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PHOTOCHEMICAL REACTIONS OF ACYLSILANES TOWARDS THE CONSTRUCTION OF CARBON-CARBON BONDS

Doutoramento em Farmácia
Química Farmacêutica e Terapêutica
Em regime de cotutela com Tampere University

João Rafael Campos do Vale

Tese orientada pelo Professor Doutor Nuno Filipe Rafael Candeias e coorientada pelo Professor Doutor Carlos Alberto Mateus Afonso, especialmente elaborada para a obtenção do grau de doutor.

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ACKNOWLEDGEMENTS

First, I would like to acknowledge my supervisor Professor Nuno Candeias for his dedication and strong commitment to organic chemistry, which continues to inspire me to study and learn as much as possible. Apart from all the help regarding scientific issues, I appreciate the tenacious friendliness that you showed me since the beginning of this journey which has now turned into a friendship I deeply cherish. Thank you for your endless patience and tireless support to all your students.

To Professor Carlos Afonso I would like to thank for believing in my abilities and motivating me to pursue a PhD in organic chemistry. You have been the backbone of my academic endeavour and an inspiration in the pursuit for knowledge. Thank you for all the professional and personal assistance that you have given me for the past seven years.

To my wife Ana, I am grateful for the love and support that you give me every single day.

To Pipsa and Raimo I would like to thank for taking me in as their *suomalainen poika*, for showing me Finland, and for the kind friendship that made the years I spent in Tampere fantastic.

To my colleagues in TUNI, I want to thank Suvi, Bene, Jagadish, Tatu, Allu and Kim for all the fantastic times spent in lab and outside it. Your friendship gave me a wonderful time in Finland.

To all my colleagues in FFUL, especially Dr. Filipa Siopa, Milene, Gomes, Oliveira, Miguel, Lídia, Juliana, Ravasco and Lopes, thank you for the long-lasting companionship.

This work was financially supported by the Fundação para a Ciência e Tecnologia (FCT) grant SFRH/BD/120119/2016 and the FCT project PTDC/QUI-

QOR/32008/2017. This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 951996.

ABSTRACT

Photochemistry is a field of chemistry which has fascinated chemists for centuries. The access to the photoexcited state of molecules allows otherwise unattainable reactivity and access to completely novel structures. The use of light as a reagent in organic synthesis can also circumvent the need of toxic or expensive reagents commonly used in traditional synthetic chemistry, making photochemistry an attractive tool in the context of Green Chemistry.

Acylsilanes are a class of compounds with rich photochemistry. They possess the unique ability to undergo photorearrangement to reactive nucleophilic siloxycarbenes. While this metal-free method for carbene generation is highly promising, the number of known efficient reactions they undergo is limited and underexplored.

In this thesis, a variety of acylsilanes have been synthesized in order to further explore and expand their known photo reactivity and obtain new complex structures via C-C bound forming photoreactions. A regioselective intramolecular [2+2]-photocycloaddition of benzoyl(allyl)silanes was developed to yield novel silacyclopentanes, compounds that may be used as silicon bioisosteres of cyclopentanes. Additionally, a novel formal (4+1)-cycloaddition of photogenerated siloxycarbene with electrophilic dienes was discovered, allowing the synthesis of highly functionalized cyclopentenes and expanding the limited reactivity of such carbenes with olefins.

During the synthesis of acylsilanes via the dithiane *umpolung* methodology an autooxidative condensation of lithiated aryl dithianes was serendipitously uncovered, which yielded complex α-thioether ketone orthothioesters, some of which present strong cytotoxic activity against glioblastoma cancer cell lines.

Keywords: Photochemistry, Acylsilanes, Carbene, Metal-free, Cyclopentanes.

RESUMO

A fotoquímica é uma área da química que tem vindo a fascinar a comunidade científica desde há vários séculos. A foto-irradiação de moléculas possibilita o acesso ao seu estado excitado, o que permite desbloquear reatividades inacessíveis por meios convencionais e sintetizar novas estruturas químicas. A fotoquímica contempla ainda a substituição de reagentes tóxicos e dispendiosos, tipicamente utilizados na síntese química tradicional, por fotões de baixo custo, facilmente acessíveis e com mínimo impacto ambiental. Nos últimos anos a fotoquímica tem aparecido na vanguarda da Química Verde, devido à introdução de novos fotocatalisadores, quer metálicos quer orgânicos, e que têm permitido abandonar a irradiação de luz ultravioleta por luz visível, tipicamente azul. Além disso, a combinação de fotoquímica com química de fluxo contínuo permitiu resolver um dos maiores desafios da fotoquímica: a baixa escalabilidade dos processos, característica inerente à baixa razão área/volume dos reatores convencionais. Estes recentes desenvolvimentos têm permitido a introdução da fotoquímica num maior número de laboratórios de química orgânica e também na indústria química para processos de grande escala.

Em particular, os acilsilanos apresentam-se como moléculas com uma fotoquímica única. Sintetizados pela primeira vez em 1957 por Brook, a sua coloração fortemente amarela, no caso de acilsilanos aromáticos, suscitou interesse no campo da fotoquímica. Rapidamente foi descoberto que, após absorção de luz, os acilsilanos sofrem um rearranjo de Brook 1,2 produzindo um siloxicarbeno reativo capaz de realizar inserções heteroátomo-hidrogénio. Esta nova metodologia verde de produção de carbenos, com total economia de átomos e sem recurso a metais de transição demonstrou o enorme potencial dos acilsilanos como reagentes precursores de carbenos para utilização em química orgânica. A procura de novos métodos de formação de carbenos é uma demanda constante, já que estes intermediários altamente reativos são utilizados frequentemente em síntese química para reações energeticamente exigentes como inserção carbono-hidrogénio e ciclopropanação. No entanto, o método mais utilizado atualmente continua a ser

por decomposição de compostos diazo, tipicamente através de catálise com metais de transição. Desde a descoberta que a irradiação de acilsilanos produz siloxicarbenos, várias reações que intercetam este intermediário reativo foram já desenvolvidas, tais como ciclopropanação de olefinas, adição a alcinos e grupos carbonilo e acoplamento cruzado com esteres borónicos. Apesar do extenso estudo que tem sido a vir a ser desenvolvido nesta química, o potencial dos acilsilanos ainda está por ser totalmente alcançado, fato demonstrado pela contínua publicação de artigos de alto impacto científico nos dois últimos anos.

O objetivo do trabalho apresentado nesta tese é explorar as propriedades fotoquímicas dos acilsilanos através do desenvolvimento de metodologias e transformações sintéticas inovadoras, permitindo o acesso a novas estruturas químicas. Mais especificamente, o trabalho foca-se em novas reações fotoquímicas de construção de ligações carbono-carbono, aproveitando o siloxicarbeno reativo gerado de forma livre de metais de transição e com total economia de átomos. As reações de formação de ligações C-C são transformações essenciais na construção de compostos orgânicos simples e complexos e são o núcleo fundamental da síntese orgânica. À medida que a química orgânica evolui, aumenta também a demanda não apenas por novas metodologias, mas também por processos mais sustentáveis e verdes. Os acilsilanos são, portanto, uma plataforma promissora capaz de combinar a sustentabilidade inerente à fotoquímica e a alta reatividade dos carbenos para atender aos requisitos modernos da química orgânica.

Este objetivo possui à partida desafios concretos, já que o carbeno obtido por fotólise de acilsilanos apresenta um dualismo de reatividade. Por um lado, reage rápida e quantitativamente com ligações polares heteroátomo-hidrogénio, como por exemplo ligações O-H. Deste modo, além da necessidade de utilizar condições anidras, todos os materiais de partida e reagentes necessitam ser protegidos ou desenhados cuidadosamente para não apresentarem estes grupos funcionais. Por outro lado, as suas reações de adição a ligações insaturadas carbono-carbono ou carbono-oxigénio são lentas ou inexistentes. O grande desafio do aproveitamento deste tipo de carbenos para formação de ligações carbono-carbono reside no desenvolvimento de parceiros reacionais racionalmente desenhados para este efeito, respeitando os requerimentos específicos associados aos acilsilanos.

Esta dissertação foca-se em três tópicos principais:

1) Síntese de acilsilanos, que irá destacar as principais estratégias utilizadas na literatura e os desafios associados à preparação deste grupo funcional. Apresentará também os resultados desta dissertação sobre a síntese de diversos acilsilanos e o racional utilizado na seleção de diferentes métodos sintéticos. Nesta fase, um elevado número de acilsilanos funcionalizados foram sintetizados, utilizando maioritariamente as estratégias umpolung de ditianos e benzotriazóis, os quais serviram como precursores para os estudos dos tópicos seguintes. Ao longo da preparação de acilsilanos através do método de ditiano, uma nova autooxidação de ditianos foi descoberta, na qual ortotioésteres de α-tioéter cetonas (TKOs) foram obtidos. O alto rendimento desta reação, assim como o seu mecanismo peculiar e a alta complexidade das estruturas obtidas suscitaram interesse para um estudo mais completo. O mecanismo da reação foi estudado e elucidado através de experiências laboratoriais apoiadas com cálculos de DFT. A reação de oxidação mostrou ser robusta para ditianos aromáticos, mas apresentar mecanismos reacionais e produtos diferentes para ditianos alquílicos ou não substituídos. Alguns TKOs, possuindo o grupo funcional fenol e metóxido, demonstraram citotoxicidade significativa contra linhas celulares cancerígenas de glioblastoma, sendo mais ativos e seletivos que o composto de referência - a cisplatina. Sendo uma classe de estruturas novas para o tratamento deste tipo de cancro, um estudo posterior mais completo de SAR poderá dar origem a compostos com relevância farmacêutica. Este trabalho deu origem às Publicações I e III, publicadas nos jornais internacionais revistos por pares *Journal of Organic Chemistry* e *Cells*, respetivamente.

2) Reações de carbenos derivados de acilsilano, que darão uma visão completa da reatividade destes intermediários gerados termo e fotoquimicamente e como têm sido usados em diferentes reações de inserção, adição e acoplamento na literatura. Além disso, apresentará a contribuição desta dissertação neste campo, uma vez que foi desenvolvida uma fotocicloadição formal (4+1) via reação de siloxicarbeno fotogerado com diciano-2-metilenobut-3-enoatos (DCMEs). DCMEs são dienos altamente eletrodeficientes que apresentam elevada reatividade como eletrófilos, característica fundamental para reagir com siloxicarbenos. Este trabalho apresenta pela primeira vez a capacidade do siloxicarbeno em realizar cicloadições em sistemas conjugados, estando este tipo de reações anteriormente limitadas a olefinas e alcinos. A reação prossegue via ciclopropanação sequencial (CP) e rearranjo vinil-ciclopropano (VCR) originando ciclopentenos altamente

funcionalizados através da construção de duas novas ligações C-C. Este tipo de cicloadição com siloxicarbenos está atualmente limitada a DCMEs, devido à escassez de métodos para a síntese de dienos altamente eletrodeficientes. No entanto, à medida que novas metodologias para a obtenção de tais dienos forem desenvolvidas, os acilsilanos poderão surgir como uma plataforma robusta para a síntese de diversos ciclopentanos, unidade química frequentemente presente em compostos com relevância medicinal e farmacêutica. Este trabalho deu origem à Publicação IV, publicado no jornal internacional revisto por pares *Journal of Organic Chemistry*.

3) [2+2]-Fotocicloadições de acilsilanos, que apresentará a escassa literatura sobre a utilização do grupo carbonilo de acilsilanos em reações de cicloadição fotoquímica com olefinas, sem fotoconversão a siloxicarbeno. Este tipo de reatividade é difícil alcançar, já que o acilsilano no seu estado foto excitado rearranja rapidamente para o siloxicarbeno mencionado anteriormente. De forma a intercetar este intermediário excitado, pré-rearranjo de Brook, é necessário um grupo funcional que reaja extremamente rápido com o grupo carbonilo. Por agora, tal cinética é possível apenas considerando reações intramoleculares. Esta tese contribuiu para a expansão deste campo desenvolvendo condições para controlar efetivamente a regioseletividade de [2+2]-fotocicloadições de acilsilanos. O protocolo desenvolvido permite a síntese de novos silaciclopentenóis via reação de formação de ligação C-C. Este trabalho deu origem à Publicação II, publicado no jornal internacional revisto por pares *Organic Chemistry Frontiers*.

Palavras-chave: Fotoquímica, Acilsilanos, Carbenos, Ciclopentanos

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Publication **II** Vale, J. R., Valkonen, A., Afonso, C. A. M., Candeias, N. R. "Synthesis of silacyclopent-2-en-4-ols via intramolecular [2 + 2] photocycloaddition of benzoyl(allyl)silanes" Org. Chem. Front., **2019**, *6*, 3793 – 3798.

Publication **III** Viswanathan, A., Musa, A., Murugesan, A., Vale, J. R., Afonso C. A. M., Mani, S. K., Yli-Harja, O., Candeias, N. R., Meenakshisundaram Kandhavelu, M., "Battling Glioblastoma: A Novel Tyrosine Kinase Inhibitor with Multi-Dimensional Anti-Tumor Effect" Cells, **2019**, *8*, 1624 – 1642.

Publication **IV** Vale, J. R., Gomes, R. F., Afonso C. A. M., Candeias, N. R., "Functionalized Cyclopentenes via the Formal [4+1] Cycloaddition of Photogenerated Siloxycarbenes from Acyl Silanes" J. Org. Chem., **2022**, *87*, 8910 – 8920.

AUTHOR'S CONTRIBUTION

I João R. Vale designed and carried out the synthesis and characterization of the compounds, interpreted the results, constructed the supporting information, and revised the manuscript. Tatu Rimpiläinen carried out part of the synthesis and characterization of the compounds. Nuno R. Candeias performed the DFT calculations, supervised the work and drafted the manuscript. Carlos A. M. Afonso supervised the work and revised the manuscript.

II João R. Vale designed and carried out the synthesis and characterization of the compounds, interpreted the results, constructed the supporting information, and drafted the manuscript. Arto Valkonen performed the X-ray crystallographic studies. Nuno R. Candeias performed the DFT calculations, supervised the work and revised the manuscript. Carlos A. M. Afonso supervised the work and revised the manuscript. All co-authors contributed to the writing of the manuscript.

III João R. Vale designed and carried out the synthesis and characterization of the compounds. Nuno R. Candeias and Carlos A. M. Afonso supervised the synthetic work. Biological studies were done by the group of Meenakshisundaram Kandhavelu (Molecular signalling group). All co-authors contributed to the writing of the manuscript.

IV João R. Vale designed and carried out the synthesis and characterization of the compounds, interpreted the results, drafted the manuscript, constructed the supporting information, and revised the manuscript. Rafael Gomes carried out part of the synthesis. Nuno R. Candeias performed the DFT calculations, supervised the work and revised the manuscript. Carlos A. M. Afonso supervised the work and revised the manuscript.

LIST OF SYMBOLS AND ABBREVIATIONS

Acac	Acetylacetonate
ACN	Acetonitrile
Ad	Adamantyl
Bt	Benzotriazolyl
Bu	Butyl
CP	Cyclopropanation
DCM	Dichloromethane
DCMEs	Dicyano-2-methylenebut-3-enoates
DFT	Density functional theory
DMAP	4-Dimethylaminopyridine
DMF	*N,N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
3,5-DNB	3,5-Dinitrobenzoyl
FDA	Food and Drug Administration
G-II	Grubbs catalyst 2nd generation
GB	Glioblastoma
HOMO	Highest occupied molecular orbital
HRMS	High resolution mass spectrometry
IC_{50}	Half-maximal inhibitory concentration
IEDDA	Inverse electro demand Diels-Alder
ISC	Intersystem crossing
LDA	Lithium diisopropylamide
LED	Light-emitting diode
LUMO	Highest unoccupied molecular orbital
*m*CPBA	*meta*-Chloroperoxybenzoic acid

MS	Molecular sieves
MTBE	Methyl *tert*-butyl ether
MW	Microwave
NBS	*N*-Bromosuccinimide
NHC	*N*-Heterocyclic carbene
NMR	Nuclear magnetic resonance
Nu	Nucleophile
PPTSA	Pyridinium *para*-toluenesulfonate
PTSA	*para*-toluenesulfonic acid
RT	Room temperature
TBAF	Tetra-*n*-butylammonium fluoride
TBDMS / TBS	*tert*-Butyldimethylsilyl
TBDPS	*tert*-Butyldiphenylsilyl
Tf	Trifluormethanosulfonyl
THF	Tetrahydrofuran
TKO	α-Thioether ketone ortothioester
TLC	Thin layer chromatography
TMS	Trimethylsilyl

1 INTRODUCTION

Photochemistry is a fascinating field of chemistry that, competing with electrochemistry, currently holds the banner of sustainable and green chemistry, and rightfully so.[1,2] The promise of replacing high-energy reagents in organic chemistry, associated with inherent toxicity, instability, and high cost, with photons that are cheap, environmentally benign, and easily assessable, has propelled the interest in photochemistry over the past decades.[3,4] Sustainability issues aside, and perhaps contributing more to the recent boom, photochemistry allows completely different reactivity profiles compared to traditional synthetic chemistry via photoexcitation and population of the excited state of molecules.[5] While typically associated with high energy irradiation such as UV light, recent developments in metal and organic photocatalysts have turned blue light irradiation as the most frequently used light source in modern photochemical reactions.[6,7] Additionally, one of the main problems associated with photochemistry is the low scalability of the processes, accounting for the low surface-to-volume ratios of common vessel reactors. These issues have been recently addressed via combining photochemistry with flow chemistry, transforming photochemistry in an interesting tool for industrial and large-scale synthesis.[8]

Regarding photoactive compounds, acylsilanes stand out as molecules with unique photochemistry.[9,10] Synthetized for the first time in 1957 by Brook,[11] it was later discovered that, after absorption of light, acylsilanes undergo 1,2-Brook rearrangement to a reactive siloxycarbene that was able to undergo heteroatom-hydrogen insertion reactions.[12,13] This novel metal-free methodology of carbene generation brought acylsilanes to the spotlight and since then, other reactions have been explored such as cyclopropanation,[14] addition to alkynes[15,16] and carbonyls,[17–19] and metal-free cross-coupling with organoboronic esters.[20] Even so, the potential of the photogenerated siloxycarbenes is far from disclosed, with many relevant articles being published this year.[14,21–23]

The objective of the work presented in this thesis is to further explore the photochemical properties of acylsilanes by developing new synthetic methodologies and transformations, allowing access to novel chemical structures. More specifically, the work was focused on novel C-C bond forming

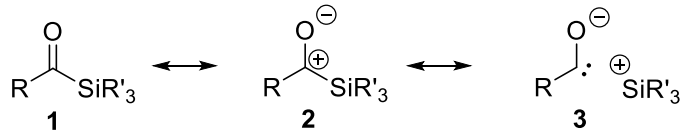
photochemical reactions, taking advantage of the reactive siloxycarbene generated in a metal-free and atom-economic manner. C-C bond-forming reactions are essential transformations in the construction of simple and complex organic compounds and are the fundamental core of organic synthesis. As the field grows, so does the demand not only for novel methodologies but for more sustainable and environmentally friendly ones. Acylsilanes are a promising platform to combine sustainability inherent to photochemistry and high reactivity of carbenes to achieve the modern demands in organic chemistry.

This dissertation will be focused on three main topics:
1) Synthesis of acylsilanes, which will highlight the main strategies used in the literature and the associated challenges involved in the preparation of this chemical motif. It will present the results of this dissertation regarding the synthesis of diverse acylsilanes and the rationale behind the selection of different synthetic methods. In addition, it will report a novel autooxidation of dithianes, common precursors to acylsilanes, which yielded stable α-thioether ketone orthothioesters (TKOs). The mechanism and scope of these unprecedented transformations were fully disclosed, and some TKOs proved to have significant cytotoxicity against glioblastoma cancer cell lines. This work led to Publications I and III.
2) Reactions of acylsilane-derived carbenes, which will give a complete overview of the reactivity of these photo- and thermogenerated intermediates and how they have been used in different insertion, addition and coupling reactions in the literature. In addition, it will present the contribution of this dissertation in this field, as a formal (4+1) photocycloaddition was developed via reaction of photogenerated siloxycarbene with dicyano-2-methylenebut-3-enoates (DCMEs). The reaction proceeds via sequential cyclopropanation (CP) and vinyl cyclopropane rearrangement (VCR) to give highly functionalised cyclopentenes via two new C-C bonds. This work led to Publication II.
3) [2+2]-photocycloadditions of acylsilanes, which will present the scarce literature on employing the carbonyl group of acylsilanes in photochemical cycloaddition reactions with olefins, without photoconversion to siloxycarbene. This thesis contributed to the expansion of this field by developing conditions to effectively control the regioselectivity of such [2+2]-photocycloadditions. The developed protocol allows the synthesis of novel silacyclopentenols via C-C bond-forming reaction. This work led to Publication IV.

2 BACKGROUND

2.1 Introduction on acylsilanes and initial investigations

Acylsilanes (**1**) are a class of compounds consisting of a carbonyl moiety bound to a silane group (Scheme 1). Although similar in structure, they present drastically distinct spectroscopic properties compared to their ketone conterparts.[24,25] The differences in electronegativity of the carbonyl carbon (X = 2.55) and the silicon atom (X = 1.90), and the larger size of silicon in comparison to carbon result in a large inductive effect releasing electron density to the carbonyl carbon. Spectroscopically, this translates into a significantly reduced carbonyl stretching frequency of acylsilanes (1618 cm^{-1} for $Ph_3SiCOPh$ versus 1692 cm^{-1} for Ph_3CCOPh), resulting in a polarization of the carbonyl group and increasing the contribution of the charge-separated resonance structure **2** (Scheme 1). The predominance of structure **2** increases the reactivity of acylsilane towards nucleophiles, to the point that acylsilanes are colloquially called sterically hindered aldehydes. In addition, acylsilanes present an abnormally long carbon-silicon bond (1.926 Å for acetyltriphenylsilane), and a 3rd non-canonical resonance form **3** has been proposed in which there is no formal bond between silicon and carbon and may explain the keenness of 1,2-silicon shifts in this class of compounds.

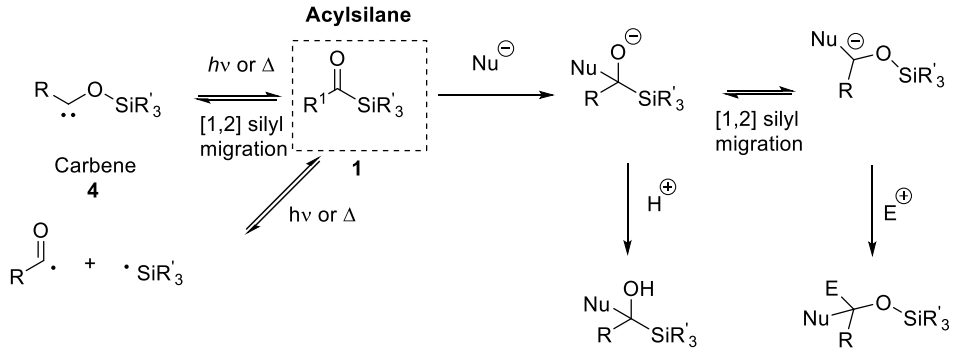


Scheme 1. Resonance structure of acylsilanes.

An important difference of acylsilanes from their ketone analogues is the significantly red-shifted (about 100 nm) absorption band of the n-π* carbonyl

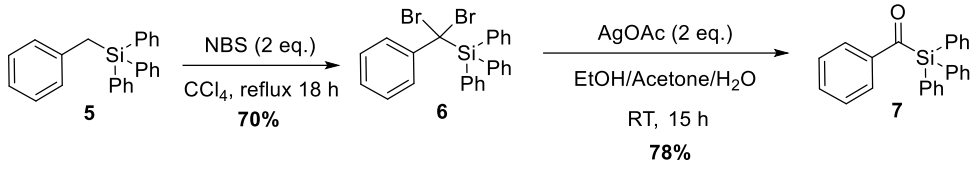
transition and its much higher molar extinction coefficient (ε = 126 M-1cm-1 for acetyltriphenylsilane and 21 M-1cm-1 for pinacolone), which is responsible for the bright yellow colour of aryl and conjugated acylsilanes.[26]

Acylsilanes have a rich and characteristic reactivity due to their ability to undergo facile 1,2-Brook rearrangements at different reaction stages, due to the large thermodynamic benefit of forming a stable oxygen-silicon bound. In fact, addition of nucleophiles to acylsilane carbonyls often leads to a silyl migration and formation of a carbanion that can be intercepted with other electrophiles or collapse intramolecularly (Scheme 2).[10]

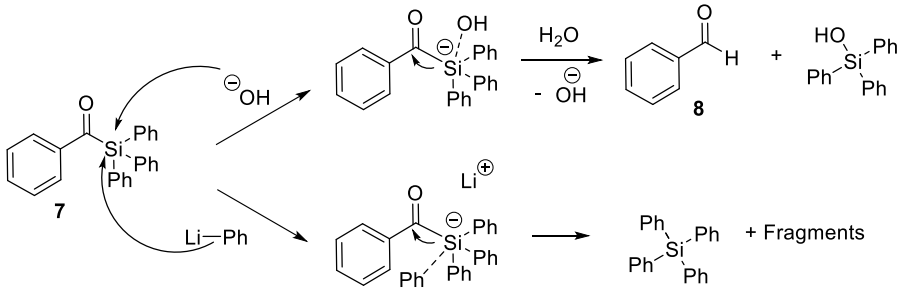


Scheme 2. Structure of acylsilanes and examples of their reactivity.

The first synthesis of acylsilanes was performed by Brook (1957), driven by curiosity about their reactivity due to the α-silicon effect, known to grant the groups attached to the α-carbon of a silane abnormal reactivity.[11] Triphenylsilyl phenyl ketone **7** was prepared via oxidation of triphenylbenzylsilane with *N*-bromosuccinamide (NBS), followed by hydrolysis with silver acetate (Scheme 3). The obtained acylsilane, yellow in colour, proved to be extremely base labile and reacted abnormally with organolithium reagents, providing products of addition to silicon instead of expectable carbonyl addition (Scheme 4).

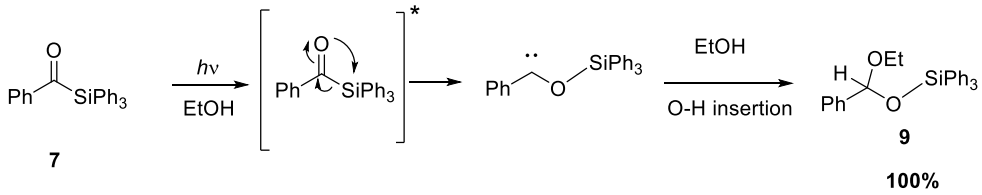


Scheme 3. First synthesis of an acylsilane, triphenylsilyl phenyl ketone, by Brook.



Scheme 4. Unusual reactivity of triphenylsilyl phenyl ketone towards hydroxy anion and phenyllithium.

In a breakthrough discovery, Brook later reported in 1967 the unusual photochemistry of acylsilanes in alcoholic solutions.[12] Upon irradiation of acylsilane **7**, mixed acetal **9** was obtained (Scheme 5) when sub stoichiometric amounts of base were used. A unique reaction mechanism was proposed in which the irradiation of the acylsilane with light promotes the formation of a reactive carbene via a [1,2]-shift, known as [1,2]-Brook rearrangement, following O-H insertion with the alcoholic solvent.



Scheme 5. Formation of a mixed acetal from photochemical isomerization of acylsilane in alcoholic solution.

The possibility of creating a reactive carbene using visible light immediately brought acylsilanes to the interest of many chemistry groups. Transition metal-free methods of creating reactive carbenes are uncommon, and nucleophilic carbenes

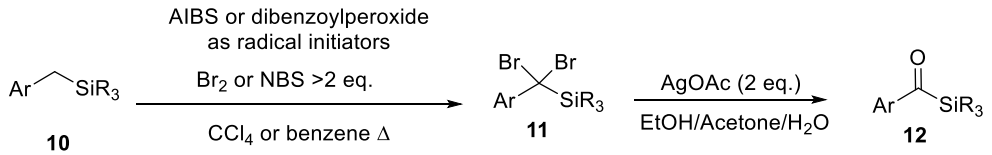
are particularly changeling to obtain, given that the common diazo-mediated metal carbenoid method works best with electron withdrawing groups bound to the carbene moiety, rendering them electrophilic.[27,28]

2.2 Synthesis of acylsilanes

With the large potential of acylsilanes and their versatility in undergoing a vast range of chemical reactions, it is vital to have synthetic methodologies that provide these molecules in a facile and efficient manner, with compatibility with different functional groups. However, the synthesis of acylsilanes has proven to be challenging. Despite the development of several methods over the years, each has its limitations and disadvantages. This section presents the most common approaches for the synthesis of acylsilanes.

2.2.1 NBS oxidation of benzylic silanes

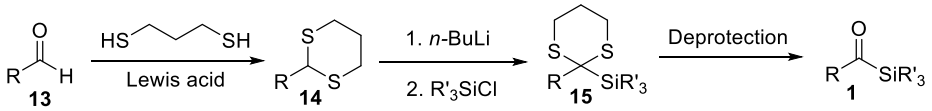
In the early stages of acylsilane chemistry, a commonly utilized strategy was the NBS oxidation of benzylic silanes **10**, followed by hydrolysis of the dibromo derivative **11** (Scheme 6).[11] This methodology propelled the initial studies on acylsilane chemistry as simple and provided direct access to benzoyl silanes. While it is still used nowadays in the synthesis of simple benzoyl silanes, it has mostly been replaced with newer alternatives as it suffers from severe scope limitations as only aromatic acylsilanes can be obtained and is incompatible with substrates that have other benzylic positions or easily oxidizable groups.



Scheme 6. Synthesis of benzoyl silanes via benzylic oxidation/hydrolysis sequence.

2.2.2 Lithium dithiane *umpolung*

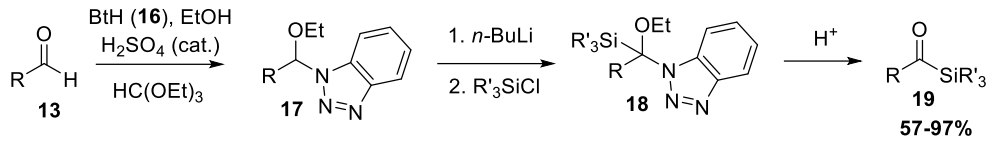
As the most commonly used procedure for the synthesis of acylsilanes, the lithium dithiane *umpolung* method involves the formation of a 1,3-dithiane from an aldehyde precursor **13**, followed by its deprotonation with a strong base, usually *n*-BuLi, and silylation with a chlorosilane (Scheme 7).[29,30] Hydrolysis of the silyldithiane **15** yields the final acylsilane **16**. Although lengthy, this methodology usually gives the desired compounds in good to excellent yields. Nevertheless, the final step can be troublesome because of the high stability of the dithiane ring. Although its deprotection works reasonably well with mercury salts such as $HgCl_2/HgO$, their toxicity and need for over-stoichiometric amounts make them unappealing reagents. Other reagents have been used to oxidize or alkylate the sulphur atoms and facilitate the hydrolysis (examples: ceric ammonium nitrate, NBS, MeI/$CaCO_3$, $I_2/CaCO_3$) but they do not work as efficiently as mercury salts and in some cases fail to give the desired acylsilane.[10] Very recently Kirihara and co-workers developed a mild procedure for the dithiane oxidation, employing catalytic amounts of $Fe(acac)_3$, NaI and hydrogen peroxide as the oxidant, obtaining aromatic and aliphatic acylsilanes in very good yields.[31] In addition to the dithiane deprotection issues, bulky or electron rich chlorosilanes seem unreactive towards the lithiated dithiane.



Scheme 7. Dithiane methodology for acylsilane synthesis.

2.2.3 Lithium benzotriazole aminal *umpolung*

A methodology similar in concept to the dithiane method (Scheme 8) was developed by Katritzky in 1996, which circumvented the difficult dithiane deprotection by utilizing the acid labile acyl anion equivalent 1-(benzotriazol-1-yl)-1-ethoxyalkanes **17**.[32] The same umpolung reactivity is explored but the final step of the synthesis is facilitated by the straightforward hydrolysis of the hemiaminal group under slightly acidic conditions.

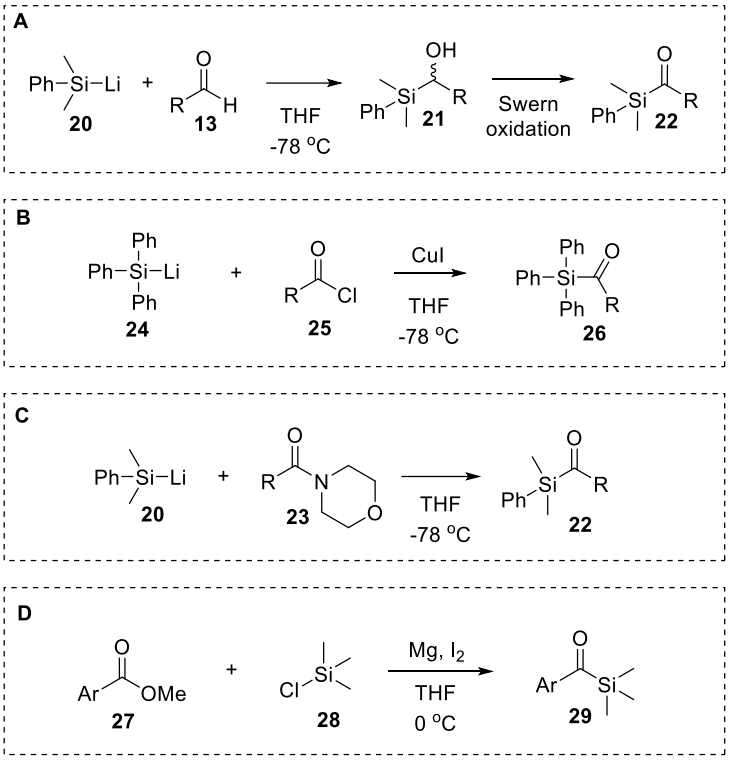


Scheme 8. Alternative method similar to dithiane approach for the synthesis of acylsilanes.

Although less stable than the parent dithianes, the benzotriazole hemiaminal intermediates **18** are still compatible with traditional silica column chromatography. Moreover, their facile deprotection allows the introduction of a wider variety of substituents on the silicon atom, such as particularly sensitive functional groups that do not resist dithiane hydrolysis conditions.

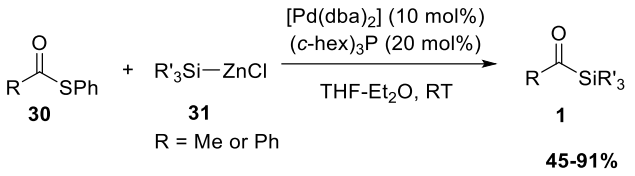
2.2.4 Metal-silyl addition to carbonyls

Due to the limitations of the previously discussed methodologies, a different approach was developed, which reverses the traditional reactivity of silanes. Metal silicon-bonded compounds can be used as nucleophilic agents to: a) add onto aldehydes **13**, resulting in a α-silyl alcohol **21**, that can be oxidized to the acylsilane **22** (Scheme 9, A)[33] or; b) add onto acyl chlorides (Scheme 9, B)[34] or equivalents such as amides (Scheme 9, C)[35] or esters (Scheme 9, D)[36], directly yielding the desired acylsilanes.



Scheme 9. Synthesis of acylsilane by addition of metal-silicon reagents to aldehydes (A), acyl chlorides (B), amides (C) and esters (D).

Although these methodologies tolerate many groups bound to the carbonyl precursor, the preparation of the metal-silyl reagents is not trivial and usually requires at least one phenyl group bound to the silicon atom to stabilize its negative charge. An interesting method was developed by Tokuyama *et. al.* that utilizes a palladium-catalysed coupling of silylzinc chlorides to thioesters (**Scheme 10**).[37] It tolerates a series of functional groups on both the thioester precursor and the silylzinc reagent, although the synthesis of the later can prove tedious.

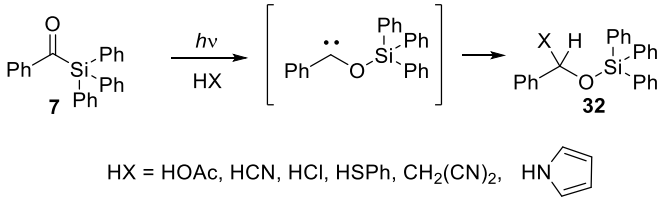


Scheme 10. Synthesis of acylsilanes by palladium-catalysed cross-coupling reaction of thiol esters and silylzinc chlorides

2.3 Reactions of acylsilane-derived carbenes

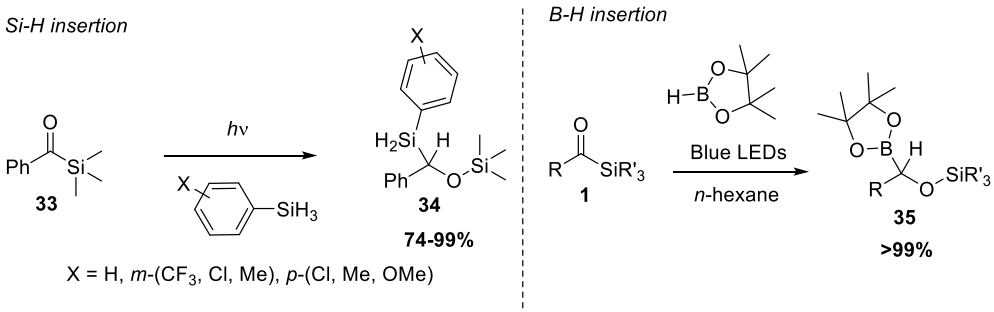
2.3.1 X-H insertion reactions of photo-generated carbenes

In addition to undergoing O-H insertion with alcohols as initially observed by Brook (Scheme 5), photogenerated siloxycarbenes were proven to undergo a variety of insertion reactions with other polar X-H labile bonds, such as amines, thiols, malonitrile and acids (Scheme 11).[13] The absence of reaction with less acidic reagents such as acetonitrile suggested a nucleophilic nature of the carbene.



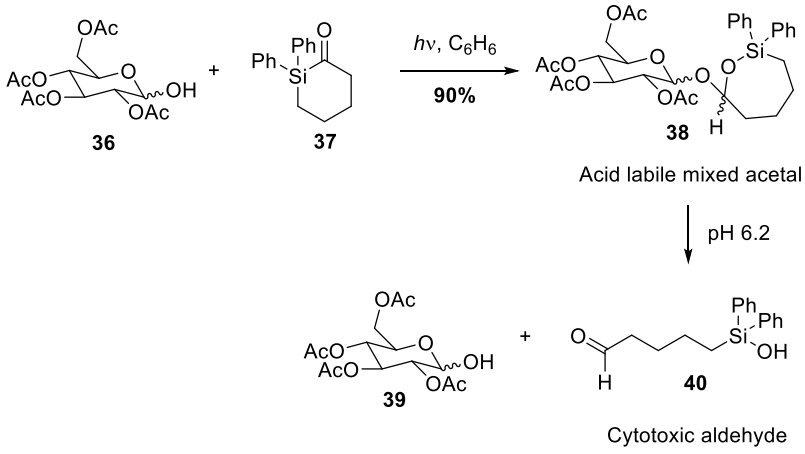
Scheme 11. Scope of the insertion reaction of carbene derived from acylsilane with polar reagents.

Two years later Watanabe *et al.* expanded the scope of the insertion reactions to a range of arylsilanes obtaining Si-H insertion products **34** in good yields (Scheme 12, left).[38] Recently, Glorius' group made the latest contribution on the matter of insertion reactions of acylsilanes by synthetizing a variety of α-alkoxyorganoboronate esters via B-H insertion of the siloxycarbene with pinacolborane to give siloxy boronate esters **35** (**Scheme 12,** right).[39]



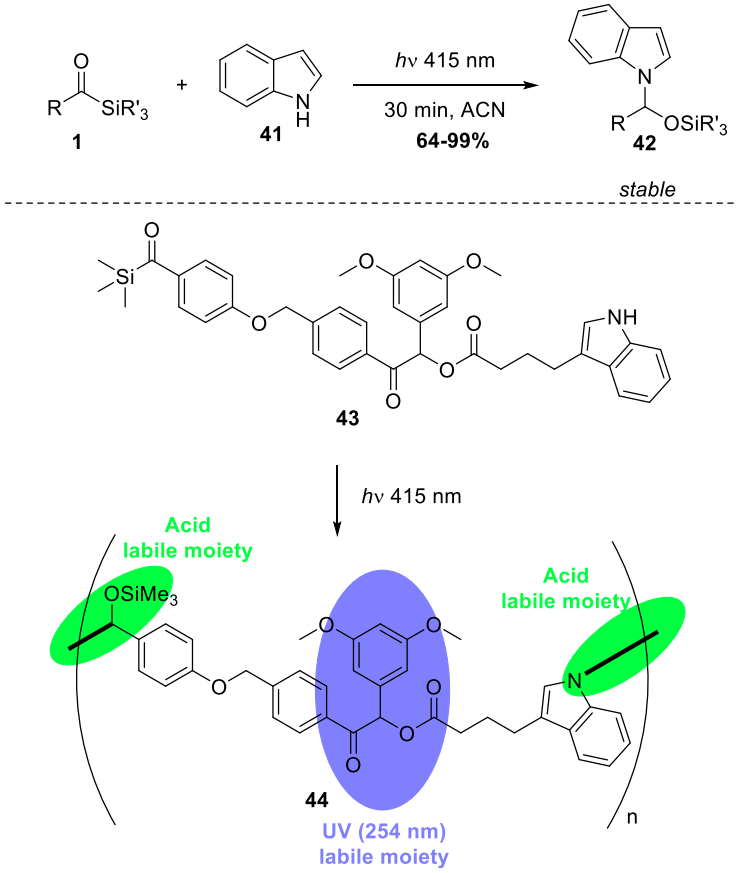
Scheme 12. Photochemical insertion reactions of siloxycarbene with phenylsilanes (left), and pinacolborane (right).

Products derived from the heteroatom-H insertion reactions of acylsilane-derived carbenes are often unstable and acid-labile, which has limited the application of such reactions. In 2004, Svarovsky *et al.* took advantage of this feature and attached glycosides **36** to an acylsilane **37** via carbene O-H insertion, producing an acid labile mixed acetal **38** (Scheme 13).[40] The increased rate of glucose transport by cancer cells facilitates the uptake of the acetal molecule which would then be hydrolysed under the acidic conditions present in the tumour environment and liberate the cytotoxic aldehyde **40** in these cells. The authors observed moderate activity against MCF-7 breast cancer cell line.



Scheme 13. Synthesis of bioactive acid-labile mixed acetals by O-H insertion of carbene.

Studer has observed in 2021 that, in contrast to the standard X-H insertion products of acylsilane-derived carbenes, N-H insertion with indoles (**41**) yields remarkably robust *N*,*O*-acetals **42** (Scheme 14), which are stable at high temperatures and in wet solvents.[41] Cleavage of this acetal moiety can be performed only under acidic conditions or via fluorine-induced desilylation. The authors utilized the atom-efficient and high yielding intramolecular N-H insertion as a photoclick reaction for the construction of polymers such as **44** possessing an acid-labile cleavable unit.

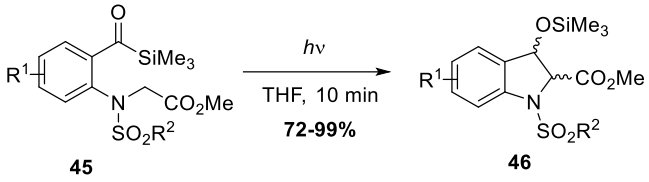


Scheme 14. N-H insertion of indoles with acylsilane-derived carbene.

2.3.2 Carbon-carbon bond forming reactions of photo-generated carbenes

2.3.2.1 C-H insertion

Examples regarding C-H insertion reactions of photogenerated acylsilanes are nevertheless extremely scarce. In addition to the intermolecular insertion with malononitrile previously mentioned (Scheme 11), only one more example of successful C-H insertion has been reported. Bolm's group successfully achieved intramolecular C-H insertion with acylsilanes **45** which possess an acidic position α- to ester and sulfonamide (Scheme 15).[42] These acylsilanes swiftly undergo 1,2-Brook rearrangement to the siloxycarbenes after irradiation which insert onto the acidic hydrogen to give indolines **46**. Unfortunately, this C-H insertion reaction is extremely limited in scope, requiring a very specific substrate, and presenting poor *cis*/*trans* selectivity.

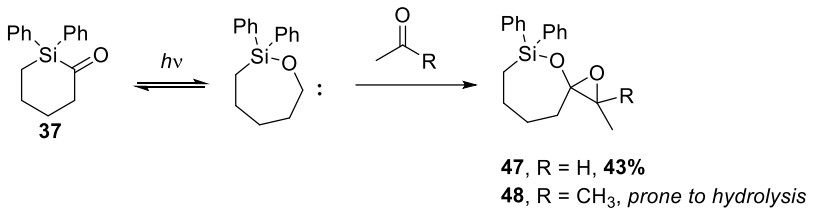


Scheme 15. Intramolecular C-H insertion of acylsilanes to give indolines.

2.3.2.2 Addition to carbonyl

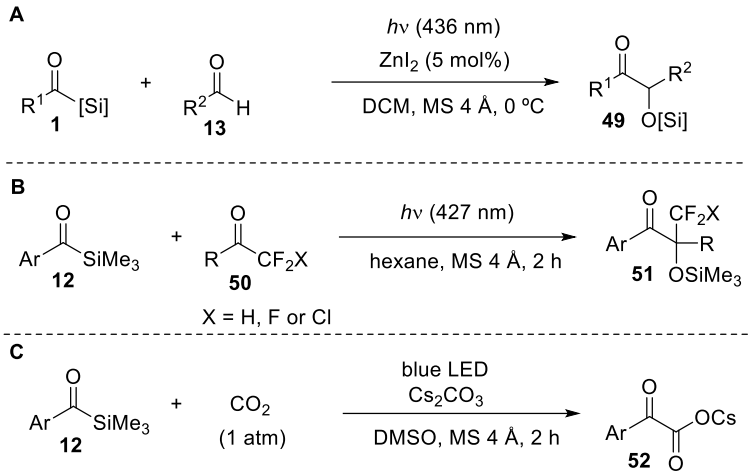
While heteroatom-H insertion reactions have been proven a useful addition to the chemical toolbox of acylsilanes, the nature of the siloxycarbene makes it so that products derived from such reactions are little more than masked carbonyls in the form of a siloxy acetal. Given the metal-free and visible light-promoted generation of carbenes from acylsilanes, it is more exciting to harness the potential of such carbenes towards the synthesis of new and stable carbon-carbon bounds. Considering the nucleophilic nature of the siloxycarbene, the carbonyl group suggests itself as a suitable electrophile. Such reactions were initially investigated by Brook, in which the carbene from an acylsilane precursor **37** was successfully captured by reaction with formaldehyde or acetone forming the corresponding oxiranes **47** and **48** (Scheme 16), in low yields and with instability problems.[43]

Nevertheless, these reactions further demonstrated the potential of the siloxycarbenes as reactive intermediates and cemented their nucleophilic character, as the electron-withdrawing nature of the addition partners was essential for reactivity.



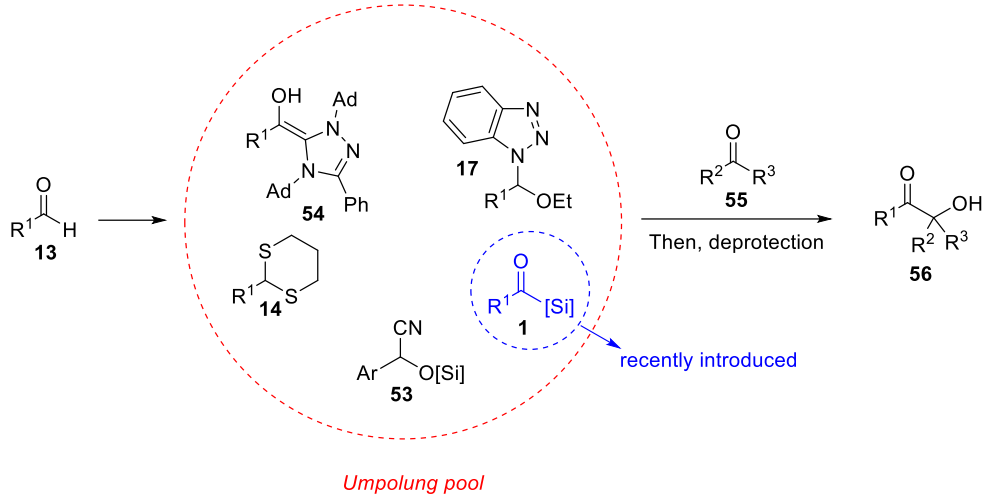
Scheme 16. Capture of carbene intermediate with acetaldehyde and acetone.

Following Brook's initial investigations, it seemed likely that the siloxycarbene derived from acylsilanes could be used in addition reactions to a variety of carbonyl functional groups. However, these carbenes proved to react sluggishly and with very specific electrophiles. In fact, efficient addition to aldehydes was only achieved nearly 50 years later by Kusama's group.[44] Contrary to Brook's results, irradiation of acylsilanes **1** in the presence of aldehydes lead to the negligible formation of addition products. The presence of Lewis acids was essential to promote efficient addition, and zinc iodide proved to be the best catalyst giving α-siloxy ketones **49** after silyl migration (Scheme 17, A). Addition to ketones is particularly challenging and only di- and tri-fluorinated ketones **50** are sufficiently electrophilic to trap efficiently and quickly the nucleophilic siloxycarbene (Scheme 17, B) and give the resulting α-siloxy ketones **51.**[18] Surprisingly, CO_2 proved to be a suitable electrophile for the siloxycarbene and allowed the synthesis of α-ketoesters after alkylation of the α-ketocarboxylate products **52** (Scheme 17, C).[19]



Scheme 17. Addition of photogenerated siloxycarbene to A: aldehydes, B: fluorinated ketones and C: carbon dioxide.

All in all, the addition of the siloxycarbene to carbonyls resembles traditional umpolung strategies used to reverse the reactivity of aldehydes, such as Corey-Seebach dithiane (**14**),[45] Kalinsky's benzotriazole aminal (**17**),[32] cyanohydrin (**53**)[46] and NHC (**54**)[47] strategies (Scheme 18). The fact that most of the methods for acylsilane synthesis employs umpolung reactivity, as discussed in chapter 2.2, vastly diminishes the importance of their carbene addition reactions, as their products could also be obtained from the acylsilane precursors, avoiding unnecessary silylation steps. For this reason, the application of acylsilanes for carbonyl addition reactions has seen virtually no use and is seen merely as a showcase of the reactivity of siloxycarbenes.



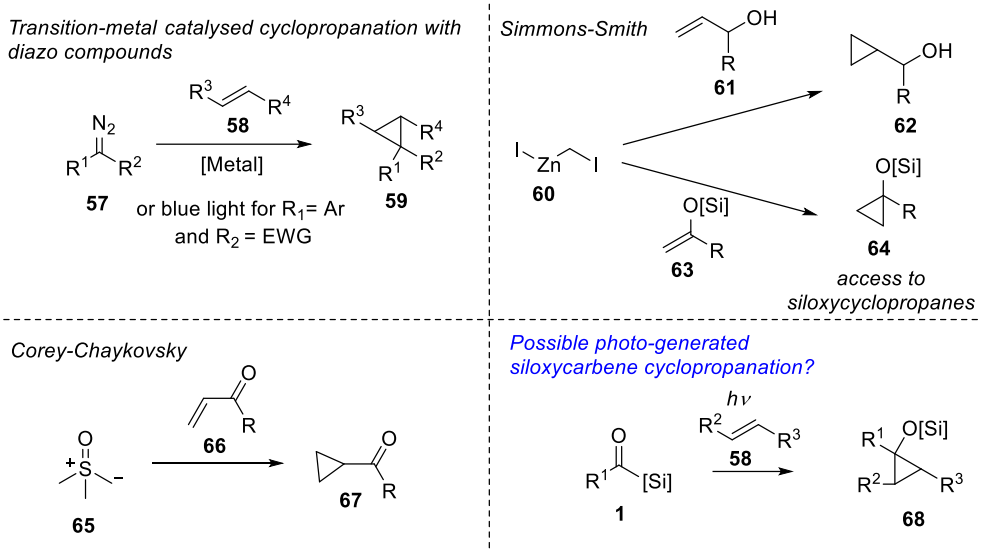
Scheme 18. Commonly used Umpolung pool for addition to carbonyls.

2.3.2.3 Addition to olefins

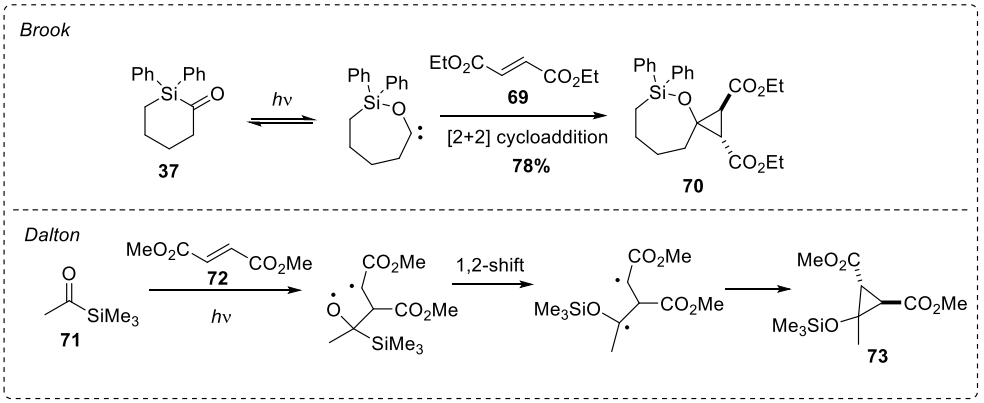
Considering traditional carbene chemistry, cyclopropanation of olefins is a classical reaction of extreme importance in the synthesis of cyclopropanes,[48] producing not only reactive intermediates in synthetic organic chemistry but a moiety present in several biologically active products.[49] One of the most studied reactions in organic chemistry is the cyclopropanation (CP) of olefins via transition metal-catalysed decomposition of diazo compounds like **57**.[50] More recently, visible light has been used as a promoter for carbene formation from donor/acceptor diazoalkanes.[51] Additional common cyclopropanation methods include the Corey-Chaykovsky reaction and the Simmons-Smith reaction, which allow functional group variability on the cyclopropane (Scheme 19).

The clean formation of siloxycarbene from irradiation of acylsilanes poses a promising novel approach to cyclopropanation reactions (Scheme 19, lower right corner). This potential was quickly realised by Brook, who observed that irradiation of an acylsilane in the presence of diethyl fumarate led to the formation of the cyclopropane product **70**.[52] While the reaction was initially proposed to go via carbene (2+1) cycloaddition (Scheme 20, top), further studies from Dalton suggested a different mechanism, involving radical addition of the singlet and/or triplet acylsilane excited state and subsequent silyl 1,2-shift followed by radical

recombination to give the cyclopentane product **73** (Scheme 20, bottom).[53] While Dalton convincingly proved that attributing the reactivity of acylsilanes with fumarates by a cycloaddition was erroneous, this work has been slept by the scientific community, and the photo-cyclopropanation of acylsilanes is generally believed to undergo via siloxycarbene intermediate.



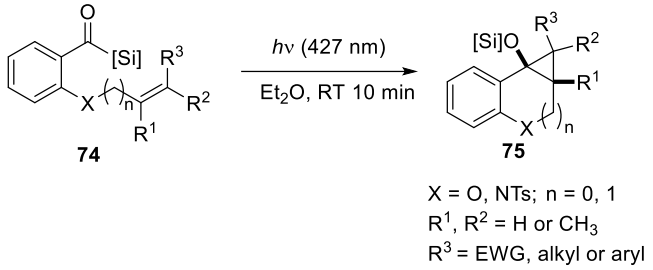
Scheme 19. Common strategies for cyclopropanation.



Scheme 20. Intermolecular photochemical reactions of acylsilanes with electron deficient olefins.

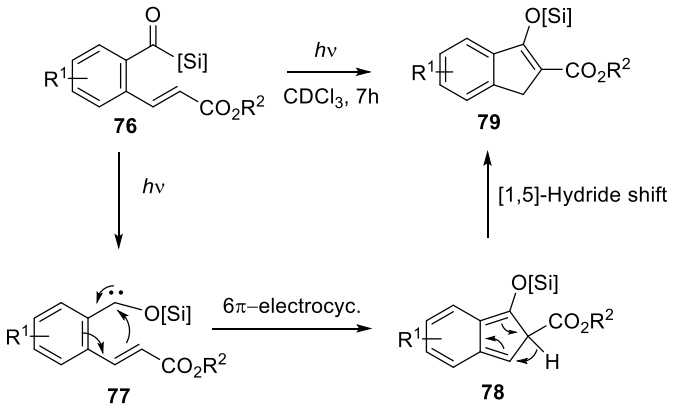
Highly activated olefins such as dialkyl fumarates and maleates were, for many years, the only olefins known to react with photoactivated acylsilanes yielding

cyclopropanes. Only recently, Priebbenow elucidated that the requirement for electron-withdrawing moieties in the olefin is less strict for the intramolecular version.[14] In fact even a few non-activated olefins (**74**) were successful in the intramolecular cyclopropanations, leading to a variety of O- and N- heterocyclic compounds (**75**) in very good yields.



Scheme 21. Intramolecular cyclopropanation of photogenerated siloxycarbene.

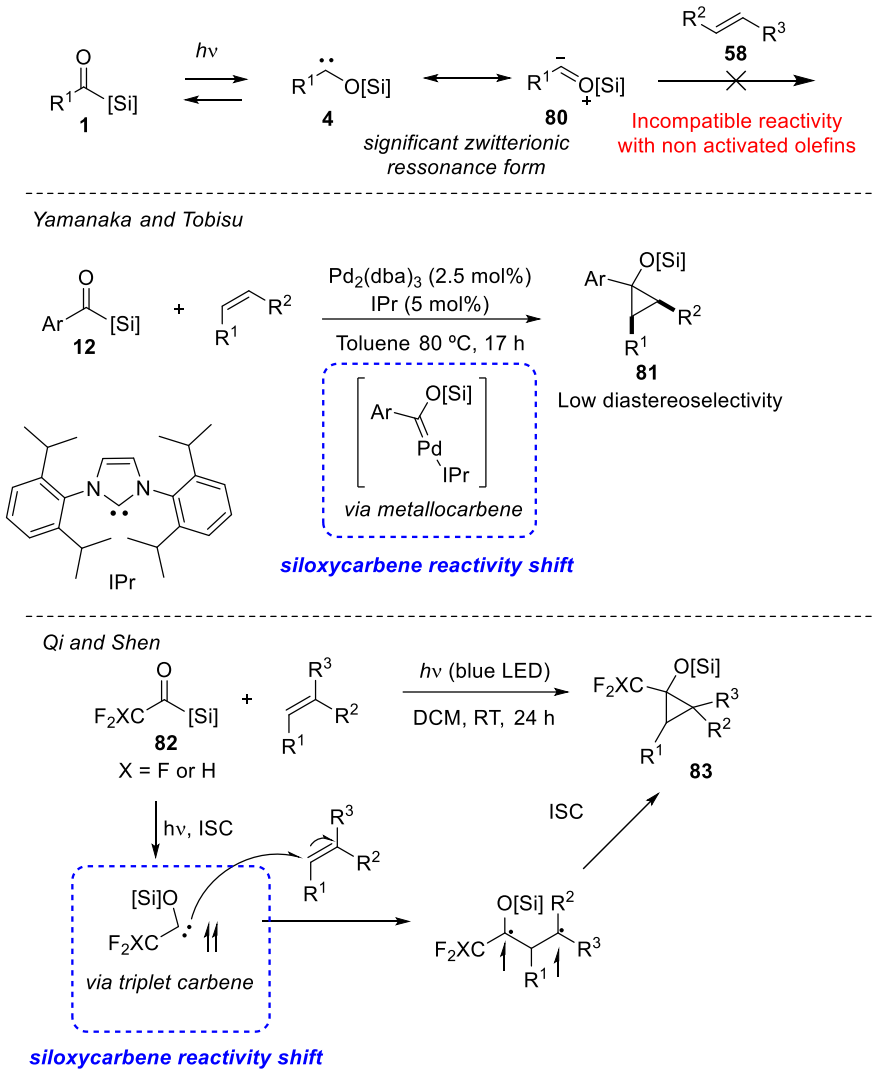
Interestingly, the photoreaction of acrylates **76**, in which the resulting siloxycarbene **77** would have to form a highly strained 4-membered ring, proceeds instead via a 6π-electrocyclization of the siloxycarbene **77** followed by a 1,5-hydride shift of the tetraene intermediate **78** to quantitively give indanone silyl enol ethers **79** in complete atom efficiency (Scheme 22).[54]



Scheme 22. Irradiation of *o*-vinyl benzoylsilanes.

Regarding intermolecular cyclopropanation, the highly nucleophilic nature of the carbene must be altered to allow reactivity with olefins other than fumarates and

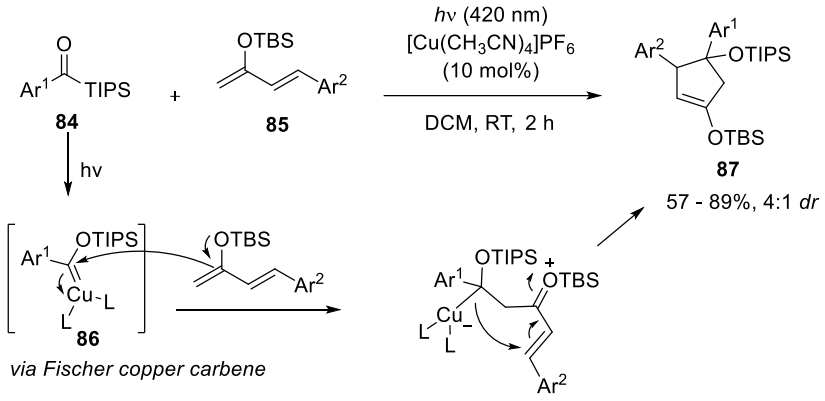
maleates, as the significant contribution of its resonance form **80** (Scheme 23) is incompatible with the electron density of nonactivated olefins. One strategy was recently employed by Yamanaka and Tobisu, in which rather than forming the siloxycarbene via photoirradiation, a palladium catalyst was used to form a metallo-siloxycarbene which reacts as electrophile with a variety of olefins to give siloxycyclopropanes **81**.[21] A similar reverse in the reactivity of acylsilanes-derived carbenes was observed by Qi and Shen.[55] Attaching a di- or trifluoromethyl group to the acylsilane (**82**) alters the traditional singlet character of the resulting photogenerated carbene to a triplet carbene which allowed intermolecular cyclopropanation with a series of non-activated olefins in a triplet di-radical pathway to give siloxycyclopropanes **83**.



Scheme 23. Reactivity mismatch between siloxycarbene and non-activated olefins and recent solutions.

Kusama's group recently expanded the potential of acylsilanes after the discovery that photogenerated siloxycarbenes complex with copper (I) to form Fischer-type copper carbene complexes like **86**.[55] The complex is formed stoichiometrically and is stable enough for *in situ* characterization, although it decomposed slowly at room temperature and could not be isolated. **^{13}C{1H} NMR** analysis of complex **86** showed a remarkable carbon signal shift of the benzylic carbon from 235 ppm in **84** to 304 ppm, suggesting a strongly de-shielded carbon characteristic of such

Fischer copper carbenes. The metallocarbene was electrophilic and reacted with highly nucleophilic dienes in a stepwise manner to form cyclopentenes **87** in good yields and moderate *dr*. The reaction supported a catalytic version in which copper metal is used sub-stoichiometric.



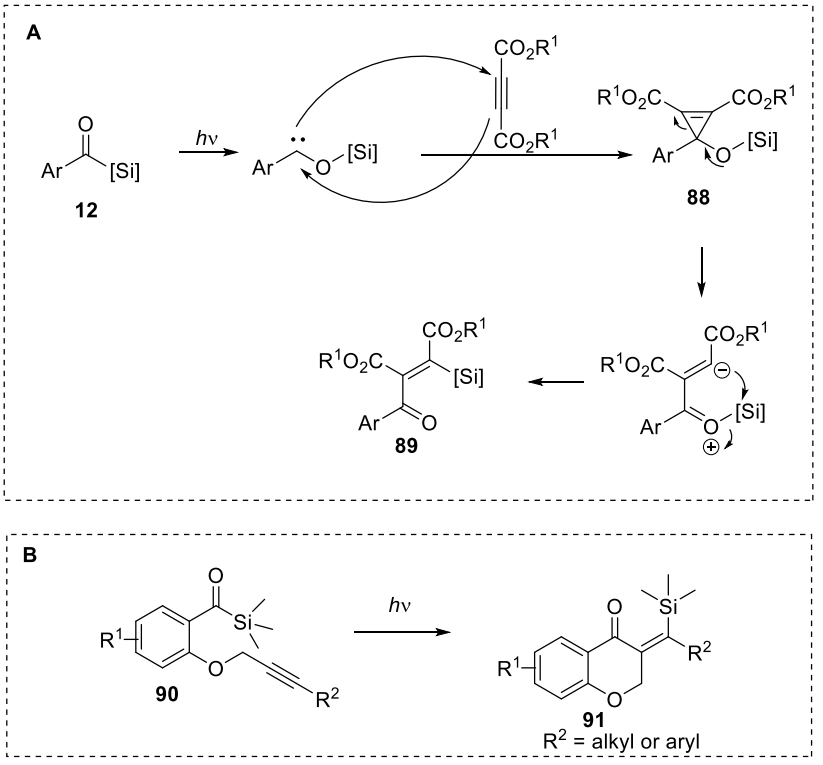
Scheme 24. Formation of copper Fisher carbene with photogenerated siloxycarbene and its reaction with electron-rich dienes.

These recent "umpolung" approaches to siloxycarbenes via complexation with transition metals are expected to quickly expand the chemical toolbox of acylsilane reactivity, as the intrinsic nucleophilic character of siloxycarbenes is modified by the transition metal, and therefore allows new types of reactivity. Considering the vast number of transition metals competent for metallocarbene chemistry, a high degree of reactivity modulation may be possible by tuning the metals and ligands to suit a particular reaction partner.

2.3.2.4 Addition to alkynes

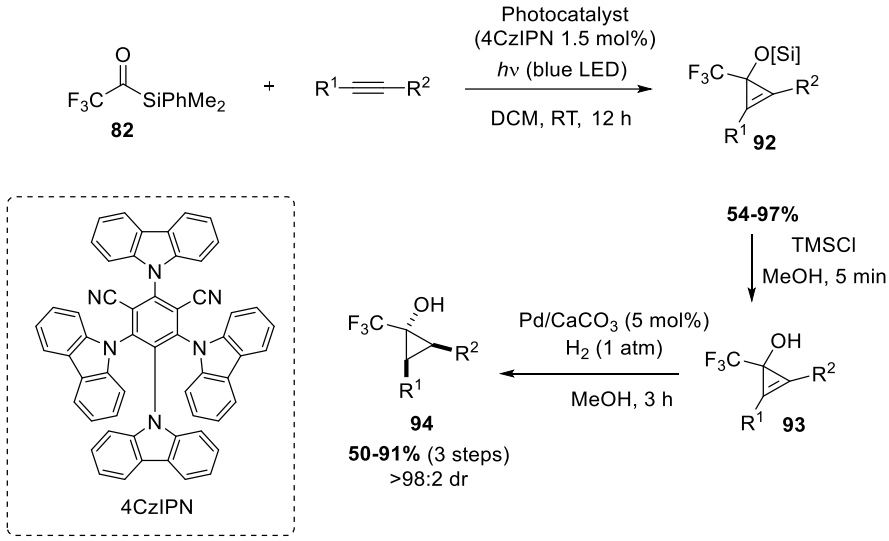
Similar to the addition to olefins, the photogenerated siloxycarbene is also capable of adding to carbon-carbon triple bonds, with similar electronic requirements. In contrast, the resulting cyclopropene intermediate has a much higher bond angle strain than the parent cyclopropane, leading to more unstable products. This was first observed by Bolm's group which reported that photochemically generated carbenes are capable of inserting in highly electron deficient internal alkynes (Scheme 25, A);[15,16] involving the initial formation of a donor-acceptor cyclopropene intermediate **88** that quickly rearranges in a highly stereo- and

regioselective manner to the silylated unsaturated ketone **89**. Again, as observed for olefins, the intramolecular variant is possible, without the requirement of highly electrophilic substituents on the alkyne (Scheme 25, B).[15]



Scheme 25. Photochemically induced cycloadditions of alkynes with acylsilanes in an intermolecular (A) and intramolecular fashion (B).

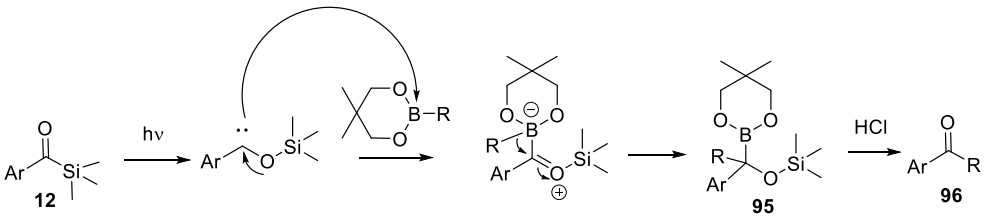
Shen group also successfully employed their previously studied trifluoracylsilanes in the cyclopropenation of the resulting siloxycarbenes with alkynes.[23] Due to the electronic nature of the donor-acceptor carbene, the reaction worked very well with non-activated terminal and internal alkynes, yielding stable siloxycyclopropenes **92** that could be desilylated (**93**) and reduced (**94**) without collapse of the three-membered ring (Scheme 26).



Scheme 26. Cyclopropenation of trifluormethylacylsilane-derived siloxycarbenes towards the synthesis of cyclopropanols in high *dr*.

2.3.2.5 Addition to organoborates

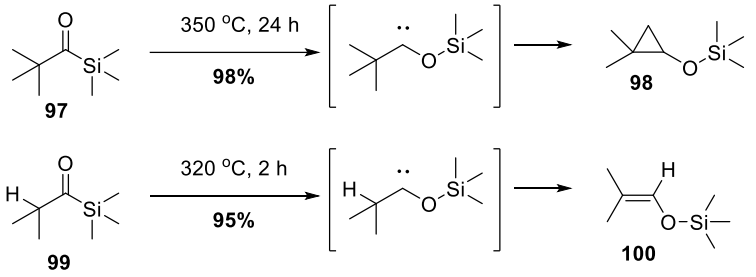
In 2010 Kusama's group observed that the photogenerated siloxycarbenes were able to undergo addition to organoboronic esters (Scheme 27).[20] A 1,2-metalate rearrangement of the addition product forms a new C-C bond and a geminal siloxy boronate ester **95**, that after autooxidation and acidic hydrolysis yields cross-coupled ketone **96**. This work was the first and only in using acylsilanes in metal-free cross-coupling reactions and showcased a unique reactivity profile of their photogenerated carbenes.



Scheme 27. Mechanism of the photochemically promoted transition metal-free cross-coupling of acylsilanes with organoboronic esters.

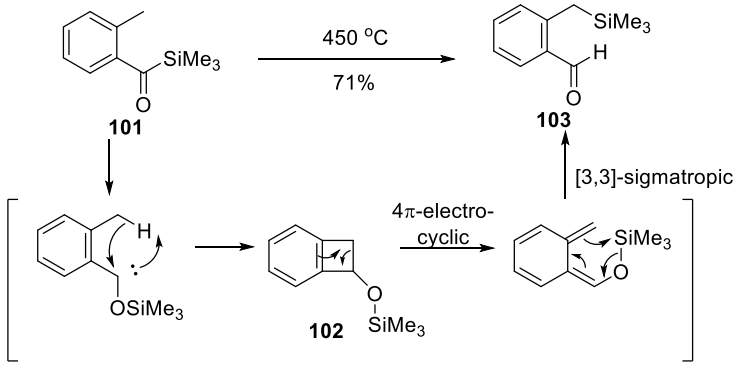
2.3.3 Thermal generation of carbenes from acylsilanes

In 1975 Brook showed that the formation of a siloxycarbene from acylsilanes also occurs under thermal conditions, typically way above 200 °C.[56] The thermolysis of acylsilanes displays different reactivity, inaccessible through photochemical conditions. For example, heating *tert*-butyl acylsilane **97** at 350 °C leads to the formation of its siloxycarbene which undergoes intramolecular C-H insertion to give cyclopropane **98** (Scheme 28). *iso*-Propyl acylsilane **99** also undergoes thermolysis to the siloxycarbene which undergoes [1,2]-hydrogen shift to give silyl enol ether **100**.



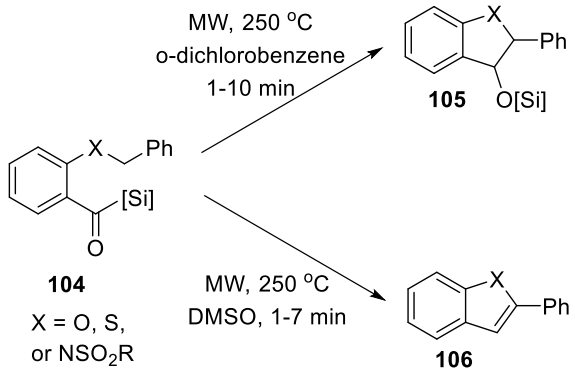
Scheme 28. Examples of intramolecular C-H insertion from thermolysis of acylsilanes.

The thermo-generated siloxycarbene is also capable of C-H insertion onto benzylic positions in an intramolecular fashion (Scheme 29 and Scheme 30).[57] Acylsilane **101** undergoes thermolysis at 450 °C and C-H insertion on the *o*-methyl group, giving the unstable cyclobutene intermediate **102** that undergoes a series of pericyclic reactions to give benzaldehyde **103** (Scheme 29).



Scheme 29. Thermally generated carbene intramolecular insertion on benzylic position.

Acylsilanes such as **104** undergo C-H insertion of benzylic position α- to the heteroatom.[42,58] Depending on the solvent, their thermolysis can yield saturated **105** or unsaturated heterocycles **106**.

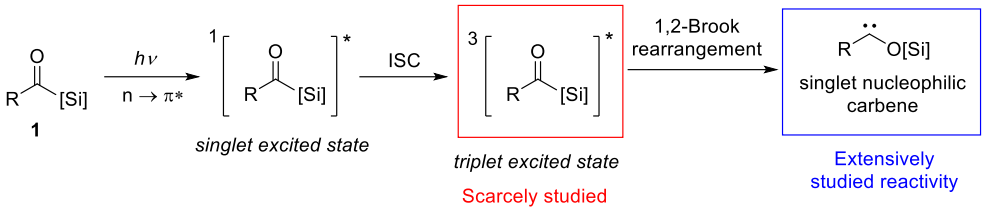


Scheme 30. Thermally generated carbene intramolecular insertion on activated benzylic position. Formation of 2,3-dihydrobenzofurans (top) and benzofurans (bottom).

Producing siloxycarbenes from the thermolysis of acylsilanes seems an attractive methodology, particularly considering that it opens the possibility of otherwise challenging reactions such as C-H insertion. However, the requirement for extremely very high temperatures for the thermal [1,2]-Brook rearrangement has limited this approach to intramolecular reactions of very specific substrates.

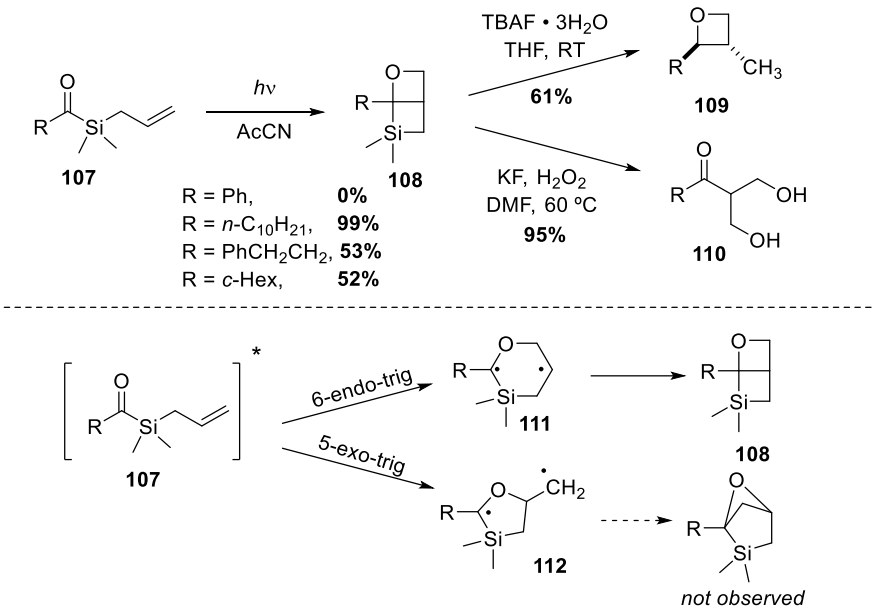
2.3.4 [2+2]-photocycloaddition of acylsilanes

The photochemistry of acylsilanes is complex and not limited to the photogeneration of siloxycarbenes. Upon absorption of light, the acylsilane undergoes a $n \rightarrow \pi^*$ transition to the S_1 excited state (Scheme 31). Then, intersystem crossing yields the triplet excited state acylsilane T_1, which can undergo the mentioned 1,2-Brook rearrangement to form the singlet siloxycarbene. Alternatively, the T_1 state of carbonyls is also a capable reactant in more traditional photochemical reactions, such as the [2+2] photochemical cycloadditions and is not limited to highly electrophilic reaction partners like the siloxycarbene, possibly adding versatility to the chemical toolbox of acylsilane photochemistry.[59]



Scheme 31. Simplified photochemical profile of acylsilanes

Although harvesting the transition state T_1 is promising for the formation of new carbon-carbon bonds, in practice, this proves challenging as the 1,2-Brook rearrangement is a fast irreversible process (to S_1 carbene). In fact, a single study was successful in harvesting this transient triplet state towards chemical reactivity. In 2008, Portella and Hammaecher synthesised a series of allyl acyl silanes **107**, which after irradiation underwent an unprecedented [2+2] photochemical cycloaddition of acylsilanes yielding oxasilabicyclo[2.2.0]hexanes **108** (Scheme 32).[60] The authors proposed a stepwise mechanism in which the carbonyl of the excited state of the acylsilane has a diradical nature and its oxygen adds to the olefin. While the addition could go via two different routes, either a 5-exo-trig, via **112**, or 6-endo-trig via **111**, the authors only observed products derived from the 6-endo-trig and point to the increased stabilization of secondary radical intermediate **111** as the culprit, presumably more stable than the primary radical alternative in **112**. The diradical then combines to yield the oxasilabicyclo[2.2.0]hexanes **108**. These products could undergo desylilation with TBAF to give oxetanes **109** and Fleming–Tamao oxidation to diol **110**. This [2+2] photocycloaddition does not allow intermolecular fashion because of the quick interconversion to the siloxycarbene which is known to be unreactive towards non-activated olefins.



Scheme 32. [2+2] photochemical cycloaddition of allylsilanes. Formation of oxetanes.

3 RESEARCH OBJECTIVES AND QUESTIONS

While a promising tool in sustainable and green organic chemistry, the chemical toolbox of siloxycarbenes is still underexplored and evading interest in the general scientific community. Recent advances in this field in high impact factor journals[14,18,19,21–23,41,55] reveal the importance of valorisation of siloxycarbenes and their still untapped potential. The main objective of this dissertation was to further explore the ability of acylsilanes to absorb blue light and rearrange to reactive siloxycarbenes in a metal-free manner. During such an endeavour the answers to a set of questions were searched, namely: i) could new C-C bond forming reactions towards the construction of novel relevant chemical structures be uncovered? ii) as the photochemical behaviour of acylsilanes is not limited to rearrangement to carbenes, would other photo transformations be attained with the same end purpose? If so, the valorisation of the developed methodologies via exploration of the chemical reactivity and biological relevance of the novel obtained chemical structures could be explored. Publications II and IV accomplished the main objective via the development of innovative photochemical transformations of acylsilanes towards the construction of novel cyclopentenes inaccessible through other methods.

The challenging synthesis of acylsilanes is still a major aspect hindering their widespread application. A consequential objective of this thesis is to employ and evaluate different synthetic methodologies of acylsilane synthesis, advance the current state of the art and elucidate the advantages and disadvantages of each method. Publications I and III reflect extensive investigations made on this topic, revealing a major side reaction in the dithiane umpolung method, the most frequently used methodology for acylsilane synthesis.

4 MATERIALS AND METHODS

4.1 General information

NMR spectra were recorded using a Bruker Fourier 300 (Bruker, Massachusetts, USA), a Bruker AVANCE III (300 MHz), a Bruker Fourier 400 (Bruker, Massachusetts, USA) or a 500 MHz JEOL ECZR instrument, using $CDCl_3$, D_2O, or $(CD_3)_2SO$ as deuterated solvent. Irradiation experiments were performed either in a Rayonet RPR-200 or in a homemade Rayonet-inspired reactor with 16 lamps (419 nm). High-resolution mass spectra were recorded using a Thermo ScientificQExactive hybrid quadrupole- Orbitrap mass spectrometer (Thermo Scientific Q Exactive Plus). Reaction mixtures were analysed by thin layer chromatography (TLC) using Merck silica gel 60F254 aluminium plates and visualized by UV light or stained with potassium permanganate, phosphomolybdic acid, vanillin stain or ceric ammonium nitrate stains. Column chromatography was performed with silica gel Geduran Si 60 (0.040−0.063 mm) purchased from Merck. All solvents were distilled before use. Dry tetrahydrofuran (THF) and dichloromethane (DCM) were obtained from the INERT PureSolv micro apparatus. Toluene was dried by standing in freshly activated 4 Å molecular sieves (20% m/v). Acetonitrile (ACN) was dried by refluxing with CaH_2. All reagents used were purchased from Fluorochem, Alfa Aesar, TCI, or Sigma-Aldrich.

4.2 Experimental Section

This section presents the general procedures for the developed transformations. The experimental details can be found in publications I-IV and as an annexe to this dissertation.

4.2.1 General procedure for autooxidation of aryldithianes

Aryl dithiane **14** (1.02 mmol, 1 equiv.) was dissolved in dry THF (5 mL) in an argon purged round-bottom flask. The solution was cooled to -78 ºC in an acetone/liquid nitrogen bath. *n*-BuLi (1.3 equiv.) solution in hexanes was added dropwise to the reaction mixture at -78 ºC. The solution was left stirring at -78 ºC for 20 minutes and then left to warm up to room temperature for 40 minutes. The argon balloon was replaced with an atmospheric air balloon and an additional needle was inserted in the septum as to allow air flow through the surface of the solution. As oxidation took place the solution warmed up and colour change was usually observed. After 1 minute the solution was quenched with 10 mL of a saturated aqueous NH_4Cl solution. 10 mL of Et_2O were added and the layers were separated. The organic phase was collected, and the aqueous phase was extracted two times with Et_2O (2 × 10 mL). The organic phases were combined and dried over $MgSO_4$. The solvent was filtered and evaporated. The products **117** were purified by flash chromatography.

4.2.2 General procedure for the synthesis of cinnamyl acylsilanes

Silyl benzotriazole hemiaminal **138** (1 mmol) was dissolved in 6 mL of dry DCM, in an argon filled round-bottom flask. The substituted styrene (5 mmol, 5 equiv.) was added to the solution, followed by 2nd generation Grubbs catalyst (1-5 mol %). The solution was refluxed overnight. The solvent was evaporated and 10 mL of hexane/ethyl acetate (9:1) mixture was added. The suspension was stirred for 10 minutes and filtered through cotton. The off-white solid, mostly composed by undesired stilbene, was washed two more times with hexane/ethyl acetate (9:1) mixture (10 mL) and filtered again. The filtrate was combined, and the solvents evaporated. The crude was passed through a small silica column (hexane/ethyl acetate mixture as eluent) to remove the remaining stilbene (highly mobile on silica). $FeCl_3$•$6H_2O$ (0.3 mmol, 0.3 equiv.) was added in one portion to an acetone solution (6 mL) of the resulting crude oil. The solution was stirred for 30 minutes, and the solvent evaporated under reduced pressure. Hexane (6 mL) was added, and the solution stirred for 10 minutes. The bright yellow liquid was filtered through cotton and the reaction flask washed with hexane (2 x 6 mL) and filtered. The filtrate was combined, and the hexane evaporated to give bright yellow oil as crude, which was purified through silica chromatography (hexane/ethyl acetate mixture as eluent) to give aroylsilanes **139** as bright yellow oils.

4.2.3 General procedure for the Photochemical cyclopropanation/Vinyl cyclopropane rearrangement of acylsilanes with DCMEs

Acylsilane **1** (0.1 mmol) and diene **145** (0.14 mmol, 1.4 equiv.) were dissolved in 0.5 mL of dry toluene in a sealed Pasteur pipette. 100 mg of molecular sieves 4 Å were added and the solution was purged with argon for 15 minutes and irradiated at 419 nm from a minimum of 24 to maximum 72 h. Reaction progress was monitored by TLC and stopped upon full consumption of acylsilane **1**. Toluene was evaporated under reduced pressure and the crude purified via silica column chromatography (eluent hexane/EtOAc) to give cyclopentenes **148**.

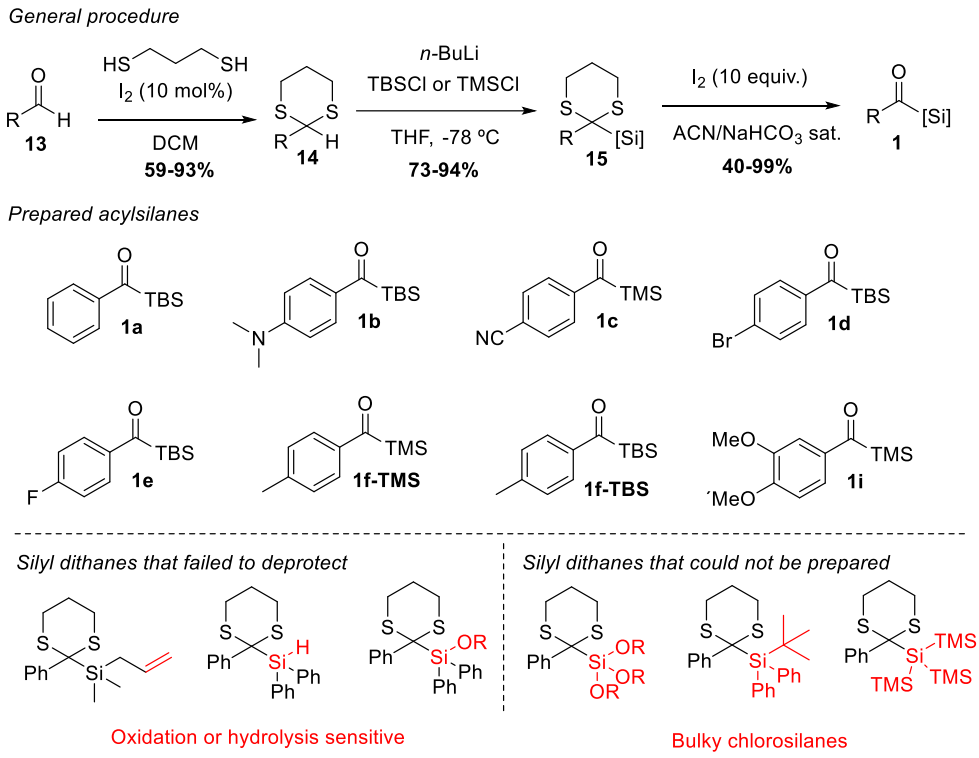
4.2.4 General procedure for the [2+2]-photocycloaddition of benzoyl(allyl)silanes

Acylsilane **139** (0.3 mmol) was dissolved in dry hexane (7 mL) under argon atmosphere, in a glass test tube. The solution was degassed with argon (until a final volume of 6 mL) and then irradiated for 5 hours. The solution was transferred to a round-bottom flask and the hexane evaporated under reduced pressure. The residue was solubilized in *t*-butanol (6 mL) at 27 °C, followed by addition of $NaHSO_4$ or PPTSA (0.03 mmol, 0.1 equiv.) and stirring at that temperature for 6 hours. The reaction was quenched with saturated aqueous K_2CO_3 (10 mL) and the product extracted with ethyl acetate (3 × 10 mL). The organic phases were combined, dried over $MgSO_4$ and filtered. The solvent was evaporated and the product isolated through silica column chromatography to give silacyclopentenols **164**.

5 RESULTS AND DISCUSSIONS

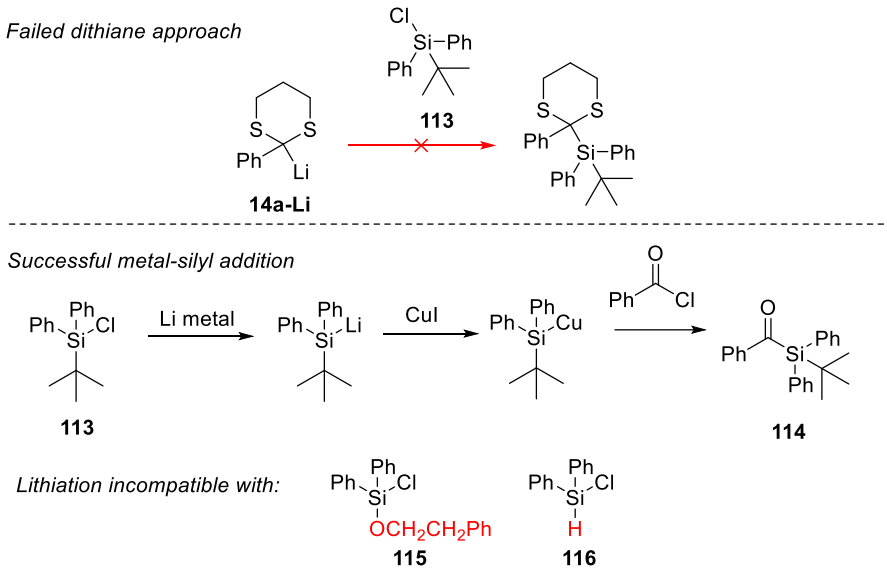
5.1 Synthesis of simple acylsilanes

The dithiane methodology proved straightforward and practical towards the synthesis of simple acylsilanes. Most dithianes **14** were obtained easily via condensation of aromatic aldehydes **13** with 1,3-propanedithiol via iodine catalysis and typically required single recrystallization as a purification method. Only highly electron-rich aromatics like 4-(dimethylamino)benzaldehyde required a stronger catalyst, namely boron trifluoride etherate. Treatment of the dithiane **14** with a slight excess of *n*-BuLi at -78 ºC and subsequent quench with chlorosilane yielded silylated dithianes **15** in good yields (Scheme 33). Deprotection of the silyl dithianes was typically achieved via oxidative hydrolysis with excess iodine, which is a much more convenient alternative to the typical mercury salt-promoted hydrolysis, which creates over-stoichiometric amounts of toxic mercury waste.



Scheme 33. Synthesis of acylsilanes via dithiane Umpolung methodology. General procedure (top) and obtained acylsilanes (bottom).

For compounds in which the silyl group was too hindered to react with a lithiated dithiane, the metal-silyl addition proved a good alternative. *tert*-Butyldiphenylchlorosilane, for example, failed to react with the lithiated dithiane. The desired acylsilane was prepared via lithiation of TBDPS-Cl followed by copper metal exchange and addition to benzoyl chloride (Scheme 34).

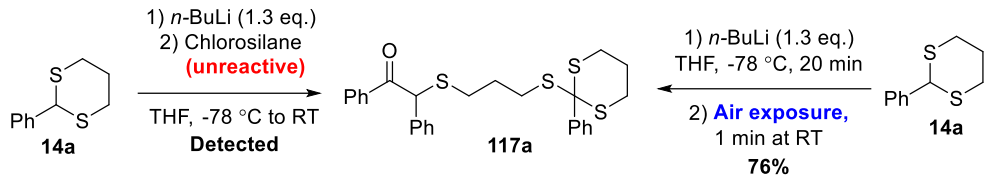


Scheme 34. Attempted synthesis of bulky diphenyl(*tert*-butyl)benzoylsilane.

Aside from the requirement of at least one phenyl group bound to chlorosilane to facilitate the formation of silyl lithium intermediate, this methodology also proved unsuitable for alkoxy chlorosilanes such as **115** and silyl hydrides (**116**) (Scheme 34), not allowing the synthesis of diversified functionalized acylsilanes.

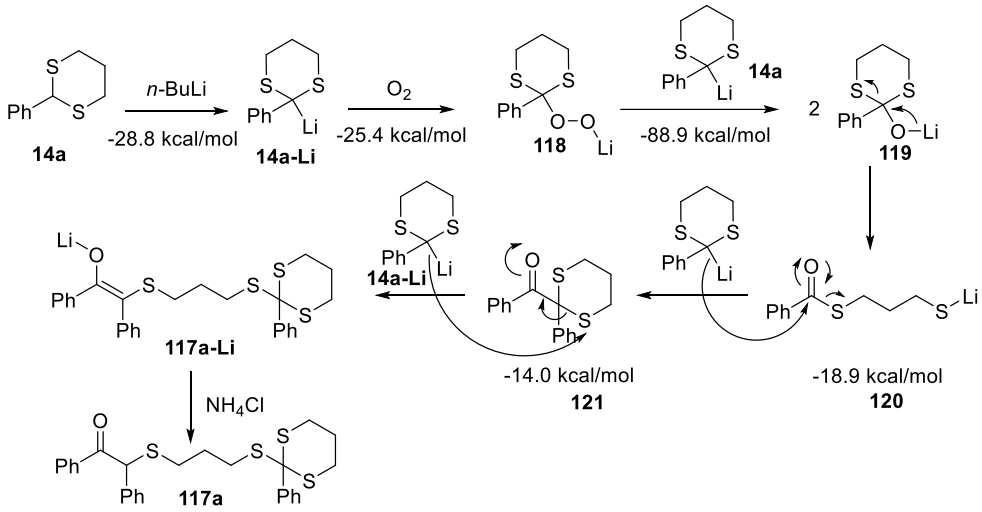
5.2 Autooxidation of lithiated dithianes

While attempting the silylation of lithiated dithiane derived from **14a**, with sterically hindered chlorosilanes, an intriguing side product **117a** was identified (Scheme 35, left). Such product, besides missing the desired silyl moiety, was consistently present when the chlorosilane used was not reactive towards the dithiane anion. Mass and NMR analysis elucidated the structure of the unexpected substance **117a** as a α-thioether ketone orthothioester, hereafter referred as TKO.



Scheme 35. Unexpected compound **117a** formed via oxidation of lithiated dithiane. Left: initial observations. Right: optimized conditions.

Since the treatment of dithiane with *n*-BuLi in the absence of a chlorosilane also lead to the formation of **117a**, it was initially thought that an oxidising impurity could be present in the old *n*-BuLi bottle, presumably *n*-BuOOLi, as seen previously by another group.[61] However, using a new bottle of *n*-BuLi did not change the outcome of the reaction. After a few studies, the source of oxygen was proven to be air. During work-up, the unreacted lithiated dithiane was briefly exposed to air before quenching with aqueous NH_4Cl, which was sufficient for the oxidation to take place. After optimization of *n*-BuLi equivalents, reaction temperature and time of air exposure, compound **117a** could be obtained in a quite satisfactory yield of 76% (Scheme 35, right). Similar structures were synthetized by a different group in 2006, obtained via the addition of a dithiane to an acyl chloride or ester,[62] which helped to rationalise the mechanism of this unprecedented one-pot oxidation of dithianes. With DFT calculations, the mechanism depicted in Scheme 36 is proposed. The initial direct oxidation step with molecular oxygen is energetically favoured with a ΔG_{form} = -25.4 kcal/mol. The lithium peroxide **118** that is formed acts again as an oxidizer for another molecule of lithiated dithiane in an extremely favoured process (ΔG_{form} = -88.9 kcal/mol), giving intermediate **119.** The opening of the latter intermediate leads to thioester **120**, being -18.9 kcal/mol more stable than the processor. Then, another molecule of lithiated dithiane adds to the thioester carbonyl, liberating a unit of dithiolate and forming intermediate **121**. A second addition of **14a-Li** to the carbonyl is highly unlikely, as there a high steric hindrance around it, as was observed by Kutateladze for ethyl derivatives. Instead, addition to the thioether is prefered, forming the enolate **117a-Li**, which after acidic quench yields **117a**.



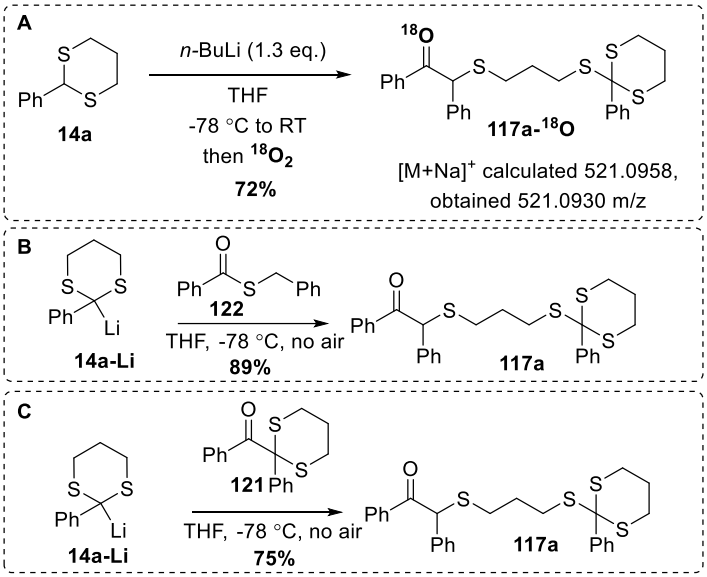
Scheme 36. Proposed reaction mechanism for the one-pot oxidation of benzyl dithiane. The energies presented below the arrows relate to ΔG_{form} of that step calculated at the PBE1PBE/6-31G(d,p) level of theory. The energies presented below the structures are related to intermediate **119.**

In order to prove the proposed mechanism, some key experiments were preformed (Scheme 37):

A. Reaction with the optimized conditions using isotopically labelled $^{18}O_2$ led to the incorporation of ^{18}O in the carbonyl of **117a**, as observed by HRMS, proving that the carbonyl oxygen source is atmospheric oxygen.

B. Reaction of lithiated **14a** with thioester **122**, in the absence of air, resulted in the clean formation of **117a**, corroborating the possibility of the thioester **120** as a reaction intermediate.

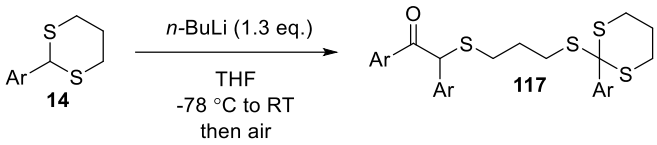
C. Reaction of lithiated **14a** with dithiane **121** led to the formation of **117a** in good yield, proving that **121** is likely a final intermediate of the reaction.

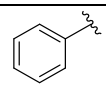
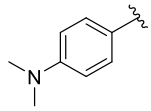
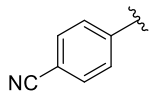
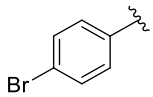
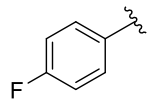
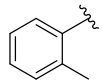
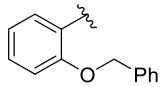
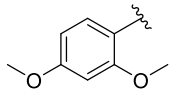
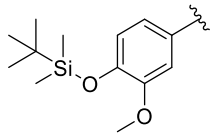
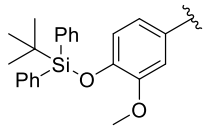
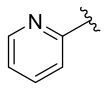


Scheme 37. A: ^{18}O labelling of compound **117a**. B: Addition of lithiated dithiane to a thioester, yielding **117a**. C: Addition of lithiated dithiane to proposed intermediate **121**, yielding **117a**.

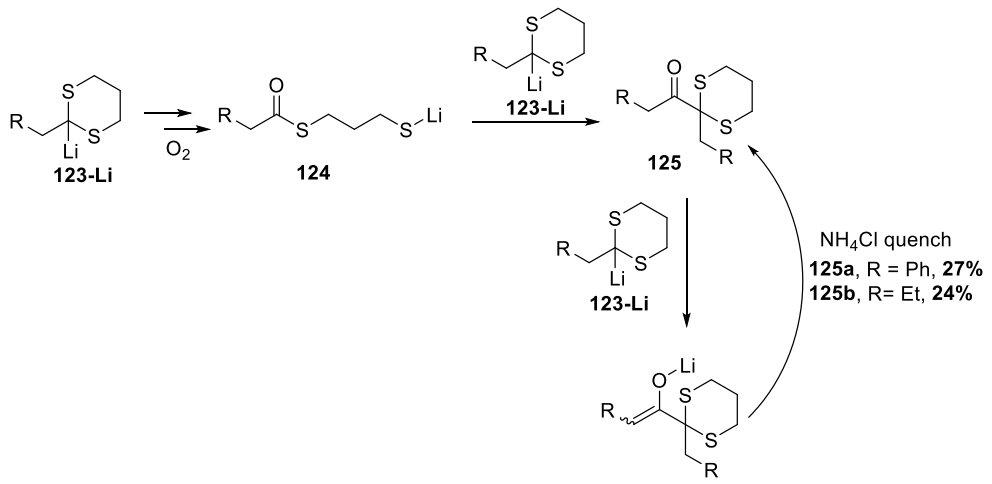
With the reaction mechanism understood, the scope of the reaction was evaluated regarding aromatic substitution on the aryl dithiane. The reaction withstands substitution on *ortho*, *meta* and *para* positions and a variety of electron-donating and slightly electron-withdrawing groups, yielding the corresponding orthothioesters **117** in good yields (Table **1**). Few examples were incompatible with the reaction conditions. Pentafluorobenzene and trifluorotoluene derivatives were unstable to the first deprotonation step as the resulting lithiated dithiane polymerizes quickly before exposure to air. Additionally, the presence of a nitro moiety in any position of the benzene ring makes it stable to the presence of O_2, leading to almost complete recovery of starting material recovery after acidic work-up. The influence of the nitro group can be attributed to the lowering of the HOMO of the corresponding lithiated dithiane and consequent lower reactivity.

Table 1. Dithiane one-pot oxidation reaction scope.



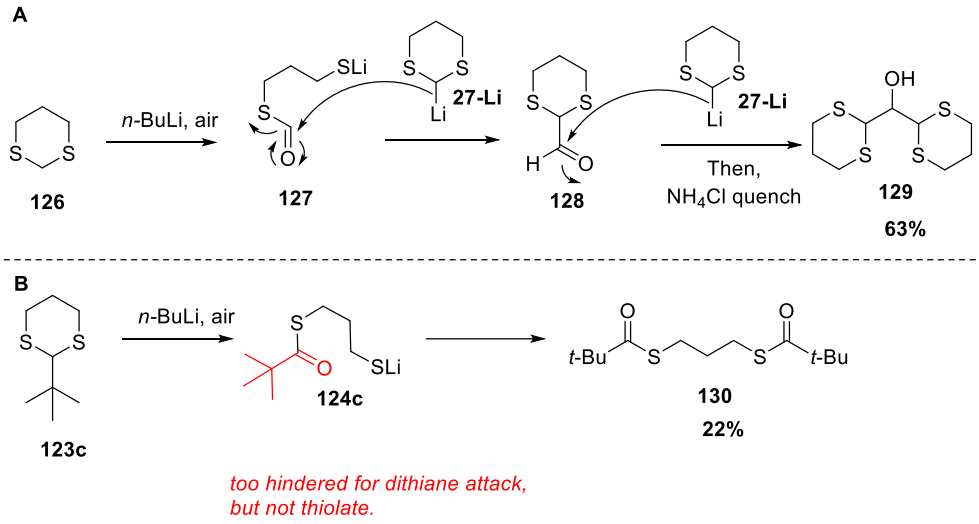
Entry	Compound	Ar	Yield (%)
1	**117a**		76
2	**117b**		64
3	**117c**		60
4	**117d**		51
5	**117e**		60
6	**117g**		69
7	**117h**		58
8	**117i**		68
9	**117j**		61
10	**117k**		89
11	**117l**		57

With non-aromatic dithiane starting materials, the reaction proceeds via a completely different mechanism. For substrates with protons α to the carbonyl, the reaction initially proceeds as with aromatic derivates with oxidation of lithiated compound **123**, thioester formation (**124**), and subsequent substitution with another unit of **123-Li**, forming α-ketodithiane **125**. However, for these substrates, **125** has an enolizable position (Scheme 38), which is deprotonated with one equivalent of **123-Li**, halting the reaction, and leading to low yields of final product **125**.



Scheme 38. Reaction pathway for non-aromatic dithianes.

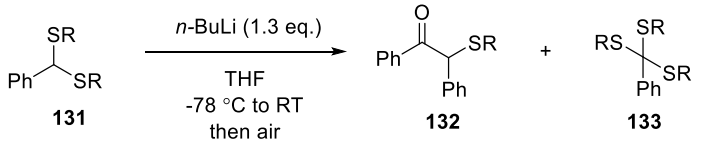
Not surprisingly, the simplest dithiane, compound **126**, also behaves differently than aromatic dithianes. Initial lithiation and air oxidation led to the formation of thioformate **127**, which could react with two equivalents of lithiated **27,** providing secondary alcohol **129** in 63% yield (Scheme 39, A). For *tert*-butyl dithiane **123c**, lithiation and oxidation gave intermediate thioester **124c**, which seems to be too sterically hindered by the *tert*-butyl moiety to be attacked by another dithiane anion molecule (Scheme 39, B). Eventually, **124c** combined via transthioesterification to give **130** in low yield.

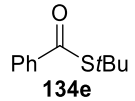


Scheme 39. Autooxidation of simple dithiane **126** (A) and *tert*-butyl dithiane **123c** (B).

The methodology was also extended to acyclic dithioacetals. In these cases, the thioacetal and α-thioether ketone moiety lack a tether, leading to the isolation of two separate molecules, α-thioether ketones **132** and orthothioesters **133** (Table 2). Orthothiosters **133** were often too chemically similar to unreacted **131** to allow separation via standard column chromatography.

Table 2. Reaction scope for acyclic dithioacetals.



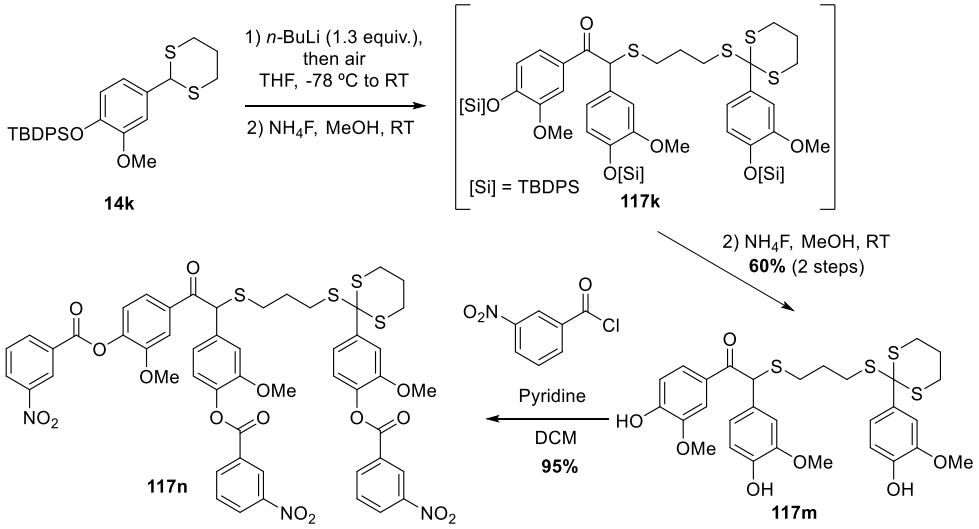
Entry	RS	Yield (%) 132	133
1	PhS (**131a**)	48	-[a]
2	*n*-BuS (**131b**)	97	72
3	$CH_3(CH_2)_{11}S$ (**131c**)	73	56
4	*sec*-BuS (**131d**)	67	-[a]
5	*t*-BuS (**131e**)	 **134e** 62%	

[a]Detected in ^{1}**H NMR** of crude, but not isolated

In conclusion, this work uncovered the unprecedented 2-aryl-2-lithium-1,3-dithianes autooxidation towards the formation of trimeric α-thioether ketone orthothioesters **117**. The reaction mechanism was fully disclosed via experimental reactions and DFT calculations. Additionally, the different behaviour of non-aromatic dithianes and non-cyclic dithioacetals was studied and fully rationalized. This comprehensive study led to Publication I.[63]

5.3 Biological activity of TKOs against Glioblastoma

Considering the prevalence of sulphur in numerous natural products and drugs,[64] including FDA-approved drugs,[65] it was interesting to explore the biological activity of TKOs prepared via autooxidation of dithianes. The compounds present an extremely sulphur-rich structure and could present a novel scaffold for bioactive molecules. An on-going collaboration with Professor Kandhavelu was explored to test the cytotoxicity of the library of thioethers against glioblastoma cells. Glioblastoma is a particularly deadly brain tumour with almost certain recurrence rate and highly resistant to current treatment. The heterogeneity of GB tumours originates a high demand for multi-target cytotoxic/anti-angiogenic agents. In addition to all the TKOS prepared for the previous work, two more derivatives were synthesized (Scheme 40), which were originally meant for attempts at obtaining a suitable X-ray crystal for definite confirmation of the structure of TKO. Tris-phenol **117m** was obtained via fluoride promoted cleavage of TBDPS protective group of the TKO **117k**, and a simple esterification with 3-nitrobenzoyl chloride yielded **117n.**



Scheme 40. Synthesis of TKO derivates for evaluation against glioblastoma cell lines.

Professor Kandhavelu's group then performed a comprehensive biological and biochemical study and identified some TKOs to be cytotoxic against glioblastoma cell line U87 (Figure 1). The tris-phenol **117m** was especially cytotoxic, surpassing the positive control cisplatin.

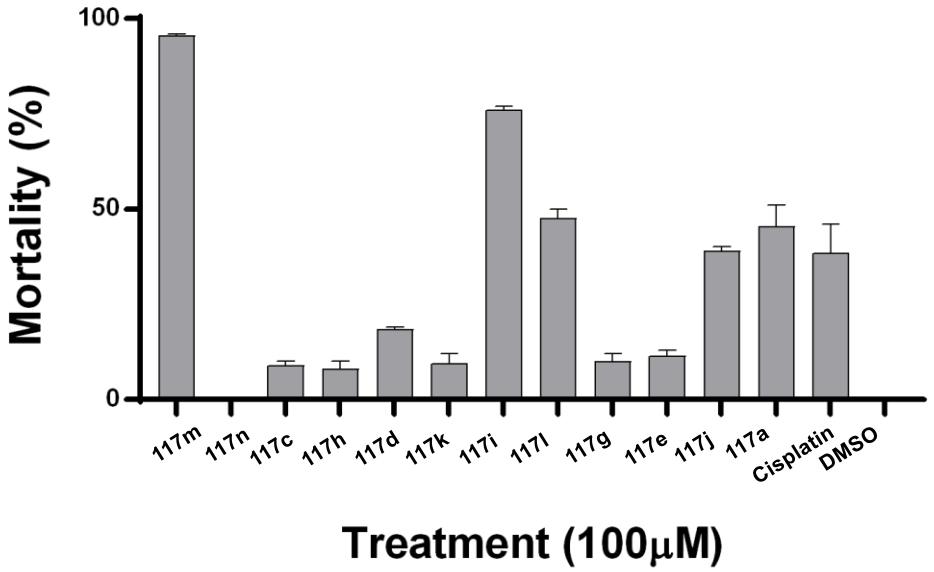


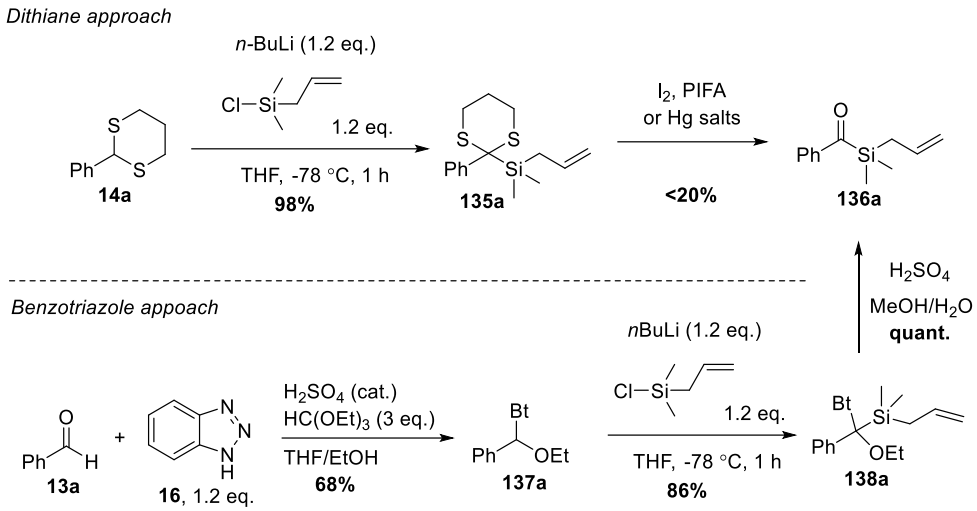
Figure 1. Mortality rate percentage on treating U87 cells with TKOs, cisplatin (positive control) and 1% DMSO (negative control), at 100 μM.

Further studies revealed **117m** to present an IC50 of 27 and 23 μM for U87 and LN229 (glioblastoma cancer cells) cell lines, respectively, a value much lower than the traditional positive control cisplatin, with IC50 of 53 and 115 μM respectively. Additionally, the cytotoxicity of **117m** in normal brain cells was significantly lower than cisplatin, with an 11% growth inhibition for **117m** whereas cisplatin presented 48% of inhibition, suggesting that **117m** is more selective than cisplatin against GB cancer cells than normal brain cells. The cytotoxicity of **117m** was attributed to being effective in weakening resistance pathways and enhancing apoptotic machinery. Additionally, **117m** acts on key genes involved in the regulation of cell cycle pathways, including multiple tyrosine kinase pathways, as demonstrated by an *in silico* docking study of **117m** with EGFR (Epidermal growth factor receptor), a tyrosine kinase receptor.

This study led to publication III,[66] as the novel TKOs showed promising as a novel pharmacological scaffold for the treatment of glioblastoma.

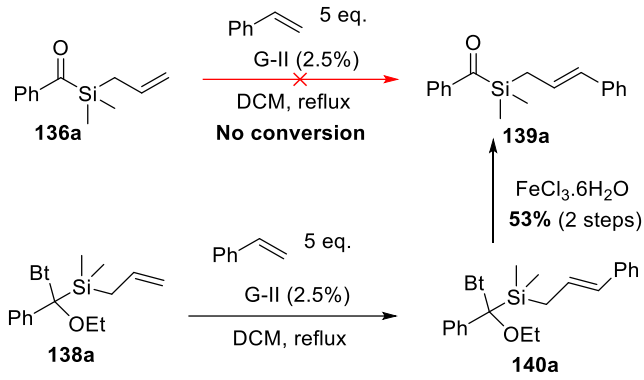
5.4 Synthesis of benzoyl(allyl)silanes

Synthesizing novel benzoyl(allyl)silanes was required for studies on the [2+2] photocycloaddition of acylsilanes, as is better described later in chapter 4.2.6. As previously, allylic silyl dithiane **135a** was synthesized via lithiation of **14a** and addition to chlorodimethyl allylsilane. Contrary to literature reports, this compound proved to be unsuitable for deprotection, consistently giving acylsilane (**136a**) in yields below 20% (Scheme 41, top). The oxidative conditions required for hydrolysis of the dithiane were also oxidizing the olefin moiety leading to a complex mixture of products with loss of the acylsilane functionality. Also, attempts at hydrolysing the dithiane with mercury salts were met with degradation, likely from oxymercuration of the olefin. At this point, with the challenge lying in the final deprotection of the dithiane moiety, the use of Katritzky methodology employing benzotriazole hemiaminal ethers was considered.[32] The facile late-stage removal of the acyl anion equivalent could overcome the dithiane strategy's main limitation. Benzotriazole hemiaminal ether **137a** was prepared via acid-catalysed condensation of benzotriazole with benzaldehyde in the presence of triethyl orthoformate. In contrast to the corresponding dithiane, for which purification is typically achieved via simple crystallization, the purification of benzotriazole required silica column chromatography, which is a minor disadvantage. From there, treatment with *n*-BuLi gave the lithiated acyl anion equivalent which was able to add to allyl chlorosilane to give **138a** in good yield. Gratifyingly, the resulting silyl benzotriazole hemiaminal ether was promptly deprotected in excellent yield to the desired benzoyl allylsilane **136a** (Scheme 41, bottom).



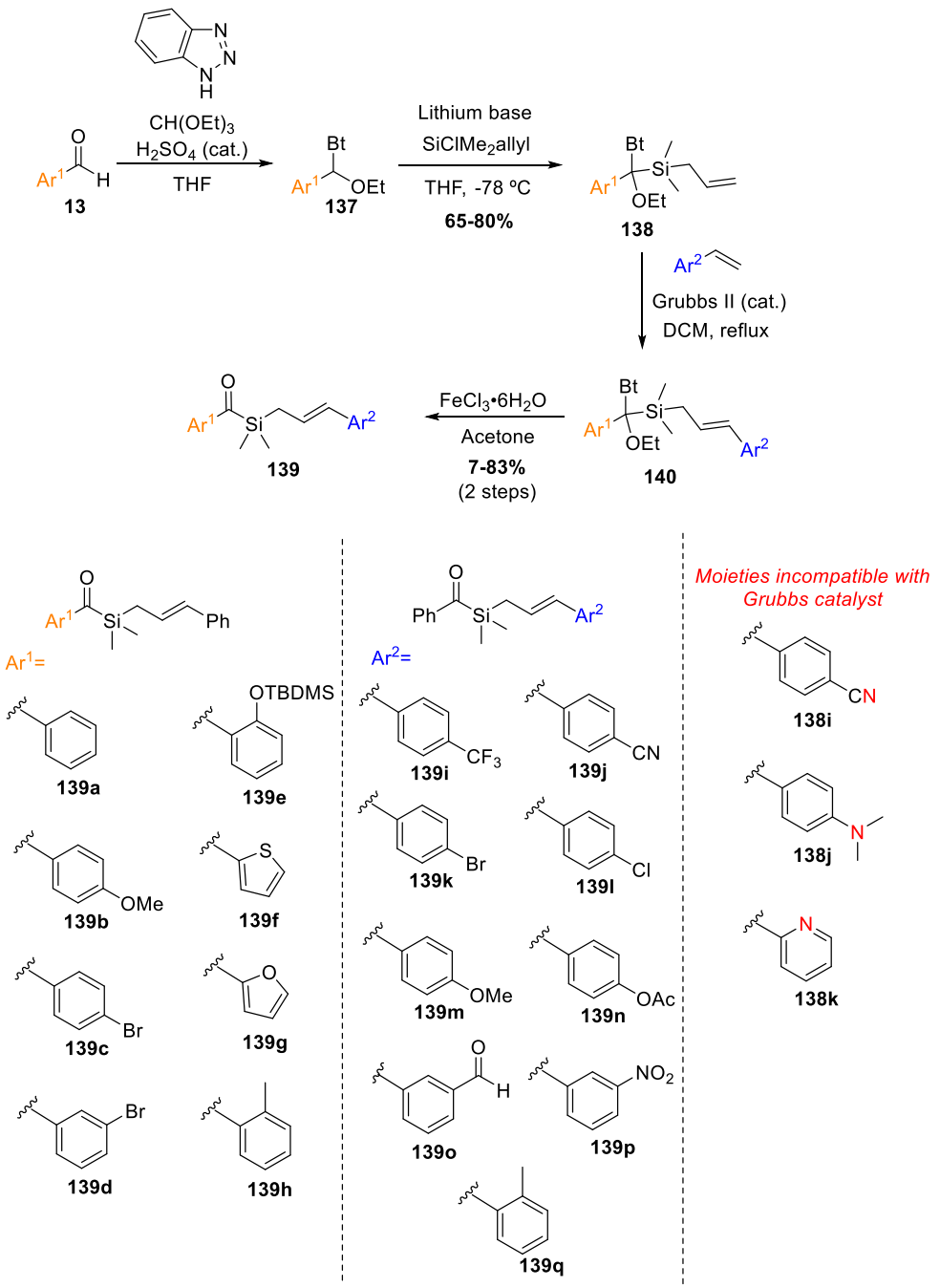
Scheme 41. Synthesis of benzoyl(ally)silane. Failed dithiane approach (top) and successful benzotriazole method (bottom).

Attempting the introduction of additional variations on the olefin moiety and obtaining novel acylsilanes, it was observed that acyl(allyl)silanes such as **136a** failed to undergo olefin metathesis with styrene using Grubbs catalyst, with starting material being recovered in most cases quantitively (Scheme 42). This has also been observed by Hammaecher, which faced the same apparent lack of reactivity of an bis-allyl acylsilane when attempting its ring-closing metathesis.[67] The authors hypothesised that the presence of acidic α-carbonyl allylic protons could be deactivating the catalyst. For the benzoyl **136a** however, no acidic hydrogens are present, which suggests that the issue lies in the carbonyl moiety. Tracing back to the structure of acylsilanes, the contribution of the resonance form **2** (Scheme 1) likely increases the basicity of the carbonyl of acylsilanes and may be the cause of catalyst deactivation. Gratifyingly, the use of the allylsilane benzotriazole intermediate **138a,** having the carbonyl moiety masked in form of a hemiaminal ether, was a suitable substrate for metathesis with a variety of styrenes further corroborating our hypothesis. Hydrolysis of the product **140a** gave the desired acylsilane **139a** in good yield.



Scheme 42. Successful synthesis of substituted benzoyl(allyl)silane **139a** via benzotriazole route.

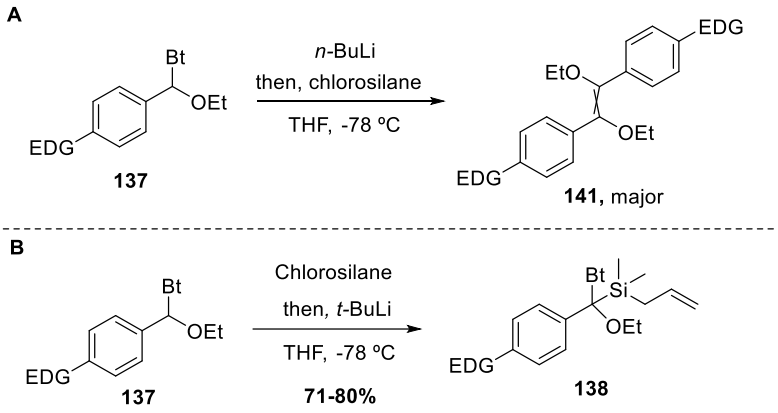
With a successful methodology in hand to obtain substituted benzoyl(allyl)silanes, a variety of acylsilanes was synthesized (Scheme 43). The diversification of the aryl moieties of the carbonyl and the styrene was done in order to study the [2+2] photocycloaddition of benzoyl(allyl)silanes, later described in chapter 4.2.6.



Scheme 43. Synthesis of substituted benzoyl(allyl)silanes.

It is worth noting that the lithiated benzotriazole hemiaminal is not as stable as the parent lithiated dithiane, and always required handling at low temperatures, due to quick decomposition at room temperature. Additionally, the lithiated species resultant from electron-donating aryl derivatives are highly unstable even at low temperatures, leading to dimerization products (**141**) before the addition of the chlorosilane (Scheme 44, A). This side reaction was circumvented by adding the electrophile before the base followed by dropwise addition of the base to slowly form lithiated **38** amenable to be trapped by the chlorosilane in solution (Scheme 44, B). The use of *t*-BuLi minimized the direct addition of the lithium base to the silyl chloride electrophile.

An additional inconvenience encountered in the synthesis of acylsilanes **139** was the incompatibility of nitrogen-based functional groups with the cross-metathesis reaction, such as nitrile (**138i**), dimethyl aniline (**138j**) and pyridine (**138k**). The deactivation of the Grubbs catalyst with nitrogen bases and *N*-heterocycles is known and still a problematic issue in this field.[68]



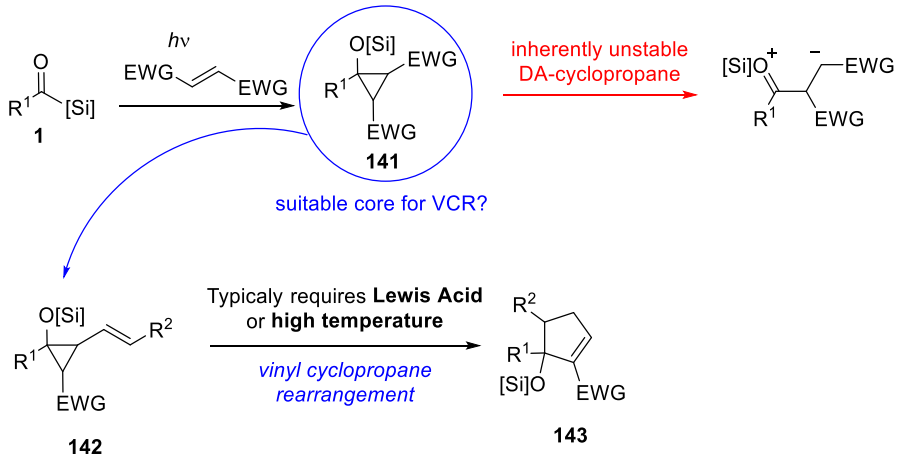
Scheme 44. Dimerization of lithiated benzotriazole anions with electron-donating substituents (A) and successful approach towards silylation (B).

Overall, the Katritzky methodology proved to be very robust in the synthesis of more complex acylsilanes bearing oxidation-sensitive moieties. In addition, the stability of the benzotriazole precursors allows additional functionalization after the introduction of the silicon moiety, namely the cross-metathesis reaction. Finally, the greatest advantage of this method is the facile hydrolysis of the acid-sensitive hemiaminal ether group to cleanly provide the desired acylsilanes, in high contrast

to the parent dithianes which typically require harsh conditions incompatible with many functional groups.

5.5 Cyclopropanation/vinyl cyclopropane rearrangement

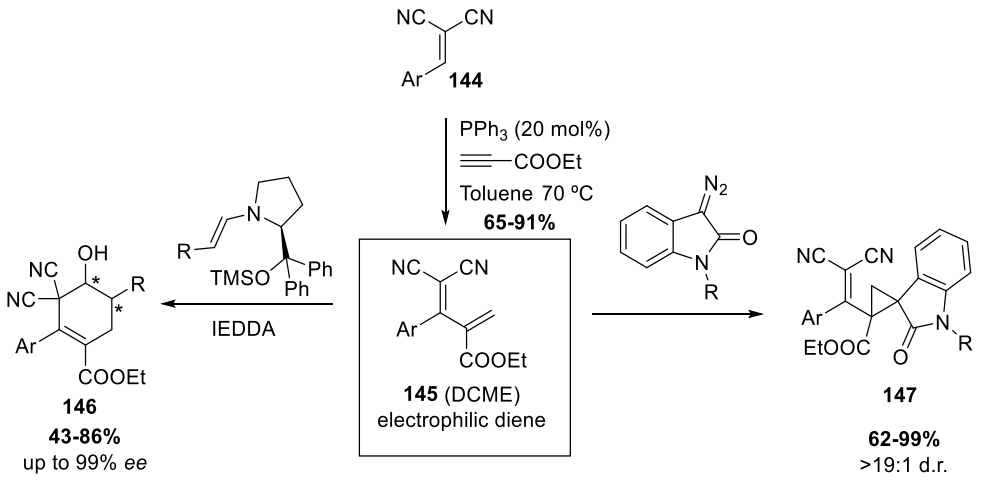
In the previous chapter 2.3.2.3 is shown the significant limitations of the metal-free cycloaddition of photogenerated siloxycarbenes regarding the strict requirements on the olefin electrophile and in the inherent instability of the resulting donor-acceptor cyclopropanes **141** (Scheme 45). Concurrently, donor-acceptor (DA) cyclopropanes, albeit less reactive than the ones presented in chapter 2.3.2.3, are common substrates for the vinyl cyclopropane rearrangement (VCR) for the synthesis of cyclopentanes.[69] The push-pull character of such cyclopropanes facilitates ring opening and eases the access of the transition state for VCR, allowing the reaction to proceed with Lewis acid catalysis at room temperature, whereas traditional VCR requires high temperatures. It was envisioned that if a suitable electrophilic diene could undergo cycloaddition with the siloxycarbene to give vinyl cyclopropanes such as **142**, they could prove suitable substrates for VCR.



Scheme 45. Taking advantage of the instability of DA cyclopropanes towards VCR.

Unfortunately, the current variety of highly electron-withdrawing dienes is very scarce, as they tend to be unstable, forming dimers or polymers. Tetrazines are the traditional electrophilic dienes used for inverse electron demand Diels-Alder

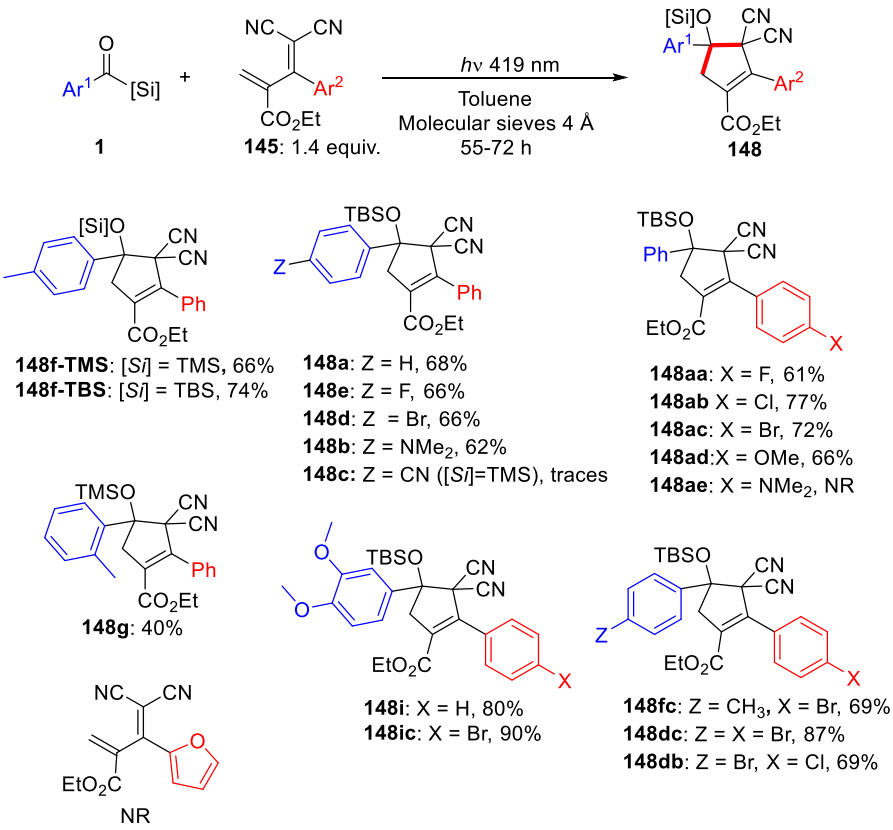
(IEDDA). Alas, tetrazines absorb light in a similar region of acylsilanes, the near UV-visible region. Irradiation of a tetrazine/acylsilane solution led to a complete recovery of both starting materials unreacted. A novel class of dienes, dicyano-2-methylenebut-3-enoates (**145**, DCMEs) has been recently developed by Wang's group. They can be prepared in good yields via PPh_3 catalysed Bayllis-Hillman type reaction of easily accessible arylidene-malononitriles **144** and alkyl propiolates (Scheme 46).[70] They are surprisingly stable and can be stored in cold for months. They proved to be excellent electrophiles for IEDDA and other cycloadditions, including cyclopropanation with carbenes to give stable cyclopropanes **147** (Scheme 46).[71]



Scheme 46. Reported synthesis of DCMEs and their cycloaddition reactions.

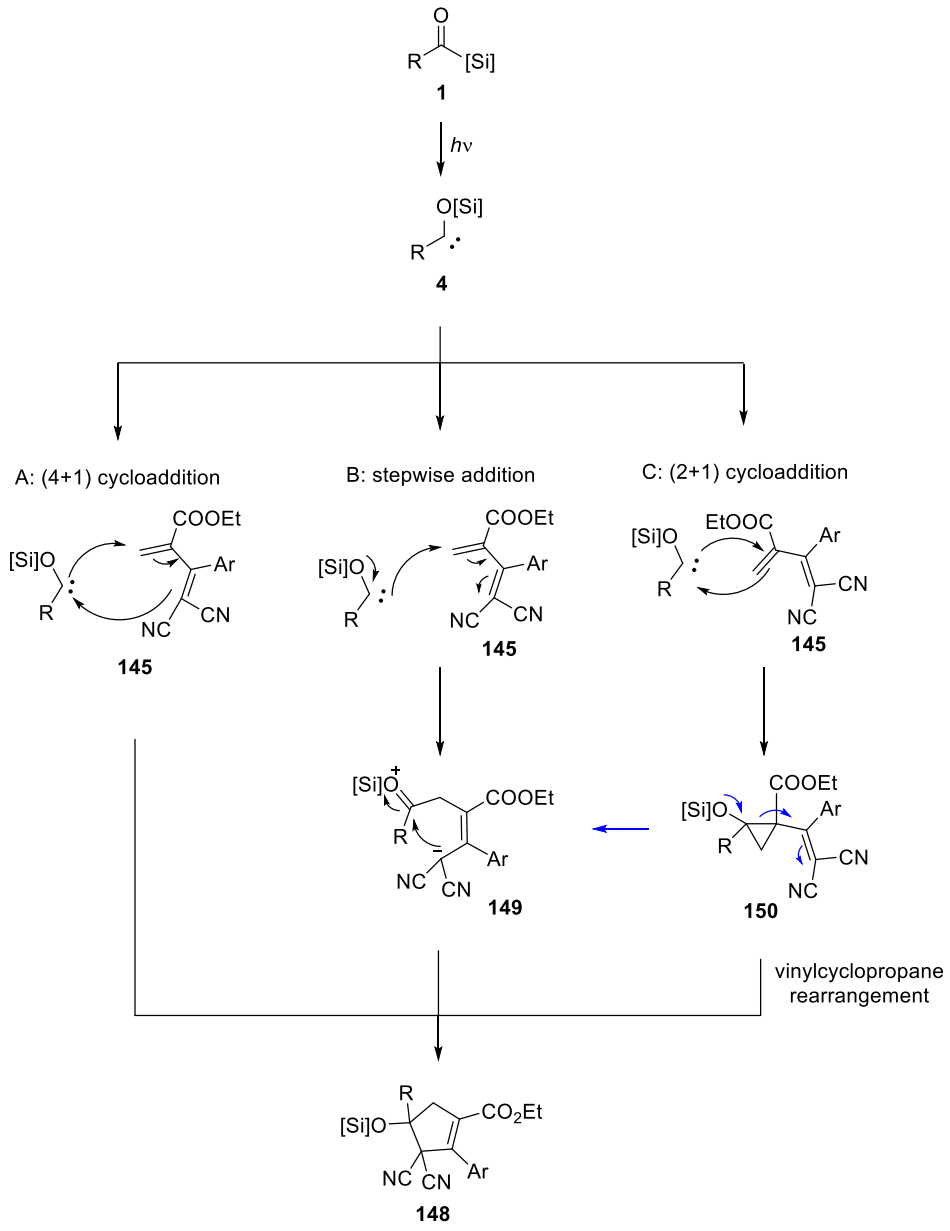
The chemical reactivity of these dienes incited us to use them in the hypothesized siloxycarbene CP/VCR sequence (Scheme 45). Gratifyingly, irradiation of acylsilanes **1** in the presence of DCME diene led to the isolation of the expected rearrangement sequence product albeit in low yield. Analysis of the reaction crude failed to identify a cyclopropane intermediate, suggesting that this VCR is a fast process at room temperature and does not require Lewis acid catalysis. Optimization of the reaction conditions regarding solvent, diene equivalents and use of molecular sieves increased the yield to synthetically useful values. The use of a moderately bulky *tert*-butyldimethyl silane proved important to the stability of the final product, preventing desilylation and ring collapse. The scope of the reaction

was expanded by changing the aromatic moiety of the acylsilane and the DCME diene, and a total of 16 examples in good yields were obtained (Scheme 47).



Scheme 47. Scope of the photochemical CP/VCR sequence.

DFT calculations were performed in order to understand the mechanism of the reaction. The reaction could potentially proceed via three distinct mechanisms (Scheme 48): A) a (4+1) cycloaddition where the two new C-C bonds are formed in a concerted manner; B) a stepwise addition of the nucleophilic carbene with olefin migration, forming a zwitterionic intermediate **149** that undergoes intramolecular addition of the anion to the oxonium carbon: and C, cyclopropanation on the geminal olefin forming the cyclopropane intermediate **150** that may either open to form the zwitterion **149** (facilitated by the DA nature of the cyclopropane) or undergo concerted VCR.



Scheme 48. Envisioned possible mechanisms for the formal (4+1) photocycloaddition of acylsilanes **1** with dienes **145**.

According to DFT calculation, the reaction starts with the interaction of singlet carbene **sc1** with diene **dn** (Figure 2). The interaction of the siloxycarbene with the diene is strengthened through the terminal alkene moiety, thus ruling out a

concerted mechanism (Scheme 48, A pathway). The cyclopropanation can occur via two different pathways, formation of the *trans* or *cis* cyclopropane, with similar activation energies of only 11.6 or 11.1 kcal/mol respectively. Forcing the carbene to undergo stepwise addition (Scheme 48, B pathway) invariably leads to the formation of the cyclopropane intermediates (Scheme 48, C pathway), following intrinsic reaction coordinates. From there, the two cyclopropane isomers seem to follow distinct reaction mechanisms. $\mathbf{cp_{trans}}$ Undergoes concerted ring enlargement to the final product through a barrier of only 14.4 kcal/mol, an instant reaction at room temperature. A similar transition state could not be found for $\mathbf{cp_{cis}}$, where a stepwise ring-opening to the zwitterion intermediate $\mathbf{int_1}$ seems to be the preferred pathway with an overall energy barrier of 15.2 kcal/mol. Both activation energies for the formation of product from *cis* and *trans* cyclopropanes are small enough for instantaneous reaction at room temperature. Such small energy barriers explain the non-detection of the cyclopropane intermediate and the unrequired need for acid catalysis or high temperatures for this VCR.

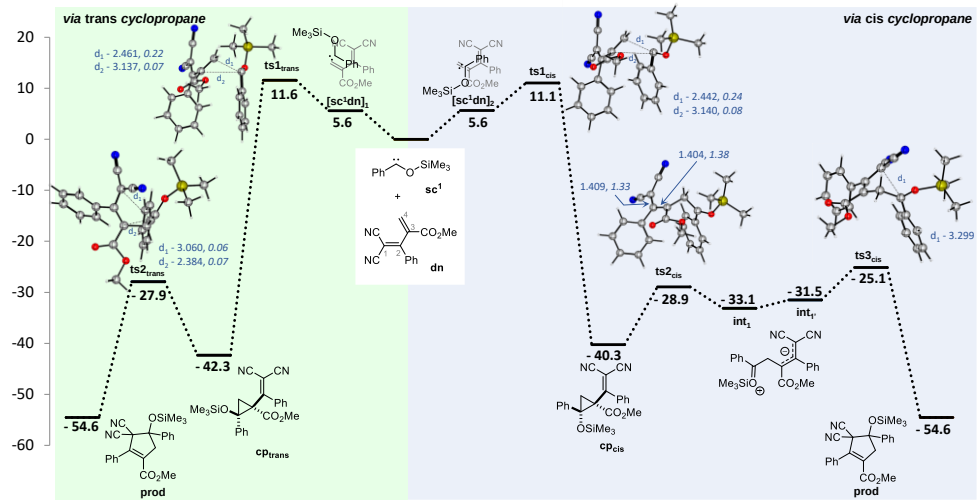
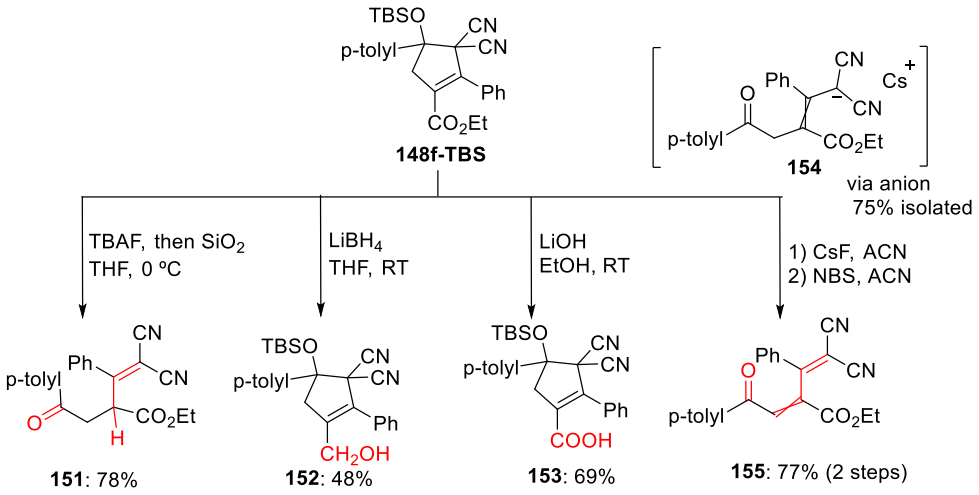


Figure 2. DFT studies on the CP/VCR sequence. Figure from *J. Org. Chem.* **2022**, *87*, 8910–8920.

The cyclopentene products could be further chemically modified in the ester functionality via hydrolysis to the acid **153** or reduced to the primary alcohol **152**. Additionally, the silyl group could be cleaved with TBAF but not without the collapse of the ring structure to give ketone **151**. If the desilylation is performed under anhydrous conditions with caesium fluoride, the anion **154** can be intercepted and oxidised with NBS to the enone **155**.



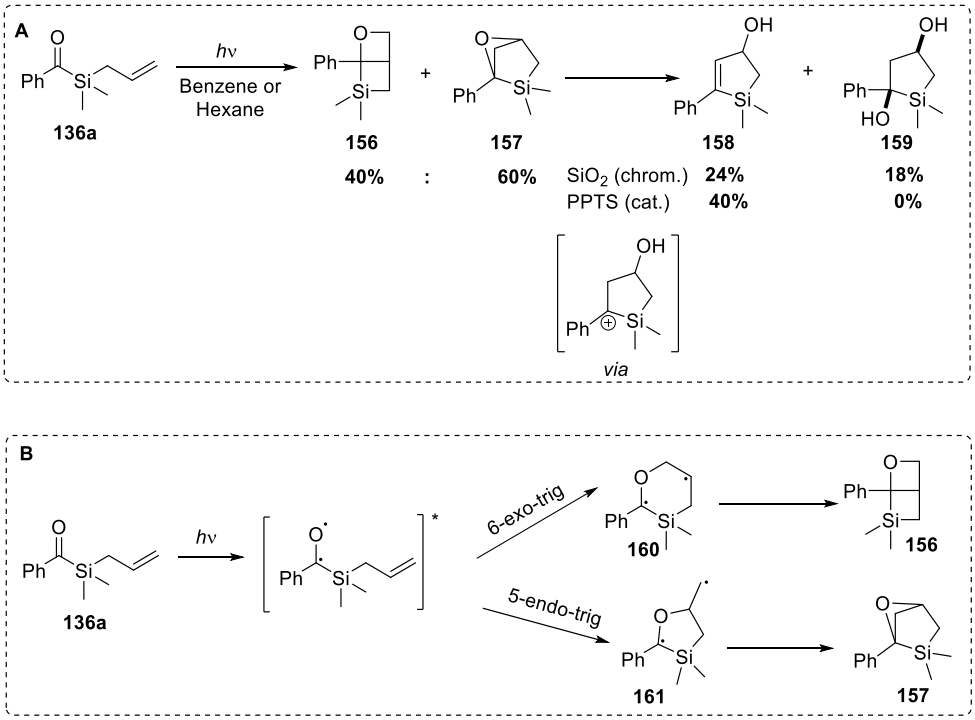
Scheme 49. Chemical modifications of cyclopentene **111f-TBS**.

In conclusion, this work expanded the reactivity profile of siloxycarbenes photogenerated from acylsilanes and presents a novel approach to the synthesis of highly functionalised cyclopentenes. DFT calculations corroborate the mechanistic hypothesis that the siloxycarbene undergoes initial cyclopropanation as the rate-limiting step and then a fast vinyl cyclopropane rearrangement delivers the cyclopropenes. The results of this unprecedented reaction sequence in acylsilane chemistry were reported as publication IV.[72]

5.6 [2+2] cycloaddition of benzoyl(allyl)silanes

While most of acylsilane photochemistry is focused on the formation of siloxycarbenes, their ketone moiety still participates, in specific cases, in more traditional carbonyl photochemistry such as [2+2]-cycloadditions. One example is the work of Portella and Hammaecher,[60] where it was reported the [2+2]-photocycloaddition reaction of benzoylallylsilanes, and is better described in Chapter 2.3.4. The authors observed exclusive regioselectivity in the 6-endo-trig pathway, which lead to the synthesis of oxasilabicyclo[2.2.0]hexanes **108** (Scheme 32). The possibility of stabilizing the 5-exo-trig intermediate via substitution of the olefin with radical stabilizing groups and shifting the reaction pathway was intriguing, as it could allow the access of yield novel silacycles. Interestingly, while Portella observed that irradiation of allyl benzoylsilane in acetonitrile gave an

intractable reaction mixture, in our hands, irradiation of benzoyl(allyl)silane **136a** in apolar dry solvents cleanly gave isomers **156** and **157** (Scheme 50, A and Figure 3). Compound **156** originates from the expected 6-endo-trig [2+2] cycloaddition, as observed by Portella for alkyl acyl(allyl)silanes, while **157** originates from the alternative 5-exo-trig pathway, which was not previously observed (Scheme 50, B). Both **156** and **157** are extremely unstable compounds and were not possible to isolate through standard silica column chromatography. This difference in stability compared to Portella´s bicycles might be due to the increased stabilization of a benzylic carbocation derived from the oxetane ring-opening. Hence, the use of apolar solvents during irradiation seems to be vital to prevent decomposition. During silica column chromatography, compound **157** undergoes acid-catalysed ring-opening to give **158** and **159**, which are formed via oxetane ring-opening and elimination and hydrolysis respectively. If the crude reaction is treated with catalytic pyridinium *p*-toluenosulphonate (PPTS) under anhydrous conditions, the elimination product **158** is formed selectively. Isomer **156** seems to decompose into various products which could not be isolated or characterized.



Scheme 50. Irradiation of **136a** in benzene or hexane (A). Proposed mechanism for the formation of **156** and **157** (B).

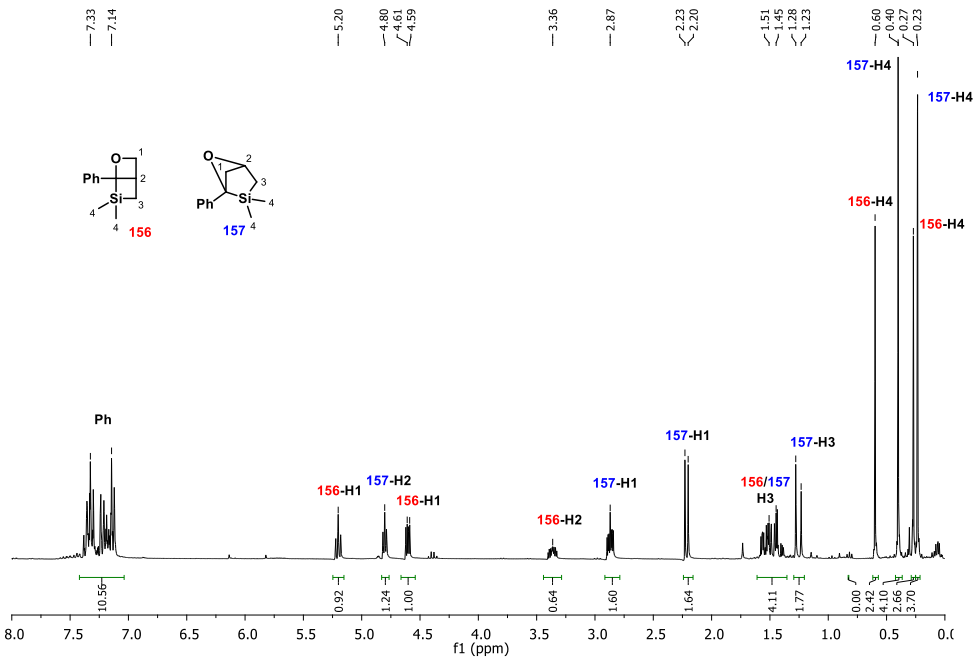
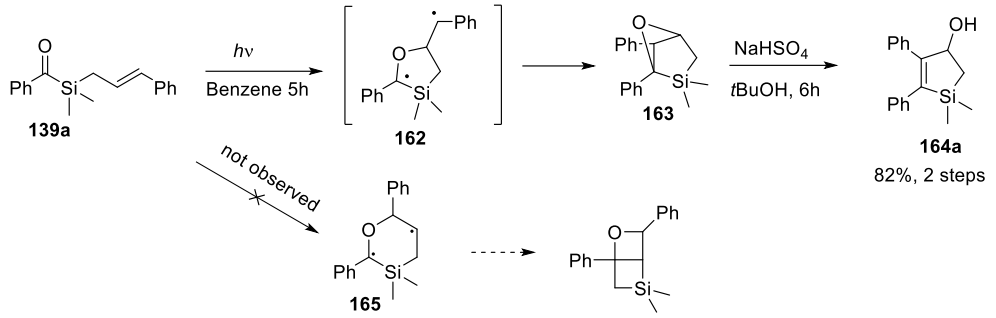


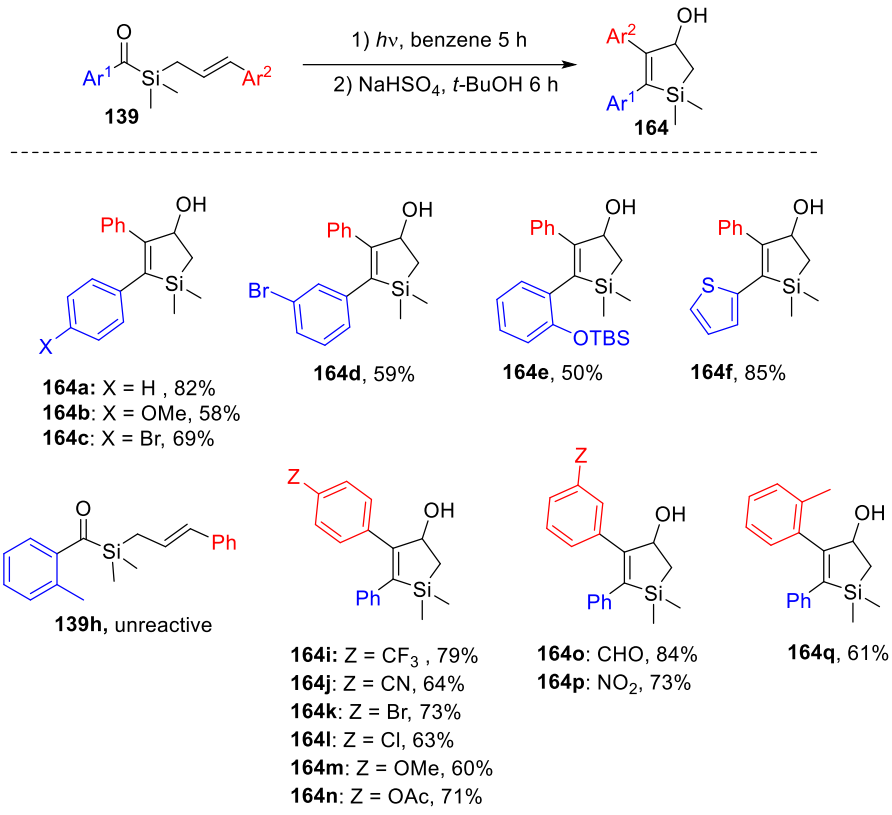
Figure 3. Crude ^{1}H NMR of irradiation of **136a** in benzene.

After validating that aryl allyl silanes can in fact undergo [2+2] cycloaddition reactions via two different pathways, acylsilane **139a** was synthesised (detailed in chapter 4.2.4) to investigate if the additional stabilization of the 5-exo-trig intermediate through benzylic stabilization of the radical would change the reaction profile. Irradiation of **139a** in dry benzene led to the exclusive formation of compound **163** as a mixture of diastereoisomers, showing a complete shift in selectivity for the 5-exo-trig pathway (Scheme 52). The bicyclic product was unstable and was quickly converted to its stable isomer **164a** by treatment with acid. The use of weakly acidic sodium hydrogen phosphate and non-nucleophilic solvent *t*BuOH was pivotal to prevent degradation and solvolysis, respectively.



Scheme 51. Highly selective [2+2] photochemical cycloaddition of **139a** via 5-exo-trig pathway. Formation of silacyclopentenol **164a** after acidic treatment.

The scope of the reaction was explored by changing the aromatic substitution on the carbonyl and the styrene and obtained 15 examples in good yields of novel silacyclopentenols **164**. The reaction is quite tolerant to different substitution patterns on both aromatic groups. The only notable exception was *o*-methyl derivative **139h** which failed to undergo cycloaddition and starting material was recovered. While steric hindrance on the *ortho* position is an attractive justification for the lack of reactivity, the bulkier *o*-siloxyether **139e** reacted as expected to give silacyclopentenol **164e** in 50% yield. Additionally, *o*-methyl substitution on the styrene part of the molecule does not seem detrimental, as **164q** was obtained in 61% yield. So far, an explanation for this result remains elusive.



Scheme 52. [2+2] photochemical cycloaddition of **139** to give silacyclopentenol **164** after acidic work-up.

DFT calculations helped to elucidate the differences in reactivity of the unsubstituted and aromatic substituted acyl(allyl)silanes (Figure 4). For the unsubstituted olefin **136a**, there is a negligible difference of 0.8 kcal/mol in the energies of the two diradical intermediates $\mathbf{br_5}$ and $\mathbf{br_6}$, which leads to a very poor reaction selectivity for both isomers. In the case of the styrene olefin **139a**, there is a 10.8 kcal/mol stabilization of the 5-exo-trig pathway intermediate $\mathbf{br_5}$, which results in complete reaction selectivity for the 5-exo-trig product **163**.

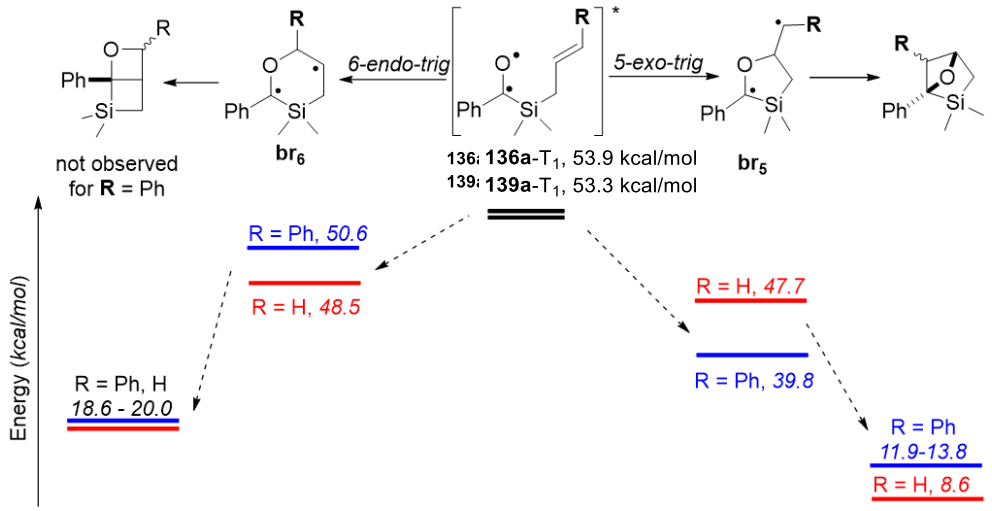
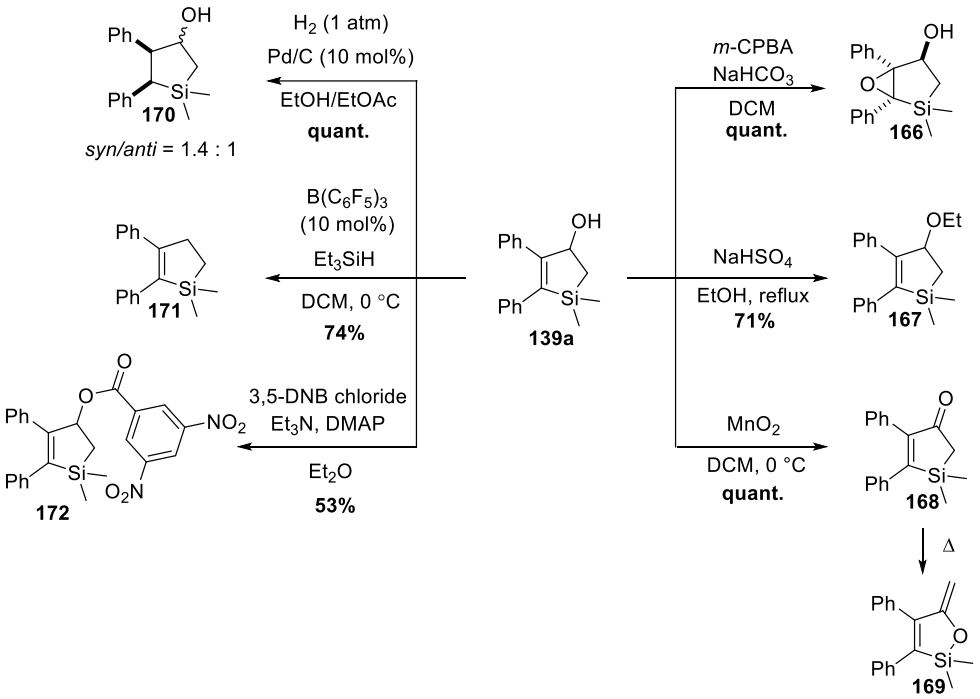


Figure 4. Different reaction profiles as given by DFT calculations, at (U)BMK/6-31+G (d, p) level of theory. Energies are presented in kcal/mol. The range of energies for the bicyclic species refer to *cis* and *trans* diastereomers.

To add value to these novel silacycles, the possibility of chemical modifications on a model compound was investigated. It was concluded that the compounds can undergo a variety of selective reactions (Scheme 53) including: diastereoselective epoxidation with *m*-CPBA (**166**); MnO_2 oxidation to the enone **168** that thermally rearranges to the silyl enol ether **169**; etherification via facile allylic carbon formation in acidic conditions to give ether **167**; reduction of the olefin with hydrogen and palladium catalyst to give silacyclopentane **170** as a mixture of diastereoisomers; alcohol reduction with boron catalyst[73] and silyl hydride yielding deoxygenated product **171** and benzoylation with 3,5-dinitrobenzoyl chloride to give ester **172**. Compound **172** gave crystals that were suitable for X-ray analysis, confirming the assigned structures of **139**.



Scheme 53. Chemical transformations of silacyclopentenol **139a**.

In conclusion, this work expanded the known reactivity of the elusive triplet state of the acylsilane and increased the scarce variety of methods available for the synthesis of stable silacyclopentanes and lead to Publication II.[74] DFT calculations helped rationalize the high degree of regioselectivity of this photo transformation.

6 CONCLUSIONS AND OUTLOOK

The work carried out during this PhD has significantly expanded the boundaries of the scientific knowledge on the photoreactivity of acylsilanes. Using blue-light mediated and metal-free approaches, new carbon-carbon bond forming reactions were developed for the synthesis of novel complex molecular structures. In this topic, an unprecedented formal (4+1) cycloaddition of photogenerated siloxycarbene with electrophilic dienes was established, via a sequential cyclopropanation/vinyl cyclopropane rearrangement. This study revealed that cyclopropanes derived from siloxycarbenes are outstanding precursors for facile vinyl cyclopropane rearrangement, allowing the synthesis of highly functionalized cyclopentenes. While previously limited to intramolecular (2+1) cyclopropanations, cycloadditions with siloxycarbenes have now been proven to work with conjugated systems, which should pave the way for the discovery of other novel transformations for the construction of carbocycles. So far, the expansion of this methodology is restrained by the scarce availability of highly electrophilic dienes. The development of novel methods for their synthesis is required in order to provide suitable partners for cycloaddition with siloxycarbenes and to expand utility of acylsilanes in synthetic chemistry.

With the same objectives in mind, a modified [2+2] photocycloaddition of acylsilanes with intramolecular olefins was developed, unravelling a novel methodology for the challenging synthesis of silacyclopentenes. The molecular construction required for total regioselectivity in such systems was elucidated and the use of UV-light was replaced with visible light by optimizing the conditions to withstand aromatic acylsilanes. This work expanded the extremely limited number of photochemical reactions of the acylsilane carbonyl without siloxycarbene intermediation. With this precedent, novel cyclic cores may now be obtained by constructing acylsilanes with intramolecular olefins installed in different positions.

Lastly, a novel autooxidation of lithiated dithianes was discovered and investigated, revealing a side reaction encountered during the preparation of acylsilanes via

dithiane umpolung methodology. This novel transformation was optimised and proved to be a very efficient method for the synthesis of sulphur-rich α-thioether ketone orthothioesters, a trimer of oxidated dithianes. Some of these molecules showed promising biological activity, being highly cytotoxic to glioblastoma cancer cell lines. SAR studies revealed the importance of a free phenol moiety on the aromatic dithiane, which opens the way for further studies of other derivatives with modifications on the phenol position and/or number of phenol groups in each aromatic group. The possibility of further decreasing the IC50 of such molecules and obtain a competitive and easily produced lead compound for the treatment of glioblastoma remains, for now, unexplored.

Currently, the number of novel transformations directly employing acylsilane derived siloxycarbenes is reaching saturation, as their reactivity are now very well understood. While the blue light irradiation of acylsilanes stands out as a promising green method to produce carbenes, the nucleophilic nature of such siloxycarbenes is limiting their application and widespread use. Very recently, this area has been rejuvenated by the discovery that siloxycarbenes can coordinate with metals in a catalytic fashion to form metallocarbenes with completely different reactivity than the parent siloxycarbenes. The reactivity shifts towards an electrophilic carbene, which might open the door for traditional carbene chemistry such as C-H insertion and other cycloadditions. A new field combining metal catalysis and visible light irradiation awaits ahead, which may once again bring acylsilanes to the spotlight of organic chemistry.

7 REFERENCES

[1] Albini, A.; Fagnoni, M. Green Chemistry and Photochemistry Were Born at the Same Time. *Green Chem.* **2004**, *6*, 1–6.

[2] Oelgemöller, M.; Jung, C.; Mattay, J. Green Photochemistry: Production of Fine Chemicals with Sunlight. *Pure Appl. Chem.* **2007**, *79*, 1939–1947.

[3] Bonfield, H. E.; Knauber, T.; Lévesque, F.; Moschetta, E. G.; Susanne, F.; Edwards, L. J. Photons as a 21st Century Reagent. *Nat. Commun.* **2020**, *11*, 2–5.

[4] Buglioni, L.; Raymenants, F.; Slattery, A.; Zondag, S. D. A.; Noël, T. Technological Innovations in Photochemistry for Organic Synthesis: Flow Chemistry, High-Throughput Experimentation, Scale-up, and Photoelectrochemistry. *Chem. Rev.* **2022**, *122*, 2752–2906.

[5] Robert, J. D.; Caserio, M. C. *Basic Principles of Organic Chemistry*, 2nd ed.; W. A. Benjamin, Inc: Menlo Park, CA, 1977.

[6] Marzo, L.; Pagire, S. K.; Reiser, O.; König, B. Visible-Light Photocatalysis: Does It Make a Difference in Organic Synthesis? *Angew. Chemie - Int. Ed.* **2018**, *57*, 10034–10072.

[7] Yoon, T. P.; Ischay, M. A.; Du, J. Visible Light Photocatalysis as a Greener Approach to Photochemical Synthesis. *Nat. Chem.* **2010**, *2*, 527–532.

[8] Williams, J. D.; Kappe, C. O. Recent Advances toward Sustainable Flow Photochemistry. *Curr. Opin. Green Sustain. Chem.* **2020**, *25*, 100351.

[9] Reich, H. J.; Kelly, M. J.; Olson, R. E.; Holtan, R. C. Silyl Ketone Chemistry. Preparation and Reactions of Unsaturated Silyl Ketones. *Tetrahedron* **1983**, *39*, 949–960.

[10] Zhang, H.-J.; Priebbenow, D. L.; Bolm, C. Acylsilanes: Valuable Organosilicon Reagents in Organic Synthesis. *Chem. Soc. Rev.* **2013**, *42*, 8540–8571.

[11] Brook, A. G. Triphenylsilyl Phenyl Ketone. *J. Am. Chem. Soc.* **1957**, *79*, 4373–4375.

[12] Brook, A. G.; Duff, J. M. The Photochemistry of Silyl Ketones in Alcohol. *J. Am. Chem. Soc.* **1967**, *89*, 454–455.

[13] Duff, J. M.; Brook, A. G. Photoisomerization of Acylsilanes to Siloxycarbenes, and Their Reactions with Polar Reagents. *Can. J. Chem.* **1973**, *51*, 2869–2883.

[14] Bunyamin, A.; Hua, C.; Polyzos, A.; Priebbenow, D. L. Intramolecular Photochemical [2+1]-Cycloadditions of Nucleophilic Siloxy Carbenes. *Chem. Sci.* **2022**, *13*, 3273–3280.

[15] Zhang, H. J.; Becker, P.; Huang, H.; Pirwerdjan, R.; Pan, F. F.; Bolm, C. Photochemically Induced Silylacylations of Alkynes with Acylsilanes. *Adv. Synth. Catal.*

2012, *354*, 2157–2161.

[16] Becker, P.; Priebbenow, D. L.; Zhang, H. J.; Pirwerdjan, R.; Bolm, C. Photochemical Intermolecular Silylacylations of Electron-Deficient Internal Alkynes. *J. Org. Chem.* **2014**, *79*, 814–817.

[17] Ishida, K.; Tobita, F.; Kusama, H. Lewis Acid-Assisted Photoinduced Intermolecular Coupling between Acylsilanes and Aldehydes : A Formal Cross Benzoin-Type Condensation. *Chem. Eur. J.* **2018**, *24*, 543–546.

[18] Priebbenow, D. L.; Pilkington, R. L.; Hearn, K. N.; Polyzos, A. Fluorinated Ketones as Trapping Reagents for Visible-Light-Induced Singlet Nucleophilic Carbenes. *Org. Lett.* **2021**, *23*, 2783–2789.

[19] Fan, Z.; Yi, Y.; Chen, S.; Xi, C. Visible-Light-Induced Catalyst-Free Carboxylation of Acylsilanes with Carbon Dioxide. *Org. Lett.* **2021**, *23*, 2303–2307.

[20] Ito, K.; Tamashima, H.; Iwasawa, N.; Kusama, H. Photochemically Promoted Transition Metal-Free Cross-Coupling of Acylsilanes with Organoboronic Esters. *J. Am. Chem. Soc.* **2011**, *133*, 3716–3719.

[21] Sakurai, S.; Inagaki, T.; Kodama, T.; Yamanaka, M.; Tobisu, M. Palladium-Catalyzed Siloxycyclopropanation of Alkenes Using Acylsilanes. *J. Am. Chem. Soc.* **2022**, *144*, 1099–1105.

[22] Zhang, Y.; Zhou, G.; Gong, X.; Guo, Z.; Qi, X.; Shen, X. Diastereoselective Transfer of Tri(Di)Fluoroacetylsilanes-Derived Carbenes to Alkenes. *Angew. Chemie - Int. Ed.* **2022**.

[23] Zhou, G.; Shen, X. Synthesis of Cyclopropenols Enabled by Visible-Light-Induced Organocatalyzed [2+1] Cyclization. *Angew. Chemie - Int. Ed.* **2022**, *61*.

[24] Brook, A. G.; Quicley, M. A.; Schwartz, N. V.; Warner, C. M. The Spectral and Chemical Properties of α-Silyl Ketones. *J. Am. Chem. Soc.* **1960**, *82*, 5102–5106.

[25] Brook, A. G.; Kivisikk, R.; LeGrow, G. E. Spectral Properties of P-Substituted Benzoyltriphenylsilanes. *Can. J. Chem.* **1965**, *43*, 1175–1183.

[26] Bock, H.; Alt, H.; Seidl, H. D-Orbital Effects in Silicon-Substituted π-Electron Systems. The Color of Silyl Ketones. *J. Am. Chem. Soc.* **1968**, *91*, 355–361.

[27] Ford, A.; Miel, H.; Ring, A.; Slattery, C. N.; Maguire, A. R.; Mckervey, M. A. Modern Organic Synthesis with A-Diazocarbonyl Compounds. *Chem. Rev.* **2015**, *115*, 9981–10080.

[28] Zhu, D.; Chen, L.; Fan, H.; Yao, Q.; Zhu, S. Recent Progress on Donor and Donor – Donor Carbenes. *Chem. Soc. Rev.* **2020**, *49*, 908–950.

[29] Davis, N. . R.; Jones, P. F.; Duff, J. M.; Brook, A. G. Synthesis of Silyl and Germyl Ketones. *J. Am. Chem. Soc.* **1967**, *89*, 431–434.

[30] Corey, E. J.; Seebach, D.; Freedman, R. Synthesis of α-Silyl Ketones via 1,3-Dithianes. *J. Am. Chem. Soc.* **1967**, *89*, 434–436.

[31] Kirihara, M.; Suzuki, S.; Ishihara, N.; Yamazaki, K.; Akiyama, T.; Ishizuka, Y. Synthesis of Acylsilanes via Catalytic Dedithioacetalization of 2-Silylated 1,3-Dithianes with 30%

Hydrogen Peroxide. *Synthesis (Stuttg).* **2017**, *49*, 2009–2014.

[32] Katritzky, A. R.; Lang, H.; Wang, Z.; Lie, Z. Convenient Syntheses of Functionalized Dialkyl Ketones and Alkanoylsilanes: 1-(Benzotriazol-1-Yl)-1-Phenoxyalkanes as Alkanoyl Anion Equivalents. *J. Org. Chem.* **1996**, *61*, 7551–7557.

[33] Paredes, M. D.; Alonso, R. On the Radical Brook Rearrangement. Reactivity of α-Silyl Alcohols, α-Silyl Alcohol Nitrite Esters, and β-Haloacylsilanes under Radical-Forming Conditions. *J. Org. Chem.* **2000**, *65*, 2292–2304.

[34] Duffaut, N.; Dunogues, J.; Biran, C.; Calas, R.; Gerval, J. Sur Une Nouvelle Synthese D'Acylsilanes. *J. Organomet. Chem.* **1978**, *161*, C23–C24.

[35] Clark, C. T.; Milgram, B. C.; Scheidt, K. A.; V, N. U.; Road, S. Efficient Synthesis of Acylsilanes Using Morpholine Amides. *Org. Lett.* **2004**, *6*, 3977–3980.

[36] Picard, J.; Calas, R.; Dunogubs, J.; Duffaut, N.; Gerval, J.; Lapouyade, P. Reductive Silylation of Benzoates: Convenient Synthesis of Aroylsilanes. *J. Org. Chem.* **1979**, *44*, 420–424.

[37] Azuma, H.; Okano, K.; Tokuyama, H. Synthesis of Acylsilanes by Palladium-Catalyzed Cross-Coupling Reaction of Thiol Esters and Silylzinc Chlorides. *Chem. Lett.* **2011**, *40*, 959–961.

[38] Watanabe, H.; Ohsawa, N.; Sawai, M.; Fukasawa, Y.; Matsumoto, H.; Nagai, Y. Photochemical Reaction of Benzoyltrimethylsilane. *J. Organomet. Chem.* **1975**, *93*, 173–179.

[39] Ye, J. H.; Quach, L.; Paulisch, T.; Glorius, F. Visible-Light-Induced, Metal-Free Carbene Insertion into B-H Bonds between Acylsilanes and Pinacolborane. *J. Am. Chem. Soc.* **2019**, *141*, 16227–16231.

[40] Svarovsky, S. A.; Taraban, M. B.; Barchi Jr, J. J. Facile Photochemical Synthesis of Mixed Siloxyacetal Glycosides as Potential pH-Sensitized Prodrugs for Selective Treatment of Solid Tumors. *Org. Biomol. Chem.* **2004**, *2*, 3155–3161.

[41] Stuckhardt, C.; Wissing, M.; Studer, A. Photo Click Reaction of Acylsilanes with Indoles. *Angew. Chemie Int. Ed.* **2021**, *60*, 18605–18611.

[42] Becker, P.; Pirwerdjan, R.; Bolm, C. Acylsilanes in Iridium-Catalyzed Directed Amidation Reactions and Formation of Heterocycles via Siloxycarbenes. *Angew. Chemie - Int. Ed.* **2015**, *54*, 15493–15496.

[43] Brook, A. G.; Pierce, J. B. Nucleophilic Attack of Siloxycarbenes on Carbonyl Groups. The Formation of Oxiranes. *Can. J. Chem.* **1971**, *49*, 1622–1628.

[44] Ishida, K.; Tobita, F.; Kusama, H. Lewis Acid-Assisted Photoinduced Intermolecular Coupling between Acylsilanes and Aldehydes: A Formal Cross Benzoin-Type Condensation. *Chem. Eur. J.* **2018**, *24*, 543–546.

[45] Gröbel, B.-T.; Seebach, D. Umpolung of the Reactivity of Carbonyl Compounds Through Sulfur-Containing Reagents. *Synthesis (Stuttg).* **1977**, *6*, 357–402.

[46] Stetter, H.; Schreckenberg, M. A New Method for Addition of Aldehydes to Activated Double Bonds. *Angew. Chemie Int. Ed.* **1973**, *12*, 81–81.

[47] Stetter, H. Catalyzed Addition of Aldehydes to Activated Double Bonds—A New Synthetic Approach. *Angew. Chemie Int. Ed.* **1976**, *15*, 639–647.

[48] Lebel, H.; Marcoux, J. F.; Molinaro, C.; Charette, A. B. Stereoselective Cyclopropanation Reactions. *Chem. Rev.* **2003**, *103*, 977–1050.

[49] Ma, S.; Mandalapu, D.; Wang, S.; Zhang, Q. Biosynthesis of Cyclopropane in Natural Products. *Nat. Prod. Rep.* **2021**, *39*, 926–945.

[50] Maas, G. Ruthenium-Catalysed Carbenoid Cyclopropanation Reactions with Diazo Compounds. *Chem. Soc. Rev.* **2004**, *33*, 183–190.

[51] Yang, Z.; Stivanin, M. L.; Jurberg, I. D.; Koenigs, R. M. Visible Light-Promoted Reactions with Diazo Compounds: A Mild and Practical Strategy towards Free Carbene Intermediates. *Chem. Soc. Rev.* **2020**, *49*, 6833–6847.

[52] Brook, A. G.; Kucera, H. W.; Pearce, R. Photolysis of 1,1-Diphenylsilacyclohexanone in Diethyl Fumarate. The Trapping of a Siloxycarbene by an Electron-Deficient Olefin. *Can. J. Chem.* **1971**, *49*, 1618–1621.

[53] Dalton, J. C.; Bourque, R. A. Mechanistic Photochemistry of Acylsilanes. 2. Reaction with Electron-Poor Olefins. *J. Am. Chem. Soc.* **1981**, *103*, 699–700.

[54] Becker, P.; Priebbenow, D. L.; Pirwerdjan, R.; Bolm, C. Acylsilanes in Rhodium(III)-Catalyzed Directed Aromatic C-H Alkenylations and Siloxycarbene Reactions with C-C Double Bonds. *Angew. Chemie - Int. Ed.* **2014**, *53*, 269–271.

[55] Takeuchi, T.; Aoyama, T.; Orihara, K.; Ishida, K.; Kusama, H. Visible-Light-Induced In Situ Generation of Fischer-Type Copper Carbene Complexes from Acylsilanes and Its Application to Catalytic [4+1] Cycloaddition with Siloxydienes. *Org. Lett.* **2021**, *23*, 9490–9494.

[56] Bassindale, A. R.; Brook, A. G.; Harris, J. Siloxycarbenes from the Thermolysis of Acylsilanes. *J. Organomet. Chem.* **1975**, *90*, C6–C8.

[57] Fund, B.; Summer, F. Thermal and Photochemical Rearrangement of (o-Tolylcarbonyl)Trimethylsilane. A 1,5-Shift of a Trimethylsilyl Group from Oxygen to Carbon. *J. Org. Chem.* **1982**, *47*, 2668–2670.

[58] Shen, Z.; Dong, V. M. Benzofurans Prepared by C-H Bond Functionalization with Acylsilanes. *Angew. Chemie Int. Ed.* **2009**, *48*, 784–786.

[59] Bourque, R. A.; Davis, P. D.; Dalton, J. C. Mechanistic Photochemistry of Acylsilanes. 1. Reaction with Alchohols. *J. Am. Chem. Soc.* **1981**, *103*, 697–699.

[60] Hammaecher, C.; Portella, C. New 6-Oxa-2-Silabicyclo[2.2.0]Hexanes by Photochemical Conversion of Acyl(Allyl)(Dimethyl)Silanes. *Chem. Commun.* **2008**, 5833.

[61] Argade, N. P.; Hazra, B. G.; Joshi, P. L. Influence of an Oxidising Impurity on Preparation of 2-Lithio-1,3-Dithiane: Isolation of Bis[2-d,3-Dithianyl)]Methanol. *Synth. Commun.* **1996**, *26*, 2797–2802.

[62] Valiulin, R. A.; Kottani, R.; Kutateladze, A. G. When Ethyl Is Infinitely Different from Methyl: Double Addition of Lithiated Dithianes to Aromatic Carboxylates Revisited. *J. Org. Chem.* **2006**, *71*, 5047–5049.

[63] Vale, J. R.; Rimpiläinen, T.; Sievänen, E.; Rissanen, K.; Afonso, C. A. M.; Candeias, N. R. Pot-Economy Autooxidative Condensation of 2-Aryl-2-Lithio-1,3-Dithianes. *J. Org. Chem.* **2018**, *83*, 1948–1958.

[64] Feng, M.; Tang, B.; H. Liang, S.; Jiang, X. *Sulfur Containing Scaffolds in Drugs: Synthesis and Application in Medicinal Chemistry*; 2016; Vol. 16.

[65] Scott, K. A.; Njardarson, J. T. Analysis of US FDA-Approved Drugs Containing Sulfur Atoms. *Top. Curr. Chem.* **2018**, *376*, 1–34.

[66] Viswanathan, A.; Musa, A.; Murugesan, A.; Vale, J.; Afonso, C.; Konda Mani, S.; Yli-Harja, O.; Candeias, N.; Kandhavelu, M. Battling Glioblastoma: A Novel Tyrosine Kinase Inhibitor with Multi-Dimensional Anti-Tumor Effect. *Cells* **2019**, *8*, 1624.

[67] Hammaecher, C.; Bouillon, J. P.; Portella, C. Towards Bis(Acylsilanes) and Cyclic Unsaturated Acylsilanes via Metathesis: An Exploratory Study. *Tetrahedron* **2009**, *65*, 5527–5534.

[68] Lafaye, K.; Bosset, C.; Nicolas, L.; Guérinot, A.; Cossy, J. Beyond Catalyst Deactivation: Cross-Metathesis Involving Olefins Containing N-Heteroaromatics. *Beilstein J. Org. Chem.* **2015**, *11*, 2223–2241.

[69] Ivanova, O. A.; Chagarovskiy, A. O.; Shumsky, A. N.; Krasnobrov, V. D.; Levina, I. I.; Trushkov, I. V. Lewis Acid Triggered Vinylcyclopropane − Cyclopentene Rearrangement. *J. Org. Chem.* **2018**, *83*, 543–560.

[70] Jiang, X.; Fu, D.; Shi, X.; Wang, R. PPh_3-Catalyzed Synthesis of Dicyano-2-Methylenebut-3-Enoates as Efficient Dienes in Catalytic Asymmetric Inverse-Electron-Demand Diels – Alder Reaction. *Chem. Commun.* **2011**, *47*, 8289–8291.

[71] Li, Q.; Zhang, X.; Xie, K.; Dai, Q.; Zeng, R.; Liu, Y.; Jia, Z.; Feng, X.; Li, J. Diastereodivergent Synthesis of Cyclopropanes via On-Water [2+1] Annulations of Diazo Compounds with Electron-Deficient Alkenes. *Green Chem.* **2019**, *21*, 2375–2379.

[72] Vale, J. R.; Gomes, R. F.; Afonso, C. A. M.; Candeias, N. R. Functionalized Cyclopentenes via the Formal [4+1] Cycloaddition of Photogenerated Siloxycarbenes from Acyl Silanes. *J. Org. Chem.* **2022**, *87*, 8910–8920.

[73] Gevorgyan, V.; Liu, J. X.; Rubin, M.; Benson, S.; Yamamoto, Y. A Novel Reduction of Alcohols and Ethers with a $HSiEt_3$/Catalytic $B(C_6F_5)_3$ System. *Tetrahedron Lett.* **1999**, *40*, 8919–8922.

[74] Vale, J. R.; Valkonen, A.; Afonso, C. A. M.; Candeias, N. R. Synthesis of Silacyclopent-2-En-4-Ols via Intramolecular [2+2] Photocycloaddition of Benzoyl(Allyl)Silanes. *Org. Chem. Front.* **2019**, *6*, 3793–3798.

PUBLICATION I

Pot-economy autooxidative condensation of 2-Aryl-2-lithio-1,3-dithianes

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Journal of Organic Chemistry, **2018**, *83*, 1948-1958

DOI: 10.1021/acs.joc.7b02896

JOC The Journal of Organic Chemistry
Article
Cite This: J. Org. Chem. 2018, 83, 1948−1958
pubs.acs.org/joc

Pot-Economy Autooxidative Condensation of 2-Aryl-2-lithio-1,3-dithianes

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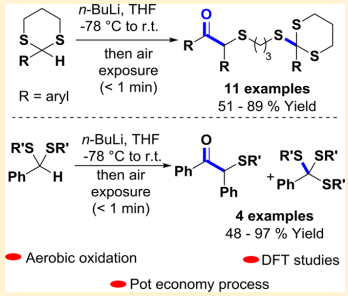
Supporting Information

ABSTRACT: The autoxidative condensation of 2-aryl-2-lithio-1,3-dithianes is here reported. Treatment of 2-aryl-1,3-dithianes with *n*-BuLi in the absence of any electrophile leads to condensation of three molecules of 1,3-dithianes and formation of highly functionalized α-thioether ketones orthothioesters in 51−89% yields upon air exposure. The method was further expanded to benzaldehyde dithioacetals, affording corresponding orthothioesters and α-thioether ketones in 48−97% yields. The experimental results combined with density functional theory studies support a mechanism triggered by the autoxidation of 2-aryl-2-lithio-1,3-dithianes to yield a highly reactive thioester that undergoes condensation with two other molecules of 2-aryl-2-lithio-1,3-dithiane.

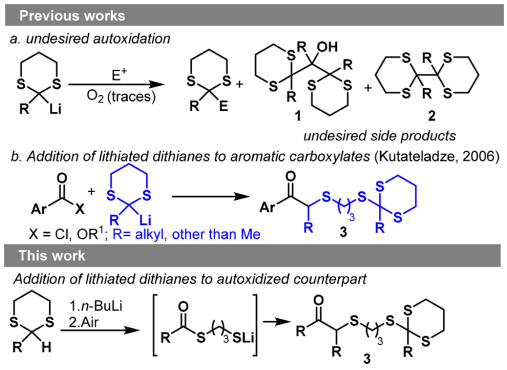


INTRODUCTION

Organolithium compounds can undergo autoxidation toward formation of highly unstable organolithium peroxides, which upon fast interaction with another organolithium leads to the ultimate formation of lithium alkoxides.[1] Oxidation of RLi with ROOLi was proven by Müller and Töpel[2] in 1939 and used in several oxidative processes,[3] and the autoxidation of organolithiums further explored in preparation of alcohols.[4]

The first reports of Corey and Seebach[5] on the use of lithiated 1,3-dithianes as synthetic equivalents to acyl anions have rapidly gathered the attention of the synthetic community. The umpolung strategy rendered by transformation of aldehydes to 2-substituted 1,3-dithianes and subsequent formation of the lithiated acyl anion equivalent have been explored for preparation of a wide array of products,[6,7] namely in natural product synthesis.[8] Other thioacetals can lead to the formation of similar acyclic lithiated anions,[9] but it was soon realized that cyclic 2-lithio-1,3-dithianes were advantageous due to their ease of preparation and general suitability.[6b] Despite the undisputable importance of 2-lithio-1,3-dithianes in synthetic chemistry, inconsistent yields and formation of side products have been reported.[10] Problems derived from its high reactivity and strong basicity have been overcome either by transmetalation,[11−13] or using less reactive silyl,[14−16] or tin[10a,17] analogues. The autoxidation of 2-lithio-1,3-dithiane (Scheme 1) upon air exposure has been reported by Wade and co-workers,[18] after observing formation of **1** and **2** in absence of an electrophile. The formation of **1** was also later reported by Argade and co-workers when preparing 2-lithio-1,3-dithiane.[19] The presence of an oxidizing impurity in older bottles of *n*-BuLi was advanced as the cause for the formation of the oxidized products. The same compound was reported to be formed in 25% yield when preparing 2-lithio-1,3-dithiane in THF, proposed by the authors to arise from the unlikely reaction of the desired intermediate with solvent.[20] Presence of dimers

Scheme 1



Received: November 15, 2017
Published: January 15, 2018

DOI: 10.1021/acs.joc.7b02896
J. Org. Chem. 2018, 83, 1948−1958

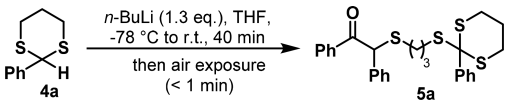
derived from single electron transfer processes have been observed in several other works,[12a,14c,21] especially in the presence of nitro substituted compounds.[22] The nucleophilic addition of 2-lithio-1,3-dithianes to acyl chlorides and esters reported by Kutateladze and co-workers[23] is one example from the vast array of dithiane umpolung reactivity of carbonyl compounds (Scheme 1). Interestingly, when an aldehyde other than acetaldehyde is used, the reaction proceeds through addition of a second dithiane molecule through ring-opening of the first installed dithiane unit.[24]

Considering the previous reports on the autoxidation of 2-lithio-1,3-dithianes, we envisioned that 2-aryl-2-lithio-1,3-dithianes could be oxidized *in situ* to yield a thioester capable of undergoing a similar attack by the excess organolithium eventually forming compounds similar to those described by Kutateladze in a pot economy.[25] Previously reported transformations of the envisioned products include desulfurizing difluorination of the α-thioether ketone and dithioketal moieties[26] or trifluoromethylation of benzylic orthothioesters.[26b,27] Orthothioesters can be converted to esters, thioesters or orthoesters[28] and α-thioether ketones have also been used in the oxidative coupling of benzyl ketones.[29]

RESULTS AND DISCUSSION

Gratifyingly, when reacting 2-phenyl-2-lithium-1,3-dithiane with *S*-benzyl benzothioate, product **5a** was obtained in 89% yield (Table 1, entry 1). The ability of the thioester group to undergo the same transformation as benzoyl chloride (entry 2) prompted us to assess the possibility for *in situ* formation of the thioester by oxidation of the lithium dithiane. Hence, the argon atmosphere of a solution of 2-phenyl-2-lithium-1,3-dithiane from **4a** was replaced by oxygen and kept for 5 min to afford the thioorthoester in 69% yield (entry 3). The simple exposure of the reaction mixture to air for 30 min allowed formation of thioorthoester **5a** in 41% yield (entry 4), which was increased to 68% by decreasing exposure to air to less than a minute (entry 5), and to 71% by forming the lithiated dithiane at 0 °C (entry 6). Modification of the stoichiometric amounts of *n*-BuLi or other solvents (entries 7–10) did not improve the reaction success. Although a fast process at 0 °C, air exposure of the organolithium at −78 °C led to only traces of product and unreacted dithiane (entry 11).

Table 1. Optimization of Reaction Conditions

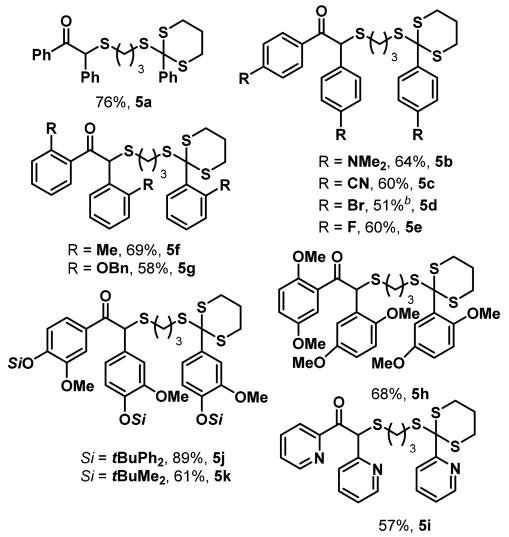


entry	deviation from reaction conditions[a]	yield (%)[b]
1	PhC(O)SBn (0.65 equiv), no air	89
2	PhC(O)Cl (0.65 equiv), no air	71
3	O_2 balloon for 5 min	69
4	30 min air exposure	41
5	rt, 20 min	68
6	0 °C to rt, 20 min	71
7	1.0 equiv *n*-BuLi, 0 °C to rt, 20 min	66
8	1.6 equiv *n*-BuLi, 0 °C to rt, 20 min	60
9	Et_2O, 0 °C to rt, 20 min	46
10	toluene	39
11	air exposure at −78 °C	traces

[a]*n*-BuLi (2.5 M in hexanes, 1.3 mmol) was added dropwise to a solution of dithiane **4a** (1 mmol) in THF (5 mL) under argon atmosphere at −78 °C. The mixture was left to reach rt after 20 min, and opened to air 1 min before addition of NH_4Cl saturated aqueous solution. [b]Isolated yield.

Finally, the optimized protocol retrieved formation of orthothioester **5a** in 76% and the scope of the method was evaluated (Scheme 2). Formation of ortholithiation derived products was not observed even in the presence of directing metalating groups. The correspondent orthothioesters derived from electron rich or electron poor aryl dithianes could be obtained in reasonable yields. Phenyl-1,3-dithianes decorated with halogens at the *para*-position were successfully transformed into the corresponding orthothioesters **5d** and **5e**, although LDA had to be used for the bromide derivative to avoid transmetalation with *n*-BuLi. TBDMS and TBDPS silyl protective groups were stable to the reaction conditions, and silyl ethers **5j** and **5k** could be obtained in up to 89% yield. A dithiane derived from 2-formylpyridine resulted in formation of **5i** in 57% yield. Despite several attempts on the autoxidative addition of nitrophenyl-1,3-dithianes, only alkylated derivatives or starting materials were obtained. Other electron deficient dithianes such as pentafluorophenyl or *para*-trifluoromethylphenyl derivatives were unstable toward the lithiation conditions tested.

Scheme 2[a]



[a]For reaction conditions see footnote *a*, Table 1. [b]LDA as base.

Acyclic benzaldehyde dithioacetals derived from primary and secondary thiols undergo the same process to yield α-thioether ketones **7** and orthothioesters **8** (Table 2). Dithioacetal **6e** derived from *tert*-butyl mercaptan failed to provide the corresponding ketone or orthothioesters likely due to steric hindrance as only thioester **9** could be obtained. The use of O_2 instead of air was observed to be detrimental for the reaction yield, as complex mixtures of products were obtained in such cases.

In order to evaluate the scope of the transformation concerning the nature of the 2-substituent of 1,3-dithianes,

DOI: 10.1021/acs.joc.7b02896
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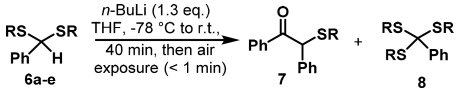
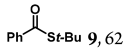
Table 2. Autooxidative Condensation of Benzaldehyde-Derived Dithioacetals

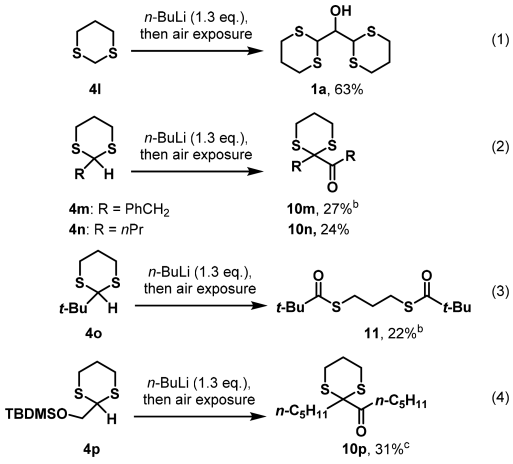


Entry[a]	R	7 Yield (%)[b]	8 Yield (%)[b]
1	Ph	**7a**, 48	**8a**, -[c]
2	*n*-Bu	**7b**, 97	**8b**, 72
3	$(CH_2)_{11}Me$	**7c**, 73	**8c**, 56
4	*sec*-Bu	**7d**, 67	**8d**, -[c]
5	*t*-Bu	 **9**, 62	

[a]For reaction conditions see footnote *a*, Table 1. [b]Isolated yield. [c]Observed in ^{1}H NMR of the crude mixture but not isolated.

several 2-alkyl-1,3-dithianes were submitted to our autoxidative conditions (Scheme 3). The autoxidation of 2-lithio-1,3-dithiane under the reaction conditions resulted in the unsurprising formation of alcohol **1a** as previously reported by Wade and co-workers (Scheme 3, eq 1).[18] 2-Alkyl substituted 1,3-dithianes undergo autoxidation to some extent, however the reaction is halted before orthothioester formation and **10** are obtained in up to 27% yields (Scheme 3, eq 2) probably due to the competitive formation of the lithium enolate of product. Similar yields of the products were observed when increasing the amount of *n*-BuLi. The presence of a bulky *t*-butyl substituent alters the outcome of the reaction. Dithioester **11**, resulting from condensation of two oxidized species was the only product identified (Scheme 3, eq 3). The autoxidative addition of 1,3-dithiane derived from silyl protected glycoaldehyde yields **10p** together with hexyl substituted 1,3-dithiane. The formation of the later is likely to occur by trapping of the ketene dithiane with *n*-butyl lithium.[30] Several attempts to apply this procedure to 2-silyl substituted 1,3-dithianes, such as 2-TMS-1,3-dithiane 2-TBDPS-1,3-dithiane, resulted in the formation of complex mixtures of unidentified products.

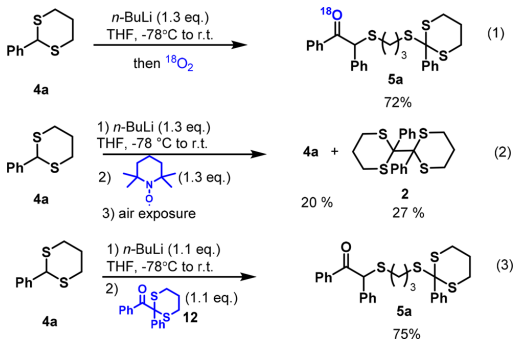
Scheme 3[a]



[a]For reaction conditions see footnote *a*, Table 1. Isolated yields. [b]Unreacted dithiane **4** was isolated as the major species. [c]2-(*n*-Hexyl)-1,3-dithiane was also isolated in 23%.

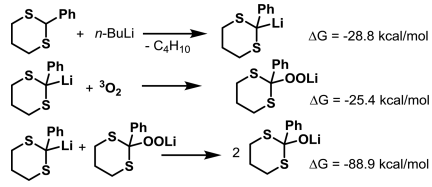
The role of atmospheric oxygen as the oxidant species in the process was confirmed by running the autoxidative condensation reaction under $^{18}O_2$, affording the ^{18}O isotopically labeled **5a** in 72% yield (Scheme 4, eq 1). Impelled by the previous suggestions that a SET mechanism could be involved, the exposure to air in the presence of TEMPO was performed (Scheme 4, eq 2). Trapped intermediates were not identified and only compound **2** was isolated, already known to derive from SET.[12a,14c,21] Notably, formation of compound **5a** was not observed, which might indicate the SET process to be a pitfall prior to the organolithium autoxidation. The presence of **12** as intermediate in the reaction was supported by its reaction with lithium dithiane derived from **4a** (Scheme 4, eq 3).

Scheme 4



In order to get some insight on the reaction mechanism, the several putative processes involved in the transformation were studied by DFT calculations.[31] The spontaneous autoxidation of the organolithium compound was verified through optimization of relevant intervenient species (Scheme 5). The process seems highly favorable, as the lithium alkoxide formation is balanced by the release of 25.4 kcal/mol upon reaction of lithium dithiane with triplet oxygen[3a] followed by release of 88.9 kcal/mol upon reaction of the lithium peroxide with lithium dithiane to form the corresponding lithium alkoxide.

Scheme 5



According to our calculations, formation of thioester **B** from lithium alkoxide **A** requires only 2.7 kcal/mol (Figure 1). The thiolate charge in thioester **B** is highly stabilized by lithium and becomes more stabilized upon interaction with a lithium

DOI: 10.1021/acs.joc.7b02896
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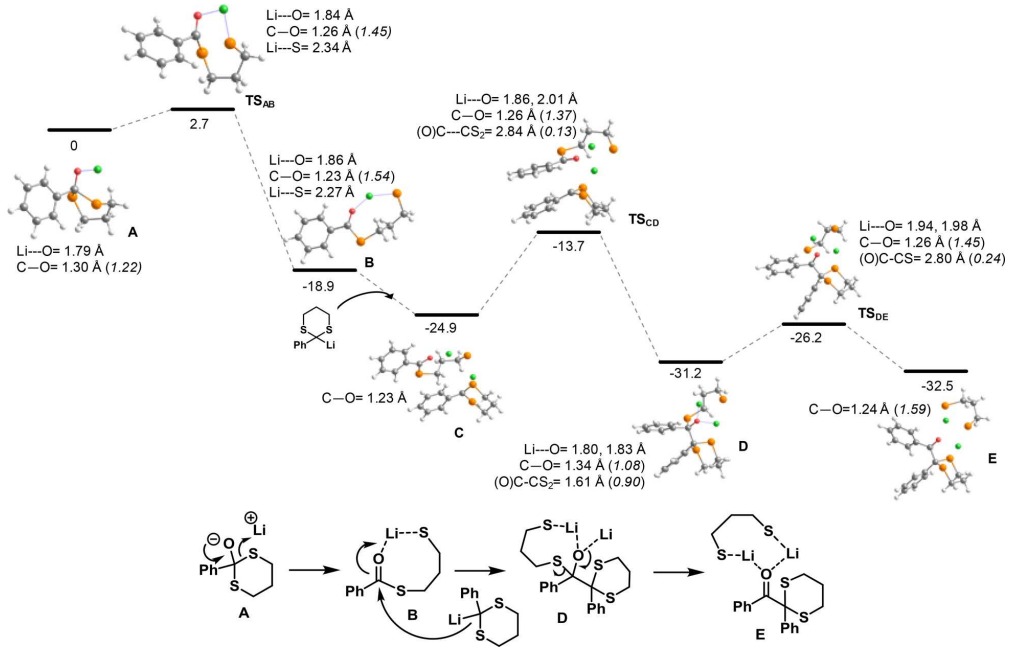

Figure 1. Free energy profile (PBE0) for deterioration of lithium alkoxide and reaction with 2-phenyl-2-lithio-1,3-dithiane, and mechanistic representation. Optimized structures of minima and transition states are presented with bond distances and Wiberg indexes (in italics) for the more relevant bonds. Free energies values are presented in kcal/mol, referring to the initial intermediate **A**.

dithiane molecule (**C**). The presence of lithium increases the C═O polarization of the thioester assisting the nucleophilic attack of a lithium dithiane molecule, and requires 11.2 kcal/mol. The transition state **TS$_{CD}$** resembles an early one, as suggested by the rather long forming C−C bond and small Wiberg index[32] (d = 2.84 Å and WI = 0.13), which becomes considerably shorter in the tetrahedral intermediate **D** (d = 1.61 Å and WI = 0.90). The collapse of intermediate **D** to the more stable pair of ketone and lithium thiolate (**E**) requires only 5.0 kcal/mol to overcome the transition state **TS$_{DE}$** energy barrier. Interaction of the lithium cations with sulfur atoms is visible in calculated **TS$_{DE}$**, although such stabilization is likely to take place by the solvent molecules. The pair of products represented in **E** is highly stabilized by interaction of lithium cations with both sulfur atoms of the thiolate and the carbonyl oxygen.

Condensation of the ketone **12** in **E** with another lithium dithiane molecule was considered, as observed experimentally (Scheme 4, eq 3), by taking the nucleophilic attack of the organolithium to a sulfur atom of the α-disubstituted ketone (Figure 2).[24] The calculated transition state for this reaction **TS$_{FG}$** is characterized by distension of the C−S bond of the ketone (2.11 Å in **TS$_{FG}$** and 1.85 Å in **F**) and formation of a new C−S bond (2.49 Å and WI = 0.29) with the lithium dithiane molecule, demanding for 11.2 kcal/mol. Weakening of the carbon−oxygen bond from **F** to **G** is visible by its length (1.23 Å in **F** and 1.29 Å in **G**) and weaker Wiberg index in the lithium enolate product **G** (WI = 1.65 in **F** and 1.31 in **G**), accompanied by strengthening of the C−C bond (1.55 Å; WI = 0.95 in **F** and 1.40 Å; WI = 1.47 in **G**). Although we cannot rule out a radical mechanism based on our calculations (as suggested by Kutateladze[23] and considered in Supporting Information), the low energy barrier determined for the ionic

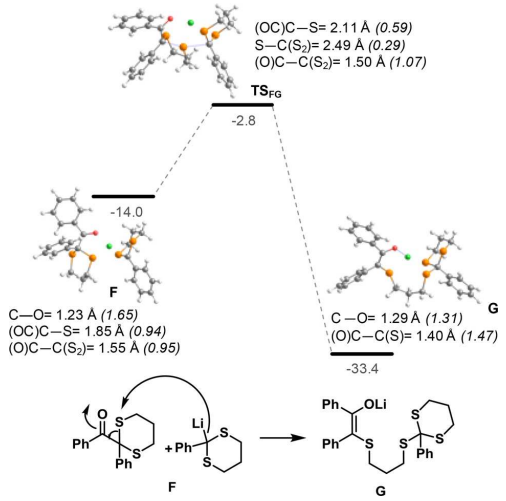

Figure 2. Free energy profile (PBE0) for nucleophilic condensation of α-disubstituted ketone with 2-phenyl-2-lithio-1,3-dithiane and mechanistic representation. Optimized structures of minima and transition states are presented with bond distances and Wiberg indexes (in italics) for the more relevant bonds. Free energies values are presented in kcal/mol, referring to the initial intermediate **A** from Figure 1.

DOI: 10.1021/acs.joc.7b02896
J. Org. Chem. 2018, 83, 1948−1958

nucleophilic attack might indicate this as the main route for formation of the orthothioester product.

CONCLUSION

In summary, we have shown that 2-aryl-2-lithium-1,3-dithianes undergo autoxidative condensation forming α-thioether ketones orthothioesters in reasonable to good yields upon aerobic oxidation. The procedure can be expanded to other benzaldehyde derived dithioacetals, affording orthothioesters and α-thioether ketones in good to excellent yields. 2-Alkyl substituted 1,3-dithianes also undergo a similar autoxidative process upon treatment with *n*-BuLi and air exposure; however, condensation of a third dithiane unit is hampered by presence of enolizable positions on the condensation intermediate. DFT calculations support a reaction mechanism that starts with the highly thermodynamic favorable autoxidation of the organolithium dithiane, leading to formation of the thioester that is further trapped by another 2-lithium-1,3-dithiane. The herein described process might be on the basis of the known limitations on the use of 2-lithio-1,3-dithianes in synthetic chemistry, and it is also a way to achieve highly functionalized and stable orthothioesters.

EXPERIMENTAL SECTION

General Remarks. Reactions were monitored through thin-layer chromatography (TLC) with commercial silica gel plates (Merck silica gel, 60 F254). Visualization of the developed plates was performed under UV lights at 254 nm and by staining with cerium ammonium molybdate, 2,4-dinitrophenylhydrazine and vanillin stains. Flash column chromatography was performed on silica gel 60 (40−63 μm) as stationary phase. Preparative TLCs were conducted on PLC silica gel 60 F254, 1 mm.^{1}H NMR spectra were recorded at 300 MHz, ^{13}C NMR spectra were recorded at 75 MHz and ^{19}F spectrum was recorded at 282 MHz in a 300 MHz Varian Mercury spectrometer, using $CDCl_3$ as solvent. Chemical shifts (δ) are reported in ppm referenced to the CDCl3 residual peak (δ 7.26) or TMS peak (δ 0.00) for ^{1}H NMR and to $CDCl_3$ (δ 77.16) for ^{13}C NMR. The following abbreviations were used to describe peak splitting patterns: s = singlet, d = doublet, t = triplet, m = multiplet. Coupling constants, *J*, were reported in Hertz (Hz). High-resolution mass spectra were recorded on a Waters ESI-TOF MS spectrometer. Tetrahydrofuran (THF) was dried by distillation under argon with sodium metal and benzophenone as indicator. Dichloromethane (DCM) was dried by distillation under argon with calcium hydride. Isotope labeled oxygen-18 (99% isotopic purity) was purchased from Sigma-Aldrich (CAS Number 32767−18−3). A small balloon was filled with oxygen-18 and used directly in the oxidation reaction.

General Procedure for Preparation of 2-Substituted 1,3-Dithianes (Method A). On the basis of a modified previously reported method,[33] aldehyde (15 mmol, 1 equiv) and 1,3-propanedithiol (3 mL, 16.5 mmol, 1.1 equiv) were dissolved in dichloromethane (50 mL) in a round-bottom flask. Iodine (381 mg, 1.5 mmol, 0.1 equiv) was slowly added do the stirring solution as to prevent vigorous boiling of the solvent. The reaction was quenched with a 2% $Na_0S_2O_3$ aqueous solution (10 mL) 30 min after complete iodine addition. Upon separation, the organic layer was washed successively with a 10% aqueous NaOH solution (10 mL), water (10 mL) and brine (10 mL). The organic solvent was dried over $MgSO_4$ and filtered. After evaporating the solvent, the product was recrystallized in isopropanol. Note: Reactions were conducted in different scales depending on availability of aldehyde starting material.

4a. Prepared according to method A. 77% yield (3.425 g, 17.45 mmol), white crystals. Obtained with same spectral characterization as previously described.[34] ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.49−7.45 (m, 2H), 7.37−7.29 (m, 3H), 5.17 (s, 1H), 3.12−3.02 (m, 2H), 2.95−2.88 (m, 2H), 2.22−2.14 (m, 1H), 2.01−1.86 (m, 1H).

4b. Prepared according to a modified previously reported method.[35] 4-(Dimethylamino)benzaldehyde (1 g, 6.7 mmol, 1 equiv) and 1,3-propanedithiol (0.74 mL, 7.4 mmol, 1.1 equiv) were dissolved in 10 mL of dry DCM in an argon purged round-bottom flask. The solution was cooled to 0 °C and $BF_3{\cdot}OEt_2$ (1.16 mL, 9.4 mmol, 1.4 equiv) was added dropwise. The solution was then left warming to room temperature for 1 h. The reaction was quenched with a 10% aqueous NaOH solution (10 mL). The layers were separated and the organic phase collected and washed with water (10 mL) and Brine (10 mL). The organic solvent was dried over $MgSO_4$ and filtered. After evaporation of the solvent, the product was recrystallized from isopropanol to give **4b** as yellow crystals in 93% yield (1.498 g, 6.26 mmol). Obtained with same spectral characterization as previously described.[36] ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.33 (d, *J* = 8.8 Hz, 2H), 6.67 (d, *J* = 8.8 Hz, 2H), 5.12 (s, 1H), 3.17−2.86 (m, 4H), 2.94 (s, 6H), 2.20−2.10 (m, 1H), 1.97−1.82 (m, 1H).

4c. Prepared according to method A. 89% yield (2.997 g, 13.54 mmol), white crystals. Obtained with same spectral characterization as previously described.[34] ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.65−7.57 (m, 4H), 5.17 (s, 1H), 3.11−3.01 (m, 2H), 2.96−2.90 (m, 2H), 2.23−2.15 (m, 1H), 2.01−1.86 (m, 1H).

4d. Prepared according to method A. 81% yield (3.628 g, 13.18 mmol), white crystals. Obtained with same spectral characterization as previously described.[34] ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.49−7.44 (m, 2H), 7.37−7.32 (m, 2H), 5.11 (s, 1H), 3.10−3.00 (m, 2H), 2.94−2.86 (m, 2H), 2.22−2.12 (m, 1H), 1.99−1.84 ppm (m, 1H).

4e. Prepared according to method A. 76% yield (1.515 g, 7.07 mmol), white crystals. Obtained with same spectral characterization as previously described.[37] ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.47−7.42 (m, 2H), 7.05−6.99 (m, 2H), 5.14 (s, 1H), 3.10−3.01 (m, 2H), 2.94−2.87 (m, 2H), 2.22−2.13 (m, 1H), 1.99−1.84 (m, 1H).

4f. Prepared according to method A. 69% yield (1.253 g, 5.96 mmol), white crystals. Obtained with same spectral characterization as previously described.[34] ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.61−7.57 (m, 1H), 7.24−7.13 (m, 3H), 5.33 (s, 1H), 3.14−3.04 (m, 2H), 2.95−2.88 (m, 2H), 2.45 (s, 3H), 2.23−2.14 (m, 1H), 2.02−1.87 (m, 1H).

4g. Prepared according to method A. 88% yield (1.681 g, 5.56 mmol), pale yellow solid. Product was isolated by flash chromatography (Hex:AcOEt, 95:5). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.60 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.47−7.30 (m, 5H), 7.21 (td, *J* = 7.8, 1.5 Hz, 1H), 7.00−6.95 (m, 1H), 6.89 (d, *J* = 8.2 Hz, 1H), 5.76 (s, 1H), 5.13 (s, 2H), 3.13−2.85 (m, 2H), 2.92−2.85 (m, 2H), 2.20−2.11 (m, 1H), 2.00−1.85 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 154.8, 137.2, 129.4, 129.3, 128.7, 128.1, 128.0, 127.3, 121.5, 112.7, 70.6, 44.2, 44.1, 32.5, 25.5. HR-MS (ESI) *m*/*z* calculated for $C_{17}H_{19}OS_2^+$ $[M + H]^+$ 303.0872, found 303.0884.

4h. Prepared according to method A. 76% yield (1.172 g, 4.57 mmol), white crystals. Obtained with same spectral characterization as previously described.[34] ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.15 (dd, *J* = 2.3, 1.2 Hz, 1H), 6.83−6.76 (m, 2H), 5.67 (s, 1H), 3.82 (s, 3H), 3.78 (s, 3H), 3.16−3.06 (m, 2H), 2.93−2.86 (m, 2H), 2.20−2.12 (m, 1H), 2.01−1.86 (m, 1H).

4i. Prepared according to a modified previously reported method.[38] Freshly distilled picolinaldehyde (1 mL, 10.51 mmol, 1 equiv) and 1,3-propanedithiol (1.16 mL, 11.56 mmol, 1.1 equiv) were dissolved in DCE (20 mL). *p*-Toluenosulfonic acid (200 mg, 1.05 mmol, 0.1 equiv) was added to the mixture and the solution refluxed for 24 h. The reaction was cooled to room temperature and quenched with a 10% aqueous NaOH solution (10 mL). The layers were separated and the organic phase collected and washed with water (10 mL) and brine (10 mL). The organic solvent was dried over $MgSO_4$ and filtered. The solvent was evaporated and the product isolated by flash chromatography (Hex:AcOEt, 70:30) to give **4i** as a yellow solid in 54% yield (1.111 g, 5.63 mmol), with same spectral characterization as previously described.[38] ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.57 (dd, *J* = 4.4, 1.5 Hz, 1H), 7.67 (td, *J* = 7.6, 1.8 Hz, 1H), 7.46 (d, *J* = 7.6 Hz, 1H), 7.22−7.18 (m, 1H), 5.35 (s, 1H), 3.11−2.92 (m, 4H), 2.23−2.13 (m, 1H), 2.05−1.90 (m, 1H).

DOI: 10.1021/acs.joc.7b02896
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4-(1,3-Dithian-2-yl)-2-methoxyphenol. Prepared according to method A and used in preparation of **4j** and **4k**. 84% yield (6.723 g, 27.73 mmol), white crystals. Obtained with same spectral characterization as previously described.[39] ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.00−6.84 (m, 2H), 6.87−6.84 (m, 1H), 5.64 (s, 1H), 5.11 (s, 1H), 3.90 (s, 3H), 3.10−2.87 (m, 2H), 2.93−2.86 (m, 2H), 2.21−2.12 (m, 1H), 1.99−1.84 (m, 1H).

4j. 4-(1,3-Dithian-2-yl)-2-methoxyphenol (0.5 g, 2.06 mmol, 1 equiv), imidazole (155 mg, 2.27 mmol, 1.1 equiv) and 4-dimethylaminopyridine (25 mg, 0.2 mmol, 0.1 equiv) were dissolved in dry DCM (10 mL), in an argon purged round-bottom flask. Then, *tert*-butyl(chloro)diphenylsilane was added dropwise to the stirring solution. The mixture was left stirring at room temperature for 24 h. The reaction was quenched with H_2O (10 mL) and the layers were separated. The organic layer was collected and washed with water (10 mL) and Brine (10 mL), dried over $MgSO_4$, filtered and evaporated. The product was purified by flash chromatography (Hex:DCM, 1:1) to yield **4j** in 93% yield (918 mg, 1.91 mmol) as a colorless thick oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.69 (dd, J = 7.6, 1.8 Hz, 4H), 7.42−7.31 (m, 6H), 6.89 (d, J = 1.8 Hz, 1H), 6.76−6.73 (m, 1H), 6.55−6.63 (m, 1H), 5.05 (s, 1H), 3.57 (s, 3H), 3.07−2.98 (m, 2H), 2.91−2.83 (m, 2H), 2.18−2.09(m, 1H), 1.96−1.81 (m, 1H), 1.10 ppm (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 150.6, 145.2, 135.5, 133.6, 132.3, 129.7, 127.6, 120.2, 120.0, 111.8, 55.5, 51.5, 32.3, 26.8, 25.2, 19.9. HR-MS (ESI) m/z calculated for $C_{27}H_{33}O_2S_2Si^+$ $[M + H]^+$ 481.1686, found 481.1687.

4k. 4-(1,3-Dithian-2-yl)-2-methoxyphenol (0.8 g, 3.30 mmol, 1 equiv), imidazole (270 mg, 3.96 mmol, 1.2 equiv) and 4-dimethylaminopyridine (42 mg, 0.34 mmol, 0.1 equiv) were dissolved in dry DCM (10 mL), in an argon purged round-bottom flask. Then, *tert*-butyldimethylsilyl chloride (597 mg, 3.96 mmol, 1.2 equiv) was added dropwise to the stirring solution. The mixture was left stirring at room temperature for 24 h. The reaction was quenched with H_2O (10 mL) and the layers were separated. The organic layer was collected and washed with water (10 mL) and Brine (10 mL), dried over $MgSO_4$, filtered and evaporated. The product was purified by flash chromatography (Hex:EtOAc, 95:5) to yield **4k** in 90% yield (1.056 mg, 2.86 mmol) as a colorless thick oil with same spectral characterization as previously described.[40] ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 6.97 (d, J = 1.8 Hz, 1H), 6.92−6.89 (m, 1H), 6.79−6.76 (m, 1H), 5.11 (s, 1H), 3.81 (s, 3H), 3.10−3.01 (m, 2H), 2.93−2.86 (m, 2H), 2.21−2.11 (m, 1H), 1.99−1.84 (m, 1H), 0.98 (s, 9H), 0.14 (s, 6H).

4l. Prepared according to a modified previously reported method.[41] In an argon purged round-bottom flask were added 10 mL of dry DCM, 5 mL of glacial acetic acid, and $BF_3{\cdot}OEt_2$ (2.47 mL, 20 mmol, 1 equiv). Then, a solution of 1,3-propanedithiol (2 mL, 20 mmol, 1 equiv) and chloromethyl methyl ether (1.67 mL, 22 mmol, 1.1 equiv) in 30 mL of dry DCM was added dropwise for 10 min at room temperature. The solution was left stirring for 3 h at room temperature, and then quenched with 40 mL of water. The layers were separated and the organic phase collected and washed with water (40 mL), a 10% aqueous NaOH solution (2 × 40 mL) and brine (40 mL). The organic solvent was dried over $MgSO_4$, filtered and evaporated. Sublimation under reduced pressure gave pure **4l** as a white solid in 32% yield (778 mg, 6.47 mmol), with same spectral characterization as previously described.[42] ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 3.78 (s, 2H), 2.84−2.80 (m, 4H), 2.11−2.03 (m, 2H).

4m. Prepared according to method A. 53% yield (560 mg, 2.66 mmol), pale green solid. 1.2 equiv of 1,3-propanedithiol were used. Obtained with same spectral characterization as previously described,[43] after purification by flash chromatography (Hex:EtOAc, 85:15). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.34−7.22 (m, 5H), 4.24 (t, J = 7.3 Hz, 1H), 3.02 (d, J = 7.3 Hz, 2H), 2.85−2.80 (m, 4H), 2.15−2.05 (m, 1H), 1.92−1.79 (m, 1H).

4n. Prepared according to a modified previously reported method.[35] Butyraldehyde (0.45 mL, 5 mmol, 1 equiv) and 1,3-propanedithiol (0.6 mL, 6 mmol, 1.2 equiv) were dissolved in 20 mL of dry DCM under argon. The solution was stirred at room temperature and $BF_3{\cdot}OEt_2$ (0.43 mL, 0.7 mmol, 0.7 equiv) was added dropwise. After 90 min, the reaction was quenched by washing the reaction mixture twice with 20 mL of 10% aqueous NaOH. The combined aqueous layers were then extracted twice with 20 mL of DCM. The organic layers were combined, washed with 25 mL of brine and dried over $MgSO_4$. The organic solvent was evaporated under reduced pressure and the resulting oil was purified by flash chromatography (hexane/EtOAc 97:3), which afforded **4n** as a colorless oil in 99% yield (808 mg, 4.98 mmol). Obtained with same spectral characterization as previously described.[34] ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 4.05 (t, J = 6.7 Hz, 1H), 2.92−2.76 (m, 4H), 2.14−2.06 (m, 1H), 1.90−1.77 (m, 1H), 1.75−1.67 (m, 2H), 1.59−1.45 (m, 2H), 0.85−0.97 (m, 3H).

4o. Prepared according to a modified previously reported method.[44] Pivalaldehyde (5 mmol, 1 equiv) and *N*-bromosuccinimide (178 mg, 1 mmol, 0.2 equiv) were dissolved in CH_2Cl_2 (25 mL). The solution was then stirred under argon at rt and 1,3-propanedithiol (1.2 equiv) was added dropwise. The reaction was monitored by TLC and quenched with 10% aqueous NaOH (25 mL) when the aldehyde was consumed (30−80 min). Aqueous and organic layers were separated and the aqueous layer was washed with CH_2Cl_2 (2 × 25 mL). The combined organic layers were washed with 25 mL brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. 62% yield (544 mg, 3.08 mmol), white solid was obtained with same spectral characterization as previously described.[34] ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 3.99 (s, 1H), 2.90−2.86 (m, 4H), 2.11−2.02 (m, 1H), 1.86−1.74 (m, 1H), 1.10 (s, 9H).

4p. Prepared according to method A. Flash chromatography gradient eluent: Hex:AcOEt (85:15 to 60:40). 33% yield (433 mg, 1.64 mmol), colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 4.17−4.17 (m, 1H), 3.85 (d, J = 6.4 Hz, 2H), 2.90−2.75 (m, 4H), 2.15−2.06 (m, 1H), 1.96−1.85 (m, 1H), 0.90 (s, 9H), 0.09 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 66.1, 48.6, 29.1, 26.2, 26.0, 18.6, −5.2. HR-MS (ESI) m/z calculated for $C_{11}H_{24}OS_2SiNa^+$ $[M + Na]^+$ 287.0930, found 287.0953.

General Procedure for Preparation of Dithioacetals 6 (Method B). On the basis of a modified previously reported method,[44] aldehyde (5 mmol, 1 equiv) and *N*-bromosuccinimide (178 mg, 1 mmol, 0.2 equiv) were dissolved in CH_2Cl_2 (25 mL). The solution was then stirred under argon at rt and thiol (2.5 equiv) was added dropwise. The reaction was monitored by TLC and quenched with 10% aqueous NaOH (25 mL) when the aldehyde was consumed (30−80 min). Aqueous and organic layers were separated and the aqueous layer was washed with CH_2Cl_2 (2 × 25 mL). The combined organic layers were washed with 25 mL brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was then purified by recrystallization or by flash chromatography.

6a. Prepared according to a modified previously reported method.[33] Benzaldehyde (0.51 mL, 5 mmol, 1 equiv) and benzenethiol (1.08 mL, 10.5 mmol, 2.1 equiv) were dissolved in $CHCl_3$ (25 mL). The solution was then stirred at rt and I_2 (0.13 g, 0.5 mmol, 0.1 equiv) was added. The reaction was monitored by TLC. When the aldehyde was consumed (30 min) the reaction was quenched with aqueous $Na_2S_2O_3$ (0.1 M, 25 mL) and then washed twice with 10% aqueous NaOH (25 mL). Aqueous and organic layers were separated and the aqueous layer was washed with $CHCl_3$ (25 mL). The combined organic layers were washed with 20 mL of H_2O, dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield the crude product. The crude product was then purified by recrystallization from hexane to afford **6a** as white crystals in 66% yield (1.01 g, 3.28 mmol) with the same spectral characterization as previously described.[45] ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.39−7.20 (m, 15H), 5.42 (s, 1H).

6b. Prepared according to method B. Flash chromatography eluent: Hex:AcOEt (97.5:2.5). 91% yield (1.218 g, 4.54 mmol), colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.45−7.42 (m, 2H), 7.34−7.22 (m, 3H), 4.87 (s, 1H), 2.63−2.46 (m, 4H), 1.58−1.48 (m, 4H), 1.42−1.30 (m, 4H), 0.87 (t, J = 7.3 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 140.7, 128.5, 127.8, 127.8, 53.3, 32.0, 31.3, 22.1, 13.7. HR-MS (ESI) m/z calculated for $C_{15}H_{23}S_2^+$ $[M - H]^+$ 267.1236, found 267.1246.

6c. Prepared according to a modified previously reported method.[33] Benzaldehyde (2 mL, 19.7 mmol, 1 equiv) and dodecanethiol (10.4

DOI: 10.1021/acs.joc.7b02896
J. Org. Chem. 2018, 83, 1948−1958

mL, 43.3 mmol, 2.2 equiv) were dissolved in dichloromethane (30 mL) in a round-bottom flask. Then, iodine (508, 2 mmol, 0.1 equiv) was slowly added do the stirring solution as to prevent vigorous boiling of the solvent. After 2 h of complete addition, the reaction was quenched with a 2% $Na_2S_2O_3$ aqueous solution (10 mL). The layers were separated and the organic layer collected and washed successively with a 10% aqueous NaOH solution (10 mL), water (10 mL) and brine (10 mL). The organic solvent was dried over $MgSO_4$ and filtered. After evaporating the solvent, the product was purified by flash chromatography (hexane) to give **6c** as a white amorphous solid in 57% yield (5.563 g, 11.29 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.45−7.42 (m, 2H), 7.35−7.22 (m, 3H), 4.86 (s, 1H), 2.62−2.45 (m, 4H), 1.59−1.49 (m, 4H), 1.35−1.24 (m, 36H), 0.90−0.86 (m, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ ppm 140.8, 128.6, 127.9, 127.8, 53.3, 32.4, 32.1, 29.8, 29.7, 29.6, 29.5, 29.3, 29.3, 29.0, 22.8, 14.3. HR-MS (ESI) m/z calculated for $C_{31}H_{55}S_2^+$ $[M - H]^+$ 491.3740, found 491.3757.

6d. Prepared according to method B. 86% yield (1.150 g, 4.29 mmol), colorless oil. Flash chromatography eluent: Hex:AcOEt (97.5:2.5). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.47 (d, J = 7.6 Hz, 2H), 7.34−7.22 (m, 3H), 4.94 (s, 1H), 2.88−2.63 (m, 2H), 1.66−1.42 (m, 4H), 1.24−1.20 (m, 6H), 0.97−0.88 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 141.1, 128.5, 127.8, 127.7, 50.8, 50.6, 42.5, 42.4, 29.5, 29.5, 20.7, 20.6, 20.6, 11.2, 11.1. HR-MS (ESI) m/z calculated for $C_{15}H_{23}S_2^+$ $[M - H]^+$ 267.1236, found 267.1243.

6e. Prepared according to method B. 87% yield (1.171 g, 4.37 mmol), white solid. Flash chromatography eluent: Hex:AcOEt (97.5:2.5). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.48−7.44 (m, 2H), 7.32−7.26 (m, 2H), 7.23−7.18 (m, J = 1.3 Hz, 1H), 5.02 (s, 1H), 1.29 (s, 18H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 144.1, 128.7, 127.7, 127.4, 48.8, 45.8, 31.3. HR-MS (ESI) m/z calculated for $C_{15}H_{23}S_2^+$ $[M - H]^+$ 267.1236, found 267.1243.

12. Prepared according to a modified previously reported method.[46] Benzil (1g, 4.76 mmol, 1.2 equiv) was dissolved in dry DCM (5 mL) in an argon purged round-bottom flask. The solution was cooled to 0 °C in an ice bath bath. A solution of 1,3-propanedithiol (398 μL, 3.96 mmol, 1 equiv) and $BF_3{\cdot}Et_2O$ (489 μL, 3.96 mmol, 1 equiv) in dry DCM (1.5 mL) was added dropwise at 0 °C. The solution was warmed to room temperature for 3 h and quenched with 10 mL of a saturated aqueous $NaHCO_3$ solution. The layers were separated and the organic phase collected. The aqueous phase was extracted with DCM (3 × 10 mL) and the organic phases combined, dried over $MgSO_4$, filtered and the solvent evaporated. The dry crude was dissolved in hot isopropanol and left cooling at room temperature. After 3 h, the product precipitated as a white solid and was filtered and washed with cold isopropanol to yield **12** as a white solid in 54% yield (641 mg, 2.13 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.69−7.66 (m, 2H), 7.57 (dd, J = 7.9, 1.5 Hz, 2H), 7.38−7.28 (m, 4H), 7.22−7.17 (m, 2H), 3.26 (ddd, J = 14.4, 12.0, 2.9 Hz, 2H), 2.80−2.73 (m, 2H), 2.17−2.08 (m, 1H), 2.01−1.86 (m, 1H). ^{13}C NMR (300 MHz, $CDCl_3$) δ ppm 192.8, 139.0, 134.5, 132.2, 130.8, 129.2, 128.8, 127.7, 127.5, 63.5, 29.3, 24.1. HR-MS (ESI) m/z calculated for $C_{17}H_{17}OS_2^+$ $[M + H]^+$ 301.0715, found 301.0734.

General Procedure for Autoxidative Addition of Dithianes 4a−c and 4e−k. Dithiane (1.02 mmol, 1 equiv) was dissolved in dry THF (5 mL) in an argon purged round-bottom flask. The solution was cooled to −78 °C in an acetone/liquid nitrogen bath. *n*-BuLi (1.3 equiv) solution in hexanes was added dropwise to the reaction mixture at −78 °C. The solution was left stirring at −78 °C for 20 min and then left to warm up to room temperature for 40 min. The argon balloon was replaced with an atmospheric air balloon and an additional needle was inserted in the septum as to allow air flow through the surface of the solution. As oxidation took place the solution warmed up and color change was usually observed. After 1 min the solution was quenched with 10 mL of a saturated aqueous NH_4Cl solution. Ten mL of Et_2O were added and the layers were separated. The organic phase was collected and the aqueous phase was extracted two times with Et_2O (2 × 10 mL). The organic phases were combined and dried over $MgSO_4$. The solvent was filtered and evaporated. The product was purified by flash chromatography.

5a. 76% yield (128 mg, 0.26 mmol), pale yellow oil. Flash chromatography eluent: Hex:AcOEt (90:10). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.96−7.90 (m, 4 H) 7.54−7.23 (m, 11 H) 5.51 (s, 1 H) 3.30 (ddt, J = 13.8, 10.8, 2.9, 2.9 Hz, 2 H) 2.75−2.68 (m, 2 H) 2.57−2.44 (m, 4 H) 2.15−2.04 (m, 1 H) 1.96−1.83 (m, 1 H) 1.76−1.66 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 195.1, 141.6, 136.7, 135.8, 133.4, 129.1, 129.0, 128.9, 128.8, 128.6, 128.5, 128.1, 128.0, 64.3, 55.6, 32.7, 30.6, 29.2, 28.4, 24.4. HR-MS (ESI) m/z calculated for $C_{27}H_{28}OS_4Na^+$ $[M + Na]^+$ 519.0915, found 519.0894.

5b. 64% yield (135 mg, 0.22 mmol), amorphous yellow solid. Flash chromatography eluent: Hex:AcOEt (60:40). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.90−7.87 (m, 2H), 7.79−7.76 (m, 2H), 7.30−7.26 (m, 2H), 6.67−6.56 (m, 6H), 5.47 (s, 1H), 3.36−3.26 (m, 2H), 3.01 (s, 6H), 2.95 (s, 6H), 2.90 (s, 6H), 2.72−2.67 (m, 2H), 2.59−2.45 (m, 4H), 2.12−2.03 (m, 1H), 1.94−1.84 (m, 1H), 1.81−1.71 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 193.5, 153.4, 150.2, 150.0, 131.3, 129.5, 129.0, 128.4, 124.9, 123.6, 112.7, 111.9, 110.7, 64.4, 54.9, 40.6, 40.5, 40.1, 32.9, 30.6, 29.4, 28.7, 24.5. HR-MS (ESI) m/z calculated for $C_{33}H_{43}N_3OS_4Na^+$ $[M + Na]^+$ 648.2181, found 648.2187.

5c. 60% yield (232 mg, 0.41 mmol), amorphous white solid. Flash chromatography eluent: Hex:AcOEt (70:30). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.05−8.02 (m, 4H), 7.75 (d, J = 8.8 Hz, 2H), 7.67−7.56 (m, 6H), 5.43 (s, 1H), 3.20 (tdd, J = 2.3, 9.9, 14.1 Hz, 2H), 2.73 (ddd, J = 2.9, 6.9, 14.2 Hz, 2H), 2.60−2.44 (m, 4H), 2.12−2.02 (m, 1H), 1.97−1.84 (m, 1H), 1.73−1.64 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 192.3, 146.8, 141.1, 138.4, 132.7, 132.4, 129.8, 129.4, 129.0, 118.5, 118.3, 117.7, 117.1, 112.4, 112.3, 63.5, 54.2, 32.4, 30.8, 29.3, 28.1, 23.9. HR-MS (ESI) m/z calculated for $C_{30}H_{25}N_3OS_4Na^+$ $[M + Na]^+$ 594.0773, found 594.0773.

5e. 60% yield (112 mg, 20 mmol), colorless oil. Flash chromatography eluent: Hex:AcOEt (94:6). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.00−7.88 (m, 4H), 7.42−7.38 (m, 2H), 7.12−7.00 (m, 6H), 5.44 (s, 1H), 3.26 (ddt, J = 13.8, 10.9, 2.6 Hz, 2H), 2.76−2.68 (m, 2H), 2.57−2.46 (m, 4H), 2.13−2.04 (m, 1H), 1.96−1.82 (m, 1H), 1.76−1.66 (m, 2H). ^{19}F NMR (282 MHz, $CDCl_3$) δ ppm −104.01 to −104.09 (m, 1F), −113.35 to −113.45 (m, 1F), −113.56 to −113.66 ppm (m, 1F). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 193.3, 167.6, 164.2, 164.2, 160.9, 137.4, 137.4, 132.3, 132.2, 131.9, 131.9, 131.8, 131.7, 130.6, 130.5, 130.1, 130.0, 116.2, 115.9, 115.5, 115.2, 63.6, 54.4, 32.7, 30.7, 29.3, 28.3, 24.2. HR-MS (ESI) m/z calculated for $C_{27}H_{25}F_3OS_4Na^+$ $[M + Na]^+$ 573.0633, found 573.0640.

5f. 66% yield (120 mg, 0.22 mmol), colorless oil. Flash chromatography eluent: Hex:AcOEt (95:5). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.97−7.94 (m, 1H), 7.42 (d, J = 5.9 Hz, 2H), 7.32−7.27 (m, 1H), 7.19−7.12 (m, 8H), 5.52 (s, 1H), 3.40−3.30 (m, 2H), 2.83 (s, 3H), 2.75−2.68 (m, 2H), 2.55−2.48 (m, 4H), 2.37 (s, 3H), 2.33 (s, 3H), 2.15−2.04 (m, 1H), 1.98−1.84 (m, 1H), 1.74−1.64 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 199.0, 138.7, 138.4, 138.0, 137.7, 136.1, 134.2, 133.8, 131.9, 131.2, 130.9, 129.2, 129.0, 128.4, 128.1, 127.6, 126.7, 125.6, 125.5, 64.9, 54.7, 32.8, 31.1, 29.2, 28.6, 24.3, 23.6, 20.8, 19.8. HR-MS (ESI) m/z calculated for $C_{30}H_{34}OS_4Na^+$ $[M + Na]^+$ 561.1385, found 561.1389.

5g. 58% yield (324 mg, 0.40 mmol), pale yellow oil. Flash chromatography eluent: Hex:AcOEt (80:20). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.87−7.85 (m, 1H), 7.59 (d, J = 7.6 Hz, 2H), 7.43 (dt, J = 7.6, 2.1 Hz, 2H), 7.36−7.13 (m, 16H), 6.94−6.76 (m, 6H), 6.12 (s, 1H), 5.17 (s, 2H), 4.95−4.79 (m, 4H), 3.32−3.24 (m, 2H), 2.71−2.64 (m, 2H), 2.40−2.30 (m, 4H), 2.07−1.96 (m, 1H), 1.94−1.80 (m, 1H), 1.56−1.46 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 198.0, 157.1, 156.8, 156.0, 137.5, 136.9, 136.4, 132.8, 130.8, 130.3, 129.8, 129.6, 129.4, 128.8, 128.7, 128.6, 128.6, 128.4, 128.1, 127.9, 127.5, 127.5, 127.3, 127.2, 125.7, 121.0, 120.8, 120.5, 114.8, 112.7, 111.8, 71.0, 70.4, 70.2, 63.1, 52.5, 32.9, 31.0, 28.9, 28.5, 24.3. HR-MS (ESI) m/z calculated for $C_{48}H_{46}O_4S_4Na^+$ $[M + Na]^+$ 837.2171, found 837.2196.

5h. 68% yield (157 mg, 0.23 mmol), colorless oil. Flash chromatography eluent: Hex:AcOEt (80:20). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.45 (d, J = 2.9 Hz, 1H), 7.13 (d, J = 3.5 Hz, 1H), 6.99 (t, J = 1.5 Hz, 1H), 6.95−6.78 (m, 4H), 6.71 (d, J = 1.8 Hz, 2H), 6.03 (s, 1H), 3.82 (s, 3H), 3.76 (s, 6H), 3.73 (s, 3H), 3.72 (s, 3H), 3.70 (s, 3H), 3.36−3.26 (m, 2H), 2.74−2.68 (m, 2H), 2.54−2.49 (m, 4H),

DOI: 10.1021/acs.joc.7b02896
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2.10−2.01 (m, 1H), 1.96−1.83 (m, 1H), 1.75−1.65 ppm (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 197.4, 153.7, 153.4, 153.2, 152.6, 152.4, 151.1, 130.7, 128.2, 126.7, 119.5, 116.0, 115.6, 115.6, 114.8, 114.2, 113.8, 113.0, 111.8, 62.5, 57.6, 56.2, 55.9, 55.8, 55.8, 52.1, 32.9, 30.9, 29.0, 28.6, 24.4. HR-MS (ESI) m/z calculated for $C_{33}H_{40}O_7S_4Na^+$ $[M + Na]^+$ 699.1549, found 699.1572.

5i. 62% yield (63 mg, 0.13 mmol), yellow oil. Flash chromatography was run with eluent Hex:AcOEt:Et_3N (50:50:2) because the compound was unstable on silica without treatment with triethylamine. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.65−8.61 (m, 1H), 8.52−8.45 (m, 2H), 8.10−8.07 (m, 1H), 7.85−7.78 (m, 2H), 7.70−7.66 (m, 3H), 7.49−7.41 (m, 1H), 7.19−7.11 (m, 2H), 6.39 (s, 1H), 3.46−3.34 (m, 2H), 2.75−2.68 (m, 2H), 2.64−2.49 (m, 2H), 2.42 (t, J = 7.3 Hz, 2H), 2.18−2.10 (m, 1H), 1.95−1.81 (m, 1H), 1.61−1.51 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 195.4, 161.0, 157.8, 152.3, 149.2, 149.1, 148.0, 137.1, 137.1, 136.8, 127.4, 124.0, 123.2, 123.2, 122.3, 122.2, 65.9, 53.2, 32.7, 31.2, 28.3, 28.2, 24.9. HR-MS (ESI) m/z calculated for $C_{24}H_{25}N_3OS_4Na^+$ $[M + Na]^+$ 522.0773, found 522.0806.

5j. 89% yield (239 mg, 0.19 mmol), amorphous white solid. Flash chromatography eluent: Hex:AcOEt (80:20). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.69−7.61 (m, 12H), 7.41−7.15 (m, 22H), 6.79 (s, 1H), 6.66−6.59 (m, 4H), 5.28 (s, 1H), 3.53 (s, 3H), 3.52 (s, 3H), 3.47 (s, 3H), 3.24−3.15 (m, 2H), 2.63 (dt, J = 14.1, 2.9 Hz, 2H), 2.45−2.32 (m, 4H), 2.06−1.96 (m, 1H), 1.87−1.75 (m, 1H), 1.63−1.54 (m, 2H), 1.10−1.08 ppm (m, 27H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 194.2, 151.1, 150.7, 150.4, 150.0, 145.2, 144.9, 135.5, 135.3, 134.5, 133.5, 133.5, 133.0, 130.2, 130.0, 129.7, 129.7, 129.6, 127.8, 127.6, 127.5, 123.0, 121.1, 120.2, 120.2, 119.7, 119.5, 112.4, 112.3, 112.2, 64.1, 55.5, 55.5, 55.4, 32.7, 30.5, 29.3, 28.4, 26.8, 26.7, 26.6, 24.4, 19.9, 19.9, 19.9. HR-MS (ESI) m/z calculated for $C_{78}H_{88}O_7S_4Si_3Na^+$ $[M + Na]^+$ 1371.4613, found 1371.4641.

5k. 61% yield (148 mg, 0.15 mmol), amorphous white solid. Flash chromatography eluent: Hex:DCM (1:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm ^{1}H NMR ($CDCl_3$, 300 MHz): d = 7.49−7.45 (m, 3H), 7.37−7.34 (m, 1H), 6.96 (d, J = 2.3 Hz, 1H), 6.85−6.74 (m, 4H), 5.43 (s, 1H), 3.80 (s, 6H), 3.77 (s, 3H), 3.33−3.24 (m, 2H), 2.74−2.67 (m, 2H), 2.58−2.44 (m, 4H), 2.12−2.05 (m, 1H), 1.94−1.82 (m, 1H), 1.74−1.65 (m, 2H), 0.98 (s, 9H), 0.97 (s, 9H), 0.96 (s, 9H), 0.15−0.11 (m, 18H) ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 194.2, 151.4, 151.1, 150.8, 150.3, 145.2, 144.9, 134.7, 130.3, 129.8, 123.3, 121.5, 120.8, 120.5, 120.4, 120.3, 112.3, 112.2, 112.1, 64.2, 55.7, 55.6, 55.5, 55.3, 32.8, 30.7, 29.4, 28.5, 25.8, 25.7, 24.5, 18.6, 18.5, −4.4, −4.5. HR-MS (ESI) m/z calculated for $C_{48}H_{76}O_7S_4Si_3Na^+$ $[M + Na]^+$ 999.3679, found 999.3645.

5d. Dithiane **4d** (281 mg, 1.02 mmol, 1 equiv) was dissolved in dry THF (5 mL) in an argon purged round-bottom flask. The solution was cooled to −78 °C in an acetone/liquid nitrogen bath. LDA (0.85 mL of a 1.5 M solution, 1.3 equiv) solution in hexanes was added dropwise to the reaction mixture at −78 °C. The solution was left stirring at −78 °C for 20 min and then left to warm up to room temperature for 40 min. The argon balloon was replaced with an atmospheric air balloon and an additional needle was inserted in the septum as to allow air flow through the surface of the solution. As oxidation took place the solution warmed up and color change was observed. After 1 min the solution was quenched with 10 mL of a saturated aqueous NH_4Cl solution. The aqueous layer was extracted three times with Et_2O (3 × 10 mL). The organic phases were combined and dried over $MgSO_4$. The solvent was evaporated and the product purified by flash chromatography (eluent Hex:AcOEt, 90:10) to afford the desired compound **5d** in 51% yield (127 mg, 0.17 mmol) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.83−7.77 (m, 4H), 7.59−7.54 (m, 2H), 7.50−7.44 (m, 4H), 7.32−7.26 (m, 2H), 5.37 (s, 1H), 3.29−3.19 (m, 2H), 2.75−2.69 (m, 2H), 2.59−2.45 (m, 4H), 2.13−2.03 (m, 1H), 1.96−1.82 (m, 1H), 1.76−1.66 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 193.5, 140.7, 135.4, 134.2, 132.2, 132.2, 131.7, 130.6, 130.5, 129.9, 128.9, 122.7, 122.4, 63.7, 54.5, 32.6, 30.7, 29.3, 28.3, 24.2. HR-MS (ESI) m/z calculated for $C_{27}H_{24}Br_3OS_4^-$ $[M - H]^-$ 728.8266, found 728.8265.

General Procedure for Autoxidative Addition of Dithioacetals 6a−6d. Dithioacetal **6** (1.02 mmol, 1 equiv) was dissolved in dry THF (5 mL) in an argon purged round-bottom flask. The solution was cooled to −78 °C in an acetone/liquid nitrogen bath. *n*-BuLi (1.3 equiv) solution in hexanes was added dropwise to the reaction mixture at −78 °C. The solution was left stirring at −78 °C for 20 min and then left to warm up to room temperature for 40 min. The argon balloon was replaced with an atmospheric air balloon and an additional needle was inserted in the septum as to allow air flow through the surface of the solution. After 1 min the solution was quenched with 10 mL of a saturated aqueous NH_4Cl solution. Ten mL of Et_2O were added and the layers were separated. The organic phase was collected and the aqueous phase was extracted two times with Et_2O (2 × 10 mL). The organic phases were combined and dried over $MgSO_4$. The solvent was filtered and evaporated. Products **7** and **8** were obtained after purification by flash chromatography.

7a. 48% yield (97 mg, 0.32 mmol), white solid. Flash chromatography eluent: Hex:AcOEt (97.5:2.5). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.94−7.90 (m, 2H), 7.49−7.44 (m, 1H), 7.38−7.17 (m, 12H), 5.85 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 194.8, 136.6, 135.6, 134.1, 133.4, 133.1, 129.0, 128.9, 128.8, 128.7, 128.1, 128.0, 60.4. HR-MS (ESI) m/z calculated for $C_{20}H_{17}OS^+$ $[M + H]^+$ 305.0995, found 305.1013. The corresponding orthothioester product, **8a** could not be isolated due to low polarity and structural similarity to **6a**. However, the following characteristic peaks for the **8a** can be observed from the NMR spectrum of a mixture with the dithioacetal. **8a**: ^{1}H NMR (300 MHz, $CDCl_3$): 7.69−7.64 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 139.4, 132.9, 128.8, 128.4, 128.3, 128.0, 127.9, 77.0.

7b. 97% yield (92 mg, 0.32 mmol), white solid. Flash chromatography eluent: Hex:AcOEt (95:5). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.99−7.96 (m, 2H), 7.53−7.23 (m, 8H), 5.55 (s, 1H), 2.56−2.42 (m, 2H), 1.58−1.48 (m, 2H), 1.41−1.29 (m, 2H), 0.85 (t, J = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 195.3, 136.9, 135.9, 133.3, 129.0, 128.9, 128.9, 128.7, 128.0, 55.5, 31.3, 31.2, 22.1, 13.7. HR-MS (ESI) m/z calculated for $C_{18}H_{21}OS^+$ $[M + H]^+$ 285.1308, found 285.1328.

8b. 72% yield (86 mg, 0.24 mmol), colorless oil. Flash chromatography eluent: Hex:AcOEt (95:5). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.87−7.84 (m, 2H), 7.35−7.21 (m, 3H), 2.58 (t, J = 7.3 Hz, 6H), 1.51−1.29 (m, 12H), 0.88−0.83 (m, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 141.8, 131.3, 127.9, 127.6, 73.5, 31.5, 30.5, 22.3, 13.7. HR-MS (ESI) m/z calculated for $C_{15}H_{23}S_2^+$ $[M - S(CH_2)_3CH_3]^+$ 267.1236, found 267.1255.

7c. 73% yield (99 mg, 0.25 mmol), pale yellow solid. Flash chromatography gradient eluent: Hex:Toluene (80:20 to 50:50). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.99−7.96 (m, 2H), 7.54−7.23 (m, 8H), 5.55 (s, 1H), 2.55−2.41 (m, 2H), 1.59−1.49 (m, 2H), 1.30−1.22 (m, 18H), 0.90−0.86 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 195.3, 136.9, 136.0, 133.3, 129.1, 129.0, 128.9, 128.7, 128.0, 55.6, 32.1, 31.6, 29.8, 29.7, 29.6, 29.5, 29.3, 29.2, 29.0, 22.8, 14.3. HR-MS (ESI) m/z calculated for $C_{26}H_{37}OS^+$ $[M + H]^+$ 397.2560, found 397.2591.

8c. 56% yield (131 mg, 0.19 mmol), white solid. Flash chromatography eluent: Hexane (100%). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.87−7.84 (m, 2H), 7.35−7.21 (m, 3H), 2.57 (t, J = 7.3 Hz, 6H), 1.54−1.44 (m, 6H), 1.31−1.24 (m, 54H), 0.90−0.86 (m, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 142.1, 128.1, 127.8, 73.7, 32.1, 32.0, 29.8, 29.8, 29.6, 29.5, 29.4, 29.3, 28.6, 22.9, 14.3. HR-MS (ESI) m/z calculated for $C_{31}H_{55}S_2^+$ $[M - S(CH_2)_{11}CH_3]^+$ 491.3740, found 491.3737.

7d. 67% yield (63 mg, 0.22 mmol), pale yellow solid. 1:1 mixture of diastereomers. Flash chromatography eluent: Hex:AcOEt (95:5). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.01−7.97 (m, 4H), 7.54−7.23 (m, 16H), 5.61 (s, 2H), 2.75−2.61 (m, 2H), 1.72−1.42 (m, 4H), 1.30 (d, J = 6.4 Hz, 3H), 1.19 (d, J = 7.0 Hz, 3H), 0.98−0.86 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 195.5, 195.4, 137.2, 135.9, 133.3, 129.0, 128.9, 128.9, 128.7, 127.9, 54.7, 54.6, 42.1, 41.9, 29.7, 29.7, 21.0, 20.6, 11.3, 11.2. HR-MS (ESI) m/z calculated for $C_{18}H_{21}OS^+$ $[M + H]^+$ 285.1308, found 285.1303. The corresponding orthothioester product **8d** could not be isolated due to low polarity and structural similarity to **6d**. However, the following characteristic peaks for **8d** can be observed

DOI: 10.1021/acs.joc.7b02896
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in NMR spectrum of the crude reaction mixture: **8d**: ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 69.3, 29.0, 20.1, 11.5.

9. Dithioacetal **6e** (0.5 mmol, 1 equiv) was dissolved in dry THF (2.5 mL) in an argon purged round-bottom flask. The solution was cooled to −78 °C in an acetone/liquid nitrogen bath. *n*-BuLi (1.3 equiv) solution in hexanes was added dropwise to the reaction mixture at −78 °C. The solution was left stirring at −78 °C for 20 min and then left to warm up to room temperature for 40 min. The argon balloon was replaced with an atmospheric air balloon and an additional needle was inserted in the septum as to allow air flow through the surface of the solution. After 1 min the solution was quenched with 5 mL of a saturated aqueous NH_4Cl solution. Five mL of Et_2O were added and the layers were separated. The organic phase was collected and the aqueous phase was extracted two times with Et_2O (2 × 5 mL). The organic phases were combined and dried over $MgSO_4$. The solvent was evaporated and the product was purified by preparative TLC (eluent: pentane) to yield **9** as a colorless oil (62%, 60 mg, 0.31 mmol) with the same spectral characterization as previously described.[47] ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.93−7.90 (m, 2H), 7.56−7.51 (m, J = 7.3 Hz, 1H), 7.44−7.39 (m, 2H), 1.58 (s, 9H).

General Procedure for Autoxidative Addition of 2-Alkyl-1,3-dithianes 4l−p. Dithiane (1.02 mmol, 1 equiv) was dissolved in dry THF (5 mL) in an argon purged round-bottom flask. The solution was cooled to −78 °C in an acetone/liquid nitrogen bath. *n*-BuLi (1.3 equiv) solution in hexanes was added dropwise to the reaction mixture at −78 °C. The solution was left stirring at −78 °C for 20 min and then left to warm up to room temperature for 40 min. The argon balloon was replaced with an atmospheric air balloon and an additional needle was inserted in the septum as to allow air flow through the surface of the solution. After 5 min the solution was quenched with 10 mL of a saturated aqueous NH_4Cl solution. Ten mL of Et_2O were added and the layers were separated. The organic phase was collected and the aqueous phase was extracted two times with Et_2O (2 × 10 mL). The organic phases were combined and dried over $MgSO_4$. The solvent was filtered and evaporated. The product was purified and separated from unreacted starting material by flash chromatography.

1a. 63% yield (47 mg, 0.18 mmol), white solid. Flash chromatography eluent: DCM (100%). Obtained with same spectral characterization as previously described.[19] ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 4.28 (s, 3H), 3.15 (s, 1H), 3.07−2.95 (m, 4H), 2.78−2.62 (m, 4H), 2.07−2.00 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 74.7, 47.4, 27.9, 27.2, 25.5.

10m. 27% yield, (45 mg, 0.14 mmol), white solid. Flash chromatography eluent: Hex:AcOEt (95:5). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.33−7.21 (m, 10H), 4.00 (s, 2H), 3.41 (s, 2 H), 2.86−2.76 (m, 2H), 2.60−2.53 (m, 2H), 1.99−1.90 (m, 1H), 1.84−1.73 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 200.6, 134.9, 134.3, 130.2, 129.9, 128.5, 128.5, 127.7, 127.0, 62.5, 44.3, 43.4, 28.0, 24.2. HR-MS (ESI) m/z calculated for $C_{19}H_{21}OS_2^+$ $[M + H]^+$ 329.1028, found 329.1052.

10n. 24% yield (29 mg, 0.12 mmol), colorless oil. Flash chromatography eluent: Hex:DCM (55:45). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 3.02−2.92 (m, 2H), 2.66−2.56 (m, 4H), 2.09−2.00 (m, 1H), 1.96−1.91 (m, 2H), 1.97−1.76 (m, 1H), 1.71−1.59 (m, 2H), 1.47−1.34 (m, 2H), 0.95−0.89 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 204.3, 61.4, 40.6, 37.8, 27.9, 25.0, 18.4, 18.0, 14.4, 13.9. HR-MS (ESI) m/z calculated for $C_{11}H_{21}OS_2^+$ $[M + H]^+$ 233.1028, found 233.1050.

11. 22% yield (61 mg, 0.22 mmol), colorless oil. Flash chromatography eluent: Hex:AcOEt (97:3). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 2.86 (t, J = 7.0 Hz, 4H), 1.79 (quin, J = 7.2 Hz, 2H), 1.20 (s, 18H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 206.6, 46.5, 29.7, 27.5, 27.5. HR-MS (ESI) m/z calculated for $C_{13}H_{25}O_2S_2^+$ $[M + H]^+$ 277.1290, found 277.1323.

10p. 31% yield (44 mg, 0.13 mmol), colorless oil. Flash chromatography gradient eluent: Hex:DCM (85:15 to 60:40). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 3.02−2.92 (m, 2H), 2.67−2.57 (m, 4H), 2.07−2.01 (m, 1H), 1.97−1.92 (m, 2H), 1.87−1.71 (m, 1H), 1.66−1.57 (m, 2H), 1.42−1.28 (m, 10H), 0.90−0.83 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 204.5, 61.5, 38.5, 35.8, 32.1, 31.6, 27.9, 25.0, 24.7, 24.1, 22.6, 22.3, 14.1, 14.0. 2-(*n*-Hexyl)-1,3-dithiane was isolated in 23% yield (44 mg, 23 mmol), colorless oil with same spectral characterization as previously described:[48] ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 4.03 (t, J = 7.0 Hz, 1H), 2.91−2.76 (m, 4H), 2.14−2.06 (m, 1H), 1.91−1.79 (m, 1H), 1.76−1.68 (m, 2H), 1.54−1.44 (m, 2H), 1.32−1.24 (m, 4H), 0.89−0.85 (m, 3H). HR-MS (ESI) m/z calculated for $C_{15}H_{29}OS_2^+$ $[M + H]^+$ 289.1654, found 289.1676.

Reaction of 4a with Benzoyl Chloride. Dithiane **4a** (200 mg, 1.02 mmol, 1 equiv) was dissolved in dry THF (5 mL) in an argon purged round-bottom flask. The solution was cooled to −78 °C in an acetone/liquid nitrogen bath. *n*-BuLi (0.53 mL of a 2.5 M solution, 1.32 mmol, 1.3 equiv) solution in hexanes was added dropwise to the reaction mixture at −78 °C. The solution was left stirring at −78 °C for 20 min and then left to warm up to room temperature for 40 min. Benzoyl chloride (77 μL, 0.66 mmol, 0.65 equiv) was added dropwise to the solution and after 2 min, while under argon, the reaction was quenched with 10 mL of a saturated aqueous NH_4Cl solution. Ten mL of Et_2O were added and the layers were separated. The organic phase was collected and the aqueous phase was extracted two times with Et_2O (2 × 10 mL). The organic phases were combined and dried over $MgSO_4$. The solvent was filtered and evaporated. The product was purified by flash chromatography (eluent Hex:AcOEt, 90:10) to afford **5a** in 71% yield (180 mg, 0.36 mmol) as a pale yellow oil.

Reaction of 4a with *S*-Benzyl Benzothioate. Dithiane **4a** (200 mg, 1.02 mmol, 1 equiv) was dissolved in dry THF (5 mL) in an argon purged round-bottom flask. The solution was cooled to −78 °C in an acetone/liquid nitrogen bath. *n*-BuLi (0.53 mL of a 2.5 M solution, 1.32 mmol, 1.3 equiv) solution in hexanes was added dropwise to the reaction mixture at −78 °C. The solution was left stirring at −78 °C for 20 min and then left to warm up to room temperature for 40 min. Then, *S*-benzyl benzothioate (151 mg, 0.66 mmol, 0.65 equiv) in dry THF (1 mL) was added dropwise to the solution. After 2 min, while under argon, the reaction was quenched with 10 mL of a saturated aqueous NH_4Cl solution. Ten mL of Et_2O were added and the layers were separated. The organic phase was collected and the aqueous phase was extracted two times with Et_2O (2 × 10 mL). The organic phases were combined and dried over $MgSO_4$. The solvent was filtered and evaporated. The product was purified by flash chromatography (eluent Hex:AcOEt, 90:10) to afford **5a** in 89% yield (226 mg, 0.45 mmol) as a pale yellow oil.

Reaction of 4a in the Presence of $^{18}O_2$. General procedure for autoxidative addition of dithianes was used, although a small ballon filled with $^{18}O_2$ was used directly in the oxidation reaction. HR-MS (ESI) m/z calculated for $C_{27}H_{28}{}^{18}OS_4Na^+$ $[M + Na]^+$ 521.0958, found 521.0930.

Reaction of 4a in the Presence of TEMPO. Dithiane **4a** (200 mg, 1.02 mmol, 1 equiv) was dissolved in dry THF (5 mL) in an argon purged round-bottom flask. The solution was cooled to −78 °C in an acetone/liquid nitrogen bath. *n*-BuLi (0.53 mL of a 2.5 M solution, 1.3 equiv) solution in hexanes was added dropwise to the reaction mixture at −78 °C. The solution was left stirring at −78 °C for 20 min and then left to warm up to room temperature for 40 min. Then, TEMPO (206 mg in 1.5 mL of dry THF, 1.12 mmol, 1.3 equiv) was added dropwise to the solution. After 2 min, the argon balloon was replaced with an atmospheric air balloon and an additional needle was inserted in the septum as to allow air flow through the surface of the solution. After 1 min the solution was quenched with 10 mL of a saturated aqueous NH_4Cl solution. Ten mL of Et_2O were added and the layers were separated. The organic phase was collected and the aqueous phase was extracted two times with Et_2O (2 × 10 mL). The organic phases were combined and dried over $MgSO_4$. The solvent was filtered and evaporated. Flash chromatography (Hex:AcOEt, 95:5) yielded starting material **4a** (20%, 39 mg, 0.20 mmol) and dimer **2** (27%, 53 mg, 0.14 mmol) as a white solid, with same spectral characterization as previously described.[49] **2**: ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.54−7.15 (m, 10H), 2.70−2.49 (m, 8H), 2.01−1.75 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 135.0, 133.0, 127.6, 127.3, 70.9, 29.0, 24.7.

Reaction of 4a with 12. Dithiane **4a** (200 mg, 1.02 mmol, 1 equiv) was dissolved in dry THF (5 mL, 0.2 M) in an argon purged round-bottom flask. The solution was cooled to −78 °C in an

DOI: 10.1021/acs.joc.7b02896
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acetone/liquid nitrogen bath. *n*-BuLi (0.45 mL of a 2.5 M solution, 1.12 mmol, 1.1 equiv) solution in hexanes was added dropwise to the reaction mixture at −78 °C. The solution was left stirring at −78 °C for 20 min and then left to warm up to room temperature for 40 min. Phenyl(2-phenyl-1,3-dithian-2-yl)methanone **12** (337 mg, 1.12 mmol, 1.1 equiv) in THF (5 mL) was added dropwise to the solution. After 2 min, while under argon, the reaction was quenched with 10 mL of a saturated aqueous NH_4Cl solution. Ten mL of Et_2O were added and the layers were separated. The organic phase was collected and the aqueous phase was extracted two times with Et_2O (2 × 10 mL). The organic phases were combined and dried over $MgSO_4$. The solvent was filtered, evaporated and the product purified by flash chromatography (eluent Hex:AcOEt, 90:10) to afford **5a** in 75% yield (381 mg, 0.77 mmol) as a pale yellow oil.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b02896.

Full accounts on computational calculations and copies of spectra for all reported compounds (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

AKA is acknowledged for the financial support to NRC (Decisions No. 287954 and 294067); FCT for financial support to JRV and CAMA (SFRH/BD/120119/2016, UID/DTP/04138/2013). CSC−IT Center for Science Ltd., Finland, is acknowledged for the allocation of computational resources.

■ REFERENCES

(1) (a) Boche, G.; Lohrenz, J. C. W. *Chem. Rev.* **2001**, *101*, 697−756. (b) Wardell, J. L. In *Comprehensive Organometallic Chemistry*; Stone, F. G. A., Abel, E. W., Eds.; Pergamon: Oxford, 1982; pp 43−120. (c) Sosnovsky, G.; Brown, J. H. *Chem. Rev.* **1966**, *66*, 529−566.

(2) Müller, E.; Töpel, T. *Ber. Dtsch. Chem. Ges. B* **1939**, *72*, 273−290.

(3) (a) Jones, A. B.; Wang, J.; Hamme, A. T.; Han, W. Oxygen. In *Encyclopedia of Reagents for Organic Synthesis*; John Wiley & Sons, 2001. (b) Boche, G.; Möbus, K.; Harms, K.; Lohrenz, J. C. W.; Marsch, M. *Chem. - Eur. J.* **1996**, *2*, 604−607. (c) Julia, M.; Saint-Jalmes, V. P.; Verpeaux, J.-N. *Synlett* **1993**, *1993*, 233−234. (d) Boche, G.; Bosold, F.; Lohrenz, J. C. W. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1161−1163.

(4) Examples on the use of oxidation of organolithiums with O_2: (a) Möller, M.; Husemann, M.; Boche, G. *J. Organomet. Chem.* **2001**, *624*, 47−52. (b) Weber, B. *Synthesis* **1999**, *1999*, 1593−1606. (c) Barluenga, J.; Foubelo, F.; Fañanás, F. J.; Yus, M. *Tetrahedron* **1989**, *45*, 2183−2192. (d) Ryckman, D. M.; Stevens, R. V. *J. Am. Chem. Soc.* **1987**, *109*, 4940−4948. (e) Hoell, D.; Schnieders, C.; Müllen, K. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 243−244. (f) Nguyen, T. H.; Chau, N. T.; Castanet, A. S.; Nguyen, K. P.; Mortier, J. *J. Org. Chem.* **2007**, *72*, 3419−3429. (g) Einhorn, J.; Luche, J.-L.; Demerseman, P. *J. Chem. Soc., Chem. Commun.* **1988**, 1350. (h) Parker, K. A.; Koziski, K. A. *J. Org. Chem.* **1987**, *52*, 674−676.

(5) (a) Corey, E. J.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 1075−1077. (b) Corey, E. J.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 1077−1078. (c) Seebach, D.; Corey, E. J. *J. Org. Chem.* **1975**, *40*, 231−237.

(6) For reviews, see: (a) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 639−649. (b) Gröbel, B.-T.; Seebach, D. *Synthesis* **1977**, *1977*, 357−402. (c) Seebach, D. *Synthesis* **1969**, *1969*, 17−36. (d) Bulman Page, P. C.; van Niel, M. B.; Prodger, J. C. *Tetrahedron* **1989**, *45*, 7643−7677. (e) Yus, M.; Nájera, C.; Foubelo, F. *Tetrahedron* **2003**, *59*, 6147−6212. (f) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 239−258. (g) Fernández de la Pradilla, R.; Viso, A., In *Comprehensive Organic Synthesis II*; Elsevier: Amsterdam, 2014; pp 157−208.

(7) Selected recent examples: (a) Smith, A. B.; Pitram, S. M.; Gaunt, M. J.; Kozmin, S. A. *J. Am. Chem. Soc.* **2002**, *124*, 14516−14517. (b) Chen, M. Z.; Micalizio, G. C. *J. Am. Chem. Soc.* **2012**, *134*, 1352−1356. (c) Yao, K.; Liu, D.; Yuan, Q.; Imamoto, T.; Liu, Y.; Zhang, W. *Org. Lett.* **2016**, *18*, 6296−6299.

(8) (a) Hurski, A. L.; Ermolovich, Y. V.; Zhabinskii, V. N.; Khripach, V. A. *Org. Biomol. Chem.* **2015**, *13*, 1446−1452. (b) Smith, A. B.; Adams, C. M. *Acc. Chem. Res.* **2004**, *37*, 365−377. (c) Henrot, M.; Richter, M. E.; Maddaluno, J.; Hertweck, C.; De Paolis, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 9587−9591. (d) Han, H.; Smith, A. B. *Org. Lett.* **2015**, *17*, 4232−4235. (e) Smith, A. B.; Condon, S. M.; McCauley, J. A. *Acc. Chem. Res.* **1998**, *31*, 35−46. (f) Das, D.; Chakraborty, T. K. *Org. Lett.* **2017**, *19*, 682−685. (g) Almalki, F. A.; Harrowven, D. C. *Eur. J. Org. Chem.* **2016**, *2016*, 5738−5746.

(9) Corey, E. J.; Seebach, D. *J. Org. Chem.* **1966**, *31*, 4097−4099.

(10) (a) Tanner, D.; Hagberg, L. *Tetrahedron* **1998**, *54*, 7907−7918. (b) Metri, P. K.; Schiess, R.; Prasad, K. R. *Chem. - Asian J.* **2013**, *8*, 488−493.

(11) (a) Cerè, V.; De Angelis, S.; Pollicino, S.; Ricci, A.; Reddy, C. K.; Knochel, P.; Cahiez, G. *Synthesis* **1997**, *1997*, 1174−1178. (b) Bulman Page, P. C.; Marchington, A. P.; Graham, L. J.; Harkin, S. A.; Wood, W. W. *Tetrahedron* **1993**, *49*, 10369−10386.

(12) (a) Claessen, R. U.; Kornilov, A. M.; Banger, K. K.; Ngo, S. C.; Higashiya, S.; Wells, C. C.; Dikarev, E. V.; Toscano, P. J.; Welch, J. T. *J. Organomet. Chem.* **2004**, *689*, 71−81. (b) Zengeya, T. T.; Kulkarni, R. A.; Meier, J. L. *Org. Lett.* **2015**, *17*, 2326−2329. (c) Adams, L. A.; Valente, M. W. N.; Williams, R. M. *Tetrahedron* **2006**, *62*, 5195−5200. (d) Wang, S. S.; Shi, X.-X.; Powell, W. S.; Tieman, T.; Feinmark, S. J.; Rokach, J. *Tetrahedron Lett.* **1995**, *36*, 513−516.

(13) (a) Ide, M.; Nakata, M. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 2491−2499. (b) Arlt, A.; Benson, S.; Schulthoff, S.; Gabor, B.; Furstner, A. *Chem. - Eur. J.* **2013**, *19*, 3596−3608. (c) Reiner, M.; Schmidt, R. R. *Tetrahedron: Asymmetry* **2000**, *11*, 319−335. (d) Braun, M.; Esdar, M. *Chem. Ber.* **1981**, *114*, 2924−2928.

(14) (a) Eger, W. A.; Grange, R. L.; Schill, H.; Goumont, R.; Clark, T.; Williams, C. M. *Eur. J. Org. Chem.* **2011**, *2011*, 2548−2553. (b) Seebach, D.; Gröbel, B. T.; Beck, A. K.; Braun, M.; Geiss, K. H. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 443−444. (c) Carey, F. A.; Court, A. S. *J. Org. Chem.* **1972**, *37*, 1926−1929. (d) Chen, M.-J.; Tsai, Y.-M. *Tetrahedron* **2011**, *67*, 1564−1574.

(15) For recent uses of 2-(trialkylsilyl)-1,3-dithiane in Peterson olefination: (a) Aggarwal, V. K.; Steele, R. M.; Ritmaleni, R.; Barrell, J. K.; Grayson, I. *J. Org. Chem.* **2003**, *68*, 4087−4090. (b) Wedel, T.; Podlech, J. *Org. Lett.* **2005**, *7*, 4013−4015. (c) Xu, H. C.; Moeller, K. D. *J. Am. Chem. Soc.* **2010**, *132*, 2839−2844. (d) Xu, H. C.; Moeller, K. D. *Org. Lett.* **2010**, *12*, 1720−1723.

(16) For recent uses of 2-(trialkylsilyl)-1,3-dithiane in Anion Relay Chemistry: (a) Ai, Y.; Kozytska, M. V.; Zou, Y.; Khartulyari, A. S.; Smith, A. B. *J. Am. Chem. Soc.* **2015**, *137*, 15426−15429. (b) Singh, G.; Aub, J. *Org. Biomol. Chem.* **2016**, *14*, 4299−4303. (c) Nguyen, M. H.; Imanishi, M.; Kurogi, T.; Smith, A. B. *J. Am. Chem. Soc.* **2016**, *138*, 3675−3678. (d) Melillo, B.; Smith, A. B. *Org. Lett.* **2013**, *15*, 2282−2285. (e) Chen, M. Z.; Gutierrez, O.; Smith, A. B. *Angew. Chem., Int. Ed.* **2014**, *53*, 1279−1282. (f) Farrell, M.; Melillo, B.; Smith, A. B. *Angew. Chem., Int. Ed.* **2016**, *55*, 232−235.

DOI: 10.1021/acs.joc.7b02896
J. Org. Chem. 2018, 83, 1948−1958

(17) Seebach, D.; Willert, I.; Beck, A. K.; Gröbel, B.-T. *Helv. Chim. Acta* **1978**, *61*, 2510−2523.
(18) Wade, P. A.; D'Ambrosio, S. G.; Murray, J. K. *J. Org. Chem.* **1995**, *60*, 4258−4259.
(19) Argade, N. P.; Hazra, B. G.; Joshi, P. L. *Synth. Commun.* **1996**, *26*, 2797−2802.
(20) Bulman-Page, P. C.; Chadwick, D. J.; van Niel, M. B.; Westwood, D. *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* **1987**, *43*, 803−804.
(21) (a) Benati, L.; Calestani, G.; Nanni, D.; Spagnolo, P.; Volta, M. *Tetrahedron* **1997**, *53*, 9269−9278. (b) Kruse, C. G.; Poels, E. K.; Van der Gen, A. *J. Org. Chem.* **1979**, *44*, 2911−2915. (c) Lipshutz, B. H.; Moretti, R.; Crow, R. *Tetrahedron Lett.* **1989**, *30*, 15−18.
(22) (a) Baarschers, W. H.; Loh, T. L. *Tetrahedron Lett.* **1971**, *12*, 3483−3484. (b) Bartoli, G.; Dalpozzo, R.; Grossi, L.; Todesco, P. E. *Tetrahedron* **1986**, *42*, 2563−2570. (c) Russell, G. A.; Jawdosiuk, M.; Makosza, M. *J. Am. Chem. Soc.* **1979**, *101*, 2355−2359. (d) Perrotta, R. R.; Winter, A. H.; Coldren, W. H.; Falvey, D. E. *J. Am. Chem. Soc.* **2011**, *133*, 15553−15558.
(23) Valiulin, R. A.; Kottani, R.; Kutateladze, A. G. *J. Org. Chem.* **2006**, *71*, 5047−5049.
(24) For a related example for formation of orthothioesters: Sih, J. C.; Graber, D. R.; Mizsak, S. A.; Scahill, T. A. *J. Org. Chem.* **1982**, *47*, 4362−4364.
(25) Hayashi, Y. *Chem. Sci.* **2016**, *7*, 866−880.
(26) (a) Shishimi, T.; Hara, S. *J. Fluorine Chem.* **2014**, *168*, 55−60. (b) Hara, S.; Monoi, M.; Umemura, R.; Fuse, C. *Tetrahedron* **2012**, *68*, 10145−10150.
(27) Matthews, D. P.; Whitten, J. P.; McCarthy, J. R. *Tetrahedron Lett.* **1986**, *27*, 4861−4864.
(28) (a) Grange, R. L.; Williams, C. M. *Tetrahedron Lett.* **2010**, *51*, 1158−1160. (b) Mamane, V.; Aubert, E.; Fort, Y. *J. Org. Chem.* **2007**, *72*, 7294−7300. (c) Smith, R. A. J.; Keng, G. S. *Tetrahedron Lett.* **1978**, *19*, 675−678.
(29) Furuta, S.; Hiyama, T. *Tetrahedron Lett.* **1996**, *37*, 7983−7986.
(30) Pan, L.; Bi, X.; Liu, Q. *Chem. Soc. Rev.* **2013**, *42*, 1251−1286.
(31) Parr, R. G.; Yang, W. *Density Functional Theory of Atoms and Molecules*; Oxford University Press: New York, 1989. Calculations performed at the PBE1PBE/6-31G(d,p) level with the use of the Gaussian 09 package. The energies reported were calculated with a polarizable continuum model (PCM) with THF as solvent. A full account on the computational details is presented as Supporting Information.
(32) (a) Wiberg, K. B. *Tetrahedron* **1968**, *24*, 1083−1096. (b) Wiberg indices are electronic parameters related to the electron density between atoms. They can be obtained from a Natural Population Analysis and provide an indication of the bond strength.
(33) Firouzabadi, H.; Iranpoor, N.; Hazarkhani, H. *J. Org. Chem.* **2001**, *66*, 7527−7529.
(34) Lai, J.; Du, W.; Tian, L.; Zhao, C.; She, X.; Tang, S. *Org. Lett.* **2014**, *16*, 4396−4399.
(35) Ghosh, S. S.; Martin, J. C.; Fried, J. *J. Org. Chem.* **1987**, *52*, 862−876.
(36) Naik, S.; Gopinath, R.; Goswami, M.; Patel, B. K. *Org. Biomol. Chem.* **2004**, *2*, 1670−1677.
(37) Page, P. C. B.; Graham, A. E.; Park, B. K. *Tetrahedron* **1992**, *48*, 7265−7274.
(38) Aloup, J.-C.; Bouchaudon, J.; Farge, D.; James, C.; Deregnaucourt, J.; Hardy-Houis, M. *J. Med. Chem.* **1987**, *30*, 24−29.
(39) Graham, A. E. *Synth. Commun.* **1999**, *29*, 697−703.
(40) Raffaelli, B.; Wähälä, K.; Hase, T. *Org. Biomol. Chem.* **2006**, *4*, 331−341.
(41) Seebach, D.; Jones, N. R.; Corey, E. J. *J. Org. Chem.* **1968**, *33*, 300−305.
(42) Wan, Y.; Kurchan, A. N.; Barnhurst, L. A.; Kutateladze, A. G. *Org. Lett.* **2000**, *2*, 1133−1135.
(43) Yu, C. J.; Li, R.; Gu, P. *Tetrahedron Lett.* **2016**, *57*, 3568−3570.
(44) Iranpoor, N.; Firouzabadi, H.; Shaterian, H. R.; Zolfigol, M. A. *Phosphorus, Sulfur Silicon Relat. Elem.* **2002**, *177*, 1047−1071.
(45) Zhang, H.; Wang, H.; Yang, H.; Fu, H. *Org. Biomol. Chem.* **2015**, *13*, 6149−6153.
(46) Afonso, C. A. M.; Barros, M. T.; Godinho, L. S.; Maycock, C. D. *Synthesis* **1991**, *1991*, 575−580.
(47) Uno, T.; Inokuma, T.; Takemoto, Y. *Chem. Commun.* **2012**, *48*, 1901−1903.
(48) Huckins, J. R.; Rychnovsky, S. D. *J. Org. Chem.* **2003**, *68*, 10135−10145.
(49) Linker, M.; Reuter, G.; Frenzen, G.; Maurer, M.; Gosselck, J.; Stahl, I. *J. Prakt. Chem./Chem.-Ztg.* **1998**, *340*, 63−72.

DOI: 10.1021/acs.joc.7b02896
J. Org. Chem. 2018, 83, 1948−1958

PUBLICATION II

Synthesis of silacyclopent-2-en-4-ols via intramolecular [2+2] photocycloaddition of benzoyl(allyl)silanes

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Organic Chemistry Fontiers, **2019**, *6*, 3793-3798

DOI: 10.1039/c9qo01028a

ORGANIC CHEMISTRY
FRONTIERS

RESEARCH ARTICLE

View Article Online
View Journal | View Issue

Cite this: *Org. Chem. Front.*, 2019, **6**, 3793

Synthesis of silacyclopent-2-en-4-ols *via* intramolecular [2 + 2] photocycloaddition of benzoyl(allyl)silanes†

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Received 21st August 2019,
Accepted 10th October 2019

DOI: 10.1039/c9qo01028a

rsc.li/frontiers-organic

Organosilicon compounds are versatile units with a wide range of uses from medicinal chemistry to the field of organic electronics. An unprecedented method for the synthesis of novel diaryl-substituted silacyclopentenols *via* blue-light promoted intramolecular [2 + 2] photocycloaddition of acyl silanes is herein disclosed. Additionally, the present findings demonstrate the influence of the olefin substituents in controlling the regioselectivity of the intramolecular Paternò–Büchi reaction, providing silacycles different from previously reported ones. The high degree of functionalization of these compounds makes them attractive precursors to other synthetically challenging silacyclopentanes.

Introduction

The incorporation of silicon into an organic molecule can alter some of its physical and chemical properties, making organosilicon compounds attractive candidates for medicinal chemistry.[1,2] Although silicon is an isostere of sp^3-hybridised carbon, replacing carbon by silicon can: alter reactivity, increase lipophilicity, induce different conformations and increase ring sizes.[1] Organosilicons have the tendency to form penta- and hexa-coordinated species[3,4] and labile Si–O, Si–N and Si–H bonds in aqueous media. Moreover, polarised C–Si bounds have increased reactivity as compared to C–C bounds. Because of these features, organosilicon compounds have shown considerable potential in the medicinal chemistry field over the past 55 years.[1] The virtually simple replacement of carbon by silicon in a known drug or scaffold has been widely explored in the design of new bioactive compounds.[5,6] Drastic changes in the pharmacological profiles of silicon bioisoster of venlafaxine,[7] haloperidol[8] and bexarotene[9] have been previously reported, including improvements in the selectivity profile or lower toxicity of the drug metabolites.

Notwithstanding the role of silicon in drug discovery,[2] organosilicon compounds have also gained notoriety in molecular electronics[10] and polymer science.[11] Conjugated organosilicon materials are particularly promising for the organic electronics and photonics field.[12] The insertion of silicon atoms in conjugated organic motifs changes the HOMO and LUMO energy levels, creating a new broad class of important semiconductors. The 5-membered conjugated silacycle silole is a particularly interesting building block in this research area and in the development of silicon-containing polymers.[13] Given the natural abundance of silicon and its lack of intrinsic toxicity, processes targeting the synthesis of organosilanes[14] and the modification of C–Si bonds are becoming more available.[15] Despite the versatility and importance of silacycles, methods for their preparation are somewhat scarce.[16] Silacyclobutanes (SCBs) are generally synthetised by the convenient intramolecular silylation of *in situ* prepared Grignard reagents.[16] Due to their high ring strain and Lewis acidity, SCBs are often used as precursors to other organosilicon compounds through ring opening/expansion reactions catalysed by transition metals.[16,17] Even though ring expansion of SCBs can also provide silacyclopentanes under specific conditions, the most direct method for their synthesis consists in the addition of metal treated 1,3-butadienes to dichlorosilanes.[18,19] The synthesis of silacyclopentenes through palladium-catalysed silylene-1,3-diene [4 + 1] cycloaddition[20] allows flexibility on substitution of the cyclopentene core.

Considering the importance of the cyclopentane motif in bioactive compounds,[21–26] we reasoned that new methods for the preparation of 5 membered-ring silacycles are needed for several fields of molecular sciences. From a synthetic perspec-

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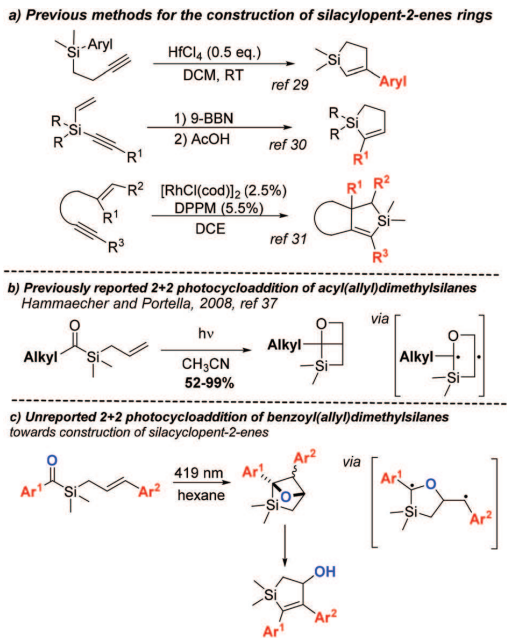
†Electronic supplementary information (ESI) available: Experimental protocols and NMR, computational and X-ray diffraction data. CCDC 1935510 and 1935511. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c9qo01028a

tive, achieving the cyclopentene moiety would be preferable due to potentially further functionalization of the double bound, such as asymmetric oxidative transformations.[27,28] Silacyclopent-2-enes are especially challenging as the ring is usually constructed from a highly functionalised silane (Scheme 1a),[29–31] imposing limitations on the degree of substitution on the cyclic core. Further modifications of silacyclopent-2-enes have also been reported[32–35] but additional functionalization of the cyclopentene ring is rare and synthetic flexibility on olefin substitution is often limited. Amongst the aforementioned scaffold, silacyclopent-2-enes bearing an allylic alcohol are of particular interest. Tomooka's group has utilised such compounds in the synthesis of various functionalised silacylclopentanes, some presenting biological activity, *via* Mitsunobu, Tsuji–Trost, and other transformations.[34,35] Additionally, similar silacyclopent-2-en-4-ols have been used in the synthesis of a polyol motif present in several natural products.[36]

In 2008, Portella *et al.* reported a photochemical [2 + 2] cycloaddition of acylsilanes (Scheme 1b).[37] Upon irradiation, acyl(allyl)silanes undergo intramolecular Paternò–Büchi reaction, producing bicyclic oxetanes in moderate to good yields and providing a new method for the synthesis of SCBs. While new 1-alky-6-oxa-2-silabicyclo[2.2.0]hexanes could be prepared by this way, irradiation of benzoyl(allyl)silane resulted in an intractable reaction mixture. Since the relative stability of the triplet biradical intermediates in the Paternò–Büchi reaction plays an important role in its stereo- and regioselectivity,[38,39] we envisioned that substitution on the olefin moiety with a radical stabilising group could tame the reactivity of the intermediates, altering the reaction profile observed by Portella. This could alter the regioselectivity of the cycloaddition, and the subsequent oxetane ring-opening would eventually yield silacyclopentenols (Scheme 1c).

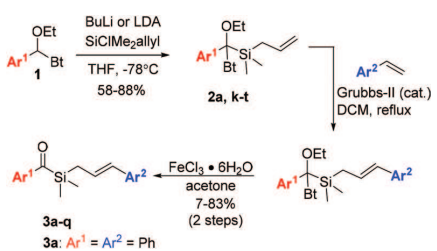
Acylsilanes have attracted immense scientific interest since their first preparation by Brook in 1957.[40] Despite the extensive research conducted on these compounds in the past few decades,[41–43] novel methodologies that utilize acylsilanes as powerful reagents in organic chemistry are still being reported.[44–46] Experimentally, the use of aromatic acylsilanes is particularly attractive as they do not undergo side reactions involving the carbonyl α-carbon.[47] Moreover, they show an absorption maximum at around 425 nm, thus allowing photoexcitation using visible blue light. The handling of acylsilanes requires special precautions as they are known to undergo Brook rearrangement to a reactive carbene after photoirradiation or thermal conditions. This carbene has been shown to undergo insertion reactions in polarised heteroatom-hydrogen bounds,[48,49] cycloadditions to aldehydes[50] and alkynes,[51,52] cross-coupling reaction with organoboronic esters[53] and even C–H insertions[54–56] under harsher conditions. Carbene formation and its subsequent reactions are then possible competitive destructive pathways to the [2 + 2] photocycloaddition. This influence can be minimised by using dry, aprotic solvents and by protecting free alcohols or amines in the acylsilane starting material.



Scheme 1 Methods for construction of silacyclopent-2-enes and photocycloaddition of acylsilanes.

Results and discussion

To investigate our hypothesis, cinnamyl silane **3a** was synthesised (Scheme 2). Initial investigations using the dithiane umpolung approach failed as the harsh conditions required for the deprotection of the dithiane moiety were incompatible with the olefin group. Inspired by Portella's success in the synthesis of acyl(allyl)silanes using benzotriazole hemiaminals as umpolung equivalents of aldehydes,[37,57] we adopted a similar synthetic pathway. This strategy, originally developed by Katritzky,[58] benefits from facile late-stage hydrolysis of the hemiaminals to the corresponding carbonyls. Olefin cross-metathesis was performed on intermediate **2a**, as the acylsilane moiety seems to inhibit the Grubbs catalyst.[57]



Scheme 2 Synthesis of benzoylsilanes **3**.

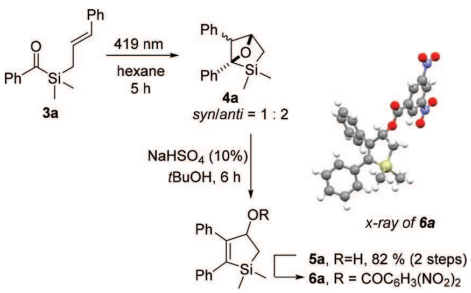
Gratifyingly, **3a** was obtained in reasonable 53% yield after hydrolysis. Compound **3a** was irradiated with blue-light for 5 hours in dry hexane, and complete consumption of the starting material was observed (Scheme 3). NMR analysis showed that oxetane **4a** was cleanly obtained as a mixture of two diastereoisomers (*syn*/*anti* = 1 : 2), resulting from the [2 + 2] photocycloaddition reaction. Notably, reverse regioselectivity in the Paternò–Büchi reaction was observed by Portella *et al.*[37] for unsubstituted acyl(allyl)silanes (Scheme 1b).

Compound **4a** proved to be unstable to silica column purification and overall acidic conditions, producing alcohol **5a** and other products. After optimization, we found that treating **4a** with catalytic $NaHSO_4$ in *tert*-butanol leads to complete and selective isomerization to **5a**, in 82% overall yield. Its structure was proven through esterification with 3,5-dinitrobenzoylchloride to yield **6a** and following single crystal X-ray diffraction analysis of the obtained ester.

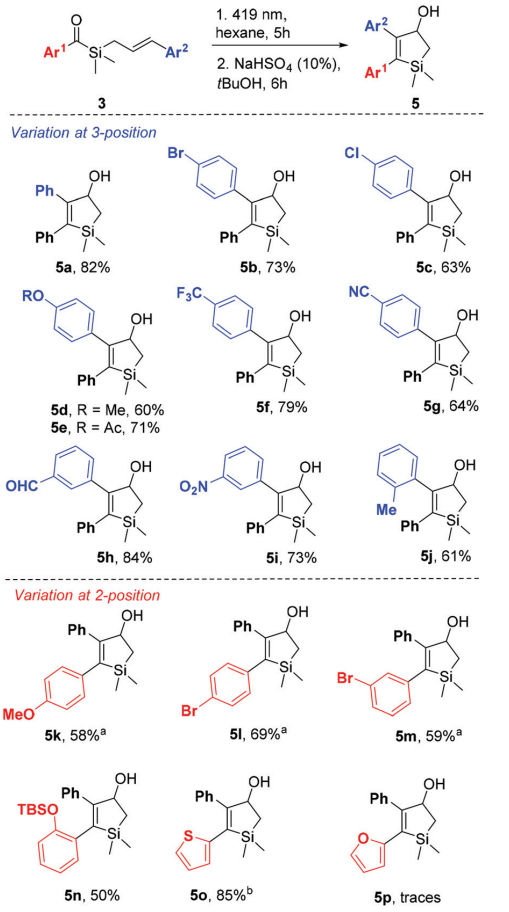
Realising the potential of the photocycloaddition–isomerization sequence as a direct and selective way to obtain 2,3-aryl-substituted silacyclopent-2-en-4-ols, we synthesised a series of acylsilanes **3** to be submitted to the same transformation (Scheme 2). Sila-hemiaminals **2** were obtained in very good yields, containing a wide range of functional groups in the aryl moiety. Nitro-substituted aromatics however failed to add to the silylchloride reagent, presumably due to the low nucleophilicity of the lithiated intermediate. Issues related with the instability of the lithiated anion of **1** bearing electron-rich groups in Ar^1 were overcome by *t*BuLi addition to a stirring solution of **1** and silyl chloride. The syntheses proceeded with cross-metathesis of intermediates **2** with styrenes. Low to moderate yields were obtained in some cases due to incomplete conversion of **2**, as the dimerization of styrene to stilbene was a fast competitive reaction. 2-Pyrididyl, 4-cyano- and 4-dimethylamine-benzene resulted in complete deactivation of the catalyst, as no reactions were observed after several days at reflux. The detrimental effect of nitrogen bases and N-heterocycles in metathesis reaction is known and still a problematic issue in this field.[59]

Despite the synthetic challenges, a series of seventeen aryl-substituted acylsilanes **3** were obtained and tested in the intramolecular [2 + 2] photocycloaddition reaction (Scheme 4). The reaction scope appears to be quite vast, withstanding electron withdrawing and electron donating substituents, as well as *ortho*, *meta* and *para* substitution. Gratifyingly, both variations at 3- and 2-positions of the 2,3-diaryl-silacyclopent-2-ene-4-ol could be performed. The reaction tolerates the presence of substituents prone for further derivatization such as acetyl (**5e**), nitrile (**5g**), aldehyde (**5h**) and silyl ether (**5n**). Formation of sulfur heterocycle derivative **5o** contrasts with its oxygen homologue **5p**, for which only traces could be observed. Also *ortho*-methyl substitution on the ketone side (Ar^1) led to the recovery of starting material even after 8 hours of irradiation.

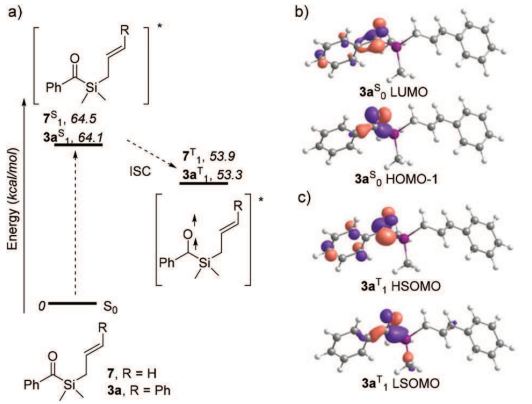
In order to better understand the dramatic change in regioselectivity of the [2 + 2] photocycloaddition of **3a** compared to its terminal olefin analogues, DFT calculations were performed and the energies of the possible biradical intermediates com-



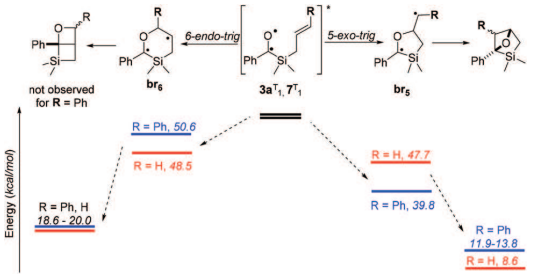
Scheme 3 [2 + 2] photocycloaddition of cinnamyl silane **3a**, acid-catalysed isomerization to **5a**, and crystal structure of 3,5-dinitrobenzoylated **6a**.



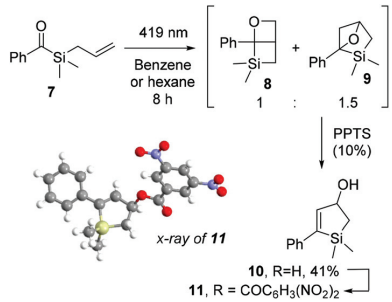
Scheme 4 Scope of the [2 + 2] photocycloaddition of benzoylsilanes **3**. [a] PPTS (10%) was used instead of $NaHSO_4$. [b] No acid treatment was needed.



Scheme 5 (a) Energy profile for excited states population of acylsilanes **3a** and **7**. Free energies of the species are indicated in italics (kcal mol^{-1}), referring to corresponding acylsilane in ground state. (b) Representation of most significant molecular orbitals involved in first vertical excitation of **3a**. (c) Single occupied orbitals of **3a**.



Scheme 6 Proposed mechanism for the intramolecular [2 + 2] photocycloaddition of acylsilanes.



Scheme 7 Irradiation of benzoyl(allyl)silane **7** and its non-regioselective [2 + 2] cycloaddition.

pared (see ESI† for details). The Paternò–Büchi photocycloaddition typically occurs through reaction of a carbonyl compound in the excited state with an alkene in the ground state. Time dependent DFT studies on **3a** and **7** show that the first vertical transition corresponds to populating the singlet excited state with comparable energies for both molecules (*ca.* 64 kcal mol^{-1}, Scheme 5a), through a carbonyl n → π* transition between HOMO−1 and LUMO, as can be observed in the case of **3a** (Scheme 5b). As triplet excited states for both molecules are generally *ca.* 11 kcal mol^{-1} more stable than their singlet counterparts, they likely undergo intersystem spin crossing. Analysis of the molecular orbitals of $\mathbf{3a}^{\mathbf{T}}_{\mathbf{1}}$ verifies that LSOMO and HSOMO correspond to the half-occupied n and π* carbonyl orbitals, respectively (Scheme 5c).

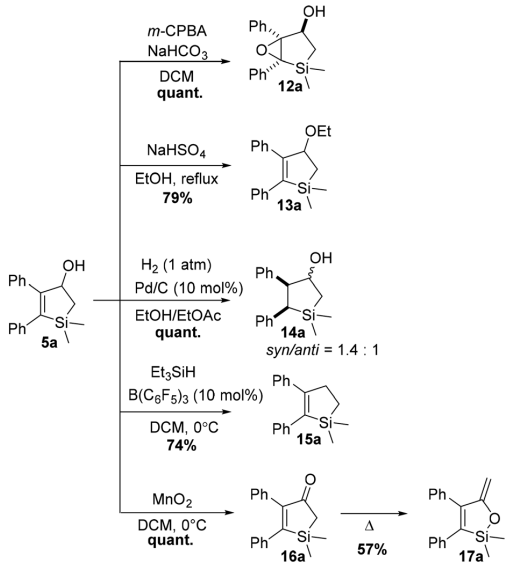
The two paths concerning the attack of the carbonyl oxygen of the triplet excited state to the olefin moiety of the allylsilane were considered‡ (Scheme 6). Comparing the formation of the two biradical species upon either *exo* and *endo* attacks of the oxygen to the cinnamyl moiety, a preference would be expected towards the former path due to stabilization of the radicals by the aromatic ring in **3a** : $\mathbf{br}_5$. The less than 1 kcal mol^{-1} difference in the stabilities of the biradicals derived from **7** nevertheless suggests two competing mechanisms. Since, when starting from aliphatic acyl(allyl)silanes, Portella *et al.* observed the exclusive formation of the 6-*endo-trig* cyclization-derived product (Scheme 1b), benzoylsilane **7** was synthesised and irradiated in order to determine the effect of the carbonyl substituent on the reaction outcome.

After irradiation of **7** in hexane for 8 hours, we observed complete and clean conversion to the structural isomers **8** and **9**, in 1 to 1.5 ratio, respectively (Scheme 7). Both compounds proved to be unstable to silica column chromatography. Indirect detection of compound **9** was possible after acid treatment with PPTS and isomerization to the isolable allylic alcohol **10** in 41% overall yield, which was further functionalised with 3,5-dinitrobenzoyl chloride to give ester **11** for X-ray diffraction analysis (Scheme 7). Despite the many attempts in isolating compound **8** or its decomposition products, we could only verify its presence through identification of characteristic peaks in ^{1}H and ^{13}C NMR spectra of the reaction mixture, in accordance with previous oxetanes characterization by Portella *et al.*[37] (Scheme 1b).

Experimentally, the lack of regioselectivity for the cycloaddition of compound **7** is in agreement with its DFT predicted reactivity, highlighting the need of a radical stabilising group connected to the olefin in order to promote complete regioselectivity towards the 5-*exo-trig* pathway.

In order to demonstrate the versatility of these unprecedented 2,3-disubstituted silacyclopentenols as precursors to other silacyclopentanes, compound **5a** was subjected to known transformations (Scheme 8). Diastereoselective epoxidation with *m*-CPBA quantitatively delivered **12a**, a candidate precursor to a series of polyols. Ethanolysis of a transient carbocation formed after acid treatment of **5a** yielded ether **13a**. In addition, olefin reduction with 1 atm of hydrogen in the pres-

‡The possible intermediates involved in the paths derived from the attack of the carbonyl carbon to the olefin moiety were also considered, although leading to biradicals considerably higher in energy (see ESI†).



Scheme 8 Examples of chemical transformations of **5a**.

ence of catalytic palladium on carbon quantitatively yields the silacyclopentanol **14a** as mixture of two diastereoisomers (*syn*/*anti* = 1.4 : 1). Finally, inspired by the structural similarity of selective COX-2 enzyme inhibitors[60] derived from cyclopentane, the removal of the hydroxyl functionality of **5a** was attempted. Gratefully, use of Yamamoto's $HSiEt_3$/catalytic $B(C_6F_5)_3$ system[61] allowed deoxygenation to **15a** in reasonable yield. The use of such compounds as bioisosteres of cyclopentanes could pave the way in the adoption of the new intramolecular [2 + 2] photocycloaddition in the silicon/carbon switch strategy. Oxidation of allylic alcohol **5a** was accomplished using excess MnO_2 in cold DCM, giving ketone **16a** quantitatively. Low temperatures are vital as **16a** proved to easily isomerize to the silyl enol ether **17a** under thermal conditions.

Conclusions

In conclusion, we have developed a methodology for the synthesis of novel 2,3-diaryl silacyclopent-2-en-4-ols. This strategy involved the synthesis of olefin-substituted benzoyl(allyl) silanes through the benzotriazole umpolung and metathesis reactions. Blue-light irradiation of these molecules promotes a [2 + 2] photocycloaddition reaction with complete regioselectivity, governed by the stability of the biradical intermediate as supported by computational calculations. Acid-promoted isomerization yields, to the best of our knowledge, the so far unavailable 2,3-disubstituted silacyclopentenols. Moreover, this study expands the rather short collection of intramolecular Paternò–Büchi reaction examples while demonstrating the influence of the olefin substituents in controlling the regioselectivity of such reaction. The obtained compounds may be used as versatile precursors to other silacyclopentanes that could find their use in the silicon/carbon switch approach in medicinal chemistry as bioisosters of bioactive cyclopentanes, or as organosilicon motifs in organic electronics.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

The Academy of Finland is duly acknowledged for financial support to N. R. C. (Decisions No. 326487 and 326486) and to A. V. (No. 314343). Fundação para a Ciência e Tecnologia (FCT) is acknowledged for financial support to JRV (SFRH/BD/120119/2016). CSC-IT Center for Science Ltd, Finland is acknowledged for the allocation of computational resources.

Notes and references

1 A. K. Franz and S. O. Wilson, *J. Med. Chem.*, 2013, **56**, 388–405.
2 E. Rémond, C. Martin, J. Martinez and F. Cavelier, *Chem. Rev.*, 2016, **116**, 11654–11684.
3 A. D. Dilman and S. L. Ioffe, *Chem. Rev.*, 2003, **103**, 733–772.
4 S. Rendler and M. Oestreich, *Synthesis*, 2005, 1727–1747.
5 R. Tacke and S. Dörrich, *Atypical Elements in Drug Design*, 1st edn, 2014.
6 R. Ramesh and D. S. Reddy, *J. Med. Chem.*, 2017, **61**, 3779–3798.
7 O. Daiss, C. Burschka, J. S. Mills, J. G. Montana, G. A. Showell, J. B. H. Warneck and R. Tacke, *Organometallics*, 2006, **25**, 1188–1198.
8 R. Tacke, F. Popp, B. Müller, B. Theis, C. Burschka, A. Hamacher, M. U. Kassack, D. Schepmann, B. Wünsch, U. Jurva and E. Wellner, *ChemMedChem*, 2008, **3**, 152–164.
9 J. B. Bauer, W. P. Lippert, S. Dörrich, D. Tebbe, C. Burschka, V. B. Christie, D. M. Tams, A. P. Henderson, B. A. Murray, T. B. Marder, S. A. Przyborski and R. Tacke, *ChemMedChem*, 2011, **6**, 1509–1517.
10 T. A. Su, H. Li, R. S. Klausen, N. T. Kim, M. Neupane, J. L. Leighton, M. L. Steigerwald, L. Venkataraman and C. Nuckolls, *Acc. Chem. Res.*, 2017, **50**, 1088–1095.
11 R. L. N. Hailes, A. M. Oliver, J. Gwyther, G. R. Whittell and I. Manners, *Chem. Soc. Rev.*, 2016, **45**, 5358–5407.
12 S. A. Ponomarenko and S. Kirchmeyer, *Adv. Polym. Sci.*, 2011, **235**, 33–110.
13 J. Chen and Y. Cao, *Macromol. Rapid Commun.*, 2007, **28**, 1714–1742.
14 J. V. Obligacion and P. J. Chirik, *Nat. Rev. Chem.*, 2018, **2**, 15–34.

15 T. Komiyama, Y. Minami and T. Hiyama, *ACS Catal.*, 2017, **7**, 631–651.
16 Q. C. Mu, J. Chen, C. G. Xia and L. W. Xu, *Coord. Chem. Rev.*, 2018, **374**, 93–113.
17 H. Chen, Y. Chen, X. Tang, S. Liu, R. Wang, T. Hu, L. Gao and Z. Song, *Angew. Chem., Int. Ed.*, 2019, **58**, 4695–4699.
18 G. Manuel, P. Mazerolles and E. T. J. Florence, *J. Organomet. Chem.*, 1971, **30**, 5–19.
19 G. K. Henry, R. Shinimoto, Q. Zhou and W. P. Weber, *J. Organomet. Chem.*, 1988, **350**, 3–8.
20 T. Ohmura, K. Masuda, I. Takase and M. Suginome, *J. Am. Chem. Soc.*, 2009, **131**, 16624–16625.
21 D. S. Straus and C. K. Glass, *Med. Res. Rev.*, 2001, **21**, 185–210.
22 S. M. Roberts, M. Gabriella and E. S. Sickle, *J. Chem. Soc., Perkin Trans. 1*, 2002, 1735–1742.
23 H. Almahli, *Curr. Top. Med. Chem.*, 2017, **17**, 2903–2912.
24 Z. Sevcikova, M. Pour, D. Novak, J. Ulrichova and J. Vacek, *Mini-Rev. Med. Chem.*, 2014, **14**, 322–331.
25 B. Heasly, *Curr. Org. Chem.*, 2014, **18**, 641–686.
26 S. P. Simeonov, P. M. Nunes, K. Guerra, V. B. Kurteva and C. A. M. Afonso, *Chem. Rev.*, 2016, **116**, 5744–5893.
27 H. C. Kolb, M. S. VanNieuwenhze and K. B. Sharpless, *Chem. Rev.*, 1994, **94**, 2483–2547.
28 A. Pfenninger, *Synthesis*, 1986, 89–116.
29 N. Asao, T. Shimada, T. Shimada and Y. Yamamoto, *J. Am. Chem. Soc.*, 2001, **123**, 10899–10902.
30 B. Wrackmeyer, O. L. Tok and R. Kempe, *Inorg. Chim. Acta*, 2005, **358**, 4183–4190.
31 T. Ohmura, I. Sasaki and M. Suginome, *Org. Lett.*, 2019, **21**, 1649–1653.
32 A. C. Stevens and B. L. Pagenkopt, *Org. Lett.*, 2010, **12**, 3658–3661.
33 D. Liu and S. A. Kozmin, *Angew. Chem., Int. Ed.*, 2001, **40**, 4757–4759.
34 K. Igawa, D. Yoshihiro, Y. Abe and K. Tomooka, *Angew. Chem., Int. Ed.*, 2016, **55**, 5814–5818.
35 K. Igawa, A. Kuroo, D. Yoshihiro, Y. Yamanaka and K. Tomooka, *Synlett*, 2017, **28**, 2445–2448.
36 D. Liu and S. A. Kozmin, *Org. Lett.*, 2002, **4**, 3005–3007.
37 C. Hammaecher and C. Portella, *Chem. Commun.*, 2008, 5833.
38 M. Abe, T. Kawakami, S. Ohata and K. Nozaki, *J. Am. Chem. Soc.*, 2004, **126**, 2838–2846.
39 F. Kong, B. Zhai and Q. Song, *Photochem. Photobiol. Sci.*, 2008, **7**, 1332–1336.
40 A. G. Brook, *J. Am. Chem. Soc.*, 1957, **79**, 4373–4375.
41 A. Ricci and A. Degl'Innocenti, *Synthesis*, 1989, 647–660.
42 P. C. B. Page, S. S. Klair and S. Rosenthal, *Chem. Soc. Rev.*, 1990, **19**, 147.
43 H.-J. Zhang, D. L. Priebbenow and C. Bolm, *Chem. Soc. Rev.*, 2013, **42**, 8540–8571.
44 J. Y. Lv, Z. Xu, Z. J. Zheng, L. Li, Y. M. Cui, J. Cao, K. F. Yang and L. W. Xu, *RSC Adv.*, 2017, **7**, 54934–54938.
45 F. G. Zhang and I. Marek, *J. Am. Chem. Soc.*, 2017, **139**, 8364–8370.
46 L. Capaldo, R. Riccardi, D. Ravelli and M. Fagnoni, *ACS Catal.*, 2018, **8**, 304–309.
47 A. G. Brook and J. M. Duff, *Can. J. Chem.*, 1973, **51**, 352–360.
48 J. M. Duff and A. G. Brook, *Can. J. Chem.*, 1973, **51**, 2869–2883.
49 H. Watanabe, T. Kogure and Y. Nagai, *J. Org. Chem.*, 1972, **43**, 285–291.
50 A. G. Brook and J. B. Pierce, *Can. J. Chem.*, 1971, **49**, 1622–1628.
51 H. J. Zhang, P. Becker, H. Huang, R. Pirwerdjan, F. F. Pan and C. Bolm, *Adv. Synth. Catal.*, 2012, **354**, 2157–2161.
52 P. Becker, D. L. Priebbenow, H. J. Zhang, R. Pirwerdjan and C. Bolm, *J. Org. Chem.*, 2014, **79**, 814–817.
53 K. Ito, H. Tamashima, N. Iwasawa and H. Kusama, *J. Am. Chem. Soc.*, 2011, **133**, 3716–3719.
54 A. R. Bassindale, A. G. Brook and J. Harris, *J. Organomet. Chem.*, 1975, **90**, C6–C8.
55 B. Fund and F. Summer, *J. Org. Chem.*, 1982, **47**, 2668–2670.
56 Z. Shen and V. M. Dong, *Angew. Chem., Int. Ed.*, 2009, **48**, 784–786.
57 C. Hammaecher, J. Bouillon and C. Portella, *Tetrahedron*, 2009, **65**, 5527–5534.
58 A. R. Katritzky, H. Lang, Z. Wang, Z. Zhang and H. Song, *J. Org. Chem.*, 1995, **60**, 7619–7624.
59 K. Lafaye, C. Bosset, L. Nicolas, A. Guérinot and J. Cossy, *Beilstein J. Org. Chem.*, 2015, **11**, 2223–2241.
60 D. B. Reitz, J. J. Li, M. B. Norton, E. J. Reinhard, J. T. Collins, G. D. Anderson, S. A. Gregory, C. M. Koboldt, W. E. Perkins, K. Seibert and P. C. Isakson, *J. Med. Chem.*, 1994, **37**, 3878–3881.
61 V. Gevorgyan, J. X. Liu, M. Rubin, S. Benson and Y. Yamamoto, *Tetrahedron Lett.*, 1999, **40**, 8919–8922.

PUBLICATION III

Battling Glioblastoma: A Novel Tyrosine Kinase Inhibitor with Multi-Dimensional Anti-Tumor Effect

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Cells, **2019**, *8*, 1624-1641

DOI: 10.3390/cells8121624

cells

MDPI

Article

Battling Glioblastoma: A Novel Tyrosine Kinase Inhibitor with Multi-Dimensional Anti-Tumor Effect

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Received: 26 November 2019; Accepted: 9 December 2019; Published: 12 December 2019

Abstract: Glioblastoma (GB), a grade IV glioma, with high heterogeneity and chemoresistance, obligates a multidimensional antagonist to debilitate its competence. Considering the previous reports on thioesters as antitumor compounds, this paper investigates on use of this densely functionalized sulphur rich molecule as a potent anti-GB agent. Bio-evaluation of 12 novel compounds, containing α-thioether ketone and orthothioester functionalities, identified that five analogs exhibited better cytotoxic profile compared to standard drug cisplatin. Detailed toxicity studies of top compound were evaluated in two cell lines, using cell viability test, apoptotic activity, oxidative stress and caspase activation and RNA-sequencing analysis, to obtain a comprehensive molecular profile of drug activity. The most effective molecule presented half maximal inhibitory concentration (IC_{50}) values of 27 μM and 23 μM against U87 and LN229 GB cells, respectively. Same compound effectively weakened various angiogenic pathways, mainly MAPK and JAK-STAT pathways, downregulating VEGF. Transcriptome analysis identified significant promotion of apoptotic genes, and genes involved in cell cycle arrest, with concurrent inhibition of various tyrosine kinase cascades and stress response genes. Docking and immunoblotting studies suggest EGFR as a strong target of the orthothioester identified. Therefore, orthothioesters can potentially serve as a multi-dimensional chemotherapeutic possessing strong cytotoxic, anti-angiogenic and chemo-sensitization activity, challenging glioblastoma pathogenesis.

Keywords: glioblastoma; thioester; anti-angiogenesis; tyrosine kinase inhibitor

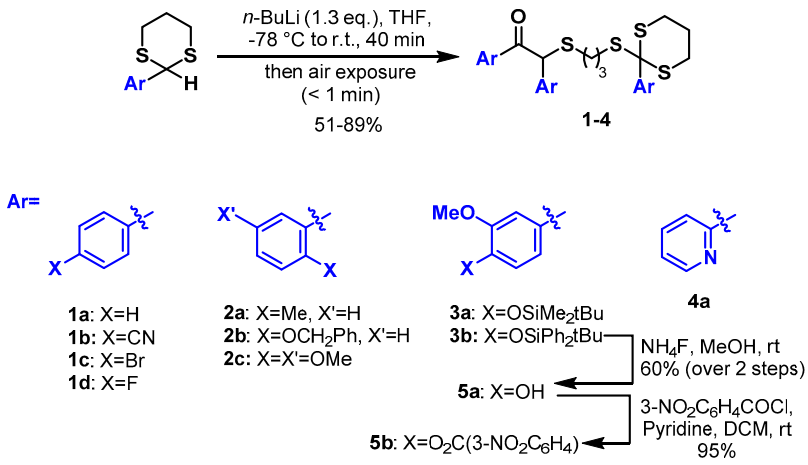
1. Introduction

Glioblastoma (GB) is a type of brain tumor with almost 100% recurrence rate and high resistance to current treatment modalities. The high heterogeneity exhibited within GB tumors render it

unresponsive to single-target cytotoxic/anti-angiogenic agents and demands a significant clinical need for new multi-dimensional oncogenic inhibitors for GB.

Angiogenesis is a significant feature of GB, attributed to the overexpression of vascular endothelial growth factor (*VEGF*). Few of the most significant proangiogenic regulators that stimulate angiogenesis indirectly by inducing *VEGF* mRNA expression include the growth factors epidermal growth factor (*EGF*), transforming growth factor (*TGF-α* and *TGF-β*), tumor necrosis factor α (*TNF-α*), keratinocyte growth factor, insulin-like growth factor I (*IGF-I*), fibroblast growth factor (*FGF*), platelet-derived growth factor/(*PDGF*), and cytokines (interleukin (*IL*)-*1α* and *IL-6*) and amplifications of *Ras*/*Raf* genes [1]. Multiple strategies have been developed to target VEGF/VEGF receptor (*VEGFR*)–mediated angiogenesis, including VEGF blockade, VEGF Trap, and suppression of VEGFR signaling via receptor tyrosine kinase inhibitors (TKIs) [2–4]. *EGFR* belongs to the *ErbB* family receptors of Class I receptor tyrosine kinases (*RTKs*). Almost 60% of glioblastoma patients have some kind of genomic alteration affecting EGFR pathway [5]. Downstream effects of *EGFR* is mediated through phosphoinositide 3-kinase (*PI3K*), mitogen-activated protein kinase (*MAPK*), signal transducer and activator of transcription 3 (*STAT3*) pathways, and *Src* family kinases [6]. A number of studies have focused on inhibiting both *VEGFR* and *EGFR* so as to improve drug efficiency, including monotherapy with a multi-targeted tyrosine kinase inhibitor (e.g., vandetanib, AEE788, BMS-690514) [7,8]. Other significant pathways regulating tumor angiogenesis directly or indirectly via VEGF includes MAPK pathway [9], JAK-STAT pathway [10,11], and PI3K-AKT [12] pathway. Thus, a multi-targeted chemoagent that can effectively sequester multiple pathways involved in VEGF regulation would be an effective solution to tackle tumor pathogenesis.

Some of us have recently reported the unprecedented autoxidative condensation of 2-aryl-2-lithio-1,3-dithianes (Scheme 1) [13]. The result of such transformation was a small library of highly functionalized molecules containing α-thioether ketones and orthothioesters functionalities, among others. Motivated by the desire to find new agents capable of multi-target inhibition as promising approaches in the development of glioblastoma cancer drugs [14], we have set to assess the antitumor properties of these intricate molecules.



Scheme 1. Synthesis and structures of studied orthothioesters.

2. Materials and Methods

2.1. Synthesis of Orthothioesters

Reactions were monitored through thin-layer chromatography (TLC) with commercial silica gel plates (Merck silica gel, 60 F254). Visualization of the developed plates was performed under UV lights

at 254 nm and by staining with cerium ammonium molybdate, 2,4-dinitrophenylhydrazine and vanillin stains. Flash column chromatography was performed on silica gel 60 (40–63 μm) as a stationary phase. NMR spectra were recorded with Varian Mercury 300 MHz or Jeol ECZR 500 instruments using $CDCl_3$ as solvent and calibrated using tetramethylsilane as internal standard. Chemical shifts (δ) are reported in ppm referenced to the $CDCl_3$ residual peak (δ 7.26) or TMS peak (δ 0.00) for ^{1}H-NMR and to $CDCl_3$ (δ 77.16) for ^{13}C-NMR. The following abbreviations were used to describe peak splitting patterns: s = singlet, d = doublet, t = triplet, m = multiplet. Coupling constants, *J*, were reported in Hertz (Hz). High-resolution mass spectra (HR-MS) were recorded on a Waters ESI-TOF MS spectrometer. Tetrahydrofuran (THF) was dried by distillation under argon with sodium metal and benzophenone as indicator. Dichloromethane (DCM) was dried by distillation under argon with calcium hydride. Structural elucidation of all compounds tested in biological assays was performed by ^{1}H and ^{13}C-NMR, and HR-MS. All compounds of interest were isolated by chromatography and their purity (>97%) assessed by NMR.

Compounds **1**–**4** were prepared and characterized as reported elsewhere [13], through autoxidative condensation of 2-aryl-2-lithium-1,3-dithianes, prepared from treatment of 2-aryl-1,3-dithianes with *n*-BuLi followed by air exposure.

5a: (4-(1,3-Dithian-2-yl)-2-methoxyphenoxy)(*tert*-butyl)diphenylsilane (1.09 g, 2.27 mmol) was dissolved in dry THF (10 mL) in an argon purged round-bottom flask. The solution was cooled to −78 °C in an acetone/liquid nitrogen bath. *n*-BuLi (1.3 equivalents) was added dropwise to the reaction mixture at −78 °C. After addition, the solution was left stirring at −78 °C for 20 min, and then left to warm up to room temperature for 40 min. The argon balloon was replaced with an atmospheric air balloon and an additional needle was inserted in the septum as to allow air flow through the surface of the solution. After one minute, the solution was quenched with saturated aqueous NH_4Cl solution (20 mL). Et_2O (20 mL) was added and the layers separated. The organic phase was collected and the aqueous phase was extracted with Et_2O (2 × 20 mL). The organic phases were combined and dried over $MgSO_4$. The solvent was filtered and evaporated to yield crude 3b. The mixture was dissolved in dry methanol (8 mL) in an argon purged round-bottom flask. Then, ammonium fluoride (95 mg, 2.56 mmol, 1.1 equivalents) was added and the solution was stirred overnight at room temperature. The methanol was evaporated and water (10 mL) was added. The aqueous phase was extracted with DCM (3 × 10 mL) and the organic phases were combined and dried over $MgSO_4$. The solvent was evaporated and the product was purified by flash chromatography, eluent hexane: ethyl acetate (1:1), to give product **5a** as an amorphous orange solid (286 mg, 0.45 mmol) in 60% yield. ^{1}H-NMR (500 MHz, $CDCl_3$) δ ppm 7.56–7.49 (m, 3H), 7.44 (dd, *J* = 8.4, 2.1 Hz, 1H), 6.98 (s, 1H), 6.89–6.82 (m, 4H), 6.07 (s, 1H), 5.68 (s, 1H), 5.61 (s, 1H), 5.45 (s, 1H), 3.90 (s, 3H), 3.89 (s, 3H), 3.86 (s, 3H), 3.27 (t, *J* = 12.5 Hz, 2H), 2.74–2.70 (m, 2H), 2.57–2.44 (m, 4H), 2.10–2.05 (m, 1H), 1.92–1.85 (m, 1H), 1.77–1.71 (m, 2H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ ppm 194.0, 150.7, 147.1, 146.8, 146.4, 145.8, 145.6, 133.3, 128.8, 128.5, 124.3, 122.1, 121.3, 114.3, 114.0, 113.9, 111.0, 110.8, 110.6, 64.3, 56.2 (×2), 56.1, 55.2, 32.8, 30.7, 29.4, 28.5, 24.4. HR-MS (ESI) *m*/*z* calculated for $C_{30}H_{34}O_7S_4Na^+$ $[M + Na]^+$ 657.1080, found 657.1068.

5b: Triphenol **5a** (100 mg, 0.158 mmol) was dissolved in dry DCM (3 mL) in an argon purged round-bottom flask. Pyridine (48 μL, 0.591 mmol, 3.75 equivalents) was added to the solution, followed by 3-nitrobenzoyl chloride (91 mg, 0.488 mmol, 3.1 equivalents). The reaction was left stirring at room temperature for 72 h. Water (10 mL) was added to the mixture and the aqueous phase was extracted with DCM (3 × 10 mL). The organic phases were combined and dried over $MgSO_4$. The solvent was evaporated and the product was purified by flash chromatography, eluent hexane: ethyl acetate (3:2), to give the benzoyl derivative **5b** as an amorphous white solid (163 mg, 0.151 mmol) in 95% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 9.02 (s, 3H), 8.51–8.48 (m, 6H), 7.76–7.67 (m, 6H), 7.62 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.25–7.08 (m, 5H), 5.56 (s, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.83 (s, 3H), 3.31 (dd, *J* = 13.3, 11.2 Hz, 2H), 2.79 (dd, *J* = 14.3, 3.6 Hz, 2H), 2.70–2.58 (m, 4H), 2.14–2.11 (m, 1H), 1.98–1.91 (m, 1H), 1.86–1.81 (m, 2H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 193.8, 162.6, 162.6, 162.2, 151.7, 151.6, 151.0, 148.5, 148.5, 143.8, 140.9, 139.5, 139.4, 136.1, 136.1, 135.9, 134.9, 131.2, 131.2, 130.8, 130.1, 130.0, 128.3, 128.1,

128.1, 125.5, 125.4, 122.9, 122.4, 122.3, 121.4, 120.6, 112.9, 112.8, 64.1, 56.3, 56.2, 56.2, 55.1, 32.8, 30.9, 29.5, 28.5, 24.3. HR-MS (ESI) *m/z* calculated for $C_{51}H_{43}N_3O_{16}S_4Na^+$ $[M + Na]^+$ 1104.1418, found 1104.1385.

2.2. Cell Culture

Human GB cell lines, U87 cells were grown in Minimum Essential Medium (MEM, Product# 51416C, Sigma-Aldrich, St. Louis, MO, USA) with 10% Fetal Bovine Serum(FBS) 2 mM sodium pyruvate (Product# S8636, Sigma-Aldrich, St. Louis, MO), 1% Penicillin-Streptomycin and 0.025 mg/mL Amphotericin B. LN229 and non-cancerous cell line, mouse embryonic fibroblast (MEF) cells were cultured in Dulbecco's Modified Eagle Medium—high glucose (DMEM, Catalog# L0102, Biowest, Riverside, CA, USA) containing 5% FBS (Product # F1051, Sigma-Aldrich, St. Louis, MO), 1% Penicillin-Streptomycin (Product # P4333, Sigma-Aldrich, St. Louis, MO) and 0.025 mg/mL Amphotericin B (Sigma-Aldrich, St. Louis, MO). U87 and LN229 are the standard cell lines derived from malignant gliomas used commonly for cytotoxicity study. MEF Cells were maintained at 37 °C in a humidified incubator supplemented with 5% CO_2. Three biological and technical repeats were used for each condition.

2.3. In Vitro Cytotoxicity Assay

Cytotoxicity assay was performed to determine the cell growth inhibitory effect of the compounds following treatment for 48 h on the GB cell lines, U87, LN229. This assay was performed in two stages. At first, a high concentration, 100 μM, of compounds were used as well as for the positive control Cisplatin, CIS (Sigma-Aldrich, USA). Following this, the top compound was selected, and different concentrations (100 μM, 75 μM, 50 μM, 25 μM, and 10 μM) of the compound were tested to determine the IC_{50}. Treated cells were harvested by centrifugation at 1200 rpm for 10 min. Cell viability was determined using trypan blue staining. The number of live and dead cells were counted using a Countess II Automated Cell Counter (Thermo Fisher Scientific, Carlsbad, CA, USA). The proliferation inhibition percentage of each sample was determined using the following formula to determine the dose-response curve. From the dose-response curve, the IC_{50} value of each compound was calculated. The cytotoxicity of the top compound and Cisplatin at a concentration of 10 μM was also evaluated in normal brain cells (MEF). Percentage of inhibition of cell proliferation was calculated using the following formula:

$$\text{Proliferation inhibition } (\%) = \frac{\textit{Mean No. of untreated cells (DMSO control)} - \textit{Mean No. of treated cells} \times 100}{\textit{Mean No. of untreated cells (DMSO control)}}$$

2.4. Double Staining Assay

U87 and LN229 cell lines were grown as described previously, followed by cells treatment with IC_{50} concentration of 5a and incubated for 48 h. Untreated (Negative) and Cisplatin (positive) controls were also maintained. Apoptosis/necrosis detection was carried out using Annexin V-FITC and PI (Thermo Fisher Scientific). The apoptosis determination was performed following the standard protocol suggest by the manufacturer. Briefly, the cells were cultured in 6-well plate with an initial cell density of 7×10^5 cells/well. The cells were incubated for 48 h with 5a, positive control and untreated cells conditions and then harvested and washed in cold phosphate buffered saline (PBS). The cell pellets were then resuspended in 1× Annexin-binding buffer provided in the kit. Consequently, 5 μL of FITC conjugated Annexin V and 1 μL of the 100 μg/mL PI working solutions were added to the 100 μL of cell suspension. The cells were incubated in dark for 15 min, at room temperature, after which the stained cells were observed for fluorescence to distinguish apoptotic cells. The image acquisition was done by using an EVOS imaging system (ThermoFisher Scientific) with 20× objective magnification. More than 300 cells were used for each analysis. The percentage of apoptosis was quantified based on the cells stained with Annexin V-FITC positive and PI negative and both Annexin V-FITC and PI

positive. The percentage of necrosis was calculated based on the cells with Annexin V-FITC negative and PI positive [15–17]. The fold change in apoptosis was calculated against the untreated cells.

2.5. Caspase Activity Assay

In-vitro caspase-3 and caspase-7 activity was determined using Caspase-Glo® 3/7 Assay Systems (Promega Corporation, Madison, WI, USA). The reagent was prepared as mentioned in the manufacturer protocol. The U87 and LN229 cells were grown overnight in a 96-well plate and were treated with an IC_{50} of 5A. Negative control, positive control and blank (medium+ Dimethyl sulfoxide (DMSO)+ dye) were also maintained. Cells were incubated at 37 °C in a humidified incubator supplemented with 5% CO_2 for 5 h and then equilibrated at room temperature for 30 min. 100 µL of Caspase-Glo 3/7 reagent was added to 100 µL of cells/well and was incubated in a dark-chamber. The luminescence signal was quantified (Chameleon Multi-label Detection Platform) at one hour after treatment. Magnitude of fold change in luminescence between treated and untreated cells were determined using the following formula:

$$Fold\ increase = \frac{F_{test} - F_{blank}}{F_{control} - F_{blank}}$$

2.6. Intracellular Redox Potential Test

To evaluate the redox potential of 5a, a comparative test, using H_2O_2 and standard drug against untreated cells, was performed using H2DCFDA (Catalog no.# D399 Life Technologies, Eugene, OR, USA). The U87 and LN229 cells were grown overnight in a 96-well plate and were treated with an IC_{50} of 5a for 5 h at 37 °C in a humidified incubator supplemented with 5% CO_2. Negative control, positive control and blank were maintained. Baseline effect due to solvent was determined as well. After 5 h of treatment, cells were harvested by centrifugation at 3000 rpm for 10 min and incubated with 200 µL of 2 µM H2DCFDA for 30 min at 37 °C in the CO_2 incubator. Cells were then washed with pre-warmed PBS and resuspended in 200 µL of pre-warmed medium. Next, 100 µL of suspension was transferred to each well, in a 96-well plate and incubated at room temperature for 20 min. Finally, fluorescence signal was measured using Chameleon Multi-label Detection Platform (Excitation 485 nm, Emission 535 nm).

2.7. RNA Isolation and Gene Expression Evaluation

Cell were incubated with IC_{50} of test compound and standard drug Cisplatin for 48 h at 37 °C in a humidified incubator supplemented with 5% CO_2. A negative control was maintained as well. All conditions were conducted in triplicated samples for the isolation of RNA. Total RNA of >9.25 ng/µL was isolated using GeneJET RNA purification kit (Catalog no #K0731), according to the manufacturer's instructions. The yield was then measured spectrophotometrically using NanoDrop-1000 (Thermoscientific, Wilmington, NC, USA). After quantification, the cells were considered for quality assessment by TapeStation. The gene expression analysis was performed by using Illumina Next Seq High throughput profiling (Illumina NextSeq 500). The sequencing produced data in bcl format which was converted into FASTQ file format.

2.8. Transcriptome Analysis

Differential expression (DE) and statistical analysis were performed using DESeq2 [18] (release 3.3) in R (version 3.2.4) (https://bioconductor.org/packages/release/bioc/vignettes/DESeq2/inst/doc/DESeq2.html). *p*-values were adjusted for multiple testing using the Benjamini-Hochberg procedure [19]. A false discovery rate adjusted *p*-value (i.e., *q*-value) < 0.05 was set for the selection of DE genes.

2.9. Phosphorylation of MAPKs and Other Serine/Threonine Kinases

The U87 cells were treated with an IC_{50} concentration of **5a** and DMSO, maintained in CO_2 humidified temperature for 48 h. The total protein was extracted using RnD protein extraction kit for the immunoblotting experiment. The phosphorylation of three families of mitogen-activated protein

kinases (*MAPKs*), including the extracellular signal-regulated kinases (*ERK1/2*), c-Jun N-terminal kinases (*JNK1-3*), and different p38 isoforms, was analyzed following the manufacturer protocol, RnD Human Phospho-MAPK array kit. In detail, cell lysates are mixed with a cocktail of biotinylated detection antibodies and incubated with Proteome Profiler Human Phospho-MAPK Array. Streptavidin-HRP and chemiluminescent detection reagents are added and the signals that are produced at each spot correspond to the amount of phosphorylated protein bound. The captured and control antibodies have been spotted in duplicate on nitrocellulose membranes. The signals are measured using ChemiPro Luminescence detection system. The relative level of phosphorylation was analysed for 26 *MAPK* proteins as described in the manufacturer's protocol.

2.10. Gene Ontology (GO) and Pathway Analysis

Gene ontology [20] and ClusterProfiler package [21] was used for pathway analyses. We performed with the over-representation test for the GO biological process and KEGG pathways [22]. The package supports the human genome. We used the binomial test and Bonferroni correction for multiple testing and displayed z-scores to indicate whether a potential regulator was activated or inhibited. We used the default settings for statistical analysis in both the KEGG pathways and GO terms. In this analysis, pathways and GO terms only with a p-value < 0.05 were included.

2.11. Evaluation of Structure-Activity Relationship

In order to make a comparative study on the binding of **5a** with different receptors, sequences and structures of six receptors taken from Protein Data Bank (PDB)—Fibroblast Growth Factor receptor (*FGFR*, PDB ID: 2FDB), Epidermal growth Factor Receptor (*EGFR*, PDB ID: 4UIP), Platelet-Derived Growth Factor Receptor (*PDGFR*, PDB ID: 1PDG), *c-MET* Receptor (PDB ID: 3DKC), c-KIT Receptors (PDB ID: 6GQK) and Vascular Endothelial Growth Factor receptors (PDB ID: 3V2A) were obtained from the Protein Data bank. To study the binding efficiency and to identify the important amino acid residues contribute to the binding, Patchdock molecular docking program was used. The default parameters were used for the molecular docking in this study. Patchdock carries out rigid docking, with surface variability implicitly addressed through liberal intermolecular penetration.

2.12. Statistical Analysis

All experiments described in the present study were performed as with three biological and technical repeats. The data were presented as the mean ± standard error of mean. Statistical analyses between two groups were performed by Student's t-test. Differences among multiple groups were tested by one-way analysis of variance following by a Dunnett's multiple comparison test (GraphPad Prism 7.04, San Diego, CA, USA). $p < 0.05$ was considered to indicate a statistically significant difference.

3. Results

3.1. Synthesis of Orthothioesters

The orthothioesters **1-4** were synthesized through autoxidative condensation of 2-aryl-2-lithium-1,3-dithianes, prepared in situ from treatment of 2-aryl-1,3-dithianes with *n*-BuLi followed by air exposure. The presence of bromide when preparing **1c** demanded for replacement of *n*-BuLi by lithium diisopropylamide (LDA) in order to avoid transmetalation. The compounds were obtained in reasonable yields and pure after quenching with NH_4Cl saturated aqueous solution, usual work-up and purification by silica chromatography. The silyl ether group in compound **3b** was cleaved by treatment with 1 equivalent of NH_4F to yield phenol **5a**. Derivatization of **5a** with *m*-nitrobenzoyl chloride delivered carboxylic ester **5b** in excellent yield. Purity evaluation results of the novel compounds are given in the Supplementary file 1.

3.2. ***5a*** *Inhibited Proliferation of Glioma Cells*

The cytotoxicity of the orthothioesters **1**-**5** against the growth of U87 GB cell line was performed with 100 μM concentration of the compounds as described in the method section. Upon evaluation of the 12 compounds depicted in Scheme 1, **5a** was identified to be the most cytotoxic compound inducing 90% cell death and **5b** was the least cytotoxic with 0% cell death. This was a 20-fold higher activity compared to the standard drug cisplatin and 31.8-fold compared to the negative control (Figure 1a) The analysis of cytotoxic data of all compounds tested shows that while the presence of halogens or nitrile in the 4-position of the aromatic rings is detrimental for cytotoxicity (as for compounds **1b**–**d**), having a methoxy group in the 3-position has an opposite effect. Compounds **2c**, **3a** and **5a**, decorated with a 3-methoxy substituent in the aromatic rings, showed cytotoxicity similar to or higher than **1a**. Compounds **3b** and **5b** on the other hand, also decorated with the same 3-methoxy substituent but having bulky substituents in the vicinal 4-position, have residual or absent cytotoxicity. No improvement on cytotoxicity was observed when replacing the aryl groups by heteroaryl such as pyridyl in **4a**. The cytotoxicity on normal brain cells, MEF, was also performed for the top compound **5a** (Figure 1b) and cisplatin at a concentration of 10 μM. The results show that **5a** have 11% of growth inhibition, whereas cisplatin have 48% of inhibition, suggesting that **5a** is more toxic to the cancer cells than the normal cells (Figure 1c).

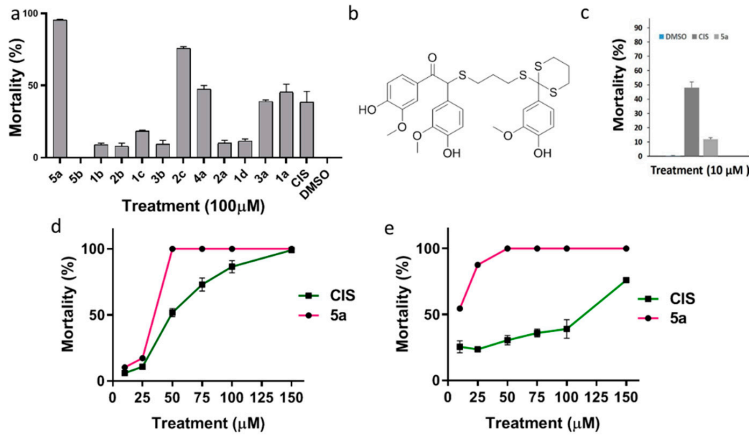


Figure 1. In vitro screening and evaluation of dose response of thioester compounds (**a**). The percentage of mortality rate on treating U87 cells with novel panel of 12 thioester derivatives along with CIS (positive control) 1% DMSO (negative control), at a 100 μM concentration (**b**). Chemical structure of the investigative drug **5a**. (**c**) Cytotoxicity analysis of non-cancerous brain cells, MEF and cisplatin at 10 μM concentration. (**d**) Dose response curve of U87 cells (left) and (**e**) LN229 (right) cells treated with the top compound (**5a**), CIS and 1% DMSO was analyzed to determine IC_{50} value. Treatment was carried out at 48h and cellular viability was measured by Trypan Blue exclusion method. Data points and error bars represent mean ± standard error of the mean (SEM) (n = 6 per group). Significant when $p < 0.05$, one-way ANOVA.

In order to investigate the in vitro anticancer activity of **5a** and to determine its IC_{50} value, we evaluated cytotoxicity against cell lines, U87 and LN229 in the presence of increasing concentrations of this compound for 24 h, ranging from 0 μM–150 μM. The viability of cells was determined according to cell counting based on Trypan Blue assay and the IC_{50} value of **5a** was determined as 27 μM in U87 cells and 23 μM in LN229 cells (Figure 1d,e). The IC_{50} value of cisplatin was identified as 53 μM in U87 cells and 115 μM in LN229.

3.3. ***5a*** *Induced Negligible Oxidative Stress and Promoted Caspase Activation*

Reactive oxygen species (ROS) mediated caspase activation of tumor cells during stress and subsequent cell death has been repeatedly reported by various studies [23,24]. In the present study, both intracellular ROS and caspase in U87 cells were quantified to verify oxidative stress and cellular response upon **5a** treatment. After exposure of U87 cells to **5a** at IC_{50} for 5 h, we detected an oxidative increase of 3.3% increase in the **5a** treated cells when compared to untreated cells. The standard drug cisplatin and positive control H_2O_2 on the other hand, marked a 4.2% and 2.2% increase in oxidative response respectively (Figure 2a). Similarly, exposure of LN229 cells to **5a** at IC_{50} for 5 h demonstrated negligible change in the treated cells when compared to untreated cells (Figure 2a). The difference between treated and untreated conditions was confirmed to be statistically insignificant per ANOVA test (p-value <0.05), establishing that the **5a** does not increase ROS in the tested GB cells.

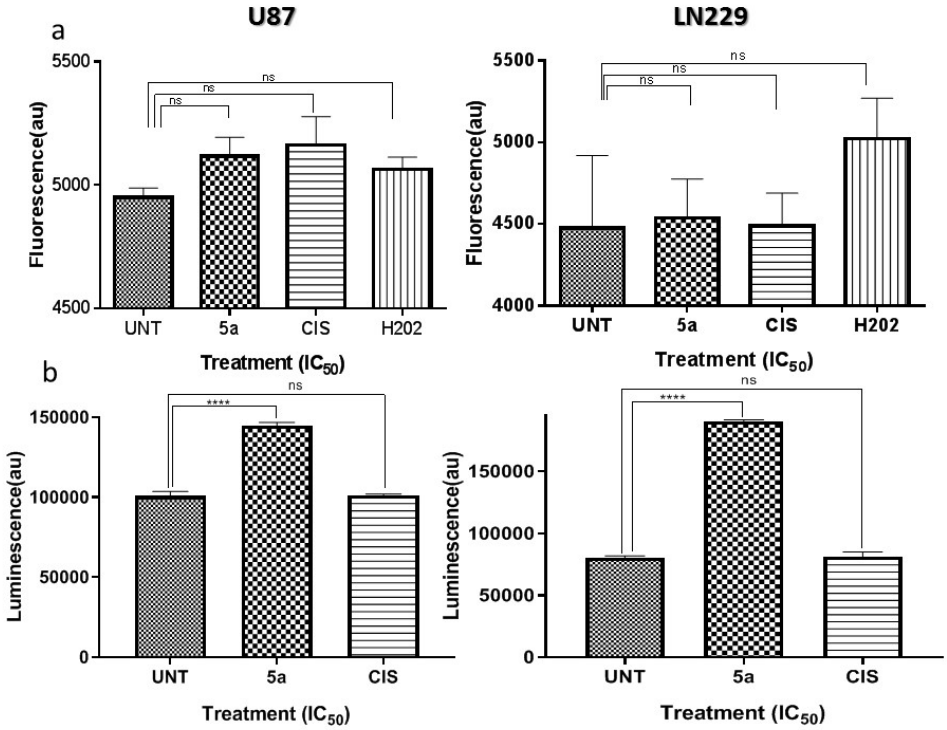


Figure 2. Comparative evaluation of oxidative stress response and caspase activation by the **5a** in two different cell lines (**a**) Effect of **5a** on intracellular reactive oxygen species (ROS) production by GB cells as interpreted by fluorescence level. Evaluation suggested no significant increase in ROS level upon drug treatment ($\alpha = 0.05$). (**b**) Caspase activity displayed by GB cells analyzed using caspase 3/7 luminescence assay. Significant increase in caspase activity of cells was observed after treatment with IC_{50} of **5a** for 5h compared to control. The values are expressed as means ± standard error of the mean (SEM) of triplicate measurements of biological repeats (n = 3). Significance: **** $p < 0.0001$.

Considering the role of Caspase activation, we determined the caspase activity of U87 cells using caspase3/7 assay after a treatment period of 5 h with **5a** at IC_{50}. Interestingly, U87 **5a**-treated cells displayed an increase of caspase 3/7, displaying a 0.43-fold increase in comparison to untreated cancer cells, whereas positive control displayed no significant increase (0.003) in caspase activity (Figure 2b). Similarly, in LN229 cells **5a**-treated cells demonstrated 1.37-fold increase with respect to untreated cells, whereas the standard drug cisplatin exhibited 0.05 fold increase in caspase levels. The difference between treated and untreated conditions was confirmed to be statistically significant per ANOVA test (p-value < 0.05).

*3.4. **5a** Enhanced Apoptosis and Cell Cycle Arrest*

Defective apoptotic machinery enhances tumor pathogenesis by permitting survival of genetically unstable cells leading to treatment resistance. To understand if the decrease in viability was due to apoptosis, we treated U87 cells with IC_{50} of 5a and we determined the apoptosis effect using double staining method.

The results revealed that **5a** was much effective in inducing apoptosis exhibiting a 3.75-fold increase in programmed cell death, whereas the standard drug cisplatin induced a 1.7-fold increase when compared to untreated cells (Figure 3a,b). To explore in detail the effect of 5a transcriptomics, data analysis was carried out, and we identified 1148 differentially expressed genes (DEGs) when **5a** is compared with untreated (negative control) samples (q-value < 0.05). We also compared the **5a** and cisplatin samples as a positive control group, both individually and combined as a single "affected" group. In these comparisons, 3132 DEGs were identified, with the largest number of DEGs identified in comparison with the cisplatin samples. In total, 595 out of 4280 DEGs were common in both comparisons. The complete lists of DEGs from the cell line analysis and all pairs of comparisons are provided in Supplementary file 2. Gene expression analysis indicated that **5a** has a multidimensional impact on various tumorogenic features, especially on tyrosine kinase signaling (Figures 4 and 5a) and was effective in increasing expression of agonists of cell death such as *DKK1*, *ADM*, *HMGA2*, and *CAV1*. In addition, downregulation of chemoprotective factors such as *HMOX1*, *HSPs*, and *CYP1B1* were detected. Adding to its cytotoxic effects, **5a** was also found to suppress mitochondrial membrane stability as evident by dysregulated levels of *HSPA1A* and *BNIP3*.

Gene expression analysis also points out that treatment of U87 cells with **5a** leads to inhibition of G1/S transition leading to cell cycle arrest. Upregulation of cell cycle inhibitory genes involved in G1/S such as *DACT1*, *SUSD2*, and *CTDSP1* signifies the efficiency of the drug as a cell cycle inhibitor (Figure 5c). Additionally, genes favoring G1/S transition such as *PLRG1* and *ADAM17* were effectively downregulated due to **5a** treatment. The cell cycle interruption is further strengthened by suppression of *CCND3* affecting the *CDK4* activity associated with this cyclin, which is necessary for cell cycle progression. Several studies have proposed that agents that interfere with DNA repair can act as a therapeutic strategy targeting double-strand break repair pathways or abrogate cell cycle checkpoints. *HMGA2* gene involved in negative regulation of double-strand break repair via non-homologous end joining was found to be risen upon the treatment with **5a** demonstrating its genotoxicity leading to the apoptotic death of cancer cells. Additionally, notable chemo-sensitizing was visible in treated cells as evident from transcriptome levels of *HSPA1*, *CLU*, and *TXN* (Table 1).

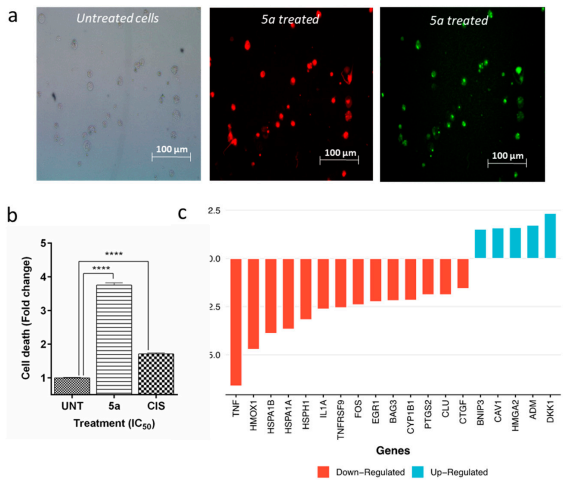


Figure 3. Evaluation of apoptotic activity induced by **5a**. (**a**). Phase contrast image of non-apoptotic cells in untreated condition (left); fluorescence image of U87 cells exhibited upon PI (middle) and Annexin V (right) staining. **5a** was found to effectively induce apoptotic cell death when compared to untreated cells. (**b**) The histogram represents quantification of apoptosis after treating the cell lines with IC_{50} of **5a**, for 48 h, in U87 cell line. Cisplatin was used as a positive control and untreated cells as negative control. The fold change of apoptosis has been calculated against untreated U87 cells. The values are expressed as means ± standard error of the mean (SEM) of triplicate measurements of biological repeats (n = 3). **** $p < 0.0001$ as produced by ANOVA test. (**c**) Key genes involved in Apoptotic process and their log2(fold-change), that are differentially expressed upon R114 treatment, compared to untreated. log 2(fold-change) cutoff = 1.5.

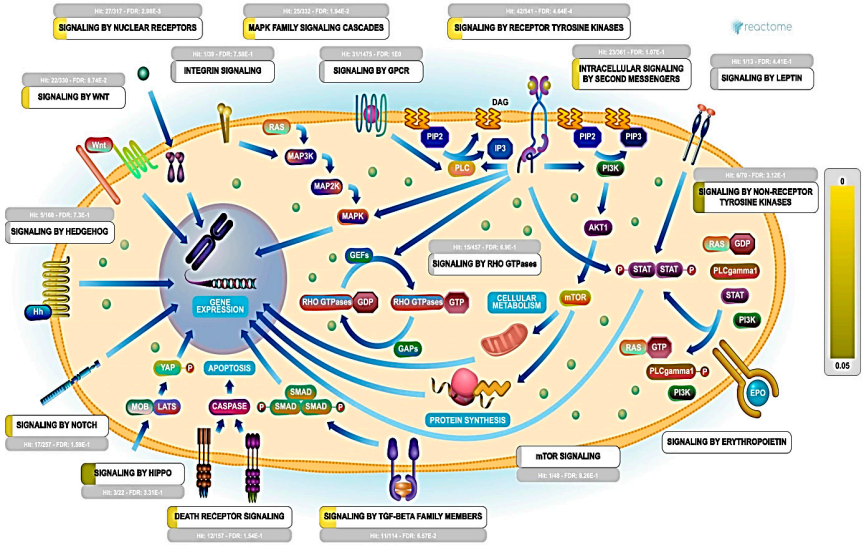


Figure 4. Representation of DEGs in major signal transduction pathways, in **5a** treated cells. The color code denotes over-representation of that pathway by DEGs. FDR represents the corrected over-representation probability. Color scale denotes the proportion of entities identified among the total entities enriched in a pathway (Image generated via the reactome pathway analysis tool; https://reactome.org/PathwayBrowser/).

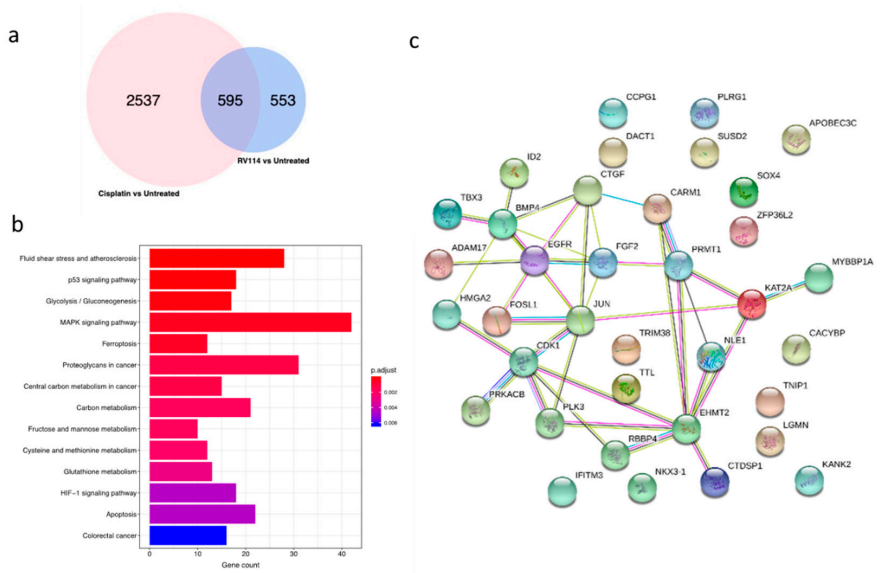


Figure 5. Transcriptional profile of **5a** compared to standard drug (**a**) Venn diagram showing 595 genes commonly differentially expressed in both treatments versus control, as assessed by RNA-seq data analysis of U87 cell line. (**b**) Visual representation of top 14 pathways associated with differentially expressed genes upon **5a** treatment with reference to control. (**c**) Gene interaction network of cell cycle genes affected upon **5a** treatment.

Table 1. Key genes affected by the top drug-like compound.

Key Genes Dysregulated in Major Pathways						
Signalling Pathways	**MAPK**	**TNF**	**PI3K-Akt**	**STAT**	**ErbB**	**NF-kB**
	AREG CASP3 CRK	CASP3 FOS IL15	AREG CCND3 CDKN1A	CCND3 CDKN1A IL15	AREG CDKN1A CRK	BCL10 IL1R1 PTGS2
Downregulated genes	FGF2 FOS	IL18R1 JUN	FGF2 MCL1	MCL1 STAT1	HBEGF JUN	RIPK1 TNF
	IL1A IL1R1 JUN LAMTOR3 PGF TNF	JUNB PTGS2 RIPK1 TNF	PGF SGK1 THBS1			
Upregulated genes	DUSP6 EGFR EPHA2 MET MYC PDGFA PDGFB RPS6KA5 STMN1 TGFA VEGFA BMP4 RASA3	JAG1 LIF RPS6KA5	BCL2L1 EGFR EPHA2 F2R GNG4 IRS1 ITGA6 MET MYC PDGFA PDGFB TGFA VEGFA	BCL2L1 EGFR LIF MYC PDGFA PDGFB PTPN2	EGFR MYC TGFA	BCL2L1

3.5. 5a Is an Anti-Angiogenic Agent

To gain more insight on anti-angiogenic efficacy of **5a**, we analyzed the modulation of genes in U87 glioma cells treated with the investigative drug. **5a** was found to adversely affect the cytokine receptor pathway exerting its effect through interaction of multiple pathways, eventually downregulating *VEGF* expression. *VEGFD* itself exhibited a $\log_2$ (fold change) of −4.5. Other key genes (*TNF*, *HMOX*, *IL1A*, *CYP1B1*, and *PTGS1*) involved in positive regulation of *VEGF* were identified to be downregulated by more than 1.75-fold. Key genes involved in inhibition of angiogenesis, including *NR2F1*, *SEM3A*, *ERRFI1*, *SPRY1*, *ADM*, *NRP1*, etc., were found to be upregulated ($\log_2$ (fold change) > 1.5). Moreover, enhancers of migration and angiogenesis such as *GPNMB*, *PTGS2*, *CD274*, and *ZNF703* were significantly downregulated suggesting suppression of tumor malignancy (Table 1 and Supplementary file 2).

5a advocates inhibition of angiogenesis targeting VEGF pathway, via multiple pro-angiogenic regulators. The mRNA levels of *VEGF* were markedly decreased in the U87 cells treated with the IC_{50} concentrations of **5a**. Moreover, other angiogenic enhancers such as *HMOX1*, *IL1A*, *CYP1B1 PGF*, and *FGF* were effectively suppressed by **5a**. Additionally, such a molecule potentially weakened angiogenesis by affecting pathways involved in the crosstalk by interrupting key regulators involved. The phosphorylation of multiple kinase proteins involved in the VEGF signaling pathway were quantified using immunoblotting. The upregulation of *CREB*, *GSK-3α/β*, *GSK-3β*, *MSK2*, *p38α*, *p38γ*, and *p53* and down regulation of *JNK1* validates that the VEGF pathway might be targeted by **5a** (Figure 6a–c).

3.6. 5a Restricts MAPK Signaling Cascade and Downregulates TNF Expression

Activation of the MAPK pathway leads to the transcription of genes that encode proteins involved in the regulation of essential cellular functions, such as cell growth, cell proliferation, and cell differentiation [25]. U87 glioma cells treated with IC_{50} concentrations of **5a** exhibited downregulation of positive regulators of MAPK pathway such as *GADDs*, *RIPK*, *CTNNB1* and *PSAP*, whereas, it enhanced the expression of inhibitors of MAPK signaling such as *MYC*, *SPRY1*, *EZR*, *RASA3* and *CAV1*. Additionally, **5a** reduced the expression of activators of ERK cascade (*TNF*, *CTGF*, *FGF*, *JUN*) and enhanced its negative modulators such as *C1QL4* and *TNIP1* (Figure 5b, Table 1 and Supplementary file 2). *TNF* exerts its biological functions by activating distinct signaling pathways such as nuclear factor κB (*NF-κB*) and c-Jun N-terminal kinase (*JNK*). We observed a significant reduction of TNF levels in 5a treated cells compared to untreated cells. Inhibitors of TNF production like *ERRIF1*, *RARA*, *VSIR* and *AXL* were found to be overexpressed explaining the reduction in TNF level. Additionally, immunoblotting revealed the phosphorylation of *CREB*, *p38*, *JNK* proteins involved in MAPK/TNF signaling pathway. The relative higher-level expression of *CREB*, *p38* and reduced expression of *JNK* protein, also validates the inhibition of MAPK signaling cascade by **5a** in U87 cells (Figure 6a–c).

3.7. 5a Negatively Affects JAK-STAT Pathway

The direct and mediated mechanisms of JAK-STAT signaling in tumor cell survival, proliferation, and invasion have made the JAK-STAT pathway a feasible target for drug development and cancer therapy. Interactions of JAK/STAT pathway with the RTK/Ras/MAPK pathway, TGF- β signaling pathway and PI3K pathway amplifies the effect mediated through the regulation of JAK-STAT signaling [26]. The current study revealed that **5a** is a strong suppressor of JAK-STAT pathway causing notable downregulation of major and downstream genes such as *STAT1*, *MCL1*, *CCND3*, *CDKN1A*, and *IL15* (Table 1 and Supplementary file 2). Upregulation of *PTPN2*, an inhibitor of *JAK* expression was observed, which is also a contributor of endoplasmic reticulum stress-induced intrinsic apoptotic signaling pathway. Additionally, upregulation of *CAV1* and *HMGA* was identified explaining the downregulation of JAK-STAT pathway. Phosphorylation analysis of multiple kinases shows the upregulation of *CREB* and *p38* proteins, suggesting a role of **5a** in inhibiting JAK-STAT signaling pathway (Figure 6a–c).

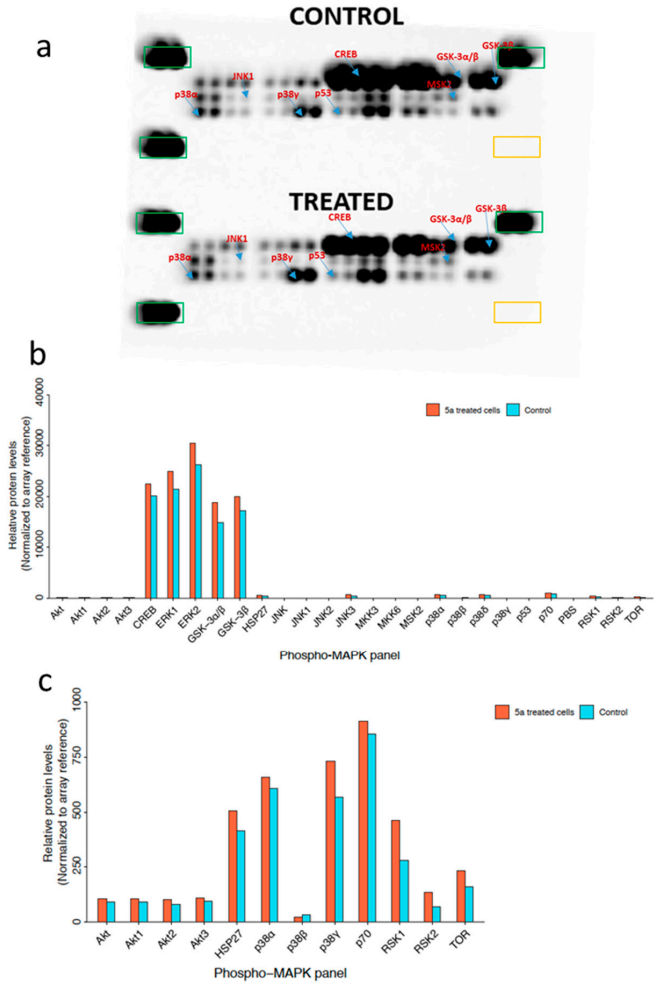


Figure 6. Analysis of phosphor–MAPK array. (**a**) The array images are shown for both DMSO control and **5a** treated cells and the eight phosphorylated proteins are marked in blue arrow. Positive reference spots are represented in green box and the negative reference spot (PBS) is represented in yellow box. (**b**) The complete set of *MAPKs* was presented according to the relative level of intensity of phosphorylation. (**c**) Absolute values of integrated pixel intensity of a few kinases are displayed for better resolution.

Several cross-family interactions among tyrosine kinases may significantly alter angiogenic signaling, leading to anti-angiogenic drug resistance. Reports say *FGF*-driven angiogenesis is blocked by *VEGF* inhibition, which suggests that *FGF* controls angiogenesis upstream of *VEGF* by modulating *VEGF* function [27]. Additionally, in the case of glioma tumorigenesis, *PDGF*- expression is assumed to contribute to the expansion of an established tumor as well as the regulation of the angiogenic switch for initial tumor development [28]. Studies also testify that there are cross family interactions between *VEGF* and *PDGFR* [29]. In addition, *cKIT* and *MET* are another two important *RTKs* to be explored as angiogenic drivers [30]. c-KIT signaling promotes cell proliferation and survival, exerting its effect through Ras-Erk pathway as well as JAK/STAT pathway [31]. Chen et al. asserted that intracrine *VEGF* function can be regulated by MET signaling and plays a significant role in controlling *VEGFR2* [32].

In this context, we sought to explore interactions between promising orthothioester 5a and six different tyrosine kinase receptors-*FGFR*, *EGFR*, *PDGFR*, *c-MET*, *cKIT*, and *VEGFR-2*, by in silico docking study. The results show that the Epidermal growth Factor Receptor shows good binding efficiency with thioester with high docking score (7256) (Figure 7a). The two-dimensional ligand interaction diagram of thioester with *EGFR* is shown in Figure 7b. Conclusively, our study evidences a multidimensional anti-tumor effect of the novel thioester drug **5a**.

a

S.No	RECEPTORS	Patchdock Score
1	FGFR	5712
2	EGFR	7256
3	PDGFR	5094
4	c-MET	6194
5	cKIT	6890
6	VEGFR2	4700

b

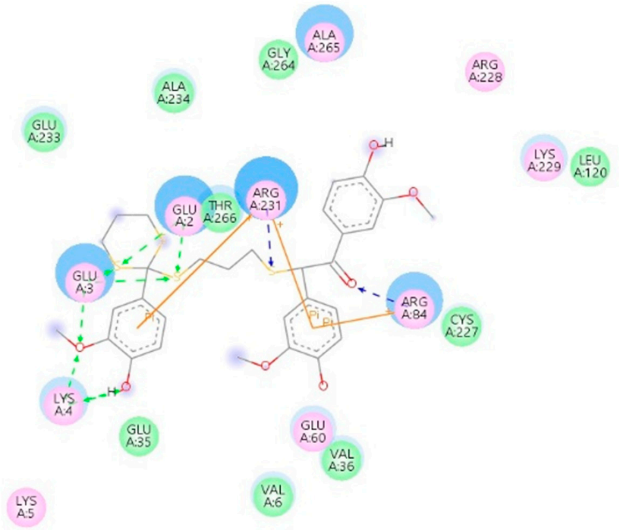


Figure 7. Docking score of **5a** with various kinase receptors (**a**) Docking analysis of various cytokine receptors (Fibroblast Growth Factor receptor—*FGFR*, PDB ID: 2FDB, Epidermal growth Factor Receptor—*EGFR*, PDB ID: 4UIP, Platelet-Derived Growth Factor Receptor—*PDGFR*, PDB ID: 1PDG, c-MET Receptor, PDB ID: 3DKC, *c-KIT* Receptor- PDB ID: 6GQK, and Vascular Endothelial Growth Factor receptors PDB ID: 3V2A) with **5a**. Docking study was carried out using the Patchdock program. (**b**) 2-dimensional interaction diagram of EGFR with ligand.

3.8. ***5a*** *Induced Phosphorylation of MAPKs and Other Serine/Threonine Kinases*

The effect of **5a** on the phosphorylation levels of three families of *MAPKs*, such as *ERK1/2*, *JNK1–3* and different p38 isoforms, was analyzed. The arrays used in the experiments are based on the analysis of kinase specific antibodies which are spotted in duplicates along with three reference spots and PBS as negative spots. The mixture of biotinylated anti-phospho-kinase antibodies and streptavidin-HRP conjugate differentiates the phosphorylated and non-phosphorylated protein between the control and **5a** treated cells. The luminescence induced by the addition of chemiluminescence reagent was captured using the ChemiPro detection system (Figure 6a). In detail, the relative levels of phosphorylation of 26 kinases such as *Akt1*, *Akt2*, *Akt3*, *Akt*, *CREB*, *ERK1*, *ERK2*, *GSK-3α/β*, *GSK-3β*, *HSP27*, *JNK1*, *JNK2*, *JNK3*,

JNK, *MKK3*, *MKK6*, *MSK2*, *p38α*, *p38β*, *p38δ*, *p38γ*, *p53*, *p70*, *RSK1*, *RSK2*, and *TOR* (Figure 7b) were analyzed. The phosphorylation level of *CREB* (Ser^{133}), *GSK-3α/β* (Ser^{21}/Ser^{9}), *GSK-3β* (Ser^{9}), *MSK2* (Ser^{360}), *p38α* (Thr^{180}/Tyr^{182}), *p38γ* (Thr^{183}/Tyr^{185}) and *p53* (Ser^{46}) were significantly increased in 5a treated U87 cells, whereas the phosphorylation level for *JNK1* (Thr^{183}/Tyr^{185}) was found to be reduced relative to the control (Figure 6c). The results suggest that the EGFR signaling pathway was suppressed by **5a**, which is confirmed by the phosphorylation of not only the *MAPKs* and other serine threonine kinases. Thus, the **5a** suppression of *EGFR* further substantiates that 5a as TK inhibitor.

4. Discussion

In order to challenge tumor recurrence and resistance of GB, agents that can synergistically confront multiple oncogenic pathways are gaining great importance in GB drug discovery. In a pursuit to identify a multi-targeted chemo-agent against glioblastoma, we assessed bioactivity of a panel of new orthothioester derivatives as anti-GB agents in vitro.

Cytotoxicity evaluation identified an orthothioester **5a**, which has inhibited tumor cell growth in a dose-dependent manner in GB cell lines. In addition, it displayed a more effective anti-tumor activity than current standard drug cisplatin in both GB cell lines U87 and LN229. Gene expression profiling revealed that this effect is due to the suppression of multiple kinase signaling pathways regulating *VEGF* levels in GB cells suggesting the possible anti-angiogenic effect. Additionally, inhibition of *HMOX1* abrogates VEGF-induced endothelial activation and subsequent angiogenesis [33]. A robust silencing of *HMOX1* observed in our study convinces curbing of VEGF-induced pathogenic angiogenesis.

Virtual binding studies using bioinformatics tools suggests *EGFR* as a key target of **5a**, exerting its effect through multiple pathways leading to the inhibition of angiogenesis, cell cycle arrest, and apoptosis. Considering previous reports that *EGFR* can activate β-catenin via receptor tyrosine kinase-PI3K/Akt pathway [34], inhibitory ligand binding on *EGFR* is expected to diminish WNT signaling. Our observation of weakened expression of *CTNNB1* and other positive regulators of WNT pathway (*DAB2*, *GSKIP*) corresponds to this notion.

The candidate drug **5a** seems to be an attractive anti-angiogenic agent acting beyond VEGF/VEGFR pathway. Notable downregulation of growth factors (*VEGFD*, *FGF2*, *PGF*, *TNF-α*) and *cytokine IL-1A* was observed in tumor cells upon treatment with 5a. FGF can act synergistically with *VEGF* to amplify tumor angiogenesis and are implicated in the emerging phenomenon of resistance to VEGF inhibition. FGFs have been reported to have potent proangiogenic effects through the stimulation and release of other proangiogenic factors [35]. **5a** was found to effectively reduce *FGF* levels, causing a synergistic anti-angiogenic effect as well as increased sensitization to *VEGF* suppression. Additionally, potent inhibition of *TNF-α* by **5a** may also contribute to its anti-angiogenic impact. Though *TNF* is widely promoted as a antineoplastic agent, its dual role as a angiogenesis promoter and inhibitor has been discussed in multiple reports [36–38]. A study by Giraudo et al. discussed the *VEGF* mediated role of *TNF-α* in the initiation and maintenance of angiogenesis and increased vascular permeability [39]. Furthermore, the investigative drug also effectively induced chemo-sensitization by suppressing stress proteins such as *HSPs, CLU, SNAI1, PTGS2,* and *MCL1*. Taken together, we postulate **5a** as a multi-targeted agent against GB signaling pathway and highlighting its significance as anti-tumor agent. Additionally, **5a** exerts its cytostatic effect via key genes involved in regulation of cell cycle pathways as observed in our experimental results. The present research thus suggests **5a** as a candidate GB chemotherapeutic with multiple anti-cancer properties.

5. Conclusions

Drugs that can act as multi-targeted agents can enhance efficacy and confront chemoresistance exhibited by GB cells. Thioesters has been investigated as an antitumor agent in multiple studies [40,41]. The present study validates potential of a novel orthothioester **5a**, as an excellent pharmacological scaffold possessing strong cytotoxic, anti-angiogenic, and chemo-sensitization activity. The compound **5a** exerted extensive killing effects on two different glioma cell lines by effectively weakening resistance

pathways and enhancing apoptotic machinery. Additionally, **5a** is a strong cytostatic agent acting on key genes involved in regulation of cell cycle pathways. In particular, the capability of **5a** to impede various pathogenic signaling cascades leading to GB pathogenesis, by acting on multiple tyrosine kinase pathways, makes it an appealing anti-GB agent. Taken together, our report provides new insights on how underexplored thioester derivatives can act as a potent pharmacological scaffold against glioblastoma.

Supplementary Materials: The following are available online at http://www.mdpi.com/2073-4409/8/12/1624/s1: NMR spectroscopy results of previously unreported compounds are attached as Supplementary file 1. List of differentially expressed genes and pathway analysis are attached as Supplementary file 2.

Author Contributions: J.R.V., C.A.M.A., and N.R.C. synthesized and characterized the compounds and A.V. executed the experiments and data analysis. S.K.M. executed docking studies. A.M (Akshaya Murugesan) executed protein studies. A.M. (Aliyu Musa) analyzed RNA-seq data. O.Y.-H. and M.K. conceived and managed all studies. All the authors contributed to writing the manuscript.

Funding: M.K., A.V., and O.Y.H. acknowledge the Academy of Finland for the project grant support (decision no. 297200) and Tampere University of Technology for Instrumental facility grant support. N.R.C. acknowledges the Academy of Finland (decision no. 287954) for the financial support. FCT is acknowledged for financial support to J.R.V., (SFRH/BD/120119/2016)

Acknowledgments: We thank Rahul Mangayil and Ville Santala for providing the access to Fluorescence Plate reader instrumental facility at Tampere University.

Conflicts of Interest: The authors declare that they have no conflicting interests.

Abbreviations

GB	Glioblastoma
TKI	Tyrosine Kinase Inhibitor
RTK	Receptor Tyrosine Kinases
ROS	Reactive Oxygen Species
GO	Gene Ontology
TLC	Thin-Layer Chromatography
DCM	Dichloromethane
TCF	Tetrahydrofuran
DE	Differential expression
DEG	Differentially expressed gene

References

1. Ferrara, N.; Gerber, H.P.; LeCouter, J. The biology of VEGF and its receptors. *Nat. Med.* **2003**, *9*, 669. [CrossRef]
2. Fuchs, C.S.; Tomasek, J.; Yong, C.J.; Dumitru, F.; Passalacqua, R.; Goswami, C.; Safran, H.; Dos Santos, L.V.; Aprile, G.; Ferry, D.R.; et al. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): An international, randomised, multicentre, placebo-controlled, phase 3 trial. *Lancet* **2014**, *383*, 31–39. [CrossRef]
3. Ferrara, N.; Hillan, K.J.; Gerber, H.P.; Novotny, W. Discovery and development of bevacizumab, an anti-VEGF antibody for treating cancer. *Nat. Rev. Drug Discov.* **2004**, *3*, 391. [CrossRef] [PubMed]
4. Holash, J.; Davis, S.; Papadopoulos, N.; Croll, S.D.; Ho, L.; Russell, M.; Boland, P.; Leidich, R.; Hylton, D.; Burova, E.; et al. VEGF-Trap: A VEGF blocker with potent antitumor effects. *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 11393–11398. [CrossRef] [PubMed]
5. Maire, C.L.; Ligon, K.L. Molecular pathologic diagnosis of epidermal growth factor receptor. *Neuro. Oncol.* **2014**, *16*, viii1–viii6. [CrossRef] [PubMed]
6. Mizoguchi, M.; Betensky, R.A.; Batchelor, T.T.; Bernay, D.C.; Louis, D.N.; Nutt, C.L. Activation of STAT3, MAPK, and AKT in malignant astrocytic gliomas: Correlation with EGFR status, tumor grade, and survival. *J. Neuropathol. Exp. Neurol.* **2006**, *556*, 1181–1188. [CrossRef] [PubMed]
7. Tabernero, J. The Role of VEGF and EGFR Inhibition: Implications for Combining Anti-VEGF and Anti-EGFR Agents. *Mol. Cancer Res.* **2007**, *5*, 203–220. [CrossRef]

8. Pennell, N.A.; Lynch, T.J. Combined Inhibition of the VEGFR and EGFR Signaling Pathways in the Treatment of NSCLC. *Oncologist* **2009**, *14*, 399–411. [CrossRef]
9. Mori, K.; Tani, M.; Kamata, K.; Kawamura, H.; Urata, Y.; Goto, S.; Kuwano, M.; Shibata, S.; Kondo, T. Mitogen-activated protein kinase, ERK1/2, is essential for the induction of vascular endothelial growth factor by ionizing radiation mediated by activator protein-1 in human glioblastoma cells. *Free Radic. Res.* **2000**, *33*, 157–166. [CrossRef]
10. Xie, T.; Wei, D.; Liu, M.; Gao, A.C.; Ali-Osman, F.; Sawaya, R.; Huang, S. Stat3 activation regulates the expression of matrix metalloproteinase-2 and tumor invasion and metastasis. *Oncogene* **2004**, *23*, 3550. [CrossRef]
11. Chen, Z.; Zhong, C.H. STAT3: A critical transcription activator in angiogenesis. *Med. Res. Rev.* **2008**, *28*, 185–200. [CrossRef] [PubMed]
12. Jiang, B.H.; Liu, L.Z. PI3K/PTEN signaling in tumorigenesis and angiogenesis. *Biochim. Biophys. Acta Proteins Proteomics* **2008**, *1784*, 150–158. [CrossRef] [PubMed]
13. Vale, J.R.; Rimpiläinen, T.; Sievänen, E.; Rissanen, K.; Afonso, C.A.M.; Candeias, N.R. Pot-economy autooxidative condensation of 2-Aryl-2-lithio-1,3-dithianes. *J. Org. Chem.* **2018**, *83*, 1948–1958. [CrossRef] [PubMed]
14. Sestito, S.; Runfola, M.; Tonelli, M.; Chiellini, G.; Rapposelli, S. New multitarget approaches in the war against glioblastoma: A mini-perspective. *Front. Pharmacol.* **2018**, *9*, 874. [CrossRef]
15. Doan, P.; Musa, A.; Candeias, N.R.; Emmert-Streib, F.; Yli-Harja, O.; Kandhavelu, M. Alkylaminophenol induces G1/S phase cell cycle arrest in glioblastoma cells through p53 and cyclin-dependent kinase signaling pathway. *Front. Pharmacol.* **2019**, *10*, 330. [CrossRef]
16. Chowdhury, S.; Kandhavelu, M.; Yli-Harja, O.; Ribeiro, A.S. An interacting multiple model filter-based autofocus strategy for confocal time-lapse microscopy. *J. Microsc.* **2012**, *245*, 265–275. [CrossRef]
17. Vaiyapuri, P.S.; Ali, A.A.; Mohammad, A.A.; Kandhavelu, J.; Kandhavelu, M. Time lapse microscopy observation of cellular structural changes and image analysis of drug treated cancer cells to characterize the cellular heterogeneity. *Environ. Toxicol.* **2015**, *30*, 724–734. [CrossRef]
18. Love, M.I.; Huber, W.; Anders, S. Moderated estimation of fold change and dispersion for RNA-seq data with DESeq2. *Genome Biol.* **2014**, *15*, 550. [CrossRef]
19. Benjamini, Y.; Hochberg, Y. Controlling the false discovery rate: A practical and powerful approach to multiple testing. *J. R. Stat. Soc. Ser. B* **1995**, *57*, 289–300. [CrossRef]
20. Ashburner, M.; Ball, C.A.; Blake, J.A.; Botstein, D.; Butler, H.; Cherry, J.M.; Davis, A.P.; Dolinski, K.; Dwight, S.S.; Eppig, J.T.; et al. Gene ontology: Tool for the unification of biology. *Nat. Genet.* **2000**, *25*, 25. [CrossRef]
21. Yu, G.; Wang, L.-G.; Han, Y.; He, Q.-Y. clusterProfiler: An R Package for Comparing Biological Themes Among Gene Clusters. *Omi. A J. Integr. Biol.* **2012**, *16*, 284–287. [CrossRef] [PubMed]
22. Ogata, H.; Goto, S.; Sato, K.; Fujibuchi, W.; Bono, H.; Kanehisa, M. KEGG: Kyoto encyclopedia of genes and genomes. *Nucleic Acids Res.* **1999**, *28*, 27–30. [CrossRef] [PubMed]
23. Izeradjene, K.; Douglas, L.; Tillman, D.M.; Delaney, A.B.; Houghton, J.A. Reactive oxygen species regulate caspase activation in tumor necrosis factor-related apoptosis-inducing ligand-resistant human colon carcinoma cell lines. *Cancer Res.* **2005**, *65*, 7436–7445. [CrossRef] [PubMed]
24. Chanvorachote, P.; Nimmannit, U.; Azad, N.; Wang, L.; Moungjaroen, J.; Lipipun, V.; Rojanasakul, Y.; Callery, P.S. Reactive Oxygen Species Mediate Caspase Activation and Apoptosis Induced by Lipoic Acid in Human Lung Epithelial Cancer Cells through Bcl-2 Down-Regulation. *J. Pharmacol. Exp. Ther.* **2006**, *319*, 1062–1069.
25. Kim, E.K.; Choi, E.J. Pathological roles of MAPK signaling pathways in human diseases. *Biochim. Biophys. Acta Mol. Basis Dis.* **2010**, *1802*, 396–405. [CrossRef]
26. Moustakas, A.; Ardley, H.C. Smad signalling network. *J. Cell Sci.* **2002**, *115*, 3355–3356.
27. Murakami, M.; Simons, M. Fibroblast growth factor regulation of neovascularization. *Curr. Opin. Hematol.* **2008**, *15*, 215. [CrossRef]
28. Plate, K.H.; Breier, G.; Farrell, C.L.; Risau, W. Platelet-derived growth factor receptor-beta is induced during tumor development and upregulated during tumor progression in endothelial cells in human gliomas. *Lab. Investig.* **1992**, *67*, 529–534.

29. Mamer, S.B.; Chen, S.; Weddell, J.C.; Palasz, A.; Wittenkeller, A.; Kumar, M.; Imoukhuede, P.I. Discovery of High-Affinity PDGF-VEGFR Interactions: Redefining RTK Dynamics. *Sci. Rep.* **2017**, *7*, 16439. [CrossRef]
30. Stankov, K.; Popovic, S.; Mikov, M. C-KIT signaling in cancer treatment. *Curr. Pharm. Des.* **2014**, *20*, 2849–2880. [CrossRef]
31. Abbaspour Babaei, M.; Kamalidehghan, B.; Saleem, M.; Huri, H.Z.; Ahmadipour, F. Receptor tyrosine kinase (c-Kit) inhibitors: A potential therapeutic target in cancer cells. *Drug Des. Devel. Ther.* **2016**, *10*, 2443–2459. [CrossRef] [PubMed]
32. Chen, T.T.; Filvaroff, E.; Peng, J.; Marsters, S.; Jubb, A.; Koeppen, H.; Merchant, M.; Ashkenazi, A. MET Suppresses Epithelial VEGFR2 via Intracrine VEGF-induced Endoplasmic Reticulum-associated Degradation. *EBioMedicine* **2015**, *2*, 406–420. [CrossRef] [PubMed]
33. Bussolati, B.; Mason, J.C. Dual role of VEGF-induced heme-oxygenase-1 in angiogenesis. *Antioxid. Redox Signal.* **2006**, *8*, 1153–1163. [CrossRef] [PubMed]
34. Hu, T.; Li, C. Convergence between Wnt-β-catenin and EGFR signaling in cancer. *Mol. Cancer* **2010**, *9*, 236. [CrossRef] [PubMed]
35. Giavazzi, R.; Sennino, B.; Coltrini, D.; Garofalo, A.; Dossi, R.; Ronca, R.; Tosatti, M.P.M.; Presta, M. Distinct role of fibroblast growth factor-2 and vascular endothelial growth factor on tumor growth and angiogenesis. *Am. J. Pathol.* **2003**, *162*, 1913–1926. [CrossRef]
36. Madhusudan, S.; Foster, M.; Mathuramalingam, S.R.; Braybrooke, J.P.; Wilner, S.; Kaur, K.; Han, C.; Hoare, S.; Balkwill, F.; Talbot, D.C.; et al. A phase II study of etanercept (Enbrel), a tumor necrosis factor α inhibitor in patients with metastatic breast cancer. *Clin. Cancer Res.* **2004**, *10*, 6528–6534. [CrossRef]
37. Cordero, J.B.; Macagno, J.P.; Stefanatos, R.K.; Strathdee, K.E.; Cagan, R.L.; Vidal, M. Oncogenic ras diverts a host TNF tumor suppressor activity into tumor promoter. *Dev. Cell* **2010**, *18*, 999–1011. [CrossRef]
38. Nabors, L.B.; Suswam, E.; Huang, Y.; Yang, X.; Johnson, M.J.; King, P.H. Tumor necrosis factor α induces angiogenic factor up-regulation in malignant glioma cells: A role for RNA stabilization and HuR. *Cancer Res.* **2003**, *63*, 4181–4187.
39. Giraudo, E.; Primo, L.; Audero, E.; Gerber, H.P.; Koolwijk, P.; Soker, S.; Klagsbrun, M.; Ferrara, N.; Bussolino, F. Tumor necrosis factor-alpha regulates expression of vascular endothelial growth factor receptor-2 and of its co-receptor neuropilin-1 in human vascular endothelial cells. *J. Biol. Chem.* **1998**, *273*, 22128–22135. [CrossRef]
40. El-Azab, A.S.; Abdel-Aziz, A.A.M.; Abou-Zeid, L.A.; El-Husseiny, W.M.; ElMorsy, A.M.; El-Gendy, M.A.; El-Sayed, M.A.A. Synthesis, antitumour activities and molecular docking of thiocarboxylic acid ester-based NSAID scaffolds: COX-2 inhibition and mechanistic studies. *J. Enzyme Inhib. Med. Chem.* **2018**, *33*, 989–998. [CrossRef]
41. Ashizawa, T.; Kawashima, K.; Kanda, Y.; Goml, K.; Okabe, M.; Ueda, K.; Tamaoki, T. Antitumor activity of KF22678, a novel thioester derivative of leinamycin. *Anticancer. Drugs* **1999**, *10*, 829–836. [CrossRef] [PubMed]

PUBLICATION IV

Functionalized Cyclopentenes via the Formal [4+1] Cycloaddition of Photogenerated Siloxycarbenes from Acyl Silanes

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Journal of Organic Chemistry, **2022**, *87*, 8910-8920

DOI: 10.1021/acs.joc.2c00591

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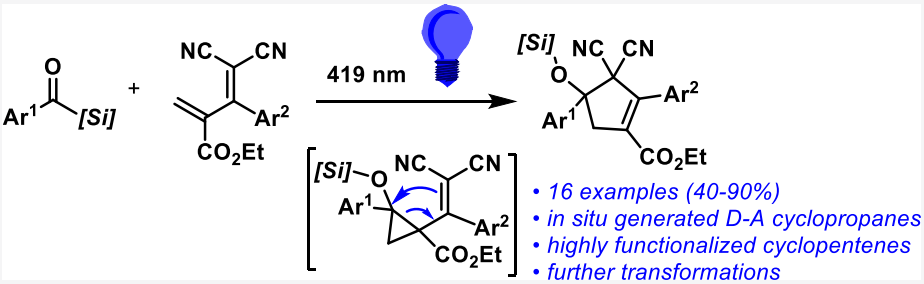


ABSTRACT: This work describes the first formal cycloaddition reaction of photogenerated nucleophilic carbenes derived from acylsilanes with electrophilic dienes. The resulting transient donor−acceptor cyclopropane rearranges to its stable and highly functionalized cyclopentene isomer in an unprecedented metal-free process. The cyclopropanation−vinyl cyclopropane rearrangement sequence was corroborated by computational calculations. The cyclopropane formation corresponds to a higher energetic barrier, and the vinylcyclopropane−cyclopentene rearrangement proceeds through different mechanisms, although of comparable energies, depending on the stereochemistry of the cyclopropane.

INTRODUCTION

Acylsilanes have recently attracted considerable attention in the field of organic synthesis mainly due to their ability to generate nucleophilic carbenes.[1−3] The metal-free UV−visible irradiation of acylsilanes presents an atom-efficient way to deliver siloxycarbenes upon a reversible 1,2-Brook rearrangement. Despite their clean production, these carbenes have seen limited applications due to their low reactivity and fast reversibility to the acylsilane precursor that can also undergo a homolytic cleavage.[4] The siloxycarbenes generated by the irradiation of acylsilanes can undergo a plethora of X−H insertions, such as O−H,[5] N−H,[6] S−H,[4] Si−H,[7,8] and B−H.[9] Although limited to its intramolecular version, C−H insertion of siloxycarbenes has been explored in the preparation of benzofurans,[10] while thermolytic methods proved synthetically nonuseful.[11,12] B−C insertion was also observed with organoboronic esters allowing an elegant photochemical transition metal-free cross-coupling.[13] The repertoire of reactions of siloxycarbenes also encompasses the nucleophilic addition to aldehydes,[14,50] trifluoromethyl ketones,[15] and carbon dioxide.[16]

Cyclopropanation, a classical carbene reaction,[17] is elusive due to the nucleophilic nature of the siloxycarbene. Activated alkynes have been shown to undergo slow inter- and intramolecular cyclopropenations following ring collapse to give β-silylated enones (Scheme 1),[18,19] while ambiphilic donor−acceptor carbenes derived from trifluoroacetylsilanes were recently explored.[53,54] Concerning olefins, only the highly electron-withdrawing dialkyl fumarate and maleate have been reported to undergo cyclopropanation,[20,21] yielding cyclopropyl silyl ethers that are prone to ring opening through hydrolysis and are therefore not synthetically useful for cyclopropane synthesis. Despite the preference for acylsilane carbonyl to react in a [2+2]-photocycloaddition reaction,[22,23] singlet nucleophilic carbenes with tethered olefins were recently shown to undergo rapid [2+1]-cycloaddition.[55] All in all, formal cyclopropanation of olefins with acylsilane-derived carbenes remains poorly explored due to the required presence of electron-withdrawing groups in the olefin which renders instability to the resulting silyl ether cyclopropanes. Recently, further advances on the topic rely heavily on transition metal catalysis. Cyclopropanation of nonactivated olefins using acylsilanes was achieved through palladium catalysis via a Fischer-type carbene complex without the involvement of a photogenerated siloxycarbene (Scheme 1, top).[24]

Received: March 14, 2022
Published: June 23, 2022

https://doi.org/10.1021/acs.joc.2c00591
J. Org. Chem. 2022, 87, 8910−8920

Scheme 1. Cycloaddition Reactions of Siloxycarbe

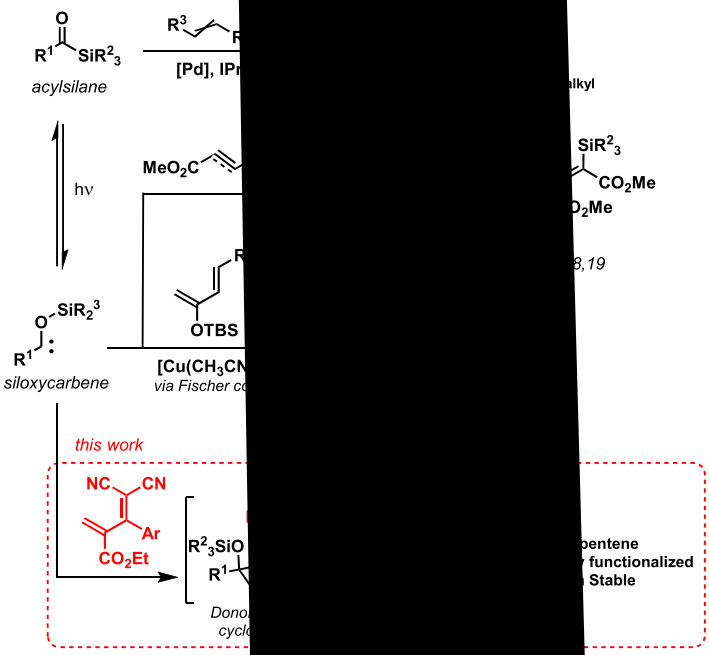
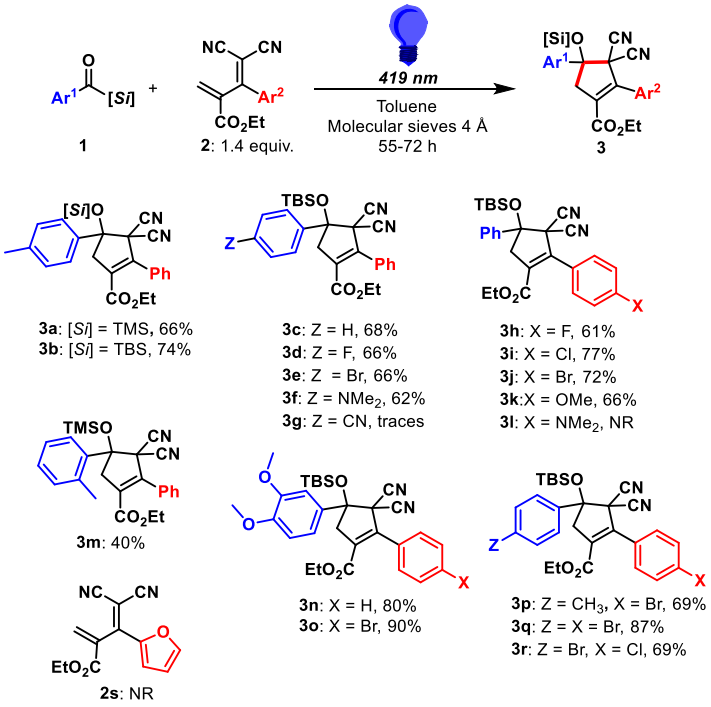


Table 1. Optimization of the Cyclopropanation−Vi **uence**

The formation of cyclopentenes through the interme ed by tuning the electronic nature of the diene. We siloxycarbenes was recently achieved via the umpolung oned that the reaction of an acylsilane-derived carbene (Scheme 1).[25] The photogenerated carbene complex an electron-withdrawing diene would lead to a donor− copper to form an electrophilic Fischer-type carbene th ceptor (D−A) cyclopropan[26−29] that would be a prone with highly electron-rich dienes in (4 + 1) cycloaddit andidate for a vinyl cyclopropane rearrangement,[30−32] circumventing the electronic mismatch between the tra ultimately forming a stable cyclopentene (Scheme 1, bottom). nucleophilic siloxycarbene and electron-rich cyclo Notwithstanding the reactivity of D−A cyclopropanes, the partner. Such findings led us to hypothesize that a m vinylcyclopropane−cyclopentene rearrangement usually re- strategy using acylsilanes to synthesize cyclopentenes c quires the presence of Lewis acids of variable strengths[33−36]

Scheme 2. Scope of the Cyclopropanation−Vinyl Cyclopropane Rearrangement Sequence



depending on the electronic nature of the cyclopropane substituents.

Dicyano-2-methylenebut-3-enoates have been previously used as electron-withdrawing dienes for the inverse-electron-demand Diels−Alder reactions,[37] and their terminal olefin was observed to undergo cyclopropanation with diazo compounds.[38] Hence, this highly electrophilic diene was considered a suitable candidate for the trapping of siloxycarbenes derived from benzoyl silanes.

RESULTS AND DISCUSSION

The studies were initiated using *p*-toluoyltrimethylsilane **1a** as a carbene precursor and diene **2a** in slight excess. Prolonged irradiation at 419 nm of a hexane/DCM solution gladly resulted in the domino production of cyclopentene **3** in a 20% yield (Table 1, entry 1), despite the absence of any Lewis acid catalyst. Additional measures taken to remove any traces of moisture, that is, using dry solvents and molecular sieves, proved futile, and *p*-tolualdehyde was the main side product.

Notably, no cyclopropane intermediate was isolated nor detected in the crude reaction mixture, indicating that the vinyl cyclopropane rearrangement is a highly favored process not requiring high temperatures or a catalyst. The use of dry toluene as a solvent and the addition of molecular sieves suppressed the aldehyde formation, and the increase in the amount of the diene to 2.8 equiv led to a cyclopentene **3** yield increasing to 70% (Table 1, entry 5). The amount of diene could be reduced by 1.4 equiv without significantly compromising the yield (Table 1, entry 6). As small amounts of the diallylated product **4** (Scheme 4) were detected in every experiment with **1a**, and suspecting the lability of the trimethylsilyl (TMS) group, benzoyl silane was decorated with a bulkier tert-butyldimethylsilyl (TBS). Despite the longer reaction times required to reach full conversion, the desilylated product was not detected, and **3b** was obtained in a slightly improved 74% yield (Table 1, entry 7). The cyclopentene structure was confirmed through X-ray diffraction analysis of product **3b** (see the Supporting Information). Irradiation of even bulkier benzoyl *t*-butyldiphenylsilane **1o** (Table 1, entry 9) led to no conversion and full recovery of the starting material. With the optimal reaction conditions cleared, we investigated the scope of the reaction by changing the aryl groups of the benzoyl silane and diene (Scheme 2). Para substitution within the aromatic ring of the benzoyl silane was well tolerated, allowing electron-donating (**3f**, **3n** and **3o**) and slightly electron-withdrawing substituents (**3d**, **3e**, **3q**, and **3r**). Meta- (**3n** and **3o**) and ortho- (**3m**) substitutions were also tolerated. Only the highly electron-withdrawing nitrile was unreactive toward the formation of cyclopentene **3g**, presumably due to the lower nucleophilicity of the generated carbene. Substitution on the aromatic ring of the diene was more challenging. Moderate electron-withdrawing groups such as halogens (**3h−3j** and **3p-r**) as well as electron-donating groups such as methoxy (**3k**) were compatible. However, highly electron-donating groups such as dimethylamine (**2l**) led to no reactivity, a result of its higher lowest unoccupied molecular orbital energy. Furan derivative **2s** was surprisingly unreactive. Nitro and nitrile derivatives would likely present suitable reactivity, as highly electron-withdrawing dienes, but their synthesis proved impossible with the used protocol.[37]

While the ring enlargement of cyclopropanes has been studied computationally for several systems,[39−41] similar studies for the expansion of vinylcyclopropanes containing an electron-

https://doi.org/10.1021/acs.joc.2c00591
J. Org. Chem. 2022, 87, 8910−8920

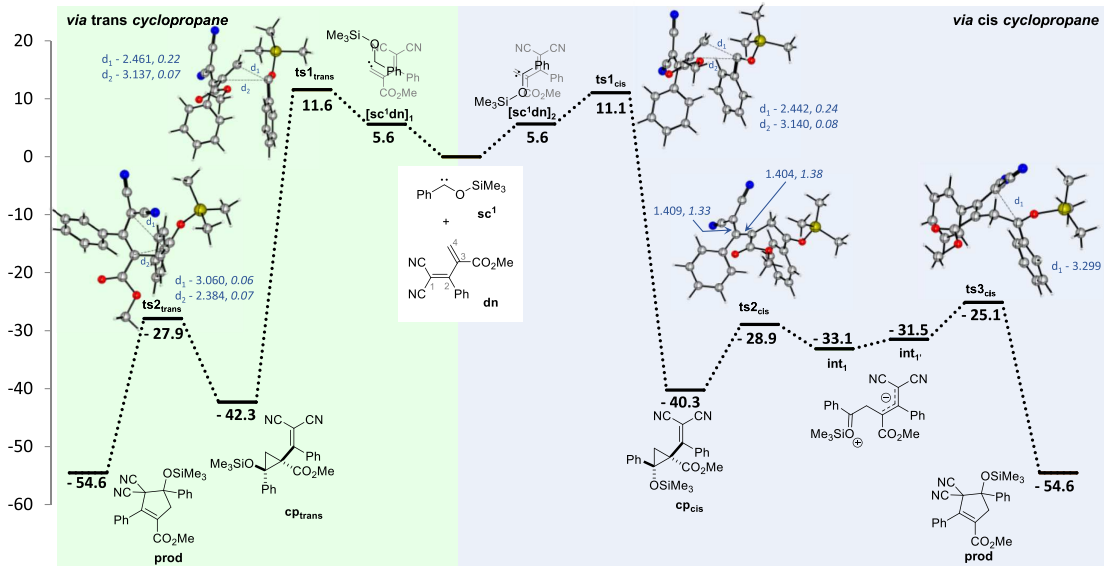
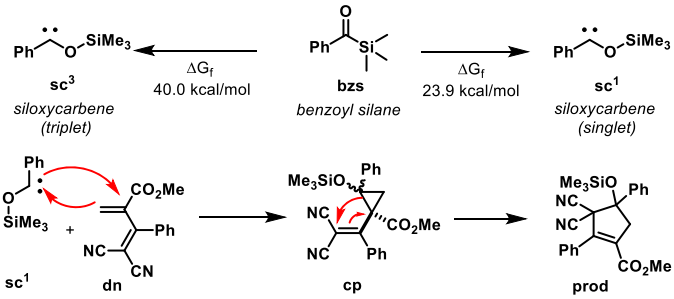


Figure 1. Free energy profile (M06-2X/6-311++G**//M06-2X/6-31+G**) and a mechanistic representation for the cyclopropanation rearrangement to cyclopentene of separated model substrates siloxycarbene **sc^1** and diene **dn**. The geometries of the minima and the transition states were optimized, and the energy values (kcal/mol) refer to the optimized **sc^1** and **dn** and include the thermal correction to Gibb's free energy in toluene. Bond lengths (in Å) and Wiberg indices (WIs; italics) of relevant bonds are presented.

Scheme 3. Thermodynamics of Benzoyl Silane-Derived Siloxycarbene Formation and Working Mechanism Investigated by DFT



deficient alkene remain elusive. Hence, mechanistic insights were obtained through computational calculations using density functional theory[42] (DFT) studies at the M06-2X/6-311++G (d, p)//M06-2X/6-31+G(d, p) level of theory (Figure 1). The comparison of energies of the two siloxycarbenes attainable from benzoyl silane shows large stability of the singlet species **sc^1** over that of the triplet **sc^3** (Scheme 3, top). The 16.1 kcal/mol difference is well in agreement with the recent study by Priebbenow.[43] The computational study proceeded considering the formation of cyclopropane derivatives **cp**, for which the two possible diastereomers were investigated (Scheme 3, bottom). Alternatively, the addition of carbene **sc1** to the terminal carbon of the diene was also considered. Despite the identification of a transition state for the C−C bond formation (with subsequent charge delocalization to the methylenemalononitrile unit), following the intrinsic reaction coordinates invariably resulted in the formation of cyclopropane derivatives. This clearly demonstrates the preference for a route that encompasses cyclopropane as an intermediate.

The interaction of the siloxycarbene with the diene is slightly unfavorable by 5.6 kcal/mol in comparison to the initial pair of reactants. In both cases, [**sc^{1}dn**]$_1$ and [**sc^{1}dn**]$_2$, a $\pi-\pi$ attractive interaction between the phenyl substituents (3.4−4.4 Å) of both species seems to hold the two reactants together. Despite the overlap of the phenyl substituents in both pairs, the location of the silyl group relative to the methylenemalononitrile differs, with [**sc^{1}dn**]$_1$ keeping the units close to each other, in contrast with [**sc^{1}dn**]$_2$ in which one is kept apart from the other. Generally, regardless of the relative geometry of the substituents of the cyclopropane derivatives, the formation of the three-membered rings accounts for the most energy-demanding step of the whole process. The formation of the two diastereomeric cyclopropane derivatives requires the transposition of energy barriers of 11.6 or 11.1 kcal/mol for the formation of the trans (**cp$_{trans}$**) or cis (**cp$_{cis}$**) diastereomer, respectively. The cyclopropanation transition states are very similar in nature and energies; the forming C−C bonds of the siloxycarbene carbon with C4 are shorter (2.44−2.46 Å) than those forming with C3

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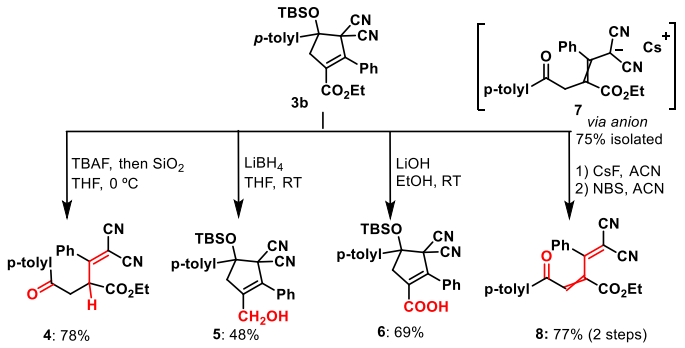
Scheme 4. Chemical Transformations of the Siloxycyclopentene Core



(3.14 Å) but still incipient as also confirmed by the weak WIs (WI = 0.1−0.2). The two diastereomeric cyclopropane derivatives differ in energy by 2.0 kcal/mol with a slight preference toward the trans diastereomer, where the repulsion between the phenyl and methylenemalononitrile substituents is diminished. The steric constraints imposed by the cyclopropane substituents are also noticeable in the C−C bond lengths as the C−C bond between the quaternary carbons is the most distended of the cyclopropane ring (1.55 Å in $\mathbf{cp}_{\mathbf{trans}}$ and 1.57 Å in $\mathbf{cp}_{\mathbf{cis}}$). The cyclopropane rearrangement to the cyclopentene differs slightly depending on the relative positions of the substituents in the cyclopropane. The $\mathbf{ts2}_{\mathbf{trans}}$ transition state was calculated for the ring enlargement of $\mathbf{cp}_{\mathbf{trans}}$, which is 14.4 kcal/mol less stable than its immediate precursor. Also, in this case, the C−C bonds involved are incipient (2.38−3.06 Å) and weak (WI = 0.1). The formation of the cyclopentane **prod** from the siloxycarbene is highly favored as determined by a ΔG_f of −54.6 kcal/mol. Despite numerous attempts to calculate a similar synchronous transition state for the ring enlargement from $\mathbf{cp}_{\mathbf{cis}}$, such a process seems more likely to proceed through charged intermediates $\mathbf{int}_1$ and $\mathbf{int}_{1'}$ due to the steric clash of the bulky phenyl and methylenemalononitrile substituents in the cis positions. Hence, the charged intermediate $\mathbf{int}_1$ is reached by the cleavage of the elongated C−C bond between the quaternary carbons of $\mathbf{cp}_{\mathbf{cis}}$ (1.57 Å in $\mathbf{cp}_{\mathbf{cis}}$ and 2.39 Å in $\mathbf{ts2}_{\mathbf{cis}}$) as the C−OSi bond becomes stronger (d = 1.38 Å; WI = 0.95 in $\mathbf{cp}_{\mathbf{cis}}$ and d = 1.28 Å; WI = 1.29 in $\mathbf{ts2}_{\mathbf{cis}}$). A change in conformation in $\mathbf{int}_1$ by rotation of the C−C bond between C3 and C4 gives rise to $\mathbf{int}_{1'}$, which undergoes C−C bond formation through a 6.4 kcal/mol energy barrier. The determined transition state $\mathbf{ts3}_{\mathbf{cis}}$ is again an early transition one as the forming C−C bond is still very incipient with a 3.30 Å length. When considering the energies involved in both pathways, that is, through each diastereomer of the cyclopropane, they likely compete with each other, and a preference for one of the diastereomeric cyclopropanes is improbable.

After the development of the protocol for the cycloaddition of photogenerated carbene with dicyano-2-methylenebut-3-enoates, we set out to investigate further transformations to the resulting cyclopentene molecules (Scheme 4). TBAF promoted the desilylation of **3b**, followed by purification via silica column chromatography which delivered the ring-opened product **4** in a good yield via acid-promoted retro-aldol. The ester moiety was selectively reduced to the primary alcohol **5** via $LiBH_4$ reduction and hydrolyzed to carboxylic acid **6** with LiOH. Attempts at palladium-catalyzed hydrogenation of olefin or its oxidation (*m*-CPBA or H_2O_2) invariably led to the recovery of the starting material, demonstrating the remarkable stability of the carbon−carbon double bond. Efforts to reduce nitrile (with DIBAL, $LiAlH_4$, or BH_3) or hydrolyze it under acidic or basic conditions led in all cases to an unidentifiable mixture of compounds. Desilylation under anhydrous conditions using CsF yielded **7** (1:0.2 trans/cis ratio), a room-temperature (RT) stable allylic anion, that could be quenched with equimolar *N*-bromosuccinimide (NBS) to yield the novel diene **8** (as an interconvertible 1:0.2 *cis*/*trans* mixture).

CONCLUSIONS

In summary, we expanded the scope of acylsilane-derived carbene reactivity toward the preparation of new highly functionalized cyclopentene scaffolds, which can be modified without disruption of the cyclic core. To the best of our knowledge, this work presents the first entry on the cycloaddition of photogenerated siloxycarbenes with dienes without the use of transition metal catalysis, paving the way for the use of easily prepared acylsilanes toward the metal-free synthesis of other cyclopentanes. While sensitive to stereochemical constraints, the metal-free cyclopropane ring expansion to cyclopentene proceeds with similar energy requirements for both diastereomeric cyclopropanes, as demonstrated by DFT calculations.

EXPERIMENTAL SECTION

General Information. NMR spectra were recorded using a Bruker Fourier 300 (Bruker, Massachusetts, USA), a Bruker AVANCE III (300 MHz), or a Bruker Fourier 400 (Bruker, Massachusetts, USA) using $CDCl_3$, D_2O, or $(CD_3)_2SO$ as a deuterated solvent. All coupling constants are expressed in hertz and chemical shifts (δ) in parts per million. Multiplicities are given as follows: s (singlet), d (doublet), dd (double doublet), dt (double triplet), t (triplet), td (triple triplet), tt (triple triplet), q (quartet), quint (quintuplet), and m (multiplet). Irradiation experiments were performed in a homemade Rayonet-inspired reactor with 16 lamps (419 nm). High-resolution mass spectra were recorded using a Thermo Scientific Q Exactive hybrid quadrupole-Orbitrap mass spectrometer (Thermo Scientific Q Exactive Plus). Reaction mixtures were analyzed by thin layer chromatography (TLC) using Merck silica gel 60F254 aluminum plates and visualized by UV light or stained with potassium permanganate or a phosphomolybdic acid stain. Column chromatography was performed with silica gel Geduran Si 60 (0.040−0.063 mm) purchased from Merck. All solvents were distilled before use. Dry tetrahydrofuran (THF) and dichloromethane (DCM) were obtained from the INERT PureSolv micro apparatus. Toluene was dried by standing in freshly activated 4 Å molecular sieves (20% m/v). Acetonitrile (ACN) was dried by refluxing

https://doi.org/10.1021/acs.joc.2c00591
J. Org. Chem. 2022, 87, 8910−8920

with CaH. All reagents used were purchased from Fluorochem, Alfa Aesar, TCI, or Sigma-Aldrich. X-ray crystallographic analysis of 3b was conducted using a Bruker D8 VENTURE diffractometer equipped with a Photon 100 complementary metal oxide semiconductor (CMOS) detector and an Oxford Cryostream cooler using graphite monochromated Mo Kα radiation (λ = 0.71073 Å). Dienes **2** were synthesized according to a reported procedure[37] and used immediately after purification. Dithianes **8** were prepared according to a reported procedure.[44,45]

*Ethyl 4,4-Dicyano-3-(4-(dimethylamino)phenyl)-2-methylenebut-3-enoate (**2l**).* Following the reported procedure,[37] **2l** was obtained in 12% yield (53 mg) as a red oil. Column eluent hexane/DCM (20:80). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.68−7.62 (m, 2H), 6.84 (s, 1H), 6.70−6.64 (m, 2H), 6.03 (s, 1H), 4.19 (q, J = 7.1 Hz, 2H), 3.10 (s, 6H), 1.20 (t, J = 7.1 Hz, 3H). ^{13}C{1H} NMR (75 MHz, $CDCl_3$): δ 167.8, 163.8, 153.7, 138.7, 133.9, 132.0, 120.6, 115.3, 114.7, 111.4, 62.1, 40.1, 14.1. HRMS m/z: $[M + H]^+$ calcd for $C_{17}H_{18}N_3O_2^+$, 296.1394; found, 296.1383.

*General Procedure for the Preparation of Silyl Dithianes **9a−f** and **9n**, Adapted from a Reported Procedure.*[46] Dithiane **8** (9.5 mmol) was dissolved in 40 mL of dry THF in a dried, argon-filled round-bottom flask. The solution was cooled to −78 °C, and nBuLi (2.5 M solution in hexanes, 1.2 equiv, 11.4 mmol) was added dropwise. The solution was stirred at −78 °C for 10 min after which *tert*-butyldimethylsilyl chloride (TBSCl; 11.4 mmol, 1.2 equiv) was added dropwise at this temperature. The solution was stirred at −78 °C for an additional 10 min and then left to warm to RT for a minimum of 1 h. The reaction was quenched with 40 mL of a saturated aqueous NH_4Cl solution. The layers were separated, and the organic phase was collected. The aqueous phase was extracted with methyl tert-butyl ether (MTBE) (2 × 40 mL), and the organic phases were combined, dried over $MgSO_4$, and filtered. After vacuum evaporation of the solvent, the crude was purified via silica column chromatography (eluent hexane/EtOAc mixture) to yield silyldithiane **9**.

*Trimethyl(2-(p-tolyl)-1,3-dithian-2-yl)silane (**9a**).*[47] Following the general procedure, **9a** was obtained in 89% yield (2.38 g) as a colorless oil. Trimethylsilyl chloride was used instead of TBSCl. Column eluent 100% hexane. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.79−7.74 (m, 2H), 7.17 (d, J = 8.0 Hz, 2H), 2.83−2.74 (m, 2H), 2.45−2.38 (m, 2H), 2.35 (s, 3H), 2.09−1.83 (m, 2H), 0.06 (s, 9H).

*tert-Butyldimethyl(2-(p-tolyl)-1,3-dithian-2-yl)silane (**9b**).* Following the general procedure, **9b** was obtained in 89% yield (2.017 g) as a colorless oil. Column eluent 100% hexane. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.83 (d, J = 8.4 Hz, 2H), 7.17 (d, J = 8.0 Hz, 2H), 2.83−2.73 (m, 2H), 2.41−2.35 (m, 2H), 2.35 (s, 3H), 2.08−1.80 (m, 2H), 0.82 (s, 9H), 0.13 (s, 6H). ^{13}C{1H} NMR (75 MHz, $CDCl_3$): δ 137.6, 135.0, 130.2, 129.2, 48.6, 28.0, 25.3, 25.3, 21.0, 19.9, −6.8. HRMS m/z: $[M + H]^+$ calcd for $C_{17}H_{29}S_2Si^+$, 325.1474; found, 325.1470.

*tert-Butyldimethyl(2-phenyl-1,3-dithian-2-yl)silane (**9c**).*[48] Following the general procedure, **9c** was obtained in 82% yield (508 mg) as a colorless oil. Column eluent 100% hexane. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.99−7.96 (m, 2H), 7.40−7.33 (m, 2H), 7.20−7.15 (m, 1H), 2.83−2.73 (m, 2H), 2.43−2.36 (m, 2H), 2.10−1.82 (m, 2H), 0.81 (s, 9H), 0.15 (s, 6H). HRMS m/z: $[M + H]^+$ calcd for $C_{16}H_{27}S_2Si^+$, 311.1318; found, 311.1313.

*tert-Butyl(2-(4-fluorophenyl)-1,3-dithian-2-yl)dimethylsilane (**9d**).*[49] Following the general procedure, **9d** was obtained in 73% yield (483 mg) as a colorless oil. Column eluent 100% hexane. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.96−7.89 (m, 2H), 7.09−7.02 (m, 2H), 2.80−2.70 (m, 2H), 2.40 (dt, J = 14.3, 3.9 Hz, 2H), 2.09−1.83 (m, 2H), 0.83 (s, 9H), 0.13 (s, 6H).

*(2-(4-Bromophenyl)-1,3-dithian-2-yl)(tert-butyl)dimethylsilane (**9e**).* Following the general procedure, **9e** was obtained in 69% yield (536 mg) as a colorless oil. A freshly prepared solution of LDA was used as a base. Column eluent 100% hexane. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.87−7.83 (m, 2H), 7.50−7.45 (m, 2H), 2.78−2.68 (m, 2H), 2.43−2.36 (m, 2H), 2.08−1.83 (m, 2H), 0.84 (s, 9H), 0.12 (s, 6H). ^{13}C{1H} NMR (75 MHz, $CDCl_3$): δ 140.5, 132.2, 131.5, 119.6, 48.4, 28.1, 25.3, 25.2, 20.0, −6.9. HRMS m/z: $[M + H]^+$ calcd for $C_{16}H_{26}BrS_2Si^+$, 389.0423; found, 389.0417.

*4-(2-(tert-Butyldimethylsilyl)-1,3-dithian-2-yl)-N,N-dimethylaniline (**9f**).* Following the general procedure, **9f** was obtained in 94% yield (667 mg) as a white amorphous solid. Column eluent hexane/EtOAc (99:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.79−7.74 (m, 2H), 6.76−6.71 (m, 2H), 2.97 (s, 6H), 2.82 (td, J = 14.1, 2.8 Hz, 2H), 2.36 (dt, J = 14.3, 3.9 Hz, 2H), 2.07−1.80 (m, 2H), 0.84 (s, 9H), 0.11 (s, 6H). ^{13}C{1H} NMR (75 MHz, $CDCl_3$): δ 148.3, 131.1, 128.0, 112.5, 48.4, 40.7, 28.1, 25.5, 25.2, 19.8, −6.8. HRMS m/z: $[M + H]^+$ calcd for $C_{18}H_{32}NS_2Si^+$, 354.1740; found, 354.1731.

*tert-Butyl(2-(3,4-dimethoxyphenyl)-1,3-dithian-2-yl)-dimethylsilane (**9n**).* Following the general procedure, **9f** was obtained in 89% yield (270 mg) as a white amorphous solid. Column eluent hexane/EtOAc (94:6). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.57 (d, J = 2.4 Hz, 1H), 7.50 (dd, J = 8.5, 2.4 Hz, 1H), 6.87 (d, J = 8.5 Hz, 1H), 3.90 (s, 3H), 3.89 (s, 3H), 2.81 (td, J = 14.0, 2.8 Hz, 2H), 2.40 (dt, J = 14.2, 3.7 Hz, 2H), 2.08−1.84 (m, 2H), 0.82 (s, 9H), 0.14 (s, 6H). ^{13}C{1H} NMR (75 MHz, $CDCl_3$): δ 148.8, 146.9, 133.2, 122.7, 113.8, 110.9, 56.1, 56.0, 48.5, 28.0, 25.4, 25.3, 19.9, −6.7. HRMS m/z: $[M + H]^+$ calcd for $C_{18}H_{31}O_2S_2Si^+$, 371.1529; found, 371.1524.

*General Procedure for the Preparation of Acylsilanes **1a-f** and **1n**, Adapted from a Reported Procedure.*[50] Dithiane **9** (3.5 mmol) was dissolved in 17 mL of ACN (sonication and gentle heating were usually required). Then, 5 mL of a saturated aqueous $NaHCO_3$ solution was added, and the mixture was cooled to 0 °C. Then, I_2 (35 mmol, 10 equiv) was added slowly in portions. After addition, the reaction was left at room temperature for 1 h. 20 mL of water was added, followed by continuous addition of $Na_2S_2O_3$. The mixture was vigorously stirred until the dark brown color of iodine faded to give a bright yellow solution. Then, the aqueous phase was extracted with MTBE (3 × 20 mL), and the organic phases were combined, dried over $MgSO_4$, and filtered. After vacuum evaporation of the solvent, the crude was purified via silica column chromatography (eluent hexane/EtOAc mixture) to yield benzoyl silane **1**.

*p-Tolyl(trimethylsilyl)methanone (**1a**).*[51] Following the general procedure, **1a** was obtained in 99% yield (677 mg) as a yellow oil. Column eluent hexane/DCM (6:4). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.59 (d, J = 8.2 Hz, 2H), 7.13−7.10 (m, 2H), 2.25 (s, 3H), 0.21 (s, 9H).

*(tert-Butyldimethylsilyl)(p-tolyl)methanone (**1b**).*[52] Following the general procedure, **1b** was obtained in 77% yield (1.117 g) as a yellow amorphous solid. Column eluent hexane/DCM (8:2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.62 (d, J = 8.1 Hz, 2H), 7.16 (d, J = 7.9 Hz, 2H), 2.30 (s, 3H), 0.86 (s, 9H), 0.26 (s, 6H). HRMS m/z: $[M + H]^+$ calcd for $C_{14}H_{23}OSi^+$, 235.1513; found, 235.1512.

*(tert-Butyldimethylsilyl)(phenyl)methanone (**1c**).*[48] Following the general procedure, **1c** was obtained in 91% yield (303 mg) as a yellow oil. Column eluent hexane/DCM (8:2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.71−7.68 (m, 2H), 7.47−7.33 (m, 3H), 0.86 (s, 9H), 0.27 (s, 6H). HRMS m/z: $[M + H]^+$ calcd for $C_{13}H_{21}OSi^+$, 221.1356; found, 221.1354.

*(tert-Butyldimethylsilyl)(4-fluorophenyl)methanone (**1d**).*[49] Following the general procedure, **1d** was obtained in 87% yield (291 mg) as a yellow oil. Column eluent hexane/EtOAc (98:2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.77−7.70 (m, 2H), 7.07−6.99 (m, 2H), 0.85 (s, 9H), 0.27 (s, 3H).

*(4-Bromophenyl)(tert-butyldimethylsilyl)methanone (**1e**).* Following the general procedure, **1e** was obtained in 87% yield (350 mg) as a yellow oil. Column eluent hexane/EtOAc (98:2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.58−7.48 (m, 4H), 0.85 (s, 9H), 0.26 (s, 6H). ^{13}C{1H} NMR (75 MHz, $CDCl_3$): δ 234.7, 141.4, 132.0, 129.2, 127.8, 26.8, 17.1, −4.6. HRMS m/z: $[M + H]^+$ calcd for $C_{13}H_{20}BrOSi^+$, 299.0461; found, 299.0460.

*(tert-Butyldimethylsilyl)(4-(dimethylamino)phenyl)methanone (**1f**).* Following the general procedure, **1f** was obtained in 40% yield (194 mg) as a yellow amorphous sold. Column eluent hexane/EtOAc (85:15). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.71−7.66 (m, 2H), 6.59−6.54 (m, 2H), 2.95 (s, 6H), 0.86 (s, 9H), 0.25 (s, 6H). ^{13}C{1H} NMR (75 MHz, $CDCl_3$): δ 230.5, 153.2, 132.4, 130.3, 110.7, 40.2, 27.0, 17.0, −4.2. HRMS m/z: $[M + H]^+$ calcd for $C_{15}H_{26}NOSi^+$, 264.1778; found, 264.1773.

https://doi.org/10.1021/acs.joc.2c00591
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*4-((Trimethylsilyl)carbonyl)benzonitrile (**1g**).* Dithiane **8g** (443 mg, 2 mmol) was dissolved in 9 mL of dry THF in a dried, argon-filled round-bottom flask. The solution was cooled to −78 °C, and *n*BuLi (0.96 mL of 2.5 M solution in hexanes, 1.2 equiv, 2.4 mmol) was added dropwise. The solution was stirred at −78 °C for 10 min after which trimethylsilyl chloride (303 μL, 2.4 mmol, 1.2 equiv) was added dropwise at this temperature. The solution was stirred at −78 °C for an additional 10 min and then left to warm to RT for a minimum of 1 h. The reaction was quenched with 10 mL of a saturated aqueous NH_4Cl solution. The layers were separated, and the organic phase was collected. The aqueous phase was extracted with MTBE (2 × 10 mL), and the organic phases were combined, dried over $MgSO_4$, and filtered. The crude containing **9g** was redissolved in 12 mL of ACN. Then, 4 mL of a saturated aqueous $NaHCO_3$ solution was added, and the mixture was cooled to 0 °C. Then, I_2 (5.08 g, 20 mmol, 10 equiv) was added slowly in portions. After addition, the reaction was left at room temperature for 1 h. Water was added (20 mL), followed by NaS_2O_3, and the mixture was vigorously stirred until the dark brown color of iodine faded to give a bright yellow solution. Then, the aqueous phase was extracted with MTBE (3 × 20 mL), and the organic phases were combined, dried over $MgSO_4$, and filtered. After vacuum evaporation of the solvent, the crude was purified via silica column chromatography eluent hexane/EtOAc (96:4) to yield acylsilane **1g** in 54% yield (220 mg, 1.08 mmol) as a bright yellow oil, as previously reported.[50] ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.89−7.86 (m, 2H), 7.79−7.76 (m, 2H), 0.38 (s, 9H).

*o-Tolyl(trimethylsilyl)methanone (**1m**).* The benzotriazole hemiaminal ether (535 mg, 2 mmol) was dissolved in dry THF (9 mL) in a dried, argon-filled round-bottom flask. The solution was cooled to −78 °C, and *n*BuLi (0.96 mL of 2.5 M solution in hexanes, 1.2 equiv, 2.4 mmol) was added dropwise. The solution was stirred at −78 °C for 10 min after which trimethylsilyl chloride (303 μL, 2.4 mmol, 1.2 equiv) was added dropwise at this temperature. The solution was stirred at −78 °C for an additional 10 min and then left to warm to RT for a minimum of 1 h. The reaction was quenched with 10 mL of a 1 M HCl solution. The layers were separated, and the organic phase was collected. The aqueous phase was extracted with MTBE (2 × 10 mL), and the organic phases were combined, dried over $MgSO_4$, and filtered. The crude oil was redissolved in 10 mL of acetone, and $FeCl_3{\cdot}6H_2O$ was added. After 1 h, acetone was evaporated, and the crude oil was dissolved in 10 mL of hexane and filtered. The liquid was evaporated under reduced pressure, and the crude was purified with the silica column chromatography eluent hexane 100% to give **1m** in 95% yield (364 mg, 1.9 mmol) as a bright yellow oil, with similar spectral characterization to those previously reported.[51] ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.58 (dd, *J* = 7.2, 1.8 Hz, 1H), 7.37−7.22 (m, 3H), 2.42 (s, 3H), 0.32 (s, 9H).

*(tert-Butyldimethylsilyl)(3,4-dimethoxyphenyl)methanone (**1n**).* Following the general procedure, **1n** was obtained in 90% yield (176 mg) as a yellow amorphous solid. Column eluent hexane/EtOAc (92:8). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.52 (dd, *J* = 8.3, 1.9 Hz, 1H), 7.36 (d, *J* = 1.9 Hz, 1H), 6.91 (d, *J* = 8.3 Hz, 1H), 3.94 (s, 3H), 3.91 (s, 3H), 0.96 (s, 9H), 0.36 (s, 6H). ^{13}C{1H} NMR (75 MHz, $CDCl_3$): δ 232.5, 153.1, 149.3, 136.7, 124.6, 110.0, 108.0, 56.2, 55.9, 26.9, 17.0, −4.3. HRMS *m*/*z*: $[M + H]^+$ calcd for $C_{15}H_{25}O_3Si^+$, 281.1567; found, 281.1561.

General Procedure for the Synthesis of Cyclopentenes 3. Acylsilane **1** (0.1 mmol) and diene **2** (0.14 mmol, 1.4 equiv) were dissolved in 0.5 mL of dry toluene in a sealed Pasteur pipette. 100 mg of molecular sieves 4 Å was added, and the solution was purged with argon for 15 min and irradiated at 419 nm from a minimum of 24 to a maximum of 72 h. Reaction progress was monitored by TLC and stopped upon full consumption of acylsilane **1**. Toluene was evaporated under reduced pressure, and the crude was purified via silica column chromatography (eluent hexane/EtOAc) to give cyclopentenes **3**.

*Ethyl 3,3-Dicyano-2-phenyl-4-(p-tolyl)-4-((trimethylsilyl)oxy)-cyclopent-1-ene-1-carboxylate (**3a**).* Following the general procedure, **3a** was obtained in 66% yield (29.5 mg) as an off-white amorphous solid. 23 h reaction. Column eluent hexane/EtOAc (95:5). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.58 (d, *J* = 8.3 Hz, 2H), 7.45−7.38 (m, 5H), 7.27 (d, *J* = 8.0 Hz, 2H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.88 (d, *J* = 17.1 Hz, 1H), 3.36 (d, *J* = 17.1 Hz, 1H), 2.40 (s, 3H), 1.07 (t, *J* = 7.1 Hz, 3H), 0.07 (s, 9H). ^{13}C{1H} NMR (75 MHz, $CDCl_3$): δ 163.6, 143.7, 140.0, 135.2, 134.5, 131.7, 129.9, 129.6, 128.5, 128.2, 126.6, 112.4, 112.1, 89.0, 61.5, 60.6, 43.4, 21.3, 13.8, 1.3. HRMS *m*/*z*: $[M + H]^+$ calcd for $C_{26}H_{29}N_2O_3Si^+$, 445.1942; found, 445.1942.

*Ethyl 4-((tert-Butyldimethylsilyl)oxy)-3,3-dicyano-2-phenyl-4-(p-tolyl)cyclopent-1-ene-1-carboxylate (**3b**).* Following the general procedure, **3b** was obtained in 74% yield (36.2 mg) as an off-white amorphous solid. 55 h reaction. Column eluent hexane/EtOAc (94:6). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.61 (d, *J* = 8.3 Hz, 2H), 7.46−7.36 (m, 5H), 7.27 (d, *J* = 7.9 Hz, 2H), 4.12 (qd, *J* = 7.1, 2.0 Hz, 2H), 3.90 (d, *J* = 17.1 Hz, 1H), 3.36 (d, *J* = 17.0 Hz, 1H), 1.07 (t, *J* = 7.1 Hz, 3H), 0.93 (s, 9H), 0.00 (s, 3H), −0.22 (s, 3H). ^{13}C{1H} NMR (75 MHz, $CDCl_3$): δ 163.5, 144.1, 140.2, 135.0, 134.5, 131.7, 129.9, 129.7, 128.6, 128.2, 126.9, 112.4, 112.3, 89.0, 61.5, 60.1, 43.1, 25.7, 21.4, 18.5, 13.9, −3.3, −3.5. HRMS *m*/*z*: $[M + H]^+$ calcd for $C_{29}H_{35}N_2O_3Si^+$, 487.2411; found, 487.2412.

*Ethyl 4-((tert-Butyldimethylsilyl)oxy)-3,3-dicyano-2,4-diphenylcyclopent-1-ene-1-carboxylate (**3c**).* Following the general procedure, **3c** was obtained in 68% yield (32.1 mg) as an off-white amorphous solid. 55 h reaction. Column eluent hexane/EtOAc (94:6). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.76−7.73 (m, 2H), 7.49−7.38 (m, 8H), 4.13 (qd, *J* = 7.1, 1.9 Hz, 2H), 3.94 (d, *J* = 17.0 Hz, 2H), 3.40 (d, *J* = 17.0 Hz, 1H), 1.08 (t, *J* = 7.1 Hz, 3H), 0.94 (s, 9H), 0.02 (s, 3H), −0.22 (s, 3H). ^{13}C{1H} NMR (75 MHz, $CDCl_3$): δ 163.4, 144.0, 138.0, 134.4, 131.6, 130.2, 129.9, 129.0, 128.6, 128.2, 126.9, 112.3, 112.2, 89.0, 61.5, 60.0, 43.0, 25.7, 18.5, 13.8, −3.3, −3.6. HRMS *m*/*z*: $[M + H]^+$ calcd for $C_{28}H_{33}N_2O_3Si^+$, 473.2255; found, 473.2255.

*Ethyl 4-((tert-Butyldimethylsilyl)oxy)-3,3-dicyano-4-(4-fluorophenyl)-2-phenylcyclopent-1-ene-1-carboxylate (**3d**).* Following the general procedure, **3d** was obtained in 66% yield (32.6 mg) as an off-white amorphous solid. 72 h reaction. Column eluent hexane/EtOAc (93:7). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.77−7.71 (m, 2H), 7.46−7.37 (m, 5H), 7.21−7.14 (m, 2H), 4.12 (qd, *J* = 7.1, 1.8 Hz, 2H), 3.89 (d, *J* = 17.1 Hz, 1H), 3.39 (d, *J* = 17.0 Hz, 1H), 1.07 (t, *J* = 7.1 Hz, 3H), 0.94 (s, 9H), 0.04 (s, 3H), −0.21 (s, 3H). ^{13}C{1H} NMR (75 MHz, $CDCl_3$): δ 165.3, 163.3, 162.0, 144.0, 134.2, 134.1, 134.1, 131.5, 130.0, 129.1, 128.9, 128.6, 128.2, 116.2, 116.0, 112.1, 112.1, 88.5, 61.5, 60.1, 43.1, 25.7, 18.5, 13.8, −3.2, −3.5. ^{19}F{1H} NMR (376 MHz, $CDCl_3$): δ −110.6. HRMS *m*/*z*: $[M]^+$ calcd for $C_{28}H_{31}FN_2O_3Si^+$, 490.2082; found, 490.2082.

*Ethyl 4-(4-Bromophenyl)-4-((tert-butyldimethylsilyl)oxy)-3,3-dicyano-2-phenylcyclopent-1-ene-1-carboxylate (**3e**).* Following the general procedure, **3e** was obtained in 66% yield (36.5 mg) as an off-white amorphous solid. 55 h reaction. Column eluent hexane/EtOAc (90:10). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.62 (s, 4H), 7.46−7.37 (m, 5H), 4.12 (qd, *J* = 7.1, 1.9 Hz, 2H), 3.87 (d, *J* = 17.1 Hz, 1H), 3.38 (d, *J* = 17.0 Hz, 1H), 1.07 (t, *J* = 7.1 Hz, 3H), 0.94 (s, 9H), 0.05 (s, 3H), −0.19 (s, 3H). ^{13}C{1H} NMR (75 MHz, $CDCl_3$): δ 163.3, 143.9, 137.1, 134.2, 132.3, 131.4, 130.0, 128.6, 128.6, 128.2, 124.6, 112.0, 112.0, 88.5, 61.6, 60.0, 42.8, 25.7, 18.5, 13.8, −3.2, −3.5. HRMS *m*/*z*: $[M + H]^+$ calcd for $C_{28}H_{32}BrN_2O_3Si^+$, 551.1360; found, 551.1361.

*Ethyl 4-((tert-Butyldimethylsilyl)oxy)-3,3-dicyano-4-(4-(dimethylamino)phenyl)-2-phenylcyclopent-1-ene-1-carboxylate (**3f**).* Following the general procedure, **3f** was obtained in 62% yield (32 mg) as an off-white amorphous solid. 48 h reaction. Column eluent hexane/DCM (65:35). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.55 (d, *J* = 8.9 Hz, 2H), 7.45−7.37 (m, 5H), 6.73 (d, *J* = 9.0 Hz, 2H), 4.11 (qd, *J* = 7.1, 2.1 Hz, 2H), 3.87 (d, *J* = 17.0 Hz, 1H), 3.33 (d, *J* = 17.0 Hz, 1H), 3.01 (s, 6H), 1.07 (t, *J* = 7.1 Hz, 3H), 0.93 (s, 9H), −0.00 (s, 3H), −0.17 (s, 3H). ^{13}C{1H} NMR (75 MHz, $CDCl_3$): δ 163.7, 151.2, 144.2, 134.5, 131.9, 129.7, 128.5, 128.2, 128.0, 124.8, 112.7, 112.5, 111.8, 89.3, 61.3, 60.3, 43.3, 40.2, 25.7, 18.5, 13.8, −3.3, −3.5. HRMS *m*/*z*: $[M + H]^+$ calcd for $C_{30}H_{38}N_3O_3Si^+$, 516.26770; found, 516.2670.

*Ethyl 4-((tert-Butyldimethylsilyl)oxy)-3,3-dicyano-2-(4-fluorophenyl)-4-phenylcyclopent-1-ene-1-carboxylate (**3h**).* Following the general procedure, **3h** was obtained in 61% yield (30.2 mg) as an off-white amorphous solid. 55 h reaction. Column eluent hexane/EtOAc (93:7). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.75−7.71 (m, 2H),

https://doi.org/10.1021/acs.joc.2c00591
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7.49−7.47 (m, 3H), 7.42−7.38 (m, 2H), 7.19−7.11 (m, 2H), 4.15 (qd, J = 7.1, 2.4 Hz, 2H), 3.92 (d, J = 17.1 Hz, 1H), 3.39 (d, J = 17.0 Hz, 1H), 1.12 (t, J = 7.1 Hz, 3H), 0.93 (s, 9H), 0.00 (s, 3H), −0.23 (s, 3H). ^{13}C{1H} NMR (75 MHz, $CDCl_3$): δ 165.3, 163.2, 162.0, 143.1, 137.8, 134.9, 130.5, 130.3, 130.3, 129.1, 127.6, 127.5, 126.9, 116.0, 115.7, 112.3, 112.1, 89.0, 61.6, 60.0, 43.0, 25.7, 18.5, 13.9, −3.3, −3.6. ^{19}F{1H} NMR (376 MHz, $CDCl_3$): δ −110.3 HRMS m/z: $[M]^+$ calcd for $C_{28}H_{31}FN_2O_3Si^+$, 490.2082; found, 490.2082.

*Ethyl 4-((tert-Butyldimethylsilyl)oxy)-2-(4-chlorophenyl)-3,3-dicyano-4-phenylcyclopent-1-ene-1-carboxylate (**3i**).* Following the general procedure, **3i** was obtained in 77% yield (39.1 mg) as an off-white amorphous solid. 55 h reaction. Column eluent hexane/EtOAc (92:8). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.74−7.71 (m, 2H), 7.50−7.42 (m, 5H), 7.36−7.33 (m, 2H), 4.15 (qd, J = 7.1, 2.3 Hz, 2H), 3.92 (d, J = 17.2 Hz, 1H), 3.39 (d, J = 17.1 Hz, 1H), 1.13 (t, J = 7.1 Hz, 3H), 0.93 (s, 9H), 0.00 (s, 3H), −0.23 (s, 3H). ^{13}C{1H} NMR (75 MHz, $CDCl_3$): δ 163.1, 142.9, 137.8, 136.2, 135.1, 130.3, 130.0, 129.7, 129.1, 129.0, 126.9, 112.2, 112.0, 89.0, 61.7, 59.8, 43.0, 25.7, 18.5, 13.9, −3.3, −3.6. HRMS m/z: $[M + H]^+$ calcd for $C_{28}H_{32}ClN_2O_3Si^+$, 507.1865; found, 507.1825.

*Ethyl 2-(4-Bromophenyl)-4-((tert-butyldimethylsilyl)oxy)-3,3-dicyano-4-phenylcyclopent-1-ene-1-carboxylate (**3j**).* Following the general procedure, **3j** was obtained in 72% yield (40.0 mg) as an off-white amorphous solid. 55 h reaction. Column eluent hexane/DCM (60:40). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.62 (s, 4H), 7.46−7.44 (m, 3H), 7.41−7.36 (m, 2H), 4.12 (qd, J = 7.1, 1.9 Hz, 2H), 3.87 (d, J = 17.1 Hz, 1H), 3.38 (d, J = 17.0 Hz, 1H), 1.07 (t, J = 7.1 Hz, 3H), 0.94 (s, 9H), 0.05 (s, 3H), −0.19 (s, 3H). ^{13}C{1H} NMR (75 MHz, $CDCl_3$): δ 163.3, 143.9, 137.1, 134.2, 132.3, 131.4, 130.0, 128.6, 128.6, 128.2, 124.6, 112.0, 112.0, 88.5, 61.6, 60.0, 42.8, 25.7, 18.5, 13.8, −3.2, −3.5. HRMS m/z: $[M]^+$ calcd for $C_{28}H_{31}BrN_2O_3Si^+$, 550.1282; found, 550.1284.

*Ethyl 4-((tert-Butyldimethylsilyl)oxy)-3,3-dicyano-2-(4-methoxyphenyl)-4-phenylcyclopent-1-ene-1-carboxylate (**3k**).* Following the general procedure, **3k** was obtained in 66% yield (33.2 mg) as an off-white amorphous solid. 72 h reaction. Column eluent hexane/EtOAc (90:10). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.76−7.72 (m, 2H), 7.50−7.45 (m, 3H), 7.40−7.35 (m, 2H), 6.99−6.94 (m, 2H), 4.16 (qd, J = 7.1, 2.0 Hz, 2H), 3.91 (d, J = 17.0 Hz, 1H), 3.84 (s, 3H), 3.37 (d, J = 17.0 Hz, 1H), 0.92 (s, 9H), 0.01 (s, 3H), −0.23 (s, 3H). ^{13}C{1H} NMR (75 MHz, $CDCl_3$): δ 163.6, 160.9, 144.1, 138.0, 133.1, 130.1, 129.9, 129.0, 127.0, 123.7, 114.0, 112.6, 112.4, 88.9, 61.4, 59.9, 55.4, 43.1, 25.7, 18.5, 14.0, −3.3, −3.6. HRMS m/z: $[M + H]^+$ calcd for $C_{29}H_{35}N_2O_4Si^+$, 503.2361; found, 503.2357.

*Ethyl 3,3-Dicyano-2-phenyl-4-(o-tolyl)-4-((trimethylsilyl)oxy)-cyclopent-1-ene-1-carboxylate (**3m**).* Following the general procedure, **3m** was obtained in 40% yield (17.7 mg) as an off-white amorphous solid. 72 h reaction. Column eluent hexane/EtOAc (93:7). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.50−7.22 (m, 9H), 4.15−4.08 (m, 2H), 3.94 (d, J = 17.0 Hz, 1H), 3.50 (d, J = 17.0 Hz, 1H), 2.70 (s, 3H), 1.04 (t, J = 7.1 Hz, 3H), 0.10 (s, 9H). ^{13}C{1H} NMR (75 MHz, $CDCl_3$): δ 163.5, 142.9, 138.9, 136.4, 135.2, 133.8, 131.6, 129.8, 129.7, 128.5, 128.3, 128.0, 126.2, 112.7, 112.3, 91.1, 61.6, 60.0, 46.2, 24.3, 13.8, 1.4. HRMS m/z: $[M + H]^+$ calcd for $C_{26}H_{29}N_2O_3Si^+$, 445.1942; found, 445.1942.

*Ethyl 4-((tert-Butyldimethylsilyl)oxy)-3,3-dicyano-4-(3,4-dimethoxyphenyl)-2-phenylcyclopent-1-ene-1-carboxylate (**3n**).* Following the general procedure, **3n** was obtained in 80% yield (42.5 mg) as an off-white amorphous solid. 48 h reaction. Column eluent hexane/EtOAc (92:8). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45−7.35 (m, 6H), 7.19 (dd, J = 8.4, 2.3 Hz, 1H), 6.90 (d, J = 8.4 Hz, 1H), 4.19−4.04 (m, 2H), 3.93 (s, 3H), 3.92 (s, 3H), 3.90 (d, J = 17.0 Hz, 1H), 3.34 (d, J = 17.0 Hz, 1H), 1.06 (t, J = 7.1 Hz, 3H), 0.95 (s, 9H), 0.03 (s, 3H), −0.18 (s, 3H). ^{13}C{1H} NMR (75 MHz, $CDCl_3$): δ 163.5, 150.3, 149.2, 144.1, 134.3, 131.7, 130.3, 129.9, 128.6, 128.1, 119.3, 112.4, 112.3, 110.5, 110.0, 89.0, 61.4, 60.3, 56.0, 55.9, 42.9, 25.7, 18.5, 13.8, −3.3, −3.5. HRMS m/z: $[M + H]^+$ calcd for $C_{30}H_{37}N_2O_5Si^+$, 533.2466; found, 533.2463.

*Ethyl 2-(4-Bromophenyl)-4-((tert-butyldimethylsilyl)oxy)-3,3-dicyano-4-(3,4-dimethoxyphenyl)cyclopent-1-ene-1-carboxylate (**3o**).* Following the general procedure, **3o** was obtained in 90% yield (54.8 mg) as an off-white amorphous solid. 48 h reaction. Column eluent hexane/EtOAc (85:15). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (d, J = 8.2 Hz, 2H), 7.35 (d, J = 2.3 Hz, 1H), 7.28 (d, J = 8.3 Hz, 2H), 7.17 (dd, J = 8.4, 2.3 Hz, 1H), 6.92 (d, J = 8.4 Hz, 1H), 4.20−4.12 (m, 2H), 3.94 (s, 6H), 3.90 (d, J = 17.2 Hz, 1H), 3.35 (d, J = 17.1 Hz, 1H), 1.14 (t, J = 7.1 Hz, 3H), 0.95 (s, 9H), 0.04 (s, 3H), −0.16 (s, 3H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$): δ 163.1, 150.3, 149.2, 142.9, 135.0, 131.9, 130.5, 130.0, 129.8, 124.4, 119.2, 112.2, 112.1, 110.5, 109.8, 89.1, 61.6, 60.0, 56.0, 55.9, 42.8, 25.6, 18.4, 13.9, −3.4, −3.6. HRMS m/z: $[M + H]^+$ calcd for $C_{30}H_{36}BrN_2O_5Si^+$, 611.1571; found, 611.1583.

*Ethyl 2-(4-Bromophenyl)-4-((tert-butyldimethylsilyl)oxy)-3,3-dicyano-4-(p-tolyl)cyclopent-1-ene-1-carboxylate (**3p**).* Following the general procedure, **3p** was obtained in 69% yield (39.0 mg) as a yellow amorphous solid. 48 h reaction. Column eluent hexane/EtOAc (85:15). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 (d, J = 8.0 Hz, 4H), 7.25 (d, J = 8.1 Hz, 4H), 4.18−4.07 (m, 2H), 3.87 (d, J = 17.1 Hz, 1H), 3.33 (d, J = 17.1 Hz, 1H), 2.38 (s, 3H), 1.10 (t, J = 7.1 Hz, 3H), 0.90 (s, 9H), −0.03 (s, 3H), −0.24 (s, 3H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$): δ 163.1, 142.9, 140.3, 135.1, 134.8, 131.9, 130.5, 129.9, 129.7, 126.8, 124.4, 112.2, 112.1, 89.0, 61.6, 59.8, 43.1, 25.7, 21.4, 18.4, 13.9, −3.3, −3.6. HRMS m/z: $[M + H]^+$ calcd for $C_{29}H_{34}BrN_2O_3Si^+$, 565.1517; found, 565.1526.

*Ethyl 2,4-Bis(4-bromophenyl)-4-((tert-butyldimethylsilyl)oxy)-3,3-dicyanocyclopent-1-ene-1-carboxylate (**3q**).* Following the general procedure, **3q** was obtained in 87% yield (52.4 mg) as a white amorphous solid. 72 h reaction. Column eluent hexane/DCM (68:32). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63−7.57 (m, 6H), 7.25 (d, J = 8.3 Hz, 2H), 4.20−4.08 (m, 2H), 3.85 (d, J = 17.1 Hz, 1H), 3.35 (d, J = 17.1 Hz, 1H), 1.11 (t, J = 7.1 Hz, 3H), 0.91 (s, 9H), 0.02 (s, 3H), −0.21 (s, 3H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$): δ 162.9, 142.7, 136.9, 134.9, 132.3, 131.9, 130.2, 129.8, 128.5, 124.7, 124.6, 111.8 (2), 88.5, 61.8, 59.7, 42.8, 25.6, 18.4, 13.9, −3.2, −3.5. HRMS m/z: $[M + H]^+$ calcd for $C_{28}H_{31}Br_2N_2O_3Si^+$, 631.0445; found, 631.0461.

*Ethyl 4-(4-Bromophenyl)-4-((tert-butyldimethylsilyl)oxy)-2-(4-chlorophenyl)-3,3-dicyanocyclopent-1-ene-1-carboxylate (**3r**).* Following the general procedure, **3r** was obtained in 69% yield (40.6 mg) as a pale oil. 72 h reaction. Column eluent hexane/DCM (70:30). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64−7.59 (m, 4H), 7.44 (d, J = 8.3 Hz, 2H), 7.33 (d, J = 8.3 Hz, 2H), 4.18−4.09 (m, 2H), 3.87 (d, J = 17.1 Hz, 1H), 3.37 (d, J = 17.1 Hz, 1H), 1.13 (t, J = 7.1 Hz, 3H), 0.93 (s, 9H), 0.03 (s, 3H), −0.20 (s, 3H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$): δ 163.0, 142.8, 136.9, 136.3, 134.9, 132.3, 129.7, 129.6, 129.0, 128.5, 124.8, 111.9 (2), 88.5, 61.8, 59.8, 42.8, 25.6, 18.4, 13.9, −3.2, −3.5. HRMS m/z: $[M + H]^+$ calcd for $C_{28}H_{31}BrClN_2O_3Si^+$, 585.0970; found, 585.0979.

*Ethyl 4,4-Dicyano-2-(2-oxo-2-(p-tolyl)ethyl)-3-phenylbut-3-enoate (**4**).* Cyclopentene **3b** (10 mg, 20 μmol) was dissolved in THF (1 mL) in a round-bottom flask. The solution was cooled to 0 °C, and TBAF·H_2O (7.1 mg, 23 μmol, 1.1 equiv) was added. After 10 min, at 0 °C, the solution was warmed to RT. Ketone **4** was purified by silica column flash chromatography with dry loading using hexane/EtOAc (80:20) as an eluent to give **4** as an amorphous off-white solid in 78% yield (5.8 mg, 16 μmol). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.72 (d, J = 8.2 Hz, 2H), 7.51−7.39 (m, 3H), 7.27−7.20 (m, 4H), 4.83 (dd, J = 8.3, 5.5 Hz, 1H), 4.31 (q, J = 7.1 Hz, 2H), 3.74 (dd, J = 18.4, 5.5 Hz, 1H), 3.17 (dd, J = 18.4, 8.4 Hz, 1H), 2.39 (s, 3H), 1.33 (t, J = 7.1 Hz, 3H). ^{13}C{1H} NMR (75 MHz, $CDCl_3$): δ 195.4, 175.2, 168.6, 145.0, 133.6, 133.3, 131.8, 129.6, 129.4, 128.3, 127.6, 112.4, 112.1, 90.0, 63.0, 47.9, 38.7, 21.8, 14.2. HRMS m/z: $[M + H]^+$ calcd for $C_{23}H_{21}N_2O_3^+$, 373.1547; found, 373.1544.

*5-((tert-Butyldimethylsilyl)oxy)-3-(hydroxymethyl)-2-phenyl-5-(p-tolyl)cyclopent-2-ene-1,1-dicarbonitrile (**5**).* Cyclopentene **3b** (20 mg, 41 μmol) was dissolved in dry THF (2 mL) in a round-bottom flask, and the resulting solution was cooled to 0 °C. $LiBH_4$ (3 mg, 135 μmol, 3.3 equiv) was added, and the reaction was warmed to RT. After 3 h, water (9.7 μL, 540 μmol, 13.2 equiv) was added, and the solution was left to stir for 5 min. Then, the solvent was evaporated, and the crude was purified by silica flash column chromatography using hexane/EtOAc as an eluent (80:20) to give alcohol **5** in 48% yield (8.8 mg, 20

https://doi.org/10.1021/acs.joc.2c00591
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μmol). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.61 (d, J = 8.3 Hz, 2H), 7.47−7.41 (m, 3H), 7.34−7.32 (m, 2H), 7.25 (d, J = 6.7 Hz, 2H), 4.44−4.33 (m, 2H), 3.76 (d, J = 17.0 Hz, 1H), 3.21 (d, J = 17.0 Hz, 1H), 2.39 (s, 3H), 0.92 (s, 9H), 0.01 (s, 3H), −0.23 (s, 3H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$): δ 144.1, 139.9, 135.9, 132.0, 131.5, 129.6, 129.4, 129.1, 128.6, 127.1, 113.6, 113.6, 89.2, 59.7, 58.7, 43.6, 25.8, 21.4, 18.5, −2.9, −3.4. HRMS m/z: $[M + H]^+$ calcd for $C_{27}H_{33}N_2O_2Si^+$, 445.2306; found, 445.2304.

4-((tert-Butyldimethylsilyl)oxy)-3,3-dicyano-2-phenyl-4-(p-tolyl)-cyclopent-1-ene-1-carboxylic Acid (6). Cyclopentenone **3b** (6 mg, 12 μmol) was dissolved in EtOH (1 mL). LiOH (20 μL of 1 M aqueous solution, 20 μmol, 2 equiv) was added, and the solution was stirred for 5 h at RT. Then, the solvent was evaporated, and the crude was purified by silica flash column chromatography using hexane/EtOAc/AcOH (60:40:0.1) as an eluent to give carboxylic acid **6** in 69% yield (3.8 mg, 8.3 μmol). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (d, J = 8.3 Hz, 2H), 7.47−7.39 (m, 5H), 7.27 (d, J = 6.6 Hz, 2H), 3.90 (d, J = 17.1 Hz, 1H), 3.36 (d, J = 17.0 Hz, 1H), 2.40 (s, 3H), 0.92 (s, 9H), −0.00 (s, 3H), −0.23 (s, 3H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$): δ 167.3, 146.3, 140.3, 134.8, 133.4, 131.3, 130.2, 129.8, 128.8, 128.2, 126.9, 112.2, 112.1, 88.9, 60.3, 43.2, 25.7, 21.4, 18.5, −3.2, −3.5. HRMS m/z: $[M + H]^+$ calcd for $C_{27}H_{31}N_2O_3Si^+$, 459.2098; found, 459.2091.

Cesium 1,1-Dicyano-3-(ethoxycarbonyl)-5-oxo-2-phenyl-5-(p-tolyl)pent-2-en-1-ide (7). Cyclopentene **3b** (10 mg, 20 μmol) was dissolved in dry ACN (1 mL) in an oven-dried round-bottom flask under an argon atmosphere. CsF (94 mg, 620 μmol, 30 equiv) was added, and the solution was left to stir for 3 h. The solvent was evaporated, and the crude mixture was redissolved in acetone. The solid CsF excess was filtered off through celite, and the filtrate was evaporated to give salt **7** as a bright yellow oil in 75% yield (7.6 mg, 15 μmol) as a 1:0.2 mixture of E/Z isomers. **7** can be converted to **4** simply via passing through a silica plug. **7a** (major): ^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ 7.94 (d, J = 8.2 Hz, 2H), 7.28 (d, J = 7.9 Hz, 2H), 7.21 (s, 5H), 4.39 (s, 2H), 3.52 (q, J = 7.1 Hz, 2H), 2.39 (s, 3H), 0.59 (t, J = 7.1 Hz, 3H). ^{13}C{1H} NMR (100 MHz, $(CD_3)_2CO$): δ 199.6, 169.8, 158.2, 144.9, 143.2, 136.8, 130.2, 129.7, 129.0, 127.9, 127.8, 125.2, 102.0, 58.7, 43.1, 40.2, 21.6, 14.1. **7b** (minor): ^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ 7.70 (d, J = 8.2 Hz, 2H), 7.29−7.20 (m, 7H), 4.06 (q, J = 7.1 Hz, 2H), 3.60 (s, 2H), 2.33 (s, 3H), 1.12 (t, J = 7.1 Hz, 3H). HRMS m/z: $[M+2H]^+$ calcd for $C_{23}H_{21}N_2O_3Si^+$, 373.1547; found, 373.1544.

Ethyl 2-(2,2-Dicyano-1-phenylvinyl)-4-oxo-4-(p-tolyl)but-2-enoate (8). Cyclopentene **3b** (20 mg, 40 μmol) was dissolved in dry ACN (2 mL) in an oven-dried round-bottom flask under an argon atmosphere. CsF (180 mg, 1.2 mmol, 30 equiv) was added, and the solution was left to stir for 3 h. Excess CsF was filtered through celite, and NBS (7.1 mg, 40 μmol, 1 equiv) was added to the filtrate solution. The bright yellow color of intermediate **7** quickly fades. The solvent was quickly evaporated. Analysis of the ^{1}H NMR crude at this stage reveals a E/Z ratio of 0.45:1. The crude was purified by silica flash column chromatography using hexane/EtOAc as an eluent (80:20) to give diene **8** in 77% yield (11.4 mg, 31 μmol) in a E/Z ratio of 1:0.2 at thermodynamic equilibrium (Figure S2). **8a** (major): ^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ 8.41 (s, 1H), 7.96 (d, J = 8.2 Hz, 2H), 7.78−7.76 (m, 2H), 7.69−7.53 (m, 3H), 7.40 (d, J = 8.2 Hz, 2H), 4.31 (q, J = 7.1 Hz, 2H), 2.43 (s, 3H), 1.24 (t, J = 7.1 Hz, 3H). ^{13}C{1H} NMR (100 MHz, $(CD_3)_2CO$): δ 189.1, 172.2, 163.4, 146.7, 139.8, 138.7, 134.4, 134.2, 133.6, 130.6, 130.2, 129.9, 129.8, 113.5, 113.4, 85.4, 63.6, 21.7, 14.1. **8b** (minor): ^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ 7.99−7.39 (m, 10H), 3.96 (q, J = 7.1 Hz, 2H), 2.43 (s, 3H), 0.89 (t, J = 7.1 Hz, 3H). HRMS m/z: $[M + H]^+$ calcd for $C_{23}H_{19}N_2O_3$, 371.1390; found, 371.1384. Note: Prolonged heating of the reaction crude at 40 °C also delivers the same relative E/Z ratio of isomers, further confirming the thermodynamic equilibrium. Identification of isomers was conducted via analysis of the ethyl ester β-hydrogen which shows characteristic lower field shift from *trans* to *cis* conformation (relative to ester) from 7.79 to 8.41 ppm.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.2c00591.

Full accounts on computational calculations, X-ray crystallographic analysis for **3b**, and ^{1}H and ^{13}C NMR copies of spectra for all novel compounds (PDF)

Accession Codes

CCDC 2142958 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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The manuscript was written through the contributions of all authors. All authors have approved the final version of the manuscript.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The Academy of Finland is acknowledged for financial support to N.R.C. (decision nos. 326487 and 326486). Fundação para a Ciência e Tecnologia (FCT) is acknowledged for financial support to J.R.V. (SFRH/BD/120119/2016) and N.R.C. under the Scientific Employment Stimulus (CEECINST/00026/2018). This work was supported through the projects UIDB/50006/2020, UIDP/50006/2020, UIDB/04138/2020, and UIDP/04138/2020 funded by FCT/MCTES through national funds. The CSC-IT Center for Science Ltd, Finland, is acknowledged for the allocation of computational resources.

■ REFERENCES

(1) Zhang, H.-J.; Priebbenow, D. L.; Bolm, C. Acylsilanes: Valuable Organosilicon Reagents in Organic Synthesis. *Chem. Soc. Rev.* **2013**, *42*, 8540−8571.

(2) Priebbenow, D. L. Silicon-Derived Singlet Nucleophilic Carbene Reagents in Organic Synthesis. *Adv. Synth. Catal.* **2020**, *362*, 1927−1946.
(3) Wang, X.; Liu, F.; Li, Y.; Yan, Z.; Qiang, Q.; Rong, Z. Q. Recent Advances in the Synthesis of Acylsilanes. *ChemCatChem* **2020**, *12*, 5022−5033.
(4) Duff, J. M.; Brook, A. G. Photoisomerization of Acylsilanes to Siloxycarbenes, and Their Reactions with Polar Reagents. *Can. J. Chem.* **1973**, *51*, 2869−2883.
(5) Svarovsky, S. A.; Taraban, M. B.; Barchi, J. J., Jr. Facile Photochemical Synthesis of Mixed Siloxyacetal Glycosides as Potential pH-Sensitized Prodrugs for Selective Treatment of Solid Tumors. *Org. Biomol. Chem.* **2004**, *2*, 3155−3161.
(6) Stuckhardt, C.; Wissing, M.; Studer, A. Photo Click Reaction of Acylsilanes with Indoles. *Angew. Chem., Int. Ed.* **2021**, *60*, 18605−18611.
(7) Watanabe, H.; Kogure, T.; Nagai, Y. The photochemical reaction of benzoyltrimethylsilane with organosilicon hydrides. *J. Org. Chem.* **1972**, *43*, 285−291.
(8) Watanabe, H.; Ohsawa, N.; Sawai, M.; Fukusawa, Y.; Matsumoto, H.; Nagai, Y. Photochemical reaction of benzoyltrimethylsilane with substituted phenylsilanes. *J. Organomet. Chem.* **1975**, *93*, 173−179.
(9) Ye, J.-H.; Quach, L.; Paulisch, T.; Glorius, F. Visible-Light-Induced, Metal-Free Carbene Insertion into B-H Bonds between Acylsilanes and Pinacolborane. *J. Am. Chem. Soc.* **2019**, *141*, 16227−16231.
(10) Shen, Z.; Dong, V. M. Benzofurans Prepared by C−H Bond Functionalization with Acylsilanes. *Angew. Chem., Int. Ed.* **2009**, *48*, 784−786.
(11) Bassindale, A. R.; Brook, A. G.; Harris, J. Siloxycarbenes from the Thermolysis of Acylsilanes. *J. Organomet. Chem.* **1975**, *90*, C6.
(12) Shih, C.; Swenton, J. S. Thermal and Photochemical Rearrangement of (o-Tolylcarbonyl)Trimethylsilane. A 1,5-Shift of a Trimethylsilyl Group from Oxygen to Carbon. *J. Org. Chem.* **1982**, *47*, 2668−2670.
(13) Ito, K.; Tamashima, H.; Iwasawa, N.; Kusama, H. Photochemically Promoted Transition Metal-Free Cross-Coupling of Acylsilanes with Organoboronic Esters. *J. Am. Chem. Soc.* **2011**, *133*, 3716−3719.
(14) Brook, A. G.; Pearce, R.; Pierce, J. B. Nucleophilic Attack of Siloxycarbenes on Carbonyl Groups. The Formation of Oxiranes. *Can. J. Chem.* **1971**, *49*, 1622−1628.
(15) Priebbenow, D. L.; Pilkington, R. L.; Hearn, K. N.; Polyzos, A. Fluorinated Ketones as Trapping Reagents for Visible-Light-Induced Singlet Nucleophilic Carbenes. *Org. Lett.* **2021**, *23*, 2783−2789.
(16) Fan, Z.; Yi, Y.; Chen, S.; Xi, C. Visible-Light-Induced Catalyst-Free Carboxylation of Acylsilanes with Carbon Dioxide. *Org. Lett.* **2021**, *23*, 2303−2307.
(17) Yang, Z.; Stivanin, M. L.; Jurberg, I. D.; Koenigs, R. M. Visible light-promoted reactions with diazo compounds: a mild and practical strategy towards free carbene intermediates. *Chem. Soc. Rev.* **2020**, *49*, 6833−6847.
(18) Zhang, H.-J.; Becker, P.; Huang, H.; Pirwerdjan, R.; Pan, F.-F.; Bolm, C. Photochemically Induced Silylacylations of Alkynes with Acylsilanes. *Adv. Synth. Catal.* **2012**, *354*, 2157−2161.
(19) Becker, P.; Priebbenow, D. L.; Zhang, H.-J.; Pirwerdjan, R.; Bolm, C. Photochemical Intermolecular Silylacylations of Electron-Deficient Internal Alkynes. *J. Org. Chem.* **2014**, *79*, 814−817.
(20) Brook, A. G.; Kucera, H. W.; Pearce, R. Photolysis of 1,1-Diphenylsilacyclohexanone in Diethyl Fumarate. The Trapping of a Siloxycarbene by an Electron-Deficient Olefin. *Can. J. Chem.* **1971**, *49*, 1618−1621.
(21) Dalton, J. C.; Bourque, R. A. Mechanistic photochemistry of acylsilanes. 2. Reaction with electron-poor olefins. *J. Am. Chem. Soc.* **1981**, *103*, 699−700.
(22) Hammaecher, C.; Portella, C. New 6-Oxa-2-Silabicyclo[2.2.0]-Hexanes by Photochemical Conversion of Acyl(Allyl)(Dimethyl)-Silanes. *Chem. Commun.* **2008**, 5833.
(23) Vale, J. R.; Valkonen, A.; Afonso, C. A. M.; Candeias, N. R. Synthesis of Silacyclopent-2-En-4-Ols via Intramolecular [2 + 2] Photocycloaddition of Benzoyl(Allyl)Silanes. *Org. Chem. Front.* **2019**, *6*, 3793−3798.
(24) Sakurai, S.; Inagaki, T.; Kodama, T.; Yamanaka, M.; Tobisu, M. Palladium-Catalyzed Siloxycyclopropanation of Alkenes Using Acylsilanes. *J. Am. Chem. Soc.* **2022**, *144*, 1099−1105.
(25) Takeuchi, T.; Aoyama, T.; Orihara, K.; Ishida, K.; Kusama, H. Visible-Light-Induced In Situ Generation of Fischer-Type Copper Carbene Complexes from Acylsilanes and Its Application to Catalytic [4 + 1] Cycloaddition with Siloxydienes. *Org. Lett.* **2021**, *23*, 9490−9494.
(26) Cavitt, M. A.; Phun, L. H.; France, S. Intramolecular Donor-Acceptor Cyclopropane Ring-Opening Cyclizations. *Chem. Soc. Rev.* **2014**, *43*, 804−818.
(27) Grover, H. K.; Emmett, M. R.; Kerr, M. A. Carbocycles from Donor-Acceptor Cyclopropanes. *Org. Biomol. Chem.* **2015**, *13*, 655−671.
(28) Augustin, A. U.; Werz, D. B. Exploiting Heavier Organochalcogen Compounds in Donor-Acceptor Cyclopropane Chemistry. *Acc. Chem. Res.* **2021**, *54*, 1528−1541.
(29) Cohen, Y.; Cohen, A.; Marek, I. Creating Stereocenters within Acyclic Systems by C-C Bond Cleavage of Cyclopropanes. *Chem. Rev.* **2021**, *121*, 140−161.
(30) Baldwin, J. E. Thermal Isomerizations of Vinylcyclopropanes to Cyclopentenes. *J. Comput. Chem.* **1998**, *19*, 222−231.
(31) Hudlicky, T.; Reed, J. W. From Discovery to Application: 50 Years of the Vinylcyclopropane-Cyclopentene Rearrangement and Its Impact on the Synthesis of Natural Products. *Angew. Chem., Int. Ed.* **2010**, *49*, 4864−4876.
(32) Meazza, M.; Guo, H.; Rios, R. Synthetic Applications of Vinyl Cyclopropane Opening. *Org. Biomol. Chem.* **2017**, *15*, 2479−2490.
(33) Coscia, R. W.; Lambert, T. H. Development of a Formal [4 + 1] Cycloaddition: Pd(OAc)2-Catalyzed Intramolecular Cyclopropanation of 1,3-Dienyl β-Keto Esters and MgI2-Promoted Vinylcyclopropane−Cyclopentene Rearrangement. *J. Am. Chem. Soc.* **2009**, *131*, 2496−2498.
(34) Wu, J.; Becerril, J.; Lian, Y.; Davies, H. M. L.; Porco, J. A.; Panek, J. S. Sequential Transformations to Access Polycyclic Chemotypes: Asymmetric Crotylation and Metal Carbenoid Reactions. *Angew. Chem., Int. Ed.* **2011**, *50*, 5938−5942.
(35) Talukdar, R.; Tiwari, D. P.; Saha, A.; Ghorai, M. K. Diastereoselective Synthesis of Functionalized Tetrahydrocarbazoles via a Domino-Ring Opening-Cyclization of Donor-Acceptor Cyclopropanes with Substituted 2-Vinylindoles. *Org. Lett.* **2014**, *16*, 3954−3957.
(36) Ivanova, O. A.; Chagarovskiy, A. O.; Shumsky, A. N.; Krasnobrov, V. D.; Levina, I. I.; Trushkov, I. V. Lewis Acid Triggered Vinylcyclopropane-Cyclopentene Rearrangement. *J. Org. Chem.* **2018**, *83*, 543−560.
(37) Jiang, X.; Fu, D.; Shi, X.; Wang, S.; Wang, R. PPh3-catalyzed synthesis of dicyano-2-methylenebut-3-enoates as efficient dienes in catalytic asymmetric inverse-electron-demand Diels-Alder reaction. *Chem. Commun.* **2011**, *47*, 8289−8291.
(38) Li, Q.-Z.; Zhang, X.; Xie, K.; Dai, Q.-S.; Zeng, R.; Liu, Y.-Q.; Jia, Z.-Q.; Feng, X.; Li, J.-L. Diastereodivergent synthesis of cyclopropanes via on-water [2 + 1] annulations of diazo compounds with electron-deficient alkenes. *Green Chem.* **2019**, *21*, 2375−2379.
(39) Sperling, D.; Reißig, H.-U.; Fabian, J. [1,3]-Sigmatropic Rearrangements of Divinylcyclopropane Derivatives and Hetero Analogs in Competition with Cope-Type Rearrangements - A DFT Study. *Eur. J. Org. Chem.* **1999**, *1999*, 1107−1114.
(40) Wang, S. C.; Troast, D. M.; Conda-Sheridan, M.; Zuo, G.; LaGarde, D.; Louie, J.; Tantillo, D. J. Mechanism of the Ni(0)-Catalyzed Vinylcyclopropane−Cyclopentene Rearrangement. *J. Org. Chem.* **2009**, *74*, 7822−7833.
(41) Schneider, T. F.; Werz, D. B. Ring-Enlargement Reactions of Donor−Acceptor-Substituted Cyclopropanes: Which Combinations are Most Efficient? *Org. Lett.* **2011**, *13*, 1848−1851.
(42) Parr, R. G.; Weitao, Y. *Density-Functional Theory of Atoms and Molecules*; Oxford University Press: New York, Oxford, 1989.

https://doi.org/10.1021/acs.joc.2c00591
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(43) Priebbenow, D. L. Insights into the Stability of Siloxy Carbene Intermediates and Their Corresponding Oxocarbenium Ions. *J. Org. Chem.* **2019**, *84*, 11813−11822.
(44) Firouzabadi, H.; Iranpoor, N.; Hazarkhani, H. Iodine Catalyzes Efficient and Chemoselective Thioacetalization of Carbonyl Functions, Transthioacetalization of O,O- and S,O-Acetals and Acylals. *J. Org. Chem.* **2001**, *66*, 7527−7529.
(45) Vale, J. R.; Rimpiläinen, T.; Sievänen, E.; Rissanen, K.; Afonso, C. A. M.; Candeias, N. R. Pot-Economy Autooxidative Condensation of 2-Aryl-2-Lithio-1,3-Dithianes. *J. Org. Chem.* **2018**, *83*, 1948−1958.
(46) Brook, A. G.; Davis, N. R.; Jones, P. F.; Duff, J. M. Synthesis of Silyl and Germyl Ketones. *J. Am. Chem. Soc.* **1967**, *89*, 431−434.
(47) Ni, Z. J.; Yang, P. F.; Ng, D. K. P.; Tzeng, Y. L.; Luh, T. Y. Unified Synthesis of Vinylsilanes and Silylated Butadienes. Nickel-Catalyzed Olefination and Silylolefination of Dithioacetals. *J. Am. Chem. Soc.* **1990**, *112*, 9356−9364.
(48) Linghu, X.; Nicewicz, D. A.; Johnson, J. S. Tandem Carbon-Carbon Bond Constructions via Catalyzed Cyanation/Brook Rearrangement/C-Acylation Reactions of Acylsilanes. *Org. Lett.* **2002**, *4*, 2957−2960.
(49) Ishida, K.; Tobita, F.; Kusama, H. Lewis Acid-Assisted Photoinduced Intermolecular Coupling between Acylsilanes and Aldehydes: A Formal Cross Benzoin-Type Condensation. *Chem.—Eur. J.* **2018**, *24*, 543−546.
(50) Fan, D.; Liu, Y.; Jia, J.; Zhang, Z.; Liu, Y.; Zhang, W. Synthesis of Chiral α-Aminosilanes through Palladium-Catalyzed Asymmetric Hydrogenation of Silylimines. *Org. Lett.* **2019**, *21*, 1042−1045.
(51) Tongco, E. C.; Wang, Q.; Surya Prakash, G. K. One-Pot Preparation of Aroylsilanes by Reductive Silylation of Methyl Benzoates. *Synth. Commun.* **1997**, *27*, 2117−2123.
(52) Lin, C.-Y.; Ma, P.-J.; Sun, Z.; Lu, C.-D.; Xu, Y.-J. Carbamoyl Anion-Initiated Cascade Reaction for Stereoselective Synthesis of Substituted α-Hydroxy-β-Amino Amides. *Chem. Commun.* **2016**, *52*, 912−915.
(53) Zhou, G.; Shen, X. Synthesis of Cyclopropenols Enabled by Visible-Light-Induced Organocatalyzed [2+1] Cyclization. *Angew. Chem. Int. Ed. Engl.* **2022**, *61*, No. e202115334.
(54) Zhang, Y.; Zhou, G.; Gong, X.; Guo, Z.; Qi, X.; Shen, X. Diastereoselective Transfer of Tri(di)fluoroacetylsilanes-Derived Carbenes to Alkenes. *Angew. Chem. Int. Ed. Engl.* **2022**, No. e202202175.
(55) Bunyamin, A.; Hua, C.; Polyzos, A.; Priebbenow, D. L. Intramolecular photochemical [2 + 1]-cycloadditions of nucleophilic siloxy carbenes. *Chem. Sci.* **2022**, *13*, 3273−3280.

NOTE ADDED AFTER ASAP PUBLICATION

This article was published ASAP on June 23, 2022. Text was updated in the second paragraph of the Introduction and references 53 through 55 were added. The corrected version was reposted on June 24, 2022.

https://doi.org/10.1021/acs.joc.2c00591
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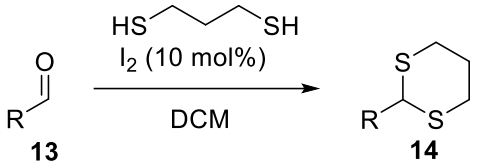
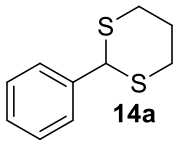
ANNEX

Synthesis of dithianes 14:



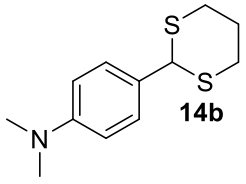
13 **14**

General procedure: Based on a modified previously reported method,[1] aldehyde (15 mmol, 1 equiv) and 1,3-propanedithiol (3 mL, 16.5 mmol, 1.1 equiv) were dissolved in dichloromethane (50 mL) in a round-bottom flask. Iodine (381 mg, 1.5 mmol, 0.1 equiv) was slowly added do the stirring solution as to prevent vigorous boiling of the solvent. The reaction was quenched with a 2% $Na_2S_2O_3$ aqueous solution (10 mL) 30 min after complete iodine addition. Upon separation, the organic layer was washed successively with a 10% aqueous NaOH solution (10 mL), water (10 mL) and brine (10 mL). The organic solvent was dried over $MgSO_4$ and filtered. After evaporating the solvent, the product was recrystallized in isopropanol. Note: Reactions were conducted in different scales depending on availability of aldehyde starting material.



14a

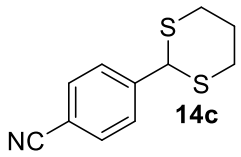
Prepared according to general procedure. 77% yield (3.425 g, 17.45mmol), white crystals. Obtained with same spectral characterization as previously described.[2] ^{1}**H NMR** (300 MHz, CDCl3): δ ppm 7.49-7.45 (m, 2H), 7.37-7.29 (m, 3H), 5.17 (s, 1H), 3.12-3.02 (m, 2H), 2.95-2.88 (m, 2H), 2.22-2.14 (m, 1H), 2.01-1.86 (m, 1H).



14b

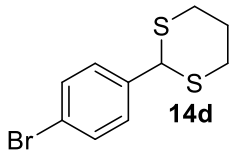
Prepared according to a modified reported method.[3] 4-(Dimethylamino)benzaldehyde (1 g, 6.7 mmol, 1 equiv.) and 1,3-propanedithiol (0.74 mL, 7.4 mmol, 1.1 equiv.) were dissolved in 10 mL of dry DCM in an argon purged round-bottom flask. The solution was cooled to 0ºC and BF_3•OEt_2

(1.16 mL, 9.4 mmol, 1.4 equiv.) was added dropwise. The solution was then left warming to room temperature for 1 hour. The reaction was quenched with a 10% aqueous NaOH solution (10 mL). The layers were separated, and the organic phase collected and washed with water (10 mL) and Brine (10 mL). The organic solvent was dried over $MgSO_4$ and filtered. After evaporation of the solvent, the product was recrystallized from isopropanol to give **14b** as yellow crystals in 93% yield (1.498 g, 6.26 mmol). Obtained with same spectral characterization as previously described.[4] ^{1}**H NMR** (300 MHz, $CDCl_3$): δ ppm 7.33 (d, J=8.8 Hz, 2H), 6.67 (d, J=8.8 Hz, 2H), 5.12 (s, 1H), 3.17-2.86 (m, 4H), 2.94 (s, 6H), 2.20-2.10 (m, 1H), 1.97-1.82 (m, 1H).



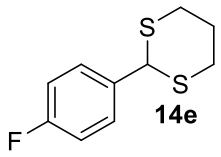
14c

Prepared according to general procedure. 89% yield (2.997 g, 13.54 mmol), white crystals. Obtained with same spectral characterization as previously described.[2] ^{1}**H NMR** (300 MHz, $CDCl_3$): δ ppm 7.65-7.57 (m, 4H), 5.17 (s, 1H), 3.11-3.01 (m, 2H), 2.96-2.90 (m, 2H), 2.23-2.15 (m, 1H), 2.01-1.86 (m, 1H).



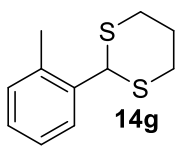
14d

Prepared according to general procedure. 81% yield (3.628 g, 13.18 mmol), white crystals. Obtained with same spectral characterization as previously described.[2] ^{1}**H NMR** (300 MHz, $CDCl_3$): δ ppm 7.49-7.44 (m, 2H), 7.37-7.32 (m, 2H), 5.11 (s, 1H), 3.10-3.00 (m, 2H), 2.94-2.86 (m, 2H), 2.22-2.12 (m, 1H), 1.99-1.84 ppm (m, 1H).



14e

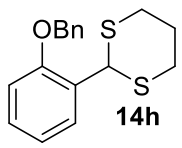
Prepared according to general procedure. 76% yield (1.515 g, 7.07 mmol), white crystals. Obtained with same spectral characterization as previously described.[5] ^{1}**H NMR** (300 MHz, $CDCl_3$): δ ppm 7.47-7.42 (m, 2H), 7.05-6.99 (m, 2H), 5.14 (s, 1H), 3.10-3.01 (m, 2H), 2.94-2.87 (m, 2H), 2.22-2.13 (m, 1H), 1.99-1.84 (m, 1H).



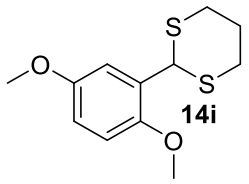
14g

Prepared according to general procedure. 69% yield (1.253 g, 5.96 mmol), white crystals. Obtained with same spectral characterization as previously described.[2] ^{1}**H NMR** (300 MHz, $CDCl_3$): δ ppm 7.61-7.57 (m, 1H), 7.24-7.13 (m, 3H), 5.33 (s, 1H),

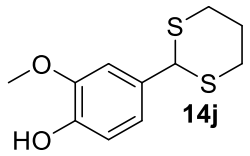
3.14-3.04 (m, 2H), 2.95-2.88 (m, 2H), 2.45 (s, 3H), 2.23-2.14 (m, 1H), 2.02-1.87 (m, 1H).



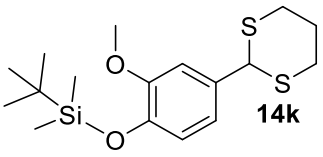
Prepared according to general procedure. 88% yield (1.681 g, 5.56 mmol), pale yellow solid. Product was isolated by flash chromatography (Hex:AcOEt, 95:5). ^{1}**H NMR** (300 MHz, $CDCl_3$): δ ppm 7.60 (dd, *J*=7.6, 1.8 Hz, 1H), 7.47-7.30 (m, 5H), 7.21 (td, *J*=7.8, 1.5 Hz, 1H), 7.00 -6.95 (m, 1H), 6.89 (d, *J*=8.2 Hz, 1H), 5.76 (s, 1H), 5.13 (s, 2H), 3.13-2.85 (m, 2H), 2.92-2.85 (m, 2H), 2.20-2.11 (m, 1H), 2.00-1.85 (m, 1H). ^{13}**C{1H} NMR** (75 MHz, $CDCl_3$): δ ppm 154.8, 137.2, 129.4, 129.3, 128.7, 128.1, 128.0, 127.3, 121.5, 112.7, 70.6, 44.2, 44.1, 32.5, 25.5. **HR-MS (ESI)** m/z calculated for $C_{17}H_{19}OS_2^+$ $[M+H]^+$ 303.0872, found 303.0884.



Prepared according to general procedure. 76% yield (1.172 g, 4.57 mmol), white crystals. Obtained with same spectral characterization as previously described.[2] ^{1}**H NMR** (300 MHz, $CDCl_3$): δ ppm 7.15 (dd, *J*=2.3, 1.2 Hz, 1H), 6.83-6.76 (m, 2H), 5.67 (s, 1H), 3.82 (s, 3H), 3.78 (s, 3H), 3.16-3.06 (m, 2H), 2.93-2.86 (m, 2H), 2.20-2.12 (m, 1H), 2.01-1.86 (m, 1H).

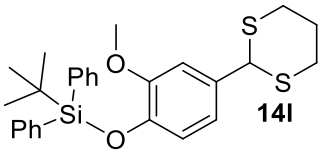


4-(1,3-Dithian-2-yl)-2-methoxyphenol **14j** wasPrepared according to the general procedure and used in preparation of **14k** and **14l**. 84% yield (6.723 g, 27.73 mmol), white crystals. Obtained with same spectral characterization as previously described.[6] ^{1}**H NMR** (300 MHz, $CDCl_3$): δ ppm 7.00-6.84 (m, 2H), 6.87-6.84 (m, 1H), 5.64 (s, 1H), 5.11 (s, 1H), 3.90 (s, 3H), 3.10-2.87 (m, 2H), 2.93-2.86 (m, 2H), 2.21-2.12 (m, 1H), 1.99-1.84 (m, 1H).



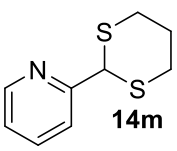
4-(1,3-Dithian-2-yl)-2-methoxyphenol (0.8 g, 3.30 mmol, 1 equiv.), imidazole (270 mg, 3.96 mmol, 1.2 equiv.) and 4-dimethylaminopyridine (42 mg, 0.34 mmol, 0.1 equiv.) were dissolved in dry DCM (10 mL), in an argon purged round-bottom flask. Then, *tert*-butyldimethylsilyl chloride (597 mg, 3.96 mmol, 1.2 equiv.) was added dropwise to the stirring solution. The mixture was left stirring at room temperature for 24 h. The reaction was quenched with H_2O

(10 mL) and the layers were separated. The organic layer was collected and washed with water (10 mL) and Brine (10 mL), dried over $MgSO_4$, filtered and evaporated. The product was purified by flash chromatography (Hex:EtOAc, 95:5) to yield **14k** in 90% yield (1.056 mg, 2.86 mmol) as a colorless thick oil with same spectral characterization as previously described.[7] ^{1}**H NMR** (300 MHz, $CDCl_3$): δ ppm 6.97 (d, *J*=1.8 Hz, 1H), 6.92-6.89 (m, 1H), 6.79-6.76 (m, 1H), 5.11 (s, 1H), 3.81 (s, 3H), 3.10-3.01 (m, 2H), 2.93-2.86 (m, 2H), 2.21-2.11 (m, 1H), 1.99-1.84 (m, 1H), 0.98 (s, 9H), 0.14 (s, 6H).



14l

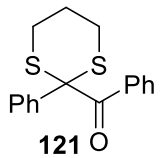
4-(1,3-Dithian-2-yl)-2-methoxyphenol (0.5 g, 2.06 mmol, 1 equiv.), imidazole (155 mg, 2.27 mmol, 1.1 equiv.) and 4-dimethylaminopyridine (25 mg, 0.2 mmol, 0.1 equiv.) were dissolved in dry DCM (10 mL), in an argon purged round-bottom flask. Then, *tert*-butyl(chloro)diphenylsilane was added dropwise to the stirring solution. The mixture was left stirring at room temperature for 24 h. The reaction was quenched with H_2O (10 mL) and the layers were separated. The organic layer was collected and washed with water (10 mL) and Brine (10 mL), dried over $MgSO_4$, filtered, and evaporated. The product was purified by flash chromatography (Hex:DCM, 1:1) to yield **14l** in 93% yield (918 mg, 1.91 mmol) as a colorless thick oil. ^{1}**H NMR** (300 MHz, $CDCl_3$): δ ppm 7.69 (dd, *J*=7.6, 1.8 Hz, 4H), 7.42-7.31 (m, 6H), 6.89 (d, *J*=1.8 Hz, 1H), 6.76-6.73 (m, 1H), 6.55-6.63 (m, 1H), 5.05 (s, 1H), 3.57 (s, 3H), 3.07-2.98 (m, 2H), 2.91-2.83 (m, 2H), 2.18-2.09(m, 1H), 1.96-1.81 (m, 1H), 1.10 ppm (s, 9H). ^{13}**C{1H} NMR** (75 MHz, $CDCl_3$): δ ppm 150.6, 145.2, 135.5, 133.6, 132.3, 129.7, 127.6, 120.2, 120.0, 111.8, 55.5, 51.5, 32.3, 26.8, 25.2, 19.9. **HR-MS (ESI)** m/z calculated for $C_{27}H_{33}O_2S_2Si^+$ $[M+H]^+$ 481.1686, found 481.1687.



14m

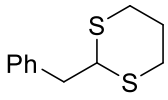
Prepared according to a modified reported method.[8] Freshly distilled picolinaldehyde (1 mL, 10.51 mmol, 1 equiv.) and 1,3-propanedithiol (1.16 mL, 11.56 mmol, 1.1 equiv.) were dissolved in DCE (20 mL). *p*-Toluenosulfonic acid (200 mg, 1.05 mmol, 0.1 equiv.) was added to the mixture and the solution refluxed for 24 hours. The reaction was cooled to room temperature and quenched with a 10% aqueous NaOH solution (10 mL). The layers were separated, and the organic phase collected and washed with water (10 mL) and brine (10 mL). The organic solvent was dried over $MgSO_4$ and

filtered. The solvent was evaporated and the product isolated by flash chromatography (Hex:AcOEt, 70:30) to give **14m** as a yellow solid in 54% yield (1.111 g, 5.63 mmol), with same spectral characterization as previously described.[38] ^{1}**H NMR** (300 MHz, $CDCl_3$): δ ppm 8.57 (dd, *J*=4.4, 1.5 Hz, 1H), 7.67 (td, *J*=7.6, 1.8 Hz, 1H), 7.46 (d, *J*=7.6 Hz, 1H), 7.22-7.18 (m, 1H), 5.35 (s, 1H), 3.11-2.92 (m, 4H), 2.23-2.13 (m, 1H), 2.05-1.90 (m, 1H).



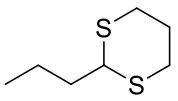
121

Prepared according to a modified reported method.[9] Benzil (1g, 4.76 mmol, 1.2 equiv.) was dissolved in dry DCM (5 mL) in an argon purged round-bottom flask. The solution was cooled to 0 °C in an ice bath bath. A solution of 1,3-propanedithiol (398 μL, 3.96 mmol, 1 equiv.) and BF_3•Et_2O (489 μL, 3.96 mmol, 1 equiv.) in dry DCM (1.5 mL) was added dropwise at 0 °C. The solution was warmed to room temperature for 3 hours and quenched with 10 mL of a saturated aqueous $NaHCO_3$ solution. The layers were separated, and the organic phase collected. The aqueous phase was extracted with DCM (3 × 10 mL) and the organic phases combined, dried over $MgSO_4$, filtered and the solvent evaporated. The dry crude was dissolved in hot isopropanol and left cooling at room temperature. After 3 hours, the product precipitated as a white solid and was filtered and washed with cold isopropanol to yield **121** as a white solid in 54% yield (641 mg, 2.13 mmol). ^{1}**H NMR** (300 MHz, $CDCl_3$): δ ppm 7.69-7.66 (m, 2H), 7.57 (dd, *J*=7.9, 1.5 Hz, 2H), 7.38-7.28 (m, 4H), 7.22-7.17 (m, 2H), 3.26 (ddd, *J*=14.4, 12.0, 2.9 Hz, 2H), 2.80-2.73 (m, 2H), 2.17-2.08 (m, 1H), 2.01-1.86 (m, 1H). ^{13}**C{1H} NMR** (300 MHz, $CDCl_3$): δ ppm 192.8, 139.0, 134.5, 132.2, 130.8, 129.2, 128.8, 127.7, 127.5, 63.5, 29.3, 24.1. **HR-MS (ESI)** m/z calculated for $C_{17}H_{17}OS_2^+$ $[M+H]^+$ 301.0715, found 301.0734.



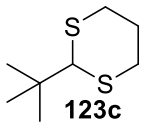
123a

Prepared according to general procedure. 53% yield (560 mg, 2.66 mmol), pale green solid. 1.2 equiv. of 1,3-propanedithiol were used. Obtained with same spectral characterization as previously described,[10] after purification by flash chromatography (Hex:EtOAc, 85:15). 1**H NMR** (300 MHz, CDCl3): δ ppm 7.34-7.22 (m, 5H), 4.24 (t, J = 7.3 Hz, 1H), 3.02 (d, J = 7.3 Hz, 2H), 2.85-2.80 (m, 4H), 2.15-2.05 (m, 1H), 1.92-1.79 (m, 1H).



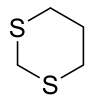
123b

Prepared according to a modified method.[3] Butyraldehyde (0.45 mL, 5 mmol, 1 equiv.) and 1,3-propanedithiol (0.6 mL, 6 mmol, 1.2 equiv.) were dissolved in 20 mL of dry DCM under argon. The solution was stirred at room temperature and BF_3•OEt_2 (0.43 mL, 0.7 mmol, 0.7 equiv.) was added dropwise. After 90 minutes, the reaction was quenched by washing the reaction mixture twice with 20 mL of 10% aqueous NaOH. The combined aqueous layers were then extracted twice with 20 mL of DCM. The organic layers were combined, washed with 25 mL of brine and dried over $MgSO_4$. The organic solvent was evaporated under reduced pressure and the resulting oil was purified by flash chromatography (hexane/EtOAc 97:3), which afforded **123b** as a colorless oil in 99% yield (808 mg, 4.98 mmol). Obtained with same spectral characterization as previously described.[2] ^{1}**H NMR** (300 MHz, $CDCl_3$): δ ppm 4.05 (t, J=6.7 Hz, 1H), 2.92-2.76 (m, 4H), 2.14-2.06 (m, 1H), 1.90-1.77 (m, 1H), 1.75-1.67 (m, 2H), 1.59-1.45 (m, 2H), 0.85-0.97 (m, 3H).



123c

Prepared according to a modified reported method.[11] Pivalaldehyde (5 mmol, 1 equiv.) and *N*-bromosuccinimide (178 mg, 1 mmol, 0.2 equiv.) were dissolved in CH_2Cl_2 (25 ml). The solution was then stirred under argon at r.t. and 1,3-propanedithiol (1.2 equiv.) was added dropwise. The reaction was monitored by TLC and quenched with 10% aqueous NaOH (25 ml) when the aldehyde was consumed (30-80 min). Aqueous and organic layers were separated, and the aqueous layer was washed with CH_2Cl_2 (2 x 25 ml). The combined organic layers were washed with 25 ml brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. 62% yield (544 mg, 3.08 mmol), white solid was obtained with same spectral characterization as previously described.[2] ^{1}**H NMR** (300 MHz, $CDCl_3$): δ ppm 3.99 (s, 1H), 2.90-2.86 (m, 4H), 2.11-2.02 (m, 1H), 1.86-1.74 (m, 1H), 1.10 (s, 9H).



126

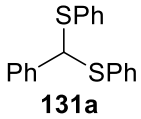
Prepared according to a modified reported method.[12] In an argon purged round-bottom flask were added 10 mL of dry DCM, 5 mL of glacial acetic acid, and BF_3•OEt_2 (2.47 mL, 20 mmol, 1 equiv.). Then, a solution of 1,3-propanedithiol (2 mL, 20 mmol, 1 equiv.) and chloromethyl methyl ether (1.67 mL, 22 mmol, 1.1 equiv.) in 30 mL of dry DCM was added dropwise for 10 min at room temperature. The solution was left stirring for 3 hours at room temperature, and then quenched with 40 mL of water. The layers were

separated and the organic phase collected and washed with water (40 mL), a 10% aqueous NaOH solution (2 × 40 mL) and brine (40 mL). The organic solvent was dried over $MgSO_4$, filtered and evaporated. Sublimation under reduced pressure gave pure **126** as a white solid in 32% yield (778 mg, 6.47 mmol), with same spectral characterization as previously described.[13] ^{1}**H NMR** (300 MHz, $CDCl_3$): δ ppm 3.78 (s, 2H), 2.84-2.80 (m, 4H), 2.11-2.03 (m, 2H).

Synthesis of dithioacetals 131:

13a **131**

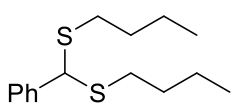
General procedure: Based on modified previously reported method.[11] Benzaldehyde **13a** (5 mmol, 1 equiv.) and *N*-bromosuccinimide (178 mg, 1 mmol, 0.2 equiv.) were dissolved in CH_2Cl_2 (25 ml). The solution was then stirred under argon at r.t. and thiol (2.5 equiv.) was added dropwise. The reaction was monitored by TLC and quenched with 10% aqueous NaOH (25 ml) when the aldehyde was consumed (30-80 min). Aqueous and organic layers were separated, and the aqueous layer was washed with CH_2Cl_2 (2 x 25 ml). The combined organic layers were washed with 25 ml brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product **131** was then purified by recrystallization or by flash chromatography.



131a

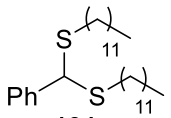
Prepared according to a modified previously reported method.[14] Benzaldehyde (0.51 ml, 5 mmol, 1 equiv.) and benzenethiol (1.08 ml, 10.5 mmol, 2.1 equiv.) were dissolved in $CHCl_3$ (25 ml). The solution was then stirred at room temperature and I_2 (0.13 g, 0.5 mmol, 0.1 equiv.) was added. The reaction was monitored by TLC. When the aldehyde was consumed (30 min) the reaction was quenched with aqueous $Na_2S_2O_3$ (0.1 M, 25 ml) and then washed twice with 10% aqueous NaOH (25 ml). Aqueous and organic layers were separated and the aqueous layer was washed with $CHCl_3$ (25 ml). The combined organic layers were washed with 20 ml of H_2O, dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield the crude product. The crude product was then purified by recrystallization from hexane to afford **131a** as white crystals in 66% yield (1.01 g, 3.28 mmol) with the same spectral characterization as

previously described.[15] ^{1}**H NMR** (300 MHz, $CDCl_3$): δ ppm 7.39-7.20 (m, 15H), 5.42 (s, 1H).



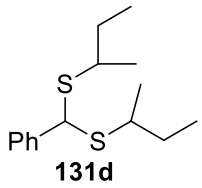
131b

Prepared according to general procedure. Flash chromatography eluent: Hex:AcOEt (97.5:2.5). 91% yield (1.218 g, 4.54 mmol), colorless oil. ^{1}**H NMR** (300 MHz, $CDCl_3$): δ ppm 7.45-7.42 (m, 2H), 7.34-7.22 (m, 3H), 4.87 (s, 1H), 2.63-2.46 (m, 4H), 1.58-1.48 (m, 4H), 1.42-1.30 (m, 4H), 0.87 (t, J = 7.3 Hz, 6H). ^{13}**C{1H} NMR** (75 MHz, $CDCl_3$): δ ppm 140.7, 128.5, 127.8, 127.8, 53.3, 32.0, 31.3, 22.1, 13.7. **HR-MS (ESI)** m/z calculated for $C_{15}H_{23}S_2^+$ $[M-H]^+$ 267.1236, found 267.1246.



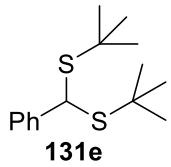
131c

Prepared according to a modified reported method.[14] Benzaldehyde (2 mL, 19.7 mmol, 1 equiv.) and dodecanethiol (10.4mL, 43.3 mmol, 2.2 equiv.) were dissolved in dichloromethane (30 mL) in a round-bottom flask. Then, iodine (508, 2 mmol, 0.1 equiv.) was slowly added do the stirring solution as to prevent vigorous boiling of the solvent. After 2 hours of complete addition, the reaction was quenched with a 2% $Na_2S_2O_3$ aqueous solution (10 mL). The layers were separated, and the organic layer collected and washed successively with a 10% aqueous NaOH solution (10 mL), water (10 mL) and brine (10 mL). The organic solvent was dried over $MgSO_4$ and filtered. After evaporating the solvent, the product was purified by flash chromatography (hexane) to give **131c** as a white amorphous solid in 57% yield (5.563 g, 11.29 mmol). ^{1}**H NMR** (300 MHz, $CDCl_3$): δ ppm 7.45-7.42 (m, 2H), 7.35-7.22 (m, 3H), 4.86 (s, 1H), 2.62-2.45 (m, 4H), 1.59-1.49 (m, 4H), 1.35-1.24 (m, 36H), 0.90-0.86 (m, 6H). ^{13}**C{1H} NMR** ($CDCl_3$, 75MHz) δ ppm 140.8, 128.6, 127.9, 127.8, 53.3, 32.4, 32.1, 29.8, 29.7, 29.6, 29.5, 29.3, 29.3, 29.0, 22.8, 14.3. **HR-MS (ESI)** m/z calculated for $C_{31}H_{55}S_2^+$ $[M-H]^+$ 491.3740, found 491.3757.



131d

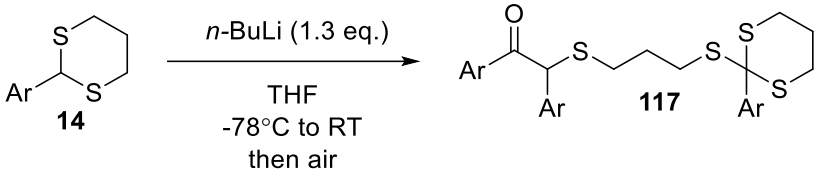
Prepared according to general procedure. 86% yield (1.150 g, 4.29 mmol), colorless oil. Flash chromatography eluent: Hex:AcOEt (97.5:2.5). ^{1}**H NMR** (300 MHz, $CDCl_3$): δ ppm 7.47 (d, J = 7.6 Hz, 2H), 7.34-7.22 (m, 3H), 4.94 (s, 1H), 2.88-2.63 (m, 2H), 1.66-1.42 (m, 4H), 1.24-1.20 (m, 6H), 0.97-0.88 (m, 6H). ^{13}**C{1H} NMR** (75 MHz, $CDCl_3$): δ ppm 141.1, 128.5, 127.8, 127.7, 50.8, 50.6, 42.5, 42.4, 29.5, 29.5, 20.7, 20.6, 20.6, 11.2, 11.1. **HR-MS (ESI)** m/z calculated for $C_{15}H_{23}S_2^+$ $[M-H]^+$ 267.1236, found 267.1243.



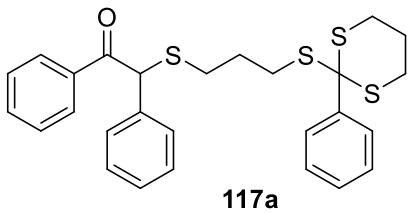
131e

Prepared according to general procedure. 87% yield (1.171 g, 4.37 mmol), white solid. Flash chromatography eluent: Hex:AcOEt (97.5:2.5). ^{1}**H NMR** (300 MHz, $CDCl_3$): δ ppm 7.48-7.44 (m, 2H), 7.32-7.26 (m, 2H), 7.23-7.18 (m, J = 1.3 Hz, 1H), 5.02 (s, 1H), 1.29 (s, 18H). ^{13}**C{1H} NMR** (75 MHz, $CDCl_3$): δ ppm 144.1, 128.7, 127.7, 127.4, 48.8, 45.8, 31.3. **HR-MS (ESI)** m/z calculated for $C_{15}H_{23}S_2^+$ $[M-H]^+$ 267.1236, found 267.1243.

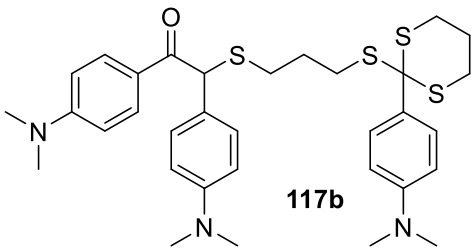
Autooxidative addition of dithianes 14:



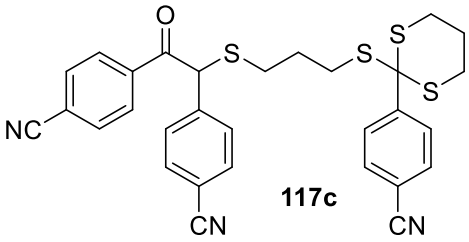
Aryl dithiane **14** (1.02 mmol, 1 equiv.) was dissolved in dry THF (5 mL) in an argon purged round-bottom flask. The solution was cooled to -78 ºC in an acetone/liquid nitrogen bath. *n*-BuLi (1.3 equiv.) solution in hexanes was added dropwise to the reaction mixture at -78 ºC. The solution was left stirring at -78 ºC for 20 minutes and then left to warm up to room temperature for 40 minutes. The argon balloon was replaced with an atmospheric air balloon and an additional needle was inserted in the septum as to allow air flow through the surface of the solution. As oxidation took place the solution warmed up and color change was usually observed. After 1 minute the solution was quenched with 10 mL of a saturated aqueous NH_4Cl solution. 10 mL of Et_2O were added and the layers were separated. The organic phase was collected, and the aqueous phase was extracted two times with Et_2O (2 × 10 mL). The organic phases were combined and dried over $MgSO_4$. The solvent was filtered and evaporated. The product **117** was purified by flash chromatography.



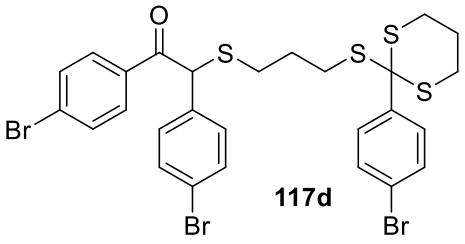
Prepared according to general procedure. 76% yield (128 mg, 0.26 mmol), pale yellow oil. Flash chromatography eluent: Hex:AcOEt (90:10). ^{1}**H NMR** (300 MHz, $CDCl_3$): δ ppm 7.96 - 7.90 (m, 4 H) 7.54 - 7.23 (m, 11 H) 5.51 (s, 1 H) 3.30 (ddt, *J*=13.8, 10.8, 2.9, 2.9 Hz, 2 H) 2.75 - 2.68 (m, 2 H) 2.57 - 2.44 (m, 4 H) 2.15 - 2.04 (m, 1 H) 1.96 - 1.83 (m, 1 H) 1.76-1.66 (m, 2 H). ^{13}**C{1H} NMR** (75 MHz, $CDCl_3$): δ ppm 195.1, 141.6, 136.7, 135.8, 133.4, 129.1, 129.0, 128.9, 128.8, 128.6, 128.5, 128.1, 128.0, 64.3, 55.6, 32.7, 30.6, 29.2, 28.4, 24.4. **HR-MS (ESI)** m/z calculated for $C_{27}H_{28}OS_4Na^+$ $[M+Na]^+$ 519.0915, found 519.0894.



Prepared according to general procedure. 64% yield (135 mg, 0.22 mmol), amorphous yellow solid. Flash chromatography eluent: Hex:AcOEt (60:40). ^{1}**H NMR** (300 MHz, $CDCl_3$): δ ppm 7.90-7.87 (m, 2H), 7.79-7.76 (m, 2H), 7.30-7.26 (m, 2H), 6.67-6.56 (m, 6H), 5.47 (s, 1H), 3.36-3.26 (m, 2H), 3.01 (s, 6H), 2.95 (s, 6H), 2.90 (s, 6H), 2.72-2.67 (m, 2H), 2.59-2.45 (m, 4H), 2.12-2.03 (m, 1H), 1.94-1.84 (m, 1H), 1.81-1.71 (m, 2H). ^{13}**C{1H} NMR** (75 MHz, $CDCl_3$): δ ppm 193.5, 153.4, 150.2, 150.0, 131.3, 129.5, 129.0, 128.4, 124.9, 123.6, 112.7, 111.9, 110.7, 64.4, 54.9, 40.6, 40.5, 40.1, 32.9, 30.6, 29.4, 28.7, 24.5. **HR-MS (ESI)** m/z calculated for $C_{33}H_{43}N_3OS_4Na^+$ $[M+Na]^+$ 648.2181, found 648.2187.

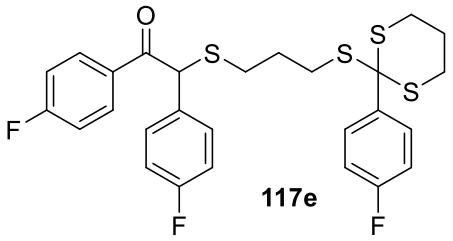


Prepared according to general procedure. 60% yield (232 mg, 0.41 mmol), amorphous white solid. Flash chromatography eluent: Hex:AcOEt (70:30). ^{1}**H NMR** (300 MHz, $CDCl_3$): δ ppm 8.05 – 8.02 (m, 4H), 7.75 (d, *J*=8.8 Hz, 2H), 7.67 - 7.56 (m, 6H), 5.43 (s, 1H), 3.20 (tdd, *J*=2.3, 9.9, 14.1 Hz, 2H), 2.73 (ddd, *J*=2.9, 6.9, 14.2 Hz, 2H), 2.60-2.44 (m, 4H), 2.12 - 2.02 (m, 1H), 1.97 - 1.84 (m, 1H), 1.73-1.64 (m, 2H). ^{13}**C{1H} NMR** (75 MHz, $CDCl_3$): δ ppm 192.3, 146.8, 141.1, 138.4, 132.7, 132.4, 129.8, 129.4, 129.0, 118.5, 118.3, 117.7, 117.1, 112.4, 112.3, 63.5, 54.2, 32.4, 30.8, 29.3, 28.1, 23.9. **HR-MS (ESI)** m/z calculated for $C_{30}H_{25}N_3OS_4Na^+$ $[M+Na]^+$ 594.0773, found 594.0773.



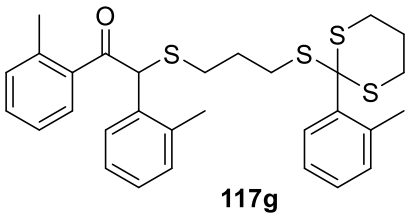
Prepared according to general procedure. LDA was used instead of *n*-BuLi. 51% yield (127 mg, 0.17 mmol), pale yellow oil. 1**H NMR** (300 MHz, CDCl3): δ ppm 7.83-7.77 (m, 4H), 7.59-7.54 (m, 2H), 7.50-7.44 (m, 4H), 7.32-7.26 (m, 2H), 5.37 (s, 1H), 3.29-3.19 (m, 2H), 2.75-2.69 (m, 2H), 2.59-2.45 (m, 4H), 2.13-2.03 (m, 1H), 1.96-1.82 (m, 1H), 1.76-1.66 (m, 2H). 13**C{1H} NMR**

(75 MHz, CDCl3): δ ppm 193.5, 140.7, 135.4, 134.2, 132.2, 132.2, 131.7, 130.6, 130.5, 129.9, 128.9, 122.7, 122.4, 63.7, 54.5, 32.6, 30.7, 29.3, 28.3, 24.2. **HR-MS (ESI)** m/z calculated for C27H24Br3OS4- [M-H]- 728.8266, found 728.8265.



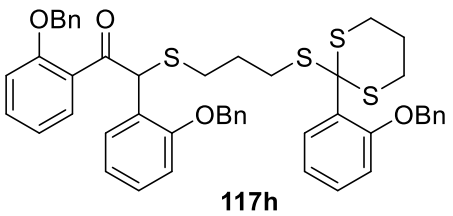
117e

Prepared according to general procedure. 60% yield (112 mg, 0.20 mmol), colorless oil. Flash chromatography eluent: Hex:AcOEt (94:6). ^{1}**H NMR** (300 MHz, $CDCl_3$): δ ppm 8.00-7.88 (m, 4H), 7.42-7.38 (m, 2H), 7.12-7.00 (m, 6H), 5.44 (s, 1H), 3.26 (ddt, *J*=13.8, 10.9, 2.6 Hz, 2H), 2.76-2.68 (m, 2H), 2.57-2.46 (m, 4H), 2.13-2.04 (m, 1H), 1.96-1.82 (m, 1H), 1.76-1.66 (m, 2H). ^{19}F NMR (282MHz, $CDCl_3$): δ ppm -104.01--104.09 (m, 1F), -113.35--113.45 (m, 1F), -113.56--113.66 ppm (m, 1F). ^{13}**C{1H} NMR** (75 MHz, $CDCl_3$): δ ppm 193.3, 167.6, 164.2, 164.2, 160.9, 137.4, 137.4, 132.3, 132.2, 131.9, 131.9, 131.8, 131.7, 130.6, 130.5, 130.1, 130.0, 116.2, 115.9, 115.5, 115.2, 63.6, 54.4, 32.7, 30.7, 29.3, 28.3, 24.2. **HR-MS (ESI)** m/z calculated for $C_{27}H_{25}F_3OS_4Na^+$ $[M+Na]^+$ 573.0633, found 573.0640.



117g

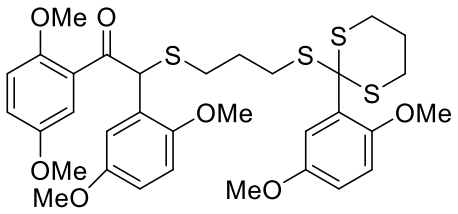
Prepared according to general procedure. 66% yield (120 mg, 0.22 mmol), colorless oil. Flash chromatography eluent: Hex:AcOEt (95:5). ^{1}**H NMR** (300 MHz, $CDCl_3$): δ ppm 7.97-7.94 (m, 1H), 7.42 (d, *J*=5.9 Hz, 2H), 7.32-7.27 (m, 1H), 7.19-7.12 (m, 8H), 5.52 (s, 1H), 3.40-3.30 (m, 2H), 2.83 (s, 3H), 2.75-2.68 (m, 2H), 2.55-2.48 (m, 4H), 2.37 (s, 3H), 2.33 (s, 3H), 2.15-2.04 (m, 1H), 1.98-1.84 (m, 1H), 1.74-1.64 (m, 2H). ^{13}**C{1H} NMR** (75 MHz, $CDCl_3$): δ ppm 199.0, 138.7, 138.4, 138.0, 137.7, 136.1, 134.2, 133.8, 131.9, 131.2, 130.9, 129.2, 129.0, 128.4, 128.1, 127.6, 126.7, 125.6, 125.5, 64.9, 54.7, 32.8, 31.1, 29.2, 28.6, 24.3, 23.6, 20.8, 19.8. **HR-MS (ESI)** m/z calculated for $C_{30}H_{34}OS_4Na^+$ $[M+Na]^+$ 561.1385, found 561.1389.



117h

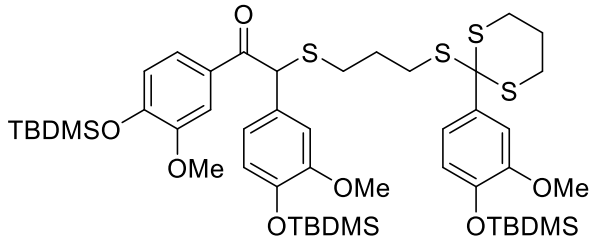
Prepared according to general procedure. 58% yield (324 mg, 0.40 mmol), pale yellow oil. Flash chromatography eluent: Hex:AcOEt (80:20). ^{1}**H NMR** (300 MHz, $CDCl_3$): δ ppm 7.87-7.85 (m, 1H), 7.59 (d,

J=7.6 Hz, 2H), 7.43 (dt, *J*=7.6, 2.1 Hz, 2H), 7.36-7.13 (m, 16H), 6.94-6.76 (m, 6H), 6.12 (s, 1H), 5.17 (s, 2H), 4.95-4.79 (m, 4H), 3.32-3.24 (m, 2H), 2.71-2.64 (m, 2H), 2.40-2.30 (m, 4H), 2.07-1.96 (m, 1H), 1.94-1.80 (m, 1H), 1.56-1.46 (m, 2H). ^{13}**C{1H} NMR** (75 MHz, $CDCl_3$): δ ppm 198.0, 157.1, 156.8, 156.0, 137.5, 136.9, 136.4, 132.8, 130.8, 130.3, 129.8, 129.6, 129.4, 128.8, 128.7, 128.6, 128.6, 128.4, 128.1, 127.9, 127.5, 127.5, 127.3, 127.2, 125.7, 121.0, 120.8, 120.5, 114.8, 112.7, 111.8, 71.0, 70.4, 70.2, 63.1, 52.5, 32.9, 31.0, 28.9, 28.5, 24.3. **HR-MS (ESI)** m/z calculated for $C_{48}H_{46}O_4S_4Na^+$ $[M+Na]^+$ 837.2171, found 837.2196.



117i

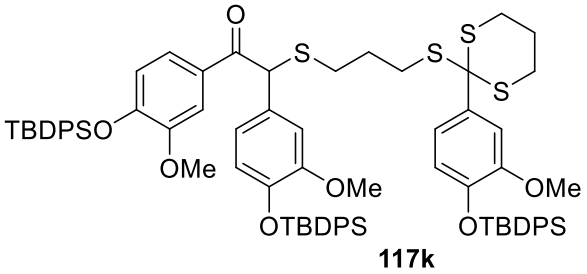
Prepared according to general procedure. 68% yield (157 mg, 0.23 mmol), colorless oil. Flash chromatography eluent: Hex:AcOEt (80:20). ^{1}**H NMR** (300 MHz, $CDCl_3$): δ ppm 7.45 (d, *J*=2.9 Hz, 1H), 7.13 (d, *J*=3.5 Hz, 1H), 6.99 (t, *J*=1.5 Hz, 1H), 6.95-6.78 (m, 4H), 6.71 (d, *J*=1.8 Hz, 2H), 6.03 (s, 1H), 3.82 (s, 3H), 3.76 (s, 6H), 3.73 (s, 3H), 3.72 (s, 3H), 3.70 (s, 3H), 3.36-3.26 (m, 2H), 2.74-2.68 (m, 2H), 2.54-2.49 (m, 4H), 2.10-2.01 (m, 1H), 1.96-1.83 (m, 1H), 1.75-1.65 ppm (m, 2H). ^{13}**C{1H} NMR** (75 MHz, $CDCl_3$): δ ppm 197.4, 153.7, 153.4, 153.2, 152.6, 152.4, 151.1, 130.7, 128.2, 126.7, 119.5, 116.0, 115.6, 115.6, 114.8, 114.2, 113.8, 113.0, 111.8, 62.5, 57.6, 56.2, 55.9, 55.8, 55.8, 52.1, 32.9, 30.9, 29.0, 28.6, 24.4. **HR-MS (ESI)** m/z calculated for $C_{33}H_{40}O_7S_4Na^+$ $[M+Na]^+$ 699.1549, found 699.1572.



117j

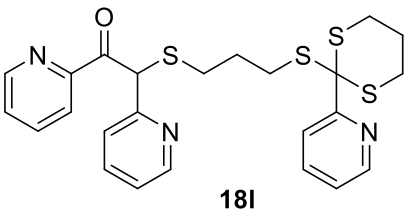
Prepared according to general procedure. 61% yield (148 mg, 0.15 mmol), amorphous white solid. Flash chromatography eluent: Hex:DCM (1:1). ^{1}**H NMR** (300 MHz, $CDCl_3$): δ ppm ^{1}**H NMR** ($CDCl_3$, 300MHz): d = 7.49-7.45 (m, 3H), 7.37-7.34 (m, 1H), 6.96 (d, *J*=2.3 Hz, 1H), 6.85-6.74 (m, 4H), 5.43 (s, 1H), 3.80 (s, 6H), 3.77 (s, 3H), 3.33-3.24 (m, 2H), 2.74-2.67 (m, 2H), 2.58-2.44 (m, 4H), 2.12-2.05 (m, 1H), 1.94-1.82 (m, 1H), 1.74-1.65 (m, 2H), 0.98 (s, 9H), 0.97 (s, 9H), 0.96 (s, 9H), 0.15-0.11 (m, 18H) ^{13}**C{1H} NMR** (75 MHz, $CDCl_3$): δ ppm 194.2, 151.4, 151.1, 150.8, 150.3, 145.2, 144.9, 134.7, 130.3, 129.8, 123.3, 121.5, 120.8, 120.5,

120.4, 120.3, 112.3, 112.2, 112.1, 64.2, 55.7, 55.6, 55.5, 55.3, 32.8, 30.7, 29.4, 28.5, 25.8, 25.7, 24.5, 18.6, 18.5, -4.4, -4.5. **HR-MS (ESI)** m/z calculated for $C_{48}H_{76}O_7S_4Si_3Na^+$ $[M+Na]^+$ 999.3679, found 999.3645.



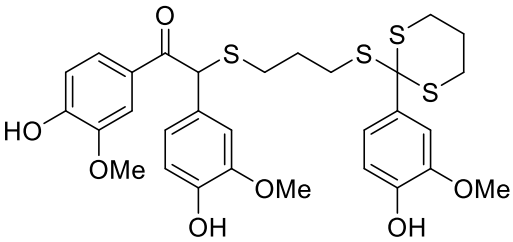
117k

Prepared according to general procedure. 89% yield (239 mg, 0.19 mmol), amorphous white solid. Flash chromatography eluent: Hex:AcOEt (80:20). ^{1}**H NMR** (300 MHz, $CDCl_3$): δ ppm 7.69-7.61 (m, 12H), 7.41-7.15 (m, 22H), 6.79 (s, 1H), 6.66-6.59 (m, 4H), 5.28 (s, 1H), 3.53 (s, 3H), 3.52 (s, 3H), 3.47 (s, 3H), 3.24-3.15 (m, 2H), 2.63 (dt, *J*=14.1, 2.9 Hz, 2H), 2.45-2.32 (m, 4H), 2.06-1.96 (m, 1H), 1.87-1.75 (m, 1H), 1.63-1.54 (m, 2H), 1.10-1.08 ppm (m, 27H). ^{13}**C{1H} NMR** (75 MHz, $CDCl_3$): δ ppm 194.2, 151.1, 150.7, 150.4, 150.0, 145.2, 144.9, 135.5, 135.3, 134.5, 133.5, 133.5, 133.0, 130.2, 130.0, 129.7, 129.7, 129.6, 127.8, 127.6, 127.5, 123.0, 121.1, 120.2, 120.2, 119.7, 119.5, 112.4, 112.3, 112.2, 64.1, 55.5, 55.5, 55.4, 32.7, 30.5, 29.3, 28.4, 26.8, 26.7, 26.6, 24.4, 19.9, 19.9, 19.9. **HR-MS (ESI)** m/z calculated for $C_{78}H_{88}O_7S_4Si_3Na^+$ $[M+Na]^+$ 1371.4613, found 1371.4641.



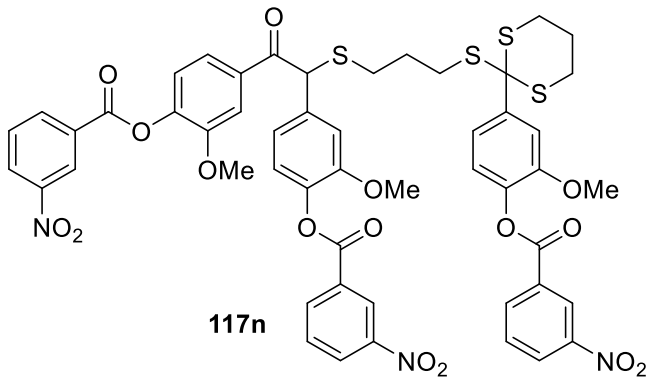
18l

Prepared according to general procedure. 62% yield (63 mg, 0.13 mmol), yellow oil. Flash chromatography was run with eluent Hex:AcOEt:Et_3N (50:50:2) because the compound was unstable in silica without treatment with triethylamine. ^{1}**H NMR** (300 MHz, $CDCl_3$): δ ppm 8.65-8.61 (m, 1H), 8.52-8.45 (m, 2H), 8.10-8.07 (m, 1H), 7.85-7.78 (m, 2H), 7.70-7.66 (m, 3H), 7.49-7.41 (m, 1H), 7.19-7.11 (m, 2H), 6.39 (s, 1H), 3.46-3.34 (m, 2H), 2.75-2.68 (m, 2H), 2.64-2.49 (m, 2H), 2.42 (t, *J*=7.3 Hz, 2H), 2.18-2.10 (m, 1H), 1.95-1.81 (m, 1H), 1.61-1.51 (m, 2H). ^{13}**C{1H} NMR** (75 MHz, $CDCl_3$): δ ppm 195.4, 161.0, 157.8, 152.3, 149.2, 149.1, 148.0, 137.1, 137.1, 136.8, 127.4, 124.0, 123.2, 123.2, 122.3, 122.2, 65.9, 53.2, 32.7, 31.2, 28.3, 28.2, 24.9. **HR-MS (ESI)** m/z calculated for $C_{24}H_{25}N_3OS_4Na^+$ $[M+Na]^+$ 522.0773, found 522.0806.



117m

After standard autoxidative addition of dithiane **14k**, the resulting crude was not purified via column chromatography but instead was dissolved in dry methanol (8 mL) in an argon purged round-bottom flask. Then, ammonium fluoride (95 mg, 2.56 mmol, 1.1 equivalents) was added and the solution was stirred overnight at room temperature. The methanol was evaporated, and water (10 mL) was added. The aqueous phase was extracted with DCM (3 × 10 mL) and the organic phases were combined and dried over MgSO4. The solvent was evaporated, and the product was purified by flash chromatography, eluent hexane: ethyl acetate (1:1), to give product **117m** as an amorphous orange solid (286 mg, 0.45 mmol) in 60% overall yield. ^{1}H-NMR (500 MHz, $CDCl_3$) δ ppm 7.56–7.49 (m, 3H), 7.44 (dd, J = 8.4, 2.1 Hz, 1H), 6.98 (s, 1H), 6.89–6.82 (m, 4H), 6.07 (s, 1H), 5.68 (s, 1H), 5.61 (s, 1H), 5.45 (s, 1H), 3.90 (s, 3H), 3.89 (s, 3H), 3.86 (s, 3H), 3.27 (t, J = 12.5 Hz, 2H), 2.74–2.70 (m, 2H), 2.57–2.44 (m, 4H), 2.10–2.05 (m, 1H), 1.92–1.85 (m, 1H), 1.77–1.71 (m, 2H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ ppm 194.0, 150.7, 147.1, 146.8, 146.4, 145.8, 145.6, 133.3, 128.8, 128.5, 124.3, 122.1, 121.3, 114.3, 114.0, 113.9, 111.0, 110.8, 110.6, 64.3, 56.2 (×2), 56.1, 55.2, 32.8, 30.7, 29.4, 28.5, 24.4. **HR-MS (ESI)** m/z calculated for $C_{30}H_{34}O_7S_4Na^+$ $[M + Na]^+$ 657.1080, found 657.1068.



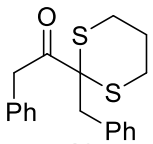
117n

Triphenol **117m** (100 mg, 0.158 mmol) was dissolved in dry DCM (3 mL) in an argon purged round-bottom flask. Pyridine (48 µL, 0.591 mmol, 3.75 equivalents) was added to the solution, followed by 3-nitrobenzoyl chloride (91 mg, 0.488 mmol, 3.1 equivalents). The reaction was left stirring at room temperature for 72 h. Water (10 mL) was added to the mixture and the aqueous phase was extracted with DCM (3 × 10 mL). The organic phases were combined and dried over MgSO4. The solvent was evaporated and the product was purified by flash chromatography, eluent hexane:

ethyl acetate (3:2), to give the benzoyl derivative **117n** as an amorphous white solid (163 mg, 0.151 mmol) in 95% yield. ^{1}**H NMR** (500 MHz, $CDCl_3$) δ ppm 9.02 (s, 3H), 8.51–8.48 (m, 6H), 7.76–7.67 (m, 6H), 7.62 (dd, J = 8.4, 2.0 Hz, 1H), 7.25–7.08 (m, 5H), 5.56 (s, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.83 (s, 3H), 3.31 (dd, J = 13.3, 11.2 Hz, 2H), 2.79 (dd, J = 14.3, 3.6 Hz, 2H), 2.70–2.58 (m, 4H), 2.14–2.11 (m, 1H), 1.98–1.91 (m, 1H), 1.86–1.81 (m, 2H). ^{13}**C{1H} NMR** (125 MHz, $CDCl_3$) δ 193.8, 162.6, 162.6, 162.2, 151.7, 151.6, 151.0, 148.5, 148.5, 143.8, 140.9, 139.5, 139.4, 136.1, 136.1, 135.9, 134.9, 131.2, 131.2, 130.8, 130.1, 130.0, 128.3, 128.1, 128.1, 125.5, 125.4, 122.9, 122.4, 122.3, 121.4, 120.6, 112.9, 112.8, 64.1, 56.3, 56.2, 56.2, 55.1, 32.8, 30.9, 29.5, 28.5, 24.3. **HR-MS (ESI)** m/z calculated for $C_{51}H_{43}N_3O_{16}S_4Na^+$ $[M + Na]^+$1104.1418, found 1104.1385.

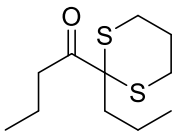
Autoxidative addition of 2-alkyl-1,3-dithianes:

General procedure: Dithiane (1.02 mmol, 1 equiv.) was dissolved in dry THF (5 mL) in an argon purged round-bottom flask. The solution was cooled to -78ºC in an acetone/liquid nitrogen bath. *n*-BuLi (1.3 equiv.) solution in hexanes was added dropwise to the reaction mixture at -78ºC. The solution was left stirring at -78ºC for 20 minutes and then left to warm up to room temperature for 40 minutes. The argon balloon was replaced with an atmospheric air balloon and an additional needle was inserted in the septum as to allow air flow through the surface of the solution. After 5 minutes the solution was quenched with 10 mL of a saturated aqueous NH_4Cl solution. 10 mL of Et_2O were added and the layers were separated. The organic phase was collected, and the aqueous phase was extracted two times with Et_2O (2 × 10 mL). The organic phases were combined and dried over $MgSO_4$. The solvent was filtered and evaporated. The product was purified and separated from unreacted starting material by flash chromatography.



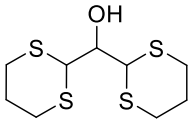
125a

Prepared according to general procedure. 27% yield, (45 mg, 0.14 mmol), white solid. Flash chromatography eluent: Hex:AcOEt (95:5). ^{1}**H NMR** (300 MHz, $CDCl_3$): δ ppm 7.33-7.21 (m, 10H), 4.00 (s, 2H), 3.41 (s, 2 H), 2.86-2.76 (m, 2H), 2.60-2.53 (m, 2H), 1.99-1.90 (m, 1H), 1.84-1.73 (m, 1H). ^{13}**C{1H} NMR** (75 MHz, $CDCl_3$): δ ppm 200.6, 134.9, 134.3, 130.2, 129.9, 128.5, 128.5, 127.7, 127.0, 62.5, 44.3, 43.4, 28.0, 24.2. **HR-MS (ESI)** m/z calculated for $C_{19}H_{21}OS_2^+$ $[M+H]^+$ 329.1028, found 329.1052.



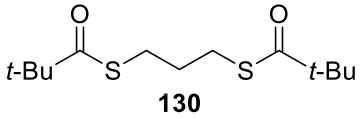
125b

Prepared according to general procedure. 24% yield (29 mg, 0.12 mmol), colorless oil. Flash chromatography eluent: Hex:DCM (55:45). ^{1}**H NMR** (300 MHz, $CDCl_3$): δ ppm 3.02-2.92 (m, 2H), 2.66-2.56 (m, 4H), 2.09-2.00 (m, 1H), 1.96-1.91 (m, 2H), 1.97-1.76 (m, 1H), 1.71-1.59 (m, 2H), 1.47-1.34 (m, 2H), 0.95-0.89 (m, 6H). ^{13}**C{1H} NMR** (75 MHz, $CDCl_3$): δ ppm 204.3, 61.4, 40.6, 37.8, 27.9, 25.0, 18.4, 18.0, 14.4, 13.9. **HR-MS (ESI)** m/z calculated for $C_{11}H_{21}OS_2^+$ $[M+H]^+$ 233.1028, found 233.1050.



129

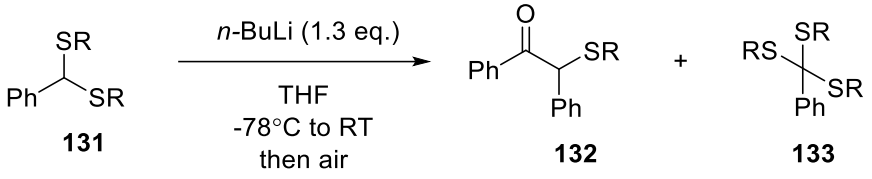
Prepared according to general procedure. 63% yield (47 mg, 0.18 mmol), white solid. Flash chromatography eluent: DCM (100%). Obtained with same spectral characterization as previously described.[19] ^{1}**H NMR** (300 MHz, $CDCl_3$): δ ppm 4.28 (s, 3H), 3.15 (s, 1H), 3.07-2.95 (m, 4H), 2.78-2.62 (m, 4H), 2.07-2.00 (m, 4H). ^{13}**C{1H} NMR** (75 MHz, $CDCl_3$): δ ppm 74.7, 47.4, 27.9, 27.2, 25.5.



130

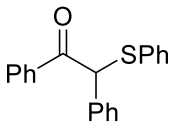
Prepared according to general procedure. 22% yield (61 mg, 0.22 mmol), colorless oil. Flash chromatography eluent: Hex:AcOEt (97:3). ^{1}**H NMR** (300 MHz, $CDCl_3$): δ ppm 2.86 (t, J=7.0 Hz, 4H), 1.79 (quin, J=7.2 Hz, 2H), 1.20 (s, 18H). ^{13}**C{1H} NMR** (75 MHz, $CDCl_3$): δ ppm 206.6, 46.5, 29.7, 27.5, 27.5. **HR-MS (ESI)** m/z calculated for $C_{13}H_{25}O_2S_2^+$ $[M+H]^+$ 277.1290, found 277.1323.

Autooxidative addition of dithioacetals 131:



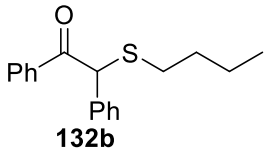
General procedure for autooxidative addition of dithioacetals **131**: Dithioacetal **32** (1.02 mmol, 1 equiv.) was dissolved in dry THF (5 mL) in an argon purged round-bottom flask. The solution was cooled to -78 ºC in an acetone/liquid nitrogen bath. *n*-BuLi (1.3 equiv.) solution in hexanes was added dropwise to the reaction mixture

at -78 ºC. The solution was left stirring at -78 ºC for 20 minutes and then left to warm up to room temperature for 40 minutes. The argon balloon was replaced with an atmospheric air balloon and an additional needle was inserted in the septum as to allow air flow through the surface of the solution. After 1 minute the solution was quenched with 10 mL of a saturated aqueous NH_4Cl solution. 10 mL of Et_2O were added and the layers were separated. The organic phase was collected, and the aqueous phase was extracted two times with Et_2O (2 × 10 mL). The organic phases were combined and dried over $MgSO_4$. The solvent was filtered and evaporated. Products **33** and **34** were obtained after purification by flash chromatography.



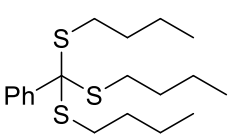
132a

Prepared according to general procedure: 48% yield (97 mg, 0.32 mmol), white solid. Flash chromatography eluent: Hex:AcOEt (97.5:2.5). ^{1}**H NMR** (300 MHz, $CDCl_3$): δ ppm 7.94-7.90 (m, 2H), 7.49-7.44 (m, 1H), 7.38-7.17 (m, 12H), 5.85 (s, 1H). ^{13}**C{1H} NMR** (75 MHz, $CDCl_3$): δ ppm 194.8, 136.6, 135.6, 134.1, 133.4, 133.1, 129.0, 128.9, 128.8, 128.7, 128.1, 128.0, 60.4. **HR-MS (ESI)** m/z calculated for $C_{20}H_{17}OS^+$ $[M+H]^+$ 305.0995, found 305.1013. The corresponding orthothioester product, **133a** could not be isolated due to low polarity and structural similarity to **131a**. However, the following characteristic peaks for the **133a** can be observed from the NMR spectrum of a mixture with the dithioacetal. **133a**: ^{1}**H NMR** (300 MHz, $CDCl_3$): 7.69-7.64 (m, 2H). ^{13}**C{1H} NMR** (75 MHz, $CDCl_3$): δ ppm 139.4, 132.9, 128.8, 128.4, 128.3, 128.0, 127.9, 77.0.



132b

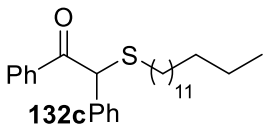
Prepared according to general procedure: 97% yield (92 mg, 0.32 mmol), white solid. Flash chromatography eluent: Hex:AcOEt (95:5). ^{1}**H NMR** (300 MHz, $CDCl_3$): δ ppm 7.99-7.96 (m, 2H), 7.53-7.23 (m, 8H), 5.55 (s, 1H), 2.56-2.42 (m, 2H), 1.58-1.48 (m, 2H), 1.41-1.29 (m, 2H), 0.85 (t, J = 7.3 Hz, 3H). ^{13}**C{1H} NMR** (75 MHz, $CDCl_3$): δ ppm 195.3, 136.9, 135.9, 133.3, 129.0, 128.9, 128.9, 128.7, 128.0, 55.5, 31.3, 31.2, 22.1, 13.7. **HR-MS (ESI)** m/z calculated for $C_{18}H_{21}OS^+$ $[M+H]^+$ 285.1308, found 285.1328.



133b

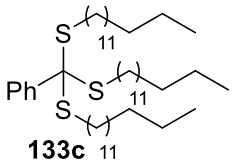
Prepared according to general procedure: 72% yield (86 mg, 0.24 mmol), colorless oil. Flash chromatography eluent: Hex:AcOEt (95:5). ^{1}**H NMR** (300 MHz, $CDCl_3$): δ ppm 7.87-7.84 (m, 2H), 7.35-7.21 (m, 3H), 2.58 (t, J = 7.3 Hz, 6H), 1.51-1.29 (m, 12H), 0.88-0.83 (m, 9H). ^{13}**C{1H} NMR** (75

MHz, $CDCl_3$): δ ppm 141.8, 131.3, 127.9, 127.6, 73.5, 31.5, 30.5, 22.3, 13.7. **HR-MS (ESI)** m/z calculated for $C_{15}H_{23}S_2^+$ $[M\text{-}S(CH_2)_3CH_3]^+$ 267.1236, found 267.1255.



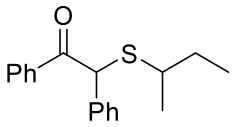
132c

Prepared according to general procedure: 73% yield (99 mg, 0.25 mmol), pale yellow solid. Flash chromatography gradient eluent: Hex:Toluene (80:20 to 50:50). ^{1}**H NMR** (300 MHz, $CDCl_3$): δ ppm 7.99-7.96 (m, 2H), 7.54-7.23 (m, 8H), 5.55 (s, 1H), 2.55-2.41 (m, 2H), 1.59-1.49 (m, 2H), 1.30-1.22 (m, 18H), 0.90-0.86 (m, 3H). ^{13}**C{1H} NMR** (75 MHz, $CDCl_3$): δ ppm 195.3, 136.9, 136.0, 133.3, 129.1, 129.0, 128.9, 128.7, 128.0, 55.6, 32.1, 31.6, 29.8, 29.7, 29.6, 29.5, 29.3, 29.2, 29.0, 22.8, 14.3. **HR-MS (ESI)** m/z calculated for $C_{26}H_{37}OS^+$ $[M+H]^+$ 397.2560, found 397.2591.



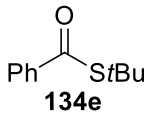
133c

Prepared according to general procedure: 56% yield (131 mg, 0.19 mmol), white solid. Flash chromatography eluent: Hexane (100%). ^{1}**H NMR** (300 MHz, $CDCl_3$): δ ppm 7.87 -7.84 (m, 2H), 7.35-7.21 (m, 3H), 2.57 (t, *J*=7.3 Hz, 6H), 1.54-1.44 (m, 6H), 1.31-1.24 (m, 54H), 0.90-0.86 (m, 9H). ^{13}**C{1H} NMR** (75 MHz, $CDCl_3$): δ ppm 142.1, 128.1, 127.8, 73.7, 32.1, 32.0, 29.8, 29.8, 29.6, 29.5, 29.4, 29.3, 28.6, 22.9, 14.3. **HR-MS (ESI)** m/z calculated for $C_{31}H_{55}S_2^+$ $[M\text{-}S(CH_2)_{11}CH_3]^+$ 491.3740, found 491.3737.



132d

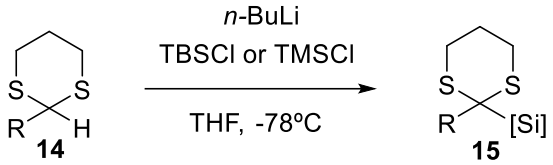
Prepared according to general procedure: 67% yield (63 mg, 0.22 mmol), pale yellow solid. 1:1 mixture of diastereomers. Flash chromatography eluent: Hex:AcOEt (95:5). ^{1}**H NMR** (300 MHz, $CDCl_3$): δ ppm 8.01-7.97 (m, 4H), 7.54-7.23 (m, 16H), 5.61 (s, 2H), 2.75-2.61 (m, 2H), 1.72-1.42 (m, 4H), 1.30 (d, J = 6.4 Hz, 3H), 1.19 (d, J = 7.0 Hz, 3H), 0.98-0.86 (m, 6H). ^{13}**C{1H} NMR** (75 MHz, $CDCl_3$): δ ppm 195.5, 195.4, 137.2, 135.9, 133.3, 129.0, 128.9, 128.9, 128.7, 127.9, 54.7, 54.6, 42.1, 41.9, 29.7, 29.7, 21.0, 20.6, 11.3, 11.2. **HR-MS (ESI)** m/z calculated for $C_{18}H_{21}OS^+$ $[M+H]^+$ 285.1308, found 285.1303. The corresponding orthothioester product **133d** could not be isolated due to low polarity and structural similarity to **131d**. However, the following characteristic peaks for **133d** can be observed in NMR spectrum of the crude reaction mixture: **133d**:^{13}**C{1H} NMR** (75 MHz, $CDCl_3$): δ ppm 69.3, 29.0 20.1, 11.5.



134e

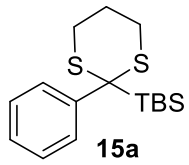
Dithioacetal **32e** (0.5 mmol, 1 equiv.) was dissolved in dry THF (2.5 mL) in an argon purged round-bottom flask. The solution was cooled to -78 ºC in an acetone/liquid nitrogen bath. *n*-BuLi (1.3 equiv.) solution in hexanes was added dropwise to the reaction mixture at -78 ºC. The solution was left stirring at -78 ºC for 20 minutes and then left to warm up to room temperature for 40 minutes. The argon balloon was replaced with an atmospheric air balloon and an additional needle was inserted in the septum as to allow air flow through the surface of the solution. After 1 minute the solution was quenched with 5 mL of a saturated aqueous NH_4Cl solution. 5 mL of Et_2O were added and the layers were separated. The organic phase was collected and the aqueous phase was extracted two times with Et_2O (2 × 5 mL). The organic phases were combined and dried over $MgSO_4$. The solvent was evaporated and the product was purified by preparative TLC (eluent: pentane) to yield **35e** as a colorless oil (62%, 60 mg, 0.31 mmol) with the same spectral characterization as previously described.[16] ^{1}**H NMR** (300 MHz, $CDCl_3$): δ ppm 7.93-7.90 (m, 2H), 7.56-7.51 (m, J = 7.3 Hz, 1H), 7.44-7.39 (m, 2H), 1.58 (s, 9H).

Synthesis of silyl-dithianes 15:



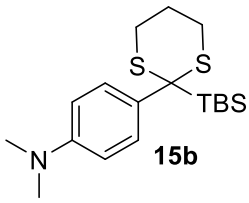
14 **15**

General procedure: Dithiane **14** (9.5 mmol) was dissolved in 40 mL of dry THF, in a dried, argon-filled round-bottom flask. The solution was cooled to -78 °C and *n*-BuLi (2.5M solution in hexanes, 1.2 equiv., 11.4 mmol) was added dropwise. The solution was stirred at -78 °C for ten minutes after which *tert*-butyldimethylsilyl chloride or trimethylsilyl chloride (11.4 mmol, 1.2 equiv.) was added dropwise at this temperature. The solution was stirred at -78 °C for an additional ten minutes and then left warming to RT for a minimum of one hour. The reaction was quenched with 40 mL of a saturated aqueous NH_4Cl solution. The layers were separated, and the organic phase was collected. The aqueous phase was extracted with MTBE (2 × 40 mL) and the organic phases combined, dried over $MgSO_4$ and filtered. After vacuum evaporation of the solvent, the crude was purified via silica column chromatography (eluent hexane/EtOAc mixture) to yield silyldithiane **15**.



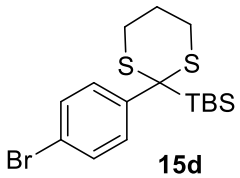
15a

Prepared according to general procedure: 82% yield (508 mg) as a colorless oil. Column eluent 100% hexane. Obtained with same spectral characterization as previously described.[17] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.99 – 7.96 (m, 2H), 7.40 – 7.33 (m, 2H), 7.20 – 7.15 (m, 1H), 2.83 – 2.73 (m, 2H), 2.43 – 2.36 (m, 2H), 2.10 – 1.82 (m, 2H), 0.81 (s, 9H), 0.15 (s, 6H). HRMS m/z: $[M+H]^+$ calculated for $C_{16}H_{27}S_2Si^+$ 311.1318, found 311.1313.



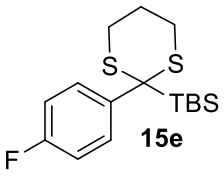
15b

Prepared according to general procedure: 94% yield (667 mg) as a white amorphous solid. Column eluent hexane/EtOAc (99:1) **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.79 – 7.74 (m, 2H), 6.76 – 6.71 (m, 2H), 2.97 (s, 6H), 2.82 (td, J = 14.1, 2.8 Hz, 2H), 2.36 (dt, J = 14.3, 3.9 Hz, 2H), 2.07 – 1.80 (m, 2H), 0.84 (s, 9H), 0.11 (s, 6H). **^{13}C{1H} NMR** (75 MHz, $CDCl_3$) δ 148.3, 131.1, 128.0, 112.5, 48.4, 40.7, 28.1, 25.5, 25.2, 19.8, -6.8. **HRMS m/z:** $[M+H]^+$ calculated for $C_{18}H_{32}NS_2Si^+$ 354.1740, found 354.1731.



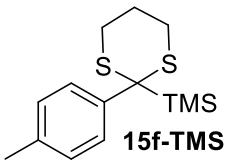
15d

Prepared according to general procedure but using a freshlyPrepared solution of LDA as base: 69% yield (536 mg) as a colorless oil. Column eluent 100% hexane. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.87 – 7.83 (m, 2H), 7.50 – 7.45 (m, 2H), 2.78 – 2.68 (m, 2H), 2.43 – 2.36 (m, 2H), 2.08 – 1.83 (m, 2H), 0.84 (s, 9H), 0.12 (s, 6H). **^{13}C{1H} NMR** (75 MHz, $CDCl_3$) δ 140.5, 132.2, 131.5, 119.6, 48.4, 28.1, 25.3, 25.2, 20.0, -6.9. **HRMS m/z:** $[M+H]^+$ calculated for $C_{16}H_{26}BrS_2Si^+$ 389.0423, found 389.0417.



15e

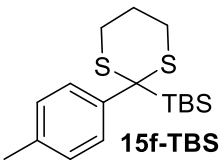
Prepared according to general procedure: 73% yield (483 mg) as a colorless oil. Column eluent 100% hexane. Obtained with same spectral characterization as previously described.[18] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.96 – 7.89 (m, 2H), 7.09 – 7.02 (m, 2H), 2.80 – 2.70 (m, 2H), 2.40 (dt, J = 14.3, 3.9 Hz, 2H), 2.09 – 1.83 (m, 2H), 0.83 (s, 9H), 0.13 (s, 6H).



15f-TMS

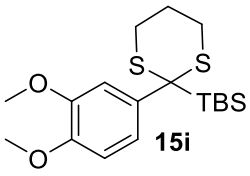
Prepared according to general procedure: 89% yield (2.38 g) as a colorless oil. Trimethylsilyl chloride was used instead of TBSCl. Column eluent 100% hexane. Obtained with same spectral characterization as previously described.[19] **^{1}H NMR**

(300 MHz, $CDCl_3$) δ 7.79 – 7.74 (m, 2H), 7.17 (d, J = 8.0 Hz, 2H), 2.83 – 2.74 (m, 2H), 2.45 – 2.38 (m, 2H), 2.35 (s, 3H), 2.09 – 1.83 (m, 2H), 0.06 (s, 9H).



15f-TBS

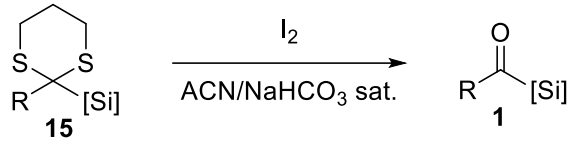
Prepared according to general procedure: 89% yield (2.017 g) as a colorless oil. Column eluent 100% hexane. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.83 (d, J = 8.4 Hz, 2H), 7.17 (d, J = 8.0 Hz, 2H), 2.83 – 2.73 (m, 2H), 2.41 – 2.35 (m, 2H), 2.35 (s, 3H), 2.08 – 1.80 (m, 2H), 0.82 (s, 9H), 0.13 (s, 6H). **^{13}C{1H} NMR** (75 MHz, $CDCl_3$) δ 137.6, 135.0, 130.2, 129.2, 48.6, 28.0, 25.3, 25.3, 21.0, 19.9, -6.8. **HRMS m/z:** $[M+H]^+$ calculated for $C_{17}H_{29}S_2Si^+$ 325.1474, found 325.1470.



15i

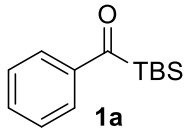
Prepared according to general procedure: 89% yield (270 mg) as a white amorphous solid. Column eluent hexane/EtOAc (94:6) **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.57 (d, J = 2.4 Hz, 1H), 7.50 (dd, J = 8.5, 2.4 Hz, 1H), 6.87 (d, J = 8.5 Hz, 1H), 3.90 (s, 3H), 3.89 (s, 3H), 2.81 (td, J = 14.0, 2.8 Hz, 2H), 2.40 (dt, J = 14.2, 3.7 Hz, 2H), 2.08 – 1.84 (m, 2H), 0.82 (s, 9H), 0.14 (s, 6H). **^{13}C{1H} NMR** (75 MHz, $CDCl_3$) δ 148.8, 146.9, 133.2, 122.7, 113.8, 110.9, 56.1, 56.0, 48.5, 28.0, 25.4, 25.3, 19.9, -6.7. **HRMS m/z:** $[M+H]^+$ calculated for $C_{18}H_{31}O_2S_2Si^+$ 371.1529, found 371.1524.

Synthesis of simple acylsilanes 1:



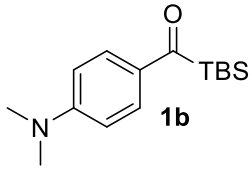
15 **1**

General procedure: Dithiane **15** (3.5 mmol) was dissolved in 17 mL of acetonitrile (sonication and gentle heating were usually required). Then, 5 mL of a saturated aqueous $NaHCO_3$ solution was added and the mixture cooled to 0°C. Then, I_2 (35 mmol, 10 equiv.) was added slowly in portions. After addition, the reaction was left at room temperature for 1 hour. 20 mL of water was added followed by continued addition of NaS_2O_3. The mixture was vigorously stirred until the dark brown color of iodine faded to give a bright yellow solution. Then, the aqueous phase was extracted with MTBE (3 × 20 mL), and the organic phases combined, dried over $MgSO_4$ and filtered. After vacuum evaporation of the solvent the crude was purified via silica column chromatography (eluent hexane/EtOAc mixture) to yield benzoylsilane **1**.



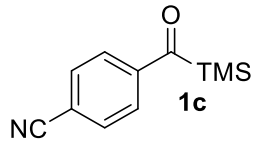
1a

Prepared according to general procedure: 91% yield (303 mg) as a yellow oil. Column eluent hexane/DCM (8:2). Obtained with same spectral characterization as previously described.[17] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.71 – 7.68 (m, 2H), 7.47 – 7.33 (m, 3H), 0.86 (s, 9H), 0.27 (s, 6H). **HRMS m/z:** $[M+H]^+$ calculated for $C_{13}H_{21}OSi^+$ 221.1356, found 221.1354.



1b

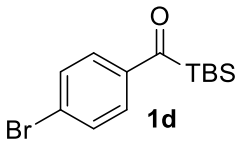
Prepared according to general procedure: 40% yield (194 mg) as a yellow amorphous sold. Column eluent hexane/EtOAc (85:15). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.71 – 7.66 (m, 2H), 6.59 – 6.54 (m, 2H), 2.95 (s, 6H), 0.86 (s, 9H), 0.25 (s, 6H). **^{13}C{1H} NMR** (75 MHz, $CDCl_3$) δ 230.5, 153.2, 132.4, 130.3, 110.7, 40.2, 27.0, 17.0, -4.2. **HRMS *m/z*:** $[M+H]^+$ calculated for $C_{15}H_{26}NOSi^+$ 264.1778, found 264.1773.



1c

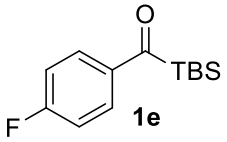
Dithiane **14c** (443 mg, 2 mmol) was dissolved in 9 mL of dry THF, in a dried, argon-filled round-bottom flask. The solution was cooled to -78 °C and *n*-BuLi (0.96 mL of 2.5M solution in hexanes, 1.2 equiv., 2.4 mmol) was added dropwise. The solution was stirred at -78 °C for ten minutes after which trimethylsilyl chloride (303 μL, 2.4 mmol, 1.2 equiv.) was added dropwise at this temperature. The solution was stirred at -78 °C for an additional ten minutes and then left warming to RT for a minimum of one hour. The reaction was quenched with 10 mL of a saturated aqueous NH_4Cl solution. The layers were separated, and the organic phase collected. The aqueous phase was extracted with MTBE (2 × 10 mL) and the organic phases combined, dried over $MgSO_4$ and filtered. The crude containing **9g** was redissolved in 12 mL of acetonitrile. Then, 4 mL of saturated aqueous $NaHCO_3$ solution was added and the mixture cooled to 0°C. Then, I_2 (5.08 g, 20 mmol, 10 equiv.) was added slowly in portions. After addition, the reaction was left at room temperature for 1 hour. Water was added (20 mL) followed by NaS_2O_3, and the mixture vigorously stirred until the dark brown color of iodine faded to give a bright yellow solution. Then, the aqueous phase was extracted with MTBE (3 × 20 mL), and the organic phases combined, dried over $MgSO_4$ and filtered. After vacuum evaporation of the solvent the crude was purified via silica column chromatography eluent hexane/EtOAc (96:4) to yield acylsilane **1c** in 54% yield (220 mg, 1.08 mmol) as a bright yellow oil. Obtained with same spectral characterization as previously

described.[20] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.89 – 7.86 (m, 2H), 7.79 – 7.76 (m, 2H), 0.38 (s, 9H).



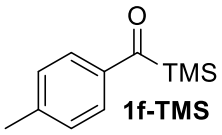
1d

Prepared according to general procedure: 87% yield (350 mg) as a yellow oil. Column eluent hexane/EtOAc (98:2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.58 – 7.48 (m, 4H), 0.85 (s, 9H), 0.26 (s, 6H). **^{13}C{1H} NMR** (75 MHz, $CDCl_3$) δ 234.7, 141.4, 132.0, 129.2, 127.8, 26.8, 17.1, -4.6. **HRMS *m/z*:** $[M+H]^+$ calculated for $C_{13}H_{20}BrOSi^+$ 299.0461, found 299.0460.



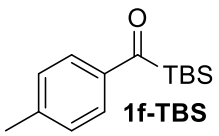
1e

Prepared according to general procedure: 87% yield (291 mg) as a yellow oil. Column eluent hexane/EtOAc (98:2). Obtained with same spectral characterization as previously described.[18] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.77 – 7.70 (m, 2H), 7.07 – 6.99 (m, 2H), 0.85 (s, 9H), 0.27 (s, 3H).



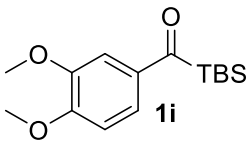
1f-TMS

Prepared according to general procedure: 99% yield (677 mg) as a yellow oil. Column eluent hexane/DCM (6:4). Obtained with same spectral characterization as previously described.[21] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.59 (d, J = 8.2 Hz, 2H), 7.13 – 7.10 (m, 2H), 2.25 (s, 3H), 0.21 (s, 9H).



1f-TBS

Prepared according to general procedure: 77% yield (1.117 g), as a yellow amorphous solid. Column eluent hexane/DCM (8:2). Obtained with same spectral characterization as previously described.[22] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.62 (d, J = 8.1 Hz, 2H), 7.16 (d, J = 7.9 Hz, 2H), 2.30 (s, 3H), 0.86 (s, 9H), 0.26 (s, 6H). **HRMS m/z:** $[M+H]^+$ calculated for $C_{14}H_{23}OSi^+$ 235.1513, found 235.1512.

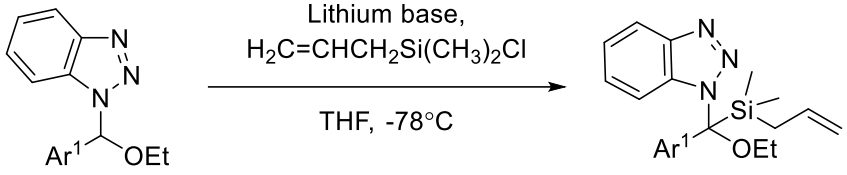


1i

Prepared according to general procedure: 90% yield (176 mg) as a yellow amorphous solid. Column eluent hexane/EtOAc (92:8). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.52 (dd, J = 8.3, 1.9 Hz, 1H), 7.36 (d, J = 1.9 Hz, 1H), 6.91 (d, J = 8.3 Hz, 1H), 3.94 (s, 3H), 3.91 (s, 3H), 0.96 (s, 9H), 0.36 (s, 6H). **^{13}C{1H} NMR** (75 MHz, $CDCl_3$) δ 232.5, 153.1, 149.3, 136.7, 124.6, 110.0, 108.0, 56.2, 55.9, 26.9, 17.0, -4.3. **HRMS m/z:** $[M+H]^+$ calculated for $C_{15}H_{25}O_3Si^+$ 281.1567, found 281.1561.

Synthesis of silyl-benzotriazole hemiaminal ethers 138:

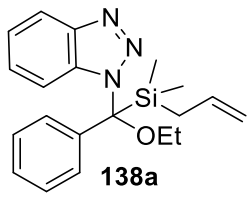
Note: Benzotriazole hemiaminal ether derivatives **137** werePrepared as previously reported[23] and used immediately after purification.



137 **138**

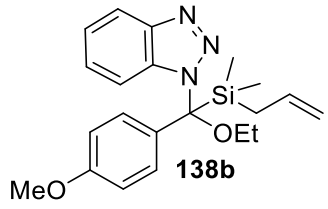
General procedure A: Benzotriazole derivative **137** (5 mmol) was dissolved in 30 mL of dry THF, in an Argon filled round-bottom flask. The solution was cooled to -78 °C with an acetone/liquid nitrogen bath. *n*-BuLi, *t*-BuLi or LDA (1.1 equiv.) was added dropwise at this temperature. After addition, the solution was left stirring for 10 minutes at -78 °C. Allyl(chloro)dimethylsilane (1.1 eq.) was then added dropwise at the same temperature. The solution was left at this temperature for 15 minutes and then slowly warmed to room temperature for one hour. The reaction was quenched with 30 mL of saturated aqueous $NaHCO_3$ and transferred to an extraction funnel. The phases were allowed to separate and the top organic phase collected. The aqueous phase was extracted with Et_2O (2 × 30 mL) and the organic phases combined, dried over $MgSO_4$ and filtered. The solvent was evaporated and the resulting crude oil purified through silica chromatography (hexane/ethyl acetate mixture as eluent) to give silyl derivatives **138** as yellow tainted clear oils.

General procedure B (used for electron rich aromatics): Benzotriazole derivative **137** (5 mmol) was dissolved in 30 mL of dry THF, in an argon filled round-bottom flask. The solution was cooled to -78 °C with an acetone/liquid nitrogen bath and allyl(chloro)dimethylsilane (1.1 eq.) added dropwise. Immediately after addition, *t*-BuLi (1.1 equiv.) was slowly added dropwise, over a period of 10 minutes. After addition, the solution was left stirring for additional 10 minutes at -78 °C and then slowly warmed to room temperature for one hour. The reaction was quenched with 30 mL of saturated aqueous $NaHCO_3$ and transferred to an extraction funnel. The phases were allowed to separate and the top organic phase collected. The aqueous phase was extracted with Et_2O (2 × 30 mL) and the organic phases combined, dried over $MgSO_4$ and filtered. The solvent was evaporated and the resulting crude oil purified through silica chromatography (hexane/ethyl acetate mixture as eluent) to give silyl derivatives **138** as yellow tainted clear oils.



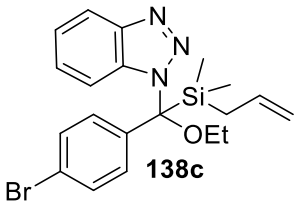
138a

Prepared according to general procedure A with *n*-BuLi as base. 86% yield (1.517 g, 4.3 mmol) as yellow tainted oil. Column eluent hexane/ethyl acetate (95:5). **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 8.06 (d, J = 8.3 Hz, 1H), 7.32 – 7.27 (m, 4H), 7.19 (t, J = 7.6 Hz, 1H), 7.03 – 7.00 (m, 2H), 6.93 (d, J = 8.3 Hz, 1H), 5.82 – 5.67 (m, 1H), 4.90 – 4.84 (m, 2H), 3.56 – 3.46 (m, 1H), 3.28 – 3.18 (m, 1H), 1.81 (t, J = 8.1 Hz, 2H), 1.12 (t, J = 6.9 Hz, 3H), 0.30 (s, 3H), 0.25 (s, 3H). **^{13}C{1H} NMR (**$CDCl_3$, 75 MHz) δ 146.5, 139.7, 134.5, 132.9, 128.2, 127.7, 127.1, 126.4, 124.2, 120.0, 114.2, 113.3, 93.7, 61.2, 22.5, 15.5, -3.0, -3.1.



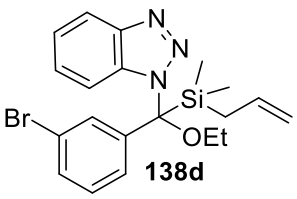
138b

Prepared according to general procedure B: 71% yield (1.362 g, 3.6 mmol) as yellow tainted oil. Column eluent hexane/ethyl acetate (92:8). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 8.05 (dt, *J* = 8.3, 0.8 Hz, 1H), 7.31 – 7.28 (m, 1.0 Hz, 1H), 7.21 – 7.18 (m, 1H), 6.98 – 6.96 (m, 1H), 6.91 (d, J = 8.2 Hz, 2H), 6.81 – 6.80 (m, 2H), 5.75 (ddt, J = 16.7, 10.1, 8.2 Hz, 1H), 4.90 – 4.85 (m, 2H), 3.79 (s, 3H), 3.53 – 3.45 (m, 1H), 3.22 – 3.16 (m, 1H), 1.85 – 1.75 (m, 2H), 1.10 (t, J = 6.9 Hz, 3H), 0.29 (s, 3H), 0.24 (s, 3H). **^{13}C{1H} NMR (**$CDCl_3$, 125 MHz) δ 159.0, 146.5, 134.6, 132.8, 131.7, 127.6, 127.0, 124.2, 119.9, 114.1, 113.4, 113.4, 93.6, 61.1, 55.3, 22.5, 15.6, -3.0, -3.1.



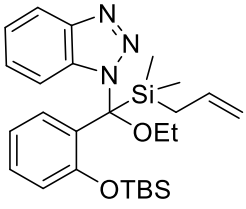
138c

Prepared according to general procedure A with LDA as base. 87% yield (1.862 g, 4.3 mmol) as yellow tainted oil. Column eluent hexane/ethyl acetate (96:4). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 8.07– 8.05 (m, 1H), 7.41 – 7.40 (m, 2H), 7.33 – 7.30 (m, 1H), 7.25 –7.21 (m, 1H), 6.97 (dt, J = 8.3, 0.9 Hz, 1H), 6.88 (d, J = 7.8 Hz, 2H), 5.79 – 5.70 (m, 1H), 4.91 – 4.87 (m, 2H), 3.55 (dq, J = 8.6, 6.9 Hz, 1H), 3.16 (dq, J = 8.6, 7.1 Hz, 1H), 1.85 – 1.74 (m, 2H), 1.11 (t, J = 6.9 Hz, 3H), 0.29 (s, 3H), 0.25 (s, 3H). **^{13}C{1H} NMR (**$CDCl_3$, 125 MHz) δ 146.6, 139.1, 134.1, 132.5, 131.3, 128.1, 127.4, 124.4, 121.8, 120.1, 114.5, 113.0, 93.4, 61.4, 22.4, 15.5, -3.1, -3.1.



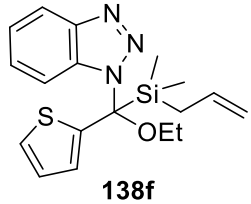
138d

Prepared according to general procedure A with LDA as base. 89% yield (1.910 g, 4.4 mmol) as yellow tainted oil. Column eluent hexane/ethyl acetate (96:4). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 8.07 (d, J = 8.4 Hz, 1H), 7.41–7.40 (m, 2H), 7.34 – 7.31 (m, 1H), 7.26 – 7.23 (m, 1H), 7.10 (t, J = 8.1 Hz, 1H), 7.01 (d, J = 8.4 Hz, 1H), 6.70 (d, J = 7.9 Hz, 1H), 5.79 – 5.71 (m, 1H), 4.92 – 4.88 (m, 2H), 3.56 (dq, J = 8.7, 6.9 Hz, 1H), 3.15 (dq, J = 8.7, 7.0 Hz, 1H), 1.86 – 1.76 (m, 2H), 1.13 (t, J = 6.9 Hz, 3H), 0.31 (s, 3H), 0.27 (s, 3H). **^{13}C{1H} NMR (**$CDCl_3$, 125 MHz) δ 146.5, 142.3, 134.0, 132.5, 130.8, 129.7, 129.3, 127.4, 124.9, 124.4, 122.6, 120.1, 114.6, 113.0, 93.1, 61.4, 22.4, 15.5, -3.0, -3.1.



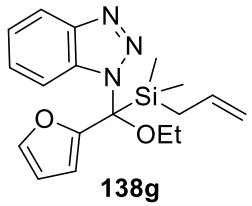
138e

Prepared according to general procedure B: 75% yield (1.817 g, 3.8 mmol) as yellow tainted oil. Column eluent hexane/ethyl acetate (96:4). Column chromatography yielded the compound with only 80% purity, which was used as such in the next synthetic step. **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 8.04 – 8.01 (m, 1H), 7.71 – 7.69 (m, 1H), 7.27 – 7.08 (m, 6H), 5.80 – 5.72 (m, 1H), 4.89 – 4.83(m, 2H), 3.18 (dq, J = 8.6, 6.9 Hz, 1H), 2.97 (dq, J = 8.7, 6.9 Hz, 1H), 1.94 – 1.82 (m, 2H), 1.02 (t, J = 6.9 Hz, 3H), 0.56 (s, 9H), 0.32 (s, 3H), 0.25 (s, 3H), -0.32 (s, 3H), -0.45 (s, 3H).



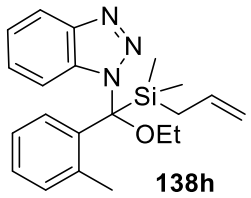
138f

Prepared according to general procedure B: 79% yield (1.418 g, 4.0 mmol) as yellow tainted oil. Column eluent hexane/ethyl acetate (96:4). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 8.06 (dt, J = 8.3, 1.0 Hz, 1H), 7.34 – 7.25 (m, 3H), 7.11 (dt, J = 8.3, 1.0 Hz, 1H), 6.90 (dd, J = 5.1, 3.7 Hz, 1H), 6.38 (dd, J = 3.6, 1.2 Hz, 1H), 5.82 – 5.73(m, 1H), 4.93 – 4.87 (m, 2H), 3.56 (dq, J = 8.6, 6.9 Hz, 1H), 3.21 (dq, J = 8.6, 7.0 Hz, 1H), 1.91 (dd, J = 13.5, 8.0 Hz, 1H), 1.83 (dd, J = 13.5, 8.3 Hz, 1H), 1.10 (t, J = 7.0 Hz, 3H), 0.38 (s, 3H), 0.33 (s, 3H). **^{13}C{1H} NMR (**$CDCl_3$, 125 MHz) δ 146.4, 144.2, 134.3, 132.7, 127.3, 127.0, 125.2, 124.4, 124.3, 120.0, 114.3, 113.1, 92.3, 61.7, 22.5, 15.5, -3.0.



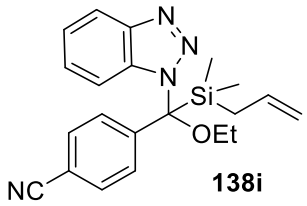
138g

Prepared according to general procedure B: 77% yield (1.321 g, 3,9 mmol) as yellow tainted oil. Column eluent hexane/ethyl acetate (96:4). **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 8.08 – 8.02 (m, 1H), 7.35 – 7.28 (m, 3H), 6.93 – 6.87 (m, 1H), 6.46 (dd, J = 3.3, 1.8 Hz, 1H), 6.38 (dd, J = 3.3, 0.7 Hz, 1H), 5.84 – 5.70 (m, 1H), 4.93 – 4.84 (m, 2H), 3.46 (dq, J = 8.6, 7.0 Hz, 1H), 3.31 (dq, J = 8.7, 6.9 Hz, 1H), 1.90 – 1.76 (m, 2H), 1.06 (t, J = 7.0 Hz, 3H), 0.30 (s, 3H), 0.25 (s, 3H). **^{13}C{1H} NMR (**$CDCl_3$, 75 MHz) δ 151.8, 146.1, 142.5, 134.4, 134.0, 127.6, 124.1, 120.0, 114.1, 112.2, 110.9, 108.6, 89.8, 61.3, 22.3, 15.5, -3.5, -3.6.



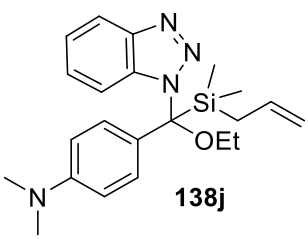
138h

Prepared according to general procedure B: 79% yield (1.439 g, 3,9 mmol) as yellow tainted oil. Column eluent hexane/ethyl acetate (96:4). **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 8.05 (d, J = 8.3 Hz, 1H), 7.32 – 7.15 (m, 5H), 7.01 (d, J = 7.5 Hz, 1H), 6.90 (d, J = 8.3 Hz, 1H), 5.83 – 5.69 (m, 1H), 4.91 – 4.85 (m, 2H), 3.40 – 3.11 (m, 1H), 3.21 – 3.11 (m, 1H), 1.96 – 1.80 (m, 2H), 1.09 (t, J = 6.9 Hz, 3H), 0.34 (s, 3H), 0.27 (s, 3H). **^{13}C{1H} NMR (**$CDCl_3$, 75 MHz) δ 146.3, 136.7, 135.2, 134.7, 133.8, 132.8, 128.1, 127.7, 127.3, 125.9, 124.2, 120.0, 114.2, 112.5, 60.8, 23.0, 15.4, -2.3, -2.6.



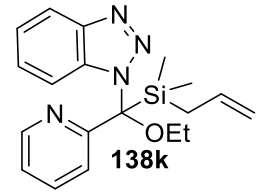
138i

Prepared according to general procedure A with LDA as base: 80% yield (1.508 g, 4.0 mmol) as yellow tainted oil. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 8.08 (dt, J = 8.3, 1.0 Hz, 1H), 7.58 (d, J = 8.8 Hz, 2H), 7.36 – 7.21 (m, 2H), 7.12 (d, J = 8.0 Hz, 2H), 6.91 (dt, J = 8.2, 1.0 Hz, 1H), 5.80 – 5.65 (m, 1H), 4.91 – 4.86 (m, 2H), 3.61 (dq, J = 8.6, 6.9 Hz, 1H), 3.16 (dq, J = 8.6, 7.0 Hz, 1H), 1.86 – 1.73 (m, 2H), 1.14 (t, J = 6.9 Hz, 3H), 0.30 (s, 3H), 0.26 (s, 3H). **^{13}C{1H} NMR (**$CDCl_3$, 75 MHz) δ 146.5, 145.4, 133.5, 132.2, 131.9, 127.5, 126.9, 124.5, 120.2, 118.5, 114.8, 112.4, 111.6, 93.3, 61.5, 22.2, 15.4, -3.1, -3.2.



138j

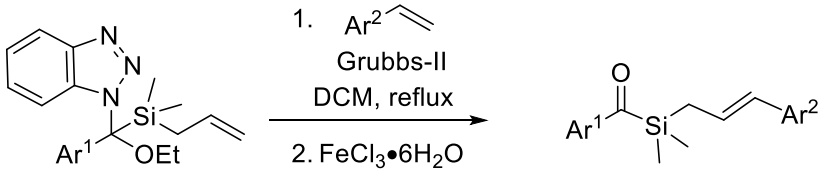
Prepared according to general procedure B: 80% yield (1.578 g, 4.0 mmol) as yellow tainted oil. Column eluent hexane/ethyl acetate/Et_3N (93:5:2). **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 8.03 (d, J = 8.3 Hz, 1H), 7.30 – 7.25 (m, 1H), 7.21 – 7.15 (m, 1H), 7.00 (d, J = 8.3 Hz, 1H), 6.84 (d, J = 8.8 Hz, 2H), 6.61 (d, J = 9.2 Hz, 2H), 5.86 – 5.70 (m, 1H), 4.90 – 4.83 (m, 2H), 3.50 – 3.41 (m, 1H), 3.30 – 3.16 (m, 1H), 2.93 (s, 6H), 1.88 – 1.76 (m, 2H), 1.09 (t, J = 6.9 Hz, 3H), 0.29 (s, 3H), 0.24 (s, 3H). **^{13}C{1H} NMR (**$CDCl_3$, 75 MHz) δ 149.8, 146.5, 134.9, 133.0, 127.2, 126.9, 126.8, 124.0, 119.8, 113.8, 113.8, 111.8, 93.8, 61.0, 40.5, 27.1, 22.6, 15.6, -3.0, -3.1.



138k

Prepared according to general procedure A using *n*-BuLi as base: 65% yield (1.143 g, 3.2 mmol) as a brown amorphous solid. Column eluent hexane/ethyl acetate/Et_3N (90:8:2). **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 8.42 – 8.39 (m, 1H), 8.04 (dt, J = 8.3, 1.0 Hz, 1H), 7.79 (td, J = 7.7, 1.8 Hz, 1H), 7.67 (dt, J = 8.0, 1.0 Hz, 1H), 7.28 – 7.11 (m, 3H), 6.58 (d, J = 8.3 Hz, 1H), 5.81 – 5.67 (m, 1H), 4.90 – 4.82 (m, 2H), 3.43 (dq, J = 8.8, 7.3 Hz, 1H), 3.27 (dq, J = 8.8, 7.0 Hz, 1H), 1.92 – 1.77 (m, 2H), 1.10 (t, J = 7.0 Hz, 3H), 0.28 (s, 3H), 0.27 (s, 3H). **^{13}C{1H} NMR (**$CDCl_3$, 75 MHz) δ 158.8, 149.2, 146.3, 136.4, 134.5, 133.3, 127.0, 123.8, 122.5, 121.6, 120.1, 114.1, 112.4, 93.5, 61.3, 22.5, 15.6, -3.1, -3.2.

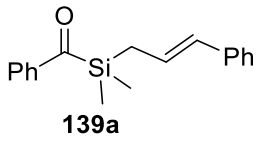
Synthesis of cinnamyl acylsilanes 139:



138 **139**

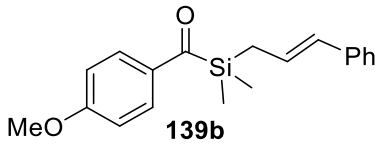
General procedure: Silyl derivative **138** (1 mmol) was dissolved in 6 mL of dry DCM, in an argon filled round-bottom flask. The substituted styrene (5 mmol, 5 equiv.) was added to the solution, followed by 2nd generation Grubbs catalyst (1-5 mol %). The solution was refluxed overnight. The solvent was evaporated and 10 mL of hexane/ethyl acetate (9:1) mixture was added. The suspension was stirred for 10

minutes and filtered through cotton. The off-white solid, mostly composed by undesired stilbene, was washed two more times with hexane/ethyl acetate (9:1) mixture (10 mL) and filtered again. The filtrate was combined and the solvents evaporated. The crude was passed through a small silica column (hexane/ethyl acetate mixture as eluent) to remove the remaining stilbene (highly mobile on silica). $FeCl_3$•$6H_2O$ (0.3 mmol, 0.3 equiv.) was added in one portion to an acetone solution (6 mL) of the resulting crude oil. The solution was stirred for 30 minutes and the solvent evaporated under reduced pressure. Hexane (6 mL) was added and the solution stirred for 10 minutes. The bright yellow liquid was filtered through cotton and the reaction flask washed with hexane (2 x 6 mL) and filtered. The filtrate was combined and the hexane evaporated to give bright yellow oil as crude, which was purified through silica chromatography (hexane/ethyl acetate mixture as eluent) to give aroylsilanes **139** as bright yellow oils.



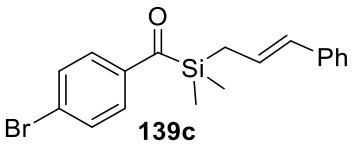
139a

Prepared according to general procedure: 53% yield (154 mg, 0.53 mmol), bright yellow oil. 1 mol% of G-II used. Column eluent hexane/ethyl acetate (96:4). **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.84 – 7.81 (m, 2H), 7.57 – 7.44 (m, 3H), 7.26 – 7.25 (m, 4H), 7.20 – 7.13 (m, 1H), 6.31 – 6.14 (m, 2H), 2.02 (d, J = 7.0 Hz, 2H), 0.42 (s, 6H). **^{13}C{1H} NMR (**$CDCl_3$, 75 MHz) δ 234.7, 141.7, 138.1, 133.0, 130.1, 128.9, 128.6, 127.8, 126.7, 125.8, 125.8, 21.8, -2.9. **HR-MS (ESI)** *m/z* calculated for $C_{18}H_{21}OSi^+$ $[M+H]^+$ 281.1356, found 281.1362.



139b

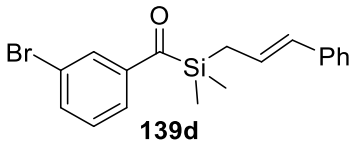
Prepared according to general procedure: 53% yield (164 mg, 0.53 mmol), pale yellow oil. 1.5 mol% of G-II used. Column eluent hexane/ethyl acetate (94:6). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.84 (dd, J = 8.7, 1.5 Hz, 2H), 7.26 (d, J = 4.2 Hz, 4H), 7.18 – 7.15 (m, 1H), 6.95 (dd, J = 8.6, 1.4 Hz, 2H), 6.30 – 6.18 (m, 2H), 3.87 (s, 3H), 2.01 (d, J = 7.7 Hz, 2H), 0.41 (s, 6H). **^{13}C{1H} NMR (**$CDCl_3$, 125 MHz) δ 231.8, 163.5, 138.1, 135.5, 130.1, 129.9, 128.6, 126.7, 126.0, 125.8, 114.0, 55.6, 21.9, -2.8. **HR-MS (ESI)** *m/z* calculated for $C_{19}H_{23}O_2Si^+$ $[M+H]^+$ 311.1462, found 311.1449.



139c

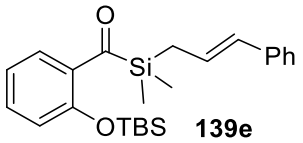
Prepared according to general procedure: 46% yield (164 mg, 0.46 mmol), bright yellow oil. 2 mol% of G-II used. Column eluent hexane/ethyl acetate (97:3). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ

7.69 (d, J = 8.5 Hz, 2H), 7.61 (d, J = 8.5 Hz, 2H), 7.29 – 7.24 (m, 4H), 7.19 – 7.16 (m, 1H), 6.27 (d, J = 15.8 Hz, 1H), 6.18 (dt, J = 15.8, 8.0 Hz, 1H), 2.01 (d, J = 8.0 Hz, 2H), 0.42 (s, 6H). **^{13}C{1H} NMR (**$CDCl_3$, 125 MHz) δ 233.6, 140.2, 137.9, 132.2, 130.2, 129.1, 128.6, 128.2, 126.8, 125.8, 125.4, 21.7, -3.0. **HR-MS (ESI)** *m/z* calculated for $C_{18}H_{20}BrOSi^+$ $[M+H]^+$ 359.0461, found 359.0474.



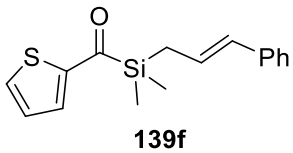
139d

Prepared according to general procedure: 37% yield (132 mg, 0.37 mmol), bright yellow oil. 2 mol% of G-II used. Column eluent hexane/ethyl acetate (97:3). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.91 (s, 1H), 7.75 (d, J = 7.7 Hz, 1H), 7.67 – 7.65 (m, 1H), 7.35 (t, J = 7.8 Hz, 1H), 7.29 – 7.25 (m, 4H), 7.19 – 7.15 (m, 1H), 6.28 (d, J = 15.8 Hz, 1H), 6.18 (dt, J = 15.8, 8.0 Hz, 1H), 2.01 (d, J = 8.0 Hz, 2H), 0.42 (s, 6H). **^{13}C{1H} NMR (**$CDCl_3$, 125 MHz) δ 233.5, 143.1, 137.9, 135.8, 130.5, 130.3, 130.2, 128.6, 126.8, 126.7, 125.8, 125.3, 123.5, 21.6, -3.0. **HR-MS (ESI)** *m/z* calculated for $C_{18}H_{20}BrOSi^+$ $[M+H]^+$ 359.0461, found 359.0483.



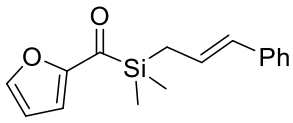
139e

Prepared according to general procedure: 42% yield (171 mg, 0.42 mmol), bright yellow oil. 2 mol% of G-II used. Column eluent hexane/ethyl acetate (96:4). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.29 – 7.22 (m, 5H), 7.17 – 7.11 (m, 2H), 6.97 (t, J = 7.4 Hz, 1H), 6.86 (d, J = 8.2 Hz, 1H), 6.21 (d, J = 15.7 Hz, 1H), 6.12 (dt, J = 15.8, 8.0 Hz, 1H), 1.92 (d, J = 7.9 Hz, 2H), 0.95 (s, 9H), 0.29 (s, 3H), 0.20 (s, 3H). **^{13}C{1H} NMR (**$CDCl_3$, 125 MHz) δ 241.8, 152.6, 138.2, 137.7, 131.5, 129.7, 128.5, 127.3, 126.6, 125.9, 125.8, 121.4, 120.6, 26.0, 21.3, 18.7, -3.8, -4.0. **HR-MS (ESI)** *m/z* calculated for $C_{24}H_{35}O_2Si_2^+$ $[M+H]^+$ 411.2170, found 411.2169.



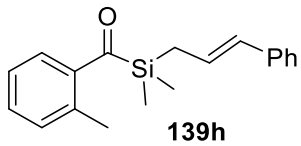
139f

Prepared according to general procedure: 36% yield (106 mg, 0.36 mmol), bright yellow oil. 2 mol% of G-II used. Column eluent hexane/ethyl acetate (97:3). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.75 – 7.74 (m, 1H), 7.66 – 7.65 (m, 1H), 7.27 (d, J = 4.3 Hz, 4H), 7.18 – 7.14 (m, 2H), 6.30 (d, J = 15.7 Hz, 1H), 6.21 (dt, J = 15.8, 7.9 Hz, 1H), 2.02 (d, J = 7.9 Hz, 2H), 0.43 (s, 6H). **^{13}C{1H} NMR (**$CDCl_3$, 125 MHz) δ 223.5, 150.9, 138.0, 133.5, 133.2, 130.1, 128.6, 128.4, 126.7, 125.8, 125.5, 21.5, -3.3. **HR-MS (ESI)** *m/z* calculated for $C_{16}H_{19}OSSi^+$ $[M+H]^+$ 287.0920, found 287.0918.



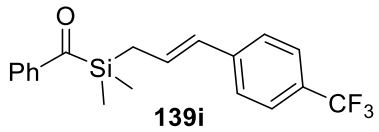
139g

Prepared according to general procedure: 39% yield (105, 0.39 mmol), bright yellow oil. 5 mol% of G-II used. Column eluent hexane/ethyl acetate (96:4). **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.61 – 7.60 (m, 1H), 7.27 (d, J = 4.0 Hz, 4H), 7.20 – 7.13 (m, 1H), 7.09 (dt, J = 3.6, 0.7 Hz, 1H), 6.54 (ddd, J = 3.6, 1.7, 0.7 Hz, 1H), 6.32 – 6.15 (m, 2H), 2.02 (d, J = 7.6 Hz, 2H), 0.39 (d, J = 0.7 Hz, 6H). **^{13}C{1H} NMR (**$CDCl_3$, 75 MHz) δ 220.2, 158.4, 146.3, 138.1, 129.9, 128.6, 126.7, 125.7, 125.6, 115.0, 112.3, 21.0, -4.1. **HR-MS (ESI)** *m/z* calculated for $C_{16}H_{19}O_2Si^+$ $[M+H]^+$ 271.1149, found 271.1143.



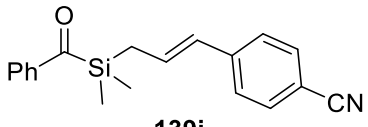
139h

Prepared according to general procedure: 59% yield (175 mg, 0.59 mmol), bright yellow oil. 2 mol% of G-II used. Column eluent hexane/ethyl acetate (98:2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.57 (dd, J = 7.5, 1.2 Hz, 1H), 7.36 – 7.32 (m, 1H), 7.30 – 7.22 (m, 6H), 7.18 – 7.14 (m, 1H), 6.25 – 6.13 (m, 2H), 2.40 (s, 3H), 1.97 (d, J = 7.5 Hz, 2H), 0.36 (s, 6H). **^{13}C{1H} NMR (**$CDCl_3$, 125 MHz) δ 241.1, 142.1, 138.1, 135.9, 132.2, 130.9, 129.9, 129.8, 128.6, 126.7, 125.7, 125.7, 125.6, 21.6, 20.7, -3.2. **HR-MS (ESI)** *m/z* calculated for $C_{19}H_{23}OSi^+$ $[M+H]^+$ 295.1513, found 295.1527.



139i

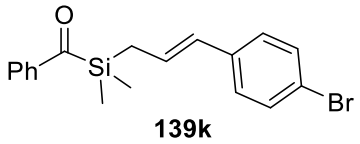
Prepared according to general procedure: 47% yield (163 mg, 0.47 mmol), bright yellow oil. 1 mol% of G-II used. Column eluent hexane/ethyl acetate (92:8). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.83 – 7.81 (m, 2H), 7.57 – 7.54 (m, 1H), 7.51 – 7.47 (m, 4H), 7.33 – 7.32 (d, J = 7.7 Hz, 2H), 6.37 – 6.27 (m, 2H), 2.06 (d, J = 7.2 Hz, 2H), 0.44 (s, 6H). **^{13}C{1H} NMR (**$CDCl_3$, 125 MHz) δ 234.4, 141.6, 141.5, 133.2, 129.0, 128.9, 128.7, 127.7, 125.8, 125.6, 125.6, 125.5, 125.5, 22.1, -2.8. **HR-MS (ESI)** *m/z* calculated for $C_{19}H_{20}F_3OSi^+$ $[M+H]^+$ 349.4477, found 349.4470.



139j

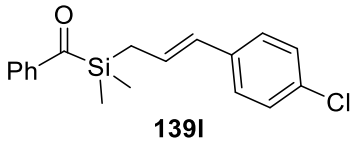
Prepared according to general procedure: 7% yield (22 mg, 0.07 mmol), bright yellow oil. 1 mol% of G-II used. Column eluent hexane/ethyl acetate (90:10). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.82 – 7.80 (m, 2H), 7.57 – 7.46 (m, 5H), 7.30 (d, J = 8.3 Hz, 2H), 6.38 (dt, J = 16.3, 8.2 Hz, 1H), 6.26 (d, J = 15.7 Hz, 1H), 2.07 (dd, J = 8.2,

0.8 Hz, 2H), 0.44 (s, 6H). **^{13}C{1H} NMR (**$CDCl_3$, 125 MHz) δ 234.1, 142.5, 141.5, 133.2, 132.4, 130.7, 128.9, 128.4, 127.6, 126.1, 119.3, 109.7, 22.4, -2.8. **HR-MS (ESI)** *m/z* calculated for $C_{19}H_{20}NOSi^+$ $[M+H]^+$ 306.1309, found 306.1315.



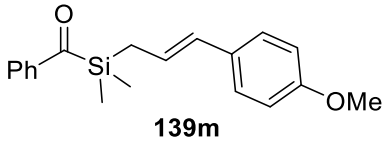
139k

Prepared according to general procedure: 55% yield (198 mg, 0.55 mmol), bright yellow oil. 1 mol% of G-II used. Column eluent hexane/ethyl acetate (97:3). **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.84 – 7.80 (m, 2H), 7.58 – 7.44 (m, 3H), 7.39 – 7.34 (m, 2H), 7.12 – 7.08 (m, 2H), 6.21 – 6.18 (m, 2H), 2.01 (dd, J = 4.8, 2.1 Hz, 2H), 0.42 (s, 6H). **^{13}C{1H} NMR (**$CDCl_3$, 75 MHz) δ 234.5, 141.6, 137.0, 133.1, 131.6, 128.9, 128.8, 127.7, 127.3, 126.8, 120.3, 21.9, -2.8. **HR-MS (ESI)** *m/z* calculated for $C_{18}H_{20}BrOSi^+$ $[M+H]^+$ 359.0461, found 359.0451.



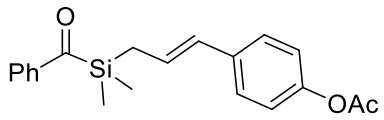
139l

Prepared according to general procedure: 83% yield (261 mg, 0.83 mmol), bright yellow oil. 1 mol% of G-II used. Column eluent hexane/ethyl acetate (97:3). **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.83 – 7.80 (m, 2H), 7.58 – 7.44 (m, 3H), 7.23 – 7.14 (m, 4H), 6.25 – 6.12 (m, 2H), 2.02 – 2.00 (m, 2H), 0.43 (s, 6H). **^{13}C{1H} NMR (**$CDCl_3$, 75 MHz) δ 234.5, 141.6, 136.5, 133.1, 132.2, 128.9, 128.8, 128.7, 127.7, 127.0, 126.7, 21.9, -2.9. **HR-MS (ESI)** *m/z* calculated for $C_{18}H_{20}ClOSi^+$ $[M+H]^+$ 315.0966, found 315.0970.



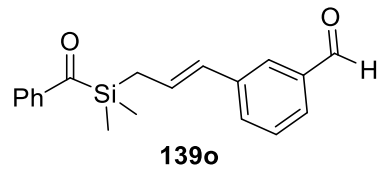
139m

Prepared according to general procedure: 30% yield (93 mg, 0.3 mmol), bright yellow oil. 1 mol% of G-II used. Column eluent hexane/ethyl acetate (95:5). **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.84 – 7.81 (m, 2H), 7.54 – 7.44 (m, 3H), 7.20 – 7.17 (m, 2H), 6.82 – 6.79 (m, 2H), 6.22 (d, J = 15.8 Hz, 1H), 6.04 (dt, J = 15.8, 8.1 Hz, 1H), 3.78 (s, 3H), 1.99 (d, J = 8.0 Hz, 2H), 0.41 (s, 6H). **^{13}C{1H} NMR (**$CDCl_3$, 75 MHz) δ 235.1, 158.7, 141.8, 133.1, 131.1, 129.6, 129.0, 127.8, 127.0, 123.5, 114.1, 55.5, 21.7, -2.8. **HR-MS (ESI)** *m/z* calculated for $C_{19}H_{23}O_2Si^+$ $[M+H]^+$ 311.1462, found 311.1464.



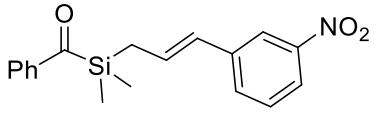
139n

Prepared according to general procedure: 26% yield (89 mg, 0.26 mmol), bright yellow oil. 1 mol% of G-II used. Column eluent hexane/ethyl acetate (85:15). **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.84 – 7.80 (m, 2H), 7.58 – 7.44 (m, 3H), 7.27 – 7.22 (m, 2H), 7.00 – 6.95 (m, 2H), 6.28 – 6.09 (m, 2H), 2.28 (s, 3H), 2.01 (d, J = 7.2 Hz, 2H), 0.42 (s, 6H). **^{13}C{1H} NMR (**$CDCl_3$, 75 MHz) δ 234.6, 169.7, 149.4, 141.6, 135.9, 133.0, 129.0, 128.9, 127.7, 126.7, 126.1, 121.6, 21.8, 21.3, -2.9. **HR-MS (ESI)** *m/z* calculated for $C_{20}H_{23}O_3Si^+$ $[M+H]^+$ 339.1411, found 339.1423.



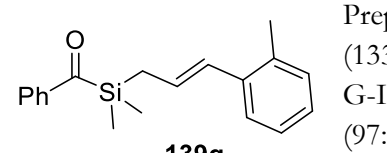
139o

Prepared according to general procedure: 43% yield (132 mg, 0.43 mmol), bright yellow oil. 1 mol% of G-II used. Gradient column eluent hexane/ethyl acetate (98:2 to 85:15). **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 9.98 (s, 1H), 7.84 – 7.39 (m, 10H), 6.34 – 6.31 (m, 2H), 2.07 – 2.05 (m, 2H), 0.44 (s, 6H). **^{13}C{1H} NMR (**$CDCl_3$, 125 MHz) δ 234.4, 192.6, 141.6, 139.0, 136.8, 133.1, 131.7, 129.3, 128.9, 128.6, 128.1, 128.0, 127. 7, 126.7, 22.0, -2.8. **HR-MS (ESI)** *m/z* calculated for $C_{19}H_{21}O_2Si^+$ $[M+H]^+$ 309.1305, found 309.1310.



139p

Prepared according to general procedure: 26% yield (84 mg, 0.26 mmol), bright yellow oil. 1 mol% of G-II used. Gradient column eluent hexane/ethyl acetate (90:10 to 85:15). **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 8.06 (t, J = 1.9 Hz, 1H), 8.01 – 7.97 (m, 1H), 7.84 – 7.81 (m, 2H), 7.58 – 7.38 (m, 5H), 6.43 – 6.26 (m, 2H), 2.07 (d, J = 7.2 Hz, 2H), 0.45 (s, 6H). **^{13}C{1H} NMR (**$CDCl_3$, 125 MHz) δ 234.1, 148.7, 141.6, 139.8, 133.2, 131.6, 129.7, 129.4, 128.9, 127.8, 127.7, 121.3, 120.3, 22.1, -2.7. **HR-MS (ESI)** *m/z* calculated for $C_{18}H_{20}NO_3Si^+$ $[M+H]^+$ 326.1207, found 326.1192.

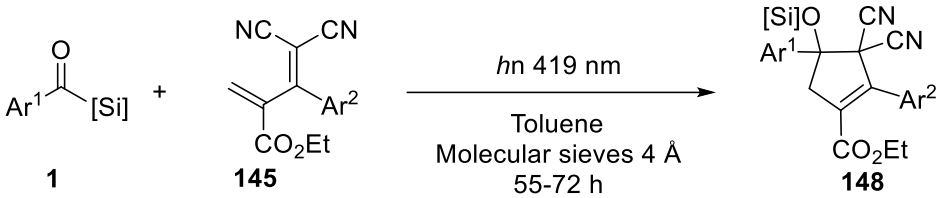


139q

Prepared according to general procedure: 45% yield (133 mg, 0.45 mmol), bright yellow oil. 1 mol% of G-II used. Column eluent hexane/ethyl acetate (97:3). **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.86 – 7.83 (m, 2H), 7.58 – 7.45 (m, 3H), 7.32 – 7.29 (m, 1H), 7.15 – 7.09 (m, 3H), 6.46 (d, J = 15.6 Hz, 1H), 6.07 (dt, J = 15.7, 8.2 Hz, 1H), 2.25

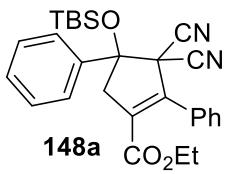
(s, 3H), 2.06 (dd, J = 8.2, 1.2 Hz, 2H), 0.44 (s, 6H). **^{13}C{1H} NMR (**$CDCl_3$, 75 MHz) δ 234.7, 141.7, 137.3, 134.7, 133.0, 130.2, 128.9, 128.1, 127.7, 127.0, 126.7, 126.1, 125.4, 22.2, 20.0, -2.9. **HR-MS (ESI)** *m/z* calculated for $C_{19}H_{23}OSi^+$ $[M+H]^+$ 295.1513, found 295.1512.

Photochemical cyclopropanation/Vinyl cyclopropane rearrangement of acylsilanes 1 with dienes 145:



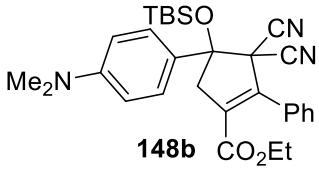
1 **145** **148**

General procedure: Acylsilane **1** (0.1 mmol) and diene **148** (0.14 mmol, 1.4 equiv.) were dissolved in 0.5 mL of dry toluene in a sealed Pasteur pipette. 100 mg of molecular sieves 4 Å were added and the solution was purged with argon for 15 minutes and irradiated at 419 nm from a minimum of 24 to maximum 72 h. Reaction progress was monitored by TLC and stopped upon full consumption of acylsilane **1**. Toluene was evaporated under reduced pressure and the crude purified via silica column chromatography (eluent hexane/EtOAc) to give cyclopentenes **148**.



148a

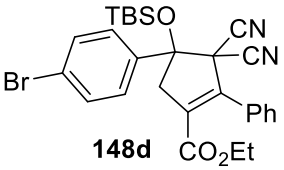
Prepared according to general procedure: 68% yield (32.1 mg) as an off-white amorphous solid. 55 h reaction. Column eluent hexane/EtOAc (94:6). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.76 – 7.73 (m, 2H), 7.49 – 7.38 (m, 8H), 4.13 (qd, J = 7.1, 1.9 Hz, 2H), 3.94 (d, J = 17.0 Hz, 2H), 3.40 (d, J = 17.0 Hz, 1H), 1.08 (t, J = 7.1 Hz, 3H), 0.94 (s, 9H), 0.02 (s, 3H), -0.22 (s, 3H). **^{13}C{1H} NMR** (75 MHz, $CDCl_3$) δ 163.4, 144.0, 138.0, 134.4, 131.6, 130.2, 129.9, 129.0, 128.6, 128.2, 126.9, 112.3, 112.2, 89.0, 61.5, 60.0, 43.0, 25.7, 18.5, 13.8, -3.3, -3.6. HRMS m/z: $[M+H]^+$ calculated for $C_{28}H_{33}N_2O_3Si$+ 473.2255, found 473.2255.



148b

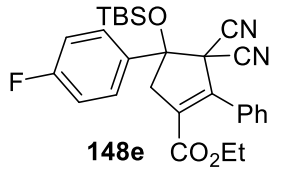
Prepared according to general procedure: 62% yield (32 mg) as an off-white amorphous solid. 48 h reaction. Column eluent hexane/DCM (65:35). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.55 (d, J = 8.9 Hz, 2H), 7.45 – 7.37 (m, 5H), 6.73 (d, J = 9.0 Hz, 2H), 4.11 (qd, J = 7.1, 2.1 Hz, 2H), 3.87 (d, J = 17.0 Hz, 1H), 3.33 (d, J = 17.0 Hz, 1H), 3.01 (s, 6H), 1.07 (t, J

= 7.1 Hz, 3H), 0.93 (s, 9H), -0.00 (s, 3H), -0.17 (s, 3H). **^{13}C{1H} NMR** (75 MHz, $CDCl_3$) δ 163.7, 151.2, 144.2, 134.5, 131.9, 129.7, 128.5, 128.2, 128.0, 124.8, 112.7, 112.5, 111.8, 89.3, 61.3, 60.3, 43.3, 40.2, 25.7, 18.5, 13.8, -3.3, -3.5. **HRMS m/z:** $[M+H]^+$ calculated for $C_{30}H_{38}N_3O_3Si^+$ 516.26770, found 516.2670.



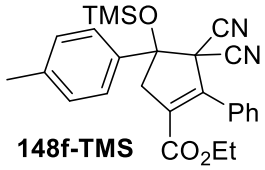
148d

Prepared according to general procedure: 66% yield (36.5 mg) as an off-white amorphous solid. 55 h reaction. Column eluent hexane/EtOAc (90:10). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.62 (s, 4H), 7.46 – 7.37 (m, 5H), 4.12 (qd, J = 7.1, 1.9 Hz, 2H), 3.87 (d, J = 17.1 Hz, 1H), 3.38 (d, J = 17.0 Hz, 1H), 1.07 (t, J = 7.1 Hz, 3H), 0.94 (s, 9H), 0.05 (s, 3H), -0.19 (s, 3H). **^{13}C{1H} NMR** (75 MHz, $CDCl_3$) δ 163.3, 143.9, 137.1, 134.2, 132.3, 131.4, 130.0, 128.6, 128.6, 128.2, 124.6, 112.0, 112.0, 88.5, 61.6, 60.0, 42.8, 25.7, 18.5, 13.8, -3.2, -3.5. **HRMS m/z:** $[M+H]^+$ calculated for $C_{28}H_{32}BrN_2O_3Si^+$ 551.1360, found 551.1361.



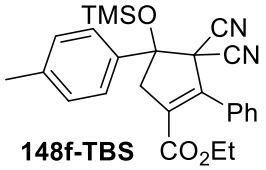
148e

Prepared according to general procedure: 66% yield (32.6 mg) as an off-white amorphous solid. 72 h reaction. Column eluent hexane/EtOAc (93:7). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.77 – 7.71 (m, 2H), 7.46 – 7.37 (m, 5H), 7.21 – 7.14 (m, 2H), 4.12 (qd, J = 7.1, 1.8 Hz, 2H), 3.89 (d, J = 17.1 Hz, 1H), 3.39 (d, J = 17.0 Hz, 1H), 1.07 (t, *J* = 7.1 Hz, 3H), 0.94 (s, 9H), 0.04 (s, 3H), -0.21 (s, 3H). **^{13}C{1H} NMR** (75 MHz, $CDCl_3$) δ 165.3, 163.3, 162.0, 144.0, 134.2, 134.1, 134.1, 131.5, 130.0, 129.1, 128.9, 128.6, 128.2, 116.2, 116.0, 112.1, 112.1, 88.5, 61.5, 60.1, 43.1, 25.7, 18.5, 13.8, -3.2, -3.5. **^{19}F{1H} NMR** (376 MHz, $CDCl_3$) δ -110.6. **HRMS m/z:** $[M]^+$ calculated for $C_{28}H_{31}FN_2O_3Si^+$ 490.2082, found 490.2082.



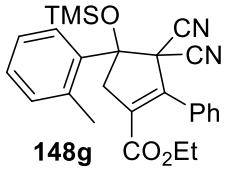
148f-TMS

Prepared according to general procedure: 66% yield (29.5 mg) as an off-white amorphous solid. 23 h reaction. Column eluent hexane/EtOAc (95:5). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.58 (d, J = 8.3 Hz, 2H), 7.45 – 7.38 (m, 5H), 7.27 (d, J = 8.0 Hz, 2H), 4.13 (q, J = 7.1 Hz, 2H), 3.88 (d, J = 17.1 Hz, 1H), 3.36 (d, J = 17.1 Hz, 1H), 2.40 (s, 3H), 1.07 (t, J = 7.1 Hz, 3H), 0.07 (s, 9H). **^{13}C{1H} NMR** (75 MHz, $CDCl_3$) δ 163.6, 143.7, 140.0, 135.2, 134.5, 131.7, 129.9, 129.6, 128.5, 128.2, 126.6, 112.4, 112.1, 89.0, 61.5, 60.6, 43.4, 21.3, 13.8, 1.3. **HRMS m/z:** $[M+H]^+$ calculated for $C_{26}H_{29}N_2O_3Si^+$ 445.1942, found 445.1942.



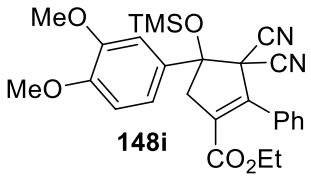
148f-TBS

Prepared according to general procedure: 74% yield (36.2 mg) as an off-white amorphous solid. 55 h reaction. Column eluent hexane/EtOAc (94:6). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.61 (d, J = 8.3 Hz, 2H), 7.46 – 7.36 (m, 5H), 7.27 (d, J = 7.9 Hz, 2H), 4.12 (qd, J = 7.1, 2.0 Hz, 2H), 3.90 (d, J = 17.1 Hz, 1H), 3.36 (d, J = 17.0 Hz, 1H), 1.07 (t, J = 7.1 Hz, 3H), 0.93 (s, 9H), 0.00 (s, 3H), -0.22 (s, 3H). **^{13}C{1H} NMR** (75 MHz, $CDCl_3$) δ 163.5, 144.1, 140.2, 135.0, 134.5, 131.7, 129.9, 129.7, 128.6, 128.2, 126.9, 112.4, 112.3, 89.0, 61.5, 60.1, 43.1, 25.7, 21.4, 18.5, 13.9, -3.3, -3.5. **HRMS m/z:** $[M+H]^+$ calculated for $C_{29}H_{35}N_2O_3Si^+$ 487.2411, found 487.2412.



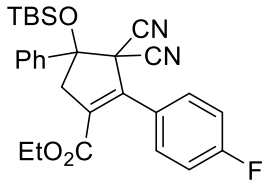
148g

Prepared according to general procedure: 40% yield (17.7 mg) as an off-white amorphous solid. 72 h reaction. Column eluent hexane/EtOAc (93:7). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.50 – 7.22 (m, 9H), 4.15 – 4.08 (m, 2H), 3.94 (d, J = 17.0 Hz, 1H), 3.50 (d, J = 17.0 Hz, 1H), 2.70 (s, 3H), 1.04 (t, J = 7.1 Hz, 3H), 0.10 (s, 9H). **^{13}C{1H} NMR** (75 MHz, $CDCl_3$) δ 163.5, 142.9, 138.9, 136.4, 135.2, 133.8, 131.6, 129.8, 129.7, 128.5, 128.3, 128.0, 126.2, 112.7, 112.3, 91.1, 61.6, 60.0, 46.2, 24.3, 13.8, 1.4. **HRMS m/z:** $[M+H]^+$ calculated for $C_{26}H_{29}N_2O_3Si^+$ 445.1942, found 445.1942.



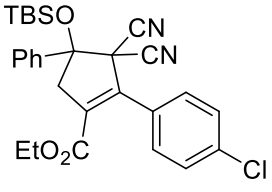
148i

Prepared according to general procedure: 80% yield (42.5 mg), off-white amorphous solid. 48 h reaction. Column eluent hexane/EtOAc (92:8). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.45 – 7.35 (m, 6H), 7.19 (dd, J = 8.4, 2.3 Hz, 1H), 6.90 (d, J = 8.4 Hz, 1H), 4.19 – 4.04 (m, 2H), 3.93 (s, 3H), 3.92 (s, 3H), 3.90 (d, J = 17.0 Hz, 1H), 3.34 (d, J = 17.0 Hz, 1H), 1.06 (t, J = 7.1 Hz, 3H), 0.95 (s, 9H), 0.03 (s, 3H), -0.18 (s, 3H). **^{13}C{1H} NMR** (75 MHz, $CDCl_3$) δ 163.5, 150.3, 149.2, 144.1, 134.3, 131.7, 130.3, 129.9, 128.6, 128.1, 119.3, 112.4, 112.3, 110.5, 110.0, 89.0, 61.4, 60.3, 56.0, 55.9, 42.9, 25.7, 18.5, 13.8, -3.3, -3.5. **HRMS m/z:** $[M+H]^+$ calculated for $C_{30}H_{37}N_2O_5Si^+$ 533.2466, found 533.2463.



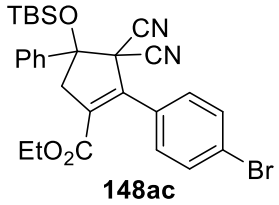
148aa

Prepared according to general procedure: 61% yield (30.2 mg) as an off-white amorphous solid. 55 h reaction. Column eluent hexane/EtOAc (93:7). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.75 – 7.71 (m, 2H), 7.49 – 7.47 (m, 3H), 7.42 – 7.38 (m, 2H), 7.19 – 7.11 (m, 2H), 4.15 (qd, J = 7.1, 2.4 Hz, 2H), 3.92 (d, J = 17.1 Hz, 1H), 3.39 (d, J = 17.0 Hz, 1H), 1.12 (t, J = 7.1 Hz, 3H), 0.93 (s, 9H), 0.00 (s, 3H), -0.23 (s, 3H). **^{13}C{1H} NMR** (75 MHz, $CDCl_3$) δ 165.3, 163.2, 162.0, 143.1, 137.8, 134.9, 130.5, 130.3, 130.3, 129.1, 127.6, 127.5, 126.9, 116.0, 115.7, 112.3, 112.1, 89.0, 61.6, 60.0, 43.0, 25.7, 18.5, 13.9, -3.3, -3.6. **^{19}F{1H} NMR** (376 MHz, $CDCl_3$) δ -110.3 **HRMS m/z:** $[M]^+$ calculated for $C_{28}H_{31}FN_2O_3Si^+$ 490.2082, found 490.2082.



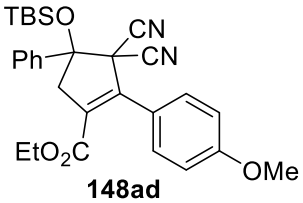
148ab

Prepared according to general procedure: 77% yield (39.1 mg) as an off-white amorphous solid. 55 h reaction. Column eluent hexane/EtOAc (92:8). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.74 – 7.71 (m, 2H), 7.50 – 7.42 (m, 5H), 7.36 – 7.33 (m, 2H), 4.15 (qd, J = 7.1, 2.3 Hz, 2H), 3.92 (d, J = 17.2 Hz, 1H), 3.39 (d, J = 17.1 Hz, 1H), 1.13 (t, J = 7.1 Hz, 3H), 0.93 (s, 9H), 0.00 (s, 3H), -0.23 (s, 3H). **^{13}C{1H} NMR** (75 MHz, $CDCl_3$) δ 163.1, 142.9, 137.8, 136.2, 135.1, 130.3, 130.0, 129.7, 129.1, 129.0, 126.9, 112.2, 112.0, 89.0, 61.7, 59.8, 43.0, 25.7, 18.5, 13.9, -3.3, -3.6. **HRMS m/z:** $[M+H]^+$ calculated for $C_{28}H_{32}ClN_2O_3Si^+$ 507.1865, found 507.1825.



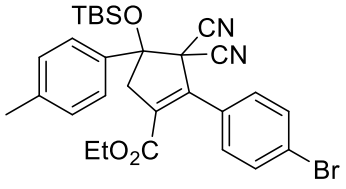
148ac

Prepared according to general procedure: 72% yield (40.0 mg) as an off-white amorphous solid. 55 h reaction. Column eluent hexane/DCM (60:40). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.62 (s, 4H), 7.46 – 7.44 (m, 3H), 7.41 – 7.36 (m, 2H), 4.12 (qd, J = 7.1, 1.9 Hz, 2H), 3.87 (d, J = 17.1 Hz, 1H), 3.38 (d, J = 17.0 Hz, 1H), 1.07 (t, J = 7.1 Hz, 3H), 0.94 (s, 9H), 0.05 (s, 3H), -0.19 (s, 3H). **^{13}C{1H} NMR** (75 MHz, $CDCl_3$) δ 163.3, 143.9, 137.1, 134.2, 132.3, 131.4, 130.0, 128.6, 128.6, 128.2, 124.6, 112.0, 112.0, 88.5, 61.6, 60.0, 42.8, 25.7, 18.5, 13.8, -3.2, -3.5. **HRMS m/z:** $[M]^+$ calculated for $C_{28}H_{31}BrN_2O_3Si^+$ 550.1282, found 550.1284.



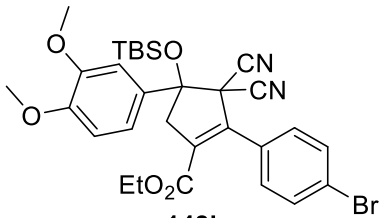
148ad

Prepared according to general procedure: 66% yield (33.2 mg) as an off-white amorphous solid. 72 h reaction. Column eluent hexane/EtOAc (90:10). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.76 – 7.72 (m, 2H), 7.50 – 7.45 (m, 3H), 7.40 – 7.35 (m, 2H), 6.99 – 6.94 (m, 2H), 4.16 (qd, J = 7.1, 2.0 Hz, 2H), 3.91 (d, J = 17.0 Hz, 1H), 3.84 (s, 3H), 3.37 (d, J = 17.0 Hz, 1H), 0.92 (s, 9H), 0.01 (s, 3H), -0.23 (s, 3H). **^{13}C{1H} NMR** (75 MHz, $CDCl_3$) δ 163.6, 160.9, 144.1, 138.0, 133.1, 130.1, 129.9, 129.0, 127.0, 123.7, 114.0, 112.6, 112.4, 88.9, 61.4, 59.9, 55.4, 43.1, 25.7, 18.5, 14.0, -3.3, -3.6. **HRMS m/z:** $[M+H]^+$ calculated for $C_{29}H_{35}N_2O_4Si^+$ 503.2361, found 503.2357.



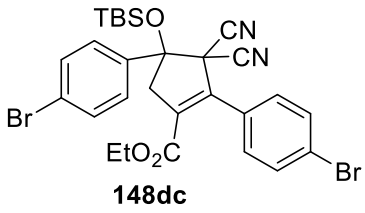
148fc

Prepared according to general procedure: 69% yield (39.0 mg), yellow amorphous solid. 48 h reaction. Column eluent hexane/EtOAc (85:15). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.57 (d, J = 8.0 Hz, 4H), 7.25 (d, J = 8.1 Hz, 4H), 4.18 – 4.07 (m, 2H), 3.87 (d, J = 17.1 Hz, 1H), 3.33 (d, J = 17.1 Hz, 1H), 2.38 (s, 3H), 1.10 (t, J = 7.1 Hz, 3H), 0.90 (s, 9H), -0.03 (s, 3H), -0.24 (s, 3H). **^{13}C{1H} NMR** (100 MHz, $CDCl_3$) δ 163.1, 142.9, 140.3, 135.1, 134.8, 131.9, 130.5, 129.9, 129.7, 126.8, 124.4, 112.2, 112.1, 89.0, 61.6, 59.8, 43.1, 25.7, 21.4, 18.4, 13.9, -3.3, -3.6. **HRMS m/z:** $[M+H]^+$ calculated for $C_{29}H_{34}BrN_2O_3Si^+$ 565.1517, found 565.1526.



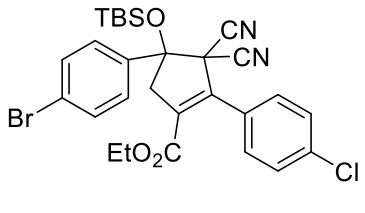
148ic

Prepared according to general procedure: 90% yield (54.8 mg), off-white amorphous solid. 48 h reaction. Column eluent hexane/EtOAc (85:15). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.61 (d, J = 8.2 Hz, 2H), 7.35 (d, J = 2.3 Hz, 1H), 7.28 (d, J = 8.3 Hz, 2H), 7.17 (dd, J = 8.4, 2.3 Hz, 1H), 6.92 (d, J = 8.4 Hz, 1H), 4.20 – 4.12 (m, 2H), 3.94 (s, 6H), 3.90 (d, J = 17.2 Hz, 1H), 3.35 (d, J = 17.1 Hz, 1H), 1.14 (t, J = 7.1 Hz, 3H), 0.95 (s, 9H), 0.04 (s, 3H), -0.16 (s, 3H). **^{13}C{1H} NMR** (100 MHz, $CDCl_3$) δ 163.1, 150.3, 149.2, 142.9, 135.0, 131.9, 130.5, 130.0, 129.8, 124.4, 119.2, 112.2, 112.1, 110.5, 109.8, 89.1, 61.6, 60.0, 56.0, 55.9, 42.8, 25.6, 18.4, 13.9, -3.4, -3.6. **HRMS m/z:** $[M+H]^+$ calculated for $C_{30}H_{36}BrN_2O_5Si^+$ 611.1571, found 611.1583.



148dc

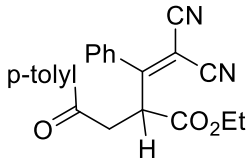
Prepared according to general procedure: 87% yield (52.4 mg), white amorphous solid. 72 h reaction. Column eluent hexane/DCM (68:32). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.63 – 7.57 (m, 6H), 7.25 (d, J = 8.3 Hz, 2H), 4.20 – 4.08 (m, 2H), 3.85 (d, J = 17.1 Hz, 1H), 3.35 (d, J = 17.1 Hz, 1H), 1.11 (t, J = 7.1 Hz, 3H), 0.91 (s, 9H), 0.02 (s, 3H), -0.21 (s, 3H). **^{13}C{1H} NMR** (100 MHz, $CDCl_3$) δ 162.9, 142.7, 136.9, 134.9, 132.3, 131.9, 130.2, 129.8, 128.5, 124.7, 124.6, 111.8 (2), 88.5, 61.8, 59.7, 42.8, 25.6, 18.4, 13.9, -3.2, -3.5. **HRMS m/z:** $[M+H]^+$ calculated for $C_{28}H_{31}Br_2N_2O_3Si^+$ 631.0445, found 631.0461.



148db

Prepared according to general procedure: 69% yield (40.6 mg), pale oil. 72 h reaction. Column eluent hexane/DCM (70:30). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.64 – 7.59 (m, 4H), 7.44 (d, J = 8.3 Hz, 2H), 7.33 (d, J = 8.3 Hz, 2H), 4.18 – 4.09 (m, 2H), 3.87 (d, J = 17.1 Hz, 1H), 3.37 (d, J = 17.1 Hz, 1H), 1.13 (t, J = 7.1 Hz, 3H), 0.93 (s, 9H), 0.03 (s, 3H), -0.20 (s, 3H). **^{13}C{1H} NMR** (100 MHz, $CDCl_3$) δ 163.0, 142.8, 136.9, 136.3, 134.9, 132.3, 129.7, 129.6, 129.0, 128.5, 124.8, 111.9 (2), 88.5, 61.8, 59.8, 42.8, 25.6, 18.4, 13.9, -3.2, -3.5. **HRMS m/z:** $[M+H]^+$ calculated for $C_{28}H_{31}BrClN_2O_3Si^+$ 585.0970, found 585.0979.

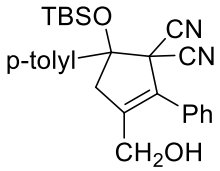
Chemical transformations of cyclopentene 148f-TBS:



151

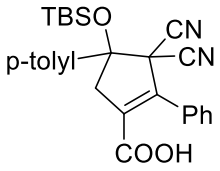
Cyclopentene **148f-TBS** (10 mg, 20 μmol) was dissolved in THF (1 mL) in a round-bottom flask. The solution was cooled to 0°C and TBAF·H_2O (7.1 mg, 23 μmol, 1.1 equiv.) was added. After 10 min at 0°C the solution was warmed to room temperature. The product was purified by silica column flash chromatography with dry loading, using hexane/EtOAc (80:20) as eluent to give **151** as an amorphous off-white solid in 78% yield (5.8 mg, 16 μmol). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.72 (d, J = 8.2 Hz, 2H), 7.51 – 7.39 (m, 3H), 7.27 – 7.20 (m, 4H), 4.83 (dd, J = 8.3, 5.5 Hz, 1H), 4.31 (q, J = 7.1 Hz, 2H), 3.74 (dd, J = 18.4, 5.5 Hz, 1H), 3.17 (dd, J = 18.4, 8.4 Hz, 1H), 2.39 (s, 3H), 1.33 (t, J = 7.1 Hz, 3H). **^{13}C{1H} NMR** (75 MHz, $CDCl_3$) δ 195.4, 175.2, 168.6,

145.0, 133.6, 133.3, 131.8, 129.6, 129.4, 128.3, 127.6, 112.4, 112.1, 90.0, 63.0, 47.9, 38.7, 21.8, 14.2. **HRMS m/z:** $[M+H]^+$ calculated for $C_{23}H_{21}N_2O_3^+$ 373.1547, found 373.1544.



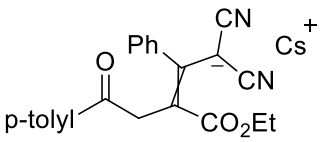
152

Cyclopentene **148f-TBS** (20 mg, 41 μmol) was dissolved in dry THF (2 mL) in a round-bottom flask and the resulting Solution cooled to 0°C. $LiBH_4$ (3 mg, 135 μmol, 3.3 equiv.) was added and the reaction warmed to room temperature. After 3 h, water (9.7 μL, 540 μmol, 13.2 equiv.) was added and the solution left stirring for 5 minutes. Then, the solvent was evaporated, and the crude purified by silica flash column chromatography, using hexane/EtOAc as eluent (80:20) to give alcohol **152** in 48% yield (8.8 mg, 20 μmol). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.61 (d, J = 8.3 Hz, 2H), 7.47 – 7.41 (m, 3H), 7.34 – 7.32 (m, 2H), 7.25 (d, J = 6.7 Hz, 2H), 4.44 – 4.33 (m, 2H), 3.76 (d, J = 17.0 Hz, 1H), 3.21 (d, J = 17.0 Hz, 1H), 2.39 (s, 3H), 0.92 (s, 9H), 0.01 (s, 3H), -0.23 (s, 3H). **^{13}C{1H} NMR** (100 MHz, $CDCl_3$) δ 144.1, 139.9, 135.9, 132.0, 131.5, 129.6, 129.4, 129.1, 128.6, 127.1, 113.6, 113.6, 89.2, 59.7, 58.7, 43.6, 25.8, 21.4, 18.5, -2.9, -3.4. **HRMS m/z:** $[M+H]^+$ calculated for $C_{27}H_{33}N_2O_2Si^+$ 445.2306, found 445.2304.



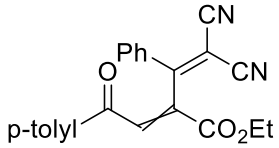
153

Cyclopentenone **148f-TBS** (6 mg, 12 μmol) was dissolved in EtOH (1 mL). LiOH (20 μL of 1 M aqueous solution, 20 μmol, 2 equiv.) was added and the solution stirred for 5 h at room temperature. Then, the solvent was evaporated and the crude purified by silica flash column chromatography, using hexane/EtOAc/AcOH (60:40:0.1) as eluent to give carboxylic acid **153** in 69% yield (3.8 mg, 8.3 μmol) **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.59 (d, J = 8.3 Hz, 2H), 7.47 – 7.39 (m, 5H), 7.27 (d, J = 6.6 Hz, 2H), 3.90 (d, J = 17.1 Hz, 1H), 3.36 (d, J = 17.0 Hz, 1H), 2.40 (s, 3H), 0.92 (s, 9H), -0.00 (s, 3H), -0.23 (s, 3H). **^{13}C{1H} NMR** (100 MHz, $CDCl_3$) δ 167.3, 146.3, 140.3, 134.8, 133.4, 131.3, 130.2, 129.8, 128.8, 128.2, 126.9, 112.2, 112.1, 88.9, 60.3, 43.2, 25.7, 21.4, 18.5, -3.2, -3.5. **HRMS m/z:** $[M+H]^+$ calculated for $C_{27}H_{31}N_2O_3Si^+$ 459.2098, found 459.2091.



154

Cyclopentene **148f-TBS** (10 mg, 20 μmol) was dissolved in dry ACN (1 mL) in an oven-dried round-bottom flask, under argon atmosphere. CsF (94 mg, 620 μmol, 30 equiv.) was added and the solution left stirring for 3 hours. The solvent was evaporated, and the crude mixture was redissolved in acetone. The solid CsF excess was filtered off through celite and the filtrate evaporated to give salt **154** as a bright yellow oil in 75% yield (7.6 mg, 15 μmol) as a 1:0.2 mixture of isomers. **154** can be converted to **151** simply via passing through silica plug. **154*major:* ^{1}H NMR** (400 MHz, $(CD_3)_2CO$) δ 7.94 (d, J = 8.2 Hz, 2H), 7.28 (d, J = 7.9 Hz, 2H), 7.21 (s, 5H), 4.39 (s, 2H), 3.52 (q, J = 7.1 Hz, 2H), 2.39 (s, 3H), 0.59 (t, J = 7.1 Hz, 3H). **^{13}C{1H} NMR** (100 MHz, $(CD_3)_2CO$) δ 199.6, 169.8, 158.2, 144.9, 143.2, 136.8, 130.2, 129.7, 129.0, 127.9, 127.8, 125.2, 102.0, 58.7, 43.1, 40.2, 21.6, 14.1. **154*minor*: ^{1}H NMR** (400 MHz, $(CD_3)_2CO$) δ 7.70 (d, J = 8.2 Hz, 2H), 7.29 – 7.20 (m, 7H) 4.06 (q, J = 7.1 Hz, 2H), 3.60 (s, 2H), 2.33 (s, 3H), 1.12 (t, J = 7.1 Hz, 3H). **HRMS m/z:** $[M+2H]^+$ calculated for $C_{23}H_{21}N_2O_3Si^+$ 373.1547, found 373.1544.

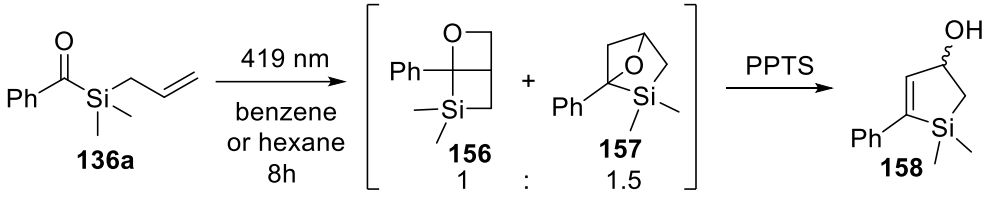


155

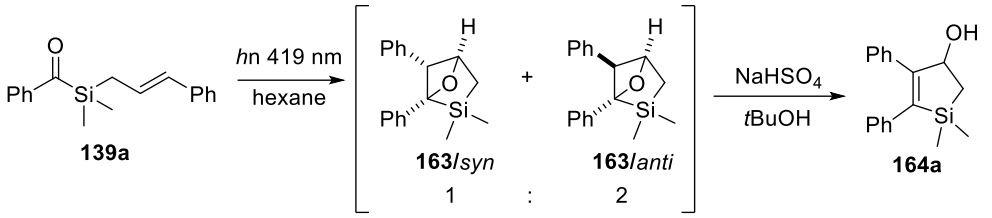
Cyclopentene **148f-TBS** (20 mg, 40 μmol) was dissolved in dry ACN (2 mL) in an oven-dried round-bottom flask, under argon atmosphere. CsF (180 mg, 1.2 mmol, 30 equiv.) was added and the solution left stirring for 3 hours. Excess CsF was filtered through celite and NBS (7.1 mg, 40 μmol, 1 equiv.) was added to the filtrate solution. The bright yellow colour of the intermediate **154** quickly faded. The solvent was quickly evaporated. Analysis of the ^{1}**H NMR** crude at this stage reveals a *E*/*Z* ratio of 0.45:1. The crude was purified by silica flash column chromatography, using hexane/EtOAc as eluent (80:20) to give diene **155** in 77% yield (11.4 mg, 31 μmol) in a *E*/*Z* ratio of 1:0.2 in thermodynamic equilibrium. **155*E*** (major): **^{1}H NMR** (400 MHz, $(CD_3)_2CO$) δ 8.41 (s, 1H), 7.96 (d, J = 8.2 Hz, 2H), 7.78 – 7.76 (m, 2H), 7.69 – 7.53 (m, 3H), 7.40 (d, J = 8.2 Hz, 2H), 4.31 (q, J = 7.1 Hz, 2H), 2.43 (s, 3H), 1.24 (t, J = 7.1 Hz, 3H). **^{13}C{1H} NMR** (100 MHz, $(CD_3)_2CO$) δ 189.1, 172.2, 163.4, 146.7, 139.8, 138.7, 134.4, 134.2, 133.6, 130.6, 130.2, 129.9, 129.8, 113.5, 113.4, 85.4, 63.6, 21.7, 14.1. **155*Z*** (minor): **^{1}H NMR** (400 MHz, $(CD_3)_2CO$) δ 7.99 – 7.39 (m, 10H), 3.96 (q, J = 7.1 Hz, 2H), 2.43 (s, 3H), 0.89 (t, *J* = 7.1 Hz, 3H). **HRMS m/z:** $[M+H]^+$ calculated for $C_{23}H_{19}N_2O_3$ 371.1390, found 371.1384. Note: Prolonged heating of the reaction crude at 40°C also delivers the same relative *E*/*Z* ratio of isomers, further confirming thermodynamic equilibrium. Identification of isomers

was conducted via analysis of the ethyl ester β-hydrogen which shows characteristic lower field shift from *trans* to *cis* conformation (relative to ester), from 7.79 to 8.41 ppm.

Photochemical [2+2] photocycloaddition of benzoyl(allyl)silanes:

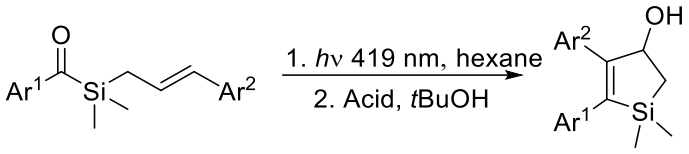


Acylsilane **136a** (50 mg, 0.245 mmol) was dissolved in dry benzene or hexane (5 mL). The solution was irradiated for 5-8h, until complete disappearance of the bright yellow colour. NMR analysis of the reaction crude at this point showed a mixture of the unstable intermediates **156** and **157**, which structures were elucidated based on spectroscopic characterization of previously reported related bicyclic structures.[24] **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.38 – 7.12 (m, 10H, **156**/**157**), 5.20 (t, J = 7.2 Hz, 1H, **156**), 4.81 (d, J = 4.6 Hz, 1H, **157**), 4.61 (dd, J = 6.4, 3.5 Hz, 1H, **156**), 3.40 – 3.33 (m, 1H, **156**), 2.90 – 2.84 (m, 1H, **157**), 2.22 (d, J = 8.3 Hz, 1H, **157**), 1.58 – 1.38 (m, 3H, **156**/**157**), 1.26 (d, J = 13.8 Hz, 1H, **157**), 0.60 (s, 3H, **156**), 0.40 (s, 3H, **157**), 0.27 (s, 3H, **156**), 0.24 (s, 3H, **157**). **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz) δ 144.5, 143.2, 128.4, 128.2, 125.9, 125.3, 123.1, 123.0, 96.3 (**156**), 89.9 (**157**), 79.3 (**156**), 79.2 (**157**), 44.6 (**157**), 42.2 (**156**), 23.5 (**157**), 17.3 (**156**), -1.3 (**156**), -3.0 (**157**), -3.0 (**156**), -4.9 (**157**).
The solution was transferred to a round-bottom flask and pyridinium *p*-toluenesulfonate (PPTSA) (65 mg, 0.257 mmol, 1.05 equiv.) was added. The reaction was stirred at room temperature for 15 minutes. The solvent was evaporated, and the product purified through alumina column chromatography, eluent hexane/ethyl acetate (80:20) to give silacyclopentenol **158** (20 mg, 0,099 mmol) as an oil in 40% yield. **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.37 – 7.30 (m, 4H), 7.25 – 7.22 (m, 1H), 6.86 (d, J = 2.3 Hz, 1H), 4.92 (s, 1H), 1.69 (s, 1H), 1.59 (dd, J = 14.6, 7.6 Hz, 1H), 0.84 (dd, J = 14.6, 5.7 Hz, 1H), 0.39 (s, 3H), 0.31 (s, 3H). **^{13}C{1H} NMR (**$CDCl_3$, 125 MHz) δ 147.3, 146.5, 139.1, 128.7, 127.3, 126.9, 126.9, 74.7, 23.7, -0.2, -1.3. **HR-MS (ESI)** *m*/*z* calculated for $C_{12}H_{15}OSi^+$ $[M]^+$ 203.0887, found 203.0905.



Acylsilane **139a** (81 mg, 0.29 mmol) was dissolved in dry hexane (7 mL) under argon atmosphere, in a glass test tube. The solution was degassed with argon (until a final volume of 6 mL) and then irradiated for 5 hours. During this time the solution's bright yellow colour disappeared to give a colourless liquid. The solution was transferred to a round-bottom flask and the hexane evaporated under reduced pressure. NMR analysis of the crude at this stage showed the presence of **163** as a 1:2 mixture of diastereoisomers. **163/***syn*: **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.60 – 6.88 (m, 10H), 5.17 (t, J = 4.8 Hz, 1H), 4.32 (d, J = 5.1 Hz, 1H), 1.53 –1.28 (m, 2H), 0.20 (s, 3H), -0.06 (s, 3H). **^{13}C{1H} NMR (**$CDCl_3$, 75 MHz) δ 141.9, 138.2, 128.7, 128.2, 127.6, 127.4, 126.8, 126.6, 94.1, 81.2, 59.19, 19.7, -1.7, -3.4. **163/***anti*: **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.39 – 6.86 (m, 10H), 4.97 (d, J = 4.3 Hz, 1H), 3.54 (s, 1H), 1.65 (dd, J = 14.0, 4.3 Hz, 1H), 1.43 (d, J = 14.0 Hz, 1H), 0.54 (s, 3H), 0.22 (s, 3H). **^{13}C{^{1}H} NMR (**$CDCl_3$, 125 MHz) δ **^{13}C{^{1}H} NMR (**$CDCl_3$, 75 MHz) δ 140.4, 138.4, 128.8, 128.1, 127.9, 126.6, 125.2, 123.2, 93.4, 84.3, 60.3, 23.3, -3.0, -4.8.

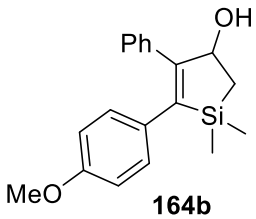
The oily crude was solubilized in *t*butanol (6 mL) at 27 °C, followed by addition of $NaHSO_4$ (0.03 mmol, 0.1 equiv.) and stirring at that temperature for 6 hours. The reaction was quenched with saturated aqueous K_2CO_3 (10 mL) and the product extracted with ethyl acetate (3 × 10 mL). The organic phases were combined, dried over $MgSO_4$ and filtered. The solvent was evaporated and the product isolated through silica column chromatography using hexane/ethyl acetate/Et_3N (90:8:2) and eluent, to give silacyclopentenol **164a** as an amorphous solid in 82% yield (66.1 mg, 0.236 mmol). **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.24 – 7.04 (m, 8H), 6.91 – 6.89 (m, 2H), 5.26 (dd, J = 7.6, 4.9 Hz, 1H), 1.81 (s, 1H), 1.61 (dd, J = 14.9, 7.7 Hz, 1H), 1.08 – 0.99 (m, 1H), 0.44 (s, 3H), 0.17 (s, 3H). **^{13}C{1H} NMR (**$CDCl_3$, 125 MHz) δ 157.2, 144.2, 140.5, 138.2, 129.1, 128.4, 128.2, 128.1, 127.3, 125.7, 77.3, 21.2, 0.1, -2.2. **HR-MS (ESI)** *m*/*z* calculated for $C_{18}H_{19}OSi^+$ $[M]^+$ 279.1200, found 279.1213.



139 **164**

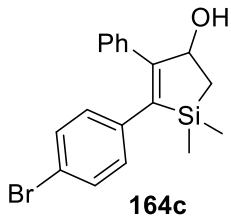
General procedure: Acylsilane **139** (0.3 mmol) was dissolved in dry hexane (7 mL) under argon atmosphere, in a glass test tube. The solution was degassed with argon (until a final volume of 6 mL) and then irradiated for 5 hours. The solution was transferred to a round-bottom flask and the hexane evaporated under reduced pressure. The residue was solubilized in *t*butanol (6 mL) at 27 °C, followed by addition of $NaHSO_4$ or PPTSA (0.03 mmol, 0.1 equiv.) and stirring at that temperature for 6 hours. The reaction was quenched with saturated aqueous K_2CO_3 (10 mL) and the product extracted with ethyl acetate (3 × 10 mL). The organic phases were combined, dried over $MgSO_4$ and filtered. The solvent was evaporated and the product isolated through silica column chromatography to give silacyclopentenol **164**.

Note: Some reactions were performed in different scale due to availability of starting material **139**.



164b

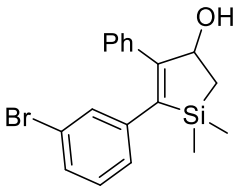
Prepared according to general procedure: 58% yield (53.8 mg, 0.172 mmol) as an amorphous solid. PPTSA used as acid. Column eluent hexane/ethyl acetate/Et_3N (83:15:2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.25 – 7.14 (m, 5H), 6.85 – 6.82 (m, 2H), 6.70 – 6.67 (m, 2H), 5.25 – 5.21 (m, 1H), 3.73 (s, 3H), 1.79 (d, J = 4.0 Hz, 1H), 1.59 (dd, J = 14.9, 7.7 Hz, 1H), 1.00 (dd, J = 14.9, 4.9 Hz, 1H), 0.45 (s, 3H), 0.18 (s, 3H). **^{13}C{1H} NMR (**$CDCl_3$, 125 MHz) δ 157.7, 156.4, 143.2, 138.5, 132.5, 129.4, 129.1, 128.5, 127.3, 113.7, 77.4, 55.2, 21.1, 0.3, -2.1. **HR-MS (ESI)** *m/z* calculated for $C_{19}H_{21}O_2Si^+$ $[M]^+$ 309.1305, found 309.1295.



164c

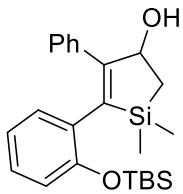
Prepared according to general procedure: 69% yield (74.3 mg, 0.207 mmol) as an amorphous solid. PPTSA used as acid. Column eluent hexane/ethyl acetate/Et_3N (84:14:2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.26 – 7.17 (m, 5H), 7.11 – 7.09 (m, 2H), 6.77 – 6.74 (m, 2H), 5.24 – 5.21 (m, 1H), 1.79 (d, J = 3.8 Hz, 1H), 1.60 (dd, J = 14.9, 7.7 Hz, 1H), 1.01 (dd, J = 14.9, 4.9 Hz, 1H), 0.41 (s, 3H), 0.15 (s, 3H). **^{13}C{1H} NMR (**$CDCl_3$,

75 MHz) δ 158.1, 143.0, 139.5, 137.8, 131.4, 129.8, 129.0, 128.5, 127.6, 119.6, 77.2, 21.2, 0.0, -2.2. **HR-MS (ESI)** *m/z* calculated for $C_{18}H_{18}BrOSi^+$ $[M]^+$ 357.0305, found 357.0317.



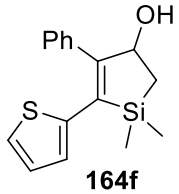
164d

Prepared according to general procedure: 59% yield (64.2 mg, 0.179 mmol) as an amorphous solid. PPTSA used as acid. Column eluent hexane/ethyl acetate/Et_3N (84:14:2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.25 – 7.19 (m, 4H), 7.12 – 7.10 (m, 2H), 7.05 (t, J = 1.8 Hz, 1H), 7.00 (t, J = 7.8 Hz, 1H), 6.79 (dt, J = 7.7, 1.3 Hz, 1H), 5.27 – 5.23 (m, 1H), 1.82 (d, J = 3.9 Hz, 1H), 1.62 (dd, J = 14.9, 7.7 Hz, 1H), 1.03 (dd, J = 14.9, 5.0 Hz, 1H), 0.44 (s, 3H), 0.18 (s, 3H). **^{13}C{1H} NMR (**$CDCl_3$, 75 MHz) δ 158.5, 142.9, 142.8, 137.6, 130.8, 129.8, 129.0, 128.7, 128.5, 127.7, 126.7, 122.3, 77.2, 21.2, -0.0, -2.2.**HR-MS (ESI)** *m/z* calculated for $C_{18}H_{18}BrOSi^+$ $[M]^+$ 357.0305, found 357.0297.



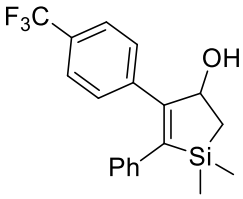
164e

Prepared according to general procedure: 50% yield (62.0 mg, 0.151 mmol) as an amorphous solid. $NaHSO_4$ used as acid. Column eluent hexane/ethyl acetate/Et_3N (90:8:2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.20 – 7.09 (m, 5H), 7.02 – 6.99 (m, 1H), 6.84 – 6.81 (m, 2H), 6.70 (d, J = 8.1 Hz, 1H), 5.38 – 5.36 (m, 1H), 1.76 (s, 1H), 1.65 (dd, J = 14.8, 7.6 Hz, 1H), 1.01 (dd, J = 14.8, 5.2 Hz, 1H), 0.90 (s, 9H), 0.34 (s, 3H), 0.15 (s, 3H), 0.12 (s, 3H), 0.00 (s, 3H). **^{13}C{1H} NMR (**$CDCl_3$, 125 MHz) δ 156.4, 137.8, 132.0, 129.5, 128.4, 128.0, 127.3, 126.6, 120.8, 118.6, 76.6, 26.1, 21.6, 18.4, -0.4, -2.1, -3.8, -4.3. **HR-MS (ESI)** *m/z* calculated for $C_{24}H_{35}O_2Si_2^+$ $[M]^+$ 411.2170, found 411.2162.



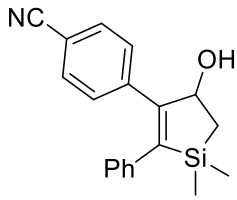
164f

Prepared according to general procedure: 85% yield (68.0 mg, 0.237 mmol) as an amorphous solid. **8o** was directly obtained without acid treatment. Column eluent hexane/ethyl acetate/Et_3N (84:14:2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.44 – 7.36 (m, 3H), 7.26 – 7.23 (m, 2H), 7.04 (dd, J = 5.1, 1.2 Hz, 1H), 6.87 – 6.85 (m, 1H), 6.82 (dd, *J* = 3.6, 1.1 Hz, 1H), 5.02 (ddd, J = 7.9, 5.2, 3.8 Hz, 1H), 1.77 (d, J = 3.8 Hz, 1H), 1.60 (dd, J = 14.9, 7.8 Hz, 1H), 1.01 (dd, J = 14.9, 5.3 Hz, 1H), 0.52 (s, 3H), 0.35 (s, 3H). **^{13}C{1H} NMR (**$CDCl_3$, 125 MHz) δ 156.4, 142.1, 139.1, 134.3, 129.2, 129.1, 128.1, 127.3, 126.3, 125.8, 78.1, 20.9, 0.1, -1.5. **HR-MS (ESI)** *m/z* calculated for $C_{16}H_{17}OSSi^+$ $[M]^+$ 285.0764, found 285.0766.



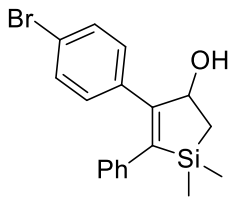
164i

Prepared according to general procedure: 79% yield (83.1 mg, 0.239 mmol) as an amorphous solid. $NaHSO_4$ used as acid. Column eluent hexane/ethyl acetate/Et_3N (83:15:2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.45 (d, J = 8.1 Hz, 2H), 7.25 (d, J = 7.9 Hz, 2H), 7.19 – 7.15 (m, 2H), 7.12 – 7.09 (m, 1H), 6.88 – 6.86 (m, 2H), 5.28 (dt, J = 7.7, 4.6 Hz, 1H), 1.71 (d, J = 4.6 Hz, 1H), 1.66 (dd, J = 14.9, 7.6 Hz, 1H), 1.03 (dd, J = 14.9, 4.9 Hz, 1H), 0.44 (s, 3H), 0.19 (s, 3H). **^{13}C{1H} NMR (**$CDCl_3$, 125 MHz) δ 155.6, 146.5, 142.2, 139.8, 129.5, 128.4, 127.9, 126.1, 125.2, 125.2, 125.2, 125.1, 77.3, 21.9, -0.1, -2.2. **HR-MS (ESI)** *m/z* calculated for $C_{19}H_{18}F_3OSi^+$ $[M]^+$ 347.1074, found 347.1060.



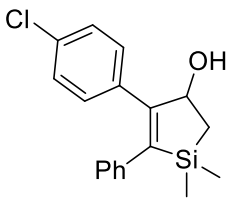
164j

Prepared according to general procedure: 64% yield (14.3 mg, 0.047 mmol) as an amorphous solid. $NaHSO_4$ used as acid. Column eluent hexane/ethyl acetate/Et_3N (68:30:2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.47 – 7.45 (m, 2H), 7.25 – 7.22 (m, 2H), 7.18 – 7.09 (m, 3H), 6.84 – 6.83 (m, 2H), 5.25 (dd, J = 7.4, 5.0 Hz, 1H), 1.69 (s, 1H), 1.66 (dd, J = 14.9, 7.6 Hz, 1H), 1.02 (dd, J = 14.9, 4.9 Hz, 1H), 0.42 (s, 3H), 0.18 (s, 3H). **^{13}C{1H} NMR (**$CDCl_3$, 125 MHz) δ 155.1, 147.6, 143.6, 139.6, 131.9, 129.9, 128.5, 127.8, 126.3, 119.1, 110.7, 77.1, 22.2, -0.2, -2.3. **HR-MS (ESI)** *m/z* calculated for $C_{19}H_{18}NOSi^+$ $[M]^+$ 304.1152, found 304.1151.



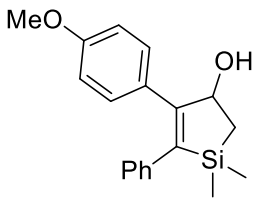
164k

Prepared according to general procedure: 73% yield (79.0 mg, 0.220 mmol) as an amorphous solid. $NaHSO_4$ used as acid. Column eluent hexane/ethyl acetate/Et_3N (82:10:2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.34 – 7.31 (m, 2H), 7.17 (ddd, J = 7.5, 6.4, 1.2 Hz, 2H), 7.12 – 7.09 (m, 1H), 7.03 – 7.00 (m, 2H), 6.89 – 6.87 (m, 2H), 5.23 (dt, J = 8.0, 4.4 Hz, 1H), 1.73 (d, J = 4.2 Hz, 1H), 1.62 (dd, J = 14.9, 7.7 Hz, 1H), 1.01 (dd, J = 14.9, 4.9 Hz, 1H), 0.43 (s, 3H), 0.17 (s, 3H). **^{13}C{1H} NMR (**$CDCl_3$, 125 MHz) δ 155.8, 145.4, 140.1, 137.1, 131.5, 130.8, 128.4, 127.9, 125.9, 121.4, 77.2, 21.6, 0.0, -2.2. **HR-MS (ESI)** *m/z* calculated for $C_{18}H_{18}BrOSi^+$ $[M]^+$ 357.0305, found 357.0297.



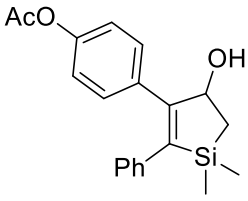
164l

Prepared according to general procedure: 63% yield (59.2 mg, 0.183 mmol) as an amorphous solid. $NaHSO_4$ used as acid. Column eluent hexane/ethyl acetate/Et_3N (90:8:2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.19 – 7.16 (m, 4H), 7.12 – 7.06 (m, 3H), 6.89 – 6.87 (m, 2H), 5.24 – 5.23 (m, 1H), 1.74 – 1.73 (m, 1H), 1.63 (dd, J = 14.9, 7.6 Hz, 1H), 1.01 (dd, J = 15.1, 4.8 Hz, 1H), 0.43 (s, 3H), 0.17 (s, 3H). **^{13}C{1H} NMR (**$CDCl_3$, 125 MHz) δ 155.8, 145.3, 140.2, 136.6, 133.1, 130.5, 128.5, 128.4, 127.9, 125.9, 77.2, 21.6, 0.0, -2.2. **HR-MS (ESI)** *m/z* calculated for $C_{18}H_{18}ClOSi^+$ $[M]^+$ 313.0810, found 313.0803.



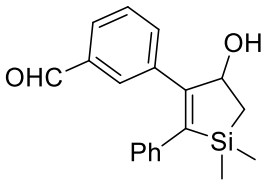
164m

Prepared according to general procedure: 60% yield (53.1 mg, 0.171 mmol) as an amorphous solid. $NaHSO_4$ used as acid. Column eluent hexane/ethyl acetate/Et_3N (86:12:2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.18 – 7.15 (m, 2H), 7.10 – 7.06 (m, 3H), 6.92 – 6.91 (m, 2H), 6.76 – 6.73 (m, 2H), 5.27 – 5.24 (m, 1H), 3.75 (s, 3H), 1.81 (s, 1H), 1.60 (dd, *J* = 14.9, 7.7 Hz, 1H), 1.01 (dd, J = 15.0, 4.9 Hz, 1H), 0.43 (s, 3H), 0.15 (s, 3H). **^{13}C{1H} NMR (**$CDCl_3$, 125 MHz) δ 158.8, 156.5, 143.2, 140.8, 130.4, 130.1, 128.3, 128.1, 125.6, 113.8, 77.1, 55.3, 21.1, 0.2, -2.2. **HR-MS (ESI)** *m/z* calculated for $C_{19}H_{21}O_2Si^+$ $[M]^+$ 309.1305, found 309.1318.



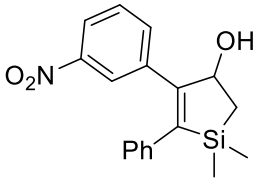
164n

Prepared according to general procedure: 71% yield (72.5 mg, 0.214 mmol) as an amorphous solid. $NaHSO_4$ used as acid. Column eluent hexane/ethyl acetate/Et_3N (78:20:2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.17 – 7.14 (m, 4H), 7.10 – 7.07 (m, 1H), 6.95 – 6.93 (m, 2H), 6.90 – 6.88 (m, 2H), 5.24 (dd, J = 7.6, 4.8 Hz, 1H), 2.26 (s, 3H), 1.82 (s, 1H), 1.60 (dd, J = 14.9, 7.7 Hz, 1H), 1.02 (dd, J = 14.9, 4.7 Hz, 1H), 0.42 (s, 3H), 0.17 (s, 3H). **^{13}C{1H} NMR (**$CDCl_3$, 125 MHz) δ 169.4, 156.0, 149.8, 144.8, 140.3, 135.7, 130.2, 128.3, 128.0, 125.8, 121.4, 77.3, 21.3, 21.3, 0.0, -2.1. **HR-MS (ESI)** *m/z* calculated for $C_{20}H_{21}O_3Si^+$ $[M]^+$ 337.1254, found 279.1268.



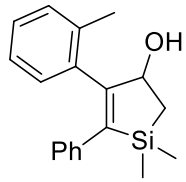
164o

Prepared according to general procedure: 84% yield (78.0 mg, 0.252 mmol) as an amorphous solid. $NaHSO_4$ used as acid. Column eluent hexane/ethyl acetate/Et_3N (78:20:2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 9.86 (s, 1H), 7.69 – 7.67 (m, 2H), 7.37 – 7.1 (m, 2H), 7.17 – 7.13 (m, 2H), 7.10 – 7.07 (m, 1H), 6.90 – 6.85 (m, 2H), 5.34 – 5.29 (m, 1H), 1.84 (s, 1H), 1.67 (dd, J = 14.9, 7.6 Hz, 1H), 1.04 (dd, J = 14.9, 4.9 Hz, 1H), 0.44 (s, 3H), 0.20 (s, 3H). **^{13}C{1H} NMR (**$CDCl_3$, 125 MHz) δ 192.4, 155.6, 146.2, 139.9, 139.4, 136.3, 135.6, 130.5, 128.9, 128.4, 128.3, 127.9, 126.0, 77.2, 21.9, -0.1, -2.2. **HR-MS (ESI)** *m/z* calculated for $C_{19}H_{19}O_2Si^+$ $[M]^+$ 307.1149, found 307.1160.



164p

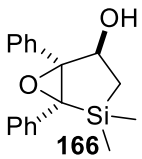
Prepared according to general procedure: 73% yield (62.4 mg, 0.192 mmol) as an amorphous solid. $NaHSO_4$ used as acid. Column eluent hexane/ethyl acetate/Et_3N (73:15:2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 8.08 – 8.07 (m, 1H), 8.01 (ddd, J = 8.2, 2.3, 1.1 Hz, 1H), 7.42 – 7.40 (m, 1H), 7.31 (t, J = 7.9 Hz, 1H), 7.19 – 7.16 (m, 2H), 7.12 – 7.09 (m, 1H), 6.88 – 6.86 (m, 2H), 5.31 (dd, J = 7.5, 4.8 Hz, 1H), 1.78 (s, 1H), 1.69 (dd, J = 14.9, 7.6 Hz, 1H), 1.05 (dd, J = 14.9, 4.9 Hz, 1H), 0.44 (s, 3H), 0.21 (s, 3H). **^{13}C{1H} NMR (**$CDCl_3$, 125 MHz) δ 154.4, 148.1, 147.6, 140.2, 139.5, 135.7, 128.9, 128.6, 127.8, 126.3, 123.9, 122.1, 77.1, 22.3, -0.3, -2.3. **HR-MS (ESI)** *m/z* calculated for $C_{18}H_{19}NO_3Si^-$ $[M]^-$ 325.1140, found 325.1136.



164q

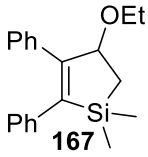
Prepared according to general procedure: 61% yield (53.5 mg, 0.182 mmol) as an amorphous solid. $NaHSO_4$ used as acid. Column eluent hexane/ethyl acetate/Et_3N (90:8:2). **^{1}H NMR** (C_6D_6, 500 MHz) δ 7.07 (dd, J = 8.2, 1.2 Hz, 2H), 7.00 – 6.96 (m, 4H), 6.92 (d, J = 7.8 Hz, 1H), 6.86 – 6.84 (m, 1H), 4.87 (s, 1H), 2.03 (s, 3H), 1.42 (dd, J = 14.8, 7.5 Hz, 2H), 1.10 (dd, J = 14.8, 4.9 Hz, 1H), 0.36 (s, 3H), 0.16 (s, 3H). **HR-MS (ESI)** *m/z* calculated for $C_{19}H_{21}OSi^+$ $[M]^+$ 293.1356, found 293.1344.

Chemical transformations of silacyclopentene 164a:



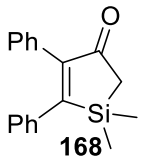
166

Silacyclopentenol **164a** (28 mg, 0.1 mmol) was dissolved in DCM (2 mL). Then, $NaHCO_3$ (20 mg, 0.24 mmol, 2.4 equiv.) was added, followed by *m*CPBA (38 mg, 0.22 mmol, 2.2 equiv.). After stirring for two hours at room temperature, the reaction was quenched with a saturated aqueous solution of Na_2SO_3 (2 mL). The layers were separated, and the organic phase collected. The aqueous phase was extracted with DCM (2 × 2 mL) and the organic fractions were combined, dried over $MgSO_4$ and filtered. The solvent was evaporated under reduced pressure to give epoxide **166** as oil in quantitative yield. **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.26 (t, J = 3.6 Hz, 2H), 7.18 (t, J = 7.4 Hz, 2H), 7.11 (dd, J = 13.1, 7.3 Hz, 3H), 7.04 – 7.00 (m, 3H), 4.97 (dd, J = 9.3, 7.8 Hz, 1H), 1.44 – 1.40 (m, 1H), 1.25 (s, 1H), 0.88 (dd, J = 14.0, 9.4 Hz, 1H), 0.36 (s, 3H), 0.30 (s, 3H). **^{13}C{1H} NMR (**$CDCl_3$, 125 MHz) δ 137.0, 134.9, 128.1, 127.9, 127.6, 127.3, 126.3, 126.3, 76.0, 74.2, 68.8, 17.4, -2.7, -5.0. **HR-MS (ESI)** *m/z* calculated for $C_{18}H_{19}OSi^+$ $[M\text{-}OH]^+$ 279.11997, obtained 279.11870.



167

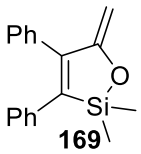
Silacyclopentenol **164a** (10 mg, 0.036 mmol) was dissolved in dry ethanol (2 mL). Then, $KHSO_4$ (10 mg, 0.073 mmol, 2 equiv.) was added and the solution was heated to 70 °C for one hour. The reaction was quenched with saturated aqueous $NaHCO_3$ (2 mL) and the product was extracted with EtOAc (3 × 2 mL). The organic phases were combined, dried over $MgSO_4$ and filtered. The solvent was evaporated, and the resulting crude purified by silica column chromatography, eluent hexane/EtOAc (97:3) to give the ether **167** in 88% yield (8.8 mg, 0.029 mmol). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.15 – 7.05 (m, 8H), 6.90 (d, J = 7.8 Hz, 2H), 4.93 (dd, J = 7.5, 4.3 Hz, 1H), 3.60 (dq, J = 14.1, 7.0 Hz, 1H), 3.41 – 3.35 (m, 1H), 1.46 (dd, J = 14.8, 7.6 Hz, 1H), 1.07 (t, J = 7.0 Hz, 3H), 1.03 – 0.99 (m, 1H), 0.39 (s, 3H), 0.18 (s, 3H). **^{13}C{1H} NMR (**$CDCl_3$, 125 MHz) δ 155.9, 144.9, 140.8, 139.0, 129.2, 128.2, 128.1, 127.6, 126.7, 125.5, 84.3, 63.8, 17.8, 15.5, -0.2, -1.8. **HR-MS (ESI)** *m/z* calculated for $C_{20}H_{23}OSi^+$ $[M\text{-}H]^+$ 307.1531, found 307.1520.



168

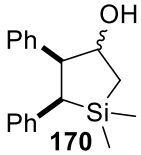
Silacyclopentenol **164a** (20 mg, 0.071 mmol) was dissolved in dry DCM (1.5 mL), under argon atmosphere. The solution was cooled to 0 °C and MnO_2 (186 mg, 2.13 mmol, 30 equiv.) was added. After stirring at 0 °C for 1 hour, the solution was filtered through celite to remove excess MnO_2. The solvent was evaporated to give pentenone

168 in quantitative yield (20 mg, 0.071 mmol). **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.27 – 7.19 (m, 6H), 7.10 – 7.07 (m, 2H), 7.04 – 7.00 (m, 2H), 2.04 (s, 2H), 0.47 (s, 6H). **^{13}C{1H} NMR (**$CDCl_3$, 75 MHz) δ 203.8, 166.1, 154.3, 138.9, 134.8, 130.2, 128.5, 128.1, 127.8, 127.7, 27.6, -2.4. **HR-MS (ESI)** *m/z* calculated for $C_{18}H_{19}OSi^+$ $[M+H]^+$ 279.11997, obtained 279.11850.



169

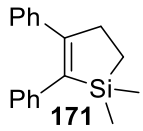
Pentenone **168** was observed to isomerize under thermal conditions to the silyl enol ether **169**, which could be isolated by passing it through a short silica column using hexane:ethyl acetate (9:1) as the eluent. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.34 – 7.30 (m, 3H), 7.20 – 7.10 (m, 5H), 6.93 – 6.89 (m, 2H), 4.67 (d, J = 1.3 Hz, 1H), 4.15 (d, J = 1.2 Hz, 1H), 0.53 (s, 6H). **^{13}C{1H} NMR (**$CDCl_3$, 75 MHz) δ 163.4, 149.5, 141.7, 137.4, 136.8, 129.8, 128.6, 128.4, 128.4, 127.6, 126.8, 91.9, -0.1. **HR-MS (ESI)** *m/z* calculated for $C_{18}H_{19}OSi^+$ $[M+H]^+$ 279.11997, obtained 279.11844.



170

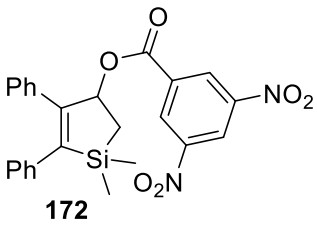
Silacyclopentenol **164a** (28 mg, 0.1 mmol) was dissolved in 1.5 mL of an ethanol/ethyl acetate mixture (3:2), under argon atmosphere, followed by addition of Pd/C (10%) (5.3 mg, 5 mol%). The argon balloon was then replaced for a hydrogen-filled balloon. The solution was stirred at room temperature for 30 min and then filtered over celite. The solvents were evaporated to give **170** as mixture of two non-isolable diastereoisomers (syn/anti = 1.4 : 1) in quantitative yield (28 mg, 0.1 mmol). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.22 – 6.73 (m, 10H+10H), 4.85 (dt, J = 11.0, 8.6 Hz, 1H/*anti*), 4.70 – 4.57 (m, 1H/*syn*), 3.74 (dd, J = 8.0, 4.6 Hz, 1H/*syn*), 3.30 (dd, J = 11.1, 7.6 Hz, 1H, *anti*), 3.00 (d, J = 8.0 Hz, 1H, *syn*), 2.71 (d, J = 7.6 Hz, 1H, *anti*), 1.77 (s, 1H,), 1.64 (dd, J = 14.7, 7.8 Hz, 1H, *anti*), 1.54 (s, 1H), 1.26 (dd, J = 14.4, 6.0 Hz, 1H/*syn*), 1.03 – 0.97 (m, 1H+1H/*syn* and *anti*), 0.40 (s, 3H, *anti*), 0.37 (s, 3H/*syn*), 0.25 (s, 3H/*syn*), 0.11 (s, 3H, *anti*). **^{13}C{1H} NMR (**$CDCl_3$, 125 MHz) δ 141.3, 141.0, 140.0, 139.0, 130.2, 130.0, 129.5, 128.5, 128.1, 128.0, 127.8, 127.8, 126.3, 126.3, 124.8, 124.2, 74.9(*syn*), 74.6(*anti*), 58.7(*anti*), 54.6(*syn*), 41.7(*anti*), 38.3(*syn*), 23.4(syn), 22.1(*anti*), 0.6(*syn*), 0.4(*anti*), -1.7(*syn*), -2.5(anti). **HR-MS (ESI)** *m/z* calculated for $C_{18}H_{21}OSi^+$ $[M-H]^+$ 281.1356, found 281.1364.

Silacyclopentenol **164a** (28 mg, 0.1 mmol) was dissolved in dry DCM (1.5 mL), under argon atmosphere. Borane catalyst $B(C_6F_5)_3$ (0.01 mmol, 10 mol%) was added to the solution, followed by dropwise addition of triethylsilane (48 μL, 0.3 mmol, 3 equiv.). The solution was left



171

stirring at room temperature for 3 hours. The solvent was evaporated, and the product purified by silica column chromatography, eluted with hexane to give **171** as a white amorphous solid in 74% yield (19.5 mg, 0,074 mmol). **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.18 – 7.04 (m, 8H), 6.93 – 6.90 (m, 2H), 3.01 – 2.96 (m, 2H), 1.02 – 0.97 (m, 2H), 0.27 (s, 6H). **^{13}C{1H} NMR (**$CDCl_3$, 75 MHz) δ 155.3, 141.6, 141.3, 140.9, 128.5, 128.3, 128.1, 127.9, 126.8, 125.1, 36.5, 9.5, -1.0.



172

Silacyclopentenol **164a** (42 mg, 0.15 mmol) was dissolved in dry DCM (2 mL). Triethylamine (27 μL, 0.19 mmol, 1.3 equiv.) was added, followed by 3,5-dinitrobenzoyl chloride (42 mg, 0.18, 1.2 equiv.). Then, dimethylaminopyridine (2 mg, 0.02 mmol, 0.1 equiv.) was added. The reaction was left stirring at room temperature for 30 minutes. The reaction was quenched with water (5 mL). DCM (5 mL) was added, and the layers separated. The organic layer was collected, and the aqueous layer washed with DCM (2 × 5 mL). The organic phases were combined and dried over $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The crude was purified by silica column chromatography, eluent hexane/ethyl acetate (94:6), to give ester **172** as a white solid (55 mg. 0.12 mmol) in 77% yield. The compound was further recrystallized from hexane/DCM to give suitable crystals for X-ray diffraction analysis. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 9.12 (t, J = 2.1 Hz, 1H), 8.84 (d, J = 2.1 Hz, 2H), 7.22 – 7.07 (m, 8H), 7.00 – 6.98 (m, 2H), 6.61 (dd, J = 7.9, 5.7 Hz, 1H), 1.93 (dd, J = 14.9, 8.0 Hz, 1H), 1.20 (dd, J = 14.9, 5.6 Hz, 1H), 0.55 (s, 3H), 0.28 (s, 3H). **^{13}C{1H} NMR (**$CDCl_3$, 75 MHz) δ 162.3, 153.2, 148.6, 147.1, 139.5, 137.5, 134.5, 129.3, 128.6, 128.4, 128.2, 128.0, 127.4, 126.2, 122.2, 82.4, 19.3, -0.1, -2.4.

Anex references

[1] Firouzabadi, H.; Iranpoor, N. Iodine Catalyzes Efficient and Chemoselective Thioacetalization of Carbonyl Functions , Transthioacetalization of O , O - and S , O - Acetals and Acylals. *J. Org. Chem.* **2001**, *66*, 7527–7529.

[2] Lai, J.; Du, W.; Tian, L.; Zhao, C.; She, X.; Tang, S. Fe-Catalyzed Direct Dithioacetalization of Aldehydes with 2-Chloro-1,3-Dithiane. *Org. Lett.* **2014**, *16*, 4396–4399.

[3] Ghosh, S. S.; Martin, J. C.; Fried, J. Total Synthesis of the Methyl Ester of the 9,11-Dithia Analog of 13,14-Dehydro-PGH2. *J. Org. Chem.* **1987**, *52*, 862–876.

[4] Naik, S.; Gopinath, R.; Goswami, M.; Patel, B. K. Chemoselective Thioacetalisation and Transthioacetalisation of Carbonyl Compounds Catalysed by Tetrabutylammonium Tribromide (TBATB). *Org. Biomol. Chem.* **2004**, *2*, 1670–1677.

[5] Page, P. C. B.; Graham, A. E.; Park, B. K. A Convenient Preparation of Symmetrical and Unsymmetrical 1,2-Diketones: Application to Fluorinated Phenytoin Synthesis. *Tetrahedron Lett.* **1992**, *48*, 7265–7274.

[6] Graham, A. E. A Simple and Convenient Catalytic Procedure for the Preparation of Dithioacetals. *Synth. Commun.* **1999**, *29*, 697–703.

[7] Raffaelli, B.; Wähälä, K.; Hase, T. Asymmetric Synthesis, Stereochemistry and Rearrangement Reactions of Naturally Occurring 7'-Hydroxylignano-9,9'-Lactones. *Org. Biomol. Chem.* **2006**, *4*, 331–341.

[8] Aloup, J.-C.; Bouchaudon, J.; Farge, D.; James, C.; Deregnaucourt, J.; Hardy-Houis, M. Synthesis and Antisecretory and Antiulcer Activities of Derivatives and Analogues of 2-(2-Pyridyl)Tetrahydrothiophene-2-Carbothioamide. *J. Med. Chem.* **1987**, *30*, 24–29.

[9] Afonso, C. A. M.; Barros, M. T.; Godinho, L. S.; Maycock, C. D. Synthesis of 2,3-Dihydro-1,4-Dithiins and 2-Alkylidene-1,4-Dithianes by 1,2-Sulfur Migration in 2-(1-Hydroxyalkyl)-1,3-Dithiolanes. *Synthesis (Stuttg).* **1991**, No. 7, 575–580.

[10] Yu, C. J.; Li, R.; Gu, P. Intermolecular Schmidt Reaction of Alkyl Azides with Acyl Silanes. *Tetrahedron Lett.* **2016**, *57*, 3568–3570.

[11] Iranpoor, N.; Firouzabadi, H.; Shaterian, H. R.; Zolfigol, M. A. 2,4,4,6-Tetrabromo-2,5-Cyclohexadienone (TABCO), N-Bromosuccinimide (NBS) and Bromine as Efficient Catalysts for Dithioacetalization and Oxathioacetalization of Carbonyl Compounds and Transdithioacetalization Reactions. *Phosphorus. Sulfur. Silicon Relat. Elem.* **2002**, *177*, 1047–1071.

[12] Seebach, D.; Jones, N. R.; Corey, E. J. A New Synthetic Route to Cyclic Mono- and Diketone Derivatives via Bisthio Carbanions. *J. Org. Chem.* **1968**, *33*, 300–305.

[13] Wan, Y.; Kurchan, A. N.; Barnhurst, L. A.; Kutateladze, A. G. Direct Transformation of 1,3-Dihalides into Dithianes and Dithiepines via a Novel One-Pot Reaction with Carbon Disulfide and Sodium Borohydride. *Org. Lett.* **2000**, *2*, 1133–1135.

[14] Firouzabadi, H.; Iranpoor, N.; Hazarkhani, H. Iodine Catalyzes Efficient and Chemoselective Thioacetalization of Carbonyl Functions , Transthioacetalization of O , O - and S , O -Acetals and Acylals Protections of Carbonyl Groups as Thioacetals Are Quite Often a Necessary Requirement in the Synthesis. *J. Org. Chem.* **2001**, *66*, 7527–7529.

[15] Zhang, H.; Wang, H.; Yang, H.; Fu, H. Rhodium-Catalyzed Denitrogenative Thioacetalization of N-Sulfonyl-1,2,3-Triazoles with Disulfides: An Entry to Diverse Transformation of Terminal Alkynes. *Org. Biomol. Chem.* **2015**, *13*, 6149–6153.

[16] Uno, T.; Inokuma, T.; Takemoto, Y. NHC-Catalyzed Thioesterification of Aldehydes by External Redox Activation. *Chem. Commun.* **2012**, *48*, 1901–1903.

[17] Linghu, X.; Nicewicz, D. A.; Johnson, J. S. Tandem Carbon-Carbon Bond Constructions via Catalyzed Cyanation/Brook Rearrangement/C-Acylation Reactions of Acylsilanes. *Org. Lett.* **2002**, *4*, 2957–2960.

[18] Ishida, K.; Tobita, F.; Kusama, H. Lewis Acid-Assisted Photoinduced Intermolecular Coupling between Acylsilanes and Aldehydes: A Formal Cross Benzoin-Type Condensation. *Chem. Eur. J.* **2018**, *24*, 543–546.

[19] Ni, Z. J.; Yang, P. F.; Ng, D. K. P.; Tzeng, Y. L.; Luh, T. Y. Unified Synthesis of Vinylsilanes and Silylated Butadienes. Nickel-Catalyzed Olefination and Silylolefination of Dithioacetals. *J. Am. Chem. Soc.* **1990**, *112*, 9356–9364.

[20] Fan, D.; Liu, Y.; Jia, J.; Zhang, Z.; Liu, Y.; Zhang, W. Synthesis of Chiral α-Aminosilanes through Palladium-Catalyzed Asymmetric Hydrogenation of Silylimines. *Org. Lett.* **2019**, *21*, 1042–1045.

[21] Tongco, E. C.; Wang, Q.; Prakash, G. K. S. One-Pot Preparation of Aroylsilanes by Reductive Silylation of Methyl Benzoates. *Synth. Commun.* **1997**, *27*, 2117–2123.

[22] Lin, C. Y.; Ma, P. J.; Sun, Z.; Lu, C. D.; Xu, Y. J. Carbamoyl Anion-Initiated Cascade Reaction for Stereoselective Synthesis of Substituted α-Hydroxy-β-Amino Amides. *Chem. Commun.* **2016**, *52*, 912–915.

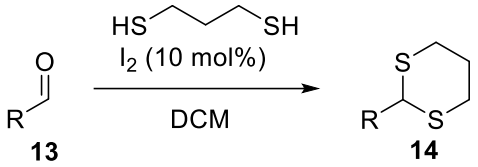
[23] Katritzky, A. R.; Lang, H.; Wang, Z.; Zhang, Z.; Song, H. Benzotriazole-Mediated Conversions of Aromatic and Heteroaromatic Aldehydes to Functionalized Ketones. *J.*

Org. Chem. **1995**, *60*, 7619–7624.

[24] Hammaecher, C.; Portella, C. New 6-Oxa-2-Silabicyclo[2.2.0]Hexanes by Photochemical Conversion of Acyl(Allyl)(Dimethyl)Silanes. *Chem. Commun.* **2008**, 5833.

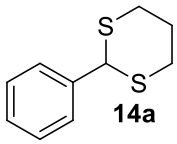
ANNEX

Synthesis of dithianes 14:



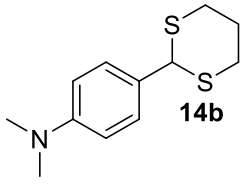
13 **14**

General procedure: Based on a modified previously reported method,[1] aldehyde (15 mmol, 1 equiv) and 1,3-propanedithiol (3 mL, 16.5 mmol, 1.1 equiv) were dissolved in dichloromethane (50 mL) in a round-bottom flask. Iodine (381 mg, 1.5 mmol, 0.1 equiv) was slowly added do the stirring solution as to prevent vigorous boiling of the solvent. The reaction was quenched with a 2% $Na_2S_2O_3$ aqueous solution (10 mL) 30 min after complete iodine addition. Upon separation, the organic layer was washed successively with a 10% aqueous NaOH solution (10 mL), water (10 mL) and brine (10 mL). The organic solvent was dried over $MgSO_4$ and filtered. After evaporating the solvent, the product was recrystallized in isopropanol. Note: Reactions were conducted in different scales depending on availability of aldehyde starting material.



14a

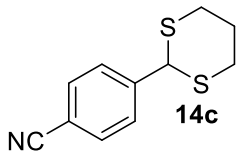
Prepared according to general procedure. 77% yield (3.425 g, 17.45mmol), white crystals. Obtained with same spectral characterization as previously described.[2] ^{1}**H NMR** (300 MHz, CDCl3): δ ppm 7.49-7.45 (m, 2H), 7.37-7.29 (m, 3H), 5.17 (s, 1H), 3.12-3.02 (m, 2H), 2.95-2.88 (m, 2H), 2.22-2.14 (m, 1H), 2.01-1.86 (m, 1H).



14b

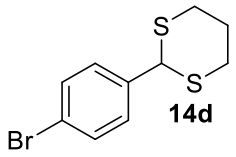
Prepared according to a modified reported method.[3] 4-(Dimethylamino)benzaldehyde (1 g, 6.7 mmol, 1 equiv.) and 1,3-propanedithiol (0.74 mL, 7.4 mmol, 1.1 equiv.) were dissolved in 10 mL of dry DCM in an argon purged round-bottom flask. The solution was cooled to 0ºC and BF_3•OEt_2

(1.16 mL, 9.4 mmol, 1.4 equiv.) was added dropwise. The solution was then left warming to room temperature for 1 hour. The reaction was quenched with a 10% aqueous NaOH solution (10 mL). The layers were separated, and the organic phase collected and washed with water (10 mL) and Brine (10 mL). The organic solvent was dried over $MgSO_4$ and filtered. After evaporation of the solvent, the product was recrystallized from isopropanol to give **14b** as yellow crystals in 93% yield (1.498 g, 6.26 mmol). Obtained with same spectral characterization as previously described.[4] ^{1}**H NMR** (300 MHz, $CDCl_3$): δ ppm 7.33 (d, J=8.8 Hz, 2H), 6.67 (d, J=8.8 Hz, 2H), 5.12 (s, 1H), 3.17-2.86 (m, 4H), 2.94 (s, 6H), 2.20-2.10 (m, 1H), 1.97-1.82 (m, 1H).



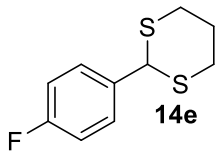
14c

Prepared according to general procedure. 89% yield (2.997 g, 13.54 mmol), white crystals. Obtained with same spectral characterization as previously described.[2] ^{1}**H NMR** (300 MHz, $CDCl_3$): δ ppm 7.65-7.57 (m, 4H), 5.17 (s, 1H), 3.11-3.01 (m, 2H), 2.96-2.90 (m, 2H), 2.23-2.15 (m, 1H), 2.01-1.86 (m, 1H).



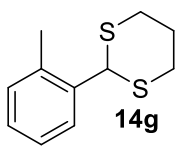
14d

Prepared according to general procedure. 81% yield (3.628 g, 13.18 mmol), white crystals. Obtained with same spectral characterization as previously described.[2] ^{1}**H NMR** (300 MHz, $CDCl_3$): δ ppm 7.49-7.44 (m, 2H), 7.37-7.32 (m, 2H), 5.11 (s, 1H), 3.10-3.00 (m, 2H), 2.94-2.86 (m, 2H), 2.22-2.12 (m, 1H), 1.99-1.84 ppm (m, 1H).



14e

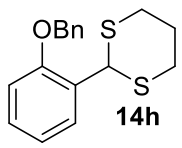
Prepared according to general procedure. 76% yield (1.515 g, 7.07 mmol), white crystals. Obtained with same spectral characterization as previously described.[5] ^{1}**H NMR** (300 MHz, $CDCl_3$): δ ppm 7.47-7.42 (m, 2H), 7.05-6.99 (m, 2H), 5.14 (s, 1H), 3.10-3.01 (m, 2H), 2.94-2.87 (m, 2H), 2.22-2.13 (m, 1H), 1.99-1.84 (m, 1H).



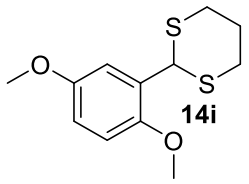
14g

Prepared according to general procedure. 69% yield (1.253 g, 5.96 mmol), white crystals. Obtained with same spectral characterization as previously described.[2] ^{1}**H NMR** (300 MHz, $CDCl_3$): δ ppm 7.61-7.57 (m, 1H), 7.24-7.13 (m, 3H), 5.33 (s, 1H),

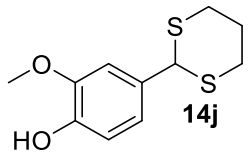
3.14-3.04 (m, 2H), 2.95-2.88 (m, 2H), 2.45 (s, 3H), 2.23-2.14 (m, 1H), 2.02-1.87 (m, 1H).



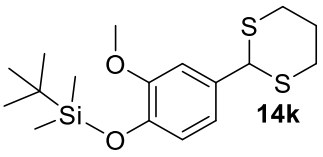
Prepared according to general procedure. 88% yield (1.681 g, 5.56 mmol), pale yellow solid. Product was isolated by flash chromatography (Hex:AcOEt, 95:5). ^{1}**H NMR** (300 MHz, $CDCl_3$): δ ppm 7.60 (dd, *J*=7.6, 1.8 Hz, 1H), 7.47-7.30 (m, 5H), 7.21 (td, *J*=7.8, 1.5 Hz, 1H), 7.00 -6.95 (m, 1H), 6.89 (d, *J*=8.2 Hz, 1H), 5.76 (s, 1H), 5.13 (s, 2H), 3.13-2.85 (m, 2H), 2.92-2.85 (m, 2H), 2.20-2.11 (m, 1H), 2.00-1.85 (m, 1H). ^{13}**C{1H} NMR** (75 MHz, $CDCl_3$): δ ppm 154.8, 137.2, 129.4, 129.3, 128.7, 128.1, 128.0, 127.3, 121.5, 112.7, 70.6, 44.2, 44.1, 32.5, 25.5. **HR-MS (ESI)** m/z calculated for $C_{17}H_{19}OS_2^+$ $[M+H]^+$ 303.0872, found 303.0884.



Prepared according to general procedure. 76% yield (1.172 g, 4.57 mmol), white crystals. Obtained with same spectral characterization as previously described.[2] ^{1}**H NMR** (300 MHz, $CDCl_3$): δ ppm 7.15 (dd, *J*=2.3, 1.2 Hz, 1H), 6.83-6.76 (m, 2H), 5.67 (s, 1H), 3.82 (s, 3H), 3.78 (s, 3H), 3.16-3.06 (m, 2H), 2.93-2.86 (m, 2H), 2.20-2.12 (m, 1H), 2.01-1.86 (m, 1H).

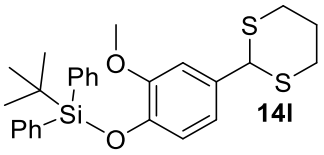


4-(1,3-Dithian-2-yl)-2-methoxyphenol **14j** wasPrepared according to the general procedure and used in preparation of **14k** and **14l**. 84% yield (6.723 g, 27.73 mmol), white crystals. Obtained with same spectral characterization as previously described.[6] ^{1}**H NMR** (300 MHz, $CDCl_3$): δ ppm 7.00-6.84 (m, 2H), 6.87-6.84 (m, 1H), 5.64 (s, 1H), 5.11 (s, 1H), 3.90 (s, 3H), 3.10-2.87 (m, 2H), 2.93-2.86 (m, 2H), 2.21-2.12 (m, 1H), 1.99-1.84 (m, 1H).



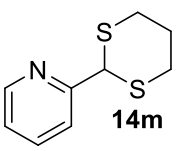
4-(1,3-Dithian-2-yl)-2-methoxyphenol (0.8 g, 3.30 mmol, 1 equiv.), imidazole (270 mg, 3.96 mmol, 1.2 equiv.) and 4-dimethylaminopyridine (42 mg, 0.34 mmol, 0.1 equiv.) were dissolved in dry DCM (10 mL), in an argon purged round-bottom flask. Then, *tert*-butyldimethylsilyl chloride (597 mg, 3.96 mmol, 1.2 equiv.) was added dropwise to the stirring solution. The mixture was left stirring at room temperature for 24 h. The reaction was quenched with H_2O

(10 mL) and the layers were separated. The organic layer was collected and washed with water (10 mL) and Brine (10 mL), dried over $MgSO_4$, filtered and evaporated. The product was purified by flash chromatography (Hex:EtOAc, 95:5) to yield **14k** in 90% yield (1.056 mg, 2.86 mmol) as a colorless thick oil with same spectral characterization as previously described.[7] ^{1}**H NMR** (300 MHz, $CDCl_3$): δ ppm 6.97 (d, *J*=1.8 Hz, 1H), 6.92-6.89 (m, 1H), 6.79-6.76 (m, 1H), 5.11 (s, 1H), 3.81 (s, 3H), 3.10-3.01 (m, 2H), 2.93-2.86 (m, 2H), 2.21-2.11 (m, 1H), 1.99-1.84 (m, 1H), 0.98 (s, 9H), 0.14 (s, 6H).



14l

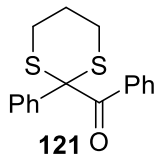
4-(1,3-Dithian-2-yl)-2-methoxyphenol (0.5 g, 2.06 mmol, 1 equiv.), imidazole (155 mg, 2.27 mmol, 1.1 equiv.) and 4-dimethylaminopyridine (25 mg, 0.2 mmol, 0.1 equiv.) were dissolved in dry DCM (10 mL), in an argon purged round-bottom flask. Then, *tert*-butyl(chloro)diphenylsilane was added dropwise to the stirring solution. The mixture was left stirring at room temperature for 24 h. The reaction was quenched with H_2O (10 mL) and the layers were separated. The organic layer was collected and washed with water (10 mL) and Brine (10 mL), dried over $MgSO_4$, filtered, and evaporated. The product was purified by flash chromatography (Hex:DCM, 1:1) to yield **14l** in 93% yield (918 mg, 1.91 mmol) as a colorless thick oil. ^{1}**H NMR** (300 MHz, $CDCl_3$): δ ppm 7.69 (dd, *J*=7.6, 1.8 Hz, 4H), 7.42-7.31 (m, 6H), 6.89 (d, *J*=1.8 Hz, 1H), 6.76-6.73 (m, 1H), 6.55-6.63 (m, 1H), 5.05 (s, 1H), 3.57 (s, 3H), 3.07-2.98 (m, 2H), 2.91-2.83 (m, 2H), 2.18-2.09(m, 1H), 1.96-1.81 (m, 1H), 1.10 ppm (s, 9H). ^{13}**C{1H} NMR** (75 MHz, $CDCl_3$): δ ppm 150.6, 145.2, 135.5, 133.6, 132.3, 129.7, 127.6, 120.2, 120.0, 111.8, 55.5, 51.5, 32.3, 26.8, 25.2, 19.9. **HR-MS (ESI)** m/z calculated for $C_{27}H_{33}O_2S_2Si^+$ $[M+H]^+$ 481.1686, found 481.1687.



14m

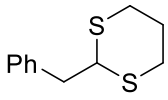
Prepared according to a modified reported method.[8] Freshly distilled picolinaldehyde (1 mL, 10.51 mmol, 1 equiv.) and 1,3-propanedithiol (1.16 mL, 11.56 mmol, 1.1 equiv.) were dissolved in DCE (20 mL). *p*-Toluenosulfonic acid (200 mg, 1.05 mmol, 0.1 equiv.) was added to the mixture and the solution refluxed for 24 hours. The reaction was cooled to room temperature and quenched with a 10% aqueous NaOH solution (10 mL). The layers were separated, and the organic phase collected and washed with water (10 mL) and brine (10 mL). The organic solvent was dried over $MgSO_4$ and

filtered. The solvent was evaporated and the product isolated by flash chromatography (Hex:AcOEt, 70:30) to give **14m** as a yellow solid in 54% yield (1.111 g, 5.63 mmol), with same spectral characterization as previously described.[38] ^{1}**H NMR** (300 MHz, $CDCl_3$): δ ppm 8.57 (dd, *J*=4.4, 1.5 Hz, 1H), 7.67 (td, *J*=7.6, 1.8 Hz, 1H), 7.46 (d, *J*=7.6 Hz, 1H), 7.22-7.18 (m, 1H), 5.35 (s, 1H), 3.11-2.92 (m, 4H), 2.23-2.13 (m, 1H), 2.05-1.90 (m, 1H).



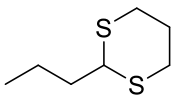
121

Prepared according to a modified reported method.[9] Benzil (1g, 4.76 mmol, 1.2 equiv.) was dissolved in dry DCM (5 mL) in an argon purged round-bottom flask. The solution was cooled to 0 °C in an ice bath bath. A solution of 1,3-propanedithiol (398 μL, 3.96 mmol, 1 equiv.) and BF_3•Et_2O (489 μL, 3.96 mmol, 1 equiv.) in dry DCM (1.5 mL) was added dropwise at 0 °C. The solution was warmed to room temperature for 3 hours and quenched with 10 mL of a saturated aqueous $NaHCO_3$ solution. The layers were separated, and the organic phase collected. The aqueous phase was extracted with DCM (3 × 10 mL) and the organic phases combined, dried over $MgSO_4$, filtered and the solvent evaporated. The dry crude was dissolved in hot isopropanol and left cooling at room temperature. After 3 hours, the product precipitated as a white solid and was filtered and washed with cold isopropanol to yield **121** as a white solid in 54% yield (641 mg, 2.13 mmol). ^{1}**H NMR** (300 MHz, $CDCl_3$): δ ppm 7.69-7.66 (m, 2H), 7.57 (dd, *J*=7.9, 1.5 Hz, 2H), 7.38-7.28 (m, 4H), 7.22-7.17 (m, 2H), 3.26 (ddd, *J*=14.4, 12.0, 2.9 Hz, 2H), 2.80-2.73 (m, 2H), 2.17-2.08 (m, 1H), 2.01-1.86 (m, 1H). ^{13}**C{1H} NMR** (300 MHz, $CDCl_3$): δ ppm 192.8, 139.0, 134.5, 132.2, 130.8, 129.2, 128.8, 127.7, 127.5, 63.5, 29.3, 24.1. **HR-MS (ESI)** m/z calculated for $C_{17}H_{17}OS_2^+$ $[M+H]^+$ 301.0715, found 301.0734.



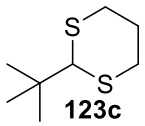
123a

Prepared according to general procedure. 53% yield (560 mg, 2.66 mmol), pale green solid. 1.2 equiv. of 1,3-propanedithiol were used. Obtained with same spectral characterization as previously described,[10] after purification by flash chromatography (Hex:EtOAc, 85:15). 1**H NMR** (300 MHz, CDCl3): δ ppm 7.34-7.22 (m, 5H), 4.24 (t, J = 7.3 Hz, 1H), 3.02 (d, J = 7.3 Hz, 2H), 2.85-2.80 (m, 4H), 2.15-2.05 (m, 1H), 1.92-1.79 (m, 1H).



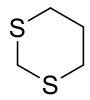
123b

Prepared according to a modified method.[3] Butyraldehyde (0.45 mL, 5 mmol, 1 equiv.) and 1,3-propanedithiol (0.6 mL, 6 mmol, 1.2 equiv.) were dissolved in 20 mL of dry DCM under argon. The solution was stirred at room temperature and BF_3•OEt_2 (0.43 mL, 0.7 mmol, 0.7 equiv.) was added dropwise. After 90 minutes, the reaction was quenched by washing the reaction mixture twice with 20 mL of 10% aqueous NaOH. The combined aqueous layers were then extracted twice with 20 mL of DCM. The organic layers were combined, washed with 25 mL of brine and dried over $MgSO_4$. The organic solvent was evaporated under reduced pressure and the resulting oil was purified by flash chromatography (hexane/EtOAc 97:3), which afforded **123b** as a colorless oil in 99% yield (808 mg, 4.98 mmol). Obtained with same spectral characterization as previously described.[2] ^{1}**H NMR** (300 MHz, $CDCl_3$): δ ppm 4.05 (t, J=6.7 Hz, 1H), 2.92-2.76 (m, 4H), 2.14-2.06 (m, 1H), 1.90-1.77 (m, 1H), 1.75-1.67 (m, 2H), 1.59-1.45 (m, 2H), 0.85-0.97 (m, 3H).



123c

Prepared according to a modified reported method.[11] Pivalaldehyde (5 mmol, 1 equiv.) and *N*-bromosuccinimide (178 mg, 1 mmol, 0.2 equiv.) were dissolved in CH_2Cl_2 (25 ml). The solution was then stirred under argon at r.t. and 1,3-propanedithiol (1.2 equiv.) was added dropwise. The reaction was monitored by TLC and quenched with 10% aqueous NaOH (25 ml) when the aldehyde was consumed (30-80 min). Aqueous and organic layers were separated, and the aqueous layer was washed with CH_2Cl_2 (2 x 25 ml). The combined organic layers were washed with 25 ml brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. 62% yield (544 mg, 3.08 mmol), white solid was obtained with same spectral characterization as previously described.[2] ^{1}**H NMR** (300 MHz, $CDCl_3$): δ ppm 3.99 (s, 1H), 2.90-2.86 (m, 4H), 2.11-2.02 (m, 1H), 1.86-1.74 (m, 1H), 1.10 (s, 9H).



126

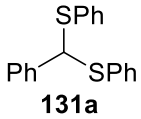
Prepared according to a modified reported method.[12] In an argon purged round-bottom flask were added 10 mL of dry DCM, 5 mL of glacial acetic acid, and BF_3•OEt_2 (2.47 mL, 20 mmol, 1 equiv.). Then, a solution of 1,3-propanedithiol (2 mL, 20 mmol, 1 equiv.) and chloromethyl methyl ether (1.67 mL, 22 mmol, 1.1 equiv.) in 30 mL of dry DCM was added dropwise for 10 min at room temperature. The solution was left stirring for 3 hours at room temperature, and then quenched with 40 mL of water. The layers were

separated and the organic phase collected and washed with water (40 mL), a 10% aqueous NaOH solution (2 × 40 mL) and brine (40 mL). The organic solvent was dried over $MgSO_4$, filtered and evaporated. Sublimation under reduced pressure gave pure **126** as a white solid in 32% yield (778 mg, 6.47 mmol), with same spectral characterization as previously described.[13] ^{1}**H NMR** (300 MHz, $CDCl_3$): δ ppm 3.78 (s, 2H), 2.84-2.80 (m, 4H), 2.11-2.03 (m, 2H).

Synthesis of dithioacetals 131:

13a **131**

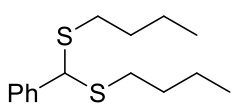
General procedure: Based on modified previously reported method.[11] Benzaldehyde **13a** (5 mmol, 1 equiv.) and *N*-bromosuccinimide (178 mg, 1 mmol, 0.2 equiv.) were dissolved in CH_2Cl_2 (25 ml). The solution was then stirred under argon at r.t. and thiol (2.5 equiv.) was added dropwise. The reaction was monitored by TLC and quenched with 10% aqueous NaOH (25 ml) when the aldehyde was consumed (30-80 min). Aqueous and organic layers were separated, and the aqueous layer was washed with CH_2Cl_2 (2 x 25 ml). The combined organic layers were washed with 25 ml brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product **131** was then purified by recrystallization or by flash chromatography.



131a

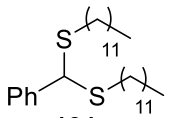
Prepared according to a modified previously reported method.[14] Benzaldehyde (0.51 ml, 5 mmol, 1 equiv.) and benzenethiol (1.08 ml, 10.5 mmol, 2.1 equiv.) were dissolved in $CHCl_3$ (25 ml). The solution was then stirred at room temperature and I_2 (0.13 g, 0.5 mmol, 0.1 equiv.) was added. The reaction was monitored by TLC. When the aldehyde was consumed (30 min) the reaction was quenched with aqueous $Na_2S_2O_3$ (0.1 M, 25 ml) and then washed twice with 10% aqueous NaOH (25 ml). Aqueous and organic layers were separated and the aqueous layer was washed with $CHCl_3$ (25 ml). The combined organic layers were washed with 20 ml of H_2O, dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield the crude product. The crude product was then purified by recrystallization from hexane to afford **131a** as white crystals in 66% yield (1.01 g, 3.28 mmol) with the same spectral characterization as

previously described.[15] ^{1}**H NMR** (300 MHz, $CDCl_3$): δ ppm 7.39-7.20 (m, 15H), 5.42 (s, 1H).



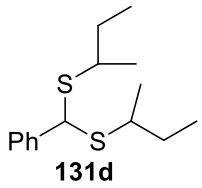
131b

Prepared according to general procedure. Flash chromatography eluent: Hex:AcOEt (97.5:2.5). 91% yield (1.218 g, 4.54 mmol), colorless oil. ^{1}**H NMR** (300 MHz, $CDCl_3$): δ ppm 7.45-7.42 (m, 2H), 7.34-7.22 (m, 3H), 4.87 (s, 1H), 2.63-2.46 (m, 4H), 1.58-1.48 (m, 4H), 1.42-1.30 (m, 4H), 0.87 (t, J = 7.3 Hz, 6H). ^{13}**C{1H} NMR** (75 MHz, $CDCl_3$): δ ppm 140.7, 128.5, 127.8, 127.8, 53.3, 32.0, 31.3, 22.1, 13.7. **HR-MS (ESI)** m/z calculated for $C_{15}H_{23}S_2^+$ $[M-H]^+$ 267.1236, found 267.1246.



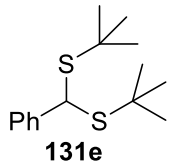
131c

Prepared according to a modified reported method.[14] Benzaldehyde (2 mL, 19.7 mmol, 1 equiv.) and dodecanethiol (10.4mL, 43.3 mmol, 2.2 equiv.) were dissolved in dichloromethane (30 mL) in a round-bottom flask. Then, iodine (508, 2 mmol, 0.1 equiv.) was slowly added do the stirring solution as to prevent vigorous boiling of the solvent. After 2 hours of complete addition, the reaction was quenched with a 2% $Na_2S_2O_3$ aqueous solution (10 mL). The layers were separated, and the organic layer collected and washed successively with a 10% aqueous NaOH solution (10 mL), water (10 mL) and brine (10 mL). The organic solvent was dried over $MgSO_4$ and filtered. After evaporating the solvent, the product was purified by flash chromatography (hexane) to give **131c** as a white amorphous solid in 57% yield (5.563 g, 11.29 mmol). ^{1}**H NMR** (300 MHz, $CDCl_3$): δ ppm 7.45-7.42 (m, 2H), 7.35-7.22 (m, 3H), 4.86 (s, 1H), 2.62-2.45 (m, 4H), 1.59-1.49 (m, 4H), 1.35-1.24 (m, 36H), 0.90-0.86 (m, 6H). ^{13}**C{1H} NMR** ($CDCl_3$, 75MHz) δ ppm 140.8, 128.6, 127.9, 127.8, 53.3, 32.4, 32.1, 29.8, 29.7, 29.6, 29.5, 29.3, 29.3, 29.0, 22.8, 14.3. **HR-MS (ESI)** m/z calculated for $C_{31}H_{55}S_2^+$ $[M-H]^+$ 491.3740, found 491.3757.



131d

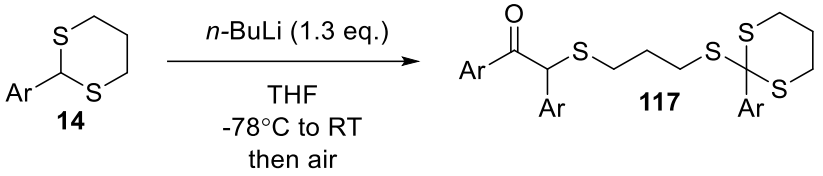
Prepared according to general procedure. 86% yield (1.150 g, 4.29 mmol), colorless oil. Flash chromatography eluent: Hex:AcOEt (97.5:2.5). ^{1}**H NMR** (300 MHz, $CDCl_3$): δ ppm 7.47 (d, J = 7.6 Hz, 2H), 7.34-7.22 (m, 3H), 4.94 (s, 1H), 2.88-2.63 (m, 2H), 1.66-1.42 (m, 4H), 1.24-1.20 (m, 6H), 0.97-0.88 (m, 6H). ^{13}**C{1H} NMR** (75 MHz, $CDCl_3$): δ ppm 141.1, 128.5, 127.8, 127.7, 50.8, 50.6, 42.5, 42.4, 29.5, 29.5, 20.7, 20.6, 20.6, 11.2, 11.1. **HR-MS (ESI)** m/z calculated for $C_{15}H_{23}S_2^+$ $[M-H]^+$ 267.1236, found 267.1243.



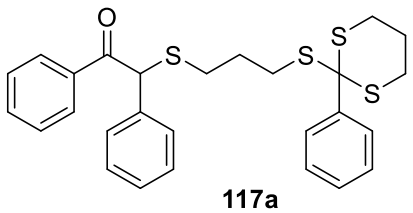
131e

Prepared according to general procedure. 87% yield (1.171 g, 4.37 mmol), white solid. Flash chromatography eluent: Hex:AcOEt (97.5:2.5). ^{1}**H NMR** (300 MHz, $CDCl_3$): δ ppm 7.48-7.44 (m, 2H), 7.32-7.26 (m, 2H), 7.23-7.18 (m, J = 1.3 Hz, 1H), 5.02 (s, 1H), 1.29 (s, 18H). ^{13}**C{1H} NMR** (75 MHz, $CDCl_3$): δ ppm 144.1, 128.7, 127.7, 127.4, 48.8, 45.8, 31.3. **HR-MS (ESI)** m/z calculated for $C_{15}H_{23}S_2^+$ $[M-H]^+$ 267.1236, found 267.1243.

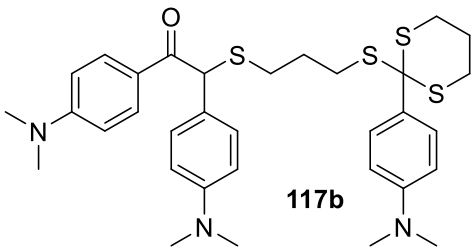
Autooxidative addition of dithianes 14:



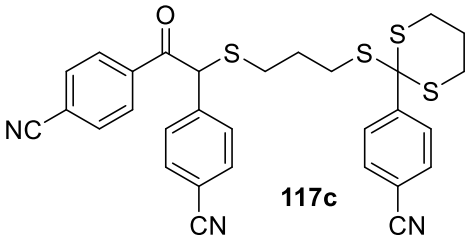
Aryl dithiane **14** (1.02 mmol, 1 equiv.) was dissolved in dry THF (5 mL) in an argon purged round-bottom flask. The solution was cooled to -78 ºC in an acetone/liquid nitrogen bath. *n*-BuLi (1.3 equiv.) solution in hexanes was added dropwise to the reaction mixture at -78 ºC. The solution was left stirring at -78 ºC for 20 minutes and then left to warm up to room temperature for 40 minutes. The argon balloon was replaced with an atmospheric air balloon and an additional needle was inserted in the septum as to allow air flow through the surface of the solution. As oxidation took place the solution warmed up and color change was usually observed. After 1 minute the solution was quenched with 10 mL of a saturated aqueous NH_4Cl solution. 10 mL of Et_2O were added and the layers were separated. The organic phase was collected, and the aqueous phase was extracted two times with Et_2O (2 × 10 mL). The organic phases were combined and dried over $MgSO_4$. The solvent was filtered and evaporated. The product **117** was purified by flash chromatography.



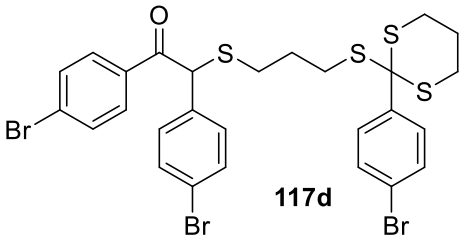
Prepared according to general procedure. 76% yield (128 mg, 0.26 mmol), pale yellow oil. Flash chromatography eluent: Hex:AcOEt (90:10). ^{1}**H NMR** (300 MHz, $CDCl_3$): δ ppm 7.96 - 7.90 (m, 4 H) 7.54 - 7.23 (m, 11 H) 5.51 (s, 1 H) 3.30 (ddt, *J*=13.8, 10.8, 2.9, 2.9 Hz, 2 H) 2.75 - 2.68 (m, 2 H) 2.57 - 2.44 (m, 4 H) 2.15 - 2.04 (m, 1 H) 1.96 - 1.83 (m, 1 H) 1.76-1.66 (m, 2 H). ^{13}**C{1H} NMR** (75 MHz, $CDCl_3$): δ ppm 195.1, 141.6, 136.7, 135.8, 133.4, 129.1, 129.0, 128.9, 128.8, 128.6, 128.5, 128.1, 128.0, 64.3, 55.6, 32.7, 30.6, 29.2, 28.4, 24.4. **HR-MS (ESI)** m/z calculated for $C_{27}H_{28}OS_4Na^+$ $[M+Na]^+$ 519.0915, found 519.0894.



Prepared according to general procedure. 64% yield (135 mg, 0.22 mmol), amorphous yellow solid. Flash chromatography eluent: Hex:AcOEt (60:40). ^{1}**H NMR** (300 MHz, $CDCl_3$): δ ppm 7.90-7.87 (m, 2H), 7.79-7.76 (m, 2H), 7.30-7.26 (m, 2H), 6.67-6.56 (m, 6H), 5.47 (s, 1H), 3.36-3.26 (m, 2H), 3.01 (s, 6H), 2.95 (s, 6H), 2.90 (s, 6H), 2.72-2.67 (m, 2H), 2.59-2.45 (m, 4H), 2.12-2.03 (m, 1H), 1.94-1.84 (m, 1H), 1.81-1.71 (m, 2H). ^{13}**C{1H} NMR** (75 MHz, $CDCl_3$): δ ppm 193.5, 153.4, 150.2, 150.0, 131.3, 129.5, 129.0, 128.4, 124.9, 123.6, 112.7, 111.9, 110.7, 64.4, 54.9, 40.6, 40.5, 40.1, 32.9, 30.6, 29.4, 28.7, 24.5. **HR-MS (ESI)** m/z calculated for $C_{33}H_{43}N_3OS_4Na^+$ $[M+Na]^+$ 648.2181, found 648.2187.

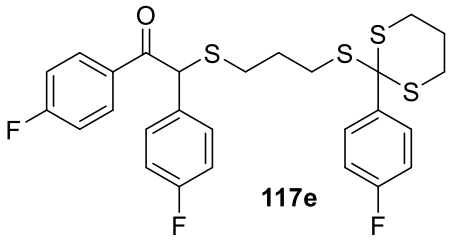


Prepared according to general procedure. 60% yield (232 mg, 0.41 mmol), amorphous white solid. Flash chromatography eluent: Hex:AcOEt (70:30). ^{1}**H NMR** (300 MHz, $CDCl_3$): δ ppm 8.05 – 8.02 (m, 4H), 7.75 (d, *J*=8.8 Hz, 2H), 7.67 - 7.56 (m, 6H), 5.43 (s, 1H), 3.20 (tdd, *J*=2.3, 9.9, 14.1 Hz, 2H), 2.73 (ddd, *J*=2.9, 6.9, 14.2 Hz, 2H), 2.60-2.44 (m, 4H), 2.12 - 2.02 (m, 1H), 1.97 - 1.84 (m, 1H), 1.73-1.64 (m, 2H). ^{13}**C{1H} NMR** (75 MHz, $CDCl_3$): δ ppm 192.3, 146.8, 141.1, 138.4, 132.7, 132.4, 129.8, 129.4, 129.0, 118.5, 118.3, 117.7, 117.1, 112.4, 112.3, 63.5, 54.2, 32.4, 30.8, 29.3, 28.1, 23.9. **HR-MS (ESI)** m/z calculated for $C_{30}H_{25}N_3OS_4Na^+$ $[M+Na]^+$ 594.0773, found 594.0773.



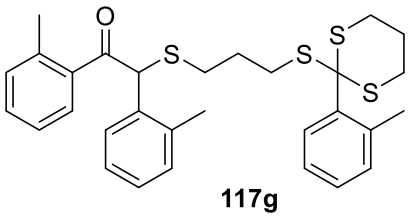
Prepared according to general procedure. LDA was used instead of *n*-BuLi. 51% yield (127 mg, 0.17 mmol), pale yellow oil. 1**H NMR** (300 MHz, CDCl3): δ ppm 7.83-7.77 (m, 4H), 7.59-7.54 (m, 2H), 7.50-7.44 (m, 4H), 7.32-7.26 (m, 2H), 5.37 (s, 1H), 3.29-3.19 (m, 2H), 2.75-2.69 (m, 2H), 2.59-2.45 (m, 4H), 2.13-2.03 (m, 1H), 1.96-1.82 (m, 1H), 1.76-1.66 (m, 2H). 13**C{1H} NMR**

(75 MHz, CDCl3): δ ppm 193.5, 140.7, 135.4, 134.2, 132.2, 132.2, 131.7, 130.6, 130.5, 129.9, 128.9, 122.7, 122.4, 63.7, 54.5, 32.6, 30.7, 29.3, 28.3, 24.2. **HR-MS (ESI)** m/z calculated for C27H24Br3OS4- [M-H]- 728.8266, found 728.8265.



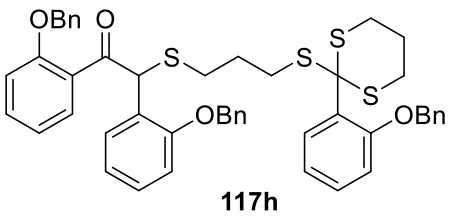
117e

Prepared according to general procedure. 60% yield (112 mg, 0.20 mmol), colorless oil. Flash chromatography eluent: Hex:AcOEt (94:6). ^{1}**H NMR** (300 MHz, $CDCl_3$): δ ppm 8.00-7.88 (m, 4H), 7.42-7.38 (m, 2H), 7.12-7.00 (m, 6H), 5.44 (s, 1H), 3.26 (ddt, *J*=13.8, 10.9, 2.6 Hz, 2H), 2.76-2.68 (m, 2H), 2.57-2.46 (m, 4H), 2.13-2.04 (m, 1H), 1.96-1.82 (m, 1H), 1.76-1.66 (m, 2H). ^{19}F NMR (282MHz, $CDCl_3$): δ ppm -104.01--104.09 (m, 1F), -113.35--113.45 (m, 1F), -113.56--113.66 ppm (m, 1F). ^{13}**C{1H} NMR** (75 MHz, $CDCl_3$): δ ppm 193.3, 167.6, 164.2, 164.2, 160.9, 137.4, 137.4, 132.3, 132.2, 131.9, 131.9, 131.8, 131.7, 130.6, 130.5, 130.1, 130.0, 116.2, 115.9, 115.5, 115.2, 63.6, 54.4, 32.7, 30.7, 29.3, 28.3, 24.2. **HR-MS (ESI)** m/z calculated for $C_{27}H_{25}F_3OS_4Na^+$ $[M+Na]^+$ 573.0633, found 573.0640.



117g

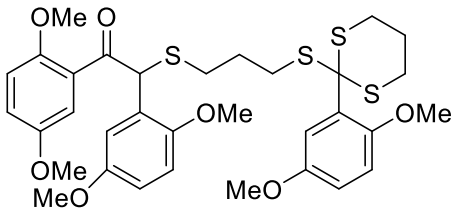
Prepared according to general procedure. 66% yield (120 mg, 0.22 mmol), colorless oil. Flash chromatography eluent: Hex:AcOEt (95:5). ^{1}**H NMR** (300 MHz, $CDCl_3$): δ ppm 7.97-7.94 (m, 1H), 7.42 (d, *J*=5.9 Hz, 2H), 7.32-7.27 (m, 1H), 7.19-7.12 (m, 8H), 5.52 (s, 1H), 3.40-3.30 (m, 2H), 2.83 (s, 3H), 2.75-2.68 (m, 2H), 2.55-2.48 (m, 4H), 2.37 (s, 3H), 2.33 (s, 3H), 2.15-2.04 (m, 1H), 1.98-1.84 (m, 1H), 1.74-1.64 (m, 2H). ^{13}**C{1H} NMR** (75 MHz, $CDCl_3$): δ ppm 199.0, 138.7, 138.4, 138.0, 137.7, 136.1, 134.2, 133.8, 131.9, 131.2, 130.9, 129.2, 129.0, 128.4, 128.1, 127.6, 126.7, 125.6, 125.5, 64.9, 54.7, 32.8, 31.1, 29.2, 28.6, 24.3, 23.6, 20.8, 19.8. **HR-MS (ESI)** m/z calculated for $C_{30}H_{34}OS_4Na^+$ $[M+Na]^+$ 561.1385, found 561.1389.



117h

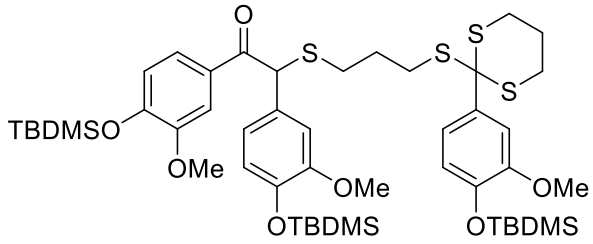
Prepared according to general procedure. 58% yield (324 mg, 0.40 mmol), pale yellow oil. Flash chromatography eluent: Hex:AcOEt (80:20). ^{1}**H NMR** (300 MHz, $CDCl_3$): δ ppm 7.87-7.85 (m, 1H), 7.59 (d,

J=7.6 Hz, 2H), 7.43 (dt, *J*=7.6, 2.1 Hz, 2H), 7.36-7.13 (m, 16H), 6.94-6.76 (m, 6H), 6.12 (s, 1H), 5.17 (s, 2H), 4.95-4.79 (m, 4H), 3.32-3.24 (m, 2H), 2.71-2.64 (m, 2H), 2.40-2.30 (m, 4H), 2.07-1.96 (m, 1H), 1.94-1.80 (m, 1H), 1.56-1.46 (m, 2H). ^{13}**C{1H} NMR** (75 MHz, $CDCl_3$): δ ppm 198.0, 157.1, 156.8, 156.0, 137.5, 136.9, 136.4, 132.8, 130.8, 130.3, 129.8, 129.6, 129.4, 128.8, 128.7, 128.6, 128.6, 128.4, 128.1, 127.9, 127.5, 127.5, 127.3, 127.2, 125.7, 121.0, 120.8, 120.5, 114.8, 112.7, 111.8, 71.0, 70.4, 70.2, 63.1, 52.5, 32.9, 31.0, 28.9, 28.5, 24.3. **HR-MS (ESI)** m/z calculated for $C_{48}H_{46}O_4S_4Na^+$ $[M+Na]^+$ 837.2171, found 837.2196.



117i

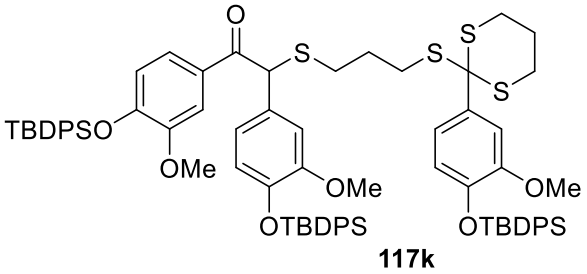
Prepared according to general procedure. 68% yield (157 mg, 0.23 mmol), colorless oil. Flash chromatography eluent: Hex:AcOEt (80:20). ^{1}**H NMR** (300 MHz, $CDCl_3$): δ ppm 7.45 (d, *J*=2.9 Hz, 1H), 7.13 (d, *J*=3.5 Hz, 1H), 6.99 (t, *J*=1.5 Hz, 1H), 6.95-6.78 (m, 4H), 6.71 (d, *J*=1.8 Hz, 2H), 6.03 (s, 1H), 3.82 (s, 3H), 3.76 (s, 6H), 3.73 (s, 3H), 3.72 (s, 3H), 3.70 (s, 3H), 3.36-3.26 (m, 2H), 2.74-2.68 (m, 2H), 2.54-2.49 (m, 4H), 2.10-2.01 (m, 1H), 1.96-1.83 (m, 1H), 1.75-1.65 ppm (m, 2H). ^{13}**C{1H} NMR** (75 MHz, $CDCl_3$): δ ppm 197.4, 153.7, 153.4, 153.2, 152.6, 152.4, 151.1, 130.7, 128.2, 126.7, 119.5, 116.0, 115.6, 115.6, 114.8, 114.2, 113.8, 113.0, 111.8, 62.5, 57.6, 56.2, 55.9, 55.8, 55.8, 52.1, 32.9, 30.9, 29.0, 28.6, 24.4. **HR-MS (ESI)** m/z calculated for $C_{33}H_{40}O_7S_4Na^+$ $[M+Na]^+$ 699.1549, found 699.1572.



117j

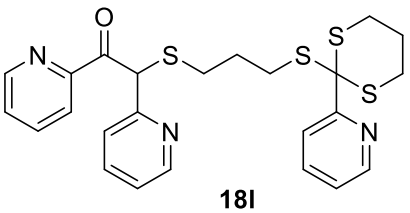
Prepared according to general procedure. 61% yield (148 mg, 0.15 mmol), amorphous white solid. Flash chromatography eluent: Hex:DCM (1:1). ^{1}**H NMR** (300 MHz, $CDCl_3$): δ ppm ^{1}**H NMR** ($CDCl_3$, 300MHz): d = 7.49-7.45 (m, 3H), 7.37-7.34 (m, 1H), 6.96 (d, *J*=2.3 Hz, 1H), 6.85-6.74 (m, 4H), 5.43 (s, 1H), 3.80 (s, 6H), 3.77 (s, 3H), 3.33-3.24 (m, 2H), 2.74-2.67 (m, 2H), 2.58-2.44 (m, 4H), 2.12-2.05 (m, 1H), 1.94-1.82 (m, 1H), 1.74-1.65 (m, 2H), 0.98 (s, 9H), 0.97 (s, 9H), 0.96 (s, 9H), 0.15-0.11 (m, 18H) ^{13}**C{1H} NMR** (75 MHz, $CDCl_3$): δ ppm 194.2, 151.4, 151.1, 150.8, 150.3, 145.2, 144.9, 134.7, 130.3, 129.8, 123.3, 121.5, 120.8, 120.5,

120.4, 120.3, 112.3, 112.2, 112.1, 64.2, 55.7, 55.6, 55.5, 55.3, 32.8, 30.7, 29.4, 28.5, 25.8, 25.7, 24.5, 18.6, 18.5, -4.4, -4.5. **HR-MS (ESI)** m/z calculated for $C_{48}H_{76}O_7S_4Si_3Na^+$ $[M+Na]^+$ 999.3679, found 999.3645.



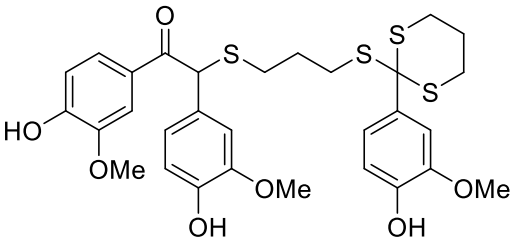
117k

Prepared according to general procedure. 89% yield (239 mg, 0.19 mmol), amorphous white solid. Flash chromatography eluent: Hex:AcOEt (80:20). ^{1}**H NMR** (300 MHz, $CDCl_3$): δ ppm 7.69-7.61 (m, 12H), 7.41-7.15 (m, 22H), 6.79 (s, 1H), 6.66-6.59 (m, 4H), 5.28 (s, 1H), 3.53 (s, 3H), 3.52 (s, 3H), 3.47 (s, 3H), 3.24-3.15 (m, 2H), 2.63 (dt, *J*=14.1, 2.9 Hz, 2H), 2.45-2.32 (m, 4H), 2.06-1.96 (m, 1H), 1.87-1.75 (m, 1H), 1.63-1.54 (m, 2H), 1.10-1.08 ppm (m, 27H). ^{13}**C{1H} NMR** (75 MHz, $CDCl_3$): δ ppm 194.2, 151.1, 150.7, 150.4, 150.0, 145.2, 144.9, 135.5, 135.3, 134.5, 133.5, 133.5, 133.0, 130.2, 130.0, 129.7, 129.7, 129.6, 127.8, 127.6, 127.5, 123.0, 121.1, 120.2, 120.2, 119.7, 119.5, 112.4, 112.3, 112.2, 64.1, 55.5, 55.5, 55.4, 32.7, 30.5, 29.3, 28.4, 26.8, 26.7, 26.6, 24.4, 19.9, 19.9, 19.9. **HR-MS (ESI)** m/z calculated for $C_{78}H_{88}O_7S_4Si_3Na^+$ $[M+Na]^+$ 1371.4613, found 1371.4641.



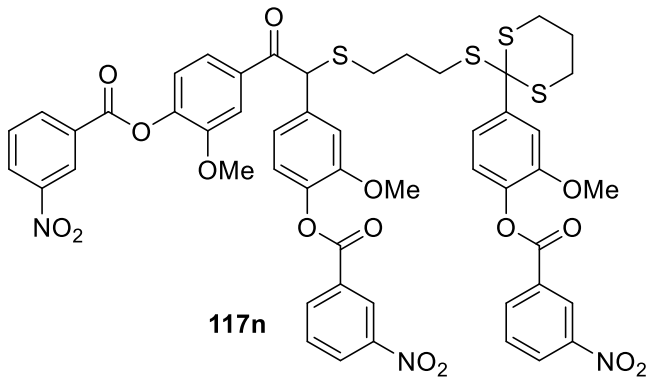
18l

Prepared according to general procedure. 62% yield (63 mg, 0.13 mmol), yellow oil. Flash chromatography was run with eluent Hex:AcOEt:Et_3N (50:50:2) because the compound was unstable in silica without treatment with triethylamine. ^{1}**H NMR** (300 MHz, $CDCl_3$): δ ppm 8.65-8.61 (m, 1H), 8.52-8.45 (m, 2H), 8.10-8.07 (m, 1H), 7.85-7.78 (m, 2H), 7.70-7.66 (m, 3H), 7.49-7.41 (m, 1H), 7.19-7.11 (m, 2H), 6.39 (s, 1H), 3.46-3.34 (m, 2H), 2.75-2.68 (m, 2H), 2.64-2.49 (m, 2H), 2.42 (t, *J*=7.3 Hz, 2H), 2.18-2.10 (m, 1H), 1.95-1.81 (m, 1H), 1.61-1.51 (m, 2H). ^{13}**C{1H} NMR** (75 MHz, $CDCl_3$): δ ppm 195.4, 161.0, 157.8, 152.3, 149.2, 149.1, 148.0, 137.1, 137.1, 136.8, 127.4, 124.0, 123.2, 123.2, 122.3, 122.2, 65.9, 53.2, 32.7, 31.2, 28.3, 28.2, 24.9. **HR-MS (ESI)** m/z calculated for $C_{24}H_{25}N_3OS_4Na^+$ $[M+Na]^+$ 522.0773, found 522.0806.



117m

After standard autoxidative addition of dithiane **14k**, the resulting crude was not purified via column chromatography but instead was dissolved in dry methanol (8 mL) in an argon purged round-bottom flask. Then, ammonium fluoride (95 mg, 2.56 mmol, 1.1 equivalents) was added and the solution was stirred overnight at room temperature. The methanol was evaporated, and water (10 mL) was added. The aqueous phase was extracted with DCM (3 × 10 mL) and the organic phases were combined and dried over MgSO4. The solvent was evaporated, and the product was purified by flash chromatography, eluent hexane: ethyl acetate (1:1), to give product **117m** as an amorphous orange solid (286 mg, 0.45 mmol) in 60% overall yield. ^{1}H-NMR (500 MHz, $CDCl_3$) δ ppm 7.56–7.49 (m, 3H), 7.44 (dd, J = 8.4, 2.1 Hz, 1H), 6.98 (s, 1H), 6.89–6.82 (m, 4H), 6.07 (s, 1H), 5.68 (s, 1H), 5.61 (s, 1H), 5.45 (s, 1H), 3.90 (s, 3H), 3.89 (s, 3H), 3.86 (s, 3H), 3.27 (t, J = 12.5 Hz, 2H), 2.74–2.70 (m, 2H), 2.57–2.44 (m, 4H), 2.10–2.05 (m, 1H), 1.92–1.85 (m, 1H), 1.77–1.71 (m, 2H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ ppm 194.0, 150.7, 147.1, 146.8, 146.4, 145.8, 145.6, 133.3, 128.8, 128.5, 124.3, 122.1, 121.3, 114.3, 114.0, 113.9, 111.0, 110.8, 110.6, 64.3, 56.2 (×2), 56.1, 55.2, 32.8, 30.7, 29.4, 28.5, 24.4. **HR-MS (ESI)** m/z calculated for $C_{30}H_{34}O_7S_4Na^+$ $[M + Na]^+$ 657.1080, found 657.1068.



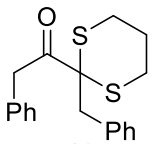
117n

Triphenol **117m** (100 mg, 0.158 mmol) was dissolved in dry DCM (3 mL) in an argon purged round-bottom flask. Pyridine (48 µL, 0.591 mmol, 3.75 equivalents) was added to the solution, followed by 3-nitrobenzoyl chloride (91 mg, 0.488 mmol, 3.1 equivalents). The reaction was left stirring at room temperature for 72 h. Water (10 mL) was added to the mixture and the aqueous phase was extracted with DCM (3 × 10 mL). The organic phases were combined and dried over MgSO4. The solvent was evaporated and the product was purified by flash chromatography, eluent hexane:

ethyl acetate (3:2), to give the benzoyl derivative **117n** as an amorphous white solid (163 mg, 0.151 mmol) in 95% yield. ^{1}**H NMR** (500 MHz, $CDCl_3$) δ ppm 9.02 (s, 3H), 8.51–8.48 (m, 6H), 7.76–7.67 (m, 6H), 7.62 (dd, J = 8.4, 2.0 Hz, 1H), 7.25–7.08 (m, 5H), 5.56 (s, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.83 (s, 3H), 3.31 (dd, J = 13.3, 11.2 Hz, 2H), 2.79 (dd, J = 14.3, 3.6 Hz, 2H), 2.70–2.58 (m, 4H), 2.14–2.11 (m, 1H), 1.98–1.91 (m, 1H), 1.86–1.81 (m, 2H). ^{13}**C{1H} NMR** (125 MHz, $CDCl_3$) δ 193.8, 162.6, 162.6, 162.2, 151.7, 151.6, 151.0, 148.5, 148.5, 143.8, 140.9, 139.5, 139.4, 136.1, 136.1, 135.9, 134.9, 131.2, 131.2, 130.8, 130.1, 130.0, 128.3, 128.1, 128.1, 125.5, 125.4, 122.9, 122.4, 122.3, 121.4, 120.6, 112.9, 112.8, 64.1, 56.3, 56.2, 56.2, 55.1, 32.8, 30.9, 29.5, 28.5, 24.3. **HR-MS (ESI)** m/z calculated for $C_{51}H_{43}N_3O_{16}S_4Na^+$ $[M + Na]^+$1104.1418, found 1104.1385.

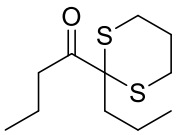
Autoxidative addition of 2-alkyl-1,3-dithianes:

General procedure: Dithiane (1.02 mmol, 1 equiv.) was dissolved in dry THF (5 mL) in an argon purged round-bottom flask. The solution was cooled to -78ºC in an acetone/liquid nitrogen bath. *n*-BuLi (1.3 equiv.) solution in hexanes was added dropwise to the reaction mixture at -78ºC. The solution was left stirring at -78ºC for 20 minutes and then left to warm up to room temperature for 40 minutes. The argon balloon was replaced with an atmospheric air balloon and an additional needle was inserted in the septum as to allow air flow through the surface of the solution. After 5 minutes the solution was quenched with 10 mL of a saturated aqueous NH_4Cl solution. 10 mL of Et_2O were added and the layers were separated. The organic phase was collected, and the aqueous phase was extracted two times with Et_2O (2 × 10 mL). The organic phases were combined and dried over $MgSO_4$. The solvent was filtered and evaporated. The product was purified and separated from unreacted starting material by flash chromatography.



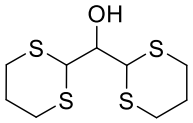
125a

Prepared according to general procedure. 27% yield, (45 mg, 0.14 mmol), white solid. Flash chromatography eluent: Hex:AcOEt (95:5). ^{1}**H NMR** (300 MHz, $CDCl_3$): δ ppm 7.33-7.21 (m, 10H), 4.00 (s, 2H), 3.41 (s, 2 H), 2.86-2.76 (m, 2H), 2.60-2.53 (m, 2H), 1.99-1.90 (m, 1H), 1.84-1.73 (m, 1H). ^{13}**C{1H} NMR** (75 MHz, $CDCl_3$): δ ppm 200.6, 134.9, 134.3, 130.2, 129.9, 128.5, 128.5, 127.7, 127.0, 62.5, 44.3, 43.4, 28.0, 24.2. **HR-MS (ESI)** m/z calculated for $C_{19}H_{21}OS_2^+$ $[M+H]^+$ 329.1028, found 329.1052.



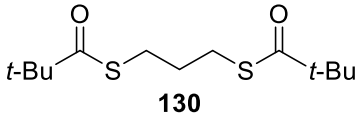
125b

Prepared according to general procedure. 24% yield (29 mg, 0.12 mmol), colorless oil. Flash chromatography eluent: Hex:DCM (55:45). ^{1}**H NMR** (300 MHz, $CDCl_3$): δ ppm 3.02-2.92 (m, 2H), 2.66-2.56 (m, 4H), 2.09-2.00 (m, 1H), 1.96-1.91 (m, 2H), 1.97-1.76 (m, 1H), 1.71-1.59 (m, 2H), 1.47-1.34 (m, 2H), 0.95-0.89 (m, 6H). ^{13}**C{1H} NMR** (75 MHz, $CDCl_3$): δ ppm 204.3, 61.4, 40.6, 37.8, 27.9, 25.0, 18.4, 18.0, 14.4, 13.9. **HR-MS (ESI)** m/z calculated for $C_{11}H_{21}OS_2^+$ $[M+H]^+$ 233.1028, found 233.1050.



129

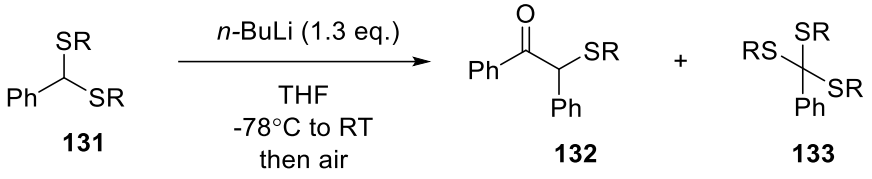
Prepared according to general procedure. 63% yield (47 mg, 0.18 mmol), white solid. Flash chromatography eluent: DCM (100%). Obtained with same spectral characterization as previously described.[19] ^{1}**H NMR** (300 MHz, $CDCl_3$): δ ppm 4.28 (s, 3H), 3.15 (s, 1H), 3.07-2.95 (m, 4H), 2.78-2.62 (m, 4H), 2.07-2.00 (m, 4H). ^{13}**C{1H} NMR** (75 MHz, $CDCl_3$): δ ppm 74.7, 47.4, 27.9, 27.2, 25.5.



130

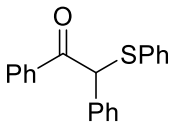
Prepared according to general procedure. 22% yield (61 mg, 0.22 mmol), colorless oil. Flash chromatography eluent: Hex:AcOEt (97:3). ^{1}**H NMR** (300 MHz, $CDCl_3$): δ ppm 2.86 (t, J=7.0 Hz, 4H), 1.79 (quin, J=7.2 Hz, 2H), 1.20 (s, 18H). ^{13}**C{1H} NMR** (75 MHz, $CDCl_3$): δ ppm 206.6, 46.5, 29.7, 27.5, 27.5. **HR-MS (ESI)** m/z calculated for $C_{13}H_{25}O_2S_2^+$ $[M+H]^+$ 277.1290, found 277.1323.

Autooxidative addition of dithioacetals 131:



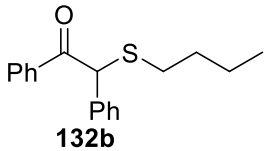
General procedure for autooxidative addition of dithioacetals **131**: Dithioacetal **32** (1.02 mmol, 1 equiv.) was dissolved in dry THF (5 mL) in an argon purged round-bottom flask. The solution was cooled to -78 ºC in an acetone/liquid nitrogen bath. *n*-BuLi (1.3 equiv.) solution in hexanes was added dropwise to the reaction mixture

at -78 ºC. The solution was left stirring at -78 ºC for 20 minutes and then left to warm up to room temperature for 40 minutes. The argon balloon was replaced with an atmospheric air balloon and an additional needle was inserted in the septum as to allow air flow through the surface of the solution. After 1 minute the solution was quenched with 10 mL of a saturated aqueous NH_4Cl solution. 10 mL of Et_2O were added and the layers were separated. The organic phase was collected, and the aqueous phase was extracted two times with Et_2O (2 × 10 mL). The organic phases were combined and dried over $MgSO_4$. The solvent was filtered and evaporated. Products **33** and **34** were obtained after purification by flash chromatography.



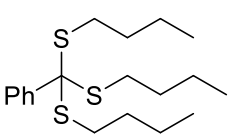
132a

Prepared according to general procedure: 48% yield (97 mg, 0.32 mmol), white solid. Flash chromatography eluent: Hex:AcOEt (97.5:2.5). ^{1}**H NMR** (300 MHz, $CDCl_3$): δ ppm 7.94-7.90 (m, 2H), 7.49-7.44 (m, 1H), 7.38-7.17 (m, 12H), 5.85 (s, 1H). ^{13}**C{1H} NMR** (75 MHz, $CDCl_3$): δ ppm 194.8, 136.6, 135.6, 134.1, 133.4, 133.1, 129.0, 128.9, 128.8, 128.7, 128.1, 128.0, 60.4. **HR-MS (ESI)** m/z calculated for $C_{20}H_{17}OS^+$ $[M+H]^+$ 305.0995, found 305.1013. The corresponding orthothioester product, **133a** could not be isolated due to low polarity and structural similarity to **131a**. However, the following characteristic peaks for the **133a** can be observed from the NMR spectrum of a mixture with the dithioacetal. **133a**: ^{1}**H NMR** (300 MHz, $CDCl_3$): 7.69-7.64 (m, 2H). ^{13}**C{1H} NMR** (75 MHz, $CDCl_3$): δ ppm 139.4, 132.9, 128.8, 128.4, 128.3, 128.0, 127.9, 77.0.



132b

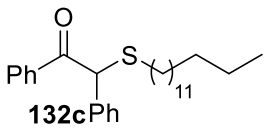
Prepared according to general procedure: 97% yield (92 mg, 0.32 mmol), white solid. Flash chromatography eluent: Hex:AcOEt (95:5). ^{1}**H NMR** (300 MHz, $CDCl_3$): δ ppm 7.99-7.96 (m, 2H), 7.53-7.23 (m, 8H), 5.55 (s, 1H), 2.56-2.42 (m, 2H), 1.58-1.48 (m, 2H), 1.41-1.29 (m, 2H), 0.85 (t, J = 7.3 Hz, 3H). ^{13}**C{1H} NMR** (75 MHz, $CDCl_3$): δ ppm 195.3, 136.9, 135.9, 133.3, 129.0, 128.9, 128.9, 128.7, 128.0, 55.5, 31.3, 31.2, 22.1, 13.7. **HR-MS (ESI)** m/z calculated for $C_{18}H_{21}OS^+$ $[M+H]^+$ 285.1308, found 285.1328.



133b

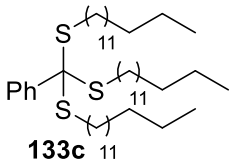
Prepared according to general procedure: 72% yield (86 mg, 0.24 mmol), colorless oil. Flash chromatography eluent: Hex:AcOEt (95:5). ^{1}**H NMR** (300 MHz, $CDCl_3$): δ ppm 7.87-7.84 (m, 2H), 7.35-7.21 (m, 3H), 2.58 (t, J = 7.3 Hz, 6H), 1.51-1.29 (m, 12H), 0.88-0.83 (m, 9H). ^{13}**C{1H} NMR** (75

MHz, $CDCl_3$): δ ppm 141.8, 131.3, 127.9, 127.6, 73.5, 31.5, 30.5, 22.3, 13.7. **HR-MS (ESI)** m/z calculated for $C_{15}H_{23}S_2^+$ $[M\text{-}S(CH_2)_3CH_3]^+$ 267.1236, found 267.1255.



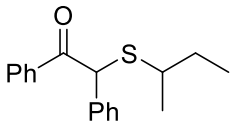
132c

Prepared according to general procedure: 73% yield (99 mg, 0.25 mmol), pale yellow solid. Flash chromatography gradient eluent: Hex:Toluene (80:20 to 50:50). ^{1}**H NMR** (300 MHz, $CDCl_3$): δ ppm 7.99-7.96 (m, 2H), 7.54-7.23 (m, 8H), 5.55 (s, 1H), 2.55-2.41 (m, 2H), 1.59-1.49 (m, 2H), 1.30-1.22 (m, 18H), 0.90-0.86 (m, 3H). ^{13}**C{1H} NMR** (75 MHz, $CDCl_3$): δ ppm 195.3, 136.9, 136.0, 133.3, 129.1, 129.0, 128.9, 128.7, 128.0, 55.6, 32.1, 31.6, 29.8, 29.7, 29.6, 29.5, 29.3, 29.2, 29.0, 22.8, 14.3. **HR-MS (ESI)** m/z calculated for $C_{26}H_{37}OS^+$ $[M+H]^+$ 397.2560, found 397.2591.



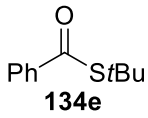
133c

Prepared according to general procedure: 56% yield (131 mg, 0.19 mmol), white solid. Flash chromatography eluent: Hexane (100%). ^{1}**H NMR** (300 MHz, $CDCl_3$): δ ppm 7.87 -7.84 (m, 2H), 7.35-7.21 (m, 3H), 2.57 (t, *J*=7.3 Hz, 6H), 1.54-1.44 (m, 6H), 1.31-1.24 (m, 54H), 0.90-0.86 (m, 9H). ^{13}**C{1H} NMR** (75 MHz, $CDCl_3$): δ ppm 142.1, 128.1, 127.8, 73.7, 32.1, 32.0, 29.8, 29.8, 29.6, 29.5, 29.4, 29.3, 28.6, 22.9, 14.3. **HR-MS (ESI)** m/z calculated for $C_{31}H_{55}S_2^+$ $[M\text{-}S(CH_2)_{11}CH_3]^+$ 491.3740, found 491.3737.



132d

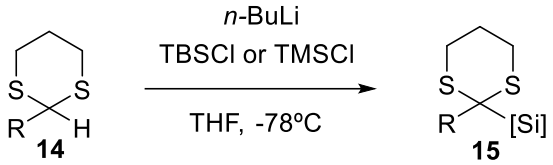
Prepared according to general procedure: 67% yield (63 mg, 0.22 mmol), pale yellow solid. 1:1 mixture of diastereomers. Flash chromatography eluent: Hex:AcOEt (95:5). ^{1}**H NMR** (300 MHz, $CDCl_3$): δ ppm 8.01-7.97 (m, 4H), 7.54-7.23 (m, 16H), 5.61 (s, 2H), 2.75-2.61 (m, 2H), 1.72-1.42 (m, 4H), 1.30 (d, J = 6.4 Hz, 3H), 1.19 (d, J = 7.0 Hz, 3H), 0.98-0.86 (m, 6H). ^{13}**C{1H} NMR** (75 MHz, $CDCl_3$): δ ppm 195.5, 195.4, 137.2, 135.9, 133.3, 129.0, 128.9, 128.9, 128.7, 127.9, 54.7, 54.6, 42.1, 41.9, 29.7, 29.7, 21.0, 20.6, 11.3, 11.2. **HR-MS (ESI)** m/z calculated for $C_{18}H_{21}OS^+$ $[M+H]^+$ 285.1308, found 285.1303. The corresponding orthothioester product **133d** could not be isolated due to low polarity and structural similarity to **131d**. However, the following characteristic peaks for **133d** can be observed in NMR spectrum of the crude reaction mixture: **133d**:^{13}**C{1H} NMR** (75 MHz, $CDCl_3$): δ ppm 69.3, 29.0 20.1, 11.5.



134e

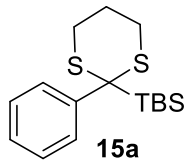
Dithioacetal **32e** (0.5 mmol, 1 equiv.) was dissolved in dry THF (2.5 mL) in an argon purged round-bottom flask. The solution was cooled to -78 ºC in an acetone/liquid nitrogen bath. *n*-BuLi (1.3 equiv.) solution in hexanes was added dropwise to the reaction mixture at -78 ºC. The solution was left stirring at -78 ºC for 20 minutes and then left to warm up to room temperature for 40 minutes. The argon balloon was replaced with an atmospheric air balloon and an additional needle was inserted in the septum as to allow air flow through the surface of the solution. After 1 minute the solution was quenched with 5 mL of a saturated aqueous NH_4Cl solution. 5 mL of Et_2O were added and the layers were separated. The organic phase was collected and the aqueous phase was extracted two times with Et_2O (2 × 5 mL). The organic phases were combined and dried over $MgSO_4$. The solvent was evaporated and the product was purified by preparative TLC (eluent: pentane) to yield **35e** as a colorless oil (62%, 60 mg, 0.31 mmol) with the same spectral characterization as previously described.[16] ^{1}**H NMR** (300 MHz, $CDCl_3$): δ ppm 7.93-7.90 (m, 2H), 7.56-7.51 (m, J = 7.3 Hz, 1H), 7.44-7.39 (m, 2H), 1.58 (s, 9H).

Synthesis of silyl-dithianes 15:



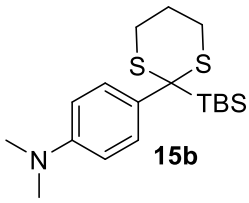
14 **15**

General procedure: Dithiane **14** (9.5 mmol) was dissolved in 40 mL of dry THF, in a dried, argon-filled round-bottom flask. The solution was cooled to -78 °C and *n*-BuLi (2.5M solution in hexanes, 1.2 equiv., 11.4 mmol) was added dropwise. The solution was stirred at -78 °C for ten minutes after which *tert*-butyldimethylsilyl chloride or trimethylsilyl chloride (11.4 mmol, 1.2 equiv.) was added dropwise at this temperature. The solution was stirred at -78 °C for an additional ten minutes and then left warming to RT for a minimum of one hour. The reaction was quenched with 40 mL of a saturated aqueous NH_4Cl solution. The layers were separated, and the organic phase was collected. The aqueous phase was extracted with MTBE (2 × 40 mL) and the organic phases combined, dried over $MgSO_4$ and filtered. After vacuum evaporation of the solvent, the crude was purified via silica column chromatography (eluent hexane/EtOAc mixture) to yield silyldithiane **15**.



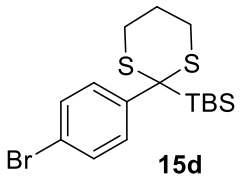
15a

Prepared according to general procedure: 82% yield (508 mg) as a colorless oil. Column eluent 100% hexane. Obtained with same spectral characterization as previously described.[17] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.99 – 7.96 (m, 2H), 7.40 – 7.33 (m, 2H), 7.20 – 7.15 (m, 1H), 2.83 – 2.73 (m, 2H), 2.43 – 2.36 (m, 2H), 2.10 – 1.82 (m, 2H), 0.81 (s, 9H), 0.15 (s, 6H). HRMS m/z: $[M+H]^+$ calculated for $C_{16}H_{27}S_2Si^+$ 311.1318, found 311.1313.



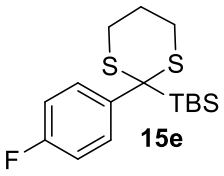
15b

Prepared according to general procedure: 94% yield (667 mg) as a white amorphous solid. Column eluent hexane/EtOAc (99:1) **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.79 – 7.74 (m, 2H), 6.76 – 6.71 (m, 2H), 2.97 (s, 6H), 2.82 (td, J = 14.1, 2.8 Hz, 2H), 2.36 (dt, J = 14.3, 3.9 Hz, 2H), 2.07 – 1.80 (m, 2H), 0.84 (s, 9H), 0.11 (s, 6H). **^{13}C{1H} NMR** (75 MHz, $CDCl_3$) δ 148.3, 131.1, 128.0, 112.5, 48.4, 40.7, 28.1, 25.5, 25.2, 19.8, -6.8. **HRMS m/z:** $[M+H]^+$ calculated for $C_{18}H_{32}NS_2Si^+$ 354.1740, found 354.1731.



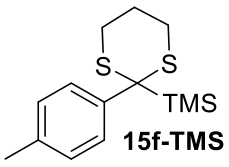
15d

Prepared according to general procedure but using a freshlyPrepared solution of LDA as base: 69% yield (536 mg) as a colorless oil. Column eluent 100% hexane. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.87 – 7.83 (m, 2H), 7.50 – 7.45 (m, 2H), 2.78 – 2.68 (m, 2H), 2.43 – 2.36 (m, 2H), 2.08 – 1.83 (m, 2H), 0.84 (s, 9H), 0.12 (s, 6H). **^{13}C{1H} NMR** (75 MHz, $CDCl_3$) δ 140.5, 132.2, 131.5, 119.6, 48.4, 28.1, 25.3, 25.2, 20.0, -6.9. **HRMS m/z:** $[M+H]^+$ calculated for $C_{16}H_{26}BrS_2Si^+$ 389.0423, found 389.0417.



15e

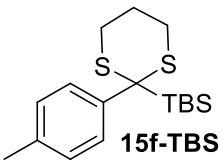
Prepared according to general procedure: 73% yield (483 mg) as a colorless oil. Column eluent 100% hexane. Obtained with same spectral characterization as previously described.[18] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.96 – 7.89 (m, 2H), 7.09 – 7.02 (m, 2H), 2.80 – 2.70 (m, 2H), 2.40 (dt, J = 14.3, 3.9 Hz, 2H), 2.09 – 1.83 (m, 2H), 0.83 (s, 9H), 0.13 (s, 6H).



15f-TMS

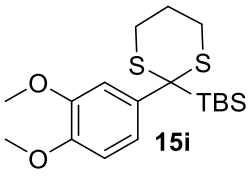
Prepared according to general procedure: 89% yield (2.38 g) as a colorless oil. Trimethylsilyl chloride was used instead of TBSCl. Column eluent 100% hexane. Obtained with same spectral characterization as previously described.[19] **^{1}H NMR**

(300 MHz, $CDCl_3$) δ 7.79 – 7.74 (m, 2H), 7.17 (d, J = 8.0 Hz, 2H), 2.83 – 2.74 (m, 2H), 2.45 – 2.38 (m, 2H), 2.35 (s, 3H), 2.09 – 1.83 (m, 2H), 0.06 (s, 9H).



15f-TBS

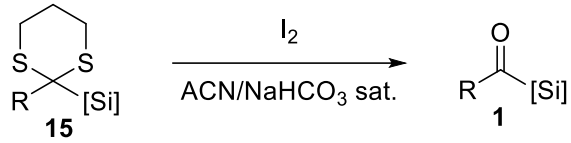
Prepared according to general procedure: 89% yield (2.017 g) as a colorless oil. Column eluent 100% hexane. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.83 (d, J = 8.4 Hz, 2H), 7.17 (d, J = 8.0 Hz, 2H), 2.83 – 2.73 (m, 2H), 2.41 – 2.35 (m, 2H), 2.35 (s, 3H), 2.08 – 1.80 (m, 2H), 0.82 (s, 9H), 0.13 (s, 6H). **^{13}C{1H} NMR** (75 MHz, $CDCl_3$) δ 137.6, 135.0, 130.2, 129.2, 48.6, 28.0, 25.3, 25.3, 21.0, 19.9, -6.8. **HRMS m/z:** $[M+H]^+$ calculated for $C_{17}H_{29}S_2Si^+$ 325.1474, found 325.1470.



15i

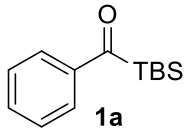
Prepared according to general procedure: 89% yield (270 mg) as a white amorphous solid. Column eluent hexane/EtOAc (94:6) **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.57 (d, J = 2.4 Hz, 1H), 7.50 (dd, J = 8.5, 2.4 Hz, 1H), 6.87 (d, J = 8.5 Hz, 1H), 3.90 (s, 3H), 3.89 (s, 3H), 2.81 (td, J = 14.0, 2.8 Hz, 2H), 2.40 (dt, J = 14.2, 3.7 Hz, 2H), 2.08 – 1.84 (m, 2H), 0.82 (s, 9H), 0.14 (s, 6H). **^{13}C{1H} NMR** (75 MHz, $CDCl_3$) δ 148.8, 146.9, 133.2, 122.7, 113.8, 110.9, 56.1, 56.0, 48.5, 28.0, 25.4, 25.3, 19.9, -6.7. **HRMS m/z:** $[M+H]^+$ calculated for $C_{18}H_{31}O_2S_2Si^+$ 371.1529, found 371.1524.

Synthesis of simple acylsilanes 1:



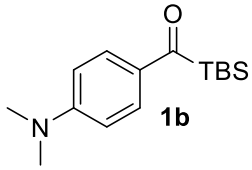
15 **1**

General procedure: Dithiane **15** (3.5 mmol) was dissolved in 17 mL of acetonitrile (sonication and gentle heating were usually required). Then, 5 mL of a saturated aqueous $NaHCO_3$ solution was added and the mixture cooled to 0°C. Then, I_2 (35 mmol, 10 equiv.) was added slowly in portions. After addition, the reaction was left at room temperature for 1 hour. 20 mL of water was added followed by continued addition of NaS_2O_3. The mixture was vigorously stirred until the dark brown color of iodine faded to give a bright yellow solution. Then, the aqueous phase was extracted with MTBE (3 × 20 mL), and the organic phases combined, dried over $MgSO_4$ and filtered. After vacuum evaporation of the solvent the crude was purified via silica column chromatography (eluent hexane/EtOAc mixture) to yield benzoylsilane **1**.



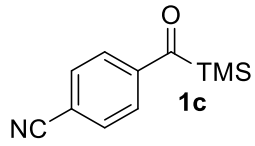
1a

Prepared according to general procedure: 91% yield (303 mg) as a yellow oil. Column eluent hexane/DCM (8:2). Obtained with same spectral characterization as previously described.[17] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.71 – 7.68 (m, 2H), 7.47 – 7.33 (m, 3H), 0.86 (s, 9H), 0.27 (s, 6H). **HRMS m/z:** $[M+H]^+$ calculated for $C_{13}H_{21}OSi^+$ 221.1356, found 221.1354.



1b

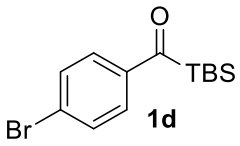
Prepared according to general procedure: 40% yield (194 mg) as a yellow amorphous sold. Column eluent hexane/EtOAc (85:15). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.71 – 7.66 (m, 2H), 6.59 – 6.54 (m, 2H), 2.95 (s, 6H), 0.86 (s, 9H), 0.25 (s, 6H). **^{13}C{1H} NMR** (75 MHz, $CDCl_3$) δ 230.5, 153.2, 132.4, 130.3, 110.7, 40.2, 27.0, 17.0, -4.2. **HRMS *m/z*:** $[M+H]^+$ calculated for $C_{15}H_{26}NOSi^+$ 264.1778, found 264.1773.



1c

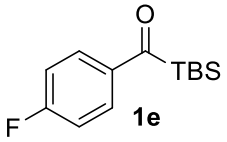
Dithiane **14c** (443 mg, 2 mmol) was dissolved in 9 mL of dry THF, in a dried, argon-filled round-bottom flask. The solution was cooled to -78 °C and *n*-BuLi (0.96 mL of 2.5M solution in hexanes, 1.2 equiv., 2.4 mmol) was added dropwise. The solution was stirred at -78 °C for ten minutes after which trimethylsilyl chloride (303 μL, 2.4 mmol, 1.2 equiv.) was added dropwise at this temperature. The solution was stirred at -78 °C for an additional ten minutes and then left warming to RT for a minimum of one hour. The reaction was quenched with 10 mL of a saturated aqueous NH_4Cl solution. The layers were separated, and the organic phase collected. The aqueous phase was extracted with MTBE (2 × 10 mL) and the organic phases combined, dried over $MgSO_4$ and filtered. The crude containing **9g** was redissolved in 12 mL of acetonitrile. Then, 4 mL of saturated aqueous $NaHCO_3$ solution was added and the mixture cooled to 0°C. Then, I_2 (5.08 g, 20 mmol, 10 equiv.) was added slowly in portions. After addition, the reaction was left at room temperature for 1 hour. Water was added (20 mL) followed by NaS_2O_3, and the mixture vigorously stirred until the dark brown color of iodine faded to give a bright yellow solution. Then, the aqueous phase was extracted with MTBE (3 × 20 mL), and the organic phases combined, dried over $MgSO_4$ and filtered. After vacuum evaporation of the solvent the crude was purified via silica column chromatography eluent hexane/EtOAc (96:4) to yield acylsilane **1c** in 54% yield (220 mg, 1.08 mmol) as a bright yellow oil. Obtained with same spectral characterization as previously

described.[20] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.89 – 7.86 (m, 2H), 7.79 – 7.76 (m, 2H), 0.38 (s, 9H).



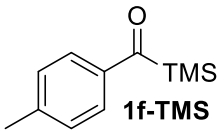
1d

Prepared according to general procedure: 87% yield (350 mg) as a yellow oil. Column eluent hexane/EtOAc (98:2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.58 – 7.48 (m, 4H), 0.85 (s, 9H), 0.26 (s, 6H). **^{13}C{1H} NMR** (75 MHz, $CDCl_3$) δ 234.7, 141.4, 132.0, 129.2, 127.8, 26.8, 17.1, -4.6. **HRMS *m/z*:** $[M+H]^+$ calculated for $C_{13}H_{20}BrOSi^+$ 299.0461, found 299.0460.



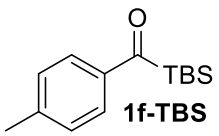
1e

Prepared according to general procedure: 87% yield (291 mg) as a yellow oil. Column eluent hexane/EtOAc (98:2). Obtained with same spectral characterization as previously described.[18] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.77 – 7.70 (m, 2H), 7.07 – 6.99 (m, 2H), 0.85 (s, 9H), 0.27 (s, 3H).



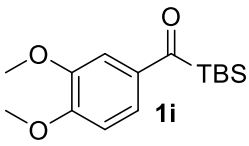
1f-TMS

Prepared according to general procedure: 99% yield (677 mg) as a yellow oil. Column eluent hexane/DCM (6:4). Obtained with same spectral characterization as previously described.[21] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.59 (d, J = 8.2 Hz, 2H), 7.13 – 7.10 (m, 2H), 2.25 (s, 3H), 0.21 (s, 9H).



1f-TBS

Prepared according to general procedure: 77% yield (1.117 g), as a yellow amorphous solid. Column eluent hexane/DCM (8:2). Obtained with same spectral characterization as previously described.[22] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.62 (d, J = 8.1 Hz, 2H), 7.16 (d, J = 7.9 Hz, 2H), 2.30 (s, 3H), 0.86 (s, 9H), 0.26 (s, 6H). **HRMS m/z:** $[M+H]^+$ calculated for $C_{14}H_{23}OSi^+$ 235.1513, found 235.1512.

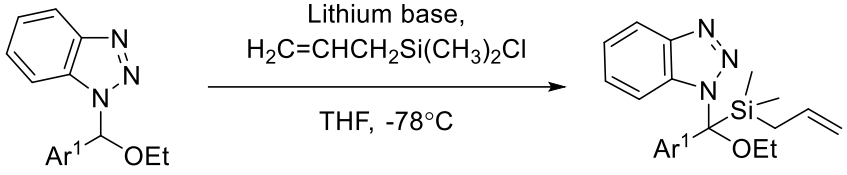


1i

Prepared according to general procedure: 90% yield (176 mg) as a yellow amorphous solid. Column eluent hexane/EtOAc (92:8). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.52 (dd, J = 8.3, 1.9 Hz, 1H), 7.36 (d, J = 1.9 Hz, 1H), 6.91 (d, J = 8.3 Hz, 1H), 3.94 (s, 3H), 3.91 (s, 3H), 0.96 (s, 9H), 0.36 (s, 6H). **^{13}C{1H} NMR** (75 MHz, $CDCl_3$) δ 232.5, 153.1, 149.3, 136.7, 124.6, 110.0, 108.0, 56.2, 55.9, 26.9, 17.0, -4.3. **HRMS m/z:** $[M+H]^+$ calculated for $C_{15}H_{25}O_3Si^+$ 281.1567, found 281.1561.

Synthesis of silyl-benzotriazole hemiaminal ethers 138:

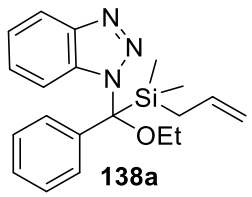
Note: Benzotriazole hemiaminal ether derivatives **137** werePrepared as previously reported[23] and used immediately after purification.



137 **138**

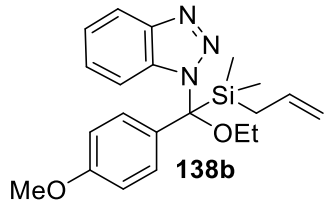
General procedure A: Benzotriazole derivative **137** (5 mmol) was dissolved in 30 mL of dry THF, in an Argon filled round-bottom flask. The solution was cooled to -78 °C with an acetone/liquid nitrogen bath. *n*-BuLi, *t*-BuLi or LDA (1.1 equiv.) was added dropwise at this temperature. After addition, the solution was left stirring for 10 minutes at -78 °C. Allyl(chloro)dimethylsilane (1.1 eq.) was then added dropwise at the same temperature. The solution was left at this temperature for 15 minutes and then slowly warmed to room temperature for one hour. The reaction was quenched with 30 mL of saturated aqueous $NaHCO_3$ and transferred to an extraction funnel. The phases were allowed to separate and the top organic phase collected. The aqueous phase was extracted with Et_2O (2 × 30 mL) and the organic phases combined, dried over $MgSO_4$ and filtered. The solvent was evaporated and the resulting crude oil purified through silica chromatography (hexane/ethyl acetate mixture as eluent) to give silyl derivatives **138** as yellow tainted clear oils.

General procedure B (used for electron rich aromatics): Benzotriazole derivative **137** (5 mmol) was dissolved in 30 mL of dry THF, in an argon filled round-bottom flask. The solution was cooled to -78 °C with an acetone/liquid nitrogen bath and allyl(chloro)dimethylsilane (1.1 eq.) added dropwise. Immediately after addition, *t*-BuLi (1.1 equiv.) was slowly added dropwise, over a period of 10 minutes. After addition, the solution was left stirring for additional 10 minutes at -78 °C and then slowly warmed to room temperature for one hour. The reaction was quenched with 30 mL of saturated aqueous $NaHCO_3$ and transferred to an extraction funnel. The phases were allowed to separate and the top organic phase collected. The aqueous phase was extracted with Et_2O (2 × 30 mL) and the organic phases combined, dried over $MgSO_4$ and filtered. The solvent was evaporated and the resulting crude oil purified through silica chromatography (hexane/ethyl acetate mixture as eluent) to give silyl derivatives **138** as yellow tainted clear oils.



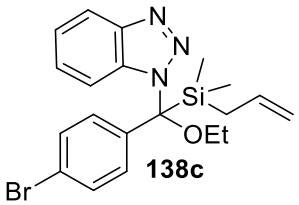
138a

Prepared according to general procedure A with *n*-BuLi as base. 86% yield (1.517 g, 4.3 mmol) as yellow tainted oil. Column eluent hexane/ethyl acetate (95:5). **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 8.06 (d, J = 8.3 Hz, 1H), 7.32 – 7.27 (m, 4H), 7.19 (t, J = 7.6 Hz, 1H), 7.03 – 7.00 (m, 2H), 6.93 (d, J = 8.3 Hz, 1H), 5.82 – 5.67 (m, 1H), 4.90 – 4.84 (m, 2H), 3.56 – 3.46 (m, 1H), 3.28 – 3.18 (m, 1H), 1.81 (t, J = 8.1 Hz, 2H), 1.12 (t, J = 6.9 Hz, 3H), 0.30 (s, 3H), 0.25 (s, 3H). **^{13}C{1H} NMR (**$CDCl_3$, 75 MHz) δ 146.5, 139.7, 134.5, 132.9, 128.2, 127.7, 127.1, 126.4, 124.2, 120.0, 114.2, 113.3, 93.7, 61.2, 22.5, 15.5, -3.0, -3.1.



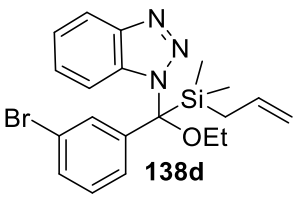
138b

Prepared according to general procedure B: 71% yield (1.362 g, 3.6 mmol) as yellow tainted oil. Column eluent hexane/ethyl acetate (92:8). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 8.05 (dt, *J* = 8.3, 0.8 Hz, 1H), 7.31 – 7.28 (m, 1.0 Hz, 1H), 7.21 – 7.18 (m, 1H), 6.98 – 6.96 (m, 1H), 6.91 (d, J = 8.2 Hz, 2H), 6.81 – 6.80 (m, 2H), 5.75 (ddt, J = 16.7, 10.1, 8.2 Hz, 1H), 4.90 – 4.85 (m, 2H), 3.79 (s, 3H), 3.53 – 3.45 (m, 1H), 3.22 – 3.16 (m, 1H), 1.85 – 1.75 (m, 2H), 1.10 (t, J = 6.9 Hz, 3H), 0.29 (s, 3H), 0.24 (s, 3H). **^{13}C{1H} NMR (**$CDCl_3$, 125 MHz) δ 159.0, 146.5, 134.6, 132.8, 131.7, 127.6, 127.0, 124.2, 119.9, 114.1, 113.4, 113.4, 93.6, 61.1, 55.3, 22.5, 15.6, -3.0, -3.1.



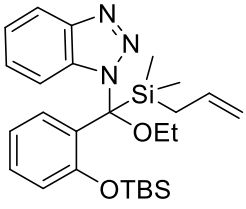
138c

Prepared according to general procedure A with LDA as base. 87% yield (1.862 g, 4.3 mmol) as yellow tainted oil. Column eluent hexane/ethyl acetate (96:4). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 8.07– 8.05 (m, 1H), 7.41 – 7.40 (m, 2H), 7.33 – 7.30 (m, 1H), 7.25 –7.21 (m, 1H), 6.97 (dt, J = 8.3, 0.9 Hz, 1H), 6.88 (d, J = 7.8 Hz, 2H), 5.79 – 5.70 (m, 1H), 4.91 – 4.87 (m, 2H), 3.55 (dq, J = 8.6, 6.9 Hz, 1H), 3.16 (dq, J = 8.6, 7.1 Hz, 1H), 1.85 – 1.74 (m, 2H), 1.11 (t, J = 6.9 Hz, 3H), 0.29 (s, 3H), 0.25 (s, 3H). **^{13}C{1H} NMR (**$CDCl_3$, 125 MHz) δ 146.6, 139.1, 134.1, 132.5, 131.3, 128.1, 127.4, 124.4, 121.8, 120.1, 114.5, 113.0, 93.4, 61.4, 22.4, 15.5, -3.1, -3.1.



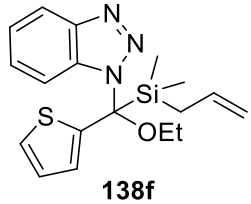
138d

Prepared according to general procedure A with LDA as base. 89% yield (1.910 g, 4.4 mmol) as yellow tainted oil. Column eluent hexane/ethyl acetate (96:4). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 8.07 (d, J = 8.4 Hz, 1H), 7.41–7.40 (m, 2H), 7.34 – 7.31 (m, 1H), 7.26 – 7.23 (m, 1H), 7.10 (t, J = 8.1 Hz, 1H), 7.01 (d, J = 8.4 Hz, 1H), 6.70 (d, J = 7.9 Hz, 1H), 5.79 – 5.71 (m, 1H), 4.92 – 4.88 (m, 2H), 3.56 (dq, J = 8.7, 6.9 Hz, 1H), 3.15 (dq, J = 8.7, 7.0 Hz, 1H), 1.86 – 1.76 (m, 2H), 1.13 (t, J = 6.9 Hz, 3H), 0.31 (s, 3H), 0.27 (s, 3H). **^{13}C{1H} NMR (**$CDCl_3$, 125 MHz) δ 146.5, 142.3, 134.0, 132.5, 130.8, 129.7, 129.3, 127.4, 124.9, 124.4, 122.6, 120.1, 114.6, 113.0, 93.1, 61.4, 22.4, 15.5, -3.0, -3.1.



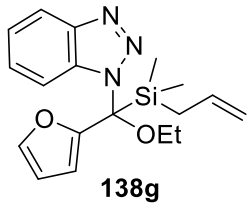
138e

Prepared according to general procedure B: 75% yield (1.817 g, 3.8 mmol) as yellow tainted oil. Column eluent hexane/ethyl acetate (96:4). Column chromatography yielded the compound with only 80% purity, which was used as such in the next synthetic step. **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 8.04 – 8.01 (m, 1H), 7.71 – 7.69 (m, 1H), 7.27 – 7.08 (m, 6H), 5.80 – 5.72 (m, 1H), 4.89 – 4.83(m, 2H), 3.18 (dq, J = 8.6, 6.9 Hz, 1H), 2.97 (dq, J = 8.7, 6.9 Hz, 1H), 1.94 – 1.82 (m, 2H), 1.02 (t, J = 6.9 Hz, 3H), 0.56 (s, 9H), 0.32 (s, 3H), 0.25 (s, 3H), -0.32 (s, 3H), -0.45 (s, 3H).



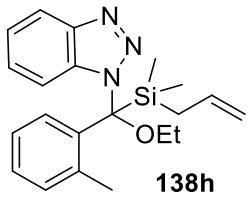
138f

Prepared according to general procedure B: 79% yield (1.418 g, 4.0 mmol) as yellow tainted oil. Column eluent hexane/ethyl acetate (96:4). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 8.06 (dt, J = 8.3, 1.0 Hz, 1H), 7.34 – 7.25 (m, 3H), 7.11 (dt, J = 8.3, 1.0 Hz, 1H), 6.90 (dd, J = 5.1, 3.7 Hz, 1H), 6.38 (dd, J = 3.6, 1.2 Hz, 1H), 5.82 – 5.73(m, 1H), 4.93 – 4.87 (m, 2H), 3.56 (dq, J = 8.6, 6.9 Hz, 1H), 3.21 (dq, J = 8.6, 7.0 Hz, 1H), 1.91 (dd, J = 13.5, 8.0 Hz, 1H), 1.83 (dd, J = 13.5, 8.3 Hz, 1H), 1.10 (t, J = 7.0 Hz, 3H), 0.38 (s, 3H), 0.33 (s, 3H). **^{13}C{1H} NMR (**$CDCl_3$, 125 MHz) δ 146.4, 144.2, 134.3, 132.7, 127.3, 127.0, 125.2, 124.4, 124.3, 120.0, 114.3, 113.1, 92.3, 61.7, 22.5, 15.5, -3.0.



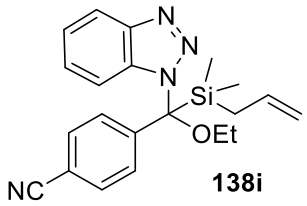
138g

Prepared according to general procedure B: 77% yield (1.321 g, 3,9 mmol) as yellow tainted oil. Column eluent hexane/ethyl acetate (96:4). **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 8.08 – 8.02 (m, 1H), 7.35 – 7.28 (m, 3H), 6.93 – 6.87 (m, 1H), 6.46 (dd, J = 3.3, 1.8 Hz, 1H), 6.38 (dd, J = 3.3, 0.7 Hz, 1H), 5.84 – 5.70 (m, 1H), 4.93 – 4.84 (m, 2H), 3.46 (dq, J = 8.6, 7.0 Hz, 1H), 3.31 (dq, J = 8.7, 6.9 Hz, 1H), 1.90 – 1.76 (m, 2H), 1.06 (t, J = 7.0 Hz, 3H), 0.30 (s, 3H), 0.25 (s, 3H). **^{13}C{1H} NMR (**$CDCl_3$, 75 MHz) δ 151.8, 146.1, 142.5, 134.4, 134.0, 127.6, 124.1, 120.0, 114.1, 112.2, 110.9, 108.6, 89.8, 61.3, 22.3, 15.5, -3.5, -3.6.



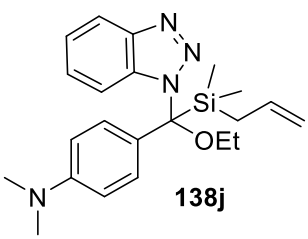
138h

Prepared according to general procedure B: 79% yield (1.439 g, 3,9 mmol) as yellow tainted oil. Column eluent hexane/ethyl acetate (96:4). **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 8.05 (d, J = 8.3 Hz, 1H), 7.32 – 7.15 (m, 5H), 7.01 (d, J = 7.5 Hz, 1H), 6.90 (d, J = 8.3 Hz, 1H), 5.83 – 5.69 (m, 1H), 4.91 – 4.85 (m, 2H), 3.40 – 3.11 (m, 1H), 3.21 – 3.11 (m, 1H), 1.96 – 1.80 (m, 2H), 1.09 (t, J = 6.9 Hz, 3H), 0.34 (s, 3H), 0.27 (s, 3H). **^{13}C{1H} NMR (**$CDCl_3$, 75 MHz) δ 146.3, 136.7, 135.2, 134.7, 133.8, 132.8, 128.1, 127.7, 127.3, 125.9, 124.2, 120.0, 114.2, 112.5, 60.8, 23.0, 15.4, -2.3, -2.6.



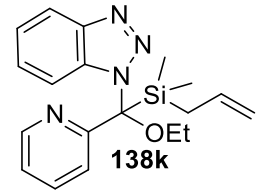
138i

Prepared according to general procedure A with LDA as base: 80% yield (1.508 g, 4.0 mmol) as yellow tainted oil. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 8.08 (dt, J = 8.3, 1.0 Hz, 1H), 7.58 (d, J = 8.8 Hz, 2H), 7.36 – 7.21 (m, 2H), 7.12 (d, J = 8.0 Hz, 2H), 6.91 (dt, J = 8.2, 1.0 Hz, 1H), 5.80 – 5.65 (m, 1H), 4.91 – 4.86 (m, 2H), 3.61 (dq, J = 8.6, 6.9 Hz, 1H), 3.16 (dq, J = 8.6, 7.0 Hz, 1H), 1.86 – 1.73 (m, 2H), 1.14 (t, J = 6.9 Hz, 3H), 0.30 (s, 3H), 0.26 (s, 3H). **^{13}C{1H} NMR (**$CDCl_3$, 75 MHz) δ 146.5, 145.4, 133.5, 132.2, 131.9, 127.5, 126.9, 124.5, 120.2, 118.5, 114.8, 112.4, 111.6, 93.3, 61.5, 22.2, 15.4, -3.1, -3.2.



138j

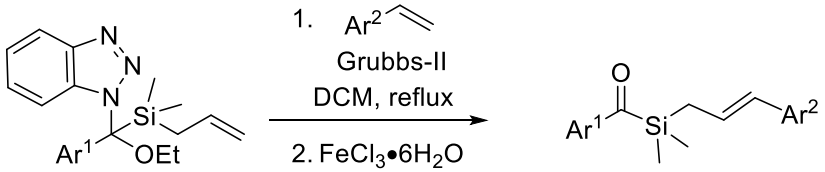
Prepared according to general procedure B: 80% yield (1.578 g, 4.0 mmol) as yellow tainted oil. Column eluent hexane/ethyl acetate/Et_3N (93:5:2). **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 8.03 (d, J = 8.3 Hz, 1H), 7.30 – 7.25 (m, 1H), 7.21 – 7.15 (m, 1H), 7.00 (d, J = 8.3 Hz, 1H), 6.84 (d, J = 8.8 Hz, 2H), 6.61 (d, J = 9.2 Hz, 2H), 5.86 – 5.70 (m, 1H), 4.90 – 4.83 (m, 2H), 3.50 – 3.41 (m, 1H), 3.30 – 3.16 (m, 1H), 2.93 (s, 6H), 1.88 – 1.76 (m, 2H), 1.09 (t, J = 6.9 Hz, 3H), 0.29 (s, 3H), 0.24 (s, 3H). **^{13}C{1H} NMR (**$CDCl_3$, 75 MHz) δ 149.8, 146.5, 134.9, 133.0, 127.2, 126.9, 126.8, 124.0, 119.8, 113.8, 113.8, 111.8, 93.8, 61.0, 40.5, 27.1, 22.6, 15.6, -3.0, -3.1.



138k

Prepared according to general procedure A using *n*-BuLi as base: 65% yield (1.143 g, 3.2 mmol) as a brown amorphous solid. Column eluent hexane/ethyl acetate/Et_3N (90:8:2). **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 8.42 – 8.39 (m, 1H), 8.04 (dt, J = 8.3, 1.0 Hz, 1H), 7.79 (td, J = 7.7, 1.8 Hz, 1H), 7.67 (dt, J = 8.0, 1.0 Hz, 1H), 7.28 – 7.11 (m, 3H), 6.58 (d, J = 8.3 Hz, 1H), 5.81 – 5.67 (m, 1H), 4.90 – 4.82 (m, 2H), 3.43 (dq, J = 8.8, 7.3 Hz, 1H), 3.27 (dq, J = 8.8, 7.0 Hz, 1H), 1.92 – 1.77 (m, 2H), 1.10 (t, J = 7.0 Hz, 3H), 0.28 (s, 3H), 0.27 (s, 3H). **^{13}C{1H} NMR (**$CDCl_3$, 75 MHz) δ 158.8, 149.2, 146.3, 136.4, 134.5, 133.3, 127.0, 123.8, 122.5, 121.6, 120.1, 114.1, 112.4, 93.5, 61.3, 22.5, 15.6, -3.1, -3.2.

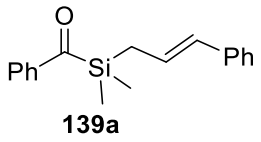
Synthesis of cinnamyl acylsilanes 139:



138 **139**

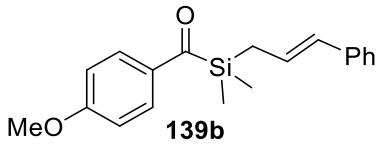
General procedure: Silyl derivative **138** (1 mmol) was dissolved in 6 mL of dry DCM, in an argon filled round-bottom flask. The substituted styrene (5 mmol, 5 equiv.) was added to the solution, followed by 2nd generation Grubbs catalyst (1-5 mol %). The solution was refluxed overnight. The solvent was evaporated and 10 mL of hexane/ethyl acetate (9:1) mixture was added. The suspension was stirred for 10

minutes and filtered through cotton. The off-white solid, mostly composed by undesired stilbene, was washed two more times with hexane/ethyl acetate (9:1) mixture (10 mL) and filtered again. The filtrate was combined and the solvents evaporated. The crude was passed through a small silica column (hexane/ethyl acetate mixture as eluent) to remove the remaining stilbene (highly mobile on silica). $FeCl_3$•$6H_2O$ (0.3 mmol, 0.3 equiv.) was added in one portion to an acetone solution (6 mL) of the resulting crude oil. The solution was stirred for 30 minutes and the solvent evaporated under reduced pressure. Hexane (6 mL) was added and the solution stirred for 10 minutes. The bright yellow liquid was filtered through cotton and the reaction flask washed with hexane (2 x 6 mL) and filtered. The filtrate was combined and the hexane evaporated to give bright yellow oil as crude, which was purified through silica chromatography (hexane/ethyl acetate mixture as eluent) to give aroylsilanes **139** as bright yellow oils.



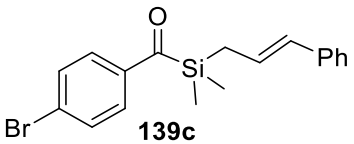
139a

Prepared according to general procedure: 53% yield (154 mg, 0.53 mmol), bright yellow oil. 1 mol% of G-II used. Column eluent hexane/ethyl acetate (96:4). **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.84 – 7.81 (m, 2H), 7.57 – 7.44 (m, 3H), 7.26 – 7.25 (m, 4H), 7.20 – 7.13 (m, 1H), 6.31 – 6.14 (m, 2H), 2.02 (d, J = 7.0 Hz, 2H), 0.42 (s, 6H). **^{13}C{1H} NMR (**$CDCl_3$, 75 MHz) δ 234.7, 141.7, 138.1, 133.0, 130.1, 128.9, 128.6, 127.8, 126.7, 125.8, 125.8, 21.8, -2.9. **HR-MS (ESI)** *m/z* calculated for $C_{18}H_{21}OSi^+$ $[M+H]^+$ 281.1356, found 281.1362.



139b

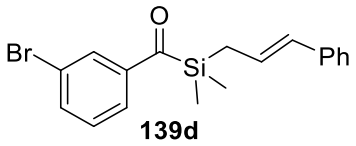
Prepared according to general procedure: 53% yield (164 mg, 0.53 mmol), pale yellow oil. 1.5 mol% of G-II used. Column eluent hexane/ethyl acetate (94:6). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.84 (dd, J = 8.7, 1.5 Hz, 2H), 7.26 (d, J = 4.2 Hz, 4H), 7.18 – 7.15 (m, 1H), 6.95 (dd, J = 8.6, 1.4 Hz, 2H), 6.30 – 6.18 (m, 2H), 3.87 (s, 3H), 2.01 (d, J = 7.7 Hz, 2H), 0.41 (s, 6H). **^{13}C{1H} NMR (**$CDCl_3$, 125 MHz) δ 231.8, 163.5, 138.1, 135.5, 130.1, 129.9, 128.6, 126.7, 126.0, 125.8, 114.0, 55.6, 21.9, -2.8. **HR-MS (ESI)** *m/z* calculated for $C_{19}H_{23}O_2Si^+$ $[M+H]^+$ 311.1462, found 311.1449.



139c

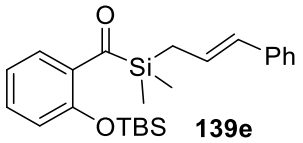
Prepared according to general procedure: 46% yield (164 mg, 0.46 mmol), bright yellow oil. 2 mol% of G-II used. Column eluent hexane/ethyl acetate (97:3). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ

7.69 (d, J = 8.5 Hz, 2H), 7.61 (d, J = 8.5 Hz, 2H), 7.29 – 7.24 (m, 4H), 7.19 – 7.16 (m, 1H), 6.27 (d, J = 15.8 Hz, 1H), 6.18 (dt, J = 15.8, 8.0 Hz, 1H), 2.01 (d, J = 8.0 Hz, 2H), 0.42 (s, 6H). **^{13}C{1H} NMR (**$CDCl_3$, 125 MHz) δ 233.6, 140.2, 137.9, 132.2, 130.2, 129.1, 128.6, 128.2, 126.8, 125.8, 125.4, 21.7, -3.0. **HR-MS (ESI)** *m/z* calculated for $C_{18}H_{20}BrOSi^+$ $[M+H]^+$ 359.0461, found 359.0474.



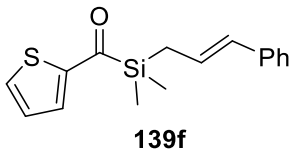
139d

Prepared according to general procedure: 37% yield (132 mg, 0.37 mmol), bright yellow oil. 2 mol% of G-II used. Column eluent hexane/ethyl acetate (97:3). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.91 (s, 1H), 7.75 (d, J = 7.7 Hz, 1H), 7.67 – 7.65 (m, 1H), 7.35 (t, J = 7.8 Hz, 1H), 7.29 – 7.25 (m, 4H), 7.19 – 7.15 (m, 1H), 6.28 (d, J = 15.8 Hz, 1H), 6.18 (dt, J = 15.8, 8.0 Hz, 1H), 2.01 (d, J = 8.0 Hz, 2H), 0.42 (s, 6H). **^{13}C{1H} NMR (**$CDCl_3$, 125 MHz) δ 233.5, 143.1, 137.9, 135.8, 130.5, 130.3, 130.2, 128.6, 126.8, 126.7, 125.8, 125.3, 123.5, 21.6, -3.0. **HR-MS (ESI)** *m/z* calculated for $C_{18}H_{20}BrOSi^+$ $[M+H]^+$ 359.0461, found 359.0483.



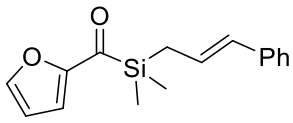
139e

Prepared according to general procedure: 42% yield (171 mg, 0.42 mmol), bright yellow oil. 2 mol% of G-II used. Column eluent hexane/ethyl acetate (96:4). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.29 – 7.22 (m, 5H), 7.17 – 7.11 (m, 2H), 6.97 (t, J = 7.4 Hz, 1H), 6.86 (d, J = 8.2 Hz, 1H), 6.21 (d, J = 15.7 Hz, 1H), 6.12 (dt, J = 15.8, 8.0 Hz, 1H), 1.92 (d, J = 7.9 Hz, 2H), 0.95 (s, 9H), 0.29 (s, 3H), 0.20 (s, 3H). **^{13}C{1H} NMR (**$CDCl_3$, 125 MHz) δ 241.8, 152.6, 138.2, 137.7, 131.5, 129.7, 128.5, 127.3, 126.6, 125.9, 125.8, 121.4, 120.6, 26.0, 21.3, 18.7, -3.8, -4.0. **HR-MS (ESI)** *m/z* calculated for $C_{24}H_{35}O_2Si_2^+$ $[M+H]^+$ 411.2170, found 411.2169.



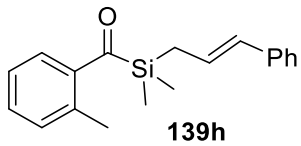
139f

Prepared according to general procedure: 36% yield (106 mg, 0.36 mmol), bright yellow oil. 2 mol% of G-II used. Column eluent hexane/ethyl acetate (97:3). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.75 – 7.74 (m, 1H), 7.66 – 7.65 (m, 1H), 7.27 (d, J = 4.3 Hz, 4H), 7.18 – 7.14 (m, 2H), 6.30 (d, J = 15.7 Hz, 1H), 6.21 (dt, J = 15.8, 7.9 Hz, 1H), 2.02 (d, J = 7.9 Hz, 2H), 0.43 (s, 6H). **^{13}C{1H} NMR (**$CDCl_3$, 125 MHz) δ 223.5, 150.9, 138.0, 133.5, 133.2, 130.1, 128.6, 128.4, 126.7, 125.8, 125.5, 21.5, -3.3. **HR-MS (ESI)** *m/z* calculated for $C_{16}H_{19}OSSi^+$ $[M+H]^+$ 287.0920, found 287.0918.



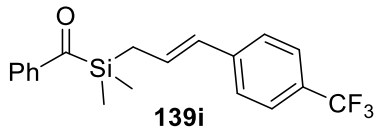
139g

Prepared according to general procedure: 39% yield (105, 0.39 mmol), bright yellow oil. 5 mol% of G-II used. Column eluent hexane/ethyl acetate (96:4). **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.61 – 7.60 (m, 1H), 7.27 (d, J = 4.0 Hz, 4H), 7.20 – 7.13 (m, 1H), 7.09 (dt, J = 3.6, 0.7 Hz, 1H), 6.54 (ddd, J = 3.6, 1.7, 0.7 Hz, 1H), 6.32 – 6.15 (m, 2H), 2.02 (d, J = 7.6 Hz, 2H), 0.39 (d, J = 0.7 Hz, 6H). **^{13}C{1H} NMR (**$CDCl_3$, 75 MHz) δ 220.2, 158.4, 146.3, 138.1, 129.9, 128.6, 126.7, 125.7, 125.6, 115.0, 112.3, 21.0, -4.1. **HR-MS (ESI)** *m/z* calculated for $C_{16}H_{19}O_2Si^+$ $[M+H]^+$ 271.1149, found 271.1143.



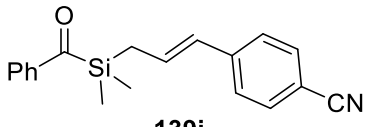
139h

Prepared according to general procedure: 59% yield (175 mg, 0.59 mmol), bright yellow oil. 2 mol% of G-II used. Column eluent hexane/ethyl acetate (98:2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.57 (dd, J = 7.5, 1.2 Hz, 1H), 7.36 – 7.32 (m, 1H), 7.30 – 7.22 (m, 6H), 7.18 – 7.14 (m, 1H), 6.25 – 6.13 (m, 2H), 2.40 (s, 3H), 1.97 (d, J = 7.5 Hz, 2H), 0.36 (s, 6H). **^{13}C{1H} NMR (**$CDCl_3$, 125 MHz) δ 241.1, 142.1, 138.1, 135.9, 132.2, 130.9, 129.9, 129.8, 128.6, 126.7, 125.7, 125.7, 125.6, 21.6, 20.7, -3.2. **HR-MS (ESI)** *m/z* calculated for $C_{19}H_{23}OSi^+$ $[M+H]^+$ 295.1513, found 295.1527.



139i

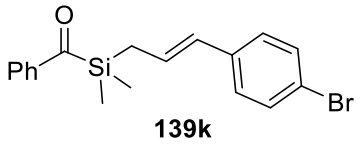
Prepared according to general procedure: 47% yield (163 mg, 0.47 mmol), bright yellow oil. 1 mol% of G-II used. Column eluent hexane/ethyl acetate (92:8). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.83 – 7.81 (m, 2H), 7.57 – 7.54 (m, 1H), 7.51 – 7.47 (m, 4H), 7.33 – 7.32 (d, J = 7.7 Hz, 2H), 6.37 – 6.27 (m, 2H), 2.06 (d, J = 7.2 Hz, 2H), 0.44 (s, 6H). **^{13}C{1H} NMR (**$CDCl_3$, 125 MHz) δ 234.4, 141.6, 141.5, 133.2, 129.0, 128.9, 128.7, 127.7, 125.8, 125.6, 125.6, 125.5, 125.5, 22.1, -2.8. **HR-MS (ESI)** *m/z* calculated for $C_{19}H_{20}F_3OSi^+$ $[M+H]^+$ 349.4477, found 349.4470.



139j

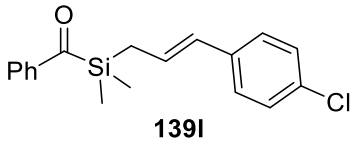
Prepared according to general procedure: 7% yield (22 mg, 0.07 mmol), bright yellow oil. 1 mol% of G-II used. Column eluent hexane/ethyl acetate (90:10). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.82 – 7.80 (m, 2H), 7.57 – 7.46 (m, 5H), 7.30 (d, J = 8.3 Hz, 2H), 6.38 (dt, J = 16.3, 8.2 Hz, 1H), 6.26 (d, J = 15.7 Hz, 1H), 2.07 (dd, J = 8.2,

0.8 Hz, 2H), 0.44 (s, 6H). **^{13}C{1H} NMR (**$CDCl_3$, 125 MHz) δ 234.1, 142.5, 141.5, 133.2, 132.4, 130.7, 128.9, 128.4, 127.6, 126.1, 119.3, 109.7, 22.4, -2.8. **HR-MS (ESI)** *m/z* calculated for $C_{19}H_{20}NOSi^+$ $[M+H]^+$ 306.1309, found 306.1315.



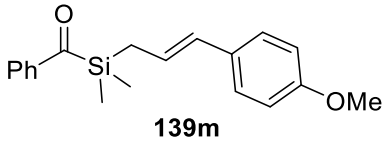
139k

Prepared according to general procedure: 55% yield (198 mg, 0.55 mmol), bright yellow oil. 1 mol% of G-II used. Column eluent hexane/ethyl acetate (97:3). **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.84 – 7.80 (m, 2H), 7.58 – 7.44 (m, 3H), 7.39 – 7.34 (m, 2H), 7.12 – 7.08 (m, 2H), 6.21 – 6.18 (m, 2H), 2.01 (dd, J = 4.8, 2.1 Hz, 2H), 0.42 (s, 6H). **^{13}C{1H} NMR (**$CDCl_3$, 75 MHz) δ 234.5, 141.6, 137.0, 133.1, 131.6, 128.9, 128.8, 127.7, 127.3, 126.8, 120.3, 21.9, -2.8. **HR-MS (ESI)** *m/z* calculated for $C_{18}H_{20}BrOSi^+$ $[M+H]^+$ 359.0461, found 359.0451.



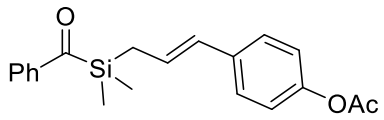
139l

Prepared according to general procedure: 83% yield (261 mg, 0.83 mmol), bright yellow oil. 1 mol% of G-II used. Column eluent hexane/ethyl acetate (97:3). **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.83 – 7.80 (m, 2H), 7.58 – 7.44 (m, 3H), 7.23 – 7.14 (m, 4H), 6.25 – 6.12 (m, 2H), 2.02 – 2.00 (m, 2H), 0.43 (s, 6H). **^{13}C{1H} NMR (**$CDCl_3$, 75 MHz) δ 234.5, 141.6, 136.5, 133.1, 132.2, 128.9, 128.8, 128.7, 127.7, 127.0, 126.7, 21.9, -2.9. **HR-MS (ESI)** *m/z* calculated for $C_{18}H_{20}ClOSi^+$ $[M+H]^+$ 315.0966, found 315.0970.



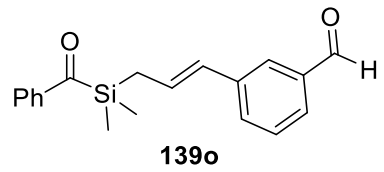
139m

Prepared according to general procedure: 30% yield (93 mg, 0.3 mmol), bright yellow oil. 1 mol% of G-II used. Column eluent hexane/ethyl acetate (95:5). **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.84 – 7.81 (m, 2H), 7.54 – 7.44 (m, 3H), 7.20 – 7.17 (m, 2H), 6.82 – 6.79 (m, 2H), 6.22 (d, J = 15.8 Hz, 1H), 6.04 (dt, J = 15.8, 8.1 Hz, 1H), 3.78 (s, 3H), 1.99 (d, J = 8.0 Hz, 2H), 0.41 (s, 6H). **^{13}C{1H} NMR (**$CDCl_3$, 75 MHz) δ 235.1, 158.7, 141.8, 133.1, 131.1, 129.6, 129.0, 127.8, 127.0, 123.5, 114.1, 55.5, 21.7, -2.8. **HR-MS (ESI)** *m/z* calculated for $C_{19}H_{23}O_2Si^+$ $[M+H]^+$ 311.1462, found 311.1464.



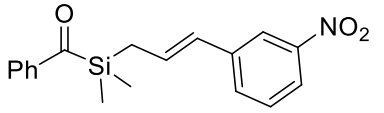
139n

Prepared according to general procedure: 26% yield (89 mg, 0.26 mmol), bright yellow oil. 1 mol% of G-II used. Column eluent hexane/ethyl acetate (85:15). **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.84 – 7.80 (m, 2H), 7.58 – 7.44 (m, 3H), 7.27 – 7.22 (m, 2H), 7.00 – 6.95 (m, 2H), 6.28 – 6.09 (m, 2H), 2.28 (s, 3H), 2.01 (d, J = 7.2 Hz, 2H), 0.42 (s, 6H). **^{13}C{1H} NMR (**$CDCl_3$, 75 MHz) δ 234.6, 169.7, 149.4, 141.6, 135.9, 133.0, 129.0, 128.9, 127.7, 126.7, 126.1, 121.6, 21.8, 21.3, -2.9. **HR-MS (ESI)** *m/z* calculated for $C_{20}H_{23}O_3Si^+$ $[M+H]^+$ 339.1411, found 339.1423.



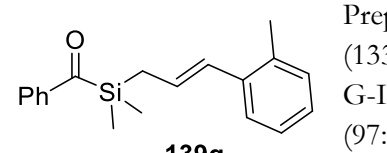
139o

Prepared according to general procedure: 43% yield (132 mg, 0.43 mmol), bright yellow oil. 1 mol% of G-II used. Gradient column eluent hexane/ethyl acetate (98:2 to 85:15). **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 9.98 (s, 1H), 7.84 – 7.39 (m, 10H), 6.34 – 6.31 (m, 2H), 2.07 – 2.05 (m, 2H), 0.44 (s, 6H). **^{13}C{1H} NMR (**$CDCl_3$, 125 MHz) δ 234.4, 192.6, 141.6, 139.0, 136.8, 133.1, 131.7, 129.3, 128.9, 128.6, 128.1, 128.0, 127. 7, 126.7, 22.0, -2.8. **HR-MS (ESI)** *m/z* calculated for $C_{19}H_{21}O_2Si^+$ $[M+H]^+$ 309.1305, found 309.1310.



139p

Prepared according to general procedure: 26% yield (84 mg, 0.26 mmol), bright yellow oil. 1 mol% of G-II used. Gradient column eluent hexane/ethyl acetate (90:10 to 85:15). **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 8.06 (t, J = 1.9 Hz, 1H), 8.01 – 7.97 (m, 1H), 7.84 – 7.81 (m, 2H), 7.58 – 7.38 (m, 5H), 6.43 – 6.26 (m, 2H), 2.07 (d, J = 7.2 Hz, 2H), 0.45 (s, 6H). **^{13}C{1H} NMR (**$CDCl_3$, 125 MHz) δ 234.1, 148.7, 141.6, 139.8, 133.2, 131.6, 129.7, 129.4, 128.9, 127.8, 127.7, 121.3, 120.3, 22.1, -2.7. **HR-MS (ESI)** *m/z* calculated for $C_{18}H_{20}NO_3Si^+$ $[M+H]^+$ 326.1207, found 326.1192.

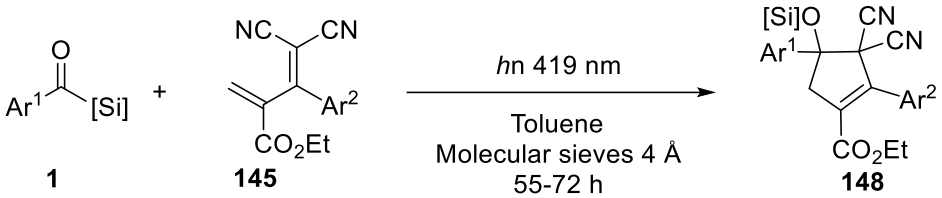


139q

Prepared according to general procedure: 45% yield (133 mg, 0.45 mmol), bright yellow oil. 1 mol% of G-II used. Column eluent hexane/ethyl acetate (97:3). **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.86 – 7.83 (m, 2H), 7.58 – 7.45 (m, 3H), 7.32 – 7.29 (m, 1H), 7.15 – 7.09 (m, 3H), 6.46 (d, J = 15.6 Hz, 1H), 6.07 (dt, J = 15.7, 8.2 Hz, 1H), 2.25

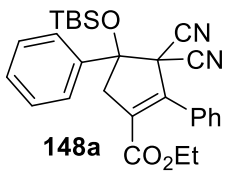
(s, 3H), 2.06 (dd, J = 8.2, 1.2 Hz, 2H), 0.44 (s, 6H). **^{13}C{1H} NMR (**$CDCl_3$, 75 MHz) δ 234.7, 141.7, 137.3, 134.7, 133.0, 130.2, 128.9, 128.1, 127.7, 127.0, 126.7, 126.1, 125.4, 22.2, 20.0, -2.9. **HR-MS (ESI)** *m/z* calculated for $C_{19}H_{23}OSi^+$ $[M+H]^+$ 295.1513, found 295.1512.

Photochemical cyclopropanation/Vinyl cyclopropane rearrangement of acylsilanes 1 with dienes 145:



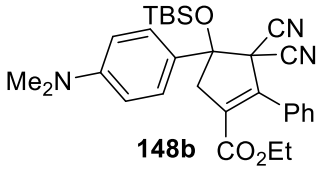
1 **145** **148**

General procedure: Acylsilane **1** (0.1 mmol) and diene **148** (0.14 mmol, 1.4 equiv.) were dissolved in 0.5 mL of dry toluene in a sealed Pasteur pipette. 100 mg of molecular sieves 4 Å were added and the solution was purged with argon for 15 minutes and irradiated at 419 nm from a minimum of 24 to maximum 72 h. Reaction progress was monitored by TLC and stopped upon full consumption of acylsilane **1**. Toluene was evaporated under reduced pressure and the crude purified via silica column chromatography (eluent hexane/EtOAc) to give cyclopentenes **148**.



148a

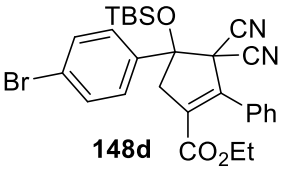
Prepared according to general procedure: 68% yield (32.1 mg) as an off-white amorphous solid. 55 h reaction. Column eluent hexane/EtOAc (94:6). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.76 – 7.73 (m, 2H), 7.49 – 7.38 (m, 8H), 4.13 (qd, J = 7.1, 1.9 Hz, 2H), 3.94 (d, J = 17.0 Hz, 2H), 3.40 (d, J = 17.0 Hz, 1H), 1.08 (t, J = 7.1 Hz, 3H), 0.94 (s, 9H), 0.02 (s, 3H), -0.22 (s, 3H). **^{13}C{1H} NMR** (75 MHz, $CDCl_3$) δ 163.4, 144.0, 138.0, 134.4, 131.6, 130.2, 129.9, 129.0, 128.6, 128.2, 126.9, 112.3, 112.2, 89.0, 61.5, 60.0, 43.0, 25.7, 18.5, 13.8, -3.3, -3.6. HRMS m/z: $[M+H]^+$ calculated for $C_{28}H_{33}N_2O_3Si$+ 473.2255, found 473.2255.



148b

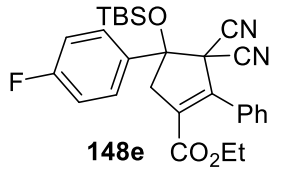
Prepared according to general procedure: 62% yield (32 mg) as an off-white amorphous solid. 48 h reaction. Column eluent hexane/DCM (65:35). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.55 (d, J = 8.9 Hz, 2H), 7.45 – 7.37 (m, 5H), 6.73 (d, J = 9.0 Hz, 2H), 4.11 (qd, J = 7.1, 2.1 Hz, 2H), 3.87 (d, J = 17.0 Hz, 1H), 3.33 (d, J = 17.0 Hz, 1H), 3.01 (s, 6H), 1.07 (t, J

= 7.1 Hz, 3H), 0.93 (s, 9H), -0.00 (s, 3H), -0.17 (s, 3H). **^{13}C{1H} NMR** (75 MHz, $CDCl_3$) δ 163.7, 151.2, 144.2, 134.5, 131.9, 129.7, 128.5, 128.2, 128.0, 124.8, 112.7, 112.5, 111.8, 89.3, 61.3, 60.3, 43.3, 40.2, 25.7, 18.5, 13.8, -3.3, -3.5. **HRMS m/z:** $[M+H]^+$ calculated for $C_{30}H_{38}N_3O_3Si^+$ 516.26770, found 516.2670.



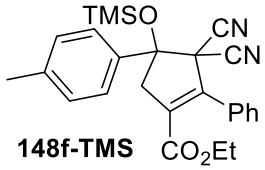
148d

Prepared according to general procedure: 66% yield (36.5 mg) as an off-white amorphous solid. 55 h reaction. Column eluent hexane/EtOAc (90:10). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.62 (s, 4H), 7.46 – 7.37 (m, 5H), 4.12 (qd, J = 7.1, 1.9 Hz, 2H), 3.87 (d, J = 17.1 Hz, 1H), 3.38 (d, J = 17.0 Hz, 1H), 1.07 (t, J = 7.1 Hz, 3H), 0.94 (s, 9H), 0.05 (s, 3H), -0.19 (s, 3H). **^{13}C{1H} NMR** (75 MHz, $CDCl_3$) δ 163.3, 143.9, 137.1, 134.2, 132.3, 131.4, 130.0, 128.6, 128.6, 128.2, 124.6, 112.0, 112.0, 88.5, 61.6, 60.0, 42.8, 25.7, 18.5, 13.8, -3.2, -3.5. **HRMS m/z:** $[M+H]^+$ calculated for $C_{28}H_{32}BrN_2O_3Si^+$ 551.1360, found 551.1361.



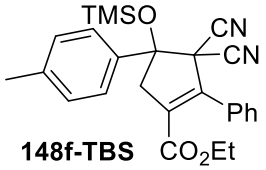
148e

Prepared according to general procedure: 66% yield (32.6 mg) as an off-white amorphous solid. 72 h reaction. Column eluent hexane/EtOAc (93:7). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.77 – 7.71 (m, 2H), 7.46 – 7.37 (m, 5H), 7.21 – 7.14 (m, 2H), 4.12 (qd, J = 7.1, 1.8 Hz, 2H), 3.89 (d, J = 17.1 Hz, 1H), 3.39 (d, J = 17.0 Hz, 1H), 1.07 (t, *J* = 7.1 Hz, 3H), 0.94 (s, 9H), 0.04 (s, 3H), -0.21 (s, 3H). **^{13}C{1H} NMR** (75 MHz, $CDCl_3$) δ 165.3, 163.3, 162.0, 144.0, 134.2, 134.1, 134.1, 131.5, 130.0, 129.1, 128.9, 128.6, 128.2, 116.2, 116.0, 112.1, 112.1, 88.5, 61.5, 60.1, 43.1, 25.7, 18.5, 13.8, -3.2, -3.5. **^{19}F{1H} NMR** (376 MHz, $CDCl_3$) δ -110.6. **HRMS m/z:** $[M]^+$ calculated for $C_{28}H_{31}FN_2O_3Si^+$ 490.2082, found 490.2082.



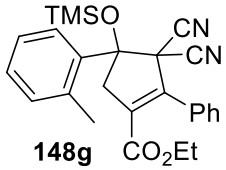
148f-TMS

Prepared according to general procedure: 66% yield (29.5 mg) as an off-white amorphous solid. 23 h reaction. Column eluent hexane/EtOAc (95:5). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.58 (d, J = 8.3 Hz, 2H), 7.45 – 7.38 (m, 5H), 7.27 (d, J = 8.0 Hz, 2H), 4.13 (q, J = 7.1 Hz, 2H), 3.88 (d, J = 17.1 Hz, 1H), 3.36 (d, J = 17.1 Hz, 1H), 2.40 (s, 3H), 1.07 (t, J = 7.1 Hz, 3H), 0.07 (s, 9H). **^{13}C{1H} NMR** (75 MHz, $CDCl_3$) δ 163.6, 143.7, 140.0, 135.2, 134.5, 131.7, 129.9, 129.6, 128.5, 128.2, 126.6, 112.4, 112.1, 89.0, 61.5, 60.6, 43.4, 21.3, 13.8, 1.3. **HRMS m/z:** $[M+H]^+$ calculated for $C_{26}H_{29}N_2O_3Si^+$ 445.1942, found 445.1942.



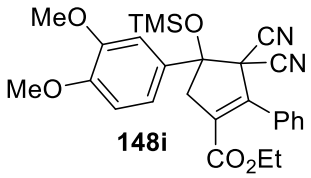
148f-TBS

Prepared according to general procedure: 74% yield (36.2 mg) as an off-white amorphous solid. 55 h reaction. Column eluent hexane/EtOAc (94:6). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.61 (d, J = 8.3 Hz, 2H), 7.46 – 7.36 (m, 5H), 7.27 (d, J = 7.9 Hz, 2H), 4.12 (qd, J = 7.1, 2.0 Hz, 2H), 3.90 (d, J = 17.1 Hz, 1H), 3.36 (d, J = 17.0 Hz, 1H), 1.07 (t, J = 7.1 Hz, 3H), 0.93 (s, 9H), 0.00 (s, 3H), -0.22 (s, 3H). **^{13}C{1H} NMR** (75 MHz, $CDCl_3$) δ 163.5, 144.1, 140.2, 135.0, 134.5, 131.7, 129.9, 129.7, 128.6, 128.2, 126.9, 112.4, 112.3, 89.0, 61.5, 60.1, 43.1, 25.7, 21.4, 18.5, 13.9, -3.3, -3.5. **HRMS m/z:** $[M+H]^+$ calculated for $C_{29}H_{35}N_2O_3Si^+$ 487.2411, found 487.2412.



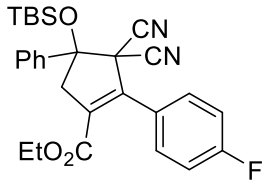
148g

Prepared according to general procedure: 40% yield (17.7 mg) as an off-white amorphous solid. 72 h reaction. Column eluent hexane/EtOAc (93:7). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.50 – 7.22 (m, 9H), 4.15 – 4.08 (m, 2H), 3.94 (d, J = 17.0 Hz, 1H), 3.50 (d, J = 17.0 Hz, 1H), 2.70 (s, 3H), 1.04 (t, J = 7.1 Hz, 3H), 0.10 (s, 9H). **^{13}C{1H} NMR** (75 MHz, $CDCl_3$) δ 163.5, 142.9, 138.9, 136.4, 135.2, 133.8, 131.6, 129.8, 129.7, 128.5, 128.3, 128.0, 126.2, 112.7, 112.3, 91.1, 61.6, 60.0, 46.2, 24.3, 13.8, 1.4. **HRMS m/z:** $[M+H]^+$ calculated for $C_{26}H_{29}N_2O_3Si^+$ 445.1942, found 445.1942.



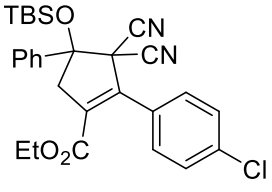
148i

Prepared according to general procedure: 80% yield (42.5 mg), off-white amorphous solid. 48 h reaction. Column eluent hexane/EtOAc (92:8). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.45 – 7.35 (m, 6H), 7.19 (dd, J = 8.4, 2.3 Hz, 1H), 6.90 (d, J = 8.4 Hz, 1H), 4.19 – 4.04 (m, 2H), 3.93 (s, 3H), 3.92 (s, 3H), 3.90 (d, J = 17.0 Hz, 1H), 3.34 (d, J = 17.0 Hz, 1H), 1.06 (t, J = 7.1 Hz, 3H), 0.95 (s, 9H), 0.03 (s, 3H), -0.18 (s, 3H). **^{13}C{1H} NMR** (75 MHz, $CDCl_3$) δ 163.5, 150.3, 149.2, 144.1, 134.3, 131.7, 130.3, 129.9, 128.6, 128.1, 119.3, 112.4, 112.3, 110.5, 110.0, 89.0, 61.4, 60.3, 56.0, 55.9, 42.9, 25.7, 18.5, 13.8, -3.3, -3.5. **HRMS m/z:** $[M+H]^+$ calculated for $C_{30}H_{37}N_2O_5Si^+$ 533.2466, found 533.2463.



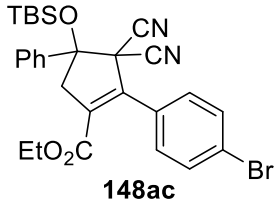
148aa

Prepared according to general procedure: 61% yield (30.2 mg) as an off-white amorphous solid. 55 h reaction. Column eluent hexane/EtOAc (93:7). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.75 – 7.71 (m, 2H), 7.49 – 7.47 (m, 3H), 7.42 – 7.38 (m, 2H), 7.19 – 7.11 (m, 2H), 4.15 (qd, J = 7.1, 2.4 Hz, 2H), 3.92 (d, J = 17.1 Hz, 1H), 3.39 (d, J = 17.0 Hz, 1H), 1.12 (t, J = 7.1 Hz, 3H), 0.93 (s, 9H), 0.00 (s, 3H), -0.23 (s, 3H). **^{13}C{1H} NMR** (75 MHz, $CDCl_3$) δ 165.3, 163.2, 162.0, 143.1, 137.8, 134.9, 130.5, 130.3, 130.3, 129.1, 127.6, 127.5, 126.9, 116.0, 115.7, 112.3, 112.1, 89.0, 61.6, 60.0, 43.0, 25.7, 18.5, 13.9, -3.3, -3.6. **^{19}F{1H} NMR** (376 MHz, $CDCl_3$) δ -110.3 **HRMS m/z:** $[M]^+$ calculated for $C_{28}H_{31}FN_2O_3Si^+$ 490.2082, found 490.2082.



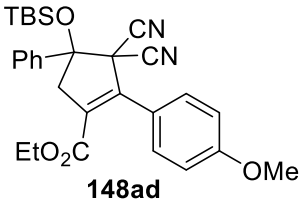
148ab

Prepared according to general procedure: 77% yield (39.1 mg) as an off-white amorphous solid. 55 h reaction. Column eluent hexane/EtOAc (92:8). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.74 – 7.71 (m, 2H), 7.50 – 7.42 (m, 5H), 7.36 – 7.33 (m, 2H), 4.15 (qd, J = 7.1, 2.3 Hz, 2H), 3.92 (d, J = 17.2 Hz, 1H), 3.39 (d, J = 17.1 Hz, 1H), 1.13 (t, J = 7.1 Hz, 3H), 0.93 (s, 9H), 0.00 (s, 3H), -0.23 (s, 3H). **^{13}C{1H} NMR** (75 MHz, $CDCl_3$) δ 163.1, 142.9, 137.8, 136.2, 135.1, 130.3, 130.0, 129.7, 129.1, 129.0, 126.9, 112.2, 112.0, 89.0, 61.7, 59.8, 43.0, 25.7, 18.5, 13.9, -3.3, -3.6. **HRMS m/z:** $[M+H]^+$ calculated for $C_{28}H_{32}ClN_2O_3Si^+$ 507.1865, found 507.1825.



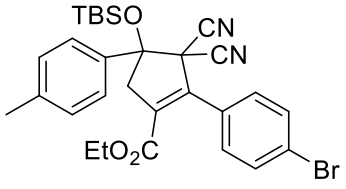
148ac

Prepared according to general procedure: 72% yield (40.0 mg) as an off-white amorphous solid. 55 h reaction. Column eluent hexane/DCM (60:40). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.62 (s, 4H), 7.46 – 7.44 (m, 3H), 7.41 – 7.36 (m, 2H), 4.12 (qd, J = 7.1, 1.9 Hz, 2H), 3.87 (d, J = 17.1 Hz, 1H), 3.38 (d, J = 17.0 Hz, 1H), 1.07 (t, J = 7.1 Hz, 3H), 0.94 (s, 9H), 0.05 (s, 3H), -0.19 (s, 3H). **^{13}C{1H} NMR** (75 MHz, $CDCl_3$) δ 163.3, 143.9, 137.1, 134.2, 132.3, 131.4, 130.0, 128.6, 128.6, 128.2, 124.6, 112.0, 112.0, 88.5, 61.6, 60.0, 42.8, 25.7, 18.5, 13.8, -3.2, -3.5. **HRMS m/z:** $[M]^+$ calculated for $C_{28}H_{31}BrN_2O_3Si^+$ 550.1282, found 550.1284.



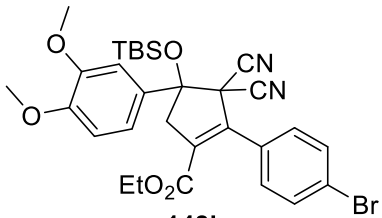
148ad

Prepared according to general procedure: 66% yield (33.2 mg) as an off-white amorphous solid. 72 h reaction. Column eluent hexane/EtOAc (90:10). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.76 – 7.72 (m, 2H), 7.50 – 7.45 (m, 3H), 7.40 – 7.35 (m, 2H), 6.99 – 6.94 (m, 2H), 4.16 (qd, J = 7.1, 2.0 Hz, 2H), 3.91 (d, J = 17.0 Hz, 1H), 3.84 (s, 3H), 3.37 (d, J = 17.0 Hz, 1H), 0.92 (s, 9H), 0.01 (s, 3H), -0.23 (s, 3H). **^{13}C{1H} NMR** (75 MHz, $CDCl_3$) δ 163.6, 160.9, 144.1, 138.0, 133.1, 130.1, 129.9, 129.0, 127.0, 123.7, 114.0, 112.6, 112.4, 88.9, 61.4, 59.9, 55.4, 43.1, 25.7, 18.5, 14.0, -3.3, -3.6. **HRMS m/z:** $[M+H]^+$ calculated for $C_{29}H_{35}N_2O_4Si^+$ 503.2361, found 503.2357.



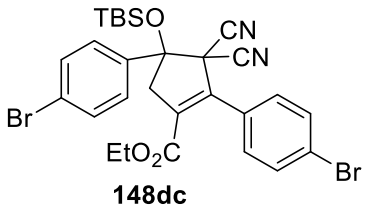
148fc

Prepared according to general procedure: 69% yield (39.0 mg), yellow amorphous solid. 48 h reaction. Column eluent hexane/EtOAc (85:15). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.57 (d, J = 8.0 Hz, 4H), 7.25 (d, J = 8.1 Hz, 4H), 4.18 – 4.07 (m, 2H), 3.87 (d, J = 17.1 Hz, 1H), 3.33 (d, J = 17.1 Hz, 1H), 2.38 (s, 3H), 1.10 (t, J = 7.1 Hz, 3H), 0.90 (s, 9H), -0.03 (s, 3H), -0.24 (s, 3H). **^{13}C{1H} NMR** (100 MHz, $CDCl_3$) δ 163.1, 142.9, 140.3, 135.1, 134.8, 131.9, 130.5, 129.9, 129.7, 126.8, 124.4, 112.2, 112.1, 89.0, 61.6, 59.8, 43.1, 25.7, 21.4, 18.4, 13.9, -3.3, -3.6. **HRMS m/z:** $[M+H]^+$ calculated for $C_{29}H_{34}BrN_2O_3Si^+$ 565.1517, found 565.1526.



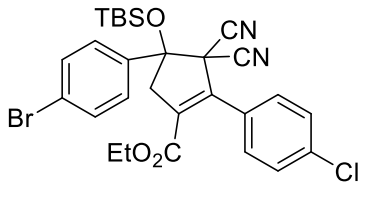
148ic

Prepared according to general procedure: 90% yield (54.8 mg), off-white amorphous solid. 48 h reaction. Column eluent hexane/EtOAc (85:15). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.61 (d, J = 8.2 Hz, 2H), 7.35 (d, J = 2.3 Hz, 1H), 7.28 (d, J = 8.3 Hz, 2H), 7.17 (dd, J = 8.4, 2.3 Hz, 1H), 6.92 (d, J = 8.4 Hz, 1H), 4.20 – 4.12 (m, 2H), 3.94 (s, 6H), 3.90 (d, J = 17.2 Hz, 1H), 3.35 (d, J = 17.1 Hz, 1H), 1.14 (t, J = 7.1 Hz, 3H), 0.95 (s, 9H), 0.04 (s, 3H), -0.16 (s, 3H). **^{13}C{1H} NMR** (100 MHz, $CDCl_3$) δ 163.1, 150.3, 149.2, 142.9, 135.0, 131.9, 130.5, 130.0, 129.8, 124.4, 119.2, 112.2, 112.1, 110.5, 109.8, 89.1, 61.6, 60.0, 56.0, 55.9, 42.8, 25.6, 18.4, 13.9, -3.4, -3.6. **HRMS m/z:** $[M+H]^+$ calculated for $C_{30}H_{36}BrN_2O_5Si^+$ 611.1571, found 611.1583.



148dc

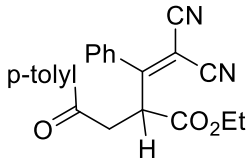
Prepared according to general procedure: 87% yield (52.4 mg), white amorphous solid. 72 h reaction. Column eluent hexane/DCM (68:32). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.63 – 7.57 (m, 6H), 7.25 (d, J = 8.3 Hz, 2H), 4.20 – 4.08 (m, 2H), 3.85 (d, J = 17.1 Hz, 1H), 3.35 (d, J = 17.1 Hz, 1H), 1.11 (t, J = 7.1 Hz, 3H), 0.91 (s, 9H), 0.02 (s, 3H), -0.21 (s, 3H). **^{13}C{1H} NMR** (100 MHz, $CDCl_3$) δ 162.9, 142.7, 136.9, 134.9, 132.3, 131.9, 130.2, 129.8, 128.5, 124.7, 124.6, 111.8 (2), 88.5, 61.8, 59.7, 42.8, 25.6, 18.4, 13.9, -3.2, -3.5. **HRMS m/z:** $[M+H]^+$ calculated for $C_{28}H_{31}Br_2N_2O_3Si^+$ 631.0445, found 631.0461.



148db

Prepared according to general procedure: 69% yield (40.6 mg), pale oil. 72 h reaction. Column eluent hexane/DCM (70:30). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.64 – 7.59 (m, 4H), 7.44 (d, J = 8.3 Hz, 2H), 7.33 (d, J = 8.3 Hz, 2H), 4.18 – 4.09 (m, 2H), 3.87 (d, J = 17.1 Hz, 1H), 3.37 (d, J = 17.1 Hz, 1H), 1.13 (t, J = 7.1 Hz, 3H), 0.93 (s, 9H), 0.03 (s, 3H), -0.20 (s, 3H). **^{13}C{1H} NMR** (100 MHz, $CDCl_3$) δ 163.0, 142.8, 136.9, 136.3, 134.9, 132.3, 129.7, 129.6, 129.0, 128.5, 124.8, 111.9 (2), 88.5, 61.8, 59.8, 42.8, 25.6, 18.4, 13.9, -3.2, -3.5. **HRMS m/z:** $[M+H]^+$ calculated for $C_{28}H_{31}BrClN_2O_3Si^+$ 585.0970, found 585.0979.

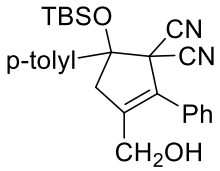
Chemical transformations of cyclopentene 148f-TBS:



151

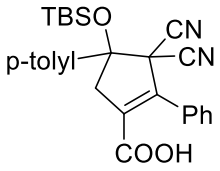
Cyclopentene **148f-TBS** (10 mg, 20 μmol) was dissolved in THF (1 mL) in a round-bottom flask. The solution was cooled to 0°C and TBAF·H_2O (7.1 mg, 23 μmol, 1.1 equiv.) was added. After 10 min at 0°C the solution was warmed to room temperature. The product was purified by silica column flash chromatography with dry loading, using hexane/EtOAc (80:20) as eluent to give **151** as an amorphous off-white solid in 78% yield (5.8 mg, 16 μmol). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.72 (d, J = 8.2 Hz, 2H), 7.51 – 7.39 (m, 3H), 7.27 – 7.20 (m, 4H), 4.83 (dd, J = 8.3, 5.5 Hz, 1H), 4.31 (q, J = 7.1 Hz, 2H), 3.74 (dd, J = 18.4, 5.5 Hz, 1H), 3.17 (dd, J = 18.4, 8.4 Hz, 1H), 2.39 (s, 3H), 1.33 (t, J = 7.1 Hz, 3H). **^{13}C{1H} NMR** (75 MHz, $CDCl_3$) δ 195.4, 175.2, 168.6,

145.0, 133.6, 133.3, 131.8, 129.6, 129.4, 128.3, 127.6, 112.4, 112.1, 90.0, 63.0, 47.9, 38.7, 21.8, 14.2. **HRMS m/z:** $[M+H]^+$ calculated for $C_{23}H_{21}N_2O_3^+$ 373.1547, found 373.1544.



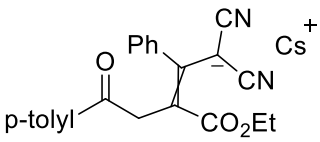
152

Cyclopentene **148f-TBS** (20 mg, 41 μmol) was dissolved in dry THF (2 mL) in a round-bottom flask and the resulting Solution cooled to 0°C. $LiBH_4$ (3 mg, 135 μmol, 3.3 equiv.) was added and the reaction warmed to room temperature. After 3 h, water (9.7 μL, 540 μmol, 13.2 equiv.) was added and the solution left stirring for 5 minutes. Then, the solvent was evaporated, and the crude purified by silica flash column chromatography, using hexane/EtOAc as eluent (80:20) to give alcohol **152** in 48% yield (8.8 mg, 20 μmol). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.61 (d, J = 8.3 Hz, 2H), 7.47 – 7.41 (m, 3H), 7.34 – 7.32 (m, 2H), 7.25 (d, J = 6.7 Hz, 2H), 4.44 – 4.33 (m, 2H), 3.76 (d, J = 17.0 Hz, 1H), 3.21 (d, J = 17.0 Hz, 1H), 2.39 (s, 3H), 0.92 (s, 9H), 0.01 (s, 3H), -0.23 (s, 3H). **^{13}C{1H} NMR** (100 MHz, $CDCl_3$) δ 144.1, 139.9, 135.9, 132.0, 131.5, 129.6, 129.4, 129.1, 128.6, 127.1, 113.6, 113.6, 89.2, 59.7, 58.7, 43.6, 25.8, 21.4, 18.5, -2.9, -3.4. **HRMS m/z:** $[M+H]^+$ calculated for $C_{27}H_{33}N_2O_2Si^+$ 445.2306, found 445.2304.



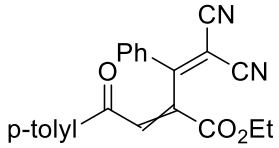
153

Cyclopentenone **148f-TBS** (6 mg, 12 μmol) was dissolved in EtOH (1 mL). LiOH (20 μL of 1 M aqueous solution, 20 μmol, 2 equiv.) was added and the solution stirred for 5 h at room temperature. Then, the solvent was evaporated and the crude purified by silica flash column chromatography, using hexane/EtOAc/AcOH (60:40:0.1) as eluent to give carboxylic acid **153** in 69% yield (3.8 mg, 8.3 μmol) **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.59 (d, J = 8.3 Hz, 2H), 7.47 – 7.39 (m, 5H), 7.27 (d, J = 6.6 Hz, 2H), 3.90 (d, J = 17.1 Hz, 1H), 3.36 (d, J = 17.0 Hz, 1H), 2.40 (s, 3H), 0.92 (s, 9H), -0.00 (s, 3H), -0.23 (s, 3H). **^{13}C{1H} NMR** (100 MHz, $CDCl_3$) δ 167.3, 146.3, 140.3, 134.8, 133.4, 131.3, 130.2, 129.8, 128.8, 128.2, 126.9, 112.2, 112.1, 88.9, 60.3, 43.2, 25.7, 21.4, 18.5, -3.2, -3.5. **HRMS m/z:** $[M+H]^+$ calculated for $C_{27}H_{31}N_2O_3Si^+$ 459.2098, found 459.2091.



154

Cyclopentene **148f-TBS** (10 mg, 20 μmol) was dissolved in dry ACN (1 mL) in an oven-dried round-bottom flask, under argon atmosphere. CsF (94 mg, 620 μmol, 30 equiv.) was added and the solution left stirring for 3 hours. The solvent was evaporated, and the crude mixture was redissolved in acetone. The solid CsF excess was filtered off through celite and the filtrate evaporated to give salt **154** as a bright yellow oil in 75% yield (7.6 mg, 15 μmol) as a 1:0.2 mixture of isomers. **154** can be converted to **151** simply via passing through silica plug. **154*major:* ^{1}H NMR** (400 MHz, $(CD_3)_2CO$) δ 7.94 (d, J = 8.2 Hz, 2H), 7.28 (d, J = 7.9 Hz, 2H), 7.21 (s, 5H), 4.39 (s, 2H), 3.52 (q, J = 7.1 Hz, 2H), 2.39 (s, 3H), 0.59 (t, J = 7.1 Hz, 3H). **^{13}C{1H} NMR** (100 MHz, $(CD_3)_2CO$) δ 199.6, 169.8, 158.2, 144.9, 143.2, 136.8, 130.2, 129.7, 129.0, 127.9, 127.8, 125.2, 102.0, 58.7, 43.1, 40.2, 21.6, 14.1. **154*minor*: ^{1}H NMR** (400 MHz, $(CD_3)_2CO$) δ 7.70 (d, J = 8.2 Hz, 2H), 7.29 – 7.20 (m, 7H) 4.06 (q, J = 7.1 Hz, 2H), 3.60 (s, 2H), 2.33 (s, 3H), 1.12 (t, J = 7.1 Hz, 3H). **HRMS m/z:** $[M+2H]^+$ calculated for $C_{23}H_{21}N_2O_3Si^+$ 373.1547, found 373.1544.

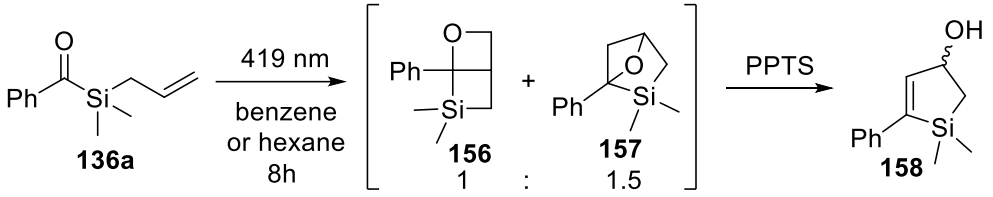


155

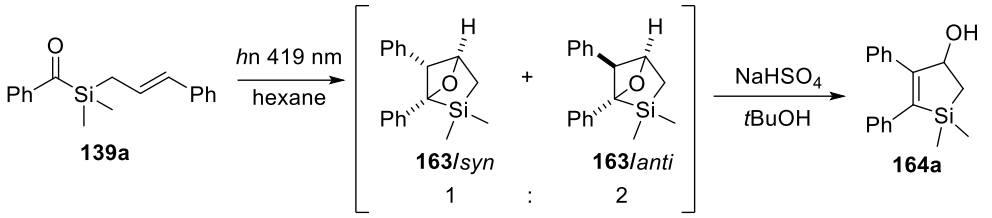
Cyclopentene **148f-TBS** (20 mg, 40 μmol) was dissolved in dry ACN (2 mL) in an oven-dried round-bottom flask, under argon atmosphere. CsF (180 mg, 1.2 mmol, 30 equiv.) was added and the solution left stirring for 3 hours. Excess CsF was filtered through celite and NBS (7.1 mg, 40 μmol, 1 equiv.) was added to the filtrate solution. The bright yellow colour of the intermediate **154** quickly faded. The solvent was quickly evaporated. Analysis of the ^{1}**H NMR** crude at this stage reveals a *E*/*Z* ratio of 0.45:1. The crude was purified by silica flash column chromatography, using hexane/EtOAc as eluent (80:20) to give diene **155** in 77% yield (11.4 mg, 31 μmol) in a *E*/*Z* ratio of 1:0.2 in thermodynamic equilibrium. **155*E*** (major): **^{1}H NMR** (400 MHz, $(CD_3)_2CO$) δ 8.41 (s, 1H), 7.96 (d, J = 8.2 Hz, 2H), 7.78 – 7.76 (m, 2H), 7.69 – 7.53 (m, 3H), 7.40 (d, J = 8.2 Hz, 2H), 4.31 (q, J = 7.1 Hz, 2H), 2.43 (s, 3H), 1.24 (t, J = 7.1 Hz, 3H). **^{13}C{1H} NMR** (100 MHz, $(CD_3)_2CO$) δ 189.1, 172.2, 163.4, 146.7, 139.8, 138.7, 134.4, 134.2, 133.6, 130.6, 130.2, 129.9, 129.8, 113.5, 113.4, 85.4, 63.6, 21.7, 14.1. **155*Z*** (minor): **^{1}H NMR** (400 MHz, $(CD_3)_2CO$) δ 7.99 – 7.39 (m, 10H), 3.96 (q, J = 7.1 Hz, 2H), 2.43 (s, 3H), 0.89 (t, *J* = 7.1 Hz, 3H). **HRMS m/z:** $[M+H]^+$ calculated for $C_{23}H_{19}N_2O_3$ 371.1390, found 371.1384. Note: Prolonged heating of the reaction crude at 40°C also delivers the same relative *E*/*Z* ratio of isomers, further confirming thermodynamic equilibrium. Identification of isomers

was conducted via analysis of the ethyl ester β-hydrogen which shows characteristic lower field shift from *trans* to *cis* conformation (relative to ester), from 7.79 to 8.41 ppm.

Photochemical [2+2] photocycloaddition of benzoyl(allyl)silanes:

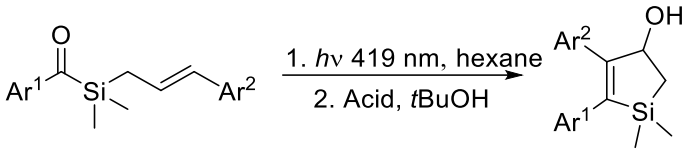


Acylsilane **136a** (50 mg, 0.245 mmol) was dissolved in dry benzene or hexane (5 mL). The solution was irradiated for 5-8h, until complete disappearance of the bright yellow colour. NMR analysis of the reaction crude at this point showed a mixture of the unstable intermediates **156** and **157**, which structures were elucidated based on spectroscopic characterization of previously reported related bicyclic structures.[24] **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.38 – 7.12 (m, 10H, **156**/**157**), 5.20 (t, J = 7.2 Hz, 1H, **156**), 4.81 (d, J = 4.6 Hz, 1H, **157**), 4.61 (dd, J = 6.4, 3.5 Hz, 1H, **156**), 3.40 – 3.33 (m, 1H, **156**), 2.90 – 2.84 (m, 1H, **157**), 2.22 (d, J = 8.3 Hz, 1H, **157**), 1.58 – 1.38 (m, 3H, **156**/**157**), 1.26 (d, J = 13.8 Hz, 1H, **157**), 0.60 (s, 3H, **156**), 0.40 (s, 3H, **157**), 0.27 (s, 3H, **156**), 0.24 (s, 3H, **157**). **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz) δ 144.5, 143.2, 128.4, 128.2, 125.9, 125.3, 123.1, 123.0, 96.3 (**156**), 89.9 (**157**), 79.3 (**156**), 79.2 (**157**), 44.6 (**157**), 42.2 (**156**), 23.5 (**157**), 17.3 (**156**), -1.3 (**156**), -3.0 (**157**), -3.0 (**156**), -4.9 (**157**).
The solution was transferred to a round-bottom flask and pyridinium *p*-toluenesulfonate (PPTSA) (65 mg, 0.257 mmol, 1.05 equiv.) was added. The reaction was stirred at room temperature for 15 minutes. The solvent was evaporated, and the product purified through alumina column chromatography, eluent hexane/ethyl acetate (80:20) to give silacyclopentenol **158** (20 mg, 0,099 mmol) as an oil in 40% yield. **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.37 – 7.30 (m, 4H), 7.25 – 7.22 (m, 1H), 6.86 (d, J = 2.3 Hz, 1H), 4.92 (s, 1H), 1.69 (s, 1H), 1.59 (dd, J = 14.6, 7.6 Hz, 1H), 0.84 (dd, J = 14.6, 5.7 Hz, 1H), 0.39 (s, 3H), 0.31 (s, 3H). **^{13}C{1H} NMR (**$CDCl_3$, 125 MHz) δ 147.3, 146.5, 139.1, 128.7, 127.3, 126.9, 126.9, 74.7, 23.7, -0.2, -1.3. **HR-MS (ESI)** *m*/*z* calculated for $C_{12}H_{15}OSi^+$ $[M]^+$ 203.0887, found 203.0905.



Acylsilane **139a** (81 mg, 0.29 mmol) was dissolved in dry hexane (7 mL) under argon atmosphere, in a glass test tube. The solution was degassed with argon (until a final volume of 6 mL) and then irradiated for 5 hours. During this time the solution's bright yellow colour disappeared to give a colourless liquid. The solution was transferred to a round-bottom flask and the hexane evaporated under reduced pressure. NMR analysis of the crude at this stage showed the presence of **163** as a 1:2 mixture of diastereoisomers. **163/***syn*: **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.60 – 6.88 (m, 10H), 5.17 (t, J = 4.8 Hz, 1H), 4.32 (d, J = 5.1 Hz, 1H), 1.53 –1.28 (m, 2H), 0.20 (s, 3H), -0.06 (s, 3H). **^{13}C{1H} NMR (**$CDCl_3$, 75 MHz) δ 141.9, 138.2, 128.7, 128.2, 127.6, 127.4, 126.8, 126.6, 94.1, 81.2, 59.19, 19.7, -1.7, -3.4. **163/***anti*: **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.39 – 6.86 (m, 10H), 4.97 (d, J = 4.3 Hz, 1H), 3.54 (s, 1H), 1.65 (dd, J = 14.0, 4.3 Hz, 1H), 1.43 (d, J = 14.0 Hz, 1H), 0.54 (s, 3H), 0.22 (s, 3H). **^{13}C{^{1}H} NMR (**$CDCl_3$, 125 MHz) δ **^{13}C{^{1}H} NMR (**$CDCl_3$, 75 MHz) δ 140.4, 138.4, 128.8, 128.1, 127.9, 126.6, 125.2, 123.2, 93.4, 84.3, 60.3, 23.3, -3.0, -4.8.

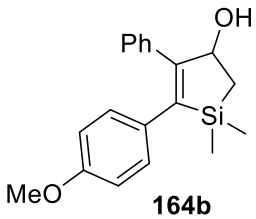
The oily crude was solubilized in *t*butanol (6 mL) at 27 °C, followed by addition of $NaHSO_4$ (0.03 mmol, 0.1 equiv.) and stirring at that temperature for 6 hours. The reaction was quenched with saturated aqueous K_2CO_3 (10 mL) and the product extracted with ethyl acetate (3 × 10 mL). The organic phases were combined, dried over $MgSO_4$ and filtered. The solvent was evaporated and the product isolated through silica column chromatography using hexane/ethyl acetate/Et_3N (90:8:2) and eluent, to give silacyclopentenol **164a** as an amorphous solid in 82% yield (66.1 mg, 0.236 mmol). **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.24 – 7.04 (m, 8H), 6.91 – 6.89 (m, 2H), 5.26 (dd, J = 7.6, 4.9 Hz, 1H), 1.81 (s, 1H), 1.61 (dd, J = 14.9, 7.7 Hz, 1H), 1.08 – 0.99 (m, 1H), 0.44 (s, 3H), 0.17 (s, 3H). **^{13}C{1H} NMR (**$CDCl_3$, 125 MHz) δ 157.2, 144.2, 140.5, 138.2, 129.1, 128.4, 128.2, 128.1, 127.3, 125.7, 77.3, 21.2, 0.1, -2.2. **HR-MS (ESI)** *m*/*z* calculated for $C_{18}H_{19}OSi^+$ $[M]^+$ 279.1200, found 279.1213.



139 **164**

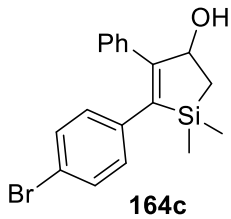
General procedure: Acylsilane **139** (0.3 mmol) was dissolved in dry hexane (7 mL) under argon atmosphere, in a glass test tube. The solution was degassed with argon (until a final volume of 6 mL) and then irradiated for 5 hours. The solution was transferred to a round-bottom flask and the hexane evaporated under reduced pressure. The residue was solubilized in *t*butanol (6 mL) at 27 °C, followed by addition of $NaHSO_4$ or PPTSA (0.03 mmol, 0.1 equiv.) and stirring at that temperature for 6 hours. The reaction was quenched with saturated aqueous K_2CO_3 (10 mL) and the product extracted with ethyl acetate (3 × 10 mL). The organic phases were combined, dried over $MgSO_4$ and filtered. The solvent was evaporated and the product isolated through silica column chromatography to give silacyclopentenol **164**.

Note: Some reactions were performed in different scale due to availability of starting material **139**.



164b

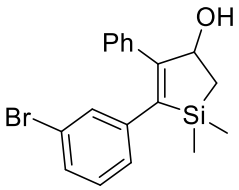
Prepared according to general procedure: 58% yield (53.8 mg, 0.172 mmol) as an amorphous solid. PPTSA used as acid. Column eluent hexane/ethyl acetate/Et_3N (83:15:2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.25 – 7.14 (m, 5H), 6.85 – 6.82 (m, 2H), 6.70 – 6.67 (m, 2H), 5.25 – 5.21 (m, 1H), 3.73 (s, 3H), 1.79 (d, J = 4.0 Hz, 1H), 1.59 (dd, J = 14.9, 7.7 Hz, 1H), 1.00 (dd, J = 14.9, 4.9 Hz, 1H), 0.45 (s, 3H), 0.18 (s, 3H). **^{13}C{1H} NMR (**$CDCl_3$, 125 MHz) δ 157.7, 156.4, 143.2, 138.5, 132.5, 129.4, 129.1, 128.5, 127.3, 113.7, 77.4, 55.2, 21.1, 0.3, -2.1. **HR-MS (ESI)** *m/z* calculated for $C_{19}H_{21}O_2Si^+$ $[M]^+$ 309.1305, found 309.1295.



164c

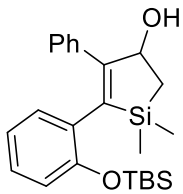
Prepared according to general procedure: 69% yield (74.3 mg, 0.207 mmol) as an amorphous solid. PPTSA used as acid. Column eluent hexane/ethyl acetate/Et_3N (84:14:2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.26 – 7.17 (m, 5H), 7.11 – 7.09 (m, 2H), 6.77 – 6.74 (m, 2H), 5.24 – 5.21 (m, 1H), 1.79 (d, J = 3.8 Hz, 1H), 1.60 (dd, J = 14.9, 7.7 Hz, 1H), 1.01 (dd, J = 14.9, 4.9 Hz, 1H), 0.41 (s, 3H), 0.15 (s, 3H). **^{13}C{1H} NMR (**$CDCl_3$,

75 MHz) δ 158.1, 143.0, 139.5, 137.8, 131.4, 129.8, 129.0, 128.5, 127.6, 119.6, 77.2, 21.2, 0.0, -2.2. **HR-MS (ESI)** *m/z* calculated for $C_{18}H_{18}BrOSi^+$ $[M]^+$ 357.0305, found 357.0317.



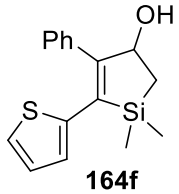
164d

Prepared according to general procedure: 59% yield (64.2 mg, 0.179 mmol) as an amorphous solid. PPTSA used as acid. Column eluent hexane/ethyl acetate/Et_3N (84:14:2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.25 – 7.19 (m, 4H), 7.12 – 7.10 (m, 2H), 7.05 (t, J = 1.8 Hz, 1H), 7.00 (t, J = 7.8 Hz, 1H), 6.79 (dt, J = 7.7, 1.3 Hz, 1H), 5.27 – 5.23 (m, 1H), 1.82 (d, J = 3.9 Hz, 1H), 1.62 (dd, J = 14.9, 7.7 Hz, 1H), 1.03 (dd, J = 14.9, 5.0 Hz, 1H), 0.44 (s, 3H), 0.18 (s, 3H). **^{13}C{1H} NMR (**$CDCl_3$, 75 MHz) δ 158.5, 142.9, 142.8, 137.6, 130.8, 129.8, 129.0, 128.7, 128.5, 127.7, 126.7, 122.3, 77.2, 21.2, -0.0, -2.2.**HR-MS (ESI)** *m/z* calculated for $C_{18}H_{18}BrOSi^+$ $[M]^+$ 357.0305, found 357.0297.



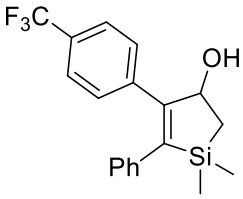
164e

Prepared according to general procedure: 50% yield (62.0 mg, 0.151 mmol) as an amorphous solid. $NaHSO_4$ used as acid. Column eluent hexane/ethyl acetate/Et_3N (90:8:2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.20 – 7.09 (m, 5H), 7.02 – 6.99 (m, 1H), 6.84 – 6.81 (m, 2H), 6.70 (d, J = 8.1 Hz, 1H), 5.38 – 5.36 (m, 1H), 1.76 (s, 1H), 1.65 (dd, J = 14.8, 7.6 Hz, 1H), 1.01 (dd, J = 14.8, 5.2 Hz, 1H), 0.90 (s, 9H), 0.34 (s, 3H), 0.15 (s, 3H), 0.12 (s, 3H), 0.00 (s, 3H). **^{13}C{1H} NMR (**$CDCl_3$, 125 MHz) δ 156.4, 137.8, 132.0, 129.5, 128.4, 128.0, 127.3, 126.6, 120.8, 118.6, 76.6, 26.1, 21.6, 18.4, -0.4, -2.1, -3.8, -4.3. **HR-MS (ESI)** *m/z* calculated for $C_{24}H_{35}O_2Si_2^+$ $[M]^+$ 411.2170, found 411.2162.



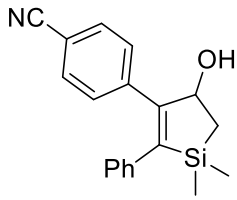
164f

Prepared according to general procedure: 85% yield (68.0 mg, 0.237 mmol) as an amorphous solid. **8o** was directly obtained without acid treatment. Column eluent hexane/ethyl acetate/Et_3N (84:14:2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.44 – 7.36 (m, 3H), 7.26 – 7.23 (m, 2H), 7.04 (dd, J = 5.1, 1.2 Hz, 1H), 6.87 – 6.85 (m, 1H), 6.82 (dd, *J* = 3.6, 1.1 Hz, 1H), 5.02 (ddd, J = 7.9, 5.2, 3.8 Hz, 1H), 1.77 (d, J = 3.8 Hz, 1H), 1.60 (dd, J = 14.9, 7.8 Hz, 1H), 1.01 (dd, J = 14.9, 5.3 Hz, 1H), 0.52 (s, 3H), 0.35 (s, 3H). **^{13}C{1H} NMR (**$CDCl_3$, 125 MHz) δ 156.4, 142.1, 139.1, 134.3, 129.2, 129.1, 128.1, 127.3, 126.3, 125.8, 78.1, 20.9, 0.1, -1.5. **HR-MS (ESI)** *m/z* calculated for $C_{16}H_{17}OSSi^+$ $[M]^+$ 285.0764, found 285.0766.



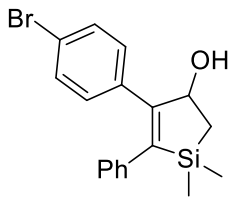
164i

Prepared according to general procedure: 79% yield (83.1 mg, 0.239 mmol) as an amorphous solid. $NaHSO_4$ used as acid. Column eluent hexane/ethyl acetate/Et_3N (83:15:2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.45 (d, J = 8.1 Hz, 2H), 7.25 (d, J = 7.9 Hz, 2H), 7.19 – 7.15 (m, 2H), 7.12 – 7.09 (m, 1H), 6.88 – 6.86 (m, 2H), 5.28 (dt, J = 7.7, 4.6 Hz, 1H), 1.71 (d, J = 4.6 Hz, 1H), 1.66 (dd, J = 14.9, 7.6 Hz, 1H), 1.03 (dd, J = 14.9, 4.9 Hz, 1H), 0.44 (s, 3H), 0.19 (s, 3H). **^{13}C{1H} NMR (**$CDCl_3$, 125 MHz) δ 155.6, 146.5, 142.2, 139.8, 129.5, 128.4, 127.9, 126.1, 125.2, 125.2, 125.2, 125.1, 77.3, 21.9, -0.1, -2.2. **HR-MS (ESI)** *m/z* calculated for $C_{19}H_{18}F_3OSi^+$ $[M]^+$ 347.1074, found 347.1060.



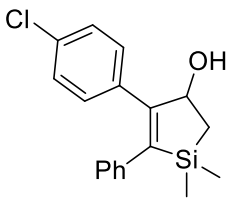
164j

Prepared according to general procedure: 64% yield (14.3 mg, 0.047 mmol) as an amorphous solid. $NaHSO_4$ used as acid. Column eluent hexane/ethyl acetate/Et_3N (68:30:2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.47 – 7.45 (m, 2H), 7.25 – 7.22 (m, 2H), 7.18 – 7.09 (m, 3H), 6.84 – 6.83 (m, 2H), 5.25 (dd, J = 7.4, 5.0 Hz, 1H), 1.69 (s, 1H), 1.66 (dd, J = 14.9, 7.6 Hz, 1H), 1.02 (dd, J = 14.9, 4.9 Hz, 1H), 0.42 (s, 3H), 0.18 (s, 3H). **^{13}C{1H} NMR (**$CDCl_3$, 125 MHz) δ 155.1, 147.6, 143.6, 139.6, 131.9, 129.9, 128.5, 127.8, 126.3, 119.1, 110.7, 77.1, 22.2, -0.2, -2.3. **HR-MS (ESI)** *m/z* calculated for $C_{19}H_{18}NOSi^+$ $[M]^+$ 304.1152, found 304.1151.



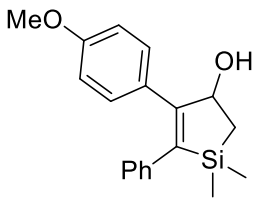
164k

Prepared according to general procedure: 73% yield (79.0 mg, 0.220 mmol) as an amorphous solid. $NaHSO_4$ used as acid. Column eluent hexane/ethyl acetate/Et_3N (82:10:2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.34 – 7.31 (m, 2H), 7.17 (ddd, J = 7.5, 6.4, 1.2 Hz, 2H), 7.12 – 7.09 (m, 1H), 7.03 – 7.00 (m, 2H), 6.89 – 6.87 (m, 2H), 5.23 (dt, J = 8.0, 4.4 Hz, 1H), 1.73 (d, J = 4.2 Hz, 1H), 1.62 (dd, J = 14.9, 7.7 Hz, 1H), 1.01 (dd, J = 14.9, 4.9 Hz, 1H), 0.43 (s, 3H), 0.17 (s, 3H). **^{13}C{1H} NMR (**$CDCl_3$, 125 MHz) δ 155.8, 145.4, 140.1, 137.1, 131.5, 130.8, 128.4, 127.9, 125.9, 121.4, 77.2, 21.6, 0.0, -2.2. **HR-MS (ESI)** *m/z* calculated for $C_{18}H_{18}BrOSi^+$ $[M]^+$ 357.0305, found 357.0297.



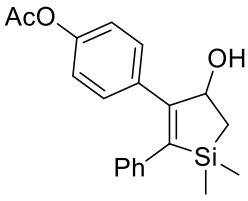
164l

Prepared according to general procedure: 63% yield (59.2 mg, 0.183 mmol) as an amorphous solid. $NaHSO_4$ used as acid. Column eluent hexane/ethyl acetate/Et_3N (90:8:2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.19 – 7.16 (m, 4H), 7.12 – 7.06 (m, 3H), 6.89 – 6.87 (m, 2H), 5.24 – 5.23 (m, 1H), 1.74 – 1.73 (m, 1H), 1.63 (dd, J = 14.9, 7.6 Hz, 1H), 1.01 (dd, J = 15.1, 4.8 Hz, 1H), 0.43 (s, 3H), 0.17 (s, 3H). **^{13}C{1H} NMR (**$CDCl_3$, 125 MHz) δ 155.8, 145.3, 140.2, 136.6, 133.1, 130.5, 128.5, 128.4, 127.9, 125.9, 77.2, 21.6, 0.0, -2.2. **HR-MS (ESI)** *m/z* calculated for $C_{18}H_{18}ClOSi^+$ $[M]^+$ 313.0810, found 313.0803.



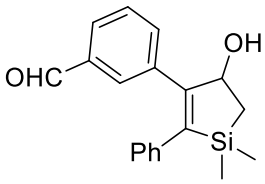
164m

Prepared according to general procedure: 60% yield (53.1 mg, 0.171 mmol) as an amorphous solid. $NaHSO_4$ used as acid. Column eluent hexane/ethyl acetate/Et_3N (86:12:2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.18 – 7.15 (m, 2H), 7.10 – 7.06 (m, 3H), 6.92 – 6.91 (m, 2H), 6.76 – 6.73 (m, 2H), 5.27 – 5.24 (m, 1H), 3.75 (s, 3H), 1.81 (s, 1H), 1.60 (dd, *J* = 14.9, 7.7 Hz, 1H), 1.01 (dd, J = 15.0, 4.9 Hz, 1H), 0.43 (s, 3H), 0.15 (s, 3H). **^{13}C{1H} NMR (**$CDCl_3$, 125 MHz) δ 158.8, 156.5, 143.2, 140.8, 130.4, 130.1, 128.3, 128.1, 125.6, 113.8, 77.1, 55.3, 21.1, 0.2, -2.2. **HR-MS (ESI)** *m/z* calculated for $C_{19}H_{21}O_2Si^+$ $[M]^+$ 309.1305, found 309.1318.



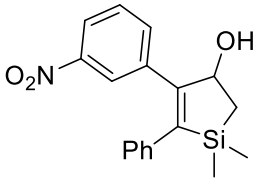
164n

Prepared according to general procedure: 71% yield (72.5 mg, 0.214 mmol) as an amorphous solid. $NaHSO_4$ used as acid. Column eluent hexane/ethyl acetate/Et_3N (78:20:2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.17 – 7.14 (m, 4H), 7.10 – 7.07 (m, 1H), 6.95 – 6.93 (m, 2H), 6.90 – 6.88 (m, 2H), 5.24 (dd, J = 7.6, 4.8 Hz, 1H), 2.26 (s, 3H), 1.82 (s, 1H), 1.60 (dd, J = 14.9, 7.7 Hz, 1H), 1.02 (dd, J = 14.9, 4.7 Hz, 1H), 0.42 (s, 3H), 0.17 (s, 3H). **^{13}C{1H} NMR (**$CDCl_3$, 125 MHz) δ 169.4, 156.0, 149.8, 144.8, 140.3, 135.7, 130.2, 128.3, 128.0, 125.8, 121.4, 77.3, 21.3, 21.3, 0.0, -2.1. **HR-MS (ESI)** *m/z* calculated for $C_{20}H_{21}O_3Si^+$ $[M]^+$ 337.1254, found 279.1268.



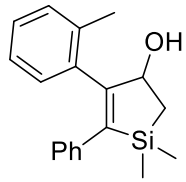
164o

Prepared according to general procedure: 84% yield (78.0 mg, 0.252 mmol) as an amorphous solid. $NaHSO_4$ used as acid. Column eluent hexane/ethyl acetate/Et_3N (78:20:2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 9.86 (s, 1H), 7.69 – 7.67 (m, 2H), 7.37 – 7.1 (m, 2H), 7.17 – 7.13 (m, 2H), 7.10 – 7.07 (m, 1H), 6.90 – 6.85 (m, 2H), 5.34 – 5.29 (m, 1H), 1.84 (s, 1H), 1.67 (dd, J = 14.9, 7.6 Hz, 1H), 1.04 (dd, J = 14.9, 4.9 Hz, 1H), 0.44 (s, 3H), 0.20 (s, 3H). **^{13}C{1H} NMR (**$CDCl_3$, 125 MHz) δ 192.4, 155.6, 146.2, 139.9, 139.4, 136.3, 135.6, 130.5, 128.9, 128.4, 128.3, 127.9, 126.0, 77.2, 21.9, -0.1, -2.2. **HR-MS (ESI)** *m/z* calculated for $C_{19}H_{19}O_2Si^+$ $[M]^+$ 307.1149, found 307.1160.



164p

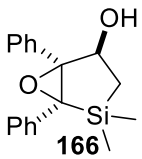
Prepared according to general procedure: 73% yield (62.4 mg, 0.192 mmol) as an amorphous solid. $NaHSO_4$ used as acid. Column eluent hexane/ethyl acetate/Et_3N (73:15:2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 8.08 – 8.07 (m, 1H), 8.01 (ddd, J = 8.2, 2.3, 1.1 Hz, 1H), 7.42 – 7.40 (m, 1H), 7.31 (t, J = 7.9 Hz, 1H), 7.19 – 7.16 (m, 2H), 7.12 – 7.09 (m, 1H), 6.88 – 6.86 (m, 2H), 5.31 (dd, J = 7.5, 4.8 Hz, 1H), 1.78 (s, 1H), 1.69 (dd, J = 14.9, 7.6 Hz, 1H), 1.05 (dd, J = 14.9, 4.9 Hz, 1H), 0.44 (s, 3H), 0.21 (s, 3H). **^{13}C{1H} NMR (**$CDCl_3$, 125 MHz) δ 154.4, 148.1, 147.6, 140.2, 139.5, 135.7, 128.9, 128.6, 127.8, 126.3, 123.9, 122.1, 77.1, 22.3, -0.3, -2.3. **HR-MS (ESI)** *m/z* calculated for $C_{18}H_{19}NO_3Si^-$ $[M]^-$ 325.1140, found 325.1136.



164q

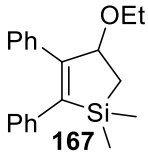
Prepared according to general procedure: 61% yield (53.5 mg, 0.182 mmol) as an amorphous solid. $NaHSO_4$ used as acid. Column eluent hexane/ethyl acetate/Et_3N (90:8:2). **^{1}H NMR** (C_6D_6, 500 MHz) δ 7.07 (dd, J = 8.2, 1.2 Hz, 2H), 7.00 – 6.96 (m, 4H), 6.92 (d, J = 7.8 Hz, 1H), 6.86 – 6.84 (m, 1H), 4.87 (s, 1H), 2.03 (s, 3H), 1.42 (dd, J = 14.8, 7.5 Hz, 2H), 1.10 (dd, J = 14.8, 4.9 Hz, 1H), 0.36 (s, 3H), 0.16 (s, 3H). **HR-MS (ESI)** *m/z* calculated for $C_{19}H_{21}OSi^+$ $[M]^+$ 293.1356, found 293.1344.

Chemical transformations of silacyclopentene 164a:



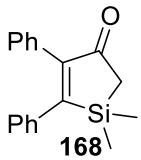
166

Silacyclopentenol **164a** (28 mg, 0.1 mmol) was dissolved in DCM (2 mL). Then, $NaHCO_3$ (20 mg, 0.24 mmol, 2.4 equiv.) was added, followed by *m*CPBA (38 mg, 0.22 mmol, 2.2 equiv.). After stirring for two hours at room temperature, the reaction was quenched with a saturated aqueous solution of Na_2SO_3 (2 mL). The layers were separated, and the organic phase collected. The aqueous phase was extracted with DCM (2 × 2 mL) and the organic fractions were combined, dried over $MgSO_4$ and filtered. The solvent was evaporated under reduced pressure to give epoxide **166** as oil in quantitative yield. **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.26 (t, J = 3.6 Hz, 2H), 7.18 (t, J = 7.4 Hz, 2H), 7.11 (dd, J = 13.1, 7.3 Hz, 3H), 7.04 – 7.00 (m, 3H), 4.97 (dd, J = 9.3, 7.8 Hz, 1H), 1.44 – 1.40 (m, 1H), 1.25 (s, 1H), 0.88 (dd, J = 14.0, 9.4 Hz, 1H), 0.36 (s, 3H), 0.30 (s, 3H). **^{13}C{1H} NMR (**$CDCl_3$, 125 MHz) δ 137.0, 134.9, 128.1, 127.9, 127.6, 127.3, 126.3, 126.3, 76.0, 74.2, 68.8, 17.4, -2.7, -5.0. **HR-MS (ESI)** *m/z* calculated for $C_{18}H_{19}OSi^+$ $[M\text{-}OH]^+$ 279.11997, obtained 279.11870.



167

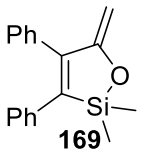
Silacyclopentenol **164a** (10 mg, 0.036 mmol) was dissolved in dry ethanol (2 mL). Then, $KHSO_4$ (10 mg, 0.073 mmol, 2 equiv.) was added and the solution was heated to 70 °C for one hour. The reaction was quenched with saturated aqueous $NaHCO_3$ (2 mL) and the product was extracted with EtOAc (3 × 2 mL). The organic phases were combined, dried over $MgSO_4$ and filtered. The solvent was evaporated, and the resulting crude purified by silica column chromatography, eluent hexane/EtOAc (97:3) to give the ether **167** in 88% yield (8.8 mg, 0.029 mmol). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.15 – 7.05 (m, 8H), 6.90 (d, J = 7.8 Hz, 2H), 4.93 (dd, J = 7.5, 4.3 Hz, 1H), 3.60 (dq, J = 14.1, 7.0 Hz, 1H), 3.41 – 3.35 (m, 1H), 1.46 (dd, J = 14.8, 7.6 Hz, 1H), 1.07 (t, J = 7.0 Hz, 3H), 1.03 – 0.99 (m, 1H), 0.39 (s, 3H), 0.18 (s, 3H). **^{13}C{1H} NMR (**$CDCl_3$, 125 MHz) δ 155.9, 144.9, 140.8, 139.0, 129.2, 128.2, 128.1, 127.6, 126.7, 125.5, 84.3, 63.8, 17.8, 15.5, -0.2, -1.8. **HR-MS (ESI)** *m/z* calculated for $C_{20}H_{23}OSi^+$ $[M\text{-}H]^+$ 307.1531, found 307.1520.



168

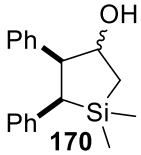
Silacyclopentenol **164a** (20 mg, 0.071 mmol) was dissolved in dry DCM (1.5 mL), under argon atmosphere. The solution was cooled to 0 °C and MnO_2 (186 mg, 2.13 mmol, 30 equiv.) was added. After stirring at 0 °C for 1 hour, the solution was filtered through celite to remove excess MnO_2. The solvent was evaporated to give pentenone

168 in quantitative yield (20 mg, 0.071 mmol). **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.27 – 7.19 (m, 6H), 7.10 – 7.07 (m, 2H), 7.04 – 7.00 (m, 2H), 2.04 (s, 2H), 0.47 (s, 6H). **^{13}C{1H} NMR (**$CDCl_3$, 75 MHz) δ 203.8, 166.1, 154.3, 138.9, 134.8, 130.2, 128.5, 128.1, 127.8, 127.7, 27.6, -2.4. **HR-MS (ESI)** *m/z* calculated for $C_{18}H_{19}OSi^+$ $[M+H]^+$ 279.11997, obtained 279.11850.



169

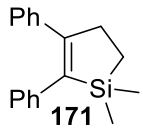
Pentenone **168** was observed to isomerize under thermal conditions to the silyl enol ether **169**, which could be isolated by passing it through a short silica column using hexane:ethyl acetate (9:1) as the eluent. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.34 – 7.30 (m, 3H), 7.20 – 7.10 (m, 5H), 6.93 – 6.89 (m, 2H), 4.67 (d, J = 1.3 Hz, 1H), 4.15 (d, J = 1.2 Hz, 1H), 0.53 (s, 6H). **^{13}C{1H} NMR (**$CDCl_3$, 75 MHz) δ 163.4, 149.5, 141.7, 137.4, 136.8, 129.8, 128.6, 128.4, 128.4, 127.6, 126.8, 91.9, -0.1. **HR-MS (ESI)** *m/z* calculated for $C_{18}H_{19}OSi^+$ $[M+H]^+$ 279.11997, obtained 279.11844.



170

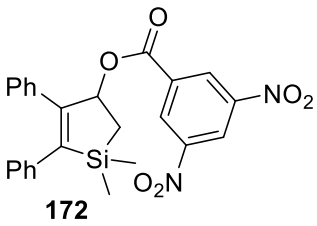
Silacyclopentenol **164a** (28 mg, 0.1 mmol) was dissolved in 1.5 mL of an ethanol/ethyl acetate mixture (3:2), under argon atmosphere, followed by addition of Pd/C (10%) (5.3 mg, 5 mol%). The argon balloon was then replaced for a hydrogen-filled balloon. The solution was stirred at room temperature for 30 min and then filtered over celite. The solvents were evaporated to give **170** as mixture of two non-isolable diastereoisomers (syn/anti = 1.4 : 1) in quantitative yield (28 mg, 0.1 mmol). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.22 – 6.73 (m, 10H+10H), 4.85 (dt, J = 11.0, 8.6 Hz, 1H/*anti*), 4.70 – 4.57 (m, 1H/*syn*), 3.74 (dd, J = 8.0, 4.6 Hz, 1H/*syn*), 3.30 (dd, J = 11.1, 7.6 Hz, 1H, *anti*), 3.00 (d, J = 8.0 Hz, 1H, *syn*), 2.71 (d, J = 7.6 Hz, 1H, *anti*), 1.77 (s, 1H,), 1.64 (dd, J = 14.7, 7.8 Hz, 1H, *anti*), 1.54 (s, 1H), 1.26 (dd, J = 14.4, 6.0 Hz, 1H/*syn*), 1.03 – 0.97 (m, 1H+1H/*syn* and *anti*), 0.40 (s, 3H, *anti*), 0.37 (s, 3H/*syn*), 0.25 (s, 3H/*syn*), 0.11 (s, 3H, *anti*). **^{13}C{1H} NMR (**$CDCl_3$, 125 MHz) δ 141.3, 141.0, 140.0, 139.0, 130.2, 130.0, 129.5, 128.5, 128.1, 128.0, 127.8, 127.8, 126.3, 126.3, 124.8, 124.2, 74.9(*syn*), 74.6(*anti*), 58.7(*anti*), 54.6(*syn*), 41.7(*anti*), 38.3(*syn*), 23.4(syn), 22.1(*anti*), 0.6(*syn*), 0.4(*anti*), -1.7(*syn*), -2.5(anti). **HR-MS (ESI)** *m/z* calculated for $C_{18}H_{21}OSi^+$ $[M-H]^+$ 281.1356, found 281.1364.

Silacyclopentenol **164a** (28 mg, 0.1 mmol) was dissolved in dry DCM (1.5 mL), under argon atmosphere. Borane catalyst $B(C_6F_5)_3$ (0.01 mmol, 10 mol%) was added to the solution, followed by dropwise addition of triethylsilane (48 μL, 0.3 mmol, 3 equiv.). The solution was left



171

stirring at room temperature for 3 hours. The solvent was evaporated, and the product purified by silica column chromatography, eluted with hexane to give **171** as a white amorphous solid in 74% yield (19.5 mg, 0,074 mmol). **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.18 – 7.04 (m, 8H), 6.93 – 6.90 (m, 2H), 3.01 – 2.96 (m, 2H), 1.02 – 0.97 (m, 2H), 0.27 (s, 6H). **^{13}C{1H} NMR (**$CDCl_3$, 75 MHz) δ 155.3, 141.6, 141.3, 140.9, 128.5, 128.3, 128.1, 127.9, 126.8, 125.1, 36.5, 9.5, -1.0.



172

Silacyclopentenol **164a** (42 mg, 0.15 mmol) was dissolved in dry DCM (2 mL). Triethylamine (27 μL, 0.19 mmol, 1.3 equiv.) was added, followed by 3,5-dinitrobenzoyl chloride (42 mg, 0.18, 1.2 equiv.). Then, dimethylaminopyridine (2 mg, 0.02 mmol, 0.1 equiv.) was added. The reaction was left stirring at room temperature for 30 minutes. The reaction was quenched with water (5 mL). DCM (5 mL) was added, and the layers separated. The organic layer was collected, and the aqueous layer washed with DCM (2 × 5 mL). The organic phases were combined and dried over $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The crude was purified by silica column chromatography, eluent hexane/ethyl acetate (94:6), to give ester **172** as a white solid (55 mg. 0.12 mmol) in 77% yield. The compound was further recrystallized from hexane/DCM to give suitable crystals for X-ray diffraction analysis. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 9.12 (t, J = 2.1 Hz, 1H), 8.84 (d, J = 2.1 Hz, 2H), 7.22 – 7.07 (m, 8H), 7.00 – 6.98 (m, 2H), 6.61 (dd, J = 7.9, 5.7 Hz, 1H), 1.93 (dd, J = 14.9, 8.0 Hz, 1H), 1.20 (dd, J = 14.9, 5.6 Hz, 1H), 0.55 (s, 3H), 0.28 (s, 3H). **^{13}C{1H} NMR (**$CDCl_3$, 75 MHz) δ 162.3, 153.2, 148.6, 147.1, 139.5, 137.5, 134.5, 129.3, 128.6, 128.4, 128.2, 128.0, 127.4, 126.2, 122.2, 82.4, 19.3, -0.1, -2.4.

Anex references

[1] Firouzabadi, H.; Iranpoor, N. Iodine Catalyzes Efficient and Chemoselective Thioacetalization of Carbonyl Functions , Transthioacetalization of O , O - and S , O - Acetals and Acylals. *J. Org. Chem.* **2001**, *66*, 7527–7529.

[2] Lai, J.; Du, W.; Tian, L.; Zhao, C.; She, X.; Tang, S. Fe-Catalyzed Direct Dithioacetalization of Aldehydes with 2-Chloro-1,3-Dithiane. *Org. Lett.* **2014**, *16*, 4396–4399.

[3] Ghosh, S. S.; Martin, J. C.; Fried, J. Total Synthesis of the Methyl Ester of the 9,11-Dithia Analog of 13,14-Dehydro-PGH2. *J. Org. Chem.* **1987**, *52*, 862–876.

[4] Naik, S.; Gopinath, R.; Goswami, M.; Patel, B. K. Chemoselective Thioacetalisation and Transthioacetalisation of Carbonyl Compounds Catalysed by Tetrabutylammonium Tribromide (TBATB). *Org. Biomol. Chem.* **2004**, *2*, 1670–1677.

[5] Page, P. C. B.; Graham, A. E.; Park, B. K. A Convenient Preparation of Symmetrical and Unsymmetrical 1,2-Diketones: Application to Fluorinated Phenytoin Synthesis. *Tetrahedron Lett.* **1992**, *48*, 7265–7274.

[6] Graham, A. E. A Simple and Convenient Catalytic Procedure for the Preparation of Dithioacetals. *Synth. Commun.* **1999**, *29*, 697–703.

[7] Raffaelli, B.; Wähälä, K.; Hase, T. Asymmetric Synthesis, Stereochemistry and Rearrangement Reactions of Naturally Occurring 7'-Hydroxylignano-9,9'-Lactones. *Org. Biomol. Chem.* **2006**, *4*, 331–341.

[8] Aloup, J.-C.; Bouchaudon, J.; Farge, D.; James, C.; Deregnaucourt, J.; Hardy-Houis, M. Synthesis and Antisecretory and Antiulcer Activities of Derivatives and Analogues of 2-(2-Pyridyl)Tetrahydrothiophene-2-Carbothioamide. *J. Med. Chem.* **1987**, *30*, 24–29.

[9] Afonso, C. A. M.; Barros, M. T.; Godinho, L. S.; Maycock, C. D. Synthesis of 2,3-Dihydro-1,4-Dithiins and 2-Alkylidene-1,4-Dithianes by 1,2-Sulfur Migration in 2-(1-Hydroxyalkyl)-1,3-Dithiolanes. *Synthesis (Stuttg).* **1991**, No. 7, 575–580.

[10] Yu, C. J.; Li, R.; Gu, P. Intermolecular Schmidt Reaction of Alkyl Azides with Acyl Silanes. *Tetrahedron Lett.* **2016**, *57*, 3568–3570.

[11] Iranpoor, N.; Firouzabadi, H.; Shaterian, H. R.; Zolfigol, M. A. 2,4,4,6-Tetrabromo-2,5-Cyclohexadienone (TABCO), N-Bromosuccinimide (NBS) and Bromine as Efficient Catalysts for Dithioacetalization and Oxathioacetalization of Carbonyl Compounds and Transdithioacetalization Reactions. *Phosphorus. Sulfur. Silicon Relat. Elem.* **2002**, *177*, 1047–1071.

[12] Seebach, D.; Jones, N. R.; Corey, E. J. A New Synthetic Route to Cyclic Mono- and Diketone Derivatives via Bisthio Carbanions. *J. Org. Chem.* **1968**, *33*, 300–305.

[13] Wan, Y.; Kurchan, A. N.; Barnhurst, L. A.; Kutateladze, A. G. Direct Transformation of 1,3-Dihalides into Dithianes and Dithiepines via a Novel One-Pot Reaction with Carbon Disulfide and Sodium Borohydride. *Org. Lett.* **2000**, *2*, 1133–1135.

[14] Firouzabadi, H.; Iranpoor, N.; Hazarkhani, H. Iodine Catalyzes Efficient and Chemoselective Thioacetalization of Carbonyl Functions , Transthioacetalization of O , O - and S , O -Acetals and Acylals Protections of Carbonyl Groups as Thioacetals Are Quite Often a Necessary Requirement in the Synthesis. *J. Org. Chem.* **2001**, *66*, 7527–7529.

[15] Zhang, H.; Wang, H.; Yang, H.; Fu, H. Rhodium-Catalyzed Denitrogenative Thioacetalization of N-Sulfonyl-1,2,3-Triazoles with Disulfides: An Entry to Diverse Transformation of Terminal Alkynes. *Org. Biomol. Chem.* **2015**, *13*, 6149–6153.

[16] Uno, T.; Inokuma, T.; Takemoto, Y. NHC-Catalyzed Thioesterification of Aldehydes by External Redox Activation. *Chem. Commun.* **2012**, *48*, 1901–1903.

[17] Linghu, X.; Nicewicz, D. A.; Johnson, J. S. Tandem Carbon-Carbon Bond Constructions via Catalyzed Cyanation/Brook Rearrangement/C-Acylation Reactions of Acylsilanes. *Org. Lett.* **2002**, *4*, 2957–2960.

[18] Ishida, K.; Tobita, F.; Kusama, H. Lewis Acid-Assisted Photoinduced Intermolecular Coupling between Acylsilanes and Aldehydes: A Formal Cross Benzoin-Type Condensation. *Chem. Eur. J.* **2018**, *24*, 543–546.

[19] Ni, Z. J.; Yang, P. F.; Ng, D. K. P.; Tzeng, Y. L.; Luh, T. Y. Unified Synthesis of Vinylsilanes and Silylated Butadienes. Nickel-Catalyzed Olefination and Silylolefination of Dithioacetals. *J. Am. Chem. Soc.* **1990**, *112*, 9356–9364.

[20] Fan, D.; Liu, Y.; Jia, J.; Zhang, Z.; Liu, Y.; Zhang, W. Synthesis of Chiral α-Aminosilanes through Palladium-Catalyzed Asymmetric Hydrogenation of Silylimines. *Org. Lett.* **2019**, *21*, 1042–1045.

[21] Tongco, E. C.; Wang, Q.; Prakash, G. K. S. One-Pot Preparation of Aroylsilanes by Reductive Silylation of Methyl Benzoates. *Synth. Commun.* **1997**, *27*, 2117–2123.

[22] Lin, C. Y.; Ma, P. J.; Sun, Z.; Lu, C. D.; Xu, Y. J. Carbamoyl Anion-Initiated Cascade Reaction for Stereoselective Synthesis of Substituted α-Hydroxy-β-Amino Amides. *Chem. Commun.* **2016**, *52*, 912–915.

[23] Katritzky, A. R.; Lang, H.; Wang, Z.; Zhang, Z.; Song, H. Benzotriazole-Mediated Conversions of Aromatic and Heteroaromatic Aldehydes to Functionalized Ketones. *J.*

Org. Chem. **1995**, *60*, 7619–7624.

[24] Hammaecher, C.; Portella, C. New 6-Oxa-2-Silabicyclo[2.2.0]Hexanes by Photochemical Conversion of Acyl(Allyl)(Dimethyl)Silanes. *Chem. Commun.* **2008**, 5833.