Dissertation zur Erlangung des Doktorgrades

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CONSTRUCTION AND TRANSFORMATION OF UNSATURATED FOUR-MEMBERED CARBO- AND HETEROCYCLES AND NEW METHODS IN BORON MEDIATED OLEFINATIONS

von

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aus

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Erklärung

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Eidesstattliche Versicherung

Diese Dissertation wurde eigenständig und ohne unerlaubte Hilfe erarbeitet.

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…….

Andreas Nicolas Baumann

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Parts of this thesis have been published in peer-reviewed journals.

1. *"Highly Diastereoselective Approach to Methylenecyclopropanes via Boron-Homologation/Allylboration Sequences*" A. N. Baumann; A. Music; K. Karaghiosoff; D. Didier, *Chem. Commun.* **2016**, 12, 2529.

2. *"Unsaturated Four-Membered Rings: Efficient Strategies for the Construction of Cyclobutenes and Alkylidenecyclobutanes"* A. N. Baumann; M. Eisold; G. M. Kiefl; S. T. Emmerling; D. Didier, *Chem. Eur. J.* **2017**, *23*, 1634.

3. *"Stereoselective Sequence toward Biologically Active Fused Alkylidenecyclobutanes"* A. N. Baumann; M. Eisold; D. Didier, *Org. Lett.* **2017**, *19*, 2114.

4. *"Methods for the Synthesis of Substituted Azetines"* A. N. Baumann; M. Eisold; A. Music; G. Haas; Y. M. Kiw; D. Didier, *Org. Lett.* **2017**, *19*, 5681.

5. *"Regiodivergent Stereoselective Access to Fused Alkylideneazetidines"* A. N. Baumann; A. Music; M. Eisold; D. Didier, *J. Org. Chem.* **2018**, *83*, 783.

6. *„Oxidative Ring Contraction of Cyclobutenes: General Approach to Cyclopropylketones including Mechanistic Insights"* A. N. Baumann; F. Schüppel; M. Eisold; A. Kreppel; R. de Vivie-Riedle; D. Didier, *J. Org. Chem.* **2018**, *83*, 4905.

7. *"One-Pot Preparation of Stable Organoboronate Reagents for the Functionalization of Unsaturated Four- and Five-Membered Carbo- and Heterocycles"* A. N. Baumann; M. Eisold; A. Music; D. Didier; *Synthesis* **2018**, *50*, 3149.

8. *„Chemodivergent and Stereoselective Access to Fused Isoxazoline Azetidines and Thietanes through [3+2]-Cycloadditions"* A. N. Baumann; F. Reiners; T. Juli; D. Didier, *Org. Lett.* **2018**, *20*, 6736.

9. *"Unsaturated Four-Membered N-Heterocycles: From Synthesis to Applications"* D. Didier; A. N. Baumann; M. Eisold, *Tetrahedron Lett*. **2018**, *59*, 3975.

10. *"Single-Pot Access to Bisorganoborinates: Applications in Zweifel Olefination"* A. N. Baumann; A. Music; P. Spieß; N. Hillgert; M. Köllen; D. Didier, *Org. Lett.* **2019**, *21*, 2189.

Parts of this thesis have been presented at scientific conferences.

ESOC - 20th European Symposium of Organic Chemistry

Stereoselective Sequence toward Biologically Active Fused Alkylidenecyclobutanes (poster presentation)

Cologne, Germany, 2017.

BOSS XV - 16th Belgian Organic Synthesis Symposium

Oxidative Ring Contraction of Cyclobutenes: General Approach to Cyclopropylketones including Mechanistic Insights (poster presentation)

Brussel, Belgium, 2018.

SFB749 - Meeting at Venice International University

Thiete-Based Macromolecules – From Synthesis to Application (poster presentation)

Venice, Italy, 2019.

ESOC - 21th European Symposium of Organic Chemistry

Electrochemical Formation of Functionalized Alkenes using Tetraorganoborates (poster presentation)

Vienna, Austria, 2019.

„Phantasie ist wichtiger als Wissen, denn Wissen ist begrenzt.”

Albert Einstein

Glossary

°C	degree Celsius
app	apparent (NMR spectroscopy)
Ar	aryl
ATR	attenuated total reflection
Boc	*tert*-butyloxycarbonyl
br	broad (NMR spectroscopy)
br	broad (IR spectroscopy)
calcd	calculated
cm	centimetre
conc.	concentrated
Cp	cyclopentadienyl
Cy	cyclohexyl
δ	chemical shift (NMR spectroscopy)
d	doublet (NMR spectroscopy)
DEP	direct evaporation probe
DG	directing group
d.r.	diastereomeric ratio
E	*trans*
E^+	electrophile
EI	electron ionization
ESI	electron spray ionization
equiv.	equivalents
Et_2O	diethyl ether
EtOAc	ethyl acetate
F	Faraday
g	gram(s)
GC	gas chromatography
GCE	Glassy-Carbon-Electrode
gem	geminal
h	hour(s)
hν	photo irradiation
HRMS	high resolution mass spectrometry
i	*iso*
J	coupling constant
M	molar
K	Kelvin
LRMS	low resolution mass spectrometry
M	molar
m	medium (IR spectroscopy)
m	multiplet (NMR spectroscopy)
*m*CPBA	*meta*-chloroperoxybenzoic acid
MeCN	acetonitrile
MeI	methyl iodide
mg	milligrams
MHz	megahertz
min	minutes
µL	microliter
mL	millilitre
mm	millimetre
mmol	millimole
m.p.	melting point
Ms	methanesulfonyl
µW	microwave irradiation
$\tilde{\nu}$	wave number
n-BuLi	butyllithium
NEt_3	triethylamine
nm	nanometre
NMR	nuclear magnetic resonance
OAc	acetate
PAA	*para*-Anisaldehyde stain
Piv	pivaloyl
Ph	phenyl
PLC	preparative layer chromatography
ppm	parts per million (NMR spectroscopy)

q	quartet (NMR spectroscopy)
quint	quintet (NMR spectroscopy)
R_f	retention factor
r.t.	room temperature
s	singlet (NMR spectroscopy)
s	strong (IR spectroscopy)
s-BuLi	*sec*-butyllithium
t	triplet (NMR spectroscopy)
TBS	*tert*-butyldimethylsilyl
TFP	tri(2-furyl)phospine
THF	tetrahydrofurane
TLC	thin layer chromatography
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl
UV	ultraviolet
vs	very strong (IR spectroscopy)
vw	very weak (IR spectroscopy)
w	weak (IR spectroscopy)
Z	*cis*

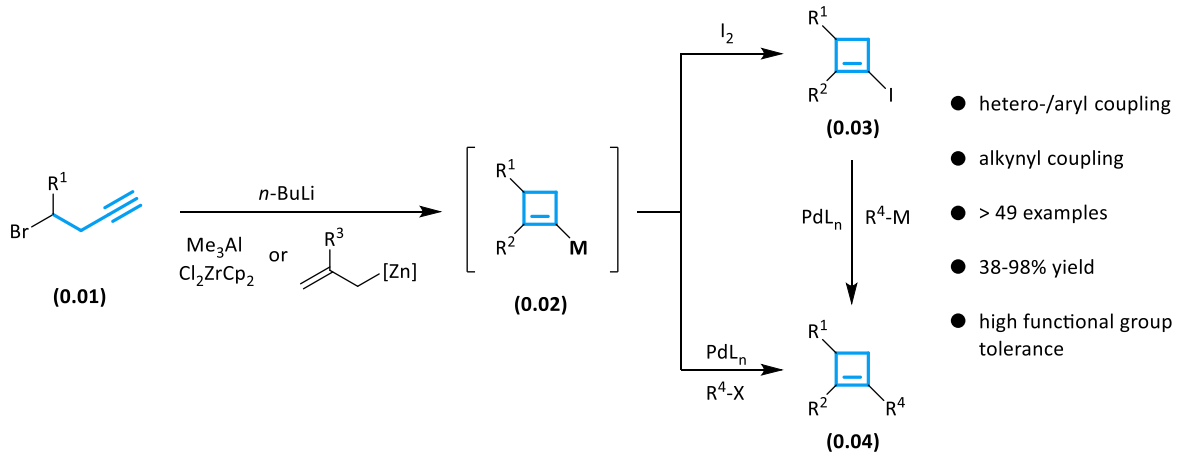
Abstract

Part A of this Ph.D. thesis describes the construction and further transformations of 4-membered unsaturated ring systems like cyclobutenes, 2-azetines and thiete dioxides. Part B presents new boron-mediated strategies in Zweifel olefinations and electrocoupling reactions.

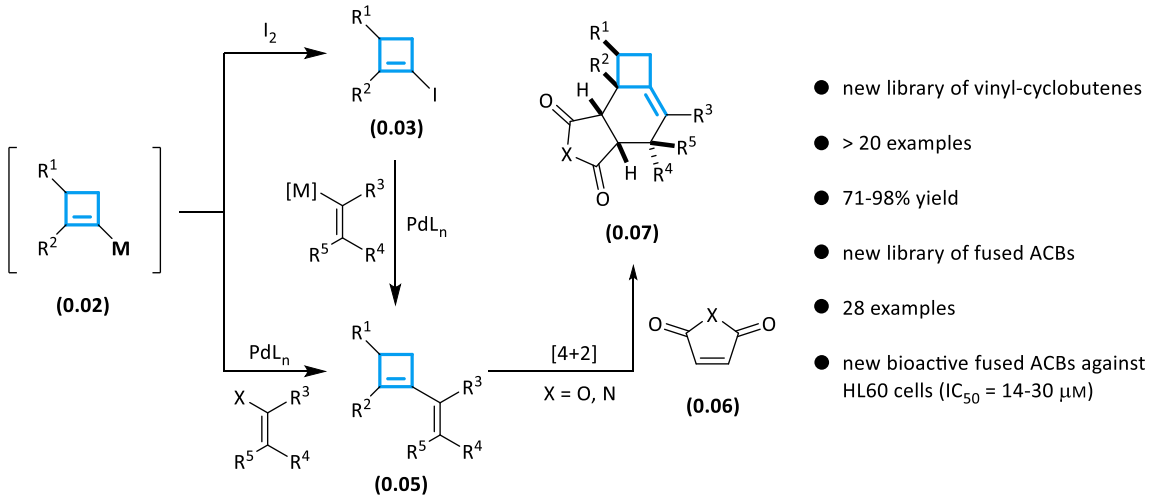
Part A

Chapter I

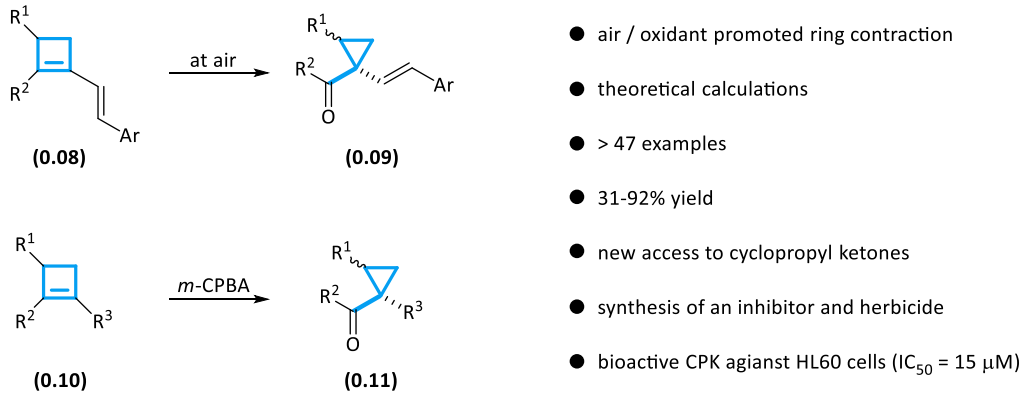
In contrast to cyclobutanes, the unsaturated variant of this important class of four-membered rings have been studied much less. Due to the strained ring structure, cyclobutenes have a unique reactivity and are therefore more difficult to access. Thus, part of this Ph.D. thesis aims to address the synthetic challenge of accessing cyclobutenes and cyclobutene-containing building blocks. Using a literature known first step, metallated cyclobutenes **0.02** could be easily accessed and were either engaged in palladium-mediated cross-coupling reactions (Suzuki-Miyaura-/Negishi cross-coupling) or converted to the corresponding iodo-cyclobutenes **0.03**. With these convenient strategies in hands, a new library of functionalized cyclobutenes **0.04** was elaborated (> 49 examples).



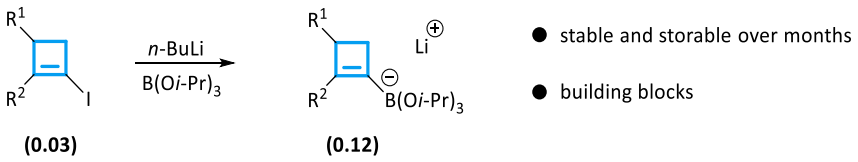
Next, a similar sequence towards vinyl-cyclobutenes **0.05** was examined. After having gained access to vinyl-cyclobutenes **0.05**, a library of alkylidenecyclobutanes (ACBs, **0.07**) was created, relying on a [4+2]-cycloaddition with activated dienophiles (**0.06**). Up to five consecutive stereocenters with great control over diastereoselectivity were constructed. Moreover, several ACBs were tested for their cytotoxicity against the leukemia cell line HL60, resulting in IC_{50} values between 14-120 μM.



Another part of this thesis focuses on an air promoted oxidative ring contraction of conjugated dienes such as **0.08** towards cyclopropyl ketones (CPKs, **0.09**). Supported by mechanistical experiments and a computational analysis of the reaction between molecular oxygen and vinylcyclobutenes **0.08**, a comprehensive overview of the mechanism was sketched. With this understanding, a universal oxidative ring contraction of cyclobutenes **0.10** with *m*-CPBA as oxidant was established and expanded to the formation of several biologically active compounds, containing the key-cyclopropyl ketone moiety.

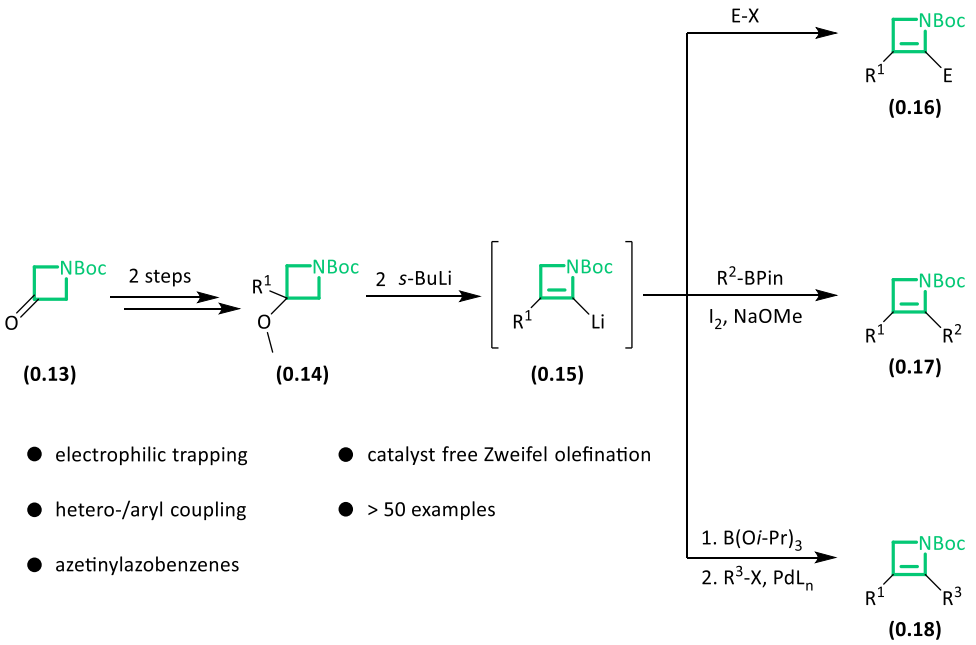


Finally, an unprecedented method for the formation of stable cyclobutene-organoborates as versatile and storable units for Suzuki-Miyaura cross-couplings was designed.



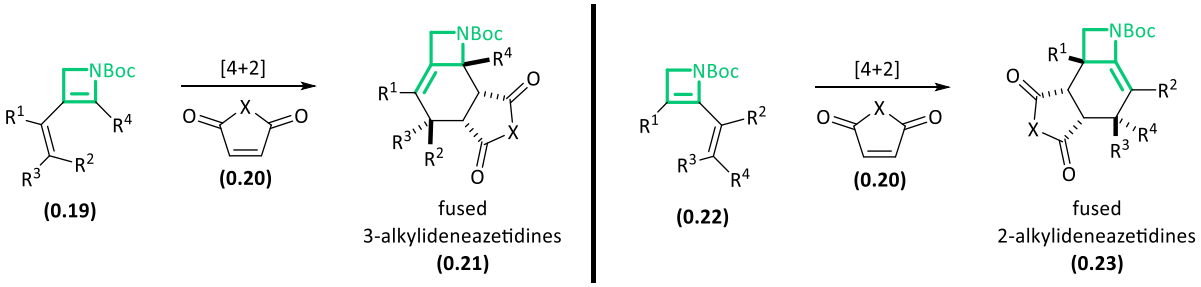
Chapter II

In contrast to the important azetidine-based β-lactams, 2-azetines have been scarcely explored, probably due to their intrinsicly higher reactivity. However, this reactivity, if used reasonably, can be exploited for the access to novel functionalized 2-azetine scaffolds. The first part of this chapter describes the straightforward synthesis of functionalized 2-azetines by an organometallic strategy.



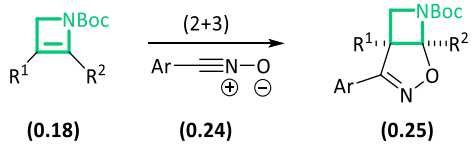
Two steps were required to access **0.14** from the commercially available 1-Boc-3-azetidinone (**0.13**). Key metallated **0.15** were obtained by simple treatment of **0.14** with two equivalents of *s*-BuLi and trapped with different electrophiles, coupled via palladium mediated Suzuki-Miyaura cross-coupling with various aromatic halides or engaged in a catalyst free Zweifel olefination. In summary, this led to a new library of more than 50 disubstituted 2-azetines (**0.16**-**0.18**).

Next, a regiodivergent and stereoselective [4+2]-cycloaddition of vinyl-azetines **0.19/0.22** with suitable dienophiles **0.20** towards unprecedented fused alkylideneazetidines **0.21/0.23** was accomplished. In a high yielding one-pot process, 26 examples were isolated in great diastereoselectivity, expanding the class of known alkylideneazetidines.



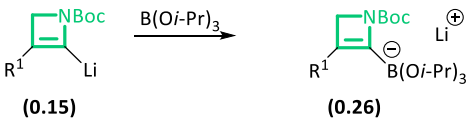
- fused alkylideneazetidines
- 26 examples
- regiodivergent and stereoselctive
- vinyl-azetidine building blocks

Following the success of those cycloadditions, a straightforward access to isoxazoline azetidines was realized, employing (2+3)-cycloadditions. Disubstituted azetines **0.18** were converted to the corresponding isoxazoline azetidines **0.25** through stereoselective and regiocontrolled (2+3)-cycloaddition with in-situ generated nitrile oxides **0.24**.



- fused isoxazoline azetidines
- up to 91%
- diastereoselective and regioselective

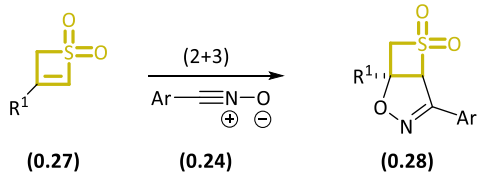
In the last part of this section, more stabilized 2-azetines were designed. The high reactivity of 2-azetinyllithium species was tempered by derivatizing it into the corresponding organoboronates **0.26**. These were stored for several months under different conditions and finally tested in Suzuki-Miyaura cross-coupling reactions. It was proven that they are most stable when kept in solution at -20 °C or neat at room temperature under inert atmosphere.



- stable for months
- storable in solution or neat
- still high yielding after months

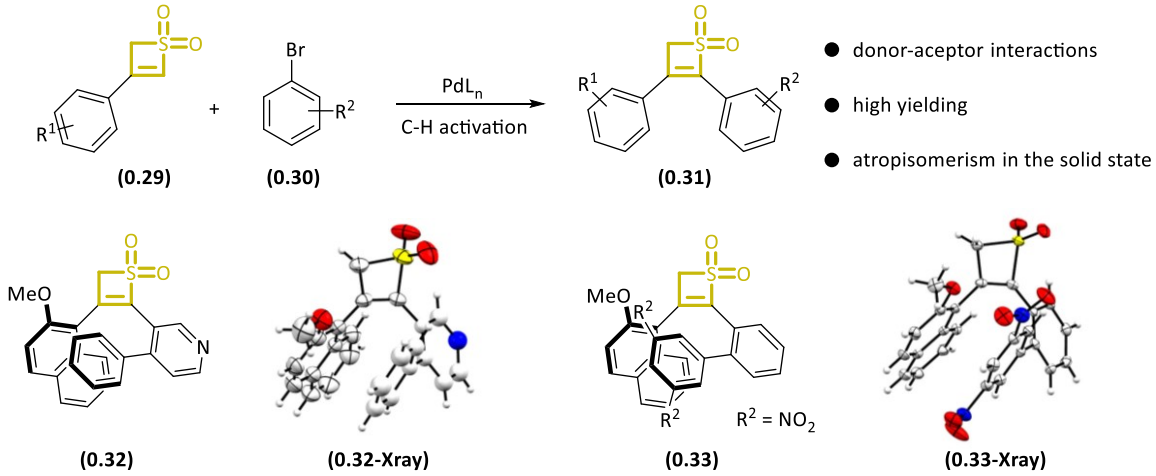
Chapter III

In this chapter, another class of 4-membered strained heterocycles was investigated, namely thiete dioxides. By using a literature known procedure based on organometallic reagents, monosubstituted thiete dioxides **0.27** were synthesized and utilized in the formation of fused, sophisticated isoxazoline thietanes. *Via* a (2+3)-cycloaddition strategy with nitrile oxides **0.24**, a new library of elaborated architectures **0.28** with excellent regio- and stereoselectivity was assembled in up to 97% yield.



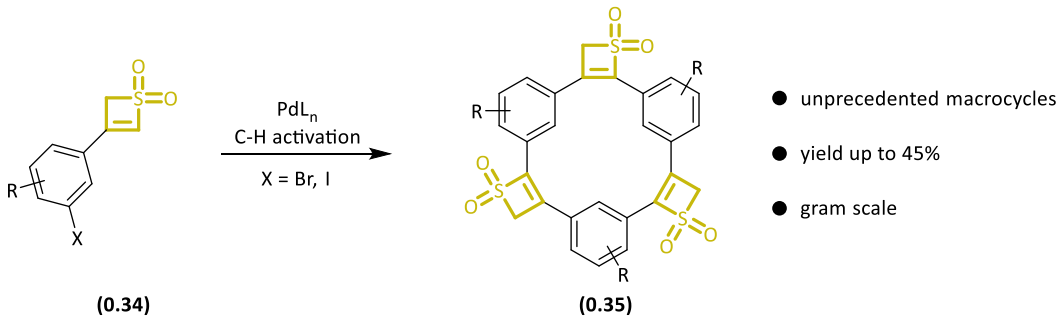
- fused isoxazoline thietanes
- high yielding up to 97%
- diastereoselective and regioselective

With the objective of developing an access to thiete-based atropisomers, C-H activation strategies – previously described in the group – were used. To reach this goal, the manipulation of the strength of π-donor-acceptor interactions between the residues of disubstituted thiete dioxides **0.31** seemed to be inevitable. Therefore, different suitable aromatic linkers were introduced by C-H activation. The corresponding crystal structures of promising thiete dioxides **0.32**/**0.33** revealed the presence of axial chirality in the solid state at room temperature.



Preliminary results on the behaviour of solvated functionalized thiete dioxides **0.31** showed, however, that the interactions responsible for atropisomerism are not strong enough to maintain chirality at ambient temperature or even at -50 °C.

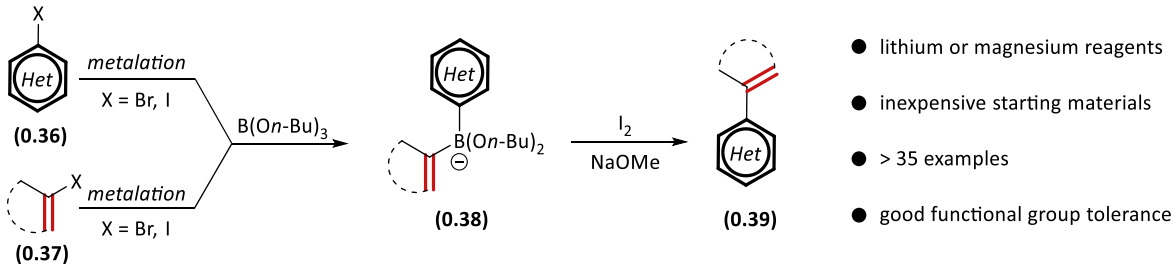
Finally, a C-H activation mediated macrocyclization of thiete dioxides is described. In this approach, C-H activation with similar congeners of mono-substituted thiete dioxides **0.34** resulted in unprecedented macrocycles **0.35** consisting of 3 thiete dioxide units.



Part B

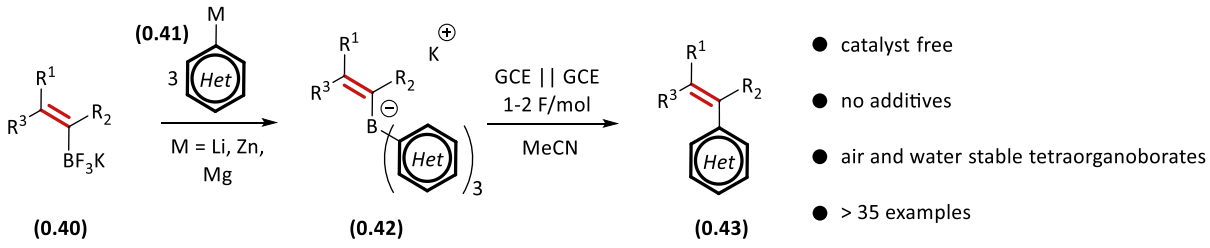
Chapter I

While the Zweifel olefination is a well-developed and explored reaction, however, most of the literature-known procedures involve the use of expensive boron pinacol esters or have a lack of practical applicability. To overcome these issues, inexpensive boron alkoxides and different organometallic reagents were used in a convergent sequence. A stoichiometrically controlled generation of bisorganoborinates **0.38** through a consecutive reaction of two different organometallic species with tri(*n*-butyl) borate led to a versatile and easily applicable new method in Zweifel olefinations.



Chapter II

In the last chapter of this Ph.D. thesis, the previously described Zweifel reaction of Chapter I (Part B) is revisited through an electrochemical approach. For this purpose, a new sequence towards mixed tetraorganoborates was engineered. Starting from commercially available potassium alkenyltrifluoroborates **0.40** followed by a treatment with various (hetero)aryl Grignard reagents **0.41**, air and water stable potassium alkenyl(hetero)triarylborates **0.42** were obtained.



After an electrochemical oxidation in acetonitrile, the coupled products **0.43** were isolated in moderate to good yields over two steps. It should be noted that no transition metal catalyst or any other additive is required in this unprecedented electrochemical coupling reaction.

Table of Content

Chapter III – Experimental Part

Part A

-

Construction and Transformation of Unsaturated Four-Membered Carbo- and Heterocycles

Chapter I

Cyclobutenes

1 Introduction

Cyclobutenes are four-membered carbocyclic architectures containing a double bond within the ring. The inherent ring strain is a key characteristic feature of this compound class. Due to that peculiar framework, the cyclobutenyl moiety is barely found in natural compounds compared to the naturally occurring cyclobutanes (**Figure 1**). Nevertheless, several compounds have been reported. For instance, the sesquiterpene taynudol (**1.01**), was isolated from the essential oils of the liverworts *Mylia taylorii* and 4,5-dehydro-5-deoxyarmillol (**1.02**) is a constituent of the inky cap of the fungus *Coprinus cinereus*.[1]

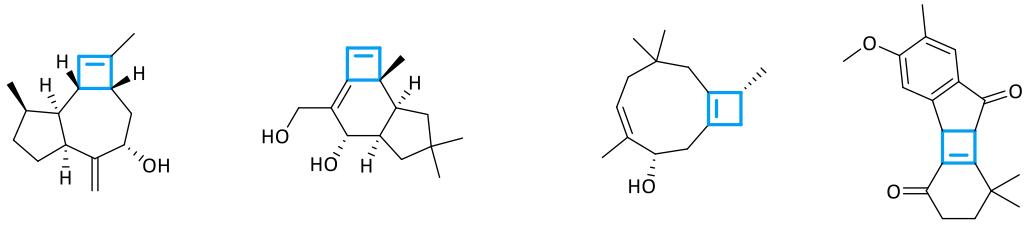


Figure 1: The cyclobutene moiety (highlighted in blue) in different natural compounds.

Further examples containing a cyclobutene pattern are capillosanol (**1.03**), which possesses a unique bicyclo[7.2.0]undecane moiety and was isolated from the soft corals *Sinularia capillosa*, and finally, neofavelanone (**1.04**), extracted and characterized from the bark of *Cnidoscolus phyllacanthus*, shows potential activity against the P-388 murine leukaemia cell line.[2]

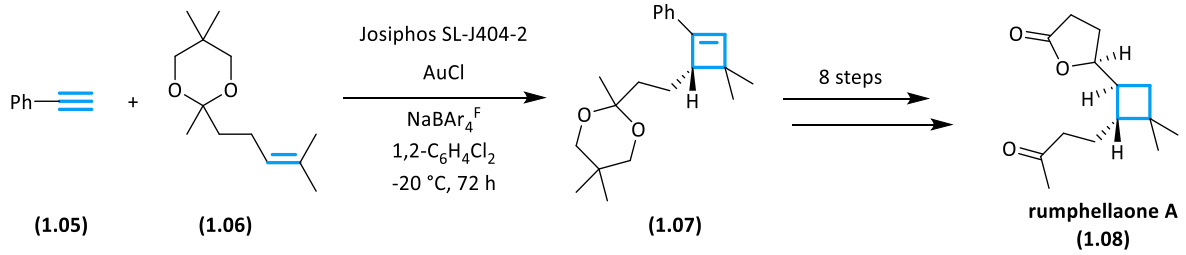
These rather complex cyclobutene-containing representatives of natural compounds clearly show the need for dependable and versatile synthetic methods toward their synthesis.

1.1 Synthesis of Cyclobutenes

Inheriting a strain-driven reactivity, cyclobutenes have served as versatile synthetic intermediates, whereupon their synthesis remain difficult.[3] The most common strategies for gaining access to the core ring are [2+2]-cycloaddition reactions, either photochemically or through metal-catalysis.[4] An

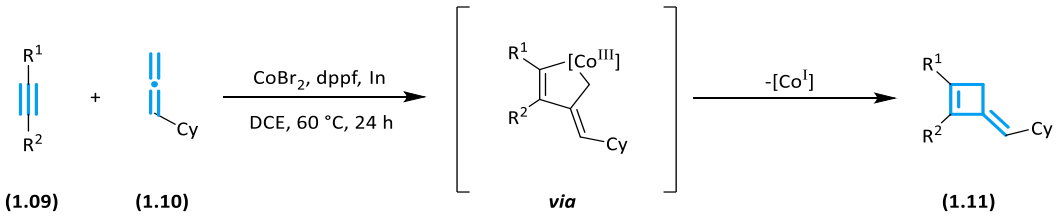
[1] S. H. Reuß; C.-L. Wu; H. Muhle; W. A. König, *Phytochemistry* **2004**, *65*, 2277; G. R. Pettit; Y. Meng; R. K. Pettit; D. L. Herald; F. Hogan; Z. A. Cichacz, *Bioorg. Med. Chem.* **2010**, *18*, 4879.
[2] S.-Y. Cheng; K.-J. Huang; S.-K. Wang; Z.-H. Wen; C.-H. Hsu; C.-F. Dai; C.-Y. Duh, *Org. Lett.* **2009**, *11*, 4830; Y. Endo; T. Ohta; S. Nozoe, *Tetrahedron Lett.* **1992**, *33*, 353.
[3] J. C. Namyslo; D. E. Kaufmann, *Chem. Rev.* **2003**, *103*, 1485.
[4] Y. Xu; M. L. Conner; M. K. Brown, *Angew. Chem. Int. Ed.* **2015**, *54*, 11918; T. Kang; S. Ge; L. Lin; X. Liu; X. Feng, *Angew. Chem. Int. Ed.* **2016**, *55*, 5541; B. M. Trost; M. Yanai; K. Hoogsteen, *J. Am. Chem. Soc.* **1993**, *115*, 5294.

example of a metal catalyzed [2+2]-cycloaddition was published by the group of Echavarren.[5] Based on an intermolecular gold-(I)-catalyzed [2+2]-cycloaddition of alkenes and terminal alkynes, the enantioselective total synthesis of rumphellaone A (**1.08**) was demonstrated (**Scheme 1**). A Josiphos digold (I) complex served as adequate catalytic system to access cyclobutene **1.07** in high yield and good enantioselectivity. With further 8 steps that have been previously described by the group of Echavarren, rumphellaone A (**1.08**) is finally obtained.[6]



Scheme 1: Intermolecular gold-(I)-catalyzed [2+2] cycloaddition towards rumphellaone A.

A more recent example of an intermolecular metal-catalyzed [2+2]-cycloaddition was published by the group of Yoshikai in 2019.[7] They described an original intermolecular [2+2]-cycloaddition between an alkyne **1.09** and an allene **1.10** using a cobalt(I)/bisphospine catalyst (**Scheme 2**). In this work, with the use of allenes (**1.10**) as cycloaddition partner, 3-alkylidenecyclobutene were accessed in good yields and high regioselectivities. A regioselective oxidative cyclization with the less substituted double bond of the allene **1.10** and the alkyne **1.09** with Co^{I} was proposed as a reaction pathway. The alkylidenecobaltacyclopentene intermediate further undergoes a reductive elimination to afford the alkylidenecyclobutene adduct **1.11**.

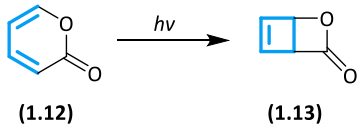


Scheme 2: Cobalt catalyzed [2+2]-cycloaddition towards the synthesis of alkylidenecyclobutenes.

In 1964 Corey and Streith investigated the internal photoaddition reaction of 2-pyrone (**1.12**), paving the way for further studies, in which the unstable and strained bicyclic lactone **1.13** was utilized (**Scheme 3**).[8] One of the central arguments that initiated further investigations was the almost

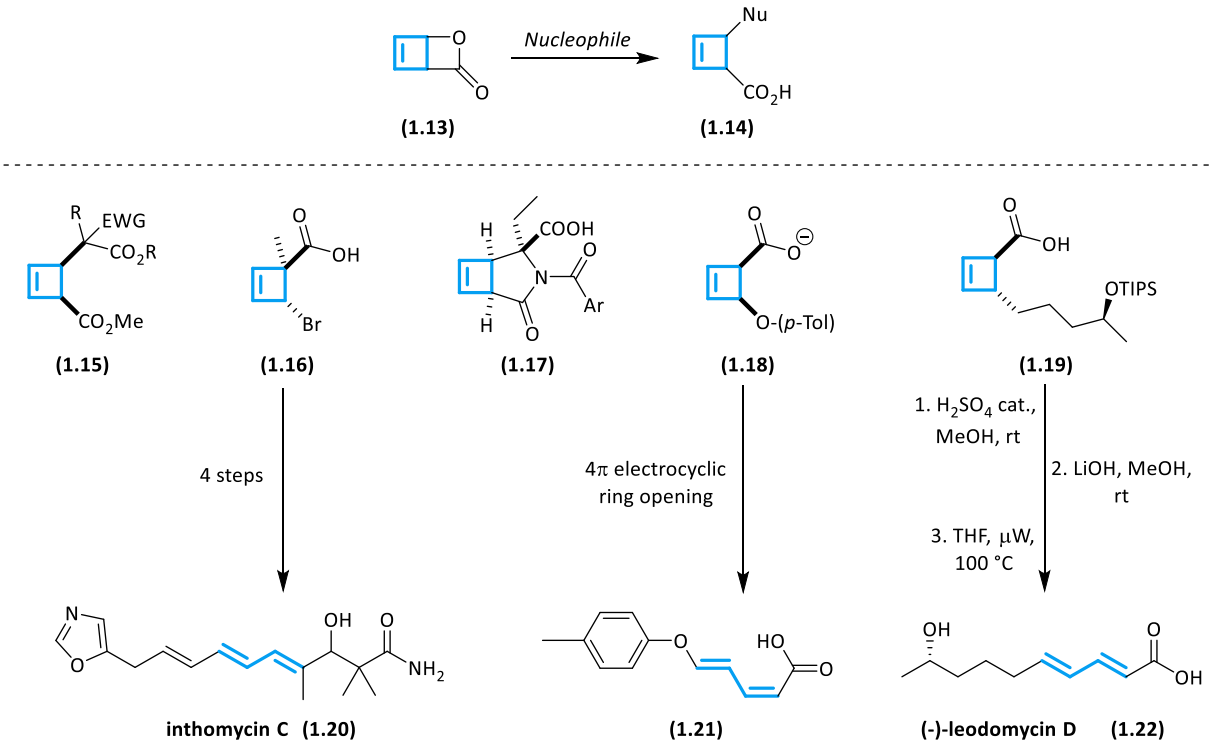
[5] C. García-Morales; B. Ranieri; I. Escofet; L. López-Suarez; C. Obradors; A. I. Konovalov; A. M. Echavarren, *J. Am. Chem. Soc.* **2017**, *139*, 13628.
[6] B. Ranieri; C. Obradors; M. Mato; A. M. Echavarren, *Org. Lett.* **2016**, *18*, 1614.
[7] W. Ding; N. Yoshikai, *Angew. Chem. Int. Ed.* **2019**, *58*, 2500.
[8] E. J. Corey; J. Streith, *J. Am. Chem. Soc.* **1964**, *86*, 950.

quantitative photochemical isomerization of readily available **1.12** to the now storable cyclobutene **1.13**.[9]



Scheme 3: Internal photoaddition of 2-pyrone (**1.12**) towards the bicyclic cyclobutene **1.13**.

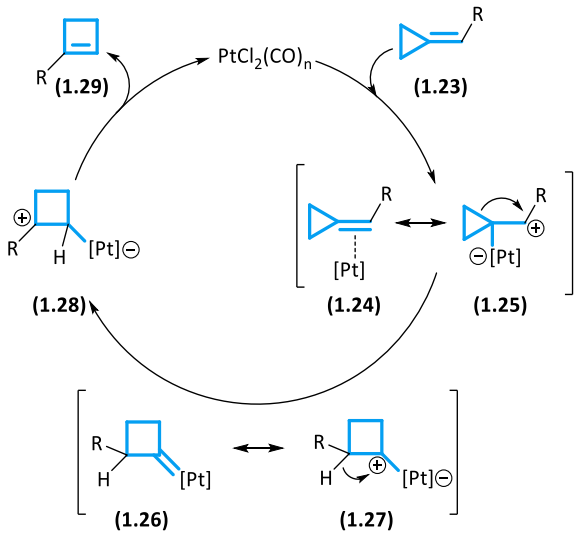
Especially the group of Maulide used this sensitive intermediate **1.13** as a starting building block in their research program.[10] Employing different nucleophiles, new cyclobutene containing molecules (**1.14**) were accessed and utilized in further transformations, as in the total synthesis of (-)-leodomycin D (**1.22**) (**Scheme 4**).[11]



Scheme 4: Transformation of the bicyclic cyclobutene **1.13** and further synthetic steps based on this transformation.

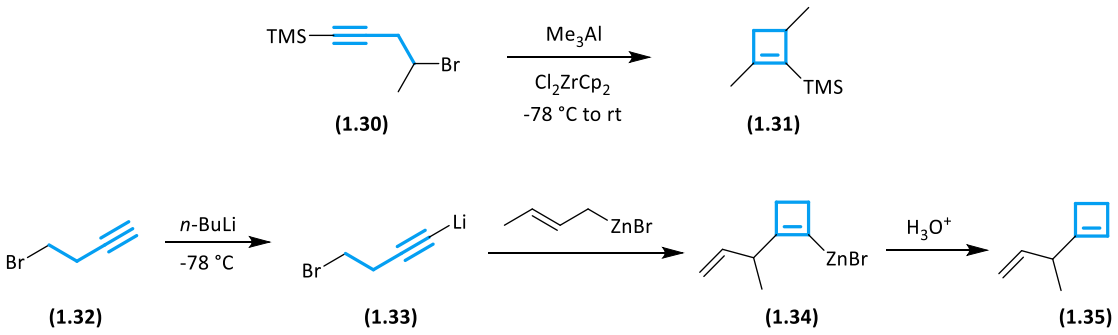
[9] F. Frébault; M. Luparia; M. T. Oliveira; R. Goddard; N. Maulide, *Angew. Chem. Int. Ed.* **2010**, *49*, 5672.
[10] A. Misale; S. Niyomchon; N. Maulide, *Acc. Chem. Res.* **2016**, *49*, 2444.
[11] F. Frébault; M. Luparia; M. T. Oliveira; R. Goddard; N. Maulide, *Angew. Chem. Int. Ed.* **2010**, *49*, 5672; C. Souris; F. Frébault; A. Patel; D. Audisio; K.N. Houk; N. Maulide, *Org. Lett.* **2013**, *15*, 3242; C. Souris; M. Luparia; F. Frébault; D. Audisio; C.Farès; R. Goddard; N. Maulide, *Chem. Eur. J.* **2013**, *19*, 6566; C. Souris; A. Misale; Y. Chen; M. Luparia; N. Maulide, *Org. Lett.* **2015**, *17*, 4486.

Another elegant method for the preparation of cyclobutenes is the enlargement of existing cyclic systems.[12] As described by the group of Fürstner, a platinum mediated rearrangement of methylenecyclopropanes can lead to mono- or disubstituted cyclobutenes (**Scheme 5**).[13]



Scheme 5: Platinum mediated ring enlargement of methylenecyclopropanes towards cyclobutenes.

In 1984, the group of Negishi employed a carbometallation strategy that allows not only the synthesis of a variety of functionalized cyclobutenes (**1.31/1.35**), but also represents the cornerstone for the synthesis of cyclobutene building blocks in this Ph.D. thesis (**Scheme 6**).[14] The intermediary cyclobutene-metal species **1.34** was therefore utilized as a new starting point for cyclobutene functionalization.



Scheme 6: Synthesis of substituted cyclobutenes by carbometalation.

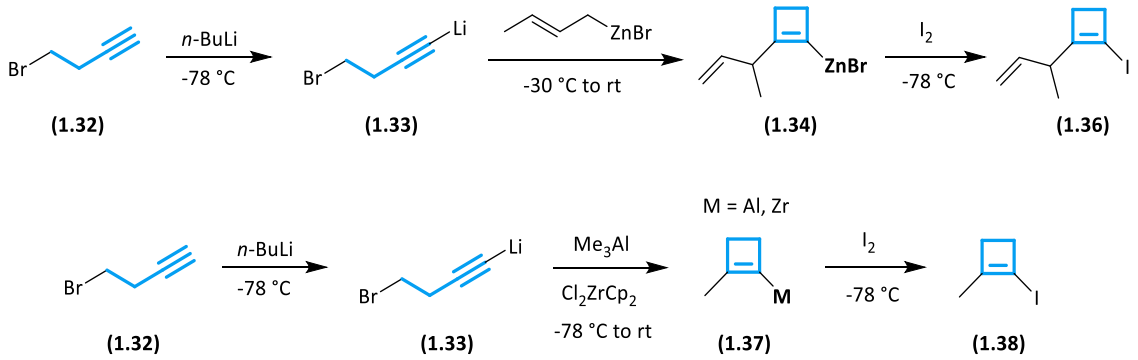
[12] C.-W. Li; K. Pati; G.-Y. Lin; S. M. A. Sohel; H.-H. Hung; R.-S. Liu, *Angew. Chem. Int. Ed.* **2010**, *49*, 9891; R. Liu; M. Zhang; G. Winston-McPherson; W. Tang, *Chem. Commun.* **2013**, *49*, 4376; A. Masarwa; A. Fürstner; I. Marek, *Chem. Commun.* **2009**, *38*, 5760; H. Xu; W. Zhang; D. Shu; J. B. Werness; W. Tang, *Angew. Chem. Int. Ed.* **2008**, *47*, 8933.

[13] A. Fürstner; C. Aïssa, *J. Am. Chem. Soc.* **2006**, *128*, 6306.

[14] L. D. Boardman; V. Bagheri; H. Sawada; E.-i. Negishi, *J. Am. Chem. Soc.* **1984**, *106*, 6105.

1.2 Synthesis of Iodo-cyclobutenes

As described in the previous chapter, many reports focus on the formation of the cyclobutene core rather than using it, as a starting base of functionalization. Iodo-cyclobutenes are a promising source for new cyclobutene-functionalization and are already well known. Additionally, their synthesis can be found in several published work.[15] Nevertheless, most of these reports lack of generality and simplicity, as many steps for their synthesis are necessary and/or too complex precursors are essential, preventing access to versatile building blocks. Inspirational is the work from Negishi between 1983 to 1996, as it describes a way of getting access to metallated cyclobutenes by using organometallic chemistry.[16]



Scheme 7: Synthesis of iodo-cyclobutenes by two different carbometalation pathways.

In both sequences (**Scheme 7**), an initial lithiation on the most acidic C-H position of the bromo-alkyne **1.32** occurs, followed by a *syn*-carbometalation that furnishes the metallated cyclobutenes **1.34/1.37**. The corresponding iodo-cyclobutenes **1.36/1.38** were obtained after iodolysis.

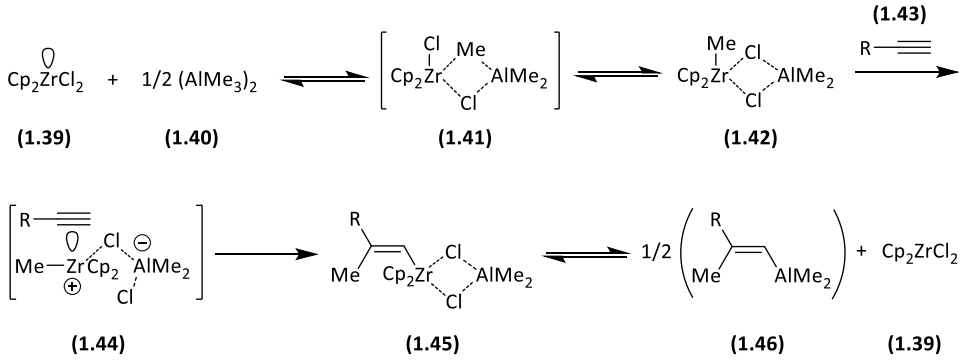
Concerning the use of a mixture of trimethylaluminium (**1.40**) and zirconocene dichloride (**1.39**), more details are given in **Scheme 8**.[17] Starting with a transmetalation of one methyl group of the trimethylaluminium (**1.40**) to the zirconium, followed by a chloride abstraction of the aluminium, the intermediary zwitterionic species **1.44** is formed. The alkyne coordinates to the cationic zirconium,

[15] H. Oda; K. Oshima; H. Nozaki, *Chem. Lett*. **1985**, 53; K. Kasai; Y. Liu; R. Hara; T. Takahashi, *Chem. Commun.* **1998**, *18*, 1989; K. Villeneuve; N. Riddell; R. W. Jordan; G. C. Tsui; W. Tam, *Org. Lett.* **2004**, *6*, 4543; E. B. Averina; R. R. Karimov; K. N. Sedenkova; Y. K. Grishin; T. S. Kuznetzova; N. S. Zefirov, *Tetrahedron* **2006**, *62*, 8814; A. Fürstner; A. Schlecker; C. W. Lehmann, *Chem. Commun.* **2007**, *41*, 4277; Y.-P. Wang; R. L. Danheiser, *Tetrahedron Lett.* **2011**, *52*, 2111; Y. Li; X. Liu; H. Jiang; B. Liu; Z. Chen; P. Zhou, *Angew. Chem. Int. Ed.* **2011**, *50*, 6341; J. He; M. L. Snapper, *Tetrahedron* **2013**, *69*, 7831; B. Alcaide; P. Almendros; C. Lázaro-Milla, *Adv. Synth. Catal.* **2017**, *359*, 2630; D. Kossler; F. G. Perrin; A. A. Suleymanov; G. Kiefer; R. Scopelliti; K. Severin; N. Cramer, *Angew. Chem. Int. Ed.* **2017**, *56*, 11490.

[16] E.-i. Negishi; L. D. Boardman; J. M. Tour; H. Sawada; C. L. Rand, *J. Am. Chem. Soc.* **1983**, *105*, 6344; L. D. Boardman; V. Bagheri; H. Sawada; E.-i. Negishi, *J. Am. Chem. Soc.* **1984**, *106*, 6105; E.-i. Negishi; L. D. Boardman; H. Sawada; V. Ragheri; A. T. Stoll; J. M. Tour; C. L. Rand, *J. Am. Chem. Soc.* **1988**, *110*, 5383; E.-i. Negishi; F. Liu; D. Choueiry; Mohamud; A. Silveira; M. Reeves, *J. Org. Chem.* **1996**, *61*, 8325; F. Liu; E.-i. Negishi, *Tetrahedron Lett.* **1997**, *38*, 1149.

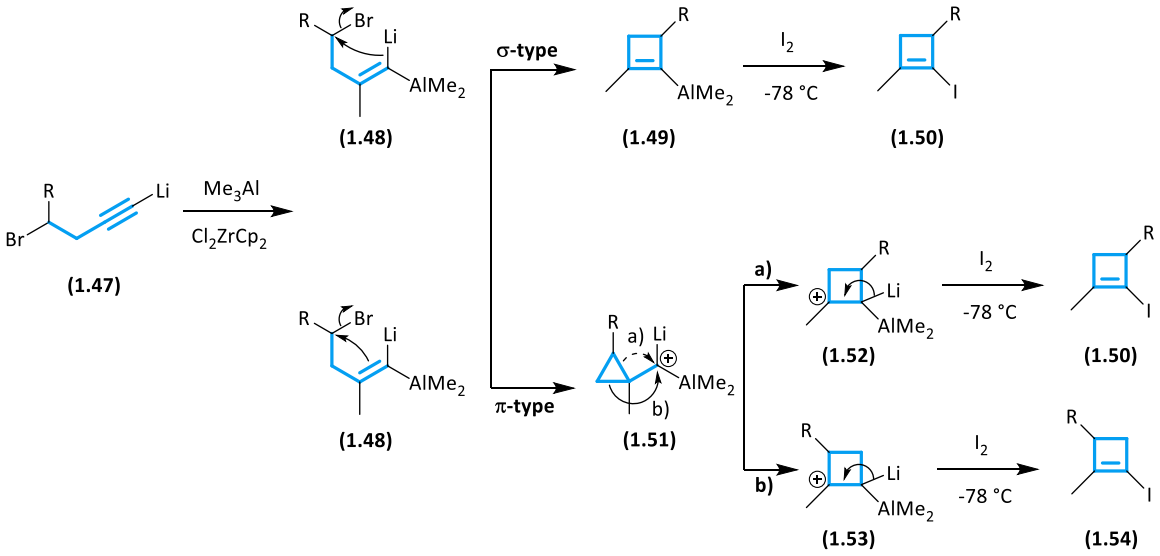
[17] S. Xu; E.-i. Negishi, *Acc. Chem. Res.* **2016**, *49*, 2158.

upon which a migratory insertion of the methyl group (bound to the zirconium) takes place. At last, a reversible transmetalation to aluminium occurs, forming the final *syn*-addition product **1.46**.



Scheme 8: Proposed mechanism of the carboalumination with zirconocene dichloride.[17]

As proposed by Negishi, the carbometalation of metallated 4-halobut-1-ynes (**1.47**) leads to a *gem*-bismetallated species **1.48** which can then undergo two different pathways for the ring closing step (**Scheme 9**). The two possible ways are differentiated by a σ- or π-type cyclization process, which after iodolysis of the metallated cyclobutene intermediate, give rise to two different regioisomers (**1.50/1.54**).



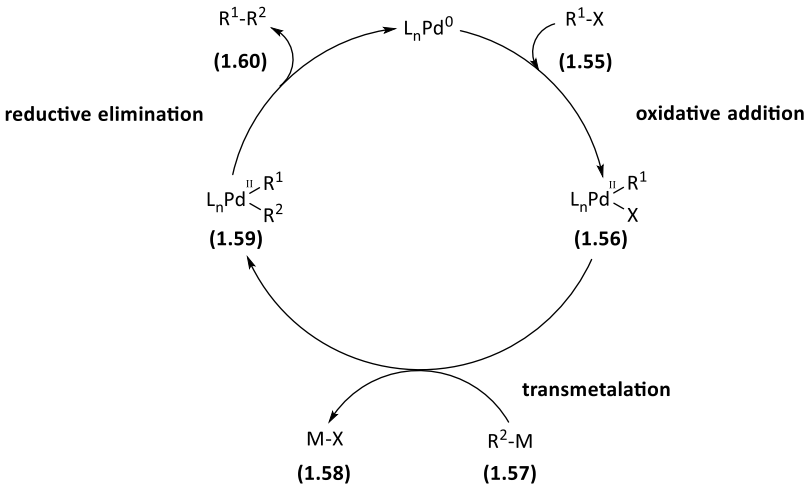
Scheme 9: Proposed pathways for the carboalumination of 4-halobut-1-ynes to iodo-cyclobutenes.

The σ-type pathway describes a S_N2-type mechanism, where the electrons of the sigma-bond between carbon and lithium attack the carbon connected to the leaving halogen towards structure **1.49**. In contrast, the π-type attack of the double bond leads intermediary to the cationic cyclopropane species **1.51**, whereupon two new routes can be described. In path **a)**, the bond connected to the R-group undergoes a Wagner-Meerwein rearrangement, giving intermediate **1.52** and ultimately providing the same regioisomer **1.50** as for the σ-type mechanism. Path **b)** describes the other possibility of a

Wagner-Meerwein rearrangement and thus, after elimination of LiBr and iodolysis, leads to the formation of regioisomer **1.54**. Negishi has shown that both pathways are possible. However, the application of such conditions in this thesis only led to one regioisomer **1.54**, additionally confirmed by X-ray crystallographic data. With this robust and simple method in hands, the iodo-cyclobutene building block, as well as the metallated cyclobutene moiety have been extensively used and will be described thereafter.

1.3 Suzuki-Miyaura and Negishi Cross-Coupling Reactions

Over last decades, several cross-coupling reactions have been reported. It is remarkable however, that the first cross coupling reaction was already demonstrated in 1869 by Glaser, where the stoichiometric use of copper for the homocoupling of metal acetylides was reported.[18] Since that early beginning, many more transition-metal-mediated cross-couplings have emerged, namely Stille, Heck, Sonogashira, Hiyama, Kumada and the two herein relevant methods, the Suzuki-Miyaura and Negishi cross-coupling reaction.[19]

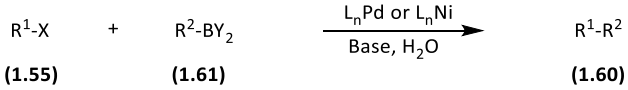


Scheme 10: General mechanism of palladium mediated cross-coupling.

In most cases palladium complexes are used as pre-catalysts. The robustness of these systems in combination with high functional group tolerance made these protocols one of the cornerstones in creating new C-C bonds and was therefore rewarded with the Nobel Prize in 2010.[20] The general accepted mechanism of a palladium mediated cross-coupling is depicted in **Scheme 10**. It consists of

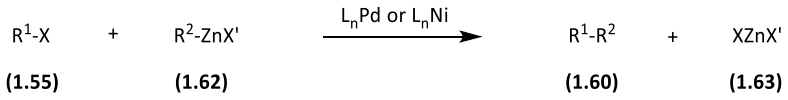
[18] C. Glaser, *Ber. Dtsch. Chem. Ges.* **1869**, *2*, 422.
[19] D. Milstein; J. K. Stille*, J. Am. Chem. Soc.* **1978**, *100*, 3636; R. F. Heck; J. P. Nolley, *J. Org. Chem.* **1972**, *37*, 2320; K. Sonogashira; Y. Tohda; N. Hagihara, *Tetrahedron Lett.* **1975**, *16*, 4467; Y. Hatanaka; T. Hiyama, *J. Org. Chem.* **1988**, *53*, 918; K. Tamao; K. Sumitani; M. Kumada, *J. Am. Chem. Soc*. **1972**, *94*, 4374; N. Miyaura; A. Suzuki, *J. Chem. Soc., Chem. Commun.* **1979**, *19*, 866; N. Miyaura; K. Yamada; A. Suzuki, *Tetrahedron Lett.* **1979**, *20*, 3437; A. O. King; N. Okukado; E.-i. Negishi, *J. Chem. Soc., Chem. Commun.* **1977**, 19, 683.
[20] E.-i. Negishi, *Angew. Chem. Int. Ed.* **2011**, *50*, 6738; A. Suzuki, *Angew. Chem. Int. Ed.* **2011**, *50*, 6722.

three steps: oxidative addition, transmetalation and reductive elimination. For the Suzuki-Miyaura coupling, an organo-boron compound (**1.61**) and an organic halide (**1.55**) are combined in the presence of a base (**Scheme 11**). As a transition metal in the catalytic cycle, palladium and nickel are mainly described in the literature.[21]



Scheme 11: General Suzuki-Miyaura cross coupling with palladium- or nickel-complexes.

In the Negishi type coupling, organozinc compounds are used (**Scheme 12**). The reaction takes place between organic halides or triflates and organozinc compounds in the presence of palladium/nickel catalysts.[22]



Scheme 12: General Negishi cross coupling with palladium- or nickel-complexes.

As both cross-couplings show great advantages in terms of versatility and functional group tolerance, they were utilized in the sophistication of the cyclobutene ring, which can be found in **Chapter I "Results"**.

1.4 Alkylidenecyclobutanes

Alkylidenecyclobutanes have historically been in discussion since 1896, when Gustavson first debrominated erythrityl bromide with zinc and identified spiropentane (**1.65**) ("vinyltrimethylene" called to that time) from the product mixture (**Scheme 13**).[23] Further studies revealed that an alkylidenecyclobutane was among the products in this mixture and methylenecyclobutane (**1.66**) could be identified for the first time.[24]

Scheme 13: Compound mixture of the debromination of erythrityl bromide with zinc.

[21] F.-S. Han, *Chem. Soc. Rev.* **2013**, *42*, 5270.
[22] S. Baba; E.-i. Negishi, *J. Am. Chem. Soc.***1976**, *98*, 6729.
[23] G. Gustavson, *J. prakt. Chem.* **1896**, *54* (2), 97; G. Gustavson, *J. prakt. Chem.* **1896**, *54* (1), 104.
[24] Philipov, *J. prakt. Chem.* **1916**, *93* (2), 163; M. J. Murray, E. H. Stevenson, *J. Am. Chem. Soc.* **1944**, *66*, 812.

Despite this long history, alkylidenecyclobutanes have attracted much less attention than their homologous alkylidenecyclopropanes, mainly due to the lower reactivity of the cyclobutane core and the difficulty for their synthesis.[25] Nevertheless, the methylenecyclobutane moiety can be found in several natural compounds (**Figure 2**).

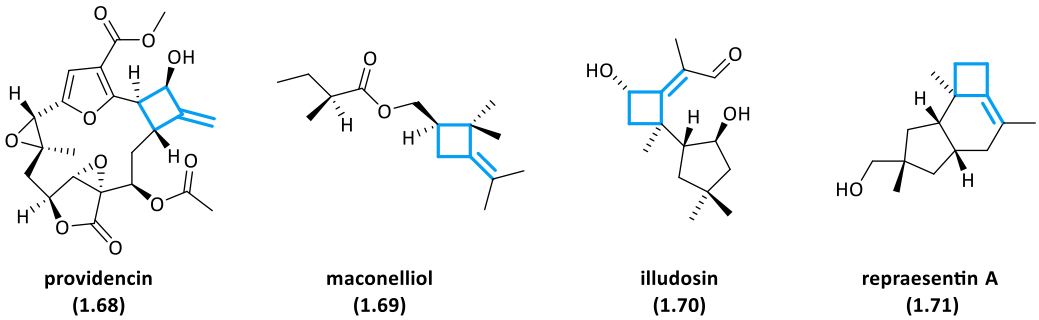
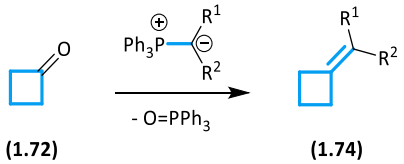


Figure 2: Natural occurring alkylidenecyclobutanes.

For instance, the cytotoxin providencin (**1.68**) which was isolated from the Caribbean gorgonian octocoral *Pseudopterogorgia kallos,* and the female sex pheromone of the pink hibiscus mealylbug namely maconelliol (**1.69**) was isolated from *Maconellicoccus hirsutus*.[26] The antibacterial illudosin (**1.70**) was isolated from the fungus *Omphalotus olearius* and belongs to the fomannosane-type sesquiterpene family.[27] Another sesquiterpene, the repraesentin A (**1.71** a protoilludane) was extracted from the fungus *Lactarius repraesentaneus* and was found to promote plant growth.[28] The particular interest in the protoilludane family has been expressed in several total syntheses and is of primary importance in this work.[29]

In general, alkylidenecyclobutanes are mainly formed by allene-alkene [2+2]-cycloaddition reactions and metal-catalyzed cyclizations.[25] Starting from preformed four-membered ring compounds, the Wittig olefination of cyclobutanones **1.72** is one of the most versatile and efficient methods for the construction of alkylidenecyclobutanes **1.74** (**Scheme 14**).[25]

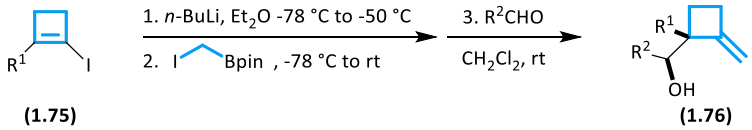
[25] A. Brandi; S. Cicchi; F. M. Cordero; A. Goti, *Chem. Rev.* **2014**, *114*, 7317.
[26] J. Marrero; A. D. Rodríguez; P. Baran; R. G. Raptis, *Org. Lett.* **2003**, *5*, 2551; A. Zhang; D. Amalin; S. Shirali; M. S. Serrano; R. A. Franqui; J. E. Oliver; J. A. Klun; J. R. Aldrich; D. E. Meyerdirk; S. L. Lapointe, *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 9601.
[27] A. Arnone; R. Cardillo; G. Nasini; O. V. de Pava, *J. Chem. Soc. Perkin. Trans. 1* **1991**, 1787; T. C. McMorris; R. Lira; P. K. Gantzel; M. J. Kelner; R. Dawe, *J. Nat. Prod.* **2000**, *63*, 1557.
[28] M. Hirota; Y. Shimizu; T. Kamo; H. Makabe; H. Shibata, *Biosci. Biotechnol. Biochem.* **2003**, *67*, 1597.
[29] M. Kögl; L. Brecker; R. Warrass; J. Mulzer, *Angew. Chem. Int. Ed.* **2007**, *46*, 9320; P. Siengalewicz; J. Mulzer; U. Rinner, *Eur. J. Org. Chem.* **2011**, *35*, 7041.



(1.72) **(1.74)**

Scheme 14: Wittig olefination of cyclobutanones towards alkylidenecyclobutanes.

Building on the previously described methodology (**"Synthesis of Iodo-cyclobutenes**") on iodo-cyclobutenes, the group of Didier engineered a sequence for the synthesis of alkylidenecyclobutanes, combining a boron-homologation and boron-allylation (**Scheme 15)**.[30]



(1.75) **(1.76)**

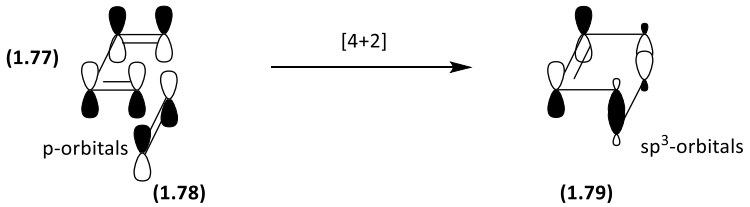
Scheme 15: Boron-homologation/boron-allylation sequence towards alkylidenecyclobutanes.

The objective was however to make this sequence more versatile and will be described in the next section of this thesis.

1.5 [4+2]-Cycloadditions of Cyclobutenes

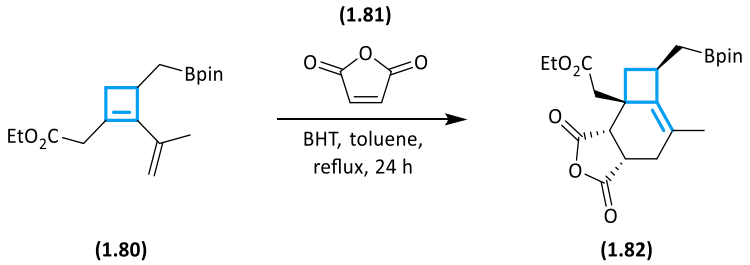
Kurt Alder and Otto Diels described a concerted pericyclic [4+2]-cycloaddition for the first time in 1928, later called the Diels-Alder reaction.[31] Forming six-membered rings, the Diels-Alder cycloaddition of a conjugated diene with a substituted dienophile is particularly useful for synthetic chemists as it provides the cycloadduct regio- and stereoselectively. In this type of cycloaddition, no intermediates are usually observed, as the reaction occurs via a single, cyclic transition state and therefore serves as an excellent example for a concerted pericyclic reaction (**Scheme 16**).[32] In that cyclic transition state, the frontier p-orbitals of the diene **1.77** (HOMO - highest occupied molecular orbital) and of the alkene **1.78** (LUMO - lowest unoccupied molecular orbital) are overlapping and finally forming two new carbon-carbon bonds. However, the reaction shown in **Scheme 16** can only be regarded as schematic since the LUMO of the inactivated ethene (**1.78**) is too high in energy for the HOMO of 1,3-butadiene (**1.77**) to allow for reactivity. Only harsh reaction conditions would lead to the desired cycloadduct.[33]

[30] M. Eisold; D. Didier, *Angew. Chem. Int. Ed.* **2015**, *54*, 15884.
[31] O. Diels; K. Alder, *Liebigs Ann. Chem.* **1928**, *460*, 98; O. Diels; K. Alder, *Ber. dtsch. Chem. Ges. A/B* **1929**, *62*, 554.
[32] M. J. S. Dewar; S. Olivella; J. J. P. Stewart, *J. Am. Chem. Soc.* **1986**, *108*, 5771.
[33] L. M. Joshel; L. W. Butz, *J. Am. Chem. Soc.***1941**, *63*, 3350.



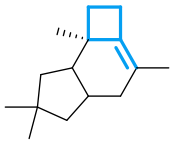
Scheme 16: [4+2]-cycloaddition of a diene and a dienophile illustrated with the involved p-orbitals (HOMO of the diene and LUMO of the dienophile).

Although countless applications exist in literature, the [4+2]-cycloaddition of cyclobutenes was not given much attention, as only the use of the cyclobutene ring as a dienophile was reported by Danyshefsky.[34] In contrast to cyclobutenes as dienophiles, Bäckvall's group reported the use of vinylcyclobutenes **1.80** in [4+2]-cycloaddition strategies (**Scheme 17**).[35] An activated dienophile, maleic anhydride (**1.81**), allowed access to fused alkylidenecyclobutanes **1.82**.



Scheme 17: [4+2]-cycloaddition of a substituted vinylcyclobutene **1.80** with maleic anhydride (**1.82**).

With this example in mind, a synthesis towards unprecedented fused 5/6/4-ring systems containing an alkylidenecyclobutane moiety was reachable. Worthy of note is the similarity with the 5/6/4-fused-ring system of protoilludanes, especially the 6-protoilludane (**1.83**), which was a target in our research program (**Figure 3**).[36]



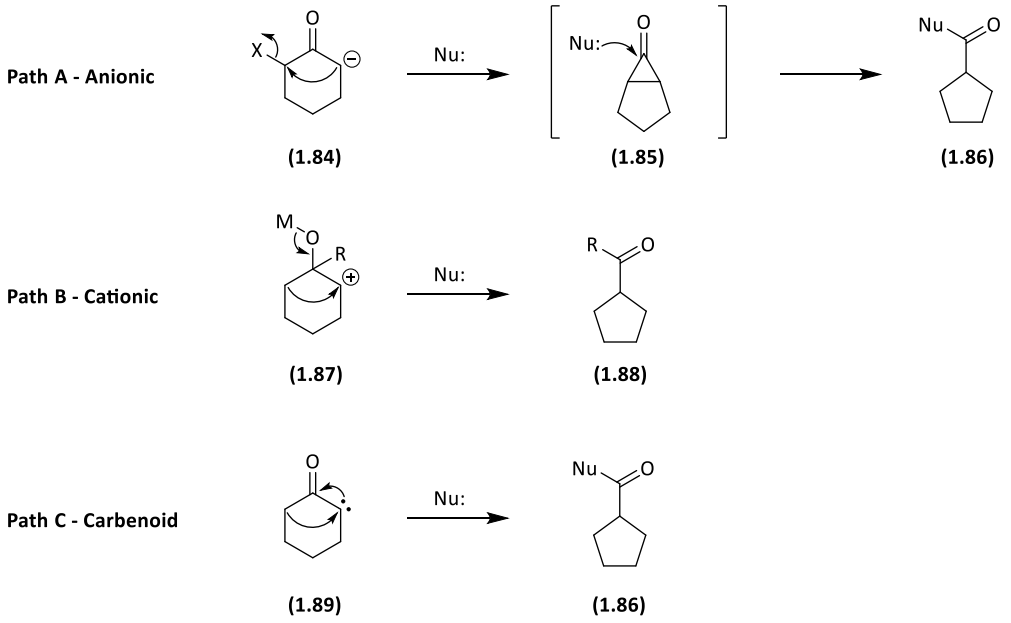
6-protoilludane
(1.83)

Figure 3: One representative of the protoilludane family: 6-protoilludane.

[34] A. G. Ross; X. Li; S. J. Danishefsky, *J. Am. Chem. Soc.* **2012**, *134*, 16080; A. G. Ross; S. D. Townsend; S. J. DAnishefsky, *J. Org. Chem.* **2013**, *78*, 204.
[35] Y. Qiu; B. Yang; C. Zhu; J.-E. Bäckvall, *Angew. Chem. Int. Ed*. **2016**, *55*, 6520.
[36] W. Oppolzer; A. Nakao, *Tetrahedron Lett.* **1986**, *27*, 5471.

1.6 Ring Contraction Reactions

Ring contraction reactions can be generally classified in three different categories based on their mechanism: anionic, cationic and carbenoid (**Scheme 18**).[37]

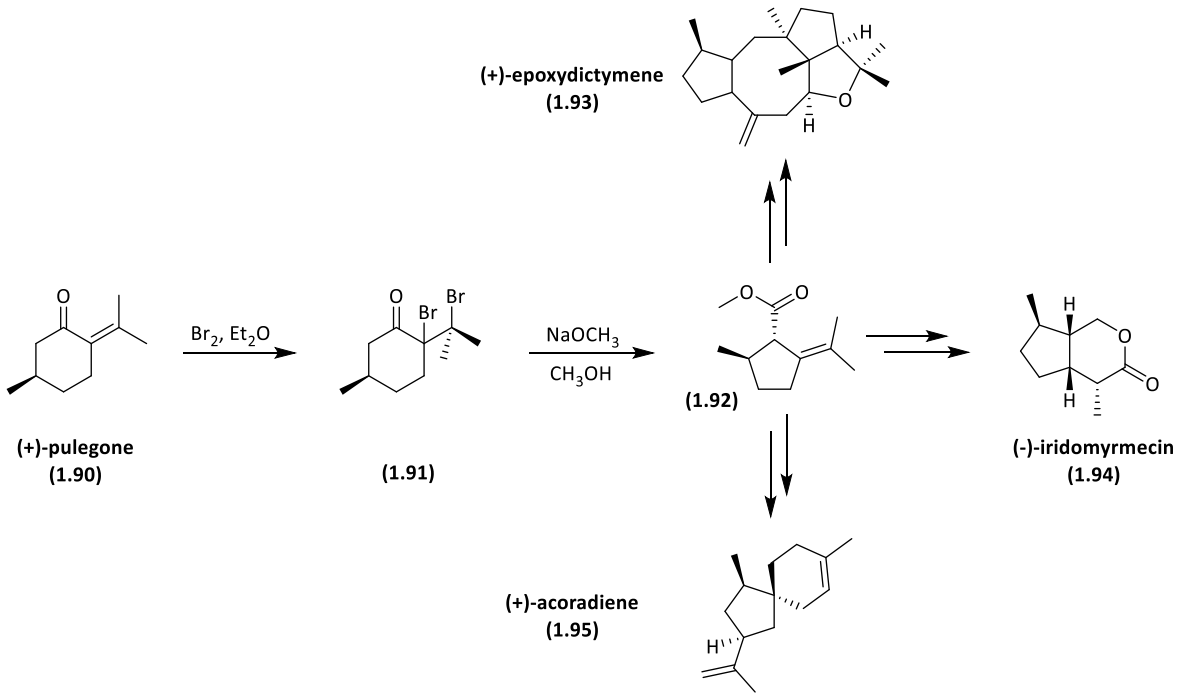


Scheme 18: Three different types of ring contraction reactions classified by their inherent mechanism.

In the anionic reaction pathway (**Path A**), a negative charge on a cyclic ring system (**1.84**) attacks a suitable leaving group resulting in a ring contraction (**1.86**). The cationic type (**Path B**) consists of a ring contraction triggered by an alkyl shift in conjunction with a carbonyl formation (**1.88**). The last one (**Path C**) contains an intermediate carbene or carbenoid **1.89** that rearranges and leads to a ring contraction. The Favorskii rearrangement on cyclic systems is a typical example of an anionic ring contraction and served as a successful tool in several natural product syntheses (**Scheme 19**).[38] In the total synthesis of (+)-epoxydictymene (**1.93**), (-)-iridomyrmecin (**1.94**) and (+)-acoradiene (**1.95**), the anionic ring contraction of dibrominated (+)-pulegone (**1.91**) in the presence of a base is the key step.

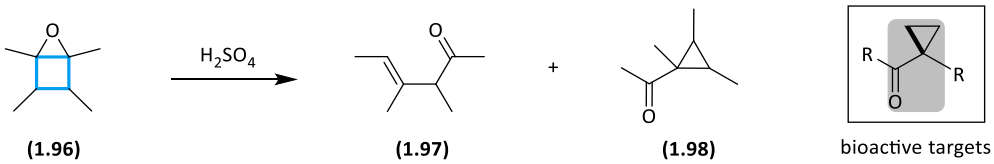
[37] *Ring Contraction Reactions in the Total Synthesis of Biologically Active Natural Products*, L. F. Silva in *Stereoselective Synthesis of Drugs and Natural Products* (Eds.: V. Andrushko, N. Andrushko), John Wiley & Sons, Inc, Hoboken, NJ, USA, **2013**, 1-20; L. F. Silva, *Tetrahedron* **2002**, *58*, 9137.

[38] A. E. Faworskii, *J. Russ. Phys. Chem.* **1894**, *26*, 559; T. F. Jamison; S. Shambayati; W. E. Crowe; S. L. Schreiber, *J. Am. Chem. Soc.* **1997**, *119*, 4353; J. Wolinsky; T. Gibson; D. Chan; H. Wolf, *Tetrahedron* **1965**, *21*, 1247; S. Kurosawa; M. Bando; K. Mori, *Eur. J. Org. Chem.* **2001**, *23*, 4395.



Scheme 19: The Favorskii rearrangement, applied in total syntheses of natural products.

In 1959, Criegee and Noll described the ring contraction of a cyclobutane epoxide **1.96** in the presence of sulfuric acid (**Scheme 20**).[39] They obtained a mixture of two different compounds from which a cyclopropyl ketone (**1.98**) was identified. Part of this Ph.D. thesis was devoted to the selective ring contraction of cyclobutenes by an oxidative ring contraction, as this rather unexplored reaction can give access to the pharmacologically important cyclopropyl ketone scaffold.[40]



Scheme 20: Early example of an oxidative ring contraction of cyclobutane-epoxides.

[39] R. Criegee; N. Noll, *Liebigs Ann. Chem.* **1959**, *627*, 1; J. M. Conia, *Angew. Chem.* **1968**, *80*, 578.
[40] For some bioactive compounds see: J. X. Qiao; S. R. King; K. He; P. C. Wong; A. R. Rendina; J. M. Luettgen; B. Xin; R. M. Knabb; R. R. Wexler; P. Y. S. Lam, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 462; C. E. Wainwright; J. S. Elborn; B. W. Ramsey; G. Marigowda; X. Huang; M. Cipolli; C. Colombo; J. C. Davies; K. De-Boeck; P. A. Flume; M. W. Konstan; S. A. McColley; K. McCoy; E. F. McKone; A. Munck; F. Ratjen; S. M. Rowe; D. Waltz; M. P. Boyle, *N. Engl. J. Med.* **2015**, *373*, 220; U. J. Ries; H. W. M. Priepke; N. H. Hauel; S. Handschuh; G. Mihm; J. M. Stassen; W. Wienen; H. Nar, *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2297.

2 Results

2.1 Unsaturated Four-Membered Rings: Efficient Strategies for the Construction of Cyclobutenes and Alkylidenecyclobutanes

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Cyclobutenes

Unsaturated Four-Membered Rings: Efficient Strategies for the Construction of Cyclobutenes and Alkylidenecyclobutanes

Michael Eisold[+], Andreas N. Baumann[+], Gabriel M. Kiefl, Sebastian T. Emmerling, and Dorian Didier*[a]

Abstract: Our recent studies of the diastereo- and enantioselective formation of strained alkylidenecycloalkanes drove us to more-thoroughly investigate the formation of four-membered rings for which only few efficient methods are described. We first developed a strategy to diversify the saturated part of the four-membered ring and applied it to a highly diastereoselective synthesis of more-elaborate alkylidenecyclobutanes, which completed our precedent studies. In parallel, cyclobutene structures were built employing simple organometallic methods and further functionalized to give a diverse range of new substitution patterns, which consequently enriched the pool of cyclobutene-based building blocks.

Introduction

Cyclobutenes (CBs) and alkylidenecyclobutanes (ACBs) are interesting structural motifs and drive continuous interest among the organic chemistry community.

CBs are rarely observed in natural architectures,[1] whereas ACBs are found in the cores of a number of natural products (Figure 1).[2] Besides their natural occurrences, CBs and ACBs have enticed curiosity for their ability to undergo transformations such as ring expansions[3] and rearrangements.[4] However, and despite growing interest, four membered-ring systems have been scarcely studied, mainly due to the difficulty in accessing their core structure. Generally obtained via [2+2] cycloaddition reactions[5] or metal-catalyzed processes,[6] the synthesis of CBs and ACBs remains a challenge in the area of organic chemistry. The development of simple and straightforward strategies to generate these strained building blocks[7] undoubtedly warrants further exploration,
because the limitation of the scope is a consequence of the lack of diverse and available methodologies.

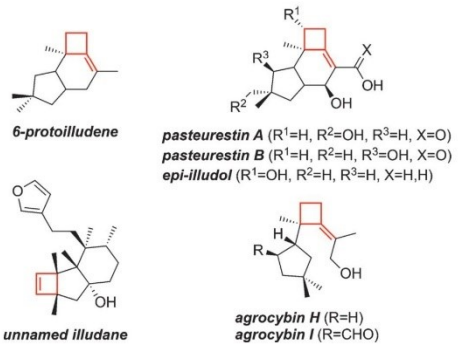


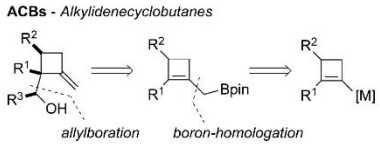
Figure 1. Naturally occurring CB- and ACB-containing substances.

Results and Discussion

Synthetic routes towards ACBs

We recently reported an efficient method for the diastereo- and enantioselective preparation of alkylidenecyclopropanes[8] and ACBs.[9] Our general approach is based on a one-pot boron-homologation/allylboration sequences. A boron homologation reaction, based on the useful and pioneering work of Matteson,[10] installs the allylic boron moiety onto a preformed cyclobutenyl metal species then simple aldehyde allylboration forms the ACB (Scheme 1).

A representative example is shown in Scheme 2. Addition of dihydrocinnamaldehyde to cyclobutenylmethylboronate **1**



Scheme 1. Retrosynthetic approach to ACBs.

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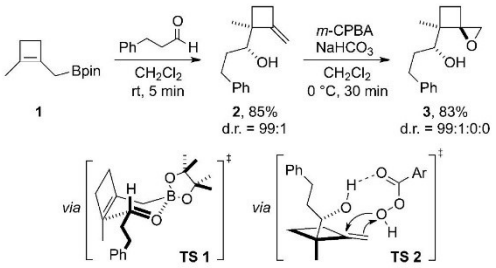
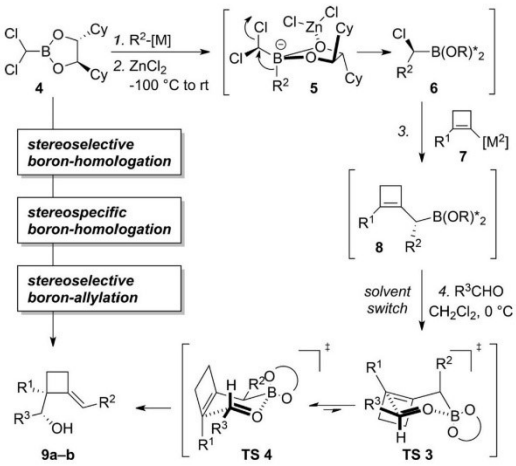
[+] Both authors contributed equally to this manuscript.

Supporting information and the ORCID for the author of this article are available on the WWW under http://dx.doi.org/10.1002/chem.201604585.



Scheme 2. ACB formation, and application of the method to the synthesis of oxaspirohexane **3**. Bpin = 4,4,5,5-tetramethyl-1,3,2-dioxaborolane.



Scheme 3. One-pot stereoselective synthesis of ACBs **9a** and **9b** (Cy = cyclohexyl).

afforded methylenecyclobutane **2** in 85% yield with perfect diasterocontrol control (diastereomeric ratio (d.r.) = 99:1) in a remarkably short time at ambient temperature. Subsequent oxidation furnished diastereomerically pure oxaspirohexane **3** in 83% yield. The high d.r. observed for the formation of **2** can be explained by a Zimmermann–Traxler transition state, in which the lateral chain of the aldehyde adopts the pseudo-equatorial position, which was initially postulated by Hoffmann for allylboration reactions (**TS 1**).[11] We also propose that, in the absence of a protic solvent, epoxidation of the alkylidene moiety takes place on the same face as the secondary alcohol by hydrogen bonding with *m*-chloroperbenzoic acid (*m*-CPBA) (**TS 2**).

This new method to easily generate ACBs proved to be quite general; a wide range of aromatic, heteroaromatic, and aliphatic aldehydes were used to generate chiral adducts with good diastereoselectivity.

Next, we developed an asymmetric version of the one-pot sequence by using chiral diols as boron ligands, which allowed enantiomerically enriched ACBs to be prepared (Scheme 3).[9b]

In this one-pot sequence, dichloromethylboronic ester **4** reacted with an organometallic nucleophile, which promoted stereoselective formation of a α-chiral chloromethylboronic ester **6** via a 1,2-metalate rearrangement. The rearrangement was controlled by the chiral diol ligand, and the selectivity was relayed through the intermediate boronate **5** by the presence of zinc chloride.[12] A second stereospecific boron homologation occurred upon addition of cyclobutenyl metal species **7** and gave α-chiral cyclobutenylmethylboronic ester **8**. Finally, an allylation reaction occurred upon addition of an aldehyde. A Zimmerman–Traxler transition state, in which both the R^2 and R^3 groups adopted pseudo-equatorial positions (**TS 4**), controlled the diastereoselectivity of the reaction.

A wide variety of novel ACBs **9a** (R^3 = aromatic) and **9b** (R^3 = aliphatic) were generated by using this diastereo- and enantioselective procedure. Figure 2 shows representative examples of the ACBs obtained in 55–79% yield with excellent diastereo- and enantiocontrol over the one-pot sequence.

Alternatively, we envisioned that the diastereoselectivity could come from the cyclobutene ring itself. In this case, propargyl bromides had to be adequately prepared to install the lateral chain R^2 (Scheme 4). To avoid the use of expensive propargylation reagents,[13] we employed readily available aldehydes and a pre-prepared storable propargylzinc reagent to form the substituted homopropargylic alcohol precursors **10**. The temperature was maintained at −78 °C, which allowed selective formation of the expected alkyne that contained only traces of the competitive allenylation compound. Subsequent tosylation of the secondary alcohols **10** followed by nucleophilic substitution afforded the corresponding homopropargylic bromides **11**. Notably, only traces of the required substituted propargyl bromides were obtained if PBr_3 or Appel's conditions were employed for direct synthesis from the corresponding alcohols; instead, the major product resulted from an elimination reaction.

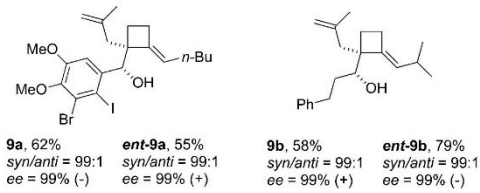
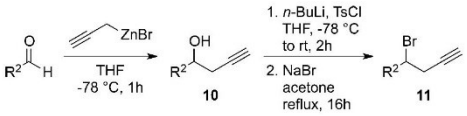


Figure 2. Representative examples of enantiomerically enriched ACBs.



Scheme 4. Synthesis of homopropargylic bromides **11** (Ts = tosyl).

The boron homologation and allylboration reactions were merged in a one-pot sequence, and ACBs **12a–l** were obtained with excellent diastereoselectivity (in all cases d.r. > 99:1:0:0).

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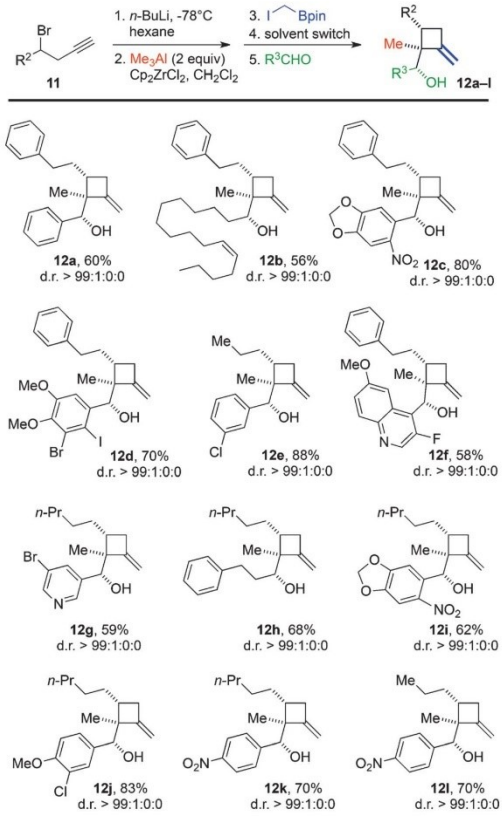
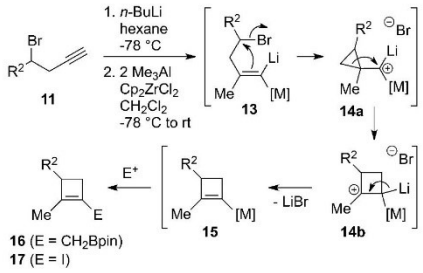
Simple propargyl bromides **11** and aromatic, heteroaromatic, and aliphatic aldehydes were employed, and the reaction furnished the expected compounds **12** with three consecutive stereocenters (one quaternary) in good yields up to 88% (Scheme 5).



Scheme 5. One-pot diastereoselective synthesis of ACBs containing a side chain.

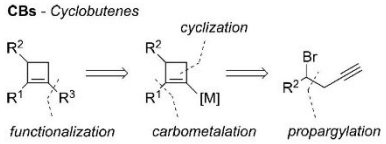
The reaction was initiated by alkyne deprotonation with *n*-butyllithium, and the remainder of the sequence was realized by a carboalumination reaction upon addition of a mixture of dichlorozirconocene and trimethylaluminium in dichloromethane (**13**). Following the mechanism proposed by Negishi,[14] a π cyclization took place to furnish *gem*-bismetalated cyclopropyl methylium intermediate **14a**. Subsequent C–C bond cleavage and migration of the methylene group gave cyclobutenylium **14b** then lithium bromide elimination gave cyclobutenyl metal species **15**. The regiochemistry of the overall cyclization process was clarified by NMR spectroscopy.[15] Finally, introduction of the appropriate electrophile gave either the cyclobutenylmethylboronic ester **16** (Scheme 6), used for the allylation sequence with an aldehyde, or the iodocyclobutene **17**, which is useful for CB functionalization.



Scheme 6. Proposed mechanism for the formation of cyclobutene derivatives.

Synthetic routes towards CBs

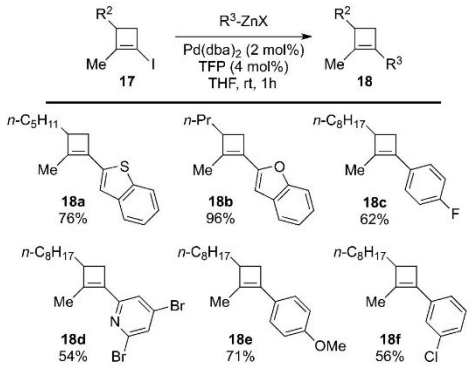
We envisioned that CBs could be functionalized later in the sequence by employing the previously generated cyclobutenyl metal species with a preinstalled R^2 moiety by following the aforementioned cyclization strategies (see above). Consequently, derivatization of the unsaturated CB was undertaken via a cyclobutenyl metal intermediate (Scheme 7).



Scheme 7. Retrosynthetic approach to CBs.

With a range of propargyl bromides **11** in hand, cyclobutene iodides **17** were simply synthesized by the addition of iodine to cyclobutenyl metal species **15**, which was generated in situ.

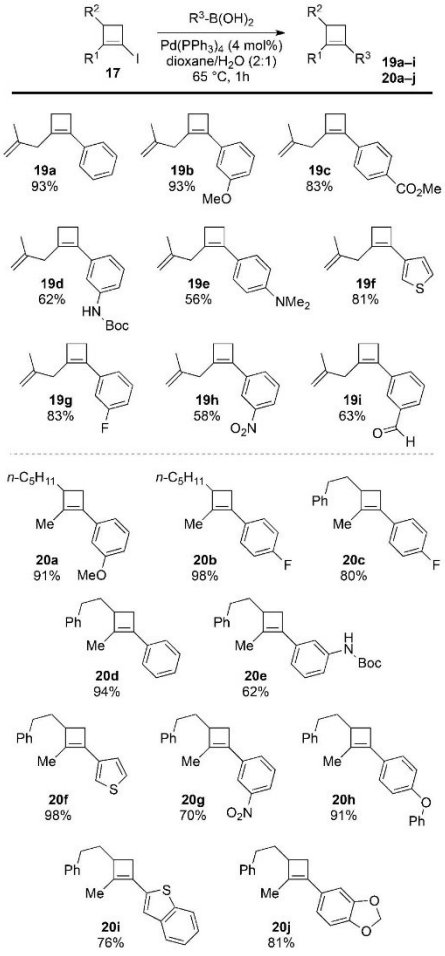
A first derivatization was undertaken by cross-coupling **17** with different zinc species in the presence of bis(dibenzylideneacetone)palladium ($Pd(dba)_2$) and tri-2-furylphosphane (TFP). The results are depicted in Scheme 8. Aromatic and hetero



Scheme 8. Derivatization of CBs via Negishi cross-coupling.

aromatic substrates were easily introduced, and substituted CBs **18a–f** were obtained in good-to-excellent yield.

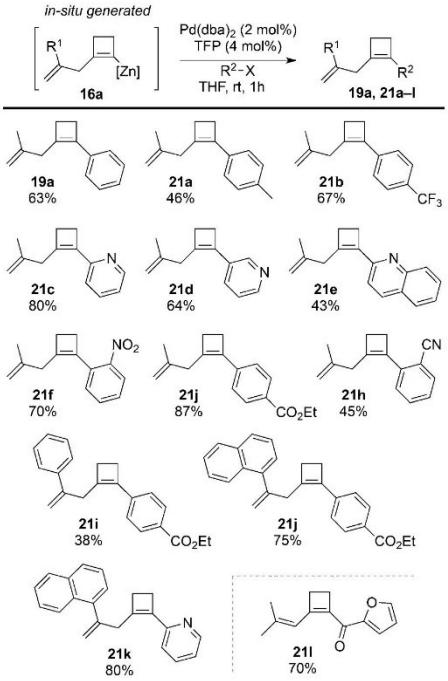
On the strength of these successful initial results, we took a step further and envisaged boronic acids as cross-coupling partners. A wide range of commercially available boronic acids were used in the Suzuki cross-coupling of cyclobutene iodides **17** in the presence of tetrakis(triphenylphosphine)palladium (4 mol%) (Scheme 9).[16] Halogen-, ether-, and nitro- substituted



Scheme 9. Derivatization of CBs via Suzuki cross-coupling

aromatic groups were introduced very efficiently, as well as *tert*-butoxycarbonyl (Boc) protected aromatic amines (**19d** and **20e**) and the even more challenging *m*-formyl phenyl group (**19i**). Functionalized four-membered rings were obtained in very good yields (up to 98%), and the system had high tolerance for a wide range of functional groups in the cross-coupling reaction (**19a–i** and **20a–j**). Unfortunately, only the starting cyclobutene iodides **17** were recovered when Suzuki cross-couplings with alkylboronic acids were attempted, and no alkyl-substituted product was obtained.

Alternatively, cyclobutenyl metal species can be generated and used in situ by employing allylzinc species. Simple insertion of zinc into the carbon–halogen bond (Scheme 10) proceeded when the condition described by Villiéras et al. were used[17].



Scheme 10. Derivatization of cyclobutenylzinc species generated in situ.

Allylzinc reagents were added to 4-bromobutyne, which initiated a carbometalation–cyclization sequence to form a new cyclobutenylzinc species in situ. First, aromatic and heteroaromatic iodides added in the presence of $Pd(dba)_2$ and TFP underwent the cross-coupling reaction and furnished substituted CBs **19a** and **21a–k** in good yields (up to 87%). Second, furoyl chloride was used in the reaction to give the conjugated cyclobutenylketone **21l**. Surprisingly, isomerization of the allylic double bond was observed, and the more-stable six-π-electron conjugated system was the sole product of the reaction.

Taking into account the propensity of 1,3-enyne systems to undergo further interesting transformations,[18] we envisaged that alkynylcyclobutenes could be highly valuable substrates

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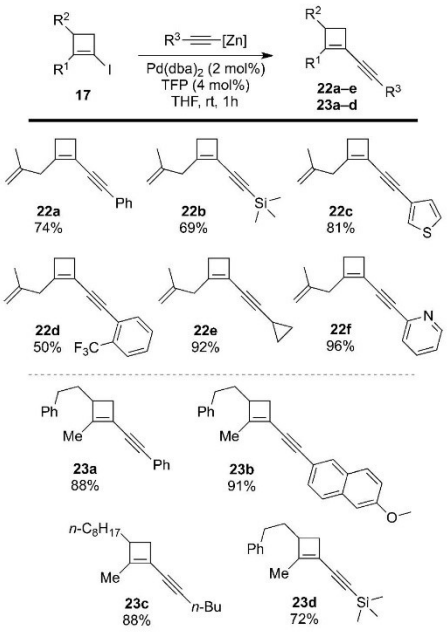
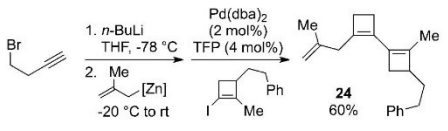


Scheme 11. Cross-coupling reactions of allylcyclobutene iodides.

for further studies. Alkynylzinc reagents—prepared by deprotonation of the corresponding terminal alkyne and subsequent transmetalation with $ZnCl_2$—underwent rapid cross-coupling reactions with a variety of allylcyclobutene iodides **17** to obtain conjugated cyclobutenyl acetylenes **22a–f** and **23a–d** in good yields (50–96%; Scheme 11), which showed the potential of this methodology to diversify the pool of previously described CBs. The Sonogashira-type cross-coupling of a cyclobutene iodide was previously described by Okamura et al.[19] The resulting cyclobutenyl acetylene was applied to a concise synthesis of (+)-sterpurene.

Finally, we applied this straightforward methodology to the synthesis of bicyclobutene **24**. A similar one-pot sequence was employed to generate the allylcyclobutenyl metal species, followed by a cross-coupling reaction that involved a cyclobutene iodide. Compound **24** was obtained in 60% yield (Scheme 12).



Scheme 12. Synthetic approach to bicyclobutene **24**.

Conclusion

We used simple organometallic chemistry to thoroughly assemble efficient routes to access substituted four-membered rings. On one hand, an unprecedented highly diastereo selective one-pot sequence produced ACBs that possessed three consecutive stereocenters, including one quaternary center. On the other hand, an efficient preparation of cyclobutenyl derivatives merged with a cross-coupling reaction generated valuable aryl-, alkynyl-, and acyl-CBs. The easily accessible routes to unsaturated four-membered-ring architectures described warrants further investigations because these structures are usually difficult to access.

Experimental Section

General procedure A: Preparation of propargyl alcohols 10

A few drops of 1,2-dibromoethane were added to a suspension of zinc dust (3.8 equiv) and lithium chloride (2.0 equiv) to activate the zinc. The reaction was kept slightly above rt (about 30–40 °C), and a solution of propargyl bromide (1.0 equiv) in THF (2.0 M) was slowly added. Upon complete addition, the mixture was stirred for 90 min at rt. The suspension was cooled to −78 °C and the appropriate aldehyde was slowly added. The mixture was allowed to react for 30 min at −78 °C then quenched by adding conc. hydrochloric acid (2.0 equiv). The mixture was allowed to reach rt overnight, and then was extracted with diethyl ether (3×50 mL). The combined organic phases were washed with a saturated aqueous solution of sodium hydrogen carbonate (50 mL) and brine (50 mL) then dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure (Caution! some products **10** are quite volatile). The crude alcohol was purified by flash column chromatography on silica gel (eluent: ethyl acetate/hexanes). See the Supporting Information for the characterization data for alcohols **10a–d**.

General procedure B: Synthesis of propargyl bromides 11 via tosylates 25

A solution of *n*BuLi (1.0 equiv) in hexanes (2.86 M) was added dropwise to a solution of alcohol **10** (1.0 equiv) in THF (0.5 M) at −78 °C. The solution was stirred for 30 mins at −78 °C then warmed to rt. A solution of 4-methylbenzene-1-sulfonyl chloride (1.1 equiv) in THF (1.0 M) was added. The reaction mixture was stirred at rt for 30 min. The mixture was poured into water (50 mL) and extracted with diethyl ether (3×50 mL). The combined organic phases were washed with brine (50 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The crude tosylate **25** was used without further purification. For data analysis, a sample of crude **25** was purified by flash column chromatography on silica gel (eluent: ethyl acetate/hexanes).

The crude tosylate **25** was dissolved in acetone (0.3 M) and lithium bromide (5.0 equiv) was added. The reaction mixture was stirred at reflux temperature for 10 h, after which time full consumption of **25** was observed (alternatively, the reaction can be performed in a pressure vessel at 65 °C for 10 h). The reaction mixture was cooled to rt then poured into water (50 mL) and extracted with hexanes (3×50 mL). The combined organic phases were washed with brine (50 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure (*Caution!* some

products **11** are quite volatile). The crude bromide was purified by flash column chromatography on silica gel (eluent: hexanes).

Compound 25a: Compound **25a** (4.21 g, quantitative) was obtained from alcohol **10a** as a colorless oil by following general procedure B. R_f=0.35 (9:1 hexanes/EtOAc, UV, $KMnO_4$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.81 (d, J=8.3 Hz, 2H), 7.34 (d, J=7.7 Hz, 2H), 4.63–4.50 (m, 1H), 2.55–2.50 (m, 2H), 2.45 (s, 3H), 1.96 (t, J=2.7 Hz, 1H), 1.70 (td, J=8.1, 6.4 Hz, 2H), 1.39–1.13 (m, 2H), 0.83 ppm (t, J=7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ=144.9, 134.1, 129.9, 128.0, 80.2, 78.6, 71.3, 35.5, 24.8, 21.8, 18.0, 13.7 ppm; IR: $\tilde{\nu}$=3289 (w), 2962 (w), 2936 (w), 2876 (vw), 1599 (w), 1496 (vw), 1460 (w), 1356 (m), 1308 (w), 1292 (w), 1188 (m), 1174 (vs), 1097 cm^{-1} (m); HRMS (EI): m/z calcd for $C_{14}H_{18}O_3S^+$: 266.0977; found: 266.0980.

Compounds 25b–d: See the Supporting Information.

Compound 11a: Compound **11a** (1.10 g, 40%) was obtained from tosylate **25a** as a colorless oil by following general procedure B. R_f=0.41 (hexanes, $KMnO_4$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=4.07 (dtd, J=8.8, 6.3, 4.5 Hz, 1H), 2.87–2.72 (m, 2H), 2.12 (t, J=2.6 Hz, 1H), 2.01–1.78 (m, 2H), 1.69–1.50 (m, 1H), 1.44 (dddd, J=13.4, 9.6, 7.4, 6.3 Hz, 1H), 0.95 ppm (t, J=7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ=80.7, 71.1, 52.3, 39.9, 29.4, 20.8, 13.5 ppm; HRMS (EI): m/z calcd for $C_7H_{11}{}^{79}Br^+$: 174.0044; found: 174.0101.

Compounds 11b–d: See the Supporting Information.

General procedure C: Synthesis of cyclobutyl iodides 17a–d

A solution of *n*BuLi (1.0 equiv) in hexanes (2.86 M) was added dropwise to a solution of 4-bromobutyne **11** (1.0 equiv) in hexanes (0.5 M) at −78 °C, and the mixture was stirred for 30 min. A second flask was charged with Cp_2ZrCl_2 (1.0 equiv) in CH_2Cl_2 (0.5 M) and a solution of trimethylaluminium (2.0 equiv) in hexanes (2.00 M) was added at rt. The mixture was stirred for 30 min. The second solution was transferred to the first at −78 °C via cannula. The resulting mixture was the allowed to stir at RT for 2 h, to form the metalated cyclobutenyl derivative **16**. The suspension was cooled to 0 °C, and a solution of iodine in THF (1.5 equiv) was added slowly via cannula. The mixture was stirred for 30 min at 0 °C then slowly poured into ice-cold hydrochloric acid (10 equiv, ≈0.5 M) with continued vigorous stirring. The aqueous phase was extracted with hexanes (3×50 mL). The combined organic phases were washed with a saturated aqueous solution of sodium hydrogen carbonate (50 mL) and brine (50 mL). The organic phase was dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure (*Caution!* some products **17** are quite volatile). The crude cyclobutyl iodide **17** was purified by flash column chromatography on silica gel (eluent: hexanes).

Compound 17a: Compound **17a** (260 mg, 59%) was obtained as a colorless oil from **11a** by following general procedure C. R_f=0.87 (hexanes, UV, $KMnO_4$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=2.97–2.81 (m, 2H), 2.38–2.29 (m, 1H), 1.58 (td, J=2.3, 1.1 Hz, 4H), 1.41–1.22 (m, 3H), 0.90 ppm (t, J=7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ=158.3, 83.0, 48.6, 43.4, 35.0, 20.7, 14.9, 14.3 ppm; IR: $\tilde{\nu}$=2958 (vs), 2931 (s), 2872 (s), 1710 (vs), 1462 (s), 1379 (s), 1211 (s), 1166 (s), 1088 cm^{-1} (s); HRMS (EI): m/z calcd for $C_8H_{13}I^+$: 236.0062; found: 236.0059.

Compounds 17b–d: See the Supporting Information.

Compound 17e

A solution of *n*BuLi (1 equiv) in hexanes (2.86 M) was added dropwise to a stirred solution of 4-bromobut-1-yne (1 equiv) in THF (0.2 M) at −78 °C. After 15 min the cooling bath was exchanged for a −30 °C bath. The temperature was held −30 °C for 5 min then (2-methylallyl)zinc bromide (1 equiv) was added dropwise. After 10 min the cooling bath was removed and the colorless solution was slowly warmed to rt over 1 h, during which time the color changed to pale yellow. The reaction mixture was treated with iodine (1 equiv) followed by a small amount (2 mL/mmol) of water. The crude mixture was extracted with diethyl ether (3×5.0 mL/mmol), and the combined organic phases were dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure at 0 °C. The crude product was purified by column chromatography on silica gel (eluent: hexanes) in the dark to obtain **17e** (945 mg, 40%) as a colorless oil. R_f=0.9 (hexanes, UV, $KMnO_4$, *p*-anisaldehyde (PAA)); ^{1}H NMR (400 MHz, $CDCl_3$): δ=4.80–4.77 (m, 1H), 4.75–4.72 (m, 1H), 2.78–2.74 (m, 2H), 2.73–2.70 (m, 2H), 2.69–2.66 (m, 2H), 1.72 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ=155.5, 141.5, 112.3, 84.5, 39.5, 36.4, 34.7, 22.7 ppm; HRMS (EI): m/z calcd for $C_8H_{11}I^+$: 233.9905; found: 233.9906.

Compound 17f

Following the procedure described above for the preparation of **17e**, *N*-bromosuccinimide (1 equiv) was employed as the electrophile and **17f** (299 mg, 32%) was obtained as a colorless oil. R_f=0.79 (hexanes, UV, $KMnO_4$, PAA); ^{1}H NMR (400 MHz, $CDCl_3$): δ=4.80–4.77 (m, 1H), 4.75–4.73 (m, 1H), 2.77–2.74 (m, 2H), 2.74–2.71 (m, 2H), 2.49 (ddd, J=4.1, 2.2, 1.0 Hz, 2H), 1.73 ppm (t, J=1.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ=146.5, 141.6, 112.2, 109.8, 37.5, 35.2, 31.0, 22.7 ppm; IR: $\tilde{\nu}$=2963 (s), 2948 (s), 2930 (vs), 2854 (m), 2362 (m), 2334 (m), 1735 (m), 1700 (m), 1653 (s), 1456 (m), 1438 (m), 1375 (m), 1261 (m), 1094 (s), 1031 (s), 1021 cm^{-1} (s); MS (EI): m/z (%): 188.0 (11) $[M]^+$, 186.0 (11) $[M]^+$, 171.0 (6), 107.1 (35), 91.1 (100), 79.1 (61), 65.1 (34), 51.0 (22); HRMS (EI): m/z calcd for $C_8H_{11}{}^{79}Br^+$: 186.0044; found: 188.0034.

General procedure D: Synthesis of alkylidenecyclobutylcarbinols 12

A solution of *n*BuLi (1.0 equiv) in hexanes (2.86 M) was added dropwise to a solution of 4-bromobutyne **11** (1.0 equiv) in hexanes (0.5 M) at −78 °C, and the mixture was stirred for 30 min. A second flask was charged with Cp_2ZrCl_2 (1.0 equiv) in CH_2Cl_2 (0.5 M) and a solution of trimethylaluminium (2.0 equiv) in hexanes (2.00 mL) was added at rt. The mixture was stirred for 30 min then transferred to the first flask at −78 °C via cannula. The resulting mixture was stirred at rt for 2 h, during which time the metalated cyclobutenyl derivative **15** formed. The reaction mixture was cooled to −78 °C and 2-(iodomethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.0 equiv) in THF (0.5 M) was added. The solution was warmed to rt over 2 h. Excess organometallic species were quenched by the careful addition of water. The boronic ester **16** was extracted with diethyl ether (3×20 mL). The combined organic phases were washed with brine (20 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (0.5 M), and the solution was cooled to 0 °C. The required aldehyde (0.5 equiv) was added neat (liquid) or as a solution in CH_2Cl_2 (solid). Upon complete consumption of the boronate intermediate **16** a saturated aqueous solution of ammonium chloride (4.0 mL/mmol) and diethyl ether (4.0 mL/mmol) were added, and the mixture was stirred vigorously. The aqueous phase was extracted with diethyl ether (3×20 mL), and the combined organic phases were washed with an aqueous solution of sodium metabisulfite (20 mL). The organic phase was dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The crude alcohol was purified by flash column

chromatography on silica gel (eluent: ethyl acetate/hexanes or diethyl ether/hexanes) to afford the pure alkylidenecyclobutylcarbinol **12**.

Compound 12a

Following general procedure D, **12a** (88 mg, 60%, d.r. = 99:1:0:0) was obtained as a colorless oil from bromide **11d** and benzaldehyde. R_f = 0.24 (95:5 hexanes/EtOAc, UV, $KMnO_4$, PAA); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.21 (m, 7H), 7.19–7.11 (m, 1H), 7.08–7.03 (m, 2H), 5.02 (t, J = 2.6 Hz, 1H), 4.84 (t, J = 2.1 Hz, 1H), 4.67 (d, J = 2.9 Hz, 1H), 2.79–2.69 (m, 1H), 2.48 (ddd, J = 14.3, 9.4, 5.3 Hz, 1H), 2.35–2.18 (m, 3H), 2.11 (d, J = 2.9 Hz, 1H, OH), 1.54–1.31 (m, 2H), 1.00 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 155.6, 142.4, 141.0, 128.5, 128.4, 127.9, 127.5, 127.2, 125.8, 106.0, 79.2, 54.1, 36.3, 33.8, 33.8, 32.3, 14.3 ppm; IR: $\tilde{\nu}$ = 3568 (vw), 3454 (vw), 3084 (vw), 3062 (vw), 3027 (w), 2963 (w), 2932 (w), 2856 (w), 1668 (w), 1603 (w), 1494 (w), 1452 (m), 1371 (w), 1296 (w), 1188 (w), 1155 (w), 1081 (w), 1034 (m), 1022 cm^{-1} (m); HRMS (EI): m/z calcd for $C_{14}H_{18}^+$: 186.1403 $[M-C_7H_7O]^+$; found: 186.1397.

Compound 12b

Following general procedure D, **12b** (120 mg, 56%, d.r. = 99:1:0:0) was obtained as a colorless oil from bromide **11d** and (*Z*)-hexadec-11-enal. R_f = 0.16 (98:2 hexanes/EtOAc, UV, $KMnO_4$, PAA); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.26 (m, 2H), 7.20–7.16 (m, 3H), 5.41–5.30 (m, 2H), 4.89 (t, J = 2.7 Hz, 1H), 4.81 (t, J = 2.1 Hz, 1H), 3.49–3.42 (m, 1H), 2.80 (ddt, J = 16.0, 9.0, 2.5 Hz, 1H), 2.55 (dddd, J = 40.8, 13.7, 10.1, 5.8 Hz, 2H), 2.22 (ddt, J = 15.9, 5.0, 2.4 Hz, 1H), 2.07–1.96 (m, 5H), 1.85–1.75 (m, 1H), 1.72–1.69 (m, 1H), 1.68–1.59 (m, 1H), 1.59–1.52 (m, 1H), 1.32–1.26 (m, 19H), 1.01 (s, 3H), 0.91–0.88 ppm (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 156.1, 142.5, 130.0, 130.0, 125.9, 105.7, 77.0, 54.1, 36.8, 34.2, 33.8, 33.0, 32.1, 31.3, 29.9, 29.9, 29.8, 29.8, 29.7, 29.5, 27.4, 27.3, 27.1, 22.5, 14.2, 13.4 ppm; IR: $\tilde{\nu}$ = 2924 (vs), 2854 (s), 1774 (w), 1668 (w), 1604 (w), 1496 (w), 1454 (m), 1375 (w), 1058 (w), 1030 cm^{-1} (w); HRMS (EI): m/z calcd for $C_{30}H_{48}O^+$: 424.3705; found: 424.3690.

Compounds 12c–l: See the Supporting Information.

Compound 18a

A freshly titrated solution of 2,2,6,6-tetramethyl piperidine lithium chloride (TMPMgCl·LiCl; 1.1 equiv) in THF (1.1 M) was added dropwise to a solution of benzo[*b*]thiophene (1.0 equiv) in THF (0.25 M) at rt. The mixture was stirred at rt for 2 h until iodolysis of an aliquot of the reaction mixture indicated that completed metalation had occurred. A solution of zinc chloride (1.1 equiv) in THF (1.0 M) was added dropwise to the reaction mixture, which was then stirred for 30 min at rt to allow full transmetalation. In a second reaction vessel, $Pd(dba)_2$ (2 mol%) and TFP (4 mol%) were dissolved in THF, and the mixture was stirred for 5 min to allow ligand exchange. Iodide **17b** (1.0 equiv) in THF (0.3 M) was added and the reaction mixture was stirred for 5 min. The zinc species (1.5 equiv) in the first flask was added immediately. The reaction mixture was stirred at rt for 2 h, and then quenched by addition of a saturated aqueous solution of ammonium chloride. The aqueous phase was extracted with diethyl ether (3×20 mL). The combined organic phases were washed with brine and dried over anhydrous magnesium sulfate. The organic phase was filtered and concentrated under reduced pressure then flash column chromatography on silica gel (eluent: hexanes) gave **18a** as a colorless oil (61 mg, 76%). R_f = 0.67 (hexanes, UV, $KMnO_4$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.77 (d, J = 7.9 Hz, 1H), 7.70 (d, J = 7.5 Hz, 1H), 7.30 (7.33–7.24, m, 2H), 7.04 (s, 1H), 2.84 (ddt, J = 11.4, 4.3, 2.2 Hz, 1H), 2.77–2.65 (m, 1H), 2.28 (dquin, J = 11.9, 2.1 Hz, 1H), 1.98 (q, J = 2.0 Hz, 3H), 1.79–1.62 (m, 1H), 1.46–1.24 (m, 7H), 0.92 ppm (t, J = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 144.8, 139.8, 139.6, 139.2, 130.9, 124.4, 124.0, 123.3, 122.3, 119.0, 42.8, 33.8, 33.0, 32.3, 27.4, 22.8, 14.3, 14.3 ppm; IR: $\tilde{\nu}$ = 3057 (vw), 2955 (m), 2920 (m), 2853 (m), 1713 (w), 1695 (w), 1667 (w), 1593 (vw), 1562 (vw), 1516 (w), 1456 (m), 1435 (m), 1372 (m), 1354 (w), 1330 (w), 1302 (m), 1250 (w), 1227 (w), 1182 (w), 1155 (m), 1130 (w), 1066 (w), 1016 cm^{-1} (w); HRMS (EI): m/z calcd for $C_{18}H_{22}S^+$: 270.1442; found: 270.1446.

Compound 18b

Compound **18b** was obtained as a colorless oil (48 mg, 96%) from iodide **17a** by using the procedure described above for **18a**. The metalation of benzofuran with TMPMgCl·LiCl was incomplete after 3 h at rt, therefore the concentration of the metalated benzofuran was determined by iodolysis followed by GC analysis. Excess zinc chloride in THF was used to promote complete transmetalation of the metalated benzofuran. R_f = 0.71 (hexanes, UV, $KMnO_4$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50 (dd, J = 7.5, 1.7 Hz, 1H), 7.45–7.40 (m, 1H), 7.28–7.14 (m, 2H), 6.46 (s, 1H), 2.83–2.70 (m, 2H), 2.23 (dq, J = 11.7, 2.0 Hz, 1H), 2.05 (q, J = 2.0 Hz, 3H), 1.76–1.65 (m, 1H), 1.48–1.30 (m, 3H), 0.99–0.91 ppm (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 154.7, 153.6, 146.5, 128.9, 126.7, 123.9, 122.7, 120.7, 111.0, 101.6, 43.2, 35.2, 32.2, 20.9, 14.7, 14.5 ppm; IR: $\tilde{\nu}$ = 2957 (w), 2920 (m), 2871 (w), 2844 (w), 2359 (vw), 2337 (vw), 1713 (w), 1708 (w), 1699 (w), 1683 (m), 1614 (w), 1559 (w), 1464 (w), 1451 (s), 1374 (w), 1356 (w), 1301 (m), 1256 (m), 1184 (m), 1156 (m), 1140 (m), 1108 (w), 1086 (w), 1025 (w), 1005 cm^{-1} (m).

Compound 18c

A solution of *n*BuLi (1.0 equiv) in hexanes (2.86 M) was added dropwise to a solution of 1-fluoro-4-iodobenzene (1.0 equiv) in THF (0.5 M) at −78 °C. The solution was stirred for 30 min at rt to allow complete halogen–metal exchange. A solution of zinc chloride (1.1 equiv) in THF (1.0 M) was added dropwise, and the solution was warmed to rt then stirred for 30 min. The amount of metalated species was determined by iodolysis and GC analysis. In a second reaction vessel, $Pd(dba)_2$ (2 mol%) and TFP (4 mol%) were dissolved in THF and the mixture was stirred for 5 min to allow ligand exchange. Iodide **17c** (1.0 equiv) in THF (0.3 M) was added. The reaction mixture was stirred for 5 min then the previously prepared zinc species (1.5 equiv) was added immediately. The reaction mixture was stirred at rt for 2 h then quenched by addition of a saturated aqueous solution of ammonium chloride. The aqueous phase was extracted with diethyl ether (3×20 mL). The combined organic phases were washed with brine and dried over anhydrous magnesium sulfate. The organic phase was filtered and concentrated under reduced pressure. Flash column chromatography on silica gel (eluent: hexanes) gave **18c** as a colorless oil (51 mg, 62%). R_f = 0.85 (hexanes, UV, $KMnO_4$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.26 (m, 2H), 7.06–6.99 (m, 2H), 2.75 (ddq, J = 12.0, 4.3, 2.1 Hz, 1H), 2.62 (dd, J = 8.7, 4.8 Hz, 1H), 2.17 (dquin, J = 12.1, 2.2 Hz, 1H), 1.96 (q, J = 2.0 Hz, 3H), 1.73–1.65 (m, 1H), 1.44–1.22 (m, 13H), 0.94–0.86 ppm (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 161.5 (d, J = 245.6 Hz), 142.3 (d, J = 2.2 Hz), 134.8, 132.8 (d, J = 3.2 Hz), 127.1 (d, J = 7.8 Hz), 115.3 (d, J = 21.4 Hz), 41.9, 33.1, 32.9, 32.1, 30.1, 29.8, 29.5, 27.7, 22.9, 14.3, 14.2 ppm; IR: $\tilde{\nu}$ = 2956 (m), 2923 (s), 2853 (m), 1716 (vw), 1690 (w), 1655 (vw), 1601 (w), 1508 (vs), 1466 (w), 1410 (w), 1376 (w), 1354 (w), 1324 (w), 1294 (w), 1230 (s), 1155 (m), 1104 (w), 1070 (vw), 1013 cm^{-1} (vw).

Compound 18 d

Compound **18 d** (67 mg, 54%) was obtained as a slightly yellow oil from iodide **17 c** by using the procedure described above for **18 a**. Complete metalation of 2,4-dibromopyridine was achieved at −25 °C after 3 h. R_f = 0.33 (hexanes, UV, $KMnO_4$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.40 (m, 1H), 7.17 (d, J = 1.4 Hz, 1H), 2.83–2.70 (m, 1H), 2.70–2.59 (m, 1H), 2.24–2.14 (m, 1H), 2.11 (q, J = 1.9 Hz, 3H), 1.74–1.61 (m, 1H), 1.44–1.16 (m, 13H), 0.88 ppm (t, J = 6.7 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 156.2, 154.1, 141.9, 133.6, 133.6, 127.1, 121.8, 42.6, 32.5, 32.4, 31.9, 29.9, 29.6, 29.3, 27.5, 22.7, 14.6, 14.2 ppm; IR: $\tilde{\nu}$ = 3098 (vw), 2954 (w), 2921 (m), 2852 (m), 1654 (m), 1554 (vs), 1520 (s), 1465 (w), 1430 (w), 1380 (w), 1368 (m), 1352 (m), 1300 (w), 1240 (vw), 1184 (w), 1151 (s), 1122 (w), 1081 cm^{-1} (m); HRMS (EI): m/z calcd for $C_{18}H_{25}{}^{79}Br_2N^+$: 413.0345; found: 413.0345.

Compound 18 e

A solution of zinc chloride (1.0 equiv) in THF (1.0 M) was added to a freshly titrated solution of (4-methoxyphenyl)magnesium bromide (1.0 equiv) in THF (0.55 M), and the mixture was stirred for 30 min at rt. In a second reaction vessel, $Pd(dba)_2$ (2 mol%) and TFP (4 mol%) were dissolved in THF (1.0 mL), and the mixture was stirred for 5 min to allow ligand exchange. Iodide **17 c** (1.0 equiv) in THF (0.3 M) was added, and the reaction mixture was stirred for 5 min then the previously prepared zinc species (1.5 equiv) was added immediately. The reaction mixture was stirred at rt for 2 h then quenched by addition of a saturated aqueous solution of ammonium chloride. The aqueous phase was extracted with diethyl ether (3×20 mL). The combined organic phases were washed with brine and dried over anhydrous magnesium sulfate. The organic phase was filtered and concentrated under reduced pressure. Flash column chromatography on silica gel (eluent: hexanes) gave **18 e** (61 mg, 71%) was obtained as a colorless oil. R_f = 0.1 (hexanes, UV, $KMnO_4$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.24 (m, 2H), 6.90–6.85 (m, 2 h), 3.81 (s, 3H), 2.73 (m, 1H), 2.62–2.55 (m, 1H), 2.15 (dt, J = 12.1, 2.1 Hz, 1H), 1.95–1.92 (m, 3H), 1.74–1.62 (m, 1H), 1.44–1.22 (m, 13H), 0.90 ppm (t, J = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 158.3, 140.4, 135.2, 129.7, 126.8, 113.9, 55.4, 41.8, 33.2, 32.9, 32.1, 30.2, 29.8, 29.5, 27.8, 22.9, 14.3, 14.2 ppm; IR: $\tilde{\nu}$ = 2955 (w), 2922 (s), 2852 (m), 1606 (m), 1673 (w), 1510 (s), 1464 (m), 1442 (w), 1418 (w) 1375 (w), 1330 (w), 1301 (w), 1391 (m), 1344 (vs), 1172 (m), 1114 (w), 1072 (w), 1038 cm^{-1} (m); HRMS (EI): m/z calcd for $C_{20}H_{30}O^+$: 286.2297; found: 286.2304.

Compound 18 f

Compound **18 f** (56 mg, 56%) was obtained as a colorless oil from 1-chloro-3-iodobenzene by using the procedure described above for **18 c**. R_f = 0.95 (hexanes, UV, $KMnO_4$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.14 (m, 4H), 2.75 (ddq, J = 12.1, 4.4, 2.2 Hz, 1H), 2.67–2.58 (m, 1H), 2.18 (dq, J = 12.1, 2.2 Hz, 1H), 1.98 (q, J = 2.0 Hz, 3H), 1.74–1.64 (m, 1H), 1.44–1.21 (m, 13H), 0.94–0.86 ppm (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 145.0, 138.2, 134.7, 134.4, 129.7, 126.4, 125.6, 123.7, 42.0, 32.9, 32.8, 32.1, 30.1, 29.8, 29.5, 27.7, 22.9, 14.4, 14.3 ppm; IR: $\tilde{\nu}$ = 2956 (m), 2924 (vs), 2853 (m), 2361 (vw), 2339 (vw), 1716 (vw), 1693 (w), 1652 (w), 1593 (m), 1562 (w), 1468 (w), 1425 (w), 1374 (w), 1325 (w), 1260 (vw), 1233 (vw), 1182 (vw), 1110 (vw), 1080 cm^{-1} (w).

General procedure E: Synthesis of aryl-CB derivatives by Suzuki cross-coupling (19/20)

Arylboronic acid (1.33 equiv) and K_2CO_3 (2.7 equiv) were added to a stirred solution of cyclobutene iodide **17** (1 equiv) in 2:1 dioxane/H_2O (0.05 M) at rt. The reaction mixture was stirred for 10 min then $Pd(PPh_3)_4$ (4 mol%) was added. The reaction mixture was stirred at 50 °C for 1 h, during which time a color change to red or black indicated a complete reaction. Water (5.0 mL) was added and the aqueous solution was extracted with diethyl ether (3×20 mL). The combined organic phases were dried over anhydrous magnesium sulfate, the solvent was removed under reduced pressure, and the crude product was purified by column chromatography on silica gel or preparative TLC to afford the aryl-CB derivative **19**/**20**.

Compound 19 a: Compound **19 a** (43 mg, 93%) was obtained as pale-yellow oil from **17 e** and phenylboronic acid by following general procedure E. R_f = 0.8 (hexanes, UV, $KMnO_4$, PAA); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.29 (m, 4H), 7.24–7.18 (m, 1H), 4.83–4.79 (m, 2H), 3.11–3.07 (m, 2H), 2.69–2.63 (m, 2H), 2.47–2.43 (m, 2H), 1.79 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 142.7, 140.4, 139.3, 136.1, 128.5, 126.8, 125.7, 111.6, 39.1, 28.4, 26.1, 23.1 ppm; IR: $\tilde{\nu}$ = 3079 (w), 3061 (w), 3027 (w), 2914 (m), 2836 (w), 1720 (w), 1714 (w), 1688 (s), 1656 (w), 1650 (m), 1644 (w), 1598 (m), 1493 (m), 1448 (m), 1426 (w), 1414 (w), 1374 (m), 1358 (w), 1335 (w), 1323 (m), 1301 (w), 1263 (m), 1245 (m), 1221 (w), 1212 (m), 1179 (w), 1107 (w), 1082 (w), 1066 (m), 1052 (w), 1020 (m), 1002 cm^{-1} (w); HRMS (EI): m/z calcd for $C_{14}H_{16}{}^+$: 184.1252; found: 184.1247.

Compound 19 b: Compound **19 b** (50 mg, 93%) was obtained as a colorless oil from **17 e** and (3-methoxyphenyl)boronic acid by following general procedure E. R_f = 0.4 (9:1 hexanes/EtOAc, UV, $KMnO_4$, PAA); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.22 (t, J = 7.9 Hz, 1H), 6.92 (d, J = 7.6 Hz, 1H), 6.86–6.84 (m, 1H), 6.75 (dd, J = 8.2, 1.8 Hz, 1H), 4.82–4.77 (m, 2H), 3.79 (s, 3H), 3.08–3.05 (m, 2H), 2.65–2.61 (m, 2H), 2.44–2.40 (m, 2H), 1.76 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.7, 142.7, 140.8, 139.2, 137.4, 129.4, 118.4, 112.4, 111.7, 111.2, 55.3, 39.1, 28.4, 26.2, 23.0 ppm; IR: $\tilde{\nu}$ = 3075 (w), 2939 (m), 2913 (m), 2833 (w), 1689 (w), 1650 (w), 1598 (m), 1576 (s), 1486 (m), 1482 (m), 1464 (m), 1452 (m), 1428 (m), 1374 (w), 1334 (m), 1285 (m), 1262 (s), 1220 (s), 1195 (m), 1175 (m), 1166 (s), 1092 (w), 1043 cm^{-1} (s); HRMS (EI): m/z calcd for $C_{15}H_{18}O^+$: 214.1358; found: 214.1350.

Compound 19 c–i: See the Supporting Information.

Compound 20 a: Compound **20 a** (49 mg, 91%) was obtained as a colorless oil from **17 b** and (3-methoxyphenyl)boronic acid by following general procedure E. R_f = 0.62 (hexanes, UV, $KMnO_4$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23 (d, J = 7.9 Hz, 1H), 6.94 (ddd, J = 7.5, 1.2, 1.2 Hz, 1H), 6.85 (dd, J = 2.6, 1.5 Hz, 1H), 6.75 (ddd, J = 8.3, 2.6, 0.9 Hz, 1H), 3.82 (s, 3H), 2.74 (ddt, J = 12.0, 4.3, 2.1 Hz, 1H), 2.65–2.56 (m, 1H), 2.17 (dt, J = 12.1, 2.1 Hz, 1H), 1.96 (q, J = 2.0 Hz, 3H), 1.73–1.62 (m, 1H), 1.44–1.23 (m, 7H), 0.95–0.86 ppm (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.7, 143.6, 137.9, 135.7, 129.4, 118.3, 112.0, 111.1, 55.3, 41.9, 33.0, 32.9, 32.3, 27.4, 22.9, 14.3, 14.3 ppm; IR: $\tilde{\nu}$ = 2955 (m), 2922 (vs), 2870 (m), 2854 (m), 1653 (w), 1604 (s), 1599 (s), 1577 (s), 1487 (m), 1465 (m), 1454 (m), 1432 (m), 1376 (w), 1372 (w), 1332 (m), 1323 (m), 1285 (s), 1250 (s), 1230 (w), 1212 (m), 1176 (m), 1167 (m), 1047 cm^{-1} (s); HRMS (EI): m/z calcd for $C_{17}H_{24}O^+$: 244.1827; found: 244.1816.

Compound 20 b: Compound **20 b** (51 mg, 98%) was obtained as a colorless oil from **17 b** and (4-fluorophenyl)boronic acid by following general procedure E. R_f = 0.88 (hexanes, UV, $KMnO_4$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.26 (m, 2H), 7.07–6.98 (m, 2H), 2.75 (ddq, J = 12.0, 4.4, 2.1 Hz, 1H), 2.65–2.57 (m, 1H), 2.17 (dquin, J = 12.1, 2.2 Hz, 1H), 1.96 (q, J = 2.0 Hz, 3H), 1.75–1.65 (m, 1H),

1.45–1.27 (m, 7H), 0.92 ppm (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 161.5 (d, J = 245.5 Hz), 142.3 (d, J = 2.3 Hz), 134.8, 132.8 (d, J = 3.2 Hz), 127.1 (d, J = 7.8 Hz), 115.3 (d, J = 21.4 Hz), 41.9, 33.0, 32.9, 32.3, 27.4, 22.9, 14.3, 14.2. ppm; IR: $\tilde{\nu}$ = 2957 (m), 2923 (m), 2855 (m), 1655 (vw), 1601 (w), 1507 (vs), 1467 (w), 1408 (vw), 1376 (w), 1324 (w), 1294 (w), 1230 (s), 1182 (vw), 1155 (m), 1104 (w), 1069 (vw), 1012 cm^{-1} (vw); HRMS (EI): m/z calcd for $C_{16}H_{21}F^+$: 232.1627; found: 232.1624.

Compounds 20 c–j: See the Supporting Information.

General procedure F: Synthesis of CB derivatives 21 and 24 by in-situ Negishi cross-coupling

*n*BuLi (1 equiv) in hexanes (2.86 M) was added dropwise to a stirred solution of 4-bromobut-1-yne (1 equiv) in THF (0.2 M) at −78 °C. After 15 min the cooling bath was exchanged for a −30 °C bath. The temperature was held at −30 °C for 5 min then the allylzinc species (1 equiv) was added dropwise. After 10 min the cooling bath was removed and the colorless solution was warmed to rt over 1 h (a color change to pale yellow was observed). During this time, in a second vessel, $Pd(dba)_2$ (4 mol%) and TFP (8 mol%) were dissolved in THF. After stirring for 10–20 min the red solution turned yellow. Aryl iodide (0.95 equiv) in THF (0.15 M) was added to the yellow catalyst solution, and the mixture was stirred for 10 min. Finally, the cyclobutenylzinc species **15** was quickly added to the flask that contained the aryl iodide, and the mixture was stirred for 1 h then quenched with water. The crude mixture was extracted diethyl ether (3 × mL) and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography on silica gel or preparative TLC to obtain the CB derivative **21**/**24**.

Compound 21 a: Compound **21 a** (56 mg, 46%) was obtained as pale-yellow oil from (2-methylallyl)zinc bromide and 1-iodo-4-methylbenzene by following general procedure F. R_f = 0.8 (hexanes, UV, $KMnO_4$, PAA); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28–7.23 (m, 2H), 7.17–7.12 (m, 2H), 4.83–4.79 (m, 2H), 3.10–3.07 (m, 2H), 2.68–2.63 (m, 2H), 2.47–2.42 (m, 2H), 2.35 (s, 3H), 1.79 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 142.8, 139.2, 139.1, 136.5, 133.4, 129.1, 125.7, 111.5, 39.1, 28.3, 26.2, 23.1, 21.4 ppm; IR: $\tilde{\nu}$ = 3077 (w), 3024 (w), 2969 (m), 2939 (s), 2914 (vs), 2872 (m), 2836 (m), 2361 (w), 2331 (vw), 1652 (m), 1511 (s), 1443 (m), 1374 (m), 1328 (w), 1112 cm^{-1} (w); HRMS (EI): m/z calcd for $C_{15}H_{18}^+$: 198.1409; found: 198.1410.

Compound 21 b: Compound **21 b** (100 mg, 67%) was obtained as a yellowish oil from (2-methylallyl)zinc bromide and 1-iodo-4-(trifluoromethyl)benzene by following general procedure F. R_f = 0.8 (9:1 hexanes/EtOAc, UV, $KMnO_4$, PAA); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.57 (d, J = 8.1 Hz, 2H), 7.41 (d, J = 8.1 Hz, 2H), 4.86–4.78 (m, 2H), 3.12–3.08 (m, 2H), 2.70–2.67 (m, 2H), 2.51–2.48 (m, 2H), 1.79 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 143.7, 142.1, 139.2 (q, J = 2.0 Hz), 138.2, 128.44 (q, J = 32.3 Hz), 125.8, 125.43 (q, J = 3.9 Hz), 124.4 (q, J = 272.7 Hz), 112.0, 39.1, 28.7, 26.1, 23.1 ppm; IR: $\tilde{\nu}$ = 3079 (vw), 2918 (w), 2840 (vw), 1650 (vw), 1616 (w), 1411 (w), 1325 (vs), 1165 (m), 1124 (m), 1112 (m), 1070 (m), 1015 cm^{-1} (w); HRMS (EI): m/z calcd for $C_{15}H_{15}F_3^+$: 252.1126; found: 252.1112.

Compounds 21 c–k: See the Supporting Information.

Compound 21 l: Compound **21 l** (40 mg, 68%) was obtained as colorless oil from (2-methylallyl)zinc bromide and furan-2-carbonyl chloride by following general procedure F. R_f = 0.3 (9:1 hexanes/EtOAc, UV, $KMnO_4$, PAA); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.59 (dd, J = 1.7, 0.8 Hz, 1H), 7.15 (dd, J = 3.5, 0.8 Hz, 1H), 6.90 (d, J = 1.4 Hz, 1H), 6.52 (dd, J = 3.6, 1.7 Hz, 1H), 3.01–2.98 (m, 2H), 2.93–2.89 (m, 2H), 1.93 (s, 3H), 1.91 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 176.0, 157.9, 153.8, 147.8, 146.2, 133.1, 120.9, 117.1, 112.1, 31.6, 29.3, 27.7, 20.1 ppm; IR: $\tilde{\nu}$ = 3145 (w), 3100 (w), 2966 (m), 2917 (m), 2853 (w), 1654 (m), 1635 (s), 1610 (s), 1569 (vs), 1560 (s), 1541 (m), 1507 (m), 1463 (vs), 1448 (m), 1437 (m), 1394 (m), 1377 (m), 1370 (m), 1343 (m), 1288 (m), 1276 (m), 1188 (m), 1151 (m), 1040 (m), 1014 cm^{-1} (m); HRMS (EI): m/z calcd for $C_{13}H_{14}O_2^+$: 202.0994; found: 202.0986.

Compound 24: Compound **24** (45 mg, 60%) was obtained as a colorless oil from (2-methylallyl)zinc bromide and (2-(3-iodo-2-methylcyclobut-2-en-1-yl)ethyl)-benzene (instead of an aryl iodide) by following general procedure F. R_f = 0.51 (hexanes, UV, $KMnO_4$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34 (tt, J = 7.1, 2.4 Hz, 2H), 7.28–7.20 (m, 3H), 4.82–4.79 (m, 1H), 4.78 (q, J = 1.5 Hz, 1H), 2.89 (s, 1H), 2.75–2.66 (m, 4H), 2.60–2.56 (m, 2H), 2.47–2.43 (m, 2H), 2.19–2.13 (m, 1H), 2.04–1.96 (m, 1H), 1.81–1.77 (m, 6H), 1.72–1.61 ppm (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 143.5, 142.9, 142.6, 139.6, 136.0, 132.8, 128.5, 128.4, 125.7, 111.3, 43.2, 38.8, 35.2, 34.1, 33.8, 29.8, 27.2, 22.8, 13.7 ppm; IR: $\tilde{\nu}$ = 3026 (w), 2912 (m), 2855 (w), 1712 (w), 1694 (w), 1651 (w), 1604 (w), 1496 (w), 1453 (m), 1440 (m), 1374 (m), 1355 (w), 1261 (w), 1198 (w), 1177 (w), 1065 (w), 1030 cm^{-1} (w); HRMS (EI): m/z calcd for $C_{21}H_{26}^+$: 278.2035; found: 278.2042.

General procedure G: Synthesis of alkynyl-CB derivatives 22 and 23 by Negishi cross-coupling

*n*BuLi (1 equiv) in hexanes (2.86 M) was added dropwise to a stirred solution of alkyne (1 equiv) in THF (0.15 M) at −78 °C. After 30 min zinc chloride (1.33 equiv) in THF (1 M) was added dropwise to the reaction mixture at −78 °C. The reaction mixture was stirred for 30 min at −78 °C. The cooling bath was removed and the system was allowed to reach rt. During this time, $Pd(dba)_2$ (4 mol%) and TFP (8 mol%) was dissolved in THF (1.0 mL) in a second flask. After 10–20 min the red solution turned yellow. Iodide **17** (0.95 equiv) in THF (0.15 M) was added to the yellow catalytic solution, which was then stirred for 10 min. Finally, the alkenylzinc species was quickly added to the second flask that contained **17**. The reaction mixture was stirred for 1 h then quenched with water. The crude mixture was extracted with diethyl ether (3 × 20 mL) and the combined organic phases were dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the crude product was purified by column chromatography on silica gel or preparative TLC to obtain the alkynyl-CB derivative **22**/**23**.

Compound 22 a: Compound **22 a** (45 mg, 74%) was obtained as pale-yellow oil from **17 e** and ethynylbenzene by following general procedure G. R_f = 0.7 (hexanes, UV, $KMnO_4$, PAA); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45–7.42 (m, 2H), 7.34–7.27 (m, 3H), 4.82–4.76 (m, 2H), 2.96–2.91 (m, 2H), 2.63–2.59 (m, 2H), 2.43–2.39 (m, 2H), 1.78 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 153.6, 142.5, 131.6, 128.4, 128.1, 123.6, 121.3, 112.2, 91.1, 84.5, 39.8, 30.1, 29.8, 22.9 ppm; IR: $\tilde{\nu}$ = 3078 (w), 2959 (w), 2916 (w), 2870 (w), 2842 (w), 1650 (w), 1594 (w), 1488 (m), 1443 (m), 1374 (w), 1322 (w), 1260 (w), 1224 (w), 1202 (w), 1178 (w), 1069 (w), 1027 cm^{-1} (w); HRMS (EI): m/z calcd for $C_{16}H_{16}^+$: 208.1252; found: 208.1253.

Compound 22 b: Compound **22 b** (41 mg, 69%) was obtained as a pale-yellow oil from **17 e** and ethynyltrimethylsilane by following general procedure G. R_f = 0.6 (hexanes, UV, $KMnO_4$, PAA); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.79–4.72 (m, 2H), 2.90–2.85 (m, 2H), 2.55–2.49 (m, 2H), 2.37–2.31 (m, 2H), 1.74 (s, 3H), 0.19 ppm (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 154.9, 142.3, 121.4, 112.2, 99.8, 96.4, 39.8, 30.0, 29.6, 22.8, 0.2 ppm; IR: $\tilde{\nu}$ = 2962 (w), 2929 (w), 2254 (vw), 2140 (vw), 1722 (w), 1713 (w), 1698 (w), 1679 (w), 1631 (w), 1620 (w), 1613 (w), 1422 (w), 1410 (w), 1392 (w), 1378 (w), 1366 (w), 1360 (w), 1252 (m), 1174 (w), 1112 cm^{-1} (w); HRMS (EI): m/z calcd for $C_{13}H_{20}Si^+$: 204.1334; found: 204.1330.

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Compounds 22c–f: See the Supporting Information.

Compound 23a: Compound **23a** (83 mg, 88%) was obtained as a colorless oil from **17d** and ethynylbenzene by following general procedure G. R_f=0.33 (hexanes, UV, $KMnO_4$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.47–7.41 (m, 2H), 7.33–7.26 (m, 5H), 7.22–7.15 (m, 3H), 2.77–2.70 (m, 1H), 2.70–2.63 (m, 3H), 2.25–2.18 (m, 1H), 2.02–1.91 (m, 1H), 1.83 (q, J=2.0 Hz, 3H), 1.72–1.60 ppm (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ=156.3, 142.5, 133.2, 131.6, 128.5, 128.5, 128.1, 125.9, 123.6, 119.0, 91.4, 84.4, 43.1, 36.5, 34.6, 34.0, 14.7 ppm; IR: $\tilde{\nu}$=3413 (w), 3062 (w), 3028 (w), 2936 (w), 2863 (w), 2366 (w), 2335 (vw), 2201 (m), 1754 (m), 1710 (s), 1703 (vs), 1672 (s), 1644 (m), 1620 (w), 1599 (m), 1582 (w), 1493 (m), 1452 (m), 1436 (w), 1434 (m), 1416 (m), 1358 (m), 1315 (m), 1266 (s), 1175 (m), 1160 (m), 1142 (m), 1100 (m), 1071 (m), 1029 (m), 1000 cm^{-1} (m); HRMS (EI): m/z calcd for $C_{21}H_{20}^{+}$: 272.1565; found: 272.1598.

Compound 23b: Compound **23b** (107 mg, 91%) was obtained as a colorless oil from **17d** and 2-ethynyl-6-methoxynaphthalene by following general procedure G. R_f=0.20 (hexanes, UV, $KMnO_4$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.88 (t, J=1.1 Hz, 1H), 7.67 (t, J=8.7 Hz, 2H), 7.46 (dd, J=8.4, 1.7 Hz, 1H), 7.30 (ddd, J=7.6, 6.4, 1.9 Hz, 2H), 7.22–7.18 (m, 3H), 7.14 (dd, J=8.9, 2.5 Hz, 1H), 7.10 (d, J=2.5 Hz, 1H), 3.92 (s, 3H), 2.76 (ddd, J=12.0, 4.5, 2.2 Hz, 1H), 2.72–2.64 (m, 3H), 2.23 (dt, J=11.9, 2.1 Hz, 1H), 2.06–1.93 (m, 1H), 1.86 (d, J=2.0 Hz, 3H), 1.74–1.61 ppm (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ=158.3, 156.0, 142.6, 134.1, 131.2, 129.4, 129.2, 128.6, 128.6, 128.5, 126.9, 125.9, 119.5, 119.1, 118.5, 105.9, 92.0, 84.1, 55.5, 43.2, 36.5, 34.6, 34.1, 14.8 ppm; IR: $\tilde{\nu}$=3060 (w), 3026 (w), 2920 (m), 2843 (w), 2363 (w), 2340 (vw), 1717 (m), 1706 (w), 1700 (m), 1684 (w), 1653 (m), 1646 (m), 1625 (s), 1600 (vs), 1559 (m), 1540 (w), 1506 (m), 1498 (s), 1482 (s), 1456 (s), 1438 (m), 1419 (w), 1411 (m), 1391 (s), 1368 (w), 1364 (w), 1336 (w), 1266 (vs), 1250 (s), 1226 (m), 1207 (vs), 1164 (s), 1135 (m), 1069 (w), 1031 cm^{-1} (s); HRMS (EI): m/z calcd for $C_{26}H_{24}O^{+}$: 352.1827; found: 352.1822.

Compounds 23c–d: See the Supporting Information.

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[15] See the Supporting Information for assignments by 2D-NMR spectroscopy.

[16] Cyclobutenebromide **17f** was synthesized by reaction of the corresponding cyclobutenylzinc species with *N*-bromosuccinimide (see the Supporting Information). Suzuki cross-coupling of **17f** with $PhB(OH)_2$ under the conditions shown in Scheme 11 furnished phenylcyclobutene **19a** in 76% yield.

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2.2 Stereoselective Sequence toward Biologically Active Fused Alkylidenecyclobutanes

Organic LETTERS

Letter

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Stereoselective Sequence toward Biologically Active Fused Alkylidenecyclobutanes

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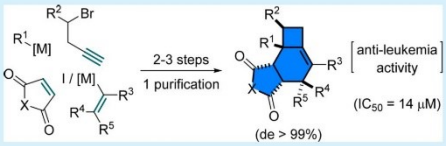
Supporting Information

ABSTRACT: Combining an efficient preparation of cyclobutenylmetal species, high-yielding cross-coupling reactions, and highly diastereoselective [4 + 2]-cycloaddition led to opening a new route toward the synthesis of fused alkylidenecyclobutanes containing up to five consecutive stereocenters. New complex architectures, analogues to protoilludane skeletons, were obtained in a very efficient manner and with a minimum number of steps starting from commercial sources and were tested for their cytotoxicity against leukemia cell lines HL60.



Among small, strained ring systems, unsaturated four-membered rings have fueled curiosity in the organic chemistry community as their selective formation remains a synthetic challenge. Over the past decade, alongside great advances in homogeneous catalysis, a growing interest in regio- and stereoselective methods has emerged,[1] featuring the importance and potential applications of such architectures.[2]

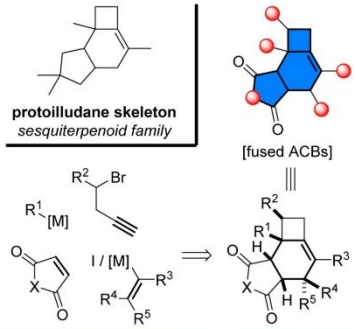
However, the study of cyclobutenes (CBs) and alkylidenecyclobutanes (ACBs) has undeniably suffered from the restricted number of strategies allowing their preparation. Recently, we have demonstrated the great ability of in situ generated cyclobutenylmetal species to undergo a subsequent cross-coupling reaction toward the formation of decorated cyclobutenes.[3] Alternatively, a stereoselective double boron homologation led to new embedded allylboron reagents that subsequently reacted with a variety of aldehydes to stereoselectively furnish enantioenriched ACBs in good to excellent yields.[4] We envisioned that opening a new and straightforward access to vinylcyclobutenes could ultimately unravel a path toward the diastereoselective synthesis of fused ACBs via a simple [4 + 2]-cycloaddition,[5] starting from readily available building blocks (Scheme 1), and leading expediently to direct heterocyclic analogues of protoilludanes, a family of sesquiterpenoids.[6]

Based on the cyclization strategy pioneered by Negishi, substituted homopropargyl bromides were employed to access the key cyclobutenylmetal intermediate (Scheme 2) through a successive deprotonation/carbometalation/π-cyclization sequence.[7]

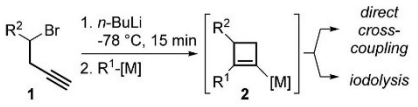
When an organozinc reagent ([M] = ZnCl) was employed for carbometalation, the possibility of a one-pot Negishi cross-coupling was explored to directly access vinylcyclobutenes in a one-pot sequence. At first, (*Z*)-alkyl-substituted alkenyl iodides **3a**–**c** were employed, giving the corresponding (*Z*)-**4a**–**c** with good yields and retention of the double-bond configuration. (*E*)-**3d** and the aryl-subsituted (*Z*)-**3e** also afforded the corresponding dienes (*E*)-**4d** and (*Z*)-**4e** with excellent yields up to 98% (Scheme 3).

Alternatively, iodolysis of the intermediate cyclobutenylmetal **2**-[**M**] gave access to corresponding iodocyclobutenes **2**-**I**, which was used as the cross-coupling partner in the presence of

Scheme 1. Retrosynthetic Approach



Scheme 2. Formation of the Key Cyclobutenylmetal Intermediate 2



R^1-[M] = 2-Me-allyl-ZnBr (1 equiv)
or Me_3Al (2 equiv) / Cp_2ZrCl_2 (1 equiv)

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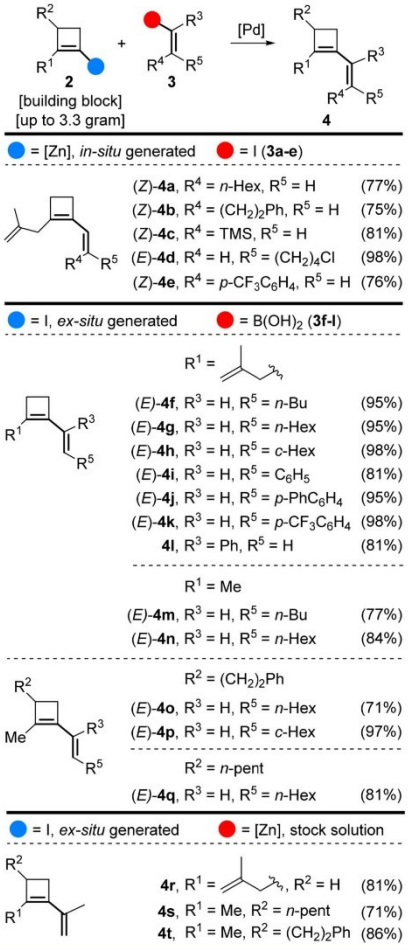
Scheme 3. Vinylcyclobutenes 4

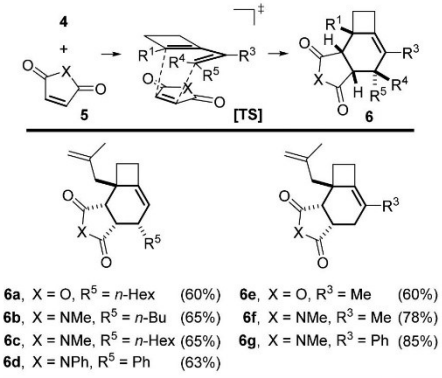


an alkenylmetal species. Employing alkyl-substituted alkenylboronic acids furnished dienes (*E*)-**4f**−**h** and (*E*)-**m**,**n** with excellent yields. Arylated alkenylboronic acids led to dienes (*E*)-**4i**−**k** with up to 98% yield. Branched alkenylboronic acids underwent a smooth Suzuki cross-coupling reaction, giving **4l** in 81% yield. Finally, **2-I** was engaged in the Negishi cross-coupling with isopropenylzinc, and the dienes **4r**−**t** were isolated in up to 86% yield.

With a solid building block synthesis, [4 + 2]-Diels−Alder cycloadditions were first attempted on isolated cyclobutane-embedded dienes **4**. Maleic anhydride **5a**, *N*-methylmaleimide **5b**, and *N*-phenylmaleimide **5c** were chosen as commercially available dienophile partners.

Having an alkyl chain as the R^5 substituent (from (*E*)-**4n**,**o**) led to generation of fused ACBs **6a**−**d** with good yields (up to 65%) and a perfect control of the diastereoselectivity (Scheme 4). A known model for the prediction of the stereochemical outcome of the [4 + 2]-cycloaddition can be proposed in which

Scheme 4. [4 + 2]-Cycloaddition toward Fused ACBs 6



orbital overlaps in the transition state [**TS**] are involved, leading to the major formation of the *endo* products **6a**−**d** (dr >99:1).[8] Changing the R^3 chain to a methyl or phenyl substituent (**4l** and **4r**) allowed for performing the cycloaddition within shorter reaction times, which we explained by a decrease in steric hindrance at the reacting carbon. Compounds **6e**−**g** were obtained in high yields up to 85% (dr >99:1).

On the basis of this successful experiment, we envisioned that the sequence could be shortened by using the crude dienes resulting from the cross-coupling reactions. Previously optimized conditions showed a complete conversion of the starting materials with a minimum amount of impurities, allowing for the direct use of the vinylcyclobutenes after simple extraction from the palladium salts. After the solvent was switched to toluene, the appropriate dienophile was added to the mixture and taken up to 90 °C for 18 h in a sealed tube. When a *cis*-iodoalkene **3** (R^4 = alkyl chain) was employed for the Negishi cross-coupling, subsequent Diels−Alder reactions with maleic anhydride led to fused ACBs **6h**,**i** with moderate yields (40−48%), while *N*-methylmaleimide gave **6j**,**k** with good yields up to 60% over three consecutive steps (cyclization−Negishi−Diels−Alder). In all cases, full control of the diastereoselectivity was observed (de >97%). Cross-coupling of 1-phenylvinylboronic acid (R^3 = Ph) gave access to **6v** after a two-step sequence (Scheme 5).

Interestingly, using cyclic alkenylboronic acids in situ generated via a Shapiro reaction from the corresponding tosyl hydrazones furnished bicyclic dienes that were engaged without purification in the Diels−Alder cycloaddition to give tetracyclic fused ACBs **6l**,**m** in moderate yields but with excellent diastereomeric ratios over three consecutive steps (Shapiro−Suzuki−Diels−Alder).[9] Initializing the sequence by direct deprotonation of 2,3-dihydrofuran followed by transmetalation to zinc and Negishi cross-coupling furnished the tetracyclic ACB **6n** after cycloaddition in 47% yield.[10] Alternatively, starting with *trans*-alkenylboronic acid in a Suzuki cross-coupling of cyclobutenyl iodides for the diene synthesis followed by a [4 + 2]-cycloaddition led to obtaining epimer structures **6o**−**u** in reasonable yields in a two-step sequence.

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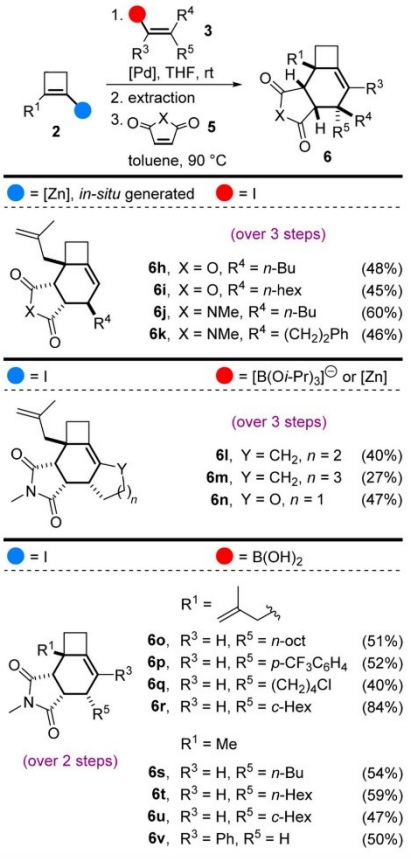
Scheme 5. [4 + 2]-Cycloaddition toward Fused Alkylidenecyclobutanes

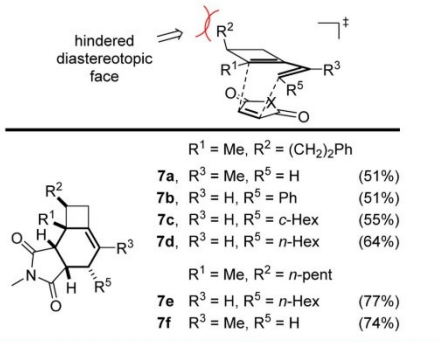


We then took a step further by performing a stereoselective [4 + 2]-cycloaddition by initially having a lateral chain on the starting diene. As described in Scheme 6, the cycloaddition should take place on the less hindered diastereotopic face of the cyclobutene, on the opposite side of R^2. Two substrates were employed in which $R^2 = (CH_2)_2Ph$ (**7a**–**d**) or *n*-pentyl (**7e**,**f**).[11] The simple addition of *N*-methylmaleimide on the crude dienes furnished the corresponding fused ACBs with up to 77% yields over two synthetic steps and with a perfect control of the diastereoselectivity induced by the presence of R^2.

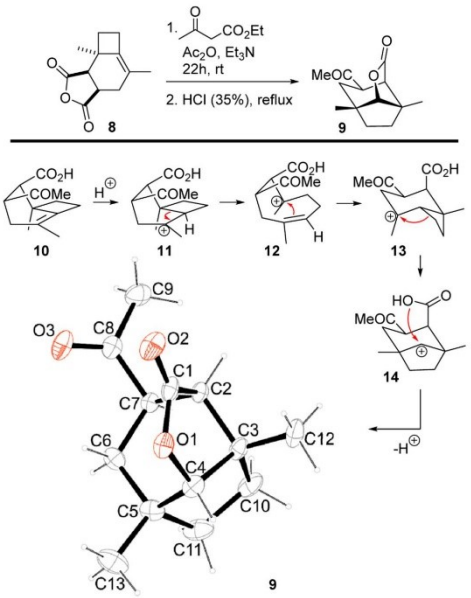
With the aim of uncovering a straightforward access to protoilludane skeleton analogues, we envisioned that the tricyclic ACB **8** could be transformed by a literature-known sequence using ethylacetoacetate to formally substitute the oxygen atom by a carbon atom.[12]

However, we surprisingly noted the formation of a new entity resulting from an unprecedented ring-enlargement rearrangement, as confirmed by X-ray analysis (Scheme 7).[8,11] We propose to explain this unusual rearrangement by

Scheme 6. Diastereoselective [4 + 2]-Cycloaddition of Chiral Dienes 4



Scheme 7. Cationic ACB Ring Enlargement



the initial protonation of the alkylidene group to give a tertiary carbocation **11**. The subsequent ring-opening–ring-closing sequence led to the more stable cyclobutane structure **13** through **12**. 1,2-Alkyl transposition gives the secondary carbocation **14**, which finally undergoes a ring-closing reaction of the carboxylic moiety and furnishes exclusively **9** as a crystalline compound.[11] Furthermore, deuteration experiments with DCl supported the initial protonation of the alkylidene as described in Scheme 7.

Finally, the utility of such a methodology was featured with bioassays on different tricylic alkylidenecyclobutanes. While a range of bacteria, fungi, and algae seemed to be resistant,

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interesting activities were observed when tested against HL60 (leukemia cell lines).

Cytotoxicity of **6f**,**g**, **6r**, **6b**,**c**, and **6p** was measured via MTT assays (Figure 1). Only a low bioactivity was obtained for a

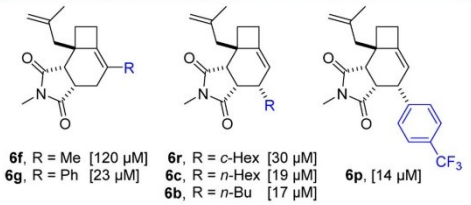

Figure 1. IC_{50} measurements of fused ACBs against HL60.

tetra-alkyl-substituted alkylidene **6f**. However, changing the side chain to a phenyl group (**6g**) drastically improved the activity against HL60 (IC_{50} = 23 μM). A reasonable cytotoxicity was measured for **6r** and **6b**,**c** possessing alkyl chains on the central ring (IC_{50} = 17−30 μM). Finally, exchanging the previous alkyl group for the *p*-CF_3-phenyl moiety (**6p**) improved the cytotoxicity to 14 μM.

In conclusion, we have demonstrated a very efficient and expedient route to access tri- and tetracyclic fused alkylidene-cyclobutanes with perfect control over the diastereoselective outcome and possessing up to five stereogenic centers, one being quaternary. Starting from readily available substrates, targets were obtained in a minimum number of steps, requiring only a single and final purification. Some of the structures showed a specific cytotoxicity against HL60, encouraging us to pursue our investigations further toward potential applications in pharmacology.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00724.

Experimental procedures and spectroscopic characterization (IR, HRMS, ^{1}H and ^{13}C NMR data, and X-ray diffraction data) of all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(8) Relative configurations resulting from [4 + 2]-cycloadditions were attested by 2D NMR studies and X-ray diffraction; see the SI.

(9) In-situ cross-coupling following the Shapiro reaction was done according to: Passafaro, M. S.; Keay, B. A. *Tetrahedron Lett.* **1996**, *37*, 429−432.

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(11) CCDC 1536131 (**7b**), CCDC 1536132 (**8**), and CCDC 1536133 (**9**) contain the supplementary crystallographic data for this paper.

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2.3 Oxidative Ring Contraction of Cyclobutenes: General Approach to Cyclopropylketones including Mechanistic Insights

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Oxidative Ring Contraction of Cyclobutenes: General Approach to Cyclopropylketones including Mechanistic Insights

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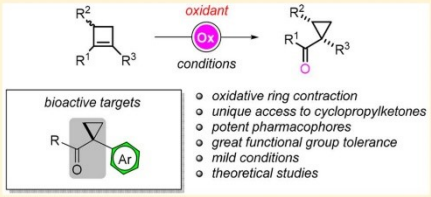
Supporting Information

ABSTRACT: An original oxidative ring contraction of easily accessible cyclobutene derivatives for the selective formation of cyclopropylketones (CPKs) under atmospheric conditions is reported. Comprehensive mechanistic studies are proposed to support this novel, yet unusual, rearrangement. Insights into the mechanism ultimately led to simplification and generalization of the ring contraction of cyclobutenes using *m*CPBA as an oxidant. This unique and functional group tolerant transformation proceeds under mild conditions at room temperature, providing access to a new library of polyfunctionalized motifs. With CPKs being attractive and privileged pharmacophores, the elaboration of such a simple and straightforward strategy represents a highly valuable tool for drug discovery and medicinal chemistry. Additionally, the described method was employed to generate a pool of bioactive substances and key precursors in a minimum number of steps.

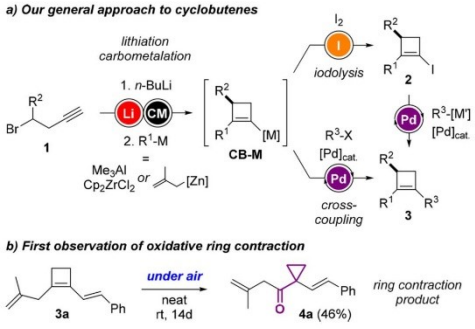


INTRODUCTION

Four-membered carbocyclic architectures, especially cyclobutenes, have recently become a source of inspiration for dependable synthetic methodologies because of their inherent ring strain.[1]

While most documented strategies are based on [2 + 2]-cycloadditions and transition-metal-catalyzed processes,[2] we have described an efficient, general, and regioselective route to cyclobutenes via the intermediate formation of an easily accessible cyclobutenylmetal species **CB-M** (Scheme 1a) from bromobutynes **1**.[3] This one-pot generated **CB-M** was then engaged either in a direct cross-coupling reaction with aryl halides or in a relayed sequence involving intermediate formation of iodocyclobutenes **2**. The synthetic approach to functionalized cyclobutenes **3** was studied in depth, leading to a unique library of diversified aryl-, heteroaryl-, alkynyl- and vinylcyclobutenes. While **CB-M** could be used in one-pot sequences to form challenging alkylidenecyclobutanes,[4] vinylcyclobutenes were transformed into strained fused ring systems.[5] Interestingly, when vinylcyclobutene **3a** was left under atmospheric conditions (Scheme 1b) a formal oxidative ring contraction was observed and cyclopropylketone (CPK) **4a** was isolated in 46% yield.

Scheme 1. Our Access Path to Cyclobutenes (a) and the First Observation of Oxidative Ring Contraction (b)



Notably, CPK-based pharmacophores can be found in a number of bioactive substances (Figure 1, **A**−**F**)[6] by exalting crucial hydrophobic interactions.[7] Efficient strategies that allow for a rapid and selective construction of these strained pharmacophores represent valuable tools for drug discovery and high throughput screenings.

Surprisingly, only a few methods are described concerning the synthesis of such structures possessing aromatic, heteroaromatic, or vinylic substituents, and those require in most cases a large number of steps with low functional group tolerance So far, formation of *gem*-disubstituted cyclopropanes has been achieved by employing preformed carbonylated cyclopropanes,[8] double alkylations with dihaloethanes,[9] Corey−Chaykovsky cyclopropanations,[10] or α-arylation of cyclopropyl nitriles[11] or, more recently, via transition-metal-catalyzed oxidative cyclopropanations of alkynes.[12] Intrigued by

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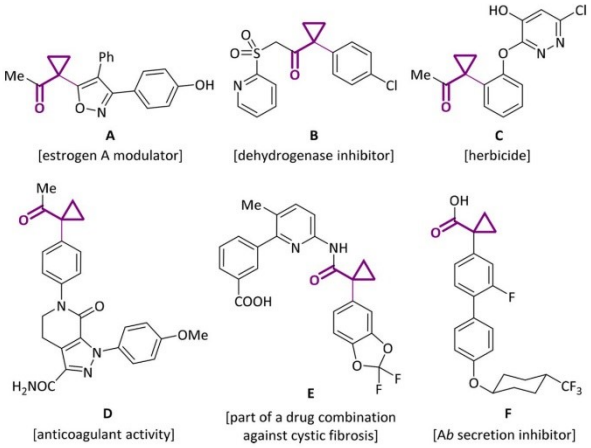
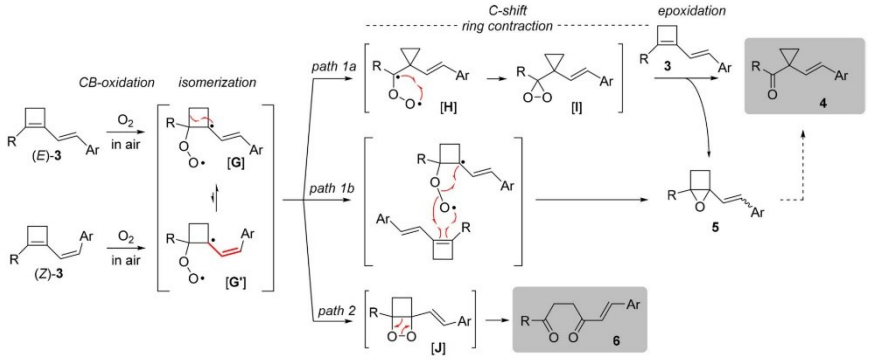


Figure 1. CPK-containing bioactive substances.[6]

Scheme 2. Proposed Mechanism for the Oxidative Ring Contraction of Cyclobutenes (Path 1) and Oxidative Ring Opening (Path 2)



the simplicity of our innovative sequence, when compared to functional group sensitive reported processes, we took on the challenge of generalizing the access to these important modules.

RESULTS AND DISCUSSION

On the Mechanism of the Oxidative Ring Contraction with O_2. After the first observation of ring contraction of cyclobutenes under air, we became interested in the generalization and application of such an uncommon reaction.[13] We thus started investigating the mechanism of the transformation to understand, and ultimately optimize, the synthesis of CPKs from cyclobutenes. Here we propose a mechanism for the oxidative addition of O_2 onto cyclobutenes, inspired by the early findings of Priesnitz et al.[13a] Fundamental mechanistic assumptions were addressed both experimentally and by quantum-chemical calculations, the details of which can be found in the Supporting Information. We describe and compare two alternative routes that can be envisioned for the formation of CPKs.

As the reaction readily occurs under air, we propose that cyclobutene (*E*)-**3** is first oxidized by the presence of triplet O_2, giving the biradical species [**G**] (Scheme 2). Importantly, we noticed that starting from either (*E*)-**3** or (*Z*)-**3** derivatives led to the same (*E*)-**4** isomer. First, the consideration of this allows for explanation of the double-bond isomerization through an intermediate π-allyl radical species, the equilibrium being displaced toward the thermodynamic *E* product [**G**]. Two paths can then be described: in path 1a, a ring contraction takes place resulting in [**H**], which leads to formation of the dioxirane [**I**]. As dioxiranes are very reactive species, we assumed that a fast epoxidation occurs, consuming an equimolar amount of the starting material **3**. However, a second route (path 1b) can be described, where **G** reacts in a concerted radical epoxidation with a molecule of the cyclobutene substrate **3**, giving the same intermediate **5** as path 1a. In parallel, path 2 can be followed in which a 1,2-dioxetane [**J**] is formed as the product of a formal

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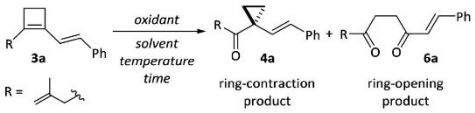
[2 + 2]-cycloaddition. A subsequent ring-opening reaction undergoes the formation of 1,4-diketone **6**.

Formation of CPKs vs 1,4-Diketones under Atmospheric Conditions. Taking into account that a carbon shift of substituted epoxides can be triggered by addition of a Lewis acid or under thermal conditions (Meinwald rearrangement),[13,14] optimizations were undertaken to favor the exclusive formation of the oxidative ring contraction product **4** (Table 1). Particular observations of such cyclobutene oxide rearrangements have been reported in the past but in most cases with low efficiency and versatility.[15]

Table 1. Condition Optimizations



entry	oxidant	solvent	temp (° C)	time (h)	conv (%)	**4a**/**6a**[a]
1	air	neat	rt	24	50	87:13
2	O_2	neat	rt	2	98	30:70
3	O_2	H_2O	rt	2	92	38:62
4	air	EtOAc	rt	48	>99	77:23
5	-[b]	neat	rt	20	0	
6	air[c]	EtOAc	rt	20	0	
7	air[d]	EtOAc	rt	20	0	
8	***air***	***neat***	***100***	***3***	***89***	***>99:1***

[a]Conversion of the starting material and ratios determined by GC. [b]Under N_2. [c]TEMPO (1 equiv) was added. [d]BHT (1 equiv) was added.

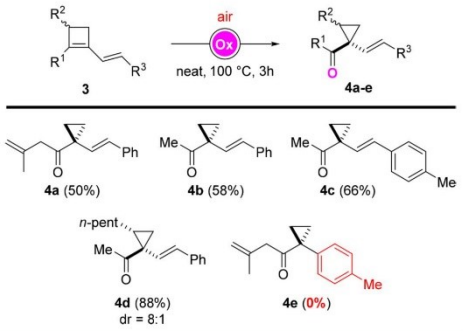
Performing the reaction neat in air led to incomplete conversion, while pure oxygen favored the formation of 1,4-diketone **6a** (entries 1 and 2), as recently exemplified by Loh and co-workers.[16] Similar ratios were observed when H_2O was used as a solvent in the presence of O_2 (entry 3), and prolonged reaction times were noted when substrates were solubilized in EtOAc (entry 4). In the absence of air (nitrogen atmosphere), no oxidation was observed, leaving the starting material unreacted (entry 5). Addition of TEMPO or BHT to the solution prevented the reaction, supporting the assumption of an initial radical addition of O_2 to the unsaturated system (entries 6 and 7), and the starting material was recovered. Taking the reaction under air up to 100 °C afforded full conversion of the starting cyclobutene in 3 h, furnishing exclusively the mono-oxidized compound **4a**, supporting the intermediate formation of cyclobutene oxide **5**, undergoing a dyotropic rearrangement at higher temperatures (entry 8).

Through a favored path 1 under thermal conditions (see Scheme 2), the exclusive formation of the desired product is the result of two converging and complementary reactions: (1) the consumption of the dioxirane [**I**] giving the ketone **4** along with the epoxide **5** and (2) the Meinwald rearrangement of the latter epoxide under thermal conditions.

With optimized conditions in hand for air-promoted oxidative ring contraction, cyclobutenes **3a**−**c** led to CPKs **4a**−**c** in good yields up to 66%. When chiral cyclobutene **3d** was used, **4d** was isolated with a good diastereoisomeric ratio (dr = 8:1 determined by ^{13}C NMR, Scheme 3).

Surprisingly, when arylcyclobutene (**3e**) was subjected to similar conditions, none of the corresponding CPK **4e** could be

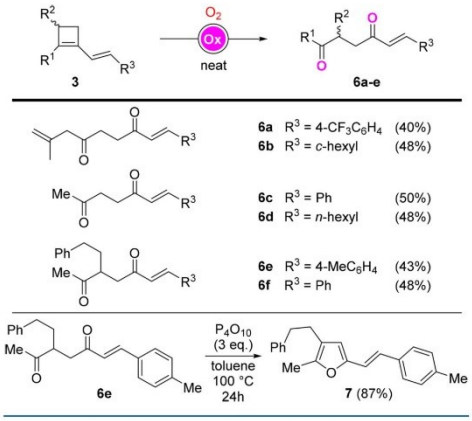
Scheme 3. Representative Examples of Air-Promoted Oxidative Ring Contraction



detected, even after prolonged reaction time (further optimizations will be disclosed later).

As depicted in Table 1, the use of pure oxygen favored a formal [2 + 2]-cycloaddition, giving a majority of 1,4-diketone **6**. The scope of this transformation was briefly explored, as such motifs present synthetic applications in organic chemistry.[16] Vinylcyclobutenes **3** were submitted to an atmosphere of dioxygen, furnishing diketones **6a**−**f** in moderate yields (Scheme 4). Moreover, **6e** was employed in a Paal−Knorr condensation to undergo the formation of trisubstituted furan **7** in 87% yield.

Scheme 4. Synthetic Scope of 1,4-Diketone Formation



Selective Formation of CPKs with Oxidants. Overcoming the limitation of the ring contraction to styryl systems required developing additional optimizations. Diverse oxidizing reagents were tested for the transformation of **3a** and **3e** into **4a** and **4e**, respectively (Table 2)

Even though DMDO afforded full conversion of **3a** at room temperature (entry 1, Table 2), many overoxidized side products were observed. When *m*CPBA was used (entries 2 and 3), complete consumption of the starting material was observed, giving the desired ring-contracted product independ-

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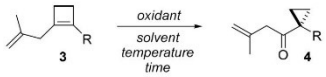
Table 2. Condition Optimizations



entry	R	oxidant	temp. (° C)	t	conv. (%)[a]
1		DMDO[b]	rt	3h	>99[c]
2		*m*CPBA[d]	0	10min	>99
3		***m*CPBA[d]**	***rt***	***10min***	***>99***
4	***p-Tol***	***m*CPBA[d]**	***rt***	***10min***	***>99***
5	*p*-Tol	*m*CPBA[e]	rt	18h	75[f]
6	*p*-Tol	*t*-BuOOH[d]	rt	18h	traces
7	*p*-Tol	AcOOH[d]	rt	18h	33
8	*p*-Tol	H_2O_2[g]	rt	18h	traces
9	*p*-Tol	NaOCl[h]	rt	18h	70[h]

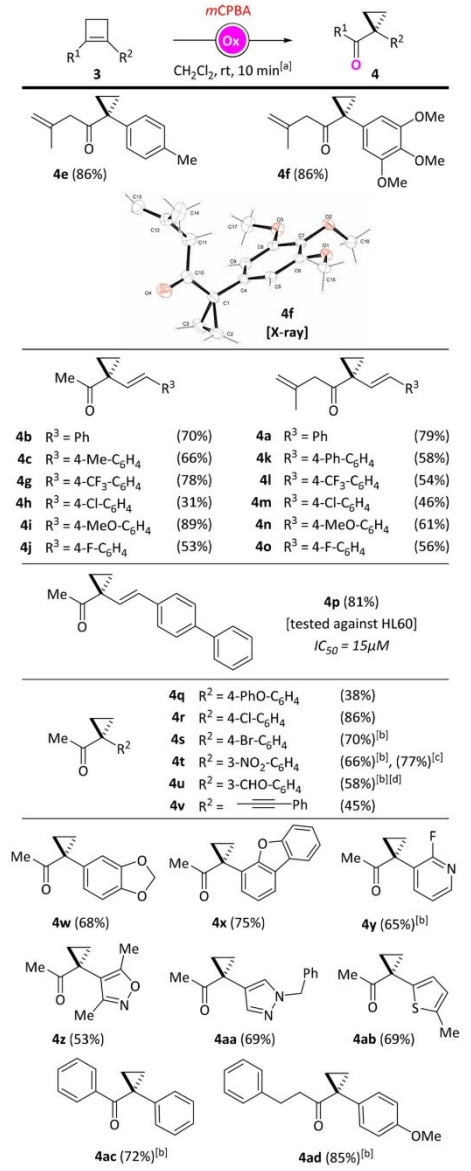
[a]Conversion of the starting material and proportions determined by GC/NMR. [b]Acetone from the in situ generation of DMDO. [c]Many side products observed. [d]1 equiv, in CH_2Cl_2 [e]$NaHCO_3$ (2 equiv) was added to the reaction. [f]75% conversion of the starting material, but in a 50:50 ratio of epoxidation product and desired product **4**; see the SI. [g]5 equiv, NaOH (0.1 equiv), in MeOH. [h](*R*,*R*)-Jacobsen's catalyst (5 mol %): 70% conversion of the starting material, but in a 30:70 ratio of epoxidation product and desired product **4**; see the SI.

ently from the temperature.[17] Interestingly, only the most activated double bond (cyclobutene) reacted during the reaction, leaving both allyl and vinyl groups untouched. Moreover, the air-stable substrate **3e** furnished the rearranged product **4e** under these optimized and mild conditions. We assumed that the Meinwald rearrangement was assisted by the presence of *m*-chlorobenzoic acid, released by the epoxidation reaction. To test this hypothesis, a similar experiment (entry 5) was conducted in the presence of $NaHCO_3$. If 75% conversion were observed, the ring contraction was partially inhibited by the presence of the base, as the cyclobutene oxide was observed in a 50:50 ratio with the desired cyclopropylketone, thus supporting the intermediary epoxide formation as well as the assistance of the acid in the ring-contraction process. Furthermore, the scope of oxidants was evaluated. While alkyl peroxide or hydrogen peroxide did not promote any oxidation, leaving the starting material unreacted (entries 6 and 8), peracetic acid afforded 33% conversion after 18h (entry 7). At last, Jacobsen's catalyst was employed in the presence of sodium hypochlorite (entry 9) and could convert 70% of the starting cyclobutene **3e** in 18 h. However, the uncontracted cyclobutene oxide was detected in a 30:70 ratio with the desired product **4**, supporting the need for acidic conditions in the Meinwald rearrangement.

To establish the scope of the transformation, a range of cyclobutenes was engaged in the oxidative ring contraction under reoptimized conditions. First, **3e**, which remained unaffected under an atmospheric environment, furnished the desired CPK **4e** in 86% yield (Scheme 5). Likewise, an electroenriched substrate led to the expected ring-contracted product **4f** in similar yield, and a crystal structure was obtained to confirm the presence of the cyclopropylketone scaffold.[18]

Vinylcyclobutenes, the oxidative ring contraction of which was established with air, underwent smooth conversion to CPKs **4a**−**c** and **4g**−**o** with peracids in similar to high yields (up to 89%).

Scheme 5. Representative Examples of *m*CPBA-Promoted Oxidative Ring Contraction



[a]*m*CPBA (1 equiv). [b]$BF_3{\cdot}OEt_2$ (1 equiv) was added to the reaction mixture. [c]The product was obtained from the corresponding 3-$NH_2C_6H_4$ derivative. [d]The aldehyde was obtained after hydrolysis, starting from the corresponding 1,3-dioxolane (see the Supporting Information).

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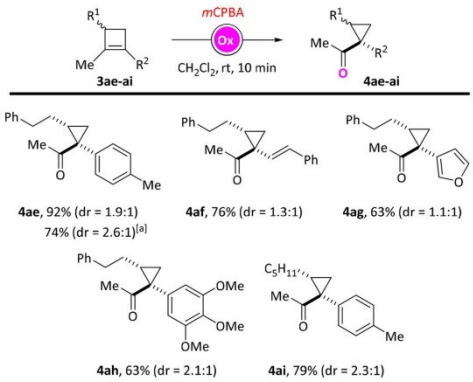
Noteworthy, the very simple CPK-containing skeleton **4p** was found to possess a moderate activity against tumor cells HL60 (IC_{50} = 15 μM; see the SI). In all cases, only the internal strained alkene reacted with the oxidant, leaving additional double bonds intact. In a second instance, aryl-substituted cyclobutenes were subjected to oxidation, yielding the corresponding adducts **4q–u** and **4w**. While electron-donor substituents underwent a direct ring contraction (**4q,r**, **4w**), the addition of a Lewis acid ($BF_3{\cdot}OEt_2$) was needed to drive the reaction to completion with electron-withdrawing groups (**4s–u**). Although an alkynyl derivative also furnished the desired product, a lower yield was obtained (**4v**, 45%). Finally, we pushed the methodology further to test the versatility of the process when using heteroarylated cyclobutenes. Dibenzofuryl, fluoropyridyl, dimethyloxazolyl, and benzylpyrazolyl substituents were tolerated, and the corresponding compounds **4w–z** were isolated in good yields up to 75%. Interestingly, the presence of a sulfur atom in the aromatic core (thiophene-yl) did not affect the course of the transformation, giving the derivative **4ab** in good yield (69%), the aromatic ring remaining unoxidized. Finally, different approaches were employed to introduce phenyl and ethylphenyl moieties on the starting cyclobutene.[19,20] Their oxidation in the presence of *m*CPBA led to diversely substituted cyclopropylketones **4ac** and **4ad**, thus extending the scope of the oxidative ring contraction to aryl and alkyl groups.

Next, we investigated the oxidative ring contraction of chiral cyclobutenes (Scheme 6).

Scheme 6. Representative Examples of *m*CPBA-Promoted Oxidative Ring Contraction



[a]−40 °C to rt, 3 h.

Employing similar oxidative conditions, cyclobutenes **3ae–ai** underwent rapid ring contraction, providing CPKs **4ae–ai** in good to excellent yields (up to 92%, **4ae**). The diastereoselectivity of the transformation seems to depend on the nature of the substrate. Only moderate to low diastereomeric ratios were observed (dr up to 2.3:1). We attributed the deficiency in stereoselectivity to a fast epoxidation, the shielding effect of the R^1 chain playing only a minor role in the stereodifferentiation of the double bond. Decreasing the temperature to −40 °C slightly improved the diastereoselectivity for the ring contraction to 2.6:1 dr (**4ae**).

Synthesis of Bioactive Targets. To further explore the synthetic utility of our methodology, we set out to access bioactive substances or their related precursors (Scheme 7). A common starting material (4-bromobutyne) was utilized to begin these syntheses. Cyclobutene iodides were formed in a one-pot process through lithiation/carboalumination/iodolysis and, after simple extraction, reacted using a palladium-catalyzed Negishi or Suzuki cross-coupling reaction to afford the corresponding arylated cyclobutenes. Further oxidation with *m*CPBA was performed on crude materials, giving CPKs **4r**, **4w**, and **4aj** in good yields (68–86%). At first, postderivatization was achieved on the methylketone moiety of **4r** by enolization/electrophilic trapping employing 2-pyridylsulfonylfluoride to provide the dehydrogenase inhibitor **B** in a single step. Second, modification of the methylketone was carried out through haloform reaction with CCl_4, providing cyclopropylcarboxylic acids **8a,b** in quantitative yields. Importantly, **8b** stands as the precursor in the lumacaftor (**E**) synthesis (potent drug against cystic fibrosis in combination with ivacaftor).[6g] Prederivatization was also envisioned and applied to the synthesis of an analogue structure of the herbicide **C** providing the deoxy-**C** herbicide in 43% yield over two steps. Initial Suzuki cross-coupling of previously iodinated **CB-M** (see Scheme 1) with (2-methoxyphenyl)boronic acid resulted in the corresponding cyclobutene **9** in 77%. Upon exposure of **9** to BBr_3, followed by nucleophilic substitution on dichloropyridazine, **10** was obtained and directly employed in the final oxidative ring contraction without purification, completing the synthesis of deoxy-C **11** in 43% yield over two steps.

Sequence To Access Cyclopropyl Aldehydes. To ensure a broader applicability of the method, we finally assembled a sequence for the formation of cyclopropylaldehydes. To achieve that goal, commercially available cyclobutanone **12** was submitted to nucleophilic addition of an arylmetal species, and the resulting alcoholate was further acetylated. β-Elimination on **15** in the presence of lithium bromide after exchanging the solvent with dimethylformamide furnished arylated cyclobutene **16**. With a sufficient purity, **16** was further engaged without purification in the oxidative ring contraction in the presence of *m*CPBA, giving the desired rearranged compounds **13a–f** (Scheme 8). Employing diversely substituted aromatic structures showcases the efficient formation of a range of cyclopropyl aldehydes in six steps from commercial sources and with a sole purification step in moderate to good yields (34 to 69%).

■ COMPUTATIONAL ANALYSIS

The proposed mechanism of the oxidative ring contraction of cyclobutene **3** (Scheme 2) was investigated theoretically for a better understanding. DFT with the B3LYP functional and the 6-31G(d) basis set of the program package Gaussian16[21] was used generally for all geometry optimizations. Only geometry point TSDK1 was computed at the CASSCF/6-31G(d) level of theory with the program package Molpro2012[22] for a correct description of the state.

The energies of the discussed reaction scheme were then obtained by applying the CASPT2 routine of the program package Molcas 8.2[23] with the ANO-L-VDZP basis set on the optimized structures. It is a common procedure to perform geometry optimizations on a low level of theory, as, e.g., DFT, and then correct the calculated energies using single-point calculations at a higher level of theory, as, e.g., the CASPT2, to include nondynamic and dynamic electron correlation.[24]

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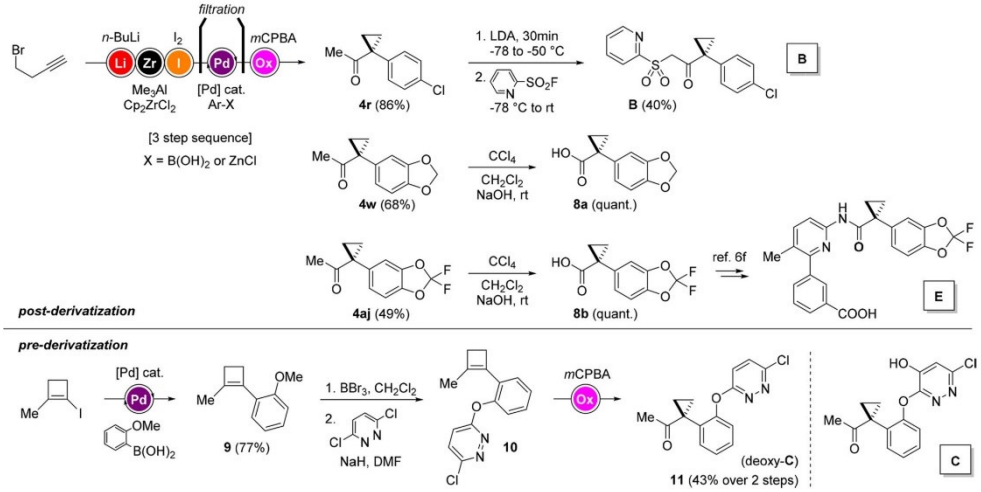
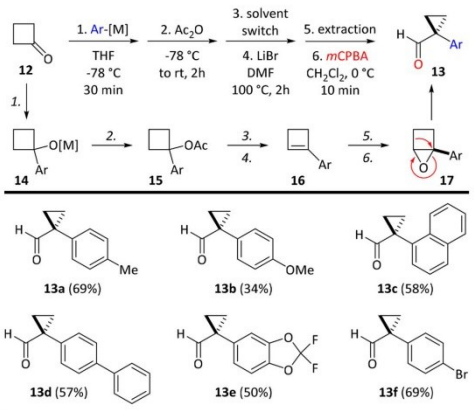
Scheme 7. Straightforward Syntheses and Formal Synthesis of Bioactive Substances through Oxidative Ring Contraction



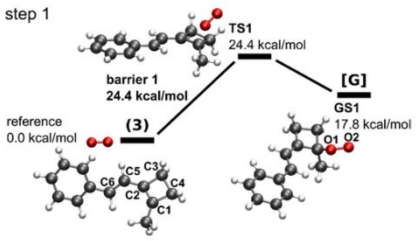
Scheme 8. Direct Access to Cyclopropyl Aldehydes from Commercially Available Cyclobutanone



Investigating the mechanism proposed in Scheme 2 computationally, we need to describe diradicalic structures. To do this correctly, we use the multireference method CASPT2. A more detailed description of the computational methods is given in the Supporting Information. Specific options for the CASPT2 calculations, as the chosen active space, are discussed there. For completeness, we also show the results at the B3LYP level of theory.

The first step of the mechanism (Scheme 9) is the same for both observed products, cyclopropane **4** and diketone **6**. Triplet oxygen ($^3O_2$) adds to the C−C double bond of the cyclobutene ring forming a C−O bond between C1 and O1 to generate the diradical GS1. The barrier for this addition lies with 24.4 kcal/mol in the possible range for a slow reaction at room temperature. At GS1, the occupied T_1 state and the S_0 state

Scheme 9. Barrier for the Addition of Triplet Oxygen ($^3O_2$) to Cyclobutene 3 at the CASPT2/ANO-L-VDZP Level of Theory[a]



[a] [G] corresponds to the nomenclature used in Scheme 2. The given energies are referenced to the energy of the educts, cyclobutene **3**, and $^3O_2$, separated at 10 Å. Additionally, the numbering of important atoms used in the following discussion is shown.

both have the equivalent electronic diradicalic character and lie energetically close with $\Delta E \approx 0.001$ eV. Figure 2 a shows the two single occupied orbitals of the S_0 and T_1 state to confirm the diradicalic character. One electron is localized at the oxygen

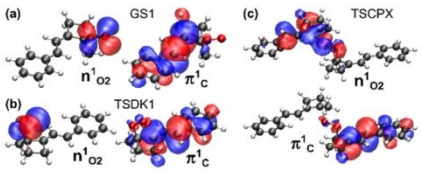


Figure 2. Single occupied orbitals of the S_0/T_1 state at (a) GS1, (b) TSDK1, and (c) TSCPX showing the diradicalic character at this geometry points.

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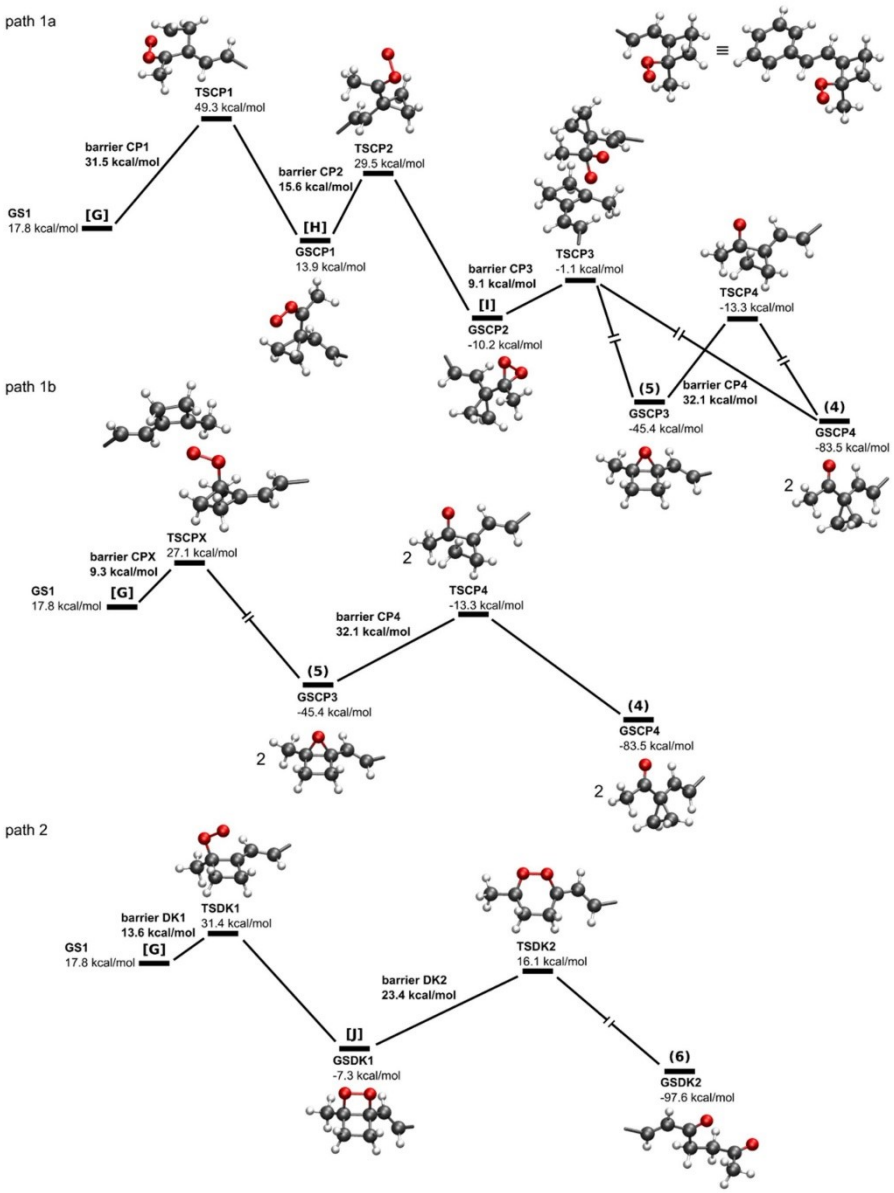
Scheme 10. Reaction Scheme for Paths 1a, 1b, and 2 of the Oxidative Ring Contraction of Cyclobutene 3 at the CASPT2/ANO-L-VDZP Level of Theory[a]



[a]The labels in brackets correspond to the nomenclature used in Scheme 2. The structures are shown without the phenyl ring. The energies are referenced to the energy of the educts, cyclobutene **3**, and $^3O_2$, separated at 10 Å.

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atom O2, and the second is delocalized over the allylic positions C2 and C6. The S_0 and T_1 states remain energetically close and keep their electronic character along the reaction path to the corresponding next transition state of each investigated pathway (Figure 2b,c). Calculations of the spin-orbit coupling suggest that intersystem crossing is possible in those regions. A detailed discussion and the calculated values are given in the Supporting Information. In the following discussion, we expect that intersystem crossing took place and all points are evaluated in the singlet ground state S_0.

Scheme 10 summarizes the results for the reaction pathways path 1a, path 1b, and path 2 discussed in Scheme 2. In path 1a, first proposed by Priesnitz,[13a] the predicted dioxirane [**I**] (GSCP2) is reached in a stepwise process. First, the cyclobutene ring is rearranged to a cyclopropane ring to form GSCP1 [**H**]. The C−C bond between C1 and C4 is broken, and a bond between C2 and C4 is built in one step via TSCP1. This is followed by the formation of the second C−O bond between C1 and O2 via TSCP2 to form dioxirane [**I**]. For the next step, Priesnitz proposed that cyclobutene **3** is epoxidized by dioxirane [**I**]. This step via TSCP3 leads to the product CPK **4** (GSCP4) and the intermediate, epoxide **5** (GSCP3). Epoxide **5** can form another CPK **4** molecule via TSCP4, which corresponds to a Meinwald rearrangement.[13,14] The first step of path 1a has a high barrier of 31.5 kcal/mol to TSCP1 accounting for a total barrier of 49.3 kcal/mol, which makes this pathway highly unlikely. Apparently, the rearrangement of the carbon bonds forming a cyclopropane ring from a cyclobutene ring is unfeasible at this point of the reaction path.

In Scheme 2 another mechanistic pathway to cyclobutene **3** was proposed (path 1b). Here, a direct epoxidation takes place after the addition of $^3O_2$ without formation of the cyclopropane ring. The diradical GS1 can epoxidize cyclobutene **3** via TSCPX to form two molecules of intermediate epoxide **5** (GSCP3). The next step of this pathway is the same as of path 1a. CPK **4** (GSCP4) is built via Meinwald rearrangement of epoxide **5**. The barrier to TSCPX is with a value of 9.1 kcal/mol a lot of smaller than the barrier to TSCP1, which makes path 1b the favored pathway toward cyclobutene **4**. The second transition state of this path (TSCP4) can be reached via a barrier of 32.1 kcal/mol, the largest barrier of this pathway. In the following, only the here proposed novel path 1b is discussed as reaction pathway leading to the product **4**.

The reaction toward the second product, diketone **6**, is described with path 2. Here, the first transition state (TSDK1) leads to a formation of a four-membered ring between the oxygen molecule and the two carbon atoms of the C−C double bond. This intermediate, dioxetane [**G**] (GSDK1), corresponds to a classical [2 + 2] cycloaddition product between $^3O_2$ and an alkene. The barrier for this step accounts for 13.6 kcal/mol. In the second step, the bonds of the four-membered dioxetane ring are rearranged via a six-membered transition state (TSDK2) to form diketone **6** (GSDK2). The corresponding barrier (23.4 kcal/mol) is of the same magnitude as the barrier for the first addition of $^3O_2$ to **3** (step 1).

Comparing both pathways (path 1b and path 2), first, confirms that the formation of both products is possible and, second, reveals a difference in 4.3 kcal/mol for the corresponding first barriers in favor of reaction path 1b. This also results in a difference of the same value in the total barriers of both pathways. Third, diketone **6** is the more stable product lying 14.1 kcal/mol lower than CPK **4**.

In contrast to dioxetane [**J**], the intermediate epoxide **5** could be detected experimentally. This can be explained by the fact that **5** (GSCP3) is around 38.1 kcal/mol more stabilized than [**J**] (GSDK1). Furthermore, comparison of the corresponding barriers to each next step reveals that the barrier to TSCP4 is around 8.7 kcal/mol larger than the barrier to TSDK2. This means, the Meinwald rearrangement via TSCP4 to generate CPK **4** happens on a slower time-scale so that intermediate **5** can be detected under the given experimental conditions. The rearrangement toward **6** is expected to happen at the same time-scale than the initial attack of $^3O_2$ to **3** since the barriers are of the same height.

All computational results are in good agreement with the experimental product distributions under different reaction conditions. Using thermodynamical conditions with a low reaction temperature and a long reaction time leads preferentially to the more stable product diketone **6**. In contrast, using kinetic conditions with a high reaction temperature and a short reaction time leads to CPK **4** whose pathway has the lower overall barrier. Furthermore, the observation of better yields of diketone **6** when the reaction is conducted under pure oxygen atmosphere (in contrast to the normal atmospheric conditions) can be explained by the theoretical results. The decisive transition state for the formation of CPK **4** (TSCPX) is a two-molecule transition-state between GS1 and educt cyclobutene **3**. When more oxygen is available for the first reaction step, the addition of $^3O_2$ to **3**, less reaction partner for GS1 is available to form epoxide **5** (GSCP2).

In summary, the proposed as well as observed intermediates are verified, and the complete proposed reaction mechanism is strongly supported by the theoretical study.

■ CONCLUSIONS

We have demonstrated a novel and efficient air-promoted oxidative ring contraction of easily generated vinyl cyclobutenes. Combining theoretical studies with experimental investigations finally led to proposing a new mechanistic path for the formation of α-substituted cyclopropylketones. These modules possessing interesting pharmacological properties, a general and selective sequence was designed starting from readily available substrates, allowing the synthesis of a wide variety of functionalized scaffolds. Such a straightforward approach undoubtedly opens an entire platform for high throughput screening in drug discovery processes.

■ EXPERIMENTAL SECTION

General Considerations. Commercially available starting materials were used without further purification unless otherwise stated. All reactions were carried out under N_2 atmosphere in flame-dried glassware. Syringes, which were used to transfer anhydrous solvents or reagents, were purged with nitrogen prior to use. CH_2Cl_2 was predried over $CaCl_2$ and distilled from CaH_2. THF was refluxed and distilled from sodium benzophenone ketyl under nitrogen. Et_2O was predried over $CaCl_2$ and passed through activated Al_2O_3 (the solvent purification system SPS-400-2 from Innovative Technologies, Inc.). Toluene was predried over $CaCl_2$ and distilled from, CaH_2. Chromatography purifications were performed using silica gel (SiO_2, 0.040−0.063 mm, 230−400 mesh ASTM) from Merck. The spots were visualized under UV (254 nm) or by staining the TLC with $KMnO_4$ solution (K_2CO_3, 10 g; $KMnO_4$, 1.5 g; H_2O, 150 mL; NaOH 10% in H_2O, 1.25 mL), PAA: *p*-anisaldehyde solution (concd H_2SO_4, 10 mL; EtOH, 200 mL; AcOH, 3 mL; *p*-anisaldehyde, 4 mL). Diastereoisomeric ratios were determined by ^1H NMR and ^{13}C NMR.

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^{13}C and ^{1}H NMR spectra were recorded on Varian Mercury 200, Bruker ARX 300, Varian VXR 400 S, and Bruker AMX 600 instruments. Chemical shifts are reported as δ values in ppm relative to residual solvent peak (^{1}H NMR) or solvent peak (^{13}C NMR) in deuterated chloroform ($CDCl_3$: δ 7.26 ppm for ^{1}H NMR and δ 77.16 ppm for ^{13}C NMR). Abbreviations for signal coupling are as follows: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), m (multiplet) and br (broad). Reaction end points were determined by GC monitoring of the reactions. Gas chromatography was performed with machines of Agilent Technologies 7890, using a column of type HP 5 (Agilent 5% phenylmethylpolysiloxane; length: 15 m; diameter: 0.25 mm; film thickness: 0.25 μm) or Hewlett-Packard 6890 or 5890 series II, using a column of type HP 5 (HewlettPackard, 5% phenylmethylpolysiloxane; length: 15 m; diameter: 0.25 mm; film thickness: 0.25 μm). High-resolution mass spectra (HRMS) and low-resolution mass spectra (LRMS) were recorded on Finnigan MAT 95Q or Finnigan MAT 90 instrument or JEOL JMS-700. Infrared spectra were recorded on a Perkin 281 IR spectrometer and samples were measured neat (ATR, Smiths Detection DuraSample IR II Diamond ATR). The absorption bands were reported in wave numbers (cm-1) and abbreviations for intensity are as follows: vs (very strong; maximum intensity), s (strong; above 75% of max. intensity), m (medium; from 50% to 75% of max. intensity), w (weak; below 50% of max. intensity) and br (broad). Melting points were determined on a Büchi B-540 apparatus and uncorrected. Single crystals were grown in small quench vials with a volume of 5.0 mL from slow evaporation of dichloromethane/hexanes mixtures at room temperature. Suitable single crystals were then introduced into perfluorinated oil and mounted on top of a thin glass wire. Data collection was performed at 100 K with a Bruker D8 Venture TXS equipped with a Spellman generator (50 kV, 40 mA) and a Kappa CCD detector operating with Mo Kα radiation (l = 0.71071 Å).

s-BuLi and *t*-BuLi were purchased as solutions in cyclohexane/hexanes mixtures from Rockwood Lithium GmbH. The commercially available Grignard reagents MeMgCl, PhMgCl, and *n*-BuMgCl were also purchased from Rockwood Lithium GmbH as solutions in THF.

The concentration of organometallic reagent from commercially purchased and synthesized reagents was determined either by titration of isopropyl alcohol using the indicator 4-(phenylazo)diphenylamine in THF for Grignard reagents or using the indicator *N*-benzylbenzamide in THF for organolithium reagents. [*s*-BuLi] = 1.31 M in cyclohexane (titration with isopropanol/1,10-phenanthroline), purchased from Rockwood Lithium GmbH. [*i*-PrMgCl·LiCl] = 1.1 M in THF (titration with iodine), purchased from Rockwood Lithium GmbH. [*n*-BuLi] = 2.44 M in cyclohexane (titration with isopropanol/1,10-phenanthroline), purchased from Rockwood Lithium GmbH.

General Procedure A for the Synthesis of Cyclobutenes ***3****.*[3] To cyclobutene iodides **2** in THF (0.2 M) were consecutively added $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (4 mol %), the appropriate organoboronic acid (1.0−2.0 equiv), and a 1 M solution of NaOH (3.0 equiv). The mixture was stirred at ambient temperature until TLC showed full consumption of the starting iodide **2** (20 min up to overnight). The reaction was quenched by addition of water, extracted with Et_2O (3 × 20 mL), and dried over $MgSO_4$. The crude product was concentrated under reduced pressure and finally filtrated through a short silica column to remove palladium salts. Crude materials were used without further purification.

General Procedure B for the Synthesis of Cyclopropylketones ***4*** *and* ***11****.* To cyclobutenes **3** in CH_2Cl_2 (0.1 M) was added *m*CPBA in CH_2Cl_2 (0.3 M, 1.0 equiv) at 0 °C. The reaction was checked after 10 min by TLC, and another portion of *m*CPBA (0.5 equiv) was added if the reaction was not complete. This step was repeated until full conversion of the substrates. The reaction was the treated by addition of NaOH (1 M) and extracted with CH_2Cl_2 (3 × 20 mL). Volatiles were removed under reduced pressure and the crude product purified by chromatography. **Procedure Ba.** The desired products **4** and **11** were obtained analytically pure. **Procedure Bb.** In the case of **4s,t,u,y,ac,ad,aj** the epoxide intermediate **5** was obtained after chromatography, as it did not undergo ring contraction. In such cases, intermediates were dissolved in Et_2O (0.3 M), and $BF_3{\cdot}OEt_2$ (1.0 equiv) was added. As completion of the rearrangement was observed after 10 min, the final products could be purified by chromatography after extraction.

General Procedure C for the Synthesis of Cyclopropylaldehydes ***13****.* To aryl halide (1.05 equiv) in THF (0.33 M) was added dropwise *n*-BuLi (1.1 eq., 2.44 m) at −78 °C under inert atmosphere, and the mixture was stirred for 15 min at this temperature. Cyclobutanone **12** (1 equiv) in THF (1 M) was added at −78 °C, and the reaction stirred for 30 min before warming to room temperature. Ac_2O (2 equiv) was added at −78 °C, and the reaction was allowed to warm to room temperature and stirred for 2 h. Volatiles were removed under vacuum, DMF (0.5 M) was added, followed by LiBr (10 equiv), and the mixture was heated to 100 °C and allowed to stir for 2 h. After completion of the transformation and monitoring by TLC, the mixture was allowed to cool to room temperature, washed with water and brine, and extracted with EtOAc. The organic phase was dried over $MgSO_4$ and the solvent removed under reduced pressure. To crude cyclobutenes **16** in CH_2Cl_2 (0.1 M) was added *m*CPBA in CH_2Cl_2 (1.0 equiv, 0.3 m) at 0 °C. The reaction was checked after 10 min by TLC, and another portion of *m*CPBA (0.5 equiv) was added if the reaction was not complete. This was repeated once if need be. The reaction was quenched by addition of NaOH (1 M) and extracted with CH_2Cl_2 (3 × 20 mL). The solvent was evaporated under reduced pressure and the crude product purified by chromatography.

Experimental Data. *1-Methoxy-4-(2-phenethylcyclobut-1-en-1-yl)benzene (****3ad****).*[19] To a solution of $(C_5H_5)_2ZrCl_2$ (1 equiv) in THF (0.2 M) was added EtMgBr (2 equiv) at −78 °C. The reaction mixture was warmed to −40 °C and stirred for 1 h. To the mixture was added (4-chlorobut-3-yn-1-yl)benzene (1 equiv) in THF (5 M) at −78 °C. The mixture was stirred for 1 h at room temperature. After being cooled to −40 °C, the reaction was quenched with iodide (2 equiv) and allowed to warm to room temperature. The mixture was poured onto an ice/1 M HCl solution, extracted with hexanes, dried with $MgSO_4$, and filtered. The solvent was removed under reduced pressure, and the crude mixture was purified over silica with hexanes as eluent (R_f = 0.7 (hexane, UV, $KMnO_4$, PAA). (2-(2-Iodocyclobut-1-en-1-yl)ethyl)benzene was then used in the following cross-coupling reaction. Therefore, LiCl (1.1 equiv) and Mg (1.6 equiv) were dried under inert atmosphere followed by addition of THF (0.4 M) and one drop of dibromoethane. The mixture was heated once to reflux to activate the Grignard. After the mixture was cooled back to room temperature, $B(Oi\text{-}Pr)_3$ (1.5 equiv) was added. (2-(2-Iodocyclobut-1-en-1-yl)ethyl)benzene (0.5 M) was added dropwise to the reaction. After 2 h, a cloudy suspension was formed. To the suspension was then added $Pd(dppf)Cl_2$ dichloromethane adduct (4 mol %), 1-iodo-4-methoxybenzene (0.80 equiv), and an aqueous solution of sodium hydroxide (1.5 equiv, 1.00 M). The reaction mixture stirred overnight and then extracted with diethyl ether (3 × 20 mL), washed with a saturated aqueous solution of sodium chloride (20 mL), dried with magnesium sulfate, filtered, concentrated, and purified via flash column chromatography to provide **3ad** (0.27 mmol, 72 mg, 55%) as a colorless oil. R_f = 0.20 (hexane, UV, $KMnO_4$, PAA). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35−7.18 (m, 7H), 6.89−6.82 (m, 2H), 3.82 (s, 3H), 2.86 (dd, J = 9.6, 6.4 Hz, 2H), 2.75−2.67 (m, 2H), 2.65−2.59 (m, 2H), 2.51−2.42 ppm (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 158.4, 142.2, 139.7, 137.3, 129.3, 128.5, 128.4, 126.9, 126.0, 113.9, 55.4, 33.7, 32.1, 27.7, 26.1 ppm. LRMS (DEP/EI-Orbitrap) m/z: 264.1 (30), 249.1 (40), 235.0 (5), 221.1 (5), 203.1 (2). HRMS (EI-Orbitrap) m/z: $[M]^+$ calcd for $C_{19}H_{20}O^+$ 264.1514, found 264.1507. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3059 (w), 3024 (w), 1780 (w), 1726 (w), 1670 (s), 1614 (vw), 1597 (m), 1578 cm^{-1} (w).

*(E)-3-Methyl-1-(1-styrylcyclopropyl)but-3-en-1-one (****4a****).* Using 1-iodo-2-(2-methylallyl)cyclobut-1-ene (**2a**) and (*E*)-styrylboronic acid according to general procedures A and Ba provided **4a** (0.20 mmol, 45 mg, 79%) as a colorless oil. R_f = 0.80 (hexane/EtOAc 9:1, UV, $KMnO_4$, PAA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42−7.31 (m, 4H), 7.29−7.22 (m, 1H), 6.83 (d, J = 15.8 Hz, 1H), 6.42 (d, J = 15.8 Hz, 1H), 4.96−4.93 (m, 1H), 4.77−4.75 (m, 1H), 3.33 (s, 2H), 1.76 (t, J = 1.1 Hz, 3H), 1.50 (dd, J = 6.9, 3.7 Hz, 2H), 1.15 ppm (dd, J = 7.1, 3.9

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Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.8, 139.5, 136.9, 131.4, 128.8, 128.2, 127.8, 126.3, 114.8, 49.9, 33.8, 22.9, 19.8 ppm. LRMS (DEP/EI-Orbitrap) m/z: 226.2 (3), 211.2 (12), 184.1 (21), 141.1 (31), 128.1 (100). HRMS (EI-Orbitrap) m/z: $[M]^+$ calcd for $C_{16}H_{18}O^+$ 226.1358, found 226.1353. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3080 (vw), 3027 (w), 2920 (w), 2852 (w), 1690 (s), 1646 (w), 1600 cm^{-1} (w).

*(E)-1-(1-Styrylcyclopropyl)ethanone (**4b**).* Using 1-iodo-2-methylcyclobut-1-ene (**2b**) and (*E*)-styrylboronic acid according to general procedures A and Ba provided **4b** (0.35 mmol, 65 mg, 70%) as a colorless oil. Compound **4b** was also obtained by following procedure A and subjecting the cross-coupling product to air at 100 °C for 3 h (58%). R_f = 0.5 (hexane/EtOAc 9:1, UV, $KMnO_4$, PAA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33−7.28 (m, 2H), 7.27−7.22 (m, 2H), 7.20−7.14 (m, 1H), 6.76 (d, J = 15.9 Hz, 1H), 6.31 (d, J = 15.9 Hz, 1H), 2.17 (s, 3H), 1.42 (dd, J = 6.6, 4.2 Hz, 1H), 1.09 ppm (dd, J = 7.3, 3.8 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.1, 136.9, 130.6, 128.8, 128.4, 127.8, 126.3, 33.9, 28.4, 19.6 ppm. LRMS (DEP/EI-Orbitrap) m/z: 186.1 (40), 171.1 (10), 157.1 (15), 143.1 (40), 128.1 (100). HRMS (EI-Orbitrap) m/z: $[M]^+$ calcd for $C_{13}H_{14}O^+$ 186.1045, found 186.1039. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3082 (vw), 3058 (vw), 3026 (w), 3006 (w), 2926 (vw), 1688 (s), 1646 (w), 1600 cm^{-1} (w).

*(E)-1-(1-(4-Methylstyryl)cyclopropyl)ethanone (**4c**).* Using **2b** and (*E*)-(4-methylstyryl)boronic acid according to general procedures A and Ba provided **4c** (0.17 mmol, 33 mg, 66%) as a colorless oil. Compound **4c** was also obtained by following procedure A and subjecting the cross-coupling product to air at 100 °C for 3 h (66%). R_f = 0.5 (hexane/EtOAc 9:1, UV, $KMnO_4$, PAA). ^{1}H NMR (400 MHz, $CDCl_3$) 7.30−7.26 (m, 2H), 7.18−7.10 (m, 2H), 6.77 (d, J = 15.8 Hz, 1H), 6.36 (d, J = 15.8 Hz, 1H), 2.34 (s, 3H), 2.25 (s, 3H), 1.48 (dd, J = 6.7, 4.0 Hz, 2H), 1.15 ppm (dd, J = 7.2, 3.6 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.4, 137.6, 134.1, 130.6, 129.5, 127.4, 126.2, 33.9, 28.5, 21.3, 19.5 ppm. LRMS (DEP/EI-Orbitrap) m/z: 200.1 (42), 185.1 (13), 157.1 (50), 142.1 (100). HRMS (EI-Orbitrap) m/z: $[M]^+$ calcd for $C_{14}H_{16}O^+$ 200.1201, found 200.1192. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3088 (vw), 3022 (w), 2922 (w), 2864 (vw), 1690 (vs), 1650 (w), 1612 (w), 1572 (vw), 1560 (vw), 1540 (vw) cm^{-1}.

*1-((1R,2R)-2-Pentyl-1-((E)-styryl)cyclopropyl)ethanone (**4d**).* Using 1-iodo-2-methyl-3-pentylcyclobut-1-ene (**2c**) and (*E*)-styrylboronic acid according to general procedures A and Ba provided **4d** (0.35 mmol, 65 mg, 70%) as a colorless oil. Compound **4d** was also obtained by following procedure A and subjecting the cross-coupling product to air at 100 °C for 3 h (88%). R_f = 0.6 (hexane/EtOAc 9:1, UV, $KMnO_4$, PAA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41−7.29 (m, 4H), 7.26−7.22 (m, 1H), 6.74 (d, J = 15.8 Hz, 1H), 6.39 (d, J = 15.8 Hz, 1H), 2.33 (s, 3H), 1.59 (dd, J = 6.8, 4.1 Hz, 1H), 1.49−1.24 (m, 9H), 1.21 (dd, J = 8.3, 4.2 Hz, 1H), 0.88 ppm (t, J = 6.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.3, 137.0, 130.6, 130.2, 128.8, 127.7, 126.3, 39.5, 35.0, 31.7, 30.6, 29.6, 27.1, 22.8, 21.0, 14.2 ppm. LRMS (DEP/EI-Orbitrap) m/z: 256.1 (8), 213.2 (15), 160.1 (50). HRMS (EI-Orbitrap) m/z: $[M]^+$ calcd for $C_{18}H_{24}O^+$ 256.1827, found 256.1823. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3645 (m), 1738 (w), 1481 (w), 1467 (m), 1441 (s), 1429 (vs) cm^{-1}.

*3-Methyl-1-(1-(p-tolyl)cyclopropyl)but-3-en-1-one (**4e**).* Using **2a** and 4,4,5,5-tetramethyl-2-(*p*-tolyl)-1,3,2-dioxaborolane according to general procedures A and Ba provided **4e** (0.22 mmol, 46 mg, 86%) as a colorless oil. R_f = 0.45 (hexane/EtOAc 9:1, UV, $KMnO_4$, PAA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28−7.24 (m, 2H), 7.15 (d, J = 7.8 Hz, 2H), 4.88−4.79 (m, 1H), 4.57−4.53 (m, 1H), 3.02 (s, 2H), 2.36 (s, 3H), 1.63 (s, 3H), 1.60 (dd, J = 7.1, 3.2 Hz, 2H), 1.15 ppm (dd, J = 7.2, 3.2 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.8, 139.7, 137.9, 137.3, 131.1, 129.4, 114.4, 50.1, 37.1, 22.8, 21.3, 19.2 ppm. LRMS (DEP/EI-Orbitrap) m/z: 214.1 (8), 159.1 (26), 131.1 (100). HRMS (EI-Orbitrap) m/z: $[M]^+$ calcd for $C_{15}H_{18}O^+$ 214.1358, found 214.1354. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3080 (vw), 2974 (w), 2922 (w), 2252 (vw), 1776 (w), 1692 (s), 1650 (w) cm^{-1}.

*3-Methyl-1-(1-(3,4,5-trimethoxyphenyl)cyclopropyl)but-3-en-1-one (**4f**).* Using **2a** and (3,4,5-trimethoxyphenyl)boronic acid according to general procedures A and Ba provided **4f** (0.22 mmol, 62 mg, 86%) as colorless solid. R_f = 0.35 (hexane/EtOAc 8:2, UV, $KMnO_4$, PAA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.58 (s, 2H), 4.84 (t, J = 1.6 Hz, 1H), 4.59 (dq, J = 2.0, 1.0 Hz, 1H), 3.86 (s, 6H), 3.85 (s, 3H), 3.06 (s, 2H), 1.69−1.55 (m, 3H), 1.58 (dd, J = 6.7, 3.5 Hz, 2H), 1.17 ppm (dd, J = 7.0, 3.5 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.4, 153.2, 139.8, 137.5, 136.4, 114.4, 108.0, 61.1, 56.3, 49.7, 38.0, 22.9, 19.3 ppm. LRMS (DEP/EI-Orbitrap) m/z: 290.1 (67), 275.1 (45), 235.1 (10), 207.1 (100), 192.1 (29), 176.1 (84), 161.1 (50). HRMS (EI-Orbitrap) m/z: $[M]^+$ calcd for $C_{17}H_{22}O_4^+$ 290.1518, found 290.1514. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2968 (w), 2940 (w), 2924 (w), 2832 (w), 1692 (m), 1586 (m) cm^{-1}. Mp (°C): 81−82.

*(E)-1-(1-(4-(Trifluoromethyl)styryl)cyclopropyl)ethanone (**4g**).* Using **2b** and (*E*)-(4-(trifluoromethyl)styryl)boronic acid according to general procedures A and Ba provided **4g** (0.19 mmol, 49 mg, 78%) as a colorless oil. R_f = 0.4 (hexane/EtOAc 9:1, UV, $KMnO_4$, PAA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, J = 8.1 Hz, 1H), 7.47 (d, J = 8.3 Hz, 1H), 6.99 (d, J = 15.9 Hz, 0H), 6.38 (d, J = 15.9 Hz, 0H), 2.23 (s, 1H), 1.55 (dd, J = 7.0, 4.3 Hz, 1H), 1.21 ppm (dd, J = 6.6, 3.9 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.3, 140.4 (q, J = 1.3 Hz), 131.3, 129.3 (q, J = 32.6 Hz), 128.7, 126.5, 125.7 (q, J = 3.8 Hz), 122.9 (q, J = 271.7 Hz), 34.0, 27.9, 19.7 ppm. LRMS (DEP/EI-Orbitrap) m/z: 254.1 (46), 225.1 (23), 191.1 (22). HRMS (EI-Orbitrap) m/z: $[M]^+$ calcd for $C_{14}H_{13}F_3O^+$ 254.0918, found 254.0913. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3044 (vw), 3012 (vw), 2932 (vw), 1692 (m), 1648 (w), 1616 (w) cm^{-1}.

*(E)-1-(1-(4-Chlorostyryl)cyclopropyl)ethanone (**4h**).* Using **2b** and (*E*)-(4-chlorostyryl)boronic acid according to general procedures A and Ba provided **4h** (0.08 mmol, 17 mg, 31%) as a colorless oil. R_f = 0.45 (hexane/EtOAc 9:1, UV, $KMnO_4$, PAA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33−7.26 (m, 4H), 6.83 (d, J = 15.9 Hz, 1H), 6.32 (d, J = 15.9 Hz, 1H), 2.22 (s, 3H), 1.51 (dd, J = 7.2, 4.4 Hz, 2H), 1.17 ppm (dd, J = 7.4, 3.6 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.7, 135.4, 133.3, 129.2, 129.2, 128.9, 127.5, 33.9, 28.1, 19.5 ppm. LRMS (DEP/EI-Orbitrap) m/z: 220.0 (46), 191.0 (11), 177.0 (30), 162.0 (21), 142.1 (100). HRMS (EI-Orbitrap) m/z: $[M]^+$ calcd for $C_{13}H_{13}ClO^+$ 220.0655, found 220.0647. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3022 (vw), 2926 (vw), 1690 (vs), 1646 (w) cm^{-1}.

*(E)-1-(1-(4-Methoxystyryl)cyclopropyl)ethanone (**4i**).* Using **2b** and (*E*)-(4-methoxystyryl)boronic acid according to general procedures A and Ba provided **4i** (0.22 mmol, 48 mg, 89%) as a colorless oil. R_f = 0.4 (hexane/EtOAc 9:1, UV, $KMnO_4$, PAA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.28 (m, 2H), 6.91−6.82 (m, 2H), 6.67 (d, J = 15.9 Hz, 1H), 6.34 (d, J = 15.8 Hz, 1H), 3.81 (s, 3H), 2.25 (s, 3H), 1.58 (s, 4H), 1.47 (dd, J = 6.9, 4.3 Hz, 3H), 1.14 ppm (dd, J = 7.5, 3.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.6, 159.4, 130.3, 129.7, 127.5, 126.2, 114.2, 55.5, 33.9, 28.6, 19.5 ppm. LRMS (DEP/EI-Orbitrap) m/z: 216.0 (95), 201.0 (22), 173.0 (81), 158.0 (100), 141.1 (35). HRMS (EI-Orbitrap) m/z: $[M]^+$ calcd for $C_{14}H_{16}O_2^+$ 216.1150, found 216.1153.

*(E)-1-(1-(4-Fluorostyryl)cyclopropyl)ethanone (**4j**).* Using **2b** and (*E*)-(4-fluorostyryl)boronic acid according to general procedures A and Ba provided **4j** (0.13 mmol, 27 mg, 53%) as a colorless oil. R_f = 0.45 (hexane/EtOAc 9:1, UV, $KMnO_4$, PAA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.28 (m, 2H), 7.06−6.96 (m, 2H), 6.75 (d, J = 15.9 Hz, 1H), 6.34 (d, J = 15.9 Hz, 1H), 2.23 (s, 3H), 1.49 (dd, J = 7.0, 3.6 Hz, 2H), 1.16 ppm (dd, J = 7.2, 3.7 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.0, 162.4 (d, J = 246.9 Hz), 133.1 (d, J = 3.4 Hz), 129.4, 128.2 (d, J = 2.3 Hz), 127.8 (d, J = 8.0 Hz), 115.7 (d, J = 21.6 Hz), 33.9, 28.2, 19.4 ppm. LRMS (DEP/EI-Orbitrap) m/z: 204.1 (34), 175.0 (11), 161.1 (39), 146.0 (100). HRMS (EI-Orbitrap) m/z: $[M]^+$ calcd for $C_{13}H_{13}FO^+$ 204.0950, found 204.0946. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3040 (vw), 3008 (vw), 2926 (vw), 1690 (s), 1652 (w), 1602 (m) cm^{-1}.

*(E)-1-(1-(2-([1,1′-Biphenyl]-4-yl)vinyl)cyclopropyl)-3-methylbut-3-en-1-one (**4k**).* Using **2a** and (*E*)-(2-([1,1′-biphenyl]-4-yl)vinyl)-boronic acid according to general procedures A and Ba provided **4k** (0.15 mmol, 44 mg, 58%) as a colorless oil. R_f = 0.5 (hexane/EtOAc 9:1, UV, $KMnO_4$, PAA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66−7.55 (m, 4H), 7.50−7.41 (m, 4H), 7.38−7.32 (m, 1H), 6.88 (d, J = 15.8 Hz, 1H), 6.46 (d, J = 15.8 Hz, 1H), 4.99−4.93 (m, 1H), 4.82−4.76

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(m, 1H), 3.35 (s, 2H), 1.78 (s, 3H), 1.53 (dd, J = 7.0, 4.0 Hz, 2H), 1.17 ppm (dd, J = 7.0, 3.0 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.7, 140.7, 140.6, 139.5, 135.9, 130.9, 128.9, 128.3, 127.5, 127.5, 127.0, 126.8, 114.8, 49.9, 33.9, 23.0, 19.8 ppm. LRMS (DEP/EI-Orbitrap) m/z:302.1 (37), 287.1 (45), 260.1 (41), 247.1 (100), 233.1 (11), 219.1 (61), 204.1 (83), 191.0 (47), 178.1 (53). HRMS (EI-Orbitrap) m/z: $[M]^+$ calcd for $C_{22}H_{22}O^+$ 302.1671, found 302.1665. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3078 (vw), 3056 (vw), 3028 (w), 2972 (vw), 2914 (vw), 1688 (s), 1646 (w), 1602 (w), 1582 (vw) cm^{-1}.

(E)-3-Methyl-1-(1-(4-(trifluoromethyl)styryl)cyclopropyl)but-3-en-1-one ***(4l)***. Using **2a** and (*E*)-(4-(trifluoromethyl)styryl)boronic acid according to general procedures A and Ba provided **4l** (0.14 mmol, 40 mg, 54%) as a colorless oil. R_f = 0.5 (hexane/EtOAc 9:1, UV, $KMnO_4$, PAA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, J = 8.2 Hz, 2H), 7.46 (d, J = 8.1 Hz, 2H), 6.97 (d, J = 15.9 Hz, 1H), 6.42 (d, J = 15.8 Hz, 1H), 4.97−4.93 (m, 1H), 4.79−4.71 (m, 1H), 3.29 (s, 2H), 1.76 (s, 3H), 1.55 (dd, J = 6.7, 3.4 Hz, 2H), 1.18 ppm (dd, J = 7.3, 3.5 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.0, 140.4 (q, J = 1.4 Hz), 139.3, 131.1, 129.6, 129.5 (q, J = 32.4 Hz), 126.5, 125.8 (q, J = 3.8 Hz), 124.3 (q, J = 271.5 Hz), 114.9, 49.6, 33.9, 22.9, 19.9 ppm. LRMS (DEP/EI-Orbitrap) m/z: 294.1 (8), 279.1 (30), 252.2 (35), 239.2 (11), 211.1 (34), 191.1 (100). HRMS (EI-Orbitrap) m/z: $[M]^+$ calcd for $C_{17}H_{17}F_3O^+$ 294.1231, found 294.1225. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3080 (vw), 2976 (vw), 2918 (vw), 1692 (m), 1648 (w) cm^{-1}.

(E)-1-(1-(4-Chlorostyryl)cyclopropyl)-3-methylbut-3-en-1-one ***(4m)***. Using **2a** and (*E*)-(4-chlorostyryl)boronic acid according to general procedures A and **Ba** provided **4m** (0.11 mmol, 29 mg, 46%) as a colorless oil. R_f = 0.5 (hexane/EtOAc 9:1, UV, $KMnO_4$, PAA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (app s, 4H), 6.81 (d, J = 15.8 Hz, 1H), 6.35 (d, J = 15.9 Hz, 1H), 4.97−4.90 (m, 1H), 4.78−4.72 (m, 1H), 3.30 (s, 3H), 1.75 (s, 2H), 1.51 (dd, J = 7.4, 3.9 Hz, 2H), 1.14 ppm (dd, J = 7.7, 3.2 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.4, 139.4, 135.4, 133.4, 130.0, 128.9, 128.9, 127.5, 114.8, 49.7, 33.8, 22.9, 19.8 ppm. LRMS (DEP/EI-Orbitrap) m/z: 260.1 (5), 245.1 (14), 218.1 (33), 205.0 (12), 177.0 (22). HRMS (EI-Orbitrap) m/z: $[M]^+$ calcd for $C_{16}H_{17}ClO^+$ 260.0968, found 260.0966. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3080 (vw), 3028 (vw), 3014 (vw), 2974 (w), 2942 (vw), 2916 (w), 1690 (vs), 1646 (m), 1592 (w) cm^{-1}.

(E)-1-(1-(4-Methoxystyryl)cyclopropyl)-3-methylbut-3-en-1-one ***(4n)***. Using **2a** and (*E*)-(4-methoxystyryl)boronic acid according to general procedures A and Ba provided **4n** (0.15 mmol, 39 mg, 61%) as a colorless oil. R_f = 0.5 (hexane/EtOAc 9:1, UV, $KMnO_4$, PAA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34−7.29 (m, 2H), 6.90−6.84 (m, 2H), 6.66 (d, J = 15.8 Hz, 1H), 6.37 (d, J = 15.9 Hz, 1H), 4.97−4.91 (m, 1H), 4.77−4.72 (m, 1H), 3.82 (s, 3H), 3.33 (s, 2H), 1.75 (app t, 3H), 1.47 (dd, J = 7.0, 4.0 Hz, 2H), 1.11 ppm (dd, J = 7.3, 3.4 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.2, 159.4, 139.6, 131.1, 129.7, 127.5, 125.9, 114.7, 114.2, 55.5, 50.0, 33.8, 23.0, 19.7 ppm. LRMS (DEP/EI-Orbitrap) m/z: 256.1 (31), 241.1 (12), 214.1 (28), 201.1 (87), 173.1 (76), 158.1 (100), 141.1 (40), 128.1 (58), 115.1 (82), 102.0 (186.1 (40), 171.1 (10). HRMS (EI-Orbitrap) m/z: $[M]^+$ calcd for $C_{17}H_{20}O_2^+$ 256.1463, found 256.1465. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2967 (w), 2944 (w), 2934 (w), 2916 (w), 1723 (w), 1690 (m), 1652 (w), 1606 (m), 1576 (w), 1528 (w), 1511 (vs) cm^{-1}.

(E)-1-(1-(4-Fluorostyryl)cyclopropyl)-3-methylbut-3-en-1-one ***(4o)***. Using **2a** and (*E*)-(4-fluorostyryl)boronic acid according to general procedures A and Ba provided **4o** (0.14 mmol, 34 mg, 56%) as a colorless oil. R_f = 0.6 (hexane/EtOAc 9:1, UV, $KMnO_4$, PAA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.30 (m, 2H), 7.07−6.97 (m, 2H), 6.74 (d, J = 15.9 Hz, 1H), 6.37 (d, J = 15.8 Hz, 1H), 4.97−4.92 (m, 1H), 4.79−4.73 (m, 1H), 3.31 (s, 3H), 1.75 (app t, 3H), 1.50 (dd, J = 7.4, 3.8 Hz, 2H), 1.13 ppm (dd, J = 7.4, 3.3 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.7, 162.5 (d, J = 247.0 Hz), 139.5, 133.1 (d, J = 3.4 Hz), 130.2, 128.0 (d, J = 2.3 Hz), 127.8 (d, J = 7.9 Hz), 115.7 (d, J = 21.6 Hz), 114.8, 49.8, 33.8, 22.9, 19.7 ppm. LRMS (DEP/EI-Orbitrap) m/z: 244.1 (100). HRMS (EI-Orbitrap) m/z: $[M]^+$ calcd for $C_{16}H_{17}FO^+$ 244.1263, found 244.1261. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3078 (vw), 2992 (vw), 2936 (vw), 1692 (s), 1652 (w), 1602 (w) cm^{-1}.

(E)-1-(1-(2-([1,1′-Biphenyl]-4-yl)vinyl)cyclopropyl)ethanone ***(4p)***. Using **2b** and (*E*)-(2-([1,1′-biphenyl]-4-yl)vinyl)boronic acid according to general procedures A and Ba provided **4p** (0.20 mmol, 53 mg, 81%) as white solid. R_f = 0.45 (hexane/EtOAc 9:1, UV, $KMnO_4$, PAA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68−7.54 (m, 4H), 7.50−7.39 (m, 4H), 7.38−7.32 (m, 1H), 6.90 (d, J = 15.9 Hz, 1H), 6.42 (d, J = 15.9 Hz, 1H), 2.27 (s, 3H), 1.52 (dd, J = 7.0, 3.9 Hz, 2H), 1.19 ppm (dd, J = 7.5, 3.7 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.1, 140.7, 140.5, 135.9, 130.1, 128.9, 128.6, 127.5, 127.5, 127.0, 126.8, 34.0, 28.4, 19.6 ppm. LRMS (DEP/EI-Orbitrap) m/z: 262.2 (100), 247.1 (5), 219.1 (80). HRMS (EI-Orbitrap) m/z: $[M]^+$ calcd for $C_{19}H_{18}O^+$ 262.1358, found 262.1352. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3028 (w), 2924 (w), 2854 (vw), 1688 (s), 1644 (w), 1600 (w) cm^{-1}.

1-(1-(4-Phenoxyphenyl)cyclopropyl)ethanone ***(4q)***. Using **2b** and (4-phenoxyphenyl)boronic acid according to general procedures A and Ba provided **4q** (0.10 mmol, 24 mg, 38%) as a colorless oil. R_f = 0.5 (hexane/EtOAc 9:1, UV, $KMnO_4$, PAA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.33 (m, 2H), 7.33−7.30 (m, 2H), 7.17−7.08 (m, 1H), 7.05−7.01 (m, 2H), 7.00−6.95 (m, 2H), 2.03 (s, 3H), 1.60 (dd, J = 6.5, 3.5 Hz, 2H), 1.17 ppm (dd, J = 6.9, 3.5 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.3, 157.0, 156.8, 135.9, 132.2, 130.0, 123.7, 119.3, 118.8, 37.0, 29.6, 19.1 ppm. LRMS (DEP/EI-Orbitrap) m/z: 252.1 (100), 209.1 (35) HRMS (EI-Orbitrap) m/z: $[M]^+$ calcd for $C_{17}H_{16}O_2^+$ 252.1150, found 252.1145. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3040 (w), 3010 (w), 1692 (s), 1590 (m) cm^{-1}.

1-(1-(4-Chlorophenyl)cyclopropyl)ethanone ***(4r)***. Using **2a** and (4-chlorophenyl)boronic acid according to general procedures A and Ba provided **4r** (0.22 mmol, 42 mg, 86%) as a colorless oil. R_f = 0.5 (hexane/EtOAc 9:1, UV, $KMnO_4$, PAA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34−7.28 (m, 1H), 2.00 (s, 1H), 1.61 (dd, J = 6.8, 3.9 Hz, 1H), 1.15 ppm (dd, J = 7.0, 3.5 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.3, 139.7, 133.5, 132.2, 128.9, 37.1, 29.4, 18.9 ppm. HRMS (EI-Orbitrap) m/z: $[M]^+$ calcd for $C_{11}H_{11}ClO^+$ 194.0498, found 194.0496.

1-(1-(4-Bromophenyl)cyclopropyl)ethanone ***(4s)***. Using **2b** and (4-bromophenyl)boronic acid according to general procedures A and Bb provided **4s** (0.18 mmol, 42 mg, 70%) as a colorless oil. R_f = 0.5 (hexane/EtOAc 9:1, UV, $KMnO_4$, PAA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50−7.46 (m, 2H), 7.26−7.22 (m, 2H), 2.00 (s, 3H), 1.61 (dd, J = 6.5, 3.8 Hz, 2H), 1.15 ppm (dd, J = 7.0, 4.0 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.4, 140.2, 132.6, 131.9, 121.6, 37.2, 29.4, 18.9 ppm. LRMS (DEP/EI-Orbitrap) m/z: 238.0 (38), 195.0 (13), 116.1 (100). HRMS (EI-Orbitrap) m/z: $[M]^+$ calcd for $C_{11}H_{11}{}^{79}BrO^+$ 237.9993, found IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 237.9987. 2958 (m), 2918 (vs), 2850 (s), 2212 (m), 1740 (m) cm^{-1}.

1-Methyl-4-(3-nitrophenyl)-5-oxabicyclo[2.1.0]pentane ***(5t)***. Using **2b** and 4,4,5,5-tetramethyl-2-(3-nitrophenyl)-1,3,2-dioxaborolane according to general procedures A and B provided intermediate **5t** (0.17 mmol, 34 mg, 66%) as a colorless oil. R_f = 0.8 (hexane/EtOAc 9:1, UV, $KMnO_4$, PAA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (t, J = 1.9 Hz, 1H), 8.13 (ddd, J = 8.1, 2.3, 1.2 Hz, 1H), 7.63 (dt, J = 7.7, 1.4 Hz, 1H), 7.53 (t, J = 7.9 Hz, 1H), 2.71−2.62 (m, 1H), 2.15−1.94 (m, 3H), 1.50 ppm (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.5, 137.3, 132.2, 129.4, 122.5, 121.4, 71.9, 68.5, 30.5, 27.3, 13.9 ppm. LRMS (DEP/EI-Orbitrap) m/z: 205.1 (40), 190.0 (100), 159.1 (20). HRMS (EI-Orbitrap) m/z: $[M]^+$ calcd for $C_{11}H_{11}NO_3^+$ 205.0739, found 205.0733.

1-(1-(3-Nitrophenyl)cyclopropyl)ethanone ***(4t)***. Treating **5t** with $BF_3{\cdot}OEt_2$ (see general procedure Bb) resulted in ring contraction, yielding **4t** (0.17 mmol, 34 mg, quant) as slightly yellow solid. Using **2b** and 3-aminobenzeneboronic acid hydrochloride according to general procedures A and Bb provided directly oxidized **4t** (0.19 mmol, 39 mg, 77%). R_f = 0.5 (hexane/EtOAc 9:1, UV, $KMnO_4$, PAA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (t, J = 2.0 Hz, 1H), 8.17 (ddd, J = 8.2, 2.3, 1.1 Hz, 1H), 7.71 (ddd, J = 7.6, 1.7, 1.1 Hz, 1H), 7.55 (t, J = 7.9 Hz, 1H), 2.01 (s, 3H), 1.71 (dd, J = 7.2, 3.6 Hz, 2H), 1.25 (dd, J = 7.2, 3.6 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.7, 148.5, 143.1, 137.2, 129.8, 125.7, 122.8, 37.6, 28.8, 18.6 ppm. LRMS (DEP/EI-Orbitrap) m/z: 205.1 (85), 146.0 (10), 115.1 (100). HRMS (EI-Orbitrap) m/z: $[M]^+$ calcd for $C_{11}H_{11}NO_3^+$ 205.0739, found

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205.0734. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3096 (vw), 3008 (vw), 1700 (m), 1688 (m), 1534 (s) cm^{-1}. Mp (°C): 106−107.

*3-(1-Acetylcyclopropyl)benzaldehyde (**4u**).* Using **2b** and 2-(3-(1,3-dioxolan-2-yl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane according to general procedures A and Bb directly provided deprotected **4u** (0.15 mmol, 27 mg, 58%) as a colorless oil. R_f = 0.2 (hexane/EtOAc 9:1, UV, $KMnO_4$, PAA). ^1H NMR (400 MHz, $CDCl_3$) δ 10.03 (s, 1H), 7.89 (t, J = 1.7 Hz, 1H), 7.82 (dt, J = 7.6, 1.5 Hz, 1H), 7.65 (ddd, J = 7.7, 1.9, 1.2 Hz, 1H), 7.54 (t, J = 7.6 Hz, 1H), 2.00 (s, 3H), 1.67 (dd, J = 6.8, 4.2 Hz, 2H), 1.22 ppm (dd, J = 7.1, 3.7 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.7, 192.2, 142.4, 137.1, 136.9, 131.5, 129.6, 129.4, 37.5, 29.2, 18.7 ppm. LRMS (DEP/EI-Orbitrap) m/z: 188.1 (100). HRMS (EI-Orbitrap) m/z: $[M]^+$ calcd for $C_{12}H_{12}O_2^+$ 188.0837, found 188.0831. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3010 (w), 1758 (w), 1720 (m), 1692 (vs), 1604 (w), 1586 (w) cm^{-1}.

*1-(1-(Phenylethynyl)cyclopropyl)ethanone (**4v**).* ((2-Methylcyclobut-1-en-1-yl)ethynyl) according to general procedure Ba provided **4v** (0.11 mmol, 21 mg, 45%) as a colorless oil. R_f = 0.5 (hexane/EtOAc 9:1, UV, $KMnO_4$, PAA). ^1H NMR (400 MHz, $CDCl_3$) δ 7.46−7.39 (m, 2H), 7.34−7.29 (m, 3H), 2.57 (s, 3H), 1.62 (dd, J = 8.2, 3.2 Hz, 2H), 1.39 ppm (dd, J = 8.1, 3.1 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.2, 131.7, 128.5, 128.3, 123.2, 90.4, 80.7, 29.7, 23.7, 23.4 ppm. LRMS (DEP/EI-Orbitrap) m/z: 184.1 (84), 141.1 (83). HRMS (EI-Orbitrap) m/z: $[M]^+$ calcd for $C_{13}H_{12}O^+$ 184.0888, found 184.0883. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2958 (w), 2930 (w), 1706 (vs), 1598 (w) cm^{-1}.

*1-(1-(Benzo[d][1,3]dioxol-5-yl)cyclopropyl)ethanone (**4w**).* Using **2b** and benzo[*d*][1,3]dioxol-5-ylboronic acid according to general procedures A and Ba provided **4w** (0.17 mmol, 35 mg, 68%) as a colorless oil. R_f = 0.4 (hexane/EtOAc 9:1, UV, $KMnO_4$, PAA). ^1H NMR (400 MHz, $CDCl_3$) δ 6.86−6.81 (m, 2H), 6.80−6.75 (m, 1H), 5.97 (s, 2H), 2.03 (s, 3H), 1.56 (dd, J = 7.0, 3.1 Hz, 2H), 1.13 ppm (dd, J = 6.9, 3.5 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) 209.4, 147.8, 147.0, 135.1, 124.1, 111.2, 108.4, 101.3, 37.4, 29.5, 19.3 ppm. LRMS (DEP/EI-Orbitrap) m/z: 204.1 (70), 161.0 (30). HRMS (EI-Orbitrap) m/z: $[M]^+$ calcd for $C_{12}H_{12}O_3^+$ 204.0786, found 204.0774.

*1-(1-(Dibenzo[b,d]furan-4-yl)cyclopropyl)ethanone (**4x**).* Using **2b** and dibenzo[*b*,*d*]furan-4-ylboronic acid according to general procedures A and Ba provided **4x** (0.19 mmol, 50 mg, 75%) as a colorless oil. R_f = 0.5 (hexane/EtOAc 9:1, UV, $KMnO_4$, PAA). ^1H NMR (400 MHz, $CDCl_3$) δ 7.98 (ddd, J = 7.7, 1.4, 0.7 Hz, 1H), 7.92 (dd, J = 7.6, 1.4 Hz, 1H), 7.62 (dt, J = 8.3, 0.9 Hz, 1H), 7.49 (ddd, J = 8.3, 7.3, 1.3 Hz, 1H), 7.41 (td, J = 7.2, 1.2 Hz, 1H), 7.36 (dd, J = 7.5, 1.0 Hz, 1H), 7.34 (t, J = 7.6 Hz, 1H), 2.03 (s, 3H), 1.80 (dd, J = 6.8, 3.9 Hz, 2H), 1.34 ppm (dd, J = 7.1, 3.7 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.5, 156.3, 155.9, 128.9, 127.5, 125.3, 124.6, 124.3, 123.1, 123.0, 120.9, 120.2, 112.1, 32.6, 29.2, 19.3 ppm. LRMS (DEP/EI-Orbitrap) m/z: 250.1 (100), 207.1 (97). HRMS (EI-Orbitrap) m/z: $[M]^+$ calcd for $C_{17}H_{14}O_2^+$ 250.0994, found 250.0995. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3056 (vw), 3010 (w), 1692 (s), 1630 (vw), 1586 (w) cm^{-1}.

*1-(1-(2-Fluoropyridin-3-yl)cyclopropyl)ethanone (**4y**).* Using **2b** and 2-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine according to general procedures A and Bb provided **4y** (0.16 mmol, 29 mg, 65%) as a colorless oil. R_f = 0.2 (hexane/EtOAc 9:1, UV, $KMnO_4$, PAA). ^1H NMR (400 MHz, $CDCl_3$) δ 8.18 (ddd, J = 4.9, 2.0, 1.1 Hz, 1H), 7.73 (ddd, J = 9.5, 7.4, 2.0 Hz, 1H), 7.20 (ddd, J = 7.4, 4.9, 1.7 Hz, 1H), 2.04 (s, 3H), 1.71 (dd, J = 7.1, 4.1 Hz, 2H), 1.19 ppm (dd, J = 7.4, 3.9 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.1, 163.1 (d, J = 240.8 Hz), 147.0 (d, J = 14.8 Hz), 142.4 (d, J = 4.8 Hz), 123.4 (d, J = 29.3 Hz), 121.8 (d, J = 4.4 Hz), 31.9 (d, J = 3.2 Hz), 28.2 (d, J = 1.3 Hz), 18.6 ppm. LRMS (DEP/EI-Orbitrap) m/z: 179.1 (100), 136.0 (88). HRMS (EI-Orbitrap) m/z: $[M]^+$ calcd for $C_{10}H_{10}FNO^+$ 179.0746, found 179.0741. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3012 (vw), 1696 (s), 1636 (vw), 1606 (m), 1578 (w) cm^{-1}.

*1-(1-(3,5-Dimethylisoxazol-4-yl)cyclopropyl)ethanone (**4z**).* Using **2b** and (3,5-dimethylisoxazol-4-yl)boronic acid according to general procedures A and Ba provided **4z** (0.13 mmol, 24 mg, 53%) as a colorless oil. R_f = 0.25 (hexane/EtOAc 9:1, UV, $KMnO_4$, PAA). ^1H NMR (400 MHz, $CDCl_3$) δ 2.37 (s, 3H), 2.24 (s, 3H), 2.04 (s, 3H), 1.65 (dd, J = 7.0, 3.0 Hz, 2H), 1.02 ppm (dd, J = 6.7, 3.4 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.6, 167.9, 160.6, 114.1, 28.8, 25.1, 18.8, 11.5, 10.5 ppm. LRMS (DEP/EI-Orbitrap) m/z: 179.1 (11), 136.1 (61). HRMS (EI-Orbitrap) m/z: $[M - H]^+$ calcd for $C_{10}H_{12}NO_2^+$ 178.0863, found 178.0859.

*1-(1-(1-Benzyl-1H-pyrazol-4-yl)cyclopropyl)ethanone (**4aa**).* Using **2b** and 1-benzyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole according to general procedures A and Ba provided **4aa** (0.17 mmol, 41 mg, 69%) as a colorless oil: R_f = 0.1 (hexane/EtOAc 9:1, UV, $KMnO_4$, PAA). ^1H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, J = 0.8 Hz, 1H), 7.39−7.31 (m, 4H), 7.24−7.20 (m, 2H), 5.28 (s, 2H), 2.08 (s, 3H), 1.53 (dd, J = 7.4, 3.7 Hz, 2H), 1.07 ppm (dd, J = 7.4, 3.7 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.9, 140.4, 136.4, 129.8, 129.0, 128.3, 127.8, 122.5, 56.3, 28.9, 27.5, 19.4 ppm. LRMS (DEP/EI-Orbitrap) m/z: 240.1 (38), 197.1 (22), 91.1 (100). HRMS (EI-Orbitrap) m/z: $[M]^+$ calcd for $C_{15}H_{16}N_2O^+$ 240.1263, found 240.1257. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3090 (w), 3008 (w), 2940 (w), 1718 (m), 1690 (vs) cm^{-1}.

*1-(1-(5-Methylthiophene-2-yl)cyclopropyl)ethanone (**4ab**).* Using **2b** and (5-methylthiophene-2-yl)boronic acid according to general procedures A and Ba provided **4ab** (0.17 mmol, 31 mg, 69%) as a colorless oil. R_f = 0.6 (hexane/EtOAc 9:1, UV, $KMnO_4$, PAA). ^1H NMR (400 MHz, $CDCl_3$) δ 6.77 (d, J = 3.4 Hz, 1H), 6.60 (dq, J = 3.4, 1.1 Hz, 1H), 2.46 (d, J = 1.1 Hz, 3H), 2.17 (s, 3H), 1.62 (dd, J = 7.2, 3.7 Hz, 2H), 1.26 ppm (dd, J = 7.2, 3.7 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.6, 142.7, 140.1, 128.0, 124.9, 31.8, 29.1, 21.1, 15.6 ppm. LRMS (DEP/EI-Orbitrap) m/z: 180.1 (90), 165.0 810), 137.0 (100), 122.0 (23). HRMS (EI-Orbitrap) m/z: $[M]^+$ calcd for $C_{10}H_{12}OS^+$ 180.0609, found 180.0608. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3010 (w), 2920 (w), 1698 (vs) cm^{-1}.

*Phenyl(1-phenylcyclopropyl)methanone (**4ac**).* 1,2-Diphenylcyclobut-1-ene (**3ac**) for the following rearrangement was synthesized according to the literature.[20] Using **3ac** according to general procedure Bc provided **4ac** (0.36 mmol, 80 mg, 72%) as yellowish oil. R_f = 0.5 (hexane/EtOAc 95:5, UV, $KMnO_4$, PAA). ^1H NMR (400 MHz, $CDCl_3$) δ 7.91−7.84 (m, 2H), 7.53−7.23 (m, 8H), 1.79 (dd, J = 7.3, 4.1 Hz, 2H), 1.48 ppm (dd, J = 7.0, 3.9 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.5, 141.1, 137.1, 132.1, 129.5, 128.7, 128.1, 128.0, 126.7, 35.2, 16.4 ppm. LRMS (DEP/EI-Orbitrap) m/z: 222.1 (80), 193.1 (5), 165 (10), 105.0 (100). HRMS (EI-Orbitrap) m/z: $[M]^+$ calcd for $C_{16}H_{14}O^+$ 222.1045, found 222.1039.

*1-(1-(4-Methoxyphenyl)cyclopropyl)-3-phenylpropan-1-one (**4ad**).* Using **3ad** according to general procedure Bc provided **4ad** (0.16 mmol, 45 mg, 85%) as a colorless oil. R_f = 0.65 (hexane/EtOAc 8:2, UV, $KMnO_4$, PAA). ^1H NMR (400 MHz, $CDCl_3$) δ 7.23 (tq, J = 6.7, 6.6, 3.4, 3.2 Hz, 4H), 7.18−7.13 (m, 1H), 7.09−7.04 (m, 2H), 6.87−6.83 (m, 2H), 3.81 (s, 3H), 2.78 (t, J = 7.6 Hz, 2H), 2.60 (t, J = 7.6 Hz, 2H), 1.57 (dd, J = 7.2, 3.5 Hz, 2H), 1.11 ppm (dd, J = 7.2, 3.5 Hz, 2H).^{13}C NMR (101 MHz, $CDCl_3$) δ 210.5, 159.0, 141.5, 132.8, 132.1, 128.5, 128.5, 126.0, 114.1, 55.4, 43.5, 36.6, 30.3, 19.2 ppm. LRMS (DEP/EI-Orbitrap) m/z: 280.0 (60), 189.1 (30), 161.0 (70). HRMS (EI-Orbitrap) m/z: $[M]^+$ calcd for $C_{19}H_{20}O_2^+$ 280.1463, found 280.1458. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3086 (vw), 3026 (w), 3003 (w), 2955 (w), 2952 (w), 2934 (w), 2931 (w), 2923 (vw), 2835 (vw), 1716 (w), 1689 (s), 1651 (vw), 1610 (m), 1579 cm^{-1} (w).

1-((1R,2R*)-2-Phenethyl-1-(p-tolyl)cyclopropyl)ethanone ((**R***)-**4ae**).* Using (2-(3-iodo-2-methylcyclobut-2-en-1-yl)ethyl)benzene (**2d**) and 4,4,5,5-tetramethyl-2-(*p*-tolyl)-1,3,2-dioxaborolane according to general procedures A and Ba provided (**R***)-**4ae** (0.15 mmol, 42 mg, 60%) as a colorless oil. R_f = 0.7 (hexane/EtOAc 9:1, UV, $KMnO_4$, PAA). ^1H NMR (400 MHz, $CDCl_3$) δ 7.32−7.27 (m, 2H), 7.24−7.17 (m, 5H), 7.15−7.11 (m, 2H), 2.80−2.71 (m, 1H), 2.69−2.61 (m, 1H), 2.35 (s, 3H), 1.95 (s, 3H), 1.91−1.80 (m, 2H), 1.76−1.66 (m, 2H), 1.15−1.05 ppm (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.3, 141.8, 139.6, 137.2, 130.5, 129.4, 128.6, 128.5, 126.0, 42.6, 36.4, 32.1, 30.9, 28.5, 21.6, 21.2 ppm. LRMS (DEP/EI-Orbitrap) m/z: 278.1 (2), 187.1 (10), 173.1 (15), 148.1 (100). HRMS (EI-Orbitrap) m/z: $[M]^+$ calcd for $C_{20}H_{22}O^+$ 278.1671, found 278.1662. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3086 (vw), 3062 (vw), 3026 (w), 3000 (w), 2922 (w), 2860 (w), 1688 (vs), 1654 (vw), 1604 (w) cm^{-1}.

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1-((1R,2S*)-2-Phenethyl-1-(p-tolyl)cyclopropyl)ethanone* ***((S*)-4ae)***. Using **2d** and 4,4,5,5-tetramethyl-2-(*p*-tolyl)-1,3,2-dioxaborolane according to general procedures A and Ba provided (***S****)-**4ae** (0.08 mmol, 23 mg, 32%) as a colorless oil. R_f = 0.6 (hexane/EtOAc 9:1, UV, $KMnO_4$, PAA). ^1H NMR (400 MHz, $CDCl_3$) δ 7.25−7.20 (m, 2H), 7.15 (s, 5H), 7.09−7.06 (m, 2H), 2.77−2.58 (m, 2H), 2.35 (s, 3H), 1.99−1.92 (m, 1H), 1.97 (s, 3H), 1.79−1.67 (m, 1H), 1.60 (ddd, J = 8.8, 3.6, 0.8 Hz, 1H), 1.00 (dd, J = 6.8, 3.6 Hz, 1H), 0.91−0.79 ppm (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.4, 142.0, 137.2, 135.0, 131.4, 129.4, 128.6, 128.4, 125.9, 42.2, 35.7, 33.0, 29.9, 29.7, 25.3, 21.3 ppm. LRMS (DEP/EI-Orbitrap) m/z: 278.1 (100). HRMS (EI-Orbitrap) m/z: $[M]^+$ calcd for $C_{20}H_{22}O^+$ 278.1671, found 278.1660. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3026 (w), 3000 (w), 2924 (w), 2858 (w), 1690 (vs) cm^{-1}.

1-((1R,2R*)-2-Phenethyl-1-((E)-styryl)cyclopropyl)ethanone* ***((R*)-4af)***. Using **2d** and (*E*)-styrylboronic acid according to general procedures A and Ba provided (***R****)-**4af** (0.11 mmol, 31 mg, 43%) as a colorless oil. R_f = 0.8 (hexane/EtOAc 9:1, UV, $KMnO_4$, PAA). ^1H NMR (400 MHz, $CDCl_3$) δ 7.37−7.23 (m, 7H), 7.23−7.16 (m, 3H), 6.68 (d, J = 15.8 Hz, 1H), 6.35 (d, J = 15.8 Hz, 1H), 2.74−2.54 (m, 2H), 2.21 (s, 3H), 1.83−1.73 (m, 2H), 1.60 (dd, J = 7.5, 4.1 Hz, 1H), 1.52−1.41 (m, 1H), 1.22 ppm (dd, J = 8.6, 4.1 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.3, 141.7, 136.9, 130.9, 129.9, 128.8, 128.8, 128.5, 127.8, 126.2, 126.1, 39.4, 36.1, 34.2, 30.6, 28.6, 21.1 ppm. LRMS (DEP/EI-Orbitrap) m/z: 290.1 (5), 199.1 (10). HRMS (EI-Orbitrap) m/z: $[M]^+$ calcd for $C_{21}H_{22}O^+$ 290.1671, found 290.1660. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3060 (w), 3026 (m), 3000 (w), 2920 (w), 1692 (vs), 1644 (w), 1602 (w) cm^{-1}.

1-((1S,2R*)-2-Phenethyl-1-((E)-styryl)cyclopropyl)ethanone* ***((S*)-4af)***. Using **2d** and (*E*)-styrylboronic acid according to general procedures A and Ba provided (***S****)-**4af** (0.08 mmol, 24 mg, 33%) as a colorless oil. R_f = 0.7 (hexane/EtOAc 9:1, UV, $KMnO_4$, PAA). ^1H NMR (400 MHz, $CDCl_3$) δ 7.36−7.25 (m, 7H), 7.24−7.18 (m, 1H), 7.15−7.09 (m, 2H), 6.39 (d, J = 15.8 Hz, 1H), 6.21 (d, J = 15.8 Hz, 1H), 2.77−2.59 (m, 2H), 2.16 (s, 3H), 1.77−1.62 (m, 2H), 1.62−1.53 (m, 2H), 1.03 ppm (dd, J = 6.2, 3.6 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.4, 141.8, 136.8, 134.3, 128.8, 128.8, 128.5, 127.9, 126.4, 126.1, 125.6, 39.4, 36.1, 32.4, 30.6, 29.3, 21.9 ppm. LRMS (DEP/EI-Orbitrap) m/z: 290.1 (4), 199.1 (53), 141.1 (10). HRMS (EI-Orbitrap) m/z: $[M]^+$ calcd for $C_{21}H_{22}O^+$ 290.1671, found 290.1663. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3060 (w), 3025 (w), 2998 (w), 2926 (w), 2922 (w), 2919 (w), 2859 (w), 1729 (w), 1691 (vs), 1655 (w), 1643 (w), 1602 (w) cm^{-1}.

1-((1R,2R*)-1-(Furan-3-yl)-2-phenethylcyclopropyl)ethanone* ***((R*)-4ag)***. Using **2d** and furan-3-ylboronic acid according to general procedures A and Ba provided (***R****)-**4ag** (0.085 mmol, 21 mg, 33%) as a colorless oil. R_f = 0.5 (hexane/EtOAc 9:1, UV, $KMnO_4$, PAA). ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 (dd, J = 1.7 Hz, 1H), 7.32−7.24 (m, 3H), 7.23−7.16 (m, 3H), 6.30 (dd, J = 1.8, 0.9 Hz, 1H), 2.74−2.56 (m, 2H), 2.06 (s, 3H), 1.92−1.72 (m, 2H), 1.63 (dd, J = 7.3, 3.5 Hz, 1H), 1.61−1.53 (m, 1H), 1.03 ppm (dd, J = 8.2, 3.5 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.9, 143.2, 141.6, 141.4, 128.7, 128.5, 127.3, 126.1, 112.1, 36.2, 33.1, 32.2, 30.5, 28.2, 21.6 ppm. LRMS (DEP/EI-Orbitrap) m/z: 254.1 (3), 163.0 (29). HRMS (EI-Orbitrap) m/z: $[M]^+$ calcd for $C_{17}H_{18}O_2^+$ 254.1307, found 254.1299. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3026 (w), 3002 (w), 2924 (w), 2860 (w), 1770 (m), 1690 (s), 1602 (w) cm^{-1}.

1-((1R,2S*)-1-(Furan-3-yl)-2-phenethylcyclopropyl)ethanone* ***((S*)-4ag)***. Using **2d** and furan-3-ylboronic acid according to general procedures A and Ba provided (***S****)-**4ag** (0.08 mmol, 19 mg, 30%) as a colorless oil. R_f = 0.4 (hexane/EtOAc 9:1, UV, $KMnO_4$, PAA). ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 (dd, J = 1.7 Hz, 1H), 7.30 (dd, J = 1.5, 0.9 Hz, 1H), 7.28−7.21 (m, 2H), 7.20−7.13 (m, 1H), 7.12−7.07 (m, 2H), 6.33 (dd, J = 1.8, 0.9 Hz, 1H), 2.75−2.59 (m, 2H), 2.11 (s, 3H), 1.94−1.81 (m, 1H), 1.68−1.58 (m, 2H), 1.28−1.17 (m, 1H), 0.93 ppm (dd, J = 6.9, 3.6 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.6, 143.3, 142.6, 141.9, 128.5, 128.5, 126.0, 122.6, 112.9, 35.6, 33.1, 32.2, 29.8, 29.4, 25.0 ppm. LRMS (DEP/EI-Orbitrap) m/z: 254.1 (29), 117.1 (17). HRMS (EI-Orbitrap) m/z: $[M]^+$ calcd for $C_{17}H_{18}O_2^+$ 254.1307, found 254.1299. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3025 (w), 2932 (w), 2926 (w), 2923 (w), 1758 (vs), 1688 (vs), 1635 (w), 1627 (w), 1602 (w) cm^{-1}.

1-((1R,2R*)-2-Phenethyl-1-(3,4,5-trimethoxyphenyl)-cyclopropyl)ethanone* ***((R*)-4ah)***. Using **2d** and (3,4,5-trimethoxyphenyl)boronic acid according to general procedures A and Ba provided (***R****)-**4ah** (0.07 mmol, 26 mg, 43%) as a colorless oil. R_f = 0.4 (hexane/EtOAc 8:2, UV, $KMnO_4$, PAA). ^1H NMR (400 MHz, $CDCl_3$) δ 7.32−7.27 (m, 2H), 7.25−7.16 (m, 3H), 6.46 (s, 2H), 3.83 (s, 3H), 3.82 (s, 6H), 2.70 (t, J = 7.3 Hz, 2H), 1.98 (s, 3H), 1.93−1.80 (m, 2H), 1.77−1.67 (m, 2H), 1.10 ppm (dd, J = 7.8, 2.9 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.1, 153.3, 141.6, 138.1, 137.3, 128.6, 128.6, 126.1, 107.4, 61.0, 56.3, 43.5, 36.2, 31.7, 30.6, 28.1, 21.7 ppm. LRMS (DEP/EI-Orbitrap) m/z: 354.2 (26), 311.2 (17), 263.1 (10), 219.1 (919, 181.1 (100), 165.1 (24). HRMS (EI-Orbitrap) m/z: $[M]^+$ calcd for $C_{22}H_{26}O_4^+$ 354.1831, found 354.1819. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2998 (w), 2936 (w), 2838 (vw), 1688 (m) cm^{-1}.

1-((1R,2S*)-2-Phenethyl-1-(3,4,5-trimethoxyphenyl)-cyclopropyl)ethanone* ***((S*)-4ah)***. Using **2d** and (3,4,5-trimethoxyphenyl)boronic acid according to general procedures A and Ba provided (***S****)-**4ah** (0.03 mmol, 12 mg, 20%) as a colorless oil. R_f = 0.3 (hexane/EtOAc 8:2, UV, $KMnO_4$, PAA). ^1H NMR (400 MHz, $CDCl_3$) δ 7.29−7.20 (m, 2H), 7.19−7.13 (m, 1H), 7.12−7.07 (m, 2H), 6.47 (s, 2H), 3.86 (s, 3H), 3.85 (s, 6H), 2.79−2.61 (m, 2H), 2.02 (s, 3H), 2.01−1.93 (m, 1H), 1.81−1.69 (m, 1H), 1.57 (dd, J = 9.0, 3.7 Hz, 1H), 1.00 (dd, J = 6.8, 3.7 Hz, 1H), 0.98−0.88 ppm (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.9, 153.3, 141.9, 137.4, 133.6, 128.5, 128.5, 126.0, 108.3, 61.1, 56.3, 43.1, 35.7, 33.0, 29.6, 29.5, 25.4 ppm. LRMS (DEP/EI-Orbitrap) m/z: 354.2 (100), 339.2 (39), 207.1 (17), 189.1 (22). HRMS (EI-Orbitrap) m/z: $[M]^+$ calcd for $C_{22}H_{26}O_4^+$ 354.1831, found 354.1822. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3000 (w), 2936 (w), 1688 (m) cm^{-1}.

1-((1R,2R*)-2-Pentyl-1-(p-tolyl)cyclopropyl)ethanone* ***((R*)-4ai)***. Using **2c** and 4,4,5,5-tetramethyl-2-(*p*-tolyl)-1,3,2-dioxaborolane according to general procedures A and Ba provided (***R****)-**4ai** (0.18 mmol, 21 mg, 55%) as a colorless oil. R_f = 0.6 (hexane/EtOAc 9:1, UV, $KMnO_4$, PAA). ^1H NMR (400 MHz, $CDCl_3$) δ 7.25−7.21 (m, 2H), 7.16−7.12 (m, 2H), 2.35 (s, 3H), 1.98 (s, 3H), 1.71−1.65 (m, 2H), 1.52−1.40 (m, 3H), 1.37−1.24 (m, 5H), 1.11−1.03 (m, 1H), 0.93−0.84 ppm (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.4, 139.9, 137.1, 130.6, 129.4, 42.6, 32.8, 31.8, 30.8, 30.0, 26.8, 22.8, 21.6, 21.3, 14.2 ppm. LRMS (DEP/EI-Orbitrap) m/z: 244.2 (56), 187.1 (10), 160.1 (14). HRMS (EI-Orbitrap) m/z: $[M]^+$ calcd for $C_{17}H_{24}O^+$ 244.1827, found 244.1820. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3000 (w), 2956 (m), 2924 (m), 2858 (m), 1692 (vs) cm^{-1}.

1-((1R,2S*)-2-Pentyl-1-(p-tolyl)cyclopropyl)ethanone* ***((S*)-4ai)***. Using **2c** and 4,4,5,5-tetramethyl-2-(*p*-tolyl)-1,3,2-dioxaborolane according to general procedures A and **Ba** provided (***S****)-**4ai** (0.08 mmol, 9 mg, 24%) as a colorless oil. R_f = 0.55 (hexane/EtOAc 9:1, UV, $KMnO_4$, PAA). ^1H NMR (400 MHz, $CDCl_3$) δ 7.16 (s, 4H), 2.36 (s, 3H), 1.96 (s, 3H), 1.93−1.84 (m, 1H), 1.61 (ddd, J = 8.8, 3.5, 0.7 Hz, 1H), 1.49−1.31 (m, 3H), 1.27−1.16 (m, 4H), 1.01 (dd, J = 6.9, 3.5 Hz, 1H), 0.87−0.78 (m, 3H), 0.57−0.44 ppm (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.7, 137.0, 135.3, 131.4, 129.3, 42.2, 31.7, 30.8, 30.3, 29.9, 29.1, 25.6, 22.7, 21.3, 14.2 ppm. LRMS (DEP/EI-Orbitrap) m/z: 244.2 (100), 187.1 (12), 169.1 (12), 160.1 (20), 145.1 (43). HRMS (EI-Orbitrap) m/z: $[M]^+$ calcd for $C_{17}H_{24}O^+$ 244.1827, found 244.1821. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3000 (w), 2956 (m), 2928 (m), 2858 (m), 1692 (vs) cm^{-1}.

(E)-8-Methyl-1-(4-(trifluoromethyl)phenyl)nona-1,8-diene-3,6-dione ***(6a)***. Using **2c** and (*E*)-(4-(trifluoromethyl)styryl)boronic acid according to general procedures A and C provided **6a** (0.10 mmol, 31 mg, 40%) as a colorless oil. R_f = 0.28 (hexane/EtOAc 9:1, UV, $KMnO_4$, PAA). ^1H NMR (400 MHz, $CDCl_3$) δ 7.64 (s, 4H), 7.58 (d, J = 16.2 Hz, 1H), 6.81 (d, J = 16.2 Hz, 1H), 4.97 (s, 1H), 4.86 (s, 1H), 3.20 (s, 2H), 2.98 (t, J = 6.1 Hz, 2H), 2.87 (t, J = 6.1 Hz, 2H), 1.77 ppm (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.4, 198.3, 140.8, 139.3, 138.0, 132.0 (q, J = 32.7 Hz), 128.5, 128.1, 126.0 (q, J = 3.8 Hz), 123.9 (q, J = 272.2 Hz), 115.4, 52.4, 35.6, 34.7, 22.8 ppm. LRMS (DEP/EI-Orbitrap) m/z: 310.2 (2), 255.1 (100), 227.1 (30), 199.1 (62). HRMS (EI-Orbitrap) m/z: $[M]^+$ calcd for $C_{17}H_{17}F_3O_2^+$

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310.1181, found 310.1168. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2973 (vw), 2917 (vw), 2854 (vw), 1714 (m), 1694 (m), 1670 (m), 1616 (m) cm^{-1}.

*(E)-1-Cyclohexyl-8-methylnona-1,8-diene-3,6-dione (**6b**).* Using **2a** and (*E*)-(2-cyclohexylvinyl)boronic acid according to general procedures A and C provided **6b** (0.12 mmol, 29 mg, 48%) as slightly yellow oil. R_f = 0.50 (hexane/EtOAc 9:1, UV, $KMnO_4$, PAA). ^1H NMR (400 MHz, $CDCl_3$) δ 6.80 (dd, J = 16.1, 6.8 Hz, 1H), 6.05 (dd, J = 16.1, 1.3 Hz, 1H), 4.95 (s, 1H), 4.84 (s, 1H), 3.18 (s, 2H), 2.85 (t, J = 6.3 Hz, 2H), 2.77 (t, J = 6.2 Hz, 2H), 2.23−2.07 (m, 1H), 1.76 (s, 3H), 1.83−1.60 (m, 4H), 1.34−1.05 ppm (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.6, 199.1, 152.7, 139.2, 127.5, 115.1, 52.3, 40.6, 35.3, 33.5, 31.7, 25.9, 25.7, 22.6 ppm. LRMS (DEP/EI-Orbitrap) m/z: 248.3 (2), 193.2 (23). HRMS (EI-Orbitrap) m/z: $[M]^+$ calcd for $C_{16}H_{24}O_2^+$ 248.1776, found 248.1772. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2926 (vs), 2853 (m), 1717 (m), 1698 (m), 1674 (s), 1650 (w), 1628 (m) cm^{-1}.

*(E)-7-Phenylhept-6-ene-2,5-dione (**6c**).* Using **2b** and (*E*)-styrylboronic acid according to general procedures A and C provided **6c** (0.13 mmol, 25 mg, 50%) as a colorless oil. R_f = 0.10 (hexane/EtOAc 9:1, UV, $KMnO_4$, PAA). ^1H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, J = 16.2 Hz, 1H), 7.56−7.51 (m, 2H), 7.42−7.36 (m, 3H), 6.76 (d, J = 16.2 Hz, 1H), 2.98 (dd, J = 6.6, 5.5 Hz, 2H), 2.83 (dd, J = 6.9, 5.7 Hz, 2H), 2.24 ppm (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.5, 198.6, 143.0, 134.5, 130.7, 129.1, 128.4, 126.1, 37.2, 34.3, 30.2 ppm. LRMS (DEP/EI-Orbitrap) m/z: 202.1 (4), 144.1 (24), 131.1 (100). HRMS (EI-Orbitrap) m/z: $[M - H]^+$ calcd for $C_{13}H_{13}O_2^+$ 201.0910, found 201.0912. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2908 (w), 1714 (vs), 1690 (s), 1664 (vs), 1614 (vs) cm^{-1}.

*(E)-Tridec-6-ene-2,5-dione (**6d**).* Using **2b** and (*E*)-oct-1-en-1-ylboronic acid according to general procedures A and C provided **6d** (0.12 mmol, 25 mg, 48%) as a colorless oil. R_f = 0.13 (hexane/EtOAc 9:1, UV, $KMnO_4$, PAA). ^1H NMR (400 MHz, $CDCl_3$) δ 6.87 (dt, J = 15.9, 6.9 Hz, 1H), 6.10 (d, J = 15.9 Hz, 1H), 2.84 (t, J = 6.3 Hz, 2H), 2.75 (t, J = 6.3 Hz, 2H), 2.21 (dd, J = 13.6, 7.0 Hz, 2H), 2.21 (s, 3H), 1.52−1.38 (m, 2H), 1.37−1.21 (m, 6H), 0.88 ppm (t, J = 6.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.6, 198.8, 148.2, 130.1, 37.1, 33.6, 32.7, 31.7, 30.2, 29.0, 28.2, 22.7, 14.2 ppm. HRMS (ESI-quadrupole pos) m/z: $[M]^+$ calcd for $C_{13}H_{22}O_2^+$: 210.1620, found 210.1622. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2956 (m), 2926 (s), 2871 (m), 2857 (m), 1718 (vs), 1700 (vs), 1675 (vs), 1630 (s) cm^{-1}.

*(E)-3-Phenethyl-7-(p-tolyl)hept-6-ene-2,5-dione (**6e**).* Using **2d** and (*E*)-(4-methylstyryl)boronic acid according to general procedures A and C provided **6e** (0.11 mmol, 34 mg, 43%) as a colorless oil. R_f = 0.3 (hexane/EtOAc 9:1, UV, $KMnO_4$, PAA). ^1H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, J = 16.2 Hz, 1H), 7.47−7.41 (m, 2H), 7.34−7.27 (m, 2H), 7.23−7.14 (m, 5H), 6.68 (d, J = 16.2 Hz, 1H), 3.29−3.14 (m, 2H), 2.84−2.71 (m, 1H), 2.68−2.54 (m, 2H), 2.38 (s, 3H), 2.29 (s, 3H), 2.03−1.90 (m, 1H), 1.84−1.69 ppm (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.4, 198.5, 143.1, 141.2, 141.1, 131.6, 129.7, 128.6, 128.4, 128.3, 126.2, 124.9, 46.6, 42.1, 33.4, 33.1, 30.0, 21.6 ppm. LRMS (DEP/EI-Orbitrap) m/z: 320.1 (2), 216.1 (26), 145.1 (100). HRMS (EI-Orbitrap) m/z: $[M]^+$ calcd for $C_{22}H_{24}O_2^+$ 320.1776, found 320.1768. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3056 (w), 3026 (w), 2924 (w), 2860 (w), 1710 (vs), 1686 (s), 1656 (s), 1602 (vs) cm^{-1}.

*(E)-3-Phenethyl-7-phenylhept-6-ene-2,5-dione (**6f**).* Using **2d** and (*E*)-styrylboronic acid according to general procedures A and C provided **6f** (0.12 mmol, 37 mg, 48%) as a colorless oil. R_f = 0.3 (hexane/EtOAc 9:1, UV, $KMnO_4$, PAA). ^1H NMR (400 MHz, $CDCl_3$) δ 7.60−7.51 (m, 3H), 7.43−7.37 (m, 3H), 7.33−7.27 (m, 2H), 7.25−7.15 (m, 3H), 6.72 (d, J = 16.3 Hz, 1H), 3.29−3.16 (m, 2H), 2.84−2.71 (m, 1H), 2.71−2.53 (m, 2H), 2.29 (s, 3H), 2.06−1.92 (m, 1H), 1.84−1.71 ppm (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.5, 198.6, 143.1, 141.3, 134.5, 130.7, 129.1, 128.7, 128.5, 128.4, 126.3, 125.9, 46.7, 42.2, 33.5, 33.2, 30.1 ppm. LRMS (DEP/EI-Orbitrap) m/z: 306.0 (2), 202.1 (40), 159.0 (10), 131.0 (100). HRMS (EI-Orbitrap) m/z: $[M]^+$ calcd for $C_{21}H_{22}O_2^+$ 306.1620, found 306.1620. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3060 (w), 3026 (w), 2928 (w), 2860 (w), 1708 (s), 1688 (m), 1658 (s), 1610 (s) cm^{-1}.

*1-(1-(4-Chlorophenyl)cyclopropyl)-2-(pyridin-2-ylsulfonyl)-ethanone (**B**).* **4r** was transformed to **6a** according to a literature procedure.[25] Purification by chromatography afforded **B** (0.06 mmol, 20 mg, 40%) as a colorless oil. R_f = 0.5 (hexane/EtOAc 5:5, UV, $KMnO_4$, PAA). ^1H NMR (400 MHz, $CDCl_3$) δ 8.70 (dt, J = 4.8, 1.2 Hz, 1H), 8.05 (dt, J = 7.9, 1.1 Hz, 1H), 7.97 (td, J = 7.7, 1.7 Hz, 1H), 7.55 (ddd, J = 7.6, 4.7, 1.2 Hz, 1H), 7.40−7.29 (m, 4H), 4.47 (s, 2H), 1.64 (dd, J = 7.3, 4.1 Hz, 2H), 1.27 ppm (dd, J = 7.1, 3.5 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.5, 157.1, 150.1, 138.3, 137.2, 134.5, 132.5, 129.5, 127.6, 122.3, 59.5, 38.0, 20.5 ppm. LRMS (DEP/EI-Orbitrap) m/z: 335.0 (3), 243.0 (13), 229.1 (11), 193.1 (43), 158.1 (21). HRMS (EI-Orbitrap) m/z: $[M - H]^+$ calcd for $C_{16}H_{13}ClNO_3S^+$ 334.0299, found 334.0288. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2918 (w), 1696 (s), 1580 (w) cm^{-1}.

*1-(Benzo[d][1,3]dioxol-5-yl)cyclopropanecarboxylic Acid (**8a**).* To a solution of **4w** (0.1 mmol) in CCl_4 (0.2 mL) and CH_2Cl_2 (0.1 mL) was added benzyltriethylammonium chloride (6 mg) followed by a dropwise addition of a 50% solution of NaOH (0.15 mL). The mixture was then stirred for 16h at rt. Water was added, and the mixture was extracted with EtOAc, concentrated under vacuum and purified on silica gel, providing **8a** (0.1 mmol, 26 mg, quant.) as white solid. R_f = 0.3 (hexane/EtOAc 6:4, UV, $KMnO_4$, PAA). ^1H NMR (400 MHz, $CDCl_3$) δ 6.83 (d, J = 1.6 Hz, 1H), 6.80 (dd, J = 7.9, 1.7 Hz, 1H), 6.73 (dd, J = 6.4, 3.3 Hz, 1H), 5.94 (s, 2H), 1.62 (dd, J = 7.0, 4.1 Hz, 3H), 1.22 ppm (dd, J = 6.9, 3.6 Hz, 2H) (COO*H* not observed). ^{13}C NMR (101 MHz, $CDCl_3$) 181.2, 147.4, 147.0, 132.7, 123.8, 111.3, 108.1, 101.2, 28.7, 17.8 ppm. LRMS (DEP/EI-Orbitrap) m/z: 206.1 (100), 161.0 (61). HRMS (EI-Orbitrap) m/z: $[M]^+$ calcd for $C_{11}H_{10}O_4^+$: 206.0579, found 206.0570. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3014 (w), 2894 (w), 2594 (w), 1684 (vs) cm^{-1}. Mp (°C): 157−158.

*2,2-Difluoro-5-(2-methylcyclobut-1-en-1-yl)benzo[d][1,3]dioxole (**12**).* To a solution of 5-bromo-2,2-difluorobenzo[*d*][1,3]dioxole in THF (0.5 M) at −10 °C was slowly added *i*PrMgCl·LiCl (1.1 M in THF) and stirred at aforesaid temperature for 60 min. The so obtained (2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)magnesium bromide was subsequently transmetalated to zinc by addition of a zinc chloride solution (1.0 M in THF) and stirring for another 60 min at −10 °C. The resulting zinc species was subjected to a Negishi cross-coupling[3] with **2b** to obtain **12**.

*1-(1-(2,2-Difluorobenzo[d][1,3]dioxol-5-yl)cyclopropyl)ethanone (**4aj**).* Using **12** according to general procedure Bb provided **4aj** (0.49 mmol, 118 mg, 49%) as a colorless oil. R_f = 0.5 (hexane/EtOAc 9:1, UV, $KMnO_4$, PAA). ^1H NMR (400 MHz, $CDCl_3$) δ 7.12−7.06 (m, 2H), 7.02 (dd, J = 7.9, 0.7 Hz, 1H), 2.01 (s, 3H), 1.61 (dd, J = 6.8, 3.9 Hz, 2H), 1.16 ppm (dd, J = 7.1, 3.9 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) 208.0, 143.8, 143.1, 137.4, 131.8 (t, J = 255.5 Hz), 126.2, 112.1, 109.5, 37.6, 29.1, 19.1 ppm. LRMS (DEP/EI-Orbitrap) m/z: 240.0 (100), 197.0 (32), 131.0 (40), 103.1 (76). HRMS (EI-Orbitrap) m/z: $[M]^+$ calcd for $C_{12}H_{10}F_2O_3^+$ 240.0598, found 240.0581.

*1-(2,2-Difluorobenzo[d][1,3]dioxol-5-yl)cyclopropanecarboxylic Acid (**8b**).* To a solution of **4aj** (0.33 mmol) in CCl_4 (0.66 mL) and CH_2Cl_2 (0.33 mL) was added benzyltriethylammonium chloride (20 mg) followed by a dropwise addition of a 50% solution of NaOH (0.5 mL). The mixture was then stirred for 16 h at rt. Water was added, and the mixture was extracted with EtOAc, concentrated under vacuum, and purified on silica gel, providing **8b** (0.33 mmol, 80 mg, quant) as white solid. R_f = 0.3 (hexane/EtOAc 6:4, UV, $KMnO_4$, PAA). ^1H NMR (400 MHz, $CDCl_3$) δ 7.08−7.03 (m, 2H), 6.98 (d, J = 8.2 Hz, 1H), 1.69 (dd, J = 7.2, 4.3 Hz, 2H), 1.25 ppm (dd, J = 7.2, 3.8 Hz, 2H) (COO*H* not observed). ^{13}C NMR (101 MHz, $CDCl_3$) 180.7, 143.6, 143.1, 134.9, 131.8 (t, J = 253.2 Hz), 125.8, 112.2, 109.1, 28.8, 17.9 ppm. LRMS (DEP/EI-Orbitrap) m/z: 242.0 (68), 224.0 (16), 196.0 (35). HRMS (EI-Orbitrap) m/z: $[M]^+$ calcd for $C_{11}H_8F_2O_4^+$ 242.0391, found 242.0382. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2886 (w), 2840 (w), 1678 (vs) cm^{-1}. Mp (°C): 179−180.

*3-Chloro-6-(2-(2-methylcyclobut-1-en-1-yl)phenoxy)pyridazine (**10**).* Using **2b** and (2-methoxyphenyl)boronic acid according to general procedure A provided **9**. The product was dissolved in CH_2Cl_2 (1.0 M) and treated with a solution of BBr_3 in CH_2Cl_2 (1.0 equiv, 1.0 M) at 30 °C. After 5 min, TLC indicated completion of the reaction.

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The reaction mixture was slowly poured onto ice-cold water and subsequently extracted with CH_2Cl_2 (3 × 20 mL) and dried over magnesium sulfate. After evaporation of solvents and purification by chromatography, pure **13** was dissolved in DMF (1.0 M). To the solution were added NaH (1.1 equiv, 60% dispersion in mineral oil) and 3,6-dichloropyridazine. After the solution was stirred for 30 min at ambient temperature, TLC indicated full consumption of the starting materials. The reaction mixture was extracted with Et_2O (3 × 20 mL), washed with a saturated aqueous solution of LiCl (20 mL) and brine (20 mL). After the organic phase was dried over magnesium sulfate and solvents were evaporated, chromatography afforded pure **10** as a colorless oil. Most fractions contained impurities, a yield was therefore not determined. R_f = 0.3 (hexane/EtOAc 8:2, UV, $KMnO_4$, PAA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, J = 9.2 Hz, 1H), 7.36−7.33 (m, 1H), 7.18−7.12 (m, 2H), 7.02−6.98 (m, 1H), 6.96 (d, J = 9.1 Hz, 1H), 2.46−2.41 (m, 2H), 2.24−2.20 (m, 2H), 1.80−1.77 ppm (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.5, 151.8, 149.6, 142.5, 133.9, 131.4, 129.0, 129.0, 128.0, 126.0, 122.4, 119.2, 31.0, 28.9, 16.6 ppm. HRMS (EI-Orbitrap) m/z: $[M]^+$ calcd for $C_{15}H_{13}ClN_2O^+$ 272.0716, found 272.0714.

1-(1-(2-((6-Chloropyridazin-3-yl)oxy)phenyl)cyclopropyl)-ethanone (11). Using **10** (also impure fractions) according to general procedure Ba provided **11** (1.00 mmol, 288 mg, 43% over two steps) as a colorless oil. R_f = 0.1 (hexane/EtOAc 8:2, UV, $KMnO_4$, PAA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, J = 9.1 Hz, 1H), 7.45−7.36 (m, 2H), 7.29 (dd, J = 7.5, 1.3 Hz, 1H), 7.19 (dd, J = 8.0, 1.3 Hz, 1H), 7.18 (d, J = 9.1 Hz, 1H), 2.08 (s, 3H), 1.43 (dd, J = 6.9, 3.8 Hz, 2H), 1.08 ppm (dd, J = 7.2, 3.9 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.2, 164.8, 153.3, 152.4, 132.9, 131.8, 131.8, 129.3, 126.4, 122.5, 120.2, 33.5, 28.9, 18.1 ppm. LRMS (DEP/EI-Orbitrap) m/z: 272.1 (9), 237.1 (100), 222.1 (30), 209.1 (15), 194.1 (18), 183.0 (10), 165.0 (12). HRMS (EI-Orbitrap) m/z: $[M]^+$ calcd for $C_{15}H_{12}ClN_2O^+$ ($[M - OH]^+$) 271.0638, found 271.0635. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3066 (w), 2972 (w), 1754 (w), 1692 (m), 1642 (w), 1614 (w), 1606 (w) cm^{-1}.

(E)-2-Methyl-5-(4-methylstyryl)-3-phenethylfuran (7). Compound **6e** was dissolved in toluene (0.1 M), and P_4O_{10} (3.0 equiv) was added. The reaction mixture was heated to 100 °C for 24 h in a pressure tube. After being cooled to room temperature, the reaction was quenched with water, extracted with Et_2O (3 × 20 mL), washed with brine (20 mL), and dried over magnesium sulfate. The organic phase was concentrated under reduced pressure and purified by column chromatography. **7** was obtained (0.10 mmol, 29 mg, 87%) as a colorless oil. R_f = 0.2 (hexane, UV, $KMnO_4$, PAA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.32 (m, 2H), 7.31−7.26 (m, 2H), 7.23−7.11 (m, 5H), 6.90 (d, J = 16.2 Hz, 1H), 6.75 (d, J = 16.2 Hz, 1H), 6.13 (s, 1H), 2.81 (dd, J = 8.7, 6.7 Hz, 2H), 2.62 (dd, J = 8.7, 6.7 Hz, 2H), 2.34 (s, 3H), 2.10 ppm (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) 150.8, 147.9, 141.8, 137.2, 134.7, 129.5, 128.7, 128.4, 126.2, 126.1, 125.2, 120.6, 115.9, 110.9, 36.8, 27.1, 21.4, 11.6 ppm. LRMS (DEP/EI-Orbitrap) m/z: 302.1 (100), 211.1 (42), 169.1 (35). HRMS (EI-Orbitrap) m/z: $[M]^+$ calcd for $C_{22}H_{22}O^+$ 302.1671, found 302.1670.

1-(p-Tolyl)cyclopropane-1-carbaldehyde (13a). Using 1-bromo-4-methylbenzene and cyclobutanone according to general procedure C provided **13a** (8.4 mmol, 1.346 g, 69%) as a colorless oil. R_f = 0.5 (hexane/EtOAc 9:1, UV, $KMnO_4$, PAA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.28 (s, 1H), 7.26−7.13 (m, 4H), 2.38 (s, 3H), 1.57 (dd, J = 3.9 Hz, 2H), 1.40 ppm (dd, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.4, 137.5, 134.6, 130.0, 129.4, 37.2, 21.2, 16.2 ppm. LRMS (DEP/EI-Orbitrap-Orbitrap) m/z: 160.1 (100), 145.1 (20). HRMS (EI-Orbitrap) m/z: $[M]^+$ calcd for $C_{11}H_{12}O^+$ 160.0888, found 160.0882. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3010 (w), 2923 (w), 2919 (w), 2822 (vw), 2818 (vw), 1705 (vs), 1517 (m) cm^{-1}.

1-(4-Methoxyphenyl)cyclopropane-1-carbaldehyde (13b). Using 1-bromo-4-methoxybenzene and cyclobutanone according to general procedure C provided **13b** (0.34 mmol, 60 mg, 34%) as a colorless oil. R_f = 0.4 (hexane/EtOAc 9:1, UV, $KMnO_4$, PAA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.22 (s, 1H), 7.25−7.20 (m, 2H), 6.93−6.87 (m, 2H), 3.81 (s, 3H), 1.54 (dd, J = 3.9 Hz, 2H), 1.37 ppm (dd, J = 3.5 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.5, 159.1, 131.4, 129.6, 114.1, 55.4, 37.0, 16.2 ppm. LRMS (DEP/EI-Orbitrap-Orbitrap) m/z: 176.1 (100), 161.1 (10), 147.1 (70), 132.1 (15). HRMS (EI-Orbitrap) m/z: $[M]^+$ calcd for $C_{11}H_{12}O_2^+$ 176.0837, found IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 176.0831. 3003 (vw), 2958 (vw), 2836 (w), 2708 (vw), 1780 (vw), 1703 (s), 1611 (m), 1579 (w), 1514 (vs) cm^{-1}.

1-(Naphthalen-1-yl)cyclopropane-1-carbaldehyde (13c). Using 1-bromonaphthalene and cyclobutanone according to general procedure C provided **13c** (0.58 mmol, 114 mg, 58%) as a colorless oil. R_f = 0.4 (hexane/EtOAc 9:1, UV, $KMnO_4$, PAA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.42 (s, 1H), 8.04−7.97 (m, 1H), 7.94−7.81 (m, 2H), 7.58−7.45 (m, 4H), 1.88−1.78 (m, 2H), 1.54−1.47 ppm (m, 2H).^{13}C NMR (101 MHz, $CDCl_3$) δ 201.7, 134.2, 134.0, 133.3, 129.0, 128.8, 128.5, 126.6, 126.1, 125.5, 124.4, 35.7, 17.2 ppm. LRMS (DEP/EI-Orbitrap-Orbitrap) m/z: 196.1 (90), 178.1 (10), 165.1 (100), 152.1 (90), 139.1 (20). HRMS (EI-Orbitrap) m/z: $[M]^+$ calcd for $C_{14}H_{12}O^+$ 196.0888, found 196.0883. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3044 (w), 3007 (vw), 2819 (vw), 2732 (vw), 2702 (vw), 1780 (vw), 1702 (s), 1595 (w) cm^{-1}.

1-([1,1′-Biphenyl]-4-yl)cyclopropane-1-carbaldehyde (13d). Using 4-bromo-1,1′-biphenyl and cyclobutanone according to general procedure C provided **13d** (0.57 mmol, 133 mg, 57%) as a colorless oil. R_f = 0.45 (hexane/EtOAc 9:1, UV, $KMnO_4$, PAA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.29 (s, 1H), 7.64−7.57 (m, 4H), 7.51−7.35 (m, 5H), 1.63 (dd, J = 4.1 Hz, 2H), 1.47 ppm (dd, J = 4.3 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.0, 140.8, 140.7, 136.5, 130.6, 128.9, 127.5, 127.2, 37.3, 16.2 ppm. HRMS (EI-Orbitrap) m/z: $[M]^+$ calcd for $C_{16}H_{14}O^+$ 222.1045, found 222.1048. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 1677 (m), 1498 (m), 1440 (w), 1427 (w) cm^{-1}.

1-(2,2-Difluorobenzo[d][1,3]dioxol-5-yl)cyclopropane-1-carbaldehyde (13e). Using 5-bromo-2,2-difluorobenzo[*d*][1,3]dioxole and cyclobutanone according to general procedure C provided **13e** (0.5 mmol, 105 mg, 50%) as a colorless oil. R_f = 0.5 (hexane/EtOAc 9:1, UV, $KMnO_4$, PAA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.07 (s, 1H), 7.09−6.89 (m, 3H), 1.59 (dd, J = 4.1 Hz, 2H), 1.41 ppm(dd, J = 3.7 Hz, 2H).^{13}C NMR (101 MHz, $CDCl_3$) δ 200.0, 143.9, 143.4, 133.5, 131.81 (t, J = 255.5 Hz), 125.6, 111.8, 109.5 ppm. LRMS (DEP/EI-Orbitrap-Orbitrap) m/z: 226.1 (80), 207.0 (5), 197.1 (15), 182.0 (5), 170.9 (5). HRMS (EI-Orbitrap) m/z: $[M]^+$ calcd for $C_{11}H_8F_2O_3^+$ 226.0442, found 226.0435.

1-(4-Bromophenyl)cyclopropane-1-carbaldehyde (13f). Using 1-bromo-4-iodobenzene and cyclobutanone according to general procedure C provided **13f** (0.69 mmol, 155 mg, 69%) as a colorless oil. R_f = 0.5 (hexane/EtOAc 9:1, UV, $KMnO_4$, PAA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.14 (s, 1H), 7.51−7.47 (m, 2H), 7.20−7.16 (m, 2H), 1.58 (dd, J = 6.9, 5.0 Hz, 2H), 1.39 ppm (dd, J = 7.8, 4.1 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.3, 136.5, 131.9, 131.9, 131.8, 37.2, 15.9 ppm. LRMS (DEP/EI-Orbitrap-Orbitrap) m/z: 226.0 (30), 197.0 (5), 181.9 (5). HRMS (EI-Orbitrap) m/z: $[M]^+$ calcd for $C_{10}H_9BrO^+$ 223.9837, found 223.9830. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 1682 (vs), 1488 (m), 1429 (m), 1420 (m) cm^{-1}.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.8b00297.

^{1}H and ^{13}C NMR spectra for all new compounds and computational details (PDF)

X-ray crystallographic data of compound **4f** (CIF)

X-ray crystallographic data of compound **4t** (CIF)

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Notes

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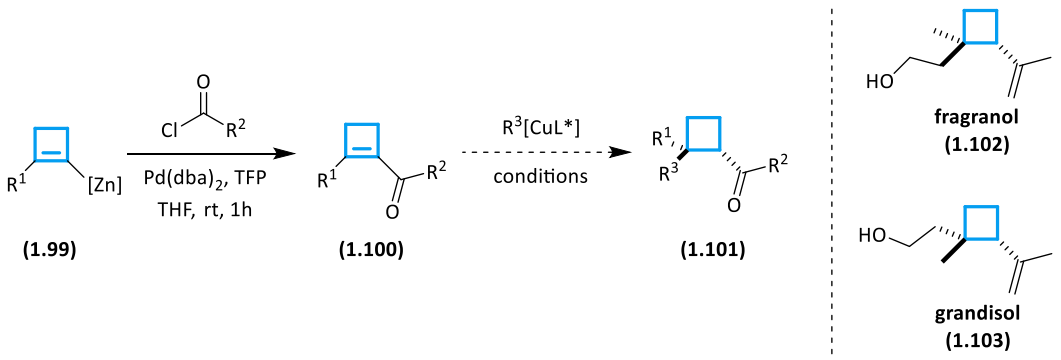
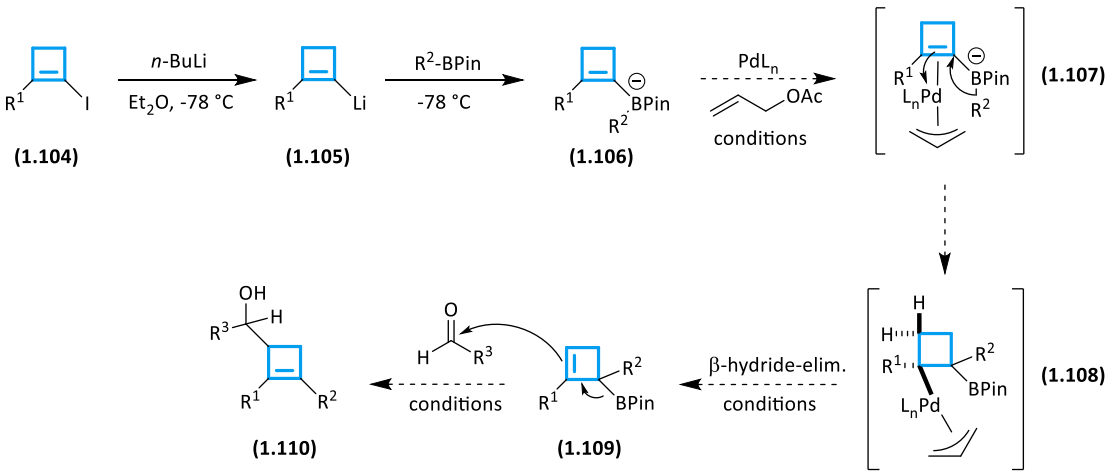
3 Outlook

Using previously described methods for the functionalization and transformation of the cyclobutenyl moiety, further applications are conceivable. For example, an asymmetric 1,4-addition of cyclobutenylketones with organocuprates in the presence of chiral ligands can lead to quaternary stereocenter-containing cyclobutanes **1.101** (**Scheme 21**). This method could ultimately give access to the enantioselective synthesis of grandisol (**1.103**) and fragranol (**1.102**), two naturally occurring pheromones.



Scheme 21: 1,4-Addition of organocuprates onto cyclobutenylketone and potential targets for total synthesis.

A further transformation of iodo-cyclobutenes **1.104** could be achieved by an initial halogen-metal exchange, followed by an introduction of a boronic ester to form organoboronate **1.106** (**Scheme 22**). The latter can be engaged in a palladium-mediated reaction, leading after β-hydride elimination to different cyclobutene-containing boronic pinacol esters **1.109**. Finally, a boron-allylation sequence with aldehydes or ketones would give access to a new library of functionalized cyclobutenes.



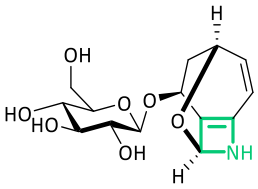
Scheme 22: Palladium mediated functionalization of iodo-cyclobutenes followed by boron-allylation with different aldehydes.

Chapter II

2-Azetines

4 Introduction

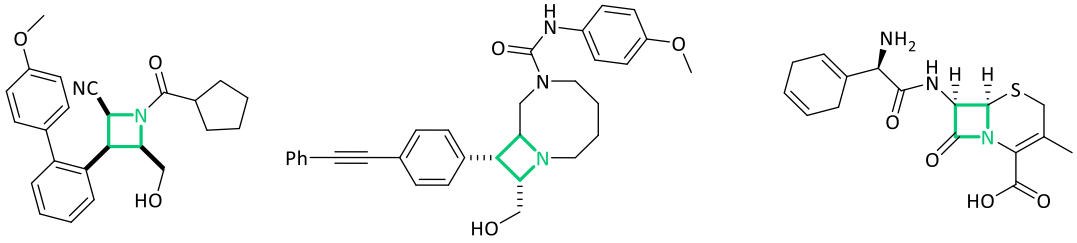
2-Azetines are remarkable and expectedly reactive structures, possessing an intrinsic ring strain within a polarized 4-membered ring moiety. Only one natural occurring compound has been discovered so far.[41] Isolated from the roots and stems of *Cleistanthus gracilis*, a 2-azetine fused with a 7-membered ring connected to a glucose moiety, was identified (**Figure 4**).



(+)-gracicleistanthoside (2.01)

Figure 4: The only natural occurring compound (+)-gracicleistanthoside, containing a 2-azetine moiety.

(+)-Gracicleistanthoside (**2.01**) was found to possess a down regulation of the TNF-α-induced synthesis of interleikin-6 in HaCaT cells without any cytotoxicity and can therefore be referred to as anti-inflammatory.[42] Additionally, 2-azetines are well suited as precursors for the synthesis of pharmacological important classes of azetidines and β-lactams. Some representative examples are depicted in **Figure 5**. For instance, the two azetidines BRD0026 (**2.02**) and BRD3444 (**2.03**) are novel antimalarial inhibitors with the potential to cure and prevent the further transmission of the disease.[43]



BRD0026 (2.02) **BRD3444 (2.03)** **cefradin (2.04)**

Figure 5: Examples of pharmacologically important azetidines and β-lactams.

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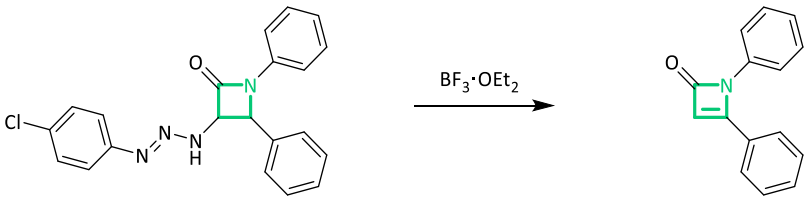
Cefradin (**2.04**) is a representative member of antibiotic cephalosporines, a huge class of β-lactam antibiotics.

However, methods for the formation and transformation of 2-azetines into important saturated derivatives are rather rare. This certainly originates from the difficulty of their synthesis.[44] To overcome this methodological gap, new ways are inevitable to provide access to highly substituted azetidines. Some relevant and known synthetic pathways will be described in the following section.

4.1 Synthesis of 2-Azetines

The synthesis of 2-azetines was pioneered by Henery-Logan and Rodricks in 1963. In their work on azetinone (**2.05**), the unsaturated β-lactam **2.06** was synthesized *via* a boron trifluoride triggered β-elimination (**Scheme 23**). The β-elimination approach is one of the most common methods for the formation of 2-azetines and double bonds in general and can be found in several reports.[45]



(2.05) **(2.06)**

Scheme 23: One of the first reported synthesis of a 2-azetine by β-elimination.

More recently, Hodgson and his group engaged the commercially available *N*-Boc-3-methoxyazetidine (**2.07**) in an α-lithiation/β-elimination sequence towards 2-substituted 2-azetines such as **2.12** (**Scheme 24**).[46] For the α-lithiation step, two equivalents of the organometallic compound *s*-BuLi, were used. Following the first α-lithiation, lithium methoxide is eliminated through β-elimination mechanism, whereupon the second equivalent of *s*-BuLi subsequently deprotonates the 2-azetine **2.09** to finally form the 2-lithiated azetine **2.10**. In this general approach, a large diversity of different electrophiles could be added to **2.10**. However, their attempt to perform a Negishi coupling through transmetalation with zinc only gave poor yields of desired coupling products.

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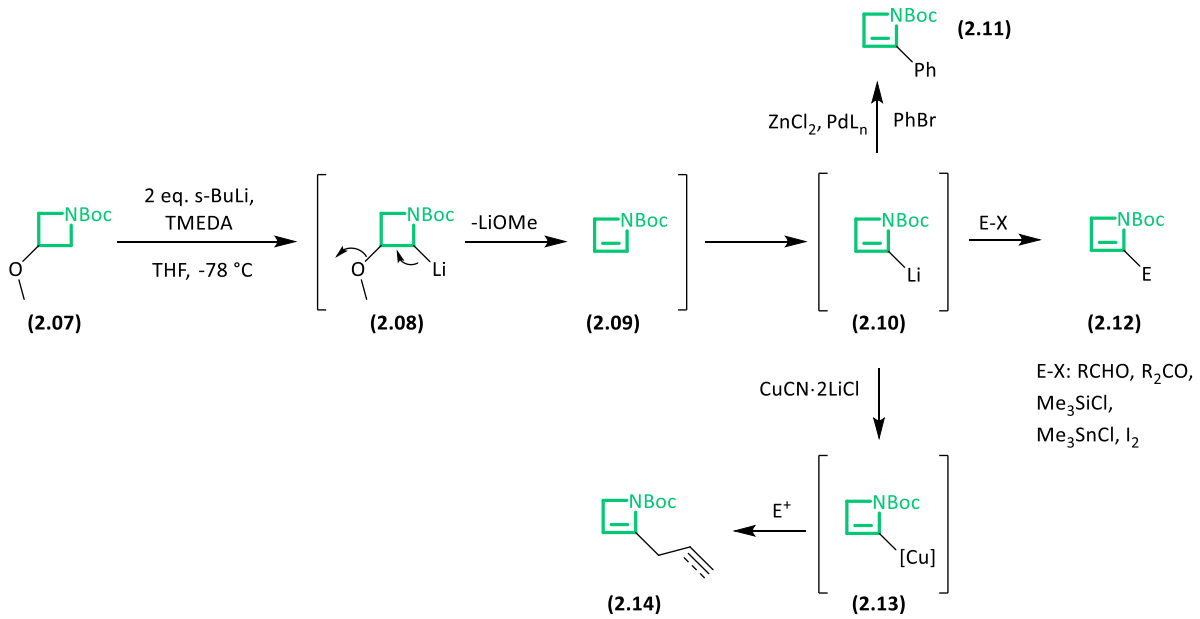
[44] For a short review see: D. Didier; A. N. Baumann; M. Eisold, *Tetrahedron Lett.* **2018**, *59*, 3975; T. W. Reidl; L. L. Anderson, *Asian J. Org. Chem.* **2019**, *8*, 931.

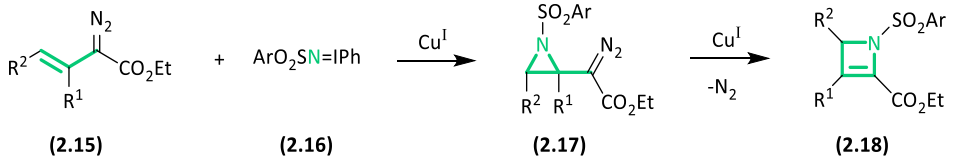
[45] F. Effenberger; R. Maier, *Angew. Chem. Int. Ed.* **1966**, *5*, 416; M. E. Jung; Y. M. Choi, *J. Org. Chem.* **1991**, *56*, 6729; P.R. Dave, R. Duddu, J. Li, R. Surapaneni, R. Gilardi, *Tetrahedron Lett.* **1998**, *39*, 5481; A. P. Marchand; D. Rajagopal; S. G. Bott; T. G. Archibald, *J. Org. Chem.* **1994**, *59*, 1608.

[46] D. M. Hodgson; C. I. Pearson; A. L. Thompson, *J. Org. Chem.* **2013**, *78*, 1098; D. M. Hodgson; C. I. Pearson; M. Kazmi, *Org. Lett.* **2014**, *16*, 856.



Scheme 24: Hodgson`s approach towards the synthesis of 2-azetines.

A different method for getting access to 2-azetines was described by the group of Barluenga, where a copper-catalyzed [3+1]-cycloaddition of alkenyldiazoacetates (**2.15**) and iminoiodinanes (**2.16**) was used (**Scheme 25**).[47] In the first catalytic step, the cycloaddition towards the aziridine **2.17** occurs, followed by extrusion of molecular nitrogen and formation of a copper-carbene complex which then undergoes a ring-enlargement of the aziridine moiety towards the final 2-azetine **2.18**.



Scheme 25: [3+1]-cycloaddition of alkenyldiazoacetates and iminoiodinanes towards 2-azetines.

Considering the different methods for the synthesis of 2-azetines, the β-elimination approach, especially the one investigated by Hodgson, was selected as a perfect headstone for the synthesis of 2-azetine building blocks and for further manipulation. Starting with a species similar to lithiated **2.10** (**Scheme 24**), various paths were developed, such as Suzuki cross couplings (see **Chapter I** "**Suzuki-Miyaura and Negishi Cross-Coupling Reactions**") or Zweifel-olefinations (see **Part B/Chapter I** "**Zweifel Olefinations**").

[47] J. Barluenga; L. Riesgo; G. Lonzi; M. Tomás; L. A. López, *Chem. Eur. J.* **2012**, *18*, 9221.

4.2 Alkylideneazetidines

Alkylideneazetidines represent a unique class of strained cyclic azetidines. Due to their difficulty of formation, only little is known about their chemistry and properties.[48] Apart from the well-known β-lactams (cephalosporines and penicillins), a few biologically active alkylideneazetidines are already known. Two of them are depicted in **Figure 6**. Polyoxin O (**2.19**) has shown antifungal activity, while 2-alkylideneazetidine **2.20** possesses inhibiting properties against leukocyte elastase and gelatinase.[49]

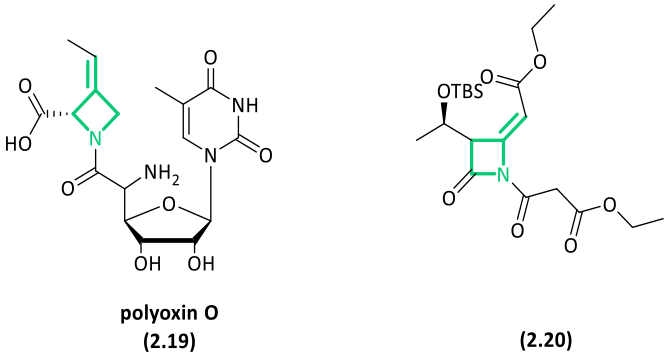
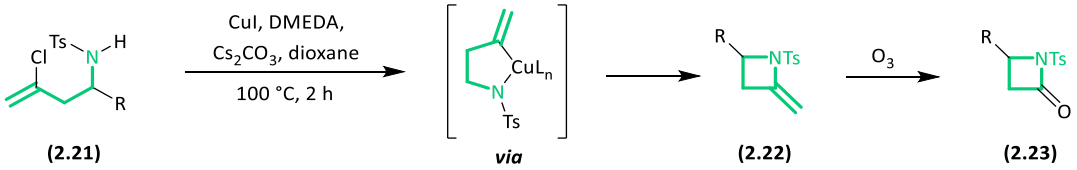


Figure 6: Some pharmacologically important alkylideneazetidines.

In 2006 Li and Lu described a well thought-through strategy for the synthesis of 2-alkylideneazetidines by employing a copper-catalyzed intramolecular *N*-vinylation (**Scheme 26**).[50] Several 2-alkylideneazetidines such as **2.22** could be accessed with remarkably high yields, and finally converted into the β-lactams **2.23** through ozonolysis.



Scheme 26: Copper-catalyzed intramolecular N-vinylation towards alkylideneazetidines.

As already described in **Chapter I** "**[4+2]-Cycloadditions of Cyclobutenes**", the Diels-Alder reaction represents a powerful tool for further transformations with cyclobutenes, in getting access to the important class of alkylidenecyclobutanes. This cycloaddition strategy was therefore applied to convert 2-azetines into fused alkylideneazetidines.

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[48] For recent examples see: D. K. Tiwari; A. Y. Shaikh; L. S. Pavase; V. K. Gumaste; A. R. A. S. Deshmukh *Tetrahedron* **2007**, *63*, 2524; K. Tehrani; N. De Kimpe, *Curr. Org. Chem.* **2009**, *13*, 854; S. Stanković; M. D'hooghe; T. Vanderhaegen; K. A. Tehrani; N. De Kimpe, *Synlett* **2014**, *25*, 75.

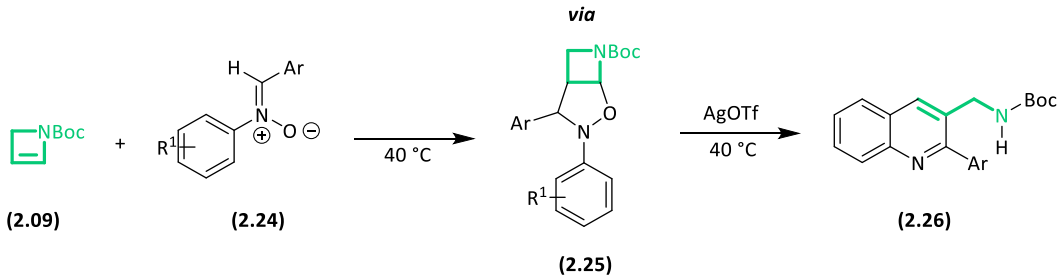
[49] J. Li; L. Li; Y. Chen; H. Tan, *Microb. Cell Fact.* **2012**, *11*, 135; G. Cainelli; P. Galletti; S. Garbisa; D. Giacomini; L. Sartor; A. Quintavalla, *Bioorg. Med. Chem.* **2003**, *11*, 5391.

[50] H. Lu; C. Li, *Org. Lett.* **2006**, *8*, 5365.

In an approach similar to the [4+2]-cycloaddition, the use of 1,3-dipoles for the derivatization of 2-azetines will be described thereafter.

4.3 (2+3)-Cycloadditions of 2-Azetines

(2+3)-Cycloaddition reactions or 1,3-dipolar cycloadditions, are widely applied in organic syntheses and are useful in opening the pathway towards more complex molecules.[51] However, the utilization of 2-azetines in 1,3-dipolar cycloaddition strategies has only been reported once in the literature (**Scheme 27**).[52] In that work, a 1,3-dipolar cycloaddition of different nitrones **2.24** with 2-azetine (**2.09**) was described. Furthermore, the cycloaddition adduct **2.25** was directly converted into 2,3-disubstituted quinolines **2.26** by a silver-catalyzed ring opening-/ring-closing-sequence.



Scheme 27: 1,3-Dipolar cycloaddition of 2-azetine and different nitrones followed by a silver-catalyzed ring opening- and closing-sequence.

On the one hand, this clearly demonstrates the applicability of azetines. On the other hand, a general method for their use in 1,3-dipolar cycloadditions is still not provided. Therefore, a more versatile and general approach in 1,3-dipolar cycloadditions was designed and combined with the sulfur analogues of azetines (thiete dioxides). This results will be presented in **Chapter III** "**Chemodivergent and Stereoselective Access to Fused Isoxazoline Azetidines and Thietanes through [3+2]-Cycloadditions**".

[51] For an overview on 1,3-dipolar cycloadditons see: L.-Y. Wang; Y. Tang, *Intermolecular 1,3-Dipolar Cycloadditions of Alkenes, Alkynes, and Allenes.* In Comprehensive Organic Synthesis II; Elsevier, **2014**; 1342−1383; T. Hashimoto; K. Maruoka, *Chem. Rev.* **2015**, *115*, 5366; M. S. Singh; S. Chowdhury; S. Koley, *Tetrahedron* **2016**, *72*, 1603.
[52] H. Yan; X. Li; C. Wang; B. Wan, *Org. Chem. Front.* **2017**, *4*, 1833.

5 Results

5.1 Methods for the Synthesis of Substituted Azetines

Organic LETTERS

Letter

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Methods for the Synthesis of Substituted Azetines

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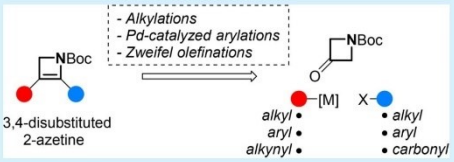
Supporting Information

ABSTRACT: Spurred on by the recent emerging interest from the chemical community for unsaturated four-membered heterocycles, an unprecedented approach to nitrogen-containing four-membered rings has been designed. 3,4-Disubstituted 2-azetines were synthesized from commercially available substrates, allowing for a straightforward access to a new library of chiral functionalized azetidines and amino alcohols. This original approach was applied to efficiently prepare functionalized azobenzenes, an emerging class of molecules with a large potential in photopharmacology.



Small, strained ring systems have recently received increased attention due to their large applicability in drug discovery and development. However, generating these systems is often limited by the availability of efficient and straightforward methods. Among them, azetidines and their unsaturated analogues 2-azetines[1−4] are particularly interesting as they represent a promising pattern for further pharmacological studies.

Apart from the well-known β-lactams penicillin and cephalosporin derivatives, several fused azetidine-containing substances have shown interesting antitumor activities[5] and antinociceptive effects[6] (Figure 1).

Fused β-lactams have also proven to be adequate precursors of azabicyclo[3.2.1]octanes.[7] In the polyoxin family, antibiotic properties were observed on 3-alkylideneazetidine-modified structures.[8]

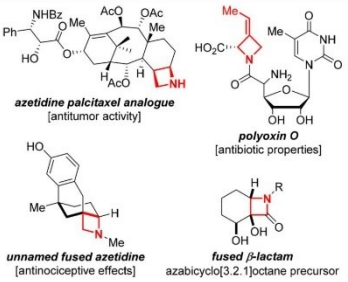


Figure 1. Examples of biologically active azetidine-containing structures or precursors.

Recently, the group of Baran et al. developed a new route for introducing 3-substituted azetidines by using the ring strain of azabicyclo[1.1.0]butane to efficiently modify lead compounds of pharmacological interests.[9] Concurrently, Carreira demonstrated the propensity of spiro-azetidines to modulate biological properties of different targets in drug discovery.[10] While smaller and larger *N*-containing heterocycles have been extensively studied,[1] only a few reports relate the general formation of azetines.[2,11]

With the ambitious objective of generalizing access to polysubstituted azetine architectures—that represent versatile building blocks en route to sophisticated azetidines—we first took on the challenge of identifying a sequence allowing for the regioselective introduction of diverse substituents at positions 3 and 4 (Scheme 1), involving a lithiated species as the key intermediate. While direct functionalization of 4-azetinyllithium could be easily performed in the presence of alkyl, silyl or carbonyl derivatives (conditions A), a more challenging arylation was designed through cross-coupling of the corresponding organoboronate derivatives, obtained through a simple transmetalation. As a matter of fact, transmetalation with $ZnCl_2$ only furnished the cross-coupled compound in low yield (27%, Hodgson et al.). Alternatively, a boron-relayed catalyst-free arylation of azetinyllithium was developed.

Starting from commercial sources of *N*-Boc-3-azetidinone **1**,[12] the introduction of the substituent at position 3 (R^1) was simply performed by employing an adequate organometallic reagent, such as organolithium, organomagnesium, or $PhMe_2SiLi$. Methylation of the resulting crude tertiary alcohol afforded **2a**−**f** in good to excellent yields over two steps (up to 98%, Scheme 2).[13] α-Lithiation of **2** assisted by coordination of the

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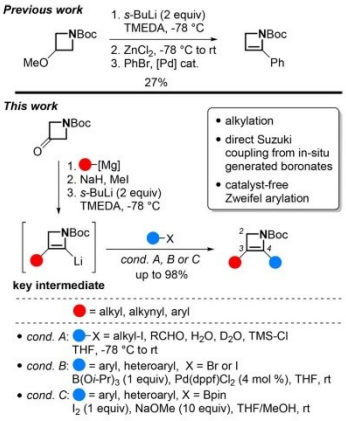
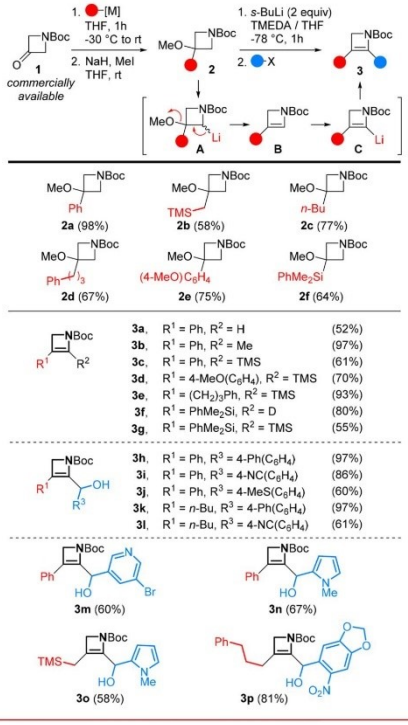
Scheme 1. Our Contribution to the Efficient Synthesis of Disubstituted Azetines



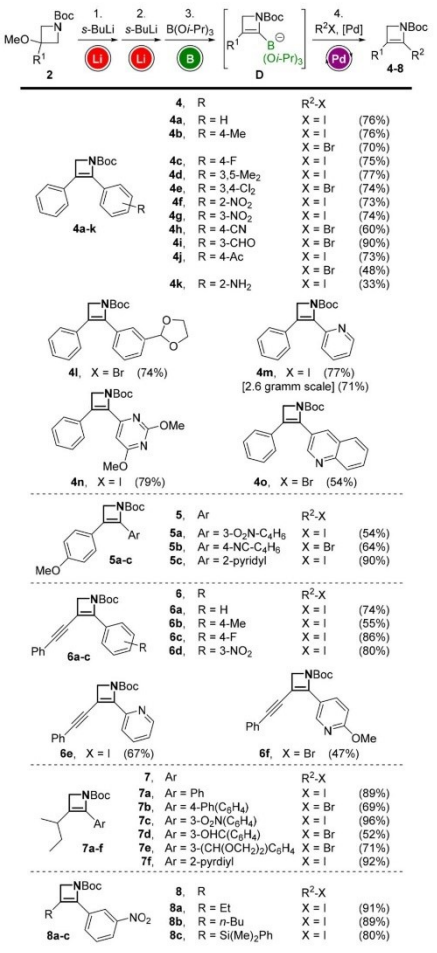
Scheme 2. Our Contribution to the Efficient Synthesis of Disubstituted Azetines



directing group (Boc) on the amine using *s*-BuLi in the presence of TMEDA triggers a β-elimination (**A**, Scheme 2) and intermediary forms a 2-azetine (**B**). With an excess of *s*-BuLi, a second α-metalation of the C(sp^2) can take place to obtain the key 4-azetinyllithium intermediate **C**. Addition of H_2O, D_2O, MeI, or TMSCl allowed the formation of 3-substituted azetines **3a**–**g** in up to 97% yield (Scheme 2). Aromatic and heteroaromatic aldehydes were also engaged as electrophiles in the reaction, furnishing azetinecarbinols **3h**–**p** with up to 97% yield.

Second, a similar sequence was designed to in situ generate a boronate derivative **D** (Scheme 3) by trapping the corresponding 4-azetinyllithium **C** with boron isopropoxide. Being a stable species at room temperature, this organoboronate is an excellent candidate to subsequently undergo a Suzuki cross-coupling in a one-pot process. Thus, following the double-lithiation/borylation sequence, a range of aromatic halides were engaged in the

Scheme 3. In Situ Generated 4-Azetinylboronates for Direct Suzuki Coupling



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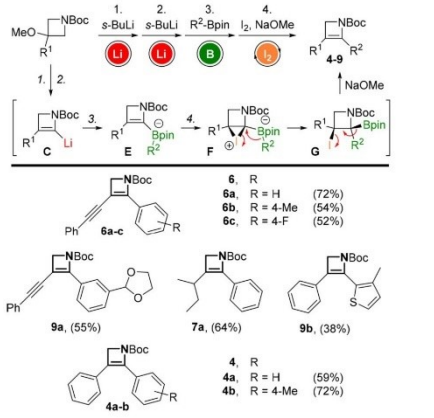
presence of $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (4 mol %) in THF, and products **4**–**8** were isolated after 48 h at room temperature. Aryl iodides reacted usually faster than the corresponding bromides, leading to the expected compounds in better yields. A wide range of aromatic halides were introduced in this strategy, using 3-arylated (**4a**–**o** and **5a**–**c**), 3-alkynyl (**6a**–**f**), and 3-alkyl substrates (**7a**–**f** and **8a**,**b**), resulting in 4-arylated structures in good to excellent yields (up to 96%). Additionally, the great functional group tolerance of organoboronates allowed us to introduce aromatic aldehydes **4i** and **7d** as well as heteroaromatic moieties (**4m**–**o**, **5c**, **6e**,**f**, and **7f**) in good yields up to 92%, independently from the nature of the substituent at position 3. Structures of these unsaturated *N*-heterocycles were supported by X-ray analysis (**6d** and **8a**).[14] Although full conversion was monitored for the formation of **4k** bearing a free amine, decomposition of the product on silica was noticed and the final azetine could only be isolated in 33% yield. In a more general manner, electron-enriched aromatics led to moderate yields due to fast decomposition (mainly ring opening products) in slightly acidic conditions during purification.

We then pushed the methodology further by developing an unprecedented catalyst-free cross-coupling of the 4-azetinyllithium species, successfully adapting the Zweifel-type olefination strategy. Boronic ester was then added to the in situ generated intermediate **C** (Scheme 4), giving the bis-organoboronate **E**.

Scheme 4. Catalyst-Free Zweifel Arylation of 4-Azetinyllithium Species

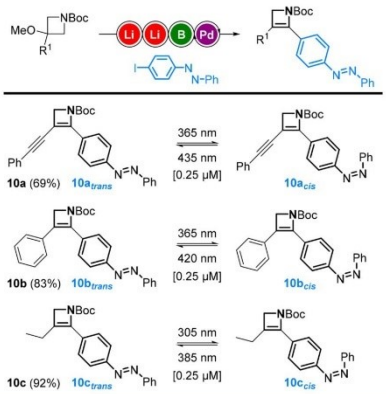


Subsequent addition of iodine furnishes an iodonium **F** that undergoes 1,2-metalate rearrangement, giving the α,β-iodoboronic ester **G**. The addition of a base finally triggers a cis-elimination, resulting in 3,4-disubstituted azetines **4**–**9**. 3-Alkyl-, alkynyl-, and arylazetinyllithium were used with aromatic boronic esters and compounds **4a**,**b**, **6a**–**c**, and **7a**, were obtained with reasonable yields (up to 72%), given the absence of a palladium catalyst. Interestingly, heteroaromatic substrates led to similar results and **9b** was isolated in 38% yield.

Considering the versatility of both arylation sequences and the recent interest brought by the community on diazobenzenes as promising photoswitchable systems for pharmacologic applications,[15] functionalization of azetines at position 4 was explored as a proof of concept.

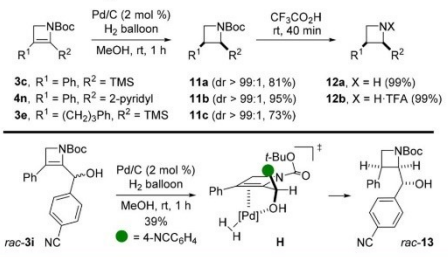
A one-pot sequence terminated by a palladium-catalyzed Suzuki coupling with 4-bromodiazobenzenes led to conjugated systems **10a**–**c** in good yields (Scheme 5). In the dark, **10a**–**c** are

Scheme 5. Application to the Synthesis of 4-Azetinylazobenzenes



present in their thermally stable *trans*-configuration. Irradiation with UV light (λ = 305–365 nm) triggers isomerization to the *cis*-configuration, while irradiation at 385–435 nm allows instant switching to the *trans*-configuration. Performing iteratively on and off photoswitching on these azetinyl-derived azobenzenes did not show any fatigue of the four-membered ring over time, proving the structural stability of the system. Finally, we showed the applicability of 3,4-substituted azetines to the formation of *syn*-2,3-disubstituted azetidines through simple hydrogenation (Scheme 6). Compounds **3e**, **3c**, and **4n** were engaged in the

Scheme 6. Straightforward Access to Stereodefined Azetidines



presence of palladium and hydrogen to give **11a**–**c** under smooth conditions in good yields and with an excellent diastereoisomeric ratio (dr >99:1).[12] Subsequent amine deprotection ultimately led to free azetidines **12a**,**b** in quantitative yields. It is worth noting that this represents a powerful approach to *syn*-azetidines, as most reports relate the formation of *anti*-azetidines.[16]

β-Amino alcohols are important functionalities in organic chemistry as they can serve as ligands in catalysis and are present in a large number of natural and bioactive substances.[17] In an attempt to synthesize stereodefined β-amino alcohols embedded in an azetidine core, we representatively demonstrated (Scheme

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6) that the reduction of chiral 4-azetinylcarbinol *rac*-**3i** could take place with high diastereoselectivities, furnishing *rac*-**13** as a single isomer (dr >99:1:0:0, the relative configuration was determined by X-ray crystallography).[14] The high degree of stereoselectivity observed in this reaction can be attributed to the coordination of the hydroxyl moiety to the palladium in the reduction process. For steric reasons, the aromatic group on the carbinol prefers to be oriented out of the plane, avoiding unfavorable interactions with the large Boc protecting group (**H**) (Scheme 6). This procedure certainly paves the way to new subclasses of chiral strained β-aminoalcohols.

In conclusion, we have demonstrated a very simple and efficient synthetic approach to novel 3,4-disubstituted azetine architectures, paving a new way toward stereodefined 2,3-azetidines. Two parallel approaches have been developed for the facile introduction of aryl and heteroaryl substituents at the position α to the nitrogen, either through a one-pot Suzuki cross-coupling or via catalyst-free arylation. Additionally, we showed the potential applicability of our system to unprecedented photoswitchable molecules, demonstrating their long-term stability. We finally illustrated an unprecedented access to stereodefined β-aminoalcohols that represent important structures in organic, organometallic and bioorganic chemistry. Paths allowing for the formation of these interesting patterns represent important advances in the chemistry of nitrogen-containing four-membered rings and their potential implications in drug-discovery processes.

■ ASSOCIATED CONTENT

Supporting Information

CThe Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02847.

Experimental procedures and characterization (IR, HRMS, and ^{1}H and ^{13}C NMR data) for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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5.2 One-Pot Preparation of Stable Organoboronate Reagents for the Functionalization of Unsaturated Four- and Five-Membered Carbo- and Heterocycles

Synthesis A. N. Baumann et al. Special Topic

One-Pot Preparation of Stable Organoboronate Reagents for the Functionalization of Unsaturated Four- and Five-Membered Carbo- and Heterocycles

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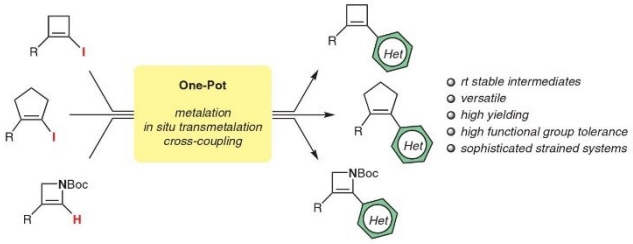

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Abstract Combining a facile preparation of organoboronates with their remarkable stability and functional group tolerance allows for the straightforward synthesis of four- and five-membered carbo- and heterocycles. While most strategies rely on the ex situ preparation of boronic acids as isolated intermediates, we demonstrate that in situ transmetalation of sensitive organometallics with boron alkoxides can lead to great stabilization of such species at room temperature. A considerable extension of the library of unsaturated strained structures is achieved through these sequences, expanding the potential applicability of such unusual building blocks.

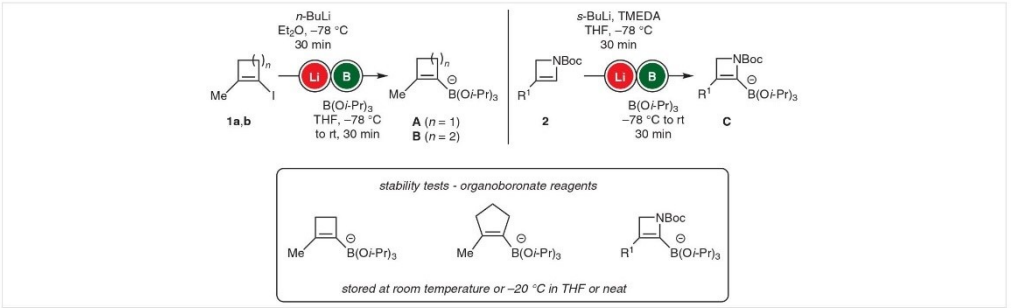
Key words cyclobutenes, cyclopentenes, azetines, organoboronates, one-pot sequences

The transition-metal-catalyzed cross-couplings of organoboronic acids with organic halides, a process developed by Suzuki et al.,[1] has become one of the most powerful tools for the creation of C–C bonds.[2] Both simplicity and functional group tolerance have made it a privileged method[3] for assembling complex structures in many fields of chemistry such as drug discovery,[4] materials science,[5] chemosensors[6] and total synthesis.[7] Spurred on by the particular stability of organoboron species, we took on the challenge of generalizing the access to classes of molecules that have been scarcely reported: strained cyclobutenes, cyclopentenes and 2-azetines. Due to their commercial availability, organoboronic acids are employed as stable substrates for numerous cross-coupling reactions. For more elaborated scaffolds however, tailor-made boronic acids must be prepared ex situ in order to be engaged in a subsequent reaction through a two-step process. For the sake of step-economy, we needed to develop a more straightforward access to the targeted compounds, avoiding an extra purification of intermediate boronic acids. Taking into account the recent work of Buchwald and co-workers on direct cross-coupling of lithium organoboronates,[8] Miyaura et al. on base-free coupling of triolborates,[9] Cammidge on coupling of ex situ generated trihydroxyborates,[10] and Knochel's group on the in situ generation of magnesium bis-organoborinates,[11] we designed different strategies in which the cross-coupling reaction would be relayed by the in situ formation of a stable intermediate boron species. Our first objective was to demonstrate the long-term stability of such strained organoboron derivatives over time, opening the strategy to reagent storage; secondly, we aimed to explore the scope and limitations of the method to complete a large library of new building blocks, being hitherto difficult to access.

Cyclobutene and cyclopentene iodides **1a**,**b** were readily prepared from procedures originally described by Negishi et al. involving π-cyclization of *gem*-bismetalated alkenes,[12] which we recently applied to the synthesis of alkylidenecyclobutanes and fused four-membered rings.[13] Halogen–lithium exchanges on **1a** and **1b** were performed employing *n*-BuLi in diethyl ether at –78 °C (as THF led to further alkylation of the newly formed cycloalkenyllithium) and the corresponding cycloalkenyl-boronates **A** and **B** were generated by addition of $B(Oi\text{-}Pr)_3$ in THF (Scheme 1).

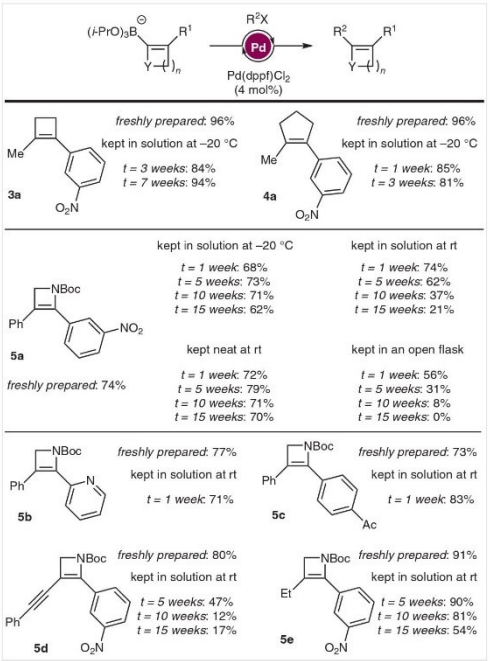
Azetinyllithium reagents were generated by α-lithiation of in situ formed azetines **2** using *s*-BuLi in the presence of TMEDA in THF at –78 °C,[14] and subsequently trapped with boron isopropoxide to give **C**.[15]

Organoboronates **A**, **B** and **C** were then stored either in solution or neat at –20 °C or room temperature before being engaged in Suzuki cross-couplings (Scheme 2).



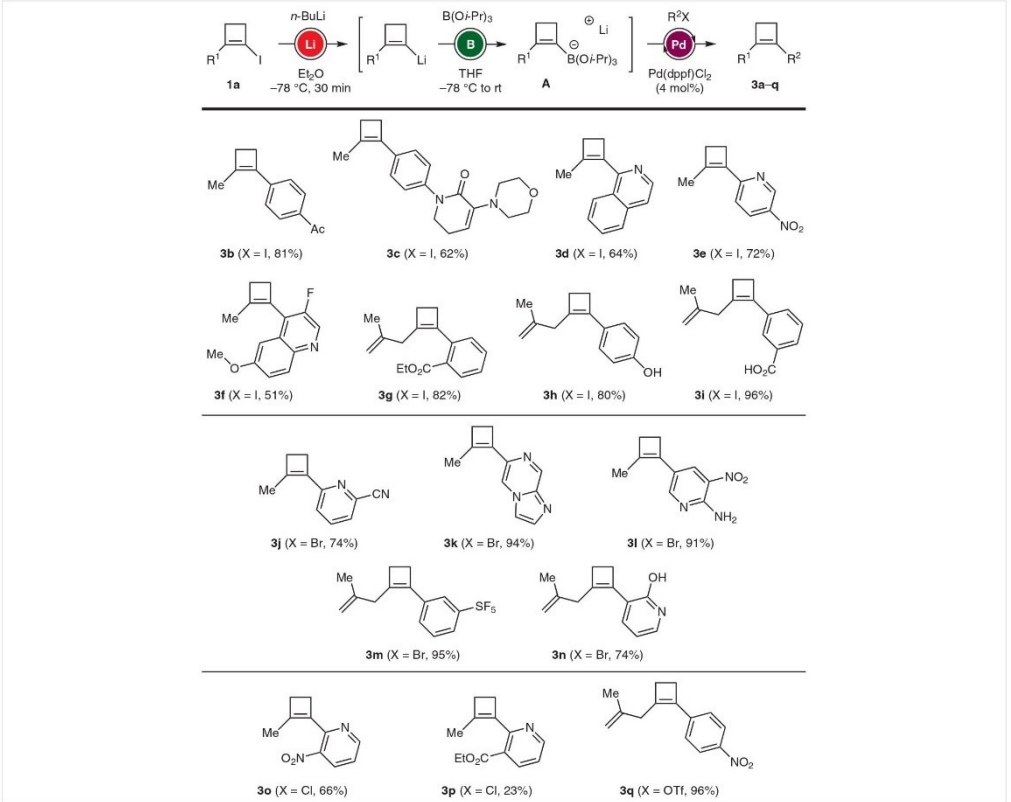
Scheme 1 Organoboronate synthesis through Li/I exchange–transmetalation or α-lithiation–transmetalation

Cyclobutenyl- and cyclopentenylboronates **A** and **B** were coupled with 1-iodo-3-nitrobenzene as a test partner. From freshly prepared solutions, both products **3a**[16] and **4a** were obtained in excellent yields (96%). Keeping solutions at –20 °C showed constancy in reactivity, delivering **3a** in 94% yield after seven weeks and **4a** (81%) after three weeks. Diverse conditions were evaluated for storage of azetinylboronates **C**. When kept in an open flask, the yields decreased drastically after only one week of storage, and a fast decrease in reactivity was also observed on storing **C** in solution at room temperature. However, reproducible results were obtained when the boronate salts were kept either in solution at –20 °C (as for **A** and **B**), or neat at room temperature. Products **5a** were isolated in constant, reasonable yields (up to 70% after fifteen weeks). Stock solutions of azetinylboronate reagents were prepared and further used in cross-coupling reactions after different storage times at room temperature. In some cases (**5b**, **5c** and **5e**), the salts gave reproducible yields after one or ten weeks of storage, showing the great potential of such reagents as building blocks. In some other cases (**5d**), the solution showed a rapid decrease of reactivity, furnishing only a 47% yield of the desired product.



Scheme 2 Stability testing of four- and five-membered carbo- and heterocyclic organoboronates

Having established the stability of strained organoboronates, we next investigated the scope of the transformation toward a new library of cyclobutenes. The protocol of Scheme 1 was used to generate in situ the cyclobutenylboronate **A**, which was then engaged directly in cross-coupling reactions in the presence of $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (Scheme 3). Aromatic and heteroaromatic iodides bearing ketone, ester, nitro or amide moieties led to the expected arylcyclobutenes **3b–g** in moderate to good yields (51 to 82%). Interestingly, an unprotected phenol and a benzoic acid furnished the desired products **3h** and **3i** in excellent yields of 80% and 96%, respectively. Not only iodides, but bromides could be engaged as cross-coupling partners with similar efficacy, furnishing **3j–n** with up to 95% yield and with exceptional functional group tolerance (SF_5, NH_2, OH). Alternatively, an aryl triflate gave a similar result (**3q**, 96%) while aryl chlorides showed decreased efficiency (**3o**,**p**, 23 to 66%).



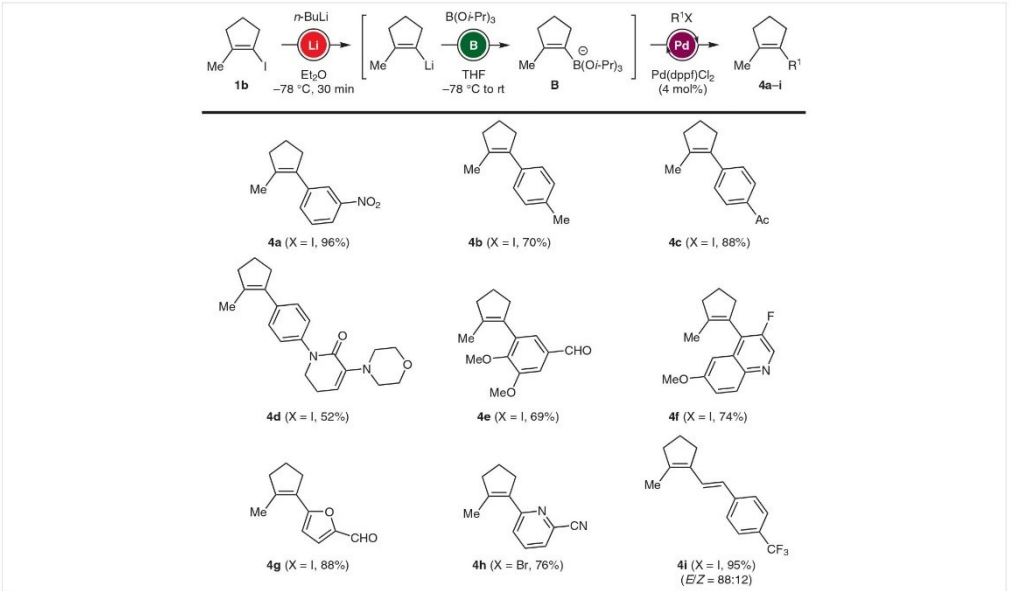
Scheme 3 In situ preparation and further Suzuki cross-coupling of cyclobutenylboronates

The study was then pursued with five-membered rings, utilizing cyclopentenyl iodides as starting materials[17] in a similar one-pot sequence (Scheme 4). Halogen–lithium exchange on **1b** was followed by transmetalation with B(O*i*-Pr)$_3$ and further palladium-catalyzed cross-coupling with diverse aromatic halides. A comparable functional group tolerance was observed for these larger cycloalkenylboronates, as ketone, nitro, amide and aldehyde moieties could be introduced, giving a wide range of unique functionalized cyclopentenes **4a–h** in moderate to excellent yields (52 to 96%).[16] When a β-styryl iodide was used, the reaction resulted in partial double bond isomerization and **4i** was obtained in 95% yield and an 82:18 *E*/*Z* ratio.

Next, we investigated the iodine–lithium exchange in the presence of boron isopropoxide. Given that the exchange reaction should proceed at a higher rate than the nucleophilic addition of *n*-BuLi to the boron atom, the presence of boron species should not perturb the exchange reaction, but rather promote the direct transmetalation of the newly generated lithium species (Scheme 5), as previously exemplified by Li et al.[18] As a result, the undesired alkylation reaction was to be suppressed without having to use Et$_2$O, avoiding the previously required mixture of solvents.

As a proof of concept, the halogen–metal exchange was performed on **1a** and **1b** in the presence of B(O*i*-Pr)$_3$ at –78 °C, and ultimately engaged in the cross-coupling reaction with a representative partner (1-iodo-3-nitrobenzene). Similar results were collected from this simplified procedure (93 to 96% yield).

Toward a more convenient setup, a step further was then taken by developing conditions that would not require low temperatures for the formation of organoboronates. We envisioned that room-temperature metal insertion in the presence of boron alkoxides should lead to the expected intermediate boron species through in situ transmetalation

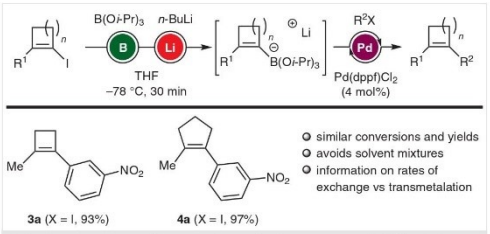


Scheme 4 In situ preparation and further Suzuki cross-coupling of cyclopentenylboronates

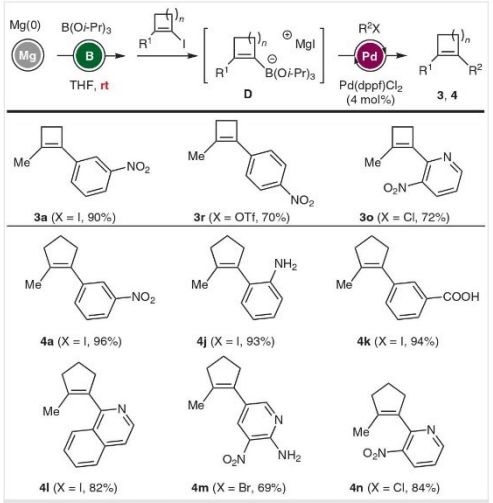
of the transitional cycloalkenylmagnesium species (Scheme 6).

Magnesium powder was then employed, furnishing the intermediary magnesium salt **D**, being an analog of **A** and **B**. Performing the full sequence at room temperature afforded the desired cross-coupling products in excellent yields, comparable to those obtained via the lithium path (up to 96%). The reaction also showed similarly high functional group tolerance, with the ability to introduce unprotected amines (**4j**, **4m**: 69 to 93%) and a carboxylic acid (**4k**, 94%).

In addition, we recently demonstrated the potential of in situ generated azetinylboronates to undergo unprecedented cross-coupling, transposing the methodology to

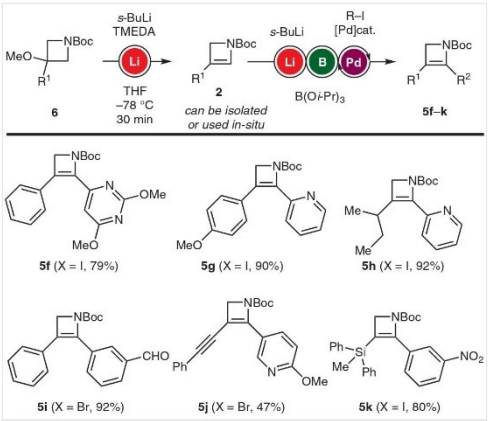


Scheme 5 Iodine–lithium exchange in the presence of $B(Oi\text{-}Pr)_3$ for direct transmetalation



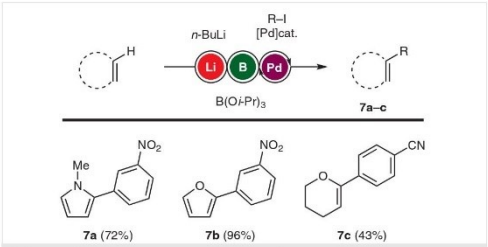
Scheme 6 Formation of organoboronates through magnesium insertion and in situ transmetalation

heterocyclic four-membered structures. A one-pot sequence was designed to access the desired boronates through a double α-lithiation of readily available azetidines **6**, followed by trapping with boron isopropoxide and palladium-catalyzed cross-coupling. Representative examples are given in Scheme 7. Alkyl, aryl, alkynyl and silyl groups were introduced at position 3, and the cross-coupling was performed using a large range of functionalized aromatic halides.[15]



Scheme 7 Single-pot access to 3,4-disubstituted azetines through a lithiation/transmetalation/cross-coupling sequence

Furthermore, we showed the applicability of this strategy to pyrroles, furans and hydropyrans to open the scope to a larger array of heterocyclic scaffolds. A simple metalation with *n*-BuLi was performed to access the initial organometallic derivatives, before transmetalation with B(O*i*-Pr)$_3$. Heteroaromatic starting materials furnished the desired cross-coupled compounds **7a**[16] and **7b** in good yields (up to 96%). However, employing hydrofuran resulted in only 43% of the substituted styrene derivative **7c** (Scheme 8).



Scheme 8 Extension to other heterocycles

In conclusion, we have assembled a new efficient one-pot sequence for the synthesis of cyclobutenes, cyclopentenes and azetines by using in situ prepared boron alkoxides possessing a remarkable functional group tolerance. Diverse conditions were successfully developed relying either on halogen/metal exchanges or on an advantageous room temperature insertion/transmetalation procedure. Through the intermediate formation of stable organoboronate building blocks, we have unlocked a wide library of unexplored strained architectures, opening modern organic chemistry to new classes of modules for further applications.

Commercially available starting materials were used without further purification unless otherwise stated. All reactions were carried out under N_2 atmospheres in flame-dried glassware. Syringes, which were used to transfer anhydrous solvents or reagents, were purged with nitrogen prior to use. CH_2Cl_2 was predried over $CaCl_2$ and distilled from CaH_2. THF was refluxed and distilled from sodium benzophenone ketyl under nitrogen. Et_2O was predried over $CaCl_2$ and passed through activated Al_2O_3 (using a solvent purification system SPS-400-2 from Innovative Technologies Inc.). Toluene was predried over $CaCl_2$ and distilled from CaH_2. *n*-BuLi was purchased from Rockwood Lithium GmbH; [*n*-BuLi] = 2.44 M in hexane (titration with isopropanol/1,10-phenanthroline).

Chromatographic purifications were performed using silica gel (SiO_2, 0.040–0.063 mm, 230–400 mesh ASTM) from Merck. The spots were visualized under UV (254 nm) or by staining the TLC plate with $KMnO_4$ solution [K_2CO_3 (10 g), $KMnO_4$ (1.5 g), H_2O (150 mL), NaOH (10% in H_2O, 1.25 mL)] or *p*-anisaldehyde (PAA) solution [concd H_2SO_4 (10 mL), EtOH (200 mL), AcOH (3 mL), *p*-anisaldehyde (4 mL)]. Melting points were determined on a Büchi B-540 apparatus and are uncorrected. Diastereoisomeric ratios were determined by ^{1}H NMR and ^{13}C NMR spectroscopy. ^{1}H and ^{13}C NMR spectra were recorded on VARIAN Mercury 200, BRUKER ARX 300, VARIAN VXR 400 S and BRUKER AMX 600 instruments. Chemical shifts are reported as δ values in ppm relative to the residual solvent peak (^{1}H NMR) or the solvent peak (^{13}C NMR) in deuterated chloroform ($CDCl_3$: δ 7.26 for ^{1}H NMR and δ 77.16 for ^{13}C NMR). Abbreviations for multiplicities are as follows: s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), m (multiplet) and br (broad). Reaction endpoints were determined by GC monitoring. Gas chromatography was performed with an Agilent Technologies 7890 instrument, using a column of type HP 5 (Agilent 5% phenylmethylpolysiloxane; length: 15 m; diameter: 0.25 mm; film thickness: 0.25 µm) or Hewlett-Packard 6890 or 5890 series II instruments, using a column of type HP 5 (Hewlett-Packard, 5% phenylmethylpolysiloxane; length: 15 m; diameter: 0.25 mm; film thickness: 0.25 µm). High-resolution mass spectra (HRMS) and low-resolution mass spectra (LRMS) were recorded on Finnigan MAT 95Q, Finnigan MAT 90 or JEOL JMS-700 instruments. Single crystals (for X-ray analysis) were grown in small quench vials with a volume of 5.0 mL from slow evaporation of dichloromethane/hexanes mixtures at room temperature. Suitable single crystals were then introduced into perfluorinated oil and mounted on top of a thin glass wire. Data collection was performed at 100 K with a Bruker D8 Venture TXS equipped with a Spellman generator (50 kV, 40 mA) and a Kappa CCD detector operating with Mo-Kα radiation (l = 0.71071 Å).

General Procedure A

To a solution of cycloalkenyl iodide (1.00 equiv) in Et_2O (0.5 M) was slowly added a solution of *n*-BuLi (2.44 M in hexane, 1.10 equiv) at –78 °C. After stirring for 30 min at the aforementioned temperature, $B(Oi\text{-}Pr)_3$ (1.15 equiv) and THF (total concn 0.25 M) were added and the resulting mixture stirred for an additional 1 h at room temperature. $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (4 mol%), the cross-coupling partner (aromatic or vinylic iodide, bromide, tosylate or chloride) (0.90 equiv) and an aqueous solution of NaOH (1.5 equiv 1.00 M) were subsequently added and the reaction mixture was stirred overnight. The crude material was extracted with Et_2O (3 × 20 mL), washed with a saturated aqueous solution of sodium chloride (20 mL), dried over magnesium sulfate, filtered, concentrated and purified via flash column chromatography.

General Procedure B

Magnesium powder (1.30 equiv) and LiCl (1.10 equiv) were placed in a reaction tube and flame-dried in vacuo three times. After cooling to ambient temperature, enough THF was added to cover the solids. The magnesium was activated by addition of a few drops of dibromoethane and heating. After cooling back to ambient temperature, $B(Oi\text{-}Pr)_3$ (1.00 equiv) was added. The cycloalkenyl iodide was added dropwise as a solution in THF (1.00 equiv, 0.5 M) and the resulting solution stirred for 2 h, after which a grey suspension had formed, which was divided into equimolar portions in new reaction tubes. To the portions were then added $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (4 mol%), the cross-coupling partner (aromatic iodide, bromide, tosylate or chloride) (0.80 equiv) and an aqueous solution of NaOH (1.5 equiv 1.00 M). The reaction mixture was stirred overnight and then extracted with Et_2O (3 × 20 mL), washed with a saturated aqueous solution of sodium chloride (20 mL), dried over magnesium sulfate, filtered, concentrated and purified via flash column chromatography.

1-Iodo-2-methylcyclopent-1-ene (1b)

Commercially available 5-iodopent-1-yne (1.93 g, 10 mmol, 1.0 equiv) was dissolved in dry pentane (30 mL) in a Schlenk tube and cooled to –78 °C. *n*-BuLi (2.39 M, 10 mmol, 1.0 equiv) was then added dropwise and the reaction mixture was stirred for 30 min before being warmed to –50 °C for 5 min. The mixture was then cooled back to –78 °C and dimethylaluminum chloride (1 M in CH_2Cl_2, 10 mmol, 1.0 equiv) was added dropwise and the resulting mixture stirred for a further 30 min. The mixture was then allowed to reach room temperature. In another Schlenk flask, zirconocene dichloride (2.93 g, 10 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (25 mL) and trimethylaluminum (2 M, 20 mmol, 2.0 equiv) was added at room temperature and the mixture stirred for 1 h. The first Schlenk flask was then cooled back to –78 °C before dropwise addition of the solution from the second Schlenk flask. The combined reaction mixture was allowed to reach room temperature and stirred for 1 h. The solvent was then removed in vacuo and a red solid remained, which was dissolved in THF (50 mL). After 30 min, complete conversion into the cyclized pentene was confirmed by GC–MS. The reaction mixture was cooled to –78 °C and iodine (5.58 g, 22 mmol, 2.2 equiv) was added portionwise. The mixture was allowed to reach room temperature and then poured into ice-cold HCl (2 M, 200 mL). The layers were separated and the aqueous layer was extracted with hexane (2 × 100 mL). The combined organics were washed with a saturated sodium thiosulfate solution. The organics were dried over $MgSO_4$, filtered and the solvent evaporated at 20 °C (60 mbar) due to the volatility of the desired product. Column chromatography (hexane) yielded the desired product as a colorless oil, which was stored at –20 °C to avoid decomposition.

Yield: 1.48 g, 7.09 mmol (71%); R_f = 0.79 (hexane; UV, $KMnO_4$, PAA).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.74–2.54 (m, 2 H), 2.31 (t, *J* = 8.5 Hz, 2 H), 2.04–1.82 (m, 2 H), 1.80–1.72 (m, 3 H).

Spectroscopic data are in agreement with the previously reported characterization.[15]

1-(2-Methylcyclobut-1-en-1-yl)-3-nitrobenzene (3a)

Using 1-iodo-2-methylcyclobut-1-ene and 1-iodo-3-nitrobenzene according to general procedure A provided **3a** as a yellow solid.

Yield: 49 mg, 0.26 mmol (96%); R_f = 0.32 (hexane/EtOAc, 98:2; UV, $KMnO_4$, PAA).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09 (t, *J* = 2.0 Hz, 1 H), 8.01 (ddd, *J* = 8.1, 2.4, 1.0 Hz, 1 H), 7.60 (dt, *J* = 7.7, 1.4 Hz, 1 H), 7.47 (t, *J* = 7.9 Hz, 1 H), 2.70–2.63 (m, 2 H), 2.52–2.42 (m, 2 H), 2.08–1.99 (m, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 148.6, 143.0, 137.7, 135.7, 131.2, 129.3, 121.0, 120.0, 30.2, 26.3, 16.5.

MS (EI): *m*/*z* (%) = 189 (11) $[M]^+$, 172 (43), 141 (67), 128 (100), 115 (58).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{11}H_{11}NO_2$: 189.0790; found: 189.0783.

Compound **3a** was also synthesized according to general procedure B.

Yield: 41 mg, 0.22 mmol (90%); mp 115–117 °C.

1-[4-(2-Methylcyclobut-1-en-1-yl)phenyl]ethan-1-one (3b)

Using 1-iodo-2-methylcyclobut-1-ene and 1-(4-iodophenyl)ethan-1-one according to general procedure A provided **3b** as a colorless oil.

Yield: 30 mg, 0.16 mmol (81%); R_f = 0.5 (hexane/EtOAc, 95:5; UV, $KMnO_4$, PAA).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.91 (d, *J* = 8.4 Hz, 2 H), 7.37 (d, *J* = 8.4 Hz, 2 H), 2.66–2.63 (m, 2 H), 2.58 (s, 3 H), 2.49–2.44 (m, 2 H), 2.05–2.02 (m, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 197.7, 143.4, 140.7, 137.1, 134.9, 128.7, 125.4, 30.3, 26.7, 26.2, 16.7.

MS (EI): *m*/*z* (%) = 186 $[M]^+$ (30), 171 (20), 143 (80), 128 (100), 115 (40).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{13}H_{14}O$: 186.1045; found: 186.1037.

1-[4-(2-Methylcyclobut-1-en-1-yl)phenyl]-3-morpholino-5,6-dihydropyridin-2(1*H*)-one (3c)

Using 1-iodo-2-methylcyclobut-1-ene and 1-(4-iodophenyl)-3-morpholino-5,6-dihydropyridin-2(1*H*)-one according to general procedure A provided **3c** as a colorless oil.

Yield: 40 mg, 0.12 mmol (62%); R_f = 0.2 (hexane/EtOAc, 6:4; UV, $KMnO_4$, PAA).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.27 (m, 4 H), 5.63 (t, *J* = 4.7 Hz, 1 H), 3.84–3.80 (m, 4 H), 3.78 (t, *J* = 6.7 Hz, 2 H), 2.93–2.86 (m, 4 H), 2.64–2.55 (m, 2 H), 2.48 (td, *J* = 6.7, 4.6 Hz, 2 H), 2.44–2.39 (m, 2 H), 2.00–1.94 (m, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 161.3, 143.8, 140.8, 139.0, 137.0, 134.1, 125.6, 124.7, 114.2, 66.7, 50.5, 48.6, 29.8, 26.1, 23.4, 16.2.

1-(2-Methylcyclobut-1-en-1-yl)isoquinoline (3d)

Using 1-iodo-2-methylcyclobut-1-ene and 1-iodoisoquinoline according to general procedure A provided **3d** as a colorless oil.

Yield: 25 mg, 0.13 mmol (64%); R_f = 0.3 (hexane/EtOAc, 9:1; UV, $KMnO_4$, PAA).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.52 (d, *J* = 5.6 Hz, 1 H), 8.30 (d, *J* = 8.5 Hz, 1 H), 7.80 (d, *J* = 7.0 Hz, 1 H), 7.67–7.63 (m, 1 H), 7.56 (ddd, *J* = 8.2, 6.8, 1.3 Hz, 1 H), 7.50 (d, *J* = 5.6 Hz, 1 H), 3.11–3.06 (m, 2 H), 2.63–2.57 (m, 2 H), 2.02 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 155.3, 147.5, 142.5, 137.8, 136.8, 129.9, 127.1, 126.9, 126.7, 126.6, 119.2, 31.1, 29.9, 17.2.

MS (EI): *m*/*z* (%) = 194 [M – H]$^+$ (100), 180 (100), 167 (30), 154 (20).

HRMS (EI): *m*/*z* [M – H]$^+$ calcd for $C_{14}H_{12}N$: 194.0970; found: 194.0962.

2-(2-Methylcyclobut-1-en-1-yl)-5-nitropyridine (3e)

Using 1-iodo-2-methylcyclobut-1-ene and 2-iodo-5-nitropyridine according to general procedure A provided **3e** as a yellow oil.

Yield: 27 mg, 0.14 mmol (72%); R_f = 0.5 (hexane/EtOAc, 9:1; UV, $KMnO_4$, PAA).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.37 (d, *J* = 2.6 Hz, 1 H), 8.39 (dd, *J* = 8.7, 2.7 Hz, 1 H), 7.26 (d, *J* = 8.7 Hz, 1 H), 2.81–2.70 (m, 2 H), 2.59–2.49 (m, 2 H), 2.21 (t, *J* = 1.9 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.2, 153.3, 145.5, 141.5, 136.8, 131.4, 119.6, 31.1, 26.1, 17.2.

MS (EI): *m*/*z* (%) = 190 [M]$^+$ (40), 175 (100), 143 (60), 129 (70).

HRMS (EI): *m*/*z* [M – H]$^+$ calcd for $C_{10}H_9N_2O_2$: 189.0664; found: 189.0656.

3-Fluoro-6-methoxy-4-(2-methylcyclobut-1-en-1-yl)quinoline (3f)

Using 1-iodo-2-methylcyclobut-1-ene and 3-fluoro-4-iodo-6-methoxyquinoline according to general procedure A provided **3f** as a colorless oil.

Yield: 25 mg, 0.10 mmol (51%); R_f = 0.3 (hexane/EtOAc, 9:1; UV, $KMnO_4$, PAA).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.60 (d, *J* = 1.7 Hz, 1 H), 7.97 (d, *J* = 9.1 Hz, 1 H), 7.30 (dd, *J* = 9.1, 2.8 Hz, 1 H), 7.26 (d, *J* = 4.1 Hz, 1 H), 3.92 (s, 3 H), 2.98–2.89 (m, 2 H), 2.72–2.58 (m, 2 H), 1.84 (d, *J* = 1.3 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 158.6, 154.0 (d, *J* = 254.5 Hz), 148.4, 141.8 (d, *J* = 2.3 Hz), 138.6 (d, *J* = 29.3 Hz), 131.4, 130.2, 128.3 (d, *J* = 3.4 Hz), 124.8 (d, *J* = 12.7 Hz), 120.8 (d, *J* = 2.7 Hz), 103.9 (d, *J* = 5.4 Hz), 55.6, 32.0, 30.5 (d, *J* = 2.8 Hz), 17.4 (d, *J* = 2.1 Hz).

MS (EI): *m*/*z* (%) = 243 [M]$^+$ (90), 228 (70), 212 (100), 200 (30).

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{15}H_{14}FNO$: 243.1059; found: 243.1053.

Ethyl 2-[2-(2-Methylallyl)cyclobut-1-en-1-yl]benzoate (3g)

Using 1-iodo-2-(2-methylallyl)cyclobut-1-ene and ethyl 2-iodobenzoate according to general procedure A provided **3g** as a yellowish oil.

Yield: 42 mg, 0.16 mmol (82%*), *with minor impurities due to the starting material (aryl-I); R_f = 0.6 (hexane/EtOAc, 9:1; UV, $KMnO_4$, PAA).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67 (d, *J* = 7.6 Hz, 1 H), 7.39 (t, *J* = 8.1 Hz, 1 H), 7.31–7.19 (m, 2 H), 4.74 (d, *J* = 6.8 Hz, 2 H), 4.31 (q, *J* = 7.1 Hz, 2 H), 2.85 (s, 2 H), 2.68–2.61 (m, 2 H), 2.46–2.36 (m, 2 H), 1.68 (s, 3 H), 1.34 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 168.6, 142.9, 141.9, 140.2, 136.1, 131.1, 130.3, 129.6, 129.4, 126.7, 111.6, 61.3, 38.2, 29.2, 28.7, 23.0, 14.4.

MS (EI): *m*/*z* (%) = 256 [M]$^+$ (10), 241 (5), 227 (5), 209 (30), 195 (100), 181 (20).

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{17}H_{20}O_2$: 256.1463; found: 256.1458.

4-[2-(2-Methylallyl)cyclobut-1-en-1-yl]phenol (3h)

Using 1-iodo-2-(2-methylallyl)cyclobut-1-ene and 4-iodophenol according to general procedure A provided **3h** as a colorless oil.

Yield: 32 mg, 0.16 mmol (80%); R_f = 0.3 (hexane/EtOAc, 8:2; UV, $KMnO_4$, PAA).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25–7.21 (m, 2 H), 6.83–6.76 (m, 2 H), 4.81 (d, *J* = 5.6 Hz, 3 H), 3.04 (s, 2 H), 2.64–2.59 (m, 2 H), 2.47–2.40 (m, 2 H), 1.78 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 154.4, 142.9, 138.6, 137.7, 129.4, 127.2, 115.3, 111.5, 39.0, 28.3, 26.2, 23.1.

MS (EI): *m*/*z* (%) = 200 [M]$^+$ (30), 185 (80), 171 (20), 158 (100), 144 (30).

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{14}H_{16}O$: 200.1201; found: 200.1195.

3-[2-(2-Methylallyl)cyclobut-1-en-1-yl]benzoic Acid (3i)

Using 1-iodo-2-(2-methylallyl)cyclobut-1-ene and 3-iodobenzoic acid according to general procedure A provided **3i** as a colorless oil.

Yield: 44 mg, 0.19 mmol (96%); R_f = 0.3 (hexane/EtOAc, 95:5; UV, $KMnO_4$, PAA).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07 (s, 1 H), 7.95 (d, *J* = 7.7 Hz, 1 H), 7.57 (d, *J* = 7.7 Hz, 1 H), 7.43 (t, *J* = 7.7 Hz, 1 H), 4.84 (s, 2 H), 3.13 (s, 2 H), 2.73–2.67 (m, 2 H), 2.53–2.46 (m, 2 H), 1.80 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.3, 142.4, 142.2, 138.2, 136.4, 129.5, 128.7, 128.3, 127.4, 111.9, 39.1, 28.6, 26.2, 23.1.

MS (EI): *m*/*z* (%) = 228 [M]$^+$ (5), 212 (10), 183 (100), 167 (20), 155 (50).

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{15}H_{16}O_2$: 228.1150; found: 228.1143.

6-(2-Methylcyclobut-1-en-1-yl)picolinonitrile (3j)

Using 1-iodo-2-methylcyclobut-1-ene and 6-bromopicolinonitrile according to general procedure A provided **3j** as a colorless oil.

Yield: 25 mg, 0.15 mmol (74%); R_f = 0.5 (hexane/EtOAc, 8:2; UV, $KMnO_4$, PAA).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72 (t, *J* = 7.8 Hz, 1 H), 7.44 (d, *J* = 7.6 Hz, 1 H), 7.31 (d, *J* = 8.1 Hz, 1 H), 2.73–2.63 (m, 2 H), 2.53–2.44 (m, 2 H), 2.16 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 155.9, 149.6, 137.0, 136.2, 133.6, 125.4, 123.0, 117.8, 30.6, 26.0, 16.8.

MS (EI): *m*/*z* (%) = 170 [M]$^+$ (20), 155 (100), 142 (10), 129 (10), 115 (10).

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{11}H_{10}N_2$: 170.0844; found: 170.0843.

6-(2-Methylcyclobut-1-en-1-yl)imidazo[1,2-*a*]pyrazine (3k)

Using 1-iodo-2-methylcyclobut-1-ene and 6-bromoimidazo[1,2-*a*]pyrazine according to general procedure A provided **3k** as a yellowish oil.

Yield: 35 mg, 0.19 mmol (94%); R_f = 0.1 (hexane/EtOAc, 5:5; UV, $KMnO_4$, PAA).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.06 (s, 1 H), 7.85 (s, 1 H), 7.75 (s, 1 H), 7.63 (s, 1 H), 2.72–2.61 (m, 2 H), 2.55–2.43 (m, 2 H), 2.15 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 144.5, 143.3, 139.8, 137.5, 135.7, 133.7, 114.1, 113.7, 30.5, 25.7, 16.5.

MS (EI): *m*/*z* (%) = 185 [M]$^+$ (70), 184 (100), 170 (100), 157 (5), 144 (5).

HRMS (EI): *m/z* [M – H]$^+$ calcd for $C_{11}H_{10}N_3$: 184.0875; found: 184.0869.

5-(2-Methylcyclobut-1-en-1-yl)-3-nitropyridin-2-amine (3l)

Using 1-iodo-2-methylcyclobut-1-ene and 5-bromo-3-nitropyridin-2-amine according to general procedure A provided **3l** as a yellow oil.

Yield: 37 mg, 0.18 mmol (91%); R_f = 0.1 (hexane/EtOAc, 8:2; UV, $KMnO_4$, PAA).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.40 (d, *J* = 2.2 Hz, 1 H), 8.25 (d, *J* = 2.1 Hz, 1 H), 6.69 (s, 2 H), 2.66–2.56 (m, 2 H), 2.50–2.40 (m, 2 H), 1.99 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 153.3, 151.7, 140.2, 132.8, 130.5, 128.0, 123.7, 30.4, 26.1, 16.5.

MS (EI): *m/z* (%) = 205 [M]$^+$ (100), 190 (90), 176 (40), 157 (60), 144 (60).

HRMS (EI): *m/z* [M]$^+$ calcd for $C_{10}H_{11}N_3O_2$: 205.0851; found: 205.0840.

Pentafluoro{3-[2-(2-methylallyl)cyclobut-1-en-1-yl]phenyl}-λ^6-sulfane (3m)

Using 1-iodo-2-(2-methylallyl)cyclobut-1-ene and (3-bromophenyl)pentafluoro-λ^6-sulfane according to general procedure A provided **3m** as a colorless oil.

Yield: 59 mg, 0.19 mmol (95%); R_f = 0.6 (hexane; UV, $KMnO_4$, PAA).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.68 (s, 1 H), 7.59–7.53 (m, 1 H), 7.45–7.36 (m, 2 H), 4.83 (d, *J* = 9.7 Hz, 2 H), 3.08 (s, 2 H), 2.73–2.63 (m, 2 H), 2.52–2.44 (m, 2 H), 1.78 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 154.3, 143.4, 142.0, 137.7, 136.8, 128.8, 128.5, 123.9, 123.3, 112.1, 39.1, 28.9, 26.2, 23.0.

MS (EI): *m/z* (%) = 310 [M]$^+$ (60), 295 (60), 282 (10), 269 (5), 253 (5).

HRMS (EI): *m/z* [M]$^+$ calcd for $C_{14}H_{15}F_5S$: 310.0815; found: 310.0807.

3-[2-(2-Methylallyl)cyclobut-1-en-1-yl]pyridin-2-ol (3n)

Using 1-iodo-2-(2-methylallyl)cyclobut-1-ene and 3-bromopyridin-2-ol according to general procedure A provided **3n** as a colorless oil.

Yield: 30 mg, 0.15 mmol (74%); R_f = 0.1 (hexane/EtOAc, 7:3; UV, $KMnO_4$, PAA).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31 (dd, *J* = 7.0, 2.0 Hz, 1 H), 7.21 (dd, *J* = 6.5, 2.0 Hz, 1 H), 6.25 (t, *J* = 6.7 Hz, 1 H), 4.79–4.74 (m, 2 H), 3.29 (s, 2 H), 2.68–2.63 (m, 2 H), 2.45–2.39 (m, 2 H), 1.75 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 162.8, 144.5, 143.9, 137.0, 135.0, 132.4, 127.7, 111.2, 106.8, 40.3, 28.5, 26.9, 23.1.

MS (EI): *m/z* (%) = 201 [M]$^+$ (100), 186 (50), 167 (30), 134 (30).

HRMS (EI): *m/z* [M]$^+$ calcd for $C_{13}H_{15}NO$: 201.1154; found: 201.1149.

2-(2-Methylcyclobut-1-en-1-yl)-3-nitropyridine (3o)

Using 1-iodo-2-methylcyclobut-1-ene and 2-chloro-3-nitropyridine according to general procedure A provided **3o** as a yellowish oil.

Yield: 25 mg, 0.13 mmol (66%).

Compound **3o** was also synthesized according to general procedure B.

Yield: 32 mg, 0.17 mmol (72%); R_f = 0.6 (hexane/EtOAc, 8:2; UV, $KMnO_4$, PAA).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.72 (dd, *J* = 4.7, 1.6 Hz, 1 H), 7.92 (dd, *J* = 8.1, 1.6 Hz, 1 H), 7.21 (dd, *J* = 8.2, 4.7 Hz, 1 H), 2.72–2.61 (m, 2 H), 2.55–2.46 (m, 2 H), 2.10 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 153.6, 151.9, 147.2, 144.4, 133.6, 131.4, 120.8, 31.6, 27.5, 17.2.

MS (EI): *m/z* (%) = 172 (5), 160 (950), 145 (30), 130 (90), 117 (100).

HRMS (EI): *m/z* [M – H]$^+$ calcd for $C_{10}H_9N_2O_2$: 189.0664; found: 189.0657.

Ethyl 2-(2-Methylcyclobut-1-en-1-yl)nicotinate (3p)

Using 1-iodo-2-methylcyclobut-1-ene and ethyl 2-chloronicotinate according to general procedure A provided **3p** as a yellowish oil.

Yield: 10 mg, 0.05 mmol (23%); R_f = 0.6 (hexane/EtOAc, 8:2; UV, $KMnO_4$, PAA).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.65 (dd, *J* = 4.8, 1.8 Hz, 1 H), 7.87 (dd, *J* = 7.8, 1.8 Hz, 1 H), 7.13 (dd, *J* = 7.8, 4.8 Hz, 1 H), 4.36 (q, *J* = 7.2 Hz, 2 H), 2.76–2.71 (m, 2 H), 2.48–2.42 (m, 2 H), 2.01 (s, 3 H), 1.38 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 168.0, 152.9, 151.1, 148.6, 137.0, 136.9, 126.0, 120.4, 61.8, 30.8, 28.3, 16.7, 14.4.

MS (EI): *m/z* (%) = 217 [M]$^+$ (10), 187 (100), 174 (15).

HRMS (EI): *m/z* [M]$^+$ calcd for $C_{13}H_{15}NO_2$: 217.1103; found: 217.1099.

1-[2-(2-Methylallyl)cyclobut-1-en-1-yl]-4-nitrobenzene (3q)

Using 1-iodo-2-(2-methylallyl)cyclobut-1-ene and 4-nitrophenyl trifluoromethanesulfonate according to general procedure A provided **3q** as a colorless oil.

Yield: 44 mg, 0.19 mmol (96%); R_f = 0.7 (hexane/EtOAc, 9:1; UV, $KMnO_4$, PAA).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.17 (d, *J* = 8.8 Hz, 2 H), 7.42 (d, *J* = 8.8 Hz, 2 H), 4.83 (d, *J* = 16.7 Hz, 2 H), 3.12 (s, 2 H), 2.84–2.61 (m, 2 H), 2.58–2.41 (m, 2 H), 1.79 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 146.9, 146.0, 141.9, 141.6, 137.8, 126.1, 124.0, 112.2, 39.3, 29.1, 26.1, 23.1.

MS (EI): *m/z* (%) = 229 [M]$^+$ (2), 212 (90), 182 (100), 168 (50), 153 (50).

HRMS (EI): *m/z* [M]$^+$ calcd for $C_{14}H_{15}NO_2$: 229.1103; found: 229.1102.

1-(2-Methylcyclobut-1-en-1-yl)-4-nitrobenzene (3r)

Using 1-iodo-2-methylcyclobut-1-ene and 4-nitrophenyl trifluoromethanesulfonate according to general procedure B provided **3r** as a yellow oil.

Yield: 32 mg, 0.17 mmol (70%); R_f = 0.29 (hexane/EtOAc, 98:2; UV, $KMnO_4$, PAA).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.19–8.09 (m, 2 H), 7.46–7.28 (m, 2 H), 2.76–2.57 (m, 2 H), 2.57–2.40 (m, 2 H), 2.15–1.96 (m, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 145.9, 145.8, 142.3, 136.3, 125.7, 124.0, 30.6, 26.2, 16.7.

MS (EI): *m/z* (%) = 189 [M]$^+$ (23), 172 (34), 143 (63), 128 (100), 115 (50), 102 (14).

HRMS (EI): *m/z* [M]$^+$ calcd for $C_{11}H_{11}NO_2$: 189.0790; found: 189.0783.

1-(2-Methylcyclopent-1-en-1-yl)-3-nitrobenzene (4a)

Using 1-iodo-2-methylcyclopent-1-ene and 1-iodo-3-nitrobenzene according to general procedure A provided **4a** as a light-yellow oil.

Yield: 39 mg, 0.19 mmol (96%); R_f = 0.2 (hexane/EtOAc, 99:1; UV, $KMnO_4$, PAA).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.13 (t, *J* = 1.9 Hz, 1 H), 8.04 (dd, *J* = 9.1, 2.1 Hz, 1 H), 7.59 (d, *J* = 7.8 Hz, 1 H), 7.48 (t, *J* = 7.9 Hz, 1 H), 2.80–2.72 (m, 2 H), 2.54 (t, *J* = 7.9 Hz, 2 H), 1.94 (quin, *J* = 7.5 Hz, 2 H), 1.88 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 148.3, 140.5, 138.7, 133.7, 132.4, 129.0, 122.4, 120.9, 40.4, 37.2, 21.9, 15.6.

MS (EI): *m*/*z* (%) = 203 [M]$^+$ (80), 188 (100), 156 (20), 141 (78), 128 (58), 115 (81).

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{12}H_{13}NO_2$: 203.0946; found: 203.0939.

Compound **4a** was also synthesized according to general procedure B.

Yield: 39 mg, 0.19 mmol (96%).

1-Methyl-4-(2-methylcyclopent-1-en-1-yl)benzene (4b)

Using 1-iodo-2-methylcyclopent-1-ene and 1-iodo-4-methylbenzene according to general procedure A provided **4b** as a colorless oil.

Yield: 24 mg, 0.14 mmol (70%); R_f = 0.7 (hexane; UV, $KMnO_4$, PAA).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44–7.29 (m, 4 H), 2.95–2.86 (m, 2 H), 2.73–2.60 (m, 2 H), 2.52 (s, 3 H), 2.07 (t, *J* = 7.5 Hz, 2 H), 2.05–1.99 (m, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 135.9, 135.7, 134.7, 134.6, 128.8, 127.6, 40.2, 37.4, 22.0, 21.3, 15.6.

MS (EI): *m*/*z* (%) = 172 [M]$^+$ (70), 157 (100), 142 (40), 129 (40), 115 (30).

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{13}H_{16}$: 172.1252; found: 172.1245.

1-[4-(2-Methylcyclopent-1-en-1-yl)phenyl]ethan-1-one (4c)

Using 1-iodo-2-methylcyclopent-1-ene and 1-(4-iodophenyl)ethan-1-one according to general procedure A provided **4c** as a colorless oil.

Yield: 35 mg, 0.18 mmol (88%); R_f = 0.3 (hexane/EtOAc, 95:5; UV, $KMnO_4$, PAA).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93 (d, *J* = 8.4 Hz, 2 H), 7.37 (d, *J* = 8.4 Hz, 2 H), 2.80–2.71 (m, 2 H), 2.60 (s, 3 H), 2.53 (t, *J* = 7.1 Hz, 2 H), 1.97–1.90 (m, 2 H), 1.88 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 197.9, 143.9, 138.5, 134.8, 134.2, 128.3, 127.7, 40.5, 37.1, 26.7, 22.0, 15.9.

MS (EI): *m*/*z* (%) = 200 [M]$^+$ (57), 185 (100), 157 (22), 142 (25), 128 (32).

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{14}H_{16}O$: 200.1201; found: 200.1195.

1-[4-(2-Methylcyclopent-1-en-1-yl)phenyl]-3-morpholino-5,6-dihydropyridin-2(1*H*)-one (4d)

Using 1-iodo-2-methylcyclopent-1-ene and 1-(4-iodophenyl)-3-morpholino-5,6-dihydropyridin-2-(1*H*)-one according to general procedure A provided **4d** as a light yellow sticky oil.

Yield: 35 mg, 0.10 mmol (52%); R_f = 0.3 (hexane/EtOAc, 1:1; UV, $KMnO_4$, PAA).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.25 (m, 4 H), 5.63 (t, *J* = 4.7 Hz, 1 H), 3.84–3.76 (m, 6 H), 2.91 (t, *J* = 4.4 Hz, 4 H), 2.75–2.66 (m, 2 H), 2.53–2.43 (m, 4 H), 1.95–1.84 (m, 2 H), 1.84 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 161.5, 143.9, 140.6, 136.6, 135.6, 134.3, 128.0, 124.5, 114.2, 66.9, 50.6, 48.7, 40.2, 37.3, 23.5, 21.9, 15.6.

MS (EI): *m*/*z* (%) = 338 [M]$^+$ (14), 320 (100), 307 (20), 281 (35), 253 (34), 239 (31), 207 (55).

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{21}H_{26}N_2O_2$: 338.1994; found: 338.1988.

3,4-Dimethoxy-5-(2-methylcyclopent-1-en-1-yl)benzaldehyde (4e)

Using 1-iodo-2-methylcyclopent-1-ene and 3-iodo-4,5-dimethoxybenzaldehyde according to general procedure A provided **4e** as a colorless oil.

Yield: 34 mg, 0.14 mmol (69%); R_f = 0.35 (hexane/EtOAc, 9:1; UV, $KMnO_4$, PAA).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.87 (s, 1 H), 7.34 (d, *J* = 1.9 Hz, 1 H), 7.24 (d, *J* = 1.9 Hz, 1 H), 3.92 (s, 3 H), 3.79 (s, 3 H), 2.76–2.61 (m, 2 H), 2.47 (t, *J* = 7.0 Hz, 2 H), 1.95 (quin, *J* = 7.5 Hz, 2 H), 1.65 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 191.6, 153.6, 152.7, 138.0, 133.6, 132.10, 132.08, 127.6, 108.7, 60.8, 56.1, 38.9, 37.8, 22.7, 15.4.

MS (EI): *m*/*z* (%) = 246 [M]$^+$ (100), 231 (27), 217 (18), 203 (18), 189 (24), 161 (26), 115 (35).

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{15}H_{18}O_3$: 246.1256; found: 246.1250.

3-Fluoro-6-methoxy-4-(2-methylcyclopent-1-en-1-yl)quinoline (4f)

Using 1-iodo-2-methylcyclopent-1-ene and 3-fluoro-4-iodo-6-methoxyquinoline according to general procedure A provided **4f** as colorless oil.

Yield: 38 mg, 0.15 mmol (74%); R_f = 0.3 (hexane/EtOAc, 9:1; UV, $KMnO_4$, PAA).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.62 (d, *J* = 9.2 Hz, 1 H), 8.00 (d, *J* = 9.2 Hz, 1 H), 7.31 (dd, *J* = 9.2, 2.8 Hz, 1 H), 6.99 (d, *J* = 2.8 Hz, 1 H), 3.89 (s, 3 H), 2.86–2.74 (m, 1 H), 2.71–2.66 (m, 1 H), 2.62 (t, *J* = 7.3 Hz, 2 H), 2.20–1.99 (m, 2 H), 1.56 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 158.9, 154.3 (d, *J* = 252.4 Hz), 142.0, 141.9, 138.9 (d, *J* = 29.3 Hz), 131.7, 129.4 (d, *J* = 3.6 Hz), 128.8 (d, *J* = 14.4 Hz), 126.7, 120.8 (d, *J* = 3.2 Hz), 104.1 (d, *J* = 5.9 Hz), 55.9, 39.2, 37.8 (d, *J* = 2.1 Hz), 23.5, 15.9.

MS (EI): *m*/*z* (%) = 257 [M]$^+$ (100), 242 (25), 226 (20), 214 (40), 198 (22), 184 (36), 172 (20).

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{16}H_{16}FNO$: 257.1216; found: 257.1210.

5-(2-Methylcyclopent-1-en-1-yl)furan-2-carbaldehyde (4g)

Using 1-iodo-2-methylcyclopent-1-ene and 5-iodofuran-2-carbaldehyde according to general procedure A provided **4g** as a crystalline solid.

Yield: 31 mg, 0.18 mmol (88%); mp 93–97 °C; R_f = 0.2 (hexane/EtOAc, 98:2; UV, $KMnO_4$, PAA).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.56 (s, 1 H), 7.23 (d, *J* = 3.7 Hz, 1 H), 6.34 (d, *J* = 3.7 Hz, 1 H), 2.80–2.65 (m, 2 H), 2.60–2.48 (m, 2 H), 2.12 (quin, *J* = 1.6 Hz, 3 H), 1.93 (quin, *J* = 7.6 Hz, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 177.0, 159.1, 151.2, 144.1, 124.1, 123.4, 109.4, 40.9, 34.4, 22.1, 16.4.

MS (EI): *m*/*z* (%) = 176 [M]$^+$ (100), 161 (50), 147 (78), 129 (21), 119 (46), 105 (22).

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{11}H_{12}O_2$: 176.0837; found: 176.0831.

6-(2-Methylcyclopent-1-en-1-yl)picolinonitrile (4h)

Using 1-iodo-2-methylcyclopent-1-ene and 6-bromopicolinonitrile according to general procedure A provided **4h** as a colorless oil.

Yield: 28 mg, 0.15 mmol (76%); R_f = 0.3 (hexane/EtOAc, 95:5; UV, $KMnO_4$, PAA).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74 = (t, *J* = 7.9 Hz, 1 H), 7.46 (d, *J* = 7.6 Hz, 1 H), 7.41 (d, *J* = 8.1 Hz, 1 H), 2.85–2.76 (m, 2 H), 2.58 (t, *J* = 7.4 Hz, 2 H), 2.10 (s, 3 H), 1.92 (quin, *J* = 7.6 Hz, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 158.8, 145.2, 136.9, 133.1, 132.4, 125.2, 125.1, 117.8, 41.3, 35.8, 21.7, 16.4.

MS (EI): *m*/*z* (%) = 184 $[M]^+$ (70), 169 (100), 155 (46), 142 (36), 129 (13), 118 (12), 103 (17).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{12}H_{12}N_2$: 184.1000; found: 184.0994.

(*E*)-1-[2-(2-Methylcyclopent-1-en-1-yl)vinyl]-4-(trifluoromethyl)benzene (4i)

Using 1-iodo-2-methylcyclopent-1-ene and (*Z*)-1-(2-iodovinyl)-4-(trifluoromethyl)benzene according to general procedure A provided **4i** (*E*/*Z* = 88:12 by crude GC, isolated *E*/*Z* = 56:44) as a colorless oil.

Yield: 48 mg, 0.19 mmol (95%); R_f = 0.56/0,68 (hexane; UV, $KMnO_4$, PAA).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.59–7.46 (m, 3 H), 7.37–7.30 (m, 1 H), 6.46–6.33 (m, 2 H), 2.36–2.28 (m, 2 H), 2.22–2.11 (m, 2 H), 1.75 (quin, *J* = 7.4 Hz, 2 H), 1.67 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 142.6 (d, *J* = 1.6 Hz), 142.3, 133.8, 129.2, 128.7 (d, *J* = 5.0 Hz), 128.0, 125.9, 124.7 (q, *J* = 3.8 Hz), 123.1 (d, *J* = 1.5 Hz), 38.6, 35.8, 22.8, 15.1.

MS (EI): *m*/*z* (%) = 252 $[M]^+$ (91), 237 (100), 209 (75), 183 (53), 159 (35), 141 (34), 115 (22).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{15}H_{15}F_3$: 252.1126; found: 252.1119.

2-(2-Methylcyclopent-1-en-1-yl)aniline (4j)

Using 1-iodo-2-methylcyclopent-1-ene and 2-iodoaniline according to general procedure B provided **4j** as a light yellow oil.

Yield: 32 mg, 0.19 mmol (93%); R_f = 0.2 (hexane/EtOAc, 95:5; UV, $KMnO_4$, PAA).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.07 (td, *J* = 7.8, 1.5 Hz, 1 H), 6.98 (dd, *J* = 7.5, 1.4 Hz, 1 H), 6.79–6.69 (m, 2 H), 3.66 (s, 2 H), 2.68–2.57 (m, 2 H), 2.48 (t, *J* = 7.3 Hz, 2 H), 1.96 (quin, *J* = 7.5 Hz, 2 H), 1.61 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 143.6, 136.9, 133.4, 129.3, 127.7, 124.9, 118.2, 115.2, 38.8, 37.9, 22.6, 15.2.

MS (EI): *m*/*z* (%) = 173 $[M]^+$ (67), 158 (22), 144 (100), 130 (53), 117 (22), 77 (20).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{12}H_{15}N$: 173.1204; found: 173.1198.

3-(2-Methylcyclopent-1-en-1yl)benzoic Acid (4k)

Using 1-iodo-2-methylcyclopent-1-ene and 3-iodobenzoic acid according to general procedure B provided **4k** as a light brown solid.

Yield: 38 mg, 0.19 mmol (94%); mp 116–120 °C; R_f = 0.4 (hexane/1% MeOH; UV, $KMnO_4$, PAA).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.39 (s, 1 H), 8.01 (s, 1 H), 7.91 (d, *J* = 7.6 Hz, 1 H), 7.47 (d, *J* = 7.4 Hz, 1 H), 7.36 (t, *J* = 7.3 Hz, 1 H), 2.72 (s, 2 H), 2.49 (s, 2 H), 1.90 (quin, *J* = 7.2 Hz, 2 H), 1.83 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.8, 139.1, 136.7, 134.1, 132.7, 129.9, 129.4, 128.2, 127.9, 40.3, 37.3, 22.0, 15.6.

MS (EI): *m*/*z* (%) = 202 $[M]^+$ (100), 187 (81), 157 (52), 128 (77), 115 (67), 77 (28).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{13}H_{14}O_2$: 202.0994; found: 202.0989.

1-(2-Methylcyclopent-1-en-1-yl)isoquinoline (4l)

Using 1-iodo-2-methylcyclopent-1-ene and 1-iodoisoquinoline according to general procedure B provided **4l** as a light yellow oil.

Yield: 34 mg, 0.16 mmol (82%); R_f = 0.2 (hexane/EtOAc, 9:1; UV, $KMnO_4$, PAA).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.53 (d, *J* = 5.7 Hz, 1 H), 7.97 (d, *J* = 8.4 Hz, 1 H), 7.82 (d, *J* = 8.2 Hz, 1 H), 7.70–7.62 (m, 1 H), 7.57–7.51 (m, 2 H), 2.97–2.82 (m, 2 H), 2.62 (t, *J* = 7.1 Hz, 2 H), 2.09 (quin, *J* = 7.5 Hz, 2 H), 1.55 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 160.2, 142.5, 139.9, 136.5, 134.5, 130.1, 127.5, 127.1, 127.0, 126.9, 119.3, 39.4, 38.6, 22.9, 15.6.

MS (EI): *m*/*z* (%) = 208 $[M - H]^+$ (100), 191 (11), 180 (40), 167 (15).

HRMS (EI): *m*/*z* $[M - H]^+$ calcd for $C_{15}H_{14}N$: 208.1126; found: 208.1120.

5-(2-Methylcyclopent-1-en-1-yl)-3-nitropyridin-2-amine (4m)

Using 1-iodo-2-methylcyclopent-1-ene and 5-bromo-3-nitropyridin-2-amine according to general procedure B provided **4m** as a yellow solid.

Yield: 30 mg, 0.14 mmol (69%); mp 177–180 °C; R_f = 0.2 (hexane/EtOAc, 9:1; UV, $KMnO_4$, PAA).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.36 (d, *J* = 2.1 Hz, 1 H), 8.31 (d, *J* = 2.0 Hz, 1 H), 6.70 (s, 2 H), 2.76–2.64 (m, 2 H), 2.51 (t, *J* = 7.1 Hz, 2 H), 1.93 (quin, *J* = 7.5 Hz, 2 H), 1.86 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 155.1, 151.7, 137.6, 133.0, 129.7, 127.9, 125.4, 40.2, 36.9, 21.8, 15.7.

MS (EI): *m*/*z* (%) = 219 $[M]^+$ (100), 204 (67), 173 (22), 158 (30).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{11}H_{13}N_3O_2$: 219.1008; found: 219.0992.

2-(2-Methylcyclopent-1-en-1-yl)-3-nitropyridine (4n)

Using 1-iodo-2-methylcyclopent-1-ene and 2-chloro-3-nitropyridine according to general procedure B provided **4n** as a yellow oil.

Yield: 26 mg, 0.17 mmol (84%); R_f = 0.3 (hexane/EtOAc, 8:2; UV, $KMnO_4$, PAA).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.79 (dd, *J* = 4.7, 1.6 Hz, 1 H), 8.15 (dd, *J* = 8.2, 1.6 Hz, 1 H), 7.34 (dd, *J* = 8.2, 4.7 Hz, 1 H), 2.84–2.70 (m, 2 H), 2.50 (t, *J* = 8.0 Hz, 2 H), 2.01 (quin, *J* = 7.5 Hz, 2 H), 1.61 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 152.9, 152.6, 146.5, 142.1, 132.2, 132.0, 121.8, 39.4, 36.7, 22.8, 15.0.

MS (EI): *m*/*z* (%) = 187 (70), 174 (35), 156 (95), 147 (100), 130 (75), 117 (65), 103 (23).

HRMS (EI): *m*/*z* $[M - H]^+$ calcd for $C_{11}H_{11}N_2O_2$: 203.0821; found: 203.0814.

1-Methyl-2-(3-nitrophenyl)-1*H*-pyrrole (7a)

To a solution of 1-methyl-1*H*-pyrrole (90 µL, 1.014 mmol) and TMEDA (200 µL, 1.33 mmol, 1.33 equiv) in Et_2O (2 mL, 0.5 M) was slowly added a solution of *n*-BuLi (410 µL, 2.44 M in hexane, 1.00 equiv) at 0 °C. After stirring for 2 h at ambient temperature, B(O*i*-Pr)$_3$ (230 µL, 1.00 mmol, 1.00 equiv) and THF (2 mL) were added and the resulting mixture stirred for another 1 h at room temperature. Pd(dppf)Cl_2 dichloromethane adduct (16 mg, 4 mol%), 1-iodo-3-nitrobenzene (125 mg, 0.5 mmol, 0.5 equiv) and an aqueous solution of sodium hydroxide (1.5 mL, 1.5 equiv 1.00 M) were subsequently added and the mixture stirred overnight. The mixture was extracted with Et_2O (3 × 20 mL), washed with a saturated aqueous solution of sodium chloride

(20 mL), dried over magnesium sulfate, filtered, concentrated and purified via flash column chromatography. Compound **7a** was obtained as a yellow solid.

Yield: 73 mg, 0.36 mmol (72%); mp 73–75 °C; R_f = 0.09 (hexane/EtOAc, 98:2; UV, $KMnO_4$, PAA).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.27 (t, *J* = 2.0 Hz, 1 H), 8.13 (ddd, *J* = 8.3, 2.3, 1.1 Hz, 1 H), 7.74 (ddd, *J* = 7.7, 1.7, 1.1 Hz, 1 H), 7.57 (t, *J* = 8.0 Hz, 1 H), 6.79 (t, *J* = 2.3 Hz, 1 H), 6.36 (dd, *J* = 3.7, 1.8 Hz, 1 H), 6.24 (dd, *J* = 3.7, 2.7 Hz, 1 H), 3.73 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 148.5, 135.0, 134.1, 132.1, 129.5, 125.4, 122.8, 121.4, 110.4, 108.5, 35.4.

MS (EI): *m*/*z* (%) = 202 $[M]^+$ (100), 156 (45), 141 (11), 128 (35), 115 (25).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{11}H_{10}N_2O_2$: 202.0742; found: 204.0736.

2-(3-Nitrophenyl)furan (7b)

To a solution of furan (75 µL, 1.014 mmol) in Et_2O (2 mL, 0.5 M) was slowly added a solution of *n*-BuLi (410 µL, 2.44 M in hexane, 1.00 equiv) at 0 °C. After stirring for 1 h at ambient temperature, B(O*i*-Pr)$_3$ (230 µL, 1.00 mmol, 1.00 equiv) and THF (2 mL) were added and the resulting mixture stirred for another 1 h at room temperature. Pd(dppf)Cl_2 dichloromethane adduct (16 mg, 4 mol%), 1-iodo-3-nitrobenzene (125 mg, 0.5 mmol, 0.5 equiv) and an aqueous solution of sodium hydroxide (1.5 mL, 1.5 equiv 1.00 M) were subsequently added and the mixture stirred overnight. The mixture was extracted with Et_2O (3 × 20 mL), washed with a saturated aqueous solution of sodium chloride (20 mL), dried over magnesium sulfate, filtered, concentrated and purified via flash column chromatography. Compound **7b** was obtained as a colorless oil.

Yield: 91 mg, 0.48 mmol (96%); R_f = 0.14 (hexane/EtOAc, 98:2; UV, $KMnO_4$, PAA).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.46 (t, *J* = 1.9 Hz, 1 H), 8.06 (dd, *J* = 8.2, 1.7 Hz, 1 H), 7.93 (d, *J* = 7.8 Hz, 1 H), 7.57–7.42 (m, 2 H), 6.79 (d, *J* = 3.5 Hz, 1 H), 6.52 (dd, *J* = 3.4, 1.8 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 151.6, 148.8, 143.4, 132.4, 129.8, 129.3, 121.7, 118.5, 112.2, 107.4.

MS (EI): *m*/*z* (%) = 189 $[M]^+$ (100), 143 (23), 131 (10), 115 (100), 102 (7).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{10}H_7NO_3$: 189.0426; found: 189.0420.

4-(3,4-Dihydro-2*H*-pyran-6-yl)benzonitrile (7c)

To a solution of 3,4-dihydro-2*H*-pyran (90 µL, 1.014 mmol) and TMEDA (50 µL, 0.33 mmol, 0.33 equiv) in Et_2O (2 mL, 0.5 M) was slowly added a solution of *n*-BuLi (550 µL, 2.44 M in hexane, 1.34 equiv) at ambient temperature. After stirring for 30 min, B(O*i*-Pr)$_3$ (230 µL, 1.00 mmol, 1.00 equiv) and THF (2 mL) were added and the resulting mixture stirred for 1 h at room temperature. Pd(dppf)Cl_2 dichloromethane adduct (16 mg, 4 mol%), 4-bromobenzonitrile (91 mg, 0.5 mmol, 0.5 equiv) and an aqueous solution of sodium hydroxide (1.5 mL, 1.5 equiv 1.00 M) were subsequently added and the mixture stirred overnight. The mixture was extracted with Et_2O (3 × 20 mL), washed with a saturated aqueous solution of sodium chloride (20 mL), dried over magnesium sulfate, filtered, concentrated and purified via flash column chromatography. Compound **7c** was obtained as a yellow oil.

Yield: 40 mg, 0.22 mmol (43%); R_f = 0.17 (hexane/EtOAc, 98:2; UV, $KMnO_4$, PAA).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65–7.59 (m, 2 H), 7.59–7.54 (m, 2 H), 5.50 (t, *J* = 4.2 Hz, 1 H), 4.17 (t, *J* = 5.3 Hz, 2 H), 2.24 (td, *J* = 6.4, 4.1 Hz, 2 H), 1.96–1.85 (m, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 150.2, 140.5, 132.0, 124.7, 119.2, 110.9, 101.0, 66.7, 22.2, 21.0.

MS (EI): *m*/*z* (%) = 185 $[M]^+$ (56), 170 (9), 156 (6), 140 (7), 130 (100), 116 (5), 102 (44).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{12}H_{11}NO$: 185.0841; found: 185.0834.

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Supporting Information

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5.3 Regiodivergent Stereoselective Access to Fused Alkylideneazetidines

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Regiodivergent Stereoselective Access to Fused Alkylideneazetidines

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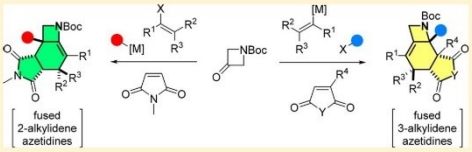
Supporting Information

ABSTRACT: Following recent advances in the generalization and simplification of 2*H*-azetine synthesis, a regiodivergent approach to fused 2- and 3-alkylideneazetines was designed via the intermediate formation of unprecedented vinylazetine structures. Concise sequences to the latter are described from which an expected unsaturated fused ring system was isolated with very high yields and regio- and stereoselectivities by [4 + 2] cycloadditions.



INTRODUCTION

Nitrogen-containing heterocycles are essential motifs in organic and medicinal chemistry[1] as their incorporation in drugs has been leading a number of synthetic studies.[2] As β-lactams have become important in pharmacology after the discovery of penicillin, a part of medicinal chemistry research has been dedicated to exploring the synthesis and biological activities of such strained four-membered heterocycles. More than antibiotic properties, azetidine-derived fused systems present a wide range of applicabilities, showing for example antiviral and antifungal activities (Figure 1).[3−5]

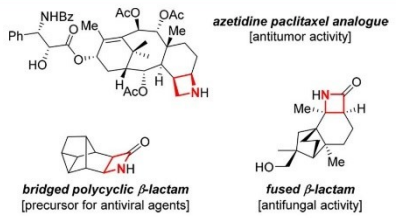
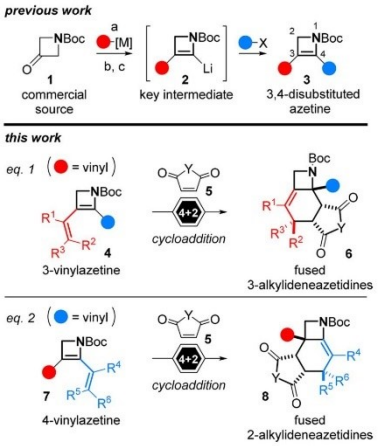


Figure 1. Selected examples of fused *N*-containing four-membered rings.

Moreover, a relatively restrained library of fused azetidines found in the literature points out the importance of these motifs as potential candidates for the treatment of a variety of diseases, including antitumor agents.[6] Although smaller and larger *N*-containing heterocycles have been intensively studied, the general formation of azetines[7] and alkylideneazetines[8] remains a challenge in organic chemistry.

En route to developing new access to sophisticated azetidine structures, we recently generalized the synthesis of 3,4-disubstituted 2-azetines **3** through the key formation of azetinyllithium intermediate **2** (Scheme 1).[9] Although direct electrophilic trapping furnished alkylated, silylated, and carbinol derivatives, transmetalation to boron followed by in situ Suzuki coupling opened unprecedented access to 4-arylated derivatives. Importantly, desired structures could be obtained in only three steps and after a sole purification. Starting from a commercial source of 3-azetidinone **1**,[10] the introduction of the substituent at position 3 can be simply done by nucleophilic 1,2-addition of an organometallic and subsequent methylation of the resulting tertiary alcohol giving then adequate substrates

Scheme 1. Past and Present Work on the Formation of Unsaturated Four-Membered *N*-Heterocycles



(a) Organolithium (M = Li) or organomagnesium (M = MgBr) were employed (1.2 equiv); reactions were performed in THF at −30 °C. (b) NaH, MeI, THF, 0 °C to rt. (c) *sec*-BuLi (2 equiv), TMEDA (1 equiv), THF, −78 °C.

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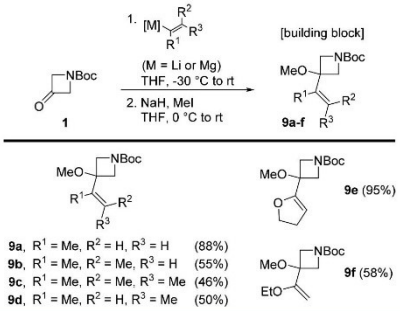
for the double α-lithiation/trapping sequence pioneered by Hodgson.[9,11] Employing either vinylmetal species (eq 1) or performing the subsequent cross-coupling with vinyl halides (eq 2) furnishes 3- and 2-vinylazetines **4** and **7**, respectively (Scheme 1). Upon addition of dienophile **5**, stereoselective [4 + 2] cycloaddition takes place, leading to fused alkylideneazetidines (AAz) **6** and **8**. The regiodivergence of the strategy simply comes from the nature of the embedded diene initially employed (3-vinylazetine **4** or 4-vinylazetine **7**).

RESULTS AND DISCUSSION

In Scheme 2, we detail the two-step preparation of 3-vinylazetidine building blocks **9a–f**.[12,13] Upon addition of an

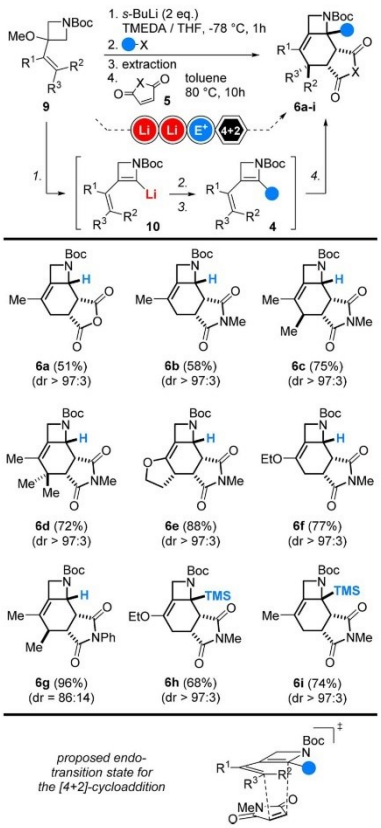
Scheme 2. Preparation of 3-Vinylazetidine Building Blocks



alkenylmetal species on **1**, tertiary alcohols are intermediary formed and further methylated without need for purification. Diverse alkenyl groups and vinyl ethers[13] were introduced, giving access to the desired substrates **9a–f** in moderate to high yields (46–95%).

Starting from these vinylazetidines **9a–f**, α-lithiation in the presence of *s*-BuLi promotes a β-elimination, and an excess amount of *s*-BuLi yields key azetinyllithium intermediate **10** that can then be trapped by the appropriate electrophile (H_2O or TMSCl, Scheme 3).[12] Resulting dienes **4** were subsequently engaged in a [4 + 2] cycloaddition with electron-deficient dienophiles **5** to afford fused AAz **6a–i** with excellent control over the stereochemical outcome of the transformation in all cases (97:3 dr).[14] Although isopropenylmetal species (R^1 = Me) led to **6a** and **6b** with good yields employing maleic anhydride or *N*-methylmaleimide, respectively, the possibility of adding a stereocenter was explored by using an in situ-generated *trans*-2-butenyllithium as the starting organometallic species. Compounds **6c** and **6g** (from *N*-phenylmaleimide) containing four consecutive stereocenters were obtained with an excellent diastereomeric ratio and up to 96% yield. A decrease in stereoselectivity was observed however when employing *N*-phenylmaleimide (**6g**, 86:14 dr). Interestingly, bulky substrates also furnished expected product **6d** in good yields. Using Feringa's deprotonation for the formation of lithiated vinyl ether[13] resulted in the formation of tetracyclic AAz **6e** and *O*-ethyl-substituted AAz **6f** in 77–88% yield. Following the double deprotonation, subsequent addition of TMSCl in the formation of **4** led to quaternary stereocenter containing AAz **6h** and **6i** in good yields and stereoselectivities.[15]

Scheme 3. Three-Step Sequence Towards Fused AAz[a]



[a]Indicated yields are calculated from compound **9** after the three-step sequence, including the extraction step; see Supporting Information.

With an efficient ex situ preparation of functionalized dienes embedded in the azetine structures in hand, we envisioned that chiral substrate **11** (Scheme 4), obtained by intermediate addition of an aldehyde, could lead to a diastereocontrolled [4 + 2] cycloaddition. Benzaldehyde was first used on 4-azetinyllithium species, furnishing the corresponding azetine carbinol **11a**, which was engaged crude in the cycloaddition with *N*-methylmaleimide. Delightfully, **12a** was isolated in good yields and with an excellent diastereomeric ratio (97:3). We propose to explain this exceptional stereoselectivity by intramolecular H-bonding between the hydroxyl moiety and the Boc group, placing the aromatic group, coming initially from the aldehyde, on one of the two diastereotopic faces. Potential allylic strain reinforces this selectivity, placing the larger group (aromatic) out of the plane. As a result, the dienophile preferentially approaches from the less hindered face of the diene. X-ray measurements on product **12g** showed H-bonding, and we assume that this interaction plays a determining role in the diastereoselectivity of the reaction, as

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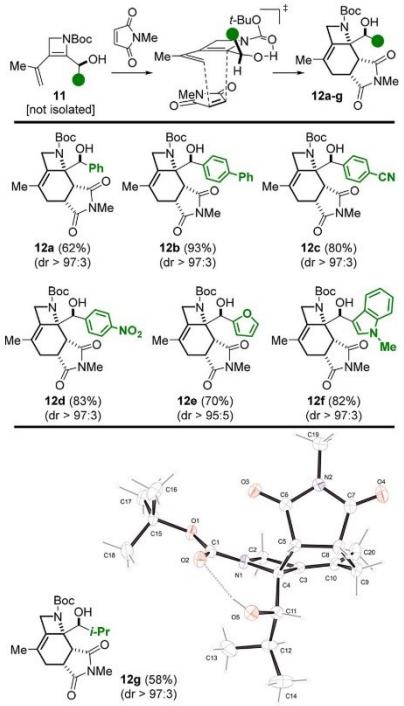
Scheme 4. Diastereoselective Approach toward AAz[a]



[a]Indicated yields are calculated from compound **9** after the three-step sequence, including the extraction step; see Supporting Information.

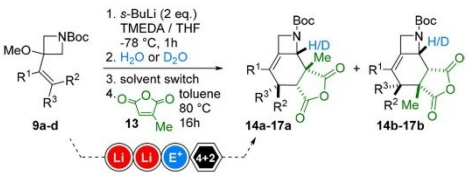
proposed in the transition state (Scheme 4).[16] Aromatic as well as heteroaromatic substrates furnished **12b–d** and **12e,f**, respectively, with similarly high yields and diastereoselectivities.

To introduce a quaternary stereocenter α to a carbonyl position, we next employed citraconic anhydride **13** as dienophile. Dienes **4g–i** and **4l** obtained after quenching with either H_2O or D_2O were employed without further purification. Interestingly, different regioselectivities were observed depending on the bulkiness of the diene engaged in the cycloaddition reaction (Scheme 5). Although the less bulky terminal diene (from **9a**) only gave moderate regioselectivities (**14a**:**14b** = 75:25), the most substituted one (from **9c**) furnished exclusively **17a** in 89% yield

As this variable regioselectivity can be easily explained by steric repulsion between the methyl group of the dienophile and the substituents at the vinylic position, *cis*- and *trans*-dimethylvinyl substrates (from **9d** and **9b**, respectively) led to intermediate regioselectivities (79:21 and 83:17, respectively). Importantly, regioisomers could be isolated separately via chromatography.

Finally, a regiodivergent approach toward fused 2-AAz was designed starting form aryl-, alkyl-, and alkynyl-substituted azetidines **18** (Scheme 6). Following the lithiation sequence described above led to the corresponding azetinylboronate upon addition of boron isopropoxide. Subsequent addition of

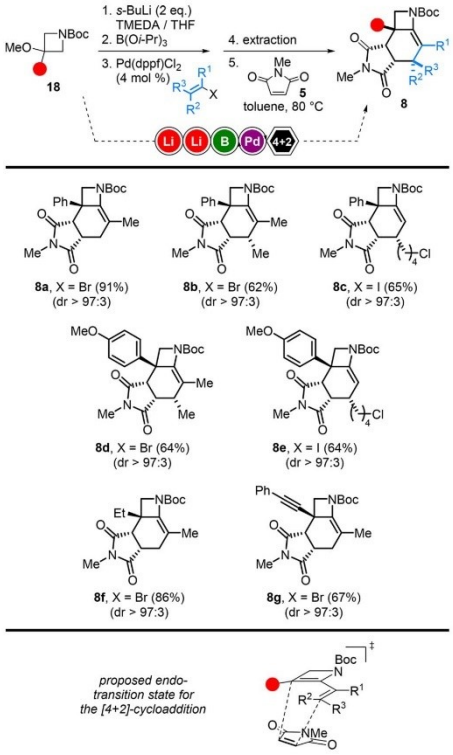
Scheme 5. Synthesis of AAz Using 3-Methylfuran-2,5-dione[a]



from **9a**	**14** (D), R^1 = Me, R^2 = H, R^3 = H	(54%)	(**14a**:**14b** = 75:25)
from **9d**	**15** (H), R^1 = Me, R^2 = H, R^3 = Me	(45%)	(**15a**:**15b** = 79:21)
from **9b**	**16** (D), R^1 = Me, R^2 = Me, R^3 = H	(62%)	(**16a**:**16b** = 83:17)
from **9c**	**17** (H), R^1 = Me, R^2 = Me, R^3 = Me	(89%)	(**17a**:**17b** = 100:0)

[a]Indicated yields are calculated from compound **9** after the three-step sequence, including the extraction step; see Supporting Information.

Scheme 6. Access to Fused 2-Alkylideneazetidines[a]



[a]Indicated yields are calculated from compound **9** after the three-step sequence, including the extraction step, see Supporting Information.

vinyl iodide or bromide furnished dienes **7** (not depicted in Scheme 6) through an in situ Suzuki cross-coupling catalyzed by $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$. These 4-vinylazetines were then directly engaged in the Diels–Alder cycloaddition with *N*-methylmaleimide **5** without further purification but after

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extracting switching the solvent to toluene. In all cases, a perfect control over the diastereoselective outcome was achieved (>97:3 dr). 3-Aryl-, alkyl-, and alkynyl-substituted substrates led to fused ring systems **8a−g** in good to excellent yields (up to 91%) containing up to four consecutive stereocenters.

■ CONCLUSIONS

In conclusion, we assembled highly stereoselective three-step sequences in which successive α-metalation, electrophilic addition, and [4 + 2] cycloaddition led to unprecedented fused tri- and tetracyclic alkylideneazetidines with up to four consecutive stereocenters. Both regioisomers could be accessed independently through this simple and efficient strategy, taking advantage of an easy and straightforward substrate preparation. Paths allowing the formation of these interesting patterns surely represent important advances in the chemistry of nitrogen-containing four-membered rings and their potential implications in drug-discovery processes.

■ EXPERIMENTAL SECTION

General Considerations. Commercially available starting materials were used without further purification unless otherwise stated. All reactions were carried out under a N_2 atmosphere in flame-dried glassware. Syringes, which were used to transfer anhydrous solvents or reagents, were purged with nitrogen prior to use. CH_2Cl_2 was predried over $CaCl_2$ and distilled from CaH_2. THF was refluxed and distilled from sodium benzophenone ketyl under nitrogen. Et_2O was predried over $CaCl_2$ and passed through activated Al_2O_3 (the solvent purification system SPS-400-2 from Innovative Technologies Inc.). Toluene was predried over $CaCl_2$ and distilled from CaH_2. Chromatography purifications were performed using silica gel (SiO_2, 0.040−0.063 mm, 230−400 mesh ASTM) from Merck. The spots were visualized under UV (254 nm) or by staining the TLC plate with $KMnO_4$ solution (10 g of K_2CO_3, 1.5 g of $KMnO_4$, 150 mL of H_2O, 1.25 mL of 10% NaOH in H_2O), *p*-anisaldehyde solution (concn 10 mLof H_2SO_4, 200 mL of EtOH, 3 mL of AcOH, 4 mL of *p*-anisaldehyde). Diastereoisomeric ratios were determined by ^{1}H NMR and ^{13}C NMR. ^{13}C and ^{1}H NMR spectra were recorded on VARIAN Mercury 200, BRUKER ARX 300, VARIAN VXR 400 S, and BRUKER AMX 600 instruments. Chemical shifts are reported as δ values in ppm relative to residual solvent peak (^{1}H NMR) or solvent peak (^{13}C NMR) in deuterated chloroform ($CDCl_3$: δ 7.26 ppm for ^{1}H NMR and δ 77.16 ppm for ^{13}C NMR). Abbreviations for signal coupling are as follows: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), m (multiplet), and br (broad). Reaction end points were determined by GC monitoring of the reactions. Gas chromatography was performed with machines from Agilent Technologies 7890 using a column of type HP 5 (Agilent 5% phenylmethylpolysiloxane, 15 m length, 0.25 mm diameter, 0.25 μm film thickness) or Hewlett-Packard 6890 or 5890 series II using a column of type HP 5 (HewlettPackard, 5% phenylmethylpolysiloxane, 15 m length, 0.25 mm diameter, 0.25 μm film thickness). High-resolution mass spectra (HRMS) and low-resolution mass spectra (LRMS) were recorded on a Finnigan MAT 95Q or Finnigan MAT 90 instrument or JEOL JMS-700. Infrared spectra were recorded on a Perkin 281 IR spectrometer, and samples were measured neat (ATR, Smiths Detection DuraSample IR II Diamond ATR). The absorption bands were reported in wave numbers (cm^{-1}), and abbreviations for intensity are as follows: vs (very strong; maximum intensity), s (strong; >75% of max. intensity), m (medium; from 50 to 75% of max. intensity), w (weak; <50% of max. intensity), and br (broad). Melting points were determined on a Büchi B-540 apparatus and uncorrected. Single crystals were grown in small quench vials with a volume of 5.0 mL from slow evaporation of dichloromethane/hexane mixtures at room temperature. Suitable single crystals were then introduced into perfluorinated oil and mounted on top of a thin glass wire. Data collection was performed at 100 K with a Bruker D8 Venture TXS equipped with a Spellman generator (50 kV, 40 mA) and a Kappa CCD detector operating with Mo Kα radiation (l = 0.71071 Å).

s-BuLi and *t*-BuLi were purchased as solutions in cyclohexane/hexane mixtures from Rockwood Lithium GmbH. The commercially available Grignard reagents MeMgCl, PhMgCl, and *n*-BuMgCl were also purchased from Rockwood Lithium GmbH as solutions in THF.

The concentration of organometallic reagent from commercially purchased and synthesized reagents was determined either by titration of isopropyl alcohol using the indicator 4-(phenylazo)diphenylamine in THF for Grignard reagents or using the indicator *N*-benzylbenzamide in THF for organolithium reagents.

[*s*-BuLi] = 1.31 M in cyclohexane (titration with isopropanol/1,10-phenanthroline) purchased from Rockwood Lithium GmbH.

[*t*-BuLi] = 2.00 M in hexane (titration with isopropanol/1,10-phenanthroline) purchased from Rockwood Lithium GmbH.

General Procedure A. For the synthesis of organomagnesium-vinyl reagents:[13] In a Schlenk flask, two equivalents of magnesium turnings were layered with either diethyl ether or THF. One seed of iodine was added for activation, and one drop of concentrated corresponding vinyl bromide was added. After ensuring that the reaction had started, the corresponding bromides were solubilized in the appropriate solvent and added dropwise at a constant rate that would keep the reaction constantly refluxing. After completed addition, the reaction was stirred for three more hours at room temperature, and the organomagnesium reagents were stored under nitrogen.

General Procedure B. for the synthesis of 3-substituted 1-Boc-3-methoxyazetidines (**9a−f, 18a−d**): Commercially available *tert*-butyl 3-oxoazetidine-1-carboxylate (**1**) (1.0 equiv, 5.0 mmol) was dissolved in THF (20 mL) and cooled to −30 °C. The corresponding vinyl-Grignard (1.3 equiv, 6.5 mmol) or vinyllithium species[13] was added dropwise, and the solution was stirred for 1 h before warming to room temperature. The reaction mixture was quenched with saturated NH_4Cl and extracted twice with diethyl ether (2 × 20 mL). The combined organic layers were dried over $MgSO_4$, and the solvents were evaporated under a vacuum. The crude alcohol was then redissolved in THF (10 mL) and cooled to 0 °C. After adding sodium hydride (1.3 equiv, 6.5 mmol) portionwise, the reaction mixture was allowed to reach room temperature and stirred for 1 h. Methyl iodide (1.3 equiv, 6.5 mmol) was then added, and the mixture was stirred for two more hours at room temperature. The reaction was quenched with methanol, and the solvents were evaporated. Purification by column chromatography on silica gel gave 3-substituted 1-boc-3-methoxyazetidines **9a−f**.

General Procedure C. For the synthesis of alkylideneazetidines (**6a−i/12a−g**): Azetidines **9a−f** (0.50 mmol, 1.0 equiv) were dissolved in THF (5.0 mL), and the solution was cooled to −78 °C. After the addition of TMEDA (1.3 mmol, 2.5 equiv), *s*-BuLi (1.3 mmol, 1.31 M, 2.5 equiv) was added dropwise, and the mixture stirred for 1 h. The reaction was then quenched with the corresponding electrophile (H_2O, TMSCl, D_2O, aldehydes), stirred for 30 min, and warmed to room temperature. After workup with saturated NH_4Cl and extraction with diethyl ether (2 × 10 mL), the organic phases were combined and dried over Na_2SO_4. The crude dienes were then redissolved in toluene (3.0 mL) and transferred into a pressure tube. The dienophile was added (1.0 mmol, 2.0 equiv), and the sealed pressure tube was heated to 80 °C for 10−24 h. Evaporation of the solvent and purification by column chromatography led to compounds **6a−i/12a−g**.

General Procedure D. For the synthesis of alkylideneazetidines (**14a−17a/14b−17b**): Azetidines **9a−d** (0.50 mmol, 1.0 equiv) were dissolved in THF (5.0 mL), and the solution was cooled to −78 °C. After the addition of TMEDA (1.3 mmol, 2.5 equiv), *s*-BuLi (1.3 mmol, 1.31 M, 2.5 equiv) was added dropwise, and the mixture was stirred for 1 h. The reaction was then quenched with the corresponding electrophile (H_2O or D_2O), stirred for 30 min, and warmed to room temperature. After workup with saturated NH_4Cl and extraction with diethyl ether (2 × 10 mL), the organic phases were combined and dried over Na_2SO_4. The crude dienes were then redissolved in toluene (3.0 mL) and transferred into a pressure tube.

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The dienophile was added (1.0 mmol, 2.0 equiv), and the sealed pressure tube was heated to 80 °C for 16 h. Evaporation of the solvent and purification by column chromatography led to compounds **14a–17a/14b–17b**.

General Procedure E. For the synthesis of alkylideneazetidines (**8a–g**): Azetidines (0.50 mmol, 1.0 equiv) were dissolved in THF (5.0 mL), and the solution was cooled to −78 °C. After the addition of TMEDA (1.3 mmol, 2.5 equiv), *s*-BuLi (1.3 mmol, 1.31 M, 2.5 equiv) was added dropwise, and the mixture was stirred for 1 h. The reaction was then quenched with 2.0 equiv of $B(Oi\text{-}Pr)_3$ and stirred for 60 min at 0 °C. After this time, $Pd(dppf)Cl_2$·DCM (4 mol %) as well as the corresponding vinyl-halogenide (X = I or Br) were added and let stir for 24 h. After workup with saturated NH_4Cl and extraction with diethyl ether (2× 10 mL), the organic phases were combined and dried over Na_2SO_4. The crude dienes were then redissolved in toluene (3.0 mL) and transferred into a pressure tube. The dienophile was added (1.0 mmol, 2.0 equiv), and the sealed pressure tube was heated to 80 °C for 10–24 h. Evaporation of the solvent and purification by column chromatography led to compounds **8a–g**.

EXPERIMENTAL DATA

***tert*-Butyl-3-methoxy-3-(prop-1-en-2-yl)azetidine-1-carboxylate (9a).** Using *tert*-butyl 3-oxoazetidine-1-carboxylate (**1**) and isopropenylmagnesium bromide according to general procedure B provided **9a** (4.40 mmol, 1.00 g, 88%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.15 (s, 1H), 5.04 (s, 1H), 3.97 (d, J = 9.0 Hz, 2H), 3.85 (d, J = 9.1 Hz, 2H), 3.06 (s, 3H), 1.67 (s, 3H), 1.44 ppm (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.7, 142.0, 114.9, 79.7, 77.8, 58.3, 56.3, 51.0, 28.5, 17.2 ppm. LRMS (ESI-quadrupole pos) m/z (%): 212.1 (1), 170.1 (32), 154.1 (8). HRMS (ESI-quadrupole pos) calcd for $C_{11}H_{18}NO_3^+$: 212.1287; found: 212.1301. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2976 (w), 2946 (w), 2884 (w), 2826 (vw), 1704 cm^{-1} (vs).

***tert*-Butyl-(*Z*)-3-(but-2-en-2-yl)-3-methoxyazetidine-1-carboxylate (9b).** Using *tert*-butyl 3-oxoazetidine-1-carboxylate (**1**) and vinyllithium according to general procedure B provided **9b** after purification on silica gel (hexane/ethyl acetate 9:1) (3.70 mmol, 900 mg, 55%) as a colorless crystalline solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.56 (q, J = 7.2, 6.8 Hz, 1H), 4.02 (d, J = 9.3 Hz, 2H), 3.92 (d, J = 9.3 Hz, 2H), 3.14 (s, 3H), 1.66 (s, 3H), 1.57 (d, J = 7.2 Hz, 3H), 1.42 ppm (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.7, 132.0, 126.7, 79.6, 76.8, 58.6, 50.8, 28.5, 21.2, 14.7 ppm. LRMS (ESI-quadrupole pos) m/z (%): 184.1 (16), 168.1 (6), 153.1 (4), 112.1 (68). HRMS (ESI-quadrupole pos) calcd for $C_9H_{14}NO_3^+$ [M − *t*-Bu]$^+$: 184.0974; found: 184.0984. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2978 (w), 2944 (w), 2884 (w), 2824 (vw), 1694 cm^{-1} (vs).

***tert*-Butyl-3-methoxy-3-(3-methylbut-2-en-2-yl)azetidine-1-carboxylate (9c).** Using *tert*-butyl 3-oxoazetidine-1-carboxylate (**1**) and vinyllithium according to general procedure B provided **9c** after purification on silica gel (hexane/ethyl acetate 9:1) (3.00 mmol, 760 mg, 46%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.01 (d, J = 9.4 Hz, 2H), 3.92 (d, J = 9.4 Hz, 2H), 3.14 (s, 3H), 1.71 (s, 3H), 1.61 (d, J = 6.4 Hz, 6H), 1.43 ppm (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.7, 133.1, 124.9, 79.6, 78.3, 58.9, 50.9, 28.5, 21.6, 16.5 ppm. LRMS (ESI-quadrupole pos) m/z (%): 198.2 (9), 184.2 (3). HRMS (ESI-quadrupole pos) calcd for $C_{10}H_{16}NO_3^+$ [M − *t*-Bu]$^+$: 198.1130; found: 198.1123. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2978 (w), 2942 (w), 2880 (w), 2822 (vw), 2244 (vw), 1704 cm^{-1} (vs).

***tert*-Butyl-(*E*)-3-(but-2-en-2-yl)-3-methoxyazetidine-1-carboxylate (9d).** Using *tert*-butyl 3-oxoazetidine-1-carboxylate (**1**) and vinyllithium according to general procedure B provided **9d** after purification on silica gel (hexane/ethyl acetate 9:1) (2.00 mmol, 482 mg, 50%) as a colorless oil. R_f = 0.5 (hexane/EtOAc 8:2, UV, $KMnO_4$, PAA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.61–5.53 (m, 1H), 3.99–3.91 (m, 2H), 3.81 (d, J = 9.0 Hz, 2H), 3.01 (s, 3H), 1.68 (d, J = 7.5 Hz, 3H), 1.53 (s, 3H), 1.43 ppm (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.8, 132.5, 123.7, 79.6, 78.9, 50.7, 28.5, 13.4, 11.0 ppm. LRMS (ESI-quadrupole pos) m/z (%): 242.2 (40), 227.1 (35), 186.1 (60), 154.0 (5). HRMS (ESI-quadrupole pos) calcd for $C_{13}H_{24}NO_3^+$: 242.1751, found 242.1751. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2976 (w), 2934 (w), 2882 (w), 2824 (vw), 1702 cm^{-1} (vs).

***tert*-Butyl-3-(4,5-dihydrofuran-2-yl)-3-methoxyazetidine-1-carboxylate (9e).** Using *tert*-butyl 3-oxoazetidine-1-carboxylate (**1**) and vinyllithium according to general procedure B provided **9e** after purification on silica gel (hexane/ethyl acetate 9:1) (3.80 mmol, 980 mg, 95%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.03 (t, J = 2.5 Hz, 1H), 4.41 (t, J = 9.4 Hz, 2H), 3.98 (d, J = 0.8 Hz, 2H), 3.93 (d, J = 9.6 Hz, 2H), 3.21 (s, 3H), 2.71 (td, J = 9.4, 2.5 Hz, 2H), 1.43 ppm (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.5, 155.4, 99.7, 79.8, 72.0, 70.8, 58.6, 57.3, 52.1, 30.2, 28.5 ppm. LRMS (ESI-quadrupole pos) m/z (%): 198.1 (16), 182.1 (6), 154.1 (5), 126.1 (75), 96.1 (44), 85.1 (11), 67.1 (9), 57.1 (100). HRMS (ESI-quadrupole pos) calcd for $C_9H_{12}NO_4^+$ [M − *t*-Bu]$^+$: 198.0766; found: 198.0754. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2976 (m), 2884 (w), 2836 (vw), 1702 cm^{-1} (vs).

***tert*-Butyl 3-(1-ethoxyvinyl)-3-methoxyazetidine-1-carboxylate (9f).** Using *tert*-butyl 3-oxoazetidine-1-carboxylate (**1**) and vinyllithium according to general procedure B provided **9f** after purification on silica gel (hexane/ethyl acetate 9:1) (2.33 mmol, 600 mg, 58%) as a colorless oil. R_f = 0.5 (hexane/EtOAc 8:2, UV, $KMnO_4$, PAA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.28–4.22 (m, 2H), 4.05 (d, J = 9.2 Hz, 2H), 3.89 (d, J = 9.2 Hz, 2H), 3.79 (q, J = 7.0 Hz, 2H), 3.21 (s, 3H), 1.44 (s, 9H), 1.33 ppm (t, J = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.8, 156.6, 84.3, 79.7, 76.0, 63.5, 51.8, 28.5, 28.5, 14.5 ppm. LRMS (ESI-quadrupole pos) m/z (%): 258.2 (100), 202.1 (50), 170.1 (10), 126.6 (2). HRMS (ESI-quadrupole pos) calcd for $C_{13}H_{24}NO_4^+$: 258.1700, found 258.1702. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2978 (w), 2934 (w), 2886 (w), 1704 (vs), 1628 cm^{-1} (w).

***tert*-Butyl-(4a*R**,7a*R**,7b*R**)-3-methyl-5,7-dioxo-4,4a,5,7,7a,7b-hexahydroisobenzofuro[4,5-*b*]azete-1(2*H*)-carboxylate (6a).** Using *tert*-butyl 3-(prop-1-en-2-yl)azete-1(2*H*)-carboxylate and maleic anhydride according to general procedure C provided **6a** (0.20 mmol, 60 mg, 51%) as a light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.72 (d, J = 9.4 Hz, 1H), 4.55 (d, J = 11.3 Hz, 1H), 4.33 (d, J = 12.2 Hz, 1H), 3.71 (t, J = 8.5 Hz, 1H), 3.41 (ddd, J = 8.9, 5.5, 1.9 Hz, 1H), 2.60 (dd, J = 15.2, 1.9 Hz, 1H), 2.25 (d, J = 16.1 Hz, 1H), 1.71 (s, 3H), 1.49 ppm (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.9, 167.8, 136.6, 127.8, 125.7, 80.9, 77.2, 62.6, 56.4, 43.1, 42.2, 29.0, 28.4, 18.5 ppm. LRMS (DEP/EI-Orbitrap) m/z: 293.3 (2), 237.2 (4), 195.2 (9). HRMS (EI-Orbitrap) calcd for $C_{15}H_{19}NO_5^+$: 293.1263; found: 293.1255. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2984 (w), 2933 (w), 2869 (vw), 1837 (w), 1773 (s), 1685 (vs), 1645 cm^{-1} (w). Mp: 170–175 °C.

***tert*-Butyl-(4a*R**,7a*R**,7b*R**)-3,6-dimethyl-5,7-dioxo-2,4,4a,5,6,7,7a,7b-octahydro-1*H*-azeto[2,3-*e*]isoindole-1-carboxylate (6b).** Using *tert*-butyl 3-(prop-1-en-2-yl)azete-1(2*H*)-carboxylate and 1-methyl-1*H*-pyrrole-2,5-dione according to general procedure C provided **6b** (0.23 mmol, 70 mg, 58%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.71 (d, J = 9.1 Hz, 1H), 4.50 (d, J = 11.3 Hz, 1H), 4.23 (d, J = 12.2 Hz, 1H), 3.44 (t, J = 8.5 Hz, 1H), 3.06 (t, J = 8.5 Hz, 1H), 2.96 (s, 3H), 2.60 (dd, J = 15.1, 1.5 Hz, 1H), 2.17 (d, J = 15.6 Hz, 1H), 1.64 (s, 3H), 1.51 ppm (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.4, 174.5, 156.7, 126.7, 125.2, 77.2, 63.9, 55.6, 42.1, 41.2, 28.8, 28.5, 25.4, 18.4 ppm. LRMS (DEP/EI-Orbitrap): m/z 306.1 (1), 250.1 (31), 233.1 (8), 206.1 (38), 191.0 (11). HRMS (EI-Orbitrap) calcd for $C_{16}H_{22}N_2O_4^+$: 306.1580; found: 306.1588. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2972 (w), 2944 (w), 2926 (w), 2881 (w), 2866 (w), 1776 (w), 1698 cm^{-1} (vs). Mp: 110–115 °C.

***tert*-Butyl-(4*R**,4a*R**,7a*R**,7b*R**)-3,4,6-trimethyl-5,7-dioxo-2,4,4a,5,6,7,7a,7b-octahydro-1*H*-azeto[2,3-*e*]isoindole-1-carboxylate (6c).** Using *tert*-butyl (*Z*)-3-(but-2-en-2-yl)azete-1(2*H*)-carboxylate and 1-methyl-1*H*-pyrrole-2,5-dione according to general procedure C provided **6c** (0.38 mmol, 120 mg, 75%) as a sticky oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.89 (dq, J = 9.5, 2.3 Hz, 1H), 4.53–4.42 (m, 1H), 4.18 (ddd, J = 12.0, 2.7, 1.2 Hz, 1H), 3.45 (t, J = 8.9 Hz, 1H), 2.93 (s, 3H), 2.88 (ddd, J = 11.9, 7.6, 1.7 Hz, 2H), 1.62 (q, J = 1.8 Hz, 3H), 1.49 (s, 9H), 1.08 ppm (d, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.0, 174.2, 157.2, 132.3, 123.9, 80.4, 63.2, 56.4, 48.4, 42.3, 36.2, 28.4, 25.3, 18.7, 17.6 ppm. LRMS (DEP/EI-Orbitrap) m/z: 264.1 (29), 247.2 (9), 220.2 (40), 205.1 (27), 153.1 (45). HRMS (EI-Orbitrap) calcd for $C_{17}H_{24}N_2O_4^+$: 320.1736; found: 320.1730. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2970 (w), 2932 (w), 2872 (vw), 1778 (w), 1694 cm^{-1} (vs).

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***tert*-Butyl-(4a*S**,7a*R**,7b*R**)-3,4,4,6-tetramethyl-5,7-dioxo-2,4,4a,5,6,7,7a,7b-octahydro-1*H*-azeto[2,3-*e*]isoindole-1-carboxylate (6d).** Using *tert*-butyl 3-(3-methylbut-2-en-2-yl)azete-1(2*H*)-carboxylate and 1-methyl-1*H*-pyrrole-2,5-dione according to general procedure C provided **6d** (0.36 mmol, 120 mg, 72%) as a yellow sticky foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.94 (dq, J = 9.9, 2.4 Hz, 1H), 4.40 (dt, J = 11.8, 2.1 Hz, 1H), 4.12−4.05 (m, 1H), 3.42 (dd, J = 9.7, 7.9 Hz, 1H), 2.85 (s, 3H), 2.67 (d, J = 7.7 Hz, 1H), 1.56 (d, J = 1.4 Hz, 3H), 1.51 (s, 3H), 1.44 (s, 9H), 0.99 ppm (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.4, 173.6, 157.8, 135.6, 124.4, 80.4, 77.2, 63.9, 56.3, 54.2, 43.6, 37.8, 28.5, 28.2, 24.8, 24.2, 14.1 ppm. LRMS (DEP/EI-Orbitrap): *m*/*z* 278.1 (16), 261.1 (9), 234.2 (20), 219.2 (52), 202.1 (5), 167.1 (92). HRMS (EI-Orbitrap) calcd for $C_{18}H_{26}N_2O_4^+$: 334.1893; found: 334.1895. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2978 (w), 2934 (vw), 2872 (vw), 2254 (vw), 1778 (w), 1696 cm^{-1} (s).

***tert*-Butyl-(5a*S*,5b*R*,8a*R*,8b*R*)-7-methyl-6,8-dioxo-2,4,5,5a,5b,6,7,8,8a,8b-decahydro-1*H*-azeto[2,3-*e*]furo[2,3-*g*]-isoindole-1-carboxylate (6e).** Using *tert*-butyl 3-(4,5-dihydrofuran-2-yl)azete-1(2*H*)-carboxylate and 1-methyl-1*H*-pyrrole-2,5-dione according to general procedure C provided **6e** (0.44 mmol, 150 mg, 88%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.89 (dd, J = 6.5, 4.4 Hz, 1H), 4.43 (t, J = 9.4 Hz, 2H), 3.86 (t, J = 7.3 Hz, 1H), 3.46 (d, J = 7.1 Hz, 1H), 3.30−3.25 (m, 1H), 3.24−3.20 (m, 1H), 2.90 (s, 3H), 2.88−2.80 (m, 2H), 2.74−2.71 (m 1H), 1.34 ppm (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.6, 175.3, 158.1, 153.6, 100.1, 80.7, 77.2, 70.1, 61.0, 53.2, 44.0, 41.1, 32.4, 28.1, 27.4, 25.1 ppm. LRMS (DEP/EI-Orbitrap) *m*/*z*: 234.2 (8), 205.1 (42), 177.1 (11). HRMS (EI-Orbitrap) calcd for $C_{17}H_{22}N_2O_5^+$: 334.1529; found: 334.1518. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2976 (w), 2932 (w), 2898 (w), 2254 (vw), 1780 (w), 1696 cm^{-1} (vs). Mp: 170−174 °C.

***tert*-Butyl-(4a*R**,7a*R**,7b*R**)-3-ethoxy-6-methyl-5,7-dioxo-2,4,4a,5,6,7,7a,7b-octahydro-1*H*-azeto[2,3-*e*]isoindole-1-carboxylate (6f).** Using *tert*-butyl 3-(1-ethoxyvinyl)azete-1(2*H*)-carboxylate and 1-methyl-1*H*-pyrrole-2,5-dione according to general procedure C provided **6f** (0.39 mmol, 130 mg, 77%) as white solid. R_f = 0.1 (hexane/EtOAc 7:3, UV, $KMnO_4$, PAA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.75−4.71 (m, 1H), 4.63 (dt, J = 11.2, 2.6 Hz, 1H), 4.42−4.37 (m, 1H), 3.72 (qd, J = 7.1, 4.1 Hz, 2H), 3.35 (s, 1H), 3.05 (t, J = 6.7 Hz, 1H), 2.95 (s, 3H), 2.62 (d, J = 15.5, 1H), 2.29−2.19 (m, 1H), 1.46 (s, 9H), 1.17 ppm (t, J = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.8, 174.4, 156.0, 145.2, 95.6, 80.2, 64.6, 64.1, 55.1, 41.8, 40.9, 28.4, 27.5, 25.3, 14.8 ppm. LRMS (ESI-quadrupole pos) *m*/*z* (%): 337.2 (40), 281.1 (100), 253.0 (5), 237.1 (2). HRMS (ESI-quadrupole pos) calcd for $C_{17}H_{25}N_2O_5^+$: 337.1758, found 337.1761. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2982 (w), 2932 (w), 2874 (w), 2252 (vw), 2154 (vw), 1778 (w), 1696 (s), 1560 cm^{-1} (vw). Mp: 120−125 °C.

***tert*-Butyl-(4*R**,4a*R**,7a*R**,7b*R**)-3,4-dimethyl-5,7-dioxo-6-phenyl-2,4,4a,5,6,7,7a,7b-octahydro-1*H*-azeto[2,3-*e*]isoindole-1-carboxylate (6g).** Using *tert*-butyl (*Z*)-3-(but-2-en-2-yl)azete-1(2*H*)-carboxylate and 1-phenyl-1*H*-pyrrole-2,5-dione according to general procedure C provided **6g** (0.48 mmol, 190 mg, 96%) as a yellowish solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43−7.36 (m, 2H), 7.34 (t, J = 7.4 Hz, 1H), 7.18−7.15 (m, 2H), 5.05−4.94 (m, 1H), 4.55 (d, J = 12.1 Hz, 1H), 4.26 (d, J = 11.4 Hz, 1H), 3.61 (t, J = 9.0 Hz, 1H), 3.08 (dd, J = 8.3, 1.6 Hz, 1H), 3.01 (q, J = 7.3 Hz, 1H), 1.67 (s, 3H), 1.48 (s, 9H), 1.13 (d, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.8, 173.1, 157.3, 132.9, 132.1, 129.2, 128.6, 126.5, 123.9, 80.5, 77.2, 63.4, 56.3, 48.6, 42.5, 36.4, 28.4, 18.3, 17.7, 14.0 ppm. LRMS (DEP/EI-Orbitrap) *m*/*z*: 282.1 (62), 265.1 (83), 248.1 (10), 237.2 (34), 221.2 (16), 207.1 (16), 194.1 (13), 172.2 (8). HRMS (EI-Orbitrap) calcd for $C_{22}H_{26}N_2O_4^+$: 382.1893; found: 382.1897. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2972 (w), 2932 (w), 2872 (w), 1780 (w), 1704 (vs), 1598 cm^{-1} (w). Mp: 145−149 °C.

***tert*-Butyl-(4a*R**,7a*S**,7b*S**)-3-ethoxy-6-methyl-5,7-dioxo-7b-(trimethylsilyl)-2,4,4a,5,6,7,7a,7b-octahydro-1*H*-azeto[2,3-*e*]isoindole-1-carboxylate (6h).** Using *tert*-butyl 3-(1-ethoxyvinyl)-4-(trimethylsilyl)azete-1(2*H*)-carboxylate and 1-methyl-1*H*-pyrrole-2,5-dione according to general procedure C provided **6h** (0.34 mmol, 140 mg, 67%) as white solid. R_f = 0.3 (hexane/EtOAc 7:3, UV, $KMnO_4$, PAA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.53 (dd, J = 11.5, 2.7 Hz, 1H), 4.46 (d, J = 12.1 Hz, 1H), 3.74 (q, J = 7.0 Hz, 2H), 3.49−3.35 (m, 1H), 2.98 (t, J = 8.6 Hz, 1H), 2.95 (s, 3H), 2.49 (d, J = 16.5 Hz, 1H), 2.31 (dd, J = 16.1, 7.4 Hz, 1H), 1.47 (d, J = 17.9 Hz, 9H), 1.17 (t, J = 7.0 Hz, 3H), 0.18 ppm (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.5, 176.5, 156.8, 145.2, 102.2, 81.9, 80.8, 65.9, 58.0, 56.7, 45.2, 42.8, 30.0, 26.8, 16.5, 0.0 ppm. LRMS (ESI-quadrupole pos) *m*/*z* (%): 363.4 (1), 351.4(50), 307.3 (100), 263.2 (20). HRMS (ESI-quadrupole pos) calcd for $C_{16}H_{23}N_2O_5Si^+$ [M − *t*-Bu]+: 351.1376; found: 351.1388. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2978 (w), 2900 (vw), 2868 (vw), 1778 (w), 1700 cm^{-1} (vs). Mp: 130−132 °C.

***tert*-Butyl-(4a*R**,7a*S**,7b*S**)-3,6-dimethyl-5,7-dioxo-7b-(trimethylsilyl)-2,4,4a,5,6,7,7a,7b-octahydro-1*H*-azeto[2,3-*e*]-isoindole-1-carboxylate (6i).** Using *tert*-butyl 3-(prop-1-en-2-yl)-4-(trimethylsilyl)azete-1(2*H*)-carboxylate and 1-methyl-1*H*-pyrrole-2,5-dione according to general procedure C provided **6i** (0.37 mmol, 140 mg, 74%) as white solid. R_f = 0.3 (hexane/EtOAc 7:3, UV, $KMnO_4$, PAA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.37 (d, J = 12.5 Hz, 1H), 4.23 (d, J = 12.3 Hz, 1H), 3.54−3.40 (m, 1H), 2.98 (t, J = 6.9 Hz, 1H), 2.94 (s, 3H), 2.46 (d, J = 15.9, 1H), 2.30−2.19 (m, 1H), 1.62 (s, 3H), 1.57−1.41 (m, 9H), 0.19 ppm (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.7, 174.9, 128.9, 123.7, 80.7, 60.5, 44.4, 41.7, 29.4, 28.6, 25.4, 21.2, 18.6, 18.6, −1.4 ppm. LRMS (DEP/EI-Orbitrap): *m*/*z* 333.3 (2), 321.8 (15), 277.2 (100), 263.2 (30). HRMS (EI-Orbitrap) calcd for $C_{19}H_{30}N_2O_4Si^+$: 378.1975; found: 378.1963. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2974 (w), 2948 (w), 2934 (w), 2902 (vw), 2864 (vw), 1778 (w), 1698 cm^{-1} (vs).

***tert*-Butyl-(4a*R**,7a*R**,7b*R**)-7b-((*S**)-hydroxy(phenyl)-methyl)-3,6-dimethyl-5,7-dioxo-2,4,4a,5,6,7,7a,7b-octahydro-1*H*-azeto[2,3-*e*]isoindole-1-carboxylate (12a).** Using *tert*-butyl 4-(hydroxy(phenyl)methyl)-3-(prop-1-en-2-yl)azete-1(2*H*)-carboxylate and 1-methyl-1*H*-pyrrole-2,5-dione according to general procedure C provided **12a** (0.44 mmol, 180 mg, 62%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16−7.07 (m, 5H), 6.32 (s, 1H), 4.56 (s, 1H), 4.14 (d, J = 8.4 Hz, 1H), 3.69 (d, J = 12.0 Hz, 1H), 3.15 (t, J = 7.4 Hz, 1H), 2.97 (d, J = 11.9 Hz, 1H), 2.83 (s, 3H), 2.53 (d, J = 15.3 Hz, 1H), 2.42 (dd, J = 15.5, 6.5 Hz, 1H), 1.43 (s, 3H), 1.35 ppm (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.4, 175.3, 157.2, 140.0, 127.8, 127.7, 126.9, 126.8, 81.1, 79.4, 77.2, 74.8, 55.6, 43.4, 41.6, 29.4, 28.4, 25.5, 18.3 ppm. LRMS (DEP/EI-Orbitrap): *m*/*z* 294.1 (100), 279.1 (48), 222.2 (8), 208.2 (23). HRMS (EI-Orbitrap) calcd for $C_{23}H_{29}N_2O_5^+$: 413.2071; found: 413.2054. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3306 (vw), 2976 (w), 2932 (w), 2868 (vw), 1776 (w), 1698 (vs), 1662 cm^{-1} (s).

***tert*-Butyl-(4a*R**,7a*R**,7b*R**)-7b-((*S**)-[1,1′-biphenyl]-4-yl-(hydroxy)methyl)-3,6-dimethyl-5,7-dioxo-2,4,4a,5,6,7,7a,7b-octahydro-1*H*-azeto[2,3-*e*]isoindole-1-carboxylate (12b).** Using *tert*-butyl (*S**)-4-([1,1′-biphenyl]-4-yl(hydroxy)methyl)-3-(prop-1-en-2-yl)azete-1(2*H*)-carboxylate and 1-methyl-1*H*-pyrrole-2,5-dione according to general procedure C provided **12b** (0.47 mmol, 227 mg, 93%) as white solid. R_f = 0.2 (hexane/EtOAc 7:3, UV, $KMnO_4$, PAA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, J = 7.7 Hz, 2H), 7.56 (d, J = 8.0 Hz, 2H), 7.45 (t, J = 7.5 Hz, 2H), 7.36 (dd, J = 7.7, 5.8 Hz, 3H), 6.51 (s, 1H), 4.75 (s, 1H), 4.32 (d, J = 8.4 Hz, 1H), 3.88 (d, J = 12.1 Hz, 1H), 3.32 (t, J = 7.7 Hz, 1H), 3.27−3.21 (m, 1H), 2.99 (s, 3H), 2.71 (dd, J = 15.7, 1.6 Hz, 1H), 2.60 (dd, J = 16.3, 7.1 Hz, 1H), 1.60 (s, 3H), 1.51 ppm (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.4, 175.3, 157.3, 140.7, 140.4, 139.2, 129.0, 127.5, 127.3, 127.1, 127.1, 126.9, 126.5, 81.3, 79.5, 74.7, 55.7, 43.5, 41.7, 29.5, 28.5, 25.6, 18.4 ppm. LRMS (DEP/EI-Orbitrap): *m*/*z* 489.3 (2). 447.3 (2), 374.2 (10), 306.2 (20). HRMS (EI-Orbitrap) calcd for $C_{29}H_{33}N_2O_5^+$: 489.2384; found: 489.2410. IR. (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3300 (vw), 2978 (vw), 2932 (vw), 2868 (vw), 2252 (vw), 1776 (w), 1700 (s), 1660 (m), 1600 (vw), 1520 cm^{-1} (vw). Mp: 165−170 °C.

***tert*-Butyl-(4a*R**,7a*R**,7b*R**)-7b-((*S**)-(4-cyanophenyl)-(hydroxy)methyl)-3,6-dimethyl-5,7-dioxo-2,4,4a,5,6,7,7a,7b-octahydro-1*H*-azeto[2,3-*e*]isoindole-1-carboxylate (12c).** Using *tert*-butyl 4-((4-cyanophenyl)(hydroxy)methyl)-3-(prop-1-en-2-yl)-azete-1(2*H*)-carboxylate and 1-methyl-1*H*-pyrrole-2,5-dione according to general procedure C provided **12c** (0.4 mmol, 175 mg, 80%) as yellow solid. R_f = 0.1 (hexane/EtOAc 7:3, UV, $KMnO_4$, PAA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, J = 8.0 Hz, 2H), 7.38 (d, J = 8.1

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Hz, 2H), 6.62 (d, J = 10.4 Hz, 1H), 4.72 (d, J = 8.6 Hz, 1H), 4.24 (d, J = 8.4 Hz, 1H), 3.87 (d, J = 12.2 Hz, 1H), 3.30 (t, J = 7.7 Hz, 1H), 3.13 (d, J = 12.3 Hz, 1H), 2.95 (s, 3H), 2.69 (d, J = 15.7, 1H), 2.54 (dd, J = 15.9, 7.4 Hz, 1H), 1.58 (s, 3H), 1.46 ppm (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.0, 174.9, 157.1, 145.8, 131.6, 128.3, 127.5, 126.2, 118.8, 111.6, 81.6, 79.1, 74.3, 55.5, 43.3, 41.4, 29.6, 28.4, 25.5, 18.4 ppm. LRMS (DEP/EI-Orbitrap): m/z 379.4 (2), 321.3 (5). HRMS (EI-Orbitrap) calcd for $C_{24}H_{28}N_3O_5^+$: 438.2023; found: 438.2013. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3286 (vw), 2980 (vw), 2254 (vw), 2230 (vw), 1776 (vw), 1700 (m), 1658 (w), 1610 cm^{-1} (vw). Mp: 160−165 °C.

***tert*-Butyl-(4a*R**,7a*R**,7b*R**)-7b-((*S**)-hydroxy(4-nitrophenyl)methyl)-3,6-dimethyl-5,7-dioxo-2,4,4a,5,6,7,7a,7b-octahydro-1*H*-azeto[2,3-*e*]isoindole-1-carboxylate (12d).** Using *tert*-butyl (*S**)-4-(hydroxy(4-nitrophenyl)-methyl)-3-(prop-1-en-2-yl)azete-1(2*H*)-carboxylate and 1-methyl-1*H*-pyrrole-2,5-dione according to general procedure C provided **12d** (0.42 mmol, 190 mg, 83%) as a yellow solid. R_f = 0.1 (hexane/EtOAc 7:3, UV, $KMnO_4$, PAA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, J = 8.6 Hz, 2H), 7.46 (d, J = 8.5 Hz, 2H), 6.71 (s, 1H), 4.79 (s, 1H), 4.28 (d, J = 8.4 Hz, 1H), 3.91 (d, J = 12.2 Hz, 1H), 3.33 (t, J = 7.2 Hz, 1H), 3.18 (d, J = 11.9 Hz, 1H), 2.99 (s, 3H), 2.73 (d, J = 15.7, 1H), 2.59 (dd, J = 15.3, 7.3 Hz, 1H), 1.61 (s, 3H), 1.50 ppm (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.0, 174.9, 157.2, 147.9, 147.6, 128.5, 127.8, 126.2, 123.0, 81.9, 79.2, 74.3, 55.6, 43.3, 41.5, 29.7, 28.4, 25.6, 18.5 ppm. LRMS (ESI-quadrupole pos) m/z (%): 458.2 (100), 402.1 (20), 251.1 (10). HRMS (ESI-quadrupole pos) calcd for $C_{23}H_{28}N_3O_7^+$: 458.1922; found: 458.1922. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3276 (vw), 2978 (w), 2934 (w), 2868 (vw), 1776 (w), 1698 (s), 1658 (m), 1606 (w), 1520 cm^{-1} (m). Mp: 152−155 °C.

***tert*-Butyl-(4a*R**,7a*R**,7b*R**)-7b-((*R**)-furan-2-yl(hydroxy)-methyl)-3,6-dimethyl-5,7-dioxo-2,4,4a,5,6,7,7a,7b-octahydro-1*H*-azeto[2,3-*e*]isoindole-1-carboxylate (12e).** Using *tert*-butyl 4-(furan-2-yl(hydroxy)methyl)-3-(prop-1-en-2-yl)azete-1(2*H*)-carboxylate and 1-methyl-1*H*-pyrrole-2,5-dione according to general procedure C provided **12e** (0.35 mmol, 140 mg, 70%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (s, 1H), 6.40 (d, J = 9.2 Hz, 1H), 6.35 (s, 1H), 6.28 (d, J = 3.1 Hz, 1H), 4.65 (d, J = 7.7 Hz, 1H), 4.20 (d, J = 8.5 Hz, 1H), 3.96 (d, J = 11.9 Hz, 1H), 3.61 (d, J = 11.9 Hz, 1H), 3.20 (t, J = 7.4 Hz, 1H), 2.96 (s, 3H), 2.61 (d, J = 15.6 Hz, 1H), 2.41 (dd, J = 15.5, 6.0 Hz, 1H), 1.58 (s, 3H), 1.47 ppm (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.3, 175.0, 157.5, 153.6, 142.1, 127.3, 125.8, 110.5, 107.8, 81.2, 78.1, 77.2, 69.8, 55.7, 43.2, 41.6, 28.9, 28.4, 25.5, 18.5 ppm. LRMS (ESI-quadrupole pos) m/z (%): 284.1 (100), 269.1 (21), 241.2 (5), 210.0 (6), 198.1 (12), 184.1 (67), 170.1 (8). HRMS (ESI-quadrupole pos) calcd for $C_{21}H_{27}N_2O_6^+$: 403.1864; found: 403.1926. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3298 (vw), 2974 (w), 2930 (w), 2870 (w), 1778 (w), 1698 (vs), 1668 cm^{-1} (s). Mp: 157−160 °C.

***tert*-Butyl-(4a*R**,7a*R**,7b*R**)-7b-((*S**)-hydroxy(1-methyl-1*H*-indol-3-yl)methyl)-3,6-dimethyl-5,7-dioxo-2,4,4a,5,6,7,7a,7b-octahydro-1*H*-azeto[2,3-*e*]isoindole-1-carboxylate (12f).** Using *tert*-butyl (*S**)-4-(hydroxy(1-methyl-1*H*-indol-3-yl)methyl)-3-(prop-1-en-2-yl)azete-1(2*H*)-carboxylate and 1-methyl-1*H*-pyrrole-2,5-dione according to general procedure C provided **12f** (0.41 mmol, 191 mg, 82%) as a brown oil. R_f = 0.1 (hexane/EtOAc 7:3, UV, KMnO4, PAA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, J = 8.3 Hz, 2H), 7.22−7.17 (m, 2H), 7.02 (t, J = 7.5 Hz, 1H), 6.29 (d, J = 11.0 Hz, 1H), 5.09 (d, J = 11.0 Hz, 1H), 4.40 (d, J = 8.5 Hz, 1H), 3.84 (d, J = 11.9 Hz, 1H), 3.79 (s, 3H), 3.36−3.26 (m, 2H), 3.00 (s, 3H), 2.78−2.65 (m, 2H), 1.52 ppm (s, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.5, 175.5, 157.7, 136.9, 128.2, 127.0, 126.9, 126.9, 121.5, 119.2, 119.1, 114.6, 109.3, 80.7, 79.7, 69.7, 56.3, 43.6, 41.8, 33.0, 29.3, 28.5, 25.5, 18.4 ppm. LRMS (DEP/EI-Orbitrap) m/z: 447.3 (2), 374.2 (10), 306.2 (20), 250.1 (100). HRMS (EI-Orbitrap) calcd for $C_{26}H_{31}N_3O_5^+$: 465.2264; found: 465.2258. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3324 (vw), 2946 (vw), 2934 (vw), 2926 (vw), 2894 (vw), 2884 (vw), 2254 (vw), 1776 (vw), 1700 (m), 1662 (w), 1616 (vw), 1548 cm^{-1} (vw).

***tert*-Butyl-(4a*R**,7a*R**,7b*R**)-7b-((*S**)-1-hydroxy-2-methyl propyl)-3,6-dimethyl-5,7-dioxo-2,4,4a,5,6,7,7a,7b-octahydro-1*H*-azeto[2,3-*e*]isoindole-1-carboxylate (12g).** Using *tert*-butyl 4-(1-hydroxy-2-methylpropyl)-3-(prop-1-en-2-yl)azete-1(2*H*)-carboxylate and 1-methyl-1*H*-pyrrole-2,5-dione according to general procedure C provided **12g** (0.29 mmol, 110 mg, 58%) as a crystalline white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.19 (s, 1H), 4.41 (d, J = 12.5 Hz, 1H), 4.26−4.12 (m, 2H), 3.28 (d, J = 4.1 Hz, 1H), 3.15 (t, J = 7.7 Hz, 1H), 2.94 (s, 3H), 2.48 (d, J = 15.5 Hz, 1H), 2.32 (d, J = 7.2 Hz, 1H), 1.98−1.85 (m, 1H), 1.58 (s, 3H), 1.48 (s, 9H), 1.02 (d, J = 6.7 Hz, 3H), 0.98 ppm (d, J = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.5, 175.6, 156.6, 127.8, 126.9, 81.1, 79.4, 77.2, 76.5, 55.6, 44.1, 41.5, 30.9, 30.0, 28.5, 25.4, 22.5, 18.4, 17.7 ppm. LRMS (DEP/EI-Orbitrap) m/z: 305.2 (8), 250.2 (56), 217.2 (8), 205.2 (100). HRMS (EI-Orbitrap) calcd for $C_{20}H_{31}N_2O_5^+$: 379.2227; found: 379.2227. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3332 (vw), 2962 (w), 2934 (w), 2870 (w), 1776 (w), 1702 (vs), 1670 cm^{-1} (m). Mp: 134−138 °C.

***tert*-Butyl-(4a*R**,7a*R**,7b*S**)-3,7a-dimethyl-5,7-dioxo-4,4a,5,7,7a,7b-hexahydroisobenzofuro[4,5-*b*]azete-1(2*H*)-carboxylate-7b-d (14a).** Using *tert*-butyl 3-(prop-1-en-2-yl)azete-1(2*H*)-carboxylate-4-d and 3-methylfuran-2,5-dione according to general procedure D provided **14a** (0.20 mmol, 62 mg, 40%) as colorless crystals. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.48 (ddd, J = 12.3, 3.0, 1.8 Hz, 1H), 4.24 (d, J = 12.3 Hz, 1H), 2.97 (dd, J = 4.4, 2.7 Hz, 1H), 2.57 (dd, J = 15.2, 2.7 Hz, 1H), 2.20 (d, J = 14.1 Hz, 1H), 1.72−1.68 (s, 3H), 1.62 (s, 3H), 1.48 ppm (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.6, 171.3, 157.1, 128.9, 125.8, 81.1, 77.2, 70.8, 56.1, 50.7, 49.8, 28.6, 28.3, 22.6, 18.5 ppm. LRMS (DEP/EI-Orbitrap) m/z: (%): 196.2 (15), 140.1 (49). HRMS (EI-Orbitrap) calcd for $C_{16}H_{20}DNO_5^+$: 308.1482; found: 308.1479; found: 322.1651. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2977 (w), 2935 (w), 2873 (vw), 1847 (w), 1779 (vs), 1697 cm^{-1} (s). Mp: 151−155 °C.

***tert*-Butyl-(4a*R**,7a*R**,7b*R**)-3,4a-dimethyl-5,7-dioxo-4,4a,5,7,7a,7b-hexahydroisobenzofuro[4,5-*b*]azete-1(2*H*)-carboxylate-7b-d (14b).** Using *tert*-butyl 3-(prop-1-en-2-yl)azete-1(2*H*)-carboxylate-4-d and 3-methylfuran-2,5-dione according to general procedure D provided **14b** (0.7 mmol, 20 mg, 14%) as colorless crystals. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.52 (d, J = 12.4 Hz, 1H), 4.30 (d, J = 12.4 Hz, 1H), 3.31 (s, 1H), 2.51 (d, J = 15.0 Hz, 1H), 2.04 (d, J = 14.9 Hz, 1H), 1.68 (s, 3H), 1.48 (s, 9H), 1.46 ppm (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.8, 167.3, 156.4, 128.4, 125.9, 80.8, 77.2, 63.2, 55.7, 50.5, 49.1, 37.9, 28.4, 24.2, 18.1 ppm. LRMS (DEP/EI-Orbitrap) m/z (%): 196.2 (15), 140.1 (49). HRMS (EI-Orbitrap) calcd for $C_{16}H_{20}DNO_5^+$: 308.1482; found: 308.1479. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2977 (w), 2935 (w), 2873 (vw), 1847 (w), 1779 (vs), 1697 cm^{-1} (s). Mp: 151−155 °C.

***tert*-Butyl-(4*S**,4a*R**,7a*R**,7b*S**)-3,4,7a-trimethyl-5,7-dioxo-4,4a,5,7,7a,7b-hexahydroisobenzofuro[4,5-*b*]azete-1(2*H*)-carboxylate (15a).** Using *tert*-butyl (*E*)-3-(but-2-en-2-yl)azete-1(2*H*)-carboxylate and 3-methylfuran-2,5-dione according to general procedure D provided **15a** (0.18 mmol, 58 mg, 36%) as a white solid. R_f = 0.5 (hexane/EtOAc 7:3, UV, KMnO4, PAA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.50−4.42 (m, 1H), 4.32 (s, 1H), 4.25 (d, J = 12.5 Hz, 1H), 2.77 (d, J = 3.1 Hz, 1H), 2.48−2.36 (m, 1H), 1.68 (s, 3H), 1.60 (s, 3H), 1.52 (s, 3H), 1.49 ppm (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.3, 171.0, 157.1, 133.0, 126.0, 81.2, 71.4, 57.2, 55.5, 51.0, 32.6, 28.4, 21.7, 14.3, 14.2 ppm. LRMS (ESI-quadrupole pos) m/z (%): 322.2 (85), 266.1 (100). HRMS (ESI-quadrupole pos) calcd for $C_{17}H_{24}NO_5^+$: 322.1649; found: 322.1651. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2998 (w), 2978 (w), 2946 (w), 2920 (w), 1846 (m), 1774 (s), 1676 cm^{-1} (vs). Mp: 169−173 °C.

***tert*-Butyl-(4*R**,4a*R**,7a*R**,7b*R**)-3,4,4a-trimethyl-5,7-dioxo-4,4a,5,7,7a,7b-hexahydroisobenzofuro[4,5-*b*]azete-1(2*H*)-carboxylate (15b).** Using *tert*-butyl (*E*)-3-(but-2-en-2-yl)azete-1(2*H*)-carboxylate and 3-methylfuran-2,5-dione according to general procedure D provided **15b** (0.05 mmol, 14 mg, 9%) as a white solid. R_f = 0.45 (hexane/EtOAc 7:3, UV, $KMnO_4$, PAA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.71 (d, J = 7.1 Hz, 1H), 4.54 (d, J = 12.5, 1H), 4.35 (d, J = 12.5 Hz, 1H), 3.37 (s, 1H), 2.25 (d, J = 7.7 Hz, 1H), 1.63 (s, 3H), 1.48 (s, 12H), 1.36 ppm (d, J = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.3, 167.7, 156.1, 131.4, 128.0, 80.7, 62.9, 56.0, 52.2, 39.8, 29.8, 28.5, 22.3, 14.0, 11.0 ppm. LRMS (ESI-quadrupole pos) m/z (%): 322.2 (85), 266.1 (100). HRMS (ESI-quadrupole pos) calcd for $C_{17}H_{24}NO_5^+$: 322.1649; found: 322.1651. IR (Diamond-

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ATR, neat) $\tilde{\nu}_{max}$: 2978 (m), 2936 (m), 2872 (m), 1854 (m), 1780 (vs), 1738 (m), 1698 (s), 1658 cm^{-1} (m).

***tert*-Butyl-(4*R**,4a*R**,7a*R**,7b*S**)-3,4,7a-trimethyl-5,7-dioxo-4,4a,5,7,7a,7b-hexahydroisobenzofuro[4,5-*b*]azete-1(2*H*)-carboxylate-7b-d (16a).** Using *tert*-butyl (*Z*)-3-(but-2-en-2-yl)azete-1(2*H*)-carboxylate-4-d and 3-methylfuran-2,5-dione according to general procedure D provided **16a** (0.25 mmol, 80 mg, 50%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.50 (d, J = 12.1 Hz, 1H), 4.25 (d, J = 12.1 Hz, 1H), 2.97 (qd, J = 7.3, 2.1 Hz, 1H), 2.85 (d, J = 2.2 Hz, 1H), 1.69 (s, 6H), 1.50 (s, 9H), 1.12 ppm (d, J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.3, 171.3, 157.4, 134.0, 124.6, 81.2, 77.2, 70.1, 56.5, 50.0, 37.7, 31.1, 28.3, 24.8, 17.7, 17.3 ppm. LRMS (DEP/EI-Orbitrap) m/z (%): 222.0 (3), 210.2 (25). HRMS (EI-Orbitrap) calcd for $C_{17}H_{22}DNO_5^+$: 322.1639; found: 322.1630. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2972 (w), 2932 (w), 2874 (w), 1854 (w), 1780 (vs), 1706 cm^{-1} (s). Mp: 170−173 °C.

***tert*-Butyl-(4*S**,4a*R**,7a*R**,7b*R**)-3,4,4a-trimethyl-5,7-dioxo-4,4a,5,7,7a,7b-hexahydroisobenzofuro[4,5-*b*]azete-1(2*H*)-carboxylate-7b-d (16b).** Using *tert*-butyl (*Z*)-3-(but-2-en-2-yl)azete-1(2*H*)-carboxylate-4-d and 3-methylfuran-2,5-dione according to general procedure D provided **16b** (0.06 mmol, 20 mg, 12%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.50 (d, J = 12.4 Hz, 1H), 4.25 (d, J = 12.0 Hz, 1H), 3.27 (s, 1H), 2.62 (q, J = 7.3 Hz, 1H), 1.69 (s, 3H), 1.48 (s, 9H), 1.42 (s, 3H), 1.01 ppm (d, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.8, 167.6, 157.3, 136.0, 123.5, 81.0, 77.2, 62.8, 53.6, 51.4, 40.8, 31.1, 28.5, 22.7, 17.7, 13.7 ppm. LRMS (DEP/EI-Orbitrap) m/z (%): 222.0 (3), 210.2 (25). HRMS (EI-Orbitrap) calcd for $C_{17}H_{22}DNO_5^+$: 322.1639; found: 322.1630. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2954 (m), 2924 (s), 2854 (m), 1852 (w), 1782 (vs), 1706 cm^{-1} (s). Mp: 170−173 °C.

***tert*-Butyl-(4a*R**,7a*R**,7b*S**)-3,4,4,7a-tetramethyl-5,7-dioxo-4,4a,5,7,7a,7b-hexahydroisobenzofuro[4,5-*b*]azete-1(2*H*)-carboxylate (17a).** Using *tert*-butyl 3-(3-methylbut-2-en-2-yl)azete-1(2*H*)-carboxylate and 3-methylfuran-2,5-dione according to general procedure D provided **17a** (0.45 mmol, 150 mg, 89%) as a yellowish solid. Only one regioisomer was isolated (ratio greater than 10:1 in crude ^{13}C NMR): ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.62−4.57 (m, 1H), 4.46 (d, J = 11.9 Hz, 1H), 4.20 (d, J = 11.8 Hz, 1H), 2.64 (s, 1H), 1.68 (s, 3H), 1.64 (s, 3H), 1.56 (s, 3H), 1.49 (s, 9H), 1.08 ppm (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.1, 170.5, 157.6, 137.2, 125.5, 81.2, 77.2, 71.2, 61.8, 56.2, 51.1, 39.5, 28.5, 28.3, 27.6, 24.3, 14.2 ppm. LRMS (DEP/EI-Orbitrap): m/z (%): 235.1 (3), 223.2 (23), 167.1 (100). HRMS (EI-Orbitrap) calcd for $C_{18}H_{24}NO_5^+$ $[M - H]^+$: 334.1654; found: 334.1646. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2976 (w), 2938 (w), 2874 (w), 1844 (w), 1780 (vs), 1702 cm^{-1} (vs). Mp: 121−125 °C.

***tert*-Butyl-3-methoxy-3-phenylazetidine-1-carboxylate (18a).** Using *tert*-butyl 3-oxoazetidine-1-carboxylate (**1**) and phenylmagnesium bromide according to general procedure B provided **18a** (7.80 mmol, 2.101 g, 98%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52−7.26 (m, 5H), 4.17 (s, 4H), 3.08 (s, 3H), 1.45 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.7, 140.0, 128.8, 128.2, 126.2, 79.9, 76.8, 59.2, 51.7, 28.5 ppm. LRMS (ESI-quadrupole pos) m/z (%): 190.1 (6), 175.1 (12). HRMS (ESI-quadrupole pos) calcd for $C_{15}H_{22}NO_3^+$: 264.1594; found: 264.1594. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2978 (w), 2950 (w), 2884 (w), 2828 (vw), 1702 cm^{-1} (vs).

***tert*-Butyl-3-methoxy-3-(4-methoxyphenyl)azetidine-1-carboxylate (18b).** Using *tert*-butyl 3-oxoazetidine-1-carboxylate (**1**) and (4-methoxyphenyl)magnesium bromide according to general procedure B provided **18b** (3.75 mmol, 1.100 g, 75%) as a colorless oil. R_f = 0.5 (hexane/EtOAc 9:1, UV, $KMnO_4$, PAA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, J = 8.5 Hz, 2H), 6.88 (d, J = 8.5 Hz, 2H), 4.11 (s, 4H), 3.77 (s, 3H), 3.00 (s, 3H), 1.41 ppm (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.3, 156.5, 131.7, 127.5, 113.9, 79.6, 76.3, 60.4, 58.4, 55.2, 51.3, 28.3 ppm. LRMS (ESI-quadrupole pos) m/z (%): 294.2 (85), 279.1 (45). HRMS (ESI-quadrupole pos) calcd for $C_{16}H_{24}NO_4^+$: 294.1700; found: 294.1702. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2974 (w), 2938 (w), 2882 (w), 2836 (vw), 1698 (vs), 1612 cm^{-1} (m).

***tert*-Butyl-3-methoxy-3-(phenylethynyl)azetidine-1-carboxylate (18c).** Commercially available phenylacetylene (1.0 equiv, 20 mmol) was dissolved in THF (60 mL) and cooled to −78 °C. After cooling, *n*-BuLi (1.0 equiv, 2.44 m, 20 mmol) was added dropwise, and the solution was stirred for 1 h before adding dropwise a solution of *tert*-butyl 3-oxoazetidine-1-carboxylate (**1**) (0.8 eq, 16 mmol, in 10 mL THF). The reaction mixture was quenched with saturated NH_4Cl and extracted twice with diethyl ether (2 × 40 mL). The combined organic layers were dried over $MgSO_4$, and the solvents were evaporated under vacuum. The crude alcohol was then redissolved in THF (60 mL) and cooled to 0 °C. After adding sodium hydride (1.0 equiv, 20 mmol) portionwise, the reaction mixture was allowed to reach room temperature and stirred for 1 h. Methyl iodide (1.0 equiv, 20 mmol) was then added, and the mixture was stirred for two more hours at room temperature. The reaction was quenched with methanol, and the solvents were evaporated. Purification by column chromatography on silica gel gave substituted 3-substituted 1-Boc-3-methoxyazetidines **18c** (11.8 mmol, 3.398 g, 74%) as a yellow solid. R_f = 0.80 (hexane/EtOAc 8:2, UV, $KMnO_4$, PAA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48−7.42 (m, 2H), 7.38−7.31 (m, 3H), 4.18 (d, J = 9.0 Hz, 2H), 4.08 (d, J = 9.0 Hz, 2H), 3.41 (s, 3H), 1.45 ppm (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.3, 131.9, 129.0, 128.5, 122.0, 87.7, 86.2, 80.1, 68.4, 61.8, 52.8, 28.5 ppm. LRMS (ESI-quadrupole pos) m/z (%): 288.1 (30), 273.1 (85), 232.1 (100). HRMS (EI-Orbitrap) calcd for $C_{17}H_{22}NO_3^+$ $[2M + H]^+$: 288.1594; found: 288.1595. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2996 (vw), 2974 (w), 2952 (w), 2932 (w), 2880 (w), 2230 (vw), 1692 (s).

***tert*-Butyl-3-ethyl-3-methoxyazetidine-1-carboxylate (18d).** Using ethylmagnesium chloride according to general procedure B afforded **18d** (7.38 g, 69%) as a colorless oil. R_f = 0.24 (10% EtOAc in hexane, PAA, $KMnO_4$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.84 (d, J = 9.0 Hz, 2H), 3.66 (d, J = 8.9 Hz, 2H), 3.20 (s, 3H), 1.78 (q, J = 7.3 Hz, 2H), 1.44 (s, 9H), 0.88 ppm (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.7, 79.7, 75.4, 58.0, 50.5, 28.5, 27.2, 7.1 ppm. LRMS (ESI-quadrupole pos) m/z (%): not found. HRMS (ESI-quadrupole pos): not found. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2976 (w), 2938 (w), 2882 (w), 1740 (m), 1704 cm^{-1} (vs).

***tert*-Butyl-(4a*S**,7a*S**,7b*S**)-3,6-dimethyl-5,7-dioxo-7b-phenyl-1,4,4a,5,6,7,7a,7b-octahydro-2*H*-azeto[3,2-*e*]isoindole-2-carboxylate (8a).** Using **18a** and 2-bromoprop-1-ene according to general procedure E provided **8a** (0.46 mmol, 174 mg, 91%) as a yellowish oil. R_f = 0.6 (hexane/EtOAc 7:3, UV, $KMnO_4$, PAA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, J = 4.3 Hz, 4H), 7.33−7.27 (m, 1H), 4.82 (d, J = 7.9 Hz, 1H), 3.64 (d, J = 7.9 Hz, 1H), 3.50 (d, J = 8.5 Hz, 1H), 3.05 (s, 3H), 2.96 (t, J = 7.3 Hz, 1H), 2.40 (d, J = 15.1 Hz, 1H), 2.23 (dd, J = 15.3, 6.4 Hz, 1H), 2.02 (s, 3H), 1.43 ppm (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.6, 177.4, 151.6, 142.2, 137.4, 129.5, 127.5, 126.1, 106.8, 81.0, 61.3, 47.4, 46.9, 42.3, 29.1, 28.4, 25.6, 18.0 ppm. LRMS (DEP/EI-Orbitrap) m/z (%): 382.3 (20), 326.2 (90), 281.2 (100). HRMS (EI-Orbitrap) calcd for $C_{22}H_{26}N_2O_4^+$ [M]+: 382.1893; found: 382.1890. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2976 (vw), 2930 (vw), 2858 (vw), 1774 (w), 1730 (w), 1700 cm^{-1} (vs).

***tert*-Butyl-(4*R**,4a*S**,7a*S**,7b*S**)-3,4,6-trimethyl-5,7-dioxo-7b-phenyl-1,4,4a,5,6,7,7a,7b-octahydro-2*H*-azeto[3,2-*e*]-isoindole-2-carboxylate (8b).** Using **18a** and (*E*)-2-bromobut-2-ene according to general procedure E provided **8b** (0.31 mmol, 123 mg, 62%) as a yellowish oil. R_f = 0.6 (hexane/EtOAc 7:3, UV, $KMnO_4$, PAA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43−7.35 (m, 4H), 7.33−7.27 (m, 1H), 4.72 (d, J = 8.0 Hz, 1H), 3.58 (dd, J = 8.1, 5.8 Hz, 2H), 3.01 (s, 3H), 2.90 (dd, J = 8.2, 5.0 Hz, 1H), 2.49 (p, J = 7.0 Hz, 1H), 1.99 (s, 3H), 1.43 (s, 9H), 1.36 ppm (d, J = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.6, 177.2, 151.6, 142.1, 138.1, 129.5, 127.5, 125.8, 111.1, 80.9, 61.5, 48.6, 48.3, 47.4, 31.8, 28.4, 25.2, 14.3, 12.8 ppm. LRMS (DEP/EI-Orbitrap) m/z (%): 355.0 (5), 295.1 (100), 265.1 (20), 182.1 (85). HRMS (EI-Orbitrap) calcd for $C_{23}H_{28}N_2O_4^+$ [M]+: 396.2049; found: 396.2040. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2976(w), 2906(vw), 1770(w), 1692 cm^{-1} (vs).

***tert*-Butyl-(4*S**,4a*S**,7a*S**,7b*S**)-4-(4-chlorobutyl)-6-methyl-5,7-dioxo-7b-phenyl-1,4,4a,5,6,7,7a,7b-octahydro-2*H*-azeto-[3,2-*e*]isoindole-2-carboxylate (8c).** Using **18a** and (*E*)-6-chloro-1-iodohex-1-ene according to general procedure E provided **8c** (0.33 mmol, 149 mg, 65%) as a yellowish oil. R_f = 0.5 (hexane/EtOAc 7:3,

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UV, KMnO4, PAA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45−7.37 (m, 4H), 7.34−7.28 (m, 1H), 5.25 (s, 1H), 4.88 (s, 1H), 3.69 (d, J = 7.8 Hz, 1H), 3.60 (d, J = 8.1 Hz, 1H), 3.52 (t, J = 6.6 Hz, 2H), 3.02−2.97 (m, 4H), 2.30 (dtd, J = 9.9, 6.0, 3.9 Hz, 1H), 1.88−1.70 (m, 4H), 1.57−1.47 (m, 2H), 1.44 ppm (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.9, 152.2, 145.0, 141.2, 134.3, 129.6, 127.7, 125.9, 100.1, 81.5, 47.8, 46.9, 46.2, 45.1, 34.5, 32.6, 31.2, 28.3, 25.6, 25.2 ppm. LRMS (DEP/EI-Orbitrap) m/z (%): 458.4 (10), 402.2 (60), 357.3 (25), 323.3 (65), 291.2 (70), 267.2 (100), 247.2 (50), 194.1 (5). HRMS (EI-Orbitrap) calcd for $C_{25}H_{31}ClN_2O_4^+$ [M]+: 458.1972; found: 458.1969. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2976 (w), 2936 (w), 2866 (vw), 1770 (w), 1694 cm^{-1} (vs).

***tert*-Butyl-(4*R**,4a*S**,7a*S**,7b*S**)-7b-(4-methoxyphenyl)-3,4,6-trimethyl-5,7-dioxo-1,4,4a,5,6,7,7a,7b-octahydro-2*H*-azeto[3,2-*e*]isoindole-2-carboxylate (8d).** Using **18b** and (*E*)-2-bromobut-2-ene according to general procedure E provided **8d** (0.32 mmol, 156 mg, 64%) as a yellowish oil. R_f = 0.45 (hexane/EtOAc 7:3, UV, $KMnO_4$, PAA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, J = 8.5 Hz, 1H), 6.89 (d, J = 8.4 Hz, 1H), 4.69 (d, J = 8.0 Hz, 0H), 3.79 (s, 1H), 3.53 (t, J = 8.6 Hz, 1H), 2.98 (s, 1H), 2.87 (dd, J = 8.1, 5.0 Hz, 1H), 2.48 (p, J = 7.0 Hz, 1H), 1.96 (s, 1H), 1.42 (s, 4H), 1.34 ppm (d, J = 7.5 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.9, 176.9, 159.0, 152.2, 145.3, 133.0, 127.0, 114.8, 99.9, 81.4, 55.4, 47.8, 46.1, 45.1, 34.4, 32.6, 31.1, 28.3, 25.6, 25.2 ppm. LRMS (DEP/EI-Orbitrap) m/z (%): 426.3 (5), 370.3 (100), 325.3 (90), 311.2 (80). HRMS (EI-Orbitrap) calcd for $C_{24}H_{30}N_2O_5^+$ [M]$^+$: 426.2155; found: 426.2155. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2976 (w), 2936 (vw), 1770 (w), 1698 (vs), 1610 cm^{-1} (vw).

***tert*-Butyl-(4*S**,4a*S**,7a*S**,7b*S**)-4-(4-chlorobutyl)-7b-(4-methoxyphenyl)-6-methyl-5,7-dioxo-1,4,4a,5,6,7,7a,7b-octahydro-2*H*-azeto[3,2-*e*]isoindole-2-carboxylate (8e).** Using **18b** and (*E*)-6-chloro-1-iodohex-1-ene according to general procedure E provided **8e** (0.32 mmol, 156 mg, 64%) as a yellowish oil. R_f = 0.4 (hexane/EtOAc 7:3, UV, $KMnO_4$, PAA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, J = 8.5 Hz, 2H), 6.90 (d, J = 8.5 Hz, 2H), 5.21 (s, 1H), 4.85 (s, 1H), 3.79 (s, 3H), 3.64 (d, J = 7.7 Hz, 1H), 3.55 (d, J = 8.2 Hz, 1H), 3.51 (t, J = 6.6 Hz, 2H), 3.04−2.92 (m, 4H), 2.34−2.24 (m, 1H), 1.77 (dqq, J = 19.3, 12.5, 6.0, 5.4 Hz, 4H), 1.57−1.45 (m, 2H), 1.43 ppm (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.6, 177.2, 158.9, 151.6, 138.4, 133.9, 126.9, 114.7, 110.8, 80.8, 61.7, 60.5, 55.4, 48.6, 47.6, 47.4, 31.6, 28.3, 25.1, 21.1, 14.3, 12.8 ppm. LRMS (DEP/EI-Orbitrap) m/z (%): 488.4 (2), 459.2 (2), 432.3 (100), 387.3 (80), 377.3 (50). HRMS (EI-Orbitrap) calcd for $C_{26}H_{33}ClN_2O_5^+$ [M]$^+$: 488.2078; found: 488.2059. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2972 (w), 2954 (w), 2936 (w), 1770 (w), 1696 cm^{-1} (vs).

***tert*-Butyl-(4a*S**,7a*S**,7b*R**)-7b-ethyl-3,6-dimethyl-5,7-dioxo-1,4,4a,5,6,7,7a,7b-octahydro-2*H*-azeto[3,2-*e*]isoindole-2-carboxylate (8f).** Using **18d** and 2-bromoprop-1-ene according to general procedure E provided **8f** (0.43 mmol, 144 mg, 86%) as a yellowish oil. R_f = 0.29 (20% EtOAc in hexane, UV, PAA, $KMnO_4$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.27 (d, J = 8.4 Hz, 1H), 3.65 (d, J = 8.4 Hz, 1H), 3.12−3.04 (m, 1H), 3.00 (s, 3H), 2.94 (d, J = 8.6 Hz, 1H), 2.44 (d, J = 2.6 Hz, 2H), 1.87 (s, 3H), 1.74−1.64 (m, 2H), 1.45 (s, 9H), 1.00 ppm (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.8, 177.7, 151.7, 138.4, 105.3, 80.8, 56.1, 44.1, 44.0, 42.3, 28.7, 28.5, 28.3, 25.5, 18.0, 8.4 ppm. LRMS (ESI-quadrupole pos) m/z (%): 335.2 (95), 279.1 (100). HRMS (ESI-quadrupole pos) calcd for $C_{18}H_{27}N_2O_4^+$: 335.1965; found: 335.1968.

***tert*-Butyl-(4a*S**,7a*S**,7b*S**)-3,6-dimethyl-5,7-dioxo-7*b*-(phenylethynyl)-1,4,4a,5,6,7,7a,7b-octahydro-2*H*-azeto[3,2-*e*]-isoindole-2-carboxylate (8g).** Using **18c** and 2-bromoprop-1-ene according to general procedure E provided **8g** (0.34 mmol, 136 mg, 67%) as a yellowish oil. R_f = 0.5 (hexane/EtOAc 7:3, UV, $KMnO_4$, PAA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45−7.38 (m, 2H), 7.36−7.28 (m, 3H), 4.84 (d, J = 8.0 Hz, 1H), 4.11 (d, J = 8.0 Hz, 1H), 3.39 (d, J = 8.5 Hz, 1H), 3.23 (ddd, J = 8.3, 6.3, 1.7 Hz, 1H), 3.01 (s, 3H), 2.87−2.77 (m, 1H), 2.51 (dd, J = 15.0, 1.7 Hz, 1H), 1.92 (s, 3H), 1.47 ppm (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.2, 175.8, 151.2, 135.7, 131.9, 128.7, 128.5, 122.4, 105.8, 88.5, 82.8, 81.4, 58.6, 46.3, 41.6, 36.8, 29.0, 28.4, 25.6, 17.8 ppm. HRMS (EI-Orbitrap) calcd for $C_{24}H_{26}N_2O_4^+$ [M]$^+$: 406.1893; found: 406.1895. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2976(w), 2960(w), 2932 (w), 2874 (vw), 1790 (w), 1776 (w), 1756 (w), 1698 cm^{-1} (vs).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b02786.

^{1}H and ^{13}C NMR spectra for all new compounds (PDF)

X-ray crystallographic data of compound **12g** (CIF)

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Notes

The authors declare no competing financial interest.

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(8) For recent examples of alkylideneazetidines, see: (a) Cainelli, G.; Galletti, P.; Garbisa, S.; Giacomini, D.; Sartor, L.; Quintavalla, A. *Bioorg. Med. Chem.* **2003**, *11*, 5391. (b) Zhao, G.-L.; Shi, M. *J. Org. Chem.* **2005**, *70*, 9975. (c) Lu, H.; Li, C. *Org. Lett.* **2006**, *8*, 5365. (d) Tiwari, D. K.; Shaikh, A. Y.; Pavase, L. S.; Gumaste, V. K.; Deshmukh, A. R. A. S. *Tetrahedron* **2007**, *63*, 2524. (e) Li, J.; Li, L.; Chen, Y.; Tan, H. *Microb. Cell Fact.* **2012**, *11*, 135. (f) Tehrani, K.; De Kimpe, N. *Curr. Org. Chem.* **2009**, *13*, 854. (g) Stanković, S.; D'hooghe, M.; Vanderhaegen, T.; Tehrani, K. A.; De Kimpe, N. *Synlett* **2014**, *25*, 75.
(9) Baumann, A. N.; Eisold, M.; Music, A.; Haas, G.; Kiw, Y. M.; Didier, D. *Org. Lett.* **2017**, *19*, 5681.
(10) Dejaegher, Y.; Kuz'menok, N. M.; Zvonok, A. M.; De Kimpe, N. *Chem. Rev.* **2002**, *102*, 29.
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(12) See fully detailed procedure in Supporting Information.
(13) Hornillos, V.; Giannerini, M.; Vila, C.; Fananas-Mastral, M.; Feringa, B. L. *Chem. Sci.* **2015**, *6*, 1394.
(14) Diastereoisomeric ratios were determined by ^{1}H NMR and GC, and the relative configuration was determined by X-ray measurements.
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(16) CCDC 1548836 (**12g**) contains the supplementary crystallographic data for this paper.

DOI: 10.1021/acs.joc.7b02786
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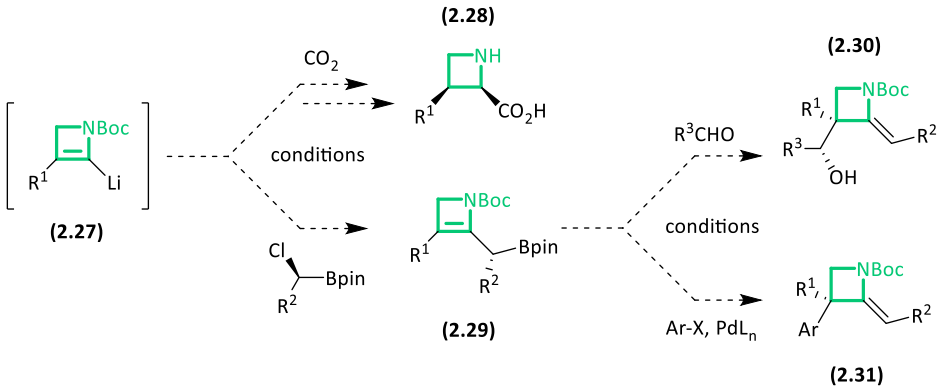
6 Outlook

With those new methods in hands, a further diversification of 2-azetine building blocks is imaginable, exemplified in two different pathways, both starting with the key intermediate **2.27** (**Scheme 28**). In the first, the azetinyllithium species **2.27** is trapped by a CO_2-source followed by an asymmetric hydrogenation and deprotection. This would ultimately lead to a new class of chiral amino acid azetidines **2.28**.



Scheme 28: Possible sequences towards a new library of functionalized azetidine-containing moieties.

The other pathway for the transformation of 2-azetines could be based on boron-related strategies, which were recently developed in the group of Didier (**Scheme 28**).[53] The previously formed azetinyllithium species **2.27** would undergo a stereospecific boron-homologation to form the azetinylmethylboronic ester **2.29**. In the next step, two routes towards the synthesis of functionalized alkylideneazetidines would be plausible. These two different approaches could open a wide library of unique structures such as **2.30**/**2.31** and allow access to further methods for the synthesis and transformation of this very important class of *N*-containing four-membered ring systems.

[53] M. Eisold; D. Didier, *Angew. Chem. Int. Ed.* **2015**, *54*, 15884; M. Eisold; D. Didier, *Org. Lett.* **2017**, *19*, 4046.

Chapter III

Thiete Dioxides

7 Introduction

The four-membered analogues to cyclobutenes and 2-azetines, containing a fully oxidized sulfur atom are called thiete dioxides (**3.01**) (**Figure 7**). Just like for the other unsaturated four-membered rings, the inherent ring strain is one of the key properties of this structure. Moreover, the sp^2-carbon next to the sulfur is polarized and therefore activated for further transformations. Not only the difference in electronegativity between sulfur and carbon, but also the presence of oxygen atoms as directing group, plays a role in this unique reactivity. Nevertheless, thiete dioxides are difficult to access and therefore scarcely examined. To the best of our knowledge, no thiete dioxide structure can be found in natural occurring compounds and the only bioactive thiete dioxide was synthesized by the group of Didier.[54] However, some of their functionalized saturated derivatives occur in nature or demonstrate their interesting properties in life-science.

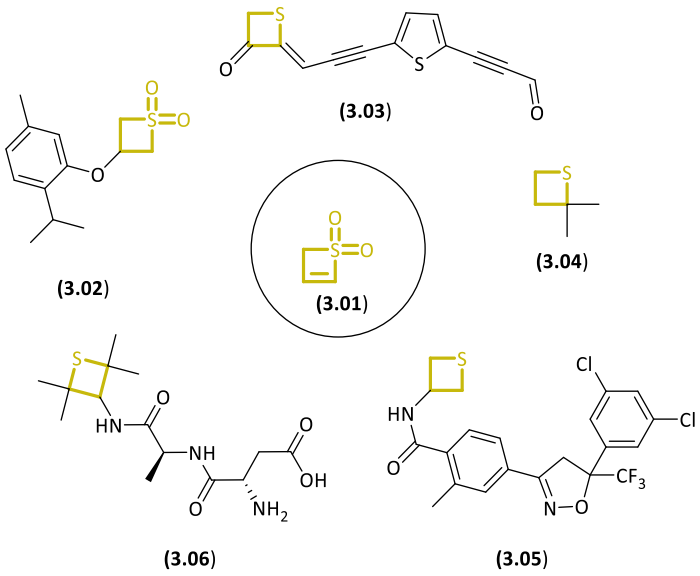


Figure 7: Thiete dioxide and some relevant structures with *S*-containing four-membered rings.

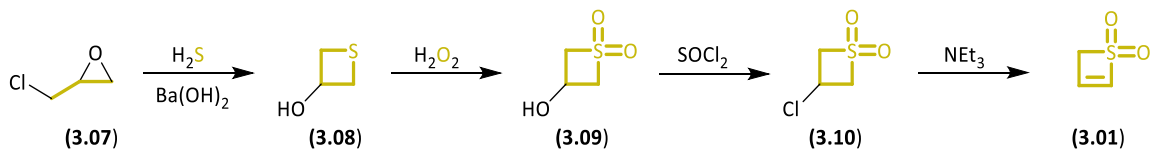
For instance, the synthetic thietane dioxide **3.02** shows high antidepressant activity in combination with low toxicity.[55] The naturally occurring alkylidenethietane **3.03** was isolated in 1975 from the roots of *Cullumia squarrossa*.[56] Unfortunately, no bioactivity experiments have been conducted so far. The saturated and volatile thietane **3.04** was found in the gland secretions of a mink and is believed to be used in communication across species, sex and age.[57] Thietane **3.05** is known as a pesticide and the

[54] M. Eisold; A. Müller-Deku; F. Reiners; D. Didier, *Org. Lett.* **2018**, *20*, 4654.
[55] E. E. Klen; I. L. Nikitina; N. N. Makarova; A. F. Miftakhova; O. A. Ivanova; F. A. Khaliullin; E. K. Alekhin, *Pharm. Chem. J.* **2017**, *50*, 642.
[56] F. Bohlmann; A. Suwita, *Chem. Ber.* **1975**, *108*, 515.
[57] J.-X. Zhang; L. Sun; Z.-B. Zhang; Z.-W. Wang; Y. Chen; R. Wang, *J. Chem. Ecol.* **2002**, *28*, 1287.

highly substituted thietane **3.06** is used as a sweetener.[58] Thiete dioxides can be suitable precursors in the formation of new and diverse thietane-containing molecules although their compound class is underrepresented in the literature. Therefore, new tools for their formation are required, as well as their implication in drug discovery.

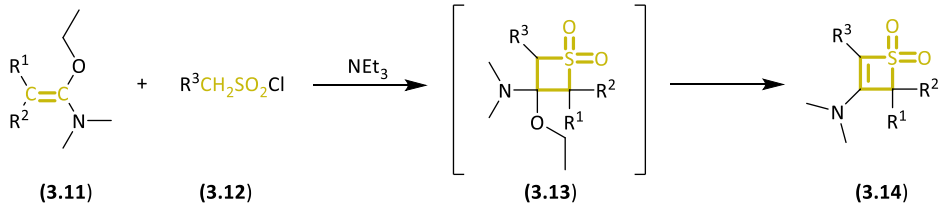
7.1 Synthesis of Thiete Dioxides

One of the first reported synthesis of the thiete dioxide core was achieved by Dittmer and Christy in 1962 (**Scheme 29**).[59] Their route disclose the use of epichlorohydrin (**3.07**) as a starting material, that was treated with a basic saturated hydrogen sulfide solution to get to 3-thietanol (**3.08**). After an oxidation with hydrogen peroxide the 3-thietanol dioxide (**3.09**) was converted into the corresponding chloride **3.10** with thionyl chloride. A final elimination step with triethylamine afforded the desired thiete dioxide **3.01** in good yield.



Scheme 29: First reported synthesis of thiete dioxide **3.01** in 1962 by Dittmer and Christy.

In the 1960s, many publications appeared with different or similar attempts for the synthesis of thiete dioxides.[60] One year after the first discovery of Dittmer in 1962, Hasek and his group used a [2+2]-cycloaddition strategy, where they used *in situ* generated sulfenes and ketene *O*,*N*- or *N*,*N*-acetals for the formation of thiete dioxides (**Scheme 30**).[61]



Scheme 30: [2+2]-Cycloaddition between in situ generated sulfenes and ketene *O*,*N*-acetal towards the formation of thiete dioxides.

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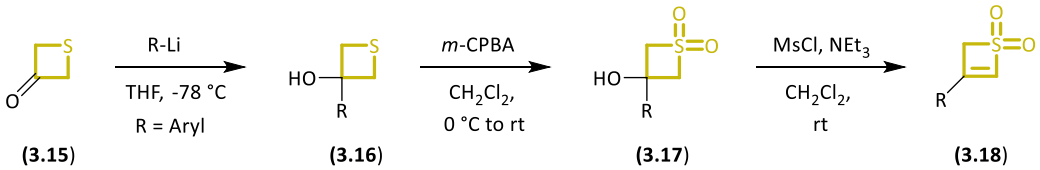
[58] P. Renold; W. Zambach; P. Maienfisch; M. Muehlebach, PCT Int. Appl. WO2009080250; T. M. Brennan; M. E. Hendrick, U.S. 4411925.
[59] D. C. Dittmer; M. E. Christy, *J. Org. Chem.* **1961**, *26*, 1324.
[60] W. E. Truce; J. R. Norell; J. E. Richman; J. P. Walsh, *Tetrahedron Lett.* **1963**, *25*, 1677; G. Opitz; H. Schempp, *Liebigs Ann. Chem.* **1965**, *684*, 103; W. E. Truce; D. J. Abraham; P. N. Son, *J. Org. Chem.* **1967**, *32*, 990; J. N. Wells; F. S. Abbott, *J. Med. Chem.* **1966**, *9*, 489.
[61] R. H. Hasek; P. G. Gott; R. H. Meen; J. C. Martin, *J. Org. Chem.* **1963**, *28*, 2496; R. H. Hasek; R. H. Meen; J. C. Martin, *J. Org. Chem.* **1965**, *30*, 1495.

The *in situ* generated sulfene can be easily prepared by the treatment of methansulfonylchloride with triethylamine. In the example of Hasek, depicted in **Scheme 30**, a ketene *O*,*N*-acetal (**3.11**) was used for the intermediary formation of the thietane **3.13**. Following a final β-elimination, the desired thiete dioxide **3.14** was obtained in moderate yield.

For the synthesis of several grams of thiete dioxides, the robust procedure of Dittmer and co-worker for the synthesis of thiete 1,1-dioxide and 3-chlorothiete 1,1-dioxide should be considered.[62] In this work, a halogenation with elemental chlorine of thietane dioxide followed by an elimination step with triethylamine produces the aforementioned thiete dioxides in good to high yields.

More recently, Burkhard demonstrated a straightforward synthesis of 3-aryl-thiete dioxides (**3.18**) (**Scheme 31**).[63] In his work, Burkhard used the commercially available thietan-3-one (**3.15**) and treated the latter with different lithiated arenes. These generated thietanoles **3.16** were then converted into the corresponding sulfones **3.17** by using *m*-CPBA as an oxidant. Finally, the desired 3-aryl-thiete dioxides **3.18** were obtained by a consecutive mesylation/β-elimination sequence using triethylamine and mesylchloride.



Scheme 31: Straightforward synthesis of 3-aryl-thiete dioxides by Burkhard.

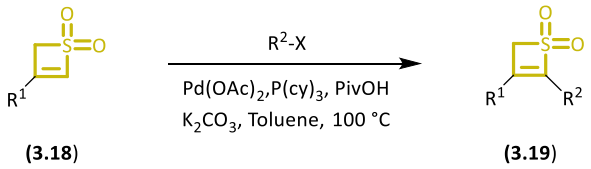
As each step is high yielding, this procedure was adopted and expanded for the synthesis of functionalized thiete dioxides as well as for their further transformations in this work.

7.2 C-H Activation of Thiete Dioxides

The well-known and extensively applied strategy of C-H activation has become a key concept for synthetic chemists all over the world.[64] Especially its use in late state functionalization drives a continuous interest in C-H activation.[65] For a replacement of a carbon-hydrogen bond with a new bond (for example to another carbon), the C-H bond needs to be activated, as this type of bond is known to be quite unreactive. As C-H bonds are ubiquitous in organic molecules, the control of the

[62] T. C. Sedergran; D. C. Dittmer, *Org. Synth.* **1984**, *62*, 210.
[63] J. A. Burkhard, *New Opportunities for Four- Membered Heterocycles: From Synthetic Studies to Unique Applications in Drug Discovery*. PhD Thesis, ETH Zürich, **2011**, DOI: 10.3929/ethz-a-006834147.
[64] For a review see: J. F. Hartwig, *Nature* **2008**, *455*, 314; K. Godula; D. Sames, *Science* **2006**, *5770*, 67; R. Giri; B.-F. Shi; K. M. Engle; N. Maugel; J.-Q. Yu, *Chem. Soc. Rev.* **2009**, *38*, 3242.
[65] P. A. Wender; M. K. Hilinski; A. V. W. Mayweg, *Org. Lett*. **2005**, *7*, 79; D. J. Abrams; P. A. Provencher; E. J. Sorensen, *Chem. Soc. Rev.* **2018**, *47*, 8925; M. S. Chen; M. C. White, *Science* **2007**, *5851*, 783.

regioselectivity plays the major role and therefore, has to be controlled using directing groups attached to the target molecule.[66] In most cases, directed C-H-bond activation is catalyzed by transition metals.[67] Recently, the group of Didier performed a palladium catalyzed C-H activation on thiete dioxides (**3.18**), in which the unique structural properties of polarization in combination with the directing group (SO_2) were exploited (**Scheme 32**).[68] This led to the unprecedented bis-functionalized structures **3.19**.



Scheme 32: C-H Activation of thiete dioxides towards disubstituted thiete dioxides by Didier.

This robust tool was further used to expand the scope of this transformation, but also to show possible applications of disubstituted thiete dioxides.

7.3 (2+3)-Cycloadditions of Thiete Dioxides

Cycloadditions can be the right choice to enhance the complexity of an existing system. Particularly, (2+3)-cycloadditions were extensively applied in organic chemistry and will be described more detailed in **Chapter II** "**(2+3)-Cycloadditions of 2-Azetines**".

1,3-Dipolar cycloadditions of thiete dioxides are rarely described in literature. One of these studies describes the crystal structure of an isoxazoline thietane.[69] Another pioneer work was done by the research groups of Rastelli and Micheli, as they reported for the first time 1,3-dipolar cycloadditions of nitrones, nitrile oxides and diazoalkanes with thiete 1,1-dioxide (**3.01**) (**Scheme 33**).[70] A special focus was set on the regiochemical behaviour of the unsubstituted thiete 1,1-dioxide. When nitrile oxides or nitrones were used as 1,3-dipoles only one regioisomer (**3.21**) was observed, whereas a mixture of **3.20** and **3.21** (approximately 1:1) was detected, conducting the cycloaddition reaction with diazoalkanes.

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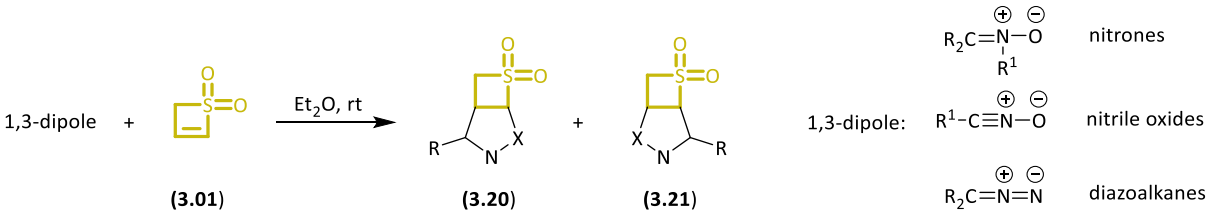
[66] For a review on bidentate directing groups see: G. Rouquet; N. Chatani, *Angew. Chem. Int. Ed.* **2013**, *52*, 11726; S. D. Sarkar; W. Liu; S. I. Kozhushkov; L. Ackermann, *Adv. Synth. Catal.* **2014**, *356*, 1461; J. Liu; G. Chen; Z. Tan, *Adv. Synth. Catal.* **2016**, *358*, 1174; L. M. Chapman; J. C. Beck; L. Wu; S. E. Reisman, *J. Am. Chem. Soc.* **2016**, *138*, 9803; A. Biafora; B. A. Khan; J. Bahri; J. M. Hewer; L. J. Goossen, *Org. Lett.* **2017**, *19*, 1232. H. M.-F. Viart; A. Bachmann; W. Kayitare; R. Sarpong, *J. Am. Chem. Soc.* **2017**, *139*, 1325.

[67] L. Ackermann; J. Pospech, *Org. Lett.* **2011**, *13*, 4153; Z.-Y. Gu; C.-G. Liu; S.-Y. Wang; S.-J. Ji, *J. Org. Chem.* **2017**, *82*, 2223; T. Yamamoto; A. Ishibashi; M. Suginome, *Org. Lett.* **2017**, *19*, 886.

[68] M. Eisold; A. Müller-Deku; F. Reiners; D. Didier, *Org. Lett.* **2018**, *20*, 4654.

[69] G. J. Gainsford; A. D. Woolhouse, *Acta Crystallogr., Sect. E: Struct. Rep. Online* **2002**, *58*, o715.

[70] P. G. De Benedetti; S. Quartieri; A. Rastelli; M. de Amici; C. de Micheli; R. Gandolfi; P. J. Gariboldi, *Chem.Soc., Perkin Trans.*2 **1982**, 95



Scheme 33: Different 1,3-dipolar cycloadditions with thiete 1,1-dioxide and the imaginable regiochemical outcome.

Consequently, some questions arose for this work: Can this method open the access to a new group of thietane dioxides? What is the regiochemical outcome of such reaction? Is there any application for fused thietane dioxides? These questions will be addressed in the result section "**Chemodivergent and Stereoselective Access to Fused Isoxazoline Azetidines and Thietanes through [3+2]-Cycloadditions**".

7.4 Atropisomerism

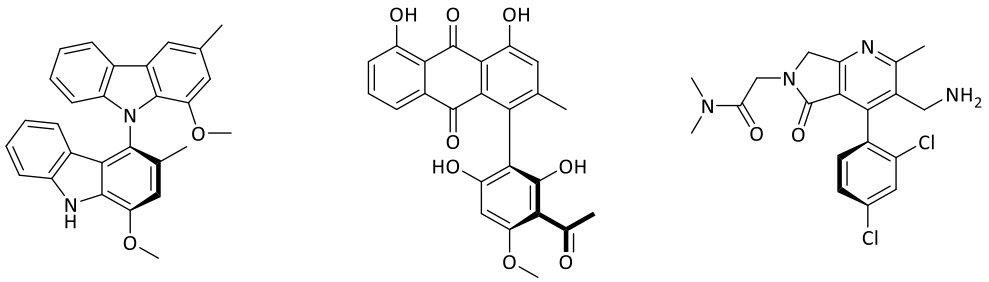
Atropisomerism is a type of stereochemistry in a molecular system that is caused by a significantly reduced free rotation around a single bond. This rotational hindrance results in axial chirality, allowing two different stereoisomers to be isolated at a given temperature.[71] Remarkably, atropisomers are often found in natural products or in drugs and are therefore of great importance in medicinal chemistry and in the development of new drugs.[72] Several representative examples are depicted in **Figure 8**. For instance, murrastifoline F (**3.22**), an alkaloidal component of *Murraya koenigii* shows that this type of stereochemistry is not limited to carbon-carbon bonds.[73] Another compound is knipholone (**3.23**), which was isolated from *Kniphofia foliosa*, with varying degrees of enantiomeric purity.[74]

[71] G. H. Christie; J. Kenner, *J. Chem. Soc., Trans.* **1922**, *121*, 614; P. Llody-Williams; E. Giralt, *Chem. Soc. Rev.* **2001**, *30*, 145; M. Ōki in *Topics in Stereochemistry* (Eds.: N. L. Allinger, E. L. Eliel, S. H. Wilen), John Wiley & Sons, Inc, Hoboken, NJ, USA, **1983**, 1-81.

[72] For a short review see: J. Clayden; W. J. Moran; P. J. Edwards; S. R. LaPlante, *Angew. Chem. Int. Ed.* **2009**, *48*, 6398; S. R. LaPlante; P. J. Edwards; L. D. Fader; A. Jakalian; O. Hucke, *ChemMedChem* **2011**, *6*, 505; A. Zask; J. Murphy; G. A. Ellestad, *Chirality* **2013**, *25*, 265; J. E. Smyth; N. M. Butler; P. A. Keller, *Nat. Prod. Rep.* **2015**, *32*, 1562; P. W. *Glunz, Bioorg. Med. Chem. Lett.* **2018**, *28*, 53; S. T. Toenjes; J. L. Gustafson, *Future Med.Chem.* **2018**, *10*, 409.

[73] C. Ito; Y. Thoyama; M. Omura; I. Kajiura; H. Furukawa, *Chem. Pharm. Bull.* **1993**, *41*, 2096.

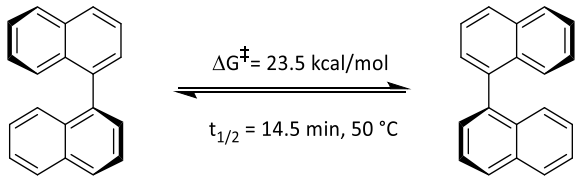
[74] E. Dagne; W. Steglich, *Phytochemistry* **1984**, *23*, 1729; J. Mutanyatta; M. Bezabih; B. M. Abegaz; M. Dreyer; R. Brun; N. Kocher; G. Bringmann, *Tetrahedron* **2005**, *61*, 8475.



murrastifoline F (3.22) | **knipholone (3.23)** | **BMS-767778 (3.24)**

Figure 8: Atropisomerism in selected naturally occurring compounds and drugs.

The not naturally occurring BMS-76778 (**3.24**) can efficiently inhibit the dipeptidyl peptidase-4 (DPP4).[75] Atropisomers not only occur in drug discovery, they are also widely used as chiral catalysts.[76] Certainly, the most famous example are the atropisomers of the 1,1'-binaphthyl series, with a racemization half-life of 14.5 minutes at 50 °C ($\Delta G^{\ddagger}$ = 23.5 kcal/mol) (**Scheme 34**).[77]



(*S*)-(3.25) **(*R*)-(3.25)**

Scheme 34: Isomerization reaction of (*S*) to (*R*)-1,1'-binaphthyl.

Many different methods exist for the synthesis of catalysts with inherent axial chirality.[78] The key requirement for axially chiral molecules is, of course, a strong steric hindrance between two groups connected by an axis. Nevertheless, some other interactions, especially the non-covalent π-

[75] R. P. Brigance; H. J. Chao; A. Fura; T. Harrity; J. Marcinkeviciene; S. P. O`Conner; J. K. Tamura; D. Xie; Y. Zhang; H. E. Klei; K. Kish; C. A. Weigelt; H. Turdi; A. Wang; R. Zahler; M. S. Kirby; L. G. Hamann; W. Meng, *J Med Chem.* **2010**, *53*, 5620; Y. Wang; L. M. Simpkins; R. P. Brigance; W. Meng; A. Wang; M. S. Kirby; C. A. Weigelt; L. G. Hamann; S. P. O´Conner, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 6273; Y. Wang; W. Wang; J. Fevig; J. Feng; A. Wang; T. Harrity; D. Egan; N. Morgan; M. Cap; A. Fura; H. E. Klei; K. Kish; C. Weigelt; L. Sun; P. Levesque; F. Moulin; Y.-X. Li; R. Zahler; M. S. Kirby; L. G. Hamann; P. Devasthale, *J. Med. Chem.* **2013**, *56*, 7343.

[76] L. Pu, *Chem. Rev.* **1998**, *98*, 2405; A. Joncour; A. Décor, S. Thoret; A. Chiaroni; O. Baudoin, *Angew. Chem. Int. Ed.* **2006**, *45*, 4149. Y.-B. Wang; P. Yu; Z.-P. Zhou; J. Zhang; J. J. Wang; S.-H. Luo; Q.-S. Gu; K. N. Houk; B. Tan, *Nat. Catal.* **2019**, *2*, 504;

[77] A. S. Cooke; M. M. Harris, *J. Chem. Soc.* **1963**, *0*, 2365;

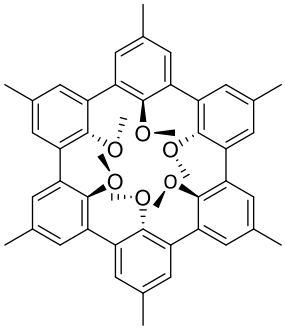
[78] For a review on the synthesis of chiral biaryls see: G. Bringmann; A. J. P. Mortimer; P. A. Keller; M. J. Gresser; J. Garner; M. Breuning, *Angew. Chem. Int. Ed.* **2005**, *44*, 5384; Y.-S. Jang; Ł. Woźniak; J. Pedroni; N. Cramer, *Angew. Chem. Int. Ed.* **2018**, *57*, 12901; C. G. Newton, E. Braconi, J. Kuziola, M. D. Wodrich, N. Cramer, *Angew. Chem. Int. Ed.* **2018**, *57*, 11040; S. Song; J. Zhou; C. Fu; S. Ma, *Nat. Commun.* **2019**, *10*, 507.

interactions, play an important role.[79] This usually weak interaction can be used for host guest systems like molecular tweezers.[80]

In summary, the importance of axial chirality can be found in many areas of chemistry and is not limited to the synthesis of novel catalysts but can also applied to drug synthesis. With this in mind, one of the objectives was the synthesis of disubstituted thiete dioxides possessing chirality through atropisomerism.

7.5 Spherands - Macrocyclic Receptors

Spherands can be classified as macrocyclic ligands with limited conformational flexibility. One of the few spherands ever described is shown in **Figure 9**. The first synthesis of this spherand (**3.26**) was reported by Donald Cram in 1979.[81] This pioneering work was later rewarded with a Nobel prize for Chemistry in 1987 with Charles Pedersen and Jean-Marie Lehn. Spherands present a high rigidity, preorganization and an electron-pair-lined cavity.[82] Consequently, they are strong complexation receptors for ions, such as lithium, sodium or potassium. Indeed, the binding constant for lithium ions is one of the strongest known so far. However, no organic molecule can be trapped, due to the small cavity of the host system.[83]



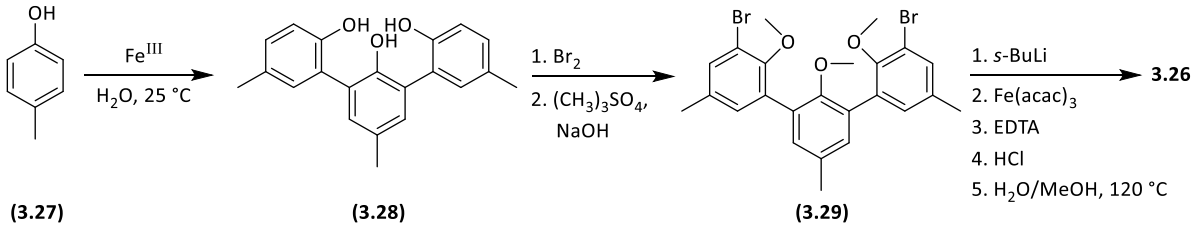
(3.26)

Figure 9: Prototypical spherand.

The typical synthesis of spherand **3.26** was described by Cram and it involves three steps, starting from *p*-cresol (**3.27**), with an overall yield of 6.3% (**Scheme 35**). In the first step, *p*-cresol was oxidatively

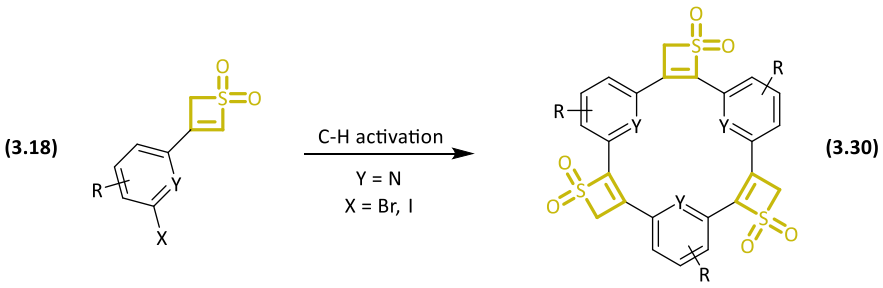
[79] For a review on non-covalent π-interactions see: A. J. Neel; M. J. Hilton; M. S. Sigman; F. D. Toste, Nature 2017, 543, 637.
[80] For review see: J. Leblond; A. Petitjean, *ChemPhysChem* **2011**, *12*, 1043 and F.-G. Klärner; T. Schrader, *Acc. Chem. Res*. **2013**, *46*, 967; M. Bosquez; A. Cambray; A. Miralrio; R.-M. del Castillo; R. Salcedo, *Comput. Theor. Chem.* **2017**, *1115*, 335.
[81] D. J Cram; T. Kaneda; R. C. Helgeson; G. M. Lein, *J. Am. Chem. Soc.* **1979**, *101*, 6752.
[82] D. J. Cram, *Angew. Chem. Int. Ed.* **1986**, *25*, 1039; L. F. Lindoy; K.-M. Park; S. S. Lee in *Supramolecular Chemistry* (Eds.: P. A. Gale, J. W. Steed), John Wiley & Sons, Ltd, Chichester, UK, **2012**, 7017.
[83] G. M. Lein; D. J. Cram, *J. Chem. Soc. Chem. Commun.* **1982**, *5*, 301; D. J. Cram; G. M. Lein; T. Kaneda; R. C. Helgeson; C. B. Knobler; E. Maverick; K. N. Trueblood, *J. Am. Chem. Soc.* **1981**, *103*, 6228.

coupled in the presence of iron^{III} to the triphenoxy moiety **3.28**. In the second step, an *ortho*-bromination was carried out, followed by a methylation of the free alcohol groups. A lithiation of structure **3.29** followed by reaction with $Fe(acac)_3$ led to the desired spherand **3.26**. Due to the use of *s*-BuLi, the spherand had to be treated with EDTA-solution to get rid of remaining lithium ions.



Scheme 35: Synthesis of spherand **3.26** (see **Figure 9**).

Following these early findings, several other spherands were synthesized and characterized with respect to host-guest interactions with different ions.[84] Motivated by these unusual structures, the synthesis of thiete based spherand analogues such as **3.30** was envisioned (**Scheme 36**). The previously described C-H activation of thiete dioxides was chosen as the appropriate tool for this purpose.



Scheme 36: Possible C-H activation of thiete dioxides towards thiete based spherand analogues.

[84] D. J. Cram; T. Kaneda; G. M. Lein; R. C. Helgeson, *J. Chem. Soc. Chem. Commun.* **1979**, *21*, 948b; D. J. Cram; R. A. Carmack; M. P. DeGrandpre; G. M. Lein; I. Goldberg; C. B. Knobler; E. F. Maverick; K. N. Trueblood, *J. Am. Chem. Soc.* **1987**, *109*, 7068; D. J. Cram, R. A. Carmack; R. C. Helgeson, *J. Am. Chem. Soc.* **1988**, *110*, 571.

8 Results

8.1 Chemodivergent and Stereoselective Access to Fused Isoxazoline Azetidines and Thietanes through [3+2]-Cycloadditions

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Chemodivergent and Stereoselective Access to Fused Isoxazoline Azetidines and Thietanes through [3 + 2]-Cycloadditions

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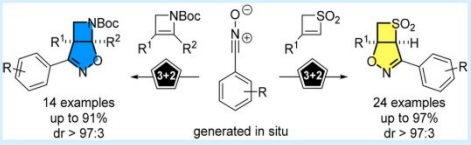
Supporting Information

ABSTRACT: By combining efficient methodologies for the preparation of substituted azetines and thietes with a highly regio- and diastereoselective [3 + 2]-cycloaddition, a straightforward pathway for the synthesis of fused isoxazoline azetidines and thietanes has been designed. With minimal steps and starting from commercial sources, a new library of elaborated architectures was synthesized opening up a new class of molecules with large potential in pharmacology. Finally, a retro [2 + 2]-cycloaddition leading to substituted isoxazoles is described.



Driven by the ever-increasing pace of drug discovery, small rings, particularly strained cyclobutenes and their heterocyclic analogs azetines and thietes, have gained increased attention due to their great range of reactivity. The unique possibilities afforded by strained bonds in organic synthesis have been dignified for decades. Recent advances by the group of Baran and Carreira demonstrated the tremendous significance of strained bioisosteres such as propellanes,[1] azetidines,[2] and oxetanes[3] in synthesis. Above all, there is an urgent need to bring such groups directly and economically onto core scaffolds. Driven by the need to push the boundaries of unexplored structural libraries, we recently reported the synthesis of new building blocks containing cyclobutenes,[4] azetines,[5] and thietes.[6] These allowed us to develop new methodologies toward the stereocontrolled formation of alkylidenecyclobutanes,[7] alkylideneazetidines,[8] and cyclopropylketones[9] formed by oxidative ring contraction of cyclobutenes.

Outlined herein is the stereoselective formation of fused isoxazoline derivatives containing azetidine- and thietane-cores by [3 + 2] dipolar cycloadditions with nitrile oxides.[10] Notably, besides the well-known β-lactams penicillin and cephalosporin, isoxazoles, isoxazolines, and the fully saturated isoxazolidine variants can be found in numerous bioactive substances[11] (Figure 1). Among these very important classes of compounds, several fused azetidine-containing substances have shown interesting tumor activities.[12] In addition, thietane cores present attractive pharmacological properties and have been used as pesticides,[13] sweetener,[14] and anticancer[15] drugs. Moreover, the oxidized thietanes were described as powerful enzyme inhibitors,[16] antidepressants,[17] antitumor agents,[18] and herbicides.[19]

Only a few reports describe the formation of the isoxazoline core fused with an azetidine/thietane[20] moiety, and with restrained variety and efficiency. To fill this gap, our general sequence for generating complexity in a modular fashion starts with the formation of substituted unsaturated azetines and thietes. In our previous work we used organometallic species such as

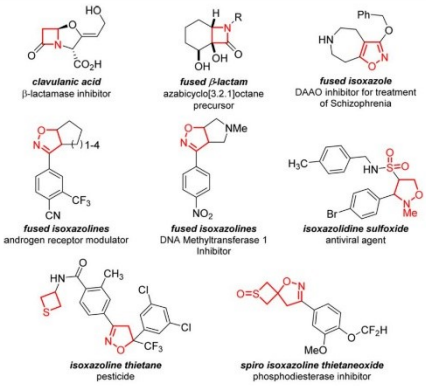


Figure 1. Few examples of biologically active fused four-and five-membered heterocycles.

Grignard or lithium reagents for 1,2-nucleophilic additions on commercially available 3-thietanone[6] **1** and 1-Boc-3-azetidinone[5] **4** (Scheme 1) to obtain the corresponding tertiary alcohols.

Following a sequence that we recently reported,[6] thiete derivatives **3** were accessed in good yields (51 to 78%) through intermediate formation of tertiary alcohols **2**. Similarly, azetines **6** were synthesized in good to excellent yields (66 to 98%), in a sequence based on a key α-lithiation of methylated alcohols **5**.[21] 3-Azetinyllithium intermediates can then be used in electrophilic trapping reactions with H_2O or with boron isopropoxide. Room temperature stable organoboronates were also used in Suzuki–

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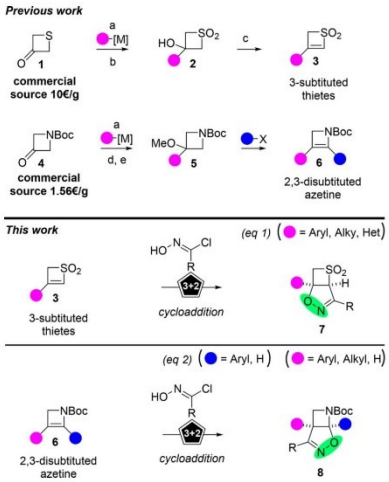
Scheme 1. Previous Work on Functionalization of Azetines and Thietes and Their Transformation in [3 + 2]-Cycloadditions[a]

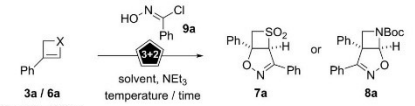


[a]For **3**/**6**: (a) Organolithium (M = Li) or organomagnesium (M = MgBr) (1.2 equiv); reactions were performed in THF at −30 °C. For **3**: (b) *m*CPBA (2 equiv), CH_2Cl_2, 0 °C to rt. (c) MsCl (3 equiv), NEt_3 (3 equiv), CH_2Cl_2, rt. For **6**: (d) NaH, MeI, THF, 0 °C to rt. (e) *s*-BuLi (2 equiv), TMEDA (1 equiv), THF, −78 °C.

Miyaura cross-coupling, affording 2,3-bis-arylated azetines.[5] With efficient access to diversely substituted azetines **6** and thietes **3**, dipolar [3 + 2]-cycloadditions were undertaken.

To tackle the ambitious formation of complex fused ring systems, we first performed optimizations to find adequate conditions for the [3 + 2]-cycloaddition. Therefore, different solvents, temperatures, techniques, and equivalents of the unexpansive or easily prepared[22] *N*-hydroxybenzimidoyl chloride **9a** were tested (Table 1). While lower temperature did not afford full conversions over prolonged periods of time (entries 4 and 5),

Table 1. Optimization in [3 + 2]-Cycloadditions



entry	solvent	NEt_3 (equiv)	temp (°C)	**9** (equiv)	time (h)	conv (%)[a] **7a**/**8a**
1	Et_2O	1	80[b]	1	16	30/25
2	Et_2O	2	80[b]	2	16	89/85
3	Et_2O	4	80[b]	2	16	94/90
4	Et_2O	4	40[b]	2	16	78/77
5	Et_2O	4	rt	2	16	68/55
6	Et_2O	6	80[b]	2	16	92/93
7	Et_2O	6	100[c]	2	2	90/89
8	CH_2Cl_2	**6**	**100**[c]	**3**	**1.5**	**97/95**
9	EtOAc	6	100[c]	3	1.5	80/81

[a]Determined by GC. [b]Pressure tube. [c]Microwave irradiations (6 bar).

reactions performed at 80 to 100 °C proved to give the expected products at higher rates. Running the transformations in pressure tubes greatly improved the overall conversions, but optimal yields were obtained under microwave irradiations (entries 1−4/6 and 7−9). Finally, the introduction of an excess of **9a** (3 equiv) proved to be inevitable, mostly due to its dimerization. It became apparent that the amount of triethylamine plays an important role, being essential to the formation of the 1,3-dipole during the reaction. Reaction times to completion were further improved by switching the solvent to dichloromethane (entry 8), while similar rates were observed when employing ethyl acetate instead of diethyl ether.

With an optimized cycloaddition sequence in hand, 3-phenylthiete **3a** was first used to establish the scope of 1,3 dipoles **9a−g** (for details, see Supporting Information, SI) and to investigate the regioselectivity and diastereoselectivity of the fused thietanes (Scheme 2). Electron-donating groups on the hydroxyl-imidoylchloride increased the yield (**7b**, 97%), whereas the presence of electron-withdrawing substituents tended to decrease the conversion into the desired compounds (**7c**, 90%). Halo-substituted hydroxyl-imidoylchloride furnished **7d−e** in good yields (up to 90%). Due to the monosubstitution of the dipolarophiles **3**, only one regioisomer (see below) together with diastereoselectivity higher than 97% was obtained. With 3-naphtylthiete **3b**, good to excellent yields were isolated (**7h−j**, up to 92%).

The scope of the transformation was established by employing a range of different substituted 3-thietes such as 4-methoxy-phenyl **3c**, 4-fluoro-phenyl **3d**, 3-bromo-phenyl **3e**, and 4- or 2-biphenyl **3f/g**, leading to a small library of unprecedented fused thietanes in good to excellent yields (**7k−v**). It is worth noting that, using **3i** led to **7w** in moderate yields (57%), X-ray crystallography supported the proposed stereochemical outcome of this transformation. Taking advantage of a simple access to substituted thietes that we developed previously, we pushed the method further by engaging 3-heteroarylated thiete **3j** with *N*-hydroxybenzimidoyl chloride **9a** and *N*-hydroxy-4-methoxybenzimidoyl chloride **9b** to isolate **7y−z** in good to excellent yields (84 to 94%). Switching the group on position 3 for a butyl chain (**3l**) furnished the corresponding thietanes **7ab−ac** in 84% and 94% yields, respectively. Unfortunately, [3 + 2] strategies on 2,3-disubstituted-thietes did not afford the desired fused ring systems.

According to this simple transformation, we started to explore [3 + 2]-cycloadditions with 3-substituted azetines.

Therefore, we used azetidines **5a−e** to form mono-substituted azetines, employing a deprotonation/elimination/deprotonation/electrophilic-trapping sequence (Scheme 3). Those azetines were directly engaged without prior purification in [3 + 2]-cycloadditions with hydroxyl-imidoyl chlorides **9a−b**. Due to the rearrangement and ring opening under slightly acidic conditions, no further purification of the 3-substituted azetines were implemented. However, for compound **8g** an isolation of the 3-azetine was possible, thus showing the efficiency of the [3 + 2]-cycloaddition by a very good yield of 91%. Without any purification at intermediate steps, arylated building blocks **5a−d** afforded sophisticated architectures **8a−f/h** in moderate to good yields as a single regioisomer and with high stereochemical ratios. It is also worth noting that the regiochemistry appears to be inverse compared to the thietes. Looking at the different regiochemical outcomes of thietes and azetines after successful [3 + 2]-cycloaddition with nitrile oxides **9a−g**, a side-inversed attack of the 1,3-dipole was observed (Figure 2). First, due to different electronic effects on the carbon atoms 2 and 3, we propose a favored approach with the congruent charge (±) of the

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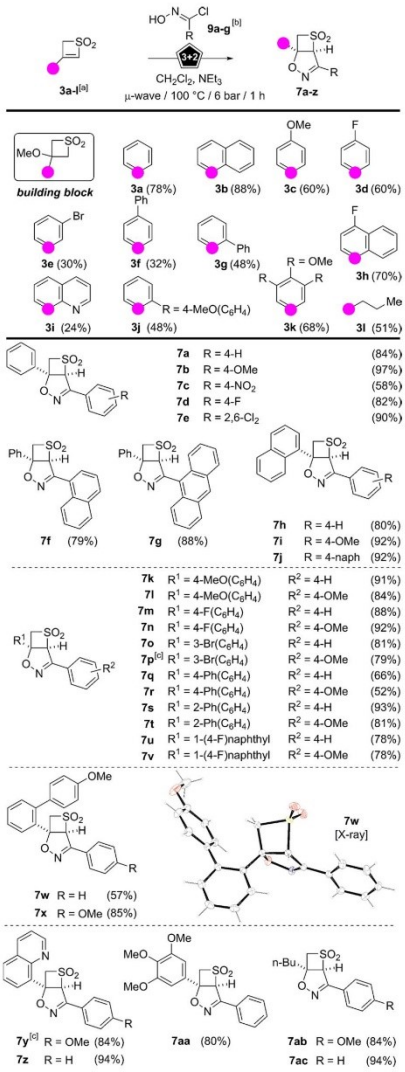
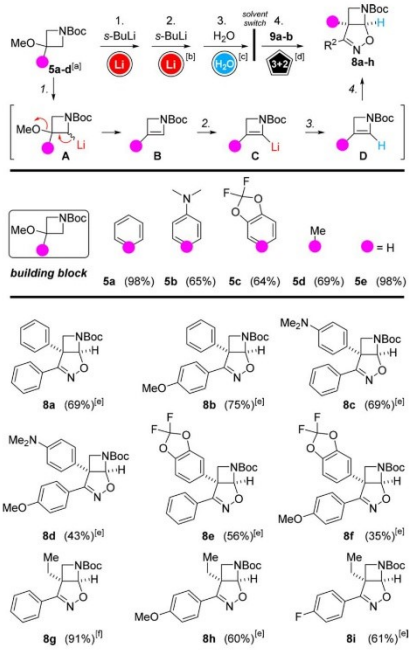
Scheme 2. [3 + 2]-Cycloaddition Towards Fused Isoxazoline Thietanes



[a]0.1 mmol scale. [b]1,3-dipole (3 equiv), CH_2Cl_2, 100 °C, 6 bar, 1 h, microwave irradiations. [c]X-ray structures are reported in the SI.

1,3-dipole to the dipolarophile, thus forming a six-electron Hückel aromatic transition state.[2,3] Second, the Boc-group in azetine structures presumably reinforces the regiocontrol through favorable steric repulsion, the transition state of which being potentially stabilized by electrostatic interactions between the two aromatic moieties and leading to one regioisomer.

Scheme 3. Lithiation/Electrophilic-Trapping/[3 + 2]-Cycloaddition Sequence Towards Fused Isoxazoline Azetidines



[a]0.5 mmol scale. [b]s-BuLi (2.0 equiv), TMEDA (2.0 equiv) THF, −78 °C, 1 h. [c]Excess, −78 °C to rt. [d]1,3-Dipole (2.5 equiv), CH_2Cl_2, 100 °C, 6 bar, 1 h, microwave irradiations. [e]Isolated yield over all steps. [f]Isolated yield for step 4.

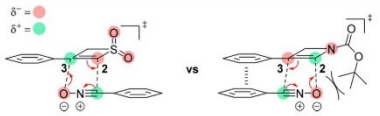


Figure 2. Proposed transition states for the [3 + 2]-cycloaddition with nitrile oxide **9a**.

Next, 2,3-disubstituted azetines were examined. In a similar sequence, azetidines **5** were employed in the formation of the lithiated intermediate **C**, and the corresponding boronate species were generated by addition of boron isopropoxide (Scheme 4). A subsequent Suzuki cross-coupling was performed in the presence of $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (4 mol %) and the appropriate coupling partner (aryl iodides). Without additional purification, the corresponding 2,3-disubstituted azetines were subjected to [3 + 2]-cycloadditions under optimized conditions. With aryl groups on both sides, poor control of the regioselectivity was witnessed, as a mixture of two regioisomers **10a/b** (1:4.5) and **11a/b** (1:3) was isolated, showing, however, excellent diastereoisomeric ratios. This observation suggests that electron densities of carbon atoms 2 and 3 are not as distinct as in monosubstituted azetines, hence decreasing regioisomeric ratios of the transformation

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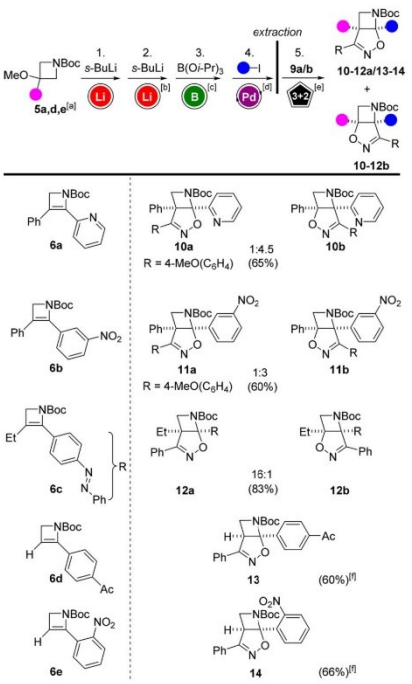
Scheme 4. [3 + 2]-Cycloaddition of 2-Substituted Azetines



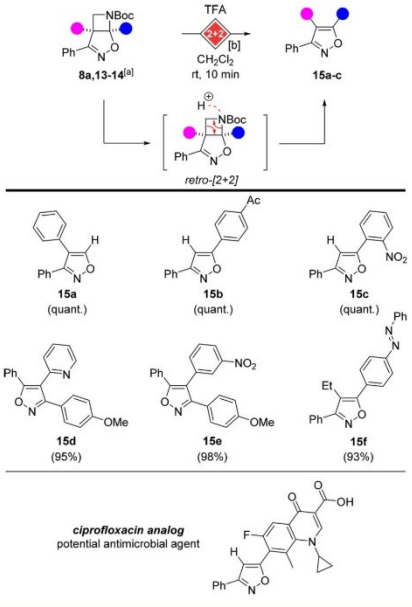
[a]0.5 mmol scale. [b]s-BuLi (2.0 equiv), TMEDA (2.0 equiv) THF, −78 °C, 1 h. [c]B(OiPr)$_3$ (1.5 equiv), −78 °C, 1 h then 0 °C, 1 h. [d]Pd(dppf)Cl$_2$.CH$_2$Cl$_2$ (4 mol %), Ar−I (1 equiv), NaOH (3 equiv), rt, 48 h. [e]1,3-Dipole (3 equiv), CH$_2$Cl$_2$, 100 °C, 6 bar, 1 h, μ-wave. [f]1,3-Dipole (2.5 equiv), CH$_2$Cl$_2$, rt, 1 h.

(Figure 2). Bearing an alkyl chain at position 3 and an aryl chain at position 2, the regioselectivity of the reaction raises to 16:1 (**12a** and **12b**), pointing out the significant role of electronic interactions in the transition state. Consequently, the disubstituted azetine **6c** furnished **12** in good yield (83%) and excellent regioisomeric ratio (16:1). In contrast, monosubstituted azetines at position 2 (**6d** and **6e**) gave exclusively one regioisomer, and **13** and **14** were isolated in 60 to 66% yields over 5 steps.

It is worth noting that the reaction already proceeded in satisfying rate at room temperature without microwave irradiation, pointing out the higher reactivity of these last systems compared to previously mentioned examples.

Considering the broad versatility of this synthetic method, we finally set out to access disubstituted isoxazoles through retro-[2+2]-cycloadditions (Scheme 5). Brønsted acid-catalyzed conditions were applied, and the transformation proceeded in quantitative yields within a few minutes at room temperature, driven by the favorable formation of an aromatic ring (**15a−c**). Additional support of the regiochemical outcome of the [3 + 2] cycloaddition was provided by unambiguous assignments of NMR signals on isoxazoles. Noteworthy, engaging previously synthesized thietanes under same conditions, no transformation to isoxazoles took place, concluding that these compounds are

Scheme 5. Retro-[2 + 2]-Cycloadditions Towards Functionalized Isoxazoles



much more stable than the azetidine derivatives. Fully substituted isoxazoles **15d−f** were also obtained in excellent yields (93 to 95%). It is important to note that isoxazole motifs are present in a number of biologically active compounds such as the analog of ciprofloxacin (Scheme 5).[24]

In summary, we have unlocked a new library of unique isoxazolines fused with azetidine or thietane moieties with great diastereoselectivity and regioselectivity. Moreover, using fused isoxazoline azetidines, a new pathway to unprecedented disubstituted isoxazoles is provided. This surely represents a valuable tool for drug discovery and opens up an entire platform for high throughput screenings.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02848.

Experimental procedures and characterization (IR, HRMS, and ^{1}H and ^{13}C NMR data) for all new compounds (PDF)

Accession Codes

CCDC 1863063−1863064 and 1872242 contain 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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Notes

The authors declare no competing financial interest.

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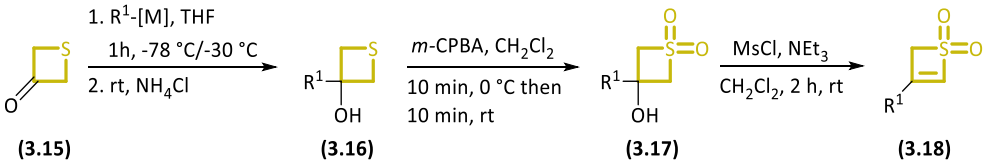
Org. Lett. 2018, 20, 6736–6740

8.2 Disubstituted Thiete Dioxides – Donor/Acceptor- Interactions towards Axial Chirality

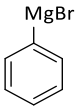
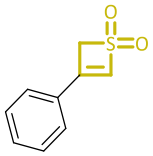
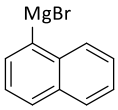
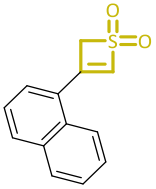
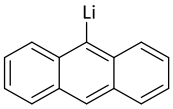
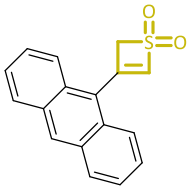
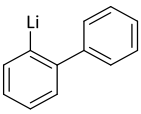
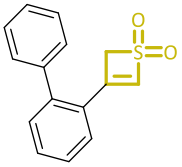
For axial chirality, appropriate substituents on thiete dioxides are necessary. Therefore, the optimized procedure of Burkhard was utilized to access mono substituted thiete dioxides **3.18** (**Scheme 38**).

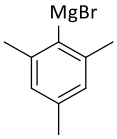
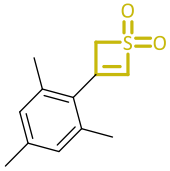
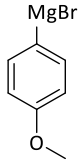
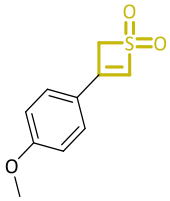
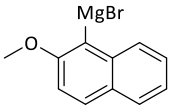
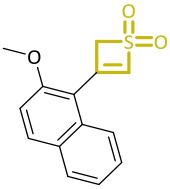
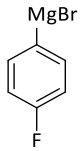
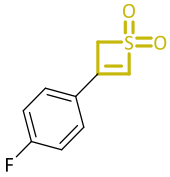
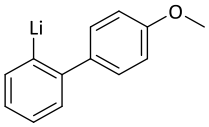
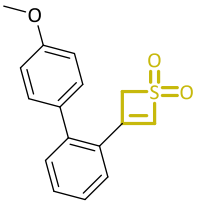
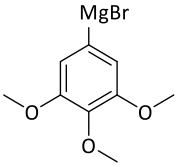
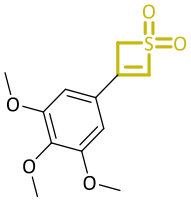
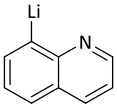
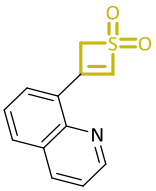


Scheme 38: Three-step sequence towards mono substituted thiete dioxides.

Using commercially available 3-thietanone (**3.15**) in a three-step sequence led to the mono substituted thiete dioxides in moderate to good yields over three steps. In most cases, organomagnesium reagents led to an increased yield compared to organolithium species (**Table 1**). 3-Phenyl-2*H*-thiete 1,1-dioxide **3.18-a** was synthesized *via* phenylmagnesium bromide giving the desired product in a high yield of 78% over three steps. On the contrary, using anthracen-9-yllithium provided thiete dioxide **3.18-c** in only 25%.

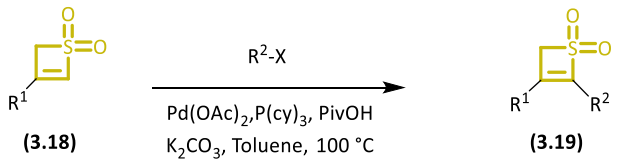
Table 1: Overview of various mono substituted thiete dioxides.

Entry	Electrophile	Organometallic reagent	Product	Yield[a]
1				**3.18-a**, 78%
2				**3.18-b**, 70%
3				**3.18-c**, 25%
4				**3.18-d**, 48%

Entry	Electrophile	Organometallic reagent	Product	Yield[a]
5				**3.18-e**, 37%
6				**3.18-f**, 60%
7				**3.18-g**, 61%
8				**3.18-h**, 60%
9				**3.18-i**, 32%
10				**3.18-j**, 68%
11[b]				**3.18-k**, 24%

[a] Yield of isolated, analytically pure product; [b] for the elimination step DAST and BF_3.OEt was used.

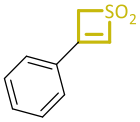
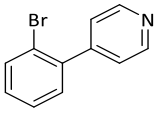
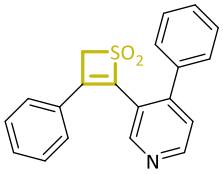
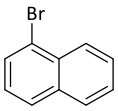
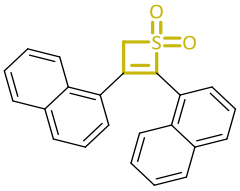
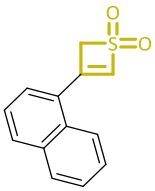
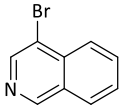
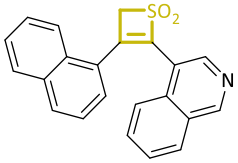
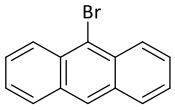
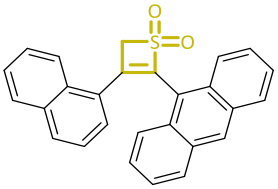
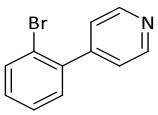
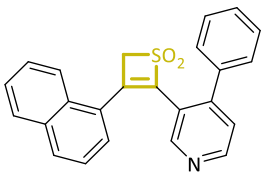
In the next step, the previously described C-H activation was chosen as the key step for the manipulation of mono substituted thiete dioxide **3.18** towards conceivable atropisomerism.[85]



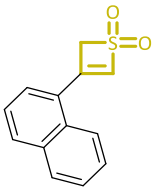
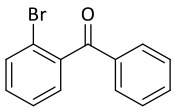
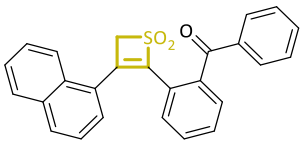
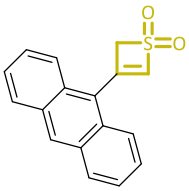
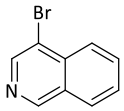
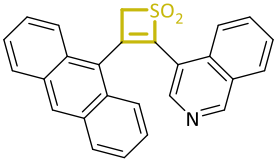
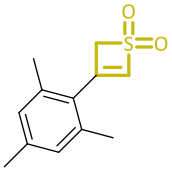
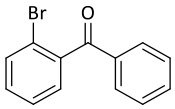
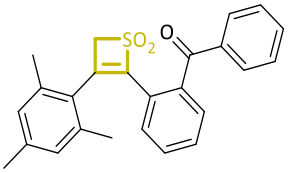
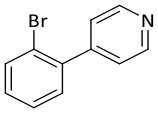
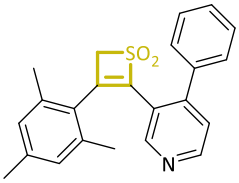
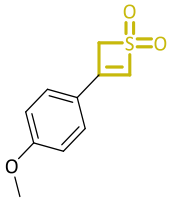
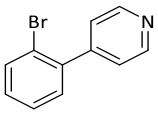
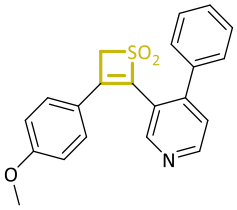
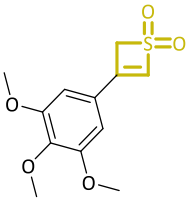
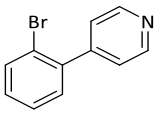
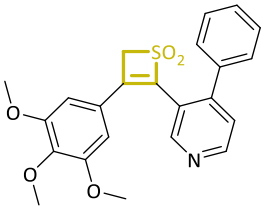
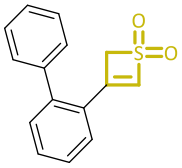
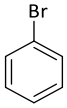
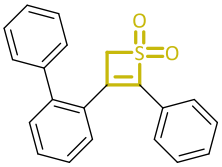
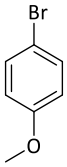
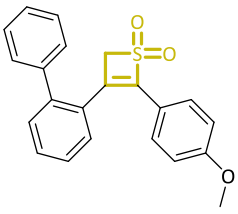
Scheme 39: C-H activation of mono substituted thiete dioxides towards disubstituted.

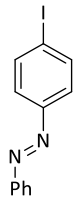
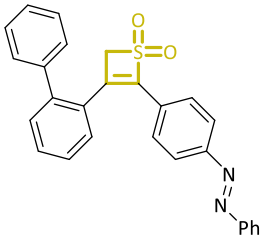
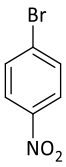
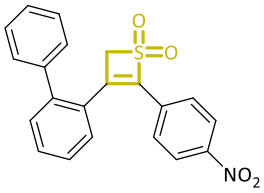
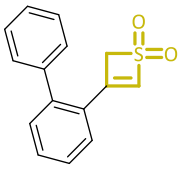
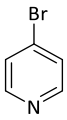
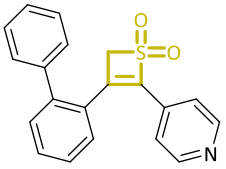
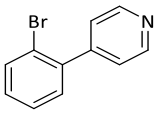
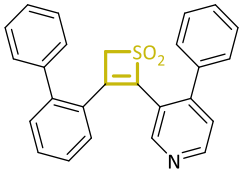
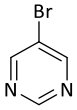
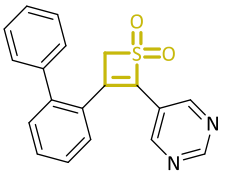
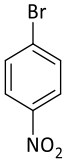
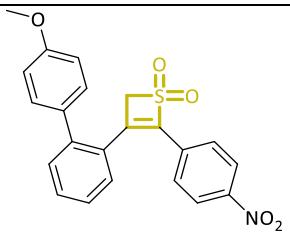
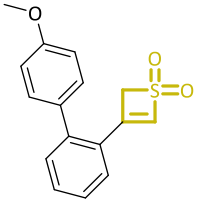
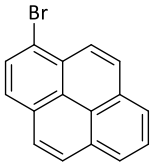
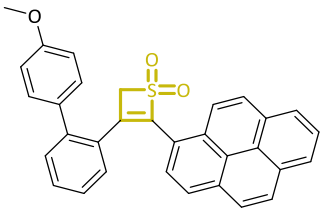
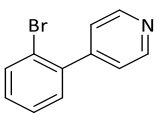
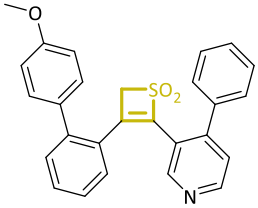
Different mono substituted thiete dioxides **3.18** were engaged in a pivalate-assisted palladium catalyzed C-H activation with a variety of aromatic halogenates (**Table 2**). This led to 23 disubstituted thiete dioxides **3.19** in up to 95%.

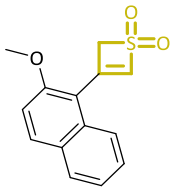
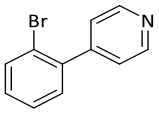
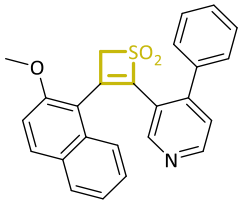
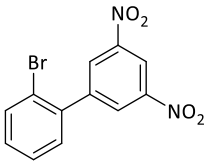
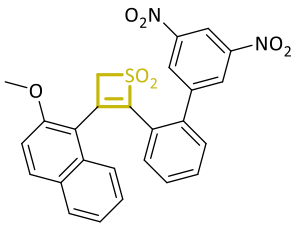
Table 2: Overview of various bis-substituted thiete dioxides.

Entry	3.18	Ar-X	Product	Yield[a]
1				**3.19-a**, 62%
2				**3.19-b**, 70%
3				**3.19-c**, 70%
4				**3.19-d**, 62%
5				**3.19-e**, 95%

[85] M. Eisold; A. Müller-Deku; F. Reiners; D. Didier, *Org. Lett.* **2018**, *20*, 4654.

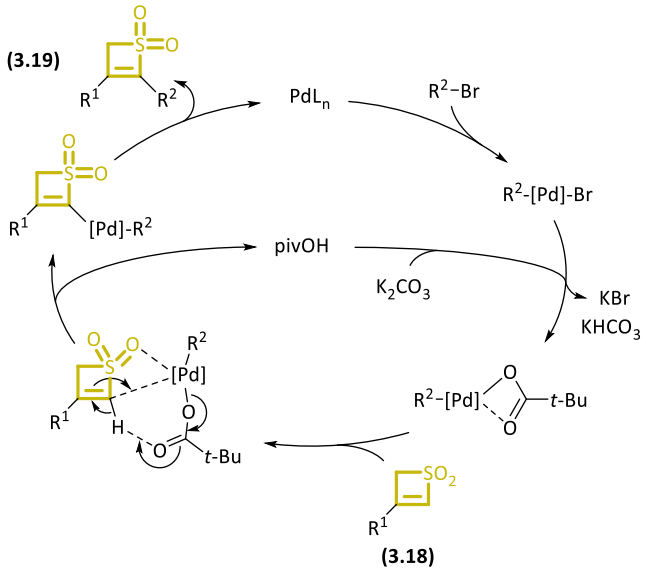
Entry	3.18	Ar-X	Product	Yield[a]
6				**3.19-f**, 85%
7				**3.19-g**, 43%
8				**3.19-h**, 71%
9				**R3.05-i**, 95%
10				**3.19-j**, 41%
11				**3.19-k**, 41%
12				**3.19-l**, 93%
13				**3.19-m**, 69%

Entry	3.18	Ar-X	Product	Yield[a]
14				**3.19-n**, 40%
15				**3.19-o**, 53%
16				**3.19-p**, 61%
17				**3.19-q**, 88%
18				**3.19-r**, 67%
19				**3.19-s**, 60%
20				**3.19-t**, 50%
21				**3.19-u**, 57%

Entry	3.18	Ar-X	Product	Yield[a]
22				**3.19-v**, 58%
23				**3.19-w**, 46%

[a] Yield of isolated, analytically pure product.

The proposed mechanism is depicted in **Scheme 40**. Experiments were conducted to determine the mechanism type of the reaction.[86] The investigations suggested that a "BIES" (base-assisted internal substitution) fits better the reaction path than the "CMD" (concerted-metalation-deprotonation) mechanism. Potassium carbonate has to be added to regenerate the pivalate by deprotonation of the corresponding acid.

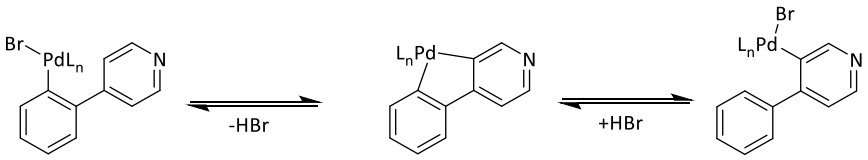


Scheme 40: Proposed catalytic cycle of the pivalate-assisted palladium catalyzed C-H activation.

It is worth noting, that when using 4-(2-bromophenyl)pyridine as the coupling partner, analytical data revealed a palladium crossover, according to the oxidative insertion step towards **3.33** (**Scheme 41**).

[86] M. Eisold; A. Müller-Deku; F. Reiners; D. Didier, *Org. Lett.* **2018**, *20*, 4654.

This migration equilibrium is already well known,[87] however, it is still surprising, that only one isomer was ever obtained after successful C-H activation.

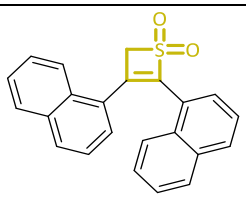
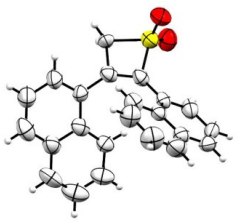
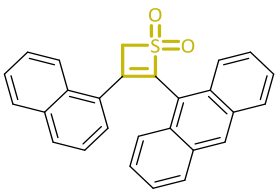
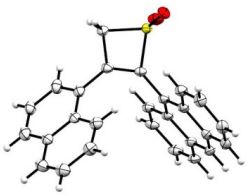


(3.31) **(3.32)** **(3.33)**

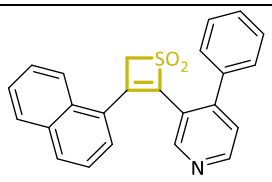
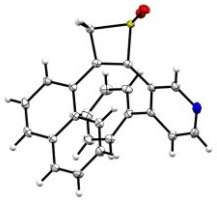
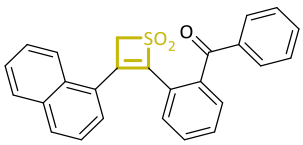
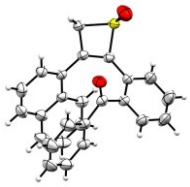
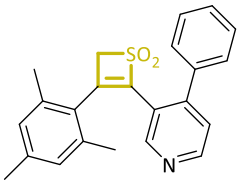
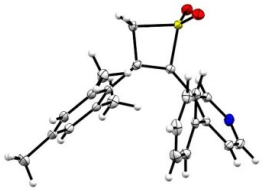
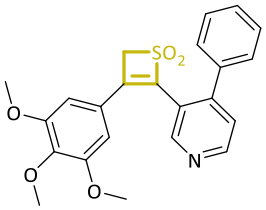
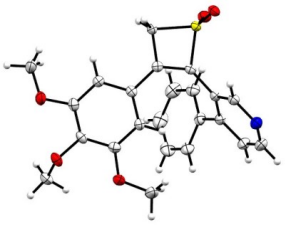
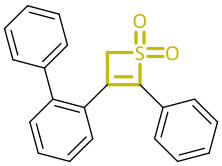
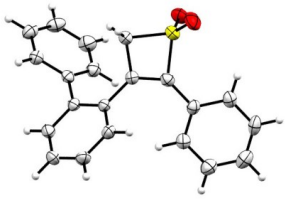
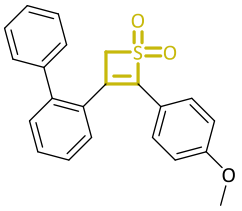
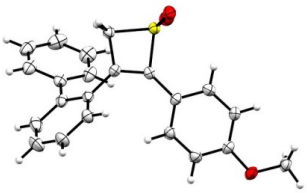
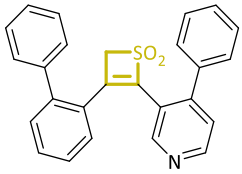
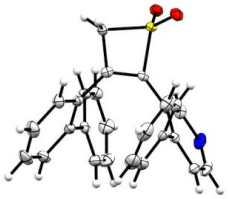
Scheme 41: 1,4-Metal shift according to the oxidative insertion of 4-(2-bromophenyl)pyridine.

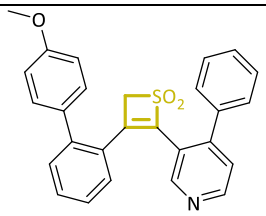
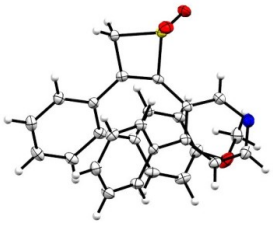
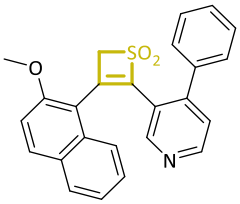
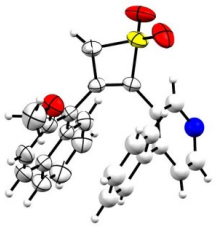
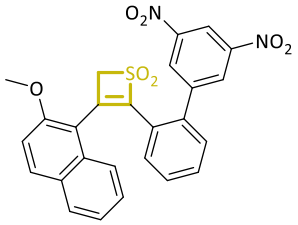
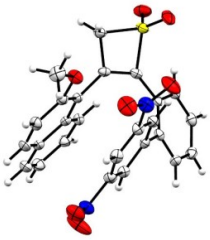
To detect atropisomerism, we tried to crystalize different disubstituted thietes **3.19** in diverse solvent ratios (hexane/dichloromethane). X-ray crystal structures are depicted in **Table 3**. First observations of axial chirality in the solid state was detected for the bi-naphthyl thiete dioxide **3.19-b**. The structure shows evident π-π-interactions between the two aromatic residues. With this results in hands, we set out to explore different moieties containing a naphthyl group on the starting material. Structures **3.19-e/f** exhibited promising interactions, whereupon in structure **3.19-d** the distance among the naphthyl and anthryl moiety was increased. Consequently, the compounds **3.19-b/e/f** were measured on a chiral HPLC at different temperatures (20 °C, -20 °C, -50 °C) to test for atropisomerism in the liquid state. Unfortunately no separation was detected as the rotational barrier is probably too low to stabilize enantiomers at the given temperature.

Table 3: Crystal structures of some disubstituted thiete dioxides.

Entry	3.19	Crystal Structure
1	 **3.19-b**	
2	 **3.19-d**	

[87] G. Karig; M.-T. Moon; N. Thasana; T. Gallagher, *Org. Lett.* **2002**, *4*, 3115.

Entry	3.19	Crystal Structure
3	 **3.19-e**	
4	 **3.19-f**	
5	 **3.19-i**	
6	 **3.19-k**	
7	 **3.19-l**	
8	 **3.19-m**	
9	 **3.19-q**	

Entry	3.19	Crystal Structure
10	 **3.19-u**	
11	 **3.19-v**	
12	 **3.19-w**	

In order to increase π-π-interactions between the residues, we set out to modulate the electron-donating/electron-withdrawing nature of the substituents. Therefore, the electron rich thiete dioxide **3.18-j** (**Table 1**) was engaged in the coupling reaction with the electron deficient 4-(2-bromophenyl)pyridine. This led to the crystal structure of **3.19-k**. Nevertheless, the distance and arrangement of the residues did not give promising results. Electron rich biaryl- or naphthyl derivatives were further used in C-H activation with electron deficient aromatic groups. However, compounds **3.19-l/m** clearly demonstrate that a linker between the residues increases the π-π electrostatic interactions. Indeed, the next thiete dioxides **3.19-(n-w)** showed stronger interactions. Especially compound **3.19-w**, with strong electron deficient NO_2-groups in close distance to the methoxy-naphthyl group, revealed strong donor/acceptor interactions. With nearly face-centred stacking and an approximate average distance of 3.5 Å an optimum for this kind of interactions was achieved.[88] As a consequence, several structures with promising axial chirality in the solid state were further studied in solution by chiral HPLC. Unfortunately, even at temperatures of -50 °C, no de-coalescence of the measured signal peak was ever observed. In conclusion, with this optimized π-π-interactions, stable

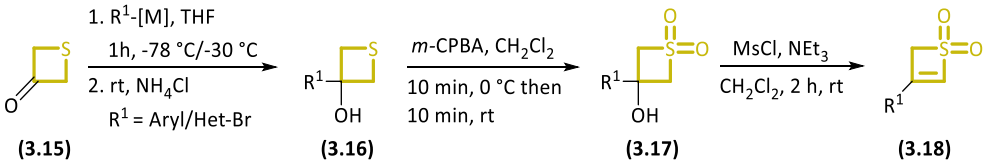
[88] C. R. Martinez; B. L. Iverson, *Chem. Sci.* **2012**, *3*, 2191.

axial chirality was found in the solid state at room temperature, but no atropisomerism could be detected in solution.

With this early findings, further explorations could lead to a new scaffold of thiete dioxide containing molecules with unknown properties.

8.3 Macrocyclic Thiete Dioxides

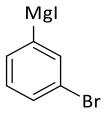
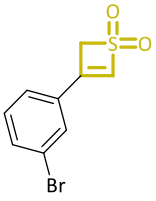
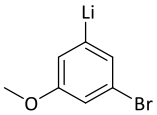
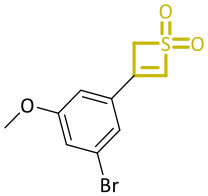
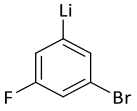
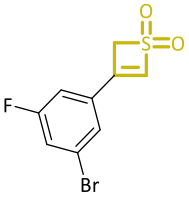
Based on the C-H activation strategy, discussed in detail in **Chapter III** "**Disubstituted Thiete Dioxides – Donor/Acceptor- Interactions towards Axial Chirality**", macrocyclic ring systems containing the thiete dioxide moiety were synthesized. Therefore, mono substituted thiete dioxides bearing a halogen on the aromatic residue had to be prepared (**Scheme 42**).

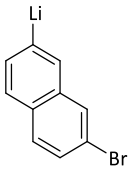
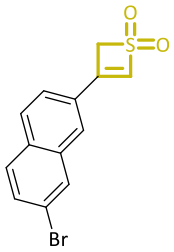
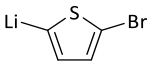
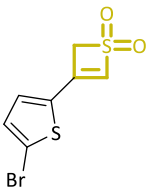


Scheme 42: Three-step sequence towards mono substituted thiete dioxides.

Compared to former obtained thiete dioxides **3.18**, the yields drastically dropped (**Table 4**). The first step is probably crucial, as a selective mono-exchange reaction of the double halogenated aromatic must be performed.

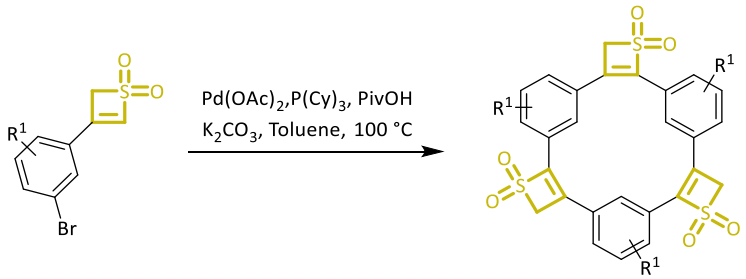
Table 4: Overview of some mono substituted thiete dioxides bearing a bromide on the aromatic residue.

Entry	Electrophile	Organometallic reagent	Product	Yield[a]
1				**3.18-l**, 62%
2				**3.18-m**, 42%
3				**3.18-n**, 35%

Entry	Electrophile	Organometallic reagent	Product	Yield[a]
4				**3.18-o**, 22%
5				**3.18-p**, 7%

[a] Yield of isolated, analytically pure product.

Acceptable yields were observed considering the three-step procedure. With this method in hands, a new scaffold of halogen bearing mono substituted thiete dioxides were synthesized, opening a new route to further transformations. Palladium-catalyzed C-H activation led to compounds **3.30** (**Scheme 43**).

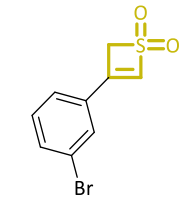
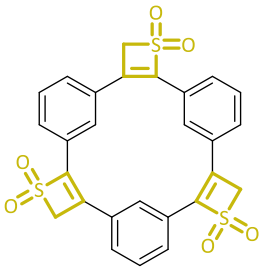
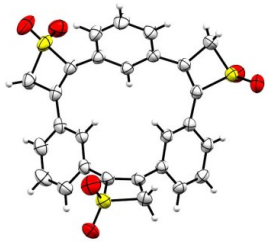
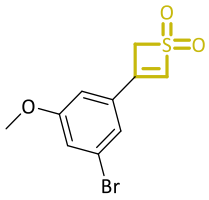
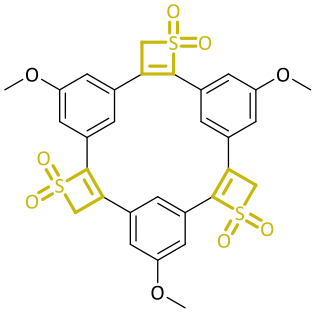
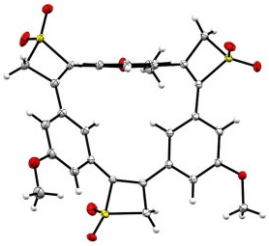
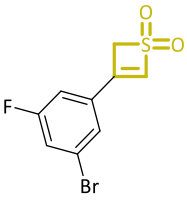
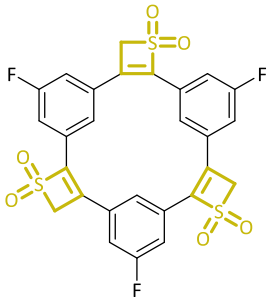
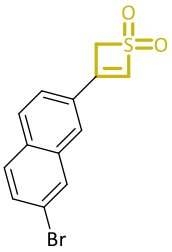
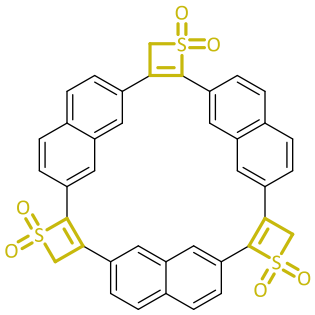


(3.18) **(3.30)**

Scheme 43: C-H activation of mono substituted thiete dioxides towards thiete dioxide macrocycles.

Cyclic thiete dioxides containing three thiete units were obtained in up to 45% (**3.30-c**) yield (**Table 5**). Considering procedures for the synthesis of related macrocyclic spherands, the yields between 20 and 45% are quite good. Moreover, a gram scale procedure of macrocycle **3.30-b** was successful conducted in similar yield of 41%. Unfortunately, the C-H activation of the thiete dioxide **3.18-p**, which would offer a coordination site in the ring cavity due to the inwards pointing sulfur atoms of the thiophene moiety, remains unsuccessful. As these structures are proved insoluble in many organic solvents as well as in water, resulting in unsatisfactory characterization by NMR. Instead, X-ray measurements and/or high-resolution mass analysis were used for characterization.

Table 5: Cyclic thiete dioxide containing macrocycles and crystal structure.

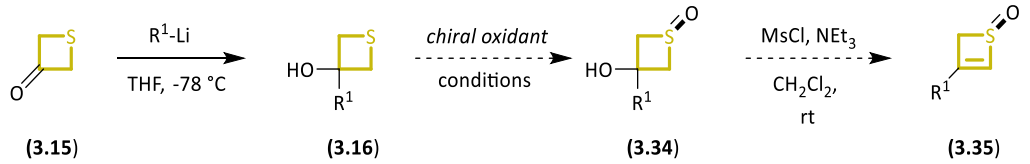
Entry	3.18	Product		Yield[a]
1				**3.30-a**, 37%
2				**3.30-b**, 42%
3				**3.30-c**, 45%
4				**3.30-d**, 20%

[a] Yield of isolated, analytically pure product.

Crystal structures confirm the cyclic structures, consisting of three thiete dioxide units. In summary, further studies are needed to deepen the knowledge about properties and applications of these cyclic structures.

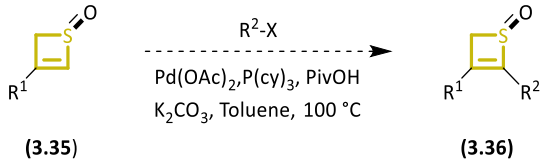
9 Outlook

Mono- or disubstituted thiete dioxides are now readily available building blocks. However, many more transformations are imaginable. Therefore, a synthesis of chiral thiete mono-oxides could open new routes for diversification and transformation towards new properties and use in drug design/modification. For the generation of chiral thiete mono-oxides a similar approach will be used as for the previously synthesized thiete dioxides (see **Chapter III** "**Synthesis of Thiete Dioxides**"). The only difference and challenge would be the use of a chiral oxidant to mono-oxidize the sulfur atom (**3.34**) without obtaining overoxidation products or mixtures (**Scheme 44**).[89]



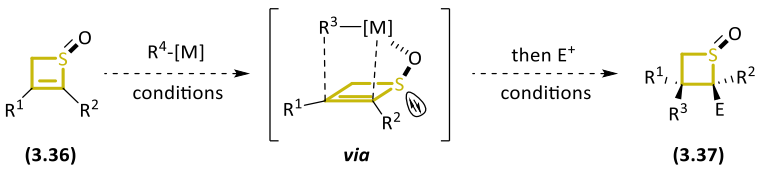
Scheme 44: Synthesis of mono substituted chiral thiete mono oxides by a chiral oxidizer.

The next step would involve the C-H activation, as demonstrated for thiete dioxides, in **Chapter III** "**C-H Activation of Thiete Dioxides**", to grant access to disubstituted chiral thiete mono oxides (**3.36**) (**Scheme 45**).



Scheme 45: C-H activation of mono substituted chiral thiete mono oxides towards disubstituted thietes.

The generation of quaternary stereocenter-containing thietanones, could be done by 1,2-addition of organometallic species to chiral thiete mono-oxides (**3.36**), followed by electrophilic trapping (**Scheme 46**). By coordination of the metal from the metallic reagent by the oxygen, the carbometalation could be diastereoselectivly controlled in a *syn*-addition. This would ultimately lead to a new library of chiral thietanes **3.37**.



Scheme 46: 1,2-Addition of organometallic species to chiral thiete mono-oxides towards chiral thietanes.

[89] For a review on chiral sulfoxides see: J. Han; V. A. Soloshonok; K. D. Klika; J. Drabowicz; A. Wzorek, *Chem. Soc. Rev.* **2018**, *47*, 1307.

Chapter IV

Experimental Part

Part A, **Chapter IV**, contains typical experimental procedures and selected examples for each topic discussed in this part. The full supporting information can be downloaded free of charge on the corresponding website of the publishing company. For unpublished results, the entire analytical data is shown.

10 General Consideration

Commercially available starting materials were used without further purification unless otherwise stated. All reactions were carried out under N_2 atmosphere in flame-dried glassware. Syringes used to transfer anhydrous solvents or reagents were purged with nitrogen prior to use. CH_2Cl_2 was pre-dried over $CaCl_2$ and distilled from CaH_2. THF was refluxed and distilled from sodium benzophenone ketyl under nitrogen. Et_2O was pre-dried over $CaCl_2$ and passed through activated Al_2O_3 (the solvent purification system SPS-400-2 from Innovative Technologies Inc.). MeCN was purchased in HPLC gradient grade (>=99.9%) from Fisher Scientific. Chromatography purifications were performed using silica gel (SiO_2, 0.040-0.063 mm, 230-400 mesh ASTM) from Merck or Florisil ($MgSiO_3$, 60-100 mesh) from APOLLO. Some samples were purified with preparative-layer plates using Merck PLC silica gel 60 F254 (2 mm). The spots were visualized under UV (254 nm) or by staining the TLC plate with $KMnO_4$ solution (3.0 g $KMnO_4$, 300 mL H_2O, 5 drops conc. H_2SO_4), *p*-anisaldehyde solution (4 mL *p*-anisaldehyde, 200 mL ethanol, 3 mL acetic acid, 10 mL conc. H_2SO_4) and/or “curcumin” stain (100 mg, 100 mL ethanol, 2 M HCl (99:1 v/v). Diastereoisomeric ratios were determined by ^{1}H NMR and ^{13}C NMR. NMR spectra were recorded on Mercury 200, Varian NMR-Systtem 600 or Bruker Avance III HD 400 MHz equipped with a CryoProbe™ spectrometers. Chemical shifts are reported as δ values in ppm relative to residual solvent peak (^{1}H NMR) or solvent peak (^{13}C NMR) in deuterated chloroform ($CDCl_3$: δ 7.26 ppm for ^{1}H NMR and δ 77.16 ppm for ^{13}C NMR) or deuterated acetonitrile (CD_3CN: δ 1.94 ppm for ^{1}H-NMR and δ 118.69 and δ 1.39 ppm for ^{13}C-NMR). Further used deuterated solvent: benzene-d_6. Abbreviations for signal coupling are as follows: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), m (multiplet), app (apparent) and br (broad). Reaction endpoints were determined by gas chromatography with *n*-undecane as an internal standard or TLC monitoring of the reactions. Gas chromatography was performed with machines of Agilent Technologies 7890, using a column of type HP 5 (Agilent 5% phenylmethylpolysiloxane; length: 15 m; diameter: 0.25 mm; film thickness: 0.25 µm) or Hewlett-Packard 6890 or 5890 series II, using a column of type HP 5 (HewlettPackard, 5% phenylmethylpolysiloxane; length: 15 m; diameter: 0.25 mm; film thickness: 0.25 µm). High-resolution mass spectra (HRMS) and low-resolution mass spectra (LRMS) were recorded on Finnigan MAT 95Q or Finnigan MAT 90 instrument or JEOL JMS-700. Infrared spectra were recorded on a Perkin 281 IR spectrometer and samples were measured neat (ATR, Smiths Detection DuraSample IR II Diamond ATR). The absorption bands were reported in wave numbers (cm^{-1}) and abbreviations for intensity are

as follows: vs (very strong; maximum intensity), s (strong; above 75% of max. intensity), m (medium; from 50% to 75% of max. intensity), w (weak; from 25% to 50% of max. intensity), vw (very weak; below 25%) and br (broad). Melting points were determined on a Büchi B-540 apparatus and are uncorrected. Single crystals were grown in small vials with a volume of 5.0 mL from slow evaporation of dichloromethane/hexanes mixtures at room temperature. Suitable single crystals were then introduced into perfluorinated oil and mounted on top of a thin glass wire.

Structure Determinations: The intensity data of **3.19-b**, **3.19-d, 3.19-e, 3.19-f, 3.19-i, 3.19-k, 3.19-l, 3.19-m, 3.19-q, 3.19-u, 3.19-w, 3.19-v, 3.30-a** and **3.30-b** was collected at a temperature of 293 K (**3.19-b**), 103 K (**3.19-d**), 100 K (**3.19-e**), 299 K (**3.19-f**), 100 K (**3.19-i**), 100 K (**3.19-k**), 143 K (**3.19-l**), 143 K (**3.19-m**), 100 K (**3.19-q**), 100 K (**3.19-u**), 143 K (**3.19-w**), 298 K (**3.19-v**), 296 K (**3.30-a**), 110 K (**3.30-b**) on a Bruker D8 Venture TXS diffractometer with a Spellman generator (50 kV, 40 mA) using Mo-K_α radiation (λ = 0.71073 Å). The structures were solved by direct methods (SHELXT)[90] and refined by full-matrix least squares techniques against F_o^2 (SHELXL-2014/7)[91].

Supporting Information available: Crystallographic data have been deposited at the Cambridge Crystallographic Data Centre: CCDC-1955894 for **3.19-b;** CCDC-1955895 for **3.19-d**; CCDC-1955896 for **3.19-e**; CCDC- 1955897 for **3.19-f**; CCDC-1955902 for **3.19-i**; CCDC- 1956145 for **3.19-k**; CCDC- 1955898 for **3.19-l**; CCDC-1955899 for **3.19-m**; CCDC-1955900 for **3.19-q**; CCDC-1955901 for **3.19-u**; CCDC-1955903 for **3.19-w**; CCDC-1955904 for **3.19-v**; CCDC-1955905 for **3.30-a**; CCDC-1955906 for **3.30-b**. Copies of the data can be obtained free of charge: https://www.ccdc.cam.ac.uk/structures/.

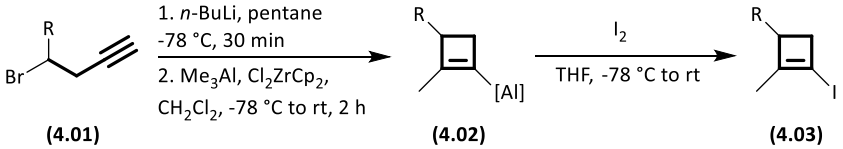
The concentration of organometallic reagent from commercially purchased and synthesized reagents was determined either by titration of isopropyl alcohol using the indicator 1,10-phenanthrolinein in THF or by using iodine dissolved in THF.

[90] G. M. Sheldrick, *Acta Cryst.* **2015**, *A71*, 3.
[91] G. M. Sheldrick, *Acta Cryst.* **2015**, *C71*, 3.

11 Experimental for Chapter I

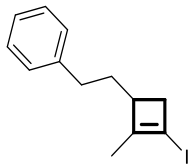
11.1 Unsaturated Four-Membered Rings: Efficient Strategies for the Construction of Cyclobutenes and Alkylidenecyclobutanes

Synthesis of cyclobutenyl aluminium species and further trapping towards iodo-cyclobutenes



(4.01) **(4.02)** **(4.03)**

To a solution of 4-bromobutyne **4.01** (10 mmol, 1.0 equiv.) in pentane (0.5 M) a solution of *n*-butyllithium (10 mmol, 1.0 equiv.) in hexane at −78 °C was added dropwise and stirred for 30 minutes. A second flask was charged with Cp_2ZrCl_2 (10 mmol, 1.0 equiv.) in CH_2Cl_2 (0.5 M) and a solution of trimethylaluminium (20 mmol, 2.0 equiv.) in hexane was added at room temperature and stirred for 30 minutes. The second solution was transferred to the first one at −78 °C via cannula. The resulting mixture was then allowed to stir at room temperature for 2 hours to form the metallated cyclobutenyl derivative **4.02**. The suspension was cooled to -78 °C and a solution of iodine in THF (15 mmol, 1.5 equiv.) was added slowly. After stirring for 30 mins at aforesaid temperature, the mixture was slowly poured onto ice-cold hydrochloric acid (10 equiv., 0.5 M HCl), while stirring vigorously. The aqueous phase was extracted with hexanes (3 × 50 mL). The combined organic phases were washed with saturated aqueous sodium hydrogen carbonate solution (50 mL) and brine (50 mL). The washed solution was dried over magnesium sulfate, filtrated and concentrated under reduced pressure at 10 °C (careful, as some products **4.03** are quite volatile). The crude cyclobutyl iodide **4.03** was purified by flash column chromatography over silica using pentanes as an eluent.

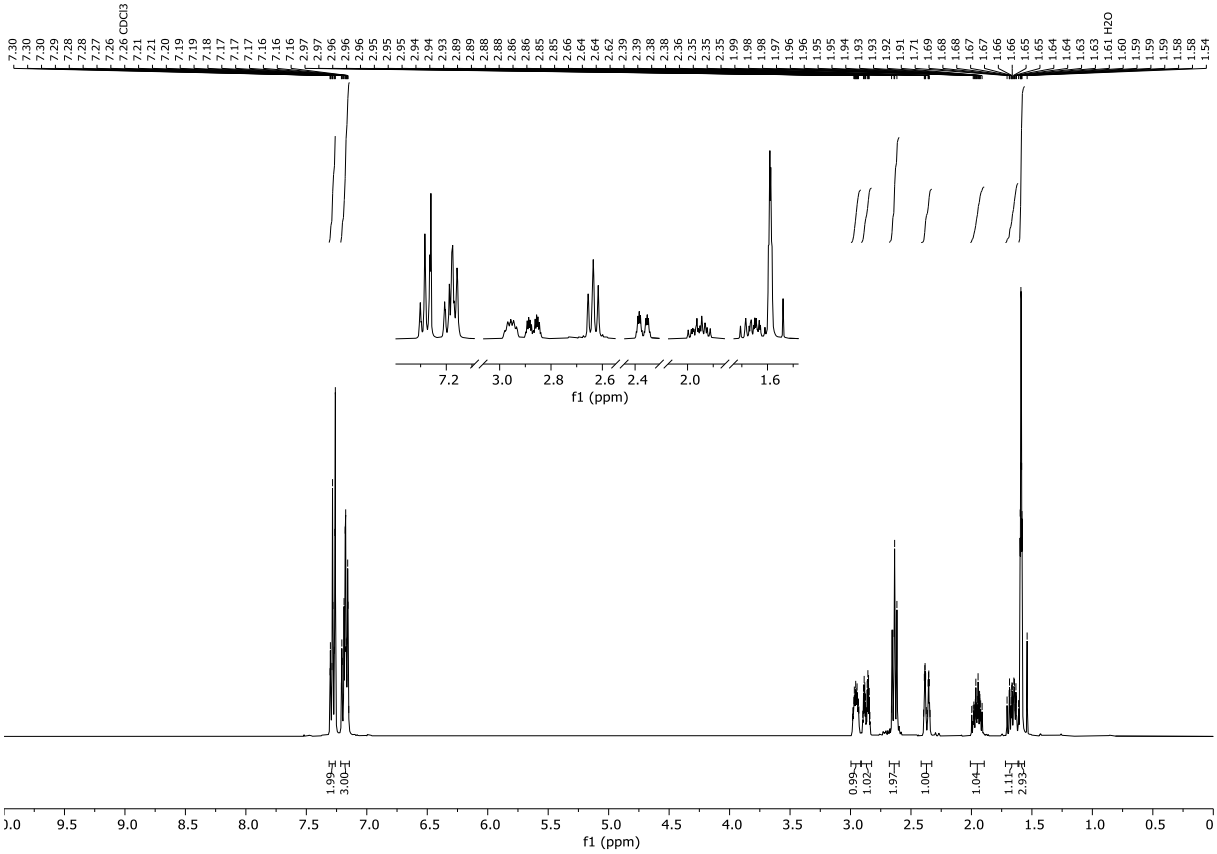


(2-(3-Iodo-2-methylcyclobut-2-en-1-yl)ethyl)benzene (selected example)

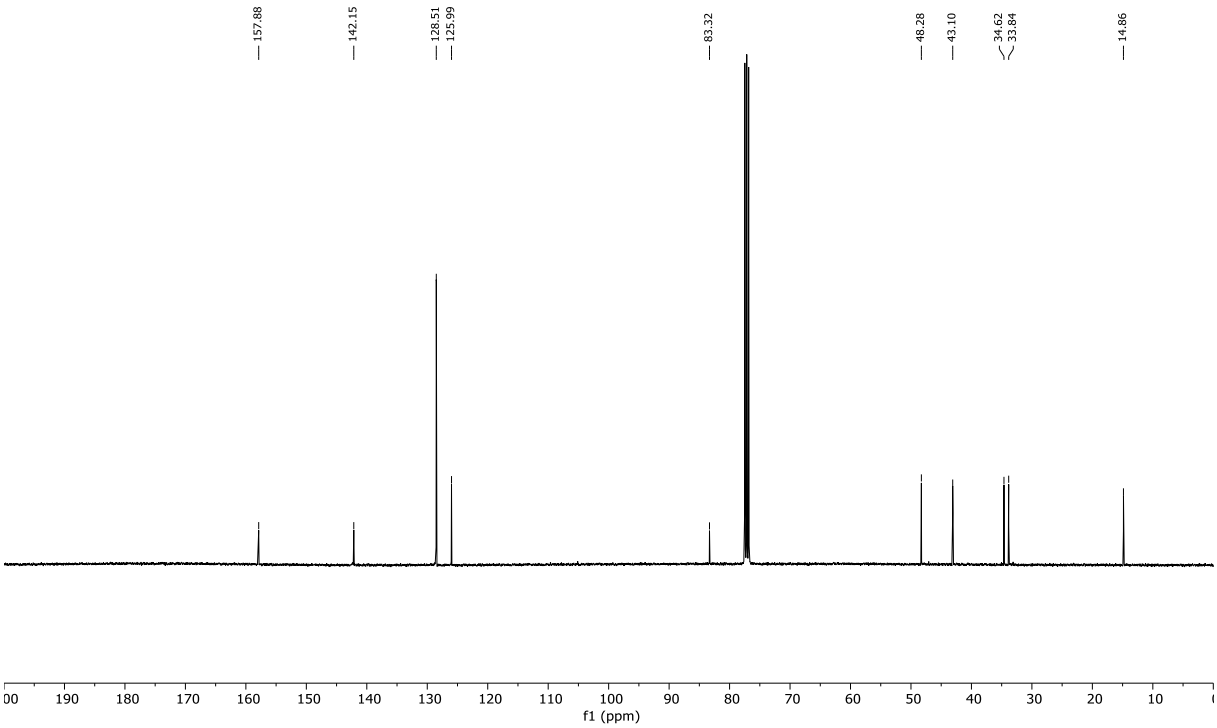
Using (3-bromohex-5-yn-1-yl)benzene provided the product (3.38 g, 62%) as a colourless oil.

***R*f** = 0.58 (hexane, UV, $KMnO_4$). **^{1}H NMR** (400 MHz, $CDCl_3$): δ: 7.31-7.25 (m, 2H), 7.22-7.14 (m, 3H), 2.96 (dtt, *J* = 9.2, 4.7, 1.4 Hz, 1H), 2.87 (ddq, *J* = 12.3, 4.5, 2.3 Hz, 1H), 2.64 (dd, *J* = 8.8, 6.9 Hz, 2H), 2.42-2.32 (m, 1H), 1.95 (dddd, *J* = 13.3, 8.4, 7.3, 4.9 Hz, 1H), 1.73-1.62 (m, 1H), 1.59 ppm (td, *J* = 2.3, 1.2 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ: 157.9, 142.2, 128.5 (2 ^{13}C signals overlapping), 126.0, 83.3, 48.3, 43.1, 34.6, 33.8, 14.9 ppm. **LRMS** (DEP/EI-Orbitrap): *m/z* [%]: 298.0 (3), 171.1 (16), 143.1 (24), 129.1 (12), 117.1 (82), 91.1 (100). **HRMS** (EI-Orbitrap): m/z: [M^+] Calcd for $C_{13}H_{15}I^+$: 298:0218, found 298:0214. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3085 (vw) 3062 (vw) 3026 (w) 2923 (m) 2847 (w) 1648 (w) 1603 (w) 1496 (m) 1453 (m) 1436 (w) 1371 (w) 1319 (vw) 1239 (m) 1181 (w) 1094 (w) 1057 (w) 1029 (w) 1022 (w) 1002 (w) 977 (m) 902 (w) 863 (w) 840 (w) 744 (m) 696 (vs) 661 cm^{-1} (m).

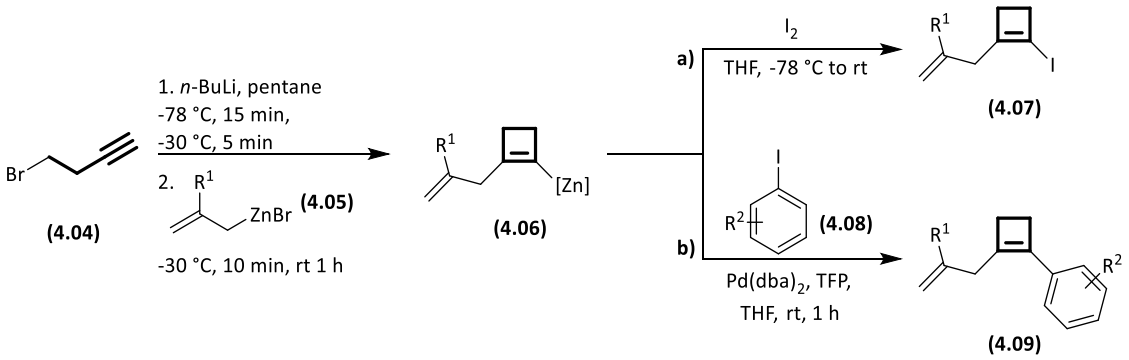
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (101 MHz, $CDCl_3$)



Synthesis of cyclobutenyl zinc species and further trapping towards iodo-cyclobutenes or *in-situ* Negishi cross-coupling



To a stirred solution of 4-bromobut-1-yne **4.04** (1 mmol, 1.0 equiv.) in THF (0.2 M) was added dropwise n-butyllithium (1 mmol, 1.0 equiv.) at -78 °C. After 15 min the cooling bath was exchanged to an -30 °C one. This temperature was maintained for 5 min before adding dropwise the allyl-zinc-species **4.05** (1 mmol, 1.0 equiv.). After 10 min the cooling bath was removed, and the colourless solution was warmed to room temperature over 1 h. The colour changed from colourless to pale yellowish.

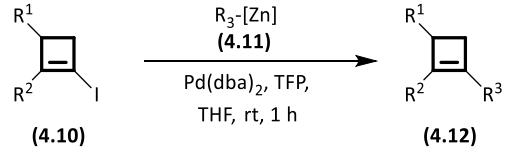
a) Formation of iodo-cyclobutenes

The reaction mixture was treated with iodine (1 mmol, 1.0 equiv.) followed by a small amount of water. The crude mixture was extracted three times with diethyl ether and dried over dry magnesium sulfate. filtrated and concentrated under reduced pressure at 10 °C. The crude cyclobutyl iodide **4.07** was purified by flash column chromatography over silica using hexanes as an eluent.

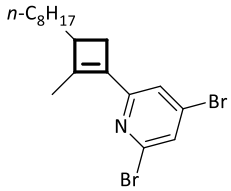
b) *In-situ* Negishi cross-coupling

$Pd(dba)_2$ (4 mol%) and TFP (8 mol%) were dissolved in THF in a second flask. After 10-20 min the red solution turned to yellow. The aryl-iodide **4.08** (0.95 mmol, 0.95 equiv.) was added in THF (0.15 M) to the yellow solution of the catalytic-system and stirred for 10 min. Finally, the cyclobutenyl-zinc-species **4.06** was quickly added to the second flask with the aryl-iodide **4.08** and stirred for 1 h. After treatment with water, the crude mixture was extracted three times with diethyl ether and dried over dry magnesium sulfate. The solvent was removed under reduced pressure and the crude was purified by column chromatography or preparative-layer plates with appropriate solvent mixture to obtain aryl-cyclobutene derivatives **4.09**.

Negishi cross-coupling of iodo-cyclobutenes



$Pd(dba)_2$ (4 mol%) and TFP (8 mol%) was dissolved in THF in a flask. After 10-20 min the red solution turned to yellow. The iodo-cyclobutene **4.10** (0.95 mmol, 0.95 equiv.) was added in THF (0.15 M) to the yellow solution of the catalytic-system and stirred for 10 min. Finally, the alkenyl-zinc-species **4.11** (1 mmol, 1.0 equiv.) was quickly added to the second flask with the cyclobutene-iodide **4.10** and stirred for 1 h. After treatment with water, the crude mixture was extracted three times with diethyl ether and dried over dry magnesium sulfate. The solvent was removed under reduced pressure and the crude was purified by column chromatography or preparative-layer plates with appropriate solvent mixture to obtain the cross-coupling product **4.12**.

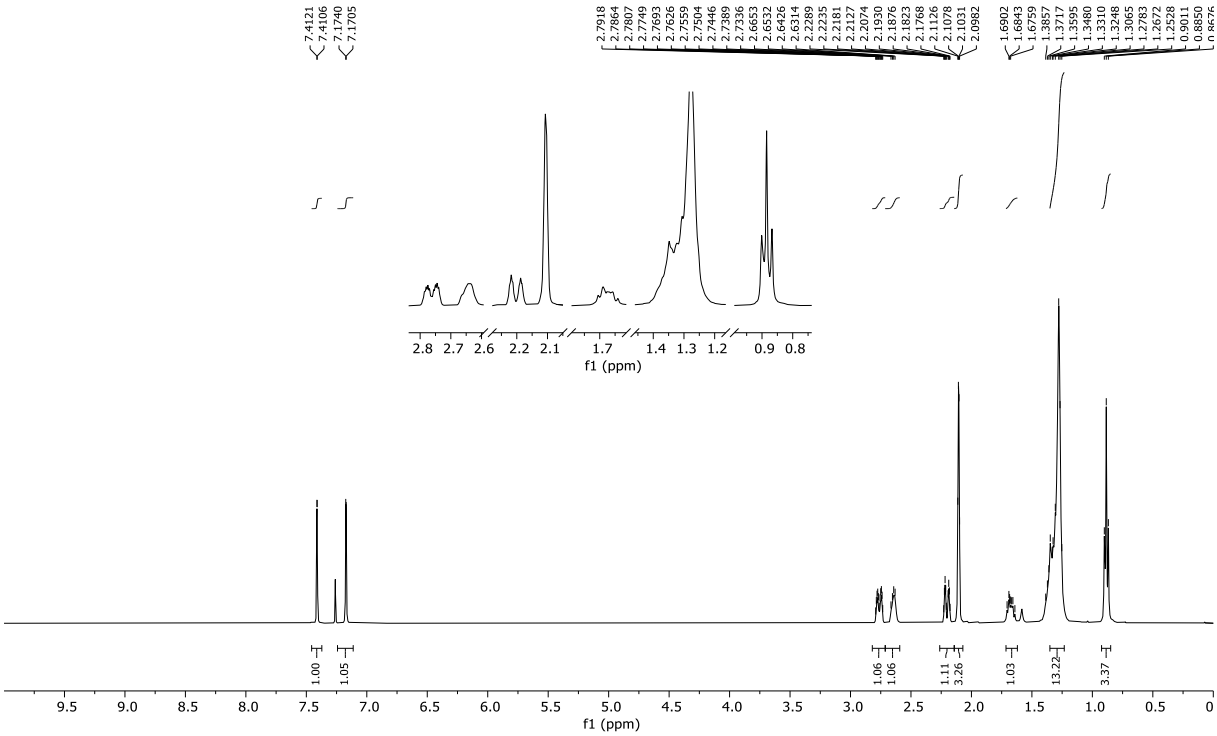


2,4-Dibromo-6-(2-methyl-3-octylcyclobut-1-en-1-yl)pyridine (selected example)

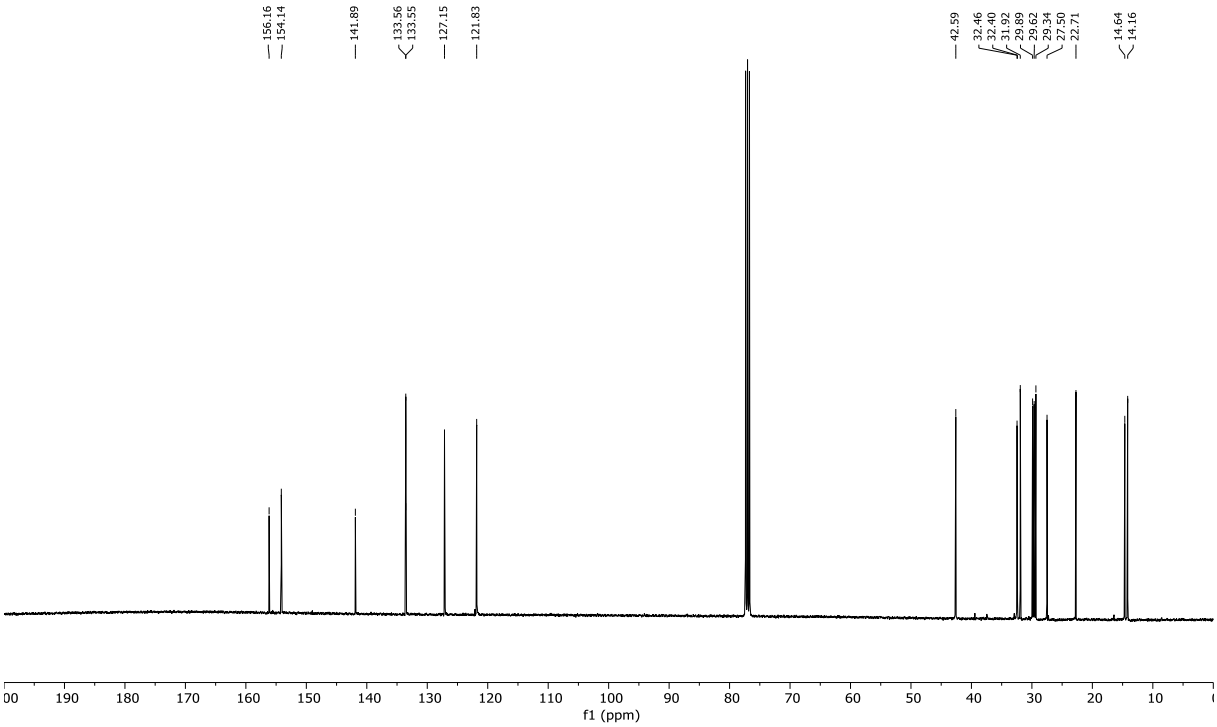
Using 1-iodo-2-methyl-3-octylcyclobut-1-ene provided the product (67 mg, 54%) as slightly yellow oil.

***R*f** = 0.33 (hexane, UV, $KMnO_4$). **^{1}H NMR** (400 MHz, $CDCl_3$): δ: 7.42-7.40 (m, 1H), 7.17 (d, *J* = 1.4 Hz, 1H), 2.83-2.70 (m, 1H), 2.70-2.59 (m, 1H), 2.24-2.14 (m, 1H), 2.11 (q, *J* = 1.9 Hz, 3H), 1.74-1.61 (m, 1H), 1.44-1.16 (m, 13H), 0.88 ppm (t, *J* = 6.7 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ: 156.2, 154.1, 141.9, 133.6, 133.6, 127.1, 121.8, 42.6, 32.5, 32.4, 31.9, 29.9, 29.6, 29.3, 27.5, 22.7, 14.6, 14.2 ppm. **LRMS** (DEP/EI-Orbitrap): *m/z* [%]: 417.1 (8), 415.2 (14), 413,3 (8), 334.2 (14), 316,0 (20), 302.0 (100). **HRMS** (EI-Orbitrap): m/z: [M^+] Calcd for $C_{18}H_{25}{}^{79}Br_2N^+$: 413.0345, found 413.0345. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3098 (vw), 2954 (w), 2921 (m), 2852 (m), 1654 (m), 1554 (vs), 1520 (s), 1465 (w), 1430 (w), 1380 (w), 1368 (m), 1352 (m), 1300 (w), 1240 (vw), 1184 (w), 1151 (s), 1122 (w), 1081 (m), 974 (vw), 867 (w), 839 (m), 773 (m), 746 (vs), 722 (w), 675 cm^{-1} (w).

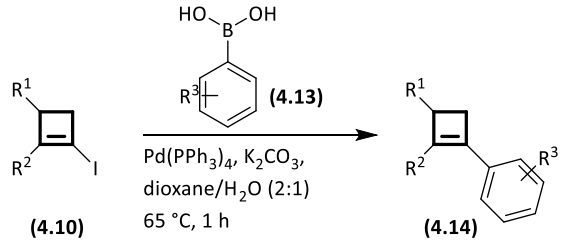
^{1}H NMR (400 MHz, $CDCl_3$)



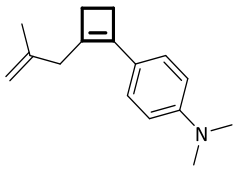
^{13}C NMR (101 MHz, $CDCl_3$)



Suzuki cross-coupling of iodo-cyclobutenes



To a stirred solution of cyclobutene-iodide **4.10** (1 mmol, 1.0 equiv.) in dioxane/H_2O (2:1) (0.05 M) arylboronic acid **4.13** (1.33 mmol, 1.33 equiv.) and K_2CO_3 (2.7 equiv.) was added at room temperature. The reaction mixture was stirred for 10 min before adding the $Pd(PPh_3)_4$ (4 mol%). The cross-coupling was performed at 50 °C for 1 h. The colour of the reaction mixture turned after completion to red or black. Finally, the reaction was treated with a small amount of water, extracted three times with diethyl ether and dried over dry magnesium sulfate. The solvent was removed under reduced pressure and the crude was purified by column chromatography or preparative-layer plates with appropriate solvent mixture to obtain aryl-cyclobutene derivatives **4.14**.

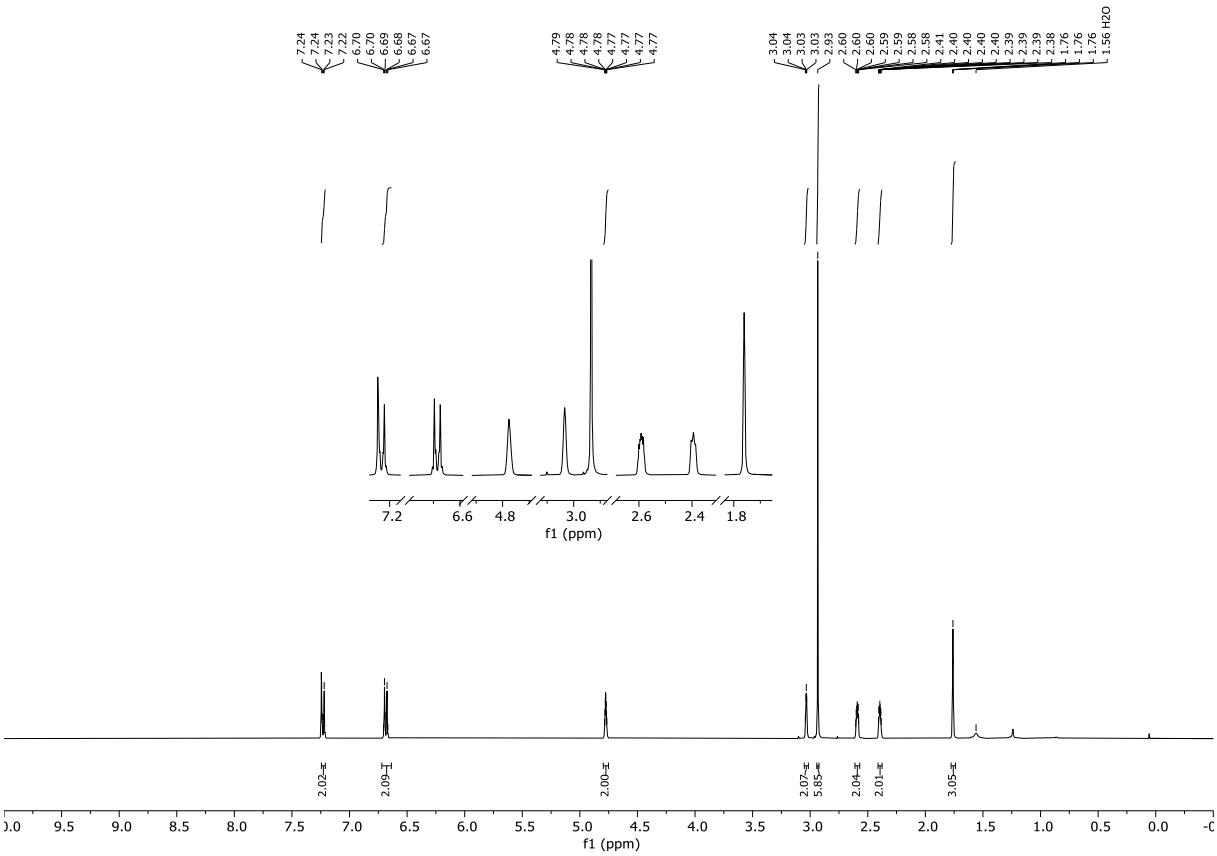


***N*,*N*-Dimethyl-4-(2-(2-methylallyl)cyclobut-1-en-1-yl)aniline (selected example)**

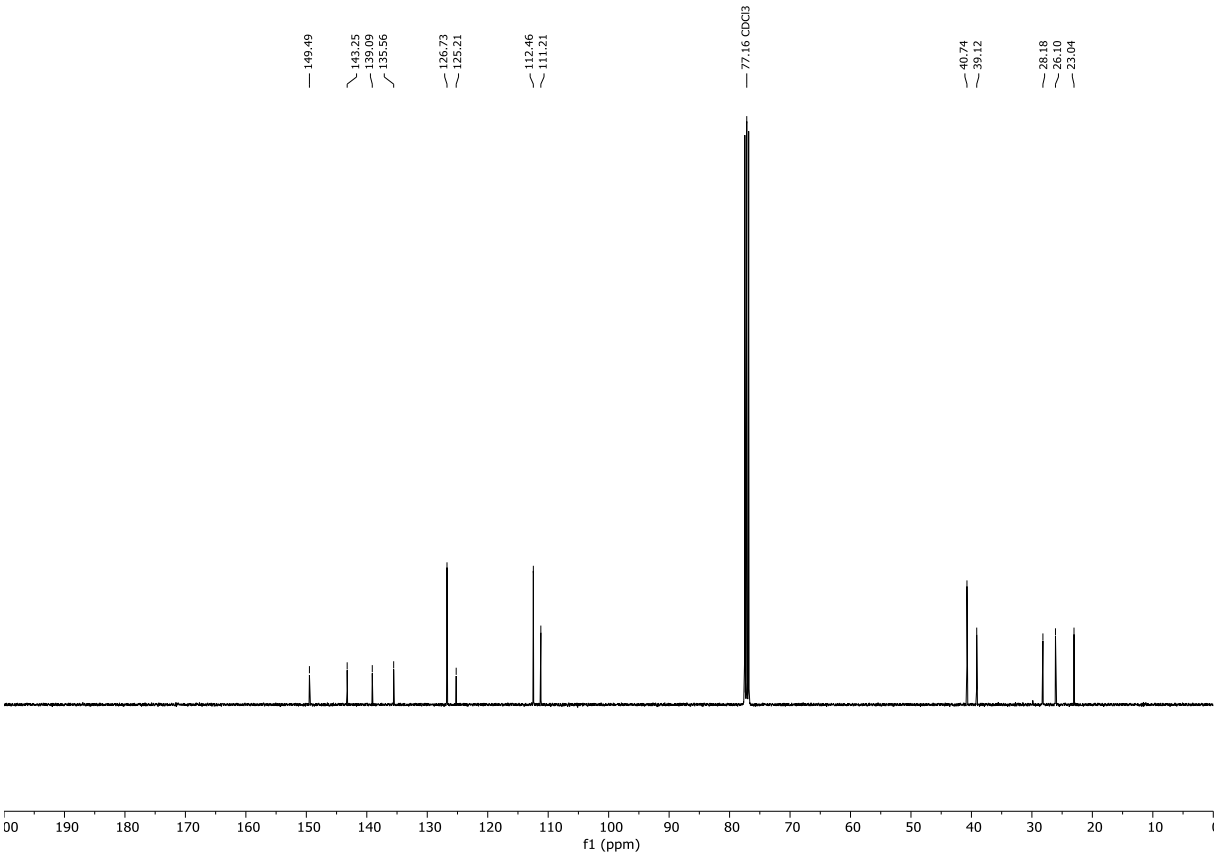
Using 1-iodo-2-(2-methylallyl)cyclobut-1-ene provided the product (32 mg, 56%) as yellow oil.

***R*$_f$** = 0.7 (9:1 hexane/EtOAc, UV, $KMnO_4$, PAA). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.24-7.21 (m, 2H), 6.71-6.66 (m, 2H), 4.79-4.76 (m, 2H), 3.05-3.02 (m, 2H), 2.93 (s, 6H), 2.62-2.57 (m, 2H), 2.42-2.38 (m, 2H), 1.76 ppm (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 149.5, 143.2, 139.1, 135.6, 126.7, 125.2, 112.5, 111.2, 77.2, 40.7, 39.1, 28.2, 26.1, 23.0 ppm. **LRMS** (DEP/EI-Orbitrap): *m/z* [%]: 226.2 (100), 212.2 (95), 197.1 (35), 183.1 (90), 170.1 (45), 155.1 (35), 141.1 (50), 128.1 (65). **HRMS** (EI-Orbitrap): m/z: [M^+] Calcd for $C_{16}H_{21}N^+$: 227.1674, found 227.1660. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3075 (w), 2966 (w), 2911 (m), 2835 (m), 1609 (s), 1520 (vs), 1480 (w), 1461 (w), 1444 (m), 1428 (w), 1353 (s), 1265 (w), 1224 (m), 1194 (m), 1167 (m), 1128 (w), 1061 (w), 946 (m), 889 (m), 820 (m), 796 (m), 598 cm^{-1} (w).

^{1}H NMR (400 MHz, $CDCl_3$)

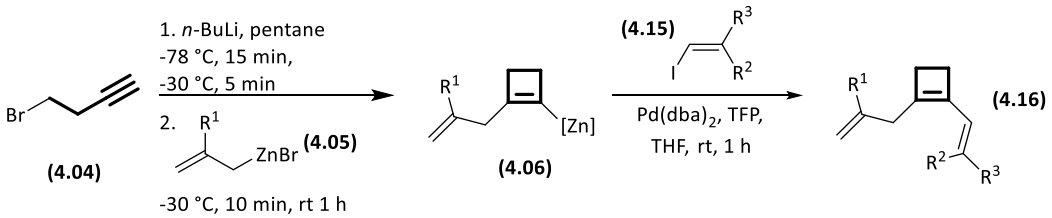


^{13}C NMR (101 MHz, $CDCl_3$)

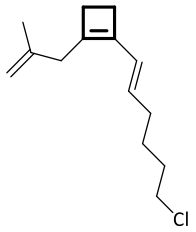


11.2 Stereoselective Sequence toward Biologically Active Fused Alkylidenecyclobutanes

Synthesis of cyclobutenyl zinc species and further *in-situ* Negishi cross-coupling



To a stirred solution of 4-bromobut-1-yne **4.04** (1 mmol, 1.0 equiv.) in THF (0.2 M) *n*-butyllithium (1 mmol, 1.0 equiv.) was added dropwise at -78 °C. After 15 min the cooling bath was exchanged to an -30 °C one. This temperature was maintained for 5 min before adding dropwise the allyl-zinc-species **4.05** (1 mmol, 1.0 equiv.). After 10 min the cooling bath was removed, and the colourless solution was warmed to room temperature over 1 h. The colour changed from colourless to pale yellowish. During that time, $Pd(dba)_2$ (4 mol%) and TFP (8 mol%) were dissolved in THF in a second flask. After 10-20 min the red solution turned to yellow. The iodo-alkene **4.15** (0.95 mmol, 0.95 equiv.) was added in THF (0.15 M) to the yellow solution of the catalytic-system and stirred for 10 min. Finally, the cyclobutenyl-zinc-species **4.06** was quickly added to the second flask with the iodo-alkene **4.15** and stirred for 1 h. After treatment with water, the crude mixture was extracted three times with diethyl ether and dried over dry magnesium sulfate. The solvent was removed under reduced pressure and the crude was purified by column chromatography or preparative-layer plates with appropriate solvent mixture to obtain vinyl-cyclobutene derivative **4.16**.

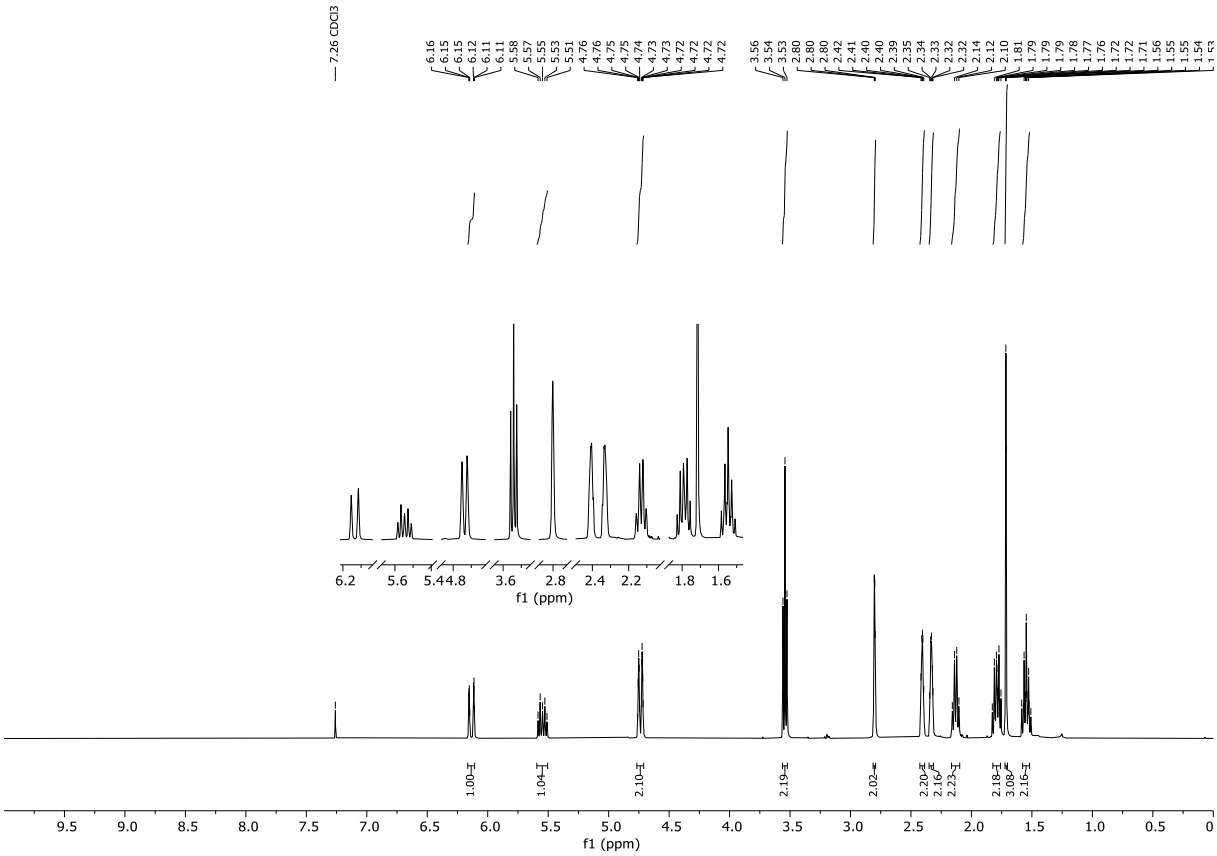


(*E*)-1-(6-Chlorohex-1-en-1-yl)-2-(2-methylallyl)cyclobut-1-ene (selected example)

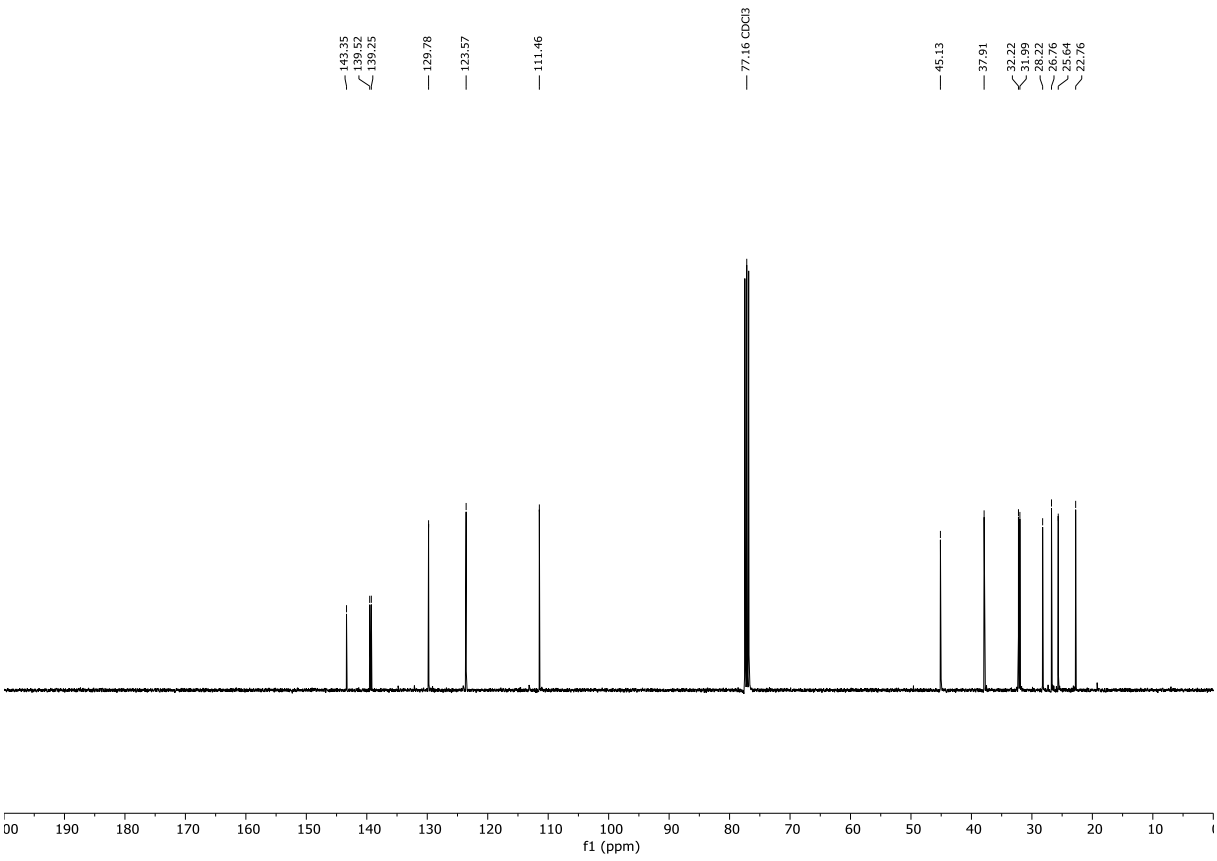
Using 4-bromobut-1-yne provided the product (0.59 mmol, 132 mg, 98%) as colorless oil.

***R*f** = 0.65 (hexane, UV, $KMnO_4$, PAA). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.13 (d, *J* = 15.5, 1H), 5.55 (dt, *J* = 14.8, 7.0 Hz, 1H), 4.76-4.71 (m, 2H), 3.54 (t, *J* = 6.7 Hz, 2H), 2.80 (s, 2H), 2.44-2.38 (m, 2H), 2.35-2.32 (m, 2H), 2.13 (q, *J* = 7.2 Hz, 2H), 1.84-1.75 (m, 2H), 1.72 (s, 3H), 1.59-1.50 ppm (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.4, 139.5, 139.3, 129.8, 123.6, 111.5, 45.1, 37.9, 32.2, 32.0, 28.2, 26.8, 25.6, 22.8 ppm. **LRMS** (DEP/EI-Orbitrap): *m/z* [%]: 224.1 (10), 209.0 (10), 147.1 (10), 133.0 (90), 119.0 (40), 105.0 (100), 91.0 (100). **HRMS** (EI-Orbitrap): m/z: $[M^+]$ Calcd for $C_{14}H_{21}Cl$ $[M]^+$: 224.1332, found 224.1333. **IR** (Diamond-ATR, neat) $_{max}$: 3076 (vw), 2937 (m), 2917 (m), 2869 (m), 2839 (w), 2361 (vw), 1722 (m), 1714 (m), 1694 (m), 1679 (m), 1650 (m), 1631 (m), 1614 (w), 1444 (m), 1434 (m), 1374 (m), 1302 (m), 1269 (m), 1222 (m), 1191 (m), 1174 (m), 1073 (m), 1060 (m), 1027 (m), 962 (vs), 891 (vs), 800 (m), 740 (m), 725 cm^{-1} (s).

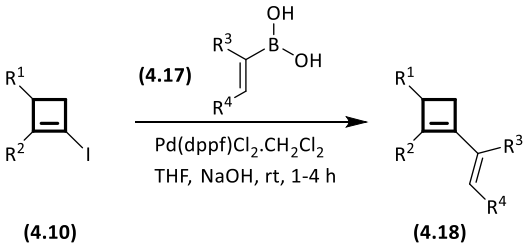
^{1}H NMR (400 MHz, $CDCl_3$)



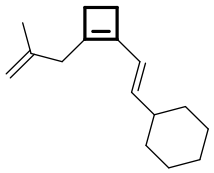
^{13}C NMR (101 MHz, $CDCl_3$)



Suzuki cross-coupling of iodo-cyclobutenes



To a stirred solution of iodo-cyclobutene **4.10** (1 mmol, 1.0 equiv.) in THF (0.7 M) was added alkenyl boronic acid **4.17** (1.5 mmol, 1.5 equiv.), Pd(dppf)Cl_2·CH_2Cl_2 (4 mol%) and NaOH (1.5 equiv.) (1.0 M) at room temperature. The reaction mixture was stirred for 1-4 h. The colour of the reaction mixture turned after completion to black. Finally, the reaction was treated with a small amount of water, extracted three times with diethyl ether and dried over magnesium sulfate. The solvent was removed under reduced pressure and the crude was purified by column chromatography with appropriate solvent mixture to obtain vinylcyclobutene **4.18**.

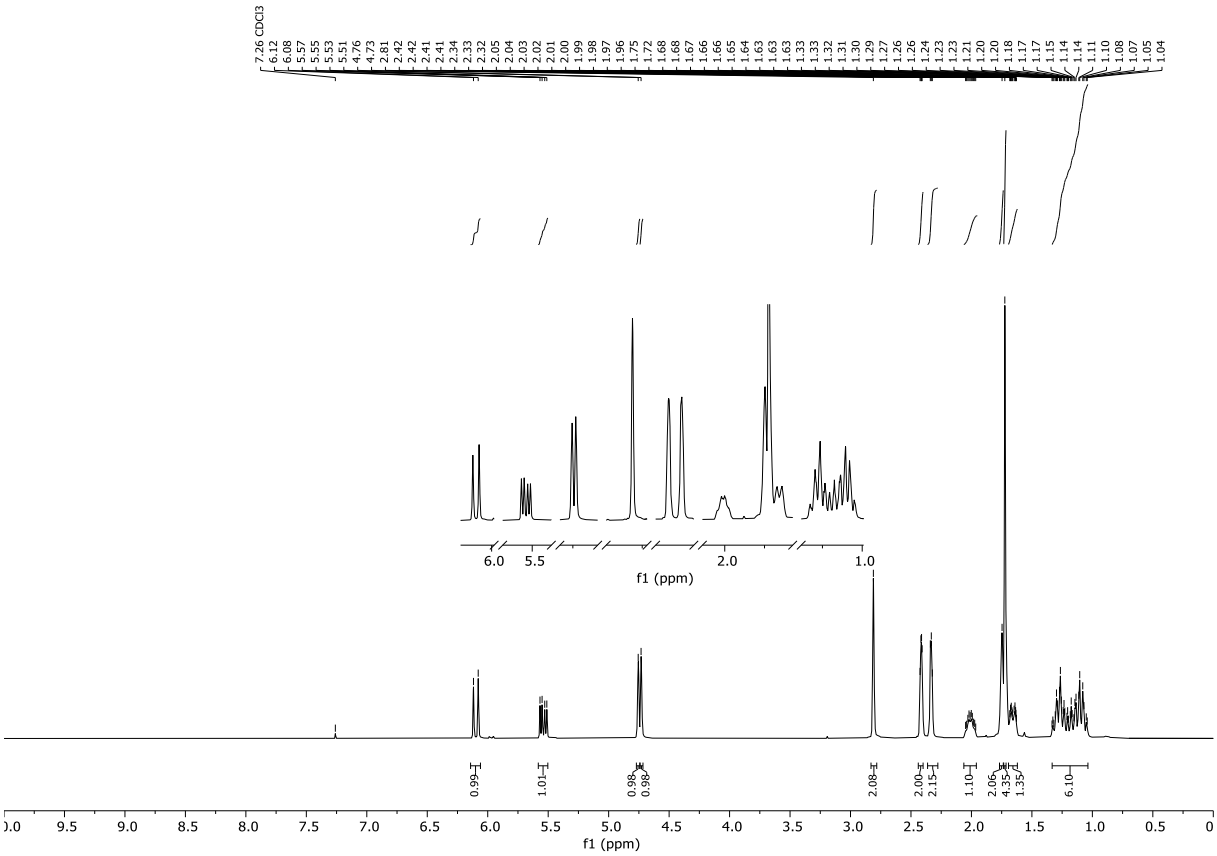


***(E)*-(2-(2-(2-Methylallyl)cyclobut-1-en-1-yl)vinyl)cyclohexane (selected example)**

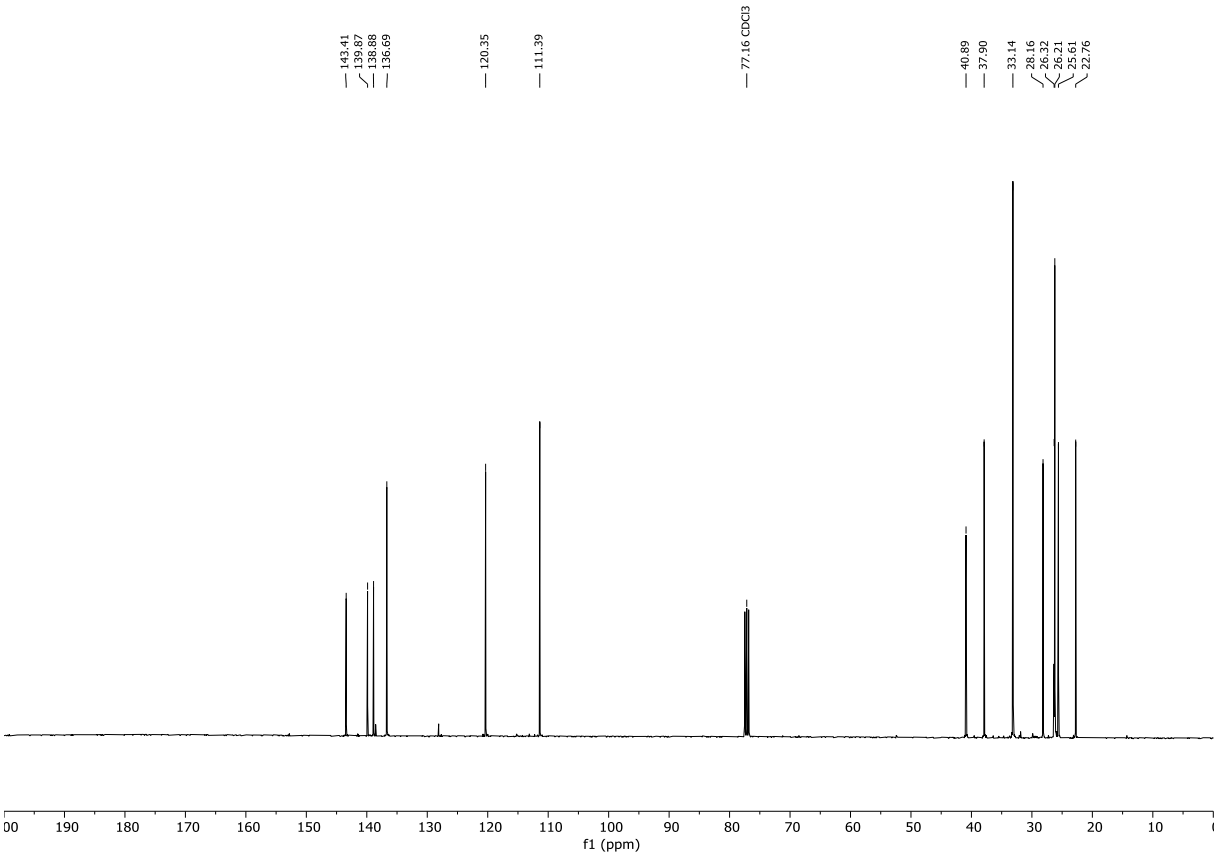
Using 1-iodo-2-(2-methylallyl)cyclobut-1-ene provided the product (0.49 mmol, 106 mg, 98%) as colorless oil.

***R*$_f$** = 0.80 (hexane, UV, $KMnO_4$, PAA). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.10 (d, *J* = 15.6 Hz, 1H), 5.54 (dd, *J* = 15.7, 6.9 Hz, 1H), 4.76 (s, 1H), 4.73 (s, 1H), 2.81 (s, 2H), 2.44-2.40 (m, 2H), 2.36-2.31 (m, 2H), 2.06-1.96 (m, 1H), 1.75 (s, 2H), 1.72 (s, 4H), 1.69-1.61 (m, 1H), 1.34-1.04 ppm (m, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.4, 139.9, 138.9, 136.7, 120.3, 111.4, 40.9, 37.9, 33.1, 28.2, 26.3, 26.2, 25.6, 22.8 ppm. **LRMS** (DEP/EI-Orbitrap): *m/z* [%]: 216.2 (15), 201.2 (5), 187.2 (2), 173.2 (5), 159.2 (10), 145.1 (15), 133.1 (75), 119.1 (40), 105.1 (85), 91.1 (100). **HRMS** (EI-Orbitrap): m/z: [M^+] Calcd for $C_{16}H_{24}$ [$M]^+$: 216.1878, found 216.1873. **IR** (Diamond-ATR, neat) $_{max}$: 2927 (vs), 2853 (m), 1715 (m), 1697 (m), 1676 (m), 1648 (w), 1627 (w), 1450 (m), 1374 (w), 1260 (w), 1188 (w), 1149 (w), 1077 (m), 1061 (w), 1022 (w), 971 (m), 892 cm^{-1} (m).

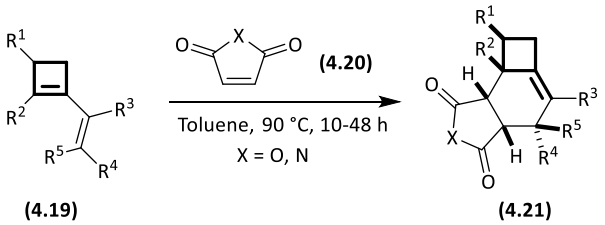
^{1}H NMR (400 MHz, $CDCl_3$)



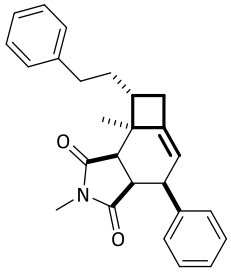
^{13}C NMR (101 MHz, $CDCl_3$)



[4+2]-Cycloaddition reaction of isolated vinyl-cyclobutenes with suitable dienophiles



Vinyl-cyclobutene **4.19** (1 mmol, 1.0 equiv.) and the corresponding cyclopentenedione derivative **4.20** (2 mmol, 2.0 equiv.) were filled into a pressure tube and dissolved in toluene (1.0 M). The tube was sealed, slowly heated to 90 °C in an oil bath and stirred for 10-48 h. The progress was monitored by gas- and by thin-layer chromatography. The reaction was stopped after complete conversion, the solvent removed under reduced pressure and the crude product was purified by column chromatography with appropriate solvent mixture to obtain fused alkylidenecyclobutanes **4.21**.

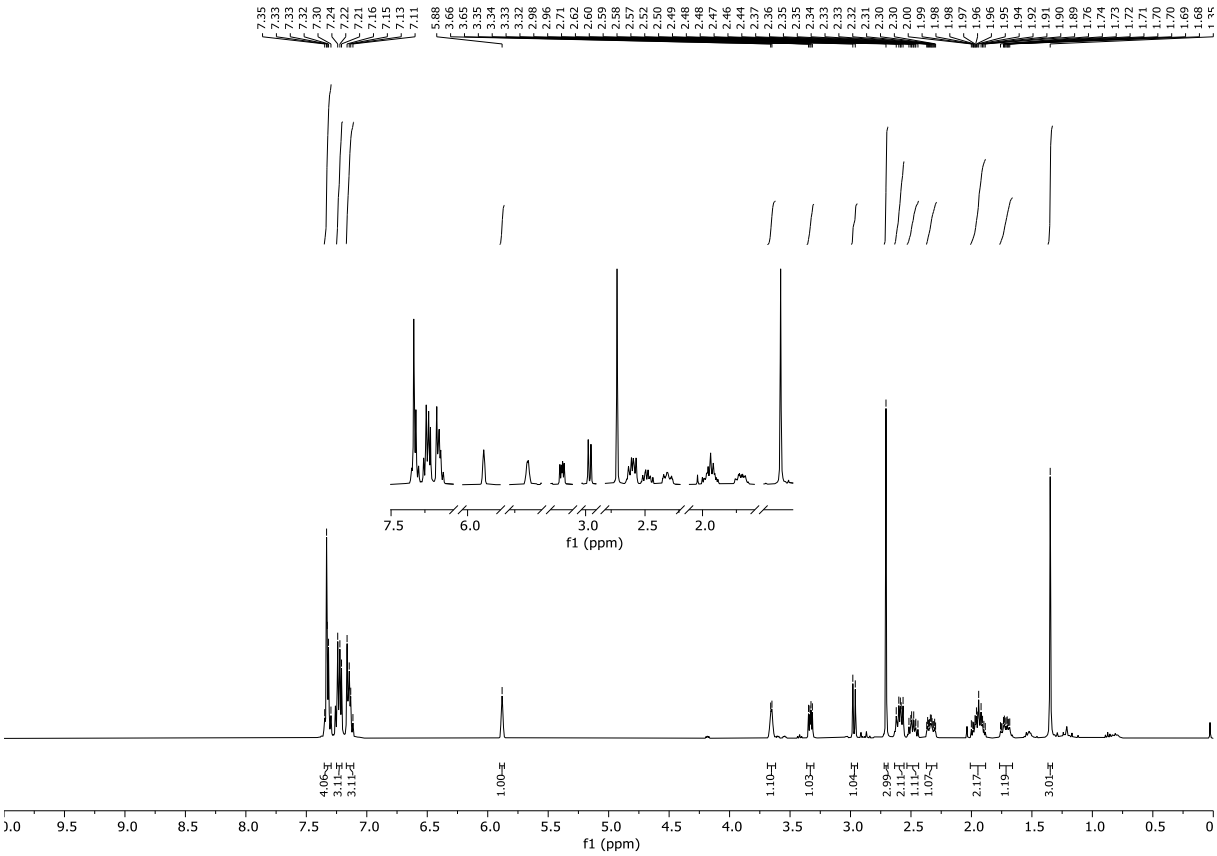


(3a*R,4*R**,7*R**,7a*R**,7b*R**)-2,7a-Dimethyl-7-phenethyl-4-phenyl-3a,4,6,7,7a,7b-hexahydro-1*H*-cyclobuta[*e*]isoindole-1,3(2*H*)-dione (selected example)**

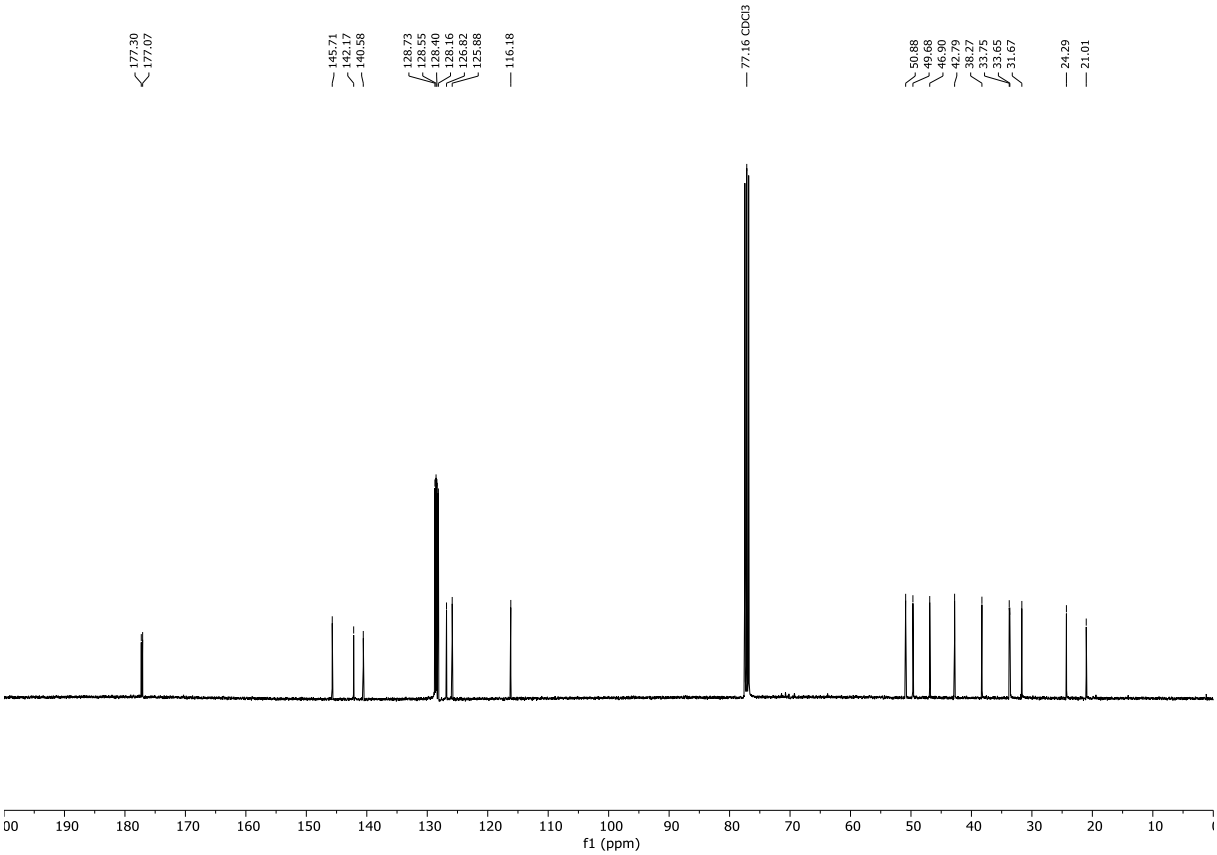
Using (*E*)-(2-(2-(2-methylallyl)cyclobut-1-en-1-yl)vinyl)benzene provided the product (0.23 mmol, 89 mg, 51%) as colourless solid.

R_f = 0.30 (8:2 hexane/EtOAc, UV, $KMnO_4$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35-7.29 (m, 4H), 7.24-7.20 (m, 3H), 7.17-7.11 (m, 3H), 5.88 (s, 1H), 3.65 (d, *J* = 4.2 Hz, 1H), 3.33 (dd, *J* = 8.1, 4.6 Hz, 1H), 2.97 (d, *J* = 8.1 Hz, 1H), 2.71 (s, 3H), 2.63-2.56 (m, 2H), 2.53-2.44 (m, 1H), 2.38-2.29 (m, 1H), 2.00-1.88 (m, 2H), 1.76-1.67 (m, 1H), 1.35 ppm (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.3, 177.1, 145.7, 142.2, 140.6, 128.7, 128.5, 128.4, 128.2, 126.8, 125.9, 116.2, 50.9, 49.7, 46.9, 42.8, 38.3, 33.7, 33.6, 31.7, 24.3, 21.0 ppm. **LRMS** (DEP/EI-Orbitrap): *m/z* [%]: 385.4 (45), 308.3 (5), 300.3 (10), 294.3 (90), 209.2 (35), 183.9 (40), 167.1 (55), 131.1 (30), 117.1 (100). **HRMS** (EI-Orbitrap): m/z: [M^+] Calcd for $C_{26}H_{27}NO_2$ [$M]^+$: 385.2042, found 385.2038. **IR** (Diamond-ATR, neat) $_{max}$: 2929 (w), 1703 (vs), 1496 (w), 1452 (w), 1432 (w), 1381 (w), 1280 (w), 1044 (w), 979 (w), 761 (w), 749 (w), 700 cm^{-1} (w). **Melting point** = 150 °C.

^{1}H NMR (400 MHz, $CDCl_3$)

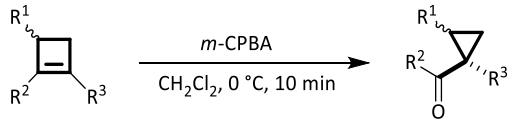


^{13}C NMR (101 MHz, $CDCl_3$)



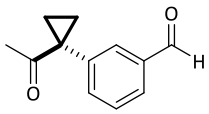
11.3 Oxidative Ring Contraction of Cyclobutenes: General Approach to Cyclopropylketones including Mechanistic Insights

Oxidative ring contraction of cyclobutenes with *m*-CPBA



(4.22) **(4.23)**

To cyclobutenes **4.22** (1 mmol, 1.0 equiv.) in CH_2Cl_2 (0.1 M) *m*-CPBA in CH_2Cl_2 (0.3 M, 1 mmol, 1.0 equiv.) was added at 0 °C. The reaction was checked after 10 min by TLC, and another portion of *m*-CPBA (0.5 mmol, 0.5 equiv.) was added if the reaction was not complete. This step was repeated until full conversion of the substrates. The reaction was then treated by addition of NaOH (1 M) and extracted with CH_2Cl_2 (3 × 20 mL). Volatiles were removed under reduced pressure and the crude product purified by column chromatography with appropriate solvent mixture to obtain cyclopropylketones or -aldehydes **4.23**.

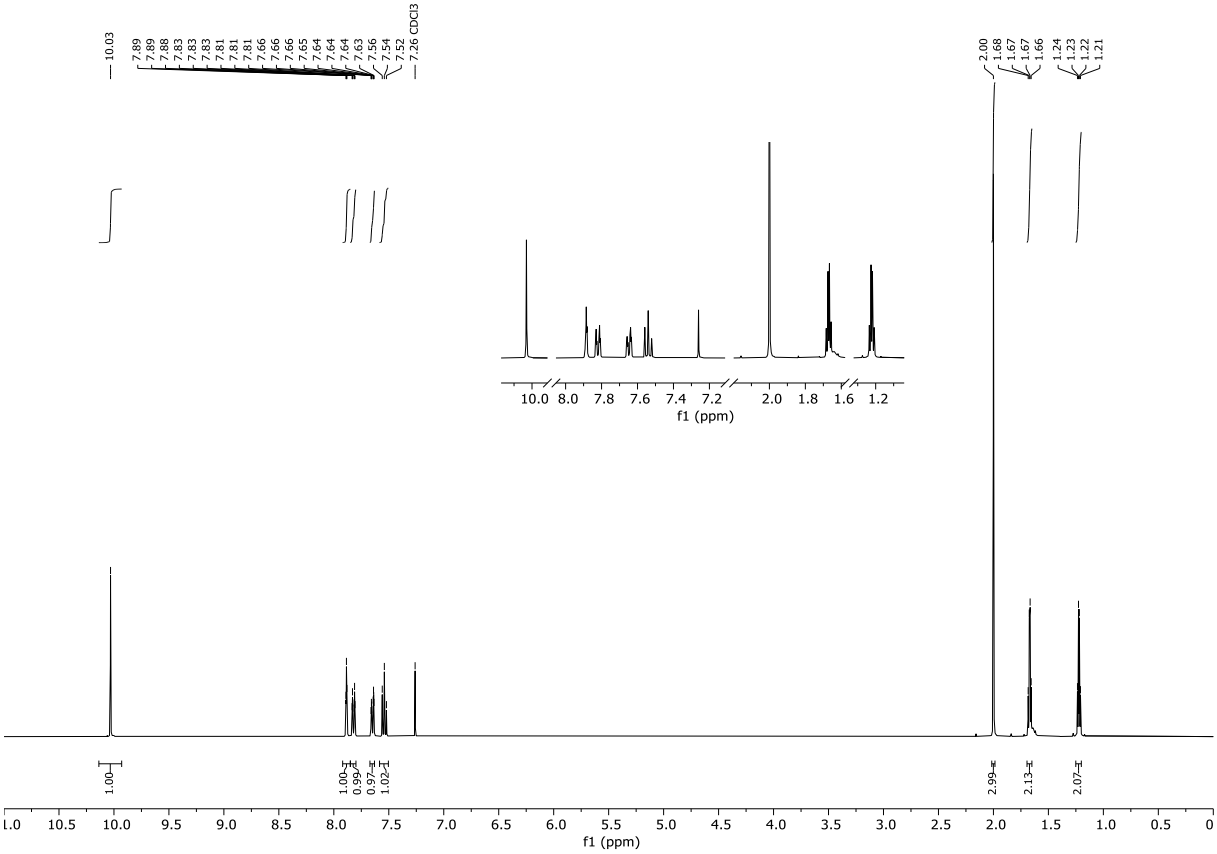


3-(1-Acetylcyclopropyl)benzaldehyde (selected example)

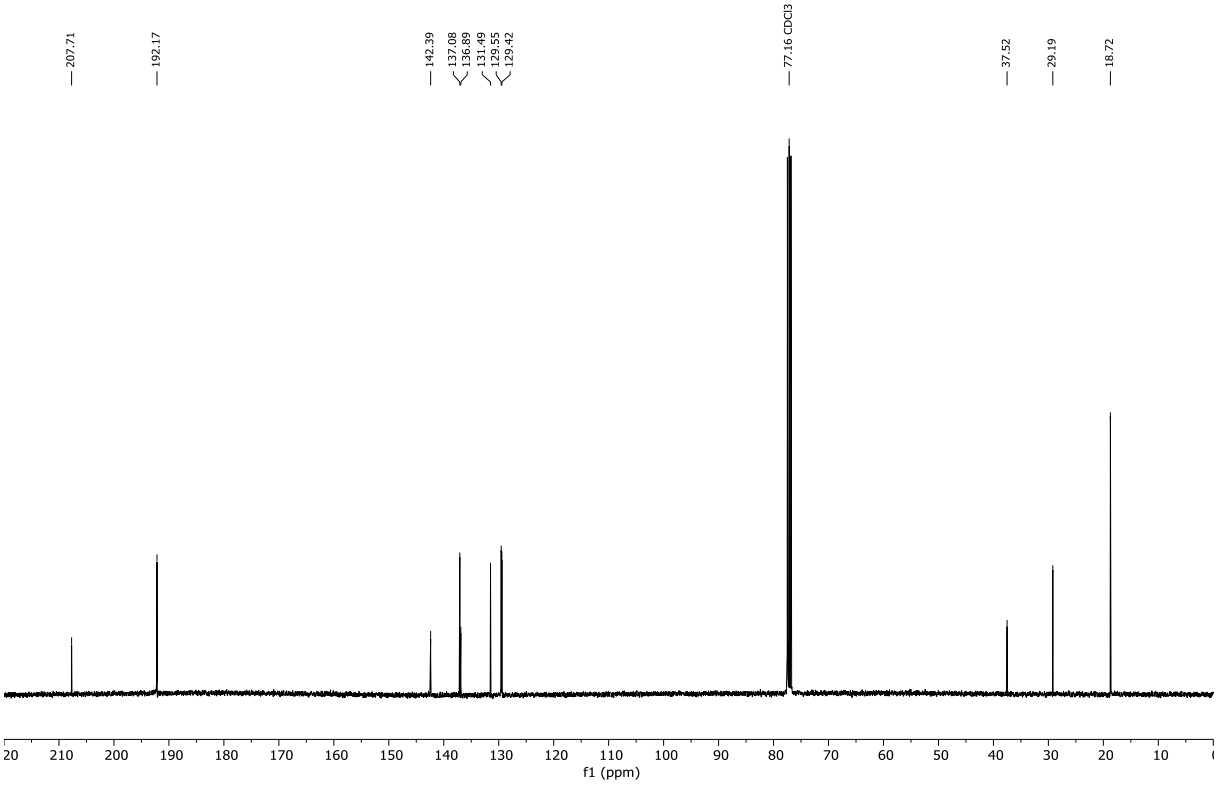
Using 3-(2-methylcyclobut-1-en-1-yl)benzaldehyde provided the product (0.15 mmol, 27 mg, 58%) as colourless oil.

***R*f** = 0.2 (hexane/EtOAc 9:1, UV, $KMnO_4$, PAA). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.03 (s, 1H), 7.89 (t, *J* = 1.7 Hz, 1H), 7.82 (dt, *J* = 7.6, 1.5 Hz, 1H), 7.65 (ddd, *J* = 7.7, 1.9, 1.2 Hz, 1H), 7.54 (t, *J* = 7.6 Hz, 1H), 2.00 (s, 3H), 1.67 (dd, *J* = 6.8, 4.2 Hz, 2H), 1.22 ppm (dd, *J* = 7.1, 3.7 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 207.7, 192.2, 142.4, 137.1, 136.9, 131.5, 129.6, 129.4, 37.5, 29.2, 18.7 ppm. **LRMS** (DEP/EI-Orbitrap): *m/z* (%): 188.1 (100). **HRMS** (EI-Orbitrap): m/z: [M^+] Calcd for $C_{12}H_{12}O_2^+$: 188.0837; found: 188.0831. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3010 (w), 1758 (w), 1720 (m), 1692 (vs), 1604 (w), 1586 cm^{-1} (w).

^{1}H NMR (400 MHz, $CDCl_3$)



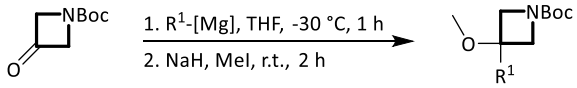
^{13}C NMR (101 MHz, $CDCl_3$)



12 Experimental for Chapter II

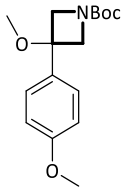
12.1 Methods for the Synthesis of Substituted Azetines

Synthesis of 3-substituted 1-Boc-3-methoxyazetidines



(4.24) **(4.25)**

Commercially available *tert*-butyl 3-oxoazetidine-1-carboxylate **4.24** (5.0 mmol, 1.0 equiv.) was dissolved in THF (0.25 M) and cooled to -30 °C. The corresponding Grignard reagent (6.5 mmol, 1.3 equiv.) was added dropwise and the solution stirred for one hour before warming to room temperature. The reaction mixture was treated with saturated NH_4Cl and extracted twice with diethyl ether (2 x 20 mL). The combined organic layers were dried over magnesium sulfate and the solvents were evaporated under vacuum. The crude alcohol was then redissolved in THF (0.5 M) and cooled to 0 °C. After adding sodium hydride (6.5 mmol, 1.3 equiv.) portion-wise, the reaction mixture was allowed to reach room temperature and stirred for one hour. Methyl iodide (6.5 mmol, 1.3 equiv.) was then added and the mixture stirred for two more hours at room temperature. The reaction was treated with methanol and the solvents were evaporated. The crude product was purified by column chromatography with appropriate solvent mixture to obtain 3-substituted 1-Boc-3-methoxyazetidines **4.25**.

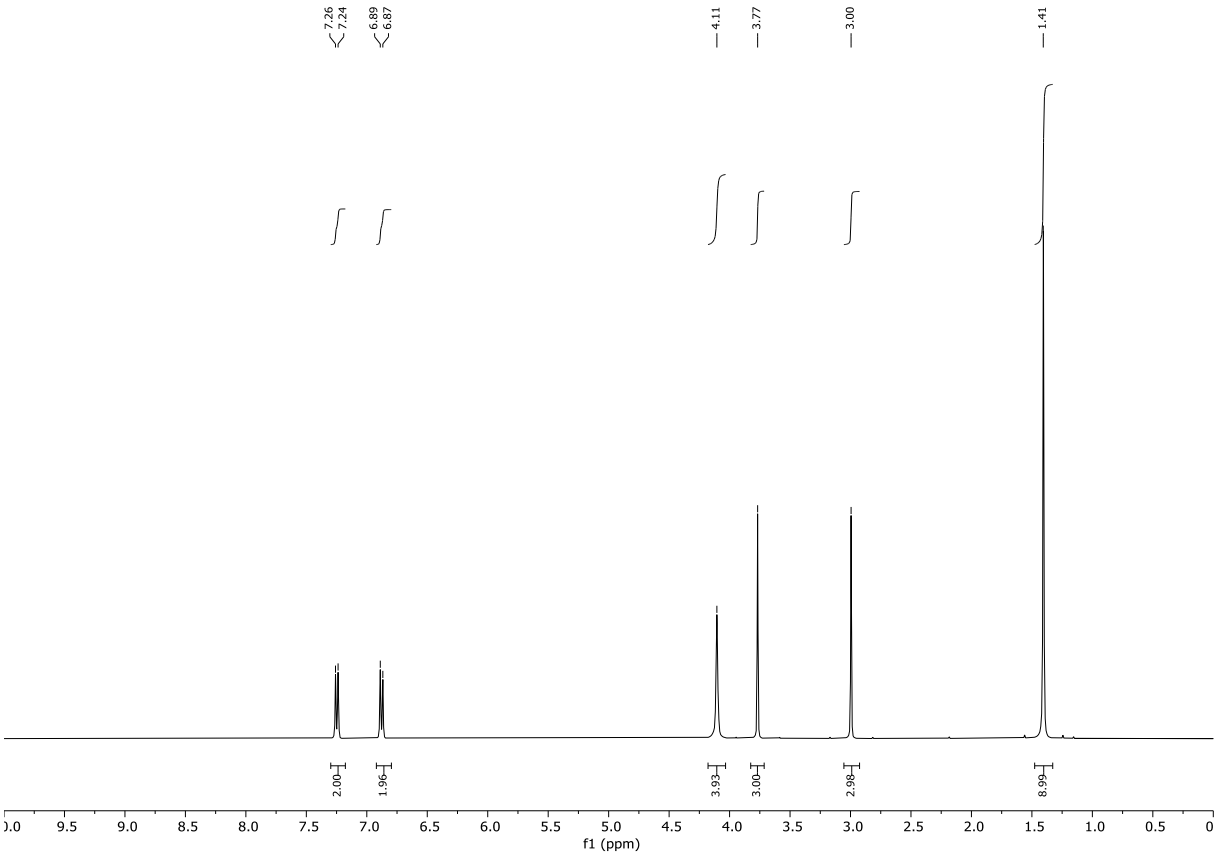


***tert*-Butyl 3-methoxy-3-(4-methoxyphenyl)azetidine-1-carboxylate (selected example)**

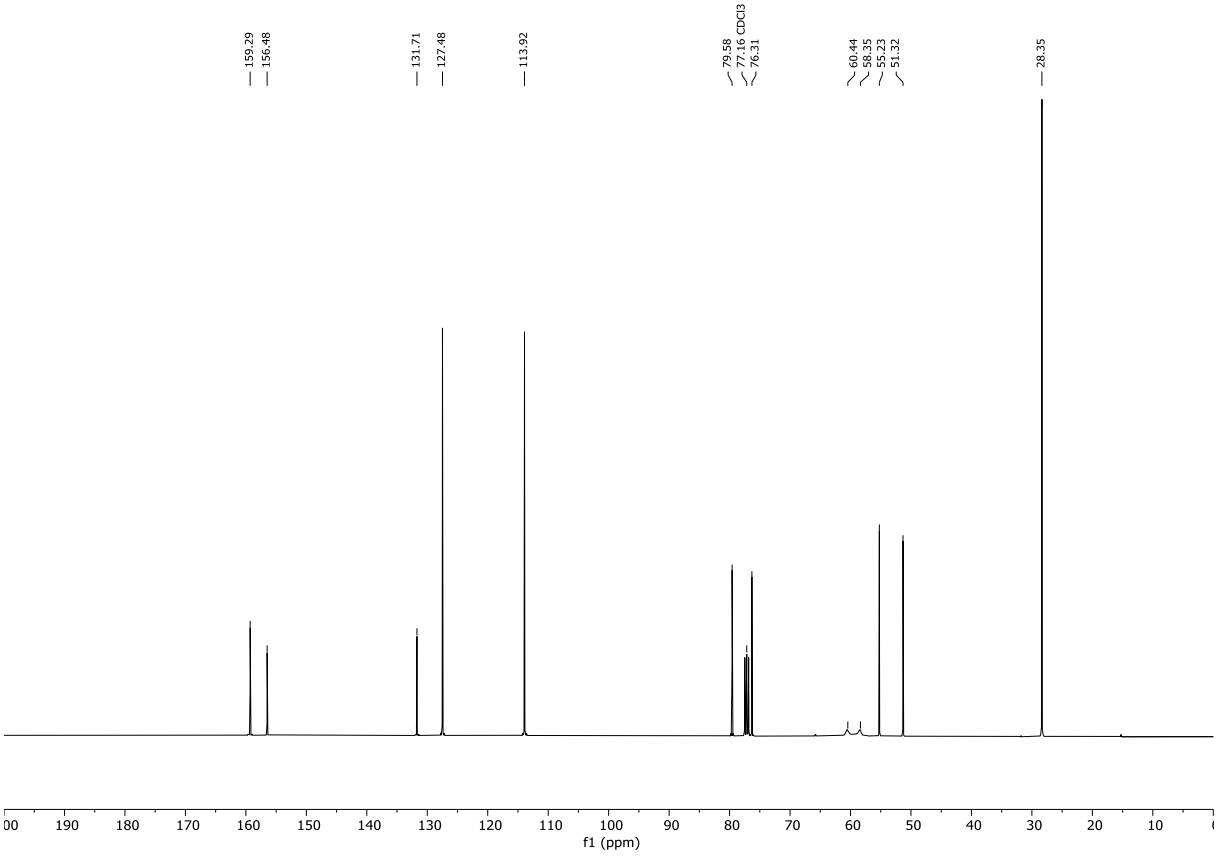
Using *tert*-butyl 3-oxoazetidine-1-carboxylate provided the product (3.75 mmol, 1.100 g, 75%) as colourless oil.

R_f = 0.5 (hexane/EtOAc 9:1, UV, $KMnO_4$, PAA). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.5 Hz, 2H), 6.88 (d, *J* = 8.5 Hz, 2H), 4.11 (s, 4H), 3.77 (s, 3H), 3.00 (s, 3H), 1.41 ppm (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.3, 156.5, 131.7, 127.5, 113.9, 79.6, 76.3, 60.4, 58.4, 55.2, 51.3, 28.3 ppm. **LRMS** (ESI-quadrupole): *m/z* (%): 294.2 (85), 279.1 (45), 206.1 (100), 162.1 (5). **HRMS** (ESI-quadrupole): m/z: Calcd for $C_{16}H_{24}NO_4^+$: 294.1700, found 294.1702. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2974 (w), 2938 (w), 2882 (w), 2836 (vw), 1698 (vs), 1612 (m), 1584 (w), 1514 (m), 1456 (m), 1390 (vs), 1366 (s), 1304 (m), 1276 (m), 1246 (vs), 1166 (s), 1148 (s), 1104 (vs), 1070 (s), 1034 (s), 1016 (m), 1002 (m), 930 (w), 860 (m), 830 (s), 808 (m), 770 (m), 732 cm^{-1} (w).

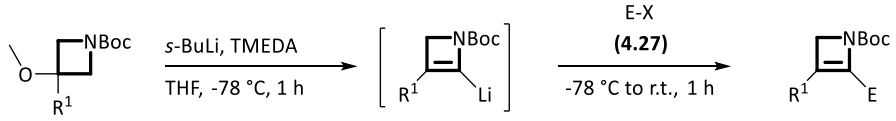
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (101 MHz, $CDCl_3$)

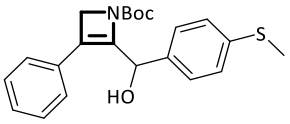


Synthesis of 2,3-substituted 1-Boc-2-azetines



(4.25) **(4.26)** **(4.28)**

Azetidines **4.25** (0.5 mmol, 1.0 equiv.) were dissolved in THF (0.1 M) and the solution was cooled down to -78 °C. After the addition of TMEDA (1.3 mmol, 2.5 equiv.), *sec*-BuLi (1.3 mmol, 2.5 equiv.) was added dropwise and the mixture was stirred for one hour. The reaction was then treated with the corresponding electrophile **4.27** (1.0 mmol, 1.0 equiv.), stirred for 30 minutes and warmed up to room temperature. After workup with saturated NH_4Cl and extraction with diethyl ether (2 x 10 mL), the organic phases were combined and dried over sodium sulfate. The solvents were evaporated, and the crude product was purified by column chromatography on preneutralized silica gel (1% NEt_3) to obtain 2,3-substituted 1-Boc-2-azetines **4.28**.

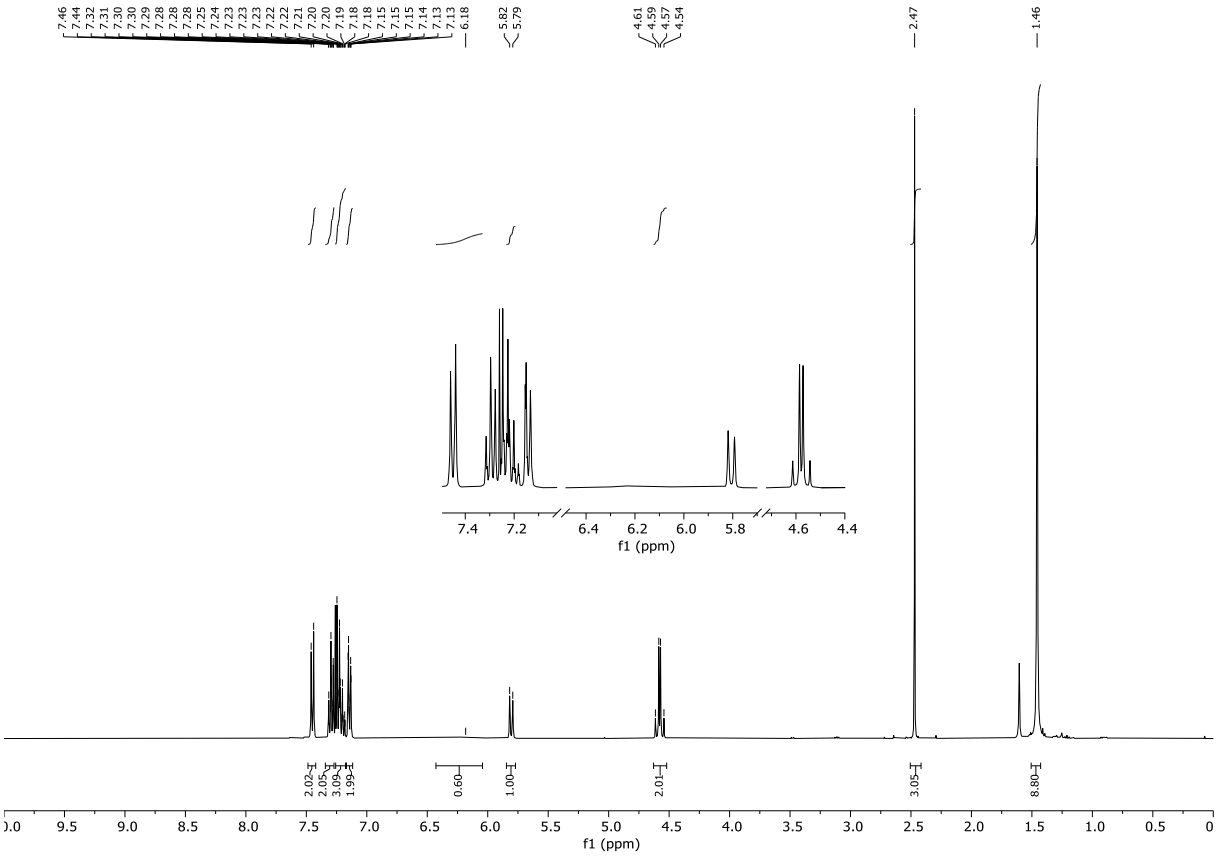


***tert*-Butyl 4-(hydroxy(4-(methylthio)phenyl)methyl)-3-phenylazete-1(*2H*)-carboxylate(selected example)**

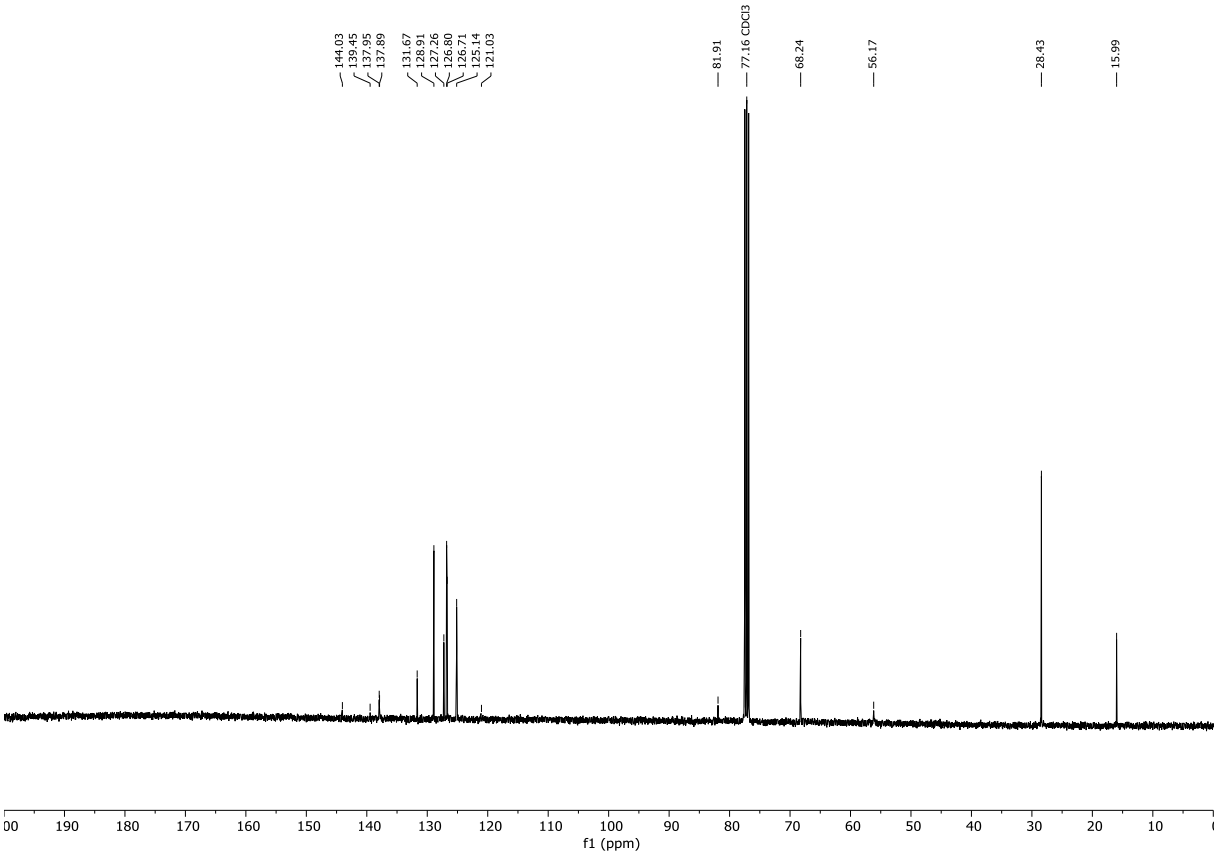
Using tert-butyl 3-methoxy-3-phenylazetidine-1-carboxylate provided the product (0.30 mmol, 115 mg, 60%) as yellow oil.

***R*f** = 0.55 (hexane/EtOAc 8:2, UV, $KMnO_4$, PAA). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.2 Hz, 2H), 7.33-7.27 (m, 2H), 7.25-7.17 (m, 3H), 7.16-7.12 (m, 2H), 6.18 (s, 1H), 5.81 (d, *J* = 10.3 Hz, 1H), 4.60 (d, *J* = 11.3 Hz, 1H), 4.56 (d, *J* = 11.2 Hz, 1H), 2.47 (s, 3H), 1.46 ppm (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 144.0, 139.5, 137.9, 137.9, 131.7, 128.9, 127.3, 126.8, 126.7, 125.1, 121.0, 81.9, 68.2, 56.2, 28.4, 16.0 ppm. **LRMS** (ESI-quadrupole): 367.2 (10), 366.2 (75), 310.0 (100), 266.1 (10). **HRMS** (ESI-quadrupole): m/z: Calcd for $C_{22}H_{24}NO_2S^+$[M-OH]$^+$: 366.1528, found 366.1525. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3334 (w), 2974 (w), 2922 (w), 2874 (w), 1672 (s), 1598 (w), 1492 (m), 1478 (m), 1448 (s), 1412 (vs) cm^{-1}(s).

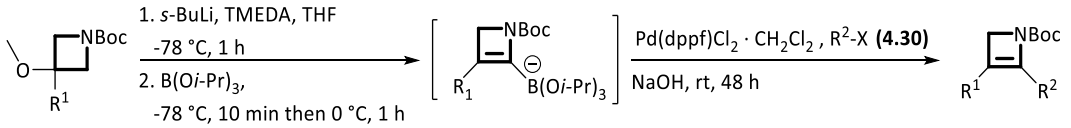
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (101 MHz, $CDCl_3$)

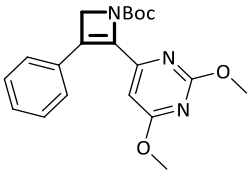


Synthesis of 2,3-substituted 1-Boc-2-azetines through Suzuki cross-coupling



(4.25) **(4.29)** **(4.31)**

Azetidines **4.25** (0.5 mmol, 1.0 equiv.) were dissolved in THF (0.1 M) and the solution was cooled down to -78 °C. After the addition of TMEDA (1.3 mmol, 2.5 equiv.), *sec*-BuLi (1.3 mmol, 2.5 equiv.) was added dropwise and the mixture stirred for one hour. B(O*i*-Pr)$_3$ (1.0 mmol, 2.0 equiv.) was then added and the resulting mixture was stirred for 10 min at -78 °C before being warmed to 0 °C and stirred for another hour. Pd(dppf)$Cl_2 \cdot CH_2Cl_2$ (4 mol%), the corresponding aryl halide **4.30** (1.0 mmol, 2.0 equiv.) and an aqueous solution of sodium hydroxide (1.5 mmol, 3.0 equiv., 1 M) were consecutively added. The reaction mixture was then stirred for 48 h at ambient temperature. After aqueous workup and extraction with diethyl ether (2 x 10 mL), the organic phases were combined and dried over sodium sulfate. The solvents were evaporated, and the crude product was purified by column chromatography on preneutralized silica gel (1% NEt_3) obtain 2,3-substituted 1-Boc-2-azetines **4.31**.

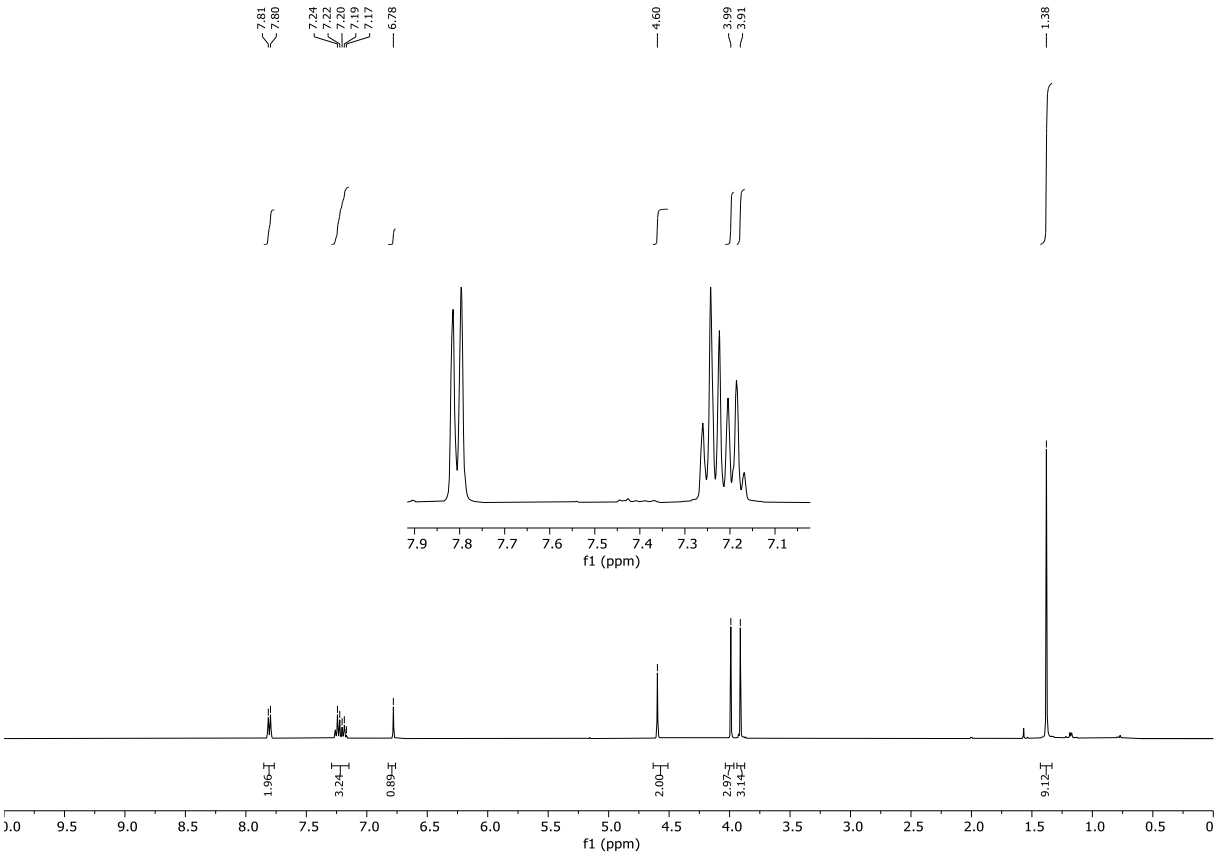


***tert*-Butyl 4-(2,6-dimethoxypyrimidin-4-yl)-3-phenylazete-1(2*H*)-carboxylate (selected example)**

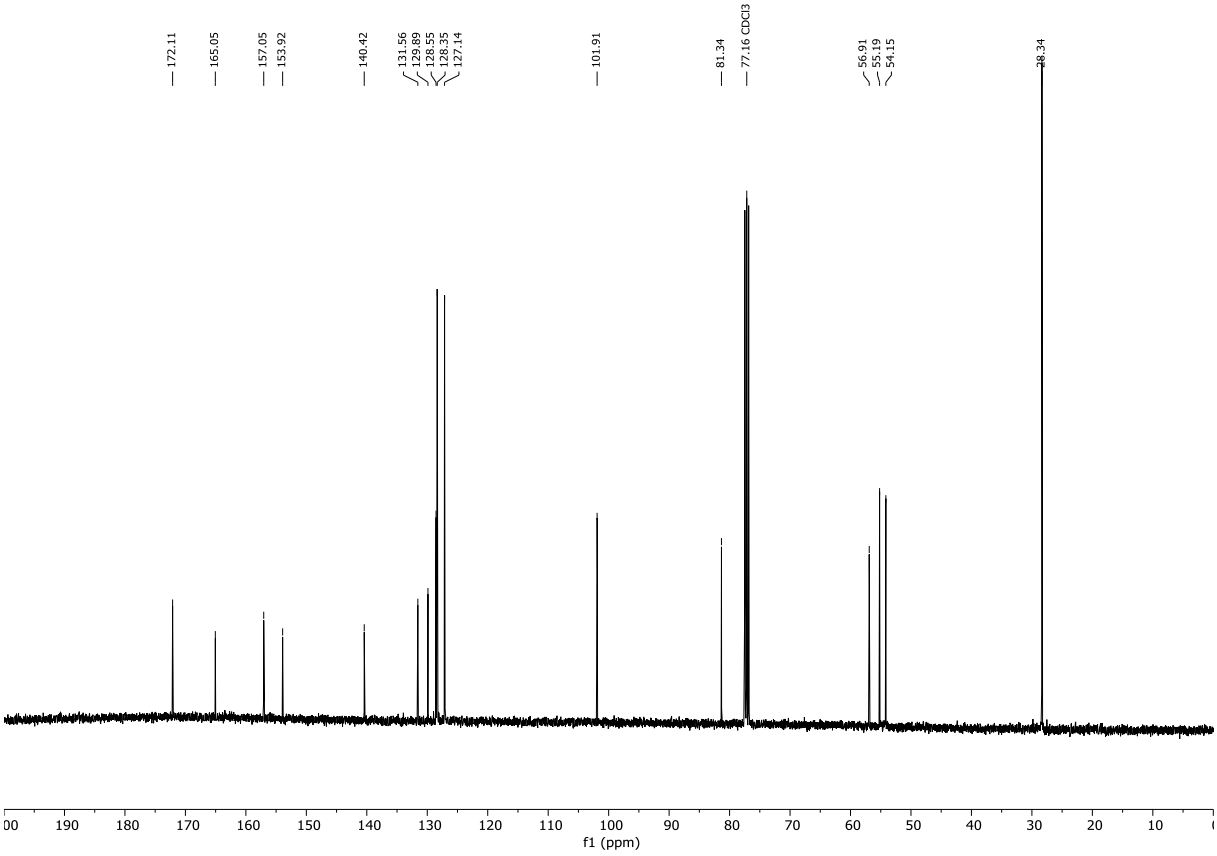
Using tert-butyl 3-methoxy-3-phenylazetidine-1-carboxylate provided the product (0.40 mmol, 146 mg, 79%) as yellow oil.

***R*$_f$** = 0.5 (hexane/EtOAc 8:2, UV, $KMnO_4$, PAA). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 7.3 Hz, 2H), 7.27-7.16 (m, 3H), 6.78 (s, 1H), 4.60 (s, 2H), 3.99 (s, 3H), 3.91 (s, 3H), 1.38 ppm (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.1, 165.1, 157.0, 153.9, 140.4, 131.6, 129.9, 128.5, 128.4, 127.1, 101.9, 81.3, 56.9, 55.2, 54.2, 28.3 ppm. **LRMS** (ESI-quadrupole): *m/z* 369.3 (15), 301.2 (5), 296.2 (10), 268.2 (100), 254.1 (10), 196.1 (15), 166.0 (40), 140.0 (55). **HRMS** (ESI-quadrupole): Calcd for $C_{20}H_{23}N_3O_4^+$: 369.1689, found 369.1684. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2978 (w), 2954 (w), 2856 (vw), 1742 (w), 1706 (s), 1626 (w), 1578 (s), 1556 (s), 1496 (w), 1476 (m), 1456 (m), 1390 (s), 1354 cm^{-1} (vs).

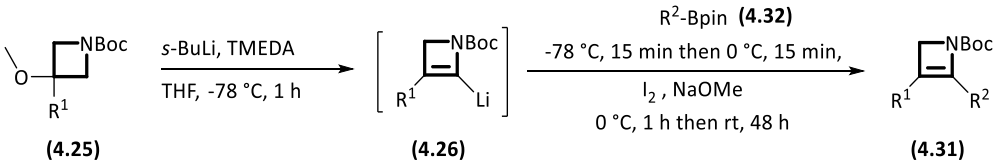
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (101 MHz, $CDCl_3$)

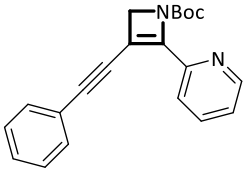


Synthesis of 2,3-substituted 1-Boc-2-azetines through Zweifel reaction



(4.25) **(4.26)** **(4.31)**

Azetidines **4.25** (0.5 mmol, 1.0 equiv.) were dissolved in THF (0.1 M) and the solution was cooled down to -78 °C. After the addition of TMEDA (1.3 mmol, 2.5 equiv.), *sec*-BuLi (1.3 mmol, 2.5 equiv.) was added dropwise and the mixture was stirred for one hour. The corresponding pinacol arylboronate **4.32** was added in THF (0.5 mmol, 1.0 equiv., 0.25 M) and the resulting mixture was stirred at -78 °C and then 0 °C for 15 min each. The mixture was then cooled back to -78 °C and a solution of iodine in THF (0.5 mmol, 1.0 equiv., 0.25 M) was added dropwise, followed by the addition of a suspension of sodium methoxide in methanol (5.0 mmol, 10 equiv., 2.5 M). The mixture was then stirred at 0 °C for 30 min and subsequently at ambient temperature overnight. After aqueous workup and extraction with diethyl ether (2 x 10 mL), the organic phases were combined and dried over sodium sulfate. The solvents were evaporated, and the crude product was purified by column chromatography on preneutralized silica gel (1% NEt_3) obtain 2,3-substituted 1-Boc-2-azetines **4.31**.

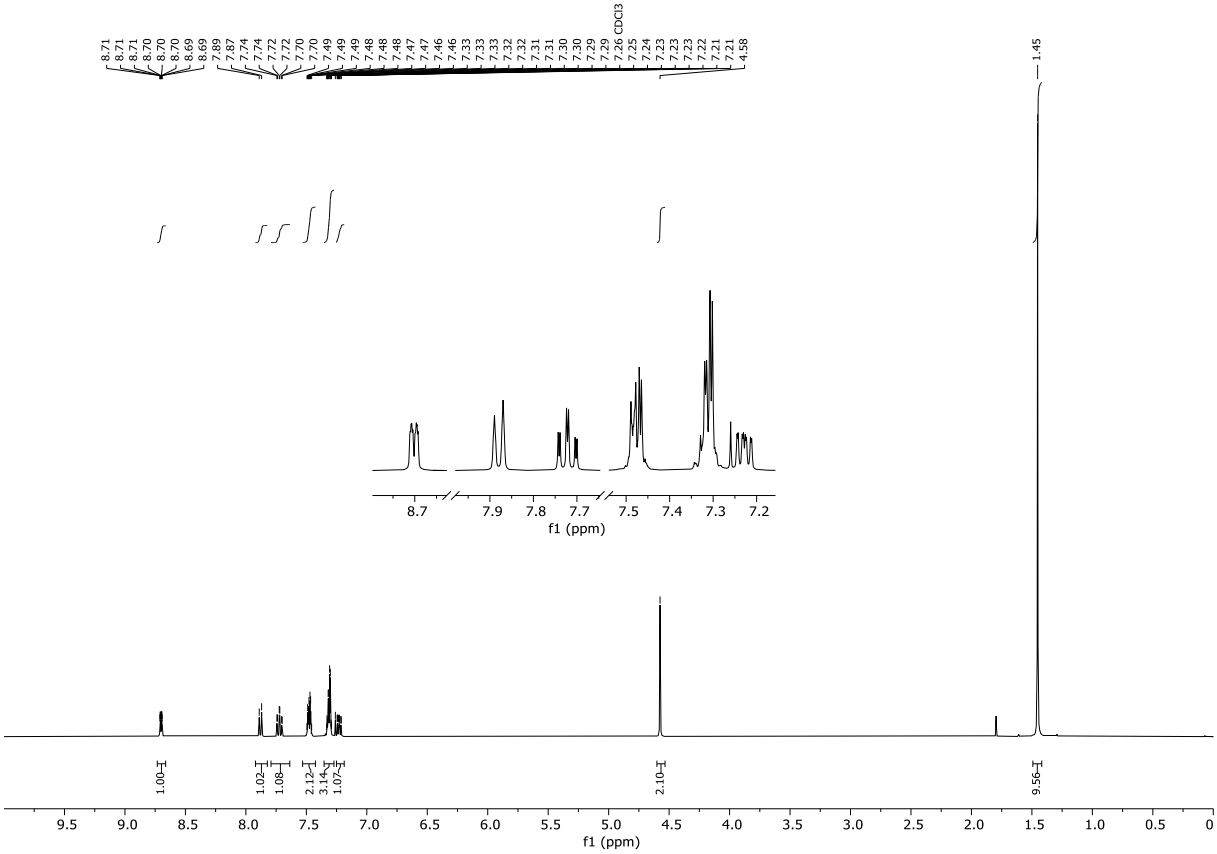


***tert*-Butyl 3-(phenylethynyl)-4-(pyridin-2-yl)azete-1(2*H*)-carboxylate (selected example)**

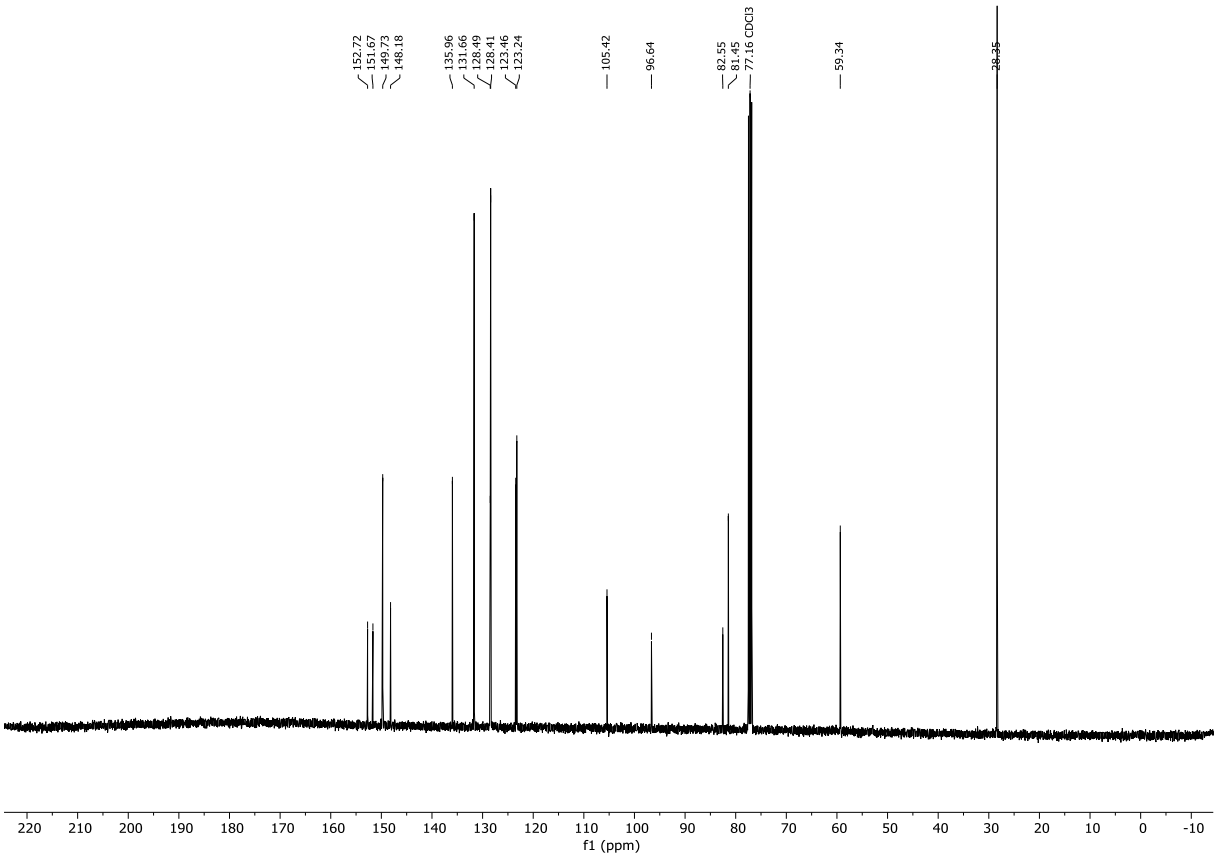
Using tert-butyl 3-methoxy-3-(phenylethynyl)azetidine-1-carboxylate provided the product (0.34 mmol, 111 mg, 67%) as orange oil.

R_f = 0.7 (hexane/EtOAc 8:2, UV, $KMnO_4$, PAA). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.70 (ddd, *J* = 4.8, 1.8, 1.0 Hz, 1H), 7.88 (d, *J* = 7.9 Hz, 1H), 7.72 (td, *J* = 7.8, 1.8 Hz, 1H), 7.53-7.43 (m, 2H), 7.36-7.29 (m, 3H), 7.23 (ddd, *J* = 7.5, 4.8, 1.2 Hz, 1H), 4.58 (s, 2H), 1.45 ppm (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 152.7, 151.7, 149.7, 148.2, 136.0, 131.7, 128.5, 128.4, 123.5, 123.2, 105.4, 96.6, 82.5, 81.4, 59.3, 28.3 ppm. **LRMS** (EI-Orbitrap): *m/z* 332.3 (20), 259.2 (5), 232.2 (100), 204.1 (10), 127.0 (5), 105.0 (15). **HRMS** (EI-Orbitrap): m/z: [M^+] Calcd for $C_{21}H_{20}N_2O_2^+$: 332.1525, found 332.1520. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2978 (w), 2944 (vw), 2934 (vw), 1708 (vs), 1654 (vw), 1646 (vw), 1628 (w), 1580 (w), 1560 (vw), 1506 cm^{-1} (vw).

^{1}H NMR (400 MHz, $CDCl_3$)

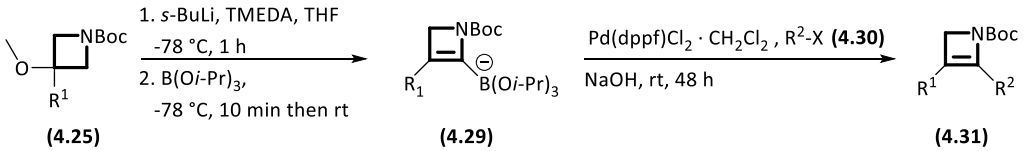


^{13}C NMR (101 MHz, $CDCl_3$)



12.2 One-Pot Preparation of Stable Organoboronate Reagents for the Functionalization of Unsaturated Four- and Five-Membered Carbo- and Heterocycles

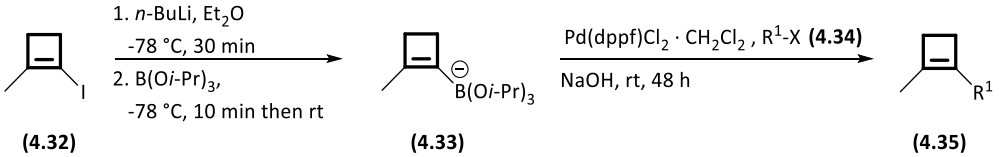
Synthesis of stable azetine-containing-borates and further stability tests *via* Suzuki-Miyaura cross-coupling



Azetidines **4.25** (10 mmol, 1.0 equiv.) were dissolved in THF (0.1 M) and the solution was cooled down to -78 °C. After the addition of TMEDA (13 mmol, 2.5 equiv.), *sec*-BuLi (13 mmol, 2.5 equiv.) was added dropwise and the mixture was stirred for one hour. B(O*i*-Pr)$_3$ (10 mmol, 2.0 equiv.) was then added and the resulting mixture was stirred for 10 min at -78 °C before being warmed to room temperature and stirred for another 1 h. The so obtained tetraorganoborates **4.29** were stored under different conditions and, regarding to stability, tested over several month *via* Suzuki-Miyaura cross-coupling reactions:

Pd(dppf)Cl$_2$ · CH$_2$Cl$_2$ (4 mol%), the corresponding aryl halide **4.30** (1.0 mmol, 2.0 equiv.) and an aqueous solution of sodium hydroxide (1.5 mmol, 3.0 equiv., 1 M) were consecutively added to the dissolved tetraorganoborate **4.29** in THF (0.5 mmol, 1.0 equiv.). The reaction mixture was then stirred for 48 h at ambient temperature. After aqueous workup and extraction with diethyl ether (2 x 10 mL), the organic phases were combined and dried over sodium sulfate. The solvents were evaporated, and the crude product was purified by column chromatography on preneutralized silica gel (1% NEt$_3$) obtain 2,3-substituted 1-Boc-2-azetines **4.31**.

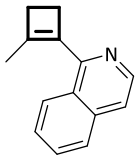
Synthesis of stable cyclobutene-containing-borates and further stability tests *via* Suzuki-Miyaura cross-coupling



To a solution of 1-iodo-2-methylcyclobut-1-ene **4.32** (10 mmol, 1.0 equiv.) in Et$_2$O (0.5 M) a solution of *n*-BuLi (11 mmol, 1.1 equiv.) was slowly added at -78 °C. After stirring for 30 min at the aforementioned temperature, B(O*i*-Pr)$_3$ (11.5 mmol, 1.15 equiv.) and THF (total concn 0.25 M) were added and the resulting mixture was stirred for an additional 1 h at room temperature. Then obtained

tetraorganoborate **4.33** was stored under different conditions and, regarding to stability, tested over several month *via* Suzuki-Miyaura cross-coupling reactions:

$Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (4 mol%), the corresponding aryl halide **4.30** (1.0 mmol, 2.0 equiv.) and an aqueous solution of sodium hydroxide (1.5 mmol, 3.0 equiv., 1 M) were consecutively added to the dissolved tetraorganoborate **4.33** in THF (0.5 mmol, 1.0 equiv.). The reaction mixture was then stirred for 48 h at ambient temperature. After aqueous workup and extraction with diethyl ether (2 x 10 mL), the organic phases were combined and dried over sodium sulfate. The solvents were evaporated, and the crude product was purified by column chromatography on silica gel to obtain functionalized cyclobutenes **4.35**.

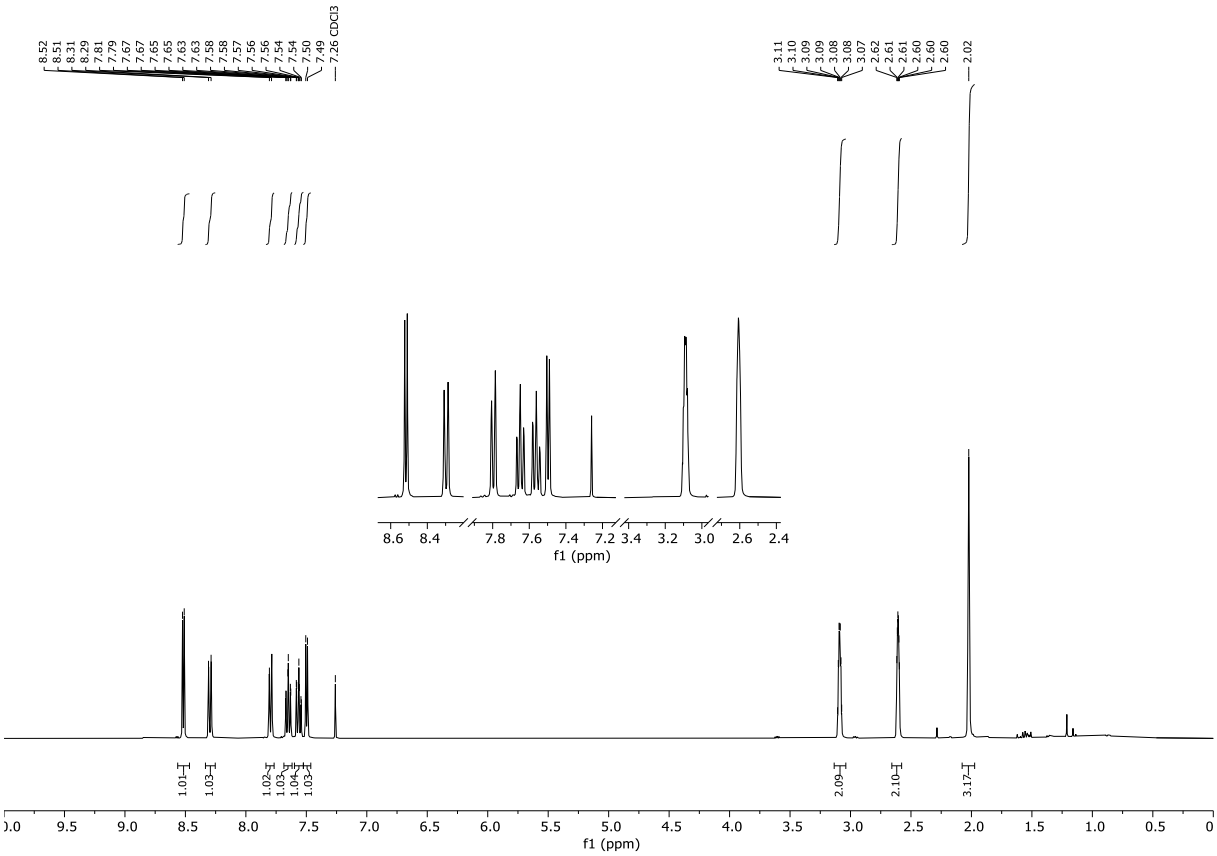


1-(2-Methylcyclobut-1-en-1-yl)isoquinoline (selected example)

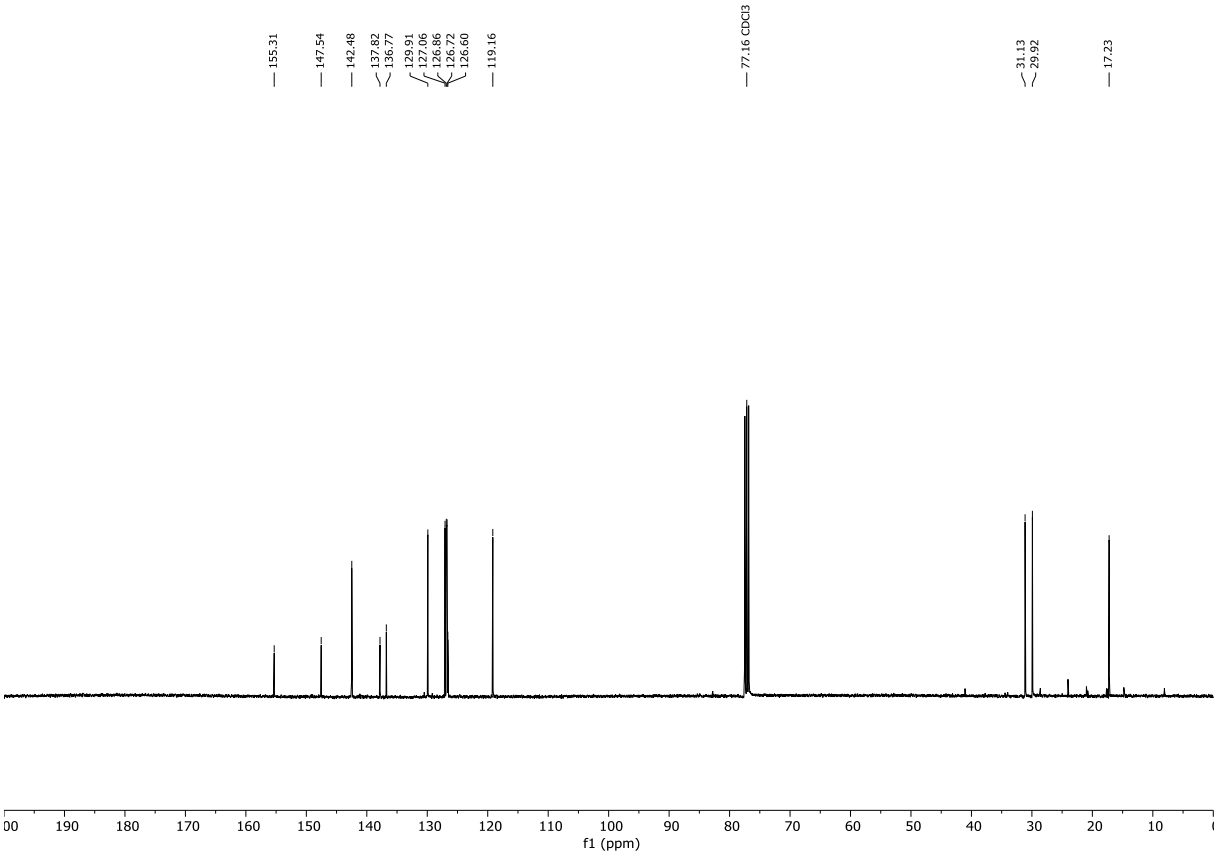
Using 1-iodo-2-methylcyclobut-1-ene provided the product (0.13 mmol, 25 mg, 64%) as a colorless oil.

R_f = 0.3 (hexane/EtOAc 9:1, UV, KMnO4, PAA). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 8.52 (d, *J* = 5.6 Hz, 1H), 8.30 (d, *J* = 8.5 Hz, 1H), 7.80 (d, *J* = 7.0 Hz, 1H), 7.67-7.63 (m, 1H), 7.56 (ddd, *J* = 8.2, 6.8, 1.3 Hz, 1H), 7.50 (d, *J* = 5.6 Hz, 1H), 3.11-3.06 (m, 2H), 2.63-2.57 (m, 2H), 2.02 ppm (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.3, 147.5, 142.5, 137.8, 136.8, 129.9, 127.1, 126.9, 126.7, 126.6, 119.2, 31.1, 29.9, 17.2 ppm. **LRMS** (EI-Orbitrap): *m/z* 194 $[M-H]^+$ (100), 180 (100), 167 (30), 154 (20). **HRMS** (EI-Orbitrap): m/z: $[M^+]$ Calcd for $C_{14}H_{12}N$: 194.0970 $[M-H]^+$; found: 194.0962.

^{1}H NMR (400 MHz, $CDCl_3$)

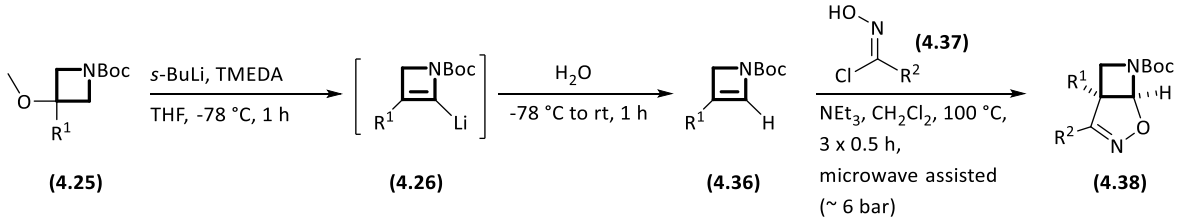


^{13}C NMR (101 MHz, $CDCl_3$)

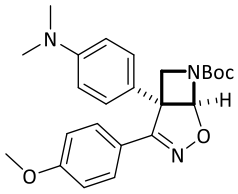


12.3 Chemodivergent and Stereoselective Access to Fused Isoxazoline Azetidines and Thietanes through [3+2]-Cycloadditions

Synthesis of fused isoxazoline azetidines with mono-substituted azetines



Azetidines **4.25** (1 mmol, 1.0 equiv.) were dissolved in THF (0.1 M) and the solution was cooled down to -78 °C. After the addition of TMEDA (1.3 mmol, 2.5 equiv.), *sec*-BuLi (1.3 mmol, 2.5 equiv.) was added dropwise and the mixture was stirred for one hour. The reaction was then treated with water (2.0 mmol, 2 equiv.), stirred for 30 minutes and warmed up to room temperature. The solvents were evaporated and the crude azetines **4.36** were dissolved in dichloromethane (0.25 M) and transferred in a BIOTAGE Microwave reaction vessel equipped with a magnetic stirring bar. Triethylamine (3 mmol, 6.0 equiv.) was added at once at room temperature followed by the corresponding chlorooxime **4.37** (1 mmol, 1 equiv.). The vial was sealed and heated in a BIOTAGE Initiator+ Robot Sixty microwave synthesizer to 100 °C (measured by the vertically focused IR temperature sensor) for 30 min. The reaction cycle was repeated another two times, each time adding additionally 1.0-2.0 equiv. of chlorooxime **4.37** (2.0-3.0 equiv. in total). The completion of the cycloaddition reaction was monitored by thin layer chromatography. After the reaction was complete, the crude mixture was extracted three times with dichloromethane. The combined organic layers were dried over magnesium sulfate, filtered and concentrated under reduced pressure. Purification of the crude products by flash column chromatography with appropriate solvent mixtures afforded the desired cycloaddition reaction products **4.38**.

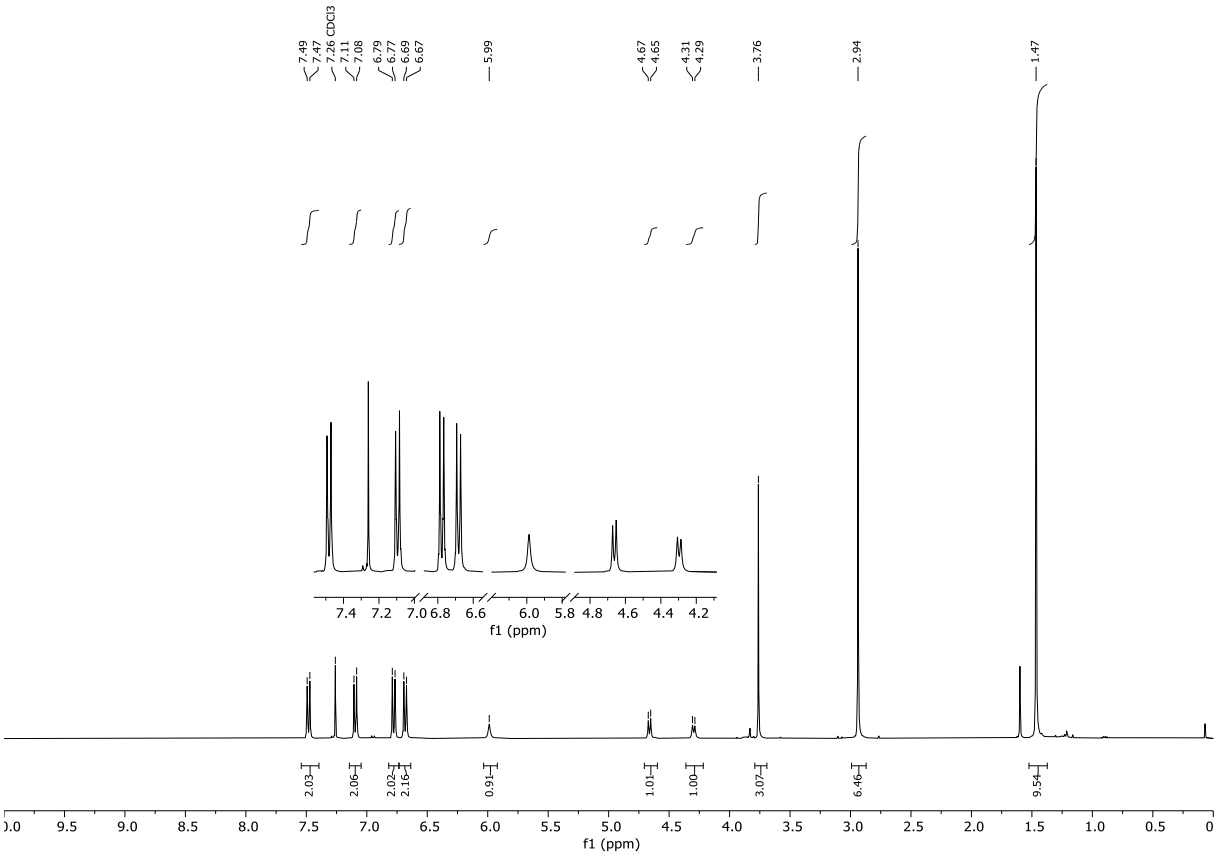


***tert*-Butyl-(1*S**,5*R**)-5-(4-(dimethylamino)phenyl)-4-(4-methoxyphenyl)-2-oxa-3,7-diazabicyclo[3.2.0]hept-3-ene-7-carboxylate (selected example)**

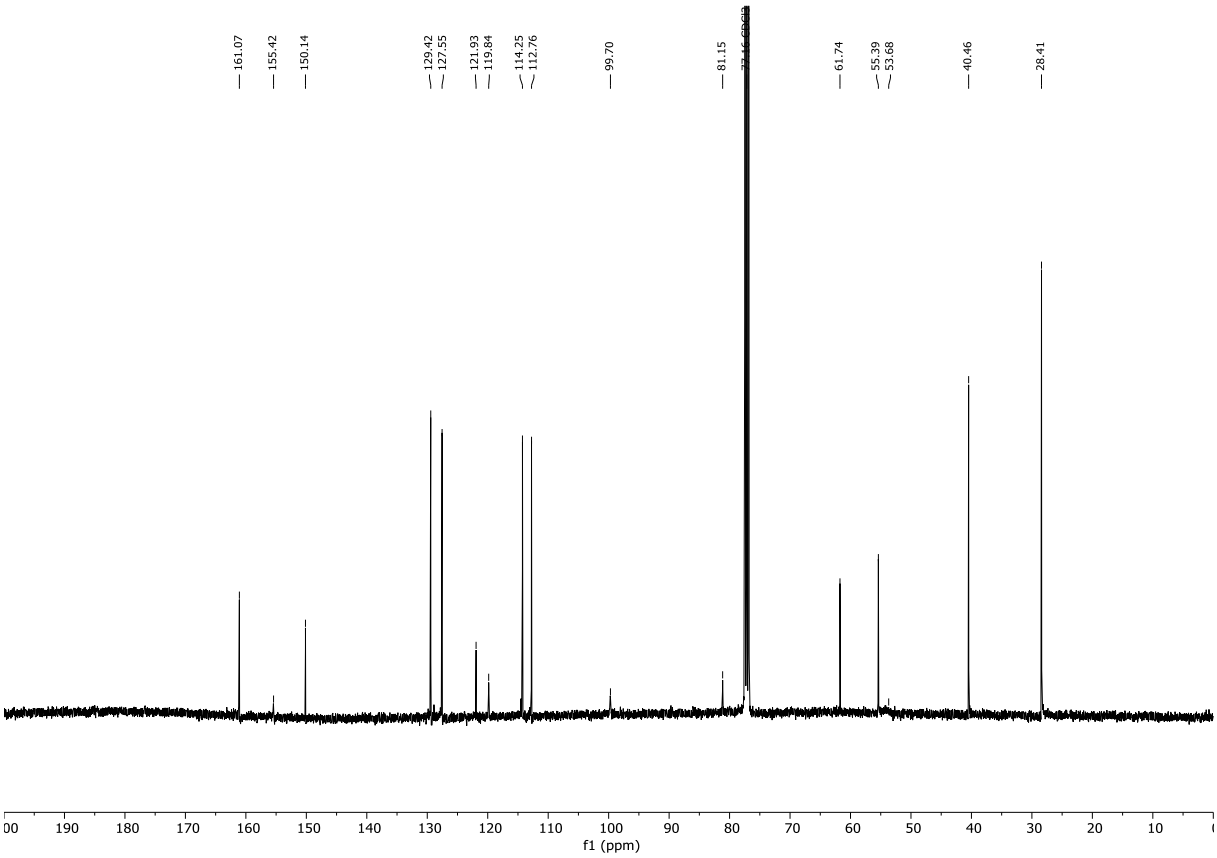
Using t*ert*-Butyl 3-(4-(dimethylamino)phenyl)-3-methoxyazetidine-1-carboxylate provided the product (0.22 mmol, 91 mg, 44%) as yellowish oil.

R_f = 0.5 (hexane/EtOAc 7:3, UV, $KMnO_4$, PAA). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.50-7.46 (m, 2H), 7.12-7.07 (m, 2H), 6.80-6.75 (m, 2H), 6.72-6.65 (m, 2H), 5.99 (s, 1H), 4.66 (d, *J* = 8.0 Hz, 1H), 4.30 (d, *J* = 8.0 Hz, 1H), 3.76 (s, 3H), 2.94 (s, 6H), 1.47 ppm (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.1, 155.4, 150.1, 129.4, 127.5, 121.9, 119.8, 114.3, 112.8, 99.7, 81.1, 61.7, 55.4, 53.7, 40.5, 28.4 ppm. **LRMS** (DEP/EI-Orbitrap): *m/z* (%): 423.5 (15), 323.3 (90), 294.2 (100). **HRMS** (EI-Orbitrap): m/z: [M^+] Calcd for $C_{24}H_{29}N_3O_4^+$: 423.2158; found: 423.2152. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2976 (w), 2934 (vw), 2897 (vw), 2838 (vw), 2251 (vw), 1703 (m), 1610 (m), 1524 (m), 1514 cm^{-1} (m).

^{1}H NMR (400 MHz, $CDCl_3$)



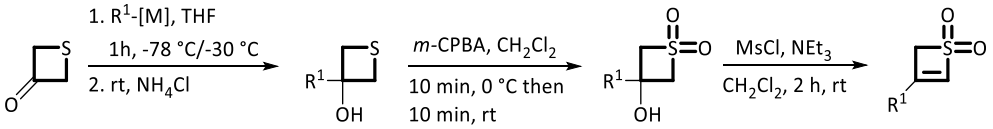
^{13}C NMR (101 MHz, $CDCl_3$)



13 Experimental for Chapter III

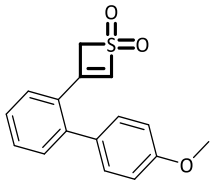
13.1 Chemodivergent and Stereoselective Access to Fused Isoxazoline Azetidines and Thietanes through [3+2]-Cycloadditions

Synthesis of mono-substituted thiete dioxides



(4.39) **(4.40)** **(4.41)** **(4.42)**

A flask was charged with thietan-3-one **4.39** (10.0 mmol, 1.0 equiv.) and THF (0.5 M) was added. The reaction mixture was cooled to -78 °C and a solution of organolithium reagent (1.30 equiv.) was added dropwise. Alternatively, the reaction mixture was cooled to -30 °C and a solution of organomagnesium reagent (1.30 equiv.) was added dropwise. After stirring for 60 min the mixture was brought to ambient temperature and treated with a solution of saturated aqueous NH_4Cl. The aqueous phase was extracted with dichloromethane (3 × 50 mL) and washed with a solution of saturated aqueous sodium chlorid (1 × 50 mL). The combined organic phases were dried over magnesium sulfate and concentrated in vacuo. The residue, containing the thietanol **4.40**, was dissolved in dichloromethane (50 mL), cooled to 0 °C and *m*-CPBA (20.0 mmol, 2.0 equiv., 77%) was added portion wise. After TLC showed full conversion of the thietanol **4.40** (approx. 10 min) water was added. The aqueous phase was extracted with dichloromethane (3 × 50 mL) and washed with a solution of saturated aqueous sodium chloride (1 × 50 mL). The combined organic phases were dried over magnesium sulfate, filtered and concentrated in vacuo. The residue, containing the thietanol dioxide **4.41**, was dissolved in dichloromethane (50 mL) and triethylamine (30 mmol, 3.0 equiv.) was added. Mesylchlorid (30 mmol, 3.0 equiv.) was subsequently added dropwise and the mixture was stirred until TLC indicated full conversion of the starting thietanol dioxide **4.41** (approx. 30 min) water was added. The aqueous phase was extracted with dichloromethane (3 × 50 mL) and washed with a solution of saturated aqueous sodium chloride (1 × 50 mL). The combined organic phases were dried over magnesium sulfate, filtered and concentrated in vacuo. The crude thiete dioxides **4.42** were purified by flash column chromatography with appropriate solvent mixtures.

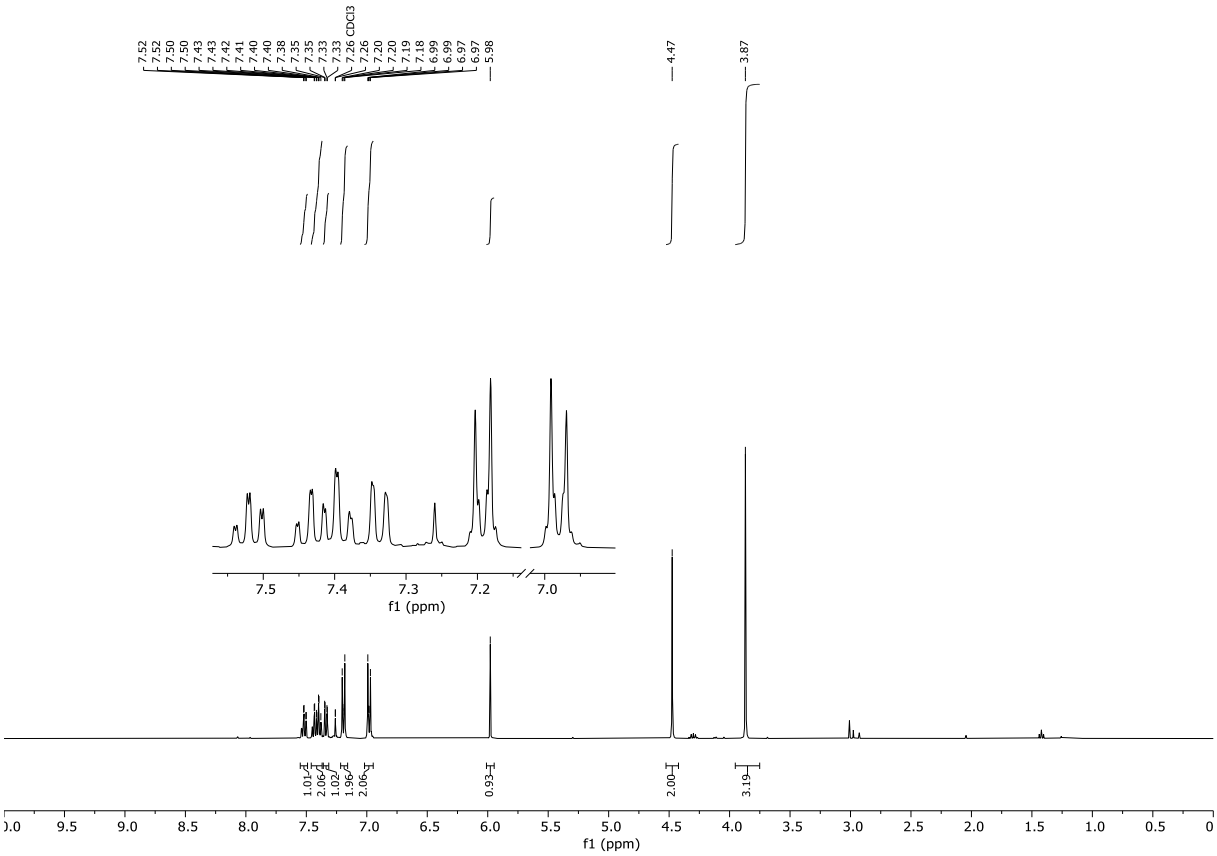


3-(4'-Methoxy-[1,1'-biphenyl]-2-yl)-*2H*-thiete 1,1-dioxide (selected example)

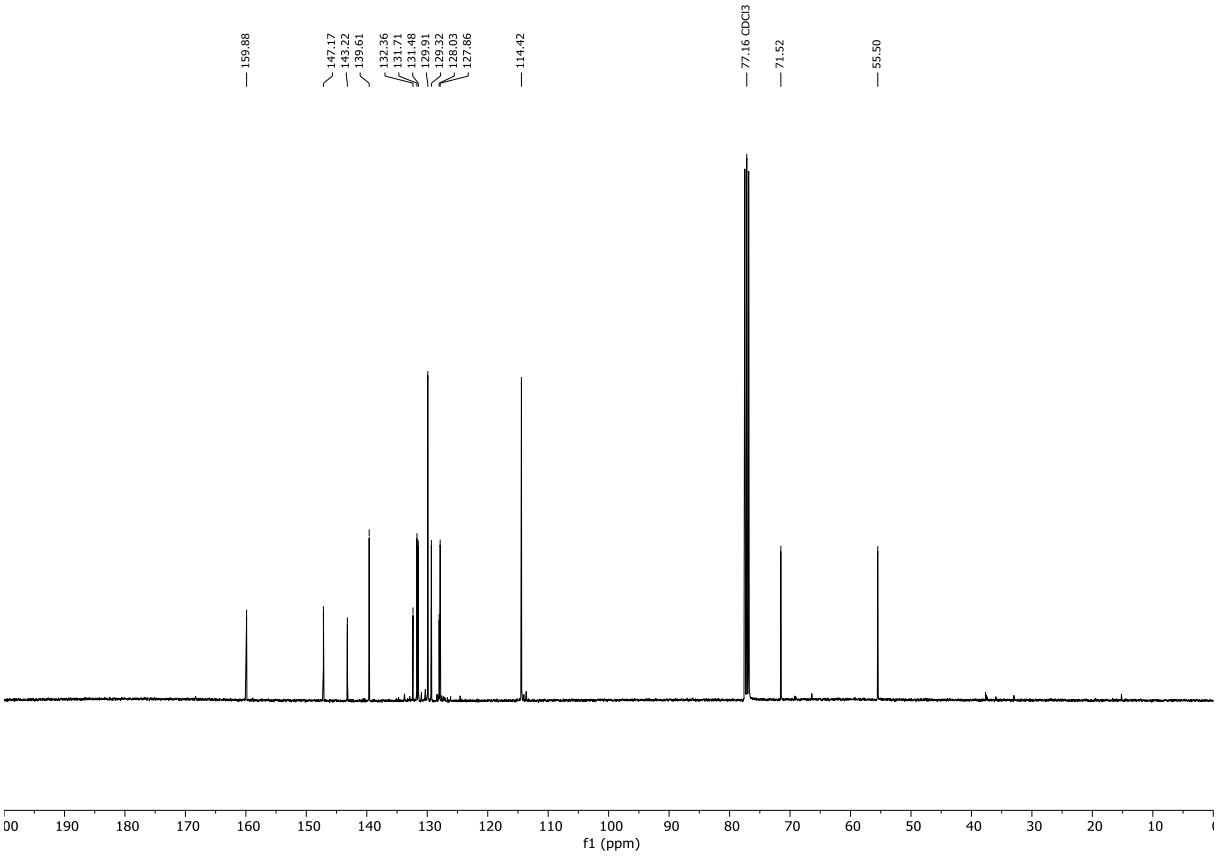
Using (4'-methoxy-[1,1'-biphenyl]-2-yl)lithium provided the product (1.37 g, 4.8 mmol, 48%) as a yellowish solid.

***R*f** = 0.25 (hexane/EtOAc 8:2, UV, $KMnO_4$, PAA). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.52 (td, *J* = 7.4, 1.6 Hz, 1H), 7.46-7.37 (m, 2H), 7.34 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.22-7.17 (m, 2H), 7.01-6.95 (m, 2H), 5.98 (s, 1H), 4.47 (s, 2H), 3.87 ppm (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.9, 147.2, 143.2, 139.6, 132.4, 131.7, 131.5, 129.9, 129.3, 128.0, 127.9, 114.4, 71.5, 55.5 ppm. **LRMS** (DEP/EI-Orbitrap): *m/z* (%): 286.1 (5), 237.1 (5), 221.0 (100), 207.0 (25). **HRMS** (EI-Orbitrap): m/z: [M]+ Calcd for $C_{16}H_{14}O_3{}^{32}S^+$: 286.0664; found: 286.0658. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2961 (w), 2958 (w), 2934 (w), 2929 (w), 2919 (w), 1610 (m), 1598 (w), 1574 (w), 1558 (w), 1516 cm^{-1} (m). **Melting point**: 120 (±2) °C.

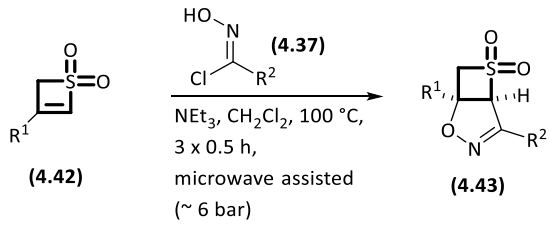
^{1}H NMR (400 MHz, $CDCl_3$)



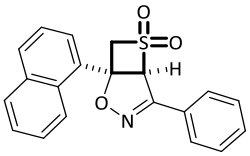
^{13}C NMR (101 MHz, $CDCl_3$)



Synthesis of fused isoxazoline thietanes with mono-substituted thiete dioxides



A 0.5-2.0 mL BIOTAGE Microwave reaction vessel equipped with a magnetic stirring bar was charged with the respective mono-substituted thiete dioxide **4.42** (0.2 mmol, 1.0 equiv.) followed by the corresponding chlorooxime **4.37** (0.2 mmol, 1.0 equiv.). The mixture was dissolved in dichloromethane (0.1 M) before triethylamine (1.2 mmol, 6.0 equiv.) was added at once at room temperature. The vial was sealed and heated in a BIOTAGE Initiator+ Robot Sixty microwave synthesizer to 100 °C (measured by the vertically focused IR temperature sensor) for 30 min. The reaction cycle was repeated another two times, each time adding additionally 1.0-2.0 equiv. of chlorooxime **4.37** (2.0-3.0 equiv. in total). The completion of the cycloaddition reaction was monitored by thin layer chromatography. After the reaction was complete, the crude mixture was extracted three times with dichloromethane. The combined organic layers were dried over magnesium sulfate, filtered and concentrated under reduced pressure. Purification of the crude products by flash column chromatography with appropriate solvent mixtures afforded the desired cycloaddition reaction products **4.43**.

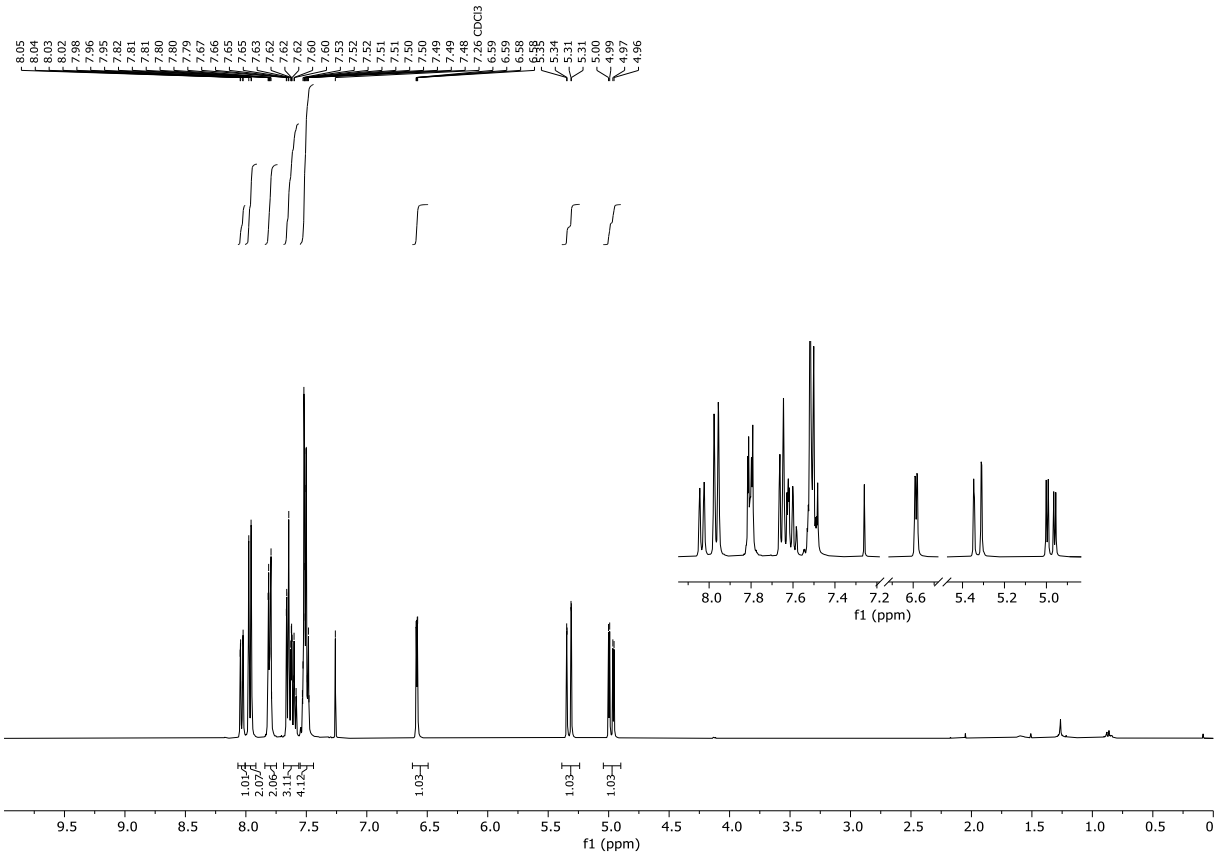


(1*S,5*S**)-1-(naphthalen-1-yl)-4-phenyl-2-oxa-6-thia-3-azabicyclo[3.2.0]hept-3-ene 6,6-dioxide (selected example)**

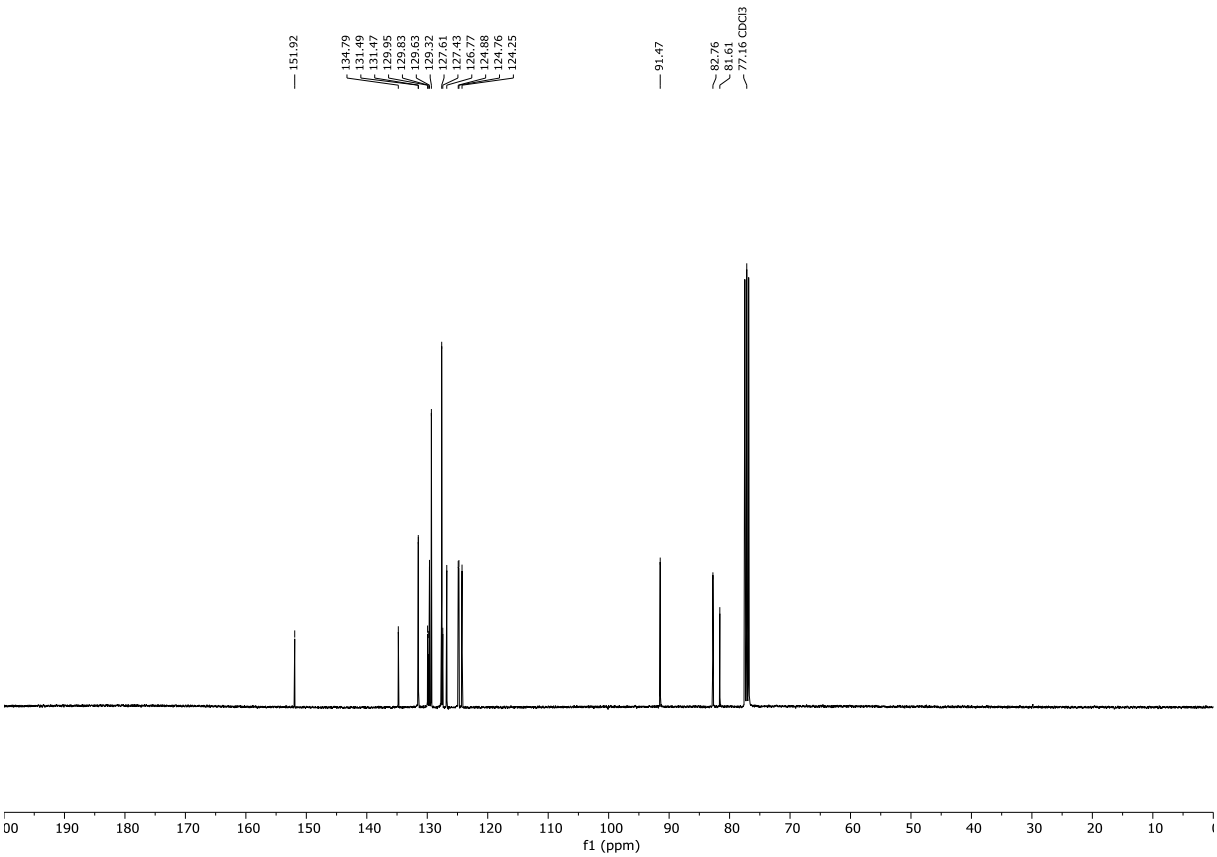
Using 3-(naphthalen-1-yl)-*2H*-thiete 1,1-dioxide provided the product (0.16 mmol, 56 mg, 80%) as white solid.

***R*f** = 0.5 (hexane/EtOAc 8:2, UV, $KMnO_4$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.4 Hz, 1H), 7.97 (d, *J* = 8.0 Hz, 2H), 7.83-7.76 (m, 2H), 7.68-7.57 (m, 3H), 7.54-7.47 (m, 4H), 6.59 (dd, *J* = 3.8, 1.3 Hz, 1H), 5.33 (dd, *J* = 14.3, 1.2 Hz, 1H), 4.98 ppm (dd, *J* = 14.4, 3.8 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 151.9, 134.8, 131.5, 131.5, 129.9, 129.8, 129.6, 129.3, 127.6, 127.4, 126.8, 124.9, 124.8, 124.3, 91.5, 82.8, 81.6 ppm. **LRMS** (DEP/EI-Orbitrap): *m/z* (%): 349.3 (10), 271.1 (100), 254.1 (5), 242.1 (3), 207.0 (30). **HRMS** (EI-Orbitrap): m/z: [M^+] Calcd for $C_{20}H_{15}NO_3S^+$: 349.0773; found: 349.0768. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3053(w), 3037(vw), 3021(w), 3018(w), 2992(vw), 2953(w), 2923(w), 2920(w), 1600(w), 1511 cm^{-1} (w). **Melting point**: 220 (±2) °C.

^{1}H NMR (400 MHz, $CDCl_3$)

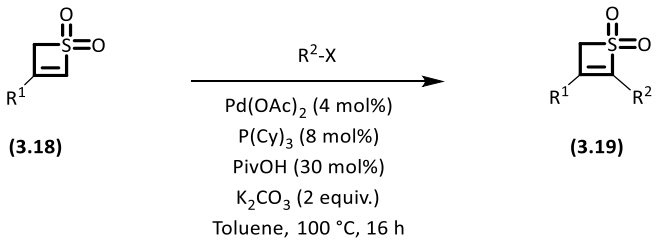


^{13}C NMR (101 MHz, $CDCl_3$)



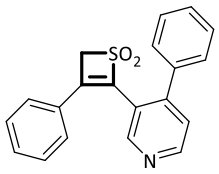
13.2 Disubstituted Thiete Dioxides – Donor/Acceptor- Interactions towards Axial Chirality

General procedure: C-H Functionalization of 2*H*-thiete 1,1- dioxides



(3.18) **(3.19)**

A pressure tube was charged with 2*H*-thiete 1,1- dioxides derivative **3.18** (0.2 mmol, 1 equiv.) and 2 mL toluene was added. Subsequently, K_2CO_3 (55 mg, 0.4 mmol, 2.0 equiv.), $Pd(Oak)_2$ (1.8 mg, 8 µmol, 4 mol%), tricyclohexylphosphane (PCy_3) (4.5 mg, 16 µmol, 8 mol%), the corresponding arylbromide (0.3 mmol, 1.5 equiv.) and a few drops of pivalic acid (~7 µL, 30 mol%) were added. The mixture was stirred at 100 °C in the sealed pressure tube until TLC showed consumption of the starting 2*H*-thiete 1,1- dioxides (approx. 16 hours). After cooling to ambient temperature, the tube was opened and a 1:1 mixture of H_2O:Et_2O (4 mL) was added. The aqueous phase was extracted with Et_2O (3 x 20 mL). The combined organic phases were dried over magnesium sulfate, filtrated, concentrated in vacuo and purified by flash-column chromatography on silica gel with the appropriate solvent mixture to obtain pure **3.19**.

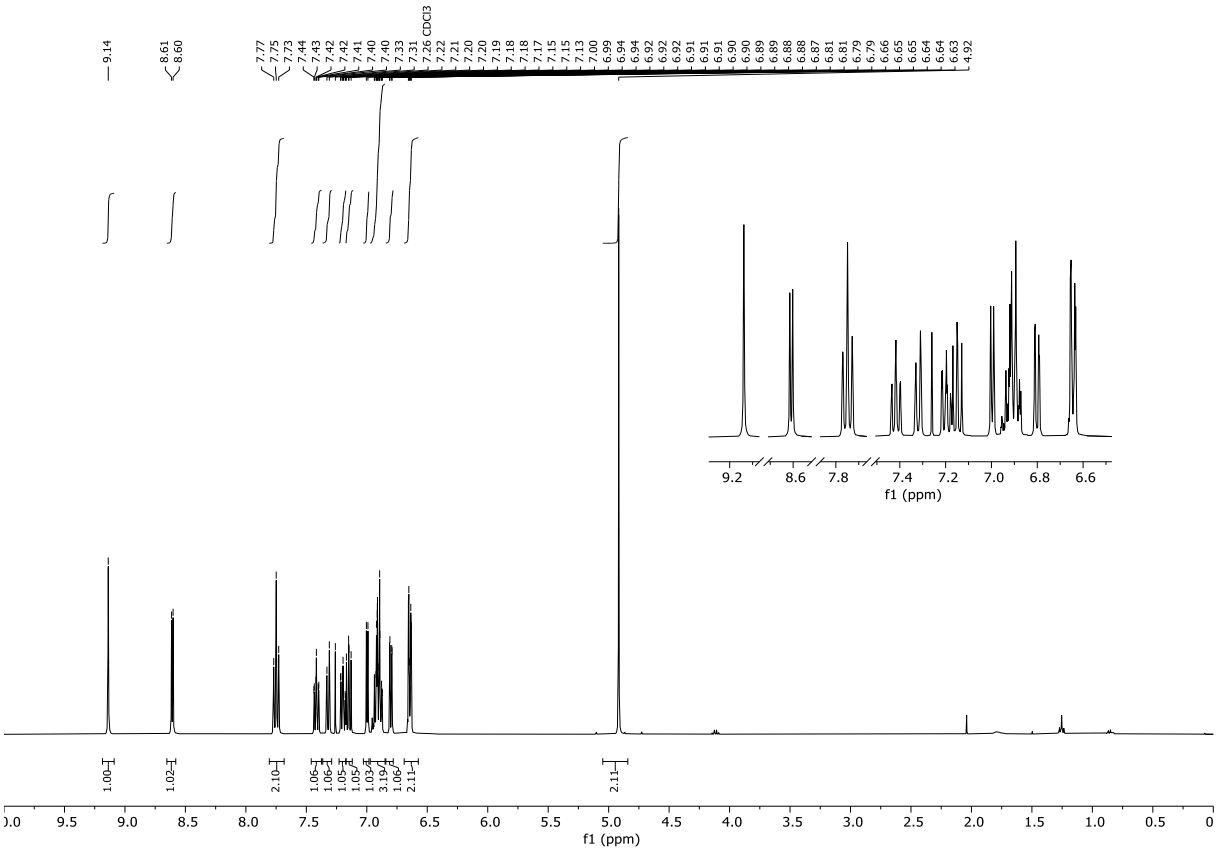


3-Phenyl-4-(4-phenylpyridin-3-yl)-2*H*-thiete 1,1-dioxide (3.19-a) (selected example)

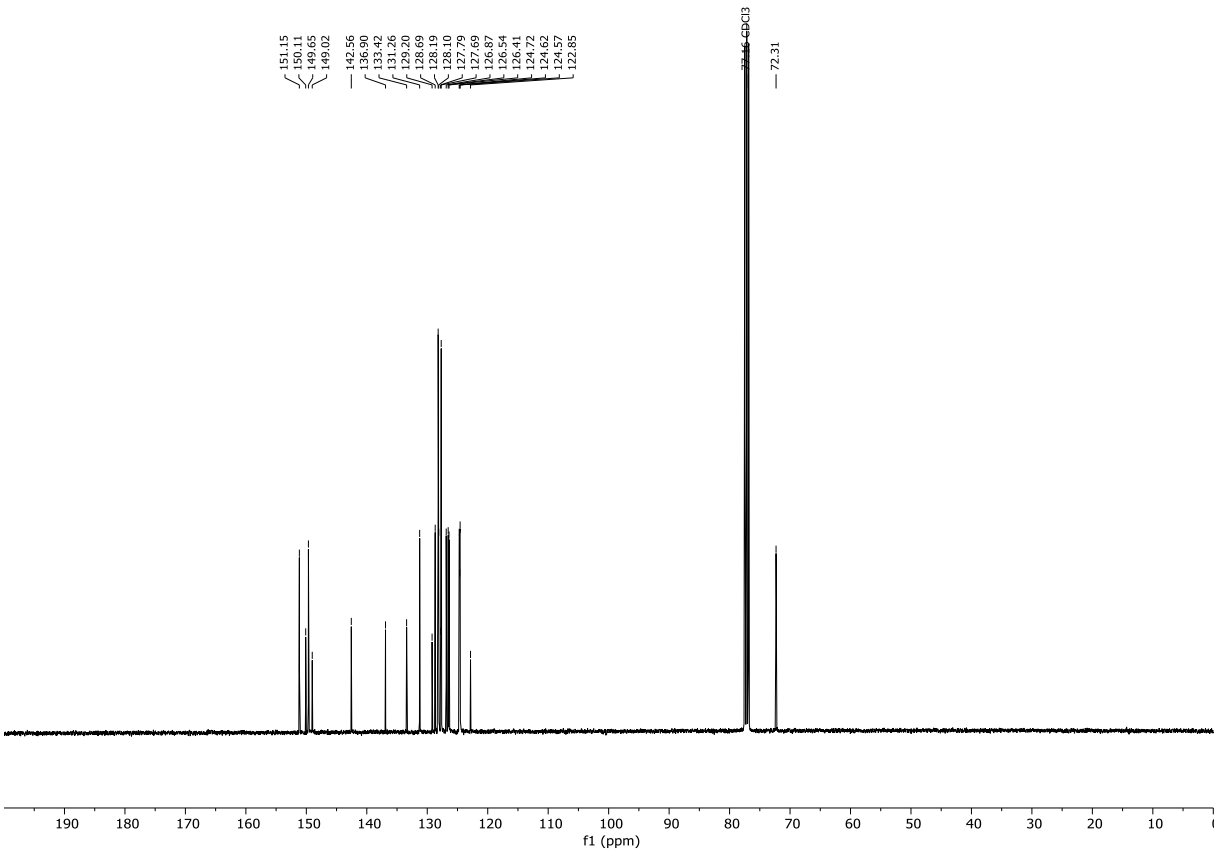
Using 4-(2-bromophenyl)pyridine according to general procedure, provided **3.19-a** (41 mg, 0.12 mmol, 62%) as a white solid.

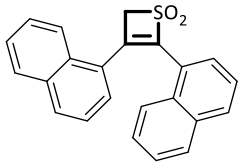
***R*f** = 0.2 (hexane/EtOAc 7:3, UV, $KMnO_4$, PAA). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.90 (s, 1H), 8.77 (d, *J* = 5.1 Hz, 1H), 7.50-7.30 (m, 4H), 7.26 (s, 5H), 7.01 (d, *J* = 7.6 Hz, 2H), 4.74 ppm (s, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 151.5, 150.5, 150.1, 146.4, 141.9, 137.1, 131.8, 129.2, 129.0, 128.8, 128.6, 128.5, 128.2, 124.7, 122.3, 69.5 ppm. **LRMS** (DEP/EI-Orbitrap): *m/z* (%): 333.1 (2), 268.1 (100), 191.1 (30). **HRMS** (EI-Orbitrap): m/z: [M-HSO_2]+ Calcd for $C_{20}H_{14}N^+$: 268.1126; found: 268.1129. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2970 (w), 2909 (w), 1582 (w), 1576 (w), 1476 (w), 1447 (w), 1405 (w), 1334 (w), 1293 (s), 1278 (m), 1262 (w), 1203 (m), 1189 (w), 1180 (w), 1132 (vs), 1104 (w), 1076 (m), 1064 (w), 1041 (w), 1022 (w), 988 (w), 958 (w), 910 (w), 851 (m), 836 (w), 780 (m), 761 cm^{-1} (s). **Melting point**: 216 (±2) °C.

^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (101 MHz, $CDCl_3$)

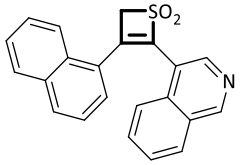




3,4-Di(naphthalen-1-yl)-2*H*-thiete 1,1-dioxide (3.19-b)

Using 1-bromonaphthalene according to general procedure, provided **3.19-b** (0.50 g, 1.4 mmol, 70%) as a brownish solid.

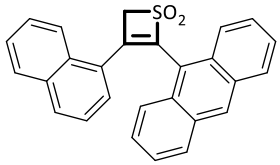
***R*f** = 0.4 (hexane/EtOAc 8:2, UV, $KMnO_4$, PAA). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.12 (dd, *J* = 8.5, 1.1 Hz, 1H), 7.91-7.74 (m, 5H), 7.59 (dd, *J* = 7.2, 1.2 Hz, 1H), 7.52 (dd, *J* = 7.2, 1.3 Hz, 1H), 7.47-7.30 (m, 5H), 7.21 (ddd, *J* = 8.4, 6.9, 1.3 Hz, 1H), 5.16 ppm (s, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 153.7, 141.2, 133.7, 133.6, 131.5, 131.1, 130.8, 129.7, 128.9, 128.6, 128.5, 128.3, 127.4, 127.3, 127.2, 126.7, 126.6, 125.5, 125.3, 125.3, 125.2, 124.7, 72.3 ppm. **LRMS** (DEP/EI-Orbitrap): *m/z* (%): 356.2 (10), 339.1 (2), 308.2 (60), 291.1 (100), 276.1 (95). **HRMS** (EI-Orbitrap): m/z: [M]+ Calcd for $C_{23}H_{16}O_2S^+$: 356.0871; found: 356.0863. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2364 (m), 2358 (m), 2344 (w), 1312 (w), 1296 (m), 1287 (s), 1276 (m), 1260 (m), 1251 (m), 1235 (m), 1218 (m), 1204 (m), 1183 (s), 1138 (s), 1114 (m), 1087 (m), 1057 (w), 981 (m), 803 cm^{-1} (m). **Melting point**: 170 (±2) °C.



4-(Isoquinolin-4-yl)-3-(naphthalen-1-yl)-2*H*-thiete 1,1-dioxide (3.19-c)

Using 4-bromoisoquinoline according to general procedure, provided **3.19-c** (50 mg, 0.14 mmol, 70%) as a white solid.

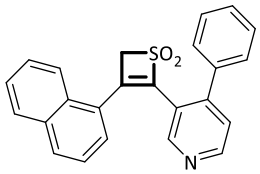
***R*f** = 0.2 (hexane/EtOAc 7:3, UV, $KMnO_4$, PAA). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.17 (s, 1H), 8.43 (s, 1H), 8.24 (d, *J* = 8.4 Hz, 1H), 7.96 (d, *J* = 8.1 Hz, 1H), 7.91 (d, *J* = 8.2 Hz, 1H), 7.82 (d, *J* = 8.2 Hz, 1H), 7.70 (t, *J* = 8.3 Hz, 2H), 7.62 (t, *J* = 7.5 Hz, 1H), 7.54 (d, *J* = 7.1 Hz, 1H), 7.49-7.44 (m, 1H), 7.40 (t, *J* = 7.3 Hz, 1H), 7.21 (t, *J* = 7.7 Hz, 1H), 5.18 ppm (s, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 154.7, 151.3, 144.4, 143.0, 133.8, 133.3, 132.1, 131.7, 129.5, 129.1, 128.4, 128.3, 128.3, 127.6, 127.4, 127.2, 126.8, 125.3, 124.7, 124.5, 119.9, 72.6 ppm. **LRMS** (DEP/EI-Orbitrap): *m/z* (%): 357.1 (40), 309.1 (90), 292.1 (100), 266.1 (30). **HRMS** (EI-Orbitrap): m/z: [M]+ Calcd for $C_{22}H_{15}NO_2S^+$: 357.0823; found: 357.0816. **Melting point**: 165 (±2) °C.



4-(Anthracen-9-yl)-3-(naphthalen-1-yl)-2*H*-thiete 1,1-dioxide (3.19-d)

Using 9-bromoanthracene according to general procedure, provided **3.19-d** (50 mg, 0.12 mmol, 62%) as a brownish solid.

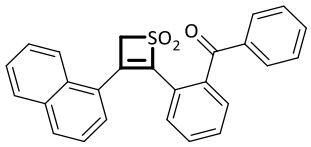
***R*f** = 0.5 (hexane/EtOAc 7:3, UV, $KMnO_4$, PAA). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.49 (s, 1H), 8.39 (d, *J* = 8.8 Hz, 2H), 7.98 (d, *J* = 8.4 Hz, 3H), 7.74 (t, *J* = 8.3 Hz, 2H), 7.52 (ddd, *J* = 8.6, 6.6, 1.4 Hz, 2H), 7.48 – 7.43 (m, 3H), 7.41 – 7.35 (m, 1H), 7.29 – 7.23 (m, 2H), 5.36 ppm(s, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 153.5, 145.8, 133.7, 131.4, 131.2, 131.0, 130.4, 130.1, 129.0, 128.9, 127.9, 127.6, 127.2, 127.1, 126.6, 125.8, 125.6, 125.2, 124.4, 120.8, 72.3 ppm. **LRMS** (DEP/EI-Orbitrap): *m/z* (%): 406.2 (15), 341.2 (100), 326.1 (20). **HRMS** (EI-Orbitrap): m/z: [M]+ Calcd for $C_{27}H_{18}O_2S^+$: 406.1028; found: 406.1023. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 1300 (s), 1205 (m), 1180 (m), 1160 (m), 1134 (vs), 1114 (m), 898 (m), 804 (m), 781 (s), 733 cm^{-1} (vs). **Melting point**: 185 (±2) °C.



3-(Naphthalen-1-yl)-4-(4-phenylpyridin-3-yl)-2*H*-thiete 1,1-dioxide (3.19-e)

Using 4-(2-bromophenyl)pyridine according to general procedure, provided **3.19-e** (73 mg, 0.19 mmol, 95%) as a white solid.

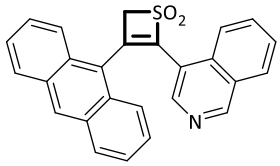
***R*f** = 0.2 (hexane/EtOAc 7:3, UV, $KMnO_4$, PAA). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.14 (s, 1H), 8.61 (d, *J* = 5.1 Hz, 1H), 7.75 (t, *J* = 8.2 Hz, 2H), 7.42 (ddd, *J* = 8.1, 6.8, 1.2 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.20 (ddd, *J* = 8.3, 6.8, 1.3 Hz, 1H), 7.17-7.13 (m, 1H), 7.00 (d, *J* = 5.1 Hz, 1H), 6.95-6.86 (m, 3H), 6.80 (dd, *J* = 7.2, 1.2 Hz, 1H), 6.67-6.63 (m, 2H), 4.92 ppm (s, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 151.2, 150.1, 149.7, 149.0, 142.6, 136.9, 133.4, 131.3, 129.2, 128.7, 128.2, 128.1, 127.8, 127.7, 126.9, 126.5, 126.4, 124.7, 124.6, 124.6, 122.8, 72.3 ppm. **LRMS** (DEP/EI-Orbitrap): *m/z* (%): 383.1 (10), 354.9 (1), 335.1 (25), 318.1 (30), 304.1 (50). **HRMS** (EI-Orbitrap): m/z: [M]+ Calcd for $C_{24}H_{17}NO_2S^+$: 383.0980; found: 383.0974. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 1708 (vs), 1435 (w), 1418 (m), 1360 (s), 1320 (m), 1221 (s), 1132 (w), 1093 (w), 777 cm^{-1} (m). **Melting point**: 215 (±2) °C.



(2-(3-(Naphthalen-1-yl)-1,1-dioxido-2*H*-thiet-4-yl)phenyl)(phenyl)methanone (3.19-f)

Using (2-bromophenyl)(phenyl)methanone according to general procedure, provided **3.19-f** (70 mg, 0.17 mmol, 85%) as a white solid.

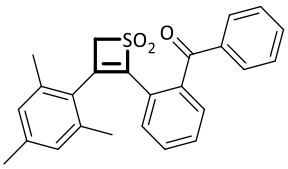
***R*f** = 0.2 (hexane/EtOAc 8:2, UV, $KMnO_4$, PAA). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.92 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.67 (dd, *J* = 8.3, 1.2 Hz, 1H), 7.63-7.53 (m, 3H), 7.46-7.34 (m, 3H), 7.29 (ddd, *J* = 8.3, 6.8, 1.4 Hz, 1H), 7.25-7.17 (m, 3H), 7.10 (t, *J* = 7.8 Hz, 2H), 7.04 (dd, *J* = 8.3, 1.5 Hz, 2H), 4.87 (s, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 194.4, 151.0, 141.3, 139.0, 135.0, 133.6, 132.9, 131.3, 131.2, 129.9, 129.8, 129.6, 129.3, 129.3, 128.9, 127.9, 127.5, 127.2, 127.1, 126.5, 126.5, 125.0, 124.8, 72.5 ppm. **LRMS** (DEP/EI-Orbitrap): *m/z* (%): 346.1 (30), 331.1 (15), 239.1 (60). **HRMS** (EI-Orbitrap): m/z: [M-SO_2]+ Calcd for $C_{26}H_{18}O^+$: 346.1358; found: 346.1359. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 1656 (s), 1299 (s), 1286 (m), 1266 (m), 1256 (m), 1184 (m), 1135 (s), 1114 (m), 927 (m), 799 (m), 777 (s), 761 (m), 704 cm^{-1} (vs). **Melting point**: 181 (±2) °C.



3-(Anthracen-9-yl)-4-(isoquinolin-4-yl)-2*H*-thiete 1,1-dioxide (3.19-g)

Using 4-bromoisoquinoline according to general procedure, provided **3.19-g** (35 mg, 0.09 mmol, 43%) as a white solid.

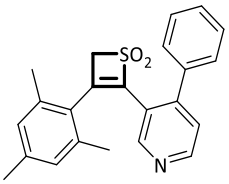
***R*f** = 0.2 (hexane/EtOAc 7:3, UV, $KMnO_4$, PAA). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.57 – 8.47 (m, 2H), 8.14 (d, *J* = 8.5 Hz, 2H), 8.03 (dd, *J* = 8.6, 1.4 Hz, 2H), 7.93 (d, *J* = 8.6 Hz, 1H), 7.68 (d, *J* = 8.3 Hz, 1H), 7.60 – 7.41 (m, 6H), 7.07 (ddd, *J* = 8.4, 6.9, 1.3 Hz, 1H), 5.19 ppm (s, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.4, 147.1, 143.4, 143.1, 136.4, 131.2, 130.5, 129.6, 129.2, 128.4, 128.1, 127.7, 127.3, 126.7, 125.9, 125.1, 124.7, 124.7, 122.4, 74.0 ppm. **HRMS** (EI-Orbitrap): m/z: [M]+ Calcd for $C_{26}H_{17}NO_2S^+$: 407.0980; found: 407.0973. **Melting point**: 180 (±2) °C.



(2-(3-Mesityl-1,1-dioxido-2*H*-thiet-4-yl)phenyl)(phenyl)methanone (3.19-h)

Using (2-bromophenyl)(phenyl)methanone according to general procedure, provided **3.19-h** (57 mg, 0.14 mmol, 71%) as a white solid.

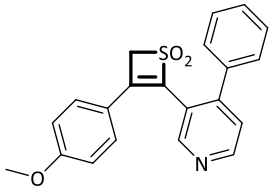
***R*f** = 0.4 (hexane/EtOAc 8:2, UV, $KMnO_4$, PAA). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 7.2 Hz, 1H), 7.63 (td, *J* = 7.6, 1.3 Hz, 1H), 7.54-7.40 (m, 4H), 7.33-7.24 (m, 3H), 6.43 (s, 2H), 4.74 (s, 2H), 2.00 ppm (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 193.7, 153.3, 142.8, 139.6, 138.7, 135.8, 134.9, 132.7, 130.9, 130.1, 129.4, 129.2, 129.0, 128.8, 127.9, 127.0, 125.6, 72.2, 21.0, 20.1 ppm. **LRMS** (DEP/EI-Orbitrap): *m/z* (%): 338.1 (70), 323.1 (40), 305.1 (20). **HRMS** (EI-Orbitrap): m/z: [M-SO_2]+ Calcd for $C_{24}H_{19}O_2^+$: 338.1671; found: 338.1680. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 1654 (m), 1447 (w), 1440 (w), 1314 (w), 1303 (vs), 1287 (m), 1269 (m), 1203 (m), 1184 (s), 1166 (w), 1156 (w), 1128 (s), 926 (m), 846 (m), 830 (w), 804 (w), 760 (s), 701 cm^{-1} (vs). **Melting point**: 162 (±2) °C.



3-Mesityl-4-(4-phenylpyridin-3-yl)-2*H*-thiete 1,1-dioxide (3.19-i)

Using 4-(2-bromophenyl)pyridine according to general procedure, provided **3.19-i** (71 mg, 0.19 mmol, 95%) as a white solid.

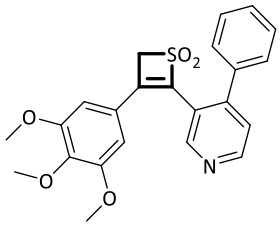
***R*f** = 0.25 (hexane/EtOAc 7:3, UV, $KMnO_4$, PAA). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.91 (s, 1H), 8.60 (d, *J* = 5.1 Hz, 1H), 7.36-7.22 (m, 3H), 7.13 (d, *J* = 5.1 Hz, 1H), 7.10-7.07 (m, 2H), 6.61 (s, 2H), 4.66 (s, 2H), 2.19 (s, 3H), 1.75 ppm (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 152.3, 150.7, 149.9, 149.7, 145.1, 139.6, 137.6, 135.6, 128.8, 128.7, 128.6, 128.1, 125.8, 125.1, 123.2, 72.3, 21.1, 20.3 ppm. **LRMS** (DEP/EI-Orbitrap): *m/z* (%): 375.1 (10), 327.1 (5), 311.1 (10), 296.1 (100). **HRMS** (EI-Orbitrap): m/z: [M]+ Calcd for $C_{23}H_{21}NO_2S^+$: 375.1293; found: 375.1294. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 1580 (m), 1478 (w), 1396 (m), 1303 (vs), 1289 (m), 1262 (m), 1244 (m), 1193 (s), 1177 (s), 1156 (m), 1128 (s), 1065 (w), 1036 (w), 982 (w), 848 (s), 825 (w), 780 (m), 764 (m), 749 (m), 734 (m), 706 cm^{-1} (s). **Melting point**: 196 (±2) °C.



3-(4-Methoxyphenyl)-4-(4-phenylpyridin-3-yl)-2*H*-thiete 1,1-dioxide (3.19-j)

Using 4-(2-bromophenyl)pyridine according to general procedure, provided **3.19-j** (30 mg, 0.08 mmol, 41%) as a white solid.

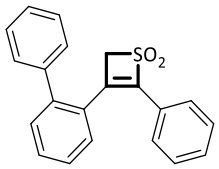
***R*f** = 0.1 (hexane/EtOAc 7:3, UV, $KMnO_4$, PAA). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.88 (s, 1H), 8.76 (d, *J* = 5.2 Hz, 1H), 7.50-7.38 (m, 3H), 7.32-7.23 (m, 3H), 6.98 (d, *J* = 8.9 Hz, 2H), 6.71 (d, *J* = 8.8 Hz, 2H), 4.69 (s, 2H), 3.78 ppm (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.4, 151.3, 150.7, 150.2, 143.5, 141.3, 137.2, 130.2, 129.1, 128.6, 128.6, 124.7, 122.6, 121.8, 114.3, 69.3, 55.6 ppm. **LRMS** (DEP/EI-Orbitrap): *m/z* (%): 363.1 (5),315.1 (5), 298.1 (10), 268.1 (20). **HRMS** (EI-Orbitrap): m/z: [M]+ Calcd for $C_{21}H_{17}NO_3S^+$: 363.0929; found: 363.0919. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2967 (w), 2909 (w), 1601 (s), 1581 (m), 1571 (m), 1516 (s), 1476 (w), 1463 (w), 1427 (m), 1397 (w), 1336 (m), 1313 (m), 1289 (s), 1267 (s), 1200 (m), 1178 (s), 1127 (vs), 1118 (vs), 1080 (m), 1073 (m), 1045 (m), 1018 (s), 988 (w), 982 (w), 958 (m), 926 (w), 853 (m), 838 (s), 814 (m), 790 (m), 778 (m), 762 (m), 746 cm^{-1} (s). **Melting point**: 223 (±2) °C.



4-(4-Phenylpyridin-3-yl)-3-(3,4,5-trimethoxyphenyl)-2*H*-thiete 1,1-dioxide (3.19-k)

Using 4-(2-bromophenyl)pyridine according to general procedure, provided **3.19-k** (35 mg, 0.08 mmol, 41%) as a white solid.

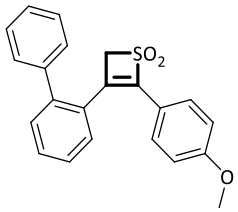
***R*f** = 0.05 (hexane/EtOAc 7:3, UV, $KMnO_4$, PAA). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.89 (s, 1H), 8.75 (d, *J* = 5.1 Hz, 1H), 7.45-7.37 (m, 3H), 7.34-7.27 (m, 3H), 6.17 (s, 2H), 4.71 (s, 2H), 3.82 (s, 3H), 3.62 ppm (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 153.2, 151.5, 150.7, 150.1, 145.8, 142.0, 141.3, 137.0, 129.1, 128.7, 128.5, 124.5, 124.5, 122.3, 105.6, 69.5, 61.1, 56.2 ppm. **LRMS** (DEP/EI-Orbitrap): *m/z* (%): 423.1 (30), 375.1 (10), 359.1 (20), 328.1 (40). **HRMS** (EI-Orbitrap): m/z: [M]+ Calcd for $C_{23}H_{21}NO_5S^+$: 423.1140; found: 423.1144. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 1579 (m), 1508 (m), 1499 (w), 1452 (m), 1414 (m), 1400 (w), 1358 (m), 1296 (s), 1241 (m), 1194 (m), 1126 (vs), 1104 (m), 1079 (m), 1004 (m), 963 (w), 947 (w), 922 (m), 914 (m), 858 (m), 829 (m), 798 (w), 782 (m), 760 (m), 743 cm^{-1} (s). **Melting point**: 208 (±2) °C.



3-([1,1'-Biphenyl]-2-yl)-4-phenyl-2*H*-thiete 1,1-dioxide (3.19-l)

Using bromobenzene according to general procedure, provided **3.19-l** (62 mg, 0.19 mmol, 93%) as a white solid.

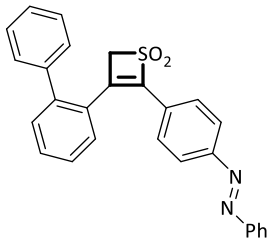
***R*f** = 0.5 (hexane/EtOAc 8:2, UV, $KMnO_4$, PAA). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.57-7.48 (m, 5H), 7.44-7.33 (m, 9H), 4.06 ppm (s, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 152.6, 141.8, 139.8, 139.2, 130.8, 130.7, 130.4, 129.7, 129.2, 129.0, 129.0, 128.7, 128.5, 127.9, 127.2, 126.9, 71.7 ppm. **LRMS** (DEP/EI-Orbitrap): *m/z* (%): 267.1 (100), 252.1 (30), 239.0 (10). **HRMS** (EI-Orbitrap): m/z: [M]+ Calcd for $C_{21}H_{16}O_2S^+$: 332.0871; found: 332.0859. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3059 (w), 3027 (w), 1964 (w), 1953 (w), 1711 (m), 1595 (w), 1493 (w), 1473 (m), 1448 (m), 1435 (w), 1362 (w), 1327 (m), 1304 (vs), 1221 (w), 1194 (s), 1176 (vs), 1130 (vs), 1076 (w), 1031 (w), 1025 (w), 1009 (w), 963 (w), 917 (w), 850 (w), 761 cm^{-1} (vs). **Melting point**: 146 (±2) °C.



3-([1,1'-Biphenyl]-2-yl)-4-(4-methoxyphenyl)-2*H*-thiete 1,1-dioxide (3.19-m)

Using 1-bromo-4-methoxybenzene according to general procedure, provided **3.19-m** (50 mg, 0.14 mmol, 69%) as a white solid.

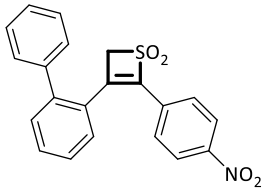
***R*f** = 0.2 (hexane/EtOAc 9:1, UV, $KMnO_4$, PAA). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.61-7.31 (m, 11H), 6.87 (d, *J* = 8.9 Hz, 2H), 4.02 (s, 2H), 3.83 ppm (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.2, 152.4, 141.8, 139.8, 136.2, 130.7, 130.4, 130.0, 129.0, 129.0, 128.8, 128.7, 128.5, 127.9, 119.4, 114.7, 71.5, 55.5 ppm. **LRMS** (DEP/EI-Orbitrap): *m/z* (%): 362.2 (5), 298.2 (40), 267.1 (40), 239.1 (20). **HRMS** (EI-Orbitrap): m/z: [M]+ Calcd for $C_{22}H_{18}O_3S^+$: 362.0977; found: 362.0971. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 1603 (m), 1511 (m), 1474 (w), 1454 (w), 1420 (w), 1298 (s), 1256 (s), 1185 (vs), 1176 (s), 1127 (s), 1075 (w), 1064 (w), 1048 (w), 1025 (s), 1007 (m), 998 (w), 985 (w), 961 (w), 925 (w), 856 (w), 831 (s), 815 (w), 786 (w), 765 (vs), 743 (s), 726 (m), 716 (m), 704 cm^{-1} (vs). **Melting point**: 152 (±2) °C.



(*E*)-3-([1,1'-Biphenyl]-2-yl)-4-(4-(phenyldiazenyl)phenyl)-2*H*-thiete 1,1-dioxide (3.19-n)

Using (*E*)-1-(4-iodophenyl)-2-phenyldiazene according to general procedure, provided **3.19-n** (35 mg, 0.08 mmol, 40%) as a red solid.

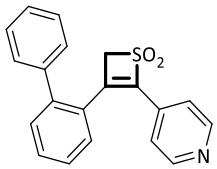
***R*f** = 0.5 (hexane/EtOAc 8:2, UV, $KMnO_4$, PAA). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.98-7.87 (m, 4H), 7.67 (d, *J* = 8.5 Hz, 2H), 7.62-7.49 (m, 6H), 7.48-7.33 (m, 6H), 4.12 ppm (s, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 153.2, 152.6, 152.0, 142.0, 140.5, 139.7, 131.7, 130.9, 130.9, 129.5, 129.3, 129.1, 129.0, 129.0, 128.8, 128.6, 128.1, 128.0, 123.7, 123.2, 71.9 ppm. **LRMS** (DEP/EI-Orbitrap): *m/z* (%): 436.1 (20), 388.1 (5), 371.1 (10), 252.1 (50). **HRMS** (EI-Orbitrap): m/z: [M]+ Calcd for $C_{27}H_{20}N_2O_2S^+$: 436.1245; found: 436.1240. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 1481 (w), 1432 (w), 1408 (w), 1324 (w), 1301 (vs), 1278 (w), 1262 (w), 1221 (w), 1191 (m), 1172 (s), 1164 (m), 1132 (s), 1123 (m), 1106 (w), 1071 (w), 1041 (w), 1027 (w), 1020 (w), 1012 (w), 1006 (w), 1000 (w), 961 (w), 916 (w), 859 (m), 835 (m), 765 (vs), 750 (m), 740 cm^{-1} (s). **Melting point**: 160 (±2) °C.



3-([1,1'-Biphenyl]-2-yl)-4-(4-nitrophenyl)-2*H*-thiete 1,1-dioxide (3.19-o)

Using 1-bromo-4-nitrobenzene according to general procedure, provided **3.19-o** (40 mg, 0.11 mmol, 53%) as a white solid.

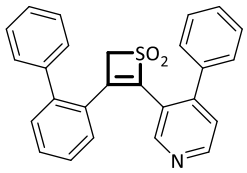
***R*f** = 0.5 (hexane/EtOAc 8:2, UV, $KMnO_4$, PAA). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.8 Hz, 2H), 7.64-7.57 (m, 3H), 7.54-7.44 (m, 3H), 7.43-7.35 (m, 3H), 7.32-7.27 (m, 2H), 4.23 ppm (s, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 150.2, 148.3, 143.5, 142.1, 139.4, 132.8, 131.5, 131.2, 129.1, 128.8, 128.8, 128.7, 128.2, 128.1, 124.4, 72.4 ppm. **LRMS** (DEP/EI-Orbitrap): *m/z* (%): 358.2 (10), 313.2 (50), 296.1 (5), 283.1 (10), 266.1 (100). **HRMS** (EI-Orbitrap): m/z: [M]+ Calcd for $C_{21}H_{15}NO_4S^+$: 377.0722; found: 377.0713. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3095 (w), 1569 (m), 1559 (m), 1432 (w), 1292 (vs), 1212 (s), 1186 (s), 1142 (m), 1127 (vs), 854 (m), 792 cm^{-1} (s). **Melting point**: 210 (±2) °C.



3-([1,1'-Biphenyl]-2-yl)-4-(pyridin-4-yl)-2*H*-thiete 1,1-dioxide (3.19-p)

Using 4-bromopyridine according to general procedure, provided **3.19-p** (40 mg, 0.11 mmol, 61%) as a yellow oil.

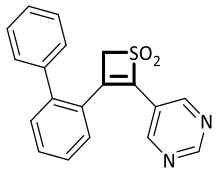
***R*f** = 0.1 (hexane/EtOAc 7:3, UV, $KMnO_4$, PAA). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.61 (d, *J* = 5.9 Hz, 2H), 7.58 (td, *J* = 7.5, 1.5 Hz, 1H), 7.53-7.48 (m, 2H), 7.46-7.36 (m, 4H), 7.35-7.27 (m, 4H), 4.18 ppm (s, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 150.6, 150.0, 144.4, 142.0, 139.4, 134.1, 131.4, 131.1, 129.1, 128.8, 128.8, 128.7, 128.1, 120.9, 72.4 ppm. **LRMS** (DEP/EI-Orbitrap): *m/z* (%): 268.1 (100), 239.1 (10), 226.1 (5). **HRMS** (EI-Orbitrap): m/z: [M]+ Calcd for $C_{20}H_{15}NO_2S^+$: 333.0823; found: 333.0827.



3-([1,1'-Biphenyl]-2-yl)-4-(4-phenylpyridin-3-yl)-2*H*-thiete 1,1-dioxide (3.19-q)

Using 4-(2-bromophenyl)pyridine according to general procedure, provided **3.19-q** (72 mg, 0.18 mmol, 88%) as white solid.

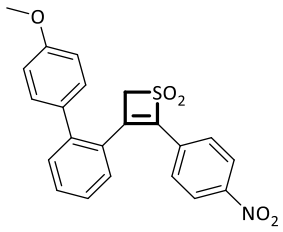
***R*f** = 0.2 (hexane/EtOAc 7:3, UV, $KMnO_4$, PAA). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.58 (d, *J* = 5.1 Hz, 1H), 8.47 (s, 1H), 7.36-7.17 (m, 7H), 7.16-7.09 (m, 4H), 7.05 (td, *J* = 7.6, 1.3 Hz, 1H), 6.79-6.69 (m, 3H), 4.22 ppm (s, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 150.6, 149.7, 149.6, 148.9, 143.7, 141.9, 139.5, 137.4, 130.4, 130.4, 128.6, 128.5, 128.5, 128.4, 128.3, 128.2, 127.4, 124.5, 122.3, 71.3 ppm. **LRMS** (DEP/EI-Orbitrap): *m/z* (%): 409.1 (5), 345.1 (50), 330.1 (20). **HRMS** (EI-Orbitrap): m/z: [M]+ Calcd for $C_{26}H_{19}NO_2S^+$: 409.1136; found: 409.1139. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 1709 (m), 1581 (m), 1481 (m), 1444 (w), 1436 (w), 1400 (w), 1362 (m), 1327 (w), 1301 (s), 1221 (m), 1192 (m), 1173 (s), 1130 (s), 1076 (w), 850 (m), 778 (m), 766 (m), 756 cm^{-1} (s). **Melting point**: 210 (±2) °C.



3-([1,1'-Biphenyl]-2-yl)-4-(pyrimidin-5-yl)-2*H*-thiete 1,1-dioxide (3.19-r)

Using 5-bromopyrimidine according to general procedure, provided **3.19-r** (45 mg, 0.13 mmol, 67%) as a yellow oil.

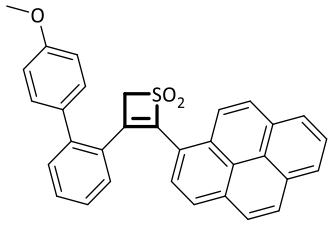
R_f = 0.4 (hexane/EtOAc 6:4, UV, $KMnO_4$, PAA). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.13 (s, 1H), 8.62 (s, 2H), 7.62-7.51 (m, 1H), 7.52-7.41 (m, 3H), 7.37-7.30 (m, 3H), 7.25-7.20 (m, 2H), 4.46 ppm (s, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.9, 154.6, 146.2, 143.5, 141.9, 139.2, 131.6, 131.3, 129.0, 128.8, 128.7, 128.5, 128.3, 128.2, 122.4, 77.2, 72.7 ppm. **LRMS** (DEP/EI-Orbitrap): *m/z* (%): 334.2 (2), 269.2 (100), 215.1 (10). **HRMS** (EI-Orbitrap): m/z: [M]+ Calcd for $C_{19}H_{14}N_2O_2S^+$: 334.0776; found: 334.0774.



3-(4'-Methoxy-[1,1'-biphenyl]-2-yl)-4-(4-nitrophenyl)-2*H*-thiete 1,1-dioxide (3.19-s)

Using 1-bromo-4-nitrobenzene according to general procedure, provided **3.19-s** (49 mg, 0.12 mmol, 60%) as a yellow oil.

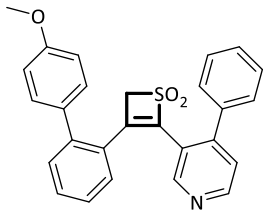
R_f = 0.5 (hexane/EtOAc 7:3, UV, $KMnO_4$, PAA). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.8 Hz, 2H), 7.63 (d, *J* = 8.8 Hz, 2H), 7.56 (td, *J* = 7.5, 1.5 Hz, 1H), 7.51-7.45 (m, 2H), 7.40 (td, *J* = 7.5, 1.4 Hz, 1H), 7.22 (d, *J* = 8.7 Hz, 2H), 6.92 (d, *J* = 8.6 Hz, 2H), 4.27 (s, 2H), 3.82 ppm (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 160.0, 150.0, 148.3, 143.7, 141.8, 132.9, 131.6, 131.5, 131.1, 130.0, 128.8, 128.6, 128.0, 127.7, 124.4, 114.5, 72.3, 55.5 ppm. **LRMS** (DEP/EI-Orbitrap): *m/z* (%): 355.1 (5), 343.1 (50), 326.9 (5), 313.1 (10). **HRMS** (EI-Orbitrap): m/z: [M]+ Calcd for $C_{22}H_{17}NO_5S^+$: 407.0827; found: 407.0821.



3-(4'-Methoxy-[1,1'-biphenyl]-2-yl)-4-(pyren-1-yl)-2*H*-thiete 1,1-dioxide (3.19-t)

Using 1-bromopyrene according to general procedure, provided **3.19-t** (49 mg, 0.10 mmol, 50%) as a yellow oil.

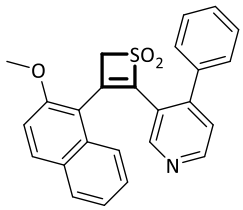
***R*f** = 0.5 (hexane/EtOAc 8:2, UV, $KMnO_4$, PAA). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.23-8.15 (m, 3H), 8.11 (d, *J* = 8.9 Hz, 1H), 8.06-7.99 (m, 4H), 7.96 (d, *J* = 7.9 Hz, 1H), 7.37 (td, *J* = 7.5, 1.3 Hz, 1H), 7.32 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.25 (d, *J* = 6.8 Hz, 1H), 7.15 (td, *J* = 7.6, 1.4 Hz, 1H), 6.99 (d, *J* = 8.6 Hz, 2H), 6.60 (d, *J* = 8.6 Hz, 2H), 4.56 (s, 2H), 3.54 ppm (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.2, 153.0, 142.3, 141.9, 132.6, 132.2, 131.2, 131.1, 130.8, 130.7, 129.8, 129.5, 129.4, 129.3, 128.9, 128.7, 127.3, 127.2, 127.0, 126.4, 126.0, 126.0, 124.8, 124.7, 124.3, 122.1, 113.9, 71.0, 55.0 ppm. **LRMS** (DEP/EI-Orbitrap): *m/z* (%): 486.1 (5), 480.1 (60). **HRMS** (EI-Orbitrap): m/z: [M]+ Calcd for $C_{32}H_{22}O_3S^+$: 486.1290; found: 486.1291.



3-(4'-Methoxy-[1,1'-biphenyl]-2-yl)-4-(4-phenylpyridin-3-yl)-2*H*-thiete 1,1-dioxide (3.19-u)

Using 4-(2-bromophenyl)pyridine according to general procedure, provided **3.19-u** (50 mg, 0.11 mmol, 57%) as white solid.

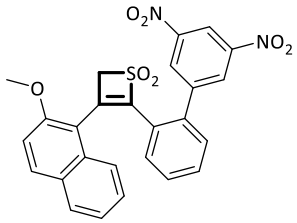
***R*f** = 0.3 (hexane/EtOAc 6:4, UV, $KMnO_4$, PAA). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.64-8.54 (m, 2H), 7.33-7.22 (m, 4H), 7.20-7.09 (m, 4H), 7.03 (td, *J* = 7.5, 1.3 Hz, 1H), 6.77 (td, *J* = 7.0, 1.7 Hz, 3H), 6.66 (d, *J* = 8.7 Hz, 2H), 4.19 (s, 2H), 3.84 ppm (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.6, 150.7, 149.8, 149.7, 148.7, 143.9, 141.7, 137.5, 131.7, 130.5, 129.8, 128.7, 128.6, 128.5, 128.5, 128.4, 126.9, 124.6, 124.5, 122.4, 114.0, 71.3, 55.5 ppm. **LRMS** (DEP/EI-Orbitrap): *m/z* (%): 439.1 (80), 389.1 (5), 375.1 (85), 360.1 (30). **HRMS** (EI-Orbitrap): m/z: [M]+ Calcd for $C_{27}H_{21}NO_3S^+$: 439.1242; found: 439.1238. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 1711 (m), 1611 (m), 1517 (m), 1483 (m), 1442 (m), 1302 (vs), 1246 (s), 1222 (m), 1192 (s), 1176 (s), 1132 (vs), 1035 (m), 834 (m), 761 (m), 755 (m), 700 cm^{-1} (m). **Melting point**: 220 (±2) °C.



3-(2-Methoxynaphthalen-1-yl)-4-(4-phenylpyridin-3-yl)-2*H*-thiete 1,1-dioxide (3.19-v)

Using 4-(2-bromophenyl)pyridine according to general procedure, provided **3.19-v** (52 mg, 0.13 mmol, 63%) as yellowish solid.

***R*f** = 0.5 (hexane/EtOAc 6:4, UV, $KMnO_4$, PAA). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.16 (s, 1H), 8.54 (d, *J* = 5.1 Hz, 1H), 7.71 (d, *J* = 9.1 Hz, 1H), 7.67 (d, *J* = 7.3 Hz, 1H), 7.23 (d, *J* = 7.6 Hz, 2H), 7.13 (ddd, *J* = 8.3, 6.7, 1.4 Hz, 1H), 7.09-7.03 (m, 1H), 6.97 (t, *J* = 7.6 Hz, 2H), 6.91 (d, *J* = 5.1 Hz, 1H), 6.85 (d, *J* = 9.1 Hz, 1H), 6.66-6.62 (m, 2H), 5.00 (s, 2H), 3.70 ppm (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.1, 151.0, 150.7, 149.7, 149.3, 140.8, 137.0, 132.7, 130.2, 128.4, 128.3, 127.6, 127.5, 127.5, 127.5, 124.8, 124.0, 123.5, 123.5, 111.8, 111.6, 72.9, 55.5 ppm. **LRMS** (DEP/EI-Orbitrap): *m/z* (%): 413.1 (10), 349.1 (10), 318.1 (30). **HRMS** (EI-Orbitrap): m/z: [M]+ Calcd for $C_{25}H_{19}NO_3S^+$: 413.1086; found: 413.1087. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 1592 (m), 1580 (m), 1510 (m), 1467 (m), 1294 (s), 1267 (s), 1249 (m), 1223 (w), 1176 (m), 1165 (vs), 1136 (s), 1106 (m), 1079 (s), 1026 (m), 998 (w), 969 (m), 909 (w), 869 (m), 856 (m), 812 (s), 778 (s), 762 (s), 748 cm^{-1} (s). **Melting point**: 190 (±2) °C.



4-(3',5'-Dinitro-[1,1'-biphenyl]-2-yl)-3-(2-methoxynaphthalen-1-yl)-2*H*-thiete 1,1-dioxide (3.19-w)

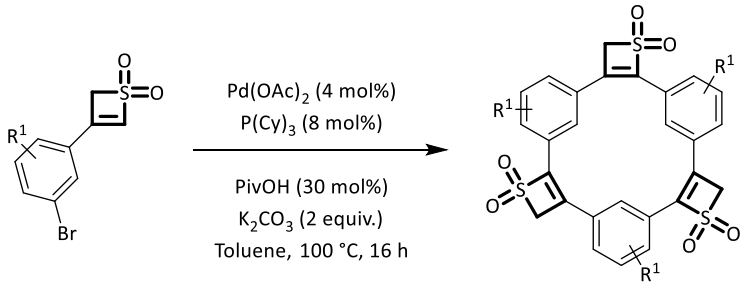
Using 2-bromo-3',5'-dinitro-1,1'-biphenyl according to general procedure, provided **3.19-w** (46 mg, 0.09 mmol, 46%) as yellowish solid.

***R*f** = 0.7 (hexane/EtOAc 6:4, UV, $KMnO_4$, PAA). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.53 (t, *J* = 2.1 Hz, 1H), 8.14 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.65 (dtt, *J* = 7.7, 5.6, 3.1 Hz, 5H), 7.48 (td, *J* = 7.6, 1.3 Hz, 1H), 7.33-7.27 (m, 1H), 7.19-7.08 (m, 2H), 7.03 (dd, *J* = 7.7, 1.2 Hz, 1H), 6.86 (d, *J* = 9.1 Hz, 1H), 4.98 (s, 2H), 3.68 ppm (s, 3H).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.1, 152.6, 147.9, 143.1, 138.2, 137.2, 133.0, 131.0, 130.3, 130.1, 130.1, 129.0, 128.9, 128.4, 128.2, 127.9, 127.1, 124.8, 123.3, 116.4, 112.1, 111.5, 72.8, 55.8 ppm. **LRMS** (DEP/EI-Orbitrap): *m/z* (%): 502.1 (100), 421.1 (95), 391.1 (30). **HRMS** (EI-Orbitrap): m/z: [M]+ Calcd for $C_{26}H_{18}N_2O_7S^+$: 502.0835; found: 502.0838. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 1548 (s), 1533 (m), 1510 (m), 1469 (w), 1360 (m), 1343 (s), 1309 (s), 1266 (s), 1246 (m), 1184 (m), 1174 (s), 1158 (m), 1138 (s),

1120 (m), 1104 (m), 1072 (s), 1048 (w), 1028 (m), 996 (w), 965 (w), 920 (w), 912 (m), 895 (w), 884 (w), 858 (w), 815 (s), 783 (m), 775 cm^{-1} (s). **Melting point**: 270 (±2) °C.

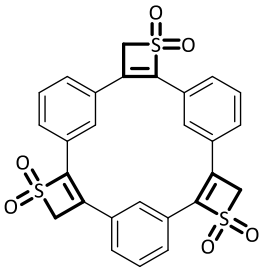
13.3 Macrocyclic Thiete Dioxides

General procedure: C-H Macrocyclization of 2*H*-thiete 1,1- dioxides



(3.18) **(3.30)**

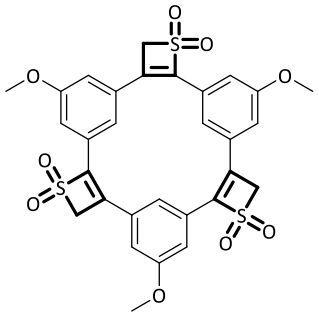
A pressure tube was charged with 2*H*-thiete 1,1- dioxides derivative **3.18** (0.2 mmol, 1 equiv.) and 2 mL toluene was added. Subsequently, K_2CO_3 (55 mg, 0.4 mmol, 2.0 equiv.), $Pd(OAc)_2$ (1.8 mg, 8 µmol, 4 mol%), tricyclohexylphosphane (PCy_3) (4.5 mg, 16 µmol, 8 mol%) and a few drops of pivalic acid (~7 µL, 30 mol%) were added. The mixture was stirred at 100 °C in the sealed pressure tube until TLC showed consumption of the starting 2*H*-thiete 1,1- dioxides (approx. 16 hours). After cooling to ambient temperature, the tube was opened and a 1:1 mixture of H_2O:CH_2Cl_2 (4 mL) was added. The aqueous phase was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic phases were dried over magnesium sulfate, filtrated, concentrated in vacuo and purified by flash-column chromatography on silica gel with the appropriate solvent mixture to obtain pure **3.30**.



***tri*-Cyclo-3-phenyl-2*H*-thiete 1,1-dioxide (3.30-a)**

Using 4-(3-bromophenyl)-2*H*-thiete 1,1-dioxide according to general procedure, provided **3.30-a** (40 mg, 0.07 mmol, 37%) as yellowish solid.

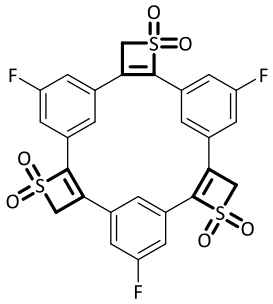
R_f = 0.2 (hexane/EtOAc 5:5, UV, $KMnO_4$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 7.9 Hz, 1H), 7.71-7.59 (m, 1H), 7.41 (d, *J* = 7.9 Hz, 1H), 4.86 ppm (s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 150.5, 139.7, 131.1, 131.0, 130.9, 129.9, 127.8, 126.6, 72.1 ppm. **HRMS** (ESI-Quadrupole): m/z: [M^+-H] Calcd for $C_{27}H_{17}O_6S_3^+$: 533.0187; found: 533.0191. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2925 (m), 2851 (w), 1295 (s), 1261 (m), 1192 (s), 1159 (m), 1127 (vs), 1041 (m), 1020 (m), 890 (m), 856 (m), 798 cm^{-1} (s). **Melting point**: 245 (±2) °C decomposition.



***tri*-Cyclo-3-(3-methoxyphenyl)-2*H*-thiete 1,1-dioxide (3.30-b)**

Using 3-(3-bromo-5-methoxyphenyl)-2*H*-thiete 1,1-dioxide according to general procedure, provided **3.30-b** (2.14 g, 3.43 mmol, 42%) as yellowish solid.

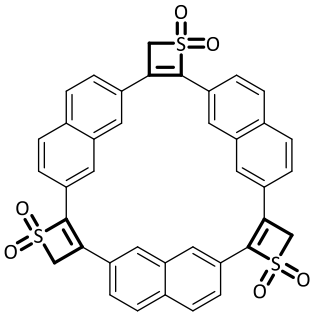
R_f = 0.2 (hexane/EtOAc 5:5, UV, $KMnO_4$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.27 (s, 3H), 7.22-7.20 (m, 3H), 6.89-6.87 (m, 3H), 4.83 (s, 6H), 3.89 ppm (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 160.8, 150.6, 139.7, 132.1, 128.8, 119.0, 116.7, 114.7, 72.1, 56.0 ppm. **HRMS** (ESI-Quadrupole): m/z: [M^+-H] Calcd for $C_{30}H_{23}O_9S_3^+$: 623.0504; found: 623.0507. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 1585 (m), 1362 (m), 1291 (s), 1261 (s), 1226 (s), 1182 (s), 1156 (m), 1129 (vs), 1064 (s), 1050 (s), 1017 (m), 1000 (s), 985 (s), 861 (m), 822 (m), 806 (m), 800 (m), 736 cm^{-1} (m). **Melting point**: 265 (±2) °C decomposition.



***tri*-Cyclo-3-(3-fluorophenyl)-2*H*-thiete 1,1-dioxide (3.30-c)**

Using 3-(3-bromo-5-fluorophenyl)-2*H*-thiete 1,1-dioxide according to general procedure, provided **3.30-c** (53 mg, 0.09 mmol, 45%) as yellowish solid.

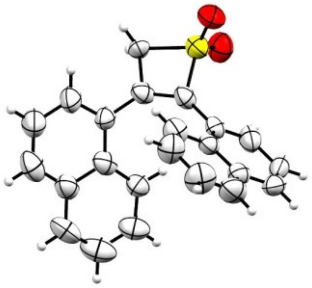
R_f = 0.65 (hexane/EtOAc 5:5, UV, $KMnO_4$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 8.3 Hz, 3H), 7.36 (s, 3H), 7.22 (d, *J* = 8.5 Hz, 3H), 4.90 ppm (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.4 (d, *J* = 253.2 Hz), 138.94, 132.95, 123.2-123.1 (m), 119.03, 118.80, 117.83, 117.59, 71.43 ppm. **HRMS** (ESI-Quadrupole): m/z: [M^+-H] Calcd for $C_{27}H_{14}F_3O_6S_3^+$: 586.9905; found: 586.9912. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 1589 (m), 1347 (m), 1308 (s), 1201 (m), 1185 (vs), 1132 (vs), 870 cm^{-1} (m). **Melting point**: 250 (±2) °C decomposition.



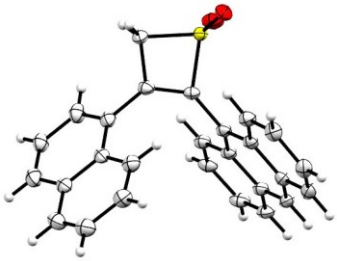
***tri*-Cyclo-3-(naphthalen-2-yl)-2*H*-thiete 1,1-dioxide (3.30-d)**

Using 3-(7-bromonaphthalen-2-yl)-2*H*-thiete 1,1-dioxide according to general procedure, provided **3.30-d** (27 mg, 0.04 mmol, 20%) as brownish solid.

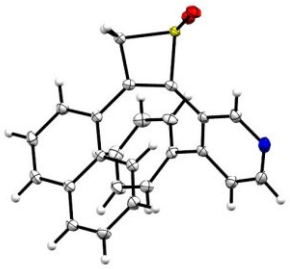
R_f = 0.8 (CH_2Cl_2/MeOH 96:4, UV, $KMnO_4$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.28 (s, 3H), 8.14 (s, 3H), 8.01 (d, *J* = 8.6 Hz, 6H), 7.93 (dd, *J* = 8.5, 1.5 Hz, 3H), 7.46 (dd, *J* = 8.5, 1.6 Hz, 3H), 4.97 ppm (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 150.7, 139.5, 134.9, 132.5, 129.8, 129.6, 128.8, 128.0, 127.8, 126.9, 126.2, 126.0, 71.9 ppm. **HRMS** (ESI-Quadrupole): m/z: [M^+-H] Calcd for $C_{39}H_{23}O_6S_3^+$: 683.0657; found: 683.0665. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 1302 (vs), 1183 (vs), 1126 (vs), 1120 (vs), 917 (m), 911 (m), 847 (s), 813 (m), 729 cm^{-1} (m). **Melting point**: 290 (±2) °C decomposition.



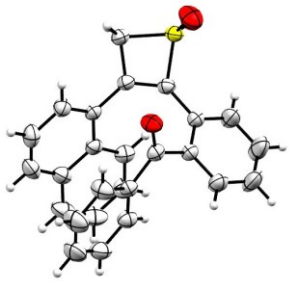
	3.19-b
net formula	$C_{23}H_{16}O_2S$
M_r/g mol^{-1}	356.42
crystal size/mm	0.100 × 0.060 × 0.030
T/K	293.(2)
radiation	MoKα
diffractometer	'Bruker D8 Venture TXS'
crystal system	triclinic
space group	'P -1'
a/Å	8.0586(5)
b/Å	13.8610(8)
c/Å	16.3574(11)
α/°	89.714(2)
β/°	78.891(3)
γ/°	89.717(2)
V/Å^3	1792.85(19)
Z	4
calc. density/g cm^{-3}	1.320
μ/mm^{-1}	0.194
absorption correction	Multi-Scan
transmission factor range	0.71–0.99
refls. measured	6116
R_{int}	0.0603
mean σ(I)/I	0.0823
θ range	3.197–25.027
observed refls.	4010
x, y (weighting scheme)	0.1008, 0.2422
hydrogen refinement	constr
refls in refinement	6116
parameters	470
restraints	0
$R(F_{obs})$	0.0728
$R_w(F^2)$	0.1926
S	1.064
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.302
min electron density/e Å^{-3}	−0.301



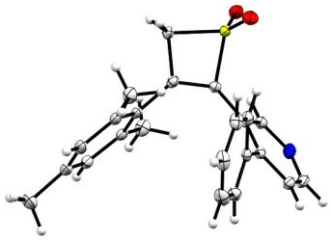
	3.19-d
net formula	$C_{27}H_{18}O_2S$
M_r/g mol^{-1}	406.47
crystal size/mm	0.100 × 0.050 × 0.040
T/K	103.(2)
radiation	MoKα
diffractometer	'Bruker D8 Venture TXS'
crystal system	monoclinic
space group	'P 1 21/c 1'
a/Å	9.8504(4)
b/Å	18.7839(6)
c/Å	10.5297(4)
α/°	90
β/°	99.0900(10)
γ/°	90
V/Å^3	1923.83(12)
Z	4
calc. density/g cm^{-3}	1.403
μ/mm^{-1}	0.191
absorption correction	Multi-Scan
transmission factor range	0.95–0.99
refls. measured	19079
R_{int}	0.0414
mean σ(I)/I	0.0352
θ range	3.271–27.099
observed refls.	3467
x, y (weighting scheme)	0.0426, 2.6914
hydrogen refinement	constr
refls in refinement	4231
parameters	271
restraints	0
$R(F_{obs})$	0.0505
$R_w(F^2)$	0.1262
S	1.041
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.848
min electron density/e Å^{-3}	−0.492



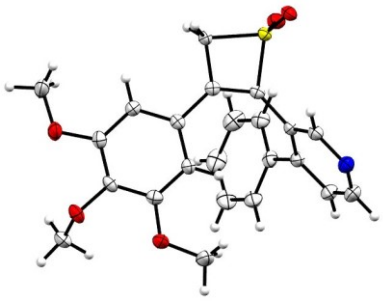
	3.19-e
net formula	$C_{24}H_{17}NO_2S$
M_r/g mol^{-1}	383.44
crystal size/mm	0.100 × 0.060 × 0.050
T/K	100.(2)
radiation	MoKα
diffractometer	'Bruker D8 Venture TXS'
crystal system	triclinic
space group	'P -1'
a/Å	8.6496(4)
b/Å	10.5111(5)
c/Å	11.7560(6)
α/°	84.633(2)
β/°	70.467(2)
γ/°	68.127(2)
V/Å^3	934.20(8)
Z	2
calc. density/g cm^{-3}	1.363
μ/mm^{-1}	0.193
absorption correction	Multi-Scan
transmission factor range	0.93–0.99
refls. measured	9803
R_{int}	0.0194
mean σ(I)/I	0.0256
θ range	3.680–27.103
observed refls.	3702
x, y (weighting scheme)	0.0376, 0.5497
hydrogen refinement	constr
refls in refinement	4084
parameters	253
restraints	0
$R(F_{obs})$	0.0328
$R_w(F^2)$	0.0858
S	1.024
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.392
min electron density/e Å^{-3}	−0.414



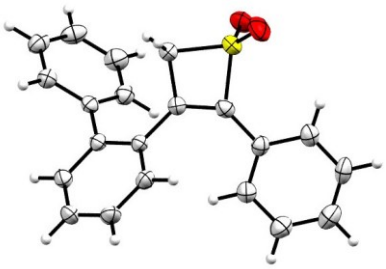
	3.19-f
net formula	$C_{26}H_{18}O_3S$
M_r/g mol^{-1}	410.46
crystal size/mm	0.090 × 0.070 × 0.050
T/K	299.(2)
radiation	MoKα
diffractometer	'Bruker D8 Venture TXS'
crystal system	monoclinic
space group	'P 1 21/c 1'
a/Å	9.6180(11)
b/Å	14.8477(16)
c/Å	15.1188(11)
α/°	90
β/°	107.960(3)
γ/°	90
V/Å^3	2053.8(4)
Z	4
calc. density/g cm^{-3}	1.327
μ/mm^{-1}	0.183
absorption correction	Multi-Scan
transmission factor range	0.95–0.99
refls. measured	18827
R_{int}	0.0478
mean σ(I)/I	0.0380
θ range	3.148–25.349
observed refls.	2888
x, y (weighting scheme)	0.0342, 1.1300
hydrogen refinement	constr
refls in refinement	3751
parameters	271
restraints	0
$R(F_{obs})$	0.0430
$R_w(F^2)$	0.1017
S	1.024
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.236
min electron density/e Å^{-3}	−0.380



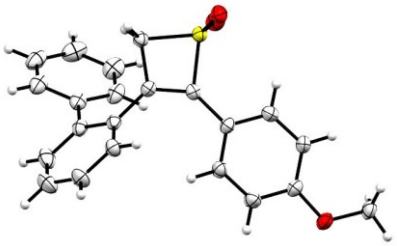
	3.19-i
net formula	$C_{23}H_{21}NO_2S$
M_r/g mol^{-1}	375.47
crystal size/mm	0.080 × 0.060 × 0.050
T/K	100.(2)
radiation	MoKα
diffractometer	'Bruker D8 Venture TXS'
crystal system	monoclinic
space group	'P 1 21/c 1'
a/Å	9.2628(3)
b/Å	18.3007(5)
c/Å	11.2957(4)
α/°	90
β/°	97.6550(10)
γ/°	90
V/Å^3	1897.73(10)
Z	4
calc. density/g cm^{-3}	1.314
μ/mm^{-1}	0.188
absorption correction	Multi-Scan
transmission factor range	0.93–0.99
refls. measured	20040
R_{int}	0.0306
mean σ(I)/I	0.0254
θ range	3.143–27.484
observed refls.	3759
x, y (weighting scheme)	0.0400, 1.1560
hydrogen refinement	constr
refls in refinement	4334
parameters	247
restraints	0
$R(F_{obs})$	0.0367
$R_w(F^2)$	0.0927
S	1.034
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.338
min electron density/e Å^{-3}	−0.433



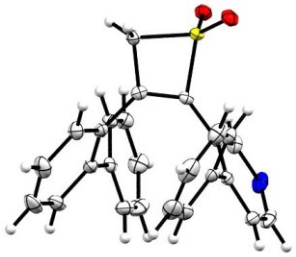
	3.19-k
net formula	$C_{23}H_{21}NO_5S$
M_r/g mol^{-1}	423.47
crystal size/mm	0.100 × 0.070 × 0.050
T/K	100.(2)
radiation	MoKα
diffractometer	'Bruker D8 Venture TXS'
crystal system	monoclinic
space group	'P 1 21/n 1'
a/Å	11.9000(4)
b/Å	10.8787(3)
c/Å	17.0090(5)
α/°	90
β/°	110.1320(10)
γ/°	90
V/Å^3	2067.39(11)
Z	4
calc. density/g cm^{-3}	1.361
μ/mm^{-1}	0.192
absorption correction	Multi-Scan
transmission factor range	0.92–0.99
refls. measured	18208
R_{int}	0.0300
mean σ(I)/I	0.0276
θ range	3.165–27.102
observed refls.	3796
x, y (weighting scheme)	0.0397, 0.9523
hydrogen refinement	constr
refls in refinement	4540
parameters	274
restraints	0
$R(F_{obs})$	0.0339
$R_w(F^2)$	0.0890
S	1.017
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.270
min electron density/e Å^{-3}	−0.406



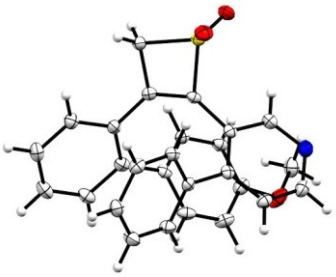
	3.19-I
net formula	$C_{21}H_{16}O_2S$
M_r/g mol^{-1}	332.40
crystal size/mm	0.362 × 0.278 × 0.221
T/K	143(2)
radiation	MoKα
diffractometer	'Oxford XCalibur'
crystal system	monoclinic
space group	'P 21/n'
a/Å	9.6709(8)
b/Å	10.5272(7)
c/Å	16.3722(13)
α/°	90
β/°	94.907(7)
γ/°	90
V/Å^3	1660.7(2)
Z	4
calc. density/g cm^{-3}	1.329
μ/mm^{-1}	0.204
absorption correction	multi-scan
transmission factor range	0.88636–1.00000
refls. measured	9249
R_{int}	0.0368
mean σ(I)/I	0.0399
θ range	4.218–24.995
observed refls.	2271
x, y (weighting scheme)	0.0398, 0.6296
hydrogen refinement	constr
refls in refinement	2916
parameters	217
restraints	0
$R(F_{obs})$	0.0398
$R_w(F^2)$	0.1047
S	1.041
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.310
min electron density/e Å^{-3}	−0.325



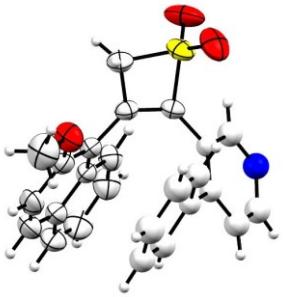
	3.19-m
net formula	$C_{22}H_{18}O_3S$
M_r/g mol^{-1}	362.42
crystal size/mm	0.296 × 0.242 × 0.103
T/K	143(2)
radiation	MoKα
diffractometer	'Oxford XCalibur'
crystal system	monoclinic
space group	'C c'
a/Å	20.6412(17)
b/Å	5.4509(3)
c/Å	17.8630(12)
α/°	90
β/°	114.456(9)
γ/°	90
V/Å^3	1829.5(2)
Z	4
calc. density/g cm^{-3}	1.316
μ/mm^{-1}	0.195
absorption correction	multi-scan
transmission factor range	0.85807–1.00000
refls. measured	4836
R_{int}	0.0318
mean σ(I)/I	0.0545
θ range	4.338–27.946
observed refls.	2912
x, y (weighting scheme)	0.0440, 0.0390
hydrogen refinement	constr
Flack parameter	−0.02(7)
refls in refinement	3200
parameters	236
restraints	2
$R(F_{obs})$	0.0399
$R_w(F^2)$	0.0965
S	1.063
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.257
min electron density/e Å^{-3}	−0.274



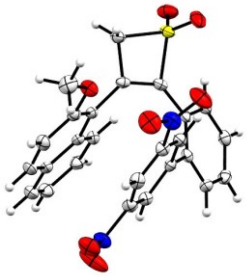
	3.19-q
net formula	$C_{26}H_{19}NO_2S$
M_r/g mol^{-1}	409.48
crystal size/mm	0.090 × 0.070 × 0.040
T/K	100.(2)
radiation	MoKα
diffractometer	'Bruker D8 Venture TXS'
crystal system	monoclinic
space group	'C 1 2/c 1'
a/Å	22.6159(5)
b/Å	8.5749(2)
c/Å	21.2839(5)
α/°	90
β/°	91.8770(10)
γ/°	90
V/Å^3	4125.35(16)
Z	8
calc. density/g cm^{-3}	1.319
μ/mm^{-1}	0.180
absorption correction	Multi-Scan
transmission factor range	0.94–0.99
refls. measured	20750
R_{int}	0.0358
mean σ(I)/I	0.0283
θ range	3.164–26.372
observed refls.	3580
x, y (weighting scheme)	0.0310, 5.1208
hydrogen refinement	constr
refls in refinement	4202
parameters	271
restraints	0
$R(F_{obs})$	0.0364
$R_w(F^2)$	0.0850
S	1.044
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.361
min electron density/e Å^{-3}	−0.404



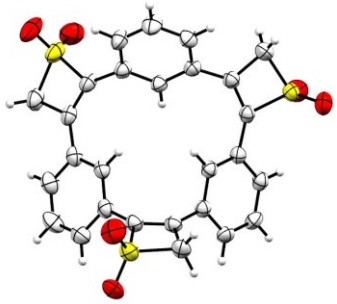
	3.19-u
net formula	$C_{27}H_{21}NO_3S$
M_r/g mol^{-1}	439.51
crystal size/mm	0.080 × 0.070 × 0.040
T/K	100.(2)
radiation	MoKα
diffractometer	'Bruker D8 Venture TXS'
crystal system	monoclinic
space group	'P 1 21/n 1'
a/Å	8.9875(2)
b/Å	13.8360(4)
c/Å	17.3172(4)
α/°	90
β/°	100.4190(10)
γ/°	90
V/Å^3	2117.91(9)
Z	4
calc. density/g cm^{-3}	1.378
μ/mm^{-1}	0.184
absorption correction	Multi-Scan
transmission factor range	0.95–0.99
refls. measured	22311
R_{int}	0.0304
mean σ(I)/I	0.0246
θ range	3.147–27.102
observed refls.	4056
x, y (weighting scheme)	0.0352, 1.3894
hydrogen refinement	constr
refls in refinement	4666
parameters	290
restraints	0
$R(F_{obs})$	0.0354
$R_w(F^2)$	0.0902
S	1.034
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.314
min electron density/e Å^{-3}	−0.461



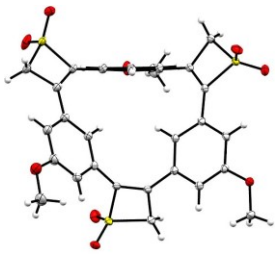
	3.19-v
net formula	$C_{25}H_{19}NO_3S$
M_r/g mol^{-1}	413.47
crystal size/mm	0.080 × 0.060 × 0.050
T/K	298.(2)
radiation	MoKα
diffractometer	'Bruker D8 Venture TXS'
crystal system	monoclinic
space group	'P 1 21/n 1'
a/Å	11.0210(7)
b/Å	15.2877(9)
c/Å	12.5569(6)
α/°	90
β/°	94.216(2)
γ/°	90
V/Å^3	2109.9(2)
Z	4
calc. density/g cm^{-3}	1.302
μ/mm^{-1}	0.180
absorption correction	Multi-Scan
transmission factor range	0.94–0.99
refls. measured	21700
R_{int}	0.0405
mean σ(I)/I	0.0302
θ range	3.246–26.371
observed refls.	3096
x, y (weighting scheme)	0.0529, 1.5771
hydrogen refinement	constr
refls in refinement	4300
parameters	261
restraints	0
$R(F_{obs})$	0.0534
$R_w(F^2)$	0.1458
S	1.032
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.277
min electron density/e Å^{-3}	−0.377



	3.19-w
net formula	$C_{26}H_{18}N_2O_7S$
M_r/g mol^{-1}	502.48
crystal size/mm	0.368 × 0.255 × 0.145
T/K	143(2)
radiation	MoKα
diffractometer	'Oxford XCalibur'
crystal system	monoclinic
space group	'P 21/n'
a/Å	7.8118(4)
b/Å	35.594(2)
c/Å	8.7474(5)
α/°	90
β/°	110.609(6)
γ/°	90
V/Å^3	2276.6(2)
Z	4
calc. density/g cm^{-3}	1.466
μ/mm^{-1}	0.195
absorption correction	multi-scan
transmission factor range	0.93787–1.00000
refls. measured	12599
R_{int}	0.0358
mean σ(I)/I	0.0466
θ range	4.242–26.370
observed refls.	3698
x, y (weighting scheme)	0.0242, 1.6852
hydrogen refinement	constr
refls in refinement	4629
parameters	326
restraints	0
$R(F_{obs})$	0.0476
$R_w(F^2)$	0.0996
S	1.068
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.315
min electron density/e Å^{-3}	−0.325



	3.30-a
net formula	$C_{27}H_{18}O_6S_3$
M_r/g mol^{-1}	534.59
crystal size/mm	0.100 × 0.060 × 0.050
T/K	296.(2)
radiation	MoKα
diffractometer	'Bruker D8Quest'
crystal system	triclinic
space group	'P -1'
a/Å	10.4939(3)
b/Å	11.1477(3)
c/Å	12.1923(3)
α/°	108.6230(10)
β/°	95.7060(10)
γ/°	97.9900(10)
V/Å^3	1322.68(6)
Z	2
calc. density/g cm^{-3}	1.342
μ/mm^{-1}	0.319
absorption correction	Multi-Scan
transmission factor range	0.95–0.98
refls. measured	25275
R_{int}	0.0251
mean σ(I)/I	0.0246
θ range	3.292–26.369
observed refls.	4706
x, y (weighting scheme)	0.0963, 0.7693
hydrogen refinement	constr
Flack parameter	?
refls in refinement	5374
parameters	325
restraints	0
$R(F_{obs})$	0.0498
$R_w(F^2)$	0.1652
S	1.086
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.410
min electron density/e Å^{-3}	−0.503



	3.30-b + $CHCl_3$
net formula	$C_{31}H_{25}Cl_3O_9S_3$
M_r/g mol^{-1}	744.04
crystal size/mm	0.100 × 0.090 × 0.080
T/K	110.(2)
radiation	MoKα
diffractometer	'Bruker D8 Venture TXS'
crystal system	triclinic
space group	'P -1'
a/Å	11.7054(6)
b/Å	12.3313(7)
c/Å	14.5166(8)
α/°	93.996(2)
β/°	102.009(2)
γ/°	106.053(2)
V/Å^3	1951.47(19)
Z	2
calc. density/g cm^{-3}	1.266
μ/mm^{-1}	0.440
absorption correction	Multi-Scan
transmission factor range	0.88–0.97
refls. measured	21459
R_{int}	0.0248
mean σ(I)/I	0.0392
θ range	2.460–28.281
observed refls.	7984
x, y (weighting scheme)	0.0514, 2.3137
hydrogen refinement	constr
refls in refinement	9597
parameters	418
restraints	0
$R(F_{obs})$	0.0440
$R_w(F^2)$	0.1192
S	1.029
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.623
min electron density/e Å^{-3}	−0.651

All but one solvent molecule $CHCl_3$ have been SQUEEZED out.

Symmetry code for figure above: i = -x, -y, 1-z.

Part B

-

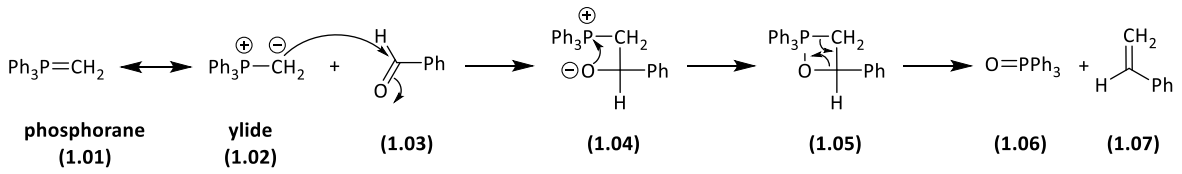
New Methods in Boron Mediated Olefinations

Chapter I

Zweifel Olefination

14 Introduction

An essential category of reaction-class is the olefination, in which two molecules are linked *via* a double bond or a new group is added to a double bond. With a long history the Wittig olefination, discovered in 1954, can be seen as the starting point of following successful transformations of various carbonyl functions into carbon-carbon double bonds.[92] Above all, the synthetically valuable reactions of Peterson, Tebbe, Horner-Wadsworth-Emmons, Takai, McMurry and Julia deserve most attention.[93] Despite using different reagents, many of these reactions show clear similarities with respect to the mechanism. The Wittig reaction is depicted in **Scheme 1**.[94] Following a nucleophilic addition of ylide **1.02** to benzaldehyde (**1.03**), the betaine **1.04** can form a cyclic oxaphosphetane **1.05**. Due to the high oxophilicity of the phosphorus atom, the oxaphosphetane **1.05** undergoes an elimination to give the triphenylphosphine oxide (**1.06**) and alkene **1.07**.



Scheme 1: Wittig olefination of methylenetriphenylphosphorane (**1.01**) and benzaldehyde (**1.02**).

In addition to these meaningful olefination reactions, substituted or functionalized alkenes are a key structural motif in naturally occurring compounds (e.g. resveratrol), in drug discovery (e.g. tamoxifen) and further transformations such as olefin metathesis.[95]

Apart from these classical olefinations, palladium-catalyzed alkenylations can be considered as a complementary tool for the synthesis of functionalized olefins.[96] As a transition-metal free variant of those, the Zweifel reaction/olefination will be described in the following section.

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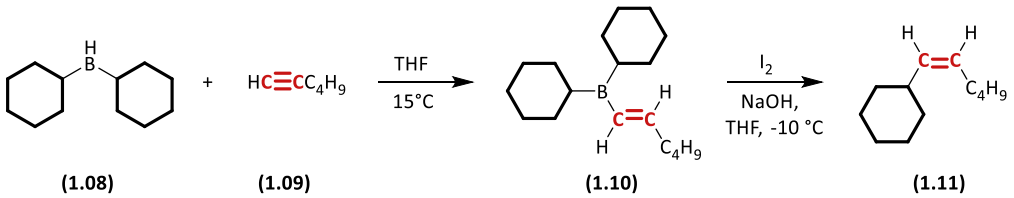
[92] G. Wittig; U. Schöllopf, *Chem. Ber.* **1954**, *87*, 1318. R. W. Hoffmann, *Angew. Chem. Int. Ed.* **2001**, *40*, 1411.
[93] D. J. Peterson; *J. Org. Chem.* **1968**, *33*, 780; F. N. Tebbe; G. W. Parshall; G. S. Reddy, *J. Am. Chem. Soc.* **1978**, *100*, 3611; L. Horner; H. Hoffmann; H. G. Wippel, *Chem. Ber.* **1958**, *91*, 61; W. S. Wadsworth; W. D. Emmons, *J. Am. Chem. Soc.* **1961**, *83*, 1733; K. Takai; K. Nitta; K. Utimoto, *J. Am. Chem. Soc.* **1986**, *108*, 7408; J. E. McMurry; M. P. Fleming, *J. Am. Chem. Soc.* **1974**, *96*, 4708; M. Julia; Y.-M. Paris, *Tetrahedron Lett.* **1973**, *14*, 4833.
[94] G. Wittig; W. Haag, *Chem. Ber.* **1955**, *88*, 1654.
[95] Resveratrol: M. Takaoka*, J. Chem. Soc. Japan* **1939**, *60*, 1090. tamoxifen: Y. Shang, *Nat. Rev. Cancer* **2006**, *6*, 360; For olefin metathesis see: D. Hughes; P. Wheeler; D. Ene, *Org. Process Res. Dev.* **2017**, *21*, 1938; O. M. Ogba; N. C. Warner; D. J. O`Leary; R. H. Grubbs, *Chem. Soc. Rev.* **2018**, *47*, 4510.
[96] E.-I. Negishi; Z. Huang; G. Wang; S. Mohan; C. Wang; H. Hattori, *Acc. Chem. Res.* **2008**, *41*, 1474.

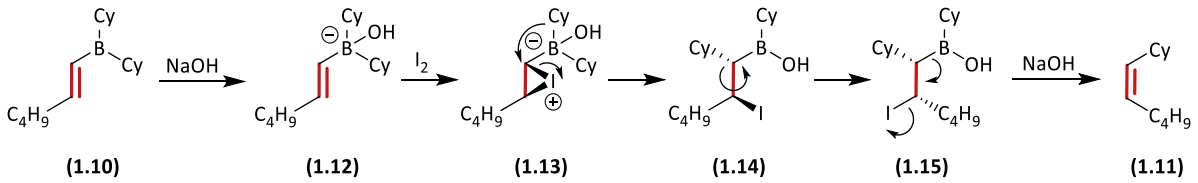
14.1 Zweifel Olefinations

In 1967 G. Zweifel and co-workers reported for the first time a stereoselective route towards substituted alkenes via a hydroboration/iodination sequence of alkynes (**Scheme 2**).[97] In this first example, 1-hexyne (**1.09**) was treated with dicyclohexylborane (**1.08**) in THF, followed by the addition of sodium hydroxide and iodine.



Scheme 2: First reported Zweifel olefination with dicyclohexylborane (**1.08**) and 1-hexyne (**1.09**).

As a key part of the proposed mechanism, an intermediary iodonium ion (**1.13**) was observed after the addition of iodine (**Scheme 3**).[98] This is followed by a 1,2-metalate rearrangement towards the uncharged compound **1.14**. For the final elimination step, the bond of the β-iodoboronic ester **1.14** must rotate in the right position for an anti-periplanar alignment (**1.15**). Finally, the addition of a base results in the formation of the desired olefin **1.11**. Notably, this method proceeds without any use of transition metals.



Scheme 3: Proposed mechanism of the Zweifel reaction (counter cations have been omitted for simplicity).

Therefore, in the following decades the Zweifel reaction was successfully applied by several research groups, like Negishi, Brown and Evans.[99] The Zweifel reaction was used in many total syntheses like the one of (-)-filiformin and debromohamigeran E by the groups of Aggarwal and Morken, respectively.[100]

More recently, Aggarwal and his group reported a general approach for the functionalization of alkenes by a Zweifel mediated strategy.[101] In this work, the use of Grignard- and organolithium

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[97] G. Zweifel; H. Arzoumanian; C. C. Whitney, *J. Am. Chem. Soc.* **1967**, *89*, 3652; G. Zweifel; N. L. Polston; C. C. Whitney, *J. Am. Chem. Soc.* **1968**, *90*, 6243. For a review on Zweifel olefinations see: R. J. Armstrong; V. K. Aggarwal, *Synthesis* **2017**, *49*, 3323.

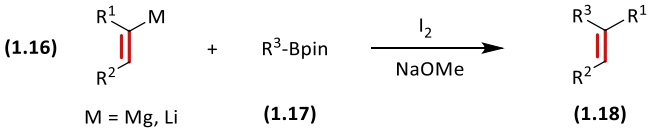
[98] R. J. Armstrong; W. Niwetmarin; V. K. Aggarwal, *Org. Lett.* **2017**, *19*, 2762.

[99] E.-I. Negishi; G. Lew; T. Yoshida, *J. Chem. Soc. Chem. Commun.* **1973**, *22*, 874; D. A. Evans; T. C. Crawford; R. C. Thomas; J. A. Walker, *J. Org. Chem.* **1976**, *41*, 3947; H. C. Brown; N. G. Bhat, *J. Org. Chem.* **1988**, *53*, 6009.

[100] D. J. Blair; C. J. Fletcher; K. M. P. Wheelhouse; V. K. Aggarwal, *Angew. Chem. Int. Ed.* **2014**, *53*, 5552; T. P. Blaisdell; J. P. Morken, *J. Am. Chem. Soc.* **2015**, *137*, 8712.

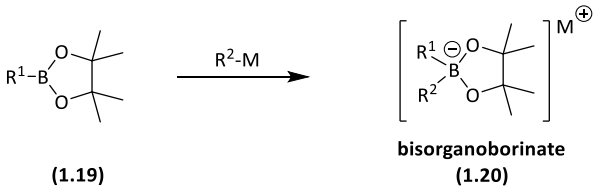
[101] R. J. Armstrong; W. Niwetmarin; V. K. Aggarwal, *Org. Lett.* **2017**, *19*, 2762.

reagents (**1.16**) with commercially available boron pinacol esters (**1.17**) was described (**Scheme 4**). A wide array of functionalized alkenes was synthesized, wherein chiral-, aryl-, and heteroaryl boron pinacol esters (**1.17**) were used as starting materials.



Scheme 4: Zweifel Olefination of boronic esters with Grignard or organolithium reagents by Aggarwal.

However, this respectable strategy is currently limited by the availability and price of the boron pinacol esters **1.19**, which are commonly used for the formation of bisorganoborinates **1.20** (**Scheme 5**).[102]



Scheme 5: General formation of bisorganoborinates.

To address these issues, we developed a general in situ method which combines various organometallic species with readily available trialkoxy-organoboronates towards bisorganoborinates.

[102] J. A. M. Mercer; C. M. Cohen; S. R. Shuken; A. M. Wagner; M. W. Smith; F. R. Moss; M. D. Smith; R. Vahala; A. Gonzalez-Martinez; S. G. Boxer; N. Z. Burns, *J. Am. Chem. Soc.* **2016**, *138*, 15845; C. Garcia-Ruiz; J. L.-Y. Chen; C. Sandford; K. Feeney; P. Lorenzo; G. Berionni; H. Mayr; V. K. Aggarwal, *J. Am. Chem. Soc.* **2017**, *139*, 15324; C. Shu; A. Noble; V. K. Aggarwal, *Angew. Chem. Int. Ed.* **2019**, *58*, 3870; A. Fawcett; T. Biberger; V. K. Aggarwal, *Nat. Chem.* **2019**, *11*, 117.

15 Results

15.1 Single-Pot Access to Bisorganoborinates: Applications in Zweifel Olefination

OL | Organic Letters

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Letter

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Single-Pot Access to Bisorganoborinates: Applications in Zweifel Olefination

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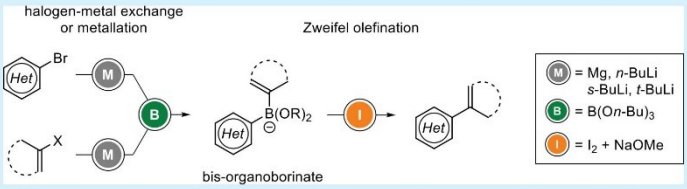
Supporting Information



ABSTRACT: Zweifel olefination is a catalyst-free reaction that serves alkene functionalization. While most methods employ commercially available boron pinacol esters, we have assembled a sequence in which the two partners of the formal coupling reaction are installed successively, starting from inexpensive boron alkoxides. The in situ formation of bisorganoborinates was accomplished by consecutive reaction of two different organometallic species. This single-pot procedure represents a great advancement in the generation of organoborinates and their involvement in C−C bond formation.

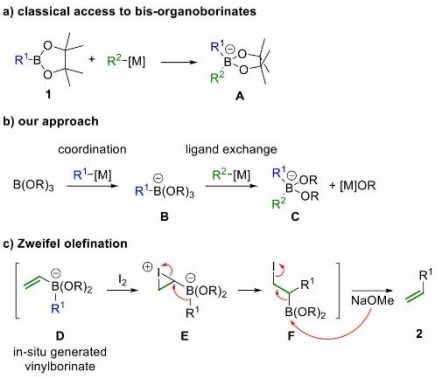
The use of boron in synthesis has spanned the community of organic chemists for a few decades. Boron-based reagents have been employed in quite a number of transformations such as stereo- and regioselective hydroborations,[1] highly functional group tolerant Suzuki cross-coupling reactions,[2] stereospecific homologations pioneered by Matteson,[3] and recently revisited by the group of Aggarwal,[4] and Zweifel olefinations.[5]

With dependable boron-related strategies in hand, we previously set out to tackle challenging strained ring-system syntheses. While boron homologations were employed to stereoselectively access alkylidenecyclobutanes[6] and cyclopropanes,[7] stable boronate complexes enabled the formation of scarcely described substituted cyclobutenes and 2-azetines.[8]

Although Zweifel olefination is an established transformation, for which we recently developed alternative organocerium reagents,[9] most reports describe the use of commercial organoboron pinacol esters **1**.[10] However, this strategy is currently limited by the availability of those reagents and their price. To overcome the need of using boron pinacol esters **1**, we thought of employing in situ generated trialkoxyorganoboronates **B** as intermediates for the formation of bisorganoborinates **C**, considering the pseudometallic character of boron to displace one of the alcoholate ligands (Scheme 1b).

Given that organoboronates **A** and **B** can be generated quantitatively by addition of boron alkoxides to organometallic species (R^1−[M]),[11] such a protocol would constitute a solid base as the first step in the in situ formation of bisorganoborinates **C**. With the possibility of performing a ligand exchange on the intermediate organoboronates, an economic alternative to the use of commercially available

Scheme 1. Our Approach to Bisorganoborinates[a]



[a]Counter-cations have been omitted for more clarity.

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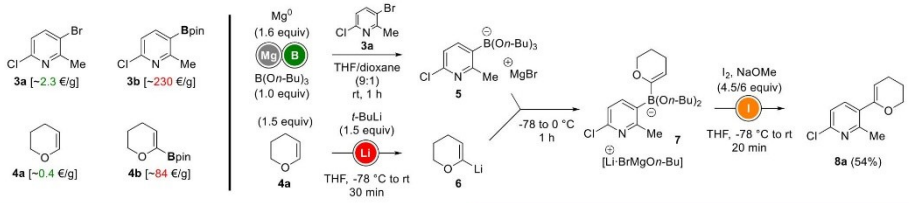
DOI: 10.1021/acs.orglett.9b00493
Org. Lett. 2019, 21, 2189–2193

Scheme 2. Proof of Concept: Coordination–Ligand Exchange–Zweifel Olefination Sequence[11]



boron pinacol esters **1** (Scheme 1a) would be unlocked with inexpensive boron alkoxides.

In the Zweifel olefination, an alkenyl-organoborinate **D** (Scheme 1c) reacts with iodine, giving an intermediate iodonium species **E** that triggers a 1,2-metalate rearrangement toward the neutral compound **F**, upon which the addition of a base promotes a β-elimination that ultimately leads to the olefin **2**.[12] The efficient formation of **D** stands as a key step in this transformation. We describe herein a one-pot sequence toward alkenyl-organoborinates **D** and their subsequent involvement in Zweifel olefination reactions.

As a proof of concept, we envisioned the formation of a Csp^2–Csp^2 bond between a pyridine moiety **3** and a 3,4-dihydropyran **4** (Scheme 2).

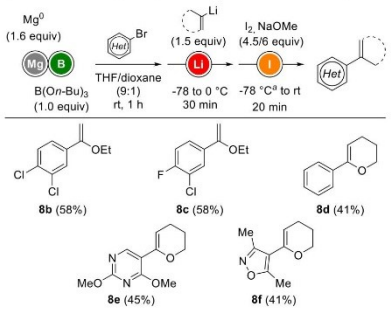
Via known strategies, the reaction requires the use of expensive boron pinacol esters (either **3b** or **4b**), while our method enables the use of cheaper substrates such as **3a** and **4a**. The intermediate 3-pyridylboronate **5** is generated by adding **3a** to a suspension of magnesium in the presence of boron *n*-butoxide (0.15 €/g),[11c,13] the reaction proceeding through metal insertion followed by coordination to the boron atom at room temperature. The presence of dioxane during this step proved to be essential to avoid formation of undesired boron species.[14,15] An ex-situ prepared solution of (3,4-dihydro-2*H*-pyran-6-yl)lithium **6**[16] is added to perform the ligand exchange, releasing an equivalent of butylate salt and giving access to the alkenylborinate **7** (Scheme 2). The intramolecular alkenylation proceeds upon addition of iodine, furnishing the heterocyclic compound **8a** in 54% yield.

As described by the group of Aggarwal,[5g] no excessive amount of alkenyllithium reagent was required for full consumption of the intermediate trialkoxyboronate as shown by ^{11}B NMR measurements.[15]

With a proof of concept in hand, we started exploring the in situ formation of bisorganoborinates through magnesium insertion/trapping reaction and further ligand exchange with alkenyllithium. Reasonable yields were obtained for insertions onto aromatic and heteroaromatic derivatives, in combination with acyclic (**8b–c**) and cyclic (**8d–f**) alkenyl ethers (Scheme 3).

However, when the ligand exchange of the second step was performed using organomagnesium reagents, an excess of the latter was required for the Zweifel product to be obtained with maximum efficiency. Three equivalents were needed in order to generate a proposed tetrakis–organoboron complex containing three alkenyl groups. ^{11}B NMR studies also demonstrated that the intermediate organoboronate species such as **B** (Scheme 1b) would remain unconsumed with lower excesses of organomagnesium reagents.[14] The boron-relayed room-temperature magnesium insertion/trapping reaction was performed on a wide range of aryl and heteroaryl bromides and

Scheme 3. Mg Insertion/Ligand Exchange with Alkenyllithium Reagents/Zweifel Olefination Sequence[a]



[a]Conducting the addition of iodine at 0 °C resulted in lower yields.

followed by exchanges of alkoxide ligands with alkenylmagnesium species (Scheme 4). The scope of the reaction was evaluated with vinyl (**9a–f**), isopropenyl (**9g–q**), and α-styrylmagnesium reagents (**9r–v**) in 45 to 89% yield. Interestingly, valuable heteroaromatic derivatives were successfully engaged in this procedure, affording sophisticated structures such as alkenyl pyrazole **9q** (50%) or pyrimidines **9n**, **9s**, and **9v** (48 to 74%).

Next, we envisioned that a Br/Li exchange (instead of Mg insertion) as a first step could be used in the formation of intermediate organoboronates (Scheme 5). *n*-Butyllithium was introduced at −78 °C on different aryl bromides, and—after formation of the organoboronate species via addition of boron butylate—the sequence was continued as above, with further introduction of 3 equiv of ex situ generated alkenylmagnesium stock solutions.

Phenanthryl, naphthyl, and carbazolyl substrates led to olefins **10a–c** in good yields up to 80%, validating the process to work with a first step of organolithium addition. The transformation being quite efficient, we pushed the challenge further and set out to perform a double, yet unprecedented Zweifel olefination on bisbrominated substrates. Double Br/Li exchange was undertaken using 2 equiv of *n*-BuLi at −78 °C. Twice the amount of further reagents was subsequently needed to drive the reaction to completion, affording bisolefinated products **10d–f** in good yields (up to 63%).

In consideration of previous results, it was expected that a procedure using sequentially two organolithium reagents would lead to desired products, and compounds **11a** and **b** were isolated in moderate yields (Scheme 6). Importantly, such a protocol allowed us to use 2 equiv of the same olefin to

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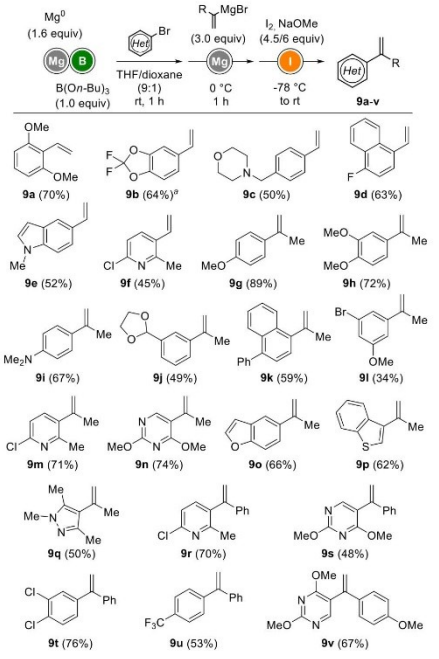
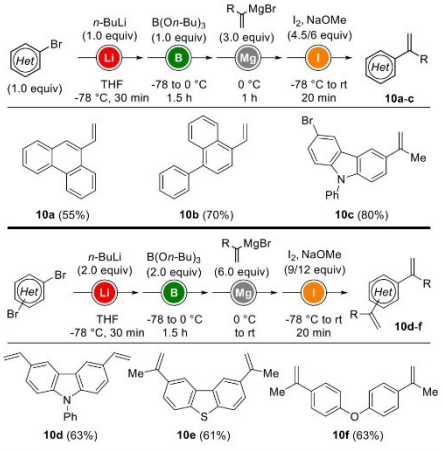
Scheme 4. Mg Insertion/Ligand Exchange with Alkenylmagnesium Reagents/Zweifel Olefination Sequence



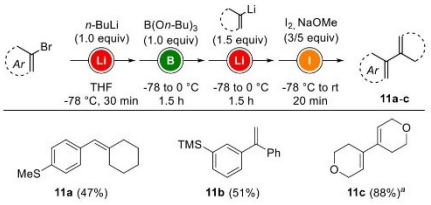
[a]Yield was determined by ^{19}F NMR vs C_6F_6 as internal standard.

Scheme 5. Br/Li Exchange/Ligand Exchange with Alkenylmagnesium Reagents/Zweifel Olefination Sequence



undergo formal dimerization (**11c**) in 88% yield, opening an efficient route toward functionalized dienes.

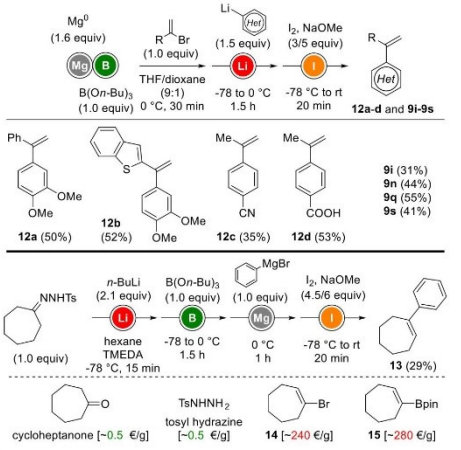
Scheme 6. Br/Li Exchange/Ligand Exchange with Alkenyllithium Reagents/Zweifel Olefination Sequence



[a]**11c** was made from 4-(3,6-dihydro-2*H*-pyran)yllithium and 0.5 equiv of $B(On\text{-}Bu)_3$ (see SI).

We finally explored the possibility of an inverse procedure in which the alkenyl group would be introduced in the first step (Scheme 7). In this case, considerable savings of alkenylmagnesium reagent—previously required in excess—would be achieved. Such a challenge was undertaken by generating an alkenylboronate from the corresponding alkenyl bromide, in the presence of magnesium and boron *n*-butoxide. An aryllithium species was then added (1.5 equiv), followed by iodine and sodium methoxide. This procedure allowed for the formation of *gem*-bisarylated alkenes **12a** and **b** in moderate yields.

Scheme 7. Zweifel Olefinations with In Situ Generated Alkenylboronates[11]



In addition, this reverse alternative provides an access to compounds that could not be obtained via previous routes, such as the nitrile derivative **12c** (35%). A challenging unprotected carboxylic acid was also engaged in in the second step of the olefination reaction. In this case, 2 equiv of *n*-BuLi was used: one to deprotonate the carboxylic acid and one to perform a halogen−metal exchange. **12d** was obtained in 53% yield. To push the methodology further, we employed a Shapiro rearrangement to produce an alkenyllithium reagent to be engaged in the Zweifel olefination. Cycloheptanyl hydrazone was chosen as a representative example, as classical

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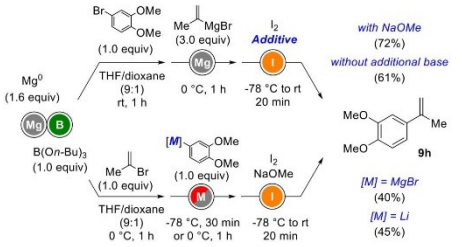
alternatives would require expensive starting materials such as 1-cycloheptenyl bromide **14** or boron pinacol ester **15**. Even though **13** was obtained in 29% yield, only inexpensive cycloheptanone and tosylhydrazine were needed as substrates in this multistep one-pot sequence.

We have shown that different transition-metal-free paths can be taken to synthesize arylated olefins without the need of purchasing expensive boron pinacol esters. In Scheme 8, we summarize and compare some of these methods, having an in situ magnesium insertion/trapping reaction as the first step. Employing classical conditions described in Scheme 4 afforded **9h** in 72% yield.

Scheme 8. Comparison of Different Methods to Access 9h



Importantly, when performing the ligand exchange in the second step on the intermediate organoboronate, magnesium butoxide (*n*-BuOMgBr) is released in the reaction mixture, and we hypothesized that this alcoholate could be used as the required base in the elimination step. Avoiding the addition of sodium methanolate confirmed this hypothesis, as **9h** was isolated in 61% yield. Alternatively, the first insertion step could be performed on the alkenyl part, preventing the use of an excessive amount of the corresponding Grignard reagent in the second step. Similar yields were obtained using either arylmagnesium or aryllithium species (40−45%).

In conclusion, we have demonstrated that a stoichiometrically controlled generation of hetero bisorganoborinates could be turned into a powerful tool for C−C bond formation. By unlocking new and complementary paths toward diversely substituted boron species, a wide array of functionalized olefins were developed, employing inexpensive substrates and reagents in combination with catalyst-free Zweifel conditions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00493.

Experimental procedures and characterization (IR, HRMS, and ^{1}H and ^{13}C NMR data) for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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DOI: 10.1021/acs.orglett.9b00493
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Moss, F. R.; Smith, M. D.; Vahala, R.; Gonzalez-Martinez, A.; Boxer, S. G.; Burns, N. Z. *J. Am. Chem. Soc.* **2016**, *138*, 15845−15848.
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(13) For references in prices, see ABCR GmbH (https://www.abcr.de/).
(14) Addition of dioxane to the reaction mixture proved to avoid the undesired formation of bisorganoboron species by inducing precipitation of mono-organoboronates in the first coordination step.
(15) See Supporting Information.
(16) Hornillos, V.; Giannerini, M.; Vila, C.; Fananas-Mastral, M.; Feringa, B. L. *Chem. Sci.* **2015**, *6*, 1394−1398.

DOI: 10.1021/acs.orglett.9b00493
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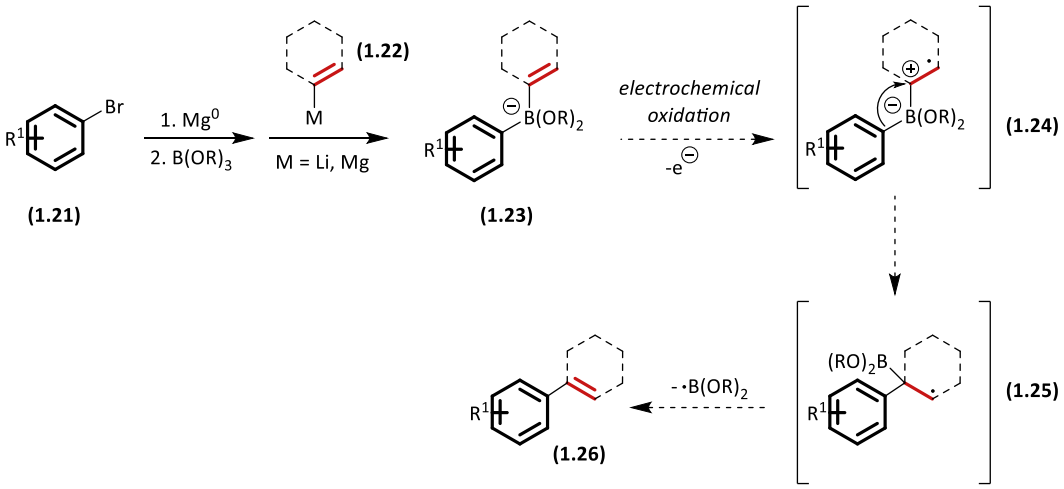
16 Outlook

With this new method for a general synthesis of bisorganoborinates in hands, combination with an unprecedented electrochemical sequence could also lead to a Zweifel-like coupling, but without the need for any additives (**Scheme 6**).



Scheme 6: Proposed electrochemical transformation of bisorganoborinates **1.23** towards coupling products **1.26** without the use of iodine/base as additive.

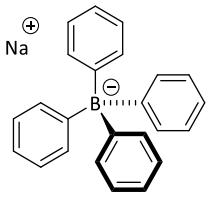
Following an *in situ* trapping of Grignard reagents as trialkoxy-organoboronates and formation of bisorganoborinates **1.23**, an electrochemical oxidation step could lead to the oxidized radical zwitter ion **1.24**. According to a 1,2-metalate rearrangement towards the radical adduct **1.25** and a final elimination of the radical $*B(OR)_2$ the desired Zweifel product **1.26** could be obtained.

Chapter II

Tetraorganoborates

17 Introduction

Tetraorganoborates are organic compounds of the formula $[BR_4]^-$, wherein the residues are tetrahedrally bound to boron. One of the most popular tetraorganoborate is sodium tetraphenyl borate (**2.01**), as it is widely used in organic and analytical chemistry (tradename: Kalignost®) (**Figure 1**).[103]

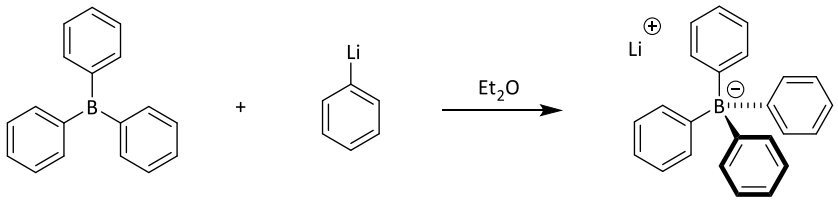


(2.01)

Figure 1: Most used tetraorganoborate in literature: sodium tetraphenyl borate, also known as Kalignost®.

17.1 Synthesis of Tetraorganoborates

The first characterized tetraorganoborate was lithium tetraphenyl borate (**2.04**), which was synthesized in 1949 by Wittig and co-workers (**Scheme 7**).[104] Different methods for the formation of lithium tetraphenylborate are reported and Wittig described the use of triphenylborane (**2.02**) and phenyllithium (**2.03**) in ether.



(2.02) **(2.03)** **(2.04)**

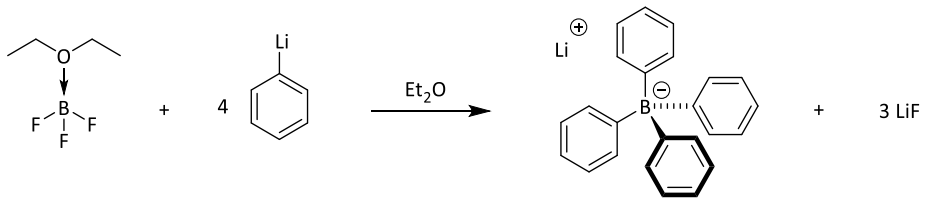
Scheme 7: First reported synthesis of lithium tetraphenylborate by Wittig.

A few years later, Wittig and Raff came up with another route towards lithium tetraphenylborate. In this case, boron trifluoride etherate complex (**2.05**) was mixed with 4 equivalents of

[103] K. Utsumi; L. Packer, *Arch. Biochem. Biophys.* **1967**, *122*, 509; P. Abley; J. Halpern, *Chem. Commun.* **1971**, *20*, 1238; P. G. Ciattini; E. Morera; G. Ortar, *Tetrahedron Lett.* **1992**, *33*, 4815; N. A. Bumagin; V. V. Bykov, *Tetrahedron* **1997**, *53*, 14437; D. Villemin; M. J. Gómez-Escalonilla; J.-F. Saint-Clair, *Tetrahedron Lett.* **2001**, *42*, 635; T. Ohe; S. Uemura, *Bull. Chem. Soc. Jpn.* **2003**, *76*, 1423; J. Yan; W. Hu; G. Rao, *Synthesis* **2006**, *6*, 0943; H. Mizuno; H. Sakurai; T. Amaya; T. Hirao, *Chem. Commun.* **2006**, *48*, 5042; L. Bai; J.-X. Wang, *Adv. Synth. Catal.* **2008**, *350*, 315. H. Zeng; R. Hua, *J. Org. Chem.* **2008**, *73*, 558; W.-J. Zhou; K.-H. Wang; J.-X. Wang; Z.-R. Gao, *Tetrahedron* **2010**, *66*, 7633; R. B. Bedford: P. B. Brenner; E. Carter; J. Clifton; P. M. Cogswell; N. J. Gower; M. F. Haddow; J. N. Harvey; J. A. Kehl; D. M. Murphy; E. C. Neeve; M. L. Neidig; J. Nunn; B. E. R. Snyder; J. Taylor, *Organometallics* **2014**, *33*, 5767; Z. Lu; R. Lavendomme; O. Burghaus; J. R. Nitschke, *Angew. Chem.* **2019**, *131*, 9171.

[104] G. Wittig; G. Keicher; A. Rückert; P. Raff, *Liebigs Ann. Chem.* **1949**, *563*, 110.

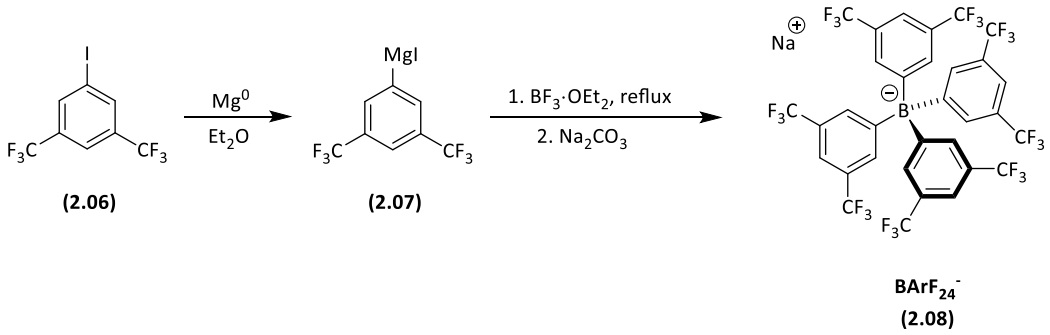
phenyllithium (**2.03**) (**Scheme 8**).[105] Moreover, an analogue method for the preparation of the sodium derivative was reported, using phenylmagnesium bromide, followed by treatment with a saturated sodium carbonate solution.



(2.05) **(2.03)** **(2.04)**

Scheme 8: Formation of lithium tetraphenylborate by the treatment of boron trifluoride etherate (**2.05**) with phenyllithium (**2.03**).

A special class of tetraorganoborates are the BARF-anions or sometimes called *Kobayashi* anions. The BARF-anions, with the formula $[BAr^F{}_4]^-$, were synthesized by Kobayashi and his group in 1984, building up on the method reported by Wittig (**Scheme 9**).[106] The Ar^F within the formula indicates the presence of fluorinated groups on the tetraorganoborate salt. Beside the work of Kobayashi, it is worth noting that the first synthesis of a BARF-Anion, the lithium tetra(pentafluorophenyl)borate ($LiBArF_{20}$) goes back to the work of Massey and Park from 1964.[107]



(2.06) **(2.07)** **$BArF_{24}^-$ (2.08)**

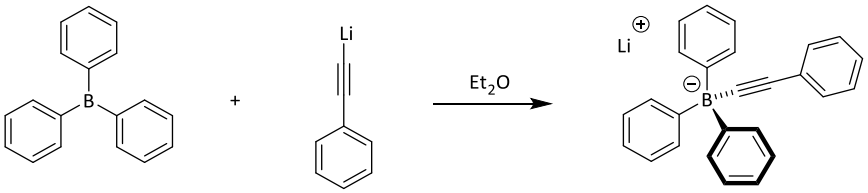
Scheme 9: Synthesis towards the BARF-anion $BArF_{24}^-$ by the group of Kobayashi.

In the synthesis reported by Kobayashi, 1-iodo-3,5-bis(trifluoromethyl)benzene (**2.06**) was used for the formation of Grignard species **2.07**, followed by a slow addition of boron trifluoride etherate (**Scheme 9**). The sodium salt of the $BArF_{24}^-$ anion was finally obtained after workup with sodium carbonate in excellent yield. In addition, Bergman and Yakelis reported in 2005 a similar preparation of $NaBArF_{24}$ but with increased safety. In this work isopropylmagnesium chloride and 1-bromo-3,5-bis(trifluoromethyl)benzene in THF were used, as (trifluoromethyl)aryl Grignards tend to exothermic

[105] G. Wittig; P. Raff, *Liebigs Ann. Chem.* **1951**, *573*, 195.
[106] H. Nishida; N. Takada; M. Yoshimura; T. Sonoda; H. Kobayashi, *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2600.
[107] A. G. Massey; A. J. Park, *J. Organometal. Chem.* **1964**, *2*, 245.

decomposition in presence of remaining magnesium metal.[108] BARF-anions are known to coordinate weaker than other commonly used anions, like BF_4^- or PF_6^-, and are therefore suitable candidates for reactions in which the nature of the anions can influence the outcome.[109]

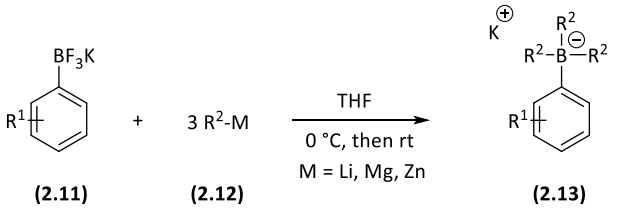
Going a step further to mixed tetraorganoborates, most procedures reported their synthesis by treatment of triarylboranes with suitable organometallic species.[110] **Scheme 10** depicts the first reaction of triphenylborane (**2.02**) with lithium phenylacetylide (**2.09**) to form the corresponding mixed tetraorganoborate **2.10**.[111]



(2.02) **(2.09)** **(2.10)**

Scheme 10: Formation of the first reported mixed tetraorganoborate by Wittig.

Another meaningful method for the selective synthesis of mixed tetraorganoborates was reported in a Japanese patent from 2016.[112] In this straightforward strategy, the commercially available organo-trifluoroborates (**2.11**) react with three equivalents of an organometallic reagent (**2.12**) to generate mixed potassium tetraorganoborates (**2.13**) (**Scheme 11**).



(2.11) **(2.12)** **(2.13)**

Scheme 11: Formation of mixed tetraorganoborates using organo-trifluoroborates and different organometallic reagents.

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[108] N. A. Yakelis; R. G. Bergman, *Organometallics* **2005**, *24*, 3579; J. L. Leazer; R. Cvetovich; F.-R. Tsay; U. Dolling; T. Vickery; D. Bachert, *J. Org. Chem.* **2003**, *68*, 3695.

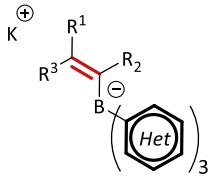
[109] S. G. Weber; D. Zahner: F. Rominger; B. F. Straub, *Chem. Commun.* **2012**, *48*, 11325; N. Hafezi; J. M. Holcroft; K. J. Hartlieb; E. J. Dale; N. A. Vermeulen; C. L. Stern; A. A. Sarjeant; J. F. Stoddard, *Angew. Chem. Int. Ed.* **2015**, *54*, 456; L. Carreras; L. Rovira; M. Vaquero; I. Mon; E. Martin; J. Benet-Buchholz; A. Vidal-Ferran, *RSC Adv.* **2017**, *7*, 32833; P. Pommerening; J. Mohr; J. Friebel; M. Oestreich, *Eur. J. Org. Chem.* **2017**, *16*, 2312.

[110] A. Suzuki; N. Miyaura; S. Abiko; M. Itoh; H. C. Brown; J. A. Sinclair; M. M. Midland, *J. Am. Chem. Soc.* ***1973***, *95*, 3080; K. Siegmann, P. S. Pregosin; L. M. Venanzi, *Organometallics* **1989**, *8*, 2659; T. Ishikawa; S. Nonaka; A. Ogawa; T. Hirao, *Chem. Commun.* **1998**, 1209. J. D. Wilkey; G. B. Schuster, *J. Am. Chem. Soc.* **1991**, *113*, 2149; M. A. Kropp; M. Baillargeon; K. M. Park; K. Bhamidapaty; G. B. Schuster, *J. Am. Chem. Soc.* **1991**, *113*, 2155; J. R. Gardinier; P. J. Pellechia; M. D. Smith, *J. Am. Chem. Soc.* **2005**, *127*, 12448; M. Asay; B. Donnadieu; T. Amaya; Y. Tsukamura; T. Hirao, *Adv. Synth. Catal.* **2009**, *351*, 1025; W. W. Schoeller; G. Bertrand, *Angew. Chem. Int. Ed.* **2009**, *48*, 4796. N. Ishida; W. Ikemoto; M. Narumi; M. Murakami, *Org. Lett*. **2011**, *13*, 3008;

[111] G. Wittig; P. Raff, *Liebigs Ann. Chem.* **1951**, *573*, 195;

[112] S. Atsushi, JP2016150925, **2016**.

Considering the simplicity of this procedure, we adopted it to access mixed alkenyl(hetero)triarylborates **2.14** and their further transformation by oxidative electrochemical coupling (**Figure 2**).

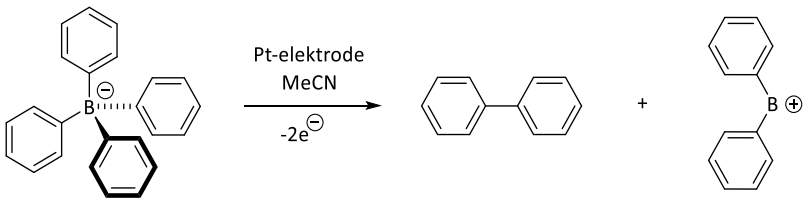


(2.14)

Figure 2: Alkenyl(hetero)triarylborates **2.14**.

17.2 Electrochemical Transformation of Tetraorganoborates

Tetraorganoborates like tetraphenylborate and particularly the BARF-anion type are well studied with respect to electrochemical properties.[113] Especially their electrochemical oxidation, first crossed by Geske in 1959, has led to unceasing interest over the following decades till now.[114] In this reaction (**Scheme 12**), a homo coupling towards biphenyl (**2.15**) is initiated by an electrochemical oxidation of tetraphenylborate (**2.14**) at a platinum electrode. Geske suggested an intramolecular two electron process.[115]



(2.15) **(2.16)** **(2.17)**

Scheme 12: Electrochemical oxidation of tetraphenylborate (counter ions have been omitted for more simplicity).

Despite the early proposal on the nature of the mechanism, it is still unclear whether it follows an inter- or intramolecular pathway. Recently, Waldvogel and his group have tried to give new mechanistical insights and therefore studied the electrochemical stability of different BARF-anions and tetraphenylborates under electrochemical conditions.[116] Cross-over experiments with two different

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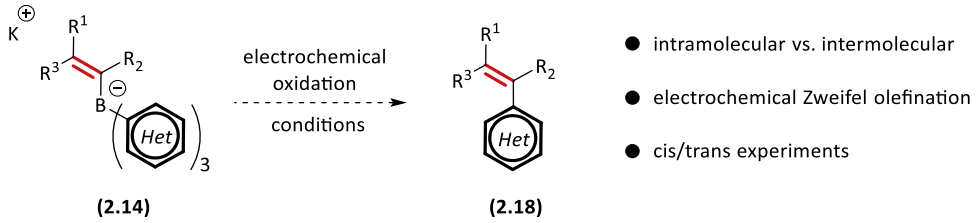
[113] F. Barrière; W. E. Geiger, *J. Am. Chem. Soc*. **2006**, *128*, 3980; W. E. Geiger; F. Barrière, *Acc. Chem. Res*. **2010**, *43*, 1030.
[114] D. H. Geske, *J. Phys. Chem.* **1959**, *63*, 1062; W. R. Turner; P. J. Elving, *Anal. Chem.* **1965**, *37*, 207; E. E. Bancroft; H. N. Blount; E. G. Janzen, *J. Am. Chem. Soc.* **1979**, *101*, 3692; J. H. Morris; H. J. Gysling; D. Reed, *Chem. Rev.* **1985**, *85*, 51. S. B. Beil; P. K. Pal; S. Chowdhury; M. G. B. Drew; D. Datta, *New J. Chem.* **2002**, *26*, 367; S. B. Beil; S. Möhle; P. Enders; S. R. Waldvogel, *Chem. Commun.* **2018**, *54*, 6128.
[115] D. H. Geske, *J. Phys. Chem.* **1962**, *66*, 1743.
[116] S. B. Beil; S. Möhle; P. Enders; S. R. Waldvogel, *Chem. Commun.* **2018**, *54*, 6128.

tetraorganoborates exclusively gave the corresponding homo coupling products without a coupling between each other, indicating an intramolecular process.

Building on this finding, we set out to develop a new route towards the formation of alkenyl(hetero)triarylborates and further investigate their electrochemical oxidation (**Scheme 13**). This would give more evidence regarding the mechanism, electrochemical stability as well as open a new pathway of boron mediated olefinations in contrast to the classical Zweifel olefinations (see **Chapter I** "**Zweifel Olefinations**").



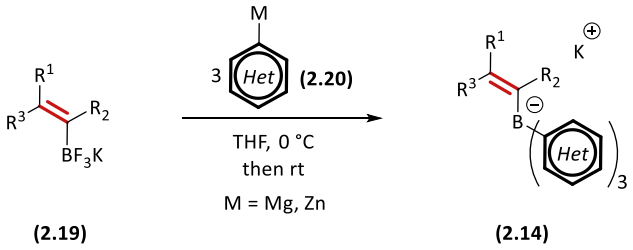
(2.14) **(2.18)**

Scheme 13: New boron mediated transformations through electrochemical oxidation of tetraorganoborates.

18 Results

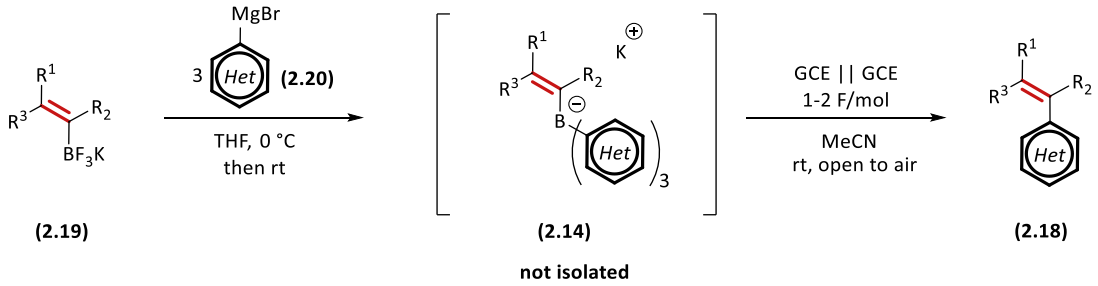
18.1 Electrochemical Formation of Functionalized Alkenes using Tetraorganoborates

As a first goal in the development of an electrochemical approach for the transformation of mixed potassium alkenyl(hetero)triarylborates **2.14**, these organic salts had to be synthesized in a versatile and practical fashion (**Scheme 14**). Therefore, organometallic species (**2.20**), like Grignard- and organozinc reagents, were engaged with commercially available alkenyl trifluoro borates (**2.19**).



Scheme 14: Synthesis of mixed potassium alkenyl(hetero)triarylborates.

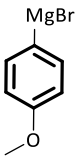
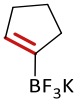
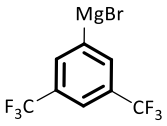
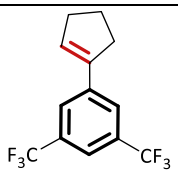
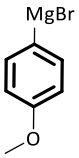
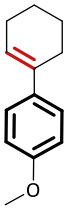
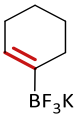
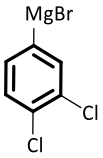
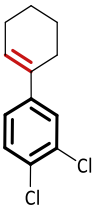
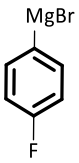
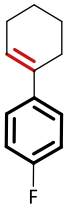
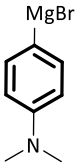
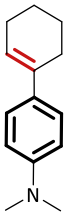
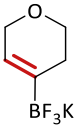
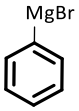
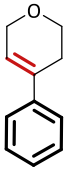
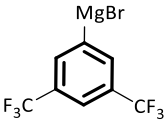
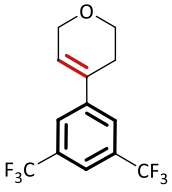
Unfortunately, due to the high solvophilicity in polar solvents, precipitation of most of these compounds was a major issue. Therefore, a more convenient and feasible two-pot procedure was designed (**Scheme 15**).

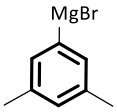
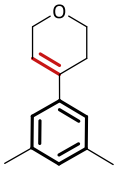
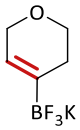
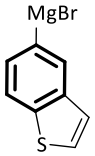
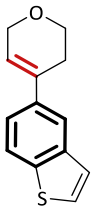
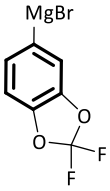
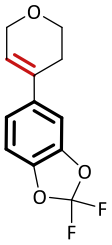
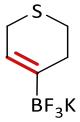
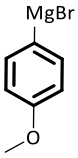
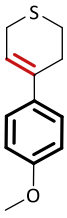
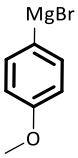
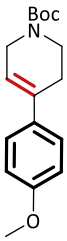
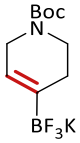
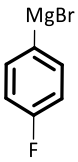
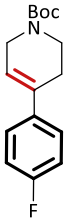
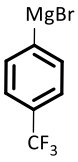
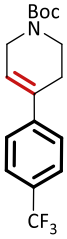


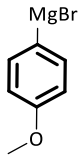
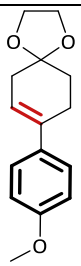
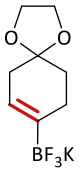
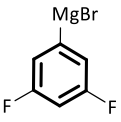
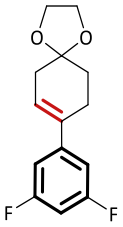
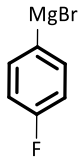
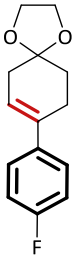
Scheme 15: Two-Pot procedure for the functionalization of alkenyl trifluoro borates by an electrochemical oxidation.

Simple workup and solvent switch from tetrahydrofuran to acetonitrile paved the way to an electrochemical oxidation step. In the electrification of tetraorganoborates, cheap and reusable glassy carbon electrodes were used. It is worth noting that no inert conditions were necessary, as the alkenyl(hetero)triarylborates **2.14** are air and water stable. With this methodology in hands, a small library of different functionalized alkenes was accessed (**Table 1**). The isolated yields vary between 23% (**2.18-j**) and 87% (**2.18-p**) over two steps.

Table 1: Functionalized alkenes by a two-pot procedure starting with alkenyl trifluoroborates.

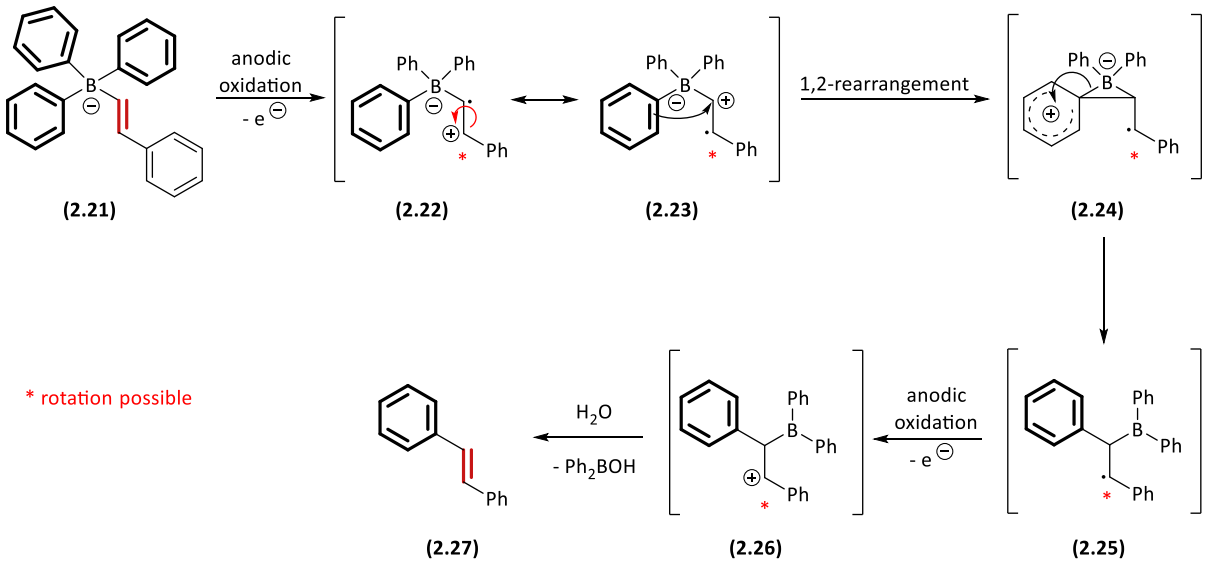
Entry	Electrophile	Organometallic reagent	Product	Yield[a]
1				**2.18-a**, 41%
2				**2.18-b**, 52%
3				**2.18-c**, 71%
4				**2.18-d**, 53%
5				**2.18-e**, 75%
6				**2.18-f**, 50%
7				**2.18-g**, 60%
8				**2.18-h**, 54%

Entry	Electrophile	Organometallic reagent	Product	Yield[a]
9				**2.18-i**, 54%
10				**2.18-j**, 23%
11				**2.18-k**, 29%
12				**2.18-l**, 77%
13				**2.18-m**, 52%
14				**2.18-n**, 56%
15				**2.18-o**, 43%

Entry	Electrophile	Organometallic reagent	Product	Yield[a]
16				**2.18-p**, 87%
17				**2.18q**, 40%
18				**2.18-r**, 86%

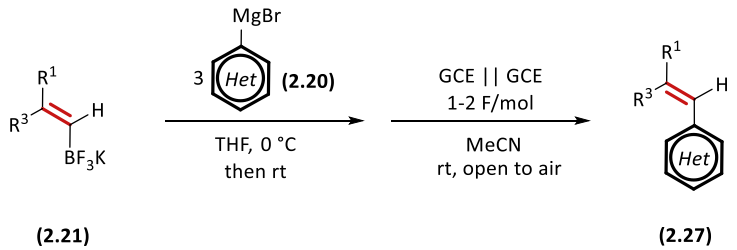
[a] Yield of isolated, analytically pure product.

In this first scope only strained alkenyl trifluoroborates were chosen as starting material, as there is no possibility of obtaining different isomers due the proposed reaction pathway (**Scheme 16**). In the mechanism given below, the reaction of an *E*-alkenyl(hetero)triarylborate **2.21** is proposed. Following an initial anodic oxidation on the alkene moiety, the generated radical cation **2.22/23** can then be attacked by one of the phenyl residues attached to the boron atom, leading to an intermediary zwitterionic structure **2.24**.



Scheme 16: Proposed intramolecular mechanism of the electrochemical oxidation of tetraorganoborates.

By regenerating the aromaticity of the zwitterionic structure **2.24**, the radical **2.25** is formed. After a second anodic oxidation, the cation **2.26** can then be attacked by a nucleophile such as water, leading to the coupled product (**2.27**). It should be noted that during the transformation, the double bond of the starting alkene (**2.21**) no longer exists. If the C-C bond rotation has time to happen, two different stereoisomers with a *Z*- or *E*-configuration can be obtained. To gain further evidence for this proposed mechanism, a second library was synthesized using *Z*- or *E*-alkenyl trifluoroborates (**Table 2**). Again, a two-pot procedure was conducted (**Scheme 17**).



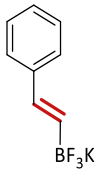
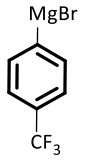
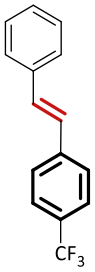
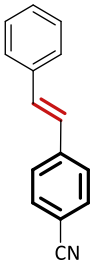
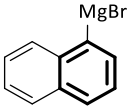
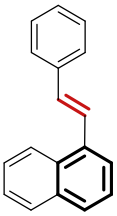
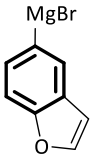
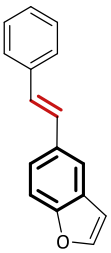
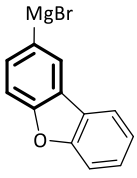
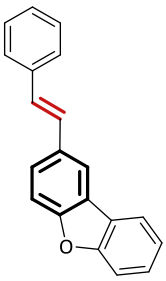
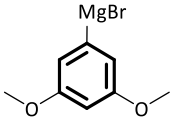
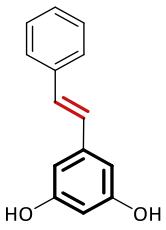
Scheme 17: Two-Pot procedure for the functionalization of *Z*- or *E*-alkenyl trifluoroborates by an electrochemical oxidation.

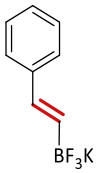
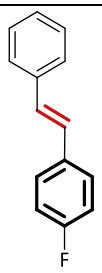
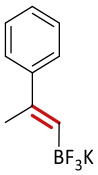
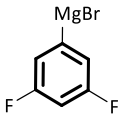
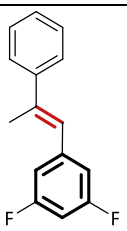
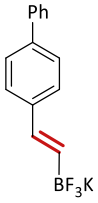
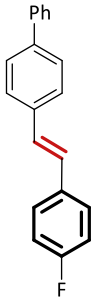
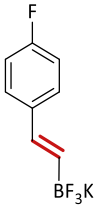
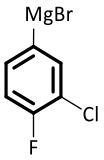
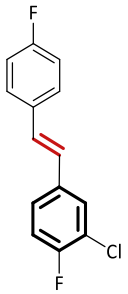
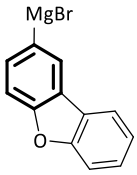
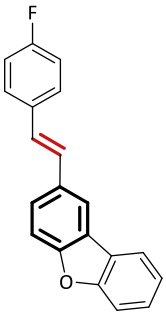
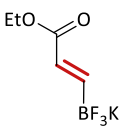
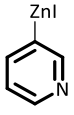
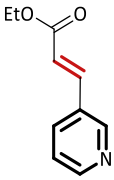
As expected, starting with *E*-alkenyl trifluoroborates, only the *E*-isomer (**2.27-a-l**) was obtained (up to 99:1 *E*/*Z* selectivity). Starting with *Z*-alkenyl trifluoroborates, the sterically favoured *E*-isomer should be formed. With lower ratios of selectivity (**2.27-m-o**) the *E*-isomers were in fact the major product, supporting the previously proposed mechanism. In contrast to the Zweifel reaction, in which a stereoinversion is usually observed the electrochemical variant strongly depends on which alkenyl trifluoroborates are used and can therefore be regarded as stereoconvergent. Furthermore, due to no coupling products between the alkenyl groups of two alkenyl(hetero)triarylborates an intermolecular reaction can be ruled out.

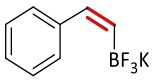
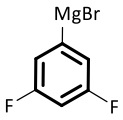
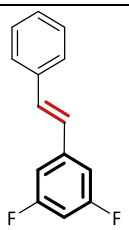
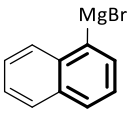
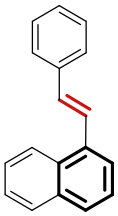
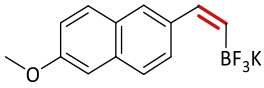
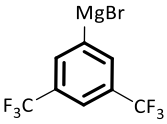
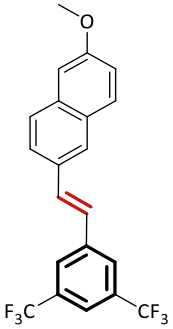
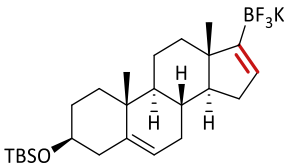
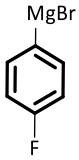
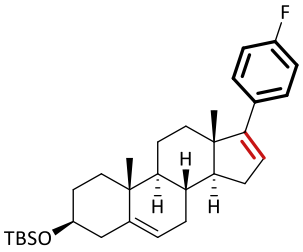
For sensitive functional groups such as nitriles, esters or pyridines the use of the corresponding organozinc species was required, but lower yields were obtained (**2.27-b/l**). Nevertheless, the use of organozinc compounds is necessary, since alkenyl trifluoroborates can be implemented, which carry more sensitive functional groups. As an application, this new method was applied for the late stage functionalization of dehydroepiandrosterone (DHEA) (**2.27-p**) and the synthesis of the naturally occurring pinosylvin (**2.27-f**).

In summary, this stereoconvergent and intramolecular transformation of alkenyl(hetero)triarylborates provided further insight into the mechanism and presents a novel route for a catalyst- and transition-metal-free coupling of alkenes with aromatic ring systems.

Table 2: Functionalized alkenes by a two-pot procedure starting with *Z*- or *E*-alkenyl trifluoroborates.

Entry	Electrophile	Organometallic reagent	Product	Yield[a]
1				**2.27-a**, 69% *E*/*Z* = 99:1[b]
2				**2.27-b**, 29% *E*/*Z* = 99:1[b]
3				**2.27-c**, 74% *E*/*Z* = 99:1[b]
4				**2.27-d**, 63% *E*/*Z* = 99:1[b]
5				**2.27-e**, 57% *E*/*Z* = 99:1[b]
6			 ***pinosylvin***	**2.27-f**[c], 42% *E*/*Z* = 99:1[b]

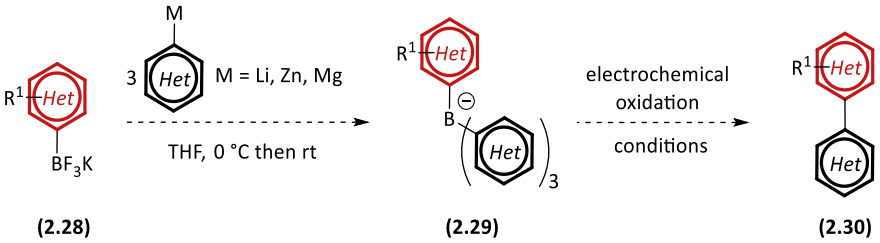
Entry	Electrophile	Organometallic reagent	Product	Yield[a]
7				**2.27-g**, 68% *E*/*Z* = 99:1[b]
8				**2.27-h**, 70% *E*/*Z* = 99:1[b]
9				**2.27-i**, 71% *E*/*Z* = 99:1[b]
10				**2.27-j**, 55% *E*/*Z* = 99:1[b]
11				**2.27-k**, 68% *E*/*Z* = 99:1[b]
12				**2.27-l**, 25% *E*/*Z* = 95:5[b]

Entry	Electrophile	Organometallic reagent	Product	Yield[a]
13				**2.27-m**, 65% *E*/*Z* = 90:10[b]
14				**2.27-n**, 57% *E*/*Z* = 93:7[b]
15				**2.27-o**, 57% *E*/*Z* = 84:16[b]
16				**2.27-p**, 57%
			DHEA-derivative	

[a] Yield of isolated, analytically pure product. [b] Determined by GC. [c] coupled product was treated with BBr_3 in DCM for the formation of unprotected OH-groups.

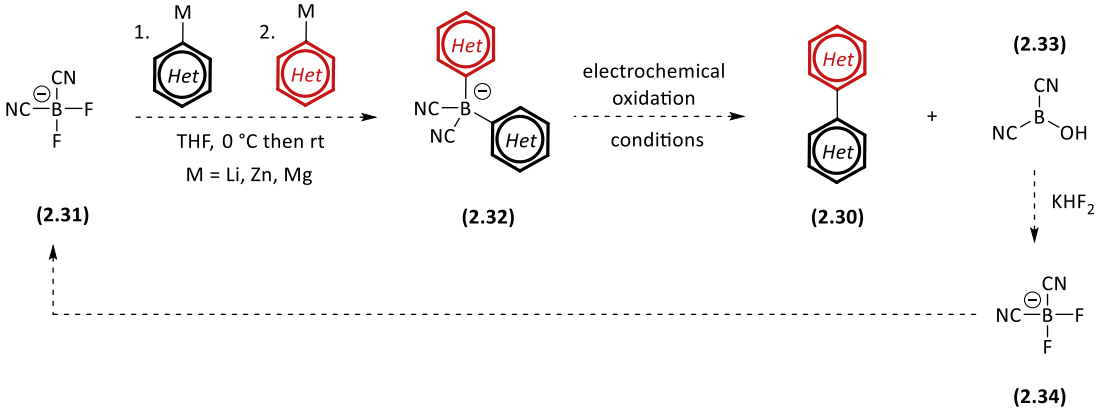
19 Outlook

According to the successful electrochemical Zweifel olefination of alkenyl(hetero)triarylborates, a biaryl coupling of tetraarylborates would be conceivable. This would lead to a scalable and catalyst free strategy (**Scheme 18**), which would open an alternative way of thinking about coupling reactions in general.



Scheme 18: Possible electrochemical oxidation of mixed tetraarylborates towards the hetero coupled biaryls.

Going a step further, a hetero coupling of tetraarylborates with a suitable dummy system would avoid the excess of organometallic reagent (**Scheme 19**). In this strategy, the easily accessible borate template **2.31** would be treated successively with the two organometallic species to be linked in the electrochemical step.[117] The mixed tetraorganoborate **2.32** would then be coupled and the remaining borinic nitrile **2.33** could be recovered by treatment with potassium bifluoride and used for another coupling step.



Scheme 19: Possible electrochemical oxidation of tetraorganoborate **2.32** by designing a reusable template.

[117] J. A. Sprenger; J. Landmann; M. Drisch; N. Ignat´ev; M. Finze, *Inorg. Chem.* **2015**, *54*, *7*, 3403.

Chapter III

Experimental Part

Part B, **Chapter II**, contains typical experimental procedures and selected examples for each topic discussed in this part. The full supporting information can be downloaded free of charge on the corresponding website of the publishing company.

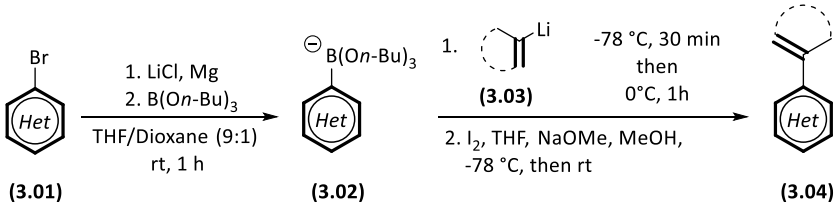
20 General Considerations

For general considerations see **Part A** - **Chapter IV** "**General Consideration**". Electrochemical oxidations on scales smaller than 1.0 mmol were performed on the IKA ElectraSyn 2.0. All used electrodes were purchased from IKA, except the RVC (reticulated vitreous carbon) electrodes which were obtained from Goodfellow (Carbon – Vitreous – 3000C Foam, Thickness: 6.35 mm, Bulk density: 0.05 g/cm^3, Porosity: 96.5%, Pores/cm: 24). Electrochemical oxidations on a scale greater than 1.0 mmol were performed on an Atlas 0931 Potentiostat – Galvanostat using a two-electrode undivided cell setup.

21 Experimental for Chapter I

21.1 Single-Pot Access to Bisorganoborinates: Applications in Zweifel Olefination

Mg-insertion/Ligand exchange with alkenyllithium reagents/Zweifel olefination sequence

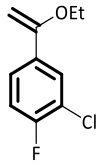


(3.01) **(3.02)** **(3.04)**

Counter-cations have been omitted for simplicity

A reaction tube was charged with lithium chloride (1.1 mmol, 1.1 equiv.) and magnesium turnings (1.6 mmol, 1.6 equiv.). Lithium chloride was dried *in vacuo* using a heat gun (600 °C, 5 min). After addition of THF/Dioxane (9:1, 1 M) and 1,2-dibromoethane (1 drop), the mixture was heated to boil with a heat gun to activate the magnesium, before tributylborate (1.0 mmol, 1.0 equiv.) was added at once. Heteroaryl/aryl bromide **3.01** (1.0 mmol, 1.0 equiv.) was dissolved in THF (1 M) and added to the activated magnesium suspension at room temperature dropwise (to hold approx. 23 °C a water bath was used). The mixture was then stirred for one hour at approx. 23 °C to yield a THF-solution of the magnesium organoboronate **3.02**. The solution was cooled to -78 °C, before the solution of alkenyllithium reagent **3.03** (1.0 - 2.0 mmol, 1.0 - 2.0 equiv.) was added dropwise. After half an hour, the reaction was warmed to 0 °C and let stir for 1 h. After the solution was cooled down again to -78 °C, iodine (3.0 mmol, 3.0 equiv.), dissolved in THF (1.5 M), was added dropwise. After 20 min, a suspension of sodium methoxide (5.0 mmol, 5.0 equiv.) in methanol (2.5 M) was added at once. After reaching

room temperature the reaction is completed. The reaction was then treated by the addition of a saturated solution of sodium thiosulfate and extracted with diethyl ether (3 x 20 mL). The combined organic phases were dried over magnesium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography with appropriate solvent mixtures to afford the desired coupling product **3.04**.

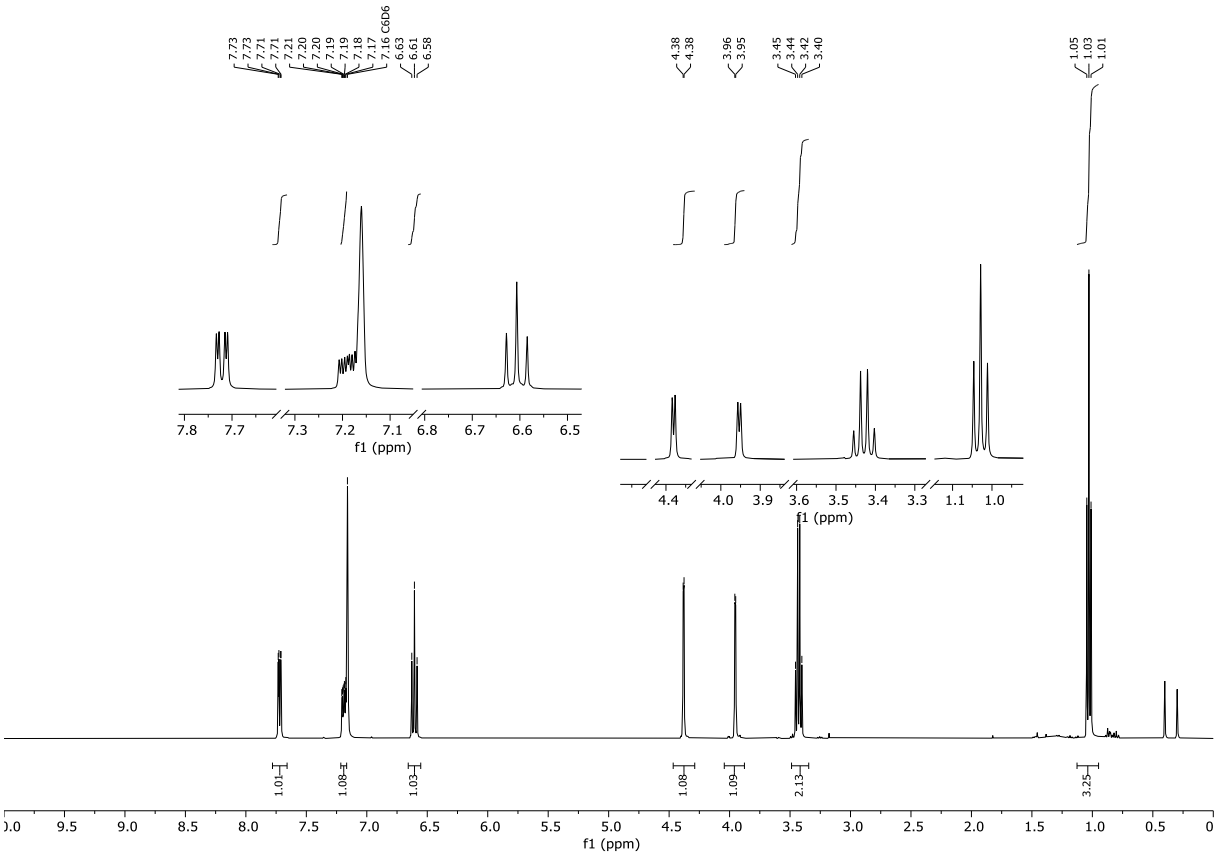


2-Chloro-4-(1-ethoxyvinyl)-1-fluorobenzene (selected example)

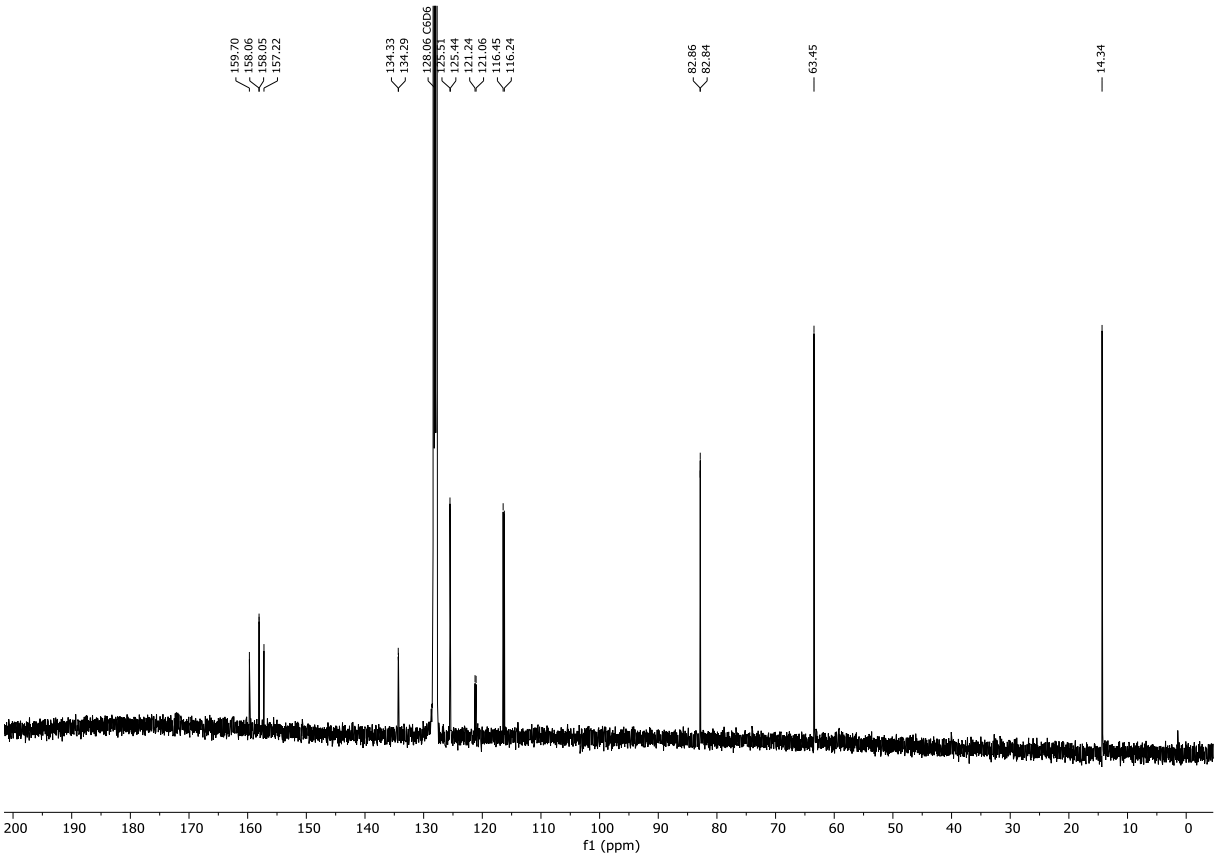
Using 4-bromo-2-chloro-1-fluorobenzene provided the product (0.58 mmol, 116 mg, 58%) as colourless oil.

***R*f** = 0.41 (hexane, UV, PAA, $KMnO_4$). **^{1}H NMR** (400 MHz, Benzene-d_6) δ 7.72 (dd, *J* = 7.2, 2.2 Hz, 1H), 7.19 (dq, *J* = 6.4, 2.3 Hz, 2H), 6.61 (t, *J* = 8.7 Hz, 1H), 4.38 (d, *J* = 2.9 Hz, 1H), 3.95 (d, *J* = 2.9 Hz, 1H), 3.43 (q, *J* = 7.0 Hz, 2H), 1.03 ppm (t, *J* = 7.0 Hz, 3H).**^{13}C NMR** (101 MHz, Benzene-d_6) δ 158.46 (d, *J* = 249.8 Hz), 158.05 (d), 134.31 (d, *J* = 3.9 Hz), 125.5, 125.4, 121.2 (d, *J* = 18.0 Hz), 116.3 (d, *J* = 21.2 Hz), 82.9 (d, *J* = 1.4 Hz), 63.5, 14.3 ppm. **LRMS** (DEP/EI-Orbitrap): *m/z* [%]: 200.0 (7), 174.0 (14), 172.0 (19), 159.0 (33), 158.0 (7), 157.0 (100), 156 (11), 130.0 (11), 129.0 (35). **HRMS** (EI-Orbitrap): m/z: [M^+] Calcd for $C_{10}H_{10}ClFO$: 200.0404; found: 200.0396. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2976 (w), 2279 (w), 1692 (w), 1593 cm^{-1} (w).

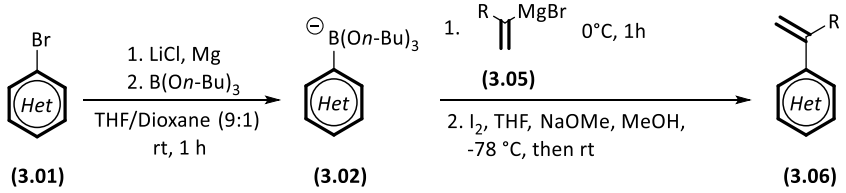
^{1}H NMR (400 MHz, benzene-d^{6})



^{13}C NMR (101 MHz, benzene-d^{6})



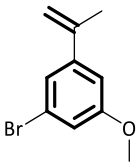
Mg-insertion/Ligand exchange with alkenylmagnesium reagents/Zweifel olefination sequence



(3.01) **(3.02)** **(3.06)**

Counter-cations have been omitted for more clarity

A reaction tube was charged with lithium chloride (1.1 mmol, 1.1 equiv.) and magnesium turnings (1.6 mmol, 1.6 equiv.). Lithium chloride was dried *in vacuo* using a heat gun (600 °C, 5 min). After addition of THF/Dioxane (9:1, 1 M) and 1,2-dibromoethane (1 drop), the mixture was heated to boil with a heat gun to activate the magnesium, before tributylborate (1.0 mmol, 1.0 equiv.) was added at once. Heteroaryl/aryl bromide **3.01** (1.0 mmol, 1.0 equiv.) was dissolved in THF (1 M) and added to the activated magnesium suspension at room temperature dropwise (to hold approx. 23 °C a water bath was used). The mixture was then stirred for one hour at approx. 23 °C to yield a THF-solution of the magnesium organoboronate **3.02**. After that a solution of alkenylmagnesium reagent **3.05** (3.0 mmol, 3.0 equiv.) was added dropwise at 0 °C and stirred for another 1 h at 0 °C. After the solution was cooled down again to -78 °C, iodine (3.0 mmol, 3.0 equiv.), dissolved in THF (1.5 M), was added dropwise. After 20 min a suspension of sodium methoxide (5.0 mmol, 5.0 equiv.) in methanol (2.5 M) was added at once. After reaching room temperature the reaction is completed. The reaction was then treated by the addition of saturated solution of sodium thiosulfate and extracted with diethyl ether (3 x 20 mL). The combined organic phases were dried over magnesium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography with appropriate solvent mixtures to afford the desired coupling product **3.06**.



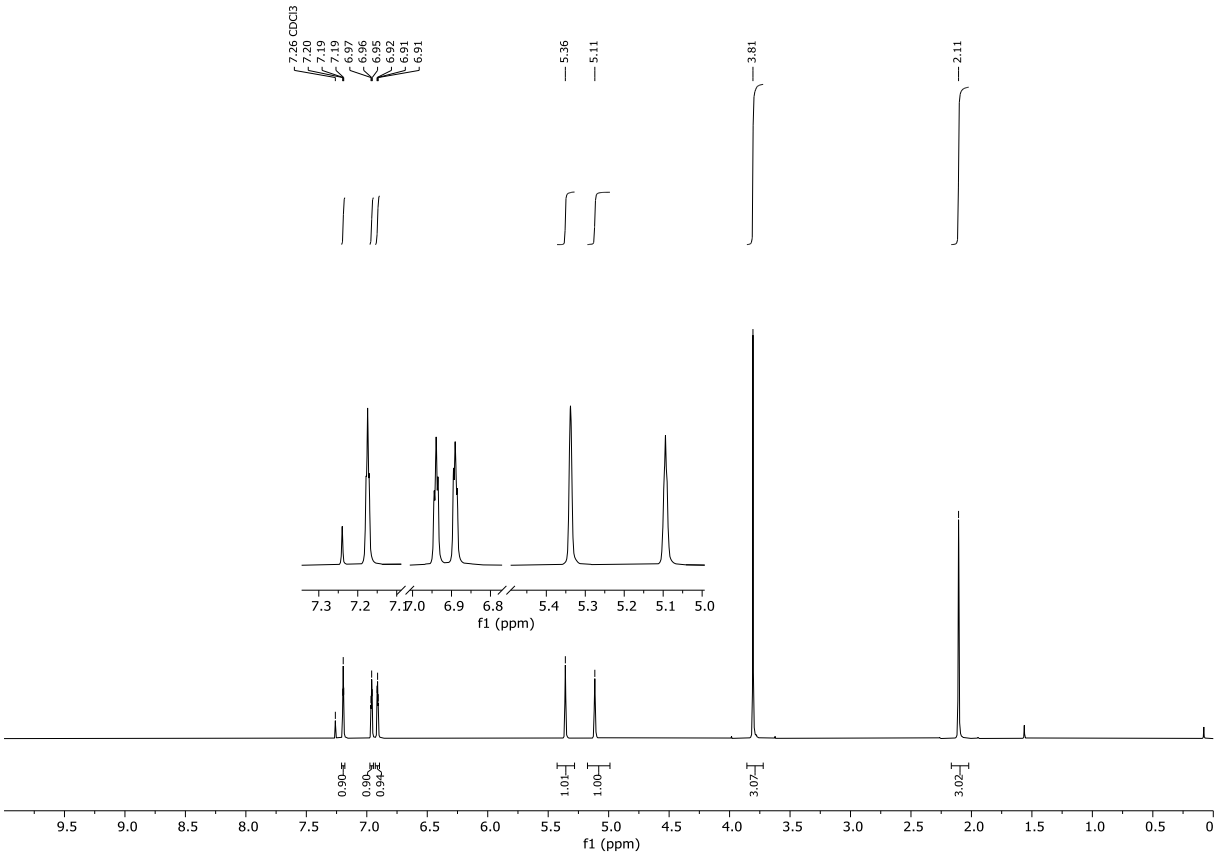
1-Bromo-3-methoxy-5-(prop-1-en-2-yl)benzene (selected example)

Using 1,3-dibromo-5-(prop-1-en-2-yl)benzene provided the product (0.34 mmol, 154 mg, 34%) as colourless oil.

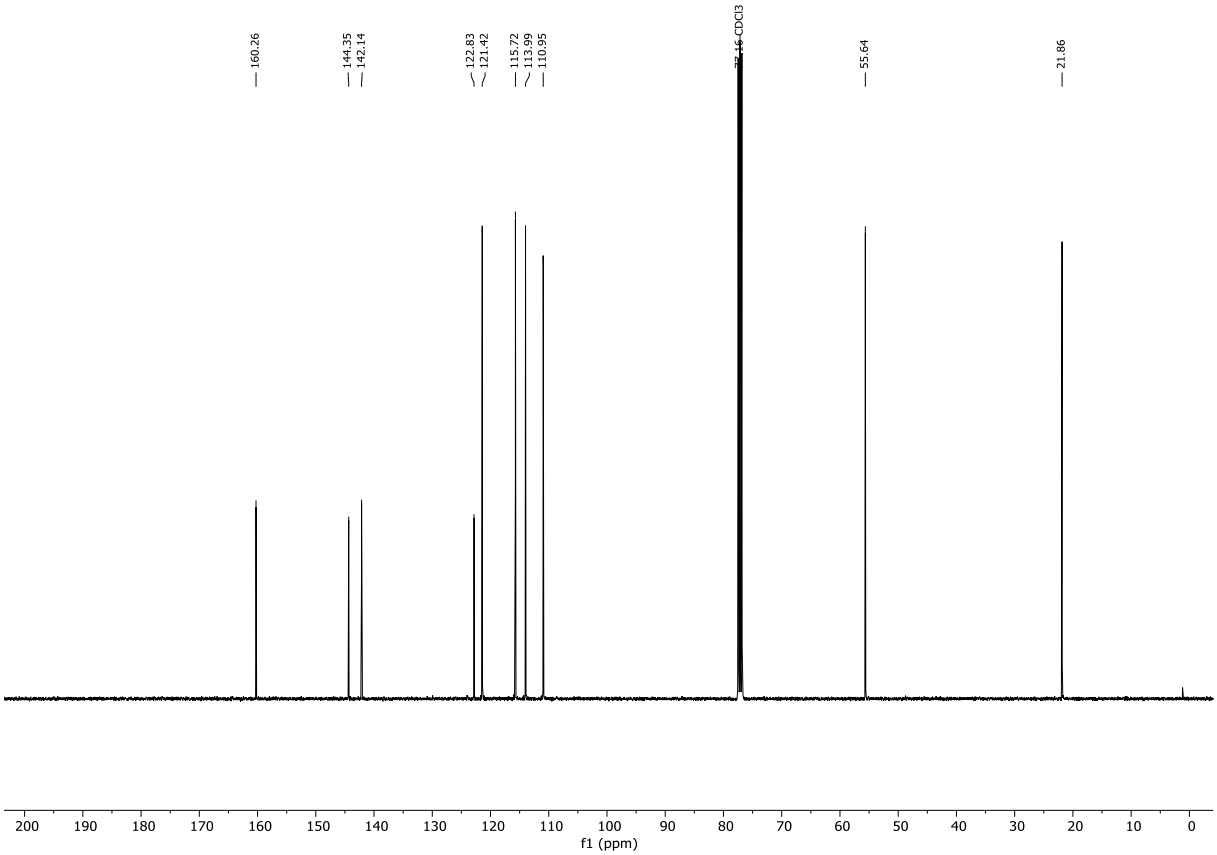
***R*f** = 0.59 (hexane/EtOAc 98:2, UV, PAA, $KMnO_4$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.17 (t, *J* = 1.6 Hz, 1H), 6.94 (t, *J* = 2.0 Hz, 1H), 6.89 (t, *J* = 1.9 Hz, 1H), 5.34 (s, 1H), 5.09 (s, 1H), 3.79 (s, 3H), 2.09 ppm (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 160.3, 144.4, 142.1, 122.8, 121.4, 115.7, 114.0, 111.0, 55.6, 21.9 ppm. **LRMS** (DEP/EI-Orbitrap): *m/z* [%]: 229.0 (11), 228.0 (98), 227.0 (11), 226 (100), 188.0 (15), 186.0 (15).

HRMS (EI-Orbitrap): m/z: [M^+] Calcd for $C_{10}H_{10}ClFO$: 200.0404; found: 200.0396. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2938 (br/w), 1599 (m), 1557 (vs), 1560 cm^{-1} (s).

^{1}H NMR (400 MHz, $CDCl_3$)



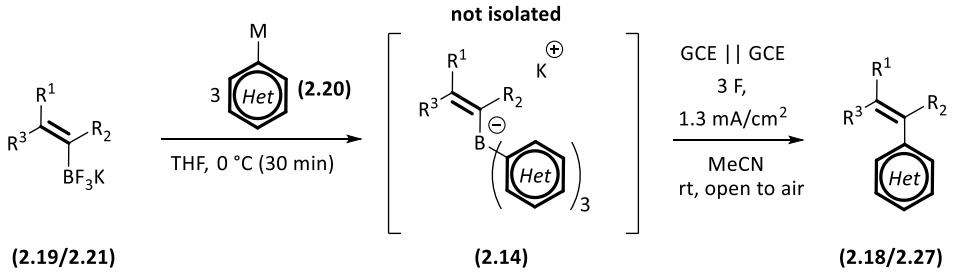
^{13}C NMR (101 MHz, $CDCl_3$)



22 Experimental for Chapter II

22.1 Electrochemical Formation of Functionalized Alkenes using Tetraorganoborates

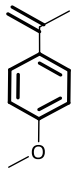
General Procedure: Two-pot Procedure for the synthesis of functionalized alkenes starting from potassium alkenyl trifluoroborate salts



A 25 mL Schlenk flask was charged with the corresponding potassium trifluoroborate salt **2.19/2.21** (0.4 mmol, 1.0 equiv.) and 2 mL of THF were added. The mixture was cooled to 0 °C and the aryl-Grignard reagent (1.2 mmol, 3.0 equiv.) was added dropwise over 30 minutes *via* syringe pump. After addition, the reaction mixture was allowed to stir for further 10 min at 0 °C and was then quenched with 5 mL of H_2O and extracted with EtOAc (3 x 40 mL). If no phase separation was observed, 5 mL of aqueous saturated K_2CO_3 solution was added. The combined organic phases were filtered and concentrated under reduced pressure. The crude tetraorganoborate **2.14** was then dissolved in 8 mL of HPLC grade MeCN and transferred into a 10 mL IKA glass vial. The reaction was started using the IKA ElectraSyn 2.0 with GCE (glassy carbon electrodes) as working and counter electrode (5 mA, 3.0 F, 1.3 mA/cm^2, 700 rpm stirring). The crude was then treated with water and extracted with diethyl ether (3 x 15 mL). The combined organic phases were dried over magnesium sulfate, filtered, concentrated under reduced pressure and purified by flash-column chromatography on silica gel with the appropriate solvent mixture to obtain pure **2.18/2.27.**

Adaptation for the use of arylzinc reagents

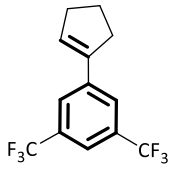
After addition of the arylzinc instead of the aryl-Grignard reagent *via* syringe pump, the reaction was heated to 40 °C for 16 hours to ensure full conversion of the potassium trifluoroborate salt into the desired salt **2.14**. General procedure was then followed to give products **2.18/2.27**.



1-Methoxy-4-(prop-1-en-2-yl)benzene (2.18-a)

Using potassium trifluoro(prop-1-en-2-yl)borate and (4-methoxyphenyl)magnesium bromide according to general procedure, provided **2.18-a** (0.16 mmol, 24 mg, 41%) as colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45-7.37 (m, 2H), 6.91-6.82 (m, 2H), 5.29 (dd, *J* = 1.6, 0.8 Hz, 1H), 5.04-4.96 (m, 1H), 3.82 (s, 3H), 2.13 ppm (dd, *J* = 1.5, 0.8 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.5, 142.7, 133.9, 126.7, 113.7, 111.3, 56.1, 22.1 ppm. Analytical data in accordance to literature.[118]



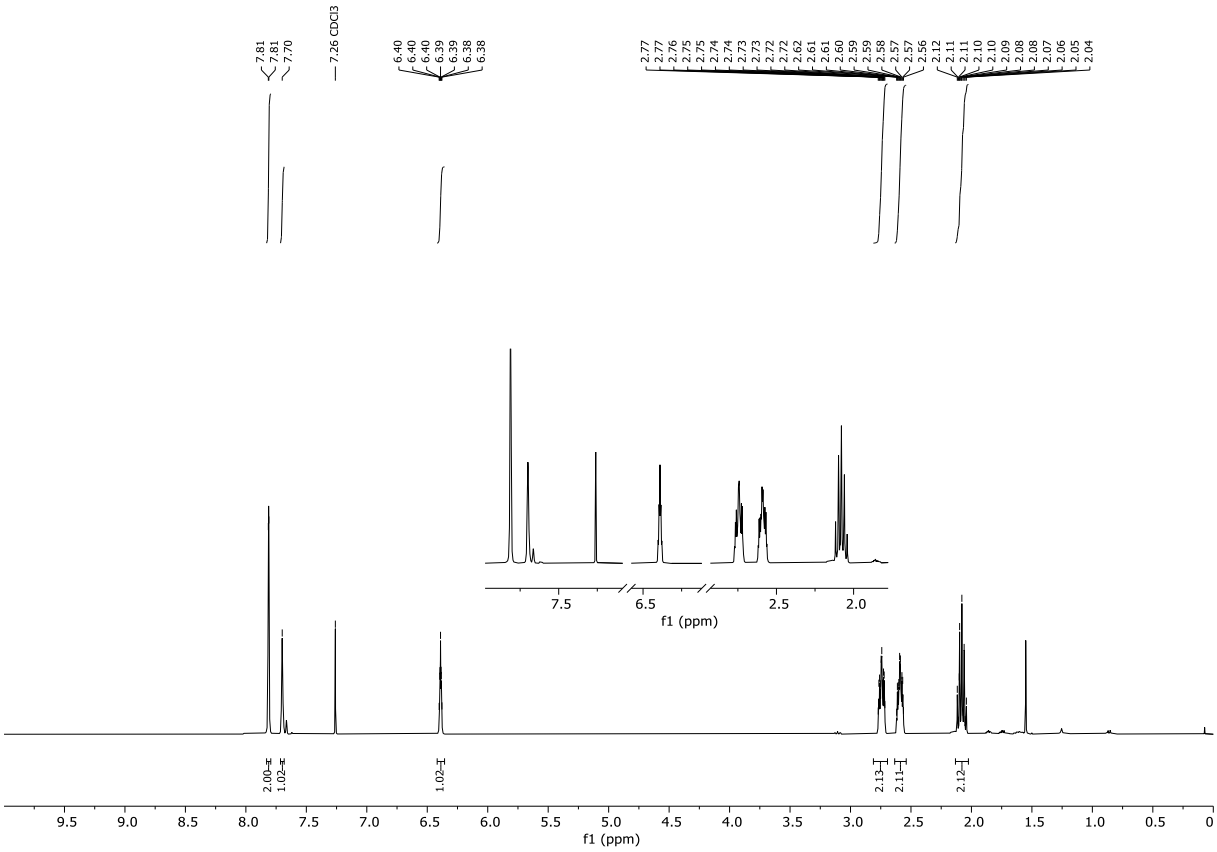
1-(Cyclopent-1-en-1-yl)-3,5-bis(trifluoromethyl)benzene (2.18-b) (selected example)

Using potassium cyclopent-1-en-1-yltrifluoroborate and (3,5-bis(trifluoromethyl)phenyl)magnesium bromide according to general procedure, provided **2.18-b** (0.21 mmol, 58 mg, 52%) as colourless oil.

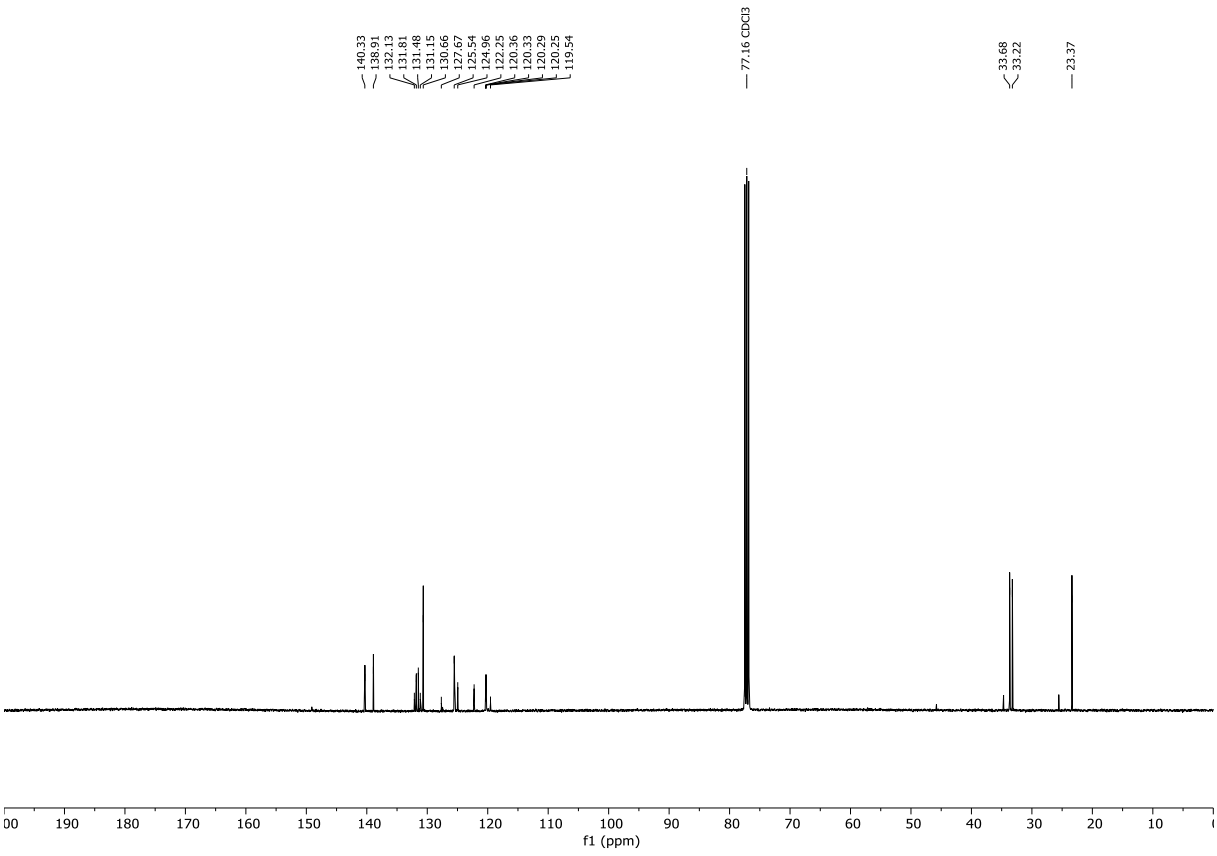
***R*$_f$** = 0.6 (hexane, UV, PAA). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.81 (s, 2H), 7.70 (s, 1H), 6.39 (td, *J* = 2.7, 1.4 Hz, 1H), 2.78-2.71 (m, 2H), 2.62-2.56 (m, 2H), 2.08 ppm (p, *J* = 7.6 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 140.3, 138.9, 131.6 (q, *J* = 32.9 Hz), 130.7, 125.5, 123.5 (q, *J* = 272.5 Hz), 120.3 (q, *J* = 3.9 Hz), 33.7, 33.2, 23.4 ppm. **LRMS** (DEP/EI-Orbitrap): *m/z* (%): 280.1 (100), 261.1 (50), 245.1 (40), 211.1 (100), 191.1 (45), 142.1 (25). **HRMS** (EI-Orbitrap): m/z: [M^+] Calcd. for $C_{13}H_{10}F_6^+$: 280.0687; found: 280.0680.

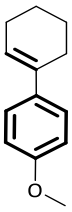
[118] W. J. Kerr; A. J. Morrison; M. Pazicky; T. Weber, *Org. Lett.* **2012**, *14*, 2250.

^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (101 MHz, $CDCl_3$)

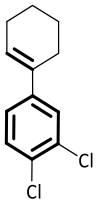




4'-Methoxy-2,3,4,5-tetrahydro-1,1'-biphenyl (2.18-c)

Using potassium cyclohex-1-en-1-yltrifluoroborate and (4-methoxyphenyl)magnesium bromide according to general procedure, provided **2.18-c** (0.28 mmol, 53 mg, 71%) as colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.29 (m, 2H), 6.90-6.82 (m, 2H), 6.03 (tt, *J* = 3.9, 1.7 Hz, 1H), 3.81 (s, 3H), 2.38 (dtd, *J* = 6.1, 3.2, 2.6, 1.4 Hz, 2H), 2.19 (dddd, *J* = 8.7, 6.3, 4.4, 2.5 Hz, 2H), 1.82-1.72 (m, 2H), 1.68-1.61 ppm (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.5, 136.0, 135.5, 126.0, 123.3, 113.6, 55.4, 27.6, 26.0, 23.2, 22.3 ppm. Analytical data in accordance to literature.[119]

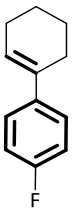


3',4'-Dichloro-2,3,4,5-tetrahydro-1,1'-biphenyl (2.18-d)

Using potassium cyclohex-1-en-1-yltrifluoroborate and (3,4-dichlorophenyl)magnesium bromide according to general procedure, provided **2.18-d** (0.21 mmol, 48 mg, 53%) as colourless oil.

***R*$_f$** = 0.80 (hexane, UV, PAA, $KMnO_4$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 2.2 Hz, 1H), 7.35 (d, *J* = 8.4 Hz, 1H), 7.20 (dd, *J* = 8.4, 2.2 Hz, 1H), 6.13 (td, *J* = 4.0, 1.9 Hz, 1H), 2.33 (tdd, *J* = 6.2, 2.5, 1.7 Hz, 2H), 2.20 (dddd, *J* = 9.2, 6.7, 4.7, 2.7 Hz, 2H), 1.82-1.72 (m, 2H), 1.70-1.58 ppm (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 142.0, 134.8, 132.3, 130.2, 130.1, 127.0, 126.7, 123.5, 27.3, 26.0, 23.0, 22.0 ppm. **LRMS** (DEP/EI-Orbitrap): *m/z* (%): 226.0 (70), 211.0 (20), 191.0 (60), 163.0 (100). **HRMS** (EI-Orbitrap): m/z: [M^+] Calcd. for $C_{12}H_{12}Cl_2^+$: 226.0316; found: 226.0309.

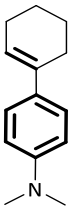
[119] M. O. Ganiu; A- H. Cleveland; J. L. Paul; R. Kartika, *Org. Lett.* **2019**, *21*, 5611.



4'-Fluoro-2,3,4,5-tetrahydro-1,1'-biphenyl (2.18-e)

Using potassium cyclohex-1-en-1-yltrifluoroborate and (4-fluorophenyl)magnesium bromide according to general procedure, provided **2.18-e** (0.30 mmol, 53 mg, 75%) as colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.29 (m, 2H), 7.03-6.92 (m, 2H), 6.06 (tt, *J* = 3.9, 1.8 Hz, 1H), 2.37 (ddq, *J* = 6.3, 4.3, 2.2 Hz, 2H), 2.20 (dtt, *J* = 8.8, 6.1, 2.6 Hz, 2H), 1.85-1.74 (m, 2H), 1.70-1.60 ppm (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.75 (d, *J* = 244.9 Hz), 138.8, 135.6, 126.37 (d, *J* = 7.7 Hz), 124.7, 114.88 (d, *J* = 21.2 Hz).,27.5, 25.8, 23.0, 22.1 ppm. Analytical data in accordance to literature.[120]

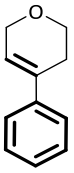


4'-Fluoro-2,3,4,5-tetrahydro-1,1'-biphenyl (2.18-f)

Using potassium cyclohex-1-en-1-yltrifluoroborate and (4-(dimethylamino)phenyl)magnesium bromide according to general procedure, provided **2.18-f** (0.20 mmol, 40 mg, 70%) as colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.27 (m, 2H), 6.74-6.65 (m, 2H), 6.00 (tt, *J* = 4.0, 1.7 Hz, 1H), 2.38 (ddt, *J* = 6.2, 3.9, 2.0 Hz, 2H), 2.19 (dtd, *J* = 8.2, 4.0, 2.2 Hz, 2H), 1.82-1.72 (m, 2H), 1.69-1.59 ppm (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 149.6, 136.1, 131.3, 125.7, 121.7, 112.6, 40.9, 27.5, 26.0, 23.3, 22.5 ppm. Analytical data in accordance to literature.[121]

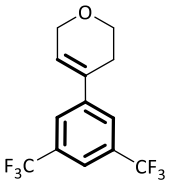
[120] K. Ishizuka; H. Seike; T. Hatakeyama; M. Nakamura, *J. Am. Chem. Soc.* **2010**, *132*, 13117.
[121] W. D. Oosterbaan; P. C. M. van Gerven; C. A. van Walree; M. Koeberg; J. J. Piet; R. W. A. Havenith; J. W. Zwikker; L. W. Jenneskens; R. Gleiter, *Eur. J. Org. Chem.* **2003**, 3117.



4-Phenyl-3,6-dihydro-2*H*-pyran (2.18-g)

Using potassium (3,6-dihydro-2*H*-pyran-4-yl)trifluoroborate and phenylmagnesium bromide according to general procedure, provided **2.18-g** (0.24 mmol, 38 mg, 60%) as colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.38 (m, 2H), 7.37-7.32 (m, 2H), 7.30-7.24 (m, 1H), 6.13 (tt, *J* = 3.0, 1.6 Hz, 1H), 4.33 (q, *J* = 2.8 Hz, 2H), 3.94 (t, *J* = 5.5 Hz, 2H), 2.74-2.34 ppm (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 140.4, 134.2, 128.6, 127.4, 124.8, 122.6, 66.0, 64.6, 27.3 ppm. Analytical data in accordance to literature.[122]

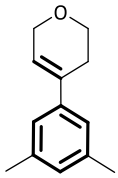


4-(3,5-Bis(trifluoromethyl)phenyl)-3,6-dihydro-2H-pyran (2.18-h)

Using potassium (3,6-dihydro-2*H*-pyran-4-yl)trifluoroborate and (3,5-bis(trifluoromethyl)phenyl) magnesium bromide according to general procedure, provided **R2.04-h** (0.22 mmol, 64 mg, 54%) as colourless oil.

***R*$_f$** = 0.3 (hexane/EtOAc 9:1, UV, PAA, $KMnO_4$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.80 (s, 2H), 7.76 (s, 1H), 6.31 (tt, *J* = 3.0, 1.6 Hz, 1H), 4.36 (q, *J* = 2.9 Hz, 2H), 3.96 (t, *J* = 5.4 Hz, 2H), 2.59-2.51 ppm (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 142.3, 132.3, 131.89 (q, *J* = 33.1 Hz), 126.3, 125.05-124.76 (m), 123.51 (d, *J* = 271.9 Hz), 121.09-120.83 (m), 65.8, 64.2, 27.1 ppm. **LRMS** (DEP/EI-Orbitrap): *m/z* (%): 296.1 (100), 278.1 (70), 267.1 (80), 254.1 (20). **HRMS** (EI-Orbitrap): m/z: [M^+] Calcd. for $C_{13}H_{10}F_6^+$: 296.0636; found: 296.0628.

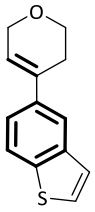
[122] B. Guo; G. Schwarzwalder; J. T. Njardarson, *Angew. Chem. Int. Ed.* **2012**, *51*, 5675.



4-(3,5-Dimethylphenyl)-3,6-dihydro-2H-pyran (2.18-i)

Using potassium (3,6-dihydro-2*H*-pyran-4-yl)trifluoroborate and (3,5-dimethylphenyl)magnesium bromide according to general procedure, provided **R2.04-i** (0.22 mmol, 64 mg, 54%) as colourless oil.

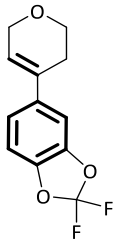
R_f = 0.35 (hexane/EtOAc 98:2, UV, $KMnO_4$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.02 (s, 2H), 6.92 (s, 1H), 6.09 (tt, *J* = 3.1, 1.6 Hz, 1H), 4.32 (q, *J* = 2.8 Hz, 2H), 3.93 (t, *J* = 5.5 Hz, 2H), 2.54-2.48 (m, 2H), 2.33 ppm (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 140.5, 138.0, 134.4, 129.1, 122.8, 122.2, 66.0, 64.7, 27.5, 21.5 ppm. **LRMS** (DEP/EI-Orbitrap): *m/z* (%): 188.1 (100), 173.1 (90), 159.1 (35), 145.1 (100).



4-(Benzo[*b*]thiophen-5-yl)-3,6-dihydro-2*H*-pyran (2.18-j)

Using potassium (3,6-dihydro-2*H*-pyran-4-yl)trifluoroborate and benzo[*b*]thiophen-5-ylmagnesium bromide according to general procedure, provided **2.18-j** (0.09 mmol, 20 mg, 23%) as colourless oil.

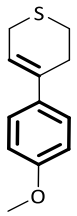
R_f = 0.60 (hexane/EtOAc 98:2, UV, PAA, $KMnO_4$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.74-7.68 (m, 2H), 7.37-7.29 (m, 2H), 7.23 (d, *J* = 5.5 Hz, 1H), 6.09 (tt, *J* = 3.0, 1.6 Hz, 1H), 4.26 (q, *J* = 2.8 Hz, 2H), 3.88 (t, *J* = 5.5 Hz, 2H), 2.59-2.46 ppm (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 140.0, 138.7, 136.9, 134.3, 124.2, 122.6, 122.4, 121.7, 119.7, 66.1, 64.7, 27.7 ppm. **HRMS** (EI-Orbitrap): m/z: [M^+] Calcd. for $C_{13}H_{12}OS^+$: 216.0609; found: 216.0604.



5-(3,6-Dihydro-2*H*-pyran-4-yl)-2,2-difluorobenzo[*d*][1,3]dioxole (2.18-k)

Using potassium (3,6-dihydro-2*H*-pyran-4-yl)trifluoroborate and (2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)magnesium bromide according to general procedure, provided **2.18-k** (0.12 mmol, 27 mg, 29%) as colourless oil.

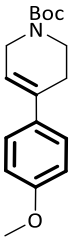
R_f = 0.30 (hexane/EtOAc 98:2, UV, PAA). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.11-7.06 (m, 2H), 7.03-6.99 (m, 1H), 6.06 (tt, *J* = 3.0, 1.6 Hz, 1H), 4.31 (q, *J* = 2.8 Hz, 2H), 3.93 (t, *J* = 5.4 Hz, 2H), 2.47 ppm (ttd, *J* = 5.5, 2.7, 1.6 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.63 (d, *J* = 120.1 Hz), 143.0, 137.1, 132.8, 131.8 (t, *J* = 255.1 Hz), 123.3, 120.1, 109.3, 106.3, 65.9, 64.5, 27.6 ppm. **LRMS** (DEP/EI-Orbitrap): *m/z* (%): 240.0 (70), 222.0 (20), 196.9 (25), 158.0 (50). **HRMS** (EI-Orbitrap): m/z: [M^+] Calcd. for $C_{12}H_{10}F_2O_3^+$: 240.0598; found: 240.0592.



4-(4-Methoxyphenyl)-3,6-dihydro-2*H*-thiopyran (2.18-l)

Using potassium (3,6-dihydro-2*H*-thiopyran-4-yl)trifluoroborate and (4-methoxyphenyl)magnesium bromide according to general procedure, provided **2.18-l** (0.31 mmol, 63 mg, 77%) as colourless oil.

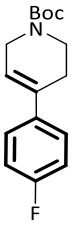
R_f = 0.5 (hexane/EtOAc 98:2, UV, PAA). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.30-7.25 (m, 2H), 6.89-6.84 (m, 2H), 6.12-6.08 (m, 1H), 3.81 (s, 3H), 3.33 (dt, *J* = 4.5, 2.3 Hz, 2H), 2.88 (t, *J* = 5.8 Hz, 2H), 2.70-2.64 ppm (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.0, 137.7, 135.6, 126.7, 120.3, 113.8, 55.4, 28.8, 26.4, 25.3 ppm. **LRMS** (DEP/EI-Orbitrap): *m/z* (%): 206.1 (100), 191.0 (5), 177.0 (60), 147.1 (75).



***tert*-Butyl 4-(4-methoxyphenyl)-3,6-dihydropyridine-1(2*H*)-carboxylate (2.18-m)**

Using potassium (1-(*tert*-butoxycarbonyl)-1,2,3,6-tetrahydropyridin-4-yl)trifluoroborate and (4-methoxyphenyl)magnesium bromide according to general procedure, provided **2.18-m** (0.21 mmol, 60 mg, 52%) as colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.29 (m, 2H), 6.93-6.83 (m, 2H), 5.94 (s, 1H), 4.05 (s, 2H), 3.81 (s, 3H), 3.63 (t, *J* = 5.7 Hz, 2H), 2.50 (s, 2H), 1.49 ppm (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.0, 133.4, 131.8, 127.8, 126.1, 113.9, 79.8, 55.4, 43.6, 40.7, 39.2, 28.6 ppm. Analytical data in accordance to literature.[123]

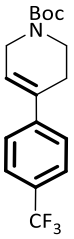


***tert*-Butyl 4-(4-fluorophenyl)-3,6-dihydropyridine-1(2*H*)-carboxylate (2.18-n)**

Using potassium (1-(*tert*-butoxycarbonyl)-1,2,3,6-tetrahydropyridin-4-yl)trifluoroborate and (4-fluorophenyl)magnesium bromide according to general procedure, provided **2.18-n** (0.22 mmol, 62 mg, 56%) as colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.29 (m, 2H), 7.06-6.98 (m, 2H), 5.97 (s, 1H), 4.09-4.02 (m, 2H), 3.63 (t, *J* = 5.7 Hz, 2H), 2.49 (s, 2H), 1.49 ppm (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.23 (d, *J* = 246.2 Hz), 155.0, 136.9, 134.8, 126.60 (d, *J* = 7.9 Hz), 115.35 (d, *J* = 21.3 Hz), 113.0, 79.9, 43.8, 39.9, 28.6, 27.7 ppm. Analytical data in accordance to literature.[124]

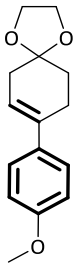
[123] A. Music; C. Hoarau; N. Hilgert; F. Zischka; D. Didier, *Angew. Chem. Int. Ed.* **2019**, *58*, 1188.
[124] D.J. Wustrow; L. D. Wise, *Synthesis* **1991**, *11*, 993.



***tert*-Butyl 4-(4-(trifluoromethyl)phenyl)-3,6-dihydropyridine-1(2*H*)-carboxylate (2.18-o)**

Using potassium (1-(*tert*-butoxycarbonyl)-1,2,3,6-tetrahydropyridin-4-yl)trifluoroborate and (4-(trifluoromethyl)phenyl)magnesium bromide according to general procedure, provided **2.18-o** (0.17 mmol, 56 mg, 43%) as colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.7 Hz, 2H), 7.46 (d, *J* = 8.1 Hz, 2H), 6.12 (s, 1H), 4.15-4.00 (m, 2H), 3.65 (t, *J* = 5.7 Hz, 2H), 2.53 (s, 2H), 1.49 ppm (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 154.9, 144.2, 134.7, 129.27 (q, *J* = 32.6 Hz), 126.77 (q, *J* = 129.9 Hz), 125.51 (q, *J* = 3.8 Hz), 125.3, 123.0, 80.0, 44.0, 39.8, 28.6, 27.4 ppm. Analytical data in accordance to literature.[125]

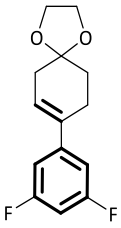


8-(4-Methoxyphenyl)-1,4-dioxaspiro[4.5]dec-7-ene (2.18-p)

Using potassium trifluoro(1,4-dioxaspiro[4.5]dec-7-en-8-yl)borate and (4-methoxyphenyl)magnesium bromide according to general procedure, provided **2.18-p** (0.35 mmol, 86 mg, 87%) as colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.31 (m, 2H), 6.88-6.81 (m, 2H), 5.90 (td, *J* = 3.9, 2.0 Hz, 1H), 4.02 (s, 4H), 3.80 (s, 3H), 2.66-2.60 (m, 2H), 2.51-2.42 (m, 2H), 1.92 ppm (t, *J* = 6.5 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.7, 135.7, 134.2, 126.4, 120.0, 113.6, 108.0, 64.6, 55.4, 36.2, 31.5, 27.0 ppm. Analytical data in accordance to literature.[126]

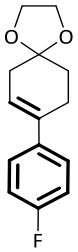
[125] Merck & Co., US6303593, **2001**, B1.
[126] A. J. Pearson; I. C. Richards; D. V. Gardner, *J. Org. Chem.* **1984**, *49*, 3887.



8-(3,5-Difluorophenyl)-1,4-dioxaspiro[4.5]dec-7-ene (2.18-q)

Using potassium trifluoro(1,4-dioxaspiro[4.5]dec-7-en-8-yl)borate and (3,5-difluorophenyl)magnesium bromide according to general procedure, provided **2.18-q** (0.16 mmol, 40 mg, 40%) as colourless oil.

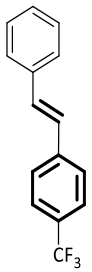
***R*f** = 0.10 (hexane/EtOAc 98:2, UV, PAA). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.95-6.85 (m, 2H), 6.66 (tt, *J* = 8.8, 2.3 Hz, 1H), 6.05 (tt, *J* = 4.0, 1.6 Hz, 1H), 4.02 (s, 4H), 2.63-2.56 (m, 2H), 2.49-2.44 (m, 2H), 1.91 ppm (t, *J* = 6.6 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.1 (dd, *J* = 246.8, 13.3 Hz), 144.9 (t, *J* = 9.2 Hz), 134.6 (t, *J* = 2.6 Hz), 124.0, 108.3-107.9 (m), 107.6, 102.1 (t, *J* = 25.6 Hz), 64.7, 36.2, 31.3, 26.6 ppm. **LRMS** (DEP/EI-Orbitrap): *m/z* (%): 252.1 (35), 237.0 (5) 164.0 (15), 151.0 (15), 86.0 (100). **HRMS** (EI-Orbitrap): m/z: [M^+] Calcd. for $C_{14}H_{14}F_2O_2^+$: 252.0962; found: 252.0956.



8-(4-Fluorophenyl)-1,4-dioxaspiro[4.5]dec-7-ene (2.18-r)

Using potassium trifluoro(1,4-dioxaspiro[4.5]dec-7-en-8-yl)borate and (4-fluorophenyl)magnesium bromide according to general procedure, provided **2.18-r** (0.34 mmol, 80 mg, 86%) as colourless oil.

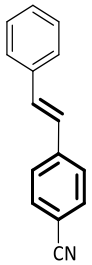
***R*f** = 0.15 (hexane/EtOAc 98:2, UV, PAA). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38-7.31 (m, 2H), 7.02-6.95 (m, 2H), 5.93 (tt, *J* = 3.9, 1.6 Hz, 1H), 4.02 (s, 4H), 2.63 (tq, *J* = 6.4, 2.1 Hz, 2H), 2.48-2.44 (m, 2H), 1.92 ppm (t, *J* = 6.5 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.1 (d, *J* = 245.4 Hz), 137.7 (d, *J* = 3.2 Hz), 135.5, 126.8 (d, *J* = 7.8 Hz), 121.6 (d, *J* = 1.4 Hz), 115.1 (d, *J* = 21.2 Hz), 107.8, 64.6, 36.2, 31.4, 27.1 ppm. **LRMS** (DEP/EI-Orbitrap): *m/z* (%): 234.1 (25), 219.1 (5), 146.0 (20), 133.0 (20), 86.0 (100). **HRMS** (EI-Orbitrap): m/z: [M^+] Calcd. for $C_{14}H_{15}FO_2^+$: 234.1056; found: 234.1049.



(*E*)-1-Styryl-4-(trifluoromethyl)benzene (2.27-a)

Using potassium (*E*)-trifluoro(styryl)borate and (4-(trifluoromethyl)phenyl)magnesium bromide according to general procedure, provided **2.27-a** (0.28 mmol, 68 mg, 69%, *E*/*Z* = 99:1) as white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (s, 4H), 7.56-7.52 (m, 2H), 7.43-7.37 (m, 2H), 7.33-7.27 (m, 1H), 7.20 (d, *J* = 16.4 Hz, 1H), 7.12 ppm (d, *J* = 16.4 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 140.9, 136.7, 131.3, 129.36 (q, *J* = 32.4 Hz), 128.9, 128.4, 127.2, 126.9, 126.7, 125.77 (q, *J* = 3.9 Hz), 123.0 ppm. Analytical data in accordance to literature.[127]

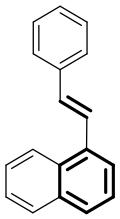


(*E*)-4-Styrylbenzonitrile (2.27-b)

Using potassium (*E*)-trifluoro(styryl)borate and (4-cyanophenyl)zinc(II) iodide according to general procedure, provided **2.27-b** (0.12 mmol, 24 mg, 29%, *E*/*Z* = 99:1) as white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69-7.61 (m, 2H), 7.61-7.57 (m, 2H), 7.56-7.52 (m, 2H), 7.43-7.37 (m, 2H), 7.36-7.29 (m, 1H), 7.22 (d, *J* = 16.3 Hz, 1H), 7.09 ppm (d, *J* = 16.3 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 141.9, 136.4, 132.6, 132.5, 129.0, 128.8, 127.0, 127.0, 126.8, 119.2, 110.7 ppm. Analytical data in accordance to literature.[128]

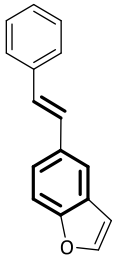
[127] S. W. Youn; B. S. Kim; A. R. Jagdale, *J. Am. Chem. Soc.* **2012**, *134*, 11308.
[128] H. Li; J. Lü; J. Lin; Y. Huang; M. Cao; R. Cao, *Chem. Eur. J.* **2013**, *19*, 15661.



(*E*)-1-Styrylnaphthalene (2.27-c)

Using potassium (*E*)-trifluoro(styryl)borate and naphthalen-1-ylmagnesium bromide according to general procedure, provided **2.27-c** (0.30 mmol, 68 mg, 74%, *E*/*Z* = 99:1) as white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, *J* = 8.0 Hz, 1H), 7.93-7.86 (m, 2H), 7.82 (d, *J* = 8.2 Hz, 1H), 7.76 (d, *J* = 6.1 Hz, 1H), 7.65-7.60 (m, 2H), 7.58-7.48 (m, 3H), 7.42 (t, *J* = 7.7 Hz, 2H), 7.34-7.29 (m, 1H), 7.17 ppm (d, *J* = 16.0 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 137.7, 135.1, 133.8, 131.9, 131.5, 128.9, 128.8, 128.2, 127.9, 126.8, 126.2, 126.0, 125.9, 125.8, 123.9, 123.8 ppm. Analytical data in accordance to literature.[129]

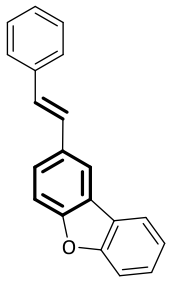


(*E*)-5-Styrylbenzofuran (2.27-d)

Using potassium (*E*)-trifluoro(styryl)borate and benzofuran-5-ylmagnesium bromide according to general procedure, provided **2.27-d** (0.25 mmol, 55 mg, 63%, *E*/*Z* = 99:1) as white solid.

***R*$_f$** = 0.3 (hexane, UV, PAA, $KMnO_4$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.72 (s, 1H), 7.62 (d, *J* = 2.2 Hz, 1H), 7.55-7.47 (m, 4H), 7.37 (t, *J* = 7.7 Hz, 2H), 7.31-7.19 (m, 2H), 7.10 (d, *J* = 16.3 Hz, 1H), 6.78 ppm (d, *J* = 2.2 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 154.8, 145.7, 137.6, 132.6, 129.1, 128.8, 128.0, 127.8, 127.5, 126.5, 123.1, 119.4, 111.7, 106.8 ppm. **LRMS** (DEP/EI-Orbitrap): *m/z* (%): 220.0 (100), 204.9 (10), 191.0 (60). **HRMS** (EI-Orbitrap): m/z: [M^+] Calcd. for $C_{16}H_{12}O^+$: 220.0888; found: 220.0882.

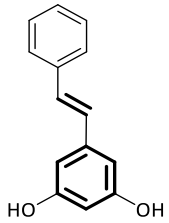
[129] M. Das; D. F. O´Shea, *Org. Lett.* **2016**, *18*, 336.



(*E*)-2-Styryldibenzo[*b*,*d*]furan (2.27-e)

Using potassium (*E*)-trifluoro(styryl)borate and dibenzo[*b*,*d*]furan-2-ylmagnesium bromide according to general procedure, provided **2.27-e** (0.23 mmol, 62 mg, 57%, *E*/*Z* = 99:1) as white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 1.8 Hz, 1H), 7.99 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.64 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.61-7.53 (m, 4H), 7.48 (ddd, *J* = 8.4, 7.3, 1.4 Hz, 1H), 7.43-7.35 (m, 3H), 7.32-7.25 (m, 2H), 7.17 ppm (d, *J* = 16.3 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 156.8, 156.0, 137.5, 132.6, 128.9, 128.7, 128.1, 127.6, 127.5, 126.5, 126.1, 124.8, 124.2, 123.0, 120.9, 118.6, 111.9, 111.9 ppm. Analytical data in accordance to literature.[130]



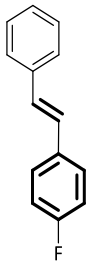
(*E*)-5-Styrylbenzene-1,3-diol (pinosylvin) (2.27-f)

Using potassium (*E*)-trifluoro(styryl)borate and (3,5-dimethoxyphenyl)magnesium bromide according to general procedure, provided (*E*)-1,3-dimethoxy-5-styrylbenzene. For removal of the methyl groups, the crude compound, after electrochemical oxidation, was dissolved in CH_2Cl_2 (4 mL), cooled down to -20 °C and treated with a solution of BBr_3 (1.6 mmol, 4 equiv.) dissolved in 1 mL CH_2Cl_2. The reaction was let warm to room temperature. After completion, the reaction was treated with water and extracted with dichloromethane (3 × 10 mL) and washed with a solution of saturated aqueous sodium chlorid (1 × 10 mL). The combined organic phases were dried over magnesium sulfate, filtered and concentrated in vacuo. The crude was purified by flash column chromatography with appropriate solvent mixture to provide **2.27-f** (0.23 mmol, 62 mg, 57%, *E*/*Z* = 99:1) as white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51-7.46 (m, 2H), 7.39-7.33 (m, 2H), 7.29-7.26 (m, 1H), 7.05 (d, *J* = 16.3 Hz, 1H), 6.96 (d, *J* = 16.3 Hz, 1H), 6.58 (d, *J* = 2.2 Hz, 2H), 6.28 (t, *J* = 2.2 Hz, 1H), 4.76 ppm (s, 2H). **^{13}C**

[130] C. Wang; I. Piel; F. Glorius, *J. Am. Chem. Soc.* **2009**, *131*, 4194.

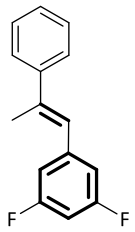
NMR (101 MHz, $CDCl_3$) δ 156.9, 140.0, 136.8, 129.6, 128.7, 127.9, 127.1, 126.6, 126.3, 106.2, 102.2 ppm. Analytical data in accordance to literature.[131]



(*E*)-1-Fluoro-4-styrylbenzene (2.27-g)

Using potassium (*E*)-trifluoro(styryl)borate and (4-fluorophenyl)magnesium bromide according to general procedure, provided **2.27-g** (0.27 mmol, 54 mg, 68%, *E*/*Z* = 99:1) as white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46-7.35 (m, 4H), 7.27 (t, *J* = 7.7 Hz, 2H), 7.21-7.13 (m, 1H), 7.03-6.92 ppm (m, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.34 (d, *J* = 247.2 Hz), 137.2, 133.51 (d, *J* = 3.3 Hz), 128.7, 128.49 (d, *J* = 2.5 Hz), 128.01 (d, *J* = 8.0 Hz), 127.7, 127.5, 126.5, 115.65 ppm (d, *J* = 21.6 Hz). Analytical data in accordance to literature.[132]



(*E*)-1,3-Difluoro-5-(2-phenylprop-1-en-1-yl)benzene (2.27-h)

Using potassium (*E*)-trifluoro(2-phenylprop-1-en-1-yl)borate and (3,5-difluorophenyl)magnesium bromide according to general procedure, provided **2.27-h** (0.28 mmol, 64 mg, 70%, *E*/*Z* = 99:1) as white solid.

***R*$_f$** = 0.6 (hexane, UV, PAA, $KMnO_4$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.56-7.46 (m, 2H), 7.43-7.36 (m, 2H), 7.35-7.29 (m, 1H), 6.94-6.83 (m, 2H), 6.74-6.66 (m, 2H), 2.28 (d, *J* = 1.4 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.97 (dd, *J* = 247.4, 13.2 Hz), 143.4, 141.62 (t, *J* = 9.7 Hz), 140.1, 128.6, 127.9, 126.2, 125.80 (t, *J* = 2.6 Hz), 112.21-111.70 (m), 102.01 (t, *J* = 25.5 Hz), 17.8 ppm. **LRMS** (DEP/EI-Orbitrap): *m/z* (%): 230.1 (100), 215.1 (80), 195.1 (20). **HRMS** (EI-Orbitrap): m/z: [M^+] Calcd. for $C_{14}H_{15}FO_2^+$: 230.0907; found: 230.0896.

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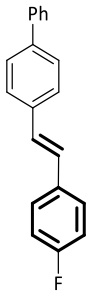
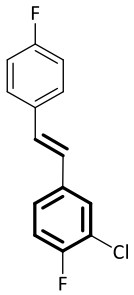
[131] J. Yang; C. Wang; Y. Sun; X. Man; Y. Li; F. Sun, *Chem. Commun.* **2019**, *13*, 1903.
[132] A. L. Isfahani; I. Mohammadpoor-Baltork; V. Mirkhani; A. R. Khosropour; M. Moghadam; S. Tangestaninejad; R. Kia, *Adv. Synth. Catal.* **2013**, *355*, 957.



(*E*)-4-(4-Fluorostyryl)-1,1'-biphenyl (2.27-i)

Using potassium (*E*)-(2-([1,1'-biphenyl]-4-yl)vinyl)trifluoroborate and (4-fluorophenyl)magnesium bromide according to general procedure, provided **2.27-i** (0.28 mmol, 78 mg, 71%, *E*/*Z* = 99:1) as white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69-7.55 (m, 6H), 7.55-7.42 (m, 4H), 7.40-7.31 (m, 1H), 7.15-7.00 ppm (m, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.35 (d, *J* = 247.2 Hz), 140.6, 140.4, 136.2, 133.50 (d, *J* = 3.3 Hz), 128.8, 128.1, 128.0, 127.5, 127.4, 126.9, 126.9, 115.67 ppm (d, *J* = 21.6 Hz). Analytical data in accordance to literature.[133]

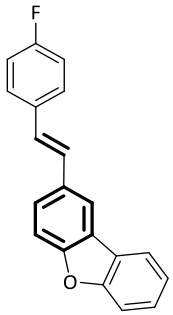


(*E*)-2-Chloro-1-fluoro-4-(4-fluorostyryl)benzene (2.27-j)

Using potassium (*E*)-trifluoro(4-fluorostyryl)borate and (3-chloro-4-fluorophenyl)magnesium bromide according to general procedure, provided **2.27-j** (0.22 mmol, 55 mg, 55%, *E*/*Z* = 99:1) as white solid.

***R*$_f$** = 0.40 (hexane, UV, $KMnO_4$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.53 (dd, *J* = 7.0, 2.2 Hz, 1H), 7.48-7.43 (m, 2H), 7.33 (ddd, *J* = 8.6, 4.6, 2.2 Hz, 1H), 7.12 (t, *J* = 8.7 Hz, 1H), 7.06 (t, *J* = 8.7 Hz, 2H), 6.99 (d, *J* = 16.3 Hz, 1H), 6.90 ppm (d, *J* = 16.3 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.7 (d, *J* = 247.8 Hz), 157.6 (d, *J* = 249.8 Hz), 134.7 (d, *J* = 3.9 Hz), 133.0 (d, *J* = 3.4 Hz), 128.7 (d, *J* = 2.4 Hz), 128.3, 128.2, 126.2 (d, *J* = 7.0 Hz), 126.1 (t, *J* = 2.1 Hz), 121.5 (d, *J* = 18.1 Hz), 116.9 (d, *J* = 21.5 Hz), 115.9 ppm (d, *J* = 21.7 Hz). **LRMS** (DEP/EI-Orbitrap): *m/z* (%): 250.0 (95), 235.0 (15), 214.1 (100), 195.1 (30).

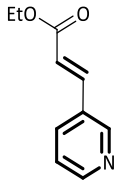
[133] Y. Liu; P. Liu; Y. Wei, *Chin. J. Chem.* **2017**, *35*, 1141.



(*E*)-2-(4-Fluorostyryl)dibenzo[*b*,*d*]furan (2.27-k)

Using potassium (*E*)-trifluoro(4-fluorostyryl)borate and dibenzo[*b*,*d*]furan-2-ylmagnesium bromide according to general procedure, provided **2.27-k** (0.27 mmol, 78 mg, 68%, *E*/*Z* = 99:1) as white solid.

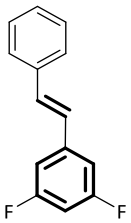
***R*f** = 0.30 (hexane, UV, PAA, $KMnO_4$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 1.8 Hz, 1H), 7.98 (d, *J* = 6.9 Hz, 1H), 7.62 (dd, *J* = 8.6, 1.8 Hz, 1H), 7.60-7.45 (m, 5H), 7.37 (td, *J* = 7.5, 1.0 Hz, 1H), 7.18 (d, *J* = 16.3 Hz, 1H), 7.14-7.05 ppm (m, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.40 (d, *J* = 246.9 Hz), 156.8, 156.0, 133.74 (d, *J* = 3.3 Hz), 132.4, 128.53 (d, *J* = 2.5 Hz), 128.00 (d, *J* = 7.8 Hz), 127.5, 126.9, 126.0, 124.9, 124.2, 123.0, 120.8, 118.5, 115.9, 115.7, 111.95 ppm (d, *J* = 4.4 Hz). **LRMS** (DEP/EI-Orbitrap): *m/z* (%): 288.1 (100), 273.0 (5), 257.1 (30). **HRMS** (EI-Orbitrap): m/z: [M^+] Calcd. for $C_{20}H_{13}FO^+$: 288.0950; found: 288.0945.



Ethyl (*E*)-3-(pyridin-3-yl)acrylate (2.27-l)

Using potassium (*E*)-(3-ethoxy-3-oxoprop-1-en-1-yl)trifluoroborate and pyridin-3-ylzinc(II) iodide according to general procedure, provided **2.27-l** (0.10 mmol, 18 mg, 25%, *E*/*Z* = 99:1) as colourless oil.

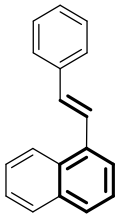
***R*f** = 0.25 (hexane/EtOAc 6:4, UV, PAA). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.75 (d, *J* = 2.2 Hz, 1H), 8.61 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.84 (dt, *J* = 7.9, 2.0 Hz, 1H), 7.67 (d, *J* = 16.1 Hz, 1H), 7.37-7.31 (m, 1H), 6.51 (d, *J* = 16.1 Hz, 1H), 4.28 (q, *J* = 7.1 Hz, 2H), 1.35 ppm (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.5, 151.1, 149.9, 141.0, 134.3, 130.4, 123.9, 120.6, 61.0, 14.4 ppm. **HRMS** (EI-Orbitrap): m/z: [M^+] Calcd. for $C_{10}H_{11}NO_2^+$: 177.0790; found: 177.0782.



(*E*)-1,3-difluoro-5-styrylbenzene (2.27-m)

Using potassium (*Z*)-trifluoro(styryl)borate and (3,5-difluorophenyl)magnesium bromide according to general procedure, provided **2.27-m** (0.26 mmol, 56 mg, 65%, *E*/*Z* = 90:10) as white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56-7.48 (m, 2H), 7.43-7.35 (m, 2H), 7.35-7.28 (m, 1H), 7.11 (d, *J* = 16.2 Hz, 1H), 7.05-6.97 (m, 3H), 6.71 ppm (tt, *J* = 8.8, 2.3 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.41 (dd, *J* = 247.5, 13.2 Hz), 140.88 (t, *J* = 9.6 Hz), 136.4, 131.4, 129.0, 128.5, 126.9, 126.62 (t, *J* = 2.9 Hz), 109.46-108.89 (m), 102.85 ppm (t, *J* = 25.7 Hz). Analytical data in accordance to literature.[134]

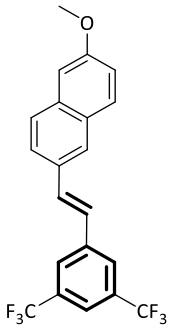


(*E*)-1-Styrylnaphthalene (2.27-n)

Using potassium (*Z*)-trifluoro(styryl)borate and naphthalen-1-ylmagnesium bromide according to general procedure, provided **2.27-n** (0.17 mmol, 37 mg, 43%, *E*/*Z* = 93:7) as white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, *J* = 8.0 Hz, 1H), 7.93-7.86 (m, 2H), 7.82 (d, *J* = 8.2 Hz, 1H), 7.76 (d, *J* = 6.1 Hz, 1H), 7.65-7.60 (m, 2H), 7.58-7.48 (m, 3H), 7.42 (t, *J* = 7.7 Hz, 2H), 7.34-7.29 (m, 1H), 7.17 ppm (d, *J* = 16.0 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 137.7, 135.1, 133.8, 131.9, 131.5, 128.9, 128.8, 128.2, 127.9, 126.8, 126.2, 126.0, 125.9, 125.8, 123.9, 123.8 ppm. Analytical data in accordance to literature.[135]

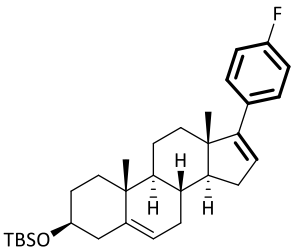
[134] T. Ismail; S. Shafi; J. Srinivas; D. Sarkar; Y. Qurishi; J. Khazir; M. S. Alam; H. M. S. Kumar, *Bioorg. Chem.* **2016**, *64*, 97.
[135] M. Das; D. F. O´Shea, *Org. Lett.* **2016**, *18*, 336.



(*E*)-2-(3,5-Bis(trifluoromethyl)styryl)-6-methoxynaphthalene (2.27-o)

Using potassium (*Z*)-trifluoro(2-(6-methoxynaphthalen-2-yl)vinyl)borate and (3,5-bis(trifluoromethyl)phenyl) magnesium bromide according to general procedure, provided **2.27-o** (0.22 mmol, 89 mg, 56%, *E*/*Z* = 84:16) as colourless oil.

***R*f** = 0.25 (hexane, UV, PAA, $KMnO_4$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.94 (s, 2H), 7.85 (s, 1H), 7.77-7.68 (m, 4H), 7.38 (d, *J* = 16.3 Hz, 1H), 7.24 (d, *J* = 15.1 Hz, 1H), 7.19-7.12 (m, 2H), 3.94 ppm (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.4, 139.8, 134.9, 132.8, 132.13 (q, *J* = 33.1 Hz), 131.5, 129.9, 129.1, 127.8, 127.6, 126.2, 124.8, 123.9, 122.2, 120.81-120.57 (m), 119.5, 106.1 ppm. **LRMS** (DEP/EI-Orbitrap): *m/z* (%): 396.1 (100), 381.0 (5), 353.0 (10), 333.0 (5). **HRMS** (EI-Orbitrap): m/z: [M^+] Calcd. for $C_{21}H_{14}F_6O_2^+$: 396.0949; found: 396.0949.



***tert*-Butyl(((*3S*,*8R*,*9S*,*10R*,*13S*,*14S*)-17-(4-fluorophenyl)-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15-dodecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl)oxy)dimethylsilane (2.27-p)**

Using potassium ((*3S*,*8S*,*9S*,*10R*,*13S*,*14S*)-3-((*tert*-butyldimethylsilyl)oxy)-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15-dodecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl)trifluoroborate and (4-fluorophenyl)magnesium bromide according to general procedure, provided **2.27-p** (0.25 mmol, 121mg, 63%) as colourless oil.

***R*f** = 0.2 (hexane/EtOAc 98:2, UV, PAA, $KMnO_4$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32 (dd, *J* = 8.7, 5.5 Hz, 2H), 7.01-6.95 (m, 2H), 5.85 (dd, *J* = 3.4, 1.8 Hz, 1H), 5.38-5.33 (m, 1H), 3.50 (tt, *J* = 11.0, 4.7 Hz, 1H), 2.34-2.15 (m, 3H), 2.09-1.96 (m, 3H), 1.85-1.41 (m, 10H), 1.33-1.20 (m, 1H), 1.06 (s, 3H), 1.03 (s, 3H), 0.90 (s, 9H), 0.07 ppm (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.9 (d, *J* = 245.4 Hz), 153.8, 141.9, 133.4

(d, *J* = 3.5 Hz), 128.2 (d, *J* = 7.7 Hz), 127.1, 120.9, 114.9 (d, *J* = 21.0 Hz), 72.6, 57.7, 50.5, 50.4, 47.2, 42.9, 37.3, 36.8, 35.4, 32.1, 31.6, 30.5, 26.0, 20.9, 19.4, 18.3, 16.6, −4.6 ppm.