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Diastereoselective Intramolecular Carbolithiation and Acylation Reactions

von

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Erklärung

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Meike Simon

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Parts of this Ph.D. Thesis have been published

A) Communications and Full Papers

1) "Diastereoselective Intramolecular Carbolithiations of Stereodefined Secondary Alkyllithiums Bearing a Remote Alkynylsilane"

M. Simon, K. Karaghiosoff, P. Knochel, *manuscript submitted*.

B) Patents

1) "Kohlenwasserstoff-Lösliche Halogen- und Thiolat- /Magnesium-Austauschreagenzien"

P. Knochel, D. S. Ziegler, M. Simon, DE 2018200805.1, *a patent application has been filed*.

“Ever tried. Ever failed. No matter. Try again. Fail again. Fail better.”

Samuel Beckett (in Worstward Ho, 1983)

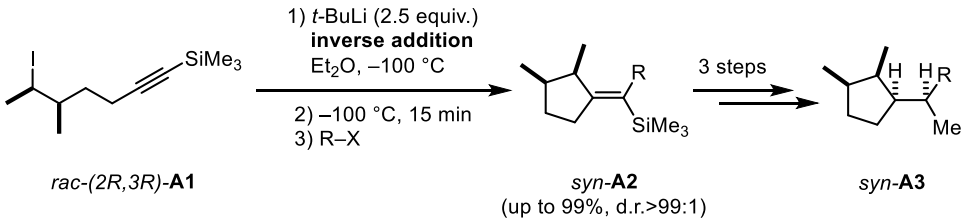
To my family

Abstract

This Ph.D. thesis describes the formation of unstabilised secondary alkyllithium reagents, and their highly diastereolective behaviour in carbolithiation and acylation reactions, and additionally details a new sulfur/metal-exchange on piperidyl thioethers.

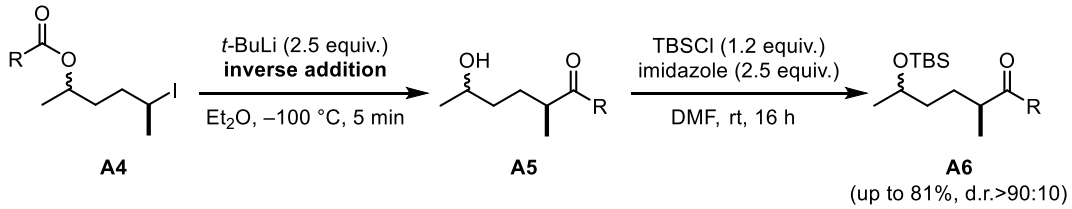
Part I: The first part of this work focuses on the diastereoselective preparation of secondary, unstabilised Li-compounds *via* an iodine/lithium-exchange at −100 °C using *t*-BuLi (inverse addition, 2.5 equiv.) and their application in intramolecular carbolithiation and acylation reactions.

The first topic describes the synthesis of various stereodefined cyclopentane derivatives. Performing a stereospecific iodine/lithium-exchange of secondary iodides, each bearing an internal alkynylsilane-moiety, generated the stereodefined Li-species. Various exo-alkylidene cyclopentane, related *cis*-bicyclo[3.3.0]octane, and *cis*-bicyclo[4.3.0]nonane derivatives were afforded in excellent diastereoselectivity by an intramolecular carbolithiation reaction. Carrying out the iodine/lithium-exchange in an enantioselective fashion, demonstrated a high potential for enantiomeric syntheses. The remaining silane-moiety was successfully transformed into an iodide, which was further modified, giving an opportunity to construct up to four contiguous stereocentres in cyclopentanes, as well as in bicyclic ring structures (Scheme A).



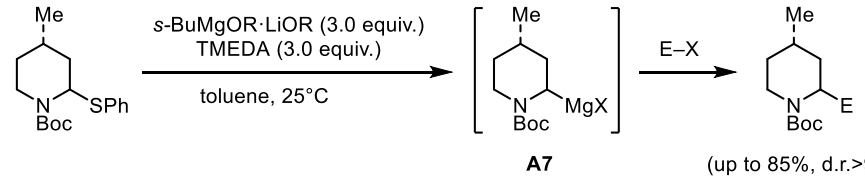
Scheme A: Example for the preparation of an exo-alkylidene cyclopentane bearing four contiguous stereocentres.

Also, an approach toward the stereoselective synthesis of ketones *via* an intramolecular acylation reaction was developed. Thus, various stereodefined organolithiums were prepared from stereodefined secondary iodoesters. The iodine/lithium-exchange was triggered by the inverse addition of *t*-BuLi (2.5 equiv.) at −100 °C in diethyl ether. The Li-reagents formed undergo a fast transfer of the acyl group, and a range of ketones were obtained, which were isolated after protection of the remaining alcohol group (Scheme B).



Scheme B: Diastereoselective acyl-transfer after an I/Li-exchange with *t*-BuLi.

Part II: The second part of this work focused on the development of a new sulfur/metal-exchange on piperidyl thioethers. The desired magnesium reagents **A7** were produced by treating piperidyl thioethers with *s*-BuMgOCH$_2$CH(Et)Bu·LiOCH$_2$CH(Et)Bu in toluene at room temperature. Reaction with various electrophiles afforded the desired products. When a second residue is present in the piperidyl ring, only the thermodynamic product is formed after quenching with electrophiles (Scheme C).



Scheme C: Reaction of thioethers with *s*-BuMgOCH$_2$CH(Et)Bu·LiOCH$_2$CH(Et)Bu in the presence of TMEDA and reaction with various electrophiles.

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List of Abbreviations

°C	degrees Celsius
Å	Ångström
acac	acetylacetonate
atm	atmosphere(s)
ATR	attenuated total reflection (IR)
Boc	*tert*-butyloxycarbonyl
Bu	butyl
CIPE	complex-induced proximity effect
COSY	correlation spectroscopy
d	day(s)
d.r.	diastereomeric ration
dba	dibenzylideneacetone
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
DMA	dimethylacetamide
DMSO	dimethylsulfoxide
DTBB	4,4′-di-*tert*-butylbiphenyl
e.g.	*exempli gratia* (for example)
e.r.	enantiomeric ratio
EI	electron ionisation
equiv.	equivalent(s)
ESI	electrospray ionisation

Et	ethyl
g	gram
GC	gas chromatography
gem-	geminal
h	hour(s)
HMBC	heteronuclear multiple bond correlation
HR-MS	high resolution mass spectrometry
HSQC	heteronuclear single quantum correlation
Hz	Hertz
INAS	intramolecular nucleophilic acyl substitution
IR	infrared spectroscopy
J	coupling constant
LDMAN	lithium 1-(dimethylamino)naphthalenide
M	molar
*m*CBPA	*meta*-chloroperbenzoic acid
Me	methyl
min	minute(s)
mL	milliliter
mmol	millimole
NIS	*N*-iodosuccinimide
NMI	*N*-methylimidazole
NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser effect correlation spectroscopy
Pd/C	palladium on charcoal

PMA	phosphomolybdic acid
PMB	*para*-methoxybenzyl
PMDTA	*N,N,N′,N″,N″*-pentamethyldiethylenetriamine
ppm	parts per million
s-	*sec-*
SET	single-electron transfer
t-	*tert-*
TBAI	tetrabutylammonium iodide
TBS	*tert*-butyldimethylsilyl
Tf	triflate
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMEDA	*N*,*N*,*N′*,*N′*-tetramethylethylenediamine
TMS	trimethylsilyl
UV	ultraviolet
δ	chemical shift in ppm downfield relative to a standard

Part I: Intramolecular Carbolithiation and Acylation Reactions of Stereodefined Secondary Alkyllithiums

1 Introduction

Lots of organic compounds, especially natural products, contain chiral centres in their molecular structure, e.g. perfumes, cosmetics, nutrients, pesticides and pharmaceuticals. Historically, those chiral compounds were isolated from natural products. Nowadays, different ways for the preparation of enantiomerically pure compounds are known: 1) synthesising the compound in its racemic form and subsequent resolution; 2) using plants or bacteria producing the desired compound; 3) synthesis starting with a natural product or 4) an asymmetric synthesis.[1] Obtaining stereoisomerically pure compounds is important for example for pharmaceuticals in terms of their mode of action. In most cases, only one of the enantiomers has the desired biological activity, while the other one is inactive or even has an inverse effect.[2] Marckwald defined the expression "asymmetric synthesis" in 1904 as follows:[3]

"Asymmetrische Synthesen sind solche, welche aus symmetrisch constituirten Verbindungen unter intermediärer Benutzung optisch-activer Stoffe, aber unter Vermeidung jedes analytischen Vorganges, optisch-active Substanzen erzeugen."

To define a transformation as asymmetric, the following criteria are useful: 1) the reaction is stereoselective; 2) if a chiral catalyst is involved, a low loading should be possible, and the catalyst should be easily separable; 3) if a chiral auxiliary is used, it should be removable without compromising the newly formed stereocentre, and recoverable in good yield without racemisation, and 4) the chiral auxiliary or catalyst should be readily and inexpensively available.[1]

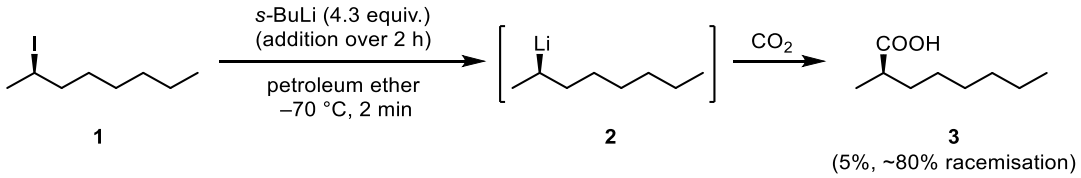
1.1 Organolithium Compounds

In 1996, Beak described organolithium reagents as the "most used organometallics in contemporary organic chemistry".[4] Lithium is the smallest of the metals and the structures of the organolithium compounds are complex due to their high tendency to aggregate.[5,6] The degree of covalence varies with temperature, solvent and structure. The C-Li bond might be best described as ionic, even if a covalent character cannot be neglected.[7]

Organolithium compounds were first prepared by Schlenk and Holtz by the reaction of lithium with a diorganomercury compound.[8] Later, Ziegler *et al.* showed that this reaction is reversible.[9] Organolithium derivatives can be prepared by deprotonation, reductive lithiation, transmetalation from Hg, Sn, Se, Te, S and P, as well as by halogen/lithium-exchange.[10]

1.2 Stereoselective Preparation of Organolithium Reagents

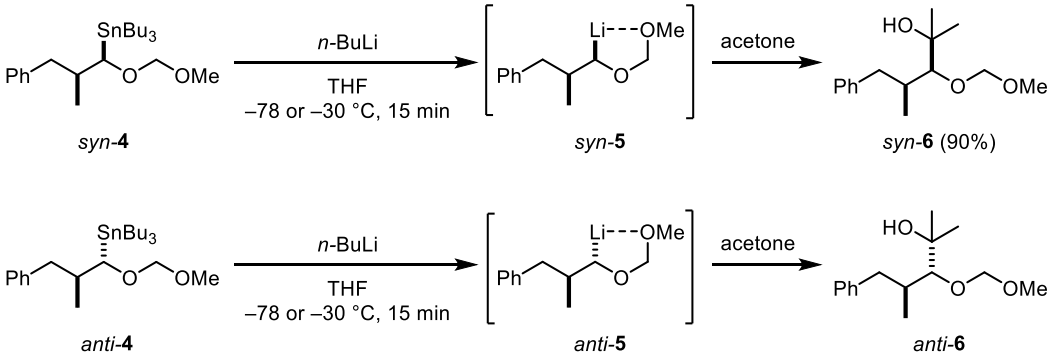
Letsinger[11] and Curtin[12] described the first chiral lithium reagents in the 1950's. Letsinger obtained acid **3** after iodine/lithium-exchange of (−)-2-iodooctane **1** using *s*-BuLi at −70 °C in petroleum ether and subsequent trapping with CO_2 in low yield and with approximately 80% racemisation (Scheme 1).[11]



Scheme 1: I/Li-exchange of (−)-2-iodooctane **1**.

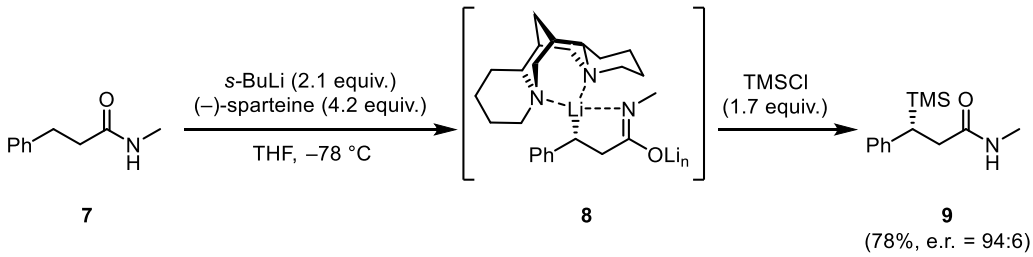
To obtain Li-compounds, which are relatively stable toward racemisation, an external stabilisation is needed. This can be achieved either by an intramolecular coordination of the Li-atom by a heteroatom or by stabilising the electron-rich C-Li bond *via* a nearby empty orbital or an electron-withdrawing group.[10]

In 1980, Still discovered the stereospecific transmetalation from Sn to Li of chiral α-alkoxystannanes. Not only was the organolithium formed stereospecifically, but also the resulting Li-species **5** were found to be configurationally stable, at least for 15 min at −30 °C. Quenching with acetone as electrophile afforded the desired product **6** (Scheme 2).[13]



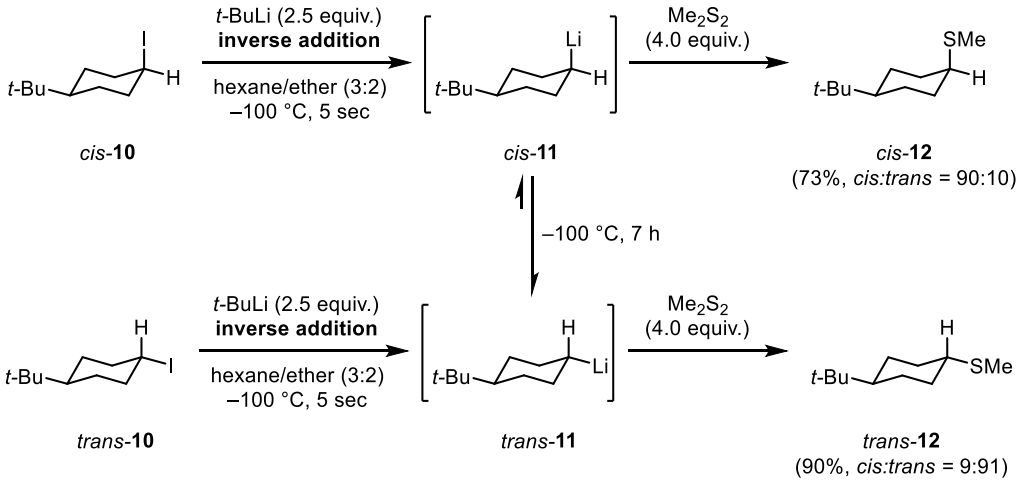
Scheme 2: Preparation of *O*-stabilised organolithiums **5** *via* Sn/Li-exchange.

Alternatively, chiral ligands, such as (−)-sparteine, were used to achieve an enantioselective deprotonation reaction. (−)-Sparteine was first reported in 1968 for the reaction of ethylmagnesium bromide with benzaldehyde.[14,15] The active conformation of (−)-sparteine, which is able to act as a bidentate ligand, is slightly higher in energy compared to its ground state.[16] Treating *N*-methyl-3-phenylpropionic acid **7** with *s*-BuLi in the presence of (−)-sparteine, the desired product **9** was isolated after trapping with TMSCl in 78% yield and with high enantioselectivity.[17]



Scheme 3: Enantioselective deprotonation of *N*-methyl-3-phenylpropionic acid amide **7** using (−)-sparteine.

About five years ago, Knochel *et al.* developed a stereoretentive iodine/lithium-exchange for the preparation of *cis*- and *trans*-cycloalkyllithiums **11** from the corresponding iodides **10**. Addition of *t*-BuLi to a solution of the iodide **10** mainly resulted in hydrolysis and elimination products. Thus, inversion of the addition order supressed the undesired hydrolysis and elimination, and the desired unstabilised secondary organolithium **11** was obtained. Reaction of the lithium reagent **11** with various electrophiles yielded the corresponding products in 23–92% yield (Scheme 4).[18]



Scheme 4: Stereoretentive I/Li-exchange and trapping with an electrophile.

This concept was later extended to secondary open-chain alkyllithium compounds functionalised at 2, 3 and 4-position (Figure 1).[19–21]

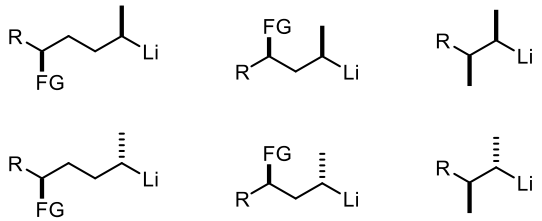
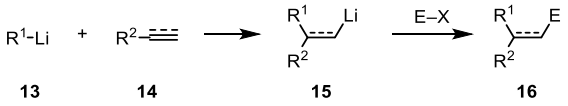


Figure 1: 1,4-, 1,3- and 1,2-functionalised secondary alkyllithiums.

1.3 Carbolithiations

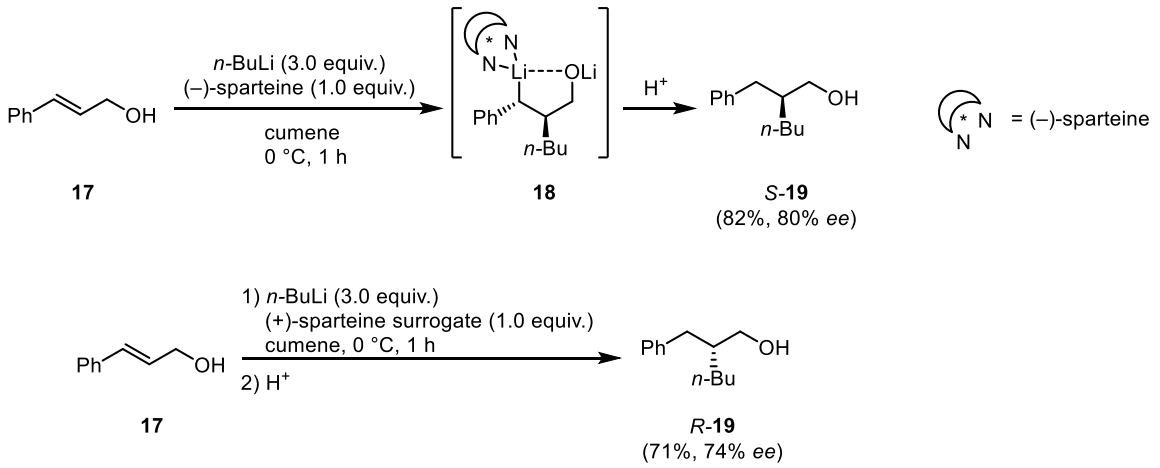
Carbolithiation reactions are defined as the addition of an organolithium reagent across an unactivated C-C π-bond, forming a new C-C and a C-Li σ-bond.[22] For these reactions the carbometalation ability of organolithium compound **13** must be higher than that of the newly formed organolithium **15** to prevent the formation of polymers. Lithium species **15** can be, for example, stabilised by conjugation or coordination.[10,23–25]



Scheme 5: General scheme of a carbolithiation reaction.

The origin of intermolecular carbolithiation reactions lies in anionic polymerisation. Ziegler[26] did pioneer work with the controlled addition of anionic initiators to nonpolar carbon-electrophiles. Theoretical calculations have shown, that the first step in the reaction of methyllithium with ethylene is the formation of a Li-π-complex with an activation energy of 18–24 kcal/mol, followed by *syn*-addition.[27]

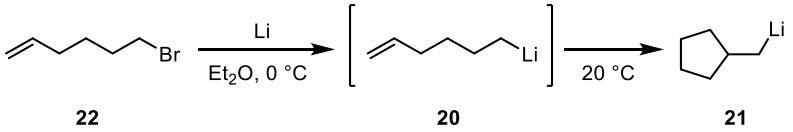
The first asymmetric intermolecular carbolithiation was developed by Marek and Normant,[28] preparing lithium species **18** under the influence of the chiral ligand (−)-sparteine (Scheme 6). This method is taking advantage of the complex-induced proximity effect (CIPE). Also, because of the chelation of Li with the oxygen, no polymerisation was observed. Furthermore, it was possible to maintain a good enantiomeric excess in the presence of only 5 mol% of (−)-sparteine. The use of a (+)-sparteine surrogate was successfully applied to the synthesis of *R*-**19** in similar yield and enantioselectivity.[29]



Scheme 6: Enantioselective carbolithiations using chiral ligands.

Intramolecular carbolithiations to alkynes can be used to prepare oligosubstituted alkenes.[30] A drawback of this reaction is that the lithium reagent can deprotonate terminal acetylenic or propargylic protons, and in some cases isomerisation products of the vinyllithium, formed during the reaction, were observed.[10]

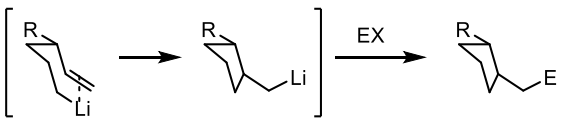
In the 1960's, Drozd *et al.* reported the isomerisation of 5-hexenyllithium (**20**) to cyclopentylmethyllithium (**21**) after reductive lithiation of 1-bromo-5-hexene (**22**) with lithium metal in ether (Scheme 7).[23]



Scheme 7: Isomerisation of 5-hexenyllithium (**21**) to cyclopentylmethyllithium (**22**).

In 1985, Bailey *et al.* carried out mechanistic studies on the cyclisation of 5-hexenyllithium (**20**) to cyclopentylmethyllithium (**21**) preparing Li-species **20** by treating 6-iodo-1-hexene with *t*-BuLi. The cyclisation can be described as a first-order process, that is therefore highly dependent on temperature. The reaction of the anionic species **21** also proceeds much slower[31] than the cyclisation of the 5-hexenyl radical.[32]

Intramolecular carbolithiations, such as 5-*exo*-trig cyclisations, proceed highly stereoselective. The entropy factor favours a monoaddition, even if the initial organolithium reagent has a higher reactivity than the carbometalated one. The cyclisation proceeds *via* a highly organised cyclic transition state. To ensure minimal steric hindrance, all moieties in the chair-like transition state are in a pseudo-equatorial position (Scheme 8).[31] The interaction of the lithium with the C-C double bond, calculated by Bailey *et al.*,[33] was later confirmed by Hofmann and Rölle by NMR.[34] However, this mechanism is not accurate enough to predict the outcome of cyclisations of secondary unsaturated organolithiums.[25]

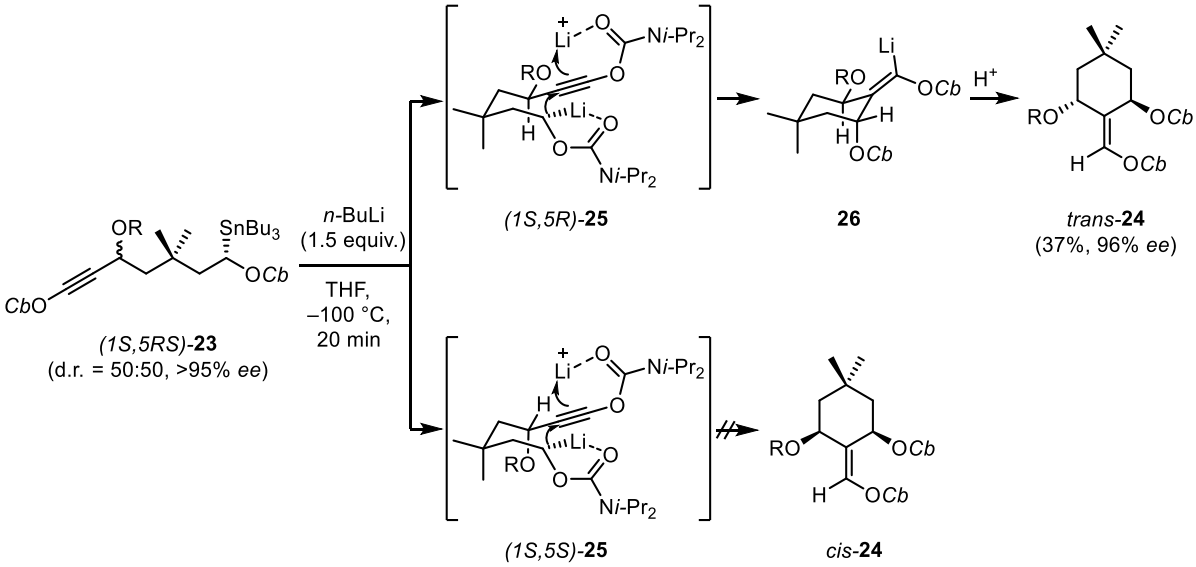


Scheme 8: Intramolecular addition of a C-Li bond across an unactivated double bond.

Intramolecular carbolithiations to alkynes allow an access to four- to six-membered carbo- and heterocycles,[25] usually with a high level of stereo- and regioselectivity, since the addition of organolithium reagent over the C-C triple bond proceeds stereospecifically.[23] Introducing an activation group at the acetylene, such as a phenyl- or a silyl-group, allows the carbolithiation to proceed faster

than with a butyl-group.[35–37] Notably Bailey,[38] Coldham,[39] and Negishi[40] generalised this kind of cyclisation.[23]

Hoppe *et al.*[41,42] used an intramolecular *trans*-cyclocarbolithiation for the preparation of four- to six-membered rings. Lithiodestannylation of (*1R,5RS)*-**23** with *n*-BuLi in THF at −100 °C and in the presence of LiCl yielded, after *anti*-selective 6-*exo-dig* cyclisation, the desired product **24**. The secondary Li-species **25**, that is formed, can be coordinated by the carbamate. It is presumed, that a 1,3,5-triaxial interaction between the TBSO-, the *Cb*O-group, and one methyl group prevents the formation of transition state *(1S,5R)*- **25** (Scheme 9).[42]

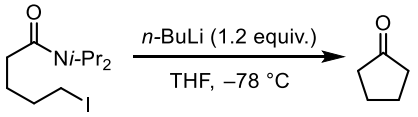


Scheme 9: Synthesis of 2-alkylidene-cyclohexane-1,3-diol **24**. *Cb*O: $(i\text{-Pr})_2NCO_2$. R = TBS.

1.4 Intramolecular Barbier-Type Reaction

A Barbier reaction[43] describes the reaction between an alkyl halide and a carbonyl group in the presence of a metal. Molle and Bauer showed, that an *in situ* formation of an organometallic is not necessarily involved in a Barbier reaction.[44]

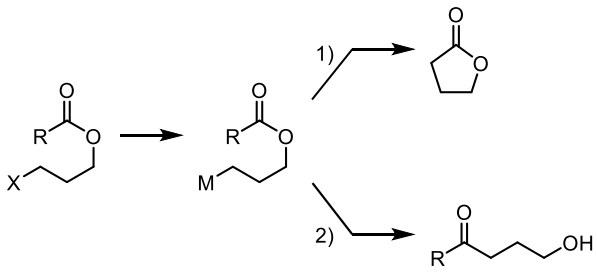
In 1985, Cooke studied the iodine/lithium-exchange of primary iodides, such as **27** and the following, intramolecular attack to an amide group, producing the cyclic ketone **28** (Scheme 10).[45]



27 **28** (71%)

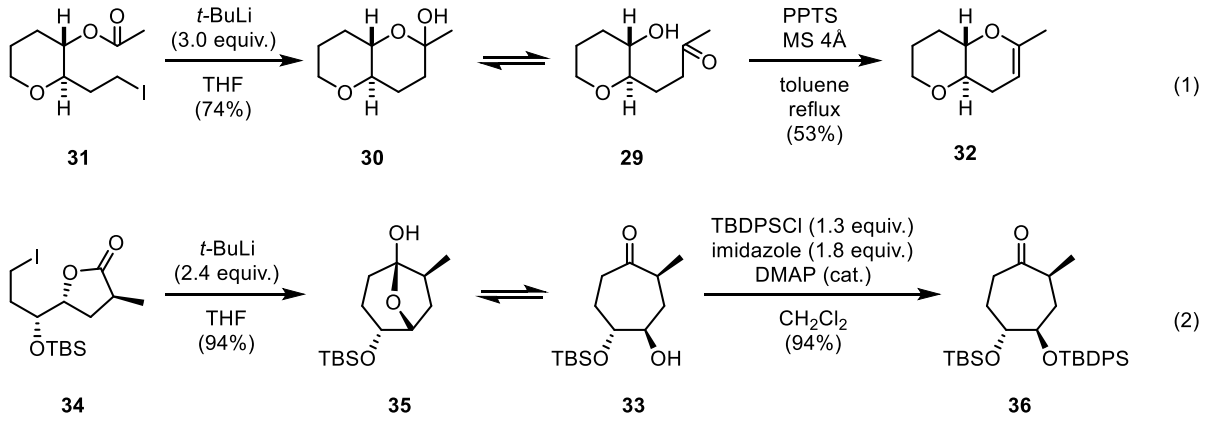
Scheme 10: I/Li-exchange of iodoamide **27** and Barbier-type cyclisation to cyclopentanone (**28**).

Such a reaction can be also performed with esters. The reaction taking place can be named as an intramolecular nucleophilic acyl substitution (INAS) reaction. INAS can be classified into two groups: 1) forming cyclic ketones, while OR or NR_2 acts as a leaving group or 2) transferring a carbon fragment from oxygen to carbon affording a hydroxyketone (Scheme 11).[46]



Scheme 11: Intramolecular nucleophilic acyl substitution.

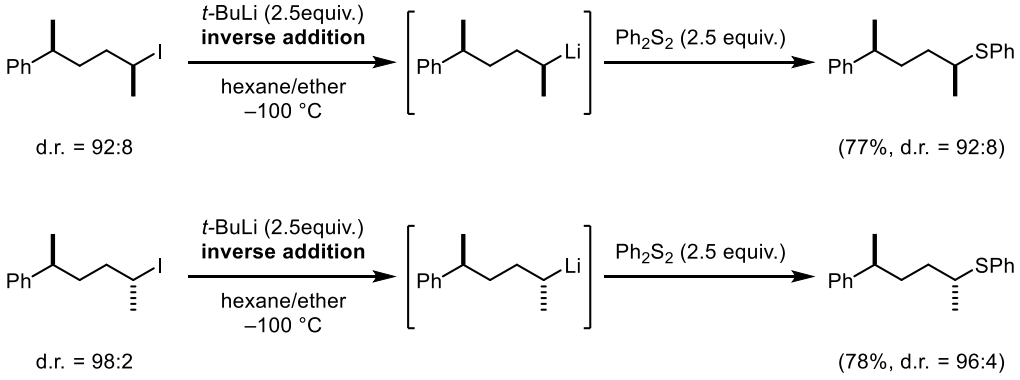
INAS reactions have also been used in natural product synthesis for targets bearing an ester group. In some cases, ketone **29**, formed during the reaction, was in fact an undesired side product beside the desired hemiacetal **30** (Scheme 12, eq. 1).[47,48] In the synthesis of (+)-Sundiversifolide, the cycloheptanone **33** formed during the reaction sequence was an important building block (Scheme 12, eq. 2).[49]



Scheme 12: Intramolecular nucleophilic acyl substitution in natural product synthesis.

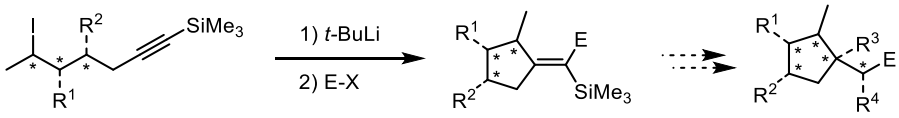
2 Project Outline

Knochel and co-workers have already demonstrated that the iodine/lithium-exchange of secondary stereodefined iodides proceeds with retention of the configuration, if no coordinating group is present in the molecule.[18,19]



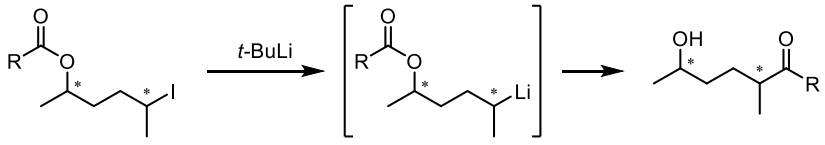
Scheme 13: Stereoretentive I/Li-exchange of secondary alkyl iodides.

With those results in mind, the first goal of this thesis was the development of a synthetic route toward the preparation of cyclopentane derivatives *via* a stereoselective iodine/lithium-exchange and intramolecular carbolithiation. The α-anion stabilising TMS-group should be transformed, allowing to synthesise cyclic systems with up to four contiguous stereocentres (Scheme 14).



Scheme 14: I/Li-exchange followed by an intramolecular carbolithiation to create structures with up to four stereocentres.

The second goal of this Ph.D. thesis was the preparation of stereodefined ketones starting from the corresponding iodoesters. An iodine/lithium-exchange, followed by an intramolecular acylation reaction, should afford the desired ketones (Scheme 15).

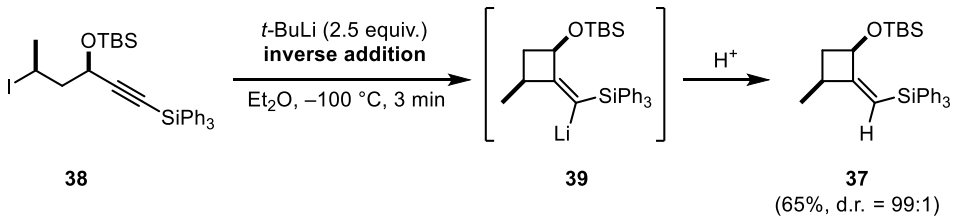


Scheme 15: I/Li-exchange and subsequent intramolecular transfer of the acyl group.

3 Results: Intramolecular Carbolithiation Reactions

3.1 Introduction

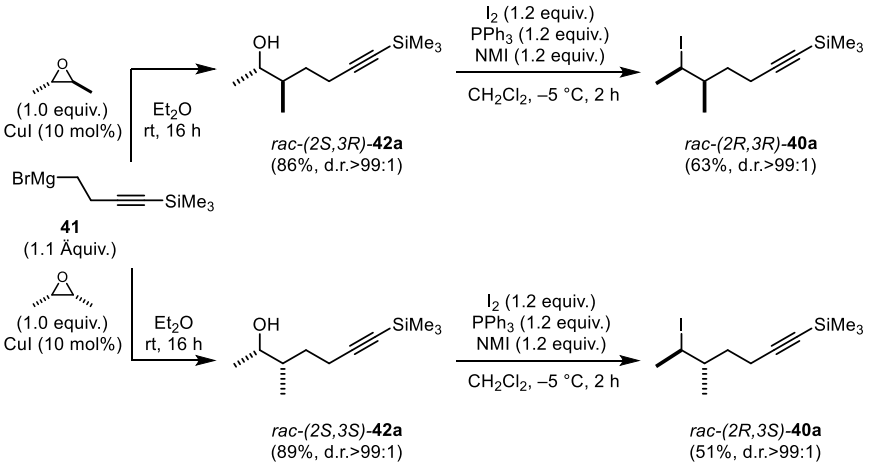
Intramolecular carbometalations of organolithiums bearing a remote alkene or alkyne have been used to prepare various carbocycles.[23–25,50–52] Pionier work from Bailey[37,38,53–55] and Negishi[56] has shown that primary alkyllithiums add intramolecularly to internal alkynes and alkynylsilanes. Hoppe[41,42] showed that optically enriched *O*-stabilized organolithium derivatives undergo *trans*-selective carbolithiations to ynol carbamates with high enantioselectivity. Recently, Knochel *et al.* have shown that non-stabilised, secondary alkyllithiums can be prepared from secondary alkyl iodides with retention of configuration.[18–20] Also, it was shown that intramolecular carbolithiations provide stereoselective access to alkylidene cyclobutanes **37** (Scheme 16).[57]



Scheme 16: Stereoselective synthesis of alkylidenecyclobutane derivatives **37**.

3.2 Synthesis of the Iodides

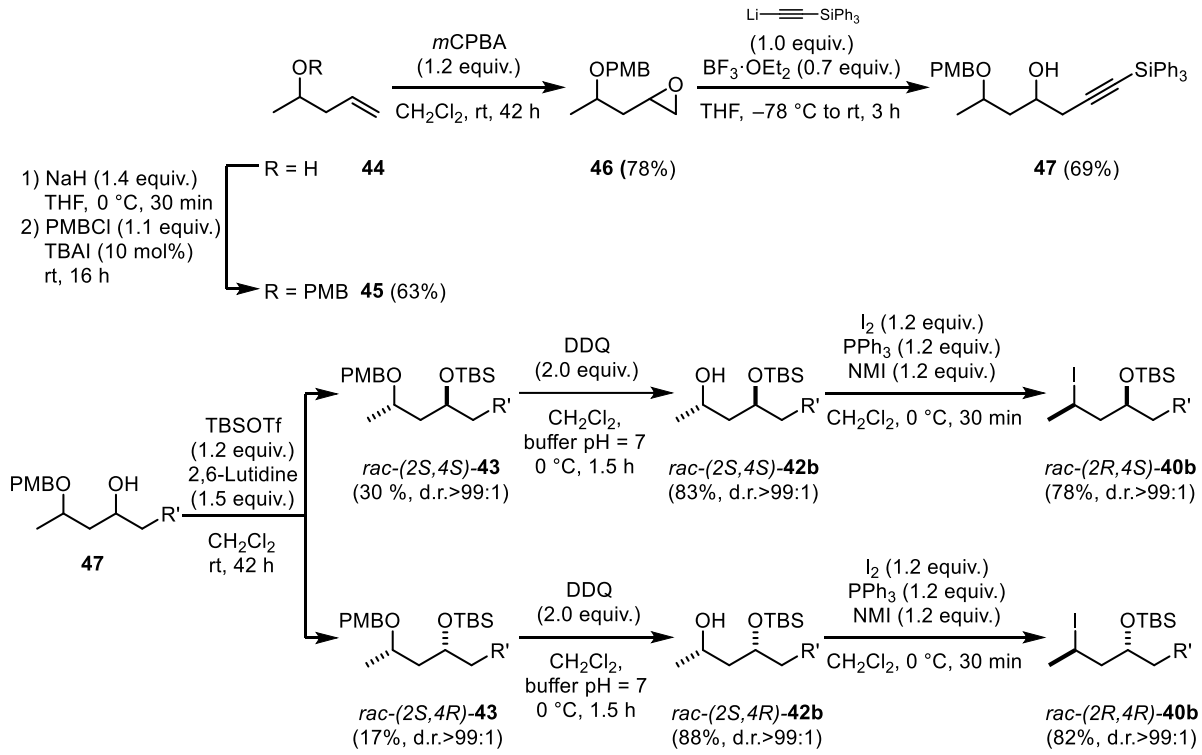
First, the secondary iodoalkynes *rac-(2R,3R)*-**40a** and *rac-(2R,3S)*-**40a** had been prepared. Copper(I)-catalysed addition of alkylmagnesium bromide **41** to *trans*- and *cis*-2,3-epoxybutane, respectively, provided the two alcohols *rac-(2S,3R)*-**42a** and *rac-(2S,3S)*-**42a** diastereoselectively in 86–89% (d.r.>99:1).[58–61] Conversion with inversion of the configuration of alcohols *rac-(2S,3R)*-**42a** and *rac-(2S,3S)*-**42a** to the corresponding iodides *rac-(2R,3R)*-**40a** and *rac-(2R,3S)*-**40a** was performed under Appel-conditions[62,63] in 51–63% (d.r.>99:1) using iodine, triphenylphosphine and *N*-methylimidazole (NMI) (Scheme 17).



Scheme 17: Stereoselective preparation of iodides *rac-(2R,3R)*-**40a** and *rac-(2R,3S)*-**40a** *via* Cu(I)-catalysed epoxide opening with Grignard reagent **41**. The diastereomeric ratio was determined by NMR-analysis.

The trimethylsilane moiety attached to the alkyne is known to stabilise an occurring α-anion during the cyclisation procedure.[64] Nevertheless, it is easily removable and transformable into various functional groups.[65–67]

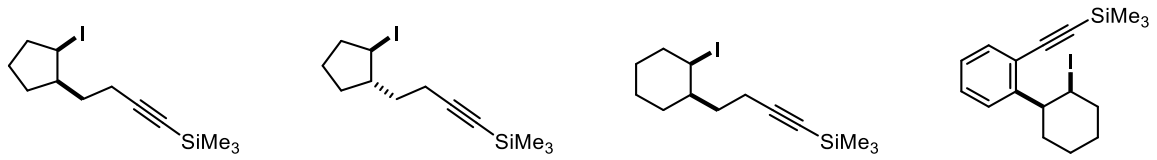
Iodides *rac-(2R,4S)*-**40b** and *rac-(2R,4R)*-**40b** were prepared stereoselectively after separation of the two diastereoisomers of intermediate **43** by column chromatography (Scheme 18). First, the alcohol group of pent-4-en-2-ol **44** was protected with PMBCl (78% yield). After epoxidation with *meta*-chloroperbenzoic acid (*m*CBPA) (78% yield), epoxide **46** was opened with ((triphenylsilyl)ethynyl)-lithium and the product **47** was isolated in 69% yield. After protection of the secondary alcohol with TBSOTf and 2,6-lutidine, the diastereoisomers of the protected diol **43** were separated by column chromatography affording *rac-(2S,4S)*-**43** in 30% yield and *rac-(2S,4R)*-**43** in 17% yield (d.r.>99:1). After PMB-deprotection of *rac-(2S,4S)*-**43** and *rac-(2S,4R)*-**43** with DDQ the corresponding alcohols *rac-(2S,4S)*-**42b** and *rac-(2S,4R)*-**42b** were obtained in 83–88% yield. Following iodination using Appel-conditions afforded iodides *rac-(2R,4S)*-**40b** and *rac-(2R,4R)*-**40b** in 78–82% yield and with excellent diastereoselectivity.



Scheme 18: Preparation of iodides *rac-(2R,4S)*-**40b** and *rac-(2S,4R)*-**40b** starting from pent-4-en-2-ol **44**.

TBAI = tetrabutylammonium iodide.

Bicyclic iodides *syn*-**40c–e** were also prepared by copper(I)-catalysed epoxide-opening using the corresponding Grignard-reagent **41**. Synthesis of the *anti*-isomers was mostly not possible. Iodination under Apple-conditions lead to the elimination product, as did the use of DCC·MeI. Conversion of a mesylate into an iodide using TMSI and $FeBr_3$ or $Fe(acac)_3$ respectively was not successful. Only iodide *anti*-**40c** could be obtained in 43% yield (d.r.<1:99) using iodine, triphenylphosphine and NMI (Figure 2).



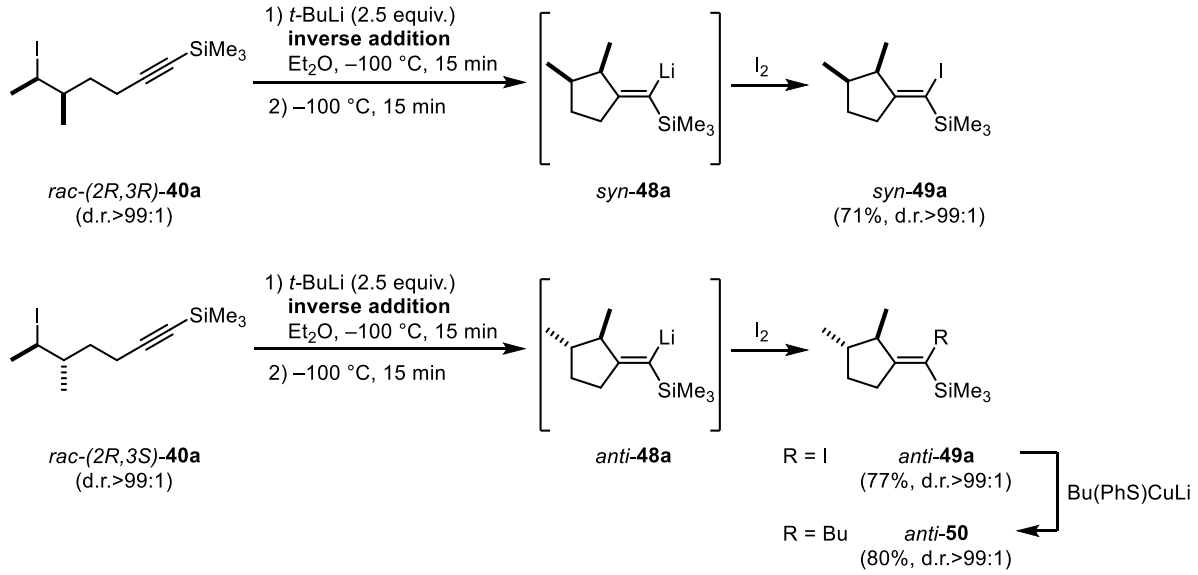
syn-**40c** (92%, d.r.>99:1) | *anti*-**40c** (43%, d.r.>99:1) | *syn*-**40d** (45%, d.r.>99:1) | *syn*-**40e** (3%, d.r.>99:1)

Figure 2: Iodides prepared for the synthesis of bi- and tricyclic structures.

3.3 Intramolecular Carbolithiation

The alkyl iodides *rac-(2R,3R)*-**40a** and *rac-(2R,3S)*-**40a** were stereoselectively converted to the Li-derivatives *syn*-**48a** and *anti*-**48a** using an iodine/lithium-exchange triggered by the inverse addition of *t*-BuLi (2.5 equiv., Et_2O, −100 °C). Quenching with iodine gave the corresponding *syn*- and *anti*-iodides

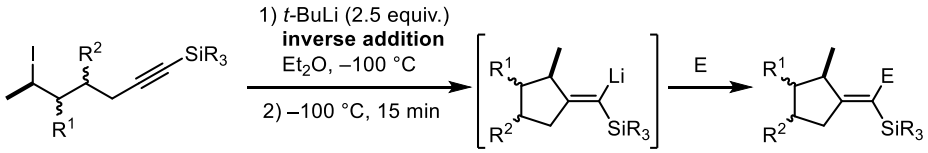
syn-**49a** and *anti*-**49a** in 71–77% yield (d.r.>99:1), indicating a high retention of configuration. Interestingly, the reaction of iodide *anti*-**49a** with Bu(PhS)CuLi[68] allowed the substitution of the iodide by a butyl moiety to afford *anti*-**50** (Scheme 19).[69]

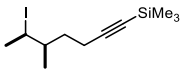
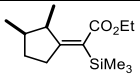
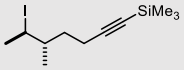
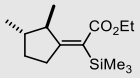
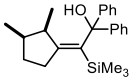
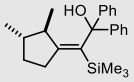
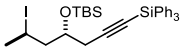
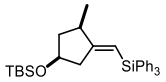
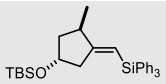


Scheme 19: Stereoselective synthesis of alkenyl iodides (*syn*-**49a** and *anti*-**49a**) from the corresponding iodides *rac-(2R,3R)*-**40a** and *rac-(2R,3S)*-**40a** *via* I/Li-exchange, intramolecular carbolithiation and trapping with iodine. The iodide of *anti*-**49a** was converted into a butyl group using Bu(PhS)CuLi.

This reaction sequence was extended to other electrophiles, such as ethyl chloroformate leading to the esters *syn*-**49b** and *anti*-**49b** in 65–77% with complete retention of the configuration (Table 1, entries 1–2). Quenching of *syn*-**48a** and *anti*-**48a** with benzophenone gave the tertiary alcohols *syn*-**49c** (65%, d.r.>99:1) and *anti*-**49c** (76%, d.r.>99:1; entries 3–4). X-ray crystallographic analysis of *syn*-**49c** confirmed the *syn*-relative stereochemistry (Figure 3). Next, 3-oxygenated substrates were examined for the intramolecular carbolithiation. Since Knochel *et al.* reported that such iodides undergo a fast equilibration after iodine/lithium-exchange providing an alkyllithium reagent in a stereoconvergent manner,[20,57] $SiMe_3$ was replaced by $SiPh_3$, which is known to facilitate carbolithiations and may therefore avoid subsequent equilibration.[70–73] To our delight, the stereoselective performance of an iodine/lithium-exchange on *rac*-(*2R,4R*)-**40b** and *rac*-(*2R,4S*)-**40b** respectively produced *syn*-**49d** (99% yield, d.r.>99:1) and *anti*-**49d** (55% yield, d.r. >99:1) after aqueous workup (entries 5–6) The *anti*-relative stereochemistry of *anti*-**49d** was confirmed by X-ray crystallographic analysis (Figure 3).

Table 1: Intramolecular diastereoselective carbolithiation leading to exo-alkylidene cyclopentane derivatives.



Entry	Substrate	Electrophile	Product [a]
1	 *rac-(2R,3R)*-**40a**	$ClCO_2Et$	 *syn*-**49b** 65%; d.r.>99:1
2	 *rac-(2R,3S)*-**40a**	$ClCO_2Et$	 *anti*-**49b** 77%; d.r. >99:1
3	*rac-(2R,3R)*-**40a**	Ph_2CO	 *syn*-**49c** 65%; d.r.>99:1
4	*rac-(2R,3S)*-**40a**	Ph_2CO	 *anti*-**49c** 76%; d.r. >99:1
5	 *rac-(2R,4R)*-**40b**	NH_4Cl	 *syn*-**49d** 99%; d.r.>99:1
6	 *rac-(2R,4S)*-**40b**	NH_4Cl	 *anti*-**49d** 55%; d.r. >99:1

[a] Yields refer to analytically pure products.

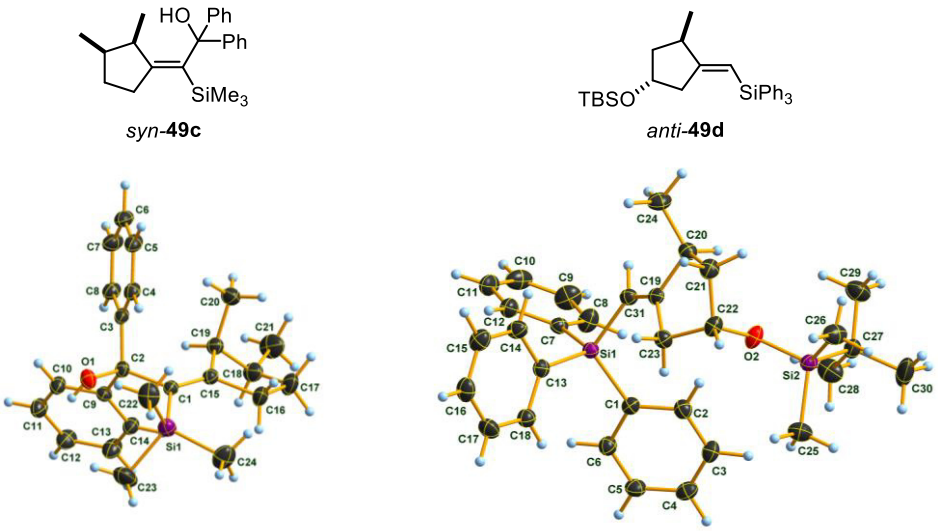
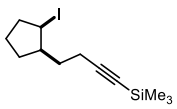
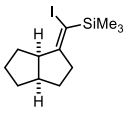


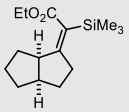
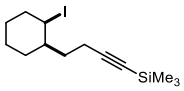
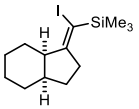
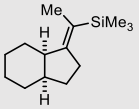
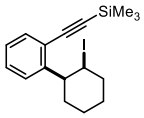
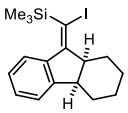
Figure 3: X-ray crystallographic structure of cyclopentane derivatives *syn*-**49c** and *anti*-**49d**.

Using the conditions described above, it was possible to prepare bicyclic and tricyclic ring systems.[54,74] Thus, the reaction of the cyclopentane iodide *syn*-**40c** with *t*-BuLi (−100 °C, 15 min) provided after iodolysis the bicyclic iodide *syn*-**51a** (63% yield, d.r.>99:1; Table 2, entry 1). Subjecting *trans*-cyclopentane iodide *anti*-**40c** to the same reaction conditions, only a negligible amount of the Li-species cyclised to the desired product *anti*-**51a**. Uncyclised iodide (28%), hydrolysis (42%) and elimination product (23%) were observed as main products during the reaction.

Alternatively, after quenching the Li-species of *syn*-**40c** with $ClCO_2Et$, ester *syn*-**51b** was obtained in 56% yield, d.r.>99:1 (entry 2). Similarly, the iodocyclohexane *syn*-**40d**, after treatment with *t*-BuLi, undergoes the expected carbolithiation leading to the bicyclic products *syn*-**51c** and *syn*-**51d** in 65–77% yield, d.r.>99:1 after iodination or quenching with methyl triflate (entry 3–4). Finally, the *syn*-phenyl-substituted cyclohexyl iodide *syn*-**40e** undergoes a carbolithiation after iodine/lithium-exchange. Iodination at −100 °C gave *syn*-**51e** in 63% yield, d.r.>99:1 (entry 6).

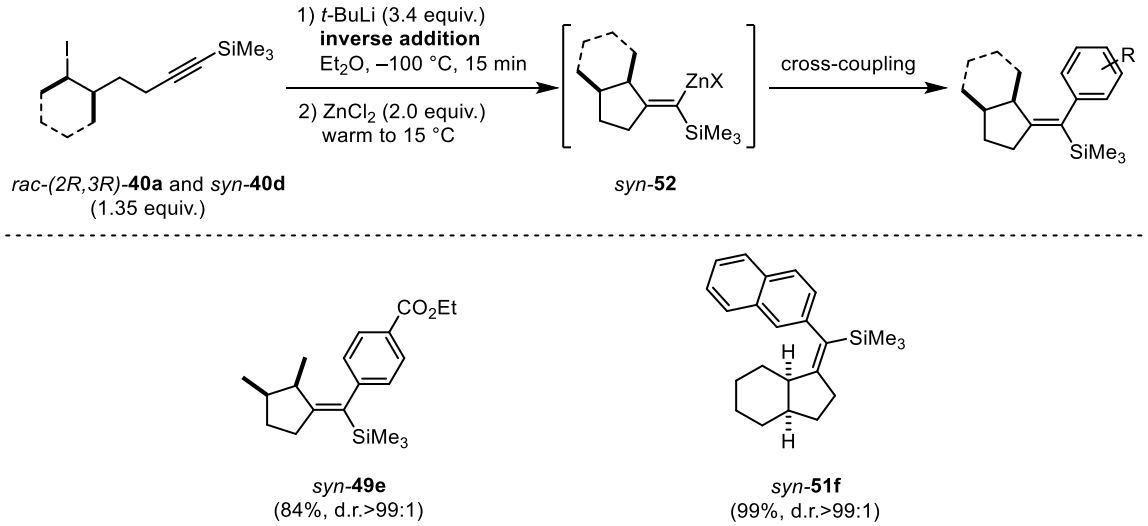
Table 2: Diastereoselective synthesis of polycyclic alkenylsilanes.

Entry	Substrate	Electrophile	Product [a]
			
1	*syn*-**40c**	I_2	*syn*-**51a** 63%; d.r.>99:1

2	*syn*-**40c**	$ClCO_2Et$	 *syn*-**51b** 56%; d.r.>99:1
3	 *syn*-**40d**	I_2	 *syn*-**51c** 65%; d.r.>99:1
4	*syn*-**40d**	$MeOSO_2CF_3$	 *syn*-**51d** 77%; d.r.>99:1
5	 *syn*-**40e**	I_2	 *syn*-**51e** 92%; d.r.>99:1

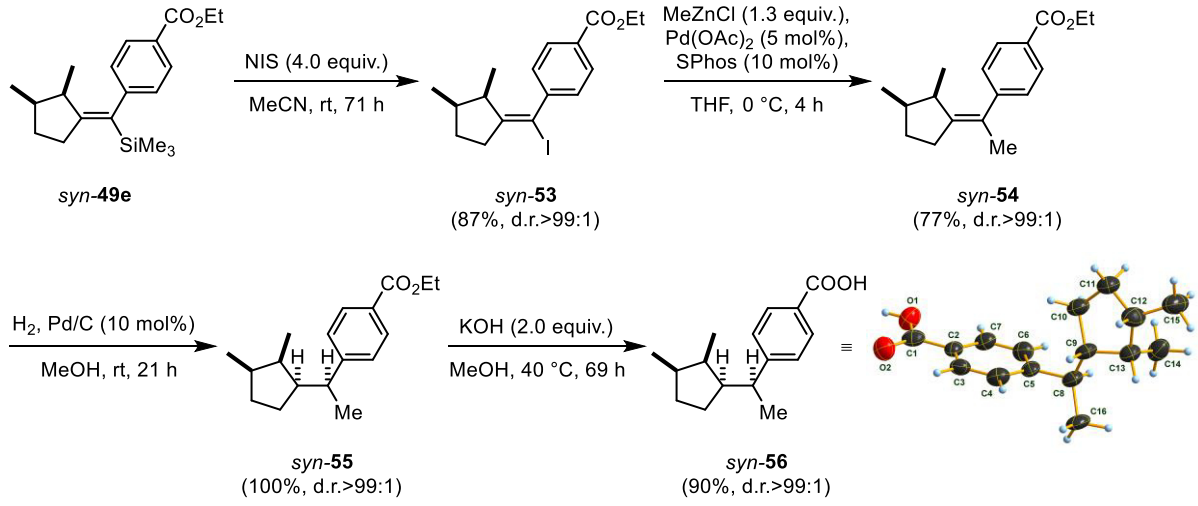
[a] Yields refer to analytically pure products.

Also, cross-coupling reactions were performed (Scheme 20). Standard carbolithiation, starting from *rac-(2R,3R)*-**40a** followed by a transmetalation with $ZnCl_2$, gave the zinc reagent *syn*-**52a**, which was cross-coupled according to Negishi[75,76] with ethyl 4-iodobenzoate using 5 mol% $Pd(OAc)_2$, 10 mol% SPhos,[77] in dimethylacetamide (DMA), affording stereoselectively the tetrasubstituted alkenylsilane *syn*-**49e** (84% yield, d.r.>99:1). Subjecting *syn*-**40d** to the same reaction conditions and a cross-coupling with 2-bromonaphthalene furnished the tetrasubstituted alkenylsilane *syn*-**51f** diastereoselectively in 99% yield, d.r.>99:1.



Scheme 20: Diastereoselective cyclisation and Negishi cross-coupling.

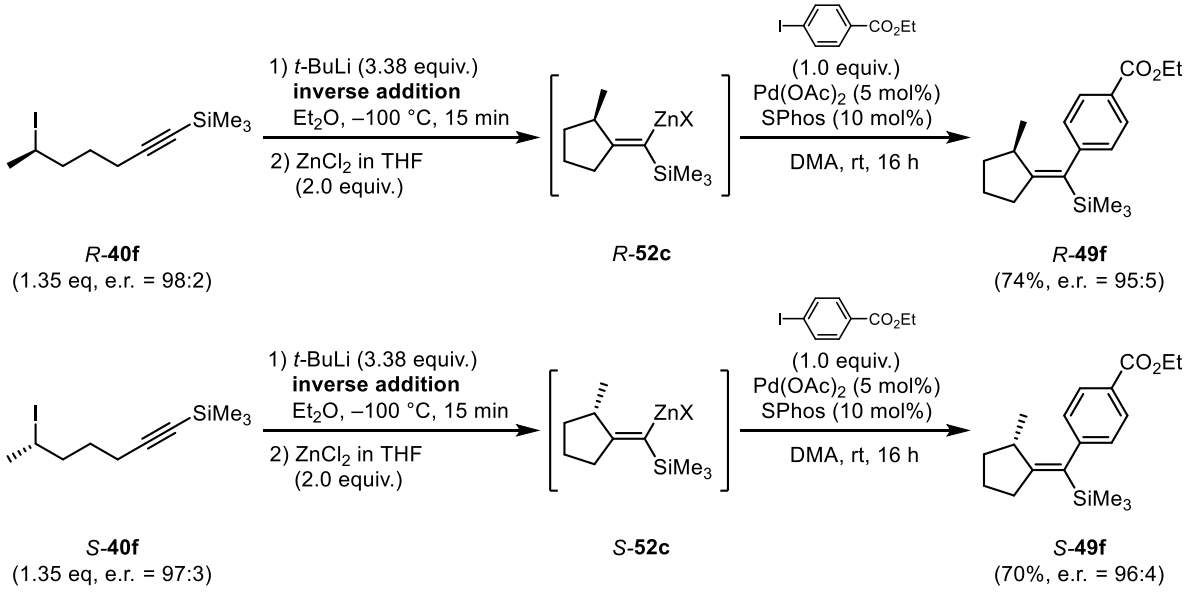
Carbolithiation products of type **49** were used to construct cyclopentanes bearing four fully controlled contiguous stereocentres. Thus, further iodination of *syn*-**49e** with *N*-iodosuccinimide (NIS) in acetonitrile provided the alkenyl iodide *syn*-**53** (87% yield, d.r.>99:1) and subsequent Negishi cross-coupling with MeZnCl lead to the tetrasubstituted olefin *syn*-**54** (77% yield, d.r.>99:1). This sequence demonstrates that the carbolithiation products can be stereoselectively converted to silyl-free tetra-substituted olefins. Pd-catalysed hydrogenation of *syn*-**54** gave the *syn*-ester *syn*-**55** (100% yield, d.r.>99:1). The structure of *syn*-**55** was confirmed by X-ray analysis of the corresponding carboxylic acid *syn*-**56,** obtained after saponification (Scheme 21).



Scheme 21: Diastereoselective preparation of cyclopentane *syn*-**55** bearing four contiguous tertiary stereocentres.

This intramolecular carbolithiation was also applied to an enantioselective synthesis (Scheme 22). After standard iodine/lithium-exchange on *R*-**40f** (e.r. = 98:2), transmetalation with $ZnCl_2$ and Negishi cross-coupling with ethyl 4-iodobenzoate, the tetrasubstituted styrene derivative *R*-**49f** was obtained in 74%

yield (e.r. = 95:5). Enantiomer *S*-**40f** (e.r. = 97:3) was exposed to the same reaction conditions, affording *S*-**49f** in 70% yield (e.r. = 96:4).



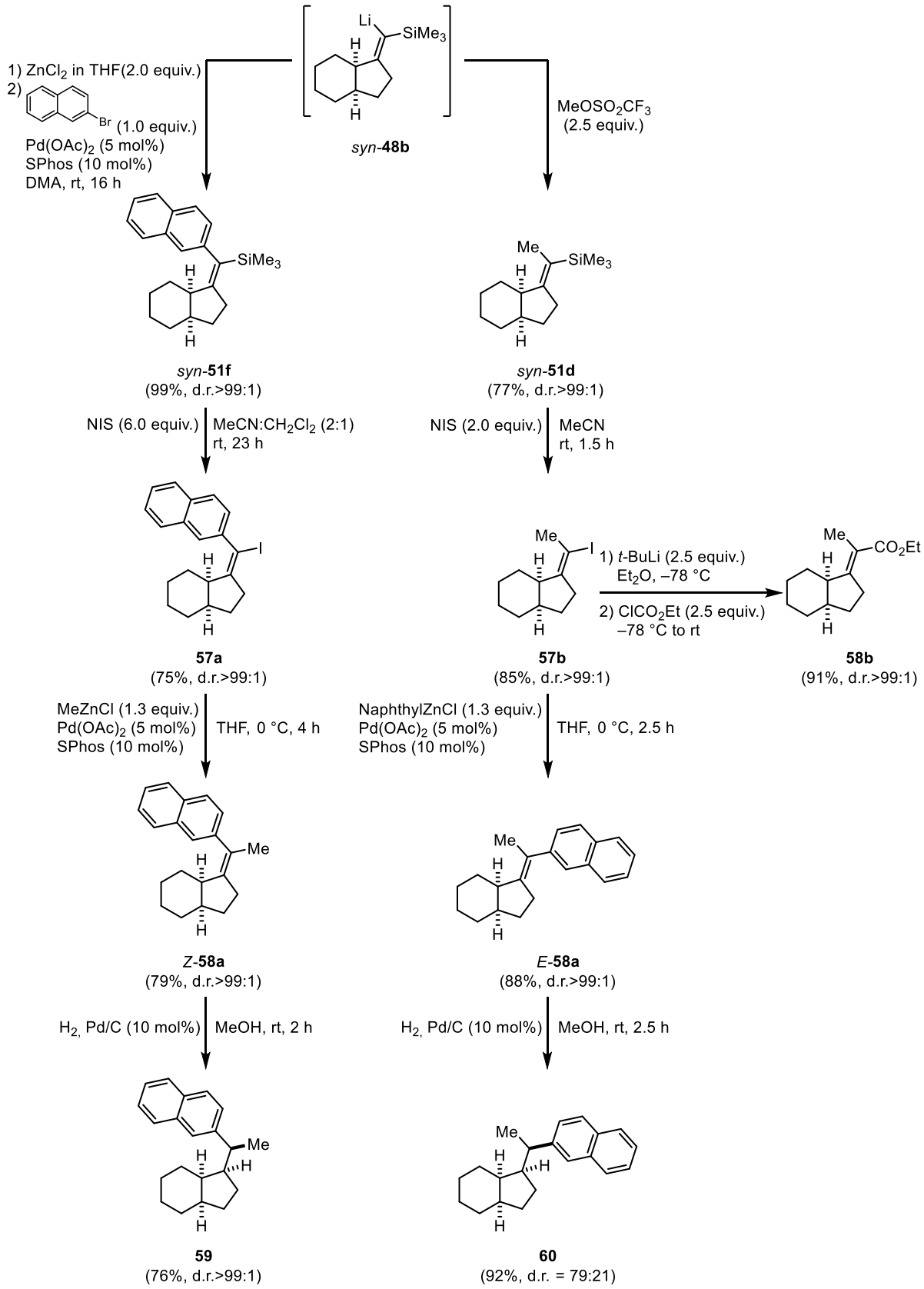
Scheme 22: Enantioselective synthesis of cyclopentane derivatives *R*-**49f** and *S*-**49f**.

Bicyclic ring systems can be build up with full stereocontrol of four contiguous centres using the described intramolecular carbolithiation (Scheme 23). Thus, the two alkenylsilanes *syn*-**51f** and *syn*-**51d** were converted with retention of configuration to the corresponding alkenyl iodides **57a** and **57b** using NIS in acetonitrile/dichloromethane at 25 °C for 2–23 h to obtain the alkenyl iodides **57a** and **57b** in 75–80% yield. The relative configuration was verified by NOESY experiments. Stereoselective Negishi cross-coupling with methylzinc chloride and 2-naphthylzinc chloride respectively (5 mol% $Pd(OAc)_2$, 10 mol% SPhos, 0 °C, 2.5–4 h) provides *Z*-**58a** and *E*-**58a** in 79–88% yield (d.r.>99:1).[a]

I/Li-exchange of the alkenyl iodide **57b** with *t*-BuLi at −78 °C and quenching with ethyl chloroformate gave ester **58b** in 91% (d.r.>99:1).[II] Exo-hydrogenation of *Z*-**58a** and *E*-**58a** using H_2 (1 atm) in the presence of 10 mol% Pd/C in MeOH (25 °C, 2–2.5 h) furnished the two epimeric *cis*-bicyclo[4.3.0]nonanes **59** and **60** in 76–92%. The relative configuration of **59** was established by X-ray analysis (Figure 4). The relative configuration of **60** was verified by NOESY experiments.

[a] The relative configuration of *Z*-**58a** and *E*-**58a** was verified by NOESY experiments.

[II] The relative configuration of **58b** was verified by NOESY experiments.



Scheme 23: Preparation of cis-bicyclic[4.3.0]nonanes bearing four contiguous stereocentres.

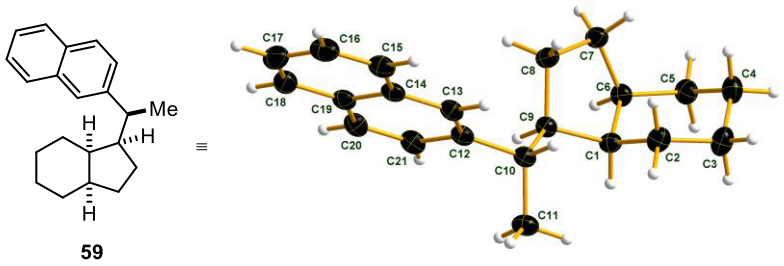
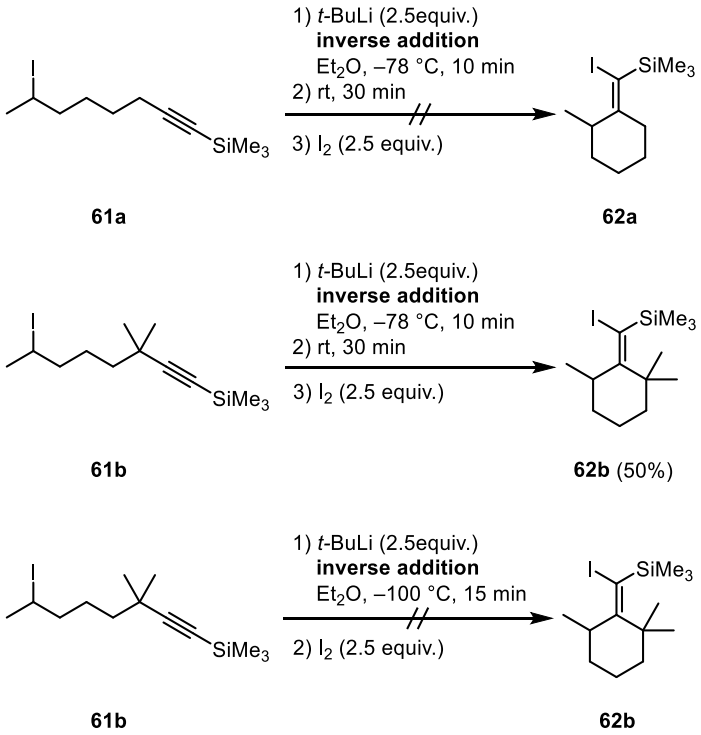


Figure 4: X-ray crystallographic structure of **59**.

3.4 Synthesis of Cyclohexane Derivatives

In a next step, we tried to apply the method to the construction of six-membered ring systems. Both, Bailey and Negishi describe an iodine/lithium-exchange reaction of 7-iodohept-1-yne with *t*-BuLi in a mixture of hexane and Et_2O at −78 °C, and a subsequent intramolecular carbolithiation, affording the cyclohexane derivatives at room temperature. The product was obtained in 48–50% yield. Bailey identified an allene formation as competitive process.[37,56]

Applying the reaction conditions described in the literature to the secondary iodide **61a**, it was not possible to detect the desired cyclisation product **62a** (Scheme 24). Therefore, *gem*-dimethyl groups were introduced at the propargylic position of the 6-heptynyl iodide to prevent an allene formation as side-product, and to benefit from the Thorpe-Ingold effect.[78] In fact, it was possible to obtain **62b** after iodine/lithium-exchange of **61b** with *t*-BuLi (2.5 equiv., −78 °C), 6-*exo*-cyclisation at room temperature and iodination.



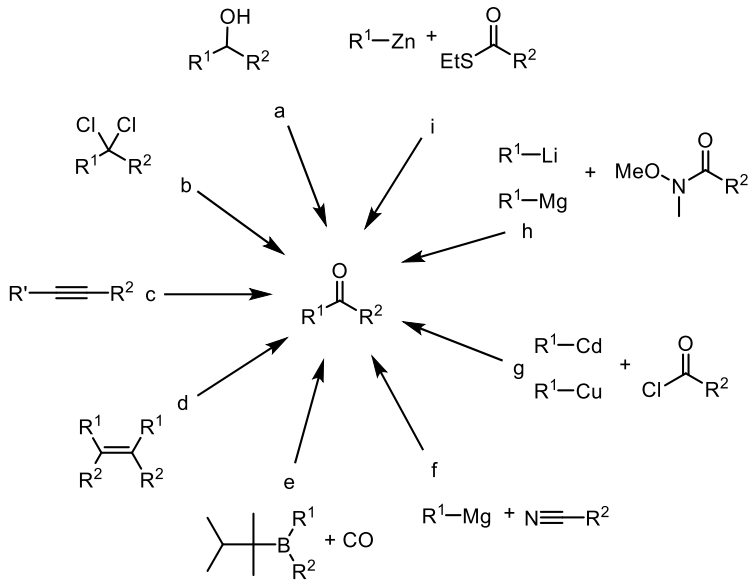
Scheme 24: Different conditions for the I/Li-exchange of secondary iodides and the intramolecular carbolithiation.

The reaction was carried out at −100 °C for 15 min, so that an iodine/lithium-exchange could be performed in a diastereoselective fashion, but no cyclisation product was observed. For this reason, new reaction conditions need to be developed to prepared cyclic compounds diastereoselectively, which contain more than five carbon atoms in the ring.

4 Results: Intramolecular Acylation Reactions

4.1 Introduction

Nowadays, lots of different methods for the preparation of ketones are known. In Scheme 25, some synthetic pathways are shown.



Scheme 25: Different methods for the preparation of aliphatic ketones.

Ketones can be prepared by: a) oxidation of secondary alcohols,[79] b) hydrolysis of *gem*-dihalides,[80] c) hydration of alkynes,[81] d) ozonolysis of alkenes,[82] e) Brown hydroboration, followed by oxidation,[83] f) reaction of Grignard reagents with nitriles, followed by hydrolysis,[84] g) acylation of organocadmium or organocopper with acid chlorides,[85,86] h) organolithiums or Grignard reagents with Weinreb amides[87] and i) a Fukuyama coupling.[88]

Ketones are present in different drugs, such as Unoprostone,[89] Megestrol acetate[90] and Oxycodone,[91] and are important intermediates in natural product synthesis because they can be further transformed into different functional groups.

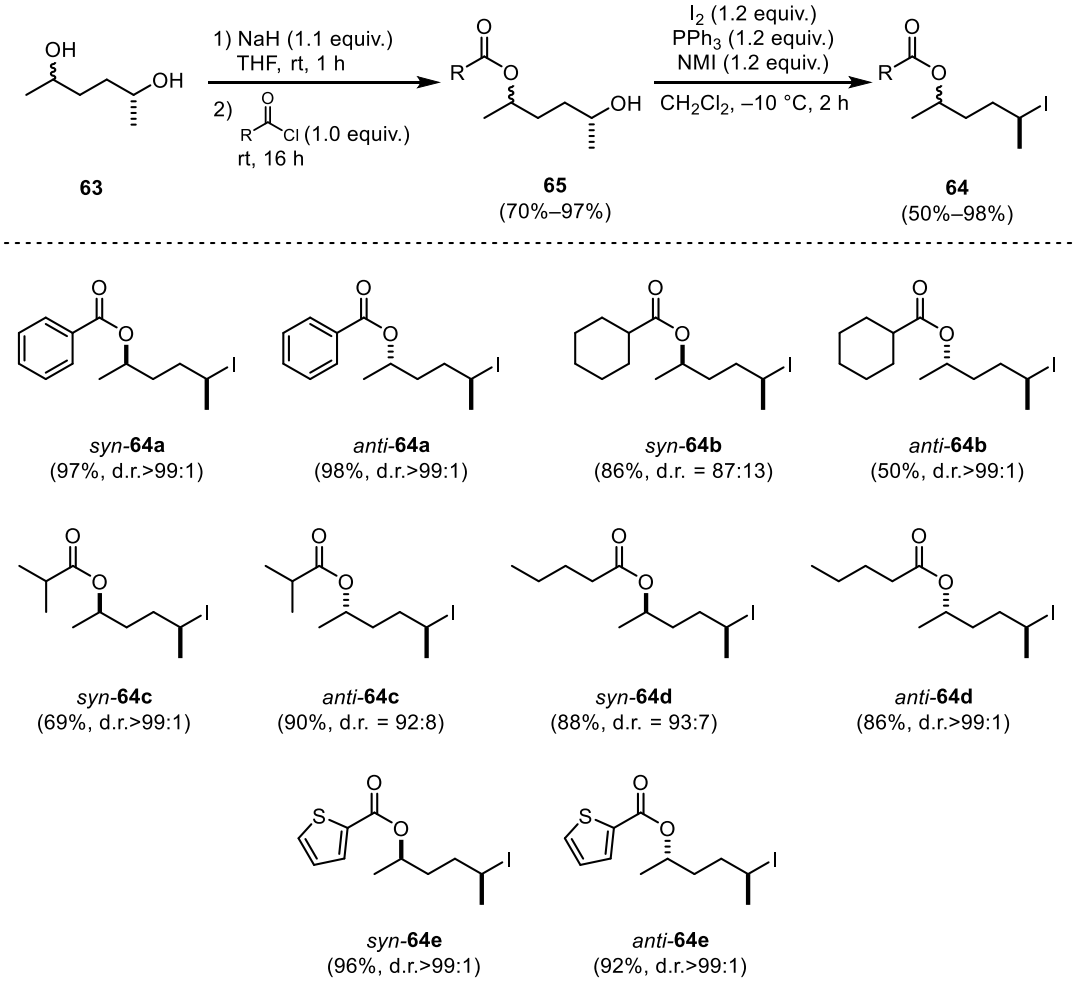
Recently, a method for the preparation of unstabilised, secondary alkyllithiums was developed by Knochel *et al*. Unfortunately, acylation reactions afforded, even after transmetalation to copper, the desired ketones only in moderate yields and with a significant loss of diastereoselectivity.[18–20,57,92]

Therefore, we developed a method for the stereoselective synthesis of ketones based on Barbier-type conditions starting from easily accessible diols. To the best of our knowledge, only primary halides have

been used so far. The method was applied to stereodefined, secondary alkyl iodides, so two stereocentres could be controlled at once.

4.2 Intramolecular Acylation Reactions of Unstabilised Secondary Alkyllithiums

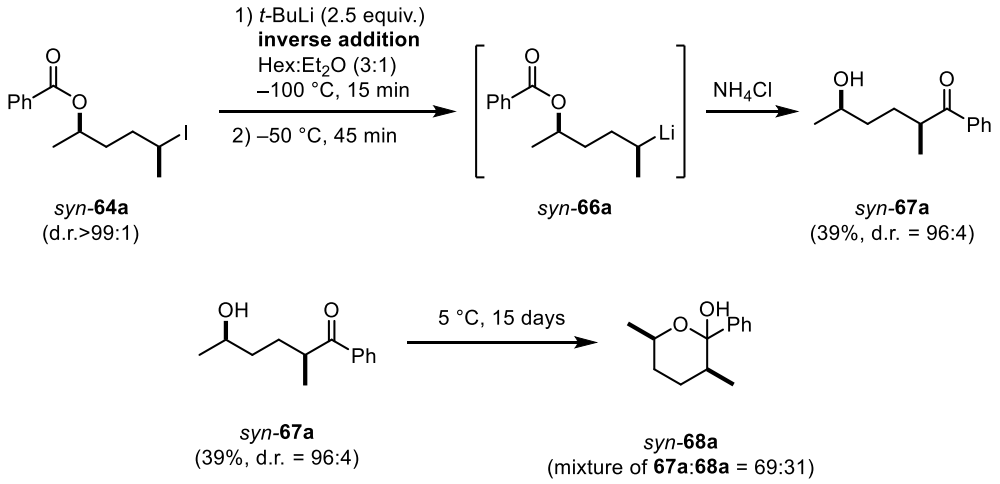
For the synthesis of the starting material, the two diastereoisomers of hexane-2,5-diol **63** were separated using the method described by Kazlauskas.[93] Afterwards, the secondary iodoesters of type **64** were prepared by esterification of alcohol **63** with different acyl chlorides to form esters of type **65** (70–97% yield, >99% retention).[III] Performing an iodination under Appel-type conditions[62,63] gave the desired iodides **64a–e** with inversion of the configuration (50–98% yield, >88% retention).



Scheme 26: Preparation of iodoesters **64** from the corresponding alcohols **63**.

[III] The percentage of the racemisation was calculated in the following way:
[d.r.(starting material)−d.r.(product)]/[d.r.(starting material)].

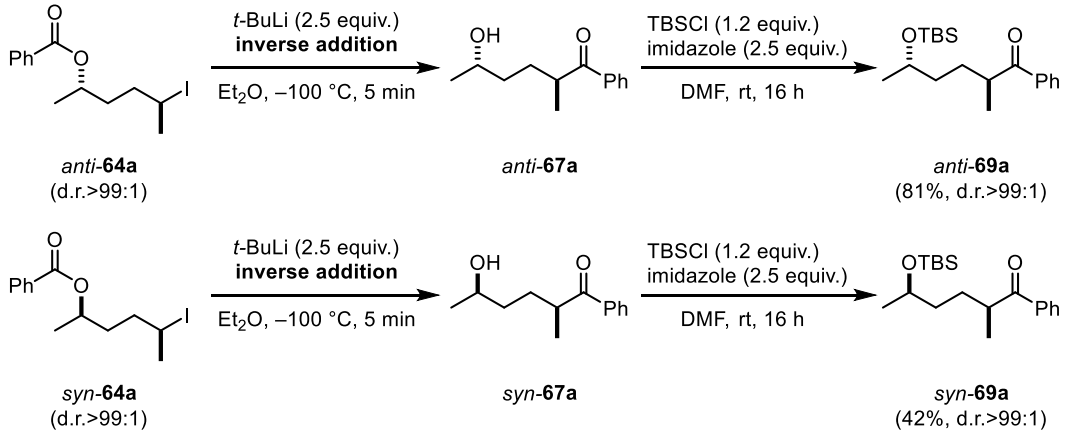
In the next step, iodide *syn*-**64a** was subjected to *t*-BuLi (2.5 equiv., inverse addition) in hexane:diethyl ether (3:1) at –100 °C for 15 min and then stirred at −50 °C for 45 min. As expected, an iodine/lithium-exchange occurred and the *t*-BuLi did not directly attack the ester group of the molecule, indicating the high speed of the exchange reaction of the iodide by *t*-BuLi.[94] After formation of the lithium species *syn*-**66a**, a [1,5]-migration of the acyl-group was observed, and the resulting ketone *syn*-**67a** was obtained after an aqueous quench in 39% yield and d.r. = 96:4 (Scheme 27).



Scheme 27: I/Li-exchange of iodide *syn*-**64a** and subsequent intramolecular transfer of the acyl group gave ketone *syn*-**67a**. After 15 d, lactol *syn*-**68a** was observed by NMR.

However, after 15 d in the fridge, ketone *syn*-**67a** was partly converted to lactol *syn*-**68a** by an intramolecular nucleophilic addition of the remaining hydroxyl group to the carbonyl group. This transformation was detected by NMR-analysis. The carbonyl signal of the keto-group was shifted in the ^{13}C-spectrum from 204.4 ppm to 104.9 ppm, where hemiacetals can be found. For that reason, all alcohols of type **67** were directly protected with a TBS-group after the reaction sequence.

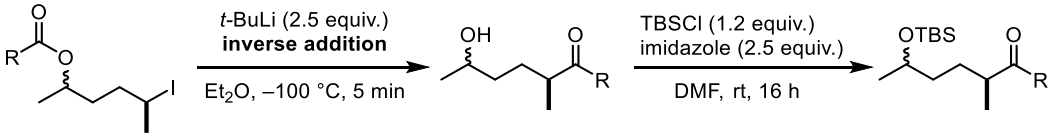
Changing the solvent system from hexane:diethyl ether (3:1) to pure diethyl ether allowed the completion of the reaction at −100 °C within 5 min and a full retention of the configuration. Thus, TBS-protected ketone *anti*-**69a** was obtained in 81% yield and d.r.>99:1. Subjecting *syn*-**64a** (d.r. >99:1) to the same reaction condition afforded *syn*-**69a** in 42% yield, d.r.>99:1 (Scheme 28).

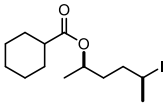
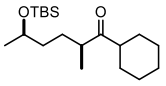
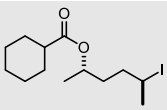
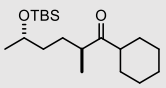


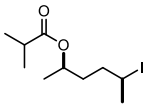
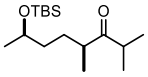
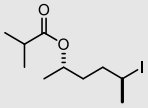
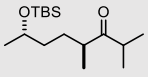
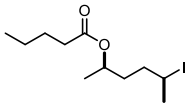
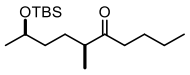
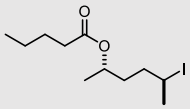
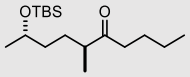
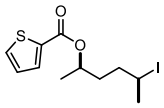
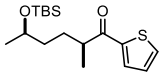
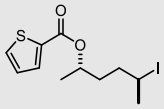
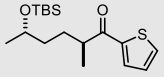
Scheme 28: Preparation of ketones *anti*-**69a** and *syn*-**69a** *via* I/Li-exchange.

The reaction sequence was extended to other starting materials as shown in Table 3. The cyclohexyl-derivatives *syn*-**64b** (d.r. = 87:13) and *anti*-**64b** (d.r.>99:1) gave, after iodine/lithium-exchange and TBS-protection, *syn*-**69b** (d.r. = 90:10) and *anti*-**69b** (d.r. = 92:8) in 34–64% yield. *i*-Propyliodoesters *syn*-**64c** (d.r.>99:1) and *anti*-**64c** (d.r. = 92:8) gave under standard conditions *syn*-**69c** (d.r.>99:1) and *anti*-**69c** (d.r. = 90:10) in 47–50% yield. The stereoselective performance of an iodine/lithium-exchange and subsequent intramolecular acylation on *syn*-**64d** (d.r. = 93:7) and *anti*-**64d** (d.r.>99:1), respectively, produced *syn*-**69d** (d.r. = 91:9) and *anti*-**69d** in 20–39% yield (d.r. = 98:2). Also, the heterocyclic iodoesters *syn*-**64e** (d.r.>99:1) and *anti*-**64e** (d.r.>99:1) were used under standard conditions to afford ketones *syn*-**69e** (d.r>99:1) and *anti*-**69e** in 21–38% yield (d.r.>99:1).

Table 3: Products obtained after I/Li-exchange and intramolecular transfer of the acyl group.

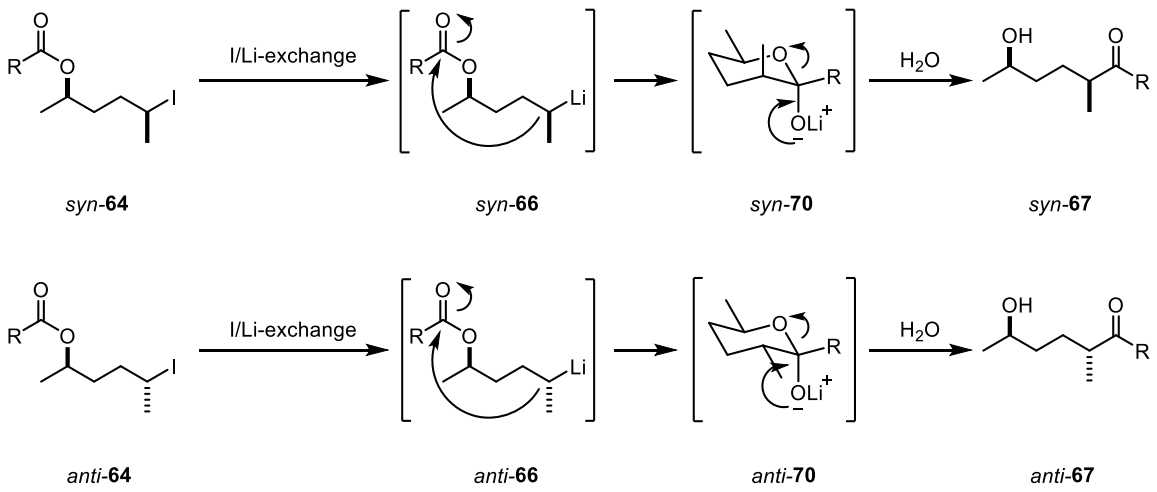


Entry	Starting Material	Product [a]
		
1	*syn*-**64b**	*syn*-**69b**
	d.r. = 87:13	34%, d.r. = 90:10
		
2	*anti*-**64b**	*anti*-**69b**
	d.r.>99:1	64%, d.r. = 92:8

		
3	*syn*-**64c**	*syn*-**69c**
	d.r.>99:1	50%, d.r.>99:1
		
4	*anti*-**64c**	*anti*-**69c**
	d.r. = 92:8	47%, d.r. = 90:10
		
5	*syn*-**64d**	*syn*-**69d**
	d.r. = 93:7	20%, d.r. = 91:9
		
6	*anti*-**64d**	*anti*-**69d**
	d.r.>99:1	39%, d.r. = 98:2
		
7	*syn*-**64e**	*syn*-**69e**
	d.r.>99:1	38%, d.r.>99:1
		
8	*anti*-**64e**	*anti*-**69e**
	d.r.>99:1	21%, d.r.>99:1

[a] Yields refer to analytically pure products.

Overall, a higher yield was observed for the *anti*-diastereomers of type **69** compared to the *syn*-diastereomers. Therefore, a cyclic transition state, as shown in Scheme 29, is proposed for the mechanism of this reaction. Considering the structure of the *anti*-diastereomer *anti*-**70**, all substituents are in an equatorial position, while in the transition state of the *syn*-diastereomer *syn*-**70**, only one methyl group is equatorial, the other is pointing axial.



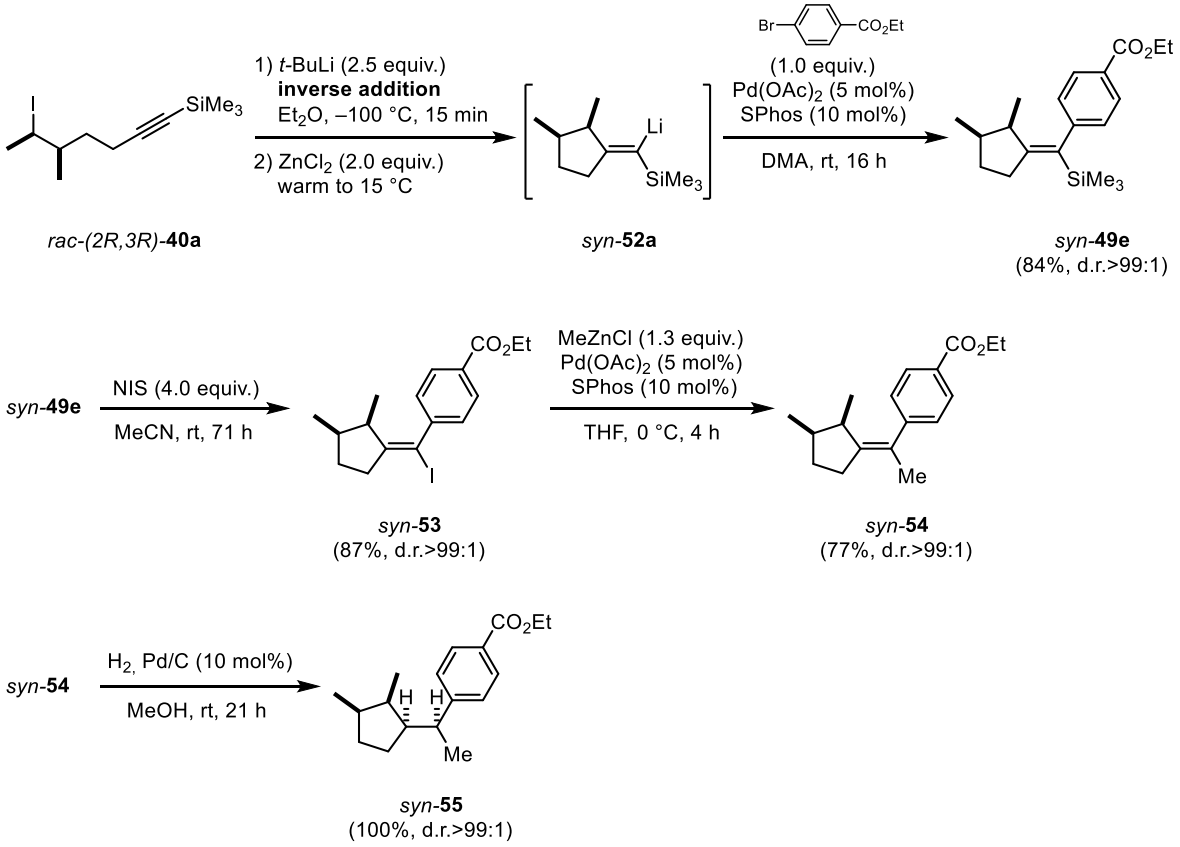
Scheme 29: Proposed mechanism including a cyclic transition state.

In summary, a useful method for the preparation of stereodefined alkyl ketones is described starting from diols that are easily accessible. After an iodine/lithium-exchange, and following transfer of the acyl group *via* a cyclic transition state, ketones **69a–e** were obtained in 21–81% yield and with high stereoretention >93%.

5 Summary and Outlook

Part I of this work focused on the diastereoselective preparation of secondary, unstabilised Li-compounds *via* an iodine/lithium-exchange at −100 °C using *t*-BuLi (inverse addition, 2.5 equiv.) and their application in intramolecular carbolithiation and acylation reactions.

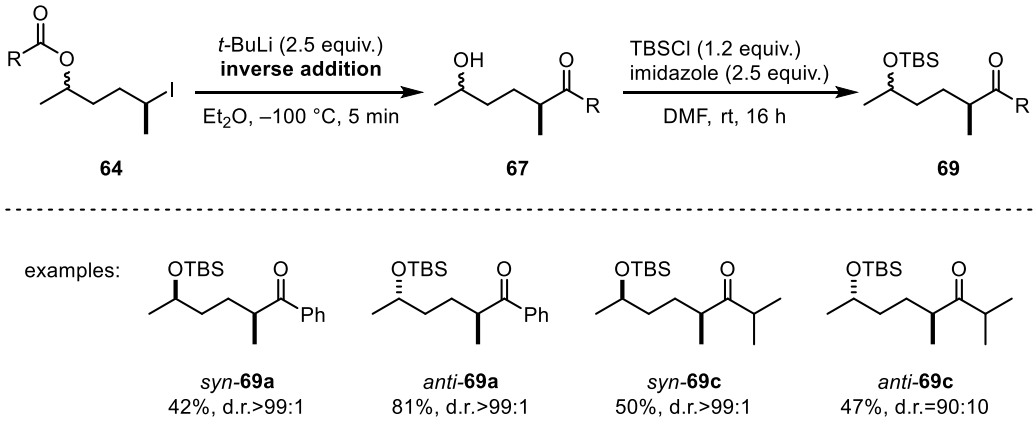
The first topic dealt with the synthesis of various stereodefined cyclopentane derivatives. First, the stereodefined Li-species were generated by iodine/lithium-exchange of secondary iodides bearing an internal alkylidynesilane-moiety. An intramolecular carbolithiation afforded the exo-alkylidene cyclopentane, related *cis*-bicyclo[3.3.0]octane and *cis*-bicyclo[4.3.0]nonane derivatives in excellent diastereoselectivity. The iodine/lithium-exchange was also carried out in an enantioselective fashion, demonstrating a high potential for enantiomeric syntheses. The remaining silane-moiety was successfully transformed into an alkyl group or an iodide, which was further modified. This gave the opportunity to construct up to four contiguous stereocentres in cyclopentanes, as well as in bicyclic ring structures (Scheme 30).



Scheme 30: Example for the preparation of an exo-alkylidene cyclopentane bearing four contiguous stereocentres.

Further applications of these intramolecular carbolithiations in natural product synthesis need to be investigated.

An approach toward the stereoselective synthesis of ketones *via* an intramolecular acylation reaction was developed. Thus, various stereodefined organolithiums were prepared from stereodefined secondary iodoesters. The inverse addition of *t*-BuLi (2.5 equiv.) at −100 °C in diethyl ether triggered the iodine/lithium-exchange. The formed Li-reagents undergo a fast transfer of the acyl group, and different ketones were obtained, which were isolated after protection of the remaining alcohol group (Scheme 31).



Scheme 31: Diastereoselective acyl-transfer after an I/Li-exchange with *t*-BuLi.

Part II: A New Arylthio/Magnesium-Exchange

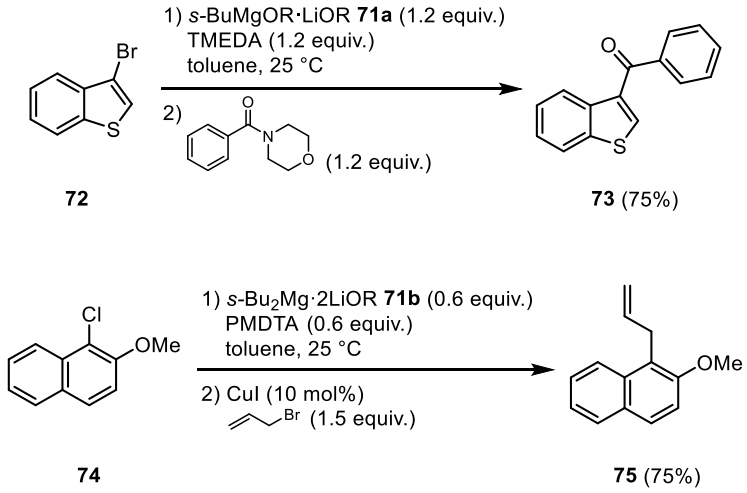
6 Introduction

6.1 Organomagnesium Reagents

Organomagnesium compounds play an important role in organic syntheses and organometallic chemistry.[95] In 1900, Victor Grignard did pioneering work on their synthesis and their broad range of applications. His discovery was honoured with the Nobel Prize in 1912.[96,97] Grignard reagents are sensitive towards air and moisture, requiring careful handling. A common method for the preparation of these reactive magnesium species is the oxidative addition of magnesium into an organohalide bond. This direct insertion can be performed with magnesium turnings, with activated metals, such as Rieke magnesium[98–102] or in the presence of lithium chloride.[103] Another possibility are metalation reactions with magnesium amides such as TMPMg·LiCl and $(TMP)_2Mg$, as reported by Knochel[104] and Eaton.[105] Alternatively, a halogen/magnesium-exchange can be performed. The first example of a bromine/magnesium-exchange reaction was reported in 1931 by Prévost.[106] The exchange reaction is an equilibrium process, in which the more stable organomagnesium compound is formed.[95] A commonly used exchange reagent is *i*-PrMgCl·LiCl (Turbo-Grignard) developed by Knochel *et al.*[107] It turned out that the lithium salt significantly accelerates the bromine/magnesium-exchange.

Only few methods have been reported, in which other than ethereal solvents, such as diethyl ether or THF, have been used. The preparation of dialkylmagnesium species with long alkyl chains has been described in hydrocarbon solvents.[108] Hevia *et al.*[109] reported potassium-alkylmagnesiates ($KMg(CH_2SiMe_3)_3$), which were prepared in hexane and benzene. They can act as a new base for the synthesis of potassium arylmagnesiates in hexane.

Knochel *et al.*[110] developed the new magnesium reagents *s*-$BuMgOCH_2CH(Et)Bu$·$LiOCH_2CH(Et)Bu$ (**71a**) and *s*-Bu_2Mg·$2LiOCH_2CH(Et)Bu$ (**71b**). Those reagents are prepared in toluene and can be used for bromine/magnesium- and chlorine/magnesium-exchanges using TMEDA (*N*,*N*,*N*′,*N*′-tetramethylethylenediamine) or PMDTA (*N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine) as an additive. Treating bromide **72** with *s*-$BuMgOCH_2CH(Et)Bu$·$LiOCH_2CH(Et)Bu$ (**71a**) in the presence of TMEDA and reaction of the Mg-species with morpholino(phenyl)methanone furnished the desired product **73** in 75% yield. After a chlorine/magnesium-exchange of **74** with *s*-Bu_2Mg·$2LiOCH_2CH(Et)Bu$ (**71b**) and PMDTA and allylation with allyl bromide in the presence of copper(I)iodide, the allylated product **75** was isolated in 75% yield (Scheme 32).[110–112]

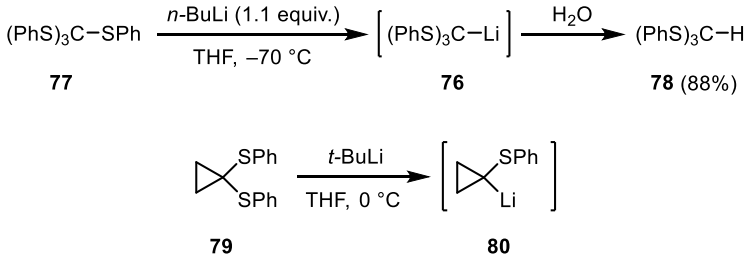


Scheme 32: Br/Mg- and Cl/Mg-exchange with the new Mg-reagents **71a** and **71b** in toluene. R = $CH_2CH(Et)Bu$.

6.2 Arylthio/Metal-Exchange

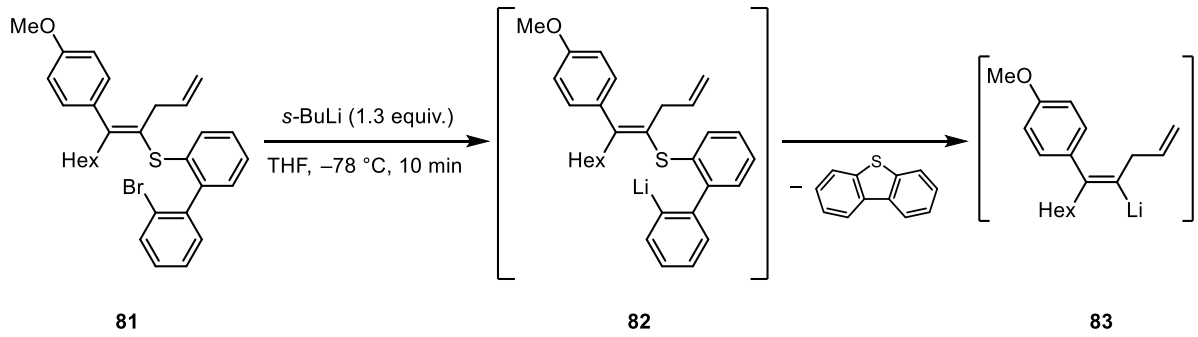
6.2.1 Lithiation with Butyllithium

Already in 1967, Arens[113] and Seebach[114] described the carbanion formation **76**, while treating tetrakis(phenylthio)methane (**77**) with *n*-butyllithium. Such a sulfur-exchange was also described later by Cohen,[115] who converted cyclopropanone dithioketals (**79**) into 1-lithio-1-(phenylthio)cyclopropanes (**80**) using *t*-BuLi (Scheme 33).



Scheme 33: ArS/Li-exchange using butyllithium.

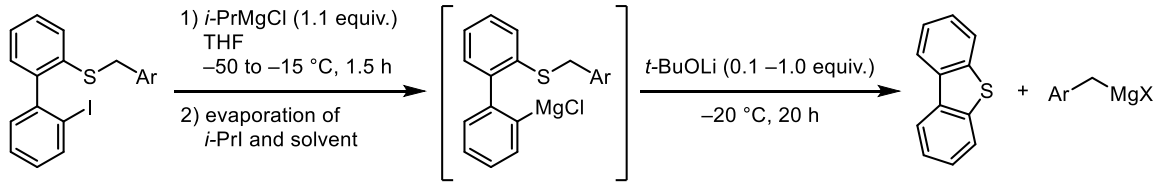
Knochel *et al.*[116] used *s*-BuLi for the stereoselective synthesis of tetrasubstituted alkene *via* a sulfur/lithium-exchange. Bromothioether **81** was treated with *s*-BuLi forming Li-species **82**. The alkenyllithium **83** was then reacted with various electrophiles (Scheme 34).



81 82 83

Scheme 34: Preparation of the alkenyllithium **83** by an intramolecular S/Li-exchange.

This methodology was originally developed for the synthesis of functionalised benzylic magnesium reagents. In this case, an iodothioether **84** was used instead of the bromothioether **81**. Therefore, it was possible to perform an iodine/magnesium-exchange at −50 to −15 °C first, followed by the intramolecular sulfur/magnesium-exchange, triggered by *t*-BuOLi at −20 °C, affording the desired benzylic magnesium species **85**.[117]

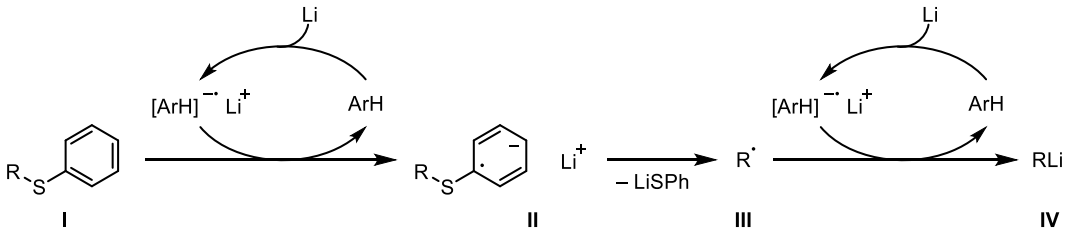


84 86 87 85

Scheme 35: Preparation of benzylic magnesium derivatives **85** by an intramolecular S/Mg-exchange.

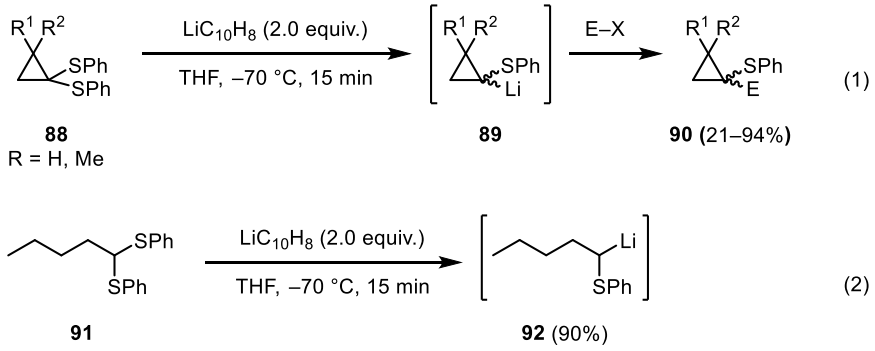
6.2.2 Reductive Lithiation and Magnesiation

Besides sulfur-exchanges using BuLi, reductive metalation can be used. A single-electron transfer (SET) with Li-metal or arene radical anions such as LiDTBB, LDMAN and lithium naphthalenide can trigger the reductive cleavage of the C-S bond. These radical anions are highly reactive and can react as reductant or as base. Considering the mechanism (Scheme 36), the arene radical anion transfers an electron to the phenyl thioether **I** generating a highly reactive radical anion **II** and the arene, which regenerated the arene radical anion in the presence of an excess of lithium. **II** dissociates to the alkyl radical **III** and lithium phenylthiolate. After a second electron transfer the desired lithium compound **IV** can be obtained and used in further reactions.[51]



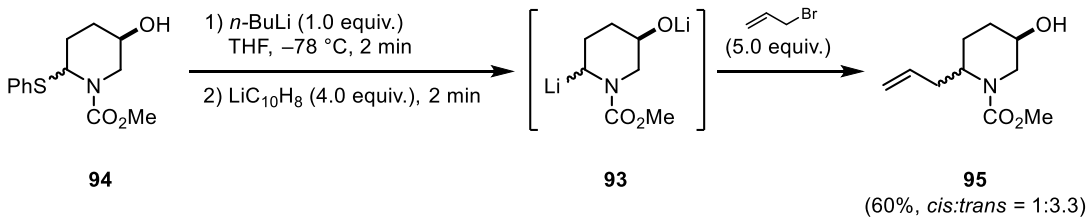
Scheme 36: Mechanism for the S/Li-exchange *via* reductive lithiation.

The first preparation of an α-functionalised organolithium by reductive lithiation was carried out by Cohen *et al.*[118] in 1978 on cyclopropane dithioketal of type **88** (Scheme 37, eq. 1). Treating **88** with lithium naphthalenide (2.0 equiv.) in THF at −70 °C afforded the sulfur-stabilised cyclopropyllithium **89**, which could be trapped with various electrophiles. At the same time Screttas and Micha-Screttas performed a comparable cleavage on *n*-BuCH(SPh)$_2$ (**91**) (Scheme 37, eq. 2).[119,120]



Scheme 37: Reductive lithiation by Cohen (eq. 1), and Screttas and Micha-Screttas (eq. 2).

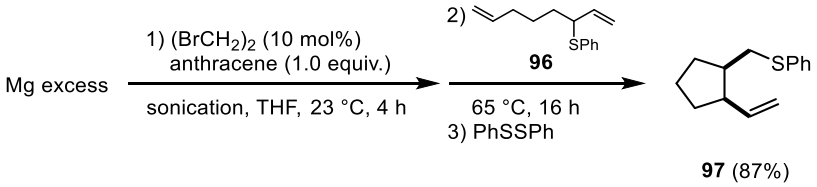
Furthermore, α-lithio cyclic ethers and amines can be prepared by reductive lithiation. Beak[121] reported that *N*-Boc 3-hydroxypiperidine does not undergo lithiation at C-2 or C-6. Later, Gallagher *et al.*[122] were able to achieve the Li-species by reductive lithiation. First, they generated the corresponding alkoxide **93** by adding *n*-BuLi to thioether **94**, followed by the addition of lithium naphthalenide (4.0 equiv.). After allylation, the desired product **95** was obtained in 60% yield, *cis:trans* = 1:3.3 (Scheme 38).



Scheme 38: C(6)-allylation of 3-hydroxypiperidine by reductive lithiation.

The large excess of lithium naphthalenide limits the variety of electrophiles.[122] In 2009, Zheng *et al.*[123] extended this procedure to the synthesis of 3-piperidinol *N*-α-carbanions.

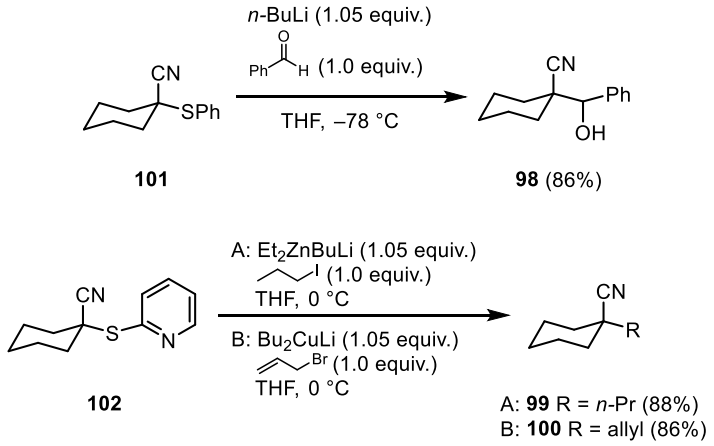
Pioneer work on reductive magnesiation was carried out by Maercker.[124] He reported that allylmagnesiums can be generated by refluxing allyl phenyl sulfides in THF with magnesium powder, which was activated by treating it with 1,2-dibromoethane or iodine. Cheng *et al.*,[125] used a mixture of magnesium powder with 10 mol% of 1,2-dibromoethane and 1.0 equiv. of anthracene in THF and sonicated the mixture for 4 h. Afterwards, the allyl phenyl sulfide **96** was added, the reaction mixture was heated to 65 °C for 16 h, and subsequent addition of the electrophile yielded product **97** in 87% yield (Scheme 39).



Scheme 39: Preparation of an allylmagnesium compound by reductive magnesiation of allyl phenyl sulfide **96** and subsequent carbomagnesiation.

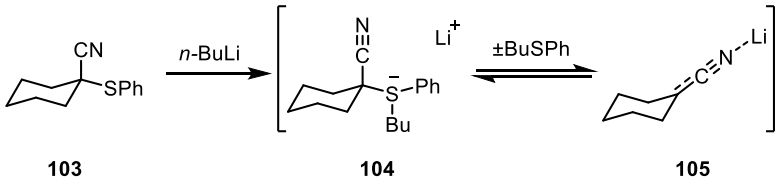
6.2.3 Arylthio/Metal-Exchange Alpha to a Nitrile

Metalated nitriles are readily prepared by an arylthio/metal-exchange. Compared with a sulfoxide/metal-exchange, a sulfide/metal-exchange requires more reactive organometallics.[126] α-Metalated nitriles are powerful nucleophiles due to the small cylindric diameter of the cyano-group and the high charge density at the formally anionic carbon. The generated metalated alkyl nitriles are largely stabilised by inductive electron withdrawal rather than through resonance.[126–129] The arylthio/metal-exchange can be achieved by the addition of *n*-BuLi, *i*-PrMgCl, Bu_3MgLi, $Et_2ZnBuLi$ or Me_2CuLi. Reaction with various electrophiles afforded the desired quaternary nitriles (*e.g.* **98**, **99**, **100**) (Scheme 40).[129] The use of *i*-PrMgCl, Bu_3MgLi, $Et_2ZnBuLi$ or Me_2CuLi was only possible using a 2-pyridylthioalkanenitrile (*e.g.* **102**) or a 2-methoxyphenylthioalkannitrile.[126,129,130]



Scheme 40: Sequential ArS/M-exchange and trapping with electrophiles.

Performing an exchange of cyclohexane derivative **103** with *n*-BuLi or Bu_3MgLi affords a three-coordinated sulfidate **104** as the predominant solution species. Mechanistic studies identified an equilibrium with **105** as reactive species, which is consistent with the loss of the stereochemically defined arylthio nitriles (Scheme 41).[126,129]

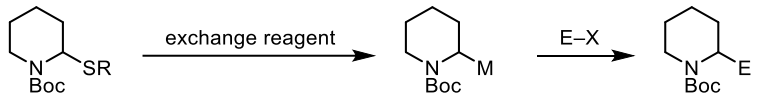


Scheme 41: Mechanism of the ArS/Li-exchange.

7 Project Outline

Arylthio/metal-exchanges are less represented in literature than the corresponding halogen/metal-exchanges. Thioethers are stable compounds, but it is therefore a more challenging task to replace them with a metal.

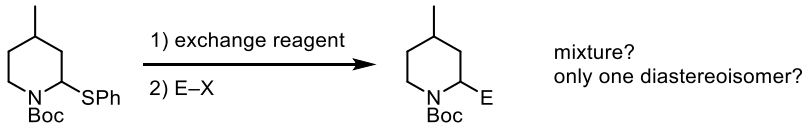
However, a method should be developed to perform an arylthio/metal-exchange (Scheme 42).



Scheme 42: S/M-exchange on Boc-protected piperidine.

N-Boc-Piperidine was chosen as a model compound because the Boc-group might coordinate the metal and would therefore stabilise the metal species. Quenching with different electrophiles would allow us to explore the scope of this methodology.

Furthermore, the use of thioethers containing a second substituent at the piperidine ring should allow us to study the stereochemical behaviour during this reaction (Scheme 43).



Scheme 43: Stereochemical behaviour during the reaction.

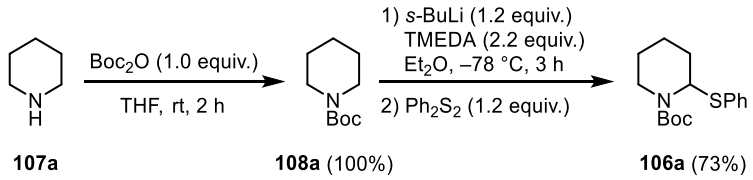
8 Results: A New Arylthio/Magnesium-Exchange

8.1 Introduction

Thioethers are stable compounds, making them a more challenging task in exchange reactions. Reductive lithiation is a common method used in the literature to prepare lithiated species of arylthioethers.[51,119,120,122,123,131]

8.2 Optimisation of the Reaction Conditions

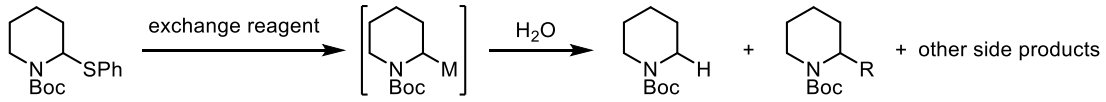
Taking up this challenge, thioether **106a** has been prepared starting from piperidine **107a**. First, the amine was protected using Boc_2O (quant.). In a second step, the thiophenyl group was introduced by deprotonation of the α-position of **108a** using *s*-BuLi and TMEDA in diethyl ether. After deprotonation at −78 °C for 3 h, the lithiated species was reacted with diphenyl disulfide (73% yield).



Scheme 44: Preparation of thioether **106a** from piperidine **107a**.

First, various reaction conditions were tested to find out which organometallic reagent would allow a smooth thiophenol/metal-exchange on thioether **106a** (Table 4). The reactions were monitored by GC using undecane as internal standard. Adding *n*-BuLi in THF at −78 °C to **106a** afforded piperidine **110a** (R = *n*-Bu) in 58% (entry 1). Changing the metal reagent to *s*-BuLi reduced the amount of **110a** (R = *s*-Bu) to 4%, but other unidentified products appeared in 22% (entry 2). *t*-BuLi in Et_2O at −78 °C showed besides starting material **106a**, piperidine **110a** (R = *t*-Bu) and other side products in 57%, 35% and 4% respectively, also 4% of the desired hydrolysis product **108a** (entry 3). No reaction could be observed using Mg-based metal reagents such as Turbo-Grignard (*i*-PrMgCl·LiCl), *n*-BuMgCl·LiCl or *n*-Bu_2Mg in THF at room temperature (entries 4–6). Using the more reactive magnesiate *n*-Bu_3Mg·2LiCl afforded **110a** (R = *n*-Bu) in 68%, but no hydrolysis product **108a** was observed (entry 7). Also using the lanthanum species Bu_2LaMe only afforded **110a** (R = *n*-Bu 53%; R = Me 17%; entry 8). Using the exchange reagent *s*-$BuMgOCH_2CH(Et)Bu$·$LiOCH_2CH(Et)Bu$ (**71a**, 1.2 equiv.) and TMEDA (1.2 equiv.) in the apolar solvent toluene at room temperature gave the desired product **108a** in 36%, remaining starting material **106a** in 49%, and 10% of **110a** (R = *s*-Bu) (entry 9).

Table 4: Screening of different organometallic reagents to perform a SPh/M-exchange on thioether **106a**.



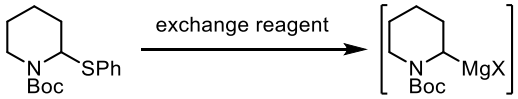
Entry	Reagent	Solvent	Temperature	Observation after 1 h[a]
1	*n*-BuLi (1.2 equiv.)	THF	−78 °C	**106a** (62%), **110a** (58%)
2	*s*-BuLi (1.2 equiv.)	THF	−78 °C	**106a** (74%), **110a** (4%), others (22%)
3	*t*-BuLi (1.2 equiv.)	Et_2O	−78 °C	**108a** (4%), **106a** (57%), **110a** (35%), others (4%)
4	*i*-PrMgCl·LiCl (1.2 equiv.)	THF	rt	no reaction
5	*n*-BuMgCl·LiCl (1.2 equiv.)	THF	rt	no reaction
6	*n*-Bu_2Mg (1.2 equiv.)	THF	rt	no reaction
7	*n*-Bu_3MgLi·LiCl (1.2 equiv.)	THF	rt	**106a** (32%), **110a** (68%)
8	Bu_2LaMe (0.7 equiv.)	THF	−30 °C	**106a** (30%), **110a** (Me: 17%; *n*-Bu 53%)
9	*s*-BuMgOR·LiOR **71a** (1.2 equiv.), TMEDA (1.2 equiv.)	toluene	rt	**108a** (36%), **106a** (49%), **110a** (10%), others (5%)

R = $CH_2CH(Et)Bu$; [a] Yields were obtained by GC-analysis.

Knochel *et al.* recently developed the preparation of Grignard reagents of type *s*-$BuMgOCH_2CH(Et)Bu \cdot LiOCH_2CH(Et)Bu$ (**71a**) and *s*-$Bu_2Mg \cdot 2LiOCH_2CH(Et)Bu$ (**71b**) in toluene. These Grignard reagents are of high interest to industry due to new reactivities in apolar solvents, as well as for ecological reasons and improved water extraction processes during the work-up.[110–112]

To determine the optimum reaction conditions for performing a thiophenol/magnesium-exchange using the magnesium reagent *s*-BuMgOR·LiOR **71a** (R = $CH_2CH(Et)Bu$) in toluene, the exchange rate of thioether **106a** was examined, which goes on to provide the corresponding Grignard reagent **109a** under various conditions (Table 5). First, magnesium alkoxide $MgOCH_2CH(Et)Bu$ (1.2 equiv.) and TMEDA (1.2 equiv.) were used, but no reaction was observed even after 6 h (entry 1). However, using *s*-BuMgOR·LiOR (**71a**, 1.2 equiv.) and TMEDA (1.2 equiv.) led to a conversion of 60%, and the desired product **108a** was observed in 45% yield (entry 2). In the absence of TMEDA, no product formation was detected. Only the alkylated piperidine derivative was observed in 36% yield (entry 3). Increasing the equivalents of exchange reagent **71a** and TMEDA to 3.0 equiv., a higher conversion (82%) of the starting material **106a** was observed, however the desired product was afforded in only 41% yield (entry 5). Adding *s*-BuMgOR·LiOR (**71a**, 3.0 equiv.) *via* a syringe pump (0.05 mL/min) to **106a** was shown to be crucial leading to **108a** in 71% (entry 6).

Table 5: Screening of different conditions to perform a SPh/M-exchange in thioether **106a** using *s*-BuMgOCH$_2$CH(Et)Bu·LiOCH$_2$CH(Et)Bu.



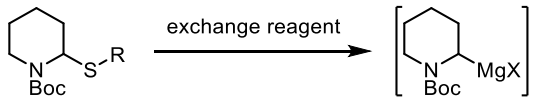
106a **109a**

Entry	Reagent	TMEDA (equiv.)	Observation after 6 h[a]
1	MgOR (1.2 equiv.)	1.2	no reaction
2	*s*-BuMgOR·LiOR (1.2 equiv)	1.2	**108a** (45%), **106a** (40%), others (15%)
3	*s*-BuMgOR·LiOR (1.2 equiv.)	–	**106a** (64%), others (36%)
4	*s*-BuMgOR·LiOR (3.0 equiv.)	3.0	**108a** (41%), **106a** (18%), others (41%)
5	*s*-BuMgOR·LiOR (3.0 equiv.)[b]	3.0	**108a** (71%), **106a** (18%), others (11%)

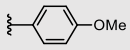
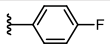
[a] Yields were obtained by GC-analysis. [b] Addition of *s*-BuMgOR·LiOR *via* syringe pump (0.05 mL/min).

Also, the behaviour of different thioethers has been studied. Thioethers **106b**–**d** have been prepared by deprotonation of Boc-protected piperidine (**108a)** with *s*-BuLi at –78 °C, and quenching with the appropriate disulfide or thiosulfonate. Thioethers **106b**–**d** were treated with the two exchange reagents *s*-BuMgOR·LiOR (**71a**) and *s*-Bu$_2$Mg·2LiOR (**71b**) to find the optimal thiolate-residue for this exchange reaction (Table 6). Subjecting the Me-thiolate **106b** to *s*-BuMgOR·LiOR (**71a**, 3.0 equiv.), the reaction showed a lower conversion compared to the Ph-thiolate derivative **106a** (Table 6, entry 1). Introduction of an electron-donating group, like OMe, to the phenyl ring leads to 57% of the desired hydrolysis product **108a** with *s*-BuMgOR·LiOR (**71a**, 3.0 equiv.) (entry 2). Using *s*-Bu$_2$Mg·2LiOR (**71b**, 1.5 equiv.) as exchange reagent in combination with TMEDA (3.0 equiv.) afforded 44% of the desired product **108a** and 30% of side products (entry 3). PMDTA (1.5 equiv.) as additive favoured the formation of side products (62%) in comparison to **108a** (6%, entry 4). Changing the thiolate residue to 4-fluorobenzene, lowered the yield of the desired product **108a** to 38% using *s*-BuMgOR·LiOR (**71a**) and TMEDA (entry 5). Surprisingly, the reaction with *s*-Bu$_2$Mg·2LiOCH$_2$CH(Et)Bu (**71b**, 1.5 equiv.) and TMEDA (3.0 equiv.) furnished 70% of the hydrolysis product **108a** and only 8% of side products were detected (entry 6). Using PMDTA (1.5 equiv.) as additive again favoured the formation of side products (65%) compared to **108a** (5%, entry 7).

Table 6: Screening of different thioethers to perform a SR/Mg-exchange in toluene and subsequent hydrolysis.



106b–d **109a**

Entry	R =	Reagent[a]	Additive	Observation after 6 h
1	Me **106b**	*s*-BuMgOR·LiOR **71a** (3.0 equiv.)	TMEDA (3.0 equiv.)	**108a** (49%), **106a** (51%)
2	 **106c**	*s*-BuMgOR·LiOR **71a** (3.0 equiv.)	TMEDA (3.0 equiv.)	**108a** (57%), **106a** (43%)
3		*s*-Bu_2Mg·2LiOR **71b** (1.5 equiv.)	TMEDA (3.0 equiv.)	**108a** (44%), **106a** (26%), others (30%)
4		*s*-Bu_2Mg·2LiOR **71b** (1.5 equiv.)	PMDTA (1.5 equiv.)	**108a** (6%), **106a** (32%), others (62%)
5	 **106d**	*s*-BuMgOR·LiOR **71a** (3.0 equiv.)	TMEDA (3.0 equiv.)	**108a** (38%), **106a** (62%)
6		*s*-Bu_2Mg·2LiOR **71b** (1.5 equiv.)	TMEDA (3.0 equiv.)	**108a** (70%), **106a** (22%), others (8%)
7		*s*-Bu_2Mg·2LiOR **71b** (1.5 equiv.)	PMDTA (1.5 equiv.)	**108a** (5%), **106a** (30%), others (65%)

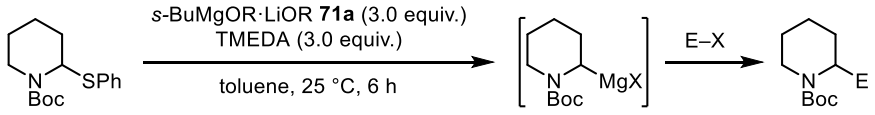
[a] Addition of exchange reagent *via* syringe pump (0.05 mL/min).

8.3 Reaction with Electrophiles

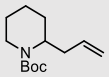
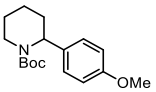
With optimised conditions in hand (*s*-BuMgOR·LiOR (**71a**, 3.0 equiv.) and TMEDA (3.0 equiv.), rt, 6 h), magnesium species **109a** was reacted with various electrophiles. After hydrolysis, *N*-Boc piperidine (**108a**) was isolated in 79% yield. Deuterolysis afforded the desired product **110b** in 70% yield. The deuterated amount of the material, determined by ^{1}H-NMR, was >97%. Direct quenching of the magnesium species **109a** with *S*-methyl phenylthiosulfonate gave thioether **106b** in 85% yield. Also, an allylation reaction with allyl bromide in the presence of CuCN·2LiCl[132] was performed, and the allylated product **110c** was obtained in 52%. Reducing the metalation time to 2 h, afforded product **110c** only in 34%.

After exchange of the phenyl thiolate of **106a**, transmetalation of the magnesium species **109a** with $ZnCl_2$ and Negishi cross-coupling with 4-iodoanisole, $Pd(dba)_2$ (5 mol%) and SPhos (10 mol%) afforded the cross-coupling product **110d** in 25% yield.

Table 7: Products obtained after SPh/Mg-exchange of thioether **106a**.

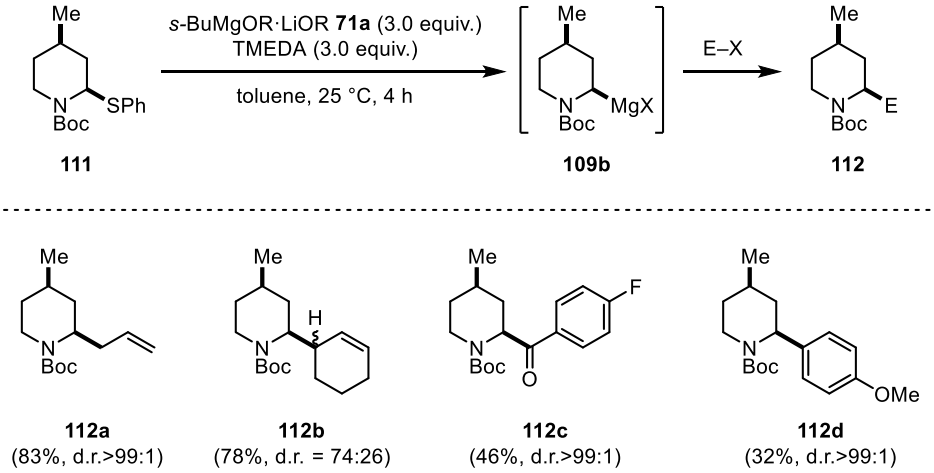


106a **109a**

Entry	Electrophile	Product [a]
1	H_2O	 **108a**; 79%
2	$AcOD/D_2O$	 **110b**; 70%
3	$MeSSO_2Ph$	 **106b**; 85%
4	allyl bromide	 **110c**; 52%[b]
5	4-iodoanisole	 **110d**; 25%[c]

[a] Yields refer to analytically pure products. [b] In the presence of CuCN·2LiCl (0.30 equiv.). [c] After transmetalation with $ZnCl_2$ and with $Pd(dba)_2$ (5 mol%), SPhos (10 mol%).

In the next step, *t*-butyl *syn*-4-methyl-2-(phenylthio)piperidine-1-carboxylate (**111**) was used as starting material to perform the developed thiophenol/magnesium-exchange reaction. The synthesis of thioether **111** was carried out in a similar way as for the other thioethers before in 72% yield (d.r.>99:1) over two steps. The optimal exchange reaction time with *s*-BuMgOR·LiOR (**71a**, 3.0 equiv.) and TMEDA (3.0 equiv.) was discovered to be 4 h at room temperature (82% conversion).



Scheme 45: SPh/Mg-exchange reaction of thioether **111** using *s*-BuMgOR·LiOR (**71a**) and TMEDA.

To our delight, subjecting this thioether **111** to standard thiophenol/magnesium-exchange conditions with *s*-BuMgOR·LiOR (**71a**) in combination with TMEDA and subsequent copper-catalysed allylation reaction with allyl bromide, only the *syn*-isomer of the allylated product **112a** was obtained in 83% yield (Scheme 45). Performing an allylation reaction of magnesium species **109b** with 3-bromocyclohexene and CuCN·2LiCl provided the allylated product **112b** in 78% yield and d.r. = 74:26. After reaction of **109b** with 4-fluorobenzoyl chloride in the presence of CuCN·2LiCl (0.3 equiv.), the acylated product **112c** was obtained in 46% (d.r.>99:1). X-ray crystallographic analysis confirmed the *syn*-relative stereochemistry (Figure 5).

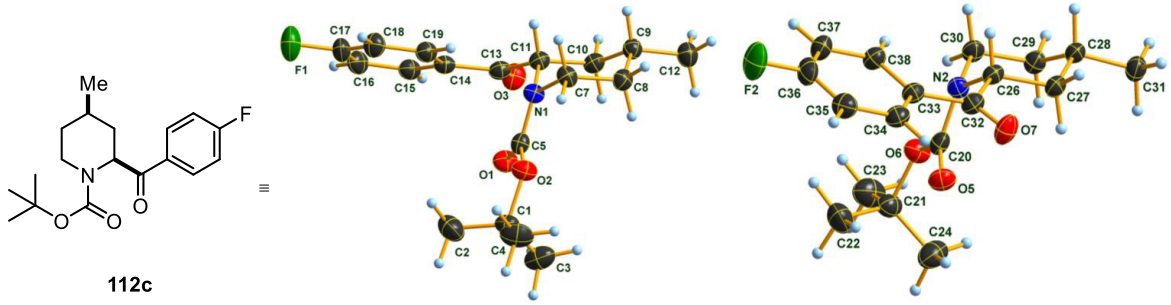


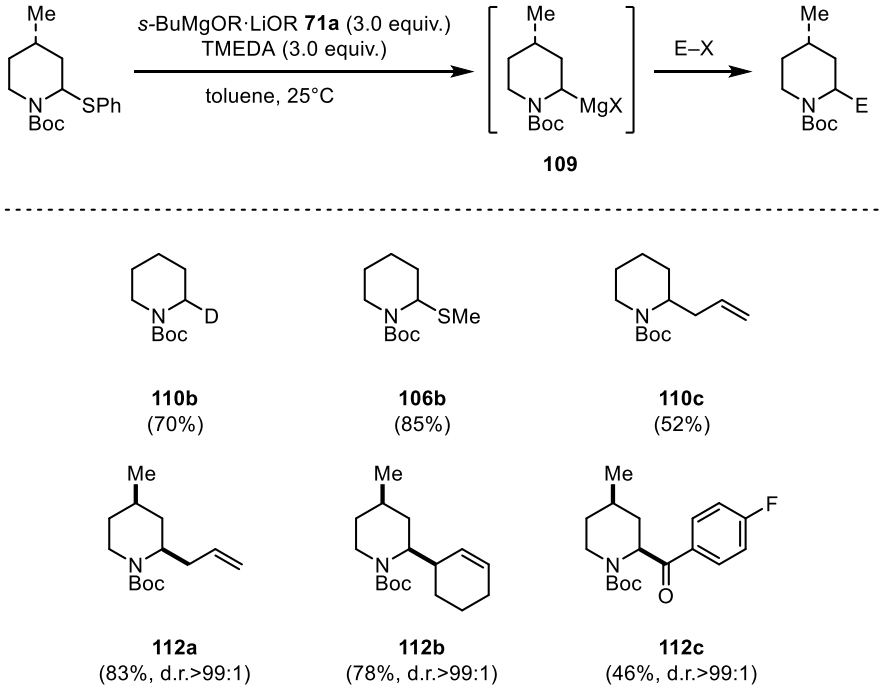
Figure 5: X-ray crystallographic structure of the acyl compound **112c**.

Transmetalation of **109b** with $ZnCl_2$ and following Negishi cross-coupling with 4-iodoanisole, $Pd(dba)_2$ (5 mol%) and SPhos (10 mol%) furnished cross-coupling product **112d** in 32% yield and d.r.>99:1 (Scheme 45).

Further studies of the thiophenol/magnesium-exchange on different heteroatom-substituted alkanes and the extension of the electrophile scope are under investigation in our laboratories.

9 Summary and Outlook

The second part of this work focused on the development of a new sulfur/metal-exchange on piperidyl thioethers. Treating piperidyl thioether **106a** and **111** with *s*-BuMgOCH$_2$CH(Et)Bu·LiOCH$_2$CH(Et)Bu (**71a**) in toluene at room temperature produced the desired magnesium species **109**. After reaction with different electrophiles the desired products were obtained. If a second residue is present in the piperidyl ring only the thermodynamic product is formed after quenching with electrophiles (Scheme 46).



Scheme 46: Treatment of thioethers with *s*-BuMgOCH$_2$CH(Et)Bu·LiOCH$_2$CH(Et)Bu **71a** in the presence of TMEDA and reaction with different electrophiles.

In further studies, the mechanism of this reaction should be examined. The scope of various electrophiles need to be extended and a thorough screening of reaction conditions will be required for the realization of such an exchange on other hetero-substituted cycloalkanes such as pyrrolidine and tetrahydropyranes.

Experimental Part

10 General Information

All air-sensitive experiments were carried out under an argon atmosphere sealed with rubber septa. All glassware was flame-dried prior to use. Air and moisture-sensitive liquids were transferred via syringe which were purged with argon prior to use. Low temperature reactions were carried out in Dewar vessel filled with cooling agents: methanol/liquid nitrogen (−100 °C), acetone/dry ice (−78 °C), water/ice (0 °C) or using a *HUBER T100* cryostat. Reaction temperatures above 23 °C were carried out in an oil bath. The reactions were monitored by GC, NMR spectroscopy or analytical thin-layer chromatography (TLC), using aluminium plates precoated with silica gel (*Merck* 60, F-254). The TLC-plates were visualised by exposure to ultraviolet light (UV) and/or stained with one of the solutions given below followed by heating with a heat gun:

Phosphomolybdic Acid (PMA): phosphomolybdic acid (10 g) in 100 mL absolute ethanol

Potassium Permanganate: $KMnO_4$ (3 g), K_2CO_3 (20 g), KOH (1.3 g) in 300 mL water

Ninhydrin: ninhydrin (750 mg) in 250 mL absolute ethanol and 25 mL acetic acid

Flash-column chromatography was performed using silica gel 60 SiO_2, 0.040–0.063 mm, 230–400 mesh ASTM) from Merck. Yields refer to chromatographically and spectroscopically (^1H and ^{13}C NMR) pure material.

Solvents and Reagents

Solvents were dried according to standard procedures by distillation over drying agents and stored under argon. Dichloromethane was predried over calcium chloride and distilled from calcium hydride. Diethyl ether was predried over calcium chloride and passed through activated aluminium oxide (solvent purification system *SPS-400-2* from *Innovative Technologies Inc.*). Tetrahydrofuran (THF) was continuously refluxed and freshly distilled from sodium benzophenone ketyl under nitrogen and stored over molecular sieves. All other reagents and solvents were purchased from chemical suppliers (*Sigma-Aldrich, Acros Organics, Alfa Aesar, ABCR, FluoroChem, TCI Europe*) and used without further purification. Solvents for crystallisation and flash-column chromatography were purchased in technical grade and distilled under reduced pressure prior to use. Organomagnesium reagents were titrated against iodine in THF.[133] Organolithium reagents were titrated against isopropanol using 1,10-phenanthroline as indicator in THF or Et_2O.[134]

$ZnCl_2$ solution (1.0 M in THF) was prepared by drying $ZnCl_2$ (27.3 g, 200 mmol) in a *Schlenk*-flask under vacuum at 150 °C for 5 h. After cooling to 25 °C, dry THF (200 mL) was added and the solution was stirred until the salts were dissolved.

CuCN·2LiCl[132] solution (1.0 M in THF) was prepared by drying CuCN (8.96 g, 100 mmol) and LiCl (8.48 g, 200 mmol) in a *Schlenk*-flask under vacuum for 5 h at 150 °C. After cooling to 25 °C, dry THF (100 mL) was added and the solution was stirred until the salts were dissolved.

Analytics

NMR spectra were recorded on a *Bruker* Avance III HD 800 MHz spectrometer equipped with a CryoProbeTM, *Bruker* Avance III HD 400 MHz spectrometer equipped with a CryoProbeTM, *Bruker* AXR300, *Varian* VXR400 S and *Bruker* AMX600 spectrometers operating at 800 MHz, 400 MHz, 300 MHz, 400 MHz and 600 MHz for proton nuclei (200 MHz, 100 MHz, 75 MHz, 100 MHz, 150 MHz for carbon nuclei), respectively. Proton chemical shifts were reported as δ values in ppm and are referenced to residual protium in the NMR solvent ($CHCl_3$: δ 7.26, C_6HD_5 7.16). Carbon chemical shifts were reported as δ values in ppm and are referenced to the carbon resonance of the NMR solvent ($CDCl_3$: δ 77.16, C_6D_6 128.06). Abbreviations for signal coupling are as follows: s singlet, d doublet, t triplet, q quartet, quint quintet, h hextet, hept heptet, m multiplet as well as br broad. The specified multiplicities of the signals correspond to the observed ones and not the theoretical ones. In addition to ^1H and ^{13}C NMR measurements, 2D NMR techniques such as homonuclear correlation spectroscopy (COSY), heteronuclear single quantum coherence (HSQC) and heteronuclear multiple bond coherence (HMBC) were used to assist signal assignment. For further elucidation of 3D structures of the product, nuclear Overhauser enhancement spectroscopy (NOESY) was conducted.

All high-resolution mass spectra (HR-MS) were measured by the analytic section of the Department of Chemistry, *Ludwig-Maximilians-Universität* München. High resolution electron impact ionization (EI) and low resolution (MS) spectra were recorded on a *Finnigan MAT 95Q* or *Finnigan MAT* 90 instrument. EI was conducted with an electron energy of 70 eV. Electrospray ionization (ESI) spectra were recorded on a *Finnigan LTQ FTICR* instrument.

Gas chromatography (GC) was performed on machines of the types *Hewlett-Packard 6890* or *5890 Series II*, and *Agilent Technologies 7890A* (*Hewlett Packard*, 5% phenylmethylpolysiloxane; length: 15 m, diameter: 0.25 mm; film thickness: 0.25 µm).

Infrared spectra (IR) were recorded from 4500 cm^{-1} to 650 cm^{-1} on a *PERKIN ELMER* Spectrum BX II FT-IR instrument. For detection a *Smiths Detection DuraSample IR II* Diamond ATR sensor was used. The absorption bands are reported in wavenumbers (cm^{-1}).

Enantiomeric ratios (e.r.) of the compounds were measured on chiral GC using a *Supelco-β-DEX 120* column. Optical rotation values were recorded on an *Anton Paar MCP 200* polarimeter. The specific rotation is calculated as follows:

$$[\alpha]_{\lambda}^{\varphi} = \frac{\alpha}{\beta \cdot d}$$

α: recorded optical rotation

β: concentration of the analyte in 10 mg/mL

d: length of the cuvette in dm

φ: measuring temperature in °C

λ: wave length in nm

The respective concentration and the solvent are given in the analytical part of the experimental description.

Melting points (m.p.) were determined on a *BÜCHI B-540* apparatus and are uncorrected.

11 Experimental Section Part I: Intramolecular Carbolithiation Reactions

Typical Procedure (TP1) for the Epoxide Opening Using Grignard Reagents

A dry and argon-flushed *Schlenk*-flask was charged with CuI (10 mol%) and dry diethyl ether (0.1 M), followed by the dropwise addition of the respective alkyl Grignard reagent (1.1 equiv.) at 0 °C. Then, the appropriate epoxide (1.0 equiv.) was added dropwise at 0 °C. After warming to room temperature, the reaction was stirred for 16 h. Saturated aqueous NH_4Cl solution was added, the phases were separated and the aqueous phase was extracted with diethyl ether. The combined organic layers were dried over $MgSO_4$. The solvents were evaporated and the crude residue was subjected to column chromatography purification on silica yielding the respective title compound.

Typical Procedure (TP2) for the Iodination of Alcohols

A dry and argon-flushed *Schlenk*-flask was charged with a solution of PPh_3 (1.2 equiv.) and *N*-methylimidazole (1.2 equiv.) in dichloromethane (0.3 M) and was cooled to −10 °C. Iodine (1.2 equiv.) was added and the resulting yellow solution was stirred for 15 min at −10 °C. The respective alcohol (1.0 equiv.) dissolved in dichloromethane (1.0 M) was added dropwise and the resulting reaction mixture was stirred for 2 h at −10 °C. The reaction mixture was quenched with saturated aqueous $NaHSO_3{\cdot}Na_2S_2O_5$ solution[IV], the phases were separated and the aqueous phase was extracted with dichloromethane. The combined organic layers were dried over $MgSO_4$ and the solvents were evaporated at 30 °C.[V] The residue was triturated three times with a mixture of pentane:diethyl ether (4:1).[VI] The residue was filtered off using a plug of silica and all organic phases were combined. All solvents were evaporated and the crude residue was subjected to column chromatography purification on silica yielding the respective title compound.

[IV] Quenching with water or unsaturated aqueous $NaHSO_3{\cdot}Na_2S_2O_5$ solution sometimes causes epimerisation of the product.

[V] Evaporation at higher temperatures (>30 °C) sometimes causes epimerisation of the product.

[VI] Removal of triphenylphosphine oxide before column chromatography is recommended to get higher yield by washing and filtering the crude product with a mixture of *n*-pentane:ethyl ether.

Typical Procedure (TP3) for the I/Li-Exchange and Subsequent Cyclisation

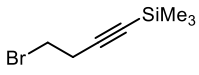
A dry and argon-flushed *Schlenk*-tube with diethyl ether (0.23 M based on *t*-BuLi) was cooled to −100 °C and charged with a solution of *t*-BuLi (in pentane, 2.5 equiv.). The appropriate alkyl iodide (1.0 equiv.) in diethyl ether (0.4 M) was added dropwise over 10 min and the reaction mixture was stirred for 15 min. After the addition of the electrophile (2.5 equiv.),[VII] the solution was stirred for 5 min at −100 °C and was then allowed to warm to room temperature. Saturated aqueous NH_4Cl solution was added, the phases were separated and the aqueous phase was extracted with diethyl ether. The combined organic layers were dried over $MgSO_4$. The solvents were evaporated and the crude residue was subjected to column chromatography purification on silica yielding the respective title compound.

Typical Procedure (TP4) for I/Li-Exchange, Intramolecular Carbolithiation and Cross-Coupling Reactions

A dry and argon-flushed *Schlenk*-tube with diethyl ether (0.23 M based on *t*-BuLi) was cooled to −100 °C and charged with a solution of *t*-BuLi (in pentane, 3.38 equiv.). The appropriate alkyl iodide (1.35 equiv.) in diethyl ether (0.4 M) was added dropwise over 10 min and the reaction mixture was stirred for 15 min. $ZnCl_2$ (1.0 M in THF, 2.0 equiv.) and THF (0.5 M based on $ZnCl_2$) were added and the reaction mixture was allowed to warm to 15 °C over 25 min. The reaction was cooled to −80 °C, SPhos (10 mol%) and a solution of the appropriate aryl iodide (1.0 equiv.) and $Pd(OAc)_2$ (5 mol%) in DMA (0.13 M based on aryl iodide) were added dropwise. The reaction was stirred at room temperature for 16 h. After the addition of saturated aqueous NH_4Cl solution, the phases were separated and the aqueous phase was extracted with diethyl ether. The combined organic layers were dried over $MgSO_4$. The solvents were evaporated and the crude residue was subjected to column chromatography purification on silica yielding the respective title compound.

[VII] If necessary, the electrophile was dissolved in 1 mL of solvent.

11.1 Preparation of the Alcohols



(4-Bromobut-1-yn-1-yl)trimethylsilane S1. PPh_3 (12.5 g, 47.6 mmol, 1.2 equiv.) was added to a solution of 4-(trimethylsilyl)but-3-yn-1-ol (5.76 g, 39.7 mmol, 1.0 equiv.) in dichloromethane (79 mL) at −20 °C. NBS (7.85 g, 43.7 mmol, 1.1 equiv.) was slowly added at this temperature and the reaction was allowed to warm to room temperature over 16 h. After the addition of a saturated aqueous $NaHCO_3$ solution the reaction mixture was extracted with diethyl ether. The combined organic layers were dried over $MgSO_4$. The crude product was purified by column chromatography on silica using pentane:diethyl ether (1000:1) as an eluent to afford **S1** as a colourless liquid (89%, 7.23 g, 35.2 mmol).

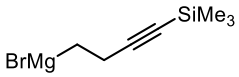
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 3.43 (t, J = 7.5 Hz, 2H), 2.77 (t, J = 7.5 Hz, 2H), 0.16 (s, 9H).

^{13}C-NMR (151 MHz, $CDCl_3$, ppm): δ = 103.3, 87.2, 29.3, 24.4, 0.1.

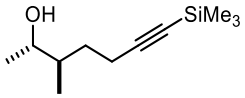
FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2960, 2899, 2178, 1418, 1328, 1271, 1250, 1212, 1055, 1044, 998, 982, 902, 837, 759, 698, 679.

MS (EI, 70 eV): *m/z* (%) = 192 (16), 190 (15), 163 (97), 161 (100), 139 (47), 137 (47), 109 (19).

HR-MS (EI, 70 eV): [$C_7H_{13}BrSi$], calcd.: 203.9970; found: 203.9949 (M^+).



Grignard reagent 41. A dry and argon-flushed flask was charged with dry LiCl (562 mg, 13.3 mmol, 1.1 equiv.) and magnesium turnings (355 mg, 14.5 mmol, 1.2 equiv.) in THF (10 mL). Bromide **S1** (2.47 g, 12.1 mmol, 1.0 equiv.) in THF (2.0 mL) was added slowly at 0 °C. The reaction mixture was allowed to stir at room temperature for 2 h. Following titration with iodine at 0 °C gave a concentration of 0.56 – 0.81 M.



Alcohol *rac-(2S,3R)*-42a. Following **TP1,** (4-(trimethylsilyl)but-3-yn-1-yl)magnesium bromide **41** (0.69 M, 10.0 mL, 6.90 mmol, 1.1 equiv.) reacts with *cis*-dimethyloxirane (466 mg, 6.27 mmol, 1.0 equiv.) and CuI (122 mg, 0.627 mmol, 10 mol%) as catalyst at 0 °C. The solution was stirred at this temperature for 16 h and was worked-up as usual. The crude product was purified by column chromatography on silica using pentane:diethyl ether (2:1) as an eluent to afford *rac-(2S,3R)*-**42a** as a colourless oil (86%, 1.07 g, 5.40 mmol, d.r.>99:1).

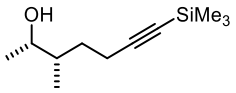
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 3.75 – 3.64 (m, 1H), 2.33 (ddd, *J* = 16.9, 8.2, 5.9 Hz, 1H), 2.20 (ddd, *J* = 17.0, 8.1, 7.4 Hz, 1H), 1.85 – 1.67 (m, 1H), 1.67 – 1.46 (m, 2H), 1.42 – 1.31 (m, 1H), 1.15 (d, *J* = 6.3 Hz, 3H), 0.90 (d, *J* = 6.8 Hz, 3H), 0.14 (s, 9H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 107.7, 84.7, 71.6, 39.5, 31.5, 19.9, 17.8, 14.7, 0.3.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3362, 2961, 2175, 1453, 1379, 1321, 1248, 1094, 1051, 1002, 923, 837, 758, 697.

MS (EI, 70 eV): *m/z* (%) = 167 (16), 165 (45), 140 (17), 139 (15), 127 (19), 112 (20), 109 (25), 97 (10), 96 (18), 83 (12), 75 (100), 73 (92), 72 (11).

HR-MS (EI, 70 eV): [$C_{10}H_{19}OSi$], calcd.: 183.1205; found: 183.1202 ([M−Me]$^+$).



Alcohol *rac-(2S,3S)*-42a. Following **TP1,** (4-(trimethylsilyl)but-3-yn-1-yl)magnesium bromide **41** (0.70 M, 13.1 mL, 9.17 mmol, 1.1 equiv.) reacts with *trans*-dimethyloxirane (620 mg, 8.34 mmol, 1.0 equiv.) using CuI (162 mg, 0.834 mmol, 10 mol%) as catalyst at 0 °C. The solution was stirred at this temperature for 16 h and was worked-up as usual. The crude product was purified by column chromatography on silica using pentane:diethyl ether (2:1) as an eluent to afford *rac-(2S,3S)*-**42a** as a colourless oil (89%, 1.47 g, 7.41 mmol, d.r.>99:1).

^{1}H-NMR (599 MHz, $CDCl_3$, ppm): δ = 3.76 (qd, *J* = 6.4, 4.2 Hz, 1H), 2.33 (ddd, *J* = 17.0, 8.0, 6.1 Hz, 1H), 2.22 (dt, *J* = 16.9, 7.7 Hz, 1H), 1.70 (dtd, *J* = 13.1, 7.7, 5.2 Hz, 1H), 1.63 – 1.47 (m, 2H),

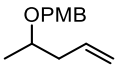
1.38 (dddd, *J* = 13.3, 8.5, 7.9, 6.1 Hz, 1H), 1.17 (d, *J* = 6.4 Hz, 3H), 0.90 (d, *J* = 6.8 Hz, 3H), 0.14 (s, 9H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 107.6, 84.8, 70.8, 39.1, 31.8, 20.4, 18.0, 13.9, 0.3.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3359, 2962, 2900, 2175, 1455, 1430, 1378, 1248, 1146, 1082, 1048, 1017, 1002, 943, 927, 870, 836, 758, 697.

MS (EI, 70 eV): *m/z* (%) = 165 (16), 140 (10), 112 (11), 109 (12), 96 (13), 85 (15), 75 (100), 73 (96), 72 (14), 57 (12), 45 (14).

HR-MS (EI, 70 eV): [$C_{10}H_{19}OSi$], calcd.: 183.1205; found: 183.1197 ([M−Me]$^+$).



1-Methoxy-4-((pent-4-en-2-yloxy)methyl)benzene 45.[135] A dry and argon-flushed *Schlenk*-flask was charged with NaH (217 mg, 5.43 mmol, 1.4 equiv.) and THF (4.5 mL). A solution of pent-4-en-2-ol **44** (400 µL, 3.88 mmol, 1.0 equiv.) in THF (1.5 mL) was added dropwise at 0 °C. The reaction mixture was stirred for 30 min at 0 °C. Then, PMBCl (590 µL, 4.27 mmol, 1.1 equiv.) and tetrabutylammonium iodide (143 mg, 0.388 mmol, 0.1 equiv.) were added at 0 °C. After warming to room temperature, the reaction mixture was stirred for 16 h. Water and saturated aqueous NaCl solution were added, the phases were separated and the aqueous phase was extracted with diethyl ether. The combined organic layers were dried over $MgSO_4$. The crude product was purified by column chromatography on silica using hexane:diethyl ether (20:1) as an eluent to afford **45** as a colourless oil (63%, 473 mg, 2.46 mmol).

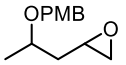
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.27 (d, *J* = 8.8 Hz, 2H), 6.87 (d, *J* = 8.1 Hz, 2H), 5.83 (ddt, *J* = 17.3, 10.3, 7.1 Hz, 1H), 5.16 – 4.96 (m, 2H), 4.47 (q, *J* = 11.4 Hz, 2H), 3.80 (s, 3H), 3.56 (dt, *J* = 6.2 Hz, 1H), 2.37 (dt, *J* = 13.2, 6.2 Hz, 1H), 2.22 (dt, *J* = 13.7, 6.8 Hz, 1H), 1.18 (d, *J* = 6.1 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 159.2, 135.3, 131.1, 129.3, 116.9, 113.9, 74.2, 70.1, 55.4, 41.0, 19.6.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2971, 2933, 2836, 1612, 1586, 1512, 1464, 1374, 1339, 1301, 1244, 1172, 1128, 1084, 1034, 1012, 913, 819, 753.

MS (EI, 70 eV): *m/z* (%) = 148 (39), 121 (100).

HR-MS (EI, 70 eV): [$C_{13}H_{18}O_2$], calcd.: 206.1307; found: 206.1301 (M^+).



Epoxide 46. A 500 mL flask was charged with **45** (6.45 g, 31.2 mmol, 1.0 equiv.) in dichloromethane (200 mL). *m*CPBA (6.20 g, 36.0 mmol, 1.15 equiv.) was added over three times at 0 °C and the reaction mixture was stirred for 42 h at room temperature. Saturated aqueous $NaHCO_3$ solution was added, the phases were separated and the aqueous phase was extracted with dichloromethane. The combined organic layers were dried over $MgSO_4$. The crude product was purified by column chromatography on silica using hexane:diethyl ether (3.5:1) as an eluent to afford a mixture of diastereomers (60:40) of **46** as a colourless oil (78%, 5.40 mg, 24.3 mmol).

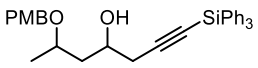
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.31 – 7.23 (m, 2H), 6.91 – 6.84 (m, 2H), 4.58 (d, *J* = 11.3 Hz, 0.5H), 4.52 (d, *J* = 11.8 Hz, 0.6H), 4.43 (d, *J* = 10.0 Hz, 0.6H), 4.41 (d, *J* = 10.1 Hz, 0.4H), 3.80 (s, 3H), 3.79 – 3.74 (m, 0.7H), 3.74 – 3.66 (m, 0.5H), 3.08 (dtd, *J* = 7.1, 4.2, 2.8 Hz, 0.6H), 3.05 – 3.01 (m, 0.4H), 2.80 (dd, *J* = 5.0, 4.0 Hz, 0.6H), 2.77 – 2.73 (m, 0.4H), 2.50 (dd, *J* = 5.0, 2.7 Hz, 0.6H), 2.48 (dd, *J* = 5.1, 2.7 Hz, 0.4H), 1.93 – 1.80 (m, 1H), 1.67 (ddd, *J* = 14.2, 5.8, 5.2 Hz, 0.4H), 1.51 (ddd, *J* = 14.3, 7.3, 4.4 Hz, 0.7H), 1.28 (d, *J* = 6.2 Hz, 1.3H), 1.25 (d, *J* = 6.2 Hz, 1.8H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = Major: 159.2, 130.9, 129.3, 113.9, 72.7, 70.5, 55.4, 50.0, 47.6, 40.4, 20.2; Minor: 159.2, 130.9, 129.3, 113.9, 72.4, 70.1, 55.4, 49.8, 47.0, 39.5, 19.8.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2969, 2933, 2912, 2865, 2837, 1612, 1586, 1512, 1463, 1443, 1410, 1375, 1339, 1301, 1244, 1172, 1128, 1100, 1069, 1032, 947, 911, 996, 938, 910, 872, 845, 818, 750.

MS (EI, 70 eV): *m/z* (%) = 137 (54), 121 (100).

HR-MS (EI, 70 eV): [$C_{13}H_{18}O_3$], calcd.: 222.1256; found: 222.1248 (M^+).



Silane 47. A dry and argon-flushed *Schlenk*-flask was charged with triphenylsilyl acetylene (8.8 g, 30.9 mmol, 1.0 equiv.) and THF (120 mL). *n*-BuLi (2.1 M in hexane, 14.8 mL, 31.1 mmol, 1.0 equiv.) was added dropwise at −78 °C and the reaction mixture was stirred at this temperature for 1 h. **46** (3.96 mL, 32.1 mmol, 1.0 equiv.) in THF (10 mL) and $BF_3{\cdot}Et_2O$ (5.10 g, 22.9 mmol, 0.74 equiv.) were added successively at −78 °C. The mixture was stirred at −78 °C for 20 min. After warming to room

temperature, the reaction was stirred for 3 h. Saturated aqueous NH_4Cl solution was added, the phases were separated and the aqueous phase was extracted with diethyl ether. The combined organic layers were dried over $MgSO_4$. The crude product was purified by column chromatography on silica using hexane:diethyl ether (3:2→5:4) as an eluent to afford a mixture of diastereomers (59:41) of **47** as a pale yellow oil (69%, 10.8 g, 21.3 mmol).

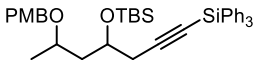
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.69 – 7.62 (m, 6H), 7.47 – 7.34 (m, 9H), 7.30 – 7.23 (m, 2H), 6.93 – 6.85 (m, 2H), 4.61 (d, *J* = 11.1 Hz, 0.4H), 4.56 (d, *J* = 11.2 Hz, 0.6H), 4.39 (d, *J* = 11.4 Hz, 0.6H), 4.37 (d, *J* = 11.2 Hz, 0.4H), 4.24 – 4.11 (m, 0.6H), 4.04 (dddd, *J* = 9.8, 7.6, 4.9, 2.4 Hz, 0.4H), 3.98 – 3.90 (m, 0.6H), 3.90 – 3.86 (m, 0.4H), 3.86 – 3.81 (m, 0.5H), 3.80 (s, 1.2H), 3.80 (s, 1.7H), 3.15 (d, *J* = 3.8 Hz, 0.5H), 2.62 (td, *J* = 16.7, 6.2 Hz, 1.4H), 2.50 (td, *J* = 16.6, 7.6 Hz, 0.6H), 2.00 – 1.90 (m, 0.4H), 1.90 – 1.84 (m, 1H), 1.82 – 1.71 (m, 0.5H), 1.26 (d, *J* = 6.3 Hz, 1.7H), 1.26 (d, *J* = 6.1 Hz, 1.3H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = Major: 159.3, 135.6, 133.9, 130.4, 130.0, 129.5, 128.1, 114.0, 108.9, 82.2, 72.4, 70.3, 67.5, 55.4, 41.7, 29.0, 19.3; Minor: 159.4, 135.6, 133.9, 130.1, 130.0, 129.6, 128.0, 114.1, 109.0, 82.1, 75.5, 70.5, 70.1, 55.4, 42.8, 29.0, 19.8.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3452, 2966, 2933, 2908, 2869, 2836, 2174, 1612, 1587, 1512, 1484, 1463, 1455, 1428, 1375, 1336, 1301, 1246, 1174, 1138 , 1111, 1032, 1009, 997, 845, 819, 741, 707, 697.

MS (EI, 70 eV): *m/z* (%) = 260 (10), 259 (34), 247 (10), 199 (32), 190 (12), 137 (50), 122 (11), 121 (100).

HR-MS (EI, 70 eV): [$C_{33}H_{34}O_3Si$], calcd.: 506.2277; found: 506.2272 (M^+).



Silane 43. A dry and argon-flushed *Schlenk*-flask was charged with **47** (10.8 g, 21.3 mmol, 1.0 equiv.) in dichloromethane (180 mL). 2,6-Lutidine (3.7 mL, 31.9 mmol, 1.5 equiv.) and TBSOTf (5.9 mL, 25.6 mmol, 1.2 equiv.) were added successively at 0 °C. After warming up to room temperature, the reaction mixture was stirred for 42 h. Saturated aqueous NH_4Cl solution was added, the phases were separated and the aqueous phase was extracted with dichloromethane. The combined organic layers were dried over $MgSO_4$. The crude product was purified by column chromatography on silica using hexane:diethyl ether (30:1) as an eluent and a second time with hexane:toluene (1:3.5) to afford *rac*-

(2S,4S)-**43** as a pale yellow oil (30%, 3.90 g, 6.28 mmol) and *rac-(2S,4R)*-**43** as a pale yellow oil (17%, 2.20 g, 3.54 mmol).

***rac-(2S,4S)*-43:**

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.67 (dd, *J* = 7.9, 1.4 Hz, 6H), 7.43 – 7.32 (m, 9H), 7.24 (d, *J* = 8.6 Hz, 2H), 6.84 (d, *J* = 8.6 Hz, 2H), 4.51 (d, *J* = 11.0 Hz, 1H), 4.31 (d, *J* = 11.0 Hz, 1H), 4.15 (ddt, *J* = 9.3, 6.1, 3.7 Hz, 1H), 3.79 (s, 3H), 3.74 (ddq, *J* = 12.2, 6.1, 3.1 Hz, 1H), 2.60 (dd, *J* = 17.0, 6.2 Hz, 1H), 2.53 (dd, *J* = 16.9, 4.2 Hz, 1H), 1.95 (ddd, *J* = 14.1, 9.0, 3.3 Hz, 1H), 1.75 (ddd, *J* = 14.1, 8.8, 3.4 Hz, 1H), 1.22 (d, *J* = 6.1 Hz, 3H), 0.88 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 159.0, 135.7, 134.1, 131.4, 129.8, 129.1, 128.0, 113.8, 109.3, 81.8, 71.8, 69.7, 67.7, 55.4, 44.9, 30.0, 26.0, 20.3, 18.2, −4.1, −4.5.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2954, 2929, 2856, 2176, 1614, 1588, 1514, 1484, 1462, 1429, 1373, 1336, 1302, 1247, 1172, 1144, 1112, 1075, 1034, 1005, 938, 908, 835, 824, 807, 775, 741, 708, 696.

MS (EI, 70 eV): *m/z* (%) = 121 (100).

HR-MS (EI, 70 eV): [$C_{39}H_{48}O_3Si_2$], calcd.: 620.3142; found: 620.3136 (M^+).

***rac-(2S,4R)*-43:**

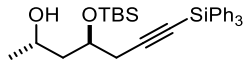
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.65 (dd, *J* = 8.0, 1.5 Hz, 6H), 7.46 – 7.31 (m, 9H), 7.21 (d, *J* = 8.6 Hz, 2H), 6.82 (d, *J* = 8.6 Hz, 2H), 4.45 (d, *J* = 11.4 Hz, 1H), 4.34 (d, *J* = 11.4 Hz, 1H), 4.05 – 3.96 (m, 1H), 3.77 (s, 3H), 3.66 (h, *J* = 6.3 Hz, 1H), 2.56 (dd, *J* = 16.9, 6.0 Hz, 1H), 2.49 (dd, *J* = 17.0, 4.8 Hz, 1H), 1.99 (dt, *J* = 13.4, 6.5 Hz, 1H), 1.79 (dt, *J* = 13.8, 6.1 Hz, 1H), 1.19 (d, *J* = 6.1 Hz, 3H), 0.85 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 159.1, 135.7, 134.1, 131.1, 129.9, 129.3, 128.0, 113.8, 109.3, 81.6, 71.5, 69.8, 68.2, 55.4, 43.7, 29.2, 25.9, 20.0, 18.1, −4.3, −4.6.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2954, 2929, 2856, 2176, 1613, 1588, 1513, 1463, 1429, 1374, 1335, 1302, 1247, 1172, 1139, 1112, 1034, 1005, 937, 908, 835, 807, 775, 741, 708, 697.

MS (EI, 70 eV): *m/z* (%) = 121 (100).

HR-MS (EI, 70 eV): [$C_{39}H_{48}O_3Si$], calcd.: 620.3142; found: 620.3138 (M^+).



Alcohol *rac-(2S,4S)*-42b. A dry and argon-flushed *Schlenk*-flask was charged with *rac-(2S,4S)*-**43** (3.90 g, 6.30 mmol, 1.0 equiv.), dichloromethane (35 mL) and phosphate buffer (20 mL, pH = 7). DDQ (2.86 g, 12.6 mmol, 2.0 equiv.) was added at 0 °C and the reaction was stirred for 1.5 h at this temperature. Saturated aqueous $NaHCO_3$ solution was added, the phases were separated and the aqueous phase was extracted with diethyl ether. The combined organic layers were dried over $MgSO_4$. The crude product was purified by column chromatography on silica using hexane:ethyl acetate (7:1) as an eluent and a second time with hexane:ethyl acetate (7:1) to afford *rac-(2S,4S)*-**42b** as a colourless oil (83%, 2.62 g, 5.25 mmol, d.r.>99:1).

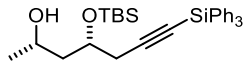
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.68 – 7.59 (m, 6H), 7.47 – 7.33 (m, 9H), 4.29 – 4.12 (m, 2H), 2.94 (d, *J* = 2.6 Hz, 1H), 2.70 (dd, *J* = 16.9, 8.0 Hz, 1H), 2.64 (dd, *J* = 16.9, 5.4 Hz, 1H), 1.89 (ddd, *J* = 14.5, 5.3, 2.2 Hz, 1H), 1.73 (ddd, *J* = 14.2, 10.1, 3.6 Hz, 1H), 1.16 (d, *J* = 6.2 Hz, 3H), 0.88 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 135.6, 133.8, 130.0, 128.1, 108.5, 82.3, 70.0, 64.4, 43.3, 28.3, 25.9, 24.0, 18.0, −4.5, −4.8.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3458, 2956, 2929, 2856, 2176, 1589, 1514, 1471, 1462, 1428, 1373, 1254, 1187, 1112, 1028, 1013, 1005, 937, 912, 835, 807, 775, 739, 707, 696.

MS (EI, 70 eV): *m/z* (%) = 283 (10), 273 (19), 259 (100), 195 (52), 159 (53), 144 (28), 129 (11), 105 (14), 75 (33).

HR-MS (EI, 70 eV): [$C_{27}H_{31}O_2Si_2$], calcd.: 443.1863; found: 443.1852 ([M−*t*-Bu]$^+$).



Alcohol *rac-(2S,4R)*-42b. A dry and argon-flushed *Schlenk*-flask was charged with *rac-(2S,4R)*-**43** (2.20 g, 3.54 mmol, 1.0 equiv.), dichloromethane (20 mL) and phosphate buffer (12 mL, pH = 7). DDQ (1.60 g, 7.09 mmol, 2.0 equiv.) was added at 0 °C and the reaction was stirred for 1 h at this temperature. Saturated aqueous $NaHCO_3$ solution was added, the phases were separated and the aqueous phase was extracted with diethyl ether. The combined organic layers were dried over $MgSO_4$. The crude product was purified by column chromatography on silica using hexane:diethyl ether (3:1) to afford *rac-(2S,4R)*-**42b** with 4-methoxybenzaldehyde as an impurity. To remove this impurity, the

resulting mixture was diluted with THF (10 mL) and tosyl hydrazine (830 mg, 4.46 mmol) was added. The reaction mixture was stirred at room temperature for 18 h. The solvents were evaporated and the crude product was purified by column chromatography on silica using hexane:diethyl ether (3:1) to afford *rac-(2S,4R)*-**42b** as a pale yellow oil (88%, 1.56 g, 3.11 mmol, d.r.>99:1).

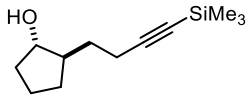
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.67 – 7.61 (m, 6H), 7.45 – 7.34 (m, 9H), 4.11 (ddt, *J* = 8.8, 6.8, 4.3 Hz, 1H), 3.99 (dqd, *J* = 8.9, 6.1, 2.7 Hz, 1H), 2.90 (s, 1H), 2.67 – 2.53 (m, 2H), 1.91 (ddd, *J* = 14.3, 4.0, 2.9 Hz, 1H), 1.78 (dt, *J* = 14.3, 9.0 Hz, 1H), 1.17 (d, *J* = 6.2 Hz, 3H), 0.89 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 135.5, 133.7, 129.9, 127.9, 108.1, 82.5, 71.4, 67.0, 44.8, 29.7, 25.7, 23.6, 17.9, −4.1, −4.8.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3430, 2956, 2929, 2856, 2177, 1589, 1484, 1471, 1462, 1428, 1361, 1255, 1187, 1112, 1082, 1026, 1014, 998, 937, 835, 806, 775, 739, 707, 696.

MS (EI, 70 eV): *m/z* (%) = 368 (41), 275 (41), 259 (100), 207 (31), 181 (21), 155 (11).

HR-MS (EI, 70 eV): [$C_{27}H_{31}O_2Si_2$], calcd.: 443.1863; found: 443.1854 ([M−*t*-Bu]$^+$).



Alcohol *anti*-42c. Following **TP1,** (4-(trimethylsilyl)but-3-yn-1-yl)magnesium bromide **41** (0.81 M, 6.10 mL, 4.94 mmol, 1.1 equiv.) reacts with cyclopentene oxide (390 mg, 4.49 mmol, 1.0 equiv.) using CuI (97 mg, 0.494 mmol, 10 mol%) as catalyst at 0 °C. The solution was stirred at this temperature for 16 h and was worked-up as usual. The crude product was purified by column chromatography on silica using pentane:diethyl ether (2:1) as an eluent to afford *anti*-**42c** as a colourless oil (69%, 652 mg, 3.10 mmol, d.r.>99:1).

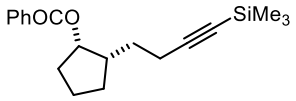
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 3.86 (q, *J* = 5.8 Hz, 1H), 2.40 – 2.20 (m, 2H), 1.99 – 1.86 (m, 2H), 1.83 – 1.63 (m, 4H), 1.63 – 1.56 (m, 2H), 1.48 (tt, *J* = 14.2, 6.6 Hz, 1H)1.24 – 1.11 (m, 1H), 0.15 (s, 9H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 107.7, 84.9, 79.0, 48.0, 34.7, 32.8, 30.3, 21.9, 18.9, 0.3.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3346, 2957, 2174, 1452, 1344, 1248, 1168, 1039, 1019, 837, 758, 697.

MS (EI, 70 eV): *m/z* (%) = 97 (11), 84 (21), 75 (100), 73 (54).

HR-MS (EI, 70 eV): [$C_{11}H_{19}OSi$], calcd.: 195.1205; found: 195.1203 ([M−Me]$^+$).



Ester *syn*-S2. DEAD (40% in toluene, 2.97 mL, 6.56 mmol, 1.0 equiv.) was added dropwise to a solution of *anti*-**42c** (1.38 g, 6.56 mmol, 1.0 equiv.) and triphenylphosphine (1.72 g, 6.56 mmol, 1.0 equiv.) in THF (24.6 mL). Then, benzoic acid (961 mg, 7.87 mmol, 1.2 equiv.) was added over a period of 30 min. After stirring at room temperature for 16 h, water (0.08 mL) was added and the mixture was concentrated *in vacuo*. The crude product was purified by column chromatography on silica using hexane:diethyl ether (9:1) as an eluent to afford *syn*-**S2** as a colourless oil (54%, 1.12 g, 3.55 mmol, d.r.>99:1).

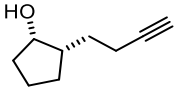
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.08 – 7.97 (m, 2H), 7.60 – 7.50 (m, 1H), 7.50 – 7.40 (m, 2H), 5.43 (td, *J* = 4.5, 1.2 Hz, 1H), 2.37 – 2.20 (m, 2H), 2.15 – 1.99 (m, 2H), 1.99 – 1.75 (m, 4H), 1.73 – 1.49 (m, 3H), 0.13 (s, 9H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 166.0, 132.7, 130.8, 129.4, 128.2, 107.0, 84.5, 78.1, 43.8, 32.6, 29.4, 28.2, 22.0, 18.8, 0.0.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2957, 2872, 2174, 1715, 1451, 1314, 1271, 1248, 1175, 1111, 1069, 1026, 838, 759, 709, 688, 670.

MS (EI, 70 eV): *m/z* (%) = 180 (12), 179 (76), 177 (39), 118 (11), 105 (100), 77 (34), 73 (36).

HR-MS (EI, 70 eV): [$C_{19}H_{25}O_2Si$], calcd.: 313.1624; found: 313.1613 ([M−H]$^+$).



Alcohol *syn*-S3. *syn*-**S2** (970 mg, 3.08 mmol, 1.0 equiv.) was treated with potassium carbonate (1.71 g, 12.3 mmol, 4.0 equiv.) in MeOH (5.6 mL). The reaction mixture was stirred at 60 °C for 16 h. A saturated aqueous solution of NH_4Cl was added. The phases were separated and the aqueous phase was

extracted with diethyl ether. The combined organic layers were dried over $MgSO_4$. The crude product was purified by column chromatography on silica using pentane:diethyl ether (3:1) as an eluent to afford *syn*-**S3** as a colourless oil (96%, 408 mg, 2.95 mmol, d.r.>99:1).

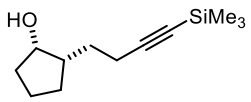
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 4.23 (td, J = 4.3, 1.5 Hz, 1H), 2.38 – 2.16 (m, 2H), 1.96 (t, J = 2.7 Hz, 1H), 1.93 – 1.71 (m, 5H), 1.71 – 1.51 (m, 3H), 1.46 – 1.31 (m, 2H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 84.9, 74.1, 68.3, 45.0, 34.9, 28.7, 27.9, 21.7, 17.4.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3398, 3304, 2940, 2869, 2116, 1450, 1434, 1328, 1297, 1145, 1107, 1040, 1008, 990, 958, 941, 855.

MS (EI, 70 eV): *m/z* (%) = 109 (60), 97 (100), 95 (30), 91 (33), 84 (65), 81 (59), 79 (80), 67 (56), 57 (73), 55 (52), 54 (36), 53 (31), 41 (83).

HR-MS (EI, 70 eV): [$C_9H_{14}O$], calcd.: 138.1045; found: 138.1048 (M^+).



Alcohol *syn*-42c. A dry and argon-flushed *Schlenk*-flask was charged with *syn*-**S3** (389 mg, 2.82 mmol, 1.0 equiv.) in THF (5.6 mL). *n*-BuLi (2.49 M, 2.32 mL, 5.77 mmol, 2.05 equiv.) was added dropwise at −78 °C. After 1 h at this temperature, TMSCl (753 µL, 5.77 mmol, 2.05 equiv.) was added and the reaction mixture was stirred at room temperature for 30 min. HCl (2 N, 2.8 mL, 5.60 mmol, 2.0 equiv.) was added. After stirring for 16 h at room temperature, the reaction mixture was neutralised with a saturated aqueous solution of $NaHCO_3$. The phases were separated and the aqueous phase was extracted with diethyl ether. The combined organic layers were dried over $MgSO_4$. The crude product was purified by column chromatography on silica using pentane:diethyl ether (2:1) as an eluent to afford *syn*-**42c** as a colourless oil (99%, 590 mg, 2.80 mmol, d.r.>99:1).

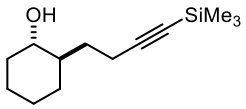
^{1}H-NMR (599 MHz, $CDCl_3$, ppm): δ = 4.29 – 4.24 (m, 1H), 2.40 – 2.32 (m, 1H), 2.28 – 2.20 (m, 1H), 1.89 – 1.50 (m, 8H), 1.53 (s, 1H), 1.44 – 1.36 (m, 1H), 0.15 (s, 9H).

^{13}C-NMR (151 MHz, $CDCl_3$, ppm): δ = 108.3, 84.8, 74.1, 45.9, 34.9, 29.2, 28.4, 22.0, 19.2, 0.2.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3377, 2957, 2901, 2870, 2173, 1430, 1328, 1248, 1143, 1104, 1026, 994, 836, 758, 697.

MS (EI, 70 eV): *m/z* (%) = 177 (23), 75 (100), 73 (70).

HR-MS (EI, 70 eV): [$C_{12}H_{21}OSi$], calcd.: 209.1362; found: 209.1358 (M^+).



Alcohol *anti*-42d. Following **TP1,** (4-(trimethylsilyl)but-3-yn-1-yl)magnesium bromide **41** (0.81 M, 6.35 mL, 5.15 mmol, 1.1 equiv.) reacts with cyclohexene oxide (4.68 mg, 4.68 mmol, 1.0 equiv.) using CuI (91 mg, 0.468 mmol, 10 mol%) as catalyst at 0 °C. The solution was stirred at this temperature for 16 h and was worked-up as usual. The crude product was purified by column chromatography on silica using pentane:diethyl ether (2:1) as an eluent to afford *anti*-**42c** as a colourless solid (77%, 804 mg, 3.58 mmol, d.r.>99:1).

m.p.: 48.6 – 50.8 °C.

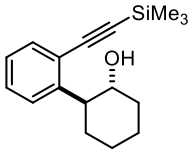
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 3.25 (td, *J* = 9.7, 4.5 Hz, 1H), 2.34 (ddd, *J* = 17.0, 8.5, 6.1 Hz, 1H), 2.22 (ddd, *J* = 17.0, 8.1, 7.1 Hz, 1H), 2.03 – 1.92 (m, 2H), 1.82 – 1.71 (m, 2H), 1.68 – 1.61 (m, 1H), 1.42 (dtd, *J* = 13.3, 8.1, 6.1 Hz, 1H), 1.36 – 1.11 (m, 4H), 1.00 – 0.87 (m, 1H), 0.14 (s, 9H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 108.2, 84.7, 74.5, 44.7, 35.9, 31.7, 30.2, 25.6, 25.0, 17.5, 0.3.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3273, 2958, 2925, 2858, 2175, 1450, 1426, 1407, 1354, 1342, 1247, 1065, 1052, 1033, 994, 987, 969, 942, 934, 836, 758, 697, 664.

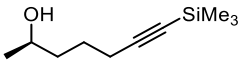
MS (EI, 70 eV): *m/z* (%) = 191 (33), 165 (28).

HR-MS (EI, 70 eV): [$C_{13}H_{24}OSi$], calcd.: 224,1596; found: 224.1593 (M^+).



Alcohol *anti*-42e. The aromatic alkynol *anti*-**42e** was prepared in two steps according to the literature in 60% yield.[136]

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.48 (ddd, *J* = 7.7, 1.4, 0.7 Hz, 1H), 7.35 – 7.27 (m, 2H), 7.16 (ddd, *J* = 7.7, 6.8, 1.9 Hz, 1H), 3.94 – 3.80 (m, 1H), 3.13 (d, *J* = 11.2 Hz, 1H), 2.21 – 2.15 (m, 1H), 1.98 – 1.84 (m, 2H), 1.84 – 1.74 (m, 1H), 1.60 – 1.52 (m, 1H), 1.49 – 1.30 (m, 4H), 0.27 (s, 9H).



Alcohol *R*-42f. Following **TP1,** (4-(trimethylsilyl)but-3-yn-1-yl)magnesium bromide **41** (0.56 M, 10.6 mL, 5.94 mmol, 1.1 equiv.) reacts with *R*-(+)-propylene oxide (320 mg, 5.396 mmol, 1.0 equiv.) using CuI (105 mg, 0.540 mmol, 10 mol%) as catalyst at 0 °C. The solution was stirred at this temperature for 16 h and was worked-up as usual. The crude product was purified by column chromatography on silica using pentane:diethyl ether (2:1) as an eluent to afford *R*-**42f** as a colourless oil (94%, 934 mg, 5.07 mmol).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 3.84 (tq, *J* = 6.1 Hz, 1H), 2.30 – 2.21 (m, 2H), 1.71 – 1.49 (m, 4H), 1.38 (s, 1H), 1.20 (d, *J* = 6.2 Hz, 3H), 0.14 (s, 9H).

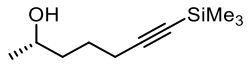
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 107.4, 84.9, 67.8, 38.5, 25.0, 23.7, 20.0, 0.3.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3345, 2962, 2174, 1456, 1408, 1374, 1326, 1248, 1183, 1128, 1086, 1055, 1026, 1015, 994, 909, 837, 758, 697.

MS (EI, 70 eV): *m/z* (%) = 151 (19), 109 (21), 96 (17), 76 (16), 75 (71), 73 (100), 71 (16), 59 (11), 45 (25), 43 (12).

HR-MS (EI, 70 eV): [$C_9H_{17}OSi$], calcd.: 169.1049; found: 169.1037 ([M−Me]$^+$).

$[\alpha]_D^{20}$ = –9° (c = 0.89, CH_2Cl_2); –8° (c = 0.90, $CHCl_3$). Lit.: –6.83° (c = 0.55, $CHCl_3$).[137]



Alcohol *S*-42f. Following **TP1,** (4-(trimethylsilyl)but-3-yn-1-yl)magnesium bromide **41** (0.67 M, 11.0 mL, 7.37 mmol, 1.1 equiv.) reacts with *S*-(−)-propylene oxide (381 mg, 6.70 mmol, 1.0 equiv.) using CuI (125 mg, 0.670 mmol, 10 mol%) as catalyst at 0 °C. The solution was stirred at this temperature overnight and was worked-up as usual. The crude product was purified by column chromatography on silica using pentane:diethyl ether (2:1) as an eluent to afford *S*-**42f** as a colourless oil (94%, 1.16 g, 6.27 mmol).

^{1}H-NMR (599 MHz, $CDCl_3$, ppm): δ = 3.89 – 3.80 (m, 1H), 2.31 – 2.23 (m, 2H), 1.69 – 1.61 (m, 1H), 1.61 – 1.52 (m, 3H), 1.31 (s, 1H), 1.21 (d, J = 6.2 Hz, 3H), 0.15 (s, 9H).

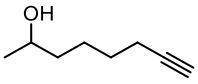
^{13}C-NMR (151 MHz, $CDCl_3$, ppm): δ = 107.4, 84.9, 67.8, 38.5, 25.0, 23.7, 20.0, 0.3.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3350, 2962, 2930, 2868, 2174, 1456, 1430, 1408, 1374, 1326, 1248, 1128, 1086, 1056, 1026, 994, 932, 910, 836, 758, 698.

MS (EI, 70 eV): *m/z* (%) = 91 (15), 79 (16), 75 (100), 73 (34).

HR-MS (EI, 70 eV): [$C_{10}H_{20}OSi$], calcd.: 184.1283; found: 184.1277 ([M−Me]$^+$).

$[\alpha]_D^{20}$ = 11° (c = 0.94, CH_2Cl_2), 11° (c = 1.01, $CHCl_3$). Lit.: 7.9° (c = 0.55, $CHCl_3$).[138]



Alcohol S4. A dry and argon-flushed flask was charged with a solution of oxalyl chloride (0.48 mL, 5.56 mmol, 1.1 equiv.) in dichloromethane (25 mL) and the solution was cooled to −78 °C. DMSO (2.4 M in dichloromethane, 5.1 mL, 12.1 mmol, 12.4 equiv.) was slowly added. After 10 min, hept-6-yn-1-ol (597 mg, 5.06 mmol, 1.0 equiv.) in dichloromethane (10 mL) was slowly added. The reaction mixture was stirred for 10 min and trimethylamine (3.4 mL, 25.3 mmol, 5.0 equiv.) was added. The solution was stirred at room temperature for 1 h. After the addition of water, the phases were separated and the aqueous phase was extracted with diethyl ether. The combined organic layers were dried over $MgSO_4$ and the solvents were evaporated.

The crude material in THF (34 mL) was treated with MeMgCl (2.62 M, 2.32 mL, 6.07 mmol, 1.2 equiv.) at −78 °C. After 10 min at this temperature, the reaction mixture was allowed to warm to room

temperature. Saturated aqueous NH_4Cl solution was added, the phases were separated and the aqueous phase was extracted with diethyl ether. The combined organic layers were dried over $MgSO_4$. The crude product was purified by column chromatography on silica using pentane:diethyl ether (1:3) as an eluent to afford alcohol **S4** as a colourless oil (85%, 545 mg, 4.32 mmol).

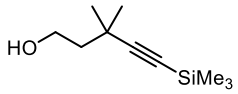
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 3.85 – 3.76 (m, 1H), 2.26 – 2.16 (m, 2H), 1.94 (t, J = 2.7 Hz, 1H), 1.60 – 1.36 (m, 7H), 1.19 (d, J = 6.2 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 84.4, 68.3, 67.9, 38.7, 28.4, 24.8, 23.5, 18.3.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3298, 2936, 2862, 1462, 1374, 1128, 1092, 1032, 932, 840.

MS (EI, 70 eV): *m/z* (%) = 95 (10), 93 (34), 91 (71), 81 (26), 79 (78), 78 (12), 77 (27), 67 (100), 65 (17).

HR-MS (EI, 70 eV): [$C_8H_{12}O$], calcd.: 124.0888; found: 124.0883 ([M−2H]$^+$).



Alcohol S5. A dry and argon-flushed flask was charged with a solution of 3-methylbut-1-yne (681 mg, 10.0 mmol, 1.0 equiv.) in diethyl ether (10.0 mL) and the solution was cooled to −20 °C. TMEDA (1.51 mL, 10 mmol, 1.0 equiv.) and *n*-BuLi (2.62 M in hexane, 7.63 mL, 20.0 mmol, 2.0 equiv.) was added slowly at this temperature. The reaction mixture was heated to 40 °C for 15 h. Then, it was cooled to −78 °C, ethylene oxide (5.49 M in THF, 5.49 mL, 13.0 mmol, 1.3 equiv.) was added dropwise. After 2 h at −78 °C, TMSCl (2.56 mL, 20 mmol, 2.0 equiv.) was added and the reaction mixture was stirred for 5 h at room temperature. HCl (2 N, 18.5 mL) was added and the solution was stirred overnight. Saturated aqueous NH_4Cl solution was added, the phases were separated and the aqueous phase was extracted with diethyl ether. The combined organic layers were dried over $MgSO_4$. The crude product was purified by column chromatography on silica using pentane:diethyl ether (2:1) as an eluent to afford alcohol **S5** as a colourless oil (26%, 487 mg, 2.64 mmol).

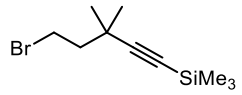
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 3.85 (dt, J = 6.1 Hz, 2H), 2.19 (t, J = 5.9 Hz, 1H), 1.70 (t, J = 6.3 Hz, 2H), 1.23 (s, 6H), 0.14 (s, 9H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 114.3, 84.9, 60.5, 45.4, 30.0, 29.6, 0.0.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3338, 2966, 2162, 1364, 1250, 1062, 1028, 992, 952, 928, 884, 838, 758, 738, 698.

MS (EI, 70 eV): *m/z* (%) = 169 (18), 151 (13), 141 (12), 140 (82), 139 (13), 123 (21), 99 (17), 97 (61), 75 (100), 73 (35).

HR-MS (EI, 70 eV): [$C_{10}H_{19}OSi$], calcd.: 183.1205; found: 183.1206 ([M−H]$^+$).



Bromide S6. A dry and argon-flushed flask was charged with a solution of PPh_3 (1.38 g, 5.26 mmol, 2.0 equiv.) and alcohol **S5** (485 mg, 2.63 mmol, 1.0 equiv.) in dichloromethane (4.0 mL). CBr_4 (1.74 g, 5.26 mmol, 2.0 equiv.) was added slowly at −78 °C. The reaction mixture was allowed to stir at room temperature for 2 h. A mixture of hexane:diethyl ether (4:1) was added and the solution was filtered through a pad of silica gel. The crude product was purified by column chromatography on silica using pentane as an eluent to afford bromide **S6** as a colourless oil (92%, 597 mg, 2.42 mmol).

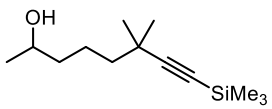
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 3.55 – 3.46 (m, 2H), 2.02 – 1.93 (m, 2H), 1.21 (s, 6H), 0.14 (s, 9H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 112.1, 84.9, 46.3, 32.6, 29.1, 29.1, 0.2.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2968, 2158, 1450, 1364, 1302, 1250, 1238, 936, 838, 758, 698, 658.

MS (EI, 70 eV): *m/z* (%) = 233 (32), 231 (31), 163 (10), 161 (10), 151 (11), 139 (100), 137 (93), 97 (32).

HR-MS (EI, 70 eV): [$C_{10}H_{19}BrSi$], calcd.: 246.0439; found: 246.0430 (M^+).



Alcohol S7. A dry and argon-flushed flask was charged with dry LiCl (113 mg, 2.66 mmol, 1.1 equiv.) and magnesium turnings (71 mg, 2.90 mmol, 1.2 equiv.) in THF (4.0 mL). A solution of bromide **S6** (598 mg, 2.42 mmol, 1.0 equiv.) in THF (0.8 mL) was added slowly at 0 °C. The reaction mixture was

allowed to stir at room temperature for 2 h. Following titration with iodine at 0 °C gave a concentration of 0.30 M for the corresponding Grignard reagent.

Following **TP1**, the Grignard reagent (0.30 M, 4.60 mL, 1.38 mmol, 1.1 equiv.) reacts with propylene oxide (73 mg, 1.25 mmol, 1.0 equiv.) using CuI (24 mg, 0.125 mmol, 10 mol%) to prepare **S7** at 0 °C. The solution was stirred at this temperature overnight and was worked-up as usual. The crude product was purified by column chromatography on silica using hexane:diethyl ether (2:1) as an eluent to afford **S7** as a colourless oil (82%, 256 mg, 1.13 mmol).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 3.83 (h, J = 6.2 Hz, 1H), 1.58 – 1.35 (m, 7H), 1.21 (d, J = 6.2 Hz, 3H), 1.18 (s, 3H), 1.18 (s, 3H), 0.13 (s, 9H).

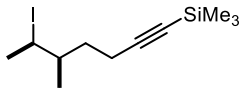
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 114.8, 83.3, 68.0, 43.1, 39.6, 31.8, 29.2, 29.1, 23.4, 21.5, 0.3.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3346, 2966, 2940, 2868, 2160, 1458, 1362, 1250, 1124, 952, 918, 838, 758, 696.

MS (EI, 70 eV): *m/z* (%) = 140 (11), 135 (21), 125 (24), 123 (17), 121 (10), 107 (14), 97 (68), 93 (20), 75 (100), 73 (65).

HR-MS (EI, 70 eV): [$C_{12}H_{23}OSi$], calcd.: 211.1518; found: 211.1510 ([M−Me]$^+$).

11.2 Iodination



Iodide *rac-(2R,3R)*-40a. Following **TP2,** *rac-(2S,3R)*-**42a** (1.20 g, 6.05 mmol, 1.0 equiv.) was used as starting material. The crude product was purified by column chromatography on silica using pentane:diethyl ether (200:1) as an eluent to afford *rac-(2R,3R)*-**40a** as a colourless oil (63%, 1.17 g, 3.80 mmol, d.r.>99:1).

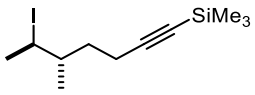
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 4.38 (qd, J = 7.0, 2.7 Hz, 1H), 2.26 (td, J = 7.2, 2.5 Hz, 2H), 1.91 (d, J = 7.0 Hz, 3H), 1.61 – 1.42 (m, 2H), 1.04 – 0.94 (m, 1H), 0.92 (d, J = 5.8 Hz, 3H), 0.14 (s, 9H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 106.7, 85.3, 40.2, 39.7, 36.0, 26.7, 17.4, 17.0, 0.3.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2961, 2860, 2175, 1444, 1380, 1307, 1248, 1192, 1182, 1115, 1054, 1042, 1019, 1007, 988, 954, 836, 758, 698.

MS (EI, 70 eV): *m/z* (%) = 185 (14), 121 (15), 107 (26), 74 (12), 73 (39), 73 (100), 73 (68), 59 (13).

HR-MS (EI, 70 eV): [$C_{11}H_{21}ISi$], calcd.: 308.0457; found: 308.0453 (M^+).



Iodide *rac-(2R,3S)*-40a. Following **TP2,** *rac-(2S,3S)*-**42a** (1.47 g, 7.41 mmol, 1.0 equiv.) was used as starting material. The crude product was purified by column chromatography on silica using pentane:diethyl ether (200:1) as an eluent to afford *rac-(2R,3S)*-**40a** as a colourless oil (51%, 1.17 g, 3.80 mmol, d.r.>99:1).

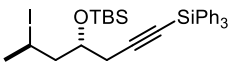
^{1}H-NMR (599 MHz, $CDCl_3$, ppm): δ = 4.35 (qd, *J* = 7.0, 3.4 Hz, 1H), 2.33 (ddd, *J* = 17.0, 7.7, 5.4 Hz, 1H), 2.21 (ddd, *J* = 17.0, 8.3, 7.3 Hz, 1H), 1.87 (d, *J* = 7.0 Hz, 3H), 1.73 (dtd, *J* = 13.2, 7.9, 3.7 Hz, 1H), 1.48 – 1.39 (m, 1H), 1.39 – 1.31 (m, 1H), 1.01 (d, *J* = 6.5 Hz, 3H), 0.15 (s, 9H).

^{13}C-NMR (151 MHz, $CDCl_3$, ppm): δ = 106.9, 85.2, 40.8, 39.1, 33.2, 25.2, 18.7, 17.9, 0.3.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2961, 2861, 2175, 1441, 1380, 1295, 1248, 1182, 1162, 1103, 1052, 1041, 987, 974, 837, 758, 698.

MS (EI, 70 eV): *m/z* (%) = 185 (12), 121 (11), 107 (19), 73 (100).

HR-MS (EI, 70 eV): [$C_{11}H_{21}ISi$], calcd.: 308.0457; found: 308.0448 (M^+).



Iodide *rac-(2R,4R)*-40b. A dry and argon flushed *Schlenk*-flask was charged with iodine (914 mg, 3.60 mmol, 1.2 equiv.) and dichloromethane (30 mL). PPh_3 (944 mg, 3.60 mmol, 1.2 equiv.) was added at 0 °C and the resulting yellow suspension was stirred for 1 h at this temperature. Then, *N*-methylimidazole (248 µL, 3.60 mmol, 1.2 equiv.) was added. After 10 min, *rac-(2S,4R)*-**42b** (1.50 g, 3.00 mmol, 1.0 equiv.) in dichloromethane (5 mL) was added dropwise and the reaction mixture was stirred for 30 min at 0 °C. The reaction mixture was quenched with saturated aqueous $NaHSO_3 \cdot Na_2S_2O_5$ solution, the phases were separated and the aqueous phase was extracted with dichloromethane. The combined organic layers were dried over $MgSO_4$ and the solvents were evaporated at 30 °C. The residue

was triturated three times with a mixture of hexane:diethyl ether (3:1). The residue was filtered off using a plug of silica and all organic phases were combined. All solvents were evaporated and the crude product was purified by column chromatography on silica using hexane:diethyl ether (70:1) as an eluent to afford *rac-(2R,4R)*-**40b** as a colourless solid (82%, 1.50 g, 2.46 mmol, d.r.>99:1).

m.p.: 89.0 – 89.8 °C.

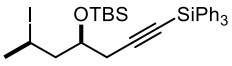
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.67 (dd, *J* = 7.9, 1.6 Hz, 6H), 7.47 – 7.34 (m, 9H), 4.28 (dqd, *J* = 13.7, 6.8, 2.5 Hz, 1H), 4.12 – 4.03 (m, 1H), 2.63 – 2.54 (m, 2H), 2.24 (ddd, *J* = 14.8, 11.4, 2.0 Hz, 1H), 1.97 (d, *J* = 6.9 Hz, 3H), 1.84 – 1.65 (m, 1H), 0.89 (s, 9H), 0.18 (s, 3H), 0.14 (s, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 135.7, 133.9, 129.9, 128.0, 108.4, 82.5, 71.3, 49.8, 29.9, 29.5, 28.2, 26.0, 18.1, −4.0, −4.1.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2955, 2929, 2855, 2173, 1484, 1468, 1428, 1374, 1363, 1257, 1221, 1163, 1127, 1111, 1104, 1057, 1032, 1004, 981, 929, 899, 836, 823, 806, 775, 740, 706, 696, 677.

MS (EI, 70 eV): *m/z* (%) = 425 (49), 259 (21), 185 (100), 105 (10), 73 (30).

HR-MS (EI, 70 eV): [$C_{27}H_{30}OISi_2$], calcd.: 553.0880; found: 553.0879 ([M−*t*-Bu]$^+$).



Iodide *rac-(2R,4S)*-40b. A dry and argon flushed *Schlenk*-flask was charged with iodine (1.52 mg, 5.99 mmol, 1.2 equiv.) and dichloromethane (50 mL). PPh_3 (1.57 g, 5.99 mmol, 1.2 equiv.) was added at 0 °C and the resulting yellow suspension was stirred for 1 h at this temperature. Then, *N*-methylimidazole (474 µL, 6.00 mmol, 1.2 equiv.) was added. After 10 min, *rac-(2S,4S)*-**42b** (2.50 g, 4.99 mmol, 1.0 equiv.) in dichloromethane (5 mL) was added dropwise and the reaction mixture was stirred for 30 min at 0 °C. The reaction mixture was quenched with saturated aqueous $NaHSO_3{\cdot}Na_2S_2O_5$ solution, the phases were separated and the aqueous phase was extracted with dichloromethane. The combined organic layers were dried over $MgSO_4$ and the solvents were evaporated at 30 °C. The residue was triturated three times with a mixture of hexane:diethyl ether (3:1). The residue was filtered off using a plug of silica and all organic phases were combined. All solvents were evaporated and the crude product was purified by column chromatography on silica using hexane:diethyl ether (70:1) as an eluent to afford *rac-(2R,4S)*-**40b** as a colourless oil (78%, 2.38 g, 3.90 mmol, d.r.>99:1).

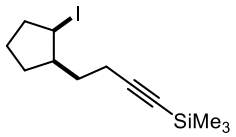
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.70 (d, J = 6.3 Hz, 6H), 7.50 – 7.36 (m, 9H), 4.27 (h, J = 6.9 Hz, 1H), 4.05 (p, J = 5.7 Hz, 1H), 2.61 (d, J = 5.1 Hz, 2H), 2.30 (qt, J = 14.4, 7.2 Hz, 1H), 2.19 (dt, J = 14.0 and 6.4, 1H), 1.92 (d, J = 6.8 Hz, 3H), 0.93 (s, 9H), 0.13 (s, 6H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 135.6, 133.9, 130.0, 128.1, 108.0, 82.5, 70.5, 49.8, 28.8, 28.4, 25.9, 24.3, 18.1, −4.3, −4.5.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2953, 2928, 2894, 2856, 2178, 1484, 1471, 1462, 1428, 1377, 1360, 1255, 1211, 1112, 1085, 1029, 998, 982, 937, 921, 835, 804, 775, 739, 707, 696.

MS (EI, 70 eV): *m/z* (%) = 425 (50), 357 (19), 305 (14), 283 (13), 259 (32), 218 (36), 185 (100), 105 (10), 73 (52).

HR-MS (EI, 70 eV): [$C_{27}H_{30}OISi_2$], calcd.: 553.0880; found: 553.0877 ([M−*t*-Bu]$^+$).



Iodide *syn*-40c. Following **TP2,** *anti*-**42c** (636 mg, 3.02 mmol, 1.0 equiv.) was used as starting material. The crude product was purified by column chromatography on silica using pentane:diethyl ether (300:1) as an eluent to afford *syn*-**40c** as a colourless oil (92%, 894 mg, 2.79 mmol, d.r.>99:1).

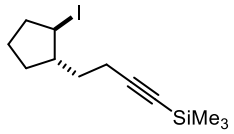
^{1}H-NMR (599 MHz, $CDCl_3$, ppm): δ = 4.57 (t, J = 4.4 Hz, 1H), 2.38 – 2.18 (m, 4H), 2.01 – 1.91 (m, 1H), 1.82 – 1.74 (m, 1H), 1.74 – 1.62 (m, 2H), 1.55 (dq, J = 14.0, 7.2 Hz, 1H), 1.43 (dtd, J = 12.3, 11.0, 6.2 Hz, 1H), 1.14 – 1.04 (m, 1H), 0.14 (s, 9H).

^{13}C-NMR (151 MHz, $CDCl_3$, ppm): δ = 106.9, 85.0, 45.9, 44.6, 39.1, 35.4, 28.9, 21.8, 18.5, 0.3.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2957, 2852, 2174, 1447, 1441, 1336, 1324, 1308, 1291, 1248, 1224, 1200, 1159, 1046, 1021, 999, 905, 836, 758, 697, 667.

MS (EI, 70 eV): *m/z* (%) = 119 (17), 73 (100).

HR-MS (EI, 70 eV): [$C_{12}H_{21}ISi$], calcd.: 320.0457; found: 320.0471 (M$^+$).



Iodide *anti*-40c. Following **TP2,** *syn*-**42c** (401 mg, 1.91 mmol, 1.0 equiv.) was used as starting material. The crude product was purified by column chromatography on silica using pentane:diethyl ether (300:1) as an eluent to afford *anti*-**40c** as a colourless oil (43%, 260 mg, 0.812 mmol, d.r.>99:1).

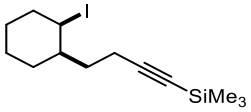
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 3.76 (q, J = 7.9 Hz, 1H), 2.38 – 2.15 (m, 4H), 2.13 – 2.02 (m, 1H), 2.02 – 1.90 (m, 1H), 1.90 – 1.80 (m, 1H), 1.80 – 1.70 (m, 1H), 1.70 – 1.57 (m, 1H), 1.42 – 1.28 (m, 1H), 1.27 – 1.14 (m, 1H), 0.15 (s, 9H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 106.8, 84.8, 50.9, 39.0, 32.8, 32.0, 29.2, 23.7, 18.5, 0.1.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2958, 2872, 2175, 1449, 1328, 1248, 1190, 1113, 1038, 1000, 907, 836, 758, 697.

MS (EI, 70 eV): *m/z* (%) = 193 (10), 185 (17), 119 (30), 73 (100), 59 (11).

HR-MS (EI, 70 eV): [$C_{12}H_{21}ISi$], calcd.: 320.0457; found: 320.0451 (M^+).



Iodide *syn*-40d. Following **TP2,** *anti*-**42d** (1.59 g, 7.08 mmol, 1.0 equiv.) was used as starting material. The crude product was purified by column chromatography on silica using pentane:diethyl ether (300:1) as an eluent to afford *syn*-**40d** as a colourless oil (45%, 1.07 g, 3.20 mmol, d.r.>99:1).

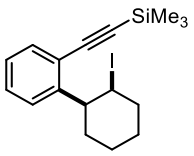
^{1}H-NMR (599 MHz, $CDCl_3$, ppm): δ = 4.77 – 4.70 (m, 1H), 2.27 – 2.17 (m, 3H), 1.81 – 1.70 (m, 3H), 1.62 – 1.54 (m, 1H), 1.52 – 1.44 (m, 2H), 1.44 – 1.24 (m, 3H), 0.71 – 0.62 (m, 1H), 0.15 (s, 9H).

^{13}C-NMR (151 MHz, $CDCl_3$, ppm): δ = 106.8, 85.3, 47.2, 41.3, 36.8, 36.5, 28.8, 25.6, 22.9, 16.7, 0.3.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2931, 2855, 2835, 2174, 1458, 1445, 1433, 1356, 1312, 1297, 1248, 1191, 1180, 1154, 1065, 1041, 994, 966, 912, 896, 886, 865, 836, 758, 697.

MS (EI, 70 eV): *m/z* (%) = 207 (29), 185 (10), 147 (22), 133 (27), 91 (14), 73 (100), 59 (11).

HR-MS (EI, 70 eV): [$C_{13}H_{23}ISi$], calcd.: 334,0614; found: 334.0608 (M^+).



Iodide *syn*-40e. Following **TP2,** *anti*-**42e** (1.81 g, 6.63 mmol, 1.0 equiv.) was used as starting material. The crude product was purified by column chromatography on silica using pentane:diethyl ether (200:1) as an eluent to afford *syn*-**40e** as a sticky yellow oil (3%, 67 mg, 0.175 mmol, d.r.>99:1).

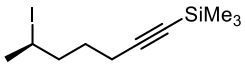
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.44 (dd, J = 7.5, 1.2 Hz, 1H), 7.31 (td, J = 7.6, 1.5 Hz, 1H), 7.18 (td, J = 7.5, 1.3 Hz, 1H), 7.13 (d, J = 8.0 Hz, 1H), 5.26 – 5.19 (m, 1H), 2.59 (dt, J = 12.1, 2.8 Hz, 1H), 2.36 – 2.26 (m, 1H), 2.05 (qd, J = 12.6, 3.5 Hz, 1H), 1.99 – 1.84 (m, 3H), 1.75 – 1.63 (m, 2H), 1.62 – 1.48 (m, 1H), 0.27 (s, 9H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 146.9, 132.5, 128.5, 127.0, 126.5, 122.1, 103.6, 99.1, 47.4, 46.3, 37.1, 27.3, 26.4, 22.3, 0.2.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2932, 2858, 2152, 1480, 1446, 1432, 1294, 1248, 1224, 1180, 1156, 1042, 988, 902, 890, 858, 838, 754, 734, 698.

MS (EI, 70 eV): *m/z* (%) = 256 (19), 255 (92), 196 (13), 195 (100), 185 (13), 185 (10), 181 (23), 167 (11), 165 (12), 73 (28).

HR-MS (EI, 70 eV): [$C_{17}H_{23}ISi$], calcd.: 382.0614; found: 382.0602 (M^+).



Iodide *R*-40f. Following **TP2,** *S*-**42f** (855 mg, 4.64 mmol, 1.0 equiv.) was used as starting material. The crude product was purified by column chromatography on silica using pentane:diethyl ether (200:1) as an eluent to afford *R*-**40f** as a colourless oil (90%, 1.23 g, 4.19 mmol, e.r.(*R*:*S*) = 98:2[VIII]).

[VIII] Flow rate = 2.1 mL/min; T = 80 °C; average velocity = 60; hold 80 °C for 20 min, 2 °C/min heating rate to 140 °C and holding for 10 min. Retention times: 48.1 min (minor), 48.3 min (major).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 4.28 – 4.15 (m, 1H), 2.31 – 2.21 (m, 2H), 1.96 – 1.84 (m, 4H), 1.80 – 1.68 (m, 2H), 1.67 – 1.55 (m, 1H), 0.15 (s, 9H).

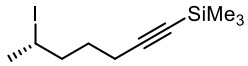
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 106.7, 85.3, 41.9, 29.5, 29.1, 28.7, 19.1, 0.3.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2958, 2900, 2864, 2834, 2174, 1444, 1430, 1408, 1378, 1326, 1298, 1274, 1248, 1218, 1204, 1186, 1138, 1116, 1090, 1056, 1032, 1022, 992, 972, 922, 906, 836, 758, 698.

MS (EI, 70 eV): *m/z* (%) = 185 (43), 127 (22), 93 (20), 75 (34), 73 (100).

HR-MS (EI, 70 eV): [$C_{10}H_{19}ISi$], calcd.: 294.0301; found: 294.0293 (M^+).

$[\alpha]_D^{20}$ = –39° (c = 0.94, CH_2Cl_2).



Iodide *S*-40f. Following **TP2,** *S*-**42f** (313 mg, 1.70 mmol, 1.0 equiv.) was used as starting material. The crude product was purified by column chromatography on silica using pentane:diethyl ether (200:1) as an eluent to afford *S*-**40f** as a colourless oil (88%, 442 mg, 1.50 mmol, e.r.(*R:S*) = 97:3[IX]).

^{1}H-NMR (599 MHz, $CDCl_3$, ppm): δ = 4.26 – 4.16 (m, 1H), 2.30 – 2.22 (m, 2H), 1.94 (d, *J* = 6.8 Hz, 3H), 1.92 – 1.86 (m, 1H), 1.79 – 1.69 (m, 2H), 1.65 – 1.57 (m, 1H), 0.15 (s, 9H).

^{13}C-NMR (151 MHz, $CDCl_3$, ppm): δ = 106.7, 85.3, 41.9, 29.6, 29.1, 28.7, 19.1, 0.3.

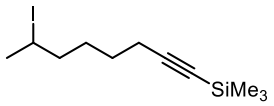
FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2958, 2863, 2174, 1444, 1378, 1326, 1298, 1248, 1218, 1187, 1139, 1116, 1090, 1032, 992, 972, 905, 837, 758, 698.

MS (EI, 70 eV): *m/z* (%) = 184 (15), 93 (12), 73 (100).

HR-MS (EI, 70 eV): [$C_{10}H_{19}ISi$], calcd.: 294.0301; found: 294.0297 (M^+).

$[\alpha]_D^{20}$ = 42° (c = 1.0, CH_2Cl_2).

[IX] Flow rate = 2.1 mL/min; T = 80 °C; average velocity = 60; hold 80 °C for 20 min, 2 °C/min heating rate to 140 °C and holding for 10 min. Retention times: 48.1 min (major), 48.4 min (minor).



Iodide 61a. Alcohol **S4** (535 mg, 4.239 mmol, 1.0 equiv.) in THF (4.2 mL) was treated with *n*-BuLi (2.62 M, 3.3 mL, 8.69 mmol, 2.05 equiv.) at −78 °C and stirred for 1 h at this temperature. TMSCl (1.13 mL, 8.69 mmol, 2.05 equiv.) was added. The reaction mixture was allowed to warm to room temperature and was stirred for 30 min. HCl (2 N, 4.2 mL) was added and the solution as stirred overnight. The reaction mixture was neutralised with saturated aqueous $NaHCO_3$ solution. The phases were separated and the aqueous phase was extracted with diethyl ether. The combined organic layers were dried over $MgSO_4$ and the solvents were evaporated.

Following **TP2**, the crude material without further purification. The crude product was purified by column chromatography on silica using hexane:diethyl ether (100:1) as an eluent to afford **61a** as a colourless oil (88%, 1.12 g, 3.62 mmol).

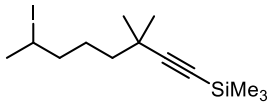
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 4.22 – 4.14 (m, 1H), 2.27 – 2.19 (m, 2H), 1.93 (d, J = 6.8 Hz, 3H), 1.90 – 1.80 (m, 1H), 1.69 – 1.43 (m, 5H), 0.15 (s, 9H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 107.0, 84.8, 42.2, 30.0, 28.8, 28.8, 27.6, 19.7, 0.1.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2938, 2860, 2174, 1444, 1378, 1248, 1136, 1042, 930, 838, 758, 696.

MS (EI, 70 eV): *m/z* (%) = 278 (11), 277 (29), 262 (28), 185 (25), 183 (28), 107 (20), 73 (100), 58 (16), 43 (31).

HR-MS (EI, 70 eV): [$C_{11}H_{21}ISi$], calcd.: 308.0457; found: 308.0444 (M^+).



Iodide 61b. Following **TP2, S7** (203 mg, 0.896 mmol, 1.0 equiv.) was used as starting material. The crude product was purified by column chromatography on silica using hexane as an eluent to afford **61b** as a colourless oil (94%, 284 mg, 0.844 mmol).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 4.28 – 4.17 (m, 1H), 1.93 (d, J = 6.8 Hz, 3H), 1.92 – 1.82 (m, 1H), 1.70 – 1.58 (m, 2H), 1.57 – 1.48 (m, 1H), 1.46 – 1.31 (m, 2H), 1.18 (s, 6H), 0.14 (s, 9H).

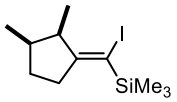
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 114.4, 83.5, 43.1, 42.2, 31.7, 30.3, 29.2, 29.0, 28.8, 25.5, 0.3.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2962, 2162, 1446, 1378, 1362, 1248, 1202, 1192, 1178, 950, 928, 890, 838, 758, 696.

MS (EI, 70 eV): *m/z* (%) = 185 (39), 136 (10), 135 (100), 123 (12), 109 (10), 107 (33), 97 (47), 93 (18), 75 (52), 73 (81).

HR-MS (EI, 70 eV): [$C_{10}H_{15}$], calcd.: 135.1174; found: 135.1168 ([M−I−$SiMe_3$−H]$^+$).

11.3 Intramolecular Carbolithiations



Cyclopentane *syn*-49a. Following **TP3,** *syn*-**40a** (91 mg, 0.295 mmol, 1.0 equiv., d.r.>99:1) reacted with *t*-BuLi (2.08 M, 0.35 mL, 0.738 mmol, 2.5 equiv.) and I_2 (188 mg, 0.738 mmol, 2.5 equiv.) in diethyl ether (1.0 mL). The crude product was purified by column chromatography on silica using pentane as an eluent to afford *syn*-**49a** as a colourless oil (71%, 64 mg, 0.208 mmol, d.r.>99:1).

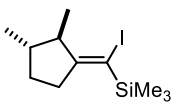
^{1}H-NMR (400 MHz, C_6D_6, ppm): δ = 2.94 (dq, *J* = 7.1 Hz, 1H), 2.31 (ddt, *J* = 17.4, 9.2, 1.4 Hz, 1H), 2.10 (ddd, *J* = 17.5, 10.7, 8.4 Hz, 1H), 1.81 (tq, *J* = 12.3, 6.1, 5.7 Hz, 1H), 1.76 – 1.67 (m, 1H), 1.41 – 1.25 (m, 1H), 0.94 (d, *J* = 7.2 Hz, 3H), 0.78 (d, *J* = 6.7 Hz, 3H), 0.26 (s, 9H).

^{13}C-NMR (101 MHz, C_6D_6, ppm): δ = 168.4, 99.7, 53.8, 36.7, 33.7, 32.7, 14.9, 11.1, 1.2.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2957, 2871, 1592, 1463, 1431, 1405, 1378, 1368, 1352, 1284, 1261, 1247, 1159, 1073, 1032, 966, 940, 909, 867, 833, 755, 746, 688, 654.

MS (EI, 70 eV): *m/z* (%) = 308 (13), 184 (15), 180 (13), 107 (18), 73 (100).

HR-MS (EI, 70 eV): [$C_{11}H_{21}ISi$], calcd.: 308.0457; found: 308.0452 (M$^+$).



Cyclopentane *anti*-49a. Following **TP3,** *anti*-**40a** (91 mg, 0.295 mmol, 1.0 equiv., d.r.>99:1) reacted with *t*-BuLi (1.96 M, 0.38 mL, 0.738 mmol, 2.5 equiv.) and I_2 (188 mg, 0.738 mmol, 2.5 equiv.) in THF

(1.0 mL). The crude product was purified by column chromatography on silica using pentane as an eluent to afford *anti*-**49a** as a colourless oil (77%, 70 mg, 0.227 mmol, d.r.>99:1).

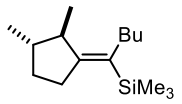
^{1}H-NMR (400 MHz, C_6D_6, ppm): δ = 2.61 – 2.48 (m, 1H), 2.39 – 2.27 (m, 1H), 2.14 (dddd, *J* = 16.5, 8.4, 6.6, 1.6 Hz, 1H), 1.78 (ddt, *J* = 12.6, 8.6, 6.5 Hz, 1H), 1.61 – 1.48 (m, 1H), 1.29 – 1.15 (m, 1H), 1.15 (d, *J* = 7.1 Hz, 3H), 0.79 (d, *J* = 6.9 Hz, 3H), 0.26 (s, 9H).

^{13}C-NMR (101 MHz, C_6D_6, ppm): δ = 167.6, 100.7, 56.7, 40.7, 33.8, 32.6, 19.8, 18.6, 1.2.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2952, 2925, 2869, 1594, 1454, 1434, 1405, 1369, 1304, 1262, 1247, 1179, 1090, 1006, 988, 922, 910, 865, 834, 755, 688.

MS (EI, 70 eV): *m/z* (%) = 308 (12), 184 (13), 181 (11), 107 (17), 73 (100).

HR-MS (EI, 70 eV): [$C_{11}H_{21}ISi$], calcd.: 308.0457; found: 308.0456 (M^+).



Cyclopentane *anti*-50. A dry and argon-flushed *Schlenk*-tube was charged with CuI (123 mg, 0.633 mmol, 3.0 equiv.) and THF (1.3 mL). A lithium thiophenolate solution (1.16 M in THF, 0.55 mL, 0.633 mmol, 3.0 equiv.) was added and the reaction mixture was stirred for 5 min. After cooling to −78 °C, *n*-BuLi (2.62 M in hexane, 0.24 mL, 0.627 mmol, 2.97 equiv) was added. After 5 min at −78 °C, a precooled solution of *anti*-**49a** (65 mg, 0.211 mmol, 1.0 equiv.) in THF (1.0 mL) was injected. The reaction mixture was stirred at −5 °C for 45 h. Saturated aqueous NH_4Cl solution was added, the phases were separated and the aqueous phase was extracted with diethyl ether. The combined organic layers were dried over $MgSO_4$. The solvents were evaporated and the crude product was purified by column chromatography on silica using pentane as an eluent to afford *anti*-**50** as a colourless oil (80%, 40 mg, 0.168 mmol, d.r.>99:1).

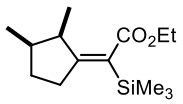
^{1}H-NMR (400 MHz, C_6D_6, ppm): δ = 2.46 – 2.34 (m, 2H), 2.34 – 2.24 (m, 2H), 2.22 – 2.11 (m, 1H), 1.84 (ddt, *J* = 12.4, 8.5, 6.3 Hz, 1H), 1.65 – 1.53 (m, 1H), 1.44 – 1.34 (m, 4H), 1.19 (dtd, *J* = 12.4, 7.2, 5.3 Hz, 1H), 1.05 (d, *J* = 7.0 Hz, 3H), 0.94 (t, *J* = 7.2 Hz, 3H), 0.90 (d, *J* = 6.9 Hz, 3H), 0.23 (s, 9H).

^{13}C-NMR (101 MHz, C_6D_6, ppm): δ = 159.0, 130.8, 45.2, 41.3, 33.9, 33.3, 32.2, 31.6, 23.5, 20.9, 20.5, 14.4, 0.5.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2952, 2926, 2870, 1612, 1456, 1404, 1372, 1246, 1056, 1004, 896, 856, 830, 754, 708, 684.

MS (EI, 70 eV): *m/z* (%) = 238 (14), 223 (21), 164 (83), 149 (18), 139 (10), 121 (17), 108 (15), 95 (21), 73 (100).

HR-MS (EI, 70 eV): [$C_{15}H_{30}Si$], calcd.: 238.2117; found: 238.2129 (M^+).



Cyclopentane *syn*-49b. Following **TP3,** *syn*-**40a** (91 mg, 0.295 mmol, 1.0 equiv., d.r.>99:1) reacted with *t*-BuLi (2.21 M, 0.33 mL, 0.738 mmol, 2.5 equiv.) and $ClCO_2Et$ (80 mg, 0.738 mmol, 2.5 equiv.). The crude product was purified by column chromatography on silica using pentane:diethyl ether (30:1) as an eluent to afford *syn*-**49b** as a colourless oil (65%, 49 mg, 0.193 mmol, d.r.>99:1).

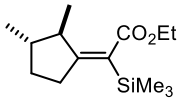
^{1}H-NMR (400 MHz, C_6D_6, ppm): δ = 4.16 – 4.01 (m, 2H), 3.09 (dq, *J* = 7.2 Hz, 1H), 2.40 (ddt, *J* = 17.9, 9.3, 1.7 Hz, 1H), 2.21 (ddd, *J* = 17.9, 10.2, 8.6 Hz, 1H), 1.87 – 1.71 (m, 1H), 1.59 – 1.47 (m, 1H), 1.25 (tdd, *J* = 12.3, 9.9, 9.1 Hz, 1H), 1.05 (t, *J* = 7.1 Hz, 3H), 1.00 (d, *J* = 7.3 Hz, 3H), 0.81 (d, *J* = 6.8 Hz, 3H), 0.25 (s, 9H).

^{13}C-NMR (101 MHz, C_6D_6, ppm): δ = 171.5, 169.2, 127.6, 59.8, 44.1, 37.4, 32.3, 30.8, 15.0, 14.5, 13.7, −0.1.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2958, 2902, 2874, 1708, 1612, 1464, 1450, 1428, 1378, 1368, 1282, 1248, 1224, 1188, 1140, 1096, 1074, 1040, 1014, 998, 980, 960, 916, 878, 834, 794, 782, 758, 716, 692.

MS (EI, 70 eV): *m/z* (%) = 238 (15), 224 (10), 223 (100), 109 (16), 195 (14), 193 (19), 179 (17), 103 (11), 75 (26), 73 (13).

HR-MS (EI, 70 eV): [$C_{14}H_{26}O_2Si$], calcd.: 254.1702; found: 254.1696 (M^+).



Cyclopentane *anti*-49b. Following **TP3,** *anti*-**40a** (91 mg, 0.295 mmol, 1.0 equiv., d.r.>99:1) reacted with *t*-BuLi (2.09 M, 0.35 mL, 0.738 mmol, 2.5 equiv.) and $ClCO_2Et$ (80 mg, 0.738 mmol, 2.5 equiv.).

The crude product was purified by column chromatography on silica using pentane:diethyl ether (20:1) as an eluent to afford *anti*-**49b** as a colourless oil (77%, 58 mg, 0.228 mmol, d.r.>99:1).

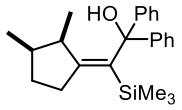
^{1}H-NMR (400 MHz, C_6D_6, ppm): δ = 4.16 – 4.00 (m, 2H), 2.69 – 2.57 (m, 1H), 2.38 (ddd, *J* = 17.0, 7.7, 5.5 Hz, 1H), 2.22 (dddd, *J* = 16.9, 8.6, 7.7, 2.0 Hz, 1H), 1.71 (ddt, *J* = 11.9, 8.7, 5.8 Hz, 1H), 1.47 (dq, *J* = 13.2, 6.7 Hz, 1H), 1.15 (d, *J* = 7.0 Hz, 3H), 1.12 – 1.01 (m, 4H), 0.83 (d, *J* = 6.8 Hz, 3H), 0.25 (s, 9H).

^{13}C-NMR (101 MHz, C_6D_6, ppm): δ = 171.5, 167.6, 128.1, 59.8, 47.7, 41.6, 32.1, 32.0, 19.7, 19.7, 14.5, –0.1.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2954, 2871, 1708, 1612, 1457, 1374, 1365, 1248, 1224, 1198, 1178, 1145, 1096, 1040, 1006, 970, 877, 835, 760, 693.

MS (EI, 70 eV): *m/z* (%) = 254 (14), 239 (24), 238 (43), 224 (17), 223 (100), 209 (28), 195 (13), 193 (23), 121 (12), 103 (40), 95 (20), 75 (43), 73 (47).

HR-MS (EI, 70 eV): [$C_{14}H_{26}O_2Si$], calcd.: 254.1702; found: 254.1697 (M^+).



Cyclopentane *syn*-49c. Following **TP3,** *syn*-**40a** (91 mg, 0.295 mmol, 1.0 equiv., d.r.>99:1) reacted with *t*-BuLi (2.16 M, 0.34 mL, 0.738 mmol, 2.5 equiv.) and benzophenone (134 mg, 0.738 mmol, 2.5 equiv.) in diethyl ether (1.0 mL). The crude product was purified by column chromatography on silica using pentane:diethyl ether (40:1) as an eluent to afford *syn*-**49c** as a colourless solid (65%, 70 mg, 0.192 mmol, d.r.>99:1). Recrystallization of the product from pentane gave crystals suitable for single crystal X-ray diffraction analysis.

m.p.: 76.4 – 84.6 °C.

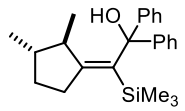
^{1}H-NMR (400 MHz, C_6D_6, ppm): δ = 7.46 – 7.40 (m, 2H), 7.32 – 7.26 (m, 2H), 7.16 – 7.12 (m, 2H), 7.11 – 7.02 (m, 4H), 2.73 – 2.51 (m, 2H), 2.37 (s, 1H), 1.78 – 1.54 (m, 3H), 1.28 – 1.08 (m, 1H), 0.67 (d, *J* = 6.4 Hz, 3H), 0.32 (d, *J* = 6.9 Hz, 3H), 0.30 (s, 9H).

^{13}C-NMR (101 MHz, C_6D_6, ppm): δ = 161.6, 148.9, 148.7, 138.3, 128.9, 128.5, 128.2, 127.9, 127.4, 127.3, 85.1, 42.2, 37.0, 32.7, 29.2, 15.5, 11.7, 4.1.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3578, 3462, 3058, 2966, 2938, 2894, 2872, 1584, 1488, 1468, 1444, 1412, 1376, 1370, 1318, 1296, 1284, 1260, 1242, 1220, 1178, 1158, 1080, 1072, 1024, 1016, 990, 982, 962, 936, 918, 906, 896, 866, 836, 764, 740, 700, 672.

MS (EI, 70 eV): *m/z* (%) = 346 (21), 331 (15), 279 (12), 274 (12), 273 (16), 272 (16), 217 (21), 184 (12), 183 (100), 178 (20), 135 (22), 105 (35), 77 (10), 75 (14), 73 (54).

HR-MS (EI, 70 eV): [$C_{24}H_{32}OSi$], calcd.: 364.2222; found: 364.2219 (M^+).



Cyclopentane *anti*-49c. Following **TP3,** *anti*-**40a** (91 mg, 0.295 mmol, 1.0 equiv., d.r.>99:1) reacted with *t*-BuLi (2.21 M, 0.33 mL, 0.738 mmol, 2.5 equiv.) and benzophenone (134 mg, 0.738 mmol, 2.5 equiv.) in diethyl ether (1.0 mL). The crude product was purified by column chromatography on silica using pentane:diethyl ether (40:1) as an eluent to afford *syn*-**49c** as a colourless oil (76%, 82 mg, 0.225 mmol, d.r.>99:1).

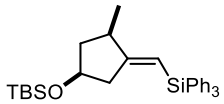
^{1}H-NMR (400 MHz, C_6D_6, ppm): δ = 7.44 – 7.38 (m, 2H), 7.26 – 7.20 (m, 2H), 7.20 – 7.17 (m, 2H), 7.14 – 7.08 (m, 1H), 7.03 – 6.98 (m, 3H), 2.62 (ddd, *J* = 15.7, 7.6, 4.8 Hz, 1H), 2.59 – 2.46 (m, 1H), 2.41 (s, 1H), 1.82 – 1.70 (m, 1H), 1.39 – 1.26 (m, 1H), 1.24 – 1.14 (m, 1H), 1.04 (dtd, *J* = 12.2, 7.9, 6.0 Hz, 1H), 0.66 (d, *J* = 6.8 Hz, 3H), 0.63 (d, *J* = 7.0 Hz, 3H), 0.26 (s, 9H).

^{13}C-NMR (101 MHz, C_6D_6, ppm): δ = 160.4, 149.7, 147.1, 139.9, 129.0, 128.8, 128.2, 127.9, 127.4, 127.3, 84.9, 43.7, 41.6, 34.3, 31.6, 21.2, 20.6, 3.6.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3610, 3084, 3060, 3024, 2950, 2924, 2898, 2868, 1584, 1490, 1446, 1408, 1370, 1280, 1260, 1246, 1180, 1158, 1094, 1082, 1048, 1030, 1002, 994, 976, 922, 898, 862, 832, 786, 760, 742, 700, 676.

MS (EI, 70 eV): *m/z* (%) = 346 (45), 331 (34), 279 (29), 274 (28), 273 (34), 272 (39), 217 (33), 183 (100), 178 (23), 135 (20), 105 (28), 73 (52).

HR-MS (EI, 70 eV): [$C_{24}H_{32}OSi$], calcd.: 364.2222; found: 364.2214 (M^+).



Cyclopentane *syn*-49d. Following **TP3,** *anti*-**40b** (176 mg, 0.288 mmol, 1.0 equiv., d.r.>99:1) reacted with *t*-BuLi (2.22 M, 0.32 mL, 0.720 mmol, 2.5 equiv.) and was quenched with saturated aqueous NH_4Cl solution. The crude product was purified by column chromatography on silica using hexane:diethyl ether (700:1) as an eluent to afford *syn*-**49d** as a colourless oil (99%, 138 mg, 0.285 mmol, d.r.>99:1).

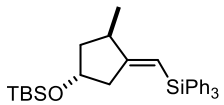
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.59 – 7.52 (m, 6H), 7.40 – 7.33 (m, 9H), 5.91 – 5.82 (m, 1H), 4.04 (p, *J* = 6.7 Hz, 1H), 2.63 – 2.51 (m, 1H), 2.18 (dd, *J* = 17.4, 6.6 Hz, 1H), 2.12 – 2.03 (m, 1H), 1.97 – 1.87 (m, 1H), 1.32 (dt, *J* = 12.3, 8.4 Hz, 1H), 1.25 (d, *J* = 6.8 Hz, 3H), 0.78 (s, 9H), −0.09 (s, 3H), −0.15 (s, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 170.3, 135.9, 135.8, 129.4, 128.0, 112.3, 72.4, 43.8, 43.5, 40.0, 26.0, 20.4, 18.2, −4.7, −4.7.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3069, 3050, 2999, 2956, 2928, 2856, 1622, 1485, 1472, 1462, 1428, 1388, 1369, 1362, 1332, 1304, 1255, 1188, 1157, 1110, 1052, 1030, 1006, 998, 938, 919, 874, 836, 808, 776, 739, 699, 670, 656.

MS (EI, 70 eV): *m/z* (%) = 427 (40), 349 (37), 333 (47), 271 (41), 269 (28), 260 (23), 259 (100), 258 (24), 257 (92), 255 (56), 197 (21), 183 (49), 179 (23), 75 (39), 73 (28).

HR-MS (EI, 70 eV): [$C_{31}H_{40}OSi_2$], calcd.: 484.2618; found: 484.2601 (M^+).



Cyclopentane *anti*-49d. Following **TP3,** *syn*-**40b** (171 mg, 0.280 mmol, 1.0 equiv., d.r.>99:1) reacted with *t*-BuLi (2.15 M, 0.33 mL, 0.700 mmol, 2.5 equiv.) and was quenched with saturated aqueous NH_4Cl solution. The crude product was purified by column chromatography on silica using hexane:diethyl ether (700:1) as an eluent to afford *anti*-**49d** as a colourless oil (55%, 75 mg, 0.155 mmol, d.r.>99:1). Recrystallization of the product from hexane gave crystals suitable for single crystal X-ray diffraction analysis.

m.p.: 79.3 – 87.5 °C.

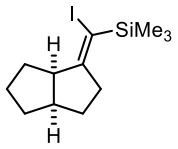
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.63 – 7.51 (m, 6H), 7.42 – 7.32 (m, 9H), 5.89 (q, *J* = 2.3 Hz, 1H), 4.13 (tt, *J* = 4.9, 2.6 Hz, 1H), 3.00 – 2.84 (m, 1H), 2.14 – 1.97 (m, 2H), 1.89 (ddt, *J* = 12.5, 7.7, 2.3 Hz, 1H), 1.39 – 1.27 (m, 1H), 1.19 (d, *J* = 7.0 Hz, 3H), 0.83 (s, 9H), -0.06 (s, 3H), -0.11 (s, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 171.3, 135.9, 135.8, 129.3, 127.9, 111.6, 71.9, 44.2, 43.9, 39.1, 26.0, 19.3, 18.2, −4.7, −4.7.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3069, 3049, 2955, 2927, 2856, 1616, 1471, 1462, 1428, 1409, 1373, 1361, 1307, 1254, 1198, 1109, 1084, 1052, 1030, 1012, 998, 947, 924, 896, 835, 802, 774, 739, 699.

MS (EI, 70 eV): *m/z* (%) = 271 (29), 259 (48), 257 (21), 255 (21), 207 (23), 199 (23), 183 (27), 181 (26), 179 (41), 91 (21), 79 (28), 78 (78), 77 (31), 75 (100).

HR-MS (EI, 70 eV): [$C_{21}H_{25}OSi_2$], calcd.: 349.1444; found: 349.1434 ([M−H−Ph−*t*-Bu]$^+$).



Bicyclo[3.3.0]octane *syn*-51a. Following **TP3,** *syn*-**40c** (96 mg, 0.300 mmol, 1.0 equiv., d.r.>99:1) reacted with *t*-BuLi (1.96 M, 0.38 mL, 0.750 mmol, 2.5 equiv.) and I_2 (191 mg, 0.750 mmol, 2.5 equiv.) in diethyl ether (1.0 mL). The crude product was purified by column chromatography on silica using pentane as an eluent to afford *syn*-**51a** as a colourless oil (63%, 61 mg, 0.190 mmol, d.r.>99:1).

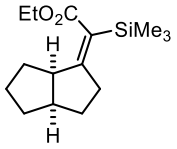
^{1}H-NMR (400 MHz, C_6D_6, ppm): δ = 3.12 (dt, *J* = 8.4 Hz, 1H), 2.47 – 2.33 (m, 1H), 2.33 – 2.10 (m, 3H), 1.72 – 1.54 (m, 2H), 1.54 – 1.44 (m, 1H), 1.44 – 1.27 (m, 3H), 1.22 – 1.07 (m, 1H), 0.27 (s, 9H).

^{13}C-NMR (101 MHz, C_6D_6, ppm): δ = 169.5, 100.4, 59.4, 43.2, 34.1, 33.7, 33.7, 32.8, 26.9, 1.4.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2946, 2864, 1596, 1448, 1432, 1405, 1313, 1260, 1246, 1204, 1176, 1084, 936, 835, 810, 756, 733, 688.

MS (EI, 70 eV): *m/z* (%) = 320 (12), 185 (14), 119 (50), 74 (15), 73 (100), 59 (25), 45 (21), 44 (12).

HR-MS (EI, 70 eV): [$C_{12}H_{21}ISi$], calcd.: 320.0457; found: 320.0456 (M^+).



Bicyclo[3.3.0]octane *syn*-51b. Following **TP3,** *syn*-**40c** (95 mg, 0.297 mmol, 1.0 equiv., d.r.>99:1) reacted with *t*-BuLi (1.96 M, 0.38 mL, 0.743 mmol, 2.5 equiv.) and $ClCO_2Et$ (81 mg, 0.743 mmol, 2.5 equiv.). The crude product was purified by column chromatography on silica using pentane:diethyl ether (20:1) as an eluent to afford *syn*-**51b** as a colourless oil (56%, 44 mg, 0.165 mmol, d.r.>99:1).

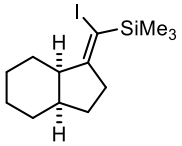
^{1}H-NMR (400 MHz, C_6D_6, ppm): δ = 4.08 (qd, *J* = 7.1, 4.3 Hz, 2H), 3.35 (td, *J* = 9.0, 6.5 Hz, 1H), 2.37 – 2.12 (m, 4H), 1.69 – 1.59 (m, 1H), 1.59 – 1.46 (m, 3H), 1.42 – 1.31 (m, 1H), 1.31 – 1.21 (m, 1H), 1.21 – 1.11 (m, 1H), 1.06 (t, *J* = 7.2 Hz, 3H), 0.26 (s, 9H).

^{13}C-NMR (101 MHz, C_6D_6, ppm): δ = 171.4, 169.3, 127.2, 59.7, 50.3, 43.5, 35.2, 33.6, 33.6, 31.4, 27.3, 14.5, 0.1.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2948, 2902, 2866, 1708, 1610, 1448, 1430, 1364, 1294, 1248, 1218, 1192, 1170, 1096, 1048, 1038, 992, 936, 910, 836, 760, 718, 692.

MS (EI, 70 eV): *m/z* (%) = 250 (36), 103 (66), 97 (42), 85 (27), 81 (33), 75 (79), 73 (100), 71 (35), 57 (80), 55 (39), 44 (83), 43 (51), 41 (47).

HR-MS (EI, 70 eV): [$C_{14}H_{22}O_2Si$], calcd.: 250.1389; found: 250.1396 ([M−H−Me]$^+$).



Bicyclo[4.3.0]nonane *syn*-51c. Following **TP3,** *syn*-**40d** (98 mg, 0.293 mmol, 1.0 equiv., d.r.>99:1) reacted with *t*-BuLi (2.08 M, 0.35 mL, 0.733 mmol, 2.5 equiv.) and I_2 (187 mg, 0.733 mmol, 2.5 equiv.) in diethyl ether (1.0 mL). The crude product was purified by column chromatography on silica using pentane as an eluent to afford *syn*-**51c** as a colourless oil (65%, 64 mg, 0.191 mmol, d.r.>99:1).

^{1}H-NMR (599 MHz, C_6D_6, ppm): δ = 2.88 (dt, *J* = 12.0, 5.9 Hz, 1H), 2.37 (ddt, *J* = 17.6, 9.3, 1.4 Hz, 1H), 2.25 – 2.18 (m, 1H), 2.14 (ddd, *J* = 17.5, 10.4, 8.7 Hz, 1H), 1.93 (dq, *J* = 12.2, 5.6 Hz, 1H),

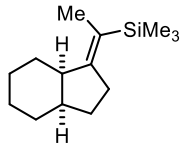
1.80 – 1.71 (m, 1H), 1.59 – 1.51 (m, 2H), 1.47 (ddq, *J* = 13.9, 4.3, 2.0 Hz, 1H), 1.44 – 1.36 (m, 1H), 1.35 – 1.29 (m, 1H), 1.23 – 1.15 (m, 1H), 1.11 (qt, *J* = 13.0, 3.1 Hz, 1H), 0.88 (qd, *J* = 13.1, 3.4 Hz, 1H), 0.27 (s, 9H).

^{13}C-NMR (151 MHz, C_6D_6, ppm): δ = 167.4, 98.4, 55.8, 37.7, 32.3, 29.2, 26.3, 25.4, 24.0, 21.1, 1.1.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2921, 2850, 1593, 1469, 1457, 1446, 1405, 1367, 1304, 1285, 1261, 1246, 1208, 1187, 1153, 1048, 1022, 940, 898, 872, 833, 794, 778, 754, 688, 657.

MS (EI, 70 eV): *m/z* (%) = 334 (25), 207 (24), 185 (15), 133 (65), 73 (100).

HR-MS (EI, 70 eV): [$C_{13}H_{23}ISi$], calcd.: 334.0614; found: 334.0610 (M^+).



Bicyclo[4.3.0]nonane *syn*-51d. Following **TP3,** *syn*-**40d** (100 mg, 0.299 mmol, 1.0 equiv., d.r.>99:1) reacted with *t*-BuLi (2.16 M, 0.35 mL, 0.748 mmol, 2.5 equiv.) and $CH_3OSO_2CF_3$ (123 mg, 0.748 mmol, 2.5 equiv.). The crude product was purified by column chromatography on silica using pentane as an eluent to afford *syn*-**51d** as a colourless oil (77%, 51 mg, 0.229 mmol, d.r.>99:1).

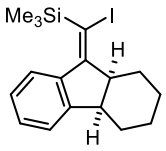
^{1}H-NMR (400 MHz, C_6D_6, ppm): δ = 2.64 (dt, *J* = 12.0, 5.9 Hz, 1H), 2.50 (dddd, *J* = 16.9, 9.1, 3.1, 1.6 Hz, 1H), 2.38 – 2.25 (m, 1H), 1.98 – 1.88 (m, 1H), 1.82 – 1.68 (m, 4H), 1.67 – 1.49 (m, 4H), 1.49 – 1.38 (m, 2H), 1.38 – 1.23 (m, 1H), 1.13 (qt, *J* = 12.3, 3.1 Hz, 1H), 1.07 – 0.92 (m, 1H), 0.20 (s, 9H).

^{13}C-NMR (101 MHz, C_6D_6, ppm): δ = 159.0, 123.2, 44.0, 38.5, 31.8, 27.1, 27.0, 26.2, 26.1, 21.4, 18.7, 0.0.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2922, 2870, 2850, 1618, 1470, 1446, 1404, 1372, 1286, 1260, 1246, 1190, 1088, 1018, 984, 936, 884, 860, 850, 830, 752, 714, 684.

MS (EI, 70 eV): *m/z* (%) = 149 (11), 148 (100), 147 (14), 133 (34), 119 (29), 106 (37), 105 (15), 91 (20), 73 (40).

HR-MS (EI, 70 eV): [$C_{14}H_{26}Si$], calcd.: 222.1804; found: 222.1797 (M^+).



Tricyclic compound *syn*-51e. Following **TP3,** *syn*-**40e** (55 mg, 0.144 mmol, 1.0 equiv., d.r.>99:1) reacted with *t*-BuLi (1.96 M, 0.18 mL, 0.360 mmol, 2.5 equiv.) and I_2 (92 mg, 0.360 mmol, 2.5 equiv.) in diethyl ether (1.0 mL). The crude product was purified by column chromatography on silica using pentane as an eluent to afford *syn*-**51e** as a colourless oil (92%, 51 mg, 0.133 mmol, d.r.>99:1).

^{1}H-NMR (400 MHz, C_6D_6, ppm): δ = 7.57 – 7.51 (m, 1H), 7.09 (tdd, *J* = 7.4, 1.2, 0.4 Hz, 1H), 7.00 (dt, *J* = 7.5, 1.2 Hz, 1H), 6.99 – 6.94 (m, 1H), 3.51 (dt, *J* = 11.5, 5.8 Hz, 1H), 3.20 (t, *J* = 5.5 Hz, 1H), 2.30 (ddt, *J* = 13.4, 5.5, 2.6 Hz, 1H), 2.02 – 1.93 (m, 1H), 1.45 – 1.38 (m, 2H), 1.32 – 1.25 (m, 1H), 1.13 – 0.81 (m, 3H), 0.39 (s, 9H).

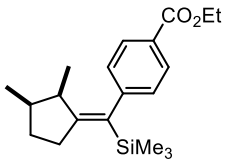
^{13}C-NMR (101 MHz, C_6D_6, ppm): δ = 165.8, 151.1, 139.2, 128.9, 126.7, 125.7, 123.8, 102.2, 61.9, 41.1, 25.7, 25.1, 24.3, 21.5, 2.4.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2924, 2852, 1602, 1562, 1460, 1446, 1406, 1378, 1360, 1328, 1302, 1248, 1156, 1090, 1024, 980, 940, 924, 906, 886, 858, 836, 824, 780, 756, 740, 718, 678.

MS (EI, 70 eV): *m/z* (%) = 383 (27), 382 (100), 255 (25), 239 (12), 196 (11), 195 (55), 185 (16), 181 (18), 167 (12), 165 (10), 73 (23).

HR-MS (EI, 70 eV): [$C_{17}H_{23}ISi$], calcd.: 382.0614; found: 382.0609 (M^+).

11.4 Cyclisation and Cross-Coupling Reactions



Cyclopentane *syn*-49e. Following **TP4,** *syn*-**40a** (127 mg, 0.411 mmol, 1.35 equiv., d.r.>99:1) reacted with *t*-BuLi (1.96 M, 0.52 mL, 1.03 mmol, 3.38 equiv.) and a $ZnCl_2$-solution (1.0 M in THF, 0.61 mL, 0.608 mmol, 2.0 equiv.). SPhos (12.3 mg, 0.030 mmol, 10 mol%), $Pd(OAc)_2$ (3.4 mg, 0.015 mmol, 5 mol%) and ethyl 4-iodobenzoate (84 mg, 0.304 mmol, 1.0 equiv.) were used for the cross-coupling

reaction. The crude product was purified by column chromatography on silica using pentane:ether (50:1) as an eluent to afford *syn*-**49e** as a colourless oil (84%, 84 mg, 0.254 mmol, d.r.>99:1).

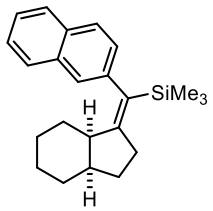
^{1}H-NMR (400 MHz, C_6D_6, ppm): δ = 8.19 (d, *J* = 8.6 Hz, 2H), 6.96 (d, *J* = 8.2 Hz, 2H), 4.17 (q, *J* = 7.1 Hz, 2H), 2.57 – 2.41 (m, 2H), 2.35 (ddd, *J* = 17.4, 10.1, 8.6 Hz, 1H), 1.91 – 1.74 (m, 1H), 1.69 – 1.59 (m, 1H), 1.33 (tt, *J* = 12.3, 9.8 Hz, 1H), 1.05 (t, *J* = 7.1 Hz, 3H), 0.79 (d, *J* = 6.8 Hz, 3H), 0.60 (d, *J* = 7.2 Hz, 3H), 0.08 (s, 9H).

^{13}C-NMR (101 MHz, C_6D_6, ppm): δ = 166.4, 162.6, 150.9, 134.1, 130.0, 128.7, 128.1, 60.6, 42.6, 37.5, 31.8, 31.2, 15.1, 14.4, 13.0, 0.1.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2956, 2872, 1716, 1604, 1464, 1448, 1432, 1404, 1378, 1366, 1304, 1268, 1246, 1204, 1172, 1108, 1096, 1072, 1020, 972, 942, 924, 886, 864, 830, 780, 754, 724, 702, 688, 664.

MS (EI, 70 eV): *m/z* (%) = 331 (16), 330 (64), 315 (14), 285 (21), 257 (49), 212 (27), 211 (32), 207 (39), 197 (15), 184 (13), 183 (32), 73 (100).

HR-MS (EI, 70 eV): [$C_{20}H_{30}O_2Si$], calcd.: 330.2015; found: 330.2005 (M^+).



Bicyclo[4.3.0]nonane *syn*-51f. Following **TP4,** *syn*-**40d** (135 mg, 0.404 mmol, 1.35 equiv., d.r.>99:1) reacted with *t*-BuLi (2.21 M, 0.46 mL, 1.01 mmol, 3.38 equiv.) and a $ZnCl_2$-solution (1.0 M in THF, 0.60 mL, 0.598 mmol, 2.0 equiv.). SPhos (12.3 mg, 0.030 mmol, 10 mol%), $Pd(OAc)_2$ (3.4 mg, 0.015 mmol, 5 mol%) and 2-bromonaphthalene (64 mg, 0.299 mmol, 1.0 equiv.) were used for the cross-coupling reaction. The crude product was purified by column chromatography on silica using pentane as an eluent to afford *syn*-**51f** as a colourless oil (99%, 84 mg, 0.296 mmol, d.r.>99:1).

^{1}H-NMR (599 MHz, C_6D_6, ppm): δ = 7.62 (d, *J* = 8.1 Hz, 1H), 7.62 – 7.55 (m, 2H), 7.48 (s, 1H), 7.24 – 7.16 (m, 2H), 7.14 (dd, *J* = 8.3, 1.7 Hz, 1H), 2.61 (ddt, *J* = 17.5, 9.6, 1.5 Hz, 1H), 2.51 – 2.32 (m, 2H), 1.96 (dq, *J* = 12.0, 6.0 Hz, 1H), 1.75 (tt, *J* = 12.6, 9.8 Hz, 1H), 1.54 – 1.43 (m, 2H),

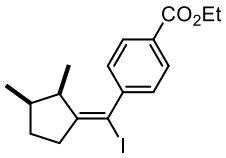
1.43 – 1.34 (m, 1H), 1.34 – 1.23 (m, 2H), 1.20 – 1.11 (m, 2H), 1.04 – 0.94 (m, 1H), 0.64 – 0.54 (m, 1H), 0.12 (s, 9H).

^{13}C-NMR (151 MHz, C_6D_6, ppm): δ = 161.5, 133.9, 133.6, 131.7, 127.9, 127.8, 127.6, 127.3, 127.2, 125.8, 124.9, 44.3, 38.2, 31.2, 26.7, 26.5, 26.3, 25.2, 20.6, −0.1.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3052, 2948, 2922, 2870, 2854, 2174, 1626, 1610, 1594, 1500, 1466, 1458, 1448, 1430, 1404, 1378, 1366, 1350, 1336, 1314, 1306, 1288, 1268, 1244, 1218, 1202, 1178, 1140, 1122, 1090, 1044, 1024, 1016, 998, 976, 962, 944, 922, 898, 888, 872, 832, 820, 804, 796, 784, 756, 742, 714, 686.

MS (EI, 70 eV): *m/z* (%) = 334 (62), 261 (39), 260 (100), 132 (26), 231 (18), 217 (20), 185 (29), 179 (30), 178 (19), 167(11), 165 (33), 141 (34), 75 (23), 73(57).

HR-MS (EI, 70 eV): [$C_{23}H_{30}Si$], calcd.: 334.2117; found: 334.2107 (M^+).



Iodide *syn*-53. *Syn*-**49e** (62 mg, 0.185 mmol, 1.0 equiv.) was treated with NIS (166 mg, 0.370 mmol, 4.0 equiv.) in acetonitrile (4.0 mL). The reaction mixture was stirred at room temperature for 71 h. The reaction process was monitored by GC. Saturated aqueous $NaHSO_3{\cdot}Na_2S_2O_5$ solution was added, the phases were separated and the aqueous phase was extracted with diethyl ether. The combined organic layers were dried over $MgSO_4$. The crude product was purified by column chromatography on silica using pentane:diethyl ether (50:1) as an eluent to afford *syn*-**53** as a colourless solid (87%, 62 mg, 0.161 mmol, d.r.>99:1).

m.p.: 52.2–53.1 °C.

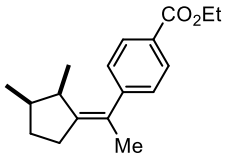
^{1}H-NMR (599 MHz, $CDCl_3$, ppm): δ = 7.99 (d, *J* = 8.6 Hz, 2H), 7.35 (d, *J* = 8.6 Hz, 2H), 4.38 (q, *J* = 7.1 Hz, 2H), 2.66 – 2.55 (m, 2H), 2.37 (ddd, *J* = 18.4, 10.0, 8.7 Hz, 1H), 2.21 – 2.11 (m, 1H), 1.85 – 1.76 (m, 1H), 1.50 (tt, *J* = 12.3, 9.7 Hz, 1H), 1.39 (t, *J* = 7.1 Hz, 3H), 0.87 (d, *J* = 6.8 Hz, 3H), 0.63 (d, *J* = 7.2 Hz, 3H).

^{13}C-NMR (151 MHz, $CDCl_3$, ppm): δ = 166.3, 158.9, 148.8, 129.7, 129.5, 128.8, 88.8, 61.2, 42.4, 40.4, 39.9, 30.4, 15.5, 14.5, 13.0.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2960, 2938, 2872, 1716, 1604, 1566, 1464, 1448, 1424, 1402, 1366, 1306, 1266, 1226, 1174, 1100, 1020, 966, 942, 904, 862, 844, 828, 808, 774, 758, 736, 710, 678.

MS (EI, 70 eV): *m/z* (%) = 257 (100), 229 (33), 211 (59), 184 (25), 169 (92), 157 (63), 155 (31), 153 (31), 143 (95), 142 (79), 141 (75), 129 (88), 128 (65), 127 (93), 115 (46).

HR-MS (EI, 70 eV): [$C_{17}H_{21}O_2I$], calcd.: 384.0586; found: 384.0580 (M^+).



Cyclopentane *syn*-54. A dry and argon-flushed *Schlenk*-tube was charged with *syn*-**53** (75 mg, 0.195 mmol,1.0 equiv.), $Pd(OAc)_2$ (2.2 mg, 0.010 mmol, 5 mol%), SPhos (8.2 mg, 0.020 mmol, 10 mol%) and THF (4.0 mL). MeZnCl (0.46 M, 0.55 mL, 0.254 mmol, 1.3 equiv.) was added dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 4 h. Saturated aqueous NH_4Cl solution was added, the phases were separated and the aqueous phase was extracted with diethyl ether. The combined organic layers were dried over $MgSO_4$. The solvents were evaporated and the crude product was purified by column chromatography on silica using pentane:diethyl ether (50:1) as an eluent to afford *syn*-**54** as a colourless oil (77%, 41 mg, 0.151 mmol, d.r.>99:1).

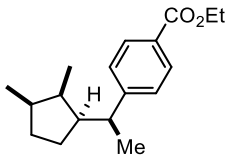
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.98 (d, *J* = 8.4 Hz, 2H), 7.25 (d, *J* = 7.1 Hz, 2H), 4.37 (q, *J* = 7.1 Hz, 2H), 2.59 – 2.40 (m, 2H), 2.38 – 2.26 (m, 1H), 1.99 (dq, *J* = 11.8, 6.7 Hz, 1H), 1.90 (q, *J* = 1.3 Hz, 3H), 1.84 – 1.72 (m, 1H), 1.48 – 1.34 (m, 4H), 0.88 (d, *J* = 6.8 Hz, 3H), 0.57 (d, *J* = 7.2 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 166.8, 150.3, 146.8, 129.6, 128.1, 128.1, 126.4, 60.9, 40.4, 38.4, 30.6, 30.0, 21.4, 15.3, 14.5, 13.4.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2958, 2936, 2912, 2870, 1716, 1606, 1464, 1448, 1432, 1402, 1368, 1306, 1268, 1174, 1098, 1058, 1018, 986, 858, 774, 740, 710.

MS (EI, 70 eV): *m/z* (%) = 272 (60), 257 (90), 199 (100), 184 (41), 159 (48), 157 (60), 156 (29), 115 (30), 105 (20), 103 (20), 95 (57), 91 (30).

HR-MS (EI, 70 eV): [$C_{18}H_{24}O_2$], calcd.: 272.1776; found: 272.1762 (M^+).



Cyclopentane *syn*-55. *Syn*-**54** (41 mg, 0.151 mmol,1.0 equiv.) and Pd/C (5%, 31 mg, 0.015 mmol, 10 mol%) in methanol (3.0 mL) were stirred under a H_2 atmosphere for 21 h. After filtration over celite, the solvent was evaporated and the crude product was purified by column chromatography on silica using pentane:diethyl ether (50:1) as an eluent to afford *syn*-**55** as a colourless oil (quant., 41 mg, 0.153 mmol, d.r.>99:1).

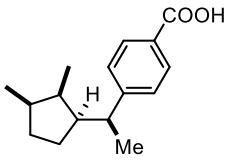
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.94 (d, *J* = 8.4 Hz, 2H), 7.24 (d, *J* = 8.3 Hz, 2H), 4.36 (q, *J* = 7.1 Hz, 2H), 2.65 – 2.52 (m, 1H), 2.10 – 1.94 (m, 3H), 1.68 – 1.56 (m, 1H), 1.38 (t, *J* = 7.1 Hz, 3H), 1.24 (d, *J* = 6.8 Hz, 3H), 1.18 – 1.08 (m, 3H), 0.94 (d, *J* = 6.5 Hz, 3H), 0.74 (d, *J* = 6.6 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 166.9, 153.4, 129.7, 128.2, 127.4, 60.8, 51.7, 42.3, 39.1, 38.5, 29.9, 28.0, 21.3, 16.3, 14.5, 7.1.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2958, 2906, 2870, 1716, 1610, 1574, 1454, 1418, 1366, 1344, 1310, 1270, 1178, 1146, 1102, 1050, 1020, 1012, 960, 856, 772, 708.

MS (EI, 70 eV): *m/z* (%) = 179 (12), 178 (100), 164 (12), 150 (24), 149 (58), 105 (18).

HR-MS (EI, 70 eV): [$C_{18}H_{26}O_2$], calcd.: 274.1933; found: 274.1925 (M^+).



Acid *syn*-56. *Syn*-**55** (42 mg, 0.153 mmol,1.0 equiv.) in methanol (2.5 mL) was treated with potassium hydroxide (40 mg, 0.712 mmol, 4.0 equiv.) and the reaction mixture was stirred at 40 °C for 69 h. Water was added, the phases were separated and the aqueous phase was extracted with diethyl ether. The aqueous phase was acidified with HCl (2 N) until a pH = 2 was reached. After extraction with diethyl ether, the combined organic layers were dried over $MgSO_4$. The solvent was evaporated and the crude product was purified by column chromatography on silica using hexane:diethyl ether (2:1; 1% HOAc) as an eluent to afford *syn*-**56** as a colourless solid (90%, 34 mg, 0.138 mmol, d.r.>99:1).

Recrystallization of the product from methanol gave crystals suitable for single crystal X-ray diffraction analysis.

m.p.: 160.6 – 163.8 °C.

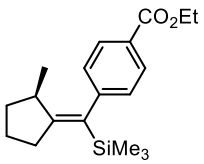
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.01 (d, *J* = 8.3 Hz, 2H), 7.28 (d, *J* = 8.3 Hz, 2H), 2.66 – 2.55 (m, 1H), 2.11 – 1.97 (m, 3H), 1.26 (d, *J* = 6.8 Hz, 3H), 1.21 – 1.09 (m, 3H), 0.95 (d, *J* = 6.5 Hz, 3H), 0.74 (d, *J* = 6.6 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 171.7, 154.6, 130.4, 127.6, 126.9, 51.7, 42.4, 39.1, 38.5, 29.9, 28.0, 21.2, 16.2, 7.1.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2958, 2940, 2902, 2868, 2672, 2598, 2540, 1678, 1608, 1574, 1468, 1454, 1426, 1378, 1358, 1340, 1316, 1286, 1178, 1144, 1130, 1108, 1052, 1010, 988, 976, 952, 908, 878, 856, 828, 814, 782, 772, 756, 736, 708, 654.

MS (EI, 70 eV): *m/z* (%) = 151 (11), 150 (100), 149 (11), 97 (18), 55 (16).

HR-MS (EI, 70 eV): [$C_{16}H_{22}O_2$], calcd.: 246.1620; found: 246.1625 (M^+).



Cyclopentane *R*-49f. Following **TP4,** *R*-**40f** (121 mg, 0.411 mmol, 1.35 equiv., e.r. = 98:2) reacted with *t*-BuLi (2.35 M, 0.44 mL, 1.03 mmol, 3.38 equiv.) and $ZnCl_2$-solution (1.0 M in THF, 0.61 mL, 0.608 mmol, 2.0 equiv.). SPhos (12.3 mg, 0.030 mmol, 10 mol%), $Pd(OAc)_2$ (3.4 mg, 0.015 mmol, 5 mol%) and ethyl 4-iodobenzoate (84 mg, 0.304 mmol, 1.0 equiv.) were used for the cross-coupling reaction. The crude product was purified by column chromatography on silica using pentane:ether (40:1) as an eluent to afford *R*-**49f** as a colourless oil (74%, 71 mg, 0.224 mmol, e.r.(*R:S*) = 95:5[X]).

[X] Flow rate = 2.1 mL/min; T = 80 °C; average velocity = 60; hold 80 °C for 20 min, 2 °C/min heating rate to 200 °C and holding for 10 min. Retention times: 84.9 min (major), 85.2 min (minor).

^{1}H-NMR (400 MHz, C_6D_6, ppm): δ = 8.19 (d, *J* = 8.6 Hz, 2H), 6.93 (d, *J* = 8.3 Hz, 2H), 4.17 (q, *J* = 7.1 Hz, 2H), 2.63 – 2.50 (m, 1H), 2.46 – 2.29 (m, 2H), 1.70 – 1.49 (m, 3H), 1.24 – 1.15 (m, 1H), 1.05 (t, *J* = 7.1 Hz, 3H), 0.68 (d, *J* = 7.1 Hz, 3H), 0.08 (s, 9H).

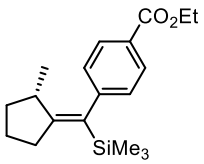
^{13}C-NMR (101 MHz, C_6D_6, ppm): δ = 165.9, 161.2, 150.2, 133.6, 129.4, 128.1, 127.6, 60.1, 37.8, 33.7, 32.3, 23.7, 19.6, 13.8, −0.4.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2954, 2868, 1716, 1604, 1462, 1448, 1432, 1404, 1366, 1304, 1280, 1268, 1246, 1218, 1172, 1108, 1096, 1022, 968, 946, 902, 890, 864, 830, 754, 724, 704, 688.

MS (EI, 70 eV): *m/z* (%) = 317 (15), 316 (70), 301 (14), 271 (16), 243 (14), 207 (15), 198 (22), 197 (26), 179 (11), 170 (19), 169 (21), 142 (15), 128 (11), 73 (100).

HR-MS (EI, 70 eV): [$C_{19}H_{28}O_2Si$], calcd.: 316.1859; found: 316.1854 (M^+).

$[\alpha]_D^{20}$ = 66° (c = 0.89, CH_2Cl_2).



Cyclopentane *S*-49f. Following **TP4,** *S*-**40f** (121 mg, 0.411 mmol, 1.35 equiv., e.r. = 97:3) reacted with *t*-BuLi (1.96 M, 0.52 mL, 1.03 mmol, 3.38 equiv.) and a $ZnCl_2$-solution (1.0 M in THF, 0.61 mL, 0.608 mmol, 2.0 equiv.). SPhos (12.3 mg, 0.030 mmol, 10 mol%), $Pd(OAc)_2$ (3.4 mg, 0.015 mmol, 5 mol%) and ethyl 4-iodobenzoate (84 mg, 0.304 mmol, 1.0 equiv.) were used for the cross-coupling reaction. The crude product was purified by column chromatography on silica using pentane:ether (40:1) as an eluent to afford *R*-**49f** as a colourless oil (70%, 67 mg, 0.212 mmol, e.r.(*R:S*) = 96:4[XI]).

^{1}H-NMR (400 MHz, C_6D_6, ppm): δ = 8.20 (d, *J* = 8.2 Hz, 2H), 6.93 (d, *J* = 8.1 Hz, 2H), 4.17 (q, *J* = 7.1 Hz, 2H), 2.62 – 2.52 (m, 1H), 2.46 – 2.29 (m, 2H), 1.70 – 1.50 (m, 3H), 1.24 – 1.15 (m, 1H), 1.04 (t, *J* = 7.1 Hz, 3H), 0.68 (d, *J* = 7.1 Hz, 3H), 0.08 (s, 9H).

[XI] Flow rate = 2.1 mL/min; T = 80 °C; average velocity = 60; hold 80 °C for 20 min, 2 °C/min heating rate to 200 °C and holding for 10 min. Retention times: 84.9 min (minor), 85.2 min (major).

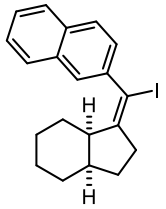
^{13}C-NMR (101 MHz, C_6D_6, ppm): δ = 166.4, 161.8, 150.8, 134.1, 130.0, 128.7, 128.1, 60.6, 38.4, 34.2, 32.9, 24.3, 20.2, 14.4, 0.1.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2954, 2869, 1716, 1603, 1563, 1502, 1463, 1403, 1367, 1305, 1279, 1268, 1247, 1218, 1173, 1107, 1096, 1021, 968, 945, 903, 889, 864, 830, 755, 725, 704, 689.

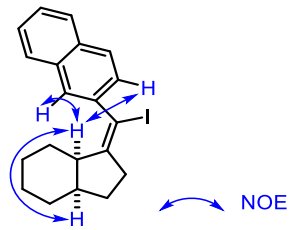
MS (EI, 70 eV): *m/z* (%) = 316 (29), 243 (11), 198 (11), 169 (12), 73 (100).

HR-MS (EI, 70 eV): [$C_{19}H_{28}O_2Si$], calcd.: 316.1859; found: 316.1852 (M^+).

$[\alpha]_D^{20}$ = –70° (c = 1.1, CH_2Cl_2).



Iodide 57a. *Syn*-**51f** (79 mg, 0.235 mmol, 1.0 equiv.) was treated with NIS (318 mg, 1.41 mmol, 6.0 equiv.) in acetonitrile (4.0 mL) and dichloromethane (2.0 mL). The reaction mixture was stirred at room temperature for 23 h. The reaction process was monitored by GC. Saturated aqueous $NaHSO_3{\cdot}Na_2S_2O_5$ solution was added, the phases were separated and the aqueous phase was extracted with diethyl ether. The combined organic layers were dried over $MgSO_4$. The crude product was purified by column chromatography on silica using pentane as an eluent to afford **57a** as a colourless oil (75%, 69 mg, 0.178 mmol, d.r.>99:1).



The relative stereochemistry was established by key NOE correlation as depicted aside.

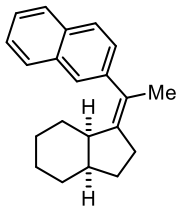
^{1}H-NMR (599 MHz, $CDCl_3$, ppm): δ = 7.84 – 7.80 (m, 2H), 7.78 (d, *J* = 8.5 Hz, 1H), 7.72 (dd, *J* = 0.5 Hz, 1H), 7.50 – 7.45 (m, 2H), 7.39 (dd, *J* = 8.4, 1.8 Hz, 1H), 2.65 (ddt, *J* = 18.1, 9.4, 1.7 Hz, 1H), 2.54 (dt, *J* = 11.6, 6.2 Hz, 1H), 2.45 (ddd, *J* = 18.4, 9.7, 8.9 Hz, 1H), 2.25 (dqd, *J* = 12.3, 7.0, 6.5, 2.6 Hz, 1H), 1.92 (tt, *J* = 12.4, 9.7 Hz, 1H), 1.69 – 1.62 (m, 1H), 1.61 – 1.54 (m, 1H), 1.49 – 1.41 (m, 2H), 1.40 – 1.30 (m, 2H), 1.27 (ddd, *J* = 14.4, 5.6, 3.0 Hz, 1H), 1.20 – 1.09 (m, 1H), 0.92 – 0.80 (m, 1H).

^{13}C-NMR (151 MHz, $CDCl_3$, ppm): δ = 157.1, 141.9, 133.1, 132.7, 128.3, 127.9, 127.8, 127.3, 127.1, 126.3, 90.5, 44.7, 40.8, 40.1, 27.0, 26.8, 26.2, 25.2, 20.8.

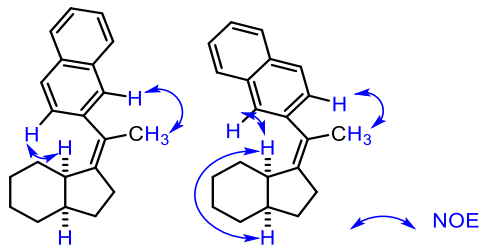
FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3052, 2920, 2850, 1644, 1628, 1594, 1572, 1502, 1466, 1456, 1444, 1422, 1380, 1364, 1342, 1314, 1306, 1288, 1268, 1248, 1230, 1214, 1202, 1186, 1172, 1152, 1142, 1124, 1096, 1072, 1060, 1048, 1040, 1022, 996, 960, 948, 938, 906, 886, 852, 836, 814, 778, 768, 756, 744, 732, 698.

MS (EI, 70 eV): *m/z* (%) = 262 (23), 261 (100), 191 (10), 179 (25), 178 (19), 167 (15), 166 (11), 165 (35), 141 (44).

HR-MS (EI, 70 eV): [$C_{20}H_{21}I$], calcd.: 388.0688; found: 388.0676 (M^+).



Bicyclo[4.3.0]nonane *Z*-58a. A dry and argon-flushed *Schlenk*-tube was charged with **57a** (69 mg, 0.178 mmol,1.0 equiv.), $Pd(OAc)_2$ (2.0 mg, 0.009 mmol, 5 mol%), SPhos (7.4 mg, 0.018mmol, 10 mol%) and THF (4.0 mL). MeZnCl (0.45 M, 0.51 mL, 0.231 mmol, 1.3 equiv.) was added dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 2 h. Saturated aqueous NH_4Cl solution was added, the phases were separated and the aqueous phase was extracted with diethyl ether. The combined organic layers were dried over $MgSO_4$. The solvents were evaporated and the crude product was purified by column chromatography on silica using pentane as an eluent to afford *Z*-**58a** as a colourless oil (79%, 39 mg, 0.141 mmol, d.r.>99:1).



The relative stereochemistry was established by key NOE correlation as depicted aside.

^{1}H-NMR (599 MHz, $CDCl_3$, ppm): δ = 7.85 – 7.76 (m, 3H), 7.62 (s, 1H), 7.49 – 7.40 (m, 2H), 7.33 (dt, *J* = 8.4, 1.6 Hz, 1H), 2.54 (ddt, *J* = 17.4, 9.7, 1.7 Hz, 1H), 2.47 – 2.34 (m, 2H), 2.13 – 2.05 (m, 1H),

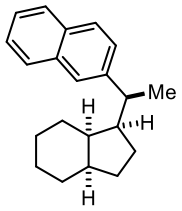
1.97 (s, 3H), 1.92 – 1.81 (m, 1H), 1.66 – 1.57 (m, 2H), 1.53 – 1.45 (m, 1H), 1.46 – 1.39 (m, 1H), 1.39 – 1.25 (m, 2H), 1.25 – 1.19 (m, 1H), 1.13 – 1.00 (m, 1H), 0.93 – 0.83 (m, 1H).

^{13}C-NMR (151 MHz, $CDCl_3$, ppm): δ = 145.0, 143.0, 133.6, 132.0, 127.9, 127.7, 127.5, 127.3, 126.7, 126.1, 125.8, 125.3, 42.8, 39.4, 29.6, 27.3, 26.8, 26.3, 25.6, 21.8, 21.1.

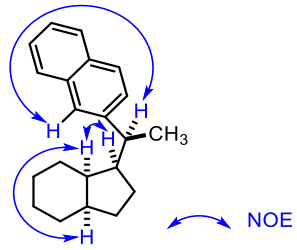
FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3054, 2918, 2850, 1628, 1598, 1502, 1468, 1444, 1430, 1372, 1342, 1266, 1248, 1230, 1196, 1188, 1156, 1142, 1128, 1076, 1056, 1036, 1018, 990, 960, 950, 932, 892, 876, 854, 816, 770, 744, 666.

MS (EI, 70 eV): *m/z* (%) = 276 (25), 182 (14), 181 (100), 179 (13), 178 (16), 166 (21), 165 (23).

HR-MS (EI, 70 eV): [$C_{21}H_{24}$], calcd.: 276.1878; found: 276.1871 (M^+).



Bicyclo[4.3.0]nonane 59. *Z*-**58a**(34 mg, 0.123 mmol,1.0 equiv.) and Pd/C (5%, 26 mg, 0.012 mmol, 10 mol%) in methanol (3.0 mL) were stirred under a H_2 atmosphere for 2 h. After filtration over celite, the solvent was evaporated and the crude product was purified by column chromatography on silica using pentane as an eluent to afford **59** as a colourless solid (76%, 26 mg, 0.093 mmol, d.r.>99:1). Recrystallization of the product from THF/MeCN gave crystals suitable for single crystal X-ray diffraction analysis.



The relative stereochemistry was established by key NOE correlation as depicted aside.

m.p.: 61.7 – 63.5 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.82 – 7.74 (m, 3H), 7.59 (s, 1H), 7.46 – 7.42 (m, 1H), 7.42 – 7.38 (m, 1H), 7.36 (dd, *J* = 8.5, 1.8 Hz, 1H), 2.71 (dq, *J* = 11.1, 6.8 Hz, 1H), 2.20 – 2.08 (m,

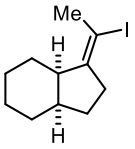
2H), 2.00 – 1.92 (m, 1H), 1.80 – 1.73 (m, 1H), 1.65 – 1.57 (m, 3H), 1.57 – 1.34 (m, 4H), 1.31 (d, J = 6.8 Hz, 3H), 1.29 – 1.05 (m, 4H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 145.6, 133.8, 132.3, 127.9, 127.7, 127.6, 126.1, 125.8, 125.6, 125.0, 51.9, 41.5, 41.3, 39.6, 28.1, 27.5, 25.8, 25.4, 21.9, 21.9, 21.2.

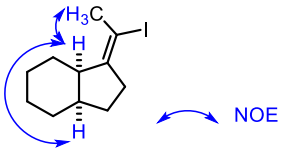
FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3052, 2920, 2868, 2854, 1600, 1508, 1470, 1452, 1444, 1380, 1270, 1020, 888, 854, 816, 744.

MS (EI, 70 eV): *m/z* (%) = 278 (15), 156 (61), 155 (100), 154 (13), 153 (23), 141 (18), 81 (19).

HR-MS (EI, 70 eV): [$C_{21}H_{26}$], calcd.: 278.2035; found: 278.2028 (M^+).



Iodide 57b. *Syn*-**51d** (84 mg, 0.378 mmol, 1.0 equiv.) was treated with NIS (174 mg, 0.756 mmol, 2.0 equiv.) in acetonitrile (4.3 mL). The reaction mixture was stirred at room temperature for 1.5 h. The reaction conversion was monitored by GC. Saturated aqueous $NaHSO_3 \cdot Na_2S_2O_5$ solution was added, the phases were separated and the aqueous phase was extracted with diethyl ether. The combined organic layers were dried over $MgSO_4$. The crude product was purified by column chromatography on silica using pentane as an eluent to afford **57b** as a colourless oil (85%, 89 mg, 0.322 mmol, d.r.>99:1).



The relative stereochemistry was established by key NOE correlation as depicted aside.

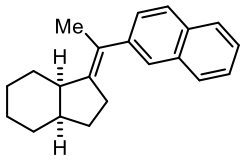
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 2.61 (dt, J = 11.7, 5.9 Hz, 1H), 2.47 (t, J = 2.1 Hz, 3H), 2.45 – 2.34 (m, 1H), 2.26 – 2.10 (m, 2H), 1.93 – 1.76 (m, 1H), 1.67 – 1.43 (m, 6H), 1.35 (qt, J = 12.9, 3.8 Hz, 1H), 1.26 – 1.04 (m, 2H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 153.3, 89.3, 43.9, 40.6, 39.6, 30.0, 27.1, 26.4, 26.2, 25.5, 20.9.

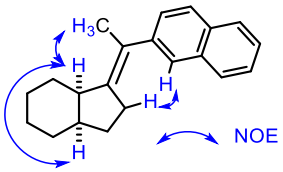
FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2920, 2848, 1652, 1468, 1458, 1444, 1426, 1374, 1250, 1212, 1172, 1158, 1122, 1076, 1058, 1036, 1020, 968, 884, 850, 828, 656.

MS (EI, 70 eV): *m/z* (%) = 276 (17), 150 (12), 149 (100), 121 (21), 107 (33), 105 (12), 95 (19), 93 (52), 91 (38), 81 (35), 79 (32), 77 (13), 67 (18).

HR-MS (EI, 70 eV): [$C_{11}H_{17}I$], calcd.: 276.0375; found: 276.0370 (M^+).



Bicyclo[4.3.0]nonane *E*-58a. A dry and argon-flushed *Schlenk*-tube was charged with **57b** (81 mg, 0.293 mmol, 1.0 equiv.), $Pd(OAc)_2$ (3.4 mg, 0.015 mmol, 5 mol%), SPhos (11.9 mg, 0.029 mmol, 10 mol%) and THF (6.0 mL). Naphthylzinc chloride (0.43 M, 0.89 mL, 0.381 mmol, 1.3 equiv.) was added dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 2.5 h. Saturated aqueous NH_4Cl solution was added, the phases were separated and the aqueous phase was extracted with diethyl ether. The combined organic layers were dried over $MgSO_4$. The solvents were evaporated and the crude product was purified by column chromatography on silica using pentane as an eluent to afford *E*-**58a** as a colourless oil (88%, 71 mg, 0.257 mmol, d.r.>99:1).



The relative stereochemistry was established by key NOE correlation as depicted aside.

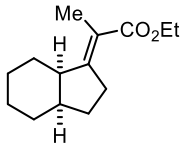
^{1}H-NMR (599 MHz, $CDCl_3$, ppm): δ = 7.82 – 7.75 (m, 3H), 7.63 (s, 1H), 7.47 – 7.38 (m, 2H), 7.36 (dd, *J* = 8.4, 1.7 Hz, 1H), 2.67 (dt, *J* = 11.7, 5.9 Hz, 1H), 2.39 (ddq, *J* = 17.4, 9.2, 1.7 Hz, 1H), 2.26 – 2.16 (m, 1H), 2.16 – 2.09 (m, 1H), 2.08 (t, *J* = 2.0 Hz, 3H), 1.84 – 1.63 (m, 5H), 1.53 – 1.43 (m, 2H), 1.43 – 1.33 (m, 1H), 1.30 – 1.15 (m, 2H).

^{13}C-NMR (151 MHz, $CDCl_3$, ppm): δ = 145.1, 142.8, 133.6, 132.0, 127.8, 127.7, 127.5, 127.0, 126.3, 126.2, 125.9, 125.3, 43.5, 39.0, 30.2, 27.0, 26.5, 25.9, 21.2.

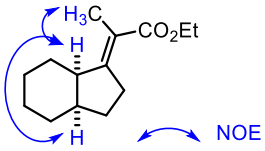
FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3054, 2920, 2848, 1628, 1598, 1502, 1468, 1456, 1444, 1432, 1374, 1344, 1266, 1194, 1188, 1166, 1154, 1142, 1128, 1078, 1056, 1036, 1020, 960, 948, 890, 854, 816, 784, 768, 744, 666.

MS (EI, 70 eV): *m/z* (%) = 276 (27), 182 (14), 181 (100), 179 (13), 178 (16), 166 (23), 165 (23).

HR-MS (EI, 70 eV): [$C_{21}H_{24}$], calcd.: 276.1878; found: 276.1871 (M^+).



Bicyclo[4.3.0]nonane 58b. A dry and argon-flushed *Schlenk*-tube was charged with **57b** (15 mg, 0.054 mmol, 1.0 equiv.) in diethyl ether (0.66 mL). *t*-BuLi (2.21 M, 0.07 mL, 0.145 mmol, 2.5 equiv.) was added dropwise at −78 °C. Ethyl chloroformate (14 µL, 0.145 mL, 2.5 equiv.) was added subsequently, the reaction was stirred at −78 °C for 5 min and was then allowed to warm to room temperature. Saturated aqueous NH_4Cl solution was added, the phases were separated and the aqueous phase was extracted with diethyl ether. The combined organic layers were dried over $MgSO_4$. The solvents were evaporated and the crude product was purified by column chromatography on silica using pentane:diethyl ether (40:1) as an eluent to afford **58b** as a colourless oil (91%, 11 mg, 0.049 mmol, d.r.>99:1).



The relative stereochemistry was established by key NOE correlation as depicted aside.

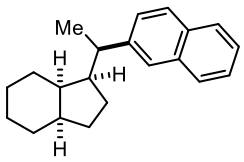
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 4.16 (q, J = 7.1 Hz, 2H), 2.91 (dddd, J = 19.8, 8.8, 3.0, 1.3 Hz, 1H), 2.72 – 2.58 (m, 2H), 2.12 – 1.99 (m, 1H), 1.88 (t, J = 2.0 Hz, 3H), 1.91 – 1.78 (m, 1H), 1.74 – 1.46 (m, 6H), 1.37 (qt, J = 13.0, 3.6 Hz, 1H), 1.29 (t, J = 7.1 Hz, 3H), 1.25 – 1.14 (m, 1H), 1.06 (qd, J = 12.9, 3.1 Hz, 1H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 168.7, 164.2, 117.9, 59.7, 45.3, 37.9, 32.3, 26.5, 26.1, 25.5, 24.7, 20.7, 15.7, 14.4.

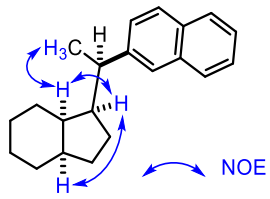
FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2926, 2858, 1710, 1638, 1446, 1304, 1284, 1270, 1214, 1180, 1124, 1096, 1076, 1048.

MS (EI, 70 eV): *m/z* (%) = 222 (36), 177 (35), 176 (100), 175 (38), 149 (37), 134 (50), 128 (53), 119 (31), 105 (31), 100 (42), 95 (33), 93 (31), 91 (46).

HR-MS (EI, 70 eV): [$C_{14}H_{22}O_2$], calcd.: 222.1620; found: 222.1613 (M^+).



Bicyclo[4.3.0]nonane 60. *E*-**58a** (71 mg, 0.257 mmol, 1.0 equiv.) and Pd/C (5%, 55 mg, 0.026 mmol, 10 mol%) in methanol (4.0 mL) and pentane (2.0 mL) were stirred under a H_2 atmosphere for 2.5 h. After filtration over celite, the solvent was evaporated and the crude product was purified by column chromatography on silica using pentane as an eluent to afford **60** as a colourless oil (92%, 66 mg, 0.237 mmol, d.r. = 79:21).



The relative stereochemistry for the major compound was established by key NOE correlation as depicted aside.

Only the chemical shifts of the major diastereomers are reported (assignment by 2D NMR analysis).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.83 – 7.75 (m, 3.0H), 7.62 (s, 1H), 7.48 – 7.33 (m, 3H), 2.78 – 2.65 (m, 1H), 2.35 – 2.24 (m, 1H), 2.12 – 1.90 (m, 2H), 1.74 – 1.47 (m, 5H), 1.46 – 1.29 (m, 5H), 1.22 (d, J = 6.9 Hz, 3H), 1.06 – 0.94 (m, 1H), 0.88 – 0.74 (m, 1H).

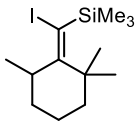
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 145.9, 133.8, 132.2, 127.9, 127.7, 127.7, 126.2, 125.8, 125.5, 125.0, 51.0, 41.9, 41.2, 39.4, 27.8, 27.3, 25.6, 25.6, 23.2, 21.9, 20.9.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3052, 2920, 2866, 2854, 1632, 1600, 1506, 1470, 1452, 1444, 1378, 1370, 1270, 1128, 1022, 956, 946, 888, 852, 816, 768, 742, 660.

MS (EI, 70 eV): *m/z* (%) = 278 (11), 156 (67), 155 (100), 154 (13), 153 (22), 141 (19), 81 (22).

HR-MS (EI, 70 eV): [$C_{21}H_{26}$], calcd.: 278.2035; found: 278.2028 (M^+).

11.5 Synthesis of Cyclohexane Derivatives



Cyclohexane 62b. A dry and argon-flushed *Schlenk*-tube with diethyl ether (3.2 mL) was cooled to −78 °C and charged with a solution of *t*-BuLi (2.49 M, 0.30 mL, 0.743 mmol, 2.5 equiv.). Iodide **61b** (100 mg, 0.297 mmol, 1.0 equiv.) in diethyl ether (0.75 mL) was added dropwise over 10 min and the reaction mixture was stirred for 10 min. Then, the reaction mixture was stirred at room temperature for 30 min. After the iodine (190 mg, 0.743 mmol, 2.5 equiv.) in diethyl ether (1.0 mL) at −78 °C, the solution was allowed to warm up to room temperature. Saturated aqueous ($NaHSO_3 \cdot Na_2S_2O_5$) solution was added, the phases were separated and the aqueous phase was extracted with diethyl ether. The combined organic layers were dried over $MgSO_4$. The crude product was purified by column chromatography on silica using pentane as an eluent to afford **62b** as a colourless oil (50%, 50 mg, 0.149 mmol).

^{1}H-NMR (400 MHz, C_6D_6, ppm): δ = 3.01 (qdd, J = 7.5, 5.4, 2.4 Hz, 1H), 1.84 – 1.74 (m, 1H), 1.58 (s, 3H), 1.56 (d, J = 0.8 Hz, 3H), 1.56 – 1.49 (m, 1H), 1.49 – 1.42 (m, 2H), 1.36 – 1.28 (m, 1H), 1.22 – 1.15 (m, 1H), 1.06 (dd, J = 7.4, 0.4 Hz, 3H), 0.32 (s, 9H).

^{13}C-NMR (101 MHz, C_6D_6, ppm): δ = 167.7, 102.2, 39.6, 38.7, 38.6, 28.4, 26.7, 26.6, 23.9, 15.8, 3.4.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2952, 2930, 2868, 1538, 1470, 1460, 1384, 1372, 1362, 1262, 1248, 1198, 868, 832, 760, 692, 680.

MS (EI, 70 eV): *m/z* (%) = 185 (14), 136 (11), 135 (100), 107 (22), 93 (20), 75 (26), 73 (70).

HR-MS (EI, 70 eV): [$C_{13}H_{25}ISi$], calcd.: 336.0770; found: 336.0767 (M^+).

11.6 Single Crystal X-Ray Analysis

Single crystals of the compounds, suitable for X-ray diffraction, were obtained by slow evaporation of solvents solutions. The crystals were introduced into perfluorinated oil and a suitable single crystal was carefully mounted on the top of a thin glass wire. Data collections were performed on an *Oxford* Xcalibur 3 diffractometer equipped with a *Spellman* generator (50 kV, 40 mA) and a Kappa CCD detector, operating with Mo-K_α radiation (λ = 0.71071 Å). Data collection was performed with the CrysAlis CCD software;[XII] CrysAlis RED software[XIII] was used for data reduction. Absorption correction using the SCALE3 ABSPACK multiscan method[XIV] was applied. The structures were solved with SHELXS-97,[XV] refined with SHELXL-97[XVI] and finally checked using PLATON.[XVII] Details for data collection and structure refinement are summarized in the tables at the different sections.

[XII] CrysAlis CCD, Oxford Diffraction Ltd., Version 1.171.27p5 beta (release 01-04-2005 CrysAlis171.NET) (compiled Apr 1 2005, 17:53:34).

[XIII] CrysAlis RED, Oxford Diffraction Ltd., Version 1.171.27p5 beta (release 01-04-2005 CrysAlis171.NET) (compiled Apr 1 2005, 17:53:34).

[XIV] SCALE3 ABSPACK – An Oxford Diffraction Program (1.0.4, gui:1.0.3) (C), Oxford Diffraction, Ltd., 2005.

[XV] Sheldrick, G. M. (1997) SHELXS-97: *Program for Crystal Structure Solution*, University of Göttingen, Germany.

[XVI] Sheldrick, G. M. (1997) SHELXL-97: *Program for the Refinement of Crystal Structures*, University of Göttingen, Germany.

[XVII] Spek, A. L. (1999) PLATON: *A Multipurpose Crystallographic Tool*, Utrecht University, Utrecht, The Netherlands.

Cyclopentane *syn*-49c.

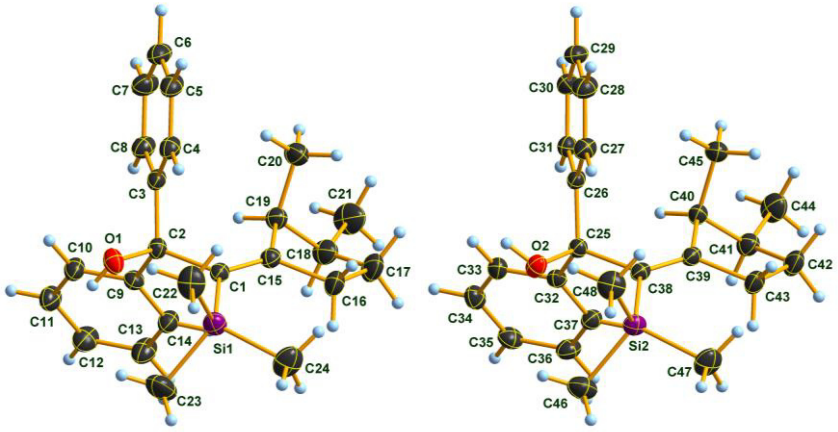


Figure 6: Molecular structure of cyclopentane *syn*-**49c** in the crystal, view of the two crystallographically independent molecules, DIAMOND[XVIII] representation; thermal ellipsoids are drawn at 50% probability level.

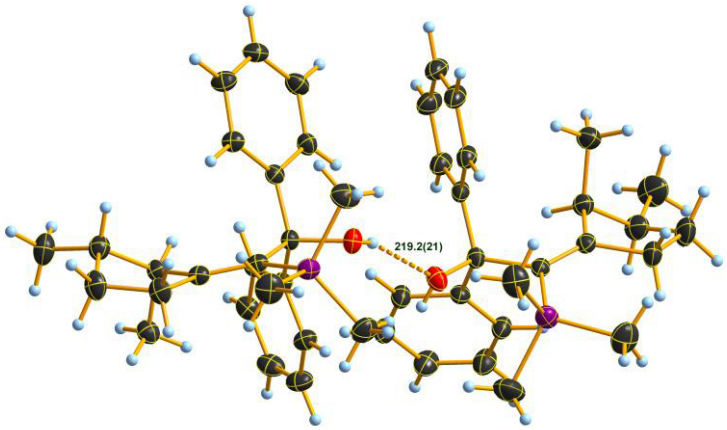


Figure 7: Hydrogen bonding in the crystal structure of cyclopentane *syn*-**49c**, DIAMOND representation; thermal ellipsoids are drawn at 50% probability level. Symmetry code for the left molecule: x, 1+y, z.

Table 8: Details for X-ray data collection and structure refinement for cyclopentane *syn*-**49c**.

Empirical formula	$C_{24}H_{32}OSi$
Formula mass	364.58
T/ K	173(2)
Crystal size [mm]	0.41 × 0.29 × 0.24
Crystal description	colorless block

[XVIII] DIAMOND, Crystal Impact GbR., Version 3.2i.

Crystal system	triclinic
Space group	*P*-1
a/ Å	11.3833(4)
b/ Å	13.4945(4)
c/ Å	14.7067(5)
α/ °	100.473(3)
β/ °	93.153(3)
γ/ °	104.257(3)
V/ Å^3	2141.24(13)
Z	4
$\rho_{calcd.}$/ g cm^{-3}	1.131
μ/ mm^{-1}	0.119
***F*(000)**	792
Θ range/ °	4.21 – 25.24
Index ranges	$-16 \le h \le 16$
	$-19 \le k \le 19$
	$-21 \le l \le 21$
Reflns. collected	42866
Reflns. obsd.	9280
Reflns. unique	13016 (R_{int} = 0.0357)
***R*$_1$, *wR*$_2$ (2σ data)**	0.0473, 0.1131
***R*$_1$, *wR*$_2$ (all data)**	0.0747, 0.1304
GOOF on *F*^{2}	1.025
Peak/hole/ e Å^{-3}	0.365 / −0.220

Cyclopentane *anti*-49d.

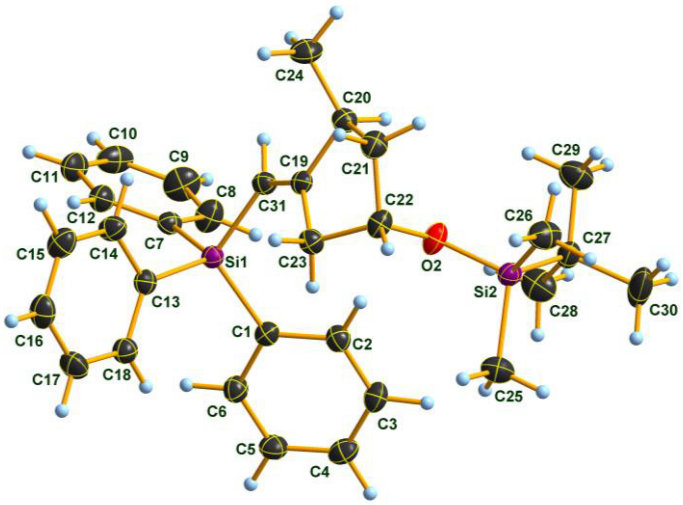


Figure 8: Molecular structure of cyclopentane *anti*-**49d** in the crystal, DIAMOND[XIX] representation; thermal ellipsoids are drawn at 50% probability level.

Table 9: Details for X-ray data collection and structure refinement for cyclopentane *anti*-**49d**.

Empirical formula	$C_{31}H_{40}OSi_2$
Formula mass	484.81
T/ K	123(2)
Crystal size [mm]	0.40 × 0.40 × 0.10
Crystal description	colorless block
Crystal system	monoclinic
Space group	*P*21/*n*
a/ Å	8.1022(3)
b/ Å	16.4356(5)
c/ Å	21.6510(7)
α/ °	90.0
β/ °	100.280(3)
γ/ °	90.0
V/ Å^3	2836.86(17)
Z	4
$\rho_{calcd.}$/ g cm^{-3}	1.135

[XIX] DIAMOND, Crystal Impact GbR., Version 3.2i.

μ/ mm^{-1}	0.146
***F*(000)**	1048
Θ range/ °	4.18 – 25.24
Index ranges	$-9 \leq h \leq 10$
	$-21 \leq k \leq 20$
	$-28 \leq l \leq 28$
Reflns. collected	24112
Reflns. obsd.	5240
Reflns. unique	7001 (R_{int} = 0.0464)
***R*$_1$, *wR*$_2$ (2σ data)**	0.0462, 0.1107
***R*$_1$, *wR*$_2$ (all data)**	0.0693, 0.1215
GOOF on *F*^{2}	1.057
Peak/hole/ e Å^{-3}	0.410 / −0.259

Acid *syn*-56.

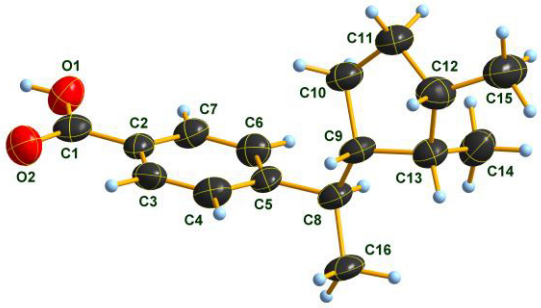


Figure 9: Molecular structure of acid *syn*-**56** in the crystal, DIAMOND[XX] representation; thermal ellipsoids are drawn at 50% probability level.

[XX] DIAMOND, Crystal Impact GbR., Version 3.2i.

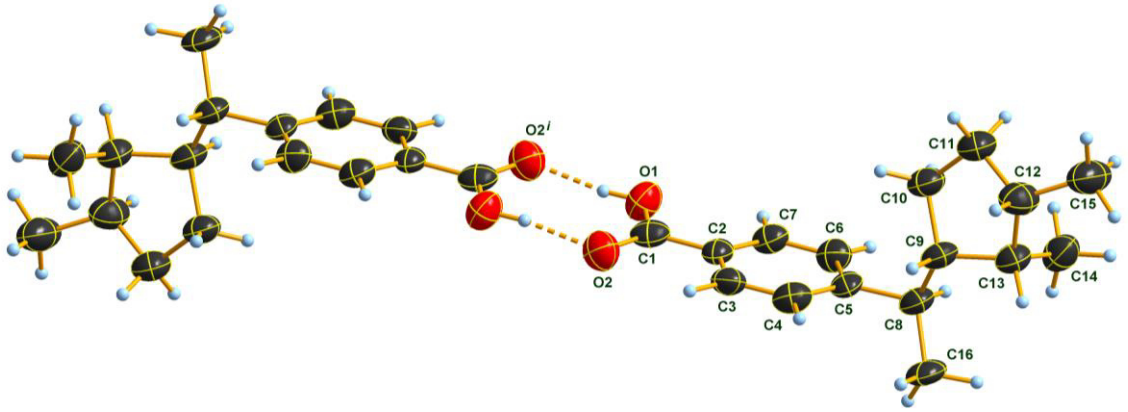


Figure 10: Hydrogen bonding in the crystal of acid *syn*-**56**, DIAMOND representation; thermal ellipsoids are drawn at 50% probability level. Symmetry code for O2^{i}: 1–x, 1–y, 1–z.

Table 10: Details for X-ray data collection and structure refinement for acid *syn*-**56**.

Empirical formula	$C_{16}H_{22}O_2$
Formula mass	246.33
T/ K	143(2)
Crystal size [mm]	0.12 × 0.06 × 0.01
Crystal description	colorless platelet
Crystal system	triclinic
Space group	*P*-1
a/ Å	6.3433(11)
b/ Å	10.0842(15)
c/ Å	12.023(2)
α/ °	101.204(13)
β/ °	101.301(15)
γ/ °	103.274(14)
V/ Å^3	710.6(2)
Z	2
$\rho_{calcd.}$/ g cm^{-3}	1.151
μ/ mm^{-1}	0.074
***F*(000)**	268
Θ range/ °	4.21 – 25.24
Index ranges	$-5 \le h \le 7$
	$-12 \le k \le 12$

	$-14 \leq l \leq 14$
Reflns. collected	4899
Reflns. obsd.	888
Reflns. unique	2783 (R_{int} = 0.0823)
R_1, wR_2 (2σ data)	0.0757, 0.0731
R_1, wR_2 (all data)	0.2632, 0.1174
GOOF on F^2	0.948
Peak/hole/ e Å^{-3}	0.169 / −0.220

Bicyclo[4.3.0]nonane 59.

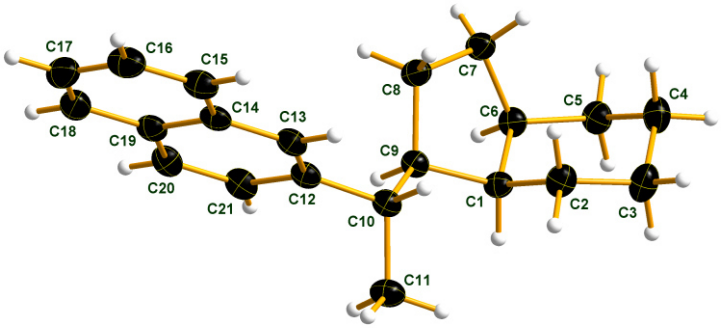


Figure 11: Molecular structure of bicyclo[4.3.0]nonane **59** in the crystal, DIAMOND[XXI] representation; thermal ellipsoids are drawn at 50% probability level.

Table 11: Details for X-ray data collection and structure refinement for bicyclo[4.3.0]nonane **59**.

Empirical formula	$C_{21}H_{26}$
Formula mass	278.42
T/ K	143(2)
Crystal size [mm]	0.39 × 0.35 × 0.17
Crystal description	colorless block
Crystal system	monoclinic
Space group	*P*21/*c*
a/ Å	5.5039(3)
b/ Å	45.1131(18)

[XXI] DIAMOND, Crystal Impact GbR., Version 3.2i.

c/ Å	7.0986(6)
α/ °	90.0
β/ °	114.343(5)
γ/ °	90.0
V/ Å^3	1605.86(18)
Z	4
$\rho_{calcd.}$/ g cm^{-3}	1.152
μ/ mm^{-1}	0.064
***F*(000)**	608
Θ range/ °	4.16 – 25.24
Index ranges	$-7 \leq h \leq 6$
	$-60 \leq k \leq 46$
	$-9 \leq l \leq 9$
Reflns. collected	14914
Reflns. obsd.	3251
Reflns. unique	3969 (R_{int} = 0.0417)
***R*$_1$, *wR*$_2$ (2σ data)**	0.0567, 0.1267
***R*$_1$, *wR*$_2$ (all data)**	0.0693, 0.1353
GOOF on *F*^{2}	1.042
Peak/hole/ e Å^{-3}	0.284 / −0.184

12 Experimental Section Part I: Intramolecular Acylation Reactions

Typical Procedure (TP5) for Esterification

A solution of the diol (1.0 equiv.) in THF (3.1 M) was added to sodium hydride (1.05 equiv.) in THF (1.0 M) at 0 °C. The reaction mixture was allowed to warm to room temperature and was stirred for 1 h. After cooling to 0 °C, the acid chloride (1.0 equiv.) was added. After 16 h at room temperature, the reaction mixture was quenched with saturated aqueous NH_4Cl solution. The phases were separated and the aqueous phase was extracted with diethyl ether. The combined organic layers were dried over $MgSO_4$. The crude product was purified by column chromatography on silica.

Typical Procedure (TP6) for Iodination

A dry and argon-flushed *Schlenk*-flask was charged with a solution of PPh_3 (1.2 equiv.) and *N*-methylimidazole (1.2 equiv.) in dichloromethane (0.3 M) and was cooled to −10 °C. Iodine (1.2 equiv.) was added and the resulting yellow solution was stirred for 15 min at −10 °C. The alcohol (1.0 equiv.) dissolved in dichloromethane (1.0 M) was added dropwise and the resulting reaction mixture was stirred for 2 h at −10 °C. The reaction mixture was quenched with saturated aqueous $NaHSO_3{\cdot}Na_2S_2O_5$ solution,[XXII] the phases were separated and the aqueous phase was extracted with dichloromethane. The combined organic layers were dried over $MgSO_4$ and the solvents were evaporated at 30 °C.[XXIII] The residue was triturated three times with a mixture of hexane:diethyl ether (4:1).[XXIV] The residue was filtered off using a plug of silica and all organic phases were combined. All solvents were evaporated and the crude residue was subjected to column chromatography purification on silica yielding the respective title compound.

Typical Procedure (TP7) for the Intramolecular Acylation and TBS-Protection

A dry and argon-flushed *Schlenk*-tube with diethyl ether (0.2 M based on *t*-BuLi) was cooled to −100 °C and charged with a solution of *t*-BuLi (in pentane, 2.5 equiv.). The appropriate alkyl iodide (1.0 equiv.) in diethyl ether (0.4 M) was added dropwise over 10 min and the reaction mixture was stirred for 5 min at −100 °C. Saturated aqueous NH_4Cl solution (10 drops) was added and the reaction mixture as allowed

[XXII] Quenching with water or unsaturated aqueous ($NaHSO_3{\cdot}Na_2S_2O_5$) solution sometimes causes epimerisation of the product.

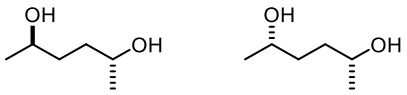
[XXIII] Evaporation at higher temperatures (>30 °C) sometimes causes epimerisation of the product.

[XXIV] Removal of triphenylphosphine oxide before column chromatography is recommended to get higher yield by washing and filtering the crude product with a mixture of hexane: ethyl ether.

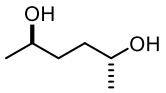
to warm to room temperature. $MgSO_4$ was added, the solution was filtrated over celite and the solvents were evaporated.

The crude mixture and imidazole (2.5 equiv.) were dissolved in DMF (0.2 M). After cooling to 0 °C, TBSCl (1.2 equiv.) was added and the reaction mixture was allowed to stir at room temperature for 16 h. Saturated aqueous NH_4Cl solution was added, the phases were separated and the aqueous phase was extracted with diethyl ether. The combined organic layers were dried over $MgSO_4$. The solvents were evaporated and the crude residue was subjected to column chromatography purification on silica yielding the respective title compound.

12.1 Preparation of the Esters



In an argon-flushed *Schlenk*-flask, thionyl chloride (3.74 mL, 51.0 mmol, 1.0 equiv.) was added dropwise to a solution of hexane-2,5-diol **63** (6.28 g, 51.0 mmol, 1.0 equiv.) in dichloromethane (50 mL) at 0 °C. The reaction mixture was stirred at room temperature for 3 h. Volatile reagents and solvents were removed at 0 °C under high vacuum using a trap. The crude product was purified and the two diastereoisomers were separated by column chromatography on silica using hexane:diethyl ether (9:1) as an eluent to afford *syn*-**S8** (16%, 1.29 g, 8.53 mmol) and *anti*-**S8** (40%, 3.28 g, 19.9 mmol) as colourless oils.[93]



***anti*-Hexane-2,5-diol *anti*-63.**[93] *anti*-**S8** (1.35 g, 8.22 mmol, 1.0 equiv.) was dissolved in aqueous NaOH (13.1 mL, 26.2 mmol, 3.2 equiv.) and the reaction mixture was refluxed for 1.5 h. The reaction mixture was saturated with sodium chloride, the phases were separated and the aqueous phase was extracted with ethyl acetate. The combined organic layers were dried over $MgSO_4$. The crude product was purified by column chromatography on silica using ethyl acetate as an eluent to afford *anti*-**63** as a colourless oil (94%, 913 mg, 7.73 mmol, d.r.>99:1).

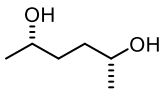
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 3.87 – 3.76 (m, 2H), 2.50 (br s, 2H), 1.64 – 1.47 (m, 4H), 1.21 (d, J = 6.2 Hz, 3H), 1.19 (d, J = 6.2 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 68.3, 35.9, 23.8.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3316, 2966, 2929, 2872, 1460, 1417, 1373, 1334, 1251, 1198, 1147, 1118, 1056, 1017, 940, 923, 901, 879, 856, 840, 822.

MS (EI, 70 eV): *m/z* (%) = 85 (100), 67 (33), 58 (10), 56 (15), 45 (40), 43 (27), 41 (39).

HR-MS (EI, 70 eV): [$C_6H_{11}O$], calcd.: 99.0810; found: 99.0804 ([M−H−H_2O]$^+$).



***syn*-Hexane-2,5-diol *syn*-63.**[93] *syn*-**S8** (1.40 g, 8.52 mmol, 1.0 equiv.) was dissolved in aqueous NaOH (13.6 mL, 27.2 mmol, 3.2 equiv.) and the reaction mixture was refluxed for 1.5 h. The reaction mixture was saturated with sodium chloride, the phases were separated and the aqueous phase was extracted with ethyl acetate. The combined organic layers were dried over $MgSO_4$. The crude product was purified by column chromatography on silica using ethyl acetate as an eluent to afford *syn*-**63** as a colourless oil (90%, 905 mg, 7.66 mmol, d.r.>99:1).

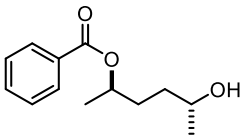
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 3.91 – 3.81 (m, 2H), 1.93 (s, 2H), 1.60 – 1.48 (m, 4H), 1.21 (d, J = 6.3 Hz, 6H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 68.0, 35.0, 23.5.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3319, 2967, 2930, 2872, 1461, 1414, 1374, 1330, 1124, 1056, 1012, 940, 896, 857, 839, 823, 761.

MS (EI, 70 eV): *m/z* (%) = 85 (100), 67 (32), 56 (15), 45 (20), 43 (17), 41 (19).

HR-MS (EI, 70 eV): [$C_6H_{11}O$], calcd.: 99.0810; found: 99.0805 ([M−H−H_2O]$^+$).



***anti*-5-Hydroxyhexan-2-yl benzoate *anti*-65a.** Following **TP5**, deprotonated diol *anti*-**63** (562 mg, 4.76 mmol, 1.0 equiv.) was reacted with benzoyl chloride (550 µL, 4.76 mmol, 1.0 equiv.). The crude product was purified by column chromatography on silica using hexane:diethyl ether (1:2) as an eluent to afford *anti*-**65a** as a colourless oil (84%, 884 mg, 3.98 mmol, d.r.>99:1).

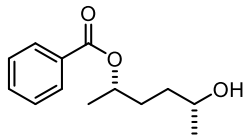
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.08 – 8.00 (m, 2H), 7.60 – 7.51 (m, 1H), 7.48 – 7.39 (m, 2H), 5.19 (dqd, J = 7.6, 6.2, 4.9 Hz, 1H), 3.85 (h, J = 6.2 Hz, 1H), 1.87 (dddd, J = 13.4, 10.4, 7.5, 5.1 Hz, 1H), 1.69 (dddd, J = 13.4, 9.7, 6.1, 5.0 Hz, 1H), 1.64 – 1.45 (m, 3H), 1.36 (d, J = 6.2 Hz, 3H), 1.21 (d, J = 6.2 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 166.2, 132.7, 130.6, 129.5, 128.3, 71.4, 67.7, 34.7, 32.1, 23.6, 20.1.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3403, 2973, 2932, 2872, 1714, 1602, 1585, 1452, 1378, 1355, 1315, 1276, 1177, 1113, 1099, 1070, 1044, 1026, 1015, 1003, 935, 920, 852, 712, 688, 674.

MS (EI, 70 eV): *m/z* (%) = 122 (100), 106 (12), 85 (12), 77 (40). 56 (16), 45 (12).

HR-MS (EI, 70 eV): [$C_{13}H_{19}O_3$], calcd.: 223.1329; found: 223.1329 ([M+H]$^+$).



***syn*-5-Hydroxyhexan-2-yl benzoate *syn*-113f.** Following **TP5**, deprotonated diol *syn*-**63** (262 mg, 2.22 mmol, 1.0 equiv.) was reacted with benzoyl chloride (260 µL, 2.22 mmol, 1.0 equiv.). The crude product was purified by column chromatography on silica using hexane:diethyl ether (1:2) as an eluent to afford *syn*-**65a** as a colourless oil (97%, 478 mg, 2.15 mmol, d.r.>99:1).

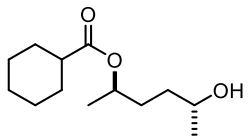
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.08 – 8.01 (m, 2H), 7.60 – 7.51 (m, 1H), 7.48 – 7.32 (m, 2H), 5.18 (h, J = 6.3 Hz, 1H), 3.90 – 3.78 (m, 1H), 1.86 – 1.70 (m, 2H), 1.65 – 1.43 (m, 2H), 1.36 (d, J = 6.3 Hz, 3H), 1.21 (d, J = 6.2 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 166.2, 132.8, 130.6, 129.5, 128.3, 71.6, 67.9, 35.0, 32.3, 23.6, 20.1.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3410, 2973, 2933, 1714, 1451, 1378, 1355, 1315, 1275, 1176, 1113, 1099, 1070, 1046, 1026, 1012, 938, 712, 688, 674.

MS (EI, 70 eV): *m/z* (%) = 123 (58), 105 (100), 77 (33).

HR-MS (EI, 70 eV): [$C_{13}H_{17}O_2$], calcd.: 205.1229; found: 205.1226 ([M−OH]$^+$).



***anti*-5-Hydroxyhexan-2-yl cyclohexanecarboxylate *anti*-65b.** Following **TP6**, deprotonated diol *anti*-**63** (244 mg, 2.07 mmol, 1.0 equiv.) was reacted with cyclohexanecarbonyl chloride (280 µL,

2.07 mmol, 1.0 equiv.). The crude product was purified by column chromatography on silica using hexane:diethyl ether (1:2) as an eluent to afford *anti*-**65b** as a colourless oil (79%, 373 mg, 1.63 mmol, d.r.>99:1).

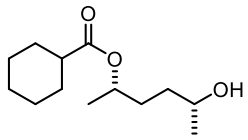
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 4.99 – 4.85 (m, 1H), 3.87 – 3.73 (m, 1H), 2.26 (tt, *J* = 11.3, 3.6 Hz, 1H), 1.93 – 1.84 (m, 2H), 1.77 – 1.39 (m, 10H), 1.32 – 1.23 (m, 3H), 1.21 (d, *J* = 4.6 Hz, 3H), 1.19 (d, *J* = 4.5 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 175.8, 70.0, 67.7, 43.4, 34.7, 32.0, 29.1, 28.9, 25.7, 25.4, 25.4, 23.6, 20.0.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3435, 2931, 2856, 1727, 1708, 1451, 1377, 1354, 1330, 1312, 1297, 1279, 1248, 1229, 1195, 1174, 1133, 1100, 1076, 1057, 1036, 1017, 947, 930, 896, 855, 845, 668, 660, 652.

MS (EI, 70 eV): *m/z* (%) = 129 (61), 83 (100).

HR-MS (EI, 70 eV): [$C_{13}H_{23}O_2$], calcd.: 211.1698; found: 211.1673 ([M−OH]$^+$).



***syn*-5-Hydroxyhexan-2-yl cyclohexanecarboxylate *syn*-65b.** Following **TP5**, deprotonated diol *syn*-**63** (248 mg, 2.10 mmol, 1.0 equiv.) was reacted with cyclohexanecarbonyl chloride (290 µL, 2.10 mmol, 1.0 equiv.). The crude product was purified by column chromatography on silica using pentane:diethyl ether (1:2) as an eluent to afford *syn*-**65b** as a colourless oil (78%, 375 mg, 1.64 mmol, d.r.>99:1).

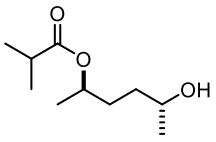
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 4.90 (h, *J* = 6.3 Hz, 1H), 3.79 (dq, *J* = 12.3, 6.2 Hz, 1H), 2.25 (tt, *J* = 11.3, 3.6 Hz, 1H), 1.88 (dtt, *J* = 12.3, 3.5, 1.7 Hz, 2H), 1.81 – 1.70 (m, 2H), 1.68 – 1.56 (m, 2H), 1.53 – 1.35 (m, 4H), 1.35 – 1.21 (m, 4H), 1.21 (d, *J* = 4.3 Hz, 3H), 1.19 (d, *J* = 4.3 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 175.8, 70.3, 67.8, 43.4, 34.9, 32.2, 29.0, 28.9, 25.7, 25.4, 25.4, 23.5, 20.0.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3432, 2932, 2856, 1728, 1710, 1451, 1378, 1354, 1330, 1312, 1297, 1278, 1248, 1229, 1195, 1174, 1131, 1076, 1059, 1037, 1019, 947, 896, 844.

MS (EI, 70 eV): *m/z* (%) = 111 (100), 101 (29), 99 (20), 85 (27), 84 (12), 67 (12), 56 (29), 55 (80), 45 (39), 43 (14), 41 (21).

HR-MS (EI, 70 eV): [$C_{13}H_{25}O_3$], calcd.: 229.1798; found: 229.1808 ([M+H]$^+$).



***anti*-5-Hydroxyhexan-2-yl isobutyrate *anti*-65c.** Following **TP5**, deprotonated diol *anti*-**63** (285 mg, 2.41 mmol, 1.0 equiv.) was reacted with isobutyryl chloride (260 µL, 2.41 mmol, 1.0 equiv.). The crude product was purified by column chromatography on silica using hexane:diethyl ether (1:2) as an eluent to afford *anti*-**65c** as a colourless oil (75%, 342 mg, 1.82 mmol, d.r.>99:1).

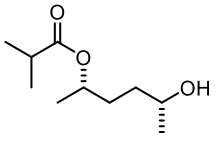
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 4.92 (dqd, *J* = 7.7, 6.2, 4.8 Hz, 1H), 3.87 – 3.74 (m, 1H), 2.51 (hept, *J* = 7.0 Hz, 1H), 1.76 – 1.65 (m, 1H), 1.62 – 1.30 (m, 4H), 1.21 (d, *J* = 6.3 Hz, 3H), 1.20 (d, *J* = 6.1 Hz, 3H), 1.16 (d, *J* = 7.0 Hz, 3H), 1.15 (d, *J* = 7.0 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 176.8, 70.2, 67.7, 34.7, 34.1, 32.0, 23.6, 19.9, 19.0, 18.9.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3422, 2973, 2935, 2877, 1729, 1712, 1470, 1462, 1385, 1378, 1359, 1335, 1266, 1196, 1161, 1123, 1096, 1072, 1045, 1015, 943, 930, 900, 892, 858, 823, 756.

MS (EI, 70 eV): *m/z* (%) = 115 (12), 89 (69), 71 (100).

HR-MS (EI, 70 eV): [$C_{10}H_{21}O_3$], calcd.: 189.1485; found: 189.1485 ([M+H]$^+$).



***syn*-5-Hydroxyhexan-2-yl isobutyrate *syn*-65c.** Following **TP5**, deprotonated diol *syn*-**63** (238 mg, 2.01 mmol, 1.0 equiv.) was reacted with isobutyryl chloride (220 µL, 2.01 mmol, 1.0 equiv.). The crude product was purified by column chromatography on silica using hexane:diethyl ether (1:2) as an eluent to afford *syn*-**65c** as a colourless oil (76%, 287 mg, 1.52 mmol, d.r.>99:1).

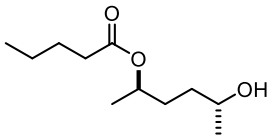
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 4.90 (h, J = 6.3 Hz, 1H), 3.86 – 3.73 (m, 1H), 2.50 (hept, J = 7.0 Hz, 1H), 1.71 – 1.53 (m, 3H), 1.53 – 1.39 (m, 2H), 1.21 (d, J = 6.3 Hz, 3H), 1.19 (d, J = 6.1 Hz, 3H), 1.15 (d, J = 7.0 Hz, 3H), 1.15 (d, J = 7.0 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 176.9, 70.5, 67.8, 34.9, 34.1, 32.2, 23.5, 19.9, 19.0, 18.9.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3432, 2973, 2935, 2877, 1730, 1713, 1470, 1462, 1385, 1335, 1266, 1197, 1162, 1126, 1097, 1070, 1046, 1012, 943, 858.

MS (EI, 70 eV): *m/z* (%) = 101 (52), 99 (18), 95 (17), 93 (10), 91 (18), 89 (20), 83 (100), 81 (25).

HR-MS (EI, 70 eV): [$C_{10}H_{19}O_2$], calcd.: 171.1385; found: 171.1379 ([M−OH]$^+$).



***anti*-5-Hydroxyhexan-2-yl pentanoate *anti*-65d.** Following **TP5**, deprotonated diol *anti*-**63** (240 mg, 2.03 mmol, 1.0 equiv.) was reacted with valeroyl chloride (250 µL, 2.03 mmol, 1.0 equiv.). The crude product was purified by column chromatography on silica using hexane:diethyl ether (1:2) as an eluent to afford *anti*-**65d** as a colourless oil (77%, 317 mg, 1.57 mmol, d.r.>99:1).

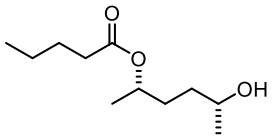
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 4.98 – 4.88 (m, 1H), 3.86 – 3.76 (m, 1H), 2.28 (dd, J = 7.5 Hz, 2H), 1.76 – 1.65 (m, 1H), 1.65 – 1.53 (m, 3H), 1.53 – 1.40 (m, 3H), 1.40 – 1.29 (m, 2H), 1.22 (d, J = 6.3 Hz, 3H), 1.20 (d, J = 6.2 Hz, 3H), 0.91 (t, J = 7.4 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 173.5, 70.4, 67.7, 34.7, 34.4, 32.0, 27.1, 23.6, 22.2, 20.0, 13.7.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3406, 2962, 2933, 2874, 1730, 1713, 1457, 1419, 1376, 1333, 1311, 1289, 1260, 1181, 1151, 1138, 1125, 1109, 1093, 1058, 1045, 1015, 942, 912, 889, 853, 754, 734, 668.

MS (EI, 70 eV): *m/z* (%) = 157 (16), 103 (47), 85 (100), 57 (37).

HR-MS (EI, 70 eV): [$C_{11}H_{21}O_2$], calcd.: 185.1542; found: 185.1541 ([M−OH]$^+$).



***syn*-5-Hydroxyhexan-2-yl pentanoate *syn*-65d.** Following **TP5**, deprotonated diol *syn*-**63** (241 mg, 2.04 mmol, 1.0 equiv.) was reacted with valeroyl chloride (250 µL, 2.04 mmol, 1.0 equiv.). The crude product was purified by column chromatography on silica using hexane:diethyl ether (1:2) as an eluent to afford *syn*-**65d** as a colourless oil (79%, 326 mg, 1.61 mmol, d.r.>99:1).

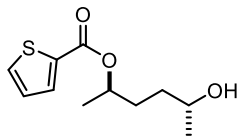
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 4.91 (h, J = 6.3 Hz, 1H), 3.86 – 3.74 (m, 1H), 2.28 (t, J = 7.5 Hz, 2H), 1.70 – 1.54 (m, 5H), 1.55 – 1.41 (m, 2H), 1.34 (dq, J = 14.6, 7.3 Hz, 2H), 1.22 (d, J = 6.3 Hz, 3H), 1.20 (d, J = 6.1 Hz, 3H), 0.91 (t, J = 7.4 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 173.6, 70.6, 67.8, 34.9, 34.4, 32.2, 27.1, 23.6, 22.2, 20.0, 13.7.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3420, 2962, 2934, 2874, 1731, 1714, 1460, 1419, 1377, 1333, 1310, 1289, 1262, 1182, 1128, 1109, 1094, 1060, 1046, 1012, 941.

MS (EI, 70 eV): *m/z* (%) = 103 (46), 85 (100), 83 (20), 57 (34), 56 (27), 55 (15), 45 (22), 43 (13), 41 (18).

HR-MS (EI, 70 eV): [$C_{11}H_{21}O_2$], calcd.: 185.1542; found: 185.1534 ([M−OH]$^+$).



***anti*-5-Hydroxyhexan-2-yl thiophene-2-carboxylate *anti*-65e.** Following **TP5**, deprotonated diol *anti*-**63** (259 mg, 2.19 mmol, 1.0 equiv.) was reacted with 2-thiophenecarbonyl chloride (240 µL, 2.19 mmol, 1.0 equiv.). The crude product was purified by column chromatography on silica using hexane:diethyl ether (1:2) as an eluent to afford *anti*-**65e** as a colourless oil (70%, 349 mg, 1.53 mmol, d.r.>99:1).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.79 (dd, J = 3.8, 1.3 Hz, 1H), 7.54 (dd, J = 5.0, 1.2 Hz, 1H), 7.10 (dd, J = 5.0, 3.7 Hz, 1H), 5.15 (dqd, J = 7.7, 6.3, 4.9 Hz, 1H), 3.85 (h, J = 6.2 Hz, 1H), 1.91 – 1.78

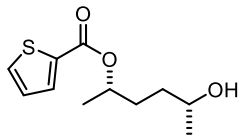
(m, 1H), 1.75 – 1.63 (m, 1H), 1.63 – 1.45 (m, 2H), 1.37 (br s, 1H), 1.35 (d, *J* = 6.3 Hz, 3H), 1.21 (d, *J* = 6.1 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 161.9, 134.4, 133.1, 132.1, 127.6, 71.8, 67.7, 34.7, 32.1, 23.6, 20.1.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3393, 1972, 2932, 1701, 1526, 1450, 1417, 1225, 1364, 1263, 1225, 1092, 1076, 1038, 1013, 932, 861, 752, 720.

MS (EI, 70 eV): *m/z* (%) = 186 (43), 184 (10), 128 (98), 112 (17), 99 (24), 85 (31), 83 (13), 82 (12), 58 (45), 56 (35), 55 (20), 45 (51), 43 (34), 41 (19).

HR-MS (EI, 70 eV): [$C_{11}H_{16}O_3S$], calcd.: 228.0820; found: 228.0820 (M^+).



***syn*-5-Hydroxyhexan-2-yl thiophene-2-carboxylate *syn*-65e.** Following **TP5**, deprotonated diol *syn*-**63** (246 mg, 2.08 mmol, 1.0 equiv.) was reacted with 2-thiophenecarbonyl chloride (230 µL, 2.08 mmol, 1.0 equiv.). The crude product was purified by column chromatography on silica using hexane:diethyl ether (1:2) as an eluent to afford *syn*-**65e** as a colourless oil (72%, 340 mg, 1.49 mmol, d.r.>99:1).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.79 (dd, *J* = 3.7, 1.3 Hz, 1H), 7.54 (dd, *J* = 5.0, 1.2 Hz, 1H), 7.10 (dd, *J* = 5.0, 3.7 Hz, 1H), 5.13 (h, *J* = 6.3 Hz, 1H), 3.83 (dqd, *J* = 7.5, 6.2, 5.0 Hz, 1H), 1.82 – 1.71 (m, 2H), 1.62 – 1.45 (m, 3H), 1.35 (d, *J* = 6.2 Hz, 3H), 1.21 (d, *J* = 6.1 Hz, 3H).

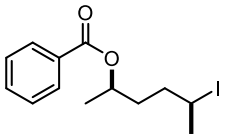
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 161.9, 134.3, 133.1, 132.1, 127.6, 72.0, 67.8, 34.9, 32.3, 23.6, 20.1.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3392, 2971, 2932, 2871, 1698, 1526, 1459, 1450, 1417, 1364, 1261, 1225, 1128, 1090, 1076, 1060, 1037, 1009, 938, 914, 861, 816, 750, 717, 660.

MS (EI, 70 eV): *m/z* (%) = 186 (82), 184 (17), 113 (20), 112 (31), 99 (31), 85 (41), 83 (17), 58 (30), 56 (24), 55 (16), 45 (35), 42 (19).

HR-MS (EI, 70 eV): [$C_{11}H_{17}O_3S$], calcd.: 229.0893; found: 229.0900 ($[M+H]^+$).

12.2 Preparation of the Iodides



***syn*-5-Iodohexan-2-yl benzoate *syn*-64a.** Following **TP6**, *anti*-**65a** (622 mg, 2.80 mmol, 1.0 equiv.) was used as starting material. The crude product was purified by column chromatography on silica using hexane:diethyl ether (20:1) as an eluent to afford *syn*-**64a** as a colourless oil (97%, 901 mg, 2.71 mmol, d.r.>99:1).

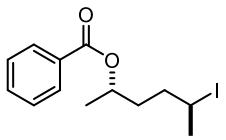
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.08 – 8.01 (m, 2H), 7.61 – 7.52 (m, 1H), 7.49 – 7.40 (m, 2H), 5.24 – 5.12 (m, 1H), 4.25 – 4.12 (m, 1H), 1.93 (d, J = 6.9 Hz, 3H), 1.91 – 1.73 (m, 4H), 1.37 (d, J = 6.2 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 166.1, 132.8, 130.5, 129.5, 128.3, 70.9, 38.8, 36.3, 29.6, 28.9, 20.1.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2977, 1715, 1450, 1379, 1355, 1314, 1275, 1228, 1176, 1111, 1070, 1046, 1026, 712, 688.

MS (EI, 70 eV): *m/z* (%) = 205 (11), 123 (17), 105 (100), 83 (39), 77 (30), 55 (24).

HR-MS (EI, 70 eV): [$C_{13}H_{17}O_2$], calcd.: 205.1229; found: 205.1223 ([M−I]$^+$).



***anti*-5-Iodohexan-2-yl benzoate *anti*-64a.** Following **TP6**, *syn*-**65a** (358 mg, 1.61 mmol, 1.0 equiv.) was used as starting material. The crude product was purified by column chromatography on silica using hexane:diethyl ether (20:1) as an eluent to afford *anti*-**64a** as a colourless oil (98%, 525 mg, 1.58 mmol, d.r.>99:1).

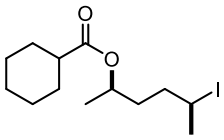
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.08 – 8.01 (m, 2H), 7.61 – 7.52 (m, 1H), 7.49 – 7.40 (m, 2H), 5.20 (dqd, J = 8.0, 6.3, 4.3 Hz, 1H), 4.21 (dqd, J = 8.5, 6.8, 4.4 Hz, 1H), 2.02 – 1.86 (m, 5H), 1.84 – 1.63 (m, 2H), 1.37 (d, J = 6.2 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 166.1, 132.8, 130.5, 129.5, 128.3, 70.4, 38.4, 36.1, 29.5, 29.0, 20.2.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2978, 2918, 1714, 1450, 1379, 1352, 1314, 1274, 1229, 1176, 1130, 1110, 1070, 1045, 1026, 711, 688.

MS (EI, 70 eV): *m/z* (%) = 205 (23), 123 (27), 106 (13), 83 (87), 77 (44), 55 (39), 41 (12).

HR-MS (EI, 70 eV): [$C_{13}H_{17}O_2$], calcd.: 205.1229; found: 205.1222 ([M−I]$^+$).



***syn*-5-Iodohexan-2-yl cyclohexanecarboxylate *syn*-64b.** Following **TP6**, *anti*-**65b** (357 mg, 1.56 mmol, 1.0 equiv.) was used as starting material. The crude product was purified by column chromatography on silica using hexane:diethyl ether (20:1) as an eluent to afford *syn*-**64b** as a colourless oil (86%, 456 mg, 1.35 mmol, d.r. = 87:13).

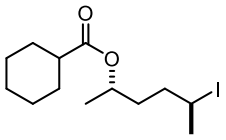
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 4.98 – 4.85 (m, 1H), 4.20 – 4.09 (m, 1H), 2.26 (tt, *J* = 11.2, 3.6 Hz, 1H), 1.92 (d, *J* = 6.8 Hz, 3H), 1.90 – 1.58 (m, 9H), 1.49 – 1.37 (m, 2H), 1.34 – 1.22 (m, 3H), 1.21 (d, *J* = 6.3 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 175.7, 69.5, 43.3, 38.7, 36.1, 29.5, 29.0, 28.9, 28.9, 25.7, 25.4, 25.4, 20.0.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2976, 2930, 2854, 1724, 1448, 1378, 1328, 1312, 1274, 1246, 1228, 1192, 1170, 1126, 1076, 1060, 1034, 986, 948, 896, 844, 760.

MS (EI, 70 eV): *m/z* (%) = 211 (12). 129 (21), 84 (11), 57 (12), 55 (61), 41 (19).

HR-MS (EI, 70 eV): [$C_{13}H_{23}O_2$], calcd.: 211.1698; found: 211.1705 ([M−I]$^+$).



***anti*-5-Iodohexan-2-yl cyclohexanecarboxylate *anti*-64b.** Following **TP5**, *syn*-**65b** (175 mg, 0.776 mmol, 1.0 equiv.) was used as starting material. The crude product was purified by column chromatography on silica using pentane:diethyl ether (20:1) as an eluent to afford *anti*-**64b** as a colourless oil (50%, 130 mg, 0.384 mmol, d.r.>99:1).

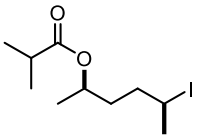
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 4.99 – 4.89 (m, 1H), 4.22 – 4.12 (m, 1H), 2.26 (tt, J = 11.3, 3.6 Hz, 1H), 1.94 – 1.70 (m, 8H), 1.68 – 1.57 (m, 3H), 1.49 – 1.36 (m, 2H), 1.35 – 1.19 (m, 7H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 175.7, 69.0, 43.3, 38.3, 35.9, 29.5, 29.1, 28.9, 28.9, 25.7, 25.4, 25.4, 20.1.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2975, 2931, 2855, 1726, 1449, 1378, 1329, 1311, 1275, 1247, 1227, 1193, 1172, 1131, 1076, 1035, 896, 845.

MS (EI, 70 eV): *m/z* (%) = 129 (13), 111 (16), 83 (100), 55 (25).

HR-MS (EI, 70 eV): [$C_{13}H_{23}O_2$], calcd.: 211.1698; found: 211.1690 ([M−I]$^+$).



***syn*-5-Iodohexan-2-yl isobutyrate *syn*-64c.** Following **TP6**, *anti*-**65c** (335 mg, 1.78 mmol, 1.0 equiv.) was used as starting material. The crude product was purified by column chromatography on silica using hexane:diethyl ether (20:1) as an eluent to afford *syn*-**64c** as a colourless oil (69%, 365 mg, 1.22 mmol, d.r.>99:1).

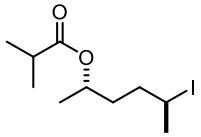
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 4.98 – 4.85 (m, 1H), 4.21 – 4.09 (m, 1H), 2.51 (hept, J = 7.0 Hz, 1H), 1.92 (d, J = 6.8 Hz, 3H), 1.87 – 1.58 (m, 4H), 1.22 (d, J = 6.3 Hz, 3H), 1.16 (d, J = 7.0 Hz, 3H), 1.15 (d, J = 7.0 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 176.7, 69.7, 38.7, 36.0, 34.1, 29.5, 28.9, 19.9, 19.0, 18.9.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2975, 2360, 2340, 1730, 1468, 1384, 1262, 1195, 1161, 1126, 1069, 668.

MS (EI, 70 eV): *m/z* (%) = 171 (14), 89 (12), 83 (100), 71 (53), 55 (46), 43 (40), 41 (19).

HR-MS (EI, 70 eV): [$C_9H_{16}O_2I$], calcd.: 283.0195; found: 283.0194 ([M−Me]$^+$).



***anti*-5-Iodohexan-2-yl isobutyrate *anti*-64c.** Following **TP6**, *syn*-**65c** (287 mg, 1.52 mmol, 1.0 equiv.) was used as starting material. The crude product was purified by column chromatography on silica using hexane:diethyl ether (20:1) as an eluent to afford *anti*-**64c** as a colourless oil (90%, 408 mg, 1.37 mmol, d.r. = 92:8).

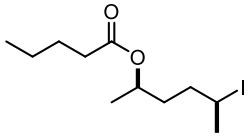
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 4.98 – 4.88 (m, 1H), 4.23 – 4.11 (m, 1H), 2.51 (hept, *J* = 7.0 Hz, 1H), 1.92 (d, *J* = 6.8 Hz, 3H), 1.89 – 1.70 (m, 2H), 1.70 – 1.58 (m, 2H), 1.22 (d, *J* = 6.3 Hz, 3H), 1.16 (d, *J* = 7.0 Hz, 3H), 1.15 (d, *J* = 7.0 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 176.7, 69.2, 38.3, 35.9, 34.1, 29.4, 28.9, 20.0, 19.0, 18.9.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2974, 2934, 2876, 1728, 1468, 1458, 1446, 1384, 1356, 1334, 1296, 1262, 1228, 1194, 1160, 1126, 1096, 1070, 1046, 1034, 984, 942, 910, 896, 852, 760.

MS (EI, 70 eV): *m/z* (%) = 185 (13), 103 (10), 85 (60), 83 (100).

HR-MS (EI, 70 eV): [$C_{10}H_{18}O_2I$], calcd.: 297.0351; found: 297.0346 ([M−H]$^+$).



***syn*-5-Iodohexan-2-yl pentanoate *syn*-64d.** Following **TP6**, *anti*-**63** (304 mg, 1.50 mmol, 1.0 equiv.) was used as starting material. The crude product was purified by column chromatography on silica using hexane:diethyl ether (20:1) as an eluent to afford *syn*-**64d** as a colourless oil (88%, 414 mg, 1.33 mmol, d.r. = 93:7).

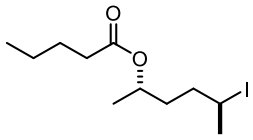
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 4.96 – 4.87 (m, 1H), 4.20 – 4.09 (m, 1H), 2.28 (dd, *J* = 7.5 Hz, 2H), 1.92 (d, *J* = 6.8 Hz, 3H), 1.86 – 1.55 (m, 6H), 1.42 – 1.28 (m, 2H), 1.22 (d, *J* = 6.2 Hz, 3H), 0.92 (t, *J* = 7.3 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 173.4, 69.9, 38.7, 36.1, 34.3, 29.5, 28.9, 27.1, 22.2, 20.0, 13.7.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2958, 2932, 2872, 1730, 1446, 1420, 1378, 1334, 1310, 1290, 1252, 1228, 1178, 1126, 1108, 1090, 1060, 1048, 1030, 986, 946, 898, 844, 758.

MS (EI, 70 eV): *m/z* (%) = 185 (15), 103 (13), 85 (69), 83 (100), 57 (33), 55(48), 41 (15).

HR-MS (EI, 70 eV): [$C_{11}H_{21}O_2$], calcd.: 185.1542; found: 185.1537 ([M−I]$^+$).



***anti*-5-Iodohexan-2-yl pentanoate *anti*-64d.** Following **TP6**, *syn*-**63** (313 mg, 1.55 mmol, 1.0 equiv.) was used as starting material. The crude product was purified by column chromatography on silica using hexane:diethyl ether (20:1) as an eluent to afford *anti*-**64d** as a colourless oil (86%, 414 mg, 1.33 mmol, d.r.>99:1).

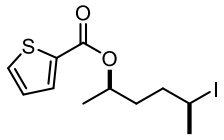
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 4.99 – 4.90 (m, 1H), 4.22 – 4.12 (m, 1H), 2.28 (dd, *J* = 7.5 Hz, 2H), 1.92 (d, *J* = 6.8 Hz, 3H), 1.89 – 1.71 (m, 2H), 1.68 – 1.54 (m, 4H), 1.40 – 1.29 (m, 2H), 1.23 (d, *J* = 6.3 Hz, 3H), 0.92 (t, *J* = 7.3 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 173.5, 69.4, 38.3, 35.9, 34.3, 29.4, 28.9, 27.1, 22.2, 20.1, 13.7.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2959, 2933, 2872, 2362, 1731, 1456, 1446, 1420, 1378, 1334, 1289, 1253, 1228, 1179, 1129, 1109, 1092, 1059, 1046, 1034, 984, 949.

MS (EI, 70 eV): *m/z* (%) = 185 (15), 103 (14), 85 (68), 83 (100), 57 (41), 55(61), 41 (27).

HR-MS (EI, 70 eV): [$C_{10}H_{18}O_2I$], calcd.: 297.0351; found: 297.0352 ([M−Me]$^+$).



***syn*-5-Iodohexan-2-yl thiophene-2-carboxylate *syn*-64e.** Following **TP6**, *anti*-**65e** (348 mg, 1.52 mmol, 1.0 equiv.) was used as starting material. The crude product was purified by column chromatography on silica using hexane:diethyl ether (20:1) as an eluent to afford *syn*-**64e** as a colourless oil (96%, 495 mg, 1.46 mmol, d.r.>99:1).

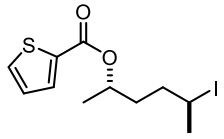
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.80 (dd, *J* = 3.8, 1.3 Hz, 1H), 7.55 (dd, *J* = 5.0, 1.3 Hz, 1H), 7.10 (dd, *J* = 5.0, 3.7 Hz, 1H), 5.22 – 5.06 (m, 1H), 4.25 – 4.10 (m, 1H), 1.93 (d, *J* = 6.9 Hz, 3H), 1.91 – 1.72 (m, 4H), 1.36 (d, *J* = 6.3 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 161.8, 134.2, 133.2, 132.2, 127.7, 71.4, 38.7, 36.2, 29.6, 28.9, 20.1.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3101, 2977, 2359, 1703, 1525, 1444, 1418, 1378, 1363, 1280, 1258, 1225, 1179, 1128, 1091, 1075, 1035, 986, 915, 861, 816, 751, 720.

MS (EI, 70 eV): *m/z* (%) = 211 (35), 129 (30), 112 (13), 83 (100), 55 (41), 41 (12).

HR-MS (EI, 70 eV): [$C_{11}H_{15}O_2S$], calcd.: 211.0793; found: 211.0792 ([M−I]$^+$).



***anti*-5-Iodohexan-2-yl thiophene-2-carboxylate *anti*-64e.** Following **TP6**, *syn*-**65e** (340 mg, 1.49 mmol, 1.0 equiv.) was used as starting material. The crude product was purified by column chromatography on silica using hexane:diethyl ether (20:1) as an eluent to afford *anti*-**64e** as a colourless oil (92%, 464 mg, 1.37 mmol, d.r.>99:1).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.79 (dd, *J* = 3.7, 1.3 Hz, 1H), 7.55 (dd, *J* = 5.0, 1.3 Hz, 1H), 7.10 (dd, *J* = 5.0, 3.7 Hz, 1H), 5.15 (dqd, *J* = 7.9, 6.3, 4.3 Hz, 1H), 4.26 – 4.16 (m, 1H), 1.98 – 1.86 (m, 5H), 1.80 – 1.64 (m, 2H), 1.36 (d, *J* = 6.3 Hz, 3H).

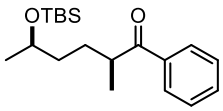
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 161.8, 134.2, 133.2, 132.2, 127.7, 70.8, 38.3, 36.0, 29.5, 28.9, 20.2.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3101, 2977, 2934, 2864, 1700, 1525, 1444, 1418, 1378, 1363, 1279, 1258, 1223, 1177, 1131, 1089, 1075, 1035, 983, 916, 897, 862, 817, 749, 718, 660.

MS (EI, 70 eV): *m/z* (%) = 211 (53), 129 (56), 112 (19), 83 (11), 41 (35).

HR-MS (EI, 70 eV): [$C_{11}H_{15}O_2S$], calcd.: 211.0793; found: 211.0778 ([M−I]$^+$).

12.3 Preparation of Ketones



Ketone *syn*-69a. Following **TP7**, iodide *syn*-**64a** (102 mg, 0.307 mmol, 1.0 equiv., d.r.>99:1) was reacted with *t*-BuLi (1.95 M, 0.39 mL, 0.768 mmol, 2.5 equiv.). TBS-protection was carried out with imidazole (53 mg, 0.758 mmol, 2.5 equiv.) and TBSCl (55 mg, 0.368 mmol, 1.2 equiv.). The crude product was purified by column chromatography on silica using hexane:diethyl ether (50:1) as an eluent to afford *syn*-**69a** as a colourless oil (42%, 41 mg, 0.128 mmol, d.r.>99:1).

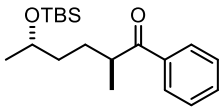
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.00 – 7.90 (m, 2H), 7.60 – 7.51 (m, 1H), 7.50 – 7.42 (m, 2H), 3.83 – 3.70 (m, 1H), 3.45 (h, *J* = 6.8 Hz, 1H), 1.84 – 1.72 (m, 1H), 1.61 – 1.51 (m, 1H), 1.45 – 1.33 (m, 2H), 1.20 (d, *J* = 6.9 Hz, 3H), 1.09 (d, *J* = 6.1 Hz, 3H), 0.86 (s, 9H), 0.02 (s, 6H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 204.4, 136.7, 132.8, 128.6, 128.2, 68.6, 40.7, 37.2, 29.8, 25.8, 23.7, 18.1, 17.4, −4.4, −4.8.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2956, 2930, 2857, 1684, 1462, 1448, 1374, 1361, 1254, 1230, 1197, 1132, 1093, 1057, 1002, 990, 971, 835, 809, 796, 774, 703, 688.

MS (EI, 70 eV): *m/z* (%) = 263 (55), 221 (19), 171 (11), 146 (11), 145 (100), 105 (26), 91 (12), 77 (22), 75 (67), 73 (34), 57 (14), 55 (11).

HR-MS (EI, 70 eV): [$C_{19}H_{31}O_2Si$], calcd.: 319.2093; found: 319.2088 ([M−H]$^+$).



Ketone *anti*-69a. Following **TP7**, iodide *anti*-**64a** (102 mg, 0.307 mmol, 1.0 equiv., d.r.>99:1) was reacted with *t*-BuLi (1.95 M, 0.39 mL, 0.768 mmol, 2.5 equiv.). TBS-protection was carried out with imidazole (53 mg, 0.758 mmol, 2.5 equiv.) and TBSCl (55 mg, 0.368 mmol, 1.2 equiv.). The crude product was purified by column chromatography on silica using pentane as an eluent to afford *anti*-**69a** as a colourless oil (81%, 80 mg, 0.250 mmol, d.r.>99:1).

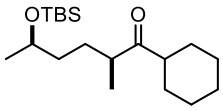
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.98 – 7.91 (m, 2H), 7.60 – 7.52 (m, 1H), 7.50 – 7.43 (m, 2H), 3.79 – 3.68 (m, 1H), 3.48 – 3.38 (m, 1H), 1.96 – 1.83 (m, 1H), 1.48 – 1.35 (m, 3H), 1.20 (d, J = 6.8 Hz, 3H), 1.10 (d, J = 6.1 Hz, 3H), 0.84 (s, 9H), 0.01 (s, 3H), –0.02 (s, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 204.3, 136.6, 132.7, 128.6, 128.2, 68.4, 40.6, 37.1, 29.6, 25.8, 23.6, 18.0, 16.9, −4.5, −4.9.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2956, 2930, 2886, 2856, 1684, 1598, 1472, 1462, 1448, 1374, 1362, 1274, 1252, 1230, 1198, 1180, 1132, 1092, 1056, 1002, 988, 968, 938, 898, 880, 832, 810, 796, 772, 702, 686, 656.

MS (EI, 70 eV): *m/z* (%) = 319 (18), 225 (11), 221 (20), 161 (29), 15 (100), 131 (17), 75 (47), 73 (10).

HR-MS (EI, 70 eV): [$C_{18}H_{29}O_2Si$], calcd.: 305.1935; found: 305.1931 ([M−Me]$^+$).



Ketone *syn*-69b. Following **TP7**, iodide *syn*-**64b** (99 mg, 0.293 mmol, 1.0 equiv., d.r. = 87:13) was reacted with *t*-BuLi (1.95 M, 0.38 mL, 0.733 mmol, 2.5 equiv.). TBS-protection was carried out with imidazole (50 mg, 0.733 mmol, 2.5 equiv.) and TBSCl (53 mg, 0.352 mmol, 1.2 equiv.). The crude product was purified by column chromatography on silica using hexane:diethyl ether (50:1) as an eluent to afford *syn*-**69b** as a colourless oil (34%, 33 mg, 0.101 mmol, d.r. = 90:10).

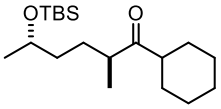
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 3.78 – 3.68 (m, 1H), 2.70 – 2.57 (m, 1H), 2.50 – 2.39 (m, 1H), 1.84 – 1.70 (m, 4H), 1.69 – 1.63 (m, 1H), 1.63 – 1.51 (m, 1H), 1.46 – 1.18 (m, 8H), 1.09 (d, J = 6.1 Hz, 3H), 1.05 – 0.99 (m, 3H), 0.87 (s, 9H), 0.03 (s, 6H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 217.7, 68.6, 49.7, 44.5, 37.3, 29.2, 28.6, 28.4, 25.8, 25.8, 25.7, 25.6, 23.8, 18.1, 16.7, −4.4, −4.8.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2930, 2856, 1708, 1472, 1462, 1450, 1374, 1362, 1256, 1134, 1100, 1056, 994, 894, 836, 808, 794, 774.

MS (EI, 70 eV): *m/z* (%) = 269 (17), 177 (21), 159 (17), 145 (100), 135 (18), 121 (12), 119 (12), 95 (22), 93 (12), 83 (13), 81 (13), 75 (69), 73 (19).

HR-MS (EI, 70 eV): [$C_{19}H_{37}O_2Si$], calcd.: 325.2563; found: 325.2554 ([M−H]$^+$).



Ketone *anti*-69b. Following **TP7**, iodide *anti*-**64b** (118 mg, 0.349 mmol, 1.0 equiv., d.r.>99:1) was reacted with *t*-BuLi (1.95 M, 0.45 mL, 0.873 mmol, 2.5 equiv.). TBS-protection was carried out with imidazole (60 mg, 0.873 mmol, 2.5 equiv.) and TBSCl (63 mg, 0.419 mmol, 1.2 equiv.). The crude product was purified by column chromatography on silica using hexane:diethyl ether (50:1) as an eluent to afford *anti*-**69b** as a colourless oil (64%, 73 mg, 0.224 mmol, d.r. = 92:8).

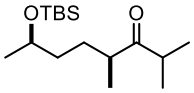
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 3.79 – 3.68 (m, 1H), 2.60 (h, *J* = 6.8 Hz, 1H), 2.50 – 2.40 (m, 1H), 1.82 – 1.60 (m, 6H), 1.39 – 1.18 (m, 8H), 1.10 (d, *J* = 6.1 Hz, 3H), 1.03 (d, *J* = 6.9 Hz, 3H), 0.87 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 217.5, 68.4, 49.5, 44.6, 37.3, 28.9, 28.6, 28.4, 25.8, 25.8, 25.7, 25.6, 23.6, 18.0, 16.4, −4.4, −4.8.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2929, 2856, 1707, 1472, 1462, 1450, 1374, 1362, 1253, 1140, 1134, 1098, 1050, 993, 939, 892, 883, 833, 808, 772, 714, 677, 662.

MS (EI, 70 eV): *m/z* (%) = 269 (16), 177 (20), 159 (16), 145 (100), 135 (18), 121 (11), 119 (19), 95 (23), 93 (11), 83 (12), 81 (13), 75 (68), 73 (17), 55 (11).

HR-MS (EI, 70 eV): [$C_{18}H_{35}O_2Si$], calcd.: 311.2406; found: 311.2398 ([M−Me]$^+$).



Ketone *syn*-69c. Following **TP7**, iodide *syn*-**64c** (83 mg, 0.278 mmol, 1.0 equiv., d.r.>99:1) was reacted with *t*-BuLi (2.15 M, 0.32 mL, 0.695 mmol, 2.5 equiv.). TBS-protection was carried out with imidazole (48 mg, 0.695 mmol, 2.5 equiv.) and TBSCl (50 mg, 0.334 mmol, 1.2 equiv.). The crude product was purified by column chromatography on silica using hexane:diethyl ether (50:1) as an eluent to afford *syn*-**69c** as a colourless oil (50%, 40 mg, 0.140 mmol, d.r.>99:1).

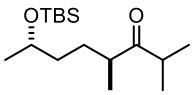
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 3.80 – 3.70 (m, 1H), 2.79 – 2.61 (m, 2H), 1.65 – 1.54 (m, 1H), 1.48 – 1.37 (m, 1H), 1.37 – 1.24 (m, 2H), 1.10 (d, J = 6.1 Hz, 3H), 1.08 (d, J = 5.4 Hz, 3H), 1.06 (d, J = 4.0 Hz, 3H), 1.06 – 1.04 (m, 3H), 0.88 (s, 9H), 0.04 (s, 6H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 218.4, 68.6, 44.5, 39.5, 37.3, 29.3, 25.8, 23.8, 18.4, 18.2, 18.1, 16.8, −4.4, −4.8.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2963, 2931, 2858, 1714, 1472, 1463, 1380, 1375, 1362, 1255, 1160, 1135, 1061, 1020, 1006, 895, 883, 836, 810, 796, 774.

MS (EI, 70 eV): *m/z* (%) = 229 (29), 187 (14), 173 (14), 169 (13), 159 (25), 155 (10), 145 (70), 141 (12), 137 (17), 119 (26), 95 (28), 81 (14), 75 (100), 73 (21).

HR-MS (EI, 70 eV): [$C_{16}H_{33}O_2Si$], calcd.: 285.2250; found: 285.2239 ([M−H]$^+$).



Ketone *anti*-69c. Following **TP7**, iodide *anti*-**64c** (90 mg, 0.301 mmol, 1.0 equiv., d.r. = 92:8) was reacted with *t*-BuLi (2.22 M, 0.34 mL, 0.753 mmol, 2.5 equiv.). TBS-protection was carried out with imidazole (52 mg, 0.753 mmol, 2.5 equiv.) and TBSCl (54 mg, 0.361 mmol, 1.2 equiv.). The crude product was purified by column chromatography on silica using hexane:diethyl ether (50:1) as an eluent to afford *anti*-**69c** as a colourless oil (47%, 40 mg, 0.140 mmol, d.r. = 90:10).

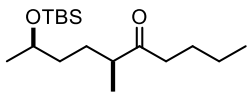
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 3.80 – 3.70 (m, 1H), 2.73 (m, 1H), 2.69 – 2.59 (m, 1H), 1.78 – 1.67 (m, 1H), 1.40 – 1.21 (m, 3H), 1.11 (d, J = 6.1 Hz, 3H), 1.08 (d, J = 5.8 Hz, 3H), 1.06 (d, J = 5.8 Hz, 3H), 1.05 (d, J = 6.9 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 218.3, 68.4, 44.5, 39.3, 37.3, 29.0, 25.8, 23.6, 18.5, 18.3, 18.1, 16.5, −4.4, −4.8.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2962, 2930, 2858, 1712, 1462, 1376, 1362, 1254, 1134, 1078, 1046, 1016, 1006, 980, 938, 894, 884, 834, 810, 772, 712, 662.

MS (EI, 70 eV): *m/z* (%) = 229 (23), 187 (22), 173 (10), 169 (15), 159 (16), 145 (80), 137 (15), 133 (10), 119 (25), 95 (31), 81 (11), 75 (100), 73 (21).

HR-MS (EI, 70 eV): [$C_{16}H_{33}O_2Si$], calcd.: 285.2250; found: 285.2243 ([M−H]$^+$).



Ketone *syn*-69d. Following **TP7**, iodide *syn*-**64d** (92 mg, 0.295 mmol, 1.0 equiv., d.r. = 93:7) was reacted with *t*-BuLi (1.95 M, 0.38 mL, 0.738 mmol, 2.5 equiv.). TBS-protection was carried out with imidazole (51 mg, 0.738 mmol, 2.5 equiv.) and TBSCl (53 mg, 0.354 mmol, 1.2 equiv.). The crude product was purified by column chromatography on silica using hexane:diethyl ether (50:1) as an eluent to afford *syn*-**69d** as a colourless oil (20%, 18 mg, 0.060 mmol, d.r. = 91:9).

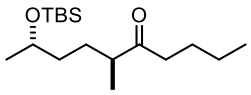
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 3.79 – 3.69 (m, 1H), 2.53 – 2.45 (m, 1H), 2.41 (td, J = 7.3, 2.9 Hz, 2H), 1.65 – 1.48 (m, 3H), 1.48 – 1.37 (m, 1H), 1.37 – 1.23 (m, 4H), 1.10 (d, J = 6.1 Hz, 3H), 1.05 (d, J = 7.0 Hz, 3H), 0.90 (t, J = 7.4 Hz, 3H), 0.87 (s, 9H), 0.03 (s, 6H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 215.0, 68.5, 46.3, 40.8, 37.1, 29.1, 25.8, 25.7, 23.7, 22.4, 18.1, 16.4, 13.8, −4.4, −4.8.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2958, 2930, 2858, 1714, 1462, 1376, 1362, 1256, 1164, 1136, 1104, 1078, 1058, 1042, 1006, 994, 896, 882, 836, 810, 774.

MS (EI, 70 eV): *m/z* (%) = 243 (35), 201 (16), 159 (15), 145 (100), 109 (11), 95 (14), 75 (67), 73 (16).

HR-MS (EI, 70 eV): [$C_{17}H_{35}O_2Si$], calcd.: 299.2406; found: 299.2392 ([M−H]$^+$).



Ketone *anti*-69d. Following **TP7**, iodide *anti*-**64d** (95 mg, 0.304 mmol, 1.0 equiv., d.r.>99:1) was reacted with *t*-BuLi (1.95 M, 0.39 mL, 0.760 mmol, 2.5 equiv.). TBS-protection was carried out with imidazole (52 mg, 0.760 mmol, 2.5 equiv.) and TBSCl (55 mg, 0.365 mmol, 1.2 equiv.). The crude product was purified by column chromatography on silica using hexane:diethyl ether (50:1) as an eluent to afford *anti*-**69d** as a colourless oil (39%, 36 mg, 0.120 mmol, d.r. = 98:2).

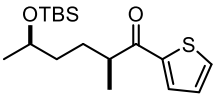
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 3.75 (h, J = 6.0 Hz, 1H), 2.54 – 2.43 (m, 1H), 2.41 (td, J = 7.2, 1.0 Hz, 2H), 1.78 – 1.67 (m, 1H), 1.59 – 1.48 (m, 2H), 1.40 – 1.23 (m, 5H), 1.10 (d, J = 6.1 Hz, 3H), 1.05 (d, J = 6.9 Hz, 3H), 0.89 (t, J = 7.3 Hz, 3H), 0.87 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 214.8, 68.3, 46.3, 40.5, 37.1, 28.9, 25.8, 25.8, 23.6, 22.4, 18.1, 16.2, 13.8, −4.4, −4.8.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2958, 2930, 2858, 1712, 1472, 1462, 1375, 1362, 1254, 1135, 1041, 1004, 939, 881, 834, 809, 773, 714, 663.

MS (EI, 70 eV): *m/z* (%) = 243 (24), 201 (22), 159 (10), 145 (100), 109 (10), 95 (11), 75 (63), 73 (13).

HR-MS (EI, 70 eV): [$C_{16}H_{33}O_2Si$], calcd.: 285.2250; found: 285.2242 ([M−Me]$^+$).



Ketone *syn*-69e. Following **TP7**, iodide *syn*-**64e** (97 mg, 0.287 mmol, 1.0 equiv., d.r.>99:1) was reacted with *t*-BuLi (2.15 M, 0.33 mL, 0.718 mmol, 2.5 equiv.). TBS-protection was carried out with imidazole (49 mg, 0.718 mmol, 2.5 equiv.) and TBSCl (52 mg, 0.344 mmol, 1.2 equiv.). The crude product was purified by column chromatography on aluminium oxide using hexane:diethyl ether (20:1) as an eluent to afford *syn*-**69e** as a colourless oil (38%, 36 mg, 0.110 mmol, d.r.>99:1).

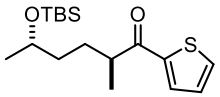
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.72 (dd, J = 3.8, 1.1 Hz, 1H), 7.63 (dd, J = 4.9, 1.1 Hz, 1H), 7.13 (dd, J = 4.9, 3.8 Hz, 1H), 3.82 – 3.70 (m, 1H), 3.26 (h, J = 6.9 Hz, 1H), 1.84 – 1.71 (m, 1H), 1.64 – 1.55 (m, 1H), 1.48 – 1.34 (m, 2H), 1.22 (d, J = 6.9 Hz, 3H), 1.09 (d, J = 6.1 Hz, 3H), 0.87 (s, 9H), 0.03 (s, 6H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 197.3, 144.3, 133.5, 131.5, 128.0, 68.6, 42.7, 37.3, 30.3, 25.8, 23.8, 18.1, 17.9, −4.5, −4.8.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2959, 2929, 2857, 1659, 1518, 1462, 1415, 1367, 1251, 1238, 1195, 1132, 1055, 1005, 988, 932, 835, 810, 774, 721, 698.

MS (EI, 70 eV): *m/z* (%) = 269 (35), 227 (28), 225 (19), 207 (14), 177 (12), 145 (89), 137 (100), 135 (13), 110 (36), 97 (11), 93 (10), 75 (69), 73 (17).

HR-MS (EI, 70 eV): [$C_{16}H_{27}O_2SSi$], calcd.: 311.1501; found: 311.1487 ([M−Me]$^+$).



Ketone *anti*-69e. Following **TP7**, iodide *anti*-**64e** (95 mg, 0.281 mmol, 1.0 equiv., d.r.>99:1) was reacted with *t*-BuLi (2.15 M, 0.33 mL, 0.703 mmol, 2.5 equiv.). TBS-protection was carried out with imidazole (48 mg, 0.703 mmol, 2.5 equiv.) and TBSCl (51 mg, 0.341 mmol, 1.2 equiv.). The crude product was purified by column chromatography on aluminium oxide using hexane:diethyl ether (50:1) as an eluent to afford *anti*-**69e** as a colourless oil (21%, 19 mg, 0.058 mmol, d.r.>99:1).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.71 (dd, *J* = 3.8, 1.1 Hz, 1H), 7.62 (dd, *J* = 5.0, 1.1 Hz, 1H), 7.13 (dd, *J* = 5.0, 3.8 Hz, 1H), 3.77 (h, *J* = 5.9 Hz, 1H), 3.29 – 3.19 (m, 1H), 1.94 – 1.85 (m, 1H), 1.48 – 1.39 (m, 3H), 1.22 (d, *J* = 6.9 Hz, 3H), 1.11 (d, *J* = 6.0 Hz, 3H), 0.85 (s, 9H), 0.02 (s, 3H), 0.00 (s, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 197.1, 144.2, 133.4, 131.4, 128.0, 68.3, 42.6, 37.2, 29.8, 25.8, 23.6, 18.1, 17.4, −4.5, −4.8.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2956, 2929, 2856, 1708, 1662, 1518, 1472, 1462, 1416, 1363, 1253, 1237, 1198, 1131, 1092, 1054, 1005, 986, 929, 835, 809, 774, 719, 662.

MS (EI, 70 eV): *m/z* (%) = 325 (68), 225 (78), 209 (26), 207 (58), 193 (42), 185 (35), 167 (26), 145 (46), 137 (100), 75 (63), 73 (22).

HR-MS (EI, 70 eV): [$C_{17}H_{29}O_2SSi$], calcd.: 325.1658; found: 325.1649 ([M−H]$^+$).

13 Experimental Section Part II: A New Arylthio/Magnesium-Exchange

Typical Procedure (TP8) for the Introduction of the Thioether

A dry and argon-flushed *Schlenk*-flask was charged with a solution of Boc-protected piperidine (1.0 equiv.) and TMEDA in diethyl ether (0.5 M) and cooled to −78 °C. *s*-BuLi was added and the resulting solution was stirred for 3 h at −78 °C. The thioether source dissolved in diethyl ether (0.8 M) was added dropwise and the resulting reaction mixture was allowed to warm to room temperature over 16 h. The reaction mixture was quenched with water, the phases were separated and the aqueous phase was extracted with diethyl ether. The combined organic layers were dried over $MgSO_4$ and the solvents were evaporated. The crude residue was subjected to column chromatography purification on silica yielding the respective title compound.

Typical Procedure (TP9) for the Preparation of *s*-BuMgOCH$_2$CH(Et)Bu·LiOCH$_2$CH(Et)Bu 71a

A dry and argon-flushed *Schlenk*-flask was charged with magnesium bis(2-ethylhexanolate) Mg[OCH$_2$CH(Et)Bu]$_2$ (0.84 M in heptane, 20.0 mL, 16.8 mmol) and cooled to 0 °C. *s*-BuLi (1.15 M in hexane, 14.6 mL, 16.8 mmol) was added dropwise. The reaction mixture was warmed to room temperature and was stirred for 2 h resulting in a slightly yellow solution. Solvents were removed *in vacuo* and dry toluene (7 mL) was added under stirring at 0 °C. Following titration with iodine at 0 °C gave a concentration of 1.0–1.3 M.

Typical Procedure (TP10) for the Preparation of *s*-Bu$_2$Mg·2LiOCH$_2$CH(Et)Bu 71b

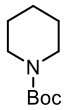
A dry and argon-flushed *Schlenk*-flask was charged with magnesium bis(2-ethylhexanolate) Mg[OCH$_2$CH(Et)Bu]$_2$ (0.84 M in heptane, 10.0 mL, 8.40 mmol) and cooled to 0 °C. *s*-BuLi (1.15 M in hexane, 14.6 mL, 16.8 mmol) was added dropwise. The reaction mixture was warmed to room temperature and was stirred for 2 h resulting in a slightly yellow solution. Solvents were removed *in vacuo* and dry toluene (3.5 mL) was added under stirring at 0 °C. Following titration with iodine at 0 °C gave a concentration of 0.90 M.

Typical Procedure (TP11) for the Exchange of the Thioether

A dry and argon-flushed *Schlenk*-tube was charged with a solution of the thioether (1.0 equiv.), TMEDA (3.0 equiv.) and undecane (10 µL/0.300 mmol), as internal standard, in toluene (0.5 M). *s*-BuMgOCH$_2$CH(Et)Bu·LiOCH$_2$CH(Et)Bu **71a** (3.0 equiv.) was added *via* syringe pump

(0.05 mL/min) and the resulting solution was stirred for the appropriate time at room temperature. The magnesium alkoxide species was reacted with the electrophile under the conditions given below. The reaction mixture was quenched with saturated aqueous NH_4Cl solution. The phases were separated and the aqueous phase was extracted with diethyl ether. The combined organic layers were dried over $MgSO_4$. The crude product was purified by column chromatography on silica.

13.1 Preparation of *N*-Boc-Protected Piperidines and Introduction of the Thioether



***N*-Boc piperidine 108a.**[139] Piperidine **107a** (19.8 mL, 200 mmol, 1.0 equiv.) was added dropwise to a solution of di-*tert*-butyl dicarbonate (42.8 mL, 200 mmol, 1.0 equiv.) in THF (146 mL) at 0 °C. The reaction mixture was stirred at room temperature for 2 h. After the addition of a saturated aqueous $NaHCO_3$ solution the reaction mixture was extracted with diethyl ether. The combined organic layers were dried over $MgSO_4$. The crude product was purified by distillation (30 °C/$1.8 \cdot 10^{-1}$ mbar) to afford **108a** as a colourless liquid (100%, 37.1 g, 200 mmol).

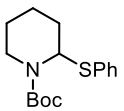
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 3.39 – 3.32 (m, 4H), 1.61 – 1.53 (m, 2H), 1.53 – 1.47 (m, 4H), 1.45 (s, 9H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 154.9, 79.0, 28.4, 27.4, 25.7, 24.5.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2978, 2934, 2856, 1690, 1474, 1448, 1418, 1392, 1364, 1282, 1268, 1258, 1238, 1212, 1176, 1144, 1118, 1068, 1026, 988, 956, 908, 868, 852, 812, 768.

MS (EI, 70 eV): *m/z* (%) = 130 (51), 129 (55), 128 (100), 126 (10), 114 (30), 112 (28), 84 (75), 69 (11).

HR-MS (EI, 70 eV): [$C_{10}H_{19}O_2N$], calcd.: 185.1416; found: 185.1408 (M^+).



Thioether 106a. Following **TP8**, *N*-Boc piperidine **108a** (3.71 g, 20.0 mmol, 1.0 equiv.) was reacted with TMEDA (6.57 mL, 44.1 mmol, 2.2 equiv.), *s*-BuLi (1.32 M, 18.2 mL, 24.0 mmol, 1.2 equiv.) and diphenyl disulfide (5.30 g, 24.0 mmol, 1.2 equiv.). The crude product was purified by column chromatography on silica using dichloromethane as an eluent to afford **106a** as a colourless oil (73%, 4.27 g, 14.6 mmol). NMR experiments show the different signals of the rotamers at 25 °C in $CDCl_3$, that merge to sharp signals at 65 °C in CD_3CN.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm, rotamers): δ = 7.55 – 7.43 (m, 2H), 7.35 – 7.20 (m, 3H), 6.04 (br s, 0.4H), 5.78 (br s, 0.6H), 4.06 (br s, 0.7H), 3.85 (s, 0.3H), 3.30 (td, *J* = 13.1, 2.8 Hz, 1H), 2.07 – 1.78 (m, 3H), 1.78 – 1.58 (m, 2H), 1.54 – 1.37 (m, 1H), 1.30 (s, 3.2H), 1.18 (d, *J* = 20.6 Hz, 5.8H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm, rotamers): δ = 153.8, 134.9, 133.9, 128.8, 127.9 & 127.4, 79.8, 64.1 & 61.7, 39.3 & 38.0, 31.2 & 30.3, 27.9, 25.4, 19.7.

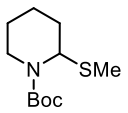
^{1}H-NMR (400 MHz, 65 °C, CD_3CN, ppm): δ = 7.52 – 7.48 (m, 2H), 7.33 – 7.28 (m, 3H), 5.91 (s, 1H), 3.94 (dd, *J* = 13.2, 2.2 Hz, 1H), 3.24 (td, *J* = 13.1, 2.9 Hz, 1H), 1.98 – 1.89 (m, 1H), 1.89 – 1.78 (m, 2H), 1.76 – 1.62 (m, 2H), 1.50 – 1.37 (m, 1H), 1.26 (s, 9H).

^{13}C-NMR (101 MHz, 65 °C, CD_3CN, ppm): δ = 155.0, 135.6, 135.3, 130.3, 129.0, 80.9, 64.7, 40.1, 32.2, 28.8, 26.5, 20.9.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2972, 2944, 2926, 1680, 1472, 1442, 1436, 1402, 1390, 1364, 1352, 1334, 1312, 1280, 1252, 1210, 1180, 1156, 1140, 1112, 1082, 1072, 1032, 1002, 982, 920, 910, 868, 824, 812, 764, 746, 704, 688.

MS (EI, 70 eV): *m/z* (%) = 183 (18), 128 (100), 127 (28), 110 (59), 109 (16), 84 (67), 83 (16), 82 (18), 57 (82), 41 (17).

HR-MS (EI, 70 eV): [$C_{16}H_{23}O_2NS$], calcd.: 293.1449; found: 293.1449 (M^+).



Thioether 106b. Following **TP8**, *N*-Boc piperidine **108a** (1.84 g, 9.93 mmol, 1.0 equiv.) was reacted with TMEDA (1.92 mL, 12.9 mmol, 1.3 equiv.), *s*-BuLi (1.15 M, 11.2 mL, 12.9 mmol, 1.3 equiv.) and dimethyl disulfide (1.34 mL, 14.9 mmol, 1.5 equiv.). The crude product was purified by column chromatography on silica using pentane:diethyl ether (9:1) as an eluent to afford **106b** as a colourless oil (50%, 1.16 g, 5.00 mmol).

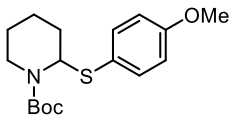
^{1}H-NMR (600 MHz, $CDCl_3$, ppm, rotamers): δ = 5.79 – 5.66 (br s, 0.3H), 5.55 (br s, 0.4H), 4.00 (br s, 0.4H), 3.86 (br s, 0.3H), 3.15 (m, 1H), 2.02 (s, 3H), 1.86 – 1.78 (m, 2H), 1.78 – 1.68 (m, 1H), 1.68 – 1.62 (m, 1H), 1.62 – 1.56 (m, 1H), 1.46 (s, 9H), 1.44 – 1.37 (m, 1H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm, rotamers): δ = 154.4, 79.9, 59.6 & 58.9, 38.7 & 37.5, 30.6, 28.3, 25.4, 19.7, 13.4.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2976, 2938, 2866, 1688, 1402, 1364, 1310, 1274, 1250, 1182, 1156, 1138, 1110, 1032, 986, 866, 760, 666.

MS (EI, 70 eV): *m/z* (%) = 184 (25), 128 (100), 84 (87), 57 (56).

HR-MS (EI, 70 eV): [$C_{11}H_{20}O_2NS$], calcd.: 230.1215; found: 230.1202 ([M−H]$^+$).



Thioether 106c. Following **TP8**, *N*-Boc piperidine **108a** (2.06 g, 11.1mmol, 1.0 equiv.) was reacted with TMEDA (2.15 mL, 14.5 mmol, 1.3 equiv.), *s*-BuLi (1.32 M, 11.0 mL, 14.5 mmol, 1.3 equiv.) and *S*-(4-methoxyphenyl) phenylthiosulfonate (4.05 g, 14.5 mmol, 1.3 equiv.). The crude product was purified by column chromatography on silica using dichloromethane as an eluent to afford **106c** as a colourless oil (51%, 1.83 g, 5.65 mmol).

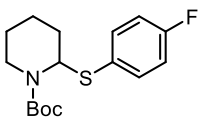
^{1}H-NMR (400 MHz, $CDCl_3$, ppm, rotamers): δ = 7.50 – 7.33 (m, 2H), 6.92 – 6.74 (m, 2H), 5.91 (br s, 0.3H), 5.66 (br s, 0.6H), 4.04 (d, *J* = 10.6 Hz, 0.6H), 3.85 (br s, 0.4H), 3.77 (s, 3H), 3.31 (td, *J* = 13.1, 2.9 Hz, 1H), 1.97 – 1.60 (m, 5H), 1.51 – 1.37 (m, 1H), 1.33 – 1.22 (br s, 3.2H), 1.16 (br s, 5.9H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm, rotamers): δ = 160.0, 153.8, 137.0 & 136.6, 124.2 & 123.7, 114.4, 79.6, 64.1 & 62.1, 55.2, 39.2 & 37.8, 30.7 & 29.9, 28.1 & 27.9, 25.4, 19.7.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2938, 1690, 1592, 1492, 1402, 1392, 1364, 1310, 1276, 1262, 1244, 1180, 1172, 1154, 1140, 1108, 1030, 980, 866, 826, 812, 798, 760, 658.

MS (EI, 70 eV): *m/z* (%) = 183 (19), 127 (92), 110 (29), 82 (70), 57 (100).

HR-MS (EI, 70 eV): [$C_{17}H_{26}O_3NS$], calcd.: 324.1628; found: 324.1626 ([M+H]$^+$).



Thioether 106d. Following **TP8**, *N*-Boc piperidine **108a** (1.99 g, 10.7 mmol, 1.0 equiv.) was reacted with TMEDA (2.08mL, 13.9 mmol, 1.3 equiv.), *s*-BuLi (1.15 M, 12.1 mL, 13.9 mmol, 1.3 equiv.) and *S*-(4-fluorophenyl) phenylthiosulfonate (4.32 g, 13.9 mmol, 1.3 equiv.). The crude product was purified

by column chromatography on silica using dichloromethane as an eluent to afford **106d** as a colourless solid (48%, 1.61 g, 5.18 mmol).

m.p.: 67.3 – 69.5 °C.

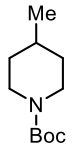
^{1}H-NMR (400 MHz, –5 °C, $CDCl_3$, ppm, rotamers): δ = 7.51 – 7.40 (m, 2H), 7.05 – 6.91 (m, 2H), 6.00 – 5.94 (m, 0.4H), 5.73 – 5.68 (m, 0.6H), 4.06 (dd, *J* = 13.1, 2.5 Hz, 0.6H), 3.83 (d, *J* = 13.0 Hz, 0.4H), 3.35 – 3.22 (m, 1H), 2.03 – 1.61 (m, 6H), 1.44 (m, 1H), 1.26 (s, 3.4H), 1.11 (s, 5.6H).

^{13}C-NMR (101 MHz, –5 °C, $CDCl_3$, ppm, rotamers): δ = 162.9 (d, *J* = 248.3 Hz) & 162.6 (d, *J* = 247.6 Hz), 153.9 & 153.6, 137.4 (d, *J* = 8.4 Hz) & 136.8 (d, *J* = 8.4 Hz), 128.5 (d, *J* = 3.3 Hz) & 127.8 (d, *J* = 3.2 Hz), 115.9 (d, *J* = 21.6 Hz) & 115.7 (d, *J* = 21.7 Hz), 79.8 & 79.8, 64.0 (d, *J* = 1.3 Hz) & 61.9 (d, *J* = 0.8 Hz), 38.9 & 37.5, 30.7 & 29.8, 28.0 & 27.7, 25.3 & 25.2, 19.7 & 19.5.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2944, 1680, 1590, 1488, 1400, 1364, 1352, 1314, 1280, 1258, 1222, 1210, 1178, 1154, 1140, 1112, 1088, 1032, 982, 866, 828, 812, 764, 716.

MS (EI, 70 eV): *m/z* (%) = 238 (16), 184 (69), 129 (18), 128 (84), 127 (25), 108 (11), 83 (14), 82 (13), 41 (17).

HR-MS (EI, 70 eV): [$C_{16}H_{20}O_2NFS$], calcd.: 309.1199; found: 309.1203 ([M−2H]$^+$).



***tert*-Butyl 4-methylpiperidine-1-carboxylate 108b.**[140] Di-*tert*-butyl dicarbonate (11.5 mL, 50.1 mmol, 1.0 equiv.) was added portionwise to a solution of 4-methylpiperidine **107b** (6.17 mL, 50.1 mmol, 1.0 equiv.) and trimethylamine (6.94 mL, 50.1 mmol, 1.0 equiv.) in dichloromethane (36 mL) at 0 °C. The reaction mixture was stirred at room temperature for 4 h. After the addition of water, the mixture was extracted with dichloromethane. The combined organic layers were dried over $MgSO_4$. The crude product was purified by distillation (41 – 43 °C/2.7 – 4.0·10^{-1} mbar) to afford **108b** as a colourless liquid (98%, 9.82 g, 49.3 mmol).

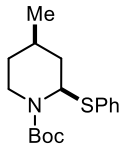
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 4.05 (d, *J* = 13.2 Hz, 2H), 2.67 (td, *J* = 12.7, 2.6 Hz, 2H), 1.59 (d, *J* = 11.2 Hz, 3H), 1.54 – 1.46 (m, 1H), 1.45 (s, 9H), 1.07 (tdd, *J* = 12.5, 11.2, 4.4 Hz, 2H), 0.93 (d, *J* = 6.5 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 154.9, 79.1, 44.0, 34.0, 30.9, 28.4, 21.8.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2924, 2848, 1690, 1446, 1416, 1392, 1378, 1364, 1304, 1276, 1258, 1238, 1212, 1174, 1146, 1084, 1004, 972, 902, 864, 830, 768.

MS (EI, 70 eV): *m/z* (%) = 144 (68), 13 (58), 142 (98), 140 (15), 128 (53), 126 (49), 98 (100), 84 (34), 57 (18).

HR-MS (EI, 70 eV): [$C_{11}H_{21}O_2N$], calcd.: 199.1572; found: 199.1564 (M^+).



Thioether 111. Following **TP8**, *tert*-butyl 4-methylpiperidine-1-carboxylate **108b** (1.99 g, 10.0 mmol, 1.0 equiv.) was reacted with TMEDA (1.80 mL, 12.0 mmol, 1.2 equiv.), *s*-BuLi (1.50 M, 8.00 mL, 12.0 mmol, 1.2 equiv.) and diphenyl disulfide (2.65 g, 12.0 mmol, 1.2 equiv.). The crude product was purified by column chromatography on silica using dichloromethane (1st column) and hexane:diethyl ether (95:5; 2nd column) as an eluent to afford **111** as a colourless oil (73%, 2.25 g, 7.31 mmol, d.r.>99:1).

^{1}H-NMR (400 MHz, –5 °C, $CDCl_3$, ppm, rotamers): δ = 7.52 – 7.45 (m, 2H), 7.32 – 7.22 (m, 3H), 6.05 (d, *J* = 4.9 Hz, 0.3H), 5.79 (d, *J* = 5.1 Hz, 0.7H), 4.12 – 4.02 (m, 0.7H), 3.89 – 3.82 (m, 0.4H), 3.40 – 3.27 (m, 1H), 2.04 – 1.88 (m, 2H), 1.74 – 1.63 (m, 1H), 1.56 – 1.44 (m, 2H), 1.26 (s, 2.9H), 1.08 (s, 6.9H), 0.93 (d, *J* = 6.4 Hz, 1.6H), 0.91 (d, *J* = 6.5 Hz, 1.4H).

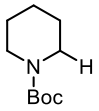
^{13}C-NMR (101 MHz, –5 °C, $CDCl_3$, ppm rotamers): δ = 153.8 & 153.6, 135.2 & 134.0, 133.4 & 133.0, 128.9 & 128.7, 128.2 & 127.6, 79.8 & 79.7, 63.9 & 61.6, 39.3 & 39.0, 38.3 & 37.7, 33.8 & 33.7, 28.0 & 27.7, 26.2 & 26.0, 21.9 & 21.8.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2974, 2930, 2874, 1692, 1404, 1392, 1364, 1294, 1248, 1156, 1124, 1088, 1066, 966, 858, 748, 734, 690, 656.

MS (EI, 70 eV): *m/z* (%) = 142 (100), 141 (21), 126 (31), 110 (36), 98 (31), 82 (23).

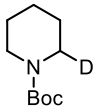
HR-MS (EI, 70 eV): [$C_{13}H_{16}ONS$], calcd.: 234.0953; found: 234.0945 ([M−O*t*-Bu]$^+$).

13.2 Thioether Exchange and Subsequent Trapping Reactions



***N*-Boc piperidine 108a.** Following **TP11**, thioether **106a** (88 mg, 0.300 mmol, 1.0 equiv.) and TMEDA (134 µL, 0.900 mmol, 3.0 equiv.) were reacted with *s*-BuMgOCH$_2$CH(Et)Bu·LiOCH$_2$CH(Et)Bu (1.10 M, 0.82 mL, 0.900 mmol, 3.0 equiv.). After a reaction time of 6 h, the reaction mixture was quenched with saturated aqueous NH_4Cl. The crude product was purified by column chromatography on silica using hexane:diethyl ether (9:1) as an eluent to afford **108a** as a colourless oil (79%, 44 mg, 0.237 mmol).

All analytical data can be accessed in section 13.1.



***N*-Boc piperidine-2-*d* 110b.** Following **TP11**, thioether **106a** (88 mg, 0.300 mmol, 1.0 equiv.) and TMEDA (134 µL, 0.900 mmol, 3.0 equiv.) were reacted with *s*-BuMgOCH$_2$CH(Et)Bu·LiOCH$_2$CH(Et)Bu (1.30 M, 0.69 mL, 0.900 mmol, 3.0 equiv.). After a reaction time of 6 h, the reaction mixture was cooled to 0 °C and quenched with AcOD/D_2O (0.10 mL each). The crude product was purified by column chromatography on silica using pentane:diethyl ether (9:1) as an eluent to afford **110b** as a colourless oil (70%, 39 mg, 0.209 mmol). The amount of the deuterated product in the isolated material is >97%.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 3.42 – 3.28 (m, 3H), 1.63 – 1.53 (m, 2H), 1.53 – 1.46 (m, 4H), 1.45 (s, 9H).

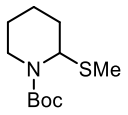
D-NMR (61 MHz, $CDCl_3$, ppm): δ = 3.4.

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 155.1, 79.2, 44.8, 44.5 (t, J = 21.1 Hz), 28.6, 25.9, 25.8, 24.6.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2976, 2934, 2856, 1688, 1476, 1444, 1414, 1392, 1364, 1336, 1314, 1300, 1270, 1254, 1164, 1132, 1084, 1070, 1040, 890, 866, 846, 768.

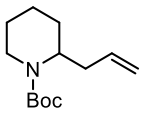
MS (EI, 70 eV): *m/z* (%) = 131 (18), 130 (38), 129 (32), 128 (11), 85 (37), 84 (12), 57 (100), 41 (18).

HR-MS (EI, 70 eV): [$C_{10}H_{18}DO_2N$], calcd.: 186.1479; found: 186.1473 (M^+).



Thioether 106b. Following **TP11**, thioether **106a** (88 mg, 0.300 mmol, 1.0 equiv.) and TMEDA (134 µL, 0.900 mmol, 3.0 equiv.) were reacted with *s*-BuMgOCH$_2$CH(Et)Bu·LiOCH$_2$CH(Et)Bu (1.14 M, 0.79 mL, 0.900 mmol, 3.0 equiv.). After a reaction time of 6 h, the reaction mixture was cooled to 0 °C and quenched with *S*-methyl phenylthiosulfonate (565 mg, 3.00 mmol, 10 equiv.). The crude product was purified by column chromatography on silica using pentane:diethyl ether (9:1) as an eluent to afford **106b** as a colourless oil (85%, 59 mg, 0.255 mmol).

All analytical data can be accessed in section 13.1.



Allyl piperidine 110c. Following **TP11**, thioether **106a** (88 mg, 0.300 mmol, 1.0 equiv.) and TMEDA (134 µL, 0.900 mmol, 3.0 equiv.) were reacted with *s*-BuMgOCH$_2$CH(Et)Bu·LiOCH$_2$CH(Et)Bu (1.30 M, 0.69 mL, 0.900 mmol, 3.0 equiv.). After a reaction time of 6 h, the reaction mixture was cooled to 0 °C and allyl bromide (259 µL, 3.00 mmol, 10 equiv.) was added. The reaction mixture was cooled to −40 °C and CuCN·2LiCl (1.0 M, 0.09 mL, 0.090 mmol, 0.3 equiv.) was added. The solution was slowly warmed to room temperature over 16 h. The crude product was purified by column chromatography on silica using pentane:diethyl ether (95:5) as an eluent to afford **110c** as a colourless oil (52%, 35 mg, 0.155 mmol).

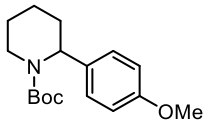
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 5.74 (ddt, *J* = 17.2, 10.1, 7.2 Hz, 1H), 5.05 (dq, *J* = 17.0, 1.5 Hz, 1H), 5.00 (ddt, *J* = 10.0, 2.0, 1.1 Hz, 1H), 4.27 (br s, 1H), 3.97 (d, *J* = 13.5 Hz, 1H), 2.76 (td, *J* = 13.2, 2.7 Hz, 1H), 2.39 (dddt, *J* = 13.8, 8.3, 7.1, 1.3 Hz, 1H), 2.29 – 2.14 (m, 1H), 1.66 – 1.53 (m, 5H), 1.45 (s, 9H), 1.42 – 1.33 (m, 1H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 155.1, 135.6, 116.5, 79.0, 50.0, 38.8, 34.4, 28.4, 27.6, 25.4, 18.8.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2976, 2934, 2858, 1686, 1448, 1408, 1392, 1364, 1320, 1266, 1244, 1166, 1144, 1094, 1078, 1068, 1032, 1008, 994, 912, 868, 766.

MS (EI, 70 eV): *m/z* (%) = 184 (17), 128 (100), 127 (14), 110 (23), 84 (59), 57 (40).

HR-MS (EI, 70 eV): [$C_{10}H_{18}O_2N$], calcd.: 184.1338; found: 184.1338 ([M−allyl]$^+$).



***N*-Boc piperidine 110d.** Following **TP11**, thioether **106a** (88 mg, 0.300 mmol, 1.0 equiv.) and TMEDA (134 µL, 0.900 mmol, 3.0 equiv.) were reacted with *s*-BuMgOCH$_2$CH(Et)Bu·LiOCH$_2$CH(Et)Bu (1.00 M, 0.90 mL, 0.900 mmol, 3.0 equiv.). After a reaction time of 6 h, the reaction mixture was cooled to −40 °C and $ZnCl_2$-solution (1.0 M in THF, 0.90 mL, 3.00 mmol, 10 equiv.) was added. After warming up to room temperature, the solution was recooled to –40 °C and SPhos (12 mg, 0.030 mmol, 10 mol%), $Pd(dba)_2$ (8.6 mg, 0.015 mmol, 5 mol%) and 4-iodoanisole (215 mg, 0.900 mmol, 3.0 equiv.) were added. The reaction was stirred at 55 °C for 16 h. The crude product was purified by column chromatography on silica using hexane:diethyl ether (9:1) as an eluent to afford **110d** as a colourless oil (25%, 22 mg, 0.076 mmol).

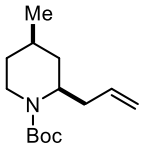
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.17 – 7.09 (m, 2H), 6.93 – 6.83 (m, 2H), 5.37 (d, *J* = 2.9 Hz, 1H), 4.07 – 3.96 (m, 1H), 3.80 (s, 3H), 2.73 (ddd, *J* = 13.5, 11.5, 3.9 Hz, 1H), 2.32 – 2.21 (m, 1H), 1.92 – 1.79 (m, 1H), 1.63 – 1.49 (m, 3H), 1.46 (s, 10H)

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 158.0, 155.5, 132.1, 127.6, 113.8, 79.4, 55.2, 52.5, 39.8, 28.4, 27.9, 25.5, 19.3.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2974, 2936, 2864, 1684, 1610, 1512, 1456, 1410, 1392, 1364, 1288, 1270, 1246, 1176, 1154, 1134, 1126, 1108, 1034, 872, 828.

MS (EI, 70 eV): *m/z* (%) = 237 (55), 236 (18), 192 (17), 191 (92), 162 (15), 134 (21), 121 (27), 83 (16), 82 (21), 57 (100), 55 (17), 44 (21), 43 (16), 41 (33).

HR-MS (EI, 70 eV): [$C_{17}H_{25}O_3N$], calcd.: 291.1834; found: 291.1822 (M$^+$).



Allyl piperidine 112a. Following **TP11**, thioether **111** (92 mg, 0.300 mmol, 1.0 equiv.) and TMEDA (134 µL, 0.900 mmol, 3.0 equiv.) were reacted with *s*-BuMgOCH$_2$CH(Et)Bu·LiOCH$_2$CH(Et)Bu (1.10 M, 0.82 mL, 0.900 mmol, 3.0 equiv.). After a reaction time of 4 h, the reaction mixture was cooled to 0 °C and allyl bromide (78 µL, 0.900 mmol, 3.0 equiv.) was added. The reaction mixture was cooled to −40 °C and CuCN·2LiCl (1.0 M, 0.09 mL, 0.090 mmol, 0.3 equiv.) was added. The solution was slowly warmed to room temperature over 16 h. The crude product was purified by column chromatography on silica using hexane:diethyl ether (95:5) as an eluent to afford **112a** as a colourless oil (83%, 59 mg, 0.248 mmol, d.r.>99:1).

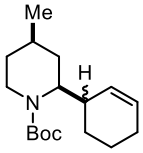
^{1}H-NMR (400 MHz, CDCl$_3$, ppm): δ = 5.77 (ddt, *J* = 17.2, 10.2, 7.2 Hz, 1H), 5.08 – 4.97 (m, 2H), 3.85 (tt, *J* = 8.3, 6.3 Hz, 1H), 3.73 (ddd, *J* = 13.9, 7.3, 3.2 Hz, 1H), 3.01 (ddd, *J* = 13.9, 10.3, 5.9 Hz, 1H), 2.40 (dddt, *J* = 14.2, 7.1, 5.9, 1.4 Hz, 1H), 2.24 (dtt, *J* = 13.5, 7.6, 1.1 Hz, 1H), 1.87 (ddtd, *J* = 13.3, 10.3, 7.2, 1.2 Hz, 1H), 1.73 – 1.68 (m, 1H), 1.68 – 1.62 (m, 1H), 1.45 (s, 9H), 1.20 – 1.12 (m, 1H), 1.12 – 1.06 (m, 1H), 0.98 (d, *J* = 6.8 Hz, 3H).

^{13}C-NMR (101 MHz, CDCl$_3$, ppm): δ = 155.4, 135.4, 116.7, 79.0, 53.0, 39.0, 37.4, 34.9, 31.1, 28.4, 26.1, 21.5.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2976, 2928, 2872, 1688, 1642, 1478, 1456, 1408, 1392, 1364, 1350, 1332, 1304, 1278, 1246, 1178, 1148, 1094, 1070, 992, 912, 866, 770.

MS (EI, 70 eV): *m/z* (%) = 142 (100), 98 (46).

HR-MS (EI, 70 eV): [C$_{10}$H$_{16}$ON], calcd.: 166.1232; found: 166.1225 ([M−O*t*-Bu]$^+$).



Allyl piperidine 112b. Following **TP11**, thioether **111** (92 mg, 0.300 mmol, 1.0 equiv.) and TMEDA (134 µL, 0.900 mmol, 3.0 equiv.) were reacted with *s*-BuMgOCH$_2$CH(Et)Bu·LiOCH$_2$CH(Et)Bu (1.10 M, 0.82 mL, 0.900 mmol, 3.0 equiv.). After a reaction time of 4 h, the reaction mixture was cooled

to 0 °C and 3-bromocyclohexene (145 mg, 0.900 mmol, 3.0 equiv.) was added. The reaction mixture was cooled to −40 °C and CuCN·2LiCl (1.0 M, 0.09 mL, 0.090 mmol, 0.3 equiv.) was added. The solution was slowly warmed to room temperature over 2.5 d. The crude product was purified by column chromatography on silica using hexane:diethyl ether (95:5) as an eluent to afford **112b** as a colourless oil (78%, 65 mg, 0.233 mmol, d.r. = 74:26).

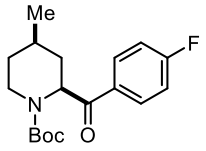
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 5.80 (dtd, *J* = 9.8, 3.6, 2.1 Hz, 0.7H), 5.72 (dq, *J* = 9.9, 3.2 Hz, 0.3H), 5.64 (dq, *J* = 10.2, 2.4 Hz, 0.7H), 5.60 – 5.52 (m, 0.3H), 3.92 – 3.71 (m, 2H), 3.02 – 2.89 (m, 1H), 2.51 – 2.34 (m, 1H), 2.05 – 1.97 (m, 2H), 1.97 – 1.89 (m, 1H), 1.83 – 1.71 (m, 2H), 1.68 – 1.53 (m, 2H), 1.53 – 1.42 (m, 10H), 1.31 – 1.18 (m, 1H), 1.13 – 1.04 (m, 1H), 1.00 (d, *J* = 6.8 Hz, 2H), 0.99 (d, *J* = 6.8 Hz, 1H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = Major: 156.0, 129.1, 127.9, 79.0, 56.6, 39.1, 37.7, 33.0, 31.0, 28.5, 26.0, 25.6, 25.4, 21.5, 20.9; Minor: 156.0, 128.9, 127.4, 79.0, 57.5, 38.8, 38.0, 32.8, 31.1, 28.4, 26.1, 25.4, 25.2, 21.7, 20.9.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2948, 2928, 2870, 1688, 1450, 1408, 1392, 1364, 1322, 1280, 1244, 1176, 1148, 1086, 1062, 770, 724.

MS (EI, 70 eV): *m/z* (%) = 206 (11), 198 (16), 143 (18), 81 (10), 41 (21).

HR-MS (EI, 70 eV): [$C_{17}H_{29}O_2N$], calcd.: 279.2198; found: 279.2216 (M^+).



***N*-Boc piperidine 112c.** Following **TP11**, thioether **111** (92 mg, 0.300 mmol, 1.0 equiv.) and TMEDA (134 µL, 0.900 mmol, 3.0 equiv.) were reacted with *s*-BuMgOCH$_2$CH(Et)Bu·LiOCH$_2$CH(Et)Bu (1.10 M, 0.82 mL, 0.900 mmol, 3.0 equiv.). After a reaction time of 4 h, the reaction mixture was cooled to −40 °C and CuCN·2LiCl (1.0 M, 0.09 mL, 0.090 mmol, 0.3 equiv.) and 4-fluorobenzoyl chloride (109 µL, 0.900 mmol, 3.0 equiv.) were added. The solution was stirred at −20 °C for 5 h. The crude product was purified by column chromatography on silica using hexane:diethyl ether (9:1) as an eluent to afford **112c** as a colourless solid (46%, 44 mg, 0.137 mmol, d.r.>99:1). Recrystallization of the product from hexane gave crystals suitable for single crystal X-ray diffraction analysis.

m.p.: 108.3 – 110.5 °C.

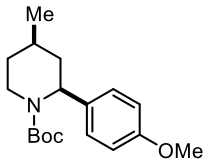
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.07 – 7.96 (m, 2H), 7.16 – 7.05 (m, 2H), 4.62 (br s, 1H), 3.86 (d, *J* = 13.2 Hz, 1H), 3.32 (ddd, *J* = 13.4, 8.9, 4.3 Hz, 1H), 2.08 – 1.95 (m, 1H), 1.84 – 1.66 (m, 2H), 1.52 – 1.41 (m, 1H), 1.38 – 1.15 (m, 10H), 0.96 (d, *J* = 6.5 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 196.3, 165.3 (d, *J* = 254.4 Hz), 155.5, 132.3, 130.8 (d, *J* = 9.1 Hz), 115.4 (d, *J* = 21.7 Hz), 80.8, 60.3, 43.2, 34.3, 32.0, 28.7, 28.0, 21.1.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1676, 1598, 1420, 1368, 1322, 1268, 1244, 1224, 1178, 1162, 1152, 1088, 994, 956, 842, 822, 772, 664.

MS (EI, 70 eV): *m/z* (%) = 204 (24), 198 (58), 143 (35), 99 (18), 97 (16), 95 (79), 75 (14), 56 (40), 55 (45), 41 (63).

HR-MS (EI, 70 eV): [$C_{18}H_{24}O_3NF$], calcd.: 321.1740; found: 321.1719 (M^+).



***N*-Boc piperidine 112d.** Following **TP11**, thioether **111** (92 mg, 0.300 mmol, 1.0 equiv.) and TMEDA (134 µL, 0.900 mmol, 3.0 equiv.) were reacted with *s*-$BuMgOCH_2CH(Et)Bu \cdot LiOCH_2CH(Et)Bu$ (1.10 M, 0.82 mL, 0.900 mmol, 3.0 equiv.). After a reaction time of 4 h, the reaction mixture was cooled to –40 °C and $ZnCl_2$-solution (1.0 M in THF, 0.90 mL, 3.00 mmol, 10 equiv.) was added. After warming to room temperature, the solution was recooled to −40 °C and SPhos (12 mg, 0.030 mmol, 10 mol%), $Pd(dba)_2$ (8.6 mg, 0.015 mmol, 5 mol%) and 4-iodoanisole (215 mg, 0.900 mmol, 3.0 equiv.) was added. The reaction was stirred at 55 °C for 2.5 d. The crude product was purified by column chromatography on silica using hexane:diethyl ether (9:1) as an eluent to afford **112d** as a colourless oil (32%, 29 mg, 0.095 mmol, d.r.>99:1).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.16 – 7.09 (m, 2H), 6.87 – 6.79 (m, 2H), 4.80 (dd, *J* = 9.8, 6.3 Hz, 1H), 3.95 (ddd, *J* = 13.7, 7.0, 3.1 Hz, 1H), 3.79 (s, 3H), 3.25 (ddd, *J* = 13.8, 10.7, 5.6 Hz, 1H), 2.04 – 1.89 (m, 2H), 1.84 – 1.75 (m, 1H), 1.55 (dt, *J* = 13.6, 10.2 Hz, 1H), 1.30 (s, 9H), 1.20 (dddd, *J* = 13.3, 7.6, 5.6, 3.0 Hz, 1H), 0.91 (d, *J* = 6.8 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 158.0, 155.9, 136.7, 126.3, 113.6, 79.3, 56.1, 55.2, 38.3, 38.2, 31.1, 28.3, 26.4, 21.5.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2950, 2930, 2872, 1686, 1512, 1456, 1402, 1364, 1292, 1280, 1242, 1172, 1148, 1126, 1112, 1090, 1034, 826, 774, 758.

MS (EI, 70 eV): *m/z* (%) = 250 (12), 249 (78), 248 (28), 232 (12), 205 (16), 204 (100), 162 (14), 135 (14), 134 (20), 121 (26), 97 (10), 96 (18), 57 (53), 41 (17).

HR-MS (EI, 70 eV): [$C_{18}H_{27}O_3N$], calcd.: 305.1991; found: 305.1992 (M^+).

13.3 Single Crystal X-Ray Analysis

Single crystals of the compounds, suitable for X-ray diffraction, were obtained by slow evaporation of solvents solutions. The crystals were introduced into perfluorinated oil and a suitable single crystal was carefully mounted on the top of a thin glass wire. Data collections were performed on an *Oxford* Xcalibur 3 diffractometer equipped with a *Spellman* generator (50 kV, 40 mA) and a Kappa CCD detector, operating with Mo-K_α radiation ($\lambda = 0.71071$ Å). Data collection and data reduction were performed with the CrysAlisPro software.[XXV] Absorption correction using the multiscan method[a)] was applied. The structures were solved with SHELXS-97, [XXVI] refined with SHELXL-97[XXVII] and finally checked using PLATON. [XXVIII] Details for data collection and structure refinement are summarized in the tables at the different sections.

_N_-Boc piperidine 112c.

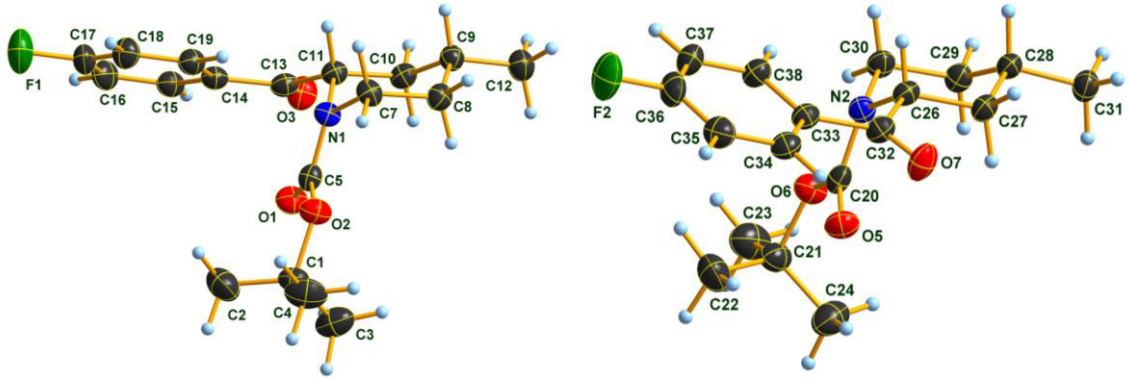


Figure 12: Molecular structure of *N*-Boc piperidine **112c** in the crystal, View of the two crystallographically independent molecules in the unit cell. DIAMOND[XXIX] representation; thermal ellipsoids are drawn at 50% probability level.

[XXV] Program package CrysAlisPro 1.171.38.46 (Rigaku OD, 2015).

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[XXIX] DIAMOND, Crystal Impact GbR., Version 3.2i.

Table 12: Details for X-ray data collection and structure refinement for *N*-Boc piperidine **112c**.

Empirical formula	$C_{18}H_{24}FNO_3$
Formula mass	321.38
T/ K	143(2)
Crystal size [mm]	0.32 × 0.16 × 0.13
Crystal description	colorless block
Crystal system	triclinic
Space group	*P*-1
a/ Å	10.4749(7)
b/ Å	12.4545(8)
c/ Å	13.7136(8)
α/ °	86.508(5)
β/ °	74.026(5)
γ/ °	88.935(5)
V/ Å^3	1716.79(19)
Z	4
$\rho_{calcd.}$/ g cm^{-3}	1.243
μ/ mm^{-1}	0.091
***F*(000)**	688
Θ range/ °	4.14 – 25.68
Index ranges	$-12 \leq h \leq 12$
	$-15 \leq k \leq 15$
	$-16 \leq l \leq 16$
Reflns. collected	12409
Reflns. obsd.	3915
Reflns. unique	6475 (R_{int} = 0.0437)
***R*$_1$, *wR*$_2$ (2σ data)**	0.0514, 0.0986
***R*$_1$, *wR*$_2$ (all data)**	0.0989, 0.1209
GOOF on *F*^{2}	0.983
Peak/hole/ e Å^{-3}	$C_{18}H_{24}FNO_3$

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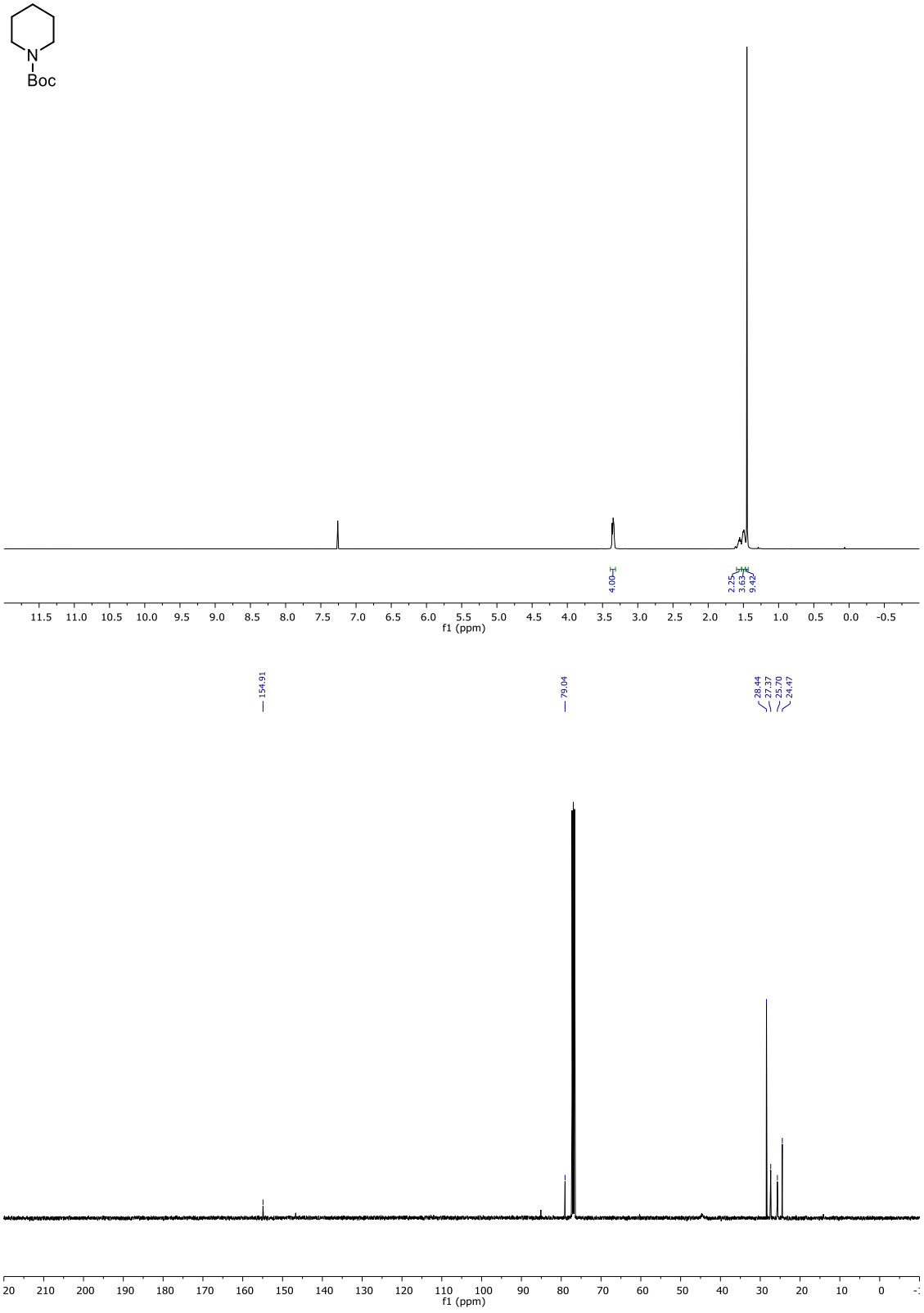
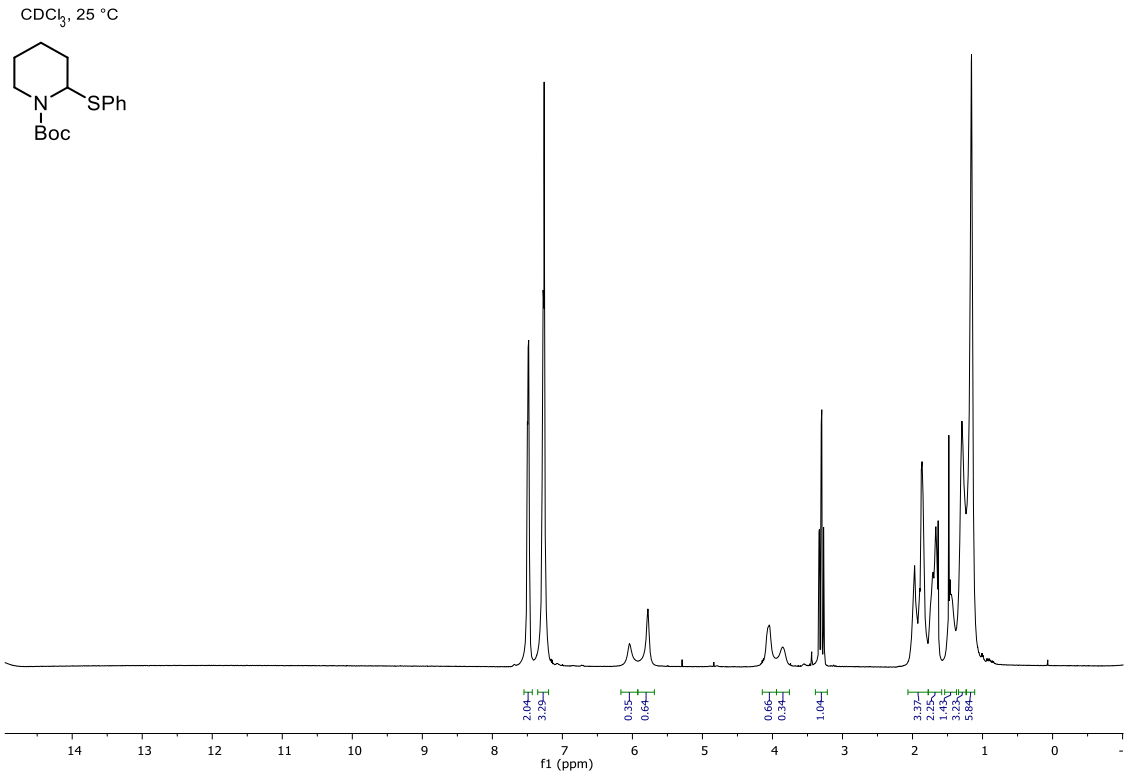
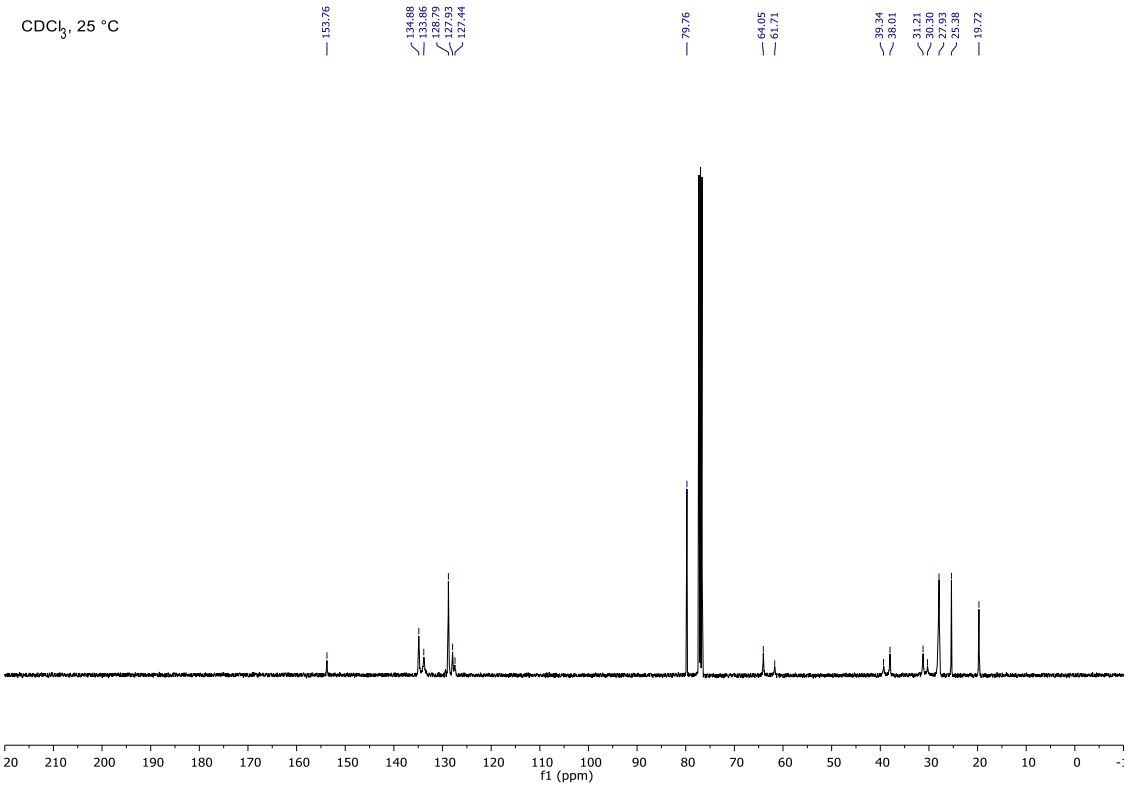
Appendix

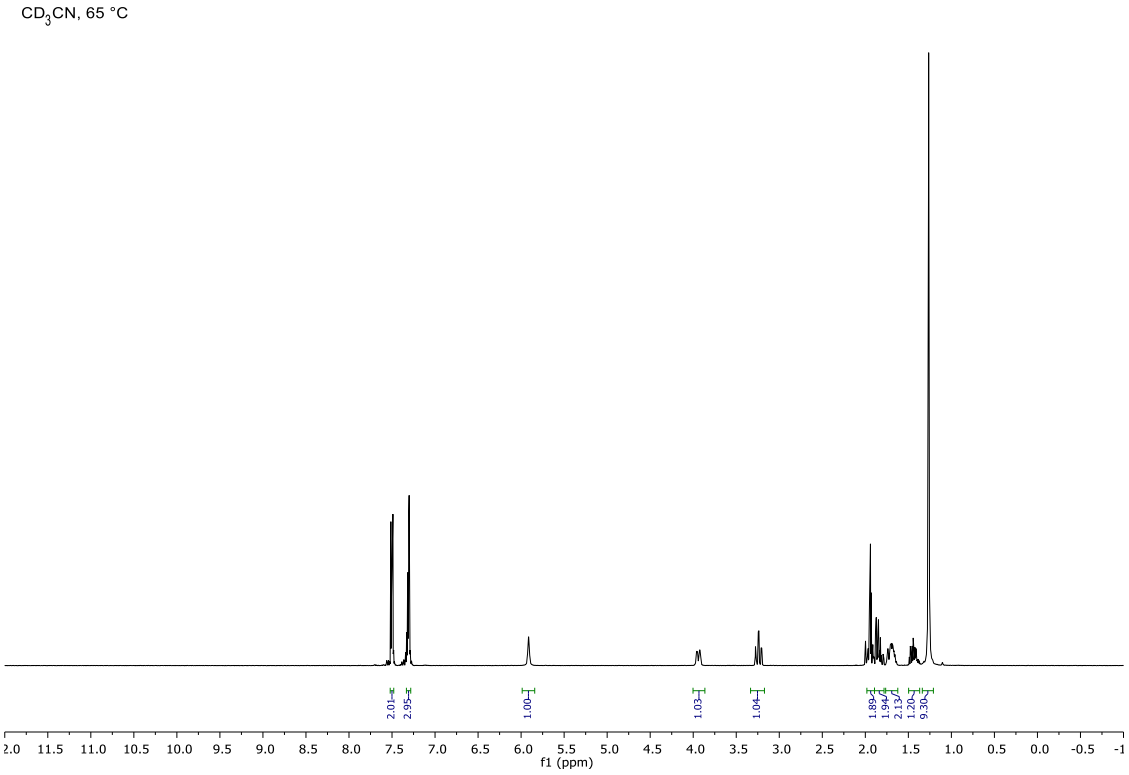
N-Boc piperidine 108a

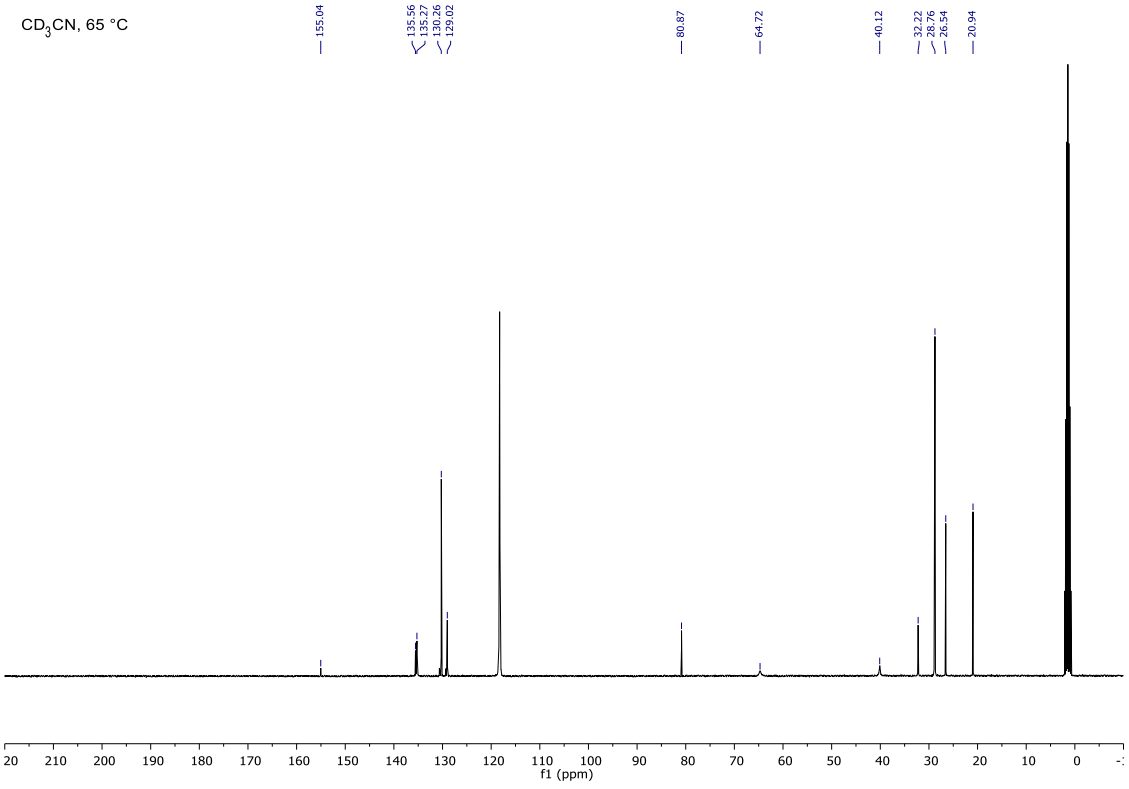


Thioether 106a

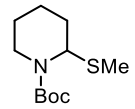


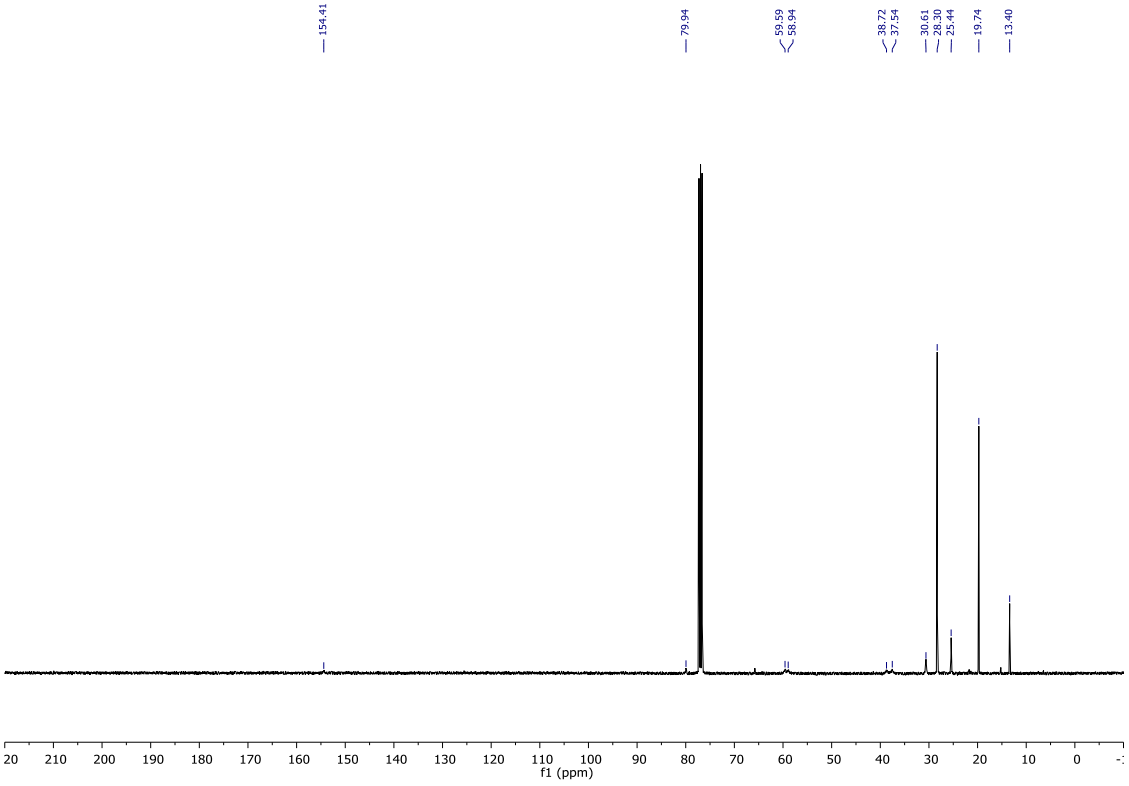



CD3CN, 65 °C
2.01
2.95
1.00
1.03
1.04
1.89
1.94
2.13
1.20
9.30
f1 (ppm)

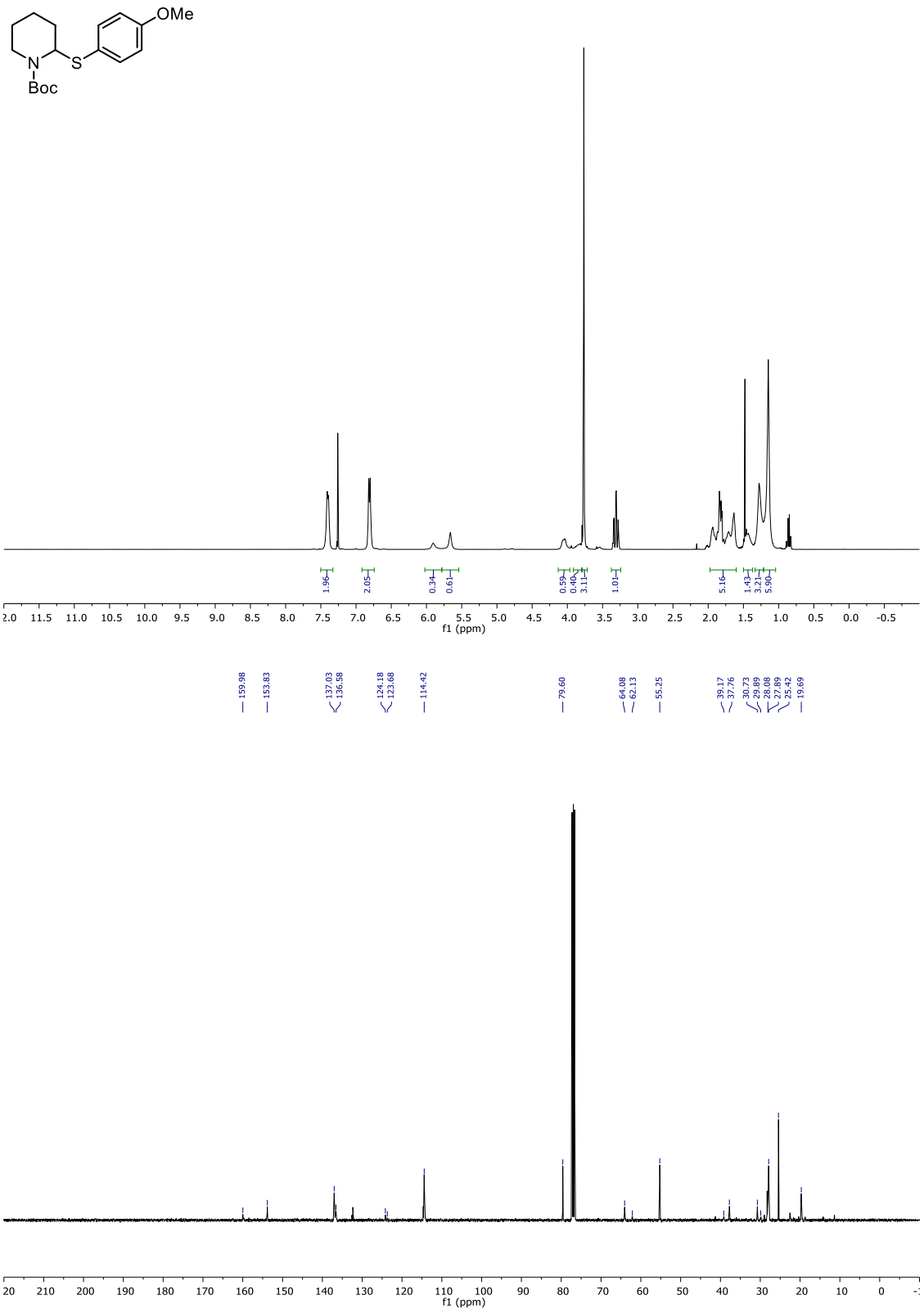

CD3CN, 65 °C
155.04
135.56
135.27
130.26
129.02
80.87
64.72
40.12
32.22
28.76
26.54
20.94
f1 (ppm)

Thioether 106b

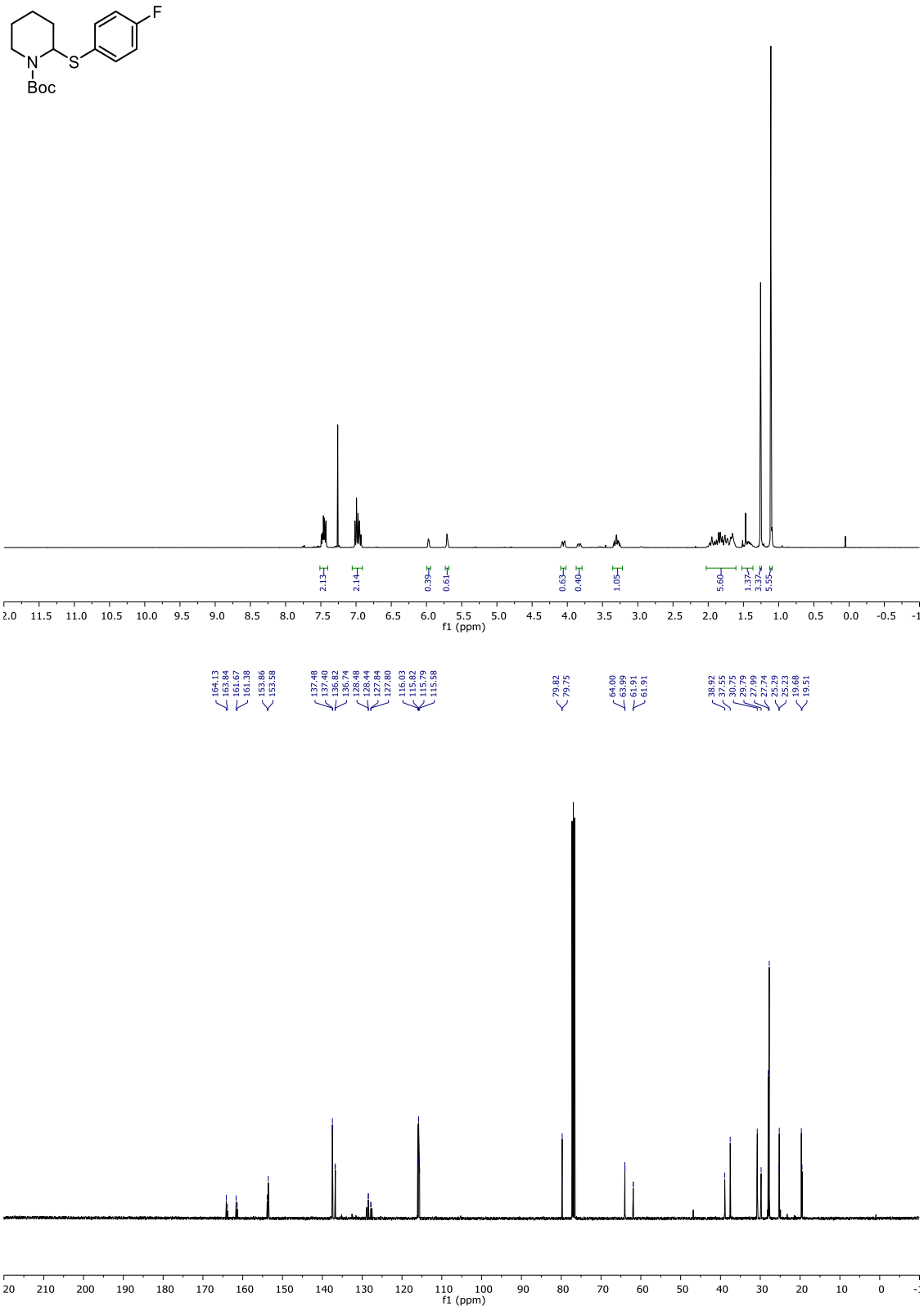




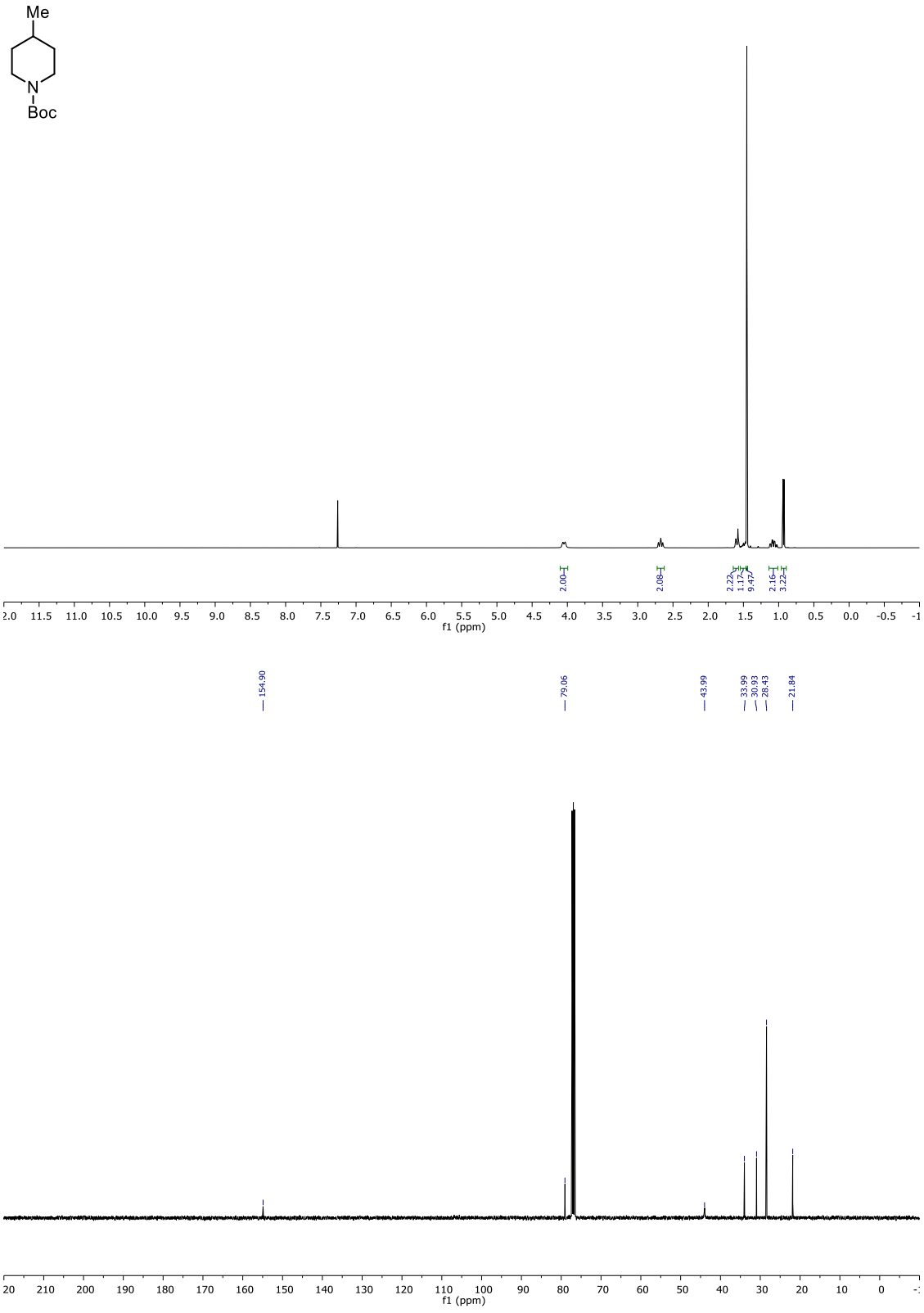
Thioether 106c



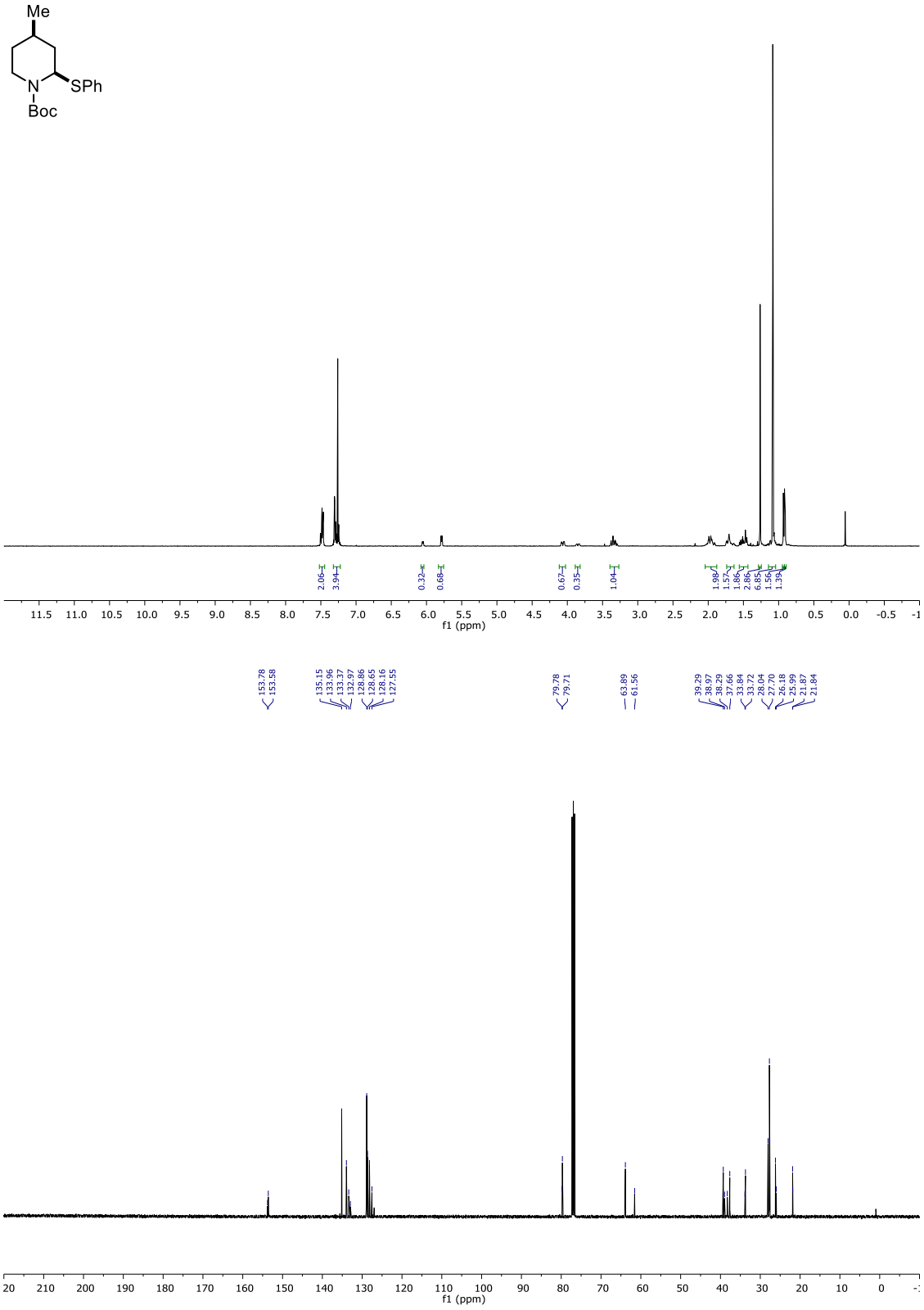
Thioether 106d



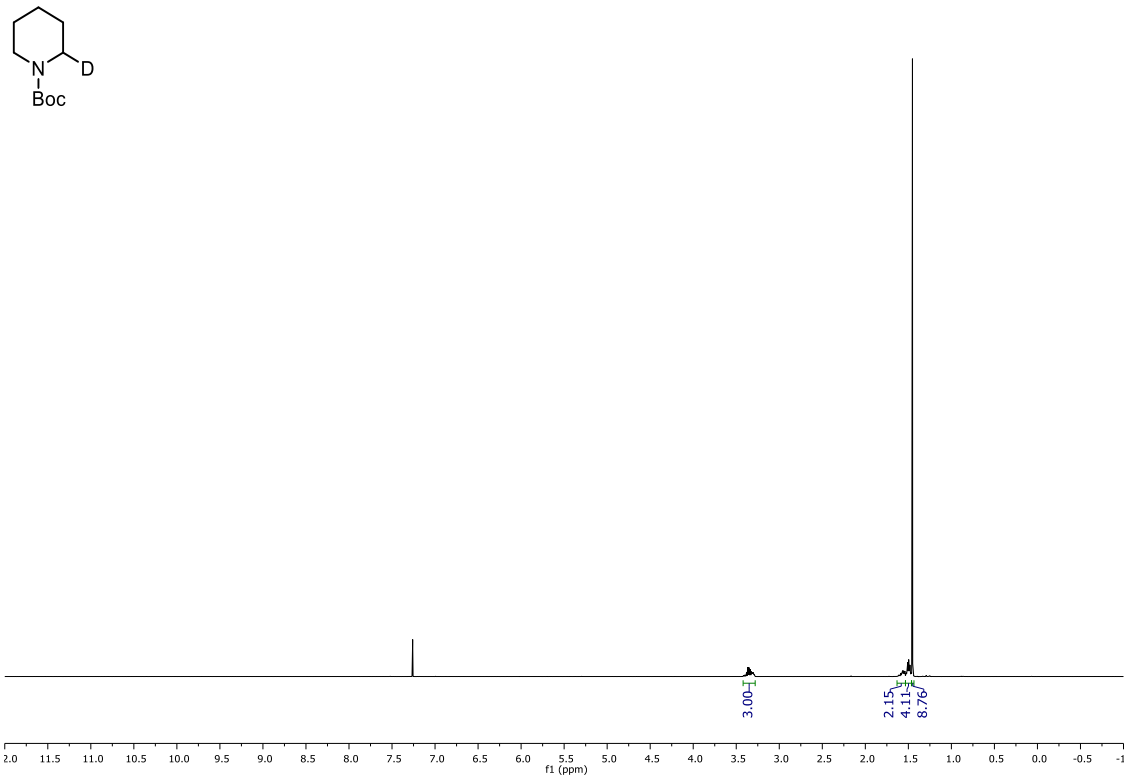
tert-Butyl 4-methylpiperidine-1-carboxylate 108b

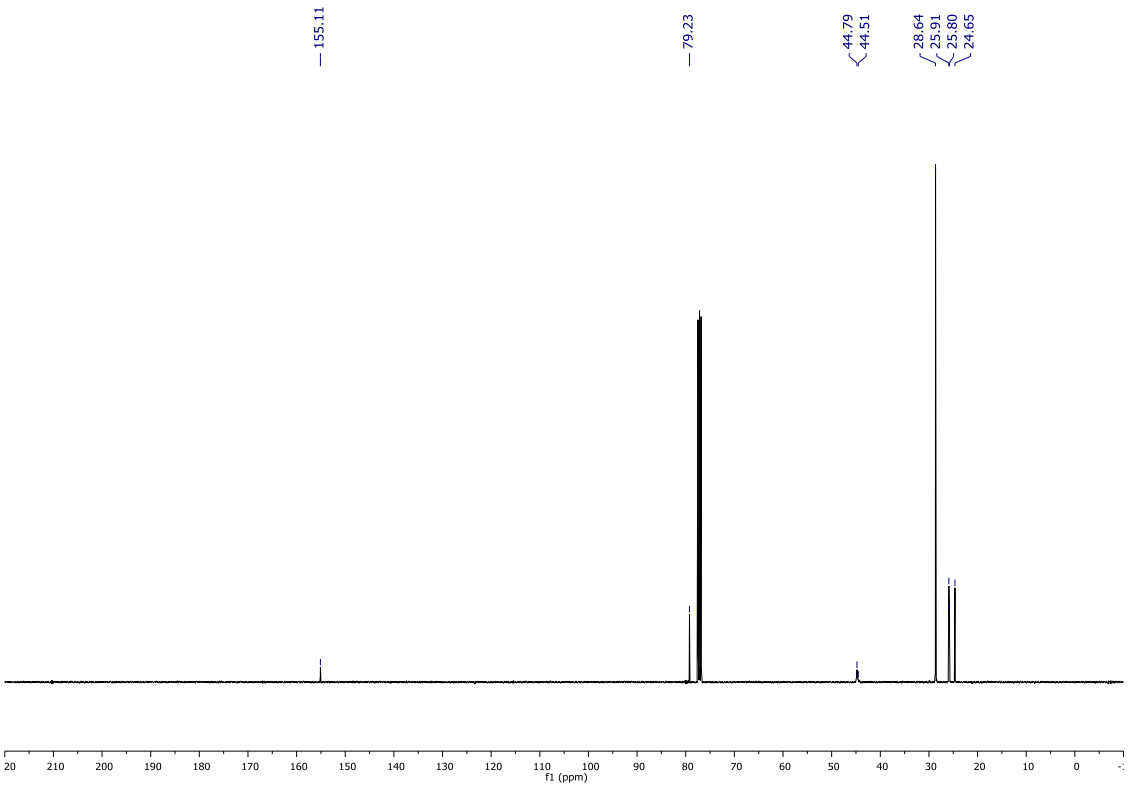


Thioether 111

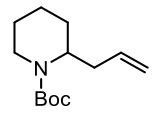


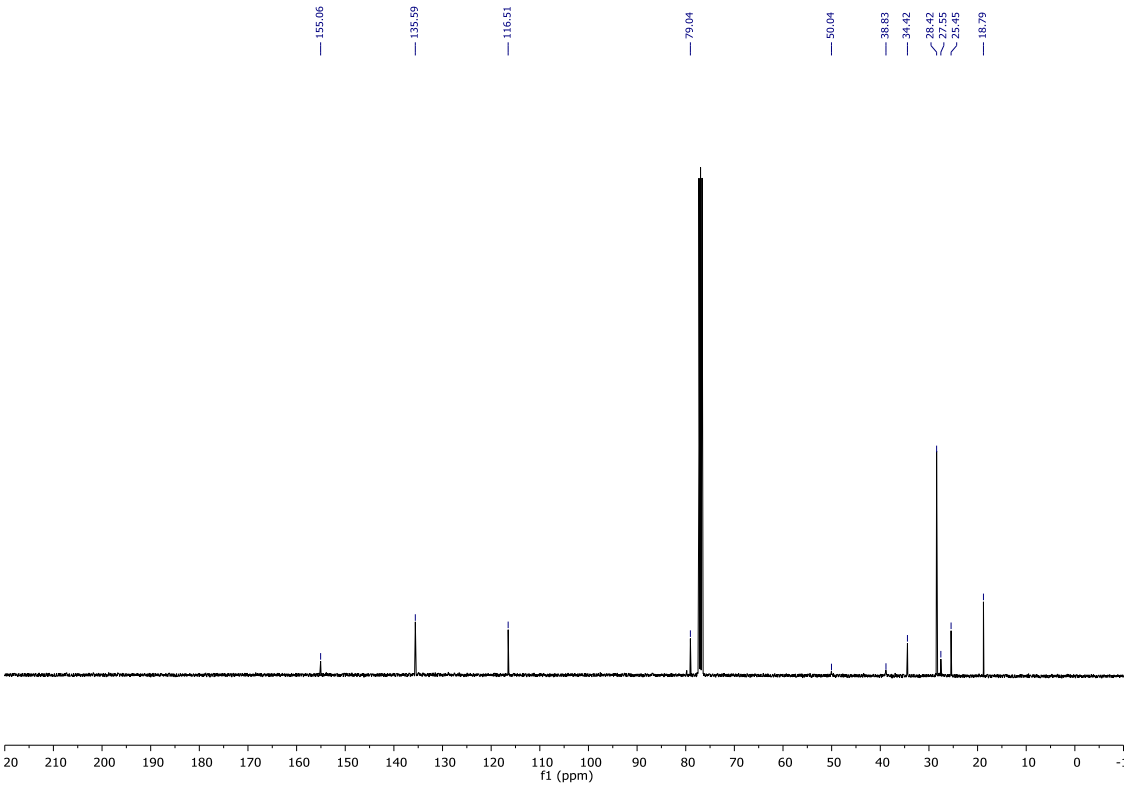
N-Boc piperidine-2-*d* 110b



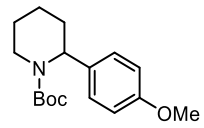


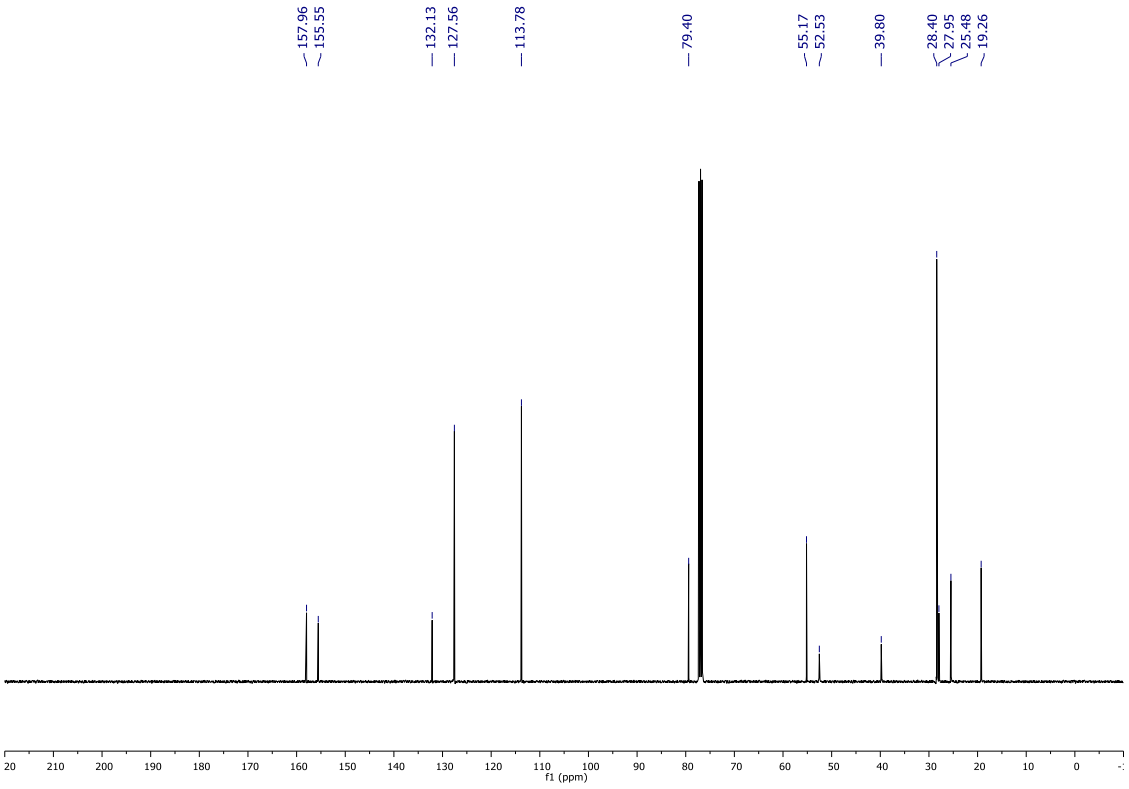
Allyl piperidine 110c



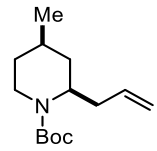


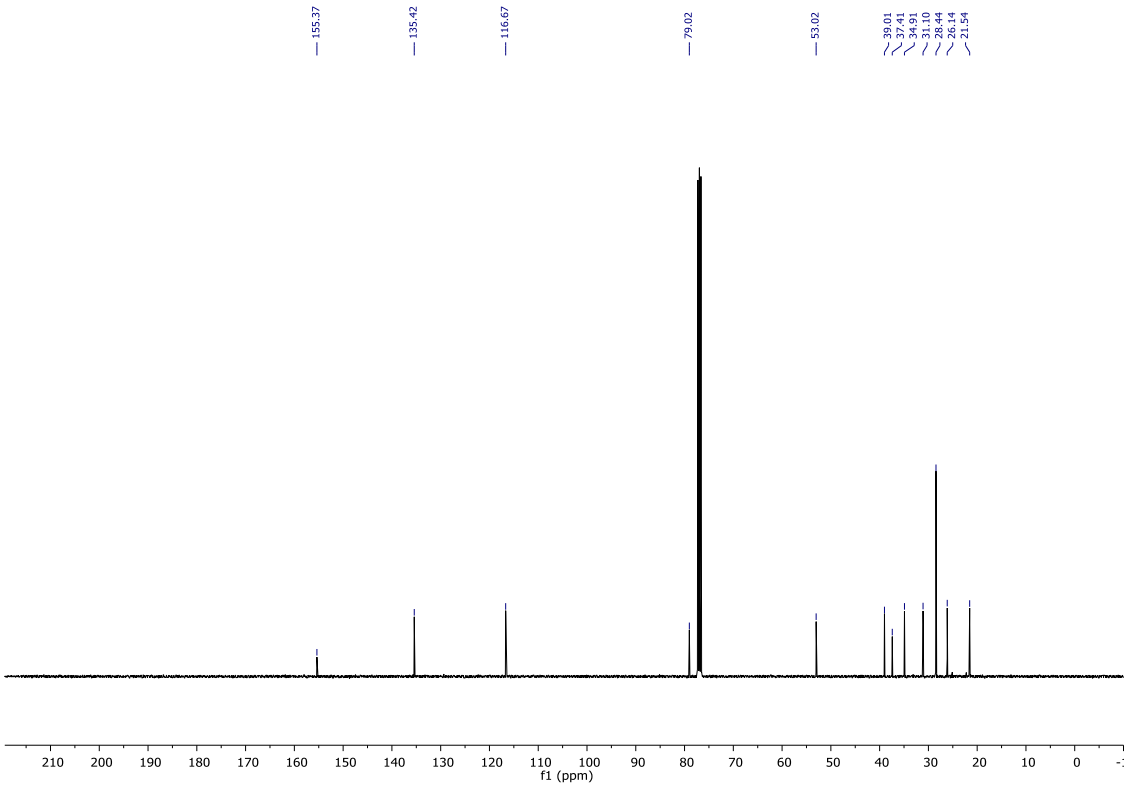
N-Boc piperidine 110d



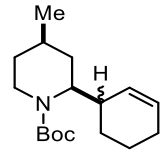


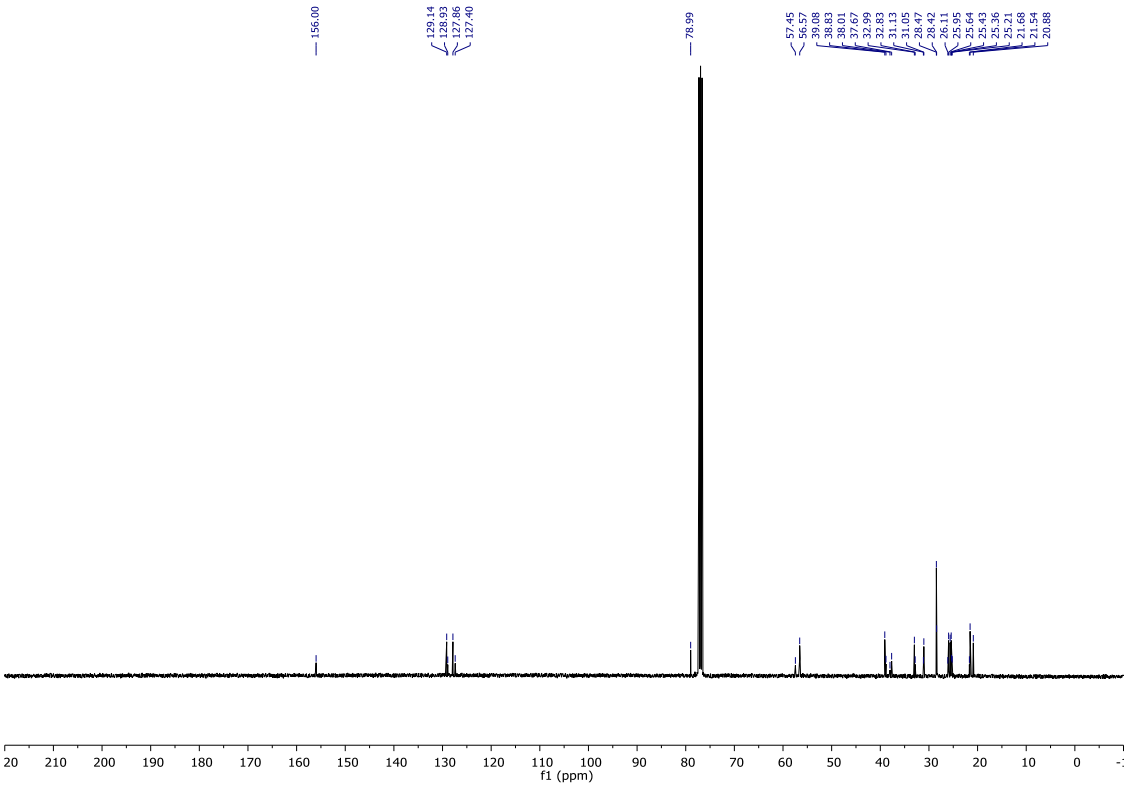
Allyl piperidine 112a



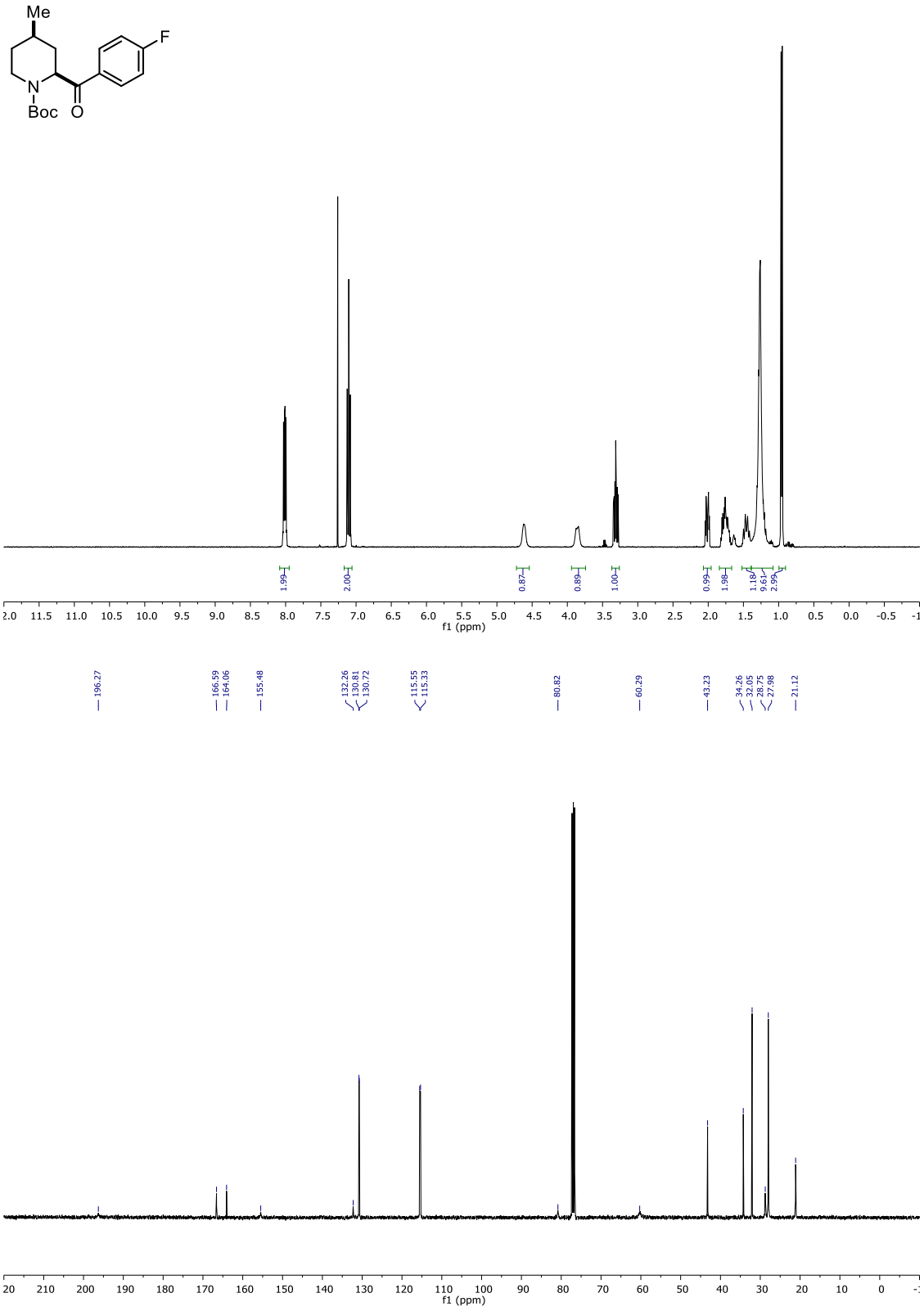


Allyl piperidine 112b





N-Boc piperidine 112c



N-Boc piperidine 112d