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Stereoselective Preparation of Chiral Secondary Alkylcopper- and Zinc Reagents. Subsequent Reactions with Allylic Substrates and Palladium-Catalyzed Cross-Couplings with Alkenyl and Aryl Halides

von

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aus

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J. Skotnitzki, A. Kremsmair, D. Keefer, Y. Gong, R. de Vivie-Riedle, P. Knochel, *Angew. Chem. Int. Ed.* **2020**, *59*, 320–324.

4) "Stereoselective *anti*-S_N2'-Substitutions of Secondary Alkylcopper-Zinc Reagents with Allylic Epoxides. Total Synthesis of (3*S*,6*R*,7*S*)-Zingiberenol"
J. Skotnitzki, A. Kremsmair, B. Kicin, R. Saeb, V. Ruf, P. Knochel, *Synthesis* **2020**, *52*, 873–881.

5) "Regio- and Diastereoselective Reaction of Chiral Secondary Alkylcopper Reagents with Propargylic Phosphates: Preparation of Chiral Allenes"
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B) Reviews:

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C) Additional publications:

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V. Morozova, **J. Skotnitzki**, K. Moriya, K. Karaghiosoff, P. Knochel, *Angew. Chem. Int. Ed.* **2018**, *57*, 5516–5519.

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It’s hard to beat someone
who never gives up!

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Abbreviations

δ	chemical shift in parts per million
Ac	acetyl
aq.	aqueous
ATR	attenuated total reflection
Bn	benzyl
n-Bu	*n*-butyl
t-Bu	*tert*-butyl
calc.	calculated
cat.	catalytic amount
d	doublet
d	deuterated
DCM	dichloromethane
Cp	cyclopentadienyl
CPhos	2-(2-dicyclohexylphosphanylphenyl)-tetramethyl-benzene-1,3-diamine
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N*,*N*′-dicyclohexylcarbodiimide
DFT	density functional theory
DIBAL-H	diisobutylaluminium hydride
DMAP	4-dimethylaminopyridine
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
ee	enantiomeric excess
EI	electron ionization
er	enantiomeric ratio
Et	ethyl
Et_2O	diethyl ether
equiv	equivalent
E-X	electrophile
GC	gas chromatography
h	hour
HMPA	hexamethylphosphoramide
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectroscopy
IR	infrared
i-Pr	*iso*-propyl
J	coupling constant
LDA	lithium diisopropylamide
m	multiplet
M	molarity: mol/L
Me	methyl
min	minute

mmol	millimole
Ms	methanesulfonyl
MS	mass spectroscopy
MTPA	methoxy(trifluoromethyl)phenylacetic acid
NHC ligand	*N*-heterocyclic carbinhe ligand
NMI	*N*-methylimidazole
NMP	1-methylpyrrolidin-2-one
NMR	nuclear magnetic resonance
OTf	trifluoromethanesulfonate
Ph	phenyl
PIDA	phenyliodine(III) diacetate
Piv	pivaloyl
ppm	parts per million
pyr	pyridine
q	quartet (NMR)
R	undefined organic substituent
rt	room temperature
s	singlet (NMR)
s	strong (IR)
sat.	saturated
t	triplet (NMR)
t	time
T	temperature
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TMEDA	*N*,*N*,*N*',*N*'-tetramethylethylenediamine
TMS	trimethylsilyl
TP	typical procedure
Ts	4-toluenesulfonyl
X	halogen (Cl, Br, I)

A. INTRODUCTION

A. Introduction

1 Overview

In 2019, the Center for Drug Evaluation and Research of the U.S. Food and Drug Administration (CDER, FDA) approved 41 novel drugs so far, including 29 small molecules (71%).[1] This emphasizes the invariable high importance of small molecules in modern drug discovery. The biological activity, for example the binding to target receptors, of these drugs is defined by their three-dimensional structure. In the past, several incidents showed that two enantiomers of a substance can have drastically different biological effects, causing severe danger to the human body, as in the cases of thalidomide[2a] or penicillamine[2b]. As a consequence, stereochemical control is an essential aspect in pharmaceutical drug design nowadays to assure the desired biological effectivness. Rivaroxaban (Xarelto®, Johnson&Johnson, anticoagulant), ibrutinib (Imbruvica®, Abbvie, protein kinase inhibitor) and pregabalin (Lyrica®, Pfizer, anticonvulsant and anxiolytic), for example, are administered as single enantiomers and among the top selling small molecule pharmaceuticals of 2018 (see Figure 1).[3]

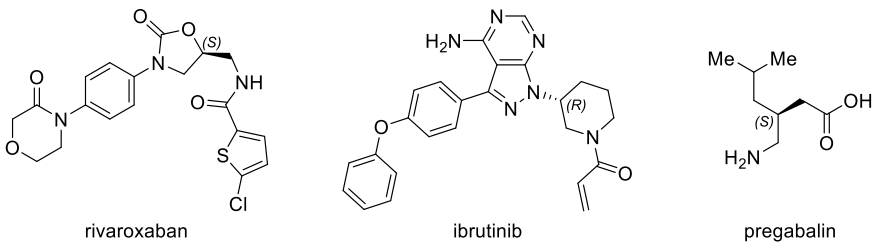


Figure 1: Structure of the chiral drugs rivaroxaban, ibrutinib and pregabalin.

In this context, the development of new synthetic methods for the preparation of chiral substances and their further functionalization is of great interest for organic synthesis to make new drugs available. The use of organometallic reagents and transition metal catalysis provides a wide range of synthetic strategies for the formation of chiral molecules.[4]

[1] As of December 2019: a) L. Urquhard, *Nat. Rev. Drug Discovery* **2019**, *18*, 329. b) L. Urquhard, *Nat. Rev. Drug Discovery* **2019**, *18*, 575. c) L. Urquhard, *Nat. Rev. Drug Discovery* **2019**, *18*, 816.
[2] a) T. Erikson, S. Björkman, B. Roth, P. Höglund, *J. Pharm. Pharmacol.* **2000**, *52*, 807–817. b) J. Peisach, W. E. Blumberg, *Mol. Pharmacol.* **1969**, *5*, 200–209.
[3] a) C. W. Lindsley, *ACS Chemical Neuroscience* **2019**, *10*, 1115–1115. b) B. J. Snellgrove, T. Steinert, S. Jaeger, *CNS Drugs* **2017**, *31*, 891–898.
[4] a) C. Elschenbroich, *Organometallics*, Wiley, **2016**. b) A. H. Cherney, N. T. Kadunce, S. E. Reisman, *Chem. Rev.* **2015**, *115*, 9587–9652.

2 Access to Stereodefined Molecules

In general, the two main strategies for the access of enantioenriched molecules are chiral resolution and asymmetric synthesis. The separation of a racemic mixture can be performed via chiral chromatography, crystallization or chemical resolution. These procedures are important tools for the preparation of optically active drugs. However, the yield of chiral resolution is limited to up to fifty percent. In contrast, enantioselective synthesis is an excellent method to access chiral molecules in high optical purity and high yields. Once a single enantiomer is accessed, there are several nucleophilic and electrophilic reactions to further functionalize the chiral substrate.

2.1 Chiral resolution

Chiral Chromatography or Crystallization

Two enantiomers can be separated due to their different interactions with a chiral stationary phase in silica flash chromatography, high performance liquid chromatography (HPLC) or gas chromatography (GC).[5] For example, oxazepam was efficiently resolved by supercritical fluid chromatography (SFC) in 2014 (see Figure 2).[6]

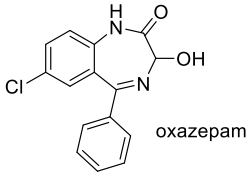
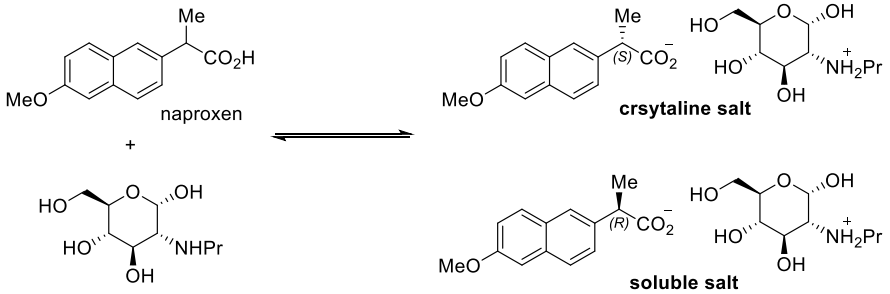


Figure 2: Structure of the racemic benzodiazepine, oxazepam.

Nevertheless, the preferred method of purification on large scale in industry is crystallization.[7] By using chiral *N*-propylglucosamine as precipitating agent, racemic naproxen can be separated leading to both enantiomers in high yield. This procedure significantly reduced the cost for the anti-inflammatory agent (*S*)-naproxen (see Scheme 1).[8]

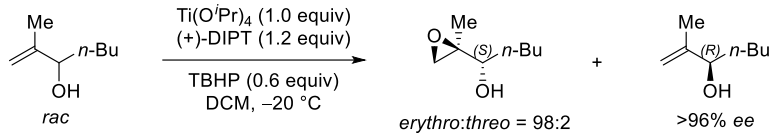


Scheme 1: Resolution of racemic naproxen via crystallization.

[5] For a recent review, see: J. Shen, Y. Okamoto, *Chem. Rev.* **2016**, *116*, 1094–1138.
[6] K. De Klerck, Y. V. Heyden, D. Mangelings, *J. Chromatogr. A* **2014**, *1326*, 110–124.
[7] A. M. Schwartz, A. S. Myerson, in *Handbook of Industrial Crystallization (Second Edition)* (Ed.: A. S. Myerson), Butterworth-Heinemann, Woburn, **2002**, pp. 1–31.
[8] P. J. Harrington, E. Lodewijk, *Org. Process Res. & Dev.* **1997**, *1*, 72–76.

Resolution

The principle of kinetic resolution depends on distinct reaction rates of two enantiomers with a chiral catalyst or reagent, leading to an enantioenriched unreacted enantiomer and a separable side product. In 1980, B. Sharpless *et al.* reported an enantioselective epoxidation of allylic alcohols by using a chiral diethyl tartrate, titanium tetraisopropoxide and *tert*-butyl hydroperoxide as oxidant.[9] This enantioselective kinetic resolution was often used for the preparation of chiral allylic alcohols (see Scheme 2)[10] and is an essential tool in natural product synthesis.[11]



Scheme 2: Enantioselective epoxidation of a racemic allylic alcohol as an example for kinetic resolution.

The importance of this work was emphasized in the awarding of the Nobel prize in chemistry 2001 to Sharpless "for his work on chirally catalyzed oxidation reactions". In the same year, W. S. Knowles and R. Noyori were also awarded "for their work on chirally catalyzed hydrogenation reactions", which represents a classic asymmetric reaction (see next chapter).[12]

2.2 Asymmetric synthesis

Isolation of natural products

A large variety of natural products are provided by biosynthetic processes in plants, animals or microorganisms. Historically, these biologically active substances were isolated and used as drugs.[13] For example, alkaloids such as morphine are extracted from the opium poppy,[14] whereas the antibiotic, penicillin G, is isolated from a microorgamism (*Penicillium chrysogenum* fungus; see Figure 3).[15]

[9] T. Katsuki, K. B. Sharpless, *J. Am. Chem. Soc.* **1980**, *102*, 5974–5976.
[10] V. S. Martin, S. S. Woodard, T. Katsuki, Y. Yamada, M. Ikeda, K. B. Sharpless, *J. Am. Chem. Soc.* **1981**, *103*, 6237–6240.
[11] a) T. R. Hoye, Z. Ye, *J. Am. Chem. Soc.* **1996**, *118*, 1801–1802. b) I. Paterson, C. De Savi, M. Tudge, *Org. Lett.* **2001**, *3*, 3149–3152. c) T. Sunazuka, T. Hirose, T. Shirahata, Y. Harigaya, M. Hayashi, K. Komiyama, S. Ōmura, A. B. Smith, *J. Am. Chem. Soc.* **2000**, *122*, 2122–2123.
[12] K. B. Sharpless, *Angew. Chem. Int. Ed.* **2002**, *41*, 2024–2032.
[13] S. D. Sarker, L. Nahar, in *Natural Products Isolation* (Eds.: S. D. Sarker, L. Nahar), Humana Press, Totowa, NJ, **2012**, pp. 1–25.
[14] a) H. N. Bennett, H. Tomas, W. R. Josephine, M. Johann, T. Dirk, *Curr. Org. Chem.* **2000**, *4*, 343–362. b) S. Galanie, K. Thodey, I. J. Trenchard, M. Filsinger Interrante, C. D. Smolke, *Science* **2015**, *349*, 1095–1100.
[15] D. A. Dias, S. Urban, U. Roessner, *Metabolites* **2012**, *2*, 303–336.

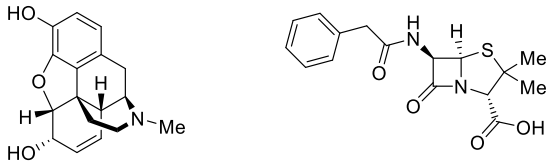
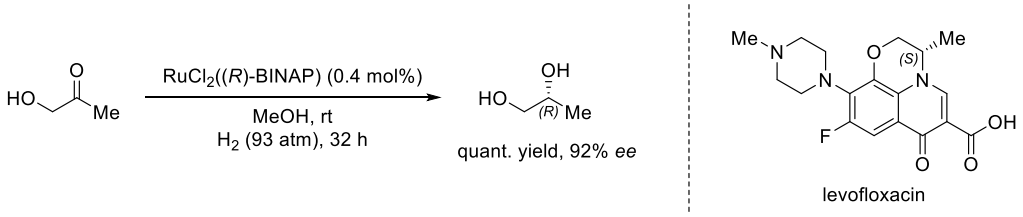


Figure 3: Structure of morphine and penicillin G as examples for drugs extracted from natural products.

In recent years, drug development from natural products has declined due to unreliable supply, changing composition and environmental issues of natural product isolation.[16] Thus, the focus shifted to the optimization and development of asymmetric synthesis.

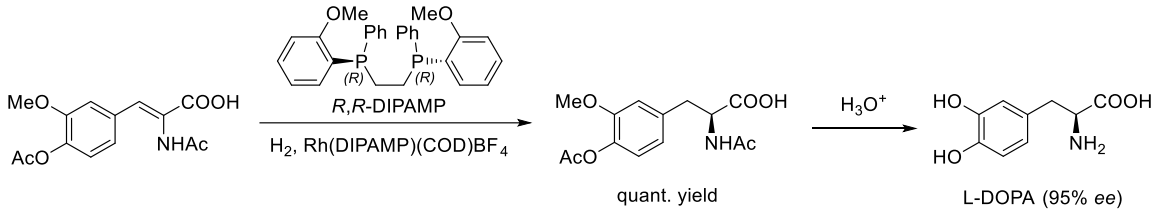
Asymmetric Reactions

Enantioselective synthesis has revolutionized modern-day chemistry and has drastically improved synthetic efficiency. In 1966, R. Noyori reported the first asymmetric hydrogenation of ketones using a Ru(II)-BINAP catalyst.[17] The chiral alcohol (*R*)-1,2-propanediol was later used for the industrial synthesis of levofloxacin, an antibacterial (see Scheme 3).[18]



Scheme 3: Asymmetric hydrogenation of achiral ketones leading to chiral secondary alcohols.

In 1977, W. S. Knowles applied the first enantioselective metal catalysis using the chiral phosphine ligand, *R,R*-DIPAMP, in an industrial scale-up synthesis of L-DOPA for Monsanto (see Scheme 4).[19]

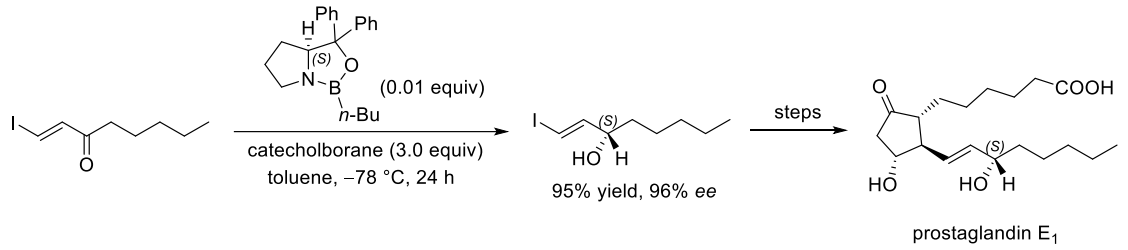


Scheme 4: Industrial synthesis of the amino acid L-DOPA.[19]

The Corey-Bakshi-Shibata (CBS) reduction is a synthetically powerful tool enabling the preparation of a broad range of chiral secondary alcohols by using catalytic amounts of oxazaborolidines in the

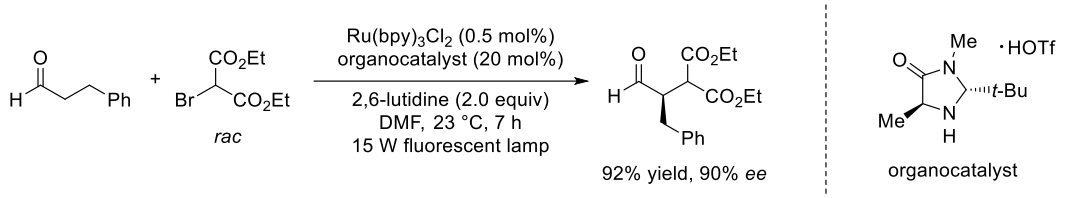
[16] J. W.-H. Li, J. C. Vederas, *Science* **2009**, *325*, 161–165.
[17] a) H. Nozaki, S. Moriuti, H. Takaya, R. Noyori, *Tetrahedron Lett.* **1966**, *7*, 5239–5244. b) H. Nozaki, H. Takaya, S. Moriuti, R. Noyori, *Tetrahedron Lett.* **1968**, *24*, 3655–3669.
[18] a) M. Kitamura, T. Ohkuma, S. Inoue, N. Sayo, H. Kumobayashi, S. Akutagawa, T. Ohta, H. Takaya, R. Noyori, *J. Am. Chem. Soc.* **1988**, *110*, 629–631. b) R. Noyori, *Angew. Chem. Int. Ed.* **2002**, *41*, 2008–2022.
[19] a) B. D. Vineyard, W. S. Knowles, M. J. Sabacky, G. L. Bachman, D. J. Weinkauff, *J. Am. Chem. Soc.* **1977**, *99*, 5946–5952. b) W. S. Knowles, *Acc. Chem. Res.* **1983**, *16*, 106–112. c) W. S. Knowles, *Angew. Chem. Int. Ed.* **2002**, *41*, 1998–2007.

presence of a borane.[20] This enantioselective reduction was used in the total synthesis of complex natural products, such as dysidiolide,[21] okadaic acid[22] or prostaglandin E_1[23] (see Scheme 5).



Scheme 5: CBS reduction in the total synthesis of prostaglandin E_1.[23]

Recently, McMillian and co-workers reported the direct asymmetric alkylation of aldehydes by using the photoredox catalyst, $Ru(bpy)_3Cl_2$, and a chiral imidazolidinone organocatalyst (see Scheme 6).[24]



Scheme 6: Asymmetric photoredox reaction.[24]

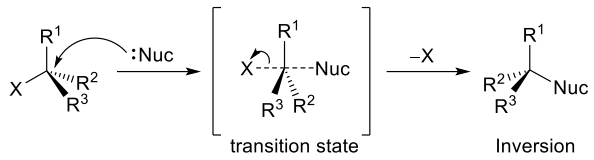
The developments in asymmetric synthesis over the past decades reformed the understanding and application of organic synthesis. These methods play a decisive role in life science of the 21th century.

2.3 Stereodefined reactions

Reactions at chiral carbon centers can lead to retention, inversion or loss of the stereochemical information. Depending on the substrate, nucleophile, solvent and leaving group, nucleophilic substitutions can proceed in a S_N1- or S_N2-reaction manner.[25] The S_N1 mechanism proceeds via an achiral carbocation leading to a racemic product, whereas the S_N2 mechanism proceeds via a concerted *anti*-substitution affording the product with inverted stereochemistry (see Scheme 7). The Mitsunobu

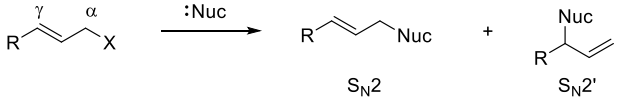
[20] a) A. Hirao, S. Itsuno, S. Nakahama, N. Yamazaki, *J. Chem. Soc., Chem. Commun.* **1981**, 315–317. b) E. J. Corey, R. K. Bakshi, S. Shibata, *J. Am. Chem. Soc.* **1987**, *109*, 5551–5553. c) E. J. Corey, R. K. Bakshi, S. Shibata, C. P. Chen, V. K. Singh, *J. Am. Chem. Soc.* **1987**, *109*, 7925–7926.
[21] E. J. Corey, B. E. Roberts, *J. Am. Chem. Soc.* **1997**, *119*, 12425–12431.
[22] S. F. Sabes, R. A. Urbanek, C. J. Forsyth, *J. Am. Chem. Soc.* **1998**, *120*, 2534–2542.
[23] a) A. Rodríguez, M. Nomen, B. W. Spur, J.-J. Godfroid, *Eur. J. Org. Chem.* **1999**, *1999*, 2655–2662. b) L. Kürti, B. Czako, *Strategic Applications of Named Reactions in Organic Synthesis*, (Eds.: E. J. Corey, K. C. Nicolaou), Elsevier Inc., Burlington, MA, **2005**, pp. 100–101.
[24] D. A. Nicewicz, D. W. C. MacMillan, *Science* **2008**, *322*, 77–80.
[25] a) L. C. Bateman, M. G. Church, E. D. Hughes, C. K. Ingold, N. A. Taher, *J. Chem. Soc. (Resumed)* **1940**, 979-1011. b) K. S. Peters, *Chem. Rev.* **2007**, *107*, 859-873. c) T. A. Hamlin, M. Swart, F. M. Bickelhaupt, *ChemPhysChem* **2018**, *19*, 1315-1330.

reaction[26], Appel reaction[27] or Mukaiyama redox-condensation[28] are well known examples, leading to an inversion of the stereochemistry.



Scheme 7: Reaction mechanism of S_N2-substitution reactions.

In allylic systems the nucleophilic substitution can occur in α- or γ-position leading to the corresponding S_N2- or S_N2'-substitution products (see Scheme 8).[29] The regio- and stereoselectivity of these allylic substitution reactions were intensively investigated and allylic substitutions were extended to various useful applications in organic synthesis.[30]



Scheme 8: Selectivity between S_N2- and S_N2'-reactions in allylic systems.

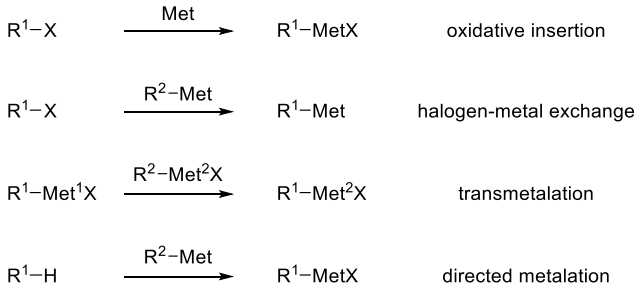
The bimolecular electrophilic S_E2 reaction proceeds, similar to the S_N2 mechanism, via a concerted transition state. However, the approach of the electrophile happens from the same site as the leaving group and thus the reaction proceeds with retention of the configuration. The trappings of chiral alkyltin-[31] or lithium reagents[32] with electrophiles are examples for a retentive S_E2-reaction.

[26] a) M. Oyo, Y. Masaaki, *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2380–2382. b) O. Mitsunobu, *Synthesis* **1981**, *1981*, 1–28. For a review, see: c) S. Fletcher, *Organic Chemistry Frontiers* **2015**, *2*, 739–752.
[27] R. Appel, *Angew. Chem. Int. Ed.* **1975**, *14*, 801–811.
[28] a) S. Taichi, K. Wataru, M. Teruaki, *Bull. Chem. Soc. Jpn.* **2003**, *76*, 1645–1667. b) T. Mukaiyama, *Angew. Chem. Int. Ed.* **2004**, *43*, 5590–5614.
[29] B. M. Trost, D. L. Van Vranken, *Chem. Rev.* **1996**, *96*, 395–422.
[30] a) T. Graening, H.-G. Schmalz, *Angew. Chem. Int. Ed.* **2003**, *42*, 2580-2584. b) B. M. Trost, M. L. Crawley, *Chem. Rev.* **2003**, *103*, 2921-2944. c) Z. Lu, S. Ma, *Angew. Chem. Int. Ed.* **2008**, *47*, 258–297.
[31] J. M. Fukuto, F. R. Jensen, *Acc. Chem. Res.* **1983**, *16*, 177–184.
[32] a) D. Hoppe, F. Hintze, P. Tebben, *Angew. Chem. Int. Ed.* **1990**, *29*, 1422–1424. b) D. Hoppe, A. Carstens, T. Krámer, *Angew. Chem. Int. Ed.* **1990**, *29*, 1424–1425. b) D. Hoppe, T. Hense, *Angew. Chem. Int. Ed.* **1997**, *36*, 2282–2316.

3 Stereodefined Organometallic Reagents and Previous Efforts

3.1 Organometallic Chemistry

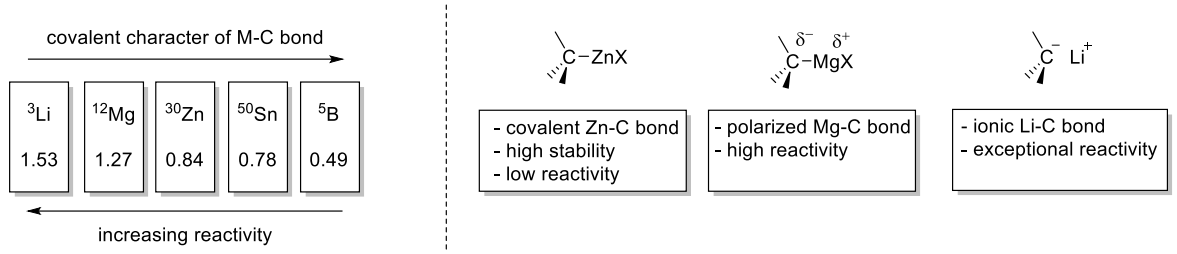
Organometallic reagents provide a versatile toolbox for the preparation and functionalization of organic molecules. In general, organometallic species can be prepared via oxidative insertion, halogen-metal exchange, transmetalation or directed metalation (see Scheme 9).[33] Furthermore, chiral organometallic reagents can be prepared via enantiospecific (stereoretention) or enantioselective reactions (use of chiral ligands).[4b,34]



Scheme 9: Preparation of organometallic reagents.

The reactivity of these organometallic reagents depend on the ionic character of the carbon-metal bond and increase with the difference of electronegativity (see Scheme 10).[35] Due to their small difference in electronegativity, organoboron,[36] -tin[37] and zinc[38] reagents have rather covalent carbon-metal bonds showing a high stability but lower reactivity. Grignard-reagents pocess a more polarized carbon-magnesium bond and as a consequence are more reactive.[39] Organolithium reagents have an ionic carbon-lithium bond and show a very high reactivity, but low stability and, therefore, lower functional group tolerance. However, organolithium reagents are widely used in organic synthesis, due to their exceptional high reactivity and commercial availability.[40]

[33] P. Knochel in *Handbook of Functionalized Organometallics* (Ed.: P. Knochel), Wiley-VCH, Weinheim, **2005**.
[34] a) S. R. Harutyunyan, T. den Hartog, K. Geurts, A. J. Minnaard, B. L. Feringa, *Chem. Rev.* **2008**, *108*, 2824–2852. b) A. Alexakis, J. E. Bäckvall, N. Krause, O. Pàmies, M. Diéguez, *Chem. Rev.* **2008**, *108*, 2796–2823.
[35] a) A. Boudier, L. O. Bromm, M. Lotz, P. Knochel, *Angew. Chem. Int. Ed.* **2000**, *39*, 4414–4435. b) E. Negishi, *Organometallics in Organic Synthesis*, Wiley, New York, **1980**
[36] a) A. Pelter, K. Smith, H. C. Brown, *Borane reagents*, Academic Press, **1988**. b) N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457–2483. c) S. R. Chemler, D. Trauner, S. J. Danishefsky, *Angew. Chem. Int. Ed.* **2001**, *40*, 4544–4568. d) A. J. J. Lennox, G. C. Lloyd-Jones, *Chem. Soc. Rev.* **2014**, *43*, 412–443.
[37] a) R. K. Ingham, S. D. Rosenberg, H. Gilman, *Chem. Rev.* **1960**, *60*, 459–539. b) A. G. Davies, *Organotin Chemistry*, Wiley, **2004**.
[38] a) E. Frankland, *Liebigs. Ann. Chem.* **1849**, *71*, 171. b) E. Negishi, L. F. Valente, M. Kobayashi, *J. Am. Chem. Soc.* **1980**, *102*, 3298–3299. c) P. Knochel, R. D. Singer, *Chem. Rev.* **1993**, *93*, 2117–2188.
[39] a) Grignard, V. *Compt. Rend. Acad. Sci.* **1900**, *130*, 1322. b) B. J. Wakefield, in *Organomagnesium Methods in Organic Synthesis* (Ed.: B. J. Wakefield), Academic Press, London, **1995**, pp. 21–71. c) D. Seyferth, *Organometallics* **2009**, *28*, 1598–1605.
[40] a) J. Clayden, *Organolithiums: Selectivity for Synthesis*, Elsevier Science, Philadelphia, **2002**, pp. 400. b) G. Wu, M. Huang, *Chem. Rev.* **2006**, *106*, 2596–2616. c) U. Wietelmann, J. Klett, *Z. Anorg. Allg. Chem.* **2018**, *644*, 194–204.



Scheme 10: Electronegativity difference of various metalorganic reagents and bond properties of organozinc-, magnesium- and lithium reagents.[35]

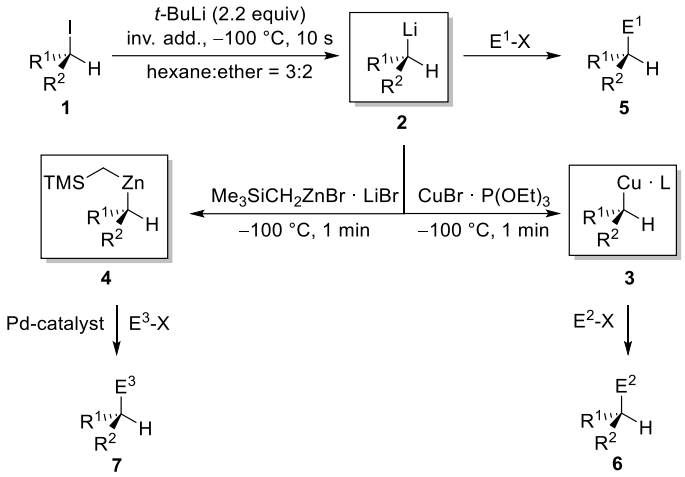
3.2 Stereoselective Preparation of Chiral Alkyllithiums

Organolithiums have been known since the beginning of the 20th century and were first used for the initiation of anionic polymerizations. They possess a highly polarized carbon-lithium bond, ensuring a high reactivity towards various electrophilic reagents.[41] These reactive organometallics were popularized in organic synthesis in ca. 1960,[42] and soon afterwards a range of heteroatom-stabilized organolithium reagents became available.[43] Seebach introduced the concept of "Umpolung", which enables the performance of C-C bond formation by a formal inversion of polarity[44] and therefore, considerably facilitates the retrosynthesis of complex organic molecules.[45] A range of elegant methods were developed for the preparation of optically enriched chiral heteroatom-stabilized organolithium reagents.[4b,32,46]

In contrast, the I/Li-exchange reaction[47] of secondary alkyl iodides of type **1** proceeds with retention of the configuration and leads to chiral non-stabilized secondary alkyllithium reagents of type **2**.[48] Reaction conditions were found, allowing a stereoselective transmetalation of **2** to either copper derivatives of type **3** using the ether soluble salt $CuBr{\cdot}P(OEt)_3$[49], or to zinc compounds of type **4** using the organozinc salt $Me_3SiCH_2ZnBr{\cdot}LiBr$. Both transmetalations proceed with retention of configuration and the resulting secondary alkyl organometallics (**2**, **3** and **4**) react stereoselectively with appropriate

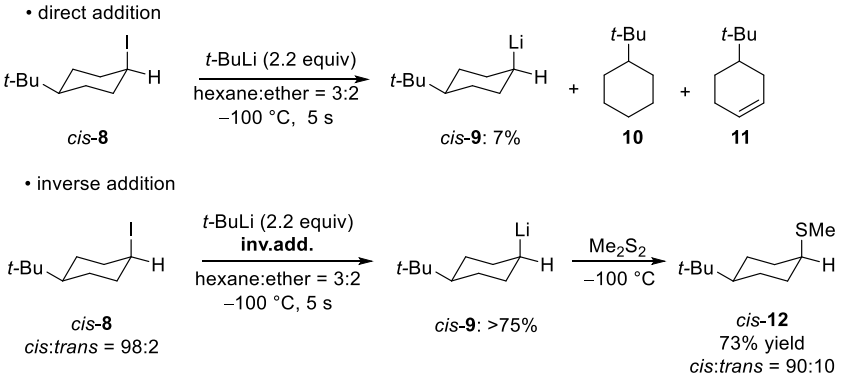
[41] M. Majewski, *et al.*: Science of Synthesis, 8a: Category 1, Organometallics, Thieme, **2005**, pp. 859.
[42] D. V. Collum, A. J. McNeil, A. Ramirez, *Angew. Chem. Int. Ed.* **2007**, 46, 3002–3017.
[43] A. T. Hase, *Umpoled Synthons: A Survey of sources and Uses in Synthesis*, John Wiley & Sons, Inc. New York, **1987**, pp. 104.
[44] D. Seebach, *Synthesis* **1969**, *1*, 17–36.
[45] D. Seebach, *Angew. Chem.* **1979**, *91*, 259–278.
[46] D. Hoppe, *Synthesis* **2009**, 43–55.
[47] a) G. Wittig, U. Pockels, H. Dröge, Chem. Ber. **1938**, *71*, 1903–1912. b) H. Gilman, W. Langham, A. L. Jacoby, *J. Am. Chem. Soc.* **1939**, *61*, 106–109. c) E. C. Ashby, T. N. Pham, *J. Org. Chem.* **1987**, *52*, 1291–1300. d) P. Beak, D. J. Allen, *J. Am. Chem. Soc.* **1992**, *114*, 3420–3425.
[48] S. Seel, G. Dagousset, T. Thaler, A. Frischmuth, K. Karaghiosoff, H. Zipse, P. Knochel, *Chem. Eur. J.* **2013**, *19*, 4614–4622.
[49] K. Moriya, M. Simon, R. Mose, K. Karaghiosoff, P. Knochel, *Angew. Chem. Int. Ed*. **2015**, *54*, 10963–10967.

electrophiles ($E^{1\text{-}3}$-X) providing a range of chiral molecules such as **5**, **6** and **7**, which are of interest for the preparation of natural products.[50]



Scheme 11: Stereoselective reactions of chiral secondary alkyllithium reagents.

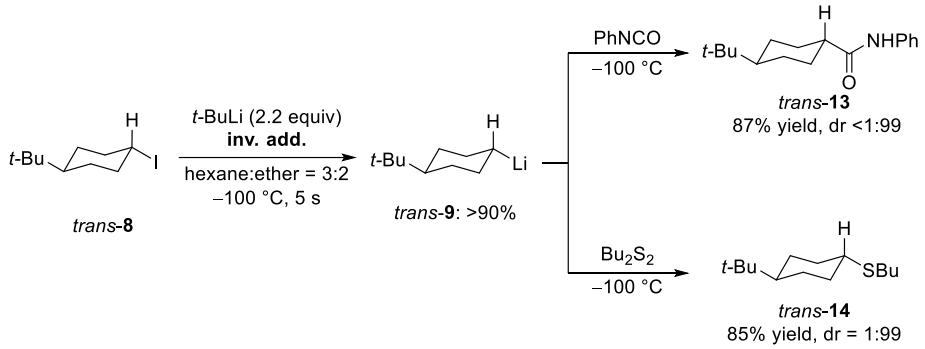
The performance of an I/Li exchange on secondary alkyl iodides using *t*-BuLi is complicated by various side reactions due to the exceptionally high reactivity of the resulting secondary alkyllithium reagents, which are very close to the reactivity of *t*-BuLi. Bailey showed that the reaction of *cis*-4-*tert*-butylcyclohexyl iodide (*cis*-**8**) with *t*-BuLi at −100 °C in a hexane/diethyl ether mixture (3:2) produced the cyclic organolithium reagent *cis*-**9** in less than 7% yield.[51] The main reaction products were the cyclohexane **10** generated by the reaction of *cis*-**9** with the iodide *cis*-**8** (protonation reaction) and the cyclohexene derivative **11** (elimination product of *cis*-**8**). These side reactions may be minimized by performing the reaction in the presence of a constant excess of *t*-BuLi. This can be experimentally realized by performing an inverse addition. Under these conditions, the lithium reagent *cis*-**9** could be generated in >75% yield. Trapping with Me_2S_2 at −100 °C provided the thioether *cis*-**12** with a diastereoselectivity of *cis*/*trans* = 90:10 (see Scheme 12).[48]



Scheme 12: Generation of the secondary alkyllithium reagent *cis*-**9** via inverse addition of *t*-BuLi.

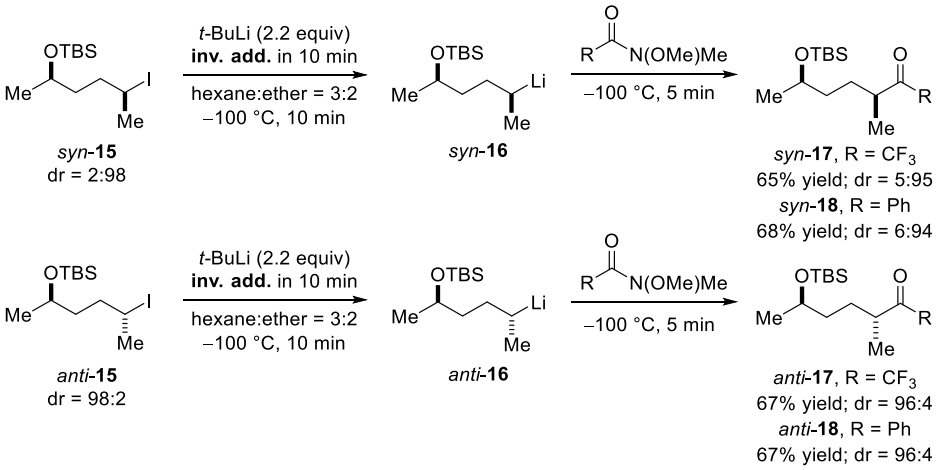
[50] V. Morozova, J. Skotnitzki, K. Moriya, K. Karaghiosoff, P. Knochel, *Angew. Chem. Int. Ed.* **2018**, *57*, 5516–5519.
[51] W. F. Bailey, J. D. Brubaker, K. P. Jordan, *J. Organomet. Chem.* **2003**, *681*, 210–214.

Further experiments demonstrated that *cis*-**9** displayed much lower thermodynamic stability than the corresponding diastereoisomer *trans*-**9** and fully equilibrated within 7 h at −100 °C. As a consequence, starting from the cyclohexyl iodide *trans*-**8** allowed the preparation of *trans*-**9**, which reacted with phenyl isocyanate or Bu_2S_2 affording the *trans*-amide **13** and the thioether *trans*-**14** in 85-87% yield with very high stereoselectivity (dr up to 99:1; see Scheme 13).[48]



Scheme 13: Stereoselective preparation of *trans*-**9** and subsequent trapping with phenyl isocyanate and dibutyl disulfide.

Remarkably, these reactions can also be extended to acyclic non-stabilized secondary alkyllithium reagents.[52] Thus, dropwise addition of the functionalized alkyl iodides *syn*-**15** and *anti*-**15** to a stirred solution of *t*-BuLi (2.2 equiv) in hexane/diethyl ether at −100 °C over 10 min afforded the corresponding alkyllithium species *syn*-**16** and *anti*-**16**. Their acylation with various Weinreb amides gave the corresponding ketones **17** and **18** with high retention of configuration (dr: ratio of *anti*/*syn* = up to 96:4; see Scheme 14).

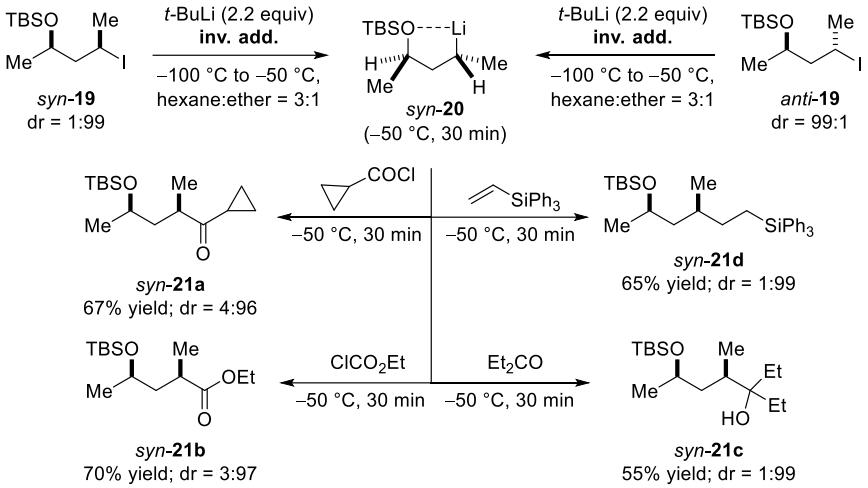


Scheme 14: Stereoselective generation of secondary open-chain alkyllithium reagents and their retentive trapping with Weinreb amides producing diastereomerically enriched ketones.

In a similar approach a broad range of diastereomerically pure non-stabilized secondary alkyl iodides were generated and, in all cases, a retentive I/Li-exchange reaction took place. Interestingly, the

[52] G. Dagousset, K. Moriya, R. Mose, G. Berionni, K. Karaghiosoff, P. Knochel, *Angew. Chem. Int. Ed*. **2014**, *53*, 1425–1429.

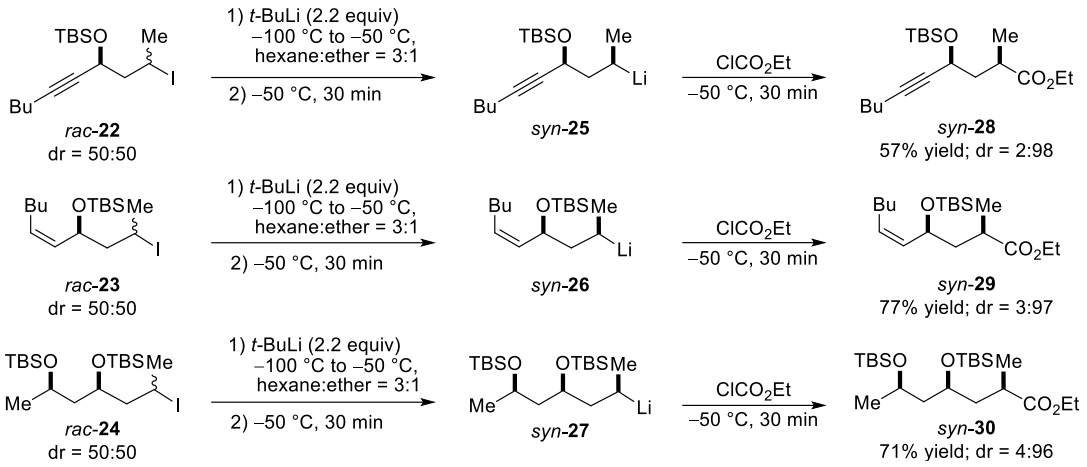
generation of *syn*-**16** or *anti*-**16** occurred without significant interaction of the remote silyl ether function (OTBS) with the carbon-lithium bond. However, the diastereoselectivity of a lithium reagent is, in fact, strongly influenced by an OTBS-group in a nearby position, as it is the case for the secondary alkyl iodides *syn*- and *anti*-**19**. Both lithium reagents, obtained after an I/Li-exchange, provided in a stereoconvergent manner the lithium species *syn*-**20**. Here, an intramolecular interaction between the silylether function and the lithium center takes place and provides a significant stabilization.[53] The prepared lithium organometallic *syn*-**20** reacted with various carbonyl derivatives, such as cyclopropylcarbonyl chloride, ethyl chloroformate and pentan-3-one, furnishing the corresponding adducts *syn*-**21a-c** in 55-70% yield. Also, the addition to triphenylethenylsilane led to the silane *syn*-**21d** in 65% yield. In all cases, the products *syn*-**21a-d** were obtained with diastereoselectivities higher than 96:4 (see Scheme 15).[53]



Scheme 15: Stereconvergent preparation of the chelate-stabilized secondary alkyllithium *syn*-**20** and its stereoselective reactions with various electrophiles.

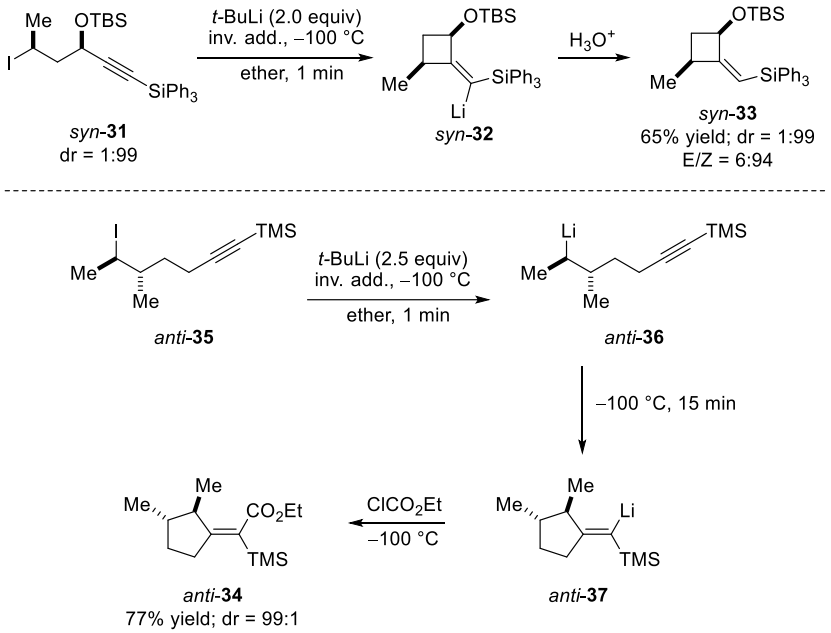
This approach can be extended to a range of γ-OTBS-substituted alkyl iodides. The epimeric mixtures of iodides *rac*-**22-24** were stereoconvergently converted to the expected secondary alkyllithium reagents *syn*-**25-27**. Further reaction with ethyl chloroformate at −50 °C furnished the desired polyfunctional esters *syn*-**28-30** in good yields and with very high diastereoselectivities (see Scheme 16).[53]

[53] K. Moriya, D. Didier, M. Simon, J. M. Hammann, G. Berionni, K. Karaghiosoff, H. Zipse, H. Mayr, P. Knochel, *Angew. Chem. Int. Ed*. **2015**, *54*, 2754–2757.



Scheme 16: Stereoconvergent synthesis of γ-OTBS-substituted secondary alkyllithium reagents *syn*-**25**-**27** and their stereoselective conversion to polyfunctional esters.

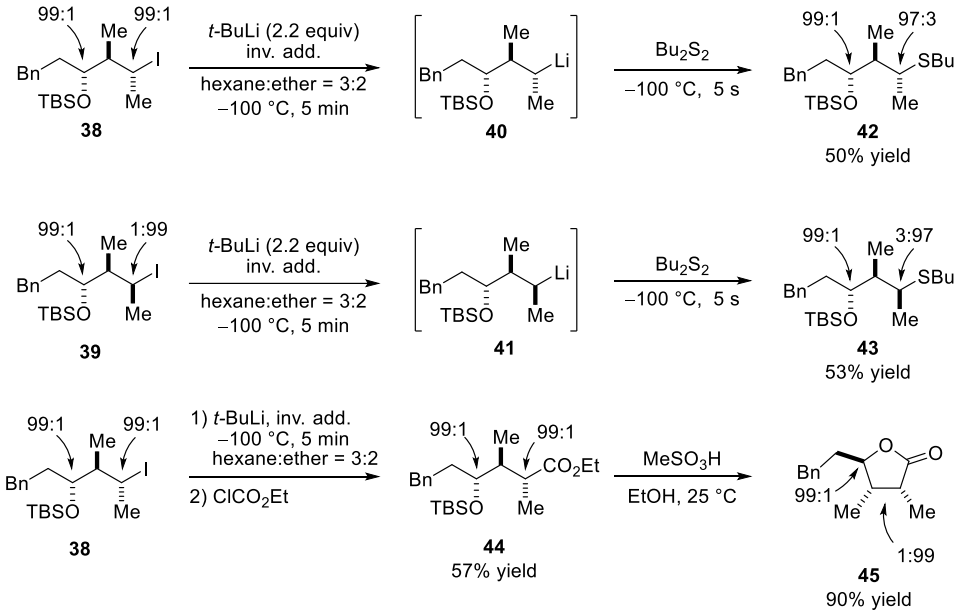
Additionally, diastereoselective intramolecular carbolithiations could be achieved at −100 °C, after an I/Li-exchange with *t*-BuLi of the alkyl iodide *syn*-**31**, if an alkynylsilane was present in a remote position. After quenching the lithiated alkenylsilane *syn*-**32** with a proton source, the *exo*-alkylidenecyclobutane *syn*-**33** was obtained in 65% yield, *E*/*Z* = 6:94 and dr = 1:99 (see Scheme 17).[54] This method could be extended to the preparation of chiral tetrasubstituted cyclopentane exo-alkylidenes, such as *anti*-**34**. Thus, the treatment of the alkyl iodide *anti*-**35** (dr >99:1) with *t*-BuLi (2.5 equiv) in diethyl ether at −100 °C followed by 15 min of stirring at −100 °C afforded the alkyllithium reagent *anti*-**36**. After cyclization to the cyclic lithiated alkenylsilane *anti*-**37** and reaction with ethyl chloroformate, the ester *anti*-**34** was obtained in 77% yield (see Scheme **17**).[55]



Scheme 17: Intramolecular carbolithiation of alkynyl silanes.

[54] K. Moriya, K. Schwaerzer, K. Karaghiosoff, P. Knochel, *Synthesis* **2016**, *48*, 3141–3154.
[55] M. Simon, K. Karaghiosoff, P. Knochel, *Org. Lett.* **2018**, *20*, 3518–3521.

An OTBS-group in the γ-position with an additional methyl group in the β-position, strongly disfavors the stereoconvergent epimerization of these open-chain secondary alkyllithiums shown in Scheme **15** and **16**. Thus, the reaction of both alkyl iodides **38** and **39** with *t*-BuLi in hexane/diethyl ether at −100 °C for 5 min provided the corresponding organolithium reagents **40** and **41**. Quenching with Bu_2S_2 afforded the thioethers **42** (50% yield; dr = 97:3) and **43** (53% yield; dr = 3:97). Similarly, **38** could be stereoselectively converted by this method (reaction with *t*-BuLi, −100 °C followed by $ClCO_2Et$) into the diastereochemically pure ester **44**, which underwent lactonization, furnishing **45** in 90% yield with full control of three adjacent chiral centers (see Scheme 18).[56]



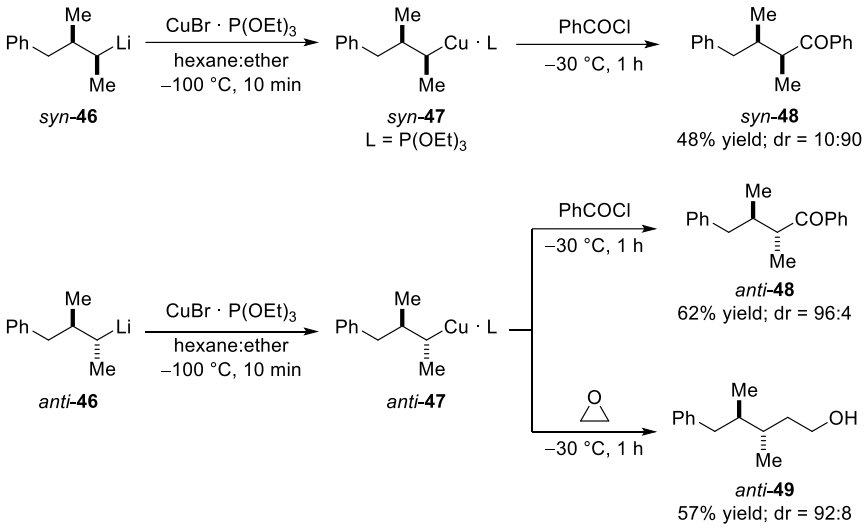
Scheme 18: Stereoselective I/Li-exchange of γ-OTBS substituted alkyl iodides **38** and **39** bearing an additional methyl group in β-position.

3.3 Preparation of Stereodefined Secondary Alkylcopper Reagents

Although, the stereoselective preparation of secondary alkyllithiums and their subsequent trapping with electrophiles allows the preparation of numerous chiral molecules, it was found that several electrophilic reagents react only unselectively with these reactive species. Subsequently, a range of transmetalation reactions to new organometallics possessing a more covalent carbon-metal bond were envisioned. For example, the acylation of organolithiums with acid chlorides is complicated by further addition reactions to the generated intermediate. However, organocopper reagents are known to react chemoselectively with acid chlorides to produce the corresponding ketones exclusively.[57] Thus, the secondary alkyl iodides *syn*-**46** and *anti*-**46** were converted into the corresponding alkylcopper reagents *syn*-**47** and *anti*-

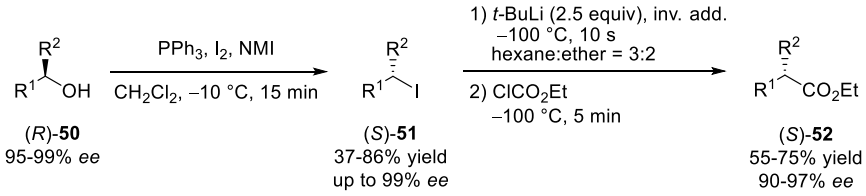
[56] V. Morozova, K. Moriya, P. Mayer, P. Knochel, *Chem. Eur. J.* **2016**, *22*, 9962–9965.
[57] a) N. Krause, *Modern Organocopper Chemistry*, Wiley-VCH Verlag GmbH, Weinheim **2002**, pp. 48. b) M. K. Eberle, G. G. Kahle, *Tetrahedron Lett.* **1980**, *21*, 2303–2304. c) C. Kim, G. M. Rubottom, *J. Org. Chem.* **1983**, *48*, 1550–1552.

47 by addition of the ether soluble copper salt CuBr·P(OEt)$_3$ at −100 °C for 10 min. Treatment of *syn*-**47** and *anti*-**47** with benzoyl chloride at −30 °C for 1 h produced the ketones *syn*-**48** and *anti*-**48** in 48-62% yield and dr >90:10. In addition, the copper reagent *anti*-**47** reacted smoothly with ethylene oxide giving the alcohol *anti*-**49** in 57% yield and dr = 92:8 (see Scheme 19).[53]



Scheme 19: Stereoretentive transmetalation of alkyllithiums to the corresponding copper reagents using CuBr·P(OEt)$_3$.

Improved transmetalation procedures were further developed.[50,58] It was shown, that a range of optically enriched alcohols of type (*R*)-**50** (95%-99% *ee*) could be converted into the corresponding secondary alkyl iodides (*S*)-**51** with full inversion of configuration. After a retentive I/Li-exchange reaction and subsequent trapping with ethyl chloroformate, the corresponding ethyl esters (*S*)-**52** were produced with >90% *ee* (see Scheme 20).[50]

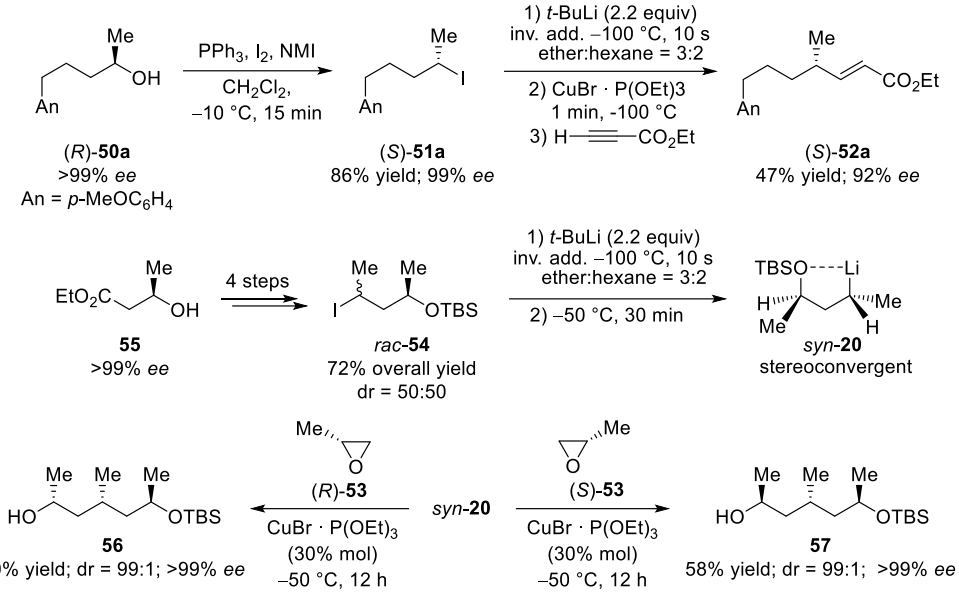


Scheme 20: Enantioselective synthesis of α-chiral esters (*S*)-**52** from optically enriched secondary alkyl alcohols (*R*)-**50**.

Thus, the optically enriched secondary alkyl alcohol (*R*)-**50a** (>99% *ee*) was converted into the corresponding alkyl iodide (*S*)-**51a** with inversion of configuration. After an I/Li-exchange and subsequent transmetalation with CuBr·P(OEt)$_3$, the intermediate alkylcopper reagent underwent a carbocupration with ethyl propiolate, affording the α,β-unsaturated (*S*)-ester **52a** in 47% yield and 92% *ee*.[50] Remarkably, the opening of chiral epoxides ((*R*)-**53** and (*S*)-**53**) with secondary alkylcopper reagents was achieved.[50] Thus, the optically enriched secondary alkyllithium *syn*-**20** (see Scheme 15) was obtained in 99% *ee* from the alkyl iodide *rac*-**54**, which was prepared from commercially available

[58] J. Skotnitzki, L. Spessert, P. Knochel, *Angew. Chem. Int. Ed*. **2019**, *58*, 1509–1514.

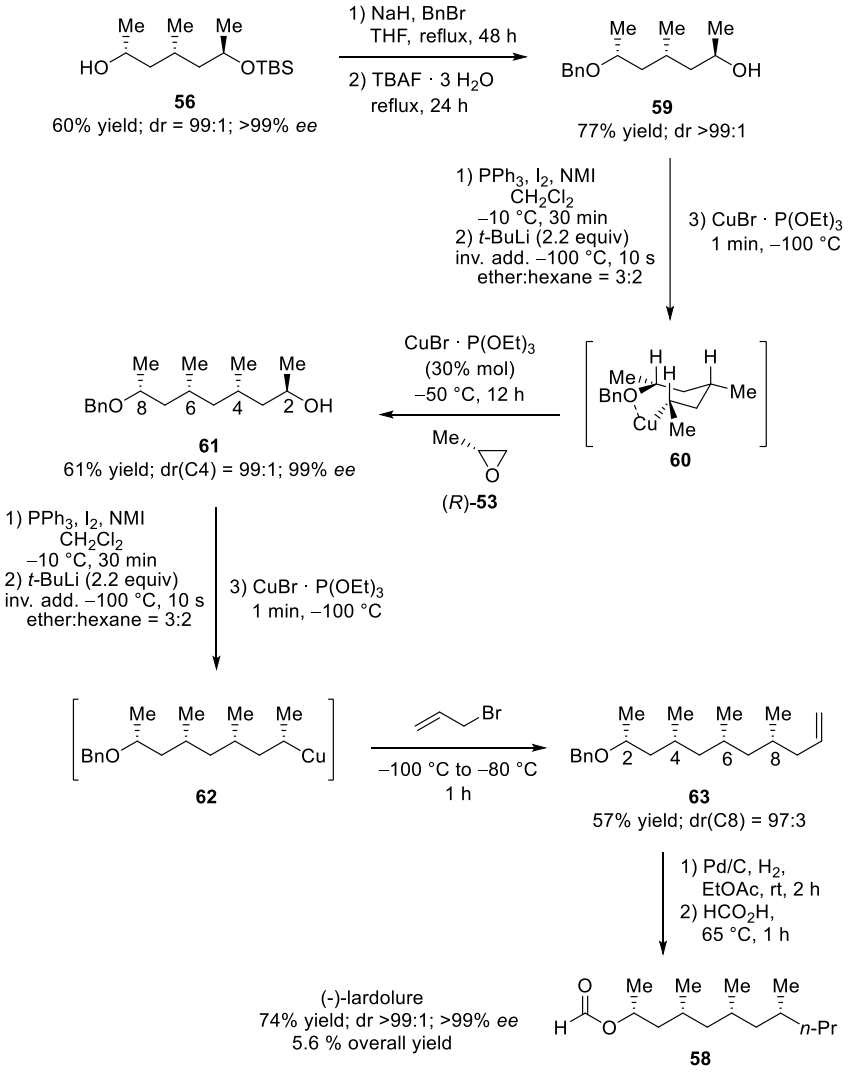
(*R*)-ethyl 3-hydroxybutyrate (**55**). In the presence of 30 mol% CuBr·P(OEt)$_3$, this chelate stabilized lithium reagent triggered a smooth opening of either (*R*)- or (*S*)-propylene oxide ((*R*)-**53** and (*S*)-**53**)) leading to the selectively protected diols **56** and **57** as diastereomerically and enantiomerically pure products (>99% *ee* and dr = 99:1; see Scheme 21).[50]



Scheme 21: Stereoselective reactions of optically pure secondary alkylcopper reagents.

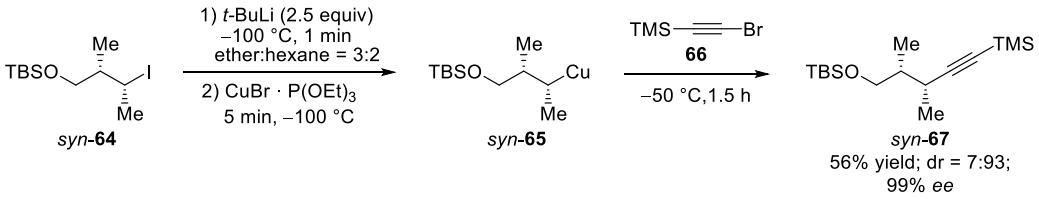
56 in particular, is of great interest as it can be used for the preparation of the pheromone (−)-lardolure (**58**).[59] Thus, after benzylation, the silyl ether was cleaved using tetra-*n*-butylammoniumfluoride (TBAF) leading to **59**. Conversion of the free alcohol into the corresponding iodide followed by the standard I/Li-exchange sequence and subsequent transmetalation with CuBr·P(OEt)$_3$, furnished the chelation-stabilized secondary alkylcopper reagent **60**. Opening of the epoxide (*R*)-**53** led to the chiral alcohol **61** in 61% yield with retention of the configuration (dr = 99:1 and >99% *ee*). The secondary alkylcoppper reagent **62** - prepared by an analogous iodination and I/Li-exchange sequence - was allylated leading to the desired product **63** in 57% yield. Reduction of the allylic system and cleavage of the benzylic alcohol followed by formylation, produced the pheromone (−)-lardolure **58** in 74% yield with a dr >99:1 and 99% *ee* (see Scheme 22).

[59] a) R. Des Mazery, M. Pullez, F. Lopez, S. R. Harutyunyan, A. J. Minnaard, B. L. Feringa, *J. Am. Chem. Soc*. **2005**, *127*, 9966–9967. b) J. S. Yadav, S. Sengupta, N. N. Yadav, C. D. Narasimha, A. A. Al Ghamdi, *Tetrahedron Lett*. **2012**, *53*, 5952–5954.



Scheme 22: Iterative enantioselective synthesis of the pheromone (−)-lardolure (**58**).

In addition, alkylcopper derivatives can undergo cross-couplings with 1-bromoalkynes providing a range of functionalized alkynes in good yields.[60] Thus, the chiral secondary alkyl iodide *syn*-**64** was converted into the corresponding copper derivative *syn*-**65**, which reacted with the bromoacetylene derivative **66**, providing the chiral alkyne *syn*-**67** in 56% yield with dr = 7:93 (see Scheme 23).[61]



Scheme 23: Cross-coupling of the chiral alkylcopper **65** with a bromoalkyne **66**.

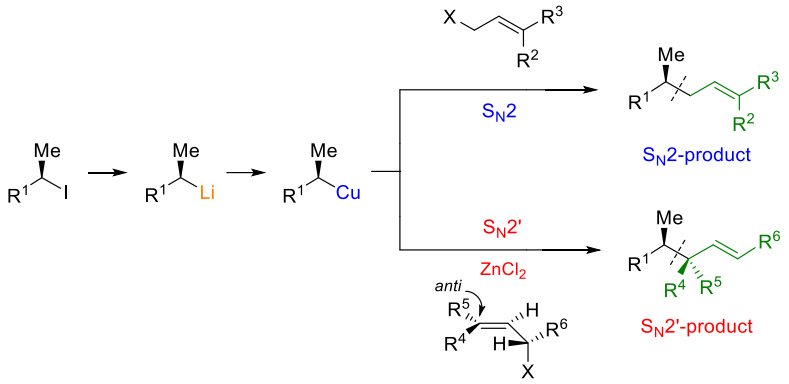
[60] a) A. Commercon, J. F. Normant, J. Villieras, *Tetrahedron* **1980**, *36*, 1215–21. b) M. C. P. Yeh, P. Knochel, *Tetrahedron Lett.* **1989**, *30*, 4799–802. c) P. Knochel, N. Millot, A. L. Rodriguez, C. E. Tucker, *Org. React.* **2001**, *58*, 417–731. d) G. Cahiez, O. Gager, J. Buendia, *Angew. Chem. Int. Ed.* **2010**, *49*, 1278–1281.

[61] This project was commenced by J. Skotnitzki during his Master thesis and finalized during his Ph.D. studies: J. Skotnitzki, V: Morozova, P. Knochel, *Org. Lett.* **2018**, *20*, 2365–2368.

Thermal and configurational studies have shown that these secondary alkylcopper are configurational stable in diethyl ether/hexane to up to −30 °C for only a short time.[61]

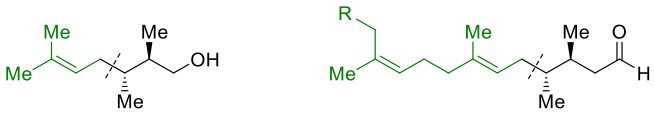
4 Objectives

As stated earlier the stability of chiral secondary alkyllithium- and copper reagents is limited to low temperatures and to the use of diethyl ether/hexane as solvents. Thus, the configurational stability and reactivity of chiral alkylcopper reagents in different solvents were to be investigated and rationalized. Next, the regioselectivity of nucleophilic substitutions of various allylic substrates was to be adjusted by the choice of temperature, solvent, the appropriate leaving group, and the organometallic reagent. Another task was the development of *anti*-S_N2'-substitutions of secondary alkylcopper reagents with chiral allylic substrates (see Scheme 24).



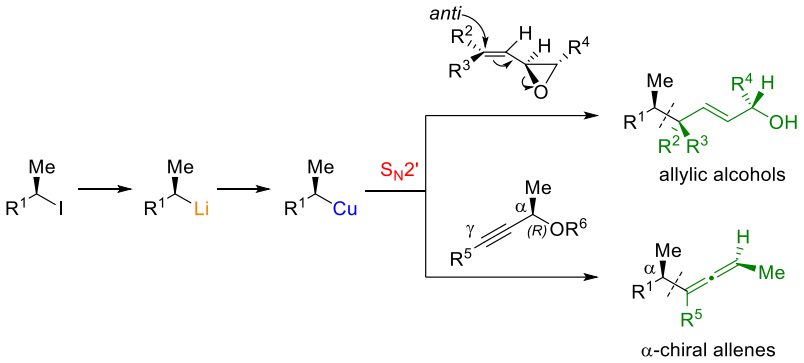
Scheme 24: Stereoselective preparation of chiral alkylcopper reagents and subsequent allylic S_N2- and *anti*-S_N2'-substitutions.

Furthermore, the total synthesis of various chiral natural products with two adjacent stereocenters was envisioned (see Scheme 25). Retrosynthetic analysis shows that these pheromones can be prepared from the corresponding chiral secondary alkyl iodides and allylic substrates *via* stereoretentive allylic S_N2-substitution reaction.



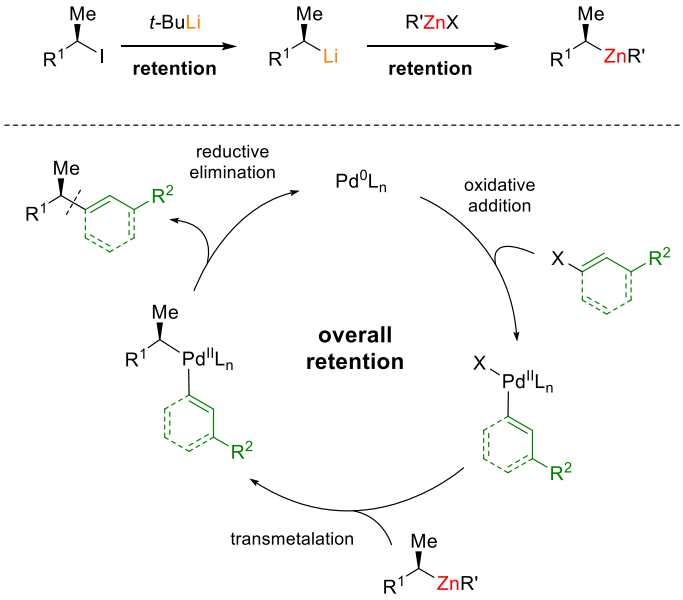
Scheme 25: Pheromones (+)-lasiol, (+)-13-norfaranal and (+)-faranal.

As an extension the regioselective reaction of these organometallic reagents with chiral allylic epoxides and propargylic substrates was to be investigated and optimized. With this method a variety of allylic alcohols and axially chiral allenes would be accessible.



Scheme 26: Stereoselective preparation of chiral alkylcopper reagents and subsequent nucleophilic substitutions leading to allylic alcohols and axially chiral allenes.

Finally, the stereoretentive preparation of chiral secondary alkylzinc reagents was to be developed. It was assumed that these chiral organozinc reagents would be suitable for a stereoselective palladium-catalyzed cross-coupling reaction with alkenyl and aryl halides (see Scheme 27).[62] Thus, various zinc transmetalation reagents and palladium catalysts were to be tested.



Scheme 27: Stereoselective preparation of chiral alkylzinc reagents and envisioned palladium-catalyzed cross-coupling reaction.

This method would enable the synthesis of α-chiral alkenes and arenes with retention of configuration, which are widely spread motifs in natural products and in pharmaceuticals.

[62] This project was developed in cooperation with A. Kremsmair: see A. Kremsmair, Dissertation, LMU Munich. D. Keefer conducted and analyzed the DFT-calculations.

B. RESULTS AND DISCUSSION

B. Results and Discussion

1 Regio- and Stereoselective Allylic Substitutions of Chiral Secondary Alkylcopper Reagents

1.1 Introduction

Absolute stereocontrol in acyclic systems is a substantial synthetic problem and of great interest for the preparation of biologically active substances. Especially the stereoselective formation of new C-C bonds is useful for organic synthesis. In general, organocopper reagents are widely used for the formation of organic molecules and easily undergo allylic substitutions leading to a variety of functionalized alkenes.[63] Furthermore, copper-catalyzed *anti*-S_N2'-allylic substitutions of organozinc reagents represent an excellent method to build up chiral centers in cyclic and acyclic systems.[64]

Herein, we wish to report that chiral secondary alkylcopper reagents of type **3** may undergo regioselective S_N2- or S_N2'-substitutions with various allylic electrophiles (**68A** or **68B**) leading to the corresponding S_N2-products **69** or to the S_N2'-products **70** with high stereoselectivity (see Scheme 28). The efficiency of this method was demonstrated in the enantioselective synthesis of three pheromones, namely (+)-lasiol **71**,[56,65] (+)-13-norfaranal **72**[66] and (+)-faranal **73**[65c,67].

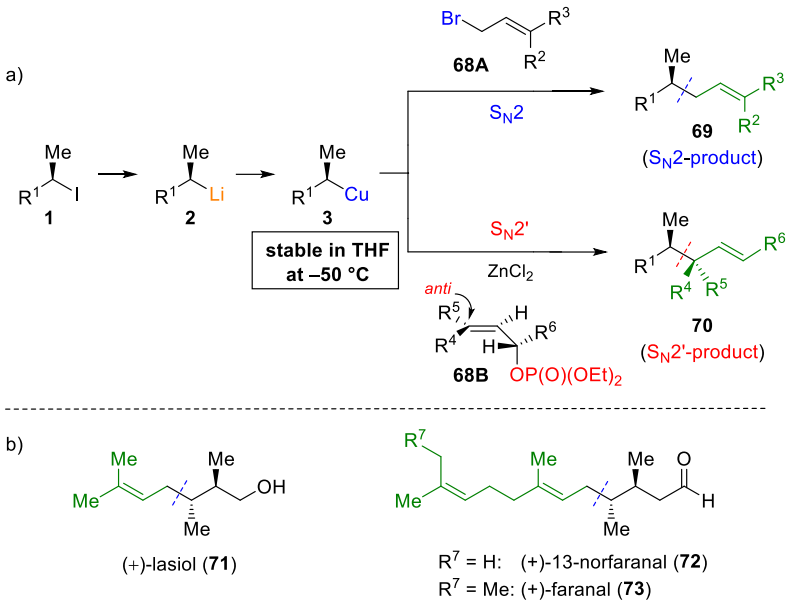
[63] a) M. van Klaveren, E. S. M. Persson, A. del Villar, D. M. Grove, J.-E. Bäckvall, G. van Koten, *Tetrahedron Lett.* **1995**, *36*, 3059−3062. b) A. Alexakis, J. E. Bäckvall, N. Krause, O. Pàmies, M. Diéguez, *Chem. Rev.* **2008**, *108*, 2796−2823. c) M. Pérez, M. Fañanás-Mastral, P. H. Bos, A. Rudolph, S. R. Harutyunyan, B. L. Feringa, *Nat. Chem.* **2011**, *3*, 377–381. d) M. Pérez, M. Fañanás-Mastral, V. Hornillos, A. Rudolph, P. H. Bos, S. R. Harutyunyan, B. L. Feringa *Chem. Eur. J.* **2012**, *8*, 11880–11883. e) V. Hornillos, S. Guduguntla, M. Pérez, M. Fañanás-Mastral, P. H. Bos, A. Rudolph, S. R. Harutyunyan, B. L. Feringa *Nat. Protoc.* **2017**, *12*, 493–505. f) S. S. Goth, S. Guduguntla, T. Kikuchi, M. Lutz, E. Otten, M. Fujita, B. L. Feringa, *J. Am. Chem. Soc.* **2018**, *140*, 7052–7055.

[64] a) T. Ibuka, H. Habashita, A. Otaka, N. Fujii, Y. Oguchi, T. Uyehara, Y. Yamamoto, *J. Org. Chem.* **1991**, *56*, 4370–4382. b) B. Breit, P. Demel, *Tetrahedron* **2000**, *56*, 2833–2846. c) H. Malda, A. W. Van Zijl, L. A. Arnold, B. L. Feringa, *Org. Lett.* **2001**, *3*, 1169–1171. d) C. A. Cullis, H. Mizutani, K. E. Murphy, A. H. Hoveyda, *Angew. Chem. Int. Ed.* **2001**, *40*, 1456–1460. e) N. Harrington-Frost, H. Leuser, M. I. Calaza, F. F. Kneisel, P. Knochel, *Org. Lett.* **2003**, *5*, 2111–2114. f) M. I. Calaza, E. Hupe, P. Knochel, *Org. Lett.* **2003**, *5*, 1059–1061. g) D. Soorukram, P. Knochel, *Org. Lett.* **2004**, *6*, 2409–2411. h) B. Breit, P. Demel, C. Studte, *Angew. Chem. Int. Ed.* **2004**, *43*, 3786–3789. i) J. E Campbell, A. H. Hoveyda, *J. Am. Chem. Soc.* **2004**, *126*, 11130–11131. j) H. Leuser, S. Perrone, F. Liron, F. F. Kneisel, P. Knochel, *Angew. Chem. Int. Ed.* **2005**, *44*, 4627–4631. k) D. Soorukram, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 3686–3689. l) C. Falciola, K. Tissot-Croset, A. Alexakis, *Angew. Chem. Int. Ed.* **2006**, *45*, 5995–5998. m) S. Perrone, P. Knochel, *Org. Lett.* **2007**, *9*, 1041–1044.

[65] a) H. A. Lloyd, T. H. Jones, A. Hefetz, J. Tengç, *Tetrahedron Lett.* **1990**, *31*, 5559–5562. b) A. A. Vasil'ev, O. Vielhauer, L. Engman, M. Pietzsch, E. P. Serebtyakov, *Russ. Chem. Bull.* **2002**, *51*, 481–487. c) A. W. Van Zijl, W. Szymanski, F. Lopez, A. J. Minnaard, B. L. Feringa, *J. Org. Chem.* **2008**, *73*, 6994–7002. d) J. Zhao, K. Burgess, *J. Am. Chem. Soc.* **2009**, *131*, 13236–13237.

[66] L. Poppe, L. Novak, P. Kolonits, A. Bata, C. Szantay, *Tetrahedron* **1988**, *44*, 1477–1487.

[67] a) S.-Y. Wei, K. Tomooka, T. Nakai, *Tetrahedron* **1993**, *49*, 1025–1042. b) K. Mori, N. Murata, *Liebigs Ann.* **1995**, 2089–2092. c) T. Okochi, K. Mori, *Eur. J. Org. Chem.* **2001**, 2145–2150. c) B. Ter Horst, B. L. Feringa, A. J. Minnaard, *Chem. Commun.* **2010**, *46*, 2535–2547.

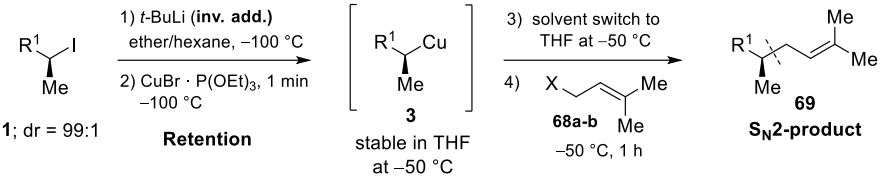


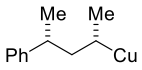
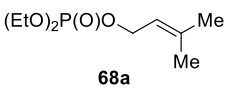
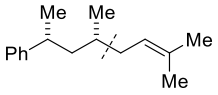
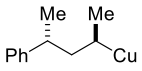
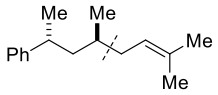
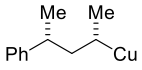
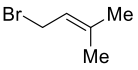
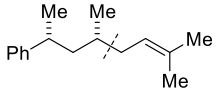
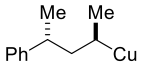
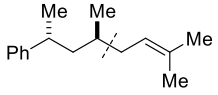
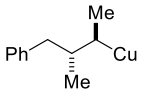
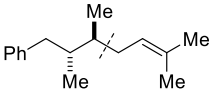
Scheme 28: a) Stereoselective allylic substitutions of chiral secondary alkylcopper reagents **3**. b) Insect pheromones **71**-**73**.

1.2 Regioselective S_N2-Substitution Reactions

As shown in Table 1, we converted *syn*-alkyl iodide *syn*-**1a** (dr = 2:98) to the corresponding alkylcopper *syn*-**3a** by performing an I/Li-exchange with *t*-BuLi in diethyl ether/hexane (2.5 equiv, –100 °C, 10 s) followed by a transmetalation with CuBr·$P(OEt)_3$ (2.0 equiv, –100 °C, 1 min). Treatment with allylic phosphate **68a** (3.0 equiv, –50 °C, 1 h) provided the S_N2-product (*syn*-**69a**) in 47% yield, but with moderate regioselectivity (S_N2/S_N2' = 80:20, dr = 10:90). After extensive experimentation, we found that removing the solvent of **3a** after its formation and replacing it by THF at –50 °C led to a configurationally stable secondary alkylcopper reagent, which reacted with **68a** with improved regio- and stereoselectivity (S_N2/S_N2' = 95:5; dr = 5:95; 56% yield; entry 1, Table 1). Similarly, the *anti*-alkyl copper reagent *anti*-**3a** furnished, under the same conditions, the *anti*-alkene *anti*-**69a** in 58% yield (S_N2/S_N2' = 96:4; dr = 95:5; entry 2). Upon replacing the phosphate **68a** with prenyl bromide (**68b**) the S_N2/S_N2' ratio was further improved (S_N2/S_N2' >99:1; entries 3 and 4). Also, the *anti*-1,2-dimethyl-substituted alkylcopper reagent *anti*-**3b** reacted with **68b** with retention of configuration, affording the alkene *anti*-**69b** (S_N2/S_N2' >99:1; dr = 98:2; entry 5).

Table 1: Diastereoselective synthesis of alkenes **69** by allylic S_N2-substitution of secondary alkylcopper species **3** with allylic phosphate **68a** and bromide **68b**.



entry	alkylcopper	electrophile	product[a]	S_N2/S_N2'
1[b]	 *syn*-**3a**	 **68a**	 *syn*-**69a**; 56%, dr = 5:95	95:5
2	 *anti*-**3a**	**68a**	 *anti*-**69a**; 58%, dr = 95:5	96:4
3[c]	 *syn*-**3a**	 **68b**	 *syn*-**69a**; 60%, dr = 3:97	>99:1
4	 *anti*-**3a**	**68b**	 *anti*-**69a**; 63%, dr = 98:2	>99:1
5	 *anti*-**3b**	**68b**	 *anti*-**69b**; 73%, dr = 98:2	>99:1

[a] The diastereoselectivity (dr; *anti*/*syn* ratio) and the regioselectivity (S_N2/S_N2') was determined by ^{1}H-NMR spectroscopy and GC analysis. [b] without solvent switch: S_N2/S_N2' = 80:20, dr = 10:90, 47% yield. [c] without solvent switch: S_N2/S_N2' = 95:5, dr = 8:92, 56% yield.

1.3 Regioselective S_N2'-Substitution Reactions

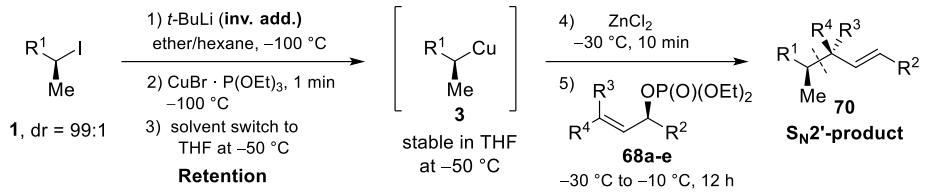
As previously shown,[64] the presence of zinc salts strongly favors the *anti*-S_N2' allylic substitution. Therefore, we added $ZnCl_2$ (1.5 equiv) to the secondary alkylcopper reagents **3** to prepare the corresponding copper-zinc reagents [RCu·ZnX_2·L] (X = Br, Cl; L = $P(OEt)_3$) *in situ*. These new organometallics enabled the performance of highly selective *anti*-S_N2'-substitutions with chiral allylic phosphates.[68]

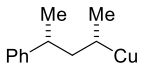
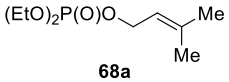
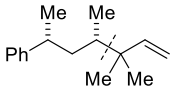
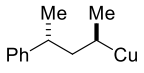
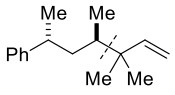
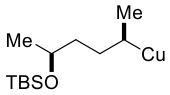
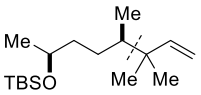
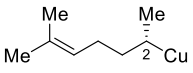
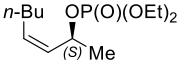
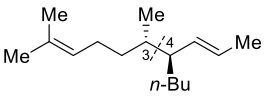
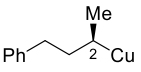
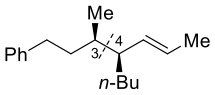
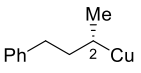
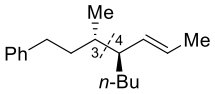
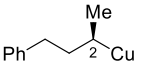
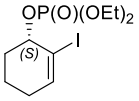
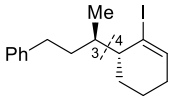
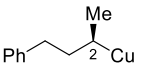
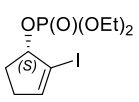
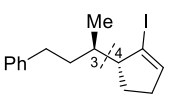
Treatment of the copper species *syn*-**3a** with $ZnCl_2$ (–30 °C, 10 min) followed by the addition of prenyl phosphate (**68a**, –30 °C to –10 °C, 12 h) afforded the S_N2'-product *syn*-**70a** in 54% yield (S_N2/S_N2' = 5:95, dr = 5:95; entry 1, Table 2). Starting from the *anti*-alkylcopper species *anti*-**3a**, the terminal alkene *anti*-**70a** was obtained in 58% yield (S_N2/S_N2' = 8:92, dr = 95:5; entry 2). Similarly, the *syn*-OTBS-substituted alkylcopper derivative *syn*-**3d** reacted with **68a** leading to the expected S_N2'-product *syn*-**70b** in 59% yield (S_N2/S_N2' = 9:91, dr = 9:91; entry 3).

Furthermore, the optically enriched secondary alkylcopper (*S*)-**3e** underwent an *anti*-S_N2'-substitution with the chiral allylic phosphate **68c** (99% *Z*, 99% *ee*)[64e,j,m] leading to 3*S*,4*S*-**70c** in 53% yield (S_N2/S_N2' <1:99, dr = 95:5, 99% *ee*; entry 4). Starting with the enantiomerically pure alkylcopper species (*R*)-**3f** and (*S*)-**3f**, the alkenes 3*R*,4*S*-**70d** (S_N2/S_N2' <1:99, dr = 10:90; entry 5) and 3*S*,4*S*-**70d** (S_N2/S_N2' <1:99, dr = 90:10; entry 6) were obtained in 56% and 54% yield. Chiral cycloallylic phosphates[64f,g,k], such as **68d** and **68e**, also underwent *anti*-S_N2'-substitutions with (*R*)-**3f** leading to the chiral cyclo-alkenyl iodides, 3*R*,4*R*-**70e** and 3*R*,4*R*-**70f**, in 59% and 54% yield (dr = 90:10; entries 7 and 8).

[68] Allylic bromides were less selective (S_N2/S_N2' = 30:70) and allylic pentafluorobenzoates almost gave no substitution product.

Table 2: Diastereoselective synthesis of alkenes **70** by allylic S_N2'-substitutions of chiral secondary alkylcopper reagents **3** with allylic phosphates **68**.

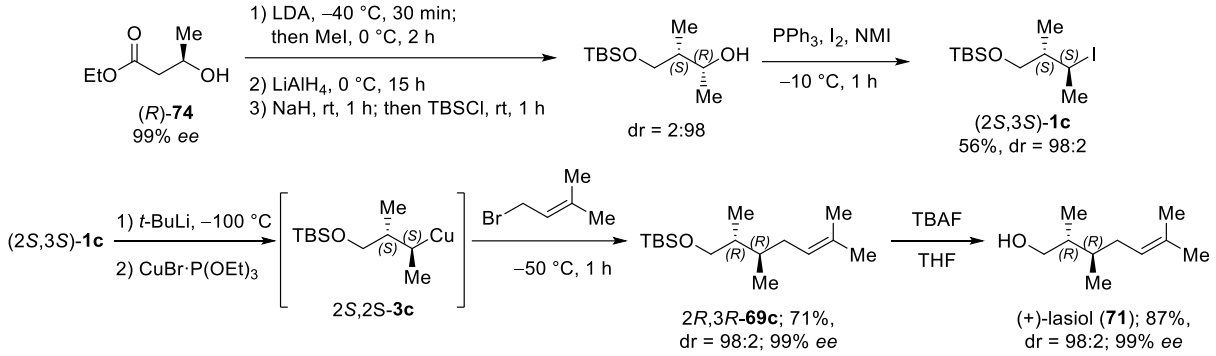


entry	alkylcopper	electrophile	product[a]	S_N2/S_N2'
1	 *syn*-**3a**	 **68a**	 *syn*-**70a**; 54%, dr = 5:95	5:95
2	 *anti*-**3a**	**68a**	 *anti*-**70a**; 58%, dr = 95:5	8:92
3	 *syn*-**3d**	**68a**	 *syn*-**70b**; 59%, dr = 9:91	9:91
4	 (*S*)-**3e**	 **68c** (99% *ee*[b])	 3*S*,4*S*-**70c**; 53%, dr = 95:5, 99% *ee*	<1:99
5	 (*R*)-**3f**	**68c**	 3*R*,4*S*-**70d**; 56%, dr = 10:90, 99% *ee*	<1:99
6	 2*S*-**3f**	**68c**	 3*S*,4*S*-**70d**; 54%, dr = 90:10, 99% *ee*	<1:99
7[b]	 (*R*)-**3f**	 **68d** (99% *ee*)	 3*R*,4*R*-**70e**; 59%, dr = 90:10, 99% *ee*[b]	<1:99
8	 (*R*)-**3f**	 **68e** (99% *ee*)	 3*R*,4*R*-**70f**; 54%, dr = 90:10, 99% *ee*	<1:99

[a] The diastereoselectivity (dr; *anti*/*syn* ratio) and the regioselectivity (S_N2/S_N2') was determined by ^{1}H-NMR spectroscopy and GC analysis. [b] The enantiomeric excess was determined by chiral GC analysis (for details: see the Experimental Part).

1.4 Total Synthesis of (+)-Lasiol

Finally, alkylcopper reagent 2*S*,3*S*-**3c**[56,61] underwent a highly selective S_N2-substitution with **68b** leading to the chiral protected alcohol 2*R*,3*R*-**69c** in 71% yield (S_N2/S_N2' >99:1, dr = 98:2, 99% *ee*; see Scheme 29). After TBS-deprotection using TBAF, the pheromone (+)-lasiol (**71**) was obtained in 87% yield (dr = 98:2, 99% *ee*[69]; 6 steps, 21% overall yield starting from (*R*)-3-hydroxybutyrate *R*-**74**)).

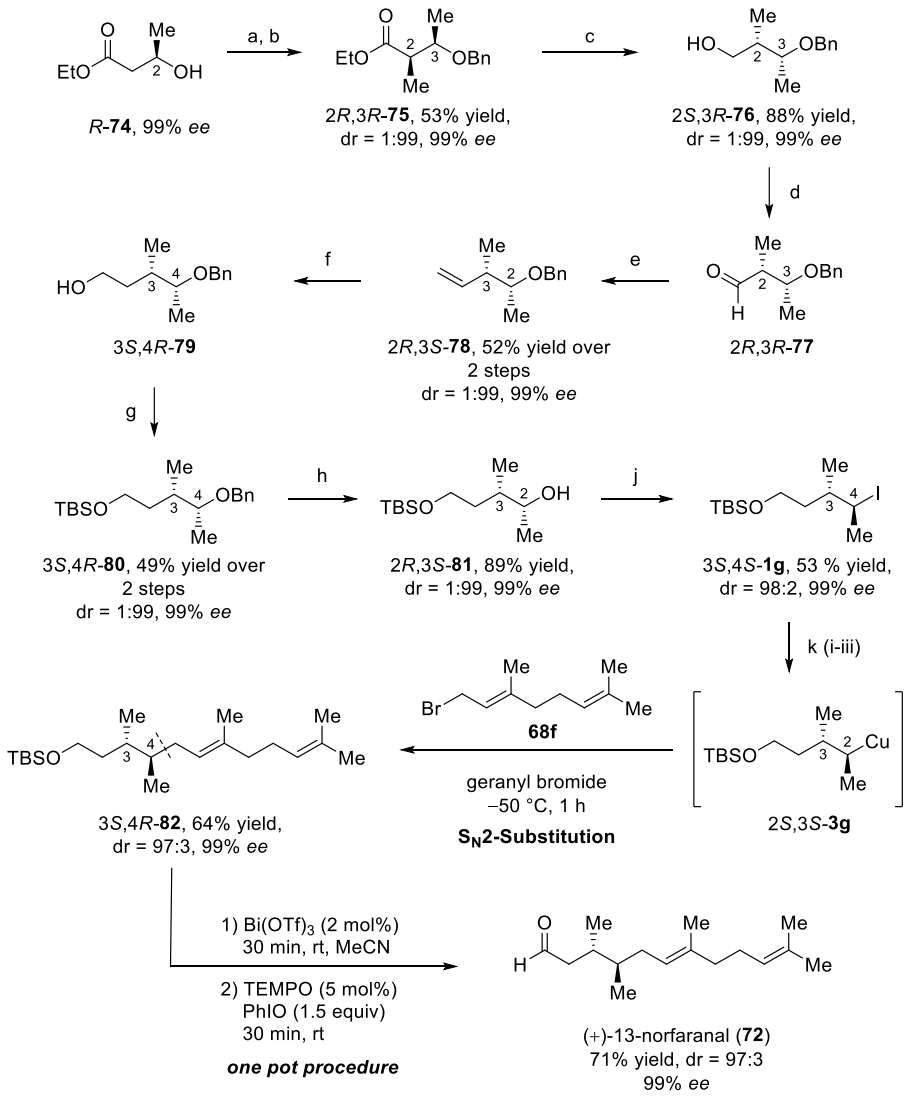


Scheme 29: Stereoselective preparation of the ant pheromone (+)-lasiol (**71**).

1.5 Total Synthesis of (+)-13-Norfaranal

Next, we used this allylic substitution for the preparation of ant pheromones, (+)-13-norfaranal (**72**) and (+)-faranal (**73**; Scheme **28**b). Thus, ethyl (*R*)-hydroxybutyrate (*R*-**74**, 99% *ee*; Scheme 30) was selectively methylated[70] and O-benzylation led to the protected ester 2*R*,3*R*-**75** in 53% yield over two steps (dr = 1:99, 99% *ee*). After $LiAlH_4$-reduction of 2*R*,3*R*-**75** (leading to 2*S*,3*R*-**76**, 88% yield, dr = 1:99, 99% *ee*), Swern oxidation (leading to 2*R*,3*R*-**77**) and Wittig olefination with $Ph_3P{=}CH_2$, the terminal alkene 2*R*,3*S*-**78** was isolated in 52% yield (dr = 1:99, 99% *ee*).

[69] The enantiomeric excess was determined by converting the alcohol into the corresponding Mosher-esters (for details, see the Experimental Part)
[70] K. Micoine, A. Fürstner, *J. Am. Chem. Soc.* **2010**, *132*, 14064–14066



Scheme 30: Enantioselective synthesis of the iodide 3*S*,4*S*-**1g** and subsequent S_N2-substitution reaction leading to (+)-13-norfaranal (**72**). Reagents and conditions: a) LDA, HMPA-THF, –40 °C, 30 min; then MeI, 0 °C, 2 h. b) benzyl 2,2,2-trichloroacetimidate, triflic acid, hexane, rt, 10 h. c) $LiAlH_4$, THF, 0 °C to rt, 15 h. d) oxalyl chloride, DMSO, NEt_3, DCM, –10 °C, 10 min. e) *n*-BuLi, Ph_3PCH_3Br, THF, rt, 10 h. f) BH_3·THF, diethyl ether, rt, 12 h; then $NaOH/H_2O_2$, 2.5 h g) imidazole, TBSCl, DCM, rt, 10 h. h) lithium naphthalenide, THF, 0 C to rt, 1 h. j) PPh_3, I_2, NMI, DCM, –10 °C, 1 h. (k) (i) *t*-BuLi, inverse addition, diethyl ether/hexane (2:3), –100 °C, 1 min. (ii): CuBr·$P(OEt)_3$, diethyl ether/hexane, –100 °C, 1 min. (iii) solvent switch to THF at –50 °C.

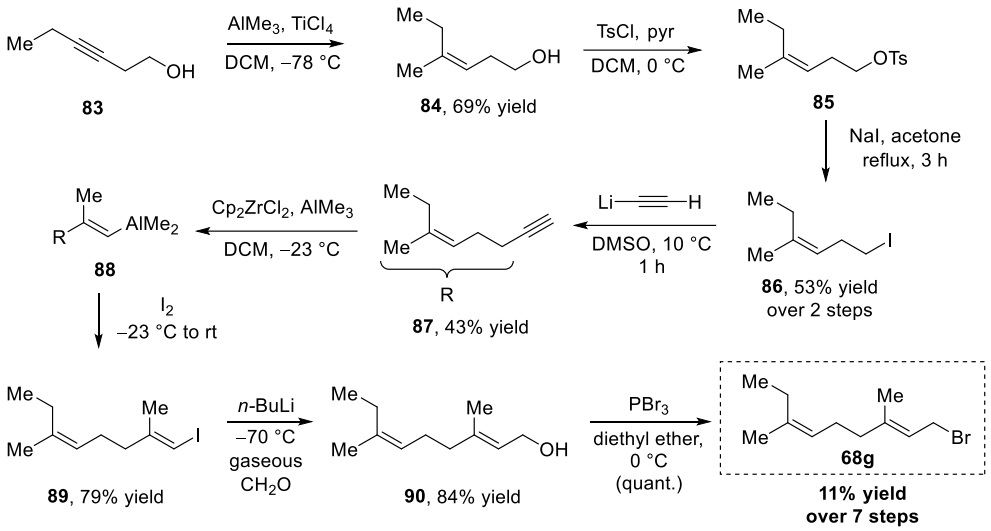
Hydroboration of 2*R*,3*S*-**78** using BH_3·THF[71] and a subsequent oxidative quench led to the primary alcohol 3*S*,4*R*-**79**, which was protected as *tert*-butylsilyl ether 3*S*,4*R*-**80** in 49% yield over two steps (dr = 1:99, 99% *ee*). After reductive debenzylation of 3*S*,4*R*-**80** with lithium naphthalenide,[72] the *syn*-alcohol 2*R*,3*S*-**81** was obtained in 89% yield (dr = 1:99, 99% *ee*[73]). Finally, the *syn*-alcohol 2*R*,3*S*-**81**

[71] S. Honzawa, N. Takahashi, A. Yamashita, T. Sugiura, M. Kurihara, M. A. Arai, S. Kato, A. Kittaka, *Tetrahedron* **2009**, *65*, 7135–7145.
[72] G. Sabitha, K. Yadagiri, M. Bhikshapathi, G. Chandrshekhar, J. S. Yadav, *Tetrahedron: Asymmetry* **2010**, *21*, 2524–2529.
[73] The enantiomeric excess was determined by converting the alcohol into the corresponding Mosher-esters (for details see the Experimental Part).

was converted into the *anti*-iodide 3*S*,4*S*-**1g** in 53% yield (dr = 98:2, 99% *ee*). The THF stable secondary alkylcopper 2*S*,3*S*-**3g** was obtained by I/Li-exchange reaction and transmetalation. Subsequent quenching of 2*S*,3*S*-**3g** with freshly prepared geranyl bromide[74] (**68**f) led to the coupling product 3*S*,4*R*-**82** (64% yield, dr = 97:3, 99% *ee*). After one-pot $Bi(OTf)_3$-catalyzed oxidative deprotection[75] of the TBS ether 3*S*,4*R*-**82**, the pheromone (+)-13-norfaranal (**72**) was isolated in 71% yield (dr = 97:3, 99% *ee*; 11 steps, 2.6% overall yield starting from (*R*)-**74**).

1.6 Total Synthesis of (+)-Faranal

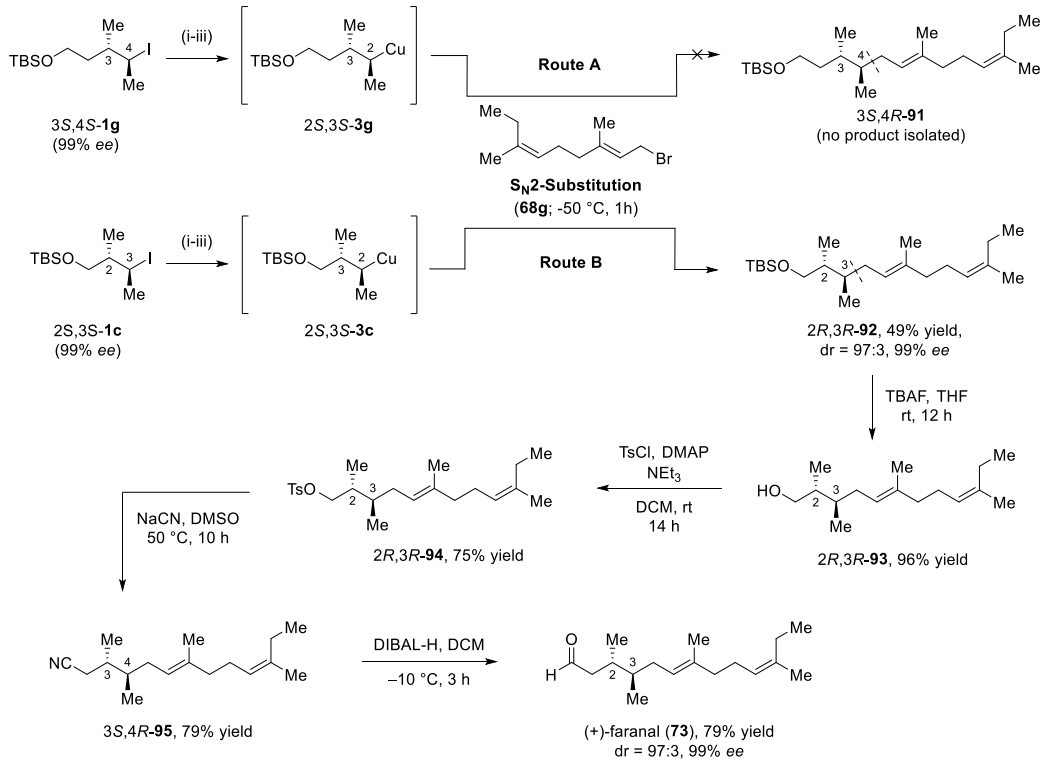
For the enantioselective synthesis of the pharaoh ant's trail pheromone, (+)-faranal **73**, the allylic bromide **68g** (Scheme 31) was prepared according to a modified literature procedure.[76]



Scheme 31: Synthesis of the geranyl derivative **68g**.

Therefore, the alcohol **83** was converted after titanium-mediated carbometalation (leading to **84** in 69% yield),[76a] tosylation (leading to **85**) and a Finkelstein reaction into the iodide **86** (53% yield over 2 steps). The reaction of **86** with lithium acetylide gave the alkyne **87** in 43% yield. The zirconium-catalyzed carbo-alumination of **87** led to the intermediate alane **88**, which afforded the iododiene **89** in 79% yield after iodination.[67b] Subsequent I/Li-exchange with *n*-BuLi followed by reaction with gaseous formaldehyde furnished the allylic alcohol **90** in 84% yield.[76b] After bromination of **90** with PBr_3[77] in quantitative yield, the geranyl derivative **68g** was isolated in 11% overall yield.

[74] The use of commercially available geranyl bromide led to a lower yield and lower diastereoselectivity.
[75] B. Barnych, J.-M. Vatèle, *Synlett* **2011**, *14*, 2048–2052.
[76] a) T.-S. Mei, H. H. Patel, M. S. Sigman, *Nature* **2014**, *508*, 340–344. b) S. Nowotny, C. E. Tucker, C. Jubert, P. Knochel, *J. Org. Chem.* **1995**, *60*, 2762–2772.
[77] S. A. Snyder, D. Treitler, *Angew. Chem. Int. Ed.* **2009**, *48*, 7899–7903.



Scheme 32: Enantioselective S_N2-substitution reaction leading to the trail pheromone (+)-faranal (**73**). (i) *t*-BuLi, inverse addition, diethyl ether/hexane (2:3), –100 °C, 1 min. (ii): $CuBr \cdot P(OEt)_3$, diethyl ether/hexane, –100 °C, 1 min. (iii) solvent switch to THF at –50 °C.

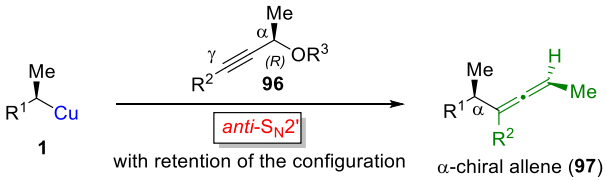
Unfortunately, the reaction of the chiral secondary alkylcopper 2*S*,3*S*-**3g** with the allylic electrophile **68g** did not afford the desired TBS-protected precursor 3*S*,4*R*-**91** of (+)-faranal (Scheme 32). Thus, we modified the synthetic route and the chiral alkylcopper reagent 2*S*,3*S*-**3c** was reacted with **68g** giving the related precursor 2*R*,3*R*-**92** in 49% yield (dr = 97:3, 99% *ee*). The protected alcohol 2*R*,3*R*-**92** was converted to (+)-faranal (**73**) by using literature procedures[78] (45% yield over 4 steps; with dr = 97:3). After TBS-deprotection using TBAF, the alcohol 2*R*,3*R*-**93** was obtained in 96% yield. The tosylation of 2*R*,3*R*-**93** led to 2*R*,3*R*-**94** in 75% yield, which reacted with sodium cyanide to the corresponding nitrile 3*S*,4*R*-**95** in 79% yield. Finally, DIBAL-H (diisobutylaluminium hydride) reduced 3*S*,4*R*-**95** after aqueous workup to the natural product (+)-faranal (**73**) in 79% yield (dr = 97:3, 99% *ee*; 12 steps, 6.9% overall yield starting from (*R*)-**74**).

[78] a) H. Zhai, M. Hrabar, R. Greis, G. Gries, R. Britton, *Chem. Eur. J.* **2016**, *22*, 6190–6193. b) A. A. Vasi'lev, L. Engman, E. P. Serebryakov, *J. Chem. Soc., Perkin Trans. 1*, **2000**, 2211–2216.

2 Stereoselective S_N2'-Reactions of Secondary Alkylcopper Reagents

2.1 Introduction

Allenes are common intermediates in organic synthesis and found in many natural products.[79] They are typically prepared by the substitution reaction of propargylic electrophiles with nucleophiles, for example organocopper reagents.[80] Thereby, these propargylic reagents bear a good leaving group, such as acetates, ethers, epoxides, phosphates or halides.[80-82] Axially chiral allenes are generally prepared from enantioenriched propargylic substrates[81] or by the use of chiral ligands[82]. The chirality transfer from the chiral propargylic substrate to the allene depends on the nature of the electrophile and nucleophile as well as on the solvent and temperature.[79e] However, the enantioselective preparation of axially chiral allenes bearing a stereocenter in α-position ("α-chiral allenes") is rather difficult and only a few examples have been reported.[83] Thereby, the stereochemistry of the α-position results from an asymmetric synthesis using chiral ligands.



Scheme 33: *Anti*-S_N2'-substitution with chiral propargylic phosphates leading to axially chiral allenes.

Herein, we wish to report the *anti*-S_N2'-substitution of secondary alkylcopper reagents **3** with chiral propargylic phosphates **96** leading to α-chiral allenes of type **97** with retention of the configuration (see Scheme 33). Remarkably, this overall *anti*-S_N2'-substitution reaction proceeded directly with the alkylcopper reagent **3** with transfer of chirality from the propargylic substrate **96** to the allene **97**.

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[79] a) Modern Allene Chemistry, Vol. 1 and 2, (Eds.: N. Krause, A. S. K. Hashmi), Wiley-VCH, Weinheim, **2004**. For reviews see: b) A. Hoffmann-Röder, N. Krause *Angew. Chem. Int. Ed.* **2004**, *43*, 1196−1216. c) S. Yu, S. Ma *Angew. Chem. Int. Ed.* **2012**, *51*, 3074−3112. d) R. K. Neff, D. E. Frantz, *ACS Catalysis* **2014**, *4*, 519−528. e) J. Ye, S. Ma, *Org. Chem. Front.* **2014**, *1*, 1210−1224.

[80] a) P. Rona, P. Crabbe, *J. Am. Chem. Soc.* **1968**, *90*, 4733−4734. b) R. S. Brinkmeyer, T. L. Macdonald, *J. C. S., Chem. Comm.* **1978**, 876−877. c) A. C. Oehlschlager, E. Czyzewska, *Tetrahedron Lett.* **1983**, *24*, 5587−5590. d) A. Alexakis, I. Marek, P. Mangeney, J. F. Normant, *Tetrahedron Lett.* **1989**, *30*, 2387−2390. e) A. Alexakis, I. Marek, P. Mangeney, J. F. Normant, *Tetrahedron* **1991**, *47*, 1677−1696. f) J. A. Marshall, K. G. Pinney, *J. Org. Chem.* **1993**, *58*, 7180−7184. g) J. P. Varghese, P. Knochel, I. Marek, *Org. Lett.* **2000**, *2*, 2849−2852.

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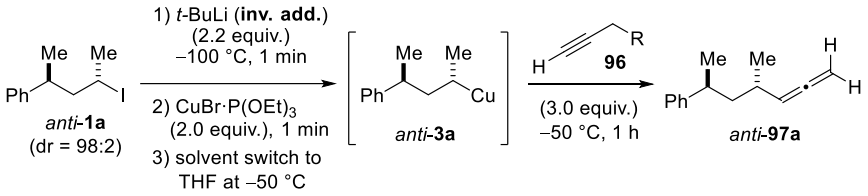
2.2 Preparation of Chiral Allenes

In preliminary experiments, we have optimized the leaving group of the propargylic electrophile for achieving the desired S_N2'-reaction. Thus, we prepared the secondary alkyllithium reagent *anti*-**2a** *via* I/Li-exchange of the corresponding alkyl iodide *anti*-**1a** at –100 °C in *n*-pentane/diethyl ether-mixture (3:2) using *t*-BuLi (2.2 equiv) followed by subsequent treatment with $CuBr{\cdot}P(OEt)_3$ (2.0 equiv) leading to alkylcopper reagent *anti*-**3a** (see Table 3). This alkylcopper reagent was configurationally stable in THF at up to –50 °C and thus, we performed a solvent switch at this temperature.[84] Subsequent addition of the propargylic bromide[85a] (**96a**, 3.0 equiv) furnished only traces of the desired allene *anti*-**97a** (see Table 3; entry 1) after stirring for 1 h at –50 °C. The use of propargylic acetate (**96b**)[85b] showed a similar result (entry 2). Switching to pentafluorobenzoate (**96c**)[85c] or diphenylphosphate (**96d**)[85d] as leaving groups afforded *anti*-**97a** in good yields, but with moderate stereoretention (48-50% yield, dr up to 93:7; entries 3 and 4).

Table 3. Stereoretentive preparation of secondary alkylcopper reagent *anti*-**3a** and subsequent reaction with various propargylic substrates **96** leading to the allene *anti*-**97a**.



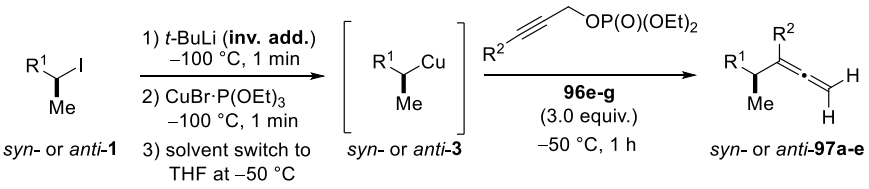
entry	electrophile	yield of *anti*-**97**a (%)[a]	dr of *anti*-**97**a[a]
1	**96a**: R = Br	traces	-
2	**96b**: R = OAc	5%	90:10
3	**96c**: R = $OCOC_6F_5$	48%	91:9
4	**96d**: R = $OP(O)(OPh)_2$	50%	93:7
5	**96e**: R = $OP(O)(OEt)_2$	59%	98:2

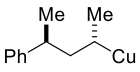
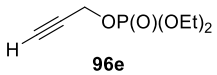
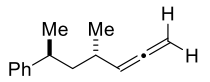
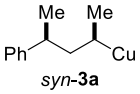
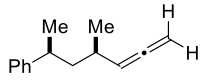
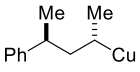
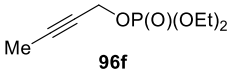
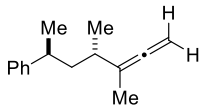
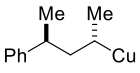
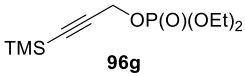
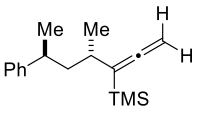
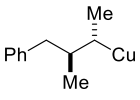
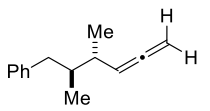
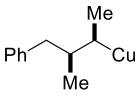
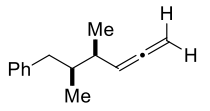
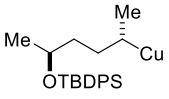
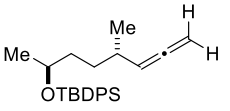
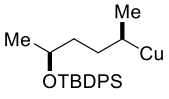
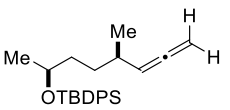
[a] The diastereoselectivity (dr; *anti*/*syn* ratio) was determined by GC-analysis using dodecane as internal standard.

[84] The reactivity and configurational stability are considerably higher in THF. For details, see: J. Skotnitzki, L. Spessert, P. Knochel, *Angew. Chem. Int. Ed.* **2019**, *58*, 1509−1514.

[85] a) Propargyl bromide is commercially available as a solution in toluene. b) Propargyl acetate is commercially available (Sigma-Aldrich). c) N. N. Solodukhin, N. E. Borisova, A. V. Churakov, K. V. Zaitsev, *J. Fluor. Chem.* **2016**, *187*, 15−23. d) J. Eisenblaetter, M. Bruns, U. Fehrenbacher, L. Barner, C. Barner-Kowollik, *Polym. Chem.* **2013**, *4*, 2406−2413. e) M. Hojo, R. Sakuragi, S. Okabe, A. Hosomi, *Chem. Comm.* **2001**, 357−358. For details, see the Experimental Part.

Table 4: Stereoselective preparation of diastereomerically pure allenes **97a-e** starting from alkyl iodides **1a**, **1b**, and **1h**.



entry	alkylcopper	electrophile **96**	product[a]
1	 *anti*-**3a**	 **96e**	 *anti*-**97a**, 55% yield, dr = 98:2
2	 *syn*-**3a**	**96e**	 *syn*-**97a**, 46% yield, dr = 6:94
3	 *anti*-**3a**	 **96f**	 *anti*-**97b**, 65% yield, dr = 97:3
4	 *anti*-**3a**	 **96g**	 *anti*-**97c**, 61% yield,[b] dr = 75:25
5	 *anti*-**3b**	**96e**	 *anti*-**97d**, 58% yield, dr = 98:2
6	 *syn*-**3b**	**96e**	 *syn*-**97d**, 42% yield, dr = 6:94
7[b]	 *anti*-**3h**	**96e**	 *anti*-**97e**, 50% yield, dr = 95:5
8	 *syn*-**3h**	**96e**	 *syn*-**97e**, 44% yield, dr = 4:96

[a] The diastereoselectivity (dr; *anti*/*syn* ratio) was determined by ^{1}H- or ^{13}C-NMR analysis. [b] The yield was determined by GC-analysis using dodecane as internal standard.

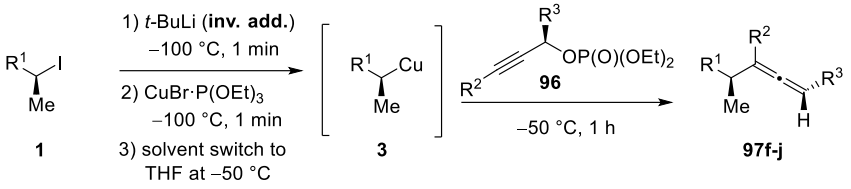
However, using the propargylic diethyl phosphate **96e**[85e] as electrophile significantly increased the stereoretention at the secondary alkylcopper center (*anti*-**97a**, 59% yield, dr = 98:2). The same reaction

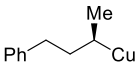
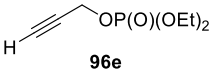
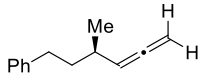
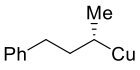
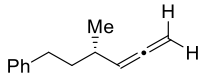
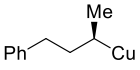
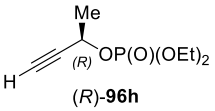
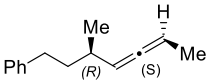
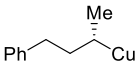
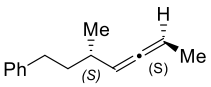
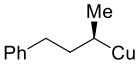
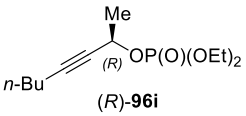
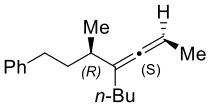
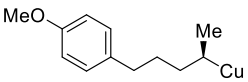
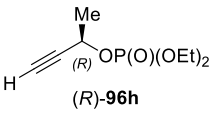
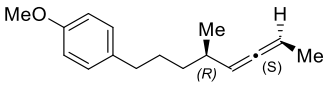
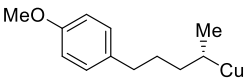
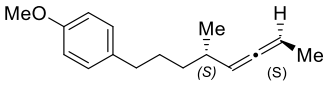
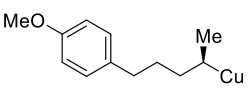
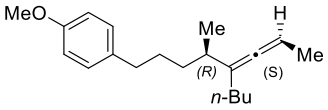
afforded *anti*-**97a** in only 40% yield and dr = 92:8 when no solvent switch was performed, demonstrating the necessity of THF as solvent. With these results in hand, we have performed stereoselective reactions with various diastereomerically pure alkyl iodides *syn*- or *anti*-**1a-d** and propargylic phosphates **96e-g** leading to allenes **97a-e** in 42-65% yield and with dr higher than 95:5 (see Table 4). In most cases, a high retention of configuration was observed. However, using the TMS-substituted propargylic phosphate **96g** as electrophile led to allene *anti*-**97c** in 61% yield with moderate diastereoselectivity (dr = 75:25; entry 4). The reaction of *anti*-**3a** with the propargylic phosphate **96f**, which contains a terminal methyl-group, led to the methyl-substituted allene *anti*-**97b** in 65% yield and dr = 97:3 (see Table 4; entry 3). Furthermore, the 1,2-substituted secondary alkylcopper reagents *anti*- and *syn*-**3b** reacted with **96e** to the corresponding allenes *anti*-**97d** (58% yield, dr = 98:2; entry 5) and *syn*-**97d** (42% yield, dr = 6:94; entry 6). The OTBS-substituted allenes *anti*-**97e** (50% yield, dr = 95:5; entry 7) and *syn*-**97e** (44% yield, dr = 4:96; entry 8) were prepared with high retention of configuration as well.

In addition, this *anti*-selective substitution was extended to optically enriched alkylcopper reagents **3f,i** (see Table 5). Thus, the reaction of the secondary alkylcopper reagent (*R*)-**3f** with propargylic phosphate **96e** furnished (*R*)-**97f** in 41% yield and er = 7:93 (see Table 5; entry 1). Analogously, the corresponding (*S*)-enantiomer (*S*)-**97f** was prepared in 48% yield and er = 90:10 (entry 2). To our delight, chiral alkylcopper reagents reacted also with higher substituted chiral propargylic phosphates **96h-i** leading to axially chiral allenes bearing a stereocenter in the α-position (see Table 5; entries 3-8). Thus, the reaction of the alkylcopper (*R*)-**3f** with enantioenriched propargylic phosphate (*R*)-**96h**, prepared from the corresponding 3-butyn-2-ol,[86] led to the α-chiral disubstituted allene (*R*,*S*)-**97g**[87] in 43% yield with high *anti*-S_N2'-substitution ratio (dr = 92:8; er = 99:1, entry 3). Similarly, the allene (*S*,*S*)-**97g** was prepared from organocopper (*S*)-**3f** and the chiral phosphate (*R*)-**96h** in 49% yield (dr = 12:88; er = 99:1;[87] entry 4). Moreover, (*R*)-oct-3-yn-2-yl diethyl-phosphate (*R*)-**96i** was prepared according to literature from the corresponding optically enriched propargylic alcohol.[58,81e,88] Subsequent reaction of alkylcopper (*R*)-**3f** with phosphate (*R*)-**96i** furnished the α-chiral trisubstituted allene (*R*,*S*)-**97h** in 59% yield (dr = 91:9, er = 99:1; entry 5). It was also possible to convert the methoxy-substituted secondary alkyl iodide (*R*)- and (*S*)-**1i** to the corresponding alkylcopper reagents (*R*)- and (*S*)-**3i** after reaction with (*R*)-**96h** the α-chiral disubstituted allenes (*R*,*S*)-**97i** (52% yield, dr = 93:7, er = 99:1; entry 6) and (*S*,*S*)-**97i** (54% yield, dr = 12:88, er = 99:1; entry 7) were obtained. Furthermore, the reaction of (*R*)-**3I** with (*R*)-**96i** led to the trisubstituted allene (*R*,*S*)-**97j** in 51% yield and good diastereoselectivity (dr = 92:8, er = 99:1; entry 8). Unfortunately, the preparation of tertiary propargylic phosphates was unsuccessful although the subsequent preparation of axially chiral tetrasubstituted allenes would have been of high interest for organic synthesis.

[86] (*R*)-(+)-3-Butyn-2-ol is commercially available (TCI; er >99:1).
[87] The enantiomeric ratio was determined by chiral GC analysis or chiral HPLC analysis. For details, see the Experimental Part.
[88] The enantiomeric ratio was determined by chiral GC analysis. For details, see reference 58.

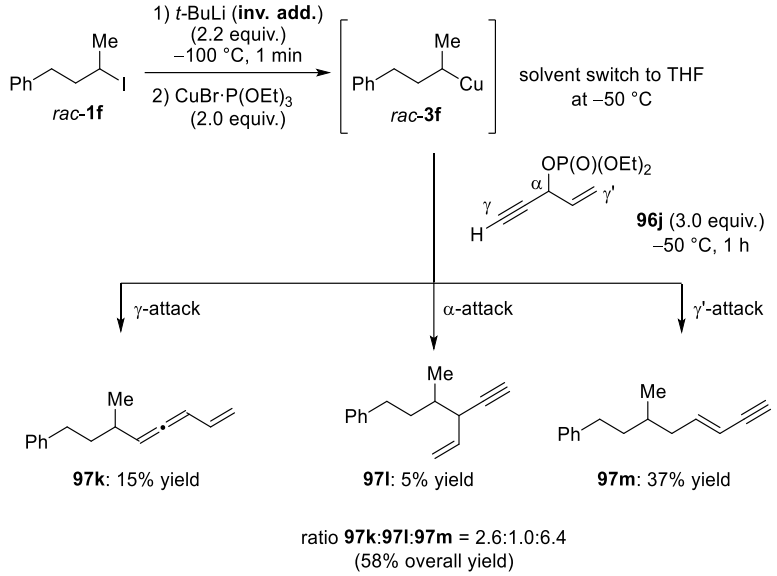
Table 5: Stereoretentive preparation of chiral allenes **97f-j** *via anti*-S_N2'-substitution reaction of chiral alkylcopper reagents **3f** and **3i** with propargylic phosphates **96e**, (*R*)-**96h** and (*R*)-**96i**.



entry	chiral alkylcopper	electrophile **96**	product of type **97**[a],[b]
1	 (*R*)-3f	 **96e**	 (*R*)-**97f**, 41% yield, er = 7:93
2	 (*S*)-**3f**	**96e**	 (*S*)-**97f**, 48% yield, er = 90:10
3	 (*R*)-3f	 (*R*)-**96h** (er = 99:1)	 (*R*,*S*)-**97g**, 43% yield (dr = 92:8; er = 99:1)
4	 (*S*)-**3f**	(*R*)-**96h** (er = 99:1)	 (*S*,*S*)-**97g**, 49% yield, (dr = 12:88; er = 99:1)
5	 (*R*)-3f	 (*R*)-**96i** (er = 99:1)	 (*R*,*S*)-**97h**, 59% yield, (dr = 91:9; er = 99:1)
6	 (*R*)-**3i**	 (*R*)-**96h** (er = 99:1)	 (*R*,*S*)-**97i**, 52% yield, (dr = 93:7; er = 99:1)
7	 (*S*)-**3i**	(*R*)-**96h** (er = 99:1)	 (*S*,*S*)-**97i**, 54% yield, (dr = 12:88; er = 99:1)
8	 (*R*)-**3i**	(*R*)-**96i** (er = 99:1)	 (*R*,*S*)-**97j**, 51% yield, (dr = 92:8; er = 99:1)

[a] The diastereoselectivity (dr; *anti*/*syn* ratio) was determined by ^{1}H- or ^{13}C-NMR analysis. [b] The enantiomeric ratio (er) was determined by chiral GC-analysis.

To get a better understanding of the regioselectivity, we prepared the racemic phosphate **96j**, which contains a propargylic and allylic moeity (see Scheme 34).[89] The nucleophilic organocopper reagent *rac*-**3f** can undergo a substitution either in the α-position (S_N2-substitution of the phosphate), the γ-position (S_N2'-attack on the propargylic site) or γ'-position (S_N2'-attack on the allylic site). Interestingly, the reaction of **3f** with **96j** afforded the allene **97k**, the S_N2-product **97l** and the alkene **97m** in 58% yield[90] with a ratio of 2.6:1.0:6.4 = γ:α:γ'. This selectivity could be explained by steric hindrance of the α-position and favoured direct S_N2'-substitution of the allylic phosphate (γ'-position) compared to the propargylic moiety (γ-position).



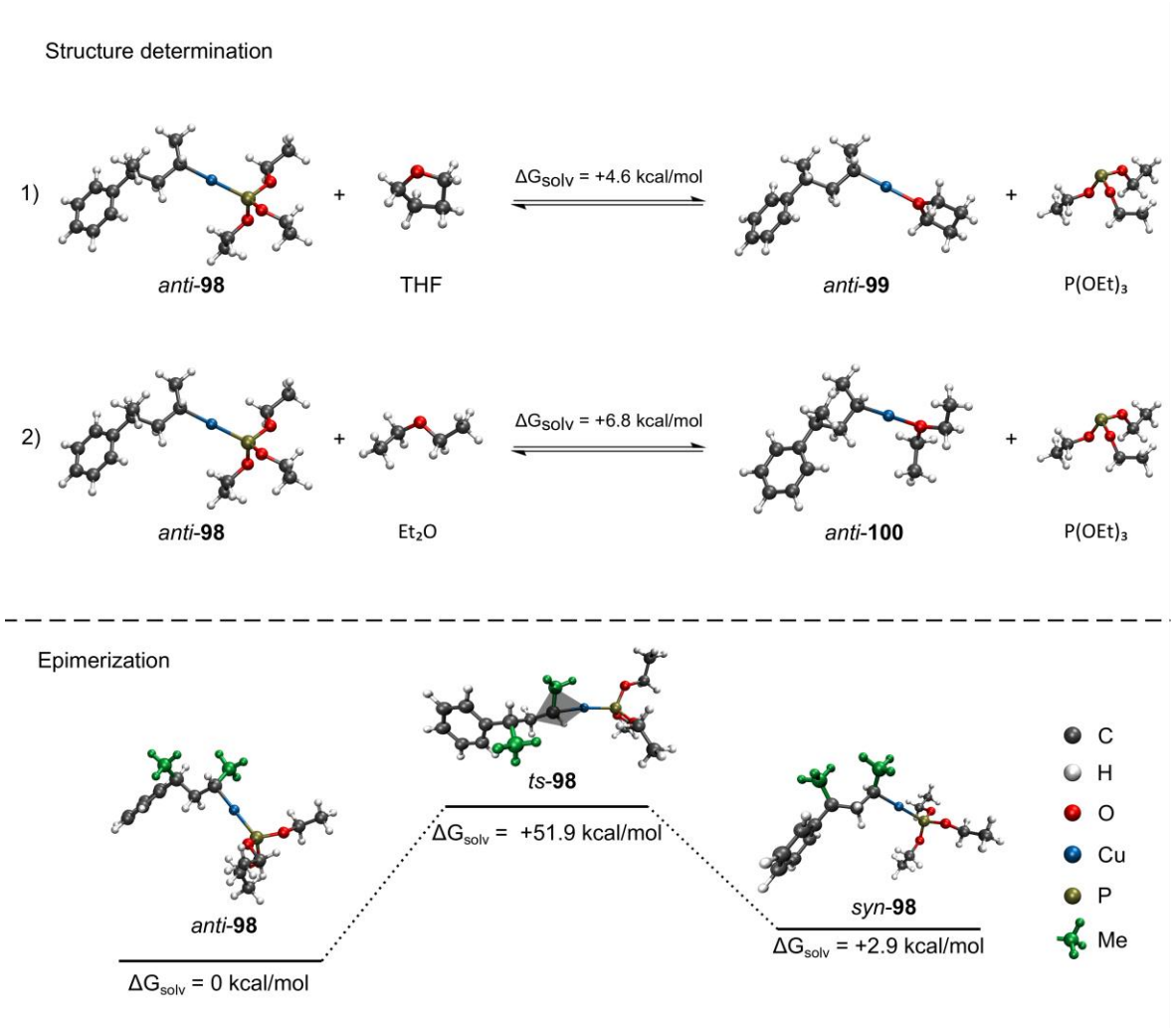
Scheme 34: Regioselective addition of secondary alkylcopper reagent **3f** to allylic and propargylic moiety containing phosphate **96j**.

2.3 Computational Calculations

Furthermore, DFT-calculations were performed to rationalize the high configurational stability of these chiral secondary alkylcopper reagents.[91] Solvation effects were accounted for by the Polarizable Continuum Model (PCM).[92] First, we determined the structure of secondary alkylcopper reagent *anti*-**3a** in solution. Thus, we calculated the free energies of *anti*-**3a** with coordination to all possible ligands, namely triethyl phosphite ($P(OEt)_3$; *anti*-**98**), tetrahydrofuran (THF; *anti*-**99**) and diethyl ether (Et_2O; *anti*-**100**; see Scheme 35, (1-2)).[93] These calculations emphasized that *anti*-**98** is the thermodynamically most stable structure. Comparison of the free energies of *anti*-**98** with the free energies of *anti*-**99** showed that the coordination to $P(OEt)_3$ is thermodynamically more stable (ΔG = +4.6 kcal/mol; see

[89] A. Czepa, T. Hofmann, *J. Agric. Food Chem.* **2004**, *52*, 4508−4514.
[90] The yield was determined by GC-analysis using dodecane as internal standard.
[91] This project was realized in cooperation with D. Keefer and F. Schueppel, who conducted and analyzed the DFT-calculations.
[92] a) M. J. Frisch *et al.* Gaussian16 Revision B.01, **2016**. b) for details of calculations, see the Experimental Part.
[93] Coordination of more than one solvent molecule decreased the free energy. For details, see the Experimental Part.

Scheme 35, (1)).[94] Similar results were obtained for the substitution of $P(OEt)_3$ with Et_2O (ΔG = +6.8 kcal/mol, (2)) showing again the high affinity of phosphor to copper. The direct comparison of *anti*-**99** and *anti*-**100** shows that the THF coordinated structure **99** is 3.9 kcal/mol more stable compared to the Et_2O coordinated structure **100**. In addition, the bond energies and bond lengths of the carbon-copper bond for *anti*-**98** (53.9 kcal/mol, 198.5 pm), *anti*-**99** (51.3 kcal/mol, 195.9 pm) and *anti*-**100** (50.6 kcal/mol, 195.8 pm) were determined showing that the carbon-copper bond is most stable when the copper is coordinated to $P(OEt)_3$.[94] Comparison of the free energies of *anti*-**98** and *syn*-**98** showed that the *anti*-isomer is thermodynamically more stable (ΔG = +2.9 kcal/mol; see Scheme 35). This result is in agreement with previous reported findings.[95]



Scheme 35: Theoretical calculations for the structure determination of *anti*-**3a** and the epimerization of secondary alkylcopper reagent *anti*-**98** to *syn*-**98**.

[94] A detailed description of the theoretical methodology, along with optimized structures and energies of all investigated compounds can be found in the the Experimental Part.
[95] J. Skotnitzki, A. Kremsmair, D. Keefer, Y. Gong, R. de Vivie-Riedle, P. Knochel, *Angew. Chem. Int. Ed.* **2020**, *59*, 320–324.

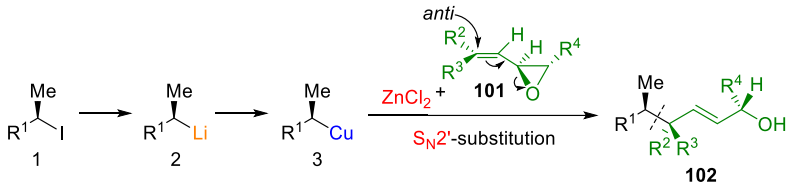
Next, we investigated the epimerization of *anti*-**98** to the corresponding *syn*-isomer *syn*-**98** *via* cleavage of the carbon-copper bond or a planar transition state *ts*-**98** (see Scheme 35). The high carbon-copper bond energy of 54.0 kcal/mol as well as the transition state energy of 51.9 kcal/mol corroborate the high stability of *anti*-**98** towards epimerization at –50 °C. However, the slight epimerization of the secondary alkylcopper reagents may be due to polymolecular exchange reactions between these copper reagents.

3 Stereoselective S_N2'-Reactions of Secondary Alkylcopper-Zinc Reagents

3.1 Introduction

Metal-catalyzed S_N2- and S_N2'-substitutions of allylic substrates are common methods for the preparation of chiral molecules.[64,96] Thereby, the chirality depends on the use of chiral ligands[96] or the use of chiral allylic substrates, which react according to an *anti*-S_N2'-substitution.[64] In addition, the control of regioselectivity of allylic substitutions is of high importance for organic synthesis and was intensively investigated.[97]

Herein, we report the stereoselective reaction of secondary alkylcopper-zinc reagents with allylic epoxides (**101**) leading to chiral allylic alcohols of type **102** (Scheme 36), which are a common motif in organic synthesis and natural products.



Scheme 36: Stereoselective preparation of chiral alkylcopper reagents (**3**) and subsequent *anti*-S_N2'-substitutions with allylic epoxides (**101**).

An example for a chiral cyclic allylic alcohol is the natural product zingiberenol (**103**) (see Figure 4).[98] Of eight possible stereoisomers only two exist in nature, (3*S*,6*R*,7*S*)- and (3*S*,6*S*,7*S*)-zingiberenol. Retrosynthetic analysis showed that (3*S*,6*R*,7*S*)-zingiberenol (**103**) can be prepared *via* an *anti*-S_N2'-substitution reaction of the chiral allylic epoxide **104** and the copper reagent **105** (prepared from the corresponding alkyl iodide **106**, see Figure 4). Starting from zingiberenol, several other natural products can be prepared using literature known transformations. Reaction of zingiberenol with AD-mix-α and subsequent epoxidation leads to the pheromone of the brown marmorated stink bug, murgantiol (**107**).[99]

[96] a) F. Bertozzi, P. Crotti, B. L. Feringa, F. Macchia, M. Pineschi, *Synthesis* **2001**, *3*, 483−486. b) C. A. Cullis, H. Mizutani, K. E. Murphy, A. H. Hoveyda, *Angew. Chem. Int. Ed.* **2001**, *40*, 1456–1460. c) B. M. Trost, M. L. Crawley, *Chem. Rev.* **2003**, *103*, 2921−2944. d) J. E. Campbell, A. H. Hoveyda, *J. Am. Chem. Soc.* **2004**, *126*, 11130–11131. e) A. W. van Zijl, W. Szymanski, F. Lopez, A. J. Minnaard, B. L. Feringa, *J. Org. Chem*. **2008**, *73*, 6994–7002. f) A. Alexakis, J. E. Bäckvall, N. Krause, O. Pàmies, M. Diéguez, *Chem. Rev.* **2008**, *108*, 2796−2823. g) M. Welker, S. Woodward, A. Alexakis, *Org. Lett.* **2010**, *12*, 576−579. h) S. S. Goth, S. Guduguntla, T. Kikuchi, M. Lutz, E. Otten, M. Fujita, B. L. Feringa, *J. Am. Chem. Soc.* **2018**, *140*, 7052–7055. i) Q. Cheng, C. Tu, H.-F. Zheng, J.-P. Qu, G. Helmchen, S.-L. You, *Chem. Rev.* **2019**, *119*, 1855−1969.

[97] a) F. Gini, F. Del Moro, F. Macchia, M. Pineschi, *Tetrahedron Lett.* **2003**, *44*, 8559−8562. b) M. Pineschi, F. Del Moro, P. Crotti, V. Di Bussolo, F. Macchia, *J. Org. Chem.* **2004**, *69*, 2099−2105. c) C. Falciola, K. Tissot-Croset, A. Alexakis, *Angew. Chem. Int. Ed.* **2006**, *45*, 5995–5998. d) M. Perez, M. Fananas-Mastral, P. H. Bos, A. S. Rudolph, R. Harutyunyan, B. L. Feringa, *Nature Chem.* **2011**, *3*, 377−381.

[98] a) M. W. Morais de Oliveria, M. Borges, C. K. Z. Andrade, R. A. Laumann, J. A. F. Barrigossi, M. C. Blassioli-Moraes, *J. Agric. Food Chem.* **2013**, *61*, 7777−7785. b) A. Khrimian, S. Shirali, F. J. Guzman, *Nat. Prod.* **2015**, *78*, 3071−3074. c) S. Shirali, F. Guzman, D. C. Weber, A. Khrimian, *Tetrahedron Lett.* **2017**, *58*, 2066−2068.

[99] a) A. Khrimian, A. Zhang, D. C. Weber, H.-Y. Ho, J. A. Aldrich, K. E. Vermillion, M. A. Siegler, S. Shirali, F. Guzman, T. C. Leskey, *J. Nat. Prod.* **2014**, *77*, 1708−1717. b) A. Khrimian, S. Shirali, K. E. Vermillion, M. A. Siegler, F. Guzman, K. Chauhau, J. A. Aldrich, D. C. Weber, *J. Chem. Ecol.* 2**014**, *40*, 1260–1268.

Further dehydration using sulfuric acid leads to the β-sesquiphellandrene (**108**) and the monocyclic sesquiterpene zingiberene (**109**).[98a]

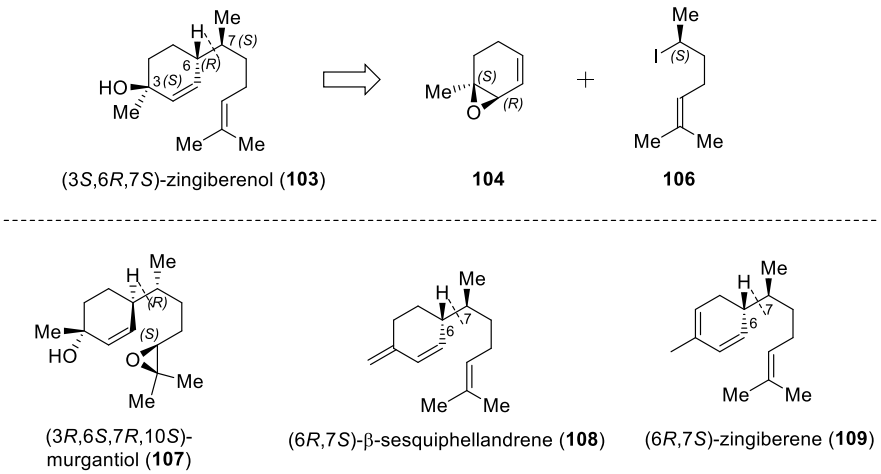
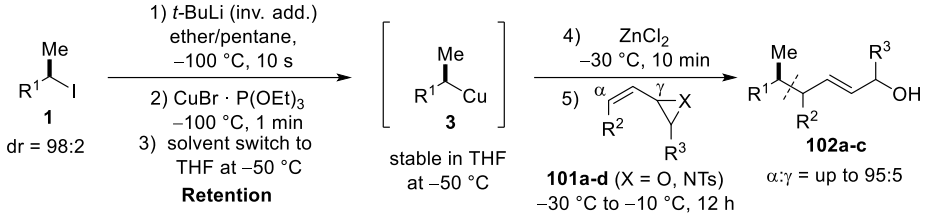


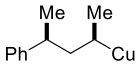
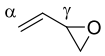
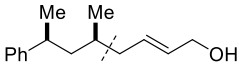
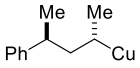
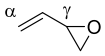
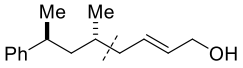
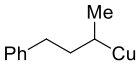
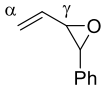
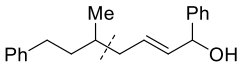
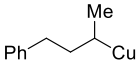
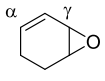
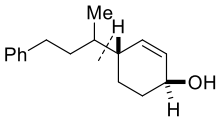
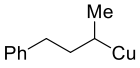
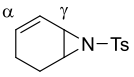
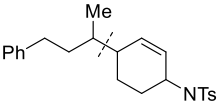
Figure 4: Retrosynthetic analysis of (3*S*,6*R*,7*S*)-zingiberenol (**103**). Structures of murgantiol (**107**), β-sesquiphellandrene (**108**), and zingiberene (**109**).

3.2 Regioselective S_N2'-Reactions of Allylic Epoxides

In preliminary experiments, the regioselectivity of S_N2'-substitution reactions of various allylic epoxides with chiral alkylcopper reagents was examined. Therefore, the diastereomerically enriched alkyl iodide *syn*-**1a** (dr = 98:2) was treated with *t*-BuLi (2.2 equiv) at –100 °C in *n*-pentane/diethyl ether affording the corresponding alkyllithium reagent *syn*-**2a**. Subsequent treatment with $CuBr \cdot P(OEt)_3$ (1.5 equiv) led to the organocopper reagent *syn*-**3a** (see Table 6). This alkylcopper reagent is configurationally stable in THF and thus, a solvent switch was performed at –50 °C.[50,54,61] The addition of $ZnCl_2$ (1.5 equiv, –30 °C, 10 min) and subsequent treatment with the allylic epoxide **101a** (3.0 equiv, –30 °C to –10 °C, 12 h) furnished the allylic alcohol *syn*-**102a** in 46% yield with retention of configuration (dr = 6:94; *E*/*Z* = 86:14; entry 1). Interestingly, the ratio of S_N2'-substitution (α-position) to S_N2-substitution (γ-position) was higher than 95:5. In the same way, the corresponding *anti*-allylic alcohol (*anti*-**102a**) was prepared with retention of configuration and high S_N2'-selectivity (54% yield; dr = 91:9; α: γ = 95:5; *E*/*Z* = 88:12; entry 2).

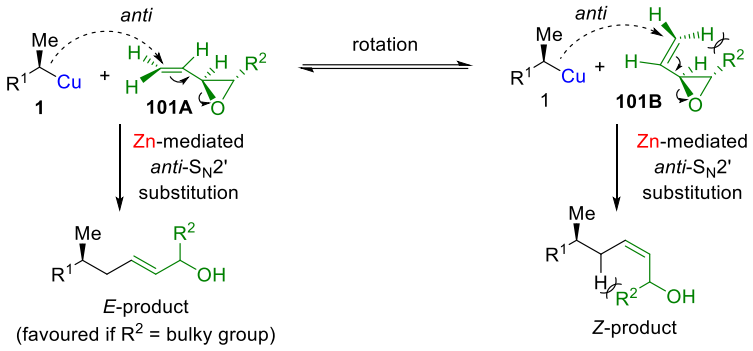
Table 6: Optimization reactions for the opening of allylic epoxides **101**.



entry	alkylcopper	electrophile	product of type **102**[a]
1	 *syn*-**3a**	 **101a**	 *syn*-**102a**, 46%, dr = 6:94, α:γ = 95:5, E/Z = 86:14
2	 *anti*-**3a**	 **101a**	 *anti*-**102a**, 54%, dr = 91:9, α:γ = 95:5, E/Z = 88:12
3	 **3f**	 **101b**	 **102b**, 43%, α:γ = 80:20, E/Z = 99:1
4	 **3f**	 **101c**	 **102c**, 51%, α:γ = 95:5
5	 **3f**	 **101d**	 **102d**, traces, α:γ = n.a.

[a] The diastereoselectivity (dr; *anti*/*syn* ratio) was determined by ^{1}H- or ^{13}C-NMR analysis.

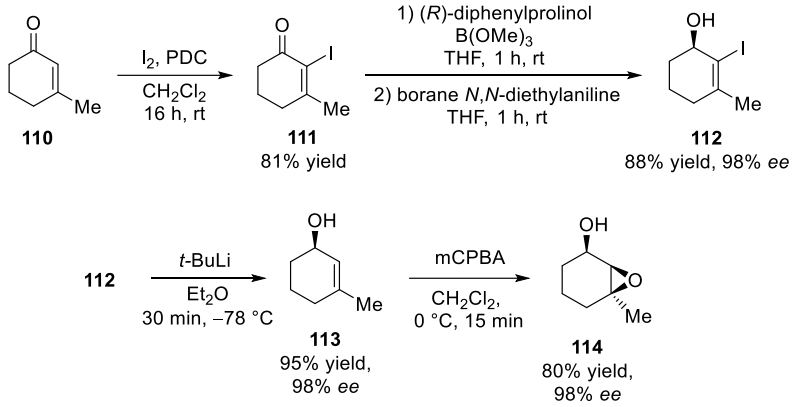
To further investigate the stereo- and regioselectivity, the *anti*-S_N2'-substitution was performed with higher substituted allylic substrates **101b-d**. Thus, 2-phenyl-3-vinyloxirane **101b** was prepared and reaction with the chiral secondary alkylcopper reagent **3f** led to the racemic allylic alcohol **102b** in moderate yield (43%) and S_N2'-selectivity (α:γ = 80:20), but with excellent *E*/*Z* ratio (99:1; entry 3)). The observed *E*/Z-ratios by using **101a** or **101b** as electrophiles are rationalized in Scheme 37. The *anti*-substitution *via* conformer **101A** affords the *E*-product, whereas the substitution of conformer **101B** results in the *Z*-product. Depending on the 1,3-allylic strain, one conformer is more favoured. If the residue R^2 of the allylic epoxide is bulky, such as the phenyl group of electrophile **101b**, the substitution proceeds *via* conformer **101A** due to steric reasons. Thus, the reaction of alkylcopper *anti*-**3a** with **101a** led to a mixture of *E*- and *Z*-products (*E*/*Z* = 88:12, see Table 6), whereas the reaction of **3f** with **101b** led exclusively to the *E*-product (*E*/*Z* = 99:1).



Scheme 37: S_N2'-susbtitution reaction *via* two different conformers **101A** or **101B** leading to the *E*- or the *Z*-product.

Switching to the cyclic allylic epoxide **101c** increased the regioselectivity significantly (**102c**, 51% yield, α:γ = 95:5; see Table 6, entry 4). We assume that the S_N2'-substitution of **101c** proceeds in a highly *anti*-S_N2'-fashion leading to **102c** as shown in Table 6 (hydroxyl group and hydrogen atom have a *syn*-orientation). Furthermore, the cyclic allylic aziridine **101d** was prepared according to literature from cyclohexadiene.[100] However, all attempts to open this allylic aziridine were unsuccessful. These preliminary experiments showed, that the *anti*-S_N2'-substitution of allylic epoxides is regioselective (α:γ = 95:5) and proceeds with retention of configuration of the secondary alkylcopper reagent.

3.3 Total Synthesis of (3*S*,6*R*,7*S*)-Zingiberenol



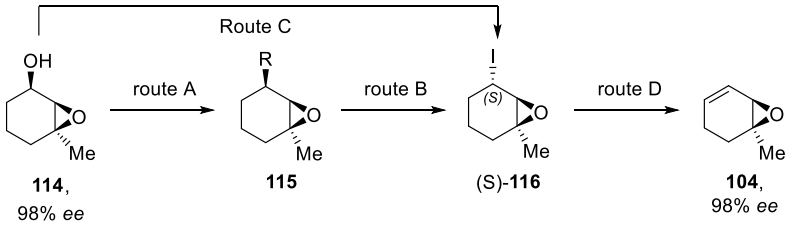
Scheme 38: Enantioselective synthesis of the precursor **114**.

Having these results in hand, the enantioselective synthesis of the chiral epoxide **104** was performed. Thus, the commercially available 3-methylcyclohex-2-en-1-one **110** was converted to the iodo-derivative **111** (81% yield) using a pyridinium dichromate (PDC) mediated iodination (see Scheme 38).[101] The bulky iodo-substituent allowed an enantioselective CBS-reduction of **111**, furnishing the chiral alcohol **112** in 88% yield and 98% *ee*.[101] Removal of the iodine *via* I/Li-exchange and subsequent protonolysis afforded the chiral allylic alcohol **113** in almost quantitative yield (95%

[100] D. Sureshkumar, S. Maity, S. Chandrasekaran, *J. Org. Chem.* **2006**, *71*, 1653–1657.
[101] S. Demay, K. Harms, Knochel, P. *Tetrahedron Lett.* **1999**, *40*, 4981–4984.

yield) and 98% *ee*. Stereoselective directed epoxidation of **113** using mCPBA afforded the chiral epoxy-alcohol **114** in 80% yield (98% *ee*).[102]

Table 7: Enantioselective elimination of the alcohol leading to the chiral allylic epoxide **104**.

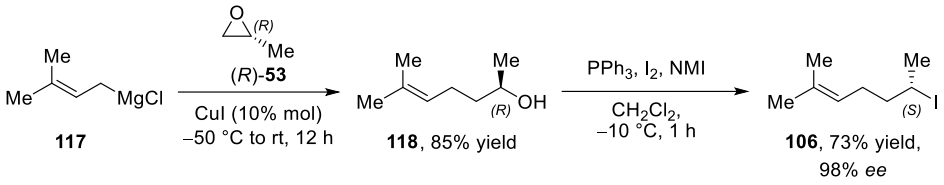


route	entry	reagents, conditions	product; yield (%)[a]
A	**1**	MsCl (4.5 equiv), NEt_3 (6.0 equiv), DCM, –10 °C	**115a**, R = OMs, 80%
	2	TsCl (4.5 equiv), NEt_3 (2.2 equiv), DCM, –10 °C	**115b**, R = OTs, 49%
	3	$(PhSe)_2$ (4.0 equiv), $NaHBH_4$ (4.0 equiv), AcOH (1.8 equiv), DMF, rt, 24 h	**115a** to **115c**, R = SePh, 42%
B	**1**	NaI (10 equiv), $NaHCO_3$ (20 equiv), THF, 65 °C	**115a** to **116**, 62%
	2	NaI (10 equiv), $NaHCO_3$ (20 equiv), THF, 65 °C	**115b** to **116**, 48%
	3	H_2O_2 (2.0 equiv), DCM, 0 °C to rt	**115c** direct to **104**, traces
C	**1**	I_2 (1.6 equiv), PPh_3 (1.6 equiv), NMI (1.6 equiv), DCM, –10 °C, 1 h	**116**, traces
	2	CI_4 (1.1 equiv), PPh_3 (1.1 equiv), NMI (1.1 equiv), DCM, 0 °C, 1 h	**116**, traces
D	**1**	DBU (5.0 equiv), THF, 60 °C, 12 h	**104**, 60%
	2	NaOEt (1.5 equiv), EtOH, 60 °C, 12 h	**104**, traces
	3	TBD (5.0 equiv), THF, 60 °C, 12 h	**104**, traces

The elimination of the hydroxyl containing epoxide **114** to the desired allylic epoxide **104** proved to be rather challenging (see Table 7). Direct elimination using the Burgess reaction[103] or elimination *via* the corresponding phenylselenide[104] was unsuccessful. Thus, we envisioned a synthetic route, in which the hydroxygroup is converted into a good leaving group R (**115**; route A) followed by S_N2-substitution to the iodide **116** (route B and C) and subsequent elimination leading to the allylic epoxide **104** (route D). After intensive screening of various leaving groups, the preparation of the mesylate **115a** (80% yield, R

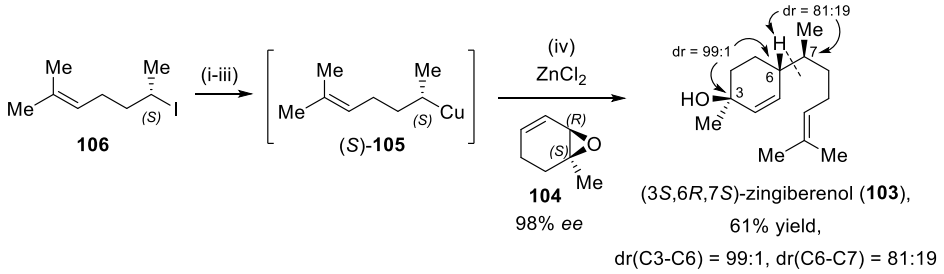
[102] K. Mori, J. I. J. Ogoche, *Liebigs Ann. Chem.* **1988**, 903–905.
[103] E. M. Burgess, H. R. J. Penton, E. A. Taylor, *J. Am. Chem. Soc.* **1970**, *92*, 5224–5225.
[104] G. Blay, L. Cardona, A. M. Collado, B. Garcia, J. R. Pedro, *J. Org. Chem.* **2006**, *71*, 4929–4936.

= OMs) followed by a Finkelstein reaction led to the desired iodide **116** (62% yield) with inversion of configuration (*S*/*R* = 80/20).[105] Subsequent elimination reaction with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as base furnished the desired epoxide **104** in 60% yield and with excellent enantiomeric excess (98% *ee*).[106]



Scheme 39: Enantioselective Synthesis of the iodide **106**.

Next, the optically enriched iodide **106** was prepared. Insertion of magnesium into commercially available 1-chloro-3-methyl-2-butene led to **117**. Subsequent copper-catalyzed epoxide opening of (*R*)-**53** led to chiral alcohol **118** in 85% yield. After inversion of the configuration *via* an Appel reaction the enantiomerically pure iodide **106** was obtained in 73% yield.[50]



Scheme 40: Synthesis of zingiberenol: (i) *t*-BuLi (2.2 equiv), inverse addition, pentane/diethyl ether = 3:2, –100 °C, 1 min. (ii): $CuBr \cdot P(OEt)_3$ (1.5 equiv), pentane: diethyl ether, –100 °C, 1 min. (iii) solvent switch to THF at –50 °C. (iv) $ZnCl_2$ (1.5 equiv), –30 °C, 10 min; then **104** (3.0 equiv), –30 °C to –10 °C, 12 h.

Finally, the secondary alkyl iodide **106** was converted into the corresponding alkylcopper reagent (*S*)-**105** under the conditions mentioned above (see Scheme 40). Subsequent zinc-mediated *anti*-S_N2'-substitution with allylic epoxide **104** led to (3*S*,6*R*,7*S*)-zingiberenol (**103**) in 61% yield (dr (C3,C6) = 99:1; and dr (C6,C7) = 81:19) with moderate selectivity at the C7-stereocenter.[107] All attempts to improve the stereoselectivity during the reaction by variation of conditions or additives, like $BF_3 \cdot OEt_2$ were unsuccessful. However, the substitution of allylic epoxide **104** proceeded in a highly *anti*-S_N2'-fashion leading to the *syn*-orientation of the hydroxyl-group and the proton (3*S*,6*R*) of zingiberenol (dr = 99:1; see Scheme 40). This emphasizes the previous assumption that opening of allylic epoxides proceeds *via* an *anti*-S_N2'-substitution reaction.

[105] K. Mori, B. G. Hazra, R. J. Pfeiffer, A. K. Gupta, B. S. Lindgren, *Tetrahedron* **1987**, *43*, 2249–2254.
[106] The enantiomeric excess was determined *via* chiral GC analysis. For details, see the Experimental Part.
[107] The stereochemistry was assigned according to literature.[99b]

4 Stereoselective Csp^3-Csp^2 Cross-Coupling Reactions of Chiral Secondary Alkylzinc Reagents with Alkenyl and Aryl Halides

4.1 Introduction

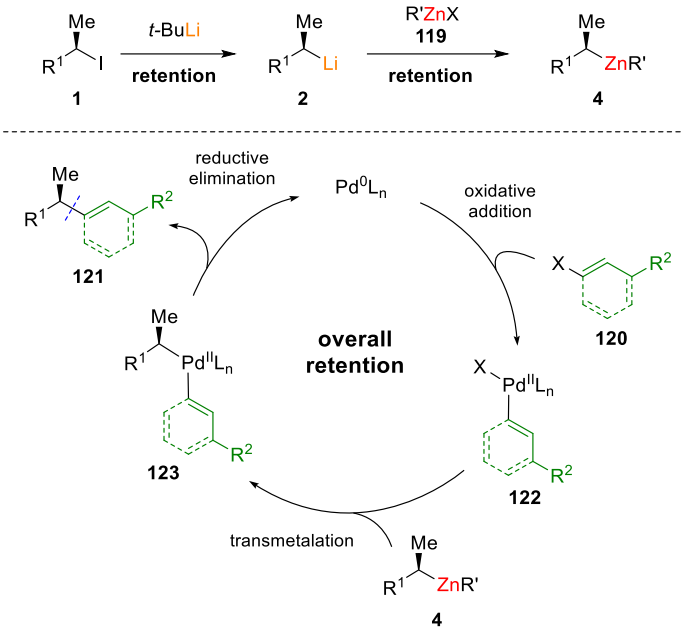
Transition-metal-catalyzed cross-coupling reactions are widely used for the construction of complex organic molecules.[108] Although a range of Csp^3-Csp^2 coupling reactions have been developed, only a few are stereoselective.[4b,109] In this context, highly stereoretentive cross-couplings of enantioenriched α-chiral alkylzinc reagents are desirable as these reagents are known for their broad functional group tolerance. However, their preparation proved to be challenging since oxidative addition of zinc powder into the carbon-halogen bond proceeds with a loss of stereoinformation.[109g] A stereoselective palladium-catalyzed cross-coupling reaction after hydroboration of trisubstituted alkenes followed by a boron-zinc exchange reaction has been reported, but proved to be of limited scope.[110] Lately, a diastereoselective palladium-catalyzed cross-coupling reaction of cyclic alkylzinc reagents, in which the stereoselectivity of the cross-coupling is thermodynamically controlled, has been reported.[111] This method leads to high selectivities only with cyclic substrates, which drastically limits the utility of such stereoselective palladium-catalyzed cross-couplings. So far, the preparation of non-stabilized optically pure open-chain organometallic reagents is a challenge for organic synthesis. Recently, we have reported that chiral secondary alkyllithiums **2** can be readily prepared from the corresponding optically enriched α-chiral secondary alkyl iodides **1** *via* a stereoretentive I/Li-exchange reaction (see Scheme 41). The configurational stability of these secondary alkyllithiums is rather moderate (ca. 1 h at –100 °C in a hexane/diethyl ether mixture).[48-56] However, transmetalation to the corresponding secondary alkylcopper reagents significantly increases this configurational stability (several hours at –50 °C in THF). These chiral alkylcopper organometallics react with activated alkynes, epoxides, 1-bromoalkynes and allylic halides with high retention of configuration.[50,58,61] Furthermore, these organocopper reagents were used in the total synthesis of several pheromones[50,58] with high control of all stereocenters.

[108] a) E.-I. Negishi, *Handbook of Organopalladium Chemistry for Organic Synthesis*; Wiley-Interscience: New York, **2002**. b) A. De Meijere, S. Bräse, M. Oestreich, *Metal-Catalyzed Cross-Coupling Reactions and More*, Wiley-VCH, Weinheim, **2013**. c) for a review see: R. Jana, T. P. Pathak, M. S. Sigman, *Chem. Rev.* **2011**, *111*, 1417−1492.

[109] a) Y. Hatanaka, T. Hiyama, *J. Am. Chem. Soc.* **1990**, *112*, 7793−7794. b) B. Hölzer, R. W. Hoffmann, *Chem. Commun.* **2003**, 732−733. c) T. K. Beng, R. E. Gawley, *Org. Lett.* **2011**, *13*, 394–397. d) L. Li, S. Zhao, A. Joshi-Pangu, M. Diane, M. R. Biscoe, *J. Am. Chem. Soc.* **2014**, *136*, 14027–14030. e) C. Sandford, V. K. Aggarwal, *Chem. Commun.* **2017**, 5481–5494. f) J. P. G. Rygus, C. M. Crudden, *J. Am. Chem. Soc.* **2017**, *139*, 18124–18137. g) S. Zhao, T. Gensch, B. Murray, Z. L. Niemeyer, M. S. Sigman, M. R. Biscoe, *Science* **2018**, *362*, 670–674.

[110] A. Boudier, P. Knochel, *Tetrahedron Lett.* **1999**, *40*, 687−690.

[111] T. Thaler, B. Haag, A. Gavryushin, K. Schober, E. Hartmann, R. M. Gschwind, H. Zipse, P. Mayer, P. Knochel, *Nat. Chem.* **2010**, *2*, 125−130.



Scheme 41: Stereoretentive preparation of secondary alkylzinc reagents **4** and subsequent palladium-catalyzed cross-coupling reaction with alkenyl or aryl halides **120**.

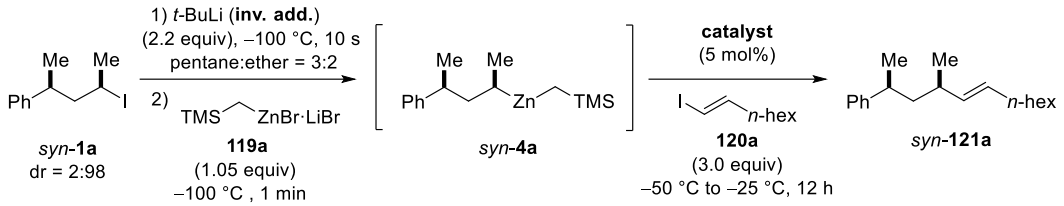
Nevertheless, the configurational stability of these chiral secondary alkylcopper reagents is restricted to low temperature reactions. Thus, we envisioned the performance of a stereoretentive transmetalation of chiral alkyllithiums of type **2** with an appropriate ether soluble zinc reagent R'ZnX (**119**), leading to the mixed dialkylzinc reagents of type **4** (see Scheme 41). These chiral mixed dialkylzinc reagents may undergo a stereoselective palladium-catalyzed cross-coupling with alkenyl and aryl halides of type **120**, which would afford α-chiral products of type **121**. To achieve such a stereoselective cross-coupling several requirements should be fulfilled: 1) both the transmetalation step (conversion of **122** to **123**) and the reductive elimination step (converting **123** to **121**) of the catalytic cross-coupling cycle have to be stereoselective; 2) the secondary dialkylzinc reagent **4** must be configurationally stable at the cross-coupling temperature and should contain a R' group, that does not participate easily in the catalytic cycle. After several preliminary experiments,[112] we chose $Me_3SiCH_2ZnBr{\cdot}LiBr$ (**119a**) as transmetalating zinc reagent since it is highly soluble in diethyl ether and readily prepared.[113] To our delight, these conditions allow a highly stereoselective cross-coupling of chiral non-stabilized open-chain secondary alkylzinc reagents with various alkenyl and aryl halides for the first time.

[112] For a detailed screening table, see the Experimental Part.
[113] a) S. H. Bertz, M. Eriksson, G. Miao, J. P. Snyder, *J. Am. Chem. Soc.* **1996**, *118*, 10906−10907. b) S. Berger, F. Langer, C. Lutz, P. Knochel, T. A. Mobley, C. K. Reddy, *Angew. Chem. Int. Ed.* **1997**, *36*, 1496−1498. c) C. Lutz, P. Knochel, *J. Org. Chem.* **1997**, *62*, 7895−7898.

4.2 Palladium-Catalyzed Cross-Coupling Reactions

Hence, we treated the diastereomerically enriched secondary alkyl iodide *syn*-**1a**[53] with *t*-BuLi (2.2 equiv) in a 3:2 mixture of pentane/diethyl ether at –100 °C for 10 s leading to an intermediate alkyllithium species (see Table 8). Addition of $Me_3SiCH_2ZnBr{\cdot}LiBr$ (**119a**; 0.95 M in diethyl ether, 1.05 equiv) at –100 °C provided the mixed dialkylzinc species *syn*-**4a**. For performing a subsequent stereoselective palladium-catalyzed cross-coupling, the choice of the palladium catalyst proved to be essential.

Table 8: Optimization for palladium-catalyzed cross-coupling reaction of racemic secondary alkylzinc reagent *syn*-**4a**.



entry	catalyst	yield of *syn*-**121a**[a]	dr of *syn*-**121a**[a]
1	$Pd(PPh_3)_4$	39%	11:89
2	$Pd(OAc)_2$/CPhos	51%	8:92
3	Pd-PEPPSI-iPent	60%	4:96
4	$Pd_2I_2(Pt\text{-}Bu_3)_2$	58%	2:98

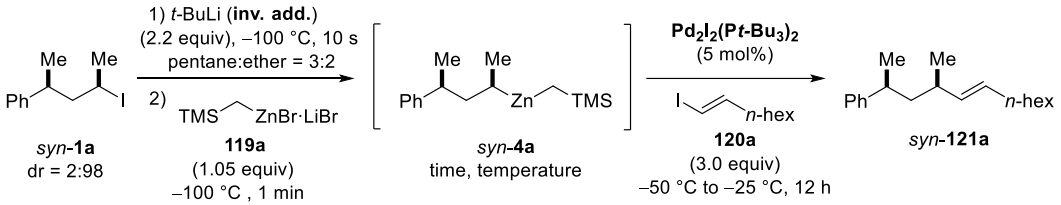
[a] The yield and diastereoselectivity (dr; *anti*/*syn* ratio) was determined by GC analysis using dodecane as internal standard.

Addition of 5 mol% $Pd(PPh_3)_4$ and (*E*)-1-iodooct-1-ene (**120a**; 3.0 equiv) as a typical substrate at –50 °C followed by warming to –25 °C and stirring for 12 h at this temperature provided the desired cross-coupling product *syn*-**121a** with a diastereoselectivity of *anti*/*syn* = 11:89 (entry 1).[114] Using the catalytic system $Pd(OAc)_2$/CPhos introduced by Buchwald for the coupling of secondary alkylzinc halides[115] improved the stereoselectivity of the cross-coupling to *anti*/*syn* = 8:92 (entry 2). A further improvement was observed with the NHC-based catalyst Pd-PEPPSI-iPent reported by Organ,[116] which provided the desired product *syn*-**121a** with a dr = 4:96 (entry 3). Finally, the Pd^I-catalyst $Pd_2I_2(Pt\text{-}Bu_3)_2$ used by Schoenebeck[117] afforded the product *syn*-**121a** with complete retention of configuration (entry 4; dr = 2:98). In order to obtain a deeper insight into the configurational stability of these chiral non-stabilized

[114] Nickel catalysts afforded only traces of *syn*-**121a**; For a detailed screening table, see the Experimental Part.
[115] a) C. Han, S. L. Buchwald, *J. Am. Chem. Soc.* **2009**, *131*, 7532−7533. b) Y. Yang, K. Niedermann, C. Han, S. L. Buchwald, *Org. Lett.* **2014**, *16*, 4638−4641.
[116] S. Çalimsiz, M. G. Organ, *Chem. Comm.* **2011**, 5181–5183; Pd-PEPPSI-iPr afforded *syn*-**121a** in 23% yield and dr = 9:91; for details see the Experimental Part.
[117] a) I. Kalvet, T. Sperger, T. Scattolin, G. Magnin, F. Schoenebeck, *Angew. Chem. Int. Ed.* **2017**, *56*, 7078–7082. b) S. T. Keaveney, G. Kundu, F. Schoenebeck, *Angew. Chem. Int. Ed.* **2018**, *57*, 12573–12577.

secondary alkylzincs of type **4**, we prepared *syn*-**4a** at –100 °C and kept it at various temperatures (–50 °C to 25 °C) for a certain time, followed by the stereoselective cross-coupling with **120a**, leading to *syn*-**121a** (see Table 9). We observed high stability of the zinc species *syn*-**4a** up to –10 °C (dr of *syn*-**121a** = 3:97). Furthermore, keeping the alkylzinc reagent *syn*-**4a** at 25 °C for 1 h and performing a palladium-catalyzed cross-coupling provided *syn*-**121a** with dr = 4:96. However, stirring *syn*-**4a** at 25 °C for 4 h led to a minimal epimerization (dr of *syn*-**121a** = 11:89). This indicated a high configurational stability of these chiral secondary mixed dialkylzinc reagents (several hours at 25 °C). With this result in hand, we slightly modified the experimental procedure to the effect that the cross-coupling reaction could be performed at room temperature. Under these conditions, Pd-PEPPSI-iPent showed superior results compared to the Pd^{I}-dimer catalyst regarding β-hydride elimination and formation of side products such as dimerization.[112]

Table 9. Stability of racemic secondary alkylzinc reagent *syn*-**4a** and subsequent cross-coupling reaction with alkenyl iodide **120a**.



entry	temperature	time	yield of *syn*-**121a**[a]	dr of *syn*-**121a**[a]
1	–50 °C	10 min	61%	3:97
2	–30 °C	10 min	58%	3:97
3	–10 °C	10 min	50%	3:97
4	25 °C	60 min	51%	4:96
5	25 °C	240 min	53%	11:89

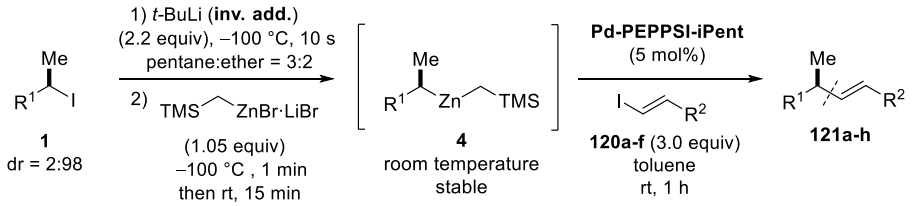
[a] The yield and diastereoselectivity (dr; *anti*/*syn* ratio) was determined by GC analysis using dodecane as internal standard.

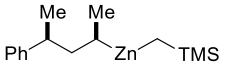
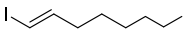
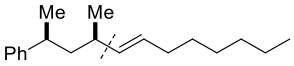
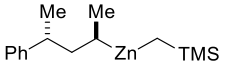
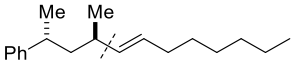
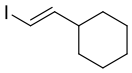
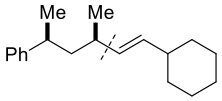
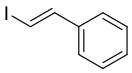
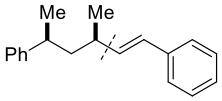
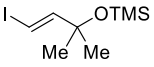
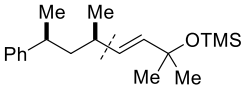
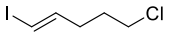
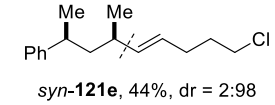
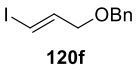
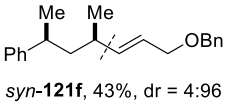
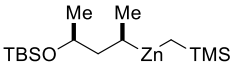
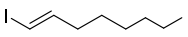
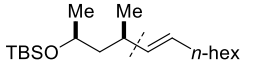
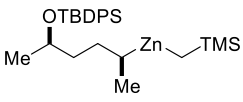
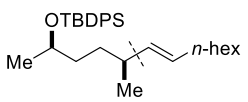
In a typical procedure, the chiral mixed dialkylzinc reagents (**4a-c**) were generated as described above and subsequently warmed to room temperature over 15 min (see Table 10). The dialkylzinc reagent was then added dropwise to a stirring solution of 5 mol% Pd-PEPPSI-iPent and the alkenyl iodide of type **120** (3.0 equiv) in toluene. After stirring for 1 h at room temperature the corresponding α-chiral cross-coupling products were isolated in up to 52% yield and with high retention of configuration (dr up to 98:2). In this way, the stereodefined alkenes *syn*-**121a**[118] and *anti*-**121a** were prepared from the corresponding iodides in 43% and 39% yield, respectively (dr = 2:98 and dr = 95:5). Interestingly, the thermodynamically more stable alkylzinc reagent *anti*-**4a** afforded the corresponding *E*-alkene *anti*-**121a** in lower yield and with less retention of configuration compared to the *syn*-product. In most other

[118] The use of octenyl bromide as electrophile afforded *syn*-**121a** in 23% yield and dr = 6:94.

cases a high retention of configuration (dr >94:6) was achieved. Thereby, the *E*/*Z*-configuration of the alkenyl iodides of type **120** turned out to be highly important. All attempts to use *Z*-alkenyl iodides as cross-coupling partners were unsuccessful presumably due to steric hindrance in the palladium(II)-intermediates **122** and **123**.[112]

Table 10. Stereoretentive cross-coupling reactions of racemic secondary alkylzinc reagents **4** with alkenyl iodides **120a-f** leading to α-chiral alkenes **121a-h**.



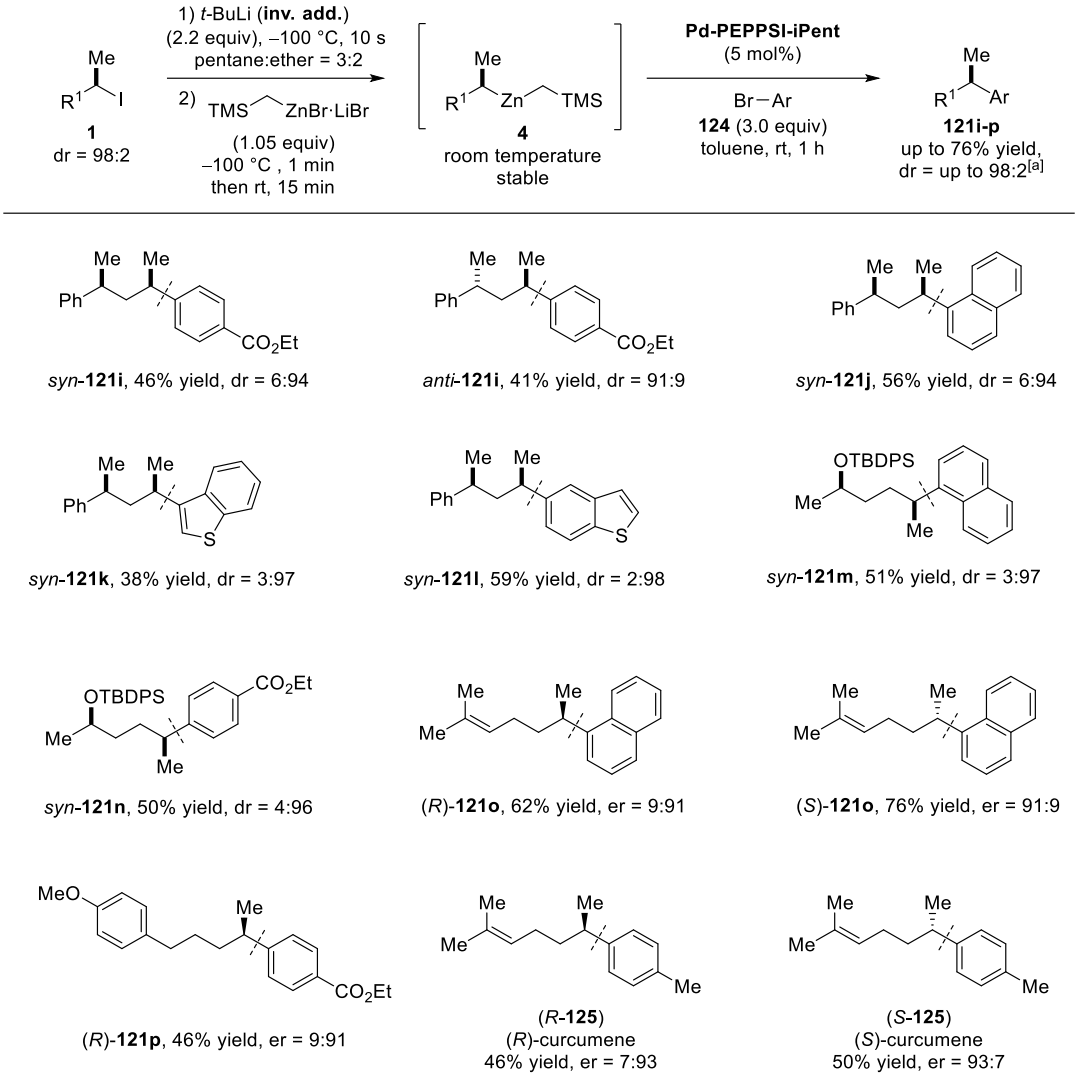
entry	alkylzinc	electrophile	product of type **121**[a]
1	 *syn*-**4a**	 **120a**	 *syn*-**121a**, 43%, dr = 2:98
2	 *anti*-**4a**	**120a**	 *anti*-**121a**, 39%, dr = 95:5
3	*syn*-**4a**	 **120b**	 *syn*-**121b**, 45%, dr = 6:94
4	*syn*-**4a**	 **120c**	 *syn*-**121c**, 52%, dr = 2:98
5	*syn*-**4a**	 **120d**	 *syn*-**121d**, 39%, dr = 6:94
6	*syn*-**4a**	 **120e**	 *syn*-**121e**, 44%, dr = 2:98
7	*syn*-**4a**	 **120f**	 *syn*-**121f**, 43%, dr = 4:96
8	 *syn*-**4j**	 **120a**	 *syn*-**121g,** 43% yield, dr = 7:93
9	 *syn*-**4h**	**120a**	 *syn*-**121h**, 46% yield, dr = 4:96

[a] The diastereoselectivity (dr; *anti*/*syn* ratio) was determined by ^{1}H-NMR spectroscopy and GC analysis.

These conditions were broadly applicable. Hence, we performed this cross-coupling reaction with other secondary alkylzinc reagents **4j,h** (see entry 8 and 9). The 1,3-functionalized secondary alkyl iodide *rac*-**1j** was prepared according to literature procedure, followed by an I/Li-exchange reaction, which after epimerization (–50 °C, 30 min) led to the chelate-stabilized lithium species.[53] Subsequent transmetalation to the corresponding dialkylzinc reagent *syn*-**4j** followed by cross-coupling with **120a** afforded the silyl-protected alkene *syn*-**121g** in 43% yield (dr = 7:93). Furthermore, the 1,4-functionalized dialkylzinc reagent *syn*-**4h** was suitable for cross-coupling reaction leading to *syn*-**121h** in 46% yield and dr = 4:96.

Since many pharmaceuticals and natural products contain aromatic moieties, the preparation of chiral arenes and heteroarenes is of great interest. Thus, we extended our method to palladium-catalyzed cross-couplings with aryl bromides of type **124** leading to the corresponding chiral arenes and heteroarenes (see Scheme 42). Various aryl bromides with electron donating and electron withdrawing substituents were used, leading to products **121i-n** (38–59% yield; dr up to 98:2). Thus, the cross-coupling reaction of *syn*-**4a** with bromothiophene derivatives[119] afforded *syn*-**121k-l** in 38–59% yield and with high retention of configuration (dr up to 98:2). In addition, 1-bromonaphthalene was used for the cross-coupling reaction with the dialkylzinc reagents *syn*-**4a** and *syn*-**4h** leading to α-chiral naphthalenes *syn*-**121j** and *syn*-**121m** in good yields (51-56% yield) and high stereoretention (dr up to 97:3). This cross-coupling was also extended to optically enriched alkylzinc reagents, leading to the corresponding α-chiral arenes (*R*)-**121o,** (*S*)-**121o** and (*R*)-**121p** (up to 76% yield, er = 9:91).[120] To demonstrate the synthetic utility of the method, we performed the natural product synthesis of the two enantiomers of α-curcumene **125**, an aromatic sesquiterpene.[121] Both enantiomers can be found in nature, e.g. in essential oils or in the pheromone produced by the red-shoulder stink bug.[122] Starting from the readily available chiral secondary alkyl iodide (*S*)- or (*R*)-**1e**,[50] the corresponding chiral secondary alkylzinc reagents (*S*)- or (*R*)-**4e** were prepared. Subsequent palladium-catalyzed cross-coupling reaction with 4-bromotoluene afforded the natural products (*S*)-curcumene [(*S*)-**125**; 50% yield; er = 93:7] and (*R*)-curcumene [(*R*)-**125**; 46% yield; er = 7:93].

[119] In this point, 2-bromothiophenes and *N*-heterocyclic halides were not suitable for cross-coupling reaction. For a detailed screening table, see the Experimental Part.
[120] The enantiomeric ratio was determined by chiral GC-analysis or chiral HPLC analysis. The (*S*)-enantiomer of **121p** was also prepared: 54% yield, er = 83:17. For details, see the Experimental Part.
[121] a) B. Rao, J. L. Simonsen, *J. Chem. Soc.* **1928**, 2496–2505. b) L. Wu, J.-C. Zhong, S.-K. Liu, F.-P. Liu, Z.-D. Gao, M. Wang, Q.-H. Bian, *Tetrahedron: Asymmetry* **2016**, *27*, 78–83.
[122] a) G. Uhde, G. Ohloff, *Helv. Chim. Acta* **1972**, *55*, 2621–2625. b) H. L. McBrien, J. G. Millar, R. E. Rice, J. S. McElfresh, E. Cullen, F. G. Zalom, *J. Chem. Ecol.* **2002**, *28*, 1797–1818.



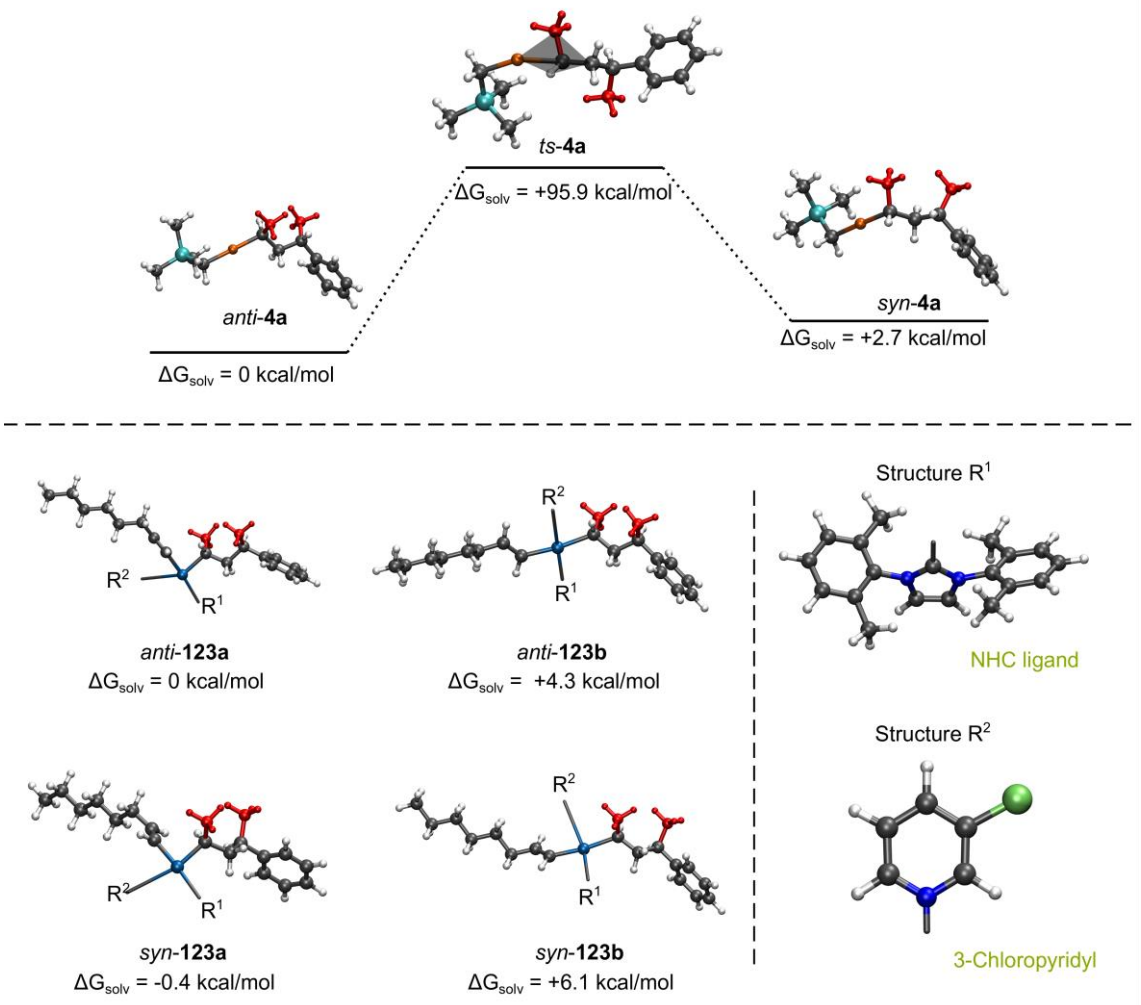
Scheme 42. Cross-coupling reaction of chiral alkylzinc reagents **4** with aryl bromides **124**, leading to α-chiral arenes and heteroarenes (**121i-p**). [a] The diastereoselectivity (dr; *anti*/*syn* ratio) was determined by ^{1}H-NMR spectroscopy and GC analysis.

4.3 Computational Calculations

Furthermore, DFT-calculations were performed to gain insight into the high retention of configuration of secondary alkylzinc reagents.[123] Therefore, the configurational stability of the chiral alkylzinc reagents *syn*-**4a** and *anti*-**4a** was investigated. Solvation effects were accounted for by the Polarizable Continuum Model (PCM) as well as by explicit treatment with diethyl ether molecules.[92] Comparison of the free energies between the two isomers showed that *anti*-**4a** is thermodynamically more stable than the corresponding alkylzinc reagent *syn*-**4a** ($\Delta G = +2.7$ kcal/mol). Coordination of one solvent molecule (diethyl ether) to the zinc site leads to a marginal rise of energy both for *syn*-**4a** and *anti*-**4a**, which suggests that solvent coordination is not relevant for the epimerization pathway. This result is in agreement with the fact that the cross-coupling reaction proceeded also in other solvents, such as toluene

[123] This project was realized in cooperation with D. Keefer, who conducted and analyzed the DFT-calculations.

or THF, with high retention of configuration.[112] We examined two possible pathways, which could lead to epimerization from *syn*-**4a** to *anti*-**4a** and vice versa, namely *via* a planar transition state *ts*-**4a** (see Scheme 43) or by cleavage of the carbon-zinc bond. Both the transition state energy of 95.9 kcal/mol and the carbon-zinc bond energy of ca. 35 kcal/mol corroborate the high stability of **4a** towards epimerization at 25 °C. Another important step in this catalytic cross-coupling cycle, in which stereoretention is crucial, is the configurational stability of the Pd^{II} intermediate **123** (see Scheme 41). We performed an analogous analysis of potential epimerization channels on **123** using Pd-PEPPSI. To stay within the computational feasibility of our quantum chemical method, we simplified the catalyst by replacing the four experimentally used isopentyl residues in Pd-PEPPSI-iPent with methyl groups. This allows slightly more steric flexibility, while the electronic nature around the Pd^{II} and the carbon stereocenter is unaltered. Starting from a tetrahedral geometry of the four ligands around the Pd^{II} center, the optimization ends in an energetic minimum which exhibits a nearly planar tetragonal structure.[92]

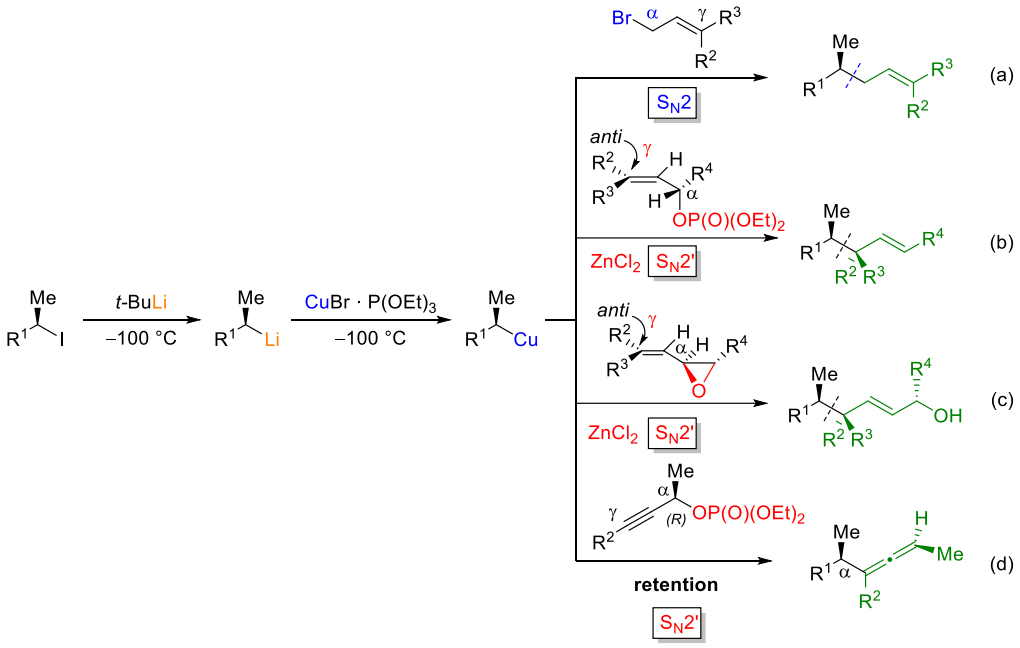


Scheme 43. Theoretical calculations of the epimerization of secondary alkylzinc reagent *anti*-**4a** to *syn*-**4a** and Pd^{II} intermediates of type **123**. Molecular geometries and Gibbs free energies ΔG_{solv} in solution. **Top:** Stabilities of *anti*-**4a** and *syn*-**4a**. **Bottom:** Stabilities of *syn*- and *anti*-**123a** and **123b**.

Thus, there are four possible species for **123**, with either the *syn*- or the *anti*-isomer in *cis* (**123a**) or *trans* (**123b**) position to the alkene (see Scheme 43). A comparison of configurational stabilities of the four species showed that the *cis*-conformer **123a** is more stable than the *trans*-conformer **123b**, which is encouraging since reductive elimination can only occur from the *cis*-configuration **123a**. Once again, the calculated high energy of the transition states *ts*-**123a** (41.8 kcal/mol; *anti*-**123a** to *syn*-**123a**) and *ts*-**123b** (39.7 kcal/mol; *anti*-**123b** to *syn*-**123b**) and carbon-palladium bonding energies of *syn*-**123a** (47.7 kcal/mol), *anti*-**123a** (47.2 kcal/mol), *syn*-**123b** (41.6 kcal/mol), and *anti*-**123b** (40.1 kcal/mol) corroborate the experimentally found retention of configuration. Interestingly, the energy barrier is significantly lower for *ts*-**123a** and *ts*-**123b** than it is for *ts*-**4a**, which suggests that a potential loss of stereoinformation occurs more likely at the Pd^{II} intermediate **123**. Nevertheless, we presume that the minimal epimerization of the secondary alkylzinc reagents may be due to polymolecular exchange reactions between these zinc reagents, which may involve the salts LiBr and LiI.

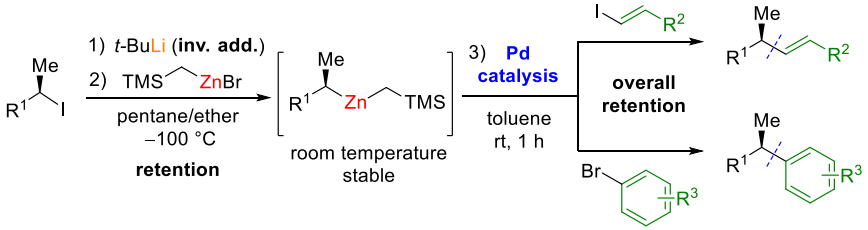
5 Summary

In this thesis the preparation of chiral secondary alkyl organometallic reagents and their application in organic synthesis was addressed. First, regioselective allylic substitutions of chiral secondary alkylcopper reagents were described (see Scheme 44, a-b). These chiral alkylcoppers underwent S_N2-substitutions with allylic bromides. The addition of $ZnCl_2$ and the use of chiral allylic phosphates allows to switch the regioselectivity towards S_N2'-substitutions. This method was extended to the regioselective substitution of allylic epoxides leading to chiral allylic alcohols with retention of configuration (Scheme 44, c). Finally, *anti*-S_N2'-substitutions of chiral alkylcopper reagents with propargylic phosphates were described affording axially chiral allenes (Scheme 44, d). DFT-calculations were performed to determine the structure of these alkylcopper reagents and rationalize their high configurational stability in THF.[91]



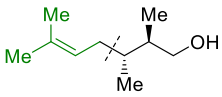
Scheme 44: Stereoretentive preparation of chiral secondary alkylcopper reagents and subsequent nucleophilic substitutions.

Furthermore, palladium-catalyzed Csp^3-Csp^2 cross-coupling reactions of chiral secondary dialkylzinc reagents with alkenyl and aryl halides at 25 °C were developed (see Scheme 45). This method provided α-chiral alkenes and arenes with very high overall retention of configuration (dr up to 98:2) and good overall yields (up to 76% for 3 reaction steps).

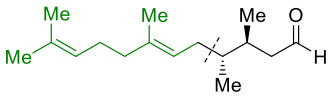


Scheme 45: Stereoretentive preparation of chiral secondary dialkylzinc reagents and subsequent palladium-catalyzed cross-coupling reactions.

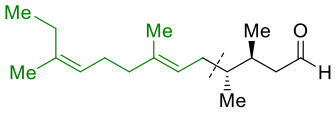
These methods were applied in efficient total syntheses of various natural products demonstrating their synthetic utility. The three ant pheromones (+)-lasiol, (+)-13-norfaranal and (+)-faranal (see Scheme 46) were prepared in high diastereoselectivity (dr up to 98:2) and in high enantioselectivity (99% *ee*) by allylic S_N2-substitution reaction of the corresponding alkylcopper reagents with allylic substrates.



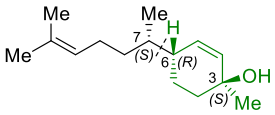
(+)-lasiol
dr = 98:2, 99% *ee*;
6 steps, 21% overall yield



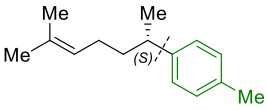
(+)-13-norfaranal
dr = 97:3, 99% *ee*;
11 steps, 2.6% overall yield



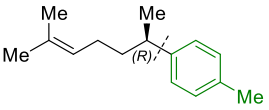
(+)-faranal
dr = 97:3, 99% *ee*;
12 steps, 6.9% overall yield



(3*S*,6*R*,7*S*)-zingiberenol
9.7% yield over 8 steps;
dr(C3-C6) = 99:1; dr(C6-C7) = 81:19



(*S*)-curcumene
er = 93:7
31% yield over 3 steps



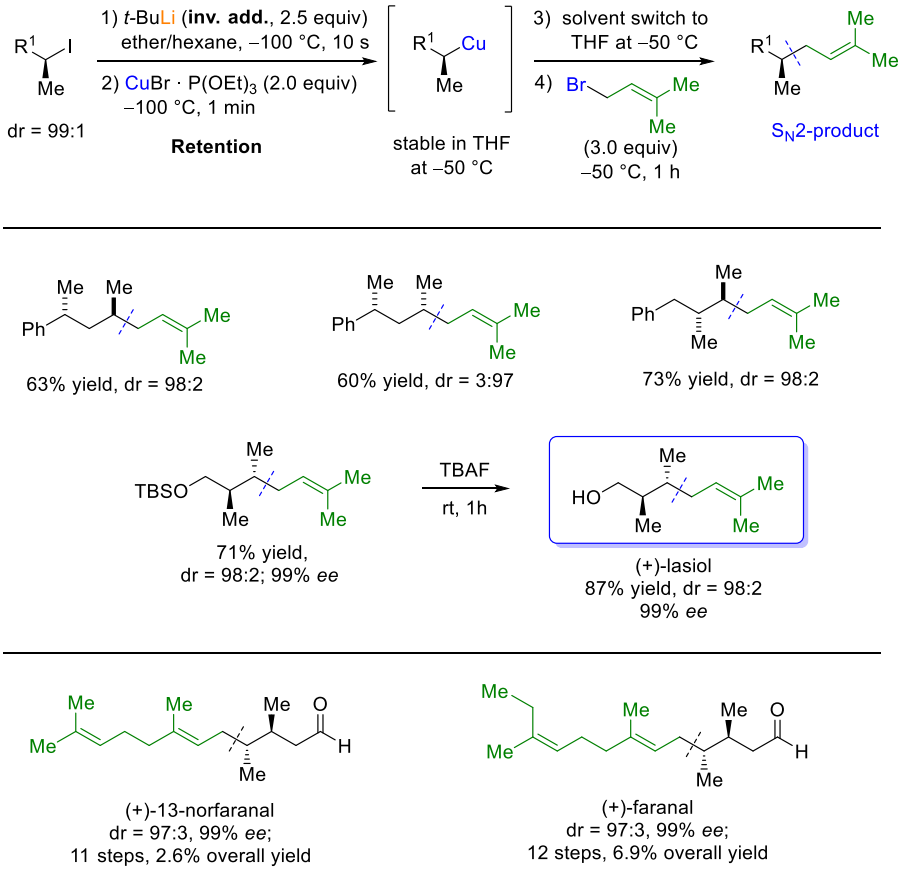
(*R*)-curcumene
er = 7:93
28% yield over 3 steps

Scheme 46: Natural products prepared *via* either nucleophilic substitution of chiral alkylcopper reagents or palladium-catalyzed cross-coupling reactions of chiral alkylzinc reagents.

The *anti*-S_N2'-substitution of chiral epoxides was used in a total synthesis of the natural product (3*S*,6*R*,7*S*)-zingiberenol in 8 steps and 9.7 % overall yield starting from commercially available 3-methyl-2-cyclohexenone. Finally, the palladium-catalyzed cross-coupling reaction of chiral alkylzinc reagents was applied in the total synthesis of the sesquiterpenes (*S*)- and (*R*)-curcumene with absolute control of stereochemistry.

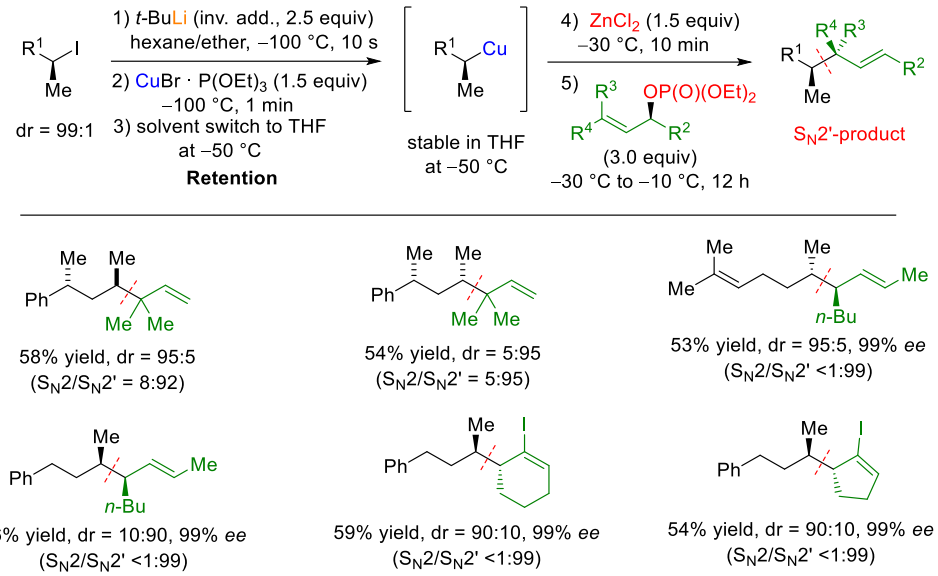
5.1 Regio- and Stereoselective Allylic Substitutions of Chiral Secondary Alkylcopper Reagents

The regio- and stereoselective allylic substitution of chiral secondary alkylcopper reagents was investigated. The reaction of these chiral alkylcopper reagents with allylic bromides in THF provided exclusively the S_N2-products (up to >99% S_N2-regioselectivity; see Scheme 47). The efficiency of this method was demonstrated in the preparation of the three ant pheromones (+)-lasiol (dr = 98:2, 99% *ee*; 6 steps, 21% overall yield), (+)-norfaranal (dr = 97:3, 99% *ee*; 11 steps, 2.6% overall yield) and (+)-faranal (dr = 97:3, 99% *ee*; 12 steps, 6.9% overall yield) starting from commercially available ethyl (*R*)-hydroxybutyrate.



Scheme 47: S_N2-substitution reactions of chiral secondary alkylcopper reagents.

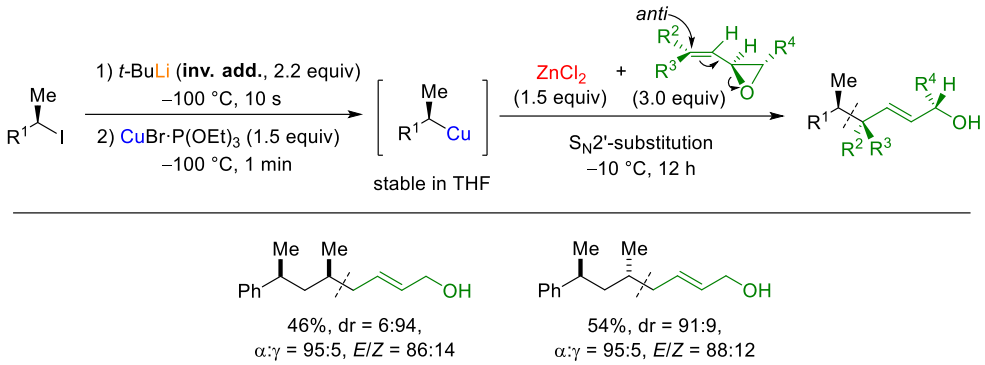
The addition of $ZnCl_2$ and the use of chiral allylic phosphates allows to switch the regioselectivity towards S_N2'-substitutions (up to >99% S_N2'-regioselectivity). These conditions enable the performance of highly selective *anti*-S_N2'-substitutions with absolute control of two adjacent stereocenters (see Scheme 48).



Scheme 48: Zinc-mediated S_N2'-substitution reactions of chiral alkylcopper reagents.

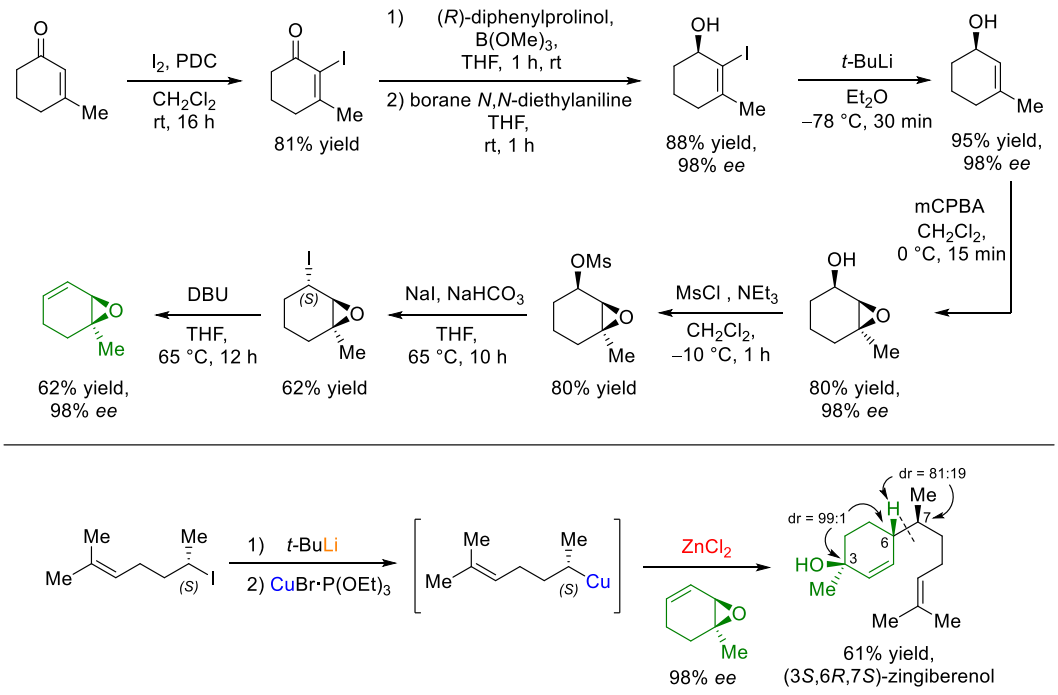
5.2 Stereoselective *anti*-S_N2'-Substitutions of Secondary Alkylcopper-Zinc Reagents with Allylic Epoxides

The stereoselective S_N2'-substitution of secondary alkylcopper-zinc reagents with allylic epoxides was described. The reaction proceeds regioselectively (α:γ > 95:5) and with retention of configuration (see Scheme 49). By using chiral cyclic epoxides highly *anti*-S_N2'-substitutions were performed.



Scheme 49: Stereoselective *anti*-S_N2'-substitutions of chiral allylic epoxides.

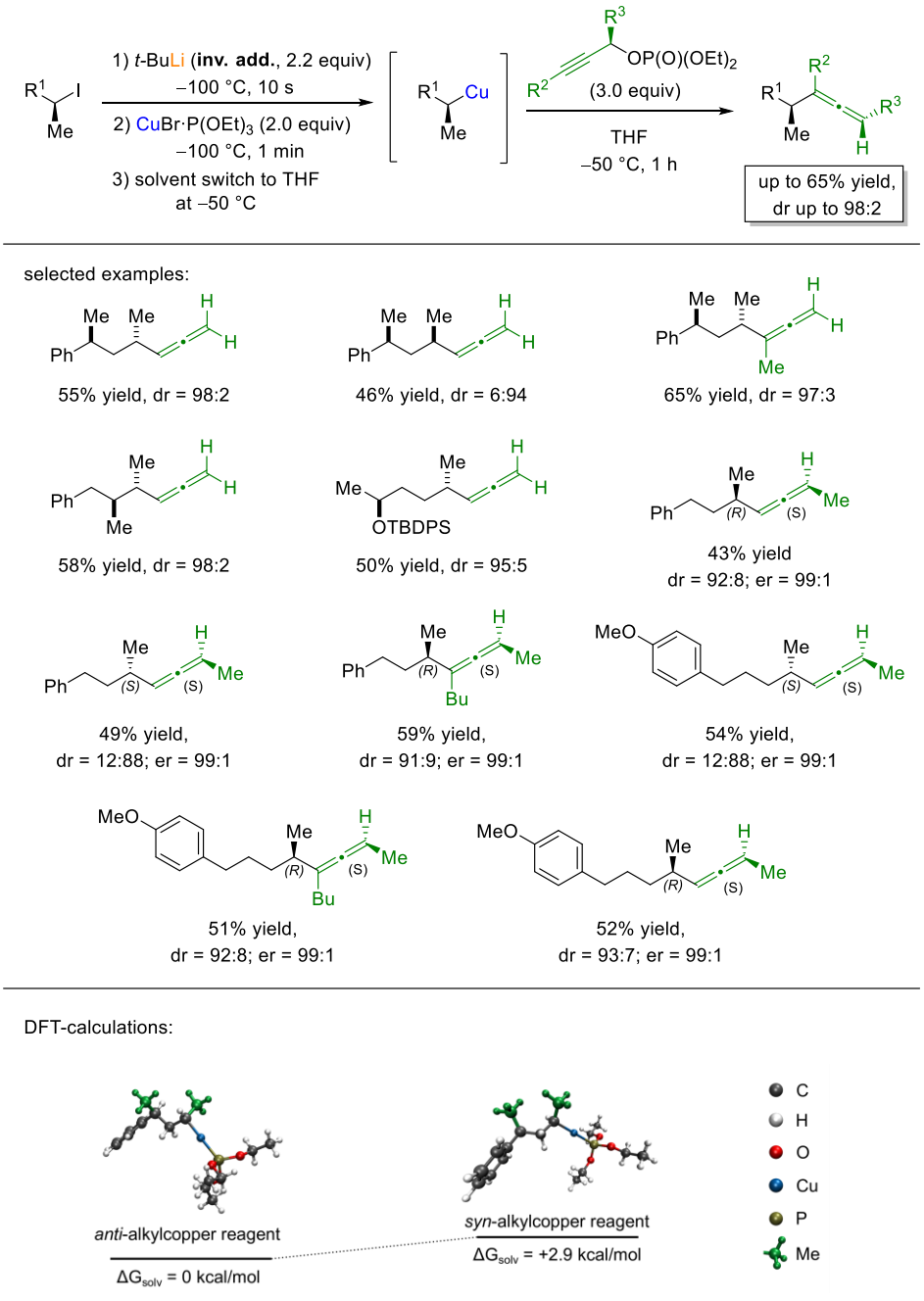
The method was used in the total synthesis of (3*R*,6*S*,7*S*)-zingiberenol in 8 steps and 9.7 % overall yield (dr (3*S*,6*R*) = 99:1; dr (6*R*,7*S*) = 81:19) starting from commercially available 3-methyl-2-cyclohexenone (see Scheme 50).



Scheme 50: Stereoselective preparation of (3*S*,6*R*,7*S*)-zingiberenol.

5.3 Regio- and Diastereoselective Reactions of Chiral Secondary Alkylcopper Reagents with Propargylic Phosphates

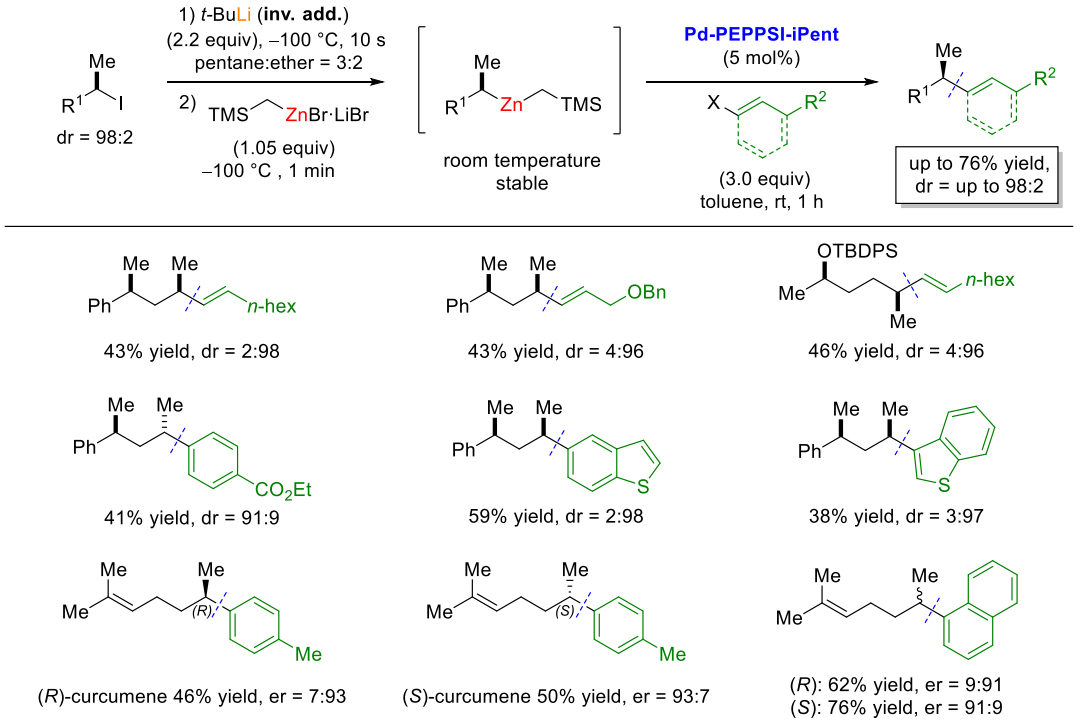
The preparation of axially chiral allenes bearing an α-chiral center was performed by *anti*-S_N2'-substitution reaction of chiral secondary alkylcopper reagents with enantioenriched propargylic phosphates (see Scheme 51). DFT-calculations emphasized that the most stable structure of the alkylcopper reagent is being coordinated by $P(OEt)_3$ instead of diethyl ether or THF. The computational calculations corroborate the high stability of these alkylcopper reagents towards epimerization at –50 °C.[91]



Scheme 51: Preparation of chiral allenes and DFT-calculations.

5.4 Stereoselective Csp^3-Csp^2 Cross-Couplings of Chiral Secondary Alkylzinc Reagents

The palladium-catalyzed cross-coupling reaction of open-chain chiral secondary dialkylzinc reagents with alkenyl and aryl halides has been developed. The configurational stability of these chiral non-stabilized dialkylzinc reagents was determined and exceeded several hours at 25 °C. DFT-calculations were performed to rationalize the high configurational stability of these dialkylzinc reagents and stereoretention during the catalytic cycle.[123] By using this method various α-chiral alkenes and arenes were prepared in up to 76% yield and dr up to 98:2 (see Scheme 52).



Scheme 52: Stereoselective cross-coupling reactions leading to α-chiral alkenes and arenes.

C. EXPERIMENTAL PART

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C. Experimental Part

1 General

All reactions were carried out with magnetic stirring and under argon atmosphere in glassware dried with a heat gun. Syringes which were used to transfer anhydrous solvents or reagents were purged with argon three times prior to use. Unless otherwise indicated, yields as stated are isolated yields of compounds and are estimated to be >95% pure as determined by ^{1}H-NMR (25 °C) and capillary gas chromatography. The ratio of diastereomers (*anti*/*syn* ratio) was determined by ^{1}H-NMR, ^{13}C-NMR spectroscopy or capillary GC.

1.1 Solvents

All solvents were dried according to standard methods by distillation over drying agents as stated below and were stored under argon atmosphere. Solvents for flash column chromatography were distilled on a vacuum evaporator prior to use.

Dichloromethane was predried over $CaCl_2$ and distilled from CaH_2.

EtOH was treated with phthalic anhydride (25 g/L) and sodium, heated to reflux for 6 h and distilled.

Diethyl ether was predried over calcium hydride and dried with the solvent purification system SPS-400-2 from INNOVATIVE TECHNOLOGIES INC or purchased from Acros (99.5% extra dry over molecular sieve).

Methanol was heated to reflux over magnesium methoxide and distilled.

***n*-pentane** was purchased from Acros (99+%, extra dry over molecular sieve)

THF was continuously refluxed and freshly distilled from sodium benzophenone ketyl under nitrogen or purchased from Acros (99.5%, extra dry over molecular sieve).

Triethylamine was dried over KOH and distilled.

Toluene was purchased from Acros (99.85%, extra dry over molecular sieve).

1.2 Chromatography

Gas chromatography was performed with machines of *Agilent* Technologies 7890, using a column of type HP 5 (*Agilent* 5% phenylmethylpolysiloxane; length: 15 m; diameter: 0.25 mm; film thickness: 0.25 μm) or *Hewlett-Packard* 6890 or 5890 series II, using a column of type HP 5 (*Hewlett-Packard*, 5% phenylmethylpolysiloxane; length: 15 m; diameter: 0.25 mm; film thickness: 0.25 μm).

Chiral gas chromatography (**GC**) was performed on the following columns:

- **Column A**: Chirasil-Dex CB, Varian, CP7502 (25.0 m x 250µm x 0.25µm), Average velocity 20, H_2-flux.
- **Column B**: β-Dex 120, Supelco, (30.0 m x 250µm x 0.25µm), Average velocity 40, H_2-flux.

Flash column chromatography was performed using SiO_2 (0.040–0.063 mm, 230–400 mesh ASTM) from Merck if not specially indicated.

Thin layer chromatography (TLC) was performed using SiO_2 pre-coated aluminium plates (Merck 60, F-254). The chromatograms were examined by 254 nm UV irradiation and/or by staining with PMA (10 g phosphormolybdic acid in 100 mL EtOH) followed by heating with a heatgun.

Preparative HPLC: For purification, an Agilent Technologies 1260 Infinity HPLC-System was used, consisting of two prep-pumps (acetonitrile/water, no additives), a MWD-detector (210 nm wavelength, 40 nm bandwidth, ref-wavelength 400 nm, ref-bandwidth 100 nm) and a fraction collector. Three different columns were used:

- Kinetix EVO C18 5 µm column (length: 150 mm, diameter: 10 mm).
- Kinetix EVO C18 5 µm column (length: 150 mm, diameter: 21.2 mm) and
- Waters XBridge Prep C8 5 µm column (length: 150 mm, diameter: 30 mm).

Chiral HPLC was performed on the following columns:

- Chiracel OD-H (length: 250 mm, diameter: 4.6 mm)
- Chiracel OJ-H (length: 250 mm, diameter: 4.6 mm)
- Chiracel AD-H (length: 250 mm, diameter: 4.6 mm)
- Chiracel OB-H (length: 250 mm, diameter: 4.6 mm)

1.3 Reagents

All reagents were obtained from commercial sources and used without further purification unless otherwise stated. Liquid reagents were distilled prior to use.

***n*-BuLi** solution in *n*-hexane was purchased from Albemarle (Chemetall).

***t*-BuLi** solution in *n*-pentane was purchased from Albemarle (Chemetall).

The concentration of *t*-BuLi (ca. 2 M in *n*-pentane) and *n*-BuLi (ca. 2.4 M in *n*-hexane) was determined by titration with dry 2-propanol and 1,10-phenanthroline as indicator in THF at −78 °C.

$CuBr{\cdot}P(OEt)_3$ was prepared according to literature.[54] The solution was prepared under Ar to obtain 3 M solution in diethyl ether. A dry and Ar-flushed 100 mL-*Schlenk*-flask was charged with a magnetic stirring bar, freshly distilled triethyl phosphite (4.98 g, 30 mmol, 5.1 mL) and toluene (30 mL). Copper (I) bromide (4.30 g, 30 mmol) was added portion wise and stirred for 1 h at rt. The light green solution was stirred 30 min at 80 °C. The cool solution was filtrated to obtain a clear solution of $CuBr{\cdot}P(OEt)_3$.

To the solution was added *i*-hexane (20 mL) and the solvent was removed under high vacuum. This step was repeated three times to obtain the purified complex without residues of toluene.

Me_3SiCH_2Li solution in *n*-pentane was purchased from Sigma Aldrich (ca. 1.0 M solution).

$ZnCl_2$ solution was prepared by drying $ZnCl_2$ (68.2 g, 500 mmol) in a *Schlenk*-flask under vacuum for 5 h at 140 °C. After cooling to 25 °C, THF (500 mL) was added and stirring was continued until the salt was dissolved.

1.4 Analytic Data

^{1}H-NMR and **^{13}C-NMR** spectra were recorded on VARIAN Mercury 200, BRUKER ARX 300, VARIAN VXR 300 S and Bruker AMX 600 instruments. Chemical shifts are reported as δ-values in ppm relative to the solvent peak in $CDCl_3$ (residual chloroform: δ 7.26 ppm for ^{1}H-NMR, δ 77.0 ppm for ^{13}C-NMR). Abbreviations for signal coupling are as follows: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), m (multiplet).

Mass spectroscopy (MS): High resolution (HRMS) and low resolution (LRMS) spectra were recorded on a FINNIGAN MAT 95Q instrument. Electron impact ionization (EI) was conducted with an ionization energy of 70 eV.

Infrared spectra (IR) were recorded from 4500 cm^{-1} to 650 cm^{-1} on a PERKIN ELMER Spectrum BX-59343 instrument. For detection a SMITHS DETECTION DuraSampl*IR* II Diamond ATR sensor was used and the absorption bands are reported in wavenumbers. The abbreviations for intensity are as follows: vs (very strong; maximum intensity), s (strong; above 75% of max. intensity), m (medium; from 50% to 75% of max. intensity), w (weak; below 50% of max. intensity) as well as br (broad).

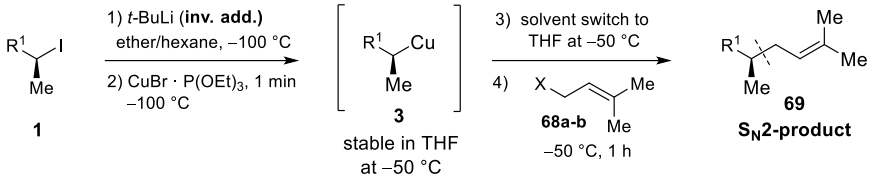
Optical rotation values were recorded on a *Perkin Elmer* 241 or *Anton Paar MCP* 500 polarimeter. The specific rotation is calculated as follows:

$$[\alpha]_{\lambda}^{\varphi} = \frac{[\alpha] \cdot 100}{c \cdot d}$$

The wavelength λ is reported in nm and the measuring temperature ϕ in °C. α represents the recorded optical rotation, c the concentration of the analyte in 10 mg/mL and d the length of the cuvette in dm. Thus, the specific rotation is given in $10^{-1}\cdot deg\cdot cm^2\cdot g^{-1}$. Usage of the sodium D line (λ = 589 nm) is indicated by D instead of the wavelength in nm. The respective concentration as well as the solvent is reported at the relevant section of the Experimental Part.

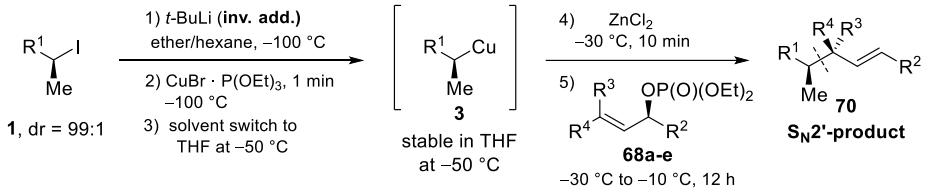
2 Regio- and Stereoselective Allylic Substitutions of Secondary Alkylcopper Reagents

2.1 Typical Procedure for the S_N2-Substitution Reactions (TP1)



A dry and Ar-flushed *Schlenk*-tube was cooled to −100 °C and charged with a solution of *t*-BuLi (0.50 mmol, 2.5 equiv) together with a mixture of diethyl ether (1.00 mL) and *n*-pentane (1.50 mL). A solution of alkyl iodide (0.20 mmol, 1.0 equiv) in diethyl ether (0.40 mL) was added dropwise for 1 min. After stirring for 10 sec, a solution of $CuBr{\cdot}P(OEt)_3$ (0.13 mL, 3 M in diethyl ether, 0.40 mmol, 2.0 equiv) was added and the reaction mixture was stirred for 1 min at −100 °C to observe the color change from yellow to green. The *Schlenk*-tube was transferred to a cooling bath (−50 °C) and the solvent was pumped away under high vacuum. After 10 min, precooled THF (2 mL) and then the allylic electrophile (0.60 mmol, 3.0 equiv) were added. The reaction mixture was stirred for 1 h at −50 °C. After quenching the reaction mixture with aq. NH_3 solution, the reaction mixture was extracted with diethyl ether (3 × 10 mL). The combined organic phases were dried over $MgSO_4$ and the solvents were evaporated. The obtained crude product was purified by flash column chromatography on silica gel to afford alkenes of type **69**.

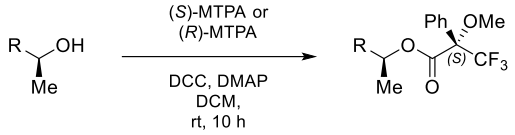
2.2 Typical Procedure for the S_N2'-Substitution Reactions (TP2)



A dry and Ar-flushed *Schlenk*-tube was cooled to −100 °C and charged with a solution of *t*-BuLi (0.50 mmol, 2.5 equiv) together with a mixture of diethyl ether (1.00 mL) and *n*-hexane (1.50 mL). A solution of iodide (0.20 mmol, 1.0 equiv) in diethyl ether (0.40 mL) was added dropwise for 1 min. After stirring for 10 sec, a solution of $CuBr{\cdot}P(OEt)_3$ (0.10 mL, 3 M in diethyl ether, 0.30 mmol, 1.5 equiv) was added and the reaction mixture was stirred for 1 min at −100 °C to observe the color change from yellow to green. The *Schlenk*-tube was transferred to a cooling bath (−50 °C) and the

solvent was pumped away under high vacuum (10 min). Precooled THF (2 mL) was added and after 10 sec, $ZnCl_2$ (0.30 mmol, 0.30 mL, 1.0 M in THF, 1.5 equiv) was added dropwise. The reaction mixture was warmed to −30 °C and stirred for 10 min. The allylic phosphate (dissolved in 0.60 mL THF) was added and the reaction mixture was warmed to−10 °C. After 12 h, the reaction mixture was quenched with aq. NH_3 solution and extracted with diethyl ether (3 × 10 mL). The combined organic phases were dried over $MgSO_4$ and the solvents were evaporated. The obtained crude product was purified by flash column column chromatography on silica gel to afford alkenes of type **70**.

2.3 Typical Procedure for Mosher Ester Analysis (TP3)



The corresponding Mosher ester were prepared according to literature procedure.[124] A dry and Ar-flushed round-bottom flask was charged with the alcohol (1.0 equiv), the (*S*)- or (*R*)-Mosher's acid (α-methoxy-α-trifluoromethylphenylacetic acid, MTPA; 3.0 equiv) and dichloromethane (0.1 M solution). DCC (3.0 equiv) and DMAP (3.0 equiv) were added subsequently and the reaction mixture was stirred for 10 h at rt. After quenching with brine, the reaction mixture was extracted with diethyl ether (3 × 10 mL). The combined organic phases were dried over $MgSO_4$ and the solvents were evaporated. The obtained crude product was purified by flash column chromatography (*i*-hexane/ethyl acetate = 40/1) on silica gel to afford the Mosher ester of type **M**.

[124] a) T. R. Hoye, C. S. Jeffrey, F. Shao, *Nat. Protoc.* **2007**, 2, 2451–2458. b) J. M. Seco, E. Quiñoá, R. Riguera, *Chem. Rev.* **2004**, 104, 17–117.

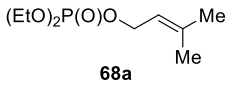
2.4 Preparation of Starting Materials

2.4.1 Secondary Alkyl Iodides

The alkyl iodides (*syn*-**1a**[53], *anti*-**1a**[53], *anti*-**1b**[56], 2*S*,3*S*-**1c**[56], *syn*-**1d**[49], (*S*)-**1e**[50], (*R*)-**1f**[50], (*S*)-**1f**[50]) were prepared from the corresponding secondary alkyl alcohols and are literature known.

2.4.2 Preparation of Chiral Allylic Phopshates

Preparation of the electrophile 68a:

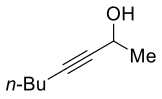


68a

Diethyl (3-methylbut-2-en-1-yl) phosphate (68a): A solution of 3-methylbut-2-en-1-ol (1.72 g, 20 mmol, 1.0 equiv), DMAP (0.24 g, 2.0 mmol, 0.10 equiv) and pyridine (1.80 mL, 22 mmol, 1.1 equiv) in dichloromethane (20.0 mL) was cooled to 0 °C. After addition of diethyl chlorophosphate (3.19 mL, 22 mmol, 1.1 equiv), the solution was allowed to warm to rt and stirred for 15 h. The reaction mixture was extracted with diethyl ether (3 x 100 mL) and purified by flash column chromatography on silica gel with *i*-hexane/ethyl acetate = 1/1 to afford **68a** (2.53 g, 11 mmol, 57% yield) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 5.40 (t, J = 7.2 Hz, 1H), 4.54 (t, J = 7.8 Hz, 2H), 4.16–4.05 (m, 4H), 1.76 (s, 3H), 1.71 (s, 3H), 1.33 (t, J = 7.1 Hz, 6H).
^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 139.5, 119.4, 64.2, 63.7, 25.9, 18.2, 16.3.
IR (ATR): $\tilde{\nu}$[cm^{-1}] = 2982 (w), 2934 (w), 2912 (w), 1740 (vw), 1674 (vw), 1478 (vw), 1446 (w), 1386 (w), 1260 (m), 1206 (w), 1166 (w), 1122 (w), 1100.

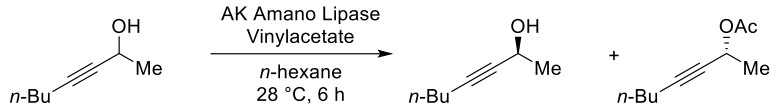
Preparation of the electrophile 68c:



Oct-3-yn-2-ol: A dry and Argon flushed *Schlenk*-flask was charged with hex-1-yne (11.8 mL, 100 mmol, 1.0 equiv) in THF (200 mL) and cooled to –78 °C. *n*-BuLi (41.8 mL, 2.63 M in *n*-hexane, 110 mmol, 1.1 equiv) was added using a syringe pump (rate: 100 mL/h) and the solution was stirred for 2.5 h. A solution of acetaldehyde (6.19 mL, 110 mmol, 1.1 equiv) in THF (40 mL) was added (rate: 120 mL/h). The solution was gradually warmed to rt and stirred for 18 h. After quenching with sat. aq. NH_4Cl solution, the reaction mixture was extracted with diethyl ether (3 x 200 mL). The combined organic phases were dried over $MgSO_4$ and the solvents were evaporated. The crude product was

purified by flash column chromatography on silica gel with *n*-pentane/diethyl ether = 3/1 to afford oct-3-yn-2-ol (11.8 g, 93.7 mmol, 94% yield) as a yellow oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 4.51 (q, *J* = 6.6 Hz, 1H), 2.29–2.12 (m, 2H), 1.54–1.44 (m, 2H), 1.43 (d, *J*= 6.5 Hz, 3H), 1.43–1.32 (m, 2H), 0.91 (t, *J* = 7.2 Hz, 3H).
^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 84.9, 82.3, 58.8, 30.9, 24.9, 22.1, 18.5, 13.7.



(*S*)-Oct-3-yn-2-ol: A dry and Ar flushed *Schlenk*-flask was charged with molecular sieves (3.30 g, 3 Å) and *n*-hexane (400 mL). Oct-3-yn-2-ol (6.66 g, 52.8 mmol, 1.0 equiv) and AK Amano Lipase (3.33 g, 0.5 w%) were added. Vinyl acetate (19.6 mL, 211 mmol, 4.0 equiv) was added dropwise and the reaction mixture was stirred for 6 h at 28 °C while monitored by chiral GC analysis. The reaction mixture was filtered and the solvent was evaporated. The crude product was purified by flash column chromatography on silica gel with *n*-pentane/diethyl ether = 10/1 (then 3/1) to afford the corresponding alcohol (*S*)-oct-3-yn-2-ol (2.19 g, 17.3 mmol, 33% yield, >99% *ee*) as a yellow oil and the corresponding acetate (*R*)-oct-3-yn-2-yl acetate (4.33 g, 25.7 mmol, 49% yield) as a pale yellow oil. The *ee* of (*S*)-oct-3-yn-2-ol was determined by chiral GC analysis

GC (Chirasil-Dex CB), 100 °C (const.); t_R (min) = 29.3 (*R*-enantiomer; minor), 30.4 (*S*-enantiomer; major). >99% *ee* (for chromatogram see Appendix).

(*S*)-Oct-3-yn-2-ol:

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 4.51 (q, *J* = 6.5 Hz, 1H), 2.23–2.15 (m, 2H), 1.54–1.44 (m, 2H), 1.42 (d, *J* = 6.5 Hz, 3H), 1.43–1.33 (m, 2H), 0.91 (t, *J*= 7.2 Hz, 3H).
^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 84.9, 82.3, 58.8, 30.9, 24.9, 22.1, 18.5, 13.7.
IR (ATR): $\tilde{\nu}$[cm^{-1}] = 3336 (w), 2978 (w), 2958 (m), 2932 (m), 2874 (m), 2248 (vw), 1456 (m), 1432 (w), 1408 (w), 1370 (m), 1330 (m), 1288 (w), 1252 (w), 1214 (vw), 1200 (vw), 1154 (s), 1106 (w), 1074 (vs), 1048 (m), 1008 (m), 986 (w), 968 (w), 958 (w), 930 (w), 894 (m), 860 (w), 778 (w), 752 (w), 728 (w), 706 (m).
MS (EI, 70 eV): m/z (%): 111 (45), 97 (100), 93 (32), 91 (64), 84 (13), 83 (11), 81 (18), 79 (61), 77 (41), 69 (65), 67 (39), 55 (24), 55 (11), 43 (13), 41 (10).
HRMS (EI) for $C_8H_{14}O$: calc. [M^+–H]: 125.0972; found: 125.0961.

(*R*)-Oct-3-yn-2-yl acetate:

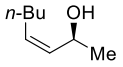
^{1}H-NMR (CDCl$_3$, 400 MHz): δ [ppm] = 5.44 (q, *J* = 6.6 Hz, 1H), 2.24–2.15 (m, 2H), 2.06 (s, 3H), 1.55–1.47 (m, 2H), 1.45 (d, *J* = 6.7 Hz, 3H), 1.43–1.33 (m, 2H), 0.90 (t, *J*= 7.2 Hz, 3H).

^{13}C{^{1}H}-NMR (CDCl$_3$, 100 MHz): δ [ppm] = 170.2, 85.7, 77.5, 61.0, 30.7, 22.1, 22.0, 21.3, 18.5, 13.7.

IR (ATR): $\tilde{\nu}$[cm^{-1}] = 2988 (vw), 2960 (w), 2936 (w), 2874 (w), 1740 (s), 1454 (w), 1434 (w), 1370 (m), 1340 (w), 1310 (w), 1230 (vs), 1168 (m), 1110 (w), 1058 (m), 1046 (m), 1016 (m), 968 (w), 956 (w), 942 (m), 846 (w), 718 (vw).

MS (EI, 70 eV): m/z (%): 126 (31), 125 (38), 111 (37), 97 (100), 93 (80), 91 (98), 84 (77), 83 (41), 79 (73), 77 (70), 69 (88), 67 (29), 55 (24).

HRMS (EI) for $C_{10}H_{16}O_2$: calc. [M^+–H]: 167.1078; found: 167.1066.

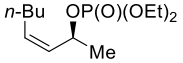


(*S*,*Z*)-Oct-3-en-2-ol: A dry and Argon flushed *Schlenk*-flask was charged with (*S*)-oct-3-yn-2-ol (1.26 g, 10 mmol, 1.00 equiv) in methanol (100 mL). Palladium on $BaSO_4$ (35 mg) and quinoline (1.00 mL, 8.5 mmol, 0.85 equiv) were added. The flask was flushed with hydrogen several times. After stirring for 25 min under a hydrogen atmosphere, the reaction mixture was filtered and the solvent was evaporated. The crude product was purified by flash column chromatography on silica gel with *n*-pentane/diethyl ether = 4/1 to afford (*S*,*Z*)-oct-3-en-2-ol (1.27 g, 9.9 mmol, 99% yield) as a colorless oil. The *ee* of (*S*,*Z*)-oct-3-en-2-ol was determined by chiral HPLC analysis of the corresponding pentafluorobenzoate.

HPLC (column: OD-H; *n*-heptane/2-propanol = 5999:1, 0.6 mL/min): t_R (min) = 8.5 (*R*), 8.7 (*S*). >99% *ee* (for chromatogram see Appendix).

^{1}H-NMR (CDCl$_3$, 400 MHz): δ [ppm] = 5.48–5.36 (m, 2H), 4.69–4.60 (m, 1H), 2.13–2.04 (m, 2H), 1.38–1.27 (m, 4H), 1.24 (d, *J* = 6.3 Hz, 3H), 0.90 (t, *J* = 7.2 Hz, 3H).

^{13}C{^{1}H}-NMR (CDCl$_3$, 100 MHz): δ [ppm] = 133.9, 131.6, 64.0, 32.0, 27.4, 23.8, 22.4, 14.1.



68c

(*S*,*Z*)-Diethyl oct-3-en-2-yl phosphate (68c): According to literature,[125] a solution of (*S*,*Z*)-oct-3-en-2-ol (513 mg, 4.0 mmol, 1.0 equiv), DMAP (49.0 mg, 0.4 mmol, 0.1 equiv) and pyridine (0.36 mL, 4.4 mmol, 1.1 equiv) in dichloromethane (5.0 mL) was cooled to 0 °C. After the addition of diethyl chlorophosphate (0.64 mL, 4.4 mmol, 1.1 equiv), the solution was allowed to warm to rt and stirred for

[125] H. Ohmiya, U. Yokobori, Y. Makida, M. Sawamura, *J. Am. Chem. Soc.* **2010**, 132, 2895–2897.

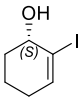
19 h. The reaction mixture was quenched with water and extracted with diethyl ether (3 x 25 mL) and purified by flash column chromatography on silica gel with *n*-pentane/diethyl ether = 1/2 to afford **68c** (820 mg, 3.1 mmol, 77% yield, 99% *ee*) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 5.60–5.18 (m, 2H), 5.37–5.11 (m, 1H), 4.21–3.94 (m, 4H), 2.19–2.07 (m, 2H), 1.37 (d, *J* = 6.3 Hz, 3H), 1.37–1.25 (m, 10H), 0.89 (t, *J* = 6.9 Hz, 3H).
^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 132.8, 130.0, 71.5, 63.6, 31.8, 27.5, 22.9, 22.5, 16.3, 14.1.

Synthesis of the electrophile 68d:[64f]

2-Iodocyclohex-2-en-1-one: According to literature,[101] PDC (2.82 g, 7.5 mmol, 0.3 equiv) and I_2 (6.35 g, 25 mmol, 1.0 equiv) were added in one portion to a solution of cyclohex-2-en-1-one (2.27 mL, 25 mmol, 1.0 equiv) in dichloromethane (150 mL). The reaction mixture was covered in aluminum-foil and stirred at rt overnight. The reaction mixture was filtered and the filtrate was washed with *n*-pentane. The organic phase was washed with 2 M HCl, with sat. aq. $NaHCO_3$, with sat. aq. $Na_2S_2O_3$ and with brine. The combined organic phases were dried over $MgSO_4$ and concentrated. The crude product was purified by flash column chromatography on silica gel with *n*-pentane/diethyl ether = 7/3 to afford 2-iodo-cyclohex-2-en-1-one (4.27 g, 19 mmol, 76% yield) as a slightly yellow solid.

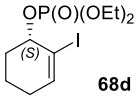
^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.77 (t, *J* = 4.4, 1H), 2.69–2.64 (m, 2H), 2.44 (td, *J* = 6.0, 4.4, 2H), 2.13–2.05 (m, 2H).
^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 192.3, 159.5, 104.0, 37.4, 30.1, 23.00.



(*S*)-2-Iodocyclohex-2-en-1-ol: A flame dried round-bottom flask was charged with a solution of (*R*)-diphenylprolinol (244 mg, 0.96 mmol, 0.05 equiv) and $B(OMe)_3$ (0.01 mL, 0.96 mmol, 0.05 equiv) in THF (20 mL). The mixture was stirred for 1 h at rt. Borane *N*,*N*-diethylaniline (3.51 mL, 19.2 mmol, 1.00 equiv) and 2-iodocyclohex-2-en-1-one (4.27 g, 19.2 mmol, 1.00 equiv; dissolved in 20 mL THF) were added dropwise. The reaction mixture was stirred for 1 h and then quenched with methanol (20 mL). The solvent was removed under reduced pressure and the obtained crude product was diluted with diethyl ether. The organic phase was washed with 7% aq. Na_2CO_3 sol., 10% aq. $KHSO_4$ sol. and brine. The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. The crude

product was purified by flash column chromatography on silica gel with *n*-pentane/diethyl ether = 3:1 to afford (*S*)-2-iodo-cyclohex-2-en-1-ol (2.83 g, 12.7 mmol, 66% yield, >99% *ee*) as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 6.50 (t, *J* = 3.8, 1H), 4.19 (t, *J* = 5.0, 1H), 2.18–2.05 (m, 2H), 1.97–2.03 (m, 2H), 1.85–1.97 (m, 1H), 1.82–1.62 (m, 2H).
^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 192.4, 159.6, 104.0, 37.4, 30.1, 23.0.



68d

(*S*)-Diethyl (2-iodocyclohex-2-en-1-yl) phosphate (68d): *N*-methylimidazole (0.76 mL, 9.6 mmol, 2.4 equiv) was added to a solution of 2-iodocyclohex-2-en-1-ol (896 mg, 4.0 mmol, 1.0 equiv) in diethyl ether (7.50 mL). The reaction mixture was cooled to 0 °C and diethyl chlorophosphate (1.46 mL, 9.6 mmol, 2.4 equiv) was added dropwise. The reaction mixture was allowed to warm to rt within 2 h and then quenched with brine. The reaction mixture was extracted with diethyl ether (3 x 10 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash column chromatography on AlOx (grade III) with *n*-pentane/diethyl ether = 1/1 to afford **68d** (976 mg, 2.7 mmol, 67% yield, >99% *ee*) as a colorless oil. The *ee* of **68d** was determined by chiral HPLC analysis.

HPLC (column: OJ-H; *n*-heptane/2-propanol = 99:1, 0.6 mL/min): t_R (min) = 21.7 (*R*), 26.4 (*S*). >99% *ee* (for chromatogram see Appendix).
^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 6.66–6.61 (m, 1H), 4.91–4.84 (m, 1H), 4.29–4.17 (m, 2H), 4.18–4.09 (m, 2H), 2.24–1.92 (m, 4H), 1.85–1.64 (m, 2H), 1.41–1.30 (m, 6H).
^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 144.1, 95.4, 78.3, 64.4, 64.0, 31.3, 29.4, 16.6, 16.3.

Synthesis of the electrophile 68e:[64f]

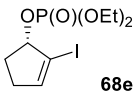
2-Iodocyclopent-2-en-1-one: PDC (2.25 g, 6.0 mmol, 0.3 equiv) and I_2 (5.06 g, 20 mmol, 1.0 equiv) were added to a solution of cyclopent-2-en-1-one (1.64 g, 20 mmol, 1.0 equiv) in dichloromethane (120 mL). The reaction mixture was covered in aluminum-foil and stirred at rt for 12 h. The reaction mixture was filtered and washed with *n*-pentane. The organic phase was washed with 2 M HCl, with sat. aq. $NaHCO_3$, with sat. aq. Na_2S2O_3 and with brine. The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel

with *n*-pentane/diethyl ether = 7/3 to afford 2-iodocyclopent-2-en-1-one (3.15 g, 15 mmol, 76% yield) as colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 8.02 (t, J = 2.9, 1H), 2.78 (ddd, J = 7.4, 2.9, 2.0, 2H), 2.53–2.50 (m, 2H).
^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 204.1, 169.6, 103.1, 31.2, 1.2.

(*S*)-2-iodocyclopent-2-en-1-ol: A flame dried round-bottom flask was charged with a solution of (*R*)-diphenylprolinol (207 mg, 0.82 mmol, 0.05 equiv) and $B(OMe)_3$ (0.01 mL, 0.82 mmol, 0.05 equiv) in THF (16.4 mL). The mixture was stirred for 1 h at rt. Borane *N*,*N*-diethylaniline (2.99 mL, 16.4 mmol, 1.00 equiv) was added and then 2-iodo-3-methylcypent-2-en-1-one (3.42 g, 16.4 mmol, 1.00 equiv; dissolved in 16 mL THF) was added dropwise. The reaction mixture was stirred for 1 h and then quenched with methanol. The solvent was removed under reduced pressure and the obtained crude product was diluted in diethyl ether. The organic phase was washed with 7% aq. Na_2CO_3 sol., 10% aq. $KHSO_4$ sol. and brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel with *n*-pentane/diethyl ether (3:1) to afford (*S*)-2-iodo-3-methylcyclopent-2-en-1-ol (2.35 g, 11.2 mmol, >99% *ee*) as a white solid. The *ee* of (*S*)-2-iodocyclopent-2-en-1-ol was determined by chiral HPLC analysis.

HPLC (column: OD-H; *n*-heptane/2-propanol = 90:10, 0.6 mL/min): t_R (min) = 13.8 (*R*), 17.8 (*S*). >99% *ee* (for chromatogram see Appendix).
^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 6.29 (td, J = 2.5, 1.0, 1H), 4.81–4.59 (m, 1H), 2.55–2.44 (m, 1H), 2.38–2.26 (m, 2H), 1.91–1.81 (m, 2H).
^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 142.8, 100.4, 82.4, 32.9, 31.6.



68e

(*S*)-Diethyl (2-iodocyclopent-2-en-1-yl) phosphate (68e): *N*-methylimidazole (0.47 mL, 6.0 mmol, 2.4 equiv) was added to a solution of 2-iodocyclopent-2-en-1-ol (525 mg, 2.5 mmol, 1.0 equiv) in diethyl ether (5.0 mL). The reaction mixture was cooled to 0 °C and diethyl chlorophosphate (0.91 mL, 6.0 mmol, 2.4 equiv) was added dropwise. The reaction mixture was warmed to rt within 2 h and then quenched with brine. The reaction mixture was extracted with diethyl ether (3 x 10 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo.* The crude product was purified by

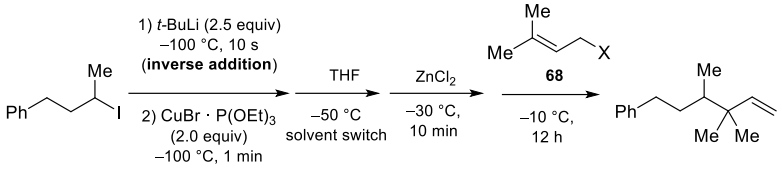
flash column chromatography on AlOx (grade III) with *n*-pentane/diethyl ether (1/1) to afford **68e** (787 mg, 2.3 mmol, 91% yield, 99% *ee*) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 6.44 (dq, J = 2.5, 1.7, 1.3, 1H), 5.31–5.25 (m, 1H), 4.25–4.17 (m, 2H), 4.16–4.10 (m, 2H), 2.61–2.49 (m, 1H), 2.43–2.18 (m, 2H), 2.17–1.90 (m, 1H), 1.36 (dtd, J = 9.4, 7.1, 1.1, 6H), 1.20 (t, J = 7.0, 2H).

^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 146.2, 93.6, 88.0, 64.3, 64.0, 33.1, 31.0, 16.3.

2.5 Optimization Reactions

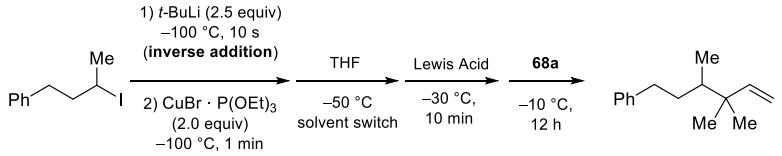
Table 11: Optimization Reactions: Variation of the leaving group.



Entry	X =	Yield[a]	S_N2'-Product[a]	S_N2-Product[a]
1	OAc	0%	-	-
2	Br	65%	70	30
4	$OCOC_6F_5$	9%	90	10
5	$OP(O)(OEt)_2$	70%	90	10

[a] determined by capillary GC with undecane as internal standard.

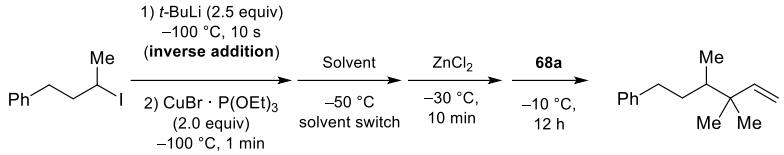
Table 12: Optimization Reactions: Variation of the lewis acid additives.



Entry	Lewis acid	Yield[a]	S_N2'-Product[a]	S_N2-Product[a]
1	ZnI_2[b]	28%	74	26
2	$Zn(OPiv)_2$ solid	45%	80	20
3	$Zn(OPiv)_2 \cdot 2LiCl$[b]	68%	90	10
3	$ZnCl_2$[b]	70%	90	10
4	no additive	65%	8	92
5	$LaCl_3$	61%	15	85
6	$BF_3 \cdot Et_2O$	48%	5	95

[a] determined by capillary GC with undecane as internal standard. [b] 1 M solution in THF.

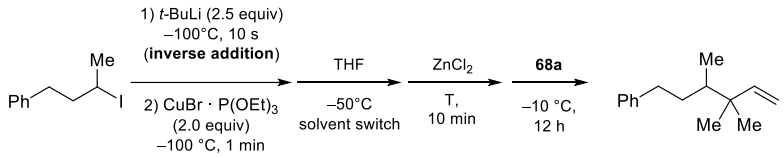
Table 13: Optimization Reactions: Variation of the solvent.



Entry	Solvent	Yield[a]	S_N2'-Product[a]	S_N2-Product[a]
1	Hexane/diethyl ether = 3/2	15%	66	34
2	toluene[b]	57%	90	10
3	THF/NMP = 2/1[b]	63%	89	11
4	THF[b]	70%	90	10

[a] determined by capillary GC with undecane as internal standard. [b] solvent switch at –50 °C.

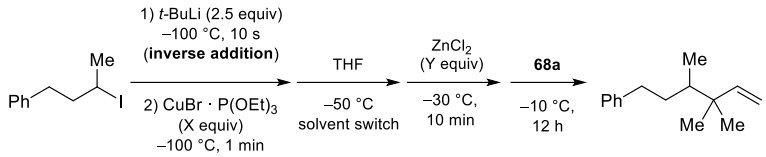
Table 14: Optimization Reactions: Variation of the temperature.



Entry	Temperature, time	Yield[a]	S_N2'-Product[a]	S_N2-Product[a]
1	–50 °C, 10 min	57%	85	15
2	–40 °C, 10 min	48%	84	16
3	–30 °C, 10 min	70%	90	10
4	–20 °C, 10 min	61%	89	11
5	–50 °C, 10 min; add **68a** then –50 °C, 12 h	29%	67	33
6	–30 °C 10 min, add **68a** then –30 °C. 12 h	51%	88	12

[a] determined by capillary GC with undecane as internal standard. [b] solvent switch at –50 °C.

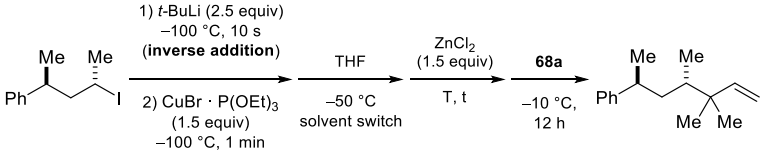
Table 15: Optimization Reactions: Equivalents.



Entry	X equiv CuBr	Y equiv $ZnCl_2$	Yield[a]	S_N2'/S_N2
1	1.2	1.2	72%	82:18
2	1.2	1.5	73%	91:9
3	1.5	1.1	67%	80:20
4	1.5	1.5	71%	93:7
5	1.5	1.7	76%	91:9
6	1.5	2.0	75%	91:9
7	1.5	3.0	46%	87:13
8	1.7	1.7	70%	88:12
9	2.0	1.1	80%	75:25
10	2.0	1.5	76%	87:13
11	2.0	2.0	70%	90:10
12	2.0	4.0	8%	40:60

[a] determined by capillary GC with undecane as internal standard.

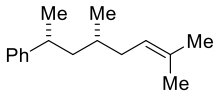
Table 16: Optimization of the reaction conditions.



Entry	Temperature	Yield[a]	S_N2'/S_N2[a]	dr [a]
1	–30 °C. 1 h	66%	90:10	92:8
2	–20 °C. 1 h	73%	87:13	92:8
3	–10 °C. 1 h	73%	86:14	89:11
4	0 °C. 1 h	65%	83:17	88:12
5	–10 °C, 10 h	62%	78:22	81:19
6	rt, 10 h	69%	78:22	82:18

[a] determined by capillary GC with undecane as internal standard.

2.6 Stereoselective Preparation of S_N2-Substitution Products



syn-**69a**

The alkene *syn*-**69a** was prepared according to **TP1** from the iodide *syn*-**1a** (dr = 2:98, 0.20 mmol, 55 mg) and electrophile **68a** (0.60 mmol, 133 mg). The crude product was purified by flash column chromatography on silica gel with *n*-pentane to afford *syn*-**69a** (0.11 mmol, 24 mg, 56% yield, dr = 5:95, S_N2/S_N2' = 95:5) as a colorless oil.

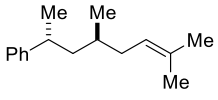
^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.31–7.26 (m, 2H), 7.20–7.14 (m, 3H), 5.07–4.98 (m, 1H), 2.86–2.72 (m, 1H), 1.95–1.86 (m, 1H), 1.83–1.71 (m, 1H), 1.69–1.66 (m, 3H), 1.56 (d, *J* = 1.8 Hz, 3H), 1.35–1.24 (m, 3H), 1.21 (d, *J* = 6.9 Hz, 3H), 0.84 (d, *J* = 6.3 Hz, 3H).

^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 147.8, 132.1, 128.4, 127.2, 125.9, 123.4, 45.5, 37.6, 35.9, 31.3, 26.0, 23.7, 19.6, 18.0.

IR (ATR): $\tilde{\nu}$[cm^{-1}] = 2955 (s), 2919 (s), 2868 (m), 2849 (m), 1493 (w), 1452 (m), 1376 (m), 1260 (m), 1085 (m), 1064 (m), 1051 (m), 1026 (m), 1022 (m), 1019 (m), 800 (m), 761 (m), 699 (vs).

MS (EI, 70 eV): m/z (%): 216 (12), 145 (86), 143 (14), 131 (13), 118 (75), 105 (100), 91 (36), 79 (13), 77 (10).

HRMS (EI) for $C_{16}H_{24}$: calc. [M$^+$]: 216.1878; found: 216.1871.



anti-**69a**

The alkene *anti*-**69a** was prepared according to **TP1** from *anti*-**1a** (dr = 99:1, 0.20 mmol, 55 mg) and electrophile **68a** (0.60 mmol, 133 mg). The crude product was purified by flash column chromatography on silica gel with *n*-pentane to afford *anti*-**69a** (0.12 mmol, 25 mg, 58% yield, dr = 95:5, S_N2/S_N2' = 96:4) as a colorless oil.

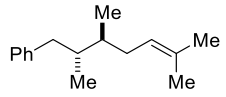
^{1}H-NMR($CDCl_3$, 400 MHz): δ [ppm] = 7.32–7.26 (m, 2H), 7.23–7.15 (m, 3H), 5.15–5.06 (m, 1H), 2.87–2.76 (m, 1H), 2.07–1.96 (m, 1H), 1.87–1.76 (m, 1H), 1.70 (d, *J* = 1.4 Hz, 3H), 1.58 (d, *J* = 1.3 Hz, 3H), 1.54–1.37 (m, 3H), 1.21 (d, *J* = 6.8 Hz, 3H), 0.84 (d, *J* = 6.1 Hz, 3H).

^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 148.5, 132.1, 128.4, 127.1, 125.9, 123.3, 45.9, 37.5, 35.3, 31.4, 26.0, 22.3, 19.9, 18.0.

IR (ATR): $\tilde{\nu}$[cm^{-1}] = 2958 (w), 2915 (m), 2869 (w), 2848 (w), 1602 (vw), 1493 (w), 1451 (m), 1376 (w), 1361 (w), 1261 (vw), 1085 (w), 1028 (w), 1010 (w), 906 (w), 852 (w), 843 (w), 761 (m), 698 (vs).

MS (EI, 70 eV): m/z (%): 216 (4), 145 (69), 131 (11), 118 (67), 117 (21), 105 (100), 103 (11), 91 (31), 79 (13), 77 (9).

HRMS (EI) for $C_{16}H_{24}$: calc. [M^+]: 216.1878; found: 216.1870.



anti-**69b**

The alkene *anti*-**69b** was prepared according to **TP1** from *anti*-**1b** (dr = 99:1, 0.20 mmol, 55 mg) and electrophile **68b** (0.60 mmol, 89 mg). The crude product was purified by flash column chromatography on silica gel with *n*-pentane to afford *anti*-**69b** (0.15 mmol, 32 mg, 73% yield, dr = 98:2, S_N2/S_N2' >99:1) as a colorless oil.

^{1}H-NMR($CDCl_3$, 400 MHz): δ [ppm] = 7.29–7.27 (m, 1H), 7.26–7.24 (m, 1H), 7.20–7.11 (m, 3H), 5.17–5.08 (m, 1H), 2.74 (dd, *J* = 13.3, 4.7 Hz, 1H), 2.24 (dd, *J* = 13.2, 9.9 Hz, 1H), 2.11 (dt, *J* = 13.0, 5.9 Hz, 1H), 1.86 (dt, *J* = 15.0, 8.2 Hz, 1H), 1.72 (s, 3H), 1.63 (s, 3H), 1.53–1.46 (m, 2H), 0.88 (d, *J* = 6.9 Hz, 3H), 0.79 (d, *J* = 6.8 Hz, 3H).

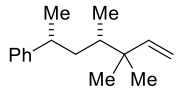
^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 142.3, 131.9, 129.3, 128.2, 125.6, 124.1, 39.7, 39.5, 38.3, 31.7, 26.0, 18.1, 16.6, 16.4.

IR (ATR): $\tilde{\nu}$[cm^{-1}] = 2956 (m), 2914 (s), 2868 (m), 1493 (w), 1451 (m), 1375 (m), 1261 (w), 1084 (w), 1015 (w), 800 (w), 760 (m), 698 (vs).

MS (EI, 70 eV): m/z (%): 216 (5), 145 (9), 131 (5), 118 (8), 105 (22), 103 (11), 91 (100), 77 (4), 69 (43), 55 (14).

HRMS (EI) for $C_{16}H_{24}$: calc. [M^+]: 216.1878; found: 216.1873.

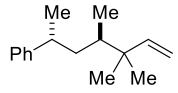
2.7 Stereoselective Preparation of S_N2'-Substitution Products



syn-**70a**

The alkene *syn*-**70a** was prepared according to **TP2** from *syn*-**1a** (dr = 2:98, 0.20 mmol, 55 mg) and electrophile **68a** (0.60 mmol, 133 mg). The crude product was purified by flash column chromatography on silica gel with *n*-pentane to afford *anti*-**70a** (0.11 mmol, 24 mg, 54% yield, dr = 5: 95, S_N2/S_N2' = 5:95) as a colorless oil.

^{1}H-NMR($CDCl_3$, 400 MHz): δ [ppm] = 7.32–7.26 (m, 2H), 7.22–7.12 (m, 3H), 5.59 (dd, *J* = 17.5, 10.8 Hz, 1H), 4.93–4.80 (m, 2H), 2.79–2.68 (m, 1H), 1.85–1.75 (m, 1H), 1.21 (d, *J* = 6.9 Hz, 3H), 1.20–1.12 (m, 1H), 0.97–0.87 (m, 1H), 0.85 (s, 3H), 0.84 (s, 3H), 0.81 (d, *J* = 6.6 Hz, 3H).
^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 148.4, 147.1, 128.4, 127.4, 125.9, 110.6, 40.0, 39.6, 39.1, 38.2, 24.8, 24.7, 23.1, 14.2.
IR (ATR): $\tilde{\nu}$[cm^{-1}] = 3027 (vw), 2957 (m), 2922 (m), 2870 (w), 2849 (w), 1493 (w), 1461 (w), 1452 (m), 1413 (w), 1376 (w), 1362 (w), 1260 (w), 1086 (w), 1069 (w), 1028 (w), 1005 (w), 907 (m), 805 (w), 761 (m), 747 (w), 699 (vs).
MS (EI, 70 eV): m/z (%): 216 (6), 145 (58), 131 (17), 118 (50), 117 (19), 105 (100), 103 (11), 91 (31), 79 (12).
HRMS (EI) for $C_{16}H_{24}$: calc. [M^+]: 216.1878; found: 216.1872.



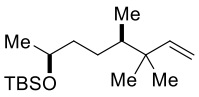
anit-**70a**

The alkene *anti*-**70a** was prepared according to **TP2** from *anti*-**2a** (dr = 98:2, 0.20 mmol, 55 mg) and electrophile **68a** (0.60 mmol, 133 mg). The crude product was purified by flash column chromatography on silica gel with *n*-pentane to afford *anti*-**70a** (0.12 mmol, 25 mg, 58% yield, dr = 95:5, S_N2/S_N2' = 8:92) as a colorless oil.

^{1}H-NMR($CDCl_3$, 400 MHz): δ [ppm] = 7.33–7.26 (m, 2H), 7.23–7.15 (m, 3H), 5.78 (dd, *J* = 17.4, 10.8 Hz, 1H), 4.98–4.86 (m, 2H), 2.75–2.64 (m, 1H), 1.72–1.56 (m, 2H), 1.47–1.33 (m, 1H), 1.20 (d, *J* = 6.8 Hz, 3H), 0.96 (s, 3H), 0.94 (s, 3H), 0.84 (d, *J* = 6.8 Hz, 3H).
^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 149.1, 148.1, 128.3, 126.8, 125.7, 110.7, 41.1, 39.9, 39.6, 37.7, 24.5, 23.3, 20.3, 14.4.
IR (ATR): $\tilde{\nu}$[cm^{-1}] = 3026 (w), 2959 (s), 2920 (s), 2871 (m), 2849 (m), 1602 (w), 1494 (w), 1461 (m), 1452 (m), 1413 (w), 1375 (m), 1362 (w), 1260 (w), 1094 (w), 1073 (w), 1070 (w), 1057 (w), 1027 (w), 1005 (w), 908 (m), 808 (w), 805 (w), 802 (w), 760 (m), 698 (vs).

MS (EI, 70 eV): m/z (%): 216 (10). 145 (74), 143 (15), 131 (15), 129 (11), 118 (73), 117 (24), 105 (100), 103 (14), 91 (38), 79 (14), 77 (11).

HRMS (EI) for $C_{16}H_{24}$: calc. [M^+]: 216.1878; found: 216.1871.



syn-**70b**

The alkene *syn*-**70b** was prepared according to **TP2** from *syn*-**2d** (dr = 1:99, 0.20 mmol, 69 mg) and electrophile **68b** (0.60 mmol, 133 mg). The crude product was purified by flash column chromatography on silica gel with *n*-pentane to afford *syn*-**70b** (0.12 mmol, 34 mg, 59% yield, dr = 9:91, S_N2/S_N2' = 9:91) as a colorless oil.

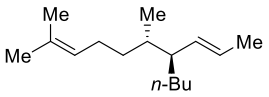
^{1}H-NMR($CDCl_3$, 400 MHz): δ [ppm] = 5.80–5.71 (m, 1H), 4.96–4.85 (m, 2H), 3.76–3.64 (m, 1H), 1.68–1.58 (m, 1H), 1.52–1.40 (m, 1H), 1.31–1.19 (m, 1H), 1.18–1.13 (m, 1H), 1.11 (d, *J* = 6.1 Hz, 3H), 0.93 (d, *J* = 3.7 Hz, 6H), 0.88 (s, 10H), 0.81 (d, *J* = 6.8 Hz, 3H), 0.04 (s, 6H).

^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 148.4, 110.7, 69.3, 39.9, 39.0, 28.4, 26.1, 24.7, 24.1, 23.4, 18.3, 14.4, –4.3, –4.6.

IR (ATR): $\tilde{\nu}$[cm^{-1}] = 2975 (m), 2928 (w), 2856 (m), 1444 (w), 1381 (m), 1350 (w), 1151 (m), 1118 (vs), 1076 (m), 1044 (w), 934 (w), 844 (w), 835 (w), 774 (w).

MS (EI, 70 eV): m/z (%): 227 (10), 151 (12), 117 (15), 109 (47), 103 (15), 95 (66), 81 (36), 75 (100), 73 (22), 7 (14).

HRMS (EI) for $C_{17}H_{36}OSi$: calc. [M^+–*t*-Bu]: 227.1831; found: 227.1823.



3*S*,4*S*-**70c**

The alkene 3*S*,4*S*-**70c** was prepared according to **TP2** from (*S*)-**2e** (er = 99:1, 0.20 mmol, 48 mg) and electrophile **68c** (0.60 mmol, 158 mg). The crude product was purified by flash column chromatography on silica gel with *n*-pentane to afford 3*S*,4*S*-**70c** (0.11 mmol, 24 mg, 53% yield, dr = 95:5, 99% *ee*, S_N2/S_N2' <1:99) as a colorless oil.

$[\alpha]_D^{20}$ = –2.4 (c = 1.0, $CHCl_3$).

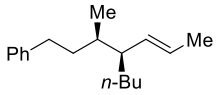
^{1}H-NMR($CDCl_3$, 400 MHz): δ [ppm] = 5.40–5.27 (m, 1H), 5.21–5.06 (m, 2H), 1.98–1.90 (m, 1H), 1.88–1.81 (m, 1H), 1.70–1.63 (m, 6H), 1.60 (d, *J* = 1.4 Hz, 3H), 1.46–1.04 (m, 10H), 0.87 (t, *J* = 6.9 Hz, 3H), 0.78 (d, *J* = 6.9 Hz, 3H).

^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 133.0, 131.1, 125.6, 125.3, 47.1, 36.6, 35.5, 32.8, 30.2, 26.0, 25.9, 23.0, 18.2, 17.8, 15.4, 14.3.

IR (ATR): $\tilde{\nu}$[cm^{-1}] = 2957 (s), 2916 (vs), 2871 (m), 2855 (s), 1453 (m), 1377 (m), 969 (vs), 934 (w), 825 (w), 729 (w).

MS (EI, 70 eV): m/z (%): 222 (8), 179 (10), 165 (11), 151 (12), 137 (20), 123 (26), 109 (100), 95 (77), 81 (58), 69 (86), 55 (18).

HRMS (EI) for $C_{16}H_{30}$: calc. [M$^+$]: 222.2348; found: 222.2340.



3*R*,4*S*-**70d**

The alkene 3*R*,4*S*-**70d** was prepared according to **TP2** from (*R*)-**2f** (er = 7:93, 0.20 mmol, 52 mg) and electrophile **68c** (0.60 mmol, 158 mg). The crude product was purified by flash column chromatography on silica gel with *n*-pentane to afford 3*R*,4*S*-**70d** (0.11 mmol, 29 mg, 56% yield, 99% *ee*, dr = 10:90, S_N2/S_N2' <1:99) as a colorless oil.

$[\alpha]_D^{20}$ = +14.3 (c = 1.0, $CHCl_3$).

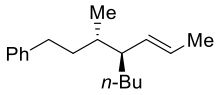
^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.32–7.25 (m, 2H), 7.21–7.15 (m, 3H), 5.37 (dq, *J* = 15.2, 6.3 Hz, 1H), 5.24–5.12 (m, 1H), 2.69–2.51 (m, 2H), 1.99–1.86 (m, 1H), 1.67 (dt, *J* = 6.3, 1.9 Hz, 3H), 1.65–1.56 (m, 3H), 1.52–1.08 (m, 6H), 0.97–0.83 (m, 6H).

^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 143.4, 132.7, 128.5, 128.4, 125.8, 125.6, 47.1, 37.5, 36.7, 33.9, 32.8, 30.2, 23.0, 18.3, 15.4, 14.3.

IR (ATR): $\tilde{\nu}$[cm^{-1}] = 3025 (w), 2956 (s), 2923 (vs), 2870 (m), 2855 (s), 1604 (w), 1496 (m), 1453 (m), 1437 (w), 1377 (m), 1030 (w), 969 (m), 745 (m), 733 (w), 728 (w), 722 (w), 717 (w), 697 (s).

MS (EI, 70 eV): m/z (%): 244 (1), 140 (28), 131 (24), 117 (34), 104 (26), 98 (22), 91 (100), 70 (11), 69 (50), 55 (10).

HRMS (EI) for $C_{18}H_{28}$: calc. [M$^+$]: 244.2191; found: 244.2185.



3*S*,4*S*-**70d**

The alkene 3*S*,4*S*-**70d** was prepared according to **TP2** from (*S*)-**2f** (er = 92:8, 0.20 mmol, 52 mg) and electrophile **68c** (0.60 mmol, 158 mg, 99% *ee*). The crude product was purified by flash column chromatography on silica gel with *n*-pentane to afford 3*S*,4*S*-**70d** (0.11 mmol, 28 mg, 54% yield, 99% *ee*, dr = 90:10, S_N2/S_N2' <1:99) as a colorless oil.

$[\alpha]_D^{20}$ = –15.7 (c = 1.0, $CHCl_3$).

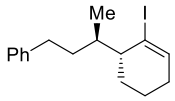
^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.32–7.26 (m, 2H), 7.22–7.15 (m, 3H), 5.41–5.30 (m, 1H), 5.24–5.12 (m, 1H), 2.78–2.65 (m, 1H), 2.54–2.42 (m, 1H), 1.87–1.77 (m, 1H), 1.67 (dd, *J* = 6.3, 1.6 Hz, 3H), 1.50–1.40 (m, 1H), 1.39–1.04 (m, 8H), 0.97–0.80 (m, 6H).

^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 143.4, 134.2, 128.5, 128.4, 125.7, 125.4, 48.4, 37.1, 35.5, 34.0, 31.4, 30.1, 23.0, 18.2, 17.3, 14.3.

IR (ATR): $\tilde{\nu}$[cm^{-1}] = 2956 (m), 2916 (vs), 2870 (m), 2848 (s), 1496 (w), 1472 (w), 1462 (m), 1453 (m), 1436 (w), 1376 (w), 970 (m), 747 (w), 743 (w), 730 (w), 698 (m), 3027 (w).

MS (EI, 70 eV): m/z (%): 244 (1), 140 (26), 131 (28), 117 (33), 104 (28), 98 (18), 91 (100), 81 (13), 69 (47), 55 (9).

HRMS (EI) for $C_{18}H_{28}$: calc. [M^+]: 244.2191; found: 244.2187.



3*R*,4*R*-**70e**

The alkene 3*R*,4*R*-**70e** was prepared according to **TP2** from (*R*)-**2f** (er = 7:93, 0.20 mmol, 52 mg) and electrophile **68d** (0.60 mmol, 216 mg, 99% *ee*). The crude product was purified by flash column chromatography on silica gel with *n*-pentane to afford 3*R*,4*R*-**70e** (0.12 mmol, 40 mg, 59% yield, 99% *ee*, dr = 90:10, S_N2/S_N2' <1:99) as a colorless oil.

$[\alpha]_D^{20}$ = +15.9 (c = 1.0, $CHCl_3$).

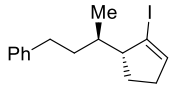
^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.34–7.27 (m, 2H), 7.25–7.16 (m, 3H), 6.59–6.51 (m, 1H), 2.76–2.55 (m, 2H), 2.48–2.27 (m, 1H), 2.16 (ddq, *J* = 10.3, 7.0, 3.5 Hz, 1H), 2.09–1.93 (m, 2H), 1.84–1.66 (m, 2H), 1.64–1.50 (m, 2H), 1.35–1.27 (m, 1H), 0.89 (t, *J* = 7.1 Hz, 1H), 0.81 (d, *J* = 6.8 Hz, 3H).

^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 142.9, 140.9, 128.5, 125.8, 109.0, 47.2, 37.4, 37.1, 34.3, 29.87, 23.9, 21.6, 13.8.

IR (ATR): $\tilde{\nu}$[cm^{-1}] = 3023 (w), 2952 (m), 2929 (s), 2887 (m), 2882 (m), 2856 (m), 1704 (w), 1700 (m), 1695 (m), 1678 (s), 1602 (w), 1495 (m), 1453 (m), 1380 (m), 1029 (w), 749 (m), 698 (vs).

MS (EI, 70 eV): m/z (%): 213 (8), 157 (7), 131 (12), 109 (36), 91 (100). 79 (14).

HRMS (EI) for $C_{16}H_{21}$: calc. [M^+–I]: 213.1643; found: 213.1637.



3*R*,4*R*-**70f**

The alkene 3*R*,4*R*-**70f** was prepared according to **TP2** from (*R*)-**2f** (er = 7:93, 0.20 mmol, 52 mg) and electrophile **68e** (0.60 mmol, 207 mg, 99% *ee*). The crude product was purified by flash column

chromatography on silica gel with *n*-pentane to afford 3*R*,4*R*-**70f** (0.11 mmol, 35 mg, 54% yield, 99% *ee*, dr = 90:10, S_N2/S_N2' <1:99) as a colorless oil.

$[\alpha]_D^{20}$ = +11.4 (c = 0.5, $CHCl_3$).

^{1}H-NMR($CDCl_3$, 400 MHz): δ [ppm] = 7.33–7.27 (m, 2H), 7.23–7.16 (m, 3H), 6.18–6.12 (m, 1H), 2.90–2.82 (m, 1H), 2.72–2.57 (m, 2H), 2.32–2.24 (m, 2H), 2.01–1.90 (m, 1H), 1.89–1.68 (m, 2H), 1.65–1.56 (m, 2H), 0.74 (d, *J* = 6.8 Hz, 3H).

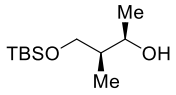
^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 142.9, 140.1, 128.5, 125.8, 101.4, 56.0, 37.8, 34.4, 34.2, 34.1, 21.5, 13.0.

IR (ATR): $\tilde{\nu}$[cm^{-1}] = 3023 (w), 3024 (w), 2957 (s), 2953 (s), 2920 (s), 2883 (m), 2870 (m), 2848 (m), 1603 (w), 1495 (m), 1453 (m), 1378 (m), 1029 (w), 806 (m), 746 (m), 698 (vs).

MS (EI, 70 eV): m/z (%): 199 (15), 143 (19), 117 (19), 95 (53), 91 (100), 66 (10).

HRMS (EI) for $C_{15}H_{19}$: calc. [M^+–I]: 199.1487; found: 199.1480.

2.8 Total Synthesis of (+)-Lasiol

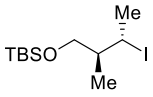


The alcohol (2*R*,3*S*)-4-((*tert*-butyldimethylsilyl)oxy)-3-methylbutan-2-ol was prepared according to literature. The enantiomeric excess and absolute configuration was determined *via* ^{1}H- and ^{13}C-NMR analysis of the corresponding (*R*)- and (*S*)-Mosher ester[124] (see chapter 2.11).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 4.04 (d, *J* = 2.4 Hz, 1H), 3.82–3.62 (m, 2H), 3.55 (dd, *J* = 10.1, 8.5 Hz, 1H), 1.68–1.60 (m, 1H), 1.17 (d, *J* = 6.3 Hz, 3H), 0.91 (s, 9H), 0.80 (d, *J* = 6.9 Hz, 3H), 0.09 (s, 6H).

^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 132.2, 123.7, 66.3, 40.4, 35.7, 31.6, 26.0, 18.0, 17.2, 14.0.

All other analytical data were in accordance with literature values.[56]



2*S*,3*S*-**1c**

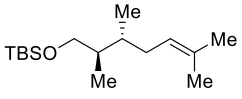
The iodide 2*S*,3*S*-**1c** was prepared according to literature (dr = 98:2, 99% *ee*).

$[\alpha]_D^{20}$ = −14.6 (c = 1.0, CH_2Cl_2).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 4.46 (qd, *J* = 7.0, 4.9 Hz, 1H), 3.59 (dd, *J* = 10.1, 6.4 Hz, 1H), 3.48 (dd, *J* = 10.1, 5.7 Hz, 1H), 1.87 (d, *J* = 7.1 Hz, 3H), 1.82 (p, *J* = 6.3 Hz, 1H), 0.99 (d, *J* = 6.8 Hz, 3H), 0.89 (s, 9H), 0.05 (d, *J* = 3.0 Hz, 6H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 77.1, 67.0, 44.6, 34.5, 26.1, 26.0, 24.8, 18.3, 15.0, -5.2, -5.3.

All other analytical data were in accordance with literature values.[56]



2*R*,3*R*-**69c**

The alkene 2*R*,3*R*-**69c** was prepared according to **TP1** from 2*S*,3*S*-**1c** (dr = 98:2, 0.20 mmol, 66 mg) and electrophile **68b** (0.60 mmol, 89 mg). The crude product was purified by flash column chromatography on silica gel with *n*-pentane to afford 2*R*,3*R*-**69c** (0.14 mmol, 38 mg, 71% yield, dr = 98:2, 99% *ee*) as a colorless oil.

$[\alpha]_D^{20}$ = +31.2 (c = 1.0, CH_2Cl_2).

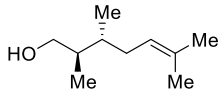
^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 5.14–5.07 (m, 1H), 3.57 (dd, *J* = 9.8, 5.6 Hz, 1H), 3.41 (dd, *J* = 9.8, 6.9 Hz, 1H), 2.07–1.95 (m, 1H), 1.84–1.72 (m, 1H), 1.72–1.68 (m, 3H), 1.59 (d, *J* = 1.3 Hz, 3H), 1.59–1.48 (m, 2H), 0.89 (s, 9H), 0.85 (dd, *J* = 8.7, 6.7 Hz, 6H), 0.04 (s, 6H).

^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 131.8, 124.1, 66.3, 40.4, 35.5, 31.5, 26.1, 26.0, 18.5, 18.0, 17.1, 14.0, -5.2.

IR (ATR): $\tilde{\nu}$[cm^{-1}] = 2956 (m), 2928 (m), 2896 (m), 2884 (m), 2858 (m), 1472 (w), 1462 (w), 1388 (w), 1378 (w), 1362 (w), 1254 (m), 1090 (s), 1030 (w), 1006 (w), 938 (w), 836 (vs), 814 (w), 774 (s), 668 (w).

MS (EI, 70 eV): m/z (%): 270 (2), 209 (24), 197 (15), 137 (27), 115 (16), 97 (20), 95 (22), 85 (35), 75 (59), 71 (57), 67 (12), 57 (100), 56 (22), 43 (69), 41 (43).

HRMS (EI) for $C_{16}H_{34}OSi$: calc. [M^+]: 270.2379; found: 270.2362.



(+)-lasiol (**71**)

(+)-Lasiol (71): A solution of TBAF (0.2 mL, 0.28 mmol, 1.0 M in THF, 2.0 equiv) was added dropwise to the alkene 2*R*,3*R*-**69c** (dr = 98:2, 0.14 mmol, 38 mg) in THF (1.0 mL). After stirring for 10 h, the reaction was quenched with brine, extracted with diethyl ether and dried over $MgSO_4$. The crude product was purified by flash column chromatography on silica gel with *n*-pentane/diethyl ether = 1/1 to afford (+)-lasiol (**71**, 0.12 mmol, 19 mg, 87% yield, dr = 98:2, 99% *ee*) as a colorless oil. The enantiomeric excess and absolute configuration were determined *via* ^{1}H- and ^{13}C-NMR analysis of the corresponding (*R*)- and (*S*)-Mosher ester[124] (see chapter 2.11).

$[\alpha]_D^{20}$ = +10.9 (c = 1.0, CH_2Cl_2). [Lit. (–)-lasiol[126]: –10.2 (c = 1.9, $CHCl_3$)].

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 5.16–5.06 (m, 1H), 3.65 (dd, *J* = 10.6, 5.4 Hz, 1H), 3.46 (dd, *J* = 10.6, 7.1 Hz, 1H), 2.03 (dt, *J*= 12.9, 5.6 Hz, 1H), 1.86–1.75 (m, 1H), 1.70 (m, 3H), 1.60 (d, *J* = 1.3 Hz, 3H), 1.59–1.49 (m, 1H), 1.35 (s, 1H), 0.93 (d, *J* = 6.8 Hz, 3H), 0.87 (d, *J* = 6.8 Hz, 3H).

^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 132.2, 123.7, 66.3, 40.4, 35.7, 31.6, 26.0, 18.0, 17.2, 14.0.

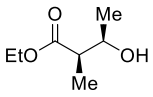
IR (ATR): $\tilde{\nu}$[cm^{-1}] = 3326 (w), 2959 (s), 2920 (s), 2914 (s), 1450 (s), 1372 (s), 1350 (m), 1230 (w), 1151 (m), 1120 (w), 1082 (m), 1039 (vs), 1025 (vs), 982 (m), 838 (m), 700 (w), 686 (m), 673 (m), 659 (w).

MS (EI, 70 eV): m/z (%): 156 (7), 123 (18), 97 (23), 85 (36), 83 (42), 71 (60), 69 (100), 57 (89), 55 (75), 44 (63), 43 (65), 41 (70).

HRMS (EI) for $C_{10}H_{20}O$: calc. [M^+]: 156.1514; found: 156.1505.

[126] A. W. Van Zijl, W. Szymanski, F. Lopez, A. J. Minnaard, B. L. Feringa, *J. Org. Chem.* **2008**, 73, 6994–7002.

2.9 Total Synthesis of (+)-13-Norfaranal



Ethyl (2*R*,3*R*)-3-hydroxy-2-methylbutanoate was prepared according to literature procedure.[70] A 500 mL *Schlenk*-flask equipped with a magnetic stirring bar was charged with THF (100 mL) and diisopropylamine (14.7 mL, 105 mmol, 2.1 equiv) and subsequently cooled to –78 °C. *n*-Butyllithium (44.3 mL, 2.48 M in *n*-hexane, 110 mmol, 2.2 equiv) was added dropwise using a syringe pump (2 mL/min). After addition, the solution was allowed to warm to –15 °C and stirred for 1 h. The solution was cooled to –78 °C. A separate round-bottom flask was charged with ethyl (*R*)-hydroxybutyrate ((*R*)-**74**, 6.50 mL, 50.0 mmol, 1.0 equiv), HMPA (14.8 mL, 85.0 mmol, 1.7 equiv) and THF (33 mL). The resulting solution was added dropwise to the reaction mixture using a syringe pump (3 mL/min) and the reaction was allowed to warm to –40 °C.

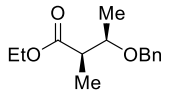
After 45 min, MeI (3.90 mL, 62.5 mmol, 1.25 equiv) was added dropwise and the reaction was allowed to warm to 0 °C and stirred for 2 h. The reaction was quenched by addition of sat. aq. NH_4Cl. 1 M HCl was added until the pH was below 7. The reaction mixture was extracted three times with ethyl acetate (3 x 50 mL). The combined organic phases were dried over $MgSO_4$ and filtered over a celite plug and concentrated under reduced pressure. The crude residue was purified by distillation (110 °C, 30 mbar) to give ethyl (2*R*,3*R*)-3-hydroxy-2-methylbutanoate (5.2 g, 35.5 mmol, 71% yield) as a colorless oil.

$[\alpha]_D^{20} = -25.2$ (c = 1.0, $CHCl_3$).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 4.17 (q, *J* = 7.1 Hz, 2 H), 3.87 (p, *J* = 5.9 Hz, 1 H), 2.71 (s, 1 H), 2.43 (p, *J* = 7.2 Hz, 1H), 1.27 (t, *J* = 7.1 Hz, 3 H), 1.22 (d, *J* = 6.4 Hz, 3 H), 1.18 (d, *J* = 7.2 Hz, 3 H).

^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 176.0, 69.5, 60.6, 46.9, 20.8, 14.2, 14.2.

All other analytical data were in accordance with literature values.[56]



2*R*,3*R*-**75**

A *Schlenk*-flask equipped with a magnetic stirring bar was charged with ethyl (2*R*,3*R*)-3-hydroxy-2-methylbutanoate (4.38 g, 30 mmol, 1.0 equiv), benzyl 2,2,2-trichloroacetimidate (6.7 mL, 36 mmol, 1.2 equiv), *i*-hexane (44 mL) and dichloromethane (22 mL). Triflic acid (1.7 mL, 5.1 mmol, 0.17 equiv) was added dropwise and the reaction was stirred overnight at rt. The reaction mixture was filtered over a pad of celite and the filtrate was washed with sat. aq. $NaHCO_3$, H_2O and brine. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by flash

column chromatography on silica gel (*i*-hexane/ethyl acetate = 19/1) to give 2*R*,3*R*-**75** (5.16 g, 22 mmol, 73% yield) as a colorless liquid.

$[\alpha]_D^{20} = -24.3$ (c = 1.5, $CHCl_3$).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.35–7.27 (m, 5 H), 4.57 (d, *J* = 11.5 Hz, 1H), 4.46 (d, *J* = 11.5 Hz, 1H), 4.21–4.05 (m, 2H), 3.86–3.70 (m, 1H), 2.67 (p, *J* = 7.2 Hz, 1H), 1.23 (t, *J* = 7.2 Hz, 3 H), 1.19 (d, *J* = 6.2 Hz, 3 H), 1.13 (d, *J* = 7.1 Hz, 3 H).

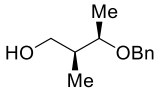
^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 175.3, 138.7, 128.4, 127.7, 127.6, 76.9, 71.1, 60.4, 45.8, 16.5, 14.4, 12.7.

IR (ATR): $\tilde{\nu}$[cm^{-1}] = 2977 (w), 2937 (w), 2934 (w), 2916 (w), 2903 (w), 2900 (w), 2897 (w), 2894 (w), 2883 (w), 2879 (w), 1731 (vs), 1496 (w), 1453 (m), 1378 (m), 1373 (m), 1342 (w), 1318 (w), 1255 (m), 1186 (s), 1163 (m), 1107 (s), 1065 (vs), 1028 (s), 986 (w), 965 (w), 915 (w), 889 (w), 862 (w), 827 (w), 823 (w), 817 (w), 812 (w), 807 (w), 796 (w), 734 (s), 696 (vs).

MS (EI, 70 eV): m/z (%): 130 (14), 115 (20), 102 (29), 91 (100), 87 (20).

HRMS (EI) for $C_{14}H_{21}O_3$: calc. [M^++H]: 237.1485; found: 237.1484.

All analytical data were in accordance with literature values.[127]



2*S*,3*R*-**76**

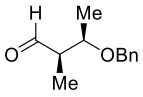
2*S*,3*R*-**76** was prepared according to a literature procedure.[127] A *Schlenk*-flask equipped with a magnetic stirring bar was charged with 2*R*,3*R*-**75** (3.40 g, 14.4 mmol, 1.0 equiv) and THF (150 mL) and subsequently cooled to 0 °C. $LiAlH_4$ (2.73 g, 72.1 mmol, 5.0 equiv) was added in small portions and the mixture was stirred overnight at rt. The reaction was quenched according to *Fieser*[128]. The crude residue was purified by flash column chromatography on silica gel (*i*-hexane/ethylacetate = 1/3) to give 2*S*,3*R*-**76** (2.43 g, 12.5 mmol, 88% yield) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.40–7.27 (m, 5H), 4.66 (d, *J* = 11.5 Hz, 1H), 4.41 (d, *J* = 11.5 Hz, 1H), 3.70–3.54 (m, 2H), 3.49 (dq, *J* = 7.3, 6.2 Hz, 1H), 3.00–2.89 (s, 1H), 1.86–1.70 (m, 1H), 1.26 (d, *J* = 6.1 Hz, 3H), 0.91 (d, *J* = 7.0 Hz, 3H).

^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 138.3, 128.7, 127.9, 127.9, 80.7, 70.9, 67.3, 41.3, 17.5, 14.2.

All other analytical data were in accordance with literature values.[127]

[127] M. Larcheveque, C. Sanner, R. Azerad, D. Buission, *Tetrahedron* **1988**, 44, 6407–6418.
[128] L. F. Fieser, M. Fieser, *Reagents for Organic Synthesis* **1967**, Wiley, New York, 581–595.



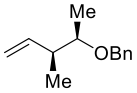
2*R*,3*R*-**77**

A S*chlenk*-flask equipped with a magnetic stirring bar was charged with oxalylchloride (3.3 mL, 45.2 mmol, 2.0 equiv) and dichloromethane (136 mL) and subsequently cooled to –78 °C. A precooled (–78 °C) solution of DMSO (4.8 mL, 67.8 mmol, 3.0 equiv) in dichloromethane (50 mL) was added dropwise to the resulting solution and the reaction was stirred for 10 min. 2*S*,3*R*-**76** (4.39 g, 22.6 mmol, 1.0 equiv) was added dropwise at –78 °C. After 10 min, NEt_3 (14 mL, 102 mmol, 4.5 equiv) was added and the reaction was allowed to warm to 0 °C and stirred for another 10 min. The reaction was quenched by addition of brine and the layers were separated. The aqueous layer was extracted three times with diethyl ether. The combined organic phases were successively washed with sat. aq. $NaHCO_3$, aq. $NaHSO_4$ (1 M), and brine, dried over $MgSO_4$ and concentrated under reduced pressure to afford 2*R*,3*R*-**77** (quant. yield) as a yellowish oil which was used in the next step without further purification.

$[\alpha]_D^{20} = -4.8$ (c = 0.5, $CHCl_3$).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 9.74 (d, *J* = 2.3 Hz, 1H), 7.37–7.27 (m, 5H), 4.63 (d, *J* = 11.7 Hz, 1H), 4.45 (d, *J* = 11.7 Hz, 1H), 3.81 (p, *J* = 6.3 Hz, 1H), 2.61–2.51 (m, 1H), 1.25 (d, *J* = 6.2 Hz, 3H), 1.09 (d, *J* = 7.2 Hz, 3H).

^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 204.6, 138.3, 128.5, 127.8, 75.4, 70.8. 51.9, 17.0, 10.3.



2*R*,3*S*-**78**

2*R*,3*S*-**78** was prepared according to a literature procedure.[129] A *Schlenk*-flask equipped with magnetic stirring bar was charged with Ph_3PCH_3Br (8.88 g, 24.9 mmol, 1.1 equiv) and THF (250 mL) and subsequently cooled to 0 °C. *n*-Butyllithium (10.9 mL, 2.48 M in *n*-hexane, 27.1 mmol, 1.2 equiv) was added dropwise. The resulting orange solution was stirred for 30 min. 2*R*,3*R*-**77** (4.35 g, 22.6 mmol, 1.0 equiv) in THF (23 mL) was added dropwise and the resulting yellow solution was stirred for 1h. The reaction was quenched by addition of methanol. *n*-Pentane was added and the reaction was filtered over a pad of celite and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (*i*-hexane/diethyl ether = 99/1) to give 2*R*,3*S*-**78** (2.25 g, 11.8 mmol, 52% yield) as a colorless liquid.

$[\alpha]_D^{20} = -17.4$ (c = 1.8, $CHCl_3$).

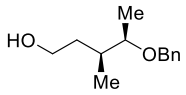
[129] L. Innis, J. M. Plancher, I. E. Markó, *Org. Lett.* **2006**, 8, 6111–6114.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.38–7.31 (m, 4H), 7.29–7.24 (m, 1H), 5.88–5.78 (m, 1H), 5.11–4.98 (m, 2H), 4.58 (d, *J* = 11.9 Hz, 1H), 4.49 (d, *J* = 11.9 Hz, 1H), 3.46 (qd, *J* = 6.5, 5.0 Hz, 1H), 2.47–2.37 (m, 1H), 1.13 (d, *J* = 6.3 Hz, 3H), 1.04 (d, *J* = 6.9 Hz, 3H).

^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 141.2, 139.2, 128.4, 127.7, 127.5, 114.5, 78.3, 70.7, 42.6, 16.2, 14.9.

IR (ATR): $\tilde{\nu}$[cm^{-1}] = 3067 (w), 3031 (w), 2974 (m), 2929 (w), 2870 (m), 1640 (w), 1497 (w), 1454 (m), 1417 (w), 1392 (w), 1374 (m), 1343 (m), 1306 (w), 1250 (vw), 1204 (w), 1189 (w), 1140 (w), 1097 (s), 1067 (s), 1028 (m), 998 (m), 912 (s), 876 (w), 734 (s), 696 (vs), 677 (w).

HRMS (EI) for $C_{13}H_{17}O$: calc. [M^+–H]: 189.1285, found: 189.1271



3*S*,4*R*-**79**

A round-bottom flask equipped with a magnetic stirring bar was charged with 2*R*,3*S*-**78** (1.05 g, 5.5 mmol, 1.0 equiv) and diethyl ether (55 mL). Borane tetrahydrofuran complex (8.3 mL, 1.0 M in THF, 8.3 mmol, 1.5 equiv) was added and the solution was stirred overnight. The reaction was quenched by addition of NaOH (2M) and H_2O_2 (30%) (2:1, 60 mL), stirred for 2.5 h and extracted with diethyl ether. The aqueous phase was extracted twice with diethyl ether and the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (*i*-hexane/ethyl acetate = 4/1) to give 3*S*,4*R*-**79** (0.78 g, 3.7 mmol, 68% yield) as a colorless liquid.

$[\alpha]_D^{20}$ = −24.5 (c = 1.2, CH_2Cl_2).

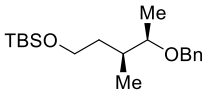
^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.37–7.27 (m, 5H), 4.60 (d, *J* = 11.6 Hz, 1H), 4.45 (d, *J* = 11.7 Hz, 1H), 3.77–3.67 (m, 1H), 3.65–3.56 (m, 1H), 3.39 (p, *J* = 6.1 Hz, 1H), 1.95 (s, 1H), 1.88–1.78 (m, 1H), 1.75–1.64 (m, 1H), 1.58–1.47 (m, 1H), 1.18 (d, *J* = 6.3 Hz, 3H), 0.95 (d, *J* = 6.9 Hz, 3H).

^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 138.8, 128.5, 127.9, 217.7, 79.0, 70.8, 60.9, 36.0, 35.4, 16.3, 15.8.

IR (ATR): $\tilde{\nu}$[cm^{-1}] = 3364 (w), 3085 (w), 3062 (w), 3029 (w), 2968 (m), 2964 (m), 2928 (m), 2901 (w), 2873 (m), 1731 (w), 1710 (w), 1496 (w), 1453 (m), 1375 (m), 1339 (w), 1307 (w), 1205 (w), 1163 (w), 1099 (s), 1056 (vs), 1027 (s), 1006 (m), 1003 (m), 973 (m), 913 (m), 888 (w), 860 (w), 856 (w), 850 (w), 733 (s).

MS (EI, 70 eV): m/z (%): 135 (6), 107 (9), 92 (15), 91 (100), 65 (5), 55 (7), 40 (4).

HRMS (EI) for $C_{13}H_{20}O_2$: calc. [M^+]: 208.1463, found: 208.1468



3*S*,4*R*-**80**

A 100 mL round-bottom flask equipped with a magnetic stirring bar was charged with 3*S*,4*R*-**79** (744 mg, 3.6 mmol, 1.0 equiv), imidazole (608 mg, 8.9 mmol, 2.5 equiv) and dichloromethane (36 mL). TBSCl (645 mg, 4.3 mmol, 1.2 equiv) was added and the reaction was stirred overnight at rt. The reaction was quenched by addition of brine (30 mL) and the layers were separated. The aqueous phase was extracted three times with dichloromethane. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (*i*-hexane/ethyl acetate = 49/1) to give 3*S*,4*R*-**80** (825 mg, 2.6 mmol, 72% yield).

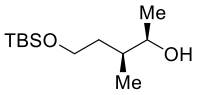
$[\alpha]_D^{20} = -10.5$ (c = 1.2, $CHCl_3$).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.37–7.30 (m, 4H), 7.28–7.22 (m, 1H), 4.54 (d, *J* = 11.8 Hz, 1H), 4.47 (d, *J* = 11.8 Hz, 1H), 3.74–3.57 (m, 2H), 3.41 (qd, *J* = 6.3, 4.8 Hz, 1H), 1.94–1.83 (m, 1H), 1.73–1.63 (m, 1H), 1.38–1.25 (m, 1H), 1.11 (d, *J* = 6.3 Hz, 3H), 0.91 (d, *J* = 7.0 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 6H).

^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 139.4, 128.4, 127.7, 127.4, 78.7, 70.5, 61.7, 36.2, 34.0, 26.1, 18.5, 15.4, 14.5, –5.1, –5.2.

IR (ATR): $\tilde{\nu}$[cm^{-1}] = 2955 (m), 2927 (m), 2882 (w), 2855 (m), 1496 (w), 1471 (w), 1462 (w), 1453 (w), 1387 (w), 1375 (w), 1360 (w), 1339 (w), 1255 (m), 1205 (w), 1171 (w), 1153 (w), 1091 (vs), 1068 (s), 1028 (m), 1004 (m), 968 (w), 959 (w), 938 (w), 899 (m), 833 (vs), 810 (m), 792 (m), 773 (vs), 732 (s), 712 (m), 695 (s), 679 (m), 674 (m), 662 (m).

HRMS (EI) for $C_{15}H_{25}O_2Si$: calc. [M^+–*t*-Bu]: 265.1618, found: 208.1628.



2*R*,3*S*-**81**

A 25 mL round-bottom flask equipped with a magnetic stirring bar was charged with naphthalene (641 mg, 5.0 mmol, 10.0 equiv) and THF (1.8 mL) and subsequently cooled to 0 °C. Lithium turnings (42.0 mg, 6.0 mmol, 12.0 equiv) were added in small portions and the reaction turned deep green upon addition. After 1.5 h, 3*S*,4*R*-**80** (101 mg, 0.5 mmol, 1.0 equiv) in THF (1.0 mL) was added dropwise and the reaction was stirred for 1 h, while being allowed to warm to ambient temperature. The reaction was quenched by addition of solid NH_4Cl. NH_3 was then allowed to evaporate. After addition of water, the reaction mixture was extracted with diethyl ether. The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by flash column

chromatography on silica gel (*i*-hexane/ethyl acetate = 4/1) to give 2*R*,3*S*-**81** (103 mg, 0.4 mmol, 89% yield, dr = 1:99, 99% *ee*). The enantiomeric excess and absolute configuration were determined *via* ^{1}H- and ^{13}C-NMR analysis of the corresponding (*R*)- and (*S*)-Mosher ester[124] (see chapter 2.11).

$[\alpha]_D^{20}$ = −8.7 (c = 1.1, $CHCl_3$).

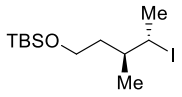
^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 3.81–3.71 (m, 1H), 3.68–3.60 (m, 1H), 3.57 (td, *J* = 6.3, 4.4 Hz, 1H), 2.95 (d, *J* = 4.3 Hz, 1H), 1.63–1.57 (m, 3H), 1.15 (d, *J* = 6.3 Hz, 3H), 0.90 (m, 12H), 0.07 (s, 6H).

^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 71.8, 61.4, 38.8, 36.2, 26.0, 20.7, 18.4, 16.6, −5.3, −5.3.

IR (ATR): $\tilde{\nu}$[cm^{-1}] = 3391 (vw), 2955 (w), 2928 (w), 2884 (w), 2881 (w), 2857 (w), 1471 (w), 1462 (w), 1386 (w), 1361 (w), 1255 (m), 1215 (w), 1088 (m), 1033 (w), 1005 (m), 990 (w), 938 (w), 922 (w), 899 (m), 834 (s), 811 (m), 774 (s), 753 (vs), 899 (m), 833 (vs), 810 (m), 792 (m), 773 (vs), 732 (s), 712 (m), 695 (s), 679 (m), 674 (m), 662 (m).

MS (EI, 70 eV): m/z (%): 232 (3), 105 (47), 83 (68), 75 (100), 57 (53), 55 (60), 41 (27).

HRMS (EI) for $C_{12}H_{28}O_2Si$: calc. [M$^+$]: 232.1859, found: 232.1858.



3*S*,4*S*-**1d**

A 25 mL *Schlenk*-flask with a magnetic stirring bar was charged with iodine (261 mg, 1.03 mmol, 1.6 equiv) and dichloromethane (5 mL) and subsequently cooled to –10 °C. PPh_3 (270 mg, 1.03 mmol, 1.6 equiv) was added and the resulting yellow solution was stirred for 1h, while being protected from light by aluminum foil. 1-Methylimidazole (82 µL, 1.03 mmol, 1.6 equiv) was added dropwise and the reaction was stirred for 10 min. 2*R*,3*S*-**81** (150 mg, 0.65 mmol, 1.0 equiv) in dichloromethane (1mL) was added dropwise. The reaction was quenched after 25 min by addition of freshly prepared sat. aq. $NaHSO_3 \cdot Na_2S_2O_5$. The phases were separated and the aqueous layer was extracted three times with dichloromethane (20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (*i*-hexane/diethyl ether = 1000/1) to give 3*S*,4*S*-**1d** (118 mg, 0.34 mmol, 53% yield, dr = 98:2, 99% *ee*).

$[\alpha]_D^{20}$ = −8.2 (c = 0.3, $CHCl_3$).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 4.39 (qd, *J* = 7.0, 2.8 Hz, 1H), 3.71–3.56 (m, 2H), 1.90 (d, *J* = 7.0 Hz, 3H), 1.62–1.51 (m, 1H), 1.44 (dt, *J* = 13.6, 6.7 Hz, 1H), 1.07–0.96 (m, 1H), 0.91 (d, *J* = 6.4 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 6H).

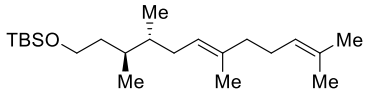
^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 60.5, 41.7, 40.4, 37.3, 26.8, 18.4, 17.2, –5.2.

IR (ATR): $\tilde{\nu}$[cm^{-1}] = 2955 (m), 2926 (m), 2894 (m), 2882 (m), 2878 (m), 2855 (m), 1719 (vw), 1471 (w), 1462 (w), 1454 (w), 1380 (w), 1377 (w), 1360 (w), 1255 (m), 1093 (s), 1035 (w), 1030 (w), 1022

(w), 1005 (m), 991 (w), 938 (w), 898 (m), 833 (vs), 809 (m), 773 (vs), 735 (w), 732 (w), 729 (w), 661 (m).

MS (EI, 70 eV): m/z (%): 215 (30), 185 (100), 157 (33), 101 (26), 89 (26), 83 (70), 75 (68), 55 (62).

HRMS (EI) for $C_8H_{18}IOSi$: calc. [M^+–*t*-Bu]: 285.0166; found: 285.0168.



3*S*,4*R*-**82**

The compound 3*S*,4*R*-**82** was prepared according to **TP1** from the iodide 3*S*,4*S*-**1d** (dr = 98:2, 0.09 mmol, 30 mg) and freshly prepared geranyl bromide (0.30 mmol, 72 mg) as electrophile. The crude product was purified by flash column chromatography on silica gel with *i*-hexane/diethyl ether = 200/1 to afford 3*S*,4*R*-**82** (0.06 mmol, 20 mg, 64% yield, dr = 97:3, 99% *ee*) as a colorless oil.

$[\alpha]_D^{20} = -10.0$ (c = 1.2, $CHCl_3$).

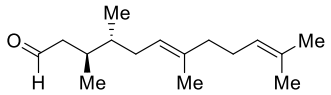
^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 5.17–5.03 (m, 2H), 3.72–3.63 (m, 1H), 3.62–3.53 (m, 1H), 2.12–1.91 (m, 5H), 1.79 (dt, *J* = 14.2, 8.4 Hz, 1H), 1.69–1.66 (m, 3H), 1.60 (d, *J* = 1.3 Hz, 3H), 1.58 (d, *J* = 1.3 Hz, 3H), 1.56–1.51 (m, 1H), 1.47–1.35 (m, 1H), 1.33–1.18 (m, 2H), 0.89 (s, 9H), 0.85 (d, *J* = 6.8 Hz, 3H), 0.81 (d, *J* = 6.9 Hz, 3H), 0.05 (s, 6H).

^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 135.3, 131.4, 124.6, 124.2, 62.3, 40.0, 38.9, 36.1, 33.8, 31.7, 26.8, 26.2, 25.9, 18.5, 17.8, 17.0, 16.2, 16.2, –5.1, –5.1.

IR (ATR): $\tilde{\nu}$[cm^{-1}] = 2955 (m), 2926 (m), 2894 (m), 2882 (m), 2878 (m), 2855 (m), 1471 (w), 1462 (w), 1454 (w), 1380 (w), 1377 (w), 1360 (w), 1255 (m), 1093 (s), 1051 (w), 1035 (w), 1030 (w), 1022 (w), 1005 (m), 991 (w), 898 (m), 833 (vs), 809 (m), 773 (vs), 735 (w), 732 (w), 729 (w), 677 (w), 661 (m).

MS (EI, 70 eV): m/z (%): 185 (28), 123 (27), 95 (54), 81 (33), 75 (45), 69 (100), 41 (44).

HRMS (EI) for $C_{22}H_{44}OSi$: calc. [M^+]: 352.3161, found: 352.3143



(+)-13-Norfaranal (**72**)

(+)-13-Norfaranal (**72**) was prepared using a literature procedure.[75] A 10 mL round-bottom flask containing 3*S*,4*R*-**82** (10.8 mg, 0.03 mmol, 1.0 equiv) was equipped with a magnetic stirring bar and charged with MeCN (1 mL) and a drop of H_2O. A spatula tip of $Bi(OTf)_3$ (~2 mg) was added and the reaction was stirred for 30 min at rt. $NaHCO_3$ (7.8 mg, 0.09 mmol, 3.0 equiv), a spatula tip of TEMPO and PIDA (15.0 mg, 0.05 mmol, 1.5 equiv) were successively added. The reaction was stirred for 30 min

and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel with *i*-hexane/ethyl acetate = 9/1 to afford (+)-13-norfaranal (**72**, 5.1 mg, 0.02 mmol, 71% yield, dr = 97:3, 99% *ee*).

$[\alpha]_D^{20}$ = +18.5 (c = 0.5, $CHCl_3$). lit:[66] $[\alpha]_D^{20}$ = +17.5 (c = 4.5, $CHCl_3$).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 9.75 (dd, *J* = 3.0, 1.6 Hz, 1H), 5.14–5.05 (m, 2H), 2.48–2.40 (m, 1H), 2.24–2.12 (m, 1H), 2.13–1.94 (m, 6H), 1.89–1.78 (m, 1H), 1.68 (d, *J* = 1.4 Hz, 3H), 1.60 (s, 3H), 1.58 (s, 3H), 1.52–1.43 (m, 1H), 0.94 (d, *J* = 6.6 Hz, 3H), 0.84 (d, *J* = 6.8 Hz, 3H).

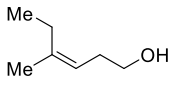
^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 230.6, 136.1, 131.5, 124.4, 123.2, 47.6, 40.0, 38.6, 32.1, 32.0, 26.7, 25.9, 17.8, 16.3, 16.1.

IR (ATR): $\tilde{\nu}$[cm^{-1}] = 2961 (s), 2919 (s), 2876 (m), 2852 (m), 2711 (w), 1725 (vs), 1668 (w), 1452 (s), 1376 (s), 1259 (m), 1151 (m), 1103 (s), 1019 (s), 982 (m), 803 (s), 1035 (w), 1030 (w), 1022 (w), 1005 (m), 991 (w), 898 (m), 833 (vs), 809 (m), 773 (vs), 735 (w), 732 (w), 729 (w), 677 (w), 661 (m).

MS (EI, 70 eV): m/z (%): 123 (29), 69 (100), 55 (27), 43 (28), 41 (51).

HRMS (EI) for $C_{16}H_{28}O$: calc. [M^+]: 236.2140, found: 236.2139.

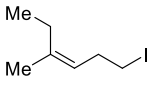
2.10 Total Synthesis of (+)-Faranal



84

(*Z*)-4-methylhex-3-en-1-ol (84): A 500 mL *Schlenk*-flask equipped with a Teflon-coated magnetic stirring bar was charged with dichloromethane (300 mL) and neat $AlMe_3$ (21.1 mL, 220 mmol, 2.2 equiv) and subsequently cooled to 0 °C. **83** (10.9 mL, 100 mmol, 1.0 equiv) was added dropwise *via* syringe. The resulting solution was cooled to –78 °C and neat $TiCl_4$ (12.1 mL, 110 mmol, 1.1 equiv) was added dropwise to the reaction mixture. The reaction was stirred at –78 °C for 2 h and quenched by dropwise addition of methanol precooled to –20 °C. An aqueous 3 M HCl solution saturated with NaCl (150 mL) was added. The reaction mixture was allowed to warm to ambient temperature and stirred for 30 min. The layers were separated and the organic phase was washed with H_2O (100 mL) and brine (100 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (*i*-hexane/ethyl acetate = 4/1) to afford **84** (7.9 g, 69.2 mmol, 69% yield).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 5.07 (t, J = 7.3 Hz, 1H), 3.59 (t, J = 6.6 Hz, 2H), 2.26 (q, J = 6.9 Hz, 2H), 2.08–2.00 (m, 3H), 1.70 (s, 3H), 0.96 (t, J = 7.6 Hz, 3H).
All other analytical data were in accordance with literature values.[130]



86

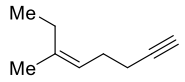
A 250 mL round-bottom flask equipped with a magnetic stirring bar was charged with **84** (10.8 g, 94.7 mmol, 1.0 equiv), dichloromethane (105 mL) and pyridine (15.3 mL, 190 mmol, 2.0 equiv) and subsequently cooled to 0 °C. TsCl (23.8 g, 125 mmol, 1.3 equiv) was added in small portions and the reaction was stirred for 3 h. The reaction was quenched by addition of water. The layers were separated and the aqueous layer was extracted once with diethyl ether (100 mL). The combined organic layers washed with 1 M HCl (100 mL), water (100 mL), brine (100 mL), dried over $MgSO_4$ concentrated under reduced pressure. The tosylate **85** was used in the next step without purification.

A 500 mL round-bottom flask equipped with a magnetic stirring bar was charged with crude **85**, NaI (21.3 g, 142 mmol, 1.5 equiv) and acetone (210 mL) and the mixture was refluxed for 3 h. The reaction was quenched by addition of H_2O and extracted with *n*-pentane. The layers were separated and the organic layer was washed sat. aq. $Na_2S_2O_3$ (200 mL), brine (200 mL) and dried over $MgSO_4$ and

[130] T.-S. Mei, H. H. Patel, M. S. Sigman, *Nature* **2014**, 508, 340–344.

concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (*n*-pentane) to give **86** (11.2 g, 50.2 mmol, 53% yield over two steps).

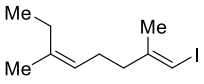
^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 5.10–5.00 (m, 1H), 3.10 (t, *J* = 7.5 Hz, 2H), 2.61–2.50 (m, 2H), 2.02 (q, *J* = 7.6 Hz, 2H), 1.69 (t, *J* = 1.3 Hz, 3H), 0.98 (t, *J* = 7.6 Hz, 3H).
^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 140.4, 122.3, 32.3, 25.1, 23.0, 13.0, 6.4.
The analytical data were in accordance with literature values.[67b]



87

A 100 mL *Schlenk*-flask equipped with a magnetic stirring bar was charged with lithium acetylide–ethylendiamine complex (4.24 g; 46.0 mmol, 1.2 equiv) and DMSO (31 mL) and subsequently cooled to 10 °C. A solution of **86** (8.6 g, 38.3 mmol, 1.0 equiv) in DMSO (15 mL) was added dropwise to the stirring suspension and stirred for 1 h. The reaction was quenched by addition of H_2O (20 mL). 1 M HCl (20 mL) was added and the mixture was extracted using *n*-pentane (50 mL). The layers were separated and the organic layer was washed with sat. aq. $NaHCO_3$ (50 mL) and brine (50 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was distilled (106 mbar, 80 °C) to give **87** (2.0 g, 16.5 mmol, 43% yield) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 5.18–5.09 (m, 1H), 2.26–2.10 (m, 4H), 2.04 (q, *J* = 7.6 Hz, 2H), 1.95 (t, *J* = 2.4 Hz, 1H), 1.70 (d, *J* = 1.4 Hz, 3H), 0.97 (t, *J* = 7.6 Hz, 3H).
^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 139.1, 122.3, 84.7, 68.3, 27.0, 25.0, 23.0, 19.3, 13.0.
IR (ATR): $\tilde{\nu}$[cm^{-1}] = 3309 (m), 3303 (m), 3300 (m), 2965 (s), 2931 (m), 2914 (m), 2874 (m), 2858 (m), 1450 (m), 1432 (m), 1376 (m), 1260 (m), 1095 (m), 1076 (m), 1059 (m), 1047 (m), 1017 (s), 857 (w), 803 (s), 686 (w).
MS (EI, 70 eV): m/z (%): 93 (100), 91 (80), 121 (63), 79 (42), 67 (29), 77 (26), 119 (22), 92 (21).
HRMS (EI) for C_9H_{13}: calc. [M^+–H]: 121.1012, found: 121.1012.
The analytical data were in accordance with literature values.[67b]



89

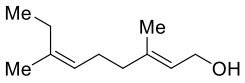
A 100 mL *Schlenk*-flask with magnetic stirring bar was charged with Cp_2ZrCl_2 (0.29 g, 1.0 mmol, 0.2 equiv), dichloromethane (20 mL) and trimethyl aluminum (15 mL, 1 M in *n*-hexane, 15 mmol, 3.0 equiv) and subsequently cooled to –23 °C. H_2O (0.14 mL, 7.5 mmol, 1.5 equiv) was added dropwise and the reaction was stirred for 10 min. **87** (0.61 g, 5.0 mmol, 1.0 equiv) in dichloromethane (10 mL)

was added and the reaction was stirred for another 10 min. I_2 (1.52 g, 6.0 mmol, 1.2 equiv) in THF (5 mL) was added and the reaction was allowed to warm to ambient temperature. Sat. aq. K_2CO_3 (5 mL) was added slowly. After 15 min $MgSO_4$ was added and the mixture was filtered. The filtrate was extracted with diethyl ether (50 mL) and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (*i*-hexane) to afford **89** (1.05 g, 4.0 mmol, 79% yield) as an oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 5.89–5.84 (m, 1H), 5.03 (td, *J* = 7.0, 1.6 Hz, 1H), 2.24–2.18 (m, 2H), 2.16–2.08 (m, 2H), 2.01 (q, *J* = 7.6 Hz, 2H), 1.84 (d, *J* = 1.1 Hz, 3H), 1.67 (q, *J* = 1.2 Hz, 3H), 0.96 (t, *J* = 7.6 Hz, 3H).

^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 148.0, 138.3, 122.8, 74.9, 40.0, 26.2, 24.9, 24.1, 23.0, 13.0.

The analytical data were in accordance with literature values.[67b]



90

A 25 mL round-bottom flask containing **89** (1.05 g, 4.0 mmol, 1.0 equiv) was charged with diethyl ether (8 mL) and subsequently cooled to –70 °C. *n*-Butyllithium (1.8 mL, 2.48 M in *n*-hexane, 4.5 mmol, 1.1 equiv) was added dropwise and the reaction was stirred for 15 min at –60 °C.

A separate 25 mL round-bottom flask was charged with paraformaldehyde (1.19 g, 39.6 mmol, 10.0 equiv) and connected to the reaction flask using Teflon tubing. At –70 °C a stream of formaldehyde obtained by heating paraformaldehyde was passed over the reaction solution. After 15 min of stirring the reaction was allowed to warm to ambient temperature. After 20 min the reaction was cooled to –20 °C and the reaction was hydrolyzed with saturated ammonium chloride solution. The layers were separated and the aqueous layer was extracted twice using *n*-pentane/diethyl ether = 1/1. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (*i*-hexane/ethyl acetate = 4/1) to give **90** (0.56 g, 3.3 mmol, 84% yield) as an oil.

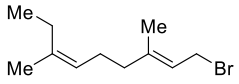
^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 5.46–5.37 (m, 1H), 5.07 (t, *J* = 6.6 Hz, 1H), 4.16 (d, *J* = 6.9 Hz, 2H), 2.10 (dd, *J* = 9.0, 6.3 Hz, 2H), 2.02 (q, *J* = 7.4 Hz, 4H), 1.68 (t, *J* = 1.4 Hz, 6H), 0.96 (t, *J* = 7.6 Hz, 3H).

^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 140.0, 137.7, 123.6, 123.4, 59.6, 40.0, 26.1, 24.9, 23.0, 16.5, 13.0.

IR (ATR): $\tilde{\nu}$[cm^{-1}] = 3309 (m), 3303 (m), 3300 (m), 2965 (s), 2931 (m), 2914 (m), 2874 (m), 2858 (m), 1450 (m), 1432 (m), 1376 (m), 1260 (m), 1095 (m), 1076 (m), 1059 (m), 1047 (m), 1017 (s), 857 (w), 803 (s), 686 (w).

MS (EI, 70 eV): m/z (%): 83 (32), 67 (9), 59 (7), 55 (100), 41 (36).

HRMS (EI) for $C_{11}H_{20}O$: calc. [M^+]: 168.1514, found: 168.1508.



68g

A 100 mL round-bottom flask equipped with a magnetic stirring bar was charged with **90** (0.56 g, 3.3 mmol, 1.0 equiv) and diethyl ether (25 mL) and subsequently cooled to –20 °C. PBr_3 (0.15 mL, 1.7 mmol, 0.5 equiv) was added dropwise and the resulting mixture was allowed to warm to 0 °C for 1 hour. The reaction was poured into ice water and extracted three times using *i*-hexane (20 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (50 mL) and brine (50 mL), dried over $MgSO_4$ and concentrated under reduced pressure to afford **68g** (0.76 g, 3.3 mmol, quant. yield).

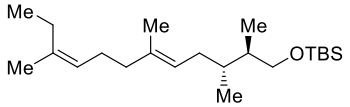
^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 5.53 (tq, J = 8.4, 1.4 Hz, 1H), 5.08–5.00 (m, 1H), 4.03 (d, J = 8.4 Hz, 2H), 2.14–2.05 (m, 4H), 2.02 (q, J = 7.6 Hz, 2H), 1.73 (d, J = 1.4 Hz, 3H), 1.67 (d, J = 1.4 Hz, 3H), 0.96 (t, J = 7.6 Hz, 3H).

^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 143.8, 137.9, 123.3, 120.6, 40.0, 29.9, 26.0, 24.9, 23.0, 16.2, 13.0.

IR (ATR): $\tilde{\nu}$[cm^{-1}] = 2964 (vs), 2931 (s), 2916 (s), 2910 (s), 2903 (s), 2874 (s), 2167 (vs), 1655 (s), 1449 (s), 1445 (vs), 1441 (s), 1376 (s), 1199 (vs), 1111 (s), 1073 (s), 1020 (s), 839 (s), 833 (s), 722 (vs), 686 (w).

MS (EI, 70 eV): m/z (%): 83 (69), 81 (26), 67 (19), 55 (100), 43 (60), 41 (32).

HRMS (EI) for $C_{11}H_{19}Br$: calc. [M^+]: 230.0670, found: 230.0664.



2*R*,3*R*-**92**

The compound 2*R*,3*R*-**92** was prepared according to **TP1** from the iodide 3*S*,4*S*-**1c** (dr = 98:2, 0.20 mmol, 98 mg) and freshly prepared electrophile **68g** (0.90 mmol, 207 mg) as electrophile. The crude product was purified by flash column chromatography on silica gel with *i*-hexane/diethyl ether = 200/1 to afford 2*R*,3*R*-**92** (0.10 mmol, 35 mg, 49% yield, dr = 97:3, 99% *ee*) as a colorless oil.

$[\alpha]_D^{20}$ = –1.2 (c = 2.0, $CHCl_3$).

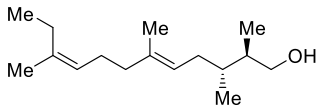
^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 5.12 (t, *J* = 7.3 Hz, 1H), 5.07 (t, *J* = 6.6 Hz, 1H), 3.57 (dd, *J* = 9.8, 5.4 Hz, 1H), 3.41 (dd, *J* = 9.9, 6.8 Hz, 1H), 2.11–1.96 (m, 7H), 1.83–1.74 (m, 1H), 1.67 (d, *J* = 1.3 Hz, 3H), 1.59 (d, *J* = 1.3 Hz, 3H), 1.57–1.54 (m, 2H), 0.96 (t, *J* = 7.6 Hz, 3H), 0.89 (s, 9H), 0.88–0.83 (m, 6H), 0.04 (s, 6H).

^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 137.2, 135.4, 124.2, 124.1, 66.3, 40.4, 40.4, 35.5, 31.4, 26.4, 26.1, 24.9, 23.0, 18.5, 17.1, 16.3, 14.0, 13.0, –5.2.

IR (ATR): $\tilde{\nu}$[cm^{-1}] = 2957 (m), 2927 (m), 2904 (m), 2897 (m), 2888 (m), 2885 (m), 2881 (m), 2874 (m), 2855 (m), 1471 (m), 1462 (m), 1387 (w), 1376 (w), 1360 (w), 1255 (m), 1251 (m), 1089 (s), 1022 (w), 1005 (w), 938 (w), 835 (vs), 814 (m), 774 (s), 667 (w).

MS (EI, 70 eV): m/z (%): 295 (27), 75 (100), 199 (95), 83 (90), 55 (80), 73 (60), 95 (53), 41 (39), 89 (26).

HRMS (EI) for $C_{22}H_{44}OSi$: calc. [M^+]: 352.3161, found: 352.3142.



2*R*,3*R*-**93**

A 5 mL round-bottom flask equipped with a magnetic stirring bar was charged with 2*R*,3*R*-**92** (20 mg, 0.06 mmol, 1.0 equiv) and THF (1 mL). A TBAF-solution (0.3 mL, 0.30 mmol, 1.0 M in THF, 5.0 equiv) was added dropwise and the resulting mixture was stirred for 12 h at rt. After quenching the reaction mixture with brine, the reaction mixture was extracted with diethyl ether (3 × 5 mL). The combined organic phases were dried over $MgSO_4$ and the solvents were evaporated. The crude product was purified by flash column column chromatography on silica gel with *i*-hexane/diethyl ether = 4/1 to afford 2*R*,3*R*-**93** (0.06 mmol, 14 mg, 96% yield, dr = 97:3, 99% *ee*) as a colorless oil.

$[\alpha]_D^{20}$ = +6.2 (c = 1.2, $CHCl_3$).

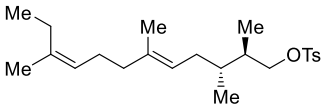
^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 5.17–5.02 (m, 2H), 3.65 (dd, *J* = 10.6, 5.3 Hz, 1H), 3.47 (dd, *J* = 10.6, 7.0 Hz, 1H), 2.12–1.96 (m, 7H), 1.87–1.76 (m, 1H), 1.67 (q, *J* = 1.3 Hz, 3H), 1.61–1.53 (m, 3H), 1.59 (d, *J* = 1.3 Hz, 3H), 0.96 (t, *J* = 7.6 Hz, 3H), 0.93 (d, *J* = 6.7 Hz, 3H), 0.87 (d, *J* = 6.7 Hz, 3H).

^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 137.3, 135.8, 124.1, 123.8, 66.4, 40.5, 35.7, 31.4, 26.4, 24.9, 23.0, 17.2, 16.3, 14.0, 13.0.

IR (ATR): $\tilde{\nu}$[cm^{-1}] = 2962 (vs), 2927 (s), 2874 (s), 2857 (m), 1669 (w), 1454 (m), 1376 (m), 1113 (w), 1025 (m), 839 (w).

MS (EI, 70 eV): m/z (%): 99 (21), 95 (34), 83 (50), 81 (27), 69 (22), 67 (21), 55 (100), 45 (17), 43 (20), 41 (57).

HRMS (EI) for $C_{16}H_{30}O$: calc. [M^+]: 238.2297, found: 238.2278.



2*R*,3*R*-**94**

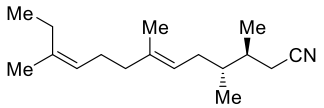
The tosylate 2*R*,3*R*-**94** was prepared according to a literature procedure.[78] To a solution of the alcohol 2*R*,3*R*-**93** (12 mg, 0.05 mmol, 1.0 equiv), TsCl (11 mg, 0.06 mmol, 1.1 equiv) and DMAP (1 mg, 0.01 mmol, 0.1 equiv) in dichloromethane (1 mL) was added triethylamine (10 mg, 0.1 mmol, 2 equiv) dropwise. The reaction mixture was stirred for 14 h at rt. After quenching the reaction mixture with 1 M aq. HCl (3 mL) and extracted with diethyl ether (3 × 5 mL) the combined organic phases were dried over $MgSO_4$ and the solvents were evaporated. The crude product was purified by flash column column chromatography on silica gel with *i*-hexane/diethyl ether = 4/1 to afford 2*R*,3*R*-**94** (0.04 mmol, 15 mg, 75% yield, dr = 97:3, 99% *ee*) as a colorless oil.

$[\alpha]_D^{20}$ = –12.2 (c = 0.7, $CHCl_3$).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.82–7.74 (m, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 5.06–4.98 (m, 2H), 3.99 (dd, *J* = 9.4, 5.5 Hz, 1H), 3.86 (dd, *J* = 9.4, 7.1 Hz, 1H), 2.45 (s, 3H), 2.10–1.86 (m, 8H), 1.83–1.70 (m, 2H), 1.68–1.64 (m, 3H), 1.52 (d, *J* = 1.3 Hz, 3H), 0.96 (t, *J* = 7.6 Hz, 3H), 0.88 (d, *J* = 7.0 Hz, 3H), 0.79 (d, *J* = 6.9 Hz, 3H).

^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 144.8, 137.3, 136.2, 133.3, 129.9, 128.0, 124.0, 122.9, 73.7, 40.3, 37.2, 35.4, 31.4, 26.3, 24.9, 23.0, 21.8, 16.7, 16.2, 14.1, 13.0.

IR (ATR): $\tilde{\nu}$[cm^{-1}] = 2963 (m), 2927 (m), 2874 (w), 2858 (w), 2854 (w), 1598 (w), 1454 (w), 1364 (m), 1188 (s), 1177 (vs), 1098 (w), 1020 (w), 964 (m), 936 (w), 932 (w), 838 (m), 814 (m), 794 (w), 791 (w), 784 (w), 778 (w), 775 (w), 772 (w), 667 (m).



3*S*,4*R*-**95**

The nitrile 3*S*,4*R*-**95** was prepared according to a literature procedure.[78] To a solution of the tosylate 2*R*,3*R*-**94** (14.5 mg, 0.04 mmol, 1.0 equiv) in DMSO (2 mL) was added NaCN (12.0 mg, 0.05 mmol, 3.0 equiv). The solution was stirred 14 h at 50 °C. After quenching the reaction mixture with ice cold water and extraction with diethyl ether (3 x 5 mL) the combined organic phases were dried over $MgSO_4$ and the solvents were evaporated. The crude product 3*S*,4*R*-**95** (0.03 mmol, 7.2 mg, 79% yield, dr = 97:3, 99% *ee*) was used in the next step without further purification.

$[\alpha]_D^{20}$ = +10.4 (c = 0.3, $CHCl_3$).

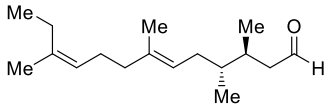
^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 5.12–5.01 (m, 2H), 2.40–2.32 (m, 1H), 2.25–2.16 (m, 1H), 2.12–1.97 (m, 8H), 1.90–1.78 (m, 2H), 1.68–1.65 (m, 3H), 1.59 (d, *J* = 1.3 Hz, 3H), 1.08 (d, *J* = 6.8 Hz, 3H), 0.96 (t, *J* = 7.6 Hz, 3H), 0.87 (d, *J* = 6.9 Hz, 3H).

^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 137.4, 136.6, 123.9, 122.5, 119.7, 40.3, 37.7, 34.9, 31.7, 29.9, 26.3, 24.9, 23.0, 21.6, 17.3, 16.3, 17.2, 16.3, 13.0.

IR (ATR): $\tilde{\nu}$[cm^{-1}] = 2961 (s), 2923 (s), 2873 (m), 2852 (m), 1740 (w), 1710 (w), 1663 (w), 1455 (m), 1428 (w), 1378 (m), 1260 (m), 1094 (s), 1090 (s), 1083 (s), 1077 (s), 1055 (m), 1019 (s), 868 (w), 865 (w), 860 (w), 853 (w), 838 (w), 797 (vs).

MS (EI, 70 eV): m/z (%): 123 (22), 99 (21), 91 (32), 83 (49), 81 (52), 79 (47), 69 (21), 67 (80), 55 (100).

HRMS (EI) for $C_{16}H_{26}N$: calc. [M^+–Me]: 232.2065; found: 232.2049.



(+)-faranal (**73**)

(+)-faranal (**73**) was prepared according to a literature procedure.[78] A solution of the cyanide 3*S*,4*R*-**95** (6.5 mg, 0.03 mmol, 1.0 equiv) in dry dichloromethane was cooled to –10 °C, and DIBAL-H (0.058 mL, 1M solution in heptane, 0.06 mmol, 2.2 equiv) was added dropwise. The reaction mixture was stirred at –10 °C for 3 h, then quenched with 15% aqueous solution of *Rochelle*'s salt and the aqueous phase was extracted with diethyl ether (3 x 5 mL). The combined organic phases were dried over $MgSO_4$ and the solvents were evaporated. The crude product was purified by flash column column chromatography (pipette column) on silica gel with *i*-hexane/diethyl ether = 100/1 to afford (+)-faranal (**73**, 0.02 mmol, 5.2 mg, 79% yield, dr = 97:3, 99% *ee*) as a colorless oil.

$[\alpha]_D^{20}$ = +16.4 (c = 0.5, $CHCl_3$).

[Lit:[66] $[\alpha]_D^{24}$ = +17.4 (c = 4.1, $CHCl_3$). Lit:[126] $[\alpha]_D^{23}$ = +16.7 (c = 1.6, $CHCl_3$)].

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 9.75 (dd, *J* = 3.1, 1.7 Hz, 1H), 5.11 (t, *J* = 7.3 Hz, 1H), 5.06 (t, *J* = 6.6 Hz, 1H), 2.44 (ddd, *J* = 15.6, 4.1, 1.7 Hz, 1H), 2.17 (ddd, *J* = 15.7, 9.5, 3.1 Hz, 1H), 2.13–1.93 (m, 8H), 1.87–1.80 (m, 1H), 1.67 (d, *J* = 1.3 Hz, 3H), 1.59 (s, 3H), 1.51–1.45 (m, 1H), 0.96–0.94 (m, 4H), 0.88 (t, *J* = 7.2 Hz, 2H), 0.84 (d, *J* = 6.8 Hz, 3H).

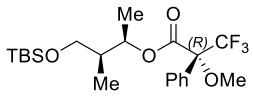
^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 203.5, 137.3, 136.1, 124.0, 123.3, 47.6, 40.3, 38.6, 32.17, 32.0, 26.4, 24.9, 23.0, 17.7, 16.3, 16.1, 13.0.

IR (ATR): $\tilde{\nu}$[cm^{-1}] = 2962 (vs), 2930 (s), 2888 (m), 2874 (s), 2863 (m), 2860 (m), 2856 (m), 2853 (m), 2359 (w), 1727 (vs), 1456 (m), 1380 (m), 1376 (m), 1261 (w), 1096 (w), 1093 (w), 1082 (w), 1078 (w), 1026 (w), 1021 (m), 804 (w).

MS (EI, 70 eV): m/z (%): 250 (1), 175 (31), 121 (43), 107 (67), 95 (73), 91 (61), 81 (100), 79 (66), 55 (58).

HRMS (EI) for $C_{17}H_{30}O$: calc. [M^+]: 250.2297; found: 250.2289.

2.11 Determination of Absolute Configuration *via* Mosher Ester Analysis



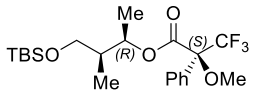
(*R*)-**M1**

The (*R*)-Mosher ester (*R*)-**M1** of (2*R*,3*S*)-4-((*tert*-butyldimethylsilyl)oxy)-3-methylbutan-2-ol (0.14 mmol, 30 mg) was prepared according to **TP3**. The crude product was purified by flash column chromatography on silica gel (*i*-hexane/ethyl acetate = 40/1) to afford the (*R*)-Mosher ester (0.10 mmol, 44 mg, 72% yield) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.54–7.49 (m, 2H), 7.43–7.35 (m, 3H), 5.20 (p, *J* = 6.4 Hz, 1H), 3.56–3.49 (m, 5H), 2.00–1.88 (m, 1H), 1.27–1.20 (m, 3H), 0.91 (d, *J*= 6.9 Hz, 3H), 0.88 (s, 9H), 0.02 (s, 6H).

^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 166.1, 132.5, 129.6, 128.5, 127.6, 77.4, 75.2, 64.4, 55.4, 40.1, 26.0, 18.4, 16.1, 12.6, –5.3, –5.4.

IR (ATR): $\tilde{\nu}$[cm^{-1}] = 2953 (m), 2927 (s), 2855 (m), 1745 (s), 1472 (m), 1463 (m), 1451 (m), 1290 (m), 1258 (s), 1184 (s), 1169 (vs), 1122 (s), 1107 (s), 1082 (s), 1057 (m), 1037 (m), 1019 (s), 993 (m), 963 (w), 836 (s), 814 (w), 776 (m), 765 (m), 716 (m), 696 (w).



(*S*)-**M1**

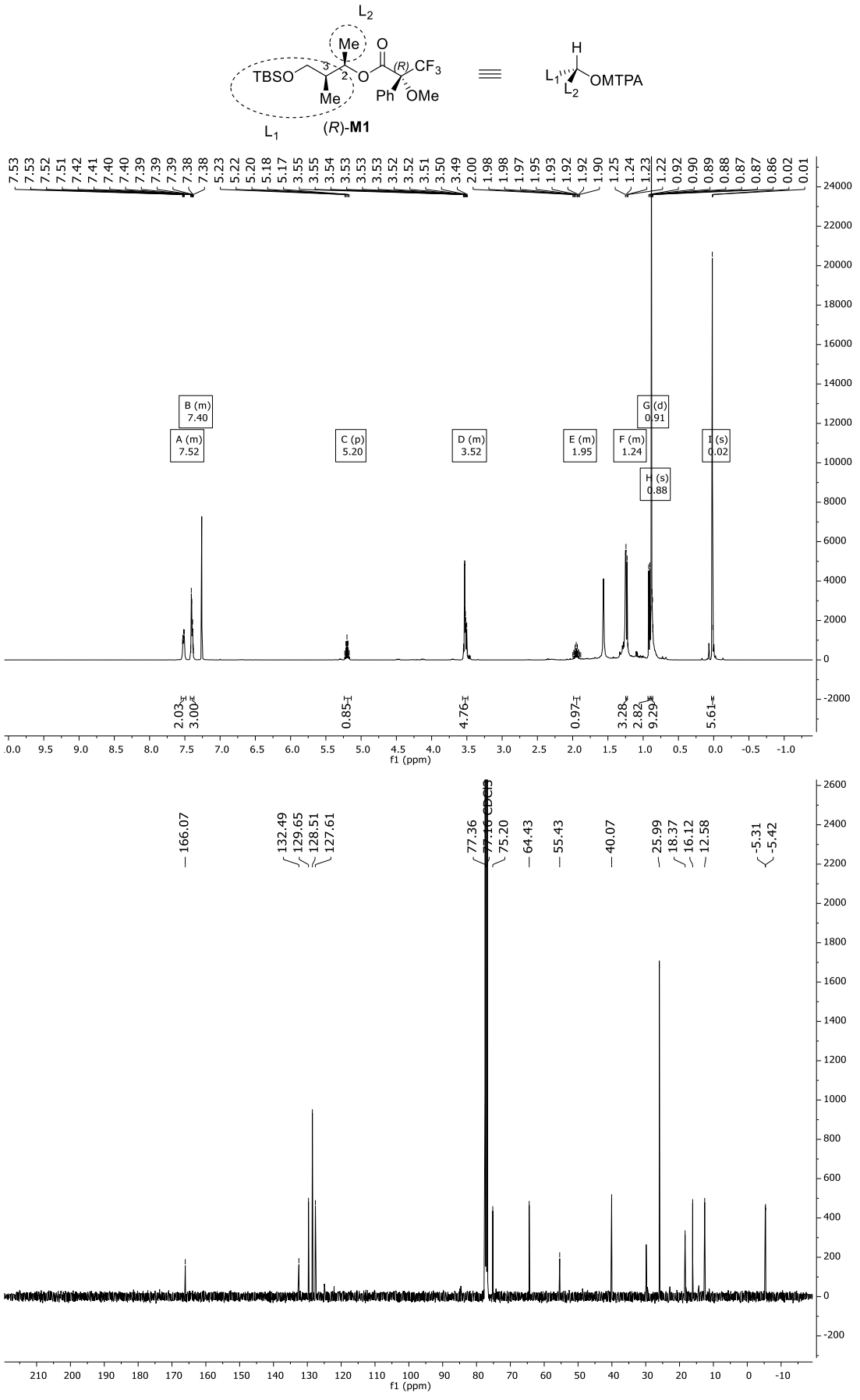
The (*S*)-Mosher ester (*S*)-**M1** of (2*R*,3*S*)-4-((*tert*-butyldimethylsilyl)oxy)-3-methylbutan-2-ol (0.14 mmol, 30 mg) was prepared according to **TP3**. The crude product was purified by flash column chromatography on silica gel (*i*-hexane/ethyl acetate = 40/1) to afford the (*S*)-Mosher ester (0.09 mmol, 39 mg, 64% yield) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.56–7.50 (m, 2H), 7.42–7.37 (m, 3H), 5.20 (p, *J* = 6.4 Hz, 1H), 3.57–3.53 (m, 3H), 3.46 (dd, *J* = 10.0, 5.6 Hz, 1H), 3.39 (dd, *J* = 10.0, 6.0 Hz, 1H), 1.91 (p, *J* = 6.4 Hz, 1H), 1.31 (d, *J* = 6.4 Hz, 3H), 0.88–0.86 (m, 12H), –0.01 (d, *J* = 2.8 Hz, 6H).

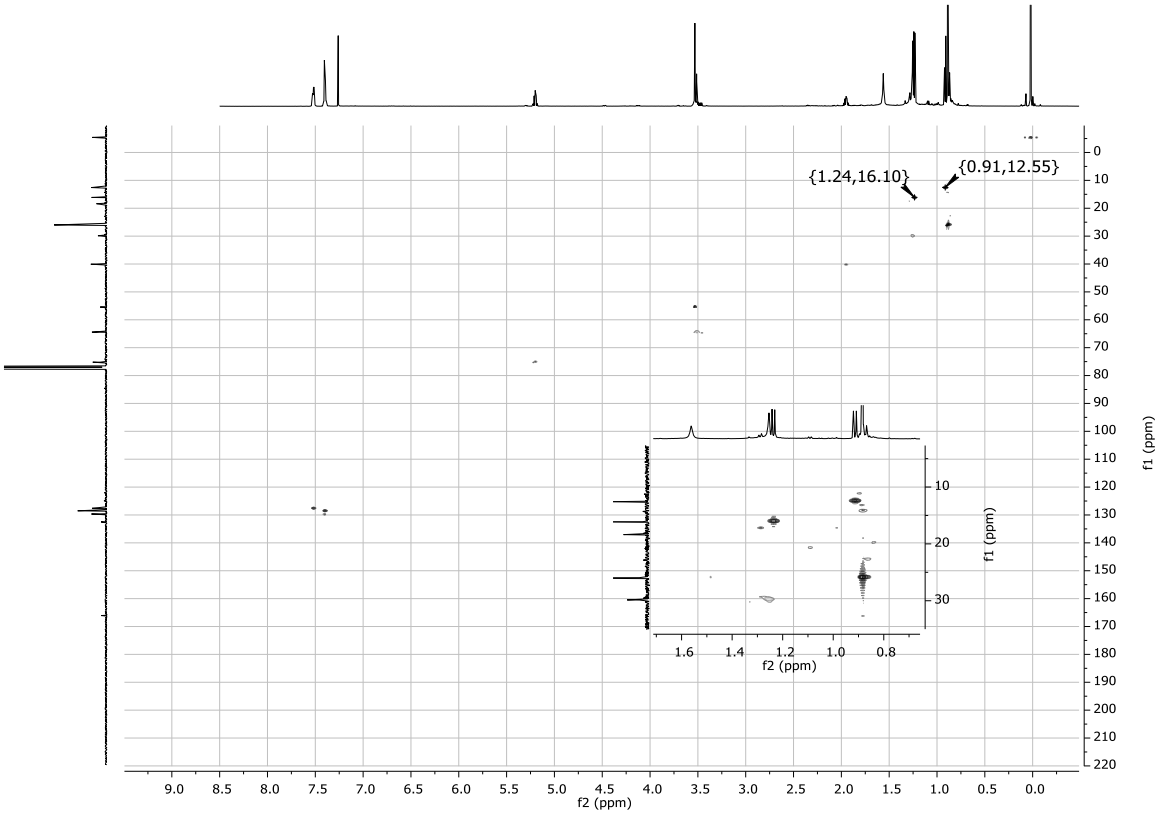
^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 165.9, 132.7, 129.6, 128.5, 127.4, 77.4, 75.2, 64.3, 55.5, 40.1, 26.0, 18.4, 16.6, 12.5, –5.3, –5.4.

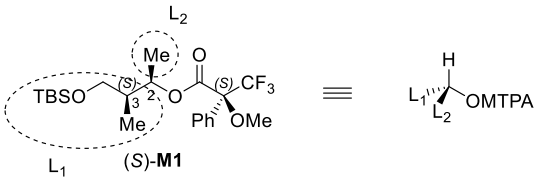
IR (ATR): $\tilde{\nu}$[cm^{-1}] = 2954 (m), 2929 (m), 2898 (w), 2888 (w), 2885 (w), 2856 (m), 1746 (s), 1472 (m), 1463 (w), 1451 (w), 1291 (m), 1258 (s), 1183 (s), 1169 (vs), 1121 (s), 1106 (s), 1082 (s), 1056 (m), 1037 (m), 1021 (s), 993 (m), 836 (s), 776 (m), 716 (m), 696 (w).

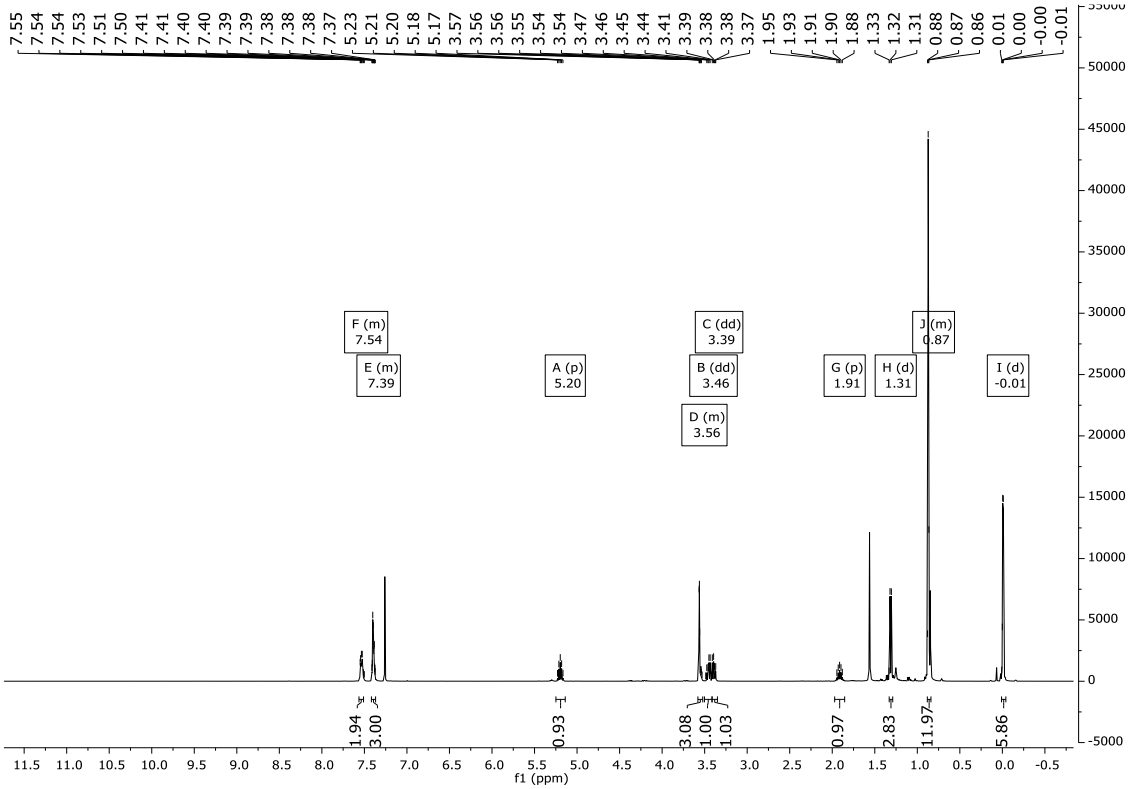
Comparison of (*R*)-M1 and (*S*)-M1

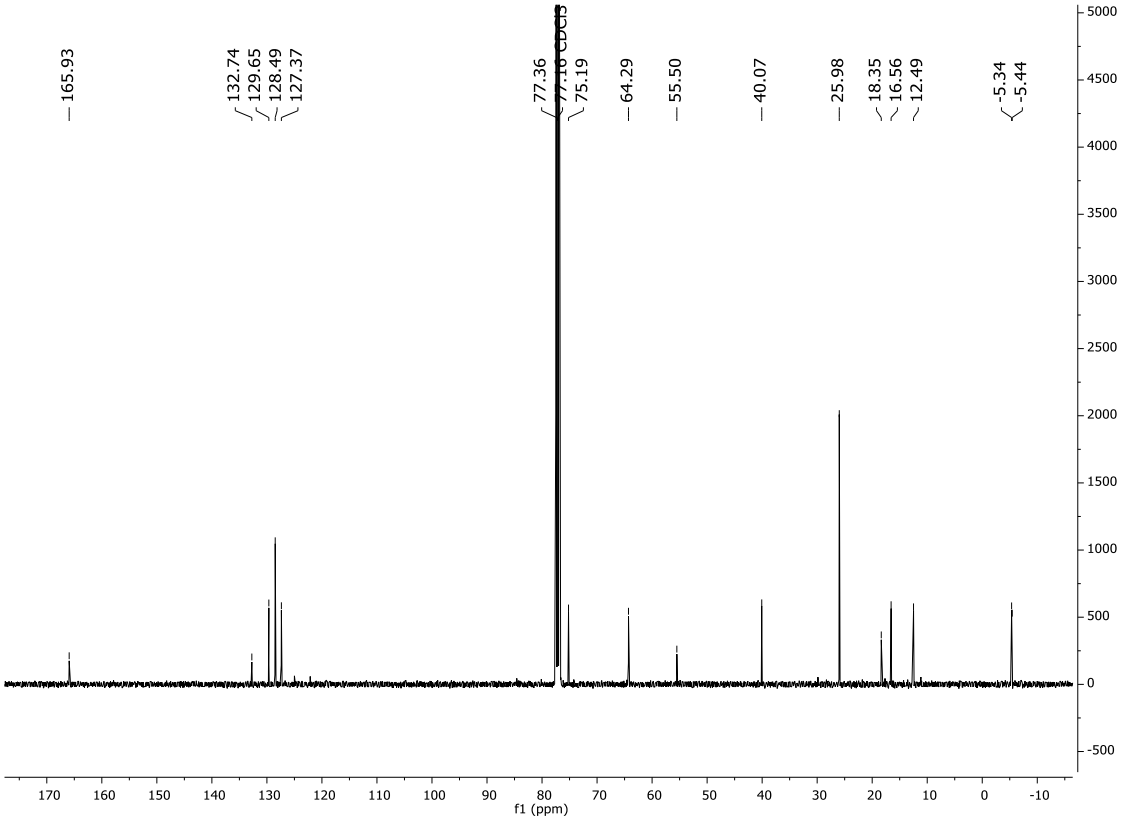


HSQC

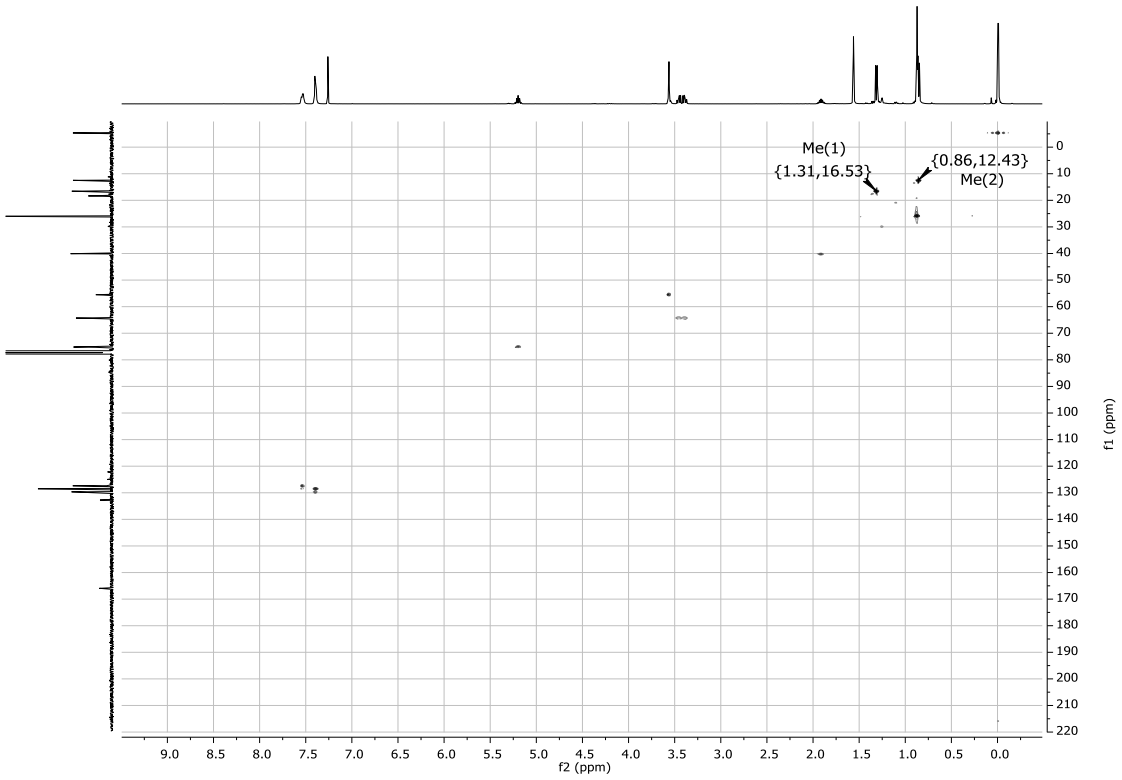


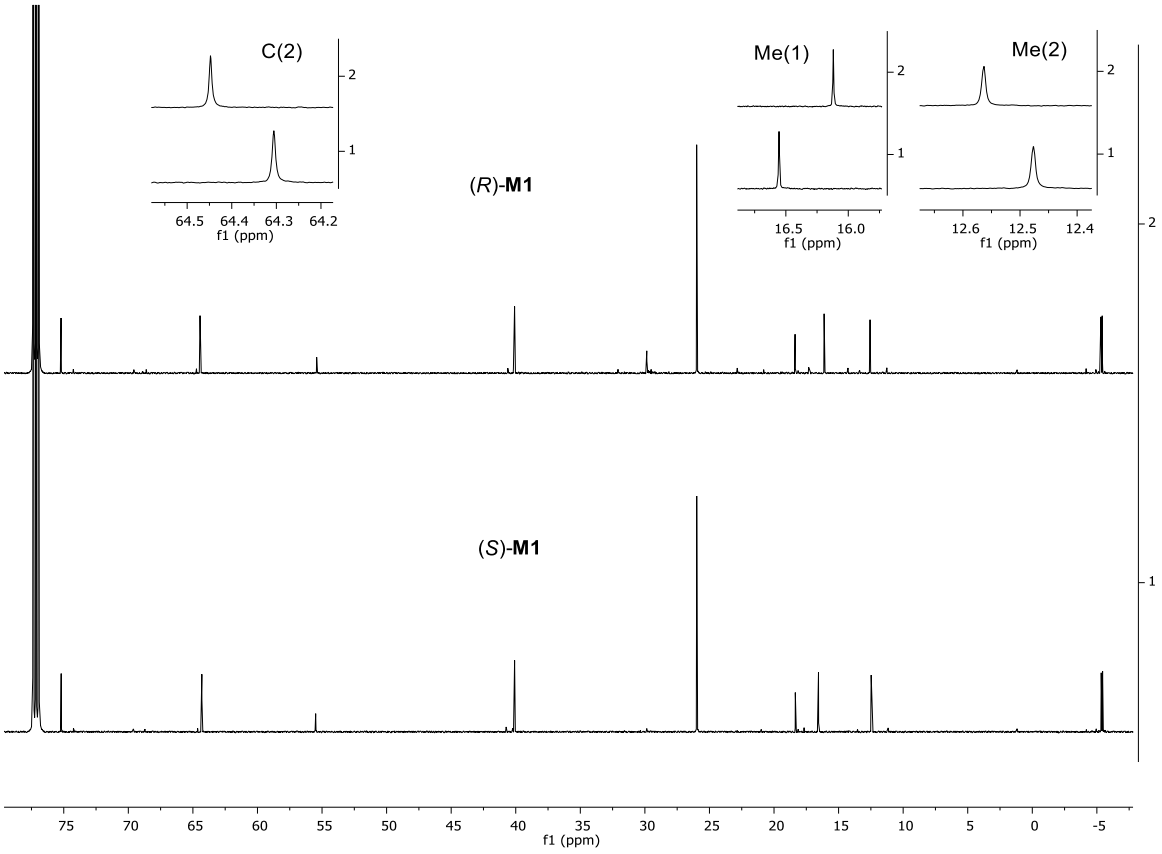

L2
Me
O
(S)
CF3
TBSO
(S)
2
O
3
Me
Ph
OMe
L1
(S)-M1
H
L1
L2
OMTPA

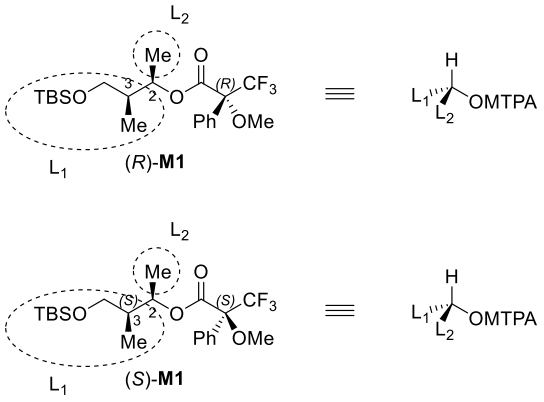

F (m) 7.54
E (m) 7.39
A (p) 5.20
C (dd) 3.39
B (dd) 3.46
D (m) 3.56
G (p) 1.91
H (d) 1.31
J (m) 0.87
I (d) -0.01
1.94
3.00
0.93
3.08
1.00
1.03
0.97
2.83
11.97
5.86
f1 (ppm)


165.93
132.74
129.65
128.49
127.37
77.36
77.16 CDCl3
75.19
64.29
55.50
40.07
25.98
18.35
16.56
12.49
-5.34
-5.44
f1 (ppm)

HSQC

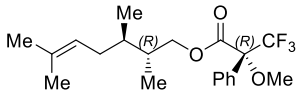






According to literature,[124] the difference $\Delta\delta^{S-R}$ of L_2 (Me(1)) should be positive and the difference $\Delta\delta^{S-R}$ of L_1 (Me(2)) should be negative. As $\Delta\delta^{S-R}$ (L_2) = 16.56–16.12 = 0.43 > 0 and $\Delta\delta^{S-R}$ (L_1) = 12.49–12.58 = –0.09 < 0, the structure and absolute stereochemistry assigned correctly.

As in the spectrum of (*R*)-**M1** any signals of (*S*)-**M1** were not found and *vice versa*, the *ee* of (2*R*,3*S*)-4-((*tert*-butyldimethylsilyl)oxy)-3-methylbutan-2-ol is >99%.



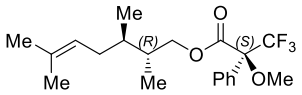
(*R*)-**M2**

The (*R*)-Mosher ester (*R*)-**M2** of (+)-lasiol (**71**, 0.05 mmol, 8 mg) was prepared according to **TP3**. The crude product was purified by flash column chromatography on silica gel (*i*-hexane/ethyl acetate = 40/1) to afford the (*R*)-Mosher ester (0.03 mmol, 9 mg, 51% yield) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.54–7.49 (m, 2H), 7.43–7.36 (m, 3H), 5.09–5.01 (m, 1H), 4.36 (dd, *J* = 10.8, 5.4 Hz, 1H), 4.11 (dd, *J* = 10.8, 7.4 Hz, 1H), 3.55 (d, *J* = 1.2 Hz, 3H), 2.04–1.94 (m, 1H), 1.86–1.75 (m, 2H), 1.71–1.66 (m, 3H), 1.57 (s, 3H), 1.51 (tdd, *J* = 9.6, 7.0, 5.0 Hz, 1H), 0.91 (d, *J* = 7.0 Hz, 3H), 0.85 (d, *J* = 7.0 Hz, 3H).

^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 166.9, 132.6, 129.7, 128.5, 127.5, 123.1, 77.4, 77.2, 77.0, 69.8, 36.9, 35.9, 31.7, 26.0, 18.0, 16.8, 14.4.

IR (ATR): $\tilde{\nu}$[cm^{-1}] = 2965 (m), 2917 (w), 2889 (w), 2879 (w), 1747 (s), 1451 (m), 1378 (w), 1290 (m), 1271 (s), 1244 (m), 1183 (s), 1169 (vs), 1122 (m), 1108 (m), 1081 (w), 1038 (m), 1022 (s), 1000 (m), 764 (w), 731 (w), 719 (m), 696 (w).



(*S*)-**M2**

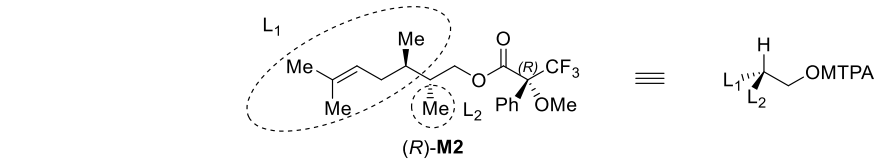
The (*S*)-Mosher ester (*S*)-**M2** of (+)-lasiol (**71**, 0.05 mmol, 8 mg) was prepared according to **TP3**. The crude product was purified by flash column chromatography on silica gel (*i*-hexane/ethyl acetate = 40/1) to afford the (*S*)-Mosher ester (0.02 mmol, 8 mg, 45% yield) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.54–7.48 (m, 2H), 7.44–7.35 (m, 3H), 5.05 (m, 1H), 4.29 (dd, *J* = 10.8, 5.3 Hz, 1H), 4.22–4.13 (m, 1H), 3.56–3.53 (m, 3H), 2.01 (dt, *J* = 12.1, 5.4 Hz, 1H), 1.88–1.74 (m, 2H), 1.69 (s, 3H), 1.57 (s, 3H), 1.49 (ddd, *J* = 13.7, 6.9, 5.0 Hz, 1H), 0.91 (d, *J* = 6.8 Hz, 3H), 0.84 (d, *J* = 6.8 Hz, 3H).

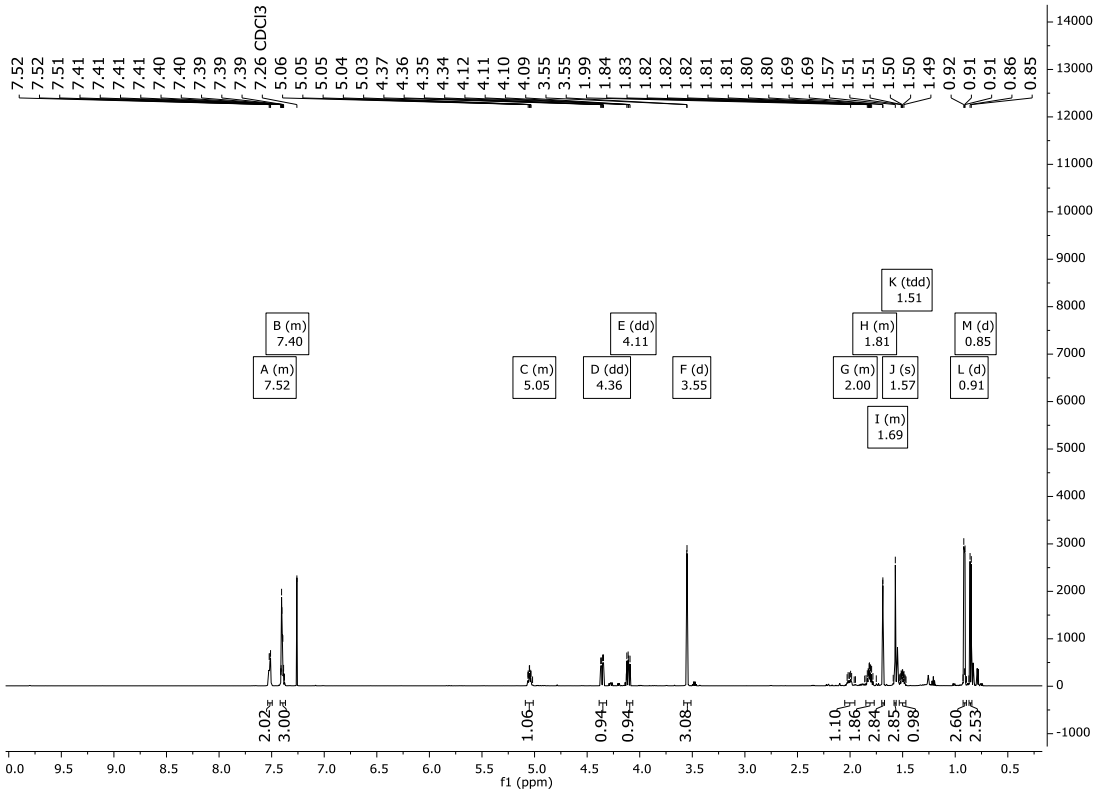
^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 166.9, 132.6, 132.5, 129.7, 128.5, 127.5, 127.5, 123.0, 69.8, 55.6, 55.6, 36.8, 35.8, 31.6, 26.0, 18.0, 16.8, 14.4.

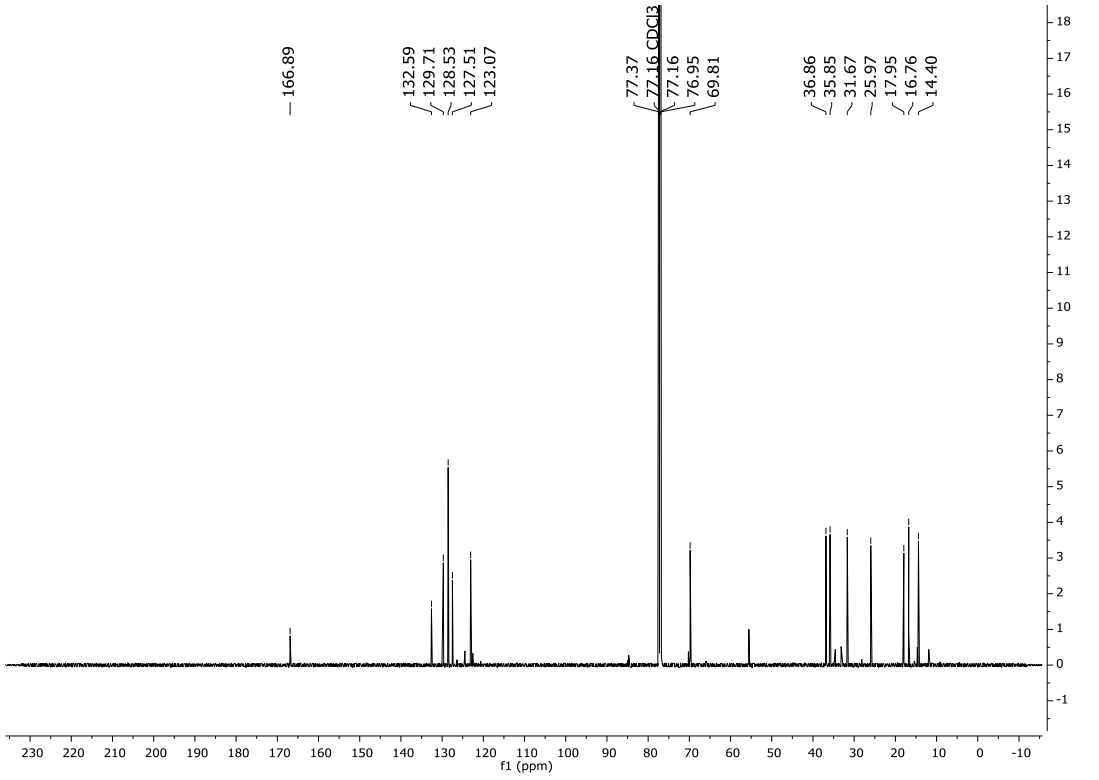
IR (ATR): $\tilde{\nu}$[cm^{-1}] = 2963 (m), 2926 (m), 2922 (m), 2918 (m), 2888 (w), 2879 (w), 2850 (w), 1747 (s), 1451 (m), 1378 (w), 1290 (m), 1272 (s), 1243 (s), 1183 (s), 1168 (vs), 1122 (m), 1108 (m), 1081 (w), 1038 (m), 1021 (s), 1000 (m), 968 (w), 916 (w), 764 (w), 730 (w), 719 (m), 696 (w).

Comparison of (*R*)-M2 and (*S*)-M2

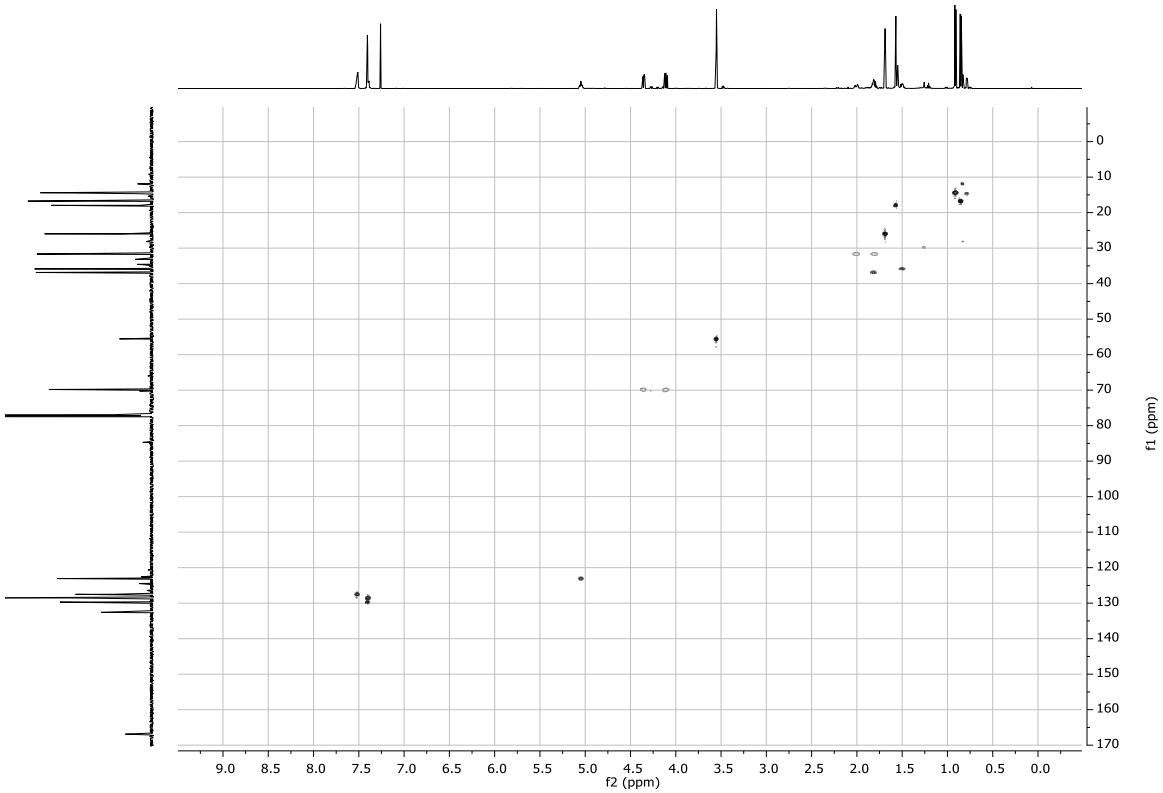


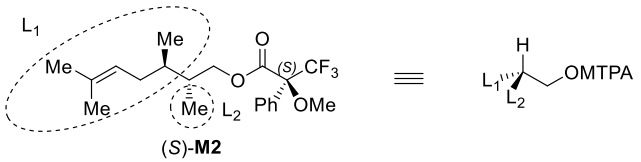
(*R*)-**M2**



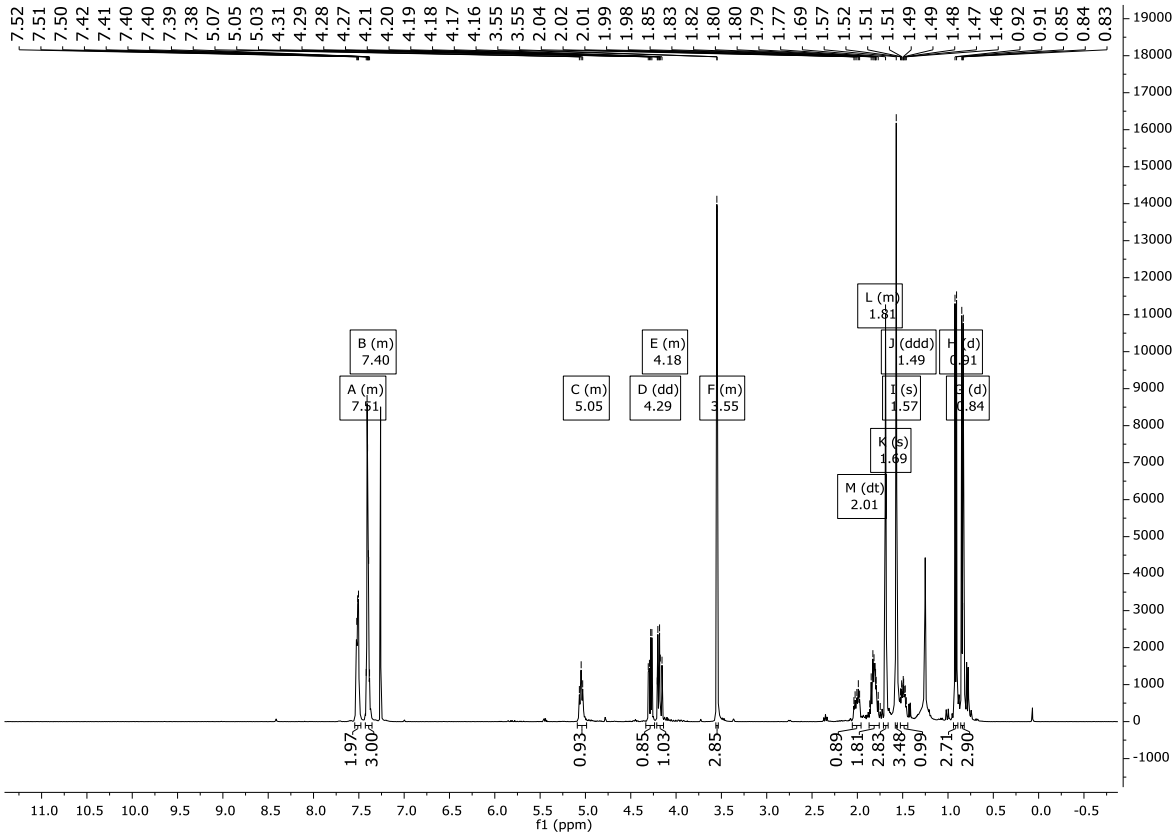


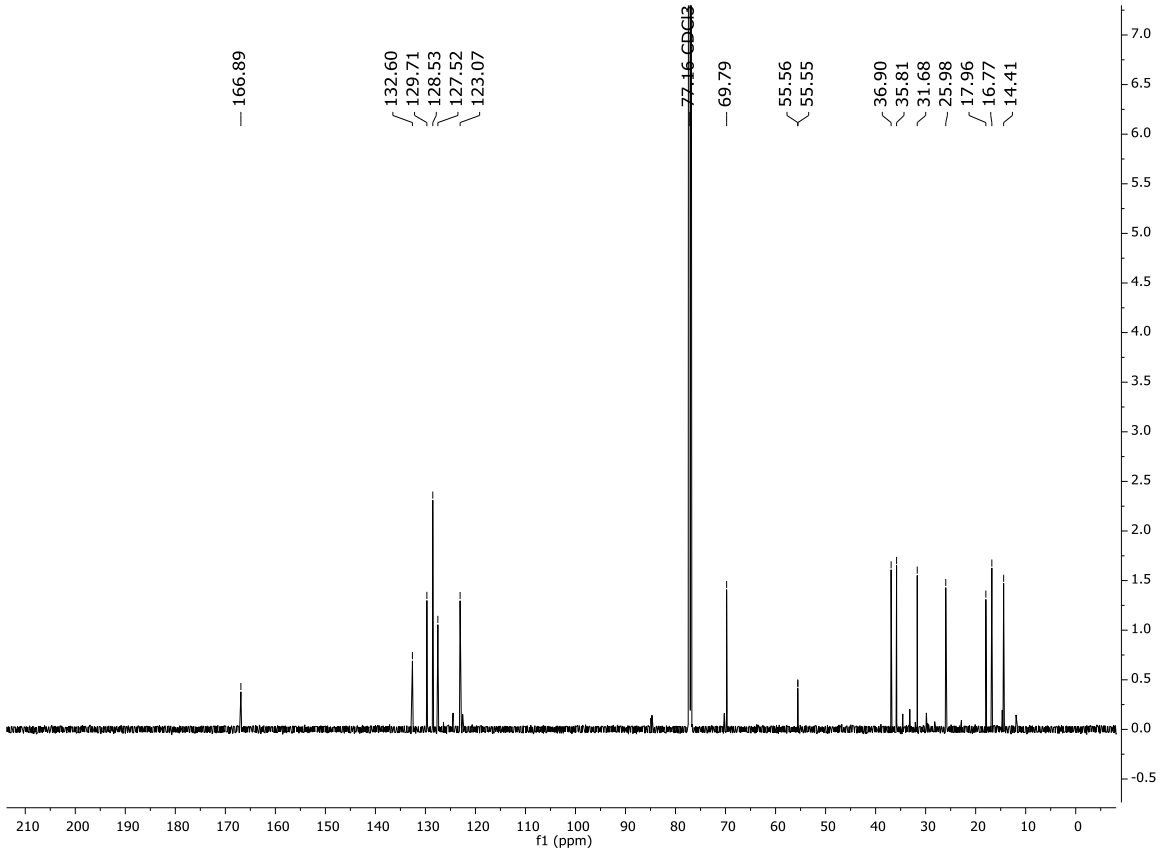
HSQC



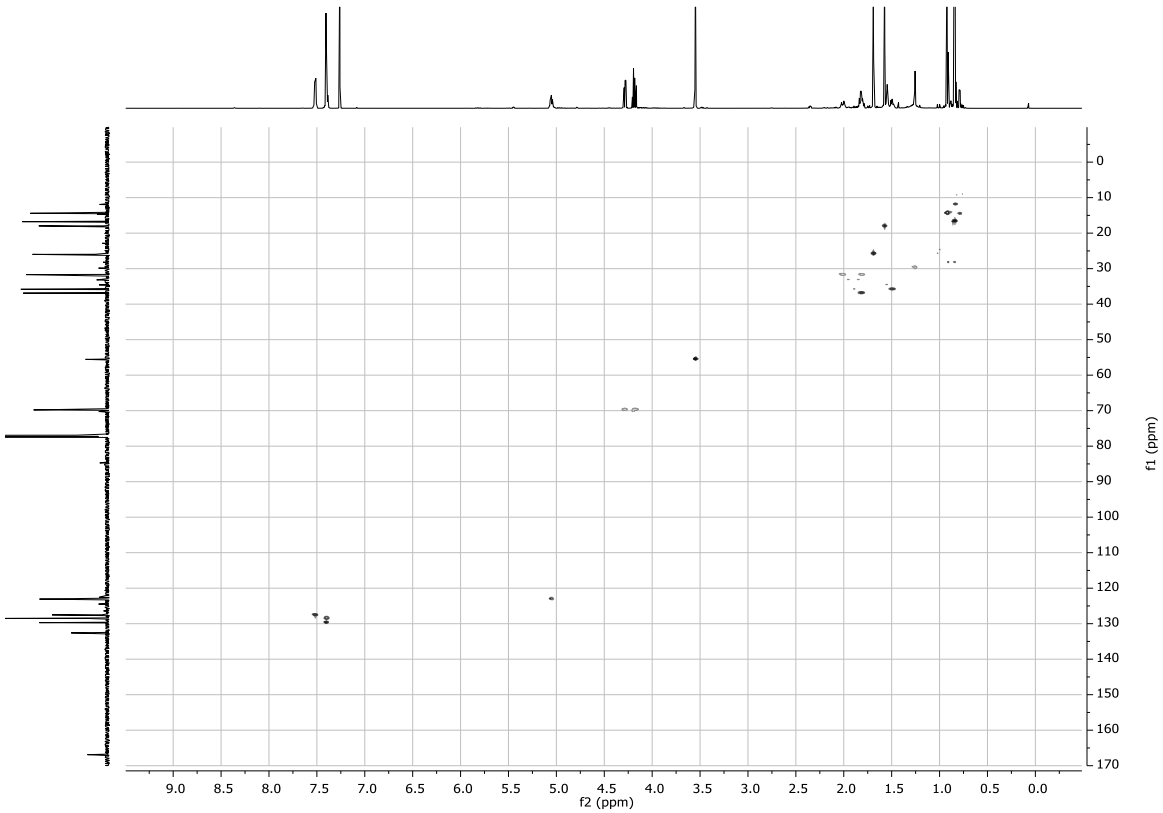

L1
Me
Me
Me
O
(S) CF3
O
Ph
OMe
Me
L2
H
L1
L2
OMTPA

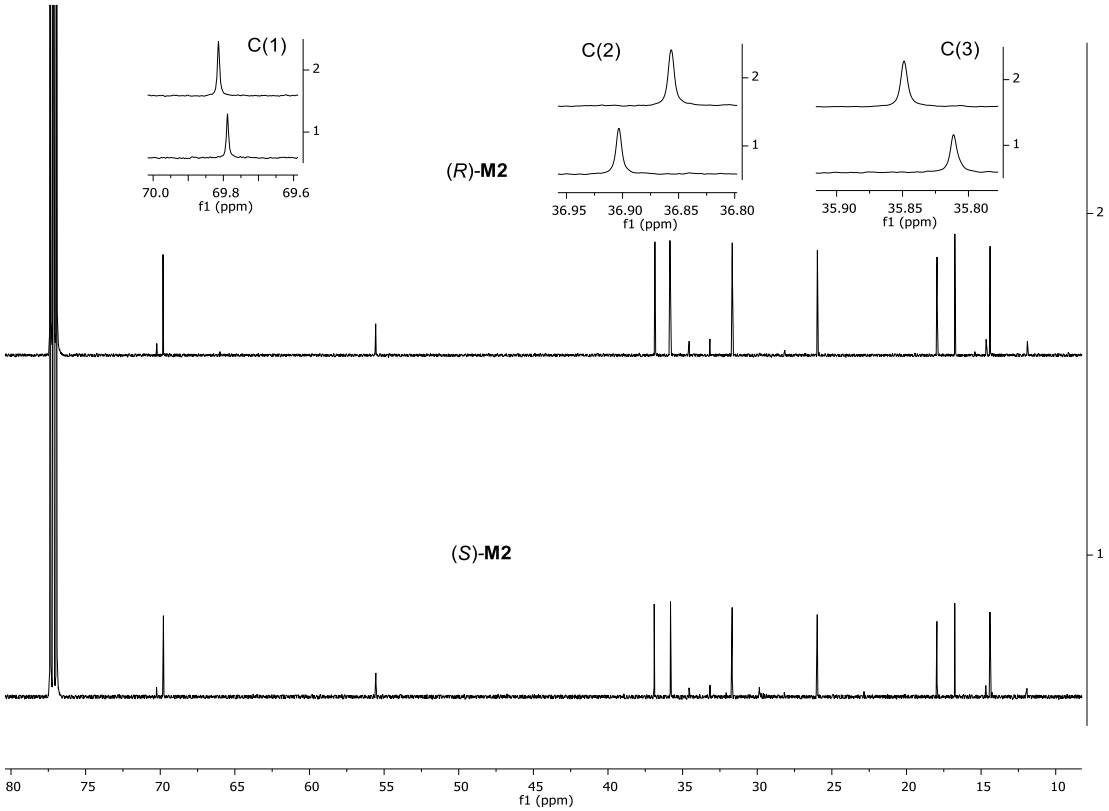
(*S*)-**M2**

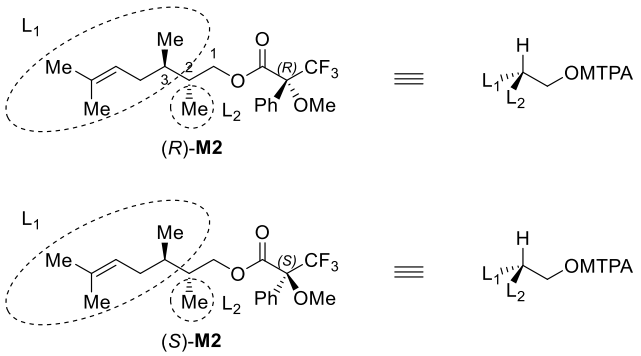

B (m) 7.40
A (m) 7.51
C (m) 5.05
D (dd) 4.29
E (m) 4.18
F (m) 3.55
L (m) 1.81
J (ddd) 1.49
I (s) 1.57
K (s) 1.69
M (dt) 2.01
f1 (ppm)


166.89
132.60
129.71
128.53
127.52
123.07
77.16 CDCl3
69.79
55.56
55.55
36.90
35.81
31.68
25.98
17.96
16.77
14.41
f1 (ppm)

HSQC

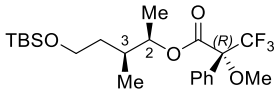






According to literature,[124] the difference $\Delta\delta^{S-R}$ of L_2 (Me(1)) should be positive and the difference $\Delta\delta^{S-R}$ of L_1 (C(3)) should be negative. As $\Delta\delta^{S-R}$ (L_2) = 0.918–0.913 = 0.05 > 0 and $\Delta\delta^{S-R}$ (L_1) = 35.81–35.85 = –0.04 < 0, the structure and absolute stereochemistry assigned correctly.

As in the spectrum of (*R*)-**M2** any signals of (*S*)-**M2** were not found and *vice versa*, the *ee* of (+)-lasiol (**71**) is >99%.



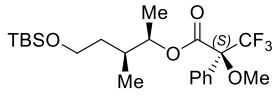
(*R*)-**M3**

The (*R*)-Mosher ester (*R*)-**M3** of 2*R*,3*S*-**81** (0.13 mmol, 30 mg) was prepared according to **TP3**. The crude product was purified by flash column chromatography on silica gel (*i*-hexane/ethyl acetate = 40/1) to afford the (*R*)-Mosher ester (0.09 mmol, 39 mg, 69% yield, dr = 1:99, 99% *ee*) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.55–7.48 (m, 2H), 7.43–7.37 (m, 3H), 5.18–5.03 (m, 1H), 3.73–3.57 (m, 2H), 3.53 (d, *J* = 1.3 Hz, 3H), 1.99–1.25 (m, 3H), 1.21 (d, *J* = 6.4 Hz, 3H), 0.92 (d, *J* = 6.9 Hz, 3H), 0.88 (s, 9H), 0.03 (s, 6H).

^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 166.2, 132.5, 129.6, 128.5, 127.6, 77.6, 60.9, 55.5, 55.5, 35.1, 34.1, 26.0, 18.4, 15.5, 14.9, –5.2, –5.3.

IR (ATR): $\tilde{\nu}$[cm^{-1}] = 3028 (w), 2975 (m), 2931 (m), 2881 (m), 2207 (w), 1669 (m), 1454 (m), 1355 (w), 1348 (w), 1329 (m), 1160 (m), 1118 (m), 1091 (m), 1052 (vs), 1007 (m), 910 (m), 734 (s), 700 (s).



(*S*)-**M3**

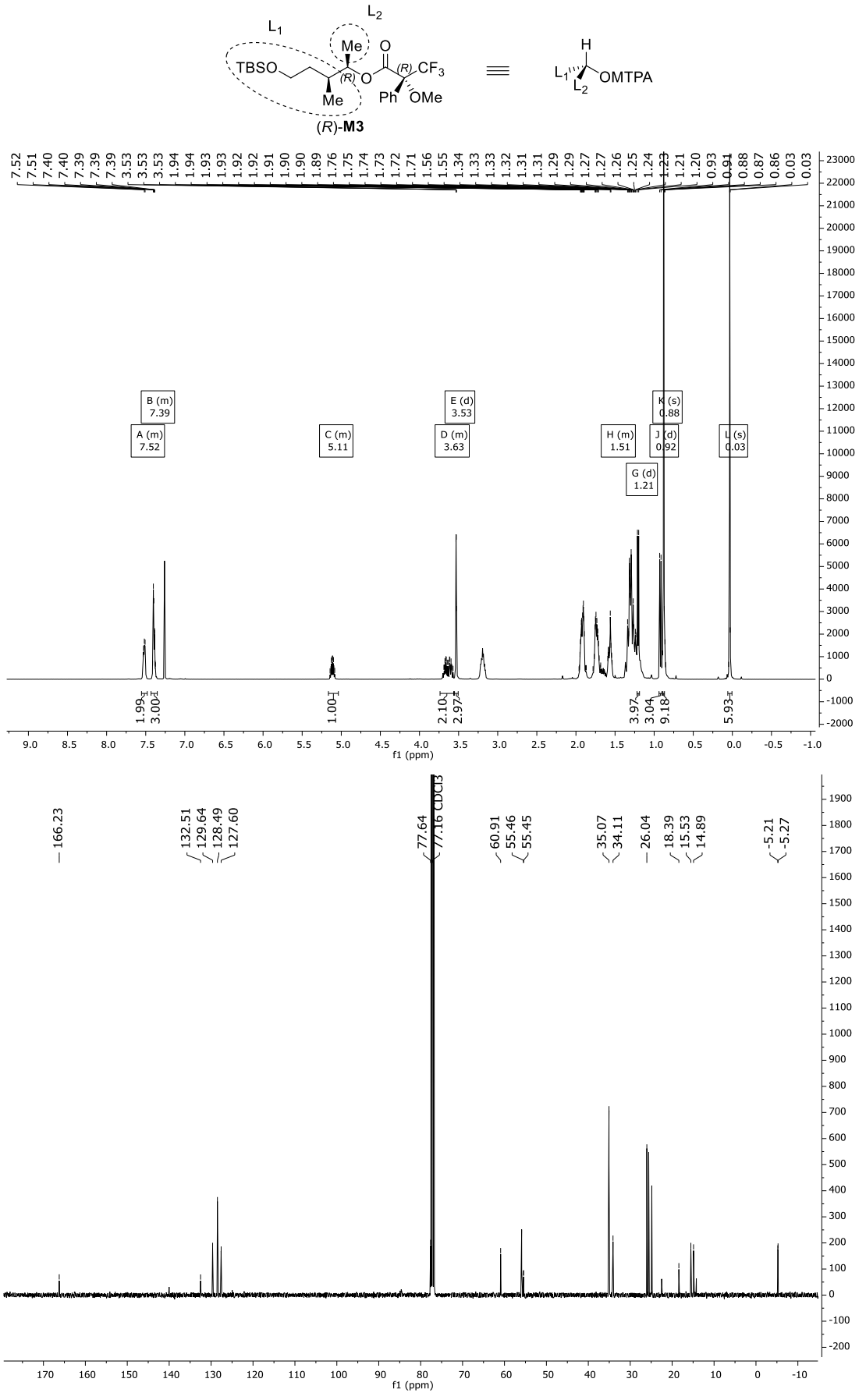
The (*S*)-Mosher ester (*S*)-**M3** of 2*R*,3*S*-**81** (0.13 mmol, 30 mg) was prepared according to **TP3**. The crude product was purified by flash column chromatography on silica gel (*i*-hexane/ethyl acetate = 40/1) to afford the (*S*)-Mosher ester (0.08 mmol, 36 mg, 62% yield, dr = 1:99, 99% *ee*) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.58–7.50 (m, 2H), 7.42–7.37 (m, 3H), 5.15–5.07 (m, 1H), 3.68–3.59 (m, 2H), 3.58–3.54 (m, 3H), 1.95–1.81 (m, 1H), 1.66–1.53 (m, 1H), 1.28 (d, *J* = 6.4 Hz, 3H), 1.26–1.18 (m, 1H), 0.88 (s, 9H), 0.84 (d, *J* = 6.8 Hz, 3H), 0.03 (s, 6H).

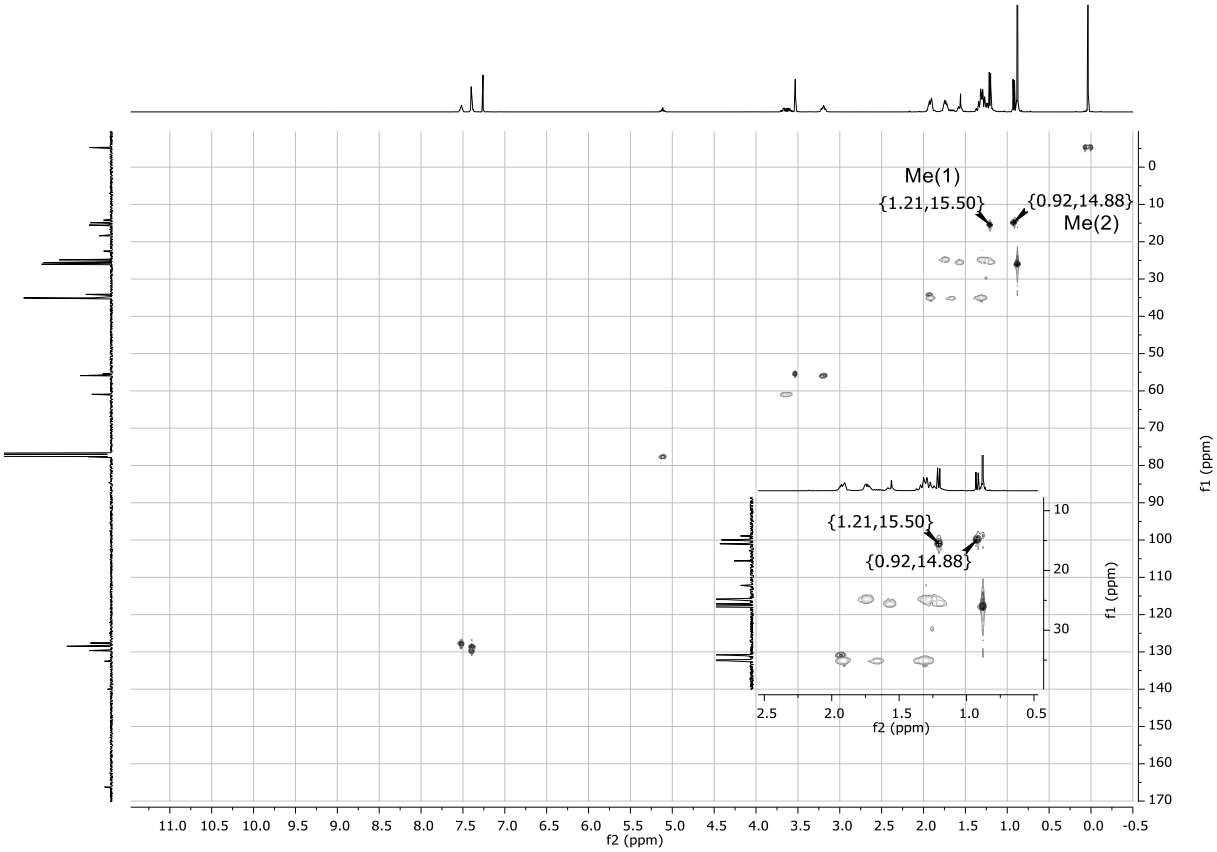
^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 166.1, 132.7, 129.6, 128.5, 127.4, 127.4, 707.6, 61.0, 55.5, 55.5, 34.9, 34.1, 26.0, 18.4, 15.9, 14.8, –5.2, –5.3.

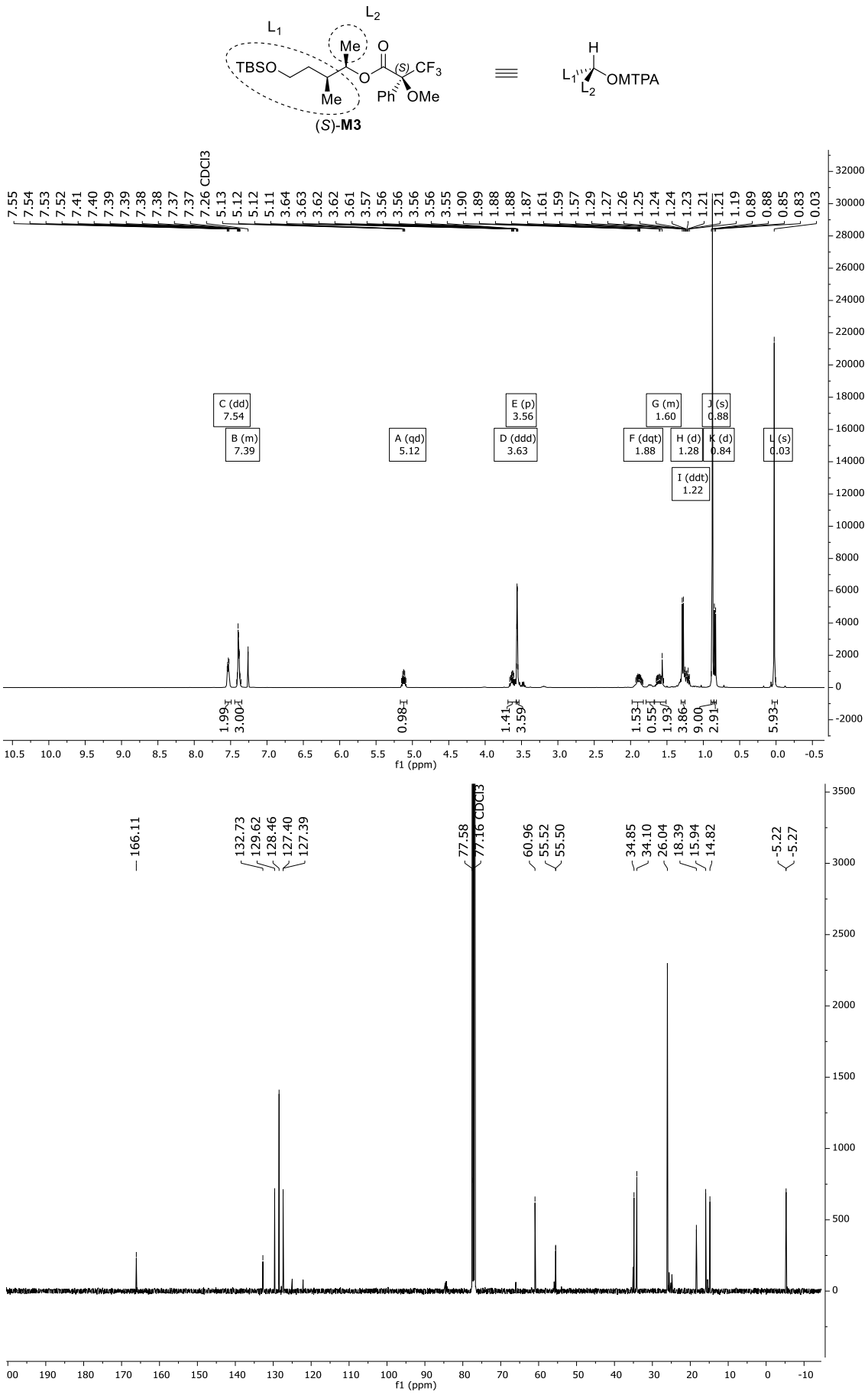
IR (ATR): $\tilde{\nu}$[cm^{-1}] = 3026 (w), 2975 (m), 2926 (m), 2877 (m), 2207 (w), 1664 (m), 1496 (w), 1454 (m), 1371 (w), 1354 (w), 1348 (w), 1329 (m), 1160 (m), 1118 (m), 1052 (vs), 1005 (m), 910 (m), 757 (w), 734 (s), 698 (s).

Comparison of (*R*)-M3 and (*S*)-M3

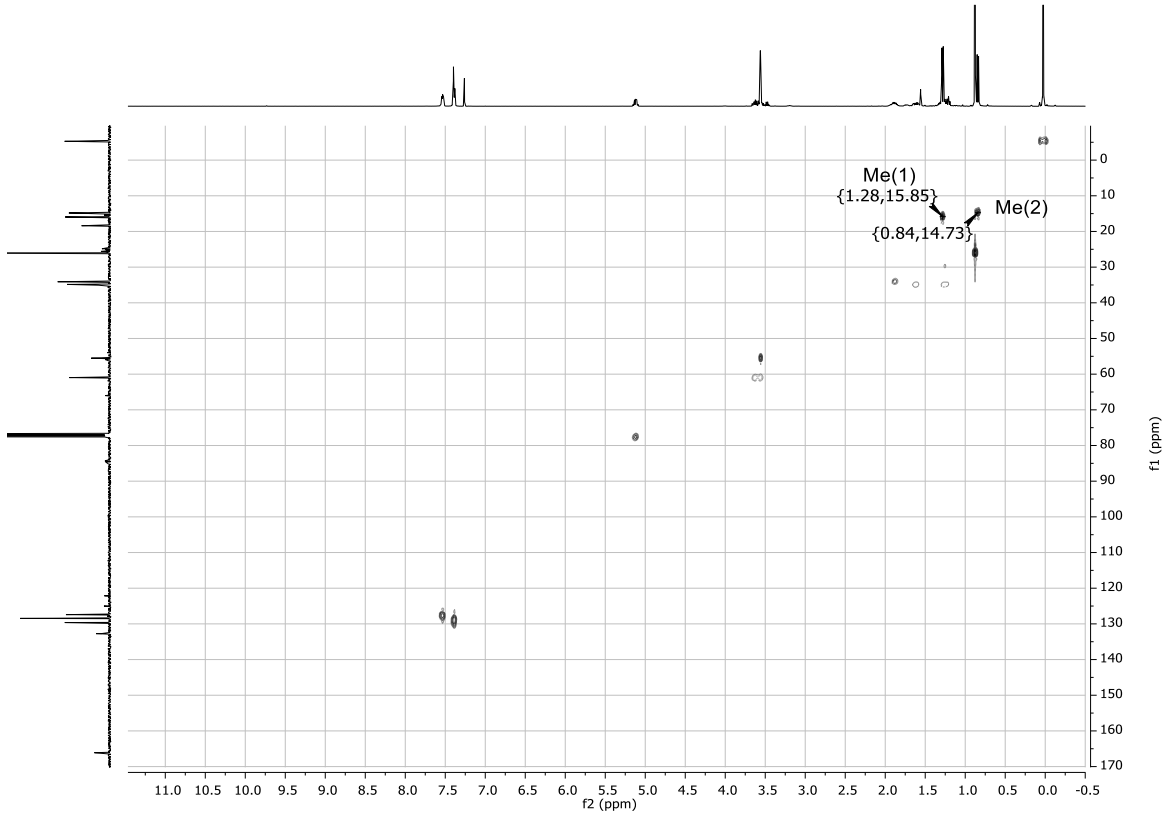


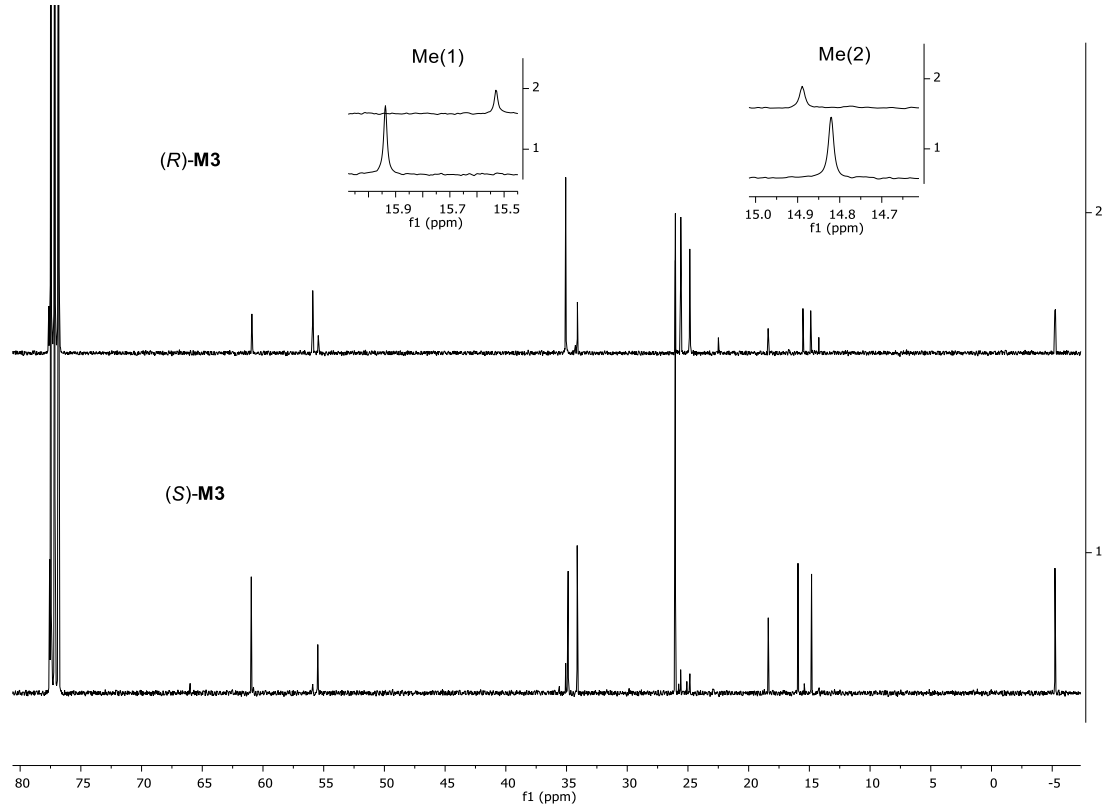
HSQC



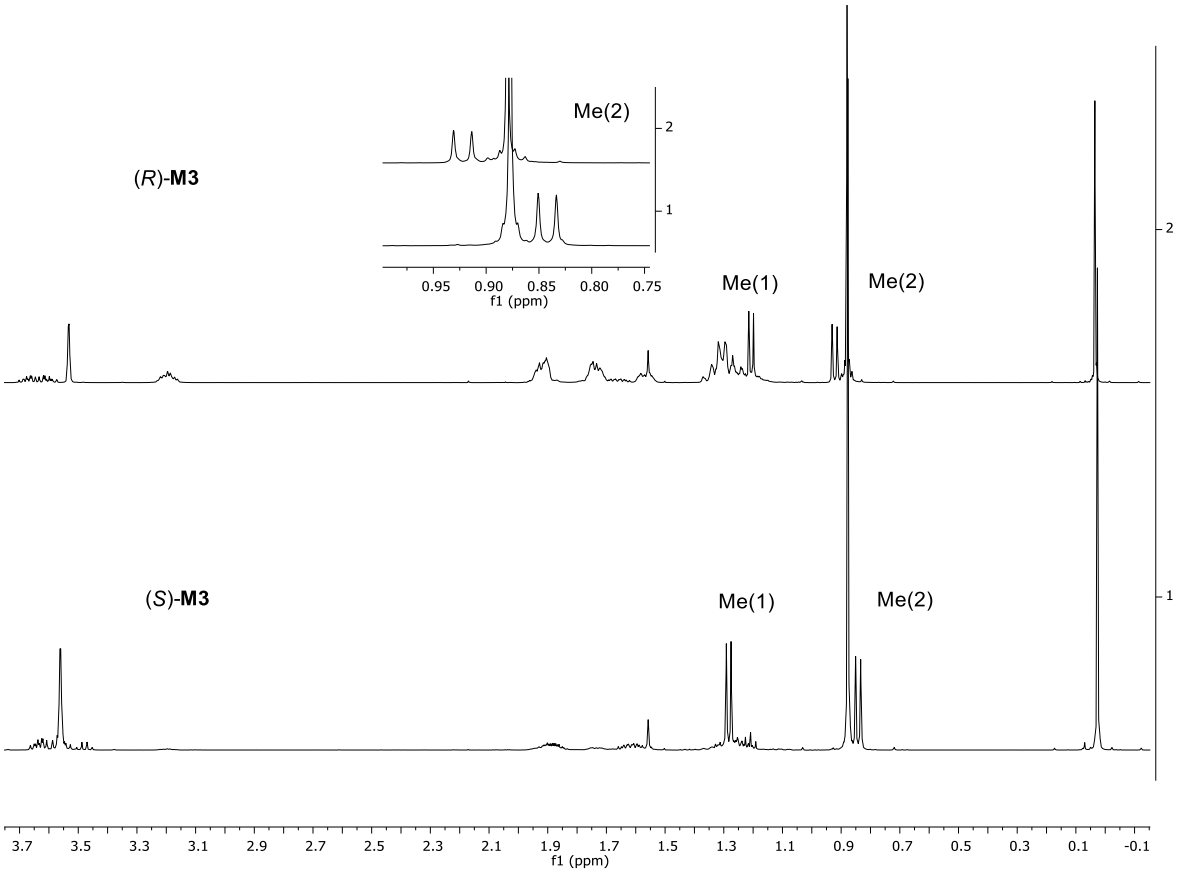

L1
L2
Me
O
TBSO
O
(S) CF3
Ph OMe
Me
(S)-M3
H
L1
L2
OMTPA
CDCl3
C (dd) 7.54
B (m) 7.39
A (qd) 5.12
E (p) 3.56
D (ddd) 3.63
G (m) 1.60
F (dqt) 1.88
H (d) 1.28
I (ddt) 1.22
J (s) 0.88
K (d) 0.84
L (s) 0.03
f1 (ppm)
166.11
132.73
129.62
128.46
127.40
127.39
77.58
77.16 CDCl3
60.96
55.52
55.50
34.85
34.10
26.04
18.39
15.94
14.82
-5.22
-5.27
f1 (ppm)

HSQC

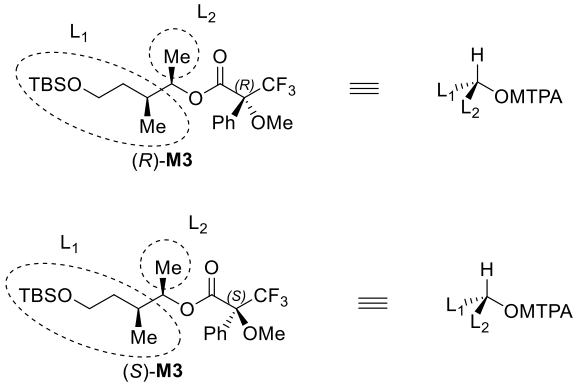




As in the spectrum of (*R*)-**M3** any signals of (*S*)-**M3** were not found and *vice versa*, the *ee* of 2*R*,3*S*-**81** is >99%.



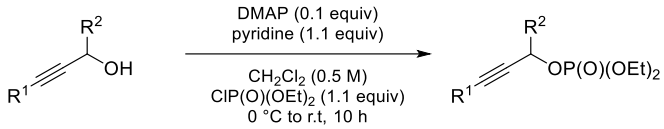
As in the spectrum of (*R*)-**M3** any signals of (*S*)-**M3** were not found and *vice versa*, the *ee* of 2*R*,3*S*-**81** is >99%.



According to literature,[124] the difference $\Delta\delta^{S-R}$ of L_2 (Me(1)) should be positive and the difference $\Delta\delta^{S-R}$ of L_1 (Me(2)) should be negative. As $\Delta\delta^{S-R}$ (L_2) = 1.28–1.21 = 0.07 > 0 and $\Delta\delta^{S-R}$ (L_1) = 0.84–0.92 = –0.08 < 0, the structure and absolute stereochemistry assigned correctly.

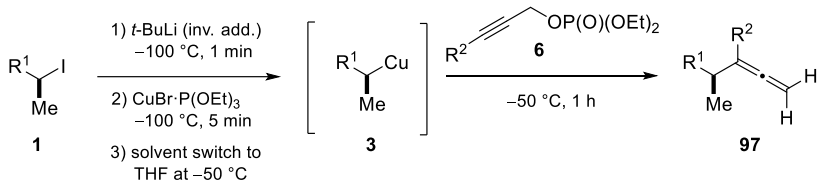
3 Stereoselective S_N2'-Reactions of Secondary Alkylcopper Reagents with Propargylic Phosphates

3.1 Typical Procedure for the Phosphorylation of Propargylic Alcohols (TP4)



According to literature,[125] a dry and Ar-flushed *Schlenk*-flask was charged with a solution of propargylic alcohol (1.0 equiv), DMAP (0.1 equiv) and pyridine (1.1 equiv) in DCM (0.5 M). After cooling to 0 °C, diethyl chlorophosphate (1.1 equiv) was added dropwise. The solution was allowed to warm to rt and stirred for 10 h. The reaction mixture was quenched with water and extracted with diethyl ether (3 x 25 mL) and purified by flash column chromatography on silica gel with *n*-pentane/diethyl ether = 1/2 to afford the desired propargylic phosphate of type **96** as a colorless oil.

3.2 Typical Procedure for the Preparation of Allenes (TP5)

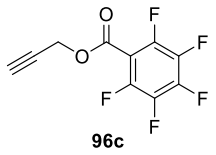


A dry and Ar-flushed *Schlenk*-tube was cooled to −100 °C and charged with a solution of *t*-BuLi (0.22 mmol, 2.2 equiv) together with a mixture of diethyl ether (1.00 mL) and n-pentane (1.50 mL). A solution of iodide 4 (0.10 mmol, 1.0 equiv) in diethyl ether (0.40 mL) was added dropwise for 1 min. After stirring for 10 sec, a solution of $CuBr{\cdot}P(OEt)_3$ (0.065 mL, 3 M in diethyl ether, 0.20 mmol, 2.0 equiv) was added and the reaction mixture was stirred for 1 min at −100 °C to observe the color change from yellow to green. The *Schlenk*-tube was transferred to a cooling bath (−50 °C) and the solvent was pumped away under high vacuum. After 10 min, precooled THF (2 mL) and then the propargylic electrophile **96** (0.30 mmol, 3.0 equiv) were added. The reaction mixture was stirred for 1 h at −50 °C. After quenching the reaction mixture with aq. NH_3 solution, the reaction mixture was extracted with diethyl ether (3 × 10 mL). The combined organic phases were dried over $MgSO_4$ and the solvents were evaporated. The obtained crude product was purified by column chromatography on silica gel to afford allenes of type **97**.

3.3 Synthesis of Alkyl Iodides and Propargylic Electrophiles

The iodides (*syn*-**1a**[53], *anti*-**1a**[53], *syn*-**1b**[56], *anti*-**1b**[56], (*R*)-**1f**[50], (*S*)-**1f**[50], *syn*-**1h**[49], *anti*-**1h**[49], (*R*)-**1i**[50], (*S*)-**1i**[50]) were prepared from the corresponding secondary alkyl alcohols and are literature known.

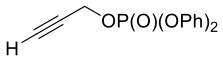
The propargyl phosphates were prepared according to literature as described in **TP4**.[125] Propargyl bromide **96a** is commercially available as a solution in toluene (Sigma Aldrich). Propargyl acetate **96b** is also commercially available (Sigma-Aldrich).



96c

The propargyl pentafluorobenzoate **96c** was prepared according to literature from propargyl alcohol (560 mg, 0.59 mL, 10 mmol).[85c] The crude product was purified by flash column chromatography on silica gel with *n*-pentane/diethyl ether = 1/2 to afford **96c** (7.8 mmol, 1.95 g, 78% yield) as a colorless oil.

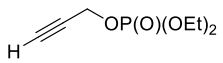
^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 4.97 (d, *J* = 2.5 Hz, 2H), 2.58 (t, *J* = 2.5 Hz, 1H).



96d

The propargyl diphenylphosphate **96d** was prepared according to literature from propargyl alcohol (560 mg, 0.59 mL, 10 mmol).[85d] The crude product was purified by flash column chromatography on silica gel with *n*-pentane/diethyl ether = 1/2 to afford **96d** (8.5 mmol, 2.45 g, 85% yield) as a colorless oil.

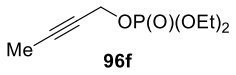
^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.40–7.29 (m, 4H), 7.28–7.15 (m, 6H), 4.85 (dd, *J* = 10.7, 2.5 Hz, 2H), 2.60 (t, *J* = 2.5 Hz, 1H).



96e

The propargyl diethylphosphate **96e** was prepared according to **TP4** from propargyl alcohol (560 mg, 0.59 mL, 10 mmol).[85e] The crude product was purified by flash column chromatography on silica gel with *n*-pentane/diethyl ether = 1/2 to afford **96e** (8.2 mmol, 1.57 g, 82% yield) as a colorless oil.

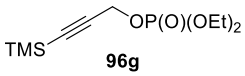
^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 4.66 (dd, *J* = 10.1, 2.5 Hz, 2H), 4.22–4.01 (m, 2H), 2.56 (t, *J* = 2.5 Hz, 1H), 1.35 (td, *J* = 7.1, 1.0 Hz, 6H).



96f

The propargyl phosphate **96f** was prepared according to **TP4** from but-2-yn-1-ol (700 mg, 0.75 mL, 10 mmol). The crude product was purified by flash column chromatography on silica gel with *n*-pentane/diethyl ether = 1/2 to afford **96f** (8.9 mmol, 1.83 g, 89% yield) as a colorless oil.

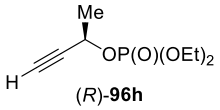
^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 4.64 (q, *J* = 2.4 Hz, 1H), 4.62 (q, *J* = 2.4 Hz, 1H), 4.19–4.07 (m, 4H), 1.87 (t, *J* = 2.4 Hz, 3H), 1.35 (td, *J* = 7.1, 0.9 Hz, 6H).



96g

The propargyl phosphate **96g** was prepared according to **TP4** from 3-(trimethylsilyl)prop-2-yn-1-ol (1.28 g, 1.48 mL, 10 mmol). The crude product was purified by flash column chromatography on silica gel with *n*-pentane/diethyl ether = 1/2 to afford **96g** (6.2 mmol, 1.54 g, 62% yield) as a colorless oil.

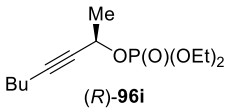
^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 4.65 (d, *J* = 10.1 Hz, 2H), 4.25–3.91 (m, 4H), 1.34 (tq, *J* = 7.1, 0.9 Hz, 6H), 0.25–0.03 (m, 9H).



(*R*)-**96h**

The chiral propargyl phosphate (*R*)-**96h** was prepared according to **TP4** from (*R*)-but-3-yn-2-ol (TCI, er >99:1; 700 mg, 0.73 mL, 10 mmol). The crude product was purified by flash column chromatography on silica gel with *n*-pentane/diethyl ether = 1/2 to afford (*R*)-**96h** (6.4 mmol, 1.31 g, 64% yield) as a colorless oil.

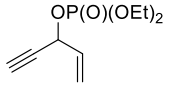
^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 5.18–5.00 (m, 1H), 4.20–4.03 (m, 4H), 2.55 (d, *J* = 2.1 Hz, 1H), 1.59 (dd, *J* = 6.7, 0.8 Hz, 3H), 1.35 (tdd, *J* = 7.1, 2.9, 1.1 Hz, 6H).



(*R*)-**96i**

The chiral propargyl phosphate (*R*)-**96i** was prepared according to **TP4** from (*R*)-oct-3-yn-2-ol (1.26 g, 10 mmol). The crude product was purified by flash column chromatography on silica gel with *n*-pentane/diethyl ether = 1/2 to afford (*R*)-**96i** (5.8 mmol, 1.52 g, 58% yield) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 5.15–5.03 (m, 1H), 4.18–4.04 (m, 4H), 2.20 (td, *J* = 7.0, 2.0 Hz, 2H), 1.54 (dd, *J* = 6.5, 0.8 Hz, 3H), 1.50–1.37 (m, 4H), 1.36–1.29 (m, 6H), 0.90 (t, *J* = 7.2 Hz, 3H).

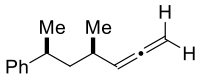


96j

The electrophile **96j** was prepared according to **TP4** from pent-1-en-4-yn-3-ol[89] (820 mg, 10 mmol). The crude product was purified by flash column chromatography on silica gel with *n*-pentane/diethyl ether = 1/2 to afford **96j** (3.5 mmol, 0.76 g, 35% yield) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 6.03–5.94 (m, 1H), 5.65–5.54 (m, 1H), 5.51–5.43 (m, 1H), 5.35 (dt, *J* = 10.2, 1.1 Hz, 1H), 4.25–3.94 (m, 4H), 2.68 (d, *J* = 2.2 Hz, 1H), 1.42–1.33 (m, 6H).

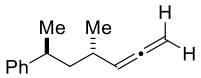
3.4 Stereoselective Preparation of Chiral Allenes



syn-**97a**

The allene *syn*-**97a** was prepared according to **TP5** from the alkyl iodide *syn*-(4-iodopentan-2-yl) benzene (*syn*-**1a**, 27.4 mg, 0.1 mmol) and electrophile **96e** (58 mg, 0.3 mmol). The crude product was purified by flash column chromatography on silica gel with pentane to afford *syn*-**97a** (0.046 mmol, 8.6 mg, 46% yield, dr = 6:94) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.32–7.27 (m, 2H), 7.21–7.15 (m, 3H), 5.02 (q, *J* = 6.7 Hz, 1H), 4.69 (dd, *J* = 6.6, 2.7 Hz, 2H), 2.83 (q, *J* = 7.2 Hz, 1H), 2.13–2.00 (m, 1H), 1.75–1.61 (m, 1H), 1.53–1.42 (m, 1H), 1.23 (d, *J* = 6.9 Hz, 3H), 1.01 (d, *J* = 6.7 Hz, 3H).
^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz): δ [ppm] = 207.6, 147.8, 128.5, 127.1, 126.0, 96.2, 75.7, 45.8, 37.5, 30.7, 22.4, 20.6.
IR (ATR): $\tilde{\upsilon}$[cm^{-1}] = 2959 (m), 2924 (vs), 2853 (m), 2360 (w), 2341 (w), 1955 (w), 1738 (w), 1493 (w), 1454 (m), 1377 (w), 1243 (w), 867 (w), 842 (m), 762 (m), 700 (s).
MS (EI, 70 eV): m/z (%): 171 (15), 157 (23), 144 (40), 143 (22), 129 (100), 128 (14), 118 (49), 117 (43), 115 (13), 105 (63), 103 (22), 91, (49), 79 (24), 78 (10), 77 (21).
HRMS (EI) for $C_{13}H_{15}$: calc. [M^+–Me]: 171.1174; found 171.1166.

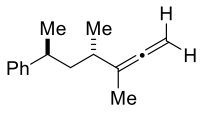


anti-**97a**

The allene *anti*-**97a** was prepared according to **TP5** from the alkyl iodide *anti*-(4-iodopentan-2-yl) benzene (*anti*-**1a**, 27.4 mg, 0.1 mmol) and electrophile **96e** (58 mg, 0.3 mmol). The crude product was purified by flash column chromatography on silica gel with pentane to afford *anti*-**97a** (0.055 mmol, 10.2 mg, 55% yield, dr = 96:4) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.34–7.26 (m, 2H), 7.20–7.17 (m, 3H), 5.04 (dt, *J* = 7.3, 6.6 Hz, 1H), 4.70–4.66 (m, 2H), 2.92–2.75 (m, 1H), 2.04–1.86 (m, 1H), 1.64–1.53 (m, 2H), 1.23 (d, *J* = 7.0 Hz, 3H), 0.96 (d, *J* = 6.7 Hz, 3H).
^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz): δ [ppm] = 207.7, 147.5, 128.5, 128.5, 127.3, 126.0, 95.8, 75.6, 46.1, 37.8, 31.0, 22.9, 21.4.
IR (ATR): $\tilde{\upsilon}$[cm^{-1}] = 3062 (vw), 3028 (w), 2960 (m), 2924 (m), 2870 (w), 2846 (w), 2360 (vw), 1956 (w), 1604 (w), 1494 (m), 1452 (m), 1376 (w), 1030 (w), 868 (w), 842 (m), 762 (m), 700 (vs).
MS (EI, 70 eV): m/z (%): 157 (17), 144 (41), 143 (20), 130 (11), 129 (100), 128 (12), 118 (32), 117 (32), 115 (12), 105 (59), 103 (23), 91 (46), 79 (26), 78 (11), 77 (23).

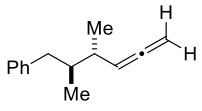
HRMS (EI) for $C_{14}H_{17}$: calc. [M^+–H]: 185.1330; found 185.1323.



anti-**97b**

The allene *anti*-**97b** was prepared according to **TP5** from the alkyl iodide *anti*-(-4-iodopentan-2-yl) benzene (*anti*-**1a**, 27.4 mg, 0.1 mmol) and electrophile **96f** (62 mg, 0.3 mmol). The crude product was purified by flash column chromatography on silica gel with pentane to afford *anti*-**97b** (0.065 mmol, 13.0 mg, 65% yield, dr = 97:3) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.32–7.26 (m, 2H), 7.22–7.11 (m, 3H), 4.59 (qd, J = 3.2, 1.6 Hz, 2H), 2.83–2.70 (m, 1H), 1.88–1.78 (m, 1H), 1.74–1.65 (m, 1H), 1.63 (t, J = 3.1 Hz, 3H), 1.54–1.47 (m, 1H), 1.22 (d, J = 7.0 Hz, 3H), 0.96 (d, J = 6.8 Hz, 3H).
^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz): δ [ppm] = 205.8, 147.8, 128.4, 127.3, 126.0, 102.5, 74.4, 44.1, 37.8, 35.1, 22.8, 20.1, 16.2.
IR (ATR): $\tilde{\upsilon}$[cm^{-1}] = 3062 (vw), 3028 (w), 2960 (m), 2924 (m), 2870 (w), 2846 (w), 2360 (vw), 1956 (w), 1604 (w), 1494 (m), 1452 (m), 1376 (w), 1054 (w), 1030 (w), 868 (w), 842 (m), 762 (m), 700 (vs).
MS (EI, 70 eV): m/z (%): 185 (13), 171 (18), 158 (52), 157 (26), 144 (11), 143 (100), 129 (14), 128 (15), 118 (68), 117 (52), 115 (14), 105 (59), 103 (22), 91 (40), 79 (35), 78 (11), 77 (26), 67 (24).
HRMS (EI) for $C_{14}H_{17}$: calc. [M^+–Me]: 185.1330; found 185.1321.



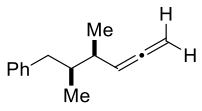
anti-**97d**

The allene *anti*-**97d** was prepared according to **TP5** from the alkyl iodide *anti*-(3-iodo-2-methylbutyl)benzene (*anti*-**1b**, 27.4 mg, 0.1 mmol) and electrophile **96e** (58 mg, 0.3 mmol). The crude product was purified by flash column chromatography on silica gel with pentane to afford *anti*-**97d** (0.058 mmol, 10.8 mg, 58% yield, dr = 98:2) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.31–7.27 (m, 2H), 7.20–7.13 (m, 3H), 5.12 (q, J = 6.8 Hz, 1H), 4.75–4.69 (m, 2H), 2.73 (dd, J = 13.4, 5.8 Hz, 1H), 2.33 (dd, J = 13.3, 8.9 Hz, 1H), 2.29–2.20 (m, 1H), 1.87–1.74 (m, 1H), 1.03 (d, J = 6.9 Hz, 3H), 0.82 (d, J = 6.8 Hz, 3H).
^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz): δ [ppm] = 208.6, 141.8, 129.3, 128.3, 125.8, 93.0, 75.3, 40.7, 40.7, 36.9, 17.6, 15.5.
IR (ATR): $\tilde{\upsilon}$[cm^{-1}] = 3028 (w), 2960 (s), 2924 (m), 2870 (w), 2366 (vw), 1956 (w), 1604 (w), 1494 (m), 1454 (m), 1376 (w), 1112 (w), 1048 (w), 1022 (w), 844 (m), 762 (m), 700 (vs).

MS (EI, 70 eV): m/z (%): 171 (19), 157 (21), 144 (11), 143 (24), 129 (13), 119 (11), 118 (43), 117 (15), 92 (15), 91 (100), 67 (14), 57 (10), 43 (35), 41 (25), 42 (21).

HRMS (EI) for $C_{14}H_{18}$: calc. [M^+]: 186.1409; found 186.1394.



syn-**97d**

The allene *syn*-**97d** was prepared according to **TP5** from the alkyl iodide *syn*-(3-iodo-2-methylbutyl)benzene (*syn*-**1b**, 27.4 mg, 0.1 mmol) and electrophile **96e** (58 mg, 0.3 mmol). The crude product was purified by flash column chromatography on silica gel with pentane to afford *syn*-**97d** (0.042 mmol, 9.2 mg, 42% yield, dr = 6:94) as a colorless oil.

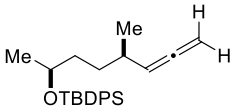
^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.30–7.25 (m, 2H), 7.20–7.06 (m, 3H), 5.11 (q, J = 6.7 Hz, 1H), 4.71 (dd, J = 6.8, 3.1 Hz, 2H), 2.79 (dd, J = 13.4, 5.3 Hz, 1H), 2.38–2.28 (m, 1H), 2.23–2.15 (m, 1H), 1.82–1.71 (m, 1H), 1.03 (dd, J = 6.9, 3.8 Hz, 3H), 0.81 (d, J = 6.8 Hz, 3H).

^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz): δ [ppm] = 208.5, 142.0, 129.5, 128.5, 128.5, 126.0, 95.2, 75.7, 41.0, 40.5, 37.3, 15.8, 15.8.

IR (ATR): $\tilde{\upsilon}$[cm^{-1}] = 3029 (w), 2959 (s), 2921 (m), 2872 (w), 2354 (vw), 1948 (w), 1604 (w), 1494 (m), 1379 (w), 1115 (w), 1047 (w), 1022 (w), 843 (m), 772 (m), 702 (vs).

MS (EI, 70 eV): m/z (%): 171 (30), 157 (39), 144 (13), 143 (53), 129 (40), 118 (57), 117 (57), 115 (12), 91 (100).

HRMS (EI) for $C_{14}H_{17}$: calc. [M^+–H]: 185.1330; found 185.1322.



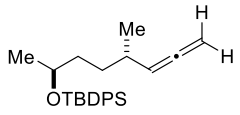
syn-**97e**

The allene *syn*-**97e** was prepared according to **TP5** from the alkyl iodide *syn*-(*tert*-butyl((5-iodohexan-2-yl)oxy)diphenylsilane) benzene (*syn*-**1c**, 46.6 mg, 0.1 mmol) and electrophile **96e** (58 mg, 0.3 mmol). The crude product was purified by flash column chromatography on silica gel with diethyl ether/pentane = 1/300 to afford *syn*-**97e** (0.044 mmol, 16.6 mg, 44% yield, dr = 4:96) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.72–7.64 (m, 4H), 7.48–7.31 (m, 6H), 4.98 (q, J = 6.7 Hz, 1H), 4.72–4.57 (m, 2H), 3.82 (q, J = 6.0 Hz, 1H), 2.10–1.99 (m, 1H), 1.53–1.37 (m, 2H), 1.34–1.25 (m, 2H), 1.09–1.03 (m, 12H), 0.94 (d, J = 6.7 Hz, 3H).

^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz): δ [ppm] = 207.5, 136.0, 135.0, 134.7, 129.6, 129.5, 127.6, 127.5, 96.1, 75.5, 69.9, 66.0, 37.0, 33.0, 32.7, 27.1, 23.4, 20.7, 19.4, 15.4.

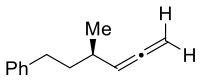
IR (ATR): ṽ[cm^{-1}] = 3071 (w), 3050 (w), 2963 (m), 2931 (m), 2858 (m), 2362 (w), 2334 (vw), 1956 (w), 1590 (vw), 1473 (w), 1462 (w), 1428 (m), 1390 (w), 1377 (w), 1362 (w), 1133 (m), 1111 (s), 1058 (m), 1030 (w), 1006 (w), 998 (m), 868 (w), 842 (w), 822 (m), 739 (m), 701 (vs), 687 (w).
MS (EI, 70 eV): m/z (%): 321 (36), 199 (100), 183 (13), 181 (10), 135 (11), 77 (6).
HRMS (EI) for $C_{21}H_{25}OSi$: calc. [M$^+$–*t*-Bu]: 321.1675; found 321.1661.



anti-**97e**

The allene *anti*-**97e** was prepared according to **TP5** from the alkyl iodide *anti*-(*tert*-butyl((5-iodohexan-2-yl)oxy)diphenylsilane) benzene (*anti*-**1c**, 46.6 mg, 0.1 mmol) and electrophile **96e** (58 mg, 0.3 mmol). The crude product was purified by flash column chromatography on silica gel with diethyl ether/pentane = 1/300 to afford *anti*-**97e** (0.050 mmol, 18.9 mg, 50% yield, dr = 95:5) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.75–7.55 (m, 4H), 7.51–7.32 (m, 6H), 5.07–4.87 (m, 1H), 4.64 (ddd, *J* = 6.7, 4.2, 2.9 Hz, 2H), 3.87–3.77 (m, 1H), 2.11–1.91 (m, 1H) 1.67–1.24 (m, 4H), 1.14–1.01 (m, 12H), 0.94 (d, *J* = 6.8 Hz, 3H).
^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz): δ [ppm] = 207.5, 136.0, 135.0, 134.7, 129.6, 129.5, 127.6, 127.5, 96.1, 96.1, 75.5, 75.5, 69.9, 69.8, 6.0, 37.0, 37.0, 33.0, 32.7, 32.6, 27.2, 23.4, 20.5, 20.4, 19.4, 15.4.
IR (ATR): ṽ[cm^{-1}] = 3071 (w), 3050 (vw), 2962 (m), 2930 (m), 2858 (m), 2360 (w), 2333 (vw), 1955 (w), 1590 (vw), 1473 (w), 1462 (w), 1428 (m), 1390 (w), 1377 (w), 1362 (w), 1132 (m), 1110 (s), 1059 (m), 1029 (w), 1006 (w), 998 (m), 868 (w), 842 (w), 822 (m), 739 (m), 701 (vs), 687 (m)
MS (EI, 70 eV): m/z (%): 321 (10), 199 (100), 135 (8), 77 (5).
HRMS (EI) for $C_{21}H_{25}OSi$: calc. [M$^+$–*t*-Bu]: 321.1675; found 321.1665.



(*R*)-**97f**

The chiral allene (*R*)-**97f** was prepared according to **TP5** from the alkyl iodide (*R*)-(3-iodobutyl) benzene ((*R*)-**1d**, 26.0 mg, 0.1 mmol) and electrophile **96e** (58 mg, 0.3 mmol). The crude product was purified by flash column chromatography on silica gel with pentane to afford (*R*)-**97f** (0.041 mmol, 7.1 mg, 41% yield, er = 7:93) as a colorless oil.

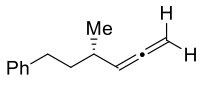
$[\alpha]_D^{20}$ = –20.0 (c = 0.5, $CHCl_3$).
^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.30–7.26 (m, 2H), 7.21–7.15 (m, 3H), 5.10 (q, *J* = 6.7 Hz, 1H), 4.73 (dd, *J* = 6.7, 2.7 Hz, 2H), 2.75–2.56 (m, 2H), 2.27–2.08 (m, 1H), 1.80–1.59 (m, 2H), 1.06 (d, *J* = 6.8 Hz, 3H).

$^{13}C\{^1H\}$-NMR ($CDCl_3$, 101 MHz): δ [ppm] = 207.7, 142.8, 128.6, 128.4, 125.8, 95.9, 75.8, 39.0, 33.7, 32.6, 20.7.

IR (ATR): ṽ[cm^{-1}] = 3063 (w), 3027 (w), 2961 (m), 2924 (m), 2856 (w), 1955 (m), 1604 (w), 1497 (m), 1454 (m), 1376 (w), 1031 (w), 868 (m), 842 (s), 746 (m), 722 (w), 698 (vs).

MS (EI, 70 eV): m/z (%): 157 (13), 144 (11), 143 (36), 129 (45), 128 (13), 115 (12), 104 (63), 103 (11), 91 (100), 79 (25), 78 (16), 77 (20), 67 (13), 65 (22).

HRMS (EI) for $C_{13}H_{16}$: calc. [M^+]: 172.1252; found 172.1242.



(*S*)-**97f**

The chiral allene (*S*)-**97f** was prepared according to **TP5** from the alkyl iodide (*S*)-(3-iodobutyl) benzene ((*S*)-**1d**, 26.0 mg, 0.1 mmol) and electrophile **96e** (58 mg, 0.3 mmol). The crude product was purified by flash column chromatography on silica gel with pentane to afford (*S*)-**97f** (0.048 mmol, 8.3 mg, 48% yield, er = 90:10) as a colorless oil.

$[\alpha]_D^{20}$ = +22.0 (c = 0.3, $CHCl_3$).

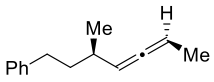
^1H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.33–7.24 (m, 2H), 7.22–7.13 (m, 3H), 5.10 (q, *J* = 6.7 Hz, 1H), 4.73 (dd, *J* = 6.6, 2.7 Hz, 2H), 2.76–2.55 (m, 2H), 2.25–2.10 (m, 1H), 1.75–1.59 (m, 2H), 1.06 (d, *J* = 6.8 Hz, 3H).

$^{13}C\{^1H\}$-NMR ($CDCl_3$, 101 MHz): δ [ppm] = 207.7, 142.8, 128.6, 128.4, 125.8, 95.9, 75.8, 39.0, 33.7, 32.6, 20.7.

IR (ATR): ṽ[cm^{-1}] = 3028 (w), 2961 (m), 2925 (m), 2855 (w), 1955 (m), 1604 (w), 1497 (w), 1454 (m), 1377 (w), 1031 (w), 907 (s), 868 (m), 843 (m), 731 (vs), 698 (vs).

MS (EI, 70 eV): m/z (%): 157 (15), 143 (40), 129 (48), 128 (14), 115 (14), 104 (65), 103 (12), 91 (100), 79 (21), 78 (15), 77 (16), 65 (19).

HRMS (EI) for $C_{13}H_{16}$: calc. [M^+]: 172.1252; found 172.1243.



(*R*,*S*)-**97g**

The chiral allene (*R*,*S*)-**97g** was prepared according to **TP5** from the alkyl iodide (*R*)-(3-iodobutyl)benzene ((*R*)-**1d**, 26.0 mg, 0.1 mmol) and electrophile (*R*)-**96h** (62 mg, 0.3 mmol). The crude product was purified by flash column chromatography on silica gel with pentane to afford (*R*,*S*)-**97g** (0.043 mmol, 8.0 mg, 43% yield, dr = 92:8) as a colorless oil.

$[\alpha]_D^{20}$ = +18.0 (c = 0.8, $CHCl_3$).

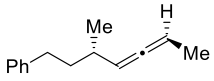
^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.31–7.26 (m, 2H), 7.22–7.13 (m, 3H), 5.17–5.08 (m, 1H), 5.07–5.01 (m, 1H), 2.74–2.51 (m, 2H), 2.16 (dtd, *J* = 13.5, 6.7, 2.6 Hz, 1H), 1.67 (dd, *J* = 6.9, 3.3 Hz, 3H), 1.65–1.58 (m, 2H), 1.04 (d, *J* = 6.8 Hz, 3H).

^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz): δ [ppm] = 203.9, 143.0, 128.6, 128.6, 128.4, 125.7, 96.2, 86.6, 39.0, 33.7, 33.1, 20.9, 14.9.

IR (ATR): ṽ[cm^{-1}] = 3027 (m), 2960 (s), 2925 (s), 2856 (m), 1497 (m), 1455 (m), 1373 (w), 872 (m), 745 (m), 720 (m), 698 (vs).

MS (EI, 70 eV): m/z (%): 171 (16), 158 (10), 157 (51), 143 (43), 129 (58), 115 (13), 104 (24), 91 (100), 82 (70), 79 (25), 77 (15), 67 (79), 65 (11).

HRMS (EI) for $C_{14}H_{19}$: calc. [M^+]: 186.1409; found 186.1400.



(*S*,*S*)-**97g**

The allene (*S*,*S*)-**97g** was prepared according to **TP5** from the alkyl iodide (*S*)-(3-iodobutyl)benzene ((*S*)-**1d**, 26.0 mg, 0.1 mmol) and electrophile (*R*)-**96h** (62 mg, 0.3 mmol). The crude product was purified by flash column chromatography on silica gel with pentane to afford (*S*,*S*)-**97g** (0.049 mmol, 9.1 mg, 49% yield, dr = 12:88) as a colorless oil.

$[\alpha]_D^{20}$ = –16.0 (c = 0.3, $CHCl_3$).

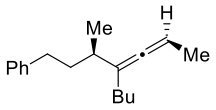
^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.33–7.26 (m, 2H), 7.22–7.15 (m, 3H), 5.11 (td, *J* = 6.7, 2.5 Hz, 1H), 5.02 (dq, *J* = 6.4, 3.2 Hz, 1H), 2.75–2.55 (m, 2H), 2.22–2.07 (m, 1H), 1.68 (dd, *J* = 6.9, 3.2 Hz, 3H), 1.66–1.58 (m, 2H), 1.04 (d, *J* = 6.8 Hz, 3H).

^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz): δ [ppm] = 203.9, 143.0, 128.6, 128.6, 128.4, 125.7, 96.1, 86.5, 39.0, 33.7, 33.3, 20.8, 15.0.

IR (ATR): ṽ[cm^{-1}] = 3027 (w), 2959 (m), 2924 (m), 2856 (w), 1604 (w), 1496 (w), 1455 (m), 1372 (w), 1031 (w), 872 (m), 761 (w), 745 (m), 717 (m), 698 (vs).

MS (EI, 70 eV): m/z (%): 157 (26), 143 (23), 129 (35), 104 (20), 91 (100), 82 (70), 79 (28), 77 (21), 67 (83), 65 (17).

HRMS (EI) for $C_{14}H_{18}$: calc. [M^+]: 186.1409; found 186.1401.



(*R*,*S*)-**97h**

The allene (*R*,*S*)-**97h** was prepared according to **TP5** from the alkyl iodide (*R*)-(3-iodobutyl)benzene ((*R*)-**1d**, 26.0 mg, 0.1 mmol) and electrophile (*R*)-**96i** (79 mg, 0.3 mmol). The crude product was purified by flash column chromatography on silica gel with pentane to afford (*R*,*S*)-**97h** (0.059 mmol, 14.3 mg, 59% yield, dr = 91:9) as a colorless oil.

$[\alpha]_D^{20}$ = +15.2 (c = 0.9, $CHCl_3$).

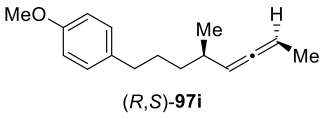
^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.31–7.26 (m, 2H), 7.23–7.14 (m, 3H), 5.16–5.02 (m, 1H), 2.73–2.50 (m, 2H), 2.02–1.88 (m, 2H), 1.80–1.70 (m, 1H), 1.67 (d, *J* = 6.9 Hz, 3H), 1.62–1.53 (m, 1H), 1.47–1.19 (m, 5H), 1.04 (d, *J* = 6.9 Hz, 3H), 0.95–0.85 (m, 3H).

^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz): 201.2, 143.3, 128.5, 128.4, 125.7, 108.4, 87.4, 37.8, 36.6, 34.3, 33.8, 30.8, 30.2, 22.6, 22.5, 20.3, 15.3, 14.2.

IR (ATR): ṽ[cm^{-1}] = 3064 (w), 3027 (w), 2957 (s), 2926 (vs), 2871 (m), 2858 (m), 2360 (w), 2340 (w), 2334 (w), 1604 (w), 1496 (w), 1455 (m), 1372 (w), 1031 (w), 770 (w), 746 (m), 698 (s).

MS (EI, 70 eV): m/z (%): 242 (16), 138 (15), 123 (13), 105 (11), 96 (28), 91 (17), 74 (93), 59 (100), 45 (44), 32 (50).

HRMS (EI) for $C_{18}H_{26}$: calc. [M^+]: 242.2035; found 242.2030.



(*R*,*S*)-**97i**

The allene (*R*,*S*)-**97i** was prepared according to **TP5** from the alkyl iodide (*R*)-1-(4-iodopentyl)-4-methoxybenzene ((*R*)-**1e**, 30.4 mg, 0.1 mmol) and electrophile (*R*)-**96h** (62 mg, 0.3 mmol). The crude product was purified by flash column chromatography on silica gel with pentane/diethyl ether = 300/1 to afford (*R*,*S*)-**97i** (0.052 mmol, 11.2 mg, 52% yield, dr = 93:7) as a colorless oil.

$[\alpha]_D^{20}$ = –6.8 (c = 0.8, $CHCl_3$).

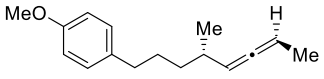
^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.13–7.05 (m, 2H), 6.89–6.73 (m, 2H), 5.06 (pd, *J* = 6.8, 2.4 Hz, 1H), 4.97 (tt, *J* = 6.4, 3.2 Hz, 1H), 3.79 (s, 3H), 2.54 (t, *J* = 7.7 Hz, 2H), 2.13 (pd, *J* = 6.8, 2.5 Hz, 1H), 1.64 (dd, *J* = 7.0, 3.2 Hz, 3H), 1.64–1.55 (m, 2H), 1.40–1.20 (m, 2H), 0.98 (d, *J* = 6.7 Hz, 3H).

$^{13}C\{^1H\}$-NMR ($CDCl_3$, 101 MHz): δ [ppm] = 203.7, 157.7, 135.0, 129.4, 113.8, 96.4, 86.3, 55.4, 36.8, 35.2, 33.6, 29.5, 20.7, 14.9.

IR (ATR): ṽ[cm^{-1}] = 2956 (m), 2922 (vs), 2891 (m), 2875 (m), 2851 (s), 1613 (m), 1513 (vs), 1465 (m), 1442 (m), 1303 (m), 1246 (m), 1178 (m), 1040 (m), 808 (w), 722 (w).

MS (EI, 70 eV): m/z (%): 148 (32), 147 (43), 134 (53), 122 (13), 121 (100), 91 (11), 74 (30), 59 (34), 45 (16), 43 (18).

HRMS (EI) for $C_{16}H_{22}O$: calc. [M^+]: 230.1671; found 230.1663.



(*S*,*S*)-**97i**

The allene (*S*,*S*)-**97i** was prepared according to **TP5** from the alkyl iodide (*S*)-1-(4-iodopentyl)-4-methoxybenzene ((*S*)-**1e**, 30.4 mg, 0.1 mmol) and electrophile (*R*)-**96h** (62 mg, 0.3 mmol). The crude product was purified by flash column chromatography on silica gel with pentane/diethyl ether = 300/1 to afford (*S*,*S*)-**97i** (0.054 mmol, 12.4 mg, 54% yield, dr = 12:88) as a colorless oil.

$[\alpha]_D^{20}$ = +9.2 (c = 1.0, $CHCl_3$).

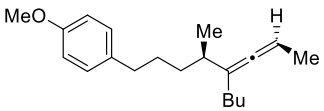
^1H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.12–7.05 (m, 2H), 6.88–6.77 (m, 2H), 5.10–5.03 (m, 1H), 5.02–4.89 (m, 1H), 3.79 (s, 3H), 2.54 (t, *J* = 7.8 Hz, 2H), 2.24–1.96 (m, 1H), 1.64 (dd, *J* = 6.9, 3.2 Hz, 3H), 1.62–1.57 (m, 2H) 1.43–1.28 (m, 2H), 0.98 (d, *J* = 6.7 Hz, 3H).

$^{13}C\{^1H\}$-NMR ($CDCl_3$, 101 MHz): 203.7, 157.7, 135.1, 129.4, 113.8, 96.4, 86.4, 55.4, 36.9, 35.3, 33.4, 29.6, 20.8, 14.9.

IR (ATR): ṽ[cm^{-1}] = 2955 (m), 2927 (s), 2892 (m), 2856 (m), 2837 (w), 1613 (m), 1513 (vs), 1463 (m), 1446 (m), 1442 (m), 1300 (m), 1245 (vs), 1177 (m), 1040 (m), 828 (m), 807 (w), 724 (w).

MS (EI, 70 eV): m/z (%): 173 (18), 159 (15), 148 (10), 147 (94), 134 (90), 121 (100), 119 (14), 117 (16), 91 (39), 77 (11).

HRMS (EI) for $C_{16}H_{22}O$: calc. [M^+]: 230.1671; found 230.1664.



(*R*,*S*)-**97j**

The allene (*R*,*S*)-**97j** was prepared according to **TP5** from the alkyl iodide (*R*)-1-(4-iodopentyl)-4-methoxybenzene ((*R*)-**1e**, 30.4 mg, 0.1 mmol) and electrophile (*R*)-**96i** (79 mg, 0.3 mmol). The crude product was purified by flash column chromatography on silica gel with pentane/diethyl ether = 200/1 to afford (*R*,*S*)-**97j** (0.051 mmol, 13.9 mg, 51% yield, dr = 92:8) as a colorless oil.

$[\alpha]_D^{20}$ = –5.0 (c = 0.4, $CHCl_3$).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.09 (dd, *J* = 8.7, 2.1 Hz, 2H), 6.88–6.74 (m, 2H), 5.03 (tdd, *J* = 6.8, 5.2, 3.6 Hz, 1H), 3.79 (s, 3H), 2.53 (dt, *J* = 8.0, 6.4 Hz, 2H), 2.01–1.92 (m, 1H), 1.90–1.82 (m, 2H), 1.61 (dd, *J* = 6.8, 1.3 Hz, 3H), 1.47–1.40 (m, 1H), 1.36–1.21 (m, 7H), 0.98 (d, *J* = 6.8 Hz, 3H), 0.92–0.74 (m, 3H).

^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz): δ [ppm] = 201.3, 157.7, 135.2, 129.4, 113.8, 108.7, 87.1, 55.4, 36.8, 35.3, 31.6, 30.3, 30.2, 29.5, 22.7, 22.6, 20.2, 15.3, 14.2, 14.2.

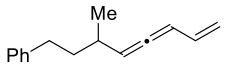
IR (ATR): ṽ[cm^{-1}] = 2956 (m), 2929 (s), 2870 (w), 2858 (m), 2835 (w), 2359 (m), 2342 (w), 1613 (w), 1513 (vs), 1464 (w), 1442 (w), 1300 (w), 1246 (vs), 1176 (w), 1040 (m), 828 (w), 817 (w), 807 (w).

MS (EI, 70 eV): m/z (%): 148 (66), 147 (100), 134 (65), 121 (78), 91 (19), 81 (18).

HRMS (EI) for $C_{20}H_{30}O$: calc. [M^+]: 286.2297: found 286.2292.

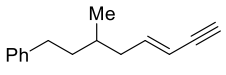
Regioselective addition of secondary alkylcopper reagent **3d** to allylic and propargylic moiety containing phosphate **96f**:

(3-methylocta-4,5,7-trien-1-yl)benzene **97k** and (*E*)-(3-methyloct-5-en-7-yn-1-yl)benzene **97m** was prepared according to **TP5** from the alkyl iodide (3-iodobutyl)benzene (**1e**, 26.0 mg, 0.1 mmol) and electrophile **96j** (65 mg, 0.3 mmol). The crude product was purified by flash column chromatography on silica gel with pentane to afford **97k** (0.022 mmol, 4.4 mg, 22% yield) and **97m** (0.036 mmol, 7.1 mg, 36% yield) as colorless oils.



97k

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.31–7.26 (m, 2H), 7.21–7.13 (m, 3H), 6.23–6.12 (m, 1H), 5.90–5.82 (m, 1H), 5.35–5.25 (m, 1H), 5.18 (d, *J* = 17.0 Hz, 1H), 5.02–4.93 (m, 1H), 2.78–2.48 (m, 2H), 2.22 (dq, *J* = 11.2, 4.6, 3.3 Hz, 1H), 1.78–1.58 (m, 2H), 1.11–1.02 (m, 3H).
IR (ATR): ṽ[cm^{-1}] = 2952 (m), 2922 (vs), 2853 (s), 2360 (w), 2342 (w), 1457 (m), 1376 (w), 1261 (w), 1099 (w), 1019 (w), 800 (w).
HRMS (EI) for $C_{15}H_{17}$: calc. [M^+–H]: 197.1330; found 197.1324.



97m

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.31–7.26 (m, 2H), 7.22–7.13 (m, 3H), 6.08–5.93 (m, 1H), 5.57–5.46 (m, 1H), 3.08 (s, 1H), 2.73–2.53 (m, 2H), 2.45–2.34 (m, 1H), 2.32–2.15 (m, 1H), 1.72–1.59 (m, 2H), 1.53–1.40 (m, 1H), 0.98 (d, *J* = 6.6 Hz, 3H).
^{13}C{^{1}H}-NMR ($CDCl_3$, 101 MHz): δ [ppm] = 144.9, 143.1, 128.7, 128.7, 128.6, 126.0, 109.4, 81.7, 81.0, 38.8, 37.6, 33.8, 33.0, 19.9.
IR (ATR): ṽ[cm^{-1}] = 3300 (m), 3026 (m), 2955 (m), 2925 (s), 2871 (m), 2859 (m), 2360 (vs), 2341 (s), 2333 (s), 1496 (w), 1455 (m), 1378 (w), 746 (m), 698 (s), 668 (m), 656 (m).
HRMS (EI) for $C_{15}H_{17}$: calc. [M^+–H]: 197.1330; found 197.1325.

4 Stereoselective S_N2'-Reactions of Secondary Alkylcopperzinc Reagents

4.1 Typical Procedure for the S_N2'-Substitution Reactions (TP6)

A dry and Ar-flushed *Schlenk*-tube was cooled to −100 °C and charged with a solution of *t*-BuLi (0.22 mmol, 2.2 equiv) together with a mixture of diethyl ether (1.00 mL) and *n*-pentane (1.50 mL). A solution of alkyl iodide **1** (0.10 mmol, 1.0 equiv) in diethyl ether (0.40 mL) was added dropwise for 1 min. After stirring for 10 sec, a solution of $CuBr{\cdot}P(OEt)_3$ (0.05 mL, 3 M in diethyl ether, 0.15 mmol, 1.5 equiv) was added and the reaction mixture was stirred for 1 min at −100 °C to observe the color change from yellow to green. The *Schlenk*-tube was transferred to a cooling bath (−50 °C) and the solvent was pumped away under high vacuum (10 min). Precooled THF (2 mL) was added and after 10 sec, $ZnCl_2$ (0.15 mmol, 0.30 mL, 1.0 M in THF, 1.5 equiv) was added dropwise. The reaction mixture was warmed to −30 °C and stirred for 10 min. The allylic epoxide **101** (0.3 mmol dissolved in 0.60 mL THF) was added and the reaction mixture was warmed to −10 °C. After 12 h, the reaction mixture was quenched with aq. NH_3 solution and extracted with diethyl ether (3 × 10 mL). The combined organic phases were dried over $MgSO_4$ and the solvents were evaporated. The obtained crude product was purified by flash column chromatography on silica gel to afford products of type **102**.

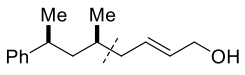
4.2 Preparation of Alkyl Iodides and Allylic Electrophiles

The iodides (*syn*-**1a**[53], *anti*-**1a**[53], *syn*-**1b**[56], *anti*-**1b**[56], (*R*)-**1f**[50], (*S*)-**1f**[50], *syn*-**1h**[49], *anti*-**1h**[49], (*R*)-**1i**[50], (*S*)-**1i**[50]) were prepared from the corresponding secondary alkyl alcohols and are literature known.

3,4-Epoxy-1-butene (**101a**) and 3,4-epoxy-1-cyclohexene (**101c**) are commercially available (Sigma Aldrich). The electrophiles 2-phenyl-3-vinyloxirane (**101b**)[96g] and 7-tosyl-7-azabicyclo[4.1.0]hept-2-ene (**101d**)[100] were prepared according to literature.

4.3 Preparation of Chiral Allylic Alcohols

syn-(_E_)-5-Methyl-7-phenyloct-2-en-1-ol (_syn_-102a)



syn-**102a**

The allylic alcohol *syn*-**102a** was prepared according to **TP6** from the alkyl iodide *syn*-**1a** (0.1 mmol, 27 mg) and electrophile **101a** (0.3 mmol, 0.024 mL). The crude product was purified by flash column chromatography on silica gel with *n*-pentane/diethyl ether = 4/1 to afford *syn*-**102a** (0.046 mmol, 10.0 mg, 46% yield) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.32–7.26 (m, 2H), 7.21–7.14 (m, 3H), 5.69–5.48 (m, 2H), 4.18–3.99 (m, 2H), 2.85–2.67 (m, 1H), 2.04–1.93 (m, 1H), 1.90–1.79 (m, 1H), 1.72–1.60 (m, 1H), 1.37–1.27 (m, 2H), 1.22 (d, *J* = 6.9 Hz, 3H), 0.86 (d, *J* = 6.0 Hz, 3H).

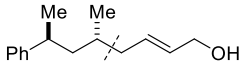
^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 147.5, 131.8, 130.4, 128.5, 127.2, 126.0, 64.0, 45.3, 40.2, 37.5, 30.5, 23.6, 19.4.

IR (ATR): $\tilde{\upsilon}$[cm^{-1}] = 3344 (m), 3026 (m), 2957 (s), 2916 (s), 2869 (m), 2142 (vw), 2010 (vw), 1603 (w), 1493 (m), 1452 (m), 1378 (m), 1084 (m), 1003 (m), 971 (s), 762 (s), 671 (vs).

MS (EI, 70 eV): m/z (%): 157 (6), 145 (100), 131 (10), 118 (47), 106 (34), 105 (47), 91 (62), 79 (19), 77 (21), 55 (6), 41 (13).

HRMS (EI) for $C_{15}H_{22}O$: calc. [M$^+$]: 218.1671; found: 218.1673.

anti-(*E*)-5-Methyl-7-phenyloct-2-en-1-ol (*anti*-102a)



anti-**102a**

The allylic alcohol *anti*-**102a** was prepared according to **TP6** from the alkyl iodide *anti*-**1a** (0.1 mmol, 27 mg) and electrophile **101a** (0.3 mmol, 0.024 mL). The crude product was purified by flash column chromatography on silica gel with *n*-pentane/diethyl ether = 4/1 to afford *anti*-**102a** (0.054 mmol, 11.8 mg, 54% yield) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.32–7.26 (m, 2H), 7.21–7.11 (m, 3H), 5.69–5.52 (m, 2H), 4.13–4.02 (m, 2H), 2.80 (q, *J* = 7.0 Hz, 1H), 2.14–2.02 (m, 1H), 1.94–1.81 (m, 1H), 1.54–1.38 (m, 3H), 1.21 (d, *J* = 6.9 Hz, 3H), 0.85 (d, *J* = 6.4 Hz, 3H).

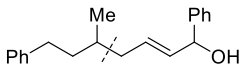
^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 148.2, 131.8, 130.5, 128.5, 127.1, 126.0, 64.0, 45.7, 39.6, 37.3, 30.7, 22.2, 19.8.

IR (ATR): $\tilde{\upsilon}$[cm^{-1}] = 3344 (m), 3026 (m), 2957 (s), 2912 (s), 2870 (m), 2141 (vw), 2009 (vw), 1603 (w), 1493 (m), 1452 (m), 1377 (m), 1084 (m), 1024 (m), 970 (s), 908 (m), 762 (s), 733 (m), 671 (vs).

MS (EI, 70 eV): m/z (%): 218 (1), 185 (2), 145 (32), 106 (11), 105 (100), 91 (14), 77 (6), 41 (4).

HRMS (EI) for $C_{15}H_{22}O$: calc. [M$^+$]: 218.1671; found: 218.1666.

(*E*)-5-Methyl-1,7-diphenylhept-2-en-1-ol (102b)



102b

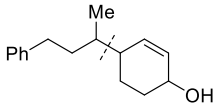
The allylic alcohol **102b** was prepared according to **TP6** from the alkyl iodide *rac*-**1f** (0.1 mmol, 26 mg) and electrophile **101b** (0.3 mmol, 44 mg). The crude product was purified by flash column

chromatography on silica gel with *n*-pentane/diethyl ether = 4/1 to afford **102b** (0.043 mmol, 12.1 mg, 43% yield) as a colorless oil and mixture of two diastereoisomers, which could not be separated.

Analytic data refer to the diastereoisomers of the α-substitution product:

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.40–7.31 (m, 8H), 7.31–7.25 (m, 6H), 7.21–7.09 (m, 6H), 5.80–5.60 (m, 4H), 5.20–5.16 (m, 2H), 2.70–2.60 (m, 2H), 2.60–2.49 (m, 2H), 2.20–2.04 (m, 2H), 2.02–1.90 (m, 2H), 1.85 (s, 1H), 1.85 (s, 1H), 1.74–1.51 (m, 4H), 1.51–1.40 (m, 2H), 0.99–0.91 (m, 6H).
^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 143.5, 143.0, 133.9, 131.0, 131.0, 128.7, 128.6, 128.5, 128.4, 127.7, 127.7, 126.3, 126.3, 125.8, 75.3, 75.3, 39.6, 39.6, 38.5, 38.5, 33.5, 33.5, 32.7, 32.7, 19.7, 19.6.
IR (ATR): ϋ[cm^{-1}] = 3354 (w), 3061 (w), 3026 (w), 2953 (w), 2921 (w), 2869 (w), 2361 (vw), 1667 (vw), 1603 (w), 1493 (m), 1453 (m), 1377 (w), 1243 (w), 1192 (w), 1068 (w), 1029 (m), 969 (m), 915 (w), 842 (w), 745 (m), 723 (m), 697 (vs).
MS (EI, 70 eV): m/z (%): 280 (8), 262 (25), 173 (12), 171 (12), 158 (29), 157 (22), 133 (26), 129 (19), 120 (25), 117 (114), 115 (17), 105 (33), 92 (11), 91 (100), 77 (22).
HRMS (EI) for $C_{20}H_{24}O$: calc. [M^+]: 280.1827; found: 280.1817.

4-Phenylbutan-2-ylcyclohex-2-en-1-ol (102c)



102c

The allylic alcohol **102c** was prepared according to **TP6** from the alkyl iodide *rac*-**1f** (0.1 mmol, 26 mg) and electrophile **101c** (0.3 mmol, 0.020 mL). The crude product was purified by flash column chromatography on silica gel with *n*-pentane/diethyl ether = 4/1 to afford **102c** (0.051 mmol, 11.7 mg, 51% yield) as a colorless oil and a mixture of diastereoisomers, which could not be separated.

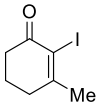
Analytic data refer to the diastereoisomers of the α-substitution product:

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.31–7.27 (m, 4H), 7.21–7.15 (m, 6H), 5.74–5.67 (m, 2H), 5.61 (tq, *J* = 10.0, 1.8 Hz, 2H), 4.28–4.16 (m, 2H), 2.75–2.61 (m, 2H), 2.61–2.43 (m, 2H), 2.25–2.00 (m, 4H), 1.78–1.62 (m, 4H), 1.58–1.32 (m, 10H), 0.92 (d, *J* = 6.5 Hz, 3H), 0.87 (d, *J* = 6.7 Hz, 3H).
^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 142.9, 133.8, 132.7, 131.9, 131.6, 128.5, 128.5, 125.8, 67.8, 40.9, 40.3, 36.7, 36.6, 36.1, 35.6, 34.1, 34.0, 33.02, 32.9, 24.1, 22.4, 16.5, 15.8.
IR (ATR): ϋ[cm^{-1}] = 3340 (m), 3025 (m), 2930 (s), 2860 (s), 1603 (w), 1496 (m), 1453 (m), 1379 (m), 1055 (s), 1040 (s), 747 (s), 735 (s), 698 (vs).
MS (EI, 70 eV): m/z (%): 212 (7), 183 (8), 131 (15), 117 (10), 108 (13), 104 (14), 93 (11), 91 (100), 79 (27).
HRMS (EI) for $C_{16}H_{22}O$: calc. [M^+]: 230.1671; found: 230.1656.

4.4 Total Synthesis of (3*S*,6*R*,7*S*)-Zingiberenol

Preparation of the allylic epoxide 104

2-Iodo-3-methylcyclohex-2-en-1-one (111)

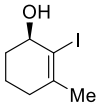


111

According to literature,[101] PDC (3.38 g, 9 mmol, 0.3 equiv) and I_2 (12.9 g, 51.0 mmol, 1.7 equiv) were added in one portion to a solution of 3-methyl-2-cyclohexenone **110** (3.40 mL, 30 mmol, 1.0 equiv) in dichloromethane (250 mL). The reaction mixture was covered in aluminum-foil and stirred at rt overnight. The reaction mixture was filtered and the filtrate was washed with *n*-pentane. The organic phase was washed with 2 M HCl, with $NaHCO_3$, with sat. aq. $Na_2S_2O_3$ and with brine. The combined organic phases were dried over $MgSO_4$ and concentrated. The crude product was purified by flash column chromatography on silica gel with *n*-pentane/diethyl ether = 7/3 to afford 2-iodo-3-methylcyclohex-2-en-1-one **111** (5.72 g, 24.3 mmol, 81% yield) as a slightly yellow solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 2.63–2.47 (m, 4H), 2.28–2.20 (m, 3H), 2.03–1.94 (m, 2H).
^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 192.3, 166.8, 107.0, 36.4, 34.3, 32.0, 22.2.
IR (ATR): $\tilde{\nu}$[cm^{-1}] = 2938 (w), 2883 (w), 2866 (w), 1672 (vs), 1589 (s), 1423 (m), 1369 (m), 1261 (s), 1190 (m), 1167 (s), 1131 (m), 968 (s), 908 (m), 781 (vs).
MS (EI, 70 eV): m/z (%): 236 (100), 208 (68), 81 (10), 79 (8), 53 (48), 41 (10).
HRMS (EI) for C_7H_9IO: calc. [M^+]: 235.9698; found: 235.9688.

(*R*)-2-Iodo-3-methylcyclohex-2-en-1-ol (112)



112

A flame dried and Ar-flushed round-bottom flask was charged with a solution of (*R*)-diphenylprolinol (232 mg, 0.91 mmol, 0.05 equiv) and $B(OMe)_3$ (0.095 mL, 0.91 mmol, 0.05 equiv) in THF (18 mL). The mixture was stirred for 1 h at rt. Borane *N*,*N*-diethylaniline (3.35 mL, 18.3 mmol, 1.00 equiv) and 2-iodo-3-methylcyclohex-2-en-1-one **111** (4.31 g, 18.3 mmol, 1.00 equiv; dissolved in 18 mL THF) were added dropwise. The reaction mixture was stirred for 1 h and then quenched with methanol (20 mL). The solvent was removed under reduced pressure and the obtained crude product was diluted with diethyl ether. The organic phase was washed with 7% aq. Na_2CO_3 sol., 10% aq. $KHSO_4$ sol. and brine. The organic phase as dried over Na_2SO_4 and concentrated under reduced pressure. The crude

product was purified by flash column chromatography on silica gel with *n*-pentane/diethyl ether = 3/1 to afford (*R*)-2-iodo-3-methylcyclohex-2-en-1-ol **112** (3.86 g, 16.2 mmol, 88% yield, 98% *ee*) as a white solid.

$[\alpha]_D^{20}$ = +54.1 (c = 4.9, $CHCl_3$).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 4.37–4.20 (m, 1H), 2.27–2.02 (m, 3H), 1.88 (s, 3H), 1.87–1.74 (m, 2H), 1.71–1.60 (m, 1H).

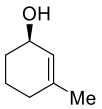
^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 143.1, 104.2, 74.0, 33.4, 31.9, 29.6, 18.6.

IR (ATR): $\tilde{\upsilon}$[cm^{-1}] = 3249 (m), 2937 (m), 2916 (m), 2907 (m), 2859 (m), 2820 (w), 1639 (m), 1420 (m), 1290 (m), 1165 (m), 1076 (m), 1065 (m), 1033 (m), 1019 (m), 999 (m), 959 (vs), 898 (m), 880 (s), 783 (s), 730 (m).

MS (EI, 70 eV): m/z (%): 238 (13), 210 (10), 111 (100), 93 (19), 91 (15), 77 (7).

HRMS (EI) for $C_7H_{11}OI$: calc. [M^+]: 237.9855; found 237.9845

(*R*)-3-Methylcyclohex-2-en-1-ol (113)



113

A flame dried and Ar-flushed round-bottom flask was charged with a solution of **112** (2.38 g, 10.0 mmol, 1.0 equiv) and diethyl ether (92 mL). After cooling to −78 °C, *t*-BuLi (23.9 mL, 45.0 mL, 4.5 equiv) was added dropwise. The mixture was stirred for 30 min and then quenched with a sat. solution of $NaHCO_3$ (30 mL). The solution was poured in 200 mL of a sat. solution of $NaHCO_3$ and extracted three times with diethyl ether. The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel with *n*-pentane/diethyl ether = 2/1 to afford (*R*)-3-methylcyclohex-2-en-1-ol **113** (1.06 g, 9.5 mmol, 95% yield, 98% *ee*) as a white solid.

$[\alpha]_D^{20}$ = +86.3 (c = 1.4, $CHCl_3$).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 5.51–5.44 (m, 1H), 4.22–4.11(m, 1H), 2.01–1.82 (m, 2H), 1.81–1.70 (m, 2H), 1.70–1.66 (m, 3H), 1.63–1.51 (m, 2H), 1.40–1.34 (m, 1H).

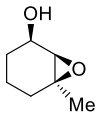
^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 138.9, 124.4, 66.0, 31.8, 30.2, 23.8, 19.1.

IR (ATR): $\tilde{\upsilon}$[cm^{-1}] = 3320 (br), 2930 (s), 2910 (m), 2859 (m), 2358 (vw), 2333 (vw), 1671 (w), 1447 (m), 1436 (m), 1376 (m), 1343 (m), 1277 (m), 1164 (m), 1074 (m), 1059 (s), 1032 (s), 1013 (m), 992 (s), 956 (vs), 905 (m), 814 (m), 706 (m).

MS (EI, 70 eV): m/z (%): 98 (11), 97 (100), 83 (16), 79 (23).

HRMS (EI) for $C_7H_{11}O^{\cdot}$: calc. [M^+–H]: 111.0810; found 111.0803.

(1*R*,2*R*,6*S*)-6-Methyl-7-oxabicyclo[4.1.0]heptan-2-ol (114)



114

A flame dried and Ar-flushed round-bottom flask was charged with a solution of **113** (1.12 g, 10.0 mmol, 1.0 equiv) in dichloromethane (70 mL) and cooled to 0 °C. *meta*-Chloroperoxybenzoic acid (mCPBA) was added dropwise as a solution in dichloromethane (50 mL). After 15 min stirring, the reaction mixture was quenched with a 10% aq. solution of Na_2CO_3 and extracted three times with dichloromethane (20 mL). The combined organic phase was washed with brine, was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel with *n*-pentane/diethyl ether = 2/1 to (1*R*,2*R*,6*S*)-6-methyl-7-oxabicyclo[4.1.0]heptan-2-ol **114** (1.02 g, 8.0 mmol, 80% yield, 98% *ee*) as a colorless oil.

$[\alpha]_D^{20}$ = +26.9 (c = 3.0, $CHCl_3$).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 4.01 (td, *J* = 5.5, 3.3 Hz, 1H), 3.15 (d, *J* = 3.3 Hz, 1H), 1.93–1.79 (m, 1H), 1.68–1.59 (m, 1H), 1.57–1.43 (m, 3H), 1.34 (s, 3H), 1.32–1.23 (m, 1H).

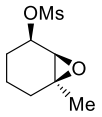
^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 66.5, 62.3, 61.7, 29.3, 28.9, 23.8, 17.6.

IR (ATR): $\tilde{\upsilon}$[cm^{-1}] = 3387 (m), 2976 (m), 2937 (m), 2862 (m), 1708 (m), 1423 (m), 1264 (m), 1074 (s), 1063 (s), 1037 (s), 1018 (s), 990 (s), 894 (s), 843 (vs), 766 (s), 669 (s), 654 (s).

MS (EI, 70 eV): m/z (%): 111 (100), 93 (68), 84 (38), 81 (19), 70 (12), 67 (46), 43 (24).

HRMS (EI) for $C_7H_{12}O_2$: calc. [M^+]: 128.0837; found 128.0830.

(1*R*,2*R*,6*S*)-6-Methyl-7-oxabicyclo[4.1.0]heptan-2-ylmethane-sulfonate (115a)



115a

A flame dried and Ar-flushed round-bottom flask was charged with a solution of **114** (0.64 g, 5.0 mmol, 1.0 equiv) and NEt_3 (2.58 mL, 30.0 mmol, 6.0 equiv) in dichloromethane (30 mL). After cooling to −10 °C, methanesulfonyl chloride (1.48 mL, 22.5 mmol, 4.5 equiv) was added dropwise. The reaction mixture was stirred for 1 h and then diluted with ethyl acetate (10 mL). The organic phase was washed 1 M HCl, sat. aq. $NaHCO_3$ and brine. The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel with *n*-pentane/diethyl ether = 1/2 to afford (1*R*,2*R*,6*S*)-6-methyl-7-oxabicyclo[4.1.0]heptan-2-ylmethane-sulfonate **115a** (0.84 g, 4.0 mmol, 80% yield, 98% *ee*) as a colorless oil

$[\alpha]_D^{20}$ = −7.0 (c = 1.5, $CHCl_3$).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 5.13–5.01 (m, 1H), 3.25 (d, J = 2.4 Hz, 1H), 3.09 (s, 3H), 1.93–1.79 (m, 1H), 1.78–1.60 (m, 4H), 1.36 (s, 3H), 1.34–1.26 (m, 1H).

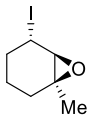
^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 78.2, 61.5, 59.4, 39.2, 27.8, 25.7, 23.9, 19.1.

IR (ATR): $\tilde{\upsilon}$[cm^{-1}] = 3519 (w), 2940 (w), 2361 (w), 2332 (w), 1452 (w), 1333 (s), 1170 (vs), 1131 (w), 1057 (m), 1006 (w), 952 (s), 933 (vs), 894 (m), 858 (m), 831 (m).

MS (EI, 70 eV): m/z (%): 111 (29), 110 (32), 95 (19), 93 (21), 84 (22), 81 (45), 79 (20), 71 (50), 70 (57), 69 (11), 67 (32), 55 (35), 53 (13), 43 (100), 41 (43).

HRMS (EI) for $C_8H_{14}O_4S$: calc. [M$^+$]: 206.0613; found 206.0609.

(1*S*,5*S*,6*S*)-5-Iodo-1-methyl-7-oxabicyclo[4.1.0]heptane (116)



116

A flame dried and Ar-flushed round-bottom flask was charged with a solution of **115a** (0.84 g, 4.0 mmol, 1.0 equiv), $NaHCO_3$ (6.7 g, 80.0 mmol, 20 equiv) and NaI (6.0 g, 40.0 mmol, 10 equiv) in THF (10 mL). The mixture was stirred for 10 h at 65 °C, then diluted with water (50 mL) and extracted three times with diethyl ether. The combined organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel with *n*-pentane/diethyl ether = 16/1 to afford (1*S*,5*S*,6*S*)-5-iodo-1-methyl-7-oxabicyclo[4.1.0]heptane **116** (590 mg, 2.5 mmol, 62% yield, 98% *ee*) as a yellow oil.

$[\alpha]_D^{20}$ = +0.3 (c = 1.9, $CHCl_3$).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 4.50 (ddd, J = 8.3, 5.9, 2.6 Hz, 1H), 3.22 (d, J = 2.7 Hz, 1H), 2.07–1.89 (m, 3H), 1.82–1.69 (m, 1H), 1.62–1.47 (m, 1H), 1.29 (s, 3H), 1.27–1.25 (m, 1H).

^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 66.3, 64.1, 32.8, 28.6, 27.8, 24.4, 21.7.

IR (ATR): $\tilde{\upsilon}$[cm^{-1}] = 3503 (br), 2935 (s), 2857 (w), 2538 (w), 1652 (w), 1441 (m), 1413 (w), 1376 (m), 1355 (w), 1295 (w), 1263 (w), 1219 (w), 1199 (w), 1135 (s), 1098 (s), 1050 (vs), 1002 (m), 962 (m), 929 (w), 890 (s), 848 (m), 766 (m), 668 (m), 656 (m).

MS (EI, 70 eV): m/z (%): 127 (67), 111 (93), 93 (100), 91 (60), 81 (17), 79 (16), 77 (23), 67 (67), 55 (9), 43 (46).

HRMS (EI) for $C_7H_{11}OI$: calc. [M$^+$]: 237.9855; found 237.9843.

(1*R*,6*S*)-6-Methyl-7-oxabicyclo[4.1.0]hept-2-ene (104)

104

A flame dried and Ar-flushed pressure tube was charged with a solution of **116** (590 mg, 2.5 mmol, 1.0 equiv) and THF (25 mL). After the addition of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU; 0.56 mL, 3.75 mmol, 1.5 equiv), the reaction mixture was stirred 12 h at 60 °C. The crude reaction mixture was product was purified by Kugelrohr distillation (45 °C-55 °C, atmoshpheric pressure) to afford (1*R*,6*S*)-6-methyl-7-oxabi-cyclo[4.1.0]hept-2-ene **104** (165 mg, 1.5 mmol, 60% yield, 98% *ee*) as a colorless oil with small impurities of THF.

$[\alpha]_D^{20} = -8.3$ (c = 1.0, THF).

^{1}H-NMR (CDCl$_3$, 400 MHz): δ [ppm] = 5.97–5.84 (m, 2H), 3.04 (dd, *J* = 3.5, 1.8 Hz, 1H), 2.21–1.86 (m, 2H), 1.72–1.53 (m, 2H), 1.42 (s, 3H).

^{13}C{^{1}H}-NMR (CDCl$_3$, 100 MHz): δ [ppm] = 132.9, 123.7, 61.2, 54.7, 26.6, 22.3, 22.0.

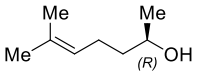
IR (ATR): $\tilde{\upsilon}$[cm^{-1}] = 3430 (m), 2964 (m), 2931 (s), 2927 (s), 2359 (m), 2328 (m), 1374 (m), 1260 (s), 1123 (s), 1103 (vs), 1091 (vs), 1087 (vs), 1071 (vs), 1058 (vs), 1042 (s), 1038 (s), 1034 (s), 1024 (s), 798 (s), 668 (s).

MS (EI, 70 eV): m/z (%): 95 (13), 91 (19), 82 (100), 81 (28), 79 (16), 69 (14).

HRMS (EI) for $C_7H_{10}O$: calc. [M^+]: 110.0732; found 110.0724.

Preparation of the iodide 106

(*R*)-6-Methylhept-5-en-2-ol (118)



118

A flame-dried and Ar-flushed *Schlenk*-flask was charged with Mg turning (0.52 g, 21.0 mmol) and THF (20 mL). After addition of I_2 (ca. 5 mg), the mixture was stirred and warmed until the color of I_2 disappeared. The allyic chloride **117** (1.94 mL, 20.0 mmol) was added in such a rate to keep a mild reflux. After the addition, the reaction mixture was stirred for 1 h at rt to obtain the corresponding Grignard reagent (67% yield, 0.67 M in THF). To a solution of the Grignard reagent (15.4 mL, 0.67 M in THF, 10.0 mmol), CuI (186 mg, 1.0 mmol) was added in one portion at 0 °C and the resulted black suspension was stirred for 5 min at 0 °C. Then (*R*)-propylene oxide (*R*)-**53** (0.70 mL, 10.0 mmol) in THF (10 mL) was added dropwise at 0 °C. The reaction mixture was warmed to rt and was stirred for 12 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution and extracted with diethyl ether (3×20 mL). The combined organic phases were dried over $NaSO_4$ and the solvents were evaporated. The crude product was purified by flash column chromatography on silica gel with *n*-pentane/diethyl ether = 2/1 to afford (*R*)-6-methylhept-5-en-2-ol **118** (1.08 g, 8.5 mmol, 85% yield, er = 99:1) as a colorless oil.

$[\alpha]_D^{23} = -14.0$ (c = 0.9, $CHCl_3$).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 5.18–5.05 (m, 1H), 3.93–3.72 (m, 1H), 2.17–1.94 (m, 2H), 1.69 (s, 3H), 1.62 (s, 3H), 1.54–1.39 (m, 2H), 1.19 (d, *J* = 6.1 Hz, 3H).

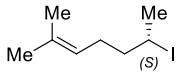
^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 132.3, 124.2, 68.1, 39.3, 25.9, 24.6, 23.6, 17.8.

IR (ATR): $\tilde{\nu}$[cm^{-1}] = 2967 (m), 2917 (m), 2859 (w), 1742 (s), 1728 (m), 1448 (w), 1395 (w), 1374 (s), 1300 (w), 1238 (vs), 1126 (m), 1113 (m), 1071 (m), 1046 (s), 952 (w), 935 (w).

MS (EI, 70 eV): m/z (%): 128 (1), 113 (9), 110 (13), 96 (8), 95 (100), 85 (10), 79 (5), 71 (5), 57 (36), 41 (6).

HRMS (EI) for $C_8H_{16}O$: calc. [M^+]: 128.1201; found 128.1194.

(*S*)-6-Iodo-2-methylhept-2-ene (106)



106

A dry and Ar-flushed *Schlenk*-flask was charged with a solution of I_2 (1.65 g, 6.5 mmol, 1.3 equiv) in dichloromethane (50 mL) and cooled to −10 °C. Triphenylphosphine (1.70 g, 6.5 mmol, 1.3 equiv) was added at −10 °C and the resulting yellow suspension was stirred for 1 h at −10 °C. Then

N-methylimidazole (0.52 mL, 0.53 g, 6.5 mmol, 1.3 equiv) was added. After 10 min of further stirring, the alcohol **118** (0.64 g, 5.0 mmol, 1.0 equiv) dissolved in dichloromethane (5 mL) was added and the reaction mixture was stirred for 1 h at −10 °C. The reaction mixture was quenched with freshly prepared sat. aq. $NaHSO_3 \cdot Na_2S_2O_5$ solution and it was extracted with dichloromethane (3 × 50 mL). The combined organic phase was dried over $MgSO_4$ and the solvents were evaporated at 30 °C. The residue was triturated three times with a mixture of *n*-pentane/diethyl ether = 4/1. The precipitate was filtered off and all organic phases were combined. The solvents were evaporated at 30 °C. The crude product was purified by flash column chromatography on silica gel with *n*-pentane to obtain (*S*)-6-iodo-2-methylhept-2-ene **106** (833 mg, 3.5 mmol, 73% yield, er = 99:1).

$[\alpha]_D^{20}$ = +89.0 (c = 0.9, $CHCl_3$).

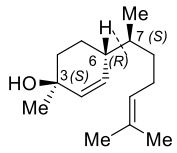
^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 5.14–4.98 (m, 1H), 4.26–4.02 (m, 1H), 2.23–1.99 (m, 2H), 1.93 (d, *J* = 6.8 Hz, 3H), 1.92–1.82 (m, 1H), 1.69 (s, 3H), 1.65 (s, 3H), 1.64–1.56 (m, 1H).

^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ = 133.1, 122.7, 43.1, 30.6, 29.1, 28.4, 25.9, 18.1.

IR (ATR): $\tilde{\upsilon}$[cm^{-1}] = 2979 (m), 2964 (s), 2914 (s), 2883 (m), 2858 (m), 1443 (s), 1376 (vs), 1231 (m), 1194 (m), 1181 (s), 1142 (s), 1136 (s), 1113 (s), 1080 (m), 843 (m), 824 (m), 805 (m), 744 (m).
MS (EI, 70 eV): m/z (%): 238 (3), 127 (5), 111 (29), 95 (5), 70 (6), 69 (100), 67 (6), 41 (14).
HRMS (EI) for $C_8H_{15}I$: calc. [M^+]: 238.0218; found 238.0213.

All analytical data were in accordance with literature values for the (*R*)-enantiomer.[50]

(3*S*,6*R*,7*S*)-Zingiberenol (103)



(3*S*,6*R*,7*S*)-zingiberenol (**103**)

The natural product **103** was prepared according to **TP6** from **106** (er = 99:1, 0.20 mmol, 48 mg) and electrophile **104** (0.60 mmol, 66 mg, 98% *ee*). The crude product was purified by flash column chromatography on silica gel with *n*-pentane/diethyl ether = 3/1 to afford (3*S*,6*R*,7*S*)-zingiberenol **8** (0.12 mmol, 26.7 mg, 61% yield, 98% *ee*; dr (3*S*,6*R*) = 99:1; dr (6*R*,7*S*) = 81:19) as a colorless oil.

$[\alpha]_D^{20}$ = −32.9 (c = 0.8, CH_2Cl_2).
The NMR data refer to the major diastereoisomer (3*S*,6*R*,7*S*)-zingiberenol:
^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 5.59–5.53 (m, 1H), 5.54–5.45 (m, 1H), 5.10 (t, *J* = 7.1 Hz, 1H), 2.16–2.06 (m, 1H), 2.04–1.78 (m, 4H), 1.67 (s, 3H), 1.60 (s, 3H), 1.52–1.44 (m, 2H), 1.42–1.31 (m, 2H), 1.22 (s, 3H), 1.20–1.08 (m, 1H), 0.81 (d, *J* = 6.8 Hz, 3H).

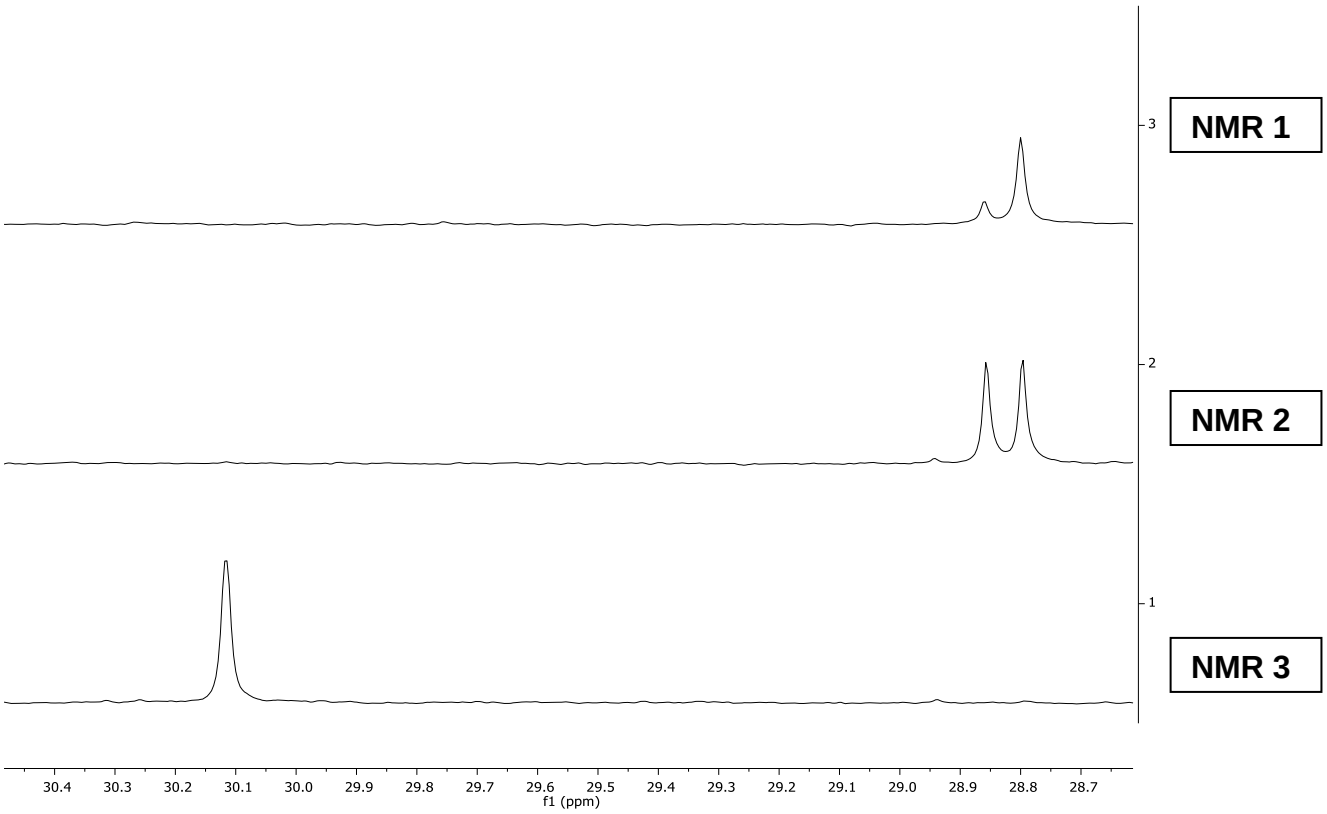
$^{13}C\{^{1}H\}$-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 135.4, 1323, 131.7, 125.2, 70.0, 40.7, 38.9, 36.8, 34.7, 28.8, 26.5, 26.0, 22.9, 17.9, 16.0.

IR (ATR): $\tilde{\upsilon}$[cm^{-1}] = 3381 (br), 2962 (vs), 2928 (vs), 2859 (s), 2363 (w), 2338 (w), 1715 (w), 1669 (w), 1456 (m), 1450 (m), 1376 (s), 1367 (m), 1120 (s), 978 (m), 916 (m), 743 (m).

MS (EI, 70 eV): m/z (%): 207 (20), 189 (11), 161 (28), 138 (15), 137 (38), 123 (33), 119 (100), 105 (30), 93 (35), 79 (18), 67 (17).

HRMS (EI) for $C_{15}H_{26}O$: calc. [M^+]: 222.1984; found 222.1975.

Determination of dr of zingiberenol [assignment of C(3), C(6) and C(7)]



NMR-spectrum 1: Synthesized product (dr(C3,C6) = 99:1; dr(C6,C7) = 81:19).

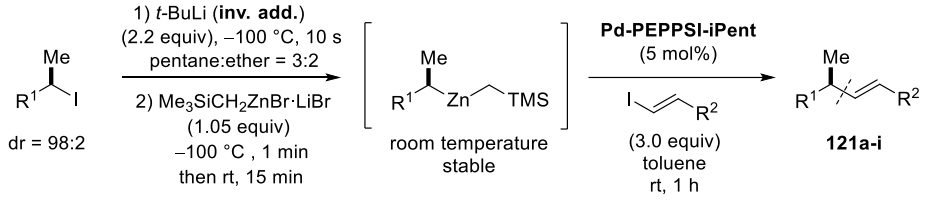
NMR-spectrum 2: mixture of (3*R*,6*S*,7*S*)-zingiberenol (left carbon) and (3*S*,6*R*,7*S*)-zingiberenol (right carbon); prepared and assigned according to literature.[99a]

NMR-spectrum 3: mixture of (3*S*,6*S*,7*S*)-zingiberenol and (3*R*,6*R*,7*S*)-zingiberenol; prepared and assigned according to literature.[99a]

Since the C(15)-peak of (3*S*,6*S*,7*S*)-zingiberenol and (3*R*,6*R*,7*S*)-zingiberenol is not found in **NMR 1**, the reaction of the copper-species (*S*)-**105** and electrophile **104** furnished exclusively the *anti*-S_N2'-product were the the OH-group of C(3) and H-atom of C(6) are on the same site.

5 Stereoselective Cross-Couplings of Chiral Alkylzinc Reagents with Alkenyl and Aryl Halides

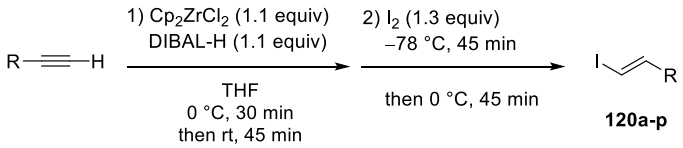
5.1 Typical Procedure for Palladium-Catalyzed Cross-Couplings (TP7)



A dry and Ar-flushed *Schlenk*-tube was charged with *n*-pentane/diethyl ether (1.3 mL/0.9 mL) and cooled to −100 °C. *t*-BuLi (2.2 equiv) was added dropwise at −100 °C. A solution of the secondary alkyl iodide (**1**, 1.0 equiv) in diethyl ether (0.4 mL) was added dropwise over a period of 60 s. Subsequently, a solution of $Me_3SiCH_2ZnBr{\cdot}LiBr$ (ca. 0.9 M, 1.05 equiv) was added dropwise and the reaction mixture was stirred for 1 min at −100 °C. The *Schlenk*-tube was then put to rt and the reaction mixture was let warm to ambient temperature. After 15 min, the reaction mixture was added dropwise to a premixed solution of Pd-PEPPSI-iPent (5 mol%) and the alkenyl iodide **120** (3.0 equiv) in toluene (1.8 mL). The reaction mixture was stirred for 1 h at rt. After quenching with sat. aq. NH_4Cl solution, the reaction mixture was extracted with diethyl ether (3 × 10 mL). The combined organic phases were dried over $MgSO_4$ and the solvents were evaporated. The obtained crude product was purified by flash column chromatography on silica gel to afford alkenes of type **121**.

5.2 Preparation of Alkyl Iodides and Alkenyl Halides

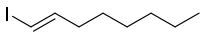
Typical procedure for alkenyl iodide synthesis (TP8)[131]



A dry and Ar-flushed *Schlenk*-flask was charged with Cp_2ZrCl_2 (1.1 equiv) followed by THF (0.5 M) and cooled to 0 ºC. DIBAL-H (1.1 equiv, 1.0 M in *n*-hexane) was added dropwise. After stirring for 30 min at 0 ºC the corresponding alkyne (1.0 equiv) was added as a solution in THF (2.0 M). The reaction mixture was warmed to rt and stirred for 45 min, at which time the solution was homogenous. The reaction mixture was then cooled to –78 ºC and a solution of iodine (1.0 M in THF, 1.3 equiv) was

[131] J. T. Edwards, R. R. Merchant, K. S. McClymont, K. W. Knouse, T. Qin, L. R. Malins, B. Vokits, S. A. Shaw, D.-H. Bao, F.-L. Wei, T. Zhou, M. D. Eastgate, P. S. Baran, *Nature* **2017**, *545*, 213–218.

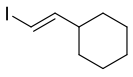
added dropwise. The resulting brown solution was stirred at –78 ºC for 45 min before warming to 0 ºC within 45 min. A *Schlenk*-flask filled with *i*-hexanes (0.2 M) and HCl (2.8 equiv) was cooled to 0 °C and the reaction mixture was carefully transferred into it with vigorous stirring. The resulting biphasic solution was seperated and the aqueous layer was extracted with *i*-hexanes (3 × 100 mL). The combined organic layer was washed with HCl (1 M, 30 mL), $NaHCO_3$ (20% aq. sol., 30 mL), $Na_2S_2O_3$ (sat. aq. sol., 30 mL) and brine (30 mL). The combined organic phases were dried with Na_2SO_4 and filtered over a pad of Celite®. Solvents were removed and the crude product was purified by flash column chromatography on silica gel to afford the corresponding alkenyl iodide **120**.



(*E*)-**120a**

The alkenyl iodide **120a** was prepared from oct-1-yne (1.1 g, 10.0 mmol) according to **TP8**. The crude product was purified by flash column chromatography on silica gel with *n*-pentane to afford (*E*)-**120a** (1.71 g, 7.2 mmol, 72 % yield) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 6.51 (dt, *J* = 14.3, 7.1 Hz, 1H), 5.97 (dt, *J* = 14.4, 1.5 Hz, 1H), 2.05 (qd, *J* = 7.2, 1.5 Hz, 2H), 1.43–1.34 (m, 2H), 1.34–1.22 (m, 6H), 0.91–0.85 (m, 3H).
^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 147.0, 74.4, 36.2, 31.7, 28.7, 28.5, 22.7, 14.2.
IR (ATR): $\tilde{\nu}$[cm^{-1}] = 2956 (m), 2925 (vs), 2870 (m), 2855 (m), 1606 (w), 1466 (w), 1458 (w), 1437 (w), 1378 (w), 1227 (w), 1214 (w), 1202 (w), 1171 (w), 943 (m), 724 (w), 660 (w).
MS (EI, 70 eV): m/z (%): 238 (25), 183 (10), 167 (37), 154 (56), 69 (100).
HRMS (EI) for $C_8H_{15}I$: calc. [M^+]: 238.0218; found: 238.0210.

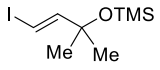


120b

The alkenyl iodide **120b** was prepared from ethynylcyclohexane (541 mg, 5.0 mmol) according to **TP8**. The crude product was purified by flash column chromatography on silica gel with *i*-hexane to afford **120b** (921 mg, 3.9 mmol, 78% yield) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 6.48 (dd, *J* = 14.4, 7.1 Hz, 1H), 5.95 (dd, *J* = 14.4, 1.2 Hz, 1H), 2.06–1.95 (m, 1H), 1.76–1.69 (m, 4H), 1.67–1.64 (m, 1H), 1.32–1.03 (m, 5H).
^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 152.4, 73.4, 44.7, 32.1, 26.1, 25.9.
IR (ATR): $\tilde{\nu}$[cm^{-1}] = 2922 (vs), 2850 (s), 1602 (w), 1448 (m), 1350 (w), 1296 (w), 1282 (w), 1260 (vw), 1240 (w), 1200 (w), 1174 (m), 1120 (w), 946 (vs), 920 (w), 892 (w), 842 (w), 758 (w), 742 (w), 710 (w), 664 (m).

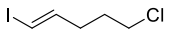
MS (EI, 70 eV): m/z (%): 180 (13), 167 (14), 127 (17), 109 (100), 81 (12), 79 (14), 67 (74).
HRMS (EI) for $C_8H_{13}I$: calc. [M^+]: 236.0062; found: 236.0057.



120d

The alkenyl iodide **120d** was prepared from trimethyl((2-methylbut-3-yn-2-yl)oxy)silane (782 mg, 5.0 mmol) according to **TP8**. The crude product was purified by flash column chromatography on silica gel with *i*-hexane/ethyl acetate = 20/1 to afford **120d** (966 mg, 3.4 mmol, 68% yield) as a colorless oil.

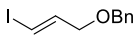
^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 6.60 (d, J = 14.4 Hz, 1H), 6.22 (d, J = 14.4 Hz, 1H), 1.29 (s, 6H), 0.12 (s, 9H).
^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 153.9, 76.4, 74.7, 30.0, 2.5.
IR (ATR): $\tilde{\nu}$[cm^{-1}] = 2976 (w), 1610 (vw), 1456 (vw), 1378 (w), 1362 (w), 1288 (vw), 1250 (m), 1232 (m), 1192 (m), 1166 (m), 1136 (m), 1034 (s), 998 (w), 944 (m), 918 (w), 888 (m), 834 (vs), 752 (m), 714 (vw), 688 (w), 658 (w).
MS (EI, 70 eV): m/z (%): 269 (44), 185 (11), 157 (75), 127 (19), 75 (73), 73 (100), 47 (30), 45 (40), 43 (20), 41 (11).
HRMS (EI) for $C_8H_{17}IOSi$: calc. [M^+−Me]: 268.9859; found: 268.9855.



120e

The alkenyl iodide **120e** was prepared from 5-chloropent-1-yne (513 mg, 5.0 mmol) according to **TP8**. The crude product was purified by flash column chromatography on silica gel with *i*-hexane/ethyl acetate = 50/1 to afford **120e** (864 mg, 3.75 mmol, 75% yield) as a colorless oil.

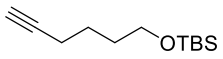
^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 6.48 (dt, J = 14.4, 7.2 Hz, 1H), 6.10 (dt, J = 14.4, 1.4 Hz, 1H), 3.54 (t, J = 6.4 Hz, 2H), 2.29–2.13 (m, 2H), 1.95–1.74 (m, 2H).
^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 144.6, 76.3, 44.0, 33.1, 31.0.
IR (ATR): $\tilde{\nu}$[cm^{-1}] = 3048 (vw), 2994 (vw), 2956 (w), 2912 (w), 2868 (vw), 2844 (w), 1606 (w), 1442 (m), 1352 (w), 1332 (vw), 1308 (w), 1294 (w), 1270 (m), 1218 (m), 1196 (m), 1144 (w), 1132 (w), 980 (w), 944 (vs), 860 (w), 780 (m), 728 (m), 660 (w).
MS (EI, 70 eV): m/z (%): 230 (75), 103 (39), 75 (29), 67 (94), 43 (23), 41 (100).
HRMS (EI) for C_5H_8ClI: calc. [M^+]: 229.9359; found: 229.9359.



120f

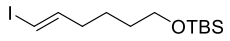
The alkenyl iodide **120g** was prepared from ((prop-2-yn-1-yloxy)methyl)benzene (219 mg, 1.5 mmol) according to **TP8**. The crude product was purified by flash column chromatography on silica gel with *i*-hexane/ethyl acetate = 10/1 to afford **120g** (280 mg, 1.02 mmol, 68% yield) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.39–7.28 (m, 5H), 6.66 (dt, *J* = 14.5, 5.7 Hz, 1H), 6.41 (dt, *J* = 14.5, 1.5 Hz, 1H), 4.52 (s, 2H), 3.96 (dd, *J* = 5.7, 1.5 Hz, 2H).
^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 142.4, 137.7, 128.5, 127.9, 127.8, 78.9, 72.3, 71.8.
IR (ATR): $\tilde{\nu}$[cm^{-1}] = 3086 (w), 3062 (w), 3030 (w), 2852 (m), 1680 (w), 1614 (m), 1496 (w), 1454 (m), 1404 (w), 1384 (w), 1354 (m), 1310 (w), 1278 (w), 1264 (w), 1242 (w), 1204 (w), 1186 (m), 1098 (vs), 1074 (s), 1028 (m), 1014 (m), 934 (m), 908 (w), 736 (s), 698 (vs), 666 (w).
MS (EI, 70 eV): m/z (%): 168 (6), 147 (7), 105 (6), 92 (31), 91 (100), 77 (7), 65 (7).
HRMS (EI) for $C_{10}H_{11}IO$: calc. [M^+]: 273.9855; found: 273.9849.



A solution of hex-5-yn-1-ol (1.96 g, 20.0 mmol) in DMF (30 mL) was cooled to 0 °C. Imidazole (3.40 g, 50.0 mmol) and *tert*-butyldimethylsilyl chloride (3.62 g, 24.0 mmol) were added to the solution. The mixture was allowed to warm to rt and stirred overnight. After quenching with a sat. aq. solution of NH_4Cl, the suspension was extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with water (1 × 100 mL) and dried over $MgSO_4$. The solvent was removed *in vacuo* and the obtained crude product was purified by short column chromatography *via* a pad of silica gel with *n*-pentane/diethyl ether = 100/1 to afford the alkyne (4.16 g, 19.6 mmol, 98% yield) as a pale yellow oil.

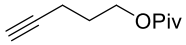
^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 3.63 (t, *J* = 6.1 Hz, 2H), 2.21 (td, *J* = 6.8, 2.6 Hz, 2H), 1.94 (t, *J* = 2.7 Hz, 1H), 1.66–1.55 (m, 4H), 0.89 (s, 9H), 0.05 (s, 6H).
^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 84.7, 68.4, 62.7, 32.0, 26.1, 25.1, 18.5, 18.4, −5.2.
IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 3315 (w), 2953 (m), 2930 (m), 2887 (w), 2858 (m), 1472 (w), 1463 (w), 1435 (vw), 1388 (w), 1361 (w), 1254 (m), 1104 (s), 1006 (w), 974 (w), 939 (vw), 881 (w), 833 (vs), 811 (m), 773 (vs), 711 (w), 661 (w).
MS (70 eV, EI): m/z (%): 155 (4), 79 (7) 77 (4), 76 (6), 75 (100).
HRMS (EI) for $C_{12}H_{24}OSi$: calc. [M^+−*t*-Bu]: 155.0892, found: 155.0885.



120g

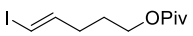
The alkenyl iodide **120g** was prepared from *tert*-butyl(hex-5-yn-1-yloxy)dimethylsilane (1.06 g, 5.0 mmol) according to **TP8**. The crude product was purified by flash column chromatography on silica gel with *i*-hexane/ethyl acetate = 50/1 to afford **120g** (1.23 g, 3.6 mmol, 72% yield) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 6.51 (dt, *J* = 14.3, 7.1 Hz, 1H), 5.98 (dt, *J* = 14.4, 1.4 Hz, 1H), 3.60 (t, *J* = 6.2 Hz, 2H), 2.07 (qd, *J* = 7.2, 1.4 Hz, 2H), 1.54–1.37 (m, 4H), 0.89 (s, 9H), 0.04 (s, 6H).
^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 146.7, 74.7, 62.9, 36.0, 32.2, 26.1, 24.8, 18.5, –5.1.
IR (ATR): $\tilde{\nu}$[cm^{-1}] = 2952 (m), 2928 (s), 2896 (m), 2858 (m), 2358 (w), 1472 (w), 1462 (w), 1388 (w), 1360 (w), 1254 (m), 1216 (w), 1204 (w), 1104 (s), 1006 (w), 978 (w), 940 (w), 836 (vs), 812 (w), 774 (s), 666 (w).
MS (EI, 70 eV): m/z (%): 283 (87), 241 (22), 185 (83), 155 (16), 81 (100), 75 (79), 73 (25).
HRMS (EI) for $C_{12}H_{25}IOSi$: calc. [M^+−Me]: 325.0485; found: 325.0481.



Pivaloyl chloride (4.10 g, 34.0 mmol) was added to 4-pentyn-1-ol (1.68 g, 20.0 mmol, 1.0 equiv) in dichloromethane (65 mL) at 0 °C. Subsequently pyridine (3.39 mL, 42.0 mmol) and DMAP (733 mg, 6.0 mmol) were added. The reaction mixture was allowed to warm to ambient temperature and stirred overnight. After quenching with a sat. aq. solution of NH_4Cl (20 mL) at 0 °C, the suspension was extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with brine (1 × 50 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure. The obtained crude product was purified by flash column chromatography on silica gel with *i*-hexane/ethyl acetate = 20/1 to afford pent-4-yn-1-yl pivalate (2.69 g, 16.0 mmol, 80% yield) as a pale yellow oil.

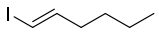
^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 4.15 (t, *J* = 6.2 Hz, 2H), 2.29 (td, *J* = 7.1, 2.7 Hz, 2H), 1.96 (t, *J* = 2.7 Hz, 1H), 1.92–1.80 (m, 2H), 1.20 (s. 9H)
^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 178.6, 83.2, 69.1, 63.0, 38.9, 27.8, 27.3, 15.4.
IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 3297 (vw), 2971 (w), 2936 (w), 2911 (w), 2874 (vw), 1726 (s), 1481 (w), 1462 (w), 1448 (w), 1436 (w), 1399 (w), 1366 (w), 1324 (vw), 1283 (m), 1230 (w), 1150 (vs), 1090 (vw), 1038 (m), 988 (vw), 940 (vw), 912 (vw), 886 (w), 864 (vw), 847 (vw), 772 (w).
MS (70 eV, EI): m/z (%): 111 (22), 103 (20), 66 (17), 57 (53), 41 (100).
HRMS (EI) for $C_{10}H_{16}O_2$: calc. [M^+−Me]: 153.0916, found: 153.0911.



120h

The alkenyl iodide **120h** was prepared from pent-4-yn-1-yl pivalate (841 mg, 5.0 mmol) according to **TP8**. The crude product was purified by flash column chromatography on silica gel with *i*-hexane/ethyl acetate = 20/1 to afford **120h** (918 mg, 3.1 mmol, 62% yield) as a colorless oil.

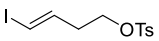
^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 6.51 (dt, J = 14.3, 7.1 Hz, 1H), 6.05 (dt, J = 14.4, 1.5 Hz, 1H), 4.05 (t, J = 6.4 Hz, 2H), 2.14 (qd, J = 7.3, 1.4 Hz, 2H), 1.79–1.67 (m, 2H), 1.19 (s, 9H).
^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 178.7, 145.3, 75.6, 63.4, 38.9, 32.7, 27.5, 27.3.
IR (ATR): $\tilde{\nu}$[cm^{-1}] = 3050 (vw), 2970 (w), 2960 (w), 2936 (w), 2908 (w), 2872 (vw), 1724 (s), 1608 (vw), 1538 (vw), 1480 (m), 1460 (w), 1398 (w), 1366 (w), 1282 (m), 1218 (w), 1148 (vs), 1036 (m), 992 (w), 946 (m), 914 (w), 888 (w), 872 (w), 850 (vw), 770 (w), 718 (vw), 658 (w).
MS (EI, 70 eV): m/z (%): 195 (5), 194 (100), 167 (11), 67 (35), 41 (23).
HRMS (EI) for $C_{10}H_{17}IO_2$: calc. [M^+−OPiv]: 194.9671; found: 194.9666.



120i

The alkenyl iodide **120i** was prepared from hex-1-yne (411 mg, 5 mmol) according to **TP8**. The crude product was purified by flash column chromatography on silica gel with *i*-hexane to afford **120i** (777 mg, 3.7 mmol, 74% yield) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 6.58–6.39 (m, 1H), 5.97 (dt, J = 14.3, 1.4 Hz, 1H), 2.09–1.96 (m, 2H), 1.40–1.30 (m, 4H), 0.92–0.77 (m, 3H).
^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 146.9, 74.4, 35.9, 30.6, 22.1, 14.0.
IR (ATR): $\tilde{\nu}$[cm^{-1}] = 2958 (vs), 2930 (vs), 2872 (m), 2858 (m), 2364 (m), 2340 (m), 1762 (m), 1748 (m), 1738 (m), 1466 (m), 1458 (m), 668 (m), 656 (m).
MS (EI, 70 eV): m/z (%): 210 (77), 168 (25), 167 (58), 154 (100), 127 (40), 83 (16), 41 (22).
HRMS (EI) for $C_6H_{11}I$: calc. [M^+]: 209.9905; found: 209.9900.



120j

The alkenyl iodide **120j** was prepared from but-3-yn-1-yl 4-methylbenzenesulfonate (1.21 g, 5.0 mmol) according to **TP8**. The crude product was purified by flash column chromatography on silica gel with *i*-hexane/ethyl acetate = 5/1 to afford **120j** (916 mg, 2.6 mmol, 52% yield) as a pale yellow oil.

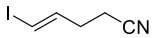
^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.84–7.69 (m, 2H), 7.44–7.28 (m, 2H), 6.34 (dt, *J* = 14.3, 7.1 Hz, 1H), 6.13 (dt, *J* = 14.5, 1.3 Hz, 1H), 4.04 (t, *J* = 6.4 Hz, 2H), 2.46 (s, 3H), 2.39 (qd, *J* = 6.5, 1.3 Hz, 2H).

^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 145.1, 140.1, 133.0, 130.1, 128.1, 78.9, 68.2, 35.4, 21.9.

IR (ATR): $\tilde{\nu}$[cm^{-1}] = 3050 (vw), 2956 (vw), 2918 (w), 2850 (w), 1598 (w), 1494 (vw), 1462 (vw), 1426 (vw), 1400 (vw), 1358 (m), 1306 (vw), 1292 (vw), 1262 (vw), 1232 (w), 1210 (vw), 1176 (vs), 1120 (vw), 1096 (w), 1040 (w), 978 (m), 944 (m), 914 (w), 834 (w), 816 (m), 778 (w), 720 (vw).

MS (EI, 70 eV): m/z (%): 225 (3), 180 (100), 167 (19), 155 (15), 91 (26).

HRMS (EI) for $C_{11}H_{13}IO_3S$: calc. [M^+−I]: 225.0585; found: 225.0578.



120k

The alkenyl iodide **120k** was prepared from pent-4-ynenitrile (396 mg, 5.0 mmol) according to **TP8**. The crude product was purified by flash column chromatography on silica gel with *i*-hexane/ethyl acetate = 5/1 to afford **120k** (652 mg, 3.15 mmol, 63% yield) as a colorless oil.

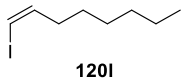
^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 6.60–6.45 (m, 1H), 6.31 (dt, *J* = 14.5, 1.2 Hz, 1H), 2.48–2.35 (m, 4H).

^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 141.5, 118.6, 79.0, 31.8, 16.7.

IR (ATR): $\tilde{\nu}$[cm^{-1}] = 3050 (w), 2924 (w), 2360 (w), 2340 (w), 2246 (w), 1608 (w), 1440 (w), 1424 (m), 1222 (m), 1198 (w), 1154 (m), 988 (w), 974 (w), 938 (vs), 862 (w), 820 (w), 810 (w), 778 (w), 762 (w), 754 (w), 746 (w), 666 (m).

MS (EI, 70 eV): m/z (%): 207 (47), 167 (100), 127 (32), 80 (13).

HRMS (EI) for C_5H_6IN: calc. [M^+]: 206.9545; found: 206.9538.



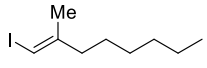
120l

The alkenyl iodide **120l** was prepared from oct-1-yne (1.1 g, 10.0 mmol) according to the literature.[132] The crude product was purified by flash column chromatography on silica gel with *n*-pentane to afford **120l** (1.33 mg, 5.6 mmol, 56% yield) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 6.17 (s, 2H), 2.21–2.06 (m, 2H), 1.37–1.19 (m, 8H), 0.96–0.79 (m, 3H).

The analytical data were in accordance with literature values.[132]

[132] D. Yang, V. A. Cwynar, D. J. Hart, J. Madanmohan, J. Lee, J. Lyons, M. Caffrey, *Organic Synth.* **2012**, *89*, 183–201.



120m

The alkenyl iodide **120m** was prepared from oct-1-yne (1.1 g, 10.0 mmol) according to the literature.[133] The crude product was purified by flash column chromatography on silica gel with *n*-pentane to afford **120m** (1.08 g, 4.3 mmol, 43%) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 5.88–5.76 (m, 1H), 2.27–2.13 (m, 2H), 1.82 (d, J = 1.1 Hz, 3H), 1.50–1.37 (m, 2H), 1.34–1.20 (m, 6H), 0.94–0.82 (m, 3H).

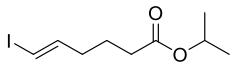
^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 148.5, 74.5, 39.8, 31.7, 28.9, 27.8, 24.0, 22.7, 14.2.

IR (ATR): $\tilde{\nu}$[cm^{-1}] = 2956 (m), 2928 (vs), 2870 (m), 2856 (m), 2362 (w), 2344 (w), 2334 (w), 1466 (w), 1376 (w), 1272 (m), 1142 (m), 908 (w), 766 (w), 734 (m), 668 (w).

MS (EI, 70 eV): m/z (%): 252 (50), 182 (86), 181 (55), 168 (50), 127 (40), 83 (55), 79 (15), 69 (100), 67 (22), 57 (15), 55 (100), 43 (29), 41 (77).

HRMS (EI) for $C_9H_{17}I$: calc. [M^+]: 252.0375; found: 252.0370.

The analytical data were in accordance with literature values.[133]



120n

The alkenyl iodide **120n** was prepared from isopropyl hex-5-ynoate (771 mg, 5 mmol) according to **TP8**. The crude product was purified by flash column chromatography on silica gel with *i*-hexane/ethyl acetate = 20/1 to afford **120n** (1.07 g, 3.8 mmol, 76% yield).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 6.49 (dt, J = 14.4, 7.2 Hz, 1H), 6.03 (dt, J = 14.4, 1.5 Hz, 1H), 5.08–4.89 (m, 1H), 2.27 (t, J = 7.4 Hz, 2H), 2.10 (qd, J = 7.3, 1.4 Hz, 2H), 1.72 (p, J = 7.4 Hz, 2H), 1.23 (d, J = 6.2 Hz, 6H).

^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 172.9, 145.6, 75.6, 67.8, 35.4, 33.8, 23.7, 22.0.

IR (ATR): $\tilde{\nu}$[cm^{-1}] = 3050 (vw), 2978 (w), 2936 (w), 1726 (vs), 1606 (w), 1468 (w), 1454 (w), 1438 (w), 1418 (w), 1374 (m), 1340 (w), 1328 (w), 1312 (w), 1288 (w), 1250 (m), 1226 (m), 1178 (s), 1078 (w), 1036 (vw), 1014 (w), 946 (m), 896 (w), 866 (vw), 822 (w), 790 (vw), 748 (vw), 720 (vw).

MS (EI, 70 eV): m/z (%): 239 (2), 223 (24), 197 (5), 223 (34), 180 (24), 155 (21), 113 (100), 71 (45), 67 (26), 42 (21).

HRMS (EI) for $C_9H_{15}IO_2$: calc. [M^+−*i*-Pr]: 238.9569; found: 238.9563.

[133] M. Davoust, F. Cantagrel, P. Metzner, J.-F. Briere, *Org. Biomol. Chem.* **2008**, *6*, 1981–1993.

120o

A 250 mL flask was charged with a solution of cyclohexanone (1.96 g, 20.0 mmol) and THF (100 mL). Potassiumbis(trimethylsilyl)amide (0.5 M solution in THF, 52 mL, 26 mmol) was added dropwise at –78 °C over a period of 5 min. After 30 min, the resulting reaction mixture was treated with diethyl chlorophosphate (4.34 mL, 30.0 mmol) and stirred for 2 h at –78 C. Subsequently, the reaction mixture was allowed to warm to ambient temperature before it was quenched with a sat. aq. NH_4Cl solution. The aqueous layer was extracted with ethyl acetate (5 × 100 mL). The combined organic phase was washed with brine, dried over $MgSO_4$ and concentrated under vacuum to afford cyclohex-1-en-1-yl diethyl phosphate (4.12 g, 17.6 mmol, 88% yield) which was used without further purification.[134]

A 250 mL flask was charged with crude cyclohex-1-en-1-yl diethyl phosphate (2.34 g, 10.0 mmol) and NaI (4.50 g, 30.0 mmol) in anhydrous dichloromethane (20 mL). TMSCl (3.82 mL, 30.0 mmol) was added dropwise and after stirring for 10 min at rt, the reaction mixture was filtrated. After quenching with a solution of sat. aq. $NaHCO_3$ and a solution of sat. aq. Na_2SO_3 the organic layer was separated. The aqueous phase was extracted with dichloromethane (3 × 50 mL) and the combined organic phases were dried over $MgSO_4$. After removing the solvent, the obtained crude product was purified by flash column chromatography on silica gel with *n*-pentane to afford **120o** (205 mg, 11.5% yield) as a colorless oil.[134]

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 6.34 (tt, J = 4.0, 1.8 Hz, 1H), 2.58–2.42 (m, 2H), 2.15–2.00 (m, 2H), 1.74–1.60 (m, 4H).

^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 137.7, 97.0, 39.5, 29.1, 25.5, 21.0.

IR (ATR): $\tilde{\nu}$[cm^{-1}] = 2926 (vs), 2852 (s), 2368 (m), 2358 (m), 2342 (m), 2332 (m), 1462 (m), 1444 (m), 1262 (m), 1248 (m), 1056 (m), 1026 (m), 990 (m).

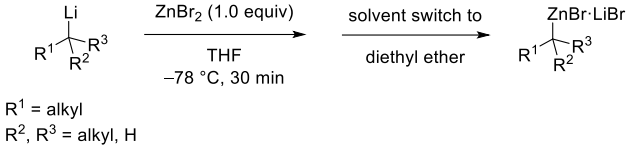
MS (EI, 70 eV): m/z (%): 208 (55), 81 (100), 79 (41).

HRMS (EI) for C_6H_9I: calc. [M^+]: 207.9749; found: 207.9740.

[134] M. Gerelle, A. J. Dalencon, M. C. Willis, *Tetrahedron Lett.* **2012**, *53*, 1954–1957.

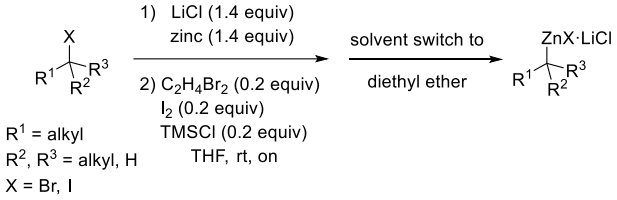
5.3 Preparation of Alkylzinc Reagents for Transmetalation

Typical procedure (transmetalation) for preparation of alkylzinc reagents (TP9)



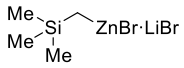
A dry and Ar-flushed *Schlenk*-tube was charged with $ZnBr_2$ (1.0 equiv) and heated at 300 °C under vacuum for 5 min. After addition of THF (30 mL), the flask was cooled to −78 °C. The alkyllithium species (1.0 equiv) was added dropwise to the reaction mixture and the reaction mixture was stirred at −78 °C for 30 min. Solvents were evaporated under argon atmosphere at 0 °C and diethyl ether (5 mL) was added. Solvents were evaporated again and this process was repeated three times. Finally, the residue was dissolved in diethyl ether (20 mL) to obtain the desired ether solution. The concentration was determined by titration of a small aliquot with iodine.[135]

Typical procedure (zinc insertion) for preparation of alkylzinc reagents (TP10)



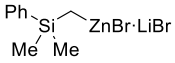
A dry and Ar-flushed *Schlenk*-flask was charged with zinc dust (1.4 equiv) and lithium chloride (1.4 equiv). After drying at 300 °C under vacuum for 5 min the reagents were dissolved in THF (ca. 0.5 M). 1,2-dibromoethane (0.1 mL) was added and the reaction mixture was carefully heated at 40 °C until gas evolution was observed. A piece of iodine and TMSCl (0.1 mL) were added to the reaction mixture and it was again heated to 40 °C. After cooling to rt the alkyl halide was added dropwise and the reaction mixture was stirred at ambient temperature overnight. Solvents were evaporated under argon atmosphere and then diethyl ether (5 mL) was added. Solvents were evaporated again and this process was repeated three times. Finally, the residue was dissolved in diethyl ether (20 mL) leading to the desired ether solution. The concentration was determined by titration of a small aliquot with iodine.[136]

[135] M. Westerhausen, B. Rademacher, W. Schwarz, J. Weidlein, *J. Organomet. Chem.* **1994**, *469*, 135–149.
[136] A. Krasovski, V. Malakhov, A. Gavryushin, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 6040–6044.



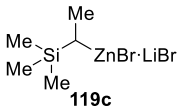
119a

The zinc reagent **119a** (0.71-0.95 M in diethyl ether) was prepared according to literature.[49] The concentration was determined by titration of a small aliquot with iodine.



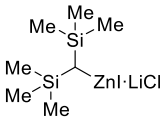
119b

The zinc reagent **119b** (0.52 M in diethyl ether) was prepared according to **TP9** starting from the freshly prepared alkyllithium reagent.[137] The concentration was determined by titration of a small aliquot with iodine.



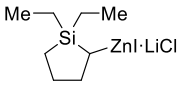
119c

The zinc reagent **119c** (0.68 M in diethyl ether) was prepared according to **TP9** starting from the freshly prepared alkyllithium reagent.[137] The concentration was determined by titration of a small aliquot with iodine.



119d

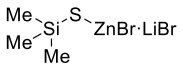
The zinc reagent **119d** (0.38 M in diethyl ether) was prepared according to **TP10** starting from the corresponding alkyl iodide. The concentration was determined by titration of a small aliquot with iodine.



119e

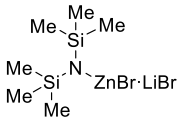
The zinc reagent **119d** (0.31 M in diethyl ether) was prepared according to **TP10** starting from the corresponding alkyl iodide.[138] The concentration was determined by titration of a small aliquot with iodine.

[137] C. Lutz, P. Jones, P. Knochel, *Synthesis* **1999**, *2*, 312–316.
[138] Joseph *et al.* U.S. Patent US 2017/0288157 A1.



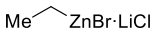
119f

The zinc reagent **119f** (0.56 M in diethyl ether) was prepared according to **TP9** starting from the freshly prepared alkyllithium reagent.[139] The concentration was determined by titration of a small aliquot with iodine.



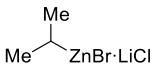
119g

The zinc reagent **119g** (0.70 M in diethyl ether) was prepared according to **TP9** starting from the freshly prepared alkyllithium reagent.[140] The concentration was determined by titration of a small aliquot with iodine.



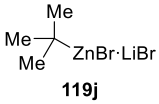
119h

The zinc reagent **119h** (0.46 M in diethyl ether) was prepared according to **TP10** starting from the corresponding alkyl bromide. The concentration was determined by titration of a small aliquot with iodine.



119i

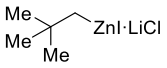
The zinc reagent **119i** (0.68 M in diethyl ether) was prepared according to **TP10** starting from the corresponding alkyl bromide. The concentration was determined by titration of a small aliquot with iodine.



119j

The zinc reagent **119j** (0.82 M in diethyl ether) was prepared according to **TP9** starting from *t*-BuLi. The concentration was determined by titration of a small aliquot with iodine.

[139] D. Taher, A. I. Wallbank, E. A. Turner, H. L. Cuthbert, J. F. Corrigan, *Eur. J. Inorg. Chem.*, **2006**, 4616–4620.
[140] D. R. Armstrong, E. Herd, D. V. Graham, E. Hevia, A. R. Kennedy, W. Clegg, L. Russo, *Dalton Trans.* **2008**, 1323–1330.

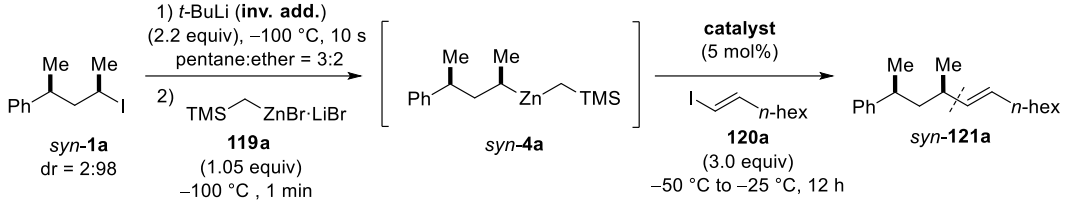


119k

The zinc reagent **119k** (0.92 M in diethyl ether) was prepared according to **TP10** starting from the corresponding alkyl iodide.[137] The concentration was determined by titration of a small aliquot with iodine.

5.4 Optimization of Reaction Conditions

Table 17: Optimization reactions: Variation of the catalyst.

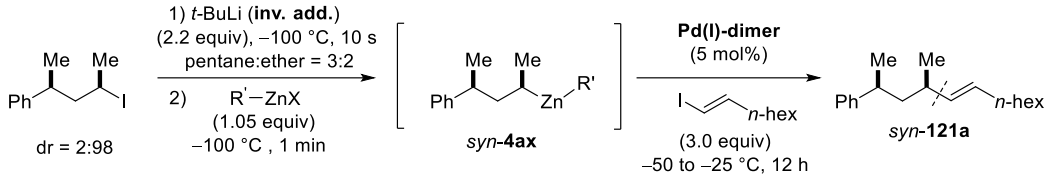


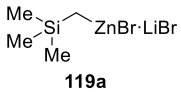
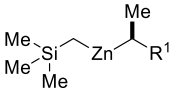
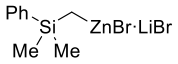
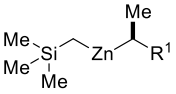
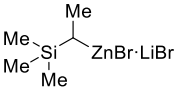
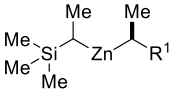
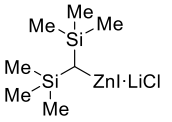
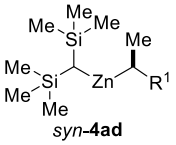
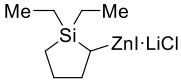
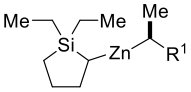
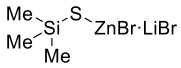
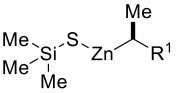
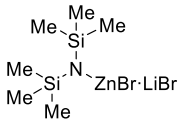
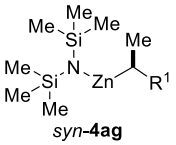
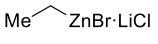
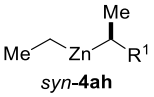
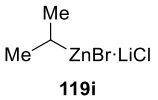
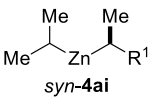
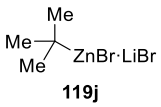
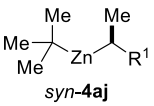
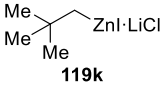
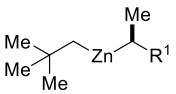
entry	catalyst	yield of *syn*-**121a**[a]	dr of *syn*-**121a**[a]	branched/linear
1	$Pd(PPh_3)_4$	39%	11:89	10:1
2	$Pd(OAc)_2$/CPhos[115]	51%	8:92	1.5:1
3	Pd-PEPPSI-iPent[116]	60%	4:96	25:1
4	Pd-PEPPSI-iPr	23%	9:91	2:1
5	$Pd_2I_2(Pt\text{-}Bu_3)_2$[117]	58%	2:98	25:1
6	$PdCl_2(Amphos)_2$[141]	0%	-	-
7	$NiCl_2(Pt\text{-}Bu_3)_2$	0%	-	-
6	$Ni(acac)_2$	0%	-	-
7	$NiCl_2(dppp)$	0%	-	-
8	$NiCl_2$/bipy[142]	0%	-	-

[a] The yield and diastereoselectivity (dr; *anti*/*syn* ratio) was determined by GC-analysis using dodecane as internal standard.

[141] A. Krasovskiy, B. H. Lipshutz, *Org. Lett.* **2011**, *13*, 3822–3825.
[142] A. Joshi-Pangu, M. Ganesh, M. R. Biscoe, *Org. Lett.* **2011**, *13*, 1218–1221.

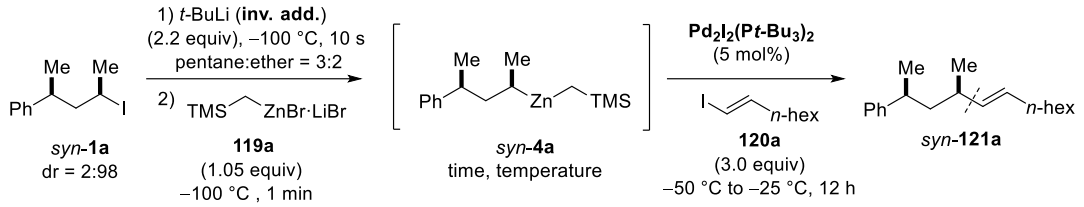
Table 18: Optimization reactions: Variation of the zinc reagent.



entry	zinc reagent	alkylzinc reagent	yield, dr of *syn*-**121a**[a]
1	 **119a**	 *syn*-**4a**	65% yield, dr = 2:98
2	 **119b**	 *syn*-**4a**	59% yield, dr = 25:75
3	 **119c**	 *syn*-**4ac**	63% yield, dr = 20:80
4	 **119d**	 *syn*-**4ad**	55% yield, dr = 50:50
5	 **119e**	 *syn*-**4ae**	41% yield, dr = 40:60
6	 **119f**	 *syn*-**4af**	10% yield, dr = 50:50
7	 **119g**	 *syn*-**4ag**	21% yield, dr = 31:69
8	 **119h**	 *syn*-**4ah**	62% yield, dr = 10:90
9	 **119i**	 *syn*-**4ai**	31% yield, dr = 12:88
10	 **119j**	 *syn*-**4aj**	44% yield, dr = 9:91
11	 **119k**	 *syn*-**4ak**	62% yield, dr = 15:85

[a] The yield and diastereoselectivity (dr; *anti*/*syn* ratio) was determined by GC analysis using dodecane as internal standard.

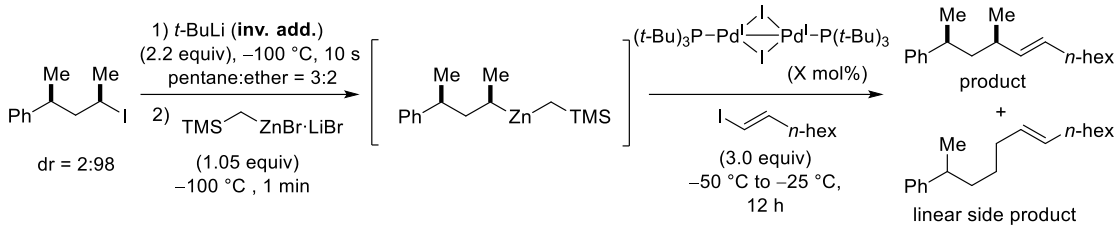
Table 19: Optimization reactions: Stability of the zinc reagent.



entry	temperature	time	yield of *syn*-**121a**[a]	dr of *syn*-**121a** [a],[b]
1	–50 °C	10 min	61%	3:97
2	–30 °C	10 min	58%	3:97
3	–10 °C	10 min	50%	3:97
4	25 °C	60 min	51%	4:96
5	25 °C	240 min	53%	11:89

[a] determined by capillary GC with dodecane as internal standard. [b] The branched/linear ratio was determined to be higher than 25:1.

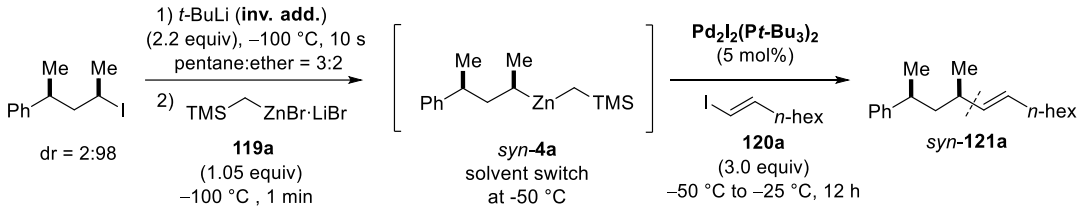
Table 20: Optimization reactions: Variation of the catalyst loading.



entry	catalyst loading	time	yield of *syn*-**121a**[a]	dr of *syn*-**121a** [a]	branched/linear
1	1 mol%	5 min	35%	2:98	-
2	1 mol%	60 min	52%	2:98	-
3	1 mol%	12 h	54%	3:97	4:1
4	5 mol%	5 min	37%	2:98	-
5	5 mol%	60 min	54%	2:98	-
6	5 mol%	12 h	58%	2:98	25:1
7	10 mol%	5 min	40%	2:98	-
8	10 mol%	60 min	54%	2:98	-
9	10 mol%	12 h	59%	4:96	30:1

[a] The yield and diastereoselectivity (dr; *anti*/*syn* ratio) was determined by GC-analysis using dodecane as internal standard.

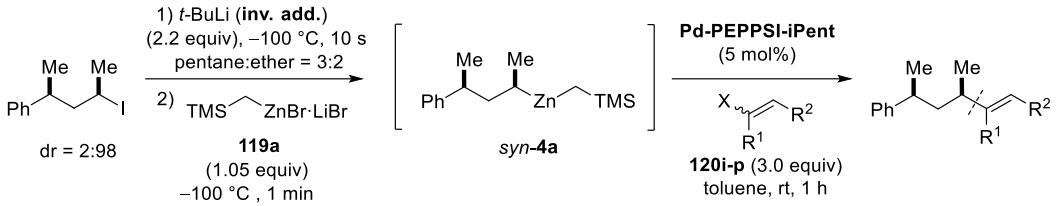
Table 21: Optimization reactions: Variation of the solvent.

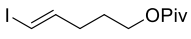
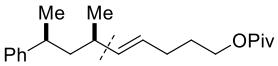
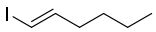
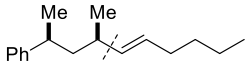
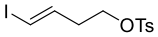
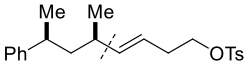
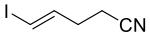
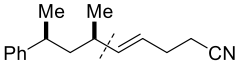
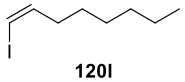
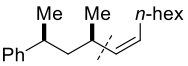
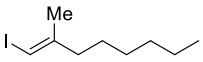
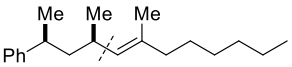
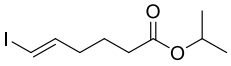
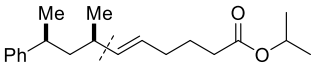
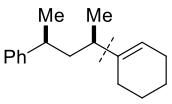
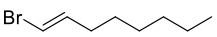
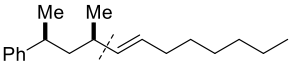


entry	solvent	time	yield of *syn*-**121a**[a]	dr of *syn*-**121a**[a],[b]
1	THF	5 min	43%	2:98
2	THF	60 min	58%	2:98
3	THF	3 h	58%	2:98
4	THF	12 h	58%	2:98
5	toluene	5 min	40%	3:97
6	toluene	60 min	63%	5:95
7	toluene	3 h	63%	5:95
8	toluene	12 h	63%	5:95

[a] The yield and diastereoselectivity (dr; *anti*/*syn* ratio) was determined by GC-analysis using dodecane as internal standard. [b] The branched/linear ratio was determined to be higher than 25:1.

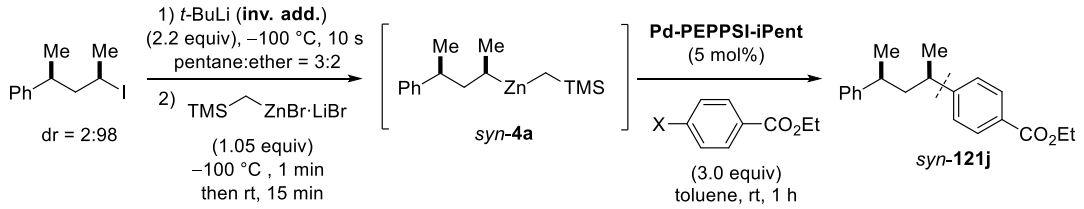
Table 22. Optimization reactions: Alkenyl halides.



entry	zinc reagent	electrophile	yield, dr of products [a]
1	*syn*-**4a**	 **120h**	 46% yield, dr = 10:90
2	*syn*-**4a**	 **120i**	 3% yield, dr = -
3	*syn*-**4a**	 **120j**	 54% yield, dr = 8:92
4	*syn*-**4a**	 **120k**	 17% yield, dr = 6:94
5	*syn*-**4a**	 **120l**	 15% yield, dr = 10:90
6	*syn*-**4a**	 **120m**	 18% yield, dr = 11:89
7	*syn*-**4a**	 **120n**	 40% yield, dr = 20:80
8	*syn*-**4a**	 **120o**	 11% yield, dr = 13:87
9	*syn*-**4a**	 **120p**	 23% yield, dr = 6:94

[a] The yield and diastereoselectivity (dr; *anti*/*syn* ratio) was determined by GC analysis using dodecane as internal standard.

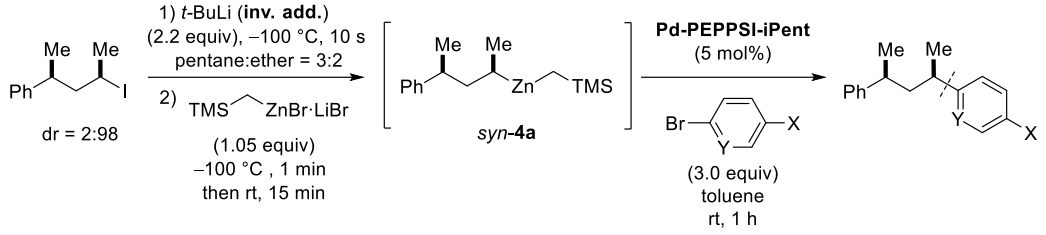
Table 23. Optimization reactions: Variation of the leaving group.

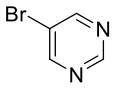
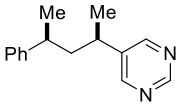
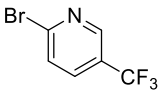
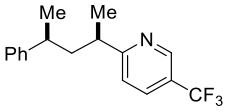
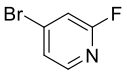
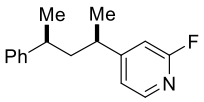
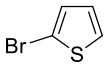
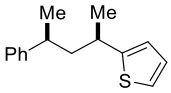
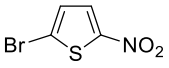
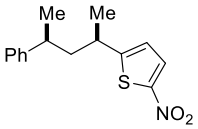
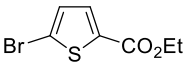
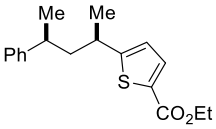
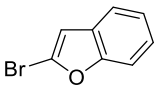
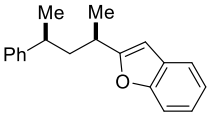
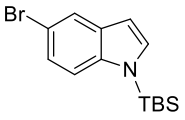
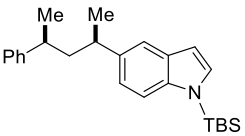
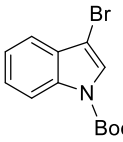
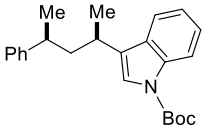


entry	X =	time	yield of *syn*-**121j**[a]	dr of *syn*-**121j**[a]
1	Cl	5 min	3%	-
2	Cl	30 min	17%	5:95
3	Cl	60 min	26%	6:94
4	Cl	12 h	34%	6:94
5	Br	5 min	12%	5:95
6	Br	30 min	34%	5:95
7	Br	60 min	40%	5:95
8	Br	12 h	48%	6:94
9	I	5 min	25%	5:95
10	I	30 min	25%	5:95
11	I	60 min	28%	9:91
12	I	12 h	29%	9:91
13	OTf	5 min	15%	6:94
14	OTf	30 min	17%	6:94
15	OTf	60 min	20%	8:92
16	OTf	12 h	24%	8:92
17	ONf	5 min	25%	6:94
18	ONf	30 min	27%	6:94
19	ONf	60 min	29%	6:94
20	ONf	12 h	29%	6:94

[a] The yield and diastereoselectivity (dr; *anti*/*syn* ratio) was determined by GC-analysis using dodecane as internal standard.

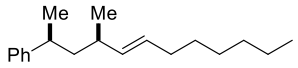
Table 24. Optimization reactions: Variation of the heteroaryl halides.



entry	electrophile	product	yield, dr of product[a]
1			0% yield, -
2			36% yield, dr = 20:80
3			0% yield, -
4			12% yield, dr = 9:91
5			traces
9			27% yield, dr = 26:74
10			traces
11			11% yield, -
12			0% yield

[a] The yield and diastereoselectivity (dr; *anti*/*syn* ratio) was determined by GC analysis using dodecane as internal standard.

5.5 Preparation of α-Chiral Alkenes and Arenes



syn-**121a**

The (*E*)-alkene *syn*-**121a** was prepared according to **TP7** from the iodide *syn*-**1a** (dr = 2:98, 0.10 mmol, 27.4 mg) and the alkenyl iodide **120a** (0.30 mmol, 71.4 mg). The crude product was purified by flash column chromatography on silica gel with *n*-pentane to afford *syn*-**121a** (0.043 mmol, 11.1 mg, 43% yield, dr = 2:98) as a colorless oil.

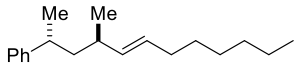
^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.32–7.26 (m, 2H), 7.21–7.14 (m, 3H), 5.35 (dt, *J* = 15.2, 6.6 Hz, 1H), 5.22 (ddt, *J* = 15.2, 7.8, 1.3 Hz, 1H), 2.74 (h, *J* = 7.0 Hz, 1H), 2.10–1.93 (m, 3H), 1.63–1.51 (m, 1H), 1.48–1.39 (m, 1H), 1.37–1.23 (m, 8H), 1.20 (d, *J* = 6.9 Hz, 3H), 0.95 (d, *J* = 6.7 Hz, 3H), 0.91–0.85 (m, 3H).

^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 148.4 136.2, 128.9, 128.4, 127.1, 125.8, 46.1, 37.4, 34.6, 32.7, 31.9, 29.8, 29.0, 22.8, 22.1, 21.2, 14.3.

IR (ATR): $\tilde{\nu}$[cm^{-1}] = 3027 (w), 2960 (m), 2925 (m), 2869 (w), 2856 (w), 2362 (vs), 2342 (s), 2220 (w), 2186 (w), 1494 (w), 1456 (w), 970 (w), 698 (m), 668 (w).

MS (EI, 70 eV): m/z (%): 145 (30), 118 (100), 117 (18), 106 (19), 105 (93), 91 (38), 79 (11).

HRMS (EI) for $C_{19}H_{30}$: calc. [M^+]: 258.2348; found: 258.2344.



anti-**121a**

The (*E*)-alkene *anti*-**121a** was prepared according to **TP7** from the iodide *anti*-**1a** (dr = 98:2, 0.10 mmol, 27.4 mg) and the alkenyl iodide **120a** (0.30 mmol, 71.4 mg). The crude product was purified by flash column chromatography on silica gel with *n*-pentane to afford *anti*-**121a** (0.039 mmol, 10.1 mg, 39% yield, dr = 95:5) as a colorless oil.

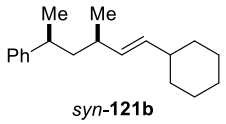
^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.31–7.25 (m, 2H), 7.20–7.12 (m, 3H), 5.37–4.98 (m, 2H), 2.82–2.70 (m, 1H), 2.01–1.94 (m, 2H), 1.92–1.84 (m, 1H), 1.61–1.53 (m, 1H), 1.49–1.41 (m, 1H), 1.40–1.23 (m, 8H), 1.20 (d, *J* = 7.0 Hz, 3H), 0.92–0.86 (m, 6H).

^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 147.8, 136.1, 129.5, 128.4, 127.4, 125.9, 46.1, 37.8, 34.8, 32.8, 31.9, 29.9, 29.0, 23.4, 22.8, 21.9, 14.3.

IR (ATR): $\tilde{\nu}$[cm^{-1}] = 2956 (m), 2924 (vs), 2854 (m), 2360 (w), 2342 (w), 1740 (w), 1494 (w), 1454 (w), 1376 (w), 1242 (w), 1020 (w), 970 (w), 762 (w), 700 (w).

MS (EI, 70 eV): m/z (%): 145 (28), 118 (100), 117 (16), 106 (19), 105 (90), 91 (37), 79 (11).

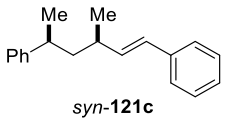
HRMS (EI) for $C_{19}H_{30}$: calc. [M^+]: 258.2348; found: 258.2344.



syn-**121b**

The (*E*)-alkene *syn*-**121b** was prepared according to **TP7** from the iodide *syn*-**1a** (dr = 2:98, 0.10 mmol, 27.4 mg) and the alkenyl iodide **120b** (0.30 mmol, 70.8 mg). The crude product was purified by flash column chromatography on silica gel with *n*-pentane to afford *syn*-**121b** (0.045 mmol, 11.5 mg, 45% yield, dr = 6:94) as a colorless oil.

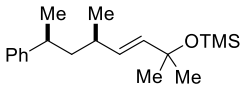
^{1}H-NMR($CDCl_3$, 400 MHz): δ [ppm] = 7.31–7.26 (m, 2H), 7.20–7.13 (m, 3H), 5.35–5.25 (m, 1H), 5.17 (ddd, *J* = 15.5, 7.7, 1.1 Hz, 1H), 2.74 (h, *J* = 7.0 Hz, 1H), 2.08–1.96 (m, 1H), 1.94–1.80 (m, 1H), 1.74–1.64 (m, 4H), 1.43 (ddd, *J* = 13.5, 8.1, 6.6 Hz, 1H), 1.32–1.22 (m, 2H), 1.20 (d, *J* = 6.9 Hz, 4H), 1.17–0.98 (m, 3H), 0.94 (d, *J* = 6.7 Hz, 3H).
^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 148.4, 135.0, 133.6, 128.4, 127.1, 125.8, 46.1, 40.8, 37.3, 34.6, 33.5, 33.4, 26.4, 26.3, 26.3, 22.0, 21.2.
IR (ATR): $\tilde{\nu}$[cm^{-1}] = 3026 (w), 2958 (m), 2922 (vs), 2850 (m), 2360 (w), 2342 (w), 1494 (w), 1450 (m), 1376 (w), 970 (m), 760 (w), 698 (s).
MS (EI, 70 eV): m/z (%): 145 (21), 118 (70), 117 (14), 105 (100), 91 (39), 79 (25), 77 (14).
HRMS (EI) for $C_{19}H_{28}$: calc. [M^+]: 256.2191; found: 256.2184.



syn-**121c**

The (*E*)-styrene *syn*-**121c** was prepared according to **TP7** from the iodide *syn*-**1a** (dr = 2:98, 0.10 mmol, 27.4 mg) and the alkenyl iodide **120c** (0.30 mmol, 69.0 mg). The crude product was purified by flash column chromatography on silica gel with *n*-pentane to afford *syn*-**121c** (0.052 mmol, 13.0 mg, 52% yield, dr = 2:98) as a colorless oil.

^{1}H-NMR($CDCl_3$, 400 MHz): δ [ppm] = 7.36–7.27 (m, 6H), 7.22–7.16 (m, 4H), 6.33 (d, *J* = 15.9 Hz, 1H), 6.07 (dd, *J* = 15.9, 8.1 Hz, 1H), 2.80 (h, *J* = 7.1 Hz, 1H), 2.27 (hept, 1H), 1.79–1.69 (m, 1H), 1.64–1.55 (m, 1H), 1.26 (d, *J* = 6.9 Hz, 3H), 1.08 (d, *J* = 6.7 Hz, 3H).
^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 148.0, 138.0, 136.8, 128.6, 128.5, 128.2, 127.1, 127.0, 126.1, 126.0, 45.8, 37.5, 35.2, 22.4, 20.8.
IR (ATR): $\tilde{\nu}$[cm^{-1}] = 3062 (w), 3026 (m), 2960 (s), 2924 (s), 2870 (m), 2362 (m), 2338 (w), 1602 (w), 1494 (m), 1452 (m), 1376 (w), 968 (m), 762 (m), 748 (s), 700 (vs).
MS (EI, 70 eV): 145 (100), 131 (71), 129 (28), 117 (40), 115 (24), 105 (63), 91 (61).
HRMS (EI) for $C_{19}H_{22}$: calc. [M^+]: 250.1717; found: 250.1722.



syn-**121d**

The (*E*)-silyl ether *syn*-**121d** was prepared according to **TP7** from the iodide *syn*-**1a** (dr = 2:98, 0.10 mmol, 27.4 mg) and the alkenyl iodide **120d** (0.30 mmol, 85.3 mg). The crude product was purified by flash column chromatography on silica gel with *n*-pentane to afford *syn*-**121d** (0.039 mmol, 11.9 mg, 39% yield, dr = 6:94) as a colorless oil.

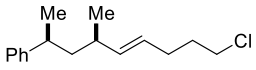
^{1}H-NMR($CDCl_3$, 400 MHz): δ [ppm] = 7.30–7.27 (m, 2H), 7.19–7.16 (m, 3H), 5.50 (dd, *J* = 15.7, 1.0 Hz, 1H), 5.35 (dd, *J* = 15.6, 7.7 Hz, 1H), 2.75 (h, *J* = 7.2 Hz, 1H), 2.05 (hept, *J* = 7.1 Hz, 1H), 1.67–1.56 (m, 1H), 1.53–1.41 (m, 1H), 1.28 (s, 6H), 1.22 (d, *J* = 7.0 Hz, 3H), 0.97 (d, *J* = 6.7 Hz, 3H), 0.10 (s, 9H).

^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 148.0, 141.7, 137.0, 132.6, 128.5, 127.1, 126.0, 73.5, 45.7, 37.4, 34.1, 31.0, 30.7, 22.5, 20.6, 2.8.

IR (ATR): $\tilde{\nu}$[cm^{-1}] = 3027 (w), 2962 (s), 2927 (m), 2871 (w), 2359 (w), 2334 (w), 1494 (w), 1454 (w), 1378 (w), 1361 (w), 1258 (m), 1249 (s), 1155 (m), 1038 (s), 997 (w), 972 (w), 862 (m), 839 (vs), 808 (w), 759 (m), 700 (m).

MS (EI, 70 eV): m/z (%): 72 (20), 59 (14), 57 (27), 43 (100), 42 (53), 41 (45).

HRMS (EI) for $C_{18}H_{29}OSi$: calc. [M^+−Me]: 289.1988; found: 289.1980.



syn-**121e**

The (*E*)-alkenyl chloride *syn*-**121e** was prepared according to **TP7** from the iodide *syn*-**1a** (dr = 2:98, 0.10 mmol, 27.4 mg) and the alkenyl iodide **120e** (0.30 mmol, 69.1 mg). The crude product was purified by flash column chromatography on silica gel with *n*-pentane to afford *syn*-**121e** (0.044 mmol, 11.0 mg, 44% yield, dr = 2:98) as a colorless oil.

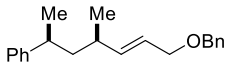
^{1}H-NMR($CDCl_3$, 400 MHz): δ [ppm] = 7.32–7.26 (m, 2H), 7.23–7.11 (m, 3H), 5.39–5.15 (m, 2H), 3.65–3.46 (m, 2H), 2.73 (q, *J* = 7.1 Hz, 1H), 2.19–2.09 (m, 2H), 2.07–1.98 (m, 1H), 1.87–1.73 (m, 2H), 1.65–1.52 (m, 1H), 1.51–1.40 (m, 1H), 1.21 (d, *J* = 6.9 Hz, 3H), 0.95 (d, *J* = 6.6 Hz, 3H).

^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 148.1, 138.0, 128.5, 127.1, 126.5, 125.9, 45.9, 44.6, 37.5, 34.6, 32.5, 29.7, 22.2, 21.0.

IR (ATR): $\tilde{\nu}$[cm^{-1}] = 3062 (w), 3027 (w), 2958 (vs), 2925 (vs), 2869 (m), 2854 (m), 2361 (w), 2334 (w), 1494 (w), 1453 (m), 1377 (w), 1291 (w), 971 (m), 762 (m), 700 (s**).**

MS (EI, 70 eV): m/z (%): 145 (30), 118 (73), 117 (16), 106 (25), 105 (100), 91 (52), 79 (11).

HRMS (EI) for $C_{16}H_{23}Cl$: calc. [M^+]: 250.1488; found: 250.1483.



syn-**121f**

The (*E*)-alkene *syn*-**121f** was prepared according to **TP7** from the iodide *syn*-**1a** (dr = 2:98, 0.10 mmol, 27.4 mg) and the alkenyl iodide **120f** (0.30 mmol, 82.2 mg). The crude product was extracted and purified by flash column chromatography. After prep-HPLC purification ($MeCN/H_2O$), the compound *syn*-**121f** (0.043 mmol, 12.7 mg, 43% yield, dr = 4:96) was obtained as a colorless oil.

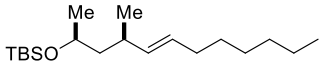
^{1}H-NMR($CDCl_3$, 400 MHz): δ [ppm] = 7.37–7.27 (m, 6H), 7.21–7.08 (m, 3H), 5.62–5.40 (m, 2H), 4.50 (s, 2H), 3.96 (d, *J* = 4.9 Hz, 2H), 2.76 (h, *J* = 7.1 Hz, 1H), 2.10 (hept, *J* = 6.7 Hz, 1H), 1.69–1.60 (m, 1H), 1.53–1.40 (m, 1H), 1.22 (d, *J* = 6.9 Hz, 3H), 0.99 (d, *J* = 6.7 Hz, 3H).

^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 147.8, 140.6, 138.6, 128.5, 128.5, 127.7, 127.1, 126.0, 124.6, 71.9, 71.1, 45.4, 37.4, 34.3, 22.5, 20.4.

IR (ATR): $\tilde{\nu}$[cm^{-1}] = 3085 (w), 3063 (w), 3028 (w), 2957 (s), 2922 (vs), 2851 (s), 2362 (w), 1738 (w), 1495 (w), 1454 (m), 1377 (w), 1362 (w), 1248 (w), 1205 (w), 1128 (w), 1099 (m), 1074 (m), 1028 (w), 1010 (w), 998 (w), 972 (m), 762 (m), 735 (m), 699 (vs).

MS (EI, 70 eV): m/z (%): 188 (16), 185 (11), 159 (21), 129 (11), 118 (22), 105 (100), 91 (95), 79 (10), 77 (11).

HRMS (EI) for $C_{21}H_{26}O$: calc. [M^+]: 294.1984; found: 294.1994.



syn-**121g**

The (*E*)-alkene *syn*-**121g** was prepared according to **TP7** from the iodide *rac*-**1j** (dr = 50:50, 0.10 mmol, 32.8 mg) and the alkenyl iodide **120a** (0.30 mmol, 71.4 mg). Thereby, the secondary alkyllithium reagent was prepared according to literature.[53] The crude product was purified by flash column chromatography on silica gel with *n*-pentane to afford *syn*-**121g** (0.043 mmol, 13.4 mg, 43% yield, dr = 7:93) as a colorless oil.

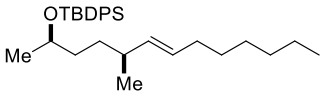
^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 5.40–5.32 (m, 1H), 5.26–5.17 (m, 1H), 3.84–3.73 (m, 1H), 2.24 (hept, *J* = 14.2, 7.0 Hz, 1H), 2.02–1.91 (m, 2H), 1.46–1.37 (m, 1H), 1.35–1.20 (m, 12H), 1.10 (d, *J* = 6.0 Hz, 3H), 0.94 (d, *J* = 6.8 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 6H).

^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 136.3, 129.1, 67.0, 47.7, 33.5, 32.8, 31.9, 29.8, 29.0, 26.1, 24.6, 22.8, 22.0, 18.3, 14.3, -3.9, -4.4.

IR (ATR): $\tilde{\nu}$[cm^{-1}] = 2958 (s), 2926 (vs), 2856 (m), 1462 (w), 1374 (w), 1364 (w), 1254 (w), 1142 (w), 1096 (w), 1054 (w), 1006 (w), 970 (w), 836 (m), 806 (w), 774 (m).

MS (EI, 70 eV): m/z (%): 255 (91), 211 (41), 169 (39), 115 (33), 103 (62), 95 (29), 75 (100).

HRMS (EI) for $C_{19}H_{40}OSi$: calc. [M^+−*t*-Bu]: 255.2144; found: 255.2138.



syn-**121h**

The (*E*)-alkene *syn*-**121h** was prepared according to **TP7** from the iodide *syn*-**1c** (dr = 1:99, 0.10 mmol, 46.6 mg) and the alkenyl iodide **120a** (0.30 mmol, 71.4 mg). The crude product was purified by flash column chromatography on silica gel with *n*-pentane to afford *syn*-**121h** (0.046 mmol, 20.7 mg, 46% yield, dr = 4:96) as a colorless oil.

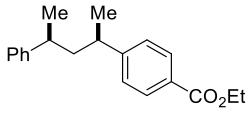
^{1}H-NMR($CDCl_3$, 400 MHz): δ [ppm] = 7.70–7.65 (m, 4H), 7.43–7.33 (m, 6H), 5.33–5.23 (m, 1H), 5.21–5.13 (m, 1H), 3.81 (h, *J* = 5.9 Hz, 1H), 2.01–1.85 (m, 3H), 1.48–1.34 (m, 2H), 1.34–1.13 (m, 12H), 1.08–1.02 (m, 12H), 0.91–0.83 (m, 6H).

^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 136.3, 136.1, 136.0, 135.2, 134.8, 129.5, 129.5, 128.8, 127.6, 127.5, 70.0, 37.3, 36.9, 32.8, 32.7, 31.9, 29.8, 29.0, 27.2, 23.4, 22.8, 21.1, 19.4, 14.3.

IR (ATR): $\tilde{\nu}$[cm^{-1}] = 3072 (w), 3050 (w), 2958 (m), 2928 (s), 2856 (m), 1472 (w), 1462 (w), 1428 (m), 1390 (w), 1378 (w), 1362 (w), 1130 (m), 1110 (s), 1066 (m), 1030 (w), 998 (w), 968 (m), 822 (w), 740 (m), 702 (vs), 688 (w).

MS (EI, 70 eV): m/z (%): 394 (13), 393 (46), 200 (14), 199 (100).

HRMS (EI) for $C_{30}H_{46}OSi$: calc. [M^+−H]: 449.3240; found: 449.3225.



syn-**121i**

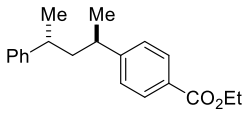
The ethyl benzoate derivative *syn*-**121i** was prepared according to **TP7** from the iodide *syn*-**1a** (dr = 2:98, 0.10 mmol, 27.4 mg) and ethyl 4-bromobenzoate **124a** (0.30 mmol, 68.7 mg). The crude product was extracted and purified by flash column chromatography. After prep-HPLC purification ($MeCN/H_2O$), the compound *syn*-**121i** (0.046 mmol, 13.6 mg, 46% yield, dr = 6:94) was obtained as a colorless oil.

^{1}H-NMR($CDCl_3$, 400 MHz): δ [ppm] = 7.98–7.94 (m, 2H), 7.32–7.26 (m, 2H), 7.23–7.18 (m, 3H), 7.16–7.07 (m, 2H), 4.37 (q, *J* = 7.1 Hz, 2H), 2.70 (h, *J* = 7.2 Hz, 1H), 2.61 (h, *J* = 7.1 Hz, 1H), 1.94 (dt, *J* = 13.7, 7.5 Hz, 1H), 1.78 (dt, *J* = 13.7, 7.6 Hz, 1H), 1.39 (t, *J* = 7.1 Hz, 3H), 1.25 (d, *J* = 3.8 Hz, 3H), 1.23 (d, *J* = 3.8 Hz, 3H).

^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 166.8, 153.2, 147.5, 129.9, 128.6, 128.4, 127.1, 127.0, 126.1, 60.9, 46.9, 37.7, 37.5, 22.3, 22.0, 14.5.

IR (ATR): $\tilde{\nu}$[cm^{-1}] = 2961 (w), 2926 (w), 2871 (w), 2362 (w), 2334 (w), 1717 (s), 1610 (w), 1494 (w), 1453 (w), 1418 (w), 1377 (w), 1367 (w), 1310 (w), 1275 (vs), 1179 (w), 1108 (m), 1021 (w), 853 (w), 775 (w), 763 (w), 701 (m).

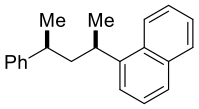
MS (EI, 70 eV): m/z (%): 251 (10), 250 (43), 207 (8), 164 (16), 105 (100), 91 (14).
HRMS (EI) for $C_{20}H_{24}O_2$: calc. [M^+]: 296.1776; found: 296.1768.



anti-**121i**

The ethyl benzoate derivative *anti*-**121i** was prepared according to **TP7** from the iodide *anti*-**1a** (dr = 98:2, 0.10 mmol, 27.4 mg) and ethyl 4-bromobenzoate **124a** (0.30 mmol, 68.7 mg). The crude product was extracted and purified by flash column chromatography. After prep-HPLC purification (MeCN/H_2O), the compound *anti*-**121i** (0.041 mmol, 12.2 mg, 41% yield, dr = 91:9) was obtained as a colorless oil.

^{1}H-NMR($CDCl_3$, 400 MHz): δ [ppm] = 8.00–7.93 (mj, 2H), 7.32–7.27 (m, 2H), 7.23–7.14 (m, 3H), 7.10–7.02 (m, 2H), 4.38 (q, *J* = 7.1 Hz, 1H), 2.59–2.49 (m, 1H), 2.49–2.37 (m, 1H), 1.96–1.80 (m, 1H), 1.40 (t, *J* = 7.1 Hz, 3H), 1.17 (dd, *J* = 6.9, 4.2 Hz, 6H).
^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 166.9, 152.9, 147.1, 129.9, 128.6, 128.5, 127.4, 127.3, 126.2, 60.9, 46.6, 38.0, 37.9, 23.5, 23.3, 14.5.
IR (ATR): $\tilde{\nu}$[cm^{-1}] = 3028 (vw), 2960 (w), 2926 (w), 2870 (w), 1718 (s), 1610 (w), 1494 (w), 1454 (w), 1418 (w), 1366 (w), 1310 (w), 1274 (vs), 1180 (w), 1106 (m), 1022 (w), 856 (w), 776 (w), 764 (w), 702 (m).
MS (EI, 70 eV): m/z (%): 251 (13), 191 (65), 178 (58), 177 (20), 163 (33), 149 (20), 131 (13), 119 (11), 106 (20), 105 (100), 91 (51).
HRMS (EI) for $C_{20}H_{24}O_2$: calc. [M^+]: 296.1776; found: 296.1768.



syn-**121j**

The naphthalene derivative *syn*-**121j** was prepared according to **TP7** from the iodide *syn*-**1a** (dr = 2:98, 0.10 mmol, 27.4 mg) and 1-bromonaphthalene **124b** (0.30 mmol, 62.1 mg). The crude product was purified by flash column chromatography on silica gel with *n*-pentane to afford *syn*-**121j** (0.056 mmol, 15.4 mg, 56% yield, dr = 6:94) as a colorless oil.

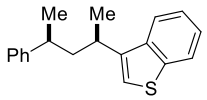
^{1}H-NMR($CDCl_3$, 400 MHz): δ [ppm] = 7.83–7.68 (m, 1H), 7.67–7.48 (m, 2H), 7.42–7.25 (m, 6H), 7.21–7.14 (m, 3H), 3.36–3.25 (m, 1H), 2.78 (qd, *J* = 6.5, 2.5 Hz, 1H), 2.02 (ddd, *J* = 14.2, 9.2, 5.4 Hz, 1H), 1.74 (ddd, 1H), 1.31 (d, *J* = 6.8 Hz, 3H), 1.17–1.10 (m, 3H).

$^{13}C\{^{1}H\}$-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 147.3, 144.1, 134.0, 131.5, 129.0, 128.6, 127.3, 126.4, 126.3, 125.7, 125.3, 123.2, 122.6, 47.2, 37.9, 23.0, 21.1.

IR (ATR): $\tilde{\nu}$[cm^{-1}] = 3061 (w), 3048 (w), 3027 (w), 2959 (m), 2924 (s), 2869 (w), 2853 (m), 2360 (w), 2340 (w), 1598 (w), 1510 (w), 1494 (w), 1453 (m), 1396 (w), 1378 (w), 797 (m), 778 (vs), 763 (m), 700 (s).

MS (EI, 70 eV): m/z (%): 274 (12), 156 (86), 155 (100), 154 (17), 153 (66), 152 (32), 141 (62), 128 (23), 115 (16), 105 (23), 91 (16).

HRMS (EI) for $C_{21}H_{22}$: calc. [M^+]: 274.1722; found: 274.1715.



syn-**121k**

The benzo[*b*]thiophene derivative *syn*-**121k** was prepared according to **TP7** from the iodide *syn*-**1a** (dr = 2:98, 0.10 mmol, 27.4 mg) and 3-bromobenzo[*b*]thiophene **124c** (0.30 mmol, 63.9 mg). The crude product was purified by flash column chromatography on silica gel with *n*-pentane to afford *syn*-**121k** (0.038 mmol, 10.7 mg, 38% yield, dr = 3:97) as a colorless oil.

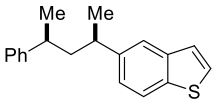
^{1}H-NMR($CDCl_3$, 400 MHz): δ [ppm] = 7.87–7.79 (m, 1H), 7.46–7.39 (m, 1H), 7.38–7.27 (m, 4H), 7.25–7.21 (m, 3H), 7.10–7.04 (m, 1H), 3.04–2.91 (m, 1H), 2.91–2.81 (m, 1H), 2.12 (ddd, *J* = 13.7, 9.3, 5.3 Hz, 1H), 1.79 (ddd, *J* = 13.7, 9.0, 5.8 Hz, 1H), 1.36 (d, *J* = 6.8 Hz, 3H), 1.27–1.24 (m, 7H)..

$^{13}C\{^{1}H\}$-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 147.2, 142.9, 140.7, 138.6, 128.6, 127.3, 126.3, 124.2, 123.8, 123.0, 121.9, 119.6, 46.2, 37.8, 30.6, 23.1, 20.4.

IR (ATR): $\tilde{\nu}$[cm^{-1}] = 3026 (w), 2959 (s), 2924 (s), 2870 (m), 2853 (m), 2360 (w), 2341 (w), 1493 (w), 1454 (m), 1428 (m), 1379 (w), 1028 (w), 838 (w), 761 (vs), 733 (s), 701 (s).

MS (EI, 70 eV): m/z (%): 207 (23), 162 (100), 161 (47), 147 (66), 128 (28), 115 (12).

HRMS (EI) for $C_{19}H_{20}S$: calc. [M^+]: 280.1286; found: 280.1279.



syn-**121l**

The benzo[*b*]thiophene *syn*-**121l** was prepared according to **TP7** from the iodide *syn*-**1a** (dr = 2:98, 0.10 mmol, 27.4 mg) and 5-bromobenzo[*b*]thiophene **124d** (0.30 mmol, 63.9 mg). The crude product was purified by flash column chromatography on silica gel with *n*-pentane to afford *syn*-**121l** (0.059 mmol, 16.5 mg, 59% yield, dr = 2:98) as a colorless oil.

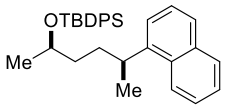
^{1}H-NMR($CDCl_3$, 400 MHz): δ [ppm] = 7.80 (d, *J* = 8.3 Hz, 1H), 7.61 (d, *J* = 1.7 Hz, 1H), 7.42 (d, *J* = 5.4 Hz, 1H), 7.32–7.27 (m, 3H), 7.22–7.14 (m, 4H), 2.78 (h, *J* = 7.1 Hz, 1H), 2.66 (h, *J* = 7.1 Hz, 1H), 2.05–1.97 (m, 1H), 1.87–1.79 (m, 1H), 1.30 (d, *J* = 6.9 Hz, 3H), 1.25 (d, *J* = 7.0 Hz, 3H).

^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 147.8, 144.0, 140.0, 137.5, 128.5, 127.1, 126.6, 126.0, 124.0, 123.9, 122.5, 121.7, 47.3, 37.5, 29.9, 22.7, 22.3.

IR (ATR): $\tilde{\nu}$[cm^{-1}] = 3026 (w), 2957 (m), 2924 (s), 2853 (m), 2360 (w), 2334 (w), 1494 (w), 1453 (m), 1438 (w), 1421 (w), 1377 (w), 1090 (w), 1053 (w), 1028 (w), 891 (w), 821 (w), 809 (w), 760 (w), 700 (vs).

MS (EI, 70 eV): m/z (%): 162 (60), 161 (30), 148 (10), 147 (100), 128 (39), 117 (11).

HRMS (EI) for $C_{19}H_{20}S$: calc. [M$^+$]: 280.1286; found: 280.1280.



syn-**121m**

The naphthalene derivative *syn*-**121m** was prepared according to **TP7** from the iodide *syn*-**1c** (dr = 1:99, 0.10 mmol, 46.6 mg) and 1-bromonaphthalene **124b** (0.30 mmol, 62.1 mg). The crude product was purified by flash column chromatography on silica gel with *n*-pentane/diethyl ether = 200/1 to afford *syn*-**121m** (0.051 mmol, 23.8 mg, 51% yield, dr = 3:97) as a colorless oil.

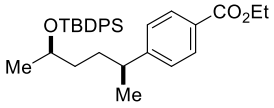
^{1}H-NMR($CDCl_3$, 400 MHz): δ [ppm] = 8.13–7.79 (m, 1H), 7.73–7.56 (m, 3H), 7.51–7.26 (m, 6H), 3.92–3.74 (m, 1H), 3.62–3.35 (m, 1H), 1.88–1.60 (m, 1H), 1.50–1.32 (m, 1H), 1.33–1.26 (m, 1H), 1.08–0.96 (m, 7H).

^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 143.9, 136.0, 136.0, 136.0, 135.0, 134.7, 134.1, 131.8, 129.6, 129.5, 129.0, 127.6, 127.6, 127.5, 127.5, 126.3, 125.8, 125.7, 125.3, 123.4, 122.6, 69.9, 37.6, 33.1, 27.2, 23.2, 22.1, 19.4.

IR (ATR): $\tilde{\nu}$[cm^{-1}] = 3070 (w), 3048 (w), 2962 (m), 2930 (s), 2857 (m), 2360 (m), 2342 (m), 1472 (w), 1461 (w), 1428 (m), 1390 (w), 1376 (w), 1362 (w), 1130 (w), 1111 (s), 1072 (m), 1052 (m), 1028 (w), 1006 (w), 998 (w), 822 (w), 797 (w), 778 (m), 740 (m), 720 (w), 702 (vs), 688 (w), 668 (w).

MS (EI, 70 eV): m/z (%): 410 (25), 409 (69), 200 (18), 199 (100), 155 (18).

HRMS (EI) for $C_{32}H_{38}OSi$: calc. [M$^+$]: 466.2692; found: 466.2704.

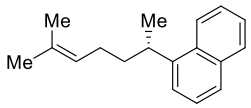


syn-**121n**

The ethyl benzoate derivative *syn*-**121n** was prepared according to **TP7** from the iodide *syn*-**1c** (dr = 1:99, 0.10 mmol, 46.6 mg) and ethyl 4-bromobenzoate **124a** (0.30 mmol, 68.7 mg). The crude product

was purified by flash column chromatography on silica gel with *n*-pentane/diethyl ether = 50/1 to afford *syn*-**121n** (0.050 mmol, 24.4 mg, 50% yield, dr = 4:96) as a colorless oil.

^{1}H-NMR($CDCl_3$, 400 MHz): δ [ppm] = 7.99–7.87 (m, 2H), 7.69–7.57 (m, 4H), 7.51–7.28 (m, 6H), 7.21–7.07 (m, 2H), 4.37 (q, *J* = 7.1 Hz, 2H), 3.78 (qd, *J* = 5.9, 2.5 Hz, 1H), 2.60 (dp, *J* = 15.2, 7.3 Hz, 1H), 1.62–1.45 (m, 3H), 1.39 (t, *J* = 7.1 Hz, 4H), 1.17 (t, *J* = 6.6 Hz, 3H), 1.04–0.96 (m, 12H).
^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 166.9, 153.2, 136.0, 136.0, 134.9, 134.6, 129.8, 129.6, 129.5, 128.3, 127.6, 127.5, 127.1, 69.6, 60.9, 40.3, 37.4, 33.6, 27.2, 23.3, 22.3, 19.4, 14.5.
IR (ATR): $\tilde{\nu}$[cm^{-1}] = 2931 (w), 2858 (w), 1716 (m), 1610 (w), 1472 (w), 1462 (w), 1428 (w), 1418 (w), 1390 (vw), 1368 (w), 1310 (w), 1275 (s), 1248 (w), 1180 (w), 1105 (s), 1053 (w), 1020 (w), 1007 (w), 907 (s), 855 (w), 822 (w), 774 (w), 731 (vs), 703 (vs).
MS (EI, 70 eV): m/z (%): 432 (34), 431 (100), 200 (13), 199 (199), 187 (12), 145 (15).
HRMS (EI) for $C_{31}H_{40}O_3Si$: calc. [M^+–H]: 487.2668; found: 487.2668.

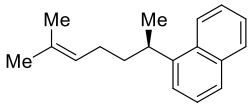


(*S*)-**121o**

The naphthalene derivative (*S*)-**121o** was prepared according to **TP7** from the iodide (*S*)-**1d** (0.10 mmol, 24 mg) and 1-bromonaphthalene **124b** (0.30 mmol, 62.1 mg). The crude product was purified by flash column chromatography on silica gel with *n*-pentane to afford (*S*)-**121o** (0.076 mmol, 18.1 mg, 76% yield, er = 91:9) as a colorless oil.

$[\alpha]_D^{20}$ = –18.6 (c = 0.4, $CHCl_3$).

^{1}H-NMR($CDCl_3$, 400 MHz): δ [ppm] = 8.16–8.08 (m, 1H), 7.87–7.83 (m, 1H), 7.73–7.67 (m, 1H), 7.54–7.37 (m, 4H), 5.18–5.10 (m, 1H), 3.61 (h, *J* = 6.9 Hz, 1H), 2.06–1.96 (m, 2H), 1.93–1.82 (m, 1H), 1.77–1.68 (m, 1H), 1.67 (q, *J* = 1.3 Hz, 3H), 1.47 (d, *J* = 1.3 Hz, 3H), 1.38 (d, *J* = 6.9 Hz, 3H).
^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 143.9, 134.1, 131.9, 131.8, 129.0, 126.3, 125.8, 125.7, 125.3, 124.6, 123.4, 122.6, 38.0, 33.2, 26.4, 25.9, 21.9, 17.8.
IR (ATR): $\tilde{\nu}$[cm^{-1}] = 3047 (w), 2963 (m), 2925 (m), 2856 (w), 1597 (w), 1510 (w), 1453 (w), 1396 (w), 1376 (w), 796 (m), 777 (vs).
MS (EI, 70 eV): m/z (%): 238 (23), 167 (17), 157 (12), 156 (100), 155 (72), 153 (46), 152 (17), 141 (68), 95 (8).
HRMS (EI) for $C_{18}H_{22}$: calc. [M^+]: 238.1722; found: 238.1715.



(*R*)-**121o**

The naphthalene derivative (*R*)-**121o** was prepared according to **TP7** from the iodide (*R*)-**1d** (0.10 mmol, 24 mg) and 1-bromonaphthalene **124b** (0.30 mmol, 62.1 mg). The crude product was purified by flash column chromatography on silica gel with *n*-pentane to afford (*R*)-**121o** (0.062 mmol, 14.8 mg, 62% yield, er = 9:91) as a colorless oil.

$[\alpha]_D^{20}$ = +18.3 (c = 0.3, $CHCl_3$).

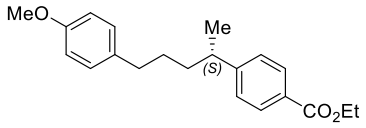
^{1}H-NMR($CDCl_3$, 400 MHz): δ [ppm] = δ 8.16–8.09 (m, 1H), 7.87–7.83 (m, 1H), 7.70 (dt, *J* = 7.9, 1.1 Hz, 1H), 7.54–7.37 (m, 4H), 5.19–5.04 (m, 1H), 3.68–3.52 (m, 1H), 2.06–1.96 (m, 2H), 1.93–1.81 (m, 1H), 1.79–1.68 (m, 1H), 1.67 (d, *J* = 1.3 Hz, 2H), 1.47 (d, *J* = 1.3 Hz, 3H), 1.38 (d, *J* = 6.9 Hz, 3H).

^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 143.9, 134.1, 131.9, 131.8, 129.0, 126.3, 125.8, 125.7, 125.3, 124.6, 123.4, 122.6, 38.0, 26.4, 25.9, 21.9, 17.8.

IR (ATR): $\tilde{\nu}$[cm^{-1}] = 3047 (w), 2963 (m), 2925 (m), 2855 (w), 1597 (w), 1511 (w), 1453 (w), 1396 (w), 1376 (w), 1255 (vw), 1108 (vw), 858 (vw), 796 (m), 777 (vs)

MS (EI, 70 eV): m/z (%): 238 (18), 167 (19), 157 (12), 155 (89), 153 (100), 152 (48), 141 (86), 128 (35), 115 (22).

HRMS (EI) for $C_{18}H_{22}$: calc. [M^+]: 238.1722; found: 238.1715.



(*S*)-**121p**

The ethyl benzoate derivative (*S*)-**121p** was prepared according to **TP7** from the iodide (*S*)-**1e** (0.10 mmol, 30.4 mg) and ethyl 4-bromobenzoate **124a** (0.30 mmol, 68.7 mg). The crude product was extracted and purified by flash column chromatography. The crude product was purified by flash column chromatography on silica gel with *n*-pentane/diethyl ether = 50/1 to afford (*S*)-**121p** (0.054 mmol, 17.6 mg, 54% yield, er = 83:17) as a colorless oil.

$[\alpha]_D^{20}$ = +6.4 (c = 0.5, $CHCl_3$).

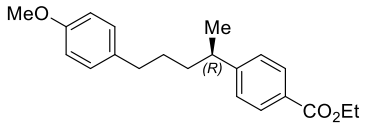
^{1}H-NMR($CDCl_3$, 400 MHz): 7.99–7.90 (m, 2H), 7.25–7.17 (m, 2H), 7.05–6.97 (m, 2H), 6.85–6.75 (m, 2H), 4.36 (q, *J* = 7.1 Hz, 2H), 3.78 (s, 3H), 2.76 (h, *J* = 7.0 Hz, 1H), 2.50 (tt, *J* = 9.3, 6.9 Hz, 2H), 1.65–1.58 (m, 2H), 1.55–1.42 (m, 2H), 1.38 (t, *J* = 7.1 Hz, 3H), 1.23 (d, *J* = 6.9 Hz, 3H).

^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): 166.9, 157.8, 153.2, 134.6, 129.8, 129.3, 128.3, 127.1, 113.8, 60.9, 55.4, 40.1, 37.8, 35.1, 29.8, 22.3, 14.5.

IR (ATR): $\tilde{\nu}$[cm^{-1}] = 2977 (w), 2936 (w), 2836 (w), 1729 (s), 1584 (w), 1463 (m), 1444 (m), 1391 (w), 1377 (w), 1349 (w), 1300 (m), 1244 (vs), 1176 (s), 1153 (s), 1115 (m), 1096 (m), 1063 (m), 1035 (s), 931 (w), 830 (m), 748 (w), 699 (m).

MS (EI, 70 eV): m/z (%): 326 (8), 121 (100), 86 (39), 84 (57), 74 (77), 59 (90), 45 (52), 42 (24).

HRMS (EI) for $C_{21}H_{26}O_3$: calc. [M$^+$]: 326.1882; found: 326.1877.



(*R*)-**121p**

The ethyl benzoate derivative (*R*)-**121p** was prepared according to **TP7** from the iodide (*R*)-**1e** (0.10 mmol, 30.4 mg) and ethyl 4-bromobenzoate **124a** (0.30 mmol, 68.7 mg). The crude product was extracted and purified by flash column chromatography. The crude product was purified by flash column chromatography on silica gel with *n*-pentane/diethyl ether = 50/1 to afford (*R*)-**121p** (0.046 mmol, 15.0 mg, 46% yield, er = 9:91) as a colorless oil.

$[\alpha]_D^{20}$ = –7.9 (c = 0.8, $CHCl_3$).

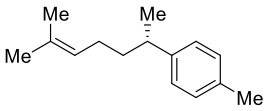
^{1}H-NMR($CDCl_3$, 400 MHz): 8.01–7.91 (m, 2H), 7.25–7.18 (m, 2H), 7.06–7.00 (m, 2H), 6.84–6.72 (m, 2H), 4.36 (q, *J* = 7.1 Hz, 2H), 3.78 (s, 3H), 2.81–2.69 (m, 1H), 2.51 (td, *J* = 7.8, 7.3, 2.5 Hz, 2H), 1.64–1.56 (m, 3H), 1.55–1.42 (m, 2H), 1.38 (t, *J* = 7.1 Hz, 3H), 1.23 (d, *J* = 6.9 Hz, 3H).

^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): 166.9, 157.8, 153.2, 134.6, 129.8, 129.3, 128.4, 127.1, 113.8, 60.9, 55.4, 40.1, 37.8, 35.1, 29.8, 22.3, 14.5.

IR (ATR): $\tilde{\nu}$[cm^{-1}] = 2958 (w), 2929 (m), 2854 (w), 1716 (s), 1611 (m), 1513 (s), 1463 (w), 1443 (w), 1418 (w), 1367 (w), 1310 (w), 1299 (w), 1275 (vs), 1246 (s), 1179 (m), 1106 (m), 1037 (w), 1021 (w), 856 (w), 831 (w), 809 (w), 775 (w), 708 (w).

MS (EI, 70 eV): m/z (%): 326 (8), 121 (100), 86 (39), 84 (57), 74 (77), 59 (90), 45 (52), 42 (24).

HRMS (EI) for $C_{21}H_{26}O_3$: calc. [M$^+$]: 326.1882; found: 326.1874.



(*S*)-curcumene (*S*-**125**)

The natural product (*S*)-**curcumene** (*S*-**125**) was prepared according to **TP7** from the iodide (*S*)-**1X** (0.10 mmol, 24 mg) and 4-bromotoluene as electrophile (0.30 mmol, 51 mg). The crude product was purified by flash column chromatography on silica gel with *n*-pentane to afford (*S*)-curcumene (*S*-**125**) (0.050 mmol, 10.1 mg, 50% yield, er = 93:7) as a colorless oil.

$[\alpha]_D^{20}$ = +35.8 (c = 0.9, $CHCl_3$).

[Lit:[143] $[\alpha]_D^{20}$ = +36.8 (c = 1.3, $CHCl_3$); Lit:[144] $[\alpha]_D^{20}$ = +37.7 (c = 0.7, $CHCl_3$).]

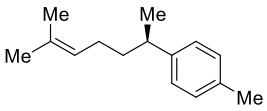
^{1}H-NMR($CDCl_3$, 400 MHz): δ [ppm] = 7.14–7.02 (m, 4H), 5.14–5.01 (m, 1H), 2.65 (h, *J* = 7.0 Hz, 1H), 2.32 (s, 3H), 1.93–1.79 (m, 2H), 1.67 (d, *J* = 1.3 Hz, 3H), 1.64–1.56 (m, 2H), 1.52 (d, *J* = 1.2 Hz, 3H), 1.21 (d, *J* = 6.9 Hz, 3H).

^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 144.8, 135.3, 131.5, 129.1, 127.0, 124.7, 39.1, 38.6, 26.3, 25.9, 22.6, 21.2, 17.8.

IR (ATR): $\tilde{\nu}$[cm^{-1}] = 3020 (w), 2961 (s), 2923 (vs), 2854 (m), 2362 (w), 2343 (w), 1515 (m), 1455 (m), 1376 (w), 1110 (w), 1020 (w), 815 (m).

MS (EI, 70 eV): m/z (%): 145 (25), 132 (100), 131 (30), 119 (58), 117 (31), 105 (34), 91 (18).

HRMS (EI) for $C_{15}H_{22}$: calc. [M^+]: 202.1722; found: 202.1714.



(*R*)-curcumene (*R*-**125**)

The natural product (*R*)-**curcumene** (*R*-**125**) was prepared according to **TP7** from the iodide (*R*)-**1X** (0.10 mmol, 24 mg) and 4-bromotoluene as electrophile (0.30 mmol, 51 mg). The crude product was purified by flash column chromatography on silica gel with *n*-pentane to afford (*R*)-curcumene (*R*-**125**) (0.046 mmol, 9.3 mg, 46% yield, er = 7:93) as a colorless oil.

$[\alpha]_D^{20}$ = –43.4 (c = 0.6, $CHCl_3$).

[Lit:[143] $[\alpha]_D^{20}$ = –44.6 (c = 1.2, $CHCl_3$); Lit:[145] $[\alpha]_D^{24}$ = –44.5 (c = 1.1, $CHCl_3$).]

^{1}H-NMR($CDCl_3$, 400 MHz): 7.15–7.03 (m, 4H), 5.13–5.03 (m, 1H), 2.65 (h, *J* = 7.0 Hz, 1H), 2.32 (s, 3H), 1.93–1.76 (m, 2H), 1.69–1.64 (m, 2H), 1.63–1.54 (m, 2H), 1.52 (d, *J* = 1.3 Hz, 3H), 1.21 (d, *J* = 7.0 Hz, 3H).

[143] L. Wu, J.-C. Zhong, S.-K. Liu, F.-P. Liu, Z.-D. Gao, M. Wang, Q.-H. Bian, *Tetrahedron Asymmetry* **2016**, *27*, 78–83.
[144] G. Uhde, G. Ohloff, *Helv. Chim. Acta* **1972**, *55*, 2621–2625.
[145] S. Song, S.-F. Zhu, S. Yang, S. Li, Q.-L. Zhou, *Angew. Chem. Int. Ed.* **2012**, *51*, 2708–2711.

$^{13}C\{^{1}H\}$-NMR ($CDCl_3$, 100 MHz): 144.8, 135.3, 131.5, 129.1, 127.0, 124.7, 39.1, 38.6, 26.3, 25.9, 22.6, 21.2, 17.8.

IR (ATR): $\tilde{\nu}$[cm^{-1}] = 3020 (w), 2961 (s), 2922 (vs), 2854 (m), 2364 (w), 2343 (w), 1518 (m), 1455 (m), 1374 (w), 1110 (w), 1020 (w), 814 (m).

MS (EI, 70 eV): m/z (%): 145 (27), 132 (100), 119 (99), 117 (62), 115 (28), 105 (57), 91 (49), 77 (12).

HRMS (EI) for $C_{15}H_{22}$: calc. [M^+]: 202.1722; found: 202.1722.

D. APPENDIX

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D. Appendix

1 Chiral Chromatograms for Determination of *ee*

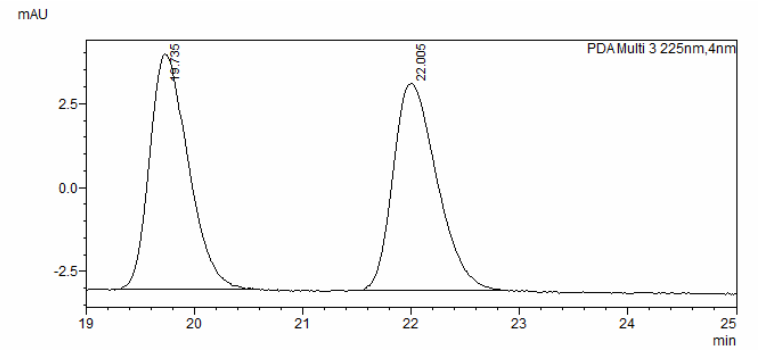
1.1 Allylic Substitution Reactions

Ethyl (*R*)-hydroxybutyrate

The *ee* of ethyl (*R*)-hydroxybutyrate [(*R*)-**74**] was determined by chiral HPLC analysis.

HPLC (column: OB-H; *n*-heptane/2-propanol, 95:5, 0.5 mL/min): t_R (min) = 19.7 (*S*), 22.0 (*R*). >99% *ee*.

Racemate:

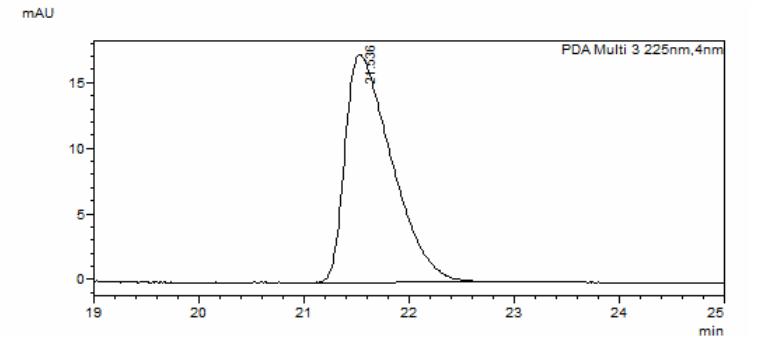


<Peak Table>

PDA Ch3 225nm

Peak#	Ret. Time	Area	Height	Area%
1	19.735	173481	7011	50.148
2	22.005	172456	6165	49.852
Total		345936	13175	100.000

(*R*)-Enatiomer:



<Peak Table>

PDA Ch3 225nm

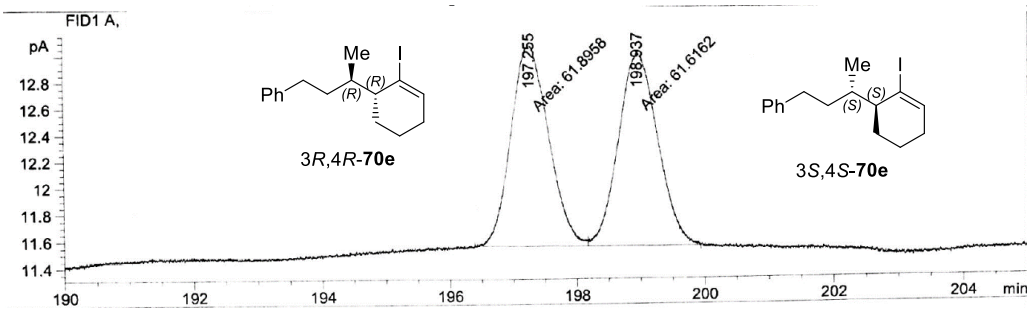
Peak#	Ret. Time	Area	Height	Area%
1	21.536	534805	17369	100.000
Total		534805	17369	100.000

3*R*,4*R*-70e:

The *ee* of 3*R*,4*R*-**70** was determined by chiral GC analysis.

GC (Chirasil-Dex CB), 80 °C (5 min), ramp of 0.4 °C/ min to 140 °C, hold for 120 min; t_R (min) = 196.9 (*R*,*R*-enantiomer; major), 198.9 (*S*,*S*-enantiomer; minor). >99% *ee*.

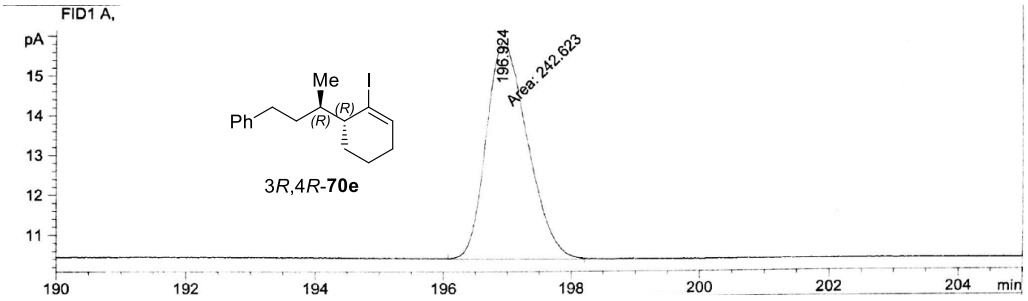
Racemate:



Signal 1: FID1 A,

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	197.255	MF	0.6802	61.89578	1.51652	50.11317
2	198.937	FM	0.7069	61.61623	1.45274	49.88683
Totals :				123.51202	2.96927	

(*R*,*R*)-Enantiomer:



Signal 1: FID1 A,

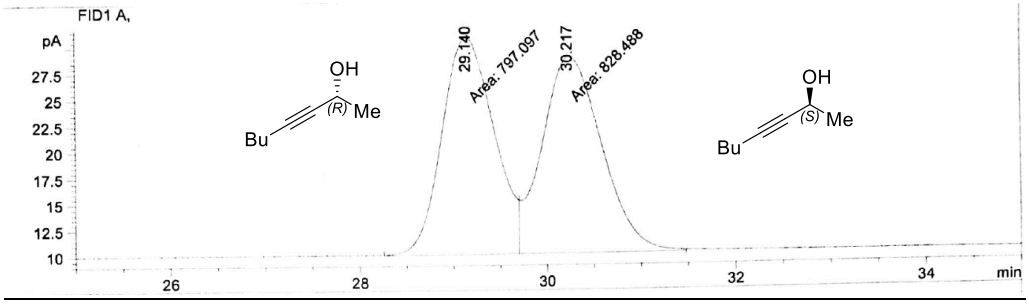
Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	196.924	MM	0.7398	242.62268	5.46617	1.000e2
Totals :				242.62268	5.46617	

(*S*)-oct-3-yn-2-ol:

The *ee* of (*S*)-oct-3-yn-2-ol was determined by chiral GC analysis

GC (Chirasil-Dex CB), 100 °C (const.); t_R (min) = 29.3 (*R*-enantiomer; minor), 30.4 (*S*-enantiomer; major). >99% *ee*.

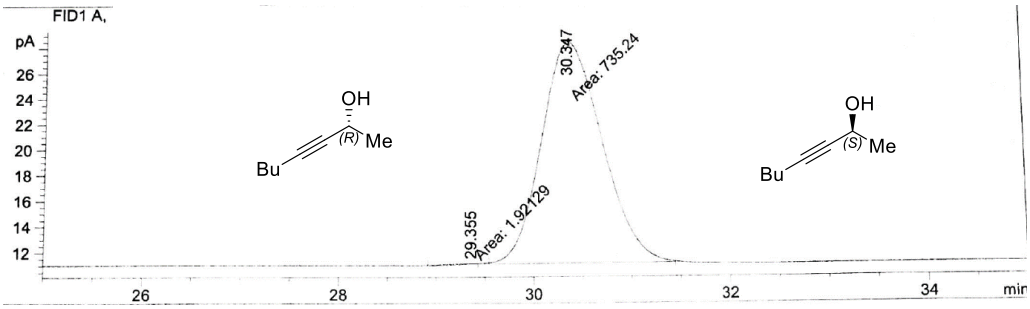
Racemate:



Signal 1: FID1 A,

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	29.140	MF	0.6418	797.09711	20.70112	49.03447
2	30.217	FM	0.7346	828.48804	18.79700	50.96553
Totals :				1625.58514	39.49812	

After 7h:



Signal 1: FID1 A,

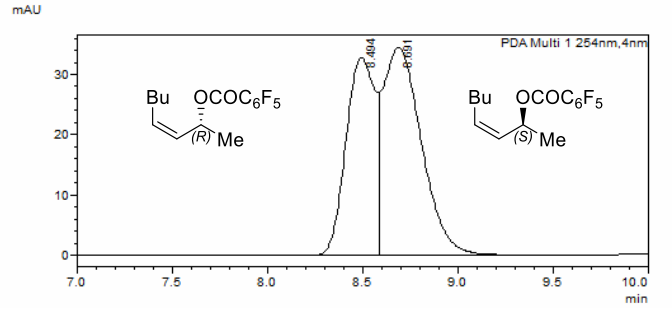
Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	29.355	MM	0.4652	1.92129	6.88331e-2	0.26063
2	30.347	MM	0.7068	735.23981	17.33797	99.73937
Totals :				737.16110	17.40680	

(*S*,*Z*)-oct-3-en-2-ol:

The *ee* of (*S*,*Z*)-oct-3-en-2-ol was determined by chiral HPLC analysis of the corresponding pentafluorobenzoate.

HPLC (column: OD-H; *n*-heptane/2-propanol = 5999:1, 0.6 mL/min): t_R *f*(min) = 8.5 (*R*), 8.7 (*S*). >99% *ee*.

Racemate:

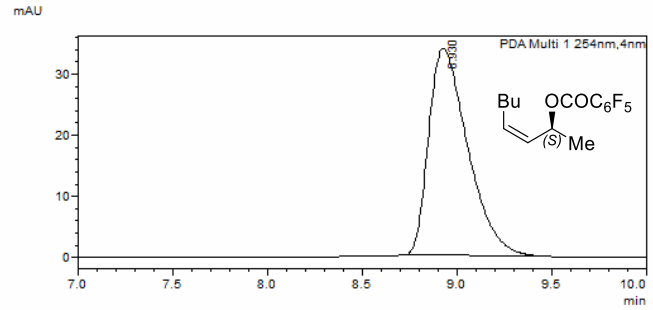


<Peak Table>

PDA Ch1 254nm

Peak#	Ret. Time	Area	Height	Area%
1	8.494	352292	32789	42.259
2	8.691	481349	34530	57.741
Total		833641	67319	100.000

(*S*)-Enatiomer:



<Peak Table>

PDA Ch1 254nm

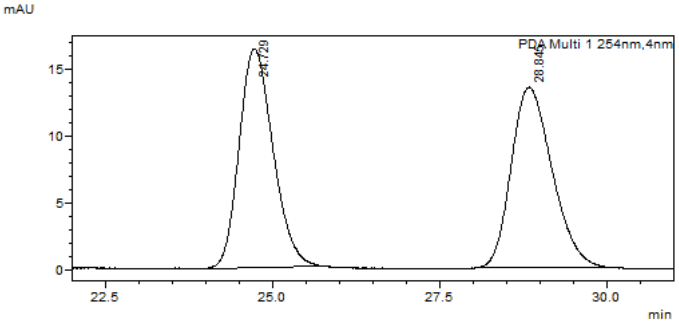
Peak#	Ret. Time	Area	Height	Area%
1	8.930	486347	33866	100.000
Total		486347	33866	100.000

(*S*)-1f, (*R*)-1f:

The *ee* values of (*S*)-**1f** and (*R*)-**1f** were determined by chiral HPLC analysis.

HPLC (column: OB-H; *n*-heptane/2-propanol = 500:1, 0.3 mL/min): t_R (min) = 24.7 (*R*), 28.8 (*S*).

Racemate:

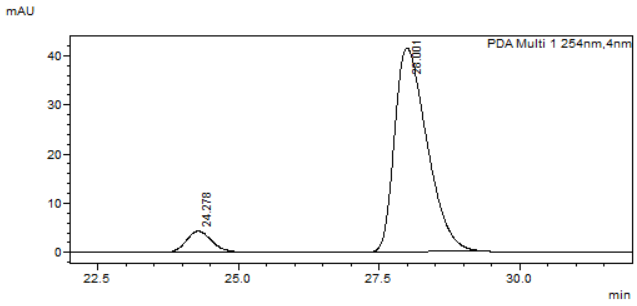


<Peak Table>

PDA Ch1 254nm

Peak#	Ret. Time	Area	Height	Area%
1	24.729	575218	16327	50.134
2	28.845	572150	13468	49.866
Total		1147368	29795	100.000

(*S*)-Enatiomer: (*S*)-**1f**, er = 93:7

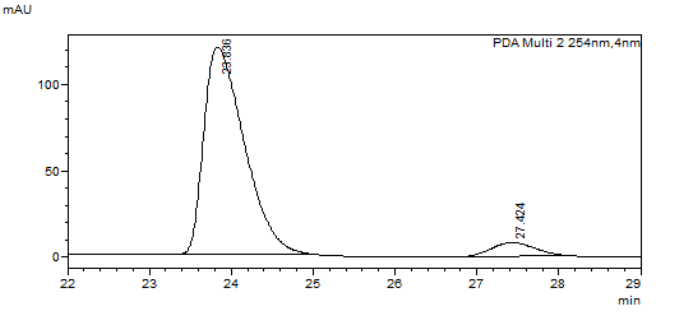


<Peak Table>

PDA Ch1 254nm

Peak#	Ret. Time	Area	Height	Area%
1	24.278	130316	4263	7.260
2	28.001	1664613	41432	92.740
Total		1794929	45695	100.000

(*R*)-Enatiomer: (*R*)-**1f**, er = 7:93



<Peak Table>

PDA Ch2 254nm

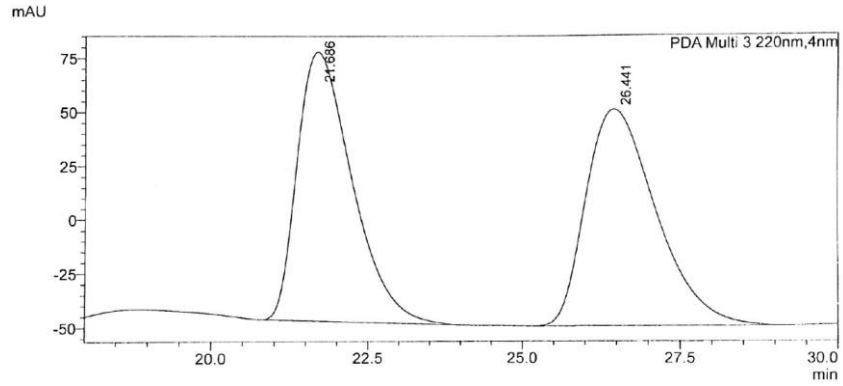
Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	23.836	4125510	120022	93.228		M	
2	27.424	299653	8003	6.772		M	
Total		4425163	128024				

Electrophile 68d:

The *ee* of **68d** was determined by chiral HPLC analysis.

HPLC (column: OJ-H; *n*-heptane/2-propanol = 99:1, 0.6 mL/min): t_R (min) = 21.7 (*R*), 26.4 (*S*). >99% *ee*; in accordance with literature values.[64f]

Racemate:

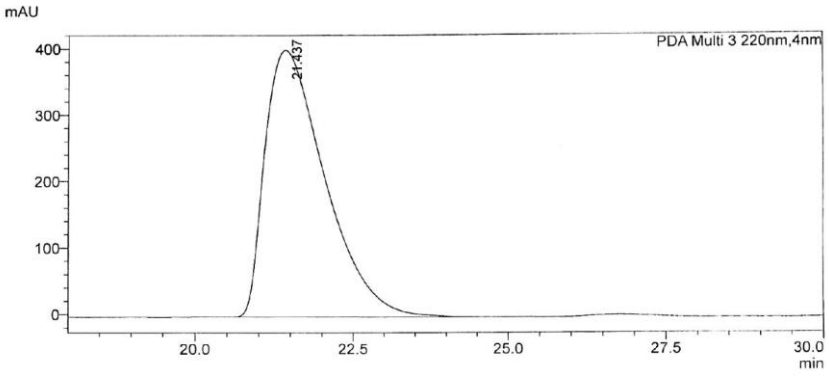


<Peak Table>

PDA Ch3 220nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark
1	21.686	7678393	125044	49.700		
2	26.441	7771150	100636	50.300		
Total		15449543	225680			

(*R*)-Enantiomer:



<Peak Table>

PDA Ch3 220nm

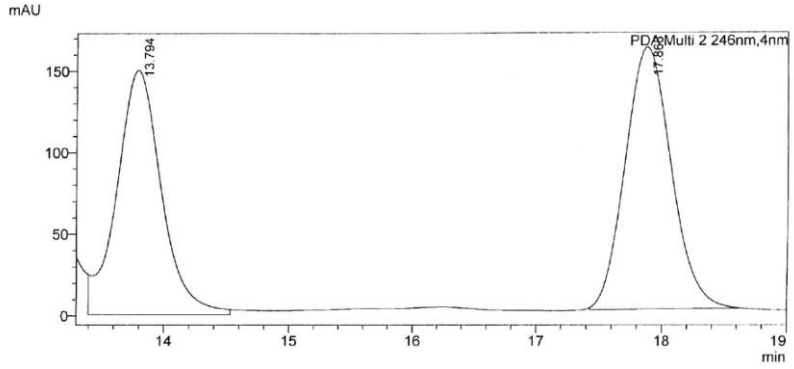
Peak#	Ret. Time	Area	Height	Area%
1	21.437	26721040	401598	100.000
Total		26721040	401598	100.000

(*S*)-2-iodocyclopent-2-en-1-ol:

The *ee* of (*R*)-2-iodocyclopent-2-en-1-ol was determined by chiral HPLC analysis.

HPLC (column: OD-H; *n*-heptane/2-propanol = 90:10, 0.6 mL/min): t_R (min) = 13.8 (*R*), 17.8 (*S*). >99% *ee*.

Racemate:

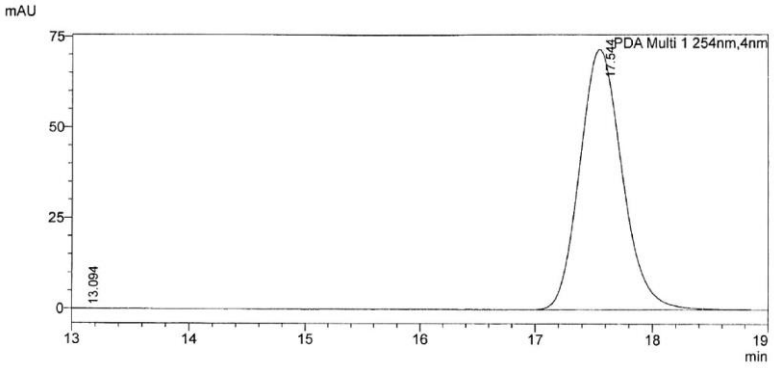


<Peak Table>

PDA Ch2 246nm

Peak#	Ret. Time	Area	Height	Area%
1	13.794	3709727	150033	47.535
2	17.868	4094551	160078	52.465
Total		7804277	310111	100.000

(*S*)-Enantiomer:



<Peak Table>

PDA Ch1 254nm

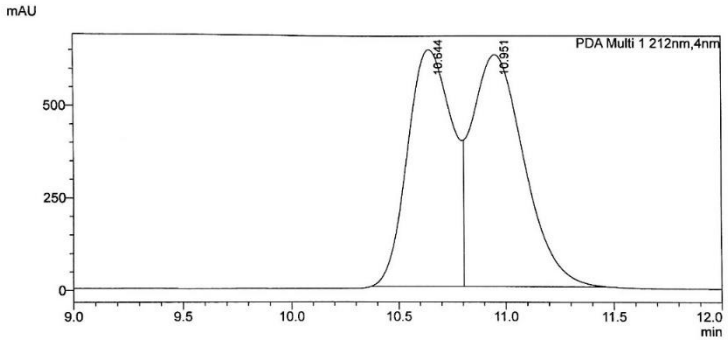
Peak#	Ret. Time	Area	Height	Area%
1	13.094	1567	100	0.087
2	17.544	1800045	71494	99.913

1.2 Preparation of Chiral Allenes

The er of (*R*)-**97f** was determined by chiral HPLC analysis.

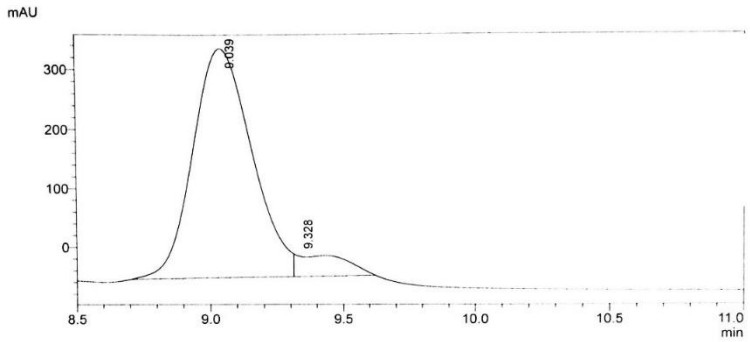
HPLC (column: OB-H; 100% *n*-heptane, 0.2 mL/min): t_R (min) = 10.7 (*R*), 10.9 (*S*). er = 93:7.

Racemate:



Peak#	Ret. Time	Area	Height	Conc.
1	10.644	9599378	646219	47.588
2	10.951	10572420	631868	52.412
Total		20171797	1278087	

(*R*)-Enantiomer:

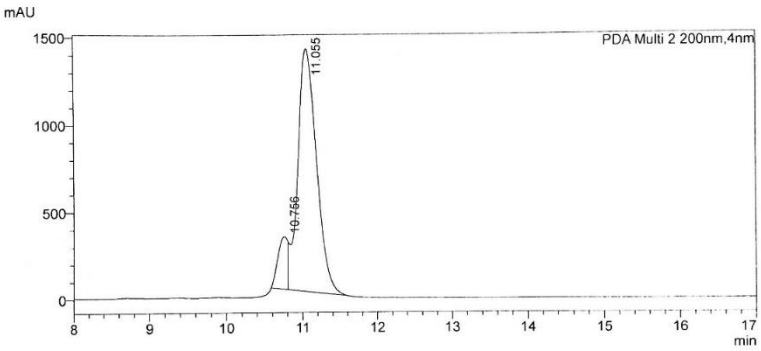


<Peak Table>

PDA Ch1 212nm

Peak#	Ret. Time	Area	Height	Area%
1	9.039	5969550	387634	92.661
2	9.328	472824	36206	7.339

(*S*)-Enantiomer:



<Peak Table>

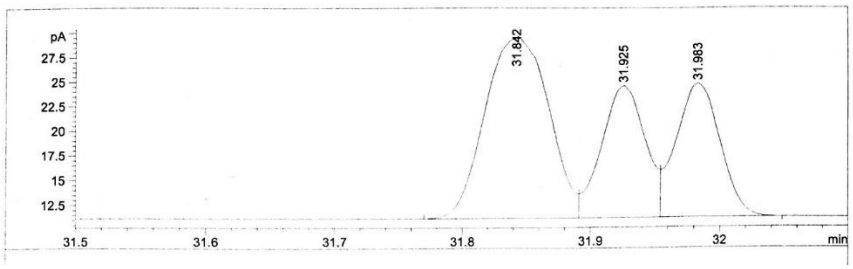
PDA Ch2 200nm

Peak#	Ret. Time	Area	Height	Conc.
1	10.756	2720167	303673	10.136
2	11.055	24117079	1393325	89.864
Total		26837246	1696998	

The er of (*R*,*S*)-**97g** was determined by chiral GC analysis.

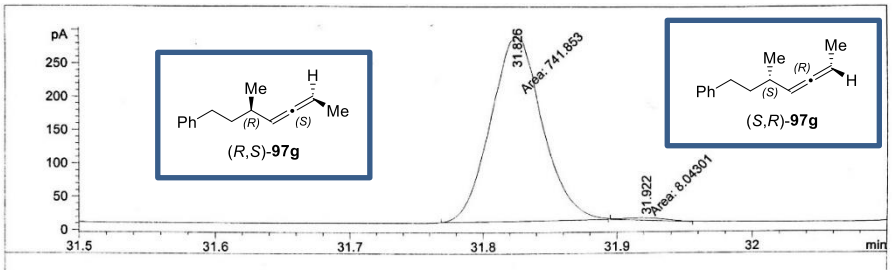
GC (Supelco β-Dex 120), 50 °C (5 min), ramp of 5 °C/ min to 180 °C, hold 20 min; t_R (min) = 31.84 ((*R*,*S*)- and (*S*,*S*)-enantiomer; major), 31.93 ((*R*,*R*)-enantiomer; minor), 31.98 ((*S*,*R*)-enantiomer; minor). er = 99:1.

Racemate:



Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	31.842	BV	0.0563	63.04992	18.25036	49.95659
2	31.925	VV	0.0364	31.25006	13.32911	24.76049
3	31.983	VB	0.0355	31.90942	13.53003	25.28292
Totals :				126.20940	45.10949	

(*R*,*S*)-Enantiomer:

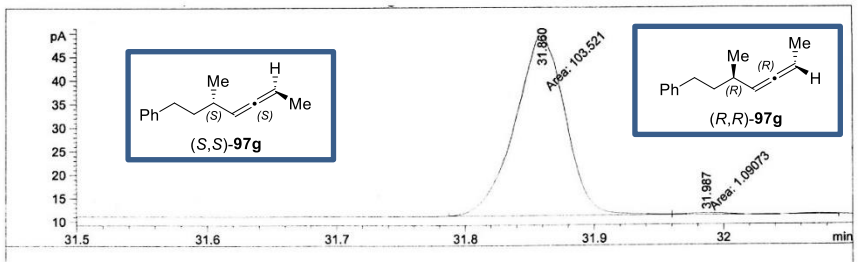


Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	31.826	MM	0.0449	741.85333	275.44794	98.92745
2	31.922	MM	0.0360	8.04301	3.72782	1.07255
Totals :				749.89634	279.17576	

(*S*,*S*)-Enantiomer:

The er of (*S*,*S*)-**97g** was determined by chiral GC analysis.

GC (Supelco β-Dex 120), 50 °C (5 min), ramp of 5 °C/ min to 180 °C, hold 20 min; t_R (min) = 31.60 ((*R*,*S*)- and (*S*,*S*)-enantiomer; major), 31.98 ((*R*,*R*)-enantiomer; minor), 31.98 ((*S*,*R*)-enantiomer; minor). er = 99:1.



Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	31.860	MF	0.0454	103.52133	38.00557	98.95735
2	31.987	FM	0.0511	1.09073	3.55708e-1	1.04265
Totals :				104.61207	38.36128	

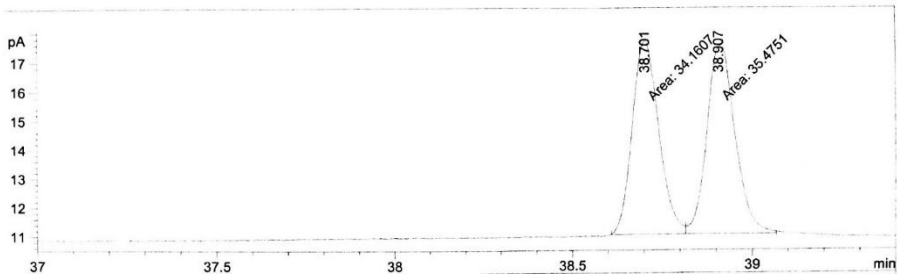
1.3 Stereoselective Cross-Couplings of Chiral Alkylzinc Reagents

(*R*)- and (*S*)-curcumene 125:

The er of (*R*)-curcumene was determined by chiral GC analysis.

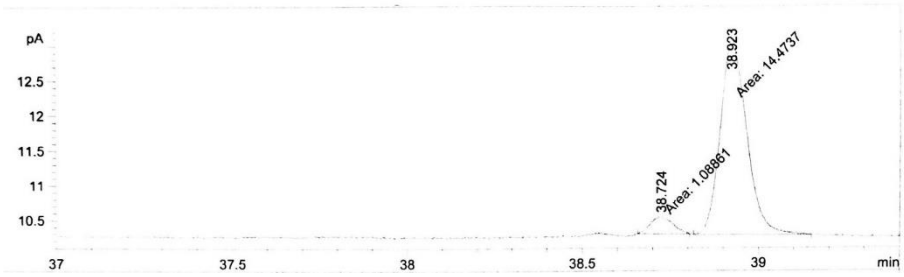
GC (Chirasil-Dex CB), 50 °C (2 min), ramp of 2 °C/ min to 145 °C; t_R (min) = 38.7 (*S*-enantiomer; minor), 38.9 (*R*-enantiomer; major). er = 7:93.

Racemate:



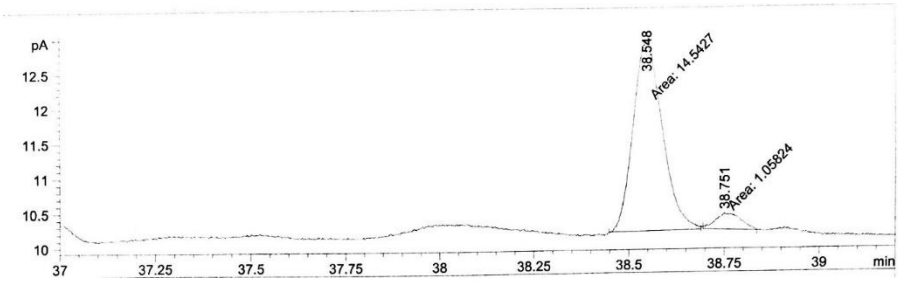
Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	38.701	MF	0.0856	34.16073	6.64748	49.05628
2	38.907	FM	0.0912	35.47507	6.48121	50.94372
Totals :				69.63580	13.12868	

(*R*)-Enantiomer: er = 7:93



Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	38.724	MM	0.0735	1.08861	2.47003e-1	6.99518
2	38.923	MM	0.0855	14.47369	2.82018	93.00482
Totals :				15.56230	3.06718	

(*S*)-Enantiomer: er = 93:7



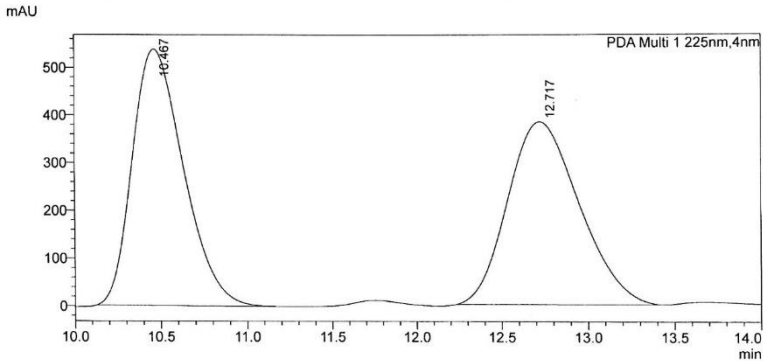
Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	38.548	MF	0.0885	14.54273	2.73937	93.21683
2	38.751	MM	0.0766	1.05824	2.30197e-1	6.78317
Totals :				15.60097	2.96957	

(*R*)- and (*S*)-121o:

The er of (*R*)-**121** was determined by chiral HPLC analysis.

HPLC (column: OJ-H; *n*-heptane/2-propanol = 99:1, 1.0 mL/min): t_R (min) = 10.7 (*R*-enantiomer; major), 12.2 (*S*-enantiomer; minor).

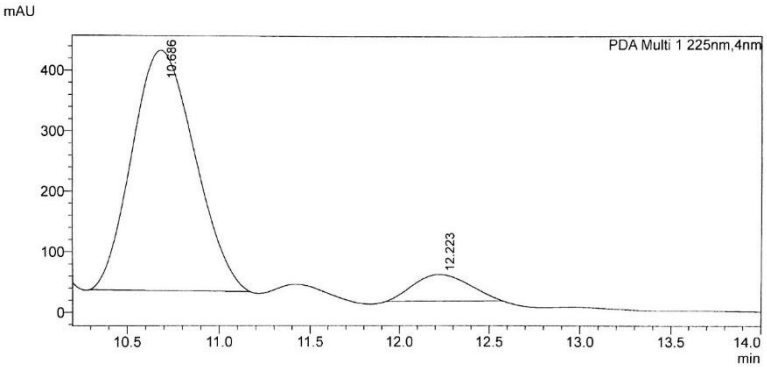
Racemate:



<Peak Table>
PDA Ch1 225nm

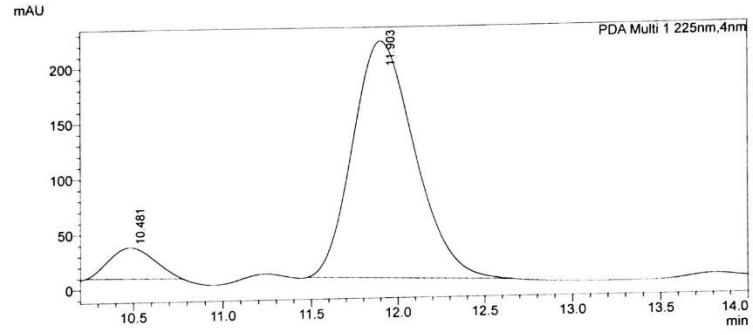
Peak#	Ret. Time	Area	Height	Area%
1	10.467	11099208	537846	50.120
2	12.717	11046146	382621	49.880

(*R*)-Enantiomer: er = 9:91



Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark
1	10.686	9420856	397586	90.696		M
2	12.223	966464	44377	9.304		M
Total		10387319	441964			

(*S*)-Enantiomer: er = 91:9



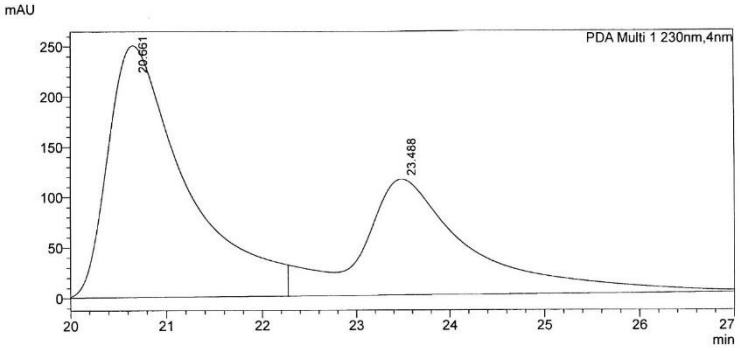
Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark
1	10.481	504189	28508	8.552		M
2	11.903	5391623	215957	91.448		M
Total		5895812	244466			

(*R*)- and (*S*)-121p:

The er of (*R*)-**121** was determined by chiral HPLC analysis.

HPLC (column: AD-H; *n*-heptane/2-propanol = 98:2, 0.5 mL/min): t_R (min) = 20.7 (*R*-enantiomer; major), 23.9 (*S*-enantiomer; minor).

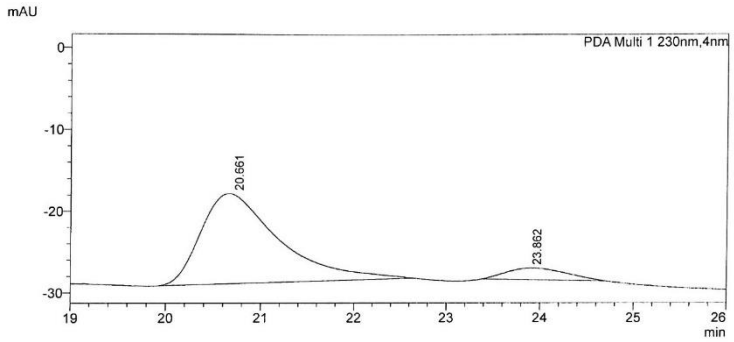
Racemate:



<Peak Table>
PDA Ch1 230nm

Peak#	Ret. Time	Area	Height	Area%
1	20.661	14156212	249814	59.898
2	23.488	9477805	115583	40.102

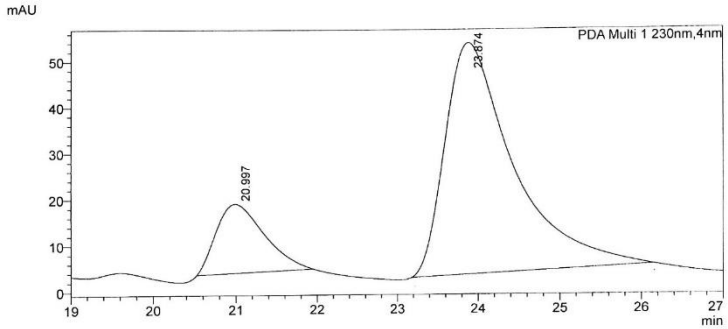
(*R*)-Enantiomer: er = 9:91



<Peak Table>
PDA Ch1 230nm

Peak#	Ret. Time	Area	Height	Area%
1	20.661	638544	11132	90.865
2	23.862	64196	1453	9.135

(*S*)-Enantiomer: er = 83:17



<Peak Table>
PDA Ch1 230nm

Peak#	Ret. Time	Area	Height	Area%
1	20.997	616959	15033	17.305
2	23.874	2948300	50389	82.695

2 Computational Calculations

All calculations were conducted with the program package GAUSSIAN16.[146,]

2.1 Secondary Alkylcopper reagents[91]

Calculation of Gibbs Free Energies:

Optimizations of minimum geometries were performed using the B3LYP functional[147] with the 6-311+G(d,p) basis set[148] for atoms C, H, O, and P, and the LANL2DZ[149] effective core potential for Cu. Solvent effects were accounted for through the Polarizable Continuum Model (PCM)[150], using the adequate dielectric constant according to the solution used in the experiment (THF for *anti*-**99** and tetralin for *anti*-**100**; *anti*-**3a** was calculated in both solutions). Tetralin was used because its dielectric constant corresponds to a 3/2 mixture of diethyl ether and pentane. The minimum structures were verified by a frequency analysis on the same level of theory by the absence of negative modes. For each geometry, a thermochemical analysis was performed at −100 °C, −50 °C and −10 °C, according to experiments. The Gibbs free energy G_{solv} in solution was extracted from the thermochemistry output for each structure ("Sum of electronic and thermal Free Energies") and is indicated below. To obtain the ΔG_{solv} values used in the results and discussion, they are compared to the Gibbs free energy of *anti*-**1a**, which was the most stable structure, according to

$$\Delta G_{solv} = G_{solv} - G_{solv}^{ref} \ . \qquad (1)$$

Calculation of transition state barriers:

The transition state *ts*-**98** for the epimerization between *syn*-**98** and *anti*-**98** was optimized on the same level of electronic structure theory as above. The PCM was not included in this case, since the transition state optimization did not converge using the PCM. Energies for the epimerization are thus given in THF applying single point calculations using the PCM at the structures optimized in the gas phase. The relative energy between *syn*-**98** and *anti*-**98** is changes by 0.5 kcal/mol when switching off the PCM for the optimization, and the transition state barrier is way higher than this difference (above 50 kcal/mol), the statement of the barrier being too high for epimerization at the investigated temperatures holds. The transition state was further verified by displacing the *ts*-**1a** structure along this mode's displacement vector in positive and negative direction, and subsequent geometry optimizations leading to *syn*-**98** and

[146] Frisch, M. J. *et al.* Gaussian16 Revision B.01. (2016).
[147] a) P. J. Stephens, F. J. Devlin, C. F. Chabalowski, M. J. Frisch, *J. Phys. Chem.* **1994**, *98*, 11623–11627. b) S. H. Vosko, L. Wilk, M. Nusair, *Can. J. Phys.* **1980**, *58*, 1200–1211. c) C. Lee, W. Yang, R. G. Parr, *Phys. Rev. B* **1988**, *37*, 785–789. d) A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648–5652.
[148] A. D. McLean, G. S. Chandler, *J. Chem. Phys.* **1980**, *72*, 5639–5648.
[149] P. J. Hay, W. R. Wadt, *J. Chem. Phys.* **1985**, *82*, 270–283.
[150] a) S. Miertuš, E. Scrocco, J. Tomasi, *Chem. Phys.* **1981**, *55*, 117–129. b) *Continuum Solvation Models in Chemical Physics*. (John Wiley & Sons, Ltd, **2007**). DOI:10.1002/9780470515235. c) J. Tomasi, B. Mennucci, R. Cammi, *Chem. Rev.* **2005**, *105*, 2999–3094.

anti-**98**, respectively. For the calculation of the IRC, the basis set was lowered from 6-311+G* to 6-31+G *.

Calculation of bond energies:

Bond dissociation energies (BDEs) of the Cu-C bond at the stereocenter were calculated from the enthalpies of formation of the participating molecular moieties according to

$$\Delta H^{\circ}(298\mathrm{K}) = \sum_{\text{products}} \Delta \mathrm{H}^{\circ}_{\mathrm{prod}}(298\mathrm{K}) - \Delta \mathrm{H}^{\circ}_{\mathrm{reactant}}(298\mathrm{K})\,. \qquad (2)$$

In all species investigated here, $\Delta H^{\circ}_{reactant}$ is the enthalpy of formation of the complete molecule (AB), and $\Delta H^{\circ}_{prod}(298K)$ are the enthalpies of formation of the two radicals (A + B) after homolytic bond cleavage. These values can be extracted from the GAUSSIAN thermochemistry output ("Sum of electronic and thermal enthalpies).

To calculate BDEs, all molecules (AB) were optimized at the UB3LYP/6-311+G* level with subsequent frequency analysis. Afterwards, both radicals A and B were optimized separately using the same method to account for relaxation effects and extracting $\Delta H^{\circ}_{prod}(298K)$ from the thermochemistry output. BDEs were calculated according to Equation 2 and values are given in Table **26**, together with the bond length of the bond before cleavage. All BDEs are well above thermally accessible energies at rt.

Table 25: Gibbs free energies (ΔG_{solv}) of investigated molecular species. ΔG_{solv} is given according to Equation 1, with *anti*-**98** as the reference.

Molecule	ΔG_{solv} (+25 °C) [kcal/mol]	ΔG_{solv} (−100 °C) [kcal/mol]	ΔG_{solv} (−50 °C) [kcal/mol]	ΔG_{solv} (−10 °C) [kcal/mol]
anti-**98**	0.0	0.0	0.0	0.0
ts-**98**	51.9	52.4	52.2	52.1
syn-**98**	2.9	2.7	2.8	2.8
anti-**99**	4.6	5.0	4.7	4.6
anti-**100**	6.8	6.8	6.8	6.8
no coordination	11.9	16.2	14.4	13.0

Table 26: Bond dissociation energies (BDEs) of the Cu-C bond of investigated molecular species. BDE values are calculated according to Equation 2.

Molecule	Bond type	Bond length [pm]	BDE (25 °C) [kcal/mol]	BDE (−50 °C) [kcal/mol]
anti-**98**	Cu-C	198.5	−53.9	−54.0
anti-**99**	Cu-C	195.8	−51.3	−51.3
anti-**100**	Cu-C	195.9	−50.6	−50.7

2.2 Secondary Alkylzinc reagents[123]

Calculation of Gibbs Free Energies for alkylzinc reagents:

Optimizations of minimum geometries were performed using the B3LYP functional[147] with the 6-311+G(d,p) basis set[148] for atoms C, H, O, Si and Cl, and the LANL2DZ[149] effective core potential for atoms Zn and Pd. Solvent effects were accounted for through the Polarizable Continuum Model (PCM)[150] using the adequate dielectric constant of the respective solvent (as indicated for each structure below). The minimum structures were verified by a frequency analysis on the same level of theory by the absence of negative modes. For each geometry, a thermochemical analysis was performed at rt, according to experiments. The Gibbs free energy G_{solv} in solution was extracted from the thermochemistry output for each structure ("Sum of electronic and thermal Free Energies") and is indicated below. To obtain the ΔG_{solv} values used in the results and discussion, they are compared to the Gibbs free energy of a reference structure (*anti*-**4a** for the Zn species in the transmetalation step and *anti*-**123a** for the Pd species in the reductive elimination step of the catalytic cross-coupling cycle) according to

$$\Delta G_{solv} = G_{solv} - G_{solv}^{ref} \ . \qquad (1)$$

Calculation of transition state barriers:

The transition state *ts*-**4a** for the epimerization between *syn*-**4a** and *anti*-**4a** was optimized on the same level of electronic structure theory as above, with the frequency analysis exhibiting exactly one mode with negative frequency. The transition state was further verified by displacing the *ts*-**4a** structure along this mode's displacement vector in positive and negative direction, and subsequent geometry optimizations leading to *syn*-**4a** and *anti*-**4a**, respectively.

The transition states *ts*-**123a** and *ts*-**123b** were computed at the B3LYP/6-31G* level of theory, as a transition state optimization for this significantly larger structure turned out to be computationally too expensive for the 6-311+G* basis set. The Gibbs free energy of the transition state was compared to the *syn*- and *anti*- minimum structures on the same level of theory. To verify this, the B3LYP/6-31G* method was also used to compute the transition state barrier of the eperimerization of *anti*-**4a** *via ts*-**4a** to *syn*-**4a** to have a benchmark for the lower basis set. Both methods qualitatively yield similar epimerization barriers, and thus the B3LYP/6-31G* method is expected to give a reasonable value for the epimerization of *anti*-**123a,b** *via ts*-**123a,b** to *syn*-**123a,b**. All values are indicated in Table 27.

Calculation of bond energies Pd-C:

Another pathway which could lead to loss of stereoinformation is the cleavage of the Zn-C bond in the transmetalation step or the Pd-C bond in the reductive elimination step. Bond dissociation energies

(BDEs) can be calculated from the enthalpies of formation of the participating molecular moieties according to

$$\Delta H^{\circ}(298\mathrm{K}) = \sum_{\text{products}} \Delta \mathrm{H}^{\circ}_{\mathrm{prod}}(298\mathrm{K}) - \Delta \mathrm{H}^{\circ}_{\mathrm{reactant}}(298\mathrm{K})\,. \qquad (2)$$

In all species investigated here, $\Delta H^{\circ}_{reactant}$ is the enthalpy of formation of the complete molecule (AB), and $\Delta H^{\circ}_{prod}(298K)$ are the enthalpies of formation of the two radicals (A + B) after homolytic bond cleavage. These values can be extracted from the GAUSSIAN thermochemistry output ("Sum of electronic and thermal enthalpies).

To calculate BDEs, all molecules (AB) were optimized at the UB3LYP/6-311+G* level with subsequent frequency analysis. Afterwards, both radicals A and B were optimized separately using the same method to account for relaxation effects and extracting $\Delta H^{\circ}_{prod}(298K)$ from the thermochemistry output. BDEs were calculated according to Equation 2 and values are given in Table 28, together with the bond length of the bond before cleavage. All BDEs are well above thermally accessible energies at rt.

Table 27: Transition state barriers for the epimerization of **123a**, **123b** and **4a**. Gibbs free energies ΔG_{solv} are indicated in kcal/mol, with *anti*-**123a** as the reference for the top two rows, and *anti*-**4a** on their respective level for the bottom two rows. For species **4a**, both basis sets qualitatively yield a similar barrier. Thus, the B3LYP/6-31G* method used for **123a** and **123b** are expected to yield reasonable values.

method	species	*anti* [kcal/mol]	*ts* [kcal/mol]	*syn* [kcal/mol]
B3LYP/6-31G*	**123a**	0.0	41.8	−1.0
B3LYP/6-31G*	**123b**	3.8	39.7	5.6
B3LYP/6-31G*	**4a**	0.0	97.0	1.5
B3LYP/6-311+G*	**4a**	0.0	95.9	2.7

Table 28: Bond dissociation energies (BDEs) of Zn-C bonds and Pd-C bonds of investigated molecular species. BDE values are calculated according to Equation 2. ΔG_{solv} is given according to Equation 1, with *anti*-**4a** as the reference for the Zinc species and *anti*-**123a** as the reference for the Palladium species.

molecule	bond type	bond length [pm]	BDE [kcal/mol]	ΔG_{solv} [kcal/mol]
anti-**4a**	Zn-C	207.5	53.1	0.0
syn-**4a**	Zn-C	207.2	49.6	2.7
anti-**4a** + 1 Et_2O	Zn-C	209.6	54.0	2.4
syn-**4a** + 1 Et_2O	Zn-C	209.2	51.8	4.2
anti-**4a** + 2 Et_2O	Zn-C	210.9	55.3	13.8
anti-**123a**	Pd-C	212.1	47.2	0.0
syn-**123a**	Pd-C	211.1	47.7	−0.4
anti-**123b**	Pd-C	220.6	41.6	4.3
syn-**123b**	Pd-C	220.8	40.1	6.1

Optimized molecular geometries:

anti-**98**

B3LYP // 6-311+G(d,p) (C,H,P,O) // LANL2DZ (Cu) // PCM (Tetrahydrofuran) // 298.15 °C

Sum of electronic and thermal Free Energies = −1429.0303 a.u.

C	−3.694868	−1.176985	−0.566547
C	−2.241846	−0.677807	−0.284884
H	−2.219448	−0.326846	0.755344
H	−2.079298	0.215041	−0.902323
C	−1.096588	−1.683810	−0.512617
H	−1.115531	−1.997783	−1.566222
C	−1.237517	−2.946976	0.357122
H	−1.232401	−2.702230	1.426519
H	−2.166395	−3.508101	0.166994
H	−0.412278	−3.646251	0.187119
C	−4.705994	−0.125020	−0.142358
C	−4.875364	1.068136	−0.860232
C	−5.480498	−0.305965	1.010634
C	−5.784710	2.038806	−0.443332
H	−4.292635	1.243210	−1.758215
C	−6.392061	0.661780	1.433977
H	−5.368448	−1.221348	1.583924
C	−6.548768	1.840738	0.707307
H	−5.898280	2.951561	−1.018826
H	−6.980947	0.492331	2.329277
H	−7.257948	2.594631	1.030714
Cu	0.674723	−0.816241	−0.291439
C	−3.886492	−1.614924	−2.028025
H	−4.914239	−1.942492	−2.209460
H	−3.666055	−0.799948	−2.724736
H	−3.219018	−2.444277	−2.273023
H	−3.874380	−2.053251	0.065183
P	2.735723	0.167099	−0.051706
O	2.872084	1.380850	1.039697
O	4.000454	−0.737531	0.423439
O	3.291092	0.745821	−1.449521
C	4.604782	1.358056	−1.629397
H	4.738796	2.126430	−0.864336
H	5.360499	0.584075	−1.485996
C	4.657000	1.942233	−3.025000
H	3.892200	2.710635	−3.157078
H	5.636748	2.397724	−3.193868
H	4.504739	1.165282	−3.777113
C	3.966349	−1.475951	1.674242
H	4.027282	−0.759944	2.497384
H	3.014741	−2.012931	1.747515
C	5.137545	−2.435666	1.686429
H	6.082470	−1.894138	1.603729
H	5.142780	−2.995409	2.625596
H	5.066987	−3.146552	0.860559
C	1.819015	2.371759	1.187539
H	1.972981	3.148201	0.433202
H	0.848534	1.899508	1.002141
C	1.890801	2.944106	2.587989

H	2.867247	3.397946	2.771701
H	1.124671	3.714574	2.709825
H	1.720054	2.166689	3.335802

anti−**99**

B3LYP // 6-311+G(d,p) (C,H,P,O) // LANL2DZ (Cu) // PCM (Tetrahydrofuran) // 298.15 °C

Sum of electronic and thermal Free Energies = −856.7173 a.u.

C	2.533305	1.098613	−0.286072
C	1.093242	0.530337	−0.079506
H	1.076444	0.043066	0.904011
H	0.951093	−0.274067	−0.811898
C	−0.074674	1.532664	−0.175773
H	−0.055910	1.987991	−1.176250
C	0.034508	2.668900	0.858148
H	0.035270	2.282377	1.884461
H	0.951031	3.269586	0.745518
H	−0.807118	3.364362	0.781157
C	3.569691	0.023026	−0.004667
C	3.766901	−1.057988	−0.876978
C	4.341272	0.066051	1.163909
C	4.700464	−2.053849	−0.593035
H	3.186794	−1.125454	−1.791010
C	5.276758	−0.928005	1.454767
H	4.207939	0.892456	1.855558
C	5.461189	−1.994127	0.575581
H	4.834787	−2.878003	−1.285710
H	5.862096	−0.866930	2.366144
H	6.188411	−2.767650	0.796105
Cu	−1.802477	0.615031	−0.087659
C	2.715910	1.733290	−1.675004
H	3.735852	2.106377	−1.806169
H	2.515860	1.014172	−2.475598
H	2.030309	2.573077	−1.809777
H	2.692494	1.885574	0.458413
O	−3.562638	−0.326899	−0.017554
C	−4.553753	−0.318513	−1.089100
C	−4.042071	−1.105901	1.120203
C	−5.823854	−0.875326	−0.454617
H	−4.648358	0.705763	−1.449385
H	−4.183626	−0.955209	−1.897106
C	−5.271612	−1.844862	0.601891
H	−3.232514	−1.760776	1.442336
H	−4.288873	−0.409879	1.926282
H	−6.464381	−1.364667	−1.189459
H	−6.395813	−0.074731	0.021777
H	−4.981707	−2.791556	0.138502
H	−5.984074	−2.057448	1.399968

***anti*-100**

B3LYP // 6-311+G(d,p) (C,H,P,O) // LANL2DZ (Cu) // PCM (Tetralin) // 298.15 °C

Sum of electronic and thermal Free Energies = −857.9087 a.u.

C	−2.078435	0.882238	1.248324
C	−0.534165	1.112083	1.277487
H	−0.281744	1.719568	0.399020
H	−0.055053	0.138968	1.113138
C	0.049821	1.770670	2.543054
H	−0.180244	1.129420	3.405563
C	−0.548592	3.162520	2.817904
H	−0.366827	3.851870	1.984711
H	−1.638032	3.139953	2.978414
H	−0.110144	3.619148	3.710574
C	−2.509726	0.372285	−0.116949
C	−2.211592	−0.929240	−0.546538
C	−3.195276	1.209959	−1.005792
C	−2.587029	−1.375439	−1.812541
H	−1.681017	−1.605999	0.114564
C	−3.573400	0.770031	−2.274737
H	−3.438139	2.222283	−0.697067
C	−3.270662	−0.527280	−2.684417
H	−2.346187	−2.387971	−2.119045
H	−4.106391	1.440352	−2.940766
H	−3.564551	−0.874569	−3.668736
Cu	2.007033	1.813022	2.482695
C	−2.553658	−0.033359	2.388882
H	−3.633500	−0.199410	2.335973
H	−2.061845	−1.010561	2.352089
H	−2.327568	0.410676	3.361059
H	−2.563307	1.854568	1.384179
O	4.037921	1.895314	2.382938
C	4.889631	0.998956	3.134363
H	4.914505	0.023762	2.638500
H	5.901454	1.418101	3.125410
C	4.368958	0.875869	4.552215
H	3.354472	0.469876	4.565129
H	5.013706	0.197685	5.117745
H	4.362198	1.846561	5.052330
C	4.625780	2.423113	1.169242
H	3.970210	3.244113	0.876790
H	5.603672	2.842876	1.428466
C	4.740957	1.397500	0.052417
H	3.763589	0.969971	−0.183702
H	5.125090	1.887684	−0.846642
H	5.426788	0.586442	0.306995

syn-**98**
B3LYP // 6-311+G(d,p) (C,H,P,O) // LANL2DZ (Cu) // 298.15 °C
Sum of electronic and thermal Free Energies = −1429.0220 a.u.

C	3.551191	−1.134768	−0.455345
C	2.260659	−0.897398	0.382029
H	1.971399	0.142613	0.192193
H	2.519691	−0.930621	1.449733
C	1.079550	−1.866986	0.113759
C	4.558599	−0.018187	−0.224258
C	5.218545	0.132455	1.004430
C	4.838597	0.911600	−1.233393
C	6.124927	1.170690	1.213929
H	5.024177	−0.568592	1.809170
C	5.745036	1.953717	−1.030389
H	4.341091	0.816242	−2.193885
C	6.393198	2.087799	0.196305
H	6.623120	1.264283	2.173122
H	5.944642	2.658090	−1.831005
H	7.099047	2.894823	0.358523
Cu	−0.667131	−0.923035	0.092982
C	4.182480	−2.522273	−0.246014
H	5.077199	−2.638661	−0.865105
H	4.473113	−2.680940	0.796608
H	3.479220	−3.311191	−0.520339
H	3.251295	−1.073917	−1.509232
P	−2.691677	0.160168	0.052654
O	−2.752245	1.653153	−0.614725
O	−3.938551	−0.517841	−0.741016
O	−3.316782	0.294074	1.533072
C	−4.620364	0.885486	1.831696
H	−4.677125	1.863008	1.347939
H	−5.389950	0.237629	1.409226
C	−4.745395	0.998047	3.335852
H	−3.965408	1.642855	3.746627
H	−5.717794	1.429477	3.588632
H	−4.672770	0.015516	3.807204
C	−3.841281	−0.840038	−2.156451
H	−3.853425	0.094396	−2.722220
H	−2.890368	−1.349519	−2.342644
C	−5.015508	−1.723762	−2.520370
H	−5.960884	−1.213564	−2.322693
H	−4.972630	−1.967140	−3.585314
H	−4.992951	−2.655935	−1.951904
C	−1.686990	2.618678	−0.390724
H	−1.872376	3.114987	0.565322
H	−0.729448	2.091926	−0.326343
C	−1.690976	3.610171	−1.535373
H	−2.654127	4.121099	−1.602706
H	−0.914268	4.361842	−1.371057
H	−1.491794	3.109732	−2.485521
C	1.051570	−3.056354	1.096470
H	1.991259	−3.629258	1.121884
H	0.861371	−2.723357	2.123359
H	0.254456	−3.764534	0.844239

H	1.203788	−2.274137	−0.901659

***ts*-98**

B3LYP // 6-311+G(d,p) (C,H,P,O) // LANL2DZ (Cu) // 298.15 °C

Sum of electronic and thermal Free Energies = −1428.9438 a.u.

C	−3.883979	−0.306324	−0.683391
C	−2.811056	0.210288	0.335418
H	−3.143236	−0.115351	1.341815
H	−2.859659	1.308511	0.342777
C	−1.401821	−0.251919	0.043226
H	−0.746045	0.657234	0.034884
C	−1.110021	−1.680357	0.511591
H	−1.451174	−1.894728	1.544368
H	−1.627882	−2.402990	−0.140160
H	−0.054719	−2.035573	0.462338
C	−5.295116	−0.068122	−0.170225
C	−5.801345	1.230652	0.013998
C	−6.131045	−1.145689	0.161824
C	−7.091994	1.442621	0.504662
H	−5.180218	2.089438	−0.229781
C	−7.425079	−0.941840	0.652523
H	−5.761341	−2.161412	0.032199
C	−7.912500	0.355970	0.826190
H	−7.458253	2.458426	0.636915
H	−8.050409	−1.797336	0.898435
H	−8.917626	0.520189	1.207101
C	−3.660632	0.293948	−2.081520
H	−4.349509	−0.138038	−2.818097
H	−3.814101	1.381501	−2.078181
H	−2.629074	0.100657	−2.396498
H	−3.752216	−1.394278	−0.767177
Cu	0.710184	−0.138902	0.410883
P	2.889231	0.045093	0.204974
O	3.599942	−1.377158	0.547939
C	5.032344	−1.589622	0.621014
H	5.502674	−1.181037	−0.281177
H	5.414049	−1.049847	1.495253
C	5.282862	−3.081778	0.748234
H	4.896658	−3.618248	−0.124781
H	6.360067	−3.272393	0.824710
H	4.795342	−3.480577	1.643732
O	3.577784	1.161904	1.150746
C	4.745021	1.977880	0.854816
H	5.630554	1.332896	0.822420
H	4.612555	2.433759	−0.129722
C	4.862686	3.021990	1.950046
H	5.738476	3.654874	1.762116
H	3.972752	3.659152	1.975351
H	4.978982	2.550698	2.931581
O	3.509625	0.501956	−1.243682
C	2.993057	−0.066337	−2.475981
H	3.416732	−1.070386	−2.597158
H	1.901786	−0.158473	−2.399937

C	3.389506	0.844064	−3.623770
H	4.478533	0.944032	−3.688230
H	3.024813	0.424160	−4.568660
H	2.953548	1.840720	−3.498618

***syn*-4a**

B3LYP // 6-311+G(d,p) (C,H,Si) // LANL2DZ (Zn) // PCM (*n*-pentane) // 298.15 °C

Sum of electronic and thermal free energies = −942.253754 a.u.

C	−2.82766400	1.11136400	0.28838300
C	−1.38804300	0.49954100	0.21026600
H	−1.47198000	−0.48059500	−0.27084600
H	−1.04030000	0.29941600	1.23322400
C	−0.33885400	1.33004700	−0.55636800
C	−3.90212200	0.04881900	0.11493200
C	−4.04085000	−1.00419000	1.03089000
C	−4.77843700	0.08693100	−0.97532900
C	−5.01894700	−1.98159800	0.86177400
H	−3.37665100	−1.06435200	1.88685300
C	−5.76108800	−0.88872600	−1.14964200
H	−4.69095300	0.89242800	−1.69803300
C	−5.88537200	−1.92826300	−0.23078600
H	−5.10618800	−2.78621700	1.58413700
H	−6.42806600	−0.83479100	−2.00342900
H	−6.64757800	−2.68810200	−0.36233200
C	−3.05821600	1.91396000	1.58393700
H	−4.04773600	2.38004800	1.58589900
H	−2.99604200	1.26413900	2.46203100
H	−2.31107000	2.70099800	1.70170000
H	−2.92850400	1.80288800	−0.55633100
C	3.09729300	−0.90405500	−1.04257000
H	3.46713500	−0.71537500	−2.05865500
H	2.77220900	−1.95250000	−1.01651100
Si	4.46516000	−0.62619400	0.20275000
C	5.10635200	1.15490400	0.08223600
H	5.46228400	1.37844800	−0.92898900
H	4.33063700	1.88773500	0.32891100
H	5.94251600	1.32194800	0.76895300
C	3.82132800	−0.91840300	1.96356800
H	3.04446300	−0.19804000	2.24178600
H	3.39433300	−1.92155800	2.06720000
H	4.62699100	−0.82739200	2.69935000
C	5.93310000	−1.79517600	−0.07677400
H	6.73029100	−1.62188400	0.65416700
H	5.62436600	−2.84202100	0.00932700
H	6.36103400	−1.65955900	−1.07522200
Zn	1.40222500	0.23247000	−0.79599700
C	−0.06210400	2.72416300	0.03080300
H	0.29533600	2.66763200	1.06579400
H	0.70255600	3.25829900	−0.54340400
H	−0.95093000	3.36942500	0.03470400
H	−0.71539200	1.46570800	−1.58081300

anti-**4a**

B3LYP // 6-311+G(d,p) (C,H,Si) // LANL2DZ (Zn) // PCM (*n*-pentane) // 298.15 °C

Sum of electronic and thermal free energies = −942.258064 a.u.

C	2.80932800	−0.94119600	0.59852400
C	1.43936400	−0.51608500	−0.01121000
H	1.60035900	−0.35471600	−1.08522400
H	1.18736200	0.46903200	0.40282900
C	0.25990900	−1.48554000	0.19584000
H	0.07067400	−1.58609700	1.27244200
C	0.51727400	−2.88842100	−0.38088600
H	0.72307300	−2.85111500	−1.45742600
H	1.37413100	−3.39308100	0.08663300
H	−0.34416400	−3.55037800	−0.24244500
C	3.89548600	0.04269700	0.19256200
C	3.94842100	1.34041500	0.72046600
C	4.86532400	−0.31906800	−0.75001100
C	4.93530500	2.24035600	0.32274800
H	3.21401200	1.65486700	1.45425500
C	5.85551700	0.57722800	−1.15276400
H	4.84613100	−1.31917700	−1.17241500
C	5.89476200	1.86275800	−0.61679800
H	4.95646700	3.23789000	0.74849100
H	6.59667800	0.26920500	−1.88247500
H	6.66405900	2.56198000	−0.92484800
C	2.73585400	−1.13301900	2.12244500
H	3.71321600	−1.40655900	2.52881800
H	2.40702500	−0.21988500	2.62827400
H	2.02993600	−1.92543300	2.38239100
H	3.08342500	−1.90555900	0.15834700
C	−3.23946900	0.16197600	−1.26372200
H	−3.72239100	−0.57676400	−1.91595700
H	−2.94421400	1.00312100	−1.90454000
Si	−4.43603300	0.74496600	0.05103800
C	−5.04625500	−0.72833800	1.07817700
H	−5.52445400	−1.48122200	0.44283900
H	−4.22854000	−1.22054100	1.61537100
H	−5.78275600	−0.41248000	1.82412900
C	−3.58339400	1.97929800	1.21333100
H	−2.75786700	1.51901600	1.76722700
H	−3.17433100	2.82894000	0.65639400
H	−4.28666800	2.37898400	1.95115900
C	−5.95239500	1.60558600	−0.69656700
H	−6.64883400	1.94100400	0.07947000
H	−5.65797700	2.48296900	−1.28148100
H	−6.49777900	0.93228900	−1.36563500
Zn	−1.49341000	−0.67659000	−0.56379900

***ts*-4a**

B3LYP // 6-311+G(d,p) (C,H,Si) // LANL2DZ (Zn) // PCM (*n*-pentane) // 298.15 °C

Sum of electronic and thermal free energies = −942.105132 a.u.

C	2.34233700	0.44842300	0.47200200
C	1.52453000	−0.51168200	−0.45256400
H	2.06215600	−1.47553300	−0.49793000
H	1.55471900	−0.09753800	−1.47130200
C	0.07171500	−0.66227700	−0.00248600
H	−0.49732500	−0.68899400	−0.99618900
C	−0.03947800	−1.79109400	1.06456000
H	0.46783200	−2.75179800	0.82566700
H	0.45682900	−1.40844600	1.97170900
H	−1.04995500	−2.06031600	1.44606500
C	3.83684900	0.34178200	0.19469200
C	4.37590800	0.71872100	−1.04165200
C	4.70974200	−0.14540300	1.17685600
C	5.74530200	0.61362100	−1.29402900
H	3.72586000	1.10085200	−1.82437400
C	6.08186500	−0.25179300	0.93110400
H	4.30734700	−0.44360800	2.14244300
C	6.61028800	0.12780600	−0.30289700
H	6.14555500	0.91263200	−2.25921900
H	6.73649000	−0.63024300	1.71171100
H	7.66814800	0.04734900	−0.49141100
C	1.82707000	1.89026600	0.36103100
H	2.32318400	2.54875800	1.08232700
H	2.00216200	2.30358000	−0.64548800
H	0.75051800	1.91133800	0.54196700
H	2.17738900	0.12274400	1.50790300
C	−3.94851900	−1.05744800	−0.24635900
H	−4.33702300	−1.68481000	0.57121500
H	−4.47362300	−1.35404600	−1.16346000
Si	−4.10678800	0.79007200	0.10715000
C	−3.35450500	1.18241900	1.79277500
H	−3.85138700	0.61950500	2.59706200
H	−2.28272000	0.93155000	1.80983400
H	−3.44717200	2.24932100	2.03282600
C	−3.11323500	1.68734900	−1.25223400
H	−2.06772200	1.22698300	−1.30692500
H	−3.60729700	1.55820600	−2.23937600
H	−2.98629100	2.79498000	−1.04652700
C	−5.93458000	1.30953400	0.07845100
H	−6.04178500	2.39005800	0.24733900
H	−6.40692600	1.07537300	−0.87941600
H	−6.49712900	0.79398400	0.86642400
Zn	−1.99161800	−1.48180800	−0.49694900

syn-**4a** + 1 diethyl ether
B3LYP // 6-311+G(d,p) (C,H,Si,O) // LANL2DZ (Zn) // PCM (*n*-pentane) // 298.15 °C
Sum of electronic and thermal free energies = −1175.870205 a.u.

C	2.77266100	−1.41704100	−0.93200100
C	1.39463000	−0.95442700	−0.34551900
H	1.58929500	−0.14481500	0.36628300
H	0.98160000	−1.77864900	0.25259100
C	0.34745200	−0.46833500	−1.36777300
C	3.94897100	−0.90398800	−0.11678600
C	4.09622300	−1.23354900	1.23880200
C	4.92374900	−0.08620300	−0.69955600
C	5.17632400	−0.76245400	1.98170900
H	3.35765800	−1.86532500	1.72141600
C	6.00890800	0.38828800	0.03911900
H	4.83323100	0.18052800	−1.74818600
C	6.13978900	0.05177400	1.38453400
H	5.26798200	−1.03222000	3.02850600
H	6.75126500	1.01886200	−0.43857600
H	6.98185200	0.41694500	1.96185800
C	2.85374700	−2.94857600	−1.09114300
H	3.79293600	−3.24726800	−1.56598500
H	2.80201200	−3.44393600	−0.11673700
H	2.02871100	−3.32581300	−1.69869400
H	2.86349700	−0.97334000	−1.93028000
C	−3.23479900	0.26719700	0.49433500
H	−3.87752100	0.94093400	−0.08874100
H	−3.10656100	0.73379600	1.48064900
Si	−4.07992200	−1.38479400	0.68658800
C	−4.40153100	−2.16754100	−1.01217800
H	−5.01087000	−1.50841100	−1.63984200
H	−3.46964400	−2.36754900	−1.55093000
H	−4.93726700	−3.11776600	−0.91719600
C	−3.00017000	−2.57004500	1.70321500
H	−2.05045800	−2.78486600	1.20206700
H	−2.76694800	−2.14584600	2.68575300
H	−3.50697700	−3.52618700	1.87015800
C	−5.75465900	−1.23834300	1.57361000
H	−6.24368600	−2.21258600	1.68252300
H	−5.63301300	−0.81331800	2.57545600
H	−6.43641300	−0.58391400	1.02035000
Zn	−1.35754600	0.26239700	−0.39966900
O	−0.76780700	2.56292300	−0.06287700
C	−1.76650200	3.57942000	0.15164600
H	−1.39521500	4.30428100	0.88344800
H	−2.61705600	3.06260500	0.59702000
C	−2.17552200	4.26876400	−1.14320300
H	−2.58232300	3.54573500	−1.85426200
H	−2.94765600	5.01594400	−0.93697400
H	−1.33376600	4.78068500	−1.61621800
C	0.59259400	3.03854500	−0.08513500
H	0.63607400	3.98879000	−0.62807300
H	1.14958800	2.30167700	−0.66466700
C	1.18269700	3.17795900	1.31155500
H	2.22270900	3.50932100	1.24125600
H	0.63830100	3.90975900	1.91361800

H	1.16742100	2.21958400	1.83561000
C	−0.02791400	−1.52422600	−2.42224100
H	−0.46456900	−2.42005100	−1.96405300
H	−0.76760900	−1.13811700	−3.13206800
H	0.82934800	−1.86083700	−3.02266700
H	0.78193500	0.38987100	−1.90149300

anti-**4a** + 1 diethyl ether
B3LYP // 6-311+G(d,p) (C,H,Si,O) // LANL2DZ (Zn) // PCM (*n*-pentane) // 298.15 °C
Sum of electronic and thermal free energies = −1175.873046 a.u.

C	−2.83768900	−0.93326400	1.18916900
C	−1.54705600	−0.33221500	0.55155500
H	−1.81246000	0.66387400	0.17423400
H	−1.31750600	−0.93162800	−0.33983800
C	−0.29990900	−0.23207400	1.44931000
H	−0.04149100	−1.24491200	1.78886700
C	−0.51969500	0.63448800	2.70091800
H	−0.77524700	1.66960200	2.44355000
H	−1.32796400	0.26495400	3.34886100
H	0.37965700	0.67733600	3.32471000
C	−4.01537600	−0.78199600	0.23955300
C	−4.10612600	−1.52536600	−0.94605300
C	−5.03563400	0.13748100	0.51217800
C	−5.17584600	−1.35624500	−1.82310200
H	−3.33495300	−2.24836400	−1.18936700
C	−6.10927700	0.31153300	−0.36150500
H	−4.98973800	0.72320600	1.42543700
C	−6.18383700	−0.43576600	−1.53520000
H	−5.22360700	−1.94556800	−2.73269700
H	−6.88784500	1.02824300	−0.12257900
H	−7.01750700	−0.30568000	−2.21625100
C	−2.63821800	−2.38884100	1.64288700
H	−3.55783700	−2.79515100	2.07282300
H	−2.34585700	−3.03336300	0.80799700
H	−1.85359000	−2.45595400	2.40020900
H	−3.07700600	−0.34084400	2.07848800
C	3.24639400	−0.12558500	−0.52955000
H	4.01374900	0.47010000	−0.01638000
H	3.20199900	0.24328900	−1.56326000
Si	3.74397100	−1.92341300	−0.52178400
C	3.87976800	−2.56464500	1.25955000
H	4.60535400	−1.97961400	1.83483200
H	2.91999400	−2.50819900	1.78352300
H	4.20726100	−3.60920600	1.28321700
C	2.45428800	−2.97016200	−1.44149300
H	1.47663500	−2.93241100	−0.94956100
H	2.32123100	−2.61747500	−2.46991700
H	2.75645800	−4.02141700	−1.49123700
C	5.42205300	−2.21806500	−1.36465300
H	5.70178300	−3.27724200	−1.35330300
H	5.40028800	−1.89092400	−2.40947700
H	6.21799300	−1.65840900	−0.86223400
Zn	1.40955500	0.29535500	0.35717800
O	1.16651200	2.55529000	−0.24633900

C	2.31690500	3.35869100	−0.58400300
H	2.06137200	4.01995200	−1.41818800
H	3.07112200	2.65428400	−0.93499600
C	2.83415700	4.15210400	0.60788600
H	3.12458600	3.48325400	1.42155400
H	3.71401000	4.73128100	0.31236700
H	2.08598000	4.85217000	0.98809100
C	−0.09832700	3.24363200	−0.32752300
H	0.02353900	4.26659800	0.04332800
H	−0.76182400	2.72013100	0.36092700
C	−0.67182900	3.23456300	−1.73738700
H	−1.63776700	3.74784800	−1.74660400
H	−0.01519800	3.74445900	−2.44669700
H	−0.82843400	2.21100700	−2.08530300

***syn*-123a**

B3LYP // 6-311+G(d,p) (C,H,N,Cl) // LANL2DZ (Pd) // PCM (*n*-pentane) // 298.15 °C

Sum of electronic and thermal free energies = −2422.005069 a.u.

Pd	0.00074800	−0.20897500	−0.78119800
C	−1.65225200	−1.39769900	0.03750300
C	−2.76568300	−2.84594800	1.42945600
C	−3.56858300	−2.61648000	0.37293500
H	−2.90663800	−3.45321300	2.30642800
H	−4.54841800	−2.99204200	0.13655500
N	−1.60408500	−2.10671000	1.21535200
N	−2.88837700	−1.73323400	−0.46505300
C	−3.50181300	−1.27479000	−1.69001000
C	−4.67036900	−0.49711400	−1.60230000
C	−2.98243000	−1.69239000	−2.92660400
C	−5.29538600	−0.11396100	−2.79349900
C	−3.64310500	−1.28649100	−4.08943600
C	−4.78850700	−0.50085500	−4.02825600
H	−6.18992100	0.49737000	−2.74301000
H	−3.24996600	−1.59671800	−5.05132600
H	−5.28578600	−0.19267000	−4.94109100
C	−0.49897400	−2.19124600	2.14119800
C	−0.19918900	−1.09955800	2.97184800
C	0.19211900	−3.41151400	2.23875400
C	0.83906000	−1.24681300	3.89718300
C	1.21683700	−3.51423000	3.18413900
C	1.54265400	−2.44144000	4.00604900
H	1.08669400	−0.41234800	4.54407300
H	1.76673900	−4.44552400	3.26571500
H	2.34349500	−2.53602000	4.73069500
C	−0.13654400	−4.59865800	1.36488800
H	0.71188900	−5.28375100	1.32511000
H	−0.99242400	−5.15999400	1.75301000
H	−0.38286900	−4.29746700	0.34589100
C	−0.95623400	0.19872100	2.88931700
H	−0.72099900	0.83148500	3.74644000
H	−0.69277600	0.73809600	1.97601200
H	−2.03655300	0.03716400	2.86975600
C	−1.74433800	−2.54229900	−3.03007200
H	−1.75891200	−3.36692300	−2.31283600
H	−1.64911900	−2.95776200	−4.03476600
H	−0.85893200	−1.93512800	−2.81630000
C	−5.28124800	−0.08410000	−0.28408000
H	−4.52792100	0.12637700	0.47395700
H	−5.88792700	0.81297700	−0.41512800
H	−5.93835600	−0.86556900	0.11178200
C	−0.99000600	1.62075600	−1.13518200
C	−2.22066300	1.93747100	−0.25583700
H	−3.13396500	1.87402300	−0.85972800
H	−2.33993300	1.20245700	0.54136100
C	−2.16867800	3.33727700	0.42155200
H	−1.24021400	3.36863200	1.00494600
C	−2.10994900	4.49945400	−0.58663800
H	−2.05334000	5.46053200	−0.06727700
H	−1.23261300	4.41158100	−1.23062800
H	−2.99468700	4.51856300	−1.22985000

C	−3.31300200	3.51804500	1.40857900
C	−3.06781000	3.56203900	2.78628900
C	−4.64220900	3.63967700	0.97884300
C	−4.10625600	3.71989400	3.70506000
H	−2.04650000	3.47628000	3.14430400
C	−5.68426500	3.79799400	1.89047000
H	−4.86760600	3.61463700	−0.08187300
C	−5.42149100	3.83792500	3.26033500
H	−3.88600600	3.75432400	4.76683800
H	−6.70370900	3.89354200	1.53146600
H	−6.23153500	3.96406200	3.97013500
C	2.58050900	−1.75623300	0.27557200
C	1.66628900	−2.99623700	−1.43151600
C	3.72088300	−2.55250000	0.27681400
H	2.48413700	−0.91871800	0.95321400
C	2.77867400	−3.82977300	−1.49214400
H	0.83011200	−3.14389300	−2.10237600
C	3.83797600	−3.60792500	−0.61876900
H	2.81546700	−4.63563800	−2.21473100
H	4.72502500	−4.22844600	−0.63377200
N	1.56438700	−1.97796500	−0.56742200
Cl	5.01254100	−2.20438700	1.41067100
C	1.64514400	0.74588100	−1.54803800
H	2.10593200	0.20267800	−2.38606600
C	2.30933300	1.83481500	−1.14113800
H	1.91753900	2.43336400	−0.31429000
C	3.60104600	2.36078400	−1.72669200
H	3.88028100	1.75272100	−2.59584800
H	3.44629700	3.38454200	−2.09997700
C	4.76914900	2.38841400	−0.72487500
H	4.96277900	1.36680400	−0.37504200
H	4.46861300	2.96200000	0.16181500
C	6.05817200	2.98601000	−1.30046000
H	6.35334100	2.41703100	−2.19208900
H	5.85905000	4.00901200	−1.64614500
C	7.22591300	3.00735900	−0.30767800
H	7.42624000	1.98461600	0.03782400
H	6.93238100	3.57657100	0.58430400
C	8.51497400	3.60503300	−0.88340600
H	8.80916800	3.03627500	−1.77412400
H	8.31556900	4.62717100	−1.22806100
C	9.67560600	3.62215900	0.11600400
H	9.92142700	2.60994800	0.45320100
H	10.57863400	4.05353000	−0.32562500
H	9.42450300	4.21316500	1.00274400
H	−0.20828500	2.33901900	−0.88483700
C	−1.29890600	1.75876700	−2.63056100
H	−1.99730300	0.99199000	−2.97577900
H	−1.76204300	2.73215400	−2.85422800
H	−0.38983600	1.67859600	−3.23079700

***anti*-123a**

B3LYP // 6-311+G(d,p) (C,H,N,Cl) // LANL2DZ (Pd) // PCM (*n*-pentane) // 298.15 °C

Sum of electronic and thermal free energies = −2422.004603 a.u.

Pd	0.14462100	0.17323100	−0.10155000
C	−1.36408700	−1.36220800	−0.60846700
C	−2.27445300	−3.43886600	−0.98727600
C	−2.88369000	−2.57962200	−1.82728700
H	−2.40429000	−4.49676800	−0.83848300
H	−3.65057600	−2.73661500	−2.56541500
N	−1.35784900	−2.69044400	−0.25282600
N	−2.33343400	−1.32152800	−1.58669400
C	−2.86354200	−0.16396600	−2.27267000
C	−4.18169300	0.22839100	−1.98086400
C	−2.10555700	0.47196300	−3.26844700
C	−4.72347800	1.29835500	−2.70034800
C	−2.68648600	1.53989300	−3.95769100
C	−3.98503500	1.95257300	−3.67899900
H	−5.73389700	1.62094100	−2.47605000
H	−2.11041700	2.04409600	−4.72589400
H	−4.42030200	2.78192800	−4.22546100
C	−0.54796200	−3.30275300	0.77181900
C	−0.91320600	−3.12894000	2.11693600
C	0.51451000	−4.13638700	0.38882700
C	−0.13336600	−3.75510300	3.09298500
C	1.26136500	−4.75121300	1.39957100
C	0.95054600	−4.55365100	2.74011300
H	−0.39080000	−3.62227000	4.13803400
H	2.09690300	−5.38593300	1.12570600
H	1.54643900	−5.03001100	3.51052200
C	0.83978900	−4.40767600	−1.06000700
H	1.86533800	−4.76698400	−1.15950200
H	0.18124200	−5.17932300	−1.47250900
H	0.72378100	−3.51683100	−1.67716000
C	−2.14200100	−2.34728000	2.50510900
H	−2.22043400	−2.26999000	3.59041500
H	−2.12809300	−1.34181500	2.08624200
H	−3.04762000	−2.84046800	2.13643900
C	−0.70129700	0.04379700	−3.59385600
H	−0.61897000	−1.04232200	−3.68399800
H	−0.36836200	0.49737500	−4.52911000
H	−0.02909400	0.35953500	−2.78947800
C	−5.02551800	−0.46299100	−0.93691400
H	−4.42771100	−0.82187200	−0.09946600
H	−5.77797600	0.22300500	−0.54661300
H	−5.55054000	−1.32652600	−1.35928400
C	−0.92834500	1.51658100	1.14106100
H	−0.53414800	2.49594200	0.86740700
C	−2.44767400	1.54341300	0.94258300
H	−2.68045100	1.74839700	−0.10641400
H	−2.87523500	0.56042000	1.16705900
C	−3.20665100	2.60034000	1.81339600
H	−2.97752900	2.38575100	2.86207200
C	−0.51665900	1.22345700	2.58816600
H	−0.92805500	1.96466100	3.29031200
H	−0.86181400	0.24201100	2.92668300

H	0.56827200	1.25005600	2.69714600
C	−2.73696100	4.03503900	1.52515500
H	−3.33216500	4.76375900	2.08294000
H	−1.69181200	4.16400400	1.81261200
H	−2.81168900	4.28013400	0.46125200
C	−4.71199400	2.43167100	1.67348800
C	−5.40310300	1.59109100	2.55765300
C	−5.45460100	3.07562200	0.67508200
C	−6.77919700	1.39634400	2.45226600
H	−4.85187300	1.08781300	3.34653500
C	−6.83281000	2.88806700	0.56588400
H	−4.95704100	3.73659300	−0.02498100
C	−7.50303900	2.04650800	1.45281500
H	−7.28725500	0.74476200	3.15540300
H	−7.38486300	3.40566400	−0.21182100
H	−8.57511900	1.90518700	1.37135900
C	2.70127600	−1.64834000	−0.01633500
C	2.46883900	−1.05720900	−2.22390900
C	3.97819500	−2.14469200	−0.25648400
H	2.27307100	−1.67408700	0.97699200
C	3.73808400	−1.53225400	−2.53875100
H	1.84791200	−0.60897600	−2.98765300
C	4.51998800	−2.09181800	−1.53440900
H	4.10911800	−1.45843200	−3.55352900
H	5.51532600	−2.46863700	−1.73268300
N	1.95283600	−1.11399100	−0.98931300
Cl	4.90003200	−2.82816500	1.07008100
C	1.56849100	1.64087500	0.05961400
H	1.40504400	2.49227700	−0.61470800
C	2.65632300	1.71429900	0.83459600
H	2.87468400	0.91414800	1.54754700
C	3.67103000	2.83704600	0.83827000
H	3.34132400	3.62456300	0.14976400
H	3.71130200	3.29525900	1.83813200
C	5.09337100	2.38800900	0.45917300
H	5.07347400	1.96287600	−0.55209700
H	5.40375600	1.57334000	1.12645400
C	6.13099500	3.51481700	0.52059100
H	5.81543900	4.33277800	−0.14052900
H	6.14879800	3.93477700	1.53492600
C	7.54647400	3.07185100	0.13325800
H	7.52935600	2.65170500	−0.88121900
H	7.86394600	2.25478700	0.79463500
C	8.58473000	4.19831900	0.19236600
H	8.26812500	5.01491900	−0.46811000
H	8.60394100	4.61755300	1.20580900
C	9.99489700	3.74530600	−0.19800900
H	10.01503700	3.35314000	−1.22006100
H	10.71024000	4.57114900	−0.14535500
H	10.35327600	2.95253800	0.46663800

***syn*-123b**

B3LYP // 6-311+G(d,p) (C,H,N,Cl) // LANL2DZ (Pd) // PCM (*n*-pentane) // 298.15 °C

Sum of electronic and thermal free energies = −2421.996657 a.u.

Pd	−0.12367300	0.09500100	0.39320800
C	0.74556700	−1.57669500	−0.32151300
C	1.34327300	−3.24176100	−1.76912100
C	1.77002400	−3.60823100	−0.54602000
H	1.42565500	−3.73259300	−2.72272700
H	2.29342200	−4.48720600	−0.21424500
N	0.71291000	−2.00702300	−1.62757400
N	1.40729000	−2.58786600	0.33370400
C	1.73985900	−2.66328500	1.73775600
C	3.09644700	−2.63778300	2.10774600
C	0.71737900	−2.86219400	2.68249500
C	3.40795200	−2.73831100	3.46778400
C	1.07967100	−2.95591000	4.02940000
C	2.41092900	−2.88305700	4.42444000
H	4.44873200	−2.70218600	3.77099900
H	0.30231100	−3.10193400	4.77146600
H	2.67115400	−2.95410900	5.47467100
C	0.03684000	−1.38715100	−2.74612700
C	0.57751300	−0.23319500	−3.33496800
C	−1.10805900	−2.01733600	−3.26365700
C	−0.08218900	0.31105400	−4.44053600
C	−1.73092500	−1.43885500	−4.37367500
C	−1.22971800	−0.28118200	−4.95617100
H	0.32056800	1.20543000	−4.90344300
H	−2.62458100	−1.90426100	−4.77506900
H	−1.72897200	0.15612000	−5.81373400
C	−1.98994900	1.83677800	2.10407900
C	−0.98736200	3.03414200	0.40522200
C	−2.69157700	2.95400300	2.53790100
H	−2.10281400	0.87747500	2.58879000
C	−1.67562300	4.18435900	0.77638200
H	−0.30092400	3.04129100	−0.42999200
C	−2.54064200	4.16105100	1.86221900
H	−3.35369000	2.87660600	3.39088800
H	−3.07638200	5.05149800	2.16517800
N	−1.14446300	1.87566700	1.06097200
Cl	−1.43170000	5.65786200	−0.13998600
C	−2.02049300	−0.71365400	−0.12803400
H	−2.15524500	−1.80047900	−0.07614600
C	−3.11851900	−0.05377000	−0.52502100
H	−3.09895300	1.03464900	−0.62828000
C	−4.45351300	−0.67066600	−0.88189100
H	−4.68912800	−0.45123100	−1.93452400
H	−4.38487500	−1.76218300	−0.79955000
C	−5.62137100	−0.16565200	−0.01626400
H	−5.65420600	0.93086300	−0.06142300
H	−5.42383900	−0.42207500	1.03218000
C	−6.98504400	−0.72871000	−0.43282500
H	−7.17815800	−0.46716200	−1.48159500
H	−6.94977800	−1.82560100	−0.39530100
C	−8.14872600	−0.23272900	0.43293800
H	−8.18655500	0.86406000	0.39456200

H	−7.95631300	−0.49320700	1.48218800
C	−9.51228600	−0.79713800	0.01750700
H	−9.47582500	−1.89275300	0.05763700
H	−9.70511300	−0.53778900	−1.03074800
C	−10.66824100	−0.29392400	0.88733800
H	−11.62495400	−0.71507000	0.56521600
H	−10.52123900	−0.56814200	1.93703200
H	−10.75261500	0.79660400	0.83991400
C	−1.67289600	−3.29107000	−2.68228400
H	−2.72930100	−3.38428000	−2.93923900
H	−1.15978100	−4.17296200	−3.08039600
H	−1.58367800	−3.31971900	−1.59683900
C	1.83285700	0.41446800	−2.81640800
H	2.17345700	1.18906500	−3.50539900
H	1.65881600	0.86737400	−1.83796100
H	2.64094700	−0.31133700	−2.69521900
C	−0.72923400	−3.00504400	2.28834900
H	−0.84765300	−3.68871600	1.44345800
H	−1.31156200	−3.39380700	3.12558400
H	−1.15364600	−2.04705400	1.98010500
C	4.22195500	−2.55486600	1.10395800
H	3.95999900	−1.96692100	0.22658200
H	5.10455100	−2.10540600	1.56163700
H	4.50948200	−3.55411100	0.75916300
C	1.69988600	1.11410200	1.10764900
C	3.11647900	0.78644800	0.58680000
H	3.67525800	0.24718600	1.36141000
H	3.08518900	0.11322600	−0.27305200
C	3.96123500	2.01908800	0.14934200
H	3.38414200	2.53622700	−0.62771700
C	4.20031400	3.03259700	1.28322500
H	4.77033500	3.89315800	0.92076900
H	3.25201400	3.39867400	1.68230100
H	4.75974400	2.58558200	2.11018700
C	5.27270200	1.59013700	−0.49305600
C	5.50279100	1.79542500	−1.85865200
C	6.28571700	0.96971200	0.25238500
C	6.69647200	1.39835800	−2.46299700
H	4.73620100	2.27762200	−2.45740100
C	7.48034900	0.57112700	−0.34399900
H	6.14218300	0.79789500	1.31380500
C	7.69193000	0.78280900	−1.70707400
H	6.84804400	1.57281800	−3.52301800
H	8.24927200	0.09595400	0.25617400
H	8.62205000	0.47450300	−2.17149300
H	1.46939500	2.13978400	0.78665600
C	1.65778700	1.07984800	2.64401100
H	1.80668200	0.06368600	3.02220100
H	2.44027800	1.70381200	3.10493600
H	0.70024500	1.43193600	3.03947400

anti-**123b**

B3LYP // 6-311+G(d,p) (C,H,N,Cl) // LANL2DZ (Pd) // PCM (*n*-pentane) // 298.15 °C

Sum of electronic and thermal free energies = −2421.99907 a.u.

Pd	−0.14162800	0.46557300	0.15088700
C	0.59704600	−0.31822500	−1.55756200
C	0.93776500	−0.57474600	−3.80497100
C	1.06994800	−1.79152200	−3.24117400
H	1.02020400	−0.25496600	−4.82932100
H	1.29160800	−2.75191400	−3.67300400
N	0.65322600	0.31974700	−2.77423800
N	0.86858400	−1.63056700	−1.87020400
C	1.12518300	−2.72140000	−0.95192200
C	2.46679900	−3.05659700	−0.69359200
C	0.06058600	−3.48007500	−0.43658800
C	2.72472500	−4.11927700	0.17821600
C	0.36882400	−4.53450900	0.42971100
C	1.68592100	−4.84489100	0.74879500
H	3.75446400	−4.37604600	0.40073200
H	−0.44167700	−5.12553600	0.84226600
H	1.90233700	−5.66521400	1.42440800
C	0.58921200	1.74655600	−3.01101500
C	1.78731000	2.47824700	−2.91951500
C	−0.61095100	2.34034600	−3.43125700
C	1.74298400	3.85197100	−3.16611500
C	−0.60549800	3.71971400	−3.67400000
C	0.55162000	4.47382500	−3.52707300
H	2.65570100	4.43204400	−3.08565400
H	−1.52585700	4.19759100	−3.99200500
H	0.53175500	5.54146600	−3.71594100
C	−1.18660700	0.62919300	3.03324600
C	−1.61404300	2.55169200	1.82759800
C	−1.81814300	1.14106800	4.15969700
H	−0.74519900	−0.35844700	3.03557200
C	−2.24740200	3.12666400	2.92419100
H	−1.53238600	3.07931900	0.88730800
C	−2.36213100	2.42099300	4.11500600
H	−1.88044700	0.54437900	5.06083500
H	−2.85807700	2.85621800	4.97307600
N	−1.08714400	1.32055000	1.88619100
Cl	−2.90298400	4.74442800	2.77904000
C	−2.08024900	0.02556600	−0.62669100
H	−2.12825800	−0.48415100	−1.59440800
C	−3.29137900	0.26018000	−0.09596700
H	−3.39039500	0.75513300	0.87237800
C	−4.62230100	−0.11289000	−0.71374900
H	−5.22124900	0.79583000	−0.87949600
H	−4.45580100	−0.55977300	−1.70137800
C	−5.45203800	−1.07840800	0.15169800
H	−5.58092800	−0.64348700	1.15149300
H	−4.88432200	−2.00630300	0.29436400
C	−6.82864300	−1.40516200	−0.43833900
H	−7.39242700	−0.47321100	−0.57703900
H	−6.69947800	−1.83329700	−1.44120500
C	−7.65411700	−2.37117300	0.41903500
H	−7.78697700	−1.94265600	1.42128200

H	−7.09026700	−3.30279900	0.55993000
C	−9.02936300	−2.70109700	−0.17278400
H	−8.89704200	−3.13104200	−1.17325800
H	−9.59321200	−1.77083900	−0.31414100
C	−9.84690700	−3.66551900	0.69183300
H	−10.82054700	−3.87991500	0.24184700
H	−9.32435300	−4.61864500	0.82273600
H	−10.02605100	−3.24806300	1.68794900
C	−1.88401000	1.56247500	−3.64103600
H	−2.52756500	2.08233500	−4.35357000
H	−1.69489200	0.55693100	−4.02016400
H	−2.42873300	1.45308700	−2.70064100
C	3.10244600	1.80669300	−2.61677700
H	3.89750800	2.54752400	−2.52153800
H	3.05766900	1.23364100	−1.69094700
H	3.38403100	1.11376700	−3.41601600
C	−1.37452400	−3.22114700	−0.80709800
H	−1.48366100	−3.01769900	−1.87486800
H	−1.98891900	−4.08891800	−0.55961700
H	−1.77116800	−2.35164000	−0.27889500
C	3.62546800	−2.36061900	−1.36529100
H	3.41594700	−1.31519800	−1.58166200
H	4.51502800	−2.40638800	−0.73593600
H	3.86550700	−2.85070900	−2.31548900
C	1.71191400	1.02836100	1.20691000
H	1.34945700	0.90887000	2.23435100
C	2.96053200	0.15372900	1.07485700
H	2.69080100	−0.89845800	1.21875800
H	3.36772500	0.22499700	0.06153700
C	4.13725300	0.47587300	2.05679500
H	4.42723600	1.51900800	1.89191300
C	1.99918800	2.51816300	0.98629800
H	2.72522700	2.92964600	1.70645000
H	2.40163500	2.71458700	−0.01199800
H	1.09381000	3.12510500	1.08483100
C	3.72397900	0.34234000	3.53128900
H	4.57570900	0.51312200	4.19609900
H	2.94940600	1.07027900	3.78159600
H	3.31958600	−0.65094900	3.75024400
C	5.35599600	−0.36453300	1.71329100
C	6.38221700	0.17278800	0.92436000
C	5.48678000	−1.69667800	2.13071900
C	7.49605400	−0.58475300	0.56341100
H	6.30777800	1.20413800	0.59250500
C	6.59923400	−2.45903500	1.77576900
H	4.71385700	−2.14739800	2.74306400
C	7.61036300	−1.90764900	0.98880100
H	8.27693000	−0.13958800	−0.04417900
H	6.67829100	−3.48570400	2.11808200
H	8.47737600	−2.49903000	0.71597200