Stereoselective Preparation and Stereochemical Behaviour of Organozinc and Organolithium Reagents

Stephanie Seel

aus

Köln

2012
**Erklärung**


**Eidesstattliche Versicherung**

Diese Dissertation wurde eigenständig und ohne unerlaubte Hilfe erarbeitet.

München, am 05. November 2012

----------------------------

Stephanie Seel

Dissertation eingereicht am: 06. November 2012

1. Gutachter: Prof. Dr. Paul Knochel
2. Gutachter: Prof. Dr. Konstantin Karaghiosoff

Mündliche Prüfung am: 01. Februar 2013
This work was carried out from November 2009 to November 2012 under the guidance of Prof. Dr. Paul Knochel at the Department Chemie und Pharmazie of the Ludwig-Maximilians-Universität, Munich.

First, I would like to thank Prof. Dr. Paul Knochel for giving me the opportunity to do my Ph.D. in his group, for his generous support and guidance in the course of my scientific research.

I am also very grateful to Prof. Dr. Konstantin Karaghiosoff for agreeing to be the second reviewer of this thesis as well as Prof. Dr. Hendrik Zipse, Prof. Dr. Heinz Langhals, Prof. Dr. Klaus Theodor Wanner and Prof. Dr. Manfred Heuschmann for their interest shown in this manuscript by accepting to be referees.

I really would like to thank Tobias Thaler and Andreas Steib for the careful correction of this manuscript.

I thank all past and present co-workers I have met in the Knochel group for their kindness and their help. Special thanks to my actual and former lab mates Dr. Tobias Thaler, Johannes Heppekausen, Andreas Steib, Dr. Hongjun Gao, Dr. Li-Na Guo, Dr. Coura Diene, Dr. Guillaume Dagousset and Dr. Elodie Sansiaume-Dagousset.

I would like to thank Tobias Thaler for his support, the fun we had in the lab and for the fruitful collaborations.

Additional thanks go to Rasmus Mose, Zhi-Liang Shen, Ning Yuan, Olesya Kuzmina, Dr. Ilaria Tirotta, Dr. John and Jen Markievicz, Lydia Klier, Klaus Groll, Kohei Moriya, Quan Chen, Dr. Christos Stathakis, Veronika Werner and Sophia Manolikakes for being fantastic colleagues.

I explicitly thank Tobias Thaler, Guillaume Dagousset, Keishi Takatsu and Kohei Moriya who have contributed to the final success of this thesis. I also thank Cong Zhang and Prof. Dr. Hendrik Zipse for the performance of DFT calculations. Moreover, I am grateful to Prof. Dr. Konstantin Karaghiosoff for the performance and design of NMR studies and his outstanding support.

I would also like to thank Renate Schröder, Simon Matthe, Dr. Vladimir Malakhov and Yulia Tsvik for their help in organizing everyday life in the lab and in the office, as well as the analytical team of the LMU for their invaluable help.

Very special thanks to my parents and my brothers for their great support throughout my studies, my Ph.D and all the other years.
Part of this Ph. D. thesis have been published:


TO MY PARENTS
# Table of Contents

Abbreviations .................................................................................................................. 1

A. Introduction .................................................................................................................. 2

1. Overview ....................................................................................................................... 2

2. Stereoselective Preparation of Organometallic Reagents .............................................. 2
   2.1. Preparation of Stereodefined Carbon-Lithium Bonds .............................................. 2
   2.2. Preparation of Stereodefined Carbon-Magnesium Bonds ....................................... 10
   2.3. Preparation of Stereodefined Carbon-Zinc Bonds ................................................... 13

3. Objectives ..................................................................................................................... 20

B. Results and Discussion .................................................................................................. 22

1. Stereoselective Preparation, Configurational Stability and Reactivity of Substituted
   Cyclohexyllithium Derivatives ....................................................................................... 23
   1.1. Introduction .............................................................................................................. 23
   1.2. Results and Discussion ......................................................................................... 23

2. Novel Insights into the Stereochemical Behaviour of Diastereomeric Cyclohexylzinc Reagents –
   Stereoconvergence through Distinct Stereochemical Pathways ..................................... 36
   2.1. Introduction .............................................................................................................. 36
   2.2. Results and Discussion ......................................................................................... 39

3. Diastereo- and Enantioselective Cross-Coupling with Functionalized Cyclohexylzinc Reagents .............................................................................................................. 47
   3.1. Synthesis of Chiral Protected Cyclohexyl Derivatives for the Enantio- and Diastereoselective
       Synthesis of 1-, 2-, 3-trisubstituted Cyclohexanes ................................................. 47
   3.2. Investigations with [2-(1,3-Dioxolane-2-y)]cyclohexyl- and [2-(5,5-Dimethyl-1,3-dioxane-2- ylcyclohexyl]zinc Compounds .................................................................................. 49
   3.3. Development of an Enantioselective Version of the Diastereoselective Cross-Coupling .... 54
   3.4. Cross-Coupling with [8-(Ethoxymethoxy)decahydronaphthalen-1-y](ethyl)zinc ............. 56

4. Highly Diastereoselective Arylations of Substituted Piperidines .................................... 59
   4.1. Introduction .............................................................................................................. 59
   4.2. Results and Discussion ......................................................................................... 60

5. Summary and Outlook .................................................................................................. 69
   5.1. Stereoselective Preparation, Configurational Stability and Reactivity of Substituted
       Cyclohexyllithium Derivatives .................................................................................. 69
   5.2. Novel Insights into the Stereochemical Behaviour of Diastereomeric Cyclohexylzinc Reagents –
       Stereoconvergence through Distinct Stereochemical Pathways .................................. 70
   5.3. Diastereo- and Enantioselective Cross-Coupling with Functionalized Cyclohexylzinc Reagents 71
   5.4. Highly Diastereoselective Arylations of Substituted Piperidines ............................. 72

C. Experimental Section .................................................................................................. 74
1. General Considerations ........................................................................................................................................ 75
   1.1. Solvents ........................................................................................................................................ 75
   1.2. Reagents ........................................................................................................................................ 75
   1.3. Chromatography ............................................................................................................................ 77
   1.4. Analytical Data .............................................................................................................................. 77

2. Stereoselective Preparation, Configurational Stability and Reactivity of Substituted Cyclohexyllithium Derivatives ............................................................................................................................................ 79
   2.1. Preparation of Starting Materials ....................................................................................................... 79
       2.1.1. Typical Procedure 1: Iodination of alcohols (TP1) ................................................................. 79
   2.2. I-Li Exchange and Subsequent Quenching with Electrophiles ...................................................... 84
       2.2.1. Typical Procedure 2: I-Li exchange and subsequent quenching with electrophiles (TP2) .... 84

3. Novel Insights into the Stereochemical Behaviour of Diastereomeric Cyclohexylzinc Reagents – Stereoconvergence through Distinct Stereochemical Pathways ................................................................................................................................. 95
   3.1. Deuterolysis and Protolysis Experiments .......................................................................................... 95
       3.1.1. Typical Procedure 3: Deuterolysis of organozinc reagents (TP 3) ........................................... 95
   3.2. Cross-Coupling Experiments ........................................................................................................ 118
       3.2.1. Typical Procedure 5: Diastereoselective cross-coupling with stereodefined cyclohexylzinc reagents produced via hydroboration and subsequent boron-zinc exchange (TP5) ................. 122
       3.2.2. Typical Procedure 6: Diastereoselective cross-coupling with non-stereodefined cyclohexylzinc iodides produced via zinc insertion into the respective cyclohexyl iodide (TP6) ............. 124

4. Diastereo- and Enantioselective Cross-Coupling with Functionalized Cyclohexylzinc Reagents 127
   4.2. Diastereoselective Cross-Coupling with Functionalized Cyclohexylzinc Derivatives ............... 127
       4.2.1. Preparation of starting materials (Scheme 34) ......................................................................... 127
       4.2.2. Typical Procedure 7: Protection with organosilyl chlorides (TP7) ........................................... 128
       4.2.3. Typical Procedure 8: Cross-coupling of silyl-protected (R)-2-iodocyclohex-2-enol derivatives (TP8) (Schemes 34 and 35) ................................................................................................................. 130
       4.2.4. Typical Procedure 9: Protection of cyclohex-2-encarboxaldehyde and acetylcycloalk-2-ene (TP9) (Schemes 37 and 38) ................................................................................................................. 134
       4.2.5. Typical Procedure 10: Preparation of alcohols via hydroboration and oxidation (TP10) (Schemes 37 and 38) ......................................................................................................................... 136
       4.2.6. Typical Procedure 11: Preparation of functionalized cyclohexyl iodides (TP11) .................... 139
   4.3. Synthesis of EOM-Protected Decahydro-1-naphthalinol ................................................................ 140
   4.4. Diastereoselective Cross-Coupling with Cyclohexylzinc Reagents Produced via Hydroboration and Subsequent Boron-Zinc Exchange (Table 7) .................................................................................. 145
   4.5. Diastereoselective Csp³-Csp² Cross-Coupling with Cyclohexylzinc Iodides (Table 8) ............ 148
   4.6. Typical Procedure 12: Enantioselective Hydroboration/Boron-Zinc Exchange with Subsequent Cross-Coupling (TP12) (Table 9) .................................................................................. 152
   4.7. Cross-Couplings with [8-(Ethoxymethoxy)decahydronaphthalin-1-yl](ethyl)zinc ................... 157
5. Highly Diastereoselective Arylations of Substituted Piperidines .................................................. 159

5.1. Preparation of Starting Materials .................................................................................................. 159

5.2. Typical Procedure 13: Cross-Coupling of (1-((t-Butoxycarbonyl)-4-methylpiperidin-2-yl)zinc Chloride (TP 13) (Table 11) ................................................................................................................. 160

5.3. Typical Procedure 14: Cross-Coupling of (1-((t-Butoxycarbonyl)-4-phenylpiperidin-2-yl)zinc Chloride (TP 14) (Table 11) ................................................................................................................. 165

5.4. Typical Procedure 15: Cross-Coupling of (1-((t-Butoxycarbonyl)-4-((triisopropylsilyl)oxy)piperidin-2-yl)zinc Chloride (TP 15) (Table 11) ................................................................................................................. 168

5.5. Typical Procedure 16: Cross-Coupling of (trans-2-((t-Butoxycarbonyl)decahydroisoquinolin-3-yl)zinc Chloride (TP 16) (Table 11) ................................................................................................................. 172

5.6. Typical Procedure 17: Cross-Coupling of (1-((t-Butoxycarbonyl)-5-methylpiperidin-2-yl)zinc Chloride (TP 17) (Table 11) ................................................................................................................. 174

5.7. Typical Procedure 18: Preparation of Piperidin-4-ylzinc Iodides (TP 18) (Table 12) ............... 176

5.8. Typical Procedure 19: Cross-Coupling of Piperidin-4-ylzinc Iodides (TP 19) (Table 12) ......... 177

5.9. Typical Procedure 20: Cross-Coupling of (1-((t-Butoxycarbonyl)-6-methylpiperidin-2-yl)zinc Chloride (TP 20) (Scheme 45) ................................................................................................................. 183

5.10. Typical Procedure 21: Synthesis of N-Tosyl Piperidines (TP 21) ................................................ 187

5.11. Typical Procedure 22: TIPS Deprotection (TP 22) ..................................................................... 192

5.12. Typical Procedure 23: Iodination (TP 23) .................................................................................. 194

D. Appendix ....................................................................................................................................... 197

1. Data of X-ray Analysis ......................................................................................................................... 198

1.1. Stereoselective Preparation, Configurational Stability and Reactivity of Substituted Cyclohexyllithium Derivatives ......................................................................................................................... 198

1.2. Highly Diastereoselective Arylations of Substituted Piperidines .................................................. 202

2. Curriculum Vitae ................................................................................................................................ 211
### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>AcOH</td>
<td>acetic acid</td>
</tr>
<tr>
<td>aq.</td>
<td>aqueous</td>
</tr>
<tr>
<td>Ar</td>
<td>aryl</td>
</tr>
<tr>
<td>Boc</td>
<td>tert-butoxycarbonyl</td>
</tr>
<tr>
<td>br</td>
<td>broad</td>
</tr>
<tr>
<td>Bu</td>
<td>butyl</td>
</tr>
<tr>
<td>nBu</td>
<td>n-butyl</td>
</tr>
<tr>
<td>tBu</td>
<td>t-butyl</td>
</tr>
<tr>
<td>calc.</td>
<td>calculated</td>
</tr>
<tr>
<td>conc.</td>
<td>concentrated</td>
</tr>
<tr>
<td>cHex</td>
<td>cyclohexyl</td>
</tr>
<tr>
<td>d</td>
<td>doublet</td>
</tr>
<tr>
<td>δ</td>
<td>chemical shifts in parts per million</td>
</tr>
<tr>
<td>dba</td>
<td>trans,trans-dibenzylideneacetone</td>
</tr>
<tr>
<td>DCC</td>
<td>N,N'-dicyclohexyl-carbodiimide</td>
</tr>
<tr>
<td>DFT</td>
<td>density functional theory</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-dimethylformamide</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-(dimethylamino)pyridine</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethyl sulfoxide</td>
</tr>
<tr>
<td>E</td>
<td>electrophile</td>
</tr>
<tr>
<td>EI</td>
<td>electron ionization</td>
</tr>
<tr>
<td>ESI</td>
<td>electrospray ionization</td>
</tr>
<tr>
<td>equiv.</td>
<td>equivalent</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
</tr>
<tr>
<td>FG</td>
<td>functional group</td>
</tr>
<tr>
<td>GC</td>
<td>gas chromatography</td>
</tr>
<tr>
<td>h</td>
<td>hour</td>
</tr>
<tr>
<td>HRMS</td>
<td>high resolution mass spectroscopy</td>
</tr>
<tr>
<td>iPr</td>
<td>iso-propyl</td>
</tr>
<tr>
<td>IR</td>
<td>infra-red</td>
</tr>
<tr>
<td>J</td>
<td>coupling constant (NMR)</td>
</tr>
<tr>
<td>LDA</td>
<td>lithium diisopropylamide</td>
</tr>
<tr>
<td>m</td>
<td>multiplet</td>
</tr>
<tr>
<td>m</td>
<td>molarity</td>
</tr>
<tr>
<td>m</td>
<td>meta</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>Met</td>
<td>metal</td>
</tr>
<tr>
<td>min</td>
<td>minute</td>
</tr>
<tr>
<td>mmol</td>
<td>millimole</td>
</tr>
<tr>
<td>M.p.</td>
<td>melting point</td>
</tr>
<tr>
<td>MS</td>
<td>mass spectroscopy</td>
</tr>
<tr>
<td>NMI</td>
<td>N-methylimidazole</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>o</td>
<td>ortho</td>
</tr>
<tr>
<td>p</td>
<td>para</td>
</tr>
<tr>
<td>PG</td>
<td>protecting group</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>q</td>
<td>quartet</td>
</tr>
<tr>
<td>R</td>
<td>organic substituents</td>
</tr>
<tr>
<td>rt</td>
<td>room temperature</td>
</tr>
<tr>
<td>RuPhos</td>
<td>dicyclohexyl(2',6'-diisopropoxy-[1,1' '-biphenyl]-2-yl)phosphine</td>
</tr>
<tr>
<td>s</td>
<td>singlet</td>
</tr>
<tr>
<td>sat.</td>
<td>saturated</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Name</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>SPhos</td>
<td>2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl</td>
</tr>
<tr>
<td>t</td>
<td>triplet</td>
</tr>
<tr>
<td>TBAF</td>
<td>tetrabutylammonium fluoride</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TBS</td>
<td>tert-butyldimethylsilyl</td>
</tr>
<tr>
<td>TBDPS</td>
<td>tert-butylidiphenylsilyl</td>
</tr>
<tr>
<td>TIPS</td>
<td>triisopropylsilyl</td>
</tr>
<tr>
<td>TMEDA</td>
<td>N,N,N',N'-tetramethylethylene-diamine</td>
</tr>
<tr>
<td>TMPP</td>
<td>tris(2,4,6-trimethoxyphenyl)-phosphate</td>
</tr>
<tr>
<td>TMS</td>
<td>trimethylsilyl</td>
</tr>
<tr>
<td>TP</td>
<td>typical procedure</td>
</tr>
<tr>
<td>Ts</td>
<td>4-toluenesulfonyl</td>
</tr>
</tbody>
</table>
A. Introduction
1. **Overview**

Due to an ever increasing demand of more complex molecular structures for the use in pharmaceutical and agrochemical industries, there is a high need for the development of novel, more efficient and, especially, more stereoselective synthetic methods.\(^1\) Thereby, one of the most important synthetic challenges is the control of the stereochemical information in a molecular framework.\(^2\) This can either be implemented by the use of stereoselective functionalizations making use of a chiral catalyst or auxiliary, as well as the stereogenic bias in a molecule or by the stoichiometric use of stereodefined reagents.\(^2\) Due to their superior reactivities and their versatile applicability, organometallic reagents are especially suitable and a considerable amount of effort has been put into the development of novel methods for the generation of stereodefined carbon-metal bonds using a wide variety of synthetic approaches.\(^3\)

2. **Stereoselective Preparation of Organometallic Reagents**

2.1. **Preparation of Stereodefined Carbon-Lithium Bonds**

Stereomeric organolithium compounds featuring a stereodefined carbon-lithium bond have been most studied.\(^4\) However, due to the low configurational stability of the C-Li bond with its high ionic character these studies were mostly restricted to stabilized reagents, such as \(\alpha\)-heteroatom substituted alkyl-\(^5\), benzylic\(^6\) or allylic organolithiums.\(^7\) Moreover, these

---


organolithium reagents can be accessed more easily via conventional stereoselective deprotonation reactions featuring chiral amine ligands, such as (-)-sparteine (1). Thus, Curtis and Beak have reported on the stereoselective generation of the configurationally stable benzylic and allylic organolithium species 2 and 3 via asymmetric deprotonation mediated by 1 (Scheme 1).\(^8\)

\(^{1}\) M. & Limat, D. Sparteine-mediated \(N\)-methylpiperidine and 2-lithio-(1999).

\(^{2}\) Curtis, M. D. & Beak, P. Asymmetric carbon-carbon bond formation in Michael reactions: conjugate addition reactions of configurationally stable benzylic and allylic organolithium species 2 and 3 via asymmetric deprotonation mediated by 1 (Scheme 1).\(^8\)


A. Introduction

Scheme 1: Generation of chiral allylic and benzylic organolithium species via (-)-sparteine-mediated enantioselective deprotonation.

Their conjugate addition to benzylideneacetylacetone (4) provided the adducts (S,S)-5 and (S,R)-6 with superior regio-, diastereo- and enantioselectivities. Hoppe et al. also showed that (-)-sparteine (1) can be used to selectively stabilize the non-heteroatom α-substituted chiral lithium indenide 7 by crystallization leading after quenching with electrophiles to the respective enantioenriched products of type 8 (Scheme 2).\textsuperscript{7c}

Scheme 2: Generation of chiral α-substituted lithium indenide 7 by crystallization with (-)-sparteine (1).

Cohen and Lin observed an interesting phenomenon based on both the configurational instability of the highly anionic C-Li bond and the stereochemical bias in substituted lithiopyrans.\textsuperscript{5a} Thus, reductive lithiation of the conformationally locked thioether 9 (axial:equatorial= 3.4:1) using lithium 1-(dimethylamino)naphthalenide (LDMAN) exclusively furnished axially substituted organolithium compound \textit{ax}-10 (Scheme 3).
Quenching with benzaldehyde (PhCHO), D$_2$O or CD$_3$CO$_2$D furnished products of type ax-11 with extraordinarily high selectivity. Remarkably, when ax-10 was warmed to -30 °C in the presence of chelating TMEDA and cooled back to -78 °C, the equatorially substituted products of type eq-11 were obtained preferentially. This showed that ax-10 had equilibrated into the more stable eq-10 via inversion of the C-Li bond. This thermodynamic control could, however, not be applied to the 3-methyl-substituted 2-lithiopyran 12. The authors suggested that the flexibility of 12 is responsible for the lacking epimerization of the C-Li bond. Thus, ax-12a in which the Li occupies the axial position can easily undergo a ring flip placing the Li moiety in the more stable equatorial position (ax-12b) thus rendering an epimerization (formation of eq-12) as observed in the conformationally locked lithiopyran 10 unnecessary for the C-Li bond to occupy its thermodynamically preferred position. Coldham et al. also made use of the configurational instability of organolithium compounds. They showed that N-Boc-2-lithiopyrrolidine (13) can be subjected to a dynamic kinetic resolution (DKR) process in the presence of the diastereomeric chiral aminoalcohol-ligands 14 and epi-14 (Scheme 4).
A. Introduction

Scheme 4: Dynamic kinetic resolution (DKR) in N-Boc-2-lithiopyrrolidine (13 and ent-13) using the chiral aminoalcohol-ligands 14 and epi-14.

Thus, deprotonation of N-Boc-pyrrolidine (15) using sBuLi in the presence of a chiral ligand led to the respective complexes between 13 and enantiomeric ent-13 with 14 or epi-14. The complex 13•14 reacted faster with Me$_3$SiCl as electrophile than the diastereomeric complex ent-13•14 leading to the chiral silane 16 with high enantioselectivity. When epi-14 was employed as ligand the ensuing complex ent-13•epi-14 reacted preferably giving a highly selective access to the opposite enantiomer of 16 (ent-16) upon quenching with Me$_3$SiCl. Another interesting dynamic resolution process based on thermodynamic control (compare Scheme 3) was observed by Coldham et al. for the N-iso-butyl-substituted lithiopyrrolidines 17 and ent-17 in conjunction with the chiral aminoalcohol ligand 14 (Scheme 5).

Scheme 5: Dynamic thermodynamic resolution (DTR) in N-iso-butyl-substituted 2-lithiopyrrolidine (17 and ent-17) using the chiral amino alcohol ligands 14.
Sn-Li exchange on stannane 18 led to the lithium species 17 and ent-17. At -78 °C addition of the chiral ligand 14 leading to the formation of the complexes 17•14 and ent-17•14 and subsequent quenching with Me3SiCl gave only racemic product (19). When the Sn-Li exchange and addition of the chiral ligand 14 was performed at ambient temperature quenching with Me3SiCl furnished 19 with high enantioselectivity (94% ee). Interestingly, quenching with a substoichiometric amount of Me3SiCl at -78 °C gave the product with low selectivity and a preference for the opposite enantiomer (ent-19). This hints at a dynamic thermodynamic resolution process in which the less stable complex ent-17•14 equilibrates into the diastereomeric complex 17•14. The energy diagrams for the dynamic thermodynamic (Scheme 5) and the dynamic kinetic resolution processes (Scheme 4) are depicted in Scheme 6.

**Dynamic thermodynamic resolution (DTR)**

**Dynamic kinetic resolution (DKR)**

**Scheme 6:** Representative energy schemes for the dynamic thermodynamic resolution (DTR) and the dynamic kinetic resolution of lithiopyrrolidines with chiral ligands.

In the latter, the difference in activation energies (ΔΔG‡) for the quenching reactions determines the overall stereoselectivity of the process with a low activation energy barrier for equilibration between 13•14 and ent-13•14. In the former, the difference in ground state energies (ΔG⁰) between the diastereomeric complexes 17•14 and ent-17•14 is responsible for the stereochemical outcome. A relatively high activation barrier for equilibration between 17•14 and ent-17•14 leads to a stable equilibrium between those complexes at lower temperatures (quenching temperature: -20 °C). Interestingly, the stereochemical paths of S22 reactions of chiral organolithium compounds are not uniform for all electrophiles. Thus, Hoppe and Hammerschmidt could show that the nature of the respective electrophiles...
determined the stereochemical outcome of the quenching of the tertiary benzylic Li-reagent 20, which was derived from 21 via deprotonation using sBuLi and TMEDA (Scheme 7).\textsuperscript{9}

\begin{scheme}
Scheme 7: Electrophile-dependent stereochemical outcome in the quenching of the chiral benzylic lithium reagent 20.
\end{scheme}

Thus, electrophiles like MeOD, HOAc and (MeO)\textsubscript{2}CO furnish the respective products of type 22 with retention of stereoconfiguration, whereas invertive substitution is observed with Me\textsubscript{3}SnCl, CO\textsubscript{2}, alkyl bromides and iodides leading to products of type \textit{ent}-23.

\begin{scheme}
Scheme 8: Hypothetical scenario with different activation barriers for invertive and retentive quenching for two distinct diastereomERIC organozinc reagents (in this simplified scheme same ground state energies are assumed for the organometallic diastereomeric reagents and diastereomeric quenching products; this does not necessarily need to be the case).
\end{scheme}

A. Introduction

Therefore, a scenario in which distinct kinetic preferences in the quenching reactions for diastereomeric organometallics in which one reacts with retention and the other with inversion of the C-metal bond is also conceivable but has not yet been reported in the literature so far. Scheme 8 shows an energy diagram for such a hypothetical scenario in which distinct activation energy barriers for the retentive and inversive substitution processes lead to different stereochemical outcomes. The stereoselective generation of unstabilized secondary alkyl lithium reagents has been far less studied. An early report by Letsinger featured an I-Li exchange on (-)-2-iodoctane (24) at -70 °C leading to stereodefined 1-methylheptyllithium (25) which was quenched with CO₂ to give the carbonic acid 26 with 80% racemization (Scheme 9). ¹⁰

![Scheme 9](image)

Scheme 9: I-Li exchange on enantiopure (-)-2-iodoctane and quenching with CO₂ at -70 °C goes along with 80% racemization.

Reich et al. reported on the stereoselective generation of the diastereomeric cyclohexyllithium compounds ax-27 and eq-27 via Te-Li exchange on tellurides ax-28 and eq-28 (Scheme 10). ¹¹ The influence of chelators such as TMEDA and PMDTA and lithium iodide salt on the configurational stability of ax-27 which tends to equilibrate into the more stable eq-27 was examined.

![Scheme 10](image)

Scheme 10: Te-Li exchange on stereodefined cyclohexyl tellurides ax-28 and eq-28 proceeds with retention of stereoconfiguration.

---

2.2. Preparation of Stereodefined Carbon-Magnesium Bonds

Stereodefined Grignard reagents have been much less studied than their organolithium counterparts. Jensen and Nakamaye reported on the stereoselective generation of endo-norbornylmagnesium bromide (endo-29) via a kinetic resolution process already as early as 1966.\(^\text{12}\) They used the greater reactivity of exo-29 towards the reduction of benzophenone to selectively remove it (Scheme 11).

![Scheme 11: Kinetic resolution of the diastereomeric norbornylmagnesium reagents exo-29 and endo-29.](image)

The remaining endo-29 was studied by NMR and trapping experiments with HgBr\(_2\) and CO\(_2\) gave the respective endo-products endo-30 and endo-31 stereospecifically with retention of configuration. In accordance with the results of Whitesides and Roberts\(^\text{13}\) only a very slow interconversion from endo-29 to exo-29 was observed showing the relatively high configurational stability of these bicyclic secondary alkyl Grignard reagents. The \((-\)\)-menthyl/neomenthyl Grignard reagents 32 and 33 represent the most extensively studied chiral organomagnesium reagents (Scheme 12).\(^\text{14}\)

---


A. Introduction

Scheme 12: Mg-insertion in either menthyl chloride \((eq-34)\) or neomenthyl chloride \((ax-34)\) results in a 1:1-mixture of the diastereomeric Grignard reagents 32 and 33; 32 can be selectively trapped using \(\text{Ph}_2\text{PCl}\).

Originally, it was believed that the insertion of Mg metal into \((-\)-menthyl chloride \((eq-34)\) would exclusively lead to the stereodefined 33, since quenching of the resulting Grignard reagent(s) with \(\text{Ph}_2\text{PCl}\) only gave equatorially substituted diastereomeric phosphine 35.\(^{15}\) A more recent investigation by Beckmann, Dakternieks and Duthie showed that, after Mg-insertion into 34, a 1:1-mixture of diastereomeric 32 and 33 ensues, which was proven by quenching the mixture with \(\text{D}_2\text{O}\).\(^{15}\) The same ratio was found when Mg-insertion was performed on the diastereomeric neomenthyl chloride \((ax-34)\). The reaction of this mixture with 0.5 equiv. of \(\text{Ph}_2\text{PCl}\) was reported to result in a kinetic resolution similar to the one shown in Scheme 11 where the more reactive and more Lewis-acidic 32 was selectively quenched and 33 remained in solution, as proven by quenching with \(\text{D}_2\text{O}\). Interestingly, the stereochemical outcome of the quenching reactions of the 32/33 mixture is highly dependent on the nature of the electrophile. Thus, Dakternieks et al. observed a 3:2-mixture of the diastereomeric stannanes 36 and 37 upon quenching with \(\text{Ph}_3\text{SnCl}\),\(^{16}\) whereas the reaction with \(\text{Me}_3\text{SnCl}\) was reported by Schumann et al. to give exclusively the equatorially substituted stannane 38 (Scheme 13).\(^{17}\)


**Scheme 13:** Quenching of the diastereomeric Grignard reagents 32 and 33 with different organotin chlorides leading to distinct stereochemical outcomes.

The addition of Lewis-bases, such as Ph$_3$P, to Ph$_3$SnCl prior to the addition of the 32/33 mixture restored selectivity presumably due to a decreased Lewis-acidity of the Ph$_3$SnCl-PPh$_3$ complex. At that time, the 32/33-mixture was still considered to consist of only 32 and an electrophile-triggered radical epimerization of 32 was proposed.$^{17}$ Hoffmann et al. developed a general and straightforward access to chiral organomagnesium reagents via a sulfoxide-magnesium exchange/ carbenoid homologation sequence using excess EtMgCl and α-chloro-substituted chiral secondary alkylsulfoxides of type 39.$^{18}$ The resulting chiral organomagnesium reagent 40 was shown to undergo racemization at -10 °C in a first order process with a half-life of only 5 h.$^{19}$ 40 was subjected to trapping and transmetalation reactions with different electrophiles (Scheme 14).$^{19}$

---


Scheme 14: Enantioselective generation of secondary alkylmagnesium reagents via sulfoxide magnesium exchange and electrophile-dependent stereochemical outcomes.

These experiments showed that the stereochemical outcome highly depends on the nature of the respective electrophile. Whereas retention of the stereoinformation hinted toward polar addition processes, losses in enantiopurity were interpreted to indicate radical single electron transfer (SET) processes.

2.3. Preparation of Stereodefined Carbon-Zinc Bonds

Reports on the generation and configurational behaviour of stereodefined organozinc reagents are scarce in the literature. Despite their usefulness for organic synthesis due to their high tolerance towards functional groups and their decreased reactivity relative to the corresponding organo-lithium and -magnesium species, their stereochemical behaviour has
A. Introduction

not yet been studied in detail. This may be due to the fact that stereodefined C-Zn bonds are not easy to generate. A first seminal investigation on the stereochemical behaviour of secondary diastereomeric organozinc reagents was published by Knochel et al. in 1994.\(^{20}\) In this article, Zn-insertion was performed on the endo- and exo-norbornyl iodides \(\text{exo-41}\) and \(\text{endo-41}\) and the resulting zinc reagents (\(42\) and \(43\)) were subjected to quenching with different electrophiles (Scheme 15).

Scheme 15: Stereoselective generation of secondary alkylzinc reagents. A phenomenon of stereoconvergent quenching or of an amide-directed Zn-insertion?

Interestingly, iodolysis of \(42\) gave the iodide \(\text{exo-44}\) with high diastereoselectivity (\(\text{exo:endo} = 95:5\)), whereas quenching of \(43\) with \(I_2\) led to a 67:33-mixture in favour of \(\text{exo-44}\). From these results it was concluded that the Zn-insertion into \(\text{exo-41}\) proceeded stereoselectively to give the stereodefined Zn-reagent \(42\), while Zn-insertion into the diastereomeric \(\text{endo-41}\) furnished a mixture of \(\text{exo-/endo-}\)-configured Zn-reagents. Further quenching reactions using \(\text{Me}_3\text{SnCl}\) and 2-(bromomethyl)hexane confirmed the observed trend. Still, when \(43\) was trapped, after transmetalation to copper, with \(\text{Me}_3\text{SnCl}\) the stereochemical outcome depended highly on the

amount of equivalents used. Thus, a 85:15 d.r. in favour of exo-45 was obtained with 1.2 equiv. Me$_3$SnCl which could be increased to 94:6 with only 0.5 equiv. of Me$_3$SnCl. Another interesting observation was made, when exo- and endo-7-iodonorcarane (exo-46 and endo-46) were subjected to Zn-insertion using Rieke-zinc (Scheme 16).

![Scheme 16](image)


In both cases, after iodolysis an exo/endo ratio of the resulting iodide (46) of 95:5 was obtained. Thus, the stereoselective formation of exo-zinc reagent 48 was concluded. When Zn-insertion was performed on cis-4-tert-butylcyclohexyl iodide 49 using Rieke-zinc and the resulting organozinc species 50 was quenched with I$_2$ the respective organic iodide products (cis-51 and trans-51) were obtained in a 35:65 cis:trans-ratio at -78 °C and in a 60:40-ratio at 25 °C (Scheme 17).

![Scheme 17](image)

Scheme 17: Stereoselective generation of secondary alkylzinc reagents? A phenomenon of stereoconvergent quenching? Dependence of the stereoselectivity on reaction conditions and electrophiles.

Trapping of 50 with AcOD resulted in a 60:40-ratio of deuterated products (cis-51 and trans-51). Quenching with D$_2$O, however, gave almost exclusively trans-51. These results underlined the influence of reaction conditions on the stereochemical outcome of the quenching reactions. The conclusion that only one Zn-species is formed in the case of 42 and 47 has still to be verified, since the zinc reagent was not directly analyzed spectroscopically. Further insights into the stereochemical behaviour of C-Zn reagents were given by the
enantioselective cross-coupling of the benzylic zinc reagents 52a-c using a chiral ferrocene-based Pd-catalyst (53) by Hayashi and Kumada (Scheme 18).\textsuperscript{21}

\textbf{Scheme 18:} Enantioselective Pd-catalyzed cross-coupling of secondary alkylzinc reagents 52a-c.

The racemic zinc reagents 52a-c were proposed to undergo a dynamic kinetic resolution process in the presence of chiral 53 thus leading to the cross-coupling product 54 with high enantioselectivities.\textsuperscript{2a} Thus, the organozinc reagents 52b-c, which were obtained via transmetalation from the Grignard reagent 55, reacted much faster and gave higher yields than 52a which was prepared via Zn-insertion into the benzylic bromide 56. Such a dynamic kinetic resolution process has also been proposed for the remotely controlled diastereoselective cross-coupling of 3- and 4-substituted cyclohexylzinc reagents (Scheme 19).\textsuperscript{22}


\textsuperscript{22} Thaler, T., Haag, B., Gavryushin, A., Schober, K., Hartmann, E., Gschwind, R., Zipse, H., Mayer, P. & Knochel, P. Highly diastereoselective Csp\textsuperscript{3}-Csp\textsuperscript{3} Negishi cross-coupling with 1,2-, 1,3- and 1,4-substituted cycloalkylzinc compounds. \textit{Nature Chem.} \textbf{2}, 125-130 (2010).
The equatorially substituted cyclohexylzinc reagent \( \text{eq-57} \) was assumed to react much faster with the arylpalladium complex \( 58 \) than \( \text{ax-57} \) thus selectively leading to the thermodynamically favoured all-equatorially substituted products of type \( \text{eq-59} \) (transmetalation and reductive elimination were assumed to proceed with retention of stereoconfiguration). An efficient way for the stereoselective generation of C-Zn bonds was disclosed by Knochel et al.: A hydroboration/B-Zn exchange sequence on trisubstituted double-bonds \( (60) \) leads to the regio- and stereodefined \( \text{trans} \)-configured organozinc reagents of type \( 61 \) (Scheme 20).\(^{23}\)

\[
\begin{align*}
\text{Scheme 20: Hydroboration/B-Zn exchange sequence for the generation of diastereomerically defined organozinc reagents.}
\end{align*}
\]

Thereby, the hydroboration proceeds with \( \text{anti} \)-Markovnikov- and \( \text{syn} \)-addition-selectivity and the B-Zn exchange with retention of stereoconfiguration. The configurational behaviour of these \( \text{trans} \)-configured organozinc reagents was examined using indanyl derivative \( \text{trans-62} \) (Scheme 21).\(^{24}\)


Scheme 21: Deterioration of the diastereoselectivity in the quenching of \textit{trans}-62 with D$_2$O in the presence of ZnBr$_2$.

When \textit{trans}-62 was quenched at -78 °C with D$_2$O almost exclusively, as expected, the \textit{trans-}deuterated product \textit{trans}-63 was formed. Prior addition of ZnBr$_2$ to \textit{trans}-62 at -78 °C for 20 min and subsequent quenching with D$_2$O, however, led to an erosion of the \textit{trans/cis} ratio to 92:8. This method was extended to an enantioselective hydroboration/B-ligand exchange/B-Zn transmetalation sequence which allowed the preparation of the enantioenriched organozinc reagent 65 which was trapped with allylic, alkynyl and propargylic bromides to furnish the products 66-68 (Scheme 22).

Scheme 22: Enantioselective conjugate functionalizations by an asymmetric hydroboration and B-Zn exchange sequence.

---

Next to Cu-mediated trapping reactions with allyl bromides, also Pd-catalyzed acylations and cross-couplings with iodoalkenes has been described (Scheme 23).^26

![Scheme 23: Enantio- and diastereoselective preparation of cyclic and acyclic organozinc reagents and subsequent Pd-catalyzed cross-coupling and acylation.](image)

The respective products were received with high diastereomeric ratios favouring the trans-configuration. Interestingly, a $^1$H-NMR-investigation by Rieke and Guijarro on the configurational stability of secondary alkylzinc reagents, in which the racemic Zn-species 69 was complexed with a chiral bisoxazoline ligand (70) to give the distinguishable diastereomeric complexes 71 and 72, showed that the C-Zn bond is configurationally extremely stable (Scheme 24).^27

![Scheme 24: High configurational stabilities for bisoxazoline-complexed diastereomeric secondary alkylzinc reagents 71 and 72.](image)

With no mentionable coalescence between these species being observed on an NMR-time scale, the authors calculated the lifetime of the inversion process to be 4130 h at 25 °C assuming a mononuclear transition state for inversion.

---


3. Objectives

One of the aims of this thesis was to develop a practical method for the preparation of stereodefined non-stabilized diastereomeric cyclohexyllithium reagents of type 73 so that their reactivities towards various electrophiles as well as their stereochemical behaviours could be investigated (Scheme 25).

![Scheme 25](image)

Scheme 25: A stereoselective method for the generation of stereodefined cyclohexyllithium reagents – studies and explanations of their stereochemical behaviours.

Also, the stereochemical behaviour of diastereomeric cyclic zinc reagents should be examined in order to elucidate the true mechanism of their remotely controlled Pd-catalyzed diastereoselective Negishi-cross-coupling with aryl halides (Scheme 26).

![Scheme 26](image)

Scheme 26: Two plausible mechanistic scenarios for the stereoconvergent cross-coupling of substituted diastereomeric cyclohexyloxyzinc reagents.

Although a dynamic kinetic resolution (DKR) mechanism had already been proposed (see Schemes 6 and 19), distinct kinetic preferences of the diastereomeric cyclohexylzinc complexes in the reaction with the arylpalladium complex cannot be ruled out (see Scheme 8).
especially since a high configurational stability of the C-Zn bond has been reported (see Scheme 24).\textsuperscript{27}

Furthermore, the highly diastereoselective cross-coupling methodology should be extended to functionalized organozinc reagents, such as substituted piperidinylzinc reagents of types 74 and 75 and cyclohexylzinc reagents bearing functionalities, such as 76 and 77 (Scheme 27). Moreover, a method for a simultaneous enantio- and diastereoselective cross-coupling should be established.

Scheme 27: Diastereoselective cross-couplings of substituted piperidinylzinc and functionalized cycloalkylzinc reagents.
B. Results and Discussion
1. Stereoselective Preparation, Configurational Stability and Reactivity of Substituted Cyclohexyllithium Derivatives

1.1. Introduction

Although the stereoselective generation and stereochemistry of α-heteroatom-substituted alkyl-, benzylic and allylic organolithium reagents are well studied, the stereoselective preparation of non-stabilized secondary alkyllithiums remains a major synthetic challenge. In this work, a practical stereoretentive synthesis to unstabilized stereodefined cyclohexyllithium reagents from the readily available organic iodides via I-Li exchange is presented. Using this approach a detailed study on the configurational stabilities, stereochemical behaviour and reactivities of various axially and equatorially substituted cyclohexyllithium reagents was performed. Thus, the stereochemical paths (S_E2 vs. S_i2) of the quenching reactions were shown to depend on the respective cyclohexyllithium diastereomer and the electrophile. In all cases, the axial cyclohexyllithium was found to almost completely equilibrate into the configurationally stable, equatorial diastereomer. This inversion process was followed for differently substituted cyclohexyllithiums over time showing distinct behaviour. DFT-calculations demonstrated that the formation of oligomeric cyclohexyllithium structures is the key determinant for the observed stereochemical preference.

1.2. Results and Discussion

Initial experiments showed that the addition of tert-butyllithium (tBuLi) to a solution of 4-tert-butyldicyclohexyl iodide (78) in hexane/ether (3:2)\(^{28}\) at -100 °C gave mainly the protonation and elimination products 79 and 80 (Scheme 28a). This is due to a very similar reactivity of tBuLi and the newly formed secondary cyclohexyllithium 81. Moreover, the mode of addition implies the presence of excess amounts of organic iodide 78 relative to

organolithium species favouring elimination side-reactions. This results in a low yield of $^{81} (<7\%$; determined by quenching experiments, see below). However, inversion of the addition order$^{26}$ led to an efficient suppression of unwanted protonation and elimination pathways and the desired secondary cyclohexyllithium $^{81}$ was obtained in 70-90% yield. Using these optimized conditions, we were able to stereoselectively access various new non-stabilized secondary cyclohexyllithiums and, consequently, to probe their stereochemical behaviours.

Scheme 28: Optimization of the I-Li exchange conditions for 4-t-butyl-cyclohexyl iodide $^{78}$ and stereoselective generation of the corresponding lithium reagents $^{trans}-(eq)-^{81}$ and $^{cis}-(ax)-^{81}$.

Thus, we have prepared the stereodefined $cis$- and $trans$-$4$-$t$-$butyl$cyclohexyl iodides $cis$-$(ax)-^{78}$ ($cis/trans= 98:2$) and $trans$-$(eq)-^{78}$ ($cis/trans= 10:90$) from the respective cyclic alcohols$^{30}$ and subjected them to the I-Li exchange conditions described above. Addition of the stereodefined cyclohexyl iodide $trans$-$(eq)-^{78}$ (1.0 equiv., 1.0 M in 3:2 hexane/ether) to a solution of $t$BuLi (2.2 equiv., 0.2 M) cooled to -100 °C instantaneously produced the $trans$-

$^{26}$ CCDC/890872 (for $\beta$-$(eq)-^{94a}$), CCDC/890873 (for $cis$-$(ax)-^{78}$), CCDC/890874 (for $neomen$-$(ax)-^{91b}$) and CCDC/890875 (for $trans$-$(eq)-^{82f}$) contain supplementary crystallographic data. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

cyclohexyllithium reagent trans-(eq)-81. Quenching with Me₂S₂ (dimethyl disulfide; 4 equiv., -100 °C, 5 min) led to the expected trans-thioether trans-(eq)-82a with retention of configuration (cis:trans= 9:91) in a 90% yield (Scheme 28c). Notably, this trans-lithium reagent trans-(eq)-81 with the Li-atom occupying an equatorial position was stable at -100 °C for several hours (probed for a period of 7 h). Subjecting cis-(ax)-78 to the same exchange reaction conditions produced the axially substituted cis-cyclohexyllithium cis-(ax)-81 (-100 °C; 5 s). Quenching with Me₂S₂ (4 equiv., -100 °C, 5 min) mainly gave the corresponding cis-thioether cis-(ax)-82a (cis:trans= 90:10) in a 73% yield. The lithium species cis-(ax)-81 bearing the Li-atom in an axial position displayed a much lower configurational stability and fully equilibrated into the stable all-equatorially substituted cyclohexyllithium trans-(eq)-81 within 7 h at -100 °C (cis:trans <3:97; see also the detailed kinetic and theoretical studies on the configurational stability below). The lower stability of cis-(ax)-81 compared to its diastereomer trans-(eq)-81 is also likely to account for the slightly decreased yield.

Next, the reactivity of trans-(eq)-81 and cis-(ax)-81 towards a variety of electrophiles was examined (Table 1). While the reactions of trans-(eq)-81 with a range of electrophiles proceeded with retention of configuration leading to the expected trans-substituted products in 85-92% yield and with excellent stereoselectivities (up to d.r. >99:1; entries 1-4; Table 1),

<table>
<thead>
<tr>
<th>Entry</th>
<th>Li-Reagent</th>
<th>Electrophile</th>
<th>Product</th>
<th>d.r. (cis:trans)a</th>
<th>Yield [%]b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>trans-(eq)-81</td>
<td>Bu₃S₂</td>
<td>trans-(eq)-82b</td>
<td>&lt;1:99</td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td>trans-(eq)-81</td>
<td>Ph-NCO</td>
<td>trans-(eq)-82c</td>
<td>&lt;1:99</td>
<td>87</td>
</tr>
<tr>
<td>3</td>
<td>trans-(eq)-81</td>
<td>F₃CCO₂D</td>
<td>trans-(eq)-82d</td>
<td>4:96c</td>
<td>85d</td>
</tr>
<tr>
<td>4</td>
<td>trans-(eq)-81</td>
<td>Me₃SnCl</td>
<td>trans-(eq)-82e</td>
<td>&lt;1:99</td>
<td>92</td>
</tr>
<tr>
<td>5</td>
<td>cis-(ax)-81</td>
<td>Bu₃S₂</td>
<td>cis-(ax)-82b</td>
<td>90:10</td>
<td>59</td>
</tr>
</tbody>
</table>
B. Results and Discussion

<table>
<thead>
<tr>
<th></th>
<th>cis-(ax)-81</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>cis-(ax)-81</td>
<td>Ph-NCO</td>
<td></td>
<td>cis-(ax)-82c</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>90:10</td>
</tr>
<tr>
<td>7</td>
<td>cis-(ax)-81</td>
<td>F₃CCO₂D</td>
<td></td>
<td>cis-(ax)-82d</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>92:8³</td>
</tr>
<tr>
<td>8</td>
<td>cis-(ax)-81</td>
<td>Me₃SnCl</td>
<td></td>
<td>trans-(eq)-82e</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>7:93</td>
</tr>
<tr>
<td>9</td>
<td>cis-(ax)-81</td>
<td>Ph₃SnCl</td>
<td></td>
<td>trans-(eq)-82f</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>8:92², f</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>cis-(ax)-81</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>cis-(ax)-81</td>
<td>Ph-NCO</td>
<td></td>
<td>cis-(ax)-82c</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>90:10</td>
</tr>
<tr>
<td>7</td>
<td>cis-(ax)-81</td>
<td>F₃CCO₂D</td>
<td></td>
<td>cis-(ax)-82d</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>92:8³</td>
</tr>
<tr>
<td>8</td>
<td>cis-(ax)-81</td>
<td>Me₃SnCl</td>
<td></td>
<td>trans-(eq)-82e</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>7:93</td>
</tr>
<tr>
<td>9</td>
<td>cis-(ax)-81</td>
<td>Ph₃SnCl</td>
<td></td>
<td>trans-(eq)-82f</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>8:92², f</td>
</tr>
</tbody>
</table>

[a] Determined via capillary GC analysis and ¹H-NMR. [b] Isolated yields. [c] Determined via ¹H-NMR. [d] Determined via capillary GC analysis. [e] The relative configuration was determined by X-ray analysis. [f] Determined via ¹¹⁷Sn-NMR.

Quenching of the configurationally labile cis-(ax)-81 was not as predictable. Trapping of cis-(ax)-81 with Bu₂S₂ (dibutyl disulfide), d-TFA and phenyl isocyanate (PhNCO) stereoselectively provided the expected cis-products (cis-(ax)-82b-d; entries 5-7; Table 1). However, quenching of cis-(ax)-81 with Me₃SnCl and Ph₃SnCl proceeded with inversion resulting mainly in the trans-substituted stannanes (trans-(eq)-82e-f; entries 8 and 9; Table 1).³¹ Due to the greater lability of cis-(ax)-81 lower yields (51-75%) are generally obtained than in the reactions of trans-(eq)-81. The configurational instability of cis-(ax)-81 also accounts for the lower observed stereoselectivities in the retentive quenching reactions (entries 5-7; Table 1).

Intrigued by these results, we became interested in the scope of substrates suitable for the I-Li exchange reaction. Therefore, we chose a variety of differently substituted cyclohexyl iodides and subjected them to the I-Li exchange conditions. First, the reactions of equatorially substituted cyclohexyl iodides, which lead to the configurationally more stable organolithium reagents, were examined (Table 2).

---

Table 2: Scope study of the I-Li exchange using equatorially substituted cyclohexyl iodides and quenching of the ensuing Li-species with electrophiles.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cyclohexyl Iodide</th>
<th>Cyclohexyllithium</th>
<th>E⁺</th>
<th>Product</th>
<th>d.r.</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>trans-(eq)-83a</td>
<td>trans-(eq)-84a</td>
<td>Bu₃S₂</td>
<td>trans-(eq)-85a</td>
<td>&lt;1:99</td>
<td>91</td>
</tr>
<tr>
<td>2</td>
<td>trans-(eq)-83b</td>
<td>trans-(eq)-84b</td>
<td>Bu₃S₂</td>
<td>trans-(eq)-85b</td>
<td>&lt;1:99</td>
<td>83</td>
</tr>
<tr>
<td>3</td>
<td>trans-(eq)-83c</td>
<td>trans-(eq)-84c</td>
<td>Bu₃S₂</td>
<td>trans-(eq)-85c</td>
<td>1:99</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td>trans-(eq)-83c</td>
<td>trans-(eq)-84c</td>
<td>Ph₂PCl, S₈</td>
<td>trans-(eq)-85d</td>
<td>2:98</td>
<td>69</td>
</tr>
<tr>
<td>5</td>
<td>trans-(eq)-83c</td>
<td>trans-(eq)-84c</td>
<td>EtSO₂Cl</td>
<td>trans-(eq)-85e</td>
<td>1:99</td>
<td>61</td>
</tr>
<tr>
<td>6</td>
<td>cis-(eq)-86a</td>
<td>cis-(eq)-87a</td>
<td>Bu₃S₂</td>
<td>cis-(eq)-88a</td>
<td>1:99</td>
<td>81</td>
</tr>
<tr>
<td>7</td>
<td>cis-(eq)-86b</td>
<td>cis-(eq)-87b</td>
<td>Bu₃S₂</td>
<td>cis-(eq)-88b</td>
<td>2:98</td>
<td>63</td>
</tr>
<tr>
<td>8</td>
<td>men-(eq)-89</td>
<td>men-(eq)-90</td>
<td>Me₂S₂</td>
<td>men-(eq)-91a</td>
<td>13:87</td>
<td>54</td>
</tr>
<tr>
<td>9</td>
<td>men-(eq)-89</td>
<td>men-(eq)-90</td>
<td>Ph₂PCl, S₈</td>
<td>men-(eq)-91b</td>
<td>10:90⁴</td>
<td>59</td>
</tr>
<tr>
<td>10</td>
<td>β(eq)-92</td>
<td>β(eq)-93</td>
<td>Me₂S₂</td>
<td>β(eq)-94a</td>
<td>1:99</td>
<td>71</td>
</tr>
<tr>
<td>11</td>
<td>β(eq)-92</td>
<td>β(eq)-93</td>
<td>Ph₂PCl, S₈</td>
<td>β(eq)-94b</td>
<td>6:94</td>
<td>80</td>
</tr>
</tbody>
</table>
Thus, the 4-methyl-substituted cyclohexyl iodide (trans-(eq)-83a) was stereoselectively converted to the organolithium reagent trans-(eq)-84a which upon trapping with Bu₂S₂ exclusively provided the trans-configured thioether trans-(eq)-85a in 91% yield (entry 1; Table 2). Replacing the methyl group with coordinating (MeO; trans-(eq)-84b) and non-coordinating (TIPS= i-Pr₃Si; trans-(eq)-84c) oxygen functionalities led, after quenching, to the expected trans-substituted products with equally high yields and diastereoselectivities (83-90%; d.r.: >99:1; entries 2-3; Table 2). Trapping of the functionalised organolithium reagent trans-(eq)-84c with Ph₂PCl and subsequent protection with S₈ gave the trans-substituted thiolphosphane trans-(eq)-85d in 69% overall yield with a d.r. of 98:2 (entry 4; Table 2). The reaction of trans-(eq)-84c with EtSO₂Cl exclusively led to the all-equatorially substituted cyclohexyl chloride trans-(eq)-85e (entry 5; Table 2). The cis-1,3-disubstituted cyclohexyl iodides cis-(eq)-86a-b smoothly underwent the I-Li exchange reaction. The resulting equatorially substituted Li-reagents cis-(eq)-87a-b were trapped with Bu₂S₂ leading to the cis-configured products cis-(eq)-88a-b with 63-81% yield and high diastereoselectivities (entries 6 and 7; Table 2). Subjection of menthyl iodide (men-(eq)-89) with a diastereomeric purity of 75:25 (menthyl(eq)/neomenthyl(ax)) to the I-Li exchange reaction resulted in the formation of mainly menthyllithium (men-(eq)-90) whose immediate quenching with Me₂S₂ or Ph₂PCl gave the menthyl derivatives men-(eq)-91a-b with improved diastereoselectivities relative to the starting material reaching from 87:13 to 90:10 (entries 8-9; Table 2). The comparatively low yields (54-59%) can be attributed to the increased basicity of men-(eq)-90 which competes more readily with tBuLi for deprotonation of the tert-butyl iodide (tBuI) side-product (compare Scheme 28) and to the presence of 25% neomenthyl iodide (neomen-(ax)-89) in the starting material which leads to an unstable axial organolithium (neomen-(ax)-90; see Table 3). I-Li exchange on cholesteryl iodide β-(eq)-92 led to the configurationally stable Li-reagent β-(eq)-93 which underwent quenching with Me₂S₂ and Ph₂PCl with retention of stereoconfiguration furnishing the products β-(eq)-94a and β-(eq)-94b with 71-80% yield and high stereoselectivities (d.r. 94:6 to 99:1; entries 10-
11, Table 2). Subjection of cholestanyl iodide $\beta$-(eq)-95 with a diastereomeric purity of 85:15 ($\beta$/$\alpha$) to the I-Li exchange and subsequent trapping of the resulting lithium compound $\beta$-(eq)-96 with Me$_2$S$_2$ gave the thioether $\beta$-(eq)-97 in 74% yield with a significantly increased diastereomeric ratio of 98:2 in favour of the $\beta$-isomer (entry 12, Table 2). Next, we examined the substrate scope of the corresponding axially substituted cyclohexyllithium reagents (cis-(ax)-84a-c, trans-(ax)-87, neomen-(ax)-90) by subjecting the respective stereochemically pure cyclohexyl iodides (cis-(ax)-83a-c, trans-(ax)-86, neomen-(ax)-89) to the I-Li exchange conditions (Table 3).

Table 3: Scope study of the I-Li exchange using axially substituted cyclohexyl iodides and quenching of the ensuing Li-species with electrophiles.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cyclohexyl Iodide</th>
<th>Cyclohexyllithium</th>
<th>E$^+$</th>
<th>Product</th>
<th>d.r. ax: eq $^a$</th>
<th>Yield [ % ]$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>cis-(ax)-83a</td>
<td>cis-(ax)-84a</td>
<td>Bu$_2$S$_2$</td>
<td>cis-(ax)-85a</td>
<td>91:9</td>
<td>74</td>
</tr>
<tr>
<td>2</td>
<td>cis-(ax)-83b</td>
<td>cis-(ax)-84b</td>
<td>Bu$_2$S$_2$</td>
<td>85b</td>
<td>52:48</td>
<td>67</td>
</tr>
<tr>
<td>3</td>
<td>cis-(ax)-83c</td>
<td>cis-(ax)-84c</td>
<td>Bu$_2$S$_2$</td>
<td>cis-(ax)-85c</td>
<td>96:4</td>
<td>79</td>
</tr>
<tr>
<td>4</td>
<td>cis-(ax)-83c</td>
<td>cis-(ax)-84c</td>
<td>Ph$_2$PCl, S$_8$</td>
<td>cis-(ax)-85d</td>
<td>92:8</td>
<td>51</td>
</tr>
<tr>
<td>5</td>
<td>cis-(ax)-83c</td>
<td>cis-(ax)-84c</td>
<td>EtSO$_2$Cl</td>
<td>cis-(ax)-85e</td>
<td>94:6</td>
<td>56</td>
</tr>
<tr>
<td>6</td>
<td>trans-(ax)-86</td>
<td>trans-(ax)-87</td>
<td>Bu$_2$S$_2$</td>
<td>trans-(ax)-88</td>
<td>89:11</td>
<td>56</td>
</tr>
<tr>
<td>7</td>
<td>neomen-(ax)-89</td>
<td>neomen-(ax)-90</td>
<td>Me$_2$S$_2$</td>
<td>neomen-(ax)-91a</td>
<td>93:7</td>
<td>23</td>
</tr>
<tr>
<td>8</td>
<td>neomen-(ax)-89</td>
<td>neomen-(ax)-90</td>
<td>Ph$_2$PCl, S$_8$</td>
<td>neomen-(ax)-91b</td>
<td>91:9$^{c,d}$</td>
<td>28</td>
</tr>
</tbody>
</table>
Thus, the 4-methyl-substituted cis-configured cyclohexyllithium cis-(ax)-84a generated from the corresponding axial iodide cis-(ax)-83a gave the expected product cis-(ax)-85a after immediate trapping (5 s) with Bu$_2$S$_2$ with predominant retention of configuration (d.r.: 91:9, 74%; entry 1 of Table 3). Remarkably, when the I-Li exchange was performed on the 4-methoxy-substituted cyclohexyl iodide cis-(ax)-83b, immediate quenching with Bu$_2$S$_2$ led to a 52:48 cis:trans-mixture of the thioether 85b (entry 2, Table 3). We reasoned that this decay in stereoselectivity could be attributed to the coordinative properties of the 4-MeO-group which may intramolecularly break the unstable C-Li bond and facilitate its isomerization to the configurationally more stable equatorially substituted organolithium trans-(eq)-84b. Indeed, complete isomerisation from cis-(ax)-84b to trans-(eq)-84b takes place within only 2.5 min at -100 °C in a hexane:ether 3:2-mixture (cis:trans 2:98; see also the detailed kinetic studies on the configurational stability below; Scheme 29b), whereas the corresponding 4-tert-butyl-substituted axial cyclohexyllithium cis-(ax)-81 requires 7 h under the same conditions to isomerise to the stable equatorial cyclohexyllithium compound trans-(eq)-81 (see also Scheme 29a). Interestingly, accelerated isomerization was not observed with an OTIPS-substituent and the desired cis-configured products cis-(ax)-85c-e were obtained upon quenching in 51-79% yield with stereoselectivities up to 96:4 (entries 3-5, Table 3). The bulky silyl group prevents the neighbouring oxygen atom from coordinating to the Li$^+$-ion. I-Li exchange on the 3-methyl-substituted trans-configured cyclohexyl iodide trans-(ax)-86 led to formation of configurationally unstable trans-(ax)-87 which upon immediate quenching with Bu$_2$S$_2$ gave the expected product trans-(ax)-88 with 56% yield and a slightly decreased d.r. of 89:11 (entry 6, Table 3). Immediate trapping of neomenthylolithium (neomen-(ax)-90), generated from neomenthyl iodide (neomen-(ax)-89), with Me$_2$S$_2$ and Ph$_2$PCL furnished the axially substituted products with good stereoselectivities (d.r. 91:9 to 93:7), however, in low

[a] Determined via capillary GC analysis and $^1$H-NMR. [b] Isolated yields. [c] Determined via $^{31}$P-NMR. [d] The relative configuration was determined by X-ray analysis.\(^{29}\)
yields (23-28%; entries 7-8, Table 3). The decreased yields are due to a highly reactive neomenthylithium species \((\text{neomen-(ax)-90})\) whose C-Li bond is weakened by the neighbouring isopropyl-group. Thus, the higher reactivity of this C-Li bond makes it a better competitor for \(t\text{BuLi}\) in the deprotonation of \(t\text{BuI}\) explaining the lower yields (compare Scheme 28a). Similar results were obtained in the quenching of the cis-2-methyl-substituted cyclohexyllithium cis-(ax)-99 which was generated from iodide cis-(ax)-98. Trapping of cis-(ax)-99 with \(\text{Bu}_2\text{S}_2\) led to the product cis-(ax)-100 with a good diastereomeric ratio of 88:12 in 34\% yield (entry 9, Table 3) underlining the higher reactivity and greater instability of 2-neighbouring isopropyl-group. Thus, the higher reactivity of this C-Li bond makes it a better competitor for formation of stabilizing oligomeric organolithium-clusters (see also DFT-analysis below).

Next, we followed the kinetics of the invertive equilibration processes under standard conditions at \(-100\, ^\circ\text{C}\) for the 4-substituted cyclohexyllithium reagents cis-(ax)-81, cis-(ax)-84a and cis-(ax)-84b (Scheme 29a-b). The ratio of axial to equatorial Li-species, determined via retentive quenching with \(\text{Me}_2\text{S}_2\) or \(\text{Bu}_2\text{S}_2\), was recorded during a time course of 7 h.
Scheme 29: Kinetic investigation on the equilibration of the configurationally unstable axially substituted cyclohexyllithium reagents into their stable equatorially substituted diastereomers.

Plotting of the percentage of the respective axial 4-substituted cyclohexyllithium species versus time resulted in near-exponential curves for cis-(ax)-81 and cis-(ax)-84a showing that inversive equilibration proceeds with first-order rate kinetics. Interestingly, the inversion process was faster for cis-(ax)-84a bearing the less bulky methyl group in position 4. Thus, after 2 h, an ax/eq-ratio of 9:91 was reached for 84a, whereas the 4-tert-butyl-substituted cyclohexyllithium 81 had only equilibrated to a ratio of 32:68 in the same time period. After 7 h, cis-(ax)-81 and cis-(ax)-84a had almost completely been converted to the diastereomERICconfigureNATioNally stable Li-species trans-(eq)-81 (ax/eq: 3:97) and trans-(eq)-84a (ax/eq: 2:98). Equilibration towards the more stable equatorially substituted cyclohexyllithium trans-(eq)-84b proceeded much faster for cis-(ax)-84b due to facilitated C-Li bond breakage via intramolecular coordination of the Li-atom to the methoxy-moiety. Here, after already 5 s, an ax/eq-ratio of 52:48 is reached. After 2.5 min cis-(ax)-84b has almost completely equilibrated to the diastereomeric isomer trans-(eq)-84b (ax/eq: 2:98). Thus, we wondered whether addition of THF, which is known to be a strongly coordinating solvent for organolithium species, to cis-(ax)-81 would similarly accelerate its equilibration to the stable trans-(eq)-81. Indeed, when 25 vol% THF were added to cis-(ax)-81 at -100 °C immediate quenching

---

with \(\text{Me}_2\text{S}_2\) already displayed an \(ax/eq\)-ratio of 9:91. Quenching after 10 min gave the product \(\text{trans-(eq)-82a}\) in 63\% isolated yield with a d.r. of 4:96.

When we turned our attention to the kinetics of C-Li bond inversion with neomenthylithium \(\text{neomen-(ax)-90}\) bearing a large isopropyl group in the neighbouring position, we were surprised to find a completely different behaviour. Its equilibration followed a sigmoidal curve. Thus, inversion was very slow during the first 4 h reaching only an \(ax/eq\)-ratio of 71:29. After 4 h, the curve’s slope got steeper showing an accelerated inversion resulting in an \(ax/eq\)-ratio of 29:71 after 7 h. This hints towards an auto-mediated process in which menthylithium \(\text{men-(eq)-90}\) promotes its own formation. With enough menthylithium \(\text{men-(eq)-90}\) (ca. 30\%) formed, inversion accelerates. However, the overall inversion proceeds much slower than for the 4-substituted cyclohexyllithiums. Almost complete inversion from \(\text{neomen-(ax)-90}\) to \(\text{men-(eq)-90}\) could be achieved when the reaction mixture was warmed, directly after I-Li exchange on \(\text{neomen-(ax)-89}\), from -100 °C to -60 °C within 50 min. Quenching of the lithium reagent with \(\text{Me}_2\text{S}_2\) gave \(\text{men-(eq)-91a}\) with a high stereoselectivity (\(ax/eq= 2:98\)) and 32\% yield. Notably, addition of 25 vol\% of THF did not speed up the equilibration from \(\text{neomen-(ax)-90}\) to \(\text{men-(eq)-90}\) at -100 °C. Instead, the \(ax/eq\)-ratio changed much more slowly over time. In this case, the kinetic behaviour was best described by a straight line. After 7 h, the \(ax/eq\)-ratio had only dropped to 84:16.

In order to explore the preference of lithium for the equatorial over the axial positions in cyclohexane ring systems, theoretical studies have been performed for 4-\(\text{tert-}
\text{butylcyclohexyllithium 81}\) in its equatorial (\(\text{trans-(eq)-81}\)) and axial (\(\text{cis-(ax)-81}\)) configurations. Following earlier theoretical work on organolithium species\(^{32,33}\) geometry optimizations have been performed at the B3LYP/6-31+G(d) level of theory. Thermal corrections to free energies at 298.15 K have been calculated at the same level using the rigid rotor/harmonic oscillator model. Single point energies have then been added at MP2(FC)/6-311+G(2d,p) level and combined with thermal corrections obtained at B3LYP/6-31+G(d) level in order to calculate free energies at 298.15 K. Interestingly, comparison of the gas phase stabilities of monomeric \(\text{trans-(eq)-81}\) and \(\text{cis-(ax)-81}\) indicated a small thermodynamic preference for the axially substituted \(\text{cis-(ax)-81}\) (Table 4) by 3.8 kJ/mol. This energy difference remains essentially unchanged at even higher levels of theory such as G3+(MP2)B3. This, however, is in clear contrast to the trapping experiments performed at

-100 °C in Et₂O/hydrocarbon solvents demonstrating a large or exclusive preference for equatorial isomers. Since the experimentally observed strong stereochemical preference for the equatorially substituted trans-(eq)-81 may be due to aggregates formed at low temperatures in weakly coordinating solvents, calculations have been additionally performed on the respective cyclohexyllithium aggregates. Comparison of the gas phase stabilities of the dimeric lithium species trans-(eq)-101 and cis-(ax)-101 shows only a small preference of 4.72 kJ/mol for the equatorial isomer (Table 4). The hexameric structures found for nBuLi³⁴ (from hexane) and cyclohexyllithium³⁵ (from benzene) indicate that higher aggregates can easily be formed in less polar solvents. The equatorial/axial preference was therefore also explored for the hexameric form of cyclohexyllithium.

Table 4: Relative gas phase stabilities of monomeric, dimeric and hexameric cyclohexyllithiums.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Structures, ΔG_{298/ax-eq} [kJ/mol]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>trans-(eq)-81, -3.8</td>
</tr>
<tr>
<td>2</td>
<td>cis-(ax)-81, +4.7</td>
</tr>
<tr>
<td>3</td>
<td>trans-(eq)-102, +71.3</td>
</tr>
<tr>
<td></td>
<td>cis-(ax)-102, +71.3</td>
</tr>
</tbody>
</table>

[a] Geometries have been optimized at the B3LYP/6-31+G(d) level in all cases. [b] Energies were determined at the MP2(FC)/6-311+G(2d,p) level.


Despite the fact that this system now lacks the tert-butyl anchor at position 4 of the cyclohexane ring, the results are nevertheless expected to be also relevant for the substituted system. The results obtained at B3LYP or MP2 level of theory are quite clear about the strong preference for the all-equatorial isomer $\text{trans-(eq)-102}$ over the all axial isomer $\text{cis-(ax)-102}$, in agreement with the conformation found in the hexameric X-ray crystal structure. The large energy difference of 71.3 kJ/mol in favour of $\text{trans-(eq)-102}$ implies a preference of 11.9 kJ/mol for the equatorial orientation in each of the six monomers. Compared to the equatorial/axial energy differences found for the respective tert-butyl cyclohexyllithium monomers ($\text{trans-(eq)-81}$ and $\text{cis-(ax)-81}$) and dimers ($\text{trans-(eq)-101}$ and $\text{cis-(ax)-101}$), this implies that the state of aggregation is the key determinant for the stereochemical preferences in substituted cyclohexyllithiums.

In summary, we have described a practical preparation of stereodefined cyclohexyllithium reagents from the corresponding organic iodides. This stereoretentive method allowed a detailed study of the configurational stabilities, stereochemical behaviours and reactivities of a wide range of axially and equatorially substituted cyclohexyllithium reagents. Thus, it was possible to stereoselectively synthesize various cis- and trans-cyclohexane derivatives by quenching with several classes of electrophiles. We have also found a clear tendency of equilibration towards the equatorially substituted lithium compounds. This thermodynamic phenomenon was explained by the formation of hexameric organolithium species which display a large difference in energy for the all-equatorial and all-axial species as proven by DFT-calculations. Polar solvents, such as THF, speed up the equilibration process for axial 4-substituted cyclohexyllithium reagents, while they display a stabilization effect on 2-substituted neomenthyllithium $\text{neomen-(ax)-90}$. An invertive reactivity pathway was found for the reaction of configurationally labile axially substituted cyclohexyllithium $\text{cis-(ax)-81}$ with organotin halides.
2. Novel Insights into the Stereochemical Behaviour of Diastereomeric Cyclohexylzinc Reagents – Stereoconvergence through Distinct Stereochemical Pathways

2.1. Introduction

Whereas the reactivities and configurational stabilities of diverse stereodefined alkyllithium\(^{36}\) and -magnesium species\(^{37}\) have been subject to extensive studies, the stereochemical behaviour of organozinc species has only been sporadically investigated. The C-Zn bond plays an exceptional role in organometallic chemistry, as it has a significantly more covalent character than C-Li and C-Mg bonds which results in a broad compatibility towards sensitive functional groups.\(^{38}\) Still, the reactivity of organozinc reagents is considerably increased compared to the corresponding organoboron reagents making them highly useful reagents for organic synthesis.\(^{38}\) A stereoselective preparation of secondary alkylzinc reagents, however, proved difficult and the B-Zn exchange reaction so far represents the only general method for generating stereodefined C-Zn bonds.\(^{39}\) Only a few more examples for the stereoselective

---


preparations of secondary alkylzinc reagents have been reported. Thus, Zn-insertion using the highly active Rieke-Zn into diastereomerically pure endo-2-acetamido-7-iodobicyclo[2.2.1]heptane was stated to proceed with retention of configuration. Stereoconvergence leading to the exo-configured organozinc species was observed with exo- and endo-7-iodonorkanes using the same conditions. However, the respective organozinc compounds have not been directly analyzed and all conclusions on their stereoconfiguration have been deduced from quenching experiments with I$_2$ and Me$_3$SnCl. Recently, a stereoconvergent remotely stereocontrolled cross-coupling between substituted cyclohexylzinc reagents and (hetero)aryl halides and alkynyl bromides was disclosed. In a preliminary mechanistic proposal, a relatively fast equilibration between the diastereomeric cyclohexylzinc reagents was assumed and the observed high diastereoselectivities in the coupling reactions were ascribed to a dynamic kinetic resolution process in which the equatorially substituted cyclohexylzinc reagent eq-103 would react faster than the axially substituted conformer ax-103 leading selectively to the Pd-intermediate eq-104 and after reductive elimination to the all equatorially substituted arylated product eq-105 (Scheme 30).
B. Results and Discussion

Scheme 30: Initial mechanistic proposal showing a dynamic kinetic resolution (DKR) process for the stereoconvergence observed in the Pd-catalyzed cross-couplings of substituted cyclohexylzinc reagents with aryl halides (a). A relatively fast equilibrium between the diastereomeric cyclohexylzinc reagents was postulated due to the results of a modified Hoffmann-test (b). NMR studies indicated that only one cyclohexylpalladium intermediate was formed with the palladium occupying the equatorial position, whereas signals for several organozinc species were found (c). The DKR proposal is based on these experimental observations.

This model suited best, at that time, the experimental results and theoretical calculations. Thus, a modified Hoffmann-test\(^{44}\) on the configurational stability of 3-methylcyclohexylzinc chloride (106) using a five-fold excess of aryl iodide (electrophile) or zinc reagent (nucleophile) was performed. Since in both cases, the same d.r. had been achieved, it was concluded that the C-Zn bond was configurationally unstable and a DKR process would be the reason for the observed stereoconvergence. In combination with the fact that only one cyclohexylpalladium intermediate was observed using \(^1\)H\(^{31}\)P-NMR, in which the Pd-moiety occupied the equatorial position, and with the DFT-calculations that showed significant energetic differences only for the cyclohexylpalladium intermediates, however, not for the corresponding cyclohexylzinc compounds, this seemed a judicious approach.

The results of the modified Hoffmann-test, still, are ambiguous due to two reasons: 1) It was performed on a Pd-catalyzed reaction. Thus, reaction with excess or substoichiometric amounts of nucleophile would always have to pass through the bottleneck of a catalytic amount of Pd-intermediate. 2) Diastereomeric organozinc compounds were examined. For two diastereomeric reagents the stereochemical course (retention vs. inversion) of substitution with electrophiles does not have to be identical, since, in contrast to the isoenergetic reaction pathways of enantiomers, the pathways for diastereomers can differ in energy. Although not yet experimentally proven, Basu and Thayumanavan had anticipated such a scenario in a seminal review on the configurational stability of organolithium compounds.\(^{36d}\) Thus, with our preliminary mechanistic investigations, we could not exclude the possibility of distinct stereochemical pathways for the two diastereomeric cyclohexylzinc derivatives in the transmetalation with Ar-PdL\(_n\)X. Importantly, the configurational stability of secondary organozinc reagents has been contradictorily discussed in the literature: Guijarro and Rieke have published a comprehensive NMR-study on the configurational stability of (R)- and (S)-

B. Results and Discussion

sec-butylzinc bromide using a chiral bisoxazoline-ligand. The resulting diastereomeric complexes displayed distinct proton signals for the methine group and could thus be probed for equilibration. An extremely slow inversion process was observed (\(t_{1/2} = 4.0\) months!). Early experiments from our laboratories with stereodefined secondary alkylzinc reagents, however, suggested that the presence of salts considerably decreased the stability of the C-Zn bond by deteriorating the observed diastereoselectivities in quenching reactions with D\(_2\)O. A DKR process and thus configurational lability were also hypothesized by Hayashi and Kumada for the enantioselective coupling of (1-phenylethyl)zinc halides with vinyl bromide using a chiral Pd-ferrocene catalyst.

2.2. Results and Discussion

Intrigued by these contradictory reports, we decided to get more deeply involved in the study of the stereochemical behaviour of diastereomeric cyclohexylzinc systems in order to disclose the true reasons for the observed stereoconvergence in their diastereoselective Negishi-couplings.

Scheme 31: Negishi-cross-coupling on the structurally identical substituted cyclohexylzinc reagents trans-(eq)-107 and 108 displaying different stereochemical purities.


In preliminary experiments, we prepared the 2-substituted cyclohexylzinc reagents \textit{trans-(eq)}-107 and 108 which are structurally identical but differ in stereochemical purity and subjected them to our Negishi-cross-coupling conditions (Scheme 31). While \textit{trans-(eq)}-107 (\textit{trans:cis}= 98:2) was stereoselectively prepared using hydroboration on 109 followed by a stereoretentive B-Zn exchange,\textsuperscript{39} 108 was obtained as a mixture of diastereomers (\textit{trans:cis}= 69:31) from LiCl-promoted Zn-insertion into the corresponding organic iodide 110.\textsuperscript{47,48} The stereochemical purity of these compounds was checked by deuterolysis with d-TFA (10 equiv.) at RT. All equatorially substituted \textit{trans-(eq)}-107 was then subjected to Negishi-cross-couplings using Pd(dba)$_2$ (2 mol%; dba: dibenzylideneacetone) and SPhos (2 mol%; dicyclohexyl(2',6'-dimethoxy-[1,1'-biphenyl]-2-yl)phosphine)\textsuperscript{49} as catalyst system with several aryl iodides at RT. The respective arylated products 111a-b were obtained after 12-24 h in 90-93\% yield (64-68\% overall yield). Their diastereomeric purity (\textit{trans:cis}= 98:2) completely reflected the stereochemical content of the starting organozinc \textit{trans-(eq)}-107. Thus, the cross-couplings had proceeded with complete retention of stereoconfiguration. When the diastereomerically undefined 108 underwent the identical cross-coupling conditions with the same aryl iodides, 111a-b were obtained with 65-83\% yield and diastereomeric ratios reaching from \textit{trans:cis} 74:26 to 88:12. The diastereomeric purity had increased compared to the starting zinc reagent 108. In addition, however, the formation of regioisomers was observed (6-14\%). Strikingly, when the cross-couplings were performed at lower temperatures (-25 °C to -10 °C), solely the all equatorially substituted, thermodynamically favourable \textit{trans}-configured products were obtained (57-83\% yield; \textit{trans:cis} >99:1). The formation of regioisomers was thereby not observed. These results made us question our previous hypothesis of a DKR-driven stereoconvergence for two main reasons: 1) The configurationally defined, equatorially substituted \textit{trans-(eq)}-107 reacted smoothly to give the products 111a-b with the same diastereomeric ratio, which does not corroborate the presumption of a fast equilibration between two thermodynamically almost equally favoured cyclohexylzinc diastereomers. 2) The observation of regioisomers in the cross-coupling reactions of stereochemically undefined 108 suggests that the axially substituted \textit{cis-(ax)}-108 diastereomer may undergo distinct reaction pathways from \textit{trans-(eq)}-108.


In order to determine whether C-Zn bonds can invert on a relatively fast time scale (hours or minutes) and whether a fast equilibration was therefore possible, we decided to probe the configurational stability of trans-(eq)-d-112 and cis-(ax)-d-112 (Scheme 32).

The remotely substituted cyclohexylzinc reagent d-112 (trans-(eq)-d-112 & cis-(ax)-d-112) which bears a tert-butyl-substituent in position 4 and a deuterium on carbon 1 geminal to the zinc enabled us to directly observe the stereochemical purity of the organozinc via \(^2\)H-NMR. The bulky tert-butyl-group also functions as an anchor for the cyclohexyl ring ensuring that the diastereomeric zinc reagents differ only in the configuration of the C-Zn bond (axial (cis) vs. equatorial (trans)). Zn-insertion into the stereodefined 4-tert-butytcyclohexyl iodides cis-d-113 and trans-d-113 resulted both in a cis:trans-mixture of d-112 (53:47). No change in the ratio was observed after 2 d at RT. EXSY-experiments showed no cross-signal for neither the deuterium in \(^2\)H- nor the deuterated carbon in \(^13\)C-NMR analysis over a period of 12 h. When the EXSY experiments were applied to 112, bearing a proton instead of the deuterium, cross-signals could be found for neither the methine proton nor carbon. A significant coalescence-shift was not observed in the \(^2\)H-NMR analysis of d-112 even upon heating to 50 °C. Subjection of d-112 to quenching with TFA immediately and even after standing for 2 d at room temperature further confirmed the observed configurational stability of the cyclohexylzinc reagents.

It was now clear to us that due to the high configurational stability of the C-Zn bond a DKR mechanism which implies an equilibration between the diastereomeric zinc reagents and thus flipping of the C-Zn bond cannot be the cause of the observed stereoconvergence in the Negishi cross-coupling (Scheme 30). The mechanistic possibilities were now limited to either an equilibration on the stage of the Pd-intermediate (eq-104; Scheme 30), a Pd-salt induced equilibration or different stereochemical pathways for the diastereomeric cyclohexylzinc.
reagents in which the equatorial C-Zn bond would react with retention and the axial C-Zn bond with inversion of stereoconfiguration in the transmetalation step selectively forming eq-104. Thus, aware of the pivotal influence of temperature on the diastereoselectivity in the Negishi-cross-coupling (Scheme 31), we decided to probe the stereochemistry of several diastereomeric cyclohexylzinc reagents in the deuterolysis with d-TFA and MeOD at different temperatures (Table 5).

![Diagram of deuterolysis of diastereomeric cyclohexylzinc reagents.]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cyclohexylzinc Reagent</th>
<th>D'/H* Source</th>
<th>Reaction Temp. [°C]</th>
<th>Products</th>
<th>d.r. (eq:ax)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>d-TFA</td>
<td>25</td>
<td></td>
<td>69:31</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>d-TFA</td>
<td>-78</td>
<td></td>
<td>99:1</td>
</tr>
<tr>
<td>3</td>
<td>108</td>
<td>MeOD</td>
<td>25</td>
<td>trans-(eq)-114 + cis-(ax)-114</td>
<td>99:1</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>d-TFA</td>
<td>25</td>
<td></td>
<td>48:52</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>d-TFA</td>
<td>-78</td>
<td></td>
<td>96:4</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>MeOD</td>
<td>25</td>
<td>trans-(eq)-116 + cis-(ax)-116</td>
<td>87:13</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>MeOD</td>
<td>0</td>
<td></td>
<td>97:3</td>
</tr>
<tr>
<td>8</td>
<td>112</td>
<td>d-TFA</td>
<td>25</td>
<td></td>
<td>67:33</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td>d-TFA</td>
<td>-78</td>
<td></td>
<td>&gt;99:1</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td>MeOD</td>
<td>25</td>
<td>trans-(eq)-117 + cis-(ax)-117</td>
<td>&gt;99:1</td>
</tr>
<tr>
<td>11</td>
<td>118</td>
<td>d-TFA</td>
<td>25</td>
<td></td>
<td>66:34</td>
</tr>
<tr>
<td>12</td>
<td></td>
<td>d-TFA</td>
<td>-78</td>
<td></td>
<td>76:24</td>
</tr>
<tr>
<td>13</td>
<td></td>
<td>MeOD</td>
<td>25</td>
<td>trans-(eq)-119 + cis-(ax)-119</td>
<td>76:24</td>
</tr>
<tr>
<td>14</td>
<td>trans-(eq)-118 + cis-(ax1)-118 + cis-(ax2)-118</td>
<td>MeOD</td>
<td>0</td>
<td>trans-(eq)-119 + cis-(ax)-119</td>
<td>90:10</td>
</tr>
<tr>
<td>15</td>
<td></td>
<td>d-TFA</td>
<td>25</td>
<td></td>
<td>65:35</td>
</tr>
<tr>
<td>16</td>
<td></td>
<td>d-TFA</td>
<td>-78</td>
<td></td>
<td>80:20</td>
</tr>
<tr>
<td>17</td>
<td></td>
<td>MeOD</td>
<td>25</td>
<td>cis-(eq)-121 + trans-(ax)-121</td>
<td>76:24</td>
</tr>
<tr>
<td>18</td>
<td></td>
<td>MeOD</td>
<td>0</td>
<td></td>
<td>90:10</td>
</tr>
</tbody>
</table>
### B. Results and Discussion

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compound</th>
<th>MeOD</th>
<th>d-TFA</th>
<th>cis-(eq)-123 + trans-(ax)-123</th>
<th>cis-(ax)-117 + trans-(eq)-117</th>
</tr>
</thead>
<tbody>
<tr>
<td>19</td>
<td>122</td>
<td>25</td>
<td>25</td>
<td>58:42</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>123</td>
<td>25</td>
<td>-78</td>
<td>79:21</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>MeOD</td>
<td>25</td>
<td>0</td>
<td>cis-(eq)-123 + trans-(ax)-123</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>MeOD</td>
<td>25</td>
<td>0</td>
<td>cis-(eq)-123 + trans-(ax)-123</td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>25</td>
<td>25</td>
<td>0</td>
<td>&gt;99:1</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>25</td>
<td>25</td>
<td>-78</td>
<td>&gt;99:1</td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>MeOD</td>
<td>25</td>
<td>0</td>
<td>&gt;99:1</td>
<td></td>
</tr>
<tr>
<td>26</td>
<td>25</td>
<td>25</td>
<td>-78</td>
<td>65:35</td>
<td></td>
</tr>
<tr>
<td>27</td>
<td>25</td>
<td>25</td>
<td>-78</td>
<td>&gt;99:1</td>
<td></td>
</tr>
<tr>
<td>28</td>
<td>MeOD</td>
<td>25</td>
<td>0</td>
<td>&gt;99:1</td>
<td></td>
</tr>
<tr>
<td>29</td>
<td>25</td>
<td>25</td>
<td>-78</td>
<td>79:21</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>25</td>
<td>25</td>
<td>-78</td>
<td>99:1</td>
<td></td>
</tr>
<tr>
<td>31</td>
<td>25</td>
<td>25</td>
<td>-78</td>
<td>90:10</td>
<td></td>
</tr>
<tr>
<td>32</td>
<td>25</td>
<td>25</td>
<td>-78</td>
<td>&gt;99:1</td>
<td></td>
</tr>
<tr>
<td>33</td>
<td>25</td>
<td>25</td>
<td>-78</td>
<td>88:12</td>
<td></td>
</tr>
<tr>
<td>34</td>
<td>25</td>
<td>25</td>
<td>-78</td>
<td>64:36</td>
<td></td>
</tr>
<tr>
<td>35</td>
<td>25</td>
<td>25</td>
<td>-78</td>
<td>63:37</td>
<td></td>
</tr>
<tr>
<td>36</td>
<td>25</td>
<td>25</td>
<td>-78</td>
<td>87:13</td>
<td></td>
</tr>
<tr>
<td>37</td>
<td>25</td>
<td>25</td>
<td>-78</td>
<td>91:9</td>
<td></td>
</tr>
</tbody>
</table>

[a] Determined via $^1$H-NMR.

Thus, quenching of 108 with d-TFA, which had resulted in a cis:trans-ratio of 31:69 at RT, led almost exclusively to the trans-configured deuterated product **trans-(eq)-114** (cis(ax):trans(eq) = 1:99) when performed at -78 °C (entries 1-2). Remarkably, replacing the strong acid d-TFA with the weak D$^+$-source MeOD furnished **trans-(eq)-114** (cis(ax):trans(eq) = 1:99) upon quenching at RT (entry 3). A similar behaviour was found for 115 bearing a less sterically demanding methyl-group in position 2 (entries 4-7). Interestingly, a cis(ax)/trans(eq)-ratio of deuterated product 116 of 13:87 was obtained when quenched with MeOD at RT (entry 6). This d.r. could be further improved to 3:97 when the reaction temperature was decreased to 0 °C (entry 7). For 112 bearing the tert-butyl anchor in position 4, the identical clear trend was observed: While quenching with d-TFA revealed the true
diastereomeric ratio of 112 (cis:trans = 33:67), exclusively trans-(eq)-117 was obtained when the reaction was performed at -78 °C (entries 8-9). Quenching with MeOD at RT gave trans-(eq)-117 with a diastereomeric purity of >99:1 (entry 10). Using 118 in which the tert-butyl anchor is replaced by a smaller methyl-group which allows the presence of an additional conformer for the axial cis-configured diastereomer cis-(ax2)-118 in which the methyl-group occupies an axial position while the C-Zn bond is oriented equatorially. Thus, the trend towards the all equatorially substituted, deuterated trans-product trans-(eq)-119 upon quenching at low temperature and with the weaker acid MeOD is less pronounced (entries 11-14). Upon quenching with MeOD at 0 °C a cis:trans-ratio of only 10:90 was achieved (entry 14). Almost identical ratios were obtained for the deuterolysis products cis-(eq)-121 and trans-(ax)-121 of the 3-methyl-substituted cyclohexylzinc reagent 120 (entries 15-18). The 3-OTBS-substituted 122, in accordance with the lower a-value of oxygen-groups on cyclohexyl rings,50 displayed a smaller bias towards equatorial deuteration, as reflected by the ratio of cis-(eq)-123 and trans-(ax)-123 (entries 19-22). With MeOD-quenching at 0 °C, however, a trans(ax):cis(eq)-ratio of 84:16 was achieved (entry 19). The rigid menthyl- (124), cholesteryl- (126) and cholestanylzinc (128) reagents showed a very strong tendency towards equatorial deuteration with both d-TFA and MeOD (entries 23-32). Thus, for menthylzinc reagent 124, which gave a 65:35 mixture of men-(eq)-125 to neomen-(ax)-125 upon trapping with d-TFA at RT, only the menthyl-diastereomer men-(eq)-125 was obtained, when the temperature was decreased to -78 °C (entry 24). Also, quenching with MeOD at RT resulted only in the formation of men-(eq)-125 (entry 25). For rigid cholesteryl- (126) and cholestanylzinc iodide (128) quenching with d-TFA at RT resulted already in α(ax):β(eq)-ratios of 18:82 and 21:79 (entries 26 and 29). Quenching with d-TFA at -78 °C and MeOD resulted in a strong preference for the equatorially deuterated products β(eq)-127 and β(eq)-129 (entries 27-28, 30-32). In order to test whether these trends hold also true for protolysis, we performed analogous quenching reactions with the deuterated cyclohexylzinc iodides d-126 and d-112 using TFA and MeOH as proton sources (entries 33-37).51 Quenching d-126 with TFA at room temperature resulted already in a d.r. of 88:12 for the equatorially protonated product, thus corroborating the tendencies which were observed with the deuterolysis of 126 before (compare entries 26 and 33). The results for protolysis of d-112 were more remarkable: While trapping of d-112 with TFA at -78 °C and at RT both resulted in the same diastereomeric ratio (cis:trans= 36:64; 37:63; entries 34-35), quenching with

---

MeOH, however, resulted in preferential equatorial protonation with cis:trans-ratios of 13:87 at RT and 9:91 at 0 °C (entries 36-37). This unequivocally proves the tendency of the axial C-Zn bond in the cis-configured diastereomer cis-(ax)-d-112 to undergo invertive quenching.

We also observed a dependence of the diastereoselectivity in the quenching reactions on the mode of addition (Scheme 33). While direct quenching of 112 with d-TFA at RT resulted in a cis:trans-ratio of 33:67, slow addition of d-TFA over 2 h gave almost exclusively trans-(eq)-117. (A test experiment showed that this result was a function of the time used for addition, not of the lower concentration of d-TFA.) The same trend was observed in the protolysis of d-112 with TFA.

![Scheme 33: Comparison of direct and slow addition of d-TFA addition to 112.](image)

Thereby, addition of TFA over 2 h led preferentially to cis-(ax)-d-112 (cis:trans= 89:11). The distinct chemical shifts of the deuterium atoms on d-112 (prepared without LiCl) and on the protonated products allowed us to follow the protolysis reaction of d-112 via $^2$H-NMR. Thus, TFA was added slowly via syringe pump and the d.r. of d-112 and the protonation product 117 was checked after several periods of time. Remarkably, the starting d.r. of d-112 (cis(ax-Zn):trans(eq-Zn)= 37:63) remained constant during addition of TFA. More strikingly even, the d.r. of the protonated compound did not alter considerably. Thus, when 5 mol% TFA were added after 2 min, already a cis(ax-H):trans(ax-H)-ratio of 83:17 was observed for 117. This ratio remained more or less the same after the addition of 20 mol% TFA after 20 min (85:15) and after 1 h, when quenching of d-112 was finished after 1 h upon a total 110 mol% TFA (87:13). Accompanying $^2$H-EXSY-NMR experiments showed no observable cross-peak, thus excluding an equilibration of the C-Zn bond on NMR timescale. These results along with the fact that only one Pd-intermediate could be observed in the cross-coupling show that the equatorial C-Zn bond must react with retention and the axial C-Zn bond with inversion of the stereoconfiguration in the transmetalation step to ArPdL$_n$X thus leading to stereoconvergence.
in the reaction. Therefore, we replace the DKR scenario with a mechanistic view in which the two diastereomeric cyclohexylzinc reagents react via distinct stereochemical (retentive vs. invertive) pathways.
3. Diastereo- and Enantioselective Cross-Coupling with Functionalized Cyclohexylzinc Reagents

3.1. Synthesis of Chiral Protected Cyclohexyl Derivatives for the Enantio- and Diastereoselective Synthesis of 1-, 2-, 3-trisubstituted Cyclohexanes

The diastereoselective cross-coupling of substituted cyclohexylzinc derivatives should be applied to chiral functionalized building blocks. For this purpose, the chiral 131 was synthesized from 2-iodocyclohex-2-enone\textsuperscript{52} (130) via CBS-catalysis\textsuperscript{53} using diethylaniline borane in 98% yield and 96% ee. Subsequent protection with tert-butyldimethylsilylchloride (TBSCI) and cross-coupling with Me\textsubscript{2}Zn-2LiCl furnished the chiral functionalized cyclohex-2enol derivative 132 in 63% yield (Scheme 34).

![Scheme 34](image)

**Scheme 34:** Synthesis of chiral precursor molecule 132 via CBS reduction of iodocyclohex-2-enone (130), TBS protection of the resulting alcohol 131 and cross-coupling with Me\textsubscript{2}Zn-2LiCl.

Consequently, 132 was subjected to hydroboration with different boranes at 25 °C. In order to determine both the diastereoselectivity and conversion, an oxidized aliquot was checked by GC analysis. Thereby, di-(S)-isopinocampheylborane afforded the highest diastereoselectivity (d.r. = 77:23) (Table 6).

![Table 6](image)

**Table 6:** Hydroboration of 132 with different boranes; optimization of the diastereoselectivity.

\textsuperscript{52} Krafft, M. E. & Cran, J. W. A convenient protocol for the α-iodination of α,β-unsaturated carbonyl compounds with I\textsubscript{2} in an aqueous medium. *Synlett* 8, 1263-1266 (2005).

B. Results and Discussion

<table>
<thead>
<tr>
<th>Entry</th>
<th>Boran</th>
<th>Conversion [%]</th>
<th>Diastereoselectivity (133 : 134)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="9-BBN" /></td>
<td>0</td>
<td>--</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="di-(R)-isopino-campheylborane" /></td>
<td>58</td>
<td>37:63</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="di-(S)-isopino-campheylborane" /></td>
<td>60</td>
<td>77:23</td>
</tr>
</tbody>
</table>

For further increasing the diastereoselectivity, substrates with sterically more challenging protecting groups (PG) and moieties (R) at the double bond were employed (135, 136, 137 in Scheme 35).

Scheme 35: Sterically hindered substrate for hydroboration with sterically hindered substituents and silyl protecting groups.

The bulkier triphenylsilyl- as well as the tert-butyldiphenylsilyl- (TBDPS-) protecting group and equally the large phenyl- and cyclohexyl moieties were supposed to increase the steric interaction between substrate and hydroborating agent and thus improve the diastereoselectivity. However, 135, 136 and 137 did not react at all with 9-BBN, with di-(S)-isopinocampheylborane or (S)-isopinocampheylborane, even at higher temperatures (60 °C) no hydroboration was observed. Since high diastereoselectivity during the hydroboration step is essential for controlling all three stereo centers, this synthetic approach was no longer pursued.
3.2. Investigations with [2-(1,3-Dioxolane-2-yl)cyclohexyl]- and [2-(5,5-Dimethyl-1,3-dioxane-2-yl)cyclohexyl]zinc Compounds

Further investigations should determine whether the stereochemical purity of the cyclohexylzinc reagents has an influence on the diastereoselectivity of the cross-coupling reactions. Therefore, the protected cyclohexenyl derivatives 138 and 139 were transformed via hydroboration followed by boron-zinc exchange using Et₂Zn into the stereodefined ethylzinc compounds 140 and 141 (Scheme 36).

Scheme 36: Hydroboration of 138 and 139 with subsequent boron-zinc exchange and cross-coupling of the freshly generated ethylzinc compounds 140 and 141.

Subsequently, 140 and 141 were reacted using Pd-catalysis (Pd(db)₂ (2 mol%) and SPhos⁵⁴ (2 mol%)) with various aryl iodides (3 equiv.). Cross-couplings of 141 resulted already at room temperature in high diastereoselectivities (d.r.= 98:2; entries 2, 4, 5 and 6 of Table 7). Thereby, it did not make a difference whether an electron-poor or -rich aryl iodide was used (compare entry 2 with entries 5 und 6 of Table 7). However, cross-couplings with 140 as a nucleophile proceeded with significantly lower diastereoselectivities (entries 1 and 3 of Table 7).

Table 7: Pd-catalyzed cross-couplings of the ethylzinc compounds 140 and 141.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Zinc Reagent</th>
<th>Aryl Iodide</th>
<th>Temperature [°C] / Time [h]</th>
<th>Yield [%] a, d.r. b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>140</td>
<td>I—O—CMe</td>
<td>25 / 12</td>
<td>71, 87:13</td>
</tr>
<tr>
<td>2</td>
<td>141</td>
<td>I—O—CMe</td>
<td>25 / 12</td>
<td>56, 98:2</td>
</tr>
</tbody>
</table>

B. Results and Discussion

<table>
<thead>
<tr>
<th></th>
<th>140</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td></td>
<td>I-</td>
<td>CO₂Et</td>
<td>-10 to 0 / 24</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>141</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td></td>
<td>I-</td>
<td>CO₂Me</td>
<td>-10 to 25 / 24</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>141</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td></td>
<td>I-</td>
<td>CF₃</td>
<td>25 / 12</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>141</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td></td>
<td>I-</td>
<td></td>
<td>25 / 12</td>
</tr>
</tbody>
</table>

[a] Isolated yield of analytically pure product. [b] Diastereoselectivity determined by capillary GC analysis before and after purification.

In the following part, the preparation and the cross-couplings of the respective non-stereodefined organozinc iodides (142, 143) will be discussed. 1-Cyclohexen-1-carbaldehyde 144 was therefore protected with the respective diols. The resulting products 138 und 139 were then converted with BH₃·THF and the hydroborated intermediates subsequently oxidized with NaBO₂·4H₂O at 0 °C furnishing the corresponding alcohols 145 and 146. Reaction with dicyclohexylcarbodiimide-iodomethane-complex (DCC-MeI)⁵⁵ in THF at 50 °C led to the cyclohexyl iodides 147 und 148.⁵⁶ Subsequent zinc insertion⁵⁷ in the presence of LiCl furnished the cyclohexyl iodides 142 and 143 in 72% and 74% yield (Scheme 37).

---

Hydroboration of the ketals 149 and 150 followed by oxidation into the respective alcohols 151 and 152 was successful, whereas the transformation into the corresponding cyclohexyl iodides (153, 154) even with an excess of DCC-MeI and longer reaction times as well as higher reaction temperatures (65 °C) had failed (Scheme 38).

Scheme 38: Attempt to synthesize the cyclohexyl iodides 153 and 154 for subsequent zinc insertion.

142 and 143 were then subjected to Pd-catalyzed cross-coupling reactions with various aryl iodides at different temperatures (Table 8). It showed that the diastereoselectivity depends strongly on the reaction temperature and the nature of the applied aryl iodide. Cross-coupling of 142 and 143 with electron-rich 4-iodoanisole proceeded already at room temperature with relatively high diastereoselectivities (d.r. = 93:7 and 98:2; entry 1 und 2 of Table 8) but lower
yields, whereas cross-coupling with electron-poor aryl iodides (methyl-4-iodobenzoate and 1-iodo-2-(trifluoromethyl)benzene; entries 3, 4, 5 and 6 of Table 8) led to a significantly decreased diastereoselectivity (d.r. = 74:26 to 90:1). Even at -10 °C, cross-couplings of 142 with methyl-4-iodobenzoate and 1-iodo-2-(trifluoromethyl)benzene furnished only diastereomeric ratios of 81:19 (entry 3 of Table 8) and 90:10 (entry 5 of Table 8). In contrast, very high diastereoselectivities combined with good yields were obtained when the cross-coupling reactions were carried out at -25 °C (entries 7 to 9 of Table 8).

![Diagram](image)

**Table 8: Cross-coupling of organozinc iodides 142 and 143 with different aryl iodides.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Zinc Reagent</th>
<th>Aryl Iodide</th>
<th>Temperature [°C] / Time [h]</th>
<th>Yield [%]a, d.r.b</th>
<th>Regioisomer</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>142</td>
<td><img src="image" alt="I-Me" /></td>
<td>25 / 12</td>
<td>44, 93:7</td>
<td>6%</td>
</tr>
<tr>
<td>2</td>
<td>143</td>
<td><img src="image" alt="I-Me" /></td>
<td>25 / 12</td>
<td>47, 98:2</td>
<td>0%</td>
</tr>
<tr>
<td>3</td>
<td>142</td>
<td><img src="image" alt="I-CO2Me" /></td>
<td>-10 / 12</td>
<td>60, 81:19</td>
<td>7%</td>
</tr>
<tr>
<td>4</td>
<td>143</td>
<td><img src="image" alt="I-CO2Me" /></td>
<td>25 / 12</td>
<td>83, 74:26</td>
<td>6%</td>
</tr>
<tr>
<td>5</td>
<td>142</td>
<td><img src="image" alt="I-CF3" /></td>
<td>-10 / 12</td>
<td>79, 90:10</td>
<td>17%c</td>
</tr>
<tr>
<td>6</td>
<td>143</td>
<td><img src="image" alt="I-CF3" /></td>
<td>25 / 12</td>
<td>65, 88:12</td>
<td>14%</td>
</tr>
<tr>
<td>7</td>
<td>143</td>
<td><img src="image" alt="I-CO2Me" /></td>
<td>-25 to -10 / 24</td>
<td>73, &gt;99:1</td>
<td>0%</td>
</tr>
<tr>
<td>8</td>
<td>143</td>
<td><img src="image" alt="I-CF3" /></td>
<td>-25 to -10 / 24</td>
<td>57, &gt;99:1</td>
<td>0%</td>
</tr>
<tr>
<td>9</td>
<td>143</td>
<td><img src="image" alt="I-CF3" /></td>
<td>-25 to -10 / 24</td>
<td>83, &gt;99:1</td>
<td>0%</td>
</tr>
</tbody>
</table>

[a] Isolated yield of analytically pure product. [b] Determined by capillary GC analysis before and after purification. [c] This regioisomer was isolated by column chromatography and analysed.
The observed divergence of diastereoselectivity in the cross-coupling reactions of the organozinc iodides 142 and 143 with electron-poor aryl iodides at higher temperatures is due to a negligible difference in reactivity between the axial and equatorial C-Zn bonds. The formation of regioisomers is due to $\beta$-hydride elimination\textsuperscript{58} which may occur on the stage of the Pd-intermediate after stereoselective transmetalation (Scheme 39).\textsuperscript{59} The fact that regioisomers are not observed with the stereodefined all equatorially substituted organozinc reagents 140 and 141, which were produced via hydroboration/B-Zn-exchange sequences, suggests that this pathway is restricted to the axially substituted cis-configured diastereomer (Probably due to an unstable axial C-Pd bond). $\beta$-Hydride elimination may additionally be responsible for the low observed diastereoselectivities (Scheme 39). These results also corroborate the hypothesis presented in Chapter 2. The results of the cross-coupling reactions with the cyclohexylzinc reagents 142 and 143 compared to those with the analogous ethylzinc compounds 140 and 141 showed that the latter proceeded already at higher temperatures with excellent diastereoselectivities. This can be attributed to the distinct stereochemistry of the zinc reagents (ZnI vs. ZnEt). While the ethylzinc compounds (140 and 141) are stereochemically defined, the organozinc iodides 142 and 143 were employed as diastereomeric mixtures (see Chapter 2 on the diverse stereochemical behaviour of diastereomeric cyclohexylzinc reagents).

\textsuperscript{58} overview article on $\beta$-hydride elimination: Lu, X. Control of $\beta$-hydride elimination making palladium-catalyzed coupling reactions more diversified. Topics in Catalysis 35, 73-86 (2005).

\textsuperscript{59} Thaler, T., Haag, B., Gavryushin, A., Schober, K., Hartmann, E., Gschwind, R., Zipse, H., Mayer, P. & Knochel, P. Highly diastereoselective Csp$^3$-Csp$^2$ Negishi cross-coupling with 1,2-, 1,3- and 1,4-substituted cycloalkylzinc compounds. Nature Chem. 2, 125-130 (2010).
After \(\beta\)-hydride elimination has taken place the resulting aryl palladium hydride complex 156 has various opportunities for rearrangement to generate cyclohexenes 139 and 157. The formation of regioisomeric cross-coupling products and their diastereomers could also be observed at temperatures >-25 °C (Table 8).

### 3.3. Development of an Enantioselective Version of the Diastereoselective Cross-Coupling

In order to develop an asymmetric version of the diastereoselective cross-coupling reaction of substituted cyclohexylzinc derivatives,\(^{59}\) a sequence of enantioselective hydroboration followed by B-Zn exchange and eventually Pd-catalyzed cross-coupling was envisioned.
Therefore, a method established by E. Hupe and P. Knochel\(^{60}\) was applied. They reacted cyclohexene \(\text{138}\) with (-)-isopinocampheylborane ((-)-IpcBH\(_2\)) at \(-10\ \degree\text{C}\) in THF, treated it with an excess of HBEt\(_2\) and performed a subsequent boron-zinc exchange with \(\text{iPr}_2\text{Zn}\). The chiral organozinc reagent \(\text{158}\) was trapped via Cu(I) mediated alkinylation with high diastereoselectivity (Scheme 40).

![Scheme 40: Enantioselective hydroboration, boron-zinc exchange with subsequent Cu mediated alkylation of the chiral cyclohexylzinc compound 158.](image)

The chiral cyclohexylzinc compounds \(\text{159} and \text{160}\) were performed using this method \textit{via} enantioselective hydroboration with subsequent boron-zinc exchange and then subjected to cross-coupling reactions with different aryl iodides (Scheme 41).

![Scheme 41: Synthesis of the chiral cyclohexylzinc reagents \(\text{159} und \text{160}\) and Palladium catalyzed cross-coupling with aryl iodides.](image)

The respective cross-coupling products were obtained with diastereoselectivities of >99:1 and enantioselectivities of 68 to 81\% ee (Table 9). This method allows the direct and stereoselective approach to functionalized 1,2-disubstituted cyclohexanes.

B. Results and Discussion

Table 9: Cross-coupling of the chiral ethylzinc reagents 159 and 160.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Zinc Reagent</th>
<th>Aryl Iodide</th>
<th>Temperature [°C] / Time [h]</th>
<th>Yield [%], d.r.</th>
<th>ee [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>159</td>
<td><img src="image" alt="I-Me" /></td>
<td>25 / 12</td>
<td>39, &gt;99:1</td>
<td>n. d.</td>
</tr>
<tr>
<td>2</td>
<td>160</td>
<td><img src="image" alt="I-Me" /></td>
<td>25 / 12</td>
<td>82, &gt;99:1</td>
<td>73</td>
</tr>
<tr>
<td>3</td>
<td>159</td>
<td><img src="image" alt="I-CO2Et" /></td>
<td>-5/ 12</td>
<td>32, &gt;99:1</td>
<td>n. d.</td>
</tr>
<tr>
<td>4</td>
<td>160</td>
<td><img src="image" alt="I-CO2Me" /></td>
<td>-10 to 0 / 24</td>
<td>82, &gt;99:1</td>
<td>81</td>
</tr>
<tr>
<td>5</td>
<td>160</td>
<td><img src="image" alt="I-CF3" /></td>
<td>-10 to 0 / 24</td>
<td>54, &gt;99:1</td>
<td>77</td>
</tr>
<tr>
<td>6</td>
<td>160</td>
<td><img src="image" alt="I" /></td>
<td>-10 to 0 / 24</td>
<td>52, &gt;99:1</td>
<td>68</td>
</tr>
</tbody>
</table>

[a] Isolated yield of analytically pure product. [b] Diastereoselectivity determined by capillary GC analysis before and after purification. [c] Enantioselectivity.

3.4. Cross-Coupling with [8-(Ethoxymethoxy)decahydronaphthalen-1-yl](ethyl)zinc

*E. Hupe* und *P. Knochel* showed that decahydro-1-naphthalenol 166 can be highly diastereoselectively functionalized via hydroboration, boron-zinc exchange and subsequent allylation (Scheme 42). Thus, two stereocentres (2 and 3) can be introduced into the molecule at the same time. Via hydroboration it is possible to determine the relative configuration between the two stereocentres 1 and 2. In his thesis, *E. Hupe* points out that the choice of alcohol-protecting groups as well as the choice of solvent during the hydroboration step are crucial for achieving high diastereoselectivities. The Cu-mediated allylation of the organozinc compound 162, which is generated via boron-zinc exchange, is highly stereoselective and forms the stereocentre 3 with a d.r. (rel. conf. of positions 2,3) >98:2. In the final product 163, all substituents of the cyclohexyl ring of the *trans*-configured decahydro-1-naphthalenol occupy equatorial positions. Thus, the thermodynamically most stable product is formed.

---


B. Results and Discussion

Scheme 42: Synthesis of decahydronaphthalenylzinc reagent 162 and stereoselective functionalization via Cu-mediated allylation; selective synthesis of the thermodynamically most stable products.

We were then wondering if it was possible to achieve similar high diastereoselectivities by cross-coupling the decahydronaphthalenylzinc compound 162 with aryl iodides. Therefore, hexahydronaphthalene (164) was synthesized starting from the chiral alcohol 131 which was transformed in the first step with diethylchlorophosphate to the phosphate 165. A subsequent S$_2$2’ reaction with the functionalized organozinc compound 166 led to the ester 167, which was cyclized after iodine-lithium exchange to give compound 164 (Scheme 43).63

Scheme 43: Synthesis of EOM-protected decahydronaphthalenol derivative 169.

Following, 164 was diastereoselective reduced via Luche-reduction64 to the alcohol 168 and protected with ethoxymethyl chloride (EOMCl). Then, according to the procedure described by E. Hupe et al., 169 was subjected to hydroboration with Et$_2$BH-SMe$_2$ complex in CH$_2$Cl$_2$ followed by a boron-zinc exchange with Et$_2$Zn.61 The resulting organozinc compound 170

---

was used in Pd-catalyzed cross-coupling with 4-iodoanisole and methyl-4-iodobenzoate (Scheme 44).

Scheme 44: Synthesis of [8-(ethoxymethoxy)decahydronaphthalen-1-yl](ethyl)zinc (170) and subsequent cross-coupling.

The results are summarized in Table 10. The conversion of the reaction was low and the diastereoselectivity moderate. Hydroboration provided a diastereoselectivity of 90:10, whereas in the cross-coupling reactions significantly lower selectivities (d.r.= 67:33 and 85:15) were achieved. In order to check whether the correct reaction conditions were used, the allylation of Scheme 42 was repeated. The allylation product 163 was isolated with a yield of 57% (lit.: 65%) and diastereoselectivities of d.r.(1,2) 97:3 and d.r.(1,3) >98:2 (lit.: 97:3 and >98:2). Thus, reproduction of the reaction was successful.

| Table 10: Pd-catalyzed cross-coupling with [8-(ethoxymethoxy)decahydronaphthalen-1-yl](ethyl)zinc (170). |
| --- | --- | --- | --- | --- |
| Entry | Zinc Reagent | Aryl Iodide | Temperature [°C] | d.r.(1,2); d.r.(1,3)a | Yield [%]b |
| 1 | 170 | - | 25 | 90:10; 67:33 | n. i. |
| 2 | 170 | - | -10 | 91:9; 85:15 | 31 |

[a] Diastereoselectivity determined by capillary GC analysis before and after purification. [b] Isolated yield of analytically pure product.
4. Highly Diastereoselective Arylations of Substituted Piperidines

4.1. Introduction

Substituted piperidines are ubiquitous structural motifs present in numerous bioactive alkaloids. In order to ensure appropriate biological activity, many of them have to be prepared in a stereodefined manner. Therefore, the development of efficient methods for the diastereoselective construction of piperidines bearing more than one stereocenter represents an important synthetic task. Still, procedures for the direct stereoselective arylation of the

---


piperidine ring are scarce.\(^67\) Only one isolated example of the diastereoselective coupling of a 6-methylpiperidin-2-yl organometallic with 4-bromoveratrole furnishing the \textit{trans}-2,6-disubstituted product has been reported.\(^67c\) So far the direct stereoselective synthesis of 2,4- and 2,5-disubstituted arylated piperidines via C\(_{sp^3}\)-C\(_{sp^2}\) cross-coupling remains a challenging problem. Recently, a highly diastereoselective couplings of several substituted cycloalkyl derivatives mediated by Pd was reported.\(^68\) Herein, we show that Pd-catalyzed cross-couplings can be efficiently used for a highly diastereoselective preparation of various disubstituted or annulated piperidines.

### 4.2. Results and Discussion


\(^{68}\) Thaler, T., Haag, B., Gavryushin, A., Schober, K.; Hartmann, E., Gschwind, R. M., Zipse, H., Mayer, P. & Knochel, P. Highly diastereoselective C\(_{sp^3}\)-C\(_{sp^2}\) Negishi cross-coupling with 1,2-, 1,3- and 1,4-substituted cycloalkylzinc compounds. \textit{Nature Chem.} \textbf{2}, 125-130 (2010).
favoured arylpalladium intermediates which after reductive elimination afford the desired aryalted products with retention of configuration (d.r. up to >99:1).\textsuperscript{68} Due to the structural importance of piperidines, we have envisioned the performance of diastereoselective cross-couplings with the related substituted piperidinylzinc compounds. By exploiting the pseudo-allylic strain induced by the protecting group at the N,\textsuperscript{69} we were able to prepare both the cis- and trans-2,4-disubstituted piperidine derivatives with excellent levels of diastereoselectivity. First, we have generated various piperidin-2-ylzinc reagents of type 1 starting from the respective piperidines 172a-e according to the procedures of Beak and Lee\textsuperscript{70} and Coldham and Leonori.\textsuperscript{67c} To our delight, the Pd-catalyzed cross-coupling of 171a-e with various aryl and heteroaryl iodides using 2% SPhos\textsuperscript{71} or 5% RuPhos\textsuperscript{72} and 2-5% Pd(dba)$_2$ as catalyst system furnished the desired α-arylated products 173 in 54-84% yield and with an exceptional level of diastereoselectivity (d.r. of 95:5 to >99:1; Table 11). Thus, cross-coupling of the 4-methyl-substituted piperidinylzinc reagent 171a with electron-rich 4-iodoanisole using 2% Pd(dba)$_2$ and 2% SPhos at 55 °C furnished exclusively the cis-configured product 173a in 78% yield (entry 1 of Table 11).\textsuperscript{73}


\textsuperscript{73} The relative configurations of 173d and 173h were directly determined via X-ray analysis. The relative configurations of 173n and 173q were determined via acidic removal of the Boc-protective group and subsequent tosylation. The crystals of the tosylates (173na and 173qa) proved suitable for X-ray analysis. See supporting information for details.
### Table 11: Diastereoselective cross-coupling of substituted piperidin-2-ylzinc reagents.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product Description</th>
<th>Yield [%]</th>
<th>d.r.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>173a: Ar: 4-MeO-C₆H₄</td>
<td>78</td>
<td>&gt;99:1&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>173b: Ar: 4-F-C₆H₄</td>
<td>81</td>
<td>95:5&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>173c: Ar: 3-Cl-C₆H₄</td>
<td>76</td>
<td>96:4&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td>173d: Ar: 3-NC-C₆H₄</td>
<td>64</td>
<td>97:3&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td>173e: Ar: 4-EtO-C₆H₄</td>
<td>67</td>
<td>98:2&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>6</td>
<td>173f: Ar: 4-pyridinyl</td>
<td>73</td>
<td>95:5&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>7</td>
<td>173g: Ar: 4-F-C₆H₄</td>
<td>64</td>
<td>97:3&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>8</td>
<td>173h: Ar: 4-NC-C₆H₄</td>
<td>79</td>
<td>&gt;99:1&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>9</td>
<td>173i: Ar: 4-MeO-C₆H₄</td>
<td>67</td>
<td>99:1&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>10</td>
<td>173j: Ar: 4-EtO-C₆H₄</td>
<td>84</td>
<td>97:3&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>11</td>
<td>173k: Ar: 4-F-C₆H₄</td>
<td>83</td>
<td>95:5&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>12</td>
<td>173l: Ar: 4-NC-C₆H₄</td>
<td>81</td>
<td>95:5&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>13</td>
<td>173m: Ar: 4-NC-C₆H₄</td>
<td>81</td>
<td>97:3&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>14</td>
<td>173n: Ar: 4-F-C₆H₄</td>
<td>69</td>
<td>&gt;99:1&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>15</td>
<td>173o: Ar: 4-NC-C₆H₄</td>
<td>54</td>
<td>&gt;99:1&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>16</td>
<td>173p: Ar: 4-MeO-C₆H₄</td>
<td>60</td>
<td>97:3&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>17</td>
<td>173q: Ar: 4-NC-C₆H₄</td>
<td>62</td>
<td>96:4&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>18</td>
<td>173r: Ar: 4-EtO-C₆H₄</td>
<td>59</td>
<td>95:5&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Isolated yield. <sup>b</sup> Determined by GC and/or <sup>1</sup>H/<sup>13</sup>C NMR analysis. <sup>c</sup> 2% Pd(dba)<sub>2</sub>, 2% SPhos, THF, 55 °C, 12 h. <sup>d</sup> 5% Pd(dba)<sub>2</sub>, 5% RuPhos, THF, 55 °C, 12 h. <sup>e</sup> 5% Pd(dba)<sub>2</sub>, 5% RuPhos, THF, 55 °C, 60 h. <sup>f</sup> 5% Pd(dba)<sub>2</sub>, 5% RuPhos, THF, 0 °C (6 h), then rt (12 h), then 40 °C (12 h).

Coupling of 171a with electron-poor aryl iodides and 4-iodopyridine under the same conditions gave the products 173b-f with d.r. from 95:5 to 98:2 (entries 2-6). The piperidinylzinc reagent 171b bearing a large phenyl ring instead of the smaller methyl substituent provided, under slightly altered conditions (5% Pd(dba)<sub>2</sub> and 5% RuPhos at 55 °C), the cis-products 173g-i with comparable yields (64-79%) and equally high.
diastereoselectivities (97:3 to >99:1; entries 7-9). Even the functionalized piperidinylzinc reagent 171c bearing an OTIPS (OSi(i-Pr)_3) group in position 4 reacted smoothly furnishing the cis-α-arylated products 173j-m with high yields (81-84%) and d.r. between 95:5 and 97:3 (entries 10-13). The method also proved applicable to the trans-decahydroisoquinolinyl scaffold. By using the method of Beak and Lee, we were able for the first time to regioselectively metalate this heterocycle at position 3. Cross-coupling of the resulting organozinc species 171d led to the stereodefined 2,4,5-trisubstituted products 173n-p in 54-69% yield with excellent d.r. (97:3 to >99:1; entries 14-16). In the case of the 5-methyl-substituted reagent 171e, lower temperatures were necessary for achieving high diastereoselectivities (Table 11). Thus, the trans-2,5-disubstituted products 173q-r were obtained in moderate yields of 59-62% with a high d.r. of 95:5 (entries 17-18).

Complementary to the diastereoselective preparation of the cis-2,4-disubstituted piperidines, we also report the synthesis of the corresponding trans-isomers by switching the positions of the substituent and the C-Zn bond. Thus, in preliminary experiments, we have prepared the 2-substituted piperidin-4-ylzinc reagent 174a via LiCl-promoted Zn-insertion into the iodide 175a and subjected it to cross-coupling with 4-iodobenzonitrile and iodobenzene using 5% TMPP_2PdCl_2 as catalyst (Table 12). The trans-coupling products 176a-b were obtained in 50-74% yield with diastereoselectivities of d.r.: 91:9 and 92:8 (entries 1 and 2 of Table 12).

By examining the NMR spectra of the N-Boc protected products 176a and 176b, we found that both revealed the presence of two Boc-conformers at room temperature. These findings are supported by DFT-analysis. The calculations also confirmed the presence of two energetically close chair and twist-boat conformers whose existence may be responsible for the observed non-perfect diastereoselectivity. Furthermore, X-ray structures of the already prepared N-Boc protected piperidines 173d and 173h (entries 4 and 8 of Table 11) showed a twisted ring conformation, whereas the structures of the N-Ts protected piperidines 173na and 173qa displayed an almost perfect chair-like structure. We, therefore, prepared the corresponding N-tosylated zinc reagent 174b. Cross-coupling of 174b with 4-iodobenzonitrile...
under the same reaction conditions led to the exclusive formation of the trans-isomer 176c in 70\% yield (entry 3). Remarkably, the couplings of the zinc reagent 174c bearing only a small methyl group in position 2 also gave the respective trans-isomers 176e-f with an excellent diastereoselectivity of d.r.: 97:3 (entries 5 and 6).

![Chemical Reaction Diagram]

**Table 12:** Diastereoselective cross-coupling of 2-substituted piperidin-4-ylzinc reagents.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Yield [%]</th>
<th>d.r.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>176a: Ar: 4-NC-C_6H_4</td>
<td>74</td>
<td>91:9</td>
</tr>
<tr>
<td></td>
<td>176b: Ar: Ph</td>
<td>50</td>
<td>92:8</td>
</tr>
<tr>
<td>2</td>
<td>176c: Ar: 4-NC-C_6H_4</td>
<td>70</td>
<td>&gt;99:1</td>
</tr>
<tr>
<td>3</td>
<td>176d: Ar: 4-MeO_2-C_6H_4</td>
<td>69</td>
<td>96:4</td>
</tr>
<tr>
<td>4</td>
<td>176e: Ar: 4-NC-C_6H_4</td>
<td>84</td>
<td>97:3</td>
</tr>
<tr>
<td>5</td>
<td>176f: Ar: 4-MeO_2-C_6H_4</td>
<td>89</td>
<td>97:3</td>
</tr>
</tbody>
</table>

[a] Isolated yield. [b] Determined by GC and/or \(^1\)H/\(^{13}\)C NMR analysis.

In order to explain the distinct stereochemical outcome of these couplings, the cis/trans stability differences between 173g and 176b together with the respective data for the Zn- and Pd-intermediates were analyzed at the B3LYP/631SVP level (Scheme 44 and Table 13).\(^{78}\) From our former studies,\(^{68}\) it was clear that the relative stabilities of the Pd-intermediates represent the crucial factor for the determination of the final diastereoselectivity of the cross-coupling.

---

\(^{78}\) The theoretical methods used herein are identical to those in ref 68 and involved the combination of the B3LYP hybrid functional with the def2-SVP all-electron basis set for Zn, the ECP-based def2-SVP basis set for Pd,\(^{21}\) and the 6-31G(d,p) basis set for all other elements.
B. Results and Discussion

Table 13: DFT calculation-based conformational analysis on the diastereomeric Zinc and Palladium complexes.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Zn- and Pd-Intermediates, ΔH°ax (kJ/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>eq-171b (C)</td>
</tr>
<tr>
<td>1</td>
<td>+15.4</td>
</tr>
<tr>
<td></td>
<td>eq-174a (TB)</td>
</tr>
<tr>
<td>2</td>
<td>-8.4</td>
</tr>
</tbody>
</table>
The stabilities of the respective Pd- and Zn-intermediates involved in the formation of the cross-coupling products 173g and 176b have been calculated using the same model as in our recent study of the analogous cyclohexyl systems.\textsuperscript{68} Whereas the diastereomeric substituted cyclohexylzinc complexes possessed very similar energies, large differences in the stabilities of the corresponding piperidinylzinc species were found. In the case of piperidin-2-ylzinc reagent 171b, the equatorial orientation of the C-Zn bond is stabilized by its coordination to the carbonyl oxygen atom of the Boc group leading to a pentacoordinated Zn-center. This results in an energetic preference for eq-171b by 15.4 kJ/mol (entry 1 of Table 13). Since pseudo-allylic strain in the 4-zincated piperidinyl species 174a dictates an axial position of the substituent at C2, axial orientation of the C-Zn bond is hampered by 1,3-diaxial repulsions resulting in ax-174a as the most stable conformer (entry 2). This underlines the “Janus-like” nature of the Boc-group showing its sterically demanding, repulsive character towards vicinal substituents, yet turning into an electrostatically attractive neighbor with Lewis-acidic metal centers present at the same position. Analogously to the cyclohexyl systems, the Pd moiety shows a preference for the equatorial position in all cases. In the piperidin-2-ylpalladium intermediates (eq-177 and ax-177; entry 1), in which the square-planar coordination sphere of Pd is not perturbed, this natural preference is magnified by a close contact between the Pd-center and the carbonyl oxygen atom of the Boc group. If, however, C2 is occupied by an aryl/alkyl substituent, 1,3-allylic strain\textsuperscript{69} takes effect and causes axial orientation (ax-178 vs. eq-178; entry 2). Without this interaction, diaxial repulsions dictate equatorial orientation of the aryl/alkyl substituent (eq-177 vs. ax-177; entry 1).\textsuperscript{68} Considering the energetic differences of the organometallic intermediates, the diastereoselectivity in the couplings of the

\begin{table}[h]
\centering
\begin{tabular}{|c|c|}
\hline
Entry & Conformation & Energy (kJ/mol) \\
\hline
3 & eq-177 (C) & +15.0 \\
\hline
4 & ax-177 (C) & -8.6 \\
\hline
\end{tabular}
\end{table}

\[\text{[a]} \text{ Ar: 4-F}_2\text{C}_6\text{H}_4. \text{ Preferred conformations are indicated as twist-boat (TB) or chair (C). [b] Calculated energetic differences (B3LYP/631SVP) between the thermodynamically lowest conformers of the two diastereomers; L: PMe}_3.\]
piperidinylzinc reagents (171 and 174) may be determined both on the stage of the respective Zn- as well as Pd-complexes. In the case of the couplings of the piperidin-2-ylzinc chlorides (171), there is strong evidence that the diastereoselectivity may already be introduced into the molecule via the lithiation step.\textsuperscript{67c,f,g,70} For the piperidin-4-ylzinc iodides (174), the stereoselectivity is most likely introduced via a selective transmetalation step between the Zn-reagent and the aryl-Pd complex leading to the thermodynamically most stable intermediate, as proposed in Chapter 2.

In continuation of our study, we found that arylations with the 6-methyl-substituted piperidin-2-ylzinc reagent 179 in the presence of Pd(dba)\textsubscript{2}/RuPhos\textsuperscript{72} as catalyst system consistently resulted in the highly stereoselective formation of the 5-arylated \textit{trans}-configured products of type 181 (d.r.: 93:7 to 96:4),\textsuperscript{79} whereas the expected \textit{trans}-2,6-disubstituted products (180)\textsuperscript{67c} were not obtained (Scheme 45). It is noteworthy that the coupling proceeded equally well with electron-rich (181b) and electron-poor aryl iodides (181c-e). We assume that this reaction proceeds via β-hydride elimination of the Pd moiety.\textsuperscript{80} The resulting ArPdL\textsubscript{2}H\textsuperscript{81} complex stays bound to the same side of the tetrahydrodropyrindinyl ring and its subsequent \textit{syn}-addition\textsuperscript{82} places the Pd in the sterically less hindered position 5. Rapid reductive elimination furnishes the observed δ-arylated 2,5-disubstituted coupling products (181). This Pd 1,2-migration/ cross-coupling sequence seems to be a function of the nature and stoichiometry of the phoshine ligand. In our case, a Pd/ RuPhos ratio of 1:1 was used. Coldham and Leonori\textsuperscript{67c} reported the use of Pd(OAc)\textsubscript{2}/ tBu\textsubscript{3}P with a ratio of 1:2 as the catalyst system, which may lead to a better stabilization of Pd(0) and thus prevent β-hydride elimination.

\textsuperscript{79} The relative configuration of 181c was determined via acidic removal of the Boc protecting group and subsequent tosylation. The crystals of the tosylate proved suitable for X-ray analysis.


Scheme 45: Pd-1,2-migration in the diastereoselective cross-coupling of \(N\)\text{-}Boc 6-methylpiperidin-2-ylzinc chloride.
5. **Summary and Outlook**

This work dealt with both the investigation and applications of the distinct stereochemical behaviours of carbon-metal bonds. Therefore, a novel practical access to stereodefined C-Li bonds was established via a stereoretentive I-Li exchange on cyclohexyl iodides which allowed a thorough examination of their configurational stabilities and the stereochemistry of their quenching with various electrophiles. Mechanistic studies on the configurational stability of the C-Zn bond in substituted cyclohexylzinc reagents showed that distinct stereochemical pathways are responsible for the observed stereoconvergence in the diastereoselective Pd-catalyzed cross-couplings. Thereby, the equatorial C-Zn bond reacts with retention and the axial C-Zn bond with inversion of its stereoconfiguration under suitable reaction conditions. The highly diastereoselective Pd-catalyzed cross-coupling methodology was extended to functionalized cyclohexyl derivatives and an enantio- and diastereoselective method for the preparation of chiral arylated functionalized cyclohexanes was developed. Highly diastereoselective cross-coupling was also established for piperidinylzinc derivatives. Selective access to both the cis- and trans-2,4-disubstituted piperidine derivatives was enabled.

5.1. **Stereoselective Preparation, Configurational Stability and Reactivity of Substituted Cyclohexyllithium Derivatives**

Although the stereoselective generation and stereochemistry of α-heteroatom-substituted alkyl-, benzylic and allylic organolithium reagents are well studied, the stereoselective preparation of non-stabilized secondary alkylolithiums has remained a major synthetic challenge. A practical stereoretentive synthesis to unstabilized stereodefined cyclohexyllithium reagents from the readily available organic iodides via I-Li exchange has been presented in this work. Using this approach a detailed study on the configurational stabilities, stereochemical behaviour and reactivities of various axially and equatorially substituted cyclohexyllithium reagents was performed. Thus, the stereochemical paths (S\text{e}2 vs. S\text{i}2) of the quenching reactions were shown to depend on the respective cyclohexyllithium diastereomer and the electrophile. In all cases, the axial cyclohexyllithium was found to almost completely equilibrate into the configurationally stable, equatorial diastereomer. This inversion process was followed for differently substituted cyclohexyllithiums over time.
showing distinct behaviour. DFT-calculations demonstrated that the formation of oligomeric
cyclohexyllithium structures is the key determinant for the observed stereochemical
preference.

Scheme 46: A new practical stereoretentive I-Li exchange reaction for the stereoselective preparation of
cyclohexyllithiums. The behaviours of the resulting diastereomeric substituted cyclohexyllithium reagents were
studied.

5.2. Novel Insights into the Stereochemical Behaviour of Diastereomeric
Cyclohexylzinc Reagents – Stereoconvergence through Distinct
Stereochemical Pathways

A novel revised mechanistic view of the stereoconvergent *Negishi*-cross-coupling of
substituted cyclohexylzinc reagents has been established through our investigations. The
observed high configurational stability of the C-Zn bond excludes a mechanism based on a
dynamic kinetic resolution process, since flipping of the C-Zn bond takes place too slowly.
Via deuterolysis and protolysis experiments, we were able to show that high
stereoselectivities can be achieved in quenching diastereomeric cyclohexylzinc reagents with
preference of the all equatorially substituted products, excluding an equilibration on the stage
of the cyclohexyl-palladium intermediates as key factor for the stereoconvergence. Moreover,
both diastereomers were observed to react with the same observable rate at the NMR time
scale in slow addition/protolysis. In combination, these crucial results along with the fact that
only one Pd-intermediate could be observed in the cross-coupling$^{68}$ show that the equatorial
C-Zn bond must react with retention and the axial C-Zn bond with inversion of the
stereoconfiguration in the transmetalation step to ArPdL$_n$X thus leading to stereoconvergence
in the reaction (Scheme 47).
Scheme 47: Substituted diastereomeric cyclohexylzinc complexes eq-103 and ax-103 which differ in the configuration of their C-Zn bond undergo distinct stereochemical pathways in the transmetallation to ArPdL-X thus leading to overall stereoconvergence in the cross-coupling reaction. The energy diagram sums up the experimental observations. The high energetic barrier between the diastereomeric zinc reagents prevents their equilibration. The fact that reaction pathways for diastereomers do not need to be isoenergetic, as is the case for enantiomers, allows distinct stereochemical reactivities. Thus, the axially configured cyclohexylzinc diastereomer reacts with inversion and the equatorially substituted one with retention of the stereoconfiguration resulting in overall stereoconvergence of the reaction.

To the best of our knowledge, this work represents the first experimental proof that diastereomeric organometallics can undergo distinct stereochemical pathways which result in the stereoselective formation of one diastereomerically defined product. We anticipate that in addition to the dynamic resolution processes which have been well established for configurationally unstable organolithiums, these observations will lead to the further understanding and development of stereoconvergent reactions for configurationally stable alkyl organometallics.

5.3. Diastereo- and Enantioselective Cross-Coupling with Functionalized Cyclohexylzinc Reagents

Cross-couplings of functionalized cyclohexylzinc reagents such as [2-(1,3-dioxolan-2-yl)cyclohexyl]- and [2-(5,5-dimethyl-1,3-dioxan-2-yl)cyclohexyl]zinc reagents (142, 143 und 140, 141) lead to high diastereoselectivities. β-Hydrde eliminations which were observed in cross-coupling reactions of the organozinc iodides 142 and 143 could be avoided by decreasing the temperature to -25 °C. Moreover, it was illustrated that cross-coupling of diorganozinc complexes 140 and 141 can be successfully performed even at higher
B. Results and Discussion

temperatures up to 25 °C without loss in diastereoselectivity. Hereby, β-hydride elimination processes did not occur which can be probably explained by the stereochemically pure nature featuring only an equatorial C-Zn bond. Cross-coupling of the chiral organozinc reagents 159 and 160 synthesized via enantioselective hydroboration, proceeded diastereoselectively and furnished the respective arylated 1,2-disubstituted cyclohexanes in moderate enantiomeric excess. Cross-coupling of [8-(ethoxymethoxy)decahydronaphthalen-1-yl](ethyl)zinc (170) was performed with moderate diastereoselectivity. Since the arylation of 170 proceeds with high stereoselectivity, β-hydride elimination processes on the step of the palladium intermediate can be responsible for the observed low diastereoselectivity.

Scheme 48: Enantio- and diastereoselective arylation via a hydroboration/B-Zn-exchange/cross-coupling sequence.

5.4. Highly Diastereoselective Arylations of Substituted Piperidines

A highly diastereoselective methodology for the preparation of various substituted piperidines via Negishi cross-couplings with (hetero)aryl iodides was developed. Depending on the position of the C-Zn bond relative to the nitrogen (position 2 vs. position 4), the stereoselectivity of the coupling can be directed either towards the trans- or the cis-2,4-disubstituted products. DFT-calculations on the relative stabilities of the Zn- and Pd-intermediates were performed to explain the high diastereoselectivities obtained. A novel Pd-1,2-migration further expands this method to the stereoselective preparation of 5-arylated 2,5-disubstituted piperidines.
**Scheme 49:** Switchable stereoselectivity in the cross-couplings of piperidinylzinc reagents and a novel diastereoselective Pd-1,2-migration.
C. Experimental Section
C. Experimental Section

1. General Considerations

All reactions were carried out with magnetic stirring and, if the reagents were air or moisture sensitive, in flame-dried glassware under argon. Syringes which were used to transfer reagents and solvents were purged with argon prior to use.

1.1. Solvents

Solvents were dried according to standard procedures by distillation over drying agents and stored under argon.

\( \text{CH}_2\text{Cl}_2 \) was predried over CaCl\(_2\) and distilled from CaH\(_2\).

DMF was heated to reflux for 14 h over CaH\(_2\) and distilled from CaH\(_2\).

1,4-Dioxane was heated to reflux for 14 h over CaH\(_2\) and distilled from CaH\(_2\).

Et\(_2\)O was predried over calcium hydride and dried with the solvent purification system SPS-400-2 from INNOVATIVE TECHNOLOGIES INC.

NEP was heated to reflux for 14 h over CaH\(_2\) and distilled from CaH\(_2\).

Pyridine was dried over KOH and distilled.

THF was continuously refluxed and freshly distilled from sodium benzophenone ketyl under nitrogen.

Toluene was predried over CaCl\(_2\) and distilled from CaH\(_2\).

Triethylamine was dried over KOH and distilled.

Solvents for column chromatography were distilled prior to use.

1.2. Reagents

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

\( \text{iPrMgCl\cdot LiCl} \) solution in THF was purchased from Rockwood Lithium (Chemetall).

\( \text{iPrMgCl} \) solution in THF was purchased from Rockwood Lithium (Chemetall).

\( \text{PhMgCl} \) solution in THF was purchased from Rockwood Lithium (Chemetall).

\( \text{nBuLi} \) solution in \( n \)-hexane was purchased from Rockwood Lithium (Chemetall).

\( \text{sBuLi} \) solution in cyclohexane was purchased from Rockwood Lithium (Chemetall).

\( \text{tBuLi} \) solution in \( n \)-pentane was purchased from Rockwood Lithium (Chemetall).
**Content determination of organometallic reagents**

The respective organometallic reagents were titrated using either the method reported by Paquette\textsuperscript{83} or Knochel\textsuperscript{84} prior to their use.

**ZnCl\textsubscript{2}** solution (1.00 M) was prepared by drying ZnCl\textsubscript{2} (100 mmol, 136 g) in a Schlenk-flask under vacuum at 140 °C for 5 h. After cooling to room temperature, 100 mL dry THF were added and stirring was continued until the salt was dissolved. The reagent was stirred under a nitrogen atmosphere.

**MgCl\textsubscript{2}** solution (0.5 M) was prepared by drying magnesium turnings (30 mmol, 0.73 g) in a Schlenk-flask under high vacuum at 140 °C for 15 min. After cooling to room temperature, 60 mL dry THF was filled in. The mixture was vigorously stirred and 1,2-dichloroethane (30 mmol, 2.38 mL) was carefully added dropwise until all magnesium filings had been consumed. The reagent was stirred under a nitrogen atmosphere.

**CuCN\textsubscript{2}LiCl** solution (1.00 m) was prepared by drying LiCl (8.48 g, 200 mmol) and CuCN (8.96 g, 100 mmol) for 5 h at 140 °C under high vacuum. After cooling to room temperature, 100 mL dry THF were added and stirring was continued until the salt was dissolved. The Schlenk-tube was wrapped in an aluminium-foil to protect from light. The reagent appears as a slightly greenish solution and has to be stored under argon.

**Preparation of a 0.7 M solution of cHexMgBr in THF**

In a dry and Ar-flushed 250 mL 3-necked flask, equipped with a reflux condenser, a dropping funnel and a magnetic stirring bar, LiCl (2.33 g, 55.0 mmol) was placed and dried over 10 min at 500 °C in high vacuum (1 mbar). After cooling to room temperature Mg turnings (1.34 g, 55.0 mmol) and 1,2-dibromoethane (0.52 g, 0.24 mL, 2.75 mmol) were added. The heterogeneous mixture was vigorously stirred before THF (38.5 mL) was added and then gently heated in order to activate the Mg surface. A solution of cyclohexyl bromide (8.15 g, 6.13 mL, 50.0 mmol) in THF (15 mL) was added dropwise and the resulting reaction mixture was stirred for 45 min at room temperature.

---


Preparation of a 7.3 M solution of \( \text{Et}_2\text{BH} \) in \( \text{SMe}_2 \)

In a dry and Ar-flushed 50 mL Schlenk-tube, equipped with a magnetic stirring bar and a septum, \( \text{BH}_3\text{SMe}_2 \) (3.80 g, 4.74 mL, 50.0 mmol) was placed and neat \( \text{BEt}_3 \) (9.80 g, 14.5 mL, 100 mmol) was added dropwise. The resulting solution was stirred at room temperature for 48 h. It was stored in a freezer (–28 °C).

Preparation of a 1.0 M solution of \((-)\)-IpcBH\(_2\) in THF

In a dry and Ar-flushed 100 mL Schlenk-tube, equipped with a magnetic stirring bar and a septum, \([(-)\text{IpcBH}_2]_2\)TMEDA-complex (5.00 g, 12.0 mmol) was dissolved in THF (24 mL) at room temperature and freshly distilled \( \text{BF}_3\text{Et}_2\text{O}\)-complex (3.40 g, 3.00 mL, 24.0 mmol) was added dropwise. The reaction mixture was stirred for 2 h and then filtrated through a Schlenk-frit into an Ar-flushed Schlenk-tube. The precipitate was washed with a small amount of THF. The solution was concentrated (0.1 mm Hg, 25 °C, 2 h) and the residue redissolved in THF (24 mL).

1.3. Chromatography

Flash column chromatography was performed using silica gel 60 (0.040-0.063 mm) from Merck.

Thin layer chromatography was performed using SiO\(_2\) pre-coated aluminium plates (Merck 60, F-254). The chromatograms were examined under UV light at 254 nm and/or by staining of the TLC plate with one of the solutions given below followed by heating with a heat gun:

- KMnO\(_4\) (3.0 g), 5 drops of conc. H\(_2\)SO\(_4\) in water (300 mL).
- Phosphomolybdic acid (5.0 g), Ce(SO\(_4\))\(_2\) (2.0 g) and conc. H\(_2\)SO\(_4\) (12 mL) in water (230 mL).

1.4. Analytical Data

NMR spectra were recorded on VARIAN Mercury 200, BRUKER AXR 300, VARIAN VXR 400 S and BRUKER AMX 600 instruments. Chemical shifts are reported as \( \delta \) values in ppm relative to the residual solvent peak of CHCl\(_3\) (\( \delta_H \) : 7.25, \( \delta_C \) : 77.0). For the characterization of the observed signal multiplicities the following abbreviations were used: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sept (septet), m (multiplet) as well as br (broad).
Mass spectroscopy: High resolution (HRMS) and low resolution (MS) spectra were recorded on a FINNIGAN MAT 95Q instrument. Electron impact ionization (EI) was conducted with an electron energy of 70 eV.

For the combination of gas chromatography with mass spectroscopic detection, a GC/MS from Hewlett-Packard HP 6890 / MSD 5973 was used.

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 DuraSamp\(\text{IR}\) II Diamond ATR sensor was used. The absorption bands are reported in wavenumbers (cm\(^{-1}\)).

Melting points (M.p.) were determined on a BÜCHI B-540 apparatus and are uncorrected.
2. Stereoselective Preparation, Configurational Stability and Reactivity of Substituted Cyclohexyllithium Derivatives

2.1. Preparation of Starting Materials

2.1.1. Typical Procedure 1: Iodination of alcohols (TP1)

A 1.0 M solution of I\(_2\) in CH\(_2\)Cl\(_2\) was prepared in a flame-dried, Ar-flushed Schlenk-flask equipped with a stirring bar and cooled to 0 °C using a Huber T100 cryostat. PPh\(_3\) (1.2 equiv.) was added portionwise. The resulting suspension was stirred for 1 h, before N-methylimidazole (NMI; 1.2 equiv.) was added. The reaction mixture became a bright yellow suspension and the respective alcohol was added portionwise. The resulting mixture was stirred for 15 h at 0 °C, then quenched with NaHSO\(_3\) sat. solution. The phases were separated and the aqueous phase was extracted with 3 x CH\(_2\)Cl\(_2\). The combined organic layers were dried over Na\(_2\)SO\(_4\) and the solvents evaporated (35 °C, rotavap, 8 mbar, <30 min). Column chromatographic purification (flash silica) was performed. The solvents were evaporated (35 °C, rotavap, 8 mbar, <30 min) and, if necessary, the product was subjected to high vacuum (10\(^{-3}\) mbar) at 30 °C in order to remove cyclohexene/elimination byproducts. The neat corresponding cyclohexyl iodides were thus obtained.

**trans-1-(tert-butyl)-4-iodocyclohexane (trans-(eq)-78)**

![Structure of trans-1-(tert-butyl)-4-iodocyclohexane](structure.png)

**column chromatography:** SiO\(_2\); i-hexane

**yield:** 3.0 g (20%), colourless oil

**d.r.:** 10:90.

\(^1\)H-NMR (300 MHz, CDCl\(_3\)) \(\delta\): 4.10 (tt, \(J\_1=12.3\) Hz, \(J\_2=4.0\) Hz, 1 H), 2.48 (d, \(J=11.9\) Hz, 2 H), 2.05–1.90 (m, 2 H), 1.72–1.61 (m, 2 H), 1.17–1.02 (m, 3 H), 0.83 (s, 9 H).

\(^{13}\)C-NMR (75 MHz, CDCl\(_3\)) \(\delta\): 46.7, 41.1, 32.6, 30.9, 30.3, 27.4.

**MS (70 eV, EI)** \(m/z\) (%): 266 (12) [M\(^+\)], 140 (14), 139 (100), 128 (12), 123 (18), 97 (15), 95 (10), 83 (45), 81 (20), 69 (20), 67 (18), 57 (65), 55 (20), 40 (16).
IR (ATR) $\tilde{\nu}$ (cm$^{-1}$): 2943 (vs), 2859 (m), 1478 (m), 1469 (m), 1448 (m), 1394 (w), 1366 (m), 1265 (w), 1258 (w), 1249 (w), 1228 (w), 1196 (w), 1188 (w), 1147 (s), 1079 (m), 996 (s), 897 (w), 810 (w), 663 (s).

HRMS (EI) for C$_{10}$H$_{19}$I (266.0531): 266.0518.

$\textit{trans}$-1-iodo-4-methoxycyclohexane ($\textit{trans}$-\textit{(eq)}-83b)

![Chemical structure of trans-1-iodo-4-methoxycyclohexane](image)

column chromatography: SiO$_2$; $i$-hexane

yield: 0.91 g (30%), colourless oil
d.r.: 5:95.

$^1$H-NMR (400 MHz, CDCl$_3$) $\delta$: 4.29–4.23 (m, 1 H), 3.28 (s, 3 H), 3.22 (tt, $J_1$=8.8 Hz, $J_2$=3.2 Hz, 1 H), 2.22–2.18 (m, 2 H), 1.92–1.83 (m, 4 H), 1.43–1.35 (m, 2 H).

$^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$: 76.6, 55.9, 36.4, 31.9, 30.7.

MS (70 eV, EI) $m/z$ (%): 240 (6) [M$^+$], 191 (28), 175 (65), 128 (21), 113 (38), 85 (40), 83 (54), 81 (100), 58 (19), 43 (14).

IR (ATR) $\tilde{\nu}$ (cm$^{-1}$): 2942, 2863, 1454, 1369, 1230, 1159, 1102, 10 10, 898, 800, 678.

HRMS (EI) for C$_7$H$_{13}$IO (240.0011): 239.9995.

$\textit{tert}$-butyl($\textit{cis}$-3-iodocyclohexyl$\textit{oxy}$)dimethylsilane ($\textit{cis}$-\textit{(eq)}-86b)

![Chemical structure of tert-butyl(cis-3-iodocyclohexyl oxy)dimethylsilane](image)

column chromatography: SiO$_2$; $i$-hexane

yield: 6.75 g (27%), colourless oil
d.r.: 97:3.

$^1$H-NMR (400 MHz, C$_6$D$_6$) $\delta$: 4.51–4.35 (m, 1 H), 3.78 (br. s., 1 H), 2.02–1.85 (m, 2 H), 1.73–1.64 (m, 2 H), 1.57–1.47 (m, 1 H), 1.33 (br. s., 3 H), 0.92 (s, 9 H), -0.02 (s, 3 H), -0.01 (s, 3 H).

$^{13}$C-NMR (101 MHz, C$_6$D$_6$) $\delta$: 69.5, 47.4, 39.0, 34.1, 28.9, 26.4, 22.9, 18.6, 4.4.

MS (70 eV, EI) $m/z$ (%): 340 (8) [M$^+$], 284 (10), 213 (12), 155 (16), 81 (100), 75 (49), 73 (17).
**IR (ATR) \( \tilde{\nu} \) (cm\(^{-1}\)):** 2929 (m), 2857 (m), 1252 (m), 1240 (m), 1152 (m), 1099 (s), 1068 (m), 1053 (s), 1032 (s), 1006 (m), 902 (m), 871 (m), 852 (m), 834 (vs), 824 (s), 799 (m), 773 (vs), 688 (m).

**HRMS (EI) for C\(_{12}\)H\(_{25}\)IOSi:** 340.0714.

**cis-1-(tert-butyl)-4-iodocyclohexane (cis-(ax)-78)**

\[
\text{[Diagram of cis-1-(tert-butyl)-4-iodocyclohexane]}
\]

- **column chromatography:** SiO\(_2\); i-hexane
- **yield:** 7.5 g (57%), white solid
- **d.r.:** 98:2.
- **m.p.:** 32.8 – 34.9 °C.
- **\(^1\)H-NMR (599 MHz, CDCl\(_3\)) \( \delta \):** 4.89 (br. s., 1 H), 2.13 (d, \( J=14.0 \) Hz, 2 H), 1.68–1.62 (m, 2 H), 1.60–1.47 (m, 4 H), 0.90 (s, 9 H).
- **\(^13\)C-NMR (151 MHz, CDCl\(_3\)) \( \delta \):** 47.8, 37.9, 36.9, 32.6, 27.4, 23.3.
- **MS (70 eV, EI) \( m/z \) (%):** 266 (8) [M\(^+\)], 140 (11), 139 (100), 123 (15), 83 (47), 81 (21), 69 (17), 67 (18), 57 (69), 55 (17), 41 (14).
- **IR (ATR) \( \tilde{\nu} \) (cm\(^{-1}\)):** 2956 (s), 2939 (vs), 2921 (m), 2885 (m), 2863 (m), 2845 (m), 2832 (m), 1482 (w), 1472 (w), 1444 (w), 1430 (m), 1418 (m), 1390 (w), 1366 (m), 1350 (w), 1308 (m), 1243 (m), 1232 (m), 1186 (s), 1016 (m), 996 (m), 851 (m), 764 (w), 652 (m).
- **HRMS (EI) for C\(_{10}\)H\(_{19}\)I:** 266.0531: 266.0530.

**cis-1-iodo-4-methoxycyclohexane (cis-(ax)-83b)**

\[
\text{[Diagram of cis-1-iodo-4-methoxycyclohexane]}
\]

- **column chromatography:** SiO\(_2\); i-hexane
- **yield:** 0.64 g (30%), colourless oil
- **d.r.:** 99:1.
- **\(^1\)H-NMR (400 MHz, CDCl\(_3\)) \( \delta \):** 4.42–4.38 (m, 1 H), 3.37–3.31 (m, 1 H), 3.30 (s, 3 H), 2.23–2.14 (m, 2 H), 1.87–1.80 (m, 2 H), 1.79–1.73 (m, 2 H), 1.67–1.61 (m, 2 H).
C. Experimental Section

$^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$: 75.6, 55.8, 34.9, 31.5, 30.3.

MS (70 eV, EI) $m/z$ (%): 240 (6) $[M^+]$, 113 (25), 81 (100), 71 (13), 58 (13), 45 (11), 43 (14), 41 (15).

IR (ATR) $\tilde{\nu}$ (cm$^{-1}$): 2939, 2859, 2820, 1446, 1371, 1229, 1163, 1101, 1089, 1001, 933, 898, 806, 675.

HRMS (EI) for C$_7$H$_{13}$IO (240.0011): 240.0003.

cis-1-iodo-2-methylcyclohexane ($cis$-(ax)-98)

![cis-1-iodo-2-methylcyclohexane](image)

column chromatography: SiO$_2$; $i$-hexane

yield: 4.7 g (48%), colourless oil

d.r.: 98:2.

$^1$H-NMR (300 MHz, C$_6$D$_6$) $\delta$: 4.26 (d, $J=2.5$ Hz, 1 H), 2.02–1.92 (m, 1 H), 1.80–1.64 (m, 1 H), 1.45 (ddddd, $J_1=12.9$ Hz, $J_2=3.7$ Hz, $J_3=3.6$ Hz, $J_4=1.4$ Hz, 1 H), 1.37–1.20 (m, 3 H), 1.17–1.08 (m, 1 H), 1.08–0.89 (m, 1 H), 0.80 (d, $J=6.6$ Hz, 3 H), 0.23–0.10 (m, 1 H).

$^{13}$C-NMR (75 MHz, C$_6$D$_6$) $\delta$: 49.7, 38.0, 37.1, 31.2, 25.7, 24.6, 23.3.

MS (70 eV, EI) $m/z$ (%): 224 (72) $[M^+]$, 98 (13), 97 (100).

IR (ATR) $\tilde{\nu}$ (cm$^{-1}$): 2956 (m), 2925 (vs), 2853 (m), 2834 (m), 1452 (m), 1442 (m), 1377 (w), 1335 (w), 1318 (w), 1290 (w), 1256 (m), 1246 (m), 1211 (m), 1162 (s), 964 (w), 955 (m), 872 (w), 815 (w), 760 (w).

HRMS (EI) for C$_7$H$_{13}$I (224.0062): 224.0053.

(1R,2R,4R)-2-iodo-1-isopropyl-4-methylcyclohexane ($men$-(eq)-89)

![1R,2R,4R-2-iodo-1-isopropyl-4-methylcyclohexane](image)

C. Experimental Section

**β-cholesteryl iodide** (β(eq)-92)


**β-cholestanyl iodide** (β(eq)-95)


(1R,2S,4R)-2-iodo-1-isopropyl-4-methylcyclohexane (neomen-(ax)-89)


**α-cholestanyl iodide** (α(ax)-95)

2.2. I-Li Exchange and Subsequent Quenching with Electrophiles

2.2.1. Typical Procedure 2: I-Li exchange and subsequent quenching with electrophiles (TP2)

(Compounds of Scheme 23, Table 1, Table 2, Table 3 and Scheme 24)

A solution of \( n \)-hexane/ether (3:2; 5.5 mL) was placed into a flame-dried and Ar-flushed Schlenk-tube equipped with a stirring bar and cooled to -100 \( ^\circ \)C using a Huber T100 cryostat. A \( \text{tBuLi} \) solution (2.2 equiv.; 1.3 M in \( n \)-hexane; 0.84 mL; 1.1 mmol) was added via syringe. After 5 min, a 1.0 M solution (0.5 M for the cholesteryl and cholestanol derivatives 92 and 95) of the respective cyclohexyl iodide (1.0 equiv.; 0.5 mmol) in \( n \)-hexane/ether (3:2) was added. The reaction was directly quenched after 4-5 s with the corresponding electrophile (4 equiv.; 0.18 mL; 2 mmol; solid \( \text{Ph}_3\text{SnCl} \) was added as a 1 M solution in \( \text{Et}_2\text{O} \)). The reaction mixture was stirred for 5 min at -100 \( ^\circ \)C before \( \text{NH}_4\text{Cl} \) sat. aq solution (2 mL) was added. After warming to room temperature the phases were separated and the aqueous phase was extracted with \( \text{Et}_2\text{O} \) (3 x 5 mL). The combined organic phases were dried over \( \text{Na}_2\text{SO}_4 \) and the solvents were evaporated. Column chromatographic purification of the crude material (flash silica) provided the respective products.

\( \text{trans-4-(tert-butyl)cyclohexyl}(\text{methyl})\text{sulfane (trans-(eq)-82a)} \) (Scheme 28)

\[
\text{trans-4-(tert-butyl)cyclohexyl}(\text{methyl})\text{sulfane (trans-(eq)-82a)}
\]

\[
\text{trans-4-} (\text{tert-butyl})\text{cyclohexyl}(\text{methyl})\text{sulfane (trans-(eq)-82a)}
\]

**column chromatography:** SiO\(_2\); \( i \)-hexane

**yield:** 84 mg (90%), colourless oil

**d.r.:** 9:91.

\( ^1\text{H-NMR (300 MHz, CDCl}_3) \): \( \delta \): 2.43 (tt, \( J_1=12.0 \) Hz, \( J_2=3.6 \) Hz, 1 H), 2.09 (s, 3 H), 2.06 (br. s., 1 H), 1.84 (d, \( J=10.0 \) Hz, 2 H), 1.36–1.15 (m, 3 H), 1.13–0.96 (m, 3 H), 0.85 (s, 9 H).

\( ^{13}\text{C-NMR (75 MHz, CDCl}_3) \): \( \delta \): 47.5, 44.9, 33.7, 32.4, 27.6, 27.5, 13.1.

**MS (70 eV, EI) m/z (%):** 186 (100) [M\(^+\)], 175 (89), 138 (49), 129 (55), 123 (48), 95 (54), 83 (55), 82 (40), 81 (87), 69 (32), 67 (31), 57 (92), 55 (35), 41 (32).
IR (ATR) $\tilde{\nu}$ (cm$^{-1}$): 2936 (vs), 2856 (s), 1478 (m), 1448 (m), 1394 (w), 1365 (s), 1275 (w), 1235 (w), 1230 (w), 1211 (w), 1174 (w), 1038 (w), 1013 (m), 1006 (m), 970 (w), 954 (w), 897 (w).

HRMS (EI) for C$_{11}$H$_{22}$S (186.1442): 186.1432.

(cis-4-(tert-butyl)cyclohexyl)(methyl)sulfane (cis-(ax)-82a) (Scheme 23)

\[
\text{column chromatography: SiO$_2$; i-hexane}
\]

yield: 68 mg (73%), colourless oil
d.r.: 90:10.

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$: 3.03 (br. s., 1 H), 2.06 (s, 3 H), 1.95 (d, $J$=14.1 Hz, 2 H), 1.66 (tt, $J_1$=13.4 Hz, $J_2$=3.7 Hz, 2 H), 1.59–1.49 (m, 2 H), 1.49–1.34 (m, 2 H), 1.07–0.96 (m, 1 H), 0.86 (s, 9 H).

$^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$: 48.4, 44.3, 32.6, 31.1, 27.5, 21.9, 14.8.

MS (70 eV, EI) $m/z$ (%): 186 (8) [M$^+$], 175 (28), 147 (25), 83 (10), 57 (22).

IR (ATR) $\tilde{\nu}$ (cm$^{-1}$): 2938 (vs), 2930 (vs), 2864 (m), 2846 (m), 1478 (m), 1467 (m), 1440 (m), 1393 (w), 1365 (s), 1312 (m), 1263 (m), 1237 (w), 1227 (w), 1214 (m), 1024 (w), 865 (w), 770 (w).

HRMS (EI) for C$_{11}$H$_{22}$S (186.1442): 186.1443.

trans-tert-butyl(4-$^2$H$_1$)cyclohexane (trans-(eq)-82d) (Table 1)

\[
\text{yield: (85%)}
\]

d.r.: 4:96.

$^2$H-NMR (61 MHz, THF) $\delta$: 1.53 (s, 1 D).
cis-tert-butyl(4-^2^H_1)cyclohexane (cis-(ax)-82d) (Table 1)

yield: 75% (GC)
d.r.: 92:8.

^2^H NMR (61 MHz, THF) δ: 0.99 (s, 1 D).

(trans-4-(tert-butyl)cyclohexyl)triphenylstannane (trans-(eq)-82f) (Table 1)

column chromatography: SiO_2; i-hexane/Et_2O 40:1

yield: 127 mg (52 %), white solid
d.r.: 8:92.
m.p.: 99.1 – 101.9 °C.

^1^H-NMR (300 MHz, CDCl_3) δ: 7.65–7.55 (m, 5 H), 7.51–7.36 (m, 10 H), 2.22 (dd, J_1=12.0 Hz, J_2=1.2 Hz, 2 H), 2.03–1.80 (m, 3 H), 1.79–1.63 (m, 2 H), 1.12–1.00 (m, 3 H), 0.84 (s, 9 H).

^1^3^C-NMR (75 MHz, CDCl_3) δ: 138.8, 137.4, 128.7, 128.4, 48.2, 32.5, 32.2, 29.9, 28.5, 27.4.

^1^1^9^Sn-NMR (149 MHz, CDCl_3) δ: 116.34 (major) -107.77 (minor).

MS (70 eV, EI) m/z (%): 490 (3) [M^+], 355 (17), 353 (16), 352 (20), 351 (100), 350 (39), 349 (76), 348 (33), 347 (45), 196 (11).

IR (ATR) \tilde{\nu} (cm^{-1}): 3061 (w), 2956 (m), 2917 (m), 2849 (m), 1480 (w), 1467 (w), 1444 (w), 1427 (m), 1390 (w), 1362 (w), 1300 (w), 1231 (w), 1190 (w), 1148 (w), 1073 (m), 1060 (w), 1023 (w), 997 (w), 874 (w), 724 (s), 697 (vs), 666 (w), 657 (w).

HRMS (EI) for C_{28}H_{34}Sn (490.1682): 490.1690.
butyl(trans-4-methoxycyclohexyl)sulfane (trans-(eq)-85b) (Table 2)

\[
\text{\textbf{C. Experimental Section}}
\]

\[
\text{column chromatography: SiO}_2 \text{ i-hexane/Et}_2\text{O 25:1}
\]

\[
yield: 84 \text{ mg (83%), colourless oil}
\]

\[
d.r.: <1:99.
\]

\[
^1\text{H-NMR (300 MHz, CDCl}_3\text{)} \delta: 3.33–3.28 (m, 1 H), 3.27 (s, 3 H), 2.69 (quint, \textit{J}=6.4 \text{ Hz, 1 H}), 2.49 (t, \textit{J}=7.5 \text{ Hz, 2 H}), 1.90–1.81 (m, 2 H), 1.72–1.66 (m, 4 H), 1.55–1.48 (m, 4 H), 1.41–1.33 (m, 2 H), 0.88 (t, \textit{J}=7.2 \text{ Hz, 3 H}).
\]

\[
^13\text{C-NMR (75 MHz, CDCl}_3\text{)} \delta: 75.7, 55.7, 42.7, 32.3, 30.3, 29.1, 28.6, 22.3, 13.9.
\]

\[
\text{MS (70 eV, EI) m/z (\%): 202 (64) [M]^+, 170 (15), 116 (23), 113 (10), 81 (70), 80 (100), 79 (14), 71 (11), 58 (14), 43 (12), 41 (10).}
\]

\[
\text{IR (ATR) \tilde{\nu} (cm}^{-1}): 2931, 2856, 1451, 1374, 1187, 1145, 1099, 933, 746.
\]

\[
\text{HRMS (EI) for C}_{11}\text{H}_{22}\text{OS (202.1391): 202.1392.}
\]

\[
\text{\textbf{tert-buty1cis-3-(butylthio)cyclohexyloxy)dimethylsilane (cis-(eq)-88b) (Table 2}}
\]

\[
\text{column chromatography: SiO}_2 \text{ i-hexane/Et}_2\text{O 40:1}
\]

\[
yield: 95 \text{ mg (63%), colourless oil}
\]

\[
d.r.: 2:98.
\]

\[
^1\text{H-NMR (400 MHz, C}_6\text{D}_6\text{) \delta: 3.55–3.43 (m, 1 H), 2.37–2.31 (m, 1 H), 2.47–2.37 (m, 3 H), 1.81 (t, \textit{J}=15.4 \text{ Hz, 2 H}), 1.56–1.45 (m, 4 H), 1.30 (dq, \textit{J}_1=15.0 \text{ Hz}, \textit{J}_2=7.5 \text{ Hz, 3 H}), 1.17–1.01 (m, 2 H), 0.98 (s, 9 H), 0.81 (t, \textit{J}=7.4 \text{ Hz, 3 H}), 0.06 (s, 6 H).
\]

\[
^13\text{C-NMR (101 MHz, C}_6\text{D}_6\text{) \delta: 71.7, 44.3, 41.9, 36.3, 33.7, 32.8, 30.3, 26.4, 24.6, 22.7, 18.6, 14.2, 4.0.}
\]

\[
^{29}\text{Si-NMR (80 MHz, C}_6\text{D}_6\text{) \delta: 16.4.}
\]

\[
\text{MS (70 eV, EI) m/z (\%): 302 (1) [M]^+, 246 (16), 245 (100), 155 (24), 147 (15), 81 (1), 75 (19).}
\]

\[
\text{IR (ATR) \tilde{\nu} (cm}^{-1}): 2930 (m), 2857 (m), 1462 (w), 1372 (w), 1255 (m), 1250 (m), 1124 (m), 1086 (s), 1006 (w), 976 (m), 878 (m), 860 (m), 846 (s), 834 (vs), 803 (m), 773 (vs), 666 (m).}
\]
HRMS (EI) for C_{16}H_{34}OSSi (302.2100): 302.2094.

\[ ((1R,2S,5R)-2-isopropyl-5-methylcyclohexyl)(methyl)sulfane \text{ (men-(eq)-91a) (Table 2)} \]

\[ \text{column chromatography: SiO}_2; \text{ } i\text{-hexane} \]

\text{yield: } 50 \text{ mg (54%), colourless oil}

d.r.: 13:87.

\[ ^1H\text{-NMR (400 MHz, } C_6D_6) \delta: 2.68–2.53 (m, 1 H), 2.25 \text{ (td, } J_1=11.2 \text{ Hz, } J_2=3.71 \text{ Hz, 1 H), 2.09–1.98 (m, 1 H), 1.80 (s, 3 H), 1.62–1.52 (m, 2 H), 1.23–1.03 (m, 3 H), 0.96–0.86 (m, 4 H), 0.84 (d, } J=6.3 \text{ Hz, 3 H), 0.80 (d, } J=6.9 \text{ Hz, 3 H), 0.77–0.69 (m, 1 H).} \]

\[ ^{13}C\text{-NMR (101 MHz, } C_6D_6) \delta: 48.0, 46.9, 43.6, 35.4, 33.8, 27.9, 25.3, 22.8, 21.9, 15.9, 12.3. \]

\[ \text{MS (70 eV, EI) } m/\text{z (]): 186 (86) [M^+]}, 138 (93), 123 (51), 97 (35), 95 (100), 85 (33), 83 (69), 82 (32), 81 (57), 71 (31), 69 (50), 57 (51), 55 (39). \]

\[ \text{IR (ATR) } \tilde{\nu} \text{ (cm}^{-1})\text{: 2954 (vs), 2918 (vs), 2869 (m), 2848 (m), 1454 (m), 1446 (m), 1385 (w), 1368 (w), 1300 (w), 1198 (w), 955 (w), 934 (w).} \]

HRMS (EI) for C_{11}H_{22}S (186.1442): 186.1440.

\[ ((1R,2S,5R)-2-isopropyl-5-methylcyclohexyl)diphenylphosphine sulfide \text{ (men-(eq)-91b) (Table 2)} \]

\[ \text{column chromatography: SiO}_2; \text{ } i\text{-hexane/Et}_2\text{O 30:1} \]

\text{yield: } 105 \text{ mg (59%), white solid}

d.r.: 10:90.

m.p.: 163.0 – 166.3 °C.

\[ ^1H\text{-NMR (400 MHz, } C_6D_6) \delta: 8.16–8.06 (m, 2 H), 8.06–7.95 (m, 2 H), 7.05–6.93 (m, 6 H), 2.63–2.55 (m, 1 H), 2.29–2.20 (m, 1 H), 1.99 \text{ (quin, } J=6.7 \text{ Hz, 1 H), 1.66 (ddd, } J_1=13.0 \text{ Hz, } J_2=6.2 \text{ Hz, } J_3=3.2 \text{ Hz, 1 H), 1.57 (d, } J=11.9 \text{ Hz, 1 H), 1.50–1.36 (m, 2 H), 1.33–1.23 (m, 1 H).} \]
C. Experimental Section

1.05 (qd, $J_1$=12.8 Hz, $J_2$=3.1 Hz, 1 H), 0.87 (d, $J$=6.6 Hz, 3 H), 0.85–0.75 (m, 1 H), 0.64 (d, $J$=6.4 Hz, 3 H), 0.39 (d, $J$=6.8 Hz, 3 H).

$^{13}$C-NMR (101 MHz, C$_6$D$_6$) $\delta$: 135.5 (d, $J$=72.8 Hz), 134.0 (d, $J$=76.3 Hz), 131.5 (d, $J$=9.0 Hz), 131.0 (d, $J$=9.6 Hz), 130.5 (d, $J$=3.0 Hz), 128.2 (d, $J$=9.8 Hz), 128.0 (d, $J$=9.5 Hz), 44.1 (d, $J$=1.7 Hz), 39.5 (d, $J$=53.7 Hz), 35.7 (d, $J$=1.1 Hz), 34.4 (d, $J$=1.7 Hz), 33.3 (d, $J$=14.2 Hz), 27.5 (d, $J$=4.1 Hz), 24.8 (d, $J$=13.1 Hz), 22.3 (d, $J$=0.7 Hz), 21.5, 15.8.

$^{31}$P-NMR (162 MHz, C$_6$D$_6$) $\delta$: 49.5, 43.6.

MS (70 eV, EI) $m/z$ (%): 356 (8) [M$^+$], 219 (26), 218 (100), 185 (11), 183 (12).

IR (ATR) $\tilde{\nu}$ (cm$^{-1}$): 2961 (m), 2953 (m), 2942 (w), 2921 (m), 2869 (w), 2844 (w), 1479 (w), 1454 (w), 1436 (m), 1308 (w), 1092 (s), 1068 (w), 1026 (w), 997 (w), 855 (w), 760 (m), 744 (s), 732 (m), 717 (m), 704 (s), 697 (vs), 688 (vs), 660 (s).

HRMS (EI) for C$_{22}$H$_{29}$PS (356.1728): 356.1727.

(β-cholesteryl)(methyl)sulfane (β-(eq)-94a) (Table 2)

![chemical structure]

column chromatography: SiO$_2$; i-hexane/CH$_2$Cl$_2$ 1:1

yield: 147 mg (71%), white solid

d.r.: 1:99.

m.p.: 127.8 – 129.6 °C.

$^1$H-NMR (400 MHz, C$_6$D$_6$) $\delta$: 5.34 (d, $J$=4.8 Hz, 1 H), 2.50–2.35 (m, 3 H), 2.04 (dt, $J_1$=12.8 Hz, $J_2$=3.2 Hz, 1 H), 1.99–1.91 (m, 1 H), 1.91–1.81 (m, 5 H), 1.75 (dt, $J_1$=13.0 Hz, $J_2$=3.2 Hz, 1 H), 1.61–1.51 (m, 4 H), 1.47–1.37 (m, 6 H), 1.31–1.05 (m, 8 H), 1.03 (d, $J$=6.6 Hz, 3 H), 0.99–0.92 (m, 12 H), 0.68 (s, 3 H).

$^{13}$C-NMR (101 MHz, C$_6$D$_6$) $\delta$: 142.4, 121.4, 57.4, 57.0, 51.1, 46.6, 43.0, 40.6, 40.5, 40.3, 37.5, 37.0, 36.6, 32.6, 32.5, 30.1, 29.0, 28.8, 25.0, 24.7, 23.4, 23.1, 21.7, 19.8, 19.4, 13.5, 12.5.

MS (70 eV, EI) $m/z$ (%): 416 (28) [M$^+$], 401 (11), 370 (11), 368 (100).

IR (ATR) $\tilde{\nu}$ (cm$^{-1}$): 2952 (s), 2928 (vs), 2911 (vs), 2899 (s), 2870 (s), 2852 (s), 1463 (s), 1444 (m), 1431 (m), 1381 (m), 1374 (m), 1366 (m), 960 (m), 825 (m), 800 (m).

HRMS (EI) for C$_{28}$H$_{48}$S (416.3477): 416.3473.
(β-cholesteryl)diphenylphosphine sulphide (β-(eq)-94b) (Table 2)

![Chemical structure](image)

column chromatography: SiO<sub>2</sub>; i-hexane/Et<sub>2</sub>O 30:1

yield: 236 mg (80%), white solid

d.r.: 6:94.

m.p.: 184.3 – 186.1 °C.

^1^H-NMR (400 MHz, C<sub>6</sub>D<sub>6</sub>) δ: 8.01–7.94 (m, 4 H), 7.07–7.02 (m, 6 H), 5.20–5.14 (m, 1 H), 3.12–3.00 (m, 1 H), 2.62–2.53 (m, 1 H), 2.28–2.15 (m, 1 H), 1.99 (d, J=12.5 Hz, 2 H), 1.92–1.72 (m, 3 H), 1.58–1.48 (m, 3 H), 1.47–1.33 (m, 8 H), 1.32–1.16 (m, 5 H), 1.16–1.03 (m, 5 H), 1.02–1.00 (m, 6 H), 0.92 (d, J=6.6 Hz, 6 H), 0.63 (s, 3 H).

^13^C-NMR (101 MHz, C<sub>6</sub>D<sub>6</sub>) δ: 141.4 (d, J=14.2 Hz), 132.7 (d, J=76.1 Hz), 132.5 (d, J=76.1 Hz), 131.6 (d, J=9.4 Hz), 131.5 (d, J=9.4 Hz), 130.9 (d, J=3.0 Hz), 130.8 (d, J=2.9 Hz), 128.4 (d, J=11.5 Hz), 128.3 (d, J=11.5 Hz), 121.0, 56.9, 56.3, 50.9 (d, J=1.4 Hz), 42.3, 40.0, 39.7, 39.3 (d, J=14.6 Hz), 39.0 (d, J=55.7 Hz), 37.2 (d, J=1.4 Hz), 36.4, 35.9, 32.2 (d, J=0.4 Hz), 31.8, 31.5, 28.4, 28.2, 24.3, 24.1, 22.8, 22.5, 21.6 (d, J=1.3 Hz), 21.0, 19.2, 18.8, 11.8.

^31^P-NMR (162 MHz, C<sub>6</sub>D<sub>6</sub>) δ: 49.0.

MS (70 eV, EI) m/z (%): 586 (12) [M<sup>+</sup>], 369 (16), 368 (27), 220 (15), 219 (73), 218 (100), 186 (16), 185 (17), 183 (17), 140 (10), 108 (11).

IR (ATR) ~ν (cm<sup>-1</sup>): 2948 (m), 2930 (s), 2888 (m), 2866 (m), 2847 (m), 1463 (m), 1436 (s), 1375 (w), 1101 (s), 827 (w), 778 (m), 751 (m), 742 (m), 732 (m), 709 (vs), 691 (vs).

HRMS (EI) for C<sub>39</sub>H<sub>55</sub>PS (586.3762): 586.3752.

(β-cholestanyl)(methyl)sulfane (β-(eq)-97) (Table 2)

![Chemical structure](image)

column chromatography: SiO<sub>2</sub>; i-hexane/CH<sub>2</sub>Cl<sub>2</sub> 20:1
C. Experimental Section

yield: 153 mg (74%), white solid

d.r.: 2:98.

m.p.: 79.4 – 81.5 °C.

$^1$H-NMR (400 MHz, C$_6$D$_6$) δ: 2.45–2.37 (m, 1 H), 2.04–1.98 (m, 1 H), 1.91 (s, 3 H), 1.89–1.80 (m, 2 H), 1.68–1.48 (m, 6 H), 1.48–1.28 (m, 6 H), 1.27–1.07 (m, 10 H), 1.03 (d, $J$=6.4 Hz, 3 H), 0.94 (d, $J$=6.6 Hz, 6 H), 0.90–0.77 (m, 2 H), 0.69 (d, $J$=11.4 Hz, 6 H), 0.56 (td, $J_1$=11.2 Hz, $J_2$=4.0 Hz, 1 H).

$^{13}$C-NMR (101 MHz, C$_6$D$_6$) δ: 57.2, 57.1, 55.1, 47.5, 45.5, 43.3, 40.8, 40.3, 39.5, 37.0, 36.6, 36.4, 36.3, 36.1, 32.8, 29.8, 29.4, 29.0, 28.8, 24.9, 24.7, 23.4, 23.1, 21.8, 19.4, 13.4, 12.7.

MS (70 eV, EI) m/z (%): 418 (100) [M$^+$], 404 (11), 372 (10), 371 (11), 278 (10), 264 (11), 263 (18), 215 (10), 107 (14), 95 (15), 93 (11), 81 (14), 69 (10), 57 (14), 55 (14), 43 (15).

IR (ATR) $\tilde{\nu}$ (cm$^{-1}$): 2954 (s), 2928 (vs), 2863 (s), 2850 (s), 2360 (w), 1739 (m), 1467 (s), 1458 (s), 1443 (m), 1424 (w), 1383 (m), 1379 (m), 1365 (m), 1350 (w), 1232 (w), 1216 (m), 1163 (w), 1155 (w), 961 (w), 954 (w).

HRMS (EI) for C$_{28}$H$_{50}$S (418.3633): 418.3626.

butyl (4-methoxycyclohexyl)sulfane (85b) (Table 3)

\[
\text{\textbf{\includegraphics[width=1cm]{butyl-sulfane.png}}}
\]

column chromatography: SiO$_2$; i-hexane/Et$_2$O 25:1

yield: 68 mg (67%), colourless oil

d.r.: 52:48.

$^1$H-NMR (300 MHz, CDCl$_3$) δ: 3.30 (s, 3 H), 3.16–3.07 (m, 1 H), 2.60–2.55 (m, 1 H), 2.50 (t, $J$=7.5 Hz, 2 H), 2.07–2.01 (m, 4 H), 1.58–1.48 (m, 2 H), 1.41–1.33 (m, 2 H), 1.32–1.21 (m, 4 H), 0.88 (t, $J$=7.2 Hz, 3 H).

$^{13}$C-NMR (75 MHz, CDCl$_3$) δ: 78.6, 55.9, 42.6, 32.3, 31.6, 30.4, 22.3, 13.9.

MS (70 eV, EI) m/z (%): 202 (90) [M$^+$], 170 (20), 145 (23), 114 (28), 113 (48), 112 (100), 111 (28), 97 (27), 81 (65), 79 (17), 41 (13).

IR (ATR) $\tilde{\nu}$ (cm$^{-1}$): 2931, 2858, 1467 (s), 1379 (m), 1187, 1109, 1099, 1024, 933, 746.

HRMS (EI) for C$_{11}$H$_{22}$OS (202.1391): 202.1386.
((1S,2S,5R)-2-isopropyl-5-methylcyclohexyl)(methyl)sulfane (neomen-(ax)-91a) (Table 3)

column chromatography: SiO$_2$; $i$-hexane
yield: 21 mg (23%), colourless oil
d.r.: 93:7.

$^1$H-NMR (400 MHz, C$_6$D$_6$) $\delta$: 2.86 (d, $J=1.9$ Hz, 1 H), 2.18–2.03 (m, 1 H), 1.93–1.86 (m, 1 H), 1.86–1.81 (m, 1 H), 1.80 (s, 3 H), 1.71–1.62 (m, 2 H), 1.38–1.27 (m, 2 H), 1.05–1.00 (m, 1 H), 0.98 (d, $J=6.3$ Hz, 3 H), 0.90 (d, $J=6.6$ Hz, 3 H), 0.89 (d, $J=6.6$ Hz, 3 H), 0.87–0.74 (m, 2 H).

$^{13}$C-NMR (101 MHz, C$_6$D$_6$) $\delta$: 49.6, 49.2, 40.4, 36.1, 30.8, 27.0, 26.8, 22.9, 21.7, 21.3, 15.4.

MS (70 eV, EI) m/z (%): 186 (52) [M$^+$], 139 (26), 138 (73), 123 (27), 101 (16), 97 (32), 96 (22), 95 (100), 94 (10), 83 (69), 82 (21), 81 (50), 79 (11), 69 (38), 68 (12), 67 (27), 61 (10), 57 (37), 55 (53), 53 (14), 43 (24), 41 (46), 39 (12), 29 (11), 27 (10).

IR (ATR) $\tilde{\nu}$ (cm$^{-1}$): 2946 (s), 2913 (vs), 2868 (m), 2840 (m), 2360 (w), 1474 (m), 1455 (m), 1383 (w), 1366 (w), 1297 (w), 1281 (w), 1264 (w), 1241 (w), 863 (w), 859 (w).

HRMS (EI) for C$_{11}$H$_{22}$S (186.1442): 186.1437.

((1S,2S,5R)-2-isopropyl-5-methylcyclohexyl)diphenylphosphine sulfide (neomen-(ax)-91b) (Table 3)

column chromatography: SiO$_2$; $i$-hexane/Et$_2$O 30:1
yield: 50 mg (28%), white solid
d.r.: 91:9.
m.p.: 139.3 – 141.3 °C.

$^1$H-NMR (400 MHz, C$_6$D$_6$) $\delta$: 8.18–8.11 (m, 2 H), 8.11–8.05 (m, 2 H), 7.06–6.96 (m, 6 H), 3.17–3.09 (m, 1 H), 3.09–2.96 (m, 1 H), 2.68–2.52 (m, 1 H), 2.09 (sxt, $J=6.6$ Hz, 1 H), 2.02–1.87 (m, 2 H), 1.66–1.42 (m, 2 H), 1.25–1.07 (m, 1 H), 0.97–0.89 (m, 1 H), 0.87 (d, $J=6.8$ Hz, 3 H), 0.67 (d, $J=6.6$ Hz, 3 H), 0.58 (d, $J=6.4$ Hz, 3 H).
\(^{13}\)C-NMR (101 MHz, C\(_6\)D\(_6\)) \(\delta\): 134.8 (d, \(J=72.9\) Hz), 134.7 (d, \(J=75.1\) Hz), 131.9 (d, \(J=9.4\) Hz), 131.6 (d, \(J=9.0\) Hz), 130.5 (d, \(J=3.0\) Hz), 130.4 (d, \(J=2.9\) Hz), 128.0 (d, \(J=11.3\) Hz), 127.9 (d, \(J=11.4\) Hz), 48.5 (br), 37.3 (br), 36.8 (d, \(J=52.1\) Hz), 34.8 (br), 29.1 (d, \(J=3.4\) Hz), 27.0 (d, \(J=3.7\) Hz), 23.4 (d, \(J=2.9\) Hz), 23.2, 21.9 (s, br), 20.9.

\(^{31}\)P-NMR (162 MHz, C\(_6\)D\(_6\)) \(\delta\): 49.5, 43.5.

MS (70 eV, EI) \(m/z\) (%): 356 (6) [M\(^+\)], 219 (25), 218 (100), 183 (10).

IR (ATR) \(\tilde{\nu}\) (cm\(^{-1}\)): 2950 (w), 2943 (m), 2936 (m), 2916 (w), 2894 (w), 2842 (w), 1476 (w), 1454 (w), 1438 (m), 1367 (w), 1090 (s), 998 (w), 756 (m), 743 (m), 716 (s), 700 (vs), 690 (vs), 680 (s).

HRMS (EI) for C\(_{22}\)H\(_{29}\)PS (356.1728): 356.1722.

butyl (cis-2-methylcyclohexyl)sulfane (cis-(ax)-100) (Table 3)

\[
\text{MeS} \quad \text{SBu}
\]

column chromatography: SiO\(_2\); i-hexane

yield: 32 mg (34%), colourless oil

d.r.: 88:12.

\(^1\)H-NMR (400 MHz, C\(_6\)D\(_6\)) \(\delta\): 2.71–2.65 (m, 1 H), 2.35 (t, \(J=7.4\) Hz, 2 H), 1.83–1.69 (m, 3 H), 1.59–1.42 (m, 5 H), 1.36–1.27 (m, 4 H), 1.27–1.14 (m, 1 H), 1.08 (d, \(J=6.8\) Hz, 3 H), 0.81 (t, \(J=7.4\) Hz, 3 H).

\(^{13}\)C-NMR (101 MHz, C\(_6\)D\(_6\)) \(\delta\): 50.6, 36.0, 32.9, 32.4, 32.1, 31.8, 24.8, 23.6, 22.7, 18.6, 14.2.

MS (70 eV, EI) \(m/z\) (%): 186 (9) [M\(^+\)], 146 (10), 145 (100), 103 (19), 97 (20), 96 (16), 87 (13), 81 (12), 61 (24), 57 (12), 55 (41), 41 (16), 29 (12).

IR (ATR) \(\tilde{\nu}\) (cm\(^{-1}\)): 2957 (s), 2927 (vs), 2870 (m), 2854 (m), 1739 (m), 1454 (m), 1445 (m), 1377 (m), 1366 (w), 1353 (w), 1228 (w), 1217 (m).

HRMS (EI) for C\(_{11}\)H\(_{22}\)S (186.1442): 186.1440.

(\(\alpha\)-cholestanyl)(methyl)sulfane (\(\alpha\)-(ax)-97) (Table 3)

\[
\begin{align*}
\text{MeS} & \quad \text{H} \\
\text{H} & \quad \text{H} \\
\text{H} & \quad \text{H}
\end{align*}
\]

column chromatography: SiO\(_2\); i-hexane
yield: 38 mg (18%), colourless oil

d.r.: 77:23.

\[^1\text{H-NMR}\ (400 \text{ MHz, } \text{C}_6\text{D}_6)\ \delta: 2.85\ (\text{br. s., } 1 \text{ H}), 1.99\ (\text{dt, } J_1=12.3 \text{ Hz, } J_2=3.1 \text{ Hz, } 1 \text{ H}), 1.89-1.83\ (\text{m, } 1 \text{ H}), 1.83\ (\text{s, } 3 \text{ H}), 1.81-1.72\ (\text{m, } 1 \text{ H}), 1.72-1.68\ (\text{m, } 1 \text{ H}), 1.66-1.49\ (\text{m, } 7 \text{ H}), 1.49-1.36\ (\text{m, } 6 \text{ H}), 1.29-1.15\ (\text{m, } 9 \text{ H}), 1.13-1.05\ (\text{m, } 4 \text{ H}), 1.01\ (\text{d, } J=6.4 \text{ Hz, } 3 \text{ H}), 0.92\ (\text{d, } J=6.4 \text{ Hz, } 6 \text{ H}), 0.75\ (\text{s, } 3 \text{ H}), 0.70-0.66\ (\text{m, } 4 \text{ H}).\]

\[^{13}\text{C-NMR}\ (101 \text{ MHz, } \text{C}_6\text{D}_6)\ \delta: 57.1, 57.0, 54.7, 47.5, 45.5, 43.3, 41.2, 40.7, 40.3, 37.0, 36.7, 36.2, 34.1, 33.9, 32.6, 29.4, 29.0, 28.8, 27.0, 24.9, 24.8, 23.4, 23.2, 21.6, 19.4, 15.4, 12.8, 12.4.\]

\text{MS (70 eV, EI)} \text{ m/z} \ (%): 418\ (51) [\text{M}^+] , 371\ (38), 370\ (100), 355\ (23), 263\ (11), 257\ (12), 217\ (13), 216\ (11), 215\ (20), 109\ (11), 107\ (13), 95\ (15), 81\ (11).

\text{IR (ATR)} \bar{\nu} \ (\text{cm}^{-1}): 2926\ (\text{vs}), 2868\ (\text{s}), 2851\ (\text{s}), 1467\ (\text{m}), 1462\ (\text{m}), 1452\ (\text{m}), 1442\ (\text{m}), 1434\ (\text{m}), 1379\ (\text{m}), 1366\ (\text{m}), 1278\ (\text{w}), 1258\ (\text{w}), 1167\ (\text{w}), 968\ (\text{w}), 952\ (\text{m}).

\text{HRMS (EI) for } \text{C}_{28}\text{H}_{50}\text{S}\ (418.3633): 418.3632.
3. Novel Insights into the Stereochemical Behaviour of Diastereomeric Cyclohexylzinc Reagents – Stereoconvergence through Distinct Stereochemical Pathways

3.1. Deuterolysis and Protolysis Experiments

3.1.1. Typical Procedure 3: Deuterolysis of organozinc reagents (TP 3)

(Compounds of Scheme 31 and Table 5)

An \textit{in vacuo} dried, Ar-flushed 10 mL Schlenk flask, equipped with a magnetic stirring bar was charged with the respective cyclohexylzinc compound (0.25 mmol, 1.0 equiv.). The flask was then cooled to the corresponding temperature, stirred for 10 min at that temperature before d-TFA (10 equiv.) or MeOD (10 equiv.) were added neat. After 20 min, the reaction was quenched with NH$_4$Cl sat. solution (2 mL). It was neutralized with NaHCO$_3$ sat. solution. Phases were separated followed by extracting the aqueous phase with 1 mL Et$_2$O (2 x). The org. phases were combined, dried over Na$_2$SO$_4$. The solution was concentrated at the rotary evaporator (careful! Products are volatile!) to 0.6 mL. These were transferred into an NMR tube and analyzed.

2-[\textit{trans}-(2-$^2$H$_1$)cyclohexyl]-5,5-dimethyl-1,3-dioxane (\textit{trans-(eq)-114})

$\&$

2-[\textit{cis}-(2-$^2$H$_1$)cyclohexyl]-5,5-dimethyl-1,3-dioxane (\textit{cis-(eq)-114})

from \textit{trans-(eq)-107} (deuterolysis at rt with d-TFA):
d.r.: 98:2.
\(^2\)H-NMR (61 MHz, THF) \(\delta\): 2.18 (s, 1 D) (major), 1.50 (s, 1 D) (minor).

from 108 (deuterolysis at rt with d-TFA):

\[
\frac{\text{millions}}{20.0}
\]

\[
\begin{array}{c|c|c}
\text{X: parts per Million: 2H} & 6.0 & 5.0 \\
 & 4.0 & 3.0 \\
 & 2.0 & 1.0 \\
 & 0 & 0 \\
\end{array}
\]

\[
\text{d.r.: 69:31.}
\]
\(^2\)H-NMR (61 MHz, THF) \(\delta\): 2.34 (s, 1 D) (major), 1.58 (s, 1 D) (minor).

(deuterolysis at -78 °C with d-TFA)
C. Experimental Section

\[ \text{d.r.: 99:1.} \]

\[ ^2\text{H-NMR (61 MHz, THF)} \quad \delta: 2.34 (s, 1 D) \text{ (major), } 1.68 (s, 1 D) \text{ (minor).} \]

(deuterolysis at rt with MeOD)
d.r.: 99:1.

\(^2\)H-NMR (61 MHz, THF) \(\delta\): 2.30 (s, 1 D) (major), 1.62 (s, 1 D) (minor).

trans-methyl(2-\(^2\)H\(_1\))cyclohexane (trans-(eq)-116)

& cis-methyl(2-\(^2\)H\(_1\))cyclohexane (cis-(eq)-116)

(deuterolysis at rt with d-TFA)

d.r.: 48:52.

\(^2\)H-NMR (61 MHz, THF) \(\delta\): 2.11 (s, 1 D) (major), 1.33 (s, 1 D) (minor).
(deuterolysis at -78 °C with d-TFA)

\[ \text{d.r.: 96:4.} \]

$^2$H-NMR (61 MHz, THF) $\delta$: 2.11 (s, 1 D) (major), 1.37 (s, 1 D) (minor).

(deuterolysis at rt with MeOD)
d.r.: 87:13.  
$^2$H-NMR (61 MHz, THF) $\delta$: 2.10 (s, 1 D) (major), 1.32 (s, 1 D) (minor).  
(deuterolysis at 0°C with MeOD)

d.r.: 97:3.  
$^2$H-NMR (61 MHz, THF) $\delta$: 2.18 (s, 1 D) (major), 1.45 (s, 1 D) (minor).
trans-tert-butyl(4-$^2$H$_1$)cyclohexane (trans-(eq)-117)
& cis-1-(tert-butyl)-4-deuterocyclohexane (cis-(eq)-117)

(deuterolysis at rt with d-TFA)

$^2$H-NMR (61 MHz, THF) $\delta$: 2.07 (s, 1 D) (major), 1.54 (s, 1 D) (minor).

d.r.: 67:33.

(deuterolysis at -78 $^\circ$C with d-TFA)

$^2$H-NMR (61 MHz, THF) $\delta$: 2.05 (s, 1 D) (major), 1.30 (s, 1 D) (minor).

d.r.: >99:1.

(deuterolysis at rt with MeOD)
d.r.: >99:1.

$^2$H-NMR (61 MHz, THF) δ: 1.90 (s, 1 D) (major), 1.30 (s, 1 D) (minor).

**trans-methyl(4-$^2$H$_1$)cyclohexane ($trans$-$eq$)-119**

& **cis-methyl(4-$^2$H$_1$)cyclohexane ($cis$-$eq$)-119**

(deuterolysis at rt with d-TFA)

d.r.: 66:34.
C. Experimental Section

\(^2\)H-NMR (61 MHz, THF) \(\delta\): 2.27 (s, 1 D) (major), 1.67 (s, 1 D) (minor).

(deuterolysis at -78 °C with d-TFA)

\[\text{d.r.: 76:24.}\]

\(^2\)H-NMR (61 MHz, THF) \(\delta\): 2.23 (s, 1 D) (major), 1.74 (s, 1 D) (minor).

(deuterolysis at rt with MeOD)
C. Experimental Section

d.r.: 76:24.
\[^{2}H\text{-NMR (61 MHz, THF)}\] $\delta$: 2.25 (s, 1 D) (major), 1.75 (s, 1 D) (minor).

(deuterolysis at 0°C with MeOD)

d.r.: 90:10.
\[^{2}H\text{-NMR (61 MHz, THF)}\] $\delta$: 1.69 (s, 1 D) (major), 1.13 (s, 1 D) (minor).
**trans-methyl(3-^2^H_1)cyclohexane (cis-(eq)-121)**

& **cis- methyl(3-^2^H_1)cyclohexane (trans-(eq)-121)**

(deuterolysis at rt with d-TFA)

\[ \text{d.r.: 65:35.} \]

\[ ^2\text{H-NMR (61 MHz, THF)} \delta: 1.54 \text{ (s, 1 D) (major), 1.12 (s, 1 D) (minor).} \]

(deuterolysis at -78 °C with d-TFA)
**C. Experimental Section**

**d.r.**: 80:20.

$^2$H-NMR (61 MHz, THF) $\delta$: 1.63 (s, 1 D) (major), 1.21 (s, 1 D) (minor).

(deuterolysis at rt with MeOD)

**d.r.**: 76:24.

$^2$H-NMR (61 MHz, THF) $\delta$: 1.62 (s, 1 D) (major), 1.19 (s, 1 D) (minor).
(deuterolysis at 0 °C with MeOD)

d.r.: 90:10.
\(^2\)H-NMR (61 MHz, THF) \(\delta\): 1.54 (s, 1 D) (major), 1.12 (s, 1 D) (minor).

**trans-**-tert-butyldimethyl((3-\(^2\)H\(_1\))cyclohexyl)oxy)silane (cis-(eq)-123)

\& **cis-**-tert-butyldimethyl((3-\(^2\)H\(_1\))cyclohexyl)oxy)silane (trans-(eq)-123)

(deuterolysis at rt with d-TFA)
d.r.: 58:42.
$^2\text{H}$-NMR (61 MHz, THF) $\delta$: 2.07 (s, 1 D) (major), 1.63 (s, 1 D) (minor).

(deuterolysis at -78 °C with d-TFA)

d.r.: 79:21.
$^2\text{H}$-NMR (61 MHz, THF) $\delta$: 2.13 (s, 1 D) (major), 1.68 (s, 1 D) (minor).
C. Experimental Section

(deuterolysis at rt with MeOD)

d.r.: 66:44.

$^2$H-NMR (61 MHz, THF) $\delta$: 2.22 (s, 1 D) (major), 1.79 (s, 1 D) (minor).

(deuterolysis at 0°C with MeOD)
d.r.: 84:16.

$^1$H-NMR (61 MHz, THF) $\delta$: 2.17 (s, 1 D) (major), 1.73 (s, 1 D) (minor).

$(1R,2R,4R)$-4-methyl-1-(1-methylethyl)(2-$^2$H)$_1$-cyclohexane (men-(eq)-125)

& $(1R,2S,4R)$-4-methyl-1-(1-methylethyl)(2-$^2$H)$_1$-cyclohexane (neomen-(ax)-125)

(deuterolysis at rt with d-TFA)

d.r.: 65:35.
\( ^2 \text{H-NMR (61 MHz, THF)} \) \( \delta: 2.13 \text{ (s, 1 D) (major), 1.43 (s, 1 D) (minor).} \)

(deuterolysis at -78 °C with d-TFA)

d.r.: >99:1.
\( ^2 \text{H-NMR (61 MHz, THF)} \) \( \delta: 2.10 \text{ (s, 1 D) (major), 1.39 (s, 1 D) (minor).} \)

(deuterolysis at rt with MeOD)
d.r.: >99:1.

$^2$H-NMR (61 MHz, THF) $\delta$: 2.13 (s, 1 D) (major), 1.56 (s, 1 D) (minor).

$\beta$-cholesteryl deuteride ($\beta$-(eq)-127) & $\alpha$-cholesteryl deuteride ($\alpha$-(ax)-127)

(deuterolysis at rt with d-TFA)
**C. Experimental Section**

D.r.: 82:18.

$^2$H-NMR (61 MHz, THF) $\delta$: 2.13 (s, 1 D) (major), 1.56 (s, 1 D) (minor).

(deuterolysis at -78 °C with d-TFA)

D.r.: >99:1.

$^2$H-NMR (61 MHz, THF) $\delta$: 2.13 (s, 1 D).
(deuterolysis at rt with MeOD)

d.r.: >99:1.
$^2$H-NMR (61 MHz, THF) $\delta$: 2.14 (s, 1 D) (major).
**β-cholestanyl deuteride (β-(eq)-129)**

& **α-cholestanyl deuteride (α-(ax)-129)**

(deuterolysis at rt with d-TFA)

- **d.r.: 79:21.**
- **2H-NMR (61 MHz, THF) δ: 1.95 (s, 1 D) (major), 1.52 (s, 1 D) (minor).**
C. Experimental Section

(deuterolysis at -78 °C with d-TFA)

\[ \delta : 1.96 \, \text{s,} \, 1 \, \text{D} \]

\[ \text{d.r.: 99:1.} \]

\(^2\text{H-NMR (61 MHz, THF)} \delta : 1.96 \, \text{s,} \, 1 \, \text{D} \]

(deuterolysis at rt with MeOD)
C. Experimental Section

\[ \text{d.r.: 90:10.} \]

$^2\text{H-NMR (61 MHz, THF)} \, \delta: 1.94 \text{ (s, 1 D) (major), 1.54 (s, 1 D) (minor).} \]

(deuterolysis at 0°C with d-TFA)

\[ \text{d.r.: >99:1.} \]

$^2\text{H-NMR (61 MHz, THF)} \, \delta: 1.94 \text{ (s, 1 D).} \]
3.1.2. Typical Procedure 4: Protolysis of deuteron-organozinc reagents (TP 4)
(Compounds of Table 5)

An in vacuo dried, Ar-flushed 10 mL Schlenk- flask, equipped with a magnetic stirring bar was charged with the respective α-deutero-cyclohexylzinc compound (0.25 mmol, 1.0 equiv.). The flask was then cooled to the corresponding temperature, stirred for 10 min at that temperature before TFA (10 equiv.) or MeOH (10 equiv.) were added neat. After 20 min, the reaction was quenched with NH$_4$Cl sat. solution (2 mL). It was neutralized with NaHCO$_3$ sat. solution. Phases were separated followed by extracting the aqueous phase with 1 mL Et$_2$O (2 x). The org. phases were combined, dried over Na$_2$SO$_4$. The solution was concentrated at the rotary evaporator (careful! Products are volatile!) to 0.6 mL. These were transferred into an NMR tube and analyzed.

\[ \text{β-cholesteryl deuteride (β-(eq)-127)} \]
\& \[ \text{α-cholesteryl deuteride (α-(ax)-127)} \]
from \[ \text{α-deuterated cholesterylzinc iodide d-126} \]

(protolysis at rt with TFA)
d.r.: 12:88.

$^2$H-NMR (61 MHz, THF) $\delta$: 1.83 (s, 1 D) (minor), 1.29 (s, 1 D) (major).

*trans*- tert-butyl($^2$H$_1$)cyclohexane (*trans*-eq)-117

& *cis*-1-(tert-butyl)-4-deuterocyclohexane (*cis*-eq)-117

from *$\alpha$*-deuterated 4-tert-butylcyclohexylzinc iodide d-112

(protolysis at rt with TFA)
**C. Experimental Section**

\( \text{d.r.: 36:64.} \)

\( _2^1 \text{H-NMR (61 MHz, THF)} \) \( \delta \): 2.08 (s, 1 D) (minor), 1.54 (s, 1 D) (major).

(protolysis at -78 °C with TFA)

\( \text{d.r.: 37:63.} \)

\( _2^1 \text{H-NMR (61 MHz, THF)} \) \( \delta \): 2.16 (s, 1 D) (minor), 1.63 (s, 1 D) (major).

(protolysis at rt with MeOH)
d.r.: 13:87.
\(^{2}H\)-NMR (61 MHz, THF) \(\delta\): 2.12 (s, 1 D) (minor), 1.52 (s, 1 D) (major).

(protolysis at 0°C with MeOH)
3.2. Cross-Coupling Experiments

3.2.1. Typical Procedure 5: Diastereoselective cross-coupling with stereodefined cyclohexylzinc reagents produced via hydroboration and subsequent boron-zinc exchange (TP5)

(Compounds of Scheme 31 and Table 7)

A dry and argon-flushed 25 mL Schlenk-flask, equipped with a magnetic stirring bar and a septum was charged with the respective cyclohexenyl derivative (1.00 mmol, 1.0 equiv.) in THF (1 mL) and cooled to 0 °C. Et$_2$BH (0.41 mL, 7.3 M in Me$_2$S, 3.00 mmol, 3.0 equiv.) was added dropwise, the reaction mixture was allowed to warm up to room temperature and stirred for 48 h at that temperature. After complete hydroboration, the mixture was concentrated (0.1 mm Hg, 25 °C, 2 h) and Et$_2$Zn (0.31 mL, 3.00 mmol, 3.0 equiv.) was added. After 3 h of stirring, a boron-zinc exchange > 85% was determined by GC-analysis of an oxidated aliquot (3 M NaOH, 30% H$_2$O$_2$). The reaction mixture was again concentrated (0.1 mm Hg, 25 °C, 1 h), the grey-black residue redissolved in THF (2 mL) and then added dropwise to a mixture of the respective electrophile (3.00 mmol, 3.0 equiv.) Pd(dba)$_2$ (11.5 mg, 0.02 mmol, 2.0 mol%) und S-Phos (8.20 mg, 0.02 mmol, 2.0 mol%) in THF (3 mL) at given temperature. After stirring for the given time and temperature the reaction mixture was quenched with sat. aq. NH$_4$Cl solution (10 mL), extracted with Et$_2$O (3 x 20 mL) and the combined organic layers were dried over MgSO$_4$. The solvents were removed in vacuo and the crude product was purified by column chromatography (SiO$_2$).
methyl-4-\((trans-2-(5,5\text{-dimethyl-1,3-dioxane-2-yl})cyclohexyl)\)benzoate (111a)

\[
\text{According to TP5, 2-cyclohex-1-enyl-5,5-dimethyl-1,3-dioxane (139) (196 mg, 1.00 mmol) was reacted via hydroboration with Et\textsubscript{2}BH, followed by a boron-zinc exchange and subsequent cross-coupling (−10 °C, 12 h; then 25 °C 12 h) with methyl-4-iodobenzoate (786 mg, 3.00 mmol). Purification by column chromatography (SiO\textsubscript{2} Et\textsubscript{2}O/n-pentane 1 : 20 then 1 : 10) furnished the title compound (213 mg, 0.64 mmol, 64 %) as a colourless solid.}
\]

\[
d.r.: 98 : 2.
\]

\[
m.p.: 81.4 °C.
\]

\[
\text{\textsuperscript{1}H-NMR (400 MHz, C\textsubscript{6}D\textsubscript{6})} \delta: 8.14 (d, J = 8.4 Hz, 2H), 7.09 (d, J = 8.2 Hz, 2H), 3.93 (d, J = 2.1 Hz, 1H), 3.47 (s, 3H), 3.32 (dd, J\textsubscript{1} = 10.8 Hz, J\textsubscript{2} = 2.8 Hz, 1H), 3.25 (dd, J\textsubscript{1} = 10.8 Hz, J\textsubscript{2} = 2.8 Hz, 1H), 2.83 (d, J = 2.3 Hz, 1H), 2.80 (d, J = 2.3 Hz, 1H), 2.67 (td, J\textsubscript{1} = 11.5 Hz, J\textsubscript{2} = 3.5 Hz, 1H), 2.32-2.36 (m, 1H), 1.83 (tt, J\textsubscript{1} = 11.5 Hz, J\textsubscript{2} = 2.7 Hz, 1H), 1.68-1.78 (m, 2H), 1.57-1.61 (m, 1H), 1.20-1.31 (m, 4H), 1.05 (s, 3H), 0.14 (s, 3H).
\]

\[
\text{\textsuperscript{13}C-NMR (101 MHz, C\textsubscript{6}D\textsubscript{6})} \delta: 166.7, 151.7, 130.1, 128.9, 101.5, 76.8, 76.8, 51.5, 47.5, 46.0, 35.2, 29.9, 26.9, 26.1, 24.7, 22.9, 21.3.
\]

\[
\text{MS (70 eV, EI) m/z (%): 196 (29), 115 (100), 97 (11), 83 (11), 71 (11), 70 (10), 69 (52), 57 (22), 56 (9), 55 (22), 45 (10), 44 (36), 43 (26), 41 (25).}
\]

\[
\text{IR (ATR) } \tilde{\nu} (\text{cm}^{-1}): 2929 (m), 2852 (m), 1717 (s), 1608 (w), 1438 (m), 1393 (m), 1270 (s), 1184 (m), 1153 (m), 1110 (vs), 1098 (s), 1030 (m), 1017 (m), 987 (m), 973 (m), 932 (m), 852 (w), 770 (s), 710 (s).
\]

\[
\text{HRMS (EI) for C}_{20}\text{H}_{28}\text{O}_{4} (332.1988): 332.1977.}
\]

\[
2-(\text{trans-2-(3-(trifluoromethyl)phenyl)cyclohexyl})-5,5\text{-dimethyl-1,3-dioxane (111b)}
\]
According to TP5, 2-cyclohex-1-enyl-5,5-dimethyl-1,3-dioxane (139) (196 mg, 1.00 mmol) was reacted via hydroboration with Et$_2$BH, followed by a boron-zinc exchange and subsequent cross-coupling (25 °C, 12 h) with 1-iodo-3-(trifluoromethyl)benzene (816 mg, 3.00 mmol). Purification by column chromatography (SiO$_2$; Et$_2$O/n-pentane 1 : 30) furnished the title compound (232 mg, 0.68 mmol, 68 %) as a colourless oil.

d.r.: 98 : 2.

$^1$H-NMR (400 MHz, C$_6$D$_6$) $\delta$: 7.53 (s, 1H), 7.26 (d, $J = 7.6$ Hz, 1H), 7.08 (d, $J = 7.6$ Hz, 1H), 6.95 (t, $J = 7.7$ Hz, 1H), 3.86 (d, $J = 2.2$ Hz, 1H), 3.29 (dd, $J_1 = 10.8$ Hz, $J_2 = 2.9$ Hz, 1H), 3.21 (dd, $J_1 = 10.9$ Hz, $J_2 = 2.8$ Hz, 1H), 2.80 (d, $J = 10.8$ Hz, 1H), 2.74 (d, $J = 11.0$ Hz, 1H), 2.62 (td, $J_1 = 11.5$ Hz, $J_2 = 3.1$ Hz, 1H), 2.27-2.30 (m, 1H), 1.76 (tt, $J_1 = 11.5$ Hz, $J_2 = 2.8$ Hz, 1H), 1.59-1.66 (m, 1H), 1.52-1.57 (m, 2H), 1.11-1.21 (m, 4H), 1.00 (s, 3H), 0.11 (s, 3H).

$^{13}$C-NMR (75 MHz, C$_6$D$_6$) $\delta$: 147.4, 131.1, 130.8 (q, $J = 31.7$ Hz), 129.0, 125.1 (d, $J = 3.4$ Hz), 123.1 (q, $J = 3.9$ Hz) 101.5, 76.8, 76.8, 47.6, 45.7, 35.1, 29.9, 26.9, 26.1, 24.9, 22.9, 21.3.

MS (70 eV, EI) $m/z$ (%): 207 (13), 196 (24), 159 (21), 115 (100), 81 (10), 69 (56), 57 (15), 56 (10), 55 (22), 45 (12), 44 (48), 43 (18), 41 (28).

IR (ATR) $\tilde{\nu}$ (cm$^{-1}$): 2930 (w), 2853 (w), 1451 (w), 1394 (w), 1328 (s), 1160 (s), 1116 (vs), 1091 (s), 1074 (s), 1042 (m), 1027 (m), 993 (m), 969 (m), 932 (w), 919 (w), 903 (w), 799 (m), 703 (m), 664 (m).

HRMS (EI) for C$_{19}$H$_{25}$F$_3$O$_2$ (342.1807): 342.1791.

### 3.2.2. Typical Procedure 6: Diastereoselective cross-coupling with non-stereodefined cyclohexylzinc iodides produced via zinc insertion into the respective cyclohexyl iodide (TP6)

(Compounds of Scheme 31 and Table 7)

In a dry and argon-flushed 25 mL Schlenk-flask, equipped with a magnetic stirring bar and a septum, first LiCl (63.6 mg, 1.50 mmol, 1.5 equiv.) then Zn (196 mg, 3.00 mmol, 3.0 equiv.) were dried under high vacuum at 500 °C for 20 min using a heat gun. After activation with 1,2-dibromoethane (5.0 mol%), THF (2 mL) was added and the reaction was initiated by carefully heating to a gentle reflux with a heat gun. Once the gas development had stopped, a solution of the respective iodide (1.00 mmol, 1.0 equiv.) in THF (1 mL) was added dropwise and the reaction mixture was stirred for 4 h at room temperature. After completion of the zinc
insertion, the reaction mixture was added dropwise to a mixture of the respective electrophile (0.70 mmol, 0.7 equiv.), Pd(dba)$_2$ (11.5 mg, 0.02 mmol, 2.0 mol%) und S-Phos (8.20 mg, 0.02 mmol, 2.0 mol%) in THF (1 mL) at the given temperature. The reaction was stirred for the given time and temperature, then quenched with sat. aq. NH$_4$Cl solution (10 mL), extracted with Et$_2$O (3 x 20 mL) and the combined organic layers were dried over MgSO$_4$. The solvents were removed in vacuo and the crude product was purified by column chromatography (SiO$_2$).

methyl-4-\(\text{(trans-2-(5,5-dimethyl-1,3-dioxan-2-yl)cyclohexyl)}\)benzoate

According to TP6, 2-\(\text{(cis-2-iodocyclohexyl)}\)-5,5-dimethyl-1,3-dioxane (148) (324 mg, 1.00 mmol) was transformed via zinc insertion to the corresponding organozinc reagent followed by subsequent cross-coupling (–25 °C, 12 h; then –10 °C, 12 h) with methyl-4-iodobenzoate (183 mg, 0.70 mmol). Purification by column chromatography (SiO$_2$; Et$_2$O/n-pentane 1 : 10) furnished the title compound (171 mg, 0.51 mmol, 73 %) as a colourless solid.

d.r.: > 99 : 1.

m.p.: 80.4 °C.

$^1$H-NMR (400 MHz, C$_6$D$_6$) $\delta$: 8.14 (d, $J = 8.4$ Hz, 2H), 7.09 (d, $J = 8.2$ Hz, 2H), 3.93 (d, $J = 2.1$ Hz, 1H), 3.47 (s, 3H), 3.32 (dd, $J_1 = 10.8$ Hz, $J_2 = 2.8$ Hz, 1H), 3.25 (dd, $J_1 = 10.8$ Hz, $J_2 = 2.8$ Hz, 1H), 2.83 (d, $J = 2.3$ Hz, 1H), 2.80 (d, $J = 2.3$ Hz, 1H), 2.67 (td, $J_1 = 11.5$ Hz, $J_2 = 3.5$ Hz, 1H), 2.32-2.36 (m, 1H), 1.83 (tt, $J_1 = 11.5$ Hz, $J_2 = 2.7$ Hz, 1H), 1.68-1.78 (m, 2H), 1.57-1.61 (m, 1H), 1.20-1.31 (m, 4H), 1.05 (s, 3H), 0.14 (s, 3H).

$^{13}$C-NMR (101 MHz, C$_6$D$_6$) $\delta$: 166.7, 151.7, 130.1, 128.9, 101.5, 76.8, 76.8, 51.5, 47.5, 46.0, 35.2, 29.9, 26.9, 26.1, 24.7, 22.9, 21.3.

MS (70 eV, EI) m/z (%): 196 (29), 115 (100), 97 (11), 83 (11), 71 (11), 70 (10), 69 (52), 57 (22), 56 (9), 55 (22), 45 (10), 44 (36), 43 (26), 41 (25).

IR (ATR) $\tilde{\nu}$ (cm$^{-1}$): 2929 (m), 2852 (m), 1717 (s), 1608 (w), 1438 (m), 1393 (m), 1270 (s), 1184 (m), 1153 (m), 1110 (vs), 1098 (s), 1030 (m), 1017 (m), 987 (m), 973 (m), 932 (m), 852 (w), 770 (s), 710 (s).

According to **TP6**, 2-(cis-2-iodocyclohexyl)-5,5-dimethyl-1,3-dioxane (148) (324 mg, 1.00 mmol) was transformed via zinc insertion to the corresponding organozinc reagent followed by subsequent cross-coupling (−25 °C, 12 h; then −10 °C, 12 h) with 1-iodo-3-(trifluoromethyl)benzene (190 mg, 0.70 mmol). Purification by column chromatography (SiO$_2$; Et$_2$O/n-pentane 1 : 30) furnished the title compound (136 mg, 0.40 mmol, 57 %) as a colourless oil.

d.r.: > 99 : 1.

$^1$H-NMR (400 MHz, C$_6$D$_6$) $\delta$: 7.53 (s, 1H), 7.26 (d, $J = 7.6$ Hz, 1H), 7.08 (d, $J = 7.6$ Hz, 1H), 6.95 (t, $J = 7.7$ Hz, 1H), 3.86 (d, $J = 2.2$ Hz, 1H), 3.29 (dd, $J_1 = 10.8$ Hz, $J_2 = 2.9$ Hz, 1H), 3.21 (dd, $J_1 = 10.9$ Hz, $J_2 = 2.8$ Hz, 1H), 2.80 (d, $J = 10.8$ Hz, 1H), 2.74 (d, $J = 11.0$ Hz, 1H), 2.62 (td, $J_1 = 11.5$ Hz, $J_2 = 3.1$ Hz, 1H), 2.27-2.30 (m, 1H), 1.76 (tt, $J_1 = 11.5$ Hz, $J_2 = 2.8$ Hz, 1H), 1.59-1.66 (m, 1H), 1.52-1.57 (m, 2H), 1.11-1.21 (m, 4H), 1.00 (s, 3H), 0.11 (s, 3H).

$^{13}$C-NMR (75 MHz, C$_6$D$_6$) $\delta$: 147.4, 131.1, 130.8 (q, $J = 31.7$ Hz), 129.0, 125.1 (d, $J = 3.4$ Hz), 123.1 (q, $J = 3.9$ Hz) 101.5, 76.8, 76.8, 47.6, 45.7, 35.1, 29.9, 26.9, 26.1, 24.9, 22.9, 21.3.

**MS (70 eV, EI)** m/z (%): 207 (13), 196 (24), 159 (21), 115 (100), 81 (10), 69 (56), 57 (15), 56 (10), 55 (22), 45 (12), 44 (48), 43 (18), 41 (28).

**IR (ATR)** $\vec{v}$ (cm$^{-1}$): 2930 (w), 2853 (w), 1451 (w), 1394 (w), 1328 (s), 1160 (s), 1116 (vs), 1091 (s), 1074 (s), 1042 (m), 1027 (m), 993 (m), 969 (m), 932 (w), 919 (w), 903 (w), 799 (m), 703 (m), 664 (m).

**HRMS (EI)** for C$_{19}$H$_{25}$F$_3$O$_2$ (342.1807): 342.1809.
4. Diastereo- and Enantioselective Cross-Coupling with Functionalized Cyclohexylzinc Reagents

4.2. Diastereoselective Cross-Coupling with Functionalized Cyclohexylzinc Derivatives

4.2.1. Preparation of starting materials (Scheme 34)

2-iodocyclohex-2-enone (130)

\[
\text{To a solution of cyclohex-2-enone (50.4 mL, 520 mmol) dissolved in 1.0 L THF/H}_2\text{O (1 : 1) was added K}_2\text{CO}_3 (86.2 g, 624 mmol), I}_2 (198 g, 780 mmol) und 4-(dimethylamino)pyridine (DMAP) (12.7 g, 104 mmol). After 2 h of stirring at 25 °C, the reaction mixture was diluted with 250 mL of EtOAc and then cooled to 0 °C. The reaction mixture was then slowly quenched with sat. aq. NaHSO}_3 solution (400 mL), the organic phase was extracted with 0.1 M HCl solution (2 x 500 mL) and the combined aqueous layers were extracted with EtOAc (3 x 200 mL). The solvent was partly evaporated in vacuo (100 mbar, 30 °C) and the residue dissolved in heptane. Crystallisation at -28 °C furnished the title compound (80.1 g, 361 mmol, 69 %) as yellow crystals.}

m.p.: 48.4 °C.

\(\text{^1H-NMR (400 MHz, C}_6\text{D}_6) \delta: 7.00 (t, J = 4.4 Hz, 1H), 2.03-2.07 (m, 2H), 1.38-1.43 (m, 2H), 1.15-1.22 (m, 2 H).}

\(\text{^13C-NMR (101 MHz, C}_6\text{D}_6) \delta: 190.6, 158.6, 104.5, 37.1, 29.4, 22.6.}

\(\text{IR (ATR) } \nu (\text{cm}^{-1}): 2936 (w), 1671 (vs), 1583 (s), 1422 (m), 1408 (m), 1328 (m), 1310 (s), 1155 (m), 1119 (s), 979 (m), 966 (vs), 914 (s), 873 (m), 802 (s), 702 (s).}

(R)-2-iodocyclohex-2-enol (131)

\[
\text{A dry and argon-flushed 500 mL 2-necked Schlenk-flask, equipped with a dropping funnel, a magnetic stirring bar and a septum, was charged with a solution of B(OMe)_3 (312 mg,}
C. Experimental Section

3.00 mmol) and (R)-diphenylprolinol (760 mg, 3.00 mmol) in THF (100 mL) and stirred for 1 h at room temperature. After addition of 2-iodocyclohex-2-enone (130) (22.2 g, 100 mmol) the reaction mixture was cooled to 0 °C and borane N,N-diethylaniline complex (17.9 g, 110 mmol) was added dropwise. The reaction mixture was then warmed to room temperature and stirred for additional 12 h. After addition of sat. aq. KHSO₄ solution (200 mL), phases were separated and the aqueous phase was extracted with Et₂O (2 x 200 mL). The combined organic layers were washed with sat. aq. KHSO₄ solution, 2 M NaOH solution and sat. aq. NaCl solution and dried over MgSO₄. Evaporation of the solvents in vacuo (> 200 mbar, 30 °C) furnished the crude product (21.2 g, 94.6 mmol, 95%), as a pale yellow oil, which was used in the next step without further purification.

\(^1\)H-NMR (400 MHz, C₆D₆) δ: 6.13 (t, J = 3.9 Hz, 1H), 3.90 (s, 1H), 1.95 (s, 1H), 1.36-1.62 (m, 6H).

\(^13\)C-NMR (101 MHz, C₆D₆) δ: 140.5, 104.6, 72.0, 32.3, 29.3, 17.7.

IR (ATR) \(\tilde{\nu}\) (cm\(^{-1}\)):
2936 (m), 2861 (w), 1626 (m), 1426 (m), 1328 (m), 1249 (m), 1161 (m), 1077 (m), 1049 (s), 988 (s), 969 (vs), 931 (m), 903 (m), 869 (m), 827 (m), 803 (s), 773 (m), 738 (s), 690 (m).

4.2.2. Typical Procedure 7: Protection with organosilyl chlorides (TP7)

A dry and Ar-flushed 250 mL Schlenk-tube, equipped with a magnetic stirring bar and a septum, was charged with a solution of alcohol (R)-2-iodocyclohex-2-enol (131) (8.96 g, 40.0 mmol, 1.0 equiv.) and imidazole (6.80 g, 100 mmol, 2.5 equiv.) in DMF (20 mL) at room temperature and the respective organosilyl chloride (50.0 mmol, 1.25 equiv.) was added. After 1 h at 25 °C, the reaction mixture was diluted with Et₂O (150 mL), the organic phase was washed with water (100 mL), 0.5 M HCl solution (120 mL) and sat. aq. NaCl solution (50 mL). The solvents were evaporated in vacuo (> 200 mbar, 40 °C) and the crude product was purified via column chromatography to give the respective title compound.

(R)-tert-butyl-(2-iodocyclohex-2-enyloxy)dimethylsilane

According to TP7, (R)-2-iodocyclohex-2-enol (131) (8.96 g, 40.0 mmol) was protected with tert-butyldimethylsilylchloride (TBSCl) (7.5 g, 50 mmol). Purification by column
chromatography (SiO$_2$; Et$_2$O/n-pentane 1 : 50) furnished the title compound (10.4 g, 30.8 mmol, 77 %) as a slightly yellow oil.

$^1$H-NMR (400 MHz, C$_6$D$_6$) $\delta$: 6.20 (d, $J = 3.7$ Hz, 1H), 4.08 (s, 1H), 1.57 (d, $J = 6.0$ Hz, 5H), 1.19-1.24 (m, 1H), 1.03 (s, 9H), 0.27 (s, 3H), 0.06 (s, 3H).

$^{13}$C-NMR (101 MHz, C$_6$D$_6$) $\delta$: 140.3, 103.8, 73.0, 33.7, 29.3, 26.2, 25.9, 18.4, 17.5, -4.0, -4.2.

MS (70 eV, EI) $m/z$ (%): 283 (11), 282 (40), 281 (30), 185 (81), 153 (41), 79 (22), 75 (100), 73 (13).

IR (ATR) $\tilde{\nu}$ (cm$^{-1}$): 2948 (m), 2928 (m), 2856 (w), 1472 (w), 1360 (w), 1250 (m), 1162 (w), 1088 (s), 1061 (m), 989 (m), 936 (w), 911 (m), 812 (s), 772 (vs), 712 (m), 695 (w), 667 (m).

HRMS (EI) for C$_{12}$H$_{23}$IOSi (338.0563): 338.0454.

(R)-(2-iodocyclohex-2-enyloxy)triphenylsilane

According to TP7, (R)-2-iodocyclohex-2-enol (131) (8.96 g, 40.0 mmol) was protected with triphenylsilylchloride (14.7 g, 50 mmol). Purification by column chromatography (SiO$_2$; Et$_2$O/n-pentane 1 : 100) furnished the title compound (11.8 g, 24.5 mmol, 61 %) as a colourless solid.

m.p.: 77.9 °C.

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$: 7.71-7.75 (m, 6H), 7.36-7.49 (m, 9H), 6.52 (t, $J = 3.9$ Hz, 1H), 4.33 (t, $J = 4.5$ Hz, 1H), 2.10-2.20 (m, 1H), 1.72-2.04 (m, 4H), 1.53-1.61 (m, 1H).

$^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$: 141.0, 135.8, 135.6, 135.4, 135.2, 134.3, 130.0, 129.8, 127.9, 127.7, 102.2, 73.8, 33.2, 29.4, 17.4.

MS (70 eV, EI) $m/z$ (%): 405 (14), 404 (25), 403 (23), 355 (15), 309 (18), 277 (27), 276 (12), 260 (25), 259 (100), 217 (22), 200 (11), 199 (58), 197 (13), 182 (11), 181 (40), 180 (10), 155 (10), 105 (13), 91 (10), 77 (17).

IR (ATR) $\tilde{\nu}$ (cm$^{-1}$): 3066 (vw), 2945 (w), 2923 (w), 1589 (vw), 1484 (vw), 1428 (m), 1176 (vw), 1160 (w), 1115 (s), 1094 (s), 1056 (m), 1019 (m), 998 (m), 936 (w), 910 (w), 897 (w), 844 (w), 811 (w), 797 (w), 739 (m), 705 (s), 697 (vs).

HRMS (EI) for C$_{24}$H$_{23}$IOSi (482.0563): 482.0553.
(R)-tert-butyl-(2-iodocyclohex-2-enyloxy)diphenylsilane

\[ \text{OTBDPS} \]

According to TP7, (R)-2-iodocyclohex-2-enol (131) (8.96 g, 40.0 mmol) was protected with tert-butylidiphenylsilylchloride (TBDPSCI) (13.7 g, 50.0 mmol). Purification by column chromatography (SiO\(_2\); Et\(_2\)O/n-pentane 1 : 50) furnished the title compound (16.1 g, 34.8 mmol, 87 %) as a colourless solid.

m.p.: \(<\ 30^\circ\text{C}.\)

\(^1\text{H-NMR (400 MHz, C}_6\text{D}_6\) \(\delta: 7.94-7.96\) (m, 2H), \(7.84-7.86\) (m, 2H), \(7.22-7.28\) (m, 6H), \(6.23\) (t, \(J = 3.7\) Hz, 1H), \(4.28\) (d, \(J = 4.4\) Hz, 1H), \(1.50-1.64\) (m, 3H), \(1.35-1.43\) (m, 2H), \(1.28\) (s, 9H), \(1.02-1.09\) (m, 1H).

\(^{13}\text{C-NMR (101 MHz, C}_6\text{D}_6\) \(\delta: 140.8, 136.8, 136.4, 136.2, 135.9, 135.2, 134.9, 133.6, 130.1, 129.9, 127.9, 127.8, 102.8, 74.1, 33.1, 29.3, 27.5, 19.9, 17.5, 1.4.

MS (70 eV, EI) \(m/z\) (%): 406 (24), 405 (100), 309 (86), 277 (10), 249 (31), 200 (15), 199 (78), 181 (22), 157 (14), 77 (12).

IR (ATR) \(\tilde{\nu}\) (cm\(^{-1}\)): 2929 (m), 2856 (m), 1106 (s), 1080 (s), 1056 (s), 1013 (s), 1005 (s), 821 (m), 794.00 (m), 740 (m), 720 (m), 699 (vs), 612(s).

HRMS (EI) for C\(_{22}\)H\(_{27}\)IOSi (462.0876): 462.0871.

4.2.3. Typical Procedure 8: Cross-coupling of silyl-protected (R)-2-iodocyclohex-2-enol derivatives (TP8) (Schemes 34 and 35)

In a dry and Ar-flushed 25 mL Schlenk-flask LiCl (5.0 equiv.) und ZnCl\(_2\) (2.5 equiv.) were dried under high vacuum at 500 °C using a heat gun for 20 min. After cooling to room temperature, anhydrous NEP (N-ethyl-2-pyrrolidone) (5.5 equiv.) was added and stirring was continued until the salts were dissolved. The solution was cooled to 0 °C, anhydrous THF (0.6 M) was added followed by dropwise addition of the freshly titrated organomagnesium solution (5.0 equiv.). After warming up to room temperature, the aryl iodide (1.0 equiv.) and bis[4-(di-tert-butylphosphine)-N,N-dimethylphenylamino]palladium-dichloride (0.5 mol%) were added and the mixture was heated to 60 °C and left to stir overnight at that temperature. The reaction mixture was then quenched with sat. aq. NH\(_4\)Cl solution, extracted with Et\(_2\)O and dried over MgSO\(_4\). The solvents were removed \textit{in vacuo} and the crude product was subjected to column chromatography.
(R)-tert-butyl(methylcyclohex-2-enyloxy)silane (132)

According to TP8, LiCl (1.70 g, 40 mmol) und ZnCl\textsubscript{2} (2.73 g, 20 mmol) were dried, dissolved in NEP (5.3 mL) and THF (13.3 mL) was added at 0 °C. After complete addition of MeMgCl (20.3 mL, 1.97 M in THF, 40 mmol) at 0 °C the reaction mixture was warmed to room temperature, (R)-tert-butyl(2-iodocyclohex-2-enyloxy)dimethylsilane (2.71 g, 8.00 mmol) and Bis[4-(di-tert-butylphosphine)-N,N-dimethylphenylamino]palladium-dichloride (28.3 mg, 0.04 mmol) were added and the mixture was heated to 60 °C and left to stir overnight at that temperature. Purification by column chromatography (SiO\textsubscript{2}; Et\textsubscript{2}O/n-pentane 1 : 50) furnished the title compound (1.48 g, 6.56 mmol, 82 %) as a colourless oil.

\textsuperscript{1}H-NMR (400 MHz, C\textsubscript{6}D\textsubscript{6}) \(\delta\): 5.42 (s, 1H), 3.96-3.97 (m, 1H), 1.88-1.92 (m, 1H), 1.77-1.80 (m, 4H), 1.65-1.72 (m, 3H), 1.37-1.44 (m, 1H), 1.00 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H).

\textsuperscript{13}C-NMR (101 MHz, C\textsubscript{6}D\textsubscript{6}) \(\delta\): 136.4, 124.4, 69.6, 33.4, 26.1, 25.9, 25.8, 21.3, 19.4, 18.3, -4.2, -4.7.

MS (70 eV, EI) \textit{m/z} (%): 226 (12), 169 (49), 93 (37), 77 (10), 75 (100), 73 (11), 41 (11).

IR (ATR) \(\tilde{\nu}\) (cm\textsuperscript{-1}): 2930 (m), 2857 (m), 1472 (w), 1462 (w), 1439 (w), 1361 (s), 1250 (m), 1152 (w), 1083 (s), 1072 (s), 1038 (m), 1019 (m), 1003 (s), 963 (w), 939 (w), 893 (s), 832 (vs), 807 (m), 771 (vs), 669 (m).

HRMS (EI) for C\textsubscript{13}H\textsubscript{26}O\textsubscript{5}Si (226.1753): 226.1754.

(R)-triphenyl-(2-phenylcyclohex-2-enyloxy)silane

According to TP8, LiCl (233 mg, 5.50 mmol) und ZnCl\textsubscript{2} (375 mg, 2.75 mmol) were dried, dissolved in NEP (0.7 mL) and THF (1.8 mL) was added at 0 °C. After complete addition of PhMgCl (3.14 mL, 1.75 M in THF, 5.50 mmol) at 0 °C the reaction mixture was warmed to room temperature, (R)-(2-iodocyclohex-2-enyloxy)triphenylsilane (531 mg, 1.10 mmol) and Bis[4-(di-tert-butylphosphine)-N,N-dimethylphenylamino]palladium-dichloride (3.54 mg, 0.005 mmol) were added and the mixture was heated to 60 °C and left to stir overnight at that
temperature. Purification by column chromatography (SiO$_2$; Et$_2$O/n-pentane 1 : 100) furnished the title compound (0.39 mg, 0.90 mmol, 82 %) as a colourless solid.

**m.p.:** 64.6 °C.

$^1$H-NMR (400 MHz, C$_6$D$_6$) $\delta$: 7.52-7.54 (m, 7H), 7.07-7.20 (m, 13H), 5.89-5.91 (m, 1H), 4.90 (d, $J = 4.0$ Hz, 1H), 1.85-2.05 (m, 3H), 1.75-1.82 (m, 1H), 1.45-1.53 (m, 1H), 1.32-1.38 (m, 1H).

$^{13}$C-NMR (101 MHz, C$_6$D$_6$) $\delta$: 142.0, 140.7, 136.3, 136.0, 135.8, 135.6, 135.5, 135.3, 130.3, 130.0, 128.5, 128.4, 127.3, 126.9, 67.9, 32.8, 26.3, 17.9, 1.4.

**MS** (70 eV, EI) $m/z$ (%): 432 (12), 354 (11), 326 (20), 289 (12), 260 (24), 259 (100), 217 (15), 199 (45), 181 (20), 156 (57).

**IR** (ATR) $\tilde{\nu}$ (cm$^{-1}$): 3060 (vw), 2933 (w), 1428 (w), 1260 (m), 1114 (s), 1106 (s), 1064 (s), 1013 (s), 800 (s), 739 (m), 705 (s), 695 (vs).

**HRMS** (EI) for C$_{30}$H$_{28}$OSi (432.1909): 432.1913.

(R)-(2-cyclohexylcyclohex-2-enyloxy)triphenylsilane (136)

According to TP8, LiCl (1.70 g, 40.0 mmol) und ZnCl$_2$ (2.73 g, 20.0 mmol) were dried, dissolved in NEP (5.3 mL) and THF (13.3 mL) was added at 0 °C. After complete addition of c-HexMgBr (60.6 mL, 0.66 M in THF, 40.0 mmol) at 0 °C the reaction mixture was warmed to room temperature, (R)-(2-iodocyclohex-2-enyloxy)triphenylsilane (3.86 g, 8.00 mmol) and Bis[4-(di-tert-butylphosphine)-N,N-dimethylphenylamino]palladium-dichloride (28.3 mg, 0.04 mmol) were added and the mixture was heated to 60 °C and left to stir for 6 h at that temperature. Purification by column chromatography (SiO$_2$; EtOAc/n-pentane 1 : 300 then 1 : 200) furnished the title compound (1.66 g, 3.78 mmol, 47 %) as a colourless oil.

$^1$H-NMR (400 MHz, C$_6$D$_6$) $\delta$: 7.78-7.84 (m, 6H), 7.20-7.21 (m, 9H), 5.54 (t, $J = 3.5$ Hz, 1H), 4.50 (d, $J = 4.4$ Hz, 1H), 2.22 (t, $J = 11.2$ Hz, 1H), 1.87-2.06 (m, 4H), 1.74-1.84 (m, 2H), 1.54-1.66 (m, 4H), 1.33-1.39 (m, 1H), 1.05-1.27 (m, 4H), 0.85-0.94 (m, 1H).

$^{13}$C-NMR (101 MHz, C$_6$D$_6$) $\delta$: 145.2, 136.0, 135.9, 135.8, 135.6, 135.1, 131.0, 130.2, 129.5, 128.1, 127.9, 122.3, 68.6, 40.6, 34.2, 33.1, 32.2, 27.3, 26.9, 25.8, 18.6.

**MS** (70 eV, EI) $m/z$ (%): 438 (12), 356 (20), 355 (68), 260 (20), 259 (100), 199 (39), 181 (10).
C. Experimental Section

IR (ATR) $\tilde{\nu}$ (cm$^{-1}$): 2923 (m), 2850 (w), 1428 (m), 1114 (s), 1058 (m), 1029 (m), 1012 (m), 997 (m), 928 (w), 801 (w), 739 (m), 708 (s), 696 (vs).

HRMS (EI) for C$_{30}$H$_{34}$OSi (438.2379): 438.2372.

(R)-tert-butyl(2-cyclohexylcyclohex-2-enyloxy)diphenylsilane (137)

According to TP8, LiCl (1.70 g, 40.0 mmol) und ZnCl$_2$ (2.73 g, 20.0 mmol) were dried, dissolved in NEP (5.3 mL) and THF (13.3 mL) was added at 0 °C. After complete addition of c-HexMgBr (60.6 mL, 0.66 M in THF, 40.0 mmol) at 0 °C the reaction mixture was warmed to room temperature, ((R)-tert-butyl-(2-iodocyclohex-2-enyloxy)diphenylsilane (3.70 g, 8.00 mmol) and Bis[4-(di-tert-butylphosphine)-N,N-dimethylphenylamino]palladium-dichloride (28.3 mg, 0.04 mmol) were added and the mixture was heated to 60 °C and left to stir for 6 h at that temperature. Purification by column chromatography (SiO$_2$; EtOAc/n-pentane 1 : 300 then 1 : 200) furnished the title compound (1.27 g, 3.04 mmol, 38 %) as a colourless solid.

m.p.: < 30 °C.

$^1$H-NMR (400 MHz, C$_6$D$_6$) $\delta$: 7.82-7.85 (m, 4H), 7.22-7.24 (m, 6H), 5.50 (t, $J$ = 3.5 Hz, 1H), 4.31 (t, $J$ = 4.2 Hz, 1H), 2.15 (t, $J$ = 11.2 Hz, 1H), 2.02 (dd, $J_1$ = 16.7 Hz, $J_2$ = 4.4 Hz, 1H), 1.75-1.95 (m, 5H), 1.59 (d, $J$ = 12.7 Hz, 3H), 1.29-1.51 (m, 4H), 1.21 (s, 9H), 1.08-1.12 (m, 2H), 0.77-0.88 (m, 1H).

$^{13}$C-NMR (101 MHz, C$_6$D$_6$) $\delta$: 145.4, 136.4, 135.1, 134.7, 129.8, 127.8, 122.0, 68.2, 40.3, 34.3, 32.9, 31.9, 27.4, 27.3, 26.9, 25.8, 19.7, 18.5.

MS (70 eV, EI) m/z (%): 362 (31), 361 (100), 201 (12), 200 (42), 199 (55).

IR (ATR) $\tilde{\nu}$ (cm$^{-1}$): 2924 (m), 2852 (m), 1427 (w), 1109 (m), 1060 (s), 1021 (s), 822 (m), 738 (m), 699 (vs), 606 (m).

HRMS (EI) for C$_{28}$H$_{38}$OSi (418.2692): 418.2682.
4.2.4. Typical Procedure 9: Protection of cyclohex-2-encarboxaldehyde and acetylcyloalk-2-ene (TP9) (Schemes 37 and 38)

A 250 mL 2-neck flask, equipped with a magnetic stirring bar, a reflux condenser, a Dean-Stark-condenser and a drying tube, was charged with the respective α,β-unsaturated carbonyl compound (45.4 mmol, 1.0 equiv.), MgSO$_4$ (5.46 g, 45.4 mmol, 1.0 equiv.), L-tartaric acid (41.5 mg, 0.27 mmol, 0.6 mol%) and benzene (60 mL). The respective diol (123 mmol, 2.7 equiv.) was added portionwise at room temperature and the reaction mixture was heated to reflux at 115 °C for 12 h. After cooling to 0 °C, NaHCO$_3$ (45.3 mg, 0.54 mmol, 1.2 mol%) was added as a solid and the reaction mixture was stirred for additional 30 min. The reaction mixture was then filtrated over NaHCO$_3$ and washed with CH$_2$Cl$_2$. The solvents were removed in vacuo and the crude product was subjected to column chromatography.

2-cyclohex-1- enyl-1,3-dioxolane (138)

According to TP9, 1-cyclohexen-1-carboxaldehyde (5.00 g, 45.4 mmol) was protected with 1,2-ethane diole (7.63 g, 6.87 mL, 123 mmol). Purification by column chromatography (SiO$_2$; Et$_2$O/n-pentane 1 : 20) furnished the title compound (6.65 g, 43.1 mmol, 95 %) as a colourless oil.

$^1$H-NMR (300 MHz, C$_6$D$_6$) $\delta$: 5.88 (m, 1H), 5.15 (s, 1H), 3.39-3.63 (m, 4H), 2.18-2.23 (m, 2H), 1.87 (qd, $J_1 = 6.0$ Hz, $J_2 = 2.5$ Hz, 2H), 1.39-1.57 (m, 4H).

$^{13}$C-NMR (75 MHz, C$_6$D$_6$) $\delta$: 135.9, 127.4, 106.9, 65.2, 25.1, 22.8, 22.6, 22.4.

MS (70 eV, EI) m/z (%): 154 (92), 153 (95), 126 (18), 125 (100), 99 (11), 43 (19).

IR (ATR) $\tilde{\nu}$ (cm$^{-1}$): 2928 (m), 2860 (m), 1684 (w), 1438 (w), 1394 (w), 1372 (w), 1300 (w), 1190 (m), 1137 (w), 1093 (s), 1071 (vs), 1042 (s), 943 (s), 837 (s), 801 (m), 690 (m).

HRMS (EI) for C$_9$H$_{14}$O$_2$ (154.0994): 154.0986.
2-cyclohex-1-enyl-5,5-dimethyl-1,3-dioxane (139)

According to TP9, 1-cyclohexen-1-carboxaldehyde (5.00 g, 45.4 mmol) was protected with 2,2-dimethylpropane-1,3-diole (12.8 g, 123 mmol). Purification by column chromatography (SiO$_2$; Et$_2$O/n-pentane 1 : 10) furnished the title compound (8.36 g, 42.6 mmol, 94%) as a colourless oil.

$^1$H-NMR (300 MHz, C$_6$D$_6$) $\delta$: 5.99 (s, 1H), 4.67 (s, 1H), 3.49 (d, $J = 10.8$ Hz, 2H), 3.21 (d, $J = 10.5$ Hz, 2H), 2.35-2.40 (m, 2H), 1.92-1.97 (m, 2H), 1.42-1.61 (m, 4H), 1.18 (s, 3H), 0.34 (s, 3H).

$^{13}$C-NMR (75 MHz, C$_6$D$_6$) $\delta$: 136.5, 125.3, 104.4, 77.2, 30.0, 25.1, 23.6, 23.1, 22.8, 22.7, 21.7.

MS (70 eV, EI) m/z (%): 196 (94), 195 (29), 167 (68), 111 (65), 110 (44), 109 (37), 81 (48), 69 (100), 67 (52), 56 (22), 55 (22), 41 (35).

IR (ATR) $\tilde{\nu}$ (cm$^{-1}$): 2929 (m), 2839 (m), 1470 (w), 1390 (m), 1362 (w), 1184 (m), 1100 (vs), 1015 (m), 979 (s), 911 (m), 838 (m), 801 (w), 644 (w).

HRMS (EI) for C$_{12}$H$_{20}$O$_2$ (196.1463): 196.1461.

2-cyclohex-1-enyl-2-methyl-1,3-dioxolane (149)

According to TP9, 1-cyclohexenylethanone (12.4 g, 100 mmol) was protected with 1,2-ethane diol (16.8 g, 15.1 mL, 270 mmol) Purification by column chromatography (SiO$_2$; Et$_2$O/n-pentane 1 : 30) furnished the title compound (10.4 g, 61.8 mmol, 62%) as a colourless oil.

$^1$H-NMR (400 MHz, C$_6$D$_6$) $\delta$: 6.02 (dt, $J_1 = 3.6$ Hz, $J_2 = 1.9$ Hz, 1H), 3.46-3.61 (m, 4H), 2.09 (qd, $J_1 = 4.0$, $J_2 = 2.0$ Hz, 2H), 1.92-1.96 (m, 2H), 1.51-1.57 (m, 5H), 1.41-1.47 (m, 2H).

$^{13}$C-NMR (101 MHz, C$_6$D$_6$) $\delta$: 138.6, 122.0, 109.6, 64.3, 25.0, 24.3, 23.1, 22.7.

MS (70 eV, EI) m/z (%): 196 (10), 153 (43), 109 (16), 87 (100), 81 (23), 43 (28).

IR (ATR) $\tilde{\nu}$ (cm$^{-1}$): 2930 (m), 2882 (m), 1668 (w), 1439 (w), 1371 (m), 1273 (w), 1194 (s), 1112 (m), 1076 (m), 1042 (vs), 947 (m), 924 (w), 863 (s), 805 (m).

HRMS (EI) for C$_{10}$H$_{16}$O$_2$ (168.1150): 168.1156.
2-cyclopent-1-enyl-2-methyl-1,3-dioxolane (150)

According to TP9, 1-cyclopentenylethanone (5.00 g, 45.4 mmol) was protected with 1,2-ethane diol (7.63 g, 6.87 mL, 123 mmol). Purification by column chromatography (SiO$_2$; Et$_2$O/n-pentane 1 : 20) furnished the title compound (5.63 g, 36.5 mmol, 80 %) as a colourless oil.

$^1$H-NMR (400 MHz, C$_6$D$_6$) $\delta$: 5.77-5.79 (m, 1H), 3.52-3.62 (m, 4H), 2.37-2.42 (m, 2H), 2.23 (tq, $J_1 = 7.4$, $J_2 = 2.3$ Hz, 2H), 1.74-1.82 (m, 2H), 1.57 (s, 3H).

$^{13}$C-NMR (101 MHz, C$_6$D$_6$) $\delta$: 146.1, 126.4, 107.7, 64.7, 32.6, 31.9, 24.4, 24.0.

MS (70 eV, EI) $m/z$ (%): 140 (25), 139 (61), 96 (13), 95 (100), 87 (25), 67 (12).

IR (ATR) $\tilde{\nu}$ (cm$^{-1}$): 2950 (w), 2886 (w), 2850 (w), 1444 (w), 1371 (m), 1296 (w), 1248 (w), 1184 (s), 1105 (m), 1034 (vs), 947 (m), 863 (s), 811 (m).

HRMS (EI) for C$_9$H$_{14}$O$_2$ (154.0994): 154.1004.

4.2.5. Typical Procedure 10: Preparation of alcohols via hydroboration and oxidation (TP10) (Schemes 37 and 38)

A 1.0 M solution of the respective olefin (1.0 equiv.) in THF was placed in a dry and argon-flushed 250 mL Schlenk-flask, equipped with a magnetic stirring bar and a septum. It was cooled to –10 °C and a 1.0 M solution of BH$_3$THF-complex (1.1 equiv.) was slowly added. The reaction mixture was then allowed to warm to 0 °C and stirred for 12 h. After completion of the hydroboration a suspension of NaBO$_3$·4 H$_2$O (13 equiv.) in MeOH/ H$_2$O (2 : 1) was carefully added. The resulting reaction mixture was stirred for 24 h at room temperature. After filtration, the filtrate was dried over Na$_2$SO$_4$ and washed with EtOAc. The solvents were removed in vacuo and the crude product was subjected to column chromatography.

trans-(1,3-dioxolane-2-yl)cyclohexan-1-ol (145)

According to TP10, 2-cyclohex-1-enyl-1,3-dioxolane (138) (2.47 g, 16.0 mmol), dissolved in THF (16 mL) was reacted with BH$_3$THF (17.6 mL, 1.0 M in THF, 17.6 mmol). The resulting mixture was then oxidatively quenched with a suspension of NaBO$_3$·4H$_2$O (32.0 g, 208 mmol)
C. Experimental Section

in MeOH/ H₂O (2 : 1) (96 mL). Purification by column chromatography (SiO₂; Et₂O/n-pentane 2 : 1 then 3 : 1) furnished the title compound (2.31 g, 13.4 mmol, 67 %) as a colourless oil.

¹H-NMR (400 MHz, C₆D₆) δ: 4.63 (d, J = 5.2 Hz, 1H), 3.73 (s, 1H), 3.67 (td, J₁ = 10.2, J₂ = 4.6 Hz, 1H), 3.33-3.40 (m, 2H), 3.17-3.25 (m, 2H), 2.09-2.16 (m, 1H), 1.81-1.85 (m, 1H), 1.46-1.66 (m, 3H), 1.30-1.40 (m, 1H), 0.95-1.13 (m, 3H).

¹³C-NMR (101 MHz, C₆D₆) δ: 107.6, 70.7, 70.7, 64.8, 64.2, 48.1, 34.9, 26.4, 25.3, 24.7.

MS (70 eV, EI) m/z (%): 171 (2), 154 (2), 125 (2), 91 (7), 82 (6), 81 (3), 74 (4), 73 (100), 67 (4), 57 (2), 45 (6).

IR (ATR) ν (cm⁻¹): 2930 (m), 2857 (m), 1450 (m), 1402 (m), 1159 (m), 1120 (s), 1063 (vs), 1030 (vs), 981 (s), 944 (s), 847 (m).

HRMS (EI) for C₉H₁₆O₃ (172.1099): 171.1031 (–H).

trans-2-(5,5-dimethyl-1,3-dioxane-2-yl)cyclohexan-1-ol (146)

According to TP10, 2-cyclohex-1-enyl-5,5-dimethyl-1,3-dioxane (139) (3.93 g, 20.0 mmol), dissolved in THF (20 mL) was reacted with BH₃THF (22.0 mL, 1.0 M in THF, 22.0 mmol). The resulting mixture was then oxidatively quenched with a suspension of NaBO₄H₂O (40.0 g, 260 mmol) in 120 mL MeOH/ H₂O (2 : 1). Purification by column chromatography (SiO₂; Et₂O/n-pentane 1 : 1 then 2 : 1) furnished the title compound (3.06 g, 14.3 mmol, 72 %) as a colourless oil.

¹H-NMR (300 MHz, C₆D₆) δ: 4.31 (d, J = 4.1 Hz, 1H), 3.85 (td, J₁ = 10.1 Hz, J₂ = 4.6 Hz, 2H), 3.32 (ddd, J₁ = 11.1 Hz, J₂ = 6.5 Hz, J₃ = 2.8 Hz, 2H), 3.25 (d, J = 6.3 Hz, 1H), 3.02 (dd, J₁ = 11.1 Hz, J₂ = 2.8 Hz, 2H), 2.12-2.18 (m, 1H), 1.81-1.87 (m, 1H), 1.50-1.73 (m, 5H), 1.31-1.45 (m, 1H), 1.06 (s, 3H), 0.25 (s, 3H).

¹³C-NMR (75 MHz, C₆D₆) δ: 105.3, 77.2, 77.0, 70.8, 48.9, 35.3, 29.9, 26.2, 25.5, 24.8, 22.8, 21.4.

MS (70 eV, EI) m/z (%): 127 (29), 115 (100), 83 (33), 81 (35), 71 (20), 69 (80), 67 (21), 57 (47), 56 (23), 55 (56), 44 (23), 43 (49), 41 (51).

IR (ATR) ν (cm⁻¹): 2924 (s), 2853 (m), 1450 (m), 1394 (m), 1161 (m), 1116 (vs), 1089 (s), 1042 (s), 1020 (vs), 985 (s), 969 (s), 927 (m), 850 (w).

HRMS (EI) for C₁₂H₂₂O₅ (214.1569): could not be determined via EI-MS.
trans-2-(2-methyl-1,3-dioxolane-2-yl)cyclohexan-1-ol (151)

\[
\text{\begin{center}
\includegraphics[width=0.2\textwidth]{trans-2-(2-methyl-1,3-dioxolane-2-yl)cyclohexan-1-ol.png}
\end{center}}
\]

According to TP10, 2-cyclohex-1-enyl-2-methyl-1,3-dioxolane (149) (5.05 g, 30.0 mmol) dissolved in THF (30 mL) was reacted with BH\(_3\)-THF (33.0 mL, 1.0 M in THF, 33.0 mmol) The resulting mixture was then oxidatively quenched with a suspension of NaBO\(_3\)/H\(_2\)O (60.0 g, 390 mmol) in 180 mL MeOH/ H\(_2\)O (2 : 1). Purification by column chromatography (SiO\(_2\); Et\(_2\)O/n-pentane 2 : 1) furnished the title compound (2.57 g, 13.8 mmol, 46 %) as a colourless oil.

\(^1\)H-NMR (400 MHz, C\(_6\)D\(_6\)) \(\delta\): 4.50 (s, 1H), 3.62 (td, \(J_1 = 10.2\) Hz, \(J_2 = 4.6\) Hz, 1H), 3.31-3.39 (m, 4H), 2.20-2.26 (m, 1H), 1.86-1.90 (m, 1H), 1.49-1.59 (m, 3H), 1.36-1.46 (m, 1H), 1.20 (s, 3H), 0.90-1.12 (m, 3H).

\(^13\)C-NMR (101 MHz, C\(_6\)D\(_6\)) \(\delta\): 112.9, 71.3, 64.4, 63.7, 51.8, 35.6, 27.2, 26.0, 25.0, 20.1.

MS (70 eV, EI) \(m/z\) (%): 171 (23), 88 (35), 87 (67), 81 (16), 71 (13), 43 (100), 41 (10).

IR (ATR) \(\tilde{\nu}\) (cm\(^{-1}\)): 3508 (w), 2930 (m), 2883 (m), 2858 (m), 1450 (m), 1381 (m), 1220 (m), 1163 (s), 1132 (s), 1101 (s), 1068 (s), 1046 (vs), 1029 (vs), 984 (m), 949 (s), 899 (m), 855 (s).

HRMS (EI) for C\(_{10}\)H\(_{18}\)O\(_3\) (186.1256): could not be determined via EI-MS.

trans-2-(2-methyl-1,3-dioxolane-2-yl)cyclopentan-1-ol (152)

\[
\text{\begin{center}
\includegraphics[width=0.2\textwidth]{trans-2-(2-methyl-1,3-dioxolane-2-yl)cyclopentan-1-ol.png}
\end{center}}
\]

According to TP10, 2-cyclopent-1-enyl-2-methyl-1,3-dioxolane (150) (1.54 g, 10.0 mmol) dissolved in THF (10 mL) was reacted with BH\(_3\)-THF (11.0 mL, 1.0 M in THF, 11.0 mmol) The resulting mixture was then oxidatively quenched with a suspension of NaBO\(_3\)/H\(_2\)O (20.0 g, 130 mmol) in 60 mL MeOH/ H\(_2\)O (2 : 1). Purification by column chromatography (SiO\(_2\); Et\(_2\)O/n-pentane 2 : 1 then 3 : 1) furnished the title compound (871 mg, 5.06 mmol, 51 %) as a colourless oil.

\(^1\)H-NMR (400 MHz, C\(_6\)D\(_6\)) \(\delta\): 4.20 (q, \(J = 7.0\) Hz, 1H), 3.43-3.44 (m, 4H), 2.62 (s, 1H), 2.07-2.13 (m, 1H), 1.95 (td, \(J_1 = 13.0\) Hz, \(J_2 = 7.0\) Hz, 1H), 1.66-1.77 (m, 2H), 1.42-1.63 (m, 3H), 1.2 (s, 3H).

\(^13\)C-NMR (101 MHz, C\(_6\)D\(_6\)) \(\delta\): 111.8, 74.5, 64.7, 64.4, 56.0, 34.8, 26.6, 22.5, 22.3.
MS (70 eV, EI) m/z (%): 157 (13), 87 (100), 71 (10), 67 (10), 57 (13), 55 (13), 43 (46), 41 (12).

IR (ATR) $\tilde{\nu}$ (cm$^{-1}$): 2955 (m), 2875 (m), 1448 (w), 1376 (m), 1250 (m), 1222 (m), 1156 (m), 1073 (s), 1030 (vs), 986 (m), 948 (m), 866 (s).

HRMS (EI) for C$_9$H$_{16}$O$_3$ (172.1099): could not be determined via EI-MS.

4.2.6. Typical Procedure 11: Preparation of functionalized cyclohexyl iodides (TP11)

In a dry and argon-flushed Schlenk-flask, equipped with a magnetic stirring bar and a septum, the respective alcohol (0.26 M in THF, 1.0 equiv.) was charged and freshly prepared DCC·MeI (2.0 equiv.) was added at room temperature. The reaction mixture was heated to 50 °C for 24 h. After completion of iodination the reaction mixture was diluted with Et$_2$O. The layers were separated, the organic phase was extracted with water and the combined aqueous layers were extracted with Et$_2$O. Then the combined organic layers were washed with sat. aq. NaHSO$_3$ solution and dried over MgSO$_4$. After removal of the solvents in vacuo the crude product was subjected to column chromatography.

2-(cis-2-iodocyclohexyl)-1,3-dioxolane (147)

According to TP11, trans-(1,3-dioxolane-2-yl)cyclohexan-1-ol (145) (1.03 g, 6.00 mmol) in THF (23 mL) was reacted with DCC·MeI (4.18 g, 12.0 mmol). The reaction mixture was heated to 50 °C for 24 h. Purification by column chromatography (SiO$_2$; Et$_2$O/n-pentane 1 : 30) furnished the title compound (1.06 g, 3.76 mmol, 63 %) as a colourless oil.

$^1$H-NMR (400 MHz, C$_6$D$_6$) $\delta$: 4.85 (s, 1H), 4.66 (d, $J = 7.0$ Hz, 1H), 3.39-3.46 (m, 2H), 3.25-3.34 (m, 2H), 1.86-1.94 (m, 2H), 1.69-1.80 (m, 1H), 1.49-1.61 (m, 2H), 1.19-1.27 (m, 2H), 0.96-1.08 (m, 1H), 0.52-0.58 (m, 1H).

$^{13}$C-NMR (101 MHz, C$_6$D$_6$) $\delta$: 108.9, 64.8, 64.7, 46.9, 39.6, 36.4, 25.2, 24.3, 22.6.

MS (70 eV, EI) m/z (%): 154 (100), 93 (13), 83 (11), 73 (63), 45 (13).

IR (ATR) $\tilde{\nu}$ (cm$^{-1}$): 2931 (m), 2860 (m), 1446 (m), 1254 (m), 1156 (s), 1130 (m), 1078 (vs), 1059 (s), 1031 (s), 979 (s), 938 (s), 891 (s), 860 (m), 829 (m), 644 (m).

HRMS (EI) for C$_9$H$_{16}$IO$_2$ (282.0117): 282.0092.
2-(cis-2-iodocyclohexyl)-5,5-dimethyl-1,3-dioxane (148)

According to TP11, trans-2-(5,5-dimethyl-1,3-dioxane-2-yl)cyclohexan-1-ol (146) (2.57 g, 12.0 mmol) in THF (46 mL) was reacted with DCC·MeI (8.36 g, 24.0 mmol). The reaction mixture was heated to 50 °C for 24 h. Purification by column chromatography (SiO$_2$; Et$_2$O/n-pentane 1 : 30) furnished the title compound (2.31 g, 7.13 mmol, 59 %) as a colourless oil.

$^1$H-NMR (300 MHz, C$_6$D$_6$) $\delta$: 4.95 (s, 1H), 4.22 (d, $J = 7.5$ Hz, 1H), 3.42 (ddd, $J_1 = 18.0$ Hz, $J_2 = 10.9$ Hz, $J_3 = 2.9$ Hz, 2H), 3.23 (d, $J = 10.9$ Hz, 1H), 3.08 (d, $J = 10.9$ Hz, 1H), 1.93-1.98 (m, 2H), 1.69-1.84 (m, 1H), 1.48-1.58 (m, 2H), 1.22-1.36 (m, 2H), 1.13 (s, 2H), 1.05 (tt, $J = 13.2$ Hz, 2H), 0.78-0.86 (m, 1H), 0.29 (s, 3H).

$^{13}$C-NMR (75 MHz, C$_6$D$_6$) $\delta$: 106.7, 77.2, 77.1, 46.7, 40.9, 36.4, 30.2, 25.3, 24.0, 23.2, 22.8, 21.5.

MS (70 eV, EI) $m/z$ (%): 197 (46), 115 (64), 111 (25), 97 (34), 83 (100), 71 (26), 69 (96), 67 (36), 57 (54), 56 (31), 55 (86), 41 (35), 39 (50).

IR (ATR) $\tilde{\nu}$ (cm$^{-1}$): 2928 (s), 2851 (m), 2116 (vs), 1713 (w), 1450 (m), 1391 (m), 1360 (m), 1300 (m), 1257 (w), 1233 (w), 1166 (m), 1150 (m), 1099 (s), 1038 (s), 1022 (s), 993 (m), 976 (s), 948 (m), 892 (m), 864 (m), 834 (w), 786 (m), 645 (m).

HRMS (EI) for C$_{12}$H$_{21}$IO$_2$ (324.0586): 323.0482 [M-H$^-$].

4.3. Synthesis of EOM-Protected Decahydro-1-naphthalinol

(R)-diethyl(2-iodocyclohex-2-en-1-yl)phosphate (165) (Scheme 43)

A dry and argon-flushed 500 mL Schlenk-flask, equipped with a magnetic stirring bar and a septum was charged with a solution of (R)-2-iodocyclohex-2-enole (131) (18.7 g, 83.5 mmol) in CH$_2$Cl$_2$ (170 mL) and cooled 0 °C. N-Methylimidazole (NMI) (13.7 g, 13.3 mL, 167 mmol) was slowly added via syringe. After complete addition, the reaction mixture was
stirred for 1 h at that temperature before a solution of diethylchlorophosphate (14.4 g, 12.1 mL, 83.5 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature and stirred for additional 7 h. The reaction mixture was then quenched with H$_2$O (150 mL), phases were separated and the aqueous phase was extracted with CH$_2$Cl$_2$ (3 x 80 mL). The combined organic layers were washed with sat. aq. NaCl solution (100 mL) and dried over MgSO$_4$. The solvents were evaporated in vacuo and the residue was subjected to column chromatography (SiO$_2$; Et$_2$O) furnishing the title compound (21.3 g, 59.2 mmol, 71 %) as a colourless oil.

$^1$H-NMR (400 MHz, C$_6$D$_6$) $\delta$: 6.16 (t, $J = 3.7$ Hz, 1H), 4.91-4.95 (m, 1H), 4.05-4.14 (m, 2H), 3.84-3.93 (m, 2H), 1.28-1.57 (m, 6H), 1.06-1.11 (m, 3H), 0.96-1.01 (m, 3H).

$^{13}$C-NMR (101 MHz, C$_6$D$_6$) $\delta$: 143.7, 96.2 (d, $J = 10.4$ Hz), 78.0 (d, $J = 4.2$ Hz), 64.0 (d, $J = 5.4$ Hz), 63.5 (d, $J = 6.2$ Hz), 31.3, 29.0, 16.5, 16.3 (d, $J = 6.5$ Hz), 16.2 (d, $J = 6.9$ Hz).

MS (70 eV, EI) m/z (%): 234 (10), 233 (100), 205 (35), 177 (40), 155 (18), 127 (25), 99 (78), 97 (24), 81 (13), 80 (14), 79 (69), 78 (14), 77 (25).

HRMS (EI) for C$_{10}$H$_{18}$IO$_4$P (359.9987): 359.9973.

1-(S)-ethyl-4-(2-iodocyclohex-2-en-1-yl)butanoate (167)

\[
\begin{align*}
\text{Ph} & \quad \text{I} \\
\quad & \quad \text{OEt}
\end{align*}
\]

In a dry and argon-flushed 500 mL Schlenk-flask LiCl (10.2 g, 240 mmol) was dried under high vacuum at 500 °C for 20 min. After addition of Zn (39.2 g, 600 mmol) the mixture was dried for additional 30 min at 170 °C under high vacuum and then cooled to room temperature. Anhydrous THF (200 mL) was filled in followed by 1,2-dibromo ethane (1.88 g, 0.87 mL, 10.0 mmol) and trimethylsilylchloride (TMSCl) (4.35 g, 5.06 mL, 40.0 mmol). The reaction was initiated by carefully heating to a gentle reflux using a heat gun and a solution of dry ethyl-4-bromobutyrate (39.0 g, 28.7 mL, 200 mmol) was added dropwise. The reaction mixture was heated to 50 °C and stirred for 12 h. After completion of the zinc insertion the resulting organozinc reagent (106 mL, 0.66 M in THF, 70.0 mmol) was slowly dropped via a cannula to a cooled solution of CuCN2LiCl (70.0 mL, 1.0 M in THF, 70.0 mmol) at –30 °C. After 30 min of stirring a solution of (R)-diethyl(2-iodocyclohex-2-en-1-yl)phosphate (165)
(12.6 g, 35.0 mmol) in N-methylpyrrolidone (63 mL) was added dropwise and the reaction mixture was allowed to warm to room temperature and stirred for additional 12 h. The reaction mixture was then quenched with sat. aq. NH₄Cl solution (500 mL, mixed with 60 mL 30 % NH₃ solution) and further stirred until all copper salts were dissolved. The phases were separated, the aqueous phase was extracted with Et₂O (3 x 250 mL), the combined organic layers were washed with sat. aq. NaCl solution (250 mL) and dried over MgSO₄. The solvents were evaporated in vacuo and the residue was subjected to column chromatography (SiO₂; Et₂O/n-pentane 1 : 20) furnishing the title compound (10.2 g, 31.7 mmol, 91 %) as colourless oil.

**¹H-NMR (400 MHz, C₆D₆) δ:** 6.18 (dt, J₁ = 4.1 Hz, J₂ = 1.5 Hz, 1H), 3.95 (q, J = 7.2 Hz, 2H), 2.07 (t, J = 7.5 Hz, 2H), 1.53–1.79 (m, 4H), 1.12–1.46 (m, 7H), 0.97 (t, J = 7.1 Hz, 3H).

**¹³C-NMR (75 MHz, C₆D₆) δ:** 172.7, 138.8, 106.5, 60.0, 45.0, 34.4, 34.3, 29.5, 28.0, 22.5, 18.5, 14.3.

**MS (70 eV, EI) m/z (%):** 195 (65), 150 (25), 149 (77), 132 (10), 131 (57), 121 (33), 107 (100), 105 (12), 93 (19), 91 (24), 81 (12), 80 (18), 79 (63), 77 (21), 67 (18), 41 (16).

**IR (ATR) ν (cm⁻¹):** 2934 (m), 2860 (w), 1731 (vs), 1445 (w), 1373 (m), 1300 (w), 1243 (m), 1176 (s), 1138 (m), 1094 (m), 1034 (m), 963 (m), 927 (w), 863 (w), 802 (w), 724 (m).

**HRMS (EI) for C₁₂H₁₉IO₂:** 322.0430; 322.0448.

**3,4,4a,5,6,7-hexahydro-1(2H)-naphthalinone (164)**

A dry and argon-flushed 1 L Schlenk-flask, equipped with a dropping funnel and a magnetic stirring bar was charged with a solution of (S)-ethyl-4-(2-iodocyclohex-2-en-1-yl)butanoate (167) (8.05 g, 25.0 mmol) in THF (500 mL) and cooled to –100 °C. Trimethylsilylchloride (TMSCI) (8.15 g, 9.49 mL, 75.0 mmol) was slowly added via syringe. After complete addition the reaction mixture was stirred for 30 min at that temperature before a solution of tBuLi (34.2 mL, 1.68 M in THF, 57.5 mmol) was added dropwise. After stirring for 12 h at –70 °C, the reaction mixture was allowed to warm to 0 °C and stirred for additional 12 h. The reaction mixture was then quenched with sat. aq. NH₄Cl solution (330 mL), extracted with Et₂O (3 x 250 mL) and the combined organic layers were dried over MgSO₄. The solvents were partly evaporated in vacuo (> 500 mbar, 40 °C) and the remainder were removed under
high vacuum at 0 °C. Purification by column chromatography (SiO$_2$; Et$_2$O/n-pentane 1 : 6) furnished the title compound (3.40 g, 22.6 mmol, 90 %) as a pale yellow oil.

$^1$H-NMR (300 MHz, C$_6$D$_6$) $\delta$: 6.78-6.82 (m, 1H), 2.37-2.46 (m, 1H), 1.77-2.02 (m, 4H), 1.36-1.55 (m, 4H), 1.09-1.34 (m, 2H), 0.80-0.96 (m, 2H).

$^{13}$C-NMR (75 MHz, C$_6$D$_6$) $\delta$: 198.2, 139.9, 134.7, 40.2, 37.9, 31.7, 30.6, 26.1, 22.7, 21.8.

MS (70 eV, EI) m/z (%): 150 (68), 135 (11), 132 (21), 122 (34), 104 (17), 94 (67), 93 (22), 91 (21), 81 (10), 80 (16), 79 (100), 77 (20), 42 (10).

IR (ATR) $\tilde{\nu}$ (cm$^{-1}$): 2925 (m), 2859 (m), 1684 (vs), 1614 (vs), 1452 (m), 1412 (w), 1352 (w), 1262 (s), 1214 (s), 1180 (m), 1154 (w), 1123 (m), 1082 (w), 1036 (w), 1012 (w), 998 (w), 970 (w), 926 (m), 903 (w), 885 (m), 862 (w), 835 (m), 798 (m), 720 (w), 643 (m).

HRMS (EI) for C$_{10}$H$_{14}$O (150.1045): 150.1036.

1,2,3,4,4a,5,6,7-Octahydro-1-naphthalinol (168)

3,4,4a,5,6,7-hexahydro-1(2H)-naphthalinone (164) (3.15 g, 21.0 mmol) was added to a solution of CeCl$_3$·7H$_2$O (52.5 mL, 0.4 M in MeOH, 21.0 mmol) at 25 °C, followed by portionwise addition of NaBH$_4$ (794 mg, 21.0 mmol). The reaction mixture was stirred for 30 min and then quenched with sat. aq. NH$_4$Cl solution (100 mL). Phases were separated, the aqueous phase was extracted with Et$_2$O (3 x 180 mL) and the combined organic layers were dried over MgSO$_4$. Evaporation of the solvents in vacuo (> 200 mbar, 40 °C) furnished the title compound (2.88 g, 18.9 mmol, 90 %) as a colourless oil, which was used in the next step without further purification.

$^1$H-NMR (300 MHz, C$_6$D$_6$) $\delta$: 5.77-5.81 (m, 1H), 3.71-3.77 (m, 1H), 1.88-1.98 (m, 3H), 1.63-1.77 (m, 2H), 1.31-1.58 (m, 4H), 1.06-1.22 (m, 2H), 0.85-0.98 (m, 2H).

$^{13}$C-NMR (75 MHz, C$_6$D$_6$) $\delta$: 143.1, 116.1, 72.4, 37.6, 36.6, 35.1, 30.9, 25.6, 24.2, 21.6.

IR (ATR) $\tilde{\nu}$ (cm$^{-1}$): 2920 (vs), 2853 (s), 1447 (m), 1354 (m), 1330 (m), 1262 (w), 1138 (m), 1102 (s), 1074 (m), 1058 (s), 1024 (m), 958 (m), 923 (w), 851 (m), 816 (m), 767 (m), 651 (s).

MS (EI, 70 eV): m/z (%) = 152 (82), 134 (31), 124 (46), 123 (100), 119 (21), 110 (87), 109 (51), 97 (25), 95 (21), 93 (33), 92 (25), 91 (49), 81 (52), 79 (60), 77 (22), 67 (36), 41 (20).

HRMS (EI) for C$_{10}$H$_{16}$O (152.1201): 152.1199.
Experimental Section

1-(ethoxymethoxy)-1,2,3,4,4a,5,6,7-octahydronaphthaline (169)

In a dry and argon-flushed 250 mL Schlenk-flask, equipped with a magnetic stirring bar and a septum, 1,2,3,4,4a,5,6,7-octahydro-1-naphthalinol (168) (2.28 g, 15.0 mmol) was dissolved in CH₂Cl₂ (30 mL) and cooled to 0 °C. After addition of diisopropylethylamine (DIPEA) (3.88 g, 4.96 mL, 30.0 mmol) the reaction mixture was stirred for 30 min at 0 °C before ethoxymethylocid (EOMCl) (2.84 g, 2.79 mL, 30.0 mmol) was dropped. The resulting solution was allowed to reach room temperature and stirred for further 12 h. After completion of the reaction saturated aq. NaCl solution (150 mL) was added, the aqueous phase was extracted with Et₂O (3 x 150 mL) and the combined organic layers were dried over MgSO₄. The solvents were evaporated in vacuo and the residue was subjected to column chromatography (SiO₂; Et₂O/n-pentane 1 : 25) furnishing the title compound (3.03 g, 14.4 mmol, 96%) as a colourless oil.

¹H-NMR (400 MHz, C₆D₆) δ: 5.94-5.97 (m, 1H), 4.69 (q, J = 7.1 Hz, 2H), 3.90-3.94 (m, 1H), 3.55-3.63 (m, 1H), 3.41-3.49 (m, 1H), 2.02-2.08 (m, 1H), 1.92-1.98 (m, 2H), 1.62-1.75 (m, 2H), 1.46-1.58 (m, 2H), 1.29-1.45 (m, 3H), 1.11-1.24 (m, 3H), 1.07 (t, J = 7.1 Hz, 3H).

¹³C-NMR (101 MHz, C₆D₆) δ: 140.7, 116.9, 94.0, 77.4, 63.3, 36.8, 35.2, 35.1, 30.8, 25.6, 24.3, 21.4, 15.4.

IR (ATR) ν (cm⁻¹): 2974 (w), 2924 (m), 2856 (m), 1447 (w), 1391 (w), 1182 (w), 1134 (m), 1113 (m), 1098 (s), 1037 (vs), 1014 (s), 947 (w), 867 (w), 847 (w), 818 (w), 629 (w).

MS (EI, 70 eV): m/z (%) = 210 (63), 181 (50), 164 (100), 151 (55), 136 (84), 136 (65), 135 (99), 134 (58), 133 (49), 123 (93), 121 (57), 110 (75), 107 (43), 105 (30), 93 (38), 91 (64), 79 (39), 59 (30).

HRMS (EI) for C₁₃H₂₂O₂: 210.1620; 210.1615.
4.4. Diastereoselective Cross-Coupling with Cyclohexylzinc Reagents Produced via Hydroboration and Subsequent Boron-Zinc Exchange (Table 7)

2-(trans-2-(4-methoxyphenyl)cyclohexyl)-1,3-dioxolane

According to TP5, 2-cyclohex-1-enyl-1,3-dioxolane (138) (154 mg, 1.00 mmol) was reacted via hydroboration with Et₂BH, followed by a boron-zinc exchange and subsequent cross-coupling (25 °C, 12 h) with 4-iodoanisole (702 mg, 3.00 mmol). Purification by column chromatography (SiO₂; Et₂O/n-pentane 1 : 10) furnished the title compound (187 mg, 0.71 mmol, 71 %) as a colourless solid.

d.r.: 87 : 13.
m.p.: 52.1 °C.

\[ \text{δ: } 7.07 (d, J = 9.7 \text{ Hz}, 2H), 6.75 (d, J = 11.0 \text{ Hz}, 2H), 4.62 (d, J = 5.2 \text{ Hz}, 1H), 3.37-3.42 (m, 2H), 3.29 (s, 3H), 3.14-3.20 (m, 2H), 2.66 (td, J₁ = 11.7 \text{ Hz}, J₂ = 3.5 \text{ Hz}, 1H), 2.09-2.15 (m, 1H), 1.98 (ddt, J₁ = 11.5 \text{ Hz}, J₂ = 3.5 \text{ Hz}, J₃ = 1.9 \text{ Hz}, 1H), 1.62-1.66 (m, 1H), 1.40-1.52 (m, 2H), 1.23-1.32 (m, 4H). \]

\[ \text{δ: } 158.6, 137.9, 128.8, 114.2, 104.4, 65.1, 65.0, 54.7, 46.3, 45.9, 36.5, 27.2, 26.1, 24.2. \]

\[ \text{MS (70 eV, EI) } m/z (%): 262 [M⁺] (25), 201 (13), 200 (48), 154 (69), 125 (12), 121 (24), 73 (100). \]

\[ \text{IR (ATR) } \tilde{\nu} (\text{cm}⁻¹): 2927 (m), 2872 (m), 1609 (m), 1511 (s), 1448 (m), 1306 (w), 1282 (m), 1245 (s), 1177 (s), 1157 (s), 1115 (s), 1097 (m), 1034 (vs), 989 (m), 946 (s), 885 (m), 824 (s), 814 (s), 756 (m), 690 (m). \]

\[ \text{HRMS (EI) for C₁₆H₂₂O₃ (262.1569): 262.1570.} \]

2-(trans-2-(4-methoxyphenyl)cyclohexyl)-5,5-dimethyl-1,3-dioxane
According to **TP5**, 2-cyclohex-1-enyl-5,5-dimethyl-1,3-dioxane (139) (196 mg, 1.00 mmol) was reacted *via* hydroboration with Et₂BH, followed by a boron-zinc exchange and subsequent cross-coupling (25 °C, 12 h) with 4-iodoanisole (702 mg, 3.00 mmol). Purification by column chromatography (SiO₂; Et₂O/n-pentane 1 : 20) furnished the title compound (171 mg, 0.56 mmol, 56 %) as a colourless solid.

d.r.: 98 : 2.

**m.p.:** 60.7 °C.

**δ** H-NMR (400 MHz, C₆D₆): 7.09 (d, J = 8.6 Hz, 2H), 6.81 (d, J = 8.8 Hz, 2H), 4.11 (d, J = 2.1 Hz, 1H), 3.38 (dd, J₁ = 10.7 Hz, J₂ = 2.9 Hz, 1H), 3.31 (s, 3H), 3.28 (dd, J₁ = 10.8 Hz, J₂ = 2.8 Hz, 1H), 2.92 (d, J = 10.7 Hz, 1H), 2.85 (d, J = 10.7 Hz, 1H), 2.70 (td, J₁ = 11.7 Hz, J₂ = 3.5 Hz, 1H), 2.38-2.42 (m, 1H), 1.89 (tt, J₁ = 11.5 Hz, J₂ = 2.6 Hz, 1H), 1.73-1.81 (m, 2H), 1.64-1.67 (m, 1H), 1.22-1.45 (m, 4H), 1.09 (s, 3H), 0.15 (s, 3H).

**13C-NMR** (101 MHz, C₆D₆): 158.6, 138.3, 128.8, 114.2, 101.8, 76.9, 54.7, 48.1, 45.1, 36.0, 30.0, 27.3, 26.4, 24.9, 23.0, 21.4.

**MS (70 eV, EI) m/z (%):** 304 (13), 200 (41), 196 (47), 147 (10), 121 (26), 115 (100), 69 (48).

**IR (ATR) V~ (cm⁻¹):** 2923 (s), 2851 (m), 1609 (w), 1512 (s), 1460 (m), 1394 (m), 1284 (m), 1247 (vs), 1176 (m), 1156 (s), 1114 (vs), 1077 (s), 1039 (s), 1026 (s), 989 (s), 967 (s), 822 (s), 814 (s).

**HRMS (EI) for C₁₉H₂₈O₃ (304.2038):** 304.2041.

**ethyl-4-(trans-2-(1,3-dioxolane-2-yl)cyclohexyl)benzoate**

According to **TP5**, 2-cyclohex-1-enyl-1,3-dioxolane (138) (154 mg, 1.00 mmol) was reacted *via* hydroboration with Et₂BH, followed by a boron-zinc exchange and subsequent cross-coupling (–10 °C, 12 h; then 0 °C, 12 h) with ethyl-4-iodobenzoate (828 mg, 3.00 mmol). Purification by column chromatography (SiO₂; Et₂O/n-pentane 1 : 10 then 1 : 1) furnished the title compound (123 mg, 0.71 mmol, 40 %) as a colourless solid.

d.r.: 80 : 20.

**m.p.:** 69.3 °C.

**δ** H-NMR (400 MHz, C₆D₆): 8.13 (d, J = 8.4 Hz, 2H), 6.97 (d, J = 8.2 Hz, 2H), 4.11 (q, J = 7.0 Hz, 2H), 3.33-3.36 (m, 2H), 2.86-2.99 (m, 3H), 2.74-2.78 (m, 1H), 2.23 (td, J₁ = 11.4 Hz,
C. Experimental Section

$J_2 = 3.1 \text{ Hz}, 1H), 1.82-1.87 (m, 1H), 1.64-1.67 (m, 1H), 1.40-1.52 (m, 2H), 1.12-1.26 (m, 4H), 0.99 (t, J = 7.1 \text{ Hz}, 3H).

$^1$H-NMR (400 MHz, C$_6$D$_6$) $\delta$: 7.16-7.21 (m, 4H), 7.04-7.09 (m, 1H), 4.06 (d, $J = 2.1 \text{ Hz}, 1H), 3.35 (dd, J_1 = 10.7 \text{ Hz}, J_2 = 2.9 \text{ Hz}, 1H), 3.25 (dd, J_1 = 10.8 \text{ Hz}, J_2 = 2.8 \text{ Hz}, 1H), 2.86 (d, J = 10.9 \text{ Hz}, 1H), 2.79 (d, J = 10.7 \text{ Hz}, 1H), 2.72 (td, J_1 = 11.8 \text{ Hz}, J_2 = 3.4 \text{ Hz}, 1H), 2.37-2.40 (m, 1H), 1.92 (tt, J_1 = 11.4 \text{ Hz}, J_2 = 2.7 \text{ Hz}, 1H), 1.72-1.79 (m, 2H), 1.59-1.64 (m, 1H), 1.23-1.44 (m, 4H), 1.00 (s, 3H), 0.11 (s, 3H).

$^1$C-NMR (101 MHz, C$_6$D$_6$) $\delta$: 146.4, 128.7, 126.4, 101.6, 76.8, 47.7, 46.0, 35.8, 29.9, 27.2, 26.3, 24.8, 23.0, 21.3.

MS (70 eV, EI) m/z (%): 273 (13), 196 (72), 170 (13), 167 (15), 159 (10), 117 (15), 116 (21), 115 (100), 91 (51), 69 (90).

IR (ATR) $\tilde{\nu}$ (cm$^{-1}$): 2926 (m), 2851 (m), 1451 (m), 1393 (m), 1153 (m), 1115 (vs), 1088 (m), 1078 (m), 1043 (m), 1025 (m), 1017 (m), 991 (m), 967 (m), 931 (m), 756 (s), 699 (vs), 644 (w).

According to TP5, 2-cyclohex-1-enyl-5,5-dimethyl-1,3-dioxane (139) (196 mg, 1.00 mmol) was reacted via hydroboration with Et$_2$BH, followed by a boron-zinc exchange and subsequent cross-coupling (25 °C, 12 h) with iodobenzene (612 mg, 3.00 mmol). Purification by column chromatography (SiO$_2$; Et$_2$O/n-pentane 1 : 20 then 1 : 10) furnished the title compound (185 mg, 0.67 mmol, 67 %) as a colourless oil.

d.r.: 98 : 2.

$^1$H-NMR (400 MHz, C$_6$D$_6$) $\delta$: 7.16-7.21 (m, 4H), 7.04-7.09 (m, 1H), 4.06 (d, $J = 2.1 \text{ Hz}, 1H), 3.35 (dd, J_1 = 10.7 \text{ Hz}, J_2 = 2.9 \text{ Hz}, 1H), 3.25 (dd, J_1 = 10.8 \text{ Hz}, J_2 = 2.8 \text{ Hz}, 1H), 2.86 (d, J = 10.9 \text{ Hz}, 1H), 2.79 (d, J = 10.7 \text{ Hz}, 1H), 2.72 (td, J_1 = 11.8 \text{ Hz}, J_2 = 3.4 \text{ Hz}, 1H), 2.37-2.40 (m, 1H), 1.92 (tt, J_1 = 11.4 \text{ Hz}, J_2 = 2.7 \text{ Hz}, 1H), 1.72-1.79 (m, 2H), 1.59-1.64 (m, 1H), 1.23-1.44 (m, 4H), 1.00 (s, 3H), 0.11 (s, 3H).

$^1$C-NMR (101 MHz, C$_6$D$_6$) $\delta$: 146.4, 128.7, 126.4, 101.6, 76.8, 47.7, 46.0, 35.8, 29.9, 27.2, 26.3, 24.8, 23.0, 21.3.

MS (70 eV, EI) m/z (%): 273 (13), 196 (72), 170 (13), 167 (15), 159 (10), 117 (15), 116 (21), 115 (100), 91 (51), 69 (90).

IR (ATR) $\tilde{\nu}$ (cm$^{-1}$): 2926 (m), 2851 (m), 1451 (m), 1393 (m), 1153 (m), 1115 (vs), 1088 (m), 1078 (m), 1043 (m), 1025 (m), 1017 (m), 991 (m), 967 (m), 931 (m), 756 (s), 699 (vs), 644 (w).
4.5. Diastereoselective Csp\(^3\)-Csp\(^2\) Cross-Coupling with Cyclohexylzinc Iodides (Table 8)

2-(trans-2-(4-methoxyphenyl)cyclohexyl)-1,3-dioxolane

According to TP6, 2-(cis-2-iodocyclohexyl)-1,3-dioxolane (147) (282 mg, 1.00 mmol) was transformed via zinc insertion to the corresponding organozinc reagent followed by subsequent cross-coupling (25 °C, 12 h) with 4-iodoanisole (164 mg, 0.70 mmol). Purification by column chromatography (SiO\(_2\); Et\(_2\)O/n-pentane 1 : 10) furnished the title compound (81 mg, 0.31 mmol, 44 %) as a colourless solid.

d.r.: 93 : 7.

m.p.: 51.6 °C.

\(^1\)H-NMR (400 MHz, C\(_6\)D\(_6\)) \(\delta\): 7.07 (d, \(J = 9.7\) Hz, 2H), 6.75 (d, \(J = 11.0\) Hz, 2H), 4.62 (d, \(J = 5.2\) Hz, 1H), 3.37-3.42 (m, 2H), 3.29 (s, 3H), 3.14-3.20 (m, 2H), 2.66 (td, \(J_1 = 11.7\) Hz, \(J_2 = 3.5\) Hz, 1H), 2.09-2.15 (m, 1H), 1.98 (ddt, \(J_1 = 11.5\) Hz, \(J_2 = 3.5\) Hz, \(J_3 = 1.9\) Hz, 1H), 1.62-1.66 (m, 1H), 1.40-1.52 (m, 2H), 1.23-1.32 (m, 4H).

\(^13\)C-NMR (101 MHz, C\(_6\)D\(_6\)) \(\delta\): 158.6, 137.9, 128.8, 114.2, 104.4, 65.1, 65.0, 54.7, 46.3, 45.9, 36.5, 27.2, 26.1, 24.2.

MS (70 eV, EI) \(m/z\) (%): 262 [M\(^+\)] (25), 201 (13), 200 (48), 154 (69), 125 (12), 121 (24), 73 (100).

IR (ATR) \(\tilde{\nu}\) (cm\(^{-1}\)): 2927 (m), 2872 (m), 1609 (m), 1511 (s), 1448 (m), 1306 (w), 1282 (m), 1245 (s), 1177 (s), 1157 (s), 1115 (s), 1097 (m), 1034 (vs), 989 (m), 946 (s), 885 (m), 824 (s), 814 (s), 756 (m), 690 (m).

HRMS (EI) for C\(_{16}\)H\(_{22}\)O\(_3\) (262.1569): 262.1573.
2-(trans-2-(4-methoxyphenyl)cyclohexyl)–5,5-dimethyl-1,3-dioxane

According to TP6, 2-(cis-2-iodocyclohexyl)-5,5-dimethyl-1,3-dioxane (148) (324 mg, 1.00 mmol) was transformed via zinc insertion to the corresponding organozinc reagent followed by subsequent cross-coupling (25 °C, 12 h) with 4-iodoanisole (164 mg, 0.70 mmol). Purification by column chromatography (SiO$_2$; Et$_2$O/n-pentane 1 : 20) furnished the title compound (100 mg, 0.33 mmol, 47 %) as a colourless solid.

d.r.: 98 : 2.
m.p.: 56.1 °C.

$^1$H-NMR (400 MHz, C$_6$D$_6$) δ: 7.09 (d, $J = 8.6$ Hz, 2H), 6.81 (d, $J = 8.8$ Hz, 2H), 4.11 (d, $J = 2.1$ Hz, 1H), 3.38 (dd, $J_1 = 10.7$ Hz, $J_2 = 2.9$ Hz, 1H), 3.31 (s, 3H), 3.28 (dd, $J_1 = 10.8$ Hz, $J_2 = 2.8$ Hz, 1H), 2.92 (d, $J = 10.7$ Hz, 1H), 2.85 (d, $J = 10.7$ Hz, 1H), 2.70 (td, $J_1 = 11.7$ Hz, $J_2 = 3.5$ Hz, 1H), 2.38-2.42 (m, 1H), 1.89 (tt, $J_1 = 11.5$ Hz, $J_2 = 2.6$ Hz, 1H), 1.73-1.81 (m, 2H), 1.64-1.67 (m, 1H), 1.22-1.45 (m, 4H), 1.09 (s, 3H), 0.15 (s, 3H).

$^{13}$C-NMR (101 MHz, C$_6$D$_6$) δ: 158.6, 138.3, 128.8, 114.2, 101.8, 76.9, 54.7, 48.1, 45.1, 36.0, 30.0, 27.3, 26.4, 24.9, 23.0, 21.4.

MS (70 eV, EI) m/z (%): 304 (9), 200 (29), 196 (37), 121 (19), 115 (100), 69 (39).

IR (ATR) $\tilde{\nu}$ (cm$^{-1}$): 2927 (m), 2850 (m), 1609 (w), 1511 (s), 1456 (m), 1394 (m), 1363 (w), 1303 (w), 1284 (m), 1246 (vs), 1175 (m), 1154 (s), 1114 (vs), 1076 (m), 1037 (s), 1026 (s), 990 (s), 967 (s), 932 (m), 910 (m), 885 (w), 822 (s), 798 (m), 754 (m), 646 (m).

HRMS (EI) for C$_{19}$H$_{28}$O$_3$ (304.2038): 304.2044.

methyl-4-(trans-2-(1,3-dioxolan-2-yl)cyclohexyl)benzoate

According to TP6, 2-(cis-2-iodocyclohexyl)-1,3-dioxolane (147) (282 mg, 1.00 mmol) was transformed via zinc insertion to the corresponding organozinc reagent followed by subsequent cross-coupling (–10 °C, 12 h) with methyl-4-iodobenzoate (183 mg, 0.70 mmol).
Purification by column chromatography (SiO$_2$; Et$_2$O/n-pentane 1 : 10 then 1 : 1) furnished the title compound (122 mg, 0.42 mmol, 60 %) as a colourless solid.

d.r.: 81 : 19.

m.p.: 56.9 °C.

$^1$H-NMR (400 MHz, C$_6$D$_6$) δ: 8.11 (d, $J = 8.5$ Hz, 2H), 7.10 (d, $J = 8.3$ Hz, 2H), 4.46 (d, $J = 1.7$ Hz, 1H), 3.49 (s, 3H), 3.27-3.42 (m, 2H), 3.05-3.19 (m, 2H), 2.63 (dt, $J_1 = 11.5$ Hz, $J_2 = 3.6$ Hz, 1H), 2.03-2.15 (m, 1H), 1.94 (ddt, $J_1 = 11.5$ Hz, $J_2 = 3.5$ Hz, $J_3 = 1.9$ Hz, 1H), 1.52-1.67 (m, 2H), 1.34-1.47 (m, 1H), 1.12-1.31 (m, 4H).

$^{13}$C-NMR (175 MHz, C$_6$D$_6$) δ: 166.7, 151.4, 130.1, 129.7, 128.8, 128.7, 104.4, 64.9, 51.4, 46.6, 45.7, 35.7, 26.9, 25.9, 24.3.

MS (70 eV, EI) m/z (%): 259 (3), 154 (22), 149 (3), 129 (3), 115 (3), 99 (3), 74 (3), 73 (100), 45 (7).

IR (ATR) $\tilde{\nu}$ (cm$^{-1}$): 2931 (m), 2853 (m), 1712 (vs), 1608 (m), 1573 (w), 1432 (m), 1314 (w), 1272 (vs), 1184 (m), 1155 (m), 1110 (s), 1096 (s), 1053 (m), 1040 (m), 1018 (m), 990 (m), 948 (s), 885 (w), 852 (w), 838 (w), 806 (w), 769 (s), 709 (s), 670 (w).

HRMS (EI) for C$_{17}$H$_{22}$O$_4$ (290.1518): 290.1493.

2-(trans-2-(3-(trifluoromethyl)phenyl)cyclohexyl)-1,3-dioxolane

According to TP6, 2-(cis-2-iodocyclohexyl)-1,3-dioxolane (147) (282 mg, 1.00 mmol) was transformed via zinc insertion to the corresponding organozinc reagent followed by subsequent cross-coupling (−10 °C, 12 h) with 1-iodo-3-(trifluormethyl)benzene (190 mg, 0.70 mmol). Purification by column chromatography (SiO$_2$; Et$_2$O/n-pentane 1 : 10) furnished the title compound (166 mg, 0.55 mmol, 79 %) as a colourless oil.

d.r.: 90 : 10.

$^1$H-NMR (400 MHz, C$_6$D$_6$) δ: 7.52 (s, 1H), 7.21 (d, $J = 7.6$ Hz, 1H), 7.06 (d, $J = 8.2$ Hz, 1H), 6.90 (t, $J = 7.7$ Hz, 1H), 4.35 (d, $J = 2.2$ Hz, 1H), 3.18-3.36 (m, 2H), 2.97-3.09 (m, 2H), 2.54 (td, $J_1 = 11.5$ Hz, $J_2 = 2.8$ Hz, 1H), 1.97-2.02 (m, 1H), 1.83 (ddt, $J_1 = 11.5$ Hz, $J_2 = 3.3$ Hz, $J_3 = 2.2$ Hz, 1H), 1.66-1.70 (m, 1H), 1.48-1.54 (m, 2H), 1.23-1.32 (m, 4H).

$^{13}$C-NMR (101 MHz, C$_6$D$_6$) δ: 147.2, 131.3, 130.8 (q, $J = 31.5$ Hz), 129.0, 124.8 (d, $J = 3.1$ Hz), 123.1 (q, $J = 3.9$ Hz), 104.3, 65.0, 64.9, 46.4, 45.8, 35.8, 26.8, 25.8, 24.5.
C. Experimental Section

**IR (ATR) \( \tilde{\nu} \) (cm\(^{-1}\))**: 2926 (m), 2855 (w), 1450 (w), 1328 (s), 1191 (w), 1159 (s), 1119 (vs), 1089 (m), 1074 (s), 1040 (m), 992 (w), 949 (m), 889 (w), 799 (m), 703 (m), 664 (m).

**HRMS (EI) for C\(_{16}\)H\(_{19}\)F\(_3\)O\(_2\) (300.1337): 300.1328.**

2-(trans-2-phenylcyclohexyl)-5,5-dimethyl-1,3-dioxane

![Chemical Structure](image)

According to TP6, 2-(cis-2-iodocyclohexyl)-5,5-dimethyl-1,3-dioxane (148) (324 mg, 1.00 mmol) was transformed via zinc insertion to the corresponding organozinc reagent followed by subsequent cross-coupling (−25 °C, 12 h; then −10 °C, 12 h) with iodobenzene (143 mg, 0.70 mmol). Purification by column chromatography (SiO\(_2\); Et\(_2\)O/n-pentane 1 : 20) furnished the title compound (158 mg, 0.58 mmol, 83 %) as a colourless oil.

**d.r.: > 99 : 1.**

**\(^1\)H-NMR (400 MHz, C\(_6\)D\(_6\))  \( \delta \):** 7.16-7.21 (m, 4H), 7.04-7.09 (m, 1H), 4.06 (d,  \( J = 2.1 \) Hz, 1H), 3.35 (dd,  \( J_1 = 10.7 \) Hz,  \( J_2 = 2.9 \) Hz, 1H), 3.25 (dd,  \( J_1 = 10.8 \) Hz,  \( J_2 = 2.8 \) Hz, 1H), 2.86 (d,  \( J = 10.9 \) Hz, 1H), 2.79 (d,  \( J = 10.7 \) Hz, 1H), 2.72 (td,  \( J_1 = 11.8 \) Hz,  \( J_2 = 3.4 \) Hz, 1H), 2.37-2.40 (m, 1H), 1.92 (tt,  \( J_1 = 11.4 \) Hz,  \( J_2 = 2.7 \) Hz, 1H), 1.72-1.79 (m, 2H), 1.59-1.64 (m, 1H), 1.23-1.44 (m, 4H), 1.00 (s, 3H), 0.11 (s, 3H).

**\(^{13}\)C-NMR (101 MHz, C\(_6\)D\(_6\))  \( \delta \):** 146.4, 128.7, 126.4, 101.6, 76.8, 47.7, 46.0, 35.8, 29.9, 27.2, 26.3, 24.8, 23.0, 21.3.

**MS (70 eV, EI) m/z (%):** 273 (13), 196 (72), 170 (13), 167 (15), 159 (10), 117 (15), 116 (21), 115 (100), 91 (51), 69 (90).

**IR (ATR) \( \tilde{\nu} \) (cm\(^{-1}\)):** 2926 (m), 2851 (m), 1451 (m), 1393 (m), 1153 (m), 1115 (vs), 1088 (m), 1078 (m), 1043 (m), 1025 (m), 1017 (m), 991 (m), 967 (m), 931 (m), 756 (s), 699 (vs), 644 (w).

**HRMS (EI) for C\(_{18}\)H\(_{26}\)O\(_2\) (274.1933): 274.1926.**
4.6. Typical Procedure 12: Enantioselective Hydroboration/ Boron-Zinc Exchange with Subsequent Cross-Coupling (TP12) (Table 9)

In a dry and argon-flushed 25 mL Schlenk-flask, equipped with a magnetic stirring bar and a septum was placed freshly prepared (–)-lpcBH$_2$ (1.20 mL, 1.0 M in THF, 1.2 mmol, 1.2 equiv.) and cooled to -25 °C. A 1.0 M solution of the respective cyclohexenyl derivative (1.00 mmol, 1.0 equiv.) in THF was added dropwise within 1 h and the resulting mixture was stirred for additional 48 h at that temperature. After complete hydroboration it was allowed to warm to room temperature and concentrated in vacuo (0.1 mm Hg, 25 °C, 2 h). Et$_2$BH (0.69 mL, 7.3 M in Me$_2$S, 5.00 mmol, 5.0 equiv.) was added and the mixture was heated to 50 °C for 12 h. The reaction mixture was then concentrated (0.1 mm Hg, 25 °C, 2 h), Et$_2$Zn (0.51 mL 5.00 mmol, 5.0 equiv.) was added dropwise via syringe and stirring was continued for 12 h at room temperature. After determination of a boron-zinc exchange > 85 % by GC-analysis of an oxidated aliquot (3 M NaOH, 30 % H$_2$O$_2$) the reaction mixture was again concentrated (0.1 mm Hg, 25 °C, 1 h), the grey-black residue redissolved in THF (2 mL) and then added dropwise to a mixture of the respective electrophile (3.00 mmol, 3.0 equiv.) Pd(db)$_2$ (11.5 mg, 0.02 mmol, 2.0 mol%) und S-Phos (8.20 mg, 0.02 mmol, 2.0 mol%) in THF (3 mL) at the indicated temperature. After stirring for the indicated time and at the indicated temperature, the mixture was quenched with sat. aq. NH$_4$Cl solution (10 mL), extracted with Et$_2$O (3 x 20 mL) and the combined organic layers were dried over MgSO$_4$. The solvents were removed in vacuo and the crude product was purified by column chromatography (SiO$_2$).

chiral 2-(trans-2-(4-methoxyphenyl)cyclohexyl)-1,3-dioxolane

According to TP12, 2-cyclohex-1-enyl-1,3-dioxolane (138) (154 mg, 1.00 mmol) was reacted via asymmetric hydroboration with (–)-IpcBH$_2$, followed by a boron-zinc exchange and subsequent cross-coupling (25 °C, 12 h) with 4-iodoanisole (702 mg, 3.00 mmol). Purification by column chromatography (SiO$_2$; Et$_2$O/n-pentane 1 : 10 then 1 : 1) furnished the title compound (103 mg, 0.39 mmol, 39 %) as a colourless solid.

d.r.: > 99 : 1.
Experimental Section

m.p.: 52.0 °C.

\(^1\)H-NMR (400 MHz, C\(_6\)D\(_6\)) \(\delta\): 7.07 (d, \(J = 9.7\) Hz, 2H), 6.75 (d, \(J = 11.0\) Hz, 2H), 4.62 (d, \(J = 5.2\) Hz, 1H), 3.37-3.42 (m, 2H), 3.29 (s, 3H), 3.14-3.20 (m, 2H), 2.66 (td, \(J_1 = 11.7\) Hz, \(J_2 = 3.5\) Hz, 1H), 2.09-2.15 (m, 1H), 1.98 (td, \(J_1 = 11.5\) Hz, \(J_2 = 3.5\) Hz, \(J_3 = 1.9\) Hz, 1H), 1.62-1.66 (m, 1H), 1.40-1.52 (m, 2H), 1.23-1.32 (m, 4H).

\(^1\)H-NMR (400 MHz, C\(_6\)D\(_6\)) \(\delta\): 7.09 (d, \(J = 8.6\) Hz, 2H), 6.81 (d, \(J = 8.8\) Hz, 2H), 4.11 (d, \(J = 2.1\) Hz, 1H), 3.38 (dd, \(J_1 = 10.7\) Hz, \(J_2 = 2.9\) Hz, 1H), 3.31 (s, 3H), 3.28 (dd, \(J_1 = 10.8\) Hz, \(J_2 = 2.8\) Hz, 1H), 2.92 (d, \(J = 10.7\) Hz, 1H), 2.85 (d, \(J = 10.7\) Hz, 1H), 2.70 (td, \(J_1 = 11.7\) Hz, \(J_2 = 3.5\) Hz, 1H), 2.38-2.42 (m, 1H), 1.89 (tt, \(J_1 = 11.5\) Hz, \(J_2 = 2.6\) Hz, 1H), 1.73-1.81 (m, 2H), 1.64-1.67 (m, 1H), 1.22-1.45 (m, 4H), 1.09 (s, 3H), 0.15 (s, 3H).

\(^\text{13}\)C-NMR (101 MHz, C\(_6\)D\(_6\)) \(\delta\): 158.6, 138.3, 128.8, 114.2, 101.8, 76.9, 54.7, 48.1, 45.1, 36.0, 30.0, 27.3, 26.4, 24.9, 23.0, 21.4.

HRMS (EI) for C\(_{16}\)H\(_{22}\)O\(_3\) (262.1569): 262.1553.

According to TP12, 2-cyclohex-1-enyl-5,5-dimethyl-1,3-dioxane (139) (196 mg, 1.00 mmol) was reacted via asymmetric hydroboration with (−)-IpcBH\(_2\), followed by a boron-zinc exchange and subsequent cross-coupling (25 °C, 12 h) with 4-iodoanisole (702 mg, 3.00 mmol). Purification by column chromatography (SiO\(_2\); Et\(_2\)O/n-pentane 1 : 20) furnished the title compound (251 mg, 0.82 mmol, 82 %) as a colourless solid.

d.r.: > 99 : 1.

m.p.: 56.0 °C.

\(^1\)H-NMR (400 MHz, C\(_6\)D\(_6\)) \(\delta\): 7.09 (d, \(J = 8.6\) Hz, 2H), 6.81 (d, \(J = 8.8\) Hz, 2H), 4.11 (d, \(J = 2.1\) Hz, 1H), 3.38 (dd, \(J_1 = 10.7\) Hz, \(J_2 = 2.9\) Hz, 1H), 3.31 (s, 3H), 3.28 (dd, \(J_1 = 10.8\) Hz, \(J_2 = 2.8\) Hz, 1H), 2.92 (d, \(J = 10.7\) Hz, 1H), 2.85 (d, \(J = 10.7\) Hz, 1H), 2.70 (td, \(J_1 = 11.7\) Hz, \(J_2 = 3.5\) Hz, 1H), 2.38-2.42 (m, 1H), 1.89 (tt, \(J_1 = 11.5\) Hz, \(J_2 = 2.6\) Hz, 1H), 1.73-1.81 (m, 2H), 1.64-1.67 (m, 1H), 1.22-1.45 (m, 4H), 1.09 (s, 3H), 0.15 (s, 3H).

\(^\text{13}\)C-NMR (101 MHz, C\(_6\)D\(_6\)) \(\delta\): 158.6, 138.3, 128.8, 114.2, 101.8, 76.9, 54.7, 48.1, 45.1, 36.0, 30.0, 27.3, 26.4, 24.9, 23.0, 21.4.

HRMS (EI) for C\(_{16}\)H\(_{22}\)O\(_3\) (262.1569): 262.1553.

chiral 2-(trans-2-(4-methoxyphenyl)cyclohexyl)-5,5-dimethyl-1,3-dioxane

![Chemical Structure](image)

According to TP12, 2-cyclohex-1-enyl-5,5-dimethyl-1,3-dioxane (139) (196 mg, 1.00 mmol) was reacted via asymmetric hydroboration with (−)-IpcBH\(_2\), followed by a boron-zinc exchange and subsequent cross-coupling (25 °C, 12 h) with 4-iodoanisole (702 mg, 3.00 mmol). Purification by column chromatography (SiO\(_2\); Et\(_2\)O/n-pentane 1 : 20) furnished the title compound (251 mg, 0.82 mmol, 82 %) as a colourless solid.

d.r.: > 99 : 1.

m.p.: 56.0 °C.

\(^1\)H-NMR (400 MHz, C\(_6\)D\(_6\)) \(\delta\): 7.09 (d, \(J = 8.6\) Hz, 2H), 6.81 (d, \(J = 8.8\) Hz, 2H), 4.11 (d, \(J = 2.1\) Hz, 1H), 3.38 (dd, \(J_1 = 10.7\) Hz, \(J_2 = 2.9\) Hz, 1H), 3.31 (s, 3H), 3.28 (dd, \(J_1 = 10.8\) Hz, \(J_2 = 2.8\) Hz, 1H), 2.92 (d, \(J = 10.7\) Hz, 1H), 2.85 (d, \(J = 10.7\) Hz, 1H), 2.70 (td, \(J_1 = 11.7\) Hz, \(J_2 = 3.5\) Hz, 1H), 2.38-2.42 (m, 1H), 1.89 (tt, \(J_1 = 11.5\) Hz, \(J_2 = 2.6\) Hz, 1H), 1.73-1.81 (m, 2H), 1.64-1.67 (m, 1H), 1.22-1.45 (m, 4H), 1.09 (s, 3H), 0.15 (s, 3H).

\(^\text{13}\)C-NMR (101 MHz, C\(_6\)D\(_6\)) \(\delta\): 158.6, 138.3, 128.8, 114.2, 101.8, 76.9, 54.7, 48.1, 45.1, 36.0, 30.0, 27.3, 26.4, 24.9, 23.0, 21.4.

HRMS (EI) for C\(_{16}\)H\(_{22}\)O\(_3\) (262.1569): 262.1553.
IR (ATR) $\tilde{v}$ (cm$^{-1}$): 2923 (s), 2851 (m), 1609 (w), 1512 (s), 1460 (m), 1394 (m), 1284 (m), 1247 (vs), 1176 (m), 1156 (s), 1114 (vs), 1077 (s), 1039 (s), 1026 (s), 989 (s), 967 (s), 822 (s), 814 (s).

HRMS (EI) for C$_{19}$H$_{28}$O$_3$ (304.2038): 304.2035.

Enantiomeric purity: 73 % ee.

HPLC: Column: AD; n-Heptan : iPrOH: 100 : 0; flux: 0.2 mL/ min.

**chiral ethyl-4-(trans-2-(1,3-dioxolan-2-yl)cyclohexyl)benzoate**

According to TP12, 2-cyclohex-1-enyl-1,3-dioxolane (138) (154 mg, 1.00 mmol) was reacted via asymmetric hydroboration with (–)-IpcBH$_2$, followed by a boron-zinc exchange and subsequent cross-coupling (–5 °C, 12 h) with ethyl-4-iodobenzoate (828 mg, 3.00 mmol). Purification by column chromatography (SiO$_2$: Et$_2$O/n-pentane 1 : 10 then 1 : 1) furnished the title compound (96.0 mg, 0.32 mmol, 32 %) as a colourless oil.

d.r.: > 99 : 1.

$^1$H-NMR (400 MHz, C$_6$D$_6$) δ: 8.13 (d, $J = 8.4$ Hz, 2H), 6.97 (d, $J = 8.2$ Hz, 2H), 4.11 (q, $J = 7.0$ Hz, 2H), 3.33-3.36 (m, 2H), 2.86-2.99 (m, 3H), 2.74-2.78 (m, 1H), 2.23 (td, $J_1 = 11.4$ Hz, $J_2 = 3.1$ Hz, 1H), 1.82-1.87 (m, 1H), 1.64-1.67 (m, 1H), 1.40-1.52 (m, 2H), 1.12-1.26 (m, 4H), 0.99 (t, $J = 7.1$ Hz, 3H).

$^{13}$C-NMR (101 MHz, C$_6$D$_6$) δ: 166.3, 151.5, 130.2, 129.8, 129.3, 74.1, 72.3, 61.8, 60.7, 47.1, 43.4, 35.3, 30.5, 26.8, 26.4, 14.3.

MS (70 eV, EI) $m/z$ (%): 261 (25), 260 (30), 245 (15), 244 (79), 216 (41), 215 (27), 203 (13), 190 (13), 185 (15), 176 (11), 172 (15), 171 (100), 163 (22), 148 (10), 143 (13), 135 (15), 131 (14), 129 (28), 119 (10), 117 (11), 115 (11), 91 (20), 81 (11), 45 (15).

IR (ATR) $\tilde{v}$ (cm$^{-1}$): 2924 (m), 2854 (m), 1714 (s), 1609 (w), 1448 (w), 1418 (w), 1367 (m), 1311 (w), 1273 (vs), 1179 (m), 1108 (s), 1060 (m), 1020 (m), 848 (w), 708 (m), 771 (m).

HRMS (EI) for C$_{18}$H$_{24}$O$_4$ (304.1675): 305.1753 [M+H$^+$].
chiral methyl-4-(trans--2-(5,5-dimethyl-1,3-dioxan-2-yl)cyclohexyl)-benzoate

According to TP12, 2-cyclohex-1-enyl-5,5-dimethyl-1,3-dioxane (139) (196 mg, 1.00 mmol) was reacted via asymmetric hydroboration with (−)-IpcBH₂, followed by a boron-zinc exchange and subsequent cross-coupling (−10 °C, 12 h; then 0 °C, 12 h) with methyl-4-iodobenzoate (786 mg, 3.00 mmol). Purification by column chromatography (SiO₂; Et₂O/n-pentane 1 : 20) furnished the title compound (251 mg, 0.82 mmol, 82 %) as a colourless solid.

d.r.: > 99 : 1.
m.p.: 78.6 °C.

¹H-NMR (400 MHz, C₆D₆) δ: 8.14 (d, J = 8.4 Hz, 2H), 7.09 (d, J = 8.2 Hz, 2H), 3.93 (d, J = 2.1 Hz, 1H), 3.47 (s, 3H), 3.32 (dd, J₁ = 10.8 Hz, J₂ = 2.8 Hz, 1H), 3.25 (dd, J₁ = 10.8 Hz, J₂ = 2.8 Hz, 1H), 2.83 (d, J = 2.3 Hz, 1H), 2.80 (d, J = 2.3 Hz, 1H), 2.67 (td, J₁ = 11.5 Hz, J₂ = 3.5 Hz, 1H), 2.32-2.36 (m, 1H), 1.83 (tt, J₁ = 11.5 Hz, J₂ = 2.7 Hz, 1H), 1.68-1.78 (m, 2H), 1.57-1.61 (m, 1H), 1.20-1.31 (m, 4H), 1.05 (s, 3H), 0.14 (s, 3H).

¹³C-NMR (101 MHz, C₆D₆) δ: 166.7, 151.7, 130.1, 128.9, 101.5, 76.8, 76.8, 51.5, 47.5, 46.0, 35.2, 29.9, 26.9, 26.1, 24.7, 22.9, 21.3.

MS (70 eV, EI) m/z (%): 196 (29), 115 (100), 97 (11), 83 (11), 71 (11), 70 (10), 69 (52), 57 (22), 56 (9), 55 (22), 45 (10), 44 (36), 43 (26), 41 (25).

IR (ATR) ν (cm⁻¹): 2929 (m), 2852 (m), 1717 (s), 1608 (w), 1438 (m), 1393 (m), 1270 (s), 1184 (m), 1153 (m), 1110 (vs), 1098 (s), 1030 (m), 1017 (m), 987 (m), 973 (m), 932 (m), 852 (w), 770 (s), 710 (s).


Enantiomeric purity: 81 %ee.

HPLC: Column: OD; n-Heptan : iPrOH: 98 : 2; flux: 0.3 mL/min.

chiral 2-(trans-2-(3-(trifluormethyl)phenyl)cyclohexyl)–5,5-dimethyl-1,3-dioxane

![chiral 2-(trans-2-(3-(trifluormethyl)phenyl)cyclohexyl)–5,5-dimethyl-1,3-dioxane](image)
According to TP12, 2-cyclohex-1-enyl-5,5-dimethyl-1,3-dioxane (139) (196 mg, 1.00 mmol) was reacted via asymmetric hydroboration with (−)-IpcBH₂, followed by a boron-zinc exchange and subsequent cross-coupling (−10 °C, 12 h; then 0 °C, 12 h) with 1-iodo-3-(trifluormethyl)benzene (816 mg, 3.00 mmol). Purification by column chromatography (SiO₂; Et₂O/n-pentane 1 : 30) furnished the title compound (186 mg, 0.54 mmol, 54 %) as a colourless oil.

d.r.: > 99 : 1.

1H-NMR (400 MHz, C₆D₆) δ: 7.53 (s, 1H), 7.26 (d, J = 7.6 Hz, 1H), 7.08 (d, J = 7.6 Hz, 1H), 6.95 (t, J = 7.7 Hz, 1H), 3.86 (d, J = 2.2 Hz, 1H), 3.29 (dd, J₁ = 10.8 Hz, J₂ = 2.9 Hz, 1H), 3.21 (dd, J₁ = 10.9 Hz, J₂ = 2.8 Hz, 1H), 2.80 (d, J = 10.8 Hz, 1H), 2.74 (d, J = 11.0 Hz, 1H), 2.62 (td, J₁ = 11.5 Hz, J₂ = 3.1 Hz, 1H), 2.27-2.30 (m, 1H), 1.76 (tt, J₁ = 11.5 Hz, J₂ = 2.8 Hz, 1H), 1.59-1.66 (m, 1H), 1.52-1.57 (m, 2H), 1.11-1.21 (m, 4H), 1.00 (s, 3H), 0.11 (s, 3H).

13C-NMR (75 MHz, C₆D₆) δ: 147.4, 131.1, 130.8 (q, J = 31.7 Hz), 129.0, 125.1 (d, J = 3.4 Hz), 123.1 (q, J = 3.9 Hz) 101.5, 76.8, 76.8, 47.6, 45.7, 43.1, 29.9, 26.9, 26.1, 24.9, 22.9, 21.3.

MS (70 eV, EI) m/z (%): 207 (13), 196 (24), 159 (21), 115 (100), 81 (10), 69 (56), 57 (15), 56 (10), 55 (22), 45 (12), 44 (48), 43 (18), 41 (28).

IR (ATR) ν (cm⁻¹): 2930 (w), 2853 (w), 1451 (w), 1394 (w), 1328 (s), 1160 (s), 1116 (vs), 1091 (s), 1074 (s), 1042 (m), 1027 (m), 993 (m), 969 (m), 932 (w), 919 (w), 903 (w), 799 (m), 703 (m), 664 (m).

HRMS (EI) for C₁₀H₁₂F₃O₂ (342.1807): 342.1786.

Enantiomeric purity: 77 % ee.

HPLC: Column: OD; n-Heptan : iPrOH: 100 : 0; flux: 0.2 mL/min.

chiral 2-(trans-2-phenylcyclohexyl)-5,5-dimethyl-1,3-dioxane

According to TP12, 2-cyclohex-1-enyl-5,5-dimethyl-1,3-dioxane (139) (196 mg, 1.00 mmol) was reacted via asymmetric hydroboration with (−)-IpcBH₂, followed by a boron-zinc exchange and subsequent cross-coupling (−10 °C, 12 h; then 0 °C, 12 h) with iodobenzene (612 mg, 3.00 mmol). Purification by column chromatography (SiO₂; Et₂O/n-pentane 1 : 20) furnished the title compound (143 mg, 0.52 mmol, 52 %) as a colourless oil.
d.r.: >99:1.

$^1$H-NMR (400 MHz, C$_6$D$_6$) δ: 7.16-7.21 (m, 4H), 7.04-7.09 (m, 1H), 4.06 (d, $J = 2.1$ Hz, 1H), 3.35 (dd, $J_1 = 10.7$ Hz, $J_2 = 2.9$ Hz, 1H), 3.25 (dd, $J_1 = 10.8$ Hz, $J_2 = 2.8$ Hz, 1H), 2.86 (d, $J = 10.9$ Hz, 1H), 2.79 (d, $J = 10.7$ Hz, 1H), 2.72 (td, $J_1 = 11.8$ Hz, $J_2 = 3.4$ Hz, 1H), 2.37-2.40 (m, 1H), 1.92 (tt, $J_1 = 11.4$ Hz, $J_2 = 2.7$ Hz, 1H), 1.72-1.79 (m, 2H), 1.59-1.64 (m, 1H), 1.23-1.44 (m, 4H), 1.00 (s, 3H), 0.11 (s, 3H).

$^{13}$C-NMR (101 MHz, C$_6$D$_6$) δ: 146.4, 128.7, 126.4, 101.6, 76.8, 47.7, 46.0, 35.8, 29.9, 27.2, 26.3, 24.8, 23.0, 21.3.

MS (70 eV, EI) m/z (%): 273 (13), 196 (72), 170 (13), 167 (15), 159 (10), 117 (15), 116 (21), 115 (100), 91 (51), 69 (90).

IR (ATR) $\tilde{\nu}$ (cm$^{-1}$): 2926 (m), 2851 (m), 1451 (m), 1393 (m), 1153 (m), 1115 (vs), 1088 (m), 1078 (m), 1043 (m), 1025 (m), 1017 (m), 991 (m), 967 (m), 931 (m), 756 (s), 699 (vs), 644 (w).

HRMS (EI) for C$_{18}$H$_{26}$O$_2$ (274.1933): 274.1933.

Enantiomeric purity: 68 % ee.

HPLC: Column: OD; n-Heptan : iPrOH: 100:0; flux: 0.2 mL/min.

4.7. Cross-Couplings with [8-(Ethoxymethoxy)decahydronaphthalin-1-yl](ethyl)zinc

4.7.1. Diastereoselective preparation of methyl-4-(8-(ethoxymethoxy)decahydronaphthalin-1-yl)benzoate (Table 10)

![Diagram](image_url)

A dry and argon-flushed 25 mL Schlenk-flask, equipped with a magnetic stirring bar and a septum was charged with a solution of 1-(ethoxymethoxy)-1,2,3,4,4a,5,6,7-octahydronaphthaline (169) (210 mg, 1.00 mmol) in CH$_2$Cl$_2$ (2 mL) and freshly prepared Et$_2$BH (0.41 mL, 7.3 M in Me$_2$S, 3.00 mmol) was added dropwise at room temperature. The reaction mixture was stirred for 48 h at that temperature. After complete hydroboration the solution was concentrated in vacuo (0.1 mm Hg, 25 °C, 2 h), Et$_2$Zn (371 mg, 0.31 mL,
3.00 mmol) was added and stirring was continued for additional 5 h at room temperature. The reaction mixture was again concentrated (0.1 mm Hg, 25 °C, 1 h), the grey-black residue redissolved in THF (2.5 mL) and then added dropwise to a mixture of methyl-4-iodobenzoate (1.31 g, 5.00 mmol), Pd(dba)$_2$ (11.5 mg, 0.02 mmol) und S-Phos (8.20 mg, 0.02 mmol) in THF (5 mL) at −10 °C. The resulting reaction mixture was left to stir overnight at this temperature before it was quenched with sat. aq. NH$_4$Cl solution (10 mL). The phases were separated, the aqueous phase was extracted with Et$_2$O (3 x 20 mL) and the combined organic layers were dried over MgSO$_4$. The solvents were evaporated in vacuo and the residue was subjected to column chromatography (SiO$_2$: Et$_2$O/n-pentane 1 : 7) furnishing the title compound (113 mg, 0.31 mmol, 31 %) as a colourless oil.

d.r. (1,2); d.r. (1,3): 91:9; 85:15.

$^1$H-NMR (400 MHz, C$_6$D$_6$) $\delta$: 8.13 (d, $J$ = 8.6 Hz, 2H), 6.96 (d, $J$ = 8.4 Hz, 2H), 3.99 (d, $J$ = 7.2 Hz, 1H), 3.60 (d, $J$ = 7.2 Hz, 1H) 3.49 (s, 3H), 3.31 (q, $J$ = 7.1 Hz, 2H), 1.48-1.60 (m, 4H), 1.08-1.47 (m, 12H), 0.89 (t, $J$ = 7.1 Hz, 3H).

$^{13}$C-NMR (101 MHz, C$_6$D$_6$) $\delta$: 167.0, 154.8, 129.4, 127.7, 95.9, 83.7, 62.9, 52.1, 51.4, 50.3, 42.0, 38.3, 35.1, 34.1, 34.0, 26.5, 24.3, 15.2.

MS (70 eV, EI) m/z (%): 300 (39), 272 (100), 271 (27), 270 (39), 269 (26), 255 (51), 240 (36), 239 (52), 177 (26), 162 (58), 150 (24), 149 (29), 131 (23), 59 (70).

IR (ATR) $\tilde{\nu}$ (cm$^{-1}$): 2924 (m), 2857 (m), 1721 (s), 1609 (m), 1434 (m), 1277 (vs), 1179 (m), 1109 (s), 1099 (s), 1044 (vs), 1017 (s), 847 (m), 771 (m), 708 (m).

HRMS (EI) for C$_{21}$H$_{30}$O$_4$ (346.2144): 346.2135.
5. Highly Diastereoselective Arylations of Substituted Piperidines

5.1. Preparation of Starting Materials

$t$-butyl 4-((triisopropylsilyl)oxy)-piperidine-1-carboxylate (172c)

To a solution of tert-butyl 4-hydroxypiperidine-1-carboxylate (100 mmol; 20.1 g) and imidazole (250 mmol; 17.0 g) in DMF (250 mL) was slowly added TIPSCl (120 mmol; 23.1 g; 25.7 mL) via syringe. The reaction mixture was stirred for further 6 h at room temperature. NaHCO$_3$ sat. aq. solution (500 mL) was added, phases were separated and the aqueous phase was extracted with Et$_2$O (4 x 300 mL). The combined organic layers were washed with brine (300 mL) and dried over Na$_2$SO$_4$. The solvents were evaporated and the residue was subjected to column chromatography (SiO$_2$; n-pentane/Et$_2$O 15:1) yielding 34.1 g (95%) of the title compound.

$^1$H-NMR (400 MHz, C$_6$D$_6$) $\delta$: 3.68 (ddd, $J_1$=10.2 Hz, $J_2$=6.8 Hz, $J_3$=3.3 Hz, 4 H), 3.27 (br. s., 1 H), 1.57 - 1.50 (m, 2 H), 1.48 (s, 9 H), 1.45 - 1.37 (m, 2 H), 1.12 - 1.01 (m, 18 H), 0.99 - 0.92 (m, 3 H).

$^{13}$C-NMR (101 MHz, C$_6$D$_6$) $\delta$: 155.1, 79.2, 67.9, 35.1, 28.9, 18.6, 18.4, 13.2, 12.9, 12.6.

MS (70 eV) m/z (%): 259 (15), 258 (77), 215 (18), 214 (100), 131 (13), 56 (12).

IR (ATR) $\tilde{\nu}$ (cm$^{-1}$): 2944 (m), 2866 (m), 1698 (vs), 1464 (m), 1420 (s), 1366 (m), 1274 (m), 1230 (s), 1172 (s), 1110 (s), 1086 (s), 1068 (s), 1044 (vs), 1012 (m), 994 (m), 882 (s), 870 (s), 850 (m), 802 (m), 678 (s), 658 (s), 632 (m).

HRMS (ESI) for C$_{19}$H$_{39}$NO$_3$SiNa$^+$ (380.2591) [M+Na$^+$]: 380.2592.

$t$-butyl 2-methyl-4-((triisopropylsilyl)oxy)piperidine-1-carboxylate

A solution of $t$-butyl 4-((triisopropylsilyl)oxy)piperidine-1-carboxylate (17 mmol; 6.08 g) and TMEDA (17 mmol; 1.97 g; 2.53 mL) in anhydrous Et$_2$O (60 mL) was cooled to -78 °C.
s-BuLi (1.07 M in hexanes) (20.4 mmol; 19.07 mL) was slowly added via syringe. The reaction mixture was stirred for 4 h at this temperature before MgCl₂ (0.5 M in THF) (8.5 mmol; 17 mL) was added. After the addition was complete, CuCN·2 LiCl (1 M in THF) (17 mmol; 17 mL) was dropped to the reaction mixture. The reaction mixture was stirred for 15 min at -78 °C before methyl iodide (17 mmol; 2.41 g; 1.06 mL) was added. The reaction mixture was kept for 4 h at -78 °C and was then allowed to warm to room temperature. NH₄Cl sat. aq. solution (100 mL) was added, the phases were separated and the aqueous phase was extracted with Et₂O (4 x 30 mL). The combined organic layers were washed with brine (50 mL) and dried over Na₂SO₄. The solvents were evaporated and the residue was subjected to column chromatography (SiO₂; i-hexane/Et₂O 10:1) yielding 4.87 g (77%) of the title compound as a colorless oil.

¹H-NMR (400 MHz, C₆D₆) δ: 4.48 (br. s., 1 H), 4.02 (br. s., 1 H), 3.91 - 3.75 (m, 1 H), 3.39 - 3.23 (m, 1 H), 1.53 - 1.35 (m, 13 H), 1.23 - 0.69 (m, 24 H).

¹³C-NMR (75 MHz, C₆D₆) δ: 155.2, 79.1, 66.1, 46.6, 37.4, 34.2, 33.9, 29.0, 19.7, 18.7, 18.4, 13.2, 12.8.

MS (70 eV) m/z (%): 371 (1) [M⁺], 273 (16), 272 (79), 230 (13), 229 (19), 228 (100), 184 (12), 142 (16), 131 (42).

IR (ATR) ν (cm⁻¹): 2942 (m), 2892 (w), 2866 (m), 1694 (s), 1464 (m), 1412 (m), 1390 (m), 1378 (m), 1364 (m), 1342 (m), 1290 (w), 1272 (w), 1250 (w), 1212 (w), 1174 (s), 1134 (m), 1112 (m), 1090 (s), 1072 (s), 1054 (vs), 1028 (m), 1004 (m), 934 (w), 918 (w), 882 (s), 864 (m), 800 (w), 768 (w), 674 (s), 656 (s).

HRMS (ESI) for C₂₀H₄₂NO₃Si⁺ (372.2934) [M+H⁺]: 372.2927.

5.2. Typical Procedure 13: Cross-Coupling of (1-(t-Butoxycarbonyl)-4-methylpiperidin-2-yl)zinc Chloride (TP 13) (Table 11)

A dry and Ar-flushed 10 mL Schlenk-tube equipped with a stirring bar was charged with a solution of t-butyl 4-methylpiperidine-1-carboxylate (1 mmol; 0.20 g) and TMEDA (1 mmol; 0.12 g; 0.45 mL) in anhydrous Et₂O (2 mL). It was cooled to -78 °C and s-BuLi (1.14 M in hexanes) (1.2 mmol; 1.05 mL) was slowly added via syringe. The reaction mixture was stirred for 4 h at this temperature before ZnCl₂ (1.0 M in THF) (1.2 mmol; 1.2 mL) was added. The reaction mixture was stirred for 15 min at -78 °C and was then warmed to room temperature. Et₂O was removed in vacuo (8 min; 1 mbar). Meanwhile, a solution of the respective aryl iodide (0.7 mmol), Pd(dba)₂ (11.5 mg; 0.02 mmol) and S-Phos (8.2 mg; 0.02 mmol) was
prepared and stirred for 10 min. The piperidinylzinc reagent was added to this mixture at room temperature. The reaction mixture was then heated to 55 °C for 15 h. NH₄Cl sat. aq. solution (20 mL) was added, the phases were separated and the aqueous phase was extracted with Et₂O (4 x 10 mL). The combined organic layers were washed with brine (10 mL) and dried over Na₂SO₄. The solvents were evaporated and the residue was subjected to column chromatography yielding the respective title compound.

cis-t-butyl 2-(4-methoxyphenyl)-4-methylpiperidine-1-carboxylate (173a)

Cross-coupling was performed according to TP13.

column chromatography: SiO₂; n-pentane/Et₂O 4:1

yield: 167 mg (78 %)
d.r.: 99:1.

1H-NMR (400 MHz, C₆D₆) δ: 7.10 (d, J=8.4 Hz, 2 H), 6.81 (d, J=8.6 Hz, 2 H), 4.91 (dd, J₁=9.4 Hz, J₂=6.4 Hz, 1 H), 4.11 (ddd, J₁=13.6 Hz, J₂=7.0 Hz, J₃=2.9 Hz, 1 H), 3.33 (s, 3 H), 3.14 (ddd, J₁=13.7 Hz, J₂=10.7 Hz, J₃=5.6 Hz, 1 H), 1.83 - 1.73 (m, 1 H), 1.66 (ddd, J₁=13.3 Hz, J₂=6.2 Hz, J₃=3.6 Hz, 1 H), 1.54 - 1.44 (m, 1 H), 1.38 (s, 9 H), 1.36 - 1.27 (m, 1 H), 0.93 - 0.84 (m, 1 H), 0.67 (d, J=6.8 Hz, 3 H).

13C-NMR (101 MHz, C₆D₆) δ: 159.1, 156.1, 137.5, 127.2, 114.3, 79.2, 56.7, 55.1, 38.8, 38.6, 31.7, 28.8, 27.0, 21.8.

MS (70 eV, EI) m/z (%): 305 (2) [M⁺], 250 (10), 249 (67), 248 (23), 205 (14), 204 (100), 162 (10), 134 (10), 121 (15), 96 (14), 57 (28).

IR (ATR) ~ (cm⁻¹): 2951 (w), 2929 (w), 1686 (vs), 1612(w), 1512 (s), 1477 (w), 1455 (m), 1403 (s), 1364 (s), 1328 (m), 1292 (m), 1279 (m), 1243 (vs), 1173 (s), 1148 (vs), 1126 (m), 1112 (m), 1090 (m), 1066 (m), 1035(s), 1000 (w),864 (m), 827 (s), 775 (m), 758 (m).

C. Experimental Section

**cis-t-butyl 4-methyl-2-(4-(trifluoromethyl)phenyl)piperidine-1-carboxylate (173b)**

![Chemical structure of cis-t-butyl 4-methyl-2-(4-(trifluoromethyl)phenyl)piperidine-1-carboxylate (173b)](image)

Cross-coupling was performed according to TP13.

**Column chromatography:** SiO2; n-pentane/Et2O 5:1

**Yield:** 195 mg (81%)

**d.r.:** 95:5

**1H-NMR (400 MHz, C6D6) δ:** 7.39 (d, J=8.0 Hz, 2 H), 7.00 (d, J=8.2 Hz, 2 H), 4.68 (dd, J1=9.8 Hz, J2=6.3 Hz, 1 H), 3.90 (dddd, J1=13.7, J2=6.6 Hz, J3=3.9 Hz, 1 H), 3.08 (dddd, J1=13.9 Hz, J2=10.0 Hz, J3=5.5 Hz, 1 H), 1.69 (dddd, J1=13.3 Hz, J2=10.0 Hz, J3=6.9 Hz, J4=6.7 Hz, 1 H), 1.55 - 1.49 (m, 1 H), 1.42 - 1.33 (m, 1 H), 1.29 (s, 9 H), 1.05 (dt, J1=13.5 Hz, J2=10.4 Hz, 1 H), 0.88 - 0.80 (m, 1 H), 0.62 (d, J=6.8 Hz, 3 H).

**13C-NMR (101 MHz, C6D6) δ:** 155.9, 150.0 (d, J=1.0 Hz), 129.1 (q, J=32.1 Hz), 126.4, 125.8 (q, J=3.8 Hz), 125.5 (q, J=271.7 Hz), 79.6, 57.3, 39.5, 38.7, 31.6, 28.6, 27.2, 21.8.

**19F-NMR (376 MHz, C6D6) δ:** -61.98 (s).

**MS (70 eV, EI) m/z (%):** 343 (1) [M⁺], 288 (19), 287 (73), 270 (16), 268 (28), 243 (15), 242 (64), 228 (12), 200 (23), 199 (10), 187 (12), 186 (15), 172 (21), 159 (30), 142 (28), 98 (24), 97 (14), 57 (100), 55 (10), 41 (22).

**IR (ATR) ν (cm⁻¹):** 2929 (w), 2871 (w), 1688 (s), 1619 (w), 1478 (w), 1455 (w), 1415 (m), 1402 (m), 1392 (m), 1378 (w), 1365 (m), 1349 (w), 1323 (vs), 1290 (w), 1278 (w), 1243 (m), 1223 (w), 1150 (s), 1120 (vs), 1111 (vs), 1090 (m), 1066 (vs), 1016 (m), 1000 (w), 971 (w), 924 (w), 863 (w), 834 (m), 815 (w), 775 (m), 759 (w), 658 (w), 605 (w).

**HRMS (EI) for C18H24F3NO2 (343.1759):** 343.1756.

**cis-t-butyl 2-(3-chlorophenyl)-4-methylpiperidine-1-carboxylate (173c)**

![Chemical structure of cis-t-butyl 2-(3-chlorophenyl)-4-methylpiperidine-1-carboxylate (173c)](image)

Cross-coupling was performed according to TP13.

**Column chromatography:** SiO2; n-pentane/Et2O 5:1

**Yield:** 165 mg (76%)
d.r.: 96:4.

m.p.: 47.3 – 49.2 °C.

$^1$H-NMR (400 MHz, C$_6$D$_6$) $\delta$: 7.24 (s, 1 H), 7.05 (d, $J$=7.04 Hz, 1 H), 6.95 - 6.81 (m, 2 H), 4.64 (dd, $J_1$=10.1 Hz, $J_2$=6.2 Hz, 1 H), 3.91 (ddd, $J_1$=13.6 Hz, $J_2$=6.7 Hz, $J_3$=3.5 Hz, 1 H), 3.09 - 3.00 (m, 1 H), 1.73 - 1.63 (m, 1 H), 1.48 - 1.44 (m, 1 H), 1.40 - 1.33 (m, 1 H), 1.31 (s, 9 H), 1.10 - 1.00 (m, 1 H), 0.84 - 0.75 (m, 1 H), 0.61 (d, $J$=6.65 Hz, 3 H).

$^{13}$C-NMR (101 MHz, C$_6$D$_6$) $\delta$: 155.9, 148.2, 134.9, 130.2, 127.0, 126.5, 124.1, 79.6, 57.3, 39.4, 38.7, 31.6, 28.7, 27.1, 21.8.

MS (70 eV, EI) m/z (%): 309 (1) [M$^+$], 255 (26), 254 (15), 253 (79), 236 (15), 210 (28), 209 (16), 208 (87), 194 (12), 192 (10), 166 (19), 153 (10), 152 (11), 142 (27), 138 (14), 125 (21), 98 (37), 97 (18), 57 (100), 41 (21).

IR (ATR) $\tilde{\nu}$ (cm$^{-1}$): 2916 (s), 2850 (m), 1682 (vs), 1476 (m), 1398 (s), 1362 (s), 1338 (m), 1284 (s), 1244 (s), 1174 (s), 1148 (vs), 1122 (s), 1098 (s), 1088 (s), 1078 (s), 1034 (m), 1004 (m), 906 (m), 864 (s), 852 (s), 790 (s), 778 (vs), 756 (s), 710 (s), 694 (vs), 676 (m).

HRMS (EI) for C$_{17}$H$_{24}$ClNO$_2$ (309.1496): 309.1487.

cis-$t$-butyl 2-(3-cyanophenyl)-4-methylpiperidine-1-carboxylate (173d)

Cross-coupling was performed according to TP13.

column chromatography: SiO$_2$; n-pentane/Et$_2$O 4:1

yield: 135 mg (64 %)

d.r.: 97:3.

m.p.: 77.8 – 79.3 °C.

$^1$H-NMR (400 MHz, C$_6$D$_6$) $\delta$: 7.22 (s, 1 H), 7.08 - 6.91 (m, 2 H), 6.76 (t, $J$=7.7 Hz, 1 H), 4.49 (dd, $J_1$=10.4 Hz, $J_2$=5.9 Hz, 1 H), 3.79 (ddd, $J_1$=13.7 Hz, $J_2$=6.6 Hz, $J_3$=3.9 Hz, 1 H), 2.98 (ddd, $J_1$=13.7 Hz, $J_2$=9.8 Hz, $J_3$=5.6 Hz, 1 H), 1.71 - 1.59 (m, 1 H), 1.40 - 1.29 (m, 2 H), 1.29 - 1.15 (m, 9 H), 0.90 (dt, $J_1$=13.1 Hz, $J_2$=10.6 Hz, 1 H), 0.83 - 0.74 (m, 1 H), 0.60 (d, $J$=6.6 Hz, 3 H).

$^{13}$C-NMR (101 MHz, C$_6$D$_6$) $\delta$: 155.1, 146.4, 129.6, 129.1, 128.9, 128.6, 118.6, 112.6, 79.0, 56.5, 39.0, 37.9, 30.8, 27.8, 26.5, 21.1.
C. Experimental Section

**MS (70 eV, EI)** m/z (%): 300 (1) [M⁺], 245 (16), 244 (37), 227 (11), 200 (32), 199 (100), 185 (17), 171 (12), 157 (24), 144 (10), 143 (15), 142 (10), 129 (16), 116 (14), 98 (20), 57 (52), 41 (17).

**IR (ATR)** $\tilde{\nu}$ (cm⁻¹): 2952 (w), 2920 (w), 2230 (w), 1682 (vs), 1482 (m), 1440 (w), 1404 (s), 1374 (m), 1364 (m), 1338 (w), 1328 (w), 1288 (m), 1248 (m), 1182 (m), 1150 (vs), 1122 (m), 1096 (m), 1010 (m), 924 (w), 874 (m), 862 (w), 798 (s), 778 (m), 758 (w), 734 (w), 694 (s), 636 (w).

**HRMS (EI)** for $\text{C}_{18}\text{H}_{24}\text{N}_{2}\text{O}_{2}$ (300.1838): 300.1860.

**cis-3-hexyl 2-(4-(ethoxycarbonyl)phenyl)-4-methylpiperidine-1-carboxylate (173e)**

Cross-coupling was performed according to TP13.

**column chromatography:** SiO₂; n-pentane/Et₂O 4:1

**yield:** 163 mg (67 %)

**d.r.:** 98:2.

**m.p.:** 108.8 – 110.3 °C.

**$^1$H-NMR (400 MHz, C₆D₆) $\delta$:** 8.20 (d, $J$=8.4 Hz, 2 H), 7.12 (d, $J$=8.4 Hz, 2 H), 4.74 (dd, $J_1$=9.7 Hz, $J_2$=6.2 Hz, 1 H), 4.15 (q, $J$=7.1 Hz, 2 H), 3.96 (dd, $J_1$=13.7 Hz, $J_2$=6.6 Hz, $J_3$=3.7 Hz, 1 H), 3.12 (ddd, $J_1$=13.7, $J_2$=10.2 Hz, $J_3$=5.4 Hz, 1 H), 1.70 (dddd, $J_1$=13.3 Hz, $J_2$=10.2 Hz, $J_3$=7.1 Hz, $J_4$=6.8 Hz, 1 H), 1.54 (dddd, $J_1$=13.4 Hz, $J_2$=5.9 Hz, $J_3$=3.9 Hz, 1 H), 1.43 - 1.36 (m, 1 H), 1.29 (s, 9 H), 1.13 (dt, $J_1$=13.4 Hz, $J_2$=10.2 Hz, 1 H), 1.03 (t, $J$=7.1 Hz, 3 H), 0.89 - 0.80 (m, 1 H), 0.61 (d, $J$=7.1 Hz, 3 H).

**$^{13}$C-NMR (101 MHz, C₆D₆) $\delta$:** 166.5, 156.0, 151.1, 130.4, 129.8, 126.0, 79.6, 61.1, 57.6, 39.4, 38.7, 31.6, 28.7, 27.2, 21.8, 14.6.

**MS (70 eV, EI)** m/z (%): 347 (1) [M⁺], 292 (15), 291 (81), 262 (16), 247 (11), 246 (55), 219 (15), 218 (100), 176 (10), 174 (11), 142 (14), 98 (20), 97 (17), 57 (42), 43 (10).

**IR (ATR)** $\tilde{\nu}$ (cm⁻¹): 2928 (w), 2920 (w), 1715 (s), 1689 (vs), 1610 (w), 1476 (w), 1455 (w), 1401 (m), 1392 (m), 1364 (s), 1350 (w), 1326 (w), 1307 (m), 1271 (vs), 1245 (s), 1222 (m), 1173 (s), 1149 (s), 1121 (s), 1101 (vs), 1066 (m), 1019 (m), 852 (m), 768 (m), 757 (m), 740 (w), 705 (m).

**HRMS (EI)** for $\text{C}_{20}\text{H}_{30}\text{NO}_4$ (347.2097): 347.2099.
cis-t-butyl 4-methyl-2-(pyridin-4-yl)piperidine-1-carboxylate (173f)

Cross-coupling was performed according to TP13.

column chromatography: SiO$_2$; Et$_2$O

yield: 141 mg (73 %)
d.r.: 95:5.

$^1$H-NMR (300 MHz, C$_6$D$_6$) δ: 8.56 (dd, $J_1$=4.6 Hz, $J_2$=1.4 Hz, 2 H), 6.79 (d, $J$=5.6 Hz, 2 H), 4.62 (dd, $J_1$=9.3 Hz, $J_2$=6.4 Hz, 1 H), 3.89 (ddd, $J_1$=13.6 Hz, $J_2$=6.6 Hz, $J_3$=3.8 Hz, 1 H), 3.03 (ddd, $J_1$=13.8 Hz, $J_2$=10.0 Hz, $J_3$=5.3 Hz, 1 H), 1.72 - 1.59 (m, 1 H), 1.54 - 1.38 (m, 2 H), 1.36 - 1.18 (m, 9 H), 1.09 - 0.97 (m, 1 H), 0.81 (dddd, $J_1$=16.9 Hz, $J_2$=5.2 Hz, $J_3$=4.1 Hz, $J_4$=3.9 Hz, 1 H), 0.58 (d, $J$=6.9 Hz, 3 H).

$^{13}$C-NMR (75 MHz, C$_6$D$_6$) δ: 155.8, 153.9, 150.7, 121.0, 79.8, 56.5, 39.3, 38.0, 31.5, 28.6, 27.1, 21.6.

MS (70 eV, EI) m/z (%): 276 (10) [M$^+$], 221 (40), 220 (78), 202 (17), 176 (55), 175 (73), 142 (35), 133 (30), 120 (17), 119 (17), 106 (16), 98 (97), 57 (100), 56 (15), 55 (19), 41 (23), 41 (23).

IR (ATR) $\tilde{\nu}$ (cm$^{-1}$): 2954 (w), 2928 (w), 1688 (vs), 1598 (m), 1478 (w), 1456 (w), 1404 (s), 1364 (s), 1338 (m), 1316 (m), 1280 (m), 1246 (s), 1228 (m), 1174 (s), 1150 (vs), 1128 (m), 1092 (m), 1064 (m), 1018 (m), 994 (m), 972 (w), 862 (m), 818 (m), 800 (m), 776 (m), 760 (m), 634 (m).

HRMS (EI) for C$_{16}$H$_{24}$N$_2$O$_2$ (276.1838): 276.1830.

5.3. Typical Procedure 14: Cross-Coupling of (1-(t-Butoxycarbonyl)-4-phenylpiperidin-2-yl)zinc Chloride (TP 14) (Table 11)

A dry and Ar-flushed 10 mL Schlenk-tube equipped with a stirring bar was charged with a solution of $t$-butyl 4-phenylpiperidine-1-carboxylate (1 mmol; 0.26 g) and TMEDA (1 mmol; 0.12 g; 0.45 mL) in anhydrous Et$_2$O (2 mL). It was cooled to -78 °C and s-BuLi (1.14 M in hexanes) (1.2 mmol; 1.05 mL) was slowly added via syringe. The reaction mixture was stirred for 4 h at this temperature before ZnCl$_2$ (1.0 M in THF) (1.2 mmol; 1.2 mL) was added. The
reaction mixture was stirred for 15 min at -78 °C and was then allowed to warm to room temperature. Et2O was removed in vacuo (8 min; 1 mbar). Meanwhile, a solution of the respective aryl iodide (0.7 mmol), Pd(dba)2 (28.8 mg; 0.05 mmol) and Ru-Phos (23.3 mg; 0.05 mmol) was prepared and stirred for 10 min. The piperidinylzinc reagent was added to this mixture at room temperature. The reaction mixture was then heated to 55 °C for 15 h. NH4Cl sat. aq. solution (20 mL) was added, the phases were separated and the aqueous phase was extracted with Et2O (4 x 10 mL). The combined organic layers were washed with brine (10 mL) and dried over Na2SO4. The solvents were evaporated and the residue was subjected to column chromatography yielding the respective title compound.

cis-t-butyl 4-phenyl-2-(4-(trifluoromethyl)phenyl)piperidine-1-carboxylate (173g)

Cross-coupling was performed according to TP14.

**column chromatography:** SiO2; toluene

**yield:** 182 mg (64 %)

**d.r.:** 97:3.

**1H-NMR (300 MHz, C6D6)** δ: 7.40 (d, J=8.3 Hz, 2 H), 7.13 (d, J=8.0 Hz, 2 H), 7.10 - 7.04 (m, 1 H), 6.98 (d, J=8.0 Hz, 2 H), 6.90 (d, J=7.2 Hz, 2 H), 4.65 (dd, J1=11.6 Hz, J2=6.1 Hz, 1 H), 3.99 (ddd, J1=13.8 Hz, J2=7.2 Hz, J3=3.9 Hz, 1 H), 3.23 (dd, J1=13.9 Hz, J2=9.5 Hz, J3=6.2 Hz, 1 H), 2.58 - 2.46 (m, 1 H), 2.06 - 1.92 (m, 1 H), 1.78 - 1.69 (m, 1 H), 1.55 - 1.45 (m, 1 H), 1.43 - 1.33 (m, 1 H), 1.29 (s, 9 H).

**13C-NMR (75 MHz, C6D6)** δ: 155.9, 149.9 (d, J=1.1 Hz), 146.4, 129.3 (q, J=32.1 Hz), 129.2, 127.4, 127.0, 126.3, 125.9 (q, J=3.9 Hz), 125.5 (q, J=271.8 Hz), 79.8, 58.4, 40.3, 39.0, 38.6, 31.8, 28.6.

**MS** (70 eV, EI) m/z (%): 405 (1) [M]+, 350 (24), 349 (100), 304 (21), 288 (10), 200 (13), 187 (12), 186 (14), 172 (10), 159 (11), 118 (32), 104 (15), 90 (19); 59 (85); 41 (11).

**IR (ATR) ν (cm⁻¹):** 2976 (w), 2932 (w), 1688 (s), 1620 (w), 1478 (w), 1454 (w), 1402 (m), 1366 (m), 1322 (vs), 1292 (m), 1248 (m), 1162 (s), 1120 (vs), 1110 (vs), 1066 (s), 1038 (w), 1016 (m), 950 (w), 878 (w), 860 (w), 836 (m), 818 (w), 760 (m), 700 (s), 662 (w).

**HRMS (EI) for C23H26F3NO2 (405.1916):** 405.1922.
cis-t-butyl 2-(4-cyanophenyl)-4-phenylpiperidine-1-carboxylate (173h)

Cross-coupling was performed according to TP14.

**column chromatography:** SiO$_2$; $n$-pentane/Et$_2$O 5:1

**yield:** 200 mg (79 %)

**d.r.:** >99:1.

**m.p.:** 137.0-138.3 °C

$^1$H-NMR (400 MHz, C$_6$D$_6$) $\delta$: 7.19 – 7.15 (m, 2 H), 7.15 - 7.06 (m, 3 H), 6.89 (d, $J$=7.0 Hz, 2 H), 6.79 (d, $J$=8.2 Hz, 2 H), 4.51 (ddd, $J_1$=11.7 Hz, $J_2$=6.0 Hz, 1 H), 3.91 (ddd, $J_1$=13.7 Hz, $J_2$=7.07 Hz, $J_3$=4.0 Hz, 1 H), 3.20 (ddd, $J_1$=13.8 Hz, $J_2$=9.3 Hz, $J_3$=6.1 Hz, 1 H), 2.52 - 2.42 (m, 1 H), 2.00 - 1.90 (m, 1 H), 1.67 - 1.60 (m, 1 H), 1.45 - 1.32 (m, 2 H), 1.27 (s, 9 H).

$^{13}$C-NMR (101 MHz, C$_6$D$_6$) $\delta$: 155.8, 150.7, 146.3, 132.6, 129.2, 127.4, 127.1, 126.4, 119.3, 111.3, 79.9, 58.6, 40.5, 39.0, 38.4, 31.7, 28.6.

**IR (ATR)** $\tilde{\nu}$ (cm$^{-1}$): 2940 (w), 2922 (w), 2842 (w), 2222 (w), 1698 (s), 1604 (w), 1446 (w), 1390 (m), 1366 (m), 1328 (m), 1280 (m), 1254 (s), 1166 (s), 1150 (vs), 1094 (w), 1024 (w), 980 (w), 858 (w), 840 (m), 782 (m), 764 (m), 756 (m), 708 (m).

**MS (70 eV, EI) m/z (%):** 363 (1) [M+H$^+$], 306 (73), 262 (35), 261 (62), 184 (19), 157 (40), 144 (27), 143 (45), 129 (28), 118 (36), 116 (18), 104 (37), 91 (25), 57 (100), 41 (26).

**HRMS (EI) for C$_{23}$H$_{27}$N$_2$O$_2$$^+$ (363.2067) [M+H$^+$]:** 363.2060.

cis-t-butyl 2-(4-(methoxycarbonyl)phenyl)-4-phenylpiperidine-1-carboxylate (173i)

Cross-coupling was performed according to TP14.

**column chromatography:** SiO$_2$; $n$-pentane/Et$_2$O 5:1

**yield:** 185 mg (67 %)
**C. Experimental Section**

**d.r.:** 99:1.

**$^1$H-NMR (400 MHz, C$_6$D$_6$) $\delta$:** 8.13 (d, $J$=8.4 Hz, 2 H), 7.11 - 6.98 (m, 5 H), 6.84 (d, $J$=7.2 Hz, 2 H), 4.63 (dd, $J_1$=11.7 Hz, $J_2$=6.0 Hz, 1 H), 4.00 (ddd, $J_1$=13.7 Hz, $J_2$=7.4 Hz, $J_3$= 3.6 Hz, 1 H), 3.47 (s, 3 H), 3.21 (ddd, $J_1$=13.8 Hz, $J_2$= 9.6 Hz, $J_3$=6.2 Hz, 1 H), 2.52 - 2.42 (m, 1 H), 2.04 - 1.85 (m, 1 H), 1.74 - 1.67 (m, 1 H), 1.55 - 1.43 (m, 1 H), 1.36 - 1.27 (m, 1 H), 1.24 (s, 9 H).

**$^{13}$C-NMR (101 MHz, C$_6$D$_6$) $\delta$:** 167.0, 155.9, 151.2, 146.6, 130.5, 129.6, 129.1, 127.5, 126.9, 126.0, 79.8, 58.8, 51.9, 40.2, 39.0, 38.5, 31.8, 28.7.

**MS (70 eV, EI) m/z (%):** 395 (1) [M$^+$], 340 (21), 339 (100), 295 (30), 294 (48), 280 (41), 190 (19), 177 (17), 176 (27), 162 (29), 118 (23), 104 (25), 91 (21); 57 (45); 41 (19).

**IR (ATR) $\tilde{\nu}$ (cm$^{-1}$):** 2950 (w), 1720 (s), 1610 (w), 1434 (m), 1402 (s), 1366 (m), 1324 (m), 1312 (m), 1276 (vs), 1248 (s), 1168 (s), 1148 (s), 1132 (s), 1104 (s), 1060 (w), 1018 (m), 950 (w), 878 (w), 854 (m), 772 (m), 758 (s), 700 (s).

**HRMS (EI) for C$_{24}$H$_{29}$NO$_4$ (395.2097):** 395.2082.

### 5.4. Typical Procedure 15: Cross-Coupling of (1-(t-Butoxycarbonyl)-4-((triisopropylsilyl)oxy)piperidin-2-yl)zinc Chloride (TP 15) (Table 11)

A dry and Ar-flushed 10 mL Schlenk-tube equipped with a stirring bar was charged with a solution of t-butyl 4-((triisopropylsilyl)oxy)piperidine-1-carboxylate (1 mmol; 0.36 g) and TMEDA (1 mmol; 0.12 g; 0.45 mL) in anhydrous Et$_2$O (2 mL). It was cooled to -78 °C and s-BuLi (1.14 M in hexanes) (1.2 mmol; 1.05 mL) was slowly added via syringe. The reaction mixture was stirred for 4 h at this temperature before ZnCl$_2$ (1.0 M in THF) (1.2 mmol; 1.2 mL) was added. The reaction mixture was stirred for 15 min at -78 °C and was then allowed to warm to room temperature. Et$_2$O was removed in vacuo (8 min; 1 mbar). Meanwhile, a solution of the respective aryl iodide (0.7 mmol), Pd(dba)$_2$ (28.8 mg; 0.05 mmol) and Ru-Phos (23.3 mg; 0.05 mmol) was prepared and stirred for 10 min. The piperidinylzinc reagent was added to this mixture at room temperature. The reaction mixture was then heated to 55 °C for 60 h. NH$_4$Cl sat. aq. solution (20 mL) was added, the phases were separated and the aqueous phase was extracted with Et$_2$O (4 x 10 mL). The combined organic layers were washed with brine (10 mL) and dried over Na$_2$SO$_4$. The solvents were evaporated and the residue was subjected to column chromatography yielding the respective title compound.
**cis-t-butyl 2-(4-(ethoxycarbonyl)phenyl)-4-((triisopropylsilyl)oxy)piperidine-1-carboxylate (173j)**

Cross-coupling was performed according to TP15.

**column chromatography:** SiO$_2$; $n$-pentane/Et$_2$O 8:1  
**yield:** 297 mg (84 %)  
**d.r.:** 97:3.

$^1$H-NMR (400 MHz, C$_6$D$_6$) $\delta$: 8.17 (d, $J$=8.4 Hz, 2 H), 7.20 (d, $J$=8.0 Hz, 2 H), 5.32 (dd, $J_I$=6.2 Hz, $J_2$=3.2 Hz, 1 H), 4.24 - 4.16 (m, 1 H), 4.13 (q, $J$=7.11 Hz, 2 H), 3.89 - 3.82 (m, 1 H), 3.45 (td, $J_I$=12.7 Hz, $J_2$=3.5 Hz, 1 H), 2.06 (dt, $J_I$=14.0 Hz, $J_2$=3.5 Hz, 1 H), 1.78 (ddd, $J_I$=14.1 Hz, $J_2$=7.1 Hz, $J_3$=3.0 Hz, 1 H), 1.58 - 1.49 (m, 1 H), 1.39 (s, 9 H), 1.31 (d, $J$=7.0 Hz, 1 H), 1.02 (t, $J$=7.0 Hz, 3 H), 0.98 - 0.77 (m, 18 H), 0.77 - 0.69 (m, 3 H).

$^{13}$C-NMR (101 MHz, C$_6$D$_6$) $\delta$: 166.6, 155.7, 149.7, 130.3, 129.4, 126.3, 79.8, 65.7, 61.0, 53.3, 37.7, 36.6, 33.5, 32.7, 30.5, 30.5, 30.2, 28.7, 23.5, 18.5, 18.4, 14.7, 14.7, 12.7.

**MS (70 eV, EI) m/z (%):** 505 (1) [M$^+$], 407 (32), 406 (100), 363 (31), 362 (91), 231 (74), 230 (85), 188 (21), 186 (85), 159 (38), 144 (23), 131 (44), 103 (21), 75 (22), 57 (29), 41 (19).

**IR (ATR) $\tilde{\nu}$ (cm$^{-1}$):** 2940 (m), 2924 (m), 2865 (m), 1717 (s), 1693 (vs), 1462 (m), 1414 (m), 1403 (m), 1390 (m), 1381 (m), 1364 (s), 1271 (vs), 1254 (m), 1214 (m), 1170 (s), 1103 (vs), 1080 (s), 1067 (s), 1044 (s), 1021 (s), 995 (m), 985 (m), 953 (m), 880 (s), 850 (m), 777 (m), 773 (m), 721 (m), 713 (m), 679 (s), 660 (s), 631 (m).

**HRMS (EI) for C$_{28}$H$_{47}$NO$_5$Si (505.3224):** 505.3221.

**cis-t-butyl 2-(4-fluorophenyl)-4-((triisopropylsilyl)oxy)piperidine-1-carboxylate (173k)**

Cross-coupling was performed according to TP15.

**column chromatography:** SiO$_2$; CH$_2$Cl$_2$  
**yield:** 275 mg (87 %)  
**d.r.:** 95:5.
C. Experimental Section

\[ \text{H-NMR (300 MHz, C}_6\text{D}_6\] \delta: 7.04 (dd, \( J_1=8.3 \) Hz, \( J_2=5.3 \) Hz, 2 H), 6.83 (t, \( J=8.7 \) Hz, 2 H), 5.30 - 5.25 (m, 1 H), 4.16 (ddd, \( J_1=13.3 \) Hz, \( J_2=4.7 \) Hz, \( J_2=2.9 \) Hz, 1 H), 3.89 - 3.83 (m, 1 H), 3.40 (td, \( J_1=12.7 \) Hz, \( J_2=3.5 \) Hz, 1 H), 2.06 - 1.97 (m, 1 H), 1.78 (ddd, \( J_1=14.1 \) Hz, \( J_2=6.9 \) Hz, \( J_2=3.3 \) Hz, 1 H), 1.63 - 1.51 (m, 1 H), 1.40 (s, 9 H), 1.11 - 1.04 (m, 1 H), 1.02 - 0.83 (m, 18 H), 0.83 - 0.73 (m, 3 H).

\[ \text{C-NMR (75 MHz, C}_6\text{D}_6\] \delta: 155.7, 162.2 (d, \( J=243.2 \) Hz), 139.9 (d, \( J=3.1 \) Hz), 127.9 (d, \( J=7.8 \) Hz), 115.4 (d, \( J=21.3 \) Hz), 79.7, 65.8, 52.8, 37.7, 36.4, 33.7, 28.8, 18.5, 18.5, 12.7.

\[ \text{F-NMR (282 MHz, C}_6\text{D}_6\] \delta: -116.44 - -116.36 (m) (minor), -117.97 - -117.82 (m) (major).

\[ \text{MS (70 eV, EI) m/z (%): 451 (1) [M^+], 309 (22), 308 (86), 187 (18), 186 (100), 177 (87), 176 (18), 174 (18), 173 (19), 159 (40), 157 (20), 156 (22), 150 (26), 144 (35), 142 (16), 131 (35), 103 (24), 75 (25), 41 (17).}

\[ \text{IR (ATR) } \tilde{\nu} \text{ (cm}^{-1}\): 2972 (w), 2932 (w), 2232 (w), 1684 (s), 1608 (w), 1570 (s), 1474 (w), 1454 (m), 1434 (w), 1410 (m), 1392 (m), 1380 (m), 1364 (s), 1338 (s), 1312 (m), 1280 (m), 1270 (m), 1248 (m), 1220 (m), 1156 (vs), 1104 (s), 1070 (m), 1056 (m), 1018 (m), 982 (s), 964 (m), 910 (m), 870 (m), 854 (m), 838 (s), 794 (m), 780 (m), 758 (m), 724 (w), 680 (m), 670 (m), 660 (m).

\[ \text{HRMS (EI) for C}_{25}\text{H}_{42}\text{FNO}_3\text{Si (451.2918): 451.2938.}

\text{cis-t-butyl 2-(4-(trifluoromethyl)phenyl)-4-((triisopropylsilyl)oxy)piperidine-1-carboxylate (173l) }

Cross-coupling was performed according to TP15.

\text{column chromatography: SiO}_2; \text{CH}_2\text{Cl}_2

\text{yield: 284 mg (81 \%) }

\text{d.r.: 95:5}

\text{m. p.: 94.8 – 95.9°C}

\[ \text{H-NMR (400 MHz, C}_6\text{D}_6\] \delta: 7.37 (d, \( J=8.2 \) Hz, 2 H), 7.10 (d, \( J=8.2 \) Hz, 2 H), 5.35 (d, \( J=5.1 \) Hz, 1 H), 4.16 (d, \( J=12.9 \) Hz, 1 H), 3.85 - 3.80 (m, 1 H), 3.39 (td, \( J_1=12.7 \) Hz, \( J_2=3.6 \) Hz, 1 H), 2.01 (d, \( J=14.3 \) Hz, 1 H), 1.73 (ddd, \( J_1=14.1 \) Hz, \( J_2=7.1 \) Hz, \( J_2=3.0 \) Hz, 1 H), 1.53 - 1.47 (m, 1 H), 1.41 (s, 9 H), 1.04 - 1.00 (m, 1 H), 0.84 - 0.80 (m, 18 H), 0.75 - 0.62 (m, 3 H).
$^{13}$C-NMR (101 MHz, CD$_6$D) $\delta$: 155.7, 148.4 (d, $J=1.0$ Hz), 128.8 (q, $J=32.3$ Hz), 126.6, 125.7 (q, $J=3.7$ Hz), 125.5 (q, $J=271.6$ Hz), 79.9, 65.5, 52.7, 37.4, 36.3, 33.4, 28.7, 18.5, 18.4, 12.7. $^{19}$F-NMR (376 MHz, CD$_6$D) $\delta$: -62.12 (s) (major), -62.20 (s) (minor).

**MS (70 eV, EI) m/z (%)**: 501 (1) [M$^+$], 403 (23), 402 (100), 358 (24), 230 (31), 186 (22), 131 (22), 57 (12).

**IR (ATR) $\tilde{\nu}$ (cm$^{-1}$)**: 2944 (m), 2868 (m), 1696 (s), 1418 (m), 1366 (m), 1328 (vs), 1164 (s), 1126 (s), 1082 (m), 1070 (m).

**HRMS (EI) for C$_{26}$H$_{42}$F$_3$NO$_3$Si (501.2886):** 501.2877.

cis-t-butyl 2-(4-cyanophenyl)-4-(((triisopropylsilyl)oxy)piperidine-1-carboxylate (173m)

![Chemical structure](attachment:structure.png)

Cross-coupling was performed according to **TP15**.

**Column chromatography**: SiO$_2$; n-pentane/Et$_2$O 4:1

**Yield**: 260 mg (81 %)

**d.r.:** 97:3.

$^1$H-NMR (400 MHz, CD$_6$D) $\delta$: 7.09 (d, $J=8.2$ Hz, 2 H), 6.90 (d, $J=8.0$ Hz, 2 H), 5.21 (d, $J=4.3$ Hz, 1 H), 4.08 (dd, $J_1=9.68$ Hz, $J_2=3.42$ Hz, 1 H), 3.79 - 3.75 (m, 1 H), 3.28 (td, $J_1=12.6$ Hz, $J_2=3.7$ Hz, 1 H), 1.89 (d, $J=14.1$ Hz, 1 H), 1.66 (ddd, $J_1=14.1$ Hz, $J_2=7.1$ Hz, $J_3=3.0$ Hz, 1 H), 1.50 - 1.41 (m, 2 H), 1.39 (s, 9 H), 0.80 (t, $J=6.9$ Hz, 18 H), 0.72 - 0.63 (m, 3 H).

$^{13}$C-NMR (101 MHz, CD$_6$D) $\delta$: 155.5, 149.4, 132.3, 126.9, 119.3, 110.8, 80.0, 65.4, 52.8, 37.3, 36.3, 33.3, 28.8, 28.7, 18.6, 18.4, 14.8, 12.9, 12.6, 12.3.

**MS (70 eV, EI) m/z (%)**: 459 (1) [M+H$^+$], 360 (19), 359 (65), 316 (27), 315 (100), 230 (18), 187 (10), 186 (58), 184 (24), 159 (19), 157 (13), 156 (14), 144 (21), 131 (11), 75 (13), 57 (10).

**IR (ATR) $\tilde{\nu}$ (cm$^{-1}$)**: 2941 (m), 2865 (m), 1691 (vs), 1461 (m), 1414 (m), 1403 (m), 1390 (m), 1381 (m), 1364 (s), 1355 (m), 1334 (m), 1281 (m), 1252 (m), 1215 (m), 1166 (s), 1127 (m), 1117 (m), 1079 (s), 1067 (s), 1043 (s), 1021 (m), 1013 (s), 985 (s), 880 (s), 873 (s), 830 (m), 796 (m), 771 (m), 746 (m), 697 (m), 680 (s), 659 (s), 641 (m), 636 (m).

**HRMS (EI) for C$_{26}$H$_{43}$N$_2$O$_3$Si$^+$ (459.3037) [M+H$^+$]:** 459.3022.
5.5. Typical Procedure 16: Cross-Coupling of (trans-2-(t-Butoxycarbonyl)decahydroisoquinolin-3-yl)zinc Chloride (TP 16) (Table 11)

A dry and Ar-flushed 10 mL Schlenk-tube equipped with a stirring bar was charged with a solution of trans-t-butyl octahydroisoquinoline-2(1H)-carboxylate (1 mmol; 0.24 g) and TMEDA (1 mmol; 0.12 g; 0.45 mL) in anhydrous Et₂O (2 mL). It was cooled to -78 °C and s-BuLi (1.14 M in hexanes) (1.2 mmol; 1.05 mL) was slowly added via syringe. The reaction mixture was stirred for 4 h at this temperature before ZnCl₂ (1.0 M in THF) (1.2 mmol; 1.2 mL) was added. The reaction mixture was stirred for 15 min at -78 °C and was then allowed to warm to room temperature. Et₂O was removed in vacuo (8 min; 1 mbar). Meanwhile, a solution of the respective aryl iodide (0.7 mmol), Pd(dba)_2 (28.8 mg; 0.05 mmol) and Ru-Phos (23.3 mg; 0.05 mmol) was prepared and cooled to 0 °C. The piperidinylzinc reagent was added to this mixture and stirred for 4 h. The reaction mixture was then warmed to room temperature and stirred for 12 h and finally heated to 55 °C for 12 h. NH₄Cl sat. aq. solution (20 mL) was added, the phases were separated and the aqueous phase was extracted with Et₂O (4 x 10 mL). The combined organic layers were washed with brine (10 mL) and dried over Na₂SO₄. The solvents were evaporated and the residue was subjected to column chromatography yielding the respective title compound.

t-butyl 3-(4-(trifluoromethyl)phenyl)octahydroisoquinoline-2(1H)-carboxylate (173n)

Cross-coupling was performed according to TP16.

column chromatography: SiO₂; n-pentane/CH₂Cl₂ 1:1 to 1:4

yield: 185 mg (69 %)
d.r.: >99:1.
m.p.: 104.1 – 105.5 °C.

¹H-NMR (599 MHz, C₆D₆) δ: 7.42 (d, J=8.2 Hz, 2 H), 7.07 (d, J=8.2 Hz, 2 H), 4.16 (dd, J₁=10.8 Hz, J₂=5.1 Hz, 1 H), 4.04 (dd, J₁=12.8 Hz, J₂=5.1 Hz, 1 H), 2.65 (dd, J₁=12.6 Hz, J₂=10.7 Hz, 1 H), 1.56 (d, J=8.0 Hz, 2 H), 1.51 (ddd, J₁=13.3 Hz, J₂=4.8 Hz, J₃=3.3 Hz, 1 H), 1.44 - 1.36 (m, 2 H), 1.17 (s, 9 H), 1.10 - 0.95 (m, 4 H), 0.79 - 0.64 (m, 3 H).
**C. Experimental Section**

\(^{13}\)C-NMR (151 MHz, \(\text{C}_6\text{D}_6\)) \(\delta\): 156.9, 151.6 (d, \(J=1.4\) Hz), 128.8 (q, \(J=32.3\) Hz), 126.5, 125.7 (q, \(J=3.6\) Hz), 125.6 (q, \(J=271.8\) Hz), 79.8, 59.6, 52.2, 41.6, 41.0, 39.9, 33.2, 31.2, 28.4, 26.7, 26.4.

\(^{19}\)F-NMR (376 MHz, \(\text{C}_6\text{D}_6\)) \(\delta\): -61.83 (s).

**MS** (70 eV, EI) \(m/z\) (%): 383 (1) \([\text{M}^+]\), 328 (24), 327 (100), 326 (10), 283 (27), 282 (67), 240 (13), 182 (11), 182 (18), 181 (17), 177 (35), 138 (40), 137 (19), 57 (60).

**IR** (ATR) \(\tilde{\nu}\) (cm\(^{-1}\)): 2920 (w), 2854 (w), 1680 (s), 1368 (m), 1326 (vs), 1306 (m), 1282 (m), 1258 (m), 1250 (m), 1160 (vs), 1142 (m), 1118 (vs), 1104 (s), 1090 (m), 1068 (vs), 1020 (m), 854 (m), 838 (s), 788 (m), 662 (m), 612 (m).

**HRMS (EI)** for \(\text{C}_{21}\text{H}_{28}\text{F}_3\text{NO}_2\) (383.2072): 383.2075.

---

**t-butyl 3-(4-cyanophenyl)octahydroisoquinoline-2(1\(H\))-carboxylate (173o)**

Cross-coupling was performed according to TP16.

**Column chromatography:** SiO\(_2\); \(n\)-pentane/Et\(_2\)O 5:1

**Yield:** 129 mg (54 %)

**d.r.:** >99:1.

**m.p.:** 83.3 – 84.6 °C.

\(^1\)H-NMR (400 MHz, \(\text{C}_6\text{D}_6\)) \(\delta\): 7.11 (m, \(J=8.4\) Hz, 2 H), 6.86 (m, \(J=8.2\) Hz, 2 H), 4.04 - 3.94 (m, 2 H), 2.56 (dd, \(J_1=12.8\) Hz, \(J_2=10.8\) Hz, 1 H), 1.55 (d, \(J=9.0\) Hz, 2 H), 1.42 - 1.33 (m, 3 H), 1.14 (s, 9 H), 1.09 - 1.01 (m, 2 H), 0.96 - 0.83 (m, 2 H), 0.77 - 0.62 (m, 3 H).

\(^{13}\)C-NMR (101 MHz, \(\text{CDCl}_3\)) \(\delta\): 156.6, 152.1, 132.2, 126.4, 119.2, 110.4, 79.7, 59.6, 52.1, 41.3, 40.7, 39.7, 32.9, 30.8, 28.2, 26.4, 26.1.

**MS** (70 eV, EI) \(m/z\) (%): 340 (1) \([\text{M}^+]\), 284 (65), 240 (37), 239 (100), 182 (37), 143 (35), 138 (37), 74 (45), 59 (73), 57 (89), 45 (51), 41 (63).

**IR** (ATR) \(\tilde{\nu}\) (cm\(^{-1}\)): 2922 (m), 2844 (w), 2230 (w), 1686 (vs), 1372 (m), 1364 (m), 1328 (m), 1306 (m), 1280 (m), 1252 (m), 1222 (m), 1162 (vs), 1140 (m), 1128 (m), 1118 (m), 1102 (m), 836 (m), 788 (m).

t-butyl 3-(4-methoxyphenyl)octahydroisoquinoline-2(1H)-carboxylate (173p)

Cross-coupling was performed according to TP16.

**column chromatography:** SiO2; n-pentane/Et2O 6:1

**yield:** 145 mg (60 %)

**d.r.:** 97:3.

**m.p.:** 73.1 – 74.7 °C.

**1H-NMR (400 MHz, C6D6) δ:** 7.19 (d, J=8.0 Hz 2 H), 6.85 (d, J=8.8 Hz, 2 H), 4.50 (dd, J=10.1 Hz, J=5.6 Hz, 1 H), 4.04 (dd, J=13.0 Hz, J=5.6 Hz, 1 H), 3.36 (s, 3 H), 2.89 (dd, J=12.9 Hz, J=9.7 Hz, 1 H), 1.75 (ddd, J=13.3 Hz, J=5.6 Hz, J=3.7 Hz, 1 H), 1.55 (d, J=8.0 Hz, 2 H), 1.44 (td, J=6.0 Hz, J=2.8 Hz, 2 H), 1.36 - 1.27 (m, 10 H), 1.14 - 1.01 (m, 3 H), 0.89 - 0.69 (m, 3 H).

**13C-NMR (101 MHz, C6D6) δ:** 159.0, 157.0, 139.0, 131.0, 127.4, 114.2, 79.2, 58.8, 55.2, 51.6, 41.1, 40.8, 39.9, 33.5, 31.6, 30.6, 28.7, 26.9, 26.6.

**MS (70 eV, EI) m/z (%):** 345 (2) [M+], 290 (20), 289 (100), 288 (36), 245 (20), 244 (85), 181 (11), 137 (10), 136 (15), 121 (18), 57 (14).

**IR (ATR) v (cm⁻¹):** 2930 (m), 2918 (m), 2854 (m), 1684 (vs), 1510 (s), 1466 (m), 1444 (m), 1390 (m), 1366 (s), 1324 (m), 1304 (m), 1278 (m), 1238 (vs), 1224 (s), 1166 (vs), 1142 (s), 1126 (s), 1102 (s), 1090 (m), 1078 (m), 1036 (s), 1018 (m), 976 (m), 876 (m), 858 (m), 828 (vs), 816 (m), 786 (s), 764 (m).

**HRMS (EI) for C₂₁H₃₁NO₃ (345.2304): 345.2296.**

### 5.6. Typical Procedure 17: Cross-Coupling of (1-(t-Butoxycarbonyl)-5-methylpiperidin-2-yl)zinc Chloride (TP 17) (Table 11)

A dry and Ar-flushed 10 mL Schlenk-tube equipped with a stirring bar was charged with a solution of t-butyl 3-methylpiperidine-1-carboxylate (1 mmol; 0.20 g) and TMEDA (1 mmol; 0.12 g; 0.45 mL) in anhydrous Et₂O (2 mL). It was cooled to -78 °C and s-BuLi (1.14 M in hexanes) (1.2 mmol; 1.05 mL) was slowly added via syringe. The reaction mixture was stirred for 4 h at this temperature before ZnCl₂ (1.0 M in THF) (1.2 mmol; 1.2 mL) was added. The
reaction mixture was stirred for 15 min at -78 °C and was then allowed to warm to room temperature. Et₂O was removed \textit{in vacuo} (8 min; 1 mbar). Meanwhile, a solution of the respective aryl iodide (0.7 mmol), Pd(dba)₂ (28.8 mg; 0.05 mmol) and Ru-Phos (23.3 mg; 0.05 mmol) was prepared and cooled to 0 °C. The piperidinylzinc reagent was added to this mixture at this temperature and stirred for 6 h. It was then kept at room temperature for further 12 h and eventually heated to 40 °C for 12 h. NH₄Cl sat. aq. solution (20 mL) was added, the phases were separated and the aqueous phase was extracted with Et₂O (4 x 10 mL). The combined organic layers were washed with brine (10 mL) and dried over Na₂SO₄. The solvents were evaporated and the residue was subjected to column chromatography yielding the respective title compound.

\textit{trans-t}-butyl 2-(4-cyanophenyl)-5-methylpiperidine-1-carboxylate (173q)

\begin{center}
\includegraphics[width=0.2\textwidth]{trans-t-butyl_2-(4-cyanophenyl)-5-methylpiperidine-1-carboxylate.png}
\end{center}

Cross-coupling was performed according to TP17. \\
\textbf{column chromatography:} SiO₂; \textit{n}-pentane/Et₂O 4:1 \\
\textbf{yield:} 128 mg (61 %) \\
\textbf{d.r.:} 96:4. (10% regioisomer)

\textbf{¹H-NMR (400 MHz, C₆D₆)}: δ: 7.04 (m, J=8.4 Hz, 2 H), 6.80 (d, J=8.0 Hz, 2 H), 5.22 (br. s., 1 H), 3.67 (d, J=13.6 Hz, 1 H), 2.70 (dd, J₁=13.4 Hz, J₂=3.7 Hz, 1 H), 1.78 - 1.67 (m, 1 H), 1.41 (s, 9 H), 1.39 - 1.28 (m, 3 H), 1.24 - 1.14 (m, 1 H), 0.90 (d, J=7.0 Hz, 3 H).

\textbf{¹³C-NMR (101 MHz, C₆D₆)}: δ: 155.4, 146.3, 137.7, 132.4, 131.8, 126.7, 118.5, 110.6, 79.0, 53.5, 45.1, 28.0, 27.7, 25.7, 23.0, 17.0.

\textbf{MS (70 eV, EI)} m/z (%): 300 (1) [M⁺], 245 (23), 244 (87), 227 (17), 200 (30), 199 (96), 143 (11), 142 (32), 129 (16), 116 (26), 98 (11), 57 (100), 43 (18), 41 (18).

\textbf{IR (ATR)} $\tilde{\nu}$ (cm⁻¹): 2960 (w), 2928 (w), 2228 (w), 1684 (s), 1476 (w), 1456 (m), 1414 (s), 1392 (m), 1364 (s), 1328 (m), 1246 (m), 1172 (s), 1142 (vs), 1102 (w), 1084 (m), 1058 (m), 1018 (w), 990 (m), 878 (w), 854 (m), 838 (m), 768 (m).

\textbf{HRMS (EI)} for C₁₈H₂₄N₂O₂ (300.1838): 300.1840.
trans-t-butyl 2-(4-(ethoxycarbonyl)phenyl)-5-methylpiperidine-1-carboxylate (173r)

Cross-coupling was performed according to TP17.

column chromatography: SiO2; n-pentane/Et3O 5:1

yield: 153 mg (63 %)

d.r.: 95:5.

\(^1\)H-NMR (400 MHz, C\textsubscript{6}D\textsubscript{6}) \(\delta\): 8.17 (d, \(J=8.4\) Hz, 2 H), 7.15 (d., 2 H), 5.41 (br. s., 1 H), 4.15 (q, \(J=7.0\) Hz, 2 H), 3.78 (d., \(J=13.4\) Hz, 1 H), 2.88 (dd, \(J_1=13.5\) Hz, \(J_2=3.6\) Hz, 1 H), 1.87 - 1.77 (m, 1 H), 1.62 - 1.54 (m, 1 H), 1.49-1.43 (m, 10 H), 1.40 - 1.27 (m, 2 H), 1.03 (t, \(J=7.1\) Hz, 3 H), 0.94 (d, \(J=7.0\) Hz, 3 H).

\(^13\)C-NMR (101 MHz, C\textsubscript{6}D\textsubscript{6}) \(\delta\): 166.5, 156.3, 147.2, 130.6, 130.5, 130.4, 129.8, 127.1, 79.6, 61.1, 54.4, 45.8, 28.8, 28.5, 26.5, 23.9, 17.8, 14.7.

MS (70 eV, EI) m/z (%): 347 (1) [M\(^+\)], 292 (16), 291 (92), 262 (17), 247 (11), 246 (53), 219 (15), 218 (100), 142 (13), 98 (12), 57 (18).

IR (ATR) \(\tilde{\nu}\) (cm\(^{-1}\)): 2964 (w), 2932 (w), 1716 (s), 1686 (vs), 1610 (w), 1476 (w), 1456 (m), 1416 (s), 1392 (m), 1364 (s), 1342 (w), 1324 (m), 1312 (m), 1270 (vs), 1246 (s), 1172 (s), 1142 (vs), 1122 (s), 1102 (vs), 1058 (m), 1018 (s), 988 (m), 892 (w), 878 (m), 864 (m), 836 (w), 766 (m), 746 (m), 724 (w), 696 (m).

HRMS (EI) for C\textsubscript{20}H\textsubscript{29}NO\textsubscript{4} (347.2097): 347.2096.

5.7. Typical Procedure 18: Preparation of Piperidin-4-ylzinc Iodides (TP 18) (Table 12)

Anhydrous LiCl (4.5 mmol; 0.19 g) was placed in an Ar-flushed flask and dried for 20 min at 150-170 °C under high vacuum (1 mbar). Zn powder (9 mmol; 0.59 g; 150 mesh, Chemetall) was added under Ar and the heterogeneous mixture of Zn and LiCl was dried again under vigorous stirring for 20 min at 150-170 °C under high vacuum (1 mbar). The reaction mixture was evacuated and refilled with Ar three times. A catalytic amount of 1,2-dibromoethane and THF (6 mL) were added. The mixture was gently heated in order to activate the Zn surface. The respective 4-iodopiperidine was added neat at room temperature. The resulting reaction mixture was stirred for 4 h at ambient temperature. It was then separated from the remaining
Zn powder via syringe filter (25 mm with 1 µm glass fiber membrane) and transferred to an Ar-flushed Schlenk flask. The concentrations of all piperidinylzinc reagents were determined via titration with I₂ (50 mg in 2 mL THF).

(1-(t-butoxycarbonyl)-2-(4-(trifluoromethyl)phenyl)-piperidin-4-yl)zinc iodide (174a)

Zn-insertion was performed according to TP18.
0.35 M (70%)

(1-tosyl-2-(4-(trifluoromethyl)phenyl)piperidin-4-yl)zinc iodide (174b)

Zn-insertion was performed according to TP18.
0.39 M (78%)

(2-methyl-1-tosylpiperidin-4-yl)zinc iodide (174c)

Zn-insertion was performed according to TP18.
0.42 M (84%)

5.8. Typical Procedure 19: Cross-Coupling of Piperidin-4-ylzinc Iodides (TP 19) (Table 12)

A dry and Ar-flushed 10 mL Schlenk-tube, equipped with a magnetic stirring bar and a septum was charged with TMPP₂PdCl₂ (0.05 mmol; 63 mg), the respective aryl iodide (0.8
mmol), THF (0.8 mL) and NEP (0.02 mL). The mixture was stirred for 5 min at room temperature and then cooled to -10 °C. The corresponding piperidin-4-ylzinc iodide (0.36 – 0.39 M solution in THF) was slowly added via syringe. The reaction mixture was kept for 12 h at -10 °C and subsequently 5 h at -5 °C. NH₄Cl sat. aq. solution (20 mL) was added, the phases were separated and the aqueous phase was extracted with CH₂Cl₂ (4 x 20 mL). The combined organic layers were washed with brine (20 mL) and dried over Na₂SO₄. The solvents were evaporated and the residue was subjected to column chromatography yielding the respective title compound.

**trans-t-butyl 4-(4-cyanophenyl)-2-(4-(trifluoromethyl)phenyl)piperidine-1-carboxylate (176a)**

![Chemical Structure](image)

Cross-coupling was performed according to TP19.

**column chromatography:** SiO₂; n-pentane/Et₂O 5:1 to 2:1

**yield:** 255 mg (74 %)

**d.r.:** 91:9.

**m.p.:** 72.9 – 74.6 °C.

**1H-NMR (400 MHz, C₆D₆) δ:** 7.42 (d, J=8.2 Hz, 2 H), 7.08 (d, J=8.2 Hz, 2 H), 7.04 (d, J=8.0 Hz, 2 H), 6.55 (d, J=8.0 Hz, 2 H), 5.59 (br. s., 1 H), 4.21 (br. s., 1 H), 2.66 - 2.57 (m, 1 H), 2.22 - 2.12 (m, 1 H), 1.93 (d, J=13.7 Hz, 1 H), 1.59 (td, J₁=13.4 Hz, J₂= 5.5 Hz, 1 H), 1.49 (s, 9 H), 1.33 - 1.20 (m, 2 H).

**13C-NMR (101 MHz, C₆D₆) δ:** 154.7, 149.7, 144.2, 131.8, 129.0 (q, J=32.5 Hz), 126.9, 126.6, 125.5 (q, J=3.7 Hz), 124.4 (q, J=271.9 Hz), 118.1, 110.9, 79.6, 52.9, 39.9, 36.9, 34.7, 32.1, 28.0.

**19F-NMR (282 MHz, C₆D₆) δ:** -62.14 (s) (minor), -62.19 (s) (major)

**MS (70 eV) m/z (%):** 330 (20), 329 (19), 328 (11), 311 (14), 227 (19), 213 (33), 207 (21), 200 (32), 188 (11), 187 (59), 186 (100), 185 (17), 173 (13).

**IR (ATR) V (cm⁻¹):** 2976 (vw), 2932 (w), 2868 (vw), 2228 (w), 1686 (s), 1620 (w), 1608 (w), 1506 (vw), 1478 (vw), 1454 (w), 1414 (m), 1366 (m), 1326 (vs), 1282 (m), 1258 (w),
trans-\textit{t}-butyl 4-phenyl-2-(4-(trifluoromethyl)phenyl)-piperidine-1-carboxylate (176b)


cross-coupling was performed according to TP19.

\textbf{Column chromatography: } SiO$_2$; CH$_2$Cl$_2$

drift: 92:8.

\textbf{\textsuperscript{1}H-NMR (400 MHz, C$_6$D$_6$) } \(\delta \): 7.41 (d, \(J=8.2\) Hz, 2 H), 7.16 - 7.02 (m, 5 H), 6.91 (d, \(J=7.4\) Hz, 2 H), 5.63 (br. s., 1 H), 4.25 (br. s., 1 H), 2.73 - 2.65 (m, 1 H), 2.38 (t, \(J=11.7\) Hz, 1 H), 2.15 (d, \(J=13.7\) Hz, 1 H), 1.83 (td, \(J_1=13.3\) Hz, \(J_2=5.5\) Hz, 1 H), 1.54 - 1.40 (m, 11 H).

\textbf{\textsuperscript{13}C-NMR (101 MHz, C$_6$D$_6$) } \(\delta \): 155.7, 146.1, 145.6, 129.7 (q, \(J=32.5\) Hz), 129.2, 127.6, 127.3, 127.1, 126.2 (q, \(J=3.9\) Hz), 126.1 (q, \(J=271.8\) Hz), 80.1, 54.1, 41.2, 37.8, 36.2, 33.7, 28.9.

\textbf{MS (70 eV, EI) } m/z (%): 405 (1) [M$^+$], 350 (22), 349 (100), 304 (21), 200 (14), 187 (10), 186 (12), 159 (10), 118 (37), 104 (15), 90 (19), 59 (89), 41 (13); 18 (25).

\textbf{IR (ATR) } \(\tilde{\nu} \) (cm$^{-1}$): 2976 (w), 2932 (w), 2868 (vw), 1688 (s), 1620 (w), 1494 (vw), 1478 (w), 1454 (w), 1414 (m), 1394 (m), 1366 (m), 1324 (vs), 1300 (m), 1282 (m), 1268 (m), 1256 (w), 1234 (m), 1214 (w), 1154(s), 1118 (vs), 1068 (s), 1016 (s), 986 (w), 964 (w), 912 (w), 888 (w), 862 (w), 838 (m), 760 (m), 730 (w), 722 (w), 698 (s), 638 (w).

\textbf{HRMS (EI) for C$_{23}$H$_{26}$F$_3$NO$_2$ (405.1916): 405.1932.}
Experimental Section

4-(trans-1-tosyl-2-(4-(trifluoromethyl)phenyl)piperidin-4-yl)benzonitrile (176c)

Cross-coupling was performed according to TP19.

Column chromatography: SiO$_2$; $n$-pentane/Et$_2$O 5:1 to 1:1

yield: 271 mg (70 %)
d.r.: >99:1.
m.p.: 181.7 – 183.3 °C.

$^1$H-NMR (400 MHz, C$_6$D$_6$) $\delta$: 7.74 (d, $J$=8.2 Hz, 2 H), 7.35 (d, $J$=8.4 Hz, 2 H), 7.07 (d, $J$=8.2 Hz, 2 H), 6.98 (m, $J$=8.4 Hz, 2 H), 6.83 (d, $J$=8.0 Hz, 2 H), 6.35 (d, $J$=8.2 Hz, 2 H), 5.38 (d, $J$=3.3 Hz, 1 H), 3.97 - 3.85 (m, 1 H), 2.69 - 2.58 (m, 1 H), 2.05 - 1.96 (m, 1 H), 1.94 (s, 3 H), 1.76 (d, $J$=13.8 Hz, 1 H), 1.51 (td, $J_1$=13.4 Hz, $J_2$=5.3 Hz, 1 H), 1.16 (qd, $J_1$=12.7 Hz, $J_2$=4.4 Hz, 1 H), 0.95 (d, $J$=12.9 Hz, 1 H).

$^{13}$C-NMR (101 MHz, C$_6$D$_6$) $\delta$: 150.0, 143.7, 143.5 (d, $J$=1.1 Hz), 139.6, 132.7, 130.3, 129.9 (q, $J$=32.2 Hz), 127.8, 127.7, 127.7, 126.3 (q, $J$=3.7 Hz), 125.2 (q, $J$=271.7 Hz), 119.1, 111.5, 55.5, 42.0, 37.0, 34.4, 31.8, 21.5.

$^{19}$F-NMR (282 MHz, C$_6$D$_6$) $\delta$: -62.16 (s).

MS (70 eV) m/z (%): 386 (37), 377 (25), 376 (100), 375 (21), 374 (16), 329 (17), 281 (10), 208 (13), 207 (56), 200 (14), 199 (12), 186 (43); 172 (13); 159 (29); 155 (21); 131 (20); 103 (10); 92 (10); 91 (73).

IR (ATR) $\tilde{\nu}$ (cm$^{-1}$): 2956 (w), 2930 (w), 2232 (m), 1612 (w), 1326 (vs), 1256 (m), 1158 (vs), 1110 (s), 1094 (s), 1072 (s), 1018 (s), 944 (m), 928 (s), 906 (m), 838 (s), 826 (s), 800 (m), 716 (s), 702 (s), 664 (vs), 650 (s).

HRMS (ESI) for C$_{26}$H$_{23}$F$_3$N$_2$O$_2$SCl $^{(519.1126)}$ [M+Cl$^-$]: 519.1122.
methyl 4-(trans-1-tosyl-2-(4-(trifluoromethyl)phenyl)piperidin-4-yl)benzoate (176d)

Cross-coupling was performed according to TP19.

column chromatography: SiO$_2$; $n$-pentane/Et$_2$O 5:1 to 1:1

yield: 286 mg (69 %)
d.r.: 97:3.
m.p.: 68.8 – 70.5 °C.

$^1$H-NMR (300 MHz, C$_6$D$_6$) $\delta$: 8.06 (d, $J$=8.2 Hz, 2 H), 7.76 (d, $J$=8.2 Hz, 2 H), 7.36 (d, $J$=8.2 Hz, 2 H), 7.14 (d, $J$=8.0 Hz, 3 H), 6.83 (d, $J$=8.0 Hz, 2 H), 6.68 (d, $J$=8.2 Hz, 2 H), 5.40 (d, $J$=3.4 Hz, 1 H), 3.94 (d, $J$=14.2 Hz, 1 H), 3.51 (s, 3 H), 2.74 - 2.63 (m, 1 H), 2.25 - 2.13 (m, 1 H), 1.94 (s, 3 H), 1.87 (br. s., 1 H), 1.63 (dd, $J_1$=13.4 Hz, $J_2$=5.3 Hz, 2 H), 1.34 - 1.25 (m, 1 H), 1.08 (d, $J$=14.6 Hz, 1 H).

$^{13}$C-NMR (75 MHz, C$_6$D$_6$) $\delta$: 166.8, 150.5, 143.7 (d, $J$=1.2 Hz), 143.6, 139.8, 130.6, 130.2, 129.8 (q, $J$=32.3 Hz), 129.7, 128.0, 127.8, 127.2, 126.3 (q, $J$=3.8 Hz), 125.3 (q, $J$=272.0 Hz), 55.7, 52.0, 42.2, 37.1, 34.4, 31.9, 21.5.

MS (70 eV, EI) $m/z$ (%): 517 (11) [M$^+$], 371 (35), 362 (24), 361 (100), 360 (27), 359 (12), 186 (21), 155 (11), 90 (22).

IR (ATR) $\tilde{\nu}$ (cm$^{-1}$): 2952 (vw), 2930 (vw), 2876 (vw), 1718 (s), 1610 (w), 1494 (vw), 1450 (w), 1436 (w), 1412 (w), 1326 (vs), 1278 (s), 1182 (w), 1156 (vs), 1114 (vs), 1096 (s), 1068 (s), 1016 (m), 954 (w), 932 (s), 908 (m), 840 (m), 816 (m), 802 (w), 770 (m), 742 (m), 716 (m), 708 (m), 690 (s), 658 (s), 646 (m).

HRMS (EI) for C$_{27}$H$_{26}$F$_3$NO$_4$S (517.1535): 517.1537.
C. Experimental Section

4-(trans-2-methyl-1-tosylpiperidin-4-yl)benzonitrile (176e)

\[
\begin{array}{c}
\text{CN} \\
\text{Ts} \\
\text{Me} \\
\text{N} \\
\text{Me}
\end{array}
\]

Cross-coupling was performed according to TP19.

**column chromatography:** SiO\(_2\); \(n\)-pentane/Et\(_2\)O 5:1 to 1:1

**yield:** 238 mg (84 %)

**d.r.:** 97:3.

**m.p.:** 106.2 – 107.1 °C.

\(^1\)H-NMR (400 MHz, C\(_6\)D\(_6\)) \(\delta\): 7.77 (d, \(J=8.2\) Hz, 2 H), 7.01 (m, \(J=8.2\) Hz, 2 H), 6.85 (m, \(J=8.0\) Hz, 2 H), 6.43 (d, \(J=8.2\) Hz, 2 H), 4.41 - 4.33 (m, \(J_1=6.2\) Hz, \(J_2=6.2\) Hz, \(J_3=6.1\) Hz, \(J_4=5.9\) Hz, 1 H), 3.86 - 3.78 (m, 1 H), 2.64 (td, \(J_1=12.9\) Hz, \(J_2=3.0\) Hz, 1 H), 2.24 - 2.15 (m, \(J_1=12.5\) Hz, \(J_2=12.5\) Hz, \(J_3=3.7\) Hz, \(J_4=3.5\) Hz, 1 H), 1.94 (s, 3 H), 1.38 (td, \(J_1=13.1\) Hz, \(J_2=5.3\) Hz, 1 H), 1.25 - 1.12 (m, 1 H), 1.12 - 1.06 (m, 1 H), 1.03 (dt, \(J_1=13.1\) Hz, \(J_2=1.6\) Hz, 1 H), 0.80 (d, \(J=6.8\) Hz, 3 H).

\(^{13}\)C-NMR (101 MHz, C\(_6\)D\(_6\)) \(\delta\): 150.6, 143.1, 139.9, 132.6, 130.1, 128.0, 127.8, 119.3, 111.3, 48.8, 40.3, 37.8, 36.5, 32.6, 21.5, 15.6.

**MS (70 eV, EI) m/z (%)**: 354 (3) [M\(^+\)], 340 (21), 339 (100), 155 (35), 90 (47), 58 (9).

**IR (ATR) \(\tilde{\nu}\) (cm\(^{-1}\))**: 2982 (vw), 2946 (vw), 2918 (vw), 2868 (vw), 2226 (w), 1604 (w), 1504 (w), 1446 (vw), 1370 (w), 1348 (w), 1332 (m), 1316 (w), 1302 (w), 1290 (w), 1276 (w), 1256 (w), 1206 (w), 1178 (w), 1158 (s), 1148 (m), 1118 (w), 1104 (w), 1092 (m), 1070 (m), 1056 (w), 1018 (w), 1012 (w), 996 (m), 972 (m), 930 (m), 880 (w), 858 (m), 848 (w), 828 (m), 816 (m), 800 (w), 722 (w), 710 (s), 698 (s), 652 (s), 624 (w).

**HRMS (EI) for C\(_{20}\)H\(_{22}\)N\(_2\)O\(_2\)S (354.1402): 354.1384.**

methyl 4-(trans-2-methyl-1-tosylpiperidin-4-yl)benzoate (176f)

\[
\begin{array}{c}
\text{CO}_2\text{Me} \\
\text{Ts} \\
\text{Me} \\
\text{N}
\end{array}
\]
Cross-coupling was performed according to TP19.

column chromatography: SiO$_2$; $n$-pentane/Et$_2$O 5:1 to 1:1

yield: 276 mg (89%)

d.r.: 97:3.

m.p.: 129.8 – 131.5 °C.

$^1$H-NMR (400 MHz, C$_6$D$_6$) $\delta$: 8.08 (d, $J$=8.4 Hz, 2 H), 7.78 (m, $J$=8.2 Hz, 2 H), 6.84 (m, $J$=8.0 Hz, 2 H), 6.75 (d, $J$=8.4 Hz, 2 H), 4.39 (qd, $J_1$=6.2 Hz, $J_2$=6.0 Hz, 1 H), 3.88 - 3.81 (m, 1 H), 3.52 (s, 3 H), 2.69 (td, $J_1$=12.9 Hz, $J_2$=3.0 Hz, 1 H), 2.36 (tt, $J_1$=12.5 Hz, $J_2$=3.6 Hz, 1 H), 1.93 (s, 3 H), 1.51 (td, $J_1$=13.1 Hz, $J_2$=5.3 Hz, 1 H), 1.36 - 1.25 (m, 1 H), 1.25 - 1.19 (m, 1 H), 1.15 (dt, $J_1$=13.1 Hz, $J_2$=1.7 Hz, 1 H), 0.84 (d, $J$=7.0 Hz, 3 H).

$^{13}$C-NMR (101 MHz, C$_6$D$_6$) $\delta$: 167.0, 151.1, 143.0, 140.0, 130.5, 130.1, 129.5, 127.8, 127.5, 51.9, 49.0, 40.5, 38.0, 36.5, 32.8, 21.5, 15.7.

MS (70 eV, EI) $m/z$ (%): 387 (3) [M$^+$], 372 (23), 371 (100), 210 (8), 155 (23), 90 (33), 58 (9).

IR (ATR) $\tilde{\nu}$ (cm$^{-1}$): 2984 (vw), 2960 (w), 2936 (w), 2910 (w), 2856 (w), 1720 (s), 1608 (w), 1596 (w), 1434 (m), 1380 (w), 1330 (m), 1280 (vs), 1252 (m), 1210 (w), 1198 (w), 1188 (w), 1174 (m), 1156 (vs), 1142 (s), 1110 (m), 1094 (s), 1070 (m), 1056 (m), 1018 (w), 994 (m), 970 (m), 958 (w), 926 (m), 882 (w), 864 (m), 848 (m), 824 (w), 814 (m), 798 (w), 770 (m), 704 (s), 684 (s), 648 (m).

HRMS (EI) for C$_{21}$H$_{25}$NO$_4$S (387.1504): 387.1512.

5.9. Typical Procedure 20: Cross-Coupling of (1-($t$-Butoxycarbonyl)-6-methylpiperidin-2-yl)zinc Chloride (TP 20) (Scheme 45)

A dry and Ar-flushed 10 mL Schlenk-tube equipped with a stirring bar was charged with a solution of $t$-butyl 2-methylpiperidine-1-carboxylate (1 mmol; 0.20 g) and TMEDA (1 mmol; 0.12 g; 0.45 mL) in anhydrous Et$_2$O (2 mL). It was cooled to -78 °C and s-BuLi (1.14 M in hexanes) (1.2 mmol; 1.05 mL) was slowly added via syringe. The reaction mixture was stirred for 4 h at this temperature before ZnCl$_2$ (1.0 M in THF) (1.2 mmol; 1.2 mL) was added. The reaction mixture was stirred for 15 min at -78 °C and was then allowed to warm to room temperature. Et$_2$O was removed in vacuo (8 min; 1 mbar). Meanwhile, a solution of the respective aryl iodide (0.7 mmol), Pd(dba)$_2$ (28.8 mg; 0.05 mmol) and Ru-Phos (23.3 mg; 0.05 mmol) was prepared and cooled to 0 °C. The piperidinylzinc reagent was added to this mixture and stirred for 12 h. The reaction mixture was then warmed to room temperature and
stirred for 12 h and finally heated to 40 °C for 12 h. NH₄Cl sat. aq. solution (20 mL) was added, the phases were separated and the aqueous phase was extracted with Et₂O (4 x 10 mL). The combined organic layers were washed with brine (10 mL) and dried over Na₂SO₄. The solvents were evaporated and the residue was subjected to column chromatography yielding the respective title compound.

**trans-t-butyl 2-methyl-5-phenylpiperidine-1-carboxylate (181a)**

Cross-coupling was performed according to TP20.

**column chromatography:** SiO₂; CH₂Cl₂

**yield:** 173 mg (90 %)

**d.r.:** 93:7.

**¹H-NMR (400 MHz, C₆D₆) δ:** 7.34 (d, J=7.6 Hz, 2 H), 7.21 (t, J=7.7 Hz, 2 H), 7.08 (t, J=7.4 Hz, 1 H), 4.41 - 4.33 (m, 2 H), 3.10 (dd, J₁=14.0 Hz, J₂=4.3 Hz, 1 H), 2.59 (br. s., 1 H), 1.75 - 1.58 (m, 3 H), 1.58 - 1.39 (m, 9 H), 1.05 (d, J=6.8 Hz, 3 H), 0.94 - 0.88 (m, 1 H).

**¹³C-NMR (101 MHz, C₆D₆) δ:** 155.2, 144.7, 128.9, 128.7, 128.3, 126.6, 126.4, 79.2, 47.3, 42.5, 38.6, 28.9, 26.3, 26.1, 16.9.

**MS (70 eV, EI) m/z (%):** 275 (1) [M⁺], 219 (29), 204 (44), 160 (24), 104 (16), 102 (17), 97 (24), 85 (24), 83 (22), 71 (31), 69 (24), 59 (26), 57 (100), 55 (28), 43 (24), 41 (25).

**IR (ATR) ν (cm⁻¹):** 2930 (m), 2920 (w), 1684 (vs), 1452 (m), 1414 (m), 1390 (m), 1364 (s), 1338 (m), 1326 (m), 1308 (m), 1278 (m), 1240 (s), 1166 (s), 1148 (s), 1116 (s), 1078 (m), 1068 (m), 1050 (m), 1036 (m), 874 (m), 860 (m), 838 (m), 828 (m), 786 (m), 766 (m), 734 (m), 698 (s), 640 (w).

**HRMS (EI) for C₁₉H₂₅NO₂ (275.1885):** 275.1874.

**trans-t-butyl 5-(4-methoxyphenyl)-2-methylpiperidine-1-carboxylate (181b)**

Cross-coupling was performed according to TP20.
column chromatography: SiO₂; n-pentane/Et₂O 8:1
yield: 130 mg (61 %)
d.r.: 94:6.

\(^1\)H-NMR (400 MHz, C\(_6\)D\(_6\)) \(\delta\): 7.27 (d, \(J=8.5\) Hz, 2 H), 6.84 (d, \(J=8.5\) Hz, 2 H), 4.42 - 4.33 (m, 2 H), 3.34 (s, 3 H), 3.14 (dd, \(J_1=13.9\) Hz, \(J_2=4.3\) Hz, 1 H), 2.64 - 2.59 (m, 1 H), 1.77 - 1.60 (m, 3 H), 1.58 - 1.52 (m, 1 H), 1.48 (s, 9 H), 1.07 (d, \(J=6.8\) Hz, 3 H).

\(^13\)C-NMR (101 MHz, C\(_6\)D\(_6\)) \(\delta\): 158.8, 155.3, 136.4, 129.2, 127.4, 114.4, 114.3, 79.2, 55.1, 47.3, 42.7, 37.8, 29.0, 28.8, 26.3, 16.9.

MS (70 eV, EI) \(m/z\) (%): 305 (13) [M\(^+\)], 249 (79), 234 (36), 232 (23), 204 (32), 190 (29), 175 (21), 148 (35), 147 (22), 134 (57), 121 (46), 102 (37), 91 (23), 58 (31), 57 (100), 43 (79), 41 (21).

IR (ATR) \(\tilde{\nu}\) (cm\(^{-1}\)): 2972 (w), 2934 (w), 1684 (vs), 1612 (m), 1512 (s), 1456 (m), 1412 (s), 1390 (m), 1364 (s), 1340 (m), 1306 (m), 1246 (vs), 1168 (vs), 1148 (vs), 1114 (s), 1090 (m), 1036 (s), 878 (m), 828 (s), 808 (m), 768 (m).

HRMS (EI) for C\(_{18}\)H\(_{27}\)NO\(_3\) (305.1991): 305.1990.

**trans-t-butyl 2-methyl-5-(4-(trifluoromethyl)phenyl)piperidine-1-carboxylate (181c)**

![Chemical Structure](image)

Cross-coupling was performed according to TP20.

column chromatography: SiO₂; CH₂Cl₂
yield: 197 mg (82 %)
d.r.: 96:4.

\(^1\)H-NMR (400 MHz, C\(_6\)D\(_6\)) \(\delta\): 7.39 (d, \(J=8.2\) Hz, 2 H), 7.18 (d, 2 H), 4.36 - 4.30 (m, 1 H), 4.26 (d, \(J=14.4\) Hz, 1 H), 2.98 (dd, \(J_1=14.1\) Hz, \(J_2=4.4\) Hz, 1 H), 2.41 (br. s., 1 H), 1.65 - 1.54 (m, 1 H), 1.49 - 1.39 (m, 9 H), 1.35 (td, \(J_1=11.6\) Hz, \(J_2=4.8\) Hz, 2 H), 1.01 (d, \(J=6.8\) Hz, 3 H), 0.85 (ddd, \(J_1=12.7\) Hz, \(J_2=4.3\) Hz, \(J_3=4.1\) Hz, 1 H).

\(^13\)C-NMR (101 MHz, C\(_6\)D\(_6\)) \(\delta\): 155.1, 148.7 (d, \(J=1.1\) Hz), 128.8 (q, \(J=32.2\) Hz), 128.0, 125.7 (q, \(J=3.8\) Hz), 125.5 (q, \(J=271.7\) Hz), 79.5, 47.1, 41.7, 38.2, 28.9, 26.1, 25.8, 16.6.

\(^19\)F-NMR (376 MHz, C\(_6\)D\(_6\)) \(\delta\): -61.92 (s) (minor), -62.05 (s) (major).

MS (70 eV, EI) \(m/z\) (%): 343 (2) [M\(^+\)], 288 (12), 287 (31), 273 (13), 272 (100), 270 (16), 242 (10), 228 (52), 172 (14), 57 (82).
IR (ATR) $\tilde{\nu}$ (cm$^{-1}$): 2980 (w), 2930 (w), 1680 (s), 1412 (m), 1366 (m), 1328 (s), 1310 (m), 1254 (m), 1236 (m), 1162 (s), 1148 (s), 1116 (vs), 1090 (s), 1070 (s), 1054 (m), 1038 (m), 1018 (m), 882 (m), 866 (m), 834 (s), 768 (m), 708 (m), 648 (m).

HRMS (EI) for C$_{18}$H$_{24}$F$_{3}$NO$_{2}$ (343.1759): 343.1757.

trans-t-butyl 5-(4-cyanophenyl)-2-methylpiperidine-1-carboxylate (181d)

\[
\begin{align*}
&\text{Cross-coupling was performed according to TP20.} \\
&\text{column chromatography: SiO$_2$; n-pentane/Et$_2$O 3:1} \\
&\text{yield: 111 mg (53 %)} \\
&\text{d.r.: 94:6.} \\
&\text{H-NMR (400 MHz, C$_6$D$_6$) $\delta$: 7.08 (d, $J$=8.4 Hz, 2 H), 6.99 (d, $J$=8.2 Hz, 2 H), 4.30 - 4.21 (m, 1 H), 4.17 (d, $J$=14.2 Hz, 1 H), 2.92 (dd, $J$$_1$=14.2 Hz, $J$$_2$=4.3 Hz, 1 H), 2.32 (br. s., 1 H), 1.61 - 1.51 (m, 1 H), 1.44 (s, 9 H), 1.34 - 1.26 (m, 2 H), 0.99 (d, $J$=6.8 Hz, 3 H), 0.87 - 0.79 (m, 1 H).} \\
&\text{C-NMR (101 MHz, C$_6$D$_6$) $\delta$: 155.0, 149.5, 132.3, 128.8, 126.8, 126.2, 119.4, 110.8, 79.6, 47.1, 41.4, 38.4, 28.9, 26.0, 25.6, 16.6.} \\
&\text{MS (70 eV, EI) m/z (%): 300 (4) [M$^+$], 245 (13), 244 (36), 229 (64), 227 (16), 200 (12), 199 (46), 185 (36), 142 (15), 130 (10), 129 (18), 58 (20), 57 (100), 43 (52), 41 (14).} \\
&\text{IR (ATR) $\tilde{\nu}$ (cm$^{-1}$): 2972 (w), 2934 (w), 2228 (w), 1682 (vs), 1608 (w), 1476 (w), 1454 (w), 1414 (s), 1392 (m), 1364 (s), 1340 (m), 1308 (m), 1256 (m), 1240 (m), 1166 (s), 1148 (s), 1118 (m), 1100 (w), 1090 (m), 1052 (m), 1038 (w), 880 (w), 864 (w), 832 (m), 770 (w).} \\
&\text{HRMS (EI) for C$_{18}$H$_{24}$N$_2$O$_2$ (300.1838): 300.1831.}
\end{align*}
\]

trans-t-butyl 2-methyl-5-(pyridin-3-yl)piperidine-1-carboxylate (181e)

\[
\begin{align*}
&\text{Cross-coupling was performed according to TP20.} \\
&\text{column chromatography: SiO$_2$; Et$_2$O}
\end{align*}
\]
yield: 116 mg (60 %)

d.r.: 95:5.

$^1$H-NMR (400 MHz, C$_6$D$_6$) δ: 8.69 (d, J=2.1 Hz, 1 H), 8.47 (dd, J$_1$=4.7 Hz, J$_2$=1.4 Hz, 1 H), 7.47 (d, J=7.8 Hz, 1 H), 6.79 (dd, J$_1$=7.8 Hz, J$_2$=4.9 Hz, 1 H), 4.31 (dd, J$_1$=9.8 Hz, J$_2$=6.3 Hz, 1 H), 4.23 (d, J=14.1 Hz, 1 H), 2.96 (dd, J$_1$=14.2 Hz, J$_2$=4.4 Hz, 1 H), 2.39 (br. s., 1 H), 1.61 - 1.52 (m, 1 H), 1.51-1.37 (m, 10 H), 1.36 - 1.29 (m, 1 H), 0.99 (d, J=6.8 Hz, 3 H), 0.88 - 0.80 (m, 1 H).

$^{13}$C-NMR (101 MHz, C$_6$D$_6$) δ: 155.1, 150.7, 148.3, 139.5, 134.8, 123.4, 79.5, 47.1, 41.8, 36.3, 28.9, 26.1, 25.6, 16.6.

MS (70 eV, EI) m/z (%): 276 (11) [M$^+$], 221 (19), 220 (21), 205 (24), 203 (25), 176 (43), 175 (15), 161 (75), 133 (16), 119 (27), 106 (40), 105 (17), 57 (100), 41 (15).

IR (ATR) $\tilde{\nu}$ (cm$^{-1}$): 2976 (w), 2934 (w), 1680 (vs), 1476 (w), 1408 (s), 1390 (m), 1382 (m), 1364 (s), 1340 (s), 1312 (m), 1296 (w), 1256 (m), 1244 (m), 1232 (m), 1182 (m), 1172 (m), 1146 (s), 1120 (s), 1088 (s), 1048 (m), 1040 (m), 1022 (m), 1000 (m), 986 (w), 912 (w), 878 (m), 862 (m), 824 (m), 802 (m), 780 (m), 770 (s), 748 (w), 726 (w), 712 (s), 640 (m), 624 (m).

HRMS (EI) for C$_{16}$H$_{24}$N$_2$O$_2$ (276.1838): 276.1834.

5.10. Typical Procedure 21: Synthesis of N-Tosyl Piperidines (TP 21)

To a solution of the respective t-butyl piperidine-1-carboxylate (Boc-protected amine) (1 equiv.) in Et$_2$O (3 mL per 1 mmol) was added trifluoroacetic acid (TFA; 40 equiv.) at 0 °C. The reaction mixture was stirred for 15 h at room temperature, then cooled to 0 °C and carefully neutralized using NaHCO$_3$ sat. aq. solution. The resulting mixture was extracted with CH$_2$Cl$_2$ (4 x). The combined organic phases were washed with brine and dried over Na$_2$SO$_4$. The solvents were removed via rotary evaporation. The crude deprotected amine (quant. yield) was added to a solution of p-tolyl-1-sulfonyl chloride (2 equiv.) and NEt$_3$ (2 equiv.) in THF (0.2 M). The reaction mixture was stirred for 15 h. NH$_4$Cl sat. aq. solution was added. The phases were separated and the aqueous layer was extracted with CH$_2$Cl$_2$ (4 x). The combined organic phases were washed with brine and dried over Na$_2$SO$_4$. The solvents were evaporated and the crude product was purified via column chromatography to give the respective title compound.
C.  Experimental Section

2-tosyl-3-(4-(trifluoromethyl)phenyl)decahydroisoquinoline (173na)

\[
\text{\begin{center}
\includegraphics[width=0.2\textwidth]{image.png}
\end{center}}
\]

Tosylation was performed according to TP21.

**Column chromatography: SiO\(_2\); CH\(_2\)Cl\(_2\)**

**Yield:** 136 mg (78 %; 0.4 mmol scale)

**M.p.:** 194.1 – 195.6 °C.

**\(^1\)H-NMR (300 MHz, CDCl\(_3\))** \(\delta\): 7.50 (d, \(J=8.3\) Hz, 2 H), 7.43 (d, \(J=8.3\) Hz, 2 H), 7.39 (d, \(J=8.0\) Hz, 2 H), 7.24 (d, \(J=8.0\) Hz, 2 H), 4.12 (dd, \(J_I=11.5\) Hz, \(J_2=3.7\) Hz, 1 H), 3.91 (dd, \(J_I=11.3\) Hz, \(J_2=3.6\) Hz, 1 H), 2.56 - 2.37 (m, 4 H), 1.95 - 1.77 (m, 3 H), 1.73 (t, \(J=3.3\) Hz, 1 H), 1.70 - 1.49 (m, 3 H), 1.47 - 1.28 (m, 2 H), 1.17 - 0.98 (m, 3 H).

**\(^1\)C-NMR (75 MHz, CDCl\(_3\))** \(\delta\): 145.7 (d, \(J=1.3\) Hz), 143.2, 134.8, 129.5, 129.2 (q, \(J=32.2\) Hz), 129.1, 128.4, 128.1, 127.9, 127.8, 127.4, 124.5 (q, \(J=3.9\) Hz), 124.1 (q, \(J=272.1\) Hz), 63.1, 53.7, 43.6, 41.0, 40.7, 32.0, 29.9, 26.0, 25.6, 21.3.

**MS (70 eV, EI)** \(m/z\) (%): 437 (12) [M\(^+\)], 293 (17), 292 (100), 283 (14), 282 (74), 281 (44), 280 (28), 159 (19), 155 (21), 91 (36), 67 (11).

**IR (ATR)** \(\tilde{\nu}\) (cm\(^{-1}\)): 2922 (w), 2900 (w), 2846 (vw), 1600 (vw), 1446 (vw), 1426 (vw), 1344 (m), 1326 (s), 1186 (w), 1160 (vs), 1126 (s), 1106 (m), 1086 (m), 1070 (m), 1046 (w), 1034 (w), 1020 (w), 968 (w), 940 (w), 914 (w), 856 (w), 848 (w), 834 (w), 812 (w), 748 (w), 728 (m), 708 (w), 666 (w), 654 (w).

**HRMS (EI)** for C\(_{23}\)H\(_{26}\)F\(_3\)NO\(_2\)S (437.1636): 437.1635.

4-(trans-5-methyl-1-tosylpiperidin-2-yl)benzonitrile (173qa)

\[
\text{\begin{center}
\includegraphics[width=0.2\textwidth]{image.png}
\end{center}}
\]

Tosylation was performed according to TP21.

**Column chromatography: SiO\(_2\); CH\(_2\)Cl\(_2\)**

**Yield:** 80 mg (75 %; 0.3 mmol scale)

**M.p.:** 113.1 – 114.4 °C.

**\(^1\)H-NMR (400 MHz, C\(_6\)D\(_6\))** \(\delta\): 7.55 (d, \(J=8.2\) Hz, 2 H), 7.01 (d, \(J=8.4\) Hz, 2 H), 6.90 (d, \(J=8.2\) Hz, 2 H), 6.77 (d, \(J=8.0\) Hz, 2 H), 4.58 (t, \(J=5.0\) Hz, 1 H), 3.25 (dd, \(J_I=12.9\) Hz, \(J_2=3.7\) Hz, 1
C. Experimental Section

1H-NMR (400 MHz, CDCl₃) δ: 7.82 (d, J=8.2 Hz, 2 H), 7.63 (d, J=8.2 Hz, 2 H), 7.56 (d, J=8.2 Hz, 2 H), 7.47 (d, J=8.2 Hz, 2 H), 7.37 (d, J=8.0 Hz, 2 H), 7.10 (d, J=8.2 Hz, 2 H), 5.52 (d, J=3.5 Hz, 1 H), 4.08 (d, J=14.2 Hz, 1 H), 3.17 - 3.08 (m, 1 H), 2.73 - 2.64 (m, 1 H), 2.49 (s, 3 H), 2.41 (d, J=13.5 Hz, 1 H), 1.91 (td, J₁=13.5 Hz, J₂=5.5 Hz, 1 H), 1.63 (d, J=12.9 Hz, 1 H), 1.51 (qd, J₁=12.7 Hz, J₂=4.5 Hz, 1 H).  

13C-NMR (101 MHz, CDCl₃) δ: 149.9, 143.7, 142.5 (d, J=0.8 Hz), 138.0, 132.5, 129.9, 129.6 (q, J=32.6 Hz), 127.4, 127.0, 127.0, 125.9 (q, J=3.7 Hz), 124.0 (q, J=272.1 Hz), 118.6, 110.7, 55.0, 41.6, 36.8, 34.1, 31.3, 21.5.

MS (70 eV, EI) m/z (%): 484 (11) [M⁺], 339 (43), 330 (25), 329 (100), 328 (24), 327 (12), 186 (23), 172 (12), 159 (11), 155 (15), 90 (30).

4-(trans-1-tosyl-2-(4-(trifluoromethyl)phenyl)piperidin-4-yl)benzonitrile (176aa)

Tosylation was performed according to TP21.

column chromatography: SiO₂; n-pentane/Et₂O 2:1

yield: 174 mg (72 %; 0.5 mmol scale)

m.p.: 182.6 – 183.1 °C.

1H-NMR (400 MHz, CDCl₃) δ: 7.82 (d, J=12.9 Hz, 2 H), 1.92 (s, 3 H), 1.60 - 1.50 (m, 1 H), 1.41 - 1.31 (m, 2 H), 1.08 (dd, J₁=13.9 Hz, J₂=9.9 Hz, J₃=4.5 Hz, J₄=4.3 Hz, 1 H), 0.71 - 0.64 (m, 1 H), 0.62 (d, J=6.9 Hz, 3 H).

13C-NMR (101 MHz, C₆D₆) δ: 146.1, 143.3, 138.3, 132.3, 129.9, 128.5, 128.0, 119.2, 111.7, 58.0, 49.6, 28.7, 27.6, 27.1, 21.5, 18.3.

MS (70 eV, EI) m/z (%): 354 (10) [M⁺], 253 (16), 252 (100), 200 (14), 199 (99), 198 (28), 197 (49), 155 (36), 129 (26), 116 (20), 91 (53), 65 (10).

IR (ATR) ν (cm⁻¹): 2952 (w), 2928 (w), 2226 (w), 1602 (w), 1456 (w), 1344 (s), 1320 (w), 1304 (w), 1162 (vs), 1096 (m), 1086 (m), 1068 (m), 1052 (m), 1020 (w), 1012 (m), 928 (m), 904 (m), 840 (m), 830 (m), 808 (s), 754 (w), 722 (vs), 656 (s).

HRMS (EI) for C₂₀H₂₂N₂O₂S (354.1402): 354.1398.
C. Experimental Section

IR (ATR) $\tilde{\nu}$ (cm$^{-1}$): 2956 (vw), 2932 (w), 2232 (w), 1606 (w), 1598 (w), 1506 (vw), 1452 (w), 1434 (w), 1412 (w), 1376 (w), 1348 (w), 1328 (vs), 1290 (m), 1256 (w), 1196 (w), 1158 (vs), 1110 (vs), 1096 (s), 1072 (s), 1034 (w), 1018 (m), 944 (m), 928 (m), 906 (m), 838 (s), 802 (w), 738 (w), 716 (m), 702 (m), 664 (s), 650 (m), 634 (w).

HRMS (EI) for C$_{26}$H$_{21}$F$_3$N$_2$O$_2$S (484.1432): 484.1439.

**trans-2-methyl-1-tosyl-5-(4-(trifluoromethyl)phenyl)piperidine (181ca)**

Tosylation was performed according to TP21.

**column chromatography:** SiO$_2$; CH$_2$Cl$_2$

**yield:** 145 mg (73 %; 0.5 mmol scale)

**m.p.:** 133.0 – 135.9 °C.

$^1$H-NMR (599 MHz, C$_6$D$_6$) $\delta$: 7.63 (d, $J$=8.2 Hz, 2 H), 7.31 (d, $J$=8.0 Hz, 2 H), 7.04 (d, $J$=8.2 Hz, 2 H), 6.77 (d, $J$=8.0 Hz, 2 H), 3.59 - 3.52 (m, 1 H), 3.43 (dd, $J_1$=12.6 Hz, $J_2$=3.8 Hz, 1 H), 3.27 (dd, $J_1$=12.6 Hz, $J_2$=5.5 Hz, 1 H), 2.51 - 2.44 (m, 1 H), 1.91 (s, 3 H), 1.48 - 1.43 (m, 1 H), 1.42 - 1.36 (m, 1 H), 1.16 (dddd, $J_1$=13.2 Hz, $J_2$=6.5 Hz, $J_3$=6.4 Hz, $J_4$=3.3 Hz, 1 H), 1.01 - 0.97 (m, 1 H) 1.02 (d, $J$=6.6 Hz, 3 H).

$^{13}$C-NMR (151 MHz, CDCl$_3$) $\delta$: 147.7 (d, $J$=1.1 Hz), 143.1, 138.4, 129.9, 129.1 (q, $J$=32.0 Hz), 128.7, 128.1, 125.8 (q, $J$=3.8 Hz), 125.5 (q, $J$=271.8 Hz), 51.5, 47.8, 39.4, 30.1, 26.8, 21.4, 17.3.

**MS (70 eV, EI) m/z (%):** 397 (2) [M$^+$], 383 (19), 382 (100), 155 (18), 91 (12).

IR (ATR) $\tilde{\nu}$ (cm$^{-1}$): 2940 (w), 2926 (w), 1686 (w), 1446 (w), 1384 (w), 1322 (s), 1300 (m), 1288 (m), 1264 (m), 1238 (m), 1196 (m), 1180 (m), 1154 (s), 1112 (vs), 1094 (s), 1082 (s), 1066 (s), 1042 (m), 1016 (m), 994 (m), 978 (m), 966 (s), 960 (m), 908 (m), 872 (m), 840 (m), 820 (s), 738 (w), 710 (s), 684 (s), 646 (s), 632 (m), 606 (m).

HRMS (EI) for C$_{20}$H$_{22}$F$_3$NO$_2$S (397.1323): 397.1320.
*cis*-1-tosyl-2-(4-(trifluoromethyl)phenyl)-4-((triisopropylsilyl)oxy)piperidine

Tosylation was performed according to TP21.

**column chromatography:** SiO₂; n-pentane/Et₂O 10:1

**yield:** 6.22 g (56 %; 20 mmol scale)

**m.p.:** 93.8 – 95.3 °C.

**¹H-NMR (400 MHz, C₆D₆) δ:** 7.68 (d, J=8.2 Hz, 2 H), 7.29 (d, J=8.2 Hz, 2 H), 7.14 (d, J=8.0 Hz, 2 H), 6.79 (d, J=8.0 Hz, 2 H), 6.51 (d, J=2.9 Hz, 1 H), 3.71 (dt, J₁=13.9 Hz, J₂=3.8 Hz, 1 H), 3.62 (br. s., 1 H), 3.55 - 3.47 (m, 1 H), 1.97 - 1.93 (m, 1 H), 1.93 (s, 3 H), 1.65 (ddd, J₁=14.2 Hz, J₂=6.6 Hz, J₃=2.9 Hz, 1 H), 1.45 - 1.36 (m, 1 H), 1.26 - 1.19 (m, 1 H), 0.97 - 0.73 (m, 18 H), 0.70 - 0.59 (m, 3 H).

**¹³C-NMR (101 MHz, C₆D₆) δ:** 146.5 (d, J=1.1 Hz), 143.2, 139.7, 130.0, 129.1 (q, J=32.2 Hz), 127.8, 127.4, 125.6 (q, J=3.8 Hz), 125.4 (d, J=271.8 Hz), 65.4, 54.8, 38.3, 37.4, 32.6, 21.4, 18.4, 18.4, 12.6.

**MS (70 eV) m/z (%)**: 514 (13), 513 (34), 512 (100), 314 (14), 310 (44), 298 (40), 296 (15), 284 (24), 272 (10), 242 (20), 159 (25), 157 (11), 155 (26), 129 (16), 101 (12), 91 (59); 87 (11); 75 (20), 61 (10).

**IR (ATR) ν (cm⁻¹):** 2938 (w), 2866 (w), 1326 (vs), 1312 (s), 1302 (m), 1162 (s), 1156 (s), 1124 (vs), 1110 (s), 1080 (s), 1070 (s), 1058 (m), 1036 (m), 1016 (s), 950 (m), 936 (s), 936 (s), 898 (m), 882 (m), 820 (m), 746 (m), 716 (s), 688 (s), 678 (s), 658 (s), 650 (s), 630 (m).

**HRMS (ESI) for C₂₉H₄₁F₃NO₅Si⁺ (556.2523) [M+H⁺]:** 556.2524.

2-methyl-1-tosyl-4-((triisopropylsilyl)oxy)piperidine

Tosylation was performed according to TP21.

**column chromatography:** SiO₂; CH₂Cl₂

**yield:** 2.77 g (65 %; 10 mmol scale)
C. Experimental Section

$^1$H-NMR (300 MHz, C$_6$D$_6$) δ: 7.80 (d, J=8.3 Hz, 2 H), 6.82 (d, J=8.0 Hz, 2 H), 4.29 - 4.18 (m, 1 H), 3.74 - 3.63 (m, 2 H), 3.48 - 3.37 (m, 1 H), 1.91 (s, 3 H), 1.56 - 1.43 (m, 2 H), 1.42 - 1.34 (m, 2 H), 1.31 (d, J=7.2 Hz, 3 H), 1.08 - 0.92 (m, 18 H), 0.92 - 0.86 (m, 3 H).

$^{13}$C-NMR (75 MHz, C$_6$D$_6$) δ: 142.7, 140.4, 130.0, 127.8, 65.9, 48.8, 37.9, 36.3, 33.6, 21.5, 19.9, 18.6, 12.7.

MS (70 eV, EI) m/z (%): 424 (1), 384 (12), 383 (26), 382 (100), 90 (1 2).

IR (ATR) ν (cm$^{-1}$): 2942 (m), 2890 (m), 2866 (m), 1598 (vw), 1494 (w), 1464 (m), 1380 (w), 1346 (m), 1328 (m), 1250 (w), 1216 (w), 1162 (vs), 1130 (s), 1106 (m), 1088 (m), 1060 (s), 1040 (s), 1018 (m), 988 (ms), 914 (s), 882 (s), 870 (s), 814 (m), 776 (m), 712 (s), 700 (s), 678 (vs), 654 (s), 642 (s).

HRMS (EI) for C$_{21}$H$_{36}$NO$_3$SSi$^+$ (410.2185) [M-CH$_3$]$^+$: 410.2207.

5.11. Typical Procedure 22: TIPS Deprotection (TP 22)

To a solution of the respective 4-((triisopropylsilyl)oxy)piperidine (1 equiv.) in THF (0.2 M) was added n-Bu$_4$NF·3 H$_2$O (2 equiv.) portionwise. The reaction mixture was stirred for 15 h at room temperature, then H$_2$O was added, the phases were separated and the aqueous phase was extracted with CH$_2$Cl$_2$ (3 x). The combined organic layers were washed with brine and dried over Na$_2$SO$_4$. The solvents were evaporated and the crude product was subjected to column chromatography.

t-butyl cis-2-(4-fluorophenyl)-4-hydroxypiperidine-1-carboxylate

Desilylation was performed according to TP22.

column chromatography: SiO$_2$; CH$_2$Cl$_2$/acetone 7:1

yield: 1.54 g (89 %; 5 mmol scale)

$^1$H-NMR (300 MHz, C$_6$D$_6$) δ: 7.37 (d, J=8.3 Hz, 2 H), 7.09 (d, J=8.3 Hz, 2 H), 5.17 (br. s., 1 H), 3.98 (ddd, J$_1$=13.6 Hz, J$_2$=5.0 Hz, J$_3$=2.8 Hz, 1 H), 3.60 - 3.48 (m, 1 H), 3.20 (td, J$_1$=12.9 Hz, J$_2$=3.5 Hz, 1 H), 1.85 - 1.72 (m, 1 H), 1.61 (ddd, J$_1$=14.4 Hz, J$_2$=6.8 Hz, J$_3$=3.2 Hz, 1 H), 1.53 - 1.41 (m, 1 H), 1.36 (s, 9 H), 1.28 - 1.14 (m, 1 H).
C. Experimental Section

$^{13}$C-NMR (75 MHz, C$_6$D$_6$) $\delta$: 155.0, 147.3 (d, $J$=1.1 Hz), 128.2 (q, $J$=32.3 Hz), 126.1, 124.8 (q, $J$=271.8 Hz), 125.0 (q, $J$=3.6 Hz), 79.3, 63.9, 52.2, 35.6, 35.5, 31.9, 27.9.

MS (70 eV, EI) m/z (%): 345 (0.3) [M$^+$], 290 (12), 289 (68), 270 (11), 244 (40), 228 (11), 200 (18), 186 (11), 172 (15), 59 (100), 41 (13), 18 (11).

IR (ATR) $\tilde{\nu}$ (cm$^{-1}$): 3438 (w), 2978 (w), 2932 (w), 1664 (s), 1620 (w), 1478 (w), 1454 (w), 1416 (m), 1394 (m), 1366 (m), 1324 (vs), 1280 (m), 1252 (m), 1210 (w), 1160 (s), 1112 (vs), 1068 (vs), 1040 (s), 1016 (m), 988 (w), 970 (w), 958 (w), 940 (m), 862 (m), 838 (m), 830 (m), 774 (w), 760 (w).

HRMS (EI) for C$_{17}$H$_{22}$F$_3$NO$_3$ (345.1552): 345.1562.

cis- 1-tosyl-2-(4-(trifluoromethyl)phenyl)piperidin-4-ol

Desilylation was performed according to TP22.

column chromatography: SiO$_2$; CH$_2$Cl$_2$/acetone 10:1 to 5:1

yield: 3.48 g (87 %; 10 mmol scale)

m.p.: 114.0 – 115.5 °C.

$^1$H-NMR (400 MHz, C$_6$D$_6$) $\delta$: 7.50 (d, $J$=8.2 Hz, 2 H), 7.21 (d, $J$=8.4 Hz, 2 H), 7.07 (d, $J$=8.2 Hz, 2 H), 6.68 (d, $J$=7.9 Hz, 2 H), 4.85 (t, $J$=4.7 Hz, 1 H), 3.51 - 3.42 (m, 1 H), 3.40 - 3.30 (m, 1 H), 3.26 (br. s., 1 H), 1.89 - 1.80 (m, 3 H), 1.64 (dt, $J$$_1$=14.3 Hz, $J$$_2$=4.1 Hz, 1 H), 1.47 (ddd, $J$=14.3 Hz, $J$$_2$=6.2 Hz, $J$$_3$=3.3 Hz, 1 H), 1.36 - 1.28 (m, 1 H), 1.06 - 0.99 (m, 1 H).

$^{13}$C-NMR (101 MHz, C$_6$D$_6$) $\delta$: 146.0 (d, $J$=1.2 Hz), 143.2, 139.2, 130.0, 129.3 (q, $J$=32.2 Hz), 127.8, 127.8, 125.5 (q, $J$=3.9 Hz), 125.4 (q, $J$=271.3 Hz), 64.6, 55.4, 38.9, 36.6, 32.1, 21.4.

$^{19}$F-NMR (376 MHz, C$_6$D$_6$) $\delta$: -62.10 (s) (major), -62.25 (s) (minor).

MS (70 eV) m/z (%): 399 (1) [M$^+$], 254 (41), 245 (16), 244 (100), 243 (13), 242 (40), 226 (35), 200 (12), 199 (13), 172 (25), 159 (19), 155 (32), 91 (61); 65 (12).

IR (ATR) $\tilde{\nu}$ (cm$^{-1}$): 2938 (w), 1622 (w), 1598 (w), 1456 (w), 1426 (w), 1326 (vs), 1260 (w), 1162 (vs), 1116 (s), 1096 (m), 1068 (s), 1046 (s), 1020 (m), 982 (m), 932 (m), 854 (m), 832 (m), 814 (s), 720 (s), 706 (m), 654 (s).

HRMS (ESI) for C$_{19}$H$_{21}$F$_3$NO$_3$S$^+$ (400.1189) [M+H$^+$]: 400.1189.
2-methyl-1-tosylpiperidin-4-ol

Desilylation was performed according to TP22.

**Column chromatography:** SiO$_2$; $n$-pentane/Et$_2$O 5:1 to Et$_2$O (neat)

**Yield:** 1.38 g (73 %; 7 mmol scale)

$^1$H-NMR (300 MHz, C$_6$D$_6$) $\delta$: 7.73 (d, $J$=8.0 Hz, 2 H), 6.80 (d, $J$=8.0 Hz, 2 H), 4.13 - 3.98 (m, 1 H), 3.60 - 3.29 (m, 3 H), 1.91 (s, 3 H), 1.53 - 1.33 (m, 2 H), 1.23 (d, $J$=6.9 Hz, 3 H), 1.17 (d, $J$=3.6 Hz, 2 H), 1.01 - 0.90 (m, 1 H).

$^{13}$C-NMR (75 MHz, C$_6$D$_6$) $\delta$: 142.8, 140.0, 130.0, 127.8, 64.8, 48.9, 37.6, 36.7, 32.9, 21.5, 19.6.

**MS (70 eV, EI) m/z (%):** 269 (3) [M$^+$], 255 (14), 254 (100), 210 (9), 155 (26), 90 (38).

**IR (ATR) $\tilde{\nu}$ (cm$^{-1}$):** 3516 (w), 2924 (w), 2882 (w), 1598 (w), 1494 (w), 1454 (w), 1424 (w), 1402 (w), 1382 (w), 1366 (w), 1344 (m), 1322 (m), 1304 (m), 1288 (m), 1234 (w), 1216 (w), 1184 (w), 1158 (s), 1148 (s), 1132 (s), 1098 (m), 1080 (s), 1056 (m), 1038 (m), 1018 (m), 1008 (w), 982 (m), 942 (m), 912 (s), 890 (w), 852 (m), 814 (m), 788 (w), 732 (w), 710 (s), 688 (vs), 642 (s).

**HRMS (EI) for C$_{13}$H$_{19}$NO$_3$S (269.1086):** 269.1078.

### 5.12. Typical Procedure 23: Iodination$^{85}$ (TP 23)

In a dry and Ar-flushed Schlenk-flask I$_2$ (1.2 equiv.) was dissolved in CH$_2$Cl$_2$ (0.6 M). The solution was cooled to 0 °C and PPh$_3$ (1.2 equiv.) was added portionwise. The resulting yellow suspension was stirred for 1 h 30 min at 0 °C before N-methyl-imidazole (NMI; 1.25 equiv.) was added. The respective piperidin-4-ol (1 equiv.) was transferred drop- or portionwise to this mixture. The reaction mixture was allowed to proceed for 6 h at 0 °C, then quenched with NaHSO$_3$ sat. aq. solution. Phases were separated and the aqueous layer was extracted with CH$_2$Cl$_2$ (3x). Solvents were evaporated and the crude product was subjected to column chromatography.

---

11-Butyl 4-iodo-2-(4-(trifluoromethyl)phenyl)piperidine-1-carboxylate (175a)

\[ \text{structural formula} \]

Iodination was performed according to TP23.

**column chromatography:** SiO\(_2\); n-pentane/Et\(_2\)O 7:1

**yield:** 2.17 g (68 %; 7 mmol scale)

\( ^1\text{H-NMR (300 MHz, C}_6\text{D}_6 \) \( \delta \): 7.26 (d, \( J=8.3 \) Hz, 2 H), 6.78 (d, \( J=8.3 \) Hz, 2 H), 5.22 (br. s., 1 H), 3.76 (d, \( J=13.0 \) Hz, 1 H), 3.53 (tt, \( J_1=12.4 \) Hz, \( J_2=3.9 \) Hz, 1 H), 2.50 (dt, \( J_1=13.6 \) Hz, \( J_2=1.8 \) Hz, 1 H), 2.26 - 2.07 (m, 2 H), 1.82 (qd, \( J_1=12.4 \) Hz, \( J_2=4.4 \) Hz, 1 H), 1.72 - 1.61 (m, 1 H), 1.41 (s, 9 H).

\( ^{13}\text{C-NMR (75 MHz, C}_6\text{D}_6 \) \( \delta \): 155.3, 143.6 (d, \( J=3.9 \) Hz), 129.6 (q, \( J=3.9 \) Hz), 125.4, 125.2 (q, \( J=272.1 \) Hz), 80.4, 56.1, 42.4, 41.7, 39.6, 28.7, 20.3.

**MS (70 eV, EI) m/\( z \) (%)**: 455 (1) [M\(^+\)], 399 (22), 328 (12), 272 (49), 228 (42), 199 (18), 159 (16), 61 (13), 59 (100), 41 (13), 18 (38).

**IR (ATR) \( \tilde{\nu} \) (cm\(^{-1}\))**: 2974 (w), 2932 (w), 2870 VW 1690 (s), 1620 (w), 1478 (w), 1452 (w), 1412 (s), 1366 (m), 1324 (vs), 1264 (m), 1248 (m), 1154 (vs), 1122 (vs), 1068 (s), 1014 (m), 1004 (m), 982 (m), 954 (m), 910 (m), 870 (w), 852 (m), 836 (m), 794 (w), 772 (m), 732 (w), 722 (w), 642 (w).

**HRMS (EI)** for C\(_{17}\)H\(_{21}\)F\(_3\)INO\(_2\) (455.0569): 455.0561.

4-iodo-1-tosyl-2-(4-(trifluoromethyl)phenyl)piperidine (175b)

\[ \text{structural formula} \]

Iodination was performed according to TP23.

**column chromatography:** SiO\(_2\); n-pentane/Et\(_2\)O 10:1

**yield:** 2.24 g (55 %; 8 mmol scale)

**m.p.:** 132.6 – 133.8 °C.

\( ^1\text{H-NMR (400 MHz, C}_6\text{D}_6 \) \( \delta \): 7.64 (d, \( J=8.2 \) Hz, 2 H), 7.25 (d, \( J=8.4 \) Hz, 2 H), 6.95 (d, \( J=8.2 \) Hz, 2 H), 6.78 (d, \( J=7.9 \) Hz, 2 H), 4.98 (d, \( J=2.9 \) Hz, 1 H), 3.51 - 3.38 (m, 2 H), 2.46 - 2.29
(m, 2 H), 1.99 (td, \( J_1 = 13.4 \) Hz, \( J_2 = 5.4 \) Hz, 1 H), 1.89 (s, 3 H), 1.66 (qd, \( J_1 = 12.6 \) Hz, \( J_2 = 4.6 \) Hz, 1 H), 1.50 - 1.43 (m, 1 H).

\(^{13}\text{C-NMR} (101 \text{ MHz, C}_6\text{D}_6) \ \delta: \ 143.8, 142.4 (d, \ J=1.2 \) Hz), 139.3, 130.3, 129.9 (q, \( J=32.3 \) Hz), 127.8, 127.6, 126.4 (q, \( J=3.7 \) Hz), 125.2 (q, \( J=272.0 \) Hz), 57.9, 43.7, 40.8, 38.3, 21.5, 19.0.

\textbf{MS (70 eV)} \ m/z (\%): 509 (1) [M\textsuperscript{+}], 383 (22), 382 (100), 226 (12), 199 (63), 186 (23), 185 (10), 184 (53), 159 (54), 155 (87), 91 (67), 65 (11), 55 (10).

\textbf{IR (ATR)} \ \tilde{\nu} \ (\text{cm}^{-1}): 1326 (vs), 1292 (m), 1154 (s), 1118 (s), 1102 (m), 1090 (s), 1070 (s), 1058 (s), 1044 (m), 1016 (m), 998 (m), 954 (s), 930 (s), 906 (m), 854 (m), 844 (m), 828 (m), 816 (s), 742 (m), 710 (s), 694 (s), 652 (vs).

\textbf{HRMS (ESI)} \text{for C}_{19}\text{H}_{19}\text{F}_3\text{INO}_2\text{SCl}^- (543.9827) [M+Cl\textsuperscript{-}]: 543.9817.

\textbf{2-methyl-4-iodo-1-tosylpiperidine (175c)}

Iodination was performed according to TP23.

\textbf{column chromatography:} SiO\textsubscript{2}; CH\textsubscript{2}Cl\textsubscript{2}

\textbf{yield:} 1.12 g (59 \%; 5 mmol scale)

\(^1\text{H-NMR} (300 \text{ MHz, C}_6\text{D}_6) \ \delta: \ 7.63 (d, \ J= 8.3 \) Hz, 2 H), 6.77 (d, \( J=8.0 \) Hz, 2 H), 4.00 - 3.84 (m, 1 H), 3.67 (tt, \( J_1=12.3 \) Hz, \( J_2=4.4 \) Hz, 1 H), 3.38 (dt, \( J_1=13.8 \) Hz, \( J_2=1.7 \) Hz, 1 H), 2.41 (ddd, \( J_1=13.7 \) Hz, \( J_2=12.2 \) Hz, \( J_3=3.2 \) Hz, 1 H), 1.99 - 1.90 (m, 1 H), 1.88 (s, 3 H), 1.81 - 1.67 (m, 1 H), 1.67 - 1.57 (m, 2 H), 0.58 (d, \( J=6.9 \) Hz, 3 H).

\(^{13}\text{C-NMR} (75 \text{ MHz, C}_6\text{D}_6) \ \delta: \ 143.1, 139.6, 130.1, 127.7, 51.4, 44.3, 42.2, 39.2, 21.5, 20.1, 15.5.

\textbf{MS (70 eV, EI)} \ m/z (\%): 379 (1) [M\textsuperscript{+}], 363 (12), 253 (15), 252 (100), 155 (51), 90 (61), 69 (10), 66 (10), 58 (17), 56 (12).

\textbf{IR (ATR)} \ \tilde{\nu} \ (\text{cm}^{-1}): 2974 (w), 2924 (w), 2870 (vw), 1598 (w), 1494 (vw), 1444 (w), 1380 (w), 1330 (s), 1285 (m), 1204 (w), 1178 (m), 1150 (vs), 1092 (s), 1070 (m), 1056 (m), 1018 (w), 1008 (m), 988 (s), 964 (w), 914 (s), 878 (w), 852 (m), 814 (s), 724 (w), 708 (m), 684 (vs), 644 (s).

\textbf{HRMS (EI)} \text{for C}_{13}\text{H}_{18}\text{INO}_2\text{S} (379.0103): 379.0118.
D. Appendix
1. Data of X-ray Analysis

1.1. Stereoselective Preparation, Configurational Stability and Reactivity of Substituted Cyclohexyllithium Derivatives

\((\beta\text{-cholesteryl})(\text{methyl})\text{sulfane} \ (\beta\text{-(eq)}-94a) \) (Table 2)
cis-1-(tert-butyl)-4-iodocyclohexane (cis-(ax)-78) (Scheme 28)

Crystal Data
Formula C_{10}H_{19}I
M_r 266.15
T[K] 173(2)
Colour, habit colorless block
Cryst. size, mm² 0.35 × 0.25 × 0.08
Crystal system monoclinic
Space group P21/c
a [Å] 17.8172(9)
b [Å] 6.0632(3)
c [Å] 10.7371(5)
α [°] 90.0
β [°] 104.538(4)
γ [°] 90.0
V [Å³] 1122.78(10)
Z 4
ρ_calcd [g cm⁻³] 1.575
μ [mm⁻¹] 2.799
F(000) 528
hkl range -21 ≤ h ≤ 21
-7 ≤ k ≤ 7
-12 ≤ l ≤ 12
Reflns. collected 9572
Reflns. obsd. 1708
Reflns. unique 1972
R_int 0.0386
Param. refined 172
θ range [°] 4.11 - 25.00
R1, wR²[I > 2σ(I)] 0.0255, 0.0635
R1, wR² (all data) 0.0326, 0.0675
((1S,2S,5R)-2-isopropyl-5-methylcyclohexyl)diphenylphosphine sulfide (neomen-(ax)-91b) (Table 3)

Crystal Data

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formula</td>
<td>C_{22}H_{29}PS</td>
</tr>
<tr>
<td>$M_r$</td>
<td>356.48</td>
</tr>
<tr>
<td>T[K]</td>
<td>100(2)</td>
</tr>
<tr>
<td>Colour, habit</td>
<td>colorless block</td>
</tr>
<tr>
<td>Cryst. size, mm$^2$</td>
<td>0.20 × 0.10 × 0.10</td>
</tr>
<tr>
<td>Crystal system</td>
<td>orthorhombic</td>
</tr>
<tr>
<td>Space group</td>
<td>$P2_12_12_1$</td>
</tr>
<tr>
<td>$a$ [Å]</td>
<td>7.6548(3)</td>
</tr>
<tr>
<td>$b$ [Å]</td>
<td>14.5175(5)</td>
</tr>
<tr>
<td>$c$ [Å]</td>
<td>18.1211(7)</td>
</tr>
<tr>
<td>$α$ [°]</td>
<td>90.0</td>
</tr>
<tr>
<td>$β$ [°]</td>
<td>90.0</td>
</tr>
<tr>
<td>$γ$ [°]</td>
<td>90.0</td>
</tr>
<tr>
<td>$V$ [Å$^3$]</td>
<td>2013.77(13)</td>
</tr>
<tr>
<td>$Z$</td>
<td>4</td>
</tr>
<tr>
<td>$ρ_{calc}$ [g cm$^{-3}$]</td>
<td>1.176</td>
</tr>
<tr>
<td>$μ$ [mm$^{-1}$]</td>
<td>0.241</td>
</tr>
<tr>
<td>$F$(000)</td>
<td>768</td>
</tr>
<tr>
<td>$hkī$ range</td>
<td>-9 ≤ $h$ ≤ 9</td>
</tr>
<tr>
<td></td>
<td>-17 ≤ $k$ ≤ 17</td>
</tr>
<tr>
<td></td>
<td>-21 ≤ $l$ ≤ 21</td>
</tr>
<tr>
<td>Reflns. collected</td>
<td>18801</td>
</tr>
<tr>
<td>Reflns. obsd.</td>
<td>3358</td>
</tr>
<tr>
<td>Reflns. unique</td>
<td>3517</td>
</tr>
<tr>
<td>$R_{int}$</td>
<td>0.0400</td>
</tr>
<tr>
<td>Param. refined</td>
<td>313</td>
</tr>
<tr>
<td>$θ$ range [°]</td>
<td>4.30 - 25.00</td>
</tr>
<tr>
<td>$R1$, $wR^2$ [$I &gt; 2\sigma(I)$]</td>
<td>0.0262, 0.0612</td>
</tr>
<tr>
<td>$R1$, $wR^2$ (all data)</td>
<td>0.0284, 0.0622</td>
</tr>
<tr>
<td>GooF</td>
<td>1.067</td>
</tr>
<tr>
<td>Peak / hole [e Å$^3$]</td>
<td>0.243, -0.178</td>
</tr>
</tbody>
</table>
(trans-4-(tert-butyl)cyclohexyl)triphenylstannane (trans-(eq)-82f) (Table 1)

Crystal Data

Formula \( \text{C}_{28}\text{H}_{34}\text{Sn} \)

\( M_r \) 489.24

\( T[K] \) 173(2)

Colour, habit colorless needle

Cryst. size, mm\(^2\) 0.30 × 0.10 × 0.05

Crystal system monoclinic

Space group \( P21/n \)

\( a \) \( [\text{Å}] \) 6.9567(4)

\( b \) \( [\text{Å}] \) 12.1094(5)

\( c \) \( [\text{Å}] \) 29.0071(12)

\( \alpha \) \( [\text{°}] \) 90.0

\( \beta \) \( [\text{°}] \) 94.261(4)

\( \gamma \) \( [\text{°}] \) 90.0

\( V \) \( [\text{Å}^3] \) 2436.8(2)

\( Z \) 4

\( \rho_{\text{calc}} \) [g cm\(^{-3}\)] 1.334

\( \mu \) [mm\(^{-1}\)] 1.059

\( F(000) \) 1008

\( hkl \) range -8 ≤ \( h \) ≤ 8

-14 ≤ \( k \) ≤ 11

-34 ≤ \( l \) ≤ 34

Reflns. collected 11403

Reflns. obsd. 3631

Reflns. unique 4270

\( R_{int} \) 0.0343

Param. refined 362

\( \theta \) range [\text{°}] 4.10 - 25.00

\( R_1, wR_2 \) [\( I > 2\sigma(I) \)] 0.0283, 0.0618

\( R_1, wR_2 \) (all data) 0.0369, 0.0649

GooF 1.023

Peak / hole [e Å\(^3\)] 0.751, -0.298
1.2. Highly Diastereoselective Arylations of Substituted Piperidines

_cis-t_-butyl 2-(3-cyanophenyl)-4-methylpiperidine-1-carboxylate (173d)_

Crystal Data

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>net formula</td>
<td>C_{18}H_{24}N_{2}O_{2}</td>
</tr>
<tr>
<td>M_r/g mol^{-1}</td>
<td>300.395</td>
</tr>
<tr>
<td>crystal size/mm</td>
<td>0.60 × 0.13 × 0.07</td>
</tr>
<tr>
<td>T/K</td>
<td>173(2)</td>
</tr>
<tr>
<td>radiation</td>
<td>MoKα</td>
</tr>
<tr>
<td>diffractometer</td>
<td>'Oxford XCalibur'</td>
</tr>
<tr>
<td>crystal system</td>
<td>triclinic</td>
</tr>
<tr>
<td>space group</td>
<td>P1bar</td>
</tr>
<tr>
<td>a/Å</td>
<td>6.3135(4)</td>
</tr>
<tr>
<td>b/Å</td>
<td>10.2813(10)</td>
</tr>
<tr>
<td>c/Å</td>
<td>13.8719(10)</td>
</tr>
<tr>
<td>α/°</td>
<td>76.283(7)</td>
</tr>
<tr>
<td>β/°</td>
<td>85.876(6)</td>
</tr>
<tr>
<td>γ/°</td>
<td>77.838(7)</td>
</tr>
<tr>
<td>V/Å³</td>
<td>854.90(12)</td>
</tr>
<tr>
<td>Z</td>
<td>2</td>
</tr>
<tr>
<td>calc. density/g cm^{-3}</td>
<td>1.16698(16)</td>
</tr>
<tr>
<td>μ/mm^{-1}</td>
<td>0.076</td>
</tr>
<tr>
<td>absorption correction</td>
<td>'multi-scan'</td>
</tr>
<tr>
<td>transmission factor range</td>
<td>0.72269–1.00000</td>
</tr>
<tr>
<td>refls. measured</td>
<td>5884</td>
</tr>
<tr>
<td>R_{int}</td>
<td>0.0355</td>
</tr>
<tr>
<td>mean σ(I)/I</td>
<td>0.0856</td>
</tr>
<tr>
<td>θ range</td>
<td>4.24–26.33</td>
</tr>
<tr>
<td>observed refls.</td>
<td>1872</td>
</tr>
<tr>
<td>x, y (weighting scheme)</td>
<td>0.0371, 0</td>
</tr>
<tr>
<td>hydrogen refinement</td>
<td>constr</td>
</tr>
<tr>
<td>refls in refinement</td>
<td>3435</td>
</tr>
<tr>
<td>parameters</td>
<td>203</td>
</tr>
<tr>
<td>restraints</td>
<td>0</td>
</tr>
<tr>
<td>R(F_{obs.})</td>
<td>0.0427</td>
</tr>
<tr>
<td>R_s(F^2)</td>
<td>0.0891</td>
</tr>
<tr>
<td>S</td>
<td>0.830</td>
</tr>
<tr>
<td>shift/error_{max}</td>
<td>0.001</td>
</tr>
<tr>
<td>max electron density/e Å^{-3}</td>
<td>0.163</td>
</tr>
</tbody>
</table>
min electron density/e Å⁻³  

-0.141

**cis-t-butyl 2-(3-cyanophenyl)-4-phenylpiperidine-1-carboxylate (173h)**

![Chemical structure of cis-t-butyl 2-(3-cyanophenyl)-4-phenylpiperidine-1-carboxylate (173h) with atom labels and molecular geometry diagram.]

**Crystal Data**

- net formula: C₂₃H₂₆N₂O₂
- Mᵣ/g mol⁻¹: 362.465
- crystal size/mm: 0.39 × 0.22 × 0.12
- T/K: 173(2)
- radiation: MoKα
- diffractometer: 'Oxford XCalibur'
- space group: P2₁/c
- a/Å: 14.5171(9)
- b/Å: 11.6682(8)
- c/Å: 12.0141(8)
- α°: 90
- β°: 98.276(7)
- γ°: 90
- V/Å³: 2013.9(2)
- Z: 4
- calc. density/g cm⁻³: 1.19548(12)
- µ/mm⁻¹: 0.076
- absorption correction: 'multi-scan'
- transmission factor range: 0.96746–1.00000
- refls. measured: 8788
- refls. in refinement: 4068
- parameters: 247
- restraints: 0
- R(Fobs) = 0.0314
- Rw(F²) = 0.0680
- S = 0.806
- shift/errormax = 0.001
max electron density/e Å\(^{-3}\) 0.156
min electron density/e Å\(^{-3}\) −0.144

2-tosyl-3-(4-(trifluoromethyl)phenyl)decahydroisoquinoline (173na)

(from Boc-protected piperidine)

Crystal Data

net formula C\(_{23}\)H\(_{26}\)F\(_3\)NO\(_2\)S

\(M_r/\text{g mol}^{-1}\) 437.519

crystal size/mm 0.51 × 0.05 × 0.02

\(T/K\) 173(2)
radiation MoK\(\alpha\)
diffractometer 'KappaCCD'
crystal system monoclinic

space group \(C2/c\)

\(a/\text{Å}\) 31.5413(5)
\(b/\text{Å}\) 5.49050(10)
\(c/\text{Å}\) 25.8592(4)
\(\alpha/°\) 90
\(\beta/°\) 110.7934(8)
\(\gamma/°\) 90

\(V/\text{Å}^3\) 4186.55(12)

\(Z\) 8

calc. density/g cm\(^{-3}\) 1.38831(4)

\(\mu/\text{mm}^{-1}\) 0.201

absorption correction none

refls. measured 12910

\(R_{int}\) 0.0338

mean \(\sigma(I)/I\) 0.0306

\(\theta\) range 3.37–25.36

observed refls. 3115

\(x, y\) (weighting scheme) 0.0296, 5.6059

hydrogen refinement constr

refls in refinement 3826

parameters 300

restraints 0

\(R(F_{\text{obs}})\) 0.0383

\(R_a(F^2)\) 0.0938

\(S\) 1.088

shift/error\(_{\text{max}}\) 0.001
max electron density/e Å\(^{-3}\) 0.223
min electron density/e Å\(^{-3}\) −0.367

F atoms disordered, split model applied, sof ratio about 1:1.

4-\((cis-5\text{-methyl-1-tosylpiperidin-2-yl})\text{benzonitrile (173qa)}\)

Crystal Data

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>net formula</td>
<td>C(<em>{20})H(</em>{22})N(_2)O(_2)S</td>
</tr>
<tr>
<td>(M_r/\text{g mol}^{-1})</td>
<td>354.467</td>
</tr>
<tr>
<td>crystal size/mm</td>
<td>0.40 × 0.08 × 0.05</td>
</tr>
<tr>
<td>(T/K)</td>
<td>173(2)</td>
</tr>
<tr>
<td>radiation</td>
<td>MoKα</td>
</tr>
<tr>
<td>diffractometer</td>
<td>'Oxford XCalibur'</td>
</tr>
<tr>
<td>crystal system</td>
<td>triclinic</td>
</tr>
<tr>
<td>space group</td>
<td>(P1)bar</td>
</tr>
<tr>
<td>(a/Å)</td>
<td>5.4884(2)</td>
</tr>
<tr>
<td>(b/Å)</td>
<td>11.8978(8)</td>
</tr>
<tr>
<td>(c/Å)</td>
<td>14.2002(7)</td>
</tr>
<tr>
<td>(α/°)</td>
<td>77.357(5)</td>
</tr>
<tr>
<td>(β/°)</td>
<td>86.323(4)</td>
</tr>
<tr>
<td>(γ/°)</td>
<td>87.651(4)</td>
</tr>
<tr>
<td>(V/Å^3)</td>
<td>902.58(8)</td>
</tr>
<tr>
<td>(Z)</td>
<td>2</td>
</tr>
<tr>
<td>calc. density/g cm(^{-3})</td>
<td>1.30429(12)</td>
</tr>
<tr>
<td>(μ/\text{mm}^{-1})</td>
<td>0.195</td>
</tr>
<tr>
<td>absorption correction</td>
<td>'multi-scan'</td>
</tr>
<tr>
<td>transmission factor range</td>
<td>0.98356–1.00000</td>
</tr>
<tr>
<td>refls. measured</td>
<td>6364</td>
</tr>
<tr>
<td>(R_{int})</td>
<td>0.0211</td>
</tr>
<tr>
<td>mean (σ(I)/I)</td>
<td>0.0554</td>
</tr>
<tr>
<td>(θ) range</td>
<td>4.36–26.34</td>
</tr>
<tr>
<td>observed refls.</td>
<td>2403</td>
</tr>
<tr>
<td>(x, y) (weighting scheme)</td>
<td>0.0431, 0</td>
</tr>
<tr>
<td>hydrogen refinement</td>
<td>constr</td>
</tr>
<tr>
<td>refls in refinement</td>
<td>3645</td>
</tr>
<tr>
<td>parameters</td>
<td>228</td>
</tr>
<tr>
<td>restraints</td>
<td>0</td>
</tr>
<tr>
<td>(R(F_{obs}))</td>
<td>0.0371</td>
</tr>
</tbody>
</table>
4-(trans-1-tosyl-2-(4-(trifluoromethyl)phenyl)piperidin-4-yl)benzonitrile (176aa)

Crystal Data

- **net formula**: C$_{26}$H$_{23}$F$_3$N$_2$O$_2$S
- **$M_r$/g mol$^{-1}$**: 484.534
- **crystal size/mm**: 0.35 × 0.04 × 0.04
- **$T/K$**: 173(2)
- **radiation**: MoKα
- **diffractometer**: 'KappaCCD'
- **crystal system**: monoclinic
- **space group**: C$_2/c$
- **$a$/Å**: 22.4013(9)
- **$b$/Å**: 14.5197(5)
- **$c$/Å**: 15.9116(7)
- **α/°**: 90
- **β/°**: 116.2671(19)
- **γ/°**: 90
- **$V$/Å$^3$**: 4641.0(3)
- **$Z$**: 8
- **calc. density/g cm$^{-3}$**: 1.38694(9)
- **μ/mm$^{-1}$**: 0.190
- **absorption correction**: none
- **refls. measured**: 14235
- **$R_{int}$**: 0.0717
- **mean σ(I)/I**: 0.0550
- **θ range**: 3.15–25.34
- **observed refls.**: 2969
- **$x$, $y$ (weighting scheme)**: 0.0316, 6.9720
- **hydrogen refinement**: constr
- **refls in refinement**: 4228
- **parameters**: 308
- **restraints**: 0
- **$R(F_{obs})$**: 0.0448
4-(trans-1-tosyl-2-(4-(trifluoro-methyl)phenyl)-piperidin-4-yl)benzonitrile (176c)

Crystal Data
net formula C_{26}H_{23}F_{3}N_{2}O_{2}S
Mr/g mol⁻¹ 484.534
crystal size/mm 0.21 × 0.15 × 0.096
T/K 173(2)
radiation MoKα
diffractometer 'KappaCCD'
crystal system monoclinic
space group C2/c
a/Å 22.3664(8)
b/Å 14.5275(6)
c/Å 15.9004(5)
α/° 90
β/° 116.2098(18)
γ/° 90
V/Å³ 4635.3(3)
Z 8
calc. density/g cm⁻³ 1.38865(9)
μ/mm⁻¹ 0.191
absorption correction none
refls. measured 10097
Rint 0.0369
mean σ(I)/I 0.0542
θ range 3.15–27.49
observed refls. 3351
x, y (weighting scheme) 0.0577, 3.2402
hydrogen refinement constr
refls in refinement 5236
parameters 308
restraints 0
R(F_{obs}) 0.0484
Crystal Data

- **net formula**: C\(_{20}\)H\(_{22}\)N\(_2\)O\(_2\)S
- **Mr/g mol\(^{-1}\)**: 354.467
- **crystal size/mm**: 0.22 × 0.16 × 0.06
- **T/K**: 173(2)
- **radiation**: MoK\(\alpha\)
- **diffractometer**: ‘Oxford XCalibur’
- **crystal system**: triclinic
- **space group**: \(P\bar{1}\)bar
- **a/Å**: 7.4047(6)
- **b/Å**: 9.5212(9)
- **c/Å**: 13.7988(11)
- **\(\alpha/°\)**: 88.074(7)
- **\(\beta/°\)**: 76.203(7)
- **\(\gamma/°\)**: 87.599(7)
- **V/Å\(^3\)**: 943.66(14)
- **Z**: 2
- **calc. density/g cm\(^{-3}\)**: 1.24751(19)
- **\(\mu/\text{mm}^{-1}\)**: 0.186
- **absorption correction**: ‘multi-scan’
- **transmission factor range**: 0.82353–1.00000
- **refls. measured**: 4869
- **R\(_{int}\)**: 0.0434
- **mean \(\sigma(I)/I\)**: 0.1372
- **0 range**: 4.29–23.29
- **observed refls.**: 1212
- **x, y (weighting scheme)**: 0.0470, 0
- **hydrogen refinement**: constr
- **refls in refinement**: 2651
- **parameters**: 228
- **restraints**: 0
- **\(R(F_{\text{obs}})\)**: 0.0539
- **\(R_w(F^2)\)**: 0.1174

4-\(\text{trans}\)-2-methyl-1-tosylpiperidin-4-yl)benzonitrile (176e)
Crystal had poor scattering strength, data collection merely up to a resolution of 0.90 Å.

trans-2-methyl-1-tosyl-5-(4-(trifluoromethyl)phenyl)-piperidine (181ca)

Crystal Data
net formula C_{20}H_{22}F_{3}NO_{2}S

Mr/g mol\(^{-1}\) 397.455

Crystal size/mm 0.37 × 0.23 × 0.17

T/K 243(2)

radiation MoK\(_\alpha\)

diffractometer ‘Oxford XCalibur’

space group P\(2_1\)/n

a/Å 10.1552(5)
b/Å 11.7039(5)
c/Å 16.2918(8)
a/° 90
β/° 98.366(4)
γ/° 90

V/Å\(^3\) 1915.76(16)

Z 4

calc. density/g cm\(^{-3}\) 1.37804(12)
µ/mm\(^{-1}\) 0.212

absorption correction ‘multi-scan’

transmission factor range 0.94343–1.00000

refls. measured 7447

R\(_{int}\) 0.0271

mean σ(I)/I 0.0604

θ range 4.30–26.33

observed refls. 2580

x, y (weighting scheme) 0.0432, 0

hydrogen refinement constr

refl.s in refinement 3883

parameters 273

restraints 10

R(F\(_{\text{obs}}\)) 0.0368

R\(_{w}\)(F\(^2\)) 0.0840
$S$ 0.881
\text{shift/error}_{\text{max}} 0.001
\text{max electron density/e Å}^{-3} 0.284
\text{min electron density/e Å}^{-3} -0.379

The F atoms of the CF$_3$ group are disordered over three sites. A split model has been applied. The sof ratios are 0.83:0.09:0.08. The F atoms on the highest occupied site have been refined anisotropically.
## 2. Curriculum Vitae

### Personal Information

<table>
<thead>
<tr>
<th>Name</th>
<th>Stephanie Seel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date of Birth</td>
<td>04.02.1983</td>
</tr>
<tr>
<td>Place of Birth</td>
<td>Köln</td>
</tr>
<tr>
<td>Citizenship</td>
<td>German</td>
</tr>
</tbody>
</table>

### Publications


### Posters
