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Enantiocontrol with Chiral Sulfoxides and Diastereocontrol in the Cross-Couplings of Substituted Cycloalkyl and Piperidinyl Derivatives

von

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Erklärung

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Parts of this Ph.D. thesis have been published

1) Tobias Thaler, Florian Geittner, Paul Knochel, "A Novel Synthetic Approach towards Chiral QUINAP", *Synlett* **2007**, 2655.

2) Tobias Thaler, Benjamin Haag, Andrei Gavryushin, Katrin Schober, Evelyn Hartmann, Ruth M. Gschwind, Hendrik Zipse, Peter Mayer, Paul Knochel, "Highly Diastereoselective Csp^3-Csp^2 Negishi Cross-Coupling with 1,2-, 1,3- and 1,4-Substituted Cycloalkylzinc Compounds", *Nature Chem.* **2010**, *2*, 125.

3) Tobias Thaler, Li-Na Guo, Peter Mayer, Paul Knochel, "Highly Diastereoselective Csp^3-Csp Cross-Couplings between 1,3- and 1,4-Substituted Cyclohexylzinc Reagents and Bromoalkynes via Remote Stereocontrol", *Angew. Chem. Int. Ed.* **2011**, *50*, 2174.

4) Tobias Thaler, Andreas K. Steib, Kimihiro Komeyama, Peter Mayer, Paul Knochel, "Highly Diastereoselective Fe-Mediated Csp^2-Csp^3 Cross-Couplings between Aryl Grignard Reagents and Cyclic Iodohydrine Derivatives", *Angew. Chem. Int. Ed.* **2011**, *50*, *in press*.

5) Stephanie Seel, Tobias Thaler, Keishi Takatsu, Cong Zhang, Hendrik Zipse, Bernd F. Straub, Paul Knochel, "Highly Diastereoselective Arylations of Substituted Piperidines via Pd-Catalyzed Csp^3-Csp^2 Cross-Couplings", *manuscript submitted*.

6) Tobias Thaler, Li-Na Guo, M. Raducan, Andreas K. Steib, Konstantin Karaghiosoff, Paul Knochel, "Sulfoxide-Alkene Hybrids: A New Class of Chiral Ligands for the Hayashi-Miyaura Reaction", *manuscript submitted*.

Dotted lines indicate equal contribution with the respective author to the manuscript.

“To understand reality is not the same as to know about outward events. It is to perceive the essential nature of things. The best-informed man is not necessarily the wisest. Indeed there is a danger that precisely in the multiplicity of his knowledge he will lose sight of what is essential. But on the other hand, knowledge of an apparently trivial detail quite often makes it possible to see into the depth of things. And so the wise man will seek to acquire the best possible knowledge about events, but always without becoming dependent upon this knowledge. To recognize the significant in the factual is wisdom.“

Dietrich Bonhoeffer

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Abbreviations

Ac	acetyl	Me	methyl
acac	acetylacetonate	Met	metal
aq.	aqueous	min	minute
Ar	aryl	mmol	millimole
Boc	*tert*-butoxycarbonyl	m.p.	melting point
br	broad	MS	mass spectroscopy
Bu	butyl	NBS	*N*-bromosuccinimide
*n*Bu	*n*-butyl	NCS	*N*-chlorosuccinimide
*s*Bu	*s*-butyl	NEP	*N*-ethyl-2-pyrrolidine
*t*Bu	*t*-butyl	NMI	*N*-methylimidazole
calc.	calculated	NMR	nuclear magnetic resonance
coe	cyclooctene	*o*	ortho
conc.	concentrated	*p*	para
*c*Hex	cyclohexyl	Ph	phenyl
δ	chemical shifts in parts per million	*i*Pr	isopropyl
d	doublet	q	quartet
dba	*trans,trans*-dibenzylideneacetone	R	organic substituent
DFT	density functional theory	rt	room temperature
DMF	*N,N*-dimethylformamide	RuPhos	dicyclohexyl(2',6'-diisopropoxy-[1,1'-biphenyl]-2-yl)phosphine
DMAP	4-(dimethylamino)pyridine		
DMSO	dimethyl sulfoxide	sat.	saturated
dppe	diphenylphosphinoethane	s	singulet
dppp	diphenylphosphinopropane	sept	septet
DPE-Phos	bis(2-diphenylphosphinophenyl)ether	SPhos	2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl
E	electrophile		
EI	electron-impact	tfp	tri-2-furylphosphine
ESI	electrospray ionization	THF	tetrahydrofuran
equiv	equivalent	TBS	*tert*-butyldimethylsilyl
Et	ethyl	TBDPS	*tert*-butyldiphenylsilyl
FG	functional group	TIPS	triisopropylsilyl
GC	gas chromatography	TMEDA	*N,N,N',N'*-tetramethylethylene-diamine
h	hour		
HRMS	high resolution mass spectroscopy	(*S*)-TMPOO	(*S*)-*N*-tosyl-phenyl-methyl-1,2,3-oxathiazolidine
IR	infra-red		
J	coupling constant (NMR)	TMPP	tris(2,4,6-trimethoxyphenyl)-phosphine
M	molarity		

m	meta	TMS	trimethylsilyl
m	multiplet	Ts	4-toluenesulfonyl

A. Introduction

1. General Introduction

Stereoselective syntheses have become indispensable for the pharmaceutical, agrochemical, flavor and fragrance industries.[1] An enantiocontrolled preparation of pharmaceuticals is often of utmost significance not only to ensure proper biological function but also to avoid deleterious side effects.[2] Thus, the synthesis of both natural and unnatural organic compounds in their optically pure forms has become an important and highly active field of research in modern organic chemistry. Many of today's syntheses aim at compounds with increasingly complex scaffolds which require an accurate control of multiple stereocenters and even of chiral axes, planes and structure-inherent chiralities.[1, 3] In order to meet these synthetic challenges a chemist must be able to benefit from a rich pool of versatile diastereo- and enantioselective transformations. Access to enantiomerically pure compounds is implemented by using one of the following main approaches:

1. Resolution of a racemic mixture:

   Classical approaches comprise separation of the enantiomers via recrystallization or reaction of the racemic mixture with a stoichiometric amount of a chiral reagent followed by isolation of the resulting diastereomers. Kinetic resolution represents a further alternative. In this approach, the racemic mixture is subjected to an enantioselective reaction with only one enantiomer being selectively transformed. In all these cases, the highest possible yield for one enantiomer cannot exceed 50%. Dynamic kinetic resolution (DKR) represents an important advancement to the latter method as it allows full production of one single enantiomer from a racemic mixture by exploiting the configurational instability of the starting material and/or the reactive intermediates.[4]

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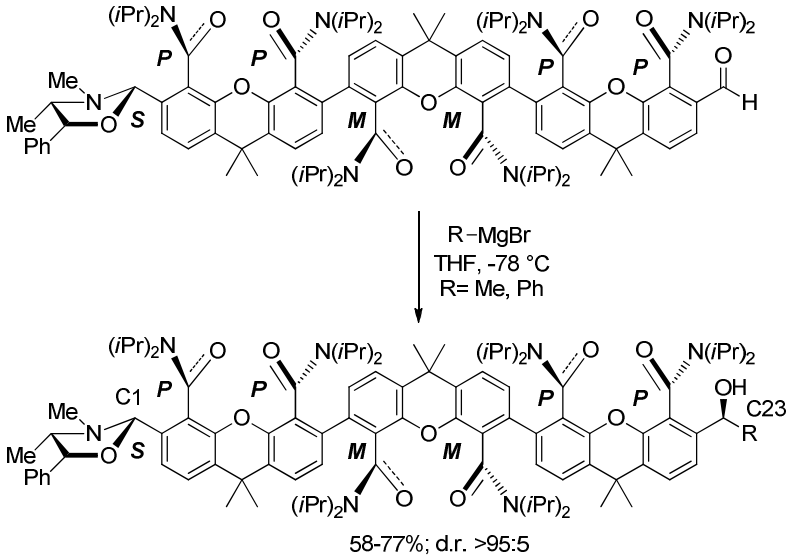
[1] (a) *Asymmetric Synthesis – The Essentials* (Eds.: M. Christmann, S. Bräse), Wiley-VCH, **2007**; (b) V. Farina, J. T. Reeves, C. H. Senanayake, J. J. Song, *Chem. Rev.* **2006**, *106*, 2734.
[2] D. Enders, R. W. Hoffmann, *Chem. Unserer Zeit* **1985**, *19*, 177.
[3] (a) M. S. Taylor, E. N. Jacobsen, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5368; (b) J. T. Mohr, M. R. Krout, B. M. Stoltz, *Nature* **2008**, *455*, 323; (c) *Comprehensive Asymmetric Catalysis*, Vol. 1-3 (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, **2000**; (d) *Comprehensive Asymmetric Catalysis*, Suppl. 1-2 (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, **2004**; (e) B. M. Trost, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5348.
[4] (a) H. Pellissier, *Tetrahedron* **2008**, *64*, 1563; (b) H. Pellissier, *Tetrahedron* **2003**, *59*, 8291; (c) F. F. Huerta, A. B. E. Minidis, J.-E. Bäckvall, *Chem. Soc. Rev.* **2001**, *30*, 321; (d) R. Noyori, M. Tokunaga, M. Kitamura, *Bull. Chem. Soc. Jpn.* **1995**, *68*, 36.

2. Synthesis from the "chiral pool" and synthesis using a chiral auxiliary:

Before the advent of efficient asymmetric synthetic methods the "chiral pool" was limited to optically active compounds provided by nature, including, most essentially, carbohydrates and amino acids, which are usually produced in only one enantiomeric form. The development of asymmetric catalysis (see below) has expanded the scope of "the chiral pool" to unnatural chiral materials.[3a, 5] Chiral auxiliaries can be viewed as chiral protective groups, as they are mostly introduced prior to the stereoselective reaction and removed afterwards.[6] Asymmetric reactions using chiral auxiliaries depend on diastereocontrol. The fact that the auxiliary-substituted products are diastereomeric additionally enables chiral resolution for very high enantiomeric purities of the final products after removal of the chiral auxiliary. Asymmetric synthesis from the chiral pool or using a chiral auxiliary is often wrongfully considered as an obsolete synthetic approach. In fact, chiral auxiliaries continue to be essential tools in modern synthetic chemistry.[1b, 6] Most of today's chiral ligand or organocatalyst syntheses are based on the use of chiral auxiliaries or the "chiral pool". Moreover, chiral auxiliaries have special properties that allow asymmetric inductions that cannot be easily achieved with asymmetric catalysis.



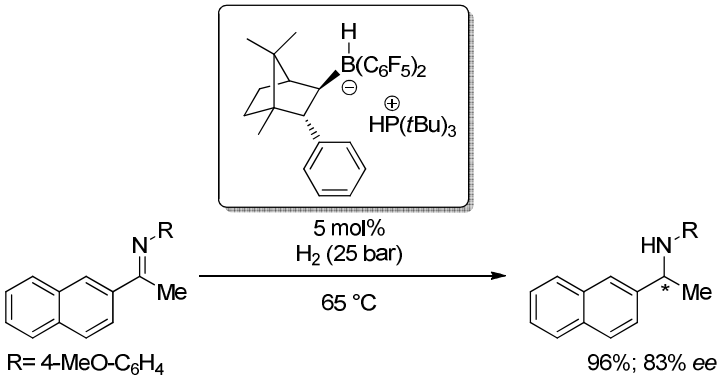
Scheme 1: Ultra-remote stereocontrol *over 22 bonds* using chiral auxiliaries.

[5] H.-U. Blaser, *Chem. Rev.* **1992**, *92*, 935.
[6] Y. Gnas, F. Glorius, *Synthesis* **2006**, 1899.

An impressive example of their potential was given by *J. Clayden et al.* who used a chiral oxazolidine auxiliary for ultra-remote stereoinduction (Scheme 1).[7]

3. Asymmetric catalysis:

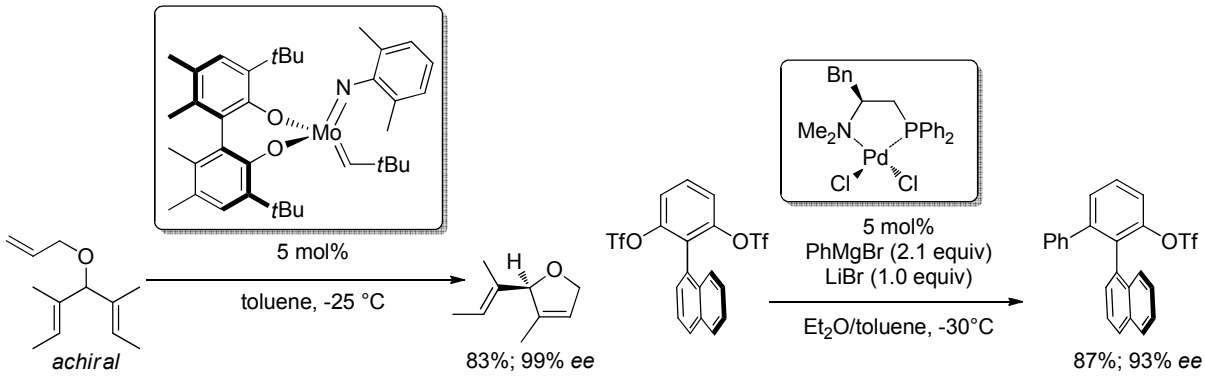
Asymmetric catalysis represents an ideal method for the induction of enantioselectivity. Here, a catalytic amount of a chiral promoter is already sufficient to produce both natural and unnatural chiral compounds in large quantities. The chirality multiplication efficiency {[(amount of major enantiomer of product) – (amount of minor enantiomer of product)]/ (amount of chiral source)} represents a measure for the competence of the chiral catalyst. This factor can theoretically be infinite for asymmetric catalysis – an important property which renders this approach superior to intra- and intermolecular chirality transfer reactions.[1a, 8] The three major fields of modern methodical organic chemistry, bioorganic chemistry, organocatalysis and organometallic chemistry, provide expedient access to asymmetric catalysis: Thus, enzymes have proved to be extremely reliable tools in asymmetric reduction, oxidation and desymmetrization processes.[9] In asymmetric organocatalysis, small amounts of a chiral organic molecule are used for enantioselective transformations.



Scheme 2: Asymmetric catalytic hydrogenation using frustrated Lewis pairs.

[7] J. Clayden, A. Lund, L. Vallverdú, M. Helliwell, *Nature* **2004**, *431*, 966.
[8] *Catalytic Asymmetric Synthesis* (Ed.: I. Ojima), Wiley-VCH, **2000**.
[9] (a) R. Wohlgemuth, *Curr. Opin. Microb.* **2010**, *13*, 283; (b) R. N. Patel, *Adv. Synth. Catal.* **2001**, *343*, 527.

Over the past decade, the significance of this methodology has immensely grown and its abilities have become multifaceted. [10] A recent example of the widespread abilities of today's asymmetric organocatalysis is the enantioselective hydrogenation with chiral frustrated Lewis pairs (Scheme 2).[11] Organometallic chemistry comprises the largest and most versatile scope of asymmetric reactions, including even asymmetric metathesis[12] and cross-coupling reactions[13] (Scheme 3). Thereby, the metal core of an organometallic species acts as the central docking site for the reactants. Asymmetry is induced by a suitable chiral ligand which partially complexes the respective metal, thus accurately defining its structural environment. The synthetic accessibility of chiral ligands, the possibility of diversifying and adapting their properties and their applicability to many distinct reactions have made their development one of the most important and popular research fields in modern organic chemistry.[14]

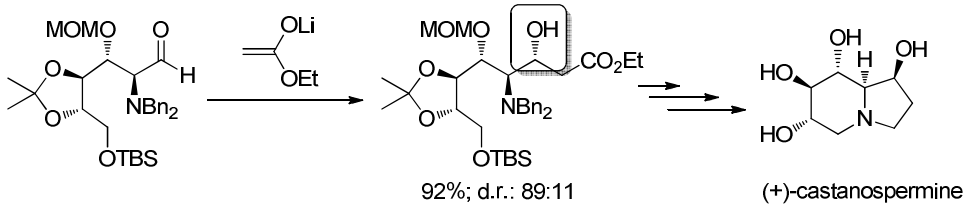


Scheme 3: Asymmetric transition-metal catalyzed metathesis and cross-coupling.

Many natural and unnatural bioactive molecules have multiple stereocenters giving rise to a large number of possible stereoisomers (2^n, where n is the number of stereocenters). Efficient control of the relationship between stereocenters and an expedient transfer of chirality throughout the

[10] (a) E. N. Jacobsen, D. W. C. MacMillan, *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 20618; (b) C. Grondal, M. Jeanty, D. Enders, *Nature Chem.* **2010**, *2*, 167; (c) A. G. Doyle, E. N. Jacobsen, *Chem. Rev.* **2007**, *107*, 5713; (d) A. Dondoni, A. Massi, *Angew. Chem. Int. Ed.* **2008**, *47*, 4638; (e) S. Jaroch, H. Weinmann, K. Zeitler, *ChemMedChem* **2007**, *2*, 1261; (f) H. Pellissier, *Tetrahedron* **2007**, *63*, 9267; (g) K. N. Houk, B. List, *Acc. Chem. Res.* **2004**, *37*, 487.
[11] D. Chen, Y. Wang, J. Klankermayer, *Angew. Chem. Int. Ed.* **2010**, *122*, 9665.
[12] H. F. T. Klare, M. Oestreich, *Angew. Chem. Int. Ed.* **2009**, *48*, 2085.
[13] (a) F. Glorius, *Angew. Chem. Int. Ed.* **2008**, *47*, 8347; (b) T. Hayashi, *J. Organomet. Chem.* **2002**, *653*, 41.
[14] M. Shibasaki, S. Matsunaga in *Asymmetric Synthesis – The Essentials* (Eds.: M. Christmann, S. Bräse), Wiley-VCH, **2007**, 47.

synthesis can only be ensured with highly diastereoselective methods.[3a, 15] Therefore, the development of diastereoselective reactions represents an important synthetic task, as exemplified by the total synthesis of the natural product (+)-castanospermine (Scheme 4).[16]



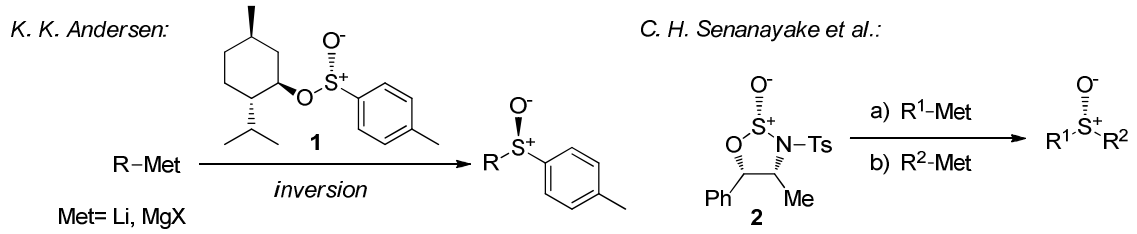
Scheme 4: Importance of diastereocontrol in the asymmetric synthesis of (+)-castanospermine.

[15] M. T. Reetz, *Chem. Rev.* **1999**, *99*, 1121.
[16] (a) H. Ina, C. Kibayashi, *Tetrahedron Lett.* **1991**, *32*, 4147; (b) H. Ina, C. Kibayashi, *J. Org. Chem.* **1993**, *58*, 52.

2. Enantiocontrol with Chiral Sulfoxides

2.1 Chiral sulfoxides as steering molecules in asymmetric synthesis

Its unique properties, such as central chirality at the sulfur, high configurational stability and the strongly polarized S-O bond make the chiral sulfinyl group a steering functionality of increasing importance in all fields of asymmetric synthesis[6, 17] and pharmaceutical research.[1b] Chiral sulfoxides can be easily accessed via the reaction of an organometallic reagent with (–)-menthyl (*S*)-*p*-toluenesulfinate (**1**) or its enantiomer , pioneered by *K. K. Andersen* as early as 1962,[18] which greatly adds to their attractiveness and usability in asymmetric reactions. The addition of the organometallic reagent occurs with inversion of the configuration at the chiral sulfur (Scheme 5). Only recently, *C. H. Senanayake et al.* extended this approach to the use of *N*-sulfonyl-1,2,3-oxathiazolidine-2-oxide derivatives, such as (*S*)-TMPOO (**2**), allowing a highly versatile construction of chiral sulfoxides.[19]



Scheme 5: Introduction of the chiral sulfinate group via reaction with organometallic reagents.

Alternative syntheses of chiral sulfoxides are mostly based on the asymmetric oxidation of sulfides.[16a] Chiral sulfoxides have proved to be suitable for the resolution of planar,[20] axial[21] and

[17] (a) E. Wojaczyńska, J. Wojaczyński, *Chem. Rev.* **2010**, *110*, 4303; (b) M. C. Carreño, G. Hernández-Torres, M. Ribagorda, A. Urbano, *Chem. Commun.* **2009**, 6129; (c) H. Pellissier, *Tetrahedron* **2006**, *62*, 5559; (d) *Organosulfur Chemistry in Asymmetric Synthesis*, (Eds.: T. Toru, C. Bolm), Wiley-VCH **2008**; (e) I. Fernandéz, N. Khiar, *Chem. Rev.* **2003**, *103*, 3651; (f) C. H. Senanayake, D. Krishnamurthy, Z.-H. Lu, Z. Han, I Gallou, *Aldrichim. Acta* **2005**, *38*, 93 and references therein.

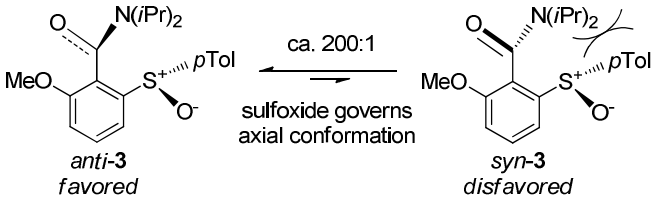
[18] (a) K. K. Andersen, *Tetrahedron Lett.* **1962**, *3*, 93; for preparation see: (b) J. M. Klunder, K. B. Sharpless, *J. Org. Chem.* **1987**, *52*, 2598; (c) Y. Watanabe, N. Mase, T. Moto-aki, T. Toru, *Tetrahedron: Asymmetry* **1999**, *10*, 737.

[19] (a) Z. Han, D. Krishnamurthy, P. Grover, Q. K. Fang, X. Su, H. S. Wilkinson, Z.-H. Lu, D. Magiera, C. H. Senanayake, *Tetrahedron* **2005**, *61*, 6386; (b) Z. Han, D. Krishnamurthy, P. Grover, H. S. Wilkinson, Q. K. Fang, X. Su, Z.-H. Lu, D. Magiera, C. H. Senanayake, *Angew. Chem. Int. Ed.* **2003**, *42*, 2032.

[20] (a) F. Rebière, O. Riant, L. Ricard, H. B. Kagan, *Angew. Chem. Int. Ed.* **1993**, *32*, 568; (b) G. J. Rowlands, *Org. Biomol. Chem.* **2008**, *6*, 1527 and references therein.

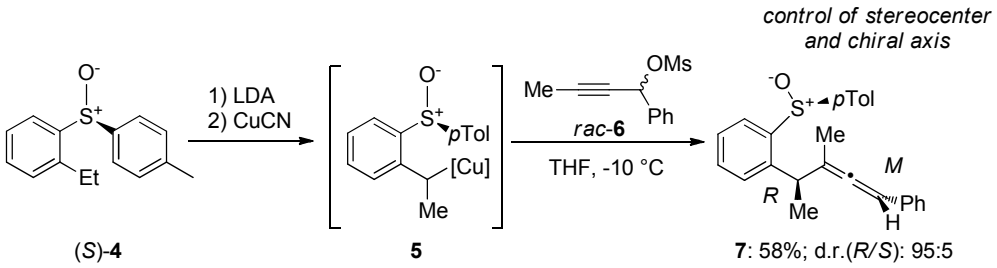
[21] (a) J. Clayden, S. P. Fletcher, J. J. W. McDouall, S. J. M. Rowbottom, *J. Am. Chem. Soc.* **2009**, *131*, 5331 and references therein; (b) J. Clayden, P. M. Kubinski, F. Sammiceli, M. Helliwell, L. Diorazio, *Tetrahedron* **2004**, *60*, 4387; (c) J. Clayden, D. Mitjans, L. H. Youssef, *J. Am. Chem. Soc.* **2002**, *124*, 5266; (d) M. S. Betson, A. Bracegirdle, J. Clayden, M. Helliwell, A. Lund, M. Pickworth, T. J. Snape, C. P. Worrall, *Chem. Commun.* **2007**, 754.

helical chiralities[22] and are therefore widely used as key-intermediates in the syntheses of chiral ligands.[17] Moreover, it was shown that the central chirality of the sulfinyl group strongly dictates the conformational preferences of atropisomers thus enabling the selective, stereocontrolled preparation of axially chiral molecules, such as amide **3** (Scheme 6).[20a, 23]



Scheme 6: Control of the chiral axis by the central chirality at the sulfinyl group.

The ability of the sulfoxide to induce remote and ultra-remote stereocontrol (see chapter 1, Scheme 1) makes it a valuable chiral auxiliary allowing highly diastereoselective transformations.[22] Its use in the synthesis of optically pure allenes with central and axial chiralities, as developed by *J. L. Garcià Ruano*, is an outstanding example of the powerful capacities of the chiral sulfinyl functionality in asymmetric induction (Scheme 7).[24]

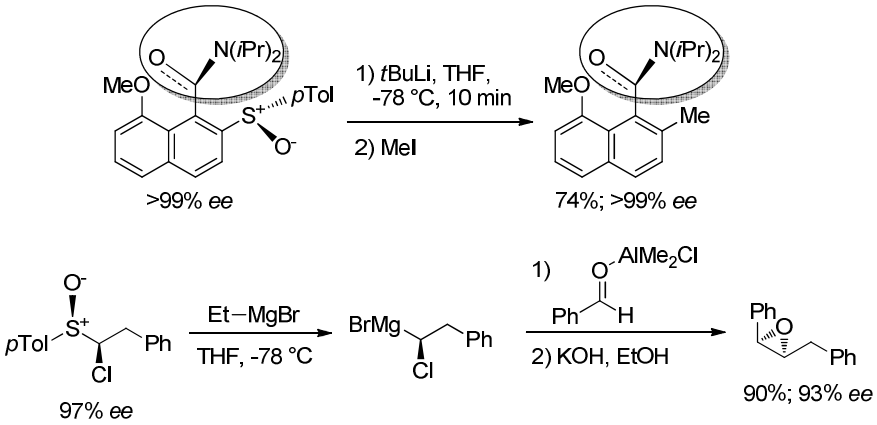


Scheme 7: Asymmetric induction with sulfoxides: simultaneous control of the stereoconfigurations of center and chiral axis.

Starting from (*S*)-**4**, deprotonation with LDA and transmetalation with CuCN·2 LiCl furnished the benzyl copper intermediate **5** whose reaction with racemic propargyl mesylates, such as *rac*-**6**, regioselectively gave the 1,1-disubstituted allene **7** in 58**%** yield with *M*-configuration at the chiral axis and *R*-configuration of the benzyl stereocenter (*R*/*S* 95:5). This result demonstrated

[22] (a) A. Latorre, A. Urbano, M. C. Carreño, *Chem. Commun.* **2009**, 6652; (b) M. C. Carreño, S. Garcìa-Cerrada, A. Urbano, *Chem. Eur. J.* **2003**, *9*, 4118.
[23] J. Clayden, N. Vassiliou, *Org. Biomol. Chem.* **2006**, *4*, 2667 and references therein.
[24] (a) J. L. García Ruano, V. Marcos, J. Alemán, *Angew. Chem. Int. Ed.* **2008**, *47*, 6836; (b) J. L. García Ruano, V. Marcos, J. Alemán, *Angew. Chem. Int. Ed.* **2009**, *48*, 3155.

that even dynamic kinetic resolution had occurred during the S_N2' reaction with the *R*-enantiomer of *rac*-**6** being the most reactive substrate. The possibility of performing sulfoxide-lithium or -magnesium exchanges is an additional highly valuable feature of the sulfinyl group. Thus, it can be considered as a "chiral halogen" functionality that can "tracelessly" be removed or replaced by other functionalities. Remarkably, the configurations of the axis in atropisomers[20a-b, 22] or even at the stereocenter[25] in the resulting organometallic reagents were shown to be relatively stable over a few minutes at low temperatures (Scheme 8).

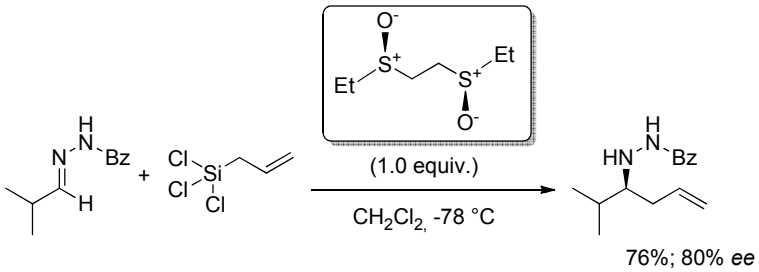


Scheme 8: Sulfoxide-lithium and sulfoxide magnesium exchange: preservation of axial and central configurations.

Recently, sulfoxides have also found applications as chiral Lewis bases inducing high enantioselectivities in the allylation of aldehydes and hydrazones with allyl trichlorosilane.[26] However, stoichiometric use of the respective chiral sulfoxide is necessary to obtain good conversions and high enantiomeric excesses (Scheme 9).

[25] (a) R. W. Hoffmann, *Chem. Soc. Rev.* **2003**, *32*, 225; (b) R. W. Hoffmann, P. G. Nell, *Angew. Chem. Int. Ed.* **1999**, *38,* 338.

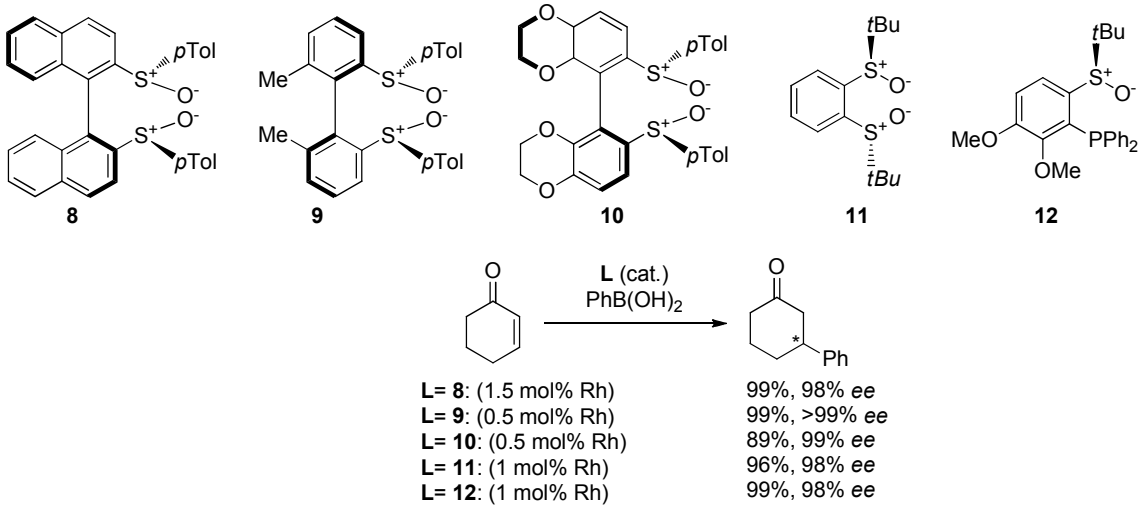
[26] (a) A. Massa, M. R. Acocella, V. De Sio, R. Villano, A. Scettri, *Tetrahedron: Asymmetry* **2009**, *20*, 202; (b) S. Kobayashi, C. Ogawa, H. Konishi, M. Sugiura, *J. Am. Chem. Soc.* **2003**, *125*, 6610; (c) A. Massa, A. V. Malkov, P. Kočovský, A. Scettri, *Tetrahedron Lett.* **2003**, *44*, 7179; (d) G. Rowlands, W. K. Barnes, *Chem. Commun.* **2003**, 2712; (e) I. Fernández, V. Valdivia, B. Gori, F. Alcudia, E. Alvarez, N. Khiar, *Org. Lett.* **2005**, *7*, 1307; (f) F. García-Flores, L. Flores-Michel, E. Juaristi, *Tetrahedron Lett.* **2006**, *47*, 8235; (g) I. Fernández, V. Valdivia, M. Pernía Leal, N. Khiar, *Org. Lett.* **2007**, *9*, 2215.



Scheme 9: Asymmetric addition of allyl trichlorosilanes to hydrazones mediated by chiral sulfoxides.

2.2 Sulfoxides as a relatively new class of chiral ligands for transition-metal catalyzed reactions

Although the coordination chemistry of sulfoxides has been well studied and despite the easy preparation and resolution of chiral sulfoxides,[27] the success story of their application as chiral ligands in enantioselective transition-metal catalyzed reactions is a rather recent one. Initially, chiral mono- and bissulfoxides were used in hydrogenation reactions, diethylzinc addition to benzaldehyde, Diels-Alder reactions and allylic substitutions.[17b,e, 28] Except for the latter two reactions, mostly low to moderate enantioselectivities were obtained. The breakthrough was achieved by the development of the axially chiral bissulfoxide ligands **8** and **9** for the Rh-catalyzed *Hayashi-Miyaura* reaction[29] by *R. Dorta et al.* (Scheme 10).[30]



Scheme 10: Chiral sulfoxide ligands for the asymmetric *Hayashi-Miyaura* reaction.

High reactivities and excellent enantioselectivities (94-99% *ee*) were obtained for the addition products. Noteworthy are the low catalyst loadings (1.5 mol% with **8** and 0.5-1.0 mol% with **9**) used in the 1,4-addition reaction. Compared to diphosphines, bissulfoxides behave as better σ-donating ligands in the Rh-catalyzed conjugate transfer of aryl boronic acids to cyclic enones.[29a]

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[27] (a) M. Calligaris, O. Carugo, *Coord. Chem. Rev.* **1996**, *153*, 83; (b) H. B. Kagan, B. Ronan, *Rev. Heteroat. Chem.* **1992**, *7*, 92.
[28] I. Fernandéz, N. Khiar in *Organosulfur Chemistry in Asymmetric Synthesis*, (Eds.: T. Toru, C. Bolm), Wiley-VCH, **2008**, 265 and references therein.
[29] Y. Takaya, M. Ogasawara, T. Hayashi, M. Sakai, N. Miyaura, *J. Am. Chem. Soc.* **1998**, *120*, 5579.
[30] (a) J. J. Bürgi, R. Mariz, M. Gatti, E. Drinkel, X. Luan, S. Blumentritt, A. Linden, R. Dorta, *Angew. Chem. Int. Ed.* **2009**, *48*, 2768; (b) R. Mariz, X. Luan, M. Gatti, A. Linden, R. Dorta, *J. Am. Chem. Soc.* **2008**, *130*, 2172.

Further chiral bissulfoxides (**10**-**11**)[31] and a sulfoxide-phosphine hybrid ligand (**12**)[32] were developed and consequently used in this type of reaction. All of them induced very high levels of enantioselectivity in the addition of arylboronic acids to cyclohexen-2-one (Scheme 10).

[31] (a) Q.-A. Chen, X. Dong, M.-W. Chen, D.-S. Wang, Y.-G. Zhou, Y.-X. Li, *Org. Lett.* **2010**, *12*, 1928; (b) J. Chen. F. Lang, X. Zhang, L. Cun, J. Zhu, J. Deng, J. Liao, *J. Am. Chem. Soc.* **2010**, *132*, 4552.
[32] F. Lang, D. Li, J. Chen, J. Chen, L. Li, L. Cun, J. Zhu, J. Deng, J. Liao, *Adv. Synth. Catal.* **2010**, *352*, 843.

3. Stereoselective Cross-Coupling Reactions

3.1 Transition-metal catalyzed cross-coupling as one of the most important C-C bond forming reactions in modern organic synthesis

Last year's Nobel prize in chemistry was awarded to the three pioneers of transition-metal catalyzed cross-coupling, *R. F. Heck*, *E.-i. Negishi* and *A. Suzuki*, who initiated, with their groundbreaking works in the 1960s and 1970s,[33] the development of one of today's most important C-C bond forming reactions: transition-metal catalyzed cross-coupling.[34] Today, this type of reaction has become an extremely valuable and well-developed method not only for complex total syntheses but also, and more significantly, for numerous industrial applications, including the syntheses of pharmaceuticals, artificial materials and agrochemicals.[34, 35] Despite outstanding achievements, the development of improved, complementary and alternative methods for cross-coupling reactions is ongoing and represents one of the most active research fields in organic synthesis today. Thereby, one of the most important synthetic challenges is the development of efficient and general methods for the cross-coupling of secondary Csp^3-centers.[36] For such reactions, the C-C bond formation is problematic due to competing β-hydride elimination and sluggish reductive elimination.[37] In addition, the issue of stereoselectivity becomes revelant for unsymmetrically substituted substrates.

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[33] (a) R. F. Heck, J. P. Nolley, *J. Org. Chem.* **1972**, *37*, 2320; (b) E. Negishi, A. O. King, N. Okukado, *J. Org. Chem.* **1977**, *42*, 1821; (c) N. Miyaura, T. Yanaga, A. Suzuki, *Synth. Commun.* **1981**, *11*, 513.

[34] X.-F. Wu, P. Anbarasan, H. Neumann, M. Beller, *Angew. Chem. Int. Ed.* **2010**, *49*, 9047.

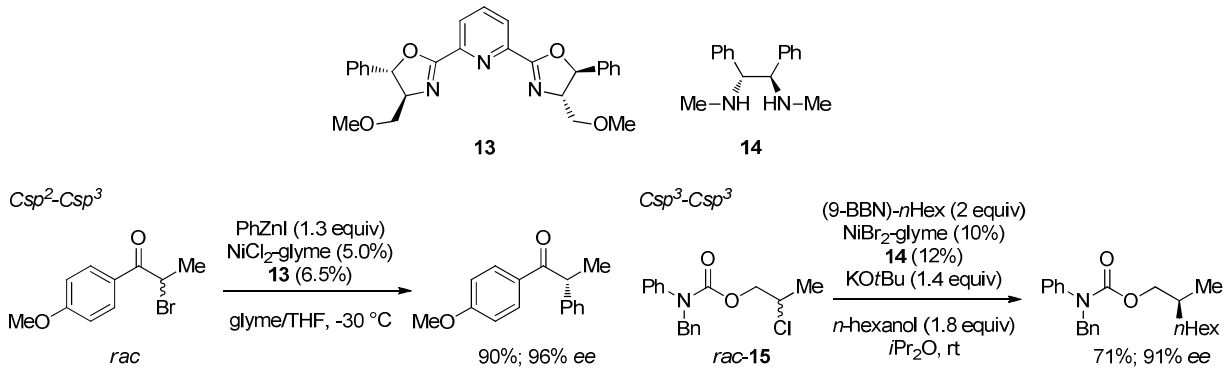
[35] (a) *Transition Metals for Organic Synthesis: Building Blocks and Fine Chemicals* (Eds.: M. Beller, C. Bolm), 2nd ed., Wiley-VCH, **2004**; (b) *Metal-Catalyzed Cross-Coupling Reactions* (Eds.: F. Diederich, P. J. Stang), Wiley-VCH, **1998**; (c) *Metal-Catalyzed Cross-Coupling Reactions* (Eds.: A. deMeijere, F. Diederich), 2nd ed., Wiley-VCH, **2004**.

[36] A. Rudolph, M. Lautens, *Angew. Chem. Int. Ed.* **2009,** *48*, 2656; (b) J. Terao, N. Kambe, *Acc. Chem. Res.* **2008,** *41*, 1545; (c) S. R. Chemler, D. Trauner, S. J. Danishefsky, *Angew. Chem. Int. Ed.* **2001,** *40* 4544; (d) J.-P. Corbet, G. Mignani, *Chem. Rev.* **2006,** *106*, 2651; (e) C. Valente, S. Baglione, D. Candito, C. J. O'Brien, M. G. Organ, *Chem. Commun.* **2008**, 735; (f) N. Hadei, E. A. B. Kantchev, C. J. O'Brien, M. G. Organ, *Org. Lett.* **2005,** *7*, 3805; (g) D. A. Powell, T. Maki, G. C. Fu,. *J. Am Chem. Soc.* **2005**, *127*, 510; (h) E.-i. Negishi, L. F. Valente, M. Kobayashi, *J. Am Chem. Soc.* **1980**, *102*, 3298; (i) T. Hayashi, M. Konishi, M. Kumada, *Tetrahedron Lett.* **1979**, 1871.

[37] T.-Y. Luh, M. K. Leung, K.-T. Wong, *Chem. Rev.* **2000**, *100*, 3187.

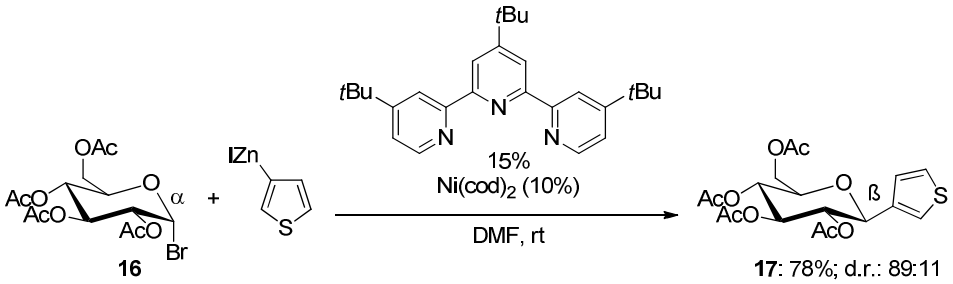
3.2 Stereoselective cross-couplings using secondary alkyl halides

Ni-catalyzed cross-couplings of various aryl/alkenyl organometallic reagents with secondary alkyl halides were shown to proceed with exceedingly high levels of enantioselectivity in the presence of chiral bi- and tridentate nitrogen ligands, such as **13** and **14** (Scheme 11).[13a, 38]



Scheme 11: Asymmetric Ni-catalyzed cross-coupling of racemic secondary alkyl halides.

Using Ni-catalysis and diamine **14** as chiral ligand even a highly enantioselective Csp^3-Csp^3 cross-coupling between primary organoboranes and secondary alkyl halides, such as the chlorohydrine derivative *rac*-**15** could be achieved.[38a] Diastereoselective Ni-catalyzed cross-couplings between aceto-α-D-bromoglucose (**16**) and various arylzinc reagents were reported by *M. R. Gagné*.[39] The arylated glucoses were obtained with d.r. up to 94:6 in favor of the β-anomer (**17**) (Scheme 12).

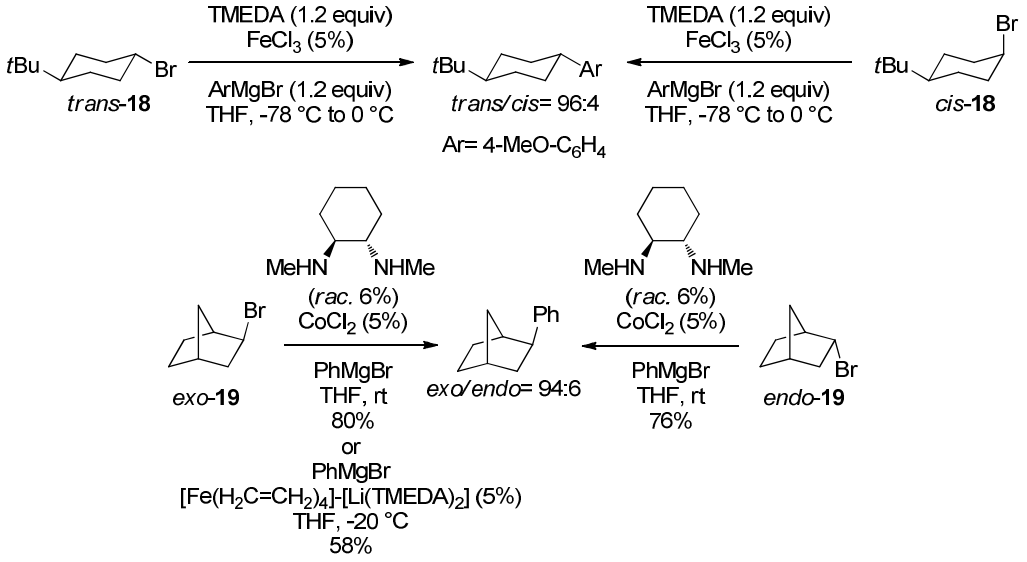


Scheme 12: Diastereoselective cross-coupling of aceto-α-D-bromoglucose (**16**).

[38] (a) N. A. Owston, G. C. Fu, *J. Am. Chem. Soc.* **2010**, *132*, 11908; (b) P. M. Lundin, G. C. Fu, *J. Am. Chem. Soc.* **2010**, *132*, 11027; (c) S. Lou, G. C. Gu, *J. Am. Chem. Soc.* **2010**, *132*, 1264; (d) P. M. Lundin, J. Esquivias, G. C. Fu, *Angew. Chem. Int. Ed.* **2009**, *48*, 154; (e) S. W. Smith, G. C. Fu, *J. Am. Chem. Soc.* **2008**, *130*, 12645; (f) B. Saito, G. C. Fu, *J. Am. Chem. Soc.* **2008**, *130*, 6694; (g) X. Dai, N. A. Strotman, G. C. Fu, *J. Am. Chem. Soc.* **2008**, *130*, 3302; (h) S. Son, G. C. Fu, *J. Am. Chem. Soc.* **2008**, *130*, 2756; (i) C. Fischer, G. C. Fu, *J. Am. Chem. Soc.* **2005**, *127*, 4594.

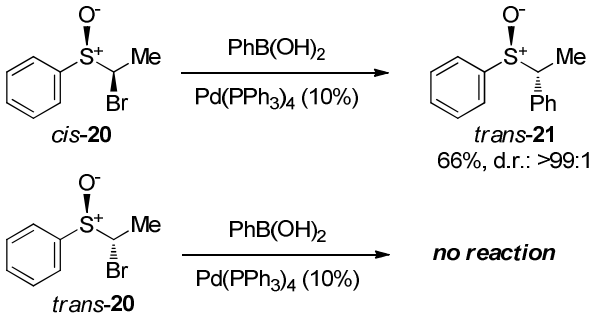
[39] H. Gong, M. R. Gagné, *J. Am. Chem. Soc.* **2008**, *130*, 12177.

Further diastereoselective cross-couplings with cyclic secondary alkyl halides (**18** and **19**) catalyzed either by Fe or Co were reported by *M. Nakamura*, *E. Nakamura*, *A. Fürstner* and *K. Oshima* (Scheme 13).[40, 41, 42]



Scheme 13: Rare examples of diastereoselective Fe- and Co-catalyzed cross-coupling of secondary alkyl halides.

Diastereoselective Pd-catalyzed cross-coupling of this type has so far only been achieved for secondary bromo sulfoxides (**20**) using organoboronic acids as nucleophiles (Scheme 14).[43]



Scheme 14: Diastereoselective Pd-catalyzed Suzuki-cross-coupling with secondary bromo sulfoxides.

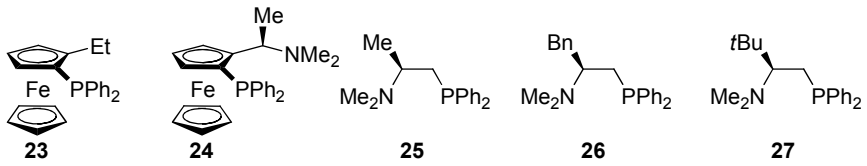
[40] (a) M. Nakamura, K. Matsuo, S. Ito, E. Nakamura, *J. Am. Chem. Soc.* **2004**, *126*, 3686; (b) M. Nakamura, S. Ito, K. Matsuo, E. Nakamura, *Synlett* **2005**, 1794;
[41] A. Fürstner, R. Martin, H. Krause, G. Seidel, R. Goddard, C. W. Lehmann, *J. Am. Chem. Soc.* **2008**, *130*, 8773.
[42] H. Ohmiya, H. Yorimitsu, K. Oshima, *J. Am. Chem. Soc.* **2006**, *128*, 1886.
[43] N. Rodríguez, C. Ramírez de Arellano, G. Asensio, M. Medio-Simon, *Chem. Eur. J.* **2007**, *13*, 4223.

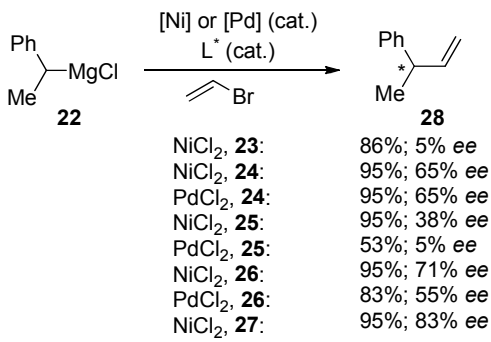
Interestingly, the reaction proceeds stereospecifically with inversion of configuration. When a mixture of the diastereomeric bromo-sulfoxides *cis*-**20** and *trans*-**20** was subjected to cross-coupling with phenylboronic acid, only the diastereomer *cis*-**20** was transformed in the cross-coupling reaction leading to *trans*-**21**. Diastereomer *trans*-**20** remained unaffected under these reaction conditions. Thus, this reaction is not stereoconvergent as the examples mentioned above and therefore requires diastereomerically pure substrates for complete conversion. The authors propose that the inversion occurs during the oxidative addition of the bromo sulfoxide to the Pd^0 center and that the reductive elimination step proceeds with retention of configuration.[44]

[44] C. Gourlaouen, G. Ujaque, A. Lledós, M. Medio-Simon, G. Asensio, F. Maseras, *J. Org. Chem.* **2009**, *74*, 4049.

3.3 Stereoselective cross-couplings using secondary alkylmagnesium and –zinc reagents

Enantioselective Ni- and Pd-catalyzed cross-coupling reactions of secondary alkylmagnesium reagents have already been known since the 1970s.[13b] In their groundbreaking studies, *M. Kumada* and *T. Hayashi* successfully subjected 1-phenylethylmagnesium chloride (**22**) to asymmetric cross-couplings with vinyl bromide using $NiCl_2$ and $PdCl_2$ in association with various optically active phosphine ligands (**23**-**27**; Scheme 15).[45]



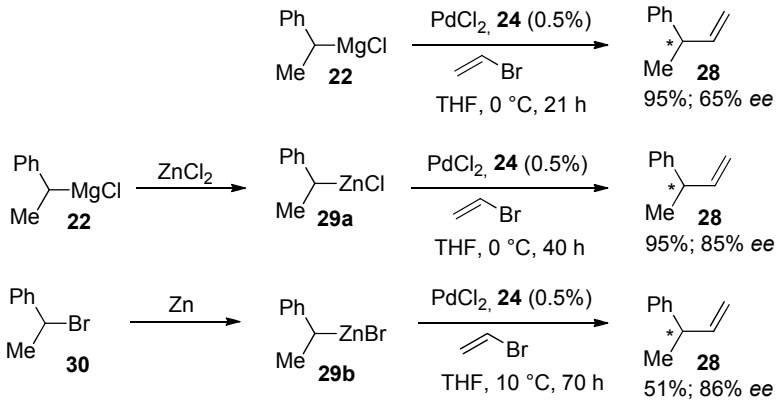


Scheme 15: Enantioselective cross-coupling of phenylethylmagnesium halides **22** with different chiral Ni- and Pd-catalysts.

Product **28** was obtained with varying degrees of enantiomeric excess. Thereby, it was found that bulky phosphine ligands with a (dialkylamino)alkyl group as second coordinating functionality (**24**, **26**-**27**) were most effective for both Ni- and Pd-catalyzed cross-couplings of **22** in terms of enantioselectivity. The use of 1-phenylethylzinc reagents (**29a-b**) in place of **22** was shown to increase the stereoselectivity (Scheme 16).[46]

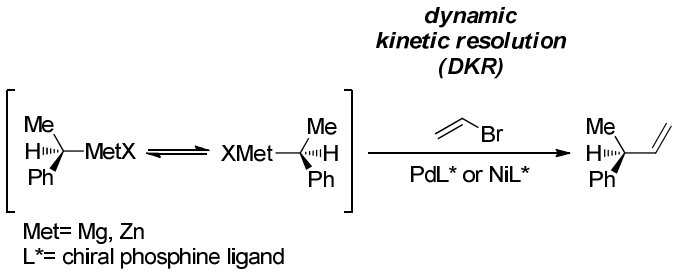
[45] (a) T. Hayashi, M. Tajika, K. Tamao, M. Kumada, *J. Am. Chem. Soc.* **1976**, *98*, 3718; (b) T. Hayashi, M. Konishi, M. Fukushima, T. Mise, M. Kagotani, M. Tajika, M. Kumada, *J. Am. Chem. Soc.* **1982**, *104*, 180; (c) T. Hayashi, M. Fukushima, M. Konishi, M. Kumada, *Tetrahedron Lett.* **1980**, *21*, 79; (d) T. Hayashi, M. Konishi, M. Fukushima, K. Kanehira, T. Hioki, M. Kuamada, *J. Org. Chem.* **1983**, *48*, 2195.

[46] (a) T. Hayashi, T. Hagihara, Y. Katsuro, M. Kumada, *Bull. Chem. Soc. Jpn.* **1983**, *56*, 363; (b) T. Hayashi, A. Yamamoto, M. Hojo, Y. Ito, *J. Chem. Soc. Chem. Commun.* **1989**, 495; (c) T. Hayashi, A. Yamamoto, M. Hojo, K. Kishi, Y. Ito, E. Nishioka, H. Miura, K. Yanagi, *J. Organomet. Chem.* **1989**, *370*, 129.



Scheme 16: Enantioselective cross-coupling of phenylethylmagnesium and –zinc halides **22** and **29a-b**.

Thus, asymmetric cross-coupling of **29a** prepared from **22** via transmetalation with $ZnCl_2$ provided the olefin **28** in >70% yield with 85-86% *ee*. Reagent **29b** obtained via the insertion of zinc metal to 1-phenylethylbromide **30** gave **28** with equal enantioselectivity, though the reaction was considerably slower (70 h vs. 40 h). Enantiocontrol in these cross-coupling reactions is exerted by a dynamic kinetic resolution (DKR) of the racemic alkylmagnesium and –zinc compounds during the transmetalation to the chiral Pd- or Ni-catalyst (Scheme 17).[47]

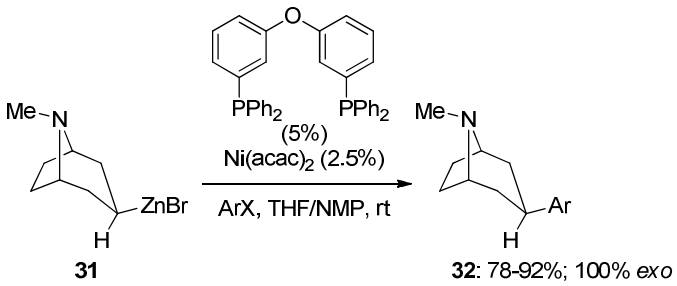


Scheme 17: Dynamic kinetic resolution of the secondary alkyl organometallics in the enantioselective cross-coupling.

Due to the relatively labile carbon-metal bond, the enantiomeric organometallic species are in a constant equilibrium. The enantiomer which is compatible with the chiral catalyst reacts preferentially and is withdrawn from the equilibrium enabling a full conversion of the racemic reagent. Thus, the higher configurational stability of C-Zn towards C-Mg bonds explains the longer reaction times for the enantioselective cross-coupling of **29a-b**. This enantioselective

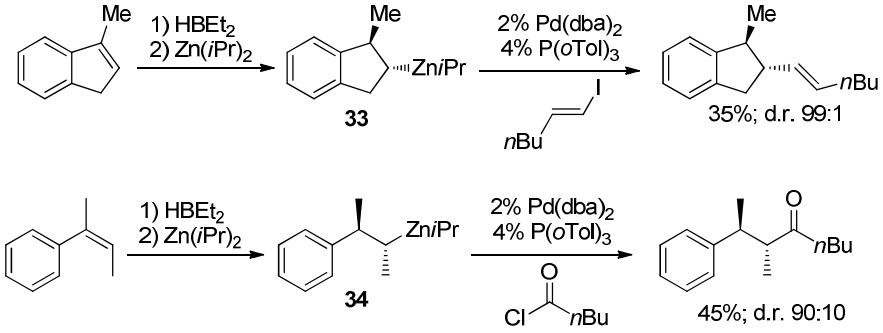
[47] T. Hayashi in *Asymmetric Synthesis – The Essentials* (Eds.: M. Christmann, S. Bräse), Wiley-VCH, **2007**, 90.

cross-coupling could also be applied to 1-(trialkylsilyl)benzyl- and –ethylmagnesium chlorides.[48] Stereoconvergent diastereoselective cross-coupling reactions are scarcely reported in the literature. A rare example is the Ni-catalyzed stereoconvergent coupling between tropan-3-ylzinc bromide (**31**) and aryl halides that resulted in an exclusive formation of the *exo*-diastereomers (**32**) (Scheme 18).[49]



Scheme 18: Ni-catalyzed stereoconvergent coupling of **31** with aryl halides.

A further report on diastereoselective cross-coupling reactions using organozinc reagents is based on hydroboration and subsequent B-Zn exchange.[50] Here, the authors suggested that the stereoselectivity is introduced by the stereodefined hydroboration, i.e. via *syn*-addition of $HBEt_2$ to the C=C bond. B-Zn exchange using Zn*i*Pr_2 was assumed to proceed with retention of configuration and to furnish configurationally stable carbon-zinc compounds (**33**-**34**).



Scheme 19: Diastereoselective hydroboration/B-Zn exchange/cross-coupling sequence.

[48] (a) T. Hayashi, M. Konishi, H. Ito, M. Kumada, *J. Am. Chem. Soc.* **1982**, *104*, 4962; (b) T. Hayashi, M. Konishi, Y. Okamoto, K. Kabeta, M. Kumada, *J. Org. Chem.* **1986**, *51*, 3772; (c) T. Hayashi, Y. Okamoto, M. Kumada, *Tetrahedron Lett.* **1983**, *24*, 807.
[49] L. Melzig, A. Gavryushin, P. Knochel, *Org. Lett.* **2007**, *9*, 5529.
[50] A. Boudier, P. Knochel, *Tetrahedron Lett.* **1999**, *40*, 687.

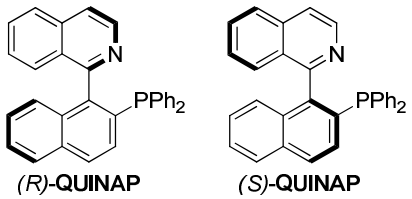
Subsequent Pd-catalyzed cross-coupling and acylation occurred with no alteration of the stereoconfiguration leading to the expected *trans*-products (Scheme 19). Stereoselective product formation was observed for both cyclic and open-chain secondary organozinc compounds.

4. Objectives

This work is divided into two main parts:

1. Enantiocontrol with chiral sulfoxides
2. Diastereocontrol in the cross-couplings of substituted cycloalkyl and piperidinyl derivatives

In the first part, the unique properties of the chiral sulfinyl group, i.e. strong polarity, central chirality, simple integration and removal, should be used to achieve a new, more straightforward synthesis and resolution of chiral QUINAP, one of the most successful *P,N*-ligands in asymmetric catalysis (Scheme 20).[51]



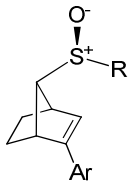
Scheme 20: Chiral QUINAP – one of the most successful *P,N*-ligands in asymmetric catalysis.

QUINAP has an atropisomeric backbone and its chirality originates from the hindered rotation between the two naphthyl-type moieties. The carbon-carbon linkage between these moieties represents a relatively flexible chiral axis which allows optimal adjustment in the formation of a complex with the respective metal and thus makes it a valuable ligand to a broad range of transition-metals.[51] Up to now, the synthesis of chiral QUINAP is difficult and costly as it is

[51] (a) J. M. Brown, D. I. Hulmes, T. P. Layzell, *J. Chem. Soc., Chem. Commun.* **1993**, 1673; (b) E. Fernandez, K. Maeda, M. W. Hooper, J. M. Brown, *Chem. Eur. J.* **2000**, *6*, 1840; (c) S. Trudeau, J. B. Morgan, M. Shrestha, J. P. Morken, *J. Org. Chem.* **2005**, *70*, 9538; (d) J. M. Brown, D. I. Hulmes, P. J. Guiry, *Tetrahedron* **1994**, *50*, 4493; (e) J. W. Faller, B. J. Grimmond, *Organometallics* **2001**, *20*, 2454; (f) C. Chen, X. Li, S. L. Schreiber, *J. Am. Chem. Soc.* **2003**, *125*, 10174; (g) X. Li, L. Kong, Y. Gao, X. Wang, *Tetrahedron Lett.* **2007**, *48*, 3915; (h) C. Koradin, K. Polborn, P. Knochel, *Angew. Chem.. Int. Ed.* **2002**, *41*, 2535; (i) C. Koradin, N. Gommermann, K. Polborn, P. Knochel, *Chem. Eur. J.* **2003**, *9*, 2797; (j) N. Gommermann, P. Knochel, *Tetrahedron* **2005**, *61*, 11418; (k) A. M. Taylor, S. L. Schreiber, *Org. Lett.* **2006**, *8*, 143; (l) T. Miura, M. Yamauchi, A. Kosaka, M. Murakami, *Angew. Chem. Int. Ed.* **2010**, *49*, 4955.

based on the use of stoichiometric amounts of $PdCl_2$.[52] A cheaper method for its resolution is therefore highly desirable.

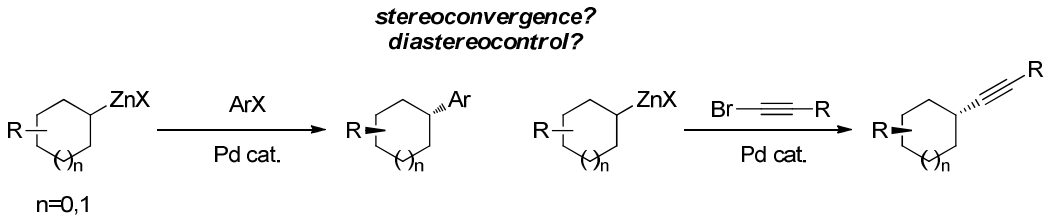
Chiral bissulfoxides have proved as efficient ligands in the Rh-catalyzed asymmetric *Hayashi-Miyaura* reaction.[30, 31] We envisioned the design of a new ligand class, chiral sulfoxide-alkene hybrids of type **35**, for this type of reaction (Scheme 21). These ligands are assumed to combine the advantages of both sulfoxide (easy preparation and resolution, strong coordination to Rh) and olefin ligands (strong influence of the chiral environment around the C=C bond on enantioselectivity). A concise synthesis of these ligands was to be designed and the ligands should be tested on their efficiency in the asymmetric Rh-catalyzed 1,4-addition to (hetero)cyclic enones.



35

Scheme 21: Sulfoxide-alkene hybrids – a new class of chiral ligands for the *Hayashi-Miyaura* reaction?

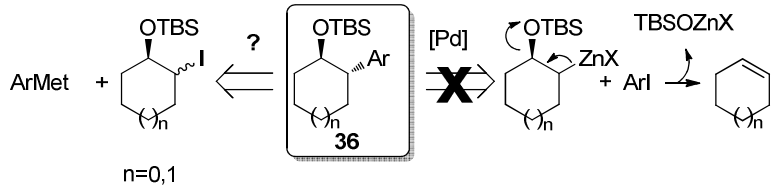
The second part of this thesis deals with diastereocontrol in the cross-coupling reactions of substituted cycloalkyl and piperidinyl derivatives. The Pd-catalyzed cross-couplings of various substituted cycloalkylzinc reagents with aryl halides and bromoalkynes were tested on diastereocontrol and stereoconvergence (Scheme 22).



Scheme 22: Diastereocontrol and stereoconvergence in the Pd-catalyzed cross-couplings of substituted cycloalkylzinc reagents?

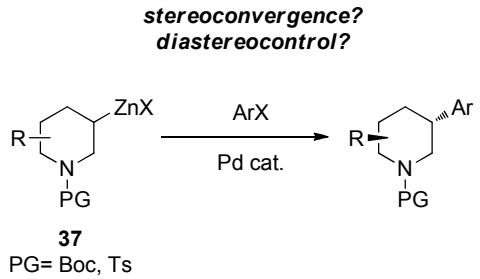
[52] C. W. Lim, O. Tissot, A. Mattison, M. W. Hooper, J. M. Brown, A. R. Cowley, D. I. Hulmes, A. J. Blacker, *Org. Proc. Res. & Dev.* **2003**, *7*, 379.

Mechanistic aspects, limits and scope of these cross-coupling reactions were to be examined. Thereby, the Pd-catalyzed Csp^3-Csp^2/Csp-coupling approach using substituted cycloalkylzinc reagents should be complemented with a diastereoselective Csp^2-Csp^3 cross-coupling of cyclic iodohydrine derivatives enabling the synthesis of molecules of type **36** which are not accessible by the former method (Scheme 23).



Scheme 23: Designing a synthesis for 2-arylated cycloalcohol derivatives of type **36**.

Finally the diastereoselective Pd-catalyzed cross-coupling was to be extended to various piperidinylzinc compounds (**37**; Scheme 24).



Scheme 24: Diastereocontrol and stereoconvergence in the Pd-catalyzed cross-couplings of substituted cycloalkylzinc reagents?

Piperidines constitute a pharmaceutically highly significant substance class.[53] Broadening the scope of their stereoselective preparation is therefore a highly important synthetic task.

[53] (a) C. de Risi, G. Fanton, G. P. Pollini, C. Trapella, F. Valente, V. Zanirato, *Tetrahedron: Asymmetry* **2008**, *19*, 131; (b) C. Escolano, M. Amat, J. Bosch, *Chem. Eur. J.* **2006**, *12*, 8198; (c) M. G. P. Buffat, *Tetrahedron* **2004**, *60*, 1701; (d) F.-X. Felpin, J. Lebreton, *Eur. J. Org. Chem.* **2003**, 3693; (e) S. Laschat, T. Dickner, *Synthesis* **2000**, 1781; (f) P. D. Bailey, P. A. Millwood, P. D. Smith, *Chem. Commun.* **1998**, 633.

B. Results and Discussion

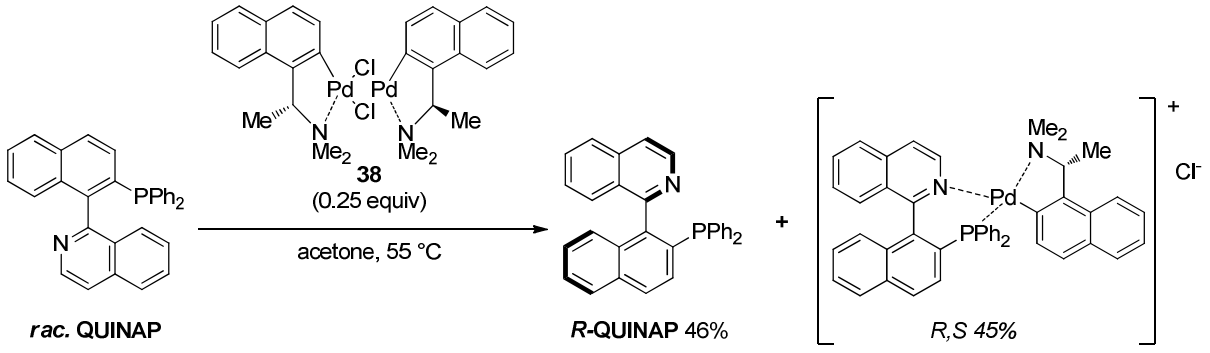
1. Enantiocontrol with Chiral Sulfoxides

1.1 A Novel Synthetic Approach towards Chiral QUINAP via Diastereomeric Sulfoxide Intermediates

1.1.1 Introduction

Since its discovery by *J. M. Brown et al.*[54] QUINAP has become one of the most outstanding chiral P,N-ligands. Its flexible chiral axis allows optimal adjustment in the formation of complexes with various metal salts. Thus, QUINAP has proved to be an excellent ligand for Pd, Ag, Cu, Ni, Ru, Rh and Ir permitting its use in a large number of asymmetric reactions, including hydro-[51a-b] and diboration,[51c] allylic alkylation,[51d] Diels-Alder reactions,[51e] [3+2]-cycloadditions,[51f] hydrogenation of olefins[51g] and Cu(I)-catalyzed synthesis of propargylamines[51h-k]. Analogues of QUINAP based on pyridine[55] and quinazoline[56] could also be successfully used as chiral ligands in many asymmetric reactions.

However, the preparation of chiral QUINAP and its derivatives, with the exception of *E. M. Carreira's* PINAP,[57] remains costly and difficult, as it is based on chiral resolution via diastereomeric cyclopalladated complexes formed with stoichiometric amounts of a complex of $PdCl_2$ and *(R)*-(+)-dimethyl[1-(1-naphthyl)ethyl]amine (**38**; Scheme **25**).[52]



Scheme 25: Costly chiral resolution of QUINAP with stoichiometric amounts of $PdCl_2$.

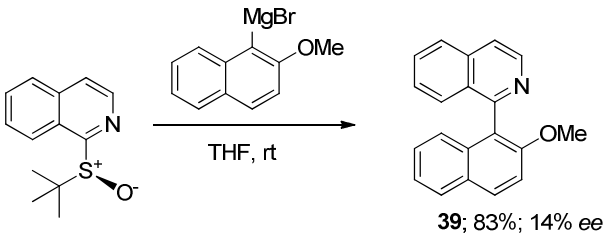
[54] (a) N. W. Alcock, , J. M. Brown, D. I. Hulmes, *Tetrahedron: Asymmetry* **1993**, *4*, 743; for QUINAP derivatives see: (b) J. M. Valk, T. D. W. Claridge, J. M. Brown, *Tetrahedron: Asymmetry* **1995**, *6*, 2597; (c) H. Doucet, J. M. Brown, *Tetrahedron: Asymmetry* **1997**, *8*, 3775.

[55] F. Y. Kwong, Q. Yang, T. C. W. Mak, A. S. C. Chan, K. S. Chan, *J. Org. Chem.* **2002**, *67*, 2769.

[56] (a) D. J. Connolly, P. M. Lacey, M. McCarthy, C. P. Saunders, A.-M. Carroll, R. Goddard, P. J. Guiry, *J. Org. Chem.* **2004**, *69*, 6572; (b) M. McCarthy, P. J. Guiry, *Tetrahedron* **1999**, *55*, 3061; (c) P. M. Lacey, C. M. McDonnell, P. J. Guiry, *Tetrahedron Lett.* **2000**, *41*, 2475.

[57] T. F. Knöpfel, P. Aschwanden, T. Ichikawa, T. Watanabe, E. M. Carreira, *Angew. Chem. Int. Ed.* **2004**, *43*, 5971.

An attempt to obtain chiral 1-(2-methoxy-1-naphthyl)isoquinoline (**39**), a key intermediate in the QUINAP synthesis, via a sulfoxide ligand coupling reaction resulted in only low enantiomeric purity (14% *ee*; Scheme 26).[58]



Scheme 26: Synthesis of **39,** a key intermediate in the present QUINAP synthesis with insufficient enantiomeric excess.

A more practical and efficient stereoselective synthesis of this important ligand is therefore highly desirable.

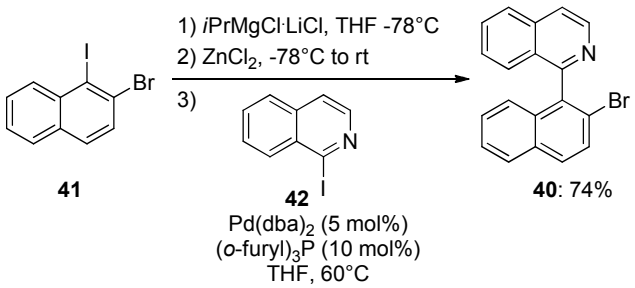
1.1.2 Novel synthesis and chiral resolution of QUINAP via chiral diastereomeric sulfoxide intermediates

We conceived a novel more expedient approach towards the synthesis of chiral QUINAP by resolution via simple chromatographic separation of diastereomeric sulfoxide intermediates: *J. Clayden et al.* have demonstrated that enantiopure sulfoxides are suited as useful intermediates for the chiral resolution of atropisomers.[21b-d] The diastereomeric character of the resulting molecule permits separation and the sulfoxide group can be easily exchanged with organolithium reagents.[21b] Therefore, we wondered, whether this method could also be applied to the resolution of QUINAP in a new synthetic approach.

First, the preparation of key intermediate **40** was envisaged (Scheme 27). The bromo-substituent in **40** allows a convenient access to the 2'-position, as it can be easily subjected to halogen-metal exchange reactions. 2-Bromo-1-iodonaphthalene (**41**), which was prepared in two steps from 1-naphthylamine via Zr(IV)-catalyzed bromination with NBS[59] and a subsequent diazotation reaction[60], was chosen as synthon for the naphthyl moiety. It was found to selectively undergo iodine-magnesium exchange with *i*PrMgCl·LiCl at -78 °C without elimination of the adjacent

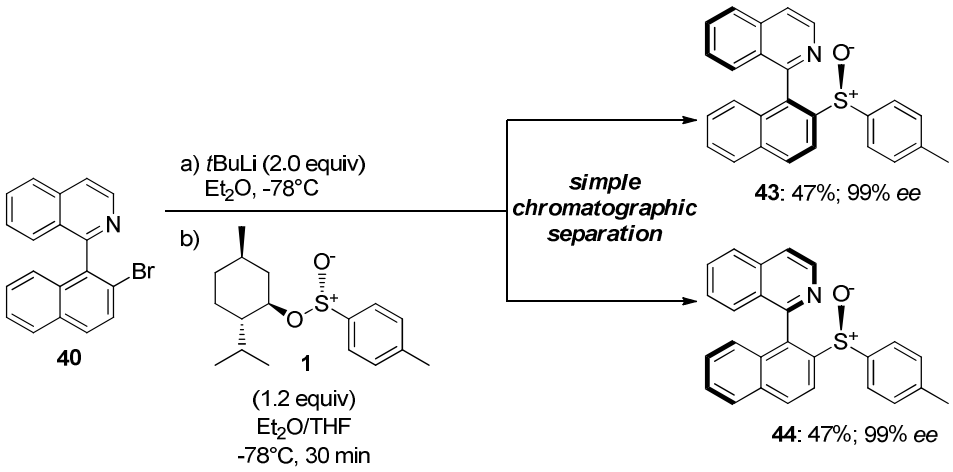
[58] R. W. Baker, S. O. Rea, M. V. Sargent, E. M. C. Schenkelaars, T. S. Tjahjandarie, A. Totaro, *Tetrahedron* **2005**, *61*, 3733.
[59] Y. Zhang, K. Shibatomi, H. Yamamoto, *Synlett* **2005**, 2837.
[60] H. H. Hodgson, D. E. Hathway, *J. Chem. Soc.* **1944**, 538.

bromide. After transmetalation with $ZnCl_2$ it was used as nucleophile in a *Negishi*-type cross-coupling reaction[33b] with 1-iodoisoquinoline **42** which was obtained via simple deprotonation of isoquinoline and subsequent trapping with iodine.[61]



Scheme 27: Preparation of 1-(2-bromo-1-naphthyl)isoquinoline (**40**).

Compound **40** was obtained with 74% yield and subjected to a bromine-lithium exchange with *t*BuLi (2.0 equiv, Et_2O, –78°C, 30 min). The resulting organolithium species was carefully reacted with (–)-menthyl (*S*)-*p*-toluenesulfinate **1** (*Andersen*-sulfinate)[18] at -78 °C. In order to preserve the configurational stability of the sulfoxide group, maintenance of this low temperature was crucial. To our delight, the resulting QUIN-sulfoxide intermediates **43** and **44** were obtained in excellent yields and could be easily separated via column chromatography (Scheme 28).[62]

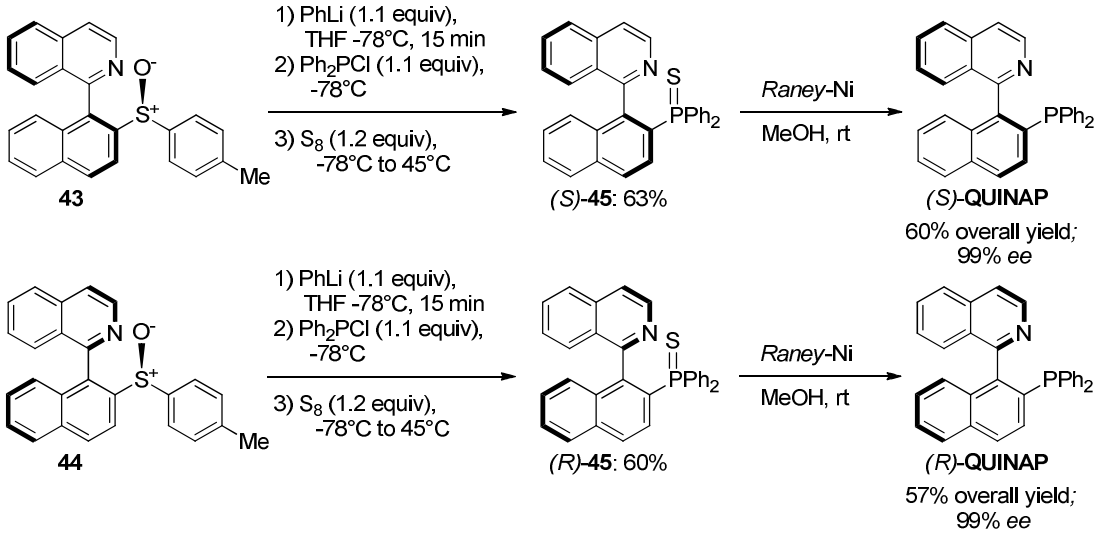


Scheme 28: Novel resolution via the chiral sulfoxide intermediates **43** and **44**.

[61] A. Krasovskiy, V. Krasovskaya, P. Knochel, *Angew.Chem. Int. Ed.* **2006**, *45*, 2958.

[62] For purification and separation of the two sulfoxide diastereomers the crude product was subjected to column chromatography with Florisil® (60-100 mesh). **44** was eluated with Et_2O/*n*-pentane 4:1. **43** was eluated with Et_2O/acetone 2:1.

Alternatively, transmetalation to $MgCl_2$ prior to the reaction with sulfinate **1** allowed the preparation of **43** and **44** with no loss of enantioselectivity (99% *ee*). Synthetic intermediates **43** and **44** were then subjected to a sulfoxide-lithium exchange reaction. Phenyllithium was chosen as exchange reagent, since it is known to minimize unwanted deprotonation of the diphenyl sulfoxide byproduct.[63] The reaction was carried out at –78°C (15 min) to ensure the atropisomeric stability of the intermediate chiral organolithium species. Quenching with Ph_2PCl and subsequent protection with sulfur afforded (*S*)-**45** and (*R*)-**45** with 60% and 63% yield (Scheme 29). Although QUINAP proved stable towards air and moisture during work-up, sulfur-protection was chosen to simplify purification by column chromatography. Subsequent desulfurisation with *Raney*-Ni gave (*S*)- and (*R*)-QUINAP in 95% yield respectively.[64]



Scheme 29: Sulfoxide-lithium exchange and QUINAP synthesis.

[63] R. J. Kloetzing, P. Knochel, *Tetrahedron: Asymmetry* **2006**, *17*, 116.
[64] D. Liu, Q. Dai, X. Zhang, *Tetrahedron* **2005**, *61*, 6460.

1.2 Sulfoxide-alkene hybrids: A new class of chiral ligands for the *Hayashi-Miyaura* reaction

1.2.1 Introduction

The Rh-catalyzed 1,4-addition of organoboronic acids to enones, also known as the *Hayashi-Miyaura* reaction,[29] has been well established as an important and versatile tool for the enantioselective formation of C-C bonds in modern asymmetric synthesis.[65] Chiral dienes[66] and most recently chiral bissulfoxides[30, 31] have proved very effective for the induction of high levels of enantioselectivity in this type of reaction. The outstanding successes of these novel ligand classes and the easy preparation[17] and resolution of chiral diastereomeric sulfoxides, which can be achieved via simple column chromatographic separation,[21, 67] led us to envision novel modular hybrid ligands of type **35** that combine both alkenes and sulfoxides as coordinative elements (Scheme 30). So far, *tert*-butylsulfinylphosphines of type **12** (Scheme 10)[32] represent the only class of chiral sulfoxide-based hybrid ligands employed in the *Hayashi-Miyaura* reaction. Alkene hybrid ligands for this reaction are restricted to either phosphorus[68] or nitrogen[69] as second coordinating moiety.

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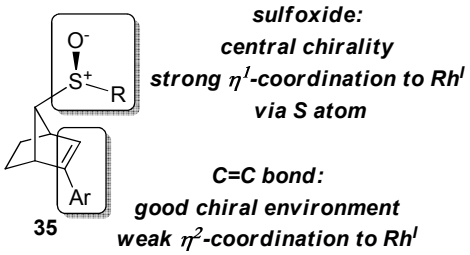
[65] For selected reviews see: (a) N. Miyaura, *Bull. Chem. Soc. Jpn.* **2008**, *81*, 1535; (b) T. Hayashi, *Russ. Chem. Bull.* **2003**, *52*, 2595; (c) T. Hayashi, *Synlett* **2001**, 879.

[66] Reviews: (a) R. Shintani, T. Hayashi, *Aldrichim. Acta* **2009**, *42*, 31; (b) C. Defieber, H. Grützmacher, E. M. Carreira, *Angew. Chem. Int. Ed.* **2008**, *47*, 4482; (c) F. Glorius, *Angew. Chem. Int. Ed.* **2004**, *6*, 3873; articles: (d) Y. Luo, A. J. Carnell, *Angew. Chem. Int. Ed.* **2010**, *49*, 2750; (e) X. Hu, Z. Cao, Z. Liu, Y. Wang, H. Du, *Adv. Synth. Catal.* **2010**, *352*, 651; ((f) Y. Wang, X. Hu, H. Du, *Org. Lett.* **2010**, *12*, 5482; (g) Z.-Q. Wang, C.-G. Feng, S.-S. Zhang, M.-H. Xu, G.-Q. Lin, *Angew. Chem. Int. Ed.* **2010**, *49*, 5780; (h) T. Gendrineau, J.-P. Genet, S. Darses, *Org. Lett.* **2009**, *11*, 3486; (i) R. Shintani, Y. Ichikawa, K. Takatsu, F.-X. Chen, T. Hayashi, *J. Org. Chem.* **2009**, *74*, 869; (j) R. Shintani, Y. Tsutsumi, M. Nagaosa, T. Nishimura, T. Hayashi, *J. Am. Chem. Soc.* **2009**, *131*, 13588; (k) X. Hu, M. Zhuang, Z. Cao, H. Du, *Org. Lett.* **2009**, *11*, 4744; (l) T. Gendrineau, O. Chuzel, H. Eijsberg, J.-P. Genet, S. Darses, *Angew. Chem. Int. Ed.* **2008**, *47*, 7669; (m) K. Okamoto, T. Hayashi, V. H. Rawal, *Org. Lett.* **2008**, *10*, 4387; (n) S. Sörgel, N. Tokunaga, K. Sasaki, K. Okamoto, T. Hayashi, *Org. Lett.* **2008**, *10*, 589; (o) C.-G. Feng, Z.-Q. Wang, C. Shao, M.-H. Xu, G.-Q. Lin, *Org. Lett.* **2008**, *10*, 4101; (p) C.-G. Feng, Z.-Q. Wang, P. Tian, M.-H. Xu, G.-Q. Lin, *Chem. Asian J.* **2008**, *3*, 1511; (q) S. Helbig, S. Sauer, N. Cramer, S. Laschat, A. Baro, W. Frey, *Adv. Synth. Catal.* **2007**, *349*, 2331; (r) G. Berthon-Gelloz, T. Hayashi, *J. Org. Chem.* **2006**, *71*, 8957; (s) Y. Otomaru, A. Kina, R. Shintani, T. Hayashi, *Tetrahedron: Asymmetry* **2005**, *16*, 1673; (t) Y. Otomaru, K. Okamoto, R. Shintani, T. Hayashi, *J. Org. Chem.* **2005**, *70*, 2503; (u) C. Defieber, J.-F. Paquin, S. Serna, E. M. Carreira, *Org. Lett.* **2004**, *6*, 3873; (v) T. Hayashi, K. Ueyama, N. Tokunaga, K. Yoshida, *J. Am. Chem. Soc.* **2003**, *125*, 11508.

[67] T. Thaler, F. Geittner, P. Knochel, *Synlett* **2007**, 2655.

[68] (a) E. Drinkel, A. Briceño, R. Dorta, R. Dorta, *Organometallics* **2010**, *29*, 2503; (b) H. Grugel, T. Minuth, M. M. K. Boysen, *Synthesis* **2010**, 3248; (c) T. Minuth, M. M. K. Boysen, *Org. Lett.* **2009**, *11*, 4212; (d) R. Mariz, A. Briceño, R. Dorta, R. Dorta, *Organometallics* **2008**, *27*, 6605; (e) W.-L. Duan, H. Iwamura, R. Shintani, T. Hayashi, *J. Am. Chem. Soc.* **2007**, *129*, 2130; (f) R. T. Stemmler, C. Bolm, *Synlett* **2007**, 1365; (g) P. Kasák, V. B. Arion, M. Widhalm, *Tetrahedron: Asymmetry* **2006**, *17*, 3084; (h) E. Piras, F. Läng, H. Rüegger, D. Stein, M. Wörle, H. Grützmacher, *Chem. Eur. J.* **2006**, *12*, 5849; (i) R. Shintani, W.-L. Duan, T. Nagano, A. Okada, T. Hayashi, *Angew. Chem. Int. Ed.* **2005**, *44*, 4611.

[69] B. T. Hahn, F. Tewes, R. Fröhlich, F. Glorius, *Angew. Chem. Int. Ed.* **2010**, *49*, 1143.

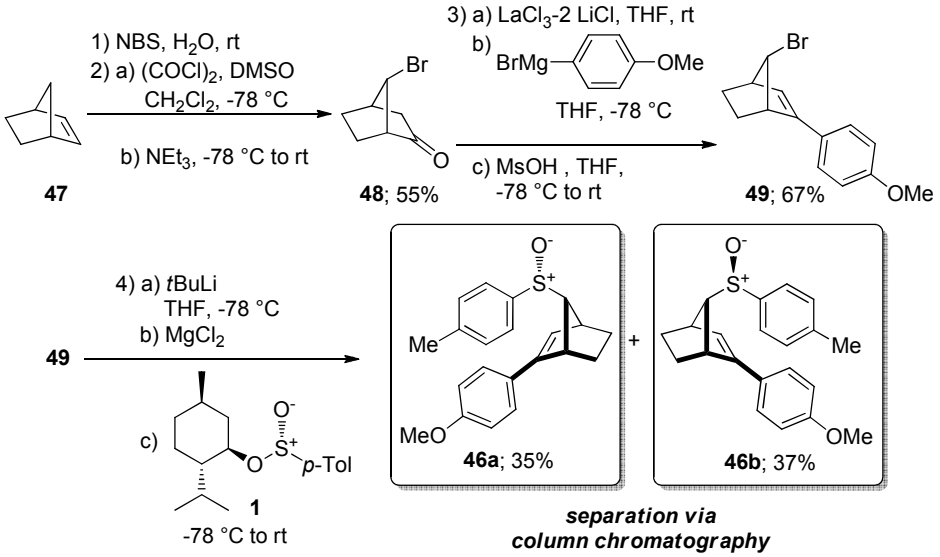


Scheme 30: Chiral heterodentate ligands comprising the unique properties of sulfoxides and C=C bonds.

Thus, this is the first synthesis of chiral sulfoxide-alkene hybrid ligands for the *Hayashi-Miyaura* reaction allowing a direct comparative study on the relative influences of the alkenyl and sulfinyl group on the reactivity and enantioselectivity of the Rh-catalyst.

1.2.2 Synthesis and resolution of the new sulfoxide-alkene hybrids

Inspired by *Hayashi's* well-studied phosphorus-olefin hybrid ligand,[68e,i] we designed the straightforward, protective-group free synthesis of **46a** and **46b** from norbornene (**47**) within only four steps (Scheme 31).



Scheme 31: Protective-group free synthesis and simple chiral resolution of the sulfoxide-alkene hybrid ligands **46a** and **46b**.

Reaction of **47** with NBS in H_2O and subsequent *Swern*-oxidation[68e,i] furnished bromoketone **48** in 55% yield. $LaCl_3 \cdot 2$ LiCl-mediated addition[70] of 4-anisylmagnesium bromide to **48** followed by acidic elimination of H_2O using MsOH (methanesulfonic acid) directly gave the racemic alkene **49** with 67% overall yield without unnecessary protection-deprotection sequences. Br/Li-exchange on **49** using *t*BuLi, subsequent transmetalation with $MgCl_2$ and quenching with the easily available (–)-menthyl (*S*)-*p*-toluene sulfinate (**1**; *Andersen*-sulfinate)[18] furnished the two diastereomeric ligands **46a** and **46b** with 72% yield and 99% *ee*[71] which could be easily separated via column chromatographic purification.[72] This feature represents a preparative advantage towards the related phosphine-olefin hybrid ligands reported by *Hayashi et al.* which have to be resolved via preparative chiral HPLC.[68e,i] ^1H and ^{13}C NMR experiments on the Rh complex of **46b** obtained by reacting it with 0.5 equivalents of $[(ethylene)_2RhCl]_2$ in d^8-1,4-dioxane clearly proved coordination of both the alkene and the sulfoxide moiety to the Rh atom with the signals for the respective C-atoms shifted upfield and split into doublets.[73]

1.2.3 Use as chiral ligands in the *Hayashi-Miyaura* reaction

In order to test the efficacy and scope of **46a** as chiral ligand in the *Hayashi-Miyaura* reaction, we prepared the Rh-complex **50a** by treating **46a** with 0.5 equivalents of $[(coe)_2RhCl]_2$ (**51**)[74] and a stoichiometric amount of $CsOH \cdot H_2O$ in 1,4-dioxane and water. The resulting *in situ* formed catalyst **50a** (2.5 mol%) was then directly used without isolation in the 1,4-addition reactions of various aryl- and alkenylboronic acids to cyclic α,β-unsaturated carbonyl compounds (Table 1). The expected chiral addition products **52-54** were obtained in 61-99% yield and with high enantioselectivities (82-97% *ee*) using only a slight excess of the respective organoboronic acid (1.2 equiv). The addition of arylboronic acids to cyclohex-2-enone typically proceeded with enantioselectivities between 90-93% *ee*. The (*S*)-configured products were obtained preferentially.[75] Lower stereoselectivities were observed with sterically more demanding (**52c;** 89% *ee*; entry 3 of Table 1) or electron-rich arylboronic acids (**52f**; 88% *ee* and **52i**; 82% *ee*; entries 6 and 9).

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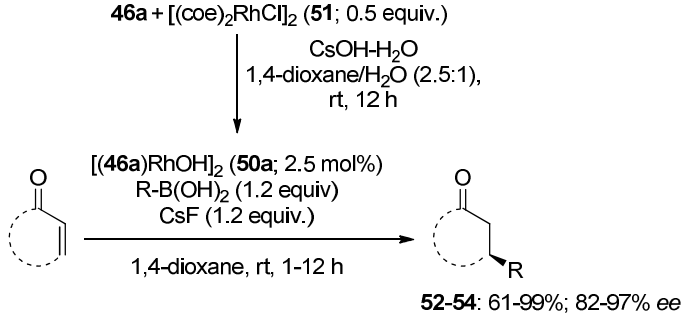
[70] A. Krasovskiy, F. Kopp, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 497.
[71] Transmetalation with $MgCl_2$ prior to reaction with the sulfinate was necessary to prevent epimerization at the chiral sulfur center.
[72] Flash column chromatography: SiO_2, CH_2Cl_2/EtOAc 2:1.
[73] See experimental section for details.
[74] A. van der Ent, A. L. Onderdelinden, *Inorg. Synth.* **1990**, *28*, 90.

Table 1: Enantioselective 1,4-addition of organoboronic acids to various electron-deficient alkenes using **46a** as chiral ligand.



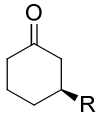
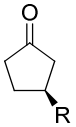
Entry		Product	Yield [%][a]	*ee* [%][b] (conf.)[c]
1		**52a**: R=Ph	98	92
2		**52b**: R=2-Et-C_6H_4	99	92
3		**52c**: R=1-naphthyl	96	89 (*S*)
4		**52d**: R=2-MeO-C_6H_4	90	90
5		**52e**: R=2-F-C_6H_4	88	90
6		**52f**: R=2,3-CH_2O_2-C_6H_3	86	88
7		**52g**: R=3-MeO-C_6H_4	93	90
8		**52h**: R=3-Cl-C_6H_4	90	90
9		**52i**: R=4-MeO-C_6H_4	85	82 (*S*)
10		**52j**: R=4-PhO-C_6H_4	90	93
11		**52k**: R=4-Cl-C_6H_4	84	93
12		**52l**: R=4-F-C_6H_4	89	92
13		**52m**: R=4-F_3C-C_6H_4	80	93
14		**52n**: R=(*E*)-PhCH=CH	66	95
15		**52o**: R=(*E*)-4-MeC_6H_4CH=CH	61	92
16		**53a**: R=Ph	85	97 (*S*)
17		**53b**: R=1-naphthyl	99	94
18		**53c**: R=2-MeO-C_6H_4	96	96
19		**53d**: R=3-Cl-C_6H_4	99	96
20		**53e**: R=4-MeO-C_6H_4	88	94
21		**53f**: R=4-Me-C_6H_4	92	96
22		**53g**: R=4-Cl-C_6H_4	99	96
23		**53h**: R=4-F_3C-C_6H_4	93	97
24		**53i**: R=(*E*)-PhCH=CH	94	95

Table 1 continued

25		**54a**: R=Ph	84	88[d] (*S*)
26		**54b**: R=4-MeO-C_6H_4	88	92[d] (*S*)
27		**54c**: R=3,5-Me_2-C_6H_3	85	97[d] (*S*)

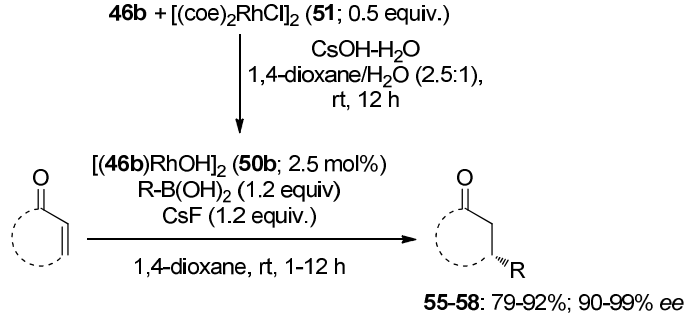
[a] Isolated yield of analytically pure product. [b] Determined via chiral HPLC analysis. See appendix for details. [c] Absolute configurations determined by comparison to chiral HPLC data reported in the literature.[75] [d] Reaction time: 12 h. Compound racemizes upon storage at room temperature.

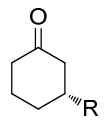
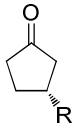
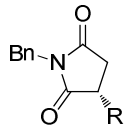
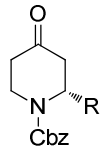
The reactions of (*E*)-styryl- and (*E*)-4-methylstyrylboronic acid with cyclohex-2-enone gave the chiral products **52n-o** with decreased yields of 61-66% and high enantiomeric excesses (92-95% *ee*; entries 14-15). With cyclopent-2-enone as substrate, excellent yields and even higher enantioselectivities were achieved (**53a-i**; 94-97% *ee*; entries 16-24). In this case, switching from aryl- to alkenylboronic acids did not result in a deterioration of the yield (**53i**; entry 24). The use of *N*-benzyl maleimide as substrate led to the chiral (*S*)-configured addition products **54a-c** with good yields (84-88%) and high enantioselectivities (88-97% *ee*; entries 25-27).

Next, we examined diastereomeric **46b** on its performance as chiral ligand in the Rh-catalyzed *Hayashi-Miyaura* reaction (Table 2). To our delight, we found that the corresponding 1,4-adducts were produced with equally high enantioselectivities and yields (79-92%; 90-99% *ee*), when **50b** was used as chiral catalyst. Remarkably, the absolute configurations of the products were opposite to those obtained with **46a** clearly hinting at a predominant stereocontrol through the chiral environment around the alkenyl moiety. Moreover, the addition of phenylboronic acid to heterocyclic Cbz-protected 2,3-dihydropyridin-4(1*H*)-one furnished **58** with 92% yield and an outstanding enantioselectivity of 99% *ee* (entry 9).

[75] Comparison with HPLC data from 66d, 66o, 30b and 68i.

Table 2: Enantioselective 1,4-addition of organoboronic acids to various electron-deficient alkenes using **46b** as chiral ligand.

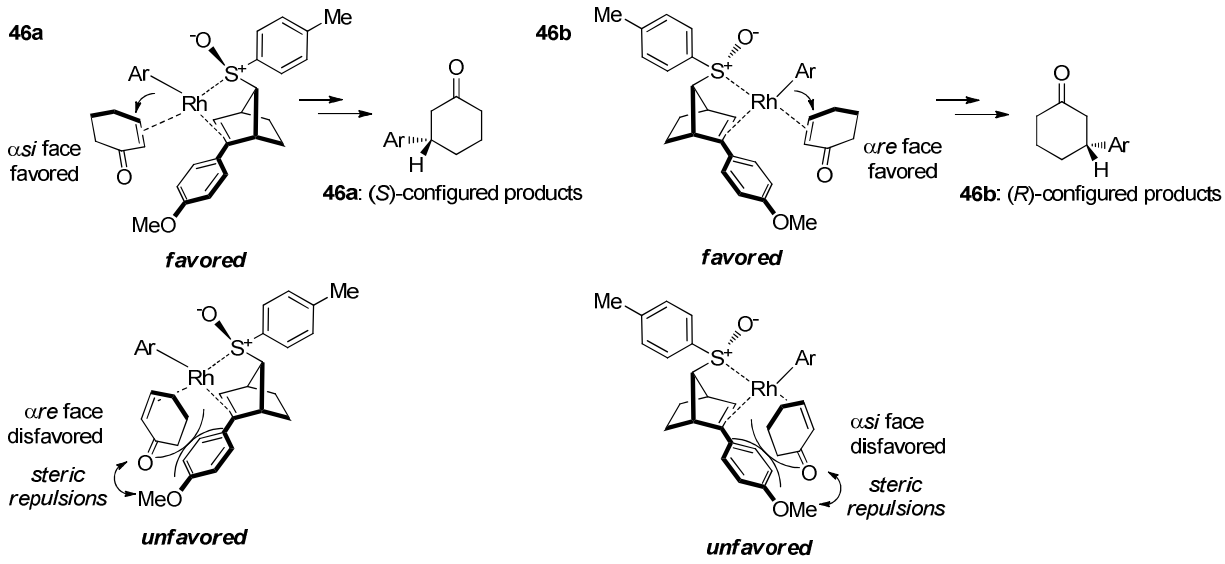


Entry		Product	Yield [%][a]	*ee* [%][b] (conf.)[c]
1		**55a**: R=Ph	87	92
2		**55b**: R=1-naphthyl	92	92 (*R*)
3		**55c**: R=4-MeO-C_6H_4	82	92 (*R*)
4		**55d**: R=4-F_3C-C_6H_4	85	90
5		**56a**: R=1-naphthyl	82	96
6		**56b**: R=4-Cl-C_6H_4	79	93
7		**56c**: R=4-F_3C-C_6H_4	83	95
8		**57**: R=3,5-Me_2-C_6H_3	80	96[d] (*R*)
9		**58**: R=Ph	92	99[e]

[a] Isolated yield of analytically pure product. [b] Determined via chiral HPLC analysis. See appendix for details. [c] Absolute configurations determined by comparison to chiral HPLC data reported in the literature.[75] [d] Reaction time: 12 h. Compound racemizes upon storage at room temperature. [e] Reaction time: 12 h.

1.2.4 Rationale for the observed stereochemical outcome

In order to rationalize the opposed stereochemical outcomes obtained with the diastereomeric ligands **46a** and **46b**, we propose the following model (Scheme 32): Since sulfinyl groups are known to be strong σ-donors to Rh,[30a] *trans*-configuration of the aryl group and the alkene moiety of the ligand in the complex can be assumed as it is reported for the related phosphine-olefin hybrid ligands.[68e]



Scheme 32: Stereochemical model explaining the opposite configurations of the addition products obtained with **46a** and **46b.**

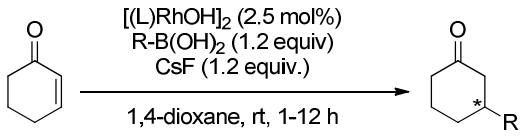
The stereoselectivity is controlled by the chiral environment around the alkenyl unit which forces the substrate, e.g. cyclohex-2-enone, via steric interactions to bind to the Rh-complex with its αsi face in the case of **46a** and with its αre face in the case of **46b**. Despite a strong coordination of the sulfinyl group to Rh the central chirality at the sulfur has only a minor influence on the observed enantioselectivities.

1.2.5 Influence of steric and electronic modulations at the ligand

Finally, we examined the influence of electronic and steric modulations at the sulfoxide-olefin hybrid ligand on reactivity and enantioselectivity of the Rh-complex in the Hayashi-Miyaura reaction. For this purpose, we prepared the analogues **59a-c** bearing different sulfinyl moieties using subsequent addition of the corresponding Grignard reagents to (*S*)-TMPOO (**2**; Scheme

5).[19] To investigate the role of the alkenyl moiety, we synthesized **60** with a more electron-rich 4-dimethylaniline substituent at the C=C double bond (Table 3). These ligands were then applied to the Rh-catalyzed 1,4-addition of various arylboronic acids to cyclohexen-2-one (Table 3). Both increasing and reducing the electron-density at the sulfoxide (**59a-b**) led to an overall deterioration of yield and enantioselectivity (entries 1-7).

Table 3: Enantioselective 1,4-addition to cyclohex-2-enone using analogues **59a-c** and **60**.



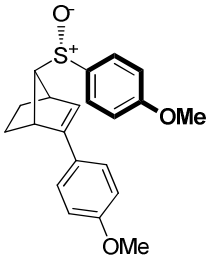
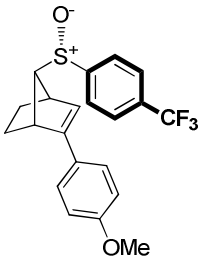
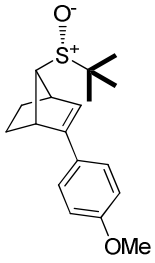
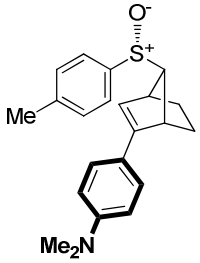
Entry	Ligand	Product	Yield [%][a]	*ee* [%][b]
1	 **59a**	**61a**: R=4-MeO-C_6H_4	57	83
2		**61b**: R=4-Me-C_6H_4	63	88
3		**61c**: R=Ph	69	81
4		**61d**: R=4-F-C_6H_4	73	90
5	 **59b**	**62a**: R=4-MeO-C_6H_4	77	84
6		**62b**: R=Ph	84	86
7		**62c**: R=4-F_3C-C_6H_4	83	91
8	 **59c**	**63**: R=Ph	no reaction	-

Table 3 continued

9		**64a**: R=3-MeO-C_6H_4	79	89
10	**60**	**64b**: R=1-naphthyl	62	90

[a] Isolated yield of analytically pure product. [b] Determined via chiral HPLC analysis. See appendix for details.

Interestingly, the use of electron-poor arylboronic acids as nucleophiles proved advantageous to yield and enantioselectivity with both ligands (entries 4 and 7). A negative effect of electron-rich arylboronic acids on the stereoselectivity was also found with **46a** as ligand (entries 6 and 9 of Table 1). With ligand **59c** bearing a sterically highly congested *t*Bu group at the sulfoxide no reaction took place (entry 8). This may be due to an impaired coordination between the sulfoxide and Rh. The alkenyl moiety alone is not sufficient for efficiently binding to the Rh atom thus underlining the vital role of the sulfinyl group for chelation and formation of the reactive complex. An increase of the electron-density at the C=C bond (**60**) led only to a deterioration of yields, without impairing the enantioselectivities (entries 9-10). These experiments show that coordination of the sulfinyl group represents a crucial factor for the formation of the reactive Rh-complex. Although binding of the alkenyl moiety to the Rh is less important for the reaction to proceed, its chiral environment predominantly dictates the stereochemical outcome.

2. Diastereocontrol in the Cross-Couplings of Substituted Cycloalkyl and Piperidinyl Derivatives

2.1 Highly diastereoselective Csp^3-Csp^2 Negishi cross-coupling with 1,2-, 1,3- and 1,4-substituted cycloalkylzinc compounds

2.1.1 Introduction

Pd-catalyzed Csp^3-cross-coupling reactions are important methods for preparing complex organic molecules.[36] The possibility of forming these C-C bonds in a stereocontrolled manner further increases their synthetic potential.[13] Thus, a number of chiral ligands for asymmetric Pd- and Ni-catalyzed cross-couplings have been successfully developed.[38, 45, 46, 48, 76] In their pioneering work, *T. Hayashi* and *M. Kumada* have shown that secondary alkyl-magnesium and -zinc reagents allow the preparation of chiral cross-coupling products.[45, 46] The Zn- or Mg-organometallics used in these reactions are configurationally labile and subject to epimerization at the carbon-metal bond.[47] We have developed highly diastereoselective Negishi cross-couplings[33b] on various substituted cycloalkylzinc reagents. An unexpected remote 1,3- and 1,4-stereocontrol was hereby observed.

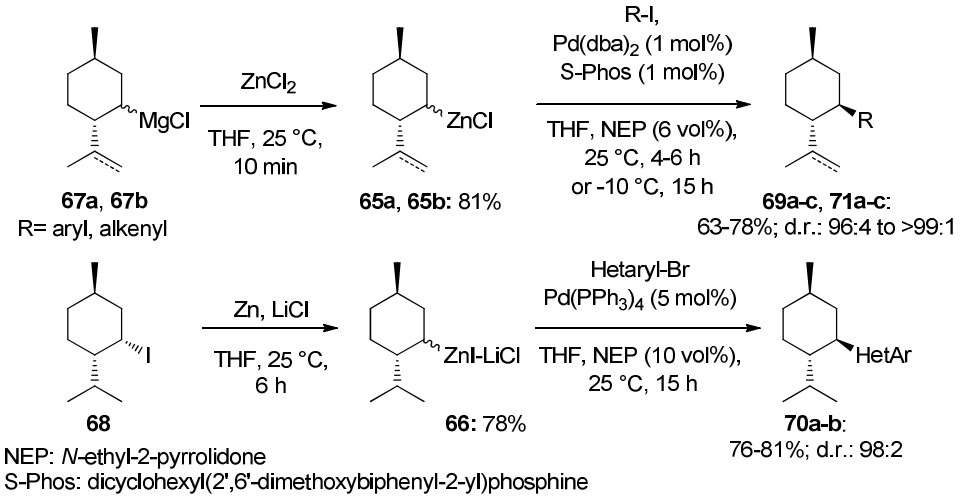
2.1.2 Pd-catalyzed cross-couplings with menthyl- and isopulegylzinc halides

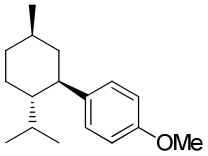
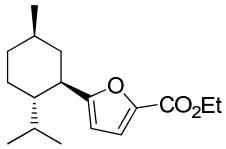
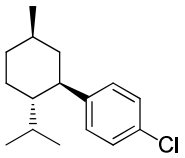
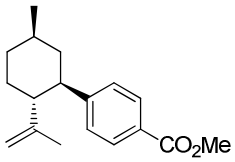
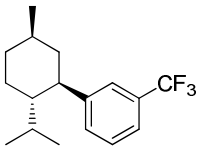
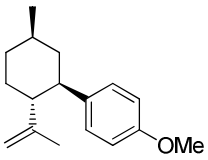
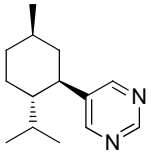
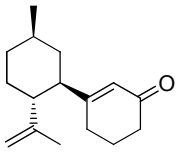
In our initial experiments, we have prepared menthylzinc halides **65** and **66** either by treating menthylmagnesium chloride[77] **67** with $ZnCl_2$ (1.1 equiv, THF, 25 °C, 10 min, 81%) or by the reaction of neomenthyl iodide **68**[78] with zinc powder and LiCl[79] (THF, rt, 6 h, 78%, Table 4). The resulting menthylzinc reagents **65** or **66** were then subjected to Pd-catalyzed cross-couplings with aryl halides at room temperature. $Pd(dba)_2$/SPhos[80] (1:1) or $Pd(PPh_3)_4$ were used as catalysts. To our delight, the *trans*-cross-coupling products were obtained with high diastereomeric purities (d.r. = 96:4 to ≥99:1) and 63-81% yields (Table 4). Thus, the reaction of menthylzinc chloride **65** with 4-iodoanisole in the presence of $Pd(dba)_2$ (1 mol%) and SPhos (1 mol%, rt, 4 h) in a mixture of THF and NEP (*N*-ethyl-2-pyrrolidone; 6 vol%) furnished the arylated menthyl-derivative **69a** in 78% yield and d.r. >99:1 (entry 1 of Table 4).

---

[76] (a) G. Cross, B. K. Vriesema, G. Boven, R. M. Kellogg, F. Van Bolhuis, *J. Organomet. Chem.* **1989,** *370*, 357; (b) J. Caeiro, J. Perez Sestelo, L. A. Sarandeses, *Chem. Eur. J.* **2008,** *14*, 741.
[77] J. Beckmann, D. Dakternieks, M. Draeger, A. Duthie, *Angew. Chem. Int. Ed.* **2006,** *45*, 6509.
[78] G. L. Lange, C. Gottardo, *Synth. Commun.* **1990**, *20*, 1473.
[79] A. Krasovskiy, V. Malakhov, A. Gavryushin, P. Knochel, *Angew. Chem. Int. Ed.* **2006,** *45*, 6040.
[80] S. D. Walker, T. E. Barder, J. R. Martinelli, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2004**, *43*, 1871.

Table 4: Cross-coupling products obtained with menthyl- and isopulegylzinc halides.



Entry	Product	Yield [%][a], d.r.[b]	Entry	Product	Yield [%][a], d.r.[b]
1	 **69a**	78, >99:1	5	 **70b**	81, 98:2[c]
2	 **69b**	71, 98:2	6	 **71a**	72, >99:1
3	 **69c**	63, 96:4	7	 **71b**	71, >99:1
4	 **70a**	76, 98:2[c]	8	 **71c**	64, 99:1[d]

[a] Isolated yield of analytically pure product. The major diastereomers are depicted. [b] Determined by capillary GC analysis before and after purification. [c] $Pd(PPh_3)_4$ (5 mol%) was used as catalyst. [d] The cross-coupling reaction was performed at -10 °C.

Similarly, the cross-coupling reactions with 1-chloro-4-iodobenzene and 1-iodo-3-(trifluoromethyl)benzene produced the expected products **69b** and **69c** with d.r. = 98:2 and 96:4, respectively (entries 2 and 3). Cross-coupling with heteroaryl bromides, either electron-poor such as 5-bromopyrimidine or electron-rich such as ethyl 5-bromofuroate, led to the desired alkylated adducts **70a-b** with d.r. = 98:2 (entries 4 and 5). The method could be extended to isopulegylzinc chloride which underwent highly diastereoselective cross-coupling reactions with methyl 4-iodobenzoate (**71a**; 72%; d.r. > 99:1), 4-iodoanisole (**71b**; 71%; d.r. > 99:1) and 3-iodo-2-cyclohexenone[81] (**71c**; 64%; d.r. = 99:1; entries 6-8). It must be noted that in all cases, the thermodynamically more favored diastereomer was formed as proven by X-ray analysis (see appendix).

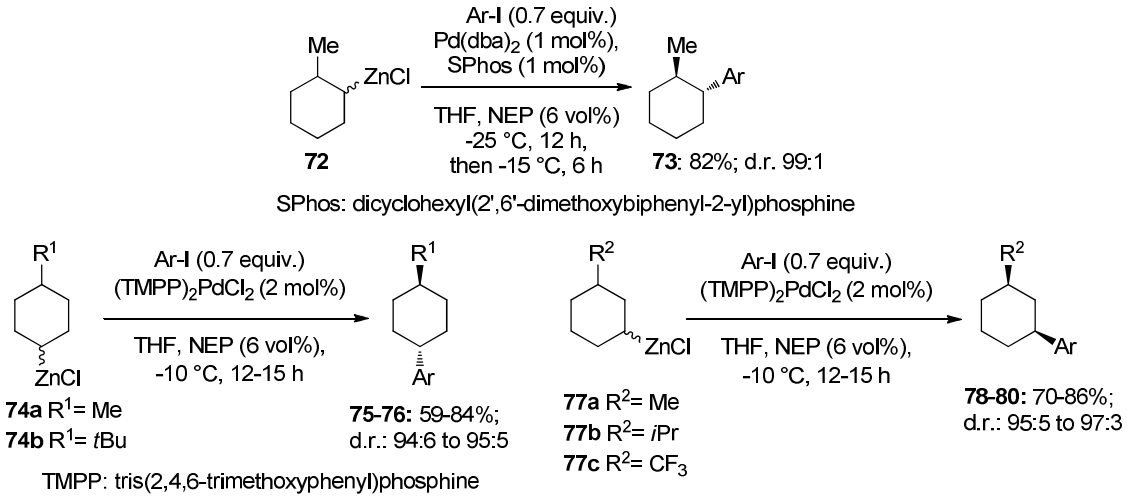
2.1.3 Extension to further substituted cycloalkylzinc reagents – observation of a remote stereocontrol

This method could be extended to 2-methylcyclohexylzinc chloride **72** (Table 5). The methyl group is less bulky than an isopropyl group and its steric influence may be expected to be less pronounced. Still, a high diastereoselectivity was observed when **72** was reacted with methyl 4-iodobenzoate in the presence of $Pd(dba)_2$ and SPhos at –25 °C. Thus, the cross-coupling product **73** was obtained with 82% yield and d.r. = 99:1 (entry 1 of Table 5). Rearrangement reactions as observed by *G. A. Molander et al.*[82] could be mostly avoided at this low temperature. Remarkably, we found that similarly high stereoselectivities were obtained with cyclohexylzinc reagents bearing substituents at position 4 such as zinc compounds **74a-b** or at position 3, such as **77a-c**. Hereby, a large steric effect cannot be expected due to the remoteness of the substituents. Thus, we have subjected 4-methylcyclohexylzinc chloride (**74a**) to a Negishi cross-coupling with methyl 4-iodobenzoate ($Pd(PPh_3)_4$, 2 mol%, rt, 15 h). The cross-coupling product **75** was obtained with a high diastereomeric ratio of 92:8 (entry 2). By screening several catalyst systems and reaction conditions, it was further possible to increase this diastereoselectivity to d.r. = 95:5 (for details see appendix). A 2:1 combination of tris(2,4,6-trimethoxyphenyl)phosphine (TMPP)[83] and $PdCl_2$ was found to be the most diastereoselective catalyst system. Using these conditions, 4-substituted cyclohexylzinc chlorides such as **74a-b** furnished the thermodynamically favored *trans*-4-substituted products (**75-76**) with diastereoselectivities up to 95:5 (entries 2-4). Similarly,

[81] J. P. Barnier, L. Blanco, *Synth. Commun.* **2003**, *33*, 2487.
[82] S. D. Dreher, P. G. Dormer, D. L. Sandrock, G. A. Molander, *J. Am. Chem. Soc.* **2008,** *130*, 9257.
[83] K. R. Dunbar, J.-S. Sun, J.-S. *J. Chem. Soc., Chem. Commun.* **1994**, 2387.

3-substituted cyclohexylzinc chlorides (**77a-c**) provided the *cis*-cross-coupling products (**78-80**) with d.r. up to 97:3 (entries 5-13). The relative stereochemistry of **78a** was determined by X-ray analysis (see appendix).

Table 5: Cross-coupling products obtained with 2-, 4- and 3-substituted cyclohexylzinc halides.



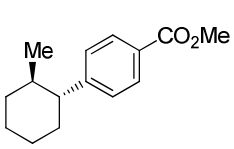
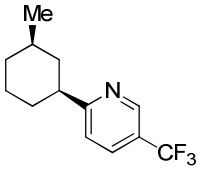
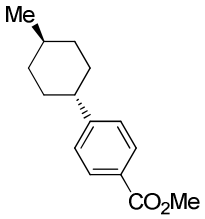
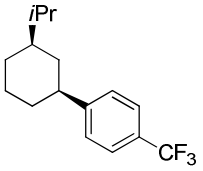
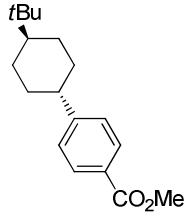
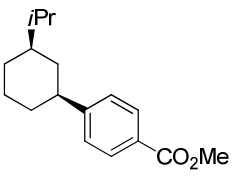
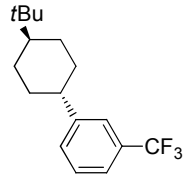
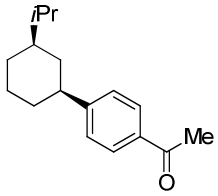
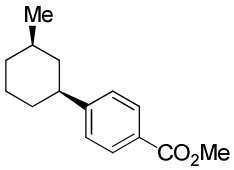
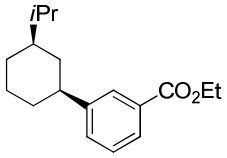
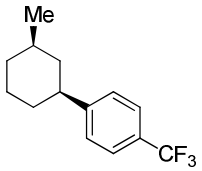
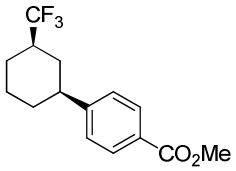
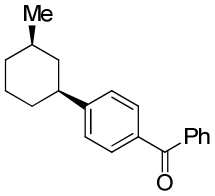
Entry	Product	Yield [%][a], d.r.[b]	Entry	Product	Yield [%][a], d.r.[b]
1	 **73**	82, 99:1[c]	8	 **78d**	85, 95:5[h]
2	 **75**	84, 95:5; 89, 92:8[d]	9	 **79a**	70, 96:4[g]
3	 **76a**	59, 95:5	10	 **79b**	86, 96:4

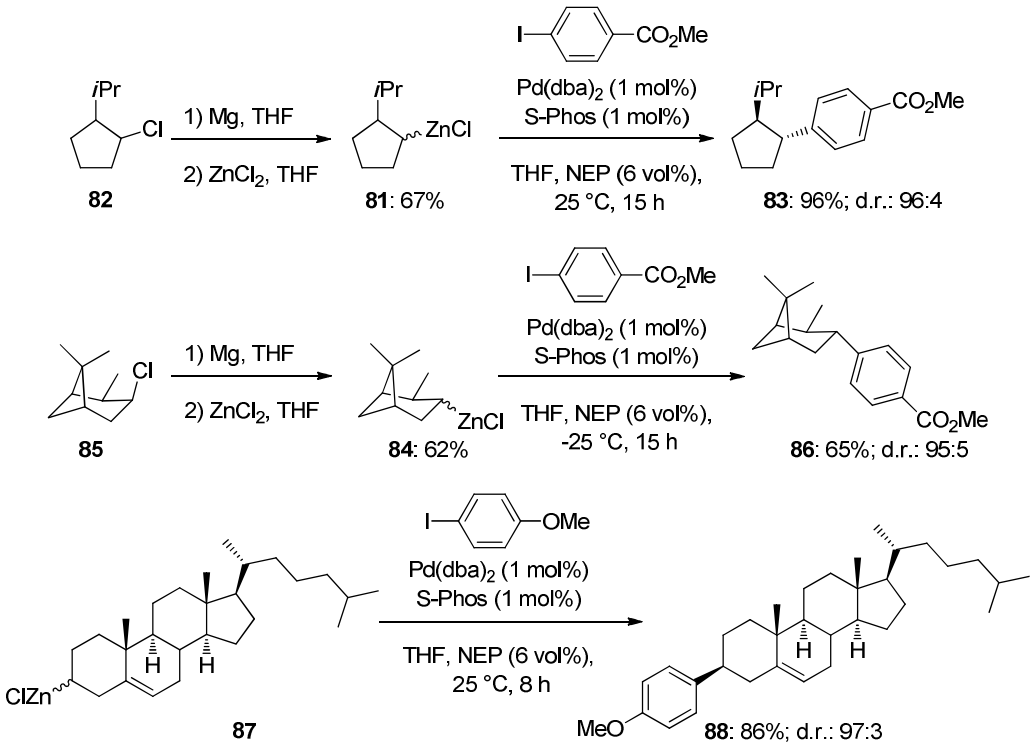
Table 5 continued

4	 **76b**	60, 94:6	11	 **79c**	71, 95:5
5	 **78a**	77, 97:3; 96:4[e]; 96:4[f]	12	 **79d**	71, 97:3[g]
6	 **78b**	70, 96:4[g]	13	 **80**	74, 96:4
7	 **78c**	81, 95:5[h]			

[a] Isolated yield of analytically pure product. The major diastereomers are depicted. [b] Determined by capillary GC analysis before and after purification. [c] 5% of regioiosmer detected. [d] The reaction was performed at rt using $Pd(PPh_3)_4$ (2 mol%) as catalyst. [e] d.r. obtained when a large excess (5 equiv) of electrophile was used. [f] d.r. obtained when a large excess of zinc reagent (5 equiv) was used. [g] The reaction was performed at –5 °C. [h] The reaction was performed with 3-methylcyclohexylzinc iodide (prepared via zinc insertion) at rt using $Pd(PPh_3)_4$ (5 mol%) as catalyst.

The diastereoselectivities were not affected by the bulkiness or the nature of the ring substituents. For example, the cross-couplings of *3-methyl*cyclohexyl- (**77a**), *3-isopropyl*cyclohexyl- (**77b**) and *3-trifluoromethyl*cyclohexylzinc chloride (**77c**) with methyl 4-iodobenzoate furnished the respective products **78a**, **79b** and **80** with similar diastereoselectivities (d.r. = 96:4 to 97:3; entries 5, 10 and 13). Remarkably, these stereoselective Negishi cross-coupling reactions could be extended to various cyclic systems, including cyclopentanes, bicyclic compounds and steroids. Thus, cross-coupling of 2-isopropylcyclopentylzinc chloride (**81**) (prepared from 1-chloro-2-

isopropylcyclopentane **82** via Mg insertion and transmetalation with $ZnCl_2$) with methyl 4-iodobenzoate furnished selectively the *trans*-product **83** (96%; d.r.= 96:4; Scheme 33).



Scheme 33: Diastereoselective cross-coupling with various cycloalkylzinc reagents.

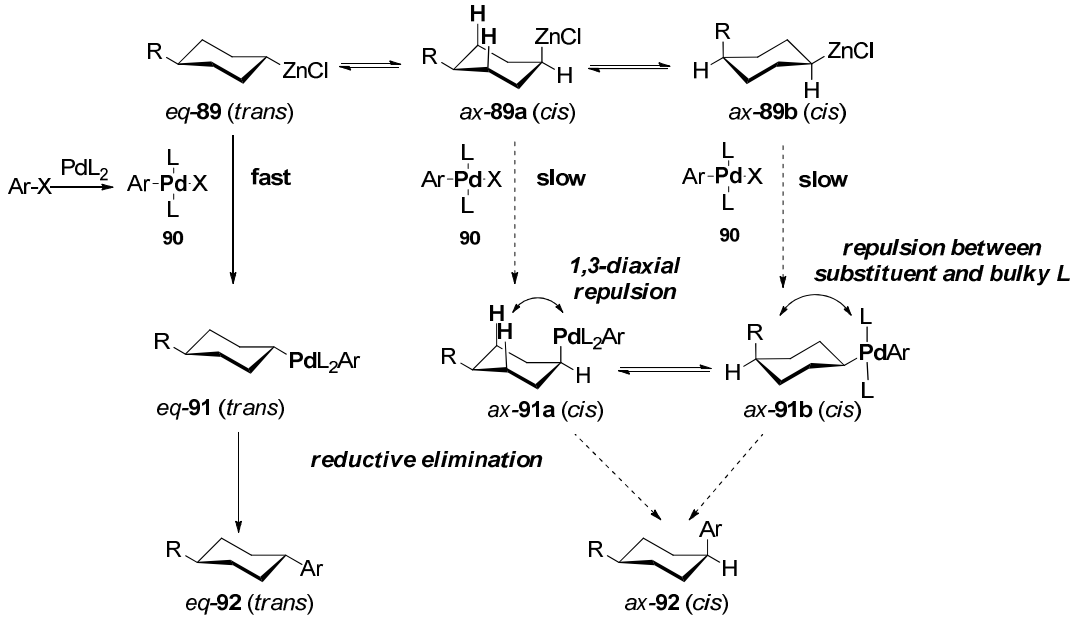
An excellent diastereoselectivity was also observed with isopinocampheylzinc chloride (**84**) (prepared analogously to **81** from isopinocampheyl chloride[84] **85**) leading to the arylated product **86** (65%; d.r. = 95:5). Finally, the cholesterylzinc chloride (**87**) (prepared from cholesteryl chloride[85]) was arylated with 4-iodoanisole resulting in the steroid **88** (86%; d.r. = 97:3; Scheme 33).

2.1.4 Mechanistic considerations

The performance of cross-coupling reactions with **77a** using a large excess (5 equiv) of methyl 4-iodobenzoate or the zinc reagent **77a** (5 equiv) led to the cross-coupling product **78a** with a similar diastereoselectivity as under standard conditions (0.7 equiv of the electrophile) (d.r. =

[84] J. Scianowski, Z. Rafinski, A. Wojtczak, *Eur. J. Org. Chem.* **2006** 3216.
[85] E. M. Kosower, S. Winstein, *J. Am. Chem. Soc.* **1956**, *78*, 4354.

96:4; compare to 97:3; see entry 5 of Table 5).[86] Based on these observations, we propose a tentative mechanism in which both diastereomeric cyclohexylzinc complexes *eq*-**89**, *ax*-**89a** and *ax*-**89b** are in equilibrium (Scheme 34). Although the carbon-zinc bond is reported to be configurationally stable,[87] it was shown that the presence of metallic salts facilitates its epimerization[88] and PdX_2, MgX_2, ZnX_2, LiCl present in the reaction mixture may be responsible for this fast equilibration.



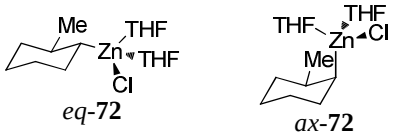
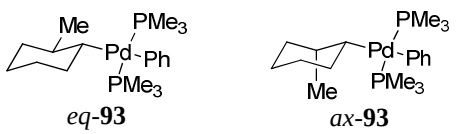
Scheme 34: Mechanistic proposal for the diastereoselective cross-coupling of substituted cycloalkylzinc reagents with aryl iodides.

The transmetalation of the zinc reagent *eq*-**89** with $ArPdL_2X$ (**90**), obtained by Pd(0)-insertion into an aryl halide (Ar-X), preferentially leads to the Pd-intermediate *eq*-**91** provided that the transmetalation occurs with retention of configuration.[89] The alternative formation of the Pd-intermediates *ax*-**91a** and *ax*-**91b** is disfavored for steric reasons. In both of these conformers either the Pd-moiety or the R-group occupies the axial position. This results in repulsive interactions with the bulky phosphine ligands on Pd (as shown by the DFT-calculations below). After reductive elimination the *trans*-product *eq*-**92** is selectively obtained from *eq*-**91** (Scheme

[86] R. Hirsch, R. W. Hoffmann, *Chem. Ber.* **1992**, *125*, 975.
[87] A. Guijarro, R. D. Rieke, *Angew. Chem. Int. Ed.* **2000**, *39*, 1475.
[88] (a) L. Micouin, M. Oestreich, P. Knochel, *Angew. Chem. Int. Ed.* **1997**, *36*, 245; (b) A. Boudier, C. Darcel, F. Flachsmann, L. Micouin, M. Oestreich, P. Knochel, *Chem. Eur. J.* **2000**, *6*, 2748.
[89] K. R. Campos, A. Klapars, J. H. Waldman, P. G. Dormer, C.-y. Chen, *J. Am. Chem. Soc.* **2006**, *128*, 3538.

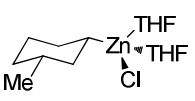
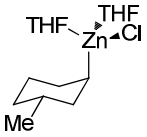
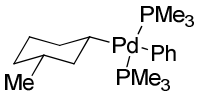
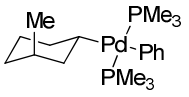
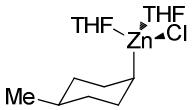
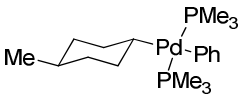
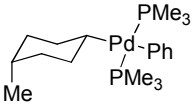
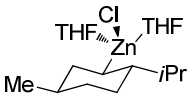
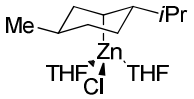
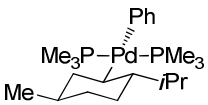
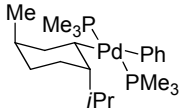
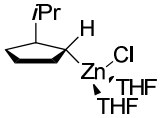
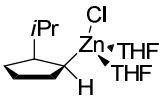
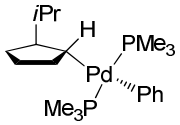
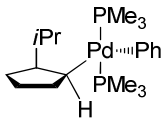
34). In order to get an insight into the energetic differences between Pd-intermediates of type **91** and to verify our mechanistic proposal, we have performed a DFT calculation-based conformational analysis on the respective organozinc and organopalladium complexes (Table 6).[90] Comparison of the energetically lowest conformers showed that only small and insignificant thermodynamical differences exist between the diastereomeric cycloalkylzinc chloride complexes (less than 0.77 kcal/mol in free energy for zinc complexes **65**, **72**, **74a, 77a** and **81**; Table 6) (for details see the appendix). However, the corresponding organopalladium complexes (**93-97**) show a significant change in thermodynamical energies favoring the diastereomers which bear all substituents in equatorial positions. The calculations demonstrated that considerable repulsive interactions between the substituents on the cycloalkyl moiety and the phosphine ligands on Pd increase the energetic gap between the diastereomeric complexes up to 9.84 kcal/mol in free energy (Table 6). This energetic increase gets experimentally significant and accounts for the diastereoselectivities observed in the cross-coupling reactions. For instance, complex *ax*-**95** bearing a methyl substituent in the axial position is strongly disfavored compared to *eq*-**95** by 2.08 kcal/mol explaining why the cross-coupling reaction only proceeds via intermediate *eq*-**95** (or via *eq*-**91** and not via *ax*-**91a** or *ax*-**91b** in Scheme 34).

Table 6: DFT calculation-based conformational analysis on the diastereomeric zinc and palladium complexes.

Entry	Organozinc complexes $\Delta G^{298}_{eq\text{-}ax}$[a], $\Delta E_{0\ ;eq\text{-}ax}$[a] [kcal/mol]	Entry	Organopalladium complexes $\Delta G^{298}_{eq\text{-}ax}$[a], $\Delta E_{0\ ;eq\text{-}ax}$[a] [kcal/mol]
	 *eq*-**72** *ax*-**72**		 *eq*-**93** *ax*-**93**
1	–0.55, –1.29	8	–4.85, –5.02

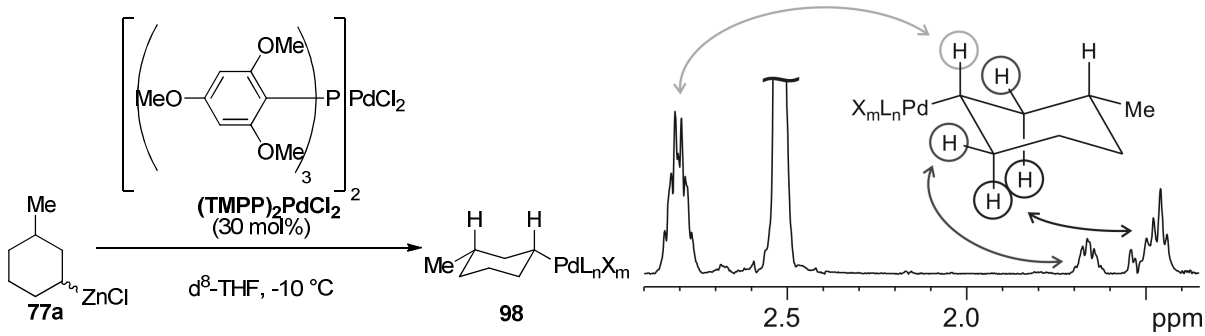
[90] DFT calculations were carried out using the Gaussian03 Rev.B.04 program package[90a] with the nonlocal hybrid B3LYP exchange-correlation functionals[90b]. The basis set denoted as 631SVP consists of the Ahlrich def2-SVP all electron basis set[90c] for Zn atoms, all electron and ECP for Pd atoms and the 6-31G(d,p) basis set[90d] for other atoms. See appendix for full details of the computational study. (a) M. J. Frisch, et al. Gaussian 03; Gaussian, Inc., Wallingford CT, **2004**; (b) R. G. Parr, W. Yang, *Density Functional Theory of Atoms and Molecules*; Oxford University Press: New York, **1989**; T. Ziegler, *Chem. Rev*. **1991**, *91*, 651; C. Lee, W. Yang, R. G. Parr, *Phys. Rev. B* **1988**, *37*, 785; A. D. Becke, *Phys. Rev. A* **1988**, *38*, 3098; (c) F. Weigend, R. Ahlrichs, *Phys. Chem. Chem. Phys.* **2005**, *7*, 3297; (d) P. C. Hariharan, J. A. Pople, *Theoret. Chimica Acta* **1973**, *28*, 213; M. M. Francl, W. J. Petro, W. J. Hehre, J. S. Binkley, M. S. Gordon, D. J. DeFrees, J. A. Pople, *J. Chem. Phys.* **1982**, *77*, 3654; V. A. Rassolov, J. A. Pople, M. A. Ratner, T. L. Windus, *J. Chem. Phys*. **1998**, *109*, 1223.

Table 6 continued

	 *eq*-**77**	 *ax*-**77**		 *eq*-**94**	 *ax*-**94**
2	–0.68, 0.10		9	–2.88, –2.59	
	 *eq*-**74**	 *ax*-**74**		 *eq*-**95**	 *ax*-**95**
3	–0.52, –0.04		10	–2.08, –2.37	
	 *eq*-**65**	 *ax*-**65**		 *eq*-**96**	 *ax*-**96**
4	–0.77, –0.36		11	–9.84, –10.08	
	 *trans*-**81**	 *cis*-**81**		 *trans*-**97**	 *cis*-**97**
5	–0.43, 0.10		12	–5.54, –5.03	

[a] Calculated energetic difference (B3LYP/631SVP) between the energetically lowest conformers of the two diastereomers.

To substantiate the results from the theoretical calculations which suggested that the diastereoselectivity is due to a fast transmetalation of the cycloalkylzinc reagent to the Pd complex *eq*-**94**, we have performed NMR studies on the reaction of 3-methylcyclohexylzinc chloride (**77a**) with $(TMPP)_2PdCl_2$ in d^8-THF (0.3 M) at –10 °C (Scheme 35). Many signals of several zinc species (**77a** and aggregates) and Pd complexes were detected in the NMR spectra. However, using $^1H^{31}P$-HMBC analysis only one ^{31}P chemical shift simultaneously displays cross-signals with the cyclohexyl and aromatic ^1H-signals.



Scheme 35: NMR-studies on the transmetalation of 3-methylcyclohexyl-zinc chloride (**77a**) to $(TMPP)_2PdCl_2$; A 1D section from the $^1H^{31}P$-HMBC spectrum is shown displaying the proton signals from the Pd intermediate **98**.[91]

This shows that *there is only one Pd-intermediate* present in a detectable amount. *J*-coupling between the proton signals in the cyclohexyl ring identified the intermediate as a structure of type **98** with the *Pd occupying the equatorial position* ($^3J_{HH}$-coupling was detected to be 11 Hz (± 0.5 Hz) which corresponds to a coupling of axial protons; for details and spectra see the appendix). These results confirm the conformational preferences of the tentative mechanism proposed in Scheme 34.

[91] The most intense of the cyclohexyl signals at δ = 2.8 ppm represents the methine signal showing the strongest coupling with the P-atom of the TMPP-ligand ($^3J_{HP}$). The neighboring methylene protons show signals in the region from δ = 1.4 ppm to 1.7 ppm with lower intensities ($^4J_{HP}$). $^3J_{HH}$-coupling of 11 Hz (± 0.5 Hz) in the methine signal which corresponds to a coupling of axial protons identifies the structure to be of type **98** with the Pd moiety occupying the equatorial position.

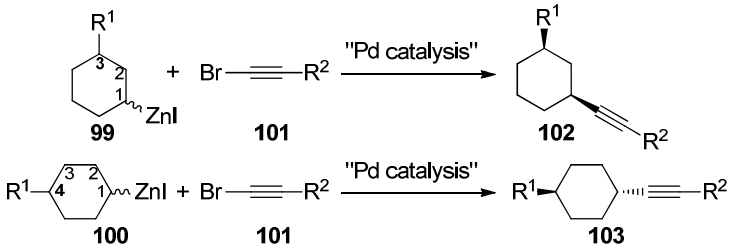
2.2 Diastereoselective Csp^3-Csp cross-couplings between 1,3- and 1,4-disubstituted cyclohexylzinc reagents and bromoalkynes via remote stereocontrol

2.2.1 Introduction

Alkynes are found in a vast array of natural products and bioactive molecules[92] and make up important constituents in many functional materials,[92c, 93] including liquid crystals[94], dyes[95] and organic light-emitting diodes (OLEDs).[96] Therefore, the development of novel methods allowing an efficient and stereoselective introduction of the alkynyl unit into organic molecules is highly desirable. Whereas for the construction of Csp-Csp^2 bonds the *Sonogashira*-reaction[97] has been well established, much less synthetic methods are available for the coupling between a Csp^3 and Csp center.[98-100] For such reactions, the C-C bond formation is problematic due to competing β-hydride elimination and sluggish reductive elimination.[37] Most of the existing procedures are based on the coupling of an alkynyl organometallic or alkyne with an alkyl halide.[98] Useful approaches for transition-metal catalyzed couplings involving alkyl organometallics have evolved only recently.[99] Such methods include oxidative coupling of primary alkylzinc reagents with terminal alkynes[99a] or alkynylstannanes[99b-c] as well as Cu-catalyzed coupling of alkylmagnesium reagents with alkynyl halides. [99d] Pd- and Cu-catalyzed decarboxylative couplings may also be

[92] (a) B. W. Gung, *C. R. Chimie* **2009**, *12*, 489; (b) A. L. K. Shi Shun, R. R. Tykwinski, *Angew. Chem. Int. Ed.* **2006**, *45*, 1034; (c) *Modern Acetylene Chemistry* (Eds.: P. J. Stang, F. Diederich), Wiley-VCH, Weinheim, **1995**.
[93] For a review on acetylenic polymers see: J. Liu, J. W. Y. Lam, B. Z. Tang, *Chem. Rev.* **2009**, *109*, 5799.
[94] (a) H. K. Bisoyi, S. Kumar, *Chem. Soc. Rev.* **2010**, *39*, 264; (b) C. T. Imrie, P. A: Henderson, *Chem. Soc. Rev.* **2007**, *36*, 2096; (c) A. L. Sadowy, R. R. Tykwinski in *Modern Supramolecular Chemistry* (Eds.: F. Diederich, P. J. Stang, R. R. Tykwinski), Wiley-VCH, Weinheim, **2008**, pp. 185-231.
[95] (a) R. Ziessel, A. De Nicola, *C. R. Chimie* **2009**, *12*, 450; (b) S. Nakatsuji, K. Nakashima, S. Akiyama, H. Nakazumi, *Dyes and Pigments* **1994**, *24*, 37.
[96] M. Kivala, F. Diederich, *Acc. Chem. Res.* **2009**, *42*, 235.
[97] (a) K. Sonogashira, Y. Tohda, N. Haghihara, *Tetrahedron Lett.* **1975**, 4467; for reviews on Csp^2-Csp cross-couplings see: (b) H. Doucet, J.-C. Hierso, *Angew. Chem. Int. Ed.* **2007**, *46*, 834; (c) H. Plenio, *Angew. Chem. Int. Ed.* **2008**, *47*, 6954.
[98] For couplings of alkynyl organometallics with alkyl halides see: (a) M. Peña-López, M. Ayán-Varela, L. A. Sarandeses, J. P. Sestelo, *Chem. Eur. J.* **2010**, *16*, 9905; (b) W. Shi, C. Liu, Z. Yu, A. Lei, *Chem. Commun.* **2007**, 2342; (c) M. Qian, E.-i. Negishi, *Tetrahedron Lett.* **2005**, *46*, 2927; (d) M. Qian, E.-i. Negishi, *Synlett* **2005**, 1789; (e) L.-M. Yang, L.-F. Huang, T.-Y. Luh, *Org. Lett.* **2004**, *6*, 1461; stereoselective couplings: (f) H. Ohmiya, H. Yorimitsu, K. Oshima, *Org. Lett.* **2006**, *8*, 3093; (g) J. Caeiro, J. P. Sestelo, L. A. Sarandeses, *Chem. Eur. J.* **2008**, *14*, 741; for couplings of alkyl halides and alkynes see: (h) O. Vechorkin, D. Barmaz, V. Proust, X. Hu, *J. Am. Chem. Soc.* **2009**, *131*, 12078; (i) G. Altenhoff, S. Würtz, F. Glorius, *Tetrahedron Lett.* **2006**, *47*, 2925; (j) M. Eckhardt, G. C. Fu, *J. Am. Chem. Soc.* **2003**, *125*, 13642.
[99] (a) M. Chen, X. Zheng, W. Li, J. He, A. Lei, *J. Am. Chem. Soc.* **2010**, *132*, 4101; (b) L. Jin, Y. Zhao, H. Wang, A. Lei, *Synthesis* **2008**, 649; (c) Y. Zhao, H. Wang, X. Hou, Y. Hu, A. Lei, H. Zhang, L. Zhu, *J. Am. Chem. Soc.* **2006**, *128*, 15048; (d) G. Cahiez, O. Gager, J. Buendia, *Angew. Chem. Int. Ed.* **2010**, *49*, 1278.

used.[100] Stereoselective versions of these reactions are scarce and have so far only been developed for Csp-Csp^3 couplings.[98f-g] From our results with the diastereoselective *Negishi*-type cross-couplings between substituted cycloalkylzinc reagents and (hetero)aryl halides (chapter **2.1**),[101] we deduced that a related cross-coupling between the cyclohexylzinc reagents (**99** or **100**) and alkynyl bromides (**101**) may be achieved, providing stereochemically defined alkynes of type **102** and **103** with 1,3- or 1,4-remote stereocontrol (Scheme 36).



Scheme 36: Diastereoselective Csp^3-Csp coupling of substituted cyclohexylzinc reagents with remote stereocontrol.

2.2.2 Diastereoselective Csp^3-Csp cross-couplings with remote stereocontrol

In a preliminary experiment, we have reacted the 3-substituted cyclohexylzinc reagent **99a** - obtained via Zn-insertion in the presence of LiCl[79] - with 1-bromophenylacetylene[102] (3a) in THF using different catalysts (Table 7). With 10 mol% CuCN·2 LiCl,[103] the expected cross-coupling product (**102a**) was obtained with a good conversion, yet only with a modest diastereoselectivity (d.r.: 68:32; entry 1 of Table 7). Switching to Pd-catalysts, we have found that the Pd complex $TMPP_2PdCl_2$,[83] provided **102a** with a high d.r. of 95:5. We also observed the formation of some regioisomeric product (ca. 4%).[104] This diastereoselectivity could be further improved by replacing the phosphine ligand TMPP with various bipyridines (**104a-b**; entry 3) and *ortho*-phenanthrolines (**105a-d**; entry 4).

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[100] (a) W.-W. Zhang, X.-G. Zhang, J.-H. Li, *J. Org. Chem.* **2010**, *75*, 5259; (b) H.-P. Bi, Q. Teng, M. Guan, W.-W. Chen, Y.-M. Liang, X. Yao, C.-J. Li, *J. Org. Chem.* **2010**, *75*, 783; (c) H.-P. Bi, L. Zhao, Y.-M. Liang, C.-J. Li, *Angew. Chem. Int. Ed.* **2009**, *48*, 792; (d) D. K. Rayabarapu, J. A. Tunge, *J. Am. Chem. Soc.* **2005**, *127*, 13510.

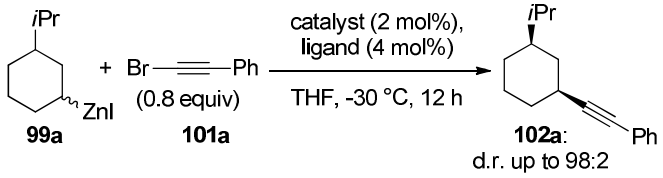
[101] T. Thaler, B. Haag, A. Gavryushin, K. Schober, E. Hartmann, R. M. Gschwind, H. Zipse, P. Mayer, P. Knochel, *Nature Chem.* **2010**, *2*, 125.

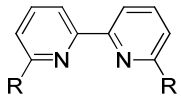
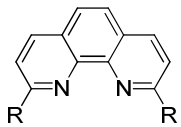
[102] Y. Zhang, R. P. Hsung, M. R. Tracey, K. C. M. Kurtz, E. L. Vera, *Org. Lett.* **2004**, *6*, 1151.

[103] (a) M. C. P. Yeh, P. Knochel, *Tetrahedron Lett.* **1989**, *30*, 4799; (b) P. Knochel, M. C. P. Yeh, S. C. Berk, J. Talbert, *J. Org. Chem.* **1988**, *53*, 2390.

[104] The Cu-catalyzed coupling only furnished the two diastereomeric products. Small amounts of regioisomers (same mass on GC-MS as the diastereomeric compounds) were only formed using Pd-catalysis.

Table 7: Optimization of the diastereoselectivity.



Entry	Catalyst	Ligand		d.r.[a]
1	10% CuCN		none	68:32
2	$PdCl_2$		**TMPP**	95:5 (4)
3	$PdCl_2$		R=H: **104a** R=Me: **104b**	**104a**: 96:4 (<3) **104b:** 98:2 (<2)
4	$PdCl_2$		R=H: **105a** R=Me: **105b** R=Ph: **105c** R=*t*Bu: **105d**	**105a**: 96:4 (<3) **105b: 98:2 (<2)** **105c**: 96:4 (<4) **105d:** 96:4 (<3)
5	$PdCl_2(PhCN)_2$		**105b**	96:4 (3)
6	$Pd(dba)_2$		**105b**	97:3 (2)
7	$Ni(acac)_2$		**105b**	87:13

[a] Determined by capillary GC analysis. The percentage of regioisomers is given in parentheses.

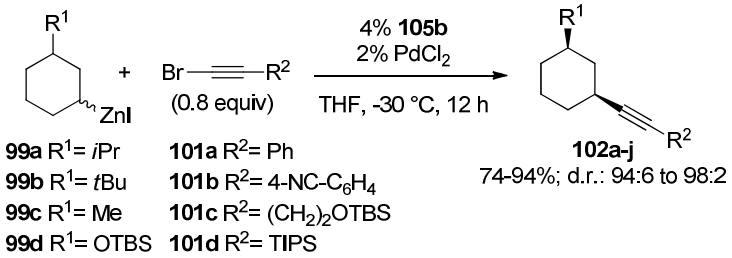
The *N*-ligands clearly proved to be superior. The commercially available and inexpensive neocuproine (**105b**)[105] combined excellent diastereoselectivity with a low formation of regioisomers (<2%). $PdCl_2$ was found to be the best Pd source and switching from Pd to Ni as catalyst resulted in a deterioration of the d.r. (d.r.: 87:13; entry 7). Bidentate *N*-ligands are known to stabilize Pd(0) more efficiently than monodentate phosphines[105b] leading to a faster reductive

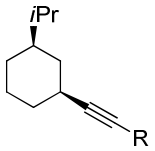
[105] (a) L. Canovese, F. Visentin, C. Santo, A. Dolmella, *J. Organomet. Chem.* **2009**, *694*, 411; (b) A. Svennebring, P. J. R. Sjöberg, M. Larhed, P. Nilsson, *Tetrahedron* **2008**, *64*, 1808; (c) K. S. Yoo, H. Cheol, K. W. Jung, *J. Am. Chem. Soc.* **2006**, *128*, 16384.

elimination thus minimizing unwanted β-hydride elimination and formation of regioisomeric products.

The 3-substituted cyclohexylzinc reagent **99a** was subsequently subjected to cross-couplings with a range of 1-bromoalkynes (**101a-d**) using the optimized catalyst system (2 mol% $PdCl_2$, 4 mol% **105b**). The expected thermodynamically preferred *cis*-1,3-disubstituted cyclohexane[106] derivatives were obtained with good yields and excellent diastereoselectivities (d.r.: 94:6 to 98:2; entries 1-5 of Table 8). Bromoalkynes bearing aromatic (**101a-b**), aliphatic (**101c**) and silyl moieties (**101d**) were successfully coupled. Increasing the steric bulk of the substituent from *i*Pr to *t*Bu at the cyclohexylzinc reagent did not have an effect on the diastereoselectivity or yield (compare **102c** (77%; d.r.: 97:3) and **102f** (74%; d.r.: 97:3); entries 3 and 6). Replacing the relatively large *i*Pr-group with the sterically much less demanding methyl group only led to a slight loss of diastereoselectivity (compare **102a** (82%; d.r.: 98:2) with **102g** (79%; d.r.: 96:4); entries 1 and 7). Functionalized cyclohexylzinc reagents bearing an OTBS ($OSiMe_2tBu$) functionality underwent the Pd-catalyzed cross-couplings with equally high diastereoselectivities (d.r.: 96:4 to 98:2; **102i-j**; entries 9-10).

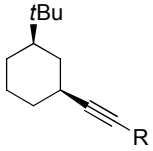
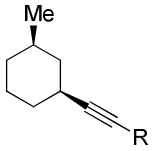
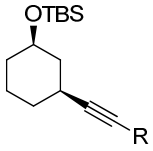
Table 8: Diastereoselective Csp^3-Csp coupling of 3-substituted cyclohexylzinc reagents.



Entry		Product	Yield [%][a] (d.r.)[b]
1		**102a**: R= Ph	82 (98:2)
2		**102b**: R= 4-NC-C_6H_4	87 (94:6)
3		**102c**: R= $(CH_2)_2$OTBS	77 (97:3)
4		**102d**: R= TIPS	79 (94:6), 76 (96:4)[c]

[106] The relative configurations of **102i** and **103h** were determined via desilylation and subsequent tosylation of the resulting alcohols. The crystals of the tosylates proved suitable for X-ray crystallography. The relative stereoconfiguration of **103b** was directly determined via X-ray crystallography. See appendix.

Table 8 continued

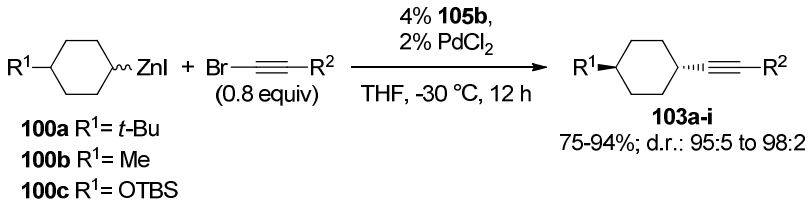
5		**102e**: R= 4-NC-C_6H_4	85 (95:5)
6		**102f**: R= $(CH_2)_2$OTBS	74 (97:3)
7		**102g**: R= Ph	79 (96:4)
8		**102h**: R= 4-NC-C_6H_4	88 (96:4)
9		**102i**: R= TIPS	81 (98:2)
10		**102j**: R= $(CH_2)_2$OTBS	94 (96:4)

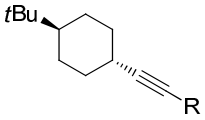
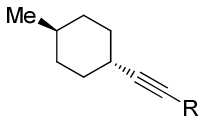
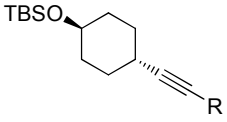
[a] Isolated yield of analytically pure product. [b] Determined by capillary GC analysis before and after purification. The percentage of regioisomers produced as byproducts was between 0-5%. See experimental section for details. [c] 4% bipyridine **104b** was used.

Next, we performed the Csp^3-Csp couplings with the 4-substituted cyclohexylzinc reagents **103a-c** (Table 9). To our delight, the diastereomeric ratios were as high as those obtained for the couplings of the 3-substituted cyclohexylzinc iodides (d.r.: 94:6 to 98:2; compare Tables 8 and 9) showing an excellent remote stereocontrol. In all cases, the thermodynamically favored *trans*-1,4-disubstituted cyclohexanes were preferentially formed (Table 9).[106] Like for the 3-substituted cyclohexylzinc reagents, the size of the respective substituents only had a minor effect on the diastereoselectivity. Thus, cyclohexylzinc reagent **100a** bearing a bulky *t*Bu-group furnished the coupling products **103a-d** with d.r. ≥96:4 (entries 1-4), while the couplings of the methyl-substituted zinc reagent **100b** resulted in a slightly lower d.r. of 95:5 (entries 5-6). Cross-couplings of the functionalized organozinc iodide **100c** also proceeded highly

diastereoselectively (d.r.: 95:5 to 96:4) providing the *trans*-configured products **103g-i** with excellent yields (88-94%; entries 7-9).

Table 9: Diastereoselective Csp^3-Csp coupling of 4-substituted cyclohexylzinc reagents.



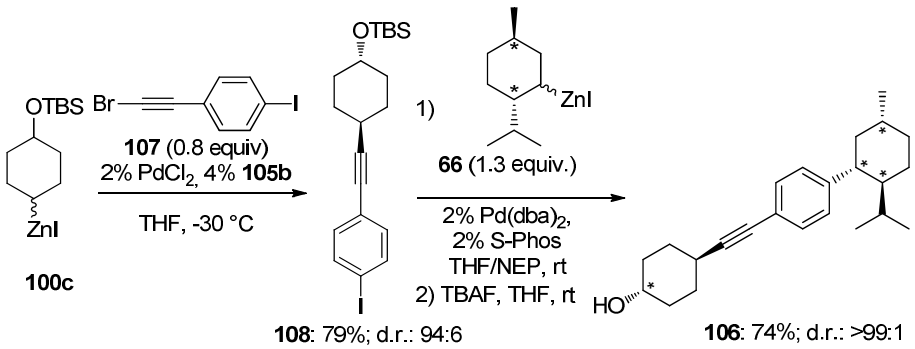
Entry		Product	Yield [%][a] (d.r.)[b]
1		**103a**: R= Ph	76 (97:3)
2		**103b**: R= 4-NC-C_6H_4	84 (96:4)
3		**103c**: R= $(CH_2)_2$OTBS	79 (98:2)
4		**103d**: R= TIPS	75 (96:4)
5		**103e**: R= $(CH_2)_2$OTBS	74 (95:5)
6		**103f**: R= TIPS	71 (95:5)
7		**103g**: R= $(CH_2)_2$OTBS	88 (96:4)
8		**103h**: R= TIPS	93 (95:5)
9		**103i**: R= 4-NC-C_6H_4	94 (96:4)

[a] Isolated yield of analytically pure product. [b] Determined by capillary GC analysis before and after purification. The percentage of regioisomers produced as byproducts was between 1-6%. See the experimental section.

trans-1,4-Disubstituted cyclohexanes,[107] including their alkynyl-substituted derivatives,[108] constitute important building blocks for liquid crystals due to their unique properties, such as low

[107] (a) R. Eidenschink, D. Erdmann, J. Krause, L. Pohl, *Angew. Chem. Int. Ed. Engl.* **1977**, *16*, 100; (b) D. Pauluth, K. Tarumi, *J. Mater. Chem.* **2004**, *14*, 1219; (c) R. Dąbrowski, *Mol. Cryst. Liq. Cryst.* **2004**, *421*, 1; (d) P. Kirsch, M. Bremer, *Angew. Chem. Int. Ed.* **2000**, *39*, 4216; (e) V. F. Petrov, S. I. Torgova, L. A. Karamysheva, S. Takenaka, *Liq. Cryst.* **1999**, *26*, 1141.
[108] (a) B. Chen, G. Sun, S. Xu, *Liq. Cryst.* **2004**, *31*, 767; (b) B. Chen, G. Sun, S. Xu, *Liq. Cryst.* **2004**, *31*, 421.

viscosity coefficients and higher optical anisotropy. The new coupling procedure offers a direct and highly stereoselective access to such compounds (Table 9). Supramolecular chirality can be induced in liquid crystals via the use of chiral dopants.[109] Since menthyl-capped dopants[110] have already been successfully applied for amplifying chirality in liquid crystals, we envisioned the synthesis of **106**, which may serve as a building block for chiral dopants due to its structural similarity to some 1,4-disubstituted cyclohexyl-based mesogens.[108] Thus, the functionalized cyclohexylzinc reagent **100c** was subjected to cross-coupling with the bromoalkyne **107** furnishing the *trans*-1,4-cyclohexylalkyne **108** (79%; d.r.: 94:6; Scheme 37). The aromatic iodo substituent of **108** allowed a further cross-coupling with (–)-menthylzinc iodide (**66**) using $Pd(dba)_2$ and SPhos[80] as catalyst system. Deprotection with TBAF furnished the rod-shaped, chiral product **106** with complete diastereoselectivity (74%; d.r.: >99:1).



Scheme 37: Sequential diastereoselective Csp^3-Csp and Csp^3-Csp^2 coupling leading to **106**, a potential building block for chiral dopants.

[109] R. Eelkema, B. L Feringa, *Org. Biomol. Chem.* **2006**, *4*, 3729.
[110] (a) J.-H. Liu, P.-C. Yang, H.-J. Hung, D.-J. Liaw, *Liq. Cryst.* **2007**, *34*, 891; (b) A. Yu. Bobrovsky, V. P. Shibaev, *Adv. Funct. Mater.* **2002**, *12*, 367; (c) R. A. Vora, A. K. Prajapati, J. B. Kevat, K. K. Raina, *Liq. Cryst.* **2001**, *28*, 983; (d) A. Yu. Bobrovsky, N. I. Boiko, V. P. Shibaev, E. Prudnikova, S. I. Torgova, *Liq. Cryst.* **2000**, *27*, 1381; (e) M. M. Green, S. Zanella, H. Gu, T. Sato, G. Gottarelli, S. K. Jha, G. P. Spada, A. M. Schoevaars, B. Feringa, A. Teramoto, *J. Am. Chem. Soc.* **1998**, *120*, 9810.

2.3 Diastereoselective Fe-mediated Csp^2-Csp^3 cross-couplings between aryl Grignard reagents and cyclic iodohydrine derivatives

2.3.1 Introduction

Transition-metal catalyzed cross-coupling reactions have been established as indispensible tools for C-C bond forming reactions in modern organic synthesis.[35] Most of these reactions depend on the use of Pd- or Ni-based complexes as catalysts. Although these metals are used in only catalytic amounts, they have the disadvantage of toxicity[111] and/or high costs.[112] Fe-mediated coupling reactions[113] were found to be a valuable alternative since Fe is one of the most abundant transition-metals and its salts are inexpensive and environmentally benign. Despite spectacular advances[114] and insights into the role of Fe in coupling reactions,[115] only few stereoselective versions of Fe-mediated or -catalyzed Csp^3-couplings are known.[40, 41, 116] Since our method for the diastereoselective cross-coupling of substituted cyclohexylzinc reagents (chapters **2.1** and **2.2**)[101, 117] could not be applied to the preparation of α-arylated cyclohexanol derivatives of type **36**, with the required zinc reagent **109** being subject to fast elimination leading to cyclohexene

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[111] (a) *Handbook on the Toxicology of Metals* (Eds.: L. Friberg, G. F. Nordberg, V. B. Vouk), Elsevier, Amsterdam, **1986**; (b) M. N. Hughes, *Compr. Coord. Chem.* **1987**, *67*, 643; (c) *Nickel and the Skin: Absorption, Immunology, Epidemology, and Metallurgy* (Eds.: J. J. Hostynek, H. I. Maibach), CRC Press, Boca Raton, **2002**.

[112] World market prices for Pd: 515 $ per ounce and Ni 10 $ per pound.

[113] (a) E. Nakamura, N. Yoshikai, *J. Org. Chem.* **2010**, *75*, 6061; (b) W. M. Czaplik, M. Mayer, J. Cvengroš, A. Jacobi von Wangelin, *ChemSusChem* **2009**, *2*, 396; (c) A. Correa, O. G. Mancheño, C. Bolm, *Chem. Soc. Rev.* **2008**, *37*, 1108; (d) B. D. Sherry, A. Fürstner, *Acc. Chem. Res.* **2008**, *41*, 1500; (e) A. Fürstner, R. Martin, *Chem. Lett.* **2005**, *34*, 624; (f) C. Bolm, J. Legros, J. Le Paih, L. Zani, *Chem. Rev.* **2004**, *104*, 6217; (g) S. M. Neumann, J. K. Kochi, *J. Org. Chem.* **1975**, *40*, 599. (h) M. Tamura, J. K. Kochi, *J. Am. Chem. Soc.* **1971**, *93*, 1487.

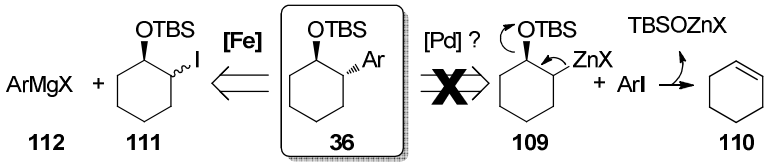
[114] (a) T. Hatakeyama, T. Hashimoto, Y. Kondo, Y. Fujiwara, H. Seike, H. Takaya, Y. Tamada, T. Ono, M. Nakamura, *J. Am. Chem. Soc.* **2010**, *132*, 10674; (b) T. Hatakeyama, S. Hashimoto, K. Ishizuka, M. Nakamura, *J. Am. Chem. Soc.* **2009**, *131*, 11949; (c) B.-J. Li, L. Xu, Z.-H. Wu, B.-T. Guan, C.-L. Sun, B.-Q. Wang, Z.-J. Shi, *J. Am. Chem. Soc.* **2009**, *131*, 14656; (d) W. M. Czaplik, M. Mayer, A. Jacobi von Wangelin, *Angew. Chem. Int. Ed.* **2009**, *48*, 607; (e) G. Cahiez, L. Foulgoc, A. Moyeux, *Angew. Chem. Int. Ed.* **2009**, *48*, 2969; (f) M. Carril, A. Correa, C. Bolm, *Angew. Chem. Int. Ed.* **2008**, *47*, 4862; (g) A. Guérinot, S. Reymond, J. Cossy, *Angew. Chem. Int. Ed.* **2007**, *46*, 6521; (h) T. Hatakeyama, M. Nakamura, *J. Am. Chem. Soc.* **2007**, *129*, 9844; (i) G. Cahiez, V. Habiak, C. Duplais, A. Moyeux, *Angew. Chem. Int. Ed.* **2007**, *46*, 4364; (j) R. B. Bedford, M. Betham, D. W. Bruce, A. A. Danopoulos, R. M. Frost, M. Hird, *J. Org. Chem.* **2006**, *71*, 1104; (k) A. Fürstner, A. Leitner, *Angew. Chem. Int. Ed.* **2002**, *41*, 609; (l) A. Fürstner, A. Leitner, M. Méndez, H. Krause, *J. Am. Chem. Soc.* **2002**, *124*, 13856.

[115] (a) S. L. Buchwald, C. Bolm, *Angew. Chem. Int. Ed.* **2009**, *48*, 5586; (b) J. Kleimark, A. Hedström, P.-F. Larsson, C. Johansson, P.-O. Norrby, *ChemCatChem* **2009**, *1*, 152; (c) D. Noda, Y. Sunada, T. Hatakeyama, M. Nakamura, H. Nagashima, *J. Am. Chem. Soc.* **2009**, *131*, 6078; (d) S. H. Wunderlich, P. Knochel, *Angew. Chem. Int. Ed.* **2009**, *48*, 9717; (e) A. Fürstner, K. Majima, R. Martin, H. Krause, E. Kattnig, R. Goddard, C. W. Lehmann, *J. Am. Chem. Soc.* **2008**, *130*, 1992.

[116] (a) S. Ito, T. Itoh, M. Nakamura, *Angew. Chem. Int. Ed.* **2011**, *50*, 454; (b) M. Nakamura, K. Matsuo, T. Inoue, E. Nakamura, *Org. Lett.* **2003**, *5*, 1373; (c) M. Nakamura, A. Hirai, E. Nakamura, *J. Am. Chem. Soc.* **2000**, *122*, 978; for a diastereoselective $CoCl_2$-catalyzed coupling see: (d) H. Ohmiya, H. Yorimitsu, K. Oshima, *J. Am. Chem. Soc.* **2006**, *128*, 1886.

[117] T. Thaler, L.-N. Guo, P. Mayer, P. Knochel, *Angew. Chem. Int. Ed.* **2011**, *manuscript accepted*.

(**110**), we envisioned a new retrosynthetic approach for their stereoselective synthesis (Scheme 38).



Scheme 38: Retrosynthesis of 2-arylcyclohexanol derivatives (**36**).

Products of type **36** are versatile building blocks for pharmaceuticals,[118] chiral ligands[119] and auxiliaries.[120] They are usually obtained by the opening of the corresponding epoxides with aryl organometallics. Enantioselective versions of this opening are of limited scope.[121] In fact, the most efficient procedures for the desymmetrization of oxacycles using aryl Grignard reagents are only reported for oxabenzonorbornadienes[122] and 2,3-disubstituted 7-oxabicyclo[2.2.1]hept-5-enes.[116b-c] These problems can be solved by an alternative retrosynthesis involving a diastereoselective coupling of the readily available iodohydrine derivative **111** with ArMgX **112** (Scheme 38).

2.3.2 Development of the Fe-mediated diastereoselective cross-coupling

In preliminary experiments, we have examined the cross-coupling of the TBS-protected iodohydrine **111** with PhMgCl in the presence of various Fe-salts (Table 10). Thus, the addition of PhMgCl to the cyclohexyl iodide (**111**, 75:25 *cis*:*trans* mixture) in the presence of 10% Fe(salen)Cl[114l, 123] exclusively resulted in the formation of protonated product (*c*HexOTBS; entry 1 of Table 10). Further attempts with Fe-salts, such as $Fe(acac)_3$[114i] and $FeCl_3$,[40a] in catalytic amounts furnished the desired cross-coupling product **36a** with 27% yield at best and diastereoselectivities between d.r.: 76:24 and 96:4 (entries 2-4).

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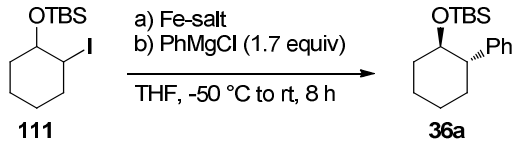
[118] R. G. Naik, V. N. Mumbaikar, R. Vasumathy, A. D. Lakdawala, M. B. Alreja, B. Lal, J. Blumbach, K. U. Weithmann, R. R. Bartlett, K. S. Joshi, S. Bal-Tembe, S. Raghavan (Hoechst AG), US 6159988, **2000**.
[119] K. Kumazawa, K. Ishihara, H. Yamamoto, *Org. Lett.* **2004**, *6*, 2551.
[120] J. K. Whitesell, *Chem. Rev.* **1992**, *92*, 953.
[121] (a) N. Oguni, Y. Miyagi, K. Itoh, *Tetrahedron Lett.* **1998**, *39*, 9023; (b) S. G. Davies, S. Wollowitz, *Tetrahedron Lett.* **1980**, *21*, 4175.
[122] R. Millet, L. Gremaud, T. Bernardez, L. Palais, A. Alexakis, *Synthesis* **2009**, 2101.
[123] R. B. Bedford, D. W. Bruce, R. M. Frost, J. W. Goodby, M. Hird, *Chem. Commun.* **2004**, 2822.

Table 10: Optimization of the conditions for the diastereoselective cross-coupling.



111 **36a**

Entry	Metal Mediator	Additive	Yield [%][a]	d.r.[a]
1[b]	10% Fe(salen)Cl	-	0[c]	n. d.
2[d]	10% $Fe(acac)_3$	20% TMEDA, 10% HMTA[e]	traces	n. d.
3[d]	5% $FeCl_3$	TMEDA (1.2 equiv)	17	76:24
4	10% $FeCl_3$	10% DPEphos	27	96:4
5	$FeCl_2$·2LiCl (0.85 equiv)	-	59 (48)	96:4
6	$FeCl_2$·2LiCl (0.85 equiv)	TMEDA (1.2 equiv)	86	83:17
7[f]	**$FeCl_2$·2LiCl (0.85 equiv)**	**4-fluorostyrene (0.5 equiv)**	**78 (61)**	**96:4**
8[g]	$FeCl_2$·2LiCl (0.85 equiv) (99.99% Fe)	4-fluorostyrene (0.5 equiv)	73 (57)	96:4
9	10% $Ni(acac)_2$	10% DPEphos	traces	n. d.

[a] Determined by capillary GC analysis. Tridecane ($C_{13}H_{28}$) was used as internal standard. Numbers in brackets indicate isolated yields. [b] 2.0 equiv of PhMgCl were used. [c] Only *c*HexOTBS was obtained. [d] 1.2 equiv of PhMgCl were used. [e] HMTA: hexamethylenetetramine [f] The use of catalytic amounts of $FeCl_2$·2 LiCl did not lead to a satisfactory conversion of **111**. [g] ICP analysis showed that no traces of other transition metals were present in the reaction mixture apart from Fe.

Significant improvements were achieved by using substoichiometric amounts (0.85 equiv) of the in THF well soluble $FeCl_2$·2 LiCl complex[115d] which preferentially gave the thermodynamically more stable *trans*-isomer[124] **36a** in 48% isolated yield (59% GC yield) and with a d.r. of 96:4

[124] The relative stereoconfiguration of **36i** was determined via X-ray crystallography.

(entry 5). The addition of TMEDA[40a] led to a deterioration of the diastereoselectivity (d.r.: 83:17; entry 6). Using 4-fluorostyrene as additive, which is known to facilitate the reductive elimination step in Ni-catalyzed cross-couplings,[125] resulted in a higher isolated yield of 61% (78% GC yield) with an excellent d.r. of 96:4 (entry 7).[126, 127] In order to elucidate whether traces of other transition metals present in the reaction mixture were responsible for the cross-coupling, we used $FeCl_2$ with a purity of 99.99% (Alfa Aesar; entry 8). Thereby, **36a** was obtained with a similar yield of 57% (73% GC yield). Using a combination of 10% $Ni(acac)_2$ and 10% DPEphos (*bis*(2-diphenylphosphinophenyl)ether)[128] as catalyst gave **36a** only in traces (<3%; entry 9).

2.3.3 Scope of the Fe-mediated diastereoselective cross-coupling

Next, we have examined the scope of the diastereoselective Fe-mediated cross-coupling using various functionalized arylmagnesium reagents (Table 11). These Grignard reagents were prepared either by LiCl-promoted insertion of Mg[129] or by a Br/Mg-exchange using *i*PrMgCl·LiCl.[130] In all cases, the thermodynamically favored *trans*-1,2-disubstituted cyclohexanols were preferentially formed with d.r. ≥95:5.[131] Arylmagnesium reagents bearing methyl and trifluoromethyl groups were efficiently coupled with high d.r. (95:5 to 99:1 ; entries 1-3). The cross-couplings of the bulky naphthalen-1-ylmagnesium bromide and the sterically congested mesitylmagnesium bromide with **111** gave the *trans*-products **36e-f** with high yields (80-90%) and excellent diastereoselectivities (d.r.: 98:2 to >99:1; entries 4-5). Grignard reagents bearing sensitive cyano-functions underwent smooth couplings with **4** furnishing the respective products **36g-h** with 62-65% yield as single diastereomers (entries 6-7).

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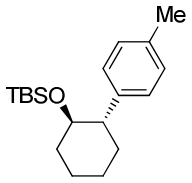
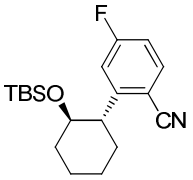
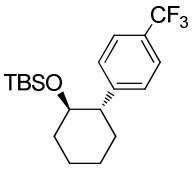
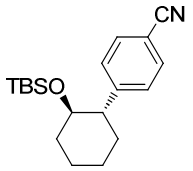
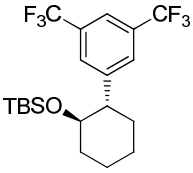
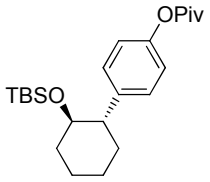
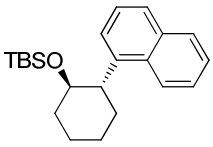
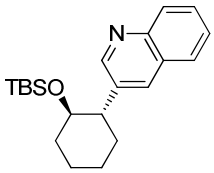
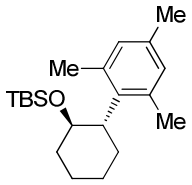
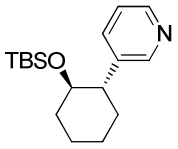
[125] A. E. Jensen, P. Knochel, *J. Org. Chem.* **2002**, *67*, 79.
[126] We assume that a low-valent diaryliron complex is the nucleophilic species in the coupling. A [4-fluorostyrene·Fe(A(r)C_6H_{10}OTBS] complex may form. Complexation with the electron-poor 4-fluorostyrene facilitates the reductive elimination process.
[127] The use of TIPS-protected 2-iodocyclohexanol led to the same d.r. (96:4) whereas protection with the bulky TBDPS-group resulted in a decreased diastereoselectivity (d.r.: 90:10).
[128] M. Kranenburg, Y. E. M. van der Burgt, P. C. J. Kamer, K. Goubitz, J. Fraanje, P. W. N. M. van Leeuwen, *Organometallics* **1995**, *14*, 3081.
[129] F. M. Piller, A. Metzger, M. A. Schade, B. A. Haag, A. Gavryushin, P. Knochel, *Chem. Eur. J.* **2009**, *15*, 7192.
[130] A. Krasovskiy, P. Knochel, *Angew. Chem. Int. Ed.* **2004**, *43*, 3333.
[131] The relative stereoconfiguration of **36i** was determined via X-ray crystallography.

Table 11: Products of the diastereoselective cross-coupling with **111**.

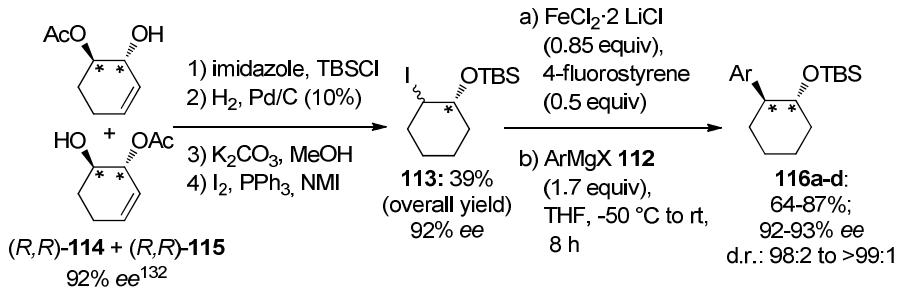
Entry	Product	Yield [%][a] (d.r.)[b]	Entry	Product	Yield [%][a] (d.r.)[b]
1	 **36b**	62 (95:5)	6	 **36g**	65 (>99:1)
2	 **36c**	67 (99:1)	7	 **36h**	62 (>99:1)
3	 **36d**	75 (97:3)	8	 **36i**	62 (95:5)
4	 **36e**	90 (98:2)	9	 **36j**	57 (>99:1)
5	 **36f**	80 (>99:1)	10	 **36k**	80 (>99:1)

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

Although a pivaloyloxy function is a well known leaving group in Fe-catalyzed cross-couplings with Grignard reagents,[114c] the reaction of (4-(pivaloyloxy)phenyl)magnesium bromide (4-$PivOC_6H_4MgBr$) with **111** exclusively led to the formation of **36i** (62%; d.r.: 95:5; entry 8). Heteroaryl Grignard reagents, such as 3-quinolinylmagnesium bromide and 3-

pyridinylmagnesium chloride, were also successfully coupled giving **36j** and **36k** as single diastereomers (entries 9-10).

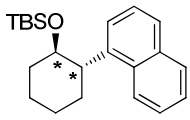
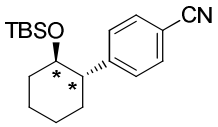
In order to underline its synthetic utility, we applied this reaction to the cross-coupling of the enantioenriched 2-iodocyclohexanol derivative **113** which was obtained from the readily prepared mixture of (*R,R*)-**114** and (*R,R*)-**115**[132] (92% ee) in only 4 steps with an overall yield of 39% (Scheme 39).



Scheme 39: Preparation and cross-coupling of the chiral 2-iodocyclohexanol **9** (NMI: *N*-methylimidazole).

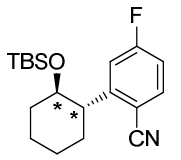
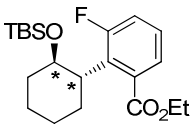
The Fe-mediated cross-couplings of **113** with various aryl Grignard reagents produced the *trans*-products **116a-d** in a stereoconvergent manner with no loss of chirality (92-93% *ee*) and excellent diasteteroselectivities (d.r.: ≥98:2; Table 12).

Table 12: Products of type **12** of the Fe-mediated cross-coupling with enantioenriched **113**.

Entry	Product	Yield[a] (d.r.)[b]	*ee*[c]
1	 **116a**	87% (98:2)	92%
2	 **116b**	64% (>99:1)	92%

[132] S. Demay, F. Volant, P. Knochel, *Angew. Chem. Int. Ed.* **2001**, *40*, 1235.

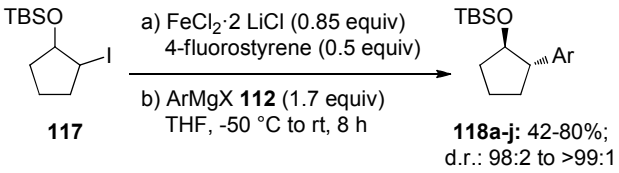
Table 12 continued

3	 **116c**	69% (>99:1)	93%
4	 **116d**	73% (>99:1)	92%

[a] Isolated yield of analytically pure product. [b] Determined by capillary GC analysis before and after purification. [c] Enantiomeric excess (*ee*) was determined by chiral HPLC. See appendix.

Thus, the reaction is suitable for an efficient propagation of stereoinformation and represents a valuable alternative to enantioselective openings of *symmetrical* epoxides.

Finally, we have tried this diastereoselective Fe-mediated coupling on the TBS-protected 2-iodocyclopentanol **117** using various functionalized (hetero)aryl Grignard reagents (Scheme 40).



Scheme 40: Diastereoselective cross-coupling of the 2-iodocyclopent-anol derivative **117**.

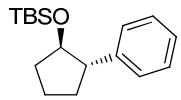
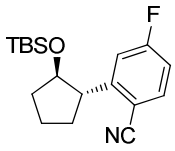
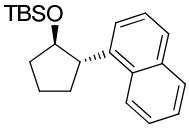
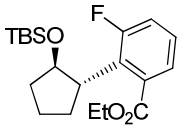
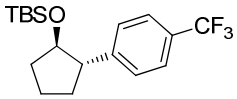
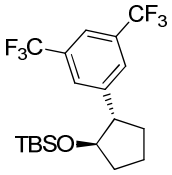
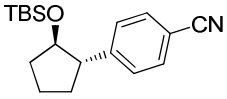
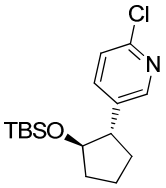
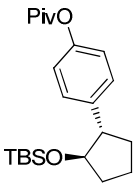
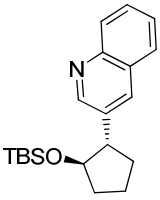
To our delight, the *trans*-coupling products[133] **118a-j** were obtained with excellent d.r. from 98:2 to >99:1 (Table 13). *trans*-2-Arylcyclopentanols are reported to constitute important building blocks for drugs treating diabetes[134] and chiral phosphine ligands.[135]

[133] The relative stereoconfiguration of **118d** was determined via desilylation. The crystals of the resulting alcohol proved suitable for X-ray crystallography.

[134] (a) E. Sher (Eli Lilly and Company), WO 2002089848, **2002**; (b) T. A. Shepherd, J. A. Aikins, D. Bleakman, B. E. Cantrell, J. P. Rearick, R: L. Simon, E. C. R. Smith, G. A. Stephenson, D. M. Zimmerman, *J. Med. Chem.* **2002**, *45*, 2101.

[135] B. E. Bosch, A. Monsees, U. Dingerdissen, P. Knochel, E. Hupe (Degussa AG), WO 2002014330, **2002**.

Table 13: Products of the diastereoselective cross-coupling with **117**.

Entry	Product	Yield [%][a] (d.r.)[b]	Entry	Product	Yield [%][a] (d.r.)[b]
1	 **118a**	56 (98:2)	6	 **118f**	68 (>99:1)
2	 **118b**	80 (>99:1)	7	 **118g**	69 (>99:1)
3	 **118c**	65 (>99:1)	8	 **118h**	68 (>99:1)
4	 **118d**	75 (>99:1)	9	 **118i**	42 (>99:1)
5	 **118e**	60 (>99:1)	10	 **118j**	60 (>99:1)

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

2.4 Diastereoselective arylations of substituted piperidines via Pd-Catalyzed Csp^3-Csp^2 cross-couplings

2.4.1 Introduction

Substituted piperidines are ubiquitous structural motifs present in numerous bioactive alkaloids.[53] In order to ensure appropriate biological activity, many of them have to be prepared in a stereodefined manner.[53] Therefore, the development of efficient methods for the diastereoselective construction of piperidines bearing more than one stereocenter represents an important synthetic task.[136] Still, procedures for the direct stereoselective arylation of the piperidine ring are scarce.[137] Only one isolated example of the diastereoselective coupling of a 2-methylpiperidinyl organometallic with 4-bromoveratrole furnishing the *trans*-2,6-disubstituted product has been reported.[137c] So far the direct stereoselective synthesis of 2,4- and 2,5-disubstituted arylated piperidines via Csp^3-Csp^2 cross-coupling remains a challenging problem. Following our series of diastereoselective cross-couplings with substituted cycloalkyl derivatives (chapters **2.1**, **2.2** and **2.3**),[101, 117, 138] we extended our investigations to the heterocyclic piperidinyl system. In chapter **2.1**, it was shown that the cross-couplings of substituted cyclohexylzinc reagents with diverse aryl halides result in the stereoconvergent formation of the thermodynamically favored arylpalladium intermediates which after reductive elimination afford

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[136] (a) A. Larivée, A. B. Charette, *Org. Lett.* **2006**, *8*, 3955; (b) T. A. Johnson, D. O. Jang, B. W. Slafer, M. D. Curtis, P. Beak, *J. Am. Chem. Soc.* **2002**, *124*, 11689; (c) M. K. S. Vink, C. A. Schortinghuis, J. Luten, J. H. van Maarseveen, H. E. Schoemaker, H. Hiemstra, F. P. J. T. Rutjes, *J. Org. Chem.* **2002**, *67*, 7869; (d) P. S. Watson, B. Jiang, B. Scott, *Org. Lett.* **2000**, *2*, 3679; (e) M. A. Wijdeven, F. L. van Delft, F. P. J. T. Rutjes, *Tetrahedron* **2010**, *66*, 5623; ((f) M.-E. Ragoussi, S. M. Walker, A. Piccanello, B. M. Kariuki, P. N. Horton, N. Spencer, J. S. Snaith, *J. Org. Chem.* **2010**, *75*, 7347; (g) M. M. A. R. Moustafa, B. L. Pagenkopf, *Org. Lett.* **2010**, *12*, 4732; (h) A. Guérinot, A. Serra-Muns, C. Gnamm, C. Bensoussan, S. Reymond, J. Cossy, *Org. Lett.* **2010**, *12*, 1808; (i) T. Urushima, D. Sakamoto, H. Ishikawa, Y. Hayashi, *Org. Lett.* **2010**, *12*, 4588; (j) M. Z. Chen, G. C. Micalizio, *Org. Lett.* **2009**, *11*, 4982; (k) J. M. Humphrey, E. P. Arnold, T. A. Chappie, J. B. Feltenberger, A. Nagel, W. Simon, M. Suarez-Contreras, N. J. Tom, B. T. O'Neill, *J. Org. Chem.* **2009**, *74*, 4525; (l) Y. Chen, C. Zhong, J. L. Petersen, N. G. Akhmedov, X. Shi, *Org. Lett.* **2009**, *11*, 2333; (m) J. L. Bilke, S. P. Moore, P. O'Brien, J. Gilday, *Org. Lett.* **2009**, *11*, 1935; (n) G. Barbe, M. St-Onge, A. B. Charette, *Org. Lett.* **2008**, *10*, 5497; (o) S. Mix, S. Blechert, *Adv. Synth. Catal.* **2007**, *349*, 157; (p) G. A. Cortez, R. R. Schrock, A. H. Hoveyda, *Angew. Chem.* **2007**, *119*, 4618; *Angew. Chem. Int. Ed.* **2007**, *46*, 4534; (q) M. Amat, O. Bassas, N. Llor, M. Cantó, M. Pérez, E. Molins, J. Bosch, *Chem. Eur. J.* **2006**, *12*, 7872; (r) G. S. Kauffman, P. S. Watson, W. A. Nugent, *J. Org. Chem.* **2006**, *71*, 8975; (s) A. Takemiya, J. F. Hartwig, *J. Am. Chem. Soc.* **2006**, *128*, 6042; (t) H. M. Peltier, J. A. Ellman, *J. Org. Chem.* **2005**, *70*, 7342; (u) H. Poerwono, K. Higashiyama, T. Yamauchi, H. Kubo, S. Ohmiya, H. Takahashi, *Tetrahedron* **1998**, *54*, 13955.

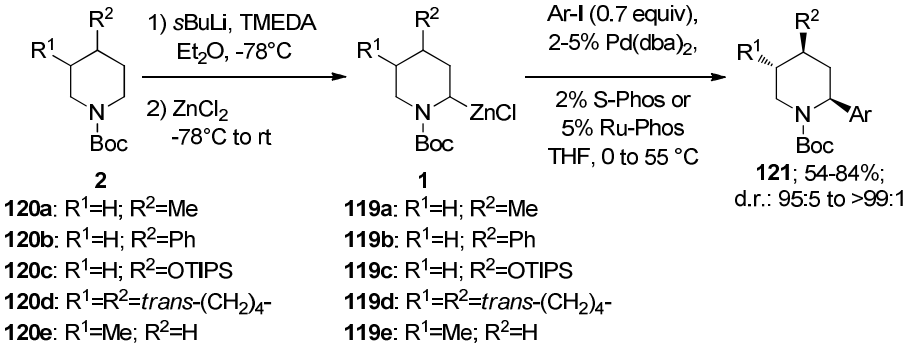
[137] (a) H. Prokopcová, S. D. Bergman, K. Aelvoet, V. Smout, W. Herrebout, B. Van der Veken, L. Meerpoel, B. U. W. Maes, *Chem. Eur. J.* **2010**, *16*, 13063; (b) S. J. Pastine, D. V. Gribkov, D. Sames, *J. Am. Chem. Soc.* **2006**, *128*, 14220; for stereoselective versions see: (c) I. Coldham, D. Leonori, *Org. Lett.* **2008**, *10*, 3923; (d) R. Shintani, N. Tokunaga, H. Doi, T. Hayashi, *J. Am. Chem. Soc.* **2004**, *126*, 6240; (e) M. Amat, J. Bosch, J. Hidalgo, M. Cantó, M. Pérez, N. Llor, E. Molins, C. Miravitlles, M. Orozco, J. Luque, *J. Org. Chem.* **2000**, *65*, 3074; (f) M. Amat, M. Pérez, A. T. Minaglia, J. Bosch, *J. Org. Chem.* **2008**, *73*, 6920.

[138] A. K. Steib, T. Thaler, P. Mayer, P. Knochel, *Angew. Chem. Int. Ed.* **2011**, *manuscript accepted*.

the desired arylated products with retention of configuration (d.r. up to >99:1).[101] 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 nitrogen,[139] we were able to prepare both the *cis*- and *trans*-2,4-disubstituted piperidine derivatives with excellent levels of diastereoselectivity.

2.4.2 Cross-coupling of 3- and 4-substituted piperidin-2-ylzinc reagents

First, we have generated various piperidin-2-ylzinc reagents of type **119** starting from the respective piperidines **120a-e** according to the procedures of *Beak*[140] and *Coldham*.[137c] To our delight, the Pd-catalyzed cross-coupling of **119a-e** with various aryl and heteroaryl iodides using 2% SPhos[80] or 5% RuPhos[141] (dicyclohexyl(2',6'-diisopropoxy-[1,1'-biphenyl]-2-yl)phosphine) and 2-5% $Pd(dba)_2$ as catalyst system furnished the desired α-arylated products **121** in 54-84% yield and with an exceptional level of diastereoselectivity (d.r. of 95:5 to >99:1; Scheme 41).



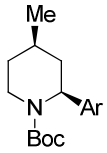
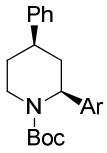
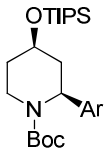
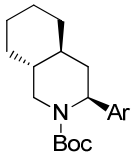
Scheme 41: Preparation and diastereoselective cross-coupling of 4- and 5-substituted *N*-Boc piperidin-2-ylzinc reagents (**119**).

Thus, cross-coupling of the 4-methyl-substituted piperidinylzinc reagent **119a** with electron-rich 4-iodoanisole using 2% $Pd(dba)_2$ and 2% SPhos at 55 °C furnished exclusively the *cis*-configured

[139] (a) H. Paulsen, K. Todt, *Angew. Chem. Int. Ed. Engl.* **1966**, *5*, 899. (b) R. A. Johnson, *J. Org. Chem.* **1967**, *33*, 3627.
[140] (a) P. Beak, W. K. Lee, *J. Org. Chem.* **1993**, *58*, 1109; (b) P. Beak, W. K. Lee, *J. Org. Chem.* **1990**, *55*, 2578.
[141] M. D. Charles, P. Schultz, S. L. Buchwald, *Org. Lett.* **2005**, *7*, 3965.

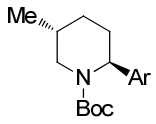
product **121a** in 78% yield (entry 1 of Table 14).[142] Coupling of **119a** with electron-poor aryl iodides and 4-iodopyridine under the same conditions gave the products **121b-f** with d.r. from 95:5 to 98:2 (entries 2-6).

Table 14: Diastereoselective cross-coupling of substituted piperdin-2-ylzinc reagents.

Entry		Product	Yield [%][a] (d.r.)[b]
1		**121a**: Ar= 4-MeO-C_6H_4	78 (>99:1)[c]
2		**121b**: Ar= 4-F_3C-C_6H_4	81 (95:5)[c]
3		**121c**: Ar= 3-Cl-C_6H_4	76 (96:4)[c]
4		**121d**: Ar= 3-NC-C_6H_4	64 (97:3)[c]
5		**121e**: Ar= 4-EtO_2C-C_6H_4	67 (98:2)[c]
6		**121f**: Ar= 4-pyridinyl	73 (95:5)[c]
7		**121g**: Ar= 4-F_3C-C_6H_4	64 (97:3)[d]
8		**121h**: Ar= 4-NC-C_6H_4	79 (>99:1)[d]
9		**121i**: Ar= 4-MeO_2C-C_6H_4	67 (99:1)[d]
10		**121j**: Ar= 4-EtO_2C-C_6H_4	84 (97:3)[e]
11[e]		**121k**: Ar= 4-F-C_6H_4	83 (95:5)[e]
12[e]		**121l**: Ar= 4-F_3C-C_6H_4	81 (95:5)[e]
13[e]		**121m**: Ar= 4-NC-C_6H_4	81 (97:3)[e]
14		**121n**: Ar= 4-F_3C-C_6H_4	69 (>99:1)[d]
15		**121o**: Ar= 4-NC-C_6H_4	54 (>99:1)[d]
16		**121p**: Ar= 4-MeO-C_6H_4	60 (97:3)[d]

[142] The relative configurations of **121d** and **121h** were directly determined via X-ray analysis. The relative configurations of **121n** and **121q** were determined via acidic removal of the Boc-protective group and subsequent tosylation. The crystals of the tosylates (**121na** and **121qa**) proved suitable for X-ray analysis. See appendix.

Table 14 continued

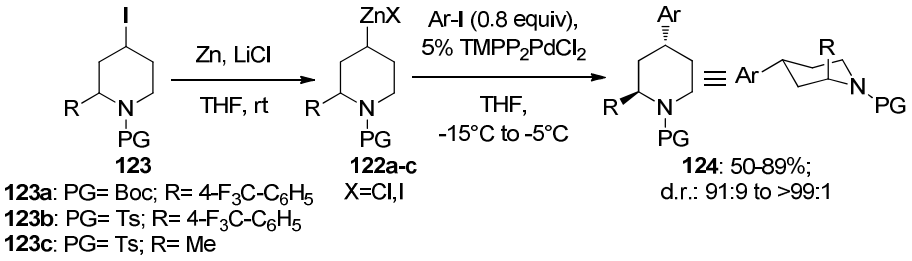
17		**121q**: Ar= 4-NC-C_6H_4	62 (96:4)[f]
18		**121r**: Ar= 4-EtO_2C-C_6H_4	59 (95:5)[f]

[a] Isolated yield of analytically pure product. [b] Determined by capillary GC or ^1H /^{13}C NMR analysis. [c] 2% $Pd(dba)_2$, 2% SPhos, THF, 55 °C, 12 h. [d] 5% $Pd(dba)_2$, 5% RuPhos, THF, 55 °C, 12 h. [e] 5% $Pd(dba)_2$, 5% RuPhos, THF, 55 °C, 60 h. [f] 5% $Pd(dba)_2$, 5% Ru-Phos, THF, 0 °C (6 h), then rt (12 h), then 40 °C (12 h).

The piperidinylzinc reagent **119b** bearing a large phenyl ring instead of the smaller methyl-substituent provided, under slightly altered conditions (5% $Pd(dba)_2$ and 5% RuPhos at 55 °C), the *cis*-products **121g-i** with comparable yields (64-79%) and equally high diastereoselectivities (97:3 to >99:1; entries 7-9). Even the functionalized piperidinylzinc reagent **119c** bearing an OTIPS ($OSi(iPr)_3$) group in position 4 reacted smoothly furnishing the *cis*-α-arylated products **121j-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 *Beak*'s method[140] we were able for the first time to regioselectively metalate this heterocycle at position 3. Cross-coupling of the resulting organozinc species **119d** led to the stereodefined 2,4,5-trisubstituted products **121n-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 **119e**, lower temperatures were necessary for achieving high diastereoselectivities (Table 14). Thus, the *trans*-2,5-disubstituted products **121q-r** were obtained in moderate yields of 59-62% with a high d.r. of 95:5 (entries 17-18).[142]

2.4.3 Cross-coupling of 2-substituted piperidin-4-ylzinc reagents

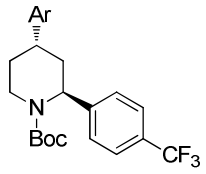
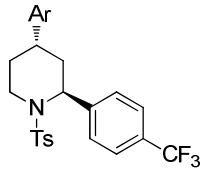
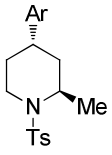
Complementary to the diastereoselective preparation of the *cis*-2,4-disubstituted piperidines, we were also able to implement the synthesis of the corresponding *trans*-isomers by switching the positions of the substituent and the C-Zn bond. Thus, in preliminary experiments, we have prepared the 2-substituted piperidin-4-ylzinc reagent **122a** via LiCl-promoted Zn-insertion into the iodide **123a**[79] and subjected it to cross-coupling with 4-iodobenzonitrile and iodobenzene using 5% $TMPP_2PdCl_2$[83] as catalyst (Scheme 42).[101]



Scheme 42: Preparation and diastereoselective cross-coupling of 2-substituted piperidin-4-ylzinc iodides (**122**).

The *trans*-coupling products **124a-b** were obtained in 50-74% yield with diastereoselectivities of d.r.: 91:9 and 92:8 (entries 1 and 2 of Table 15).[143]

Table 15: Diastereoselective cross-coupling of 2-substituted piperidin-4-ylzinc reagents.

Entry	Product	Yield [%][a] (d.r.)[b]
1	 **124a**: Ar= 4-NC-C_6H_4	74 (91:9)
2	**124b**: Ar= Ph	50 (92:8)
3	 **124c**: Ar= 4-NC-C_6H_4	70 (>99:1)
4	**124d**: Ar= 4-MeO_2C-C_6H_4	69 (96:4)
5	 **124e**: Ar= 4-NC-C_6H_4	84 (97:3)
6	**124f**: Ar= 4-MeO_2C-C_6H_4	89 (97:3)

[a] Isolated yield of analytically pure product. [b] Determined by capillary GC or ^1H /^{13}C NMR analysis.

[143] The relative configuration of **124a** was determined via acidic removal of the Boc-protective group and subsequent tosylation. The crystals of the tosylate proved suitable for X-ray analysis. The relative configurations of **124c** and **124e** were directly determined via X-ray analysis. See appendix for details.

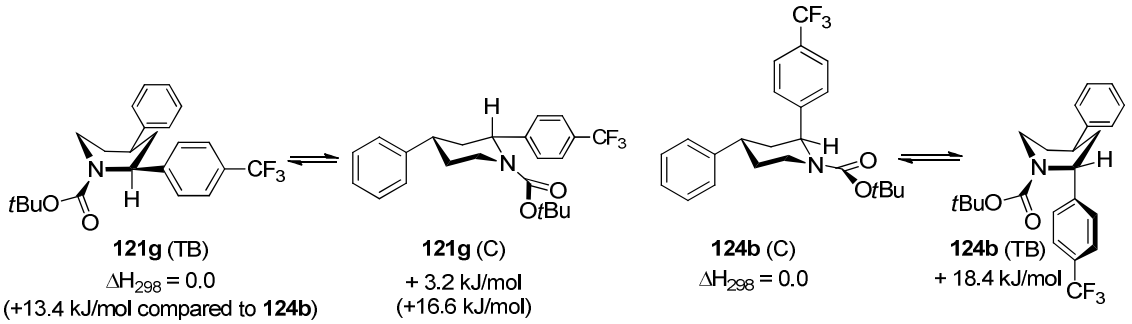
By examining the NMR spectra of the *N*-Boc protected products **124a** and **124b**, we found that both revealed the presence of two Boc-conformers at room temperature. These findings are supported by DFT-analysis.[144] Furthermore, X-ray structures of the already prepared *N*-Boc protected piperidines **121d** and **121h**[142] (entries 6 and 8 of Table 14) showed a twisted ring conformation, whereas the structures of the *N*-Ts protected piperidines **121na** and **121qa**[142] displayed an almost perfect chair-like structure. We, therefore, prepared the corresponding *N*-tosylated zinc reagent **122b**. Cross-coupling of **122b** with 4-iodobenzonitrile under the same reaction conditions led to the *exclusive formation* of the *trans*-isomer **124c** in 70% yield (entry 3). Remarkably, the couplings of the zinc reagent **122c** bearing only a small methyl group in position 2 also gave the respective *trans*-isomers **124e-f** with an excellent diastereoselectivity of d.r.: 97:3 (entries 5 and 6).

2.4.4 Mechanistic considerations

In order to explain the distinct stereochemical outcome of these couplings, the *cis*/*trans* stability differences between **121g** and **124b** together with the respective data for the Zn- and Pd-intermediates were analyzed at the B3LYP/631SVP level (Scheme 43 and Table 16).[145] From our former studies (chapter **2.1**),[101] 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. The stabilities of the products (**121g** and **124b**) and of the corresponding zinc intermediates have been calculated in order to refine our mechanistic picture. In contrast to the corresponding cyclohexanes, in which an overall equatorial substitution pattern is thermodynamically preferred,[101] the pseudo-allylic strain in *N*-Boc piperidines caused by the partial double-bond character of the amide bond forces the substituent vicinal to the nitrogen into an axial orientation.[139] Therefore, *cis*-isomer **121g** was found to be significantly less stable (by 13.4 kJ/mol) than *trans*-isomer **124b**. Detailed DFT conformational analysis (chair vs. twist boat) shows that the energy difference between the chair and twist boat conformation is negligible for **121g**, whereas it is large for **124b**.

[144] ^{1}H and ^{13}C NMR analyses of **124a** and **124b** at 70 °C showed an average spectrum of the two conformers. This finding is supported by the conformational analysis of product **124b** at the B3LYP/6-31G(d,p) level.

[145] The theoretical methods used herein are identical to those in chapter **2.1**[90] and involve the combination of the B3LYP hybrid functional with the def2-SVP all-electron basis set on Zn, the ECP-based def2-SVP basis set on Pd, and the 6-31G(d,p) basis set on all other elements.

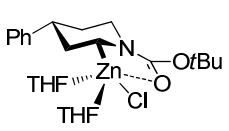
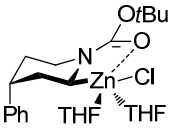
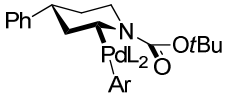
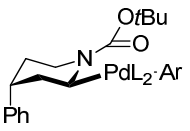
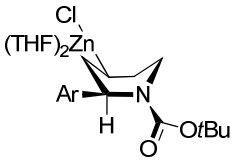
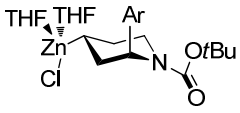
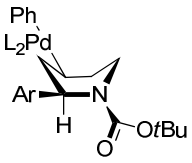
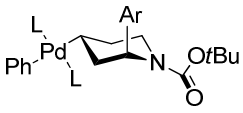


Scheme 43: DFT-conformational analysis of *cis*-isomer **121g** and *trans*-isomer **124b**. Conformations are indicated as twist-boat (TB) or chair (C).

The stabilities of the respective Pd- and Zn-intermediates involved in the formation of the cross-coupling products **121g** and **124b** have been calculated using the same model as in our recent study of the analogous cyclohexyl systems (chapter **2.1**).[101] 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 **119b**, 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*-**119b** by 15.4 kJ/mol (entry 1 of Table 16). Since pseudo-allylic strain in the 4-zincated piperidinyl species **122a** 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*-**122a** 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*-**125** and *ax*-**125**; entry 1), in which the square-planar coordination sphere of Pd is not perturbed, this natural preference is augmented 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[139] takes effect and causes axial orientation (*ax*-**126** vs. *eq*-**126**; entry 2). Without this interaction, diaxial repulsions dictate equatorial orientation of the aryl/alkyl substituent (*eq*-**125** vs. *ax*-**125**; entry 1).

Table 16: DFT calculation-based conformational analysis on the diastereomeric zinc and palladium complexes.

Entry	Zn-intermediates[a] $\Delta H^{298}_{ax\text{-}eq}$ [kJ/mol][b]		Pd-intermediates[a,c] $\Delta H^{298}_{ax\text{-}eq}$ [kJ/mol][b]	
	 *eq*-**119b** (C)	 *ax*-**119b** (C)	 *eq*-**125** (C)	 *ax*-**125** (C)
1	+15.4		+15.0	
	 *eq*-**122a** (TB)	 *ax*-**122a** (C)	 *eq*-**126** (TB)	 *ax*-**126** (C)
2	-8.4		-8.6	

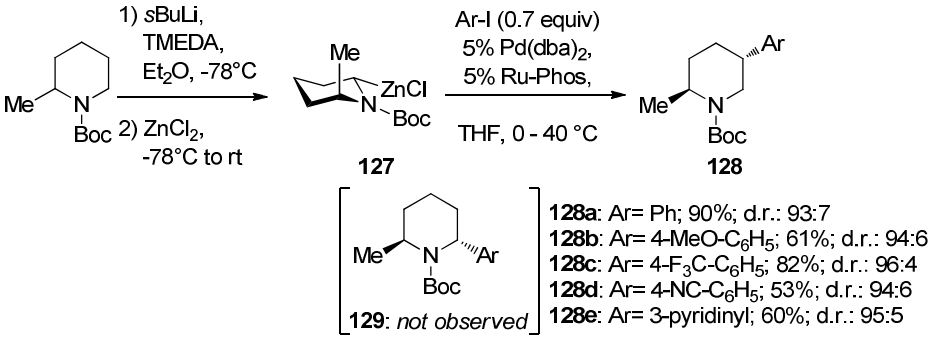
[a] Ar= 4-F_3C-C_6H_4. Preferred conformations are indicated as twist-boat (TB) or chair (C). [b] Calculated energetic differences (B3LYP/631SVP) between the thermodynamically lowest conformers of the two diastereomers. [c] L= PMe_3.

Considering the energetic differences of the organometallic intermediates, the diastereoselectivity in the couplings of the piperidinylzinc reagents (**119** and **122**) is always determined on the stage of the respective Pd-complexes via a selective transmetalation step leading to the thermodynamically most stable intermediate, as proposed for the cyclohexyl systems (chapter **2.1**).[101]

2.4.5 Diastereoselective Pd-1,2-migration

In continuation of our study, we found by performing cross-couplings with the 2-methyl-substituted piperidin-2-ylzinc reagent **127**, a consistent highly stereoselective formation of the 5-arylated *trans*-configured products of type **128** (d.r.: 93:7 to 96:4),[146] whereas the expected *trans*-2,6-disubstituted product **129** was not obtained (Scheme 44). It is noteworthy that the coupling proceeded equally well with electron-rich (**128b**) and electron-poor aryl iodides (**128c-e**).

[146] The relative configuration of **128c** was determined via acidic removal of the Boc-protective group and subsequent tosylation. The crystals of the tosylate proved suitable for X-ray analysis.



Scheme 44: Diastereoselective cross-coupling of 6-substituted *N*-Boc piperidin-2-ylzinc chloride (**127**) – observation of a 1,2-migration.

We assume that this reaction proceeds via β-hydride elimination of the Pd moiety.[147] The resulting $ArPdL_2H$[148] complex stays bound to the same side of the tetrahydropyridinyl ring and its subsequent *syn*-addition[149] places the Pd in the sterically less hindered position 5. Rapid reductive elimination furnishes the observed δ-arylated 2,5-disubstituted coupling products (**128**).

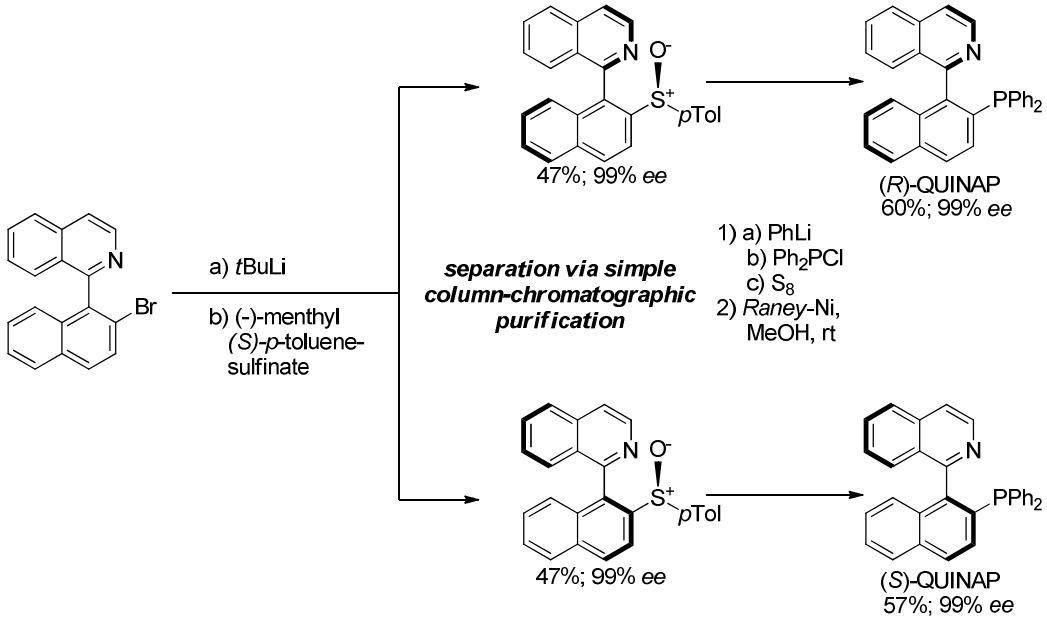
[147] (a) R. Ogawa, Y. Shigemori, K. Uehara, J. Sano, T. Nakajima, I. Shimizu, *Chem. Lett.* **2007**, *36*, 1338. (b) G. C. Lloyd-Jones, P. A. Slatford, *J. Am. Chem. Soc.* **2004**, *126*, 2690 and references therein.
[148] (a) I. D. Hills, G. C. Fu, *J. Am. Chem. Soc.* **2004**, *126*, 13178; (b) V. V. Grushin, *Chem. Rev.* **1996**, *96*, 2011; (c) R. F. Heck, *Acc. Chem. Res.* **1979**, *12*, 146.
[149] (a) A. F. Schmidt, V. V. Smirnov, *Kinet. Catal.* **2003**, *44*, 518; (b) P. M. Henry, G. A. Ward, *J. Am. Chem. Soc.* **1972**, *94*, 673.

3. Summary

This work dealt with two different subjects: enantiocontrol with chiral sulfoxides and diastereocontrol in the cross-coupling reactions of substituted cycloalkyl and piperidinyl derivatives. The enantiocontrol exerted by chiral sulfoxides was used for the design of a novel enantioselective synthesis of chiral QUINAP and the preparation and use of new chiral sulfoxide-alkene hybrid ligands in the *Hayashi-Miyaura* reaction. The diastereocontrol in the Pd-catalyzed cross-couplings of substituted cycloalkylzinc reagents was thoroughly examined and its scope was extended to the use of 1,3- and 1,4-substituted cyclohexylzinc reagents. These diastereoselective cross-couplings were shown to be applicable to both (hetero)aryl halides and alkynyl bromides. The diastereoselective synthesis of cyclic 2-arylalcohol derivatives which are not accessible via this method was achieved by developing a complementary Fe-mediated cross-coupling of aryl Grignard reagents with protected cyclic 2-iodohydrines. Finally, the diastereoselective Pd-catalyzed cross-coupling was applied to various substituted piperidinylzinc reagents allowing a convenient and stereoselective access to the pharmacologically important class of arylated piperidines. Thereby, a stereoselective 1,2-Pd migration was discovered in the cross-coupling of 6-methyl substituted piperidin-2-ylzinc chloride with aryl iodides.

3.1 Novel enantioselective QUINAP synthesis via diastereomeric sulfoxide intermediates

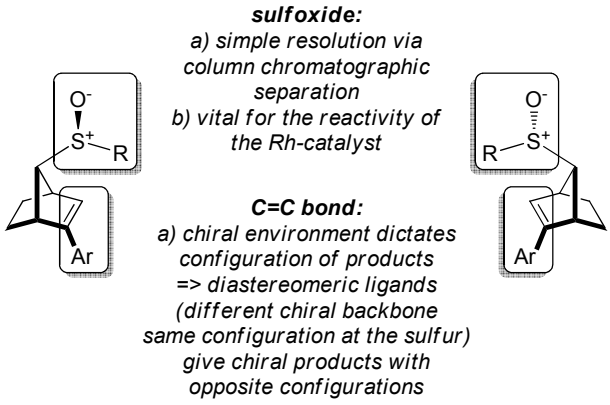
In summary, we have developed a novel practical resolution of chiral QUINAP avoiding the use of half-equivalents of Pd salts. Both (*S*)- and (*R*)-QUINAP were efficiently obtained (Scheme 45). In terms of yields, time and effort, this approach readily competes with the conventional preparation.[52] Furthermore, the chiral organolithium intermediate gives the possibility for the preparation of various QUINAP analogues, as it may be trapped with a broad range of electrophiles.



Scheme 45: Novel synthesis of chiral QUINAP via chiral sulfoxide-intermediates.

3.2 Development of sulfoxide-alkene hybrids as a novel class of chiral ligands for the *Hayashi-Miyaura* reaction

We have developed a concise, protective group free synthesis of sulfoxide-alkene hybrid ligands which combine the properties of chiral sulfoxide and olefin ligands (Scheme 46). Chiral resolution is achieved via simple column chromatographic separation of the diastereomeric ligands which can both be efficiently used in the *Hayashi-Miyaura* reaction furnishing the chiral products with excellent yields, equally high enantioselectivities and opposite stereoconfigurations.

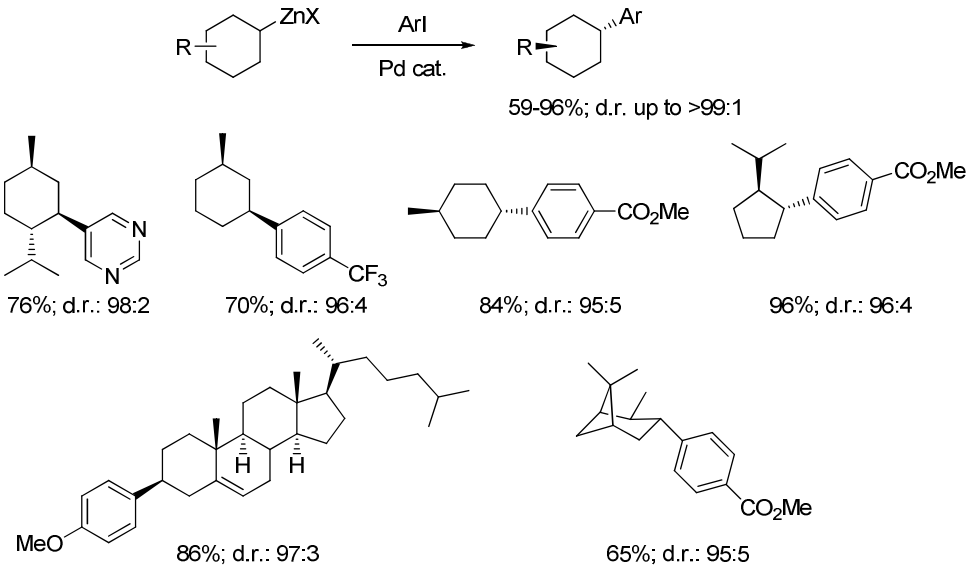


Scheme 46: New chiral ligand class combining the properties of sulfoxide and alkene ligands.

Experiments with analogues of **46a** and **46b** with different steric and electronic properties showed that coordination of the sulfinyl group represents a crucial factor for efficient chelation and formation of the reactive Rh-complex. Although efficient binding of the alkenyl moiety to the Rh is less important for the reaction to proceed, its chiral environment dictates the stereochemical outcome.

3.3 Diastereoselective Csp^3-Csp^2 cross-couplings with 1,2-, 1,3- and 1,4-substituted cycloalkylzinc compounds

A highly diastereoselective method for the cross-coupling of variously substituted cycloalkylzinc reagents with aryl and heteroaryl halides using Pd-catalysis has been successfully developed. Remarkably, not only substituents in position 2 strongly influence the diastereoselectivity of the cross-coupling, but also substituents in positions 3 and 4 of the cyclohexyl ring. Excellent diastereoselectivities are also obtained for bicyclic systems, cyclopentane derivatives and steroids (Scheme 47).

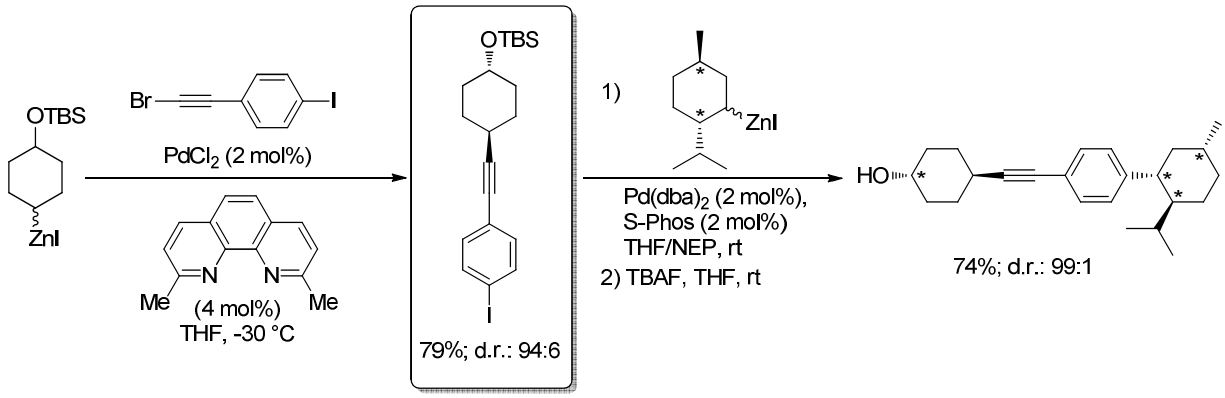


Scheme 47: Pd-catalyzed diastereoselective cross-coupling of substituted cycloalkylzinc reagents.

In order to understand the origin of this diastereoselectivity, we performed NMR experiments on a Pd-intermediate and DFT calculations which clearly show that remote substituents (e.g. in position 4) exert a strong influence on the stability of the resulting Pd-intermediates. Based on these results, a tentative mechanism has been proposed.

3.4 Diastereoselective Csp^3-Csp cross-couplings between 1,3- and 1,4-substituted cyclohexylzinc reagents and bromoalkynes

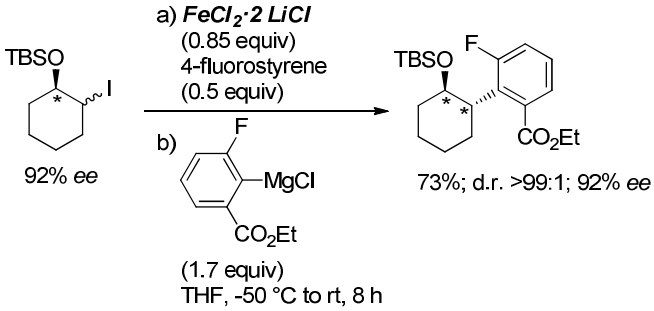
A general and highly diastereoselective method for the Pd-catalyzed cross-coupling of 3- and 4-substituted cyclohexylzinc reagents with alkynyl bromides via remote stereocontrol was developed. With the easily available and inexpensive *ortho*-phenanthroline-derivative neocuproine as ligand, diastereomeric ratios of up to 98:2 were achieved. The method can be used for the synthesis of building blocks which may be relevant for the synthesis of liquid crystal mesogens and their chiral dopants (Scheme 48).



Scheme 48: Sequential diastereoselective Csp^3-Csp and Csp^3-Csp^2 coupling for the preparation of potential chiral dopants for liquid crystals.

3.5 Diastereoselective Fe-mediated Csp^2-Csp^3 cross-couplings

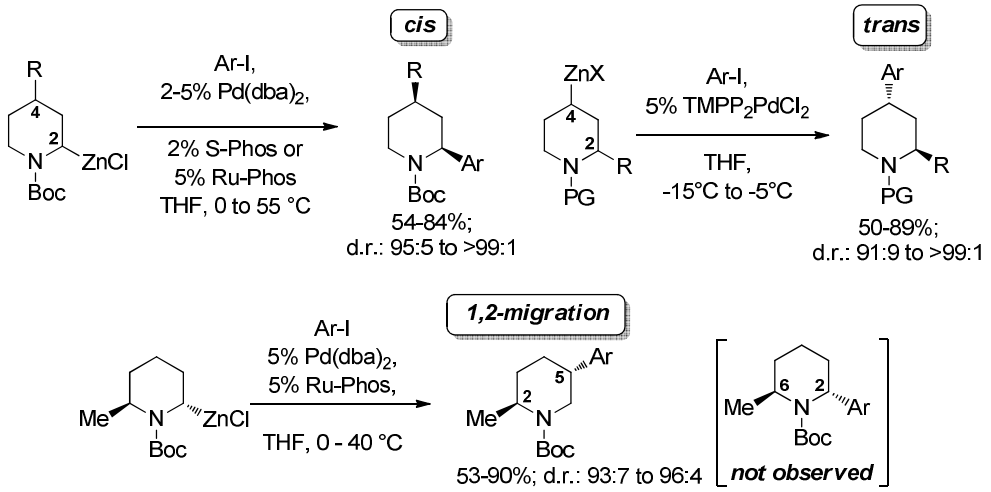
A highly diastereoselective method for the Fe-mediated cross-coupling of cyclic TBS-protected iodohydrines with aryl Grignard reagents was disclosed with Fe being truly the mediating transition-metal in the coupling. The method can be applied to a broad range of functionalized (hetero)arylmagnesium reagents furnishing the respective *trans*-2-arylcycloalcohol derivatives with d.r. up to >99:1. The stereoconvergent cross-coupling of chiral TBS-protected 2-iodocyclohexanol provides the corresponding 2-arylcyclohexanols with no loss of chirality (Scheme 49). Therefore, this method represents a valuable alternative to the enantioselective opening of *symmetrical* epoxides.



Scheme 49: Diastereoselective Fe-mediated cross-coupling.

3.6 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. At will, either the *trans*- or the *cis*-2,4-disubstituted piperidines can be obtained by choosing the position of the reactive C-Zn bond (C2 vs. C4; Scheme 50). DFT-calculations on the relative stabilities of the Pd-intermediates show that the stereoselectivity is determined by a selective formation of the respective thermodynamically most stable Pd-complex. A novel Pd-1,2-migration further expands this method to the stereoselective preparation of 5-arylated 2,5-disubstituted piperidines (Scheme 50).



Scheme 50: Directable diastereoselective cross-coupling of substituted piperidinylzinc reagents and Pd-1,2-migration.

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 or nitrogen. Syringes which were used to transfer reagents and solvents were purged with argon or nitrogen prior to use.

1.1. Solvents

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

CH_2Cl_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_2O 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

***i*PrMgCl·LiCl** solution in THF was purchased from Chemetall.

***i*PrMgCl** solution in THF was purchased from Chemetall

PhMgCl solution in THF was purchased from Chemetall

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

***s*BuLi** solution in cyclohexane was purchased from Chemetall.

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

PhLi solution was prepared by slowly adding *t*BuLi (1.5 M in *n*-pentane; 2.2 ml; 3.3 mmol) to a solution of iodobenzene (0.337 g; 1.65 mmol) in anhydrous Et_2O (3 ml) at -78 °C under argon atmosphere. The reaction mixture was stirred for 10 min at -78°C before it was allowed to reach

room temperature. The solvents were subsequently removed *in vacuo* until a white precipitate remained. The flask was then flushed with argon and recooled to -78°C. Anhydrous THF (3 ml) were carefully added and the mixture was then allowed to warm to 0°C in order to receive a homogeneous solution. The reagent was not stored but immediately used in the respective reaction.

Content determination of organometallic reagents:

The respective organometallic reagents were titrated using either the method reported by *Paquette*[150] or *Knochel*[151] prior to their use.

$ZnCl_2$ solution (1.0 M) was prepared by drying $ZnCl_2$ (100 mmol, 136 g) in a *Schlenk*-flask under high vacuum at 140 °C for 5 h. After cooling to room temperature, anhydrous THF (100 mL) was added and stirring was continued until the salt was dissolved. The reagent was stirred under a nitrogen atmosphere.

$MgCl_2$ solution (0.5 M) was prepared by drying magnesium turnings (0.73 g, 30 mmol) in a *Schlenk*-flask under high vacuum at 140 °C for 15 min. After cooling to room temperature anhydrous THF (60 mL) was filled in. The mixture was vigorously stirred and 1,2-dichloroethane (2.38 mL, 30 mmol) was carefully added dropwise until all magnesium filings had been consumed (15 h; caution, exothermic reaction! , gas development). The reagent was stirred under a nitrogen atmosphere.

$FeCl_2 \cdot 2LiCl$ solution (1.0 M) was prepared by drying LiCl (110 mmol, 4.7 g) in a *Schlenk*-flask under high vacuum at 150 °C for 3 h. After cooling to room temperature under argon, $FeCl_2$ (50 mmol, 6.34 g) was added under a nitrogen atmosphere inside a glove-box. The *Schlenk*-flask was further heated to 130 °C for 5 h under high vacuum, cooled to room temperature and charged with anhydrous THF (50 mL) under argon. The mixture has to be stirred for approximately 4 h until all solids are dissolved. The reagent appears as a dark brown solution that is stable for several weeks at room temperature.

$CuCN \cdot 2LiCl$ solution (1.0 M) was prepared by drying CuCN (80.0 mmol, 7.17 g) and LiCl (160 mmol, 6.77 g) in a *Schlenk*-tube under high vacuum at 140 °C for 5 h. After cooling to room temperature, anhydrous THF (80 mL) was added under argon and stirring was continued until the

[150] H.-S. Lin, L. A. Paquette, *Synth. Commun.* **1994**, *24*, 2503.
[151] A. Krasovskiy, P. Knochel, *Synthesis* **2006**, 890.

salt was dissolved. The Schlenk-tube was wrapped in an aluminum-foil to protect from light. The reagent appears as a slightly greenish solution and has to be stored under argon.

$LaCl_3 \cdot 2LiCl$ solution (0.3 M in THF) was purchased from Chemetall.

1.3. Chromatography

Flash column chromatography was performed using silica gel 60 (0.040-0.063 mm) from Merck or Florisil® (60-100 mesh) from Alfa Aesar.

Thin layer chromatography was performed using SiO_2 pre-coated aluminum 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:

- K_2CO_3 (40 g), $KMnO_4$ (6.0 g) in H_2O (600 mL), then 10% NaOH (5 mL) was added.
- Phosphomolybdic acid (5.0 g), $Ce(SO_4)_2$ (2.0 g) and conc. H_2SO_4 (12 mL) in H_2O (230 mL).
- Phosphomolybdic acid (16.0 g) in EtOH (40 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 δ-values in ppm relative to the residual solvent peaks of $CHCl_3$ (δ_H : 7.25, δ_C : 77.0), benzene (δ_H : 7.16, δ_C : 128.4), THF (δ_{H1} : 1.73, δ_{H2} : 3.58, δ_{C1} : 25.4, δ_{C2} : 67.6) or 1,4-dioxane (δ_H : 3.53, δ_C : 66.7). 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) spectra were either recorded on a FINNIGAN MAT 95Q (EI) or a Thermo Finnigan LTQ FT instrument (ESI). Electron impact ionization (EI) was conducted with an electron energy of 70 eV. Electrospray ionization (ESI) was conducted with an IonMax ion-source equipped with an ESI head. ESI spectroscopy was performed with a voltage of 4 kV at the spray capillary tube, a heating filament temperature of 250 °C and a nitrogen gas flow of 25 units.

For the combination of gas chromatography with mass spectroscopic detection (low resolution spectra), 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 DuraSampl*IR* II Diamond ATR sensor was used. The absorption bands are reported in wavenumbers (cm^{-1}).

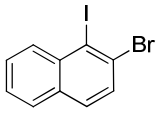
Melting points (m.p.) were determined on a BÜCHI B-540 apparatus and are uncorrected.

High Performance Liquid Chromatography (HPLC) was performed using a Gynkotec-HPLC (GINA 50) with a diode-array UV-VIS detector. Chiral columns: OD, OD-H, OJ, OB-H, AD, AD-H and AS-H (Daicel Chemical Industries) with *n*-heptane/*i*-propanol as mobile phase. Racemic compounds were used for optimizing the operation conditions for the resolution of the enantiomers and diastereomers.

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

2. Novel Synthesis of Chiral QUINAP.

2.1. Preparation of 2-bromo-1-iodonaphthalene



2-Bromo-1-naphthylamine[59] (6.2 g; 28 mmol) was suspended in a mixture of H_2O (220 mL) and H_2SO_4 (8.5 mL). The suspension was then cooled to 0°C by an ice bath and $NaNO_2$ (2.0 g; 29 mmol) was added portionwise (caution: spontaneous, exothermic reaction!). The reaction mixture was stirred for 1 h at 0°C before the excess of $NaNO_2$ was removed by addition of urea (1.6 g; 27 mmol). The reaction mixture was then carefully treated with KI (14.1 g; 85 mmol) under vigorous stirring at the same temperature. After 4 h of stirring at 0°C the reaction was allowed to warm to room temperature and was left to stir overnight. 100 mL Et_2O were added to the dark reddish suspension on the next day. The layers were separated and the aqueous phase was extracted with Et_2O (4 x 70 mL). The combined organic layers were washed with sat. $Na_2S_2O_3$ solution (2 x 25 mL), dried over $MgSO_4$ and the solvent was removed by a rotary evaporator. The resulting dark reddish solid was then subjected to purification via column chromatography (SiO_2; *n*-pentane) yielding the title compound as yellow crystals (6.6 g; 71%).

m. p.: 62–63 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ: 8.27 (d, *J*=7.9 Hz, 1H), 7.78 (d, *J*=7.9 Hz, 1H), 7.72 (s, 2H), 7.63-7.52 (m, 2H).

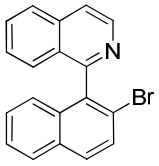
^{13}C-NMR ($CDCl_3$, 75 MHz): δ: 137.0, 134.2, 132.2, 130.2, 129.9, 129.0, 128.7, 127.0, 106.9.

MS (70 eV, EI): m/z (%): 335 (11), 334 (96), 333 (11), 332 (100) [$M+H^+$], 207 (24), 205 (24), 125.8 (68).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3087 (vw), 3065 (vw), 3050 (vw), 3014 (vw), 2984 (vw), 2445 (vw), 2299 (vw), 2076 (vw), 1956 (vw), 1937 (vw), 1925 (vw), 1904 (vw), 1838 (vw), 1820 (vw), 1809 (vw), 1753 (vw), 1724 (vw), 1698 (vw), 1669 (vw), 1614 (vw), 1579 (w), 1545 (m), 1493 (s), 1472 (vw), 1440 (vw), 1418 (vw), 1384 (vw), 1360 (vw), 1340 (w), 1300 (s), 1269 (vw), 1246 (s), 1206 (vw), 1165 (w), 1148 (vw), 1134 (w), 1103 (m), 1028 (w), 989 (vw), 958 (w), 941 (vs), 894 (vw), 862 (m), 843 (vw), 826 (m), 809 (vs), 762 (vs), 741 (vs), 650 (s), 619 (m).

HR MS (EI) for $C_{10}H_6BrI$ (331.8698): 331.8670.

2.2. Preparation of 1-(2-bromonaphthalen-1-yl)isoquinoline (40)



A 0.5 M solution of 2-bromo-1-iodonaphthalene (2.93 g; 8.8 mmol) in THF was placed in a dry and Ar-flushed *Schlenk*-flask equipped with a magnetic stirring bar. It was cooled to –78°C and a 1.2 M solution of *i*PrMgCl·LiCl (7.40 mL; 8.8 mmol) was slowly added. The reaction was allowed to proceed for 45 min at the same temperature before a 1.0 M solution of $ZnCl_2$ in THF (8.80 mL; 8.8 mmol) was slowly dropped to the yellowish mixture. After stirring for 30 min the reaction mixture was allowed to warm to 0°C and was then cannulated to a solution containing 1-iodoisoquinoline (2.04 g; 8.0 mmol), $Pd(dba)_2$ (0.230 g; 0.4 mmol) and tri(2-furyl)phosphine (*tfp*) in 16 mL dry THF. The resulting mixture was subsequently heated to 60°C and left to stir overnight at that temperature. After completion of the cross-coupling reaction (checked by GC-MS), the reaction was cooled to room temperature and sat. NH_4Cl solution (20 mL) was added. The layers were separated and the aqueous phase was extracted with 4 x CH_2Cl_2 (20 mL). The combined organic layers were first washed with brine (20 mL), then dried over $MgSO_4$. The solvents were removed *in vacuo*. The blackish crude product was subjected to column chromatography yielding the title compound as slightly yellow powder (1.98 g; 74%).

m. p.: 164–166 °C.

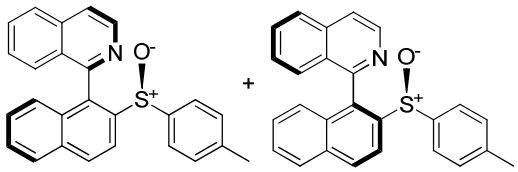
^{1}H-NMR ($CDCl_3$, 600 MHz): δ: 8.74 (d, *J*=5.7 Hz, 1 H), 7.95 (d, *J*=8.2 Hz, 1 H), 7.90 (d, *J*=8.2 Hz, 1 H), 7.86 (d, *J*=8.8 Hz, 1 H), 7.80 (d, *J*=5.7 Hz, 1 H), 7.78 (d, *J*=8.8 Hz, 1 H), 7.72 - 7.67 (m, 1 H), 7.50 - 7.46 (m, 1 H), 7.44 - 7.40 (m, 2 H), 7.32 - 7.27 (m, 1 H), 7.05 (d, *J*=8.6 Hz, 1 H).

^{13}C-NMR ($CDCl_3$, 150 MHz): δ: 159.4, 142.6, 136.7, 136.3, 133.9, 132.3, 130.4, 130.0, 129.8, 128.1, 127.8, 127.6, 127.2, 127.0, 126.8, 126.2, 125.9, 121.5, 120.6.

MS (70 eV, EI): m/z (%): 336 (11), 335 (60), 334 (100) [$M+H^+$], 333 (62) [M^+], 332 (88), 255 (11), 254 (46), 253 (63), 252 (46), 252 (19), 226 (11), 224 (10), 127 (39), 127 (4), 126 (15), 126 (21).

IR (ATR) $\tilde{\nu}$ **(cm^{-1}):** 3065 (w), 3052 (w), 2916 (vw), 1988 (vw), 1955 (vw), 1924 (vw), 1840 (vw), 1788 (vw), 1714 (vw), 1620 (w), 1581 (m), 1557 (m), 1502 (m), 1498 (m), 1449 (w), 1426 (vw), 1418 (vw), 1406 (w), 1377 (vw), 1340 (w), 1319 (m), 1310 (m), 1275 (w), 1258 (w), 1239 (w), 1205 (w), 1159 (w), 1135 (w), 1114 (m), 1070 (w), 1044 (w), 1024 (vw), 1012 (w), 994 (vw), 974 (vw), 963 (vw), 952 (m), 879 (w), 864 (m), 838 (s), 828 (vs), 818 (vs), 798 (m), 790 (m), 774 (m), 756 (vs), 744 (vs), 692 (s), 678 (m), 665 (m), 633 (s), 618 (w), 602 (m), 577 (m).
HR MS (EI) for $C_{19}H_{12}BrN$ (333.0153): 333.0129.

2.3. Preparation and resolution of (R_a)-1-(2-((*S*)-*p*-tolylsulfinyl)naphthalen-1-yl)isoquinoline (44) and (S_a)-1-(2-((*S*)-*p*-tolylsulfinyl)naphthalen-1-yl)isoquinoline (43)



44 **43**

A 0.2 M solution of 1-(2-bromo-1-naphthyl)isoquinoline (**40**) (3.34 g; 10 mmol) in anhydrous Et_2O was placed in a flame-dried *Schlenk*-flask equipped with a magnetic stirring bar under Ar-atmosphere. The solution was cooled to –78 °C and *t*BuLi (1.5 M in *n*-pentane; 13.4 mL; 20 mmol) was added dropwise. The reaction mixture was stirred for additional 30 min at -78°C before it was allowed to reach room temperature. It was then slowly and very carefully added to a 0.2 M solution of (–)-menthyl (*S*)-*p*-toluenesulfinate[18] (**1**; 3.53 g; 12 mmol) in THF which was kept at –78°C under Ar atmosphere. The reaction was left to proceed at –78 °C for 30 min before it was quenched with 2 M NaOH (10 mL) at –78 °C. (Alternatively, the organolithium reagent can be transmetalated with $MgCl_2$ (0.5 M in THF) at –78 °C before reacting with **1**. In this case, the reaction time does not need to be controlled and the reaction mixture can be allowed to warm to room temperature without epimerization at the sulfur.) It was then allowed to warm to room temperature and transferred to a separation funnel. The layers were separated and the aqueous layer was extracted with 3x CH_2Cl_2 (10 mL). The combined organic layers were washed with brine (5 mL) and dried over $MgSO_4$. The solvents were removed *in vacuo*. For purification and separation of the two sulfoxide diastereomers, the crude product was subjected to column chromatography with Florisil® (60-100 mesh). **44** was eluated with a Et_2O : *n*-pentane mixture of

4 : 1. **43** was eluated with a Et_2O : acetone mixture of 2 : 1. The two diastereomers were obtained as slightly yellow crystals yielding 1.89 g (47%) of **43** and 1.89 g (47%) of **44**.

(R_a)-1-(2-((*S*)-*p*-tolylsulfinyl)naphthalen-1-yl)isoquinoline (44)

m. p.: 148-150 °C.

^{1}H-NMR ($CDCl_3$, 600 MHz): δ: 8.72 (d, *J*=5.7 Hz, 1 H), 8.07 (d, *J*=8.8 Hz, 1 H), 7.99 - 7.95 (m, 2 H), 7.91 (d, *J*=8.2 Hz, 1 H), 7.84 (d, *J*=5.7 Hz, 1 H), 7.75 - 7.71 (m, 1 H), 7.61 (d, *J*=8.2 Hz, 2 H), 7.58 (d, *J*=8.4 Hz, 1 H), 7.52 - 7.56 (m, 1 H), 7.46 - 7.52 (m, 1 H), 7.32 - 7.37 (m, 1 H), 7.18 - 7.22 (m, 3 H), 2.32 (s, 3 H).

^{13}C-NMR ($CDCl_3$, 150 MHz): δ: 156.2, 142.8, 142.7, 141.3, 141.2, 135.9, 135.4, 134.0, 132.1, 130.1, 129.8, 129.2, 128.5, 128.3, 127.4, 127.2, 127.0, 127.0, 126.8, 126.3, 125.7, 121.2, 120.3, 21.1.

MS (70 eV, EI): m/z (%): 394 (28), 393 (100) [M^+], 374 (18), 373 (15), 343 (10), 342 (33), 285 (19), 283 (14), 254 (18), 253 (27), 252 (15).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3052 (w), 2921 (w), 2858 (vw), 1920 (b, vw), 1725 (vw), 1620 (vw), 1583 (w), 1556 (w), 1495 (w), 1450 (w), 1425 (vw), 1404 (w), 1376 (vw), 1342 (vw), 1315 (w), 1274 (vw), 1258 (w), 1237 (vw), 1205 (vw), 1179 (vw), 1165 (vw), 1140 (vw), 1120 (vw), 1082 (m), 1041 (vs), 1016 (m), 954 (m), 876 (w), 810 (vs), 780 (w), 746 (vs), 704 (w), 694 (s), 680 (w), 670 (m), 638 (s), 621 (w), 608 (vw), 574 (w).

HR MS (EI) for $C_{26}H_{19}NOS$ (393.1187): 393.1175.

(S_a)-1-(2-((*S*)-*p*-tolylsulfinyl)naphthalen-1-yl)isoquinoline (43)

m. p.: 99-101 °C.

^{1}H-NMR ($CDCl_3$, 600 MHz): δ: 8.79 (d, *J*=5.7 Hz, 1 H), 8.36 (d, *J*=8.8 Hz, 1 H), 8.21 (d, *J*=8.8 Hz, 1 H), 7.96 (d, *J*=8.2 Hz, 1 H), 7.84 (d, *J*=8.2 Hz, 1 H), 7.80 (d, *J*=5.7 Hz, 1 H), 7.55 (t, *J*=7.5 Hz, 1 H), 7.52 (t, *J*=7.2 Hz, 1 H), 7.28 - 7.24 (m, 1 H), 7.04 (d, *J*=8.6 Hz, 1 H), 7.01 (t, *J*=7.6 Hz, 1 H), 6.79 (d, *J*=8.2 Hz, 2 H), 6.69 - 6.65 (m, 3 H), 2.07 (s, 3 H).

^{13}C-NMR ($CDCl_3$, 150 MHz): δ: 156.9, 143.1, 142.0, 141.9, 140.6, 136.2, 136.2, 134.5, 131.9, 130.9, 130.8, 129.7, 128.7, 128.3, 128.3, 127.9, 127.5, 127.0, 126.9, 126.8, 124.8, 121.2, 120.5, 21.3.

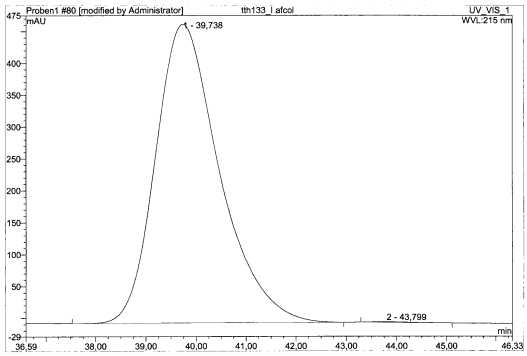
MS (70 eV, EI): m/z (%): 394 (28), 393 (100) [M^+], 375 (15), 374 (13), 343 (30), 285 (16), 283 (12), 254 (15), 253 (22), 252 (11).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3052 (vw), 2921 (vw), 2856 (vw), 1914 (b, vw), 1731 (vw), 1620 (vw), 1595 (vw), 1582 (w), 1556 (w), 1494 (w), 1450 (vw), 1437 (w), 1401 (w), 1372 (w), 1338 (vw), 1318 (m), 1257 (w), 1237 (w), 1194 (w), 1178 (w), 1164 (w), 1140 (vw), 1118 (w), 1082 (m), 1045 (vs), 1038 (vs), 1014 (s), 954 (m), 869 (w), 824 (s), 806 (vs), 779 (m), 746 (vs), 720 (s), 695 (vs), 670 (s), 637 (vs), 622 (s), 608 (m), 586 (m), 569 (m).

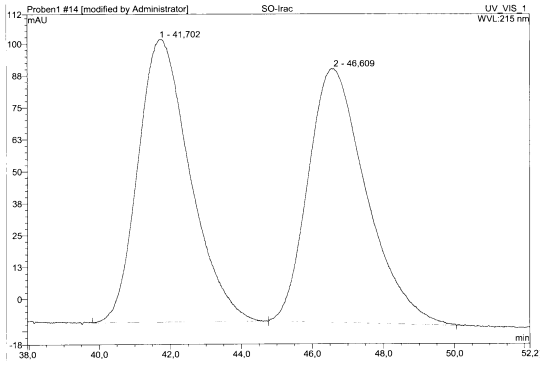
HR MS (EI) for $C_{26}H_{19}NOS$ (393.1187): 393.1197.

HPLC Data:

44: Chiralcel AD; *n*-heptane : *i*-propanol 80:20; flow: 0.5 mL/min

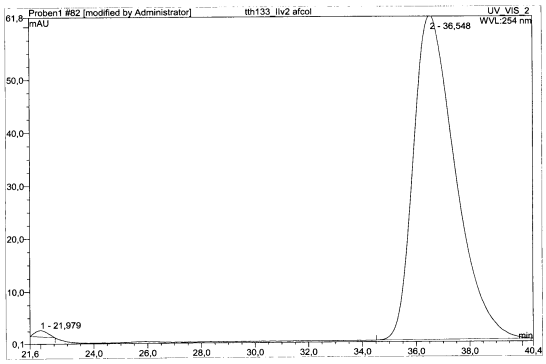


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	39,74	n.a.	468,974	692,954	99,90	n.a.	BMB
2	43,80	n.a.	0,765	0,706	0,10	n.a.	BMB*
Total:			469,739	693,661	100,00	0,000	

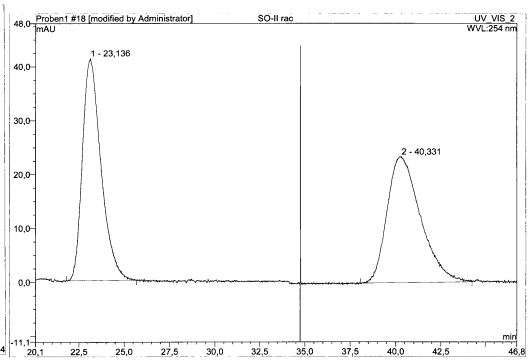


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	41,70	n.a.	110,715	187,141	49,86	n.a.	BMb*
2	46,61	n.a.	99,510	188,204	50,14	n.a.	bMB*
Total:			210,225	375,345	100,00	0,000	

43: Chiralcel AD; *n*-heptane : *i*-propanol 80:20; flow: 1.0 mL/min

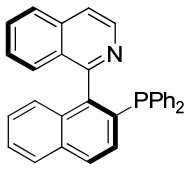


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	21,98	n.a.	1,214	0,688	0,61	n.a.	BMB*
2	36,55	n.a.	61,486	111,291	99,39	n.a.	BMB*
Total:			62,700	111,979	100,00	0,000	



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	23,14	n.a.	41,244	49,312	49,66	n.a.	BMB*
2	40,33	n.a.	23,423	49,980	50,34	n.a.	BMB*
Total:			64,667	99,292	100,00	0,000	

2.4 Enantioselective preparation of (S_a)-1-(2-(diphenylphosphino)naphthalen-1-yl)isoquinoline ((*S*)-QUINAP)



In a dry and Ar-flushed *Schlenk*-flask equipped with a stirring bar, iodobenzene (0.337 g; 1.65 mmol) was diluted in 3 mL Et_2O. The solution was then cooled to –78 °C and *t*BuLi (1.5 M in *n*-pentane; 2.2 mL; 3.3 mmol) was added dropwise. The reaction was stirred for 10 min at –78 °C before it was allowed to warm to room temperature. The solvents were subsequently removed *in vacuo* until a white precipitate remained. The flask was then flushed with Ar and cooled to –78 °C. 3 mL THF were carefully added and the mixture was then allowed to warm to 0°C in order to receive a homogeneous solution. The solution was then again cooled to –78 °C. A 0.5 M solution of **43** (0.590 g; 1.50 mmol) was added dropwise. The reaction was left to stir for 15 min at –78 °C before a 1.0 M solution of Ph_2PCl (0.397 g; 1.80 mmol) was slowly added. The reaction mixture was additionally stirred for 15 min at –78 °C before sulfur (0.063 g; 1.95 mmol) was added. The reaction mixture was then heated to 45 °C and left to stir overnight at that temperature. The reaction mixture was then cooled to room temperature and quenched with 10 mL NH_4Cl sat. solution before it was transferred to a separation funnel. The layers were separated and the aqueous phase was extracted with 3x 10 mL CH_2Cl_2. The combined organic layers were washed with brine (5 mL) and dried over $MgSO_4$. The solvents were removed *in vacuo* and the crude product was subjected to purification via column chromatography (SiO_2; Et_2O : *n*-pentane 1 : 2). The product was then redissolved in CH_2Cl_2 and 0.3 mL $MeSO_3H$ was added. The product was then filtrated over SiO_2 using pure Et_2O in order to remove the impurities and 5 mL NEt_3 in Et_2O in order to wash down the product. After removal of the solvents the product was redissolved in CH_2Cl_2 and transferred to a separation funnel. The organic phase was washed with NH_4Cl sat. solution (5 mL). The aqueous phase was extracted with 3x 10 mL CH_2Cl_2. The combined organic layers were dried over $MgSO_4$. The solvent was evaporated. (*S*)-**45** was directly subjected to desulfurisation with *Raney*-Ni: Therefore, *Raney*-Ni (30 equiv) was placed in a N_2-flushed flask. It was washed five times with MeOH and finally suspended in MeOH. A solution of (*S*)-**45** in MeOH/THF was then dropped to the *Raney*-Ni suspension. The

reaction was left to stir overnight at room temperature. Filtration and removal of the solvent yielded (*S*)-QUINAP (0.395 g; 60%; *99% ee*) as a white solid. The preparation of (*R*)-QUINAP was analogous (0.376 g; 57%; *99% ee*).

m. p.: 224.6-226.8 °C. (217.4-218.6 °C for (*R*)-QUINAP)

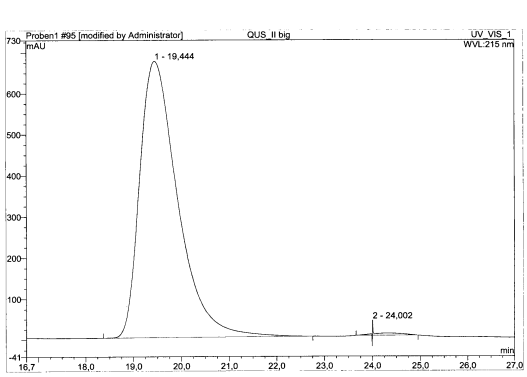
^{1}H-NMR ($CDCl_3$, 600 MHz): δ: 8.62 (d, *J*=5.5 Hz, 2 H), 7.89 (t, *J*=8.0 Hz, 3 H), 7.74 (d, *J*=5.5 Hz, 2 H), 7.63 - 7.56 (m, 2 H), 7.49 - 7.44 (m, 2 H), 7.42 (dd, J_1=8.5 Hz, J_1=3.0 Hz, 1 H), 7.30-7.17 (m, 7 H), 7.17 - 7.12 (m, 2 H), 7.09 (d, *J*=8.60 Hz, 1 H).

^{13}C-NMR ($CDCl_3$, 150 MHz): δ: 160.4 (d, *J*=6.7 Hz), 144.4, 144.1, 142.2, 137.39 (d, *J*=12.3 Hz), 137.29 (d, *J*=11.5 Hz), 135.9, 134.81 (d, *J*=13.5 Hz), 133.7 (d, *J*=20.2 Hz), 133.6, 133.2 (d, *J*=18.5 Hz), 132.6 (d, *J*=7.8 Hz), 130.0-126.6, 120.3 (due to the complexity of the P-C couplings in this spectrum not all coupling constants could be accurately attributed; data correspond to those given in the literature: 54a).

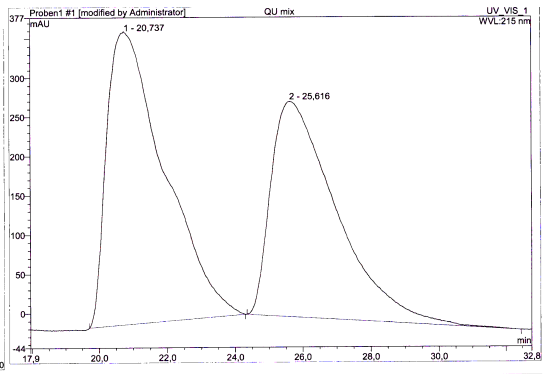
HPLC Data (for a better resolution the phosphines were reprotected with sulfur):

Chiralcel OD-H; *n*-heptane : *i*-propanol 90:10; flow: 0.5 mL/min

(*S*)-QUINAP:



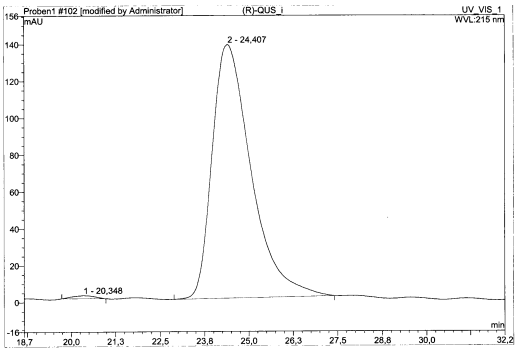
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	19,44	n.a.	673,407	618,291	99,31	n.a.	BMB
2	24,00	n.a.	36,562	4,279	0,69	n.a.	BMB*
Total:			709,969	622,570	100,00	0,000	



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	20,74	n.a.	374,251	733,376	54,45	n.a.	BMB*
2	25,62	n.a.	274,261	613,549	45,55	n.a.	BMB*
Total:			648,512	1346,925	100,00	0,000	

mix of (*R*)- and (*S*)-QUINAP (not racemic)

(*R*)-QUINAP:



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	20,35	n.a.	1,652	1,212	0,68	n.a.	BMB*
2	24,41	n.a.	137,779	175,959	99,32	n.a.	BMB*
Total:			139,432	177,171	100,00	0,000	

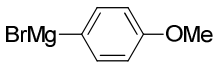
3. Sulfoxide-Alkene Hybrid Ligands: Preparation and Use in the *Hayashi-Miyaura* Reaction.

3.1. Preparation of aryl Grignard reagents

Mg-Insertion:

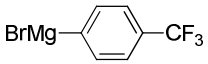
A dry and Ar-flushed 50 mL Schlenk-tube, equipped with a stirring bar and a septum, was charged with anhydrous LiCl (25 mmol; 1.06 g) and heated to 130 °C under high vacuum (1 mbar) for 3 h. After cooling to room temperature under Ar, Mg turnings (25 mmol; 608 mg), 1,2-dibromoethane (0.1 ml) and freshly distilled THF (20 mL) were added. The reaction mixture was shortly heated to reflux and was cooled to room temperature under Ar. Under vigorous stirring the respective aryl bromide (20 mmol) was added slowly at the appropriate temperature. The reaction mixture was stirred under Ar overnight and was titrated by using a stoichiometric amount of iodine (50 mg) in THF (2 mL).[129]

(4-Methoxyphenyl)magnesium bromide:



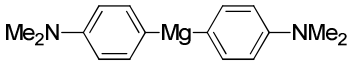
0.81 M in THF (81%); reaction temperature: 40 °C

(4-(Trifluoromethyl)phenyl)magnesium bromide:



0.68 M in THF (68%); reaction temperature: 0 °C. (Caution: Mg filings (no Mg powder) must be used in order to avoid an uncontrollable reaction).

Bis(4-(dimethylamino)phenyl)magnesium:

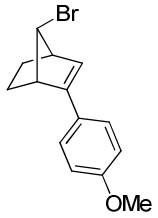


A dry and Ar-flushed 250 mL Schlenk-flask, equipped with a stirring bar and a septum, was charged with a solution of 4-bromo-*N*,*N*-dimethylaniline (4.0 g; 20 mmol) in 20 mL THF. The solution was cooled to –78 °C and *t*BuLi (1.89 M in *n*-pentane; 21.2 mL; 40 mmol) was added dropwise via syringe. The reaction was stirred for 1.5 h at –78 °C, before $MgCl_2$ (0.5 M in THF; 20 mL; 10 mmol) was added. The mixture was allowed to reach room temperature. The resulting solution was titrated by using a stoichiometric amount of iodine (50 mg) in THF (2 mL) indicating a concentration of 0.31 M (62%).

3.2. Preparation of 7-bromo-2-arylbicyclo[2.2.1]hept-2-enes

A dry and Ar-flushed 500 mL Schlenk-flask, equipped with a stirring bar and a septum, was charged with 7-bromobicyclo[2.2.1]heptan-2-one (**48**; 3.77 g; 20 mmol)[68e,i] and a solution of $LaCl_3 \cdot 2$ LiCl in THF (0.33 M; 90 mL; 30 mmol).[70] The mixture was stirred at room temperature for 1 h. Then, the solution was cooled to –78 °C and a solution of the respective aryl Grignard reagent (30 mmol) was added dropwise. After stirring for 1 h at –78 °C, the cold bath was removed and the mixture was allowed to reach room temperature within 1 h. The reaction mixture was further stirred for 2 h at room temperature. It was then cooled to –78 °C and MsOH (methanesulfonic acid; 4.68 mL; 72 mmol) was added dropwise and the mixture was allowed to reach room temperature. After 1.5 h, the clear yellow solution was quenched with NEt_3 (9.9 mL; 72 mmol). The mixture was filtrated and the precipitate was washed with Et_2O (3x). NH_4Cl sat. solution (250 mL) was added to the filtrate. Phases were separated and the aqueous phase was extracted with Et_2O (3x 100 mL). The recombined organic phases were dried over Na_2SO_4 and the solvents were evaporated. The crude product was subjected to purification via column chromatography.

7-Bromo-2-(4-methoxyphenyl)bicyclo[2.2.1]hept-2-ene (49)



yellow oil (67%)

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.40 (d, *J*=8.8 Hz, 2 H), 6.89 (d, *J*=8.8 Hz, 2 H), 6.16 (d, *J*=2.9 Hz, 1 H), 4.02 (d, *J*=0.7 Hz, 1 H), 3.82 (s, 3 H), 3.44 (d, *J*=1.0 Hz, 1 H), 3.17 (br. s., 1 H), 2.00 - 1.85 (m, 2 H), 1.38 - 1.21 (m, 2 H).

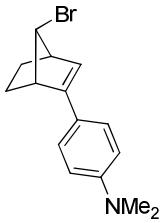
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 159.1, 144.9, 127.7, 126.5, 124.1, 114.0, 65.2, 55.3, 50.9, 50.5, 25.0, 23.0.

MS (70 eV, EI) *m/z* (%): 278 (6) [M^+], 200 (5), 199 (39), 172 (12), 171 (100), 156 (5), 128 (8), 121 (4).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 1678 (s), 1610 (s), 1598 (vs), 1570 (s), 1506 (vs), 1306 (s), 1294 (s), 1248 (vs), 1222 (s), 1176 (vs), 1036 (s), 868 (s), 838 (s), 804 (vs), 788 (s), 750 (s), 702 (s), 608 (s).

HRMS (EI) for **$C_{14}H_{15}BrO$** (278.0306): 278.0297.

4-(7-Bromobicyclo[2.2.1]hept-2-en-2-yl)-N,N-dimethylaniline



slightly red solid (71%)

m.p.: 100.4 – 101.3 °C.

^{1}H-NMR (400 MHz, C_6D_6) δ: 7.36 (d, *J*=9.0 Hz, 2 H), 6.57 (d, *J*=9.0 Hz, 2 H), 5.97 (d, *J*=2.9 Hz, 1 H), 3.68 (s, 1 H), 3.29 (d, *J*=1.2 Hz, 1 H), 2.90 (br. s., 1 H), 2.52 (s, 6 H), 1.50 - 1.36 (m, 2 H), 1.07 - 0.95 (m, 2 H).

^{13}C-NMR (101 MHz, C_6D_6) δ: 150.7, 146.2, 127.1, 124.4, 122.3, 113.2, 65.8, 52.5, 52.1, 40.5, 25.8, 23.6.

MS (70 eV, EI) *m/z* (%): 291 (8) [M^+], 213 (5), 212 (29), 185 (15), 184 (100), 183 (4), 168 (10), 139 (6), 115 (5), 92 (7), 91 (7), 58 (12), 43 (35).

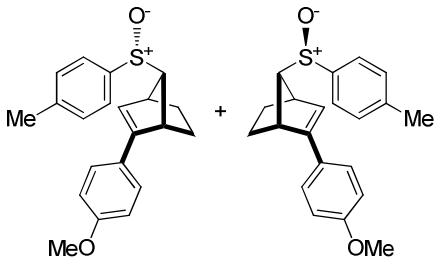
IR (ATR) $\tilde{\nu}$ **(cm^{-1}):** 2970 (m), 2942 (m), 2870 (m), 2800 (w), 1612 (vs), 1520 (vs), 1480 (m), 1460 (m), 1444 (m), 1364 (s), 1340 (m), 1298 (m), 1284 (w), 1230 (s), 1198 (s), 1188 (s), 1172 (m), 1160 (m), 1116 (s), 1064 (m), 946 (m), 866 (w), 824 (m), 806 (s), 794 (s), 786 (vs), 746 (s), 720 (m), 700 (m).

HRMS (EI) for **$C_{15}H_{18}BrN$** (291.0623): 291.0603.

3.3. Preparation and resolution of sulfoxide-alkene ligands using Andersen-sulfinate (1)

A dry and Ar-flushed 250 mL Schlenk-flask, equipped with a stirring bar and a septum, was charged with a solution of the respective 7-bromo-2-arylbicyclo[2.2.1]hept-2-ene (8 mmol) in THF (16 mL) and cooled to –78 °C. *t*BuLi (1.89 M in *n*-pentane; 9.31 mL; 17.6 mmol) was slowly added via syringe and the mixture was stirred for 2 h. A solution of $MgCl_2$ in THF (0.5 M; 18 mL; 9 mmol) was added and the mixture was further stirred at -78 °C for 30 min before a solution of the *Andersen*-sulfinate[18] (**1**; 2.65 g; 9 mmol) in THF (9 mL) was added dropwise. After 4 h at –78 °C, the reaction mixture was allowed to slowly reach room temperature. H_2O (100 mL) was added. Phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3x 50 mL). The recombined phases were washed with brine (50 mL) and dried over Na_2SO_4. The solvents were evaporated and the crude product was subjected to column chromatography yielding the pure diastereomeric chiral sulfoxides.

(1*R*,4*S*,7*R*)-2-(4-Methoxyphenyl)-7-((*R*)-p-tolylsulfinyl)-bicyclo[2.2.1]hept-2-ene (46a) and (1*S*,4*R*,7*S*)-2-(4-methoxyphenyl)-7-((*R*)-p-tolylsulfinyl)-bicyclo[2.2.1]hept-2-ene (46b)



46a **46b**

46a: white solid (35%)

m.p.: 213.1 – 214.2 °C.

^{1}H-NMR (300 MHz, C_6D_6) δ: 7.61 (d, *J*=8.0 Hz, 2 H), 7.39 (d, *J*=8.8 Hz, 2 H), 6.95 (d, *J*=7.8 Hz, 2 H), 6.79 (d, *J*=8.8 Hz, 2 H), 5.96 (d, *J*=2.7 Hz, 1 H), 4.07 (d, *J*=1.9 Hz, 1 H), 3.32 (s, 3 H), 2.77 (s, 1 H), 2.45 (br. s., 1 H), 2.01 (s, 3 H), 1.56 - 1.45 (m, 1 H), 1.31 – 1.21 (m, 1 H), 1.12 – 1.03 (m, 1 H), 0.97 – 0.88 (m, 1 H).

^{13}C-NMR (75 MHz, C_6D_6) δ: 160.4, 146.4, 144.7, 141.0, 130.2, 127.9, 127.7, 125.0, 124.5, 114.8, 88.0, 55.2, 46.5, 45.4, 27.7, 25.0, 21.5.

MS (70 eV, EI) *m/z* (%): 338 (6) [M^+], 323 (9), 322 (37), 294 (6), 200 (16), 199 (100), 198 (22), 185 (7), 184 (11), 172 (10), 171 (72), 156 (7), 135 (8), 128 (10), 121 (13), 67 (6).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2974 (w), 2926 (w), 1610 (w), 1594 (w), 1506 (m), 1490 (m), 1466 (m), 1456 (w), 1442 (w), 1296 (w), 1272 (w), 1258 (m), 1246 (m), 1222 (m), 1184 (w), 1176 (m), 1120 (w), 1110 (w), 1080 (m), 1030 (vs), 1012 (s), 992 (m), 972 (w), 840 (m), 828 (w), 808 (s), 800 (s).

HRMS (EI) for **$C_{21}H_{22}O_2S$** (338.1340): 338.1344.

46b: white solid (37%)

m.p.: 173.5 – 174.5 °C.

^{1}H-NMR (300 MHz, C_6D_6) δ: 7.57 (d, *J*=8.0 Hz, 2 H), 7.20 (d, *J*=8.8 Hz, 2 H), 6.89 (d, *J*=8.0 Hz, 2 H), 6.80 (d, *J*=8.8 Hz, 2 H), 6.07 (d, *J*=2.9 Hz, 1 H), 3.66 (br. s., 1 H), 3.33 (s, 3 H), 2.87 - 2.71 (m, 2 H), 1.98 (s, 3 H), 1.60 - 1.49 (m, 1 H), 1.28 - 1.17 (m, 1 H), 1.10 - 1.01 (m, 1 H), 0.94 - 0.84 (m, 1 H).

^{13}C-NMR (75 MHz, C_6D_6) δ: 160.2, 146.0, 144.6, 141.1, 130.2, 127.9, 127.1, 125.3, 124.9, 114.8, 88.3, 55.2, 46.3, 45.8, 27.3, 25.6, 21.5.

MS (70 eV, EI) *m/z* (%): 338 (19) [M^+], 322 (25), 200 (10), 199 (68), 198 (15), 184 (12), 172 (14), 171 (100), 156 (10), 135 (28), 128 (15), 121 (18).

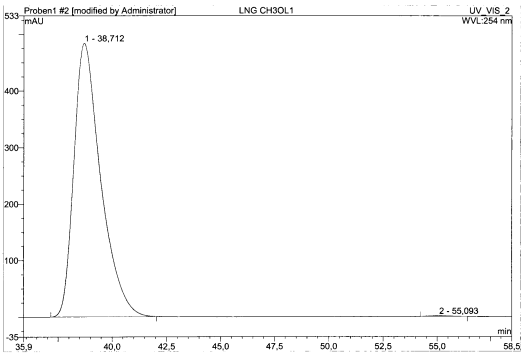
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2982 (vw), 2934 (w), 1612 (w), 1598 (w), 1572 (w), 1508 (m), 1492 (w), 1464 (w), 1446 (w), 1416 (w), 1294 (w), 1276 (w), 1246 (s), 1222 (w), 1210 (w), 1194 (w), 1182 (m), 1124 (w), 1110 (w), 1082 (w), 1030 (vs), 1014 (m), 990 (w), 964 (w), 950 (w), 842 (w), 814 (s), 794 (s), 704 (w).

HRMS (EI) for $C_{21}H_{22}O_2S$ (338.1340): 338.1325.

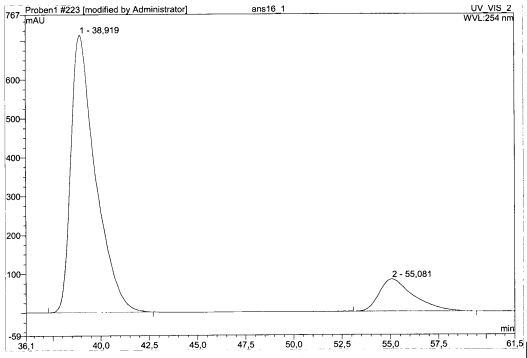
HPLC Data:

Chiralcel AD; *n*-heptane : *i*-propanol 80:20; flow: 0.3 mL/min

46a:

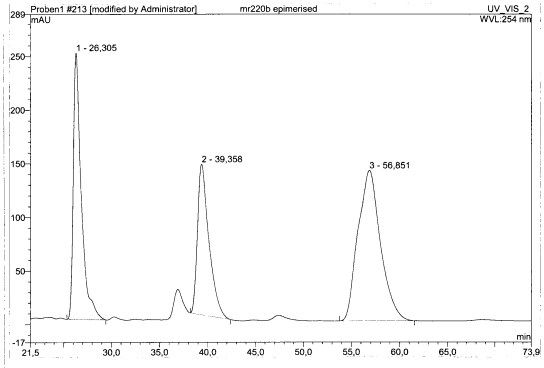


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	38,71	n.a.	484,084	699,756	99,81	n.a.	BMB
2	55,09	n.a.	1,092	1,325	0,19	n.a.	BMB*
Total:			485,176	701,082	100,00	0,000	



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	38,92	n.a.	713,643	1060,593	86,18	n.a.	BMB
2	55,08	n.a.	83,099	170,052	13,82	n.a.	BMB*
Total:			796,742	1230,645	100,00	0,000	

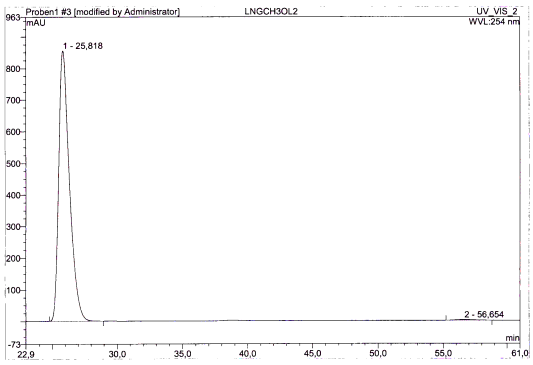
without transmetalation to $MgCl_2$ (72% *ee*)



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	26,31	n.a.	248,593	242,063	29,75	n.a.	BMB*
2	39,36	n.a.	140,488	193,461	23,78	n.a.	BMB*
3	56,85	n.a.	140,313	378,011	46,47	n.a.	BMB
Total:			529,395	813,535	100,00	0,000	

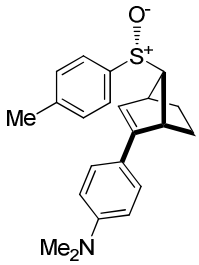
after acidic epimerization of **46a** (HCl 1 M in CH_2Cl_2) shows **46a**, **46b** and their enantiomers

46b:



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	25,82	n.a.	855,166	823,249	99,47	n.a.	BMB
2	56,65	n.a.	2,488	4,367	0,53	n.a.	BMB*
Total:			857,654	827,616	100,00	0,000	

***N*,*N*-Dimethyl-4-((1*R*,4*S*,7*R*)-7-((*R*)-p-tolylsulfinyl)bicyclo-[2.2.1]hept-2-en-2-yl)aniline (60)**



white solid (28%; only one diastereomer isolated)

m.p.: 224.7 – 226.9 °C.

^{1}H-NMR (400 MHz, d$_8$-THF) δ: 7.50 (d, *J*=8.2 Hz, 2 H), 7.37 (d, *J*=8.8 Hz, 2 H), 7.31 (d, *J*=7.8 Hz, 2 H), 6.70 (d, *J*=9.0 Hz, 2 H), 6.11 (d, *J*=2.5 Hz, 1 H), 3.84 (d, *J*=2.0 Hz, 1 H), 2.94 (s, 6 H), 2.64 (s, 2 H), 2.38 (s, 3 H), 1.91 - 1.80 (m, 1 H), 1.79 - 1.73 (m, 1 H), 1.28 - 1.16 (m, 2 H).

^{13}C-NMR (101 MHz, d$_8$-THF) δ: 151.3, 146.9, 145.2, 141.4, 130.3, 127.2, 125.0, 123.9, 122.6, 113.1, 88.2, 46.4, 45.6, 40.6, 30.7, 28.3, 21.4.

MS (70 eV, EI) *m/z* (%): 352 (5) [M$^+$], 212 (18), 184 (47), 168 (9), 148 (19), 91 (9), 67 (9), 58 (27), 43 (100).

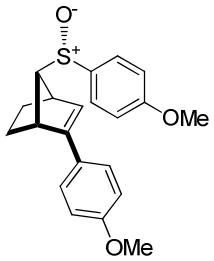
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2924 (w), 2866 (w), 1612 (m), 1520 (m), 1492 (m), 1460 (w), 1444 (w), 1364 (m), 1274 (w), 1234 (w), 1218 (w), 1200 (m), 1190 (m), 1178 (w), 1116 (w), 1078 (m), 1032 (vs), 1014 (m), 976 (w), 952 (w), 868 (w), 826 (m), 812 (s), 794 (vs), 706 (w).

HRMS (EI) for **$C_{22}H_{25}NOS$** (352.1657): 352.1644.

3.4. Preparation and resolution of sulfoxide-alkene ligands using (*S*)-TMPOO (2)

A dry and Ar-flushed 50 mL *Schlenk*-tube, equipped with a stirring bar and a septum, was charged with a solution of the 7-bromo-2-(4-methoxyphenyl)bicyclo[2.2.1]hept-2-ene (**49**; 0.838 g; 3 mmol) in THF (6 mL) and cooled to –78 °C. *t*BuLi (1.89 M in *n*-pentane; 3.49 mL; 6.6 mmol) was slowly added via syringe and the mixture was stirred for 2 h. A solution of $MgCl_2$ in THF (0.5 M; 13.2 mL; 6.6 mmol) was added. Meanwhile, a dry and Ar-flushed 100 mL *Schlenk*-flask, equipped with a stirring bar and a septum, was charged with a solution of (*S*)-TMPOO[19] (1.11 g; 3.15 mmol) in THF (8.4 mL) and cooled to –78 °C. The cold Grignard reagent, which was further kept at –78 °C was transferred to the (*S*)-TMPOO solution dropwise using a Teflon-cannula. After the addition was finished, the reaction mixture was stirred for further 2 h before the respective second Grignard reagent (3.3 mmol) was added. The reaction mixture was stirred for 1.5 h at –78 °C and was then allowed to warm to room temperature. The reaction was quenched with $NaHCO_3$ sat. solution (8 mL). H_2O (20 mL) was added and phases were separated. The aqueous phase was extracted with EtOAc (3x 40 mL). The combined organic layers were washed with brine (50 mL) and dried over Na_2SO_4. The solvents were evaporated and the crude products were subjected to column chromatography yielding the respective pure diastereomeric chiral sulfoxide.

(1*S*,4*R*,7*S*)-2-(4-methoxyphenyl)-7-((*S*)-(4-methoxyphenyl)-sulfinyl)bicyclo[2.2.1]hept-2-ene (59a)



white solid (31%; only one diastereomer isolated)

m.p.: 184.8 – 186.2 °C.

^{1}H-NMR (400 MHz, C_6D_6) δ: 7.55 (d, *J*=8.8 Hz, 2 H), 7.34 (d, *J*=8.8 Hz, 2 H), 6.74 (d, *J*=8.8 Hz, 2 H), 6.69 (d, *J*=8.8 Hz, 2 H), 5.92 (d, *J*=2.7 Hz, 1 H), 4.01 (d, *J*=1.8 Hz, 1 H), 3.28 (s, 3 H) ,

3.16 (s, 3 H), 2.73 (s, 1 H), 2.38 (br. s., 1 H), 1.56 - 1.45 (m, 1 H), 1.30 - 1.21 (m, 1 H), 1.08 - 1.00 (m, 1 H), 0.94 - 0.85 (m, 1 H).

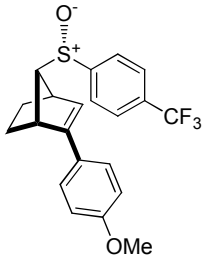
^{13}C-NMR (101 MHz, C_6D_6) δ: 161.5, 159.6, 145.7, 137.9, 127.2, 126.9, 125.9, 123.8, 114.4, 114.1, 87.5, 54.6, 54.5, 45.8, 44.7, 27.0, 24.4.

MS (70 eV, EI) *m/z* (%): 354 (4) [M^+], 338 (26), 200 (16), 199 (100), 198 (18), 197 (11), 184 (13), 172 (14), 171 (89), 156 (10), 155 (10), 135 (12), 128 (17), 121 (23), 91 (19), 67 (22).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2967 (w), 2945 (vw), 1594 (m), 1577 (w), 1508 (m), 1493 (m), 1307 (w), 1295 (w), 1245 (s), 1176 (m), 1084 (m), 1027 (vs), 1009 (m), 1004 (m), 993 (m), 838 (m), 823 (s), 817 (m), 802 (s), 796 (m), 789 (m), 616 (w), 609 (m).

HRMS (EI) for **$C_{21}H_{22}O_3S$** (354.1290): 354.1282.

(1*S*,4*R*,7*S*)-2-(4-methoxyphenyl)-7-((*S*)-(4-(trifluoromethyl)-phenyl)sulfinyl)bicyclo[2.2.1]hept-2-ene (59b)



white solid (19%; only one diastereomer isolated)

m.p.: 152.6 – 152.6 °C.

^{1}H-NMR (300 MHz, C_6D_6) δ: 7.47 (d, *J*=8.0 Hz, 2 H), 7.38 (d, *J*=8.8 Hz, 2 H), 7.30 (d, *J*=8.3 Hz, 2 H), 6.80 (d, *J*=8.8 Hz, 2 H), 5.92 (d, *J*=2.7 Hz, 1 H), 3.99 (d, *J*=1.7 Hz, 1 H), 3.33 (s, 3 H), 2.60 (s, 1 H), 2.30 (br. s., 1 H), 1.53 - 1.42 (m, 1 H), 1.29 - 1.19 (m, 1 H), 1.10 - 1.02 (m, 1 H), 0.97 - 0.88 (m, 1 H).

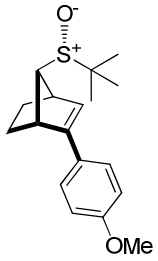
^{13}C-NMR (75 MHz, C_6D_6) δ: 160.5, 152.1 (d, *J*=1.3 Hz), 146.4, 132.7 (q, *J*=32.5 Hz), 127.7, 127.6, 126.3 (q, *J*=3.6 Hz), 125.3, 124.8 (q, *J*=272.9 Hz), 124.2, 114.9, 87.6, 55.2, 46.6, 45.2, 27.7, 24.8.

MS (70 eV, EI) *m/z* (%): 392 (13) [M^+], 376 (22), 199 (56), 184 (10), 172 (13), 171 (100), 135 (33), 128 (13), 121 (14).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2974 (w), 2960 (w), 2936 (w), 1606 (w), 1596 (w), 1508 (s), 1468 (w), 1458 (w), 1400 (w), 1332 (s), 1306 (m), 1296 (s), 1274 (m), 1258 (m), 1248 (s), 1220 (m), 1174 (s), 1162 (s), 1150 (s), 1122 (vs), 1102 (s), 1084 (m), 1062 (s), 1042 (vs), 1028 (vs), 1012 (s), 974 (m), 870 (w), 832 (s), 818 (m), 804 (s), 712 (w), 702 (m), 610 (w).

HRMS (EI) for **$C_{21}H_{19}F_3O_2S$** (392.1058): 392.1060.

(1*S*,4*R*,7*S*)-7-((*S*)-tert-butylsulfinyl)-2-(4-methoxyphenyl)-bicyclo[2.2.1]hept-2-ene (59c)



white solid (17%; only one diastereomer isolated)

m.p.: 105.4 – 106.6 °C.

^{1}H-NMR (400 MHz, C_6D_6) δ: 7.45 (d, *J*=8.8 Hz, 2 H), 6.76 (d, *J*=8.8 Hz, 2 H), 5.95 (d, *J*=2.9 Hz, 1 H), 3.94 (br. s., 1 H), 3.31 (s, 3 H), 2.70 (s, 1 H), 2.61 (br. s., 1 H), 1.66 - 1.52 (m, 2 H), 1.20 - 1.07 (m, 2 H), 1.02 (s, 9 H).

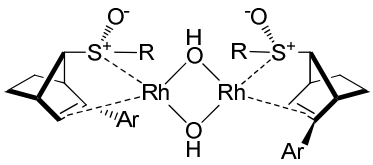
^{13}C-NMR (101 MHz, C_6D_6) δ: 160.3, 146.6, 128.0, 128.0, 123.9, 114.7, 75.9, 55.2, 52.7, 46.6, 46.5, 28.6, 24.0, 23.5.

MS (70 eV, EI) *m/z* (%): 304 (9) [M$^+$], 249 (10), 248 (65), 231 (14), 200 (21), 199 (100), 198 (20), 197 (33), 185 (38), 184 (10), 172 (35), 171 (98), 156 (12), 153 (10), 150 (25), 135 (23), 128 (21), 121 (11), 57 (14).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2944 (w), 2872 (vw), 1612 (vw), 1598 (w), 1520 (m), 1464 (w), 1446 (w), 1364 (w), 1296 (w), 1274 (w), 1262 (w), 1244 (m), 1224 (w), 1186 (m), 1126 (w), 1026 (vs), 994 (w), 878 (w), 846 (m), 816 (s), 804 (m), 786 (w).

HRMS (EI) for **$C_{18}H_{24}O_2S$** (304.1497): 304.1493.

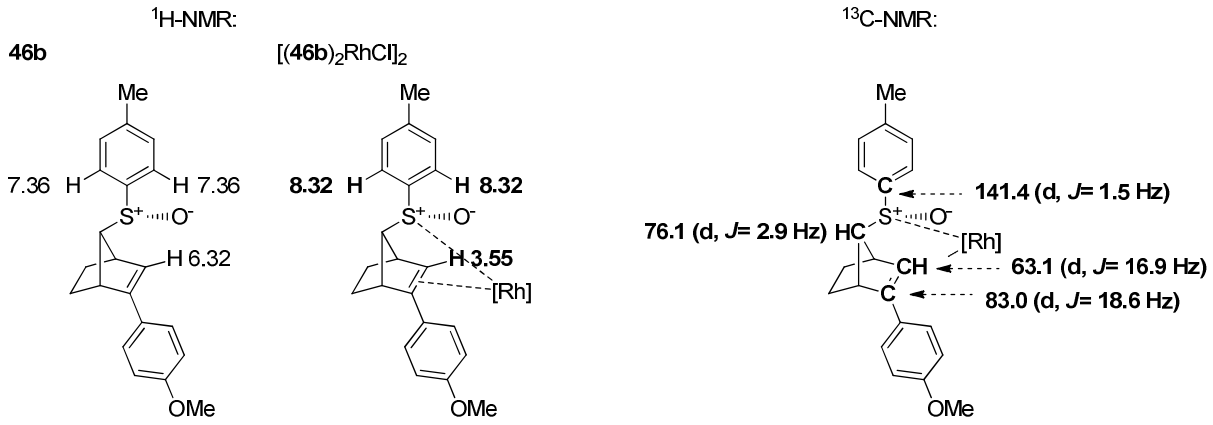
3.5. *In situ* preparation of the chiral sulfoxide-alkene hybrid/Rh catalysts



An Ar-flushed 10 mL *Schlenk*-tube, equipped with a stirring bar and a septum, was charged with a solution of the respective chiral sulfoxide-alkene hybrid ligand (200 µmol) and $[Rh(coe)_2Cl]_2$[74] (72 mg; 100 µmol) in 1,4-dioxane (2 mL). $CsOH \cdot H_2O$ (34 mg; 200 µmol) along with 0.8 mL H_2O (HPLC grade) was added. The resulting suspension was stirred overnight at room temperature. The next day, a clear yellow solution had formed.

3.6. NMR experiments

For NMR experiments **46b** (34 mg; 100 µmol) and $[Rh(ethylene)_2Cl]_2$ were mixed in d^8-1,4-dioxane (1 mL). The suspension was stirred for 12 h until a clear orange solution had formed which was immediately subjected to NMR measurements. The results of the NMR-experiments in d^8-dioxane showing the coordinative sites in the Rh-complex of **46b** through *signal shifts* in the ^{1}H- and *doublet-splittings* in the ^{13}C-spectrum are summarized below:



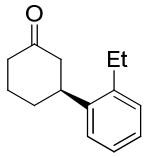
3.7. Enantioselective *Hayashi-Miyaura* reaction

An Ar-flushed 10 mL *Schlenk*-tube, equipped with a stirring bar and a septum, was charged with a solution of the respective electron-deficient alkene (0.5 mmol), the corresponding boronic acid (0.6 mmol) and CsF (0.6 mmol) in 1,4-dioxane (1.5 mL). A solution of the catalyst (see **3.5**) in 1,4-dioxane (0.036 M; 0.35 mL; 12.5 µmol) was slowly added to the reaction mixture. After the addition was complete, the mixture was warmed to room temperature. Progress of the reaction

was followed via TLC analysis. After all the starting material was consumed, Et_2O (6 mL) was added to the reaction mixture along with SiO_2. The solvents were removed and the product was subjected to column chromatography.

3.7.1 Compounds of Table 1

(*S*)-3-(2-Ethylphenyl)cyclohexanone (52b):



colorless oil 0.100 g (99%)

^{1}H-NMR (400 MHz, C_6D_6) δ: 7.14 - 7.04 (m, 2 H), 7.04 – 6.93 (m, 2 H), 3.02 - 2.93 (m, 1 H), 2.48 - 2.42 (m, 1 H), 2.37 (q, *J*=7.5 Hz, 2 H), 2.29 - 2.23 (m, 1 H), 2.15 (t, *J*=13.4 Hz, 1 H), 1.88 (td, J_1=13.3 Hz, J_2= 6.0 Hz, 1 H), 1.62 - 1.52 (m, 2 H), 1.42 - 1.22 (m, 2 H), 0.99 (t, *J*=7.6 Hz, 3 H).

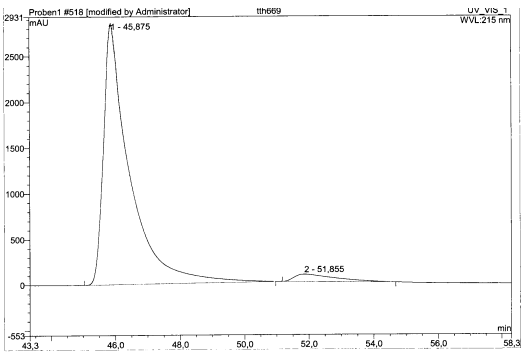
^{13}C-NMR (101 MHz, C_6D_6) δ: 207.8, 141.9, 140.7, 128.8, 126.4, 126.2, 125.5, 48.7, 40.8, 39.4, 32.5, 25.5, 25.4, 15.6.

MS (70 eV, EI) *m/z* (%): 202 (86) [M^+], 173 (33), 160 (12), 159 (100), 145 (45), 145 (32), 132 (12), 131 (17), 129 (14), 128 (10), 118 (12), 117 (54), 115 (20), 91 (11).

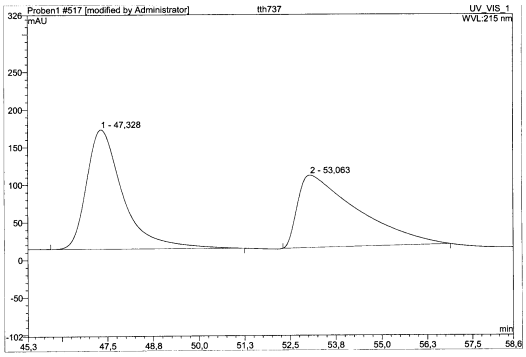
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2962 (m), 2934 (m), 2872 (w), 1708 (vs), 1490 (w), 1448 (m), 1420 (w), 1374 (w), 1364 (w), 1344 (w), 1314 (w), 1286 (w), 1252 (w), 1222 (m), 1182 (w), 1052 (w), 1032 (w), 972 (w), 914 (vw), 884 (vw), 796 (w), 788 (w), 752 (s), 714 (w), 650 (w).

HRMS (EI) for **$C_{14}H_{18}O$** (202.1358): 202.1346.

HPLC Data: Chiralcel OD-H; *n*-heptane : *i*-propanol 99:1; flow: 0.3 mL/min

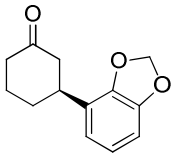


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	45,87	n.a.	2858,701	2668,319	95,75	n.a.	BMB*
2	51,85	n.a.	81,504	118,373	4,25	n.a.	BMB*
Total:			2940,205	2786,692	100,00	0,000	



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	47,33	n.a.	158,810	183,669	50,37	n.a.	BMB*
2	53,06	n.a.	96,381	180,944	49,63	n.a.	BMB*
Total:			255,192	364,613	100,00	0,000	

(*S*)-3-(Benzo[d][1,3]dioxol-4-yl)cyclohexanone (52f):



colorless crystals 0.094 g (86%)

m.p.: 78.8 – 79.9 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 6.83 - 6.69 (m, 2 H), 6.69 - 6.58 (m, 1 H), 5.93 (s, 2 H), 3.01 – 2.84 (m, 1 H), 2.60 - 2.29 (m, 4 H), 2.20 - 1.97 (m, 2 H), 1.86 - 1.65 (m, 2 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 210.7, 147.8, 146.1, 138.4, 119.4, 108.2, 106.9, 100.9, 49.2, 44.4, 41.0, 33.0, 25.3.

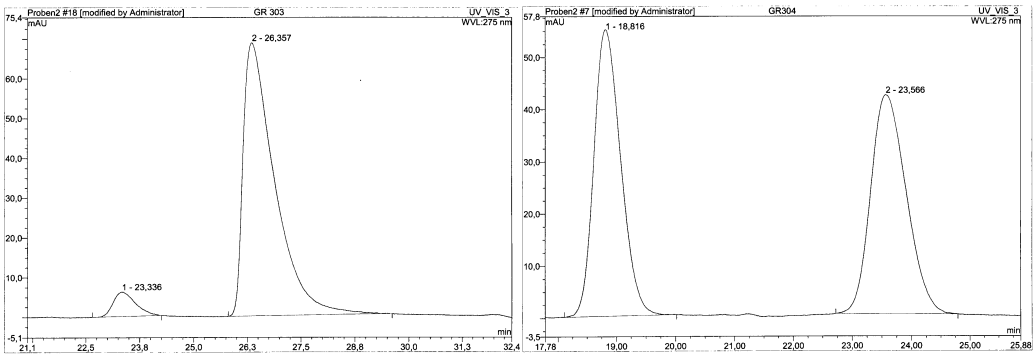
MS (70 eV, EI) *m/z* (%): 218 (100) [M^+], 175 (14), 162 (10), 161 (57), 148 (36), 147 (14), 135 (22), 103 (11), 89 (10).

IR (ATR) $\widetilde{\nu}$ **(cm^{-1}):** 2956 (m), 2918 (m), 2852 (m), 1702 (vs), 1608 (w), 1504 (s), 1486 (s), 1440 (s), 1414 (m), 1350 (w), 1250 (m), 1218 (vs), 1188 (s), 1090 (m), 1030 (vs), 974 (m), 928 (vs), 902 (m), 874 (s), 860 (m), 810 (vs), 774 (m), 748 (m).

HRMS (EI) for $C_{13}H_{14}O_3$ (218.0943): 218.0952.

HPLC Data:

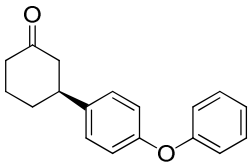
Chiralcel AS-H; *n*-heptane : *i*-propanol 80:20; flow: 1.0 mL/min



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	23,34	n.a.	6,191	3,689	5,92	n.a.	BMB*
2	26,36	n.a.	68,744	58,654	94,08	n.a.	BMB*
Total:			74,935	62,343	100,00	0,000	

No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	18,82	n.a.	54,930	29,085	49,88	n.a.	BMB*
2	23,57	n.a.	41,962	29,220	50,12	n.a.	BMB*
Total:			96,892	58,304	100,00	0,000	

(*S*)-3-(4-Phenoxyphenyl)cyclohexanone (52j):



colorless crystals 0.120 g (90%)

m.p.: 99.3 – 100.5 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.34 (t, *J*=8.0 Hz, 2 H), 7.19 (d, *J*=8.4 Hz, 2 H), 7.11 (t, *J*=7.4 Hz, 1 H), 7.02 (d, *J*=7.9 Hz, 2 H), 6.98 (d, *J*=8.6 Hz, 2 H), 3.01 (dddd, J_1=15.5 Hz, J_2=7.8 Hz, J_3=3.8 Hz, J_4=3.7 Hz, 1 H), 2.66 - 2.32 (m, 4 H), 2.24 - 2.03 (m, 2 H), 1.92 - 1.70 (m, 2 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 210.8, 157.2, 155.8, 139.2, 129.7, 127.7, 123.2, 118.9, 118.8, 49.0, 44.0, 41.1, 32.9, 25.4.

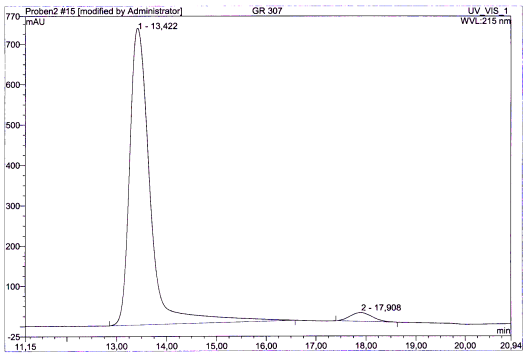
MS (70 eV, EI) *m/z* (%): 266 (100) [M^+], 223 (16), 210 (11), 209 (79), 196 (25), 183 (12), 116 (22), 115 (27), 97 (14), 85 (16), 83 (11), 77 (16), 71 (24), 69 (14), 57 (32), 43 (14).

IR (ATR) $\tilde{\nu}$ **(cm^{-1}):** 2944 (w), 2922 (w), 1702 (s), 1588 (m), 1504 (s), 1486 (s), 1456 (m), 1446 (m), 1422 (w), 1366 (w), 1250 (s), 1234 (vs), 1222 (vs), 1198 (s), 1180 (m), 1166 (m), 1110 (w), 1068 (w), 910 (w), 870 (m), 828 (m), 802 (m), 784 (m), 752 (m), 738 (m), 694 (s).

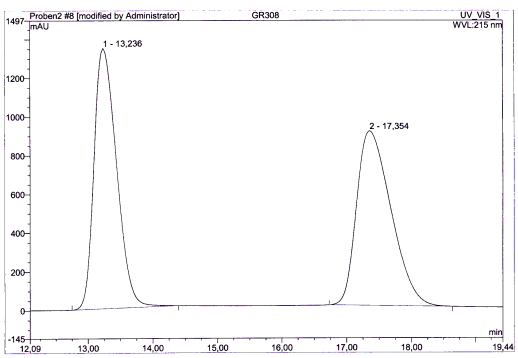
HRMS (EI) for **$C_{18}H_{18}O_2$** (266.1307): 266.1296.

HPLC Data:

Chiralcel AS-H; *n*-heptane : *i*-propanol 80:20; flow: 1.0 mL/min



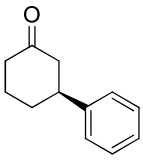
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	13,42	n.a.	736,335	349,237	96,92	n.a.	BMB*
2	17,91	n.a.	21,646	11,099	3,08	n.a.	BMB*
Total:			757,981	360,336	100,00	0,000	



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	13,24	n.a.	1344,604	543,308	49,51	n.a.	BMB*
2	17,35	n.a.	901,542	554,074	50,49	n.a.	BMB*
Total:			2246,146	1097,382	100,00	0,000	

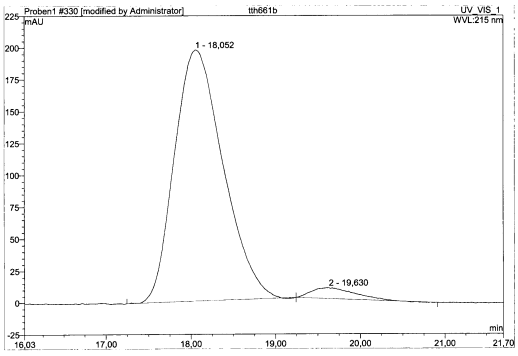
Compounds known in the literature:[30, 31, 32, 66, 68]

(*S*)-3-Phenylcyclohexanone (52a):

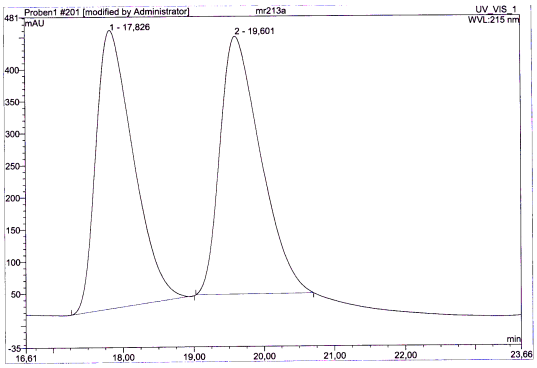


HPLC Data:

Chiralcel AD; *n*-heptane : *i*-propanol 90:10; flow: 0.3 mL/min

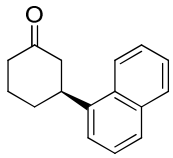


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	18,05	n.a.	196,998	131,413	96,34	n.a.	BMb*
2	19,63	n.a.	8,680	4,991	3,66	n.a.	bMB*
Total:			205,678	136,404	100,00	0,000	



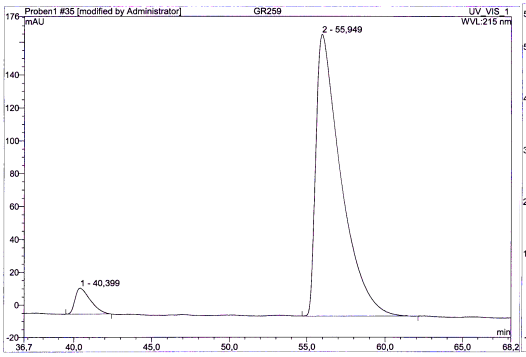
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	17,83	n.a.	434,607	266,657	49,67	n.a.	BMB*
2	19,60	n.a.	402,679	270,232	50,33	n.a.	BMB*
Total:			837,286	536,889	100,00	0,000	

(*S*)-3-(Naphthalen-1-yl)cyclohexanone (52c):



HPLC Data:

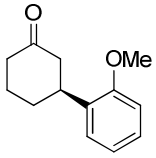
Chiralcel OD-H; *n*-heptane : *i*-propanol 95:5; flow: 0.5 mL/min



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	40,40	n.a.	15,964	18,158	5,40	n.a.	BMB*
2	55,95	n.a.	171,574	318,143	94,60	n.a.	BMB*
Total:			187,538	336,302	100,00	0,000	

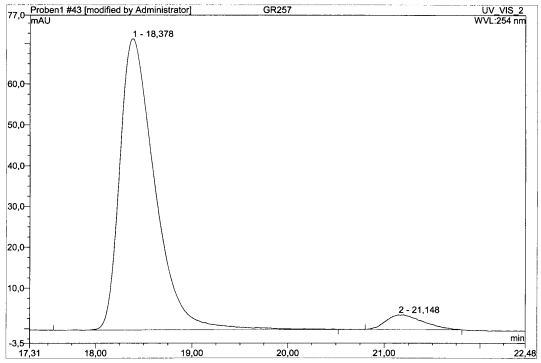
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	35,59	n.a.	494,569	1111,658	50,15	n.a.	BMB
2	54,00	n.a.	465,478	1104,947	49,85	n.a.	BMB
Total:			960,047	2216,605	100,00	0,000	

(*S*)-3-(2-Methoxyphenyl)cyclohexanone (52d):



HPLC Data:

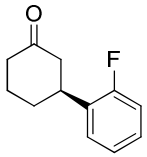
Chiralcel OD-H; *n*-heptane : *i*-propanol 95:5; flow: 0.5 mL/min



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	18,38	n.a.	71,414	30,051	94,94	n.a.	BMB*
2	21,15	n.a.	3,631	1,600	5,06	n.a.	BMB*
Total:			75,045	31,652	100,00	0,000	

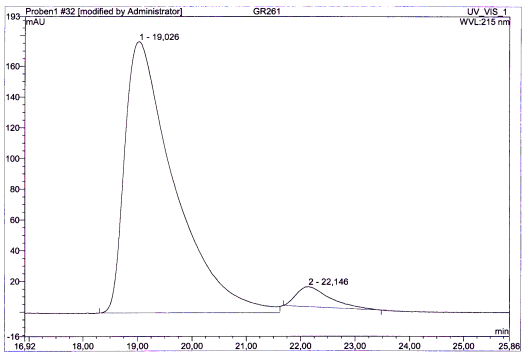
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	18,26	n.a.	124,540	52,469	49,97	n.a.	BMB
2	20,31	n.a.	88,759	52,540	50,03	n.a.	BMB
Total:			213,299	105,009	100,00	0,000	

(*S*)-3-(2-Fluorophenyl)cyclohexanone (52e):

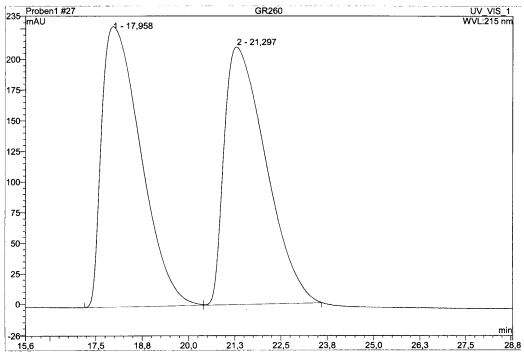


HPLC Data:

Chiralcel AD; *n*-heptane : i-propanol 99.5:0.5; flow: 1.0 mL/min

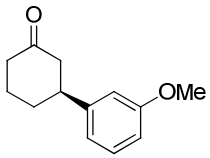


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	19,03	n.a.	176,675	185,824	95,23	n.a.	BM *
2	22,15	n.a.	13,079	9,315	4,77	n.a.	BMB*
Total:			189,754	195,139	100,00	0,000	



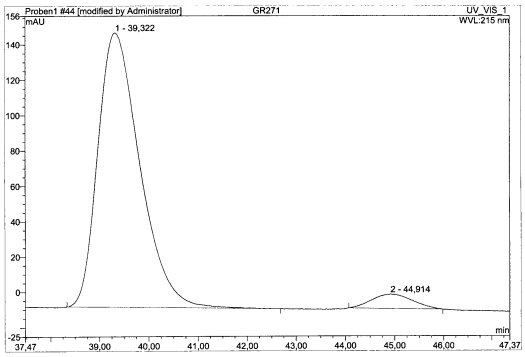
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	17,96	n.a.	229,108	280,606	50,35	n.a.	BM
2	21,30	n.a.	210,513	276,682	49,65	n.a.	MB
Total:			439,621	557,288	100,00	0,000	

(*S*)-3-(3-Methoxyphenyl)cyclohexanone (52g):

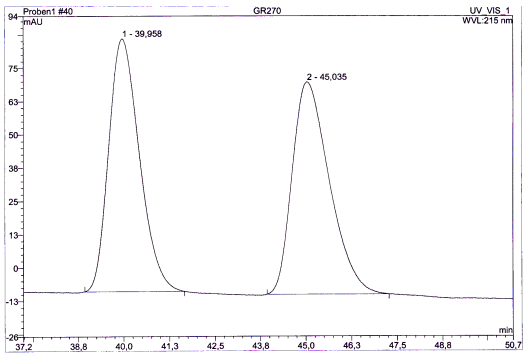


HPLC Data:

Chiralcel OD-H; *n*-heptane : *i*-propanol 99:1; flow: 1.0 mL/min

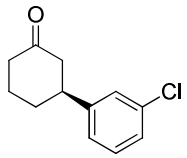


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	39,32	n.a.	155,145	153,274	95,24	n.a.	BMB*
2	44,91	n.a.	8,111	7,658	4,76	n.a.	BMB*
Total:			163,256	160,932	100,00	0,000	



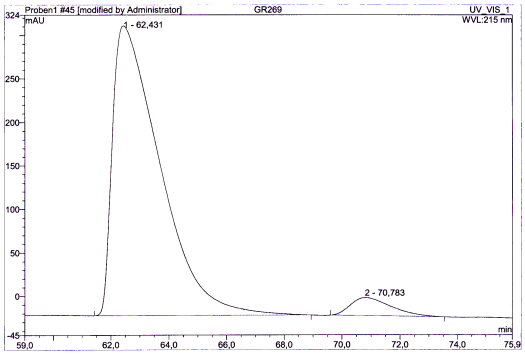
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	39,96	n.a.	94,954	92,628	49,54	n.a.	BMB
2	45,04	n.a.	79,757	94,334	50,46	n.a.	BMB
Total:			174,711	186,963	100,00	0,000	

(*S*)-3-(3-Chlorophenyl)cyclohexanone (52h):

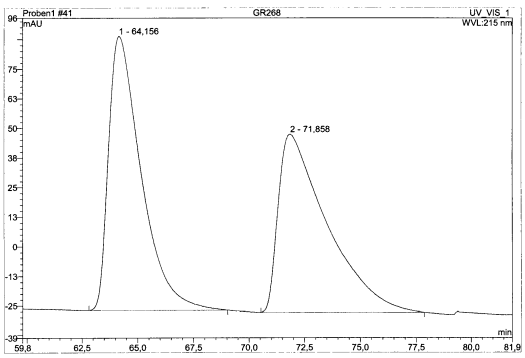


HPLC Data:

Chiralcel OD-H; *n*-heptane : *i*-propanol 99.5:0.5; flow: 0.5 mL/min

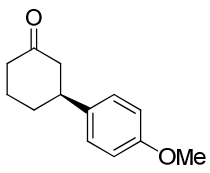


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	62,43	n.a.	333,226	633,801	94,99	n.a.	BMB*
2	70,78	n.a.	20,722	33,409	5,01	n.a.	BMB*
Total:			353,948	667,210	100,00	0,000	



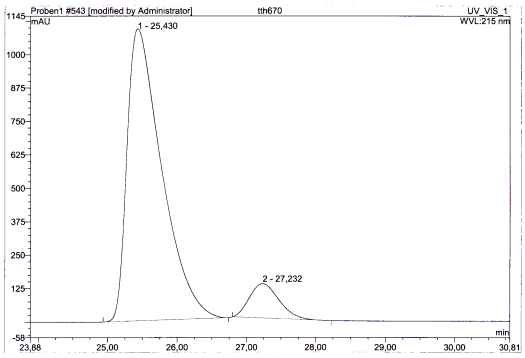
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	64,16	n.a.	115,752	195,982	50,56	n.a.	BMB
2	71,86	n.a.	75,535	191,626	49,44	n.a.	BMB
Total:			191,287	387,608	100,00	0,000	

(*S*)-3-(4-Methoxyphenyl)cyclohexanone (52i):

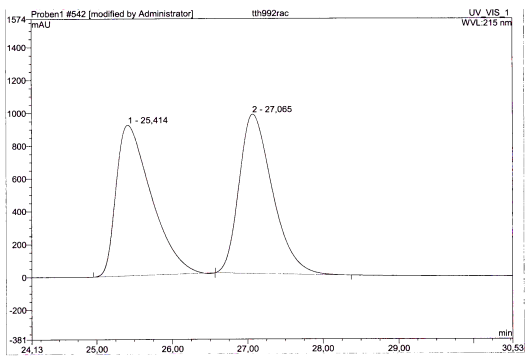


HPLC Data:

Chiralcel AD-H; *n*-heptane : *i*-propanol 98:2; flow: 0.5 mL/min

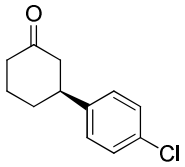


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	25,43	n.a.	1091,691	628,811	90,85	n.a.	BMB*
2	27,23	n.a.	128,261	63,300	9,15	n.a.	BMB*
Total:			1219,953	692,110	100,00	0,000	



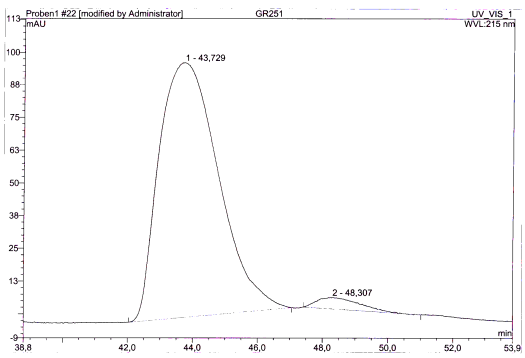
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	25,41	n.a.	917,254	493,341	49,75	n.a.	BMB*
2	27,06	n.a.	968,955	498,386	50,25	n.a.	BMB*
Total:			1886,209	991,727	100,00	0,000	

(*S*)-3-(4-Chlorophenyl)cyclohexanone (52k):

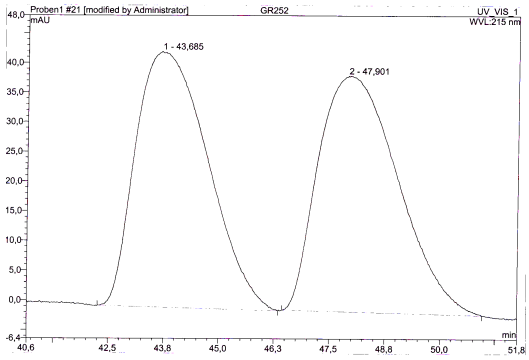


HPLC Data:

Chiralcel OJ; *n*-heptane : *i*-propanol 99:1; flow: 0.5 mL/min

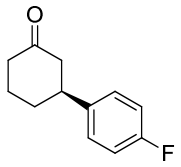


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	43,73	n.a.	97,375	206,483	96,82	n.a.	BMB*
2	48,31	n.a.	4,394	6,791	3,18	n.a.	BMB*
Total:			101,769	213,274	100,00	0,000	



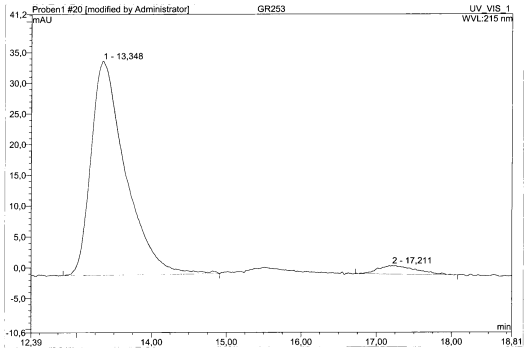
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	43,69	n.a.	43,095	81,516	49,63	n.a.	BMB*
2	47,90	n.a.	39,725	82,744	50,37	n.a.	BMB*
Total:			82,820	164,260	100,00	0,000	

(*S*)-3-(4-Fluorophenyl)cyclohexanone (52l):

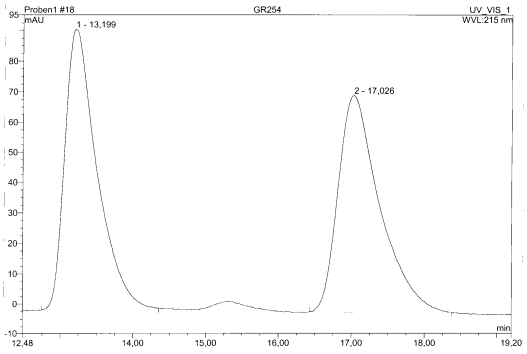


HPLC Data:

Chiralcel AD; *n*-heptane : *i*-propanol 99:1; flow: 1.0 mL/min

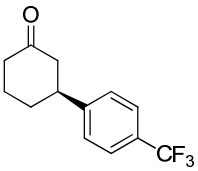


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	13,35	n.a.	34,793	18,528	95,91	n.a.	BMB*
2	17,21	n.a.	1,418	0,791	4,09	n.a.	BMB*
Total:			36,211	19,319	100,00	0,000	



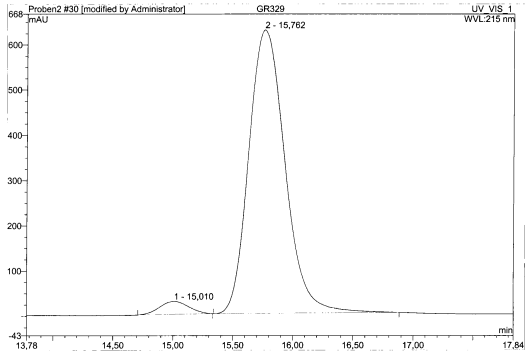
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	13,20	n.a.	92,297	47,222	50,18	n.a.	BMB
2	17,03	n.a.	71,375	46,877	49,82	n.a.	BMB
Total:			163,672	94,099	100,00	0,000	

(*S*)-3-(4-(Trifluoromethyl)phenyl)cyclohexanone (52m):

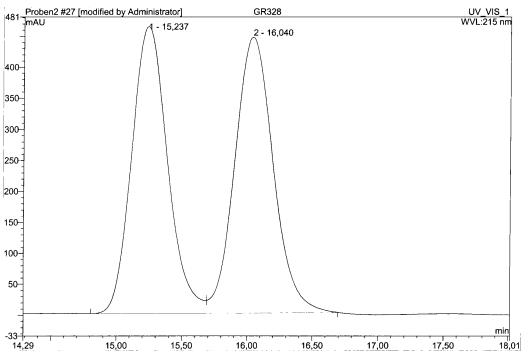


HPLC Data:

Chiralcel OD-H; *n*-heptane : *i*-propanol 90:10; flow: 0.5 mL/min

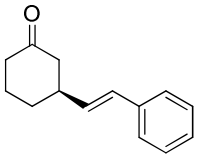


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	15,01	n.a.	28,495	7,896	3,47	n.a.	BMB*
2	15,76	n.a.	626,798	219,415	96,53	n.a.	BMB*
Total:			655,293	227,311	100,00	0,000	



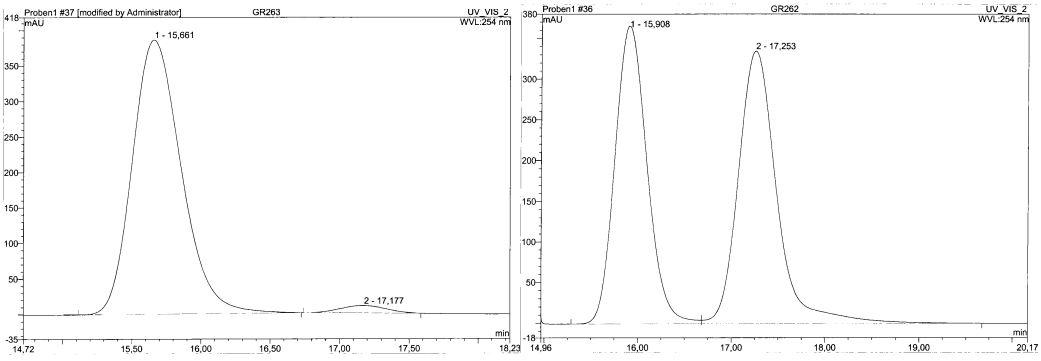
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	15,24	n.a.	462,863	147,526	49,23	n.a.	BM *
2	16,04	n.a.	444,581	152,142	50,77	n.a.	MB*
Total:			907,444	299,668	100,00	0,000	

(*S*,*E*)-3-Styrylcyclohexanone (52n):



HPLC Data:

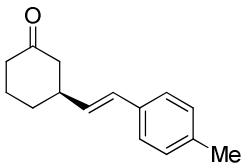
Chiralcel OD-H; *n*-heptane : *i*-propanol 98:2; flow: 1.0 mL/min



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	15,66	n.a.	386,060	157,767	97,57	n.a.	BMB
2	17,18	n.a.	10,461	3,928	2,43	n.a.	BMB*
Total:			396,521	161,695	100,00	0,000	

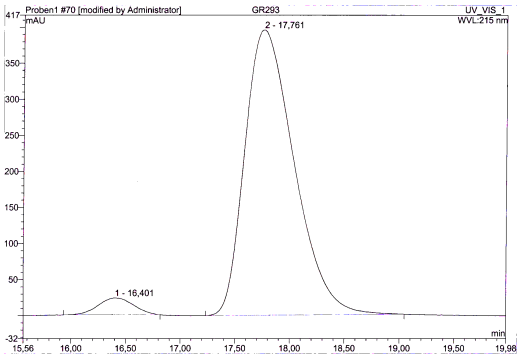
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	15,91	n.a.	365,770	145,458	47,77	n.a.	BM
2	17,25	n.a.	334,847	159,028	52,23	n.a.	MB
Total:			700,616	304,486	100,00	0,000	

(*S*,*E*)-3-(4-Methylstyryl)cyclohexanone (52o):

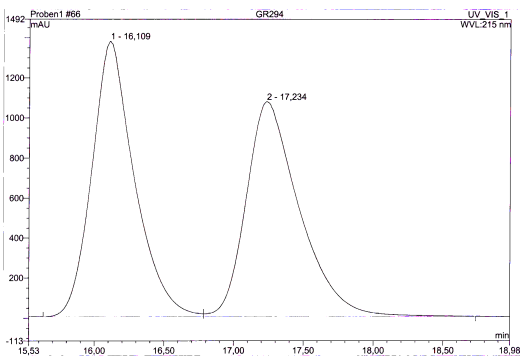


HPLC Data:

Chiralcel OD-H; *n*-heptane : *i*-propanol 99:1; flow: 1.0 mL/min

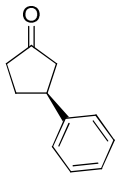


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	16,40	n.a.	23,455	8,686	4,02	n.a.	BMB*
2	17,76	n.a.	395,861	207,309	95,98	n.a.	BMB
Total:			419,316	215,995	100,00	0,000	



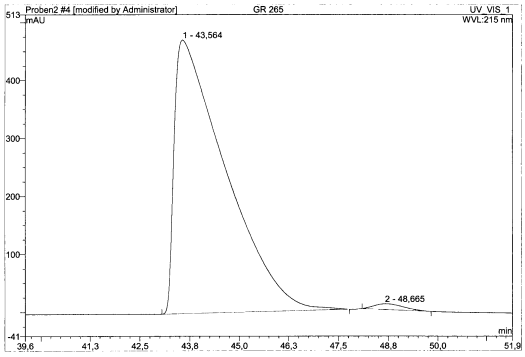
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	16,11	n.a.	1374,753	485,328	50,72	n.a.	BM
2	17,23	n.a.	1072,360	471,525	49,28	n.a.	MB
Total:			2447,114	956,853	100,00	0,000	

(*S*)-3-Phenylcyclopentanone (53a):

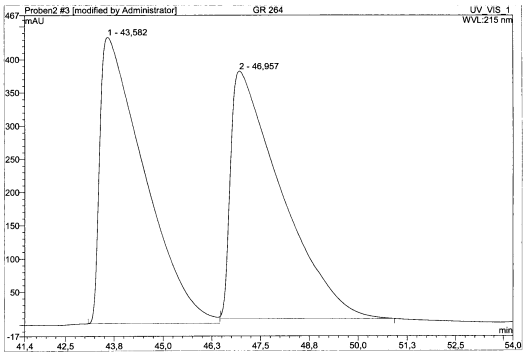


HPLC Data:

Chiralcel OB-H; *n*-heptane : *i*-propanol 99:1; flow: 0.5 mL/min

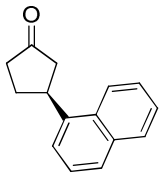


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	43,56	n.a.	472,239	706,999	98,81	n.a.	BMB*
2	48,66	n.a.	9,977	8,500	1,19	n.a.	BMB*
Total:			482,216	715,499	100,00	0,000	



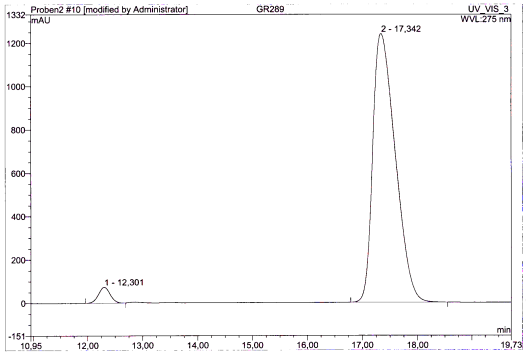
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	43,58	n.a.	431,683	567,373	50,17	n.a.	BM *
2	46,96	n.a.	373,334	563,512	49,83	n.a.	MB*
Total:			805,016	1130,885	100,00	0,000	

(*S*)-3-(Naphthalen-1-yl)cyclopentanone (53b):

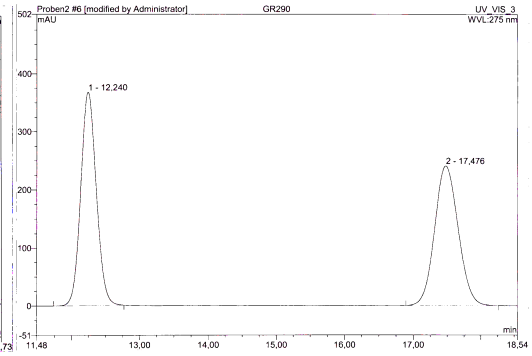


HPLC Data:

Chiralcel AS-H; *n*-heptane : *i*-propanol 80:20; flow: 0.7 mL/min

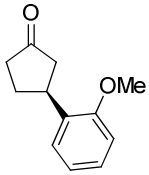


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	12,30	n.a.	72,955	17,879	2,96	n.a.	BMB*
2	17,34	n.a.	1240,831	585,984	97,04	n.a.	BMB*
Total:			1313,785	603,863	100,00	0,000	



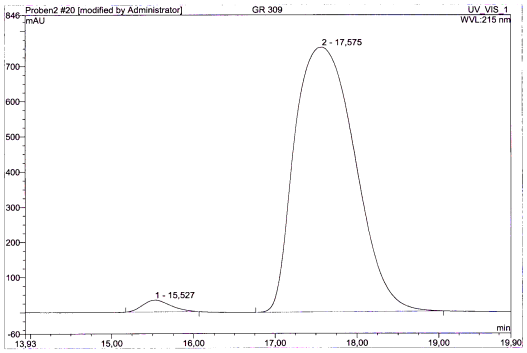
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	12,24	n.a.	367,369	97,661	50,17	n.a.	BMB*
2	17,48	n.a.	240,847	97,013	49,83	n.a.	BMB*
Total:			608,217	194,674	100,00	0,000	

(*S*)-3-(2-Methoxyphenyl)cyclopentanone (53c):

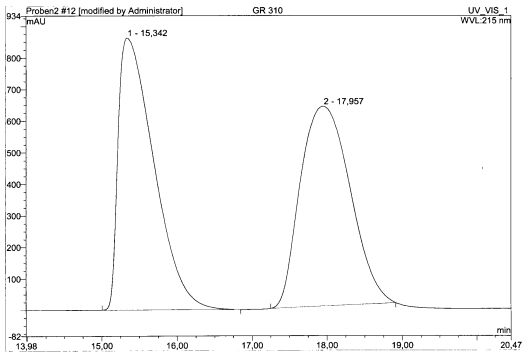


HPLC Data:

Chiralcel OB-H; *n*-heptane : *i*-propanol 90:10; flow: 0.7 mL/min

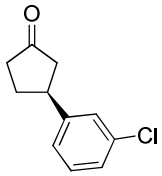


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	15,53	n.a.	33,515	13,164	2,01	n.a.	BMB*
2	17,57	n.a.	753,200	642,563	97,99	n.a.	BMB*
Total:			786,716	655,727	100,00	0,000	



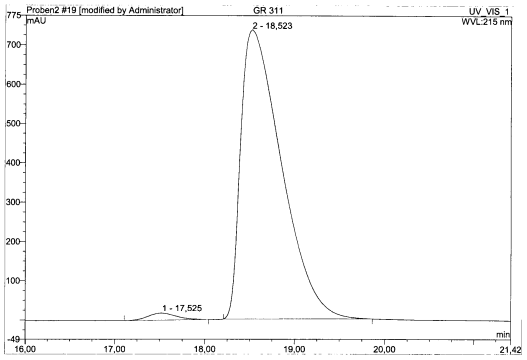
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	15,34	n.a.	863,000	474,051	49,31	n.a.	BMB*
2	17,96	n.a.	633,704	487,262	50,69	n.a.	BMB*
Total:			1496,703	961,313	100,00	0,000	

(*S*)-3-(3-Chlorophenyl)cyclopentanone (53d):

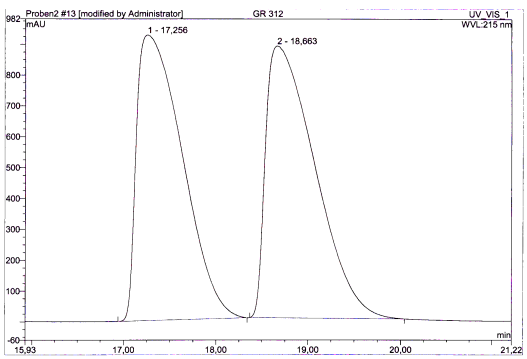


HPLC Data:

Chiralcel OB-H; *n*-heptane : *i*-propanol 90:10; flow: 0.7 mL/min

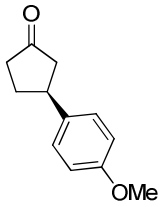


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	17,52	n.a.	17,880	6,466	1,64	n.a.	BMB*
2	18,52	n.a.	735,924	388,524	98,36	n.a.	BMB*
Total:			753,804	394,990	100,00	0,000	



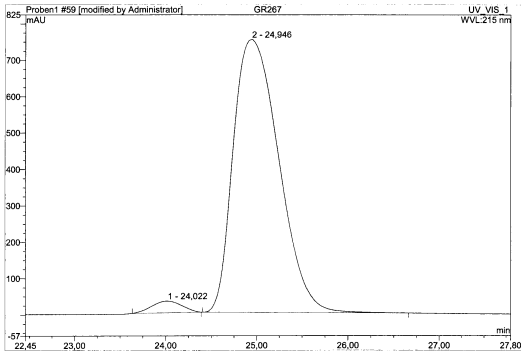
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	17,26	n.a.	926,337	530,386	49,20	n.a.	BMB*
2	18,66	n.a.	881,861	547,564	50,80	n.a.	BMB*
Total:			1808,198	1077,950	100,00	0,000	

(*S*)-3-(4-Methoxyphenyl)cyclopentanone (53e):

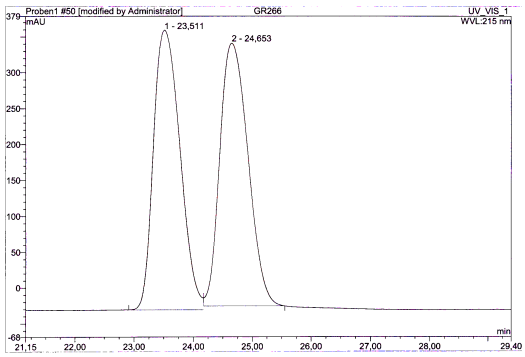


HPLC Data:

Chiralcel OD-H; *n*-heptane : *i*-propanol 95:5; flow: 0.5 mL/min

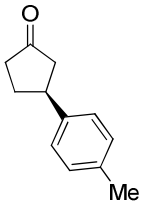


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	24,02	n.a.	32,131	12,270	2,73	n.a.	BMB*
2	24,95	n.a.	750,315	437,335	97,27	n.a.	BMB*
Total:			782,446	449,605	100,00	0,000	



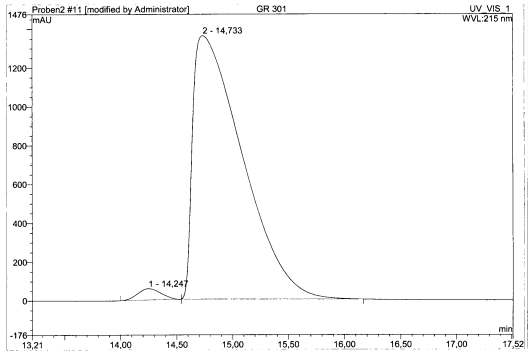
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	23,51	n.a.	390,167	202,315	49,89	n.a.	BM *
2	24,65	n.a.	366,642	203,230	50,11	n.a.	MB*
Total:			756,809	405,545	100,00	0,000	

(*S*)-3-(*p*-Tolyl)cyclopentanone (53f):

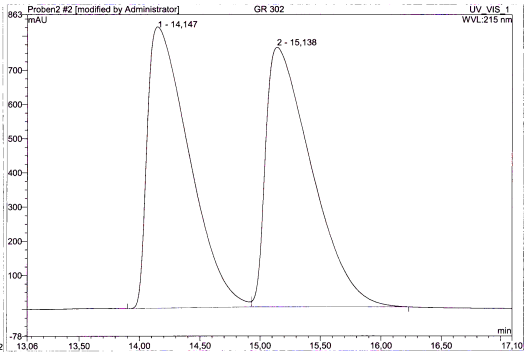


HPLC Data:

Chiralcel OB-H; *n*-heptane : *i*-propanol 95:5; flow: 0.7 mL/min

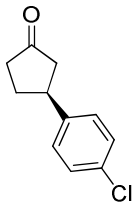


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	14,25	n.a.	58,582	13,882	1,94	n.a.	BMb*
2	14,73	n.a.	1359,642	701,284	98,06	n.a.	bMB*
Total:			1418,223	715,166	100,00	0,000	



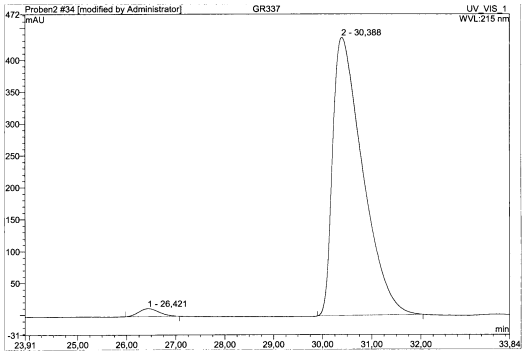
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	14,15	n.a.	823,557	329,626	49,49	n.a.	BM *
2	15,14	n.a.	760,584	336,375	50,51	n.a.	MB*
Total:			1584,142	666,002	100,00	0,000	

(*S*)-3-(4-Chlorophenyl)cyclopentanone (53g):

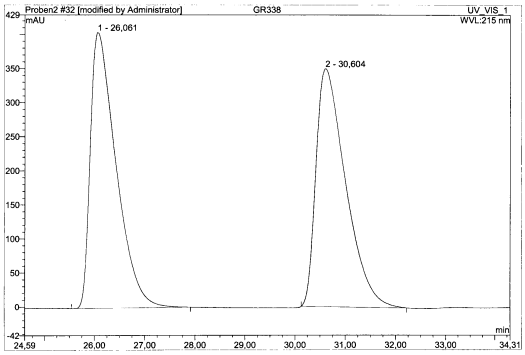


HPLC Data:

Chiralcel OB-H; *n*-heptane : *i*-propanol 90:10; flow: 0.5 mL/min

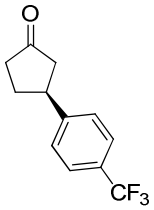


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	26,42	n.a.	12,359	5,858	1,87	n.a.	BMB*
2	30,39	n.a.	436,689	307,479	98,13	n.a.	BMB*
Total:			449,048	313,337	100,00	0,000	



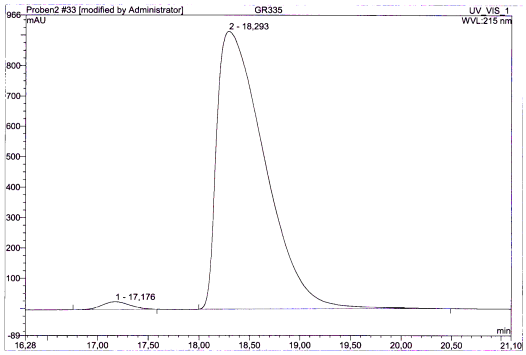
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	26,06	n.a.	404,686	239,906	50,15	n.a.	BMB*
2	30,60	n.a.	349,416	238,456	49,85	n.a.	BMB*
Total:			754,102	478,361	100,00	0,000	

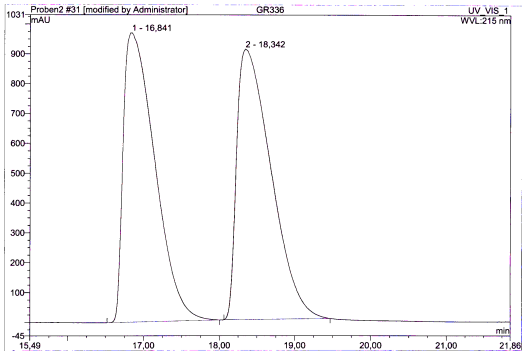
(*S*)-3-(4-(Trifluoromethyl)phenyl)cyclopentanone (53h):



HPLC Data:

Chiralcel OB-H; *n*-heptane : *i*-propanol 90:10; flow: 0.5 mL/min

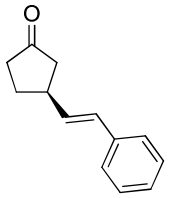




No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	17,18	n.a.	25,432	8,060	1,58	n.a.	BMB*
2	18,29	n.a.	915,354	501,940	98,42	n.a.	BMB*
Total:			940,786	510,000	100,00	0,000	

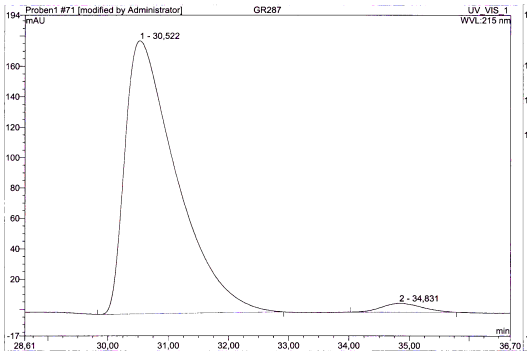
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	16,84	n.a.	970,380	465,800	49,35	n.a.	BMB*
2	18,34	n.a.	906,881	478,027	50,65	n.a.	BMB*
Total:			1877,261	943,828	100,00	0,000	

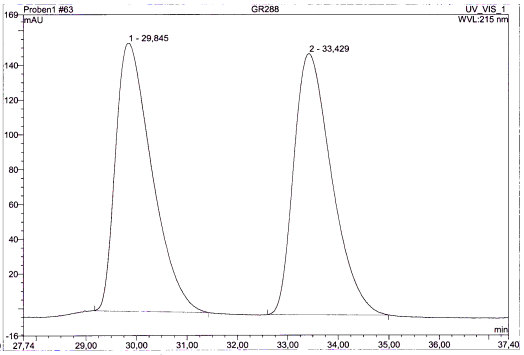
(*S*,*E*)-3-Styrylcyclopentanone (53i):



HPLC Data:

Chiralcel OD-H; *n*-heptane : *i*-propanol 99:1; flow: 1.0 mL/min

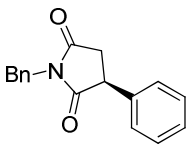




No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	30,52	n.a.	179,790	177,514	97,53	n.a.	BMB*
2	34,83	n.a.	5,882	4,505	2,47	n.a.	BMB*
Total:			185,672	182,018	100,00	0,000	

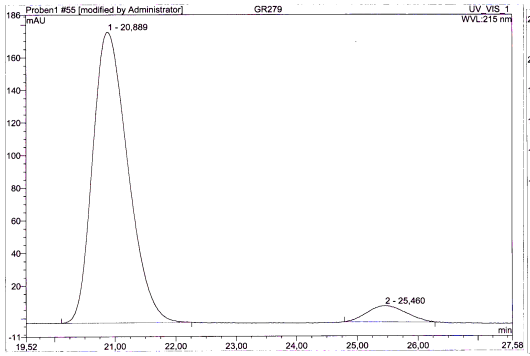
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	29,85	n.a.	154,272	127,953	49,44	n.a.	BMB
2	33,43	n.a.	150,397	130,853	50,56	n.a.	BMB
Total:			304,670	258,806	100,00	0,000	

(*S*)-1-Benzyl-3-phenylpyrrolidine-2,5-dione (54a):

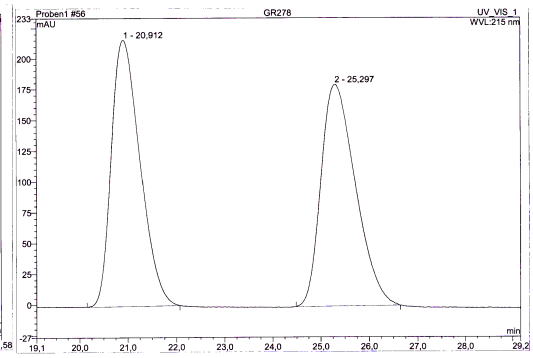


HPLC Data:

Chiralcel OD-H; *n*-heptane : *i*-propanol 90:10; flow: 1.0 mL/min

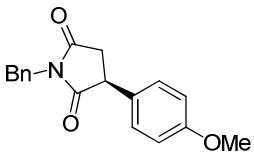


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	20,89	n.a.	178,364	120,107	94,25	n.a.	BMB*
2	25,46	n.a.	10,036	7,332	5,75	n.a.	BMB*
Total:			188,400	127,439	100,00	0,000	



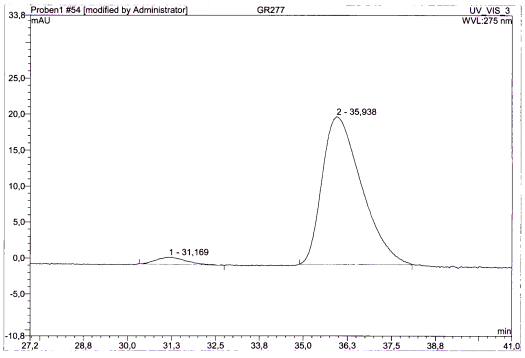
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	20,91	n.a.	216,838	148,680	49,95	n.a.	BMB
2	25,30	n.a.	180,323	148,987	50,05	n.a.	BMB
Total:			397,162	297,667	100,00	0,000	

(*S*)-1-Benzyl-3-(4-methoxyphenyl)pyrrolidine-2,5-dione (54b):

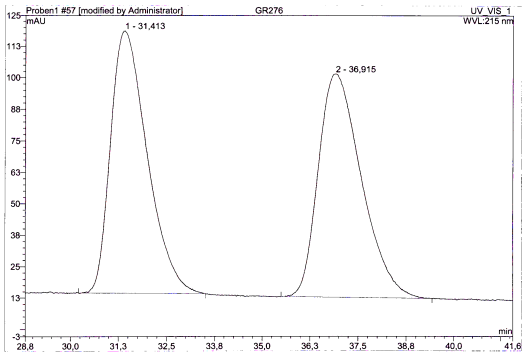


HPLC Data:

Chiralcel OD-H; *n*-heptane : *i*-propanol 90:10; flow: 1.0 mL/min

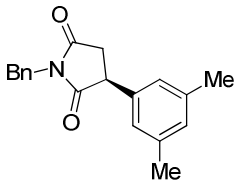


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	31,17	n.a.	1,012	0,983	3,58	n.a.	BMB*
2	35,94	n.a.	20,532	26,454	96,42	n.a.	BMB
Total:			21,545	27,438	100,00	0,000	



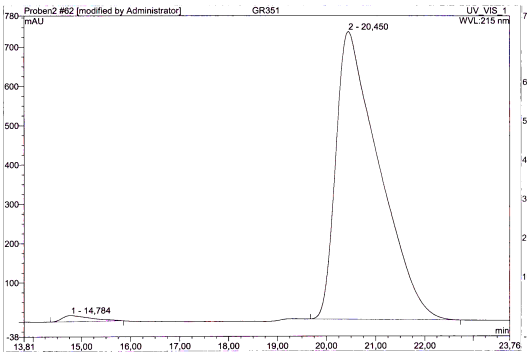
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	31,41	n.a.	104,246	115,257	49,98	n.a.	BMB*
2	36,92	n.a.	88,695	115,361	50,02	n.a.	BMB*
Total:			192,940	230,618	100,00	0,000	

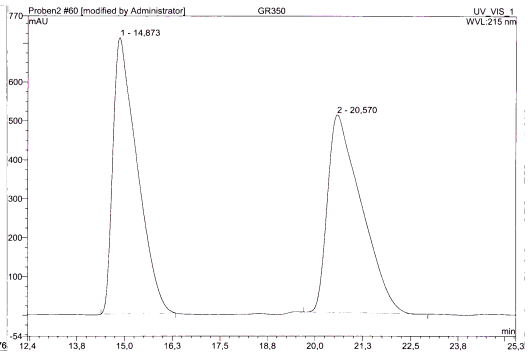
(*S*)-1-Benzyl-3-(3,5-dimethylphenyl)pyrrolidine-2,5-dione (54c):



HPLC Data:

Chiralcel AD-H; *n*-heptane : *i*-propanol 95:5; flow: 1.0 mL/min



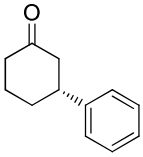


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	14,78	n.a.	15,824	10,576	1,40	n.a.	BMB*
2	20,45	n.a.	734,654	746,341	98,60	n.a.	BMB*
Total:			750,478	756,917	100,00	0,000	

No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	14,87	n.a.	710,604	521,982	49,93	n.a.	BMB*
2	20,57	n.a.	509,225	523,411	50,07	n.a.	BMB*
Total:			1219,829	1045,394	100,00	0,000	

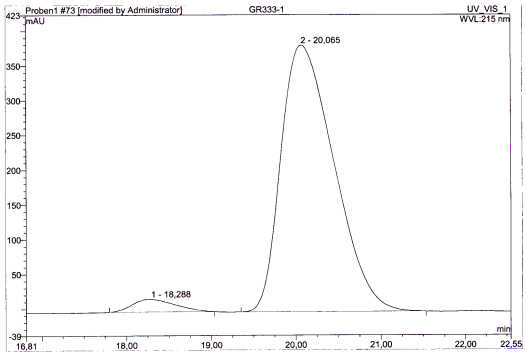
3.7.2 Compounds of Table 2

(*R*)-3-Phenylcyclohexanone (55a):



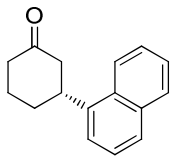
HPLC Data:

Chiralcel AD; *n*-heptane : *i*-propanol 90:10; flow: 0.3 mL/min



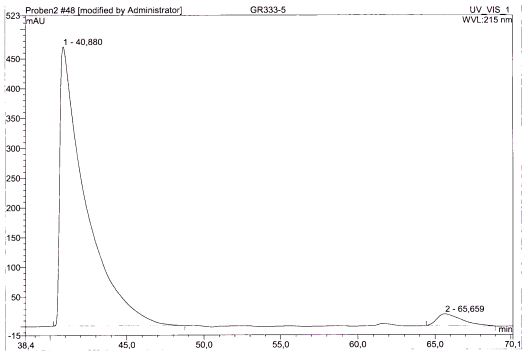
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	18,29	n.a.	18,770	10,866	3,74	n.a.	BMB*
2	20,07	n.a.	384,093	279,344	96,26	n.a.	BMB*
Total:			402,863	290,210	100,00	0,000	

(*R*)-3-(Naphthalen-1-yl)cyclohexanone (55b):



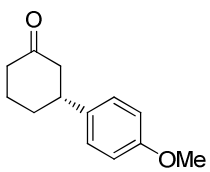
HPLC Data:

Chiralcel OD-H; *n*-heptane : *i*-propanol 95:5; flow: 0.5 mL/min



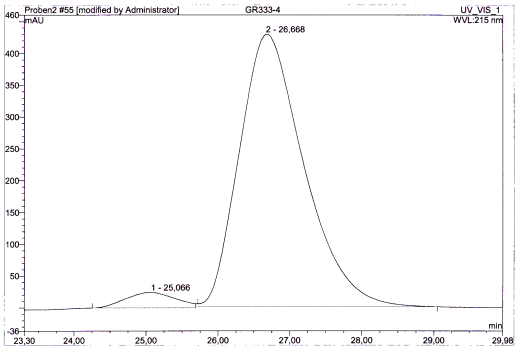
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	40,88	n.a.	469,118	911,025	95,99	n.a.	BMB*
2	65,66	n.a.	20,240	38,017	4,01	n.a.	BMB*
Total:			489,358	949,042	100,00	0,000	

(*R*)-3-(4-Methoxyphenyl)cyclohexanone (55c):



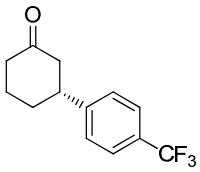
HPLC Data:

Chiralcel AD-H; *n*-heptane : *i*-propanol 98:2; flow: 0.5 mL/min



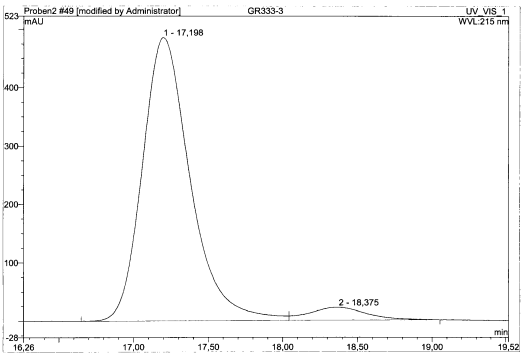
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	25,07	n.a.	24,353	19,371	4,16	n.a.	BM *
2	26,67	n.a.	428,709	446,819	95,84	n.a.	MB*
Total:			453,062	466,190	100,00	0,000	

(*R*)-3-(4-(Trifluoromethyl)phenyl)cyclohexanone (55d):



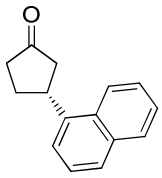
HPLC Data:

Chiralcel OD-H; *n*-heptane : *i*-propanol 95:5; flow: 0.5 mL/min



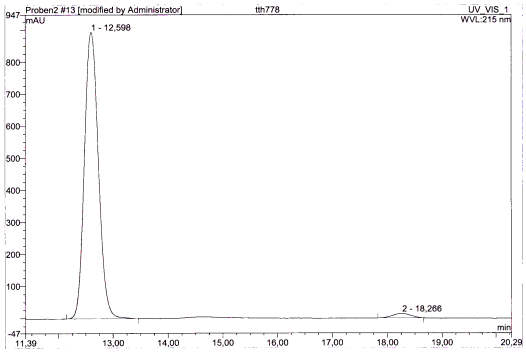
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	17,20	n.a.	485,240	179,678	94,96	n.a.	BM *
2	18,38	n.a.	21,716	9,538	5,04	n.a.	MB*
Total:			506,956	189,216	100,00	0,000	

(*R*)-3-(Naphthalen-1-yl)cyclopentanone (56a):



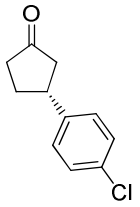
HPLC Data:

Chiralcel AD-H; *n*-heptane : *i*-propanol 80:20; flow: 0.7 mL/min



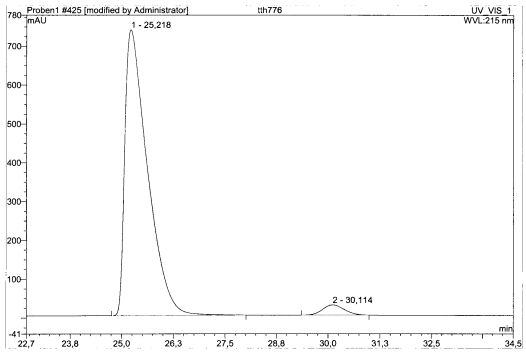
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	12,60	n.a.	893,939	266,100	98,02	n.a.	BMB
2	18,27	n.a.	14,037	5,375	1,98	n.a.	BMB*
Total:			907,976	271,475	100,00	0,000	

(*R*)-3-(4-Chlorophenyl)cyclopentanone (56b):



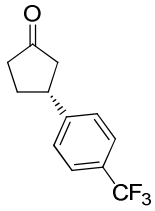
HPLC Data:

Chiralcel OB-H; *n*-heptane : *i*-propanol 90:10; flow: 0.5 mL/min



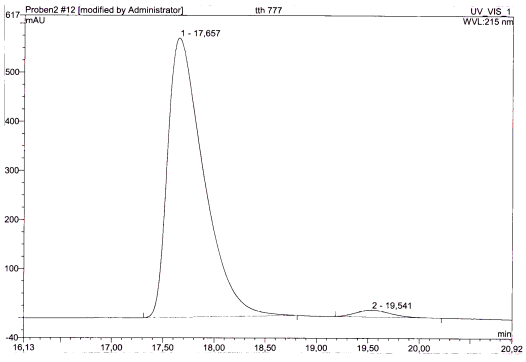
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	25,22	n.a.	736,322	464,810	96,68	n.a.	BMB
2	30,11	n.a.	26,330	15,959	3,32	n.a.	BMB*
Total:			762,652	480,769	100,00	0,000	

(*R*)-3-(4-(Trifluoromethyl)phenyl)cyclopentanone (56c):



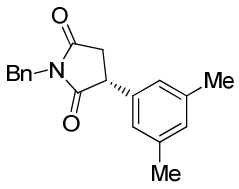
HPLC Data:

Chiralcel OB-H; *n*-heptane : *i*-propanol 90:10; flow: 0.5 mL/min



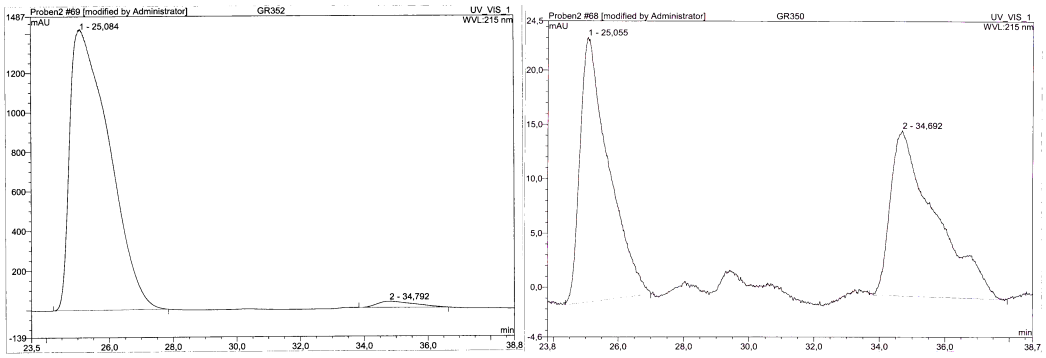
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	17,66	n.a.	568,653	231,351	97,72	n.a.	BMB
2	19,54	n.a.	13,798	5,407	2,28	n.a.	BMB*
Total:			582,450	236,758	100,00	0,000	

(*R*)-1-Benzyl-3-(3,5-dimethylphenyl)pyrrolidine-2,5-dione (57):



HPLC Data:

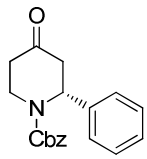
Chiralcel AD-H; *n*-heptane : *i*-propanol 95:5; flow: 0.6 mL/min



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	25,08	n.a.	1424,253	2041,539	98,00	n.a.	BMB*
2	34,79	n.a.	30,764	41,626	2,00	n.a.	BMB*
Total:			1455,017	2083,165	100,00	0,000	

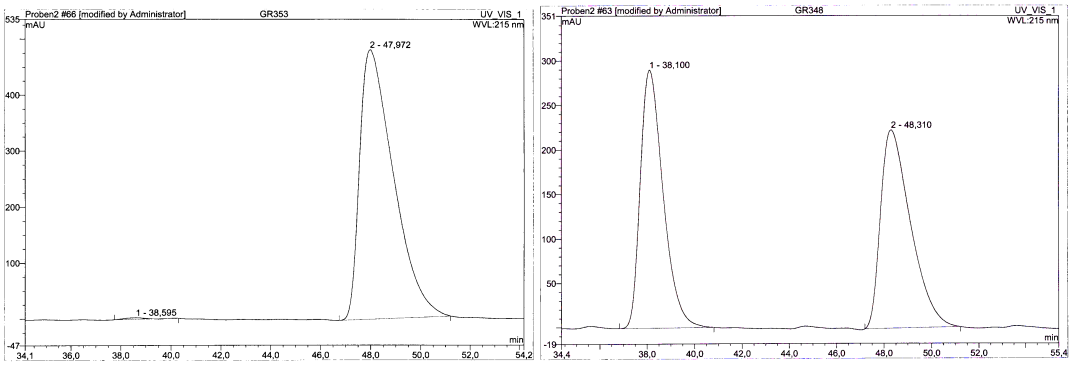
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	25,05	n.a.	24,367	24,915	50,47	n.a.	BMB*
2	34,69	n.a.	15,256	24,449	49,53	n.a.	BMB*
Total:			39,623	49,364	100,00	0,000	

(*R*)-Benzyl 4-oxo-2-phenylpiperidine-1-carboxylate (58):



HPLC Data:

Chiralcel OD-H; *n*-heptane : *i*-propanol 90:10; flow: 0.6 mL/min

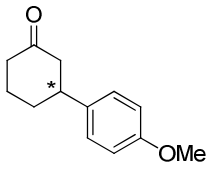


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	38,59	n.a.	2,750	2,265	0,30	n.a.	BMB*
2	47,97	n.a.	481,918	751,427	99,70	n.a.	BMB*
Total:			484,669	753,693	100,00	0,000	

No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	38,10	n.a.	290,500	324,426	49,89	n.a.	BMB*
2	48,31	n.a.	223,503	325,805	50,11	n.a.	BMB*
Total:			514,004	650,231	100,00	0,000	

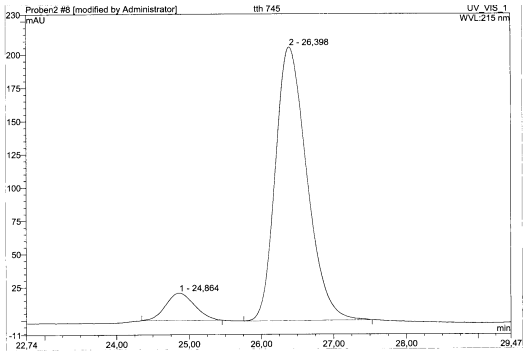
3.7.3 Compounds of Table 3

3-(4-Methoxyphenyl)cyclohexanone (61a):



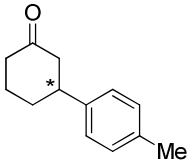
HPLC Data:

Chiralcel AD-H; *n*-heptane : *i*-propanol 98:2; flow: 0.5 mL/min



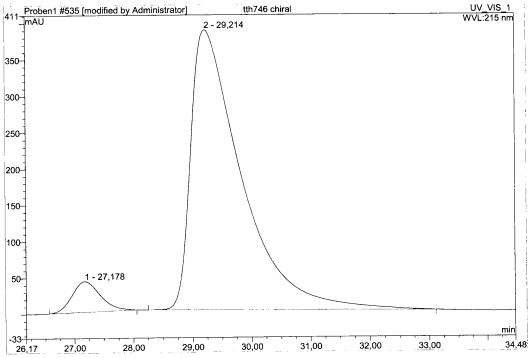
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	24,86	n.a.	20,581	9,428	8,31	n.a.	BMB*
2	26,40	n.a.	205,798	104,039	91,69	n.a.	BMB
Total:			226,379	113,467	100,00	0,000	

3-(*p*-Tolyl)cyclohexanone (61b):

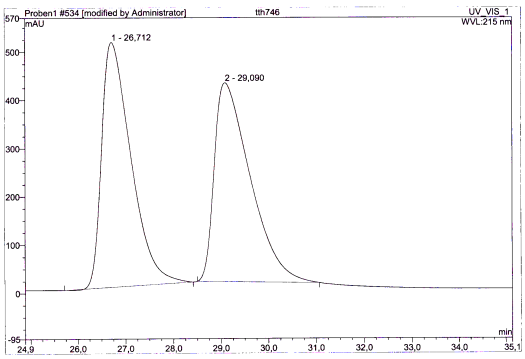


HPLC Data:

Chiralcel AS-H; *n*-heptane : *i*-propanol 95:5; flow: 0.5 mL/min

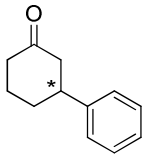


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	27,18	n.a.	42,365	23,747	5,81	n.a.	BMB*
2	29,21	n.a.	385,344	385,160	94,19	n.a.	BMB
Total:			427,709	408,907	100,00	0,000	



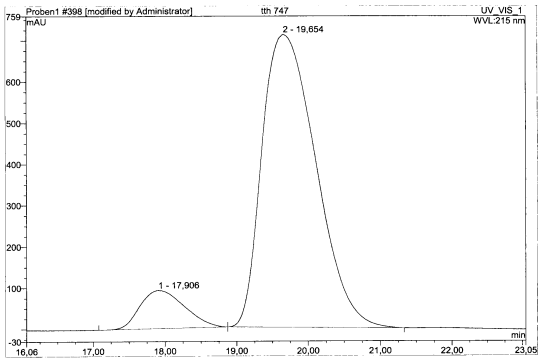
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	26,71	n.a.	506,774	359,787	49,87	n.a.	BMB*
2	29,09	n.a.	411,942	361,715	50,13	n.a.	BMB*
Total:			918,716	721,502	100,00	0,000	

3-Phenylcyclohexanone (61c):



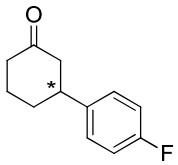
HPLC Data:

Chiralcel AD; *n*-heptane : *i*-propanol 90:10; flow: 0.3 mL/min



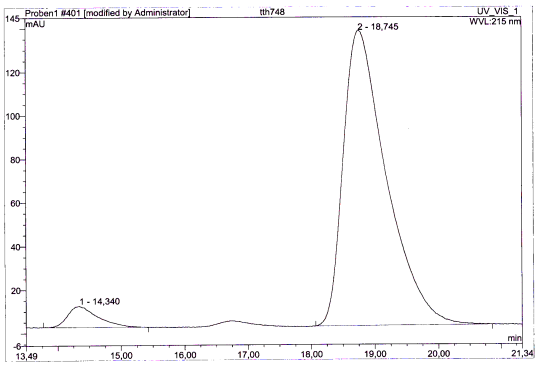
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	17,91	n.a.	92,961	66,265	9,65	n.a.	BMb*
2	19,65	n.a.	711,067	620,089	90,35	n.a.	bMB*
Total:			804,028	686,354	100,00	0,000	

3-(4-Fluorophenyl)cyclohexanone (61d):



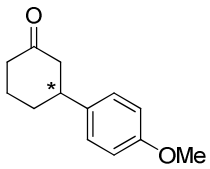
HPLC Data:

Chiralcel AD; *n*-heptane : *i*-propanol 99:1; flow: 1.0 mL/min



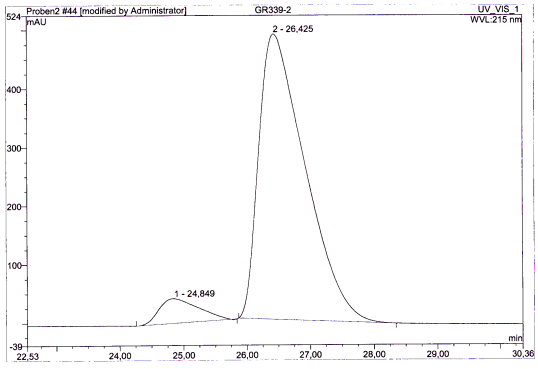
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	14,34	n.a.	9,734	5,413	4,84	n.a.	BMB*
2	18,75	n.a.	135,720	106,322	95,16	n.a.	BMB*
Total:			145,454	111,735	100,00	0,000	

3-(4-Methoxyphenyl)cyclohexanone (62a):



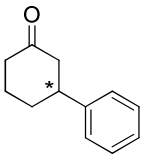
HPLC Data:

Chiralcel AD-H; *n*-heptane : *i*-propanol 98:2; flow: 0.5 mL/min



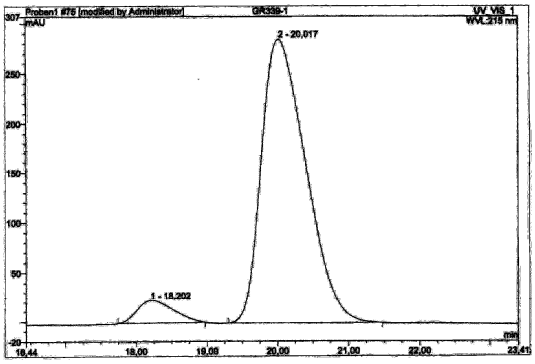
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	24,85	n.a.	42,312	30,040	6,76	n.a.	BMB*
2	26,42	n.a.	487,127	414,186	93,24	n.a.	BMB*
Total:			529,439	444,226	100,00	0,000	

3-Phenylcyclohexanone (62b):



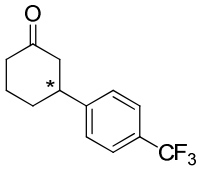
HPLC Data:

Chiralcel AD; *n*-heptane : *i*-propanol 90:10; flow: 0.3 mL/min



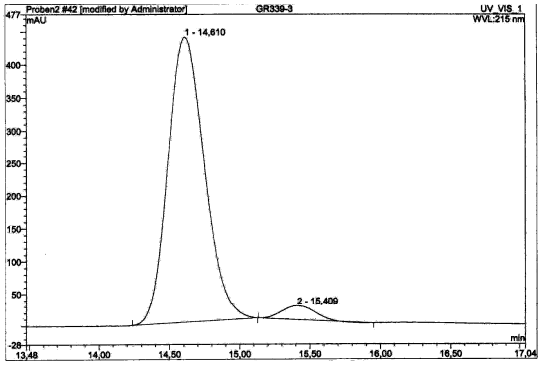
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	18,20	n.a.	23,306	13,654	6,13	n.a.	BMB*
2	20,02	n.a.	286,095	209,128	93,87	n.a.	BMB*
Total:			309,400	222,782	100,00	0,000	

3-(4-(Trifluoromethyl)phenyl)cyclohexanone (62c):



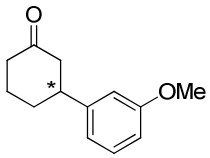
HPLC Data:

Chiralcel OD-H; *n*-heptane : *i*-propanol 90:10; flow: 0.5 mL/min



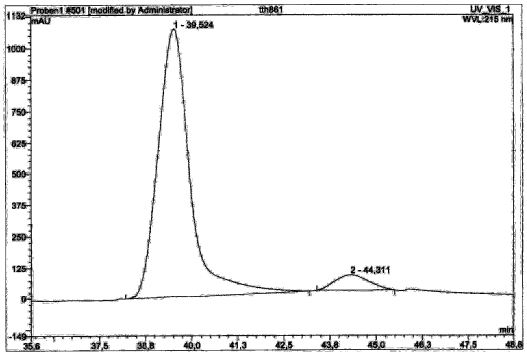
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	14,61	n.a.	436,000	131,316	95,76	n.a.	BMB*
2	15,41	n.a.	21,622	5,810	4,24	n.a.	BMB*
Total:			457,621	137,126	100,00	0,000	

3-(3-Methoxyphenyl)cyclohexanone (64a):



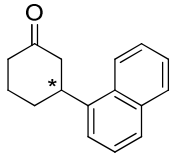
HPLC Data:

Chiralcel OD-H; *n*-heptane : *i*-propanol 99:1; flow: 1.0 mL/min



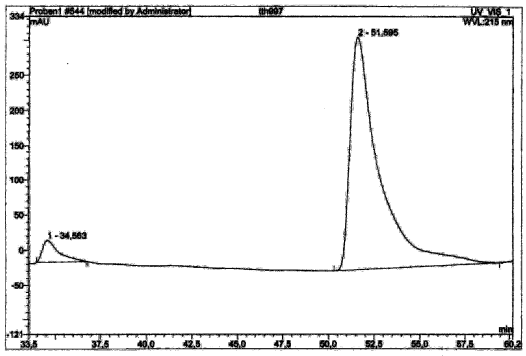
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	39,52	n.a.	1069,379	1069,176	94,39	n.a.	BMB
2	44,31	n.a.	60,357	63,561	5,61	n.a.	BMB*
Total:			1129,736	1132,736	100,00	0,000	

3-(Naphthalen-1-yl)cyclohexanone (64b):



HPLC Data:

Chiralcel OD-H; *n*-heptane : *i*-propanol 95:5; flow: 0.5 mL/min

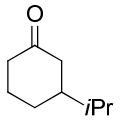


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	34,56	n.a.	30,804	33,356	5,16	n.a.	BMB*
2	51,60	n.a.	332,344	613,069	94,84	n.a.	BMB
Total:			363,148	646,425	100,00	0,000	

4. Pd-Catalyzed Diastereoselective Csp^3-Csp^2 Cross-Coupling Reactions.

4.1 Preparation of starting materials

Synthesis of 3-isopropylcyclohexanone

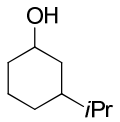


To a stirred solution of CuI (5.71 g; 30 mmol) and LiCl (2.52 g; 60 mmol) in THF and cooled to 0 °C, was added 2-cyclohexenone (28.8 g; 300 mmol) and TMSCl (41.4 mL; 300 mmol) and the stirring was continued for 1 h before the mixture was cooled to –78 °C. Then, *i*PrMgCl·LiCl (1.30 M in THF; 242 mL; 315 mmol) was added within 45 min and the stirring was continued for 4 h. Sat. NH_4Cl aq. solution (200 mL) was added and the reaction mixture was allowed to warm to rt. Most of the solvents were removed under reduced pressure. The residue was extracted with Et_2O (3 x 150 mL). The combined organic phases were washed several times with sat. NH_4Cl aq. solution (3 x 50 mL) until the aqueous phase remained colorless. The combined organic phases were then washed with brine and dried (Na_2SO_4). Solvents were removed on the rotary evaporator. The crude product was treated with a mixture of EtOH and H_2O (1:1; 80 mL) and HCl (2 M; 50 mL) and stirred at room temperature overnight. Et_2O (200 mL) was added and the phases were separated. The aqueous phase was extracted with 3 x 100 mL Et_2O. The combined organic phases were dried (Na_2SO_4). The solvents were removed via rotary evaporation to give 3-isopropylcyclohexanone as a colorless liquid (41 g) in 97% yield.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.33 (t, *J*=13.8 Hz, 1 H), 2.24-2.18 (m, 1 H), 2.06-2.02 (m, 1 H), 1.83 (d, *J*=13.4 Hz, 1 H), 1.61-1.50 (m, 1 H), 1.37-1.30 (m, 1 H), 0.88-0.86 (m, 1 H).
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 212.6, 45.4, 45.3, 41.4, 32.4, 28.3, 25.5, 19.5, 19.3.
MS (70 eV, EI) *m/z* (%): 140 (18) [M^+], 98 (10), 97 (100), 96 (10), 82 (19), 69 (36), 55 (14), 55 (26), 41 (34).
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2958 (m), 2871 (m), 1709 (vs), 1464 (w), 1448 (w), 1423 (w), 1387 (w), 1369 (w), 1347 (w), 1314 (m), 1258 (w), 1226 (m), 1197 (w), 1122 (w), 1058 (w), 902 (w), 871 (w), 565 (w).

HRMS (EI) for **$C_9H_{16}O$** (140.1201): 140.1194.

Synthesis of 3-isopropylcyclohexanol



$LiAlH_4$ (3.42 g; 90 mmol) was suspended in Et_2O (90 mL). The suspension was heated to reflux for 1 h. After cooling to 0 °C, a solution of 3-isopropylcyclohexanone (41 g; 296 mmol) in 24 ml Et_2O was added dropwise. After the addition was complete, the reaction mixture was heated to reflux (12 h). The reaction mixture was cooled to 0 °C and carefully quenched via addition of a 1:1 mixture of NaOH (2 M) and H_2O (7 mL). Additional 20 mL of H_2O were added along with 24 g of Celite. The suspension was stirred for 2 h at room temperature and filtered. The precipitate was washed with Et_2O (4 x 200 mL). The solvent was removed via rotary evaporation to give 3-isopropylcyclohexanol (37.5 g) as a colorless liquid in 89% yield.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.54 (tt, J_1=10.7 Hz, J_2=4.3 Hz, 1 H), 1.94 (d, J=12.4 Hz, 2 H), 1.81-1.70 (m, 2 H), 1.59 (ddd, J_1=12.8 Hz, J_2=1.5 Hz, J_3=1.3 Hz, 1 H), 1.45 (dd, J_1=12.6 Hz, J_2=6.8 Hz, 1 H), 1.25-1.06 (m, 3 H), 0.97-0.77 (m, 8 H). (mixture of diastereomers; signals of the major isomer are given)

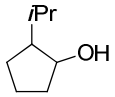
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 71.3, 42.7, 39.2, 35.9, 32.6, 28.6, 24.2, 19.8, 19.6. (mixture of diastereomers; signals of the major isomer are given)

MS (70 eV, EI) *m/z* (%): 124 (18), 109 (21), 99 (16), 83 (13), 82 (42), 81 (100), 80 (12), 69 (18), 66 (17), 57 (33), 55 (37), 43 (19), 43 (10), 41 (31).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3328 (m), 2929 (vs), 2856 (s), 1705 (w), 1463 (m), 1450 (m), 1385 (m), 1368 (m), 1088 (m), 1043 (vs), 978 (m).

HRMS (EI) for **$C_9H_{18}O$** (142.1358): 142.1349.

Synthesis of 2-isopropylcyclopentanol[152]



To a solution of $CuBr \cdot SMe_2$ (6.2 g; 30 mmol) in THF (300 mL) cooled to –30 °C was added *i*PrMgCl-LiCl (1.23 M in THF; 312 mL; 384 mmol) over 45 min. After the addition was complete, the mixture was stirred for 30 min and cyclopentene oxide (25 g; 300 mmol) was added. The reaction mixture was stirred for 1 h at –30 °C and was then warmed to room temperature (12 h). The reaction mixture was quenched with sat. NH_4Cl aq. solution (200 mL). Phases were separated and the aqueous phase was extracted with Et_2O (3 x 200 mL). The combined organic layers were dried (Na_2SO_4) and the solvents were evaporated. The crude product was distilled to give 2-isopropylcyclopentanol (22.3 g) as a colorless liquid in 59% yield.

(Mixture of diastereomers; signals of the major isomer are given)

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.95 (dt, J_1=6.6 Hz, J_2=4.7 Hz, 1 H), 1.87-1.76 (m, 2 H), 1.70-1.61 (m, 1 H), 1.60-1.41 (m, 5 H), 1.26-1.13 (m, 1 H), 0.96 (d, J=6.6 Hz, 3 H), 0.86 (d, J=6.6 Hz, 3 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 77.1, 55.7, 35.9, 30.8, 28.3, 22.8, 21.5, 20.2.

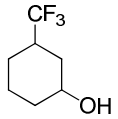
MS (70 eV, EI) *m/z* (%): 109 (22), 95 (88), 85 (14), 82 (19), 81 (18), 69 (79), 68 (30), 67 (46), 57 (100), 56 (53), 55 (35), 44 (22), 43 (69), 41 (64).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3335 (m), 3332 (m), 2953 (vs), 2870 (s), 1466 (m), 1449 (m), 1385 (m), 1367 (m), 1342 (m), 1316 (m), 1163 (m), 1079 (m), 1026 (s), 987 (m), 967 (m), 931 (m), 913 (m), 848 (m).

HRMS (EI) for **$C_8H_{16}O$** (128.1201): 128.1205.

[152] C. M. Grise, L. Barriault, *Org. Lett.* **2006**, *8*, 5905.

Synthesis of 3-(trifluoromethyl)cyclohexanol

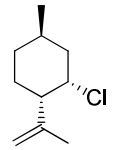


This compound was prepared from commercially available 3-(trifluoromethyl)phenol according to literature procedure.[153]

4.2 Preparation of cycloalkyl chlorides

To a suspension of *N*-chlorosuccinimide (1.3 equiv) in THF (0.5 M) cooled to 0 °C was carefully added a solution of PPh_3 (1.0 equiv) in THF (1.5 M). After the addition was complete the respective cycloalcohol was added. After 4 h, the reaction mixture was allowed to warm to room temperature and was stirred overnight. The reaction mixture was carefully concentrated *in vacuo* (some cycloalkyl chlorides are volatile!). The residue was treated with *n*-pentane. The precipitate was filtered off and washed with *n*-pentane. Removal of *n*-pentane and distillation of the resulting oils furnished the respective chlorides with up to 72% yield.

(1*S*,2*S*,4*R*)-2-Chloro-1-isopropenyl-4-methylcyclohexane



colorless oil (72%)

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 4.87 (d, *J*=1.2 Hz, 1 H), 4.73 (s, 1 H), 4.53 (d, *J*=1.7 Hz, 1 H), 2.15-2.06 (m, 2 H), 2.01-1.86 (m, 1 H), 1.85-1.70 (m, 5 H), 1.64-1.58 (m, 1 H), 1.45 (ddd, J_1=14.1 Hz, J_2=11.7 Hz, J_3=2.9 Hz, 1 H), 1.04-0.89 (m, 4 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 145.8, 111.2, 62.0, 48.0, 43.1, 34.5, 25.9, 24.1, 21.8, 21.7.

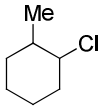
MS (70 eV, EI) *m/z* (%): 138 (31), 123 (100), 96 (88), 95 (38), 94 (31), 83 (25), 82 (48), 81 (27), 69 (59), 68 (42), 67 (62), 56 (24), 55 (77), 54 (31), 53 (26), 43 (47), 41 (67).

[153] I. M. Zalesskaya, A. N. Blakitnyi, E. P. Saenko, Y. A. Fialkov, L. M. Yagupol'skii, *Zh. Org. Khim.* **1980**, *16*, 1194.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2949 (m), 2928 (m), 2868 (m), 1647 (m), 1455 (m), 1444 (m), 1375 (m), 1297 (m), 1276 (m), 1246 (m), 1179 (w), 994 (w), 949 (m), 902 (m), 887 (vs), 860 (m), 683 (vs), 668 (w).

HRMS (EI) for **$C_{10}H_{19}Cl$** (174.1175): 174.1197.

1-Chloro-2-methylcyclohexane



colorless liquid (40%)

(Mixture of diastereomers; signals of the major isomer are given)

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 4.26 (d, *J*=2.9 Hz, 1 H), 2.07-1.91 (m, 1 H), 1.84-1.62 (m, 4 H), 1.50-1.35 (m, 3 H), 1.33-1.18 (m, 1H), 0.98 (d, *J*=6.8 Hz, 3 H).

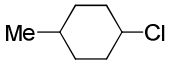
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 66.7, 37.0, 34.3, 28.5, 24.9, 20.3, 19.2.

MS (70 eV, EI) *m/z* (%): 97 (11), 96 (52), 81 (100), 70 (15), 67 (11), 55 (25).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2932 (s), 2857 (m), 1445 (m), 1269 (m), 961 (m), 876 (w), 821 (m), 766 (m), 685 (vs).

HRMS (EI) for **$C_7H_{13}Cl$** (132.0706): 132.0703.

1-Chloro-4-methylcyclohexane



colorless liquid (41%)

(Mixture of diastereomers; signals of the major isomer are given)

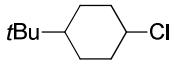
^{1}H-NMR (600 MHz, $CDCl_3$) δ: 4.39 (s, 1 H), 1.96-1.94 (m, 2 H), 1.79-1.73 (m, 2 H), 1.52-1.41 (m, 5 H), 0.92 (d, *J*=6.0 Hz, 3 H).

^{13}C-NMR (150 MHz, $CDCl_3$) δ: 59.8, 37.2, 34.8, 33.7, 31.5, 29.0, 21.9.

MS (70 eV, EI) *m/z* (%): 97 (11), 96 (40), 81 (100), 68 (16), 67 (15), 55 (41), 54 (13), 41 (23).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2947 (m), 2923 (s), 2856 (m), 1456 (m), 1441 (m), 1428 (w), 1377 (w), 1367 (w), 1357 (w), 1310 (w), 1268 (w), 1255 (s), 1217 (w), 1148 (w), 1113 (w), 1028 (w), 972 (w), 967 (w), 961 (w), 952 (m), 873 (w), 868 (w), 852 (s), 790 (w), 749 (w), 740 (w), 709 (vs).
HRMS (EI) for **$C_7H_{13}Cl$** (132.0706): 132.0696.

1-Chloro-4-*tert*-butylcyclohexane



colorless liquid (52 %)

(Mixture of diastereomers; signals of the major isomer are given)

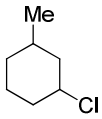
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 4.47-4.45 (m, 1 H), 2.06-2.00 (m, 2 H), 1.77-1.66 (m, 2 H), 1.60-1.45 (m, 4 H), 1.07-0.94 (m, 1 H), 0.86 (s, 9 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 60.0, 47.7, 34.5, 32.6, 27.4, 20.9.

MS (70 eV, EI) *m/z* (%): 123 (26), 81 (12), 57 (100), 56 (48), 41 (66).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2945 (vs), 2906 (s), 2867 (s), 2841 (m), 1738 (w), 1479 (s), 1441 (s), 1365 (vs), 1314 (m), 1263 (s), 1025 (s), 999 (s), 904 (m), 860 (vs), 770 (s), 692 (vs).
HRMS (EI) for **$C_{10}H_{19}Cl$** (174.1175): 174.1174.

1-Chloro-3-methylcyclohexane



colorless liquid (40%)

(Mixture of diastereomers; signals of the major isomer are given)

^{1}H-NMR (600 MHz, $CDCl_3$) δ: 4.46 (s, 1 H), 1.93 (d, *J*=12.6 Hz, 2 H), 1.78 (d, *J*=10.3 Hz, 1 H), 1.68 (d, *J*=9.5 Hz, 2 H), 1.55 (d, *J*=3.1 Hz, 1 H), 1.42 (d, *J*=11.7 Hz, 1 H), 0.97-0.88 (m, 4H).

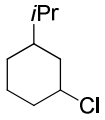
^{13}C-NMR (150 MHz, $CDCl_3$) δ: 60.0, 45.9, 42.4, 37.0, 34.1, 34.0, 26.4, 21.7, 20.3.

MS (70 eV, EI) *m/z* (%): 97 (14), 96 (40), 96 (74), 82 (12), 81 (22), 68 (30), 67 (34), 55 (100), 54 (20), 53 (11), 41 (12), 40 (31).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2929 (s), 2866 (m), 2843 (m), 1457 (m), 1446 (m), 1427 (w), 1378 (w), 1267 (s), 1106 (w), 1037 (w), 974 (w), 960 (w), 876 (m), 862 (s), 848 (m), 839 (w), 771 (m), 740 (m), 684 (vs).

HRMS (EI) for **$C_7H_{13}Cl$** (132.0706): 132.0698.

1-Chloro-3-isopropylcyclohexane



colorless liquid (54%)

(Mixture of diastereomers; signals of the major isomer are given)

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 4.54-4.52 (m, 1 H), 1.99-1.88 (m, 2 H), 1.81-1.37 (m, 7 H), 1.06-0.93 (m, 1 H), 0.87 (d, *J*=1.9 Hz, 3 H), 0.84 (d, *J*=1.9 Hz, 3 H).

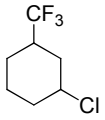
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 60.6, 37.6, 37.3, 34.2, 32.0, 28.9, 20.4, 19.7, 19.5.

MS (70 eV, EI) *m/z* (%): 124 (36), 109 (15), 82 (20), 81 (100), 80 (27), 67 (17), 55 (10), 43 (10), 41 (20).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2955 (vs), 2935 (vs), 2887 (m), 2870 (s), 1464 (m), 1447 (m), 1430 (m), 1386 (m), 1368 (m), 1268 (s), 904 (m), 862 (m), 680 (s), 577 (s).

HRMS (EI) for **$C_9H_{17}Cl$** (160.1019): 160.1003.

1-Chloro-3-(trifluoromethyl)cyclohexane



colorless liquid (37%)

(Mixture of diastereomers; signals of the major isomer are given)

^{1}H-NMR (600 MHz, $CDCl_3$) δ: 4.6 (s, 1 H), 2.66-2.56 (m, 1 H), 2.2 (d, *J*=14.1 Hz, 1 H), 2.00-1.92 (m, 2 H), 1.86-1.81 (m, 1 H), 1.78-1.67 (m, 3 H), 1.36-1.24 (m, 1 H).

^{13}C-NMR (150 MHz, $CDCl_3$) δ: 127.7 (q, *J*=278.2 Hz), 57.5, 36.3 (q, *J*=27.0 Hz), 32.99, 32.8 (d, *J*=2.7 Hz), 24.3 (d, *J*=2.4 Hz), 18.6.

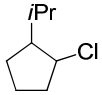
^{19}F-NMR (282 MHz, $CDCl_3$) δ: –73.5 (d, J=9.0 Hz; major isomer), –73.7 (d, J=9.0 Hz; minor isomer).

MS (70 eV, EI) *m/z* (%): 152 (17), 150 (88), 135 (21), 131 (46), 130 (56), 111 (14), 81 (100), 41 (13).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2952 (w), 2874 (w), 1459 (w), 1452 (w), 1434 (w), 1393 (m), 1353 (w), 1340 (m), 1313 (w), 1297 (m), 1254 (s), 1217 (w), 1202 (m), 1152 (s), 1115 (s), 1086 (vs), 1056 (m), 1039 (m), 987 (m), 975 (w), 913 (m), 893 (m), 770 (w), 752 (m), 734 (w), 729 (w), 724 (w), 710 (s), 695 (w), 690 (w), 678 (m), 663 (m).

HRMS (EI) for **$C_7H_{10}ClF_3$** (186.0423): 186.0419

1-Chloro-2-isopropylcyclopentane (82)



colorless liquid (70%)

(Mixture of diastereomers; signals of the major isomer are given)

^{1}H-NMR (600 MHz, $CDCl_3$) δ: 4.43 (t, J=3.5 Hz, 1 H), 2.06 (ddd, J_1=13.9 Hz, J_2=8.6 Hz, J_3=2.3 Hz, 1 H), 2.02-1.95 (m, 1 H), 1.93-1.88 (m, 1 H), 1.84-1.80 (m, 1 H), 1.70-1.65 (m, 1 H), 1.54-1.46 (m, 1 H), 1.31-1.22 (m, 1 H), 0.96 (d, J=6.7 Hz, 3 H), 0.91 (d, J=6.7 Hz, 3 H), 0.89-0.85 (m, 1 H).

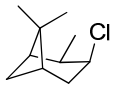
^{13}C-NMR (150 MHz, $CDCl_3$) δ: 67.2, 54.9, 36.6, 30.1, 26.9, 21.7, 21.6, 21.3.

MS (70 eV, EI) *m/z* (%): 110 (25), 95 (49), 81 (19), 70 (14), 69 (65), 68 (100), 67 (81), 66 (12), 56 (47), 55 (29), 43 (34), 41 (48).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2958 (vs), 2872 (s), 1468 (m), 1436 (m), 1386 (m), 1368 (m), 1322 (m), 1260 (m), 928 (m), 904 (m), 605 (m).

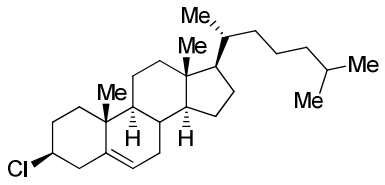
HRMS (EI) for **$C_8H_{15}Cl$** (146.0862): 146.0848.

(1*R*,2*R*,3*S*,5*S*)-3-Chloro-2,6,6-trimethylbicyclo[3.1.1]heptane (85)



This compound was prepared from commercially available (1*R*,2*R*,3*R*,5*S*)-(–)-isopinocampheol according to literature procedure.[84]

(3β)-3-Chlorocholest-5-ene

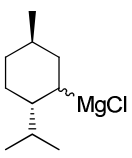


This compound was prepared from commercially available cholesterol according to literature procedure.[85]

4.3 Preparation of cycloalkylmagnesium chlorides

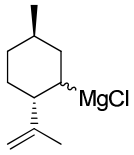
In an Ar-flushed *Schlenk*-flask equipped with a magnetic stirring bar, a reflux condenser and a dropping funnel, Mg turnings (1.2 equiv) were suspended in THF (0.7 mL per 1 mmol Mg). A catalytic amount of 1,2-dibromoethane (5 mol%) was added. The mixture was heated to reflux and a solution of the respective cyclohexyl or cyclopentyl chloride (1.0 equiv) in THF (0.3 mL per 1 mmol cycloalkyl chloride) was added dropwise. After the addition was complete, the reaction was stirred without further heating. For the Mg insertion into isopulegyl and cholesteryl chloride the reaction mixture was refluxed until all starting material was converted (checked by GC analysis). The concentrations of all cycloalkylmagnesium chlorides were determined via titration with I_2 (150 mg in 2 mL THF).

(–)-Menthylmagnesium chloride (67a)



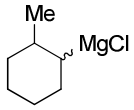
0.64 M solution in THF (73%)

(–)-Isopulegylmagnesium chloride (67b)



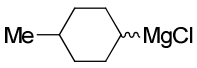
0.62 M solution in THF (71%)

2-Methylcyclohexylmagnesium chloride



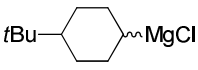
0.63 M solution in THF (72%)

4-Methylcyclohexylmagnesium chloride



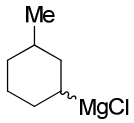
0.70 M solution in THF (80%)

4-*tert*-Butylcyclohexylmagnesium chloride



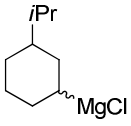
0.71 M solution in THF (81%)

3-Methylcyclohexylmagnesium chloride



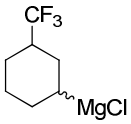
0.74 M solution in THF (84%)

3-Isopropylcyclohexylmagnesium chloride



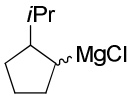
0.70 M solution in THF (80%)

3-Trifluoromethylcyclohexylmagnesium chloride



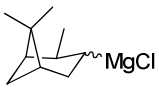
0.65 M solution in THF (74%)

2-Isopropylcyclopentylmagnesium chloride



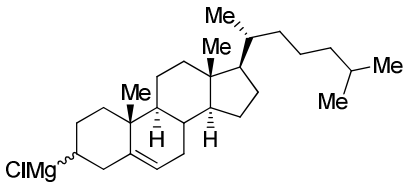
0.62 M solution in THF (71%)

(*R*)-Isopinocampheylmagnesium chloride



0.54 M solution in THF (62%)

Cholesterylmagnesium chloride

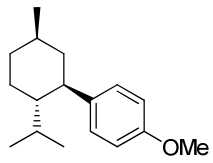


0.42 M solution in THF (48%)

4.4 Cross-coupling of menthyl-, isopulegyl-, isopinocampheyl-, cholesteryl-, 2-methylcyclohexyl- and 2-isopropylcyclopentylzinc chlorides

A dry and Ar-flushed 10 mL *Schlenk*-tube, equipped with a magnetic stirring bar and a septum, was charged with $ZnCl_2$ (1.2 mmol; 1.2 mL of a 1.0 M THF solution) and NEP (*N*-ethyl-2-pyrrolidone) (0.12 mL; 10 vol%). A solution of the respective cycloalkylmagnesium chloride (1.0 mmol) in THF was added at room temperature. The reaction mixture was stirred for 10 min. Meanwhile, in a second dry and argon-flushed 10 mL *Schlenk*-flask, a solution of $Pd(dba)_2$ (0.01 mmol; 5.75 mg), SPhos (0.01 mmol; 4.11 mg) and the respective aryl iodide (0.7 mmol) in THF (0.7 mL) was stirred for 5 min, cooled to the appropriate temperature (see Tables 4 and 5 and Scheme 33) and the organozinc reagent was added. The reaction progress was monitored by GC analysis. Conversion was complete after 6-12 h. The reaction mixture was quenched with sat. NH_4Cl aq. solution (2 mL). Water was added (2 mL). Phases were separated and the aqueous phase was extracted with Et_2O (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and the solvents were evaporated. The crude product was purified via column chromatography.

1-[(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl]-4-methoxybenzene (69a)



colorless crystals (78%)

m.p.: 81.6 – 83.2 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.07 (d, *J*=8.5 Hz, 2 H), 6.83 (d, *J*=8.5 Hz, 2 H), 3.78 (s, 3 H), 2.37 (td, J_1=11.5 Hz, J_2=3.3 Hz, 1 H), 1.83-1.70 (m, 3 H), 1.52-1.35 (m, 3 H), 1.16-0.97 (m, 3 H), 0.88 (d, *J*=6.6 Hz, 3 H), 0.79 (d, *J*=6.8 Hz, 3 H), 0.66 (d, *J*=6.8 Hz, 3 H).

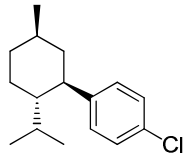
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 157.5, 138.8, 138.2, 128.2, 116.3, 113.6, 55.1, 47.6, 47.0, 45.6, 35.3, 33.3, 27.3, 24.6, 22.5, 21.5, 15.3.

MS (70 eV, EI) *m/z* (%): 246 (41) [M^+], 162 (11), 161 (100), 121 (36), 44 (11).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2952 (m), 2904 (m), 2871 (w), 2841 (w), 1608 (m), 1524 (s), 1456 (m), 1387 (w), 1367 (w), 1299 (m), 1243 (vs), 1176 (m), 1105 (m), 1032 (s), 831 (m), 817 (m), 754 (w), 637 (w).

HRMS (EI) for **$C_{17}H_{26}O$** (246.1984): 246.1980.

1-Chloro-4-[(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl]benzene (69b)



colorless liquid (71%)

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.27 (d, *J*=8.6 Hz, 2 H), 7.11 (d, *J*=8.4 Hz, 2 H), 2.43 (td, J_1=11.5 Hz, J_2=3.4 Hz, 1 H), 1.86-1.74 (m, 3 H), 1.55-1.36 (m, 3 H), 1.22-1.00 (m, 3 H), 0.91 (d, *J*=6.6 Hz, 3 H), 0.82 (d, *J*=6.8 Hz, 3 H), 0.68 (d, *J*=6.8 Hz, 3 H).

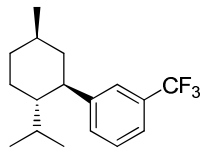
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 145.1, 131.1, 128.8, 128.4, 47.4, 45.2, 35.2, 33.2, 27.4, 24.5, 22.5, 21.5, 15.3.

MS (70 eV, EI) *m/z* (%): 250 (67) [M^+], 167 (28), 166 (11), 165 (95), 140 (29), 139 (15), 138 (100), 127 (22), 125 (77), 115 (11).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2969 (m), 2953 (s), 2917 (s), 2869 (m), 2845 (m), 1739 (vs), 1492 (s), 1455 (s), 1366 (s), 1217 (s), 1092 (s), 1014 (s), 1014 (s), 826 (s), 809 (s), 719 (m), 689 (m).

HRMS (EI) for **$C_{16}H_{23}Cl$** (250.1488): 250.1481.

1-[(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl]-3-(trifluoromethyl)benzene (69c)



colorless liquid (63%)

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.43-7.32 (m, 4 H), 2.50 (td, J_1=11.7 Hz, J_2=3.4 Hz, 1 H), 1.85-1.73 (m, 3 H), 1.52-1.43 (m, 1 H), 1.39-1.31 (m, 1 H), 1.21-0.99 (m, 3 H), 0.94-0.84 (m, 4 H), 0.80 (d, J=7.0 Hz, 3 H), 0.66 (d, J=6.8 Hz, 3 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 147.6, 130.9-130.7 (m), 130.4, 128.7, 126.1, 124.1-124.0 (m), 122.6-122.5 (m), 47.9, 47.3, 45.2, 35.1, 33.2, 27.5, 24.5, 22.4, 21.4, 15.3 (due to low resolution of the spectrum, coupling constants could not be accurately attributed).

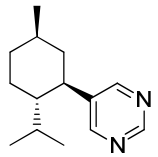
^{19}F-NMR (376 MHz, $CDCl_3$) δ: –62.47 (s; minor isomer), –62.50 (s; major isomer).

MS (70 eV, EI) *m/z* (%): 284 (66) [M^+], 214 (31), 199 (71), 185 (29), 173 (47), 172 (76), 159 (85), 125 (21), 112 (33), 111 (23), 97 (24), 95 (21), 85 (14), 84 (14), 83 (49), 81 (26), 71 (21), 70 (21), 69 (100), 57 (50), 56 (26), 55 (48), 44 (16), 43 (31), 41 (31).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2955 (m), 2918 (m), 2871 (w), 1739 (m), 1447 (m), 1369 (m), 1324 (vs), 1227 (m), 1176 (m), 1162 (s), 1123 (vs), 1073 (s), 896 (m), 798 (s), 703 (s), 664 (m).

HRMS (EI) for **$C_{17}H_{23}F_3$** (284.1752): 284.1752.

5-[(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl]pyrimidine (70a)



slightly yellow liquid (76%)

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 9.02 (s, 1 H), 8.52 (s, 2 H), 2.42 (td, J_1= 11.8 Hz, J_2= 3.4 Hz, 1 H), 1.84-1.72 (m, 2 H), 1.53-1.41 (m, 2 H), 1.35-1.26 (m, 1 H), 1.20-0.97 (m, 3 H), 0.89-0.63 (m, 9 H).

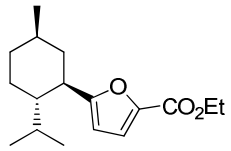
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 156.7, 156.1, 139.1, 46.9, 44.6, 43.1, 34.8, 33.0, 27.6, 24.3, 22.2, 21.3, 15.1.

MS (70 eV, EI) *m/z* (%): 218 (42) [M^+], 133 (18), 107 (100), 94 (22), 69 (15), 55 (16).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2956 (w), 2920 (w), 1559 (m), 1412 (m), 907 (m), 729 (vs).

HRMS (EI) for **$C_{14}H_{22}N_2$** (**218.1783**): **218.1776**.

Ethyl 5-[(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl]-2-furoate (70b)



colorless liquid (81%)

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.05 (d, J = 3.4 Hz, 1 H), 6.06 (d, J = 3.4 Hz, 1 H), 4.31 (q, J = 7.0 Hz, 2 H), 2.64 (td, J_1= 11.5 Hz, J_2= 3.5 Hz, 1 H), 1.86-1.66 (m, 3 H), 1.56-1.40 (m, 2 H), 1.34 (t, J = 7.0 Hz, 3 H), 1.15-0.95 (m, 4 H), 0.89-0.69 (m, 9 H).

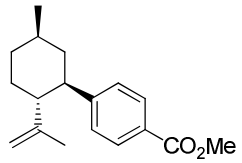
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 164.8, 158.9: 142.8, 118.8, 106.8, 60.5, 46.3, 41.6, 41.3, 34.7, 32.7, 28.4, 24.6, 22.3, 21.1, 15.7, 14.4.

MS (70 eV, EI) *m/z* (%): 278 (64) [M^+], 233 (34), 193 (47), 166 (100), 138 (39), 91 (21).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2954 (m), 1723 (s), 1297 (vs), 1140 (s), 1121 (s), 1014 (s), 760 (s).

HRMS (EI) for **$C_{17}H_{26}O_3$** (**278.1882**): **278.1891**.

Methyl 4-[(1*R*,2*R*,5*R*)-2-isopropenyl-5-methylcyclohexyl]benzoate (71a)



colorless crystals (72%)

m.p.: 85.7 – 87.1 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.91 (d, J=8.2 Hz, 2 H), 7.19 (d, J=8.2 Hz, 2 H), 4.50 (d, J=7.3 Hz, 2 H), 3.87 (s, 3 H), 2.62 (td, J=11.6 Hz, 3.2 Hz, 1 H), 2.26 (td, J=11.5 Hz, 3.2 Hz, 1 H), 1.84-1.75 (m, 3 H), 1.58-1.42 (m, 5 H), 1.20-1.07 (m, 2 H), 0.92 (d, 6.5 Hz, 3 H).

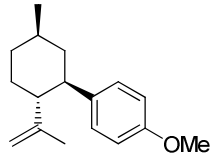
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 167.1, 152.6, 147.8, 129.5, 127.7, 127.5, 111.4, 52.8, 50.8, 48.1, 44.2, 35.0, 33.0, 32.6, 22.4, 19.7.

MS (70 eV, EI) *m/z* (%): 272 (26) [M^+], 229 (25), 213 (100), 201 (24), 157 (25), 150 (33), 149 (84), 145 (29), 143 (44), 131 (47), 129 (30), 128 (26), 123 (93), 115 (26), 109 (44), 105 (21), 95 (26), 91 (25), 81 (39), 77 (22), 69 (21), 68 (23), 67 (25), 55 (33), 40 (30).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2944 (m), 2918 (s), 2864 (m), 2846 (m), 1730 (m), 1718 (vs), 1608 (m), 1454 (m), 1446 (m), 1430 (m), 1312 (m), 1288 (vs), 1276 (vs), 1190 (m), 1178 (m), 1114 (s), 1096 (s), 882 (m), 852 (m), 768 (s), 704 (s).

HRMS (EI) for **$C_{18}H_{24}O_2$** (272.1776): 272.1769.

1-[(1*R*,2*R*,5*R*)-2-Isopropenyl-5-methylcyclohexyl]-4-methoxybenzene (71b)



colorless liquid (71%)

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.05 (d, *J*=8.5 Hz, 2 H), 6.79 (d, *J*=8.5 Hz, 2 H), 4.54 (d, *J*=5.3 Hz, 2 H), 3.77 (s, 3 H), 2.52 (td, J_1=11.5 Hz, J_2=3.2 Hz, 1 H), 2.22 (td, J_1=11.5 Hz, J_2=3.3 Hz, 1 H), 1.83-1.75 (m, 3 H), 1.56-1.42 (m, 5 H) , 1.17-1.01 (m, 2 H), 0.92 (d, *J*=6.3 Hz, 3 H).

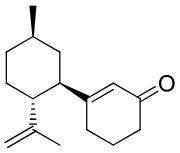
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 157.5, 148.6, 138.3, 128.2, 113.4, 111.0, 55.1, 52.1, 47.1, 45.1, 35.2, 33.1, 32.9, 22.5, 19.7.

MS (70 eV, EI) *m/z* (%): 244 (100) [M^+], 229 (13), 201 (11), 192 (12), 187 (14), 173 (23), 162 (12), 161 (82), 134 (18), 121 (45), 91 (16), 44 (26).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2946 (m), 2916 (s), 2866 (m), 2858 (m), 2840 (m), 1610 (m), 1522 (s), 1454 (s), 1442 (s), 1374 (m), 1302 (m), 1278 (m), 1260 (s), 1244 (vs), 1176 (s), 1098 (m), 1036 (s), 900 (m), 886 (s), 820 (s), 802 (s), 586 (m), 566 (m).

HRMS (EI) for **$C_{17}H_{24}O$** (244.1827): 244.1830.

(1'*R*,2'*R*,5'*R*)-2'-Isopropenyl-5'-methyl-1,1'-bi(cyclohexan)-1-en-3-one (71c)



colorless liquid (64%)

^{1}H-NMR (400 MHz, C_6D_6) δ: 5.92 (s, 1 H), 4.65 (s, 1 H), 4.56 (s, 1 H), 2.21-2.08 (m, 2 H), 1.94-1.79 (m, 3 H), 1.74-1.66 (m, 1 H), 1.57-1.47 (m, 4 H), 1.45 (s, 3 H), 1.37 (ddd, J_1=12.7 Hz, J_2=5.0 Hz, J_3=3.2 Hz, 1 H), 1.21-1.11 (m, 2 H), 0.82-0.69 (m, 5 H).

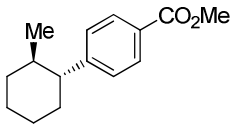
^{13}C-NMR (150 MHz, $CDCl_3$) δ: 197.7, 167.3, 148.1, 126.7, 111.4, 49.7, 48.8, 40.2, 38.0, 34.9, 32.4, 32.1, 26.4, 23.1, 22.6, 18.9.

MS (70 eV, EI) *m/z* (%): 232 (100) [M^+], 217 (24), 199 (43), 189 (23), 176 (24), 175 (25), 173 (25), 161 (34), 159 (28), 148 (50), 133 (26), 123 (47), 123 (23), 119 (32), 110 (23), 107 (31), 105 (52), 93 (38), 91 (40), 81 (49), 79 (34), 77 (25), 67 (27), 55 (26), 40 (27).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2970 (m), 2946 (s), 2921 (s), 2867 (m), 1739 (vs), 1668 (vs), 1619 (m), 1455 (s), 1373 (s), 1350 (s), 1323 (m), 1230 (s), 1217 (s), 1134 (m), 1111 (m), 965 (m), 884 (vs), 758 (m).

HRMS (EI) for **$C_{16}H_{24}O$** (232.1827): 232.1820.

Methyl 4-(*trans*-2-methylcyclohexyl)benzoate (73)



colorless liquid (82%)

^{1}H-NMR (400 MHz, C_6D_6) δ: 8.15 (d, *J*=8.2 Hz, 2 H), 6.97 (d, *J*=8.2 Hz, 2 H), 3.53 (s, 3 H), 1.89 (t, *J*=11.2 Hz, 1 H), 1.72-1.60 (m, 4 H), 1.39-1.31 (m, 1 H), 1.29-1.15 (m, 3 H), 0.98-0.89 (m, 1 H), 0.61 (d, *J*=6.5 Hz, 3 H).

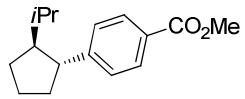
^{13}C-NMR (101 MHz, C_6D_6) δ: 166.8, 152.2, 130.1, 128.7, 52.6, 52.4, 37.6, 35.8, 35.4, 27.0, 26.8, 20.8.

MS (70 eV, EI) *m/z* (%): 232 (75) [M^+], 201 (17), 176 (11), 173 (17), 163 (18), 162 (100), 150 (14), 149 (11), 131 (34), 115 (12).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2922 (m), 1720 (s), 1609 (m), 1435 (m), 1273 (vs), 1190 (m), 1179 (m), 1111 (s), 1101 (s), 1019 (w), 848 (w), 771 (m), 756 (m), 707 (m).

HRMS (EI) for $\mathbf{C_{15}H_{20}O_2}$ (232.1463): 232.1465.

Methyl 4-[*trans*-2-isopropylcyclopentyl]benzoate (83)



colorless liquid (96%)

^{1}H-NMR (300 MHz, C_6D_6) δ: 8.14 (d, *J*=8.0 Hz, 2 H), 7.03 (d, *J*=8.0 Hz, 2 H), 3.53 (s, 3 H), 2.48 (q, *J*=8.4 Hz, 1 H), 1.94-1.82 (m, 1 H), 1.75-1.39 (m, 6 H), 1.35-1.23 (m, 1 H), 0.75 (d, *J*=6.7 Hz, 3 H), 0.72 (d, *J*=6.7 Hz, 3 H).

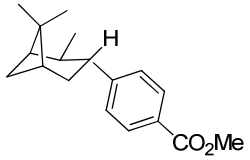
^{13}C-NMR (75 MHz, C_6D_6) δ: 166.7, 152.6, 130.1, 127.8, 54.3, 52.5, 50.2, 36.9, 30.6, 28.5, 24.8, 22.2, 18.9.

MS (70 eV, EI) *m/z* (%): 246 (86) [M^+], 215 (24), 163 (17), 162 (100), 150 (23), 149 (24), 131 (17), 131 (45), 128 (13), 117 (11), 116 (13), 115 (27), 103 (10), 91 (12).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2952 (m), 2870 (w), 1720 (s), 1609 (m), 1435 (m), 1274 (vs), 1179 (m), 1111 (s), 1101 (s), 1019 (m), 968 (w), 852 (w), 771 (m), 706 (s).

HRMS (EI) for $\mathbf{C_{16}H_{22}O_2}$ (246.1620): 246.1620.

Methyl 4-[(1*R*,2*R*,3*R*,5*R*)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]benzoate (86)



colorless liquid (65%)

^{1}H-NMR (300 MHz, C_6D_6) δ: 8.17 (d, *J*=8.3 Hz, 2 H), 7.13 (d, *J*=8.4 Hz, 2 H), 3.55 (s, 3 H), 2.93-2.84 (m, 1 H), 2.41-2.33 (m, 1 H), 2.31-2.21 (m, 1 H), 1.99-1.85 (m, 2 H), 1.82-1.74 (m, 2 H), 1.21 (s, 3 H), 1.05 (s, 3 H), 0.98 (d, *J*=9.9 Hz 1 H), 0.92 (d, *J*=7.2 Hz, 3 H).

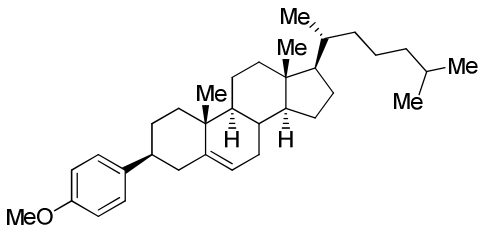
^{13}C-NMR (75 MHz, C_6D_6) δ: 166.7, 154.7, 130.2, 128.6, 128.5, 52.5, 48.2, 45.8, 45.2, 42.1, 39.2, 37.4, 35.1, 30.2, 28.6, 23.0, 21.0.

MS (70 eV, EI) *m/z* (%): 272 (11) [M^+], 241 (15), 229 (17), 218 (14), 217 (100), 216 (11), 204 (21), 203 (19), 190 (27), 185 (20), 176 (13), 171 (13), 163 (11), 149 (12), 143 (21), 131 (23), 129 (22), 128 (20), 117 (11), 115 (18), 110 (18), 95 (23), 91 (10), 83 (48), 69 (10), 59 (10), 55 (16), 41 (14).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2949 (w), 2924 (m), 2901 (m), 2870 (w), 1720 (s), 1609 (m), 1453 (w), 1434 (m), 1418 (w), 1384 (w), 1372 (w), 1309 (w), 1274 (vs), 1178 (m), 1141 (w), 1105 (s), 1018 (m), 968 (w), 850 (w), 827 (w), 769 (m), 752 (m), 706 (s).

HRMS (EI) for **$C_{18}H_{24}O_2$** (272.1776): 272.1780.

(3β)-3-(4-Methoxyphenyl)cholest-5-ene (88)



white solid (86%)

m.p.: 123.2 – 125.0 °C.

^{1}H-NMR (600 MHz, $CDCl_3$) δ: 7.15 (d, *J*=8.6 Hz, 2 H), 6.84 (d, *J*=8.6 Hz, 2 H), 5.34 (d, *J*=4.8 Hz, 1 H), 3.78 (s, 3 H), 2.50-2.44 (m, 1 H), 2.39 (td, J_1=13.2 Hz, J_2=2.1 Hz, 1 H), 2.16 (d, *J*=13.4 Hz, 1 H), 2.04-1.94 (m, 3 H), 1.84 (ddd, J_1=13.1 Hz, J_2=9.5 Hz, J_3=3.6 Hz, 1 H), 1.74-1.67 (m, 2 H), 1.62-1.44 (m, 7 H), 1.40-1.33 (m, 3 H), 1.28-1.10 (m, 7 H), 1.07 (s, 3 H), 1.04-0.99 (m, 3 H), 0.93 (d, *J*=6.7 Hz, 3 H), 0.87 (d, *J*=2.4 Hz, 3 H), 0.87 (d, *J*=2.4 Hz, 3 H), 0.70 (s, 3 H).

^{13}C-NMR (150 MHz, $CDCl_3$) δ: 157.8, 143.1, 139.3, 127.7, 127.5, 120.0, 114.1, 113.7, 56.8, 56.2, 55.2, 50.5, 44.9, 42.3, 40.9, 39.9, 39.8, 39.5, 36.9, 36.2, 35.8, 31.9, 31.9, 30.2, 28.3, 28.0, 24.3, 23.8, 22.8, 22.6, 21.0, 19.6, 18.7, 11.9.

MS (70 eV, EI) *m/z* (%): 476 (100) [M^+], 474 (15), 461 (23), 330 (21), 329 (74), 148 (36), 147 (73), 134 (70), 121 (22), 121 (56), 119 (19), 109 (18), 107 (25), 105 (16), 95 (29), 91 (19), 83 (17), 81 (21), 71 (16), 69 (23), 57 (28), 55 (27), 42 (24), 40 (19).

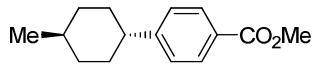
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2962 (m), 2953 (m), 2928 (s), 2898 (s), 2879 (s), 2864 (m), 2852 (m), 1509 (vs), 1464 (s), 1460 (s), 1441 (m), 1255 (s), 1240 (s), 1234 (s), 1175 (s), 1039 (s), 822 (vs), 802 (s), 766 (m), 591 (m).

HRMS (EI) for **$C_{34}H_{52}O$** (476.4018): 476.4015.

4.5 Cross-coupling of 4- and 3-substituted cyclohexylzinc reagents

A dry and Ar-flushed 10 mL *Schlenk*-tube, equipped with a magnetic stirring bar and a septum, was charged with 1.2 mL (1.2 mmol) of a solution of $ZnCl_2$ in THF (1.0 M) and NEP (*N*-ethyl-2-pyrrolidone) (0.12 mL; 10 vol%). A solution of the respective 4- or 3-substituted cyclohexylmagnesium chloride (1.0 mmol) in THF was added at room temperature. The reaction was stirred for 10 min. Meanwhile, in a second dry and Ar-flushed 10 mL *Schlenk*-flask, a solution of $TMPP_2PdCl_2$ (0.02 mmol; 25 mg) and the respective aryl iodide (0.7 mmol) in THF (0.7 mL) was prepared and cooled to the appropriate temperature (see Table 5). Subsequently, the organozinc reagent was slowly added. The reaction progress was monitored by GC analysis. Conversion was complete after 12 h. The reaction mixture was quenched with sat. NH_4Cl aq. solution (2 mL). Water was added (2 mL). Phases were separated and the aqueous phase was extracted with Et_2O (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and the solvents were evaporated. The crude product was purified via column chromatography.

Methyl 4-(*trans*-4-methylcyclohexyl)benzoate (75)



colorless crystals (84%)

m.p.: 56.5 – 58.0 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.98 (d, *J*=8.0 Hz, 2 H), 7.29 (d, *J*=8.0 Hz, 2 H), 3.91 (s, 3 H), 2.53 (t, *J*=12.0 Hz, 1 H), 1.87 (t, *J*=14.1 Hz, 4 H), 1.56-1.43 (m, 3 H), 1.16-1.03 (m, 2 H), 0.96 (d, *J*=6.6 Hz, 3 H).

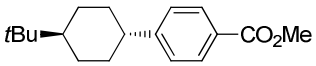
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 167.2, 153.3, 129.6, 127.8, 127.0, 126.9, 52.9, 44.3, 35.4, 34.0, 32.3, 31.8, 28.3, 27.4, 22.6.

MS (70 eV, EI) *m/z* (%): 232 (85) [M^+], 201 (36), 176 (21), 175 (14), 173 (49), 163 (16), 162 (100), 149 (18), 145 (11), 137 (11), 131 (55), 117 (24), 116 (12), 115 (21), 105 (16), 103 (13), 95 (13), 91 (42), 81 (17), 77 (13), 69 (13), 57 (15), 55 (25), 41 (19).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2945 (m), 2921 (m), 2846 (m), 1716 (vs), 1609 (m), 1439 (s), 1416 (m), 1275 (s), 1193 (m), 1178 (s), 1112 (s), 1103 (s), 1018 (m), 956 (m), 850 (s), 833 (m), 807 (m), 773 (vs), 759 (s), 706 (vs).

HRMS (EI) for **$C_{15}H_{20}O_2$** (232.1463): 232.1450.

Methyl 4-(*trans*-4-*tert*-butylcyclohexyl)benzoate (76a)



colorless crystals (59%)

m.p.: 112.3 – 114.4 °C.

^{1}H-NMR (300 MHz, C_6D_6) δ: 8.19 (d, *J*=7.8 Hz, 2 H), 7.07 (d, *J*=7.8 Hz, 2 H), 3.54 (s, 3 H), 2.21 (t, *J*=11.9 Hz, 1 H), 1.78-1.71 (m, 4 H), 1.27-1.17 (m, 3 H), 0.95-0.83 (m, 11 H).

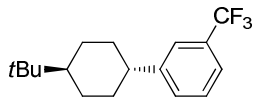
^{13}C-NMR (75 MHz, C_6D_6) δ: 166.8, 153.2, 130.1, 127.2, 52.5, 47.7, 44.7, 34.6, 32.4, 27.7, 27.7.

MS (70 eV, EI) *m/z* (%): 274 (40) [M^+], 243 (13), 219 (16), 218 (100), 217 (17), 163 (13), 162 (37), 159 (24), 150 (10), 149 (24), 131 (18), 91 (10), 57 (32).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2946 (m), 2916 (m), 2853 (w), 1719 (vs), 1609 (m), 1433 (m), 1366 (m), 1275 (vs), 1179 (m), 1106 (s), 1017 (m), 958 (m), 820 (w), 769 (m), 705 (s).

HRMS (EI) for **$C_{18}H_{26}O_2$** (274.1933): 274.1926.

1-(*trans*-4-*tert*-Butylcyclohexyl)-3-(trifluoromethyl)benzene (76b)



colorless liquid (60%)

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.45-7.37 (m, 4 H), 2.56-2.45 (m, 1 H), 1.98-1.89 (m, 4 H), 1.54-1.38 (m, 2 H), 1.26-1.08 (m, 3 H), 0.89 (s, 9 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 148.6, 130.5 (q, *J*=31.8 Hz), 130.3, 126.2, 124.4 (q, *J*=272.2 Hz), 123.5 (q, *J*=3.4 Hz), 122.6 (q, *J*=4.0 Hz), 47.6, 44.4, 34.6, 32.6, 32.5, 27.6.

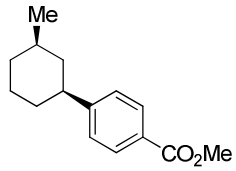
^{19}F-NMR (376 MHz, $CDCl_3$) δ: –62.48 (s, minor isomer), –62.53 (s, major isomer).

MS (70 eV, EI) *m/z* (%): 284 (10) [M^+], 228 (62), 173 (11), 172 (48), 159 (19), 57 (100), 56 (10), 41 (11).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2969 (m), 2940 (m), 2858 (w), 1739 (s), 1449 (m), 1365 (s), 1329 (s), 1230 (m), 1217 (m), 1200 (m), 1161 (s), 1122 (vs), 1074 (s), 908 (w), 892 (m), 798 (m), 701 (s), 667 (m).

HRMS (EI) for **$C_{17}H_{23}F_3$** (284.1752): 284.1739.

Methyl 4-[*cis*-3-methylcyclohexyl]benzoate (78a)



colorless crystals (77%)

m.p.: 52.3 – 53.2 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.98 (d, *J*=8.0 Hz, 2 H), 7.29 (d, *J*=8.0 Hz, 2 H), 3.91 (s, 3 H), 2.62 (t, *J*=11.7 Hz, 1 H), 1.88 (d, *J*=10.2 Hz, 3 H), 1.77 (d, *J*=13.1 Hz, 1 H), 1.63-1.30 (m, 4 H), 1.12 (q, *J*=12.0 Hz, 1 H), 0.96 (d, *J*=6.6 Hz, 3 H).

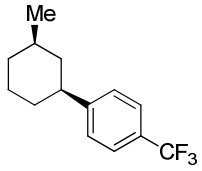
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 167.2, 153.2, 129.7, 127.7, 126.8, 52.9, 44.5, 42.8, 34.7, 33.6, 33.0, 26.5, 22.8.

MS (70 eV, EI) *m/z* (%): 232 (100) [M^+], 201 (45), 189 (25), 176 (13), 173 (57), 163 (15), 162 (79), 150 (28), 149 (46), 131 (20), 131 (53), 129 (13), 117 (26), 115 (20), 105 (28), 103 (14), 95 (14), 91 (53), 83 (15), 81 (21), 77 (16), 69 (17), 55 (26), 41 (21).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2919 (s), 1716 (s), 1609 (m), 1438 (s), 1277 (vs), 1193 (m), 1179 (s), 1103 (s), 1018 (s), 958 (s), 852 (m), 840 (m), 830 (m), 801 (m), 779 (m), 760 (vs), 703 (vs), 666 (m).

HRMS (EI) for **$C_{15}H_{20}O_2$** (232.1463): 232.1456.

1-[*cis*-3-Methylcyclohexyl]-4-(trifluoromethyl)benzene (78b)



colorless liquid (70%)

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.53 (d, *J*=8.0 Hz, 2 H), 7.30 (d, *J*=8.0 Hz, 2 H), 2.65-2.55 (m, 1 H), 1.90-1.73 (m, 4 H), 1.63-1.27 (m, 4 H), 1.09 (q, *J*=12.3 Hz, 1 H), 0.94 (d, *J*=6.6 Hz, 3 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 152.8 (d, *J*=1.0 Hz), 128.1 (q, *J*=32.2 Hz), 127.1, 125.2 (q, *J*=3.8 Hz), 124.4 (q, *J*=271.7 Hz), 44.3, 42.9, 34.7, 33.7, 33.0, 26.5, 22.8.

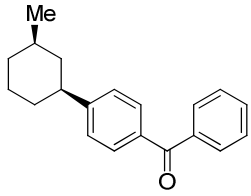
^{19}F-NMR (282 MHz, $CDCl_3$) δ: –62.27 (s).

MS (70 eV, EI) *m/z* (%): 242 (38) [M^+], 199 (23), 186 (12), 185 (11), 173 (13), 172 (100), 159 (39), 83 (20), 81 (11), 69 (10), 55 (23), 41 (14).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2950 (w), 2922 (m), 2898 (w), 2854 (w), 1620 (w), 1458 (w), 1448 (w), 1420 (w), 1322 (vs), 1188 (w), 1162 (s), 1120 (vs), 1106 (s), 1086 (m), 1066 (s), 1018 (m), 832 (s), 814 (w), 656 (m), 602 (m).

HRMS (EI) for **$C_{14}H_{17}F_3$** (242.1282): 242.1278.

{4-[*cis*-3-Methylcyclohexyl]phenyl}(phenyl)methanone (78c)



colorless oil (81%)

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.82-7.70 (m, 4 H), 7.65-7.53 (m, 2 H), 7.50-7.42 (m, 2 H), 7.35-7.26 (m, 1 H), 2.67-2.57 (m, 1 H), 1.89-1.25 (m, 8 H), 1.10-1.06 (m, 1 H), 0.94 (d, *J*= 6.0 Hz, 1 H).

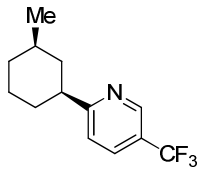
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 196.5, 152.9, 137.9, 135.2, 132.1, 130.4, 129.9, 128.2, 126.8, 44.5, 42.8, 34.7, 33.6, 33.0, 26.5, 22.8.

MS (70 eV, EI) *m/z* (%): 278 (100) [M^+], 201 (73), 181 (12), 131 (12), 105 (54), 77 (23).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2922 (w), 1656 (s), 1605 (w), 1315 (m), 1278 (s), 922 (w), 700 (vs).

HRMS (EI) for **$C_{20}H_{22}O$** (278.1671): 278.1670.

2-[(*cis*-3-Methylcyclohexyl]-5-(trifluoromethyl)pyridine (78d)



yellow oil (85%)

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.78-8.75 (m, 1 H), 7.80 (dd, J_1= 8.3 Hz, J_2= 1.9 Hz, 1 H), 7.25 (d, J = 8.3 Hz, 1 H), 2.79 (tt, J_1= 12.0 Hz, J_2= 3.3 Hz, 1 H), 1.93-1.82 (m, 3 H), 1.77-1.65 (m, 1 H), 1.60-1.36 (m, 3 H), 1.18 (q, J= 6.6 Hz, 1 H), 1.18 (d, J = 6.6 Hz, 3 H).

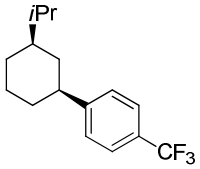
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 170.3, 146.0, 132.0 (d, J = 13 Hz), 124.1 (q, J = 33 Hz), 123.7 (q, J = 272 Hz), 46.5, 41.1, 34.6, 32.7, 26.2, 22.7.

MS (70 eV, EI) *m/z* (%): 243 (100) [M^+], 228 (45), 214 (22), 200 (76), 174 (54), 161 (23).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2924 (w), 1606 (m), 1324 (vs), 1120 (vs), 1080 (s), 1015 (m), 840 (w).

HRMS (EI) for **$C_{13}H_{16}F_3N$** (243.1235): 243.1237.

1-[*cis*-3-Isopropylcyclohexyl]-4-(trifluoromethyl)benzene (79a)



colorless liquid (70%)

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.54 (d, J=8.0 Hz, 2 H), 7.32 (d, J=8.3 Hz, 2 H), 2.63-2.53 (m, 1 H), 1.95-1.75 (m, 4 H), 1.54-1.23 (m, 4 H), 1.20-1.12 (m, 1 H), 1.08-0.98 (m, 1 H), 0.89 (d, J=2.7 Hz, 3 H), 0.88 (d, J=2.7 Hz, 3 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 152.0 (d, J=1.3 Hz), 128.1 (q, J=32.2 Hz), 127.2, 125.2 (q, J=3.8 Hz), 124.4 (q, J=271.7 Hz), 44.7, 44.3, 37.7, 34.1, 33.0, 29.2, 26.6, 19.8, 19.7.

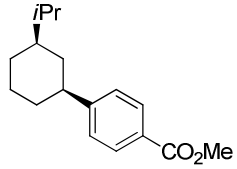
^{19}F-NMR (282 MHz, $CDCl_3$) δ: –62.27 (s).

MS (70 eV, EI) *m/z* (%): 270 (86) [M^+], 228 (13), 227 (56), 226 (13), 185 (52), 173 (20), 172 (60), 159 (100), 83 (10), 81 (22).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2958 (w), 2926 (m), 2856 (w), 1620 (w), 1322 (vs), 1162 (s), 1120 (vs), 1106 (s), 1068 (s), 1016 (m), 832 (s), 654 (w), 604 (m).

HRMS (EI) for $\mathbf{C_{16}H_{21}F_3}$ (270.1595): 270.1605.

Methyl 4-[*cis*-3-isopropylcyclohexyl]benzoate (79b)



colorless liquid (86%)

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.98 (d, J=8.3 Hz, 2 H), 7.30 (d, J=8.5 Hz, 2 H), 3.92 (s, 3 H), 2.64-2.54 (m, 1 H), 1.96-1.77 (m, 4 H), 1.55-1.25 (m, 4 H), 1.23-1.15 (m, 1 H), 1.05 (td, J_1=12.1 Hz, J_2=3.6 Hz, 1 H), 0.95-0.89 (m, 6 H).

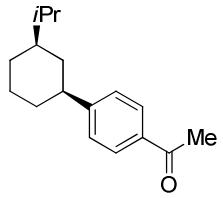
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 167.1, 153.4, 137.7, 131.0, 129.7, 127.8, 126.9, 52.9, 44.8, 44.3, 37.5, 34.0, 33.0, 29.2, 26.6, 19.7, 19.7.

MS (70 eV, EI) *m/z* (%): 260 (100) [M^+], 229 (29), 218 (11), 217 (48), 201 (18), 185 (28), 163 (27), 162 (57), 150 (24), 149 (98), 137 (13), 131 (39), 129 (12), 117 (12), 115 (16), 105 (41), 103 (12), 91 (23), 81 (19), 77 (10), 69 (10), 59 (11), 55 (16), 41 (15).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2952 (w), 2924 (m), 2854 (w), 1720 (vs), 1610 (m), 1434 (m), 1274 (vs), 1246 (m), 1178 (m), 1110 (s), 1102 (s), 1020 (m), 850 (m), 768 (m), 706 (s).

HRMS (EI) for $\mathbf{C_{17}H_{24}O_2}$ (260.1776): 260.1767.

1-{4-[*cis*-3-Isopropylcyclohexyl]phenyl}ethanone (79c)



colorless liquid (71%)

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.88 (d, J=8.3 Hz, 2 H), 7.29 (d, J=8.3 Hz, 2 H), 2.62-2.57 (m, 4 H), 1.91-1.74 (m, 4 H), 1.52-1.22 (m, 4 H), 1.20-1.12 (m, 1 H), 1.02 (td, J_1=12.1 Hz, J_2=3.4 Hz, 1 H), 0.89 (d, J=8.3 Hz, 3 H), 0.86 (d, J=8.3 Hz, 3 H).

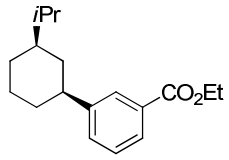
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 197.8, 153.7, 135.1, 128.5, 128.4, 127.2, 127.0, 44.8, 44.3, 37.5, 33.9, 33.0, 29.2, 26.6, 26.5, 19.7, 19.7.

MS (70 eV, EI) *m/z* (%): 244 (74) [M^+], 230 (63), 229 (100), 229 (100), 229 (72), 147 (11), 134 (14), 133 (36), 131 (29), 115 (12), 105 (18), 103 (10), 91 (17), 77 (10), 55 (13), 43 (96), 41 (14).

IR (ATR) $\widetilde{\nu}$ (cm^{-1}): 2924 (m), 2854 (m), 1682 (vs), 1606 (s), 1414 (m), 1358 (m), 1266 (vs), 1182 (m), 956 (m), 826 (s), 594 (vs).

HRMS (EI) for **$C_{17}H_{24}O$** (244.1827): 244.1830.

Ethyl 3-[*cis*-3-isopropylcyclohexyl]benzoate (79d)



colorless liquid (71%)

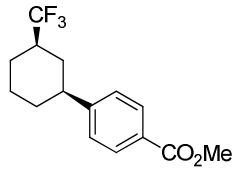
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.89-7.83 (m, 2 H), 7.43-7.31 (m, 2 H), 4.37 (q, J=7.2 Hz, 2 H), 2.61-2.52 (m, 1 H), 1.92-1.73 (m, 4 H), 1.50-1.35 (m, 6 H), 1.27-1.13 (m, 2 H), 1.02 (td, J_1=12.3, J_2=3.6 Hz, 1 H), 0.93-0.85 (m, 6 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 166.9, 148.3, 131.5, 130.4, 128.3, 128.0, 127.1, 60.9, 44.6, 44.4, 37.8, 34.1, 33.0, 29.2, 26.7, 19.8, 19.7, 14.4.

MS (70 eV, EI) *m/z* (%): 274 (100) [M^+], 231 (25), 229 (40), 203 (14), 185 (13), 177 (19), 176 (48), 164 (20), 163 (62), 159 (14), 149 (19), 135 (17), 131 (23), 129 (15), 119 (45), 117 (29), 115 (16), 105 (14), 103 (13), 91 (41), 81 (24), 69 (14), 55 (20), 41 (15).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2956 (w), 2924 (m), 2854 (w), 2360 (w), 2342 (w), 1716 (vs), 1446 (m), 1366 (m), 1274 (vs), 1192 (s), 1106 (s), 1024 (m), 924 (w), 868 (w), 816 (w), 752 (s), 696 (m).
HRMS (EI) for **$C_{18}H_{26}O_2$** (274.1933): 274.1929.

Methyl 4-[*cis*-3-(trifluoromethyl)cyclohexyl]benzoate (80)



colorless liquid (74%)
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.00 (d, *J*=8.3 Hz, 2 H), 7.29 (d, *J*=8.5 Hz, 2 H), 3.92 (s, 3 H), 2.69-2.60 (m, 1 H), 2.30-2.18 (m, 1 H), 2.14-2.01 (m, 3 H), 1.96-1.93 (m, 1 H), 1.63-1.29 (m, 4 H).
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 167.0, 152.2, 129.9, 128.4, 127.5 (q, *J*= 278.6 Hz), 126.8, 52.0, 43.1, 42.3 (q, *J*=26.6 Hz), 33.1, 32.0 (q, *J*=2.3 Hz), 25.0, 24.5 (q, *J*=2.5 Hz).
^{19}F-NMR (282 MHz, $CDCl_3$) δ: –73.85 (d, *J* = 9.4 Hz).
MS (70 eV, EI) *m/z* (%): 286 (90) [M^+], 256 (15), 255 (100), 228 (13), 227 (97), 175 (13), 162 (11), 149 (29), 131 (13), 130 (21), 129 (10), 115 (16), 103 (11), 91 (85), 77 (12), 59 (13).
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2946 (w), 2866 (w), 1718 (s), 1610 (w), 1436 (m), 1391 (w), 1276 (s), 1252 (s), 1207 (m), 1163 (s), 1139 (m), 1109 (s), 1102 (s), 1089 (vs), 1040 (w), 1019 (m), 974 (m), 938 (w), 850 (m), 770 (m), 706 (s), 692 (s), 580 (w).
HRMS (EI) for **$C_{15}H_{17}F_3O_2$** (286.1181): 286.1182.

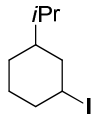
5. Pd-Catalyzed Diastereoselective Csp^3-Csp Cross-Coupling Reactions.

5.1 Preparation of starting materials

Preparation of cyclohexyl iodides[78]

A dry and N_2-flushed *Schlenk*-flask, equipped with a magnetic stirring bar and a septum, was charged with a solution of I_2 (1.2 equiv) in CH_2Cl_2 (0.5 M) and cooled to 0 °C. PPh_3 (1.1 equiv) was carefully added at this temperature. The resulting bright yellow suspension was stirred for 1.5 h. Then, *N*-methylimidazole (NMI; 1.25 equiv) was added. After 10 min of further stirring, the respective cyclohexanol (1.0 equiv) was added. After 4 h the reaction mixture was allowed to warm to room temperature and was stirred overnight. The reaction mixture was quenched with NH_4Cl sat. aq. solution. The phases were separated and the aqueous layer was extracted with 3 x CH_2Cl_2. The combined organic layers were washed with brine and dried over Na_2SO_4. The solvents were evaporated and the crude product was subjected to column chromatography furnishing the neat cyclohexyl iodide with up to 62% yield.

1-Iodo-3-isopropylcyclohexane



colorless liquid (62%) (store at -30 °C)

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 4.94 (t, J=3.3 Hz, 1 H), 2.12 - 2.00 (m, 2 H), 1.82 - 1.60 (m, 4 H), 1.54 - 1.41 (m, 2 H), 1.30 (ddd, J_1=14.3 Hz, J_2=10.8 Hz, J_3=3.3 Hz, 1 H), 1.15 - 1.01 (m, 1 H), 0.87 (d, J=6.6 Hz, 6 H). (Mixture of diastereomers; signals of the major diastereomer are given)

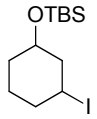
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 39.9, 39.7, 37.3, 36.7, 31.8, 29.1, 22.8, 19.8, 19.7.

MS (70 eV, EI) *m/z* (%): 252 (1) [M^+], 125 (64), 83 (41), 81 (17), 69 (100), 67 (17), 57 (30), 55 (40), 43 (29), 41 (45).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2954 (vs), 2928 (vs), 2872 (s), 2832 (m), 1464 (m), 1456 (m), 1444 (m), 1434 (m), 1426 (m), 1386 (m), 1368 (m), 1270 (m), 1256 (m), 1240 (vs), 1204 (m), 1174 (m), 1162 (s), 898 (m), 850 (m), 642 (m).

HRMS (EI) for **$C_9H_{17}I$** (252.0375): 252.0371.

***tert*-Butyl((3-iodocyclohexyl)oxy)dimethylsilane**



slightly yellow liquid (56%)

^{1}H-NMR (400 MHz, C_6D_6) δ: 4.47 - 4.40 (m, 1 H), 3.78 (br. s., 1 H), 2.01 - 1.90 (m, 2 H), 1.74 - 1.65 (m, 2 H), 1.56 - 1.47 (m, 1 H), 1.33 (br. s., 2 H), 1.15 - 1.02 (m, 1 H), 0.92 (s, 9 H), -0.01 (s, 3 H), -0.02 (s, 3 H).

(Mixture of diastereomers; signals of one diastereomer are given)

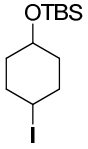
^{13}C-NMR (101 MHz, C_6D_6) δ: 71.37, 69.53, 68.54, 50.64, 47.42, 39.73, 38.95, 35.94, 35.37, 34.12, 32.54, 28.96, 26.48, 26.36, 25.85, 24.91, 24.16, 22.94, 18.59, 18.55, -4.14, -4.18, -4.40, -4.42.

MS (70 eV, EI) *m/z* (%): 340 (2) [M^+], 284 (12), 283 (100), 185 (10), 155 (18), 81 (80), 75 (32), 73 (12).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2930 (m), 2886 (w), 2856 (m), 1472 (w), 1462 (w), 1448 (w), 1252 (m), 1152 (m), 1140 (w), 1100 (m), 1082 (m), 1070 (m), 1052 (m), 1034 (m), 1006 (m), 988 (w), 978 (w), 966 (w), 902 (m), 872 (m), 854 (m), 834 (vs), 800 (m), 772 (vs), 688 (m), 672 (m), 654 (m).

HRMS (EI) for **$C_{12}H_{25}IOSi$** (340.0719): 340.0703.

***tert*-Butyl((4-iodocyclohexyl)oxy)dimethylsilane**



slightly yellow liquid (52%)

^{1}H-NMR (400 MHz, C_6D_6) δ: 3.93 (t, J=8.6 Hz, 1 H), 3.68 - 3.49 (m, 1 H), 2.20 (d, J=9.8 Hz, 1 H), 1.99 - 1.86 (m, 1 H), 1.70 - 1.52 (m, 4 H), 1.19 (ddd, J_1=12.8 Hz, J_2=8.7 Hz, J_3=4.0 Hz, 2 H), 0.96 - 0.91 (m, 9 H), -0.02 (s, 6 H).

(Mixture of diastereomers; signals of one diastereomer are given)

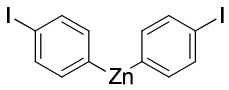
^{13}C-NMR (101 MHz, C_6D_6) δ: 68.8, 67.6, 35.9, 35.3, 35.0, 32.5, 31.1, 26.5, 26.4, 24.9, 18.6, 18.6, -4.1, -4.1, -4.2, -4.3.

MS (70 eV, EI) *m/z* (%): 339 (1) [M-H$^-$], 282 (23), 155 (11), 81 (100), 75 (48), 74 (30), 73 (13), 59 (44), 45 (30), 41 (14).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2950 (m), 2930 (m), 2886 (w), 2856 (m), 1472 (w), 1462 (w), 1440 (w), 1370 (w), 1362 (w), 1252 (m), 1232 (w), 1222 (w), 1166 (w), 1156 (w), 1092 (s), 1042 (s), 1006 (m), 992 (m), 874 (m), 830 (vs), 810 (m), 772 (vs), 678 (m), 656 (m).

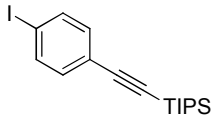
HRMS (EI) for **$C_{12}H_2IOSi^+$** (339.0641) [M-H$^-$]: 339.0649.

Preparation of bis(4-iodophenyl)zinc



A dry and Ar-flushed 100 mL *Schlenk*-flask, equipped with a magnetic stirring bar and a septum, was charged with a solution of 1,4-diiodobenzene (9.9 g; 30 mmol) in THF (30 mL) and cooled to –78 °C. At that temperature, a solution of *i*PrMgCl·LiCl (1.16 M in THF; 33 mmol; 28.4 mL) was slowly added via syringe. After complete addition, the reaction mixture was stirred for 1.5 h at –78 °C before a solution of $ZnCl_2$ in THF (1.0 M; 16.5 mL; 16.5 mmol) was added dropwise. After stirring for 15 min at –78 °C, the reaction mixture was allowed to warm to room temperature. The solvents (THF and isopropyl iodide from the I-Mg exchange reaction) were removed via high vacuum (1 mbar; 3 h). The residue was redissolved in THF (60 mL). Titration of an aliquot of the resulting organozinc with I_2 (50 mg in 2 mL THF) gave a concentration of 0.20 M (80%).

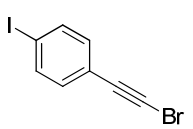
Synthesis of ((4-iodophenyl)ethynyl)triisopropylsilane



A dry and Ar-flushed 500 mL *Schlenk*-flask, equipped with a magnetic stirring bar and a septum, was charged with a solution of (bromoethynyl)triisopropylsilane[102] (5.22 g; 20 mmol) in THF (120 mL) and cooled to –78 °C. CuCN·2 LiCl[103] solution (1 M in THF; 20 mL; 20 mmol) was added and the reaction mixture was stirred for 30 min. Then, bis(4-iodophenyl)zinc (0.2 M in THF; 50 mL; 10 mmol) was slowly added via syringe. The reaction mixture was stirred for 6 h at –78 °C. NH_4Cl sat. aq. solution (200 mL) was added. Phases were separated and the aqueous phase was extracted with Et_2O (3 x 50 mL). The combined organic layers were washed with brine (100 mL) and dried over Na_2SO_4. The solvents were evaporated and the crude product was subjected to column chromatography (SiO_2; *n*-pentane) furnishing 3.30 g (43%) of the title compound as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.65 (d, *J*=8.3 Hz, 2 H), 7.20 (d, *J*=8.3 Hz, 2 H), 1.14 (s, 21 H).
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 137.3, 133.5, 123.0, 106.0, 94.1, 92.4, 18.6, 11.3.
MS (70 eV, EI) *m/z* (%): 384 (12) [M^+], 342 (18), 341 (100), 313 (22), 299 (23), 285 (30), 271 (47).
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2942 (m), 2890 (w), 2864 (m), 2156 (w), 1482 (m), 1468 (m), 1236 (w), 1224 (w), 1214 (w), 1006 (m), 996 (m), 882 (m), 818 (s), 666 (vs), 654 (s).
HRMS (EI) for **$C_{17}H_{25}ISi$** (384.0770): 384.0770.

Synthesis of 1-(bromoethynyl)-4-iodobenzene (107)[154]



To a solution of ((4-iodophenyl)ethynyl)triisopropylsilane (2.69 g; 7 mmol) in MeCN (70 mL) were subsequently added NBS (1.50 g; 8.4 mmol) and AgF (1.07 g; 8.4 mmol) in the dark. The

[154] T. Lee, H. R. Kang, S. Kim, S. Kim, *Tetrahedron* **2006**, *62*, 4081.

reaction mixture was stirred for 3 h at room temperature and then filtered through a pad of Celite. The pad was washed with Et_2O (3 x 100 mL). The combined filtrates were dried over Na_2SO_4. The solvents were evaporated and the crude product was purified via column chromatography (SiO_2; *n*-pentane) furnishing 1.45 g (67%) of the title compound as white crystals

m.p.: 104.3 - 105.8 **°C**

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.66 (d, *J*=8.3 Hz, 2 H), 7.17 (d, *J*=8.3 Hz, 2 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 137.5, 133.4, 122.2, 94.7, 79.2, 52.5.

MS (70 eV, EI) *m/z* (%): 306 (67) [M^+], 181 (58), 179 (63), 100 (95), 99 (59), 98 (35), 74 (100), 50 (46).

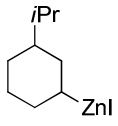
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2194 (w), 1896 (w), 1638 (w), 1574 (w), 1478 (m), 1456 (w), 1386 (m), 1262 (w), 1234 (w), 1054 (w), 1006 (m), 836 (m), 812 (vs), 776 (w).

HRMS (EI) for **C_8H_4BrI** (305.8541): 305.8528.

5.2 Preparation of cyclohexylzinc compounds

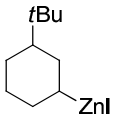
Anhydrous LiCl (0.38 g; 9 mmol) was placed in a dry and N_2-flushed 25 mL *Schlenk*-tube and dried over 20 min at 150-170 °C at high vacuum (1 mbar). Zn powder (1.18 g; 18 mmol) was added under N_2 and the heterogeneous mixture of Zn and LiCl was dried one more time at 150-170 °C for 20 min under high vacuum. The reaction flask was evacuated and refilled with N_2 three times. 1,2-Dibromoethane (0.02 mL) and THF (12 mL) was added. The mixture was then gently heated in order to activate the Zn surface. The respective cyclohexyl iodide (6 mmol) was added neat at room temperature. The resulting reaction mixture was stirred for 6 h. The solution was then separated from the remaining Zn powder via syringe filter (25 mm with 1 µm glass fiber membrane) and transferred to a dry N_2-flushed Schlenk-tube.[79] The concentrations of all cyclohexylzinc reagents were determined via titration of a small aliquot with I_2 (50 mg in 2 mL THF).

(3-Isopropylcyclohexyl)zinc iodide:



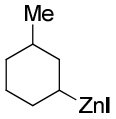
0.36 M (72%)

(3-(*tert*-Butyl)cyclohexyl)zinc iodide:



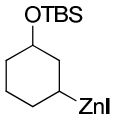
0.38 M (76%)

(3-Methylcyclohexyl)zinc iodide:



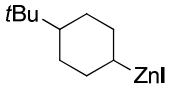
0.39 M (78%)

(3-((*tert*-Butyldimethylsilyl)oxy)cyclohexyl)zinc iodide:



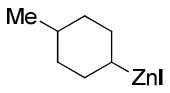
0.42 M (84%)

(4-(*tert*-Butyl)cyclohexyl)zinc iodide:



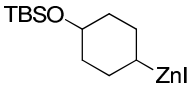
0.40 M (80%)

(4-Methylcyclohexyl)zinc iodide:



0.41 M (82%)

(4-((*tert*-Butyldimethylsilyl)oxy)cyclohexyl)zinc iodide:

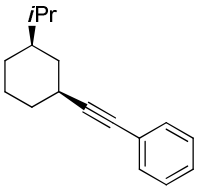


0.35 M (70%)

5.3 Cross-coupling of 3-, and 4-substituted cyclohexylzinc compounds with alkynynl bromides

A dry and N_2-flushed 10 mL *Schlenk*-tube, equipped with a magnetic stirring bar and a septum, was charged with a solution of the respective alkynyl bromide (0.4 mmol), $PdCl_2$ (10 μmol; 1.8 mg) and neocuproine (**105b**; 20 μmol; 4.2 mg) in THF (1.5 mL) and cooled to –30 °C. A solution of the respective cyclohexylzinc iodide in THF (0.5 mmol) was slowly added at this temperature. The reaction mixture was stirred for 12 h. NH_4Cl sat. aq. solution (5 mL) was added. Phases were separated and the aqueous phase was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with brine (10 mL) and dried over Na_2SO_4. The solvents were evaporated and the alkynylated product was purified via column chromatography.

((*cis*-3-Isopropylcyclohexyl)ethynyl)benzene (102a)



colorless oil (82%; regioisomer: <2%)

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.48 - 7.35 (m, 2 H), 7.34 - 7.21 (m, 3 H), 2.52 - 2.39 (m, 1 H), 2.12 - 1.98 (m, 2 H), 1.87 - 1.77 (m, 1 H), 1.70 (d, *J*=12.5 Hz, 1 H), 1.56 - 1.41 (m, 1 H), 1.39 -

1.24 (m, 2 H), 1.20 - 1.05 (m, 2 H), 0.99 (td, J_1=12.1 Hz, J_2=3.3 Hz, 1 H), 0.90 (d, J=6.7 Hz, 6 H).

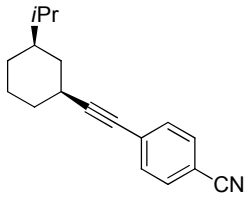
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 131.5, 128.1, 127.4, 124.0, 94.8, 43.6, 79.9, 36.4, 33.2, 32.8, 30.6, 28.9, 26.0, 19.7, 19.6.

MS (70 eV, EI) *m/z* (%): 226 (41) [M^+], 211 (100), 183 (95), 155 (40), 142 (27), 141 (52), 130 (22), 129 (32), 91 (24).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2954 (m), 2928 (m), 2856 (m), 1598 (w), 1490 (m), 1460 (w), 1444 (m), 1386 (w), 1368 (w), 1070 (w), 912 (w), 754 (vs), 690 (s), 668 (w).

HRMS (EI) for **$C_{17}H_{22}$** (226.1722): 226.1711.

4-((*cis*-3-Isopropylcyclohexyl)ethynyl)benzonitrile (102b)



slightly yellow oil (87%; regioisomer: <2%)

^{1}H-NMR (599 MHz, $CDCl_3$) δ: 7.56 (d, J=8.2 Hz, 2 H), 7.46 (d, J=8.1 Hz, 2 H), 2.45 (td, J_1=11.2 Hz, J_2=3.3 Hz, 1 H), 2.02 (d, J=7.4 Hz, 2 H), 1.85 - 1.79 (m, 1 H), 1.70 (d, J=12.1 Hz, 1 H), 1.52 - 1.43 (m, 1 H), 1.37 - 1.24 (m, 2 H), 1.18 - 1.10 (m, 2 H), 1.00 - 0.92 (m, 1 H), 0.89 (d, J=6.9 Hz, 6 H).

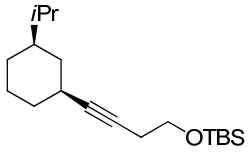
^{13}C-NMR (152 MHz, C_6D_6) δ: 132.1, 131.8, 129.1, 118.6, 110.7, 99.8, 78.8, 43.5, 36.1, 32.9, 32.8, 30.6, 28.8, 25.9, 19.6, 19.5.

MS (70 eV, EI) *m/z* (%): 259 (15), 258 (71), 215 (18), 214 (100), 131 (27), 75 (11), 57 (18), 56 (18).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2954 (m), 2930 (m), 2856 (m), 2226 (m), 1604 (m), 1500 (m), 1462 (w), 1448 (w), 1368 (w), 838 (vs).

HRMS (EI) for **$C_{18}H_{21}N$** (252.1674): 252.1664.

***tert*-Butyl((4-(*cis*-3-isopropylcyclohexyl)but-3-yn-1-yl)oxy)dimethylsilane (102c)**



slightly yellow oil (77%; regioisomer: 2%)

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.69 (t, J=7.2 Hz, 2 H), 2.38 (td, J_1=7.2 Hz, J_2=2.1 Hz, 2 H), 2.16 (dd, J_1=7.5 Hz, J_2=1.9 Hz, 1 H), 1.90 (ddd, J_1=5.8 Hz, J_2=3.9 Hz, J_3=1.5 Hz, 2 H), 1.80 - 1.71 (m, 1 H), 1.64 (d, J_1=12.4 Hz, 1 H), 1.48 - 1.37 (m, 1 H), 1.24 - 1.14 (m, 2 H), 1.11 - 0.93 (m, 3 H), 0.91 (s, 9 H), 0.86 (d, J=6.8 Hz, 6 H), 0.08 (s, 6 H).

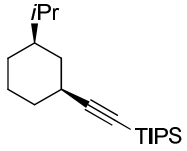
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 86.2, 76.2, 62.5, 43.6, 36.8, 33.6, 32.8, 30.1, 29.0, 26.0, 25.9, 23.2, 19.7, 19.5, 18.4, –5.2.

MS (70 eV, EI) *m/z* (%): 252 (9) [M-*t*Bu]$^+$, 175 (8), 75 (28), 59 (8), 58 (34), 57 (10), 43 (100), 41 (9).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2954 (m), 2928 (m), 2856 (m), 1472 (w), 1462 (w), 1252 (m), 1102 (s), 1058 (w), 916 (w), 860 (m), 834 (vs), 812 (m), 774 (vs), 738 (w), 664 (w).

HRMS (EI) for **$C_{15}H_{27}OSi$** (252.1831) [M-*t*Bu]$^+$: 252.1837.

Triisopropyl((*cis*-3-isopropylcyclohexyl)ethynyl)silane (102d)



colorless oil (79%; regioisomer: <4%)

^{1}H-NMR (599 MHz, $CDCl_3$) δ: 2.27 - 2.22 (m, 1 H), 1.98 - 1.94 (m, 2 H), 1.77 - 1.73 (m, 1 H), 1.65 (d, J=13.19 Hz, 1 H), 1.47 - 1.39 (m, 2 H), 1.29 - 1.19 (m, 3 H), 1.10 - 1.04 (m, 18 H), 1.04 - 0.99 (m, 4 H), 0.87 (d, J=3.1 Hz, 3 H), 0.86 (d, J=3.1 Hz, 3 H).

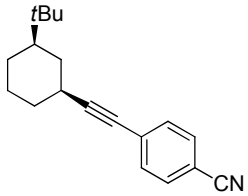
^{13}C-NMR (152 MHz, $CDCl_3$) δ: 114.2, 78.6, 43.6, 36.7, 33.6, 32.8, 31.1, 28.9, 26.0, 19.7, 19.7, 18.6, 11.3.

MS (70 eV, EI) *m/z* (%): 306 (1) [M$^+$], 264 (3), 263 (100), 235 (2), 221 (1), 207 (2), 193 (2), 73 (1).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2956 (m), 2938 (m), 2894 (m), 2864 (m), 2170 (w), 1462 (m), 1448 (w), 996 (w), 882 (m), 676 (vs), 666 (vs).

HRMS (EI) for **$C_{20}H_{38}Si$** (306.2743): 306.2739.

4-((*cis*-3-(*tert*-Butyl)cyclohexyl)ethynyl)benzonitrile (102e)



slightly yellow oil (85%;regioisomer: 2%)

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.56 (d, *J*=8.3 Hz, 2 H), 7.46 (d, *J*=8.3 Hz, 2 H), 2.50 - 2.40 (m, 1 H), 2.15 - 1.96 (m, 2 H), 1.88 - 1.74 (m, 2 H), 1.41 - 1.23 (m, 2 H), 1.22 - 0.94 (m, 3 H), 0.88 (s, 9 H).

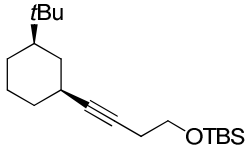
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 132.1, 131.8, 129.1, 118.6, 110.7, 99.9, 78.9, 47.6, 34.0, 32.8, 32.5, 30.9, 27.4, 26.5, 26.1.

MS (70 eV, EI) *m/z* (%): 265 (23) [M^+], 209 (40), 208 (32), 180 (11), 166 (12), 141 (32), 140 (11), 57 (100), 40 (17).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2940 (m), 2860 (m), 2226 (m), 1604 (m), 1500 (m), 1478 (w), 1462 (w), 1448 (m), 1406 (w), 1394 (w), 1366 (m), 1268 (w), 1240 (w), 1176 (w), 1104 (w), 930 (w), 838 (vs).

HRMS (EI) for **$C_{19}H_{23}N$** (265.1830): 265.1820.

***tert*-Butyl((4-(*cis*-3-(*tert*-butyl)cyclohexyl)but-3-yn-1-yl)oxy)dimethylsilane (102f)**



colorless oil (74%; regioisomer: <3%)

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.69 (t, *J*=7.2 Hz, 2 H), 2.38 (td, J_1=7.2 Hz, J_2=1.9 Hz, 2 H), 2.16 (t, *J*=8.5 Hz, 1 H), 1.99 (d, *J*=11.4 Hz, 1 H), 1.89 (d, *J*=6.8 Hz, 1 H), 1.82 - 1.67 (m, 2 H), 1.28 - 1.14 (m, 2 H), 1.13 - 0.93 (m, 3 H), 0.91 (s, 9 H), 0.85 (s, 9 H), 0.08 (s, 6 H).

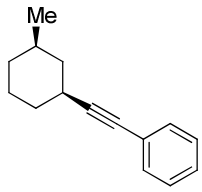
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 86.2, 76.3, 62.4, 47.6, 34.8, 33.5, 32.5, 30.4, 27.5, 26.6, 26.3, 25.9, 23.2, 18.4, -5.2.

MS (70 eV, EI) *m/z* (%): 321 (1) [M-H$^-$], 265 (28), 189 (11), 147 (17), 137 (15), 133 (12), 123 (11), 115 (11), 97 (10), 95 (16), 89 (40), 83 (26), 81 (16), 75 (79), 73 (100), 69 (17), 67 (10), 59 (14), 57 (98), 55 (18), 43 (13), 41 (20).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2948 (m), 2930 (m), 2858 (m), 1472 (w), 1462 (w), 1366 (w), 1252 (m), 1100 (s), 1058 (w), 918 (w), 862 (m), 834 (vs), 812 (m), 774 (vs), 738 (w), 664 (w).

HRMS (EI) for **$C_{20}H_{37}OSiN$** (321.2614) [M-H$^-$]: 321.2613.

((*cis*-3-Methylcyclohexyl)ethynyl)benzene (102g)



colorless oil (79%; regioisomer: <1%)

^{1}H-NMR (599 MHz, $CDCl_3$) δ: 7.40 (dd, J_1=7.7 Hz, J_2=1.4 Hz, 2 H), 7.31 - 7.23 (m, 3 H), 2.50 - 2.42 (m, 1 H), 2.04 (d, J=11.2 Hz, 2 H), 1.81 - 1.75 (m, 1 H), 1.69 (dd, J_1=13.0 Hz, J_2=1.4 Hz, 1 H), 1.45 - 1.37 (m, 1 H), 1.36 - 1.27 (m, 2 H), 1.12 (q, J=12.3 Hz, 1 H), 0.94 (d, J=6.6 Hz, 3 H), 0.92 - 0.86 (m, 1 H).

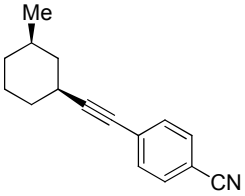
^{13}C-NMR (152 MHz, $CDCl_3$) δ: 131.5, 128.1, 127.4, 124.1, 94.6, 79.9, 41.7, 34.4, 32.8, 32.3, 30.3, 25.8, 22.6.

MS (70 eV, EI) *m/z* (%): 198 (100) [M$^+$], 183 (36), 169 (28), 156 (29), 155 (60), 143 (20), 142 (46), 141 (72), 130 (21), 129 (35), 128 (57), 115 (44), 102 (21), 91 (25).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2946 (m), 2924 (m), 2854 (m), 1492 (w), 1458 (w), 1444 (m), 754 (vs), 690 (s), 668 (w).

HRMS (EI) for **$C_{15}H_{18}$** (198.1409): 198.1401.

4-((*cis*-3-Methylcyclohexyl)ethynyl)benzonitrile (102h)



colorless oil (88%; regioisomer: –)

^{1}H-NMR (599 MHz, $CDCl_3$) δ: 7.55 (d, J=8.2 Hz, 2 H), 7.44 (d, J=8.1 Hz, 2 H), 2.47 (tt, J_1=11.6 Hz, J_2=3.4 Hz, 1 H), 2.06 - 1.94 (m, 2 H), 1.77 (dt, J_1=6.4 Hz, J_2=3.1 Hz, 1 H), 1.68 (d, J=12.9 Hz, 1 H), 1.44 - 1.37 (m, 1 H), 1.36 - 1.24 (m, 2 H), 1.09 (q, J=12.1 Hz, 1 H), 0.92 (d, J=6.6 Hz, 3 H), 0.91 - 0.85 (m, 1 H).

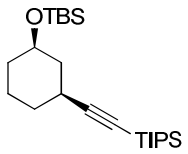
^{13}C-NMR (152 MHz, $CDCl_3$) δ: 132.0, 131.8, 129.1, 118.6, 110.7, 99.6, 78.8, 41.2, 34.2, 32.4, 32.2, 30.3, 25.7, 22.5.

MS (70 eV, EI) *m/z* (%): 223 (96) [M^+], 194 (50), 180 (52), 168 (33), 167 (65), 166 (55), 154 (68), 153 (61), 142 (27), 140 (34), 127 (45), 116 (32), 107 (31), 94 (87), 79 (29), 78 (27), 77 (69), 55 (45), 46 (100), 41 (81).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2924 (m), 2854 (m), 2224 (m), 1604 (m), 1500 (m), 1458 (m), 1446 (w), 836 (vs).

HRMS (EI) for **$C_{16}H_{17}N$** (223.1361): 223.1359.

***tert*-Butyldimethyl((*cis*-3-((triisopropylsilyl)ethynyl)-cyclohexyl)oxy)silane (102i)**



colorless oil (81%; regioisomer: 5%)

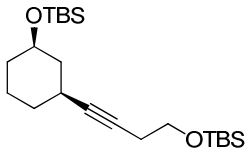
^{1}H-NMR (400 MHz, C_6D_6) δ: 3.37 - 3.28 (m, 1 H), 2.28 (d, J=12.5 Hz, 1 H), 2.13 (tt, J_1=12.2 Hz, J_2=3.5 Hz, 1 H), 1.78 (d, J=13.1 Hz, 1 H), 1.70 (d, J=11.9 Hz, 1 H), 1.60 - 1.52 (m, 1 H), 1.44 - 1.37 (m, 1 H), 1.20 - 1.16 (m, 18 H), 1.14 - 1.05 (m, 4 H), 0.95 (s, 9 H), 0.93 - 0.81 (m, 2 H), 0.01 (s, 6 H).

^{13}C-NMR (101 MHz, C_6D_6) δ: 113.6, 79.8, 71.0, 43.3, 36.2, 33.3, 30.3, 26.4, 24.4, 19.3, 18.6, 12.0, –4.09.

MS (70 eV, EI) *m/z* (%): 394 (1) [M^+], 352 (23), 339 (12), 338 (32), 337 (100), 296 (11), 295 (35), 267 (10), 253 (18), 203 (12), 161 (18), 147 (11), 133 (21), 129 (14), 120 (10), 119 (11), 115 (11), 112 (21), 87 (15), 81 (33), 75 (58), 73 (41), 59 (30).

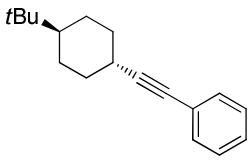
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2938 (m), 2892 (w), 2862 (m), 2172 (w), 1464 (m), 1372 (w), 1360 (w), 1252 (m), 1142 (w), 1126 (w), 1098 (s), 1076 (m), 1056 (s), 1026 (w), 1018 (w), 1006 (w), 996 (w), 894 (w), 880 (s), 860 (s), 834 (vs), 814 (m), 774 (s), 666 (vs), 650 (s).
HRMS (EI) for **$C_{23}H_{46}OSi_2$** (394.3087): 394.3083.

***tert*-Butyl((*cis*-3-(4-((*tert*-butyldimethylsilyl)oxy)but-1-yn-1-yl)cyclohexyl)oxy)dimethylsilane (102j)**



colorless oil (94%; regioisomer: 5%)
^{1}H-NMR (400 MHz, C_6D_6) δ: 3.66 (t, *J*=6.9 Hz, 2 H), 3.43 - 3.35 (m, 1 H), 2.40 (td, J_1=7.0 Hz, J_2=2.1 Hz, 2 H), 2.31 (d, *J*=12.5 Hz, 1 H), 2.20 (t, *J*=12.1 Hz, 1 H), 1.84 (d, *J*=11.7 Hz, 1 H), 1.74 (d, *J*=12.3 Hz, 1 H), 1.57 (d, *J*=11.1 Hz, 1 H), 1.49 - 1.42 (m, 1 H), 1.29 - 1.14 (m, 3 H), 0.97 (s, 9 H), 0.96 (s, 9 H), 0.04 (s, 12 H).
^{13}C-NMR (101 MHz, C_6D_6) δ: 85.4, 77.6, 71.1, 63.0, 43.9, 36.3, 33.3, 29.4, 26.5, 26.4, 24.4, 24.0, 18.9, 18.6, -4.06, –4.08, –4.79.
MS (70 eV, EI) *m/z* (%): 396 (1) [M^+], 341 (10), 340 (26), 339 (100), 249 (11), 208 (12), 207 (66), 147 (56), 133 (20), 131 (12), 105 (15), 91 (14), 89 (15), 81 (14), 75 (72), 73 (85), 59 (12).
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2930 (m), 2886 (w), 2858 (m), 1472 (w), 1464 (w), 1360 (w), 1252 (m), 1092 (s), 1006 (w), 900 (w), 880 (m), 860 (m), 832 (vs), 814 (m), 772 (vs), 666 (m).
HRMS (EI) for **$C_{22}H_{44}O_2Si_2$** (396.2880): 396.2886.

((*trans*-4-(*tert*-Butyl)cyclohexyl)ethynyl)benzene (103a)



colorless oil (76%; regioisomer: 3%)

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.48 - 7.35 (m, 2 H), 7.33 - 7.20 (m, 3 H), 2.36 (tt, J_1=12.0 Hz, J_2=3.5 Hz, 1 H), 2.14 (d, J=12.4 Hz, 2 H), 1.90 - 1.76 (m, 2 H), 1.53 - 1.36 (m, 2 H), 1.12 - 0.98 (m, 3 H), 0.88 (s, 9 H).

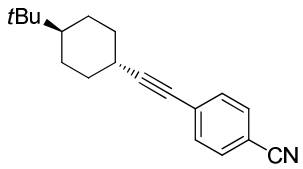
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 131.5, 128.1, 127.4, 124.1, 94.6, 80.0, 47.3, 33.7, 32.4, 30.4, 27.5, 26.9.

MS (70 eV, EI) *m/z* (%): 240 (11) [M^+], 155 (12), 141 (11), 136 (33), 131 (14), 130 (100), 129 (14), 128 (15), 121 (11), 115 (16), 57 (13).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2944 (m), 2856 (m), 1490 (m), 1478 (w), 1468 (w), 1444 (m), 1392 (w), 1366 (m), 1234 (w), 1070 (w), 1048 (w), 1026 (w), 964 (w), 928 (w), 914 (w), 898 (w), 754 (vs), 690 (s), 668 (w).

HRMS (EI) for **$C_{18}H_{24}$** (240.1878): 240.1878.

4-((*trans*-4-(*tert*-Butyl)cyclohexyl)ethynyl)benzonitrile (103b)



white crystals (84%; regioisomer: 3%)

m. p.: 103.8 – 105.5 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.56 (d, J=8.5 Hz 2 H), 7.45 (d, J=8.3 Hz ,2 H), 2.37 (tt, J_1=12.0 Hz, J_2=3.6 Hz, 1 H), 2.11 (d, J=13.6 Hz, 2 H), 1.89 - 1.76 (m, 2 H), 1.50 - 1.34 (m, 2 H), 1.10 - 0.96 (m, 3 H), 0.86 (s, 9 H).

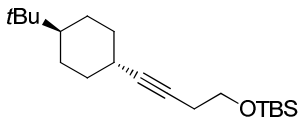
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 132.1, 131.8, 129.1, 118.6, 110.7, 99.7, 78.9, 47.3, 33.3, 32.4, 30.4, 27.4, 26.8.

MS (70 eV, EI) *m/z* (%): 265 (6) [M^+], 209 (16), 180 (13), 166 (11), 156 (12), 155 (100), 153 (13), 140 (12), 136 (45), 121 (11), 57 (58), 40 (17).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2948 (m), 2938 (m), 2928 (s), 2858 (m), 2226 (m), 1604 (m), 1502 (m), 1448 (m), 1390 (w), 1364 (s), 1234 (w), 1178 (m), 966 (w), 894 (m), 832 (vs).

HRMS (EI) for **$C_{19}H_{23}N$** (265.1830): 265.1822.

***tert*-Butyl((4-(*trans*-4-(*tert*-butyl)cyclohexyl)but-3-yn-1-yl)oxy)dimethylsilane (103c)**



slightly yellow oil (79%; regioisomer: <5%)

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.69 (t, J=7.2 Hz, 2 H), 2.37 (td, J_1=7.2 Hz, J_2=2.1 Hz, 2 H), 2.14 - 2.03 (m, 1 H), 1.98 (d, J=12.4 Hz, 2 H), 1.81 - 1.68 (m, 2 H), 1.36 - 1.21 (m, 2 H), 1.10 - 0.93 (m, 3 H), 0.91 (s, 9 H), 0.83 (s, 9 H), 0.08 (s, 6 H).

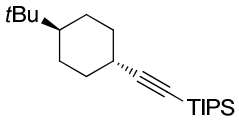
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 86.0, 76.3, 62.5, 47.4, 34.0, 32.4, 29.9, 27.5, 26.9, 25.9, 23.2, 18.4,–5.2.

MS (70 eV, EI) *m/z* (%): 265 (1) $[M\text{-}t\text{Bu}]^+$, 81 (2), 72 (3), 69 (2), 67 (2), 59 (5), 58 (33), 57 (8), 55 (4), 44 (2), 43 (3), 43 (100),42 (7), 41 (6).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2930 (m), 2858 (m), 1472 (w), 1464 (w), 1450 (w), 1364 (w), 1252 (m), 1236 (w), 1100 (s), 1058 (w), 1006 (w), 916 (w), 898 (w), 882 (w), 832 (vs), 812 (m), 774 (vs), 734 (w), 664 (w).

HRMS (EI) for $\mathbf{C_{16}H_{29}OSi^+}$ (265.1988) $[M\text{-}t\text{Bu}]^+$: 265.1996.

((*trans*-4-(*tert*-Butyl)cyclohexyl)ethynyl)triisopropylsilane (103d)



slightly yellow oil (75%;regioisomer: 2%)

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.23 - 2.11 (m, 1 H), 2.06 (d, J=12.4 Hz, 2 H), 1.82 - 1.70 (m, 2 H), 1.47 - 1.24 (m, 3 H), 1.11 - 1.03 (m, 20 H), 0.99 (dd, J_1=8.9 Hz, J_2=3.5 Hz, 3 H), 0.84 (s, 9 H).

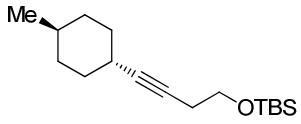
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 114.1, 78.7, 47.4, 34.0, 32.4, 30.8, 27.5, 26.9, 18.6, 11.3.

MS (70 eV, EI) *m/z* (%): 320 (1), 279 (5), 278 (27), 277 (100), 249 (10), 235 (5), 221 (9), 207 (6), 99 (3), 73 (3), 59 (3), 57 (4).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2940 (s), 2892 (m), 2864 (s), 2174 (w), 1464 (m), 1450 (w), 1366 (m), 1234 (w), 1076 (w), 1066 (w), 1016 (w), 996 (m), 882 (s), 860 (w), 756 (w), 678 (vs), 668 (vs), 638 (m).

HRMS (EI) for **$C_{21}H_{40}Si$** (320.2899): 320.2905.

***tert*-Butyldimethyl((4-(*trans*-4-methylcyclohexyl)but-3-yn-1-yl)oxy)silane (103e)**



slightly yellow oil (74%;regioisomer: 3%)

^{1}H-NMR (400 MHz, C_6D_6) δ: 3.68 (t, J=7.1 Hz, 2 H), 2.42 (td, J_1=7.0 Hz, J_2=2.1 Hz, 2 H), 2.22 - 2.09 (m, 1 H), 2.06 - 1.94 (m, 2 H), 1.53 - 1.37 (m, 4 H), 1.16 - 1.06 (m, 1 H), 1.04 - 0.97 (m, 1 H), 0.96 (s, 9 H), 0.74 (d, J=6.6 Hz, 3 H), 0.72 - 0.65 (m, 1 H), 0.04 (s, 6 H).

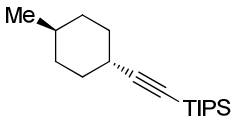
^{13}C-NMR (101 MHz, C_6D_6) δ: 86.4, 77.4, 63.1, 35.1, 34.3, 32.5, 30.4, 26.5, 24.1, 23.0, 18.9, –4.8.

MS (70 eV, EI) *m/z* (%): 223 (70) [M-*t*Bu]$^+$, 149 (15), 147 (40), 129 (37), 121 (11), 105 (13), 101 (22), 93 (10), 91 (10), 89 (19), 81 (16), 75 (100), 73 (33), 59 (11).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2950 (m), 2928 (m), 2858 (m), 1472 (w), 1462 (w), 1448 (w), 1252 (m), 1100 (s), 1058 (w), 916 (w), 876 (w), 834 (vs), 810 (m), 774 (vs), 730 (w), 664 (w).

HRMS (EI) for **$C_{13}H_{23}OSi^+$** (223.1528) [M-*t*Bu]$^+$: 223.1505.

Triisopropyl((*trans*-4-methylcyclohexyl)ethynyl)silane (103f)



colorless oil (71%; regioisomer: 4%)

^{1}H-NMR (400 MHz, C_6D_6) δ: 2.07 (tt, J_1=11.6 Hz, J_2=3.7 Hz, 1 H), 1.93 (dd, J_1=13.5 Hz, J_2=3.4 Hz, 2 H), 1.49 - 1.41 (m, 2 H), 1.41 - 1.31 (m, 2 H), 1.29 - 1.16 (m, 18 H), 1.15 - 1.06 (m, 4 H), 0.77 - 0.69 (m, 3 H), 0.69 - 0.57 (m, 2 H).

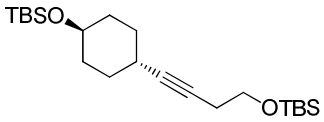
^{13}C-NMR (101 MHz, C_6D_6) δ: 114.9, 79.5, 34.9, 34.0, 32.3, 31.1, 22.9, 19.3, 12.1.

MS (70 eV, EI) *m/z* (%): 278 (1) [M^+], 236 (21), 235 (100), 207 (23), 193 (19), 179 (23), 165 (27).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2940 (m), 2924 (s), 2892 (m), 2864 (s), 2170 (w), 1462 (m), 1448 (m), 1382 (w), 1366 (w), 1236 (w), 1092 (w), 1074 (w), 1056 (w), 1010 (w), 996 (w), 918 (w), 882 (s), 836 (w), 670 (vs), 656 (s), 642 (m).

HRMS (EI) for **$C_{18}H_{34}Si$** (278.2430): 278.2448.

***tert*-Butyl((*trans*-4-(4-((*tert*-butyldimethylsilyl)oxy)but-1-yn-1-yl)cyclohexyl)oxy)-dimethylsilane (103g)**



slightly yellow oil (88%; 6%)

^{1}H-NMR (400 MHz, C_6D_6) δ: 3.68 (t, J=7.0 Hz, 2 H), 3.56 (ddd, J_1=12.5 Hz, J_2=8.5 Hz, J_3=3.4 Hz, 1 H), 2.41 (td, J_1=7.0 Hz, J_2=1.9 Hz, 2 H), 2.25 (br. s., 1 H), 1.96 (dt, J_1=9.3 Hz, J_2=3.9 Hz, 2 H), 1.89 - 1.78 (m, 2 H), 1.49 - 1.38 (m, 2 H), 1.33 - 1.23 (m, 2 H), 0.97 (s, 9 H), 0.96 (s, 9 H), 0.04 (s, 6 H), 0.02 (s, 6 H).

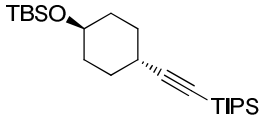
^{13}C-NMR (101 MHz, C_6D_6) δ: 85.5, 77.8, 70.4, 63.1, 34.8, 31.1, 29.3, 26.5, 26.4, 24.1, 18.9, 18.6, –4.15, –4.80.

MS (70 eV, EI) *m/z* (%): 396 (1) [M^+], 340 (13), 339 (49), 207 (12), 147 (33), 133 (19), 131 (11), 91 (11), 89 (10), 75 (100), 73 (56).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2930 (m), 2898 (w), 2886 (w), 2858 (m), 1472 (w), 1464 (w), 1252 (m), 1094 (s), 1058 (w), 1046 (m), 1006 (w), 916 (w), 896 (w),878 (w), 852 (m), 832 (vs), 814 (m), 772 (vs), 732 (w), 666 (m).

HRMS (EI) for **$C_{22}H_{44}O_2Si_2$** (396.2880): 396.2858.

***tert*-Butyldimethyl((*trans*-4-((triisopropylsilyl)ethynyl)-cyclohexyl)oxy)silane (103h)**



colorless oil (92%; regioisomer: 6%)

^{1}H-NMR (400 MHz, C_6D_6) δ: 3.52 - 3.57 (m, 1 H), 2.23 (br. s., 1 H), 1.91 - 1.81 (m, 4 H), 1.42 - 1.35 (m, 2 H), 1.31 - 1.24 (m, 2 H), 1.24 - 1.18 (m, 18 H), 1.15 - 1.08 (m, 3 H), 0.96 (s, 9 H), 0.02 (s, 6 H).

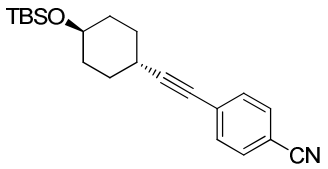
^{13}C-NMR (101 MHz, C_6D_6) δ: 113.1, 79.4, 69.1, 33.5, 29.5, 29.1, 25.7, 18.6, 17.9, 11.3, –5.0.

MS (70 eV, EI) *m/z* (%): 394 (6) [M^+], 352 (22), 352 (78), 338 (16), 337 (50), 309 (13), 261 (15), 233 (11), 181 (15), 157 (11), 153 (14), 133 (10), 129 (16), 119 (34), 112 (16), 75 (100), 73 (40), 59 (18).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2938 (s), 2892 (m), 2864 (s), 2168 (w), 1462 (m), 1382 (w), 1362 (w), 1252 (m), 1098 (s), 1048 (s), 1028 (m), 1006 (m), 996 (m), 962 (w), 876 (m), 858 (s), 834 (vs), 816 (m), 772 (vs), 700 (w), 674 (vs), 610 (w).

HRMS (EI) for **$C_{23}H_{46}OSi_2$** (394.3087): 394.3087.

4-((*trans*-4-((*tert*-Butyldimethylsilyl)oxy)cyclohexyl)-ethynyl)benzonitrile (103i)



slightly yellow oil (94%; regioisomer: 4%)

^{1}H-NMR (400 MHz, C_6D_6) δ: 7.01 (d, *J*=8.4 Hz, 2 H), 6.82 (m, *J*=8.4 Hz, 2 H), 3.59 - 3.52 (m, 1 H), 2.37 - 2.29 (m, 1 H), 1.96 - 1.87 (m, 2 H), 1.84 - 1.76 (m, 2 H), 1.45 - 1.34 (m, 2 H), 1.33 - 1.23 (m, 2 H), 0.98 (s, 9 H), 0.04 (s, 6 H).

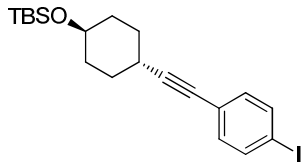
^{13}C-NMR (101 MHz, C_6D_6) δ: 132.4, 132.3, 129.0, 118.8, 111.9, 98.8, 80.4, 69.9, 34.4, 30.1, 29.6, 26.4, 18.6, -4.2.

MS (70 eV, EI) *m/z* (%): 339 (1) [M^+], 283 (21), 282 (100), 206 (31), 75 (82).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2948 (m), 2928 (m), 2898 (w), 2856 (m), 2226 (w), 1604 (w), 1500 (w), 1472 (w), 1462 (w), 1450 (w), 1374 (w), 1248 (m), 1094 (s), 1042 (m), 1006 (w), 896 (w), 876 (m), 856 (s), 830 (vs), 796 (m), 772 (s), 670 (m), 654 (w).

HRMS (EI) for **$C_{21}H_{29}NOSi$** (339.2018): 339.2007.

***tert*-Butyl((*trans*-4-((4-iodophenyl)ethynyl)cyclohexyl)-oxy)dimethylsilane (108)**



The reaction was carried out at a 4 mmol scale.

orange oil (79%; regioisomer: >4%)

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.61 (d, *J*=8.6 Hz, 2 H), 7.11 (d, *J*=8.3 Hz, 2 H), 3.74 - 3.61 (m, 1 H), 2.57 - 2.43 (m, 1 H), 2.16 - 1.95 (m, 2 H), 1.95 - 1.80 (m, 2 H), 1.57 - 1.31 (m, 4 H), 0.90 (s, 9 H), 0.07 (s, 6 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 136.8, 132.7, 123.1, 94.8, 92.6, 79.2, 69.2, 33.7, 29.5, 28.6, 25.4, 17.7, –5.1.

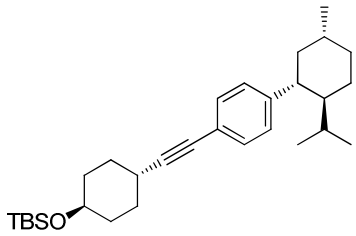
MS (70 eV, EI) *m/z* (%): 440 (1) [M^+], 384 (18), 383 (75), 308 (23), 307 (100), 256 (24), 254 (12), 182 (12), 181 (24), 180 (12), 75 (90), 73 (15).

IR (ATR) $\tilde{\nu}$ **(cm^{-1}):** 2928 (m), 2896 (w), 2856 (m), 1482 (m), 1472 (w), 1462 (w), 1452 (w), 1250 (m), 1096 (s), 1058 (m), 1046 (m), 1024 (m), 1006 (m), 942 (w), 874 (m), 854 (s), 834 (vs), 818 (vs), 772 (vs), 740 (w), 730 (w), 668 (m).

HRMS (EI) for **$C_{20}H_{29}IOSi$** (440.1032): 440.1023.

5.4 Preparation of (1*R*,4*r*)-4-((4-((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl)-phenyl)ethynyl)cyclohexanol (106)

***tert*-Butyl(((1*R*,4*r*)-4-((4-((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl)phenyl)ethynyl)-cyclohexyl)-oxy)dimethylsilane**

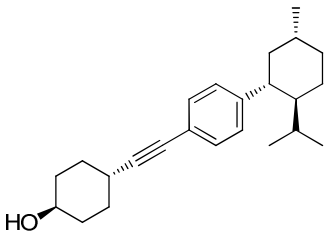


In a dry and N_2-flushed 10 mL *Schlenk*-tube, a solution of $Pd(dba)_2$ (20 µmol, 11.5 mg), S-Phos (20 µmol, 8.2 mg) and *tert*-butyl((*trans*-4-((4-iodophenyl)ethynyl)cyclohexyl)-

oxy)dimethylsilane (**108**; 0.7 mmol, 0.308 g) in THF (0.7 mL) and NEP (*N*-ethylpyrrolidone) (0.2 mL) was stirred for five minutes, before menthylzinc iodide (**11**) was added. The reaction progress was monitored by gas chromatography (GC) analysis. Conversion was complete after six hours. The reaction mixture was quenched with saturated NH_4Cl aq. solution (2 mL), and water was added (2 mL). The phases were separated and the aqueous phase extracted with Et_2O (3 × 10 mL). The combined organic layers were dried over Na_2SO_4 and the solvents were evaporated. The crude product was purified via column chromatography (SiO_2; *n*-pentane:Et_2O 80:1) furnishing the title compound (0.250 g; 79%) as an orange oil (d.r. > 99:1; >4% regioisomer).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.31 (d, *J*=8.0 Hz, 2 H), 7.08 d, *J*=8.0 Hz, 2 H), 3.70 - 3.64 (m, 1 H), 2.53 - 2.47 (m, 1 H), 2.40 (td, J_1=11.5 Hz, J_2=3.3 Hz, 1 H), 2.10 - 2.00 (m, 2 H), 1.95 - 1.88 (m, 2 H), 1.85 - 1.71 (m, 4 H), 1.52 - 1.35 (m, 6 H), 1.17 - 0.98 (m, 4 H), 0.94 - 0.84 (m, 11 H), 0.78 (d, *J*=6.9 Hz, 3 H), 0.65 (d, *J*=6.8 Hz, 3 H), 0.07 (s, 6 H).
^{13}C-NMR (101 MHz, $CDCl_3$) δ: 146.3, 132.0, 131.5, 127.4, 126.6, 121.1, 92.8, 80.5, 69.8, 47.9, 47.4, 45.0, 35.3, 34.2, 33.2, 30.2, 29.0, 27.4, 25.9, 25.8, 24.5, 22.50, 21.5, 18.2, 18.1, 15.3, –4.7.
MS (70 eV, EI) *m/z* (%): 452 (4) [M^+], 396 (20), 395 (67), 320 (39), 319 (100), 268 (87), 181 (46), 139 (22), 129 (30), 128 (23), 83 (90), 75 (79), 73 (20), 69 (34), 57 (33), 55 (25).
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2948 (m), 2928 (m), 2858 (m), 1472 (w), 1462 (w), 1452 (w), 1368 (w), 1362 (w), 1252 (m), 1096 (s), 1046 (m), 1024 (w), 1006 (w), 874 (m), 856 (s), 832 (vs), 772 (s), 668 (m).
HRMS (EI) for **$C_{30}H_{48}OSi$** (452.3474): 452.3482.

Preparation of (1*R*,4*r*)-4-((4-((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl)-phenyl)ethynyl)cyclohexanol (106)



To a solution of *tert*-butyl(((1*R*,4*r*)-4-((4-((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl)phenyl)-ethynyl)cyclohexyl)-oxy)dimethylsilane (0.5 mmol; 0.226 g) in THF (7.5 mL), TBAF·3 H_2O (tetrabutylammonium fluoride trihydrate) (1.0 mmol; 0.316 g) was added. The reaction mixture was stirred overnight at room temperature. NH_4Cl sat. aq. solution (10 mL) was added. Phases were separated and the organic phase was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvents were evaporated and the crude product was purified via column chromatography (SiO_2; *n*-pentane:Et_2O 10:1) furnishing the title compound as a slightly yellow, highly viscous substance (94%).

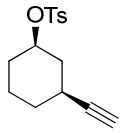
^{1}H-NMR (400 MHz, C_6D_6) δ: 7.48 (d, *J*=8.2 Hz, 2 H), 6.91 (d, *J*=8.0 Hz, 2 H), 3.39 - 3.30 (m, 1 H), 2.38 - 2.30 (m, 1 H), 2.26 (td, *J*=11.55, 3.41 Hz, 1 H), 2.02 - 1.91 (m, 2 H), 1.83 - 1.76 (m, 2 H), 1.74 - 1.62 (m, 3 H), 1.52 - 1.38 (m, 4 H), 1.35 - 1.26 (m, 2 H), 1.17 - 1.07 (m, 2 H), 1.04 - 0.89 (m, 3 H), 0.86 (d, *J*=6.6 Hz, 3 H), 0.77 (d, *J*=7.0 Hz, 3 H), 0.65 (d, *J*=6.8 Hz, 3 H).
^{13}C-NMR (101 MHz, C_6D_6) δ: 146.8, 132.5, 122.5, 93.5, 81.9, 69.4, 48.6, 47.9, 45.6, 35.9, 34.6, 33.8, 31.2, 29.9, 28.1, 25.2, 23.1, 22.0, 15.9.
MS (70 eV, EI) *m/z* (%): 338 (26) [M^+], 311 (24), 310 (100), 268 (67), 183 (21), 181 (39), 172 (88), 165 (21), 155 (26), 143 (27), 141 (37), 130 (21), 129 (61), 128 (41), 83 (78), 69 (35), 57 (31), 55 (27), 41 (22).
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3340 (w), 2928 (vs), 2866 (s), 1502 (m), 1452 (s), 1366 (m), 1104 (m), 1068 (vs), 1034 (m), 1000 (m), 832 (vs), 818 (m).
HRMS (EI) for **$C_{24}H_{34}O$** (338.2610): 338.2605.

5.5 Preparation of tosylates for X-ray analysis

To a solution of the respective TBS-protected cyclohexanol (**102i** or **103h**) (0.25 mmol; 98.7 mg) in THF (1.5 mL), TBAF·3 H_2O (tetrabutylammonium fluoride trihydrate) (1.0 mmol; 0.316 g) was added. The reaction mixture was stirred overnight at room temperature. NH_4Cl sat. aq. solution (10 mL) was added. Phases were separated and the organic phase was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvents were evaporated. The crude product was dissolved in a mixture CH_2Cl_2 (1 mL) and pyridine (0.25 mL). 4-DMAP (4-dimethylaminopyridine; 0.25 mmol; 30.5 mg) and TsCl (*p*-tolylsulfonyl chloride; 0.80 mmol; 0.152 g) were added and the reaction mixture was stirred

overnight at room temperature. NH_4Cl sat. aq. solution (10 mL) was added. Phases were separated and the organic phase was extracted with CH_2Cl_2 (3 x 20 mL). The solvents were evaporated and the crude product was purified via column chromatography.

***cis*-3-Ethynylcyclohexyl 4-methylbenzenesulfonate**



colorless crystals (71%)

m. p.: 81.6 – 83.0 °C.

^{1}H-NMR (400 MHz, C_6D_6) δ: 7.77 (d, *J*=8.4 Hz, 2 H), 6.71 (d, *J*=8.0 Hz, 2 H), 4.36 - 4.26 (m, 1 H), 2.27 - 2.21 (m, 1 H), 1.83 (s, 3 H), 1.81 - 1.72 (m, 3 H), 1.52 - 1.41 (m, 2 H), 1.18 - 1.02 (m, 2 H), 0.94 - 0.83 (m, 1 H), 0.65 - 0.53 (m, 1 H).

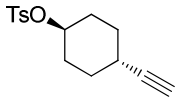
^{13}C-NMR (101 MHz, C_6D_6) δ: 144.4, 136.2, 130.1, 86.7, 79.8, 69.3, 39.2, 32.5, 31.8, 28.4, 23.4, 21.5.

MS (70 eV, EI) *m/z* (%): 278 (1) [M^+], 214 (22), 173 (12), 155 (20), 132 (19), 106 (13), 105 (13), 91 (100), 79 (11), 78 (17), 65 (14).

IR (ATR) $\tilde{\nu}$ **(cm^{-1}):** 3270 (m), 1358 (m), 1342 (m), 1188 (s), 1176 (s), 1096 (m), 938 (s), 922 (vs), 892 (s), 882 (s), 852 (s), 826 (s), 810 (s), 794 (m), 784 (m), 698 (s), 686 (s), 664 (vs).

HRMS (EI) for **$C_{15}H_{18}O_3S$** (278.0977): 278.0977.

***trans*-4-Ethynylcyclohexyl 4-methylbenzenesulfonate**



colorless crystals (73%)

m. p.: 56.1 – 57.6 °C.

^{1}H-NMR (400 MHz, C_6D_6) δ: 7.75 (d, *J*=8.4 Hz, 2 H), 6.72 (d, *J*=8.0 Hz, 2 H), 4.50 - 4.39 (m, 1 H), 1.93 (d, *J*=2.3 Hz, 1 H), 1.84 (s, 3 H), 1.80 - 1.68 (m, 3 H), 1.63 - 1.54 (m, 2 H), 1.32 - 1.23 (m, 2 H), 1.16 - 1.07 (m, 2 H).

^{13}C-NMR (101 MHz, C_6D_6) δ: 144.4, 136.2, 130.1, 128.2, 87.0, 79.9, 69.5, 30.4, 29.0, 27.6, 21.5.

MS (70 eV, EI) *m/z* (%): 278 (1) [M^+], 173 (27), 172 (16), 155 (37), 123 (12), 107 (11), 106 (100), 92 (22), 91 (55), 91 (74), 79 (31), 78 (64), 77 (19), 67 (13), 65 (42), 41 (15).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3292 (w), 3282 (m), 2956 (w), 1598 (w), 1444 (m), 1376 (w), 1348 (s), 1320 (m), 1304 (m), 1292 (m), 1258 (m), 1240 (w), 1188 (m), 1172 (vs), 1152 (m), 1122 (m), 1096 (s), 1058 (m), 1048 (m), 1034 (m), 1018 (m), 956 (s), 930 (s), 904 (s), 874 (m), 858 (vs), 810 (vs), 786 (s), 706 (m), 666 (vs), 642 (vs), 618 (s).

HRMS (EI) for **$C_{15}H_{18}O_3S$** (278.0977): 278.0971.

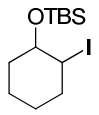
6. Fe-Mediated Diastereoselective Csp^2-Csp^3 Cross-Coupling Reactions.

6.1 Preparation of starting materials

Preparation of cyclohexyl iodides

A suspension of I_2 (1.2 equiv) in CH_2Cl_2 (0.8 M) was cooled to 0 °C and PPh_3 (1.1 equiv) was added portionwise. The reaction mixture was stirred for 1 h at 0 °C. *N*-methylimidazole (NMI; 1.25 equiv) was added, followed by dropwise addition of the respective cycloalcohol (1.0 equiv). The reaction mixture was warmed to room temperature and stirred for 1 h. NH_4Cl sat. aq. solution was added, the phases were separated and the aqueous phase was extracted with 3x CH_2Cl_2. The combined organic layers were washed with brine and dried over Na_2SO_4. The solvents were evaporated and the residue was subjected to column chromatography (SiO_2; *i*-hexane) yielding the title compound.[78]

***tert*-butyl((2-iodocyclohexyl)oxy)dimethylsilane (36)**



colorless oil (47%)

(Mixture of diastereomers; signals of the major diastereomer are given)

^{1}H-NMR (300 MHz, $CDCl_3$) δ:4.53 - 4.39 (m, 1 H), 3.36 (s br., 1 H), 2.32 - 2.20 (m, 1 H), 1.96 - 1.84 (m, 1 H), 1.79 - 1.60 (m, 3 H), 1.57 - 1.30 (m, 3 H), 0.95 (s, 9 H), 0.14 (s, 3 H), 0.08 (s, 3 H).

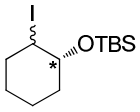
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 71.7, 42.3, 34.1, 33.4, 25.9, 25.3, 21.4, 18.2, –4.3, –4.5.

MS (70 eV, EI) *m/z* (%): 325 (1) $[M\text{-}CH_3]^+$, 284 (14), 283 (100), 215 (11), 185 (29), 155 (28), 83 (10), 81 (40), 75 (40), 73 (19), 71 (11), 69 (13), 57 (26), 55 (14), 40 (12).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2932 (m), 2856 (m), 1250 (m), 1166 (m), 1100 (s), 1074 (m), 1060 (m), 1030 (m), 1020 (m), 894 (m), 868 (m), 834 (vs), 806 (m), 774 (vs), 678 (m), 668 (m).

HRMS (EI) for **$C_{11}H_{22}OISi$** $[M\text{-}CH_3]^+$ (325.0485): 325.0413.

***tert*-Butyl(((1*R*)-2-iodocyclohexyl)oxy)dimethylsilane (113)**



colorless oil (45%)

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 4.52 - 4.41 (m, 1 H), 3.36 (s br., 1 H), 2.32 - 2.20 (m, 1 H), 1.96 - 1.85 (m, 1 H), 1.78 - 1.55 (m, 4 H), 1.48 - 1.34 (m, 2 H), 0.95 (s, 9 H), 0.14 (s, 3 H), 0.08 (s, 3 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 71.8, 42.3, 34.1, 33.4, 25.9, 25.3, 21.4, 18.2, –4.3, –4.5.

MS (70 eV, EI) *m/z* (%): 325 (1) $[M\text{-}CH_3]^+$, 284 (13), 283 (77), 191 (13), 190 (19), 185 (29), 176 (12), 175 (100), 155 (45), 91 (11), 81 (45), 75 (89), 73 (16), 71 (12), 57 (63), 55 (12), 43 (11).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2934 (m), 2856 (m), 1250 (m), 1168 (m), 1100 (s), 1072 (m), 1060 (m), 1028 (m), 1020 (m), 984 (m), 894 (m), 868 (s), 834 (vs), 806 (m), 774 (vs), 678 (m),668 (m).

HRMS (EI) for **$C_{11}H_{22}OISi$** $[M\text{-}CH_3]^+$ (325.0485): 325.0492.

***tert*-Butyl((2-iodocyclopentyl)oxy)dimethylsilane (117)**

colorless oil (48%)

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 4.43 (ddd, J_1=6.26, J_2=3.55, J_3=3.27 Hz, 1 H), 4.06 - 3.98 (m, 1 H), 2.41 - 2.28 (m, 1 H), 2.16 – 1.97 (m, 2 H), 1.80 (quint, J=7.39 Hz, 2 H), 1.60 - 1.49 (m, 1 H), 0.89 (s, 9 H), 0.10 (s, 3 H), 0.07 (s, 3 H).

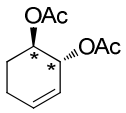
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 82.5, 35.8, 35.0, 32.3, 25.8, 22.3, 18.0, –4.5, –4.8.

MS (70 eV, EI) *m/z* (%): 311 (2) $[M\text{-}CH_3]^+$, 272 (2), 271 (4), 270 (100), 269 (2), 185 (72), 141 (41), 99 (5), 75 (21), 52 (4).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2954 (m), 2928 (m), 2856 (w), 1252 (m), 1132 (w), 1112 (m), 1076 (s), 1036 (m), 1020 (m), 1006 (m), 880 (s), 832 (vs), 810 (m), 774 (vs), 668 (m).

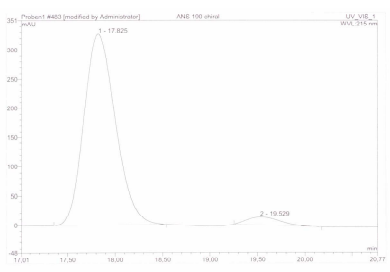
HRMS (EI) for **$C_{10}H_{20}IOSi$** (311.0328) $[M\text{-}CH_3]^+$: 311.0331

(1*R*,2*R*)-cyclohex-3-ene-1,2-diyl diacetate (obtained from the mixture of (*R*,*R*)-10 and (*R*,*R*)-11 via acetylation using Ac_2O in pyridine)[132]

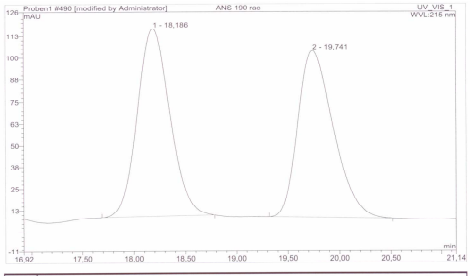


HPLC Data:

Chiralcel OD-H; *n*-heptane : *i*-propanol 98:2; flow: 0.3 mL/min

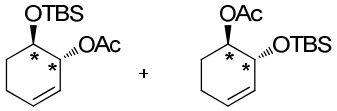


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	17,82	n.a.	326,253	125,052	96,14	n.a.	BMB*
2	19,53	n.a.	12,413	5,022	3,86	n.a.	BMB*
Total:			338,666	130,075	100,00	0,000	



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	18,19	n.a.	107,381	39,356	50,81	n.a.	BMB*
2	19,74	n.a.	95,347	38,101	49,19	n.a.	BMB*
Total:			202,728	77,457	100,00	0,000	

Preparation of (1*R*,2*R*)-2-((*tert*-butyldimethylsilyl)oxy)cyclohex-3-en-1-yl acetate and (1*R*,6*R*)-6-((*tert*-butyldimethylsilyl)oxy)cyclo- hex-2-en-1-yl acetate:



To a solution of a mixture of (1*R*,2*R*)-2-hydroxycyclohex-3-en-1-yl acetate (**10**) and (1*R*,6*R*)-6-hydroxycyclohex-2-en-1-yl acetate (**11**)[132] (24.46 mmol; 3.82 g) and imidazole (49.00 mmol; 3.34 g) in DMF (50 mL) was slowly added TBSCl (26.90 mmol; 4.05 g). The reaction mixture was stirred overnight at room temperature. NH_4Cl sat. aq. solution (150 mL) and Et_2O (50 mL) were added, phases were separated and the aqueous phase was extracted with Et_2O (3 x 50 mL). The combined organic layers were washed with brine (100 mL) and dried over Na_2SO_4. The solvents were evaporated and the residue was subjected to column chromatography (SiO_2; *n*-pentane/Et_2O 15:1) yielding 5.95 g (90%) of the title compound as a colorless oil.

(Mixture of regioisomers; signals of only one regioisomer are given)

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 5.90 - 5.78 (m, 1 H), 5.78 - 5.67 (m, 1 H), 4.82 (ddd, J_1=10.37, J_2=6.77, J_3=3.32 Hz, 1 H), 4.23 (dd, J_1=4.56, J_2=2.07 Hz, 1 H), 2.15 (td, J_1=8.78, J_2=4.01 Hz, 2 H), 2.06 (s, 3 H), 1.77 - 1.60 (m, 2 H), 0.89 (s, 9 H), 0.09 - 0.05 (m, 6 H).

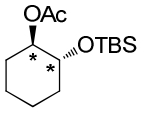
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 170.4, 128.3, 124.6, 74.6, 69.7, 29.2, 25.7, 23.7, 21.3, 18.1, –4.6 –4.7.

MS (70 eV, EI) *m/z* (%): 213 (4) [M-*t*Bu]$^+$, 184 (4), 159 (5), 152 (3), 135 (10), 127 (5), 118 (10), 117 (100), 79 (24), 75 (32), 73 (10), 43 (8).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2954 (w), 2930 (w), 2858 (w), 1736 (s), 1370 (m), 1236 (s), 1098 (s), 1048 (m), 1034 (m), 1006 (m), 988 (w), 948 (w), 934 (w), 888 (m), 864 (m), 832 (vs), 816 (m), 774 (vs), 748 (w), 724 (w), 680 (w), 666 (w), 654 (w), 642 (w).

HRMS (EI) for **$C_{10}H_{17}O_3Si$** (213.0947) [M-*t*Bu]$^+$: 213.0931.

Preparation of (1*R*,2*R*)-2-((*tert*-butyldimethylsilyl)oxy)cyclohexyl acetate:



(1*R*,2*R*)-2-((*tert*-butyldimethylsilyl)oxy)cyclohex-3-en-1-yl acetate and (1*R*,6*R*)-6-((*tert*-butyldimethylsilyl)oxy)cyclo- hex-2-en-1-yl acetate (22.00 mmol; 5.95 g) were dissolved in EtOAc (150 mL). Pd/C (10% Pd) (0.60 g) was added and the reaction mixture was reduced with H_2 (1 atm) for 6 h at room temperature. The reaction mixture was filtered and the solvent was evaporated, yielding 5.99 g (99%) of the title compound as a colorless oil.

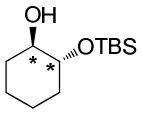
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 4.62 (td, J_1=8.78, J_2=4.56 Hz, 1 H), 3.61 - 3.52 (m, 1 H), 2.04 (s, 3 H), 2.01 – 1.93 (m, 1 H), 1.90 - 1.82 (m, 1 H), 1.71 - 1.62 (m, 2 H), 1.45 - 1.25 (m, 4 H), 0.87 (s, 9 H), 0.06 (s, 3 H), 0.05 (s, 3 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 170.4, 76.7, 72.3, 33.7, 29.6, 25.7, 23.4, 23.4, 21.4, 17.9, –4.6, –4.8.

MS (70 eV, EI) *m/z* (%): 273 (24) [M+H$^+$], 213 (92), 197 (9), 173 (28), 156 (100), 117 (80), 116 (12), 115 (8), 77 (18), 75 (11).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2932 (m), 2858 (w), 1736 (s), 1370 (m), 1236 (vs), 1106 (s), 1048 (s), 1038 (m), 1024 (m), 1006 (w), 952 (m), 874 (s), 832 (vs), 816 (m), 774 (s), 668 (m).
HRMS (EI) for **$C_{14}H_{29}O_3Si$** (273.1886) [M+H$^+$]: 273.1880.

Preparation of (1*R*,2*R*)-2-((*tert*-butyldimethylsilyl)oxy)cyclohexanol:



(1*R*,2*R*)-2-((*tert*-butyldimethylsilyl)oxy)cyclohexyl acetate (22.00 mmol; 5.99 g) was dissolved in MeOH (150 mL) and K_2CO_3 (44.00 mmol; 6.08 g) was added. The reaction mixture was stirred overnight at room temperature. It was then concentrated *in vacuo* and NH_4Cl sat. aq. solution (150 mL) and Et_2O (150 mL) were added. The phases were separated and the aqueous layer was extracted with Et_2O (3 x 50 mL). The combined organic phases were washed with brine (50 mL) and dried over Na_2SO_4. The solvents were evaporated yielding 4.95 g (98%) of the title compound as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.34 (d, J=5.81 Hz, 2 H), 2.29 (s br., 1 H), 1.98 (dd, J_1=5.94, J_2=3.18 Hz, 1 H), 1.90 - 1.81 (m, 1 H), 1.73 - 1.61 (m, 2 H), 1.31 - 1.21 (m, 4 H), 0.91 (s, 9 H), 0.10 (s, 3 H), 0.09 (s, 3 H).
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 77.2, 75.5, 33.5, 31.5, 25.8, 24.4, 24.1, 18.0, –4.1,–4.7.
MS (70 eV, EI) *m/z* (%): 215 (2) [M-CH_3]$^+$, 174 (17), 173 (100), 171 (8), 155 (15), 131 (9), 105 (48), 81 (44), 79 (8), 76 (5), 75 (74), 73 (11).
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2930 (m), 2858 (m), 1250 (m), 1090 (s), 1080 (s), 1072 (s), 1050 (m), 946 (m), 876 (s), 832 (vs), 814 (m), 774 (s), 668 (m).
HRMS (EI) for **$C_{11}H_{23}O_2Si$** (215.1467) [M-CH_3]$^+$: 215.1440.

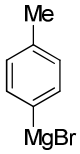
6.2 Preparation of (hetero)arylmagnesium reagents

6.2.1 Mg-insertion into (hetero)aryl halides

A dry and Ar-flushed 50 mL Schlenk-tube, equipped with a stirring bar and a septum, was charged with anhydrous LiCl (6.25 mmol; 265 mg) and heated to 130 °C under high vacuum (1

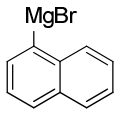
mbar) for 3 h. After cooling to room temperature under Ar, Mg turnings (6.25 mmol; 152 mg), 1,2-dibromoethane (0.02 ml) and freshly distilled THF (10 mL) were added. The reaction mixture was shortly heated to reflux and was cooled to room temperature under Ar. Under vigorous stirring the respective (hetero)aryl bromide (5 mmol) was added slowly at the appropriate temperature. The reaction mixture was stirred under Ar overnight and was titrated by using a stoichiometric amount of iodine (50 mg) in THF (2 mL).[129]

_p_-Tolylmagnesium bromide



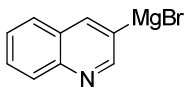
0.39 M (78%)
reaction temperature: 25 °C

Naphthalen-1-ylmagnesium bromide



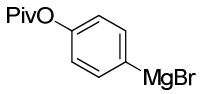
0.45 M (90%)
reaction temperature: 25 °C

Quinolin-3-ylmagnesium bromide



0.42 M (84%)
reaction temperature: 0 °C

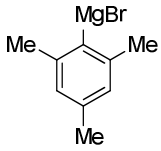
(4-(Pivaloyloxy)phenyl)magnesium bromide



0.38 M (76%)

reaction temperature: –20 °C

Mesitylmagnesium bromide



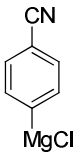
0.43 M (86%)

reaction temperature: 25 °C

6.2.1 Br/Mg-exchange reaction using *i*PrMgCl·LiCl on (hetero)aryl bromides

A dry and Ar-flushed 25 mL *Schlenk*-tube, equipped with a stirring bar and a septum, was charged with a solution of the respective bromide (1 equiv) in THF (2.0 M solution). The exchange reagent *i*PrMgCl·LiCl (1.1 equiv; 1.20 M) was added dropwise at the appropriate temperature. The reaction mixture was stirred at the same temperature, and the completion of the Br/Mg-exchange was checked by GC-analysis, using tridecane ($C_{13}H_{28}$) as internal standard. After completion of the reaction, the resulting solution was titrated by using a stoichiometric amount of iodine (50 mg) in THF (2 mL). [130]

(4-Cyanophenyl)magnesium chloride

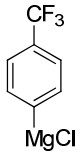


0.68 M (96%)

reaction temperature: 0 °C

reaction time: 3 h

(4-(Trifluoromethyl)phenyl)magnesium chloride

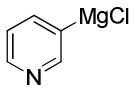


0.67 M (95%)

reaction temperature: 0 °C

reaction time: 2 h

Pyridin-3-ylmagnesium chloride

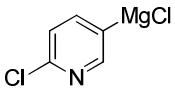


0.61 M (87%)

reaction temperature: 0 °C

reaction time: 3 h

(6-Chloropyridin-3-yl)magnesium chloride

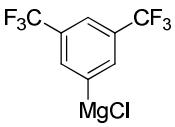


0.65 M (92%)

reaction temperature: –20 °C

reaction time: 3 h

(3,5-Bis(trifluoromethyl)phenyl)magnesium chloride

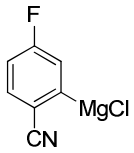


0.70 M (99%)

reaction temperature: 0 °C

reaction time: 2 h

(2-Cyano-5-fluorophenyl)magnesium chloride

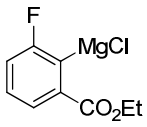


0.69 M (98%)

reaction temperature: –20 °C

reaction time: 30 min

(2-(Ethoxycarbonyl)-6-fluorophenyl)magnesium chloride



0.70 M (99%)

reaction temperature: –78 °C

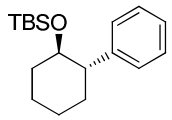
reaction time: 1 h

6.3 Diastereoselective $FeCl_2$-mediated Csp^2-Csp^3 cross-coupling with the TBS-protected cyclic iodohydrine derivatives

A dry and Ar-flushed 10 mL *Schlenk*-tube, equipped with a stirring bar and a septum, was charged with a solution of $FeCl_2 \cdot 2$ LiCl (1.0 M in THF; 0.43 mmol; 0.43 mL) and anhydrous THF (0.5 mL). The respective protected 2-iodocycloalcohol (0.5 mmol) and 4-fluorosytrene (0.25 mmol; 30.5 mg) were added via syringe. The reaction mixture was cooled to -50 °C and a solution of the corresponding Grignard reagent (0.85 mmol) was added dropwise via syringe. The reaction mixture was stirred for 1 h at this temperature and was then allowed to warm to room temperature overnight. It was then quenched with NH_4Cl sat. aq. solution (20 mL) and Et_2O (20 mL) was added, the phases were separated and the aqueous phase was extracted with Et_2O (4 x

20 mL). The combined organic layers were dried over Na_2SO_4. The solvents were evaporated and the residue was subjected to column chromatography yielding the respective title compound.

***tert*-Butyldimethyl((*trans*-2-phenylcyclohexyl)oxy)silane (36a)**



colorless oil (61 %)

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.32 - 7.09 (m, 5 H), 3.53 (td, J_1=9.8 Hz, J_2=4.4 Hz, 1 H), 2.44 (ddd, J_1=12.7 Hz, J_2=9.5 Hz, J_3=3.5 Hz, 1 H), 1.99 (ddd, J_1=8.0 Hz, J_2=4.6 Hz, J_3=4.4 Hz, 1 H), 1.88 - 1.78 (m, 2 H), 1.78 - 1.69 (m, 1 H), 1.61 - 1.59 (m, 1 H), 1.45 - 1.25 (m, 3 H), 0.66 (s, 9 H), –0.20 (s, 3 H), –0.53 (s, 3 H).

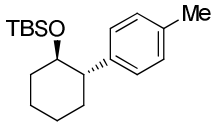
^{13}C-NMR (101 MHz, $CDCl_3$) δ: 145.0, 128.3, 127.9, 126.0, 75.9, 53.0, 36.7, 32.8, 26.0, 25.7, 25.3, 17.8, –4.7, –5.7.

MS (70 eV, EI) *m/z* (%): 289 (1) $[M-H]^+$, 235 (5), 234 (17), 233 (100), 157 (4), 135 (2), 129 (2), 115 (2), 91 (5), 75 (12).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2928 (m), 2856 (m), 1248 (m), 1094 (s), 982 (m), 880 (s), 854 (s), 834 (vs), 810 (m), 772 (vs), 752 (s), 698 (vs), 666 (m).

HRMS (EI) for **$C_{18}H_{29}OSi$** (289.1988) $[M-H]^+$: 289.1984.

***tert*-Butyldimethyl((*trans*-2-(*p*-tolyl)cyclohexyl)oxy)silane (36b)**



colorless oil (62 %)

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.10 (s, 4 H), 3.54 (td, J_1=9.6 Hz, J_2=4.6 Hz, 1 H), 2.49 - 2.39 (m, 1 H), 2.33 (s, 3 H), 2.05 - 1.97 (m, 1 H), 1.89 - 1.73 (m, 3 H), 1.64 - 1.54 (m, 1 H), 1.46 - 1.32 (m, 3 H), 0.70 (s, 9 H), –0.17 (s, 3 H), –0.48 (s, 3 H).

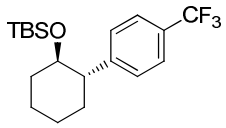
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 142.0, 135.3, 128.5, 128.2, 76.0, 52.6, 36.7, 32.9, 26.1, 25.7, 25.3, 21.0, 17.9, –4.7, –5.6.

MS (70 eV, EI) *m/z* (%): 304 (1) [M^+], 249 (5), 248 (18), 247 (100), 171 (5), 149 (4), 129 (2), 105 (15), 75 (33), 73 (7).

IR (ATR) $\tilde{\nu}$ **(cm^{-1}):** 2928 (m), 2856 (m), 1472 (w), 1248 (m), 1092 (s), 984 (m), 882 (m), 856 (s), 846 (m), 828 (vs), 810 (s), 772 (vs), 666 (m).

HRMS (EI) for **$C_{19}H_{32}OSi$** (304.2222): 304.2183.

***tert*-Butyldimethyl((*trans*-2-(4-(trifluoromethyl)phenyl)cyclohexyl)oxy)silane (36c)**



slightly yellow oil (67 %)

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.53 (d, *J*=8.0 Hz, 2 H), 7.32 (d, *J*=8.0 Hz, 2 H), 3.56 (td, J_1=9.4 Hz, J_2=4.4 Hz, 1 H), 2.59 - 2.48 (m, 1 H), 2.09 - 1.95 (m, 1 H), 1.91 - 1.74 (m, 3 H), 1.62 - 1.54 (m, 1 H), 1.47 - 1.26 (m, 3 H), 0.65 (s, 9 H), –0.15 (s, 3 H), –0.52 (s, 3 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 149.3 (d, *J*=1.1 Hz), 128.6, 128.4 (q, *J*=32.3 Hz), 124.8 (q, *J*=3.9 Hz), 124.4 (q, *J*=271.8 Hz), 75.8, 53.0, 36.6, 32.5, 25.9, 25.5, 25.1, 17.8, –4.5, –5.7.

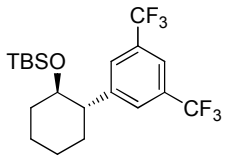
^{19}F-NMR (282 MHz, $CDCl_3$) δ: –62.3 (s).

MS (70 eV, EI) *m/z* (%): 359 (1) [M+H^+], 339 (21), 302 (100), 301 (68), 207 (96), 179 (41), 159 (42), 140 (15), 129 (12), 127 (30), 109 (10), 101 (16), 75 (11).

IR (ATR) $\tilde{\nu}$ **(cm^{-1}):** 2930 (m), 2858 (w), 1324 (vs), 1250 (m), 1162 (m), 1122 (s), 1094 (s), 1070 (s), 1018 (w), 984 (m), 882 (m), 846 (s), 830 (vs), 812 (m), 772 (s), 668 (w), 658 (m), 604 (m).

HRMS (EI) for **$C_{19}H_{30}OF_3Si$** (359.2013) [M+H^+]: 359.1843.

((*trans*-2-(3,5-Bis(trifluoromethyl)phenyl)cyclohexyl)oxy)(*tert*-butyl)dimethylsilane (36d)



colorless oil (75 %)

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.75 - 7.65 (m, 3 H), 3.57 (td, J_1=9.7 Hz, J_2=4.4 Hz, 1 H), 2.70 - 2.59 (m, 1 H), 2.05 (d, J=2.5 Hz, 1 H), 1.95 - 1.79 (m, 3 H), 1.68 - 1.57 (m, 1 H), 1.48 - 1.37 (m, 3 H), 0.65 (s, 9 H), –0.12 (s, 3 H), –0.52 (s, 3 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 147.7, 131.2 (q, J=33.0 Hz), 128.5 (d, J=2.5 Hz), 123.6 (q, J=272.4 Hz), 120.1 (sept, J=3.9 Hz), 75.7, 53.0, 36.5, 32.3, 25.7, 25.4, 25.0, 17.6, –4.5, –5.9.

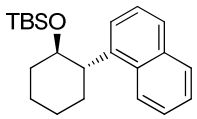
^{19}F-NMR (282 MHz, $CDCl_3$) δ: –62.9 (s).

MS (70 eV, EI) *m/z* (%): 426 (1) [M^+], 370 (19), 369 (100), 301 (14), 275 (6), 227 (4), 209 (11), 195 (2), 159 (2), 133 (3), 75 (7), 57 (2).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2932 (w), 2860 (w), 1382 (m), 1366 (w), 1276 (vs), 1260 (m), 1170 (s), 1130 (vs), 1098 (s), 1006 (w), 924 (m), 898 (w), 874 (s), 832 (s), 814 (m), 774 (s), 706 (m), 682 (s), 668 (w), 656 (w).

HRMS (EI) for **$C_{20}H_{28}OF_6Si$** (426.1814): 426.1655.

***tert*-Butyldimethyl((*trans*-2-(naphthalen-1-yl)cyclohexyl)oxy)silane (36e)**



colorless oil (90 %)

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.31 (d, J=8.5 Hz, 1 H), 7.88 - 7.82 (m, 1 H), 7.73 (d, J=7.4 Hz, 1 H), 7.55 - 7.40 (m, 4 H), 3.77 (br s., 1 H), 3.49 (t, J=9.5 Hz, 1 H), 2.16 - 2.08 (m, 1 H), 2.00 - 1.86 (m, 2 H), 1.85 (dd, J_1=8.6 Hz, J_2=2.4 Hz, 1 H), 1.81 - 1.72 (m, 1 H), 1.65 - 1.46 (m, 3 H), 0.49 (s, 9 H), –0.22 (s, 3 H), –0.81 (s, 3 H).

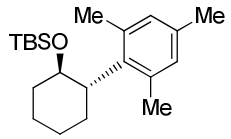
^{13}C-NMR (101 MHz, $CDCl_3$) δ: 142.1, 133.7, 133.3, 128.3, 126.2, 125.3, 125.2, 125.0, 124.5, 123.0, 77.2, 45.9, 37.1, 33.2, 26.4, 25.4, 25.4, 17.5, –4.9, –5.9.

MS (70 eV, EI) *m/z* (%):339 (1) [M-H]$^+$, 325 (1), 284 (20), 283 (100), 210 (3), 208 (4), 179 (3), 165 (4), 141 (8), 75 (11), 73 (3).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2928 (m), 2856 (m), 1248 (m), 1096 (s), 1084 (m), 972 (m), 880 (m), 862 (m), 832 (s), 814 (m), 792 (m), 772 (vs), 666 (m).

HRMS (EI) for **$C_{22}H_{31}OSi$** (339.2149) [M-H]$^+$: 339.2136.

tert-Butyl((_trans_-2-mesitylcyclohexyl)oxy)dimethylsilane (36f)



colorless oil (80 %)

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 6.76 (d, J=10.57 Hz, 2 H), 4.11 - 4.03 (m, 1 H), 3.07 – 2.98 (m, 1 H), 2.43 (s, 3 H), 2.33 (s, 3 H), 2.22 (s, 3 H), 2.05 - 1.95 (m, 2 H), 1.82 - 1.69 (m, 3 H), 1.38 - 1.27 (m, 3 H), 0.65 (s, 9 H), –0.13 (s, 3 H), –0.48 (s, 3 H).

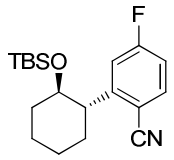
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 138.2, 137.3, 135.4, 134.7, 130.8, 128.9, 72.3, 48.2, 37.6, 29.8, 26.8, 25.5, 25.3, 22.3, 21.7, 20.6, 17.7, -4.6, -5.7.

MS (70 eV, EI) *m/z* (%): 332 (1) [M^+], 276 (22), 275 (100), 199 (7), 157 (7), 143 (3), 133 (35), 105 (3), 75 (78), 73 (13).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2950 (m), 2928 (m), 2856 (m), 1472 (w), 1248 (m), 1090 (s), 988 (m), 880 (m), 848 (s), 834 (vs), 802 (m), 772 (vs), 666 (m).

HRMS (EI) for **$C_{21}H_{36}O_1Si_1$** (332.2535): 332.2520.

2-(_trans_-2-((_tert_-Butyldimethylsilyl)oxy)cyclohexyl)-4-fluorobenzonitrile (36g)



colorless oil (65 %)

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.59 (dd, J_1=8.6 Hz, J_2=5.5 Hz, 1 H), 7.10 - 6.93 (m, 2 H), 3.70 - 3.54 (m, 1 H), 3.01 (t, J=10.2 Hz, 1 H), 2.07 - 1.96 (m, 1 H), 1.94 - 1.73 (m, 3 H), 1.62 - 1.28 (m, 4 H), 0.66 (s, 9 H), –0.08 (s, 3 H), –0.42 (s, 3 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 165.2 (d, J=255 Hz), 152.7 (d, J=8.4 Hz), 134.8 (d, J=9.5 Hz), 117.8, 114.6 (d, J=21.3 Hz), 114.1 (d, J=22.7 Hz), 110.0, 75.5, 52.1, 36.2, 32.2, 25.5, 25.4, 24.8, 17.6, –4.3, –5.7.

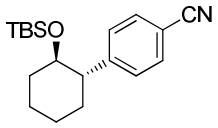
^{19}F-NMR (282 MHz, $CDCl_3$) δ: –102.6 - –102.7 (m) (minor), –103.9 - –104.2 (m) (major).

MS (70 eV, EI) *m/z* (%): 332 (1) $[M-H]^+$, 276 (100), 277 (21), 202 (20), 134 (5), 101 (5), 61 (2), 59 (10), 57 (8), 41 (8).

IR (ATR) $\tilde{\nu}$ **(cm^{-1}):** 2930 (m), 2858 (m), 2226 (w), 1608 (m), 1586 (m), 1492 (w), 1472 (w), 1464 (w), 1450 (w), 1362 (w), 1290 (w), 1274 (w), 1242 (m), 1228 (w), 1178 (w), 1160 (w), 1130 (w), 1096 (w), 1004 (m), 944 (m), 902 (w), 870 (s), 834 (vs), 818 (s), 796 (m), 774 (s), 690 (m), 668 (m).

HRMS (EI) for **$C_{19}H_{27}ONFSi$** (332.1852) $[M-H]^+$: 332.1844.

4-(*trans*-2-((*tert*-Butyldimethylsilyl)oxy)cyclohexyl)benzonitrile (36h)



slightly yellow oil (62 %)

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.56 (d, J=8.1 Hz, 2 H), 7.30 (d, J=8.3 Hz, 2 H), 3.54 (td, J_1=9.7 Hz, J_2=4.5 Hz, 1 H), 2.52 (ddd, J_1=12.5 Hz, J_2=9.7 Hz, J_3=3.2 Hz, 1 H), 2.09 - 1.94 (m, 1 H), 1.90 - 1.76 (m, 2 H), 1.68 - 1.12 (m, 5 H), 0.64 (s, 9 H), –0.15 (s, 3 H), –0.52 (s, 3 H).

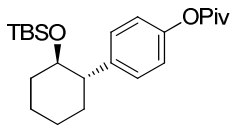
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 150.9, 131.7, 129.1, 119.2, 109.7, 75.5, 53.3, 36.5, 32.3, 25.7, 25.5, 25.0, 17.7, -4.5, –5.6.

MS (70 eV, EI) *m/z* (%): 316 (12) $[M+H^+]$, 310 (14), 267 (10), 258 (30), 238 (5), 199 (18), 177 (7), 176 (100), 171 (4), 75 (10),

IR (ATR) $\tilde{\nu}$ **(cm^{-1}):** 2928 (m), 2856 (m), 2228 (w), 1608 (w), 1472 (w), 1462 (w), 1250 (m), 1128 (w), 1090 (s), 982 (m), 882 (m), 848 (s), 830 (vs), 814 (m), 772 (s), 666 (m).

HRMS (EI) for **$C_{19}H_{30}ONSi$** (316.2096) $[M+H^+]$: 316.2080.

4-(*trans*-2-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)phenyl pivalate (36i)



colorless crystals (62 %)

m.p.: 74.4 – 75.6 °C.

^{1}H-NMR (600 MHz, $CDCl_3$) δ: 7.19 (d, J=8.5 Hz, 2 H), 6.95 (d, J=8.5 Hz, 2 H), 3.52 (td, J_1=9.8 Hz, J_2=4.2 Hz, 1 H), 2.46 (ddd, J_1=12.7 Hz, J_2=9.5 Hz, J_3=3.6 Hz, 1 H), 2.03 - 1.98 (m, 1 H), 1.88 - 1.78 (m, 2 H), 1.75 (d, J=12.6 Hz, 1 H), 1.58 - 1.52 (m, 1 H), 1.47 - 1.39 (m, 2 H), 1.39 - 1.34 (m, 9 H), 1.33 - 1.26 (m, 1 H), 0.71 (s, 9 H), –0.16 (s, 3 H), –0.46 (s, 3 H).

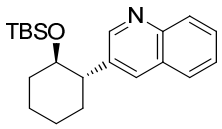
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 177.1, 149.4, 142.3, 129.0, 120.8, 75.9, 52.4, 39.0, 36.7, 32.8, 27.2, 26.0, 25.7, 25.2, 17.9, –4.8, –5.5.

MS (70 eV, EI) *m/z* (%): 390 (1) [M^+], 335 (25), 334 (100), 333 (48), 249 (31), 235 (9), 181 (8), 75 (15), 73 (10), 57 (66).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2928 (m), 2856 (w), 1754 (s), 1506 (w), 1250 (m), 1196 (m), 1164 (m), 1120 (vs), 1078 (s), 984 (m), 896 (m), 882 (m), 860 (m), 848 (s), 834 (s), 814 (m), 802 (m), 776 (vs), 668 (m).

HRMS (EI) for **$C_{23}H_{38}O_3Si$** (390.2590): 390.2543.

3-(*trans*-2-((*tert*-Butyldimethylsilyl)oxy)cyclohexyl)quinoline (36j)



slightly yellow oil (57 %)

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.81 (d, J=2.1 Hz, 1 H), 8.07 (d, J=8.3 Hz, 1 H), 7.91 (d, J=1.7 Hz, 1 H), 7.75 (d, J=8.1 Hz, 1 H), 7.64 (td, J_1=7.7 Hz, J_2=1.2 Hz, 1 H), 7.50 (t, J=7.4 Hz, 1 H), 3.64 (td, J_1=9.6 Hz, J_2=4.4 Hz, 1 H), 2.68 (ddd, J_1=12.6 Hz, J_2=9.6 Hz, J_3=3.5 Hz, 1 H), 2.09 - 2.01 (m, 1 H), 1.97 - 1.70 (m, 4 H), 1.52 - 1.32 (m, 3 H), 0.61 (s, 9 H), –0.19 (s, 3 H), –0.64 (s, 3 H).

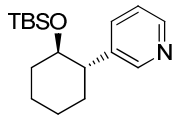
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 152.1, 147.1, 137.6, 133.9, 129.1, 128.4, 128.1, 127.3, 126.3, 75.9, 50.5, 36.6, 32.2, 25.9, 25.5, 25.1, 17.7, –4.6, –5.6.

MS (70 eV, EI) *m/z* (%): 341 (1) [M^+], 326 (4), 285 (21), 284 (100), 210 (41), 186 (4), 167 (4), 142 (14), 115 (4), 41 (19).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2928 (m), 2856 (m), 1250 (m), 1092 (s), 964 (m), 876 (s), 834 (vs), 816 (m), 772 (vs), 748 (s), 666 (m), 618 (m).

HRMS (EI) for **$C_{21}H_{31}ONSi$** (341.2175): 341.2188.

3-(*trans*-2-((*tert*-Butyldimethylsilyl)oxy)cyclohexyl)pyridine (36k)



yellow oil (80 %)

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.37 - 8.52 (m, 2 H), 7.50 (ddd, J_1=7.8 Hz, J_2=1.7 Hz, J_3=1.5 Hz, 1 H), 7.20 (dd, J_1=7.7 Hz, J_2=4.9 Hz, 1 H), 3.52 (td, J_1=9.7 Hz, J_2=4.6 Hz, 1 H), 2.47 (ddd, J_1=12.6 Hz, J_2=9.6 Hz, J_3=3.3 Hz, 1 H), 2.05 - 1.97 (m, 1 H), 1.90 - 1.74 (m, 3 H), 1.65 - 1.54 (m, 1 H), 1.44 - 1.28 (m, 3 H), 0.66 (s, 9 H), –0.16 (s, 3 H), –0.50 (s, 3 H).

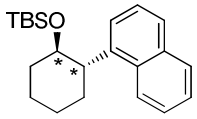
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 150.1, 147.4, 140.2, 135.4, 123.0, 75.7, 50.5, 36.5, 32.2, 25.8, 25.6, 25.1, 17.7, –4.5, –5.6.

MS (70 eV, EI) m/z (%): 290 (3) $[M\text{-}H]^+$, 276 (12), 236 (16), 234 (41), 161 (10), 160 (100), 130 (6), 92 (10), 75 (57), 73 (22), 59 (7), 41 (7).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2928 (m), 2856 (m), 1424 (m), 1250 (m), 1090 (s), 982 (m), 880 (s), 854 (s), 834 (vs), 824 (s), 812 (s), 772 (vs), 714 (s), 666 (m).

HRMS (EI) for **$C_{17}H_{28}ONSi$** (290.1945) $[M\text{-}H]^+$: 290.1960.

***tert*-Butyldimethyl(((1*R*,2*S*)-2-(naphthalen-1-yl)cyclohexyl)-oxy)silane (116a):**



colorless oil (87 %)

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.29 (d, J=8.0 Hz, 1 H), 7.86 - 7.80 (m, 1 H), 7.71 (dd, J_1=7.2 Hz, J_2=1.7 Hz, 1 H), 7.52 - 7.40 (m, 4 H), 3.81 - 3.71 (m, 1 H), 3.52 - 3.41 (m, 1 H), 2.14 - 2.06 (m, 1 H), 1.98 - 1.81 (m, 3 H), 1.63 - 1.30 (m, 4 H), 0.47 (s, 9 H), –0.25 (s, 3 H), –0.83 (s, 3 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 142.1, 133.8, 133.3, 128.3, 126.2, 125.3, 125.2, 125.0, 124.5, 123.1, 77.2, 45.9, 37.2, 33.2, 26.4, 25.4, 25.3, 17.5, –4.8, –5.9.

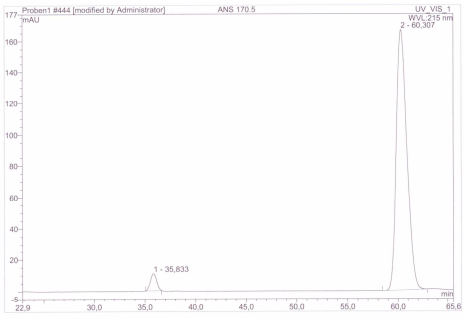
MS (70 eV, EI) m/z (%): 340 (1) $[M^+]$, 284 (20), 283 (100), 209 (3), 207 (4), 185 (3), 179 (3), 165 (4), 152 (2), 141 (12), 75 (23).

IR (ATR) $\tilde{\nu}$ **(cm^{-1}):** 2928 (m), 2856 (m), 1472 (w), 1248 (m), 1096 (s), 1084 (m), 972 (m), 880 (m), 862 (m), 832 (s), 814 (m), 792 (m), 772 (vs), 728 (w), 666 (m), 630 (w).

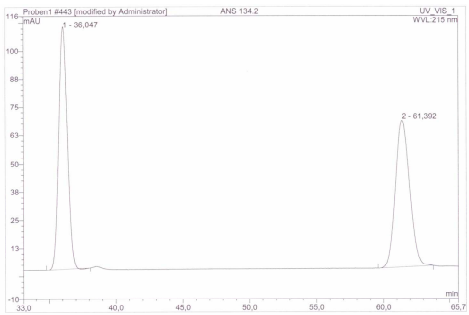
HRMS (EI) for **$C_{22}H_{32}OSi$** (340.2222): 340.2218.

HPLC Data:

Chiralcel OD-H; *n*-heptane : *i*-propanol 100:0; flow: 0.5 mL/min

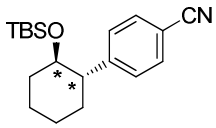


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	35,83	n.a.	10,666	7,595	3,57	n.a.	BMB*
2	60,31	n.a.	166,535	204,859	96,43	n.a.	BMB*
Total:			177,201	212,454	100,00	0,000	



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	36,05	n.a.	107,601	81,161	50,09	n.a.	BMB*
2	61,39	n.a.	64,736	80,876	49,91	n.a.	BMB*
Total:			172,338	162,037	100,00	0,000	

4-((1*S*,2*R*)-2-((*tert*-Butyldimethylsilyl)oxy)cyclohexyl)-benzonitrile (116b):



colorless oil (64 %)

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.56 (d, *J*=8.3 Hz, 2 H), 7.31 (d, *J*=8.3 Hz, 2 H), 3.54 (td, J_1=9.7 Hz, J_2=4.6 Hz, 1 H), 2.58 - 2.48 (m, 1 H), 2.06 - 1.97 (m, 1 H), 1.89 - 1.73 (m, 3 H), 1.63 - 1.55 (m, 1 H), 1.44 - 1.28 (m, 3 H), 0.69 - 0.61 (m, 9 H), –0.15 (s, 3 H), –0.52 (s, 3 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 150.9, 131.8, 129.1, 119.3, 109.8, 75.6, 53.3, 36.5, 32.3, 25.7, 25.5, 25.0, 17.8, –4.4, –5.6.

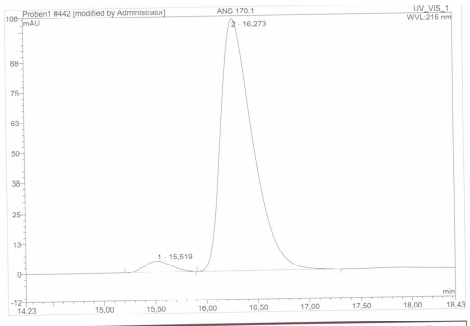
MS (70 eV, EI) m/z (%): 314 (1) $[M-H]^+$, 260 (5), 259 (20), 258 (100), 142 (1), 116 (5), 77 (1), 75 (31), 59 (2), 57 (2).

IR (ATR) $\tilde{\nu}$ **(cm^{-1}):** 2928 (m), 2856 (m), 2228 (w), 1608 (w), 1472 (w), 1250 (m), 1128 (w), 1090 (s), 982 (m), 882 (m), 848 (s), 830 (vs), 814 (m), 772 (s), 666 (m).

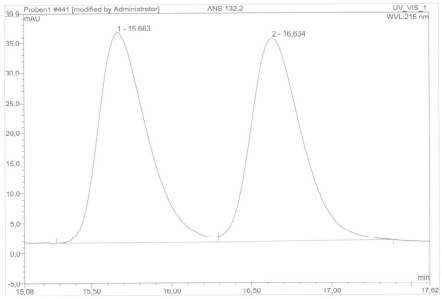
HRMS (EI) for **$C_{19}H_{28}ONSi$** (314.1945) $[M-H]^+$: 314.1946.

HPLC Data:

Chiralcel OD-H; *n*-heptane : *i*-propanol 100:0; flow: 0.5 mL/min

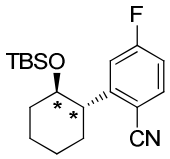


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	15,52	n.a.	4,456	1,376	3,54	n.a.	BMB*
2	16,27	n.a.	103,949	37,487	96,46	n.a.	BMB*
Total:			108,405	38,863	100,00	0,000	



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	15,66	n.a.	34,892	12,219	49,76	n.a.	BM *
2	16,63	n.a.	33,827	12,338	50,24	n.a.	MB*
Total:			68,720	24,556	100,00	0,000	

2-((1*S*,2*R*)-2-((*tert*-Butyldimethylsilyl)oxy)cyclohexyl)-4-fluorobenzonitrile (116c):



white solid (69 %)

m.p.: 57.0 – 58.1 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.60 (dd, J_1=8.4 Hz, J_2=5.7 Hz, 1 H), 7.08 – 6.94 (m, 2 H), 3.63 (d, *J*=9.1 Hz, 1 H), 3.01 (t, *J*=9.9 Hz, 1 H), 2.02 (d, *J*=11.3 Hz, 1 H), 1.92 - 1.83 (m, 2 H), 1.78 (d, *J*=5.5 Hz, 1 H), 1.59 - 1.35 (m, 4 H), 0.66 (s, 9 H), –0.07 (s, 3 H), –0.42 (s, 3 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 165.2 (d, *J*=255.1 Hz), 152.7 (d, *J*=8.3 Hz), 134.8 (d, *J*=9.7 Hz), 117.8, 114.6 (d, *J*=22.2 Hz), 114.1 (d, *J*=22.8 Hz), 110.0, 75.5, 52.1 (d, *J*=1.4 Hz), 36.3, 32.2, 25.5, 25.4, 24.9, 17.6, –4.2, –5.7.

^{19}F-NMR (282 MHz, $CDCl_3$) δ: -104.0 - -104.1 (m).

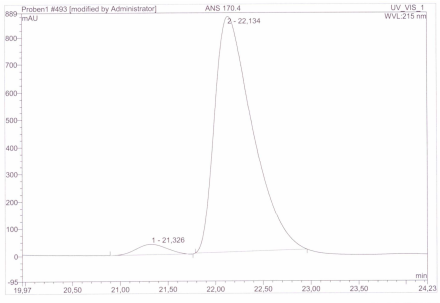
MS (70 eV, EI) m/z (%): 318 (3) $[M\text{-}CH_3]^+$, 283 (10), 278 (7), 277 (27), 276 (100), 202 (34), 175 (9), 75 (60), 73 (14), 57 (13), 41 (8).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2928 (m), 2856 (m), 2226 (w), 1608 (m), 1584 (w), 1490 (m), 1472 (w), 1274 (w), 1244 (m), 1088 (s), 1004 (m), 944 (m), 872 (s), 836 (vs), 814 (s), 794 (m), 772 (vs), 688 (m), 668 (m).

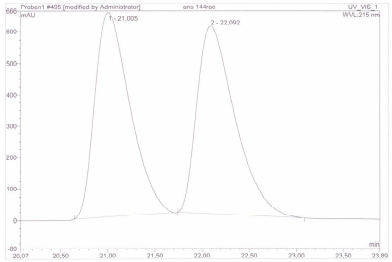
HRMS (EI) for **$C_{18}H_{25}ONFSi$** (318.1689) $[M\text{-}CH_3]^+$: 318.1679.

HPLC Data:

Chiralcel OD-H; *n*-heptane : *i*-propanol 100:0; flow: 0.3 mL/min

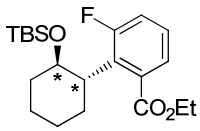


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	21,33	n.a.	37,767	13,778	3,35	n.a.	BMB*
2	22,13	n.a.	861,361	397,270	96,65	n.a.	BMB*
Total:			899,128	411,048	100,00	0,000	



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	21,00	n.a.	650,925	279,975	49,99	n.a.	BMB*
2	22,09	n.a.	597,685	280,115	50,01	n.a.	BMB*
Total:			1248,610	560,090	100,00	0,000	

Ethyl 2-((1*S*,2*R*)-2-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)-3-fluorobenzoate (116d):



colorless oil (73 %)

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.39 (d, *J*=7.7 Hz, 1 H), 7.22 - 7.05 (m, 2 H), 4.36 (qd, J_1=7.1 Hz, J_2=2.6 Hz, 2 H), 4.03 - 4.12 (m, 1 H), 3.21 - 3.31 (m, 1 H), 1.86 - 2.01 (m, 3 H), 1.70 - 1.82 (m, 2 H), 1.27 - 1.42 (m, 6 H), 0.61 (s, 9 H), –0.10 (s, 3 H), –0.42 (s, 3 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 168.2 (d, *J*=3.6 Hz), 162.0 (d, *J*=246.4 Hz), 135.6 (d, *J*=6.9 Hz), 131.7 (d, *J*=14.2 Hz), 126.8 (d, *J*=9.3 Hz), 124.9 (d, *J*=3.0 Hz), 118.5 (d, *J*=24.0 Hz), 72.4 (d, *J*=5.1 Hz), 61.1, 47.5, 37.0, 29.8 (d, *J*=4.1 Hz), 26.0, 25.5, 25.0, 17.6, 14.3, –4.3, –5.8.

^{19}F-NMR (282 MHz, $CDCl_3$) δ: –112.1 (d, *J*=9.5 Hz).

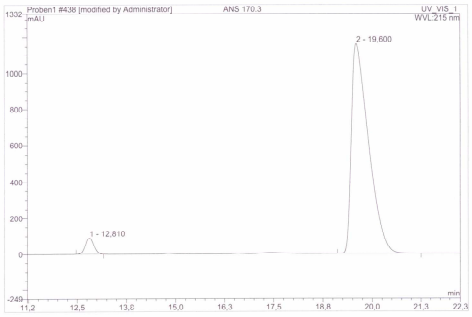
MS (70 eV, EI) m/z (%): 379 (1) $[M-H]^+$, 335 (8), 325 (8), 324 (28), 323 (100), 277 (91), 203 (13), 185 (23), 147 (7), 75 (22), 73 (16).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2930 (m), 2856 (m), 1724 (s), 1450 (m), 1286 (m), 1258 (vs), 1228 (m), 1178 (m), 1144 (m), 1112 (s), 1092 (vs), 1026 (m), 988 (m), 940 (m), 882 (s), 854 (s), 832 (vs), 810 (m), 772 (vs), 754 (vs), 666 (m).

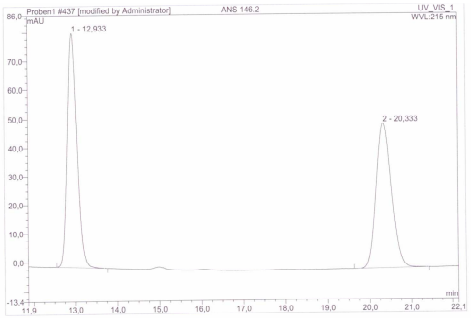
HRMS (EI) for **$C_{21}H_{32}O_3FSi$** (379.2110) $[M-H]^+$: 379.2080.

HPLC Data:

Chiralcel OD-H; *n*-heptane : *i*-propanol 100:0; flow: 0.5 mL/min

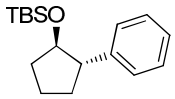


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	12,81	n.a.	89,082	22,253	3,66	n.a.	BMB*
2	19,60	n.a.	1162,045	585,112	96,34	n.a.	BMB
Total:			1251,127	607,365	100,00	0,000	



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	12,93	n.a.	81,499	21,645	50,12	n.a.	BMB*
2	20,33	n.a.	50,599	21,542	49,88	n.a.	BMB*
Total:			132,098	43,187	100,00	0,000	

***tert*-Butyldimethyl((*trans*-2-phenylcyclopentyl)oxy)silane (118a):**



colorless oil (56 %)

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.30 - 7.15 (m, 5 H), 4.02 (q, *J*=7.0 Hz, 1 H), 2.91 - 2.84 (m, 1 H), 2.12 – 1.95 (m, 2 H), 1.88 - 1.61 (m, 4 H), 0.78 (s, 9 H), –0.19 (s, 3 H), –0.24 (s, 3 H).

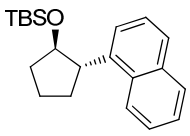
^{13}C-NMR (101 MHz, $CDCl_3$) δ: 144.0, 128.1, 127.7, 126.0, 81.6, 54.4, 34.8, 30.9, 25.8, 21.9, 18.0, –5.0, –5.1.

MS (70 eV, EI) m/z (%): 261 (2) $[M\text{-}CH_3]^+$, 221 (5), 220 (21), 219 (100), 143 (15), 115 (6), 91 (9), 75 (66), 73 (10).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2956 (m), 2928 (m), 2856 (w), 1472 (w), 1250 (m), 1114 (s), 1088 (m), 1070 (m), 1006 (w), 888 (m), 860 (m), 834 (vs), 774 (vs), 754 (s), 698 (vs), 668 (m).

HRMS (EI) for **$C_{16}H_{25}OSi$** (261.1675) $[M\text{-}CH_3]^+$: 261.1681.

***tert*-Butyldimethyl((*trans*-2-(naphthalen-1-yl)cyclopentyl)oxy)silane (118b):**



colorless oil (80 %)

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.30 (d, *J*=8.2 Hz, 1 H), 7.91 - 7.84 (m, 1 H), 7.74 (d, *J*=8.1 Hz, 1 H), 7.57 - 7.38 (m, 4 H), 4.34 (q, *J*=6.1 Hz, 1 H), 3.91 - 3.84 (m, 1 H), 2.37 - 2.29 (m, 1 H), 2.13 - 1.87 (m, 4 H), 1.84 - 1.76 (m, 1 H), 0.80 (s, 9 H), –0.17 (s, 3 H), –0.28 (s, 3 H).

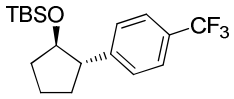
^{13}C-NMR (101 MHz, $CDCl_3$) δ: 140.6, 133.8, 132.7, 128.5, 126.4, 125.4, 125.4, 125.3, 124.4, 122.7, 81.3, 49.0, 35.1, 31.3, 25.7, 22.5, 17.9, –5.0, –5.1.

MS (70 eV, EI) m/z (%): 326 (1) [M^+], 270 (22), 269 (100), 195 (8), 193 (18), 191 (9), 165 (12), 141 (16), 115 (4), 75 (66), 73 (11), 57 (3).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2954 (w), 2928 (w), 2856 (w), 1472 (w), 1250 (m), 1114 (m), 1094 (m), 1078 (m), 1062 (m), 1032 (w), 1006 (w), 890 (m), 864 (m), 834 (s), 810 (m), 794 (m), 772 (vs), 730 (w), 668 (m).

HRMS (EI) for **$C_{21}H_{30}OSi$** (326.2066): 326.2053.

***tert*-Butyldimethyl((*trans*-2-(4-(trifluoromethyl)phenyl)cyclopentyl)oxy)silane (118c):**



slightly yellow oil (65 %)

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.55 (d, *J*=8.0 Hz, 2 H), 7.35 (d, *J*=8.0 Hz, 2 H), 4.03 (q, *J*=7.0 Hz, 1 H), 2.96 (q, *J*=7.8 Hz, 1 H), 2.16 - 1.99 (m, 2 H), 1.94 - 1.62 (m, 4 H), 0.79 (s, 9 H), –0.15 (s, 3 H), –0.23 (s, 3 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 148.3 (d, *J*=1.1 Hz), 128.4 (q, *J*= 32.0 Hz), 127.9, 125.0 (q, *J*= 3.9 Hz), 124.4 (q, *J*= 272.1 Hz), 81.4, 54.2, 34.8, 30.8, 25.7, 21.8, 18.0, –4.9, –5.1.

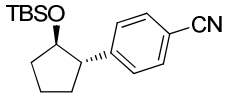
^{19}F-NMR (282 MHz, $CDCl_3$) δ: –62.3 (s).

MS (70 eV, EI) m/z (%): 344 (1) [M^+], 329 (2), 288 (33), 287 (94), 194 (11), 193 (100), 159 (8), 153 (4), 127 (7), 75 (46), 73 (13).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2956 (w), 2930 (w), 2858 (w), 1620 (w), 1472 (w), 1324 (vs), 1252 (m), 1164 (m), 1122 (vs), 1084 (m), 1068 (s), 1018 (m), 1006 (w), 890 (m), 860 (m), 832 (vs), 774 (s), 668 (m), 604 (m).

HRMS (EI) for **$C_{18}H_{27}OF_3Si$** (344.1783): 344.2131.

4-(*trans*-2-((*tert*-Butyldimethylsilyl)oxy)cyclopentyl)benzonitrile (118d):



slightly yellow oil (75 %)

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.58 (d, *J*=8.3 Hz, 2 H), 7.33 (d, *J*=8.0 Hz, 2 H), 4.00 (q, *J*=7.3 Hz, 1 H), 3.00 - 2.87 (m, 1 H), 2.16 – 1.95 (m, 2 H), 1.93 - 1.61 (m, 4 H), 0.78 (s, 9 H), –0.16 (s, 3 H), –0.25 (s, 3 H).

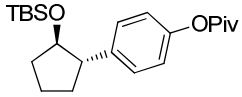
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 149.8, 131.9, 128.4, 119.1, 109.8, 81.4, 54.5, 34.7, 30.5, 25.6, 21.7 17.9, –4.9, –5.2.

MS (70 eV, EI) m/z (%): 300 (1) $[M\text{-}H]^+$, 245 (18), 244 (100), 168 (2), 142 (2), 116 (6), 101 (1), 75 (38), 73 (10),59 (3), 57 (2), 41 (3).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2956 (m), 2930 (w), 2856 (w), 2228 (w), 1608 (w), 1472 (w), 1250 (m), 1114 (m), 1084 (m), 1006 (w), 890 (m), 860 (m), 832 (vs), 774 (vs), 668 (m).

HRMS (EI) for **$C_{18}H_{26}ONSi$** (300.1789) $[M\text{-}H]^+$: 300.1763.

4-(*trans*-2-((*tert*-Butyldimethylsilyl)oxy)cyclopentyl)phenyl pivalate (118e):



colorless oil (60 %)

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.23 (d, *J*=8.4 Hz, 2 H), 6.98 (d, *J*=8.6 Hz, 2 H), 4.02 (q, *J*=6.9 Hz, 1 H), 2.94 - 2.85 (m, 1 H), 2.14 - 1.97 (m, 2 H), 1.88 - 1.65 (m, 4 H), 1.37 (s, 9 H), 0.81 (s, 9 H), –0.15 (s, 3 H), –0.19 (s, 3 H).

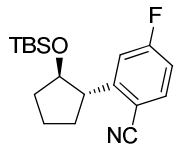
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 177.1, 149.4, 141.3, 128.4, 121.0, 81.5, 53.8, 39.0, 34.7, 30.9, 27.2, 25.8, 21.8, 18.0, –4.9, –5.0.

MS (70 eV, EI) m/z (%): 376 (1) $[M^+]$, 320 (20), 319 (100), 235 (17), 217 (5), 161 (6), 85 (5), 75 (39), 73 (24), 57 (78), 41 (6).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2956 (w), 2930 (w), 1754 (m), 1508 (m), 1472 (w), 1250 (m), 1200 (m), 1166 (m), 1112 (vs), 1028 (w), 1018 (w), 890 (m), 862 (m), 834 (s), 814 (m), 774 (s), 668 (w).

HRMS (EI) for **$C_{22}H_{36}O_3Si$** (376.2434): 376.2389.

2-(*trans*-2-((*tert*-Butyldimethylsilyl)oxy)cyclopentyl)-4-fluorobenzonitrile (118f):



colorless oil (68 %)

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.62 (dd, J_1=8.5 Hz, J_2=5.6 Hz, 1 H), 7.08 - 6.95 (m, 2 H), 4.14 (q, *J*=7.3 Hz, 1 H), 3.42 - 3.31 (m, 1 H), 2.28 - 2.16 (m, 1 H), 2.08 - 1.66 (m, 5 H), 0.78 (s, 9 H), –0.11 (s, 3 H), –0.23 (s, 3 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 165.2 (d, *J*=255.0 Hz), 152.9 (d, *J*=8.3 Hz), 135.1 (d, *J*=9.6 Hz), 117.7, 114.6 (d, J=19.4 Hz), 114.3 (d, *J*=19.6 Hz), 109.3 (d, *J*=3.1 Hz), 81.2, 52.8 (d, *J*=1.4 Hz), 34.7, 30.9, 25.6, 21.7, 17.8, –4.9, –5.2.

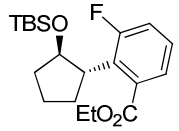
^{19}F-NMR (282 MHz, $CDCl_3$) δ: –103.4 - –103.6 (m).

MS (70 eV, EI) m/z (%): 319 (1) [M^+], 286 (3), 263 (18), 262 (100), 188 (12), 186 (2), 171 (1), 134 (2), 101 (1), 75 (22), 73 (8), 57 (2).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2956 (m), 2930 (w), 2884 (w), 2858 (w), 2226 (w), 1608 (m), 1582 (m), 1490 (m), 1472 (m), 1464 (w), 1362 (w), 1250 (m), 1234 (m), 1186 (w), 1156 (w), 1118 (s), 1096 (m), 1060 (w), 1006 (w), 984 (w), 940 (w), 870 (s), 834 (vs), 774 (vs), 690 (m), 668 (m).

HRMS (EI) for **$C_{18}H_{26}ONFSi$** (319.1768): 319.1676.

Ethyl 2-(*trans*-2-((*tert*-butyldimethylsilyl)oxy)cyclopentyl)-3-fluorobenzoate (118g):



colorless oil (69 %)

^{1}H-NMR (600 MHz, $CDCl_3$) δ: 7.43 (d, *J*=7.1 Hz, 1 H), 7.20 (td, J_1=8.0 Hz, J_2=5.2 Hz, 1 H), 7.15 - 7.10 (m, 1 H), 4.49 - 4.44 (m, 1 H), 4.41 - 4.30 (m, 2 H), 3.61 - 3.54 (m, 1 H), 2.19 - 2.10 (m, 1 H), 2.04 (dq, J_1=12.8 Hz, J_2=6.5 Hz, 1 H), 1.92 - 1.79 (m, 3 H), 1.67 - 1.61 (m, 1 H), 1.38 (t, *J*=7.1 Hz, 3 H), 0.74 (s, 9 H), –0.20 (s, 3 H), –0.31 (s, 3 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 167.9 (d, *J*=4.0 Hz), 162.0 (d, *J*=246.5 Hz), 135.2 (d, *J*=6.0 Hz), 131.6 (d, *J*=14.0 Hz), 127.0 (d, *J*=9.4Hz), 124.9 (d, *J*=3.1 Hz), 118.5 (d, *J*=23.3 Hz), 79.0 (d, *J*=4.8 Hz), 61.2, 48.5 (d, *J*=2.0 Hz), 36.0, 30.3 (d, *J*=4.0 Hz), 25.7, 22.9, 17.9, 14.2, –5.2, –5.3.

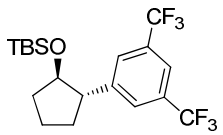
^{19}F-NMR (282 MHz, $CDCl_3$) δ: –112.0 (d, J=9.5 Hz).

MS (70 eV, EI) m/z (%): 365 (1) $[M-H]^+$, 310 (11), 309 (49), 264 (18), 263 (100), 235 (9), 221 (6), 189 (21), 171 (23), 159 (5), 133 (5), 75 (11), 73 (9).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2956 (m), 2930 (m), 2856 (w), 1724 (s), 1472 (w), 1454 (m), 1284 (s), 1250 (s), 1182 (m), 1128 (s), 1112 (s), 1084 (m), 1062 (m), 1026 (m), 1006 (m), 936 (m), 892 (m), 866 (m), 834 (vs), 814 (m), 774 (vs), 758 (vs), 668 (m).

HRMS (EI) for **$C_{20}H_{30}O_3FSi$** (365.1953) $[M-H]^+$: 365.1941.

((*trans*-2-(3,5-Bis(trifluoromethyl)phenyl)cyclopentyl)oxy)(*tert*-butyl)dimethylsilane (118h):



colorless oil (68 %)

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.76 - 7.67 (m, 3 H), 3.99 (q, *J*=7.6 Hz, 1 H), 3.07 - 2.96 (m, 1 H), 2.18 - 2.03 (m, 2 H), 1.94 - 1.78 (m, 3 H), 1.77 - 1.66 (m, 1 H), 0.78 (s, 9 H), –0.13 (s, 3 H), –0.26 (s, 3 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 146.4, 131.4 (q, *J*=32.8 Hz), 127.8, 123.5 (q, *J*=272.6 Hz), 120.1 (sept, *J*=3.9 Hz), 81.2, 53.8, 34.5, 29.8, 25.6, 21.3, 17.8, –4.8, –5.4.

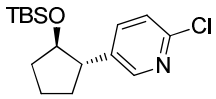
^{19}F-NMR (282 MHz, $CDCl_3$) δ: –62.9 (s).

MS (70 eV, EI) m/z (%): 397 (3) $[M-CH_3]^+$, 356 (17), 355 (100), 261 (7), 259 (5), 235 (7), 209 (3), 133 (4), 77 (6), 75 (11), 73 (11), 57 (5).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2958 (w), 2932 (w), 1384 (m), 1276 (s), 1260 (m), 1170 (s), 1130 (vs), 890 (m), 866 (m), 836 (s), 774 (s), 706 (w), 682 (m), 670 (w).

HRMS (EI) for **$C_{18}H_{23}OF_6Si$** (397.1422) $[M-CH_3]^+$: 397.1422.

5-(*trans*-2-((*tert*-Butyldimethylsilyl)oxy)cyclopentyl)-2-chloropyridine (118i):



slightly yellow oil (48 %)

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.26 (d, *J*=2.4 Hz, 1 H), 7.52 (dd, J_1=8.2 Hz, J_2=2.5 Hz, 1 H), 7.25 (d, *J*=8.2 Hz, 1 H), 3.96 (q, *J*=7.1 Hz, 1 H), 2.93 - 2.82 (m, 1 H), 2.19 - 1.97 (m, 3 H), 1.83 - 1.66 (m, 3 H), 0.79 (s, 9 H), –0.12 (s, 3 H), –0.21 (s, 3 H).

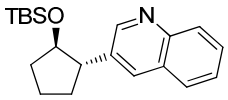
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 149.2, 149.2, 138.1, 137.6, 123.7, 81.1, 52.0, 34.5, 30.1, 25.7, 21.5, 17.9, –4.8, –5.0.

MS (70 eV, EI) m/z (%): 296 (3) $[M\text{-}CH_3]^+$, 256 (39), 254 (97), 180 (11), 144 (15), 117 (7), 86 (36), 84 (54), 75 (100), 59 (15), 57 (10), 47 (13), 42 (12).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2954 (m), 2930 (m), 2856 (w), 1470 (m), 1456 (m), 1250 (m), 1106 (s), 1086 (m), 1024 (m), 1006 (w), 890 (m), 860 (m), 832 (vs), 774 (vs), 742 (m), 668 (m).

HRMS (EI) for **$C_{15}H_{23}ONClSi$** (296.1237) $[M\text{-}CH_3]^+$: 296.1234.

3-(*trans*-2-((*tert*-Butyldimethylsilyl)oxy)cyclopentyl)quinoline (118j):



slightly yellow oil (60 %)

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.85 (d, *J*=2.2 Hz, 1 H), 8.09 (d, *J*=8.3 Hz, 1 H), 7.95 (d, *J*=1.8 Hz, 1 H), 7.77 (d, *J*=8.1 Hz, 1 H), 7.65 (td, J_1=7.7 Hz, J_2=1.2 Hz, 1 H), 7.52 (t, *J*=7.2 Hz, 1 H), 4.14 (q, *J*=7.1 Hz, 1 H), 3.16 - 3.05 (m, 1 H), 2.23 - 2.14 (m, 1 H), 2.10 - 2.01 (m, 1 H), 1.96 - 1.68 (m, 4 H), 0.79 (s, 9 H), –0.15 (s, 3 H), –0.25 (s, 3 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 152.5, 147.1, 136.5, 133.2, 129.1, 128.5, 128.1, 127.3, 126.4, 81.1, 52.9, 34.7, 30.3, 25.7, 21.8, 17.9, –4.8, –5.0.

MS (70 eV, EI) m/z (%): 327 (1) $[M^+]$, 312 (3), 271 (18), 270 (100), 196 (62), 194 (6), 167 (6), 142 (7), 115 (3), 75 (25), 73 (12).

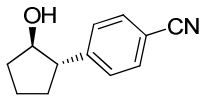
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2954 (m), 2928 (m), 2856 (w), 1494 (w), 1472 (w), 1250 (m), 1112 (s), 1084 (m), 1006 (w), 896 (m), 870 (s), 834 (vs), 814 (m), 774 (vs), 748 (vs), 668 (m), 618 (w).

HRMS (EI) for **$C_{20}H_{29}ONSi$** (327.2018): 327.2006.

6.4 TBS-deprotection for X-ray analysis

A dry and 4-(*trans*-2-((*tert*-butyldimethylsilyl)oxy)cyclopentyl)- benzonitrile (**118d**; 1.66 mmol; 0.50 g) was dissolved in THF (4 ml) and $Bu_4NF \cdot 3\,H_2O$ (4.98 mmol; 1.57 g) was added. The reaction mixture was stirred at room temperature overnight. NH_4Cl sat. aq. solution (20 ml) and Et_2O (20 ml) were added, the phases were separated and the aqueous phase was extracted with Et_2O (3 x 20 mL). The combined organic layers were dried over Na_2SO_4. The solvents were evaporated and the residue was subjected to column chromatography (SiO_2; *n*-pentane/Et_2O 1:1) yielding 0.29 g (93%) of the title compound as a white solid.

4-(*trans*-2-Hydroxycyclopentyl)benzonitrile



m.p.: 72.7 – 73.9 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.60 (d, *J*=8.25 Hz, 2 H), 7.38 (d, *J*=8.25 Hz, 2 H), 4.18 (q, *J*=7.03 Hz, 1 H), 3.06 – 2.82 (m, 1 H), 2.34 - 2.00 (m, 2 H), 1.97 - 1.63 (m, 4 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 149.3, 132.3, 128.2, 118.9, 110.1, 80.2, 54.2, 34.5, 31.7, 21.8.

MS (70 eV, EI) *m/z* (%): 187 (66) [M^+], 169 (65), 168 (44), 154 (100), 143 (46), 131 (34), 129 (47), 116 (54), 105 (15), 89 (16), 57 (25).

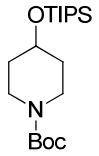
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3462 (m), 2956 (m), 2870 (w), 2234 (m), 1606 (m), 1504 (w), 1328 (m), 1300 (m), 1176 (w), 1090 (s), 1072 (m), 834 (vs).

HRMS (EI) for **$C_{12}H_{13}ON$** (187.0997): 187.0991.

7. Diastereoselective Pd-Catalyzed Cross-Coupling Reactions of Piperidinylzinc Reagents

7.1 Preparation of starting materials

tert-Butyl 4-((triisopropylsilyl)oxy)piperidine-1-carboxylate



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_2O (4 x 300 mL). The combined organic layers were washed with brine (300 mL) and dried over Na_2SO_4. The solvents were evaporated and the residue was subjected to column chromatography (SiO_2; *n*-pentane/Et_2O 15:1) yielding 34.1 g (95%) of the title compound.

^{1}H-NMR (400 MHz, C_6D_6) δ: 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).

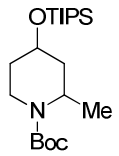
^{13}C-NMR (101 MHz, C_6D_6) δ: 155.1, 79.2, 67.9, 35.1, 28.9, 18.6, 18.4, 13.2, 12.9, 12.6.

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 **$C_{19}H_{39}NO_3SiNa^+$** (380.2591) [M+Na$^+$]: 380.2592.

***tert*-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_2O (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 $MgCl_2$ (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. NH_4Cl sat. aq. solution (100 mL) was added, the phases were separated and the aqueous phase was extracted with Et_2O (4 x 30 mL). The combined organic layers were washed with brine (50 mL) and dried over Na_2SO_4. The solvents were evaporated and the residue was subjected to column chromatography (SiO_2; *i*-hexane/Et_2O 10:1) yielding 4.87 g (77%) of the title compound as a colorless oil.

^{1}H-NMR (400 MHz, C_6D_6) 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).

^{13}C-NMR (75 MHz, C_6D_6) 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).

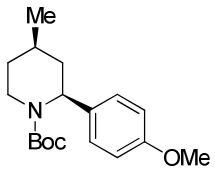
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2942 (m), 2892 (w), 2866 (m), 1694 (s), 1464 (m), 1412 (m), 1390 (m), 1378 (m), 1364 (m), 1342 (m), 1290 (w), 1272 (w), 1250 (w), 1212 (w), 1174 (s), 1134 (m), 1112 (m), 1090 (s), 1072 (s), 1054 (vs), 1028 (m), 1004 (m), 934 (w), 918 (w), 882 (s), 864 (m), 800 (w), 768 (w), 674 (s), 656 (s).

HRMS (ESI) for $C_{20}H_{42}NO_3Si^+$ (372.2934) [M+H^+]: 372.2927.

7.2 Cross-coupling of (1-(*tert*-butoxycarbonyl)-4-methylpiperidin-2-yl)zinc chloride (119a)

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 (**120a**; 1 mmol; 0.20 g) and TMEDA (1 mmol; 0.12 g; 0.45 mL) in anhydrous Et_2O (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 warmed to room temperature. Et_2O 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 SPhos (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. NH_4Cl sat. aq. solution (20 mL) was added, the phases were separated and the aqueous phase was extracted with Et_2O (4 x 10 mL). The combined organic layers were washed with brine (10 mL) and dried over Na_2SO_4. The solvents were evaporated and the residue was subjected to column chromatography yielding the respective title compound.

***cis-tert*-Butyl 2-(4-methoxyphenyl)-4-methylpiperidine-1-carboxylate (121a)**



colorless oil (78 %)

^{1}H-NMR (400 MHz, C_6D_6) δ: 7.10 (d, J=8.4 Hz, 2 H), 6.81 (d, J=8.6 Hz, 2 H), 4.91 (dd, J_1=9.4 Hz, J_2=6.4 Hz, 1 H), 4.11 (ddd, J_1=13.6 Hz, J_2=7.0 Hz, J_3=2.9 Hz, 1 H), 3.33 (s, 3 H), 3.14 (ddd, J_1=13.7 Hz, J_2=10.7 Hz, J_3=5.6 Hz, 1 H), 1.83 - 1.73 (m, 1 H), 1.66 (ddd, J_1=13.3 Hz, J_2=6.2 Hz, J_3=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).

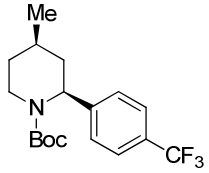
^{13}C-NMR (101 MHz, C_6D_6) δ: 159.1, 156.1, 137.5, 127.2, 114.3, 79.2, 56.7, 55.1, 38.8, 38.6, 31.7, 28.8, 27.0, 21.8.

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) $\tilde{\nu}$ **(cm^{-1}):** 2952 (w), 2929 (w), 1686 (vs), 1612(w), 1522 (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).

HRMS (EI) for **$C_{18}H_{27}NO_3$** (305.1991): 305.1977.

***cis-tert*-Butyl 4-methyl-2-(4-(trifluoromethyl)phenyl)piperidine-1-carboxylate (121b)**



colorless oil (81 %)

^{1}H-NMR (400 MHz, C_6D_6) δ: 7.39 (d, *J*=8.0 Hz, 2 H), 7.00 (d, *J*=8.2 Hz, 2 H), 4.68 (dd, J_1=9.8 Hz, J_2=6.3 Hz, 1 H), 3.90 (ddd, J_1=13.7, J_2=6.6 Hz, J_3=3.9 Hz, 1 H), 3.08 (ddd, J_1=13.9 Hz, J_2=10.0 Hz, J_3=5.5 Hz, 1 H), 1.69 (dddd, J_1=13.3 Hz, J_2=10.0 Hz, J_3=6.9 Hz, J_4=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, J_1=13.5 Hz, J_2=10.4 Hz, 1 H), 0.88 - 0.80 (m, 1 H), 0.62 (d, *J*=6.8 Hz, 3 H).

^{13}C-NMR (101 MHz, C_6D_6) 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.

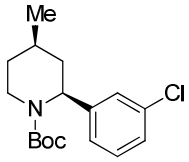
^{19}F-NMR (376 MHz, C_6D_6) δ: –61.98 (s).

MS (70 eV, EI) *m/z* (%): 343 (1) [M^+], 288 (19), 287 (73), 270 (16), 268 (11), 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) $\tilde{\nu}$ **(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 **$C_{18}H_{24}F_3NO_2$** (343.1759): 343.1756.

***cis-tert*-Butyl 2-(3-chlorophenyl)-4-methylpiperidine-1-carboxylate (121c)**



colorless crystals (76 %)

m.p.: 47.3 – 49.2 °C.

^{1}H-NMR (400 MHz, C_6D_6) δ: 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).

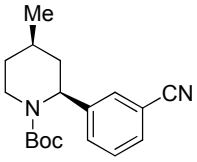
^{13}C-NMR (101 MHz, C_6D_6) δ: 155.9, 148.2, 134.9, 130.2, 127.0, 126.5, 124.1, 79.6, 57.3, 39.4, 38.7, 31.6, 28.7, 27.1, 21.8.

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-tert*-Butyl 2-(3-cyanophenyl)-4-methylpiperidine-1-carboxylate (121d)**



colorless crystals (64 %)

m.p.: 77.8 – 79.3 °C.

^{1}H-NMR (400 MHz, C_6D_6) δ: 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).

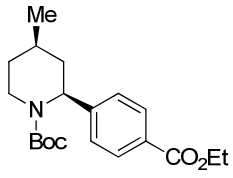
^{13}C-NMR (101 MHz, C_6D_6) δ: 155.1, 146.4, 129.6, 129.1, 128.9, 128.6, 118.6, 112.6, 79.0, 56.5, 39.0, 37.9, 30.8, 27.8, 26.5, 21.1.

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 **$C_{18}H_{24}N_2O_2$** (300.1838): 300.1860.

cis-tert-Butyl 2-(4-(ethoxycarbonyl)phenyl)-4-methylpiperidine-1-carboxylate (121e)



white solid (67 %)

m.p.: 108.8 – 110.3 °C.

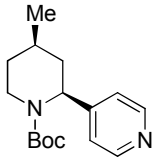
^{1}H-NMR (400 MHz, C_6D_6) δ: 8.20 (d, J=8.4 Hz, 2 H), 7.12 (d, J=8.4 Hz, 2 H), 4.74 (dd, J_1=9.7 Hz, J_2=6.2 Hz, 1 H), 4.15 (q, J=7.1 Hz, 2 H), 3.96 (ddd, J_1=13.7 Hz, J_2=6.6 Hz, J_3=3.7 Hz, 1 H), 3.12 (ddd, J_1=13.7, J_2=10.2 Hz, J_3=5.4 Hz, 1 H), 1.70 (dddd, J_1=13.3 Hz, J_2=10.2 Hz, J_3=7.1 Hz, J_4=6.8 Hz, 1 H), 1.54 (ddd, 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, C_6D_6) δ: 166.5, 156.0, 152.1, 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), 1715 (s), 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 **$C_{20}H_{29}NO_4$** (347.2097): 347.2099.

***cis-tert*-Butyl 4-methyl-2-(pyridin-4-yl)piperidine-1-carboxylate (121f)**



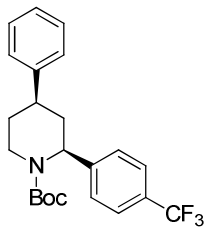
slightly yellow oil (73 %)
^{1}H-NMR (300 MHz, C_6D_6) δ: 8.56 (dd, J_1=4.6 Hz, J_2=1.4 Hz, 2 H), 6.79 (d, J=5.6 Hz, 2 H), 4.62 (dd, J_1=9.3 Hz, J_2=6.4 Hz, 1 H), 3.89 (ddd, J_1=13.6 Hz, J_2=6.6 Hz, J_3=3.8 Hz, 1 H), 3.03 (ddd, J_1=13.8 Hz, J_2=10.0 Hz, J_3=5.3 Hz, 1 H), 1.72 - 1.59 (m, 1 H), 1.54 - 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_6D_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 **$C_{16}H_{24}N_2O_2$** (276.1838): 276.1830.

7.3 Cross-coupling of (1-(*tert*-butoxycarbonyl)-4-phenylpiperidin-2-yl)zinc chloride (119b)

A dry and Ar-flushed 10 mL *Schlenk*-tube equipped with a stirring bar was charged with a solution of *tert*-butyl 4-phenylpiperidine-1-carboxylate (**120b**; 1 mmol; 0.26 g) and TMEDA (1 mmol; 0.12 g; 0.45 mL) in anhydrous Et_2O (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_2O 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 RuPhos (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. NH_4Cl sat. aq. solution (20 mL) was added, the phases were separated and the aqueous phase was extracted with Et_2O (4 x 10 mL). The combined organic layers were washed with brine (10 mL) and dried over Na_2SO_4. The solvents were evaporated and the residue was subjected to column chromatography yielding the respective title compound.

***cis-tert*-Butyl 4-phenyl-2-(4-(trifluoromethyl)phenyl)piperidine-1-carboxylate (121g)**



colorless oil (64 %)

^{1}H-NMR (300 MHz, C_6D_6) 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, J_1=11.6 Hz, J_2=6.1 Hz, 1 H), 3.99 (ddd, J_1=13.8 Hz, J_2=7.2 Hz, J_3=3.9 Hz, 1 H), 3.23 (ddd, J_1=13.9 Hz, J_2=9.5 Hz, J_3=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).

^{13}C-NMR (75 MHz, C_6D_6) 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.

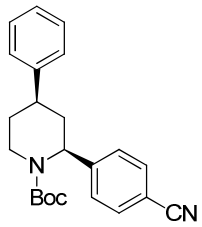
^{19}F-NMR (282 MHz, C_6D_6) δ: –61.30 (s) (minor), –61.94 (s) (major).

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) $\tilde{\nu}$ **(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 **$C_{23}H_{26}F_3NO_2$** (405.1916): 405.1922.

***cis-tert*-Butyl 2-(4-cyanophenyl)-4-phenylpiperidine-1-carboxylate (121h)**



colorless crystals (79 %)

m.p.: 137.0-138.3 °C

^{1}H-NMR (400 MHz, C_6D_6) δ: 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), 4.52 (dd, 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_1= 9.3 Hz, J_1=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).

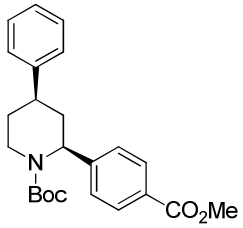
^{13}C-NMR (101 MHz, C_6D_6) δ: 155.8, 150.7, 146.3, 132.6, 129.2, 127.4, 127.1, 126.4, 119.3, 111.3, 79.9, 58.6, 40.5, 39.0, 38.4, 31.7, 28.6.

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 **$C_{23}H_{27}N_2O_2^+$** (363.2067) [M+H$^+$]: 363.2060.

***cis-tert*-Butyl 2-(4-(methoxycarbonyl)phenyl)-4-phenylpiperidine-1-carboxylate (121i)**



colorless oil (67 %)

^{1}H-NMR (400 MHz, C_6D_6) δ: 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_6D_6) δ: 167.0, 155.9, 152.2, 146.6, 130.5, 129.6, 129.1, 127.5, 126.9, 126.0, 79.8, 58.8, 52.9, 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) $\widetilde{\nu}$ **(cm^{-1}):** 2950 (w), 1720 (s), 1690 (vs), 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).

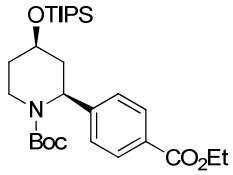
HRMS (EI) for $C_{24}H_{29}NO_4$ (395.2097): 395.2082.

7.3 Cross-coupling of (1-(*tert*-butoxycarbonyl)-4-((triisopropylsilyl)oxy)piperidin-2-yl)zinc chloride (119c)

A dry and Ar-flushed 10 mL Schlenk-tube equipped with a stirring bar was charged with a solution of *tert*-butyl 4-((triisopropylsilyl)oxy)piperidine-1-carboxylate (**120c**; 1 mmol; 0.36 g) and TMEDA (1 mmol; 0.12 g; 0.45 mL) in anhydrous Et_2O (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_2O 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 RuPhos (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_4Cl sat. aq. solution (20 mL) was added, the phases were separated and the aqueous phase was extracted with Et_2O (4 x 10 mL). The combined organic layers were washed with brine (10 mL) and dried over Na_2SO_4. The solvents were evaporated and the residue was subjected to column chromatography yielding the respective title compound.

***cis-tert*-Butyl 2-(4-(ethoxycarbonyl)phenyl)-4-((triisopropylsilyl)oxy)piperidine-1-carboxylate (121j)**



colorless oil (84 %)

^{1}H-NMR (400 MHz, C_6D_6) δ: 8.17 (d, J=8.4 Hz, 2 H), 7.20 (d, J=8.0 Hz, 2 H), 5.32 (dd, J_1=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_1=12.7 Hz, J_2=3.5 Hz, 1 H), 2.06 (dt, J_1=14.0 Hz, J_2=3.5 Hz, 1 H), 1.78 (ddd, J_1=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).

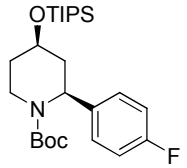
^{13}C-NMR (101 MHz, C_6D_6) δ: 166.6, 155.7, 149.7, 130.3, 129.4, 126.3, 79.8, 65.7, 61.0, 53.3, 37.7, 36.6, 33.5, 32.7, 30.5, 30.5, 30.2, 28.7, 23.5, 18.5, 18.4, 14.7, 14.7, 12.7.

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 **$C_{28}H_{47}NO_5Si$** (505.3224): 505.3221.

***cis-tert*-Butyl 2-(4-fluorophenyl)-4-((triisopropylsilyl)oxy)piperidine-1-carboxylate (121k)**



colorless oil (87 %)

^{1}H-NMR (300 MHz, C_6D_6) δ: 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_3=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_3=3.3 Hz, 1 H), 1.63 - 1.52 (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).

^{13}C-NMR (75 MHz, C_6D_6) δ: 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.

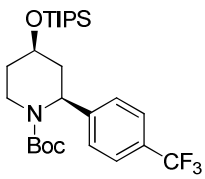
^{19}F-NMR (282 MHz, C_6D_6) δ: –116.44 - –116.36 (m) (minor), -117.97 - –117.82 (m) (major).

MS (70 eV, EI) *m/z* (%): 452 (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).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2972 (w), 2932 (w), 2232 (w), 1684 (s), 1608 (w), 1508 (w), 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).

HRMS (EI) for **$C_{25}H_{42}FNO_3Si$** (452.2918): 452.2938.

***cis-tert*-Butyl 2-(4-(trifluoromethyl)phenyl)-4-((triisopropylsilyl)oxy)piperidine-1-carboxylate (121l)**



colorless crystals (81 %)

m. p.: 94.8 – 95.9°C

^{1}H-NMR (400 MHz, C_6D_6) δ: 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_3=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, C_6D_6) δ: 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.

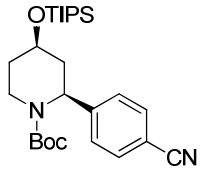
^{19}F-NMR (376 MHz, C_6D_6) δ: –62.12 (s) (major), –62.20 (s) (minor).

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 **$C_{26}H_{42}F_3NO_3Si$** (501.2886): 501.2877.

cis-tert-Butyl 2-(4-cyanophenyl)-4-((triisopropylsilyl)oxy)piperidine-1-carboxylate (121m)



slightly yellow oil (81 %)

^{1}H-NMR (400 MHz, C_6D_6) δ: 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, C_6D_6) δ: 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, 18.4, 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 (14), 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

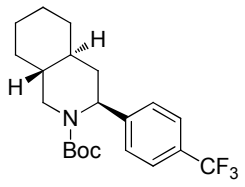
(m), 1079 (s), 1067 (s), 1043 (s), 1021 (m), 1013 (s), 985 (s), 880 (s), 873 (s), 830 (m), 796 (m), 771 (m), 746 (m), 697 (m), 680 (s), 659 (s), 641 (m), 636 (m).

HRMS (EI) for $\mathbf{C_{26}H_{43}N_2O_3Si^+}$ (459.3037) [M+H$^+$]: 459.3022.

7.4 Cross-coupling of (*trans*-2-(*tert*-butoxycarbonyl)decahydroisoquinolin-3-yl)zinc chloride (119d)

A dry and Ar-flushed 10 mL *Schlenk*-tube equipped with a stirring bar was charged with a solution of *trans*-*tert*-butyl octahydroisoquinoline-2(1H)-carboxylate (**120d**; 1 mmol; 0.24 g) and TMEDA (1 mmol; 0.12 g; 0.45 mL) in anhydrous Et_2O (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_2O 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 RuPhos (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. NH_4Cl sat. aq. solution (20 mL) was added, the phases were separated and the aqueous phase was extracted with Et_2O (4 x 10 mL). The combined organic layers were washed with brine (10 mL) and dried over Na_2SO_4. The solvents were evaporated and the residue was subjected to column chromatography yielding the respective title compound.

tert-Butyl 3-(4-(trifluoromethyl)phenyl)octahydroisoquinoline-2(1*H*)-carboxylate (121n)



colorless crystals (69 %)

m.p.: 104.1 – 105.5 °C.

^{1}H-NMR (599 MHz, C_6D_6) δ: 7.42 (d, J=8.2 Hz, 2 H), 7.07 (d, J=8.2 Hz, 2 H), 4.16 (dd, J_1=10.8 Hz, J_2=5.1 Hz, 1 H), 4.04 (dd, J_1=12.8 Hz, J_2=5.1 Hz, 1 H), 2.65 (dd, J_1=12.6 Hz, J_2=10.7 Hz, 1

H), 1.56 (d, *J*=8.0 Hz, 2 H), 1.52 (ddd, J_1=13.3 Hz, J_2=4.8 Hz, J_3=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).

^{13}C-NMR (152 MHz, C_6D_6) δ: 156.9, 152.6 (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.

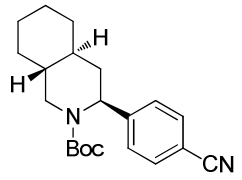
^{19}F-NMR (376 MHz, C_6D_6) δ: –61.83 (s).

MS (70 eV, EI) *m/z* (%): 383 (1) [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 $C_{21}H_{28}F_3NO_2$ (383.2072): 383.2075.

tert-Butyl 3-(4-cyanophenyl)octahydroisoquinoline-2(1*H*)-carboxylate (121o)



colorless crystals (54 %)

m.p.: 83.3 – 84.6 °C.

^{1}H-NMR (400 MHz, C_6D_6) δ: 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).

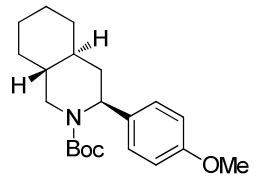
^{13}C-NMR (101 MHz, $CDCl_3$) δ: 156.6, 152.1, 132.2, 126.4, 119.2, 110.4, 79.7, 59.6, 52.1, 41.3, 40.7, 39.7, 32.9, 30.8, 28.2, 26.4, 26.1.

MS (70 eV, EI) *m/z* (%): 340 (1) [M^+], 284 (65), 240 (37), 239 (100), 182 (37), 143 (35), 138 (37), 74 (45), 59 (73), 57 (89), 45 (52), 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).

HRMS (EI) for $C_{21}H_{28}N_2O_2$ (340.2152): 340.2152.

***tert*-Butyl 3-(4-methoxyphenyl)octahydroisoquinoline-2(1*H*)-carboxylate (121p)**



colorless crystals (60 %)

m.p.: 73.1 – 74.7 °C.

^{1}H-NMR (400 MHz, C_6D_6) δ: 7.19 (d, J=8.0 Hz 2 H), 6.85 (d, J=8.8 Hz, 2 H), 4.50 (dd, J_1=10.1 Hz, J_2=5.6 Hz, 1 H), 4.04 (dd, J_1=13.0 Hz, J_2=5.6 Hz, 1 H), 3.36 (s, 3 H), 2.89 (dd, J_1=12.9 Hz, J_2= 9.7 Hz, 1 H), 1.75 (ddd, J_1=13.3 Hz, J_2=5.6 Hz, J_3=3.7 Hz, 1 H), 1.55 (d, J=8.0 Hz, 2 H), 1.44 (td, J_1=6.0 Hz, J_2=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).

^{13}C-NMR (101 MHz, C_6D_6) δ: 159.0, 157.0, 139.0, 131.0, 127.4, 114.2, 79.2, 58.8, 55.2, 52.6, 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) $\tilde{\nu}$ **(cm^{-1}):** 2930 (m), 2918 (m), 2854 (m), 1684 (vs), 1520 (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).

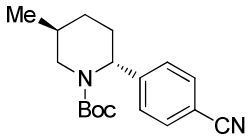
HRMS (EI) for **$C_{21}H_{31}NO_3$** (345.2304): 345.2296.

7.5 Cross-coupling of (1-(*tert*-butoxycarbonyl)-5-methylpiperidin-2-yl)zinc chloride (119e)

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 (**120e**; 1 mmol; 0.20 g) and TMEDA (1 mmol; 0.12 g; 0.45 mL) in anhydrous Et_2O (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_2O 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 RuPhos (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. NH_4Cl sat. aq. solution (20 mL) was added, the phases were separated and the aqueous phase was extracted with Et_2O (4 x 10 mL). The combined organic layers were washed with brine (10 mL) and dried over Na_2SO_4. The solvents were evaporated and the residue was subjected to column chromatography yielding the respective title compound.

***trans-tert*-Butyl 2-(4-cyanophenyl)-5-methylpiperidine-1-carboxylate (121q)**



colorless oil (61 %; 10 % regioisomer)

^{1}H-NMR (400 MHz, C_6D_6) 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, J_1=13.4 Hz, J_2=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).

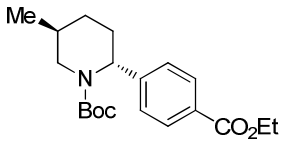
^{13}C-NMR (101 MHz, C_6D_6) δ: 155.4, 146.3, 137.7, 132.4, 131.8, 126.7, 118.5, 110.6, 79.0, 53.5, 45.1, 28.0, 27.7, 25.7, 23.0, 17.0.

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).

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).

HRMS (EI) for **$C_{18}H_{24}N_2O_2$** (300.1838): 300.1840.

***trans-tert*-Butyl 2-(4-(ethoxycarbonyl)phenyl)-5-methylpiperidine-1-carboxylate (121r):**



colorless oil (63 %)

^{1}H-NMR (400 MHz, C_6D_6) δ: 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_6D_6) δ: 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).

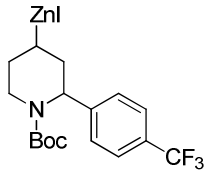
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2964 (w), 2932 (w), 1716 (s), 1686 (vs), 1610 (w), 1476 (w), 1456 (m), 1416 (s), 1392 (m), 1364 (s), 1342 (w), 1324 (m), 1312 (m), 1270 (vs), 1246 (s), 1172 (s), 1142 (vs), 1122 (s), 1102 (vs), 1058 (m), 1018 (s), 988 (m), 892 (w), 878 (m), 864 (m), 836 (w), 766 (m), 746 (m), 724 (w), 696 (m).

HRMS (EI) for **$C_{20}H_{29}NO_4$** (347.2097): 347.2096.

7.6 Preparation of piperidin-4-ylzinc iodides

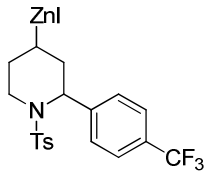
Anhydrous LiCl (4.5 mmol; 0.19 g) was placed in an Ar-flushed flask and dried for 20 min at 150-170 °C under high vacuum (1 mbar). Zn powder (9 mmol; 0.59 g; 150 mesh, Chemetall) was added under Ar and the heterogeneous mixture of Zn and LiCl was dried again under vigorous stirring for 20 min at 150-170 °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 I_2 (50 mg in 2 mL THF).[79]

(1-(*tert*-Butoxycarbonyl)-2-(4-(trifluoromethyl)phenyl)-piperidin-4-yl)zinc iodide (122a)



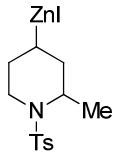
0.35 M (70%)

(1-Tosyl-2-(4-(trifluoromethyl)phenyl)piperidin-4-yl)zinc iodide (122b)



0.39 M (78%)

(2-Methyl-1-tosylpiperidin-4-yl)zinc iodide (122c)

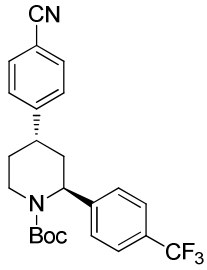


0.42 M (84%)

7.7 Cross-coupling of piperidin-4-ylzinc iodides (122a-c)

A dry and Ar-flushed 10 mL *Schlenk*-tube, equipped with a magnetic stirring bar and a septum was charged with $TMPP_2PdCl_2$ (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. NH_4Cl sat. aq. solution (20 mL) was added, the phases were separated and the aqueous phase was extracted with CH_2Cl_2 (4 x 20 mL). The combined organic layers were washed with brine (20 mL) and dried over Na_2SO_4. The solvents were evaporated and the residue was subjected to column chromatography yielding the respective title compound.

***trans-tert*-Butyl 4-(4-cyanophenyl)-2-(4-(trifluoromethyl)phenyl)piperidine-1-carboxylate (124a)**



colorless crystals (74 %)

m.p.: 72.9 – 74.6 °C.

^{1}H-NMR (300 MHz, C_6D_6) δ: 7.39 (d, *J*=8.3 Hz, 2 H), 7.03 (d, *J*=8.3 Hz, 2 H), 6.97 (d, *J*=7.7 Hz, 2 H), 6.44 (d, *J*=8.0 Hz, 2 H), 5.78 (s, 1 H), 5.40 (s, 1 H), 4.40 (s, 1 H), 4.03 (s, 1 H), 2.54 (d, *J*=10.2 Hz, 1 H), 2.04 (br. s., 1 H), 1.84 (d, *J*=13.8 Hz, 1 H), 1.50 (dd, J_1=14.0 Hz, J_2=5.1 Hz, 9 H), 1.18 - 1.10 (m, 1 H).

^{13}C-NMR (101 MHz, C_6D_6) 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.

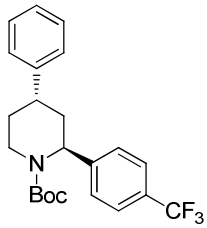
^{19}F-NMR (282 MHz, C_6D_6) δ: –62.14 (s) (minor), –62.19 (s) (major)

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) $\tilde{\nu}$ (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), 1236 (w), 1218 (w), 1156 (vs), 1118 (vs), 1068 (s), 1016 (m), 986 (w), 968 (w), 912 (w), 886 (w), 862 (w), 834 (s), 810 (w), 770 (w), 728 (w), 722 (w).

HRMS (ESI) for $C_{24}H_{25}F_3N_2O_2Cl^-$ (465.1557) [M+Cl$^-$]: 465.1564.

***trans-tert*-Butyl 4-phenyl-2-(4-(trifluoromethyl)phenyl)-piperidine-1-carboxylate (124b)**



colorless oil (50 %)

^{1}H-NMR (400 MHz, C_6D_6) δ: 7.37 (d, *J*=8.2 Hz, 2 H), 7.13 (d, *J*=7.6 Hz, 2 H), 7.11 – 6.97 (m, 3 H), 6.87 (d, *J*=7.4 Hz, 2 H), 5.83 (s, 1 H), 5.44 (s, 1 H), 4.48 (d, *J*=8.8 Hz, 1 H), 4.07 (d, *J*=9.9 Hz, 1 H), 2.63 (d, *J*=6.6 Hz, 1 H), 2.35 - 2.24 (m, 1 H), 2.09 (dd, J_1=13.7 Hz, J_2=1.8 Hz, 1 H), 1.79 (td, J_1=13.3 Hz, J_2=5.2 Hz, 1 H), 1.65 - 1.35 (m, 9 H).

^{13}C-NMR (101 MHz, C_6D_6) δ: 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.

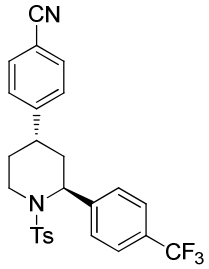
^{19}F-NMR (376 MHz, C_6D_6) δ: –62.15 (s).

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).

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).

HRMS (EI) for $C_{23}H_{26}F_3NO_2$ (405.1916): 405.1932.

4-(*trans*-1-Tosyl-2-(4-(trifluoromethyl)phenyl)piperidin-4-yl)benzonitrile (124c)



white crystals (70 %)

m.p.: 181.7 – 183.3 °C.

^{1}H-NMR (400 MHz, C_6D_6) δ: 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), 1.52 (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_6D_6) δ: 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.

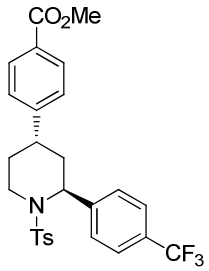
^{19}F-NMR (282 MHz, C_6D_6) δ: –62.16 (s).

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), 1412 (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 **$C_{26}H_{23}F_3N_2O_2SCl^-$** (529.1126) [M+Cl$^-$]: 529.1122.

Methyl 4-(*trans*-1-tosyl-2-(4-(trifluoromethyl)phenyl)-piperidin-4-yl)benzoate (124d)



colorless crystals (69 %)

m.p.: 68.8 – 70.5 °C.

^{1}H-NMR (300 MHz, C_6D_6) δ: 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), 3.52 (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_6D_6) δ: 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.

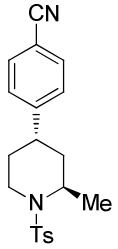
^{19}F-NMR (282 MHz, C_6D_6) δ ppm –62.22 (s).

MS (70 eV, EI) *m/z* (%): 527 (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 **$C_{27}H_{26}F_3NO_4S$** (527.1535): 527.1537.

4-(*trans*-2-methyl-1-tosylpiperidin-4-yl)benzonitrile (124e)



colorless crystals (84 %)

m.p.: 106.2 – 107.1 °C.

^{1}H-NMR (400 MHz, C_6D_6) δ: 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_1= 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).

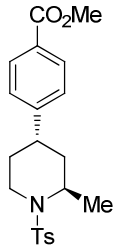
^{13}C-NMR (101 MHz, C_6D_6) δ: 150.6, 143.1, 139.9, 132.6, 130.1, 128.0, 127.8, 119.3, 111.3, 48.8, 40.3, 37.8, 36.5, 32.6, 21.5, 15.6.

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 **$C_{20}H_{22}N_2O_2S$** (354.1402): 354.1384.

Methyl 4-(*trans*-2-methyl-1-tosylpiperidin-4-yl)benzoate (124f)



colorless crystals (89 %)

m.p.: 129.8 – 131.5 °C.

^{1}H-NMR (400 MHz, C_6D_6) δ: 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), 1.52 (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_6D_6) δ: 167.0, 152.1, 143.0, 140.0, 130.5, 130.1, 129.5, 127.8, 127.5, 52.9, 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), 1304 (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).

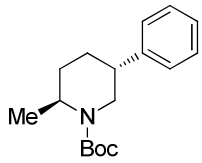
HRMS (EI) for **$C_{21}H_{25}NO_4S$** (387.1504): 387.1522.

7.8 Cross-coupling of (1-(*tert*-butoxycarbonyl)-6-methylpiperidin-2-yl)zinc chloride (127) – Pd-1,2-migration

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_2O (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_2O 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 RuPhos (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. NH_4Cl sat. aq. solution (20 mL) was added, the phases were separated and the aqueous phase was extracted with Et_2O (4 x 10 mL). The combined organic layers were washed with brine (10 mL) and dried over Na_2SO_4. The solvents were evaporated and the residue was subjected to column chromatography yielding the respective title compound.

***trans-tert*-Butyl 2-methyl-5-phenylpiperidine-1-carboxylate (128a)**



colorless oil (90 %)

^{1}H-NMR (400 MHz, C_6D_6) 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, J_1=14.0 Hz, J_2=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).

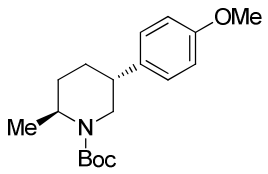
^{13}C-NMR (101 MHz, C_6D_6) δ: 155.2, 144.7, 128.9, 128.7, 128.3, 126.6, 126.4, 79.2, 47.3, 42.5, 38.6, 28.9, 26.3, 26.1, 16.9.

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) $\tilde{\nu}$ (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 **$C_{19}H_{25}NO_2$** (275.1885): 275.1874.

***trans-tert*-Butyl 5-(4-methoxyphenyl)-2-methylpiperidine-1-carboxylate (128b)**



colorless liquid (61 %)

^{1}H-NMR (400 MHz, C_6D_6) δ: 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).

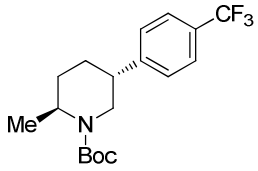
^{13}C-NMR (101 MHz, C_6D_6) δ: 158.8, 155.3, 136.4, 129.2, 127.4, 114.4, 114.3, 79.2, 55.1, 47.3, 42.7, 37.8, 29.0, 28.8, 26.3, 16.9.

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), 1522 (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-tert*-Butyl 2-methyl-5-(4-(trifluoromethyl)phenyl)piperidine-1-carboxylate (128c)**



colorless oil (82 %)

^{1}H-NMR (400 MHz, C_6D_6) δ: 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_6D_6) δ: 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.

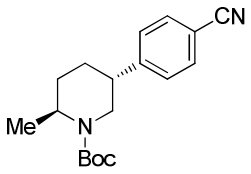
^{19}F-NMR (376 MHz, C_6D_6) δ: –61.92 (s) (minor), –62.05 (s) (major).

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 **$C_{18}H_{24}F_3NO_2$** (343.1759): 343.1757.

***trans-tert*-Butyl 5-(4-cyanophenyl)-2-methylpiperidine-1-carboxylate (128d)**



colorless oil (53 %)

^{1}H-NMR (400 MHz, C_6D_6) δ: 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 - 1.52 (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).

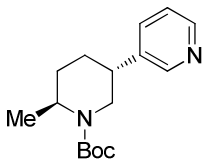
^{13}C-NMR (101 MHz, C_6D_6) δ: 155.0, 149.5, 132.3, 128.8, 126.8, 126.2, 119.4, 110.8, 79.6, 47.1, 41.4, 38.4, 28.9, 26.0, 25.6, 16.6.

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).

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).

HRMS (EI) for **$C_{18}H_{24}N_2O_2$** (300.1838): 300.1831.

***trans-tert*-Butyl 2-methyl-5-(pyridin-3-yl)piperidine-1-carboxylate (128e)**



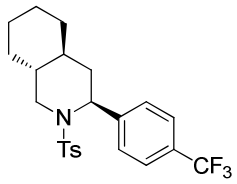
yellow oil (60 %)

^{1}H-NMR (400 MHz, C_6D_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), 1.52-1.37 (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_6D_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 **$C_{16}H_{24}N_2O_2$** (276.1838): 276.1834.

7.9 Synthesis of *N*-tosyl piperidines

To a solution of the respective *t*-butyl piperidine-1-carboxylate (Boc-protected amine) (1 equiv) in Et_2O (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_2Cl_2 (4 x). The combined organic phases were washed with brine and dried over Na_2SO_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 (TsCl; 2 equiv) and NEt_3 (2 equiv) in THF (0.2 M). The reaction mixture was stirred for 15 h. NH_4Cl sat. aq. solution was added. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (4 x). The combined organic phases were washed with brine and dried over Na_2SO_4. The solvents were evaporated and the crude product was purified via column chromatography to give the respective title compound.

2-Tosyl-3-(4-(trifluoromethyl)phenyl)decahydroisoquinoline (121na)



white crystals (78 %; 0.4 mmol scale)

m.p.: 194.1 – 195.6 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 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_1=11.5 Hz, J_2=3.7 Hz, 1 H), 3.91 (dd, J_1=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).

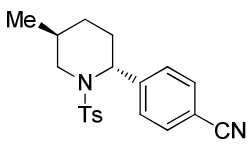
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 145.7 (d, *J*=1.3 Hz), 143.2, 134.8, 129.5, 129.2 (q, *J*=32.2 Hz), 129.1, 128.4, 128.1, 127.9, 127.8, 127.4, 124.5 (q, *J*=3.9 Hz), 124.1 (q, *J*=272.1 Hz), 63.1, 53.7, 43.6, 41.0, 40.7, 32.0, 29.9, 26.0, 25.6, 21.3.

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 **$C_{23}H_{26}F_3NO_2S$** (437.1636): 437.1635.

4-(*trans*-5-Methyl-1-tosylpiperidin-2-yl)benzonitrile (121qa)



white crystals (75 %; 0.3 mmol scale)

m.p.: 113.1 – 114.4 °C.

^{1}H-NMR (400 MHz, C_6D_6) δ: 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_1=12.9 Hz, J_2=3.7 Hz, 1 H),

2.98 (dd, J_1=12.9 Hz, J_2=5.3 Hz, 1 H), 1.92 (s, 3 H), 1.60 - 1.50 (m, 1 H), 1.41 - 1.31 (m, 2 H), 1.08 (dddd, J_1=13.9 Hz, J_2=9.9 Hz, J_3=4.5 Hz, J_4=4.3 Hz, 1 H), 0.71 - 0.64 (m, 1 H), 0.62 (d, J=6.9 Hz, 3 H).

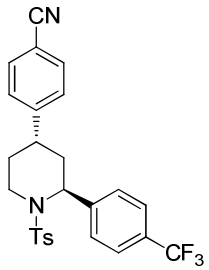
^{13}C-NMR (101 MHz, C_6D_6) δ: 146.1, 143.3, 138.3, 132.3, 129.9, 128.5, 128.0, 119.2, 111.7, 58.0, 49.6, 28.7, 27.6, 27.1, 21.5, 18.3.

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) $\tilde{\nu}$ (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 **$C_{20}H_{22}N_2O_2S$** (354.1402): 354.1398.

4-(*trans*-1-Tosyl-2-(4-(trifluoromethyl)phenyl)piperidin-4-yl)benzonitrile (124aa)



white crystals (72 %; 0.5 mmol scale)

m.p.: 182.6 – 183.1 °C.

^{1}H-NMR (400 MHz, $CDCl_3$) 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, J_1=13.5 Hz, J_2=5.5 Hz, 1 H), 1.63 (d, J=12.9 Hz, 1 H), 1.52 (qd, J_1=12.7 Hz, J_2=4.5 Hz, 1 H).

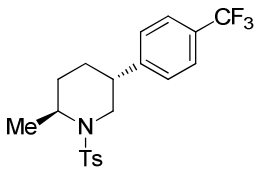
^{13}C-NMR (101 MHz, $CDCl_3$) δ: 149.9, 143.7, 142.5 (d, J=0.8 Hz), 138.0, 132.5, 129.9, 129.6 (q, J=32.6 Hz), 127.4, 127.0, 127.0, 125.9 (q, J=3.7 Hz), 124.0 (q, J=272.1 Hz), 118.6, 110.7, 55.0, 41.6, 36.8, 34.1, 31.3, 21.5.

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).

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 **$C_{26}H_{23}F_3N_2O_2S$** (484.1432): 484.1439.

***trans*-2-Methyl-1-tosyl-5-(4-(trifluoromethyl)phenyl)-piperidine (128ca)**



white crystals (73 %; 0.5 mmol scale)

m.p.: 133.0 – 135.9 °C.

^{1}H-NMR (599 MHz, C_6D_6) δ: 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), 2.52 - 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).

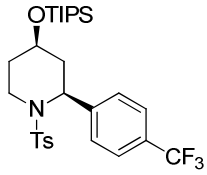
^{13}C-NMR (152 MHz, $CDCl_3$) δ: 147.7 (d, *J*=1.1 Hz), 143.1, 138.4, 129.9, 129.1 (q, *J*=32.0 Hz), 128.7, 128.1, 125.8 (q, *J*=3.8 Hz), 125.5 (q, *J*=271.8 Hz), 52.5, 47.8, 39.4, 30.1, 26.8, 21.4, 17.3.

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 **$C_{20}H_{22}F_3NO_2S$** (397.1323): 397.1320.

***cis*-1-Tosyl-2-(4-(trifluoromethyl)phenyl)-4-((triisopropylsilyl)oxy)piperidine**



colorless crystals (56 %; 20 mmol scale)

m.p.: 93.8 – 95.3 °C.

^{1}H-NMR (400 MHz, C_6D_6) 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), 5.19 (d, *J*=2.9 Hz, 1 H), 3.71 (dt, J_1=13.9 Hz, J_2=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, J_1=14.2 Hz, J_2=6.6 Hz, J_3=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).

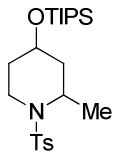
^{13}C-NMR (101 MHz, C_6D_6) δ: 146.5 (d, *J*=1.1 Hz), 143.2, 139.7, 130.0, 129.1 (q, *J*=32.2 Hz), 127.8, 127.4, 125.6 (q, *J*=3.8 Hz), 125.4 (d, *J*=271.8 Hz), 65.4, 54.8, 38.3, 37.4, 32.6, 21.4, 18.4, 18.4, 12.6.

MS (70 eV) *m/z* (%): 524 (13), 523 (34), 522 (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) $\tilde{\nu}$ **(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 $C_{28}H_{41}F_3NO_3SSi^+$ (556.2523) [M+H$^+$]: 556.2524.

2-Methyl-1-tosyl-4-((triisopropylsilyl)oxy)piperidine



viscous oil (65 %; 10 mmol scale)

^{1}H-NMR (300 MHz, C_6D_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_6D_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 (12).

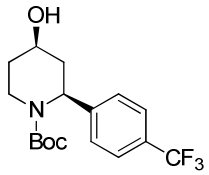
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2942 (m), 2890 (m), 2866 (m), 1598 (vw), 1494 (w), 1464 (m), 1380 (w), 1346 (m), 1328 (m), 1250 (w), 1216 (w), 1162 (vs), 1130 (s), 1106 (m), 1088 (m), 1060 (s), 1040 (s), 1018 (m), 988 (m), 966 (vs), 914 (s), 882 (s), 870 (s), 814 (m), 776 (m), 712 (s), 700 (s), 678 (vs), 654 (s), 642 (s).

HRMS (EI) for **$C_{21}H_{36}NO_3SSi^+$** (410.2185) $[M\text{-}CH_3]^+$: 410.2207.

7.10 TIPS-deprotection

To a solution of the respective 4-((triisopropylsilyl)oxy)piperidine (1 equiv) in THF (0.2 M) was added *n*$Bu_4NF \cdot 3\ H_2O$ (2 equiv) portionwise. The reaction mixture was stirred for 15 h at room temperature, then H_2O was added, the phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvents were evaporated and the crude product was subjected to column chromatography.

***tert*-Butyl *cis*-2-(4-fluorophenyl)-4-hydroxypiperidine-1-carboxylate**



viscous oil (89 %; 5 mmol scale)

^{1}H-NMR (300 MHz, C_6D_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).

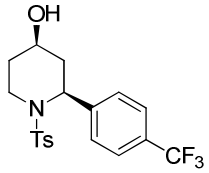
^{13}C-NMR (75 MHz, C_6D_6) δ: 155.0, 147.3 (d, *J*=1.1 Hz), 128.2 (q, *J*=32.3 Hz), 126.1, 124.8 (q, *J*=271.8 Hz), 125.0 (q, *J*=3.6 Hz), 79.3, 63.9, 52.2, 35.6, 35.5, 31.9, 27.9.

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 **$C_{17}H_{22}F_3NO_3$** (345.1552): 345.1562.

***cis*-1-Tosyl-2-(4-(trifluoromethyl)phenyl)piperidin-4-ol**



white crystals (87 %; 10 mmol scale)

m.p.: 114.0 – 115.5 °C.

^{1}H-NMR (400 MHz, C_6D_6) δ: 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), 3.52 - 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_6D_6) δ: 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.

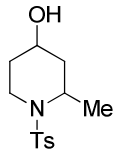
^{19}F-NMR (376 MHz, C_6D_6) δ: –62.10 (s) (major), –62.25 (s) (minor).

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 **$C_{19}H_{21}F_3NO_3S^+$** (400.1189) [$M+H^+$]: 400.1189.

2-Methyl-1-tosylpiperidin-4-ol



viscous oil (73 %; 7 mmol scale)

^{1}H-NMR (300 MHz, C_6D_6) δ: 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_6D_6) δ: 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).

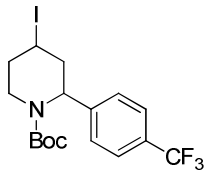
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3526 (w), 2924 (w), 2882 (w), 1598 (w), 1494 (w), 1454 (w), 1424 (w), 1402 (w), 1382 (w), 1366 (w), 1344 (m), 1322 (m), 1304 (m), 1288 (m), 1234 (w), 1216 (w), 1184 (w), 1158 (s), 1148 (s), 1132 (s), 1098 (m), 1080 (s), 1056 (m), 1038 (m), 1018 (m), 1008 (w), 982 (m), 942 (m), 912 (s), 890 (w), 852 (m), 814 (m), 788 (w), 732 (w), 710 (s), 688 (vs), 642 (s).

HRMS (EI) for **$C_{13}H_{19}NO_3S$** (269.1086): 269.1078.

7.11 Iodination

In a dry and Ar-flushed *Schlenk*-flask I_2 (1.2 equiv) was dissolved in CH_2Cl_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_2Cl_2 (3x). Solvents were evaporated and the crude product was subjected to column chromatography.[78]

***tert*-Butyl 4-iodo-2-(4-(trifluoromethyl)phenyl)piperidine-1-carboxylate (123a)**



yellow oil (68 %; 7 mmol scale)

^{1}H-NMR (300 MHz, C_6D_6) δ: 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).

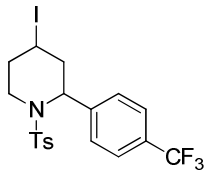
^{13}C-NMR (75 MHz, C_6D_6) δ: 155.3, 143.6 (d, *J*=1.1 Hz), 129.6 (q, *J*=32.3 Hz), 129.0, 127.2, 126.3 (q, *J*=3.9 Hz), 125.4, 125.2 (q, *J*=272.1 Hz), 80.4, 56.1, 42.4, 41.7, 39.6, 28.7, 20.3.

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 (w), 910 (m), 870 (w),852 (m), 836 (m), 794 (w), 772 (m), 732 (w), 722 (w), 642 (w).

HRMS (EI) for $C_{17}H_{21}F_3INO_2$ (455.0569): 455.0561.

4-iodo-1-tosyl-2-(4-(trifluoromethyl)phenyl)piperidine (123b)



slightly yellow crystals (55 %; 8 mmol scale)

m.p.: 132.6 – 133.8 °C.

^{1}H-NMR (400 MHz, C_6D_6) δ: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), 3.52 - 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).

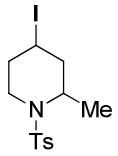
^{13}C-NMR (101 MHz, C_6D_6) δ: 143.8, 142.4 (d, J=1.2 Hz), 139.3, 130.3, 129.9 (q, J=32.3 Hz), 127.8, 127.6, 126.4 (q, J=3.7 Hz), 125.2 (q, J=272.0 Hz), 57.9, 43.7, 40.8, 38.3, 21.5, 19.0.

MS (70 eV) *m/z* (%): 509 (1) [M^+], 383 (22), 382 (100), 226 (12), 199 (63), 186 (23), 185 (10), 184 (53), 159 (54), 155 (87), 91 (67), 65 (11), 55 (10).

IR (ATR) $\tilde{\nu}$ (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).

HRMS (ESI) for **$C_{19}H_{19}F_3INO_2SCl^-$** (543.9827) [M+$Cl^-$]:543.9817.

2-Methyl-4-iodo-1-tosylpiperidine (123c)



yellow oil (59 %; 5 mmol scale)

^{1}H-NMR (300 MHz, C_6D_6) δ: 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}C-NMR (75 MHz, C_6D_6) δ: 143.1, 139.6, 130.1, 127.7, 52.4, 44.3, 42.2, 39.2, 21.5, 20.1, 15.5.

MS (70 eV, EI) *m/z* (%): 379 (1) [M^+], 363 (12), 253 (15), 252 (100), 155 (52), 90 (61), 69 (10), 66 (10), 58 (17), 56 (12).

IR (ATR) $\tilde{\nu}$ **(cm^{-1}):** 2974 (w), 2924 (w), 2870 (vw), 1598 (w), 1494 (vw), 1444 (w), 1380 (w), 1330 (s), 1302 (m), 1258 (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).

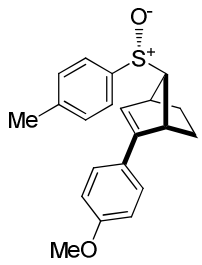
HRMS (EI) for **$C_{13}H_{18}INO_2S$** (379.0103): 379.0118.

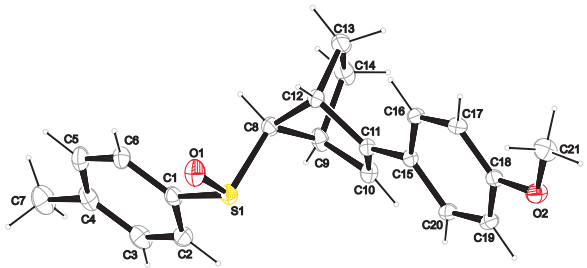
D. Appendix

1. X-ray Structures

1.1 Sulfoxide-alkene hybrid ligands

(1*R*,4*S*,7*R*)-2-(4-Methoxyphenyl)-7-((*R*)-p-tolylsulfinyl)-bicyclo[2.2.1]hept-2-ene (46a):



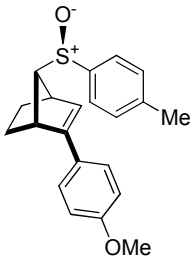


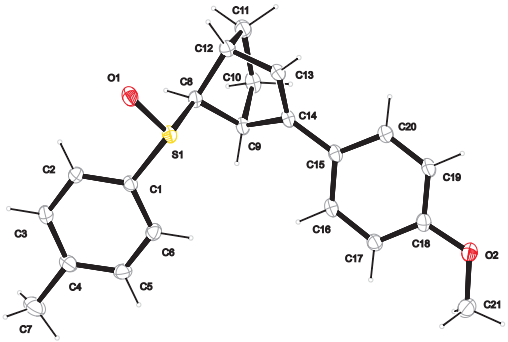
Crystal data

net formula	$C_{21}H_{22}O_2S$
M_r/g mol^{-1}	338.464
crystal size/mm	0.21 × 0.19 × 0.09
T/K	200(2)
radiation	MoKα
diffractometer	'KappaCCD'
crystal system	monoclinic
space group	$P2_1$
a/Å	6.44350(10)
b/Å	7.4994(2)
c/Å	18.0502(4)
α/°	90
β/°	90.3361(15)
γ/°	90
V/Å^3	872.21(3)
Z	2
calc. density/g cm^{-3}	1.28877(4)
μ/mm^{-1}	0.195
absorption correction	none
refls. measured	7321
R_{int}	0.0237
mean σ(I)/I	0.0417
θ range	3.16–27.47

observed refls.	3559
x, *y* (weighting scheme)	0.0433, 0.0402
hydrogen refinement	constr
Flack parameter	−0.05(6)
refls in refinement	3995
parameters	219
restraints	1
$R(F_{obs})$	0.0356
$R_w(F^2)$	0.0852
S	1.052
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.147
min electron density/e Å^{-3}	−0.280

(1*S*,4*R*,7*S*)-2-(4-methoxyphenyl)-7-((*R*)-p-tolylsulfinyl)-bicyclo[2.2.1]hept-2-ene (46b)





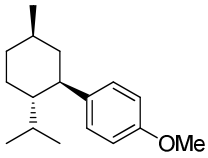
Crystal data

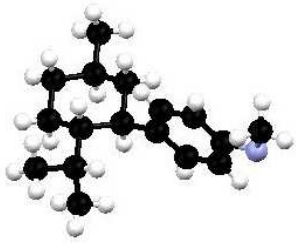
net formula	$C_{21}H_{22}O_2S$
M_r/g mol^{-1}	338.464
crystal size/mm	0.14 × 0.05 × 0.04
T/K	173(2)
radiation	MoKα
diffractometer	'KappaCCD'
crystal system	orthorhombic
space group	$P2_12_12_1$
a/Å	6.3806(2)
b/Å	13.0486(2)
c/Å	21.0871(5)
α/°	90
β/°	90
γ/°	90

V/Å^3	1755.67(7)
Z	4
calc. density/g cm^{-3}	1.28052(5)
μ/mm^{-1}	0.194
absorption correction	none
refls. measured	11548
R_{int}	0.0433
mean σ(I)/I	0.0315
θ range	3.27–25.34
observed refls.	2912
x, y (weighting scheme)	0.0465, 0.1943
hydrogen refinement	constr
Flack parameter	−0.06(7)
refls in refinement	3215
parameters	219
restraints	0
$R(F_{obs})$	0.0330
$R_w(F^2)$	0.0840
S	1.078
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.216
min electron density/e Å^{-3}	−0.216

1.2 Products of the diastereoselective cross-coupling of cycloalkylzinc reagents with aryl halides

1-[(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl]-4-methoxybenzene (69a)



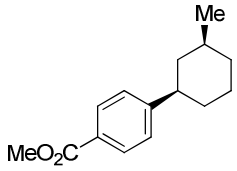


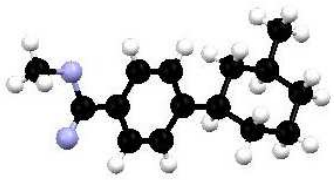
Crystal data

net formula	$C_{17}H_{26}O$
M_r/g mol^{-1}	246.388
crystal size/mm	0.25 × 0.23 × 0.18
T/K	200(2)
radiation	MoKα
diffractometer	'KappaCCD'
crystal system	orthorhombic
space group	$P2_12_12_1$
a/Å	6.5955(2)
b/Å	7.8820(2)
c/Å	29.1769(8)
α/°	90
β/°	90
γ/°	90
V/Å^3	1526.78(7)
Z	4
calc. density/g cm^{-3}	1.07898(5)
μ/mm^{-1}	0.064
absorption correction	none
refls. measured	10226
R_{int}	0.0382
mean σ(I)/I	0.0278
θ range	3.17–26.03
observed refls.	1415
x, y (weighting scheme)	0.0524, 0.1045

hydrogen refinement	constr
Flack parameter	−2(2)
refls in refinement	1748
parameters	167
restraints	0
$R(F_{obs})$	0.0386
$R_w(F^2)$	0.0972
S	1.075
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.117
min electron density/e Å^{-3}	−0.152

Methyl 4-[*cis*-3-methylcyclohexyl]benzoate (78a)



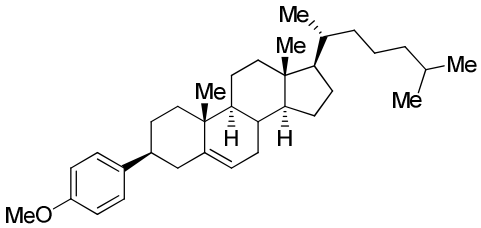


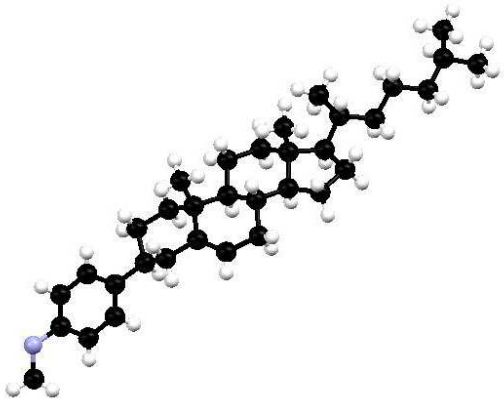
Crystal data

net formula	$C_{15}H_{20}O_2$
M_r/g mol^{-1}	232.318
crystal size/mm	0.25 × 0.15 × 0.08
T/K	200(2)
radiation	MoKα
diffractometer	'KappaCCD'
crystal system	monoclinic
space group	*C*2/*c*
a/Å	15.7972(5)
b/Å	6.3827(2)
c/Å	26.2140(8)
α/°	90
β/°	96.5673(19)
γ/°	90
V/Å^3	2625.78(14)
Z	8
calc. density/g cm^{-3}	1.17536(6)
μ/mm^{-1}	0.076

absorption correction	none
refls. measured	8464
R_{int}	0.0438
mean σ(I)/I	0.0439
θ range	3.18–26.01
observed refls.	1767
x, y (weighting scheme)	0.0937, 0.7066
hydrogen refinement	constr
refls in refinement	2560
parameters	157
restraints	0
$R(F_{obs})$	0.0574
$R_w(F^2)$	0.1739
S	1.047
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.359
min electron density/e Å^{-3}	−0.162

(3β)-3-(4-Methoxyphenyl)cholest-5-ene (88)





Crystal data

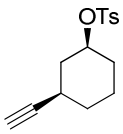
net formula	$C_{34}H_{52}O$
M_r/g mol^{-1}	476.776
crystal size/mm	0.29 × 0.18 × 0.15
T/K	200(2)
radiation	MoKα
diffractometer	'KappaCCD'
crystal system	monoclinic

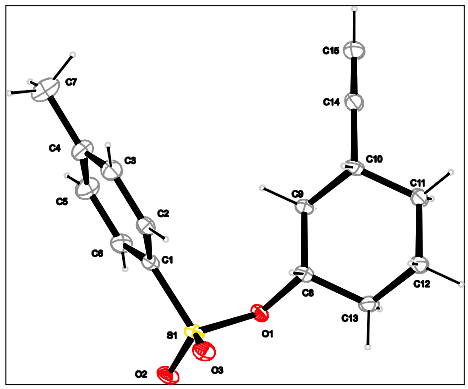
space group	$P2_1$
a/Å	16.2591(5)
b/Å	9.4526(3)
c/Å	18.8939(5)
α/°	90
β/°	95.5080(18)
γ/°	90
V/Å^3	2890.41(15)
Z	4
calc. density/g cm^{-3}	1.09565(6)
μ/mm^{-1}	0.063
absorption correction	none
refls. measured	19089
R_{int}	0.0537
mean σ(I)/I	0.0438
θ range	3.16–25.05
observed refls.	4138
x, y (weighting scheme)	0.0663, 0.3301
hydrogen refinement	constr
Flack parameter	0(2)
refls in refinement	5439
parameters	643
restraints	1
$R(F_{obs})$	0.0462
$R_w(F^2)$	0.1221
S	1.031
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.189
min electron density/e Å^{-3}	−0.228

Flack parameter meaningless, 4744 Friedel pairs merged.

1.3 Products of the diastereoselective cross-coupling of cycloalkylzinc reagents with alkynyl bromides

cis-3-Ethynylcyclohexyl 4-methylbenzenesulfonate



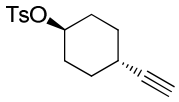


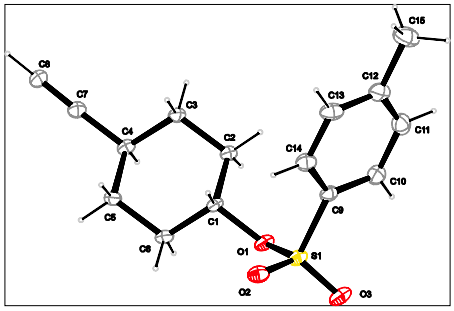
Crystal data

net formula	$C_{15}H_{18}O_3S$
M_r/g mol^{-1}	278.368
crystal size/mm	0.33 × 0.20 × 0.06
T/K	200(2)
radiation	MoKα
diffractometer	'Oxford XCalibur'
crystal system	monoclinic
space group	*C*2/*c*
a/Å	19.7276(13)
b/Å	5.8406(5)
c/Å	25.346(3)
α/°	90
β/°	92.474(8)
γ/°	90
V/Å^3	2917.7(5)
Z	8
calc. density/g cm^{-3}	1.2674(2)
μ/mm^{-1}	0.223
absorption correction	'multi-scan'
transmission factor range	0.89479–1.00000
refls. measured	4971
R_{int}	0.0503

mean σ(*I*)/*I*	0.1020
θ range	4.34–25.17
observed refls.	1533
x, *y* (weighting scheme)	0.0722, 0
hydrogen refinement	constr
refls in refinement	2568
parameters	173
restraints	0
$R(F_{obs})$	0.0749
$R_w(F^2)$	0.1694
S	1.090
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.492
min electron density/e Å^{-3}	−0.297

trans-4-Ethynylcyclohexyl 4-methylbenzenesulfonate



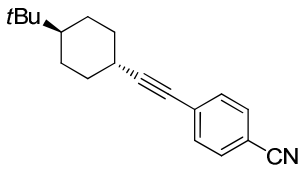


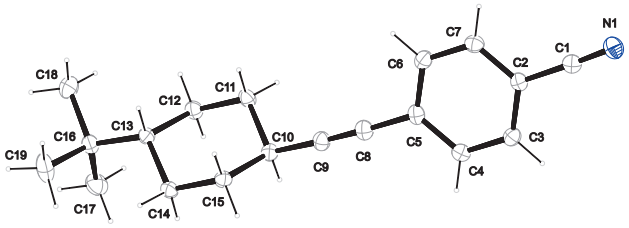
Crystal data

net formula	$C_{15}H_{18}O_3S$
M_r/g mol^{-1}	278.368
crystal size/mm	0.30 × 0.22 × 0.18
T/K	173(2)
radiation	MoKα
diffractometer	'Oxford XCalibur'
crystal system	triclinic
space group	*P*1bar
a/Å	6.5644(6)
b/Å	9.8375(9)
c/Å	12.2208(11)
α/°	69.467(8)
β/°	76.561(8)

γ/°	84.673(7)
V/Å^3	718.76(11)
Z	2
calc. density/g cm^{-3}	1.28623(20)
μ/mm^{-1}	0.226
absorption correction	'multi-scan'
transmission factor range	0.84382–1.00000
refls. measured	5283
R_{int}	0.0411
mean σ(I)/I	0.0778
θ range	4.21–26.35
observed refls.	1804
x, y (weighting scheme)	0.0564, 0
hydrogen refinement	constr
refls in refinement	2899
parameters	173
restraints	0
$R(F_{obs})$	0.0476
$R_w(F^2)$	0.1139
S	0.885
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.382
min electron density/e Å^{-3}	−0.348

4-((*trans*-4-(*tert*-Butyl)cyclohexyl)ethynyl)benzonitrile (103b)





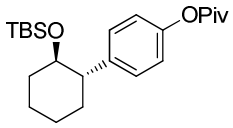
Crystal data

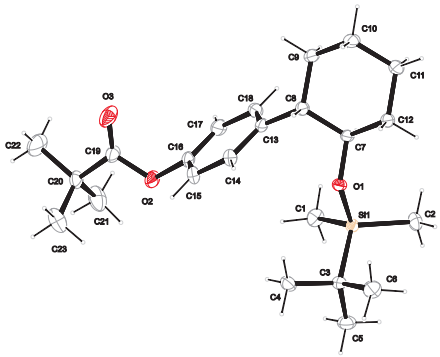
net formula	$C_{19}H_{23}N$
M_r/g mol^{-1}	265.393
crystal size/mm	0.15 × 0.13 × 0.05
T/K	173(2)
radiation	MoKα
diffractometer	'KappaCCD'

crystal system	triclinic
space group	*P*1bar
a/Å	9.1411(3)
b/Å	9.3602(3)
c/Å	10.5855(4)
α/°	96.576(2)
β/°	113.547(2)
γ/°	98.372(2)
V/Å^3	806.43(5)
Z	2
calc. density/g cm^{-3}	1.09297(7)
μ/mm^{-1}	0.063
absorption correction	none
refls. measured	7170
R_{int}	0.0293
mean σ(*I*)/*I*	0.0452
θ range	3.28–27.82
observed refls.	2380
x, *y* (weighting scheme)	0.0556, 0.1610
hydrogen refinement	constr
refls in refinement	3744
parameters	184
restraints	0
$R(F_{obs})$	0.0527
$R_w(F^2)$	0.1381
S	1.030
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.159
min electron density/e Å^{-3}	−0.182

1.4 Products of the diastereoselective Fe-mediated cross-coupling

4-(*trans*-2-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)phenyl pivalate (36i)



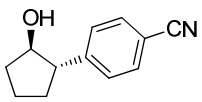


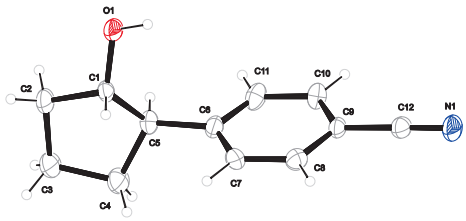
Crystal data

net formula	$C_{23}H_{38}O_3Si$
M_r/g mol^{-1}	390.632
crystal size/mm	0.37 × 0.10 × 0.08
T/K	173(2)
radiation	MoKα
diffractometer	'KappaCCD'
crystal system	monoclinic
space group	$P2_1/c$
a/Å	6.10750(10)
b/Å	14.1338(3)
c/Å	27.6415(5)
α/°	90
β/°	96.5671(11)
γ/°	90
V/Å^3	2370.42(8)
Z	4
calc. density/g cm^{-3}	1.09460(4)
μ/mm^{-1}	0.117
absorption correction	none
refls. measured	15796
R_{int}	0.0342
mean σ(I)/I	0.0368
θ range	3.24–27.50
observed refls.	4067
x, y (weighting scheme)	0.0713, 1.4216

hydrogen refinement	constr
refls in refinement	5417
parameters	252
restraints	0
$R(F_{obs})$	0.0559
$R_w(F^2)$	0.1563
S	1.021
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.716
min electron density/e Å^{-3}	−0.258

4-(*trans*-2-Hydroxycyclopentyl)benzonitrile





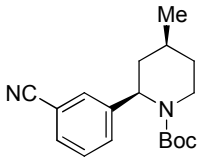
Crystal data

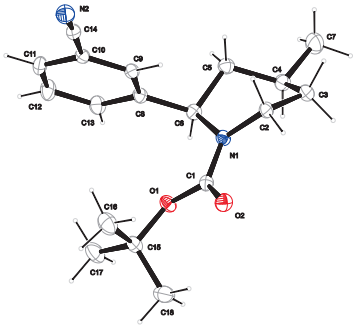
net formula	$C_{12}H_{13}NO$
M_r/g mol^{-1}	187.238
crystal size/mm	0.34 × 0.31 × 0.21
T/K	173(2)
radiation	MoKα
diffractometer	'Oxford XCalibur'
crystal system	monoclinic
space group	$P2_1/c$
a/Å	6.3875(4)
b/Å	9.6599(6)
c/Å	16.5535(8)
α/°	90
β/°	91.420(5)
γ/°	90
V/Å^3	1021.08(10)
Z	4
calc. density/g cm^{-3}	1.21800(12)
μ/mm^{-1}	0.078

absorption correction	'multi-scan'
transmission factor range	0.98653–1.00000
refls. measured	6866
R_{int}	0.0326
mean σ(I)/I	0.0530
θ range	4.22–26.32
observed refls.	1210
x, y (weighting scheme)	0.0625, 0
hydrogen refinement	constr
refls in refinement	2059
parameters	147
restraints	0
$R(F_{obs})$	0.0522
$R_w(F^2)$	0.1311
S	1.009
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.199
min electron density/e Å^{-3}	−0.243

1.6 Products of the diastereoselective cross-coupling of piperidinylzinc reagents

cis-tert-Butyl 2-(3-cyanophenyl)-4-methylpiperidine-1-carboxylate (121d)



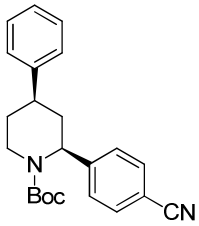


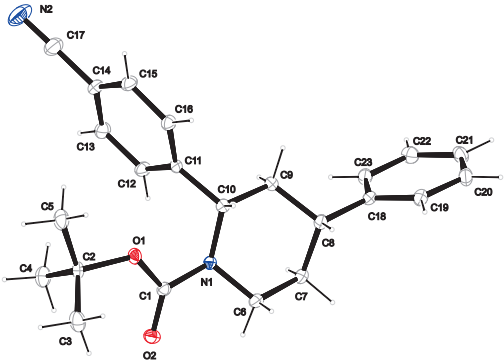
Crystal data

net formula	$C_{18}H_{24}N_2O_2$
M_r/g mol^{-1}	300.395
crystal size/mm	0.60 × 0.13 × 0.07
T/K	173(2)
radiation	MoKα
diffractometer	'Oxford XCalibur'
crystal system	triclinic
space group	P1bar
a/Å	6.3135(4)
b/Å	10.2813(10)
c/Å	13.8719(10)
α/°	76.283(7)
β/°	85.876(6)
γ/°	77.838(7)
V/Å^3	854.90(12)
Z	2
calc. density/g cm^{-3}	1.16698(16)
μ/mm^{-1}	0.076
absorption correction	'multi-scan'
transmission factor range	0.72269–1.00000
refls. measured	5884
R_{int}	0.0355
mean σ(I)/I	0.0856
θ range	4.24–26.33
observed refls.	1872
x, y (weighting scheme)	0.0371, 0

hydrogen refinement	constr
refls in refinement	3435
parameters	203
restraints	0
$R(F_{obs})$	0.0427
$R_w(F^2)$	0.0891
S	0.830
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.163
min electron density/e Å^{-3}	−0.141

cis-tert-Butyl 2-(4-cyanophenyl)-4-phenylpiperidine-1-carboxylate (121h)



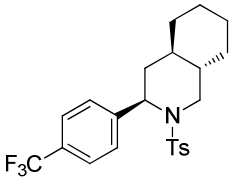


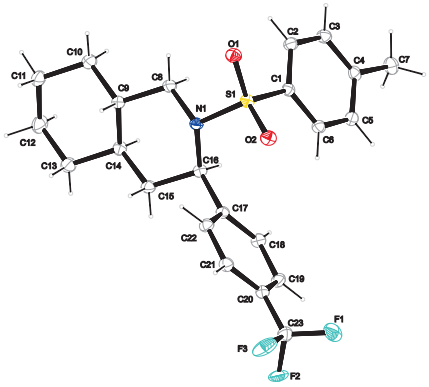
Crystal data

net formula	$C_{23}H_{26}N_2O_2$
M_r/g mol^{-1}	362.465
crystal size/mm	0.39 × 0.22 × 0.12
T/K	173(2)
radiation	MoKα
diffractometer	'Oxford XCalibur'
crystal system	monoclinic
space group	$P2_1/c$
a/Å	14.5271(9)
b/Å	11.6682(8)
c/Å	12.0141(8)
α/°	90
β/°	98.276(7)
γ/°	90
V/Å^3	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
R_{int}	0.0314
mean σ(I)/I	0.0756
θ range	4.23–26.32
observed refls.	2310
x, y (weighting scheme)	0.0279, 0
hydrogen refinement	constr
refls in refinement	4068
parameters	247
restraints	0
$R(F_{obs})$	0.0352
$R_w(F^2)$	0.0680
S	0.806
shift/error$_{max}$	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 (121na)





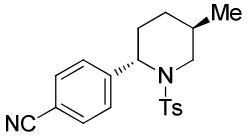
Crystal data

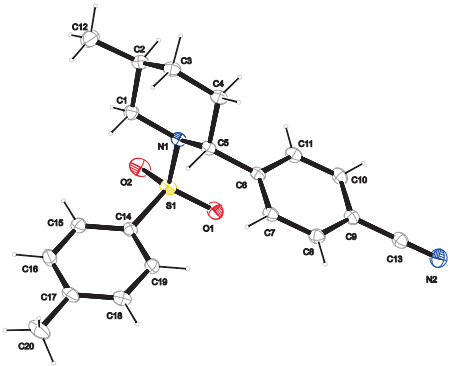
net formula	$C_{23}H_{26}F_3NO_2S$
M_r/g mol^{-1}	437.529
crystal size/mm	0.52 × 0.05 × 0.02
T/K	173(2)
radiation	MoKα
diffractometer	'KappaCCD'

crystal system	monoclinic
space group	*C*2/*c*
a/Å	31.5413(5)
b/Å	5.49050(10)
c/Å	25.8592(4)
α/°	90
β/°	110.7934(8)
γ/°	90
V/Å^3	4186.55(12)
Z	8
calc. density/g cm^{-3}	1.38831(4)
μ/mm^{-1}	0.201
absorption correction	none
refls. measured	12910
R_{int}	0.0338
mean σ(*I*)/*I*	0.0306
θ 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
$R(F_{obs})$	0.0383
$R_w(F^2)$	0.0938
S	1.088
shift/error$_{max}$	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-(*trans*-5-Methyl-1-tosylpiperidin-2-yl)benzonitrile (121qa)



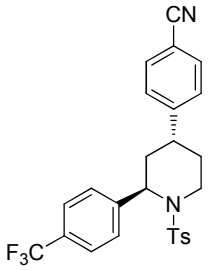


Crystal data

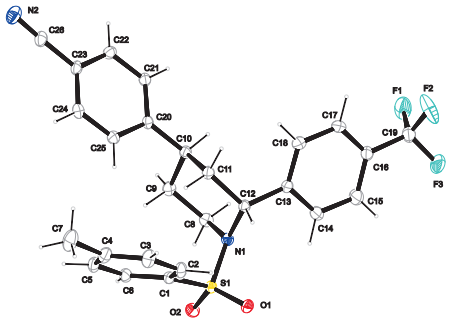
net formula	$C_{20}H_{22}N_2O_2S$
M_r/g mol^{-1}	354.467
crystal size/mm	0.40 × 0.08 × 0.05
T/K	173(2)
radiation	MoKα
diffractometer	'Oxford XCalibur'
crystal system	triclinic
space group	*P*1bar
a/Å	5.4884(2)
b/Å	11.8978(8)
c/Å	14.2002(7)
α/°	77.357(5)
β/°	86.323(4)
γ/°	87.652(4)
V/Å^3	902.58(8)
Z	2
calc. density/g cm^{-3}	1.30429(12)
μ/mm^{-1}	0.195
absorption correction	'multi-scan'
transmission factor range	0.98356–1.00000
refls. measured	6364
R_{int}	0.0211
mean σ(I)/I	0.0554
θ range	4.36–26.34
observed refls.	2403
x, y (weighting scheme)	0.0431, 0
hydrogen refinement	constr

refls in refinement	3645
parameters	228
restraints	0
$R(F_{obs})$	0.0371
$R_w(F^2)$	0.0847
S	0.886
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.209
min electron density/e Å^{-3}	−0.269

4-(*trans*-1-Tosyl-2-(4-(trifluoromethyl)phenyl)piperidin-4-yl)benzonitrile (124aa)



(prepared from Boc-protected piperidine via deprotection and tosylation)

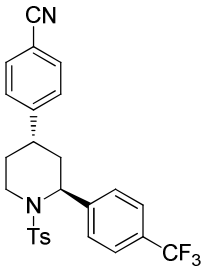


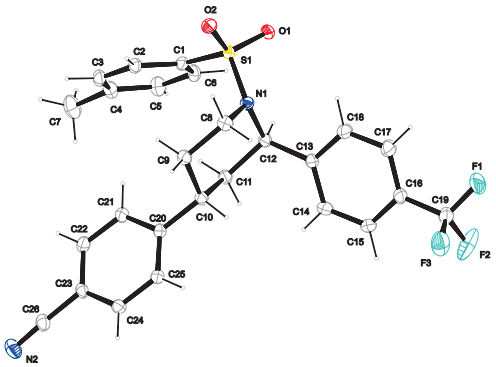
Crystal data

net formula	$C_{26}H_{23}F_3N_2O_2S$
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	14.5297(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
$R_w(F^2)$	0.1096
S	1.009
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.298
min electron density/e Å^{-3}	−0.337

4-(*trans*-1-Tosyl-2-(4-(trifluoromethyl)phenyl)piperidin-4-yl)benzonitrile (124c)



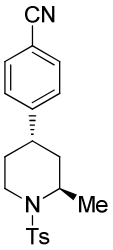


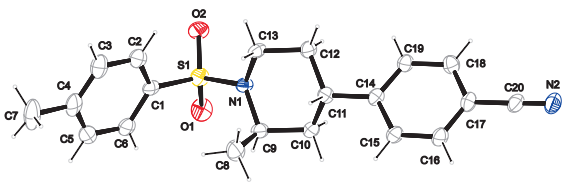
Crystal data

net formula	$C_{26}H_{23}F_3N_2O_2S$
M_r/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/Å^3	4635.3(3)
Z	8
calc. density/g cm^{-3}	1.38865(9)
μ/mm^{-1}	0.191
absorption correction	none
refls. measured	10097
R_{int}	0.0369
mean σ(*I*)/*I*	0.0542
θ range	3.15–27.49
observed refls.	3352
x, *y* (weighting scheme)	0.0577, 3.2402
hydrogen refinement	constr
refls in refinement	5236
parameters	308
restraints	0
$R(F_{obs})$	0.0484
$R_w(F^2)$	0.1319
S	1.037
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.361
min electron density/e Å^{-3}	−0.378

4-(*trans*-2-methyl-1-tosylpiperidin-4-yl)benzonitrile (124e)





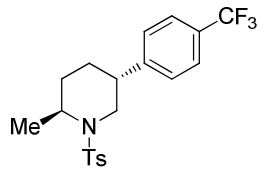
Crystal data

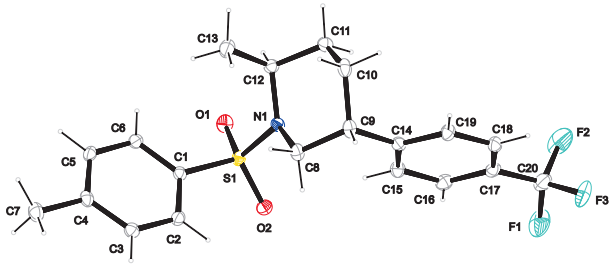
net formula	$C_{20}H_{22}N_2O_2S$
M_r/g mol^{-1}	354.467
crystal size/mm	0.22 × 0.16 × 0.06

T/K	173(2)
radiation	MoKα
diffractometer	'Oxford XCalibur'
crystal system	triclinic
space group	*P*1bar
a/Å	7.4047(6)
b/Å	9.5212(9)
c/Å	13.7988(11)
α/°	88.074(7)
β/°	76.203(7)
γ/°	87.599(7)
V/Å^3	943.66(14)
Z	2
calc. density/g cm^{-3}	1.24752(19)
μ/mm^{-1}	0.186
absorption correction	'multi-scan'
transmission factor range	0.82353–1.00000
refls. measured	4869
R_{int}	0.0434
mean σ(I)/I	0.1372
θ range	4.29–23.29
observed refls.	1212
x, y (weighting scheme)	0.0470, 0
hydrogen refinement	constr
refls in refinement	2652
parameters	228
restraints	0
$R(F_{obs})$	0.0539
$R_w(F^2)$	0.1174
S	0.831
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.205
min electron density/e Å^{-3}	−0.200

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 (128ca)





Crystal data

net formula	$C_{20}H_{22}F_3NO_2S$
M_r/g mol^{-1}	397.455
crystal size/mm	0.37 × 0.23 × 0.17
T/K	243(2)
radiation	MoKα
diffractometer	'Oxford XCalibur'
crystal system	monoclinic
space group	$P2_1/n$
a/Å	10.1552(5)
b/Å	11.7039(5)
c/Å	16.2918(8)
α/°	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
refls in refinement	3883
parameters	273
restraints	10

$R(F_{obs})$	0.0368
$R_w(F^2)$	0.0840
S	0.881
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.284
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. Ligand Screening and NMR Experiments for the Pd-Catalyzed Cross-Coupling of Substituted Cycloalkylzinc Reagents with Aryl Halides

Catalyst screening for the cross-coupling reaction:

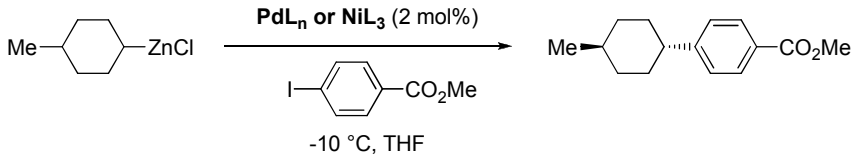


Table A. Screening for the most diastereoselective cross-coupling catalyst.

Entry	Source of transition-metal	Ligand	Ratio metal:ligand	time	d.r.
1	$Pd(PPh_3)_4$	PPh_3	1:4	48 h	92:8
2	$PdCl_2$	P(*o*-tolyl)$_3$	1:2	15 h	90:10
3	$Pd(dba)_2$	SPhos	1:1	15 h	87:13
4	PEPPSI-IPr[b]	IPr[b]	1:1	15 h	90:10
5	**$PdCl_2$**	**TMPP[c]**	**1:2**	**15 h**	**95:5**
6	$PdCl_2$	*t*Bu$_3$P	1:2	15 h	80:20
7	$Ni(acac)_2$	tris(2,4-di-tert-butylphenyl) phosphite	1:3	15 h	79:21

[a]Determined by capillary GC analysis.

[b]PEPPSI: Pyridine, Enhanced, Precatalyst, Preparation, Stabilization and Initiation.[155] IPr: 1,3-bis-{2,6-diisopropylphenyl}imidazolylidene.

[c]TMPP: tris(2,4,6-trimethoxyphenyl)phosphine[83]

NMR studies:

All NMR spectra were recorded on a *Bruker Avance 600* spectrometer equipped with a 5 mm broadband triple resonance Z-gradient probe. Temperature stability was controlled by a *Bruker BVTE 3900* temperature unit. NMR data were processed and evaluated with *TOPSPIN 2.1*. The temperature was regulated via a *BVTE 3900*-unit. ^{1}H-Spectra were calibrated using TMS as standard. ^{31}P-Spectra were calibrated using an external H_3PO_4-standard.

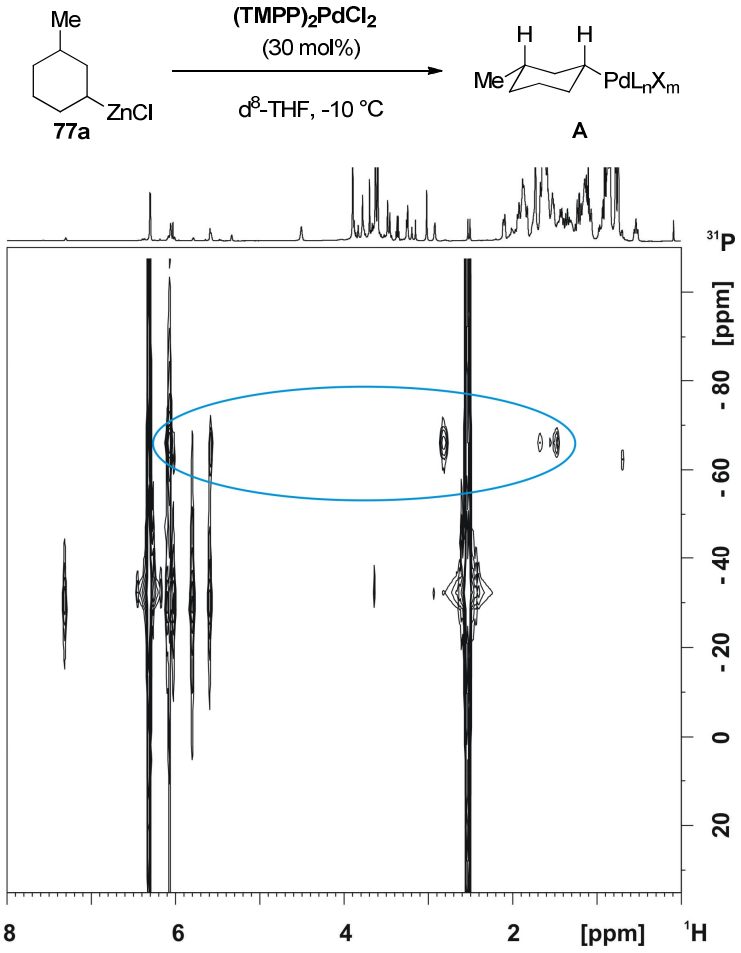


Figure 1: ^{1}H^{31}P-HMBC of **10a** and TMPP (3:1) in d_8-THF at 263 K.

[155] M. G. Organ, S. Avola, I. Dubovyk, N. Hadei, E. A. B. Kantchev, C. J. O'Brien, C. Valente, *Chem. Eur. J.* **2006**, *12*, 4749.

Figure 1 shows a section from the $^{1}H^{31}P$-HMBC. As highlighted by the labelling, only one single species in the reaction mixture displays ^{1}H-^{31}P couplings with protons in the aromatic and cyclohexyl region. Thus, it can be unambiguously shown, that only one single intermediate which contains both the P-ligand and the cyclohexyl moiety is formed.

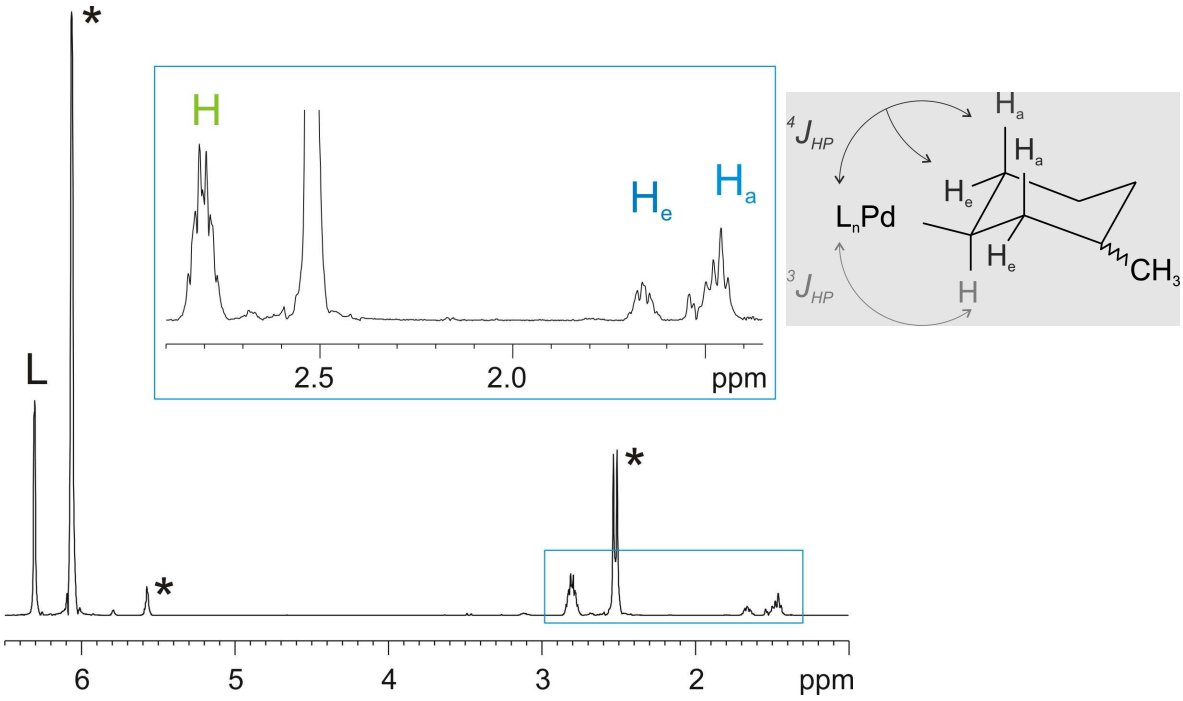
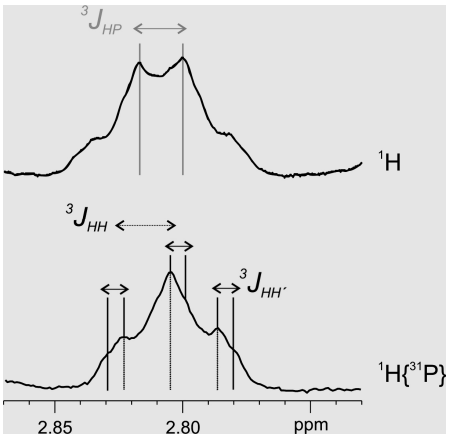


Figure 2: 1D-section from the $^{1}H^{31}P$-HMBC (see **Figure 1**). Signals labelled with * can be ascribed to T1 noise.

Figure 2 shows a 1D-section of the $^{1}H^{31}P$-HMBC (**Figure 1**) in the region of the intermediate. The aromatic signal δ = 6.3 ppm can be ascribed to the P-ligand, the signals δ = 2.8 ppm as well as in the region from δ = 1.4 ppm to 1.7 ppm can be ascribed to the cyclohexyl moiety. Since in this HMBC the signal intensity is proportional to J_{HX} under certain conditions, the cyclohexyl signals can be differentiated ($^{4}J_{HX} < {}^{3}J_{HX}$). The most intense of the cyclohexyl signals at δ = 2.8 ppm represents the methine signal showing the strongest coupling with the P of the TMPP-ligand ($^{3}J_{HP}$). The neighboring methylene protons show signals in the region from δ = 1.4 ppm to 1.7

ppm with lower intensities ($^4J_{HP}$). Due to the Karplus equation[156], the axial and equatorial protons can be distinguished.



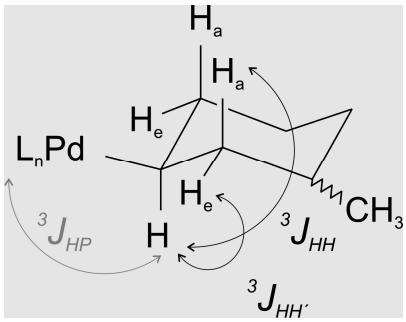


Figure 3: Sections from the ^{1}H-NMR spectra coupled to ^{31}P (above) and decoupled (below) at 263 K in d^8-THF in the region of the methine signal.

Figure 3 shows two ^{1}H-NMR spectra in the region of the methine signal, coupled to ^{31}P (above) and decoupled from ^{31}P (below). By comparing the two spectra the $^3J_{HP}$ coupling constant can be determined. The pseudo-triplet in the decoupled spectrum displays at a closer look two different coupling constants. The larger coupling is ca. 11 Hz and can be ascribed to an axial-axial $^3J_{HH}$-coupling.[156] Thus, one can conclude that the methine proton must occupy the axial position. If the methine proton occupied an equatorial position, only equatorial-axial or equatorial-equatorial couplings would occur, whose coupling constants are around 2-5 Hz.

[156] M. Hesse, H. Meier, B. Zeeh, *Spektroskopische Methoden in der organischen Chemie*, Thieme, **2005**.

3. Curriculum Vitae

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ADDRESS	Laubenweg. 9
	82061 Neuried
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	0049 89 218077691 (Lab)
EMAIL	Tobias.Thaler@cup.uni-muenchen.de
DATE OF BIRTH	1st September 1981
NATIONALITY	German

Education

April 2007 – Jan 2011	PhD student in the fields of organometallic chemistry and asymmetric synthesis under the supervision of Prof. Dr. Paul Knochel at the Ludwig-Maximilians-Universität (LMU Munich)
Feb. 2005 – Feb 2007	Master of Science (MSc) program in chemistry at the Ludwig-Maximilians-Universität (LMU Munich). Main subjects: organic chemistry and physical chemistry. Minor subject: biochemistry. Graduation as Master of Science (MSc) in chemistry; GPA (scale 1–5, 1.0–1.15 being excellent): 1.08 (excellent)
Aug. 2006 – Feb. 2007	Master's thesis in the field of organic chemistry under the supervision of Prof. Dr. Paul Knochel: "A Novel Approach to the Synthesis of Chiral QUINAP"; Grade: 1.0 (excellent)
Aug. – Dec. 2005	Research visit at Lundbeck A/S in Valby, Copenhagen (Denmark)

Oct. 2001 – Oct.2004	Bachelor of Science (BSc) program in chemistry and biochemistry at the Ludwig-Maximilians-Universität (LMU Munich)
	Graduation as Bachelor of Science (BSc) in chemistry and biochemistry; GPA (scale 1–5, 1.0–1.15 being excellent): 1.60 (good)
Aug. – Oct. 2004	Bachelor's thesis in the field of organic chemistry under the supervision of Prof. Dr. Paul Knochel: "Enantioselective Reformatsky Reaction"; Grade: 1.0 (excellent)
1992-2001	Abitur (diploma from German secondary school qualifying for university admission) Gymnasium Fuerstenried-West (Grammar School), Munich Main subjects: English, French; GPA (1-6, 1.0–1.5 being very good): 1.10 (very good) Best of class 2001 (at Gymnasium Fuerstenried-West)

Additional Programs and Courses

December 2010	Recipient of the "Römer-Stipendium" (fellowship awarded at the LMU) for outstanding achievements during the PhD thesis
March 2010	Participation at the international symposium of the SFB 749 at Kloster Irsee and presentation entitled "Stereocontrol with Substituted Cycloalkylzinc Reagents"
May 2009	Plant tour at the BASF AG (Ludwigshafen) and presentation entitled "Diastereoselective Cross-Coupling with Substituted Cycloalkylzinc Reagents"
March 2009	Participation at the symposium of the SFB 749 at

	Wildbad Kreuth and presentation entitled "Organometallics – Synthesis, Selectivity and Dynamics"
March 2008	Participation at CarLa Winter School organised by BASF and CarLa Heidelberg; selected for poster presentation ("A Novel Synthetic Approach Towards Chiral QUINAP via Diastereomeric Sulfoxide Intermediates")
	Participation at the symposium of the SFB 749 at Wildbad Kreuth.
Dec. 2007	Recipient of the "Römer-Stipendium" (fellowship awarded at the LMU) for an excellent master's thesis
Aug. 2007	Participation at Roche Continents Youth! Arts! Science!
July – Aug. 2000	Participation at the "Deutsche Schüler Akademie" (summer academy for specially talented students) in Roßleben; Course: Spanish language and culture
July –Sep. 1999	Participation at a student exchange with Denmark School in Jerusalem (Israel)
April – July 1998	Participation at a student exchange with Lycée Fourcade in Gardanne (France)
July – Sep. 1997	Participation at a student exchange with George Watson's College in Edinburgh (UK)

Additional Activities

Jan. 07 – December 2010	Contributor to the *Synfacts* magazine

May 2007 – December 2010	Assisting Professor Knochel with lectures and training courses in organometallic chemistry and stereoselective synthesis
Oct. 2005 – Feb. 2007	Tutor in physical chemistry at the LMU
April – July 2005	Tutor in organic chemistry at the LMU

Additional Skills

Languages	German: native speaker English: fluent, written and spoken French: fluent; written and spoken Italian: everyday competence Russian: everyday competence Danish: working knowledge Spanish: basic knowledge

Leisure Interests

Travelling, cultures, philosophical and religious books, saxophone, music of the 60s and 70s, soccer

Munich, 1st January 2011

Publications

1. Ralf J. Kloetzing, Tobias Thaler, Paul Knochel, "An Improved Asymmetric Reformatsky Reaction Mediated by (–)-*N*,*N*-Dimethylaminoisoborneol", *Org. Lett.* **2006**, *8*, 1125-1128.

2. Tobias Thaler, Florian Geittner, Paul Knochel, "A Novel Synthetic Approach towards Chiral QUINAP via Diastereomeric Sulfoxide Intermediates", *Synlett* **2007**, 2655-2658.

3. Tobias Thaler, Paul Knochel, "Copper-Catalyzed Asymmetric Michael Addition of Magnesium, Zinc, and Aluminum Organometallic Reagents: Efficient Synthesis of Chiral Molecules", *Angew. Chem. Int. Ed.* **2009**, *48*, 645-648.

4. Tobias Thaler, Hongjun Ren, Nina Gommermann, Giuliano C. Clososki, Christoph J. Rohbogner, Stefan H. Wunderlich, Paul Knochel, "New Catalytic Cu-, Pd- and Stoichiometric Mg-, Zn-Mediated Bond Activations" in *Activating Unreactive Substrates* (Eds.: C. Bolm, F. E. Hahn), Wiley-VCH, Weinheim **2009**, 359-377.

5. Tobias Thaler, Benjamin Haag, Andrei Gavryushin, Katrin Schober, Evelyn Hartmann, Ruth M. Gschwind, Hendrik Zipse, Peter Mayer, Paul Knochel, "Highly Diastereoselective Csp^3-Csp^2 Negishi Cross-Coupling with 1,2-, 1,3- and 1,4-Substituted Cycloalkylzinc Compounds", *Nature Chem.* **2010**, *2*, 125-130.

6. Paul Knochel, Tobias Thaler, Coura Diene, "Pd-, Ni-, Fe-, and Co-Catalyzed Cross-Couplings Using Functionalized Zn-, Mg-, Fe-, and In-Organometallics", *Isr. J. Chem.* **2010**, *50*, 547-557.

7. Tobias Thaler, Li-Na Guo, Peter Mayer, Paul Knochel, "Highly Diastereoselective Csp^3-Csp Cross-Couplings between 1,3- and 1,4-Substituted Cyclohexylzinc Reagents and Bromoalkynes via Remote Stereocontrol", *Angew. Chem. Int. Ed.* **2011**, *50*, 2174-2177.

8. Tobias Thaler, Andreas K. Steib, Kimihiro Komeyama, Peter Mayer, Paul Knochel, "Highly Diastereoselective Fe-Mediated Csp^2-Csp^3 Cross-Couplings between Aryl Grignard Reagents and Cyclic Iodohydrine Derivatives", *Angew. Chem. Int. Ed.* **2011**, *50*, *in press*.

9. Stephanie Seel, Tobias Thaler, Keishi Takatsu, Cong Zhang, Hendrik Zipse, Bernd F. Straub, Paul Knochel, "Highly Diastereoselective Arylations of Substituted Piperidines via Pd-Catalyzed Csp^3-Csp^2 Cross-Couplings", *manuscript submitted*.

10. Tobias Thaler, Li-Na Guo, M. Raducan, Andreas K. Steib, Konstantin Karaghiosoff, Paul Knochel, "Sulfoxide-Alkene Hybrids: A New Class of Chiral Ligands for the Hayashi-Miyaura Reaction", *manuscript submitted*.