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Copper(I)-mediated *anti*-S_N2' Allylic Substitution Reactions with Diorganozinc Reagents

von

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Erklärung

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Ehrenwörtliche Versicherung

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1. H. Leuser, S. Perrone, F. Liron, F. F. Kneisel, P. Knochel, "Highly Enantioselective Preparation of Alcohols and Amines Attached to a Tertiary Center *via* Copper-mediated Diastereoselective Allylic S_N2'-Substitutions", *Angew. Chem. Int. Ed.* **2005**, *44*, 4627-4631; *Angew. Chem.* **2005**, *117*, 4703-4707.

2. S. Perrone, P. Knochel, "Highly Diastereoselective Preparation of (*E*)-Alkenylsilanes bearing an α-Chiral Center", *manuscript in preparation.*

3. S. Perrone, A. Metzger, P. Knochel, "Chiral Cyanohydrins as Efficient Building Blocks for Copper(I)-mediated *anti*-S_N2' Allylic Substitutions", *manuscript in preparation.*

“There is a center of excellence, it’s in yourself.”

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Abbreviations

[α]	specific rotation [expressed without units; the actual units, deg mL/(g dm), are understood]
Ac	acetyl
acac	acetylacetone
AcOH	acetic acid
anhyd	anhydrous
Ar	aryl
Bn	benzyl
Boc	*tert*-butoxycarbonyl
bp	boiling point
br	broad
Bu	butyl
n-Bu	*n*-butyl
s-Bu	*sec*-butyl
t-Bu	*tert*-butyl
calcd.	calculated
CH_2Cl_2	dichloromethane
concd	concentrated
δ	chemical shift in parts per million
d	doublet
dba	*trans*,*trans*-dibenzylideneacetone
DIBALH	diisobutylaluminium hydride
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
dppf	1,1'-bisdiphenylphosphin-ferrocene
dr	diastereomeric ratio
ee	enantiomeric excess
equiv.	equivalent
EI	electron-impact
Et	ethyl
FAB	fast-atom bombardment
FG	functional group
GC	gas chromatography
h	hour
Hex	hexyl
c-Hex	cyclohexyl
HMPT	hexamethylphosphorous triamide
HRMS	high resolution mass spectroscopy
IR	infra-red
J	coupling constant (NMR)
M	molarity
m	meta
m	multiplet
m-CPBA	*m*-chloroperoxybenzoic acid
Me	methyl
Met	metal
min	minute
mol.	mole
mp.	melting point
MS	mass spectroscopy
NBS	*N*-bromosuccinimide
NMR	nuclear magnetic resonance
Nu	nucleophile
o	ortho
p	para
Pent	pentyl
PG	protecting group
Ph	phenyl
Piv	pivaloyl
i-Pr	iso-propyl
q	quartet
rt	room temperature
s	singlet
t	triplet
TBAF	tetrabutylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
TES	triethylsilyl
Tf	triflate
TFA	trifluoroacetic acid
tfp	*tri*-(2-furyl)phosphine
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	*N*,*N*,*N'*,*N'*-tetramethylethylenediamine
TMS	trimethylsilyl
TMP	2,2,6,6-tetramethylpiperidyl
TP	typical procedure
Ts	4-toluenesulfonyl

Theoretical Part

1 Introduction

1.1 Overview

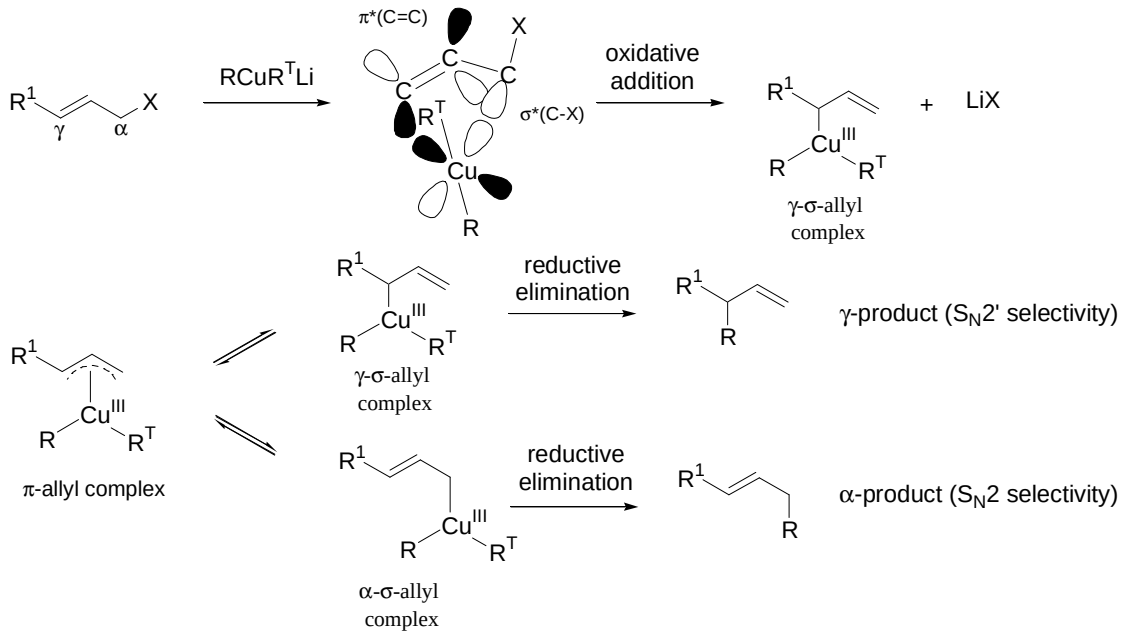
Chemistry distinguishes itself from other disciplines in approaching scientific questions by its ability to design structures for functions unfettered by what is available. A key enabling aspect is the effectiveness of synthetic methodology to solve problems of selectivity, a feature that is particularly noted when dealing with biological problem.[1] Providing an efficient synthesis to complex molecules requires minimizing the number of steps, any side reactions, and purification protocols. Among the most challenging issues is obtaining enantiomerically pure compounds for which asymmetric catalysis constitutes a core competency.[2]

1.1.1 Copper-catalyzed asymmetric allylic substitutions

While the most widely used asymmetric reactions involve hydrogenations,[3] epoxidations[4] or dihydroxylations,[5] these reactions form only one type of bond, either C-H or C-O bond, and usually involve one type of enantiodiscrimination, differentiating enantiotopic faces of a prochiral olefin or carbonyl group. Especially useful are stereoselective synthetic methods involving the formation of a new C-C bond. Among various substitution reactions, palladium-catalyzed allylic substitutions[6] have been used with considerable success.[7] However, the narrow range of nucleophiles (only stabilized nucleophiles can be used) as well as the low regioselectivity observed in non-symmetrical allylic systems have hampered the

[1] (a) R. Noyori, "*Asymmetric Catalysis in Organic Synthesis*", Wiley, New York, **1994**; (b) G.-Q. Lin, Y.-M. Li, A. S. C. Chan, "*Principles and Applications of Asymmetric Synthesis*", Wiley-Interscience, New York, **2001**; (c) R. E. Gawley, J. Aubé, "*Principles of Asymmetric Synthesis*", Pergamon, Oxford, **1996**.
[2] B. M. Trost, *J. Org. Chem.* **2004**, *69*, 5813.
[3] T. Ohkuma, M. Kitamura, R. Noyori, "*Asymmetric Hydrogenation*" in "*Catalytic Asymmetric Synthesis*", 2nd Edition, Wiley-VCH, New York, **2000**, 1.
[4] (a) Q.-H. Xia, H.-Q. Ge, C.-P. Ye, Z.-M. Liu, K.-X. Su, *Chem. Rev.* **2005**, *105*, 1603; (b) Y. Shi, *Acc. Chem. Res.* **2004**, *37*, 488.
[5] H. C. Kolb, K. B. Sharpless, "*Asymmetric Dihydroxylation*" in "*Transition Metals for Organic Synthesis*", 2nd Edition, Wiley-VCH, Weinheim, **2004**, *2*, 275.
[6] For recent reviews on asymmetric allylic alkylation with various metals, see: (a) H. Miyabe, Y. Takemoto, *Synlett* **2005**, 1641; (b) B. M. Trost, M. L. Crawley, *Chem. Rev.* **2003**, *103*, 2921; (c) R. Takeuchi, *Synlett* **2002**, 1954.
[7] (a) B. M. Trost, D. L. Van Vranken, *Chem. Rev.* **1996**, *96*, 395; (b) T. Hayashi, M. Kawatsura, Y. Uozumi, *J. Chem. Soc., Chem. Commun.* **1997**, 561; (c) J. P. Janssen, G. Helmchen, *Tetrahedron Lett.* **1997**, *38*, 8025; (d) R. Pretôt, A. Pfaltz, *Angew. Chem. Int. Ed.* **1998**, *37*, 323; (e) B. M. Trost, I. Hachiya, *J. Am. Chem. Soc.* **1998**, *120*, 1104. (f) G. Helmchen, A. Pfaltz, *Acc. Chem. Res.* **2000**, *33*, 336.

general use of this reaction. Alternatively, copper(I)-catalyzed allylic substitutions[8] do not suffer from these limitations[9] and allow the use of hard nucleophiles including Grignard and organozinc reagents, thus being complementary to palladium catalysis. Moreover, copper-catalyzed substitution reactions usually proceed with high S_N2' regioselectivity both in cyclic and acyclic systems, which may allow the generation of stereogenic centers. This control can easily be understood through the usually accepted reaction mechanism[10] pictured in Scheme 1.



Scheme 1. Mechanism of the copper-mediated allylic substitution.

Initial formation of a π-complex is followed by an oxidative addition on the γ carbon. The resulting γ σ-allylcopper(III) complex may suffer a rapid reductive elimination to afford the γ-product. If, alternatively, this step is not fast enough, this γ σ-allylcopper(III) complex can undergo a σ–π–σ isomerization into an α σ-allylcopper(III) complex, through a π-allylcopper(III) complex. Reductive elimination through the less hindered α σ-allylcopper(III) complex will afford the α-product. The control of the regioselectivity depends on the non-

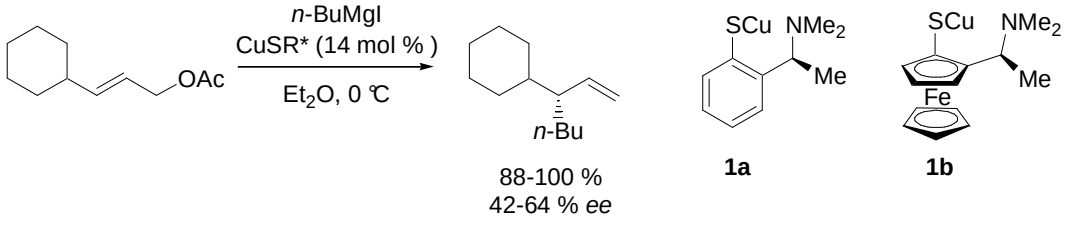
[8] For recent reviews on asymmetric Cu-catalyzed allylic alkylation, see: (a) A. Alexakis, C. Malan, L. Lea, K. Tissot-Croset, D. Polet, C. Falciola, *Chimia* **2006**, *60*, 124; (b) H. Yorimitsu, K. Oshima, *Angew. Chem. Int. Ed.* **2005**, *44*, 4435. (c) A. Kar, N. P. Argade, *Synthesis* **2005**, 2995.

[9] (a) B. H. Lipshutz, S. Sengupta, *Org. React.* **1992**, *41*, 135; (b) R. J. Anderson, C. A. Henrick, J. B. Siddall, R. Zurflüh, *J. Am. Chem. Soc.* **1972**, *94*, 5379; (c) T. L. Underiner, H. L. Goering, *J. Org. Chem.* **1988**, *53*, 1140; (d) T. L. Underiner, H. L. Goering, *J. Org. Chem.* **1991**, *56*, 2563; (e) N. Krause, A. Gerold, *Angew. Chem. Int. Ed.* **1997**, *36*, 186.

[10] (a) A. S. E. Karlström, J. E. Bäckvall, *Chem. Eur. J.* **2001**, *7*, 1981; (b) E. J. Corey, N. W. Boaz, *Tetrahedron Lett.* **1984**, *25*, 3063; (c) M. Yamanaka, S. Kato, E. Nakamura, *J. Am. Chem. Soc.* **2004**, *126*, 6287.

transferable group R^T. A halide or cyanide group usually allows high γ-selectivity, whereas an alkyl group (as in R_2CuLi) allows an equilibration, thus favoring the substitution at the least sterically hindered carbon.[11]

With simple substrates, such as the one shown in Scheme 1, the γ-allylation generates a new stereogenic carbon. Therefore, it was tempting to control the reaction to make it enantioselective.[12] *Bäckvall* and *van Koten* were the first to report an asymmetric allylic substitution catalyzed by a chiral copper complex in 1995.[13] Thus, the chiral arenethiolatocopper(I) **1a** catalyzed the asymmetric allylic substitution of allylic acetate with butylmagnesium iodide with a moderate enantioselectivity of 42 % later improved to 64 % with the new catalyst **1b**[14] (Scheme 2). The enantiomeric excess of the product heavily depended on many factors including the coordinating ability of the leaving group in allylic substrates, the temperature, and the method of substrate addition and the Grignard reagent. Their observation underscored the difficulty in developing a reaction proceeding with high selectivity.



Scheme 2. First copper-catalyzed asymmetric allylic substitution of *Bäckvall*.[13]

A breakthrough in copper-catalyzed asymmetric allylic substitution came in 1999, when *Dübner* and *Knochel* focused on dialkylzincs as an alkyl source.[15] To attain a high enantioselectivity, the system required a high ratio of ligand to copper, very low temperatures, and the presence of bulky alkyl groups on zinc. For instance, the reaction of cinnamyl chloride with dineopentylzinc using a catalysis by $CuBr{\cdot}Me_2S$/**3a** (1:10) at −90 °C afforded

[11] (a) J. Levisalles, M. Rudler-Chauvin, H. Rudler, *J. Organomet. Chem.* **1977**, *136*, 103; (b) J. P. Marino, D. M. Floyd, *Tetrahedron Lett.* **1979**, *20*, 675; (c) C. C. Tseng, S. D. Paisley, H. L. Goering, *J. Org. Chem.* **1986**, *51*, 2884 and 2892; (d) J. E. Bäckvall, M. Sellén, B. Grant, *J. Am. Chem. Soc.* **1990**, *112*, 6615; (e) J. E. Bäckvall, E. S. M. Persson, A. Bombrun, *J. Org. Chem.* **1994**, *59*, 4126.

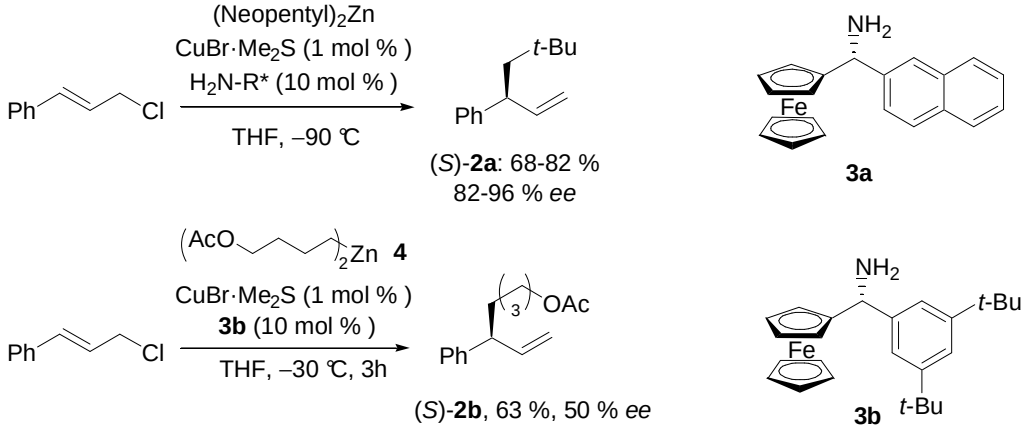
[12] A. S. E. Karlström, J. E. Bäckvall, "*Modern Organocopper Chemistry*", Ed. N. Krause, Wiley-VCH, Weinheim, **2001**, 259-288.

[13] M. van Klaveren, E. S. M. Persson, A. del Villar, D. M. Grove, J. E. Bäckvall, G. van Koten, *Tetrahedron Lett.* **1995**, *36*, 3059.

[14] (a) A. S. E. Karlström, F. F. Huerta, G. J. Meuzelaar, J. E. Bäckvall, *Synlett* **2001**, 923; (b) G. J. Meuzelaar, A. S. E. Karlström, M. van Klaveren, E. S. M. Persson, A. del Villar, J. E. Bäckvall, *Tetrahedron* **2000**, *56*, 2895.

[15] (a) F. Dübner, P. Knochel, *Angew. Chem. Int. Ed.* **1999**, *38*, 379; (b) F. Dübner, P. Knochel, *Tetrahedron Lett.* **2000**, *41*, 9233.

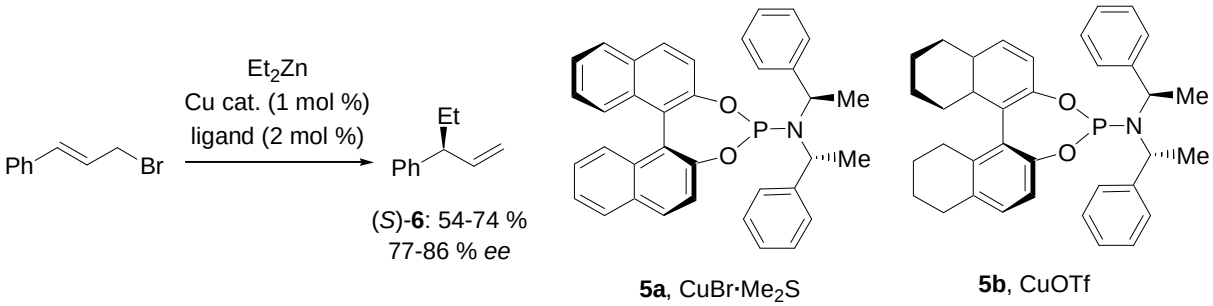
the chiral alkene (*S*)-**2a** with 82 % *ee* (γ/α 95/5, 68 %, Scheme 3). No enantioselectivity was observed when an alkylzinc chloride (RZnCl) was used instead of the corresponding dialkylzinc (R_2Zn).[16] Later, ligand **3b** proved to be more effective in this reaction and **2a** was obtained in 96 % *ee* (γ/α 98/2, 82 %). However, the dineopentylzinc reagent still gave the best results. The use of linear dialkylzincs such as dipentylzinc and functionalized dialkylzinc like **4** afforded the corresponding products with approximately 44–65 % *ee*. Despite the necessity of bulky alkyl groups, the work of *Dübner* and *Knochel* contributed to the acceleration of the development of copper-catalyzed asymmetric allylic substitution reactions.



Scheme 3. Copper-catalyzed asymmetric allylic substitutions by *Dübner* and *Knochel*.[15]

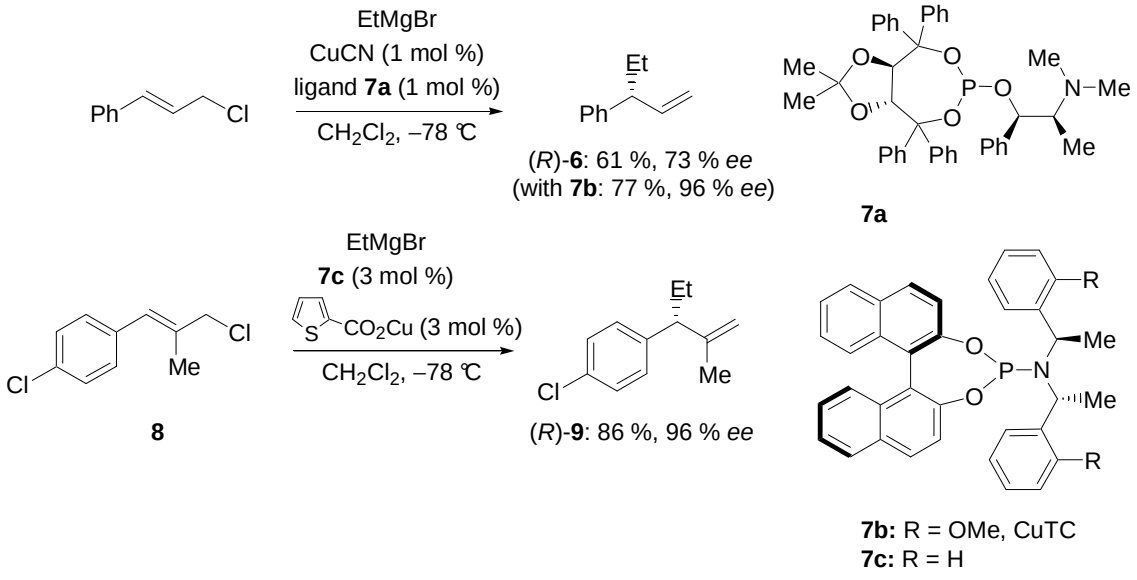
Highly enantioselective allylic substitutions with linear alkylzinc reagents remained a major challenge, but *Feringa* proposed the use of binaphthol-base phosphoramidite ligands as a chiral ligand (Scheme 4).[17] Cinnamyl bromide was the best substrate, the corresponding chloride being too sluggish. The structure of the first ligand **5a** was later modified to **5b** (2 % loading) to improve the results. The reaction was run in THF, with CuOTf (1 %), and afforded the olefin (*S*)-**6** in 82 % *ee* (γ/α 98/2, 82 % yield). Better *ee*s were obtained on cinnamyl-type substrates bearing electron-withdrawing groups but in all cases, the regioselectivity remained high.

[16] P. J. Goldsmith, S. J. Teat, S. Woodward, *Angew. Chem. Int. Ed.* **2005**, *44*, 2235.
[17] (a) H. Malda, A. W. van Zijl, L. A. Arnold, B. L. Feringa, *Org. Lett.* **2001**, *3*, 1169; (b) A. W. van Zijl, L. A. Arnold, A. J. Minnaard, B. L. Feringa, *Adv. Synth. & Catal.* **2004**, *346*, 413.



Scheme 4. Asymmetric allylic substitutions with phosphoramidite ligands by *Feringa*.[17]

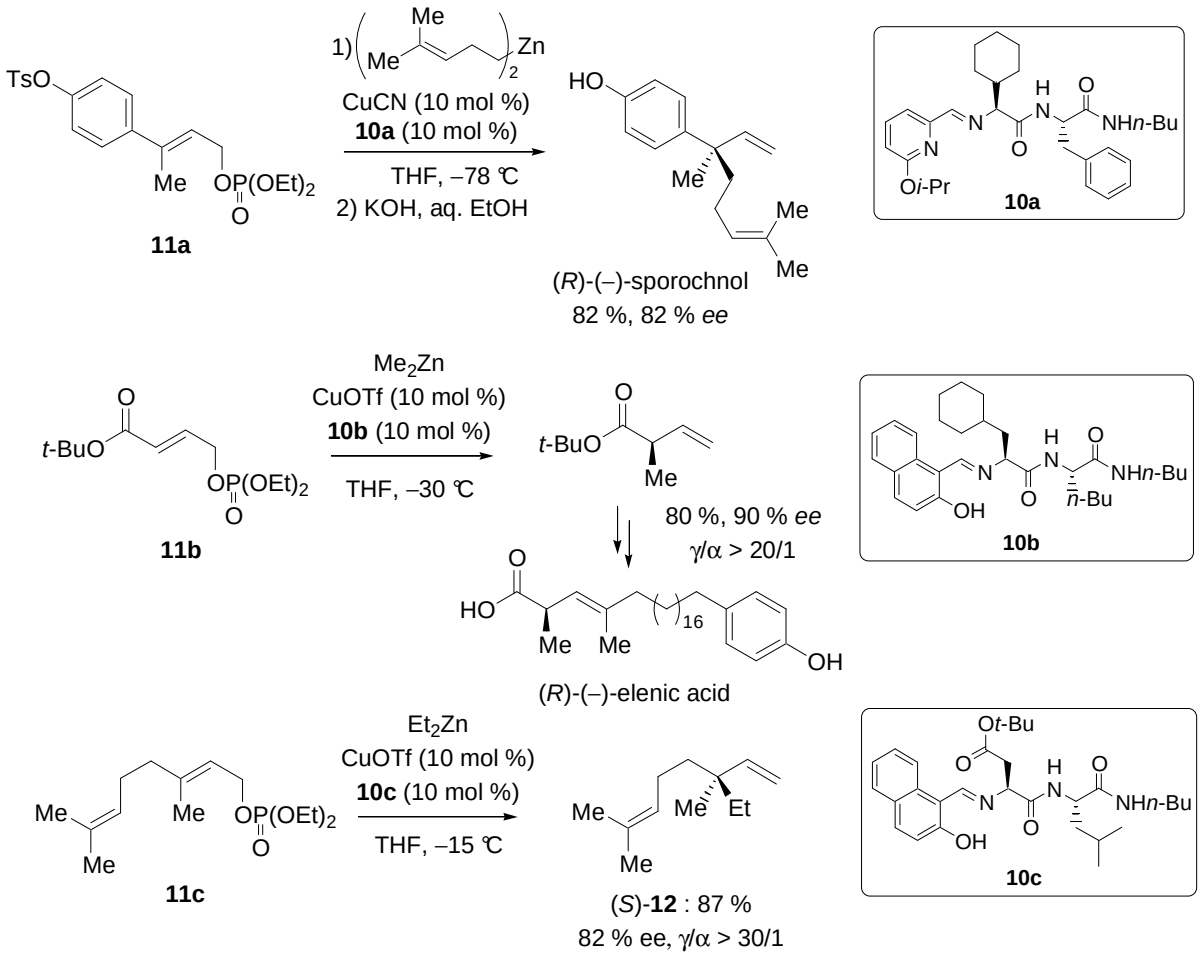
Independently, *Alexakis*[18] developed a system similar to that reported by *Feringa* for the reaction of Grignard reagents using the chiral phosphite ligand **7a** (Scheme 5). Recently, a highly effective phosphoramidite ligand **7b** was developed and provided good results, both in term of enantio- and regioselectivity (96 % *ee*, γ/α 90/10).[19] Furthermore, they showed that it was not only limited to disubstituted olefinic systems but it could be extended to more sterically hindered ones. [20] Indeed, β-disubstituted allylic chloride **8** reacted with ethylmagnesium bromide in the presence of copper(I) thiophene-2-carboxylate complex (3 mol %) and the ligand **7c** (3 mol %) affording (*R*)-**9** in excellent regioselectivity (γ/α 98/2) and with 96 % *ee* (Scheme 5).



Scheme 5. Asymmetric allylic substitutions using chiral phosphite ligands and Grignard reagents by *Alexakis*.[18-20]

[18] (a) A. Alexakis, C. Malan, L. Lea, C. Benhaim, X. Fournioux, *Synlett* **2001**, 927; (b) A. Alexakis, K. Croset, *Org. Lett.* **2002**, *4*, 4147.
[19] (a) K. Tissot-Croset, D. Polet, A. Alexakis, *Angew. Chem. Int. Ed.* **2004**, *43*, 2426; (b) K. Tissot-Croset, A. Alexakis, *Tetrahedron Lett.* **2004**, *45*, 7375.
[20] C. Falciola, K. Tissot-Croset, A. Alexakis, *Angew. Chem. Int. Ed.* **2006**, *45*, 5995.

Apart from phosphorus ligands, *Hoveyda* introduced the use of various peptide based chiral ligands.[21] By screening a library of modular ligands, efficient ligands could be synthesized. Dipeptide ligands such as **10** permitted an easy access to the asymmetric syntheses of compounds bearing a quaternary carbon atom and α-alkyl-β,γ-unsaturated esters starting from allylic phosphates such as **11a–11c** (Scheme 6)**.** The reactions were successfully applied to the syntheses of natural products such as (*R*)-(−)-sporochnol[21a] and the topoisomeras II inhibitor, (*R*)-(−)-elenic acid (Scheme 6).[21b]

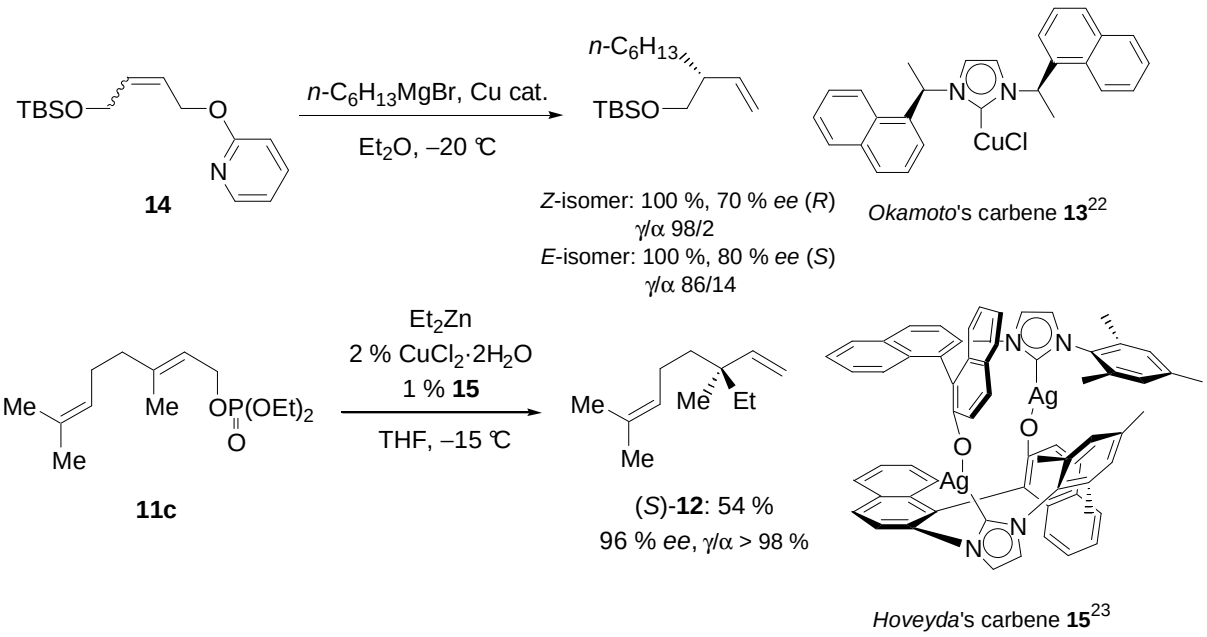


Scheme 6. Asymmetric allylic substitutions with oligopeptide ligands by *Hoveyda*.[21]

Carbene-copper complexes proved to be efficient ligands for the allylic substitution as shown recently by *Okamoto*.[22] The sterically demanding ligand **13** gave the highest *ee* values (Scheme 7). The 2-pyridyloxy group of **14** as well as the acetoxy group were good leaving groups for this type of allylic substitutions. Although a moderate level of enantioselectivity

[21] (a) C. A. Luchaco-Cullis, H. Mizutani, K. E. Murphy, A. H. Hoveyda, *Angew. Chem. Int. Ed.* **2001**, *40*, 1456; (b) K. E. Murphy, H. Hoveyda, *J. Am. Chem. Soc.* **2003**, *125*, 4690; (c) M. A. Kacprzynski, H. Hoveyda, *J. Am. Chem. Soc.* **2004**, *126*, 10676; (d) K. E. Murphy, H. Hoveyda, *Org. Lett.* **2005**, *7*, 1255.
[22] S. Tominaga, Y. Oi, T. Kato, D. K. An, S. Okamoto, *Tetrahedron Lett.* **2004**, *45*, 5585.

(up to 70 % *ee*) was observed in preliminary results, modular carbene ligands exhibited interesting properties. Indeed, *Hoveyda*[23] developed a new chiral bidentate carbene-based ligand and used it for the substitution reactions with allylic substrats (Scheme 7). Therefore, the chiral diene (*S*)-**12** bearing a quaternary center was obtained in 96 % *ee* (previously 82 % *ee*) when the allylic phosphate **11c** was reacted with diethylzinc in the presence of the dinuclear silver complex **15** and $CuCl_2 \cdot 2H_2O$ (air and moisture insensitive).



Scheme 7. Copper-carbene complexes for asymmetric allylic substitutions.

[23] A. O. Larsen, W. Leu, C. N. Oberhuber, J. E. Campbell, A. H. Hoveyda, *J. Am. Chem. Soc.* **2004**, *126*, 11130.

1.1.2 Transfer of chirality

The copper-catalyzed asymmetric allylic substitution is without any doubt a very powerful and versatile tool to build new stereogenic centers. When the chiral information is contained in the copper catalyst, the method suffers from generality since the chiral ligand-complex has to be optimized for each class of allylic substrates. On the other hand, when the chiral information is contained in the allylic electrophile,[24] the transfer of chirality has the advantage of being highly predictable. The diastereoselective synthesis in which a chiral allylic electrophile is used is more appealing and should be generally applicable since allylic alcohols can be readily prepared in optically enriched form by several asymmetric syntheses.[1,25,26]

A reliable alternative strategy for the predictable installation of a new stereocenter is a 1,3-chirality transfer from a more readily accessible stereogenic center. Allylic substitutions with organometallic carbon nucleophiles, particularly the copper-mediated allylic substitution, provide a more general solution if the regio- and stereoselectivity could be controlled. These reactions generally proceed by *anti* attack of the nucleophile with respect to the leaving group.[10] Indeed, allylic substrates of type **16** undergo *anti*-S_N2' substitution *via* two conformations (**16A** and **16B**), either of them displays an antiperiplanar arrangement of the copper reagent and the leaving group (Scheme 8).[27] The substitution *via* the conformer **16A** affords the *trans*-alkene (*trans*-**17**), the substitution *via* the conformer **16B** results in the formation of a *cis*-alkene (*cis*-**17**). Notice that the configuration at the carbon atom C(1) is the opposite in products *trans*-**17** and *cis*-**17.**

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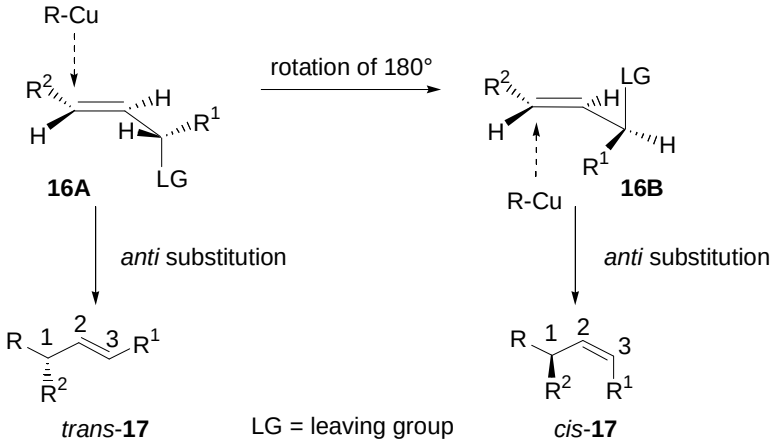
[24] (a) J. L. Belelie, J. M. Chong, *J. Org. Chem.* **2001**, *66*, 5552; (b) T. Ibuka, H. Habashita, A. Otaka, N. Fujii, Y. Oguchi, T. Uyehara, Y. Yamamoto, *J. Org. Chem.* **1991**, *56*, 4370; (c) Y. Yamamoto, M. Tanaka, T. Ibuka, Y. Chounan, *J. Org. Chem.* **1992**, *57*, 1024; (d) J. P. Marino, A. Viso, J.-D. Lee, R. Fernandez de la Pradilla, P. Fernandez, M. B. Rubio, *J. Org. Chem.* **1997**, *62*, 645; (e) J. H. Smitrovich, K. A. Woerpel, *J. Org. Chem.* **2000**, *65*, 1601. (f) C. Spino, C. Beaulieu, *Angew. Chem. Int. Ed.* **2000**, *39*, 1930; (g) C. Spino, C. Beaulieu, J. Lafreniere, *J. Org. Chem.* **2000**, *65*, 7091.

[25] (a) Y. Gao, J. M. Klunder, R. M. Hanson, H. Masamune, S. Y. Ko, K. B. Sharpless, *J. Am. Chem. Soc.* **1987**, *109*, 5765; (b) P. R. Carlier, W. S. Mungall, G. Schröder, K. B. Sharpless, *J. Am. Chem. Soc.* **1988**, *110*, 2978; (c) E. J. Corey, R. K. Bakshi, S. Shibata, *J. Am. Chem. Soc.* **1987**, *109*, 5551; (d) E. J. Corey, C. J. Helal, *Angew. Chem. Int. Ed.* **1998**, *37*, 1986; (e) S. Wallbaum, J. Martens, *Tetrahedron: Asymmetry* **1992**, *3*, 1475.

[26] For enzymatic methods see for example: (a) C. H. Wong, G. M. Whitesides, "*Enzymes in Synthetic Organic Chemistry*", Pergamon, Oxford, **1994**; (b) O. Pamies, J. E. Bäckvall, *Chem. Rev.* **2003**, *103*, 3247.

[27] (a) T. Ibuka, T. Taga, H. Habashita, K. Nakai, H. Tamamura, N. Fujii, Y. Chounan, H. Nemoto, Y. Yamamoto, *J. Org. Chem.* **1993**, *58*, 1207; (b) R. W. Hoffmann, *Chem. Rev.* **1989**, *89*, 1841; (c) Y. Yamamoto, "*Methods of Organic Chemistry*", Houben-Weyl, Vol. E21, Thieme, Stuttgart, **1995**, 2011; (d) B. Breit, P. Demel, "*Modern Organocopper Chemistry*", Ed. N. Krause, Wiley-VCH, Weinheim, **2002**, 188.



Scheme 8. *Anti*-S_N2' substitutions with organocopper reagents on allylic substrates.

The simultaneous control of the regio- and stereochemistry is a difficult problem to solve. Progress has been made in this area where substrates containing a directing leaving group, such as carbamates[28] and benzothiazoles,[29] are used. *Breit* solved this problem very elegantly by using the *ortho*-diphenylphosphanylbenzoate group (*o*-DPPB) as a directing leaving group.[30] Regioselective, stereospecific and stereodivergent construction of quaternary carbon stereogenic centers[31] could be carried out through *o*-DPPB-directed copper-mediated allylic substitution with Grignard reagents. Furthermore, the stereochemical outcome of the reaction could be reversed through an oxidative on/off switch with regard to the directing power of the *o*-DPPB group[32] (Scheme 9). Thus, both enantiomers of the substitution product could be prepared from a single enantiomer of the substrate. As shown in Scheme 9, the reaction of the *o*-DPPB ester (−)-**18a** with EtMgX in the presence of $CuBr \cdot Me_2S$ proceeded with excellent regio- and stereoselectivity to afford (−)-**19a** with almost perfect 1,3-chirality transfer. As expected, the reaction proceeded through a *syn* substitution pathway with respect to the leaving group. The *o*-DPPB group acted as a directing group through the coordination of the phosphorus center to the organocopper reagent (**20a**).

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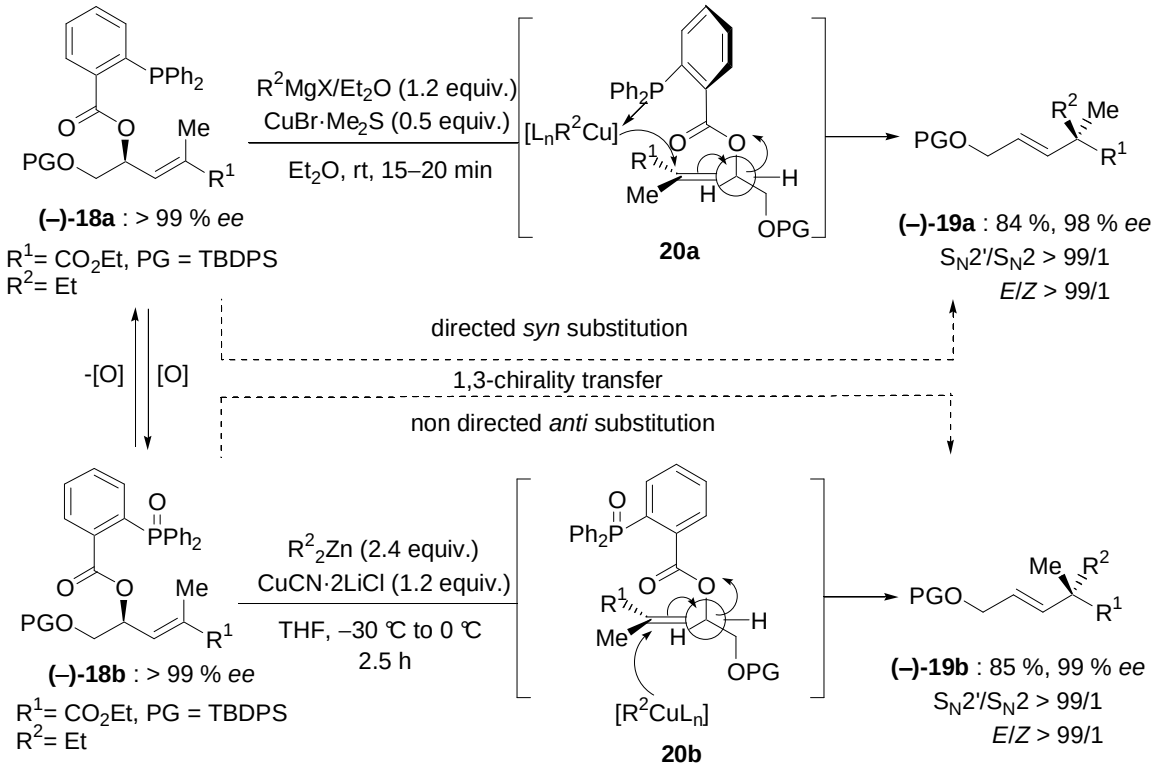
[28] (a) C. Gallina, *Tetrahedron Lett.* **1982**, *23*, 3094; (b) J. H. Smitrovich, K. A. Woerpel, *J. Am. Chem. Soc.* **1998**, *120*, 12998.

[29] (a) P. Barsanti, V. Calò, L. Lopez, G. Marchese, F. Naso, G. Pesce, *J. Chem. Soc., Chem. Commun.* **1978**, 1085; (b) V. Calò, L. Lopez, W. F. Carlucci, *J. Chem. Soc., Pekin Trans. 1* **1983**, 2953; (c) S. Valverde, M. Barnabé, S. Garcia-Ochoa, A. M. Gòmez, *J. Org. Chem.* **1990**, *55*, 2294.

[30] (a) P. Demel, M. Keller, B. Breit, *Chem. Eur. J.* **2006**, *12*, 6669; (b) B. Breit, P. Demel, *Adv. Synth. & Catal.* **2001**, *343*, 429; (c) B. Breit, P. Demel, *Tetrahedron* **2000**, *56*, 2833; (d) B. Breit, *Chem. Eur. J.* **2000**, *6*, 1519; (e) B. Breit, *Angew. Chem. Int. Ed.* **1998**, *37*, 525.

[31] For recent reviews on enantioselective construction of quaternary stereocenters, see: (a) J. Christoffers, A. Baro, *Adv. Synth. & Catal.* **2005**, *347*, 1473; (b) J. Christoffers, A. Mann, *Angew. Chem. Int. Ed.* **2001**, *40*, 4591; (c) E. Corey, A. Guzman-Perez, *Angew. Chem. Int. Ed.* **1998**, *37*, 388.

[32] (a) B. Breit, P. Demel, C. Studte, *Angew. Chem. Int. Ed.* **2004**, *43*, 3785, (b) Breit, C. Herber, *Angew. Chem. Int. Ed.* **2004**, *43*, 3790.



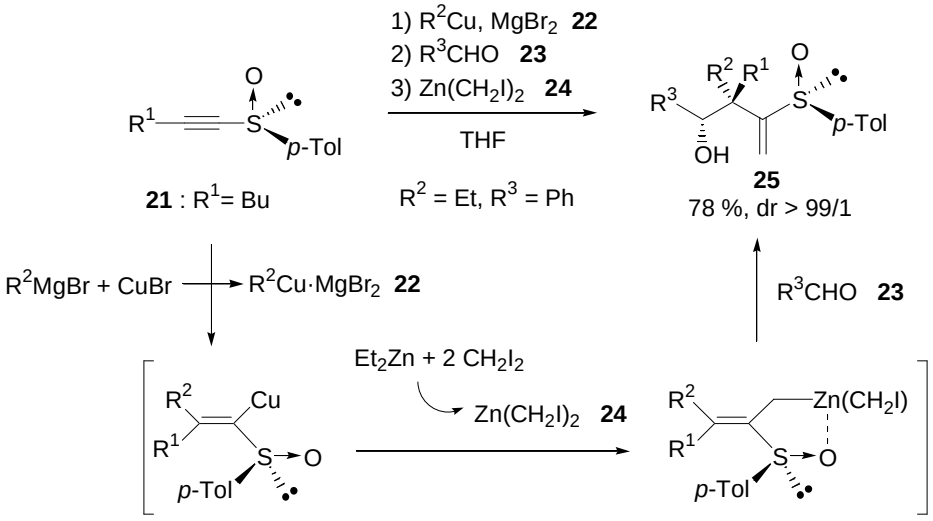
Scheme 9. Stereodivergent allylic substitutions with organocopper reagents by using a switchable directing/non directing leaving group.[32]

Similarly, the treatment of (−)-**18b** with diethylzinc in the presence of CuCN·2LiCl furnished the *anti*-S_N2' substitution product (−)-**19b** in good yield and perfect transfer of chirality giving access to the opposite enantiomer (Scheme 9). The reaction proceeded through a non-directed *anti*-attack of the nucleophile with respect to the leaving group (**20b**). By means of an oxidation of the phosphane functionality, the directing effect of the *o*-DPPB group was simply turned off, suppressing its coordinating effect on the copper reagent. However, when (−)-**18a** was subjected to reaction conditions identical to those used for (−)-**18b**, allylic substitution did not occur. Evidently, the oxidation of the phosphane functionality served not only as a directing power, but it also enhanced the leaving-group ability of the benzoate group to make non-directed *anti*-substitutions possible. This methodology has also been applied to cyclic substrates with similar efficency.[32]

An alternative option for the formation of a new stereogenic center is the use of chiral auxiliaries.[33] In this case the asymmetry is induced by the auxiliary already present in the substrate. This strategy has been exploited by *Marek* in a multi-component approach for the

[33] (a) P. O'Brien, *J. Chem. Soc., Pekin Trans. 1* **2001**, 95; (b) J. Seyden-Penne, "*Chiral Auxiliaries and Ligands in Asymmetric Synthesis*", Wiley, New York, **1995**; (c) D. Enders, M. Knopp, R. Schiffers, *Tetrahedron: Asymmetry* **1996**, *7*, 1847.

creation of chiral quaternary centers[34] (Scheme 10). The remarkable combination of a regio- and stereoselective carbometalation reaction, an *in situ* homologation of the resulting organocopper with the zinc carbenoid, an intramolecular chelation of the zinc moiety by the sulfinyl group, and a diastereoselective allylation reaction led to the preparation of chiral homoallylic alcohols with quaternary and tertiary centers in a single pot operation from a common alkyne precursor. Thus, the successive reaction of chiral alkynyl sulfoxide **21** with organocopper reagent **22**, aldehyde **23** and *bis*(iodomethylzinc) carbenoid **24** afforded in a single step the homoallylic alcohol **25** containing two adjacent new stereogenic centers in high diastereoselectivity.

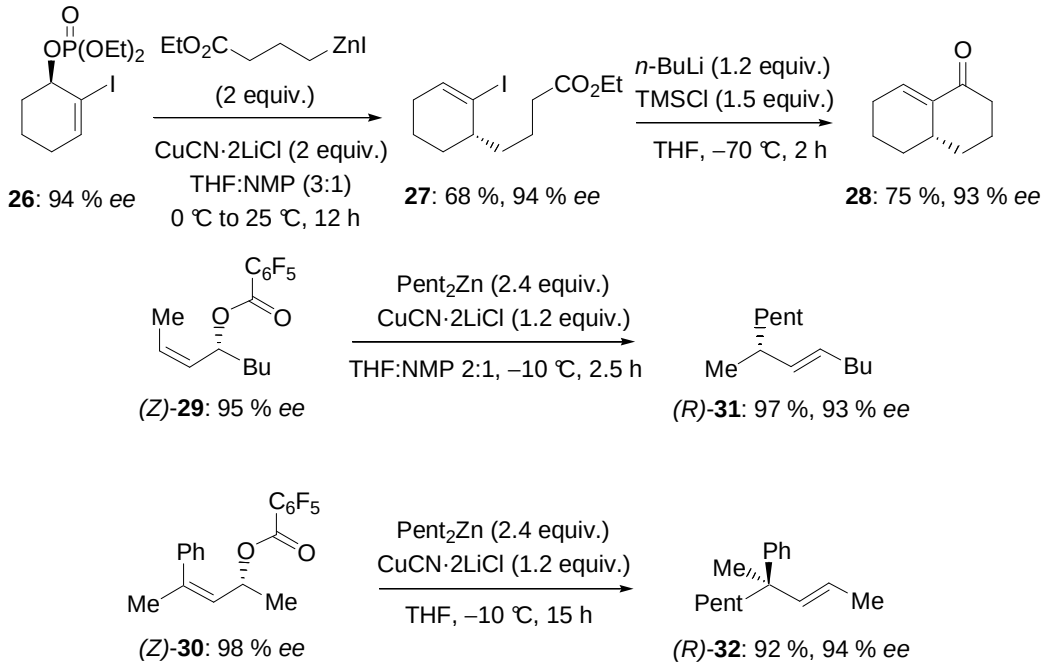


Scheme 10. Use of a chiral auxiliary in a multi-component approach for the creation of chiral quaternary centers.[34]

Recently, our group found that copper-catalyzed allylic substitutions with functionalized diorganozincs proceed with high *anti*-S_N2' selectivity (Scheme 11). Thus, the reaction of the chiral cyclic phosphate (**26**) with 3-carbethoxypropylzinc iodide in the presence of CuCN·2LiCl furnished the *anti*-S_N2' product **27** with perfect transfer of chirality.[35] Subsequent treatment with *n*-BuLi and TMSCl afforded the bicyclic enone **28** in 93 % *ee*. This reaction could successfully be extended to open-chain systems[36] (Scheme 11). In this case, the chiral pentafluorobenzoate derivative proved to be an appropriate leaving group. Allylic substitution of di- (**29**) and trisubstituted (**30**) allylic benzoates afforded respectively

[34] (a) G. Sklute, D. Amsallem, A. Shabli, J. P. Varghese, I. Marek, *J. Am. Chem. Soc.* **2003**, *125*, 11776; (b) G. Sklute, I. Marek, *J. Am. Chem. Soc.* **2006**, *128*, 4642.
[35] M. I. Calaza, E. Hupe, P. Knochel, *Org. Lett.* **2003**, *5*, 1059.
[36] N. Harrington-Frost, H. Leuser, M. I. Calaza, F. F. Kneisel, P. Knochel, *Org. Lett.* **2003**, *5*, 2111.

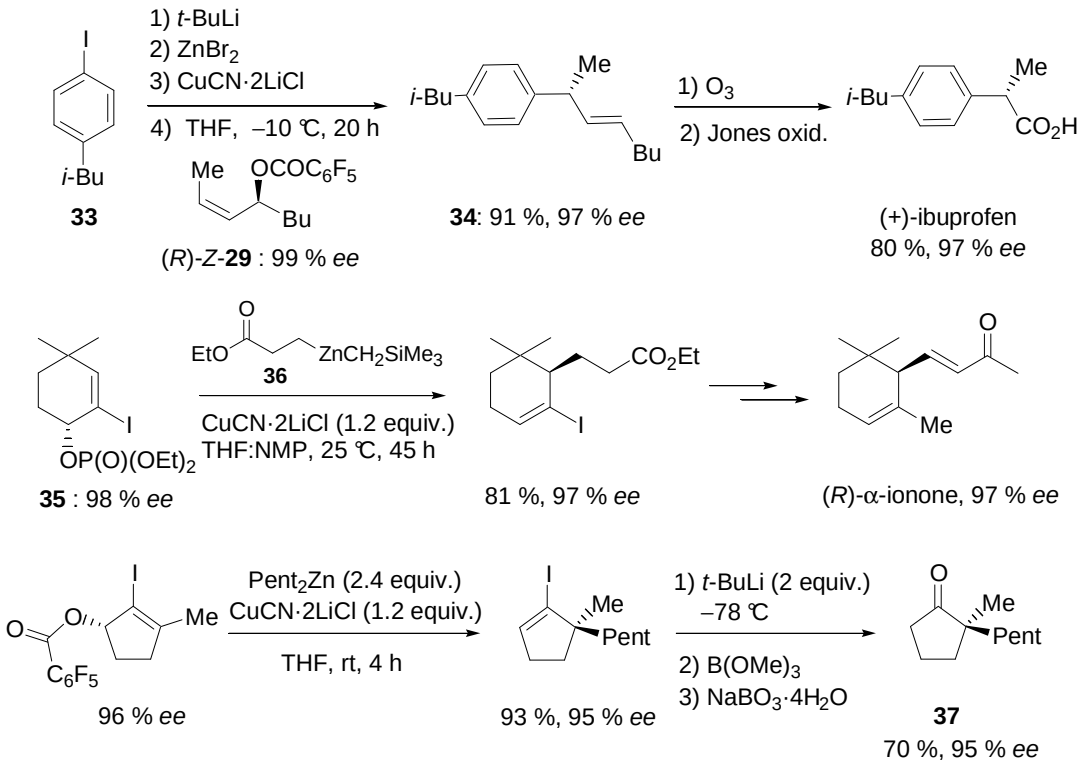
alkenes bearing a tertiary (**31**) or a quaternary (**32**) new stereogenic center with high enantioselectivity.



Scheme 11. Copper(I)-catalyzed *anti*-S_N2' allylic substitutions with functionalized diorganozincs in cyclic and acyclic systems.

The attractiveness of this method was exemplified by the synthesis of (+)-ibuprofen, an important anti-inflammatory agent[37], from the allylic benzoate (*Z*)-**29** and the aryl iodide **33** (Scheme 12).[36] Iodine-lithium exchange followed by a transmetalation to zinc with $ZnBr_2$ generated an intermediate zinc reagent that, in the presence of CuCN·2LiCl, reacted in an *anti*-S_N2' fashion with (*Z*)-**29** to afford the substituted product **34** in 97 % *ee*. Subsequent modifications leaded to the formation of (+)-ibuprofen in 80 % yield and 97 % *ee*. In a similar manner, the enantioselective synthesis of (*R*)-α-ionone[38] could be achieved starting from the chiral allylic phosphate **35** and the mixed diorganozinc **36** (Scheme 12). Finally it was possible to prepare α-alkylated cyclic ketones bearing a stereogenic center in the α position such as **37**[39], which is an important structural unit formed in numerous natural products. This two step sequence involved a stereoselective *anti*-S_N2' allylic substitution followed by the oxidation of an intermediate cycloalkenyllithium using $(Me_3SiO)_2$ or $(MeO)_3B/NaBO_3 \cdot 4H_2O$ (Scheme 12).

[37] (a) R. Akkari, M. Calmes, N. Mai, M. Rolland, J. Martinez, *J. Org. Chem.* **2001**, *66*, 5859; (b) A. Chen, L. Ren, C. M. Crudden, *J. Org. Chem.* **1999**, *64*, 9704.
[38] (a) D. Soorukram, P. Knochel, *Org. Lett.* **2004**, *6*, 2409; (b) "*Rompp Encyclopedia Natural Product*", Eds. W. Steglich, B. Fugmann, S. Lang-Fugmann, Thieme Verlag, Stuttgart, **2000**.
[39] D. Soorukram, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 3686.

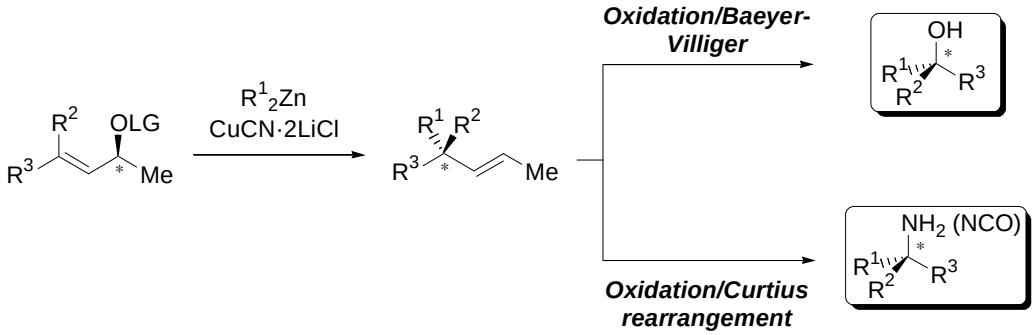


Scheme 12. Application to the synthesis of (+)-ibuprofen, (*R*)-α-ionone and the preparation of cyclic ketones bearing an α-stereogenic center.

1.2 Objectives

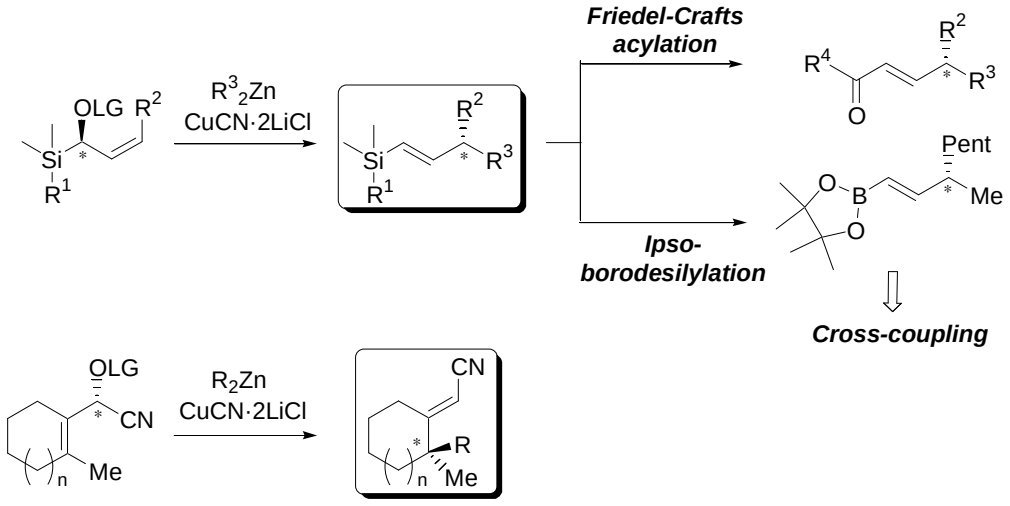
As previously mentioned, an absolute stereocontrol in acyclic systems is an important synthetic problem. This work will be focused on enantioselective allylic substitution reactions mainly on acyclic systems and without directing leaving group. It will be a continuation of the work already developed in the group. However, new research directions will be tackled:

- the preparation of enantiomerically enriched tertiary alcohols and amines *via* copper(I)-mediated allylic substitutions (Scheme 13).



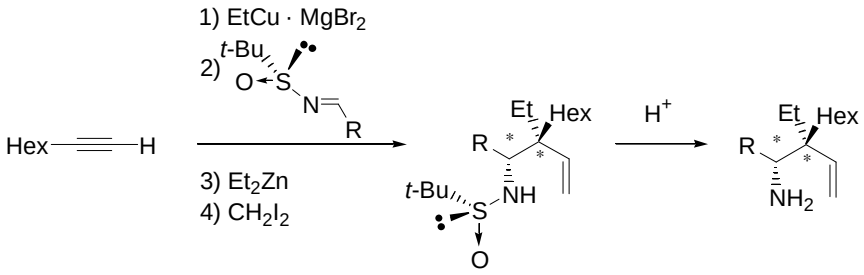
Scheme 13. Preparation of enantiomerically enriched tertiary alcohols and amines.

- the scope determination of the allylic substitution by increasing the complexity in the target molecules and introducing functionalities and therefore allowing applications in synthesis. This will be demonstrated by the preparation of (*E*)-alkenylsilanes and unsaturated nitriles bearing a stereogenic center in α position and their derivatizations (Scheme 14).



Scheme 14. Preparation of (*E*)-alkenylsilanes and unsaturated nitriles bearing an α-stereogenic center.

- finally, a reaction studied during a stay at the Technion at Haifa[40] for the generation of chiral quaternary center by a multi-component approach will be presented (Scheme 15).



Scheme 15. Multi-component approach for the generation of chiral quaternary center.

[40] Work carried out in the group of Prof. I. Marek, Haifa, Israel (25.04.2005-27.06.2005).

2 Results and Discussion

2.1 Preparation of enantiomerically enriched tertiary alcohols and amines

2.1.1 Introduction

The asymmetric preparation of tertiary alcohols or amines is an important synthetic problem which has been the subject of numerous studies.[41,42] As described in the first part, copper-catalyzed S_N2' allylic substitutions are well suited for setting up chiral centers both in cyclic and acyclic systems.[9,12,43] Only a few of these reactions have been applied to the elaboration of quaternary carbon centers.[30-32] Our group has recently developed efficient *anti*-S_N2' allylic substitution reactions on acyclic system using pentafluorobenzoates of trisubstituted allylic alcohols which produces quaternary centers with an almost complete transfer of the chiral information[36] (Scheme 16). Herein, we will demonstrate how this method can be generalized to the preparation of various types of substituted quaternary centers. Applications of this method illustrate the utility of this method. The synthesis of chiral tertiary alcohols of type **38** and amines or isocyanates bearing a tertiary chiral center such as **39** and **40** will be prepared in high enantiomeric excess starting from chiral allylic substitution products of type **41** which are obtained from the allylic benzoates of type **42** (Scheme 17).

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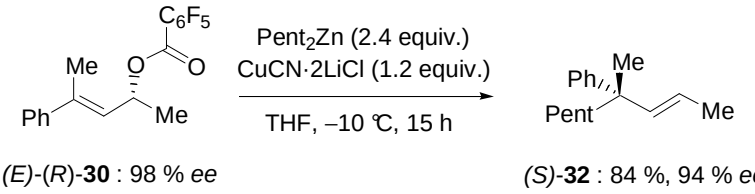
[41] (a) D. J. Ramon, M. Yus, *Angew. Chem. Int. Ed.* **2004**, *43*, 284. (b) B. Weber, D. Seebach, *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 84. (c) B. Weber, D. Seebach, *Tetrahedron* **1994**, *50*, 6117. (d) P. I. Dosa, G. C. Fu, *J. Am. Chem. Soc.* **1998**, *120*, 445. (e) C. Bolm, J. P. Hildebrand, K. Muniz, N. Hermanns, *Angew. Chem. Int. Ed.* **2001**, *40*, 3284. (f) P. G. Cozzi, *Angew. Chem. Int. Ed.* **2003**, *42*, 2895. (g) B. Jiang, Z. Chen, X. Tang, *Org. Lett.* **2002**, *4*, 3451. (h) D. J. Ramon, M. Yus, *Tetrahedron Lett.* **1998**, *39*, 1239. (i) D. J. Ramon, M. Yus, *Tetrahedron* **1998**, *54*, 5651. (j) M. Yus, D. J. Ramon, O. Prieto, *Tetrahedron: Asymmetry* **2003**, *14*, 1103. (k) C. Garcia, L. K. Larochelle, P. J. Walsh, *J. Am. Chem. Soc.* **2002**, *124*, 10970; l) S.-J. Jeon, P. J. Walsh, *J. Am. Chem. Soc.* **2003**, *125*, 9544. (m) M. Yus; D. J. Ramon, O. Prieto, *Tetrahedron: Asymmetry* **2002**, *13*, 2291. (n) M. Yus, D. J. Ramon, O. Prieto, *Eur. J. Org. Chem.* **2003**, 2745. (o) O. Prieto, D. J. Ramon; M. Yus, *Tetrahedron: Asymmetry* **2003**, *14*, 1955. (p) C. Garcia, P. J. Walsh, *Org. Lett.* **2003**, *5*, 3641. (q) E. F. DiMauro, M. C. Kozlowski, *J. Am. Chem. Soc.* **2002**, *124*, 12668. (r) E. F. DiMauro, M. C. Kozlowski, *Org. Lett.* **2002**, *4*, 3781.

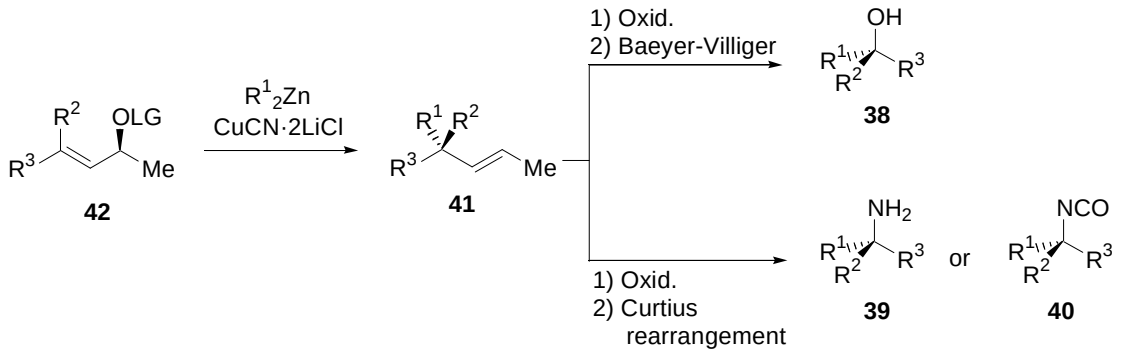
[42] (a) J. L. Wood, G. A. Moniz, D. A. Pflum, B. M. Stoltz, A. A. Holubec, H.-J. Dietrich, *J. Am. Chem. Soc.* **1999**, *121*, 1784. (b) D. A. Cogan, J. A. Ellman, *J. Am. Chem. Soc.* **1999**, *121*, 268. (c) H. Li, P. Walsh, *J. Am. Chem. Soc.* **2004**, *126*, 6538. (d) E. Cleator, C. F. McCusker, F. Steltzer, S. V. Ley, *Tetrahedron Lett.* **2004**, *45*, 3077. (e) B. M. Trost, N. G. Andersen, *J. Am. Chem. Soc.* **2002**, *124*, 14320. (f) S. Casolari, D. D´Addario, E. Tagliavini, *Org. Lett.* **1999**, *1*, 1061.

[43] (a) Y. Yamamoto, S. Yamamoto, H. Yatagai, K. Maruyama, *J. Am. Chem. Soc.* **1980**, *102*, 2318. (b) E. Nakamura, K. Sekiya, M. Arai, S. Aoki, *J. Am. Chem. Soc.* **1989**, *111*, 3091. (c) M Arai, B. H. Lipshutz, E. Nakamura, *Tetrahedron* **1992**, *48*, 5709. (d) M. Arai, E. Nakamura, B. H. Lipshutz, *J. Org. Chem.* **1991**, *56*, 5489. (e) M. Arai, T. Kawasuji, E. Nakamura, *J. Org. Chem.* **1993**, *58*, 5121. (f) M. Arai, T. Kawasuji, E. Nakamura, *Chem. Lett.* **1993**, 357. (g) A. Yanagisawa, Y. Noritake, N. Nomura, H. Yamamoto, *Synlett* **1991**, 251.



(E)-(*R*)-**30** : 98 % *ee* *(S)*-**32** : 84 %, 94 % *ee*

Scheme 16. Cu(I)-mediated *anti*-S_N2' allylic substitution of an allylic pentafluorobenzoate derived from a trisubstituted allylic alcohol with dialkylzinc.[36]



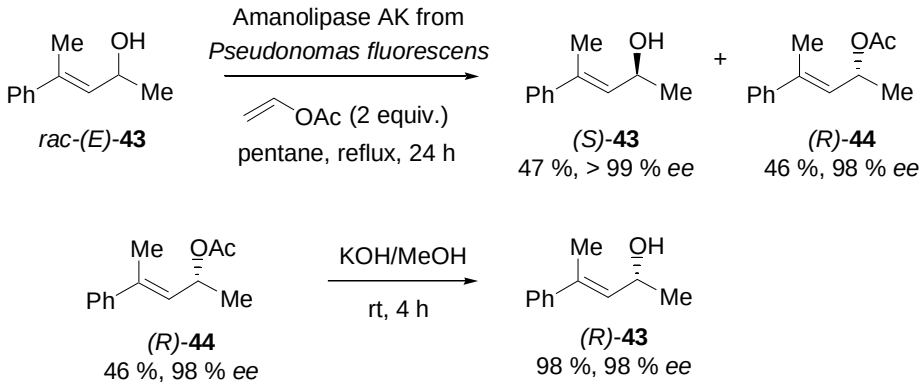
Scheme 17. Enantioselective preparation of tertiary alcohols, amines and isocyanates bearing a tertiary chiral carbon center.

2.1.2 Enantioselective preparation of quaternary centers *via* copper(I)-mediated *anti*-S_N2' allylic substitution

A highly enantioselective preparation of the allylic alcohol derivative is crucial because it will determine the enantiomeric excess obtained after the transfer of chirality. The chirality can be introduced by chemical methods[25] or by an enzymatic resolution of the racemic allylic alcohol.[26,44] We have chosen to use the enzymatic resolution as it is very well described on allylic substrates and because it has become a practical and general method for preparing allylic alcohols in almost pure enantiomeric form. Indeed, the allylic alcohol **43**[45] could be enzymatically resolved by amano lipase AK[46] in the presence of vinyl acetate in refluxing pentane to give (*S*)-**43** in 47 % yield and > 99 % *ee* (Scheme 18). Moreover, the acetate (*R*)-**44** was formed in comparable yields and 98 % *ee*. It can be easily hydrolyzed into the alcohol (*R*)-**43**. This method constitutes a large improvement for the chiral starting material

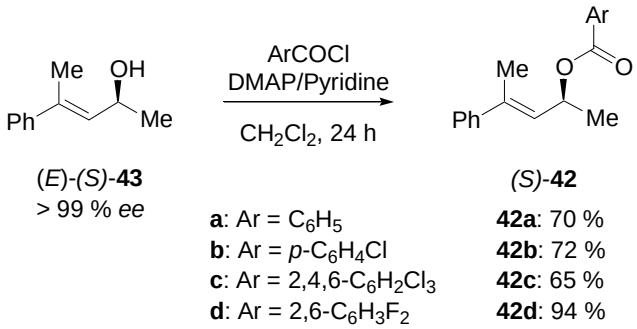
[44] (a) K. Burgess, L. D. Jennings, *J. Am. Chem. Soc.* **1991**, 6129. (b) U. Kazmaier, F. L. Zumpe, *Eur. J. Org. Chem.* **2001**, 4067.
[45] For the synthesis of alcohol **43**, see: (a) J. P. Guthrie, X. P. Wang, *Can. J. Chem.* **1992**, *70*, 1055. (b) J.-L. Luche, L. Rodriguez-Hahn, P. Crabbé, *J. Chem. Soc., Chem. Commun.* **1978**, *14*, 601.
[46] Commercially available from Aldrich.

preparation compared to classical chemical methods. In fact, the Sharpless kinetic resolution[25a] gives theoretically at best 50 % yield and up to 98 % *ee*, but requires a much more complex protocol as the enzymatic resolution itself. Another advantage of using enzymatic methods is that the acetate (easily separable by column chromatography) is also formed in excellent enantioselectivity. The yield of the enzymatic resolution is now almost quantitative. This is not the case in the Sharpless kinetic resolution.



Scheme 18. Enzymatic resolution of allylic alcohol **43**.

The allylic alcohol **43** was derivatized into derivatives bearing a leaving group (**42**). First of all, a short study was undertaken in order to determine the most appropriate leaving group. A number of substituted benzoate were prepared and the resulting substrates were tested in a standard allylic substitution reaction with dipentylzinc and CuCN·2LiCl (Scheme 19 and Table 1).

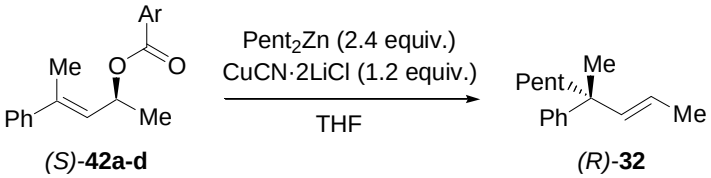


Scheme 19. Preparation of various substituted allylic benzoates of type **43**.

The pentafluorobenzoate leaving group constituted the reference with 94 % *ee* (entry 1, Table 1). We have found that unsubstituted benzoate **42a** (entry 2) as well as chloro-substituted benzoates **42b** and **42c** (entry 3 and 4) gave rise to uncomplete reactions. Interestingly, the presence of only two fluorine atoms on the aromatic ring (**42d**, entry 5) was sufficient to achieve an appropriate leaving group ability and gave a better *ee* (98 %). 2,6-

Difluorobenzoates which is more stable and cheaper, constitute a viable alternative to the pentafluorobenzoate leaving group.

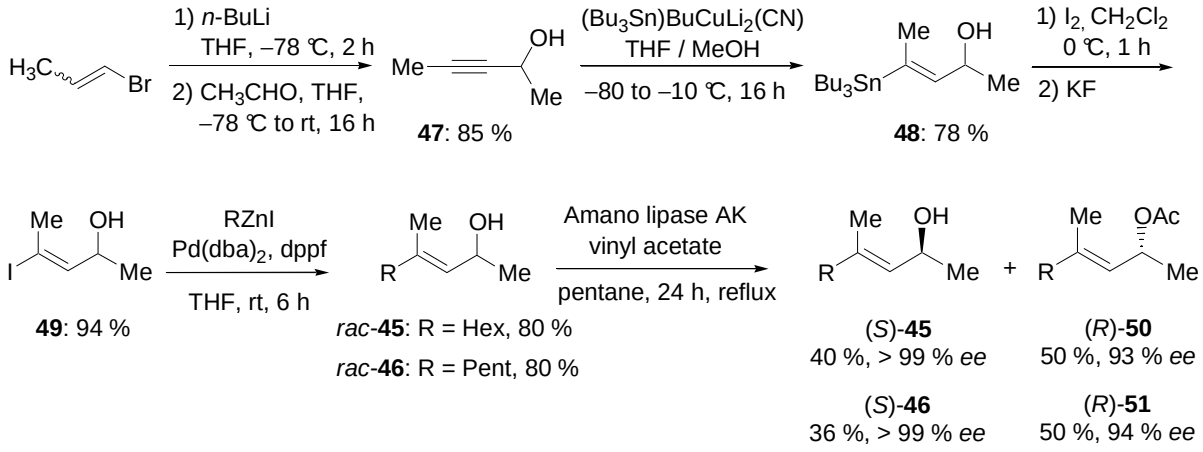
Table 1. S_N2' reactions on allylic benzoates **30** and **42a-d** with $Pent_2Zn$ and CuCN·2LiCl.



(S)-**42a-d** *(R)*-**32**

Entry	Substrates	Conditions	**Yield** (%)	***ee*** (%)	**Observations**
1	(*R*)-**30**	–30 to –10 °C, 15 h	84	94	
2	(*S*)-**42a**	rt, 24 h	30	-	47 % conversion **42a** recovered
3	(*S*)-**42b**	rt, 24 h	55	-	65 % conversion **42b** recovered
4	(*S*)-**42c**	rt, 24 h	48	-	35 % conversion
5	(*S*)-**42d**	–30 to –10 °C, 15 h	85	98	

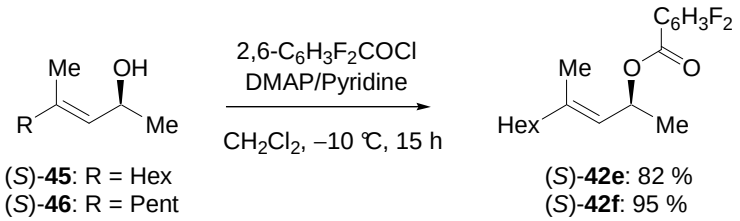
The new chiral allylic substrates (*E*)-**45** and (*E*)-**46** were synthesized as depicted in Scheme 20. Propynyllithium was prepared as described by *Suffert*[47] and reacted with acetaldehyde. Alcohol **47** was obtained in good yield and underwent a chemo-, regio- and stereoselective stannylcupration[48] leading to the γ-stannylated allylic alcohol **48** in 78 % yield.



Scheme 20. Synthesis of the chiral allylic alcohols (*S*)-**45** and (*S*)-**46**.

[47] J. Suffert, D. Toussaint, *J. Org. Chem.* **1995**, *60*, 3550.
[48] J.-F. Betzer, F. Delaloge, B. Muller, A. Pancrazi, J. Prunet, *J. Org. Chem.* **1997**, *62*, 7768.

Iodolysis[49] of the alkenylstannane **48** afforded the alkenyliodide **49** in 94 % yield. This iodide **49** was then reacted in a Negishi cross-coupling reaction[50] with hexylzinc iodide (for *rac*-**45**) or with pentylzinc iodide (for *rac*-**46**) in the presence of $Pd(dba)_2$ and dppf yielding the expected methyl alkyl substituted allylic alcohols *rac*-**45** and *rac*-**46**. Enzymatic resolution of these two allylic alcohols with amano lipase AK afforded the pure allylic alcohol (*S*)-**45** and (*S*)-**46** enantiomers in 36-40 % as well as the acetates (*R*)-**50** and (*R*)-**51** respectively in 93 % *ee* and 94 % *ee*. Finally, the allylic alcohols were transformed in their 2,6-difluorobenzoate derivatives (*S*)-**42e** and (*S*)-**42f** in high yields (Scheme 21).



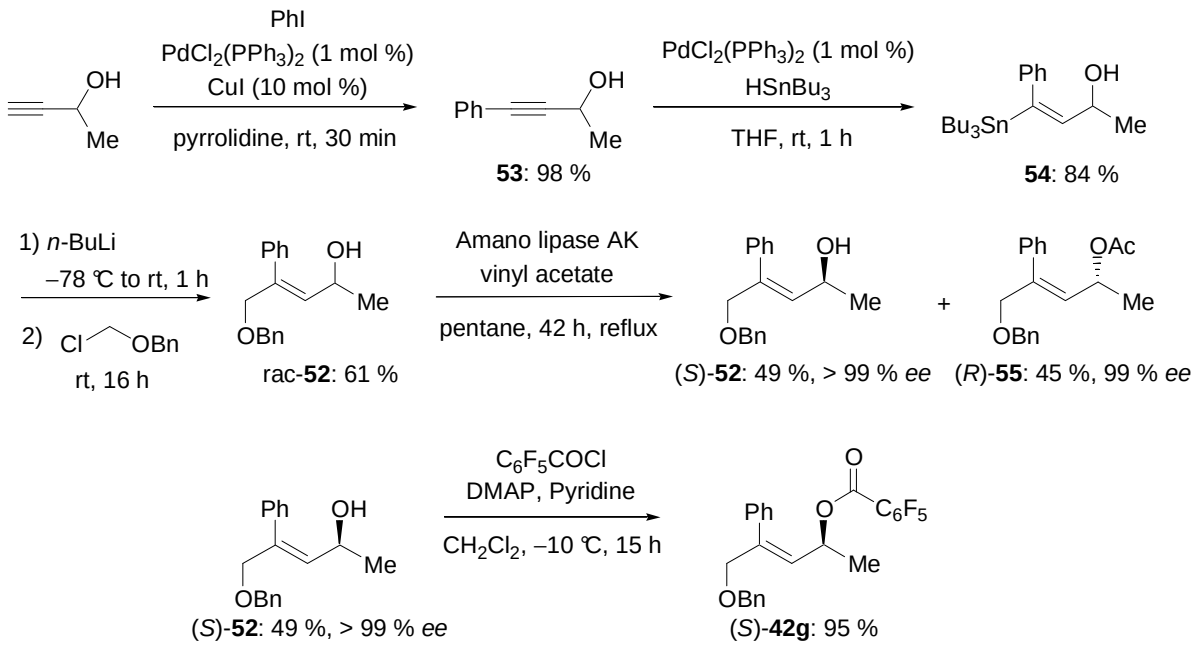
(*S*)-**45**: R = Hex
(*S*)-**46**: R = Pent

(*S*)-**42e**: 82 %
(*S*)-**42f**: 95 %

Scheme 21. Synthesis of the chiral benzoate derivatives (*S*)-**42e** and (*S*)-**42f**.

Secondly, the heteroatom containing allylic alcohol (*S*)-**52** was synthesized in four steps as follows (Scheme 22). Iodobenzene underwent a smooth Sonogashira cross-coupling reaction[51] with but-3-yn-2-ol yielding the propargylic alcohol **53** in 98 % yield. This alcohol was subjected to a Pd-catalyzed hydrostannylation [52] and yielded regioselectively the alkenylstannane **54** in 84 % yield. The allylic alcohol **54** was then reacted with *n*-BuLi (2 equiv.) and benzyl(chloromethyl)ether, yielding *rac*-**52** in 61 % yield. Enzymatic resolution of *rac*-**52** with amano lipase AK afforded the pure (*S*)-**52** enantiomer in 49 % yield as well as the acetate (*R*)-**55** in 99 % *ee* and 45 % yield. Finally, the allylic alcohol (*S*)-**52** was converted to the pentafluorobenzoate derivative (*S*)-**42g** in 95 % yield.

[49] H. X. Zhang, F. Guibé, G. Balavoine, *J. Org. Chem.* **1990**, *55*, 1857.
[50] H. Matsushita, E. Negishi, *J. Org. Chem.* **1982**, *47*, 4161.
[51] M. Alami, F. Ferri, G. Linstrumelle, *Tetrahedron Lett.* **1993**, *34*, 6403.
[52] F. Liron, M. Gervais, J.-F. Peyrat, M. Alami, J.-D. Brion, *Tetrahedron Lett.* **2003**, *44*, 2789.

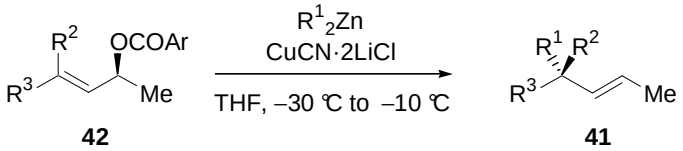


Scheme 22. Synthesis of the chiral benzoate derivative (*S*)-**42g**.

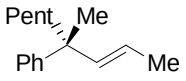
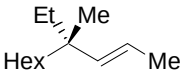
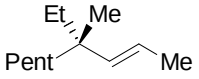
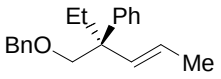
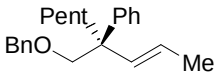
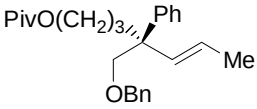
Having these new benzoate derivatives (*S*)-**42e**, (*S*)-**42f** and (*S*)-**42g** in enantiopure form in hand, we have tested them in the copper(I)-catalyzed allylic substitution. The allylic benzoate (*S*)-**42d** (entry 1, Table 2) and the difluorobenzoate (*S*)-**42e** was reacted with diethylzinc (2.4 equiv.) and CuCN·2LiCl (1.2 equiv.) in THF at −30 °C to −10 °C for 14 h providing the (*E*)-alkene **41a** (88 %, 98 % *ee*, entry 2) bearing a chiral quaternary center with three different alkyl substituents. (*S*)-**42f** reacted similarly but yielded the corresponding (*E*)-alkene **41b** in slightly lower *ee* (96 % *ee*, 80 % yield, entry 3). Interestingly, functionalized allylic benzoate (*S*)-**42g** (99 % *ee*) reacted with Et_2Zn (69 %, 96 % *ee*, entry 4), $Pent_2Zn$ (90 %, 96 % *ee*, entry 5) and even with the functionalized diorganozinc ($[PivO(CH_2)_3]_2Zn$, 60 %, 98 % *ee*, entry 6) providing in each case the corresponding (*E*)-alkenes in high enantioselectivity.

This substitution reaction proceeded with a reliable transfer of chirality and this behaviour was rather general. In all cases, no products derived from S_N2 substitution could be detected (γ:α > 99:1) and pure (*E*)-substituted products were obtained (*E:Z* > 99:1). The *anti*-S_N2'allylic substitution constitutes a powerful tool to build chiral quaternary centers with high enantiopuritiy.

Table 2. S_N2' allylic substitution reactions on benzoate substrates **42d-g**.[53]



42 **41**

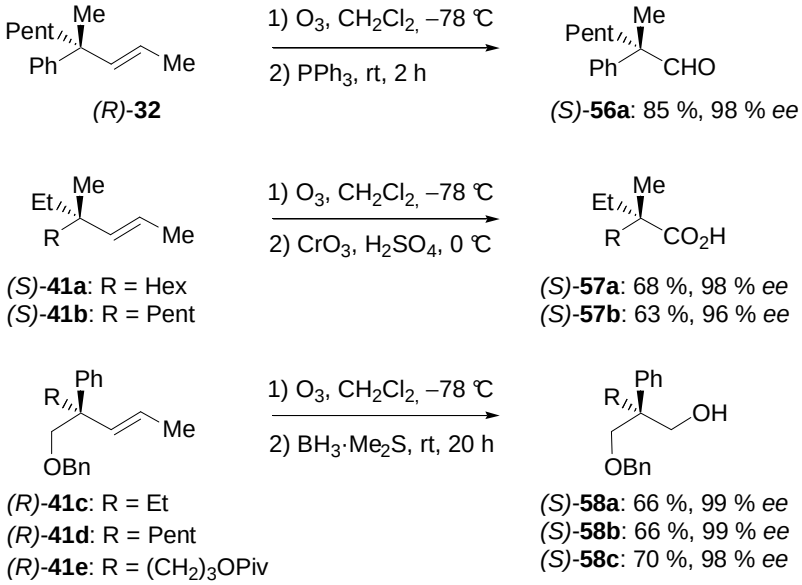
Entry	Allylic substrates *ee* (%)[a]	R_2Zn (R)	(*E*)-Alkenes	Yield (%)[b]	*ee* (%)[a]
	(*S*)-**42d** (> 99)				
1	Ar = 2,6-$C_6H_3F_2$	Pent	(*R*)-**32**	85	98
	(*S*)-**42e** (> 99)				
2	Ar = 2,6-$C_6H_3F_2$	Et	(*S*)-**41a**	88	98
	(*S*)-**42f** (> 99)				
3	Ar = 2,6-$C_6H_3F_2$	Et	(*S*)-**41b**	80	96
	(*S*)-**42g** (> 99)				
4	Ar = C_6F_5	Et	(*R*)-**41c**	69	99
	(*S*)-**42g** (> 99)				
5	Ar = C_6F_5	Pent	(*R*)-**41d**	90	99
	(*S*)-**42g** (> 99)				
6	Ar = C_6F_5	$PivO(CH_2)_3$	(*R*)-**41e**	60	98

[a] The enantiomeric excess was determined by HPLC or GC analysis on the derivatized product. In each case the racemic product was prepared for HPLC or GC calibration. [b] Yield of analytically pure product.

Generally, the enantiomeric excess was not determined on alkenes of type **41**. These products showed no separation ability neither on chiral GCs nor HPLCs. In all cases, they were derivatized either into the corresponding aldehydes **56** (using PPh_3),[54] carboxylic acids **57** (using Jones'reagent)[55] or into the primary alcohols **58** (using $BH_3 \cdot Me_2S$)[56] by an ozonolysis reaction (Scheme 23). Thus, the *ee* of (*R*)-**32** was determined on the aldehyde (*S*)-

[53] H. Leuser, S. Perrone, F. Liron, F. F. Kneisel, P. Knochel, *Angew. Chem. Int. Ed.* **2005**, *44*, 4627.
[54] (a) O. Lorenz, C. R. Parks, *J. Org. Chem.* **1965**, *30*, 1976. (b) D. P. Higley, R. W. Murray, *J. Am. Chem. Soc.* **1976**, *98*, 4526.
[55] J. L. Belelie, J. M. Chong, *J. Org. Chem.* **2001**, *66*, 5552.
[56] L. A. Flippin, D. W. Gallagher, K. Jalali-Araghi, *J. Org. Chem.* **1989**, *54*, 1430.

56.[57] The olefins (*R*)-**41a** and **b** were converted into the corresponding carboxylic acids (*S*)-**57a** and **b**. Finally, the *ee*s of **41c-e** were determined on the primary alcohols **58a-c**.



(*R*)-**32**

(*S*)-**56a**: 85 %, 98 % *ee*

(*S*)-**41a**: R = Hex
(*S*)-**41b**: R = Pent

(*S*)-**57a**: 68 %, 98 % *ee*
(*S*)-**57b**: 63 %, 96 % *ee*

(*R*)-**41c**: R = Et
(*R*)-**41d**: R = Pent
(*R*)-**41e**: R = $(CH_2)_3OPiv$

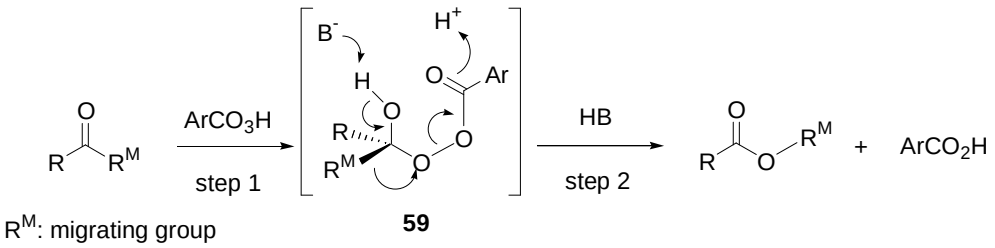
(*S*)-**58a**: 66 %, 99 % *ee*
(*S*)-**58b**: 66 %, 99 % *ee*
(*S*)-**58c**: 70 %, 98 % *ee*

Scheme 23. Derivatization of alkenes **32** and **41a-e** by an ozonolysis reaction following either by an oxidative or reductive workup.

2.1.3 Synthesis of enantiomerically enriched tertiary alcohols *via* an oxidation / Baeyer-Villiger rearrangement sequence

There have been many reports[58] on the Baeyer-Villiger reaction since its discovery in 1899 by *Adolf Baeyer* and *Victor Villiger*.[59] The mechanism of the Baeyer-Villiger reaction was first studied by *Criegee*[60] about 60 years ago. As shown in Scheme 24, the stepwise process consists of an initial nucleophilic attack of the peroxy acid at the carbonyl carbon (step 1) to form an intermediate species **59** known as the Criegee adduct. This step is followed by a 1,2-migration of one of the alkyl groups (R^M) on oxygen with the cleavage of the peroxy bond and the concomitant release of the carboxylate anion (step 2). The second step determines the properties of the overall reaction because the migration proceeds with retention of the configuration of the migrating group.

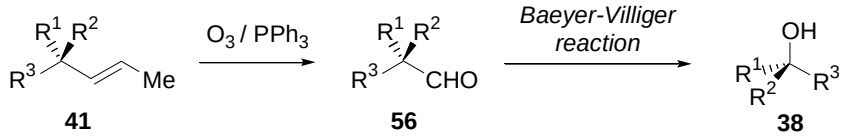
[57] For examples of chiral chromatograms, see appendix section in the experimental part.
[58] (a) C. H. Hassall, *Org. React.* **1957**, *9*, 73. (b) M. Hudlicky, "*Oxidation in Organic Chemistry*", American Chemical Society, Washington, **1990**, 186. For recent reviews, see: (c) G.-J. ten Brink, I. W. C. E. Arends, R. A. Sheldon, *Chem. Rev.* **2004**, *104*, 4105. (d) M. Renz, B. Meunier, *Eur. J. Org. Chem.* **1999**, 737. (e) G. Strukul, *Angew. Chem. Int. Ed.* **1998**, *37*, 1198.
[59] A. Baeyer, V. Villiger, *Ber. Dtsch. Chem. Ges.* **1899**, *32*, 3625.
[60] R. Criegee, *Justus Liebigs Ann. Chem.* **1948**, *560*, 127.



Scheme 24. Mechanism of the Baeyer-Villiger reaction described by Criegee.[61]

A wide range of peroxy-acids were used as oxidants for the reaction. *m*-Chloro peroxybenzoic acid (*m*-CPBA) is widely used because of its stability, but also hydrogen peroxide (H_2O_2, environmentally friendly) or *tert*-butoxyperoxide (*t*-BuOOH) have found applications.[62] The Baeyer-Villiger reaction tolerates the presence of many functional groups and the regiochemistry of the reaction can be normally controlled by reference to the scale of migratory aptitude (*t*-alkyl > cyclohexyl > *s*-alkyl > benzyl > phenyl > *n*-alkyl > cyclopentyl > methyl). It proceeds stereoselectively, so that the migrating chiral carbon atoms retains its absolute configuration.

Based on these considerations, we envisioned, the conversion of chiral alkenes of type **41** into chiral tertiary alcohols of type **38** *via* the aldehyde intermediate **56** (Scheme 25). Indeed, if we combine the previous oxidation step (ozonolysis then PPh_3) together with a stereoselective Baeyer-Villiger reaction, it will provide chiral tertiary alcohols of the type **38**, which are difficult to prepare otherwise. The copper-mediated allylic substitution reaction will ensure a high enantiomeric excess of the corresponding alkene and the oxidation / Baeyer-Villiger reaction will introduce a heteroatom directly attached to a stereogenic center.

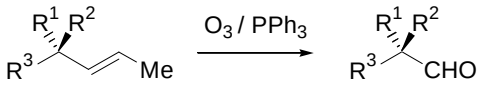


Scheme 25. Oxidation / Baeyer-Villiger reaction sequence for the preparation of chiral tertiary alcohols.

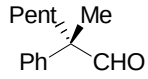
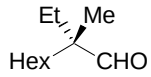
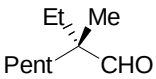
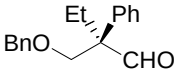
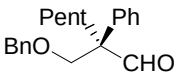
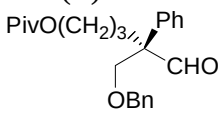
First, the previously prepared alkenes of type **32** and **41** were ozonolyzed by ozone and subsequently treated with triphenylphosphine (1.3 equiv.) to afford the corresponding aldehyde **56a-f** in reasonable yields (Table 3).

[61] G. R. Krow, *Org. React.* **1993**, *43*, 251.
[62] H. Nemoto, H. Ishibashi, K. Fukumoto, *Heterocycles* **1992**, *33*, 549.

Table 3. Preparation of aldehydes **56a-f** by ozonolysis reaction with a reductive workup.



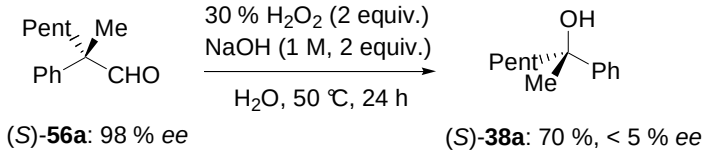
41 **56**

Entry	(*E*)-Alkenes	Adehydes	Yield (%)[b]	*ee* (%)[a]
1	(*R*)-**32**	 (*S*)-**56a**	85	98
2	(*S*)-**41a**	 (*S*)-**56b**	65	98
3	(*S*)-**41b**	 (*S*)-**56c**	63	96
4	(*R*)-**41c**	 (*R*)-**56d**	62	99
5	(*R*)-**41d**	 (*R*)-**56e**	66	99
6	(*R*)-**41e**	 (*R*)-**56f**	76	98

[a] The enantiomeric excess was determined by HPLC or GC. In each case the racemic product was prepared for HPLC or GC calibration. [b] Yield of analytically pure product.

Two oxidants were chosen to perform the Baeyer-Villiger reaction: *m*-CPBA, a stable and widely used oxidation reagent in organic synthesis, and H_2O_2, which produces water as by-product simplifying the workup procedure and being the most environmentally friendly oxidant. In a preliminary experiment, aldehyde **56a** (98 % *ee*) was reacted with H_2O_2 [63] (30 % solution, 2 equiv.) and NaOH (1 M solution, 2 equiv.) in water at 50 °C for 24 h and afforded, the expected tertiary alcohol **38a** in 70 % yield (Scheme 26). Unfortunately, the rearrangement did not occur with retention of the chiral information and gave rise to the tertiary alcohol **38a** in its racemic form.

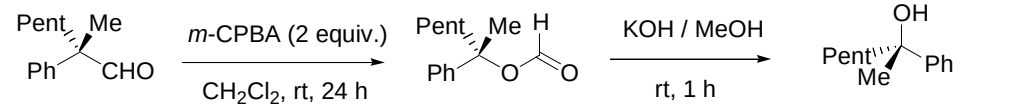
[63] M. B. Hocking, *Can. J. Chem.* **1973**, *51*, 2384.



(*S*)-**56a**: 98 % *ee* (*S*)-**38a**: 70 %, < 5 % *ee*

Scheme 26. Baeyer-Villiger reaction with hydrogen peroxide in basic conditions.

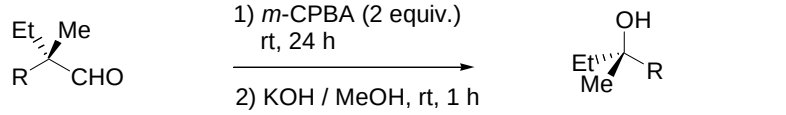
The same experiment was performed with *m*-CPBA (2 equiv.) in dichloromethane[64] (rt, 24 h). It furnished first the formyl ester intermediate **60**, which after saponification gave the tertiary alcohol **38a** in 70 % yield (Scheme 27). In this case the rearrangement occurred with perfect retention of configuration and **38a** was obtained in 97 % *ee*.



(*S*)-**56a**: 98 % *ee* **60**: 70 % (*S*)-**38a**: 95 %, 97 % *ee*

Scheme 27. Baeyer-Villiger reaction with *m*-CPBA.

In a second experiment, the aldehydes **56b** and **56c**, containing only alkyl residues, were subjected to the same reaction conditions in order to produce the corresponding tertiary alcohols **38b** and **38c**. Surprisingly the alcohol **38b** was obtained in only 36 % *ee* and the alcohol **38c** was obtained in 86 % *ee* (Scheme 28).



(*S*)-**56b**: R = Hex, 98 % *ee*
(*S*)-**56c**: R = Pent, 96 % *ee*

(*S*)-**38b**: R = Hex, 36 % *ee*
(*S*)-**38c**: R = Pent, 86 % *ee*

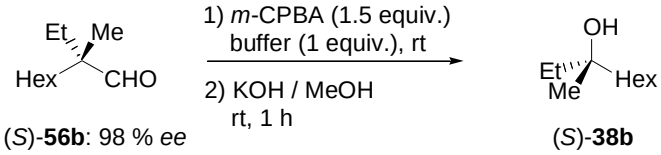
Scheme 28. Baeyer-Villiger reaction with *m*-CPBA on aldehydes **56b** and **56c**.

A possible explanation for the loss of enantioselectivity are the acidic conditions of the Baeyer-Villiger reaction. Tertiary alcohols and their corresponding formates (60) are acid sensitive. Various buffer systems were tested on the aldehyde **56b**.[65] We have found that the addition of a buffer immediately increased the enantiomeric excess but also reducs

[64] I. M. Godfrey, M. V. Sargent, J. A. Elix, *J. Chem. Soc., Perkin Trans. 1*, **1974**, 1353.
[65] P. F. Hudelik, G. Nagendrappa, T. Yimenu, E. T. Zeller, E. Chin, *J. Am. Chem. Soc.* **1980**, *102*, 6894.

impressively the reaction time from 24 h to 6 h (88 % *ee*, entry 2, Table 4). Na_2HPO_4 gave the best result with 93 % *ee* and a reaction time reduced to 2 h (entry 4).

Table 4. Use of a buffer in the Baeyer-Villiger reaction.

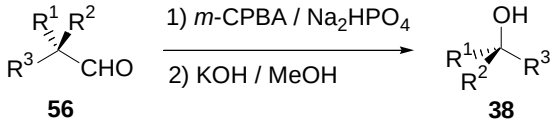


(*S*)-**56b**: 98 % *ee* (*S*)-**38b**

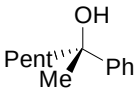
Entry	**Conditions**	***ee*** (%)	**Reaction time** (h)	**Observations**
1	*m*-CPBA (1.5) no buffer	36	24	-
2	Phosphate buffer (pH 7)	88	6	Emulsion
3	$NaHCO_3$	86	2	Suspension
4	Na_2HPO_4	93	2	Suspension

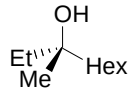
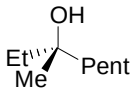
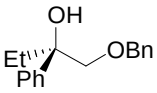
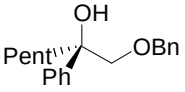
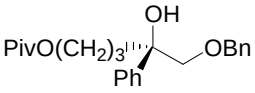
Having found the optimized conditions for the Baeyer-Villiger reaction, alkenes **56c-f** were converted into the corresponding tertiary alcohols as summarized in Table 5. Aldehyde (*S*)-**56c** were transformed into the corresponding tertiary alcohol (*S*)-**38c** in 92 % *ee* and in 76 % yield (entry 3). Polyfunctional products such as the selectively deprotected 1,2-diols **38d-f** (entry 4-6) bearing a tertiary hydroxyl group were prepared in high enantioselectivity. This sequence appears to be general for the preparation of chiral tertiary alcohols.

Table 5. Tertiary alcohols obtained by Baeyer-Villiger rearrangement.



56 **38**

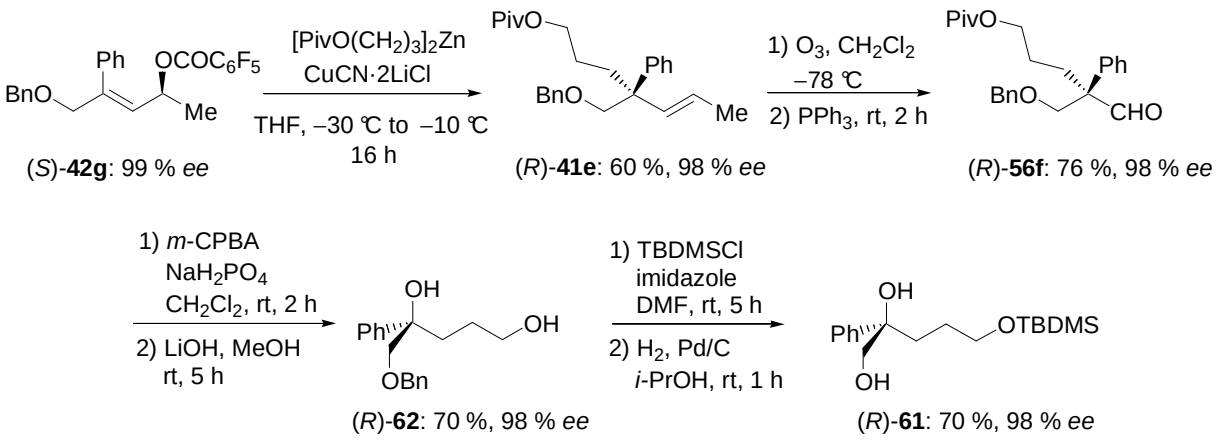
Entry	**Aldehydes** *ee* (%)	**Tertiary alcohols**	**Yield** (%)[b]	***ee*** (%)[a]
				
1	(*S*)-**56a** (98)	(*S*)-**38a**	70	97

Entry	Aldehydes *ee* (%)	Tertiary alcohols	Yield (%)[b]	*ee* (%)[a]
				
2	(*S*)-**56b** (98)	(*S*)-**38b**	68	93
				
3	(*S*)-**56c** (96)	(*S*)-**38c**	76	92
				
4	(*R*)-**56d** (99)	(*R*)-**38d**	70	99
				
5	(*R*)-**56e** (99)	(*R*)-**38e**	77	98
				
6	(*R*)-**56f** (98)	(*R*)-**38f**	76	98

[a] The enantiomeric excess was determined by HPLC or GC. In each case the racemic product was prepared for HPLC or GC calibration. [b] Yield of analytically pure product.

This methodology was applied for the preparation of the chiral 1,2-diol **61** which is a key intermediate of the combined NK_1 and NK_2 tachykinin receptor antagonist (Scheme 29).[66] Thus, the S_N2' substitution of $(PivO(CH_2)_3)_2Zn$ in the presence of CuCN·2LiCl (THF, –50 °C to –10 °C, 6 h) provided the chiral alkene **41e** in 60 % yield and 98 % *ee*. The ozonolysis of the alkene **41e** followed by reductive workup afforded the chiral aldehyde **56f** in 76 % yield and 98 % *ee*. Baeyer-Villiger oxidation in the presence of NaH_2PO_4 in CH_2Cl_2 (rt, 2 h) followed by the saponification of the two ester functions provided the diol **62** in 70 % yield and 98 % *ee*. Quantitative protection of the remote primary alcohol as a TBDM-silyl ether (TBDMSCl, imidazole, DMF, rt, 5 h) provided an intermediate tertiary alcohol which after a hydrogenolysis over Pd/C in *iso*-propanol (H_2 (1 atm), 25 °C, 1 h) furnished the expected intermediate **61** of a tachykinin receptor antagonist in 70 % yield and 98 % *ee*.

[66] T. Nishi, T. Fukazawa, K. Ishibashi, K. Nakajima, Y. Sugioka, Y. Iio, H. Kurata, K. Ithoh, O. Mukaiyama, Y. Satoh, T. Yamaguchi, *Bioorg. Med. Chem. Lett.* **1999**, *9*, 875.



Scheme 29. Preparation of the tertiary alcohol **61**, a key derivative in the synthesis of the combined NK_1 and NK_2 tachykinin receptor antagonist.

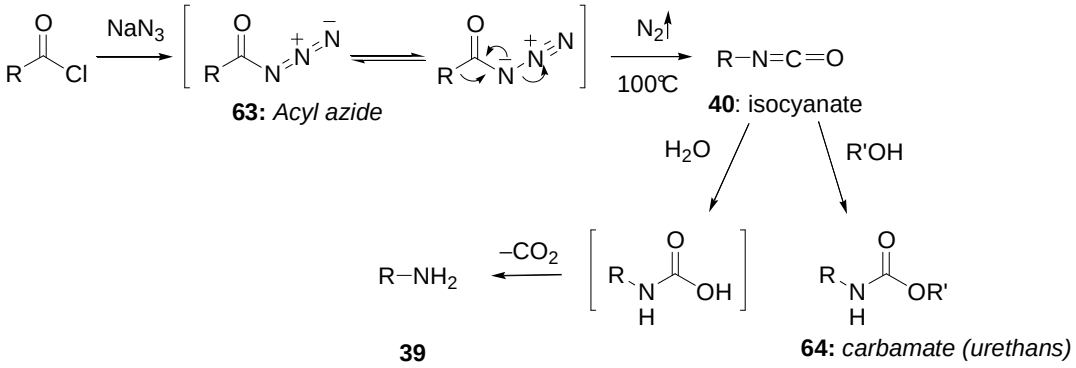
2.1.4 Synthesis of enantiomerically enriched tertiary amines *via* an oxidation / Curtius rearrangement sequence

Since the preparation of the first organic azide (phenyl azide, by *Griess* in 1864), these energy-rich intermediates have enjoyed considerable interest.[67] *Curtius* discovered the rearrangement of acyl azide into the corresponding isocyanate.[68] Azides have been used for the synthesis of heterocycles such as triazoles and tetrazoles which are functional groups presents in pharmaceuticals. Moreover the formation of the intermediate isocyanate opens the access to many other compounds of great interest nowadays like carbamates and amines. The properties of organic azides make them valuable intermediates in organic synthesis.[69]

The Curtius rearrangement is a concerted process in which the migration occurs simultaneously with the loss of nitrogen (Scheme 30). The migrating group retains its configuration. The temperature required for the reaction is ca. 100 °C. The acyl azide intermediates **63** are prepared by the treatment of acid chlorides with sodium azide. Azides rearrange in inert solvents like toluene and chloroform leading to isocyanates **40**. In the presence of reagents like alcohols, urethans **64** are formed. Amines **39** or their salts are obtained after the isocyanate hydrolysis.

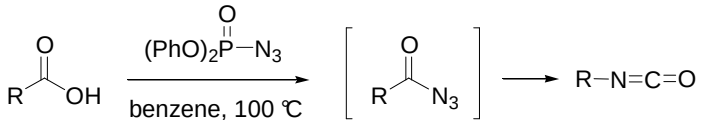
---

[67] (a) P. A. S. Smith, *Org. React.* **1946**, *3*, 337. (b) S. Bräse, C. Gil, K. Knepper, V. Zimmermann, *Angew. Chem. Int. Ed.* **2005**, *44*, 5188. (c) E. F. V. Scriven, K. Turnbull, *Chem. Rev.* **1988**, *88*, 297.
[68] (a) T. Curtius, *Ber. Dtsch. Chem. Ges.* **1890**, *23*, 3023. (b) T. Curtius, *J. Prakt. Chem.* **1894**, *50*, 275.
[69] (a) "*Chemistry of Halides, Pseudo-halides and Azides*", Part 1 and 2, Ed. S. Patai, Wiley, Chichester, **1995**. (b) "*Azides and Nitrenes – Reactivity and Utility*", Ed. E. F. V. Scriven, Academic Press, New York, **1984**.



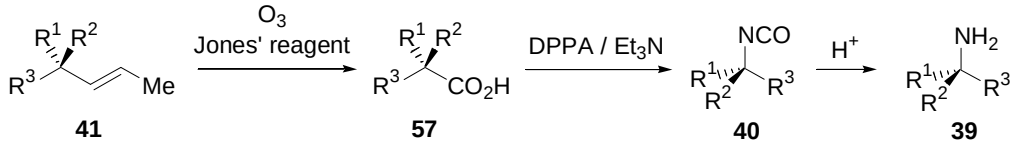
Scheme 30. The Curtius rearrangement.[68]

The reaction can also be carried out directely on carboxylic acids using diphenylphosphoryl azide (DPPA)[70] and triethylamine in refluxing solvent to give isocyanates (Scheme 31).



Scheme 31. Curtius rearrangement of carboxylic acids with diphenylphosphoryl azide.

An oxidation / Curtius rearrangement sequence should allow the synthesis of enantiomerically enriched tertiary amines **39** *via* the carboxylic acid **57** and the isocyanate **40** (Scheme 32).



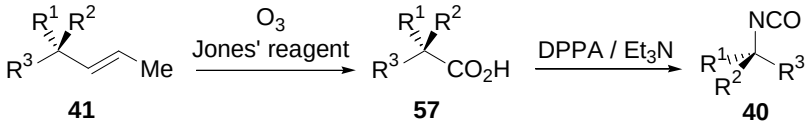
Scheme 32. Oxidation / Curtius rearrangement sequence for the enantioselective preparation of tertiary amines.

The alkenes **32**, **41a, 41c** and **41d** were cleaved by the action of ozone and subsequently treated with Jones' reagent (CrO_3/H_2SO_4) affording the corresponding carboxylic acids **57a-d** in 60-68 % yield (Table 6). They were heated with $(PhO)_2P(O)N_3$ in toluene for 1 h in the presence of Et_3N and afforded the isocyanates **40a-d** in 68-95 % yield. Moreover, the rearrangement occurred with full retention of the chiral information. In all cases, no loss of

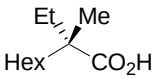
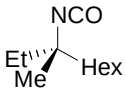
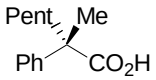
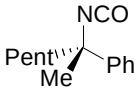
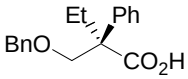
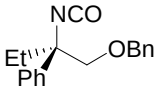
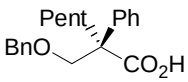
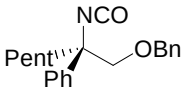
[70] (a) T. Shioiri, K. Ninomiya, S. Yamada, *J. Am. Chem. Soc.* **1972**, *94*, 6203. (b) D. Kim, S. M. Weinreb, *J. Org. Chem.* **1978**, *43*, 125.

the enantiomeric excess was observed (Table 6). The isocyanates were stable compounds and can be easily isolated.

Table 6. Preparation of carboxylic acids **57** and isocyanates **40** by ozonolysis/ Curtius rearrangement sequence.



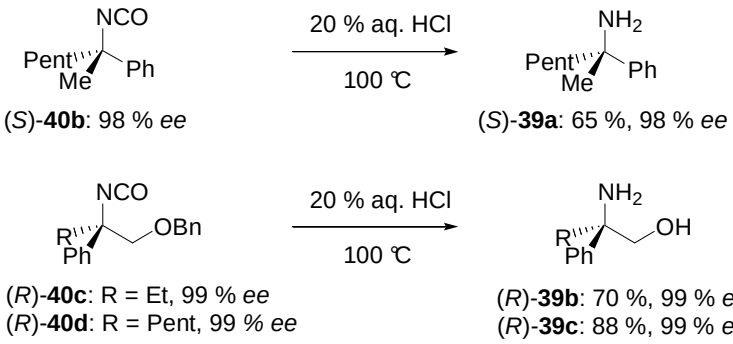
41 **57** **40**

Entry	(*E*)-Alkenes (*ee* %)	Carboxylic Acids	Yield (%)[b]	Isocyanates	Yield (%)[b]	*ee* (%)[a]
1	(*S*)-**41a** (98)	 (*S*)-**57a**	68	 (*S*)-**40a**	68	98
2	(*R*)-**32** (98)	 (*S*)-**57b**	79	 (*S*)-**40b**	95	98
3	(*R*)-**41c** (99)	 (*R*)-**57c**	65	 (*R*)-**40c**	85	99
4	(*R*)-**41d** (99)	 (*R*)-**57d**	60	 (*R*)-**40d**	88	99

[a] The enantiomeric excess was determined by HPLC or GC. In each case the racemic product was prepared for HPLC or GC calibration. [b] Yield of analytically pure product

Representatively, isocyanates **40b**, **40c** and **40d** were hydrolyzed in refluxing 1 N HCl and afforded the corresponding amines **39a-c**[71] (Scheme 33). Interestingly, compounds **40c** and **40d** were converted in a single step into chiral amino-alcohols **39b** (70 %) and **39c** (88 %). This sequence proved to be a powerful tool to prepare chiral tertiary amines and chiral amino-alcohols,[72] which are of interest for the pharmaceutical industry.

[71] J. M. Elliott, M. Jason, J. L. Castro, G. G. Chicchi, L. C. Cooper, K. Dinnell, G. J. Hollingworth, M. P. Ridgill, W. Rycroft, M. M. Kurtz, D. E. Shaw, C. J. Swain, K.-L. Tsao, L. Yang, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1755.
[72] (a) S. C. Bergmeier, *Tetrahedron* **2000**, *56*, 2561. (b) D. J. Ager, I. Prakash, D. R. Schaad, *Aldrichimica Acta* **1997**, *30*, 3.



Scheme 33. Conversion of isocyanates into amines and amino-alcohols.

2.1.5 Conclusion

We have shown that an excellent transfer of chirality is observed in copper(I)-mediated allylic substitution reactions. Quaternary centers can be generated in high enantioselectivity. In addition, further derivatization of these chiral alkenes, allowed the preparation of more functionalized aldehydes, carboxylic acids or diols.

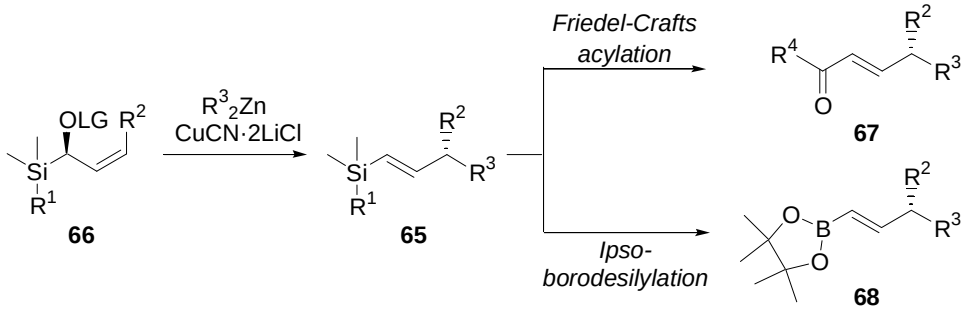
We have developed a straightforward sequence for the synthesis of tertiary alcohols in high enantioselectivity by an oxidation reaction followed by a Baeyer-Villiger rearrangement. Moreover, we have shown that a Curtius rearrangement on the corresponding chiral carboxylic acids provided a stereoselective approach to amines bearing a chiral tertiary center or to chiral amino-alcohol derivatives.

2.2 Preparation of (*E*)-alkenylsilanes bearing an α-chiral center

2.2.1 Introduction

Organosilicium chemistry[73] has found many applications in the development of organic methodology, total synthesis and industrial applications. Organosilanes are interesting building blocks in organic synthesis due to the large number of transformations that the C–Si bond can undergo. Alkenylsilanes have been widely recognized as intermediates for many applications.[74] They have been particularly used in palladium-catalyzed cross coupling reactions since the pioneering work of *Hiyama*[75,76] and then increasingly investigated in the recent years. Their preparation remains a challenging task and over the last few decades considerable effort has been made to find new routes towards them.

In the second part of this work, we will present a method toward the enantioselective preparation of (*E*)-alkenylsilanes of type **65** containing an α stereogenic center *via* a copper(I)-mediated *anti*-S_N2' allylic substitution of pentafluorobenzoate derivatives **66** (Scheme 34). Then, we will show how compounds of type **65** could be usefully derivatized into α,β-unsaturated ketones of type **67** (Friedel-Crafts acylation) or into the boronic ester derivatives **68** (*ipso*-borodesilylation).



Scheme 34. Enantioselective preparation of (*E*)-alkenylsilanes and their derivatizations.

[73] (a) E. Colvin, "*Silicon in Organic Synthesis*" Butterworth, New York, **1981**; (b) W. P. Weber, "*Silicon Reagents for Organic Synthesis"* in "*Reactivity and Structure Concepts in Organic Chemistry 14"*, Springer-Verlag, Berlin Heidelberg, **1983**; (c) M. A. Brook, "*Silicon in Organic, Organometallic, and Polymer Chemistry"*, Wiley, New York, **2000**; (d) I. Fleming, "*Science of Synthesis*", Thieme, Stuttgart, vol. 4, **2002**, 685.

[74] For reviews, see for example: (a) S. E. Denmark, R. F. Sweis, *Chem. Pharm. Bull.* **2002**, *50*, 1531; (b) S. E. Denmark, R. F. Sweis, *Acc. Chem. Res.* **2002**, *35*, 835.

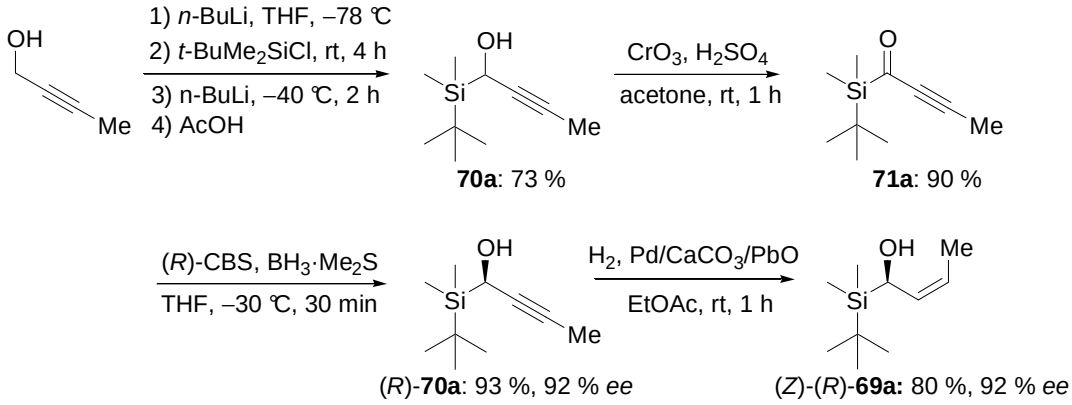
[75] (a) T. Hiyama, "*Metal Catalyzed Cross-Coupling Reactions"*, Chapter 10, Ed. F. Diederich, P. J. Stang, Wiley-VCH, Weinheim, **1998**; (b) T. Hiyama, E. Shirakawa, *Topics in Current Chemistry* **2002**, *219*, 61; (c) Y. Hatanaka, T. Hiyama, *Synlett* **1991**, 845.

[76] (a) B. M. Trost, M. R. Machacek, Z. T. Ball, *Org. Lett.* **2003**, *5*, 1895; (b) J. C. Anderson, S. Anguille, R. Bailey, *Chem. Commun.* **2002**, 2018; See also the work of Yoshida: (c) K. Itami, K. Mitsudo, T. Kamei, T. Koike, T. Nokami, J. Yoshida, *J. Am. Chem. Soc.* **2000**, *122*, 12013; (d) K. Itami, T. Nokami, J. Yoshida, *J. Am. Chem. Soc.* **2001**, *123*, 12013; (e) K. Itami, T. Nokami, Y. Ishimura, K. Mitsudo, T. Kamei, J. Yoshida, *J. Am. Chem. Soc.* **2001**, *123*, 11585.

2.2.2 Enantioselective copper(I)-mediated *anti*-S_N2' allylic substitution

It is possible to prepare alkenylsilanes bearing an α-chiral center *via* an *anti*-S_N2' allylic substitution reaction. To answer this question we chose to insert a silicon atom in the allylic position and in the α position of the leaving group because, after the substitution reaction, it would gave rise to an alkenylsilane intermediate. As mentioned previously, alkenylsilanes are of great interest in organic synthesis.

As the substituents on the silicon atom may have a great influence on the reactivity of the resulting alkenylsilane, we decided to prepare two different α-hydroxysilanes. The first one contained only alkyl groups on the silicon atom (**69a**, *t*-$BuMe_2Si$-) and the second one contained a phenyl residue (**69b**, $PhMe_2Si$-). This silane **69a** was synthesized starting from the α-hydroxysilane **70a** which was prepared *via* a retro-Brook rearrangement reaction from 2-butyn-1-ol[77] and TBDMSCl (Scheme 35). Subsequent Jones oxidation gave the silyl ketone **71a** in 90 % yield whose enantioselective reduction with $BH_3 \cdot Me_2S$ complex in the presence of the Corey-Bakshi-Shibata catalyst (*R*)-2-methyl-CBS-oxazaborolidine[78] gave the alcohol (*R*)-**70a** in 92 % and 92 % *ee*.[79] (*Z*)-Hydroxysilane (*R*)-**69a** was obtained by hydrogenation using the Lindlar catalyst ($Pd/CaCO_3/PbO$)[77] in 80 % yield.

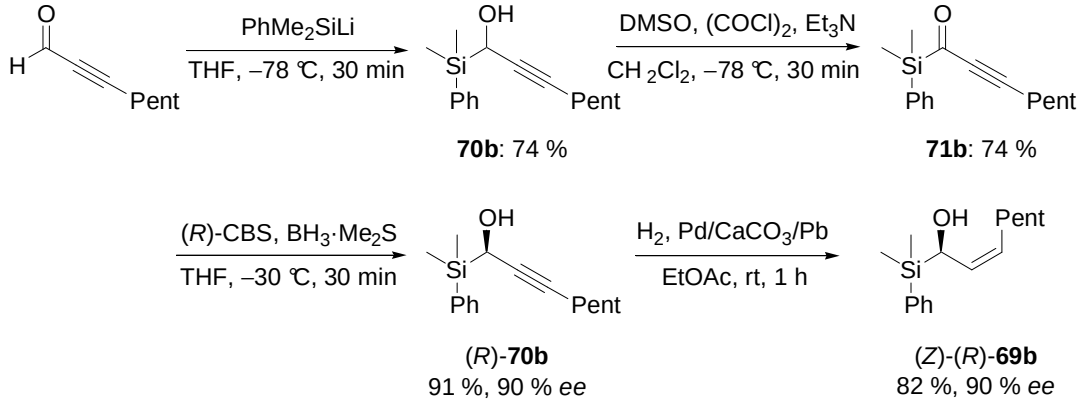


Scheme 35. Synthesis of (*Z*)-hydroxy silane **69a**.

The preparation of α-hydroxysilane **69b** was prepared in a similar way starting from the α-hydroxysilane **70b**, which was prepared by the reaction of 2-octynal with

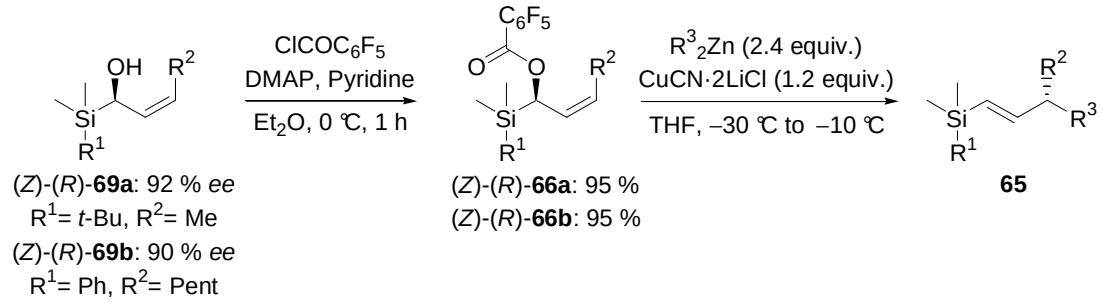
[77] K. Sakaguchi, M. Higashino, Y. Ohfune, *Tetrahedron* **2003**, *59*, 6647.
[78] (a) E. J. Corey, R. K. Bakshi, S. Shibata, *J. Am. Chem. Soc.* **1987**, *109*, 5551; (b) E. J. Corey, C. J. Helal, *Angew. Chem. Int. Ed.* **1998**, *37*, 1986.
[79] B. K. Guintchin, S. Bienz, *Organometallics* **2004**, *23*, 4944.

phenyldimethylsilyllithium ($PhMe_2SiLi$)[80] (Scheme 36). Swern oxidation[79] gave the silyl ketone **71b** (74 %) and subsequent CBS reduction led to the chiral propargylic alcohol (*R*)-**70b** in 91 % and 90 % *ee*. Hydrogenation with Lindlar catalyst afforded the allylic silane (*Z*)-(*R*)-**69b** in 82 % yield and 90 % *ee*.



Scheme 36. Synthesis of (*Z*)-hydroxysilane **69b**.

The allylic alcohols **69a** and **69b** were converted into the allylic pentafluorobenzoates **66**, which turned to be the more efficient leaving group in this case, and were tested in the allylic substitution reaction (Scheme 37).



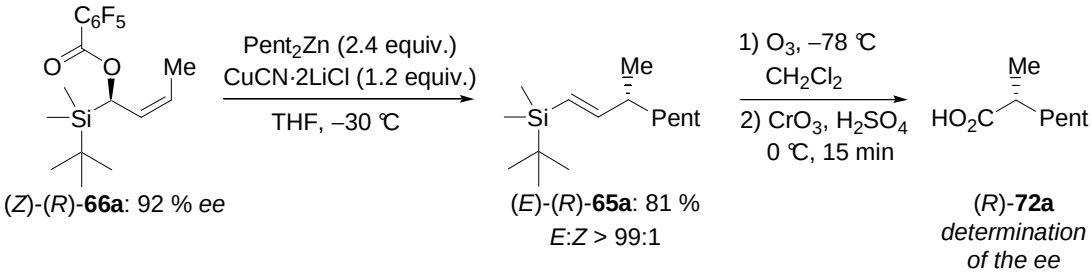
Scheme 37. Transformation into the pentafluorobenzoate derivative and allylic substitution.

The first experiment was run with the benzoate **66a** using the standard conditions (see paragraph 2.1) with dipentylzinc (2.4 equiv.) in the presence of CuCN·2LiCl (1.2 equiv.) in THF at −30 °C to −10 °C. The convertion was complet after 1 h at −10 °C and afforded the corresponding (*E*)-alkenylsilane (*R*)-**65a** in 81 % yield and 82 % *ee* (entry 1, Table 7). The transfer of chirality was low compared to the results obtained with related systems. We decided to modify the reaction conditions by adding NMP as a cosolvent since such solvent

[80] (a) D. J. Ager, I. Fleming, S. K. Patel, *J. Chem. Soc., Perkin Trans. 1* **1981**, 2520; (b) A. Romero, K. A. Woerpel, *Org. Lett.* **2006**, *8*, 2127.

has a beneficial effect for disubstituted allylic systems.[36] Also the temperature played a crucial role (see Table 7). Indeed, by lowering the temperature, the enantiomeric excess became better. At −30 °C, we have reached 84 % *ee* (entry 2), at −50 °C, 86 % (entry 3) and finally by starting at −78 °C and warming up slowly to −50 °C, we could obtain a *ee* value of 90 % after 24 h (entry 4). The *ee* could not be determined on the alkenylsilane **65a** directly, but the corresponding carboxylic acid derivative **72a** was used.

Table 7. Optimization of the allylic substitution on substrate **66a**.



(*Z*)-(*R*)-**66a**: 92 % *ee*

(*E*)-(*R*)-**65a**: 81 %
E:*Z* > 99:1

(*R*)-**72a**
determination of the ee

Entry	Temperature	Solvent	Reaction time	*ee* (%)[a]
1	−30 °C to −10 °C	THF	1 h	82
2	−30 °C	THF:NMP (2:1)	3 h	84
3	−50 °C	THF:NMP (2:1)	10 h	86
4	−78 °C to −50 °C	THF:NMP (2:1)	24 h at −50 °C	90

[a] The enantiomeric excess was determined by HPLC or GC analysis on the derivatized product. In each case the racemic product was prepared for HPLC or GC calibration.

Earlier studies have emphasized that on disubstituted allylic systems the *Z*-isomer is the one that gave higher *ee* values because it displays considerable 1,3-strain[27,36]. The relevant reactive conformers are those having the leaving group anti-periplanar to the olefin plan (e.g. the conformers **A**-**D**, Figure 1). Indeed, for the two conformers **A** and **B** of the *Z*-isomer the energy of conformer **B** is so high, that only the reaction pathway including the conformer **A** is involved. In the case of the *E*-isomer, the two conformers **C** and **D** are much closer in energy, so that both pathways are possible. In this case a mixture of *E* and *Z*-products is obtained.

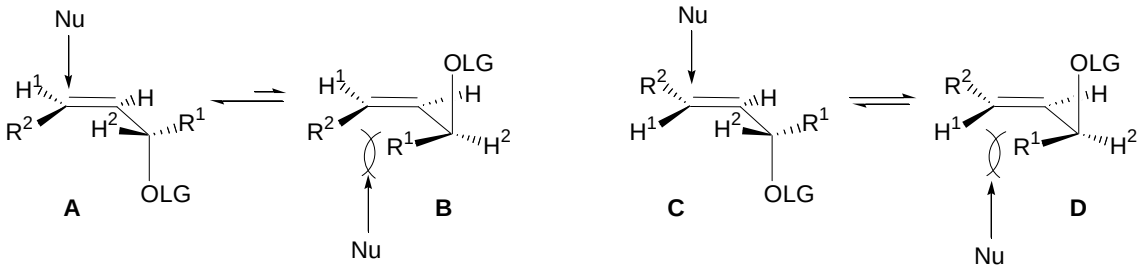
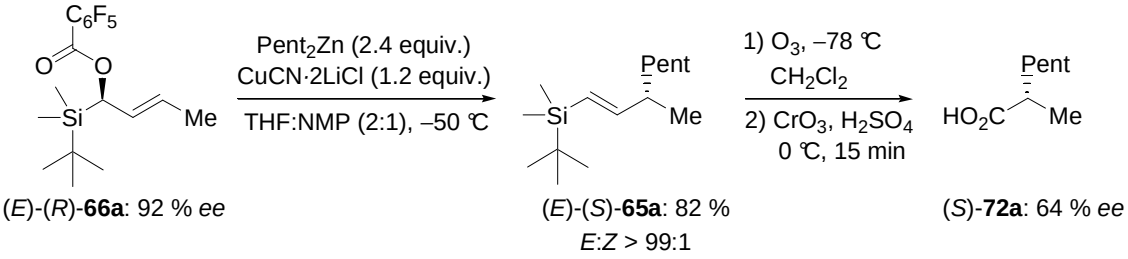


Figure 1. 1,3-Allylic strain of the *E* and *Z*-isomer of disubstituted alkene.

In the present case, when (*E*)-(*R*)-**66a** was reacted with $Pent_2Zn$ in the presence of CuCN·2LiCl it afforded (*E*)-(*S*)-**65a** in similar yield but in only 64 % *ee*. Note that it gave the opposite enantiomer (Scheme 38).



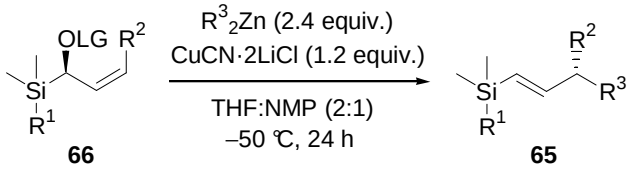
Scheme 38. S_N2' allylic substitution on (*E*)-(*R*)-**66a**.

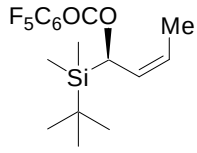
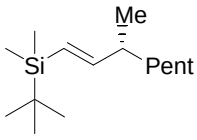
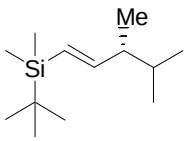
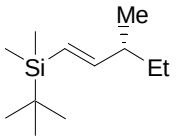
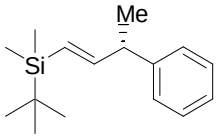
Under the same reaction conditions, the (*Z*)-pentafluorobenzoate **66a** was reacted with various diorganozincs as summarized in Table 8. Thus, a secondary diorganozinc like *i*-Pr_2Zn (entry 2, Table 8) reacted in high *anti*-S_N2' regioselectivity (no S_N2 product observed) and gave the corresponding alkenylsilane **65b** in 90 % yield and 90 % *ee*. Smaller diorganozinc like Et_2Zn gave excellent results (**65c**: 89 %, 88 % *ee*, entry 3) even though the difference between the two substituents was rather small. The substitution was not only limited to alkyl groups but tolerated also aryl substituents. Thus, Ph_2Zn reacted smoothly with the allylic benzoate **66a** in the presence of CuCN·2LiCl affording the alkenylsilane **65d** with the same level of enantioselectivity (86 %, 89 % *ee*, entry 4). More interestingly, functionalized diarylzinc reagents[81] reacted similarly providing the corresponding methyl benzoate ester **65e** (65 %, 89 % *ee*, entry 5) and *o*-methoxy benzene **65f** (60 %, 90 % *ee*, entry 6). A zinc reagent such as $[Ph(CH_2)_2]_2Zn$ led to moderate results due to its lower reactivity and higher temperature required (–30 °C to rt, 24 h, 60 %, 84 % *ee*, entry 7). Another limitation was found with functionalized diorganozincs such as $[PivO(CH_2)_3]_2Zn$. The alkenylsilane **65h** was

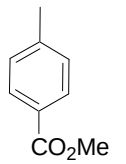
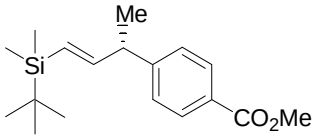
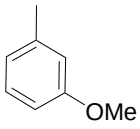
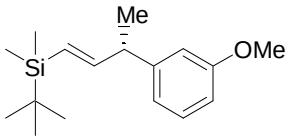
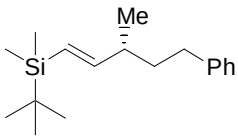
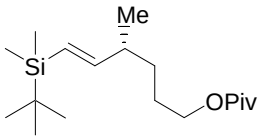
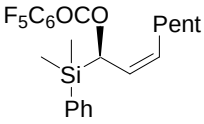
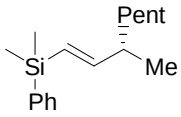
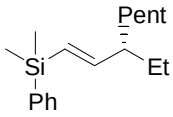
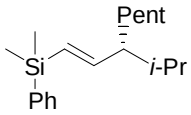
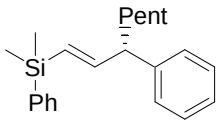
[81] F. F. Kneisel, M. Dochnahl, P. Knochel, *Angew. Chem. Int. Ed.* **2004**, *43*, 1017.

obtained with 80 % *ee* and 73 % yield (entry 8). In fact, this diorganozinc required higher temperatures (−30 °C to rt, 24 h) to undergo the substitution. Modification of the substituents on the silicon atom (from *t*-Bu to Ph residue) did not affect the quality of the transfer of chirality. Thus, the (*Z*)-pentafluorobenzoate **66b** (entry 9) was added to a solution of Me_2Zn (2.4 equiv.) and CuCN·2LiCl (1.2 equiv.) and reacted smoothly at −30 °C for 16 h affording the expected substituted alkenylsilane **65i** with almost no loss of the enantiomeric excess (89 % *ee*) and in excellent yield (95 %). Et_2Zn (86 %, 89 % *ee*, entry 10), *i*-Pr_2Zn (89 %, 87 % *ee*, entry 11) as well as Ph_2Zn (93 %, 89 % *ee*, entry 12) gave excellent results although the addition of *i*-Pr_2Zn showed a poorer transfer (only 87 % *ee* recovered) probably due to the steric hindrance.

Table 8. Preparation of (*E*)-alkenylsilanes **65a-l** by allylic substitution of allylic silanes **66a** and **b**.



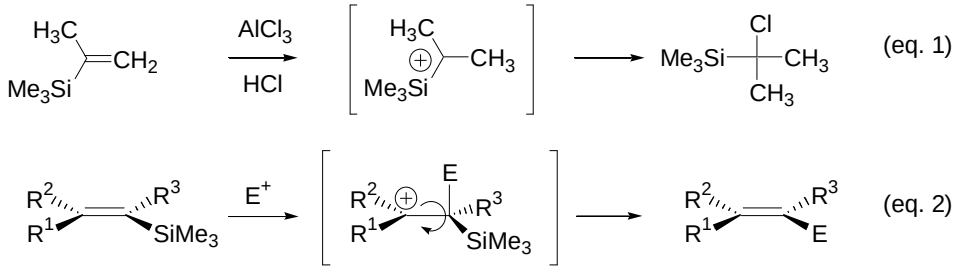
Entry	Allyl substrate *ee* (%)[a]	R_2Zn (R)	(*E*)-Alkenylsilane	Yield (%)[b]	*ee* (%)[a]
					
1	**66a** (92)	Pent	**65a**	81	90
					
2	**66a**	*i*-Pr	**65b**	90	90
					
3	**66a**	Et	**65c**	89	88
					
4	**66a**	Ph	**65d**	86	89

Entry	Allyl substrate *ee* (%)[a]	R_2Zn (R)	(*E*)-Alkenylsilane	Yield (%)[b]	*ee* (%)[a]
5	**66a**		 **65e**	65	89[c]
6	**66a**		 **65f**	60	90[c]
7	**66a**	$(CH_2)_2Ph$	 **65g**	60	84[d,e]
8	**66a**	$PivO(CH_2)_3$	 **65h**	73	80[d,e]
9	 **66b** (90)	Me	 **65i**	95	89
10	**66b**	Et	 **65j**	86	89
11	**66b**	*i*-Pr	 **65k**	89	87[d]
12	**66b**	Ph	 **65l**	93	89[d]

[a] The enantiomeric excess was determined by HPLC or GC analysis on the derivatized product. In each case the racemic product was prepared for HPLC or GC calibration. [b] Yield of analytically pure product. [c] The ee was determined on the silane by HPLC. [d] The ee was determined on the corresponding α,β-unsaturated ketone, see table 9. [e] –30 °C to rt, 24 h.

2.2.3 Derivatization of (*E*)-alkenylsilanes

Alkenylsilanes react with a wide range of electrophiles to give products of substitution or addition. The stereochemical result of such substitutions depends on a number of factors. The regiochemistry of the substitution / addition reaction is controlled by the β-effect[82] which ensures that the carbonium ion is formed at the carbon in the β position to the silyl group. Exeptions occur for vinyltrialkylsilanes, like the isopropenyltrimethylsilane, in which the carbocation is not formed in the β-position but in α to the silicon atome and gave the α-chloroisopropyltrimethylsilane (Scheme 39, equation 1).[83] Usually, the substitution takes place at the silicon-bearing carbon when polysubstituted alkenylsilanes are used and in most cases with retention of configuration. Indeed, the β-silyl cation formed is best stabilized if the carbon-silicon σ-bond is coplanar with the adjacent vacant π-orbital and a rotation around the carbon-carbon single bond takes place. The overall result of the reaction is retention of the configuration at the double bond (Scheme 39, equation 2).



Scheme 39. Regioselectivity of the substitution on alkenylsilanes.

The next three sections will present some of the possible derivatizations of (*E*)-alkenylsilanes **65** resulting from S_N2' allylic substitutions.

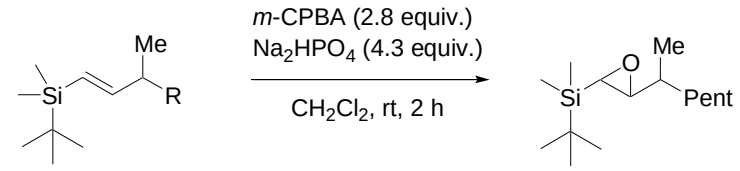
a) Epoxidation:

The epoxidation of alkenylsilanes with peracids, such as *m*-CPBA yielding the α-silyl epoxide is a well known reaction. Thus, alkenylsilane **65a** was oxidized with *m*-CPBA (2.8 equiv.) in the presence of Na_2HPO_4 (4.3 equiv.) in CH_2Cl_2 (rt, 2 h) and furnished the silyl

[82] (a) W. Hanstein, T. G. Taylor, *Tetrahedron Lett.* **1967**, 4451; (b) J. Chandrasekhar, W. L. Jorgensen, *J. Am. Chem. Soc.* **1985**, *107*, 1496; (c) A. W. P. Jarvie, *Organomet. Chem. Rev. A* **1970**, *6*, 153; (d) J. B. Lambert, *Tetrahedron* **1990**, *46*, 2677.

[83] (a) L. H. Sommer, D. L. Bailey, G. M. Goldberg, C. E. Buck, T. S. Bye, F. J. Evans, F. C. Whitmore, *J. Am. Chem. Soc.* **1954**, *76*, 1613; (b) K. E. Koenig, W. P. Weber, *J. Am. Chem. Soc.* **1973**, *95*, 3416.

epoxide **73a** as a mixture of diastereomers (60:40, Scheme 43). No diastereoselectivity was observed in the epoxidation neither on the silyl epoxide **73b** nor on **73d** containing a larger γ substituent like *i*-Pr or Ph (Scheme 40).



(*E*)-(*R*)-**65a**: R = Pent
(*E*)-(*R*)-**65b**: R = *i*-Pr
(*E*)-(*R*)-**65c**: R = Et
(*E*)-(*R*)-**65d**: R = Ph

73a: d:r = 60:40
73b: d:r = 60:40
73c: d:r = 55:45
73d: d:r = 50:50

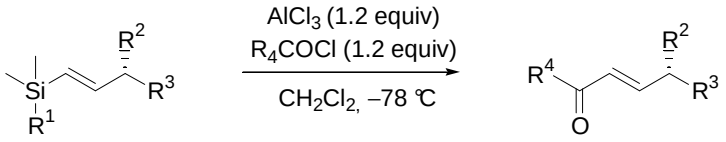
Scheme 40. Epoxidation reaction of (*E*)-alkenylsilanes **65a-d**.

b) Friedel-Crafts acylation:

Alkenylsilanes of type **65** underwent Friedel-Crafts acylation[84] reactions in which the acyl group replaced the silyl group providing a synthesis of α,β-unsaturated ketones. Thus, the alkenylsilane **65a** (entry 1 of Table 9) was typically treated with $AlCl_3$ (1.1 equiv.) and benzoyl chloride (1.1 equiv.) in CH_2Cl_2 at −78 °C and after 3 h at 25 °C afforded the corresponding (*E*)-α,β-unsaturated ketone **67a** with full retention of the chiral information (65 %, 90 % *ee*). Various acid chlorides could be similarly reacted with alkenylsilanes **65**. For example, aliphatic acid chloride like the bulky pivaloyl chloride (entry 2) or acetyl chloride (entry 3) were added with retention of the (*E*) stereochemistry (90 % *ee* respectively for **67b** and **67c**). Interestingly substituted α,β-unsaturated furyl ketone **67d** (entry 4) could be easily prepared with high enantioselectivity (66 % yield, 90 % *ee*) by this method. Similarly, alkenylsilanes of type **65i-l** (entry 8 to 11) gave the corresponding α,β-unsaturated ketones **67j** (80 %, 89 % *ee*, entry 9), **67k** (86 %, 87 % *ee*, entry 10) and **67l** (75 %, 89 % *ee*, entry 11) when treated with $AlCl_3$ and benzoyl chloride, with full retention of the enantiopurity. Interestingly the fluoro-substituted α,β-unsaturated ketone **67h** (entry 8) was prepared in high enantioselectivity (68 % yield, 89 % *ee*) by this method.

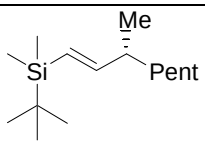
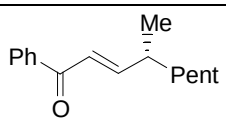
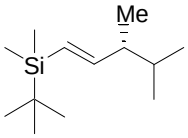
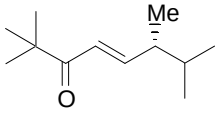
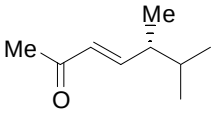
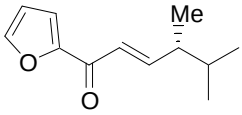
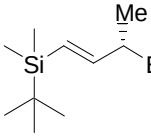
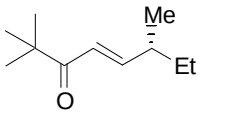
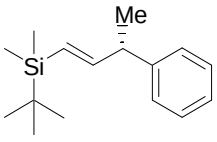
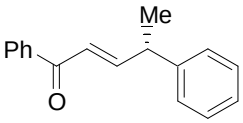
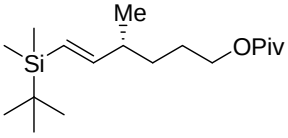
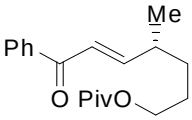
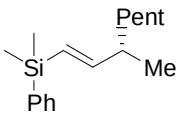
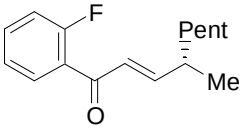
[84] (a) L. A. Paquette, W. E. Fristad, D. S. Dime, T. R. Bailey, *J. Org. Chem.* **1980**, *45*, 3017; (b) H. Zhao, M.-Z. Cai, *Syn. Commun.* **2003**, *33*, 1643.

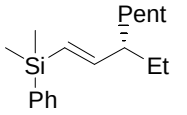
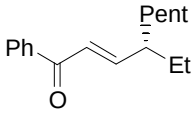
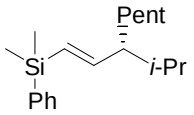
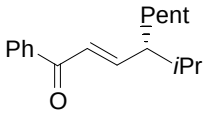
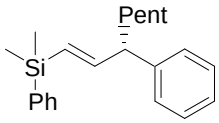
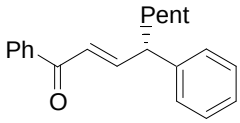
Table 9. Preparation of (*E*)-α,β-unsaturated ketones **67a-k** by Friedel-Crafts acylation on alkenylsilanes **65a-l**.



65: R^1= *t*-Bu or Ph

(*E*)-**67**

Entry	(*E*)-Alkenylsilane (*ee* %)	(*E*)-α,β Unsaturated ketone	Yield (%)[b]	*ee* (%)[a]
1	 **65a** (90)	 **67a**	65	90
2	 **65b** (90)	 **67b**	62	90
3	**65b** (90)	 **67c**	68	90
4	**65b** (90)	 **67d**	66	90
5	 **65c** (88)	 **67e**	78	88
6	 **65d** (89)	 **67f**	71	89
7	 **65h** (80)	 **67g**	65	80
8	 **65i** (89)	 **67h**	68	89

Entry	(*E*)-Alkenylsilane (*ee* %)	(*E*)-α,β Unsaturated ketone	Yield (%)[b]	*ee* (%)[a]
9	 **65j** (89)	 **67i**	80	89
10	 **65k** (87)	 **67j**	86	87
11	 **65l** (89)	 **67k**	75	89

[a] The enantiomeric excess was determined by HPLC or GC analysis. In each case the racemic product was prepared for HPLC or GC calibration. [b] Yield of analytically pure product.

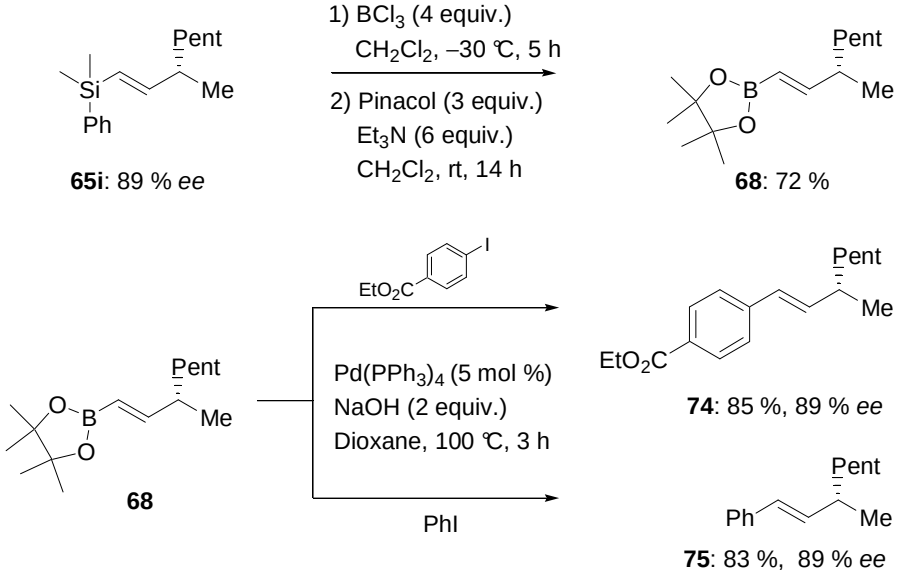
c) *Ipso*-borodesilylation and cross-coupling reaction:

Organosilanes were previously thought to be too unreactive to be effective cross-coupling partners. The small electronegativity difference between silicon and carbon as well as the absence of low lying empty orbitals resulted in a relatively weak nucleophilic reagent for cross-couplings. The use of fluorosilanes was therefore a significant breakthrough, demonstrating that in the presence of a nucleophilic promoter (usually TBAF), these compounds are converted to a pentacoordinate "ate" species, which was postulated to undergo the coupling reaction due to its enhanced polarization at the carbon-silicon bond. Because silicon-based compounds are generally non-toxic, have a low molecular weight, and are easily incorporated into molecules by a variety of methods, the need of developing other silicon-based cross-coupling systems was recognized. Indeed, a drawback of this cross-coupling is that it suffers from generality.[74]

With our systems, any attempts to cross-couple the alkenylsilane derivatives failed. The activation of the silyl group is crucial to undergo a cross-coupling reaction. For instance, the alkenylsilane **65a**, containing only alkyl residues, seemed practically inert to all type of activations (TBAF or Ag_2O). Moreover, there are very few reports of cross-coupling reactions of trisubstituted alkyl silanes, the only exception being the TMS group[85]. In the case of the

[85] T. Nokami, Y. Tomida, T. Kamei, K. Itami, J. Yoshida, *Org. Lett.* **2006**, *8*, 729.

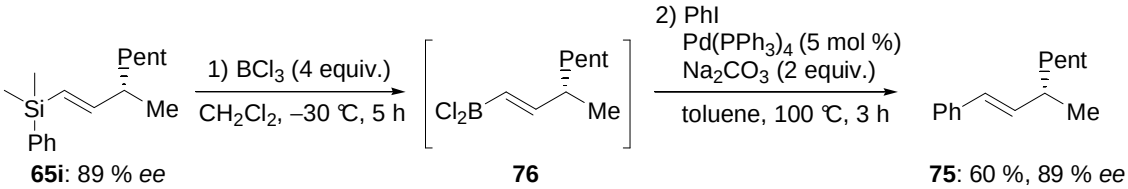
phenyldimethylalkenylsilane, it appeared to be more labile but no cross-coupling product could be isolated. Although, alkenylsilane **65i** reacted with silicon coupling promoter like TBAF or *t*-BuOK/crown ether (18-C-6)[86], no cross-coupling was observed. However, the unsaturated silane **65i** could be successfully borodesilylated.[87] Thus, treatment of alkenylsilane **65i** with BCl_3 (5 h at –30 °C) in CH_2Cl_2 followed by derivatization with pinacol in presence of triethylamine (one-pot) afforded the alkenyl boronopinacolate **68** in 72 % yield and with perfect retention of the stereochemistry (Scheme 41). Obviously, the boronate could serve as coupling partner for the Suzuki-Miyaura cross-coupling reaction.[88] The boronate **68** (Scheme 41) was first reacted with *para*-ethyl iodobenzoate in the presence $Pd(PPh_3)_4$ (5 mol %, 3 h at reflux in dioxane) to give the aryl substituted alkene **74** in 85 % yield with retention of the stereochemistry. The cross-coupling occurred under similar conditions when reacted with PhI and gave the phenyl substituted alkene **75** in 83 % yield.



Scheme 41. *Ipso*-borodesilylation of **65i** and successive Suzuki-Miyaura cross-coupling.

In addition, an *in situ ipso*-borodesilylation-cross-coupling procedure[87] could be performed, in a one-pot operation. Thus, in the presence of BCl_3 (5 h, –30 °C) the alkenylsilane **65h** (Scheme 42) was converted into the dichloroborane **76**, which reacted in the typical Suzuki-Miyaura conditions with phenyliodide and palladium(0) to afford the expected disubstituted alkene **75** in 60 % yield.

[86] J. C. Anderson, A. Flaherty, *J. Chem. Soc., Perkin Trans 1* **2000**, 3025.
[87] (a) F. Babudri, G. M. Farinola, V. Fiandanese, L. Mazzone, F. Naso, *Tetrahedron* **1998**, *54*, 1085; (b) K. Itami, T. Kamei, J. Yoshida, *J. Am. Chem. Soc.* **2003**, *125*, 14670; (c) Z. Zhao, V. Snieckus, *Org. Lett.* **2005**, *7*, 2523.
[88] N. Miyaura, A. Suzuki, *Chem. Rev*. **1995**, *95*, 2457.



65i: 89 % *ee* **76** **75**: 60 %, 89 % *ee*

Scheme 42. Sequential *ipso*-borodesilylation of **65i** followed by *in situ* Suzuki-Miyaura cross-coupling under Pd-catalyzed conditions.

2.2.4 Conclusion

In this second part, we have developed a highly diastereo- and enantioselective method to prepared (*E*)-alkenylsilanes bearing an α-chiral center *via* copper(I)-mediated *anti*-S_N2' allylic substitution. Chiral allylic silane substrates reacted with a variety of diorganozinc reagents with excellent transfer of chirality. The preparation of alkyl, aryl or functionalized substituted alkenylsilanes was therefore possible.

These resulting compounds turned to be very versatile building blocks and could be readily transformed into α,β-unsaturated ketones by Friedel-Crafts acylation reactions or into the corresponding boronates by *ipso*-borodesilylation reaction and then undergo cross-coupling reactions. However, a phenyl substituent on the silicon atom is required to undergo the *ipso*-borodesilylation. Finally, we showed that the *ipso*-borodesilylation/cross-coupling reaction could also be carried out as a one-pot operation.

2.3 S_N2' Allylic substitutions on chiral cyanohydrins derivatives

2.3.1 Introduction

Cyanohydrins occupy a unique place at the interface between chemistry and biology. On one hand, cyanohydrins have a considerable synthetic potential as chiral building blocks in organic synthesis. On the other hand, they have a distinguished enzymatic history: cyanohydrins became substrates for hydroxynitrile lyases (HNLs).[89] Advances in recent years have increased both their exploitation of the production and utilization of enantiomerically enriched cyanohydrins.[90] Chiral cyanohydrins are widespread in nature in the form of the respective glycosides and serve roughly 3000 plants and many insects as antifeedants. For organic chemists, this class of compounds offers a high synthetic potential for making other chiral compounds accessible. The development of simple synthetic procedure for such compounds, which also entail a high degree of stereoselectivity, therefore has prime importance. To this end, chiral cyanohydrins may serve as stereochemically pure starting materials.

The stereoselective syntheses of cyanohydrins can be achieved either by chemical or by enzymatic procedures. The most important chemical methods are the diastereoselective addition of trimethylsilyl cyanide and related cyanide-transfer agents to chiral aldehydes,[91] and the enantioselective addition of trimethylsilyl cyanide to aldehydes in the presence of chiral catalysts.[92] Enzymatic procedures include the oxynitrilase-catalyzed enantioselective addition of HCN to aldehydes,[93] the enantioselective hydrolysis of cyanohydrin ester racemates with esterases, and the enantioselective esterification of cyanohydrin racemates with lipases.[94]

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[89] (a) A. Hickel, M. Hasslacher, H. Griengl, *Physiol. Plant.* **1996**, *98*, 891; (b) H. Wajant, F. Effenberger, *Biol. Chem.* **1996**, *377*, 611.

[90] For reviews on cyanohydrins, see: (a) M. North, *Synlett*, **1993**, 807; (b) F. Effenberger, *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1555; (c) R. J. H. Gregory, *Chem. Rev*. **1999**, *99*, 3649.

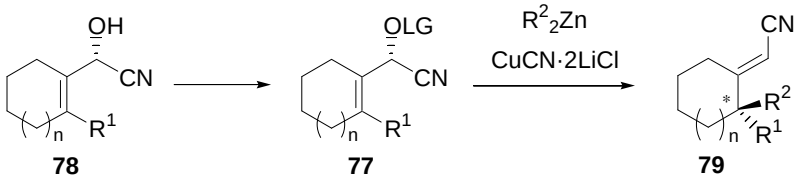
[91] J. L. García Ruano, A. M. Martín Castro, J. H. Rodríguez, *J. Org. Chem.* **1992**, *57*, 7235.

[92] (a) H. Deng, M. P. Ister, M. L. Snapper, H. A. Hoveyda, *Angew. Chem. Int. Ed.* **2002**, *41*, 1009; (b) C. A. Krueger, K. W. Kuntz, C. D. Dzierba, W. D. Wirschun, J. D. Gleason, M. L. Snapper, H. A. Hoveyda, *J. Am. Chem. Soc.* **1999**, *121*, 4284; (c) M. S. Sigman, E. N. Jacobsen, *J. Am. Chem. Soc.* **1998**, *120*, 5315; (d) S. S. Kim, G. Rajagopal, D. H. Song, *J. Organomet. Chem.* **2004**, *689*, 1734; (e) S. K. Tian, R. Hong, L. Deng, *J. Am. Chem. Soc.* **2003**, *125*, 9900; (f) M. Hayashi, Y. Miyamoto, S. Inoue, N. Oguni, *J. Org. Chem.* **1993**, *58*, 1515; (g) J. Casas, A. Baeza, C. Nájera, J. M. Sansano, J. M. Saá, *Eur. J. Org. Chem.* **2006**, 1949.

[93] See for examples: (a) L. M. van Langen, R. P. Selassa, F. van Rantwijk, R. A. Sheldon, *Org. Lett.* **2005**, *7*, 327; (b) H. Griengl, N. Klempier, P. Pöchlauer, M. Schmidt, N. Shi, A. A. Zabelinskaja-Mackova, *Tetrahedron* **1998**, *54*, 14477; (c) F. Effenberger, T. Ziegler, s. Förster, *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 458.

[94] (a) F. Effenberger, B. Gutterer, T. Ziegler, E. Eckhardt, R. Aichholz, *Liebigs Ann. Chem.* **1991**, *47*, 54; (b) E. Santaniello, P. Ferraboschi, P. Grisenti, A. Manzocchi, *Chem. Rev*. **1992**, *92*, 1071; (c) X. Liu, B. Qin, X. Zhou,

Still in the perspective to widen the scope of the copper(I)-mediated S_N2' allylic substitution reaction, it appeared natural to use cyanohydrin derivatives as starting materials. As mentioned previously, they are now easily available in enantiopure form and can undergo many synthetic reactions.[95] Therefore, we chose to start from cyclic allylic systems of type **77** containing a leaving group in the α-position of the cyano group, which are readily available from the corresponding chiral cyanohydrin **78**. *O*-benzoated cyanohydrin **77** should be able to undergo a diastereo- and enantiospecific allylic substitution reaction to form the γ-substituted α,β-unsaturated nitriles of type **78** bearing a new stereogenic center in the γ position (Scheme 43).



Scheme 43. Stereoselective S_N2' allylic substitution reaction on enantiomerically enriched *O*-benzoated cyanohydrins **77**.

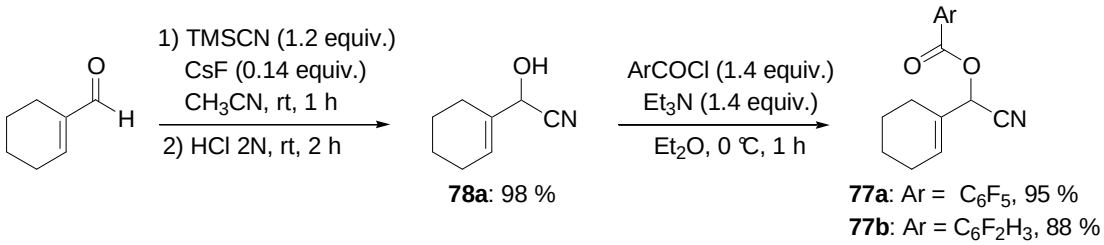
2.3.2 Enantioselective copper(I)-mediated *anti*-S_N2' allylic substitution

a) Cyclohexenyl derivative:

We started our study with the racemic cyanohydrin **78a**, which was prepared form the reaction of commercially available cyclohexenyl carbaldehyde with TMSCN in the presence of catalytic amount of cesium fluoride followed by acidic cleavage of the silyl group in 98 % yield (Scheme 44). Esterification of the hydroxyl group with various acid chlorides provided the racemic *O*-benzoated cyanohydrins **77a-c** in 88-95 % yield and allowed us to identify the best leaving group for this substrate.

B. He, X. Feng, *J. Am. Chem. Soc.* **2005**, *127*, 12224; (d) J. Casas, C. Nájera, J. M. Sansano, J. M. Saá, *Tetrahedron* **2004**, *60*, 10487; (e) T. Ooi, T. Miura, K. Takaya, H. Ichikawa, K. Maruoka, *Tetrahedron* **2001**, *57*, 867.

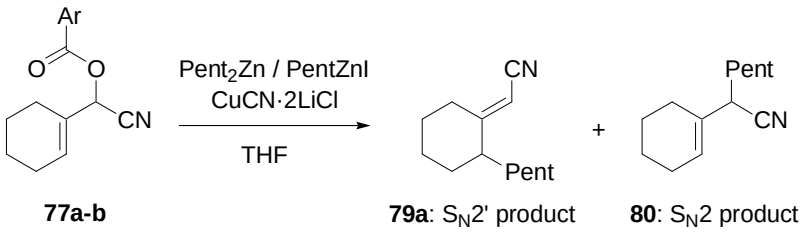
[95] (a) D. R. Deardorff, C. M. Taniguchi, S. A. Tafti, H. Y. Kim, S. Y. Choi, K. J. Downey, T. V. Nguyen, *J. Org. Chem.* **2001**, *66*, 7191; (b) E. Menéndez, R. Brieva, F. Rebolledo, V. Gotor, *J. Chem. Soc., Chem. Commun.* **1995**, 989; (c) M. Hayashi, T. Yoshiga, K. Nakatani, K. Ono, N. Oguni, *Tetrahedron* **1994**, *50*, 2821; (d) A. Baeza, J. Casas, C. Nájera, J. M. Sansano, *J. Org. Chem.* **2006**, *71*, 3837.



Scheme 44. Preparation of different *O*-benzoated cyclohexenyl cyanohydrins **77a-b**.

When substrates **77a-b** were reacted in the standard conditions with $Pent_2Zn$ and CuCN·2LiCl, in all cases no selectivity between the S_N2' and S_N2 substitution could be achieved and a 1:1 mixture of regioisomers (**79a** and **80)** was obtained (Table 10, entry 1-3). Though the best selectivity was obtained with the 2,6-difluorobenzoate leaving group **77b** in the favour of the S_N2 product (38:62, entry 2), a ratio of only 20:80 (S_N2':S_N2) could be reached under optimized conditions and with the use of PentZnCl (2 equiv., NMP as co-solvent, 48 h, entry 5). Therefore, we envisioned the synthesis of methyl-substituted cycloalkenyl derivatives that will increase the 1,3-allylic strain in the molecule and thus favore one conformer (cf. Figure 1).

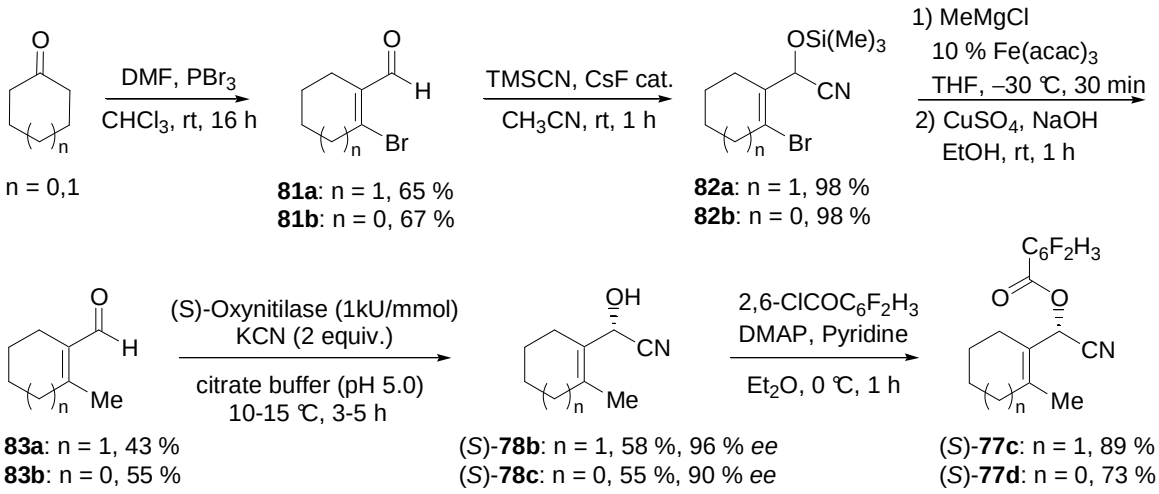
Table 10. Optimization of the allylic substitution on substrates **77a-b**.



Entry	Substrates 77 (Ar)	Conditions	Zinc reagent	S_N2':S_N2	Conversion (%)
1	**77a** (C_6F_6)	–30 °C, 1 h	$Pent_2Zn$	46:54	100
2	**77b** ($C_6F_2H_3$)	–30 °C, 1 h	$Pent_2Zn$	38:62	100
3	**77b** ($C_6F_2H_3$)	–30 °C to rt, 24 h	PentZnI	20:80	40
4	**77b** ($C_6F_2H_3$)	0 °C to rt, 16 h + NMP	PentZnI	25:75	> 70
5	**77b** ($C_6F_2H_3$)	0 °C to rt, 48 h + NMP	PentZnI (2 equiv.)	20:80	> 90
6	**77b** ($C_6F_2H_3$)	0 °C to rt, 48 h + DMPU	PentZnI (2 equiv.)	28:72	> 90

b) Methyl-cycloalkenyl derivatives:

Two starting materials were synthesized: the γ-methylated cyclopentenyl **77c** and the γ-methylated cyclohexenyl **77c** cyanohydrin derivatives (Scheme 45). In both cases, the synthesis started from the commercial cycloalkanones, which were reacted with DMF and PBr_3 to give the β-bromoaldehydes **81** in 65-67 % yield.[96] CsF-catalyzed silylcyanation with trimethylsilyl cyanide afforded the *O*-silylated cyanohydrins **82** in 98 % yield, which were subsequently reacted in an iron-mediated cross-coupling reaction[97] with MeMgCl and, after basic workup in the presence of copper sulfate, furnished the β-methylated aldehydes **83** in 43-55 % yield.[98] Enantioselective (*S*)-oxynitrilase-catalyzed[99] addition of KCN (2 equiv.) to **83** in citrate buffer,[100] yielded the chiral (*S*)-cyanohydrins in excellent enantiomeric excess ((*S*)-**78b**: 96 % *ee*, 58 % and (*S*)-**78c**: 90 % *ee*, 55 %). Finally, esterification with 2,6-difluorobenzoyl chloride furnished the benzoated derivatives **77c** and **77d** in 73-89 % yield.



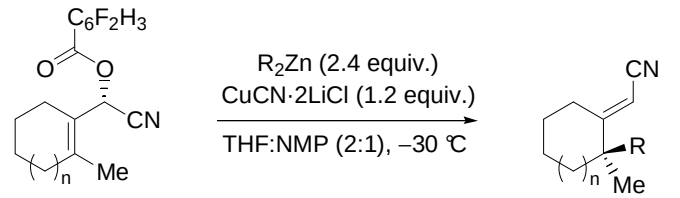
Scheme 45. Synthesis of methyl-cycloalkenyl derivatives **77c** and **77d**.

Substitution on **77c** with $Pent_2Zn$ (2.4 equiv., NMP as cosolvent, –30 °C to 0 °C) mediated by copper(I)-salt afforded in 5 h the γ-substituted unsaturated nitrile **79b** with complete transfer of chirality and good yield (96 % *ee*, 75 %, entry 1 of Table 11). The presence of a substituent in the γ-position was crucial to obtain good selectivity. No traces of

[96] (a) B. Salem, E. Delort, P. Klotz, J. Suffert, *Org. Lett.* **2003**, *5*, 2307; (b) Y. Zhang, J. W. Herndon, *Org. Lett.* **2003**, *5*, 2307.
[97] G. Cahiez, H. Avedissian, *Synthesis* **1998**, 1199.
[98] The poor yield obtained in this reaction might be explained by the high volatility of the compounds.
[99] (*S*)-Oxynitrilase aus *Manihot esculenta*, commercially available from Fluka or Julich Chemical Solutions.
[100] (a) N. Klempier, U. Pichler, H. Griengl, *Tetrahedron: Asymmetry* **1995**, *6*, 845; (b) H. Griengl, N. Klempier, P. Pöchlauer, M. Schmidt, N. Shi, A. A. Zabelinskaja-Mackova, *Tetrahedron* **1998**, *54*, 14477.

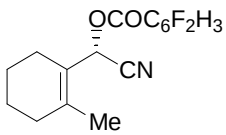
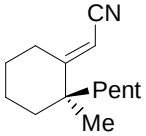
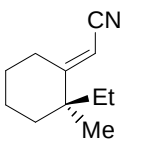
the S_N2 product could be detected and the substitution afforded only the *E*-isomer of **79b** (2D ^{1}H-NMR). Therefore, **77c** reacted similarly with Et_2Zn (entry 2, 96 % *ee*, 65 %) and $[PivO(CH_2)_3]_2Zn$ (entry 3, 96 % *ee*, 65 %) with high transfer of chirality and in good yield. Although the substitution occurred in excellent enantioselectivity, it was limited to primary alkyl substituents. Indeed, reactions with more sterically hindered groups like *i*-Pr_2Zn, *c*-Hex_2Zn or Ph_2Zn were not selective and afforded the corresponding products in poor yield. However, this was not the case for the cyclopentyl derivative **77d**, which tolerated also secondary substituents. Thus, the substitution of **77d** with $Pent_2Zn$ or Et_2Zn in the presence of CuCN·2LiCl afforded the corresponding substituted compounds **79e** (entry 4 of Table 11, 90 % *ee*, 91 %) and **79f** (entry 5, 90 % *ee*, 80 %). The substitution proceeded with excellent enantioselectivity with secondary diorganozinc reagents to furnish the sterically hindered cycloalkenes **79g** (entry 6, 90 % *ee*, 75 %) and **79h** (entry 7, 90 % *ee*, 60 %). Functionalized diorganozincs like $[Ph(CH_2)_2]_2Zn$ (entry 8) or $[PivO(CH_2)_3]_2Zn$ (entry 9) reacted similarly with **77e** and afforded **79i** in 40 % yield and **79j** in 71 % yield both with full retention of the chiral information.

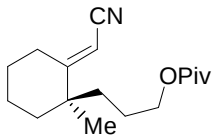
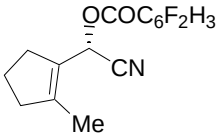
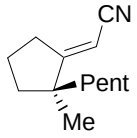
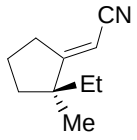
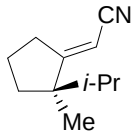
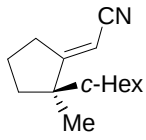
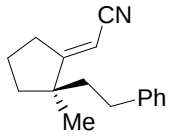
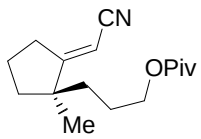
Table 11. S_N2' allylic substitutions on substrates **77c** and **77d**.



(*S*)-**77c**: n = 1
(*S*)-**77d**: n = 0

(*E*)-**79**: n = 0, 1

Entry	Allyl substrate *ee* (%)[a]	R_2Zn (R)	(*E*)-Unsaturated nitrile	Yield (%)[b]	*ee* (%)[a]
1	 **77c** (96)	Pent	 **79b**	75	96
2	**77c** (96)	Et	 **79c**	65	96

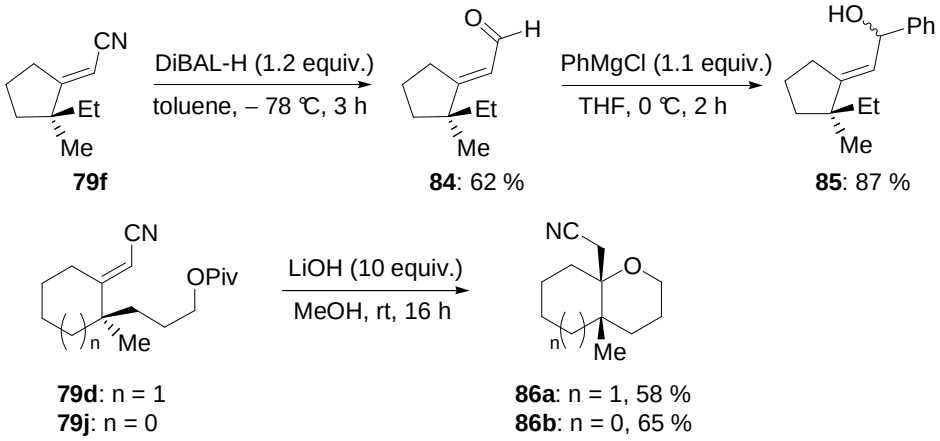
Entry	**Allyl substrate** *ee* (%)[a]	**R_2Zn** (R)	**(*E*)-Unsaturated nitrile**	**Yield** (%)[b]	***ee*** (%)[a]
					
3	**77c** (96)	$PivO(CH_2)_3$	**79d**	65	96
					
4	**77d** (90)	Pent	**79e**	91	90
					
5	**77d** (90)	Et	**79f**	80	90
					
6	**77d** (90)	*i*-Pr	**79g**	75	90
					
7	**77d** (90)	*c*-Hex	**79h**	60	90
					
8	**77d** (90)	$(CH_2)_2Ph$	**79i**	40	90
					
9	**77d** (90)	$PivO(CH_2)_3$	**79j**	71	90

[a] The enantiomeric excess was determined by HPLC or GC analysis. In each case the racemic product was prepared for HPLC or GC calibration. [b] Yield of analytically pure product.

2.3.3 Derivatization of unsaturated nitriles

With the chiral unsaturated nitriles of type **79** in hand, we explored the reactivity of these derivatives. First, one possible site of modification is at the nitrile function. For example, the reduction of **79f** with DiBAL-H [101] gave rise to the corresponding α,β-unsaturated ketone **84** in 62 % yield (Scheme 46), which was then reacted with phenyl Grignard reagent to afford the corresponding racemic allylic alcohol **85** in 87 % yield. With **85** we have now a new allylic system that might undergo enantioselective substitution reactions when chiral.

The functionalized unsaturated nitriles **79d** and **79j** were treated with lithium hydroxide in order to cleave the pivaloyl group (Scheme 46). Surprisingly, it afforded in a single step the bicyclic compounds **86** in 58-65 % yield. In both cases, the free alcohols could not be isolated and cyclized spontaneously in a diastereoselective manner. The *syn* stereochemistry was confirmed by a NOE effect between the CH_3 and the CH_2 group adjacent to the nitrile function. Unsaturated nitrile compounds were already known to undergo selective conjugated additions but exclusively intramolecularly.[102] Indeed, conjugated additions of Grignard or copper reagents suffer from selectivity.[103]



79f

84: 62 %

85: 87 %

79d: n = 1
79j: n = 0

86a: n = 1, 58 %
86b: n = 0, 65 %

Scheme 46. Derivatization of α,β-unsaturated nitrile **79f, d** and **j**.

[101] (a) D. V. Johnson, H. Griengl, *Tetrahedron* **1997**, *53*, 617; (b) K.-M. Wu, M. M. Midland, W. H. Okamura, *J. Org. Chem.* **1990**, *55*, 4381.
[102] T. F. Jamison, S. Shambayati, W. E. Crowe, S. L. Schreiber, *J. Am. Chem. Soc.* **1997**, *119*, 4353.
[103] For a very interesting review on the reactivity of unsaturated nitriles, see: F. F. Fleming, Q. Wang, *Chem. Rev.* **2003**, *103*, 2035.

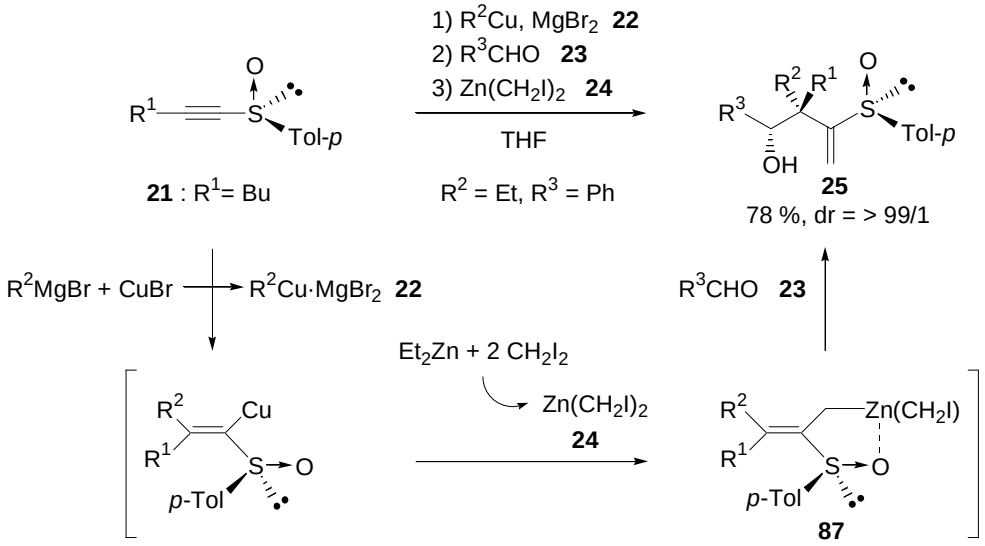
2.3.4 Conclusion

In conclusion, we have shown that enantiomerically enriched *O*-benzoated cyanohydrins constitute a substrate of choice for the copper(I)-mediated S_N2' allylic substitution. First, they are easily available in their optically pure form either by chemical or enzymatic methods and second, they react with remarkable selectivity with diorganozinc reagents in the presence of CuCN·2LiCl. In every case we could show that the substitution occurred with perfect transfer of the chiral information (no loss of the enantiomeric excess was observed) and led to an interesting class of compounds: α,β-unsaturated nitriles bearing a stereogenic center in the γ position.

2.4 Multi-component approach to build quaternary centers[40]

2.4.1 Introduction

One of the major challenges in synthesis nowadays is to assemble target molecules from readily available starting materials in a one-step operation, and in a simple and straightforward manner.[104] *Marek* has recently developed a new approach based on a four-component reaction.[34] The regio- and stereospecific carbocupration of chiral alkynyl sulfoxides **21**, followed by *in situ* methylene homologation of the alkenylcopper **24** and finally the allylation reaction of **87** with aldehydes **23** provided, in a one-pot operation, the homoallylic alcohol **25** in excellent diastereoselectivities (Scheme 47).



Scheme 47. Multi-component approach for the generation of chiral quaternary centers.

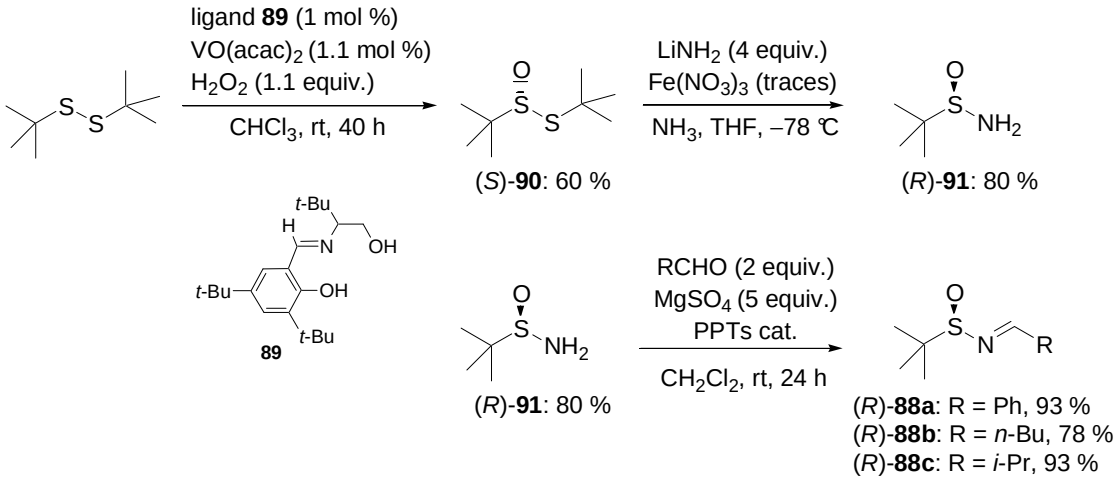
The use of a chiral sulfinyl moiety plays a unique role as chiral auxiliaries for the creation of new stereogenic centers.[105] We decided to further exploit the directing properties of chiral sulfinyl groups and therefore to incorporate it, not in the nucleophilic, but in the electrophilic partner. *Davis*[106] and later *Ellman*[107] demonstrated that the sulfinyl group serves

[104] (a) N. Chinkov, a. Levin, I. Marek, *Angew. Chem. Int. Ed.* **2006**, *45*, 465; (b) D. J. Ramon, M. Yus, *Angew. Chem. Int. Ed.* **2005**, *44*, 1602.
[105] (a) G. H. Posner, "*The Chemistry of Sulphones and Sulfoxides*", Eds. S. Patai, Z. Rappoport, C. J. M. Stirling, Wiley, Chichester, **1988**; (b) I. Fernandez, N. Khiar, *Chem. Rev.* **2003**, *103*, 3651; (c) C. H. Senanayake, D. Krishnamurthy, Z.-H. Lu, Z. Han, I. Gallou, *Aldrichimica Acta* **2005**, *38*, 93.
[106] F. A. Davis, R. E. Reddy, J. M. Szewezyk, G. V. Reddy, P. S. Portonovo, H. Zhang, D. Fanelli, R. T. Reddy, P. Zhou, P. J. Carroll, *J. Org. Chem.* **1997**, *62*, 2555.

as an ideal auxiliary on imine electrophiles because it activated the imine for nucleophilic addition, provided diastereofacial selectivity. The chiral auxiliary can be easily removed by treatment with mild acidic solution to give the free amine.

2.4.2 Multi-component reaction mediated by chiral sulfinimine auxiliaries

We started our study by synthesizing the electrophile containing the chiral sulfinyl auxiliary. The *tert*-butanesulfinimines **88** were synthesized in 3 steps and in 91 % *ee* using the procedure reported by *Ellman*[108] (Scheme 48). It started with the asymmetric catalytic oxidation of *tert*-butyl disulfide mediated by vanadium and scalemic α-branched amine ligand **89** and provided the *tert*-butylthiosulfinate **90** (60 %). Addition of lithium amide in ammonia to thiosulfinate **90** afforded the *tert*-butansulfinamide **91** in 80 % yield and finally the direct condensation with different aldehydes in the presence of $MgSO_4$ furnished the *tert*-butansulfinimines **88a-c** in high yield.

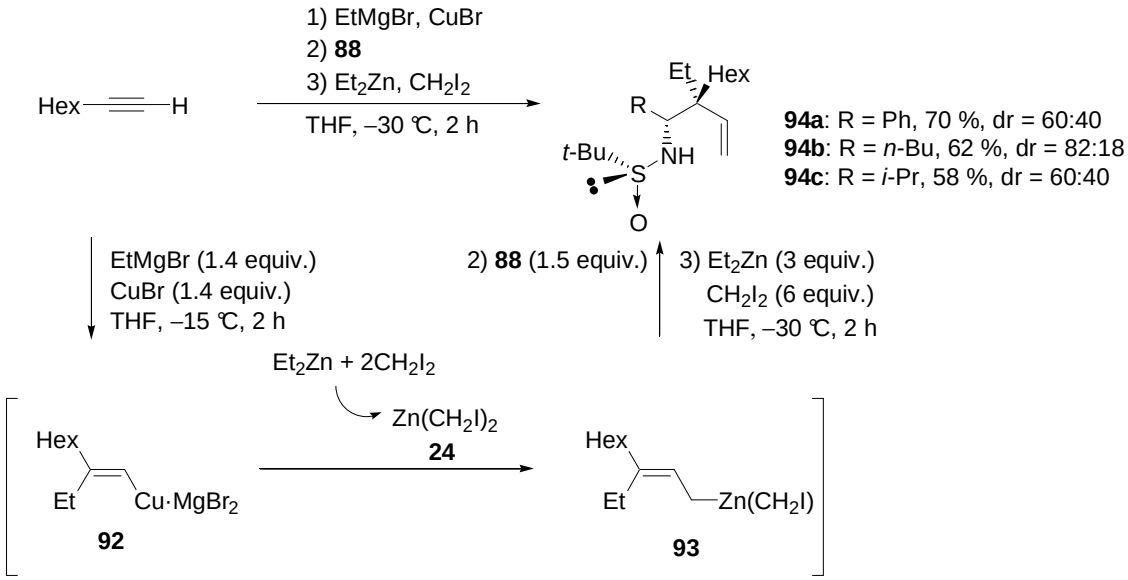


Scheme 48. Preparation of chiral *tert*-butansulfinimines **88a-c**.

These electrophiles were tested in the multi-component reaction as described previously. First the regio- and stereospecific carbocupration reaction of 1-octyne with ethylcopper, easily prepared from EtMgCl bromide and CuBr (1.4 equiv.), provided the corresponding metalated β,β-alkylated ethylenic copper **92** in quantitative yield (Scheme 49).[109] The reaction mixture

[107] (a) J. A. Ellman, *Pure & App. Chem.* **2003**, *75*, 39; (b) J. A. Ellman, T. D. Owens, T. P. Tang, *Acc. Chem. Res.* **2002**, *35*, 984.
[108] G. Liu, D. A. Cogan, J. A. Ellman, *J. Am. Chem. Soc.* **1997**, *119*, 9913.
[109] (a) W. E. Truce, M. J. J. Lusch, *J. Org. Chem.* **1974**, *39*, 3174; (b) W. E. Truce, M. J. J. Lusch, *J. Org. Chem.* **1978**, *43*, 2252; (c) V. Fiandanese, G. Marchese, F. Naso, *Tetrahedron Lett.* **1978**, 5131.

was then treated with the sulfinimine **88** (1.5 equiv.) followed by the successive addition of Et_2Zn (3 equiv.) and CH_2Cl_2 (6 equiv.).[110] As the alkenylcopper and the zinc carbenoid were not reactive enough to add to the electrophile, **92** was readily homologated by a methylene unit with the carbenoid **24**, affording *in situ* a highly reactive allylic zinc and copper species **93**[111] that reacted with the electrophile. Unfortunately, under these conditions, the reaction turned to be poorly selective. Indeed, the reaction with phenyl- and *iso*-propyl-substituted sulfinimines **88a** and **88c** led to the homoallylic amine **94a** and **94c** as a mixture of two diastereomers in a 60:40 ratio. The reaction with *n*-butyl derivative was slightly better and gave the corresponding product **94b** in a mixture of about 80:20.

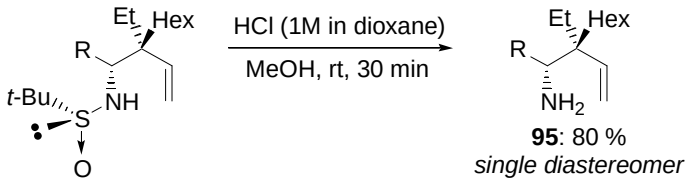


Scheme 49. Sequential carbocupration – allylation reaction on 1-octyne with chiral sulfinimines **88a-c**.

These disappointing results suggest that the enantiofacial choice of the allylation reaction could not be controlled by the chiral auxiliary contained in the electrophile. However, the reaction was diastereoselective and gave, after acidic cleavage of the sulfinate moiety, the corresponding amine **95** as a single diastereomer (Scheme 50). It also showed that no 1,3-

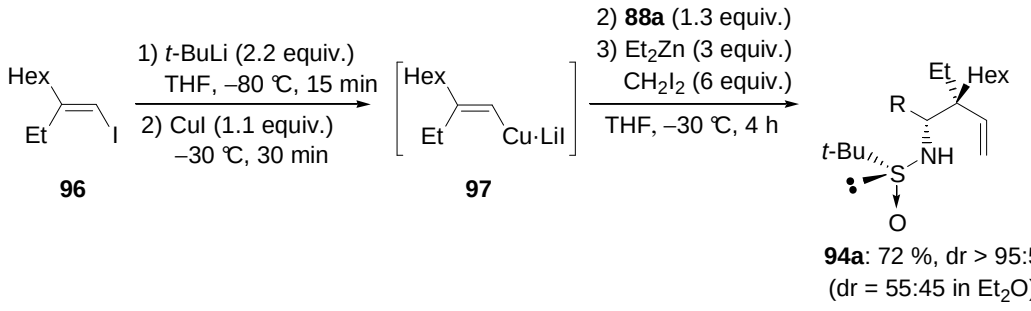
[110] (a) A. B. Charette, J. F. Marcoux, C. Molinaro, A. Beauchemin, C. Brochu, E. Isabel, *J. Am. Chem. Soc.* **2000**, *122*, 4508; (b) S. E. Denmark, S. P. O'Connor, *J. Org. Chem.* **1997**, *62*, 3390.
[111] (a) J. P. Varghese, P. Knochel, I. Marek, *Org. Lett.* **2000**, *2*, 2849; (b) I. Marek, *Tetrahedron* **2002**, *58*, 9463; (c) S. Achyutha Rao, M. J. Rozema, P. Knochel, *J. Org. Chem.* **1993**, *58*, 2694; (d) P. Wipf, C. Kendall, *Org. Lett.* **2001**, *3*, 2773.

metal shift (metallotropic equilibrium) [112] took place during the reaction, which most substituted allylic zinc reagents are sensitive to.



Scheme 50. Cleavage of the *t*-butylsulfinate chiral auxiliary.

We decided to further investigate this reaction and we found that, by using a lithium salt instead of the magnesium salt, a dramatic effect on the diastereoselectivity was observed. We started from the alkenyliodide **96**, easily prepared by a carbocupration reaction with EtCu on 1-ocytne followed by iodolysis. First, iodine-lithium exchange reaction with *t*-BuLi (2.2 equiv.) followed by transmetallation to copper(I) (CuI, 1.1 equiv.) provided the alkenylcopper species **97** in quantitative yield (Scheme 51). The reaction mixture was then treated with the chiral phenyl-substituted sulfinimine **88a** (1.3 equiv.) followed by the successive addition of diethylzinc (3 equiv.) and methylene iodide (6 equiv.) to afford the homoallylic amine **94a** in excellent diastereoselectivity (dr > 95:5). Note, that not only the salt had an effect on the selectivity of the reaction but also the solvent. When the reaction was performed in diethyl ether, the product was formed as a 1:1 mixture of diastereomers.



Scheme 51. Sequential carbocupration – allylation reaction in the presence of lithium salt.

[112] (a) P. Jones, P. Knochel, *J. Org. Chem.* **1999**, *64*, 186; (b) I. Marek, P. R. Schreiner, J. F. Normant, *Org. Lett.* **1999**, *1*, 929.

The selectivity can be rationalized by a chairlike transition state conducted by the chelating and directing effect of the chiral sulfinyl group (Figure 2).

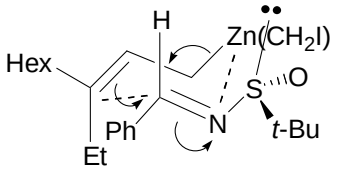


Figure 2. Postulated transition state for the allylation reaction.

In conclusion, we could show that chiral sulfinyl auxiliaries are efficient directing group. They could be adapted to a multi component approach (carbometallation–homologation–allylation reaction) for the formation of homoallylic amine derivatives containing chiral quaternary centers in high diastereoselectivity by using the sulfinyl moiety as a chiral auxiliary on the electrophilic counterpart.

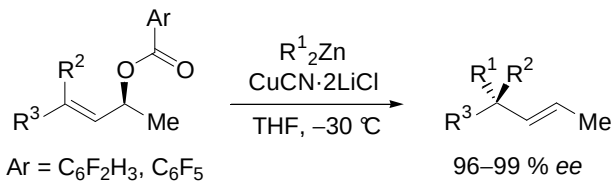
3 Summary and Outlook

This work has been focused on the use of the copper(I)-mediated *anti*-S_N2' allylic substitution reactions with non directing leaving groups. This proved to be a general and highly reliable method for the preparation of new chiral stereogenic centers in high enantioselectivity. Moreover a particular effort was made to apply this method to more complex systems, and compounds like alcohols, amines, alkenylsilanes or unsaturated nitriles could be successfully prepared in their enantiomerically enriched form.

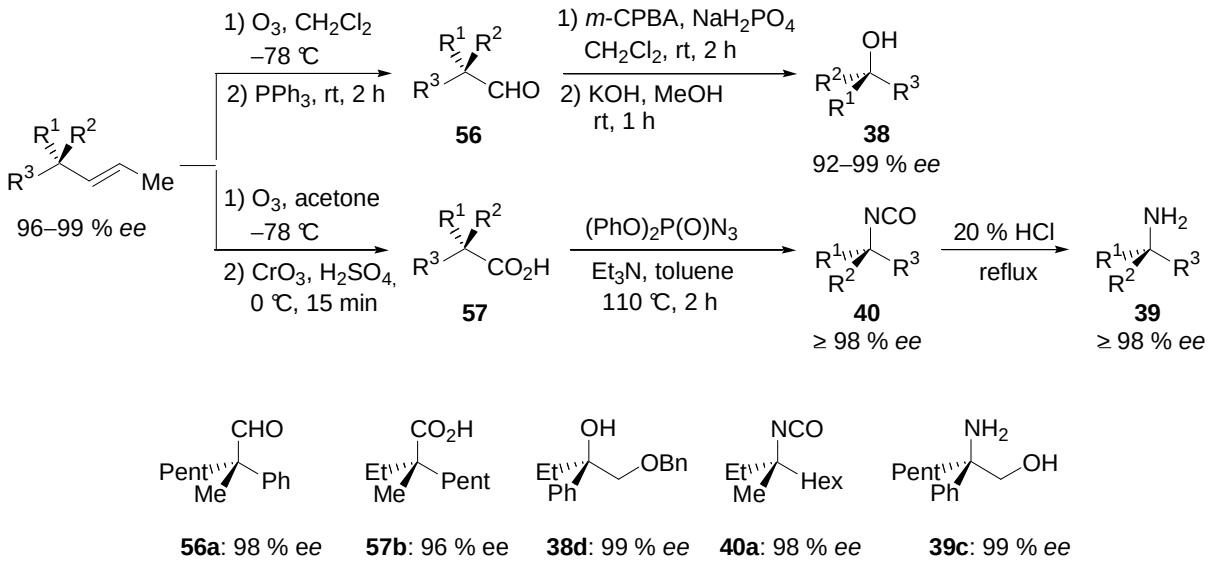
3.1 Enantioselective preparation of tertiary alcohols and amines

Excellent transfer of chirality was observed in copper(I)-mediated allylic substitution reactions. This approach to all-carbon substituted quaternary centers was generally applicable and a wide range of alkenes bearing a stereogenic center in α position could be prepared in high enantioselectivity. In addition, derivatization of alkenes resulting from the S_N2' allylic substitution, allowed us to access more functionalized compounds like aldehydes (**56**), carboxylic acids (**57**) or diols.

In addition, we have developed a straightforward sequence for the synthesis of tertiary alcohols (**38**) in high enantioselectivity by an oxidation reaction followed by a Baeyer-Villiger rearrangement. Moreover, we have shown that a Curtius rearrangement on the corresponding chiral carboxylic acids provided a stereoselective approach to amines (**39**) bearing a chiral tertiary center or to chiral amino-alcohol derivatives. These sequences are summarized in the following scheme 52 and 53.



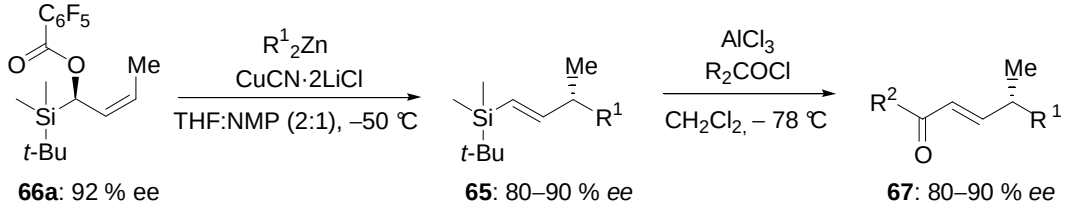
Scheme 52. Copper(I)-mediated S_N2' allylic substitutions and derivatization of the resulting alkenes.



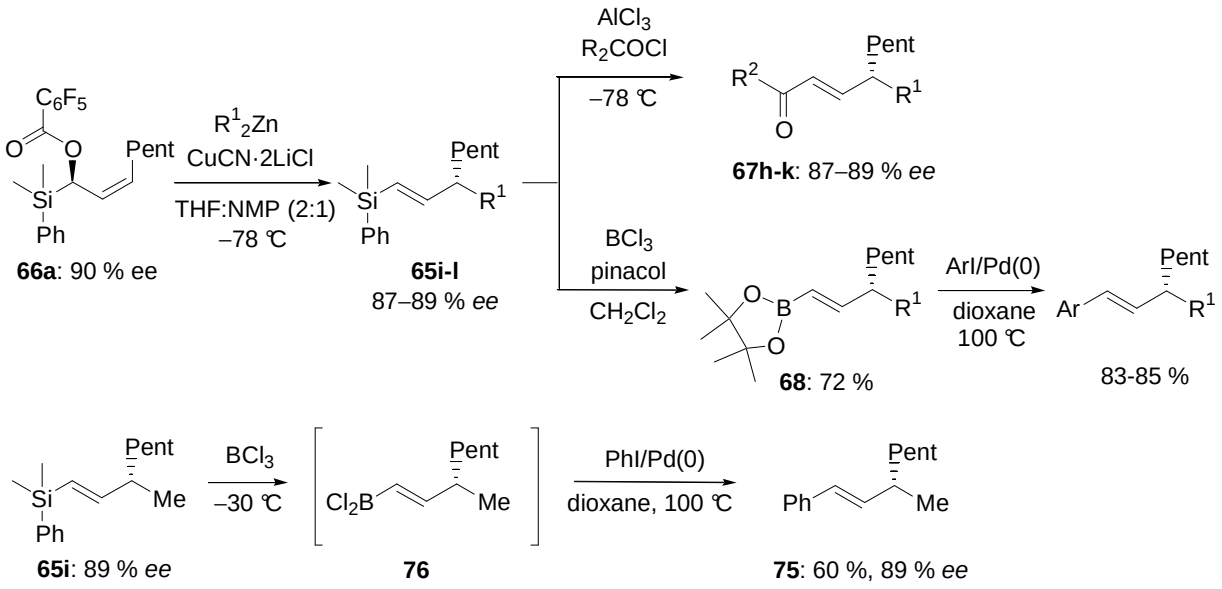
Scheme 53. Copper(I)-mediated S_N2' allylic substitutions and derivatization of the resulting alkenes.

3.2 Preparation of (*E*)-alkenylsilanes bearing an α-stereogenic center

In a second part, we have developed a highly stereoselective method to prepared (*E*)-alkenylsilanes of type **65** bearing an α-chiral center *via* copper(I)-mediated *anti*-S_N2' allylic substitution (Scheme 54). These resulting compounds turned to be very versatile building blocks and could be readily transformed into α,β-unsaturated ketones **67** by Friedel-Crafts acylation reaction or into the corresponding boronates **68** by *ipso*-borodesilylation reaction and then undergo cross-coupling reactions (Scheme 55). However, a phenyl residue on the silicon atom was required to undergo the *ipso*-borodesilylation. Finally, we showed that the *ipso*-borodesilylation/cross-coupling sequence was also possible in a one-pot operation.



Scheme 54. Preparation of (*E*)-alkenylsilanes bearing an α-chiral center and their derivatizations.

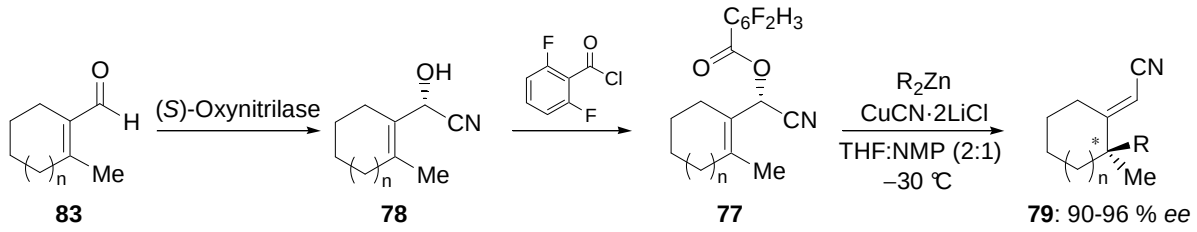


Scheme 55. Preparation of (*E*)-alkenylsilanes bearing an α-chiral center and their derivatizations (continue).

In addition, it would be interesting to study the tolerance of other groups at the place of the silicon atom, since the S_N2' allylic substitution seemed to tolerate the presence of functionalities at this position. For example, the introduction of a boron atom at the place of the silicon atom would be of interest as the resulting compounds would find many applications in organic synthesis.

3.3 S_N2' Allylic substitutions on chiral *O*-benzoated cyanohydrins

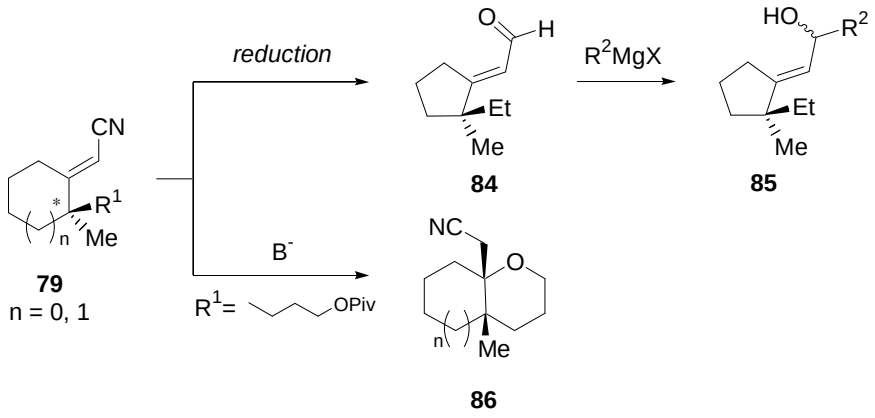
We could demonstrate that enantiomerically enriched *O*-benzoated cyanohydrins **77** constituted a substrate of choice for the copper(I)-mediated S_N2' allylic substitution. They were easily available in their optically pure form by an enantioselective addition of KCN to the aldehyde **83** mediated by the (*S*)-oxynitrilase enzyme. They reacted with remarkable selectivity with diorganozinc reagents in the presence of CuCN·2LiCl. In every case, we could show that the substitution occurred with perfect transfer of the chiral information and led to an interesting class of compounds: the α,β-unsaturated nitriles **79** bearing a stereogenic center in the γ position (Scheme 56).



83 **78** **77** **79**: 90-96 % *ee*

Scheme 56. Preparation of enantiomerically enriched *O*-benzoated cyanohydrins **77** and their allylic substitution reactions.

Unsaturated nitriles turned to have interesting reactivity and could be transformed into the corresponding α,β-unsaturated ketones **84** or into allylic alcohol systems **85** after addition of a Grignard reagent. In addition, they underwent an interesting stereoselective *syn* cyclization that leaded to bicyclic compounds **86**. These reactions are summarized in the following scheme.

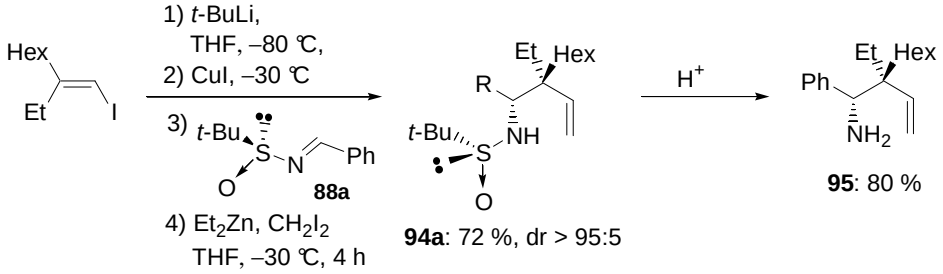


Scheme 57. Reactions of α,β-unsaturated nitriles **79**.

Further applications of unsaturated nitriles would be a fascinating aspect to explore. Particularly the stereoselective cyclization they are able to undergo could provide an access to the synthesis of polycyclic natural products. On the other hand, additional studies on the reactivity and selectivity of allylic alcohol **85** toward a second copper(I)-mediated S_N2' allylic substitution might be very interesting.

3.4 Multi-component approach to build quaternary centers

Finally, we could show, in the collaboration with Prof. Ilan Marek, that chiral sulfinyl auxiliaries are efficient directing groups in the generation of stereodefined quaternary carbon centers when they are contained in the electrophile. Following the multi component approach (carbometallation – homologation – allylation reaction) we could synthesize and apply successfully the chiral *tert*-butylsulfinimine derivative **88a** as electrophile for the preparation of the homoallylic sulfinyl amine **94a** in high diastereoselectivity (Scheme 58).



Scheme 58. Sequential carbocupration – allylation reaction on 1-octyne with chiral sulfinimines **88a**.

This short study constitutes an encouraging result. However, the applicability and the limitations have still to be further investigated.

Experimental Part

1 General considerations

Unless otherwise stated, all reactions were carried out with magnetic stirring and, if air or moisture sensitive, in flame-dried glassware and under argon. Syringes used to transfer reagents and solvent were purged with argon prior to use.

Solvents

Solvents were dried according to standard methods by distillation over drying agents as follows: dichloromethane, DMF, NMP and pentane (CaH_2), THF, diethylether and DME (Na/benzophenone), toluene (Na), methanol, ethanol and isopropanol (Mg), pyridine and triethylamine (KOH).

Reagents

Reagents of > 98 % purity were used without further purification. The following reagent were prepared according to literature procedure: Bu_3SnH, [113] TBDMSCl, [114] $Pd(dba)_2$, [115] $Pd(PPh_3)_4$,[115] Jones reagent.[116]

$CuCN{\cdot}2LiCl$[117] solution (1.0 M) was prepared by drying CuCN (896 mg, 10 mmol) and LiCl (848 mg, 20 mmol) in a Schlenk flask under vacuum for 5 h at 140 °C. After cooling to rt, dry THF (10 mL) was added and stirring was continued until the salts were dissolved.

Organolithium reagents:
n-Buthyllithium was used as 1.5 M solution in hexane (Chemetall).
t-Buthyllithium was used as 1.5 M solution in pentane (Chemetall).

Organozinc reagents:

Me_2Zn	was used as 2.0 M solution in toluene (Aldrich).
Et_2Zn	was used neat from a secured bottled (Witco).
i-Pr_2Zn[118]	was prepared by Mg/Zn exchange from *i*-PrMgBr and $ZnBr_2$, as a solution in diethylether (5-7 M).
n-$Pent_2Zn$[119]	was prepared by Mg/Zn exchange from *n*-PentMgBr and $ZnBr_2$, pure, 4.8 M.
n-PentZnI[120]	was prepared by zinc insertion from *n*-PentI, as a solution in THF (1-2 M).
n-HexZnI[120]	was prepared by zinc insertion from *n*-HexI, as a solution in THF (1-2 M).

Content determination of organometallic reagent:
Organolithium and organomagnesium solution were titrated according to the literature procedures.[121] The concentration of organozinc solutions were determined by back titration of iodine with an aqueous $Na_2S_2O_3$ solution.

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[113] K. Hayashi, J. Iyoda, I. Shiihara, *J. Organomet. Chem.* **1967**, *10*, 81.
[114] E. J. Corey, A. Venkateswarlu, *J. Am. Chem. Soc.* **1972**, *94*, 6190.
[115] E.-I. Negishi, "*Handbook of Organopalladium Chemistry for Organic Synthesis*", Wiley, New York, **2002**.
[116] J. Meinwald, J. Crandall, W. E. Hymans, *Organic Synthesis Coll.* **1973**, *5*, 866.
[117] P. Knochel, M. C. P. Yeh, S. C. Berk, J. Talbert, *J. Org. Chem.* **1988**, *53*, 2390.
[118] A. Boudier, PhD Thesis, LMU München, **2001**.
[119] F. Dübner, PhD Thesis, LMU München, **2000**.
[120] (a) P. Knochel, P. Jones, "*Organozinc Reagents : A Practical Approach*", Oxford Press, 1999; (b) P. Knochel, N. Millot, A. L. Rodriguez, C. E. Tucker, *Org. React.* **2001**, *58*, 417.
[121] (a) H. S. Lin, L. A. Paquette, *Synth. Commun.* **1994**, *24*, 2503. (b) A. Krasovskiy, P. Knochel, *Synthesis* **2006**, *5*, 890.

Chromatography

Thin layer chromatography (TLC) was performed using aluminium plates coated with SiO_2 (Merck 60, F-254). The spots were visualized by UV light and by treating the plate with different solutions:

- $KMnO_4$ (3 g), K_2CO_3 (20 g), KOH (0.3 g) in water (300 mL)
- Phosphomolybdic acid (10 g) in absolute ethanol (100 mL)
- Cerium molybdate: phosphomolybdic acid (5 g), $Ce(SO_4)_2$ (2 g), conc. H_2SO_4 (12 mL) in water (230 mL).

Flash column chromatography was performed using SiO_2 60 (0.040-0.063 mm; 230-400 mesh ASTM) from Merck and the amount of silicagel was calculated according to the recommendations of W. C. Still.[122]

Analytical data

Melting points were uncorrected and measured on a Büchi B-540 apparatus.

NMR spectra were recorded on a Varian Mercury 200, VXR 400S and on a Bruker ARX 300, AMX 600 instruments. Chemical shifts (δ/ppm) were given relative to $CDCl_3$ (7.26 ppm, for ^{1}H-NMR, 77.0 ppm for ^{13}C-NMR).
For the characterization of the observed signal multiplicities the following abbreviations were applied: s (singlet), d (doublet), dd (doublet doublet), dt (doublet triplet), t (triplet), q (quartet), m (multiplet) and br (broad).

Infrared spectra were recorded from 4000-400 cm^{-1} on a Nicolet 510 FT-IR or a Perkin-Elmer 281 IR spectrometer or BX FT-IR System with a Smith Durasampl IR II, ATR unit in substance. Samples were measured either as neat or as a film between sodium plates for liquids and as potassium tablets for solids. The absorption bands were reported in wave numbers (ν/cm^{-1}).

Optical rotations were measured on a Perkin-Elmer 241 polarimeter.

Mass spectroscopy: mass spectra were recorded on a Finnigan MAT 95Q or a Finnigan 90 instrument for electro impact ionization (EI). High resolution mass spectra (HRMS) were recorded on the same instruments. Fast atom bombardment (FAB) samples were recorded in either a 2-nitrobenzyl alcohol or a glycerine-matrix.

Determination of the enantiomeric excess

Gas chromatography (GC) was performed on the following columns:

- Chiraldex B-PH, Astec, G0112-18 (30.0 m x 250 μm x 0.00 μm),
- Chirasil-L-val, Varian, CP7495 (25.0 m x 250 μm x 0.12 μm),
- Chirasil-Dex CB, Varian, CP7502 (25.0 m x 250 μm x 0.25 μm), 12.10 psi, 2.8 mL/min, H_2-flux.
- TFA-γ-Cyclodextrin, Astec, G 9105-18 (30.0 m x 250 μm x 0.00 μm), 10.86 psi, 2.1 mL/min, H_2-flux.

[122] W. C. Still, M. Khan, A. Mitra, *J. Org. Chem.* **1978**, *43*, 2923.

High Performance Liquid Chromatography (HPLC) was performed on a Dionex instrument with a UV/vis diode array detector on the following columns (eluent: *i*-PrOH/*n*-hexane, isocratic):

- Chiralcel OD-H
- Chiralcel OD
- Chiralcel AD.

2 Typical procedures (TP)

2.1 Typical procedure for the copper(I)-mediated S_N2' allylic substitutions with dialkylzinc reagents (TP1) [36]

The dialkylzinc reagent (1.2 mmol, 2.4 equiv.) was added to a stirred solution of CuCN·2LiCl (1 M in THF, 0.6 mL, 0.6 mmol, 1.2 equiv.) at −30 °C and under an argon atmosphere. The resulting mixture was stirred for another 45 min, before the allylic fluorobenzoate (0.5 mmol, 1.0 equiv.) was added dropwise as a solution in THF (0.8 mL) and the reaction mixture was allowed to warm to −10 °C within 1.5 h. The reaction mixture was stirred at −10 °C until the conversion was complete, then aq. sat. NH_4Cl (5 mL) was added and the quenched reaction mixture was poured into an Erlenmeyer flask containing 25 % aq. ammonia (2 mL), aq. sat. NH_4Cl (50 mL) and Et_2O (50 mL). The mixture was stirred until the copper salts had dissolved. The aqueous phase was extracted with Et_2O (3 x 80 mL) and the combined extracts were washed with brine (80 ml) and dried over $MgSO_4$. The solvent was evaporated *in vacuo* and the residue was purified by flash chromatography.

2.2 Typical procedure for the copper(I)-mediated S_N2' allylic substitutions with diarylzinc reagents (TP2) [81]

Preparation of the diarylzinc reagent (1mmol of R_2Zn):

The aryl iodide (1.0 equiv.) and Li(acac) (0.1 equiv.) were dissolved in dry NMP (1.5 mL) before *i*-Pr_2Zn (1.1 mmol, 0.55 equiv.) was added at 0 °C. The reaction mixture was stirred at room temperature and the completion of the iodine-zinc exchange was checked by GC analysis using tetradecane as internal standard.

S_N2' substitution:

The freshly prepared diarylzinc reagent (2.4 equiv.) was cooled at −30 °C and CuCN·2LiCl solution (1 M in THF, 1.2 equiv.) was added. The resulting mixture was stirred at −30 °C for 45 min, and then the pentafluorobenzoate (1.0 equiv.) was added dropwise as a solution in THF. The reaction mixture was stirred at the required temperature until the conversion was complete (15-25 h) and saturated aqueous NH_4Cl solution (5 mL) was added. The quenched reaction mixture was poured into 25 % aq. ammonia (2 mL), aq. sat. NH_4Cl (50 mL) and Et_2O (50 mL) and stirred at 25 °C until the copper salts had dissolved, then extracted with Et_2O (3 x 50 mL). The combined extracts were washed with water, brine and dried over Mg_2SO_4. The solvent was evaporated *in vacuo* and the residue was purified by flash chromatography.

2.3 Typical procedure for the derivatization into the aldehyde by ozonolysis (TP3) [54]

Ozone was bubbled through a solution of alkene (1.2 mmol, 1.0 equiv.) in CH_2Cl_2 (30 mL) at −78 °C until the solution turned blue (3-10 min), then nitrogen was bubbled through until it became colourless again. PPh_3 (1.5 mmol, 1.3 equiv.) was added in one portion and the mixture was stirred under a nitrogen atmosphere and was allowed to warm to rt within 1 h. It was then diluted with Et_2O (10 ml) and washed with water, then brine, and dried over $MgSO_4$. The solvent was evaporated *in vacuo* and the residue was purified by flash chromatography.

2.4 Typical procedure for the derivatization into the carboxylic acid by ozonolysis (TP4) [55]

Ozone was bubbled through a solution of alkene (2.0 mmol) in acetone (10 mL) at −78 °C until the solution turned blue (3-10 min), then nitrogen was bubbled through until it became colourless again. At 0 °C Jones reagent (2.0 mL, 2.67 M, 5.4 mmol, 2.7 equiv.) was added dropwise until the orange colour persisted. The mixture was stirred for 1 h at 20 °C and then *i*-PrOH (8 mL) was added until the mixture turned green. The solvents were evaporated and the residue was dissolved in H_2O/Et_2O (1/4). Acido/basic workup afforded the desired carboxylic acid.

2.5 Typical procedure for the preparation of tertiary alcohols by Baeyer-Villiger rearrangement (TP5) [64,65]

To a solution of aldehyde (0.8 mmol, 1 equiv.) in CH_2Cl_2 (2mL) were added dried *m*-CPBA (260 mg, 1.2 mmol, 1.5 equiv.) and Na_2HPO_4 (113mg, 0.8 mmol, 1 equiv.). The reaction was stirred at rt for 24 h. It was quenched with water and extracted with Et_2O (3 x 50 mL). The organic layer was dried over $MgSO_4$, concentrated *in vacuo* and purified by flash chromatography.
To a solution of the resulting formate (0.5 mmol, 1 equiv.) in MeOH (2 mL) was added KOH (62 mg, 1.0 mmol, 2 equiv.). After being stirred at rt for 1 h, the reaction mixture was diluted with Et_2O (10 mL), washed with brine and dried over $MgSO_4$. The solvent was evaporated *in vacuo* and the residue was purified by flash chromatography.

2.6 Typical procedure for the preparation of tertiary isocyanates (and tertiary amines) by Curtius rearrangement (TP6) [70,71]

A mixture of the acid (0.56 mmol, 1.0 equiv.), diphenyl azidophosphate (231 mg, 0.84 mmol, 1.5 equiv.) and triethylamine (85 mg, 0.84 mmol, 1.5 equiv.) in toluene (5 mL) was heated at reflux for 2 h. The reaction mixture was cooled down to rt and toluene was evaporated *in vacuo*. The residue was taken up in Et_2O (50 mL) and washed with water (3 x 50 mL). The organic layer was dried over $MgSO_4$, concentrated *in vacuo* and purified by flash chromatography.
The free tertiary amine was obtained by refluxing the isocyanate in 20 % HCl (5 mL) for 24 h. Acido/basic workup afforded the tertiary amine.

2.7 Typical procedure for the preparation of allylic benzoates (TP7) [123]

The acyl chloride (1.4 mmol, 1.4 equiv.) was added at 0 °C to a stirred mixture of the allylic alcohol (1.0 mmol), pyridine (0.12 mL, 1.4 mmol, 1.4 equiv.) and DMAP (24 mg, 0.19 mmol, 0.14 equiv.) in CH_2Cl_2 or Et_2O (10 mL). The resulting mixture was stirred at 0 °C for 1 h, then water (10 mL) was added and the mixture was extracted twice with Et_2O (20 mL). The combined extracts were washed with saturated, aq. $NaHCO_3$ solution, then with brine, and dried over $MgSO_4$. The solvent was evaporated *in vacuo* and the residue was purified by flash chromatography.

[123] G. Höfle, W. Steglich, H. Vorbrüggen, *Angew. Chem.* **1978**, *90*, 602.

2.8 Typical procedure for the enzymatic resolution of allylic alcohols (TP8) [44]

The racemic allylic alcohol (18.0 mmol, 1.0 equiv.) was mixed with vinyl acetate (3.7 mL, 40.0 mmol, 2.2 equiv.) and the enzyme amano lipase AK form *Pseudomonas fluorescens*[124] (3.0 g) in pentane (50 mL) and stirred slowly at 36 °C. The reaction was followed by chiral GC or HPLC analysis (ca. 24 h). The reaction mixture was filtrated, concentrated *in vacuo* and the residue was purified by flash chromatography.

2.9 Typical procedure for the Friedel-Crafts acylations (TP9) [84]

In a flame-dried flask equipped with a magnetic stirring bar, an argon inlet, and a septum was placed dry CH_2Cl_2 (2mL) and anhydrous $AlCl_3$ (1.1 equiv.). This suspension was cooled to −78 °C before the acyl chloride (1.1 equiv.) was added, followed by the alkenylsilane (1.0 equiv.) as a solution in dichloromethane (2mL). The reaction mixture was stirred at room temperature or at −40 °C until completion (2-5 h) and then poured into diluted HCl (20 mL) and diluted with Et_2O. The aqueous phase was extracted with Et_2O (3 x 20 mL) and the combined extracts were washed with Na_2CO_3 saturated solution, brine and dried over Mg_2SO_4. The solvent was evaporated *in vacuo* and the residue was purified by flash chromatography.

2.10 Typical procedure for the enzymatic-catalyzed reaction with (*S*)-Oxynitrilase (TP10) [100]

To a suspension of the enzyme (*S*)-Oxynitrilase from *Manihot esculenta*[125] (>3000 units/mL, 200 to 400 units/mmol of substrate) in 5.0 mL of citrate buffer (10 mM citric acid/20 mM Na_2HPO_4, pH 5) was added the aldehyde (1 mmol, 1 equiv.) and the reaction mixture was cooled down to 5-10 °C. KCN (2 mmol, 2.0 equiv.) was then added as a solution in citrate buffer (8.0 mL, pH 5) under vigorous stirring within 20 min. The pH has to be carefully maintained at 5 to obtain a good enantioselectivity. The pH can be adjusted by the addition of citric acid. The conversion into the product was monitored by TLC (3-6 h). The aqueous phase was extracted with Et_2O (3 x 20 mL) and the combined organic phases were dried over Mg_2SO_4. The solvent was evaporated *in vacuo* and the residue was purified by flash chromatography.

2.11 Typical procedure for the epoxidation of alkenylsilanes (TP11)

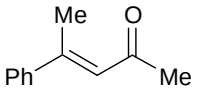
The alkenylsilane (1 equiv.) was added as a solution in CH_2Cl_2 (1 mL) to a suspension of *m*-CPBA (2.8 equiv.) and Na_2HPO_4 (4.3 equiv.) in CH_2Cl_2 (4 mL) at 0 °C. The reaction mixture was stirred for 2 h at rt before being filtered and washed with pentane. The organic phases were washed with $NaHCO_3$, brine and dried over $MgSO_4$. The solvent was evaporated *in vacuo* and the residue was purified by flash chromatography.

[124] Commercially available from Aldrich.
[125] Commercially available from Fluka or Julich Chiral Solutions.

3 Preparation of Chiral Tertiary Alcohols and Tertiary Amines

3.1 Starting materials

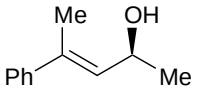
(3*E*)-4-Phenylpent-3-en-2-one:



Prepared from 2,4-pentandione and phenylmagnesium bromide according to a procedure by *Wang*.[45a]

^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 7.52-7.44 (m, 2H), 7.43-7.30 (m, 3H), 6.53-6.49 (m, 1H), 2.54 (d, ^3J = 1.5 Hz, 3H), 2.30 (s, 3H).
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 198.9, 153.9, 142.5, 129.1, 128.5, 126.5, 124.5, 32.2, 18.3.
IR (film, ν/cm^{-1}): 1960, 1890, 1680, 1600, 1570.
MS (EI, 70 eV), *m/z* (%): 159 (100, $[M-H]^+$), 145 (71), 115 (83), 102 (7), 91 (27), 77 (7), 63 (6), 51 (8).

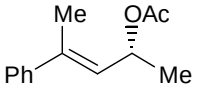
(2*S*,3*E*)-4-Phenylpent-3-en-2-ol ((*S*)-43):



Prepared from (3*E*)-4-phenyl-pent-3-en-2-one (1.60 g, 10.0 mmol, 1.0 equiv.) in a Luche reduction procedure[45b] with $CeCl_3 \cdot 7H2O$ (3.73 g, 10.0 mmol, 1.0 equiv.) and $NaBH_4$ (378 mg, 10 mmol, 1.0 equiv.). Purification by flash chromatography (pentane/Et_2O, 7:3) afforded *rac*-**43** (1.46 g, 9.0 mmol, 90 %) as a racemate and as a colourless oil.
Enzymatic resolution of *rac*-**43** according to **TP8** in presence of amano lipase AK and vinyl acetate (24 h at reflux in pentane) yielded (*S*)-**43** (686 mg, 47 %, > 99 % *ee*) after purification by flash chromatography (pentane/Et_2O, 9:1). The *ee* of (*S*)-**43** was determined by GC analysis.

$[\alpha]_D^{20}$ = + 24 (c = 1.86, EtOH).
GC (column: Chiraldex B-PH, 120 °C): t_R(min) = 54.6 (*R*), 58.6 (*S*).
^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 7.44-7.22 (m, 5H), 5.81 (dq, ^3J = 8.4 Hz, ^3J = 1.2 Hz, 1H), 4.76 (dq, ^3J = 8.4 Hz, ^3J = 6.1 Hz, 1H), 2.11 (d, ^3J = 1.2 Hz, 3H), 1.70-1.65 (m, 1H), 1.35 (d, ^3J = 6.1 Hz, 3H).
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 142.9, 136.2, 131.9, 128.3, 127.2, 125.8, 65.2, 23.5, 16.1.
IR (film, ν/cm^{-1}): 3290, 1950, 1890, 1760, 1640, 1600, 1580.
MS (EI, 70 eV), *m/z* (%): 162 (2, $[M]^+$), 147 (20), 129 (9), 115 (16), 105 (47), 91 (31), 77 (17), 69 (14), 43(21).
HRMS for $C_{11}H_{14}O$ (162.1045 $[M]^+$): found: 162.1056.

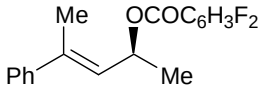
(2*R*,3*E*)-4-Phenylpent-3-en-2-yl acetate ((*R*)-44):



(*R*)-**44** was obtained as a by-product from the enzymatic resolution of *rac*-**43** as a colourless oil (938 mg, 46 %, 99 % *ee*). The *ee* was determined on the corresponding allylic alcohol ((*R*)-**43**) after hydrolysis under basic conditions (KOH, 1.5 equiv. in MeOH) of the acetate.

$[\alpha]_D^{20}$ = + 98.2 (c = 1.5, EtOH).
^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 7.44-7.22 (m, 5H), 5.67 (m, 2H), 2.04 (s, 3H), 1.96 (s, 3H), 1.29 (d, ^3J = 6.3 Hz, 3H).
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 170.8, 143.1, 138.3, 128.6, 127.9, 127.8, 126.3, 68.7, 21.8, 21.2, 16.7.
IR (film, ν/cm^{-1}): 2979, 1738, 1370, 1241, 1042, 758, 697.
MS (EI, 70 eV, *m/z* (%)): 204.1 (7, $[M]^+$), 161 (43), 147 (35), 129 (100), 115 (13), 105 (10), 91 (16), 43 (28), 77 (5).
HRMS for $C_{13}H_{16}O_2$ (204.1150 $[M]^+$): found: 204.1151.

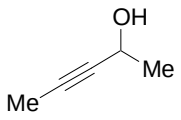
(2*S*,3*E*)-4-Phenylpent-3-en-2-yl 2,6-difluorobenzoate ((*S*)-42d):



Prepared according to **TP7** from (*S*)-**43** (370 mg, 2.28 mmol, > 99 % *ee*), 2,6-difluorobenzoyl chloride (563 mg, 3.19 mmol), pyridine (0.27 mL, 3.42 mmol) and DMAP (28 mg, 0.2 mmol). Purification by flash chromatography (pentane/Et_2O, 98:2 + 1 % Et_3N) yielded (*S*)-**42d** (647 mg, 94 %) as a colourless liquid.

$[\alpha]_D^{25}$ = −13.1 (c = 1.5, EtOH).
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.26-7.45 (m, 3H), 6.90-6.98 (m, 2H), 6.0 (m, 1H), 5.81-5.86 (dq, ^3J = 8.0 Hz, ^4J = 1.2 Hz, 1H), 2.2 (s, 3H), 1.52 (d, ^3J = 6.2 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 162.7, 161.4, 159.3, 142.6, 139.0, 132.3 (2C), 128.2, 127.5, 126.7, 125.9, 111.8 (2C), 70.4, 20.7, 16.4.
IR (film, ν/cm^{-1}): 2932, 1731, 1625, 1470, 1288, 1110, 1013.
MS (EI, 70 eV), *m/z* (%): 302 (4, $[M]^+$), 161 (20), 145 (28), 141 (100), 129 (46), 113 (14), 91 (9).
HRMS for $C_{18}H_{16}F_2O_2$ (302.1118 $[M^+]$): found: 302.1108.

Pent-3-yn-2-ol (47): [47]

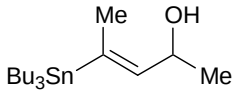


To a solution of 1-bromo-1-propene (28.2 g, 19.9 mL, 233 mmol, 1.55 equiv.) in THF (200 mL) was added *n*-BuLi (206 mL, 330 mmol, 1.6 M in Hexane, 2.2 equiv.) at −78 °C within 1.5 h and let under stirring for another 2 h. Acetaldehyde (6.6 g, 8.4 mL, 150 mmol, 1.0 equiv.) was added as a solution in THF (50 mL) at the same temperature within 30 minutes. It

is warmed up to room temperature and quenched with NH_4Cl sat. solution. The aqueouse phase was extracted 3 x with ether. The organic layer was dried ($MgSO_4$), concentrated *in vacuo* and distillation (0.1 mbar, 30 °C) afforde **47** (10.7 g, 85 %) as a colourless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 4.40-4.50 (m, 1H), 2.29 (br, 1H), 1.80 (d, ^3J = 2.10Hz, 3H), 1.38 (d, ^3J = 6.52 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 81.4, 79.9, 58.4, 24.5, 3.4.
IR (film, ν/cm^{-1}): 3351, 2982, 2922, 1448, 1370, 1160, 1079, 1000, 887.
MS (EI, 70 eV), *m/z* (%): 83 ([M-H]$^+$, 3), 69 (100), 51 (4).

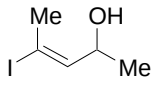
(2*E*)-2-Tributylstannyl-pent-2-en-4-ol (48): [48, 126]



To a precooled (–80 °C) suspension of CuCN (5.5 g, 60 mmol, 2 equiv.) in THF (100 mL) was added dropwise *n*-BuLi (1.6 M in hexanes, 75 mL, 120 mmol, 4 equiv.). The dark yellow solution was stirred at –80 °C for 20 min. $HSnBu_3$ (40 mL 120 mmol, 4 equiv.) was slowly added. The golden solution was stirred at –80 °C for 20 min and then MeOH (30 mL) was added. The dark red solution was warmed to –50 °C for 10 min and then cooled again to –80 °C. **47** (2.52 g, 30 mmol, 1 equiv.) was added as a solution in THF (30 mL). The solution was warmed to –10 °C and stirred overnight. It was quenched with water (300 mL), filtered (Celite) and extracted with Et_2O (3 x 50 mL). The organic layer was dried ($MgSO_4$), concentrated *in vacuo* and purified by flash chromatography (pentane/Et_2O, 100/0 to 1/1). **48** (4.5 g, 60 %) was obtained as a colourless oil.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 5.51 (dq, ^3J = 1.8 Hz, ^3J = 8.1 Hz, ^3J(H,Sn) = 67 Hz, 1H), 4.70-4.63 (m, 1H), 1.83 (d, ^3J = 1.8 Hz, ^3J(H,Sn) = 48 Hz, 3H), 1.42-1.15 (m, 15H), 0.85-0.80 (m, 15H).
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 145.1, 140.6, 63.9, 29.5, 28.1, 23.7, 19.7, 14.4, 9.6.
IR (film, ν/cm^{-1}): 3330, 2960, 1460.
MS (EI, 70 eV), *m/z* (%): 319 ([M-Bu]$^+$, 100), 263 (71), 207 (52), 177 (48).
EA for $C_{17}H_{36}OSn$ (C, 54.42 %; H, 9.67 %): found: C, 54.36 %; H, 9.70 %).

(3*E*)-4-Iodopent-3-en-2-ol (49): [49]



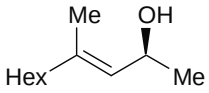
Under light exclusion, **48** (3.74 g, 10.0 mmol, 1 equiv.) in CH_2Cl_2 (100 ml) was cooled to 0 °C and I_2 (3.05 g, 12.0 mmol, 1.2 equiv.) was added. After 1 h at 0 °C, sat. aq. KF (50 ml) was added. After workup and purification by flash chromatography (pentane/Et_2O, 8:2 + 1 Vol. % Et_3N), **49** (1.91 g, 9.0 mmol, 90 %) was obtained as a colourless liquid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 6.21 (dq, ^3J = 8.51, 1.44 Hz, 1H), 4.51 (dq, ^3J = 8.51, 6.30 Hz, 1H), 2.44 (d, ^3J = 1.44 Hz, 1H), 1.91 (br, 1H), 1.24 (d, ^3J = 6.30 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 144.8, 96.9, 65.6, 28.1, 22.9.
IR (film, ν/cm^{-1}): 3326, 2972, 2920, 1638, 1428, 1375, 1138, 1061, 1043, 856, 644.

[126] W. Adam, P. Klug, *Synthesis* **1994**, 567.

MS (EI, 70 eV), *m/z* (%): 212 (M^+, 2), 197 (12), 170 (2), 127 (9), 85 (28), 69 (18), 57 (7), 43 (100).
HRMS for C_5H_9IO (211.9698 $[M]^+$): found: 211.9672.
EA for C_5H_9IO (C, 28.32 %, H, 4.28 %): found: C, 28.47 %; H, 4.29 %.

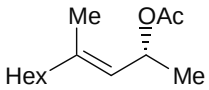
(2*S*,3*E*)-4-Methyldec-3-en-2-ol ((*S*)-45):



Prepared from **49** (424 mg, 2.0 mmol) and *n*-HexZnI (4.6 ml, 1.3 M in THF, 6.0 mmol, 3.0 equiv.) in a Negishi cross-coupling reaction.[50] Reaction conditions: 5 h at rt. Purification by flash chromatography (pentane/Et_2O, 8:2 + 1 % Et_3N) yielded *rac*-**45** (272 mg, 80 %) as a pale yellow liquid.
Enzymatic resolution of *rac*-**45** according to **TP8** in presence of amano lipase AK from and vinyl acetate (24h at reflux in pentane) yielded (*S*)-**45** (40 %, > 99 % *ee*). The *ee* of (*S*)-**45** was determined by GC analysis (see appendix).

$[\alpha]_D^{25} = -6.7$ (c = 1.5, EtOH).
GC (column: Chiraldex B-PH, 100 °C): t_R(min) = 28.1 (*R*), 32.8 (*S*).
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 5.20 (dq, ^3J = 8.6 Hz, ^4J = 1.4 Hz, 1H), 4.56 (m, 1H), 1.96 (t, ^3J = 8.0 Hz, 3H), 1.65 (s, 3H), 1.20-1.42 (m, 12H), 0.80 (t, ^3J = 6.0 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 136.7, 127.5, 63.5, 69.4, 38.1, 30.4, 27.6, 26.3, 22.3, 21.3, 15.0, 12.8.
IR (film, ν/cm^{-1}): 3339, 2928, 2857, 1058.
MS (EI, 70 eV), *m/z* (%): 170 (<1, $[M]^+$), 155 (4), 85 (100), 71 (13), 67 (7), 55 (5)
HRMS for $C_{11}H_{22}O$ (170.1671 $[M]^+$): found: 170.1680.

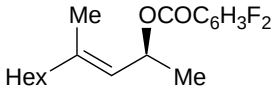
(2*R*,3*E*)-4-Methyldec-3-en-2-yl acetate ((*R*)-50):



(*R*)-**50** was obtained as a by-product from the enzymatic resolution of *rac*-**45** as a colourless oil (50 %, 77 % *ee*). The *ee* was determined on the corresponding allylic alcohol (*R*)-**45** after hydrolysis under basic conditions (KOH, 1.5 equiv. in MeOH) of the acetate.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 5.60 (m, 1H), 5.14 (d, ^3J = 8.6 Hz, 1H), 2.00-1.93 (m, 5H), 1.67 (s, 3H), 1.38-1.22 (m, 11H), 0.87 (t, ^3J = 6.8 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 170.8, 140.3, 124.8, 68.6, 39.8, 32.1, 29.2, 27.9, 23.0, 21.8, 21.3, 16.9, 14.4.
IR (film, ν/cm^{-1}): 2959, 2930, 2858, 1737, 1455, 1369, 1243, 1043, 806.
MS (EI, 70 eV), *m/z* (%): 212 (<1, $[M]^+$), 170 (7), 155 (15), 152 (30), 137 (13), 123 (14), 109 (15), 95 (86), 85 (88), 82 (100), 67 (43), 55 (26), 43 (66).
HRMS for $C_{13}H_{24}O_2$ (212.1776 $[M]^+$): found: 212.1767.

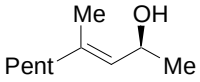
(2*S*,3*E*)-4-Methyldec-3-en-2-yl 2,6-difluorobenzoate ((*S*)-42e):



Prepared according to **TP7** from (*S*)-**45** (340 mg, 2.0 mmol, > 99 % *ee*), 2,6-difluorobenzoyl chloride (495 mg, 2.8 mmol), pyridine (0.25 ml, 3.0 mmol) and DMAP (24 mg, 0.2 mmol). Reaction conditions: 15 h at −10 °C. Purification by flash chromatography (pentane/Et_2O, 98:2 + 1 % Et_3N) yielded (*S*)-**42e** (565 mg, 91 %) as a colourless liquid.

$[\alpha]_D^{25}$ = + 49.0 (c = 1.5, EtOH).
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.26-7.40 (m, 1H), 6.82-6.87 (m, 2H), 5.8 (m, 1H), 5.16-5.20 (dq, ^3J = 9.0 Hz, ^4J = 3.0 Hz, 1H), 1.91-1.96 (t, ^3J = 6.0 Hz, 3H), 1.32 (d, ^3J = 6.0 Hz 3H), 1.20-1.23 (m, 8H), 0.80 (t, ^3J = 6.0 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 161.2, 160.0, 157.8, 140.1, 131.1, 122.8, 110.7, 111.8, 69.4, 38.4, 30.7, 27.8, 26.5, 21.6, 19.9, 15.6, 13.0.
IR (film, ν/cm^{-1}): 2930, 1732, 1625, 1470, 1288, 1119, 1013.
MS (EI, 70 eV), *m/z* (%): 310 (<1, $[M]^+$), 152 (18), 141 (100), 95 (25), 82 (32), 69 (11), 55 (7).
HRMS for $C_{18}H_{24}F_2O_2$ (310.1744 $[M^+]$): found: 310.1720.

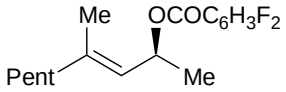
(2*S*,3*E*)-4-Methyl-3-nonen-2-ol ((*S*)-46):



49 (5.09 g, 24.0 mmol, 1.0 equiv.) was reacted in a Negishi cross-coupling reaction[50] with *n*-PentZnI (72 mmol, 14.4 mL, 5 M in THF, 3 equiv.) for 14 h at 40 °C. Purification by flash chromatography (pentane/Et_2O, 8:2 + 1 % Et_3N) afforded *rac*-**46** (3.38 g, 19.2 mmol, 80 %) as a colourless liquid.
Rac-**46** (2.81 g, 18.0 mmol, 1.0 equiv.) was resolved by enzymatic resolution according to **TP8** with vinyl acetate (3.7 mL, 40.0 mmol, 2.2 equiv.) and amano lipase AK (3.0 g) in pentane (50 mL). Reaction conditions: 20 h at 36 °C. Workup and purification by flash chromatography (pentane/Et_2O, 9:1 + 1 % Et_3N) afforded (*S*)-**46** (1.01 g, 6.4 mmol, 36 %, > 99 % *ee*) as a colourless liquid. The *ee* of (*S*)-**46** was determined by GC analysis.

$[\alpha]_D^{25}$ = – 30.9 (c = 2.07, $CDCl_3$).
GC (column: Chiraldex B-PH, 100 °C): t_R(min) = 15.1(*R*), 17.3 (*S*).
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 5.14-5.24 (m, 1H), 4.55 (dq, ^3J = 8.40 Hz, ^3J = 6.19 Hz, 1H), 1.95 (t, ^3J = 7.74 Hz, 2H), 1.64 (d, ^3J = 1.33 Hz, 3H), 1.61 (br, 1H), 1.17-1.43 (m, 6H), 1.21 (d, ^3J = 6.19 Hz, 3H), 0.87 (t, ^3J = 7.19 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 137.8, 128.9, 64.7, 39.4, 31.4, 27.3, 23.6, 22.5, 16.2, 14.0.
IR (film, ν/cm^{-1}): 3341, 2929, 1455, 1380, 1103, 1058, 866.
MS (EI, 70 eV), *m/z* (%): 156 (M^+, 1), 141(5), 95 (6), 85 (100), 82 (6), 71 (11).
HRMS for $C_{10}H_{20}O$ (156.1514 $[M]^+$): found: 156.1509.

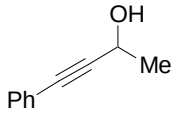
(2*S*,3*E*)-4-Methyl-3-nonen-2-yl-2,6-difluorobenzoate ((*S*)-42f):



Prepared according to **TP7** from (*S*)-**46** (654mg, 4.2 mmol, 1.0 equiv., > 99 % *ee*), pyridine (541 µL, 6.7 mmol, 1.6 equiv.), DMAP (159 mg, 1.3 mmol, 0.3 equiv.), 2,6-difluorbenzoylchloride (1.183 g, 841 µl, 6.7 mmol, 1.6 equiv.) and CH_2Cl_2 (40 ml). After workup, (*S*)-**42f** was obtained quantitatively as a colourless liquid.

$[\alpha]_D^{25}$ = + 21.7 (c = 3.15, $CDCl_3$).
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.30-7.43 (m, 1H), 6.86-6.99 (m, 2H), 5.88 (dq, ^3J = 8.74 Hz, ^3J = 6.41 Hz, 1H), 5.25 (dq, ^3J = 8.85 Hz, ^3J = 1.33 Hz, 1H), 2.01 (dt, ^3J = 7.74 Hz, 0.66 Hz, 2H), 1.76 (d, ^3J = 1.33 Hz, 3H), 1.41 (d, ^3J = 6.41 Hz, 3H), 1.18-1.48 (m, 6H), 0.88 (t, ^3J = 7.08 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 160.5 (dd, ^1J(C,F) = 255.6 Hz, ^1J(C,F) = 6.5 Hz, 2C), 161.0, 141.1, 132.1 (t, ^1J(C,F) = 10.27 Hz, 1C), 123.8, 111.5-112.2 (m, 2C), 70.4, 39.3, 31.3, 27.2, 22.5, 20.9, 16.6, 14.0.
IR (film, ν/cm^{-1}): 2932, 1732, 1625, 1593, 1470, 1289, 1120, 1037, 795.
MS (EI, 70 eV), *m/z* (%): 296 (<1, $[M]^+$), 225 (1), 158 (18), 141 (100), 95 (34), 82 (43), 67 (27), 55 (11).
HRMS for $C_{17}H_{22}F_2O_2$ (296.1588 $[M]^+$): found: 296.1562.

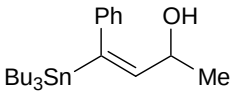
4-Phenylbut-3-yn-2-ol (53):



Prepared from iodobenzene and but-3-yn-2-ol according to a procedure by *Linstrumelle*.[51]

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 7.45-7.40 (m, 2H), 7.32-7.28 (m, 3H), 4.76 (q, ^3J = 6.6 Hz, 1H), 2.30 (s, 1H, OH), 1.55 (d, ^3J = 6.6 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 132.9, 129.4, 127.9, 122.6, 91.2, 83.9, 58.7, 24.0.

(1*E*)-1-Tributylstannyl-1-phenyl-but-1-en-3-ol (54): [52]

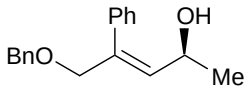


To a solution of **53** (45 mmol, 1 equiv.) and bis(triphenylphosphine) palladium chloride (300 mg, 0.5 mmol, 0.01 equiv.) in THF (50 mL) was added dropwise $HSnBu_3$ (15 mL, 55 mmol, 1.2 equiv.). The mixture was stirred at rt for 30 minutes. The solvents were evaporated *in vacuo* and the residue was purified by flash chromatography (pentane/Et_2O, 9:1). It yielded **54** (14 g, 80 %) as a single regio- and stereoisomer as a colourless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.21-7.14 (m, 2H), 7.07-7.02 (m, 1H), 6.87-6.82 (m, 2H), 5.72 (d, ^3J = 8.4 Hz, ^3J(H,Sn) = 63 Hz, 1H), 4.34-4.27 (m, 1H), 1.40-1.33 (m, 6H), 1.23-1.13 (m, 9H), 0.84-0.76 (m, 15H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 147.3, 145.2, 144.7, 128.5, 126.8, 125.5, 65.5, 29.3, 27.6, 23.9, 14.0, 10.3.

IR (film, ν/cm^{-1}): 3340, 2960, 2930, 1460.
MS (EI, 70 eV), *m/z* (%): 381 (100, [M–Bu]$^+$), 325 (19), 307 (14), 249 (38), 177 (34), 147 (39), 131 (67).
HRMS for $C_{22}H_{38}Osn$ (381.1240 [M–Bu]$^+$): found: 381.1243.

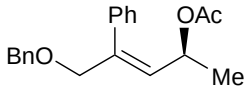
(4*S*,2*E*)-1-Benzyloxy-2-phenyl-pent-2-en-4-ol ((*S*)-52):



To a cooled (–50 °C) solution of **54** (4.4 g, 10 mmol, 1 equiv.) in THF (20 mL) was added *n*-BuLi (14 mL, 1.5 M in hexanes, 20 mmol, 2 equiv.). The first equivalent was added very slowly to deprotonate selectively the alcohol without carrying out the Sn-Li exchange reaction. After the end of the addition, the mixture was warmed to rt and stirred for 1 h. It was cooled again to –50 °C and benzyl(chloromethyl) (2 g, 12 mmol, 1.2 equiv.) was added. The solution was warmed to rt and stirred overnight. It was quenched with water (50 mL) and extracted with Et_2O (3 x 15 mL). The organic layer was dried ($MgSO_4$), concentrated *in vacuo* and purified by flash chromatography (pentane/Et_2O, 7:3). It yielded *rac*-**52** (1.28 g, 48 %) as a yellow oil.
Enzymatic resolution of *rac*-**52** according to **TP8** in presence of amano lipase AK from and vinyl acetate (24 h at reflux in pentane) followed by purification by flash chromatography (pentane/Et_2O, 9:1) yielded (*S*)-**52** (49 %, > 99 % *ee*) as a colourless oil. The *ee* of (*S*)-**52** was determined by HPLC analysis.

$[\alpha]_D^{20}$ = – 13 (c = 1.05, CH_2Cl_2).
HPLC (column: OD-H; *n*-heptane/*i*-PrOH, 95:5, 0.6 mL/min): t_R(min) = 25.95 (*R*), 47.47 (*S*).
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.34-7.18 (m, 10H), 5.91 (dd, ^3J = 0.3 Hz, ^3J = 8.1 Hz, 1H), 4.64 (m, 1H), 4.49 (s, 2H), 4.42 (d, ^3J = 10.2 Hz, 1H), 4.31 (d, ^3J = 11.1 Hz, 1H), 2.00 (br. s, 1H), 1.26 (d, ^3J = 6.3 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 141.1, 138.3, 138.1, 137.7, 128.9, 128.7, 128.4, 128.3, 127.9, 126.7, 73.1, 68.0, 64.7, 23.7.
IR (film, ν, cm^{-1}): 3400, 2970, 1490, 1450, 1370, 1090.
MS (EI, 70 eV), *m/z* (%): 265 ([M–3H]$^+$, 0.03); 159 (43), 145 (19), 131 (26), 91 (100).
HRMS for $C_{18}H_{20}O$ (265.1229 [M–3H]$^+$): found: 265.1242.

(2*R*,3*E*)-5-(Benzyloxy)-4-phenylpent-3-en-2-yl acetate ((*R*)-55):

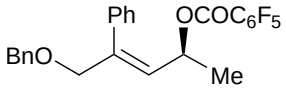


(*R*)-**55** was obtained as a by-product from the enzymatic resolution of *rac*-**52** as a colourless oil (45 %, 99 % *ee*). The *ee* was determined on the corresponding allylic alcohol (*R*)-**52** after hydrolysis under basic conditions (KOH, 1.5 equiv. in MeOH) of the acetate.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.36-7.18 (m, 10H), 5.82-5.68 (m, 2H), 4.49 (d, ^3J = 11.6 Hz, 1H), 4.44 (s, 2H), 4.32 (d, ^3J = 11.6 Hz, 1H), 1.96 (s, 3H), 1.30 (d, ^3J = 6.3 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 170.7, 140.8, 139.2, 138.4, 132.4, 128.7, 128.7, 128.3, 128.0, 128.0, 126.9, 72.7, 68.1, 67.5, 21.7, 21.5.
IR (film, ν, cm^{-1}): 3062-2870, 1731, 1241, 1072, 698.
MS (EI, 70 eV), *m/z* (%): 310 (< 0.1, [M]$^+$), 250 (17), 159 (98), 144 (49), 129 (41), 115 (12), 91 (100), 65 (8), 43 (32).

HRMS for $C_{20}H_{22}O_3$ (310.1569 $[M]^+$): found: 310.1882.

(4*S*,2*E*)-[1-Benzyloxy-2-phenylpent-2-en-4-yl] pentafluorobenzoate ((*S*)-42g):

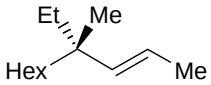


Prepared according to **TP7** from (*S*)-**52** (80 mg, 1.4 mmol, > 99 % *ee*, 1 equiv.), DMAP (20 mg, 0.14 mmol, 0.1 equiv.), pyridine (0.2 mL, 2.1 mmol, 1.5 equiv.), pentafluorobenzoyl chloride (460 mg, 2 mmol, 1.4 equiv.) and CH_2Cl_2 (3 mL). After work up (*S*)-**42g** (480 mg, 95 %) was obtained as a pale yellow oil and used without further purification.

$[\alpha]_D^{20}$ = + 8 (c = 0.7, CH_2Cl_2).
^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 7.44-7.41 (m, 2H), 7.36-7.26 (m, 8H), 6.12-6.05 (m, 1H), 5.94 (m, 1H), 4.66 (m, 1H), 4.56 (m, 1H), 4.46 (d, ^3J = 11.6 Hz, 1H), 1.52 (d, ^3J = 6.4 Hz, 3H).
^{13}C-NMR ($CDCl_3$, 100 MHz): δ = 157.3, 145.0 (m, 2CF), 142.9 (m, CF), 140.3 (m, 2CF), 140.3, 140.2, 137.9, 130.4, 128.4 (2 x 2C), 127.9, 127.8, 127.7, 126.6, 72.5, 70.9, 67.4, 20.9.
IR (film, ν/cm^{-1}): 3060, 2870, 1740, 1650, 1520, 1500, 1340, 1230.
MS (EI, 70 eV), *m/z* (%): 462 (M^+, 0.06), 194 (66), 159 (23), 144 (30), 129 (22), 91 (100).
HRMS for $C_{24}H_{19}F_5O_3$ (462.1255 $[M]^+$): found: 462.1270.

3.2 Products of the S_N2' Allylic Substitution: Alkenes

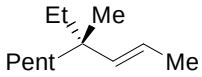
(4*S*,2*E*)-4-Ethyl-4-methyldec-2-ene ((*S*)-41a):



Prepared according to **TP1** from (*S*)-**42e** (470 mg, 1.51 mmol, > 99 % *ee*), Et_2Zn (0.37 mL, 3.63 mmol) and CuCN·2LiCl (1.81 ml, 1 M in THF, 1.81 mmol). Reaction conditions: 16 h, –30 °C. Purification by flash chromatography (100 % pentane) yielded (*S*)-**41a** (242 mg, 88 %, 98 % *ee*) as a colourless liquid. The *ee* of (*S*)-**41a** was determined by GC analysis after transformation into the corresponding carboxylic acid (*S*)-**57a.**

$[\alpha]_D^{25}$ = – 7.0 (c = 1.35, EtOH).
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.75 (t, ^3J = 7.2 Hz, 3H), 0.87 (m, 6H), 1.19-1.28 (m, 12H), 1.66 (m, 3H), 5.26 (m, 2H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 140.6, 121.7, 41.3, 39.0, 33.8, 32.3, 30.6, 24.4, 23.3, 23.1, 18.6, 14.5, 8.8.
IR (film, ν/cm^{-1}): 2930, 2856, 1461, 1378, 973.
MS (EI, 70 eV), *m/z* (%): 182 ($[M]^+$, 3), 153 (33), 111 (7), 97 (100), 83 (20), 69 (57), 55(44), 40 (12).
HRMS for $C_{13}H_{26}$ (182.2035 $[M]^+$): found: 182.2035.

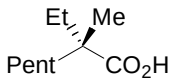
(4*S*,2*E*)-4-Ethyl-4-methyl-2-nonene ((*S*)-41b):



According to **TP1**, (*S*)-**42f** (1.052 g, 3.55 mmol, > 99 % *ee*) was reacted with Et_2Zn (892 µl, 8.52 mmol, 2.4 equiv.) and CuCN·2LiCl (4.26 mL, 4.26 mmol, 1.2 equiv.) in THF (5 mL) at –30 °C for 14 h. After workup, the crude product was purified by flash chromatography (100 % pentane). (*S*)-**41b** (478 mg, 2.84 mmol, 80 %, 96 % *ee*) was obtained as a colourless liquid.

$[\alpha]_D^{24} = -6.5$ (c = 1.45, $CDCl_3$).
^{1}H-NMR (600 MHz, $CDCl_3$): δ = 5.23-5.31 (m, 2H), 1.65-1.72 (m, 3H), 1.12-1.32 (m, 10H), 0.83-0.91 (m, 6H), 0.76 (t, ^3J = 7.4 Hz, 3H).
^{13}C-NMR (150 MHz, $CDCl_3$): δ = 140.2, 121.3, 40.9, 38.6, 33.5, 32.8, 23.7, 22.9, 22.7, 18.2, 14.1, 8.5.
IR (film, ν/cm^{-1}): 2930, 1462, 1378, 973.
MS (EI, 70 eV), *m/z* (%): 168 ([M]$^+$, 3), 139 (19), 97 (100), 83 (29), 69 (66), 55 (78), 41(35).
HRMS for $C_{12}H_{24}$ (168.1878 [M]$^+$): found: 168.1891.

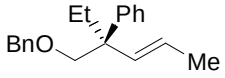
The *ee* of (*S*)-**41b** was determined by GC analysis after transformation into (2*S*)-2-ethyl-2-methylheptanoic acid (*S*)-**57b**:



According to **TP4**, (*S*)-**41b** (84 mg, 0.50 mmol, 1.0 equiv.) was ozonolyzed at –78 °C in acetone (20 mL). After treatment of the ozonide with Jones reagent (1.4 mL, 2.7 M, 1.4 mmol, 2.7 equiv.) at 0 °C and stirring for another 15 min, the reaction mixture was quenched with *i*-PrOH (5 ml). Acido/basic workup yielded (*S*)-**57b** (63 mg, 73 %, 96 % *ee*) as a colourless liquid.

$[\alpha]_D^{25} = -4.8$ (c = 1.67, $CDCl_3$).
GC (column: Chiraldex B-PH; 130 °C const.): t_R(min) = 31.2 (*S*), 32.3 (*R*).
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 9.98-10.62 (br, 1H), 1.55-1.77 (m, 2H), 1.37-1.55 (m, 2H), 1.16-1.37 (m, 6H), 1.12 (s, 3H), 0.79-0.96 (m, 6H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 184.3, 46.1, 38.7, 32.3, 31.7, 24.1, 22.5, 20.5, 14.0, 8.8.
IR (film, ν/cm^{-1}): 2936, 1699, 1464, 1262.
MS (EI, 70 eV), *m/z* (%): 173 (2, [M+H]$^+$), 144 (3), 127 (18), 115 (5), 102 (62), 87 (61), 85 (40), 71 (84), 57 (74), 43 (100), 41 (72).
HRMS for $C_{10}H_{21}O_2$ (173.1541 [M+H]$^+$): found: 173.1547.

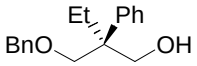
(4*R*,2*E*)-4-Benzyloxymethyl-4-phenyl-hex-2-ene ((*R*)-41c):



Prepared according to **TP1** from (*S*)-**42g** (1.8 g, 4 mmol, > 99 % *ee*, 1 equiv.), Et_2Zn (1 mL, 10 mmol, 2.4 equiv.) and CuCN·2LiCl (5.2 mL, 1.0 M in THF, 5.2 mmol, 1.3 equiv.). Reaction conditions: 12 h, –10 °C. Purification by flash chromatography (pentane/Et_2O, 95:5) yielded (*R*)-**41c** (690 mg, 69 %, 96 % *ee*) as a colourless oil.

$[\alpha]_D^{20}$ = – 13 (c = 0.69, CH_2Cl_2).
^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 7.36-7.20 (m, 10H), 5.68 (dq, ^3J = 1.6 Hz, ^3J = 15.6 Hz, 1H), 5.48 (dq, ^3J = 6.4 Hz, ^3J = 16 Hz, 1H), 4.51 (s, 2H), 3.73 (d, ^3J = 9.6 Hz, 1H), 3.65 (d, ^3J = 9.2 Hz, 1H), 1.99-1.86 (m, 2H), 1.77 (dd, ^3J = 1.6 Hz, ^3J = 6.8 Hz, 3H). 0.78 (t, ^3J = 7.2 Hz, 3H).
^{13}C-NMR ($CDCl_3$, 100 MHz): δ = 145.0, 138.7, 136.2, 128.2, 127.8, 127.7, 127.4, 127.3, 125.8, 124.2, 75.5, 73.3, 48.4, 28.9, 18.5, 8.7.
IR (film, ν/cm^{-1}): 3030, 2960, 2930, 2860, 1740, 1500, 1450, 1100.
MS (EI, 70 eV), *m/z* (%): 280 (M^+, 0.02), 159 (100), 132 (14), 117 (39), 91 (35).
HRMS for $C_{20}H_{24}O$ (280.1823 $[M]^+$): 280.1825.

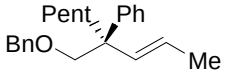
The *ee* of (*R*)-**41c** was determined by HPLC analysis after transformation into (2*S*)-2-benzyloxymethyl-2-phenyl-butan-1-ol (*S*)-**58a**:



A solution of (*R*)-**41c** (280 mg, 1 mmol, 1 equiv.) in CH_2Cl_2 (15 mL) was cooled to –78 °C and ozone was bubbled through it until the solution turned blue. N_2 was then bubbled to remove the excess ozone. The colourless solution was warmed to rt and $BH_3 \cdot Me_2S$ (neat, 0.4 mL, 10 M, 4 mmol, 4 equiv.) was added. The solution was stirred at 20 °C for 24 h, then it was carefully quenched with water (30 mL). The mixture was extracted with Et_2O (3 x 10 mL). The organic layer was dried ($MgSO_4$), concentrated *in vacuo* and purified by flash chromatography (pentane/Et_2O, 7:3). (*S*)-**58a** (190 mg, 66 %, 99 % *ee*) was obtained as a colourless solid.

mp.: 56–58 °C.
$[\alpha]_D^{20}$ = – 10 (c = 1, CH_2Cl_2).
HPLC (column: OD-H; *n*-heptane/*i*-PrOH = 97/3, 0.6 mL/min): t_R(min) = 28.7 (*S*), 34.5 (*R*).
^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 7.29-7.15 (m, 10H), 4.50 (d, ^3J = 2.7 Hz, 1H), 3.95-3.80 (m, 3H), 3.67 (d, ^3J = 9 Hz, 1H), 2.39 (m, 1H), 1.71 (dq, ^3J = 2.1 HZ, ^3J = 7.5 Hz, 2H), 0.59 (t, ^3J = 7.5 Hz, 3H).
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 142.2, 138.3, 128.9, 128.8, 128.2, 128.0, 127.3, 126.7, 76.1, 74.1, 69.4, 47.4, 27.3, 8.3.
IR (KBr disk, ν/cm^{-1}): 3430, 3030, 2960, 2880, 1500, 1450, 1090.
MS (EI, 70 eV), *m/z* (%): 271 ($[M+H]^+$, 0.3), 149 (13), 132 (76), 147 (14), 91 (100).
HRMS for $C_{18}H_{22}O_2$ (271.1607 $[M+H]^+$): found: 271.1653.

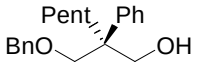
(4*R*,2*E*)-4-Benzyloxymethyl-4-phenyl-non-2-ene ((*R*)-41d):



According to **TP1**, compound (*S*)-**42g** (430 mg, 1 mmol, > 99 % *ee*, 1 equiv.) was reacted with $Pent_2Zn$ (0.5 mL, 4.5 M, 2.4 mmol, 2.4 equiv.) and CuCN·2LiCl (1.30 mL, 1.30 mmol, 1.3 equiv.) in THF (3 mL) at –10 °C for 12 h. After workup, the crude product was purified by flash chromatography (pentane/Et_2O, 95:5). (*R*)-**41d** (290 mg, 90 %, 99 % *ee*) was obtained as a colourless oil.

$[\alpha]_D^{20}$ = – 9 (c = 0.68, CH_2Cl_2).
^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 7.25-7.10 (m, 10H), 5.57 (dq, ^4J = 1.5 Hz, ^3J = 15.9 Hz, 1H), 5.35 (dq, ^3J = 6.3 Hz, ^3J = 15.9 Hz, 1H), 4.40 (s, 2H), 3.61 (d, ^3J = 8.7 Hz, 1H), 3.54 (d, ^3J = 9.0 Hz, 1H), 1.76-1.71 (m, 2H), 1.66 (dd, ^3J = 1.5 Hz, ^3J = 6.3 Hz, 3H), 1.18-0.93 (m, 6H), 0.76 (t, ^3J = 6.6 Hz, 3H).
^{13}C-NMR ($CDCl_3$, 100 MHz): δ = 145.3, 138.7, 136.5, 128.2, 127.8, 127.5, 127.4, 127.3, 125.8, 123.9, 75.9, 73.3, 48.1, 36.5, 32.7, 23.7, 22.6, 18.5, 14.1.
IR (film, ν, cm^{-1}): 3030, 2960, 2860, 1740, 1500, 1450, 1100.
MS (EI, 70 eV), *m/z* (%): 322 (< 0.1, $[M]^+$), 201 (100), 145 (33), 131 (100), 91 (91).
HRMS for $C_{23}H_{30}O$ (322.2297 $[M]^+$): found: 322.2317.

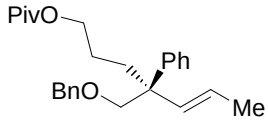
The *ee* of (*R*)-**41d** was determined by HPLC analysis after transformation into (2*S*)-2-benzyloxymethyl-2-phenylbutan-1-ol (*S*)-**58b**:



A solution of (*R*)-**41d** (342 mg, 1 mmol, 1 equiv.) in CH_2Cl_2 (10 mL) was cooled to –78 °C and ozone was bubbled through it until the solution turned blue. N_2 was then bubbled to remove the excess ozone. The colourless solution was warmed to rt and $BH_3 \cdot Me_2S$ (neat, 0.4 mL, 10 M, 4 mmol, 4 equiv.) was added. The solution was stirred at 20 °C for 24 h and then it was carefully quenched with water (30 mL). The mixture was extracted with Et_2O (3 x 10 mL). The organic layer was dried ($MgSO_4$), concentrated *in vacuo* and purified by flash chromatography (pentane/Et_2O, 7:3) afforded (*S*)-**58b** (230 mg, 66 %, 99 % *ee*) as a colourless oil.

$[\alpha]_D^{20}$ = – 13 (c = 1, CH_2Cl_2).
HPLC (column: OD-H; *n*-heptane/*i*-PrOH = 97/3, 0.6 mL/min): t_R(min) = 18.8 (*S*), 24.1 (*R*).
^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 7.30-7.12 (m, 10H), 4.50 (d, ^3J = 4.2 Hz, 2H), 3.93-3.79 (m, 3H), 3.65 (d, ^3J = 9.0 Hz, 1H), 2.60 (br. s., 1H), 1.66-1.61 (m, 2H), 1.14-1.08 (m, 4H), 0.94-0.90 (m, 2H), 0.73 (t, ^3J = 6.9 Hz, 3H).
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 142.6, 138.3, 128.9, 128.8, 128.2, 128.0, 127.1, 126.7, 76.4, 74.1, 69.8, 47.2, 34.8, 32.9, 23.4, 22.8, 14.4.
IR (film, ν/cm^{-1}): 3440, 2950, 1500, 1450, 1100.
MS (EI, 70 eV), *m/z* (%): 312 (M^+, 0.08); 191 (14); 174 (20); 118 (92); 91 (100).
HRMS for $C_{21}H_{28}O_2$ (312.2139 $[M]^+$): found: 312.2114.

(4*R*,5*E*)-4-(Benzyloxymethyl)-4-phenylhept-5-enyl pivalate ((*R*)-41e):

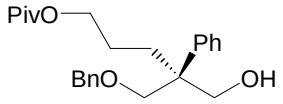


Prepared according to **TP1** from (*S*)-**42g** (930 mg, 2.0 mmol, > 99 % *ee*), $[PivO(CH_2)_3]_2Zn$ 2.45 M solution (1.95 mL, 4.8 mmol) and CuCN·2LiCl 1M solution (2.4 mL, 2.4 mmol). Reaction conditions: 16 h, –30 °C to –10 °C. Purification by flash chromatography (pentane/Et_2O, 98:2) yielded (*R*)-**41e** (472 mg, 60 %, 98 % *ee*) as a colourless liquid.

$[\alpha]_D^{25}$ = + 7.7 (c = 1.925, CH_2Cl_2).
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.19-7.31 (m, 10H), 5.65 (dd, ^3J = 15.8 Hz, ^4J = 1.2 Hz, 1H), 5.50 (dq, ^3J = 15.8 Hz, ^3J = 6.0 Hz, 1H), 4.8 (s, 2H), 3.71 (d, ^2J = 9.0 Hz, 1H), 3.59 (d,

^2J = 9.0 Hz, 1H), 1.88-1.98 (m, 2H), 1.75 (dd, ^3J = 7.8 Hz, ^4J = 1.2 Hz, 3H), 1.41-1.52 (m, 2H), 1.18 (s, 9H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 178.9, 145.0, 138.9, 136.3, 128.6, 128.4, 127.9, 127.8, 127.8, 126.4, 124.8, 76.1, 73.7, 65.2, 48.2, 39.1, 32.9, 27.6, 24.1, 18.8.
IR (film, ν/cm^{-1}): 2956, 1727, 1453, 1157, 698.
MS (EI, 70 eV), *m/z* (%): 394 (3, $[M]^+$), 171 (100), 91 (60).
HRMS for $C_{26}H_{34}O_3$ (394.2508 $[M]^+$): found: 394.2469.

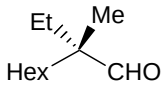
The *ee* of (*R*)-**41e** was determined by HPLC analysis after transformation into (4*S*)-4-((benzyloxy)methyl)-5-hydroxy-4-phenylpentyl pivalate (*S*)-**58c**:



$[\alpha]_D^{25}$ = + 8.2 (c = 1.1, CH_2Cl_2).
HPLC (column: OD-H; *n*-heptane/*i*-PrOH = 95/5, 0.6 mL/min): t_R(min) = 27.8 (*R*), 30.5 (*S*).
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.15-7.28 (m, 10H), 4.5 (s, 2H), 3.78-3.93 (m, 5H), 3.6 (d, ^2J = 9.2 Hz, 1H), 2.2 (br s, 1H, OH), 1.8 (m, 2H), 1.3 (m, 2H), 1.09 (s, 9H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 178.9, 142.0, 138.1, 130.0, 128.9 (2C), 128.2, 128.0, 127.0, 76.0, 74.1, 69.4, 65.0, 46.9, 39.1, 30.6, 27.6, 23.4.
IR (film, ν/cm^{-1}): 3469, 2958, 1726, 1454, 1160, 698.
MS (EI, 70 eV), *m/z* (%): 352.2 (<1, $[M–CH_4O]^+$), 161 (45), 144 (100), 91 (24).
HRMS for $C_{26}H_{34}O_3$ (352.2038 $[M–CH_4O]^+$): found: 352.2031.

3.3 Tertiary aldehydes and carboxylic acids

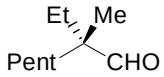
(2*S*)-2-Ethyl-2-methyloctanal ((*S*)-56b):



According to **TP3**, alkene (*S*)-**41a** (350 mg, 1.92 mmol) was ozonolyzed at −78 °C and stirred with PPh_3 (553 mg, 2.11 mmol) at 0 °C for 2 h. Purification by flash chromatography (pentane/Et_2O, 98:2) yielded (*S*)-**56b** (212 mg, 65 %, 98 % *ee*) as a colourless liquid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 9.35 (s, 1H), 1.20-1.45 (m, 4H), 1.18 (m, 8H), 0.92 (s, 3H), 0.80 (m, 6H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 206.1, 48.3, 34.1, 30.7 (2C), 28.9, 26.9, 22.9, 21.6, 16.6, 7.3.
IR (film, ν/cm^{-1}): 2929, 1722, 1438, 1183, 1120, 722, 541.
MS (EI, 70 eV), *m/z* (%): 171 (2, $[M+H]^+$), 141 (24), 99 (17), 85 (100), 71 (82), 57 (94), 43 (41).
HRMS for $C_{11}H_{22}O$ (171.1749 $[M+H]^+$): found: 171.1776.

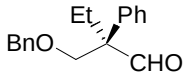
(2*S*)-2-Ethyl-2-methylheptanal ((*S*)-56c):



According to **TP3**, alkene (*S*)-**41b** (84 mg, 0.50 mmol, 1.0 equiv.) was ozonolyzed at −78 °C and stirred with PPh_3 (315 mg, 1.20 mmol, 1.2 equiv.) at 0 °C for 2 h. After workup and flash chromatography (pentane/Et_2O, 98:2), (*S*)-**56c** (50 mg, 0.32 mmol, 63 %) was obtained as a colourless liquid.

$[\alpha]_D^{25}$ = – 2.4 (c = 2.43, CH_2Cl_2).
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 9.42 (s, 1H), 1.38-1.63 (m, 4H), 1.07-1.36 (m, 6H), 0.99 (s, 6H), 0.76-0.92 (m, 6H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 207.1, 49.3, 35.1, 32.5, 27.9, 23.6, 22.5, 17.6, 14.0, 8.3.
IR (film, ν/cm^{-1}): 2932, 1728, 1462, 1384.
MS (EI, 70 eV), *m/z* (%): 157 (2, $[M+H]^+$), 127 (26), 86 (56), 85 (73), 71 (100), 57 (56), 55 (13), 42 (46), 39 (24).
HRMS for $C_{12}H_{25}$ (157.1592 $[M+H]^+$): found: 157.1574.

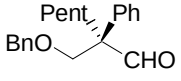
(2*R*)-2-Benzyloxymethyl-2-phenylbutanal ((*R*)-56d):



According to **TP3**, alkene (*R*)-**41c** (660 mg, 2.4 mmol, 1 equiv.) was ozonolyzed at −78 °C and stirred with PPh_3 (780 mg, 3 mmol, 1.3 equiv.) at rt for 24 h. After workup and flash chromatography (pentane/Et_2O, 95/5), (*R*)-**56d** (365 mg, 58 %, 99 % *ee*) was obtained as a colourless oil.

$[\alpha]_D^{20}$ = +18 (c = 1, CH_2Cl_2).
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 9.52 (s, 1H), 7.29-7.17 (m, 8H), 7.11-7.08 (m, 2H), 4.46 (s, 2H), 3.96 (d, ^3J = 9.3 Hz, 1H), 3.79 (d, ^3J = 9.3 Hz, 1H), 2.00 (dq, ^3J = 1.8 Hz, ^3J = 7.5 Hz, 2H), 0.66 (t, ^3J = 7.5 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 202.4, 138.3, 137.5, 129.1, 128.8, 128.1, 128.0, 127.9, 127.8, 73.9, 70.6, 59.0, 24.5, 8.4.
IR (film, ν/cm^{-1}): 3030, 2970, 2860, 2710, 1730, 1500, 1450.
MS (EI, 70 eV), *m/z* (%): 268 (M^+, 0.11), 238 (13), 132 (35), 117 (11), 91 (100).
HRMS for $C_{18}H_{20}O_2$ (268.1463, M^+): found: 268.1522.

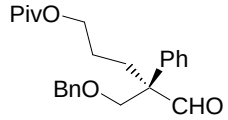
(2*R*)-2-Benzyloxymethyl-2-phenylbutanal ((*R*)-56e):



According to **TP3**, alkene (*R*)-**41d** (800 mg, 2.5 mmol, 1 equiv.) was ozonolyzed at −78 °C and stirred with PPh_3 (760 mg, 3 mmol, 1.2 equiv.) at rt for 24 h. After workup and flash chromatography (pentane/Et_2O, 95/5), (*R*)-**56e** (520 mg, 66 %, 99 % *ee*) was obtained as a colourless oil.

$[\alpha]_D^{20}$ = +15 (c = 1.05, CH_2Cl_2).
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 9.51 (s, 1H); 7.30-7.08 (m, 10H), 4.45 (s, 2H), 3.95 (d, ^3J(H,H) = 9.3 Hz, 1H), 3.79 (d, ^3J(H,H) = 9.3 Hz, 1H), 1.92 (t, ^3J(H,H) = 6.0 Hz, 2H), 1.17-1.15 (m, 4H), 1.00-0.96 (m, 2H), 0.75 (m, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 202.4, 138.3, 137.8, 129.1, 128.7, 128.1, 127.9, 127.8, 127.7, 73.9, 71.0, 58.7, 32.7, 23.6, 22.8, 14.4.
IR (film, ν/cm^{-1}): 3030, 2930, 2710, 1730, 1450.
MS (EI, 70 eV), *m/z* (%): 310 (M^+, 0.05); 118 (39); 91 (100).
HRMS for $C_{18}H_{20}O_2$ (310.1919, M^+): found: 310.1926.

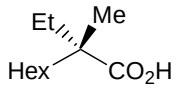
(4*R*)-5-(Benzyloxy)-4-formyl-4-phenylpentyl pivalate ((*R*)-56f):



Prepared according to **TP3** form alkene (*R*)-**41e** (700 mg, 1.77 mmol, 98 % *ee*) was ozonolyzed at −78 °C and stirred with PPh_3 (558 mg, 2.13 mmol) at 0 °C for 2 h. Purification by flash chromatography (pentane/Et_2O, 9:1) yielded (*R*)-**56f** (212 mg, 76 %, 98 % *ee*) as a colourless liquid.

$[\alpha]_D^{25}$ = – 26.5 (c = 1.07, CH_2Cl_2).
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 9.05 (s, 1H), 7.06-7.31 (m, 10H), 4.47 (s, 2H), 4.0 (d, ^3J = 9.3 Hz, 2H), 3.9 (t, ^3J = 6.3 Hz, 2H), 3.8 (d, ^3J = 9.3 Hz, 2H), 2.0 (t, ^3J = 8.4 Hz, 2H), 1.2 (m, 2H), 1.09 (s, 9H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 201.6, 178.8, 138.1, 137.0, 129.3, 128.8, 128.2, 128.0 (2C), 127.7, 74.0, 70.6, 64.7, 58.3, 39.1, 28.2, 27.6, 23.3.
IR (film, ν/cm^{-1}): 2969, 1726, 1285, 1161, 749, 699.
MS (EI, 70 eV), *m/z* (%): 382 (<1, $[M]^+$), 352 (6), 144 (52), 159 (14), 129 (17), 91 (100).
HRMS for $C_{24}H_{30}O_4$ (382.2144, $[M]^+$): found: 382.2167.

(2*S*)-2-Ethyl-2-methyloctanoic acid ((*S*)-57a):

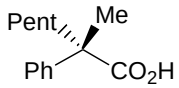


According to **TP4**, alkene (*S*)-**41a** (364 mg, 2.0 mmol) was ozonolysed in acetone (10 mL) at −78 °C and subsequently treated with Jones reagent (1.9 ml, 5.4 mmol, 2.7 equiv.). After acido/basic workup (*S*)-**57a** (212 mg, 68 %, 98 % *ee*) was obtained as a colourless liquid.

$[\alpha]_D^{25}$ = – 4.0 (c = 1.4, EtOH).
GC (Chiraldex B-PH; 120 °C (60 min), 1 °C/min, 140 °C (15min)): t_R(min) = 78.7 (*S*), 79.9 (*R*).
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.7-1.5 (m, 2H), 1.5-1.3 (m, 2H), 1.19 (m, 4H), 1.05 (s, 3H), 0.79 (m, 6H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 183.4, 45.1, 37.7, 30.7 (2C), 28.8, 22.5, 21.6, 19.5, 13.0, 7.8.
IR (film, ν/cm^{-1}): 2859, 1698, 1463, 1258, 939.
MS (EI, 70 eV), *m/z* (%): 187 (<1, $[M+H]^+$), 158 (5), 141 (25), 129 (4.1), 102 (100), 87 (58), 71 (18), 57 (62).

HRMS for $C_{11}H_{22}O_2$ (187.16989 $[M+H]^+$): found: 187.1687.

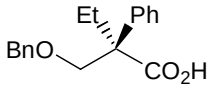
(2*S*)-2-Methyl-2-phenylheptanoic acid ((*S*)-57b):



According to **TP4**, alkene (*R*)-**32a** (432 mg, 2.0 mmol) was ozonolysed in acetone (10 mL) at –78 °C and subsequently treated with Jones reagent (1.9 mL, 5.4 mmol, 2.7 equiv.). After acido/basic workup (*S*)-**57b** (212 mg, 79 %, 98 % *ee*) was obtained as a colourless liquid.

$[\alpha]_D^{25}$ = + 8.1 (c = 1.3, EtOH).
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.16-7.32 (m, 5H), 1.80-2.09 (m, 2H), 1.49 (s, 3H), 1.17-1.20 (m, 6H), 0.77 (t, ^3J = 6.9 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 183.0, 143.5, 128.8, 127.2, 126.6, 50.4, 39.3, 32.7, 24.7, 22.8 (2C), 14.4.
IR (film, ν/cm^{-1}): 2955, 1699, 1273, 697.
MS (EI, 70 eV), *m/z* (%): 220 (1, $[M]^+$), 175 (34), 150 (19), 132 (12), 118 (20), 105 (100), 91 (60), 77 (17).
HRMS for $C_{14}H_{20}O_2$ (220.1463 $[M]^+$): found: 220.1466.

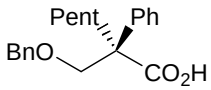
(2*R*)-2-(Benzyloxymethyl)-2-phenylbutanoic acid ((*R*)-57c):



According to **TP4**, alkene (*R*)-**41c** (840 mg, 3.0 mmol) was ozonolysed in acetone (10 mL) at –78 °C and subsequently treated with Jones reagent (2.8 ml, 8.1 mmol, 2.7 equiv.). After acido/basic workup (*R*)-**57c** (542 mg, 65 %, 99 % *ee*) was obtained as a colourless liquid.

$[\alpha]_D^{25}$ = – 8.6 (c = 1.4, EtOH).
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.15-7.27 (m, 10H), 4.47 (s, 2H), 3.98 (d, ^2J = 9.0 Hz, 1H), 3.82 (d, ^2J = 9.0 Hz, 1H), 2.09 (q, ^3J = 7.5 Hz, 2H), 0.68 (t, ^3J = 7.5 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 180.1, 140.0, 138.2, 128.8 (2C), 128.1, 128.0, 127.4, 127.1, 74.0, 71.6, 55.6, 26.9, 8.9.
IR (film, ν/cm^{-1}): 2972, 1704, 1498, 1259, 1102, 697.
MS (EI, 70 eV), *m/z* (%): 284 (<1, $[M]^+$), 254 (10), 163 (14), 132 (13), 107 (19), 91 (100).
HRMS for $C_{18}H_{20}O_3$ (284.1412 $[M]^+$): found: 284.1378.

(2*R*)-2-(Benzyloxymethyl)-2-phenylheptanoic acid ((*R*)-57d):

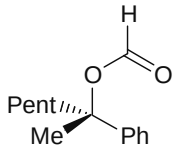


According to **TP4**, alkene (*R*)-**41d** (322 mg, 1.4 mmol) was ozonolysed in acetone (10 mL) at –78 °C and subsequently treated with Jones reagent (1.3 mL, 3.78 mmol, 2.7 equiv.). After acido/basic workup (*R*)-**57d** (273 mg, 60 %, 99 % *ee*) was obtained as a colourless liquid.

$[\alpha]_D^{25} = -5.8$ (c = 1.95, EtOH).
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.15-7.27 (m, 10H), 4.47 (s, 2H), 3.97 (d, ^2J = 9.0 Hz, 1H), 3.83 (d, ^2J = 9.0 Hz, 1H), 2.02 (m, 2H), 1.13 (m, 6H), (t, ^3J = 6.6 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 179.3, 140.3, 138.12, 128.8 (2C), 128.1, 128.0, 127.3, 127.0, 74.0, 72.0, 55.2, 34.3, 32.6, 24.1, 22.8, 14.4.
IR (film, ν/cm^{-1}): 2956, 1703, 1453, 1263, 1099, 697.
MS (EI, 70 eV), *m/z* (%): 326 (<1, $[M]^+$), 159 (46), 118 (30), 91 (100).
HRMS for $C_{21}H_{26}O_3$ (326.1882, $[M]^+$): found: 326.1864.

3.4 Tertiary alcohols, amines and isocyanates

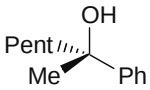
(2*S*)-2-Phenylheptan-2-yl formate ((*S*)-60):



Prepared according to **TP5** from aldehyde (*S*)-**56a** (163 mg, 0.8 mmol, 98 % *ee*), *m*-CPBA (207 mg, 1.2 mmol). Purification by flash chromatography (pentane/Et_2O, 98/2) yielded (*S*)-**60** (123 mg, 70 %) as a colourless liquid.

$[\alpha]_D^{25}$ = + 11.6 (c = 1.65, EtOH)
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.08 (s, 1H), 7.18-7.27 (m, 5H), 2.0 (m, 2H), 1.79 (s, 3H), 1.15 (m, 6H), 0.76 (t, ^3J = 6.9 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 160.9, 144.5, 128.7, 127.6, 125.3, 85.6, 43.0, 32.2, 25.6, 23.6, 22.8, 14.3.
IR (film, ν/cm^{-1}): 2932, 1730, 1180, 762, 700.
MS (EI, 70 eV), *m/z* (%): 192 (3, $[M]^+$), 174 (11), 149 (46), 121 (100), 118 (40), 91 (28), 77 (10).
HRMS for $C_{14}H_{20}O_2$ (220.1463 $[M]^+$): found: 220.1456.

(2*S*)-2-Phenylheptan-2-ol ((*S*)-38a):

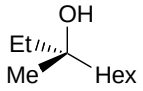


Basic hydrolysis of the formate (*S*)-**60** and purification by flash chromatography (pentane/Et_2O, 9:1) yielded (*S*)-**38a** (107 mg, 98 %, 97 % *ee*) as a colourless liquid. The *ee* was determined by GC analysis.

$[\alpha]_D^{25}$ = + 9.3 (c = 1.67, EtOH)
GC (column: Chiraldex B-PH; 100 °C (30 min), 0.5 °C/min, 120 °C (60 min)): t_R(min) = 78.3 (*R*), 79.7 (*S*).
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.10-7.36 (m, 5H), 1.70 (m, 2H), 1.57 (s, 3H), 1.13-1.17 (m, 6H), 0.76 (t, ^3J = 6.9 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 144.5, 128.9, 127.7, 126.1, 86.9, 40.2, 32.5, 23.9, 22.9, 22.8, 14.4.

IR (film, ν/cm^{-1}): 3418, 2954, 1447, 1374, 763, 699.
MS (EI, 70 eV), *m/z* (%): 192 (<1, [M]$^+$), 174 (3), 131 (14), 121 (100), 118 (34), 91 (8), 77 (5), 43 (13).
HRMS for $C_{13}H_{20}O$ (192.1514 [M]$^+$): found: 192.1511.

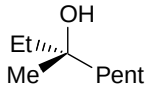
(3*S*)-3-Methylnonan-3-ol ((*S*)-38b):



Prepared according to **TP5** from aldehyde (*S*)-**56b** (264 mg, 1.55 mmol, 98 % *ee*), *m*-CPBA (320 mg, 1.86 mmol) and Na_2HPO_4 (219 mg, 1.55 mmol). Reaction time: 2 h. Basic hydrolysis of (3*S*)-3-methylnonan-3-yl formate and purification by flash chromatography (pentane/Et_2O, 9:1) yielded (*S*)-**38b** (166 mg, 68 %, 93 % *ee*) as a colourless liquid. The *ee* was determined by GC analysis.

[α]$_D^{25}$ = + 1.4 (c = 1.32, CH_2Cl_2).
GC (column: Chirasil Dex; 90 °C const.): t_R(min) = 17.3 (*S*); 18.2 (*R*).
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.42-1.18 (m, 12H), 1.07 (s, 3H), 0.82 (m, 6H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 71.9, 40.4, 33.2, 30.9, 28.9, 25.4, 22.8, 21.6, 13.1, 7.2.
IR (film, ν/cm^{-1}): 3391, 2930, 1462, 1377, 1151, 909.
MS (EI, 70 eV), *m/z* (%): 143 (<1, [M-CH_3]$^+$), 129 (18), 115 (61), 97 (15), 73 (100), 69 (14).
HRMS for $C_{10}H_{22}O$ (143.1436 [M-CH_3]$^+$): found: 143.1437.

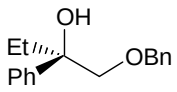
(3*S*)-3-Methyloctan-3-ol ((*S*)-38c):



Prepared according to **TP5** from aldehyde (*S*)-**56c** (260 mg, 1.67 mmol, 96 % *ee*), *m*-CPBA (345 mg, 2.0 mmol) and Na_2HPO_4 (237 mg, 1.67 mmol). Reaction time: 2 h. Basic hydrolysis of (3*S*)-3-methyloctan-3-yl formate and purification by flash chromatography (pentane/Et_2O, 9:1) yielded (*S*)-**38c** (176 mg, 76 %, 92 % *ee*) as a colourless liquid. The *ee* was determined by GC analysis.

[α]$_D^{25}$ = – 1.5 (c = 1.23, EtOH).
GC (Chirasil Dex, 70 °C const.): t_R(min) = 27.1 (*S*); 28.5 (*R*).
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.42-1.21 (m, 10H), 1.07 (s, 3H), 0.75-0.85 (m, 6H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 71.9, 40.3, 33.2, 31.5, 25.4, 22.5, 21.7, 13.0, 7.2.
IR (film, ν/cm^{-1}): 3390, 2933, 1462, 1377, 1152, 902.
MS (EI, 70 eV), *m/z* (%): 143 (<1, [M-H]$^+$), 129 (18), 115 (61), 97 (15), 73 (100), 69 (14).
HRMS for $C_9H_{20}O$ (143.1436 [M-H]$^+$): found: 143.1416.

(1*R*)-1-Benzyloxymethyl-1-phenylpropan-1-ol ((*R*)-38d):

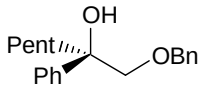


Prepared according to **TP5** from aldehyde (*R*)-**56d** (210 mg, 0.8 mmol, 99 % *ee*), *m*-CPBA (206 mg, 1.2 mmol) and Na_2HPO_4 (113 mg, 0.8 mmol). Reaction time: 2 h. Basic hydrolysis of (1*R*)-[1-benzyloxymethyl-1-phenyl-propan-1-yl] formate and purification by flash

chromatography (pentane/Et_2O, 8:2) yielded (*R*)-**38d** (143 mg, 70 %, 99 % *ee*) as a colourless oil. The *ee* was determined by GC analysis.

$[\alpha]_D^{20}$ = −14 (c = 1.02, CH_2Cl_2).
HPLC (column: OD-H; *n*-heptane/*i*-PrOH = 98/2, 0.2 mL/min): t_R(min) = 49.0 (*R*); 53.3 (*S*).
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.34-7.15 (m, 10H), 4.45 (s, 2H), 3.58 (d, ^3J = 9.0 Hz, 1H), 3.53 (d, ^3J = 9.0 Hz, 1H), 2.64 (br s, 1H), 1.92-1.80 (m, 1H), 1.77-1.68 (m, 1H), 0.67 (t, ^3J = 7.2 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 144.1, 138.3, 128.8, 128.4, 128.1, 128.0, 127.1, 125.9, 77.9, 76.8, 73.9, 32.2, 7.9.
IR (film, ν/cm^{-1}): 3560, 2930, 1450, 1100.
MS (EI, 70 eV), *m/z* (%): 256 (<1, M^+), 135 (100), 91 (25).
HRMS for $C_{17}H_{20}O_2$ (256.1464, M^+): found: 256.1485.

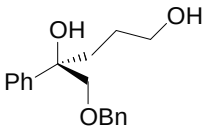
(1*R*)-1-Benzyloxymethyl-1-phenylhexan-1-ol ((*R*)-38e):



Prepared according to **TP5** from aldehyde (*R*)-**56e** (310 mg, 1 mmol, 99 % *ee*), *m*-CPBA (206 mg, 1.2 mmol) and Na_2HPO_4 (141 mg, 1 mmol). Reaction time: 2 h. Basic hydrolysis of (1*R*)-[1-benzyloxymethyl-1-phenyl-hexan-1-yl] formate and purification by flash chromatography (pentane/Et_2O, 8:2) yielded (*R*)-**38e** (229 mg, 77 %, 99 % *ee*) as a colourless oil. The *ee* was determined by GC analysis.

$[\alpha]_D^{20}$ = − 8 (c = 1.1, CH_2Cl_2).
HPLC (column: OD-H; *n*-heptane/*i*-PrOH = 98/2, 0.2 mL/min): t_R(min) = 40.0 (*S*); 42.8 (*R*).
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.34-7.14 (m, 10H), 4.45 (s, 2H), 3.57 (d, ^3J = 9.0 Hz, 1H), 3.52 (d, ^3J = 9.0 Hz, 1H), 2.73 (br. s., 1H), 1.84-1.68 (m, 2H), 1.29-1.05 (m, 3H), 1.00-0.89 (m, 1H), 0.73 (t, ^3J = 6.6 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 144.5, 138.3, 128.8, 128.4, 128.1, 128.0, 127.0, 125.8, 78.1, 76.6, 73.9, 39.6, 32.6, 23.2, 22.9, 14.4.
IR (film) (ν/cm^{-1}): 3560, 3480, 2930, 1450.
MS (EI, 70 eV), *m/z* (%): 298 (0.1, M^+), 177 (100), 91 (45).
HRMS for $C_{20}H_{26}O_2$ (298.1933, M^+): found: 298.1957.

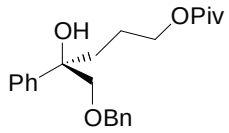
(4*R*)-5-Benzyloxy-4-phenylpentan-1,4-diol ((*R*)-62):



Prepared according to **TP5** from aldehyde (*R*)-**56f** (640 mg, 1.67 mmol, 98 % *ee*), *m*-CPBA (558 mg, 2.17 mmol) and Na_2HPO_4 (237 mg, 1.67 mmol). Reaction time: 2 h. Basic hydrolysis (LiOH) of 2,2-dimethyl-propionic acid (*R*)-5-benzyloxy-4-formyloxy-4-phenyl-pentyl ester and purification by flash chromatography (pentane/Et_2O, 9:1) yielded (*R*)-**62** (166 mg, 70 %, 98 % *ee*) as a colourless liquid.

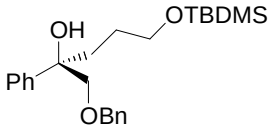
$[\alpha]_D^{25}$ = + 8.7 (c = 2.025, CH_2Cl_2).
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.14-7.34 (m, 10H), 4.44 (s, 2H), 3.55 (s, 2H), 3.47 (t, ^3J = 6.3 Hz, 2H), 2.5 (s br., 1H, OH), 1.8-2.0 (m, 2H), 1.2-1.6 (m, 2H), 1.2 (s br., 1H, OH).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 142.6, 136.8, 127.4, 127.1, 126.8, 126.6, 125.8, 124.4, 76.9, 75.1, 72.5, 62.1, 34.8, 25.6.
IR (film, ν/cm^{-1}): 3391, 2927, 1452, 1075, 699.
MS (FAB), *m/z* (%): 309 (12, $[M+Na]^+$), 287 ($[M+H]^+$, 3), 251 (13), 154 (56), 91 (100).
HRMS for $C_{18}H_{22}O_3$ (309.1467 $[M+Na]^+$): found: 309.1501.

The *ee* of (*R*)-**62** was determined by HPLC analysis on (4*R*)-5-(benzyloxy)-4-hydroxy-4-phenylpentyl pivalate (*R*)-**38f**:



$[\alpha]_D^{25}$ = + 3.5 (c = 0.918, CH_2Cl_2).
HPLC (column: OD-H; *n*-heptane/*i*-PrOH = 95/5, 0.6 mL/min): t_R(min) = 15.5 (*R*), 19.4 (*S*).
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.14-7.34 (m, 10H), 4.45 (s, 2H), 3.87-3.90 (m, 2H), 3.0 (s broad, 1H), 3.53 (s, 2H), 1.86-1.96 (m, 1H), 1.70-1.80 (m, 1H), 1.52-1.66 (m, 1H), 1.23-1.36 (m, 1H), 1.08 (s, 9H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 178.9, 143.8, 138.2, 128.8, 128.6, 128.2, 128.0, 127.3, 125.7, 78.1, 76.3, 73.9, 64.9, 39.1, 35.7, 27.6, 23.1.
IR (film, ν/cm^{-1}): 3499, 2960, 1725, 1285, 1161, 700.
MS (EI, 70 eV), *m/z* (%): 371.1 (<1, $[M+H]^+$), 353 (3), 251 (17), 147 (15), 91 (100).
HRMS for $C_{23}H_{30}O_4$ (371.2222 $[M+H]^+$): found: 371.2243.

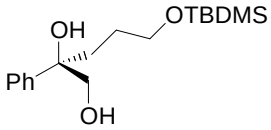
(2*R*)-1-Benzyloxy-5-(tert-butyldimethylsilanyloxy)-2-phenylpentan-2-ol:



Prepared from (*R*)-**62** (390 mg, 1.36 mmol), *tert*-butyldimethylchlorsilane (245 mg, 1.63 mmol) and imidazole (130 mg, 1.9 mmol) in DMF. Reaction conditions: 5 h at rt. Standard work up yielded the TBDM-silyl ether (544 mg, 98 %, 98 % *ee*) as a colourless liquid.

$[\alpha]_D^{25}$ = + 5.8 (c = 2.025, CH_2Cl_2).
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.23-7.35 (m, 10H), 4.53 (s, 2H), 3.60 (s, 2H), 3.54 (t, ^3J = 6.2 Hz, 2H), 1.93-2.0 (m, 2H), 1.23-1.58 (m, 2H), 0.86 (s, 9H), 0.00 (s, 6H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 144.5, 138.5, 128.7, 128.4, 128.0 (2C), 127.0, 126.0, 78.4, 76.4, 73.8, 63.9, 36.0, 27.0, 26.3, 18.7, –5.
IR (film, ν/cm^{-1}): 3436, 2953, 2857, 1096, 836, 699.
MS (FAB), *m/z* (%): 401 (26, $[M+H]^+$), 291 (23), 2791 (303), 251 (43), 161 (34), 147 (44), 91 (100).
HRMS for $C_{24}H_{36}O_3Si$ (401.2512 $[M+H]^+$): found: 401.2518.

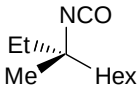
(2*R*)-5-(tert-Butyldimethylsilanyloxy)-2-phenylpentan-1,2-diol ((*R*)-61):



Hydrogenation of (2*R*)-1-Benzyloxy-5-(tert-butyl-dimethyl-silanyloxy)-2-phenyl-pentan-2-ol (150 mg, 0.37 mmol) with Pd/C in *i*-PrOH yielded (*R*)-**61** (80 mg, 70 %, 98 %) as a colourless liquid.

$[\alpha]_D^{25}$ = + 2.6 (c = 2.32, CH_2Cl_2).
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.4 (m, 5H), 4.3 (s br., 1H, OH), 3.6 (m, 4H), 2.1 (s br., 1H, OH), 2.05 (m, 2H), 1.45 (m, 2H), 0.85 (s, 9H), 0.0 (s, 6H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 144.5, 128.6, 127.2, 126.1, 79.7, 71.6, 64.3, 36.0, 26.8, 26.3, 18.7, –5.1.
IR (film, ν/cm^{-1}): 3391, 2954, 1255, 1096, 836, 701.
MS (FAB), *m/z* (%): 333.2 (36, $[M+Na]^+$), 301 (38), 279 (100), 262 (28), 201 (27), 161 (67), 91 (22).
HRMS for $C_{17}H_{30}O_3Si$ (333.1862 $[M+Na]^+$): found: 333.1834.

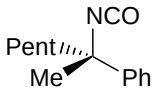
(3*S*)-3-Isocyanato-3-methylnonane ((*S*)-40a):



Prepared according to **TP6** from acid (*S*)-**57a** (80 mg, 0.43 mmol, 98 % *ee*), $(PhO)_2P(O)N_3$ (140 mg, 0.51 mmol) and Et_3N (65 mg, 0.64 mmol). Reaction time: 2 h. Purification by flash chromatography (pentane/Et_2O, 98/2) yielded (*S*)-**40a** (54 mg, 68 %, 98 % *ee*) as a colourless liquid. The *ee* was determined by GC analysis (see appendix).

$[\alpha]_D^{25}$ = – 1.0 (c = 0.85, CH_2Cl_2).
GC (column: Chirasil Dex; 90 °C const.): t_R(min) = 15.5 (*R*), 16.0 (*S*).
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.4-1.6 (m, 4H), 1.84 (s, 3H), 1.22 (m, 8H), 0.8 (m, 6H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 121.1, 60.5, 40.9, 33.9, 30.7, 28.5, 25.9, 23.0, 21.6, 13.0, 7.5.
IR (film, ν/cm^{-1}): 2933, 2259, 1725, 1462, 1260, 1097, 804.
MS (EI, 70 eV), *m/z* (%): 143 (<1, $[M–H]^+$), 154 (43), 98 (100), 69 (28), 55 (21), 41 (8).
HRMS for $C_{11}H_{21}NO$ (182.1545 $[M–H]^+$): found: 182.1512.

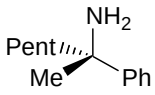
(2*S*)-2-Isocyanato-2-phenylheptane ((*S*)-40b):



Prepared according to **TP6** from acid (*S*)-**57b** (124 mg, 0.56 mmol, 98 % *ee*), $(PhO)_2P(O)N_3$ (231 mg, 0.84 mmol) and Et_3N (85 mg, 0.84 mmol). Reaction time: 2 h. Purification by flash chromatography (pentane/Et_2O, 98/2) yielded (*S*)-**40b** (120 mg, 98 %, 98 % *ee*) as a colourless liquid. The *ee* was determined by GC analysis.

$[\alpha]_D^{25}$ = + 14.3 (c = 1.7, EtOH).
GC (column: Chiraldex B-PH; 100 °C const.): t_R(min) = 57.8 (*S*), 61.9 (*R*).
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.26-7.29 (m, 5H), 1.78-1.82 (m, 2H), 1.62 (s, 3H), 1.4-1.6 (m, 6H), 0.76 (t, ^3J = 6.9 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 143.7, 127.4, 126.0, 123.8, 121.7, 63.4, 44.3, 30.7 (2C), 23.1, 21.4, 12.9.
IR (film, ν/cm^{-1}): 2934, 2261, 763, 698.
MS (EI, 70 eV), *m/z* (%): 217 ([M]$^+$, <1), 146 (100), 118 (6), 77 (9), 41 (3).
HRMS for $C_{14}H_{19}NO$ (217.1467 [M]$^+$): found: 217.1461.

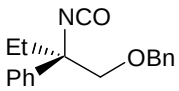
(1*S*)-1-Methyl-1-phenylhexylamine ((*S*)-39a):



(*S*)-**40b** (50 mg, 0.23 mmol) was refluxed in 20 % HCl for 24 h. Acido/basic work up yielded (*S*)-**39a** (30 mg, 65 %, 98 % *ee*) as a colourless oil.

$[\alpha]_D^{25}$ = – 2.8 (c = 1.4, EtOH).
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.13-7.38 (m, 5H), 1.63-1.65 (m, 4H), 1.62 (s, 3H), 1.38 (s, 3H), 1.13-1.18 (m, 6H), 0.75 (t, ^3J = 6.9 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 149.4, 128.5, 126.4, 125.5, 55.4, 45.6, 32.7, 31.4, 24.4, 22.9, 14.4.
IR (film) (ν/cm^{-1}): 3085, 2859, 1601, 1445, 820, 764, 699.
MS (EI, 70 eV), *m/z* (%): 190 (<1, [M–H]$^+$), 120 (100), 104 (3), 77 (2).
HRMS for $C_{13}H_{21}N$ (190.1596 [M–H]$^+$): found: 190.1594.

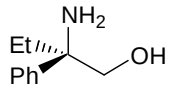
(2*R*)-2-Isocyanato-1-benzyloxy-2-phenylbutane ((*R*)-40c):



Prepared according to **TP6** from acid (*R*)-**57c** (457 mg, 1.66 mmol, 99 % *ee*), $(PhO)_2P(O)N_3$ (660 mg, 2.4 mmol) and Et_3N (243 mg, 2.4 mmol). Reaction time: 2 h. Purification by flash chromatography (pentane/Et_2O, 98/2) yielded (*R*)-**40c** (382 mg, 85 %, 99 % *ee*) as a colourless liquid. The *ee* was determined by HPLC analysis.

$[\alpha]_D^{25}$ = – 18.1 (c = 1.58, CH_2Cl_2).
HPLC (column: AD; *n*-heptane/*i*-PrOH = 99.5/0.5, 0.3 mL/min): t_R(min) = 19.3 (*R*), 22.1 (*S*).
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.16-7.30 (m, 10H), 4.50 (s, 2H) 3.59 (d, ^3J(H,H) = 9.3 Hz, 1H), 3.51 (d, ^3J(H,H) = 9.3 Hz, 1H), 2.09 (q, ^3J(H,H) = 7.2 Hz, 1H), 1.82 (q, ^3J(H,H) = 7.2 Hz, 1H), 0.70 (t, ^3J(H,H) = 7.2 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 140.9, 138.1, 128.8 (2C), 128.1, 128.0, 127.8, 126.2, 120.6, 78.3, 73.9, 69.0, 32.8, 8.6.
IR (film, ν/cm^{-1}): 2936, 2247, 1093, 698.
MS (EI, 70 eV), *m/z* (%): 281 ([M]$^+$, <1), 252 (1), 160 (100), 91 (43).
HRMS for $C_{18}H_{19}NO_2$ (281.1416 [M]$^+$): found: 281.1425.

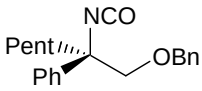
(2*R*)-2-Amino-2-phenylbutan-1-ol ((*R*)-39b):



(*R*)-**40c** (382 mg, 1.4 mmol) was refluxed in 20 % HCl for 24 h. Acido/basic work up yielded (*R*)-**39b** (163 mg, 70 %, 99 % *ee*) as a yellow solid.

$[\alpha]_D^{25} = -5.2$ (c = 1.34, CH_2Cl_2).
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.17-7.34 (m, 5H), 3.60 (s, 2H) 2.09 (br, 3H), 1.76 (q, ^3J = 7.2 Hz, 1H), 1.69 (q, ^3J = 7.2 Hz, 1H), 0.63 (t, ^3J = 7.2 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 144.7, 128.8, 127.1, 126.2, 71.1, 60.1, 32.1, 8.1.
IR (film, ν/cm^{-1}): 3420, 2960, 1043, 764, 703.
MS (EI, 70 eV), *m/z* (%): 162 (3, $[M-3H]^+$), 134 (100), 104 (17), 91 (18), 77 (10), 56(10).
HRMS for $C_{10}H_{15}NO$ (162.0919 $[M-3H]^+$): found: 162.091

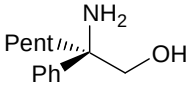
(2*R*)-2-Isocyanato-1-benzyloxy-2-phenylheptane ((*R*)-40d):



Prepared according to **TP6** from acid (*R*)-**57d** (360 mg, 1.1 mmol, 99 % *ee*), $(PhO)_2P(O)N_3$ (454 mg, 1.65 mmol) and Et_3N (167 mg, 1.65 mmol). Reaction time: 2 h. Purification by flash chromatography (pentane/Et_2O, 98:2) yielded (*R*)-**40d** (312 mg, 88 %, 99 % *ee*) as a colourless liquid. The *ee* was determined by HPLC analysis.

$[\alpha]_D^{25} = -5.6$ (c = 1.63, CH_2Cl_2).
HPLC (column: AD, *n*-heptane/*i*-PrOH = 99.5/0.5, 0.3 mL/min): t_R(min) = 17.6 (*R*), 20.2 (*S*).
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.16-7.30 (m, 10H), 4.50 (s, 2H) 3.58 (d, ^3J = 9.3 Hz, 1H), 3.49 (d, ^3J = 9.3 Hz, 1H), 1.98-2.08 (m, 1H), 1.73-1.83 (m, 1H), 1.12-1.18 (m, 6H), 0.73 (t, ^3J = 6.6 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 141.2, 138.1, 128.8 (2C), 128.1, 128.0, 127.5, 127.7, 126.0, 78.5, 73.8, 68.5, 39.8, 32.2, 23.8, 22.8, 8.6.
IR (film, ν/cm^{-1}): 2931, 2250, 1101, 698.
MS (EI, 70 eV), *m/z* (%): 324 (<1, $[M+H]^+$), 202 (100), 91 (75).
HRMS for $C_{21}H_{25}NO_2$ (324.1964 $[M+H]^+$): found: 324.1991.

(2*R*)-2-Amino-2-phenylheptan-1-ol ((*R*)-39c):



(*R*)-**40d** (219 mg, 0.67 mmol) was refluxed in 20 % HCl for 24 h. Acido/basic work up yielded (*R*)-**39c** (124 mg, 88 %, 99 % *ee*) as a yellow solid.

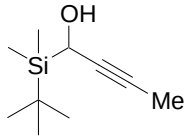
$[\alpha]_D^{25} = +9.8$ (c = 1.22, EtOH).
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.17-7.34 (m, 5H), 3.60 (s, broad, 2H) 2.09 (broad, 3H), 1.55-1.90 (m, 2H), 1.11-1.19 (m, 6H), 0.74 (t, ^3J = 6.6 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 143.7, 127.4, 125.6, 124.7, 70.1, 58.3, 38.2, 31.2, 22.0, 21.4, 13.0.

IR (film, ν/cm^{-1}): 3089, 2958, 1601, 760, 702.
MS (EI, 70 eV), *m/z* (%): 208 (<1, $[M+H]^+$), 176 (100), 136 (8), 91 (4).
HRMS for $C_{13}H_{21}NO$ (208.1701 $[M+H]^+$): found: 208.1722.

4 Preparation of (*E*)-Alkenylsilanes

4.1 Starting materials

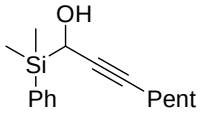
1-(tert-Butyldimethylsilanyl)-but-2-yn-1-ol (*rac*-70a):



This compound was prepared starting from 2-butyn-1-ol (700 mg, 10.0 mmol) according to the literature procedure.[77] After purification by chromatography (pentane/Et_2O, 20:1) **70a** (1.36 g, 7.42 mmol, 74 %) was obtained as a pale yellow oil.

^{1}H-NMR ($CDCl_3$, 300MHz): δ = 4.18 (q, ^5J = 2.66 Hz, 1H), 1.89 (d, ^5J = 2.66 Hz, 3H), 0.97 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H).
^{13}C-NMR ($CDCl_3$, 75MHz): δ = 84.4, 80.5, 55.5, 27.2, 17.3, 4.2, –7.6, –8.2.
MS (EI, 70 eV), *m/z* (%):184 (0.75, M^+), 141 (5), 115 (6), 99 (20), 73 (100), 59 (7).
IR (neat, ν/cm^{-1}): 3448, 2960, 2900, 2864, 2310, 1696, 1590, 1466, 1250, 976, 838, 782.
HRMS for $C_{10}H_{20}OSi$ $[M]^+$: 184.1283, found: 184.1263.

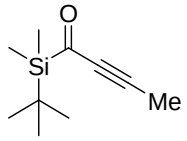
1-(Dimethylphenylsilanyl)-oct-2-yn-1-ol (*rac*-70b): [80]



To a solution of $PhMe_2SiCl$ (1.84 mL, 11.0 mmol, 1.1 equiv) in anhydrous THF (30 mL) was added lithium wire (560 mg, 80 mmol, 8.0 equiv). The dark purple suspension was stirred at 24 °C for 18 h. The resulting $PhMe_2SiLi$[80a] solution was transferred by canula to a clean flask and cooled to −78 °C. 2-Octynal (1.42 mL, 10 mmol) in 5 mL THF was then added dropwise. The solution was stirred for 30 min at −78 °C before being poured into aqueous NH_4Cl (50 mL). The resultant layers were separated and the aqueous phase was extracted with Et_2O (3 x 50 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and the solvent was evaporated under vacuo. Purification by chromatography (pentane/Et_2O, 9:1) afforded *rac*-**70b** (1.91 g, 7.35 mmol, 73 %) as a pale yellow oil.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 7.61-7.65 (m, 2H), 7.43-7.34 (m, 3H), 4.25 (t, ^5J = 2.42 Hz, 1H), 2.26-2.21 (td, ^5J = 2.42 Hz, ^3J = 7.04 Hz, 2H) 1.54-1.27 (m, 7H), 0.92-0.87 (t, ^3J = 7.0 Hz, 3H), 0.43 (s, 3H), 0.42 (s, 3H).
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 135.5, 134.3, 129.6, 127.8, 89.0, 80.0, 56.2, 31.0, 28.5, 22.1, 19.0, 13.9, –5.5, –5.8.
IR (neat, ν/cm^{-1}): 3421, 3070, 2956, 2930, 2859, 1696, 1457, 1427, 1378, 1329, 1247, 1112, 972, 830, 783, 732, 696 cm^{-1}.
MS (EI, 70 eV), *m/z* (%): 260.16 (5, M^+), 245 (30), 215 (100), 189 (82), 135 (30), 75 (16)
HRMS for $C_{16}H_{24}OSi$ $[M^+]$: 260.1596, found: 260.1602.

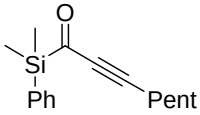
1-(tert-Butyldimethylsilanyl)-but-2-yn-1-one (71a):



This compound was prepared starting from **70a** (720 mg, 3.9 mmol) according to the literature procedure.[77] Purification by chromatography (pentane/Et_2O, 40:1) afforded **71a** (634 mg, 3.39 mmol, 90 %) as yellow oil.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 1.87 (s, 3H), 0.75 (s, 9H), 0.00 (s, 6H).
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 98.7, 89.2, 85.4, 26.7, 17.2, 4.8, –7.1.
IR (neat, ν/cm^{-1}): 2957, 2936, 2892, 2280, 2192, 1594, 1466, 1252, 1142, 840, 820, 804, 780.
MS (EI, 70 eV), *m/z* (%):181 (0.10, M^+), 167 (4), 126 (17), 97 (54), 73 (100), 59 (9).
HRMS for $C_{10}H_{17}OSi$ $[M–H]^+$: 181.1049, found: 181.1023.

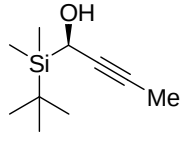
1-(Dimethylphenylsilanyl)-oct-2-yn-1-one (71b): [79]



DMSO (1.45 mL, 20.4 mmol, 1.7 equiv) was added to a solution of oxalyl chloride (1.55 mL, 18 mmol, 1.5 equiv) in CH_2Cl_2 (40 mL) at –78 °C. After 10 min **70b** (3.0 g, 11.5 mmol) was added dropwise as a solution in CH_2Cl_2 (10 mL) followed by Et_3N (6.24 mL, 44.4 mmol, 3.7 equiv) after 15 min. The resulting mixture was stirred for another 30 minutes. Extraction with Et_2O and purification by chromatography (pentane/Et_2O, 95:5) afforded **71b** (2.18 g, 8.48 mmol, 74 %) as a yellow oil.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 7.60-7.57 (m, 2H), 7.42-7.36 (m, 3H), 2.38 (t, ^3J = 7.2 Hz, 2H), 1.57-1.48 (m, 2H), 1.35-1.30 (m, 4H), 0.91-0.86 (t, ^3J = 7.2 Hz, 3H), 0.54 (s, 6H)
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 134.1, 133.5, 129.9, 127.9, 104.7, 84.8, 30.9, 27.4, 22.0, 19.3, 13.8, –5.0.
IR (neat, ν/cm^{-1}): 2932, 2957, 2181, 1591, 1428, 1249, 1112, 782, 696.
MS (EI, 70 eV), *m/z* (%): 258 (2, M^+), 257 (7), 243 (8), 215 (71), 202 (50), 135 (100), 105 (8).
HRMS for $C_{16}H_{22}OSi$ $[M^+]$:258.1440, found: 258.1444.

(1*R*)-1-(tert-Butyldimethylsilanyl)-but-2-yn-1-ol ((*R*)-70a): [79]

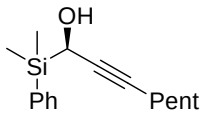


Ketone **71a** (1.49 g, 8.18 mmol) in THF (40 mL) was cooled to –30 °C and (*R*)-2-methyl-CBS-oxazaborolidine (1.0 M in toluene, 8.2 mL, 8.2 mmol) was added, followed by dropwise addition of $BH_3{\cdot}Me_2S$ complex (0.46 mL, 4.9 mmol) as a solution in THF (5 mL). The mixture was stirred at –30 °C for 30 min and quenched with MeOH (20 mL). The organic phase was extracted with Et_2O (3 x 50 mL), dried over $MgSO_4$ and the solvent was

evaporated under vacuo. Purification by chromatography (pentane/Et_2O, 20:1) afforded (*R*)-**70a** (1.39 g, 7.55 mmol, 92 %, 92 % *ee*) as a pale yellow oil.

$[\alpha]_D^{20}$ = + 62.8 (c = 1.32, CH_2Cl_2).
For analytical data see *rac*-**70a**.

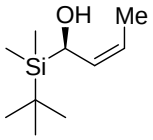
(1*R*)-1-(Dimethylphenylsilanyl)-oct-2-yn-1-ol ((*R*)-70b):



Prepared following the same procedure as for (*R*)-**70a**, with the ketone **71b** (2.14 g, 8.29 mmol), (*R*)-2-methyl-CBS-oxazaborolidine (1.0 M in toluene, 8.3 mL, 8.3 mmol) and $BH_3{\cdot}Me_2S$ complex (0.47 mL, 4.97 mmol) as a solution in THF (5 mL). Purification by chromatography (pentane/Et_2O, 9:1) afforded (*R*)-**70b** (1.96 g, 7.54 mmol, 91 %, 90 % *ee*) as a yellow oil.

$[\alpha]_D^{20}$ = + 57.6 (c = 1.45, $CHCl_3$). For analytical data see *rac*-**70b**.

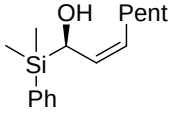
(1*R*,2*Z*)-1-(tertButyldimethyl-silanyl)-but-2-en-1-ol ((*R*)-69a):



This compound was prepared starting from (*R*)-**70a** (368 mg, 2.0 mmol) according to the literature procedure.[77] Purification by chromatography (pentane/Et_2O, 40:1) afforded (*R*)-**69a** (297 mg, 1.60 mmol, 80 %, 92 % *ee*) as a colourless oil. The *ee* was determined by GC analysis.

$[\alpha]_D^{20}$ = + 82.3 (c = 0.87, CH_2Cl_2).
GC (Chirasil-Dex CB), 70 °C (1 min), ramp of 2 °C/ min to 100 °C; t_R(min) = 20.09 (*R*), 21.41 (*S*).
^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 5.51-5.43 (m, 2H), 4.46 (d, ^3J = 10.41 Hz, 1H), 1.60 (d, ^3J = 6.55 Hz, 3H), 0.92 (s, 9H), 0.00 (s, 3H), –0.09 (s, 3H).
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 132.2, 123.0, 61.9, 26.9, 17.4, 13.9, –7.4, –8.4.
IR (neat, ν/cm^{-1}): 3370, 2930, 2859, 1722, 1523, 1464, 1351, 1251, 1168, 959, 841.
MS (EI, 70 eV), *m/z* (%):186.1423 (0.04, M^+), 129 (17), 115 (3), 75 (13), 73 (100), 59 (5).
HRMS for $C_{10}H_{22}OSi$ $[M]^+$: 186.1440, found: 186.1423.

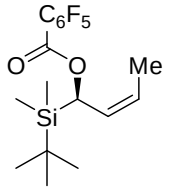
(1*R*,2*Z*)-1-(Dimethylphenylsilanyl)-oct-2-en-1-ol ((*R*)-69b):



Prepared following the same procedure as for (*R*)-**69a**, starting from (*R*)-**70b** (3.38 g, 13 mmol). Purification by chromatography (pentane/Et_2O, 95:5) afforded (*R*)-**69b** (2.77 g, 10.57 mmol, 82 %, 90 % *ee*) as a colourless oil. The *ee* was determined by GC analysis.

$[\alpha]_D^{20}$ = + 86.2 (c = 1.54, $CHCl_3$).
GC (Chirasil-Dex CB), 140 °C constant; t_R(min) = 38.15 (*R*, major), 40.78 (*S*, minor).
^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 7.60-7.57 (m, 2H), 7.39-7.26 (m, 3H), 5.49-5.32 (m, 2H), 4.45 (d, ^3J = 9.6 Hz, 1H), 2.04-1.92 (m, 1H), 1.83-1.72 (m, 1H), 1.28-1.21 (m, 6H), 0.87 (t, ^3J = 7.26 Hz, 3H), 0,36 (s, 3H, CH_3), 0,33 (s, 3H, CH_3).
^{13}C-NMR ($CDCl_3$, 75 MHz): δ =136.2, 134.2, 130.0, 129.8, 129.3, 127.7, 63.5, 31.5, 29.3, 27.8, 22.5, 14.0, –5.48, –5.97.
IR (neat, ν/cm^{-1}): 3419, 2925, 2956, 2855, 1427, 1246, 1112, 962, 812, 697.
MS (EI, 70 eV), *m/z* (%): 262.1761 (0.15, M^+), 247 (4), 219 (1), 135 (100), 75 (3).
HRMS for $C_{16}H_{26}OSi$ [M^+]: 262.1753, found: 262.1761.

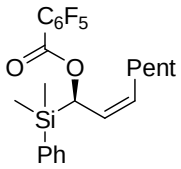
(1*R*,2*Z*)-1-(tert-Butyldimethylsilanyl)-but-2-enyl pentafluorobenzoate ((*R*)-66a):



Prepared according to **TP7** from (*R*)-**69a** (226 mg, 1.2 mmol), pentafluorobenzoyl chloride (0.23 mL, 1.68 mmol), DMAP (20.5 mg, 0.17 mmol) and pyridine (0.14 mL, 1.68 mmol). Purification by chromatography (pentane/Et_2O, 98:2 + 1 % Et_3N) afforded (*R*)-**66a** (433 mg, 1.14 mmol, 95 %, 92 % *ee*) as a colourless oil.

$[\alpha]_D^{20}$ = – 17.1 (c = 1.59, CH_2Cl_2).
^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 5.90 (d, ^3J = 10.33 Hz, 1H), 5.67-5.47 (m, 2H), 1.77 (dd, ^3J = 6.69 Hz, ^4J = 1.44 Hz, 3H), 0.90 (s, 9H), 0.04 (s, 3H), 0.00 (s, 3H).
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 159.4, 147.3, 143.9, 139.7, 136.4, 127.3, 109.1, 68.1, 27.1, 17.3, 14.0, –7.7, –11.0.
IR (neat, ν/cm^{-1}): 2932, 2860, 1737, 1651, 1524, 1503, 1471, 1422, 1333, 1251, 1225, 1149, 1104, 1005, 946, 806, 768.
MS (EI, 70 eV), *m/z* (%): 380 (0.09, M^+), 323 (17), 269 (25), 194 (24), 185 (9), 73 (100), 59 (9).
HRMS for $C_{17}H_{21}F_5O_2Si$ $[M]^+$: 380.1231, found: 380.1242.

(1*R*,2*Z*)-1-(Dimethylphenylsilanyl)-oct-2-enyl pentafluorobenzoate ((*R*)-66b):



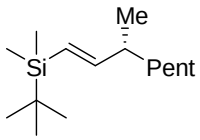
Prepared according to **TP7** from (*R*)-**69b** (1.52 g, 5.8 mmol), pentafluorobenzoyl chloride (1.12 mL, 8.12 mmol), DMAP (100 mg, 0.81 mmol) and pyridine (0.66 mL, 8.12 mmol). Purification by chromatography (pentane/Et_2O, 99:1 + 1 % Et_3N) afforded (*R*)-**66b** (2.51 g, 5.51 mmol, 95 %, 90 % *ee*) as a colourless oil.

$[\alpha]_D^{20}$ = – 7.94 (c = 1.36, $CHCl_3$)
^{1}H-NMR ($CDCl_3$, 600 MHz): δ = 7.55-7.54 (m, 2H), 7.40-7.34 (m, 3H), 5.92 (d, 1H, ^3J = 10.24 Hz), 5.49-5.45 (m, 1H), 5.39 (t, ^3J = 10.38 Hz, 1H), 2.10-2.04 (m, 1H), 1.82-1.78 (m, 1H), 1.29-1.17 (m, 6H), 0.87 (t, ^3J = 7.26 Hz, 3H), 0.41 (s, 3H), 0.40 (s, 3H).

^{13}C-NMR ($CDCl_3$, 150 MHz): 159.02, 146.10, 144.39, 143.87, 142.07, 138.46, 136.8, 134.6, 134.1, 133.2, 129.7, 127.8, 124.2, 108.85, 69.5, 31.4, 28.9, 27.9, 22.4, 13.9, –5.5, –5.6.
IR (neat, ν/cm^{-1}): 2958, 2929, 2858, 1733, 1651, 1522, 1495, 1427, 1330, 1250, 1219, 1113, 996, 942, 808, 771, 733, 698.
MS (EI, 70 eV), *m/z* (%): 456.15 (8, M^+), 441 (14), 427 (78), 378 (22), 331 (25), 269 (100), 194 (22), 135 (54), 121 (7).
HRMS for $C_{23}H_{25}F_5O_2Si$ [M^+]: 456.1544, found: 456.1517.

4.2 Products of the S_N2' Allylic Substitution: (*E*)-alkenylsilanes

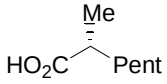
(3*R*,1*E*)-tert-Butyldimethyl-(3-methyloct-1-enyl) silane ((*R*)-65a):



Prepared according to **TP1** using the pentafluorobenzoate (*R*)-**66a** (380 mg, 1.0 mmol, 92 % *ee*), THF (1.0 mL), dipentylzinc solution (4.8 M in THF, 0.5 mL, 2.4 mmol, 2.4 equiv), CuCN·2LiCl (1.0 M in THF, 1.2 mL, 1.2 mmol, 1.2 equiv) and NMP (1.3 mL). The resulting mixture was stirred at –78 °C to –50 °C for 24 h. After purification by flash chromatography (100 % pentane), (*R*)-**65a** was obtained as a colourless oil (194 mg, 0.81 mmol, 81 %, 90 % *ee*).

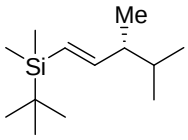
$[\alpha]_D^{20}$ = – 21.9 (c = 1.29, CH_2Cl_2)
^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 5.88 (dd, ^3J = 7.16 Hz, ^3J = 18.65 Hz, 1H), 5.35 (dd, ^4J = 1.09 Hz, ^3J = 18.65 Hz, 1H), 2.10-2.15 (m, 1H), 1.26 (m, 8H), 0.97 (d, ^3J = 6.72 Hz, 3H), 0.86 (s, 9H), 0.003 (s, 6H).
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 154.5, 124.1, 40.6, 36.5, 31.9, 26.9, 26.4, 22.6, 20.2, 16.5, 14.1, –5.9, –6.1.
IR (neat, ν/cm^{-1}): 2954, 2927, 2856, 1614, 1247, 991, 829.
MS (EI, 70 eV), *m/z* (%): 240.23 (0.23, $[M]^+$), 225 (3), 183 (100), 141 (2), 127 (4), 113 (10), 99 (7), 59 (13).
HRMS for $C_{15}H_{32}Si$ [M^+]: 240.2273, found: 240.2287.

The *ee* of (*R*)-**65a** was determined by GC analysis after transformation into (2*R*)-2-methylheptanoic acid[36] (*R*)-**72a** according to **TP4**:



$[\alpha]_D^{20}$ = – 15.6 (c = 0.55, EtOH).
GC (Chirasil-Dex CB), 70 °C (1 min), ramp of 2 °C/ min to 140 °C; t_R(min) = 28.05 (*S*), 28.97 (*R*).
^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 2.46 (qt, *J* = 7.2 Hz, 6.9 Hz, 1H), 1.20-1.50 (m, 7H), 1.62-1.75 (m, 1H), 1.18 (d, *J* = 7.2 Hz, 3H), 0.84-0.93 (m, 3H).
^{13}C-NMR ($CDCl_3$, 75 MHz): 183.0, 39.3, 33.5, 31.7, 26.8, 22.5, 16.8, 14.0.
IR (neat, ν/cm^{-1}): 3600-2200, 1710.

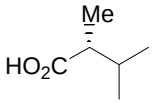
(3*R*,1*E*)-tert-Butyl-(3,4-dimethylpent-1-enyl)-dimethyl silane ((*R*)-65b):



Prepared according to **TP1** using (*R*)-**66a** (353 mg, 0.93 mmol, 92 % *ee*), THF (1.0 mL), diisopropylzinc solution (5.9 M in Et_20, 0.42 mL, 2.16 mmol, 2.4 equiv), CuCN·2LiCl (1.0 M in THF, 1.1 mL, 1.11 mmol, 1.2 equiv) and NMP (1.0 mL). The resulting mixture was stirred at –78 °C to –50 °C for 24 h. After purification by flash chromatography (100 % pentane), (*R*)-**65b** was obtained as a colourless oil (177 mg, 0.84 mmol, 90 %, 90 % *ee*).

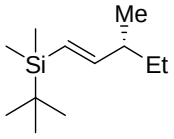
$[\alpha]_D^{20}$ = – 29.2 (c = 1.185, CH_2Cl_2)
^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 5.92 (dd, ^3J = 7.39 Hz, ^3J = 18.68 Hz, 1H), 5.54 (dd, ^4J = 1.11 Hz, ^3J = 18.68 Hz, 1H), 2.01-1.94 (m, 1H), 1.57-1.51 (m, 1H), 0.95 (d, ^3J = 6.81 Hz, 3H), 0.86 (s, 9H), 0.86-0.83 (m, 6H), 0.004 (s, 6H).
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 153.2, 125.7, 47.3, 33.1, 26.8, 20.2, 20.1, 17.2, 16.9, –5.56, –5.64.
IR (neat, ν/cm^{-1}): 2956, 2928, 2856, 1614, 1248, 993, 830.
MS (EI, 70 eV), *m/z* (%): 212.20 (0.69, M^+), 197 (3), 156 (15), 155 (100), 127 (5), 113 (13), 99 (14), 85 (12), 73 (25), 59 (16).
HRMS for $C_{13}H_{28}Si$ [M^+]: 212.1960, found: 212.1964.

The *ee* of (*R*)-**65b** was determined by GC analysis after transformation into (2*R*)-2-3-dimethylbutanoic acid[127] (*R*)-**72b** according to **TP4**:



GC (Chirasil-Dex CB), 50 °C (1 min), ramp of 2 °C/ min to 140 °C; t_R(min) = 27.80 (*S*), 28.59 (*R*).
^{1}H-NMR ($CDCl_3$, 300 MHz): 10.3 (s, broad, 1H), 2.14-2.05 (m, 2H), 1.14 (d, ^3J = 6.9 Hz, 3H), 1.10 (d, ^3J = 6.3 Hz, 3H), 0.99 (d, ^3J = 6.3 Hz, 3H).
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 184.0, 46.7, 31.7, 21.5, 19.5, 14.0.
IR (neat, ν/cm^{-1}): 2986, 2928, 2896, 1654, 1448, 773.

(3*R*,1*E*)-tert-Butyldimethyl-(3-methyl-pent-1-enyl) silane ((*R*)-65c):

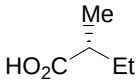


Prepared according to **TP1** using (*R*)-**66a** (380 mg, 1 mmol, 92 % *ee*), THF (1.0 mL), diethylzinc solution (0.24 mL, 2.4 mmol, 2.4 equiv), CuCN·2LiCl (1.0 M in THF, 1.2 mL, 1.2 mmol, 1.2 equiv) and NMP (1.0 mL). The resulting mixture was stirred at –78 °C to –50 °C for 24 h. After purification by flash chromatography (100 % pentane), (*R*)-**65c** was obtained as a colourless oil (176 mg, 0.89 mmol, 89 %, 88 % *ee*).

[127] Registry N°: [27855-05-06] for (+)-(*R*)-2,3 dimethylbutanoic acid, P. A. Levene, R. E. Marker, *J. Biol. Chem.* **1935**, *111*, 299.

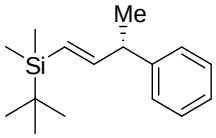
$[\alpha]_D^{20}$ = – 26.3 (c = 1.10, CH_2Cl_2)
^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 5.88 (dd, ^3J = 7.06 Hz, ^3J = 18.66 Hz, 1H), 5.54 (dd, ^4J = 1.13 Hz, ^3J = 18.66 Hz, 1H), 2.07-2.03 (m, 1H), 1.34-1.27 (m, 1H), 0.97 (d, ^3J = 6.73 Hz, 3H), 0.86 (s, 9H), 0.004 (s, 6H).
^{13}C-NMR ($CDCl_3$, 75 MHz): 154.2, 124.4, 42.2, 29.3, 26.4, 19.7, 16.5, 11.7, –5.9, –6.0.
IR (neat, ν/cm^{-1}): 2955, 2928, 2856, 1615, 1248, 991, 829.
MS (EI, 70 eV), *m/z* (%): 198.17 (1.21, M^+), 183 (3), 141 (100), 127 (3), 113 (12), 99 (14), 85 (21), 73 (25), 59 (19).
HRMS for $C_{12}H_{26}Si$ [M^+]: 198.1804, found: 198.1781.

The *ee* of (*R*)-**65c** was determined by GC analysis after transformation into (2*R*)-2-methylbutanoic acid[128] (*R*)-**72c** according to **TP4**:



GC (Chirasil-Dex CB), 50 °C (1 min), ramp of 2 °C/ min to 140 °C; t_R(min) = 22.58 (*S*), 23.14 (*R*).
^{1}H-NMR ($CDCl_3$, 300 MHz): 11.5 (s, broad, 1H), 2.47-2.38 (m, 1H), 1.78-1.49 (m, 2H), 1.21 (d, *J* = 7.0 Hz, 3H), 0.95 (t, *J* = 7.3 Hz, 3H).
^{13}C-NMR ($CDCl_3$, 75 MHz): 183.5, 41.2, 26.7, 16.5, 13.9.
IR (neat, ν/cm^{-1}): 2980, 2945, 2880, 1652, 1468, 1100, 829, 785.

(3*S*,1*E*)-tert-Butyldimethyl-(3-phenyl-but-1-enyl) silane ((*S*)-65d):

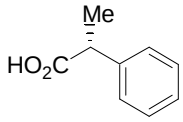


Prepared according to **TP1** using (*R*)-**66a** (328 mg, 0.86 mmol, 92 % *ee*), THF (1.0 mL), diphenylzinc solution (1.0 M in toluene, 2.61 mL, 2.59 mmol, 3.0 equiv). The toluene of the diphenylzinc solution was evaporated under vacuo at 25 °C and replaced by NMP (1.2 mL) and then CuCN·2LiCl (1.0 M in THF, 1.29 mL, 1.2 mmol, 1.5 equiv) was added to this solution at –30 °C. It is stirred for 45 min before the pentafluorobenzoate **66a** was added. The resulting mixture was stirred at –30 °C to 0 °C for 24 h. After purification by flash chromatography (100 % pentane), (*S*)-**65d** was obtained as a colourless oil (182 mg, 0.74 mmol, 86 %, 89 % *ee*).

$[\alpha]_D^{20}$ = – 4.0 (c = 1.15, CH_2Cl_2)
^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 7.34-7.29 (m, 2H), 7.22-7.18 (m, 3H), 6.21 (dd, ^3J = 5.95 Hz, ^3J = 18.67 Hz, 1H), 5.54 (dd, ^4J = 1.53 Hz, ^3J = 18.67 Hz, 1H), 3.05 (m, 1H), 1.37 (d, ^3J = 6.02 Hz, 3H), 0.88 (s, 9H), 0.02 (s, 6H).
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 152.1, 145.7, 128.4, 127.4, 125.9, 125.0, 45.6, 26.5, 20.8, 16.6, –6.04, –6.09.
IR (neat, ν/cm^{-1}): 2953, 2931, 2853, 1674, 1602, 1471, 1245, 1006, 828, 700.
MS (EI, 70 eV), *m/z* (%): 246.18 (0.74, M^+), 231 (1), 189 (100), 145 (4), 135 (23), 105 (5), 73 (35), 59 (32).
HRMS for $C_{16}H_{26}Si$ [M^+]: 246.1804, found: 246.1810.

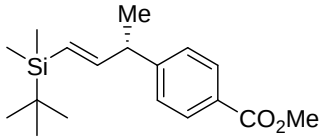
[128] Registry N°: [1730-91-2] for (+)-(*S*)-2-methylbutanoic acid (Aldrich catalogue).

The *ee* of (*S*)-**65d** was determined by GC analysis after transformation into (2*R*)-2-phenylpropanoic acid[36] (*S*)-**72d** according to **TP4**:



[α]$_D$ ^{20} = – 62.1 (c = 0.45, $CHCl_3$)[129]
GC (Chirasil-Dex CB), 70 °C (1 min), ramp of 2 °C/ min to 140 °C; t_R(min) = 42.37 (*S*), 43.61 (*R*).
^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 7.24-7.40 (m, 5H), 3.74 (q, *J* = 7.0 Hz, 1H), 1.52 (d, *J* = 7.0 Hz, 3H).
^{13}C-NMR ($CDCl_3$, 100 MHz): 180.3, 139.8, 128.7, 127.6, 127.4, 45.3, 18.1.
IR (neat, ν/cm^{-1}): 3690-2210, 1950, 1710, 1600, 1590.

4-[(1*S*,2*E*)-3-(tert-Butyldimethylsilanyl)-1-methyl-allyl] methylbenzoate ((*S*)-65e):

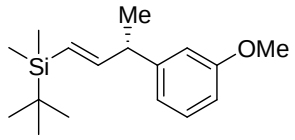


Prepared according to **TP2** using (*R*)-**66a** (266 mg, 0.7 mmol, 92 % *ee*), THF (1.0 mL), Ar_2Zn (prepared from 4-iodomethylbenzoate (880 mg, 3.36 mmol, 4.8 equiv), *i*-Pr_2Zn (0.31 mL, 1.84 mmol, 2.4 equiv) and Li(acac) (35 mg, 0.33 mmol, 0.48 equiv)), CuCN·2LiCl (1.0 M in THF, 0.84 mL, 0.84 mmol, 1.2 equiv) and NMP (2.0 mL). The resulting mixture was stirred at –30 °C to 25 °C for 24 h. After purification by flash chromatography (100 % pentane), (*S*)-**65e** was obtained as a colourless oil (138 mg, 0.45 mmol, 65 %, 89 % *ee*). The ee was determined by HPLC analysis.

[α]$_D$^{20} = + 1.5 (c = 1.37, acetone)
HPLC (column: OD-H; *n*-heptane 100 %, 0.5 mL/min): t_R(min) = 26.27 (*R*), 33.04 (*S*).
^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 7.97 (d, ^3J = 8.42, 2H), 7.25 (d, ^3J = 8.17, 2H), 6.15 (dd, ^3J = 5.95 Hz, ^3J = 18.66 Hz, 1H), 5.67 (dd, ^4J = 1.51 Hz, ^3J = 18.66 Hz, 1H), 3.90 (s, 3H), 3.55 (m, 1H), 1.37 (d, ^3J = 7.02 Hz, 3H), 0.85 (s, 9H), 0.006 (s, 6H).
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 167.1, 151.1, 129.8, 128.0, 127.4, 126.1, 51.9, 45.6, 26.4, 20.5, 16.5, –6.11.
IR (neat, ν/cm^{-1}): 2950, 2922, 2856, 1722, 1607, 1459, 1434, 1275, 1110, 828.
MS (EI, 70 eV), *m/z* (%): 304.18 (0.36, M^+), 273 (3), 247 (100), 193 (4), 157 (9), 89 (2), 73 (7), 59 (5).
HRMS for $C_{18}H_{28}O_2Si$ [M^+]: 304.1859, found: 304.1840.

[129] Aldrich catalogue: (*R*)-(-)-2-phenylpropanoic acid (98 % *ee*): $[\alpha]_D^{20}$ = – 72 (c = 1.6, $CHCl_3$).

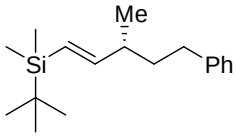
(3*S*,1*E*)-tert-Butyl-[3-(3-methoxyphenyl)-but-1-enyl] dimethyl silane ((*S*)-65f):



Prepared according to **TP2** using (*R*)-**66a** (285 mg, 0.75 mmol, 92 % *ee*), THF (1.0 mL), Ar_2Zn (prepared from 3-iodoanisol (842 mg, 3.60 mmol, 4.8 equiv), *i*-Pr_2Zn (0.33 mL, 1.98 mmol, 2.4 equiv) and Li(acac) (38 mg, 0.36 mmol, 0.48 equiv)), CuCN·2LiCl (1.0 M in THF, 0.90 mL, 0.90 mmol, 1.2 equiv) and NMP (2.0 mL). The resulting mixture was stirred at –30 °C to 25 °C for 24 h. After purification by flash chromatography (100 % pentane), (*S*)-**65f** was obtained as a colourless oil (124 mg, 0.45 mmol, 60 %, 90 % *ee*). The *ee* was determined by HPLC analysis.

$[\alpha]_D^{20}$ = + 4.0 (c = 0.3, acetone)
HPLC (column: OD-H; *n*-heptane 100 %, 0.5 mL/min): t_R(min) = 12.95 (*R*), 15.08 (*S*).
^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 7.24-7.18 (m, 2H), 6.80-6.71 (m, 2H), 6.17 (dd, ^3J = 5.96 Hz, ^3J = 18.66 Hz, 1H), 5.67 (dd, ^4J = 1.48 Hz, ^3J = 18.66 Hz, 1H), 3.78 (s, 3H), 3.45 (m, 1H), 1.34 (d, ^3J = 7.02 Hz, 3H), 0.86 (s, 9H), 0.00 (s, 6H).
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 159.6, 151.9, 147.4, 129.2, 125.1, 119.8, 113.1, 111.3, 55.1, 45.6, 26.5, 20.7, 16.6, –6.04, –6.11.
IR (neat, ν/cm^{-1}): 2950, 2928, 2851, 1596, 1462, 1248, 1152, 1045, 828, 778, 699.
MS (EI, 70 eV), *m/z* (%): 276.19 (4, M^+), 220 (15), 219 (100), 204 (15), 189 (6), 165 (12), 159 (3), 135 (3), 89 (2), 73 (11), 59 (7).
HRMS for $C_{17}H_{28}OSi$ [M^+]: 276.1909, found: 276.1906.

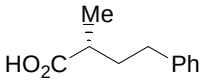
(3*R*,1*E*)-tert-Butyldimethyl-(3-methyl-5-phenylpent-1-enyl) silane ((*R*)-65g):



Prepared according to **TP1** from (*R*)-**66a** (380 mg, 1.0 mmol, 92 % *ee*), THF (1.0 mL), $[Ph(CH_2)_2]_2Zn$ (1.5 M in THF, 1.6 mL, 2.4 mmol, 2.4 equiv), CuCN·2LiCl (1.0 M in THF, 1.2 mL, 1.2 mmol, 1.2 equiv) and NMP (2.0 mL). The resulting mixture was stirred at **–**30 °C to 25 °C for 6 days. After purification by flash chromatography (100 % pentane), (*R*)-**65g** was obtained as a colourless oil (164 mg, 60 %, 84 % *ee*).

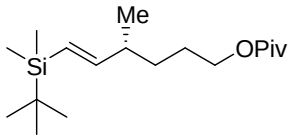
$[\alpha]_D^{20}$ = –17.4 (c = 1.14, $CHCl_3$)
^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 7.30-7.14 (m, 5H), 5.93 (dd, ^3J = 7.20 Hz, ^3J = 18.66 Hz, 1H), 5.62 (dd, ^4J = 1.04 Hz, ^3J = 18.6 Hz, 1H), 2.65-2.51 (m, 2H), 2.25-2.10 (m, 1H), 1.67-1.59 (m, 2H), 1.04 (d, ^3J = 6,7 Hz, 3H), 0.89 (s, 9H), 0.056 (s, 3H), 0.049 (s, 3H).
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 154.1, 142.8, 128.4, 128.2, 125.6, 125.1, 40.2, 38.4, 33.7, 26.4, 20.2, 16.5, –5.9, –6.0.
IR (neat, ν/cm^{-1}): 2951, 2926, 2854, 1613, 1454, 1246, 827, 696.
MS (EI, 70 eV), *m/z* (%):259.19 (24, M^+), 217 (100), 173 (1), 157 (5), 135 (3), 91 (12), 73 (10), 59 (13).
HRMS for $C_{17}H_{27}Si$ [$M–CH_3$]$^+$: 259.1882, found: 259.1897.

The *ee* of (*R*)-**65g** was determined by GC analysis after transformation into (2*R*)-2-methyl-4-phenylbutanoic acid[130] (*R*)-**72e** according to **TP4**:



GC (Chirasil-Dex CB), 70 °C (1 min), ramp of 2 °C/ min to 140 °C; t_R(min) = 57.03 (*S*), 59.56 (*R*).
^{1}H-NMR ($CDCl_3$, 200 MHz): δ = 1.20 (dd, ^3J = 7.5 Hz, ^3J = 6.0 Hz, 3H), 1.5-2.3 (m, 1H), 2.67 (t, ^3J = 8.0 Hz, 2H), 2.46 (q, ^3J = 7.5 Hz, 1H), 7.2 (m, 5H).

(4*R*,5*E*)-6-(tert-Butyldimethylsilanyl)-4-methylhex-5-enyl-2,2-dimethylpropionate ((*R*)-65h):

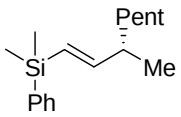


Prepared according to **TP1** using (*R*)-**66a** (268 mg, 0.70 mmol, 92 % *ee*), THF (1.0 mL), $[PivO(CH_2)_3]_2Zn$ (1.40 M in THF, 1.20 mL, 1.68 mmol, 2.4 equiv.), CuCN·2LiCl solution (1.0 M in THF, 0.84 mL, 0.84 mmol, 1.2 equiv) and NMP (1.5 mL). The resulting mixture was stirred at –30 °C to 24 °C for 24 h. After purification by flash chromatography (98:2 pentane/Et_2O), (*R*)-**65h** was obtained as a colourless oil (160 mg, 73 % yield, 80 % *ee*).

$[\alpha]_D^{20}$ = – 17.8 (c = 1.29, $CHCl_3$)
^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 5.85 (dd, ^3J = 7.16 Hz, ^3J = 18.60 Hz, 1H), 6.85 (d, ^3J = 18.61 Hz, 1H), 4.03 (t, ^3J = 6.54 Hz, 2H), 2.20-2.11 (m, 1H), 1.62-1.54 (m, 2H), 1.38-1.31 (m, 2H), 1.19 (s, 9H), 0.99 (d, ^3J = 6.71 Hz, 3H), 0.85 (s, 9H), 0.00 (s, 6H).
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 178.6, 153.5, 125.1, 64.4, 40.2, 38.7, 32.6, 27.2, 26.4, 26.4, 20.2, 16.5, –6.1, –6.0.
IR (neat): 2954, 2928, 2856, 1730, 1614, 1462, 1283, 1151, 992, 827.
MS (EI, 70 eV), *m/z* (%): 255 (4), 213 (9), 159 (100), 144 (6), 111 (3), 73 (9), 57 (12), 41 (4).
HRMS for $C_{14}H_{23}O_2Si$ $[M–C_4H_9]^+$: 255.1780, found: 255.1789.

The *ee* of **65h** was determined by GC analysis after transformation into **67g** according to **TP9**.
HPLC (column: OD-H; *n*-heptane / *i*-PrOH 95:5, 0.5 ml/min): t_R/min 13.47 (*R*), 16.32 (*S*).
For analytical data see compound **67g**.

(3*S*,1*E*)-Dimethyl-(3-methyl-oct-1-enyl)-phenyl silane ((*S*)-65i):

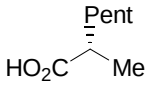


Prepared according to **TP1** from (*R*)-**66b** (2.35 g, 5.15 mmol, 90 % *ee*), THF (3.0 mL), dimethylzinc solution (2.0 M in toluene, 6.2 mL, 12.36 mmol, 2.4 equiv), CuCN·2LiCl (1.0 M in THF, 6.2 mL, 6.2 mmol, 1.2 equiv) and NMP (8.0 mL). The resulting mixture was stirred at –30 °C for 16 h and warmed up at 0 °C (5 h). After purification by flash chromatography (100 % pentane), (*S*)-**65i** was obtained as a colourless oil (1.27 g, 4.89 mmol, 95 %, 89 % *ee*).

[130] P. Anastasis, I. Freer, K. H. Overton, D. Picken, D. S. Rycroft, S. B. Singh, J. Chem. Soc. Perkin Trans. I, 1987, 2427.

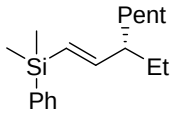
$[\alpha]_D^{20}$ = + 20.6 (c = 1.37, $CHCl_3$)
^{1}H-NMR ($CDCl_3$, 600 MHz): δ = 7.55-7.53 (m, 2H), 7.37-7.35 (m, 3H), 6.02 (dd, ^3J = 7.07 Hz, ^3J = 18.63 Hz, 1H), 5.71 (dd, ^4J = 1.08 Hz, ^3J = 18.63 Hz , 1H), 2.21-2.17 (m, 1H), 1.33-1.28 (s, 6H), 1.00 (d, ^3J = 6.73 Hz, 3H), 0.90 (t, ^3J = 7.10 Hz, 3H), 0.33 (s, 3H).
^{13}C-NMR ($CDCl_3$, 150 MHz): δ = 155.2, 139.5, 133.8, 128.7, 127.6, 124.7, 40.3, 36.4, 31.9, 26.9, 22.6, 19.9, 14.1, –2.33, –2.35.
IR (neat, ν/cm^{-1}): 2956, 2925, 2856, 1614, 1427, 1246, 1112, 990, 821, 727, 696.
MS (EI, 70 eV), *m/z* (%): 260.19 (7.05, M^+), 246 (9), 245 (45), 201 (12), 189 (7), 161 (37), 147 (11), 135 (100), 121 (46), 73 (7), 59 (7)
HRMS for $C_{17}H_{28}Si$ [M^+]: 260.1960, found: 260.1953.

The *ee* of (*S*)-**65i** was determined by GC analysis (see appendix) after transformation into (2*S*)-2-methylheptanoic acid (*S*)-**72a** according to **TP4**:



GC (Chirasil-Dex CB), 70 °C (1 min), ramp of 2 °C/ min to 140 °C; t_R(min) = 27.54 (*S*), 28.71 (*R*). For analytical data see derivatization of compound **72a**.

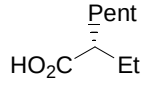
(3*S*,1*E*)-(3-Ethyl-oct-1-enyl)-dimethylphenyl silane ((*S*)-65j):



Prepared according to **TP1** from (*R*)-**66b** (534 mg, 1.17 mmol, 90 % *ee*), THF (1.0 mL), diethylzinc solution (0.3 mL, 2.8 mmol, 2.4 equiv.), CuCN·2LiCl (1.0 M in THF, 1.4 mL, 1.4 mmol, 1.2 equiv.) and NMP (1.4 mL). The resulting mixture was stirred at –30 °C for 16 h. After purification by flash chromatography (100 % pentane), (*S*)-**65j** was obtained as a colourless oil (275 mg, 1.00 mmol, 86 %, 89 % *ee*).

$[\alpha]_D^{20}$ = + 3.6 (c = 1.15, $CHCl_3$)
^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 7.57-7.53 (m, 2H), 7.37-7.36 (m, 3H), 5.88 (dd, ^3J = 7.85 Hz, ^3J = 18.58 Hz, 1H), 5.73 (d, ^3J = 18.58 Hz, 1H), 1.96-1.94 (m, 1H), 1.44-1.24 (m, 10H), 0.92-0.79 (m, 6H), 0.34 (s, 6H)
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 153.7, 139.6, 133.8, 128.7, 127.6, 127.1, 48.6, 34.4, 31.9, 27.5, 26.9, 22.6, 14.1, 11.7, –2.3.
MS (EI, 70 eV), *m/z* (%): 274.21 (6.41, M^+), 259 (26), 215 (9), 203 (2), 161 (22), 148 (9), 135 (100), 121 (36), 105 (4), 59 (6).
IR (neat, ν/cm^{-1}): 2956, 2919, 2852, 1612, 1462, 1245, 1111, 992, 819, 729, 698.
HRMS for $C_{18}H_{30}Si$ [M^+]: 274.2117, found: 274.2130.

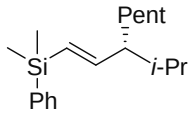
The *ee* of (*S*)-**65j** was determined by GC analysis after transformation into (2*S*)-2-ethylheptanoic acid[131] (*S*)-**72f** according to **TP4**:



[131] A. Behr, V. A. Brehme, *Adv. Synth. Catal.* **2002**, *344*, 525.

GC (Chirasil-Dex CB), 70 °C (1 min), ramp of 2 °C/ min to 140 °C; t_R(min) = 31.49 (*S*), 32.24 (*R*).
^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 11.77 (s, 1H), 2.29 (m, 1H), 1.58 (m, 2H), 1.50 (m, 2H), 1.41 (m, 2H), 1.24-1.30 (m, 4H), 0.89 (t, ^3J = 7.4Hz, 3H), 0.83 (t, ^3J = 7.1Hz, 3H).
^{13}C-NMR ($CDCl_3$, 100 MHz): 183.4, 47.2, 31.7, 27.0, 25.2, 22.5, 13.9, 11.7.
MS (EI, 70 eV), *m/z* (%): 158 (3, M^+), 130 (11), 101 (26), 88 (100), 73 (54), 55 (11), 43 (14), 41 (15).

(3*R*,1*E*)-(3-Isopropyl-oct-1-enyl)-dimethylphenyl silane ((*R*)-65k):



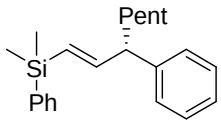
Prepared according to **TP1** from (*R*)-**66b** (455 mg, 1.0 mmol, 90 % *ee*), THF (1.0 mL), diisopropylzinc solution (5.9 M in Et_20, 0.4 mL, 2.4 mmol, 2.4 equiv), CuCN·2LiCl (1.0 M in THF, 1.2 mL, 1.2 mmol, 1.2 equiv) and NMP (1.3 mL). The resulting mixture was stirred at –50 °C to –30 °C for 16 h. After purification by flash chromatography (100 % pentane), (*R*)-**65k** was obtained as a colourless oil (258 mg, 0.89 mmol, 89 %, 87 % *ee*).

$[\alpha]_D^{20}$ = + 4.7 (c = 1.10, $CHCl_3$)
^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 7.56-7.53 (m, 2H), 7.37-7.35 (m, 3H), 5.89 (dd, ^3J = 8.48 Hz, ^3J = 18.65 Hz, 1H), 5.70 (d, ^3J = 18.65 Hz, 1H), 1.87-1.80 (m, 1H), 1.68-1.52 (m,1H), 1.31-1.22 (m, 8H), 0.91-0.83 (m, 6H), 0.34 (s, 6H).
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 151.9, 139.6, 133.8, 128.7, 128.3, 127.6, 53.6, 31.9, 31.6, 27.3, 22.7, 20.7, 19.2, 14.1, –2.2.
IR (neat, ν/cm^{-1}): 2955, 2926, 2871, 1613, 1465, 1427, 1246, 1112, 995, 817, 727, 697.
MS (EI, 70 eV), *m/z* (%): 288.22 (5, M^+), 273 (21), 245 (8), 229 (5), 211 (4), 161 (15), 135 (100), 121 (26), 73 (4), 59 (7).
HRMS for $C_{19}H_{32}Si$ [M^+]: 288.2273, found: 288.2267.

The *ee* of (*R*)-**65k** was determined by GC analysis after transformation into **67j** according to **TP9**.

HPLC (column: OD-H; *n*-heptane 100 %, 0.5 mL/min): t_R(min) = 46.93 (*S*), 50.70 (*R*).
For analytical data see compound **67j**.

(3*S*,1*E*)-Dimethylphenyl-(3-phenyl-oct-1-enyl)-silane ((*S*)-65l):



Prepared according to **TP1** from (*R*)-**66b** (677 mg, 1.48 mmol, 90 % *ee*), THF (1.0 mL), diphenylzinc solution (1.0 M in toluene, 3.6 mL, 3.6 mmol, 2.4 equiv). The toluene of the diphenylzinc solution was evaporated under vacuo at 25 °C and replaced by NMP (1.5 mL) and then the solution of CuCN·2LiCl (1.0 M in THF, 1.8 mL, 1.8 mmol, 1.2 equiv) was added to this solution at –30 °C. It is stirred for 45 min before the pentafluorobenzoate **66b** was added. The resulting mixture was stirred at –30 °C for 16 h and warmed up to 0°C (5 h). After purification by flash chromatography (100 % pentane), (*S*)-**65l** was obtained as a colourless oil (410 mg, 1.27 mmol, 86 %, 89 % *ee*).

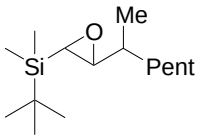
$[\alpha]_D^{20}$ = + 15.1 (c = 1.35, $CHCl_3$)
^{1}H-NMR ($CDCl_3$, 600 MHz): δ = 7.52-7.50 (m, 2H), 7.36-7.30 (m, 5H), 7.22-7.18 (m, 3H), 6.24 (dd, ^3J = 7.04 Hz, ^3J = 18.56 Hz, 1H), 5.78 (dd, ^4J = 1.17 Hz, ^3J = 18.56 Hz, 1H), 3.33-3.30 (m, 1H), 1.76-1.68 (m, 2H), 1.29-1.28 (m, 6H), 0.87 (t, ^3J = 6.72 Hz, 3H) 0.32 (s, 6H).
^{13}C-NMR ($CDCl_3$, 150 MHz): δ = 152.1, 144.5, 139.2, 133.8, 128.8, 128.3, 127.7, 127.6, 126.6, 126.0, 52.5, 35.4, 31.8, 27.2, 22.5, 14.0, –2.40, –2.44.
IR (neat, ν/cm^{-1}): 2955, 2927, 2856, 1600, 1452, 1427, 1246, 1113, 989, 820, 728, 698,.
MS (EI, 70 eV), *m/z* (%): 322.21 (6, M^+), 307 (25), 251 (11), 244 (11), 229 (4), 197 (8), 173 (28), 161 (73), 136 (14), 135 (100), 121 (18), 105 (3), 91 (4), 59 (3).
HRMS for $C_{22}H_{30}Si$ [M^+]: 322.2117, found: 322.2132.

The *ee* of **65l** was determined by GC analysis (see appendix) after transformation into **67k** according to **TP3**.

HPLC (column: OD-H; *n*-heptane/*i*-PrOH 98:2, 0.5 mL/min): t_R(min) = 13.18 (*R*), 14.96 (*S*).
For analytical data see compound **67k**.

4.3 Products of the Epoxidation

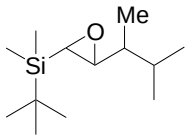
tert-Butyldimethyl-[3-(1-methylhexyl)-oxiranyl]-silane (73a):



Prepared according to **TP11** using (*rac*)-**65a** (120 mg, 0.5 mmol), *m*-CPBA (241 mg, 1.4 mmol), Na_2HPO_4 (305 mg, 2.15 mmol) and CH_2Cl_2 (5 mL). Purification by flash chromatography (pentane/Et_2O, 98:2) afforded the epoxide **73a** (100 mg, 78 %) as a colourless oil and as a mixture of two diastereomers (a:b, 60:40).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 2.56-2.48 (m, 1H), 2.12 (d, ^3J = 3.57 Hz, 1Ha), 2.03 (d, ^3J = 3.57 Hz, 1Hb), 1.35-1.26 (m, 9H), 1.06 (s, 3Ha), 1.06 (s, 3Hb), 0.96 (s, 9Ha), 0.95 (s, 9Hb), 0.90-0.86 (m, 3H), 0.00 (s, 3Hb), -0.03 (s, 3Ha), –0.06 (s, 3Ha), –0.08 (s, 3Hb).
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 60.7 (a), 49.9 (a), 48.3 (b), 38.0 (b), 35.1, 33.7, 32.2, 32.1, 26.8, 26.7, 26.5, 22.6, 17.7 (a), 16.7, 16.1, 14.1 (a), 14.0 (b), –8.1 (a), –8.2 (b), –8.4 (a), –8.5 (b).
IR (neat, ν/cm^{-1}): 2961, 2922, 2856, 1462, 1248, 828.
MS (EI, 70 eV), *m/z* (%): 241 (< 1, $[M–CH_3]^+$), 199 (8), 129 (11), 115 (11), 75 (100).
HRMS for $C_{14}H_{29}OSi$ $[M–CH_3]^+$: 241.1988, found: 241.1982.

tert-Butyl-[3-(1,2-dimethylpropyl)-oxiranyl]-dimethylsilane (73b):

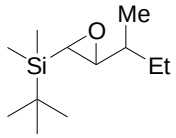


Prepared according to **TP11** *rac*-**65b** (127 mg, 0.6 mmol), *m*-CPBA (288 mg, 1.68 mmol), Na_2HPO_4 (366 mg, 2.58 mmol) and CH_2Cl_2 (5 mL). Purification by flash chromatography

(pentane/Et_2O, 98:2) afforded the epoxide **73b** (92 mg, 72 %) as a colourless oil and as a mixture of two diastereomers (a:b, 60:40).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 2.60 (2d, ^3J = 3.6 Hz, 1Ha), 2.53 (2d, ^3J = 3.6 Hz, 1Hb), 2.13 (d, ^3J = 3.6 Hz, 1Ha), 1.98 (d, ^3J = 3.57 Hz, 1Hb), 1.78-1.58 (m, 1Ha,b), 1.02-1.97 (m, 3H), 0.95 (s, 9Ha), 0.95 (s, 9Hb), 0.94-0.88 (m, 6H), –0.01 (s, 3Hb), –0.03 (s, 3Ha), –0.05 (s, 3Ha), –0.08 (s, 3Hb).
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 59.5, 59.0, 50.8, 47.9, 44.4, 44.0, 31.7, 31.4, 26.5, 20.4 (a,b), 19.6, 19.2, 16.6, 14.4, 12.8, –7.8 (a), –8.2 (b), –8.4 (a), –8.6 (b).
IR (neat, ν/cm^{-1}): 2950, 2922, 2856, 1739, 1464, 1250, 831, 789.
MS (EI, 70 eV), *m/z* (%): 213 (6, $[M–CH_3]^+$), 185 (2), 171 (4), 95 (11), 75 (100), 59 (12).
HRMS for $C_{12}H_{25}OSi$ $[M–CH_3]^+$: 213.1675, found: 213.1662.

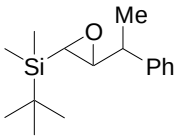
tert-Butyl-(3-sec-butyloxiranyl)-dimethylsilane (73c):



Prepared according to **TP11** using *rac*-**65c** (119 mg, 0.6 mmol), *m*-CPBA (288 mg, 1.68 mmol), Na_2HPO_4 (366 mg, 2.58 mmol) and CH_2Cl_2 (5 mL). Purification by flash chromatography (pentane/Et_2O, 98:2) afforded the epoxide **73c** (104 mg, 82 %) as a colourless oil and as a mixture of two diastereomers (a:b, 55:45).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 2.55 (2d, ^3J = 3.6 Hz, 1Ha), 2.51 (2d, ^3J = 3.6 Hz, 1Hb), 2.12 (d, ^3J = 3.6 Hz, 1Ha), 2.03 (d, ^3J = 3.57 Hz, 1Hb), 1.65-1.14 (m, 3H), 1.06 (s, 3Ha), 1.04 (s, 3Hb), 0.96 (s, 9Ha), 0.95 (s, 9Hb), 0.89 (s, 3H), 0.90-0.86 (m, 3H), 0.00 (s, 3Hb), –0.02 (s, 3Ha), –0.05 (s, 3Ha), –0.08 (s, 3Hb).
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 60.5 (a,b), 49.8, 49.1, 39.6, 39.5, 27.8, 26.6 (a,b), 26.5, 17.2, 16.7, 16.6, 11.6, 11.5, –8.1 (a), –8.2 (b), –8.4 (a), –8.5 (b).
IR (neat, ν/cm^{-1}): 2955, 2927, 2856, 1452, 1246, 820.
MS (EI, 70 eV), *m/z* (%): 214 (< 1, M^+), 157 (3), 101 (2), 75 (100), 73 (16).
HRMS for $C_{12}H_{26}OSi$ $[M^+]$: 214.1753, found: 214.1739.

tert-Butyldimethyl-[3-(1-phenyl-ethyl)-oxiranyl] silane (73d):



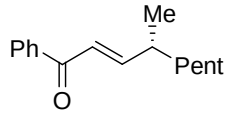
Prepared according to **TP11** *rac*-**65d** (93 mg, 0.4 mmol), *m*-CPBA (178 mg, 1.04 mmol), Na_2HPO_4 (226 mg, 1.59 mmol) and CH_2Cl_2 (5 mL). Purification by flash chromatography (pentane/Et_2O, 98:2) afforded the epoxide **73d** (75 mg, 77 %) as a colourless oil and as a mixture of two diastereomers (a:b, 50:50).

^{1}H-NMR ($CDCl_3$, 600 MHz): δ = 7.51-7.40 (m, 5H), 3.05 (2d, ^3J = 3.6 Hz, 1Ha), 3.00 (2d, ^3J = 3.6 Hz, 1Hb), 2.84 (quint., ^3J = 7.2 Hz, 1Ha), 2.72 (quint., ^3J = 7.2 Hz, 1Hb), 2.37 (d, ^3J = 3.6 Hz, 1Ha), 2.35 (d, ^3J = 3.6 Hz, 1Hb), 1.62 (d, ^3J = 7.2 Hz, 3Ha), 1.51 (d, ^3J = 7.2 Hz, 3Hb), 1.14 (s, 9Ha), 0.99 (s, 9Hb), 0.17 (s, 3Ha), 0.15 (s, 3Hb), 0.10 (s, 3Ha), 0.10 (s, 3Hb).

^{13}C-NMR ($CDCl_3$, 150 MHz): δ = 143.4, 142.9, 128.4, 127.3 (a,b), 126.6 (a,b), 60.7, 60.5, 49.7, 49.0, 44.1, 43.3, 26.5, 26.3, 17.8, 16.8, 16.7, 16.5, –8.1 (a,b), –8.5, –8.7.
IR (neat, ν/cm^{-1}): 2961, 2928, 2856, 1462, 1248, 831, 693.
MS (EI, 70 eV), *m/z* (%): 262 (< 1, M^+), 247 (14), 205 (7), 135 (100), 105 (23), 75 (45).
HRMS for $C_{16}H_{26}OSi$ [M^+]: 262.1753, found: 262.1767.

4.4 α,β-Unsaturated Ketones

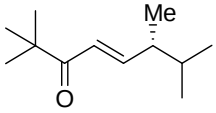
(4*R*,2*E*)- 4-Methyl-1-phenylnon-2-en-1-one ((*R*)-67a):



Prepared according to **TP9** from **65a** (146 mg, 0.60 mmol, 90 % *ee*), $AlCl_3$ (100 mg, 0.73 mmol, 1.2 equiv.), benzoylchloride (0.085 mL, 0.73 mmol, 1.2 equiv.) and CH_2Cl_2 (4.0 mL). The resulting mixture was stirred at –78 °C to rt for 3 h. After purification by flash chromatography (pentane/Et_2O, 98:2), (*R*)-**67a** was obtained as a colourless oil (90 mg, 0.40 mmol, 65 %, 90 % *ee*).

$[\alpha]_D^{20}$ = + 6.97 (c = 0.97, $CHCl_3$)
^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 7.94-7.90 (m, 2H), 7.58-7.43 (m, 3H), 6.96 (dd, ^3J = 7.65 Hz, ^3J = 15.47 Hz, 1H), 6.82 (dd, ^4J = 0.78 Hz, ^3J = 15.47 Hz, 1H), 2.45-2.36 (m, 1H), 1.27-1.44 (m, 8H), 1.11 (d, ^3J = 6.71 Hz, 3H), 0.88 (t, ^3J = 6.90 Hz, 3H).
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 191.1, 155.4, 138.1, 132.5, 128.5, 128.4, 124.1, 37.1, 36.1, 31.8, 26.9, 22.5, 19.5, 14.0.
IR (neat, ν/cm^{-1}): 2956, 2925, 2855, 1669, 1619, 1447, 1277, 1217, 1013, 982, 694.
MS (EI, 70 eV), *m/z* (%): 230.16 (20, M^+), 201 (6), 173 (38), 159 (13), 133 (9), 120 (22), 105 (100), 91 (10), 77 (31), 55 (5).
HRMS for $C_{16}H_{22}O$ [M^+]: 230.1671, found: 230.1651.

(6*R*,4*E*)-2,2,6,7-Tetramethyloct-4-en-3-one ((*R*)-67b):

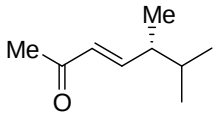


Prepared according to **TP9** from **65b** (201 mg, 0.95 mmol, 90 % *ee*), $AlCl_3$ (160 mg, 1.14 mmol, 1.2 equiv.), pivaloyl chloride (144 mg, 1.14 mmol, 1.2 equiv.) and CH_2Cl_2 (4.0 mL). The resulting mixture was stirred at –78 °C to rt for 3 h. After purification by flash chromatography (pentane/Et_2O, 98:2), (*R*)-**67b** was obtained as a colourless oil (107 mg, 0.59 mmol, 62 %, 90 % *ee*).

$[\alpha]_D^{20}$ = – 32.4 (c = 1.23, $CHCl_3$)
^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 6.85 (dd, ^3J = 8.34 Hz, ^3J = 15.30 Hz, 1H), 6.43 (dd, ^4J = 1.09 Hz, ^3J = 15.30 Hz, 1H), 2.16-2.08 (m, 1H), 1.68-1.58 (m, 1H), 1.15 (s, 9H), 1.01 (d, ^3J = 6.82 Hz, 3H), 0.88 (t, ^3J = 6.90 Hz, 3H).
^{13}C-NMR ($CDCl_3$, 75 MHz): 204.4, 151.5, 123.3, 137, 43.1, 42.8, 32.6, 26.2, 19.8, 19.7, 16.4.
IR (neat, ν/cm^{-1}): 2961, 2873, 1687, 1625, 1475, 1462, 1367, 1075, 987, 863.

MS (EI, 70 eV), *m/z* (%): 182. 16 (7, M^+), 125 (166), 113 (3), 97 (12), 83 (20), 69 (18), 55 (100), 41 (10).
HRMS for $C_{12}H_{22}O$ [M^+]: 182.1671, found: 182.1668.

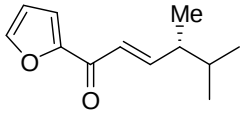
(5*R*,3*E*)-5,6-Dimethylhept-3-en-2-one ((*R*)-67c):



Prepared according to **TP9** from **65b** (127 mg, 0.6 mmol, 90 % *ee*), $AlCl_3$ (97 mg, 0.73 mmol, 1.2 equiv.), acetyl chloride (57 mg, 0.73 mmol, 1.2 equiv.) and CH_2Cl_2 (3.0 mL). The resulting mixture was stirred at –78 °C to –30 °C for 3 h. After purification by flash chromatography (pentane/Et_2O, 9:1), (*R*)-**67c** was obtained as a colourless oil (56 mg, 0.40 mmol, 68 %, 90 % *ee*).

$[\alpha]_D^{20}$ = – 26.3 (c = 1.05, $CHCl_3$)
^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 6.72 (dd, ^3J = 8.16 Hz, ^3J = 15.99 Hz, 1H), 6.03 (dd, ^4J = 1.09 Hz, ^3J = 15.99 Hz, 1H), 2.25 (s, 3H), 2.17-2.10 (m, 1H), 1.69-1.62 (m, 1H), 1.03 (d, ^3J = 6.80 Hz, 3H), 0.88 (t, ^3J = 6.73 Hz, 3H).
^{13}C-NMR ($CDCl_3$, 100 MHz): δ =198.8, 152.6, 130.4, 43.0, 32.6, 26.9, 19.9, 19.7, 16.3.
IR (neat, ν/cm^{-1}): 2960, 2930, 2874, 1674, 1624, 1459, 1359, 1253, 982.
MS (EI, 70 eV), *m/z* (%): 140.12 (11, M^+), 125 (25), 107 (9), 98 (100), 97 (58), 83 (76), 70 (18), 55 (22), 42 (70).
HRMS for $C_9H_{16}O$ [M^+]: 140.1201, found: 140.1200.

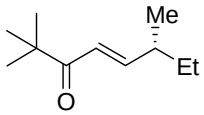
(4*R*,2*E*)-1-Furan-2-yl-4,5-dimethylhex-2-en-1-one ((*R*)-67d):



Prepared according to **TP9** from **65b** (127 mg, 0.6 mmol, 90 % *ee*), $AlCl_3$ (97 mg, 0.73 mmol, 1.2 equiv.), furoyl chloride (95 mg, 0.73 mmol, 1.2 equiv.) and CH_2Cl_2 (3.0 mL). The resulting mixture was stirred at –78 °C to rt for 10 h. After purification by flash chromatography (pentane/Et_2O, 98:2), (*R*)-**67d** was obtained as a colourless oil (76 mg, 0.40 mmol, 66 %, 90 % *ee*).

$[\alpha]_D^{20}$ = – 28.2 (c = 0.95, $CHCl_3$)
^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 7.61 (dd, ^3J = 1.69 Hz, ^4J = 0.75 Hz, 1H), 7.23 (dd, ^3J = 3.58 Hz, ^4J = 0.75 Hz, 1H), 7.10 (dd, ^3J = 8.30 Hz, ^3J = 15.49 Hz, 1H), 6.75 (dd, ^4J = 1.13 Hz, ^3J = 15.49 Hz, 1H), 6.55 (dd, ^4J = 1.71 Hz, ^3J = 3.55 Hz, 1H), 2.25-2.20 (m, 1H), 1.72-1.65 (m, 1H), 1.07 (d, ^3J = 6.79 Hz, 3H), 0.91 (t, ^3J = 6.75 Hz, 3H), 0.89 (t, ^3J = 6.75 Hz, 3H).
^{13}C-NMR ($CDCl_3$, 100 MHz): 178.2, 153.4, 146.4, 123.9, 117.4, 112.2, 43.3, 32.7, 19.9, 19.7, 16.3.
IR (neat, ν/cm^{-1}): 2960, 2928, 2873, 1665, 1618, 1568, 1465, 1394, 1009, 756.
MS (EI, 70 eV), *m/z* (%): 192.11 (57, M^+), 177 (55), 150 (43), 134 (14), 121 (100), 110 (63), 95 (85), 79 (19), 55 (11), 43 (14).
HRMS for $C_{12}H_{16}O_2$ [M^+]: 192.1150, found: 192.1161.

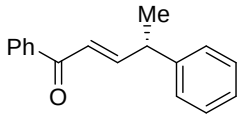
(6*R*,4*E*)-2,2,6-Trimethyloct-4-en-3-one ((*R*)-67e):



Prepared according to **TP9** from **65c** (168 mg, 0.85 mmol, 88 % *ee*), $AlCl_3$ (125 mg, 0.93 mmol, 1.2 equiv.), pivaloyl chloride (112 mg, 0.93 mmol, 1.2 equiv.) and CH_2Cl_2 (4.0 mL). The resulting mixture was stirred at –78 °C to rt for 3 h. After purification by flash chromatography (pentane/Et_2O, 98:2), (*R*)-**67e** was obtained as a colourless oil (111 mg, 0.60 mmol, 78 %, 88 % *ee*).

$[\alpha]_D^{20}$ = – 18.4 (c = 1.25, $CHCl_3$)
^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 6.81 (dd, ^3J = 7.98 Hz, ^3J = 15.30 Hz, 1H), 6.44 (dd, ^4J = 1.10 Hz, ^3J = 15.30 Hz, 1H), 2.41-2.16 (m, 1H), 1.41-1.36 (m, 2H), 1.15 (s, 9H), 1.04 (d, ^3J = 6.73 Hz, 3H), 0.86 (t, ^3J = 7.42 Hz, 3H).
^{13}C-NMR ($CDCl_3$, 100 MHz): 204.6, 152.6, 122.5, 42.9, 38.4, 28.8, 26.2, 19.2, 11.6.
IR (neat, ν/cm^{-1}): 2963, 2930, 2873, 1689, 1623, 1477, 1457, 1351, 1076, 985.
MS (EI, 70 eV), *m/z* (%): 168.15 (4, M^+), 111 (100), 83 (1), 69 (5), 55 (5), 41 (5).
HRMS for $C_{11}H_{20}O$ [M^+]: 168.1514, found: 168.1528.

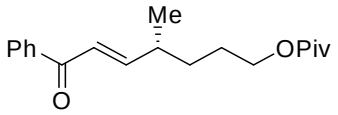
(4*S*,2*E*)-1,4-Diphenylpent-2-en-1-one ((*S*)-67f):



Prepared according to **TP9** from **65d** (90 mg, 0.36 mmol, 89 % *ee*), $AlCl_3$ (53 mg, 0.43 mmol, 1.2 equiv.), benzoylchloride (0.046 mL, 0.43 mmol, 1.2 equiv.) and CH_2Cl_2 (3.0 mL). The resulting mixture was stirred at –78 °C to rt for 3 h. After purification by flash chromatography (pentane/Et_2O, 9:1), (*S*)-**67f** was obtained as a colourless oil (60 mg, 0.26 mmol, 71 %, 89 % *ee*). The *ee* was determined by HPLC analysis.

$[\alpha]_D^{20}$ = – 5.6 (c = 1.06, $CHCl_3$)
HPLC (column: OD-H), *n*-heptane / *i*-PrOH 98:2, 0.5 mL/min.
^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 7.91-7.88 (m, 2H), 7.57-7.52 (m, 1H), 7.47-7.43 (m, 2H), 7.36-7.33 (m, 2H), 7.27-7.24 (m, 3H), 7.21 (dd, ^3J = 6.77 Hz, ^3J = 15.48 Hz, 1H), 6.84 (dd, ^4J = 1.48 Hz, ^3J = 15.48 Hz, 1H), 3.77-3.70 (m, 1H), 1.51(d, ^3J = 7.05 Hz, 3H).
^{13}C-NMR ($CDCl_3$, 100 MHz): 191.1, 153.1, 143.4, 137.9, 132.6, 128.7, 128.5, 128.4, 127.4,
IR (neat, ν/cm^{-1}): 3060, 3027, 2967, 2929, 2872, 1667, 1616, 1447, 1286, 1252, 1212, 1006, 759.
MS (EI, 70 eV), *m/z* (%): 236. 11 (9, M^+), 221 (5), 207 (2), 157 (2), 131 (19), 115 (12), 105 (100), 91 (14), 77 (39), 50 (3).
HRMS for $C_{17}H_{16}O$ [M^+]: 236.1201, found: 236. 1178.

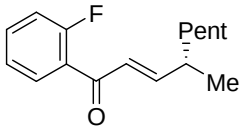
(4*R*,5*E*)-4-Methyl-7-oxo-7-phenylhept-5-enyl 2,2-dimethylpropionate ((*R*)-67g):



Prepared according to **TP9** from **65h** (90 mg, 0.30 mmol), $AlCl_3$ (48 mg, 0.36 mmol, 1.2 equiv.), benzoylchloride (0.04 mL, 0.36 mmol, 1.2 equiv.) and CH_2Cl_2 (3.0 mL). The resulting mixture was stirred at –78 °C to 25 °C for 3 h. After purification by flash chromatography (9:1 pentane/Et_2O), (*R*)-**67g** was obtained as a colourless oil (60 mg, 0.19 mmol, 65 % yield, 80 % *ee*). The *ee* was determined by HPLC analysis.

$[\alpha]_D^{20}$ = – 8.0 (c = 1.20, $CHCl_3$)
HPLC (column: OD-H; *n*-heptane/*i*-PrOH 95:5, 0.5 mL/min): t_R(min) = 13.47 (*R*), 16.32 (*S*).
^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 7.94-7.91 (m, 2H), 7.57-7.53 (m, 1H), 7.48-7.44 (m, 2H), 6.94 (dd, ^3J = 7.56 Hz, ^3J = 15.45 Hz, 1H), 6.85 (d, ^3J = 15.90 Hz, 1H), 4.05 (t, ^3J = 6.47 Hz, 2H), 2.43-2.41 (m, 1H), 1.69-1.62 (m, 2H), 1.52-1.46 (m, 2H), 1.19 (s, 9H), 1.13 (d, ^3J = 6.72 Hz, 3H).
^{13}C-NMR ($CDCl_3$, 100 MHz): δ = 190.8, 178.5, 154.2, 137.8, 132.6, 128.4, 124.4, 64.0, 38.6, 36.7, 32.2, 27.1, 26.3, 19.5.
IR (neat): 2960, 2871, 1724, 1670, 1620, 1282, 1151, 696.
MS (EI, 70 eV), *m/z* (%): 302.18 (5), 217 (6), 171 (6), 157 (6), 120 (9), 105 (100), 77 (28), 57 (43), 41 (16).
HRMS for $C_{19}H_{26}O_3$ [M^+]:302.1882, found: 302.1888.

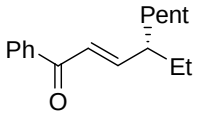
(4*S*,2*E*)-1-(2-Fluorophenyl)-4-methylnon-2-en-1-one ((*S*)-67h):



Prepared according to **TP9** from **65i** (340 mg, 1.3 mmol, 89 % *ee*), $AlCl_3$ (208 mg, 1.56 mmol, 1.2 equiv.), 2-fluorobenzoylchloride (0.18 mL, 1.56 mmol, 1.2 equiv.) and CH_2Cl_2 (5.0 mL). The resulting mixture was stirred at –78 °C to –40 °C for 4 h. After purification by flash chromatography (pentane/Et_2O, 98:2), (*S*)-**67h** was obtained as a colourless oil (220 mg, 0.88 mmol, 68 %, 89 % *ee*).

$[\alpha]_D^{20}$ = + 17.7 (c = 1.08, $CHCl_3$)
^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 7.69 (dt, ^4J = 1.82 Hz, ^3J = 7.50 Hz, 1H), 7.54-7.47 (m, 1H), 7.24 (t, ^3J = 7.53 Hz, 1H), 7.18-7.11 (m, 1H), 6.87 (dd, ^4J = 1.89 Hz, ^3J = 15.56 Hz, 1H), 6.66 (dd, ^4J = 2.67 Hz, ^3J = 15.56 Hz, 1H), 2.45-2.37 (m, 1H), 1.47-1.30 (m, 8H), 1.08 (d, ^3J = 6.72 Hz, 3H), 0.88 (t, ^3J = 6.90 Hz, 3H).
^{13}C-NMR ($CDCl_3$, 75 MHz): δ =190.0, 162.6, 159.2, 155.8, 133.5, 130.8, 127.8, 124.3, 116.5, 116.2, 36.9, 36.0, 31.8, 26.8, 22.5, 19.4, 14.0.
IR (neat, ν/cm^{-1}): 2958, 2926, 2856, 1670, 1616, 1451, 1285, 1209, 763.
MS (EI, 70 eV), *m/z* (%): 248.15 (15, M^+), 191 (29), 177 (12), 163 (5), 151 (8), 138 (12), 123 (100), 109 (17), 95 (17), 55 (8), 43 (10).
HRMS for $C_{16}H_{21}FO$ [M^+]: 248.1576, found: 248.1564.

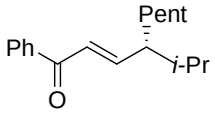
(4*S*,2*E*)-4-Ethyl-1-phenylnon-2-en-1-one ((*S*)-67i):



Prepared according to **TP9** from **65j** (200 mg, 0.72 mmol, 89 % *ee*), $AlCl_3$ (115 mg, 0.86 mmol, 1.2 equiv.), benzoylchloride (0.10 mL, 0.86 mmol, 1.2 equiv.) and CH_2Cl_2 (5.0 mL). The resulting mixture was stirred at –78 °C to 0 °C for 6 h. After purification by flash chromatography (pentane/Et_2O, 95:5), (*S*)-**67i** was obtained as a colourless oil (140 mg, 0.58 mmol, 80 %, 89 % *ee*).

$[\alpha]_D^{20}$ = + 8.4 (c = 1.055, $CHCl_3$)
^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 7.94-7.91 (m, 2H), 7.55-7.44 (m, 3H), 6.84-6.82 (m, 2H), 2.21-2.13 (m, 1H), 1.55-1.27 (m, 10H), 0.92-0.85 (m, 6H).
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 190.9, 154.3, 138.1, 132.5, 128.5, 128.4, 125.8, 45.0, 34.1, 31.9, 27.3, 27.0, 22.5, 14.1, 11.8.
IR (neat, ν/cm^{-1}): 2958, 2927, 2856, 1669, 1618, 1447, 1361, 1284, 1248, 1213, 983, 769, 694, 658.
MS (EI, 70 eV), *m/z* (%): 244.18 (48, M^+), 215 (27), 187 (45), 173 (23), 159 (14), 124 (14), 120 (22), 105 (100), 91 (10), 77 (21).
HRMS for $C_{17}H_{24}O$ [M^+]: 244.1827, found: 244.1838.

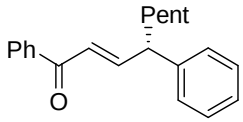
(4*S*,2*E*)- 4-Isopropyl-1-phenylnon-2-en-1-one ((*S*)-67j):



Prepared according to **TP9** from **67k** (269 mg, 0.93 mmol, 87 % *ee*), $AlCl_3$ (150 mg, 1.12 mmol, 1.2 equiv.), benzoylchloride (0.13 mL, 0.86 mmol, 1.2 equiv.) and CH_2Cl_2 (5.0 mL). The resulting mixture was stirred at –78 °C to –30 °C for 3 h. After purification by flash chromatography (pentane/Et_2O, 98:2), (+)-(*S*)-**67j** was obtained as a colourless oil (206 mg, 0.80 mmol, 86 %, 87 % *ee*). The *ee* was determined by HPLC analysis.

$[\alpha]_D^{20}$ = + 12.1 (c = 1.22, $CHCl_3$)
HPLC (column: OD-H; *n*-heptane 100 %, 0.5 mL/min): t_R(min) = 46.93 (*S*), 50.70 (*R*).
^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 7.94-7.91 (m, 2H), 7.58-7.44 (m, 3H), 6.92-6.77 (m, 2H), 2.11-2.00 (m, 1H), 1.81-1.64 (m, 1H), 1.58-1.27 (m, 8H), 0.94 (d, ^3J = 6.76 Hz, 3H), 0.92 (m, 6H).
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 190.7, 152.8, 138.2, 132.5, 128.5, 128.4, 126.7, 49.9, 31.9, 31.8, 31.6, 27.4, 22.5, 20.7, 19.3, 14.1.
IR (neat, ν/cm^{-1}): 2955, 2927, 2871, 2856, 1668, 1620, 1465, 1447, 1369, 1255, 1214, 1009, 986, 771, 694, 661.
MS (EI, 70 eV), *m/z* (%): 258.19 (36, M^+), 215 (59), 187 (37), 159 (61), 145 (23), 133 (20), 120 (45), 105 (100), 91 (14), 77 (30), 43 (13).
HRMS for $C_{18}H_{26}O$ [M^+]: 258.1984, found: 258.1992.

(4*S*,2*E*)-1,4-Diphenylnon-2-en-1-one ((*S*)-67k):

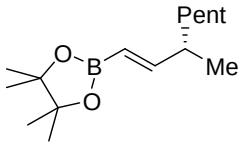


Prepared according to **TP9** from **65l** (300 mg, 0.93 mmol), $AlCl_3$ (149 mg, 1.11 mmol, 1.2 equiv.), benzoylchloride (0.13 mL, 1.11 mmol, 1.2 equiv.) and CH_2Cl_2 (8.0 mL). The resulting mixture was stirred at –78 °C to rt for 3 h. After purification by column chromatography (pentane/Et_2O, 95:5), (*S*)-**67k** was obtained as a colourless oil (203 mg, 0.70 mmol, 75 %, 89 % *ee*). The ee was determined by HPLC analysis (see appendix).

$[\alpha]_D^{20}$ = + 18.3 (c = 1.22, $CHCl_3$)
HPLC (column: OD-H; *n*-heptane/*i*-PrOH 98:2, 0.5 mL/min): t_R(min) = 13.18 (*R*), 14.96 (*S*).
^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 7.92-7.89 (m, 2H), 7.59-7.54 (m, 1H), 7.49-7.44 (m, 2H), 7.38-7.33 (m, 2H), 7.28-7.24 (m, 3H), 7.20 (dd, ^3J = 7.88 Hz, ^3J = 15.43 Hz, 1H), 6.85 (d, ^3J = 15.43 Hz, H), 3.53 (q, ^3J = 7.58 Hz, 1H), 1.87-1.84 (m, 2H), 1.32-1.31 (m, 6H), 0.89 (t, ^3J = 6.52 Hz, 3H)
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 190.9, 152.4, 142.5, 137.9, 132.6, 128.7, 128.5, 128.4, 127.7, 126.7, 125.1, 49.1, 35.2, 31.7, 27.2, 22.5, 14.0.
IR (neat, ν/cm^{-1}): 2954, 2927, 2856, 1667, 1615, 1447, 1282, 1250, 1010, 982, 757, 694.
MS (EI, 70 eV), *m/z* (%): 292.18 (8), 274 (3), 235 (7), 187 (8), 172 (15), 117 (24), 105 (100), 77 (18).
HRMS for $C_{21}H_{24}O$ [M^+]: 292.1827, found: 292.186.

4.5 Procedure for the *ipso*-borodesilylation [87]

(3*S*,1*E*)-4,4,5,5-Tetramethyl-2-(3-methyl-oct-1-enyl)-[1,3,2]dioxaborolane ((*S*)-68):



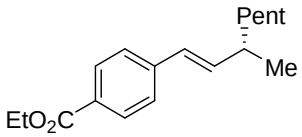
In flame-dried flask equipped with a magnetic stirring bar, an argon inlet, and a septum was placed **65i** (780 mg, 3.0 mmol, 89 % *ee*) and dry dichloromethane (2 mL). This solution was cooled to –30 °C and BCl_3 (1.0 M solution in CH_2Cl_2, 12.0 mL, 12.0 mmol, 4.0 equiv.) was added dropwise. The resulting mixture was stirred at –30 °C for 5 h before a solution of pinacol (1.06 g, 9.0 mmol, 3.0 equiv.) and Et_3N (2.54 mL, 18.0 mmol, 6.0 equiv.) in dichloromethane (5 mL) was added. After stirring the mixture at 24 °C for 16 h, saturated aqueous Na_2CO_3 (ca. 8 mL) was added. The aqueous phase was extracted with Et_2O (3 x 20 mL) and the combined extracts were washed with brine and dried over Mg_2SO_4. Evaporation of the solvents and purification by flash chromatography (pentane/Et_2O, 98:2) afforded (*S*)-**68** (544 mg, 2.16 mmol, 72 %) as a colourless oil.

$[\alpha]_D^{20}$ = + 14.6 (c = 1.12, $CHCl_3$).
^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 6.52 (dd, ^3J = 7.18 Hz, ^3J = 18.03 Hz, 1H), 5.37 (d, ^3J = 18.03 Hz, 1H), 2.19-2.16 (m, 8H), 1.25 (m, 12H), 0.98 (d, ^3J = 6.74, 3H), 0.88 (t, ^3J = 6.90, 3H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ = 160.2, 82.9, 39.4, 36.1, 31.9, 26.9, 24.8, 22.6, 19.5, 14.0.
IR (neat, ν/cm^{-1}): 2958, 2926, 2857, 1636, 1461, 1359, 1318, 1144, 998, 970, 849, 656.
MS (EI, 70 eV), *m/z* (%): 252 (10, M^+), 237 (19), 195 (32), 153 (26), 139 (27), 124 (34), 109 (10), 101 (33), 84 (100), 69 (15), 40 (15).
HRMS for $C_{15}H_{29}BO_2$ [M^+]: 252.2261, found: 252.2267.

4.6 Procedure for the Suzuki-Miyaura cross-coupling reaction with aryliodide [87]

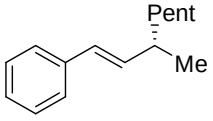
(3*S*,1*E*)-4-(3-Methyloct-1-enyl)-ethyl benzoate ((*S*)-74):



To a solution of $Pd(PPh_3)_4$ (60 mg, 0.05 mmol, 5 mol %), in dioxane (5.0 mL) was added 4-Ethyl-iodobenzoate (276 mg, 1.0 mmol, 1.0 equiv.), **68** (252 mg, 1 mmol) and NaOH (2.0 M in water, 1 mL, 2.0 mmol, 2.0 equiv.) at 25 °C. The resulting mixture was stirred at 100 °C for 3 h. After cooling the reaction mixture to room temperature water (ca. 4.0 mL) was added. The aqueous phase was extracted with Et_2O (3 x 20 mL) and the combined organic phases were dried over Mg_2SO_4. Evaporation of the solvents and purification by flash chromatography (pentane/Et_2O, 98:2) afforded (*S*)-**74** (233 mg, 0.85 mmol, 85 %, 89 % *ee*) as a colourless oil.

[α]$_D^{20}$ = + 40.2 (c = 1.06, $CHCl_3$).
^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 7.96 (d, ^3J = 8.40 Hz, 2H), 7.38 (d, ^3J = 8.40 Hz, 2H), 6.37 (d, ^3J = 15.94 Hz, 1H), 6.22 (dd, ^3J = 7.71 Hz, ^3J = 15.88 Hz, 1H), 4.36 (q, ^3J = 7.11 Hz, 2H), 2.37-2.19 (m, 1H), 1.39 (t, ^3J = 7.13 Hz, 3H), 1.31-1.28 (m, 8H), 1.08 (d, ^3J = 6.75 Hz, 3H), 0.88 (t, ^3J = 6.85 Hz, 3H).
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 166.5, 142.4, 139.8, 129.8, 128.5, 127.2, 125.7, 60.7, 37.3, 36.9, 31.9, 27.0, 22.6, 20.4, 14.3, 14.0.
IR (neat, ν/cm^{-1}): 2956, 2925, 2855, 1714, 1606, 1458, 1269, 1176, 1098, 1019, 969, 763.
MS (EI, 70 eV), *m/z* (%): 274 (30, M^+), 229 (23), 203 (44), 176 (31), 159 (29), 148 (15), 131 (100), 129 (28), 115 (21), 91 (9).
HRMS for $C_{18}H_{26}O_2$ [M^+]: 274.1933, found: 274.1925.

(3*S*,1*E*)-(3-Methyloct-1-enyl)-benzene ((*S*)-75):



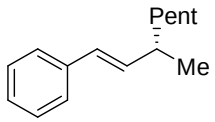
To a solution of $Pd(PPh_3)_4$ (55 mg, 0.047 mmol, 5 mol %), in was dioxane (5.0 mL) was added iodobenzene (194 mg, 0.95 mmol, 1.0 equiv.), **68** (240 mg, 0.95 mmol) and NaOH (2.0 M in water, 0.95 mL, 1.9 mmol, 2.0 equiv.) at 25 °C. The resulting mixture was stirred at 100 °C for 3 h. After cooling the reaction mixture to room temperature water (ca. 4.0 mL) was added. The aqueous phase was extracted with Et_2O (3 x 20 mL) and the combined organic

phases were dried over Mg_2SO_4. Evaporation of the solvents and purification by flash chromatography (100 % pentane) afforded (*S*)-**75** (160 mg, 0.79 mmol, 83 %, 89 % *ee*) as a colourless oil.

$[\alpha]_D^{20}$ = + 42.6 (c = 1.65, $CHCl_3$)
^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 7.40-7.19 (m, 5H), 6.37 (d, ^3J = 15.88 Hz, 1H), 6.13 (dd, ^3J = 7.90 Hz, ^3J = 15.88 Hz, 1H), 2.36-2.25 (m, 1H), 1.39-1.32 (m, 8H), 1.11 (d, ^3J = 6.76 Hz, 3H), 0.92 (t, ^3J = 6.89 Hz, 3H).
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 138.0, 137.1, 128.4, 127.9, 126.7, 125.9, 37.3, 37.1, 32.0, 27.1, 22.6, 20.7, 14.1.
IR (neat, ν/cm^{-1}): 2955, 2924, 2855, 1493, 1449, 963, 744, 690.
MS (EI, 70 eV), *m/z* (%): 202.17 (21), 145 (2), 131 (100), 104 (26), 91 (26), 77 (2), 41 (2).
HRMS for $C_{15}H_{22}BO_2$ [M^+]: 202.1721, found: 202.1729.

4.7 Procedure for the one-pot *ipso*-borodesilylation – cross-coupling reaction [87]

(3*S*,1*E*)-(3-Methyloct-1-enyl)-benzene ((*S*)-75):



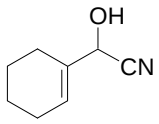
In flame-dried flask equipped with a magnetic stirring bar, an argon inlet, and a septum was placed **65i** (120 mg, 0.5 mmol, 89 % *ee*) and dry dichloromethane (0.5 mL). This solution was cooled to –30 °C and BCl_3 (1.0 M solution in CH_2Cl_2, 2.0 mL, 2.0 mmol, 4.0 equiv.) was added dropwise and the resulting mixture was stirred at –30 °C for 5 h. The solvent was evaporated at reduced pressure and the residue was dissolved in toluene (5 mL). Then a solution of iodobenzene (102 mg, 0.5 mmol, 1.0 equiv.) and $Pd(PPh_3)_4$ (28 mg, 0.025 mmol, 5 mol %) in toluene (3 mL) was added at 25 °C followed by Na_2CO_3 (2.0 M solution in water, 0.5 mL, 1.0 mmol, 2.0 equiv.). The resulting mixture was stirred at 90 °C for 5 h. After cooling the reaction mixture to room temperature water (ca. 4.0 mL) was added. The aqueous phase was extracted with Et_2O (3 x 10 mL) and the combined organic phases were dried over Mg_2SO_4. Evaporation of the solvents and purification by flash chromatography (100 % pentane) afforded (*S*)-**75** (60 mg, 0.30 mmol, 60 %, 89 % *ee*) as a colourless oil.

For compound **74** and **75** the *ee* were checked by transformation into (2*S*)-2-Methylheptanoic acid (*S*)-**72a** by ozonolysis (**TP4**) and showed no loss the enantiomeric excess.

5 Preparation of Unsaturated Nitriles

5.1 Starting materials

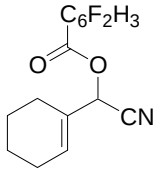
Cyclohex-1-enyl-hydroxy-acetonitrile (78a):



To a solution of cyclohexencarbaldehyde (1.14 mL, 10.0 mmol) in acetonitrile (40 mL) was added CsF (0.212 g, 1.40 mmol) and trimethylsilylcyanid (1.60 mL, 12.0 mmol) at rt. After 1 h the reaction mixture was poured into an Erlenmeyer containing HCl (2 M, 50 mL) and Et_2O (50 mL) and vigorously stirred for 2 h at rt. The water phase was extracted 3 x with Et_2O (50 mL) and the combined organic phases were washed with brine, dried over $MgSO_4$ and the solvent was evaporated under vacuo. **78a** was obtained as a pale yellow oil (.37 g, 10.0 mmol, 100 %) and used without further purification.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 5.99 (s, 1H), 4.74 (d, ^3J = 6.85 Hz, 1H), 2.41 (d, ^3J = 6.93 Hz, 1H), 2.16-1.98 (m, 4H), 1.68-1.50 (m, 4H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 133.1, 128.9, 118.8, 66.2, 25.35, 24.6, 22.5, 22.1.
IR (neat, ν/cm^{-1}): 3422, 2928, 2862, 1643, 1437, 1278, 1138, 1023, 918.
MS (EI, 70 eV): *m/z* (%) = 137 (7, $[M]^+$), 110 (16), 81 (100), 68 (10), 53 (16).

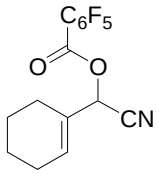
Cyano(cyclohexenyl)methyl 2,6-difluorobenzoate (77a):



Prepared according to **TP7** from **78a** (1.37 g, 10.0 mmol), Et_3N (1.97 mL, 14.0 mmol), 2,6-difluorbenzoylchlorid (1.76 mL, 14.0 mmol) and Et_2O (60 mL). Purification by flash chromatography (pentane/Et_2O, 9:1) afforded **77a** (2.46 g, 8.8 mmol, 88 %) as a colourless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.53-7.43 (m, 1H), 6.99 (t, ^3J = 8.36 Hz, 2H), 6.20 (s, 1H), 5.99 (s, 1H), 2.21-2.12 (m, 4H), 1.75-1.60 (m, 4H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 162.8 (d), 159.8, 159.3 (d), 134.0 (t), 132.1, 129.0, 115.2, 112.4 (d), 112.1 (d), 109.0 (t), 66.2, 25.1, 24.2, 21.9, 21.5.
MS (EI, 70 eV): *m/z* (%) = 277 (9, $[M]^+$), 141 (100), 136 (14), 119 (23), 109 (13), 104 (13), 81 (36), 79 (26).
HRMS for$C_{15}H_{13}F_2NO_2$ $[M]^+$: 277.0914, found: 277.0912.

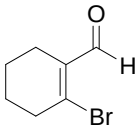
Cyano(cyclohexenyl)methyl 2,3,4,5,6-pentafluorobenzoate (77b):



Prepared according to **TP7** from **78a** (122 mg, 0.84 mmol), Et_3N (0.18 mL, 1.26 mmol), pentafluorbenzoyl chlorid (0.17 mL, 1.24 mmol) and Et_2O (5.0 mL). Standard workup afforded **77b** (264 mg, 0.79 mmol, 95 %) as a pale yellow oil and used without further purification.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 6.21 (s, 1H), 5.97 (s, 1H), 2.20-2.14 (m, 4H), 1.74-1.60 (m, 4H).
IR (neat, ν/cm^{-1}): 2935, 1741, 1620, 1257, 1234, 1022, 940, 798.
MS (EI, 70 eV): *m/z* (%) = 331 (8, $[M]^+$), 194 (100), 168 (38), 136 (34), 119 (29), 104 (30), 81 (57), 79 (51).
HRMS for$C_{15}H_{10}F_5NO_2$ $[M]^+$: 331.0632, found: 331.0642.

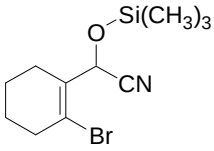
2-Bromo-cyclohex-1-ene carbaldehyde (81a):



Prepared according to a procedure by *Suffert*.[96]

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 10.0 (s, 1H), 2.76-2.69 (m, 2H), 2.29-2.23 (m, 2H), 1.76-1.64 (m, 4H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 190.5, 154.5, 140.6, 29.8, 25.9, 22.5, 20.6.
IR (neat, ν/cm^{-1}): 2937, 2859, 1673, 1616, 916, 701.
MS (EI, 70 eV): *m/z* (%) = 187 (81, $[M]^+$), 175 (14), 159 (13), 109 (39), 79 (100), 53 (24).

(2-Bromo-cyclohex-1-enyl)-trimethylsilanyloxy acetonitrile (82a):

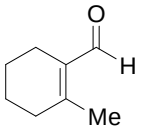


To a solution of **81a** (1.34 g, 7.09 mmol, 1.0 equiv.) in acetonitrile (40 mL) was added CsF (0.150 g, 0.99 mmol, 0.15 equiv.) and trimethylsilylcyanid (1.14 mL, 8.51 mmol, 1.1 equiv.) and the resulting mixture was stirred at rt for 1 h. The organic phase was taken up in Et_2O and washed with brine, dried over $MgSO_4$ and the solvent was evaporated under vacuo. **82a** was obtained as a pale yellow oil (2.042 g, 7.09 mmol, 100 %) and used without further purification.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 5.59 (s, 1H), 2.51-2.53 (m, 2H), 2.38-2.26 (m, 2H), 1.73-1.70 (m, 4H), 0.21 (s, 9H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 132.2, 124.1, 118.5, 65.3, 37.0, 26.0, 24.6, 22.0, 0.0.

IR (neat, ν/cm^{-1}): 2958, 2855, 1653, 1253, 1090, 1070, 840.
MS (EI, 70 eV): *m/z* (%) = 287 (0.56, [M]$^+$), 274 (44), 247 (18), 196 (43), 136 (60), 118 (65), 109 (100), 81 (63), 73 (50).
HRMS for $C_{11}H_{18}BrNOSi$ [M]$^+$, ^{79}Br: 287.0341, found: 287.0324.

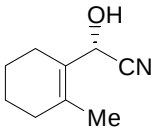
2-Methyl-cyclohex-1-ene carbaldehyde (83a): [97]



To a solution of **82a** (2.042 g, 7.09 mmol, 1.0 equiv.) and Fe(acac)$_3$ (0.250 g, 0.71 mmol, 10 mol %) in a mixture of THF (15 mL) and NMP (12.5 mL, ca. 10 equiv.) was added at −30 °C MeMgCl (2.74 mL, 2.85 M, 7.80 mmol, 1.4 equiv.). The resulting mixture was stirred at this temperature for another 30 min and then poured into Erlenmeyer with diluted HCl/Et_2O (100 mL/100 mL). It was vigorously stirred until the TMS group had been cleaved (ca. 2 h). The aqueous phase was extracted with Et_2O (3 x 100 mL), dried over $MgSO_4$ and the solvent was evaporated under vacuo.
The crude hydroxy-(2-methyl-cyclopent-1-enyl)-acetonitrile was diluted in EtOH (20 mL) and $CuSO_4 \cdot 5H_2O$ (1.77 g, 7.1 mmol, 1.0 equiv.) followed by NaOH solution (14 mL, 1.0 M, 2.0 equiv.) were added at rt and stirred for 1 h.[132] The aqueous phase was extracted with Et_2O (3 x 50 mL), dried over $MgSO_4$ and the solvent was evaporated under vacuo. Purification by flash chromatography (pentane/Et_2O, 9:1) afforded **83a** (380 mg, 3.05 mmol, 43 % for 2 steps) as a pale yellow oil.

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 10.12 (s, 1H), 2.18 (m, 2H), 2.15 (m, 2H), 2.10 (s, 3H), 1.60-1.57 (m, 4H).
^{13}C-NMR (150 MHz, $CDCl_3$): δ = 191.3, 156.3, 133.9, 34.4, 22.4, 22.2, 21.9, 18.53.
IR (neat, ν/cm^{-1}): 2933, 2862, 1659, 1632, 1448, 1237, 1141.
MS (EI, 70 eV): *m/z* (%): 124 (100, [M]$^+$), 109 (46), 95 (12), 81 (27), 79 (18), 67 (49).
HRMS for $C_8H_{12}O$ [M]$^+$: 124.0888, found: 124.0883.

(2*S*)-Hydroxy-2-(2-methylcyclohex-1-enyl) acetonitrile ((*S*)-78b):

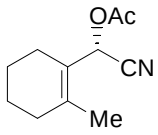


Prepared according to **TP10** from **83a** (310 mg, 2.5 mmol), KCN (325 mg, 5.0 mmol in 20 mL of the buffer), (S)-Oxynitrilase (500 units), and the citrate buffer (12 mL). Reaction time: 3 h. Purification by flash chromatography (pentane/Et_2O, 9:1 + 1 % Et_3N) afforded (*S*)-**78b** (166 mg, 1.1 mmol, 58 %) as a pale yellow oil.

$[\alpha]_D^{20}$ = + 22.4 (c = 0.85, $CHCl_3$)
^{1}H-NMR (600 MHz, $CDCl_3$): δ = 5.35 (d, ^3J = 5.24 Hz, 1H), 2.77 (d, ^3J = 5.24 Hz, 1H), 2.20 (m, 2H), 2.00 (m, 2H), 1.72 (s, 3H), 1.67-1.57 (m, 4H).
^{13}C-NMR (150 MHz, $CDCl_3$): δ = 136.0, 1.25.3, 119.3, 61.1, 32.4, 24.5, 22.7, 22.5, 19.3.
IR (neat, ν/cm^{-1}): 3422, 2928, 2862, 1643, 1437, 1278, 1138, 1023, 918.

[132] C.-Y. Liu, H. Ren, P. Knochel, *Org. Lett.* **2006**, *8*, 617.

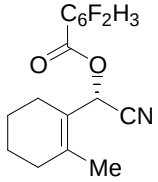
The *ee* of (*S*)-**78b** was determined by GC analysis after transformation into (2*S*)-cyano(2-methylcyclohex-1-enyl)methyl acetate:



Prepared according to **TP7** from (*S*)-**78b** (302 mg, 2.0 mmol), Et_3N (0.36 mL, 2.6 mmol), acetyl chloride (0.18 mL, 2.6 mmol) and Et_2O (10 mL). Purification by flash chromatography (pentane/Et_2O, 98:2) afforded the acetate (289 mg, 1.5 mmol, 75 %, 96 % *ee*) as a colourless oil.

$[\alpha]_D^{20}$ = + 19.3 (c = 0.66, $CHCl_3$)
GC (Chirasil-Dex CB), 100 °C constant; t_R(min) = 31.35 (*R*), 32.82 (*S*).
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 6.26 (s, 1H), 2.22-2.16 (m, 2H), 2.12 (s, 3H), 2.03-2.02 (m, 2H), 1.75 (s, 3H), 1.69-1.57 (m, 4H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 168.9, 137.9, 122.0, 116.3, 60.8, 32.2, 24.7, 22.3, 22.2, 20.4, 19.3.
IR (neat, ν/cm^{-1}): 2933, 2862, 1747, 1437, 1371, 1209, 1143, 1014, 946.
MS (EI, 70 eV): *m/z* (%) = 193 (5, $[M]^+$), 150 (7), 133 (68),118 (100), 93 (60), 91 (39), 79 (22), 43 (62).
HRMS for $C_{11}H_{15}NO_2$ $[M]^+$: 193.1103, found: 193.1110.

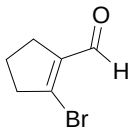
(2*S*)-Cyano(2-methylcyclohex-1-enyl)methyl 2,6-difluorobenzoate ((*S*)-77c):



Prepared according to **TP7** from (*S*)-**78b** (0.711 g, 4.70 mmol), Et_3N (0.93 mL, 6.58 mmol), 2,6-Difluorbenzoylchlorid (0.83 mL, 6.58 mmol) and Et_2O (30 mL). Purification by flash chromatography (pentane/Et_2O, 9:1) afforded (*S*)-**77c** (1.22 g, 4.18 mmol, 89 %) as a colourless oil.

$[\alpha]_D^{20}$ = – 16.1 (c = 0.70, $CHCl_3$)
^{1}H-NMR (600 MHz, $CDCl_3$): δ = 7.50-7.45 (m, 1H), 6.98 (t, ^3J = 8.35 Hz, 2H), 6.53 (s, 1H), 2.32-2.22 (m, 2H), 2.07 (m, 2H), 1.85 (s, 3H), 1.73-1.60 (m, 4H).
^{13}C-NMR (150 MHz, $CDCl_3$): δ = 161.9 (d), 160.2 (d), 159.6, 138.8, 133.9 (t), 112.3 (d), 112.2 (d), 62.1, 32.3, 24.7, 22.3, 22.2, 19.5.
IR (neat, ν/cm^{-1}): 2931, 1742, 1623, 1472, 1290, 1253, 1233, 1097, 1056, 1014, 931, 798.
MS (EI, 70 eV): *m/z* (%) = 291 (1, $[M]^+$), 141 (100), 133 (19), 118 (10), 93 (9), 79 (6).
HRMS for $C_{16}H_{15}NO_2F_2$ $[M]^+$: 291.1071, found: 291.1061.

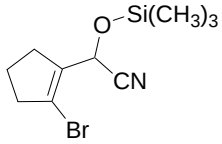
2-Bromo-cyclopent-1-ene carbaldehyde (81b):



Prepared according to a procedure by *Suffert*.[96]

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 9.88 (s, 1H), 2.93-2.83 (m, 2H), 2.56-2.46 (m, 2H), 2.01 (m, 2H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 189.1, 141.3, 140.0, 42.5, 29.2, 21.3.
IR (neat, ν/cm^{-1}): 2955, 2832, 1668, 1604, 1329, 1243, 1074, 918, 720.
MS (EI, 70 eV): *m/z* (%) = 173 (68, $[M]^+$), 144 (9), 95 (39), 67 (100), 65 (79), 41(26).
HRMS for C_6H_7BrO $[M]^+$, ^{79}Br: 173.9680, found: 173.9691.

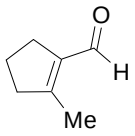
(2-Bromo-cyclopent-1-enyl)-trimethylsilanyloxy acetonitrile (82b):



Prepared following the same procedure as for **82a**, from **81b** (4.66 g, 17.0 mmol), CsF (387 mg, 2.55 mmol), trimethylsilylcyanid (2.5 mL, 18.7 mmol) and acetonitrile (60 mL). After workup, **82b** was obtained as a pale yellow oil (4.42 g, 16.1 mmol, 95 %) and used without further purification.

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 5.35 (s, 1H), 2.72-2.68 (m, 2H), 2.59-2.53 (m, 2H), 2.05-1.98 (m, 2H), 0.21 (s, 9H).
^{13}C-NMR (150 MHz, $CDCl_3$): δ = 136.2, 122.3, 118.3, 59.9, 40.7, 30.5, 21.7, 0.0.
IR (neat, ν/cm^{-1}): 2958, 2855, 1653, 1253, 1090, 1070, 840.
MS (EI, 70 eV): *m/z* (%) = 273 (0.61, $[M]^+$), 259 (22), 194 (27), 136 (71), 95 (100), 75 (62).
HRMS for $C_{10}H_{16}BrNOSi$ $[M]^+$, ^{79}Br: 273.0185, found: 273.0185.

2-Methyl-cyclopent-1-ene carbaldehyde (83b): [97]

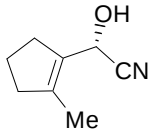


Prepared following the same procedure as for **83a**, from **82b** (4.42 g, 16.1 mmol) and $Fe(acac)_3$ (569 mg, 1.61 mmol), MeMgCl (7.9 mL, 22.5 mmol, 2.85 M), THF (30 mL) and NMP (25 mL.
Liberation of the aldehyde occurred following the same procedure as for **83a**, from hydroxy-(2-methyl-cyclopent-1-enyl)-acetonitrile, $CuSO_4 \cdot 5H_2O$ (4.0 g, 16.0 mmol), NaOH solution (30 mL, 1.0 M) and EtOH (40 mL). Purification by flash chromatography (pentane/Et_2O, 9:1) afforded **83b** (584 mg, 5.31 mmol, 33 %) as a pale yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 10.02 (s, 1H), 2.59-2.54 (m, 4H), 2.15 (s, 3H), 1.89-1.84 (m, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 188.4, 162.8, 138.4, 41.1, 30.4, 21.5, 14.5.
IR (neat, ν/cm^{-1}): 2951, 1705, 1664, 1437, 1380, 1183, 1115, 1046.
MS (EI, 70 eV): *m/z* (%): 110 (100, $[M]^+$), 109 (40), 95 (40), 81 (72), 79 (44), 67 (45), 53 (32), 41 (32).
HRMS for $C_7H_{11}O$ $[M]^+$: 110.0732, found: 110.0725.

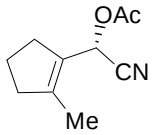
(2S)-Hydroxy-2-(2-methylcyclopent-1-enyl) acetonitrile ((*S*)-78c):



Prepared according to **TP10** with **83b** (440 mg, 4.0 mmol), KCN (520 mg, 8.0 mmol in 20 mL of the buffer), (S)-Oxynitrilase (1000 Units), and the citrate buffer (12 mL). Reaction time: 5 h. Purification by flash chromatography (pentane/Et_2O, 9:1 + 1 % Et_3N) afforded (*S*)-**78c** (300 mg, 2.2 mmol, 55 %) as a pale yellow oil.

$[\alpha]_D^{20}$ = + 29.1 (c = 1.39, $CHCl_3$)
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 5.24 (d, ^3J = 5.48 Hz, 1H), 3.51, (d, ^3J = 5.48 Hz, 1H), 2.58-2.49 (m, 2H), 2.39-2.34 (m, 2H), 1.90-1.80 (m, 2H), 1.72 (s, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 141.4, 128.6, 118.7, 57.6, 38.8, 31.6, 21.2, 13.8.
IR (neat, ν/cm^{-1}): 3420, 2917, 2847, 1676, 1437, 1383, 1258, 1177, 1061, 1019, 891.

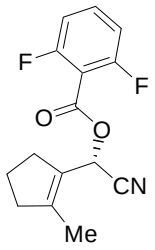
The *ee* of (*S*)-**78c** was determined after transformation into the (2*S*)-cyano(2-methylcyclopent-1-enyl)methyl acetate:



Prepared according to **TP7** from (*S*)-**78c** (192 mg, 1.4 mmol), Et_3N (0.28 mL, 1.96 mmol), acetyl chloride (0.25 mL, 1.96 mmol) and Et_2O (10 mL). Purification by flash chromatography (pentane/Et_2O, 9:1) afforded the acetate (210 mg, 1.18 mmol, 84 %, 90 % *ee*) as a colourless oil.

$[\alpha]_D^{20}$ = + 24.5 (c = 0.76, $CHCl_3$)
GC (Chirasil-Dex CB), 100 °C const.; t_R(min) = 13.74 (*S*), 14.96 (*R*).
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 6.09 (s, 1H), 2.45-2.53 (m, 2H), 2.30-2.36 (m, 2H), 2.05 (s, 3H), 1.76-1.88 (m, 2H), 1.70 (m, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 169.3, 144.4, 125.8, 116.2, 58.05, 39.15, 32.5, 21.5, 20.7, 14.4.
IR (neat, ν/cm^{-1}): 2922, 2853, 1748, 1370, 1213, 1014, 947.
MS (EI, 70 eV): *m/z* (%) = 179 (16, $[M]^+$), 136 (14), 119 (70), 104 (100), 92 (37), 79 (47).
HRMS for $C_{10}H_{13}NO_2$ $[M]^+$: 179.0946, found: 179.0959.

(2S)-Cyano(2-methylcyclopent-1-enyl)methyl 2,6-difluorobenzoate ((*S*)-77d):

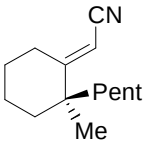


Prepared according to **TP7** from (*S*)-**78c** (685 g, 5.0 mmol), Et_3N (0.98 mL, 7.0 mmol), 2,6-difluorbenzoylchlorid (0.87 mL, 7.0 mmol) and Et_2O (50 mL). Purification by flash chromatography (pentane/Et_2O, 9:1) afforded (*S*)-**77d** (1.00 g, 3.65 mmol, 73 %) as a colourless oil.

$[\alpha]_D^{20}$ = – 8.5 (c = 1.19, $CHCl_3$)
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.53-7.43 (m, 1H), 6.98 (t, ^3J = 8.4 Hz, 2H), 6.42 (s, 1H), 2.65-2.59 (m, 2H), 2.45-2.40 (m, 2H), 1.97-1.87 (m, 2H), 1.85 (s, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 163.1, 159.9 (d, CF), 145.0, 133.9 (t, CF), 125.3, 115.4, 112.2 (d, CF), 58.9, 38.9, 32.1, 21.3, 14.3.
IR (neat, ν/cm^{-1}): 2955, 2851, 1739, 1624, 1470, 1289, 1250, 1100, 1009, 798.
MS (EI, 70 eV): *m/z* (%) = 277 (7.80, $[M]^+$), 159 (8), 141 (100), 119 (89), 104 (41), 79 (30).
HRMS for $C_{15}H_{13}NO_2F_2$ $[M]^+$: 277.0914, found: 277.0889.

5.2 Products from the S_N2' allylic substitution: Unsaturated nitriles

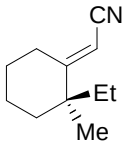
(2*S*,*E*)-2-(2-methyl-2-pentylcyclohexylidene) acetonitrile ((*S*)-79b):



Prepared according to **TP1** from (*S*)-**77c** (650 mg, 2.25 mmol), CuCN·2LiCl (1.0 M in THF, 2.7 mL, 2.7 mmol), $Pent_2Zn$ (4.8 M in THF, 1.12 mL, 5.4 mmol), NMP (4.0 mL) and THF (1.5 mL). The resulting mixture was stirred at –30 °C to 0 °C for 5 h. Purification by flash chromatography (pentan/Et_2O, 98:2) afforded (*S*)-**79b** as a pale yellow oil (346 mg, 1.68 mmol, 75 %, 96 % *ee*). The *ee* was determined by GC analysis.

$[\alpha]_D^{20}$ = – 37.8 (c = 0.72, $CHCl_3$)
GC (Chirasil-Dex CB), 100 °C (5 min), ramp of 2 °C/ min to 140 °C; t_R(min) = 29.07 (*R*), 29.33 (*S*).
^{1}H-NMR (600 MHz, $CDCl_3$): δ = 5.02 (s, 1H), 2.81-2.77 (m, 2H), 2.28-2.22 (m, 2H), 1.87-1.83 (m, 2H), 1.71-1.64 (m, 6H), 1.57-1.20 (m, 4H), 1.02 (s, 3H), 0.87(t, ^3J = 7.2 Hz, 3H).
^{13}C-NMR (150 MHz, $CDCl_3$): δ = 174.5, 117.6, 91.9, 41.1, 40.3, 37.6, 32.4, 30.4, 27.8, 24.9, 23.3, 22.5, 21.2, 14.0.
IR (neat, ν/cm^{-1}): 2928, 2856, 2214, 1739, 1613, 1500, 1453, 1379, 1325, 1228, 995, 820.
MS (EI, 70 eV): *m/z* (%) = 205 (9, $[M]^+$), 190 (14), 176 (12), 148 (15), 134 (100), 107 (46), 93 (25), 79 (25), 55 (16), 43 (26).
HRMS for $C_{13}H_{21}N$ $[M]^+$: 205.1830, found: 205.1842.

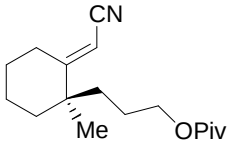
(2*S*,*E*)-2-(2-ethyl-2-methylcyclohexylidene) acetonitrile ((*S*)-79c):



Prepared according to **TP1** from (*S*)-**77c** (650 mg, 2.25 mmol), CuCN·2LiCl (1.0 M in THF, 2.7 mL, 2.7 mmol), Et_2Zn (0.54 mL, 5.40 mmol), NMP (4.0 mL) and THF (1.5 mL). The resulting mixture was stirred at –30 °C to 0 °C for 5 h. Purification by flash chromatography (pentan/Et_2O, 98:2) afforded (*S*)-**79c** as a pale yellow oil (238 mg, 1.46 mmol, 65 %, 96 % *ee*). The *ee* was determined by GC analysis.

$[\alpha]_D^{20}$ = – 72.8 (c = 0.48, $CHCl_3$)
GC (Chirasil-Dex CB), 100 °C (5 min), ramp of 2 °C/ min to 140 °C; t_R(min) = 18.87 (*S*), 19.65 (*R*).
^{1}H-NMR (600 MHz, $CDCl_3$): δ = 5.03 (s, 1H), 2.79 (dt, ^3J = 4.1 Hz, ^2J = 14.05 Hz, 1H), 2.31-2.20 (m, 1H), 1.88-1.24 (m, 8H) 1.02 (s, 3H), 0.72(t, ^3J = 7.5 Hz, 3H)
^{13}C-NMR (150 MHz, $CDCl_3$): δ = 174.3, 117.6, 92.1, 41.3, 39.9, 30.4, 30.0, 27.7, 24.3, 21.3, 8.0.
IR (neat, ν/cm^{-1}): 2963, 2862, 2215, 1613, 1449, 1383, 816.
MS (EI, 70 eV): *m/z* (%) = 163 (19) [M^+], 148 (19), 134 (100), 107 (36), 93 (21), 79 (25), 68 (13), 55 (10).
HRMS for$C_{10}H_{15}N$ [$M]^+$: 163.1361, found: 163.1350.

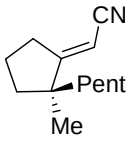
(2*R*,*E*)-3-(2-(cyanomethylene)-1-methylcyclohexyl) propyl pivalate ((*R*)-79d):



Prepared according to **TP1** from (*S*)-**77c** (583 mg, 2.0 mmol), CuCN·2LiCl (1.0 M in THF, 2.4 mL, 2.4 mmol), [$PivO(CH_2)_3]_2Zn$ (1.4 M in THF, 3.4 mL, 4.8 mmol), NMP (3.7 mL) and THF (1.5 mL). The resulting mixture was stirred at –30 °C to rt for 24 h. Purification by flash chromatography (pentan/Et_2O, 98:2) afforded (*S*)-**79d** as a pale yellow oil (360 mg, 1.3 mmol, 65 %, 96 % *ee*).

$[\alpha]_D^{20}$ = – 17.5 (c = 0.43, $CHCl_3$)
GC (Chirasil-Dex CB), 100 °C (5 min), ramp of 2 °C/ min to 160 °C; t_R(min) = 56.54 (*S*), 57.34 (*R*).
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 5.09 (s, 1H), 4.01 (t, ^3J = 6.2 Hz, 2H), 2.81 (dt, ^3J = 4.2 Hz, ^2J = 14.8 Hz, 1H), 2.30-2.20 (m, 1H), 1.90-1.25 (m, 12H), 1.19 (s, 9H), 1.05 (s, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 178.4, 173.6, 117.3, 92.6, 64.3, 40.7, 40.2, 38.7, 33.7, 30.4, 27.2, 24.8, 23.2, 21.2.
IR (neat, ν/cm^{-1}): 2933, 2867, 2214, 1725, 1613, 1453, 1283, 1152, 732.
MS (EI, 70 eV): *m/z* (%) = 277 (3, [$M]^+$), 193 (22), 175 (29), 147 (32), 134 (73), 85 (32), 57 (100), 41 (29).
HRMS for $C_{17}H_{27}NO_2$ [$M]^+$: 277.2042, found: 277.2017.

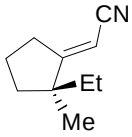
(2*S*,*E*)-2-(2-Methyl-2-pentylcyclopentylidene) acetonitrile ((*S*)-79e):



Prepared according to **TP1** from (*S*)-**77d** (610 mg, 2.2 mmol), CuCN·2LiCl (1.0 M in THF, 2.6 mL, 2.64 mmol), $Pent_2Zn$ (1.1 mL, 5.28 mmol), NMP (2.6 mL), THF (1.5 mL). The resulting mixture was stirred at –30 °C to 0 °C for 2 h. Purification by flash chromatography (pentan/Et_2O, 9:1) afforded (*S*)-**79e** as a pale yellow oil (382 mg, 2.0 mmol, 91 %, 90 % *ee*). The *ee* was determined by GC analysis.

$[\alpha]_D^{20}$ = – 15.9 (c = 1.49, $CHCl_3$).
GC (Chirasil-Dex CB), 100 °C (5 min), ramp of 2 °C/ min to 140 °C; t_R(min) = 23.45 (*R*), 23.93 (*S*).
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 5.02 (t, ^3J = 2.55 Hz, 1H), 2.81-2.56 (m, 2H), 1.78-1.66 (m, 2H), 1.66-1.53 (m, 2H), 1.34-1.16 (m, 8H), 1.04 (s, 3H), 0.87 (t, ^3J = 6.75 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 181.9, 117.9, 89.9, 47.6, 40.4, 38.9, 34.0, 32.6, 26.1, 24.4, 22.7, 22.1, 14.3.
IR (neat, ν/cm^{-1}): 2928, 2862, 2214, 1629, 1456, 1374, 806.
MS (EI, 70 eV): *m/z* (%) = 191 (8, $[M]^+$), 176 (11), 162 (8), 148 (12), 121 (89), 120 (100), 106 (12), 93 (23), 79 (25).
HRMS for $C_{13}H_{21}N$ $[M]^+$: 191.1674, found: 191.1651.

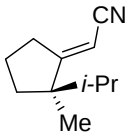
(2*S*,*E*)-(2-ethyl-2-methylcyclopentylidene) acetonitrile ((*S*)-79f):



Prepared according to **TP1** from (*S*)-**77d** (1.386 g, 5.0 mmol), CuCN·2LiCl (1.0 M in THF, 6.0 mL, 6.0 mmol), Et_2Zn (1.2 mL, 12.0 mmol), NMP (5.1 mL) and THF (3 mL). The resulting mixture was stirred at –30 °C to 0 °C for 2 h. Purification by flash chromatography (pentan/Et_2O, 9:1) afforded (*S*)-**79f** as a pale yellow oil (0.600 g, 4.0 mmol, 80 %). The *ee* was determined by GC analysis.

$[\alpha]_D^{20}$ = – 23.8 (c = 1.12, $CHCl_3$).
GC (Chirasil-Dex CB), 70 °C (1 min), ramp of 1 °C/ min to 100 °C; t_R(min) = 37.09 (*S*), 38.74 (*R*).
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 5.03 (t, ^3J = 2.86 Hz, 1H,), 2.83-2.59 (m, 2H), 1.80-1.71 (m, 4H), 1.46-1.38 (q, ^3J = 7.62 Hz, 2H), 1.05 (s, 3H), 0.85 (t, ^3J = 7.62 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 181.7, 117.9, 89.9, 47.9, 38.4, 34.1, 32.7, 25.6, 22.1, 9.0.
IR (neat, ν/cm^{-1}): 2961, 2878, 2214, 1635, 1459, 1382, 1168, 1006, 806.
MS (EI, 70 eV): *m/z* (%) = 149 (9, $[M]^+$), 134 (8), 120 (100), 93 (21), 79 (15).
HRMS for$C_{10}H_{15}N$ $[M]^+$: 149.1204, found: 149.1200.

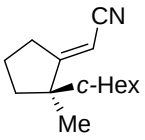
(2*R*,*E*)-(2-Isopropyl-2-methylcyclopentylidene) acetonitrile ((*R*)-79g):



Prepared according to **TP1** from (*S*)-**77d** (277 mg, 1.0 mmol), CuCN·2LiCl (1.0 M in THF, 1.2 mL, 1.2 mmol), *i*Pr_2Zn (0.40 mL, 5.9 M in Et_2O, 2.4 mmol), NMP (1.3 mL) and THF (1.0 mL). The resulting mixture was stirred at –30 °C to 0 °C for 2 h. Purification by flash chromatography (pentan/Et_2O, 9:1) afforded (*R*)-**79g** as a pale yellow oil (122 mg, 0.75 mmol, 75 %, 90 % *ee*). The *ee* was determined by GC analysis.

$[\alpha]_D^{20}$ = – 58.7 (c = 1.15, $CHCl_3$).
GC (Chirasil-Dex CB), 100 °C (5 min), ramp of 2 °C/ min to 140 °C; t_R(min) = 17.16 (*S*), 17.80 (*R*).
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 5.02 (t, ^3J = 2.8 Hz, 1H), 2.88-2.76 (m, 1H), 2.56-2.42 (m, 1H), 1.85-1.58 (m, 4H), 1.45-1.34 (m, 1H), 1.02 (s, 3H), 0.88 (d, ^3J = 6.77 Hz, 3H), 0.79 (d, ^3J = 6.77 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 182.0, 118.0, 90.1, 51.1, 35.2, 35.1, 34.4, 25.6, 22.4, 18.1.
IR (neat, ν/cm^{-1}): 2961, 2875, 2214, 1709, 1623, 1464, 1375, 1007, 794.
MS (EI, 70 eV): *m/z* (%) = 163 (0.35, $[M]^+$), 121 (100), 120 (42), 106 (15), 79 (10).
HRMS for $C_{11}H_{13}N$ $[M]^+$: 163.1361, found: 163.1359.

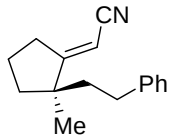
(2*R*,*E*)-(2-cyclohexyl-2-methylcyclopentylidene) acetonitrile ((*R*)-79h):



Prepared according to **TP1** from (*S*)-**77d** (330 mg, 1.2 mmol), CuCN·2LiCl (1.0 M in THF, 1.45 mL, 1.45 mmol), *c*-Hex_2Zn (1.0 M in THF, 2.9 mL, 2.9 mmol), NMP (3.0 mL) and THF (1.5 mL). The resulting mixture was stirred at –30 °C to 0 °C for 5 h. Purification by flash chromatography (pentan/Et_2O, 9:1) afforded (*R*)-**79h** as a pale yellow oil (145 mg, 0.72 mmol, 60 %, 90 % *ee*). The *ee* was determined by GC analysis.

$[\alpha]_D^{20}$ = – 6.3 (c = 0.73, $CHCl_3$).
GC (Chirasil-Dex CB), 100 °C (5 min), ramp of 2 °C/ min to 140 °C; t_R(min) = 38.48 (*R*), 39.36 (*S*).
^{1}H-NMR (600 MHz, $CDCl_3$): δ = 5.00 (t, ^3J = 2.2 Hz, 1H), 2.84-2.79 (m, 1H), 2.47 (d quint., ^3J = 2.93 Hz, ^3J = 8.88 Hz, 1H), 1.87-1.53 (m, 9H), 1.41-1.37 (m, 1H), 1.28-1.06 (m, 5H), 1.02 (s, 3H), 0.88-0.98 (m, 2H).
^{13}C-NMR (150 MHz, $CDCl_3$): δ = 182.0, 118.0, 90.1, 50.9, 46.0, 35.4, 35.1, 27.9, 27.0, 26.9, 26.6, 25.6, 22.5.
IR (neat, ν/cm^{-1}): 2928, 2851, 2214, 1626, 1448, 1374, 811.
MS (EI, 70 eV): *m/z* (%) = 203 (1, $[M]^+$), 121 (100), 94 (3), 83 (8), 79 (4), 77 (3), 55 (16).
HRMS for $C_{14}H_{21}N$ $[M]^+$: 203.1674, found: 203.1656.

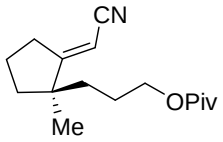
(2*R*,*E*)-(-2-Methyl-2-phenethylcyclopentylidene) acetonitrile ((*R*)-79i):



Prepared according to **TP1** from (*S*)-**77d** (138 mg, 0.5 mmol), CuCN·2LiCl (1.0 M in THF, 0.6 mL, 0.6 mmol), $[Ph(CH_2)_2]_2Zn$ (1.5 M in THF, 0.80 mL, 1.2 mmol), NMP (1.0 mL) and THF (1.0 mL). The resulting mixture was stirred at –30 °C to rt for 36 h. Purification by flash chromatography (pentan/Et_2O, 9:1) afforded (*R*)-**79i** as a pale yellow oil (45 mg, 0.2 mmol, 40 %, 90 % *ee*). The *ee* was determined by GC analysis.

$[\alpha]_D^{20}$ = – 5.8 (c = 0.69, $CHCl_3$).
GC (Chirasil-Dex CB), 100 °C (5 min), ramp of 2 °C/ min to 160 °C; t_R(min) = 49.21 (*R*), 50.24 (*S*).
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.31-7.14 (m, 5H), 5.09 (t, ^3J = 2.55 Hz, 1H), 2.91-2.46 (m, 4H), 1.88-1.58 (m, 6H), 1.14 (s, 3H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 181.4, 142.2, 128.7, 128.4, 126.2, 117.8, 90.3, 47.7, 42.5, 38.9, 34.0, 31.3, 26.1, 22.2.
IR (neat, ν/cm^{-1}): 3026, 2958, 2864, 2214, 1631, 1603, 1496, 1454, 806, 739, 698.
MS (EI, 70 eV): *m/z* (%) = 225 (12, $[M]^+$), 121 (16), 134 (9), 105 (100), 104 (63), 91 (64), 79 (18), 77 (18), 65 (15).
HRMS for $C_{16}H_{19}N$ $[M]^+$: 225.1517, found: 225.1487.

(2*R*,*E*)-3-(-2-(Cyanomethylene)-1-methylcyclopentyl) propyl pivalate ((*R*)-79j):

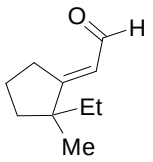


Prepared according to **TP1** from (*S*)-**77d** (1.22 g, 4.40 mmol), CuCN·2LiCl (1.0 M in THF, 5.30 mL, 5.28 mmol), $[PivO(CH_2)_3]_2Zn$ (1.4 M in THF, 7.54 mL, 10.56 mmol), NMP (7.4 mL) and THF (2.0 mL). The resulting mixture was stirred at –30 °C to rt for 36 h. Purification by flash chromatography (pentan/Et_2O, 9:1) afforded (*R*)-**79j** as a pale yellow oil (640 mg, 2.43 mmol, 71 %, 90 % ee). The *ee* was determined by GC analysis.

$[\alpha]_D^{20}$ = – 12.9 (c = 0.56, $CHCl_3$).
GC (Chirasil-Dex CB), 100 °C (5 min), ramp of 2 °C/ min to 160 °C; t_R(min) = 45.65 (*S*), 46.64 (*R*).
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 5.04 (t, ^3J = 2.48 Hz, 1H), 4.10-4.00 (m, 2H), 2.84-2.55 (m, 2H), 1.80-1.67 (m, 3H), 1.62-1.52 (m, 3H), 1.48-1.40 (m, 2H), 1.19 (s, 9H), 1.07 (s, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 181.1, 178.7, 117.7, 90.4, 64.5, 47.3, 39.0, 38.8, 36.4, 33.9, 27.5, 26.1, 24.3, 22.1.
IR (neat, ν/cm^{-1}): 2960, 2872, 2215, 1724, 1633, 1480, 1460, 1284, 1150, 1034.
MS (EI, 70 eV): *m/z* (%) = 263 (0.57; $[M]^+$), 179 (6), 161 (9), 146 (15), 133 (22), 120 (36), 119 (14), 93 (12), 85 (17), 79 (14), 57 (100).
HRMS for $C_{16}H_{25}NO_2$ $[M]^+$: 263.1877, found: 263.1885.

5.3 Derivatization of the unsaturated nitriles

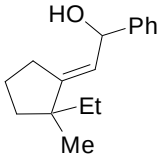
(2-Ethyl-2-methylcyclopentylidene) acetaldehyde (84): [101]



To a solution of **77d** (149 mg, 1.0 mmol, 1.0 equiv.) in toluene (5.0 mL) was added DIBAL-H (1.0 M in toluene, 1.2 mL, 1.2 mmol, 1.2 equiv.) at −78 °C and the mixture was stirred for 3 h. Ethyl acetate was added to quench the excess of DIBAL-H. After filtration the aqueous phase was extracted 3 x with Et_2O. The combined organic phases were washed with brine, dried over $MgSO_4$ and the solvent was evaporated under vacuo. Purification by flash chromatography (pentan/Et_2O, 9:1) afforded **84** as a colourless oil (95 mg, 0.62 mmol, 62 %).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.88 (d, ^3J = 8.00 Hz, 1H), 5.79 (dt, ^4J = 2.40 Hz, ^3J = 7.98 Hz, 1H), 3.04-2.96 (m, 1H), 2.83-2.74 (m, 1H), 1.84-1.65 (m, 3H), 1.51-1.41 (m, 3H), 1.05 (s, 3H), 0.83 (t, ^3J = 7.48 Hz, 3H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 192.3, 180.9, 121.8, 48.2, 36.8, 32.5, 30.7, 25.5, 22.7, 8.8.
IR (neat, ν/cm^{-1}): 2961, 1733, 1675, 1457, 1153.
MS (EI, 70 eV): *m/z* (%) = 152 (11, $[M]^+$), 137 (8), 123 (100), 95 (16), 67 (10), 55 (8).
HRMS for$C_{10}H_{16}O$ $[M]^+$: 152.1201, found: 152.1196.

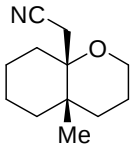
2-(2-Ethyl-2-methylcyclopentylidene)-1-phenylethanol (85):



To a solution of **84** (76mg, 0.5 mmol, 1 equiv.) in THF (5 mL) was added PhMgCl (0.55 mL, 1.04 M in THF, 0.55 equiv.) at 0 °C and stirred at rt for 2 hours. The reaction mixture was quenched with NH4Cl and the aqueous phase was extracted with Et_2O (3x), dried with MgSO4 and the solvent was evaporated under vacuo. Purification by flash chromatography (pentan/Et_2O, 9:1) afforded **85** as a colourless oil (100 mg, 0.62 mmol, 87 %).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.40-7.23 (m, 5H), 5.39-5.32 (m, 2H), 2.66-2.27 (m, 2H), 1.81-1.58 (m, 4H), 1.47-1.26 (m, 4H), 1.04 and 0.96 (2s, 3H), 0.86 and 0.74 (2t, ^3J = 7.48 Hz, 3H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 154.2, 144.1, 128.4, 127.2, 125.8, 121.9, 72.2, 45.6, 38.2, 33.0, 29.7, 26.1, 22.4, 9.1.
IR (neat, ν/cm^{-1}): 3422, 2843, 1676, 1455, 1383, 1160, 1024, 890.
MS (EI, 70 eV): *m/z* (%) = 230 (12, $[M]^+$), 212 (21), 183 (37), 120 (34), 110 (73), 105 (100), 81 (50), 77 (25).
HRMS for$C_{16}H_{22}O$ $[M]^+$: 230.1671, found: 230.1676.

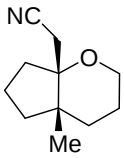
(4a-Methyl-octahydro-chromen-8a-yl) acetonitrile (86a):



To a solution of **77d** (221 mg, 0.8 mmol, 1.0 equiv.) in MeOH (5.0 mL) was added $LiOH \cdot H_2O$ (336 mg, 8.0 mmol, 10 equiv.) at rt and stirred for 1.5 h. The reaction mixture was quenched with water and the aqueous phase was extracted 3 x with Et_2O. The combined organic phases were washed with brine, dried over $MgSO_4$ and the solvent was evaporated under vacuo. Purification by flash chromatography (pentan/Et_2O, 9:1) afforded **86a** as a pale yellow oil (85 mg, 0.44 mmol, 55 %).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.87-3.82 (m, 1H), 3.66-3.60 (m, 1H), 2.76 (d, ^2J = 16.7 Hz, 1H), 2.67 (d, ^2J = 16.7 Hz, 1H), 1.75-1.32 (m, 12H), 0.91 (s, 3H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 117.1, 76.2, 61.3, 43.4, 35.3, 34.8, 27.46, 23.3, 21.9, 21.6, 21.4, 21.2.
IR (neat, ν/cm^{-1}): 2932, 2861, 2247, 1446, 1083, 1030.
MS (EI, 70 eV): *m/z* (%) = 192 (14, $[M-H]^+$), 178 (32), 153 (100), 137 (11), 97 (5), 85 (6), 67 (6), 55 (6).
HRMS for $C_{12}H_{18}NO$ $[M]^+$: 192.1388, found: 192.1390.

(4a-Methyl-hexahydro-cyclopenta[b]pyran-7a-yl) acetonitrile (86b):



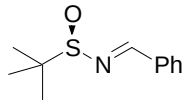
To a solution of **77j** (210 mg, 0.8 mmol, 1.0 equiv.) in MeOH (5.0 mL) was added $LiOH \cdot H_2O$ (336 mg, 8.0 mmol, 10 equiv.) at rt and stirred for 1.5 h. The reaction mixture was quenched with water and the aqueous phase was extracted 3 x with Et_2O. The combined organic phases were washed with brine, dried over $MgSO_4$ and the solvent was evaporated under vacuo. Purification by flash chromatography (pentan/Et_2O, 9:1) afforded **86b** as a pale yellow oil (90 mg, 0.5 mmol, 63 %).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 3.81-3.74 (m, 1H), 3.53-3.43 (m, 1H), 2.85 (d, ^2J = 16.8 Hz, 1H), 2.35 (d, ^2J = 16.8 Hz, 1H), 2.19-2.00 (m, 2H), 1.94-1.58 (m, 5H), 1.45-1.17 (m, 3H), 0.85 (s, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 117.8, 82.8, 61.8, 42.5, 36.5, 34.8, 30.2, 25.5, 21.3, 20.8, 18.9.
IR (neat, ν/cm^{-1}): 2961, 2862, 2247, 1648, 1555, 1475, 1110, 1075, 1025.
MS (EI, 70 eV): *m/z* (%) = 180 (2, $[M+H]^+$), 162 (2), 150 (2), 139 (100), 111 (15), 93 (15), 81 (12), 68 (36).
HRMS for $C_{11}H_{17}NO$ $[M+H]^+$: 180.1388, found: 180.1390.

6 Multi-component reaction with chiral sulfinimine

6.1 Preparation of the sulfinimines electrophiles

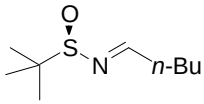
(*R*)-*N*-(Benzylidene)-tert-butansulfinamide ((*R*)-88a):



Prepared according to a procedure by *Ellman*.[108]

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.52 (s, 1H), 7.86-7.83 (m, 2H), 7.51-7.44 (m, 3H), 1.24 (s, 9H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 162.6, 134.0, 132.3, 129.2, 128.8, 57.6, 22.5.

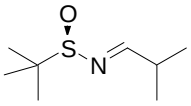
(*R*)-*N*-(Butylidene)-tert -butansulfinamide ((*R*)-88b):



Prepared according to a procedure by *Ellman*.[108]

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.05 (t, ^{3}J = 4.8 Hz, 1H), 2.53-2.47 (m, 2H), 1.61-1.54 (m, 2H), 1.40-1.33 (m, 2H), 1.17 (s, 9H), 0.93-0.87 (m, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 170.2, 56.8, 36.1, 27.6, 22.6, 22.4, 14.1.

(*R*)-*N*-(Benzylidene)-tert-butansulfinamide ((*R*)-88c):

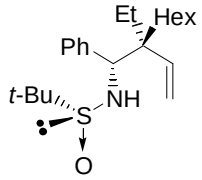


Prepared according to a procedure by *Ellman*.[108]

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.96 (d, ^{3}J = 4.2 Hz, 1H), 2.72-2.66 (m, 1H), 1.15 (s, 9H), 1.15-1.13 (m, 6H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 175.4, 58.2, 36.6, 24.1, 20.7.

6.2 Typical procedure of the preparation of homoallylic sulfinamide in the presence of lithium salt

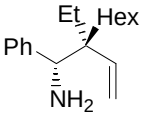
_N_-(2-Ethyl-2-hexyl-1-phenylbut-3-enyl)-tert-butansulfinamide (94a):



t-BuLi (1.3 mL, 1.7 M in pentane, 2.2 mmol, 2.2 equiv.) was added dropwise to a solution of vinyl iodide (226 mg, 1 mmol, 1 equiv.) in THF (8 mL) at −80 °C and stirred for another 15 min at this temperature. The reaction mixture is then warmed up to −40 °C and CuI (210 mg, 1.1 mmol, 1.1 equiv.) was added as a solid. The reaction was stirred for 30 minutes at −30 °C before (*R*)-**88a** (272 mg in 2 mL THF, 1.3 mmol, 1.3 equiv.), CH_2I_2 (0.48 mL, 6 mmol, 6 equiv.) and Et_2Zn (3 mL, 1.0 M in hexane, 3 mmol, 3 equiv.) were added consecutively at −50 °C. The reaction mixture was then warmed up to −30 °C and stirred for another 4 hours before NH_4Cl/NH_4OH (2:1) solution was added. The aqueous was extracted with EtOAc (3x), washed with NH_4Cl sat. sol., dried over Na_2SO_4 and the solvent was evaporated under vacuo. Purification by flash chromatography afforded **94a** in 72 % yield and > 95 % *de*.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.29-7.15 (m, 5H), 5.67 (2d, ^3J = 11.1 Hz, 1H), 5.29 (dd, ^3J = 11.1 Hz, ^4J = 1.5 Hz, 1H), 5.06 (dd, ^3J = 11.1 Hz, ^4J = 1.5 Hz, 1H), 4.13 (d, ^3J = 10.5 Hz, 1H), 3.66 (d, ^3J = 10.5 Hz, 1H), 1.85-1.70 (m, 1H), 1.60-1.45 (m, 1H), 1.27-1.09 (m, 19H), 0.88-0.78 (m, 6H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 141.9, 139.7, 128.3, 127.3, 126.9, 115.7, 63.9, 56.1, 46.5, 33.2, 31.3, 29.4, 23.1, 22.9, 22.2, 13.5, 6.9.
HRMS for$C_{22}H_{37}NOS$ $[M]^+$: 363.2596, found: 363.2590.

2-Ethyl-2-hexyl-1-phenylbut-3-enylamine (95): [108]



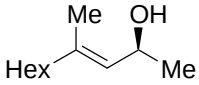
HCl (1 mL, 4 M in dioxane) was added to a solution of the 95a (ca. 0.5 mmol) in MeOH (1 mL) and stirred at rt for 30 minutes. The reaction mixture was evaporated under vacuo and the residue was taken up in Et_2O and washed 3 x with sat. sol. of $NaHCO_3$, dried over Na_2SO_4 and the solvent was evaporated under vacuo. It afforded the pure **95** as a single diastereomer.

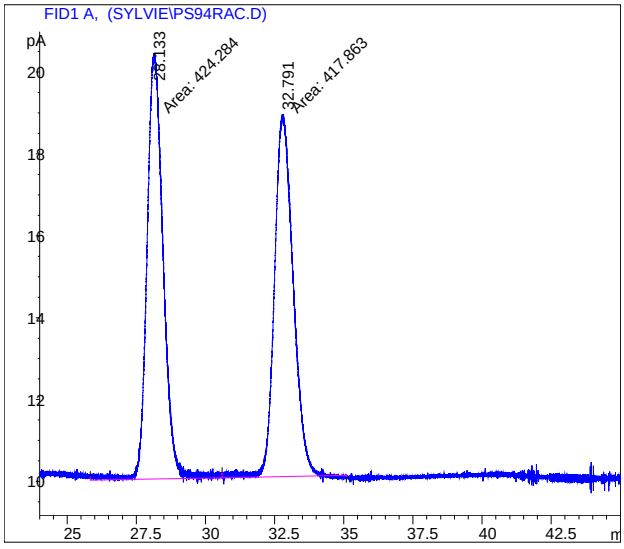
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.28-7.17 (m, 5H), 5.61 (2d, ^3J = 11.1 Hz, 1H), 5.22 (dd, ^3J = 11.1 Hz, ^4J = 1.8 Hz, 1H), 4.98 (dd, ^3J = 11.1 Hz, ^4J = 1.8 Hz, 1H), 3.80 (br. s, 1H), 1.90 (br. s, 2H), 1.80-1.75 (m, 1H), 1.59-1.39 (m, 1H), 1.27-1.13 (m, 10H), 0.90-0.80 (m, 6H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 143.2, 142.2, 128.3, 127.5, 126.4, 115.5, 60.0, 46.2, 33.6, 31.8, 30.0, 29.6, 23.5, 22.6, 14.1, 7.6.
HRMS for$C_{17}H_{29}N$ $[M-H]^+$: 258.2222, found: 258.2216.

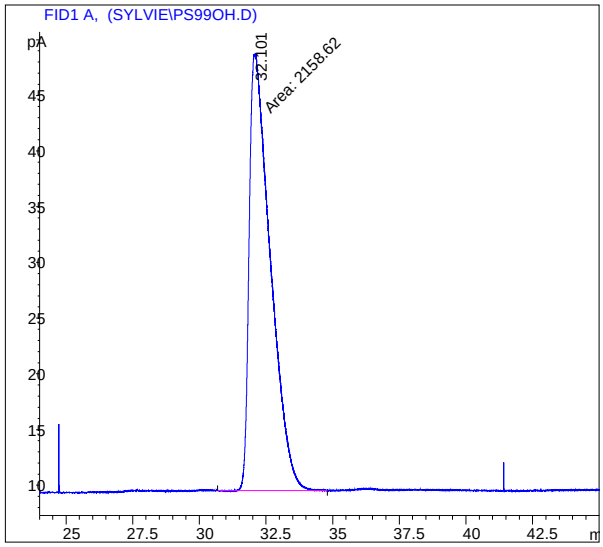
7 Appendix: Selected Chiral Chromatograms for determination of the *ee*

(2*S*,*E*)-4-Methyldec-3-en-2-ol ((*S*)-45):

GC (Chiraldex B-PH), 100 °C constant.

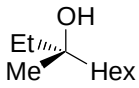


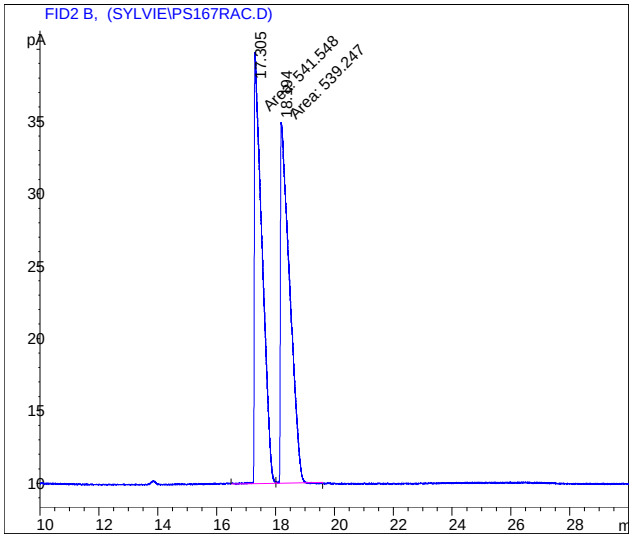


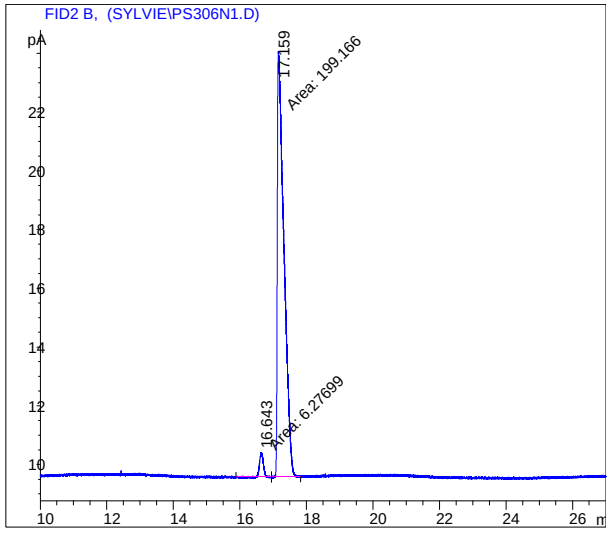


(3*S*)-3-Methylnonan-3-ol ((*S*)-38b):

GC (Chirasil-Dex CB), 90 °C constant.

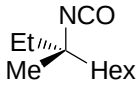


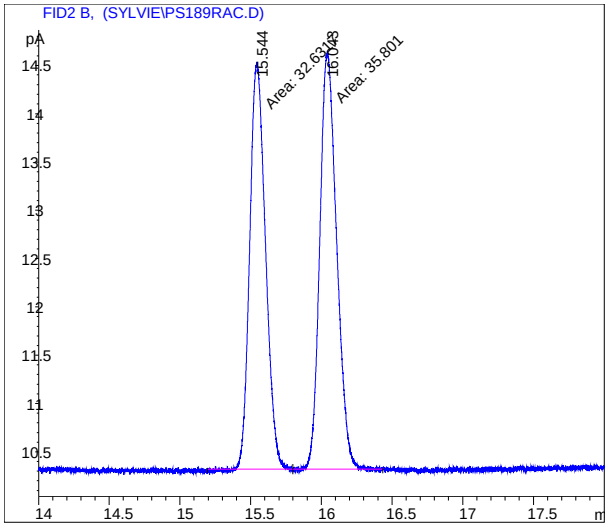


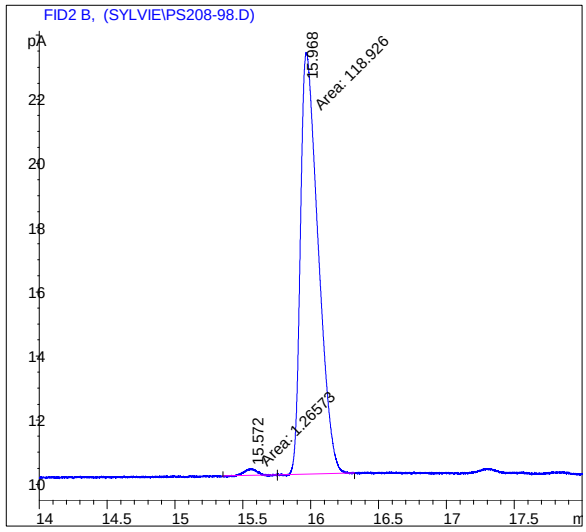


(3*S*)-3-Isocyanato-3-methylnonane ((*S*)-40a):

GC (Chirasil-Dex CB), 90 °C constant.

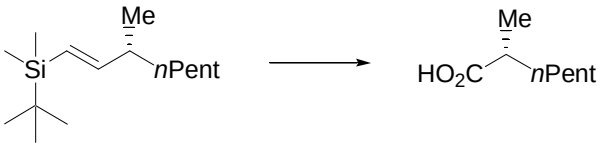


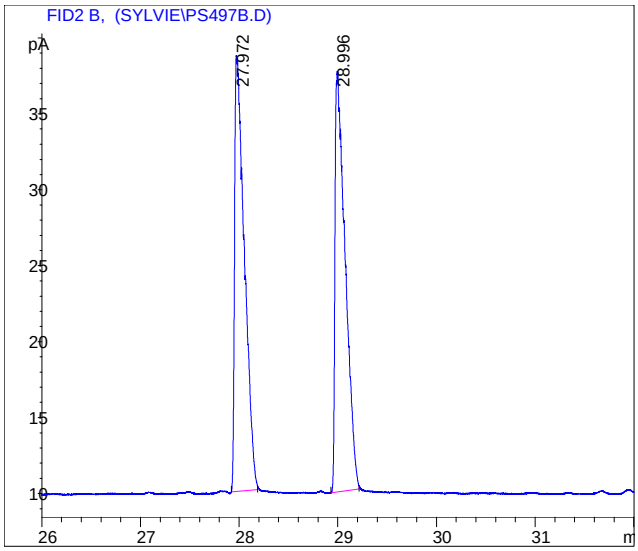


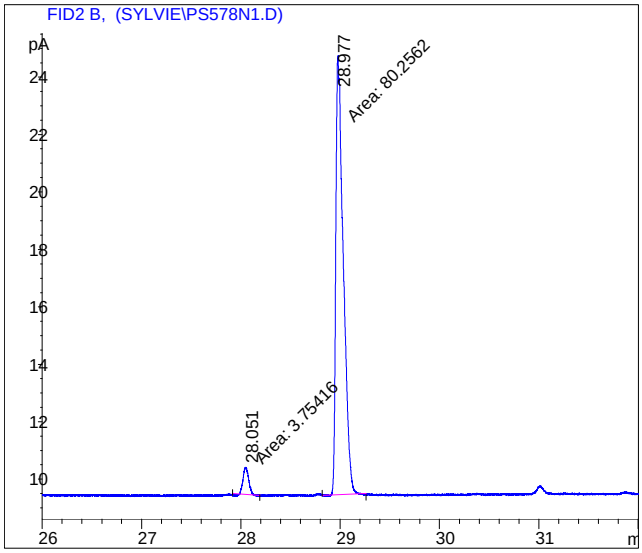


(2*R*)-2-Methylheptanoic acid: determination of the *ee* for (*R*)-**72a**

GC (Chirasil-Dex CB), 70 °C (1 min), ramp of 2 °C/min to 140 °C.

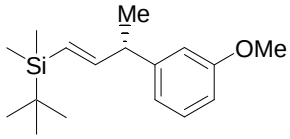


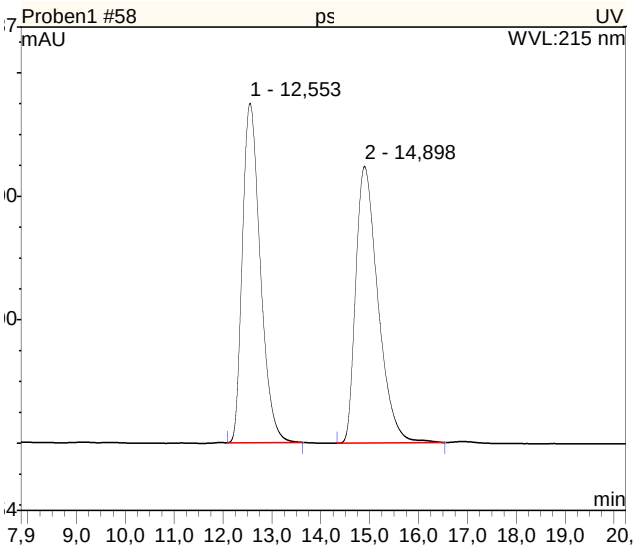


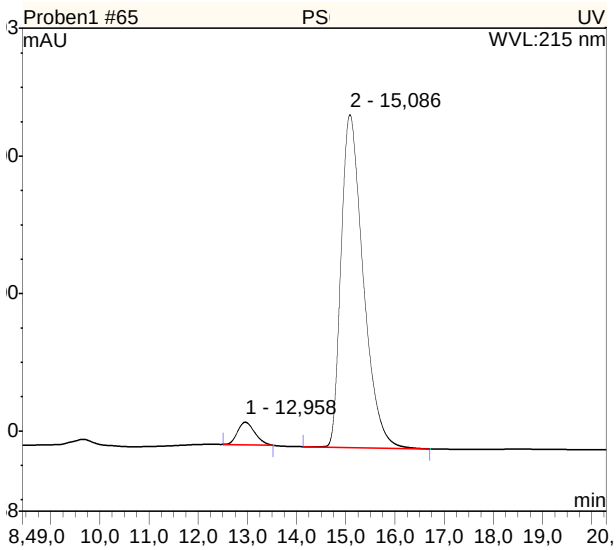


(3*S*,1*E*)-tert-Butyl-[3-(3-methoxy-phenyl)-but-1-enyl]-dimethyl silane ((*S*)-65f):

HPLC (OD-H), *n*-heptane 100 %, 0.5 mL/min.

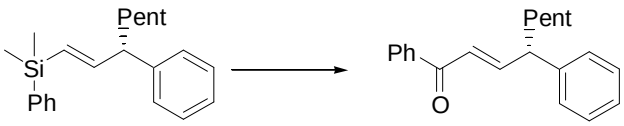


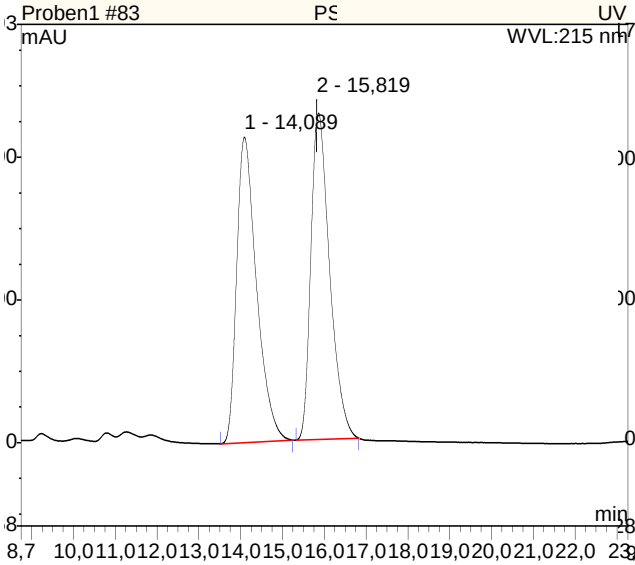


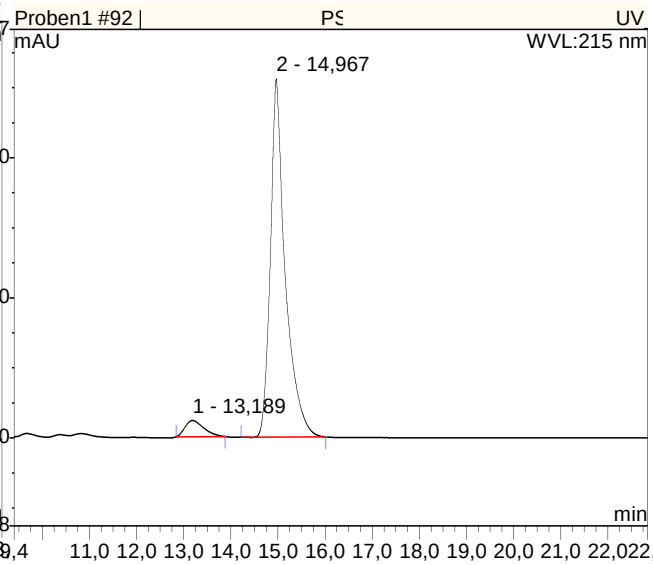


(4*S*,2*E*)-1,4-Diphenylnon-2-en-1-one (67j): determination of the *ee* for **65l**

HPLC (column: OD-H), *n*-heptane/*i*-PrOH 98:2, 0.5 mL/min.

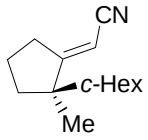


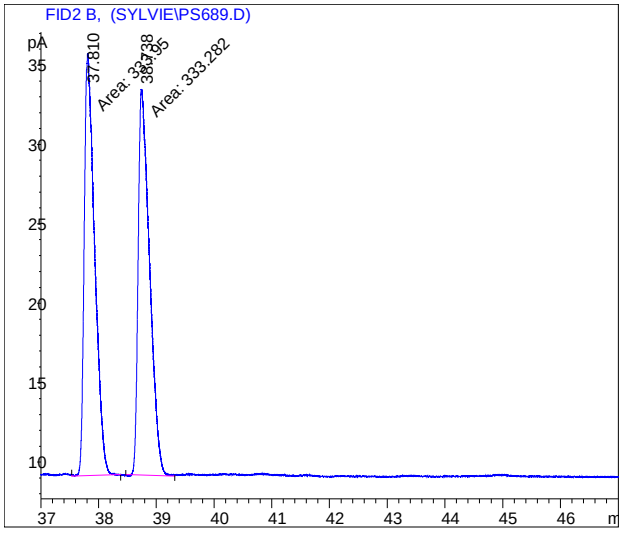


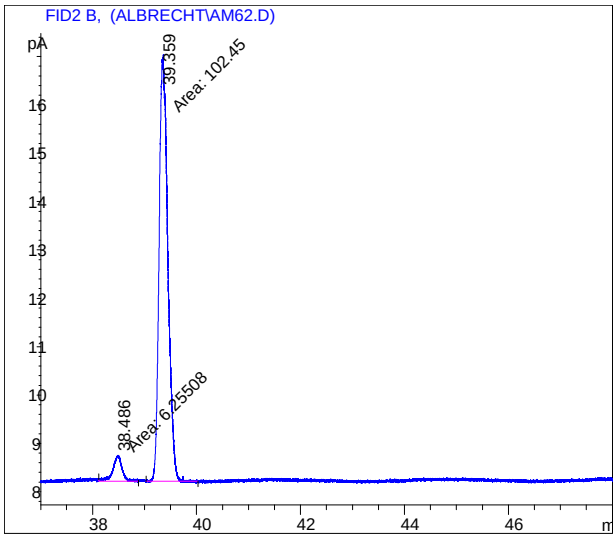


(2*R*,*E*)-(-2-Cyclohexyl-2-methylcyclopentylidene) acetonitrile ((*R*)-79h):

GC (Chirasil-Dex CB), 100 °C (5 min), ramp of 2 °C/min to 140 °C.

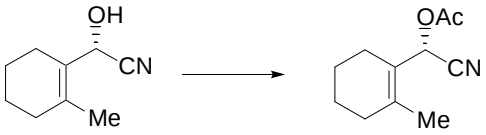


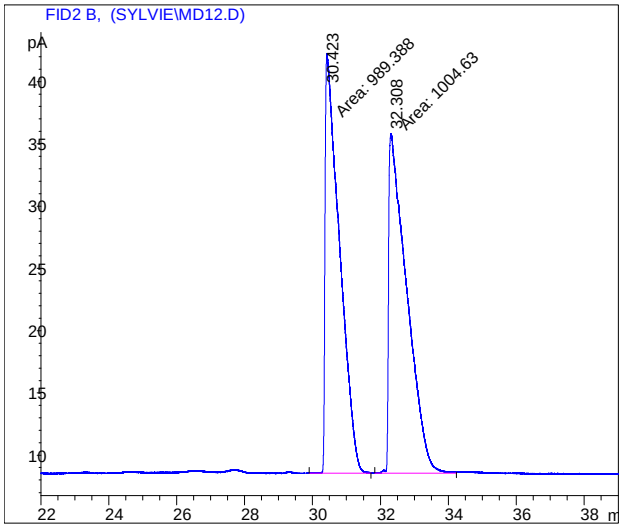


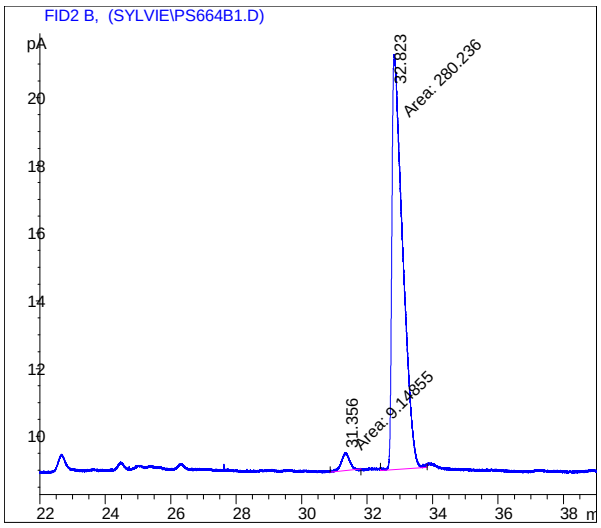


(2*S*)-Cyano(2-methylcyclohex-1-enyl) methyl acetate: determination of the ee for (*S*)-**78b**

GC (Chirasil-Dex CB), 100 °C constant.







Curriculum Vitae

Name:	Sylvie Perrone	Marital Status:	Single
Date of Birth:	June, 28th 1978	Mother language:	French
Nationality:	Dual Swiss and Italian	Other language:	Italian (bilingual)
Place of birth:	Geneva, Switzerland		English (fluent)
			German (fluent)

EDUCATION

Nov./2003-Dec./2006	**Ludwig-Maximilians-Universität** **Department Chemie und Biochemie** Ph.D. under the supervision of Prof. Dr. Paul Knochel	München, D
Oct./2001-July/2003	**University of Geneva** **Department of Chemistry** Post-graduate degree in chemistry "Diplôme de Chimiste"	Geneva, CH
Oct./1997-Mai/2001	**University of Geneva** **Department of Chemistry** Graduate degree in chemistry "Licence ès Sciences Chimiques"	Geneva, CH
Sept./1993-June/1997	**Collège Rousseau** High School degree with distinction (Maturité Fédérale type D)	Geneva, CH

RESEARCH AND WORK EXPERIENCE

Since Nov./2003	**Ludwig-Maximilians-Universität** **Department of Organic Chemistry** Ph.D. under the supervision of Prof. Dr. Paul Knochel Topic: Copper(I)-mediated *anti*-S_N2' allylic substitution reactions with diorganozinc reagents. Teaching assistant in the organic chemistry practical courses for undergraduate students.	München, D
May-June/2005	**Technion Institute of Technology** 2 month exchange program in the research group of Prof Dr. Ilan Marek Topic: Multi-component reactions for the diastereoselective synthesis of chiral quaternary centres based on chiral sulfoxides.	Haifa, Il
Nov./2002-Feb./2003	**University of Geneva** **Department of Organic Chemistry** Diploma work under the supervision of Prof. Dr. Ernst Peter Kündig Topic: Synthesis of enediynes using arene-$Cr(CO)_3$ complexes and attempt toward Bergman cyclization	Geneva, CH

Nov./2001-Oct./2002 **Serono Pharmaceutical Research Institute** Geneva, CH
Department of Medicinal Chemistry
One year student research program.
Topic: Synthesis of photoaffinity labelling probes of sulfonamides based on benzophenone and diazirine photoprobes for JNK3

PUBLICATIONS

1. H. Leuser, S. Perrone, F. Liron, F. F. Kneisel, P. Knochel, "Highly Enantioselective Preparation of Alcohols and Amines Attached to a Tertiary Center *via* Copper-mediated Diastereoselective Allylic S_N2'-Substitutions", *Angew. Chem. Int. Ed.* **2005**, *44*, 4627-4631.

2. S. Perrone, P. Knochel, "Highly Enantioselective Preparation of (*E*)-Alkenylsilanes bearing an α-Chiral Center", *Org. Lett.* **2006**, *submitted*

3. S. Perrone, A. Metzger, P. Knochel, "Chiral Cyanohydrins as Efficient Building Blocks for Copper(I)-mediated S_N2' Allylic Substitutions", *manuscript in preparation*.

4. S. Perrone, T. Rückle, J.-P. Gotteland, "Synthesis of Photoaffinity Labelling Probes of Sulfonamides Based on Benzophenone and Diazirine Photophores for JNK3", *J. Med. Chem.* **2006**, *submitted*.

5. P. Knochel, H. Leuser, L.-Z. Gong, S. Perrone, F. F. Kneisel, "Polyfunctional Zinc Organometallics for Organic Synthesis", *in* Handbook of Functionalized Organometallics, Chapter 7, Ed. P. Knochel, Wiley-VCH, Weinheim, **2005**.

6. P. Knochel, H. Leuser, L.-Z. Gong, S. Perrone, F. F. Kneisel, "Functionalized Organozinc Compounds", *in* The Chemistry of Organozinc Compounds, Chapter 8, Patai Series, Eds. Z. Rappoport, I. Marek, John Wiley & Sons, Chichester, **2006**.

7. P. Knochel, S. Perrone, N. Grenouillat, "Zinc and Cadmium", *in* Comprehensive Organometallic Chemistry III, Vol. 9, Chapter 4, Ed. P. Knochel, Elsevier, **2006**, *in press*.

POSTERS AND ORAL COMMUNICATION

1. S. Perrone and P. Knochel, "Synthesis of Enantiomerically enriched Tertiary Alcohols and Amines by Zn/Cu-mediated Allylic Substitution Reactions" (Poster), **3rd Industrie Tag**, Munich, Germany, 15th October, 2004.

2. S. Perrone and P. Knochel, "Highly Enantioselective Preparation of Tertiary Alcohols and Amines *via* Copper-mediated Diastereoselective Allylic Substitution" (Poster P366, Poster award), 13th International Symposium on Organometallic Chemistry directed Towards Organic Synthesis (**OMCOS-13**), Geneva, Switzerland, 17th-21st, July 2005.

3. S. Perrone and P. Knochel, "Copper-mediated Diastereoselective Allylic Substitution: An access to Highly Functionalized Molecules" (Oral Communication), 16th International Conference on Organic Synthesis (**ICOS-16**), Merida, Mexico, 11th-15th, June 2006.

4. S. Perrone and P. Knochel, "Highly Enantioselective Preparation of (*E*)-Vinyl silanes and Unsaturated Nitriles containing an α-Chiral Center *via* Copper(I)-mediated Allylic Substitutions" (Poster), **4th Industrie Tag**, Munich, Germany, 5th October, 2006.