Dissertation zur Erlangung des Doktorgrades
der Fakultät für Chemie und Pharmazie
der Ludwig-Maximilians-Universität München

Copper(I)-Mediated Regio- and Stereoselective Allylic Substitutions and Their Applications to Natural Product Syntheses

Von

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München 2006

Erklärung

Diese Dissertation wurde im Sinne von § 13 Abs. 3 bzw. 4 der Promotionsordnung vom 29. Januar 1998 von Professor Dr. Paul Knochel betreut.

Ehrenwörtliche Versicherung

Diese Dissertation wurde selbständig, ohne unerlaubte Hilfe erarbeitet.

München, 6.11.2006

Darunee Soorukram

Dissertation eingereicht am 6.11.2006

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2. Gutachter: Prof. Dr. Thomas Lindel

Mündliche Prüfung am 4.12.2006

This work was carried out from June 2003 to July 2006 under the supervision of Professor Dr. Paul Knochel at the Department Chemie und Pharmazie of the Ludwig-Maximilians-Universität, München.

Firstly, I would like to express my appreciation to Prof. Dr. Paul Knochel for giving me the great opportunity to do my PhD in his group and for his encouragement throughout the course of this work.

I am grateful to Prof. Dr. Thomas Lindel for agreeing to be my "Zweigutachter", as well as Prof. Dr. Hans Rudolf Pfaendler, Prof. Dr. Konstantin Karaghiosoff and Prof. Dr. Manfred Heuschmann for their interest for this manuscript.

I also would like to thank Dr. Lutz Ackermann, Dr. Srinivas Reddy Dubbaka and Sylvie Perrone for the careful correction of this manuscript.

I thank Ludwig-Maximilians-Universität, München and the DFG for financial support.

Furthermore, I would like to thank all the students and post-docs who came and went throughout my PhD for their suggestions, support and friendships which have made my time in Germany an enjoyable and worthwhile experience. I would especially like to thank Dr. Tanasri Bunlaksananusorn, Dr. Isabel M. Calaza, Dr. Xiaoyin Yang, Dr. Ioannis Sapountzis, Dr. Nina Gommermann, Dr. Tobias Korn, Dr. Helena Leuser, Andrei Gavryshin, Murthy Cheemala, Christiane Kofink, Christina Despotopoulou, Christoph Rohbogner, Marc Morsin, Wenwei Lin, Ching-Yaun Liu, Sylvie Perrone, Armin Stoll, Christian Rahut, Hongjun Ren, Felix Kopp, Simon Matthe, Dr. Arkady Krasovskiy, Valeria Krasovskaya, Nadege Boudet, Ludwig Kaspar and Robert Born for their support and friendships.

I thank Vladimir Malakov and Beatrix Cammelade for their professional administrative assistance facilitates my life in the group and in Germany. I thank the analytical team, Dr. D. Stephenson, Dr. C. Dubler, Dr. W. Spahl, B. Tschuk, T. Bruck, H. Schulz and G. Kaser for their invaluable help, and also Yulia Tavik for the measurement of HPLC spectra.

Finally, none of this would have been possible without the constant love and encouragement of my family. I would like to thank them especially my mother, brother and sisters for their great love, kind understanding and unquestioning support, as well as my friends for their friendship and support throughout my time in Germany.

Parts of this Ph.D. thesis have been published

1. Calaza, I. M.; Yang, X.; Soorukram, D.; Knochel, P. "Stereoselective S_N2-Substitutions Using Polyfunctional Lithium Arylcuprates Prepared by an Iodine-Copper Exchange" *Org. Lett*. **2004**, *6*, 529.

2. Soorukram, D.; Knochel, P. "Enantioselective Synthesis of α-Ionone Derivatives Using an Anti S_N2' Substitution of Functionalized Zinc Organometallics" *Org. Lett.* **2004**, *6*, 2409.

3. Soorukram, D.; Knochel, P. "Copper-Catalyzed Preparation of Ketones Bearing a Stereogenic Center in α Position" *Angew. Chem. Int. Ed.* **2006**, *45*, 3686.

4. Soorukram, D.; Knochel, P. "A Practical Synthesis of Optically Active α-Substituted Ketones in High Enantiomeric Excess" *Synthesis (Accepted).*

5. Soorukram, D.; Knochel, P. "Formal Enantioselective Synthesis of (+)-Estrone" *Manuscript submitted for publication.*

6. Soorukram, D.; Metzger, A.; Knochel, P. "Copper(I)-Mediated Regio- and Stereoselective Allylic Substitutions and Applications to Natural Products Syntheses" *Manuscript in preparation.*

Table of Contents

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Experimental Part

1. General introduction

The continuous search for biologically active molecules in the pharmaceutical and agrochemical industries is one of the largest research areas, in which synthetic organic chemistry plays a fundamental role. Most biologically active molecules are synthesized in chemical laboratories and not extracted from plants, therefore there is a constant need for the development of new methods for selective carbon-carbon and carbon-heteroatom bond forming reactions. Such procedures should ideally be mild and highly tolerant towards a wide range of functional groups. The development of asymmetric metal-catalyzed reactions has played a significant role for the access to biologically relevant molecules. Among the most widely used reactions such as hydrogenations, [1] epoxidations [2] or dihydroxylations, [3] asymmetric allylic substitutions are also considered as a powerful method to access to biologically active molecules.

1.1 Transition metal-catalyzed allylic substitutions

Synthetic methods, which allow the stereoselective construction of a carbon skeleton in a predictable and reliable fashion, are of great value in organic synthesis. Among the methodologies that chemists use to create stereogenic centers, allylic substitution is of considerable importance. Transition metal-catalyzed (or -mediated) allylic substitutions are particularly important and have become versatile synthetic methodologies in contemporary

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[1] a) Rautenstrauch, V.; Hoang-Chong, X.; Churlaud, R.; Abdur-Rashid, K.; Morris, R. H. *Chem. Eur. J.* **2003**, *9*, 4954; b) Blaser, H.-U.; Malan, C.; Pugin, B.; Spindler, F.; Steiner, H.; Studer, M. *Adv. Synth. Catal.* **2003**, *345*, 103; c) Everaere, K.; Mortreux, A.; Carpentier, J.-F. *Adv. Synth. Catal.* **2003**, *345*, 67; d) Saluzzo, C.; Lemaire, M. *Adv. Synth. Catal.* **2002**, *344*, 915; e) Fan, Q. H.; Li, Y. M.; Chan, A. S. C. *Chem. Rev.* **2002**, *102*, 3385; f) Palmer, M. J.; Wills, M. *Tetrahedron Asymmetry* **1999**, *10*, 2045; g) Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97; h) Noyori, R. *Angew. Chem. Int. Ed.* **2002**, *41*, 2008.

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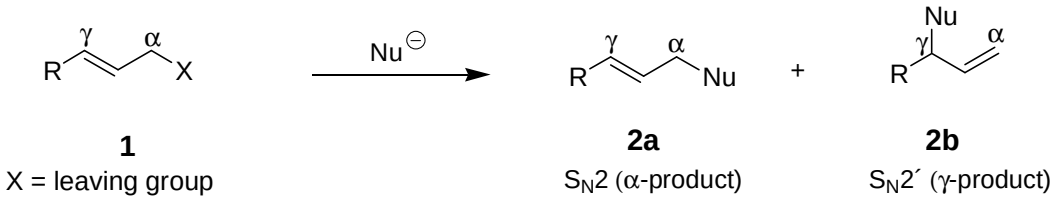
[3] For reviews, see: a) Kolb, H. C.; Van nieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev*. **1994**, *94*, 2483; b) Johnson, R. A. *Catalytic asymmetric dihydroxylation discovery and development*, in: *Catalytic Asymmetric Synthesis*, (Eds.; Ojima, I.; Sharpless, K. B.), VCH, New York, **2000**, 357; c) Wang, Z.-M.; Sharpless, K. B. *J. Org. Chem*. **1994**, *59*, 8302; d) Ahrgren, L.; Sutin, L. *Org. Process Res. Dev*. **1997**, *1*, 425; e) Lu, X.; Xu, Z.; Yang, G. *Org. Process Res. Dev.* **2000**, *4*, 575; f) Bolm, C.; Gerlach, A. *Eur. J. Org. Chem.* **1998**, 21 ; g) Song, C. E.; Lee, S. G. *Chem. Rev.* **2002**, *102*, 3495; h) Vos, D. E. D.; Dams, M.; Sels, B. F.; Jacobs, P. A. *Chem. Rev.* **2002**, *102*, 3615; i) Kolb, H. C.; Anderson, P. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1994**, *116*, 1278.

organic chemistry.[4] The allylic substitution of the substrate **1** with a carbon nucleophile can give two different products, the S_N2-product or α-product (**2a**) or the S_N2'-product or γ-product (**2b**) (Scheme 1). These two products are formed by the direct displacement of a leaving group in **1** through an S_N2 reaction affording **2a** or by the displacement of a leaving group in **1** involving an allylic shift of the double bond affording the regioisomer **2b** (Scheme 1).



Scheme 1. Regioselectivity of the allylic substitution reaction.

Because of this regioselectivity issue, the development of methods allowing a selective C–C bond formation have been extensively studied and it has been shown that the regioselectivities of these processes depend on a variety of factors: i.e. metal ion, ligand, nucleophile, leaving group and reaction conditions. A selective C–C bond formation at the γ-position has attracted more interest, since, in addition to the formation of a new C–C bond in the allylic substitution, a new stereogenic center is created (for Nu ≠ R, Nu ≠ vinyl and R ≠ H) (Scheme 1).

A variety of organometallic compounds undergo nucleophilic substitutions on allylic substrates. Palladium has been often used as a catalyst for these reactions. Palladium-catalyzed allylic substitutions and their asymmetric version have been extensively studied and widely used in a variety of total syntheses.[5] However, in spite of the success achieved with

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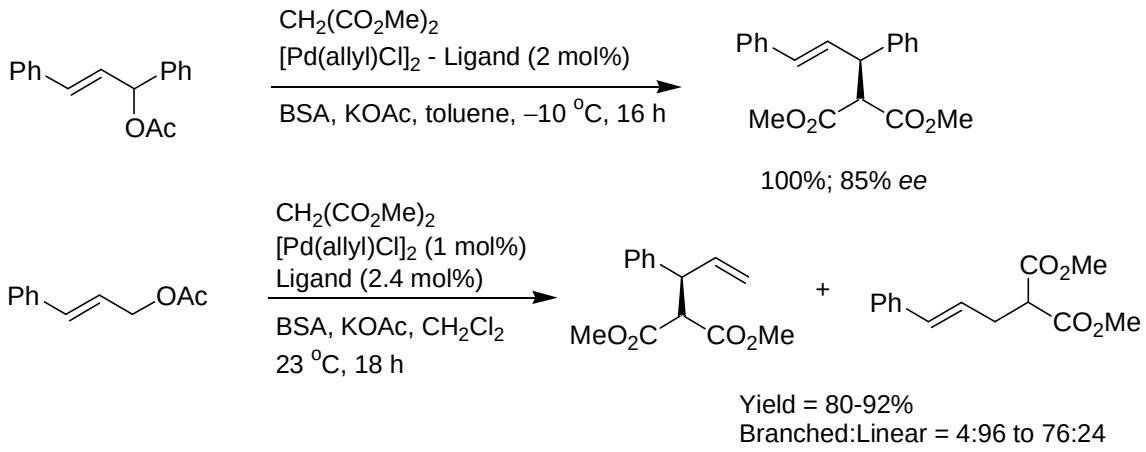
[4] a) Trost, B. M.; Lee, C. in *Catalytic Asymmetric Synthesis*, 2nd ed.; (Ed.; Ojima, I.), Wiley-VCH, New York, **2000**, 593; b) Pfaltz, A.; Lautens, M. in *Comprehensive Asymmetric Catalysis I-III*, (Eds.; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H.), Springer, Berlin, **1999**, 833; c) Fristrup, P.; Jensen, T.; Hoppe, J.; Norrby, P.-O. *Chem. Eur. J.* **2006**, *12*, 5352; d) Tan, Z.; Negishi, E. *Angew. Chem. Int. Ed.* **2006**, *45*, 762; e) Hayashi, S.; Hirano, K.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2006**, *128*, 2210; f) Watson, I. D. G.; Yudin, A. K. *J. Am. Chem. Soc.* **2005**, *127*, 17516; g) Hegedus, L. in *Organometallic in Synthesis*, (Ed.; Schlosser, M.), Wiley, New York, **1994**, 385.

[5] a) Diederich, F.; Stang, P. J. Eds. *Metal-catalyzed Cross-coupling Reactions*, Wiley-VCH, Weinheim, **1998**; b) Tsuji, J. *Palladium Reagents and Catalysts. Innovations in Organic Synthesis*, John Wiley & Sons, New York, **1995**, 290; c) Godleski, S. A. in *Comprehensive Organic Synthesis*, (Ed.; Trost, B. M.), Perganon Press, New York, **1991**, *Vol. 4*, 585; d) Farina, V.; Drishnamurthy, V.; Scott, W. J. in *Organic Reactions*, (Ed.; Paquette, L. A.), John Wiley & Sons, New York, **1997**, *Vol. 50*, 1; e) Hegedus, L. S. *Coord. Chem. Rev.* **1996**, *147*, 443; f) Suzuki, A.; Miyaura, N. *Chem. Rev.* **1995**, *95*, 2457; g) Reiser, O. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 547; h) Trost, B. M.; VanVranken, D. L. *Chem. Rev.* **1996**, *96*, 395; i) Frost, C. G.; Howarth, J.; Williams, J. M. J. *Tetrahedron: Asymmetry* **1992**, *3*, 1089; j) Consiglio, G.; Waymouth, R. M. *Chem. Rev.* **1989**, *89*, 257.

palladium-catalyzed allylic substitution reactions, this research area is still challenging. For example, the control of the regio- and enantioselectivities for unsymmetrically substituted allylic substrates, especially for monosubstituted ones, remain an unsolved problem, because the nucleophile usually attacks the terminal carbon in these substrates, when palladium complexes are used as catalyst (Scheme 2).[6, 7]



Scheme 2. Regioselectivity for palladium-catalyzed substitution reaction.[6, 7]

Numerous nucleophiles have been used in palladium-catalyzed allylic substitution reactions.[8] However, the reaction is more difficult with non-stabilized carbanions, such as organozinc compounds[9] and Grignard reagents.[10] Further, for unsymmetrically substituted allylic derivatives (Scheme 2) the situation is more complex and challenging, as both regio- and enantioselectivity need to be controlled. Accordingly, metals, such as nickel (Scheme 3),[11] iridium (Scheme 4),[12] molybdenum (Scheme 5),[13] ruthenium (Scheme 6),[14] tungsten

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7 Prétôt, R.; Pfaltz, A. *Angew. Chem. Int. Ed.* **1998**, *37*, 323.

8 Keinan, E.; Sahai, M. *J. Chem. Soc., Chem. Comm.* **1984**, *10*, 648.

9 Knochel, P.; Calaza, M. I.; Hupe, E. *Carbon-Carbon Bond-Forming Reactions Mediated by Organozincs Reagents* in *Metal-Catalyzed Cross-Coupling Reactions*, (Eds.; de Meijere, A.; Diederich, F.), Wiley-VCH, Weinheim, **2004**, *Vol. 2*, 619.

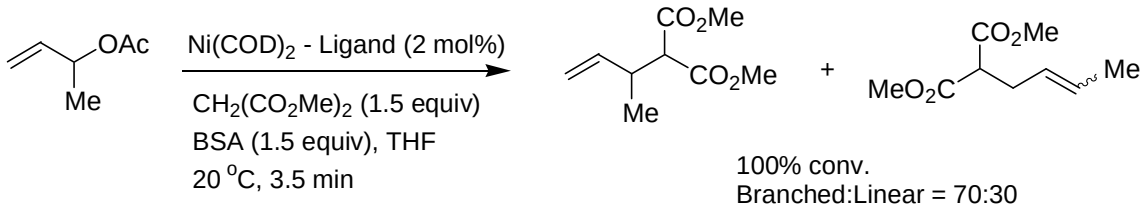
10 Knochel, P.; Sapountzis, I.; Gommermann, N. *Carbon-Carbon Bond Forming Reactions Mediated by Organomagnesium Reagents* in *Metal-Catalyzed Cross-Coupling Reactions*, (Eds.; de Meijere, A.; Diederich, F.), Wiley-VCH, Weinheim, **2004**, *Vol. 2*, 671.

11 a) Bricout, H.; Carpentier, J.-F.; Mortreux, A. *Tetrahedron Lett.* **1996**, *37*, 6105; b) Chung, K.-G.; Miyake, Y.; Uemura, S. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2725.

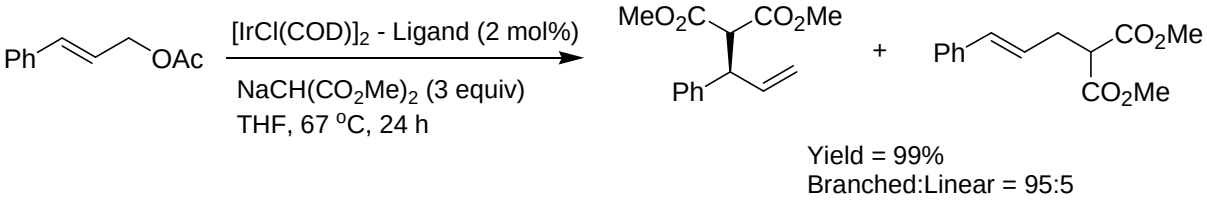
12 a) Garcia-Yebra, C.; Janssen, J. P.; Rominger, F.; Helmchen, G. *Organometallics* **2004**, *23*, 5459; b) Fuji, K.; Kinoshita, N; Tanaka, K.; Kawabata, T. *Chem. Commun.* **1999**, 2289; For a review, see: c) Takeuchi, R. *Synlett* **2002**, 1954.

13 a) Belda, O.; Moberg, C. *Acc. Chem. Res.* **2004**, *37*, 159; b) Trost, B. M.; Hachiya, I. *J. Am. Chem. Soc*. **1998**, *120*, 1104; c) Lloyd-Jones, G. C.; Krska, S. W.; Hughes, D. L.; Gouriou, L.; Bonnet, V. D.; Jack, K.; Sun, Y.;

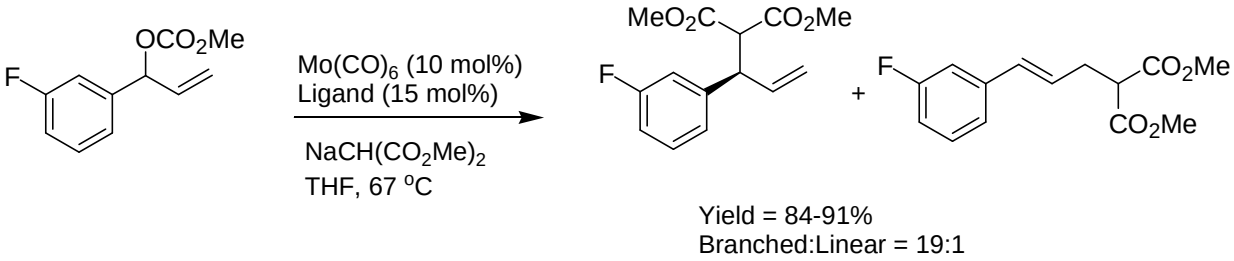
(Scheme 7),[15] rhodium (Scheme 8)[16] and copper (Scheme 9-13)[17] have emerged as efficient systems.



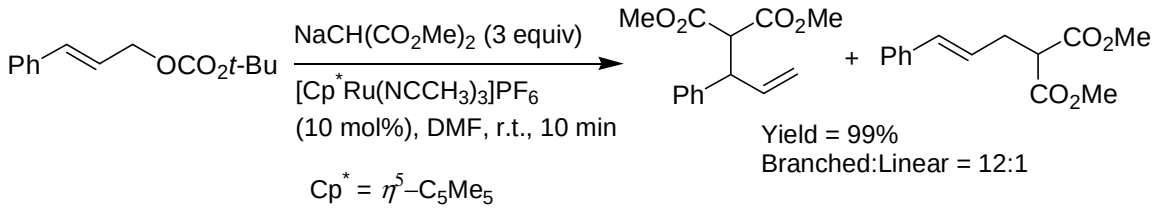
Scheme 3. Regioselectivity for nickel-catalyzed substitution reaction.[11a]



Scheme 4. Regioselectivity for iridium-catalyzed substitution reaction.[12a]



Scheme 5. Regioselectivity for molybdenum-catalyzed substitution reaction.[13f]



Scheme 6. Regioselectivity for ruthenium-catalyzed substitution reaction.[14a]

Reamer, R. A. *J. Am. Chem. Soc.* **2004**, *126*, 702; d) Glorius, F.; Pfaltz, A. *Org. Lett.* **1999**, *1*, 141; e) Glorius, F.; Neuburger, M.; Pfaltz, A. *Helv. Chim. Acta* **2001**, *84*, 3178; f) Palucki, M.; Um, J. M.; Yasuda, N.; Conlon, D. A.; Tsay, F.-R.; Hartner, F. W.; Hsiao, Y.; Marcune, B.; Karady, S.; Hughes, D. L.; Dormer, P. G.; Reider, P. J. *J. Org. Chem.* **2002**, *67*, 5508.

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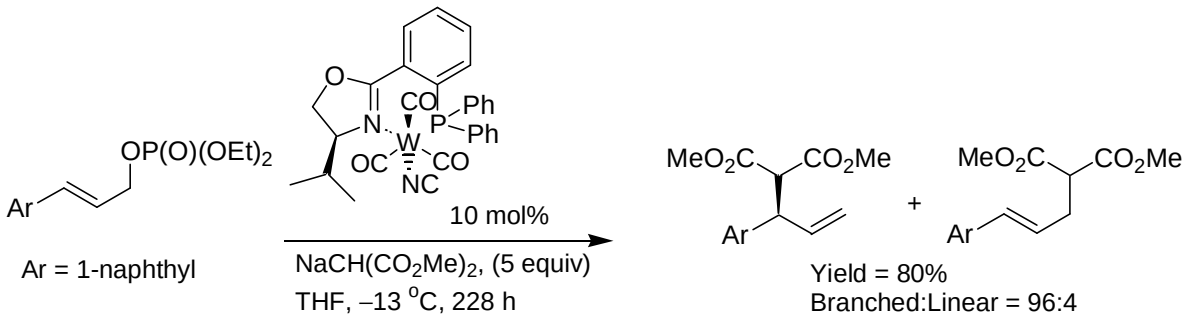
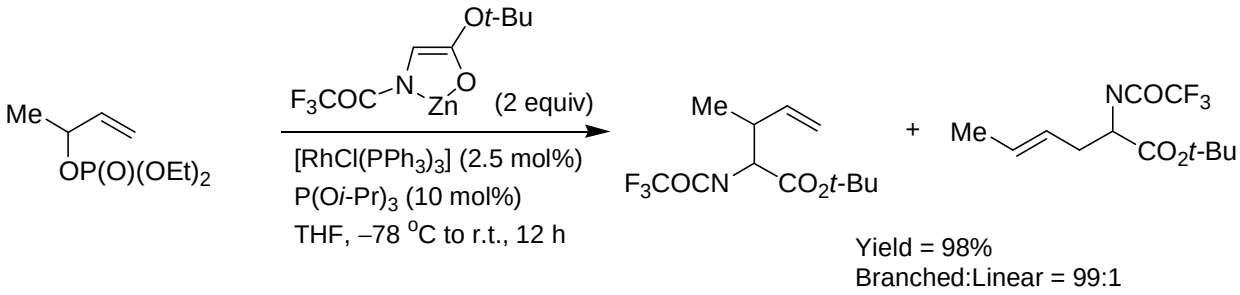
[17] Karlström, A. S. E.; Bäckvall, J.-E. in *Modern Organocopper Chemistry*, (Ed.; Krause, N.), Wiley-VCH, Weinheim, Germany, **2002**, 259.



Scheme 7. Regioselectivity for tungsten-catalyzed substitution reaction.[15a]



Scheme 8. Regioselectivity for rhodium-catalyzed substitution reaction.[16c]

1.2 Enantioselective copper-catalyzed (and -mediated) allylic substitution reactions

Copper(I) salts are generally less expensive than the corresponding palladium(II) salts,[18] and are widely used in organic synthesis.[19] Copper(I)-catalyzed and -mediated allylic substitution reactions allow the use of nucleophiles including organozinc compounds and Grignard reagents, thus being complementary to palladium catalysis. Moreover, copper(I)-catalyzed allylic substitution reactions usually proceed with high S_N2'regioselectivity.[20] Copper(I)-catalyzed allylic substitutions attracted considerable attention, and valuable investigations have been carried out to elucidate their mechanisms.

The chiral information in copper-catalyzed allylic substitution reactions can be contained either in the allylic electrophile[21] or in the chiral copper catalyst.[22] For the later

[18] Price from Aldrich catalog 2005-2006: $PdCl_2$ (99%); 1 g = 65.40 Euro, CuCl (≥98%); 100 g = 29.30 Euro.

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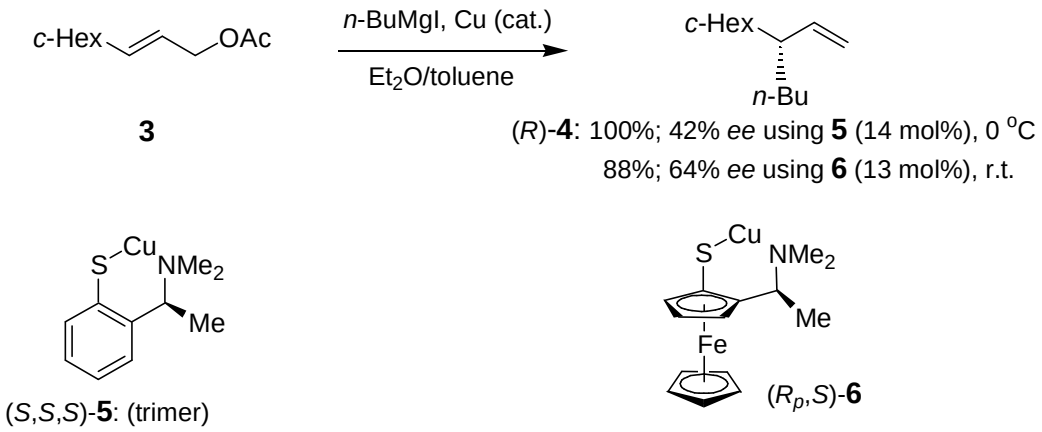
[21] a) Belelie, J. L.; Chong, J. M. *J. Org. Chem.* **2001**, *66*, 5552; b) Ibuka, T.; Habashita, H.; Otaka, A.; Fujii, N.; Oguchi, Y.; Uyehara, T.; Yamamoto, Y. *J. Org. Chem.* **1991**, *56*, 4370; c) Marino, J. P.; Viso, A.; Lee, J.-D.; de

approach, the first report appeared in 1995 by Bäckvall, van Koten and co-workers.[22a] They disclosed the copper-catalyzed asymmetric allylic substitution of allylic acetate **3** using butylmagnesium iodide providing the product (*R*)-**4** using the chiral arenethiolato-copper(I) complex **5** (Scheme 9).



Scheme 9. The first copper-catalyzed asymmetric allylic substitution by Bäckvall, van Koten and co-workers.[22a]

The enantiomeric excess of the product, such as **4**, heavily depends on several factors including the coordinating ability of the leaving group in the allylic substrate, the reaction temperature and the sequence of substrate addition. Subsequently, the enantiomeric excess of 64% was achieved by using the chiral copper catalyst **6** (Scheme 9).[22b-c]

A breakthrough in copper-catalyzed asymmetric allylic substitutions was reported in 1999, when Dübner and Knochel used dialkylzincs as an alkyl source in the presence of a novel copper/ferrocenyl amine catalysts (Scheme 10).[22d-e] To reach high enantioselectivities, the catalytic system required a high ratio of ligand to copper, very low reaction temperatures

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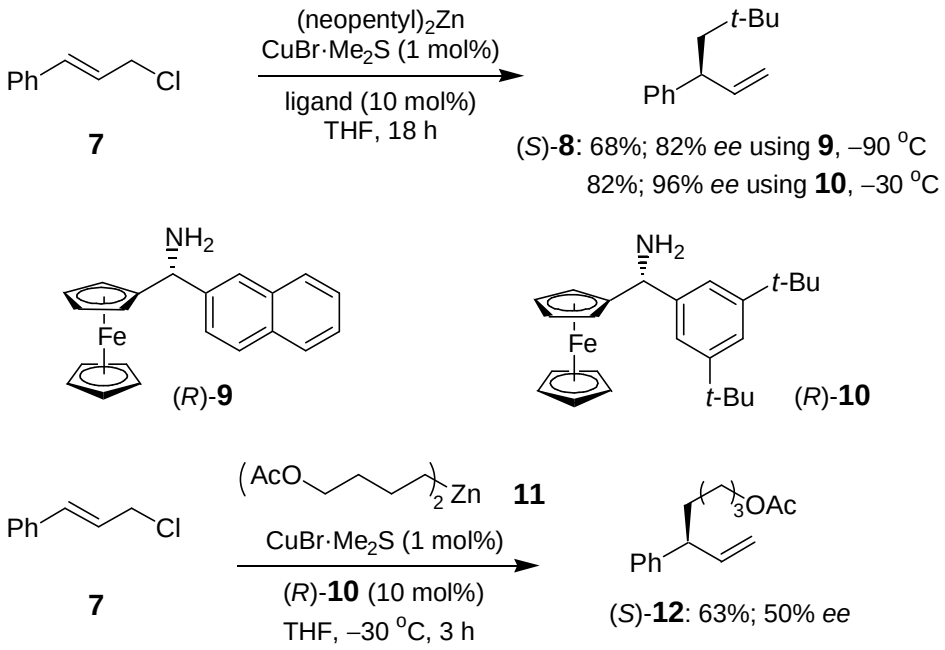
la Pradilla, R. F.; Fernandez, P.; Rubio, M. B. *J. Org. Chem.* **1997**, *62*, 645; d) Smitrovich, J. H.; Woerpel, K. A. *J. Org. Chem.* **2000**, *65*, 1601; e) Spino, C.; Beaulieu, C. *J. Am. Che. Soc.* **1998**, *120*, 11832; f) Spino, C.; Beaulieu, C. *Angew. Chem., Int. Ed.* **2000**, *39*, 1930; g) Spino, C.; Beaulieu, C.; Lafreniere, J. *J. Org. Chem.* **2000**, *65*, 7091; h) Denmark, S. E.; Marble, L. K. *J. Org. Chem.* **1990**, *55*, 1984; i) Fleming, I.; Winter, S. B. D. *Tetrahedron Lett.* **1995**, *36*, 1733; j) Tiecco, M.; Testaferri, L.; Santi, C.; Tomassini, C.; Bonini, R.; Marini, F.; Bagnoli, L; Temperini, A. *Org. Lett*. **2004**, *6*, 4751.

[22] a) van Klaveren, M.; Persson, E. S. M.; del Villar, A.; Grove, D. M.; Bäckvall, J.-E.; van Koten, G. *Tetrahedron Lett.* **1995**, *36*, 3059; b) Karlström, A. S. E.; Huerta, F. F.; Meuzelaar, G. J.; Bäckvall, J.-E. *Synlett* **2001**, 923; c) Meuzelaar, G. J.; Karlström, A. S. E.; van Klaveren, M.; Persson, E. S. M.; del Villar, A.; van Koten, G.; Bäckvall, J.-E. *Tetrahedron* **2000**, *56*, 2895; d) Dübner, F.; Knochel, P. *Angew. Chem. Int. Ed.* **1999**, *38*, 379; e) Dübner, F.; Knochel, P. *Tetrahedron Lett.* **2000**, *41*, 9233; f) Alexakis, A.; Malan, C.; Lea, L.; Benhain, C.; Fournioux, X. *Synlett* **2001**, 927; g) Alexakis, A.; Croset, K. *Org. Lett*. **2002**, *4*, 4147; h) Malda, H.; van Zijl, A. W.; Arnold, L. A.; Feringa, B. L. *Org. Lett*. **2001**, *3*, 1169; i) Luchaco-Cullis, C. A.; Mizutani, H.; Murphy, K. E.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2001**, *40*, 1456.

and the presence of bulky alkyl groups on zinc. For instance, the reaction of cinnamyl chloride (**7**) with dineopentylzinc provided the product (*S*)-**8** with 82% *ee* under catalysis by CuBr·Me_2S/**9** (1:10) at –90 °C. By using the chiral ligand **10**, the reaction could be carried out at higher temperature, and the enantiomeric excess was increased up to 96% *ee*. However, the use of unbranched dialkylzinc reagents such as dipentylzinc or the functionalized dialkylzinc **11** afforded the corresponding products, such as (*S*)-**12**, with only 44-65% *ee* (Scheme 10).

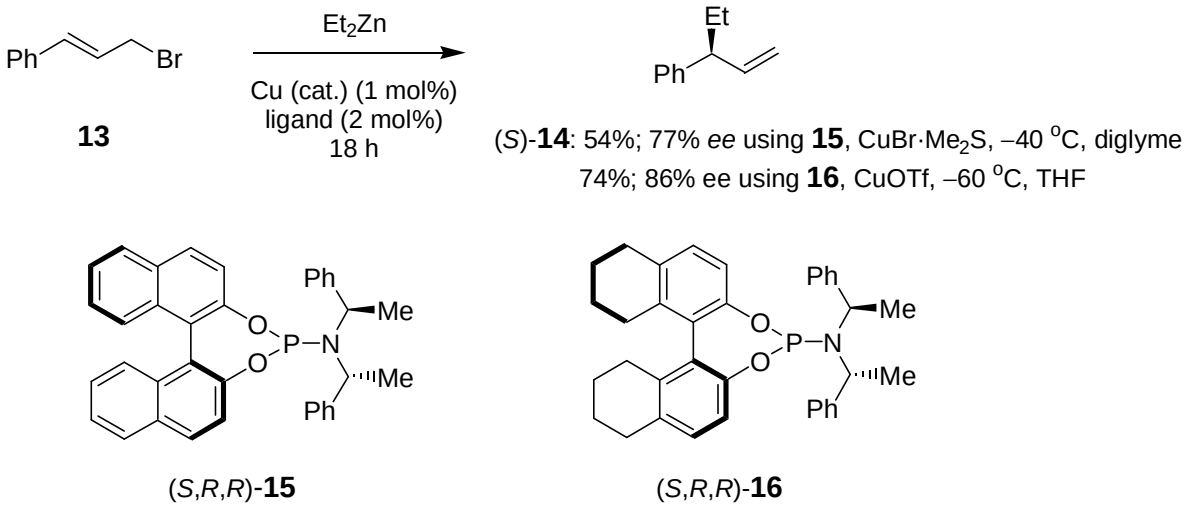


Scheme 10. Copper-catalyzed asymmetric allylic substitution by Dübner and Knochel.[22d-e]

Despite the necessity of bulky alkyl groups on zinc, the work of Dübner and Knochel was an important milestone in copper-catalyzed asymmetric allylic substitutions.

Highly enantioselective allylic substitutions with linear dialkylzincs remained a major challenge, until Feringa and co-workers proposed chiral phosphoramidites as ligands (Scheme 11).[22h] Treatment of cinnamyl bromide (**13**) with diethylzinc in the presence of CuBr·Me_2S and phosphoramidite **15** in diglyme at –40 °C afforded (*S*)-**14** with 77% *ee*. Using phosphoramidite **16** with CuOTf in THF led to improved enantioselectivities (86% *ee*).[23]

[23] van Zijl, A. W.; Arnold, L. A.; Minnaard, A. J.; Feringa, B. L. *Adv. Synth. Catal*. **2004**, *346*, 413.



Scheme 11. Copper-catalyzed asymmetric allylic substitution by Feringa and co-workers.[22h]

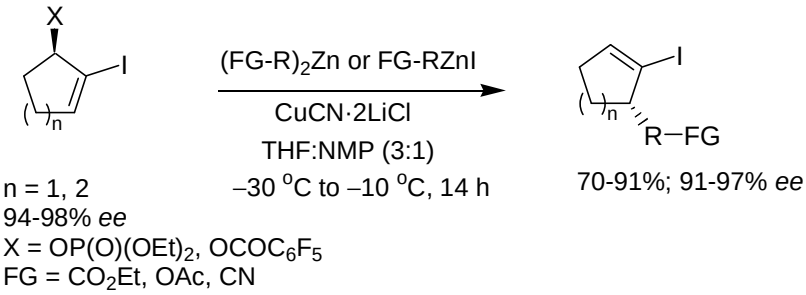
Recently, an increasing number of copper-catalyzed asymmetric allylic substitutions have emerged.[24] However, asymmetric allylic substitutions catalyzed by chiral copper complexes suffer also from a poor scope, and the corresponding chiral copper complexes have to be optimized for each class of allylic substrates. Moreover, the deliberate use of functionalized alkylzinc halides (RZnX) instead of dialkylzinc reagents (R_2Zn) led to poor enantioselectivities.[22d-e] Therefore, syntheses relying on generally applicable chiral allylic electrophiles are more appealing,[21] since allylic alcohols can be readily prepared in optically enriched form by several asymmetric syntheses.[25] Furthermore, the transfer of chirality using chiral precursors has the advantage of being rather predictable. Based on this approach, Calaza and Knochel recently reported the use of various functionalized diorganozincs and organozinc halides in the presence of CuCN·2LiCl[26] for enantioselective *anti*-S_N2' substitutions with chiral cyclic 2-iodo-allylic alcohol derivatives leading to the substitution products in high yields and up to 97% *ee* (Scheme 12).[27]

[24] Ochima, K.; Yorimitsu, H. *Angew. Chem. Int. Ed*. **2005**, *44*, 4435; and references cited therein.

[25] a) Lin, G.-Q.; Li, Y.-M.; Chan, A. S. C. *Principles and Applications of Asymmetric Synthesis*, Wiley-Interscience, New York, **2001**; b) Gawley, R. E.; Aube, J. *Principles of Asymmetric Synthesis*, Pergamon, Oxford, **1996**; c) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*, Wiley, New York, **1994**; d) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765; e) Carlier, P. R.; Mungall, W. S.; Schröder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 2978.

[26] Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2390.

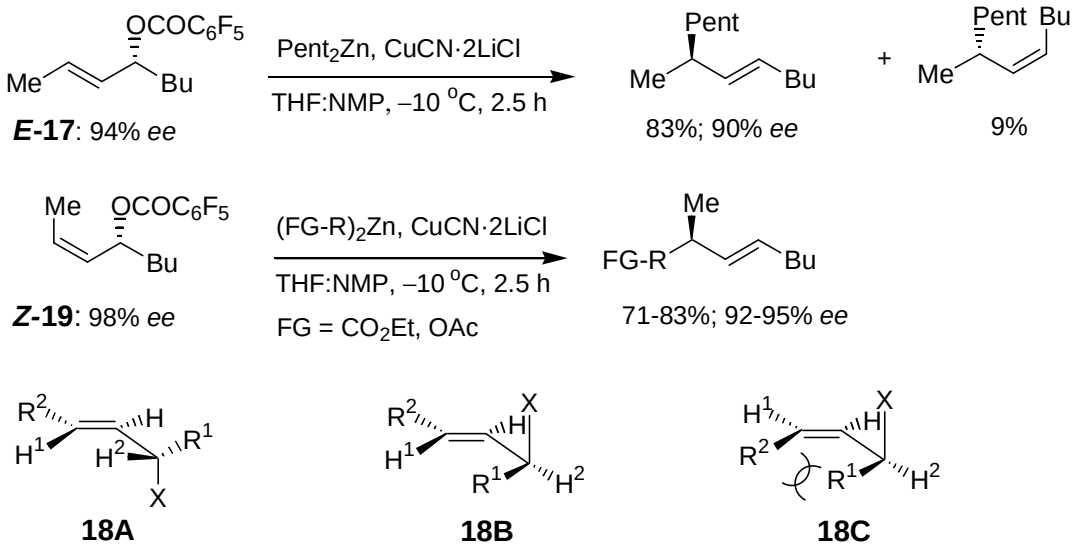
[27] Calaza, M. I.; Hupe, E.; Knochel, P. *Org. Lett.* **2003**, *5*, 1059.



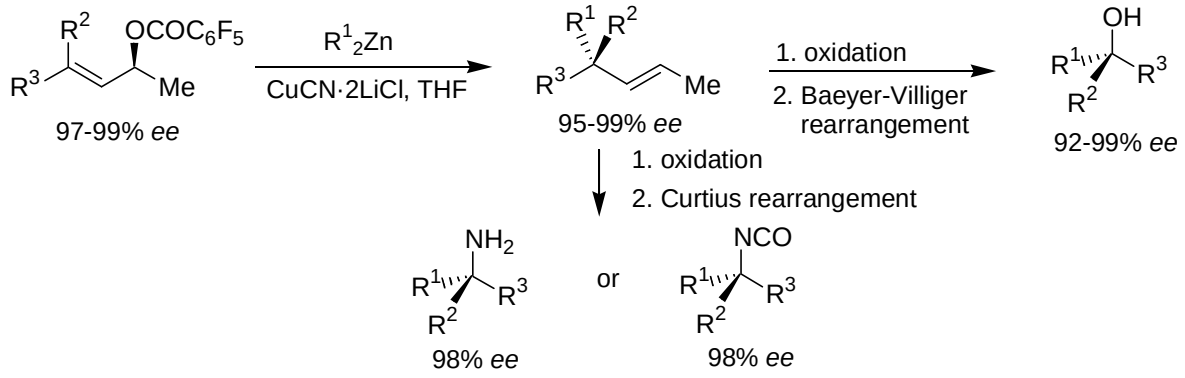
Scheme 12. Stereoselective *anti*-S_N2'substitutions of chiral cyclic 2-iodo-allylic alcohol derivatives with organozinc reagents. [27]

The reaction proved also to be generally applicable for open-chain substrates. The reaction of the (*E*)-allylic pentafluorobenzoate **17** (94% *ee*) with dipentylzinc produced the expected (*E*)-substituted product in 83% yield with 90% *ee* as well as ca. 9% yield of the (*Z*)-product (Scheme 13). [28] The formation of the (*Z*)-product results from an *anti*-substitution of the zinc-copper reagent via a conformation of type **18B** (Scheme 13). By comparing the allylic 1,3-strain[29] of the two possible conformations (**18A** and **18B**) that can undergo an *anti*-S_N2'substitution, a higher allylic 1,3-strain (between H^1 and R^1) in conformer **18B** (Scheme 13) disfavored the substitution reaction via this conformer. To disfavor this conformation further, the (*Z*)-allylic pentafluorobenzoate was used. With such a substrate, the disfavoured conformation of type **18C** displays considerable allylic 1,3-strain.[29] The (*Z*)-allylic pentafluorobenzoates **19** reacted with various linear functionalized zinc-copper reagents with high *anti*-S_N2'selectivity allowing excellent stereocontrol for the synthesis of acyclic alkenes (Scheme 13). Interestingly, this substitution reaction can be applied to the elaboration of stereoselective chiral quaternary centers. The reactions of trisubstituted (*Z*)-allylic pentafluorobenzoates furnished the substitution products with high enantiomeric excesses (Scheme 14). [30] The applications of this method for the preparation of natural products as well as of chiral tertiary alcohols, amines and isocyanates bearing a tertiary chiral center with high enantioselectivities were also subsequently reported (Scheme 14).[28, 30]

[28] Harrington-Frost, N.; Leuser, H.; Calaza, M. I.; Kneisel, F. F.; Knochel, P. *Org. Lett.* **2003**, *5*, 2111.
[29] Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841.
[30] Leuser, H.; Perrone, S.; Liron, F.; Kneisel, F. F.; Knochel, P. *Angew. Chem. Int. Ed.* **2005**, *44*, 4627.



Scheme 13. Stereoselective *anti*-S_N2'substitutions of (*Z*)-allylic pentafluorobenzoates with polyfunctionalized zinc-copper reagents.[28]



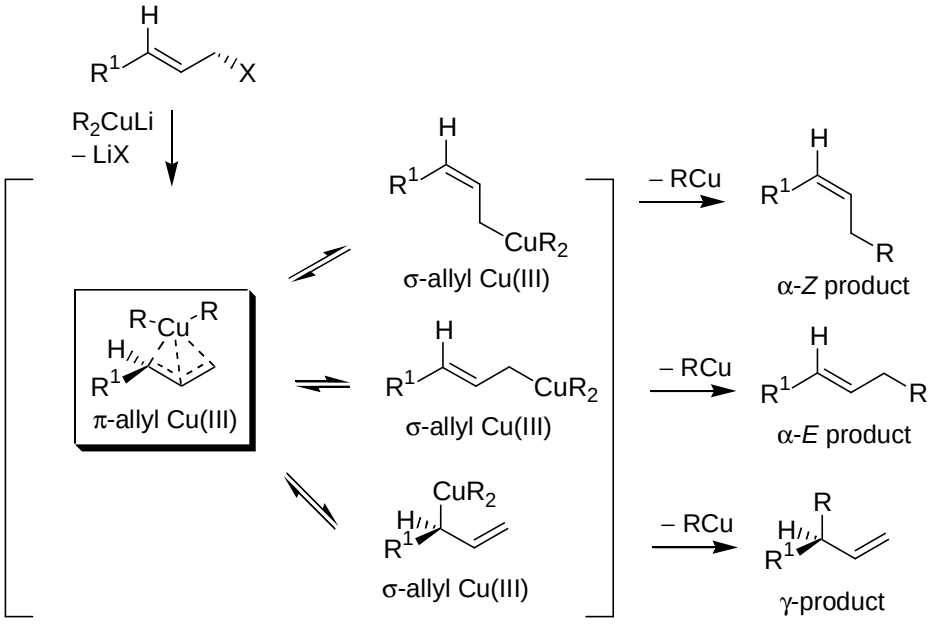
Scheme 14. Stereoselective *anti*-S_N2'allylic substitutions of the trisubstituted allylic pentafluorobenzoates and applications to the preparation of chiral tertiary alcohols, amines and isocyanates.[30]

As mentioned above, copper-catalyzed or -mediated allylic substitution reactions usually proceed with high S_N2'regioselectivity with various allylic electrophiles. Further, it has been shown that organocuprates will undergo *anti*-S_N2'reaction with allylic carboxylates,[20a-b] sulfonates,[20c-d] halides, [20e] and phosphates.[31] The allylic substitution reaction between an allylic ester and a lithium dialkylcuprate is presently considered to involve three

[31] Yanagisawa, A.; Noritake, Y.; Nomura, N.; Yamamoto, H. *Synlett*, **1991**, 251.

steps (Scheme 15).[20, 32] The initial loss of the leaving group generates a π–allylcopper(III) intermediate, in which the memory of the position of the leaving group is lost. This intermediate equilibrates with a σ-allylcopper(III) intermediates, from which a mixture of α- and γ-allylation products form. The formation of *E*- and *Z*-products has been taken as evidence of the presence of the σ-allylcopper(III) intermediates, and the regioselecitvity has been considered to depend on the reactivity of these intermediates from which the allylation products form.

Recently, based on the reports that Lewis acid favors *anti* and γ-selective reaction[33] and on the study in mechanism and regioselectivity of reductive elimination of π–allylcopper(III) intermediates by E. Nakamura,[34] the mechanism of allylic substitutions was proposed to occur via an enyl[σ+π]-complex without going through a π–allylcopper(III) complex (Scheme 16).

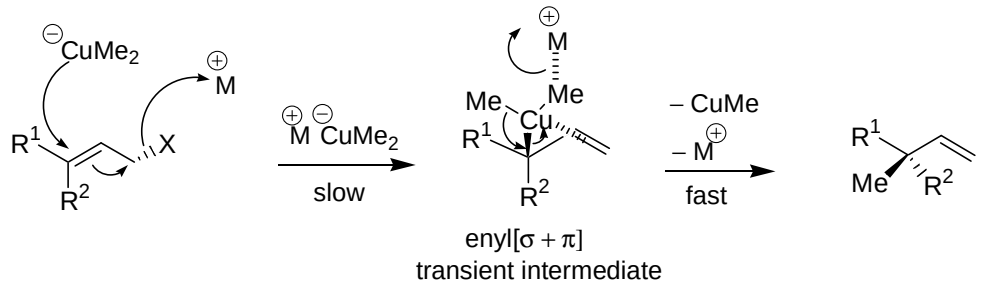


Scheme 15. Conventional mechanism of allylic carboxylates with lithium diorganocuprate.[32]

[32] a) Karlstorm, A.; Sofia, E.; Bäckvall, J.-E. *Chem. Eur. J.* **2001**, *7*, 1981; b) Keinan, E.; Bosch, E. *J. Org. Chem.* **1986**, *51*, 4006.

[33] a) Nakamura, E.; Sekiya, K.; Arai, M.; Aoki, S. *J. Am. Chem. Soc.* **1989**, *111*, 3091; b) Arai, M.; Nakamura, E. *J. Org. Chem.* **1991**, *56*, 5489; c) Yamamoto, Y.; Yamamoto, S.; Yatagai, H.; Maruyama, K. *J. Am. Chem. Soc.* **1980**, *102*, 2318.

[34] Yamamoto, M.; Kato, S.; Nakamura, E. *J. Am. Chem. Soc.* **2004**, *126*, 6287.

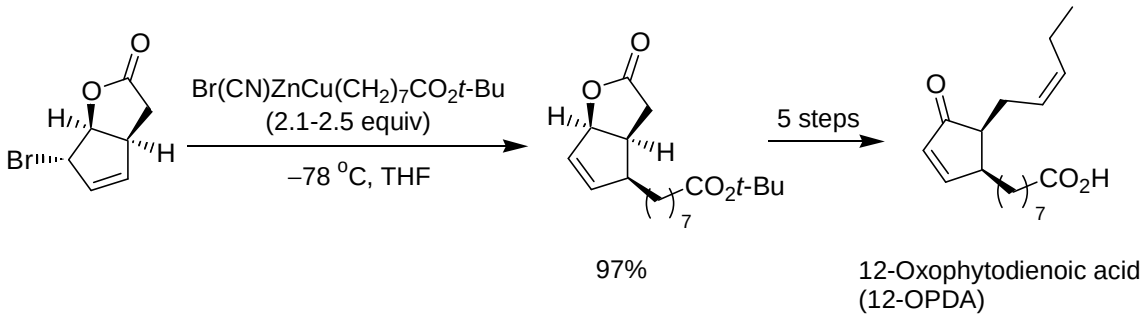


Scheme 16. Model pathway of allylic substitution reaction of a Lewis acid (M^+) complexed diorganocuprate by E. Nakamura.[34]

1.3 Applications of allylic substitutions to natural product syntheses

Stereoselective allylic substitution reactions serve as a powerful method for total syntheses of natural products. While there are only few reports on the use of acyclic electrophiles in asymmetric allylic substitution reactions, the majority of applications to total synthesis use cyclic electrophiles, particularly five- or six-membered rings.[35]

To introduce the carboxyalkyl side chain selectively *cis* to the lactone function of jasmonoids, an *anti*-S_N2' substitution reaction with zinc cyanocuprates was used by Helmchen and Ernst.[36] They synthesized the desired product, as starting material for the enantioselective synthesis of 12-oxyphytodienoic acid, a biosynthetic precursor for jasmonoids (Scheme 17).[37]



Scheme 17. Synthetic route to enantiomerically pure jasmonoids by Helmchen.[36]

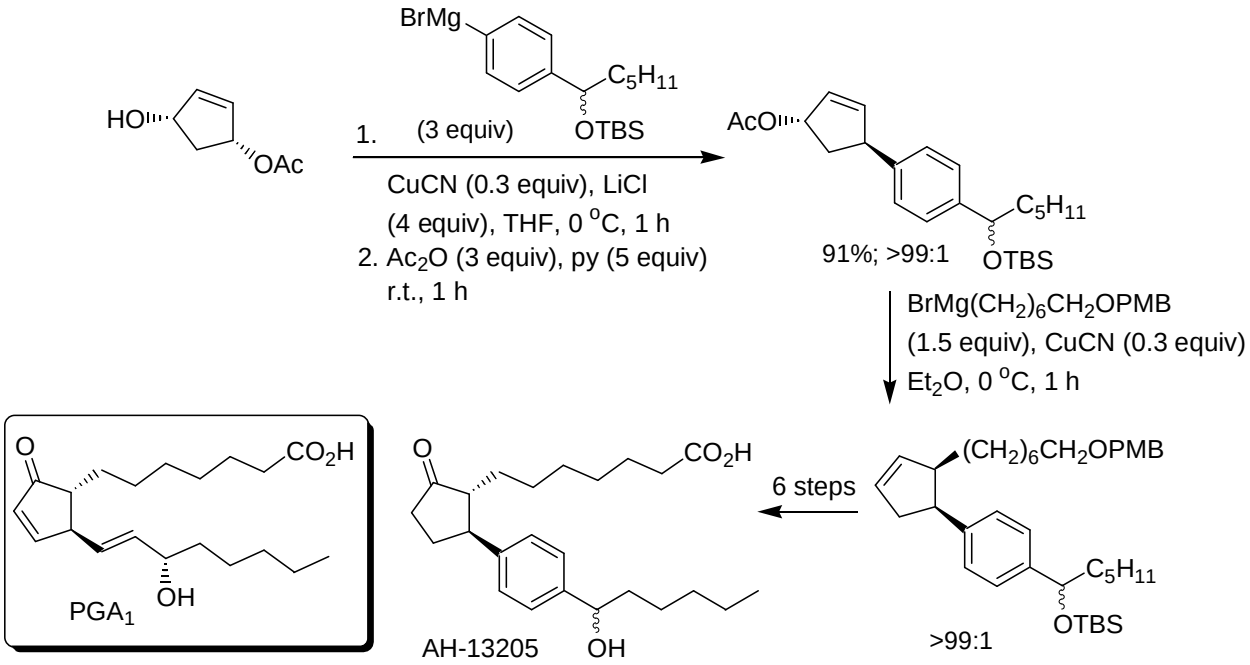
---

[35] a) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921; b) Mori, M.; Kuroda, S.; Zhang, C.-S.; Sato, Y. *J. Org. Chem.* **1997**, *62*, 5265; c) Nishimata, T.; Mori, M. *J. Org. Chem.* **1998**, *63*, 7586f; d) Nishimata, T.; Yamagudhi, K.; Mori, M. *Tetrahedron Lett.* **1999**, *40*, 5713

[36] Ernst, M.; Helmchen, G. *Angew. Chem. Int. Ed.* **2002**, *41*, 4054.

[37] Reviews: a) Sarkar, T. K.; Ghorai, B. K. *J. Indian. Chem. Soc.* **1999**, *76*, 693; b) Helmchen, G.; Goeke, A.; Lauer, G.; Urmann, M.; Fries, J. *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 1024; c) Sarkar, T. K.; Mukherjee, B.; Gosh, S. K. *Tetrahedron* **1998**, *54*, 3243; d) Fehr, C.; Galindo, J. *Angew. Chem. Int. Ed.* **2000**, *39*, 569.

Recently, Y. Kobayashi and co-workers developed a new reagent for obtaining high regio- and stereoselectivities in the allylic displacement of 4-cyclopenten-1,3-diol monoacetate with aryl- and alkenylmagnesium bromides.[38] This protocol was successfully utilized as the key step in the synthesis of AH-13205, which is an analogue of PGA_1 (Scheme 18).[39]



Scheme 18. Synthesis of AH-13205, an analogue of PGA_1.

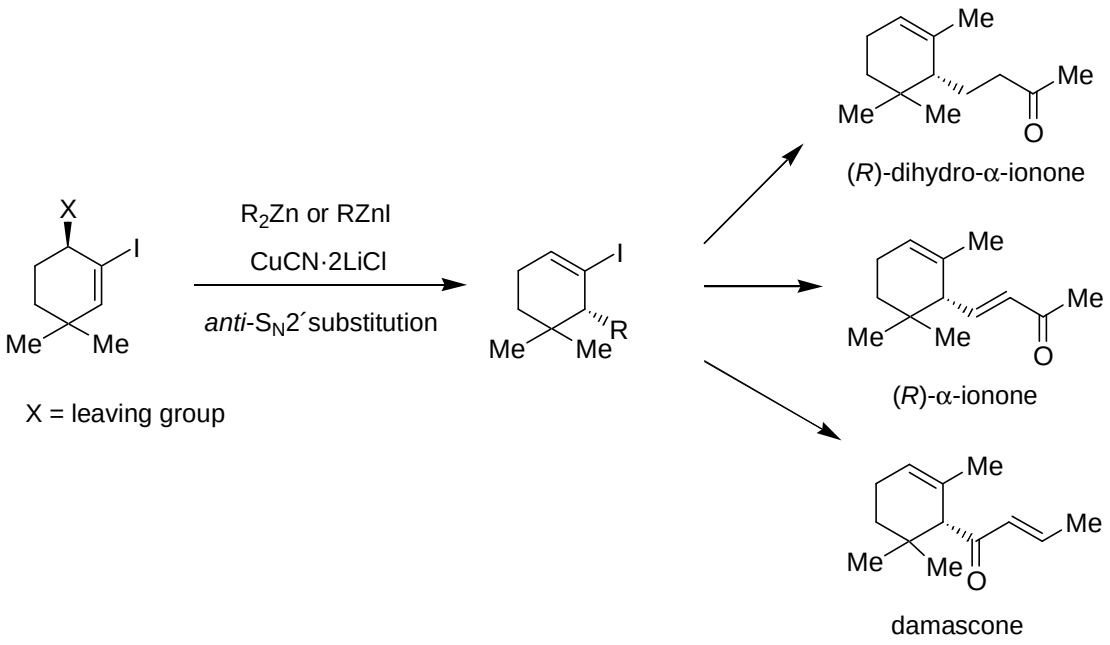
2. Objectives

Reagents for highly regio- and stereoselective allylic substitution reactions have been developed and their application to natural product synthesis has flourished. Therefore, the first objective of this project was to develop reaction conditions that allow copper-mediated stereoselective allylic substitutions with organozinc reagents and sterically hindered allylic electrophiles. This should lead to the core structure of interesting natural products, such as damascone, α-ionone and their derivatives (Scheme 19).

---

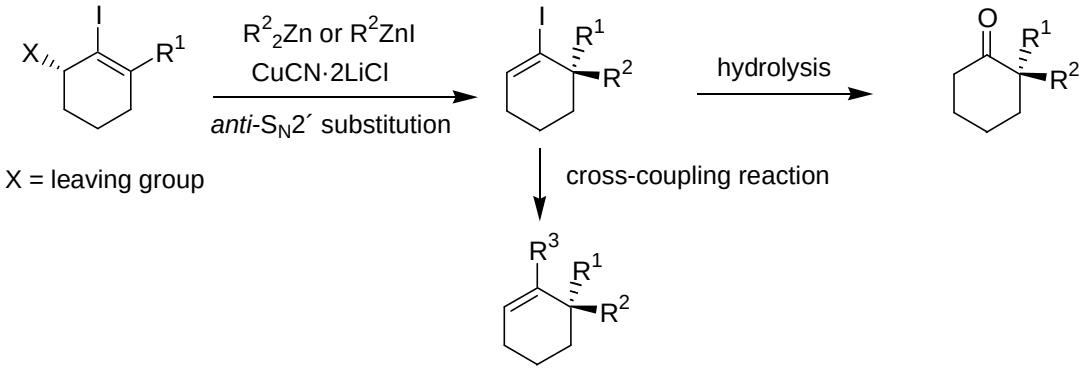
[38] a) Kobayashi, Y. *Curr. Org. Chem.* **2003**, *7*, 133; b) Hattori, H.; Abbas, A. A.; Kobayashi, Y. *Chem. Commun.* **2004**, 884; c) Ito, M.; Matsuumim M.; Murugesh, M. G.; Kobayashi, Y. *J. Org. Chem*. **2001**, *66*, 5881; d) Ainai, T.; Ito, M.; Kobayashi, Y. *Tetrahedron Lett.* **2003**, *44*, 3983; e) Kobayashi, Y.; Nakata, K.; Ainai, T. *Org. Lett*. **2005**, *7*, 183.

[39] a) Nials, A. T.; Vardey, C. J.; Denyer, L. H.; Thomas, M.; Sparrow, S. J.; Shephere, G. D.; Coleman, R. A. *Cardiovasc. Drug Rev.* **1993**, *11*, 165; b) Spada, C. S.; Nieves, A. L.; Woodward, D. F. *Ecp. Eye Tes*. **2002**, *75*, 155; c) Nials, A. T.; Coleman, R. A.; Hartley, D.; Sheldrick, R. L. G. *Br. J. Pharmacol.* **1991**, *102*, 24P; d) Coleman, R. A.; Kennedy, I.; Sheldrick, R. L. G. *Br. J. Pharmacol.* **1987**, *91*, 323P.



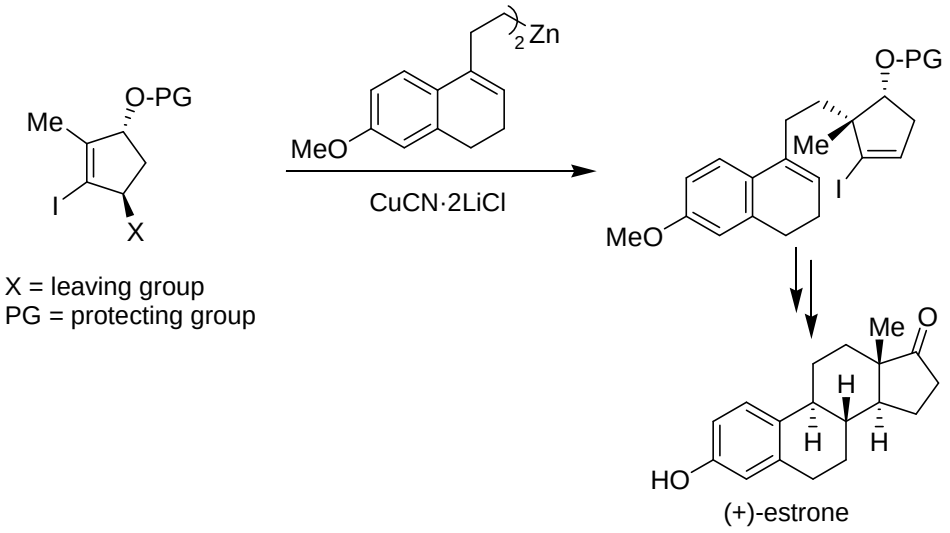
Scheme 19. Allylic substitution with sterically hindered allylic electrophiles and applications to natural product syntheses.

The previously reported use of 2-iodo-substituted cyclic allylic alcohol derivatives as precursors for stereoselective allylic substitutions would allow the synthesis of chiral iodocycloalkenyl compounds in high enantioselectivities. These types of compounds show great potential in organic synthesis. They contain a vinyl iodide moiety in the α-position to the stereogenic center, which could be, for example, further functionalized by transition metal-catalyzed cross coupling or iodine/metal-exchange reactions. It is also interesting to transform these chiral compounds to chiral ketones. Therefore, the second objective of the project was the application of chiral iodocycloalkenyl compounds to the preparation of chiral compounds such as chiral ketones (Scheme 20).



Scheme 20. Applications of chiral iodocycloalkenyl compounds to the preparation of chiral compounds.

Finally, another objective was to apply the copper(I)-catalyzed stereoselective allylic substitution reactions using organozinc reagents to the asymmetric synthesis of (+)-estrone. The key step of our proposed synthesis will be using the enantioselective *anti*-S_N2'substitution to install the chiral quaternary carbon center in the target molecule (Scheme 21).



Scheme 21. Synthesis of (+)-estrone via an asymmetric S_N2'allylic substitution.

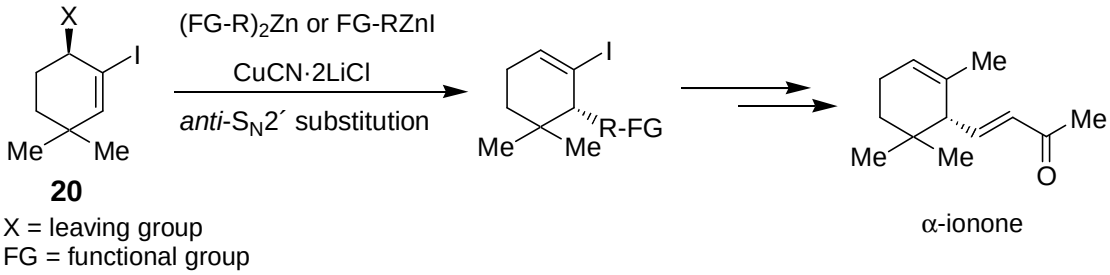
Results and Discussion

1. Copper(I)-mediated enantioselective *anti*-S_N2'substitution reactions with cyclic allylic alcohol derivatives

1.1 Introduction

Copper(I)-catalyzed or -mediated asymmetric allylic substitutions using organozinc reagents as nucleophiles have been developed in our group.[22d-e, 27, 28, 30] Following the successful works mentioned above which allowed an excellent transfer of chirality, it is of interest to perform an allylic substitution reaction with cyclic allylic systems, such as **20**, which may be used for the preparation of natural products (Scheme 22).[40]

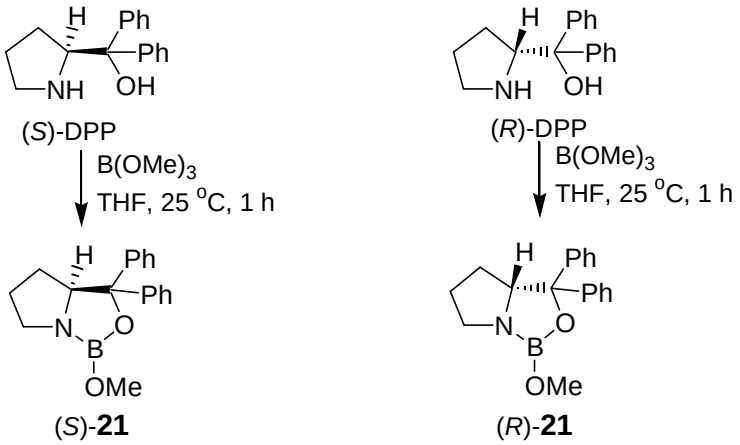
[40] Soorukram, D.; Knochel, P. *Org. Lett.* **2004**, *6*, 2409.



Scheme 22. Enantioselective allylic substitution of the cyclic allylic alcohol derivative **20** leading to α-ionone.

1.2 Preparation of the chiral cyclic allylic alcohol (24)

Asymmetric reduction of prochiral ketones is a commonly used method for preparing allylic alcohols.[25, 41] Recently, the preparation of various chiral 2-iodocycloalk-2-en-1-ols with high optically pure form has been carried out in our group.[27, 42] The use of the MeO-CBS catalyst [43] ((*S*)- or (*R*)-**21**; 5 mol%, prepared *in situ* by treatment of (*S*)- or (*R*)-diphenylprolinol (DPP) and $B(OMe)_3$ at 25 °C for 1 h, Scheme 23) and borane *N*,*N*-diethylaniline complex (1 equiv) allowed the reproducible preparation of various chiral 2-iodocycloalk-2-en-1-ols in high yields and % *ee* (up to 99% *ee*). Notably, the catalytic system is stable at room temperature (25 °C), which allows a convenient and stereoselective reduction of the corresponding prochiral ketones.



Scheme 23. Preparation of the MeO-CBS catalysts, (*S*)- and (*R*)-**21**.

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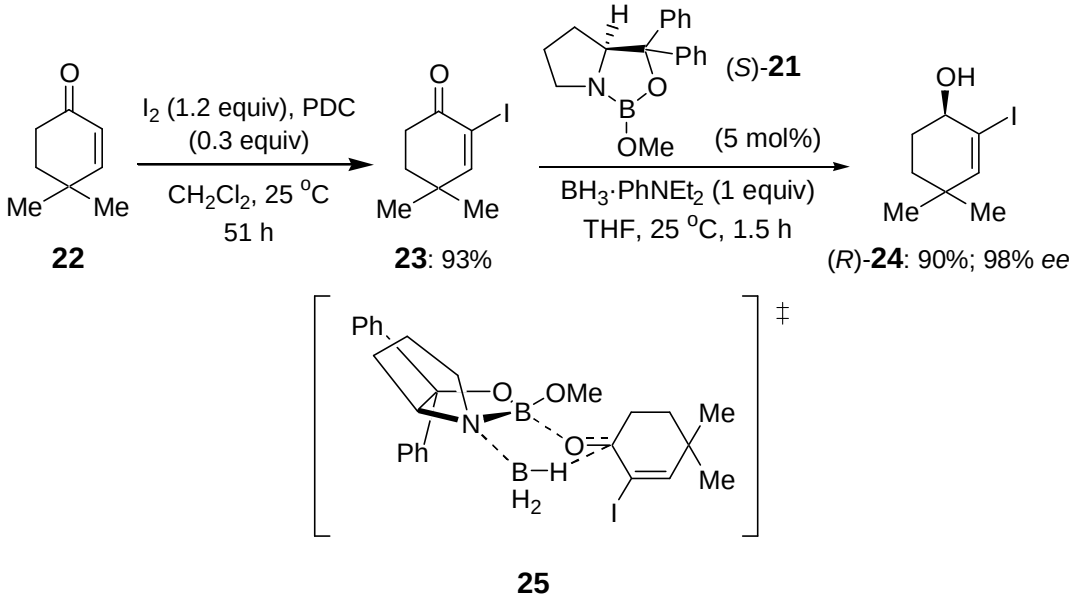
[41] For the asymmetric reduction with the CBS-method see: a) Corey, E. J.; Helal, C. J. *Angew. Chem. Int. Ed.* **1998**, *37*, 1986; b) Wallbaum, S.; Martens, J. *Tetrahedron: Asymmetry* **1992**, *3*, 1475.

[42] Gavryushin, A.; Calaza, M. I.; Knochel, P. *Unpublished results.*

[43] Cho, B. T. *Tetrahedron* **2006**, *62*, 7621; and references cited therein.

Thus, treatment of the (*S*)-MeO-CBS catalyst ((*S*)-**21**; 5 mol%) and borane *N*,*N*-diethylaniline complex (1 equiv) with 2-iodo-4,4-dimethylcyclohex-2-en-1-one (**23**), readily obtained from the ketone **22** after an iodination reaction[44] in 93% yield, in THF at 25 °C for 1.5 h afforded the allylic alcohol (1*R*)-2-iodo-4,4-dimethylcyclohex-2-en-1-ol (**24**) in 90% and 98% *ee*[45] (HPLC: Chiralcel OD-H, heptane:*i*-PrOH = 98:2, flow rate 0.3 mL/min) (Scheme 24). The stereochemical outcome observed for the allylic alcohol (*R*)-**24** could be explained by the transition state **25** depicted in Scheme 24.

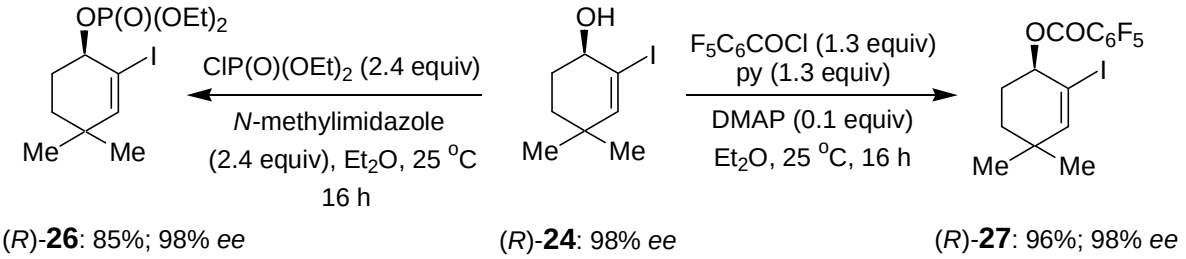


Scheme 24. Preparation of the chiral allylic alcohol (*R*)-**24**.

Having the chiral allylic alcohol (*R*)-**24** with high enantiomeric excess in hand, our attention was focused on the transformation of the hydroxy group into a leaving group. It was known that the nature of the leaving group is an important factor, influencing the regio- and stereoselectivity of allylic substitution reactions.[20, 21] In previous studies, selective *anti*-S_N2' substitutions proceeded smoothly to give the substitution products in good yields and high enantioselectivities using either a phosphate ($-OP(O)(OEt)_2$)[27] or a pentafluorobenzoate ($-OCOC_6F_5$)[27, 28, 30] as leaving groups. Although allylic phosphates gave better yields of the substitution products, in some cases for example the 5-membered analogue, the difficulties associated with the purification of the allylic phosphates and their decreased stability limited their use. Moreover, the higher reactivity of phosphates as leaving groups compared to

[44] Bovonsombat, P.; Angara, G. J.; NcNelis, E. *Tetrahedron Lett.* **1994**, *35*, 6787.
[45] Kamatani, A.; Overman, L. E. *Org. Lett.* **2001**, *3*, 1229.

pentafluorobenzoates led to a lower selectivity in these transformations. In order to investigate the effect of the leaving groups for performing selective *anti*-S_N2'substitution with sterically hindered systems using mixed zinc-copper reagents, the corresponding allylic phosphate (*R*)-**26**,[31] and pentafluorobenzoate (*R*)-**27** were prepared as depicted in Scheme 25.



(*R*)-**26**: 85%; 98% *ee* (*R*)-**24**: 98% *ee* (*R*)-**27**: 96%; 98% *ee*

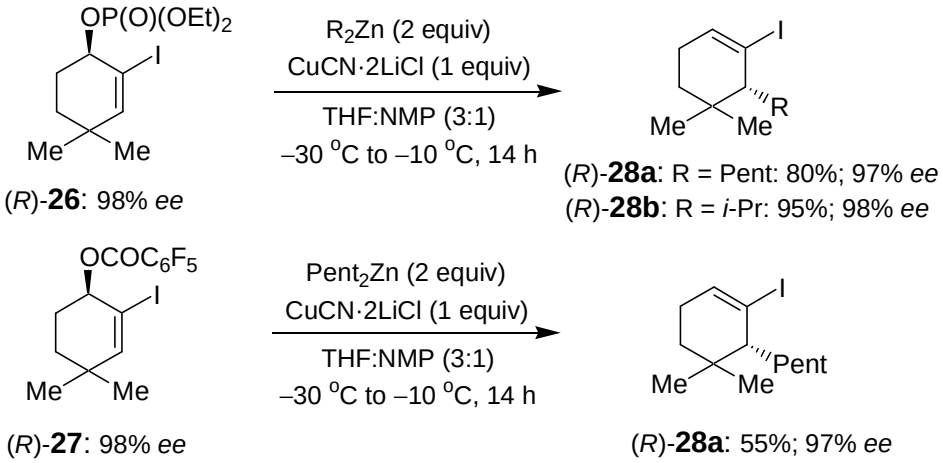
Scheme 25. Preparation of the allylic phosphate (*R*)-**26** and pentafluorobenzoate (*R*)-**27**.

Allylic alcohol (*R*)-**24** was converted into the allylic phosphate (*R*)-**26** by treatment with diethyl chlorophosphate (2.4 equiv) and *N*-methylimidazole (2.4 equiv) in Et_2O. Surprisingly, unlike for the 5-membered analogue, the resulting phosphate could be purified by chromatography on silica gel to give the allylic phosphate (*R*)-**26** in 85% with 98% *ee*. Similarly, the allylic pentafluorobenzoate (*R*)-**27** was obtained in 96% with 98% *ee* after treatment of the allylic alcohol (*R*)-**24** with pentafluorobenzoyl chloride (1.3 equiv), pyridine (1.3 equiv) and DMAP (0.1 equiv) in Et_2O. It should be noted that the allylic phosphate (*R*)-**26** and pentafluorobenzoate (*R*)-**27** are stable and can be stored at 4 °C for several months without decomposition.

1.3 Enantioselective *anti*-S_N2' substitution reactions of sterically hindered allylic phosphate (*R*)-26 and pentafluorobenzoate (*R*)-27 with diorganozincs (R_2Zn)

In a preliminary experiment, the allylic phosphate (*R*)-**26** was treated with dipentylzinc (2 equiv) and CuCN·2LiCl (1 equiv) in a 3:1 solvent mixture of THF and NMP[46] at reaction temperatures from –30 to –10 °C for 14 h. Thereby, the formation of the *anti*-substitution product (*R*)-**28a** was obtained in 80% yield and 97% *ee* (Scheme 26).

[46] We have observed that NMP strongly enhances the reactivity of zinc-copper reagents.



Scheme 26. Comparison between allylic phosphate (*R*)-**26** and pentafluorobenzoate (*R*)-**27**.

Despite the presence of a quaternary center bearing two methyl groups in α-position, the *anti*-S_N2'product was obtained selectively and no product derived from a S_N2 substitution could be detected. To compare the effect of the leaving group, the allylic pentafluorobenzoate (*R*)-**27** was also treated with dipentylzinc under the same reaction conditions. In this case, the desired product (*R*)-**28a** was obtained with the same high enantioselectivity (97% *ee*), but only in 55% of isolated yield.

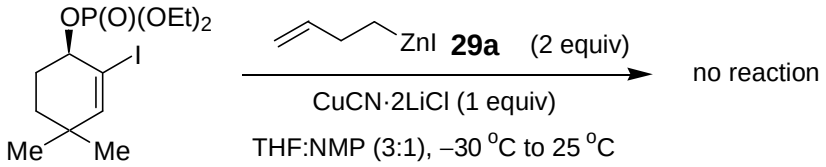
Interestingly, the substitution reactions between the allylic phosphate (*R*)-**26** and dialkylzinc reagents under our reaction conditions showed high regio- and enantioselectivities. Thus, the reaction between the allylic phosphate (*R*)-**26** and more sterically hindered secondary dialkylzincs such as *i*-Pr_2Zn (2 equiv), in the presence of CuCN·2LiCl (1 equiv), also afforded only the *anti*-S_N2' product (*R*)-**28b** in 95% yield and 98% *ee* (Scheme 26).

1.4 Enantioselective *anti*-S_N2'substitution reactions of sterically hindered allylic phosphate (*R*)-26 with mixed diorganozincs $RZnCH_2SiMe_3$

Since allylic substitution reactions of sterically hindered allylic phosphate (*R*)-**26** with a range of functionalized organozinc reagents[47] were planned, 3-buten-1-ylzinc iodide (**29a**)

[47] a) Knochel, P.; Millot, N.; Rodriguez, A. L. *Org. React.* **2001**, *58*, 417; b) Yeh, M. C. P.; Knochel, P. *Tetrahedron Lett.* **1988**, *29*, 2395; c) Knochel, P.; Singer, R. D. *Chem. Rev*. **1993**, *93*, 2117; d) Knochel, P.; Jones, P. *Organozinc Reagents. A practical approach*, Oxford University Press, **1999**; e) Rao, S. A.; Knochel, P. *J. Am. Chem. Soc*. **1991**, *113*, 5735.

was prepared by the direct insertion of activated zinc[47d] to 4-iodobut-1-ene.[48] The resulting zinc reagent **29a** was then reacted with the allylic phosphate (*R*)-**26** (Scheme 27).



(*R*)-**26**: 98% *ee*

Scheme 27. Attempts to react the allylic phosphate (*R*)-**26** with alkylzinc iodide **29a**.

Unfortunately, under the standard reaction conditions which were used for dialkylzinc reagents (Scheme 26), the substitution did not take place even at 25 °C. GC-analysis of the crude reaction mixture showed only unchanged starting material (*R*)-**26**. This result indicated that for an allylic substitution of the sterically hindered allylic phosphate (*R*)-**26**, highly reactive zinc reagents are required.

Since the reactivity of mixed diorganozincs (R^1ZnR^2) is comparable to the one of diorganozincs (R_2Zn), the organozinc $RZnCH_2SiMe_3$[49] (**30a**; R: CH_2=$CHCH_2CH_2$–) was prepared by the addition of a commercially available solution of Me_3SiCH_2Li (1 M in pentane, 1 equiv) to freshly prepared but-3-en-1-ylzinc iodide (**29a**) (Scheme 28). After stirring at –40 °C for 1 h, the resulting mixture was ready to be used.

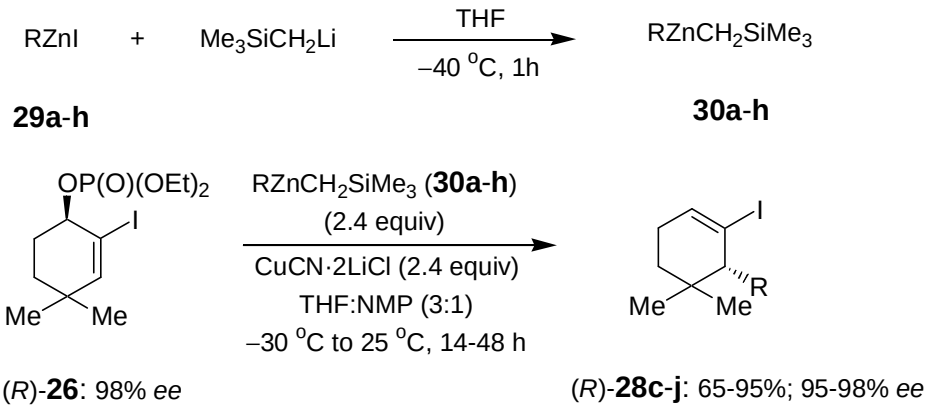
The reaction between the mixed zinc reagent **30a** (2.4 equiv) and the allylic phosphate (*R*)-**26** in the presence of CuCN·2LiCl (2.4 equiv) in a 3:1 solvent mixture of THF and NMP at reaction temperatures from –30 °C to 25 °C gave the desired *anti*-S_N2'substitution product (*R*)-**28c** in 85% yield and 98% *ee* (Scheme 28, Table 1, entry 1). It is worth noting that this mixed zinc reagent allows a selective transfer of the but-2-enyl substituent.[50] The Me_3SiCH_2 group is too unreactive to be transferred and acts only as a spectator ligand. It is also important to note that for allylic substitutions a low reaction temperature is usually crucial for high enantioselectivity. However, following our protocol (Scheme 28) the reaction could be

[48] Hoarau, S.; Fauchere, J. L.; Pappalardo, L.; Roumestant, M. L.; Viallefont, P. *Tetrahedron: Asymmetry* **1996**, *7*, 2585.

[49] Berger, S.; Langer, F.; Lutz, C.; Knochel, P.; Mobley, T. A.; Reddy, C. K. *Angew. Chem. Int. Ed.* **1997**, *36*, 1496.

[50] a) Lutz, C.; Knochel, P. *J. Org. Chem.* **1997**, *62*, 7895; b) Reddy, C. K.; Knochel, P. *Angew. Chem. Int. Ed.* **1996**, *35*, 1700; c) Bertz, S. H.; Eriksson, M.; Miao, G.; Snyder, J. P. *J. Am. Chem. Soc.* **1996**, *118*, 10906; d) Jones, P.; Reddy, C. K.; Knochel, P. *Tetrahedron* **1998**, *54*, 1471.

carried out at reaction temperatures from –30 °C to 25 °C without erosion of enantiomeric excess.

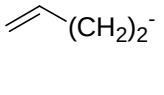
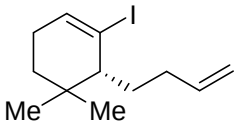
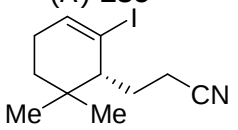
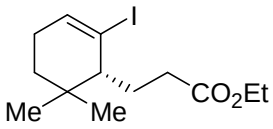
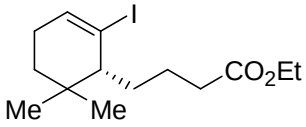
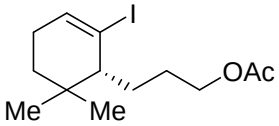
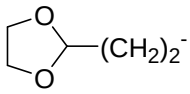
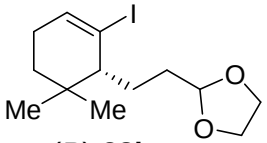
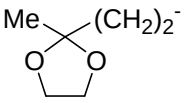
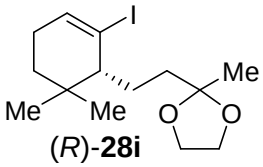
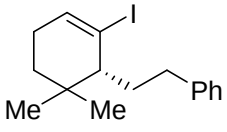


Scheme 28. Preparation and enantioselective *anti*-S_N2' substitution of mixed diorganozincs $RZnCH_2SiMe_3$ (**30a-h**).

Under the optimized reaction conditions, the reaction of mixed zinc reagents **30a-h** (2.4 equiv) with the allylic phosphate (*R*)-**26** in the presence of CuCN·2LiCl (2.4 equiv) in a 3:1 solvent mixture of THF and NMP at reaction temperatures from –30 °C to 25 °C for 14-48 h produced the desired *anti*-S_N2'substitution products **28c-j**. Despite the steric hindrance of the two adjacent methyl groups, a remarkably selective formation of only the S_N2'-products in yields between 65 and 95% and enantioselectivities of 95-98% was observed (Table 1 and Scheme 28).

Excellent transfer of chirality was achieved. Remarkably, a range of functionalized zinc reagents (**30b-h**) can be used (entries 2-8). The less reactive 2-cyanoethyl(trimetylsilylmethyl)zinc reagent (**30b**) required a reaction time of 40 h but provided the expected nitrile **28d** in 73% yield with a slight erosion of the optical purity (95% *ee*, entry 2). Ester-substituted diorganozincs such as **30c-e** (entries 3-5) reacted perfectly affording the *anti*-S_N2'substitution products (**28e-g**) in 97-98% *ee*. Whereas aldehyde and ketone functionalities are not tolerated in this procedure, the use of the corresponding acetal and ketal was viable under our mild reaction conditions, leading to the desired *anti*-S_N2'substitution products (**28h** and **28i**) in 71-90% yield with 98% *ee* (entries 6 and 7).

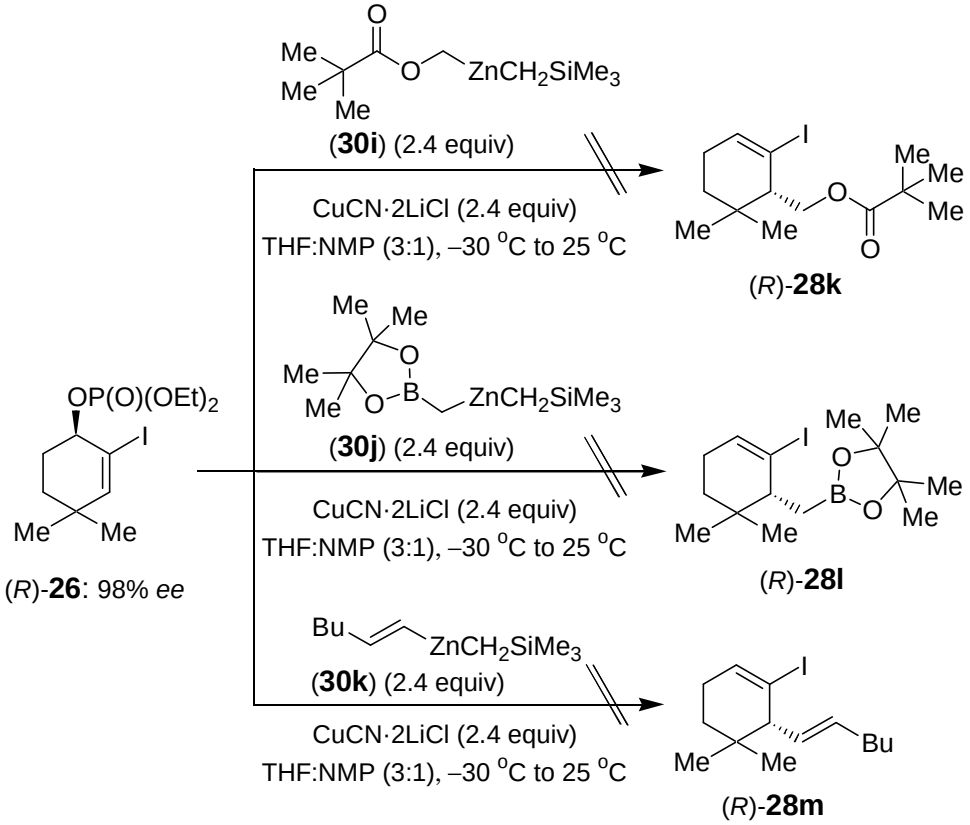
Table 1. Allylic substitution products **28c-j** obtained by the reaction of the mixed diorganozincs **30a-h** with the allylic phosphate (*R*)-**26** in the presence of CuCN·2LiCl.

Entry	$RZnCH_2SiMe_3$ (R)	Product of type (*R*)-**28**	Yield [%][a]	*ee* [%][b]
1	 **30a**	 (*R*)-**28c**	85	98
2	$NC(CH_2)_2$ **30b**	 (*R*)-**28d**	73	95
3	$EtO_2C(CH_2)_2$ **30c**	 (*R*)-**28e**	81	97
4	$EtO_2C(CH_2)_3$ **30d**	 (*R*)-**28f**	82	98
5	$AcO(CH_2)_3$ **30e**	 (*R*)-**28g**	65	97
6	 **30f**	 (*R*)-**28h**	90	98
7	 **30g**	 (*R*)-**28i**	71	98
8	$Ph(CH_2)_2$ **30h**	 (*R*)-**28j**	95	98

[a] Isolated yield of analytical pure product.

[b] The enantiomeric excess was determined by capillary GC-analysis using chiraldex B-PH and chiraldex CB columns. In all cases, the analysis was calibrated with a sample of the racemate.

Unfortunately, attempts to react the mixed dialkylzinc reagents **30i**,[51] **30j**[52] and **30k**[53] with the allylic phosphate (*R*)-**26** under the standard reaction conditions did not give any conversion as judged by the NMR and GC-analysis (Scheme 29).



Scheme 29. Attempts to react the mixed dialkylzinc reagents **30i**, **30j** and **30k** with allylic phosphate (*R*)-**26**.

1.5 Applications

Several of the products of type **28** can be used for the preparation of optically active α-ionone derivatives (Figure 1).[54] This group of natural products are among the most important fragrance constituents due to their distinctive fine violet and rose scents. They are formed by the oxidative degradation of carotenes and are widely distributed in vegetables and

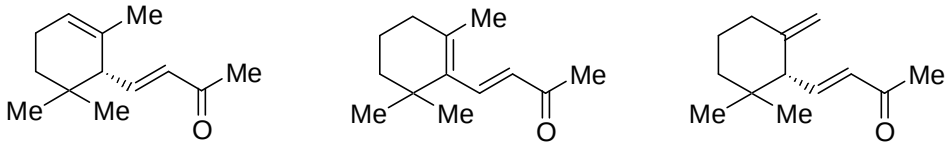
[51] For the preparation of RZnI see: a) Knochel, P.; Chou, T.-S.; Jubert, C.; Rajagopal, D. *J. Org. Chem*. **1993**, *58*, 588; b) Knochel, P.; Chou, T.-S.; Chen, H.-G.; Yeh, M.-C. P.; Rozema, M. J. *J. Org. Chem.* **1989**, *54*, 5202.

[52] For the preparation of RZnI see: a) Knochel, P. *J. Am. Chem. Soc.* **1990**, *112*, 7431; b) Rozema, M. J.; Sidduri, A.-R.; Knochel, P. *J. Org. Chem.* **1992**, *57*, 1956.

[53] Prepared by iodine/lithium-exchange reaction of the corresponding alkenyl iodide, subsequent transmetallation to the corresponding zinc organometallic by treatment with a $ZnBr_2$ solution, and reaction of the resulting alkenylzinc bromide with $LiCH_2SiMe_3$.

[54] Serra, S.; Fuganti, C.; Brenna, E. *Helv. Chim. Acta* **2006**, *89*, 1110; and references cited therein.

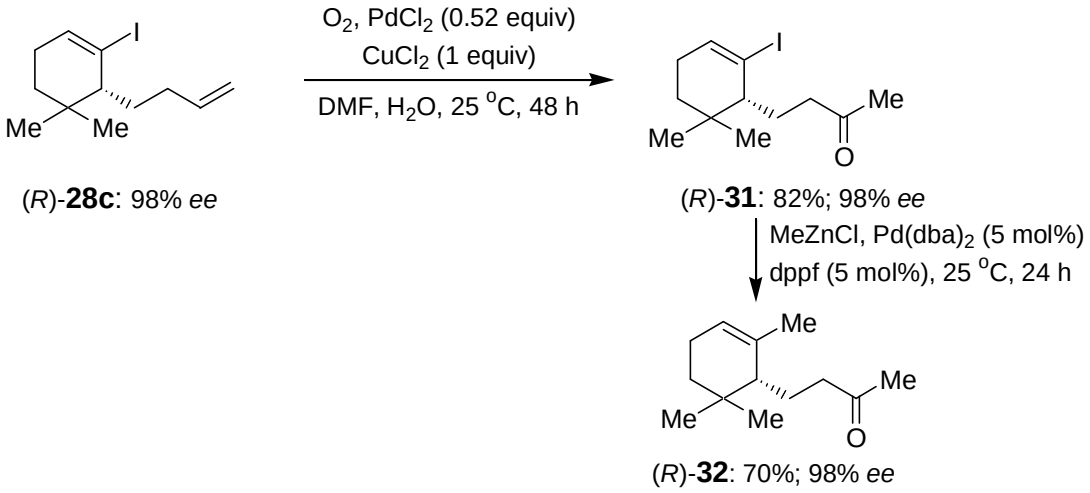
fruits, especially in tea and tobacco.[55] The α- and β-ionones are widely used as flavour ingredients [56] and as starting material in several industrial processes, whereas regioisomerically and enantiomerically pure α- and γ-ionones are suitable building blocks for the synthesis of various natural products.



(*R*)-α-Ionone β-Ionone (*R*)-γ-Ionone

Figure 1. Ionone derivatives.

Thus, palladium-catalyzed oxidation[57] of the terminal alkene of cyclohexenyl iodide (*R*)-**28c** provided the ketone (*R*)-**31** in 82% yield (98% *ee*). Cross-coupling reaction between ketone (*R*)-**31** and MeZnCl in the presence of $Pd(dba)_2$ (5 mol%) and *bis*-diphenylphosphinoferrocene (dppf)[58] (5 mol%) led to (*R*)-dihydro-α-ionone (**32**) in 70% yield and 98% *ee* (Scheme 30).



(*R*)-**28c**: 98% *ee*

(*R*)-**31**: 82%; 98% *ee*

(*R*)-**32**: 70%; 98% *ee*

Scheme 30. Synthesis of (*R*)-dihydro-α-ionone (**32**).

---

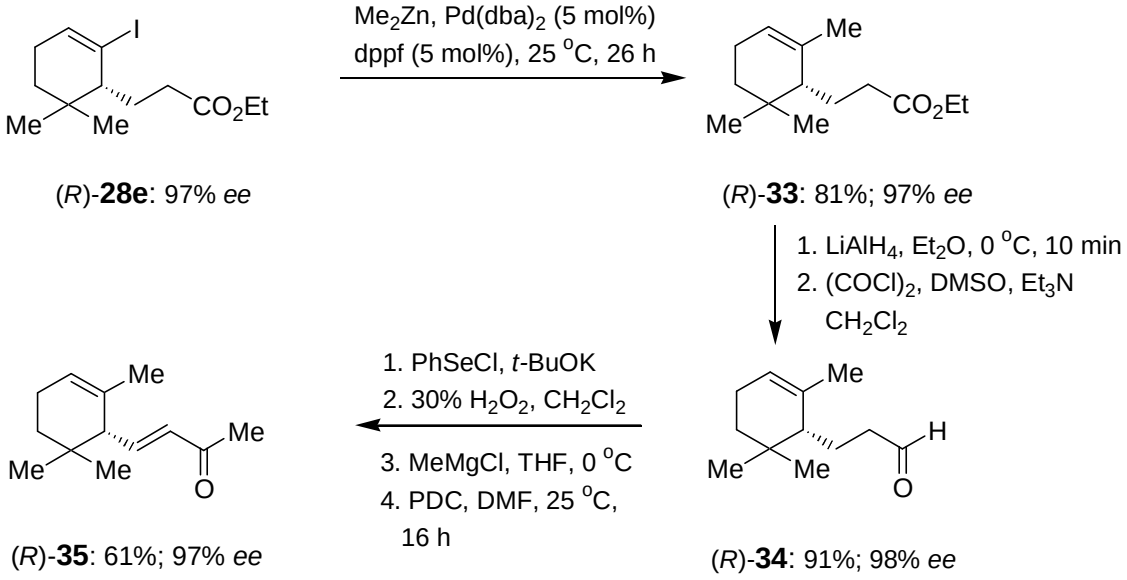
[55] a) Brenna, E.; Fuganti, C.; Serra, S.; Kraft, P. *Eur. J. Org. Chem.* **2002**, 967; b) See also: Fehr, C.; Galindo, J. *Helv. Chim. Acta* **1995**, *78*, 539; c) Fehr, C. *Angew. Chem. Int. Ed.* **1996**, *35*, 2567; d) Fehr, C.; Guntern, O. *Helv. Chim. Acta* **1992**, *75*, 1023.

[56] Bauer, K.; Garbe, D.; Surburg, H. *Common Fragrance and Flavor Materials*, 4th ed.; Wiley-VCH, Weinheim, Germany, **2001**.

[57] a) Henry, P. M. in *Handbook of Organopalladium Chemistry for Organic Synthesis*, (Ed.; Negishi, E.), Wiley-Interscience, New York, **2002**; *Vol. 2*, 2119; b) Feringa, B. L. *Transition Metals for Organic Synthesis*, (Eds.; Beller, M.; Bolm, C.), Wiley-VCH, Weinheim, **1998**, *Vol 2*, 307; c) Tsuji, J. *Synthesis* **1984**, 369.

[58] a) Green, L.; Chauder, B.; Snieckus, V. J. *Heterocycl. Chem.* **1999**, *36*, 143; b) Negishi, E.; Valente, L. F.; Kobayashi, M. *J. Am. Chem. Soc.* **1980**, *102*, 3298; c) Kobayashi, M.; Negishi, E. *J. Org. Chem.* **1980**, *45*, 5223; d) Negishi, E. *Acc. Chem. Res.* **1982**, *15*, 340; e) Tamaru, Y.; Ochiai, H.; Nakamura, T.; Yoshida, Z. *Tetrahedron Lett.* **1986**, *27*, 955; f) Klement, I.; Rottländer, M.; Tucker, C. E.; Majid, T. N.; Knochel, P.; Venegas, P.; Cahiez, G. *Tetrahedron* **1996**, *52*, 7201.

(*R*)-α-Ionone (**35**) was best prepared from the iodoester (*R*)-**28e** (Scheme 31). Negishi cross-coupling[57, 58] with Me_2Zn ($Pd(dba)_2$ (5 mol%), dppf (5 mol%), 25 °C, 26 h) provided the desired methylated product (*R*)-**33** in 81% yield. Reduction of this intermediate with $LiAlH_4$ followed by Swern oxidation gave aldehyde (*R*)-**34** with an overall yield of 91% and 98% *ee*. Phenylselenation with PhSeCl and *t*-BuOK followed by oxidation and elimination (30% aq. H_2O_2, CH_2Cl_2, 25 °C) furnished the expected unsaturated aldehyde intermediate. The synthesis of (*R*)-**35** was completed by the addition of MeMgCl in THF at 0 °C followed by oxidation with PDC in DMF (25 °C, 16 h), affording (*R*)-α-ionone (**35**) in 61% yield and 97% *ee*.[59] Attempts of using the iodoacetal (*R*)-**28i** as starting material for the synthesis of (*R*)-**35** were complicated by acid-catalyzed cyclization side-reactions.



Scheme 31. Synthesis of (*R*)-α-ionone (**35**).

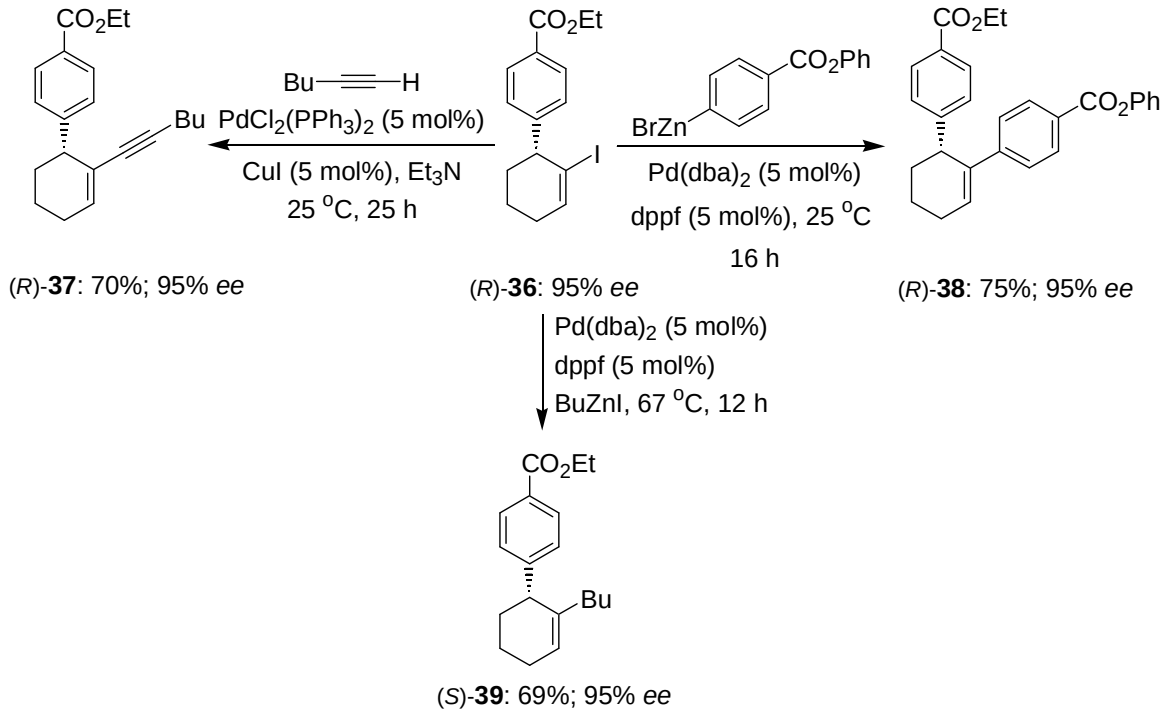
2. Copper(I)-mediated stereoselective *anti*-S_N2' substitution reactions and their applications

2.1 Application to cross-coupling reactions

The allylic substitution products are interesting, because they contain a double bond, which is a versatile functional group in organic synthesis. Particularly, the products which

[59] a) Mori, K.; Puapoomchareon, P. *Liebigs Ann. Chem.* **1991**, 1053; b) Mori, K.; Khlebnikov, V. *Liebigs Ann. Chem.* **1993**, 77; c) Mori, K. *Synlett* **1995**, 1097.

were obtained from the use of 2-iodo-substituted cyclic allylic precursors are valuable, since they contain an alkenyl iodide moiety adjacent to the chiral center, which can be used for various further transformations. It can be replaced by various groups using cross-coupling reactions (Scheme 32).



Scheme 32. Cross-coupling reactions of compound (*R*)-**36**.

Thus, treatment of the cyclohexenyl iodide (*R*)-**36** (95% *ee*), obtained from a stereoselective S_N2 allylic substitution reaction of functionalized lithium arylcuprate [60] prepared by I/Cu exchange, [61] with hex-1-yne in the presence of a catalytic amounts of $PdCl_2(PPh_3)_2$ (5 mol%), CuI (5 mol%)[57, 58, 62] provided the expected enyne (*R*)-**37** in 70% yield (Scheme 32). Similarly, the reaction of (*R*)-**36** with 4-phenoxycarbonylphenylzinc bromide[63] in the presence of $Pd(dba)_2$ (5 mol%) and dppf (5 mol%) furnished the desired Negishi cross-coupling[57, 58, 64] product (*R*)-**38** in 75% yield. Finally, a cross-coupling reaction with BuZnI led to the product (*R*)-**39** in 69% yield (Scheme 32). These cross-coupling

[60] a) Calaza, I. M.; Yang, X.; Soorukram, D.; Knochel, P. *Org. Lett*. **2004**, *6*, 529; b) Yang, X. *Dissertation*, Ludwig-Maximilians-Universität München, **2005**.

[61] a) Piazza, C.; Knochel, P. *Angew. Chem. Int. Ed.* **2002**, *41*, 3263; b) Piazza, C. *Dissertation*, Ludwig-Maximilians-Universität München, **2002**.

[62] a) Qing, F.-L.; Gao, W.-Z. *Tetrahedron Lett.* **2000**, *41*, 7727; b) Marshall, J. A.; Pinney, K. G. *J. Org. Chem.* **1993**, *58*, 7180.

[63] Staubitz, A.; Dohle, W.; Knochel, P. *Synthesis* **2003**, 233.

[64] a) Negishi, E.; Matsushita, M.; Kobayashi, M.; Rand, C. L. *Tetrahedron Lett*. **1983**, *24*, 3822; b) Negishi, E.; Owczarczyk, Z. *Tetrahedron Lett.* **1991**, *32*, 6683.

reactions indicated that the carbon-iodine bond can be readily converted into Csp^2-Csp^3, Csp^2-Csp^2 and Csp^2-Csp bonds.

2.2 Application to the synthesis of chiral ketones bearing an α-stereogenic center

2.2.1 Introduction

The enantioselective preparation of α-alkylated cyclic and acyclic ketones is an important reaction,[65] since chiral α-alkylated carbonyl moieties are present in numerous natural products.[66] Asymmetric alkylation reactions, for example, the alkylation of chiral nucleophiles, the alkylation with chiral electrophiles or the alkylation using chiral additives, are commonly used methods in the synthesis of this class of compounds.

For the alkylation reactions of ketone enolates, the regio- and stereoselectivity of enolate formation are essential for the overall selectivity of the alkylation reaction. The regioselectivity of ketone deprotonation was extensively investigated.[67, 68] The alkylation of metalated azaenolates, for example employing metalated imines, hydrazones, 4,5-dihydrooxazoles, 4,5-dihydroisoxazoles, 5,6-dihydro-4*H*-1,2-oxazines and 2,5-dialkoxy-3,6-dihydropyrazines, is a commonly used method for the asymmetric synthesis of enantiomerically enriched carbonyl compounds. A generalized reaction sequence for this methodology is outlined in Scheme 33. However, this method has limitations with respect to the preparation of α-arylsubstituted ketones.

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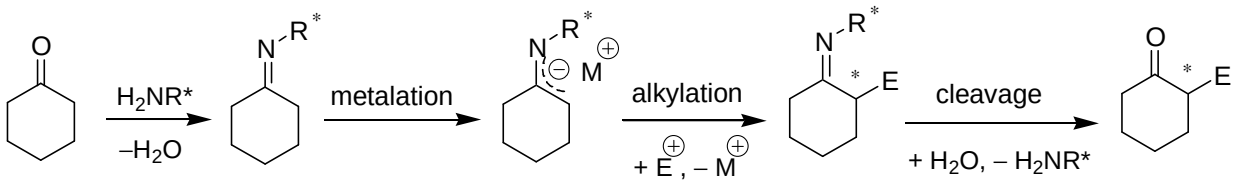
65 a) Fey, P.; Hartwig, W. in *Stereoselective Synthesis*, (Eds.; Helmchen, G.; Hoffmann, R. W.; Mulzer, J.; Schaumann, E.), Thieme Verlag, Stuttgart, **1996**, *Vol 2*, 969 and 994; b) Corey, E. J.; Enders, D. *Tetrahedron Lett*. **1976**, *17*, 11; c) Corey, E. J.; Enders, D. *Chem. Ber*. **1978**, *111*, 1337; 1362; d) Doyle, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc*. **2005**, *127*, 62; e) Luchaco-Cullis, C. A.; Hoveyda, A. H. *J. Am. Chem. Soc*. **2002**, *124*, 8192; f) Liao, S.; Collum, D. B. *J. Am. Chem. Soc*. **2003**, *125*, 15114; g) Job, A.; Janeck, C. F.; Bettray, W.; Peters, R.; Enders, D. *Tetrahedron* **2002**, *58*, 2253; h) Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc*. **1997**, *119*, 6496; i) Nakamura, M.; Hatakeyama, T.; Hara, K.; Nakamura, E. *J. Am. Chem. Soc*. **2003**, *125*, 6362; j) Hirata, T.; Shimoda, K.; Kawano, T. *Tetrahedron: Asymmetry* **2000**, *11*, 1063; k) Ohta, T.; Miyake, T.; Seido, N.; Kumobayashi, H.; Takata, S. *J. Org. Chem*. **1995**, *60*, 357; l) Hamada, T.; Chieffi, A.; Åhman, J.; Buchwald, S. L. *J. Am. Chem. Soc*. **2002**, *124*, 1261; m) Fox, J. M.; Huang, X.; Chieffi, A.; Buchwald, S. L. *J. Am. Chem. Soc*. **2000**, *122*, 1360.

66 a) Enders, D.; Eichenauer, H. *Angew. Chem*. **1979**, *91*, 425; b) Enders, D.; Kipphardt, H.; Fey, P. *Org. Synth*. **1987**, *65*, 183; c) Zhou, Y.; Kim, Y.; Mohammed, K. A.; Jones, D. K.; Muhammad, I.; Dunbar, D. H.; Nagle, D. G. *J. Nat. Prod*. **2005**, *68*, 947; d) Awale, S.; Shrestha, S. P.; Tezuka, Y.; Ueda, J.; Matsushige, K.; Kadota, S. *J. Nat. Prod*. **2005**, *68*, 858.

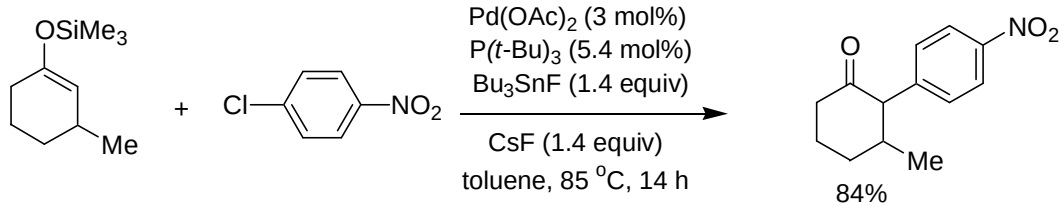
67 a) Evans, D. A. in *Asymmetric Synthesis*, (Ed.; Morrison, J. D.), Academic, New York, *Vol. 3*, 1; and references cited therein; b) d' Angelo, J. *Tetrahedron* **1976**, *32*, 2979; c) Caine, D. in *Carbon-Carbon Bond Formation*, (Ed.; Augustine, R. L.), Marcel Dekker, New York, **1979**, *Vol. 1*, 85; d) Pollack, R. M. *Tetrahedron* **1989**, *45*, 4913; and references cited therein.

68 a) House, H. O. *Modern Synthetic reactions*, 2nd ed.; Benjamin/Cummings, Menlo Park, California **1972**, Chapter 9, 492; b) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry, Part B: Reactions and Synthesis*, 2nd ed.; Plenum, New York, **1983**, Chapter 1, 1.



Scheme 33. Classical sequence for the preparation of enantiomerically enriched 2-substituted cycloalkanones.

Recently, palladium-catalyzed cross couplings of ketone enolates were developed and provided a general way to prepare α-arylated ketones.[69] Especial noteworthy are couplings with silyl enol ethers,[70] which are less basic and nucleophilic than alkali metal enolates, reported by Verkade and Hartwig.[71] With this method, couplings of silyl enol ethers, both derived from cyclic and acyclic ketones, with a wide range of aryl bromides and chlorides to form α-arylated ketones were realized (Scheme 34).



Scheme 34. Palladium-catalyzed cross-coupling of silyl enol ethers with aryl bromides and chlorides, providing α-arylated ketones.

Based on a copper(I)-mediated allylic substitution of the substrates **40** providing the enantiomerically enriched cycloalkenyl iodides **41**, our attention was turned to the application of these compounds for the preparation of chiral ketones **43** through the intermediate **42**. The approach is outlined in Scheme 35.

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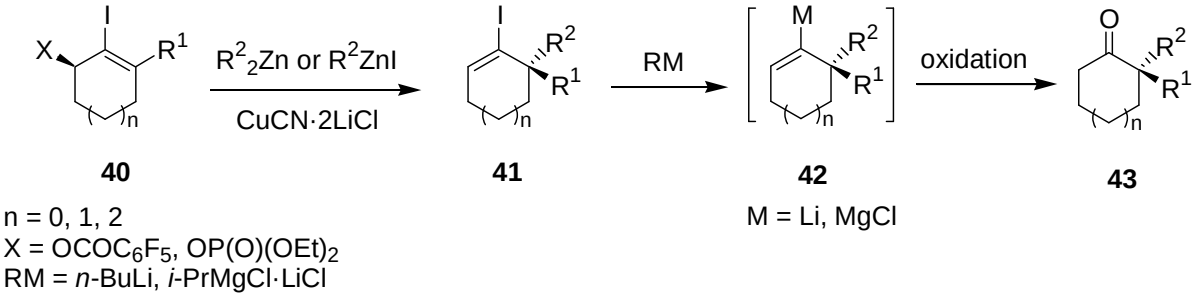
[69] a) For a review on palladium-catalyzed α-arylation of carbonyl compounds and nitriles, see: Culkin, D. A.; Hartwig, J. F. *Acc. Chem. Res*. **2003**, *36*, 234; see also: b) Chae, J.; Yun, J.; Buchwald, S. L. *Org. Lett*. **2004**, *6*, 4809.

[70] For palladium-catalyzed coupling reactions of silyl enol ethers, see: a) Kuwajima, I.; Urabe, H. *J. Am. Chem. Soc.* **1982**, *104*, 6831; b) Kuwajima, I.; Nakamura, E. *Acc. Chem. Res.* **1985**, *18*, 181. For palladium-catalyzed coupling reactions of silyl ketene acetals, see: c) Galarini, R.; Musco, A.; Pontellini, R. *J. Mol. Catal*. **1992**, *72*, L11; d) Agnelli, F.; Sulikowski, G. A. *Tetrahedron Lett.* **1998**, *39*, 8807; e) Hama, T.; Liu, X.; Culkin, D. A.; Hartwig, J. F. *J. Am. Chem. Soc*. **2003**, *123*, 11176.

[71] Su, W.; Raders, S.; Verkade, J. G.; Liao, X.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **2006**, *45*, 5852.



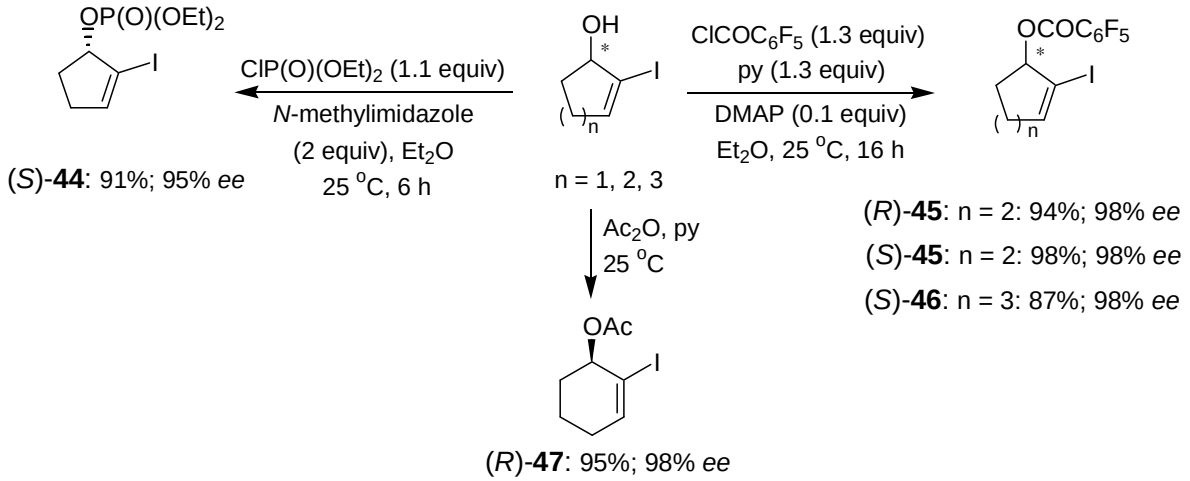
Scheme 35. Synthesis of chiral ketones bearing an α-stereogenic center through a copper(I)-mediated allylic substitution.

Chiral ketones **43** bearing an α-stereogenic center should be obtained with high enantioselectivity by oxidation of the intermediate chiral cycloalkenylmetallic species **42**. These organometallic species could be generated from the corresponding cycloalkenyl iodides **41** by an iodine/metal-exchange. The enantiomerically enriched cycloalkenyl iodides **41** were prepared by a copper(I)-mediated *anti*-S_N2'-allylic substitution with zinc organometallics, starting from the corresponding allylic alcohol derivatives **40**.[72]

2.2.2 Synthesis of enantiomerically enriched cycloalkenyl iodides

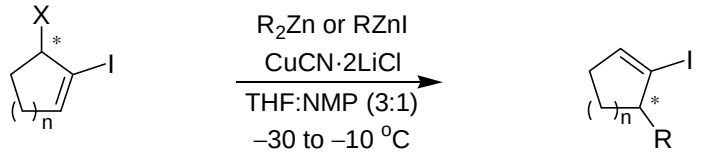
Chiral 2-iodo-substituted cyclic allylic precursors were prepared in high enantiomeric excess as shown in Scheme 36.[27, 40] (*S*)-2-Iodocyclopent-2-en-1-yldiethylphosphate (**44**) was obtained in 91% and 95% *ee* (HPLC: Chiralcel OJ, heptane:*i*-PrOH = 99:1, flow rate 0.6 mL/min) by treatment of the corresponding allylic alcohol with diethylchlorophosphate. Both enantiomers of pentafluorobenzoates (*R*)- and (*S*)-**45** were obtained in 94-98% yield with 98% *ee* by the reaction of the corresponding allylic alcohols with pentafluorobenzoyl chloride. Similarly, pentafluorobenzoate (*S*)-**46** was obtained in 87% yield and 98% *ee*. Allylic acetate (*R*)-**47** was also prepared in 95% yield and 98% *ee*. Chiral cycloalkenyl iodides **48a**-**h** were prepared by stereoselective *anti*-S_N2' substitution reactions of the cyclic electrophiles (*S*)-**44**,[27] (*R*)- and (*S*)-**45** or (*S*)-**46** with various diorganozincs and organozinc halides in the presence of CuCN·2LiCl as shown in Scheme 37. The results are summarized in Table 2.

[72] Soorukram, D.; Knochel, P. *Angew. Chem. Int. Ed.* **2006**, *45*, 3686.



Scheme 36. Preparation of chiral starting materials **44**-**47**.

Primary as well as secondary diorganozinc reagents underwent the substitution reactions with the substrates derived from 5-, 6- and 7-membered rings in the presence of CuCN·2LiCl in a 3:1 solvent mixture of THF:NMP at reaction temperatures from –30 °C to –10 °C. Thereby, *anti*-S_N2' substitution products **48a**-**c** (entries 1-3) were synthesized in good yields and high enantioselectivities. The complete transfer of chirality from the cyclic allylic precursors to the products of type **48** proved also that neither a *syn*-S_N2'substitution nor a S_N2 substitution occurred, since these reactions would lower the optical purity of substitution products **48**. Remarkably, a range of organozinc halides underwent *anti*-S_N2'substitutions with comparable selectivities and yields of isolated products (Scheme 37, and entries 4-8, Table 2).

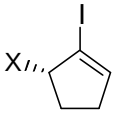
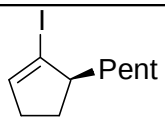
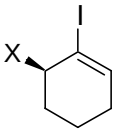
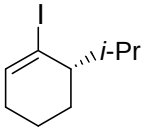
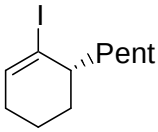
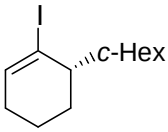
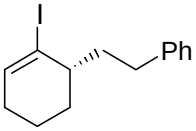
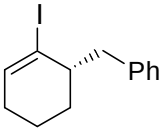
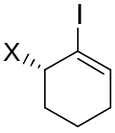
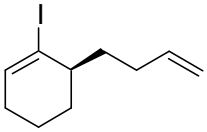
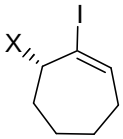
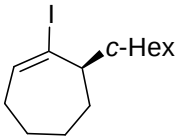


(*S*)-**44**: n = 1; X = $OP(O)(OEt)_2$; 95% *ee*
(*S*)- and (*R*)-**45**: n = 2; X = $OCOC_6F_5$; 98% *ee*
(*S*)-**46**: n = 3; X = $OCOC_6F_5$; 98% *ee*

48a-**h**: 50-97%; 91-99% *ee*

Scheme 37. An *anti*-S_N2'substitutions of chiral cyclic phosphate and pentafluorobenzoates using organozinc reagents.

Table 2. Enantiomerically enriched cycloalkenyl iodides **48a-h**

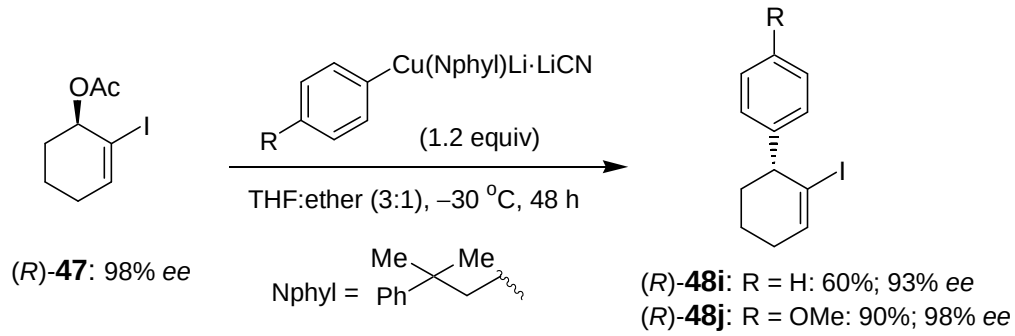
Entry	Allylic substrate	Zinc reagent	Product of type **48**	Yield [%][a]	*ee* [%][b]
1	 (*S*)-**44**: X = $OP(O)(OEt)_2$	$Pent_2Zn$	 (*S*)-**48a**	96	94
2	 (*R*)-**45**: X = $OCOC_6F_5$	*i*-Pr_2Zn	 (*S*)-**48b**	97	94[c]
3	(*R*)-**45**	$Pent_2Zn$	 (*R*)-**48c**	90	99
4	(*R*)-**45**	*c*-HexZnI	 (*S*)-**48d**	90	98[c]
5	(*R*)-**45**	$Ph(CH_2)_2ZnI$	 (*S*)-**48e**	85	99
6	(*R*)-**45**	$PhCH_2ZnI$	 (*S*)-**48f**	50	91
7	 (*S*)-**45**: X = $OCOC_6F_5$	$CH_2=CH(CH_2)_2ZnI$	 (*R*)-**48g**	85	98
8	 (*S*)-**46**: X = $OCOC_6F_5$	*c*-HexZnI	 (*R*)-**48h**	87	96

[a] Isolated yield of analytical pure product.

[b] The enantiomeric excess was determined by capillary GC-analysis using chirasil-Dex CB column. In all cases, the analysis was calibrated with a sample of the racemate.

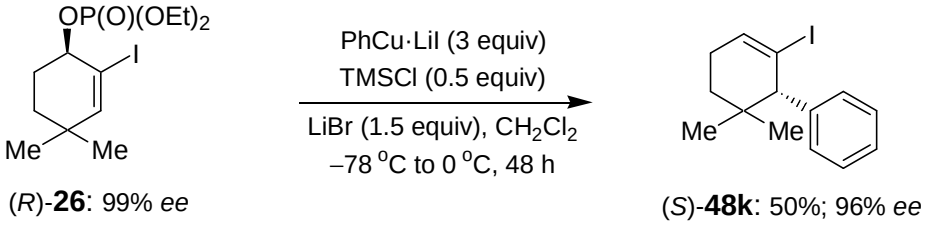
[c] The enantiomeric excess was determined for the corresponding ketone **52**.

Chiral aryl substituted cycloalkenyl iodides (*R*)-**48i** and (*R*)-**48j** were prepared using a stereoselective S_N2 allylic substitution reactions of chiral 2-iodo-1-cyclohex-2-enyl acetate (*R*)-**47** with lithium arylcuprates,[60] prepared from an I/Cu-exchange (Scheme 38).[61] Treatment of lithium arylcuprates with acetate (*R*)-**47** in a 3:1 solvent mixture of THF:ether at –30 °C provided chiral aryl substituted cycloalkenyl iodides (*R*)-**48i** and (*R*)-**48j**, respectively in 60% (93% *ee*) and 90% (98% *ee*). It is noteworthy that a low reaction temperature was required to obtain high enantioselectivities (Scheme 38).



Scheme 38. Stereoselective S_N2 allylic substitution of arylcuprates with acetate (*R*)-**47**.

Chiral cycloalkenyl iodide (*S*)-**48k** was synthesized regio- and stereoselectively as shown in Scheme 39. Thus, the reaction between phenylcopper with the allylic phosphate (*R*)-**26** in the presence of TMSCl (0.5 equiv) and LiBr (1.5 equiv) in CH_2Cl_2 at reaction temperatures from –78 °C to 0 °C [73] afforded (*S*)-**48k** in moderate yield (50%) and 96% *ee* (Scheme 39).

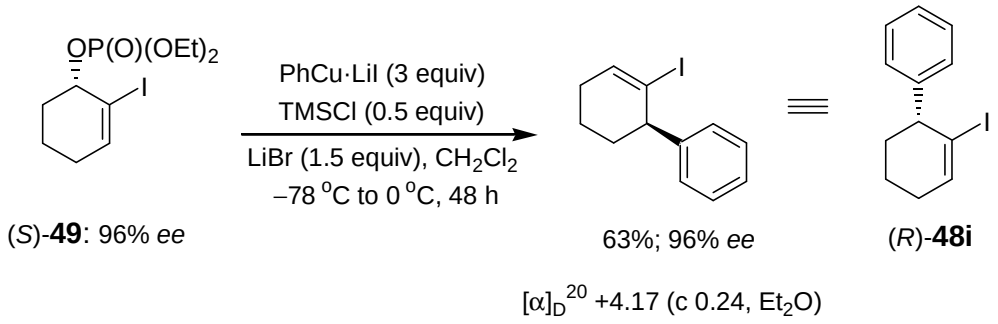


Scheme 39. Stereoselective *anti*-S_N2' allylic substitution with PhCu·LiI and allylic phosphate (*R*)-**26**.

The *anti*-S_N2' mechanism was established by using these reaction conditions for the preparation of the known compound (*R*)-**48i**. Treatment of the allylic phosphate (*S*)-**49** (96%

[73] Asao, N.; Lee, S.; Yamamoto, Y.; *Tetrahedron Lett.* **2003**, *44*, 4265.

ee) with PhCu·LiI afforded the substituted product in 63% yield (Scheme 40). Comparison of the optical rotation led to the conclusion that the substituted product obtained from this reaction has the same configuration as (*R*)-**48i**.



(*S*)-**49**: 96% *ee*

63%; 96% *ee*

(*R*)-**48i**

$[\alpha]_D^{20}$ +4.17 (c 0.24, Et_2O)

Scheme 40. Experiment to probe the *anti*-S_N2' substitution mechanism.

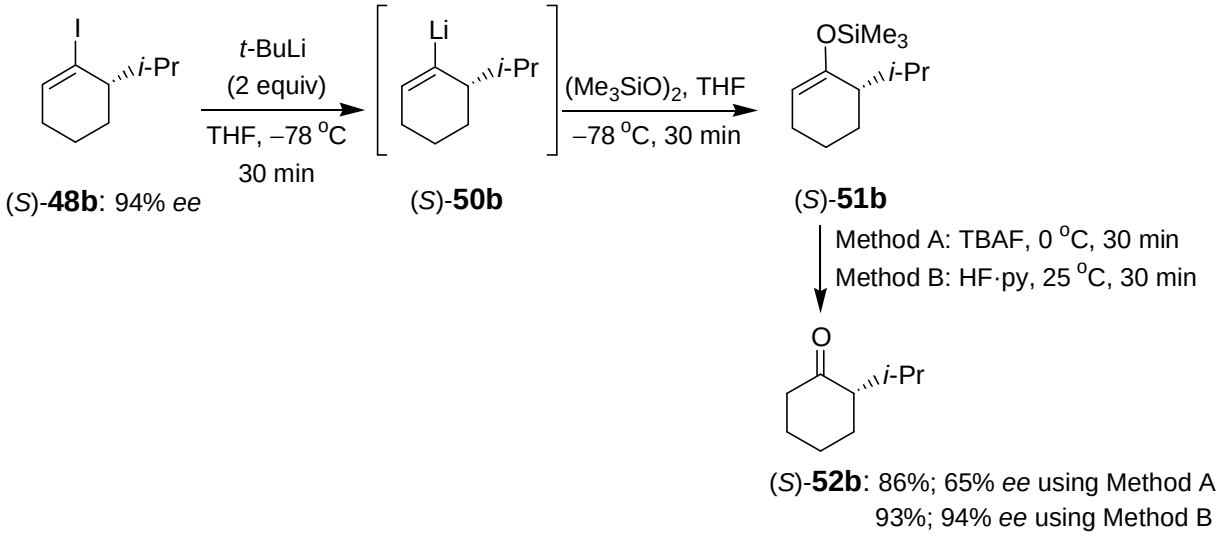
2.2.3 Oxidation reaction using dioxybis(trimethylsilane) [$(Me_3SiO)_2$]

Having chiral cycloalkenyl iodides of type **48** in hand, our attention was focused on an exchange reaction of the alkenyl iodide moiety. The cycloalkenyl iodide (*S*)-**48b** was used as a model compound to optimize the reaction conditions. Treatment of the cycloalkenyl iodide (*S*)-**48b** (94% *ee*) with *t*-BuLi (2 equiv) at –78 °C in THF[74] for 30 min provided the corresponding alkenyllithium intermediate (*S*)-**50b** quantitatively (determined by GC-analysis of hydrolyzed reaction aliquots). This intermediate smoothly reacted with dioxybis(trimethylsilane) [$(Me_3SiO)_2$][75] (1.5 equiv) at –78 °C (30 min) to afford the desired silyl enol ether (*S*)-**51b** (Scheme 41). Purification of the silyl enol ethers can be troublesome, and therefore a one-pot protocol was carried out. Initially, the deprotection of the resulting silyl enol ether (*S*)-**51b** to give the corresponding ketone (*S*)-**52b** was performed using a TBAF solution (1 M in THF, 0 °C, 30 min, Method A). However, the desired product (*S*)-**52b** was obtained in high yield (86%), but only with 65% ee (capillary GC-chirasildex CB column) (Scheme 41). This racemization occurs under the basic reaction conditions of the silyl enol ether cleavage. To our delight, using a HF·pyridine complex in a solvent mixture of

[74] a) Negishi, E.; Swanson, D. R.; Rousset, C. J. *J. Org. Chem.* **1990**, *55*, 5406; b) Bailey, W. F.; Nurmi, T. T.; Patricia, J. J.; Wang, W. *J. Am. Chem. Soc.* **1987**, *109*, 2442; c) Bailey, W. F.; Patricia, J. J.; Nurmi, T. T.; Wang, W. *Tetrahedron Lett.* **1986**, *27*, 1861; d) Bailey, W. F.; Patricia, J. J.; Nurmi, T. T. *Tetrahedron Lett.* **1986**, *27*, 1865; e) Bailey, W. F.; Rossi, K. *J. Am. Chem. Soc.* **1989**, *111*, 765; f) Bailey, W. F.; Ovaska, T. V.; Leipert, T. K. *Tetrahedron Lett.* **1989**, *30*, 3901; g) Bailey, W. F.; Ovaska, T. V. *Tetrahedron Lett.* **1990**, *31*, 627; h) Wu, G.; Cederbaum, F. E.; Negishi, E. *Tetrahedron Lett.* **1990**, *31*, 493.

[75] a) Ricci, A.; Seconi, G.; Curci, R. in *Advances in Silicon Chemistry*, (Ed.; Larson, G. L.), JAI, Greenwich, CT, **1996**, *Vol. 3*, 63; b) Bis(trimethylsilyl)peroxide [$(Me_3SiO)_2$] was purchased from ABCR Product List.

pyridine:THF[76] (25 °C, 30 min, Method B) led to an improved yield and high enantiomeric excess. Thereby, the ketone (*S*)-**52b** was obtained in 93% yield and 94% *ee* after purification (Scheme 41, Table 3, entry 2).

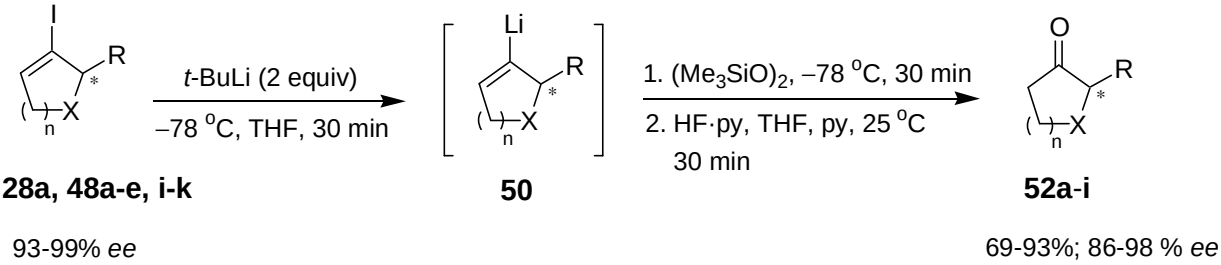


Scheme 41. Preparation of chiral ketone by oxidation of alkenyllithium **50b** with $(Me_3SiO)_2$.

Using these optimized reaction conditions, various chiral cycloalkanones were prepared as summarized in Scheme 42 and Table 3. The cyclopentenyl iodide (*S*)-**48a** (94% *ee*) was converted into the chiral cyclopentanone (*S*)-**52a** in 70% yield and 93% *ee* (entry 1, Table 3). Various primary and secondary 2-alkylsubstituted cyclohexanones were obtained in 94-98% *ee* (entries 2-4). The preparation of 2-arylcyclohexanones is more difficult, since the α-protons to the aromatic ring and to the carbonyl group are much more acidic and easily undergo racemization. Thus, the preparation of (*R*)-2-phenylcyclohexanone (**52e**) furnished the crude product with 90% *ee*. However, during the purification by column chromatography, a slight erosion of the enantiomeric excess was observed and the ketone (*R*)-**52e** was obtained in pure form (70% yield) with 86% *ee* (entry 5). A cyclohexanone (*R*)-**52f** bearing a *para*-methoxyphenyl substituent proved to be especially sensitive toward racemization and attempts to purify it by chromatography either on silica gel or alumina led to a considerable racemization (5-24% *ee* were obtained after purification). However, recrystallization of this ketone from diethyl ether provided the pure product (*R*)-**52f** in 81% yield and 86% *ee* (entry 6). (*S*)-5,5-Dimethyl-6-phenyl-1-iodocyclohexene (**48k**) was converted into the ketone (*R*)-

[76] Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Clardy, J.; Stout, T. J. *J. Am. Chem. Soc*. **1990**, *112*, 7001.

52i in 69% yield and 92% *ee* (entry 8). Also a chiral heptanones were prepared by this procedure. Thus, the cycloheptenyl iodide (*R*)-**48h** was converted into (*R*)-2-cyclohexylcycloheptanone (**52h**) in 76% yield and 96% *ee* (entry 9).

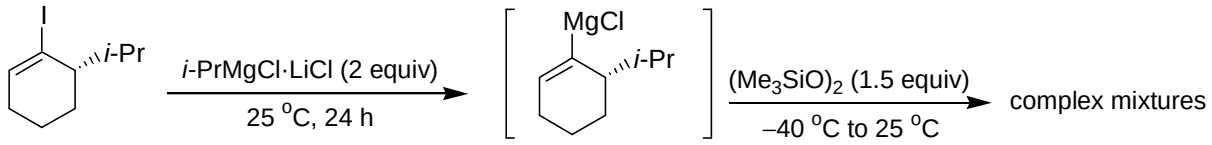


28a, 48a-e, i-k **50** **52a-i**

93-99% *ee* 69-93%; 86-98 % *ee*

Scheme 42. Preparation of chiral ketones of type **52**.

It is known that organomagnesium reagents have a less polarized carbon-metal bond than the corresponding lithium compounds. On the contrary, they show a broader range of remarkable functional group tolerance.[9, 77, 78] In order to expand the scope of our protocol, the exchange reaction using highly reactive Grignard reagent *i*-PrMgCl·LiCl[79] was studied. The iodine/magnesium-exchange reaction proceeded smoothly. Thus, treatment of the cyclohexenyl iodide (*S*)-**48b** with *i*-PrMgCl·LiCl (2 equiv) at 25 °C for 24 h provided the resulting cycloalkenylmagnesium derivative (*S*)-**53** in 95% yield (determined by GC-analysis of hydrolyzed reaction aliquots). Unfortunately, attempts to react the magnesium intermediate (*S*)-**53** with $(Me_3SiO)_2$ (1.5 equiv) at low reaction temperature (–40 °C) did not give rise to the desired silyl enol ether. GC-analysis of the hydrolyzed reaction mixture showed only the hydrolyzed Grignard reagent. Complex mixtures were obtained when the reaction mixture was allowed to warm up to 25 °C (Scheme 43).

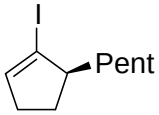
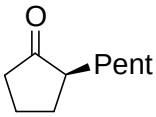
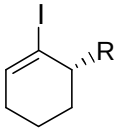
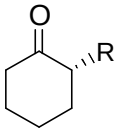
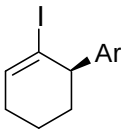
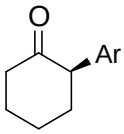
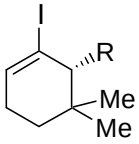
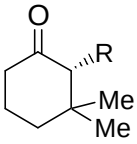
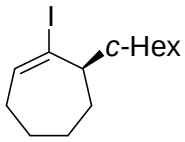
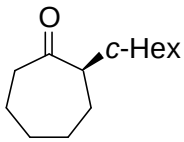


(*S*)-**48b**: 94% *ee* (*S*)-**53**: 95%

Scheme 43. Attempts to react the cycloalkenylmagnesium intermediate (*S*)-**53** with $(Me_3SiO)_2$.

[77] Ren, H.; Krasovskiy, A.; Knochel, P. *Org. Lett.* **2004**, *6*, 4215.
[78] Knochel, P.; Dohle, W.; Gommermann, N.; Kneisel, F. F.; Kopp, F.; Korn, T.; Sapountzis, I. Vu, V. A. *Angew. Chem. Int. Ed.* **2003**, *42*, 4302.
[79] Krasovskiy, A.; Knochel, P. *Angew. Chem. Int. Ed.* **2004**, *43*, 3333.

Table 3. Preparation of chiral ketones of type **52** by oxidation using $(Me_3SiO)_2$.

Entry	Cycloalkenyl iodide	*ee* [%][a]	Product of type **52**	Yield [%][b]	*ee* [%][a]
1	 (*S*)-**48a**	94	 (*S*)-**52a**	70	93[c]
					
2	(*S*)-**48b**: R = *i*-Pr	94	(*S*)-**52b**: R = *i*-Pr	93	94
3	(*S*)-**48c**: R = Pent	99	(*R*)-**52c**: R = Pent	91	97
4	(*S*)-**48d**: R = *c*-Hex	98	(*S*)-**52d**: R = *c*-Hex	88	98
					
5	(*R*)-**48i**: Ar = Ph	93	(*R*)-**52e**: Ar = Ph	70	86
6	(*R*)-**48j**: Ar = *p*-MeO-Ph	98	(*R*)-**52f**: Ar = *p*-MeO-Ph	81	86
					
7	(*R*)-**28a**: R = Pent	99	(*R*)-**52g**: R = Pent	84	93
8	(*S*)-**48k**: R = Ph	96	(*S*)-**52h**: R = Ph	69	92
9	 (*R*)-**48h**	96	 (*R*)-**52i**	76	96

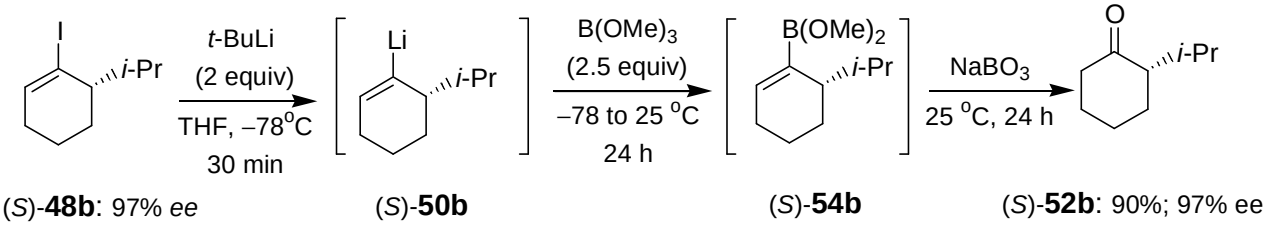
[a] The enantiomeric excess was determined by HPLC- (OD-H column) or capillary GC-analysis (chirasildex CB column). In all cases, the analysis was calibrated with a sample of the racemate.

[b] Isolated yield of analytical pure product.

[c] The enantiomeric excess was determined for the corresponding lactone after Baeyer-Villiger oxidation.

2.2.4 Oxidation reaction using $B(OMe)_3$/ $NaBO_3 \cdot 4H_2O$

Although the oxidation of the alkenyllithium derivatives **50** with $(Me_3SiO)_2$ proceeded in good yields and excellent enantioselectivities, we were concerned about a potential up-scaling and safety issues associated with this oxidation procedure. Therefore, the alternative protocols for an oxidation of the alkenyllithium intermediates **50** were also investigated. Transmetallation of lithium derivative (*S*)-**50b** to a cycloalkenyl(dimethoxy)borane (*S*)-**54b** then further oxidation of this intermediate was examined. Thus, lithium intermediate (*S*)-**50b** was treated with $B(OMe)_3$ [80] (2.5 equiv, –78 °C to 25 °C, 24 h) to give the resulting cycloalkenyl(dimethoxy)borane (*S*)-**54b** which was further oxidized with $NaBO_3 \cdot 4H_2O$ [81] (25 °C, 24 h) (Scheme 44). Thereby, cyclohexanone (*S*)-**52b** was obtained in comparable yield (90%) and with slightly higher enantiomeric excess (97% *ee*; Table 4, entry 2) compared to the one obtained from the oxidation of the alkenyllithium (*S*)-**50b** with $(Me_3SiO)_2$ (93%, 94% *ee*; Table 3, entry 2).



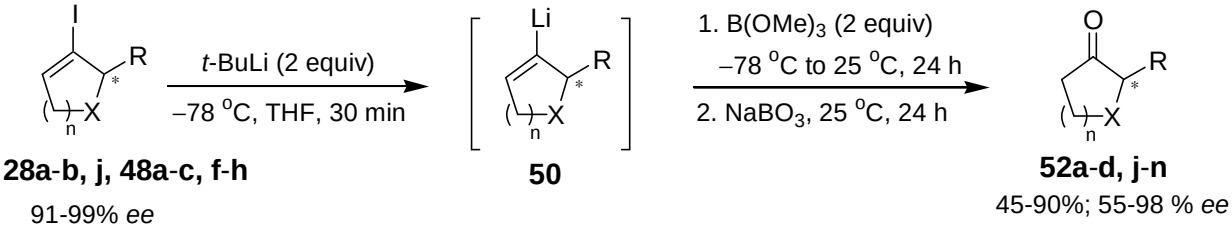
(*S*)-**48b**: 97% *ee* (*S*)-**50b** (*S*)-**54b** (*S*)-**52b**: 90%; 97% ee

Scheme 44. Oxidation of intermediate **50b** using $B(OMe)_3$ and $NaBO_3 \cdot 4H_2O$.

Under these optimized reaction conditions, several cyclohexenyl iodides of type **48** were converted into the chiral ketones **52** in good yields and high enantioselectivities (Scheme 45 and Table 4). A comparison of the two methods (**52a**, **52b**, **52g** and **52i**) shows that similar enantioselectivities were obtained for cyclohexanones and cycloheptanones, while for cyclopentanone (*S*)-**52a**, an enantioselectivity of only 81% *ee* was obtained using boron-based reagents (entry 1, Table 4). Various chiral cyclohexanones bearing either a primary or a secondary alkyl substituent in an α-position can be prepared in 45-65% yield with 55-98% *ee*.

[80] See for example: a) Speicher, A.; Backes, T.; Grosse, S. *Tetrahedron Lett.* **2005**, *61*, 11692; b) Ley, S. V.; Dixon, D. J.; Guy, R. T.; Rodriguez, F.; Sheppard, T. D. *Org. Biomol. Chem.* **2005**, *3*, 4095.

[81] a) Austad, B. C.; Hart, A. C.; Burke, S. D. *Tetrahedron* **2002**, *58*, 2011; b) Nan-Sheng, L.; Piccirille, J. A. *J. Org. Chem.* **2004**, *69*, 4751; c) Voight, E. A.; Seradj, H.; Roethle, P. A.; Burke, S. D. *Org. Lett.* **2004**, *6*, 4045.



28a-b, j, 48a-c, f-h
91-99% *ee*

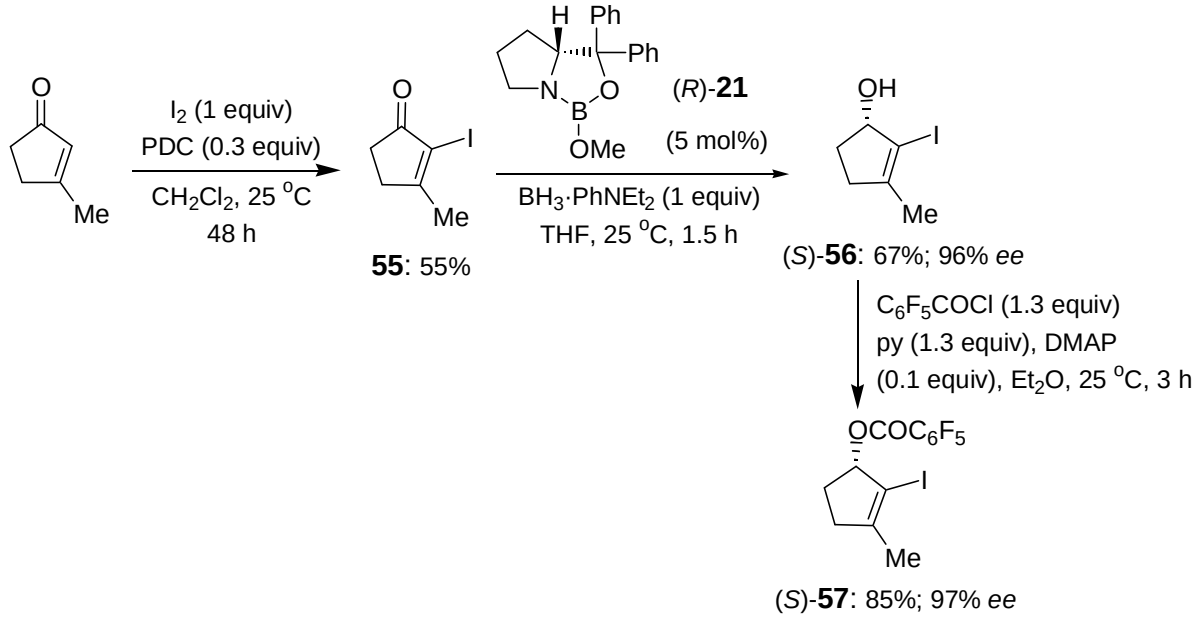
50

52a-d, j-n
45-90%; 55-98 % *ee*

Scheme 45. Preparation of ketones of type **50** using $B(OMe)_3$ and $NaBO_3 \cdot 4H_2O$.

The asymmetric formation of quarternary centers is an important problem in organic synthesis.[82] As mentioned above, our group had developed a protocol for the preparation of these compounds via asymmetric allylic substitutions of open-chain substrates in good yields and high enantioselectivities.[28, 30] The use of a pentafluorobenzoate as leaving group along with dialkylzinc reagents in the presence of CuCN·2LiCl proved essential for the success of the substitution. The reaction of these copper-zinc reagents with 2-iodo-substituted cyclic allylic pentafluorobenzoates followed by oxidation afforded the ketones bearing a chiral quaternary center in the α-position to the carbonyl moiety.

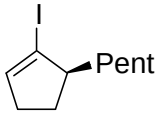
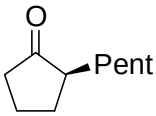
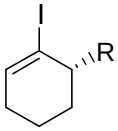
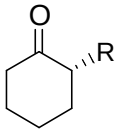
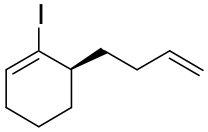
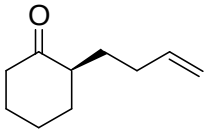
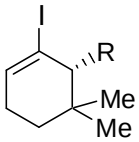
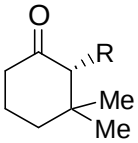
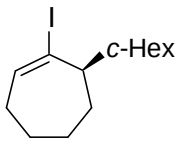
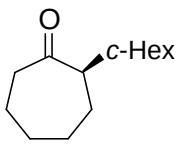
Asymmetric reduction of the ketone **55** with the MeO-CBS catalyst (*R*)-**21** provided the allylic alcohol (*S*)-**56** in 67% yield and 96% *ee*. Treatment of the allylic alcohol (*S*)-**56** with pentafluorobenzoyl chloride gave the desired cyclic allylic pentafluorobenzoate (*S*)-**57** in 85% yield with 97% *ee* (HPLC; Chiralcel OD-H, heptane:*i*-PrOH = 95:5, flow rate 0.5 mL/ min) (Scheme 46).



Scheme 46. Synthesis of allylic pentafluorobenzoate (*S*)-**57**.

[82] Corey, E. J.; Guzman-Perez, A. *Angew. Chem. Int. Ed.* **1998**, *37*, 389.

Table 4. Preparation of chiral ketones of type **52**.

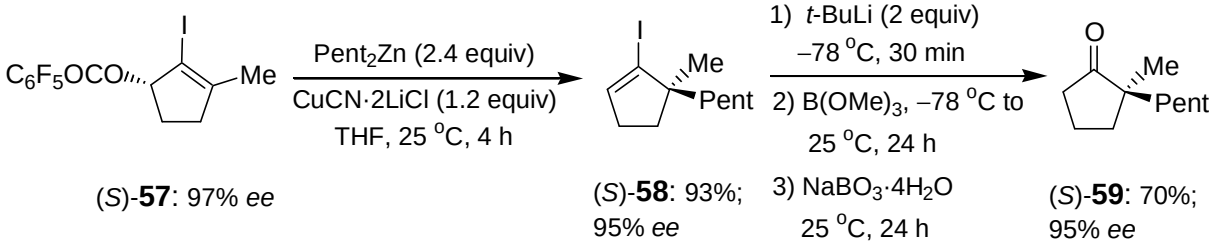
Entry	Cycloalkenyl iodide	*ee* [%][a]	Product of type **52**	Yield [%][b]	*ee* [%][a]
1	 (*S*)-**48a**	94	 (*S*)-**52a**	90	81[c]
					
2	(*S*)-**48b**: R = *i*-Pr	97	(*S*)-**52b**: R = *i*-Pr	90	97
3	(*S*)-**48e**: R = CH_2CH_2Ph	99	(*S*)-**52j**: R = CH_2CH_2Ph	61	95
4	(*S*)-**48f**: R = CH_2Ph	91	(*S*)-**52k**: R = CH_2Ph	45	55
5	 (*R*)-**48g**	98	 (*R*)-**52l**	46	90
					
6	(*R*)-**28a**: R = Pent	99	(*R*)-**52g**: R = Pent	86	98
7	(*R*)-**28b**: R = *i*-Pr	98	(*R*)-**52m**: R = *i*-Pr	56	98
8	(*R*)-**28j**: R = CH_2CH_2Ph	98	(*R*)-**52n**: R = CH_2CH_2Ph	65	97
9	 (*R*)-**48h**	98	 (*R*)-**52i**	86	98

[a] The enantiomeric excess was determined by capillary GC-analysis using chirasildex CB column. In all cases, the analysis was calibrated with a sample of the racemate.

[b] Isolated yield of analytical pure product.

[c] The enantiomeric excess was determined for the corresponding lactone after Baeyer-Villiger oxidation.

Thus, the reaction of allylic pentafluorobenzoate (*S*)-**57** with $Pent_2Zn$ (2.4 equiv) and CuCN·2LiCl (1.2 equiv) in THF at 25 °C provided the *anti*-S_N2' substitution product (*S*)-**58** in 93% yield and 95% *ee* (Scheme 47). Less than 5% of the S_N2-substitution product was observed. It should be noted, that unlike for open-chain substrates, the addition of allylic pentafluorobenzoate (*S*)-**57** to the solution of the mixed zinc-copper reagents was carried out at 25 °C in order to suppress the competitive S_N2 substitution reaction. The synthesis of the corresponding ketone (*S*)-**59** was accomplished by the following sequence in 70% yield and 95% *ee*: (1) iodine/lithium-exchange reaction of (*S*)-**58**, (2) transmetallation with $B(MeO)_3$ and (3) oxidation with $NaBO_3 \cdot 4H_2O$ (Scheme 47).

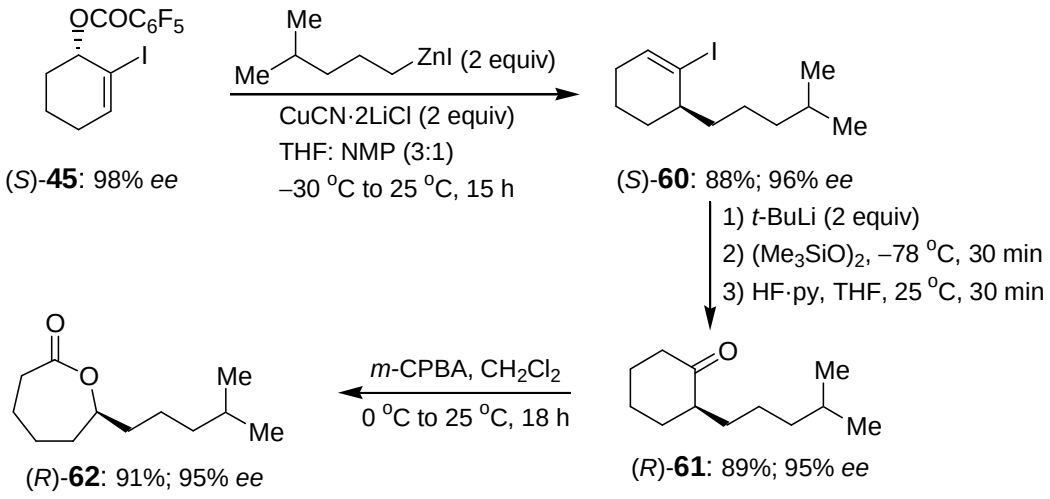


Scheme 47. Preparation of ketone (*S*)-**59** bearing a quaternary stereogenic center.

2.2.5 Application: preparation of a chiral caprolactone

As an application of this methodology, the allylic pentafluorobenzoate (*S*)-**45** (98% *ee*) was treated with $(CH_3)_2CH(CH_2)_3ZnI$ (2 equiv) in the presence of CuCN·2LiCl (2 equiv) in a 3:1 solvent mixture of THF:NMP at reaction temperatures from –30 °C to 25 °C providing the *anti*-S_N2' substitution product (*S*)-**60** in 88% yield and 96% *ee* (Scheme 48). The iodine/lithium-exchange reaction with subsequent oxidation of the corresponding lithium compound using $(Me_3SiO)_2$ followed by deprotection of the intermediate silyl enol ether furnished the ketone (*R*)-**61** in 89% yield and 95% *ee*. Baeyer-Villiger oxidation of the ketone (*S*)-**61** with *meta*-chloroperbenzoic acid (*m*-CPBA) gave (*R*)-10-methyl-6-undecanolide (**62**), which is a caprolactone isolated from the marine streptomycete (isolate B6007)[83] in 91% yield and 95% *ee*.

[83] Striyzke, K.; Schulz, S.; Laatsch, H.; Helmke, E.; Beil, W. *J. Nat. Prod.* **2004**, *67*, 395.



Scheme 48. Preparation of (*R*)-10-methyl-6-undecanolide (**62**).

3. Formal total synthesis of (+)-estrone via asymmetric allylic substitution

3.1 Introduction

The total synthesis of steroids represents an attractive research area due to their valuable biological activity and various pharmacological applications.[84] Since the synthesis of estrone (**63**; Figure 2) by Anner and Miescher in 1948,[85] and the syntheses of nonaromatic steroids, such as cortisone (**64**) and aldosterone (**65**) in the 1950s, a plethora of ingenious approaches were explored to synthesize members of steroid family. For more than 30 years, the synthesis of estrone (**63**) has held special interest for organic chemists,[86] partly because of the follicular hormone activity of estrone itself, and partly because estrone is an important precursor in the production of 19-norsteroids,[87] which has been used as an oral contraceptive. Several of the most widely applied pharmaceuticals contain estrogens[88] and millions of women use estradiol in oral contraceptives.[89]

In the past decades, many approaches were reported towards this female sex hormone. Attention has focused on the development of asymmetric syntheses of estrone itself and

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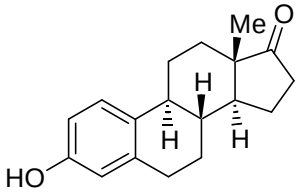
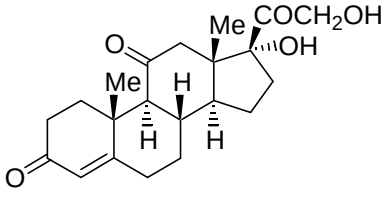
84 For biological properties, see: Anstead, G. M.; Carlson, K. E.; Katzenellenbogen, J. A. *Steroids* **1997**, *62*, 268.
85 Anner, G.; Miescher, K. *Helv. Chim. Acta* **1948**, *31*, 2173.
86 Akhrem, A. A.; Titov, Y. A. *Total Steroid Synthesis*, Plenum Press, New York, **1970**.
87 Pappo, R. in *The Chemistry and Biochemistry of Steroids*, (Ed.; Kharasch, N.), Intra-Science Research Foundation, Santa Monica, California., *Vol. 3*, **1969**, 123.
88 Simonsen, L. L. P. *Pharm. Times* **1994**, April, 18.
89 Djerassi, C. *Science* **1989**, *245*, 356.

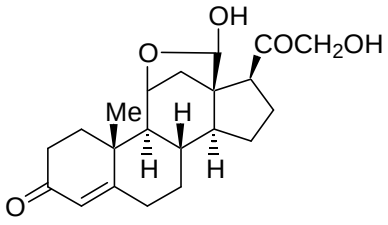
related compounds.[90] Among them are the cationic polyolefinic cyclization,[91] the more recent transition metal-mediated reactions of polyenynes,[92] biogenetic-type electrophilic cyclizations of polyene precursors[93] and the thermally induced radical cyclization of enyne-allenes.[94] They all allow the construction of the steroidal skeleton in a single step. However, the preparation of the precursors is probably rather tedious. The number of total syntheses of steroids is rather limited compared to the nearly countless reports, dealing with the partial synthesis of steroids and selective functionalization reactions at almost every position of the steroidal tetracycle.[95]



(+)-estrone (**63**)



cortisone (**64**)



aldosterone (**65**)

Figure 2. Representative steroids.

Recently reported examples for enantioselective syntheses of (+)-estrone are given in the following schemes. K. Ogasawara described an approach to (+)-estrone starting from a

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[90] a) Danishefsky, S.; Cain, P. *J. Am. Chem. Soc.* **1976**, *98*, 4975; b) Cohen, N.; Banner, B. L.; Blount, J. F.; Tsai, T.; Saucy, G. *J. Org. Chem*. **1973**, *38*, 3229; c) Eder, U.; Sauer, G.; Wlechert, R. *Angew. Chem. Int. Ed. Engl.* **1971**, *10*, 496; d) Cohen, N.; Banner, B. L.; Elchel, W. F.; Parrish, D. R.; Saucy, G.; Cassal, J.-M.; Meier, W.; Fürst, A. *J. Org. Chem.* **1975**, *40*, 681. e) Steglich, W.; Fugmann, B.; Lang-Fugmann, S. Eds. *Römpp Encyclopedia Natural Products*, Thieme Verlag, Stuttgart, **2000**; f) Corey, E. J.; Cheng, X.-M. *The Logic of Chemical Synthesis*, John Wiley & Sons, New York, **1989**; For the total syntheses of steroids, see: g) Zeelen, F. J. *Nat. Prod. Rep.* **1994**, *11*, 607; h) Groen, M. B.; Zeelen, F. J. *Recl. Trav. Chim. Pays-Bas* **1986**, *105*, 465.

[91] a) Corey, E. J.; Virgil, S. C.; Cheng, H.; Baker, C. H.; Matsuda, S. P. T.; Singh, V.; Sarshar, S. *J. Am. Chem. Soc.* **1995**, *117*, 11819; b) Johnson, W. S.; Fletcher, V. R.; Chenera, B.; Bartlett, W. R.; Tham, F. S.; Kullnig, R. K. *J. Am. Chem. Soc.* **1993**, *115*, 497; c) Nicolaou, K. C.; Barnette, W. E.; Ma, P. *J. Org. Chem.* **1980**, *45*, 1463.

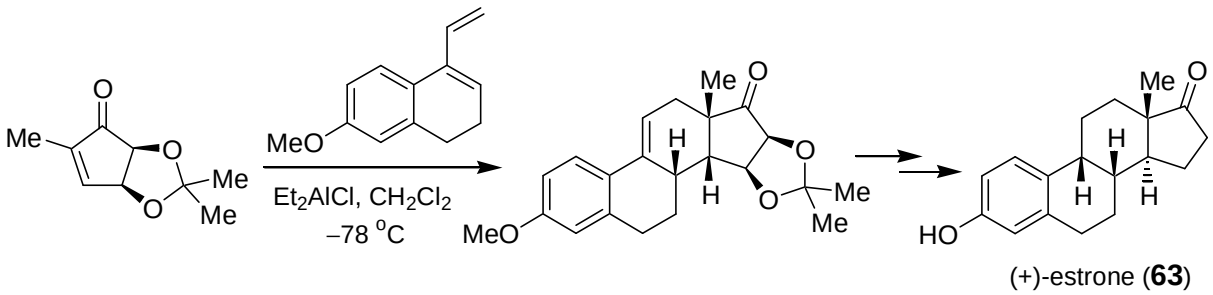
[92] a) Crigg, R.; Rasul, R.; Savic, V. *Tetrahedron Lett.* **1997**, *38*, 1825; b) Bao, J.; Dragisich, V.; Wenglowsky, S.; Wulff, W. D. *J. Am. Chem. Soc.* **1991**, *113*, 9873; c) Zhang, Y.; Wu G.; Agnel, G.; Negishi, E. *J. Am. Chem. Soc.* **1990**, *112*, 8590; d) Vollhardt, K. P. C. *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 539; e) Vollhardt, K. P. C. *Pure Appl. Chem.* **1985**, *57*, 1819; f) Lecker, S. H.; Nguyen, N. H.; Vollhardt, K. P. C. *J. Am. Chem. Soc*. **1986**, *108*, 856; g) Sugihara, T.; Copéret, C.; Owczarczyk, Z.; Harding, L. S.; Negishi, E. *J. Am. Chem. Soc.* **1994**, *116*, 7923; h) Gauthier, V.; Cazes, B.; Gore, J. *Tetrahedron Lett.* **1991**, *32*, 915; i) Trost, B. M.; Shi, Y. *J. Am. Chem. Soc.* **1993**, *115*, 9421.

[93] a) van Tamelen, E. E.; Holten, R. A.; Hopla, R. E.; Konz, W. E. *J. Am. Chem. Soc.* **1972**, *94*, 8228; b) van Tamelen, E. E.; Anderson, R. J. *J. Am. Chem. Soc.* **1972**, *94*, 8225; c) Johnson, W. S.; Wiedhaup, K.; Brady, S. F.; Olson, G. L. *J. Am. Chem. Soc*. **1974**, *96*, 3979; d) Fish, P. V.; Johnson, W. S.; Jones, G. S.; Tham, F. S.; Kullnig, R. K. *J. Org. Chem.* **1994**, *59*, 6150; e) Corey, E. J.; Lin, S. *J. Am. Chem. Soc.* **1996**, *118*, 8765.

[94] Andemichael, Y. W.; Huang, Y.; Wang, K. K. *J. Org. Chem.* **1993**, *58*, 1651.

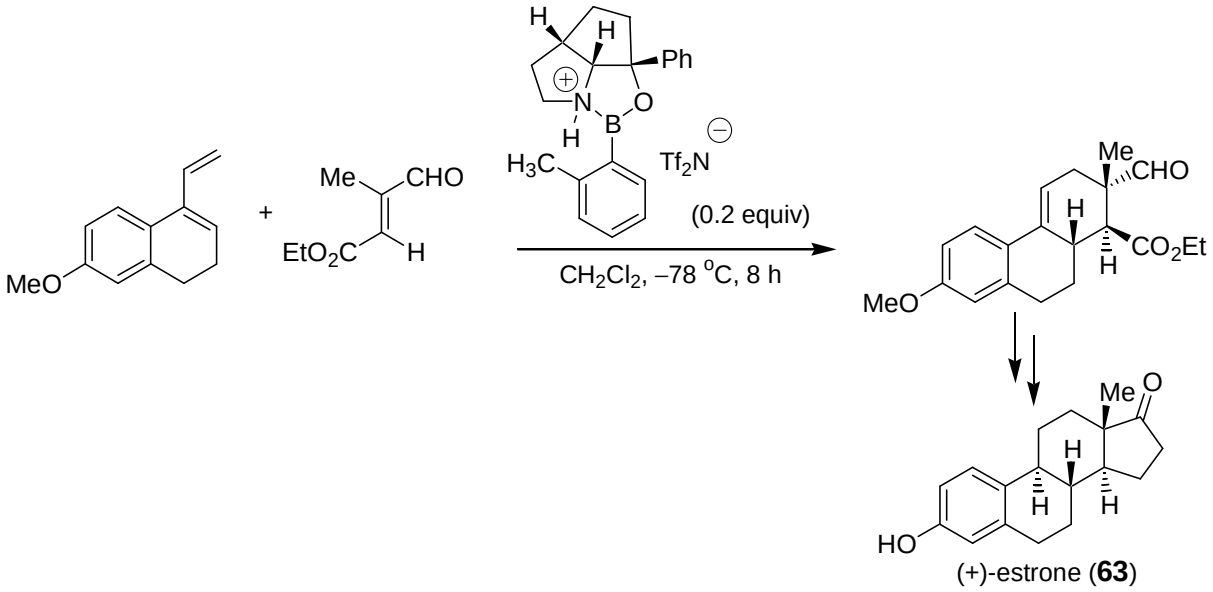
[95] Hanson, J. R. *Steroids* **1996**, *13*, 373.

chiral dioxycyclopentenone building block for a Diels-Alder reaction with Dane's diene in the presence of a Lewis acid (Scheme 49).[96]



Scheme 49. Synthesis of (+)-estrone by K. Ogasawara.

E. J. Corey reported the enantioselective synthesis of estrone using the enantioselective [4+2]-cycloaddition, catalyzed by a chiral oxazaborolidinium salt, as the key step to construct the estrone skeleton. The synthesis of (+)-estrone by E. J. Corey, which is reminiscent of Ogasawara's synthesis, is outlined in Scheme 50.[97]



Scheme 50. Synthesis of (+)-estrone by E. J. Corey.

L. F. Tietze described a highly efficient total synthesis of enantiomerically pure estrone using two successive Heck reactions as key steps for the construction of the steroidal skeleton (Scheme 51).[98]

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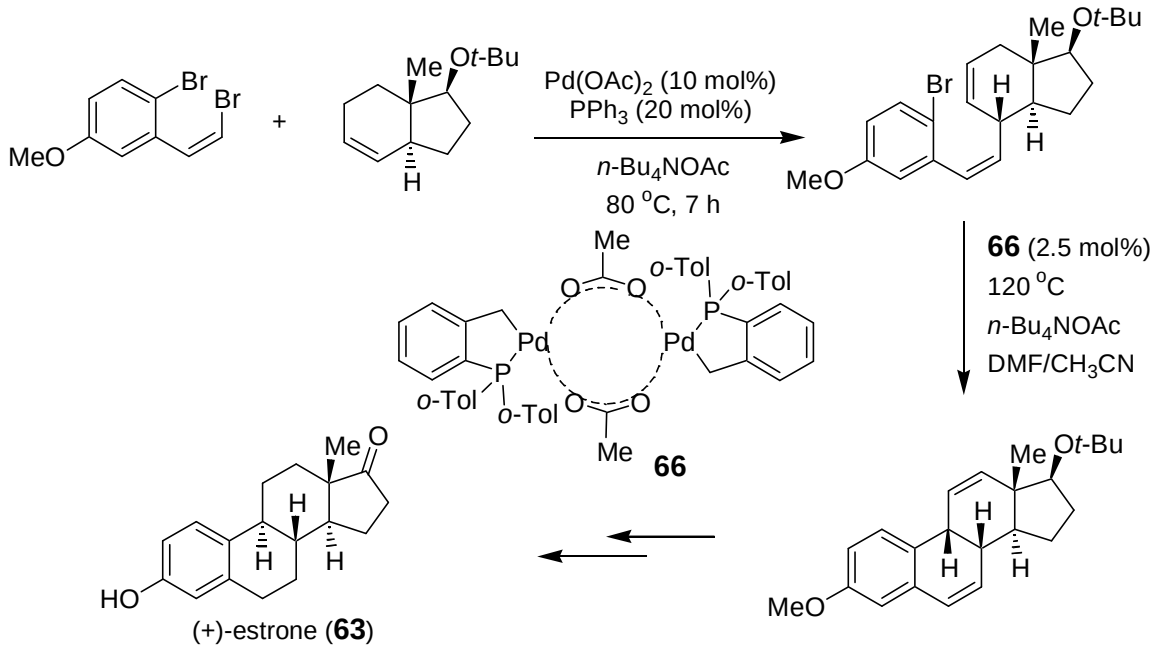
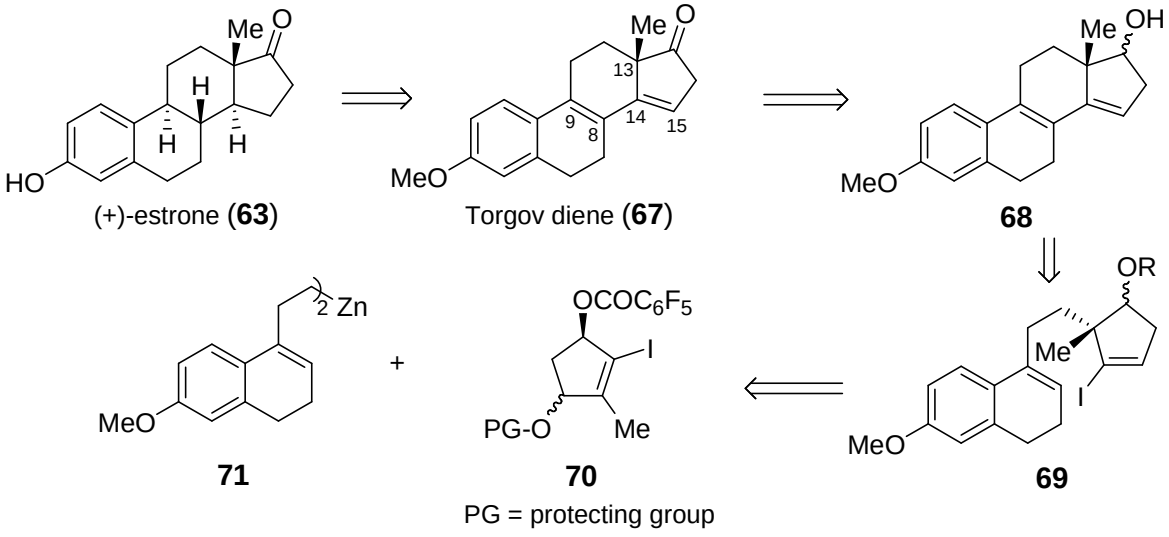
96 Tanaka, K.; Nakashima, H.; Taniguchi, T.; Ogasawara, K. *Org. Lett.* **2000**, *2*, 1915.
97 Hu, Q.-Y.; Rege, P. D.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 5984.
98 Tietze, L. F.; Nöbel, T.; Spescha, M. *J. Am. Chem. Soc.* **1998**, *120*, 8971.



Scheme 51. Synthesis of (+)-estrone by L. F. Tietze.

Due to our interest in the applications of copper(I)-mediated asymmetric allylic substitution reactions of chiral electrophiles with organozinc reagents to natural products synthesis, the remarkable ability of this method, especially to install the chiral quaternary carbon center at position 13, for the enantioselective synthesis of (+)-estrone was demonstrated (Scheme 52).

3.2 Retrosynthesis



Scheme 52. Retrosynthetic analysis of (+)-estrone (**63**) using an asymmetric allylic substitution as a key-step.

(+)-Estrone (**63**) could be obtained from the Torgov diene (**67**) by a reported sequence: (1) stereospecific reduction of the 14,15- and 8,9-double bond of **67**, respectively and (2) HBr-catalyzed ether cleavage.[99] The Torgov diene (**67**) should be obtained by an oxidation of the intermediate **68**, which would be obtained through palladium-catalyzed Heck reaction of the cycloalkenyl iodide **69**. Compound **69** may be generated via stereoselective *anti*-S_N2' substitution reaction of allylic pentafluorobenzoate **70** with the dialkylzinc reagent **71** in the presence of CuCN·2LiCl (key step of the synthesis).

3.3 Synthesis of the chiral polyfunctional cyclopentenol derivative 70

3.3.1 Synthesis of a cyclic electrophile starting from racemic starting materials

Our attention was first focused on the synthesis of the racemic substituted cyclopentenone **76**. The synthesis was accomplished in a straightforward manner starting from 2,5-dimethylfuran (**72**) (Scheme 53). An oxidation followed by the ring opening reaction using magnesium methylperphthalate (MMPP) proved to give efficiently the *cis*-3-hexene-2,5-dione (**73**).[100] Cyclization of the diketone **73** under basic reaction conditions followed by a rearrangement gave 4-hydroxy-3-methylcyclopent-2-en-1-one (*rac*-**74**). The direct protection of the secondary alcohol was necessary to facilitate the purification. Thus, the crude secondary alcohol *rac*-**74** was treated with TBSCl (1.2 equiv) and imidazole (1.5 equiv) in DMF to give the cyclopentenone *rac*-**75** in 30% overall yield starting from the furan **72**. Finally, the cyclopentenone *rac*-**75** was converted into α-iodocyclopentenone *rac*-**76** in 77% yield by treatment with I_2 (2.5 equiv) and PDC (0.3 equiv) in CH_2Cl_2 at 25 ^oC for 46 h.

Considering the envisioned approach to (+)-estrone via asymmetric *anti*-S_N2'substitution (Scheme 52), the (*R*)-configuration needed to be installed at carbonyl carbon (C-1) of the cyclopentenone *rac*-**76**. Asymmetric reduction using (*S*)-MeO-CBS catalyst was used for this purpose (Scheme 54). Thus, treatment of the cyclopentenone *rac*-**76** with *in situ* prepared (*S*)-MeO-CBS catalyst (5 mol%) and borane *N*,*N*-diethylaniline complex (1 equiv) afforded the two diastereomers, (1*R*, 4*S*)-**77a** and (1*R*, 4*R*)-**77b** (Scheme 54).

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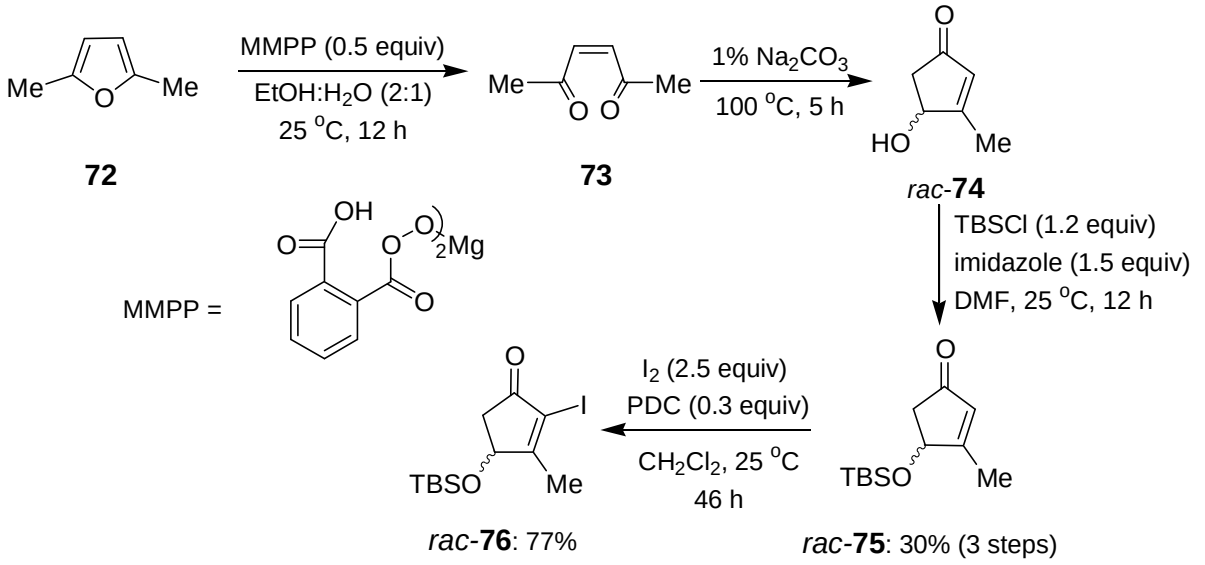
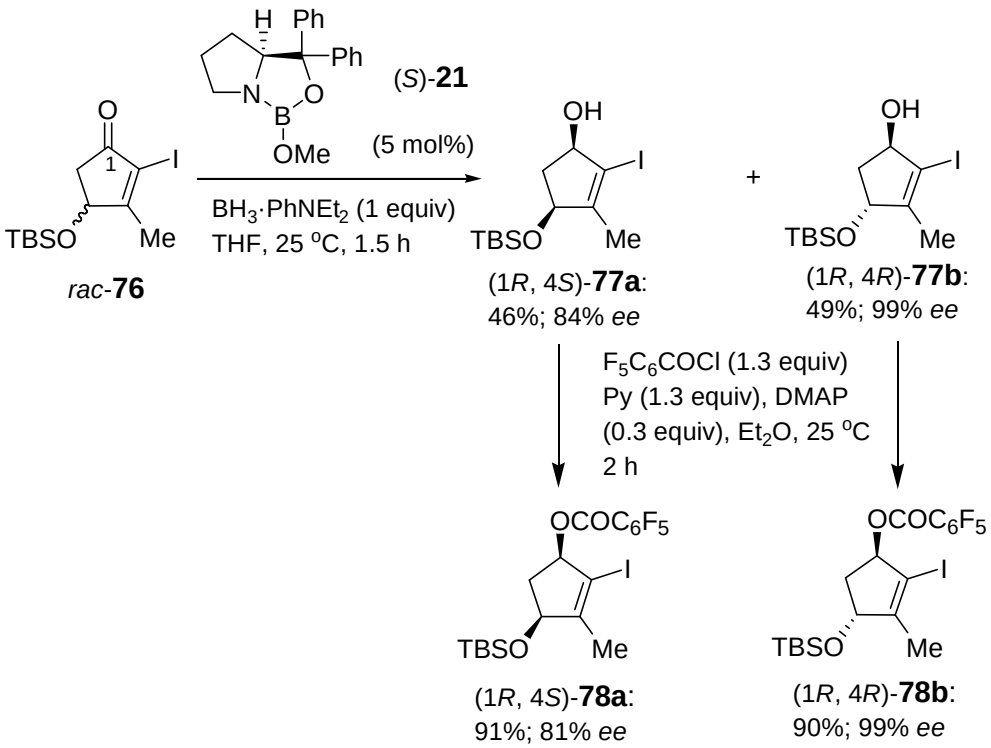
[99] Quinkert, C.; Grosso, M. D.; Doring, A.; Doring, W.; Schenkel, R. I.; Bauch, M.; Dambacher, G. T.; Bats, J. W.; Zimmermann, G.; Durner, G. *Helv. Chim. Acta* **1995**, *78*, 1345.

[100] Adembri, G.; Giorgi, G.; Lampariello, R. L.; Paoli, M. L. Sega, A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2649.



Scheme 53. Synthesis of the substituted cyclopentenone *rac*-**76**.



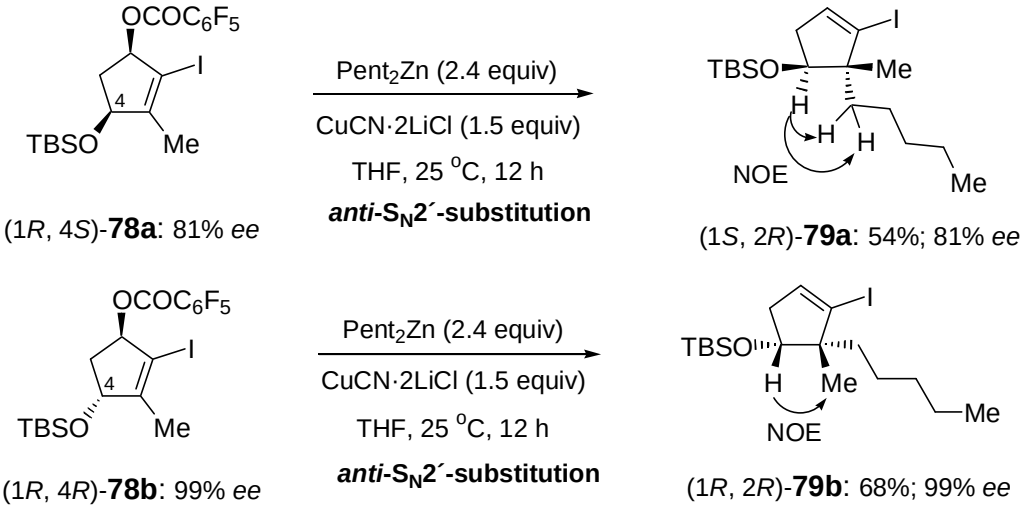
Scheme 54. Synthesis of allylic pentafluorobenzoates (1*R*, 4*S*)-**78a** and (1*R*, 4*R*)-**78b**.

Fortunately, they could be separated by column chromatography and (1*R*, 4*S*)-**77a** and (1*R*, 4*R*)-**77b** were obtained, respectively, in 46% with 84% *ee* (HPLC; Chiralcel OD, heptane:*i*-PrOH = 99:1, flow rate 0.4 mL/min) and 49% with 99% *ee* (HPLC; Chiralcel OD, heptane:*i*-PrOH = 95:5, flow rate 0.5 mL/min). Thereafter, both diastereomers were transformed separately into the corresponding pentafluorobenzoates (1*R*, 4*S*)-**78a**, and (1*R*,

4*R*)-**78b**. The pentafluorobenzoate (1*R*, 4*S*)-**78a** was obtained in 91% with 81% *ee*. The pentafluorobenzoate (1*R*, 4*R*)-**78b** was obtained in 90% with 99% *ee* (Scheme 54).

3.3.2 Determination of the relative configuration of the starting materials

Attempts to determine the absolute configurations at C-4 of (1*R*, 4*S*)-**77a** and (1*R*, 4*R*)-**77b** as well as of (1*R*, 4*S*)-**78a** and (1*R*, 4*R*)-**78b** by 2D-NMR experiments failed. It proved also difficult to obtain a single crystal suitable for crystal X-ray diffraction analysis. However, the absolute stereochemistry could be established through an *anti*-S_N2' substitution reaction (Scheme 55). Thus, allylic pentafluorobenzoates (1*R*, 4*S*)-**78a** and (1*R*, 4*R*)-**78b** were subjected to the standard reaction conditions for the *anti*-S_N2'substitution reaction using dipentylzinc (2.4 equiv) in the presence of CuCN·2LiCl (1.5 equiv) at 25 °C. The products (1*S*, 2*R*)-**79a** and (1*R*, 2*R*)-**79b** were obtained after purification, respectively, in 54% with 81% *ee* and 68% with 99% *ee*. The NOE NMR-experiment for the product (1*S*, 2*R*)-**79a** showed a correlation between the proton on carbon, bearing the –OTBS group, and the methylene protons of the pentyl substitutent. Therefore, we concluded that the stereocenter at C-4 of allylic pentafluorobenzoate (1*R*, 4*S*)-**78a** derived from allylic alcohol (1*R*, 4*S*)-**77a** possess (*S*)-configuration.



(1*R*, 4*S*)-**78a**: 81% *ee*

(1*S*, 2*R*)-**79a**: 54%; 81% *ee*

(1*R*, 4*R*)-**78b**: 99% *ee*

(1*R*, 2*R*)-**79b**: 68%; 99% *ee*

Scheme 55. Determination of the absolute configuration using *anti*-S_N2'substitution reactions.

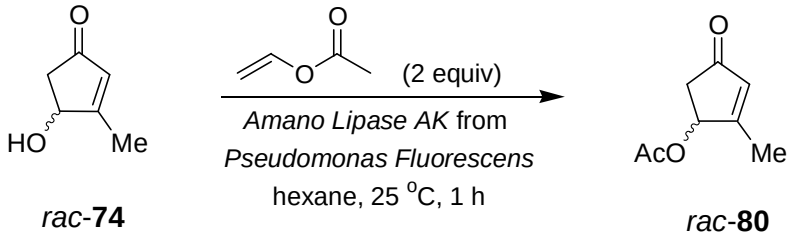
In contrast, the stereocenter at C-4 of allylic pentafluorobenzoate (1*R*, 4*R*)-**78b** derived from allylic alcohol (1*R*, 4*R*)-**77b** was shown to possess (*R*)-configuration using the same method (Scheme 55). These results indicate that only one isomer of the allylic alcohol

77 can be utilized for the envisioned enantioselective synthesis of (+)-estrone. Therefore, we explored the alternative methods to access enantiomerically pure alchol (1*R*, 4*R*)-**77b** in high yields.

3.3.3 Synthesis of an enantiomerically pure allylic alcohol by enzymatic resolution

We needed an efficient method for obtaining large quantities of enantiomerically pure (1*R*, 4*R*)-**77b** derived from pure (4*R*)-**74**. Therefore, an enzymatic resolution protocol was studied. Furthermore, the high enantioselectivity of the process also might allow the conversion of the undesired by-product (4*S*)-**74** to the desired (4*R*)-**74** enantiomer with high stereospecificity via a Mitsunobu reaction.[101] Thus our initial efforts were directed towards a lipase resolution.[102]

Enzymatic resolution of various racemic allylic alcohols[103] using *Amano Lipase AK* from *Pseudomonas Fluorescens*[104] was carried out previously in our group and excellent results (99% *ee* of the resulting alcohols) were obtained. [105] Thus, 4-hydroxy-3-methylcyclopent-2-en-1-one (*rac*-**74**) was first exposed to the slightly modified reaction conditions from those reported using *Amano Lipase AK* from *Pseudomonas Fluorescens* in the solution of vinyl acetate in hexane (Scheme 56).



rac-**74** *rac*-**80**

Scheme 56. Enzymatic resolution of *rac*-**74** using *Amano Lipase AK* from *Pseudomonas Fluorescens*.

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101 a) Mitsunobu, O. *Synthesis* **1981**, 1; b) Hughes, D. L. *Org. React.* **1992**, *42*, 335.

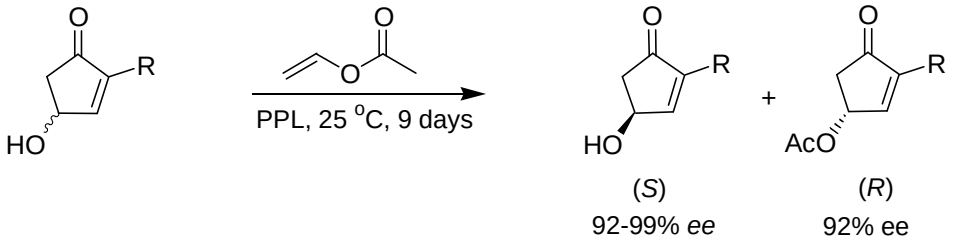
102 a) Azerad, R.; Buisson, D. *Current Opinion in Biotechnology* **2000**, *111*, 565; b) Muralidhar, R. V.; Marchant, R.; Nigam, P. *J. Chem. Technol. Biotechnol.* **2001**, *76*, 3; c) Ikunaka, M. *Catalysis Today* **2004**, *96*, 93.

103 a) Kamal, A.; Sandbhor, M.; Shaik, A. A.; Sravanthi, V. *Tetrehedron: Asymmetry* **2003**, *14*, 2839; b) Burgess, K. Jennings, L. D. *J. Am. Chem. Soc.* **1990**, *112*, 7434; c) Brenna, E.; Caraccia, N.; Fuganti, C.; Fuganti, D.; Grasselli, P. *Tetrahedron: Asymmetry* **1997**, *8*, 3801; d) Nakamura, K.; Takenaka, K. *Tetrahedron: Asymmetry* **2002**, *13*, 415; e) Kazmaier, U.; Zumpe, F. L. *Eur. J. Org. Chem.* **2001**, *21*, 4067; f) Ghanem, A.; Schurig, V. *Tetrahedron: Asymmetry* **2003**, *14*, 57; g) Raminelli, C.; Comasseto, J. V.; Andrae, L. H.; Porto, A. L. M. *Tetrahedron: Asymmetry* **2004**, *15*, 3117; h) Kazlauskas, R.; Weissfloch, A. N. E.; Rappaport, A. T.; Cuccia, L. A. *J. Org. Chem.* **1991**, *56*, 2656.

104 Commercially available from Aldrich (50 g = 74.34 Euro).

105 Leuser, H. *Dissertation*, Ludwig-Maximilians-Universität München, **2005**.

The progress of the reaction was monitored by TLC. In contrast to acyclic substrates, rather disappointing results were obtained for our substrate. The reaction was completed within only 1 h at 25 °C to give the acetate *rac*-**80** in quantitative yield. The failure of this procedure to afford the (4*R*)-**74** in sufficient optical purity forced us to probe alternative lipases. Numerous enzymes were reported for the resolution of allylic alcohols,[106] including an efficient porcine pancreatic lipase (PPL)-catalyzed acetylations of a variety of 2-alkyl-4-hydroxycyclopent-2-en-1-ones reported by Babiak and Wong.[107] They described the excellent optical purities for the derived (*R*)-acetate (≥92% *ee*) as well as the recovered (*S*)-alcohols (≥92% ee; Scheme 57).



Scheme 57. PPL-catalyzed acetylation of 2-alkyl-4-hydroxycyclopent-2-en-1-ones by Babiak and Wong.[107]

To our delight, this enzyme also provided satisfactory results for the cyclopentenone substrate *rac*-**74** at 25 °C (Scheme 58). Thus, the alcohol *rac*-**74** was dissolved in vinyl acetate, and the resulting solution was treated with enzyme PPL. Acetate (*R*)-**80** was isolated by column chromatography in 26% yield and 91% *ee* (HPLC; Chiralcel OJ, heptane:*i*-PrOH = 90:10, flow rate 0.5 mL/min). The unreacted alcohol (*S*)-**74** recovered in 58% was again submitted to the enzymatic resolution conditions giving the additional acetate (*R*)-**80** in 20% yield with 91% *ee* and the unreacted alcohol (*S*)-**74** (90% *ee*). Acetate (*R*)-**80** was combined and deacetylated according to the procedure of Wong[107] (guanidine, MeOH) to give the desired alcohol (*R*)-**74** in 71% yield and 91% *ee*. The undesired alcohol (*S*)-**74** was inverted via a Mitsunobu protocol ((i) PPh_3 (2 equiv), DEAD (2 equiv), HCO_2H (2 equiv), 25 °C, 12 h, (ii) MeOH, Al_2O_3, 25 °C, 5 h)[107] to afford the additional alcohol (*R*)-**74** in 75% yield and 91% *ee*.

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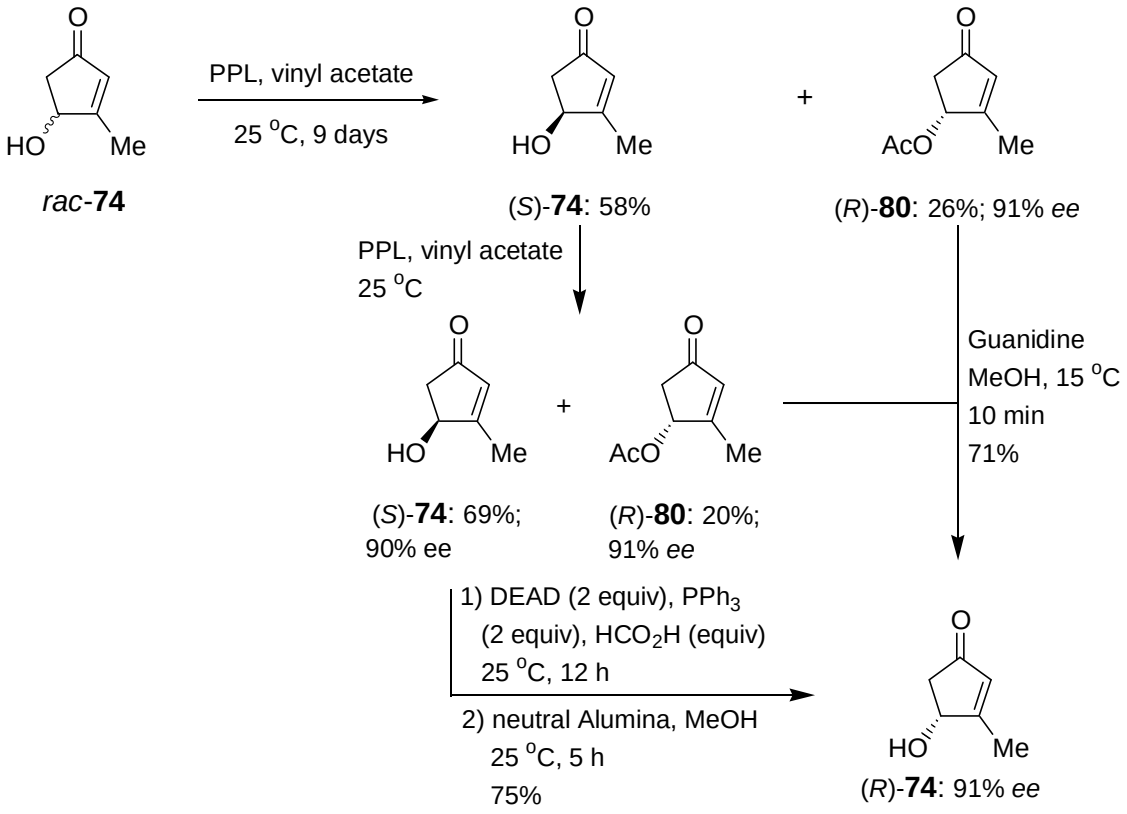
[106] Davies, H. G.; Green, R. H.; Kelly, D. R.; Roberts, S. M. *Biotransformations in Preparative Organic Chemistry*, Academic Press, San Diego, CA, **1989**, 51.

[107] Babiak, K. A.; Ng, J. S.; Dygos, J. H.; Weyker, C. L.; Wang, Y.-F.; Wong, C.-H. *J. Org. Chem.* **1990**, *55*, 3377.



Scheme 58. Enzymatic resolution of the alcohol *rac*-**74** via porcine pancreatic lipase (PPL) in vinyl acetate.

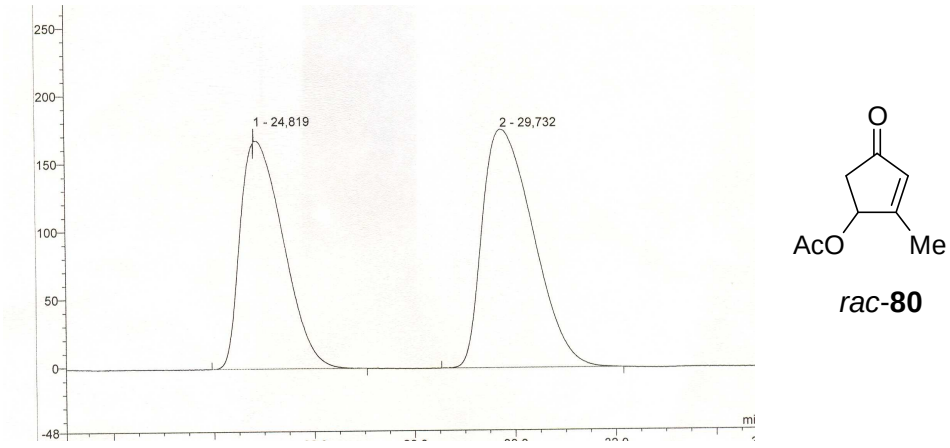


Figure 3. The separation of *rac*-**80** by HPLC (Chiralcel OJ; heptane:*i*-PrOH = 90:10, flow rate 0.5 mL/min).

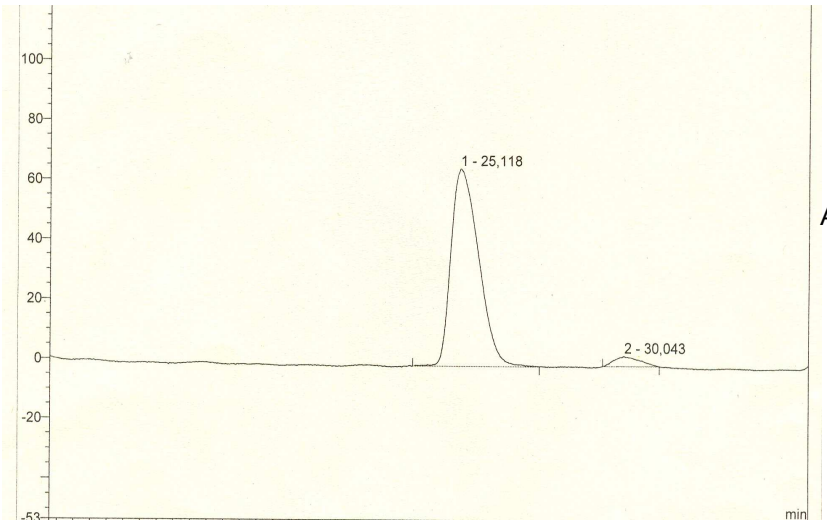


Figure 4. The acetate (*R*)-**80** (91% *ee*) obtained from enzymatic resolution using PPL and vinyl acetate.

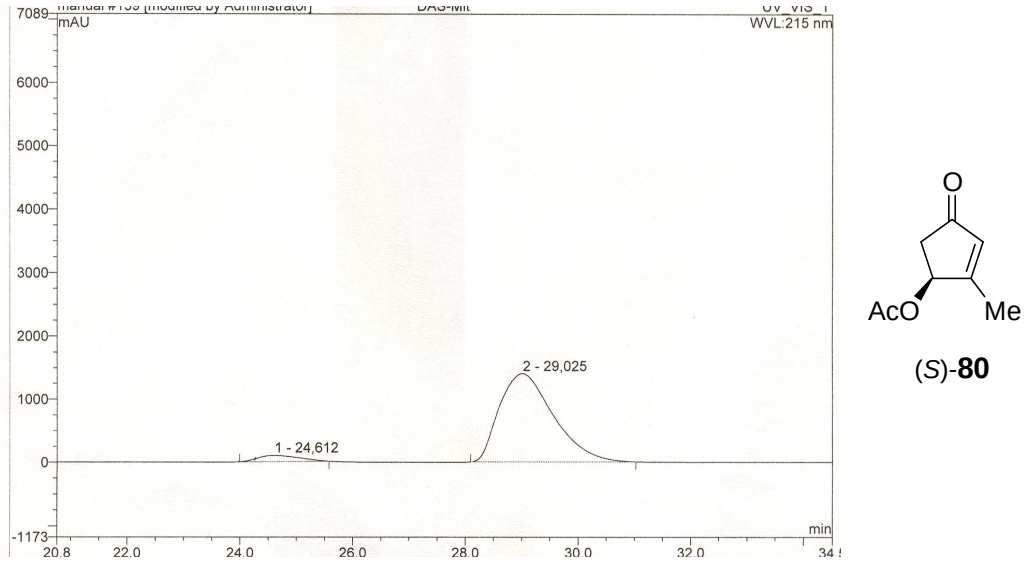
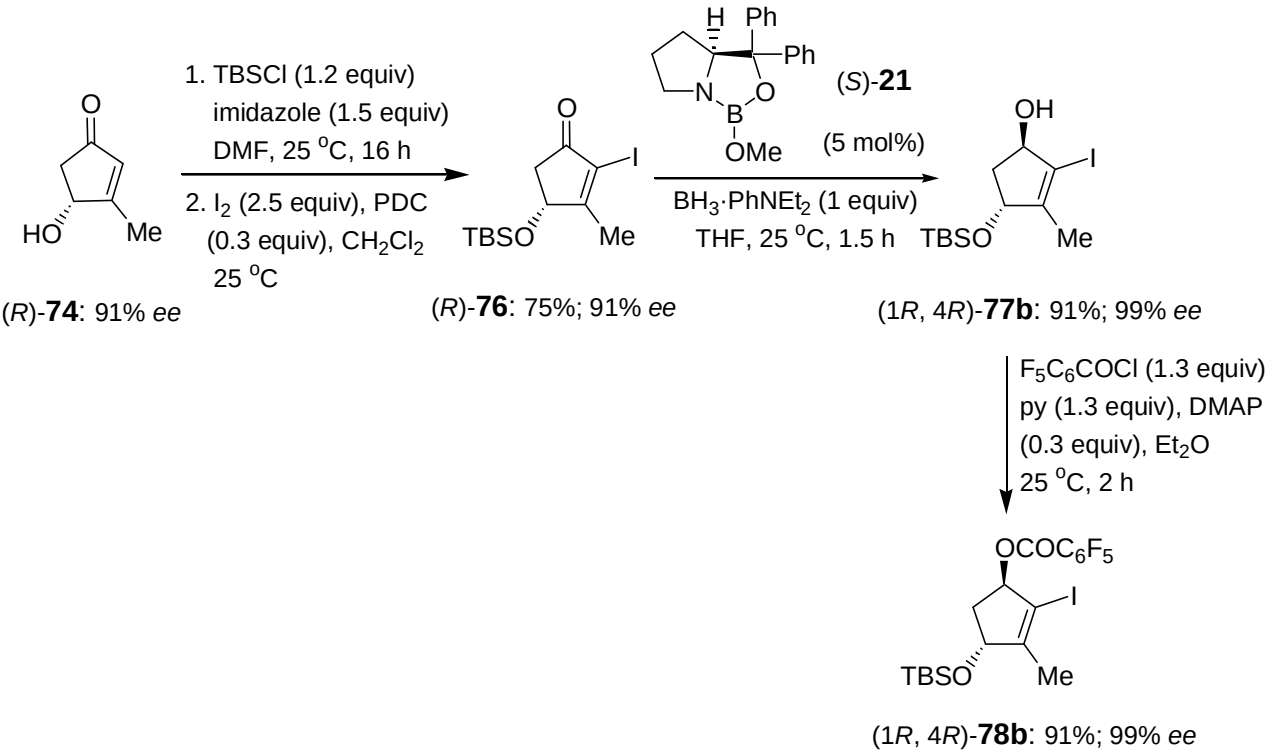


Figure 5. The remaining alcohol (*S*)-**80** (91% *ee*, determined from corresponding acetate) from enzymatic resolution using PPL and vinyl acetate.

With chiral cyclopentenone (*R*)-**74** in hand, the syntheses of enantiomerically pure (1*R*, 4*R*)-**77b** and (1*R*, 4*R*)-**78b** were accomplished as summarized in Scheme 59. Following the same sequence described previously, chiral cyclopentenone (*R*)-**74** was smoothly converted into the ketone (*R*)-**76** in 75% with 91% *ee*[108] by the protection of the secondary

[108] Determined for the alcohol **77**.

alcohol using TBSCl followed by the iodination reaction. Asymmetric reduction of the ketone (*R*)-**76** with (*S*)-MeO-CBS catalyst afforded chiral allylic alcohol (1*R*, 4*R*)-**77b** in 91% yield and 99% *ee* as the major product, which could be separated from the minor diastereomer (1*R*, 4*S*)-**77a** (≤ 5%). Finally, chiral allylic alcohol (1*R*, 4*R*)-**77b** was transformed into the corresponding pentafluorobenzoate (1*R*, 4*R*)-**78b** in 91% yield and 99% *ee*.



Scheme 59. Synthesis of enantiomerically pure allylic pentafluorobenzoate (1*R*, 4*R*)-**78b**.

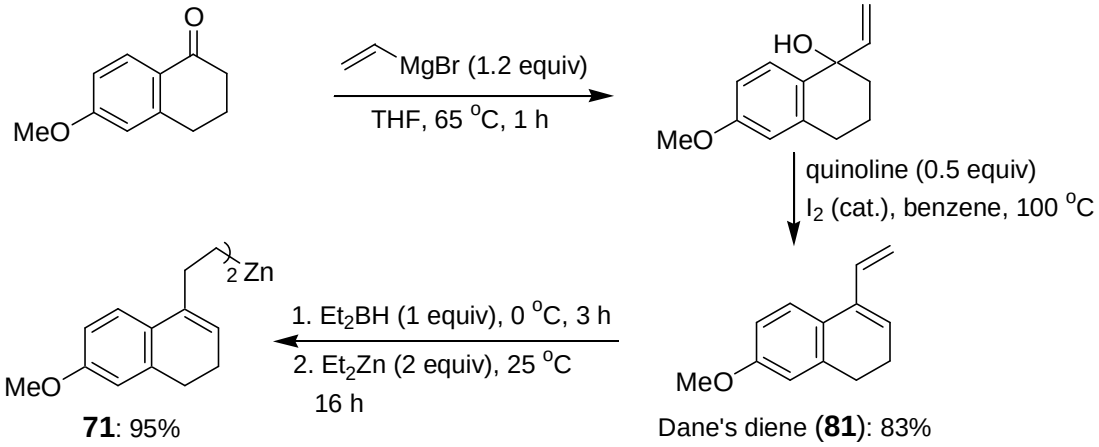
3.4 Synthesis of the diorganozinc reagent

For our approach, the dialkylzinc **71** was required. This was synthesized from Dane's diene (**81**)[109] as depicted in Scheme 60. Dane's diene was prepared according to a literature procedure.[110] Treatment of commercially available 6-methoxytetralone with vinylmagnesium bromide afforded an allylic alcohol, which was directly submitted to a dehydration reaction using quinoline (0.5 equiv) and I_2 (cat.) in benzene providing Dane's diene (**81**) in 83% yield.

[109] a) Dane, E.; Eder, K. *Liebigs Ann. Chem.* **1939**, *539*, 207; b) Dane, E.; Schmitt, J. *Liebigs Ann. Chem.* **1938**, *536*, 196; c) Dane, E.; Schmitt, J. *Liebigs Ann. Chem.* **1939**, *537*, 246. For the recent use of Dane's dienne for the syntheses of steroids see: d) Rigby, J. H.; Warshakoon, N. C.; Payen, A. J. *J. Am. Chem. Soc*. **1999**, *121*, 8237; e) Hanada, K.; Miyazawa, N.; Ogasawara, K. *Chem. Pharm. Bull*. **2003**, *51*, 104; f) Tsogoeva, S. B.; Durner, G.; Bolte, M.; Gobel, M. *Eur. J. Org. Chem*. **2003**, 1661.

[110] Symmes, Jr., C.; Quin, L. D. *J. Org. Chem.* **1979**, *44*, 1048.

The selective hydroboration of Dane's diene was conveniently performed using Et_2BH, readily prepared by mixing $BH_3 \cdot Me_2S$ and Et_3B in the ratio 1:2.[111] This hydroboration product was used for a transmetallation to zinc using neat Et_2Zn to give the dialkylzinc reagent **71** in 95% yield (determined by GC-analysis of the hydrolyzed reaction aliqouts).



Scheme 60. Preparation of the dialkylzinc reagent **71**.

3.5 Formal total enantioselective synthesis of (+)-estrone

3.5.1 Enantioselective *anti*-S_N2' substitution reaction

With enantiomerically enriched allylic pentafluorobenzoate (1*R*, 4*R*)-**78b** and the dialkylzinc reagent **71** in hand, our attention was focused on the selective *anti*-S_N2'substitution reaction. Preliminary experiments indicated that beneficial results were obtained by premixing the dialkylzinc **71** (2.4 equiv) and CuCN·2LiCl (2.4 equiv) at 0 °C for 10 min followed by the addition of a solution of allylic pentafluorobenzoate in THF at 25 °C. Under these optimized reaction conditions, allylic pentafluorobenzoate (1*R*, 4*R*)-**78b** was treated with dialkylzinc **71** (2.4 equiv) and CuCN·2LiCl (2.4 equiv) at 25 °C to afford the *anti*-S_N2'substitution product (1*R*, 2*R*)-**82** in 66% yield. The removal of the TBS-group provided the corresponding alcohol (1*R*, 2*R*)-**83** in 95% yield, which has allowed us to determine the enantiopurity by HPLC-analysis (Chiralcel OJ, heptane:*i*-PrOH = 85:15, flow rate 0.5 mL/min) as well as to confirm the relative stereochemistry of the adjacent methyl and hydroxyl groups by NOE NMR-experiments (Scheme 61).

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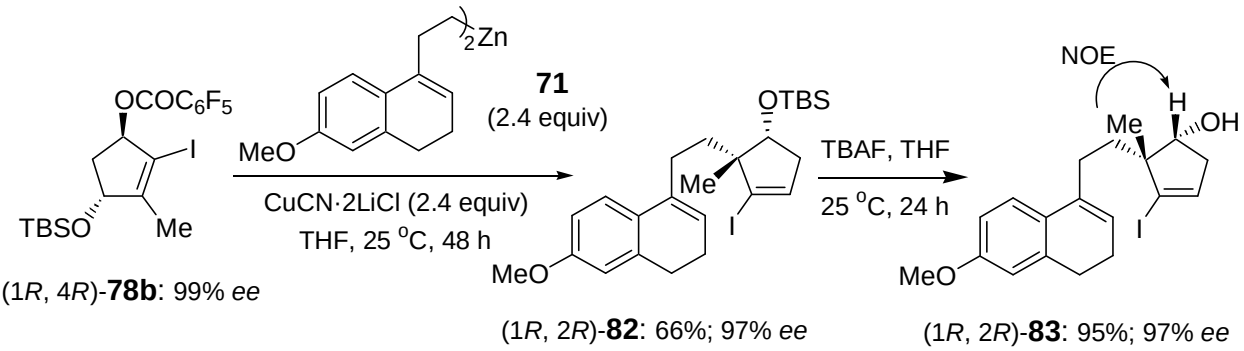
111 Langer, F.; Schwink, L.; Devasagayaraj, A.; Chavant, P.; Knochel, P. *J. Org. Chem*. **1996**, *61*, 8229.



Scheme 61. Stereoselective *anti*-S_N2'substitution of pentafluorobenzoate (1*R*, 4*R*)-**78b**.

3.5.2 Formation of the C-ring of the steroidal skeletal

3.5.2.1 Attempted formation of the C-ring of the steroidal skeletal using a Heck reaction

The next step of our envisioned (+)-estrone synthesis was the cyclization of the cycloalkenyl iodide (1*R*, 2*R*)-**82** to form the tetracyclic compound **84** (Scheme 62). A Heck reaction was our first choice. The palladium-catalyzed vinylation and ary halides was first reported 30 years ago independently by Mizoroki and Heck.[112] The application of this powerful reaction to natural product syntheses has flourished recently.[113, 114]

Treatment of the cycloalkenyl iodide (1*R*, 2*R*)-**82** with $Pd(OAc)_2$ (15 mol%) in the presence of Ph_3P (30 mol%) and Ag_2CO_3 (1.1 equiv) in THF at 65 °C for 12 h followed by the deprotection of TBS-group using a TBAF solution (1 M in THF) provided a single isomer of the product **85** in 57% isolated yield (Scheme 62). The structure of **85** was established by NMR experiments. It should be noted that compound **85** is not very stable and decomposes in chloroform solution at 25 °C.

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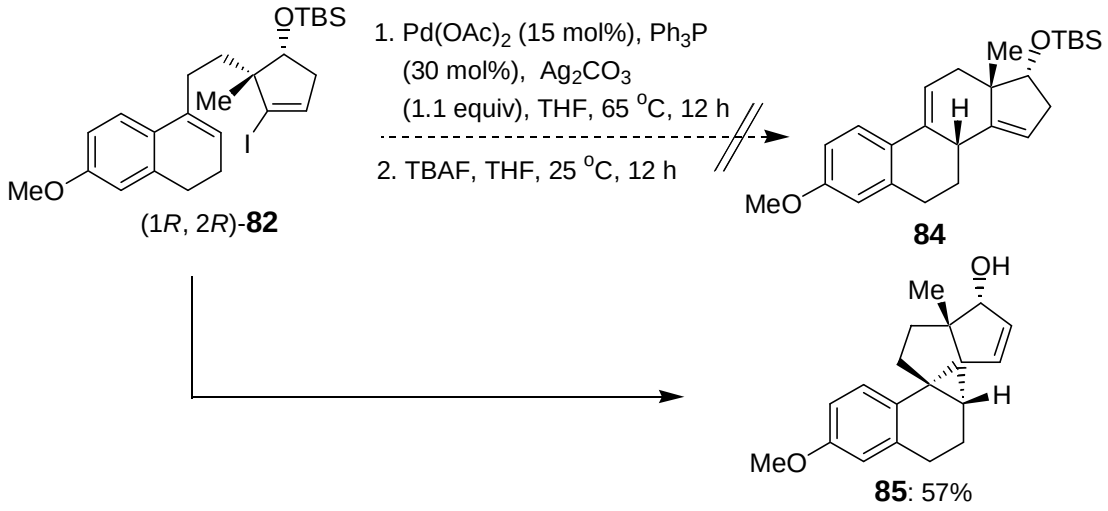
[112] a) Mizoroki, T.; Mori, K.; Ozaki, A. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 581; b) Heck, R. F.; Nolley, J. P., Jr. *J. Org. Chem.* **1972**, *37*, 2320.

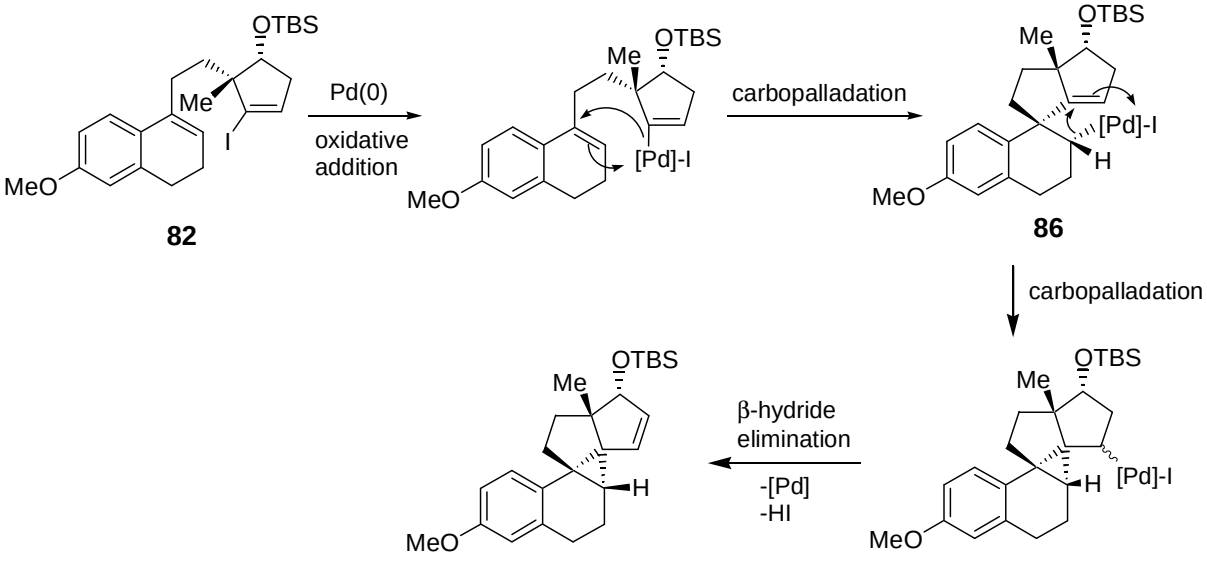
[113] Selected reviews include: a) de Meijere, A.; Meyer, F. E. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2379; b) Bräse, S.; de Meijere, A. in *Metal-Catalyzed Cross Coupling Reactions*, (Eds.; Stang, P. J.; Diederich, F.), Wiley-VCH, Weinheim, **1998**, Chapter 3; c) Link, J. T.; Overman, L. E. in *Metal-Catalyzed Cross Coupling Reactions*, (Eds.; Stang, P. J.; Diederich, F.), Wiley-VCH, Weinheim, **1998**; Chapter 6; d) Link, J. T. *Organic Reactions*, Wiley, NJ, **2002**, *Vol. 60*, Chapter 2.

[114] For recent reviews of the asymmetric Heck reaction, see: a) Shibasaki, M.; Vogl, E. M. *J. Organomet. Chem.* **1999**, *576*, 1; b) Donde, Y.; Overman, L. E. in *Catalytic Asymmetric Synthesis*, (Ed.; Ojima, I.), Wiley-VCH, New York, **2000**, Chaper 8G.



Scheme 62. Attempted formation of the C-ring of the steroidal skeletal using a Heck reaction.

A proposed mechanism for the formation of the product **85** is shown in Scheme 63. First occurs an oxidative addition of Pd(0)-catalyst into the C-I bond followed by a carbopalladation [115] leading to the tetracyclic intermediate **86**. We assume that the stereochemical outcome of this step might result from the attack of the palladium(II) salt to the alkene, which puts the angular methyl group at C-13 in an axial position. As a next step, we assume that a second carbopalladation takes place to form the cyclopropane ring followed by β-hydride elimination.

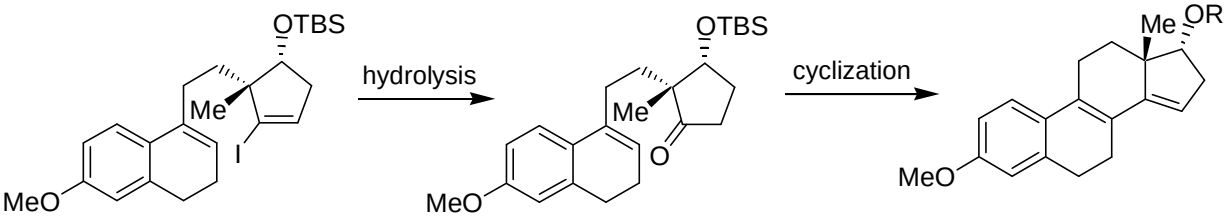


Scheme 63. Proposed mechanism of the Heck reaction.

115 Negishi, E.; Copéret, C.; Ma, S.; Liou, S.-Y.; Liu, F. *Chem. Rev.* **1996**, *96*, 365.

3.5.2.2 Formation of the C-ring of the steroidal skeletal via a ketone intermediate

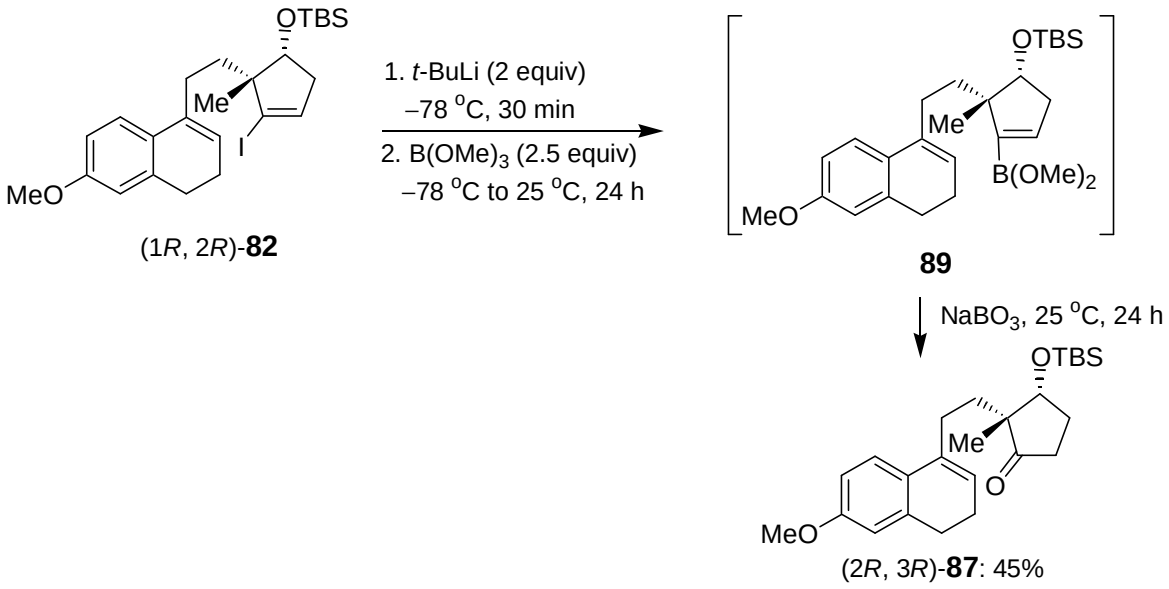
The failure of the Heck reaction forced us to change our synthesis.[116] The alkenyl iodide (1*R*, 2*R*)-**82** was converted to a carbonyl group, according to our protocol developed in chapter 2.[72] The resulting ketone (2*R*, 3*R*)-**87** should be selectively cyclized under acidic reaction conditions to form the C-ring of the steroidal skeletal **88** (Scheme 64).



(1*R*, 2*R*)-**82** (2*R*, 3*R*)-**87** **88**

Scheme 64. Envisioned synthesis of **88**.

Thus, the cycloalkenyl iodide (1*R*, 2*R*)-**82** was treated with *t*-BuLi (2 equiv) at −78 °C for 30 min, and then reacted with $B(OMe)_3$ to provide the intermediate **89**, which was oxidized by $NaBO_3$ to give the ketone (2*R*, 3*R*)-**87** in 45% yield (Scheme 65).

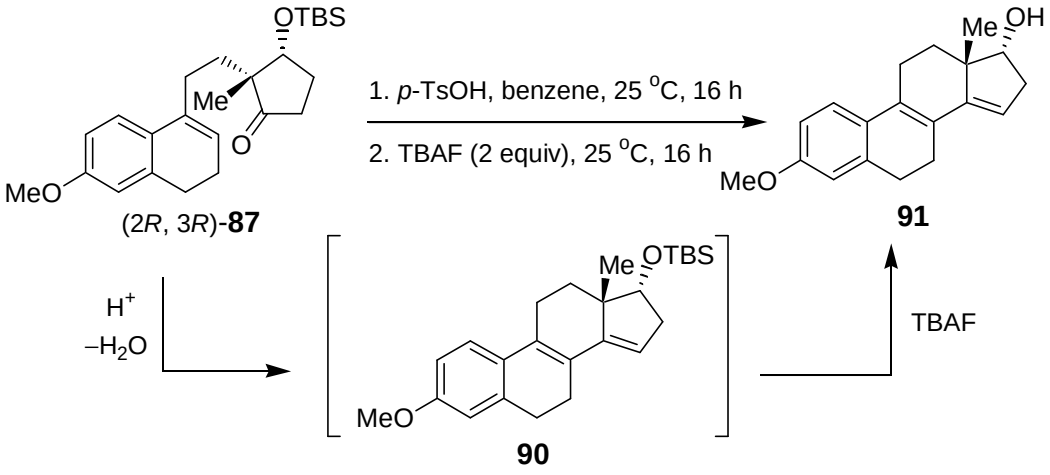


(1*R*, 2*R*)-**82** **89** (2*R*, 3*R*)-**87**: 45%

Scheme 65. Transformation of the cycloalkenyl iodide (1*R*, 2*R*)-**82** to the ketone (2*R*, 3*R*)-**87**.

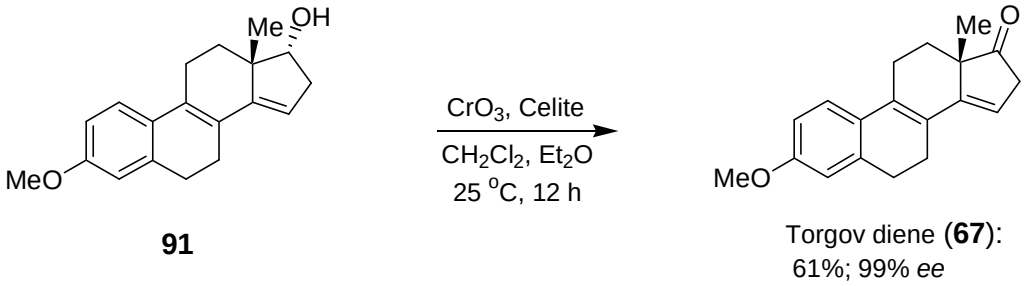
[116] Radical cyclization reactions failed for substrate **82** as well.

The ketone (2*R*, 3*R*)-**87** was then subjected to the cyclization reaction conditions. Upon stirring with anhydrous *p*-TsOH in dry benzene at 25 °C for 16 h,[117] the ring closure followed by the dehydration gave the tetracyclic intermediate **90**, which was directly treated with a TBAF solution for the deprotection of the secondary alcohol (Scheme 66).



Scheme 66. Cyclization of the ketone (2*R*, 3*R*)-**87**.

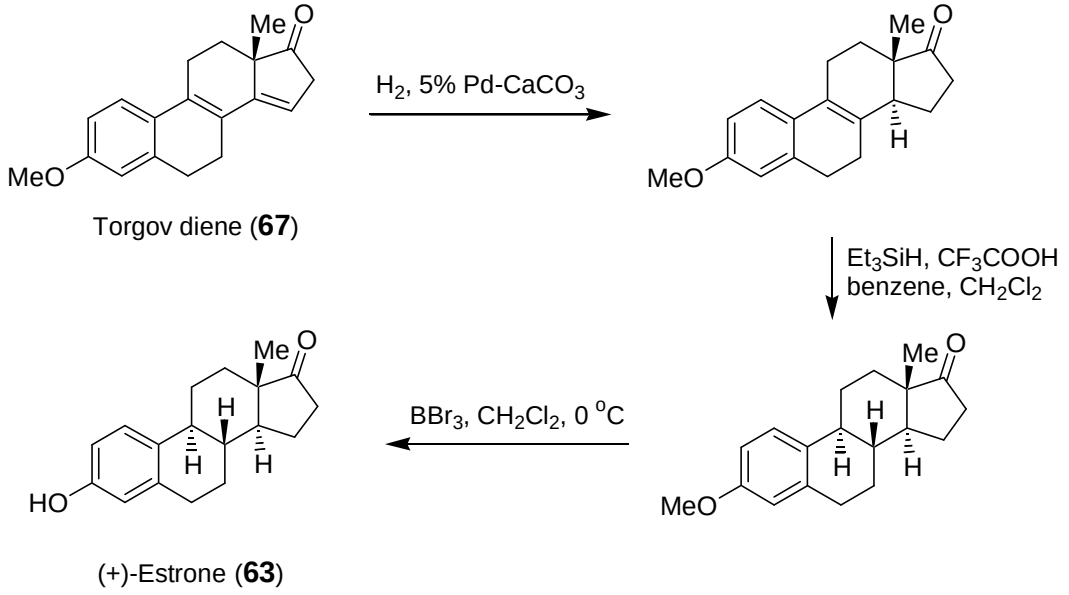
The crude alcohol **91** is unstable at 25 °C and decomposes during the purification by chromatography. Therefore, it was directly further oxidized with CrO_3 in the presence of Celite[118] to give the Torgov diene (**67**), mp = 141-144 °C, $[\alpha]_D$ –95.6 (c 0.5, $CHCl_3$) [lit.: mp = 145-146 °C, $[\alpha]_D$ –102.6 (c 0.904, $CHCl_3$)],[96, 99] in 61% yield starting from (2*R*, 3*R*)-**87** with 99% *ee*[119] (Scheme 67).



Scheme 67. Synthesis of the Torgov diene (**67**) from an oxidation of the alcohol **91**.

[117] Kuo, C. H.; Taub, D.; Wendler, N. L. *J. Org. Chem*. **1968**, *33*, 3126.
[118] Gilchrist, T. L.; Summersell, R. J. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2603.
[119] Racemate Torgov diene was generously obtained from Schering Company, Berlin, Germany.

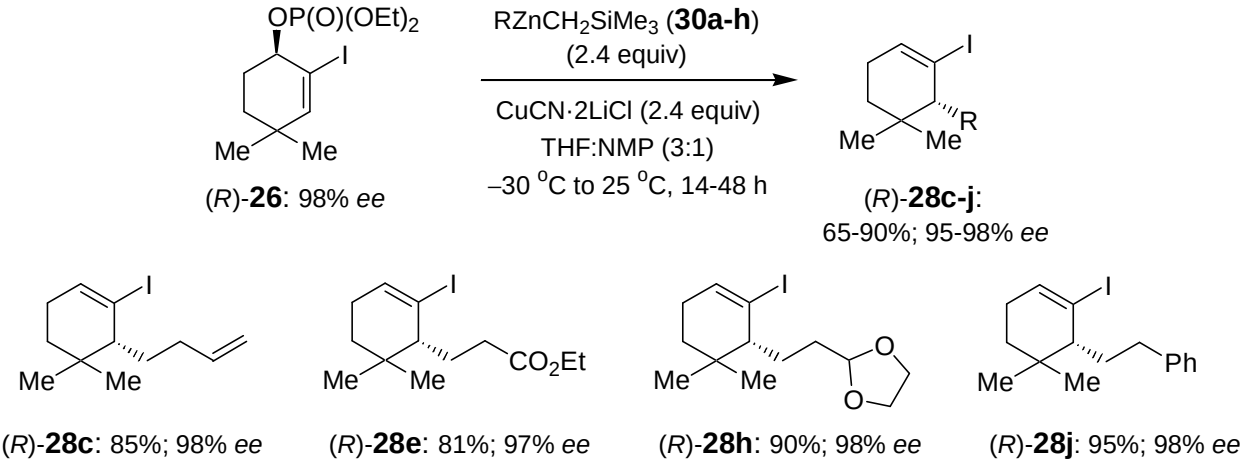
The conversion of the Torgov diene (**67**) into (+)-estrone (**63**) has been previously reported by Quinkert and Ogasawara in 3 steps and 32-37% yield (Scheme 68).[96, 99]



Scheme 68. Synthesis of (+)-estrone from the Torgov diene by Ogasawara[96] and Quinkert.[99]

4. Summary

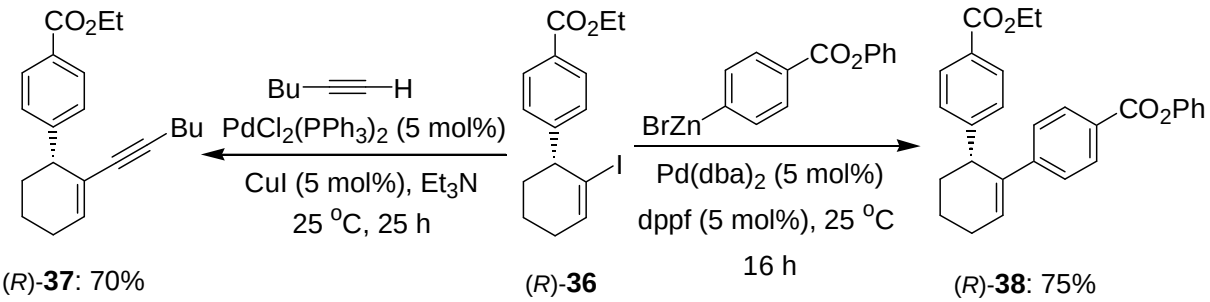
This work focused on the copper(I)-mediated stereoselective *anti*-allylic substitution reactions using organozinc reagents and chiral cyclic phosphates or pentafluorobenzoates. The applications of this method to the preparation of natural products were also reported. In a first project, the remarkable ability of mixed zinc-copper organometallics prepared from mixed diorganozincs $RZnCH_2SiMe_3$ and CuCN·2LiCl to undergo stereoselective *anti*-S_N2'substitutions with sterically hindered substrates was reported. Excellent transfer of the chirality was observed and a range of functionalized zinc reagents could be used (Scheme 69). As applications, the odoriferous (*R*)-dihydro-α-ionone (**32**) and (*R*)-α-ionone (**35**) were prepared by this method (Figure 6).



Scheme 69. Enantioselective *anti*-S_N2' substitution with $RZnCH_2SiMe_3$.

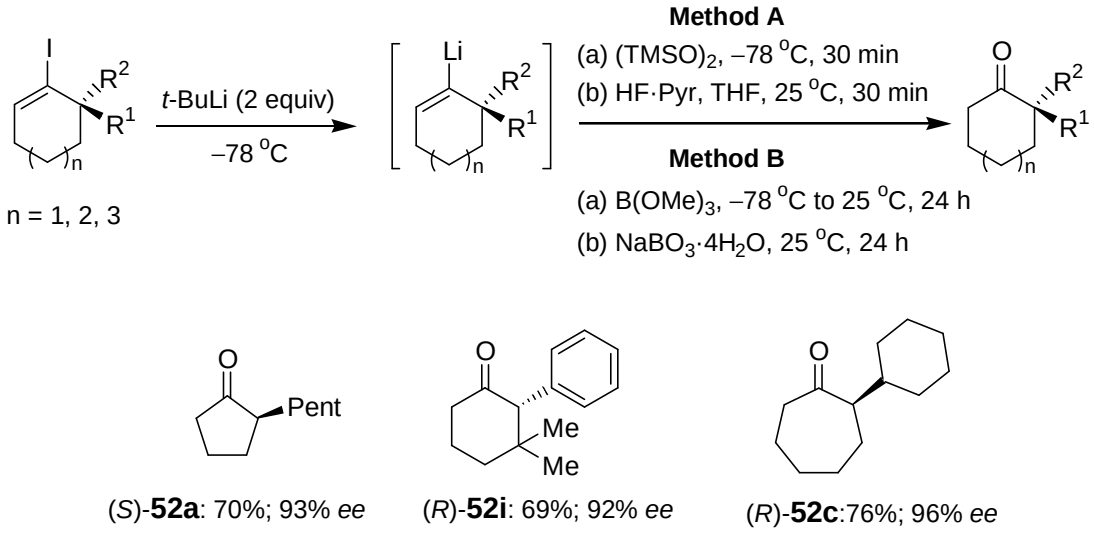
Figure 6. (*R*)-dihydro-α-ionone (**32**) and (*R*)-α-ionone (**35**).

In a second project, a transformation of the carbon-iodine bond to Csp^2-Csp^3, Csp^2-Csp^2 and Csp^2-Csp bonds via cross-coupling reaction was demonstrated (Scheme 70).



Scheme 70. Cross-coupling reactions of compound (*R*)-**36**.

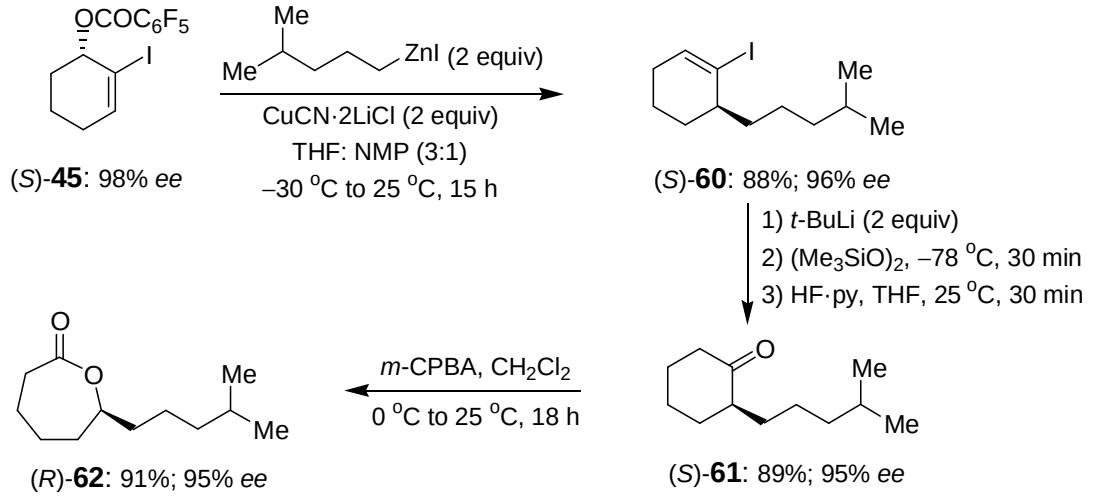
Further, a short sequence for the preparation of various chiral ketones bearing an α-stereogenic center with high enantioselectivity was developed. The reaction sequence involved a I/Li-exchange reaction followed by an oxidation of the intermediate cycloalkenyllithium species using $(Me_3SiO)_2$ or $(MeO)_3B/NaBO_3·4H_2O$ (Scheme 71).



(*S*)-**52a**: 70%; 93% *ee* (*R*)-**52i**: 69%; 92% *ee* (*R*)-**52c**:76%; 96% *ee*

Scheme 71. Synthesis of chiral ketones.

The utility of this method has been demonstrated in a short synthesis of (*R*)-10-methyl-6-undecanolide (**62**) with an excellent enantioselectivity (Scheme 72).

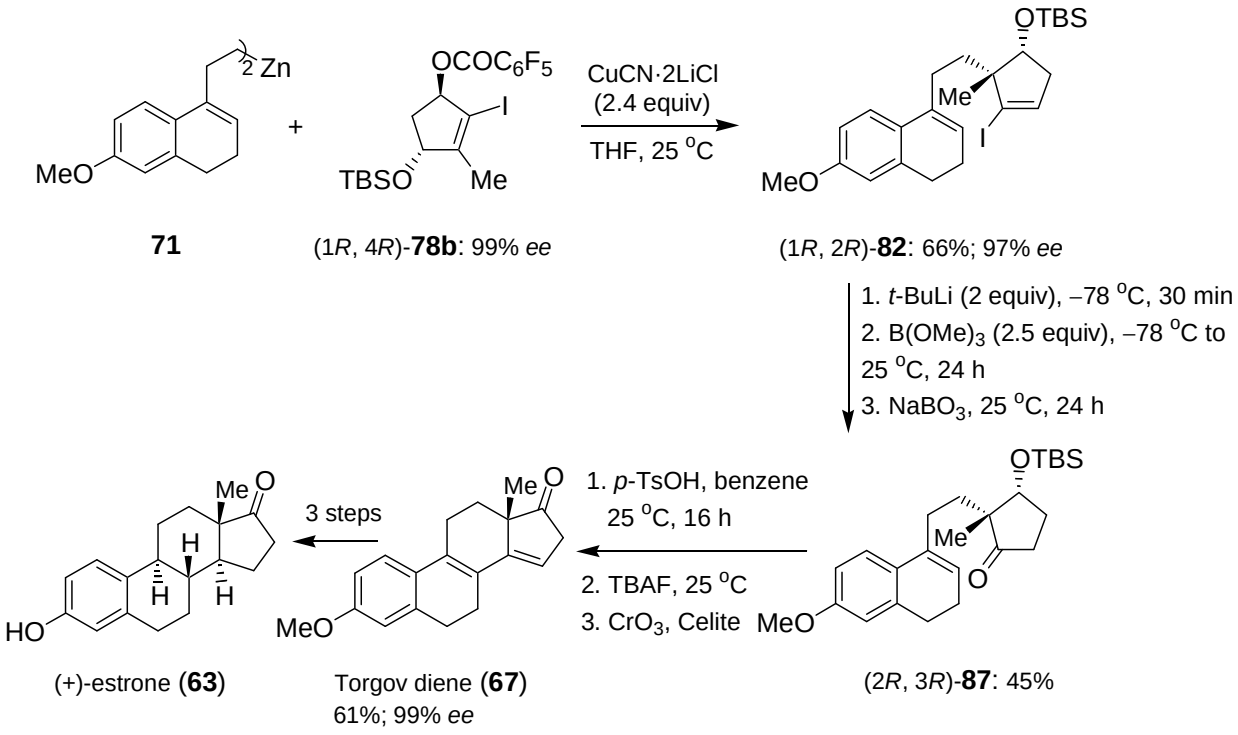


(*S*)-**45**: 98% *ee* (*S*)-**60**: 88%; 96% *ee* (*S*)-**61**: 89%; 95% *ee* (*R*)-**62**: 91%; 95% *ee*

Scheme 72. Application to the preparation of (*R*)-10-methyl-6-undecanolide (**62**).

As an application to a more complex natural product, the asymmetric allylic substitution reaction was applied to the enantioselective synthesis of the Torgov diene (**67**) which is a known intermediate for (+)-estrone synthesis. Thus, the Torgov diene (**67**) was synthesized through a copper(I)-mediated *anti*-S_N2'-substitution reaction in 9 steps and 12%

yield starting from chiral allylic alcohol (*R*)-**74**. This represents a formal total synthesis of (+)-estrone (**63**) in 12 steps and 4% yield (Scheme 73).



Scheme 73. Synthesis of (+)-estrone (**63**).

Experimental Part

1. General conditions

All reactions were carried out with a magnetic stirring and, if air or moisture sensitive, in a flamed-dried glassware under a nitrogen or an argon atmosphere. The syringes which were used to transfer the reagents and the solvents were purged with nitrogen or argon prior to use.

Solvents

The solvents were dried according to standard methods by distillation over drying agents as stated below and were stored under argon or nitrogen. Benzene, dichloromethane and toluene were predried over calcium chloride and were distilled from calcium hydride. DMF was heated at reflux for 14 h over calcium hydride and was distilled. Ethanol was treated with phthalic anhydride (25 g/L) and sodium, heated at reflux for 6 h and distilled. Methanol was treated with magnesium turnings (20 g/L), heated at reflux for 6 h and distilled. NMP was heated at reflux for 6 h over calcium hydride and distilled. Pyridine and triethylamine were dried over potassium hydroxide and distilled. Tetrahydrofuran (THF) was continuously heated at reflux and freshly distilled from sodiumbenzophenone ketyl under nitrogen.

Reagents

• Reagents of >98% purity were used as obtained.
• *n*-Butyllithium was used as a solution in hexane.
• *t*-Butyllithium was used as a solution in pentane.
• a CuCN·2LiCl solution (1.0 M in THF) was prepared by drying CuCN (896 mg, 10.0 mmol) and LiCl (848 mg, 20.0 mmol) in a Schlenk flask under high vacuum for 5 h at 120 °C. After cooling to 25 °C, under an argon atmosphere, dry THF (10 mL) was added and the stirring was continued until the salts were dissolved.
• a $ZnBr_2$ solution (1.50 M in THF) was prepared by drying $ZnBr_2$ (3.40 g, 15.0 mmol) in a Schlenk flask under high vacuum for 5 h at 120 °C. After cooling to 25 °C, under an argon atmosphere, dry THF (10 mL) was added and the stirring was continued until the salt was dissolved.
• The following reagents and substances were prepared according to literature procedures: 2-iodocyclopent-2-en-1-one,[27] (*S*)-2-iodocyclopent-2-en-1-ol (95% *ee*),[27] 2-iodocyclohex-2-en-1-one, [27] (*R*) and (*S*)-2-iodocyclohex-2-en-1-ol (98% *ee*),[27] Et_2BH[111]

Content determination of organometallic reagents

The organolithium and organomagnesium solutions were titrated using the method of Paquette[120] and Knochel[121] prior to use. The concentration of the organozinc solutions were determined by back titration of iodine with an aqueous $Na_2S_2O_3$ solution.

Chromatography

• Thin layer chromatography (TLC) was performed using aluminium plates covered with SiO_2 (Merck 60, F-254). The chromatograms were developed under UV light and/or by treatment of the TLC plate with one of the solutions below followed by gentle heating with a heat gun:

- $KMnO_4$ (0.3 g), K_2CO_3 (20 g) and KOH (0.3 g) in water (300 mL)

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120 Lin, H.-S.; Paquette, L. A. *Synth. Commun.* **1994**, *24*, 2503.
121 Krasovskiy, A.; Knochel, P. *Synthesis* **2006**, *5*, 890.

- Phosphormolybdic acid (5.0 g), $Ce(SO_4)_2$ (2.0 g) and 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) or Al_2O_3 (grade III) from Merck. The diameters of the columns and the amount of silica gel were calculated according to the recommendations of W. C. Still.[122]

Analytical data

• **Melting points** were determined on a Büchi B-540 apparatus and are uncorrected.
• **NMR** spectra were recorded on Brucker ARX 200, AC 300 or WH 400 instruments. Chemical shifts are reported as δ-values in ppm relative to the deuterated solvent peak: $CDCl_3$ (δ_H: 7.27, δ_C: 77.0) and Benzene-d_6 (δ_H: 7.16, δ_C: 128.0).
For the characterization of the observed signal multiplicities the following abbreviations were applied: s (singlet), d (doublet), dd (double doublet), dt (double triplet), t (triplet), m (multiplet), br (broad).
• **Optical rotation values** were measured on the Perkin-Elmer 241 polarimeter.
• **Infrared** spectra were recorded from 4000-400 cm^{-1} on a Nicolet 510 FT-IR or a Perkin-Elmer 281 IR spectrometer. The absorption bands are reported in wave number (cm^{-1}). For the band characterization the following abbreviations were applied: br (broad), s (strong), m (medium), w (weak).
• **Gas Chromatography** (GC): Hewlett-Packard 6890. Chiral columns: Chiraldex B-PH (30.0 mm x 0.25 mm), Chirasil-Dex CB (25 mm x 0.25 mm). Carrier gas: H_2.
• **High Performance Liquid Chromatography (HPLC)** was performed using Gynkotec-HPLC with a diode-array UV-VIS detector. Chiral columns: OD-H, OD, OJ and AD (Diacel Chemical Industries) with *n*-heptane/*i*-propanol as mobile phase. Racemic compounds were used for optimizing the operating conditions for the resolution of the enantiomer and diastereomer peaks.
• **Electron impact mass** (EI, 70 eV) spectra were recorded on a Finnigan MAT 95Q or Finnigan 90 instrument. High resolution mass spectra (HRMS) were recorded on the same instrument. The combination of gas chromatography with mass spectroscopic detection, a GC/MS from Hewlett-Packard HP 6890/MSD 5973 was used.
• **Elemental Analysis** was carried out on a Heraeus CHN-Rapid-Elementanalyzer in the microanalytical laboratories of the Department für Chemie und Pharmazie, Ludwig-Maximilians Universität München.

2. Typical Procedures (TP)

2.1 Typical procedure for the synthesis of 2-iodocycloalk-2-en-1-ones (TP 1) [38]

A flame-dried round bottom flask equipped with a magnetic stirring bar, a nitrogen inlet and a rubber septum was charged with cycloalk-2-en-1-one (1.0 equiv) and CH_2Cl_2. Pyridinium dichromate (PDC) (0.30 equiv) and I_2 (1.0 equiv) were added to the resulting solution. The reaction flask was covered with an aluminium foil and the reaction mixture was stirred at 25 ^oC. The progress of the reaction was monitored by thin-layer chromatography (TLC) or gas chromatography (GC). After the complete consumption of the starting material, the reaction mixture was filtrated, and the residue was washed with pentane. The combined organic layer was washed with 2 M HCl, a saturated $NaHCO_3$ solution, a saturated $Na_2S_2O_3$ solution, brine and dried over $MgSO_4$ anhydrous. The crude product was purified by column chromatography to afford the desired product.

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

2.2 Typical procedure for the asymmetric reduction of 2-iodocycloalk-2-en-1-ones (TP 2)

A flame-dried round bottom flask equipped with a magnetic stirring bar, an argon inlet and a rubber septum was charged with (*R*)- or (*S*)-diphenylprolinol (5 mol%), THF and $B(OMe)_3$ (5 mol%). The reaction mixture was stirred at 25 °C for 1 h. The borane-*N*,*N*-diethylaniline complex (1.0 equiv) was added followed by the slow addition of THF solution of 2-iodocycloalk-2-en-1-ones (1.0 equiv) at 25 °C. The reaction mixture was stirred at 25 °C for 1 h, and then was carefully quenched with MeOH. The solvents were evaporated under high vacuum. The remaining oil was diluted with Et_2O, washed with 7% Na_2CO_3 aqueous solution, 10% $KHSO_4$ aqueous solution, brine and dried over Na_2SO_4 anhydrous. Evaporation of the solvents and purification by column chromatography afforded the desired chiral allylic alcohol.

2.3 Typical procedure for *anti*-S_N2' substitutions of mixed dialkylzinc reagents $RZnCH_2SiMe_3$ (TP 3)

A flame-dried round bottom flask equipped with a magnetic stirring bar, an argon inlet and a rubber septum was charged with freshly prepared alkylzinc halide (a solution in THF, 2.40 equiv) and cooled to –40 °C, and then the solution of $TMSCH_2Li$ (1.0 M in pentane, 2.40 equiv) was added dropwise. The reaction mixture was stirred for 1 h at –40 °C then warmed up to –30 °C. A solution of CuCN·2LiCl (1.0 M solution in THF, 2.40 equiv) and NMP (sufficient to give an overall ratio of the solvent mixture of THF:NMP = 3:1) were added successively to the resulting mixture. The reaction mixture was stirred at –30 °C for 30 min. Diethyl (1*R*)-2-iodo-4,4-dimethylcyclohex-2-en-1-yl phosphate was added dropwise as a solution in THF. The reaction mixture was slowly warmed up to 25 °C during the time stated for each compound. A saturated aqueous NH_4Cl solution (20 mL) was added followed by 25% aqueous ammonia solution (1 mL). The reaction mixture was stirred at 25 °C until the copper salts had dissolved. The mixture was extracted with Et_2O (3 x 20 mL). The combined organic phase was washed with brine and dried over Na_2SO_4. Evaporation of the solvents and the purification by column chromatography afforded the desired product.

2.4 Typical procedure for *anti*-S_N2' substitutions of dialkylzincs (TP 4)

A flame-dried round bottom flask equipped with a magnetic stirring bar, an argon inlet and a rubber septum was charged with a CuCN·2LiCl solution (1.0 M in THF, 2.24 equiv), NMP (sufficient to give an overall ratio of the solvent mixture of THF:NMP = 3:1), and then the reaction mixture was cooled to –30 °C. Dialkylzinc (2.24 equiv) was added dropwise to the resulting mixture. The reaction mixture was stirred at –30 °C for 30 min, and then the pentafluorobenzoate or the diethylphosphate (1.0 equiv) was added dropwise as a solution in THF. The reaction mixture was stirred and allowed to warm to –10 °C until the conversion was complete (15-25 h). A saturated aqueous NH_4Cl solution (20 mL) was added followed by 25% aqueous NH_3 solution. The reaction mixture was stirred at 25 °C until the copper salts had dissolved, and then was extracted with Et_2O (3 x 20 mL). The combined organic phase was washed with brine and dried over Na_2SO_4. Evaporation of the solvents and the purification by column chromatography afforded the desired cycloalkenyl iodide.

2.5 Typical procedure for *anti*-S_N2' substitutions of alkylzinc halides (TP 5)

A flame-dried round bottom flask equipped with a magnetic stirring bar, an argon inlet and a rubber septum was charged with a CuCN·2LiCl solution (1.0 M in THF, 2.0 equiv) then

cooled to –30 °C. The alkylzinc halide (2.0 equiv) was added to a solution. The resulting mixture was stirred at –30 °C for 30 min, and then the pentafluorobenzoate (1.0 equiv) was added dropwise as a solution in NMP (sufficient to give an overall ratio of the solvent mixture of THF:NMP = 3:1). The reaction mixture was stirred and warmed to the indicated temperature. A saturated aqueous NH_4Cl solution (20 mL) was added followed by 25% aqueous NH_3 solution. The reaction mixture was stirred at 25 °C until the copper salts had dissolved then was extracted with Et_2O (3 x 20 mL). The combined organic phase was washed with brine and dried over Na_2SO_4. Evaporation of the solvents and purification by column chromatography afforded the desired cycloalkenyl iodide.

2.6 Typical procedure for S_N2 substitutions of arylcuprates (TP 6)

A flame-dried round bottom flask equipped with a magnetic stirring bar, an argon inlet and a rubber septum was charged with CuCN (0.11 g, 1.20 mmol) and dry THF (2 mL), was then cooled to 0 °C. Freshly titrated solution of $PhMe_2CCH_2Li$ (0.50 M in Et_2O, 5 mL, 2.40 mmol) was added dropwise to the resulting suspension. The resulting mixture was stirred at 25 °C for 10 min, and then was cooled to 0 °C. A solution of aryl iodide (1.20 mmol) in THF (2 mL) was added to the resulting solution of $(PhMe_2CCH_2)_2Cu(CN)Li$, and the mixture was stirred at 0 °C until I/Cu-exchange was complete (30 min). The reaction mixture was cooled to –40 °C, and a solution of (1*R*)-2-iodocyclohex-2-en-1-yl acetate (0.27 g, 1.0 mmol) in THF (1.5 mL) was added dropwise. The reaction mixture was stirred at the temperature indicated in each case. A saturated aqueous NH_4Cl solution (20 mL) was added followed by 25% aqueous NH_3 solution (1 mL). The reaction mixture was stirred at 25 °C until the copper salts had dissolved then was extracted with Et_2O (3 x 20 mL). The combined organic phase was washed with brine and dried over Na_2SO_4. Evaporation of the solvents and purification by column chromatography afforded the desired cycloalkenyl iodide.

2.7 Typical procedure for the preparation of chiral ketones bearing α-stereogenic center by the oxidation using $(TMSO)_2$ (TP 7)

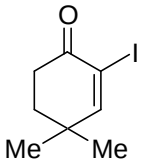
A flame-dried round bottom flask equipped with a magnetic stirring bar, an argon inlet and a rubber septum was charged with a cycloalkenyl iodide (0.50 mmol, 1.0 equiv) and THF (4.0 mL). The reaction mixture was cooled to –78 °C, and then *t*-BuLi (1.60 M in pentane, 0.63 mL, 1.0 mmol, 2.0 equiv) was added dropwise. The reaction mixture was stirred at –78 °C for 30 min, then $(TMSO)_2$ (neat, 0.16 mL, 0.75 mmol, 1.50 equiv) was added (Caution: explosion, the reagent must be transferred by using a plastic syringe and a Teflon needle and was added slowly). The reaction mixture was continuously stirred at –78 °C for 30 min, was then poured into water, and extracted with pentane (3 x 25 mL). The combined organic phase was dried over $MgSO_4$. The solvents were evaporated and the crude product was used in the next step without further purification. A flame-dried round bottom flask equipped with a magnetic stirring bar, an argon inlet and a rubber septum was charged with dry pyridine (0.40 mL) and a HF·pyridine complex (70%) (0.02 mL, 0.50 mmol, 1.0 equiv). A THF (2 mL) solution of the crude silyl enol ether was added dropwise at 25 °C. The reaction mixture was stirred for 30 min at 25 °C, was then poured into water, and extracted with Et_2O (3 x 25 mL). The combined organic phase was washed with brine and dried over $MgSO_4$. The solvents were evaporated and the crude product was purified indicated in each case to give the desired chiral ketone.

2.8 Typical procedure for the preparation of chiral ketones bearing α-stereogenic center by the oxidation using $B(OMe)_3/NaBO_3·4H_2O$ (TP 8)

A flame-dried round bottom flask equipped with a magnetic stirring bar, an argon inlet and a rubber septum was charged with a cycloalkenyl iodide (0.50 mmol, 1.0 equiv) and THF (4 mL). The reaction mixture was cooled to –78 °C, and then *t*-BuLi (1.60 M in pentane, 0.63 mL, 1.0 mmol, 2.0 equiv) was added dropwise. The reaction mixture was stirred at –78 °C for 30 min, then $B(OMe)_3$ (neat, 0.14 mL, 1.25 mmol, 2.50 equiv) was added dropwise. The reaction mixture was slowly warmed to 25 °C and stirred for 24 h, then a suspension of $NaBO_3 \cdot 4H_2O$ (10.0 equiv, 769 mg, 5.0 mmol) in H_2O (6 mL) was added at 25 °C. After stirring at 25 °C for 24 h, the mixture was poured into water, extracted with Et_2O (3 x 25 mL). The combined organic phase was washed with brine and dried over $MgSO_4$. The solvents were evaporated and the crude product was purified by column chromatography to give the desired chiral ketone.

3. Copper(I)-mediated enantioselective *anti*-S_N2' substitution reactions with sterically hindered cyclic allylic alcohol derivatives

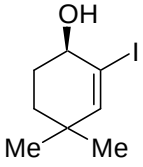
2-Iodo-4,4-dimethylcyclohex-2-en-1-one (23)



Prepared according to TP 1 using 4,4-dimethylcyclohex-2-en-1-one (2.64 mL, 20.0 mmol), CH_2Cl_2 (130 mL), PDC (2.26 g, 6.0 mmol) and I_2 (5.08 g, 20.0 mmol). The reaction mixture was stirred at 25 °C for 26 h. Additional I_2 (1.0 g, 3.9 mmol) was added and the reaction mixture was stirred for additional 25 h. The crude product was purified by column chromatography (silica gel, 8% Et_2O:pentane) to afford the product **23** as a pale yellow oil (4.64 g, 93% yield).
The data were in agreement with those reported.[123]

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.46 (s, 1H), 2.71-2.63 (m, 2H), 1.96-1.89 (m, 2H), 1.21-1.17 (m, 6H) ppm.
^{13}C NMR ($CDCl_3$, 75 MHz): δ = 192.3, 168.5, 102.2, 38.4, 36.4, 33.7, 27.79, 27.76 ppm.
IR (film): 2960 (m), 2927 (m), 2865 (m), 1690 (s), 1584 (m), 1468 (m), 1320 (m), 1144 (m), 802 (m) cm^{-1}.
MS (EI, 70 eV), *m/z* (%): 250 (M^+, 55), 235 (6), 222 (9), 207 (6), 123 (100), 95 (13), 80 (20), 67 (23), 55 (9).

(1*R*)-2-Iodo-4,4-dimethylcyclohex-2-en-1-ol (24)



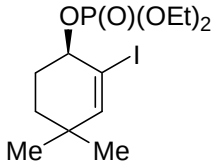
Prepared according to TP 2 using (*S*)-diphenylprolinol (167 mg, 0.66 mmol, 5 mol%), THF (14 mL) and $B(OMe)_3$ (78 µL, 0.66 mmol, 5 mol%). The reaction mixture was stirred at 25 °C for 1 h. Then the borane-*N*,*N*-diethylaniline complex (2.35 mL, 13.2 mmol, 1.0 equiv) was

[123] Souza, F. E. S.; Sutherland, H. S.; Carlini, R.; Rodrigo, R. *J. Org. Chem.* **2002**, *67*, 6568.

added followed by the slow addition of the solution of 2-iodo-4,4-dimethylcyclohex-2-en-1-one (**23**) (3.30 g, 13.2 mmol) in THF (14 mL) over 1 h. The reaction mixture was continuously stirred for 1 h, then was carefully quenched with MeOH (6 mL). The crude product was purified by column chromatography (silica gel, 20% Et_2O:pentane) to afford the product (*R*)-**24** as a colourless oil (3.01 g, 90% yield).

HPLC (Chiralcel OD-H; heptane:*i*-PrOH = 98:2, 0.3 mL/min): t_R/min = 27.61 (minor), 33.78 (major); 98% *ee*.
$[\alpha]_D^{20}$ +41.6 (c 0.9, CH_2Cl_2)
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 6.17 (s, 1H), 4.06 (t, *J* = 5.2 Hz, 1H), 2.05-1.91 (m, 2H), 1.85-1.74 (m, 1H), 1.62-1.51 (m, 1H), 1.48-1.38 (m, 1H), 0.97 (s, 3H), 0.93 (s, 3H) ppm.
^{13}C NMR ($CDCl_3$, 75 MHz): δ = 150.7, 102.9, 72.4, 37.8, 32.6, 29.23, 29.21, 28.4 ppm.
IR (film): 3370 (br), 2956 (s), 2935 (s), 2863 (s), 1043 (s) cm^{-1}.
MS (EI, 70 eV), *m/z* (%): 252 (M^+, 25), 125 (100), 100 (61), 107 (80), 95 (51), 79 (33), 69 (18), 55 (38).
$C_8H_{13}IO$ HRMS (EI): Calcd.: 252.0011
Found: 252.0038

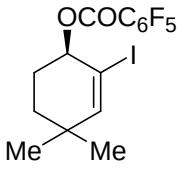
Diethyl (1*R*)-2-iodo-4,4-dimethylcyclohex-2-en-1-yl phosphate (26)



N-Methylimidazole (0.95 mL, 12.0 mmol, 2.40 equiv) was added to the solution of (1*R*)-2-iodo-4,4-dimethylcyclohex-2-en-1-ol (**24**) (1.26 g, 5.0 mmol) in dry Et_2O (9 mL). The reaction mixture was cooled to 0 °C (ice-bath), and then the diethyl chlorophosphate (1.74 mL, 12.0 mmol, 2.40 equiv) was added dropwise. The ice-bath was removed and the reaction mixture was stirred at 25 °C for 16 h, then was quenched with a saturated NaCl solution (20 mL) and extracted with Et_2O (3 x 20 mL). The combined organic phase was dried over Na_2SO_4 anhydrous. The crude product was purified by column chromatography (silica gel, 50% Et_2O:pentane) to afford the product (*R*)-**26** as a colourless oil (1.65 g, 85% yield).

GC (Chiraldex B-PH, 30 mm x 0.25 mm); conditions: 40 °C (2 min), ramp of 20 °C/min to 160 °C (90 min): t_R/min = 65.714 (major), 68.826 (minor); 98% *ee*.
$[\alpha]_D^{20}$ +27.5 (c 1.1, CH_2Cl_2)
^{1}H NMR ($CDCl_3$, 600 MHz): δ = 6.21 (s, 1H), 4.70-4.65 (m, 1H), 4.17-4.05 (m, 2H), 4.05-3.91 (m, 2H), 2.00-1.86 (m, 2H), 1.57-1.47 (m, 1H), 1.40-1.30 (m, 1H), 1.28-1.17 (m, 6H), 0.90 (s, 3H), 0.85 (s, 3H) ppm.
^{13}C NMR ($CDCl_3$, 150 MHz): δ = 153.5, 94.1, 78.2, 64.5, 64.1, 37.5, 31.3, 29.4, 28.5, 27.4, 16.5, 16.4 ppm.
IR (film): 2959 (m), 1275 (s), 1028 (s), 983 (s) cm^{-1}.
MS (EI, 70 eV), *m/z* (%): 261 (100), 155 (45), 127 (41), 107 (78), 99 (62), 91 (45), 79 (22).
$C_{12}H_{22}IO_4P$ HRMS (EI): Calcd.: 388.0300
Found: 388.0259
$C_{12}H_{22}IO_4P$ Anal. Calcd.: C 37.13, H 5.71
Found: C 37.14, H 5.73

(1*R*)-2-Iodo-4,4-dimethylcyclohex-2-en-1-yl 2,3,4,5,6-pentafluorobenzoate (27)



Pyridine (1.30 equiv, 7.80 mmol, 0.60 mL), DMAP (0.10 equiv, 0.60 mmol, 73 mg) and pentafluorobenzoyl chloride (1.30 equiv, 7.80 mmol, 1.10 mL) were added to a solution of (1*R*)-2-iodo-4,4-dimethylcyclohex-2-en-1-ol (**24**) (1.48 g, 5.87 mmol) in dry Et_2O (30 mL) at 25 °C. The reaction mixture was stirred at 25 °C for 2 h, then was quenched with a saturated NH_4Cl solution (20 mL) and extracted with Et_2O (3 x 20 mL). The combined organic phase was washed with brine and dried over Na_2SO_4 anhydrous. The crude product was purified by column chromatography (silica gel, 2% Et_2O:pentane) to afford the product (*R*)-**27** as a white solid (2.52 g, 96% yield).

mp = 51.3-53.2 °C

GC (Chiraldex CB, 25 mm x 0.25 mm); conditions: 60 °C (1 min), ramp of 20 °C/min to 160 °C: t_R/min = 19.878 (major), 20.931 (minor); 98% *ee*.

$[\alpha]_D^{20}$ +52.8 (c 0.375, CH_2Cl_2)

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 6.39 (s, 1H), 5.57 (t, *J* = 4.26 Hz, 1H), 2.17-2.03 (m, 1H), 2.00-1.88 (m, 1H), 1.65-1.43 (m, 2H), 1.00 (s, 3H), 0.97 (s, 3H) ppm.

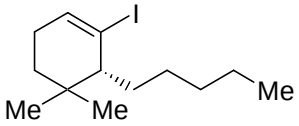
^{13}C NMR ($CDCl_3$, 150 MHz): δ = 157.3, 153.4, 146.0, 143.9, 142.5, 140.6, 138.3, 135.0, 89.8, 75.4, 36.2, 30.2, 28.2, 25.97, 25.94 ppm.

IR (neat): 1733 (s), 1651 (w), 1498 (s), 1338 (s), 1221 (s), 998 (s), 966 (s), 888 (m), 739 (s) cm^{-1}.

MS (EI, 70 eV), *m/z* (%): 319 (44), 195 (100), 167 (8), 107 (6), 92 (10).

$C_{15}H_{12}F_5IO_2$ HRMS (EI): Calcd.: 319.0757 $[M-I]^+$
Found: 319.0724 $[M-I]^+$

(6*R*)-1-Iodo-5,5-dimethyl-6-pentylcyclohex-1-ene (28a)



Prepared according to TP 4 by using diethyl (1*R*)-2-iodo-4,4-dimethylcyclohex-2-en-1-yl phosphate (**26**) (194 mg, 0.50 mmol, 1.0 equiv), THF (0.8 mL), a CuCN·2LiCl solution (1.0 M in THF, 0.56 mL, 0.56 mmol, 1.12 equiv), NMP (1.3 mL) and the dipentylzinc solution (4.8 M in THF, 0.23 mL, 1.12 mmol, 2.24 equiv). The reaction mixture was warmed to –10 °C and stirred for 14 h. Purification by column chromatography (silica gel, pentane) afforded the product (*R*)-**28a** as a colourless oil (122 mg, 80% yield).

GC (Chiraldex B-PH, 30 mm x 0.25 mm); conditions: 125 °C constant: t_R/min = 19.079 (minor), 19.965 (major); 97% *ee*.

$[\alpha]_D^{20}$ +60.2 (c 1.25, CH_2Cl_2)

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 6.12 (t, *J* = 3.8 Hz, 1H), 2.05-1.95 (m, 2H), 1.92-1.86 (m, 1H), 1.50-1.38 (m, 3H), 1.38-1.10 (m, 7H), 0.92 (s, 3H), 0.88 (s, 3H), 0.83 (t, *J* = 6.7 Hz, 3H) ppm.

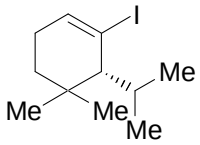
^{13}C NMR ($CDCl_3$, 75 MHz): δ = 136.3, 106.0, 56.8, 35.5, 32.9, 32.3, 30.8, 29.6, 28.4, 28.0, 27.4, 22.9, 14.5 ppm.

IR (film): 2955 (s), 2929 (s), 2870 (s), 1466 (m), 1385 (w), 1365 (w), 924 (w), 828 (w), 742 (w) cm^{-1}.

MS (EI, 70 eV), *m/z* (%): 306 (M^+, 29), 251 (10), 250 (98), 236 (40), 180 (22), 179 (12), 123 (22), 109 (31), 93 (33), 81 (100), 67 (79), 55 (19).

$C_{13}H_{23}I$	HRMS (EI):	Calcd.: 306.0844
		Found: 306.0818
$C_{13}H_{23}I$	Anal.	Calcd.: C 50.99, H 7.57
		Found: C 51.19, H 7.68

(6*R*)-1-Iodo-6-isopropyl-5,5-dimethylcyclohex-1-ene (28b)

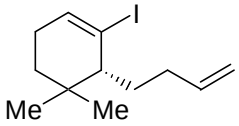


Prepared according to TP 4 by using diethyl (1*R*)-2-iodo-4,4-dimethylcyclohex-2-en-1-yl phosphate (**26**) (388 mg, 1.0 mmol), THF (1.6 mL), the diisopropylzinc solution (5.10 M in THF, 0.44 mL, 2.24 mmol, 2.24 equiv), a CuCN·2LiCl solution (1.0 M in THF, 2.24 mL, 2.24 mmol, 2.24 equiv) and NMP (1.3 mL). The reaction mixture was stirred at –30 °C for 21 h. After purification by column chromatography (silica gel, pentane), the cyclohexenyl iodide (*R*)-**28b** was obtained as a colourless oil (265 mg, 95% yield).
The separation of the enantiomers was not possible under a variety of conditions in chiral HPLC or capillary GC. The enantiomeric excess was determined for the corresponding ketone (*R*)-**52j**.

$[\alpha]_D^{20}$ +81.7 (c 0.36, CH_2Cl_2)
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 6.32 (t, *J* = 3.6 Hz, 1H), 2.15-1.98 (m, 4H), 1.60-1.40 (m, 1H), 1.20-1.08 (m, 1H), 1.15 (d, *J* = 7.1 Hz, 3H), 1.00 (d, *J* = 7.1 Hz, 3H), 0.94 (s, 3H), 0.89 (s, 3H) ppm.
^{13}C NMR ($CDCl_3$, 75 MHz): δ = 137.5, 99.8, 62.0, 37.0, 29.8, 28.9, 28.7, 28.5, 27.7, 25.0, 21.1 ppm.
IR (film): 2956 (s), 2927 (s), 2870 (s), 1463 (s), 1386 (m), 1366 (m), 1325 (w), 1253 (w) cm^{-1}.
MS (EI, 70 eV), *m/z* (%): 278 (M^+, 68), 236 (17), 222 (100), 151 (17), 108 (46), 95 (60), 77 (14), 67 (13).

$C_{11}H_{19}I$	HRMS (EI):	Calcd.: 278.0531
		Found: 278.0513

(6*R*)-6-(But-3-en-1-yl)-1-iodo-5,5-dimethylcyclohex-1-ene (28c)

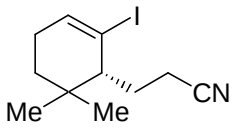


Prepared according to TP 3 by using freshly prepared 3-butenylzinc iodide[47] (1.59 M solution in THF, 2.30 mL, 3.60 mmol, 2.40 equiv), $TMSCH_2Li$ (1.0 M in pentane, 3.60 mL, 3.60 mmol, 2.40 equiv), a solution of CuCN·2LiCl (1.0 M solution in THF, 3.60 mL, 3.60 mmol, 2.40 equiv), NMP (2.2 mL) and the solution of diethyl (1*R*)-2-iodo-4,4-dimethylcyclohex-2-en-1-yl phosphate (**26**) (582 mg, 1.50 mmol, 1.0 equiv) in THF (1.5 mL). The reaction mixture was slowly warmed up to 25 °C and stirred for 14 h. Purification by column chromatography (silica gel, pentane) afforded the product (*R*)-**28c** as a colourless oil (371 mg, 85% yield).

GC (Chiraldex B-PH, 30 mm x 0.25 mm); conditions: 125 °C constant: t_R/min = 14.418 (minor), 15.151 (major); 98% *ee*.
$[\alpha]_D^{20}$ +81.2 (c 1.20, CH_2Cl_2)
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 6.21 (t, *J* = 3.8 Hz, 1H), 5.84-5.70 (m, 1H), 5.02-4.86 (m, 2H), 2.14-1.90 (m, 4H), 1.66-1.36 (m, 3H), 1.22-1.10 (m, 2H), 0.93 (s, 3H), 0.90 (s, 3H) ppm.
^{13}C NMR ($CDCl_3$, 75 MHz): δ = 139.2, 136.7, 114.9, 105.3, 56.0, 35.5, 34.1, 31.5, 30.7, 28.4, 27.9, 27.4 ppm.
IR (film): 2954 (s), 2921 (s), 2871 (s), 1640 (m), 1446 (m), 1386 (m), 1366 (m), 1327 (w), 992 (m), 911 (s) cm^{-1}.
MS (EI, 70 eV), *m/z* (%): 249 (3), 248 (32), 236 (20), 193 (8), 163 (43), 121 (11), 107 (46), 91 (47), 79 (100), 66 (47), 55 (16).

$C_{12}H_{19}I$	HRMS (EI):	Calcd.: 290.0531
		Found: 290.0561
$C_{12}H_{19}I$	Anal.	Calcd.: C 49.67, H 6.60
		Found: C 49.53, H 6.73

3-[(1*R*)-2-Iodo-6,6-dimethylcyclohex-2-en-1-yl]propanenitrile (28d)

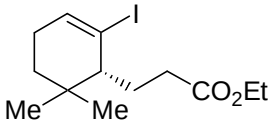


Prepared according to TP 3 by using freshly prepared 2-cyanoethylzinc iodide[47] (1.15 M solution in THF, 2.10 mL, 2.40 mmol, 2.40 equiv), $TMSCH_2Li$ (1.0 M in pentane, 2.40 mL, 2.40 mmol, 2.40 equiv), a solution of CuCN·2LiCl (1.0 M solution in THF, 2.40 mL, 2.40 mmol, 2.40 equiv), NMP (1.8 mL) and the solution of diethyl (1*R*)-2-iodo-4,4-dimethylcyclohex-2-en-1-yl phosphate (**26**) (388 mg, 1.0 mmol, 1.0 equiv) in THF (1 mL). The reaction mixture was slowly warmed up to 25 °C and stirred for 40 h. Purification by column chromatography (silica gel, 25% Et_2O:pentane) afforded the product (*R*)-**28d** as a colourless oil (211 mg, 73% yield).

GC (Chiraldex B-PH, 30 mm x 0.25 mm); conditions: 40 °C (2 min), ramp of 20 °C/min to 160 °C: t_R/min = 34.912 (minor), 35.911 (major); 95% *ee*.
$[\alpha]_D^{20}$ +70.4 (c 1.0, CH_2Cl_2)
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 6.36 (t, *J* = 3.4 Hz, 1H), 2.53-2.44 (m, 2H), 2.14-1.78 (m, 5H), 1.50-1.20 (m, 2H), 1.01 (s, 3H), 0.96 (s, 3H) ppm.
^{13}C NMR ($CDCl_3$, 75 MHz): δ = 140.0, 121.5, 102.9, 56.8, 37.0, 32.3, 29.5, 29.3, 29.2, 28.8, 18.9 ppm.
IR (film): 2958 (s), 2922 (s), 2873 (s), 2246 (m), 1732 (w), 1633 (m), 1445 (m), 1427 (m), 1388 (m), 919 (m) cm^{-1}.
MS (EI, 70 eV), *m/z* (%): 289 (M^+, 1), 261 (2), 233 (8), 162 (100), 146 (9), 132 (7), 121 (31), 106 (70), 91 (28), 79 (59), 65 (16), 53 (13).

$C_{11}H_{16}IN$	HRMS (EI):	Calcd.: 289.0327
		Found: 289.0304
$C_{11}H_{16}IN$	Anal.	Calcd.: C 45.96, H 5.58, N 4.84
		Found: C 45.97, H 5.63, N 4.68

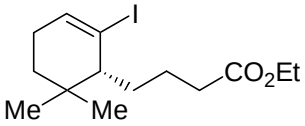
Ethyl 3-[(1*R*)-2-iodo-6,6-dimethylcyclohex-2-en-1-yl]propanoate (28e)



Prepared according to TP 3 by using freshly prepared 2-carboethoxyethylzinc iodide[47] (1.64 M solution in THF, 0.80 mL, 1.20 mmol, 2.40 equiv), $TMSCH_2Li$ (1.0 M in pentane, 1.20 mL, 1.20 mmol, 2.40 equiv), a solution of CuCN·2LiCl (1.0 M solution in THF, 1.20 mL, 1.20 mmol, 2.40 equiv), NMP (1 mL) and the solution of diethyl (1*R*)-2-iodo-4,4-dimethylcyclohex-2-en-1-yl phosphate (**26**) (194 mg, 0.50 mmol, 1.0 equiv) in THF (1 mL). The reaction mixture was slowly warmed up to 25 °C and stirred for 45 h. Purification by column chromatography (silica gel, 10% Et_2O:pentane) afforded the product (*R*)-**28e** as a colourless oil (134 mg, 81% yield).

GC (Chiraldex B-PH, 30 mm x 0.25 mm); conditions: 40 °C (2 min), ramp of 20 °C/min to 160 °C: t_R/min = 28.641 (minor), 29.421 (major); 97% *ee*.
$[\alpha]_D^{20}$ +62.7 (c 0.95, CH_2Cl_2)
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 6.17 (t, *J* = 3.8 Hz, 1H), 3.99 (q, *J* = 7.2 Hz, 2H), 2.32-2.22 (m, 2H), 1.98-1.76 (m, 4H), 1.74-1.60 (m, 1H), 1.40-1.26 (m, 1H), 1.16-1.04 (m, 1H), 1.12 (t, *J* = 7.2 Hz, 3H), 0.85 (s, 3H), 0.82 (s, 3H) ppm.
^{13}C NMR ($CDCl_3$, 75 MHz): δ = 172.1, 135.8, 101.7, 59.0, 53.9, 33.8, 32.4, 28.9, 26.7, 26.2, 25.7, 25.3, 12.9 ppm.
IR (film): 2957 (m), 2922 (m), 2873 (m), 1737 (s), 1446 (m), 1367 (m), 1324 (m), 1253 (m), 1178 (m) cm^{-1}.
MS (EI, 70 eV), *m/z* (%): 291 (5), 248 (4), 209 (100), 163 (38), 121 (47), 107 (16), 93 (22), 79 (22), 55 (6).
$C_{13}H_{21}IO_2$ HRMS (EI): Calcd.: 337.0665 $[M+H]^+$
Found: 337.0644 $[M+H]^+$

Ethyl 4-[(1*R*)-2-iodo-6,6-dimethylcyclohex-2-en-1-yl]butanoate (28f)

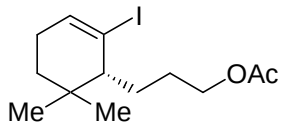


Prepared according to TP 3 by using freshly prepared 3-carboethoxypropylzinc iodide[47] (1.52 M solution in THF, 1.60 mL, 2.40 mmol, 2.40 equiv), $TMSCH_2Li$ (1.0 M in pentane, 2.40 mL, 2.40 mmol, 2.40 equiv), a solution of CuCN·2LiCl (1.0 M solution in THF, 2.40 mL, 2.40 mmol, 2.40 equiv), NMP (1.8 mL) and the solution of diethyl (1*R*)-2-iodo-4,4-dimethylcyclohex-2-en-1-yl phosphate (**26**) (388 mg, 1.0 mmol, 1.0 equiv) in THF (1 mL). The reaction mixture was slowly warmed up to 25 °C and stirred for 48 h. Purification by column chromatography (silica gel, 20% CH_2Cl_2:pentane) afforded the product (*R*)-**28f** as a colourless oil (286 mg, 82% yield).

GC (Chiraldex B-PH, 30 mm x 0.25 mm); conditions: 40 °C (2 min), ramp of 20 °C/min to 160 °C: t_R/min = 38.837 (minor), 40.045 (major); 98% *ee*.
$[\alpha]_D^{20}$ +42.5 (c 0.80, CH_2Cl_2)
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 6.19 (t, *J* = 3.8 Hz, 1H), 4.06 (q, *J* = 7.2 Hz, 2H), 2.23 (t, *J* = 7.4 Hz, 2H), 2.08-1.94 (m, 2H), 1.94-1.86 (m, 1H), 1.70-1.34 (m, 5H), 1.22-1.10 (m, 1H), 1.18 (t, *J* = 7.2 Hz, 3H), 0.91 (s, 3H), 0.89 (s, 3H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 172.5, 135.4, 103.7, 59.2, 55.1, 34.1, 33.8, 30.3, 29.3, 27.0, 26.5, 26.0, 23.7, 13.3 ppm.
IR (film): 2957 (m), 2921 (m), 2872 (m), 1735 (s), 1446 (m), 1368 (m), 1250 (m), 1179 (m), 856 (m) cm^{-1}.
MS (EI, 70 eV), *m/z* (%): 351 [$(M+H)^+$, 8], 305 (7), 223 (100), 193 (11), 177 (22), 167 (18), 121 (11), 93 (26), 41 (22).
$C_{14}H_{23}IO_2$ Anal. Calcd.: C 48.01, H 6.62
Found: C 47.53, H 6.97

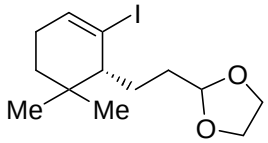
3-[(1*R*)-2-Iodo-6,6-dimethylcyclohex-2-en-1-yl]propyl acetate (28g)



Prepared according to TP 3 by using freshly prepared 3-acetoxypropylzinc iodide[47] (1.59 M solution in THF, 1.50 mL, 2.40 mmol, 2.40 equiv), $TMSCH_2Li$ (1.0 M in pentane, 2.40 mL, 2.40 mmol, 2.40 equiv), a solution of CuCN·2LiCl (1.0 M solution in THF, 2.40 mL, 2.40 mmol, 2.40 equiv), NMP (1.8 mL) and the solution of diethyl (1*R*)-2-iodo-4,4-dimethylcyclohex-2-en-1-yl phosphate (**26**) (388 mg, 1.0 mmol, 1.0 equiv) in THF (1 mL). The reaction mixture was slowly warmed up to 25 °C and stirred for 46 h. Purification by column chromatography (silica gel, 5% Et_2O:pentane) afforded the product (*R*)-**28g** as a colourless oil (218 mg, 65% yield).

GC (Chiraldex B-PH, 30 mm x 0.25 mm); conditions: 40 °C (2 min), ramp of 20 °C/min to 160 °C: t_R/min = 32.538 (minor), 33.254 (major); 97% *ee*.
$[\alpha]_D^{20}$ +57.6 (c 0.75, CH_2Cl_2)
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 6.23 (t, *J* = 3.8 Hz, 1H), 4.07-3.93 (m, 2H), 2.06-1.90 (m, 3H), 1.99 (s, 3H), 1.72-1.36 (m, 5H), 1.22-1.12 (m, 1H), 0.93 (s, 3H), 0.90 (s, 3H) ppm.
^{13}C NMR ($CDCl_3$, 75 MHz): δ = 171.5, 137.0, 104.8, 65.1, 56.2, 35.5, 30.7, 28.6, 28.4, 28.3, 28.0, 27.3, 21.4 ppm.
IR (film): 2955 (m), 2920 (m), 2872 (m), 1741 (s), 1449 (w), 1365 (m), 1241 (s), 1043 (m) cm^{-1}.
MS (FAB), *m/z* (%): 337 [$(M+H)^+$, 8], 277 (100), 248 (46), 220 (29), 149 (89).
$C_{13}H_{21}IO_2$ HRMS (EI): Calcd.: 336.0586
Found: 336.0615

2-{2-[(1*R*)-2-Iodo-6,6-dimethylcyclohex-2-en-1-yl]ethyl}-1,3-dioxolane (28h)



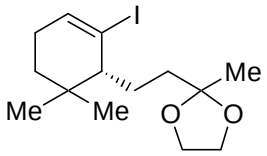
Prepared according to TP 3 by using freshly prepared [2-(1,3-dioxolan-2-yl)ethyl]zinc iodide[47] (1.72 M solution in THF, 1.40 mL, 2.40 mmol, 2.40 equiv), $TMSCH_2Li$ (1.0 M in pentane, 2.40 mL, 2.40 mmol, 2.40 equiv), a solution of CuCN·2LiCl (1.0 M solution in THF, 2.40 mL, 2.40 mmol, 2.40 equiv), NMP (1.8 mL) and the solution of diethyl (1*R*)-2-iodo-4,4-dimethylcyclohex-2-en-1-yl phosphate (**26**) (388 mg, 1.0 mmol, 1.0 equiv) in THF (1 mL). The reaction mixture was slowly warmed up to 25 °C and stirred for 41 h. Purification by

column chromatography (silica gel, 10% Et_2O:pentane) provided the product (*R*)-**28h** as a colourless oil (303 mg, 90% yield).

GC (Chiraldex B-PH, 30 mm x 0.25 mm); conditions: 40 °C (2 min), ramp of 20 °C/min to 160 °C: t_R/min = 42.135 (minor), 43.020 (major); 98% *ee*.
$[\alpha]_D^{20}$ +63.8 (c 0.95, CH_2Cl_2)
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 6.23 (t, *J* = 3.8 Hz, 1H), 4.78 (t, *J* = 4.5 Hz, 1H), 3.94-3.88 (m, 2H), 3.82-3.76 (m, 2H), 2.08-1.94 (m, 3H), 1.74-1.62 (m, 3H), 1.61-1.54 (m, 1H), 1.47-1.40 (m, 1H), 1.18-1.14 (m, 1H), 0.93 (s, 3H), 0.91 (s, 3H) ppm.
^{13}C NMR ($CDCl_3$, 75 MHz): δ = 137.1, 105.2, 104.6, 65.28, 65.22, 56.1, 35.5, 33.6, 30.7, 28.6, 28.1, 27.4, 26.2 ppm.
IR (film): 2955 (s), 2873 (s), 1142 (s), 1087 (m), 1038 (s), 943 (m) cm^{-1}.
MS (EI, 70 eV), *m/z* (%): 335 [$(M-H)^+$, 8], 330 (72), 248 (51), 204 (67), 99 (69), 73 (100).

$C_{13}H_{21}IO_2$	HRMS (EI):	Calcd.: 335.0508 $[M-H]^+$
		Found: 335.0519 $[M-H]^+$
$C_{13}H_{21}IO_2$	Anal.	Calcd.: C 46.44, H 6.30
		Found: C 46.75, H 6.39

2-{2-[(1*R*)-2-Iodo-6,6-dimethylcyclohex-2-en-1-yl]ethyl}-2-methyl-1,3-dioxolane (28i)

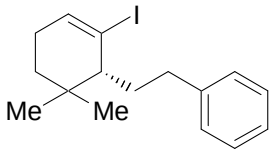


Prepared according to TP 3 by using freshly prepared [2-(2-methyl-1,3-dioxolan-2-yl)ethyl]zinc iodide[47] (1.35 M solution in THF, 0.90 mL, 1.20 mmol, 2.40 equiv), $TMSCH_2Li$ (1.0 M in pentane, 1.20 mL, 1.20 mmol, 2.40 equiv), a solution of CuCN·2LiCl (1.0 M solution in THF, 1.20 mL, 1.20 mmol, 2.40 equiv), NMP (1.0 mL) and the solution of diethyl (1*R*)-2-iodo-4,4-dimethylcyclohex-2-en-1-yl phosphate (**26**) (194 mg, 0.50 mmol, 1.0 equiv) in THF (1 mL). The reaction mixture was slowly warmed up to 25 °C and stirred for 48 h. Purification by column chromatography (silica gel, 10% Et_2O:pentane) provided the product (*R*)-**28i** as a colourless oil (125 mg, 71% yield).

GC (Chiraldex B-PH, 30 mm x 0.25 mm); conditions: 40 °C (2 min), ramp of 20 °C/min to 160 °C: t_R/min = 42.098 (minor), 43.023 (major); 98% *ee*.
$[\alpha]_D^{20}$ +62.8 (c 0.58, CH_2Cl_2)
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 6.31 (t, *J* = 3.8 Hz, 1H), 4.02-3.92 (m, 4H), 2.18-2.04 (m, 2H), 2.02-1.98 (m, 1H), 1.82-1.58 (m, 4H), 1.56-1.46 (m, 1H), 1.37 (s, 3H), 1.28-1.20 (m, 1H), 1.01 (s, 3H), 0.99 (s, 3H) ppm.
^{13}C NMR ($CDCl_3$, 75 MHz): δ = 136.5, 110.0, 104.6, 64.60, 64.58, 55.9, 38.1, 35.1, 30.4, 28.2, 27.7, 27.0, 25.9, 23.6 ppm.
IR (film): 2955 (s), 2874 (s), 1448 (m), 1376 (m), 1253 (m), 1217 (m), 1138 (m), 1056 (s), 855 (s) cm^{-1}.
MS (EI, 70 eV), *m/z* (%): 350 (M^+, 4), 248 (10), 121 (4), 99 (7), 87 (100), 79 (7).

$C_{14}H_{23}IO_2$	HRMS (EI):	Calcd.: 350.0743
		Found: 350.0743
$C_{14}H_{23}IO_2$	Anal.	Calcd.: C 48.01, H 6.62
		Found: C 48.52, H 6.13

{2-[(1*R*)-2-Iodo-6,6-dimethylcyclohex-2-en-1-yl]ethyl}benzene (28j)

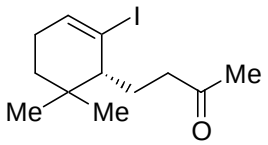


Prepared according to TP 3 by using freshly prepared 2-phenylethylzinc iodide[47] (1.60 M solution in THF, 1.25 mL, 2.0 mmol, 2.0 equiv), $TMSCH_2Li$ (1.0 M in pentane, 2.0 mL, 2.0 mmol, 2.0 equiv), a solution of CuCN·2LiCl (1.0 M solution in THF, 2.0 mL, 2.0 mmol, 2.0 equiv), NMP (1.8 mL) and the solution of diethyl (1*R*)-2-iodo-4,4-dimethylcyclohex-2-en-1-ylphosphate (**26**) (388 mg, 1.0 mmol, 1.0 equiv) in THF (2 mL). The reaction mixture was stirred at –30 °C for 41 h. After purification by column chromatography (silica gel, pentane), the product (*R*)-**28j** was obtained as a colourless oil (323 mg, 95% yield).

GC (Chirasil-Dex CB, 25 mm x 0.25 mm); conditions: 60 °C (1 min), ramp of 20 °C/ min to 160 °C; t_R (min) = 29.682 (minor), 30.429 (major); 98% *ee*.
$[\alpha]_D^{20}$ +63 (c 0.38, CH_2Cl_2)
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.28-7.06 (m, 5H), 6.25 (t, *J* = 3.54 Hz, 1H), 2.72-2.52 (m, 2H), 2.14-1.92 (m, 3H), 1.88-1.66 (m, 2H), 1.52-1.40 (m, 1H), 1.24-1.12 (m, 1H), 0.97 (s, 3H), 0.94 (s, 3H) ppm.
^{13}C NMR ($CDCl_3$, 75 MHz): δ = 143.1, 136.9, 128.8 (2 carbons), 128.7 (2 carbons), 126.2, 105.1, 56.3, 36.2, 35.5, 34.6, 31.0, 28.4, 28.0, 27.4 ppm.
IR (film): 2866 (s), 2916 (s), 1495 (w), 1452 (m), 920 (m) cm^{-1}.
MS (EI, 70 eV), *m/z* (%): 340 (M^+, 2), 284 (5), 236 (88), 213 (12), 157 (73), 129 (20), 109 (33), 104 (54), 91 (100).

$C_{16}H_{21}I$	HRMS (EI):	Calcd.: 340.0688
		Found: 340.0692
$C_{16}H_{21}I$	Anal.	Calcd.: C 56.48, H 6.22
		Found: C 56.19, H 6.10

4-[(1*R*)-2-Iodo-6,6-dimethylcyclohex-2-en-1-yl]butan-2-one (31)

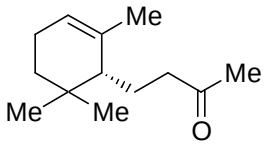


The mixture of (6*R*)-6-(but-3-en-1-yl)-1-iodo-5,5-dimethylcyclohexene ((*R*)-**28c**) (145 mg, 0.50 mmol), $PdCl_2$ (46 mg, 0.26 mmol, 0.52 equiv) and $CuCl_2$ (67 mg, 0.50 mmol, 1.0 equiv) in the solvent mixture of DMF (1.5 mL) and water (0.15 mL) was stirred under an oxygen atmosphere for 48 h at 25 °C. The reaction mixture was diluted with Et_2O (25 mL) and washed with water. The organic phase was dried over an anhydrous Na_2SO_4. The solvents were evaporated. The residual oil was purified by column chromatography (silica gel, 10% Et_2O:pentane) to afford the product (*R*)-**31** as a pale yellow oil (126 mg, 82% yield).

GC (Chiraldex B-PH, 30 mm x 0.25 mm); conditions: 40 °C (2 min), ramp of 20 °C/min to 160 °C: t_R/min = 23.303 (minor), 23.736 (major); 98% *ee*.
$[\alpha]_D^{20}$ +71 (c 0.57, CH_2Cl_2)

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 6.26 (t, *J* = 3.9 Hz, 1H), 2.60-2.40 (m, 2H), 2.11 (s, 3H), 2.09-1.80 (m, 4H), 1.71-1.60 (m, 1H), 1.48-1.35 (m, 1H), 1.24-1.14 (m, 1H), 0.94 (s, 3H), 0.89 (s, 3H) ppm.
^{13}C NMR ($CDCl_3$, 75 MHz): δ = 208.9, 137.6, 103.5, 55.5, 43.5, 35.6, 30.7, 30.3, 28.3, 28.0, 27.4, 25.8 ppm.
IR (film): 2956 (m), 2921 (m), 2872 (m), 1716 (s), 1429 (m), 1386 (m), 1161 (m) cm^{-1}.
MS (EI, 70 eV), *m/z* (%): 248 (20), 233 (8), 179 (100), 161 (10), 121 (45), 105 (16), 93 (34), 79 (23), 65 (8), 55 (8).
$C_{12}H_{19}IO$ Anal. Calcd.: C 47.07, H 6.25
Found: C 47.16, H 6.42

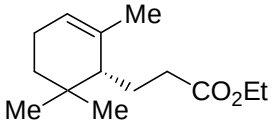
4-[(1*R*)-2,6,6-Trimethylcyclohex-2-en-1-yl]butan-2-one [(*R*)-dihydro-α-ionone; 32]



$ZnCl_2$ (136 mg, 1.0 mmol) was dried by gentle heating under high vacuum. After cooling to 25 °C under an argon atmosphere, the resulting solid was dissolved in THF (0.5 mL). The resulting mixture was treated with MeLi (1.40 M in Et_2O, 0.70 mL, 1.0 mmol). After stirring at 25 °C for 15 min, the resulting solution was transferred to a flame-dried round bottom flask which was charged with the mixture of (*R*)-**31** (100 mg, 0.33 mmol), $Pd(dba)_2$ (9 mg, 17 μmol, 5 mol%), and dppf (9 mg, 17 μmol, 5 mol%) in THF (1 mL). The reaction mixture was stirred at 25 °C for 24 h, then was diluted with Et_2O (25 mL) and washed with water. The organic phase was dried over an anhydrous Na_2SO_4. The solvents were evaporated. The residual oil was purified by column chromatography (silica gel, 10% Et_2O:pentane) to afford the product (*R*)-**32** as a pale yellow oil (44 mg, 70% yield).

GC (Chiraldex B-PH, 30 mm x 0.25 mm); conditions: 100 °C constant: t_R/min = 41.143 (minor), 45.071 (major); 98% *ee*.
$[\alpha]_D^{20}$ +149 (c 0.55, EtOH)
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 5.27 (br, s, 1H), 2.44-2.34 (m, 2H), 2.06 (s, 3H), 1.94-1.84 (m, 2H), 1.76-1.62 (m, 1H), 1.62-1.45 (m, 4H), 1.43-1.27 (m, 2H), 1.12-1.01 (m, 1H), 0.84 (s, 3H), 0.89 (s, 3H) ppm.
^{13}C NMR ($CDCl_3$, 75 MHz): δ = 209.5, 135.9, 121.4, 89.2, 48.8, 44.1, 32.9, 31.9, 30.3, 28.0, 24.8, 23.9, 23.3 ppm.
IR (film): 2957 (s), 2917 (s), 2870 (s), 1716 (s), 1449 (m), 1363 (s), 1160 (m) cm^{-1}.
MS (EI, 70 eV), *m/z* (%): 194 (M^+, 1), 176 (18), 161 (6), 136 (84), 121 (100), 107 (23), 95 (97), 81 (44), 67 (20), 55 (18).
$C_{13}H_{22}O$ HRMS (EI): Calcd.: 194.1671
Found: 194.1654

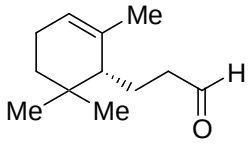
Ethyl 3-[(1*R*)-2,6,6-trimethylcyclohex-2-en-1-yl]propanoate (33)



A flame-dried round bottom flask equipped with a magnetic stirring bar, an argon inlet and a rubber septum was charged with ethyl 3-[(1*R*)-2-iodo-6,6-dimethylcyclohex-2-en-1-yl]propanoate ((*R*)-**28e**) (347 mg, 1.03 mmol), $Pd(dba)_2$ (30 mg, 0.05 mmol, 5 mol%), dppf (28 mg, 0.05 mmol, 5 mol%) and THF (2 mL). Me_2Zn (2.0 M in toluene, 1.50 mL, 3.10 mmol, 3.0 equiv) was added dropwise to the resulting suspension. The resulting mixture was stirred at 25 °C for 26 h. The reaction mixture was quenched by the dropwise addition of a saturated NH_4Cl solution. The mixture was extracted with Et_2O (3 x 25 mL). The combined organic phase was washed with water, dried over an anhydrous Na_2SO_4. The solvents were evaporated. The residual oil was purified by column chromatography (silica gel, 5% Et_2O:pentane) to afford ethyl 3-[(1*R*)-2,6,6-trimethylcyclohex-2-en-1-yl]propanoate[124] (**33**) as a pale yellow oil (186 mg, 81% yield).

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 5.26 (br, s, 1H), 4.04 (q, *J* = 7.2 Hz, 2H), 2.26 (t, *J* = 8.0 Hz, 2H), 1.94-1.84 (m, 2H), 1.80-1.66 (m, 1H), 1.65-1.43 (m, 4H), 1.44-1.26 (m, 2H), 1.18 (t, *J* = 7.2 Hz, 3H), 1.11-0.99 (m, 1H), 0.85 (s, 3H), 0.80 (s, 3H) ppm.
^{13}C NMR ($CDCl_3$, 75 MHz): δ = 174.4, 136.0, 121.4, 60.6, 48.9, 34.9, 33.0, 31.9, 28.0, 27.9, 26.2, 23.8, 23.3, 14.6 ppm.
IR (film): 2959 (m), 2871 (m), 1737 (s), 1448 (m), 1375 (m), 1256 (m), 1180 (m), 1158 (m) cm^{-1}.
MS (EI, 70 eV), 224 (M^+, 38), 209 (61), 179 (17), 168 (100), 163 (26), 136 (21), 121 (61), 107 (19), 94 (84), 81 (45).

3-[(1*R*)-2,6,6-Trimethylcyclohex-2-en-1-yl]propanal (34)



A solution of $LiAlH_4$ (1.0 M in Et_2O, 1.41 mL, 1.41 mmol, 2.0 equiv) was added dropwise to the solution of ethyl 3-[(1*R*)-2,6,6-trimethylcyclohex-2-en-1-yl]propanoate (**33**) (160 mg, 0.71 mmol) in dry Et_2O (2.5 mL) at 0 °C. The reaction mixture was vigorously stirred for 10 min, then was carefully quenched with $Na_2SO_4 \cdot 10H_2O$. The precipitate was removed by filtration, and the filtrate was concentrated to afford the corresponding alcohol as a colourless oil. A solution of DMSO (0.11 mL) in CH_2Cl_2 (0.40 mL) was added dropwise to a stirred solution of oxalyl chloride (0.07 mL, 0.82 mmol) in CH_2Cl_2 (2.6 mL) under a nitrogen atmosphere at –60 °C. After stirring for 5 min, a solution of the alcohol obtained as described above in the solvent mixture of CH_2Cl_2:DMSO (3:1, 1.0 mL) was added dropwise. The reaction mixture was stirred for additional 20 min, then dry Et_3N (0.50 mL, 3.56 mmol) was added at –60 °C and the stirring was continued for additional 10 min. The reaction mixture was warmed to 25 °C, and water was added. The organic layer was separated, and the aqueous phase was further extracted with Et_2O (3 x 25 mL). The combined organic phase was washed with water, dried over an anhydrous Na_2SO_4. The solvents were evaporated. The residual oil was purified by column chromatography (silica gel, 5% Et_2O:pentane) to afford the product (*R*)-**34** as a colourless oil (117 mg, 91% yield).

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 9.74 (t, *J* = 1.8 Hz, 1H), 5.35 (br, s, 1H), 2.53-2.41 (m, 2H), 2.04-1.90 (m, 2H), 1.90-1.30 (m, 7H), 1.22-1.06 (m, 1H), 0.92 (s, 3H), 0.87 (s, 3H) ppm.
IR (film): 2955 (s), 2917 (s), 2870 (m), 1727 (s), 1450 (w) cm^{-1}.

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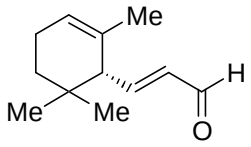
[124] Fernandez-Mateos, A.; CoCa, G. P.; Gonzalez, R. R.; Hernandez, C. T. *J. Org. Chem*. **1996**, *61*, 9097.

MS (EI, 70 eV), *m/z* (%): 180 (M^+, 4), 165 (2), 147 (8), 136 (100), 121 (62), 109 (19), 93 (48), 81 (90), 68 (42), 55 (31).
$C_{12}H_{20}O$ HRMS (EI): Calcd.: 180.1514
Found: 180.1519

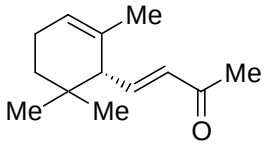
(2*E*)-3-[(1*R*)-2,6,6-Trimethylcyclohex-2-en-1-yl]acrylaldehyde



Phenylselenyl chloride (107 mg, 0.56 mmol, 1.30 equiv) and potassium *tert*-butoxide (71 mg, 0.63 mmol) were added to the solution of the aldehyde (*R*)-**34** (75 mg, 0.42 mmol) in THF (5 mL) at –78 °C. The reaction mixture was stirred at –78 °C under a nitrogen atmosphere for 1 h. Additional potassium *tert*-butoxide (71 mg, 0.63 mmol) was added at –78 °C, and the reaction mixture was stirred at –78 °C for additional 2 h. Additional potassium *tert*-butoxide (141 mg, 1.26 mmol) was added at –78 °C, and the mixture was stirred at –78 °C for additional 2 h. The reaction mixture was poured into a saturated NH_4Cl solution and extracted with Et_2O (3 x 20 mL). The combined organic layer was washed with brine, dried over an anhydrous Na_2SO_4. The solvents were evaporated. The residual oil was purified by column chromatography (silica gel, 5% Et_2O:pentane) to give a selenylated compound as a pale yellow oil. A hydrogen peroxide solution (30% solution in water, 0.05 mL) was added to the solution of the resulting selenylated compound obtained as described above in CH_2Cl_2 (4 mL). The reaction mixture was stirred at 25 °C for 20 min, then was treated with a saturated $NaHCO_3$ solution, extracted with Et_2O (3 x 25 mL). The combined organic phase was dried over an anhydrous $MgSO_4$. Purification by column chromatography (silica gel, 15% Et_2O:pentane) afforded (2*E*)-3-[(1*R*)-2,6,6-trimethylcyclohex-2-en-1-yl]acrylaldehyde as a pale yellow oil (51 mg, 70% yield).

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 9.46 (d, *J* = 7.9 Hz, 1H), 6.61 (dd, *J* = 15.5, 9.7 Hz, 1H), 6.04 (dd, *J* = 15,5, 7.9 Hz, 1H), 5.47 (br, s, 1H), 2.36 (d, *J* = 9.7 Hz, 1 H), 2.04-1.95 (m, 2H), 1.53-1.48 (m, 3H), 1.46-1.33 (m, 1H), 1.24-1.13 (m, 1H), 0.88 (s, 3H), 0.81 (s, 3H) ppm.
^{13}C NMR ($CDCl_3$, 75 MHz): δ = 194.2, 159.8, 134.4, 131.9, 123.5, 54.9, 33.0, 31.5, 28.2, 27.1, 23.4, 23.1 ppm.
IR (film): 2959 (m), 2918 (m), 1693 (s), 1450 (w), 1122 (m) cm^{-1}.
MS (EI, 70 eV), *m/z* (%): 178 (M^+, 22), 163 (13), 122 (70), 107 (100), 93 (64), 79 (51), 65 (9), 53 (10).
$C_{12}H_{18}O$ HRMS (EI): Calcd.: 178.1358
Found: 178.1377

(3*E*)-4-[(1*R*)-2,6,6-Trimethylcyclohex-2-en-1-yl]but-3-en-2-one (α-ionone; 35)

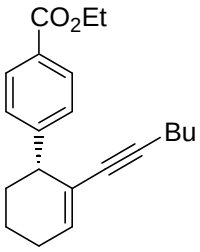


MeMgCl (2.95 M in THF, 0.12 mL) was added to a solution of (2*E*)-3-[(1*R*)-2,6,6-trimethylcyclohex-2-en-1-yl]acrylaldehyde obtained as described above (51 mg, 0.29 mmol) in THF (3 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 15 min under a nitrogen

atmosphere, then was poured into a saturated NH_4Cl solution, extracted with Et_2O (3 x 20 mL). The combined organic phase was dried over an anhydrous Na_2SO_4.The solvents were evaporated to give the corresponding alcohol as colourless oil. Pyridinium dichromate (PDC) (219 mg, 0.58 mmol) and Celite (219 mg) were added to a solution of the resulting alcohol obtained as described above in DMF (3 mL). The reaction mixture was stirred at 25 ^oC for 16 h under a nitrogen atmosphere. The reaction mixture was filtered. The solvents were evaporated then the crude material was purified by column chromatography (silica gel, 15% Et_2O:pentane) to give the product (*R*)-**35** as a colourless oil (48 mg, 87% yield).
GC (Chiraldex B-PH, 30 mm x 0.25 mm); conditions: 100 ^oC constant: t_R/min = 46.128 (minor), 50.609 (major); 97% *ee*.
$[\alpha]_D^{20}$ +43 (c 0.75, $CHCl_3$)
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 6.61 (dd, *J* = 15.9, 6.1 Hz, 1H), 6.04 (d, *J* = 15.9 Hz, 1H), 5.49 (br, s, 1H), 2.32-2.23 (m, 1H), 2.25 (s, 3H), 2.08-2.00 (m, 2H), 1.58-1.54 (m, 3H), 1.50-1.40 (m, 1H), 1.26-1.18 (m, 1H), 0.92 (s, 3H), 0.85 (s, 3H) ppm.
^{13}C NMR ($CDCl_3$, 100 MHz): δ = 198.4, 149.0, 132.3, 131.9, 122.7, 54.3, 32.5, 31.2, 27.8, 26.9, 26.8, 23.0, 22.8 ppm.
IR (film): 2958 (m), 2918 (m), 2867 (m), 1697 (m), 1676 (s), 1620 (m), 1436 (m), 1364 (m), 1252 (s), 988 (m) cm^{-1}.
MS (EI, 70 eV), *m/z* (%): 192 (M^+, 21), 177 (10), 136 (44), 121 (100), 109 (19), 93 (60), 77 (20).
$C_{13}H_{20}O$ HRMS (EI): Calcd.: 192.1514
Found: 192.1512

4. Copper(I)-mediated stereoselective *anti*-S_N2' substitution reactions and their convertions

Ethyl 4-[(1*R*)-2-hex-1-yn-1-ylcyclohex-2-en-1-yl]benzoate (37)

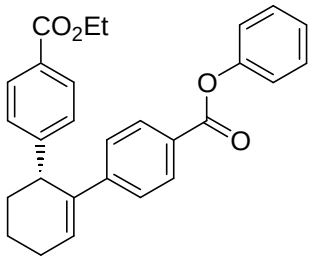


A flame-dried round bottom flask equipped with a magnetic stirring bar, an argon inlet and a rubber septum was charged with $PdCl_2(PPh_3)_2$ (35 mg, 0.05 mmol), CuI (10 mg, 0.05 mmol) and THF (2 mL). A solution of ethyl 4-[(1*R*)-2-iodocyclohex-2-en-1-yl]benzoate (**36**) (335 mg, 1.20 mmol, 95% *ee*) in THF (2 mL) was added dropwise to the resulting mixture. The reaction mixture was stirred at 25 ^oC for 5 min, then dry Et_3N (304 mg, 3.0 mmol) and hex-1-yne (90 mg, 1.10 mmol) were added consecutively. The resulting yellow solution was stirred at 25^oC for 25 h. The reaction mixture was quenched with a saturated aqueous NH_4Cl solution (20 mL) and extracted with Et_2O (3 x 20 mL). The combined organic phase was washed with brine and dried over Na_2SO_4. Evaporation of the solvents and the purification by column chromatography (silica gel, Et_2O:pentane, 80:1) afforded the product (*R*)-**37** as a colourless oil (205 mg, 70% yield).

$[\alpha]_D^{20}$ +1.4 (c 0.7, CH_2Cl_2)

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.92-7.86 (m, 2H), 7.24-7.18 (m, 2H), 6.22-6.17 (m, 1H), 4.30 (q, *J* = 7.1 Hz, 2H), 3.46-3.40 (m, 1H), 2.16-2.08 (m, 2H), 2.04-1.88 (m, 3H), 1.64-1.40 (m, 4H), 1.36-1.24 (m, 2H), 1.22-1.10 (m, 2H), 1.10-0.96 (m, 2H), 0.67 (t, *J* = 7.2 Hz, 3H) ppm.
^{13}C NMR ($CDCl_3$, 75 MHz): δ = 167.1, 150.8, 135.7, 129.7 (2 carbons), 128.7 (2 carbons), 123.2, 89.5, 81.9, 61.1, 45.8, 32.4, 31.1, 28.7, 26.1, 22.0, 19.5, 19.2, 14.7, 13.9 ppm.
IR (film): 2933 (m), 1719 (s), 1610 (m), 1275 (s), 1178 (m), 1102 (m), 1022 (m) cm^{-1}.
MS (EI, 70 eV), *m/z* (%): 310 (M^+, 100), 295 (7), 281 (23), 265 (44), 253 (19), 237 (42), 225 (12), 209 (12), 195 (43), 181 (51), 165 (72), 152 (33), 134 (28), 119 (29), 115 (29), 103 (35), 91 (41), 77 (17).
$C_{21}H_{26}O_2$ HRMS (EI): Calcd.: 310.1933
Found: 310.1946

Ethyl phenyl 4,4'-(1*R*)-cyclohex-2-ene-1,2-diyldibenzoate (38)

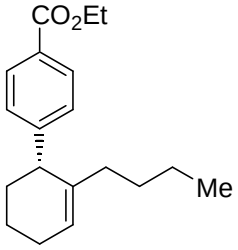


A flame-dried round bottom flask equipped with a magnetic stirring bar, an argon inlet and a rubber septum was charged with benzoic acid 4-iodo phenyl ester (243 mg, 0.75 mmol) and THF (1 mL), and cooled to –20 °C. *i*-PrMgCl (1.45 M in THF, 0.8 mL) was added dropwise, and the resulting mixture was stirred at –20 °C for 30 min. A solution of $ZnBr_2$ (1.5 M in THF, 1.5 mL) was added dropwise to the resulting mixture. After stirring at –20 °C for 15 min, the reaction mixture was warmed up to 25 °C and stirred for 30 min, and then was cannulated to the flame-dried round bottom flask which was charged with $Pd(dba)_2$ (14 mg, 5 mol%), dppf (14 mg, 5 mol%), ethyl 4-[(1*R*)-(2-iodocyclohex-2-en-1-yl)] benzoate (**36**) (178 mg, 0.50 mmol, 95% *ee*) and THF (3 mL). The reaction mixture was stirred at 25 °C for 16 h, then was quenched with a saturated aqueous NH_4Cl solution (20 mL) and extracted with Et_2O (3 x 20 mL). The combined organic phase was washed with brine and dried over Na_2SO_4 anhydrous. Evaporation of the solvents and the purification by column chromatography (silica gel, 10% Et_2O:pentane) afforded the product (*R*)-**38** as a white solid (160 mg, 75% yield).

mp = 128 °C
$[\alpha]_D^{20}$ –95 (c 0.6, CH_2Cl_2)
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.10-8.04 (m, 2H), 7.88-7.82 (m, 2H), 7.58-7.50 (m, 1H), 7.44-7.36 (m, 1H), 7.24-7.18 (m, 4H), 6.98-6.92 (m, 2H), 6.38-6.32 (m, 1H), 4.26 (q, *J* = 7.1 Hz, 2H), 4.02-3.94 (m, 2H), 2.32-2.20 (m, 2H), 2.12-1.98 (m, 1H), 1.82-1.70 (m, 1H), 1.58-1.42 (m, 2H), 1.28 (t, *J* = 7.1 Hz, 3H) ppm.
^{13}C NMR ($CDCl_3$, 75 MHz): δ = 167.0, 165.5, 150.9, 149.9, 139.7, 137.0, 133.9 (2 carbons), 130.5 (2 carbons), 129.9 (2 carbons), 129.0 (2 carbons), 128.9 (2 carbons), 128.7 (2 carbons), 127.2 (2 carbons), 121.6 (2 carbons), 61.1, 43.2, 32.9, 26.4, 17.9, 14.7 ppm.
IR (film): 2934 (m), 1731 (s), 1720 (s), 1609 (m), 1506 (m), 1275 (s), 1205 (s), 1173 (s), 1102 (m), 1082 (m), 1065 (m), 1024 (m), 741 (s) cm^{-1}.
MS (EI, 70 eV), *m/z* (%): 426 (M^+, 5), 115 (2), 106 (8), 105 (100), 78 (2), 77 (19), 51 (2).
$C_{28}H_{26}O_4$ HRMS (EI): Calcd.: 426.1831

		Found: 426.1812
$C_{28}H_{26}O_4$	Anal:	Calcd.: C 78.85, H 6.14
		Found: C 78.59, H 6.25

Ethyl 4-[(1*S*)-2-butylcyclohex-2-en-1-yl]benzoate (39)

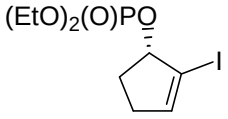


A solution of iodobutane (0.64 g, 3.50 mmol) in THF (1.5 mL) was added to the zinc foil (690 mg, 10.0 mmol) previously activated with 1,2-dibromoethane (79 μL) and TMSCl (49 μL) in THF (1 mL). The reaction mixture was heated at 40 °C for 4 h. GC–analysis of a hydrolyzed reaction aliquot showed the complete formation of the zinc reagent. A flame-dried round bottom flask was charged with $Pd(dba)_2$ (14 mg, 0.03 mmol), dppf (14 mg, 0.03 mmol) and THF (1 mL). Then the solution of ethyl 4 [(1*R*)-(2-iodocyclohex-2-en-1-yl) benzoate (**36**) (0.18 mg, 0.50 mmol, 95% *ee*) in THF (2 mL) was added dropwise followed by the addition of freshly prepared butylzinc iodide obtained as described above (1.40 M in THF, 1.5 mL). The reaction mixture was heated at 67 °C for 12 h. After cooling to 25 °C, the reaction mixture was quenched with a saturated aqueous NH_4Cl solution (20 mL) and extracted with Et_2O (3 x 20 mL). The combined organic phase was washed with brine and dried over Na_2SO_4 anhydrous. Evaporation of the solvents and the purification by column chromatography (silica gel, pentane:Et_2O = 100:2) afforded the product (*S*)-**39** as a colourless oil (99 mg, 69% yield).

$[\alpha]_D^{20}$ –74 (c 1.25, CH_2Cl_2)
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.92-7.86 (m, 2H), 7.20-7.14 (m, 2H), 5.66-5.62 (m, 1H), 4.29 (q, *J* = 6.9 Hz, 2H), 3.36-3.28 (m, 1H), 2.08-1.96 (m, 2H), 1.94-1.82 (m, 1H), 1.80-1.00 (m, 12H), 0.74 (t, *J* = 6.9 Hz, 3H) ppm.
^{13}C NMR ($CDCl_3$, 75 MHz): δ = 165.7, 150.2, 137.0, 128.4 (2 carbons), 127.5 (2 carbons), 127.2, 123.0, 59.7, 43.1, 34.6, 31.7, 28.9, 24.4, 21.4, 17.8, 13.4, 13.0 ppm.
IR (film): 2930 (m), 1720 (s), 1609 (m), 1276 (s), 1177 (m), 1102 (s), 1023 (m).
MS (EI, 70 eV), *m/z* (%): 286 (M^+, 100), 241 (34), 229 (91), 216 (24), 215 (24), 201 (12), 171 (39), 157 (31), 141 (32), 129 (60), 115 (28), 91 (24), 77 (14).

$C_{19}H_{26}O_2$	HRMS (EI):	Calcd.: 286.1933
		Found: 286.1915

Diethyl (1*S*)-2-iodocyclopent-2-en-1-yl phosphate (44)

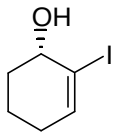


N-Methylimidazole (0.74 mL, 9.36 mmol, 2.0 equiv) was added to the solution of (1*S*)-2-iodocyclopent-2-en-1-ol (983 mg, 4.68 mmol) in dry CH_2Cl_2 (10 mL). The reaction mixture was cooled to 0 °C, and then chloro diethylphosphate (0.75 mL, 5.15 mmol, 1.10 equiv) was

added dropwise. The reaction mixture was stirred at 25 °C for 6 h, then was poured into the pH 7 buffer, extracted with CH_2Cl_2 (3 x 20 mL), and dried over Na_2SO_4 anhydrous. After the evaporation of the solvents, the crude product was purified by column chromatography (Alumina grade III, Et_2O, 0.1% Et_3N) to afford the product (*S*)-**44** as a colourless oil (1.48 g, 91% yield).

HPLC (Chiralcel OJ, heptane:*i*-PrOH = 99:1, 0.6 mL/min); t_R (min) = 30.296 (major), 38.945 (minor); 95% *ee*.
$[\alpha]_D^{20}$ –4.7 (c 1.4, CH_2Cl_2)
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 6.45-6.40 (m, 1H), 5.30-5.25 (m, 1H), 4.24-4.08 (m, 4H), 2.60-2.48 (m, 1H), 2.43-2.26 (m, 2H), 2.17-2.06 (m, 1H), 1.39-1.31 (m, 6H) ppm.
^{13}C NMR ($CDCl_3$, 75 MHz): δ = 146.4, 93.9, 88.2, 64.5, 64.3, 33.3, 31.2, 16.6, 16.5 ppm.
IR (neat): 2983 (m), 2932 (w), 1443 (w), 1393 (w), 1265 (s), 1165 (m), 1027 (s), 989 (s), 818 (m), 571 (w) cm^{-1}.
MS (EI, 70 eV), *m/z* (%): 219 (M^+-I, 100), 209 (6), 194 (14), 192 (51), 163 (51), 155 (28), 138 (3), 127 (24), 111 (5), 99 (37), 83 (20), 66 (22), 65 (45).
$C_9H_{16}IO_4P$ HRMS (EI): Calcd.: 344.9753 $[M-H]^+$
Found: 344.9747 $[M-H]^+$

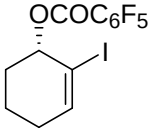
(1*S*)-2-Iodocyclohex-2-en-1-ol



Prepared according to TP 2 using (*R*)-diphenylprolinol (127 mg, 0.50 mmol, 5 mol%), THF (10 mL), $B(OMe)_3$ (60 µL, 0.50 mmol, 5 mol%), borane-*N*,*N*-diethylaniline complex (1.78 mL, 10.0 mmol, 1.0 equiv) and 2-iodocyclohex-2-en-1-one (2.22 g, 10.0 mmol) in THF (10 mL). The reaction mixture was continuously stirred for 1 h then was carefully quenched with MeOH (7 mL). The crude product was purified by column chromatography (silica gel, 25% Et_2O:pentane) to afford (1*S*)-2-iodocyclohex-2-en-1-ol as a colourless oil (1.94 g, 87% yield).

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 6.44 (t, *J* = 4.09 Hz, 1H), 4.13 (t, *J* = 4.92 Hz, 1H), 2.20-1.53 (m, 7H) ppm.
^{13}C NMR ($CDCl_3$, 75 MHz): δ = 141.4, 104.0, 72.5, 32.3, 29.8, 18.1 ppm.
IR (film): 3369 (br), 2939 (s), 2862 (m), 1426 (m), 1329 (m), 1078 (m), 1051 (s), 971 (s) cm^{-1}.
MS (EI, 70 eV), *m/z* (%): 224 (M^+, 36), 206 (4), 196 (17), 127 (10), 97 (100), 79 (21), 67 (13), 55 (15).
C_6H_9IO HRMS (EI): Calcd.: 223.9698
Found: 223.9711
C_6H_9IO Anal: Calcd.: C 32.17, H 4.05
Found: C 32.06, H 3.90

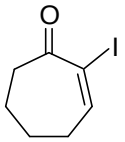
(1*S*)-2-Iodocyclohex-2-en-1-yl 2,3,4,5,6-pentafluorobenzoate (45)



Pyridine (1.30 equiv, 10.4 mmol, 0.84 mL), DMAP (0.10 equiv, 0.80 mmol, 98 mg) and pentafluorobenzoyl chloride (1.30 equiv, 10.4 mmol, 1.50 mL) were added to the solution of (1*S*)-2-iodocyclohex-2-en-1-ol (1.79 g, 7.98 mmol) in dry Et_2O (40 mL) at 25 °C. The reaction mixture was stirred at 25 °C for 16 h, and then was quenched with a saturated NH_4Cl solution (20 mL) and extracted with Et_2O (3 x 20 mL). The combined organic phase was washed with brine and dried over Na_2SO_4 anhydrous. The crude product was purified by column chromatography (silica gel, 5% Et_2O:pentane) to afford the product (*S*)-**45** as a colourless oil (3.27 g, 98% yield).

HPLC (Chiralcel OD-H, heptane:*i*-PrOH = 98:2, 0.2 mL/min); t_R (min) = 30.3 (minor), 33.1 (major); 98% *ee*.
$[\alpha]_D^{20}$ –57 (c 1.4, CH_2Cl_2)
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 6.65 (dd, *J* = 4.4, 3.5 Hz, 1H), 5.65-5.55 (m, 1H), 2.22-2.10 (m, 2H), 2.05-1.92 (m, 2H), 1.73-1.64 (m, 2H) ppm.
^{13}C NMR ($CDCl_3$, 75 MHz): δ = 158.3, 147.0, 145.1, 145.0, 143.6, 141.4, 139.4, 135.9, 92.3, 76.5, 29.9, 29.1, 16.8 ppm.
IR (neat): 2949 (m), 1738 (s), 1652 (s), 1525 (s), 1504 (s), 1425 (m), 1341 (s), 1225 (s), 1102 (m), 998 (s) cm^{-1}.
MS (EI, 70 eV), *m/z* (%): 292 (M^+-I, 12), 291 (90), 247 (5), 206 (4), 196 (22), 195 (100), 167 (31), 148 (3), 117 (15), 80 (8), 79 (31), 77 (17).
$C_{13}H_8F_5IO_2$ Anal: Calcd.: C 37.35, H 1.93
Found: C 37.40, H 1.93

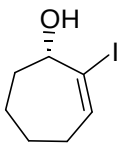
2-Iodocyclohept-2-enone



The solution of I_2 (21.3 g, 4.20 equiv, 84.0 mmol) in the solvent mixture of pyridine:CCl_4 (1:1, 84 mL) was added dropwise to the solution of cyclohept-2-en-1-one (2.20 mL, 20.0 mmol) in the solvent mixture of pyridine:CCl_4 (1:1, 84 mL) at 0 °C under a nitrogen atmosphere. The reaction mixture was warmed to 25 °C and stirred for 48 h. The reaction mixture was diluted in Et_2O (200 mL), washed with H_2O (100 mL), 1 M HCl (2 x 40 mL), H_2O (40 mL), a saturated $Na_2S_2O_3$ and dried over $MgSO_4$ anhydrous. Purification by column chromatography (silica gel, 20% Et_2O:pentane) provided 2-iodocyclohept-2-enone as a yellow oil (2.42 g, 51% yield).
The analytical data were in agreement with those reported.[125]

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.60 (t, *J* = 6.41 Hz, 1H), 2.80-2.64 (m, 2H), 2.50-2.32 (m, 2H), 1.90-1.74 (m, 4H) ppm.
MS (EI, 70 eV), *m/z* (%): 236 (M^+, 100), 207 (21).

(1*S*)-2-Iodocyclohep-2-ten-1-ol

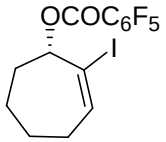


[125] Mayasundari, A.; Young, D. G. J. *Tetrahedron Lett.* **2001**, *42*, 203.

Prepared according to TP 2 using (*R*)-diphenylprolinol (63 mg, 0.25 mmol, 5 mol%), THF (5 mL), $B(OMe)_3$ (0.03 mL, 0.25 mmol, 5 mol%), borane-*N*,*N*-diethylaniline complex (0.89 mL, 5.0 mmol, 1.0 equiv) and 2-iodocyclohept-2-en-1-one (1.18 g, 5.0 mmol) in THF (5 mL). The reaction mixture was continuously stirred for 1 h, and then was carefully quenched with MeOH (2 mL). The crude product was purified by column chromatography (silica gel, 10% Et_2O:pentane) to afford (1*S*)-2-iodocyclohept-2-en-1-ol as a pale yellow oil (610 mg, 51% yield).

GC (Chirasil-Dex CB, 25 mm x 0.25 mm); conditions: 60 °C (1 min), ramp of 2 °C/min to 160 °C: t_R/min = 40.879 (minor), 41.100 (major); 99% *ee*.
$[\alpha]_D^{20}$ –51 (c 0.24, CH_2Cl_2)
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 6.61-6.55 (m, 1H), 4.31-4.25 (m, 1H), 2.20-1.40 (m, 9H) ppm.
^{13}C NMR ($CDCl_3$, 75 MHz): δ = 142.9, 110.4, 77.3, 33.1, 30.8, 26.0, 24.7 ppm.
IR (film): 3369 (br), 2939 (s), 2862 (m), 1426 (m), 1329 (m), 1078 (m), 1051 (s), 971 (s) cm^{-1}.
MS (EI, 70 eV), *m/z* (%): 238 (M^+, 27), 220 (54), 196 (5), 127 (9), 111 (51), 93 (66), 77 (41), 67 (49), 55 (100).
$C_7H_{11}IO$ HRMS (EI): Calcd.: 237.9855
Found: 237.9860

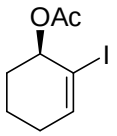
(1*S*)-2-Iodocyclohept-2-en-1-yl 2,3,4,5,6-pentafluorobenzoate (46)



Pyridine (1.30 equiv, 0.26 mL, 3.25 mmol), DMAP (0.10 equiv, 30 mg, 0.25 mmol) and pentafluorobenzoyl chloride (1.30 equiv, 0.47 mL, 3.25 mmol) were added to the solution of (1*S*)-2-iodocyclohept-2-en-1-ol (595 mg, 2.50 mmol) in dry Et_2O (13 mL) at 25 °C. The resulting suspension was stirred at 25 °C for 16 h. The reaction mixture was poured into a saturated NH_4Cl solution (20 mL), extracted with Et_2O (3 x 20 mL). The combined organic phase was washed with brine and dried over Na_2SO_4 anhydrous. The crude product was purified by column chromatography (silica gel, 2% Et_2O:pentane) to afford the product (*S*)-**46** as a pale yellow oil (941 mg, 87% yield).

GC (Chirasil-Dex CB, 25 mm x 0.25 mm); conditions: 60 °C (1 min), ramp of 2 °C/min to 160 °C: t_R/min = 61.867 (minor), 62.530 (major); 98% *ee*.
$[\alpha]_D^{20}$ –68 (c 0.36, CH_2Cl_2)
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 6.74 (t, *J* = 6.69 Hz, 1H), 5.78-5.70 (m, 1H), 2.26-1.50 (m, 8H) ppm.
^{13}C NMR ($CDCl_3$, 75 MHz): δ = 158.4, 148.0, 147.6, 145.5, 144.2, 139.8, 136.5, 108.5, 97.3, 83.1, 30.9, 30.4, 26.1, 24.3 ppm.
IR (film): 2937 (s), 2864 (m), 1736 (s), 1652 (s), 1524 (s), 1499 (s), 1452 (m), 1422 (m), 1332 (s), 1227 (s), 1006 (s), 945 (m) cm^{-1}.
MS (EI, 70 eV), *m/z* (%): 305 (M^+-I, 22), 195 (100), 167 (5), 117 (2), 93 (6), 77 (4).
$C_{14}H_{10}F_5IO_2$ HRMS (EI): Calcd.: 305.0601 $[M-I]^+$
Found: 305.0585 $[M-I]^+$

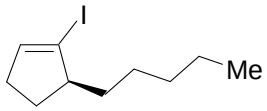
(1*R*)-2-Iodocyclohex-2-en-1-yl acetate (47)



Acetic anhydride (3.5 mL) was added to a solution of (1*R*)-2-iodocyclohex-2-en-1-ol (1.48 g, 6.61 mmol) in pyridine (5.9 mL) at 25 °C. The reaction mixture was stirred at 25 °C for 2 h, then was diluted with Et_2O, washed with 2 M HCl (50 mL), H_2O, a saturated aqeous $NaHCO_3$ solution, brine and dried over Na_2SO_4 anhydrous. The crude product was purified by column chromatography (10% Et_2O:pentane) to give the product (*R*)-**47** as a colourless oil (1.61 g, 91% yield).

GC (TFA gamma-cyclodextrin); conditions: 40 °C (2 min), ramp of 20 °C/ min to 150 °C; t_R(min) = 10.24 (major), 11.04 (minor); 98% *ee*.
$[\alpha]_D^{20}$ +22 (c 1.08, $CHCl_3$)
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 6.65-6.64 (m, 1H), 5.40-5.39 (m, 1H), 2.11 (s, 3H), 2.11-1.70 (m, 6H) ppm.
^{13}C NMR ($CDCl_3$, 75 MHz): δ = 170.5, 143.9, 95.8, 73.8, 30.3, 29.5, 21.6, 17.8 ppm.
IR (film): 2944 (w), 1735 (s), 1427 (w), 1371 (m), 1233 (s), 977 (m), 917 (w), 730 (w) cm^{-1}.
MS (EI, 70 eV), *m/z* (%): 206 (M-AcO-H$^+$, 4), 139 (85), 126 (15), 97 (100), 79 (47), 55 (4).
$C_8H_{11}IO_2$ Anal.: Calcd.: C 36.11, H 4.17
Found: C 36.38, H 4.06

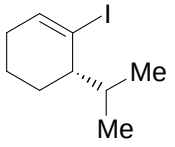
(5*S*)-1-Iodo-5-pentylcyclopent-1-ene (48a)



Prepared according to TP 4 by using diethyl (1*S*)-2-iodocyclopent-2-en-1-yl phosphate (**44**) (95% *ee*, 346 mg, 1.0 mmol), THF (1.6 mL), the dipentylzinc solution (5.70 M in THF, 0.40 mL, 2.24 mmol, 2.24 equiv), a CuCN·2LiCl solution (1.0 M in THF, 2.24 mL, 2.24 mmol, 2.24 equiv) and NMP (1.3 mL). The reaction mixture was warmed to –10 °C and stirred for 15 h. After purification by column chromatography (silica gel, pentane), the cyclopentenyl iodide (*S*)-**48a** was obtained as a colourless oil (253 mg, 96% yield).

GC (Chirasil-Dex CB, 25 mm x 0.25 mm); conditions: 60 °C (1 min), ramp of 5 °C/ min to 160 °C; t_R(min) = 16.296 (major), 16.446 (minor); 94% *ee*.
$[\alpha]_D^{20}$ +13 (c 0.31, CH_2Cl_2)
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 6.10-6.00 (m, 1H), 2.68-2.47 (m, 1H), 2.35-2.10 (m, 2H), 2.08-1.90 (m, 2H), 1.68-1.42 (m, 3H), 1.40-0.98 (m, 5H), 0.92-0.75 (m, 3H) ppm.
^{13}C NMR ($CDCl_3$, 75 MHz): δ = 139.6, 102.6, 52.4, 34.9, 33.7, 32.4, 28.7, 26.6, 23.0, 14.5 ppm.
IR (film): 2956 (s), 2926 (s), 2854 (s), 1466 (m), 1378 (w) cm^{-1}.
MS (EI, 70 eV), *m/z* (%): 264 (M$^+$, 45), 194 (37), 193 (38), 137 (21), 95 (21), 81 (43), 67 (96), 66 (100).
$C_{10}H_{17}I$ HRMS (EI): Calcd.: 264.0375
Found: 264.0382

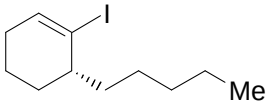
(6*S*)-1-Iodo-6-isopropylcyclohex-1-ene (48b)



Prepared according to TP 4 by using (1*R*)-2-iodocyclohex-2-en-1-yl 2,3,4,5,6-pentafluorobenzoate ((*R*)-**45**) (98% *ee*, 2.09 g, 5.0 mmol), THF (8 mL), a CuCN·2LiCl solution (1.0 M in THF, 11.2 mL, 11.2 mmol, 2.24 equiv), NMP (7 mL) and the diisopropylzinc solution (5.10 M in THF, 2.20 mL, 11.2 mmol, 2.24 equiv). The reaction mixture was warmed to –10 °C and stirred for 16 h. Purification by column chromatography (silica gel, pentane) afforded the product (*S*)-**48b** as a colourless oil (1.21 g, 97% yield).
The separation of the enantiomers was not possible under a variety of conditions in chiral HPLC or capillary GC. The enantiomeric excess was determined for the corresponding ketone (*S*)-**52b**.

$[\alpha]_D^{20}$ –79 (c 1.12, CH_2Cl_2)
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 6.60-6.45 (m, 1H), 2.32-2.17 (m, 2H), 2.08-1.94 (m, 2H), 1.80-1.63 (m, 2H), 1.61-1.47 (m, 2H), 0.96 (d, *J* = 6.6 Hz, 3H), 0.75 (d, *J* = 6.6 Hz, 3H) ppm.
^{13}C NMR ($CDCl_3$, 75 MHz): δ = 140.4, 109.0, 48.7, 32.2, 29.7, 23.6, 21.3, 20.4, 15.5 ppm.
IR (film): 2959 (s), 2859 (s), 1682 (w), 1464 (m), 1386 (w), 1368 (w), 1030 (w), 1003 (w), 805 (w), 692 (w) cm^{-1}.
MS (EI, 70 eV), *m/z* (%): 250 (M^+, 91), 208 (30), 123 (68), 79 (100), 67 (23).
$C_9H_{15}I$ HRMS (EI): Calcd.: 250.0218
Found: 250.0214

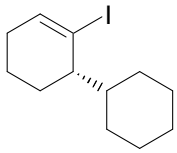
(6*R*)-1-Iodo-6-pentylcyclohex-1-ene (48c)



Prepared according to TP 4 by using (1*R*)-2-iodocyclohex-2-en-1-yl 2,3,4,5,6-pentafluorobenzoate ((*R*)-**45**) (98% *ee*, 418 mg, 1.0 mmol), THF (1.6 mL), a CuCN·2LiCl solution (1.0 M in THF, 2.24 mL, 2.24 mmol, 2.24 equiv), NMP (1.3 mL) and the dipentylzinc solution (5.70 M in THF, 0.40 mL, 2.24 mmol, 2.24 equiv). The reaction mixture was warmed to –10 °C and stirred for 16 h. Purification by column chromatography (silica gel, pentane) afforded the product (*R*)-**48c** as a colourless oil (250 mg, 90% yield).

GC (Chirasil-Dex CB, 25 mm x 0.25 mm); conditions: 40 °C (1 min), ramp of 20 °C/ min to 160 °C; t_R(min) = 9.535 (minor), 9.625 (major); 99% *ee*.
$[\alpha]_D^{20}$ –2.3 (c 1.12, CH_2Cl_2)
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 6.40-6.30 (m, 1H), 2.31-2.19 (m, 1H), 2.10-1.93 (m, 2H), 1.87-1.51 (m, 5H), 1.45-1.10 (m, 7H), 0.94-0.75 (m, 3H) ppm.
^{13}C NMR ($CDCl_3$, 75 MHz): δ = 138.2, 107.3, 44.9, 34.6, 31.8, 29.6, 28.1, 26.4, 22.6, 18.4, 14.1 ppm.
IR (film): 2929 (s), 2857 (s), 1683 (w), 1456 (m), 961 (w) cm^{-1}.
MS (EI, 70 eV), *m/z* (%): 278 (M^+, 38), 208 (26), 151 (16), 109 (17), 95 (96), 91 (10), 81 (100), 77 (21), 69 (11), 67 (39), 55 (12).
$C_{11}H_{19}I$ HRMS (EI): Calcd.: 278.0531
Found: 278.0503

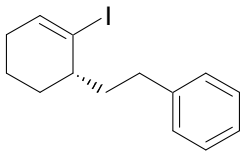
(6*S*)-6-Cyclohexyl-1-iodocyclohex-1-ene (48d)



Prepared according to TP 5 by using (1*R*)-2-iodocyclohex-2-en-1-yl 2,3,4,5,6-pentafluorobenzoate ((*R*)-**45**) (98% *ee*, 418 mg, 1.0 mmol), THF (1.6 mL), a CuCN·2LiCl solution (1.0 M in THF, 2.24 mL, 2.24 mmol, 2.24 equiv), NMP (1.3 mL) and cyclohexylzinc iodide (1.96 M in toluene, 1.14 mL, 2.24 mmol, 2.24 equiv). The reaction mixture was warmed to –10 °C and stirred for 16 h. Purification by column chromatography (silica gel, pentane) afforded the product (*S*)-**48d** as a colourless oil (261 mg, 90% yield).
The separation of the enantiomers was not possible under a variety of conditions in chiral HPLC or capillary GC. The enantiomeric excess was determined for the corresponding ketone (*S*)-**52d**.

$[\alpha]_D^{20}$ –76 (c 1.12, CH_2Cl_2)
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 6.55-6.40 (m, 1H), 2.32-2.12 (m, 1H), 2.09-0.84 (m, 17H) ppm.
^{13}C NMR ($CDCl_3$, 75 MHz): δ = 140.3, 108.6, 48.6, 43.1, 31.2, 29.7, 27.1, 26.7, 26.6, 26.5, 25.2, 21.4 ppm.
IR (film): 1925 (s), 2851 (s), 1448 (m), 986 (w) cm^{-1}.
MS (EI, 70 eV), *m/z* (%): 290 (M^+, 51), 208 (100), 163 (24), 121 (2), 105 (3), 91 (12), 83 (56), 81 (63), 79 (41), 67 (12), 55 (44).
$C_{12}H_{19}I$ HRMS (EI): Calcd.: 290.0531
Found: 290.0505

{2-[(1*S*)-2-Iodocyclohex-2-en-1-yl]ethyl}benzene (48e)

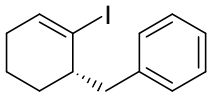


Prepared according to TP 5 by using (1*R*)-2-iodocyclohex-2-en-1-yl 2,3,4,5,6-pentafluorobenzoate ((*R*)-**45**) (98% *ee*, 418 mg, 1.0 mmol), NMP (1.1 mL), 2-phenylethylzinc iodide (1.60 M in THF, 1.25 mL, 2.0 mmol, 2.0 equiv) and a CuCN·2LiCl solution (1.0 M in THF, 2.0 mL, 2.0 mmol, 2.0 equiv). The reaction mixture was slowly warmed up to 25 °C and stirred for 48 h. Purification by column chromatography (silica gel, pentane) afforded the product (*S*)-**48e** as a colourless oil (266 mg, 85% yield).

GC (Chirasil-Dex CB, 25 mm x 0.25 mm); conditions: 60 °C (1 min), ramp of 20 °C/ min to 160 °C; t_R (min) = 25.323 (minor), 25.960 (major); 99% *ee*.
$[\alpha]_D^{20}$ –3.1 (c 0.36, CH_2Cl_2)
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.28-7.06 (m, 5H), 6.34 (dt, *J* = 1.55, 3.90 Hz, 1H), 2.72-2.60 (m, 1H), 2.54-2.40 (m, 1H), 2.34-2.22 (m, 1H), 2.10-1.94 (m, 3H), 1.88-1.74 (m, 1H), 1.74-1.48 (m, 4H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 142.5, 139.2, 128.8 (2 carbons), 128.7 (2 carbons), 126.2, 106.8, 44.8, 36.8, 33.3, 30.0, 28.5, 19.1 ppm.
IR (film): 2933 (s), 2858 (m), 1496 (m), 1454 (m), 1327 (w) cm^{-1}.
MS (EI, 70 eV), *m/z* (%): 312 (M^+, 7), 208 (22), 185 (100), 156 (4), 143 (16), 129 (12), 117 (32), 104 (54), 91 (73), 79 (21).
$C_{14}H_{17}I$ HRMS (EI): Calcd.: 312.0375
Found: 312.0382

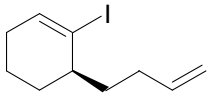
{[(1*S*)-2-Iodocyclohex-2-en-1-yl]methyl}benzene (48f)



Prepared according to TP 5 by using (1*S*)-2-iodocyclohex-2-en-1-yl 2,3,4,5,6-pentafluorobenzoate ((*R*)-**45**) (98% *ee*, 418 mg, 1.0 mmol), NMP (1.2 mL), benzylzinc iodide (0.81 M in THF, 2.50 mL, 2.0 mmol, 2.0 equiv) and a CuCN·2LiCl solution (1.0 M in THF, 1.0 mL, 1.0 mmol, 1.0 equiv). The reaction mixture was warmed up to 25 °C and stirred for 5 days. Purification by column chromatography (silica gel, pentane) afforded the product (*S*)-**48f** as a colourless oil (149 mg, 50% yield).

GC (Chirasil-Dex CB, 25 mm x 0.25 mm); conditions: 60 °C (1 min), ramp of 205 °C/ min to 160 °C; t_R (min) = 17.395 (minor), 17.803 (major); 91% *ee*.
$[\alpha]_D^{20}$ +12 (c 0.34, CH_2Cl_2)
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.26-7.16 (m, 2H), 7.16-7.08 (m, 3H), 6.36 (dt, *J* = 1.22, 4.09 Hz, 1H), 3.20 (dd, *J* = 2.34, 13.11 Hz, 1H), 2.54-2.44 (m, 1H), 2.37 (dd, *J* = 2.34, 13.11 Hz, 1H), 2.07-1.95 (m, 2H), 1.66-1.41 (m, 4H) ppm.
^{13}C NMR ($CDCl_3$, 75 MHz): δ = 140.7, 139.4, 129.5 (2 carbons), 128.7 (2 carbons), 126.5, 106.1, 47.8, 41.0, 30.0, 27.6, 17.9 ppm.
IR (film): 2930 (m), 1494 (m), 1452 (m), 964 (m), 739 (s) cm^{-1}.
MS (EI, 70 eV), *m/z* (%): 298 (M^+, 61), 206 (50), 171 (100), 129 (14), 115 (9), 91 (90), 79 (39).
$C_{13}H_{15}I$ HRMS (EI): Calcd.: 298.0218
Found: 298.0224

(6*R*)-6-(But-3-en-1-yl)-1-iodocyclohex-1-ene (48g)

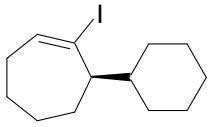


Prepared according to TP 5 by using (1*S*)-2-iodocyclohex-2-en-1-yl 2,3,4,5,6-pentafluorobenzoate ((*S*)-**45**) (98% *ee*, 836 mg, 2.0 mmol), NMP (2.2 mL), but-3-en-1-ylzinc iodide (2.11 M in THF, 2.12 mL, 4.48 mmol, 2.24 equiv) and a CuCN·2LiCl solution (1.0 M in THF, 4.48 mL, 4.48 mmol, 2.40 equiv). The reaction mixture was warmed up to 25 °C and stirred for 66 h. Purification by column chromatography (silica gel, pentane) afforded the product (*R*)-**48g** as a colourless oil (445 mg, 85% yield).

GC (Chirasil-Dex CB, 25 mm x 0.25 mm); conditions: 60 °C (1 min), ramp of 5 °C/ min to 160 °C; t_R (min) = 17.665 (major), 17.955 (minor); 98% *ee*.
$[\alpha]_D^{20}$ –2.1 (c 0.34, CH_2Cl_2)

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 6.32 (dt, *J* = 1.44, 4.09 Hz, 1H), 5.84-5.66 (m, 1H), 5.04-4.86 (m, 2H), 2.32-2.18 (m, 1H), 2.18-2.04 (m, 1H), 2.02-1.88 (m, 3H), 1.88-1.66 (m, 2H), 1.66-1.46 (m, 3H), 1.42-1.28 (m, 1H) ppm.
^{13}C NMR ($CDCl_3$, 75 MHz): δ = 139.0, 138.8, 115.2, 107.0, 44.6, 34.2, 31.3, 30.0, 28.3, 18.8 ppm.
IR (film): 2931 (m), 1449 (m), 1327 (m), 992 (m), 959 (m), 908 (s) cm^{-1}.
MS (EI, 70 eV), *m/z* (%): 262 (M^+, 3), 220 (100), 208 (15), 135 (32), 107 (5), 93 (34), 79 (33), 67 (10).
$C_{10}H_{15}I$ HRMS (EI): Calcd.: 262.0218
Found: 262.0219

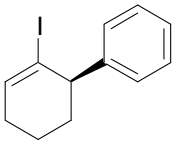
(7*R*)-7-Cyclohexyl-1-iodocyclohep-1-tene (48h)



Prepared according to TP 5 by using (1*S*)-2-iodocyclohep-2-ten-1-yl 2,3,4,5,6-pentafluorobenzoate ((*S*)-**46**) (98% *ee*, 432 mg, 1.0 mmol), NMP (1.3 mL), cyclohexylzinc iodide (1.01 M in THF, 1.98 mL, 2.0 mmol, 2.0 equiv) and a CuCN·2LiCl solution (1.0 M in THF, 2.0 mL, 2.0 mmol, 2.0 equiv). The reaction mixture was warmed to –10 °C and stirred for 16 h. Purification by column chromatography (silica gel, pentane) afforded the product (*R*)-**48h** as a colourless oil (264 mg, 87 % yield).
The separation of the enantiomers was not possible under a variety of conditions in chiral HPLC or capillary GC. The enantiomeric excess was determined for the corresponding ketone (*R*)-**52i**.

$[\alpha]_D^{20}$ –19 (c 0.31, CH_2Cl_2)
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 6.60-6.50 (m, 1H), 2.58-2.48 (m, 1H), 2.30-2.16 (m, 1H), 2.10-2.00 (m, 1H), 1.96-1.52 (m, 11H), 1.48-1.10 (m, 5H), 0.96-0.80 (m, 1H) ppm.
^{13}C NMR ($CDCl_3$, 75 MHz): δ = 141.8, 107.4, 59.6, 39.3, 32.4, 30.7, 30.4, 27.2, 26.9 (2 carbons), 26.71, 26.68, 25.5 ppm.
IR (film): 2922 (s), 2850 (s), 1446 (s) cm^{-1}.
MS (EI, 70 eV), *m/z* (%): 304 (M^+, 32), 222 (44), 177 (13), 121 (6), 95 (100), 83 (47).
$C_{13}H_{21}I$ HRMS (EI): Calcd.: 304.0688
Found: 304.0702

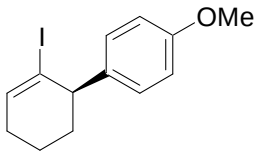
[(1*R*)-2-Iodo-2-cyclohexen-1-yl]benzene (48i)



According to TP 6, the suspension of CuCN (108 mg, 1.20 mmol, 1.20 equiv) in THF (2 mL) was treated with $PhMe_2CCH_2Li$ (0.50 M in Et_2O, 5.0 mL, 2.40 mmol, 2.0 equiv). A solution of phenyl iodide (245 mg, 1.20 mmol, 1.20 equiv) in THF (2 mL) was added to the resulting solution of $(PhMe_2CCH_2)_2Cu(CN)Li$. After the completion of I/Cu-exchange, a solution of (1*R*)-2-iodocyclohex-2-en-1-yl acetate (**47**) (98% *ee*, 266 mg, 1.0 mmol) in THF (1.5 mL) was added dropwise. The reaction mixture was stirred at –40 °C for 5 days. After purification

by column chromatography (silica gel, pentane), the cyclohexenyl iodide (*R*)-**48i** was obtained as a colourless oil (171 mg, 60% yield).
GC (Chirasil-Dex CB, 25 mm x 0.25 mm); conditions: 60 °C (2 min), ramp of 20 °C/ min to 160 °C; t_R(min) = 12.453 (major), 12.701 (minor); 93% *ee*.
$[\alpha]_D^{20}$ +4.2 (c 0.24, Et_2O)
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.35-7.00 (m, 5H), 6.62-6.56 (m, 1H), 3.70-3.56 (br, s, 1H), 2.16-2.00 (m, 3H), 1.80-1.66 (m, 1H), 1.66-1.50 (m, 2H) ppm.
^{13}C NMR ($CDCl_3$, 75 MHz): δ = 144.5, 140.6, 128.7 (3 carbons), 127.0 (2 carbons), 101.7, 53.0, 34.1, 29.7, 18.2 ppm.
IR (film): 2935 (s), 1492 (m), 1451 (m), 986 (m), 700 (s) cm^{-1}.
MS (EI, 70 eV), *m/z* (%): 284 (M^+, 100), 206 (38), 157 (41), 129 (55), 115 (30), 91 (47), 77 (13).
$C_{12}H_{13}I$ HRMS (EI): Calcd.: 284.0062
Found: 284.0035

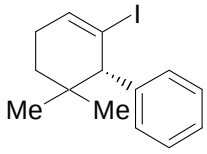
1-[(1*R*)-2-Iodo-2-cyclohexen-1-yl]-4-methoxybenzene (48j)



According to TP 6, the suspension of CuCN (54 mg, 0.60 mmol, 1.20 equiv) in THF (1 mL) was treated with $PhMe_2CCH_2Li$ (0.50 M in Et_2O, 2.40 mL, 1.20 mmol, 2.0 equiv). A solution of 4-iodoanisole (140 mg, 0.60 mmol, 1.20 equiv) in THF (1 mL) was added to the resulting solution of $(PhMe_2CCH_2)_2Cu(CN)Li$. After the completion of I/Cu-exchange, a solution of (1*R*)-2-iodocyclohex-2-en-1-yl acetate (**47**) (98% *ee*, 133 mg, 0.50 mmol) in THF (0.75 mL) was added dropwise. The reaction mixture was stirred at –30 °C for 42 h. After purification by column chromatography (silica gel, 2% Et_2O:pentane), the cyclohexenyl iodide (*R*)-**48j** was obtained as a colourless oil (141 mg, 90% yield).

GC (Chirasil-Dex CB, 25 mm x 0.25 mm); conditions: 60 °C (1 min), ramp of 20 °C/ min to 160 °C; t_R(min) = 27.756 (major), 28.758 (minor); 98% *ee*.
$[\alpha]_D^{20}$ +15 (c 1.04, CH_2Cl_2)
^{1}H NMR ($CDCl_3$, 300 MH_Z): δ = 7.04 (d, *J* = 8.4 Hz, 2H), 6.79 (d, *J* = 8.4 Hz, 2H), 6.56 (m, 1H), 3.73 (s, 3H), 3.57 (m, 1H), 2.12-1.54 (m, 6H) ppm.
^{13}C NMR ($CDCl_3$, 75 MH_Z): δ = 158.7, 140.4, 136.7 (2 carbons), 129.7 (2 carbons), 114.1, 102.5, 55.6, 52.2, 34.1, 29.7, 18.2 ppm.
IR (film): 2933 (s), 2832 (s), 1610 (s), 1510 (s), 1463 (s), 1302 (m), 1249 (s), 1176 (s), 1036 (s), 828 (m), 602 (w) cm^{-1}.
MS (EI, 70 eV), *m/z* (%): 314 (M^+, 100), 286 (4), 208 (18), 187 (31), 171 (10), 159 (24), 144 (22), 121 (43), 108 (23), 77 (11).
$C_{13}H_{15}IO$ HRMS (EI): Calcd.: 314.0168
Found: 314.0150

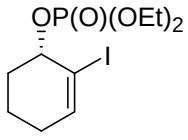
[(1*S*)-2-Iodo-6,6-dimethylcyclohex-2-en-1-yl]benzene (48k)



n-BuLi (1.60 M in hexane, 3.30 mL, 5.25 mmol, 1.05 equiv) was added dropwise to a solution of phenyl iodide (0.56 mL, 5.0 mmol, 5.0 equiv) in Et_2O (4 mL) at –78 °C, and then the reaction mixture was stirred for 10 min at –78 °C. A CuI·2LiCl solution (1.0 M in THF, 5.0 mL, 5.0 mmol, 5.0 equiv) and LiBr (130 mg, 1.50 equiv) were added to the resulting PhLi solution. The reaction mixture was stirred at 0 °C for 10 min, and then the solvents were removed under high vacuum. A CH_2Cl_2 (2 mL) was added and the reaction mixture was stirred for 5 min at 0 °C. After the removal of CH_2Cl_2, additional CH_2Cl_2 (10 mL) was added and the mixture was cooled to –78 °C. TMSCl (0.06 mL, 0.50 equiv) and a CH_2Cl_2 (1 mL) solution of (1*R*)-4,4-dimethyl-2-iodocyclohex-2-en-1-yl diethylphosphate (**26**) (99% *ee*, 388 mg, 1.0 mmol) were added. The reaction mixture was warmed to 0 °C and stirred for 5 days. A saturated aqueous NH_4Cl solution (20 mL) was added followed by 25% aqueous NH_3 solution (1 mL). The reaction mixture was stirred at 25 °C until the copper salts had dissolved, then was extracted with Et_2O (3 x 20 mL). The combined organic phase was washed with brine and dried over Na_2SO_4 anhydrous. Evaporation of the solvents and the purification by column chromatography (silica gel, pentane) afforded the product (*S*)-**48k** as a colourless oil.

GC (Chirasil-Dex CB, 25 mm x 0.25 mm); conditions: 40 °C (2 min), ramp of 20 °C/ min to 160 °C; t_R(min) = 15.239 (major), 15.435 (minor); 96% *ee*.
$[\alpha]_D^{20}$ +171 (c 0.26, CH_2Cl_2)
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.28-7.16 (m, 3H), 7.14-7.05 (m, 2H), 6.49 (t, *J* = 3.87 Hz, 1H), 3.23 (s, 1H), 2.23-2.14 (m, 2H), 1.60-1.42 (m, 1H), 1.22-1.12 (m, 1H), 1.08 (s, 3H), 0.53 (s, 3H) ppm.
^{13}C NMR ($CDCl_3$, 75 MHz): δ = 148.1, 145.1, 135.4 (2 carbons), 134.8, 134.5 (2 carbons), 108.9, 72.2, 43.3, 36.9, 36.8, 35.5, 34.7 ppm.
IR (film): 2925 (m), 1452 (m), 937 (m), 745 (s), 700 (s) cm^{-1}.
MS (EI, 70 eV), *m/z* (%): 312 (M^+, 63), 256 (100), 185 (7), 155 (5), 129 (67), 91 (8).
$C_{14}H_{17}I$ HRMS (EI): Calcd.: 312.0375
Found: 312.0360

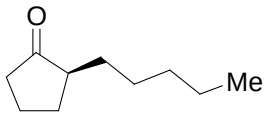
Diethyl (1*S*)-2-iodocyclohex-2-en-1-yl phosphate (49)



N-Methylimidazole (0.95 mL, 12.0 mmol, 2.40 equiv) was added to the solution of (1*S*)-2-iodocyclohex-2-en-1-ol (1.12 g, 5.0 mmol) in dry Et_2O (9 mL). The reaction mixture was cooled to 0 °C, and then diethyl chlorophosphate (1.74 mL, 12.0 mmol, 2.40 equiv) was added dropwise. The reaction mixture was stirred at 25 °C for 16 h, then was quenched with a saturated NaCl solution (20 mL) and extracted with Et_2O (3 x 20 mL). The combined organic phase was dried over Na_2SO_4 anhydrous. The crude product was purified by column chromatography (silica gel, 50% Et_2O:pentane) to afford the product (*S*)-**49** as a colourless oil (1.53 g, 85% yield).
HPLC (Chiralcel OJ, heptane:*i*-PrOH = 99:1, 0.6 mL/min); t_R (min) = 21.16 (major), 25.51 (minor); 94% *ee*.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 6.61 (t, *J* = 4.0 Hz, 1 H), 4.89-4.73 (m, 1H), 4.24-4.03 (m, 4H), 2.21-1.91 (m, 4 H), 1.82-1.63 (m, 2 H), 1.37-1.29 (m, 6 H) ppm.
^{13}C NMR ($CDCl_3$, 75 MHz): δ = 144.3, 95.6, 78.4, 64.6, 64.2, 31.5, 29.6, 18.7, 16.8, 16.5 ppm.
IR (film): 1273 (s), 1033 (s), 988 (s) cm^{-1}.
MS (EI, 70 eV), *m/z* (%): 356 (1), 315 (1), 233 (100), 205 (24), 177 (30), 155 (12), 127 (15), 99 (47), 79 (50), 67 (3).
$C_{10}H_{18}IO_4P$ HRMS (EI): Calcd.: 359.9987
Found: 359.9977

(2*S*)-2-Pentylcyclopentanone (52a)

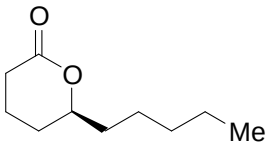


a) Prepared according to TP 7 from (5*S*)-1-iodo-5-pentylcyclopent-1-ene (**48a**) (250 mg, 0.95 mmol), THF (7.6 mL), *t*-BuLi (1.45 M in pentane, 1.31 mL, 1.90 mmol, 2.0 equiv), $(TMSO)_2$ (neat, 0.31 mL, 1.43 mmol, 1.50 equiv). The resulting silyl enol ether in THF (3.9 mL) was treated with a HF·pyridine complex (70%) (0.04 mL, 0.95 mmol) in dry pyridine (0.8 mL). After purification by column chromatography (silica gel, 10% Et_2O:pentane), the ketone (*S*)-**52a** was obtained as a colourless oil (102 mg, 70% yield).

b) Prepared according to TP 8 from (5*S*)-1-iodo-5-pentylcyclopent-1-ene (**48a**) (132 mg, 0.50 mmol), THF (4 mL), *t*-BuLi (1.60 M in pentane, 0.63 mL, 1.0 mmol), $B(OMe)_3$ (neat, 0.14 mL, 1.25 mmol, 2.50 equiv) and a suspension of $NaBO_3·4H_2O$ (10.0 equiv, 769 mg, 5.0 mmol) in H_2O (6 mL). After purification by column chromatography (silica gel, 10% Et_2O:pentane), the ketone (*S*)-**52a** was obtained as a colourless oil (69 mg, 90% yield).
The separation of the enantiomers was not possible under a variety of conditions in chiral HPLC or capillary GC. The enantiomeric excess was determined for the corresponding lactone (see below).

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.30-1.87 (m, 6H), 1.85-1.60 (m, 2H), 1.55-1.38 (m, 1H), 1.35-1.10 (m, 6H), 0.90-0.75 (m, 3H) ppm.
^{13}C NMR ($CDCl_3$, 75 MHz): δ = 221.9, 49.5, 38.5, 32.1, 30.0 (2 carbons), 27.6, 22.9, 21.1, 14.4 ppm.
IR (film): 2959 (m), 2930 (m), 2858 (m), 1739 (s), 1454 (w), 1154 (m) cm^{-1}.
MS (EI, 70 eV), *m/z* (%): 154 (M^+, 7), 112 (1), 111 (1), 97 (13), 84 (100), 69 (4), 55 (9).
$C_{10}H_{18}O$ HRMS (EI): Calcd.: 154.1358
Found: 154.1362

(6*S*)-6-Pentyltetrahydro-2*H*-pyran-2-one

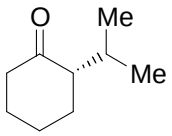


MMPP (396 mg, 0.80 mmol, 2.0 equiv) and $NaHCO_3$ (67 mg, 0.80 mmol, 2.0 equiv) were added to a solution of (2*S*)-2-pentylcyclopentanone (**52a**) (62 mg, 0.40 mmol) in a solvent mixture of MeOH:H_2O (1:1, 3.2 mL) at 25 °C. The reaction mixture was stirred at 25 °C for

18 h. The reaction mixture was poured into a saturated NH_4Cl solution, extracted with Et_2O (3 x 20 mL). The combined organic phase was washed with brine and dried over Na_2SO_4 anhydrous. The crude product was purified by column chromatography (silica gel, 50% Et_2O:pentane) to give the lactone as a colourless oil (67 mg, 99% yield).

GC (Chiralsil-Dex CB, 25 mm x 0.25 mm); conditions: 60 °C (1 min), ramp of 0.5 °C/ min to 160 °C; t_R (min) = 116.883 (major), 117.466 (minor); 93 % *ee*.
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 4.27-4.15 (m, 1H), 2.58-2.45 (m, 1H), 2.44-2.29 (m, 1H), 1.94-1.12 (m, 12H), 0.92-0.74 (m, 3H) ppm.
^{13}C NMR ($CDCl_3$, 75 MHz): δ = 172.4, 81.0, 36.2, 32.0, 29.8, 28.2, 25.0, 22.9, 18.9, 14.3 ppm.
IR (film): 2932 (s), 1738 (s), 1464 (m), 1245 (s), 1052 (m), 1036 (m) cm^{-1}.
MS (EI, 70 eV), *m/z* (%): 170 (M^+, 1), 152 (3), 134 (2), 114 (12), 99 (100), 71 (41), 55 (26).
$C_{10}H_{18}O_2$ HRMS (EI): Calcd.: 171.1385 $[M+H]^+$
Found: 171.1383 $[M+H]^+$

(2*S*)-2-Isopropylcyclohexanone (52b)

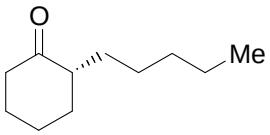


a) Prepared according to TP 7 from (6*S*)-1-iodo-6-isopropylcyclohexene (**48b**) (125 mg, 0.50 mmol), THF (4 mL), *t*-BuLi (1.60 M in pentane, 0.63 mL, 1.0 mmol), $(TMSO)_2$ (neat, 0.16 mL, 0.75 mmol, 1.50 equiv). The resulting silyl enol ether in THF (2 mL) was treated with a HF·pyridine complex (70%) (0.02 mL, 0.50 mmol) in dry pyridine (0.4 mL). After purification by column chromatography (silica gel, 10% Et_2O:pentane), the ketone (*S*)-**52b** was obtained as a colourless oil (65 mg, 93% yield, 94% *ee*).
The deprotection of the corresponding silyl enol ether by using a TBAF solution: A TBAF solution (1.0 M in THF, 0.50 mL, 1.0 equiv) was added dropwise to the solution of the crude silyl enol ether (0.5 mmol) in THF (2 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h then was poured into water, extracted with Et_2O (3 x 25 mL). The combined organic phase was washed with brine and dried over $MgSO_4$ anhydrous. After purification by column chromatography (silica gel, 10% Et_2O:pentane), the ketone (*S*)-**52b** was obtained as a colourless oil (86% yield, 65% *ee*).
b) Prepared according to TP 8 from (6*S*)-1-iodo-6-isopropylcyclohexene (**48b**) (125 mg, 0.50 mmol), THF (4 mL), *t*-BuLi (1.60 M in pentane, 0.63 mL, 1.0 mmol), $B(OMe)_3$ (neat, 0.14 mL, 1.25 mmol, 2.50 equiv) and a suspension of $NaBO_3 \cdot 4H_2O$ (10.0 equiv, 769 mg, 5.0 mmol) in H_2O (6 mL). After purification by column chromatography (silica gel, 10% Et_2O:pentane), the ketone (*S*)-**52b** was obtained as a colourless oil (63 mg, 90% yield, 97% *ee*).

GC (Chirasil-Dex CB, 25 mm x 0.25 mm); conditions: 40 °C (1 min), ramp of 5 °C/ min to 150 °C; t_R(min) = 15.141 (minor), 15.196 (major).
$[\alpha]_D^{20}$ –58 (c 0.24, MeOH)
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.36-1.40 (m, 10 H), 0.83 (d, *J* = 2.88 Hz, 3 H), 0.81 (d, *J* = 2.88 Hz, 3 H) ppm.
^{13}C NMR ($CDCl_3$, 75 MHz): δ = 213.8, 57.6, 42.4, 29.5, 28.3, 26.7, 24.6, 21.4, 19.4 ppm.
IR (film): 2935 (s), 2867 (m), 1709 (s), 1448 (w), 1121 (w) cm^{-1}.
MS (EI, 70 eV), *m/z* (%): 140 (M^+, 27), 125 (37), 111 (8), 98 (100), 83 (34), 69 (39), 55 (47).

$C_9H_{16}O$ HRMS (EI): Calcd.: 140.1201
Found: 140.1197

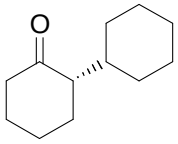
(2*R*)-2-Pentylcyclohexanone (52c)



Prepared according to TP 7 from (6*R*)-1-iodo-6-pentylcyclohexene (**48c**) (278 mg, 1.0 mmol), THF (8 mL), *t*-BuLi (1.60 M in pentane, 1.25 mL, 2.0 mmol), $(TMSO)_2$ (neat, 0.32 mL, 1.50 mmol). The resulting silyl enol ether in THF (4 mL) was treated with a HF·pyridine complex (70%) (0.04 mL, 1.0 mmol) in dry pyridine (0.8 mL). After purification by column chromatography (silica gel, 10% Et_2O:pentane), the ketone (*R*)-**52c** was obtained as a colourless oil (153 mg, 91% yield, 97% *ee*).

GC (Chirasil-Dex CB, 25 mm x 0.25 mm); conditions: 40 °C (1 min), ramp of 4 °C/ min to 150 °C; t_R (min) = 23.818 (minor), 23.911 (major).
$[\alpha]_D^{20}$ –22 (c 1, MeOH)
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.37-2.12 (m, 3H), 2.09-1.85 (m, 2H), 1.84-1.50 (m, 4H), 1.39-1.05 (m, 8H), 0.80-0.75 (m, 3H) ppm.
^{13}C NMR ($CDCl_3$, 75 MHz): δ = 213.9, 51.1, 42.3, 34.2, 32.3, 29.7, 28.4, 27.2, 25.2, 22.9, 14.4 ppm.
IR (film): 2931 (s), 2859 (m), 1712 (s), 1449 (m), 1378 (w), 1312 (w), 1122 (w) cm^{-1}.
MS (EI, 70 eV), *m/z* (%): 168 (M^+, 6), 158 (1), 139 (1), 135 (1), 125 (1), 111 (13), 98 (100), 83 (18), 70 (15), 55 (15).
$C_{11}H_{20}O$ HRMS (EI): Calcd.: 168.1514
Found: 168.1516

(2*S*)-2-Cyclohexylcyclohexanone (52d)

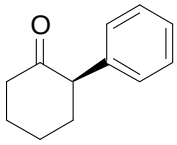


Prepared according to TP 7 from (6*S*)-6-cyclohexyl-1-iodocyclohexene (**48d**) (290 mg, 1.0 mmol), THF (8 mL), *t*-BuLi (1.60 M in pentane, 1.25 mL, 2.0 mmol), $(TMSO)_2$ (neat, 0.32 mL, 1.50 mmol). The resulting silyl enol ether in THF (4 mL) was treated with a HF·pyridine complex (70%) (0.04 mL, 1.0 mmol) in dry pyridine (0.8 mL). After purification by column chromatography (silica gel, 10% Et_2O:pentane), the ketone (*S*)-**52d** was obtained as a colourless oil (158 mg, 88% yield, 98% *ee*).

GC (Chirasil-Dex CB, 25 mm x 0.25 mm); conditions: 40 °C (1 min), ramp of 2 °C/ min to 150 °C; t_R(min) = 49.300 (major), 49.691 (minor).
$[\alpha]_D^{20}$ –61 (c 0.4, MeOH)
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.31-2.07 (m, 2H), 2.02-1.90 (m, 1H), 1.88-1.34 (m, 12H), 1.26-0.68 (m, 5H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 214.0, 56.9, 42.2, 36.4, 31.9, 29.73, 29.67, 28.3, 26.86 (2 carbons), 26.79, 24.4 ppm.
IR (film): 2925 (s), 2852 (s), 1709 (s), 1449 (m), 1129 (w) cm^{-1}.
MS (EI, 70 eV), *m/z* (%): 180 (M^+, 1), 137 (3), 123 (2), 98 (100), 83 (15), 67 (11), 55 (11).
$C_{12}H_{20}O$ HRMS (EI): Calcd.: 180.1514
Found: 180.1513

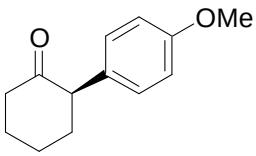
(2*R*)-2-Phenylcyclohexanone (52e)



Prepared according to TP 7 from [(1*R*)-2-iodocyclohex-2-en-1-yl]benzene (**48i**) (85 mg, 0.30 mmol), THF (2.4 mL), *t*-BuLi (1.60 M in pentane, 0.38 mL, 0.60 mmol, 2.0 equiv), $(TMSO)_2$ (neat, 0.1 mL, 0.45 mmol, 1.50 equiv). The resulting silyl enol ether in THF (1.2 mL) was treated a with HF·pyridine complex (70%) (0.012 mL, 0.30 mmol) in dry pyridine (0.4 mL). After purification by column chromatography (silica gel, 10% Et_2O:pentane), the ketone (*R*)-**52e** was obtained as a colourless oil (37 mg, 71% yield, 86% *ee*).

GC (Chirasil-Dex CB, 25 mm x 0.25 mm); conditions: 60 °C (2 min), ramp of 2 °C/ min to 160 °C; t_R (min) = 44.795 (minor), 44.945 (major).
$[\alpha]_D^{20}$ +68 (c 0.284, CH_2Cl_2)
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.27-7.18 (m, 2H), 7.17-7.10 (m, 1H), 7.07-6.99 (m, 2H), 3.50 (dd, *J* = 5.25, 11.7 Hz, 1H), 2.47-2.27 (m, 2H), 2.23-2.10 (m, 1H), 2.10-1.97 (m, 1H), 1.97-1.81 (m, 2H), 1.80-1.63 (m, 2H) ppm.
^{13}C NMR ($CDCl_3$, 75 MHz): δ = 210.6, 139.1, 128.9 (2 carbons), 128.7 (2 carbons), 127.3, 57.8, 42.6, 35.5, 28.2, 25.7 ppm.
IR (film): 2948 (m), 2930 (m), 1701 (s), 1499 (w), 1446 (m), 1309 (w), 1126 (m), 758 (m), 701 (m) cm^{-1}.
MS (EI, 70 eV), *m/z* (%): 174 (M^+, 42), 130 (100), 117 (52), 104 (33), 91 (28), 78 (10), 65 (5), 51 (6).
$C_{12}H_{14}O$ HRMS (EI): Calcd.: 174.1045
Found: 174.1055

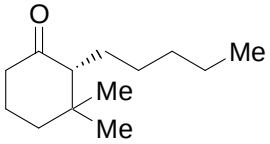
(2*R*)-2-(4-Methoxyphenyl)cyclohexanone (52f)



Prepared according to TP 7 from 1-[(1*R*)-2-iodocyclohex-2-en-1-yl]-4-methoxybenzene (**48j**) (146 mg, 0.46 mmol), THF (4 mL), *t*-BuLi (1.45 M in pentane, 0.63 mL, 0.92 mmol, 2.0 equiv), $(TMSO)_2$ (neat, 0.15 mL, 0.69 mmol, 1.50 equiv). The resulting silyl enol ether in THF (3 mL) was treated with a HF·pyridine complex (70%) (0.02 mL, 0.46 mmol, without additional pyridine). After recrystalization (Et_2O), the ketone (*R*)-**52f** was obtained as a white solid (76 mg, 81% yield, 86% *ee*).

HPLC (Chiralcel OD-H, heptane:*i*-PrOH = 90:10, 0.6 mL/min); t_R (min) = 15.71 (minor), 18.75 (major).
mp = 64.6-66.7 °C
$[\alpha]_D^{20}$ +15 (c 0.26, CH_2Cl_2)
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.02-6.93 (m, 2H), 6.84-6.74 (m, 2H), 3.70 (s, 3H), 3.47 (dd, *J* = 5.7, 11.7 Hz, 1H), 2.50-2.28 (m, 2H), 2.23-2.11 (m, 1H), 2.10-1.98 (m, 1H), 1.98-1.82 (m, 2H), 1.82-1.63 (m, 2H) ppm.
^{13}C NMR ($CDCl_3$, 75 MHz): δ = 211.0, 158.8, 131.2, 129.8 (2 carbons), 114.2 (2 carbons), 57.0, 55.6, 42.6, 35.7, 28.2, 25.8 ppm.
IR (film): 2949 (m), 2927 (m), 1705 (s), 1615 (w), 1516 (s), 1448 (w), 1254 (s), 1180 (m), 1124 (m), 1032 (m), 829 (m), 812 (m) cm^{-1}.
MS (EI, 70 eV), *m/z* (%): 204 (M^+, 59), 176 (17), 160 (14), 147 (100), 134 (28), 121 (34), 91 (24), 77 (11), 65 (9).
$C_{13}H_{16}O_2$ HRMS (EI): Calcd.: 204.1150
Found: 204.1132

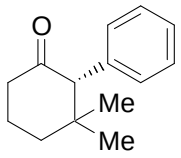
(2*R*)-3,3-Dimethyl-2-pentylcyclohexanone (52g)



a) Prepared according to TP 7 from (6*R*)-5,5-dimethyl-1-iodo-6-pentylcyclohexene (**28a**) (129 mg, 0.42 mmol), THF (4 mL), *t*-BuLi (1.45 M in pentane, 0.58 mL, 2.0 equiv), $(TMSO)_2$ (neat, 0.14 mL, 0.63 mmol, 1.50 equiv). The resulting silyl enol ether in THF (2 mL) was treated with a HF·pyridine complex (70%) (0.017 mL, 0.42 mmol) in dry pyridine (0.35 mL). After purification by column chromatography (silica gel, 10% Et_2O:pentane), the ketone (*R*)-**52g** was obtained as a colourless oil (69 mg, 84% yield, 93% *ee*).
b) Prepared according to TP 8 from (6*R*)-5,5-dimethyl-1-iodo-6-pentylcyclohexene (**28a**) (153 mg, 0.50 mmol), THF (4 mL), *t*-BuLi (1.60 M in pentane, 0.63 mL, 1.0 mmol), $B(OMe)_3$ (neat, 0.14 mL, 1.25 mmol, 2.50 equiv) and a suspension of $NaBO_3 \cdot 4H_2O$ (10.0 equiv, 769 mg, 5.0 mmol) in H_2O (6 mL). After purification by column chromatography (silica gel, 10% Et_2O:pentane), the ketone (*R*)-**52g** was obtained as a colourless oil (84 mg, 86% yield, 98% *ee*).

GC (Chirasil-Dex CB, 25 mm x 0.25 mm); conditions: 60 °C (1 min), ramp of 10 °C/ min to 160 °C; t_R (min) = 10.991 (minor), 11.080 (major).
$[\alpha]_D^{20}$ –23 (c 0.41, Et_2O)
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.27-2.05 (m, 2H), 2.00-1.90 (m, 1H), 1.83-1.63 (m, 2H), 1.62-1.40 (m, 3H), 1.25-1.05 (m, 6H), 1.04-0.83 (m, 4H), 0.82-0.70 (m, 3H), 0.66 (s, 3H) ppm.
^{13}C NMR ($CDCl_3$, 75 MHz): δ = 212.2, 59.6, 39.2, 37.9, 36.9, 30.4, 27.6, 27.0, 22.7, 21.5, 21.1, 20.9, 12.4 ppm.
IR (film): 2956 (s), 2872 (m), 1711 (s), 1460 (m), 1369 (w), 1261 (w), 1079 (w) cm^{-1}.
MS (EI, 70 eV), *m/z* (%): 196 (M^+, 1), 181 (12), 153 (3), 139 (4), 126 (18), 111 (100), 83 (3), 69 (7).
$C_{13}H_{24}O$ HRMS (EI): Calcd.: 196.1827
Found: 196.1831

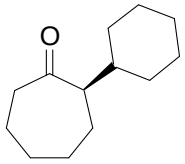
(2*S*)-3,3-Dimethyl-2-phenylcyclohexanone (52h)



Prepared according to TP 7 from (6*S*)-5,5-dimethyl-1-iodo-6-phenylcyclohexene (**48k**) (156 mg, 0.50 mmol), THF (4 mL), *t*-BuLi (1.45 M in pentane, 0.69 mL, 1.0 mmol, 2.0 equiv), $(TMSO)_2$ (neat, 0.16 mL, 0.75 mmol, 1.50 equiv). The resulting silyl enol ether in THF (2 mL) was treated with a HF·pyridine complex (70%) (0.02 mL, 0.50 mmol) in dry pyridine (0.4 mL). After recrystalization (Et_2O), the ketone (*S*)-**52h** was obtained as a white solid (70 mg, 69% yield, 93% *ee*).

GC (Chirasil-Dex CB, 25 mm x 0.25 mm); conditions: 40 °C (2 min), ramp of 20 °C/ min to 160 °C; t_R (min) = 13.120 (major), 13.441 (minor).
mp = 68.8-71.5 °C
$[\alpha]_D^{20}$ –123 (c 0.24, CH_2Cl_2)
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.29-7.16 (m, 3H), 7.16-7.08 (m, 2H), 3.41 (s, 1H), 2.48-2.28 (m, 2H), 2.00-1.62 (m, 4H), 0.85 (s, 3H), 0.78 (s, 3H) ppm.
^{13}C NMR ($CDCl_3$, 75 MHz): δ = 209.9, 135.3, 131.5 (2 carbons), 127.8 (2 carbons), 127.2, 67.8, 41.8, 41.2, 41.0, 31.0, 22.9, 22.5 ppm.
IR (film): 2959 (m), 2929 (m), 1702 (s), 1494 (w), 1456 (w), 1365 (m), 1173 (m), 1076 (m) cm^{-1}.
MS (EI, 70 eV), *m/z* (%): 202 (M^+, 100), 146 (17), 133 (71), 118 (21), 98 (42), 91 (19), 69 (22).
$C_{14}H_{18}O$ HRMS (EI): Calcd.: 202.1358
Found: 202.1352

(2*R*)-2-Cyclohexylcycloheptanone (52i)

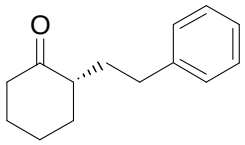


a) Prepared according to TP 7 from (7*R*)-7-cyclohexyl-1-iodocycloheptene (**48h**) (152 mg, 0.50 mmol), THF (4 mL), *t*-BuLi (1.60 M in pentane, 0.63 mL, 1.0 mmol, 2.0 equiv), $(TMSO)_2$ (neat, 0.16 mL, 0.75 mmol, 1.50 equiv). The resulting silyl enol ether in THF (2 mL) was treated with a HF·pyridine complex (70%) (0.02 mL, 0.50 mmol) in dry pyridine (0.4 mL). After purification by column chromatography (silica gel, 10% Et_2O:pentane), the ketone (*R*)-**52i** was obtained as a colourless oil (74 mg, 76% yield, 97% *ee*).

b) Prepared according to TP 8 from (7*R*)-7-cyclohexyl-1-iodocycloheptene (**48h**) (122 mg, 0.4 mmol), THF (3.2 mL), *t*-BuLi (1.60 M in pentane, 0.50 mL, 0.80 mmol), $B(OMe)_3$ (neat, 0.11 mL, 1.0 mmol, 2.50 equiv) and a suspension of $NaBO_3 \cdot 4H_2O$ (10.0 equiv, 615 mg, 4.0 mmol) in H_2O (4.8 mL). After purification by column chromatography (silica gel, 10% Et_2O:pentane), the ketone (*R*)-**52i** was obtained as a colourless oil (47 mg, 60% yield, 97% *ee*).

GC (Chirasil-Dex CB, 25 mm x 0.25 mm); conditions: 60 °C (1 min), ramp of 2 °C/ min to 160 °C; t_R (min) = 44.308 (minor), 44.411 (major).
$[\alpha]_D^{20}$ +87 (c 0.284, CH_2Cl_2)
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.45 (dt, *J* = 2.88, 12.0 Hz, 1H), 2.32-2.21 (m, 1H), 2.19-2.07 (m, 1H), 1.94-1.72 (m, 4H), 1.71-1.38 (m, 7H), 1.38-1.00 (m, 6H), 1.00-0.80 (m, 2H) ppm.
^{13}C NMR ($CDCl_3$, 75 MHz): δ = 217.5, 59.6, 43.1, 40.9, 31.7, 30.5, 30.3, 28.2, 28.1, 26.76 (2 carbons), 26.73, 26.0 ppm.
IR (film): 2924 (s), 2852 (s), 1702 (s), 1450 (s), 1342 (m), 1323 (m), 1166 (m), 936 (m) cm^{-1}.
MS (EI, 70 eV), *m/z* (%): 194 (M^+, 1), 151 (3), 123 (3), 112 (100), 97 (11), 84 (14), 67 (8).
$C_{13}H_{22}O$ HRMS (EI): Calcd.: 194.1671
Found: 194.1740

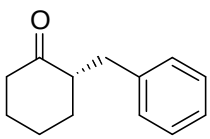
(2*S*)-2-(2-Phenylethyl)cyclohexanone (52j)



Prepared according to TP 8 from {2-[(1*S*)-2-iodocyclohex-2-en-1-yl]ethyl}benzene (**48e**) (156 mg, 0.50 mmol, 1.0 equiv), THF (4 mL), *t*-BuLi (1.60 M in pentane, 0.63 mL, 1.0 mmol, 2.0 equiv), $B(OMe)_3$ (neat, 0.14 mL, 1.25 mmol, 2.50 equiv) and a suspension of $NaBO_3 \cdot 4H_2O$ (769 mg, 5.0 mmol, 10.0 equiv) in H_2O (6 mL). After purification by column chromatography (silica gel, 10% Et_2O:pentane), the ketone (*S*)-**52j** was obtained as a colourless oil (62 mg, 61% yield, 95% *ee*).

GC (Chirasil-Dex CB, 25 mm x 0.25 mm); conditions: 60 °C (1 min), ramp of 2 °C/ min to 160 °C; t_R (min) = 50.501 (minor), 50.712 (major).
$[\alpha]_D^{20}$ –6.4 (c 0.28, CH_2Cl_2)
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.24-7.16 (m, 2H), 7.14-7.06 (m, 3H), 2.56 (t, *J* = 7.85 Hz, 2H), 2.38-2.28 (m, 1H), 2.28-2.14 (m, 2H), 2.14-2.02 (m, 2H), 2.02-1.92 (m, 1H), 1.84-1.72 (m, 1H), 1.70-1.48 (m, 2H), 1.48-1.28 (m, 2H) ppm.
^{13}C NMR ($CDCl_3$, 75 MHz): δ = 213.5, 142.5, 128.8 (2 carbons), 128.7 (2 carbons), 126.2, 50.3, 42.5, 34.4, 33.6, 31.6, 28.4, 25.3 ppm.
IR (film): 2931 (m), 1705 (s), 1449 (m), 1128 (m), 748 (m), 698 (s) cm^{-1}.
MS (EI, 70 eV), *m/z* (%): 202 (M^+, 6), 129 (1), 117 (3), 104 (9), 98 (100), 91 (9), 83 (8), 70 (8), 65 (4).
$C_{14}H_{18}O$ HRMS (EI): Calcd.: 202.1358
Found: 202.1369

(2*S*)-2-Benzylcyclohexanone (52k)

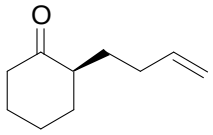


Prepared according to TP 8 from {[(1*S*)-2-iodocyclohex-2-en-1-yl]methyl}benzene (**48f**) (87 mg, 0.29 mmol, 1.0 equiv), THF (2.3 mL), *t*-BuLi (1.60 M in pentane, 0.40 mL, 0.58 mmol,

2.0 equiv), $B(OMe)_3$ (neat, 0.08 mL, 0.73 mmol, 2.50 equiv) and a suspension of $NaBO_3 \cdot 4H_2O$ (446 mg, 2.90 mmol, 10.0 equiv) in H_2O (3.5 mL). After purification by column chromatography (silica gel, 10% Et_2O:pentane), the ketone (*S*)-**52k** was obtained as a colourless oil (25 mg, 45% yield, 55% *ee*).

GC (Chirasil-Dex CB, 25 mm x 0.25 mm); conditions: 60 °C (1 min), ramp of 2 °C/ min to 160 °C; t_R (min) = 45.702 (minor), 46.003 (major).
$[\alpha]_D^{20}$ –20 (c 0.24, CH_2Cl_2)
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.25-7.15 (m, 2H), 7.15-7.04 (m, 3H), 3.16 (dd, *J* = 4.64, 13.71 Hz, 1H), 2.55-2.41 (m, 1H), 2.41-2.18 (m, 3H), 2.05-1.89 (m, 2H), 1.81-1.70 (m, 1H), 1.69-1.42 (m, 2H), 1.37-1.17 (m, 1H) ppm.
^{13}C NMR ($CDCl_3$, 75 MHz): δ = 212.9, 140.8, 129.5 (2 carbons), 128.7 (2 carbons), 126.3, 52.9, 42.5, 35.9, 33.8, 28.4, 25.4 ppm.
IR (film): 2933 (m), 1705 (s), 1495 (m), 1448 (m), 1128 (m), 731 (s), 698 (s) cm^{-1}.
MS (EI, 70 eV), *m/z* (%): 188 (M^+, 99), 159 (25), 145 (17), 131 (18), 117 (26), 104 (13), 97 (35), 91 (100), 78 (9), 65 (11).
$C_{13}H_{16}O$ HRMS (EI): Calcd.: 188.1201
Found: 188.1214

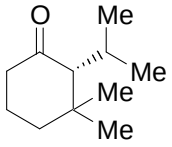
(2*R*)-2-But-3-enylcyclohexanone (52l)



Prepared according to TP 8 from (6*R*)-6-(but-3-en-1-yl)-1-iodocyclohexene (**48g**) (131 mg, 0.50 mmol, 1.0 equiv), THF (4 mL), *t*-BuLi (1.60 M in pentane, 0.63 mL, 1.0 mmol, 2.0 equiv), $B(OMe)_3$ (neat, 0.14 mL, 1.25 mmol, 2.50 equiv) and a suspension of $NaBO_3 \cdot 4H_2O$ (769 mg, 5.0 mmol, 10.0 equiv) in H_2O (6 mL). After purification by column chromatography (silica gel, 10% Et_2O:pentane), the ketone (*R*)-**52l** was obtained as a colourless oil (35 mg, 46% yield, 90% *ee*).

GC (Chirasil-Dex CB, 25 mm x 0.25 mm); conditions: 60 °C (1 min), ramp of 5 °C/ min to 160 °C; t_R (min) = 13.799 (major), 13.955 (minor).
$[\alpha]_D^{20}$ +15 (c 0.26, CH_2Cl_2)
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 5.80-5.62 (m, 1H), 5.00-4.84 (m, 2H), 2.37-2.15 (m, 3H), 2.10-1.71 (m, 6H), 1.69-1.50 (m, 2H), 1.40-1.12 (m, 2H) ppm.
^{13}C NMR ($CDCl_3$, 75 MHz): δ = 213.6, 138.9, 115.1, 50.2, 42.4, 34.2, 31.6, 28.9, 28.4, 25.3 ppm.
IR (film): 2931 (m), 1708 (s), 1448 (m), 1126 (m), 995 (m), 908 (s) cm^{-1}.
MS (EI, 70 eV), *m/z* (%): 152 (M^+, 8), 123 (1), 111 (2), 98 (100), 83 (18), 70 (23), 67 (9), 55 (13).
$C_{10}H_{16}O$ HRMS (EI): Calcd.: 152.1201
Found: 152.1196

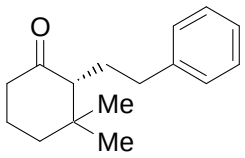
(2*R*)-3,3-Dimethyl-2-isopropylcyclohexanone (52m)



Prepared according to TP 8 from (6*R*)-5,5-dimethyl-1-iodo-6-isopropylcyclohexene (**28b**) (139 mg, 0.50 mmol, 1.0 equiv), THF (4 mL), *t*-BuLi (1.60 M in pentane, 0.63 mL, 1.0 mmol, 2.0 equiv), $B(OMe)_3$ (neat, 0.14 mL, 1,25 mmol, 2.50 equiv) and a suspension of $NaBO_3 \cdot 4H_2O$ (769 mg, 5.0 mmol, 10.0 equiv) in H_2O (6 mL). After purification by column chromatography (silica gel, pentane), the ketone (*R*)-**52m** was obtained as a colourless oil (47 mg, 56% yield, 98% *ee*).

GC (Chirasil-Dex CB, 25 mm x 0.25 mm); conditions: 60 °C (1 min), ramp of 5 °C/ min to 160 °C; t_R (min) = 13.746 (major), 13.908 (minor).
$[\alpha]_D^{20}$ +112 (c 0.26, CH_2Cl_2)
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.28-2.23 (m, 2H), 2.06-1.94 (m, 1H), 1.92-1.87 (br, d, *J* = 6.2 Hz, 1H), 1.85-1.75 (m, 2H), 1.75-1.65 (m, 1H), 1.44-1.36 (m, 1H), 1.03 (d, *J* = 6.78 Hz, 3H), 1.01 (s, 3H), 0.94 (s, 3H), 0.93 (d, *J* = 6.78 Hz, 3H) ppm.
^{13}C NMR ($CDCl_3$, 75 MHz): δ = 215.0, 67.4, 41.5, 38.8, 37.3, 29.6, 27.6, 26.8, 25.1, 22.5, 21.6 ppm.
IR (film): 2957 (m), 1704 (s), 1462 (m), 1388 (m), 1370 (w), 1222 (w), 1071 (w) cm^{-1}.
MS (EI, 70 eV), *m/z* (%): 168 (M^+, 26), 153 (25), 135 (11), 125 (27), 111 (100), 98 (18), 83 (20), 69 (23), 55 (16).
$C_{11}H_{20}O$ HRMS (EI): Calcd.: 168.1514
Found: 168.1525

(2*R*)-3,3-Dimethyl-2-(2-phenylethyl)cyclohexanone (52n)

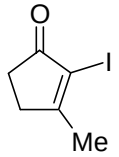


Prepared according to TP 8 from {2-[(1*R*)-2-iodo-6,6-dimethylcyclohex-2-en-1-yl]ethyl}benzene (**28j**) (170 mg, 0.50 mmol, 1.0 equiv), THF (4 mL), *t*-BuLi (1.60 M in pentane, 0.63 mL, 1.0 mmol, 2.0 equiv), $B(OMe)_3$ (neat, 0.14 mL, 1,25 mmol, 2.50 equiv) and a suspension of $NaBO_3 \cdot 4H_2O$ (769 mg, 5.0 mmol, 10.0 equiv) in H_2O (6 mL). After purification by column chromatography (silica gel, 10% Et_2O:pentane), the ketone (*R*)-**52n** was obtained as a colourless oil (75 mg, 65% yield, 97% *ee*).

GC (Chirasil-Dex CB, 25 mm x 0.25 mm); conditions: 60 °C (1 min), ramp of 2 °C/ min to 160 °C; t_R (min) = 52.226 (minor), 52.735 (major).
$[\alpha]_D^{20}$ –9 (c 0.3, CH_2Cl_2)
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.26-7.16 (m, 2H), 7.16-7.06 (m, 3H), 2.70-2.56 (m, 1H), 2.36-2.12 (m, 3H), 2.08 (br, d, *J* = 10.62 Hz, 1H), 2.03-1.64 (m, 3H), 1.62-1.44 (m, 3H), 0.93 (s, 3H), 0.69 (s, 3H) ppm.
^{13}C NMR ($CDCl_3$, 75 MHz): δ = 213.6, 142.8, 128.8 (2 carbons), 128.7 (2 carbons), 126.1, 60.6, 41.8, 40.1, 39.6, 35.3, 29.8, 26.4, 23.6, 22.4 ppm.
IR (film): 2956 (w), 1705 (s), 1455 (w), 746 (m), 698 (s) cm^{-1}.
MS (EI, 70 eV), *m/z* (%): 230 (M^+, 1), 126 (28), 111 (100), 104 (3), 91 (9), 77 (1), 69 (3).

$C_{16}H_{22}O$	HRMS (EI):	Calcd.: 230.1671.
		Found: 230.1684.
$C_{16}H_{22}O$	Anal.	Calcd.: C 83.43, H 9.63
		Found: C 83.10, H 9.69

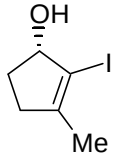
2-Iodo-3-methylcyclopent-2-en-1-one (55)



Prepared according to TP 1 from 3-methylcyclopent-2-en-1-one (4.90 mL, 50.0 mmol), CH_2Cl_2 (300 mL), PDC (5.64 g, 15.0 mmol) and I_2 (12.7 g, 50.0 mmol). The crude product was purified by column chromatography (silica gel, 10% Et_2O:pentane) to afford the product **55** as a white solid (6.16 g, 55% yield).
The data were in agreement with those reported.[126]
mp = 44.6-46.9 °C
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.75-2.66 (m, 2H), 2.56-2.48 (m, 2H), 2.16 (s, 3H) ppm.
^{13}C NMR ($CDCl_3$, 75 MHz): δ = 204.0, 180.2, 103.0, 34.70, 33.58, 22.49 ppm.
IR (film): 1695 (s), 1600 (s), 1426 (m), 1259 (m), 1156 (m) cm^{-1}.
MS (EI, 70 eV), *m/z* (%): 222 (M^+, 100), 207 (4), 179 (3), 166 (2), 95 (13), 67 (22), 65 (6), 41 (17).

C_6H_7IO	HRMS (EI):	Calcd.: 221.9542
		Found: 221.9536

(1*S*)-2-Iodo-3-methylcyclopent-2-en-1-ol (56)

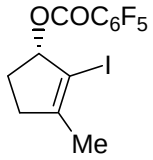


Prepared according to TP 2 from (*R*)-diphenylprolinol (253 mg, 1.0 mmol, 5 mol%), THF (20 mL), $B(OMe)_3$ (0.12 mL, 1.0 mmol, 5 mol%), borane-*N*,*N*-diethylaniline complex (3.56 mL, 20.0 mmol, 1.0 equiv) and the solution of 2-iodo-3-methylcyclopent-2-en-1-one (**55**) (4.44 g, 20.0 mmol) in THF (20 mL). The reaction mixture was continuously stirred for 1 h then was carefully quenched with MeOH (9 mL). The crude product was purified by column chromatography (silica gel, 25% Et_2O:pentane) to afford the product (*S*)-**56** as a white solid (3.0 g, 67% yield).
GC (Chirasil Dex CB, 25 mm x 0.25 mm); conditions: 60 °C (1 min), ramp of 20 °C/min to 160 °C: t_R/min = 6.868 (major), 6.960 (minor); 96% *ee*.
mp = 92.6-94.6 °C
$[\alpha]_D^{20}$ –16 (c 0.5, CH_2Cl_2)
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 4.68-4.58 (m, 1H), 2.54-2.38 (m, 1H), 2.36-2.16 (m, 2H), 1.94-1.76 (m, 2H), 1.75 (s, 3H) ppm.
^{13}C NMR ($CDCl_3$, 75 MHz): δ = 148.7, 99.0, 83.2, 35.6, 32.3, 19.6 ppm.
IR (film): 3401 (s), 2936 (s), 1435 (m), 1102 (m), 1056 (m), 1008 (m) cm^{-1}.

[126] Shipe, W. D.; Sorensen, E. J. *Org. Lett*. **2002**, *4*, 2063.

MS (EI, 70 eV), *m/z* (%): 224 (M^+, 64), 208 (6), 127 (5), 97 (100), 79 (16), 67 (8), 53 (12).
C_6H_9IO HRMS (EI): Calcd.: 223.9698
Found: 223.9696
C_6H_9IO Anal. Calcd.: C 32.17, H 4.05
Found: C 32.40, H 3.81

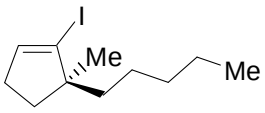
(1*S*)-2-Iodo-3-methylcyclopent-2-en-1-yl 2,3,4,5,6-pentafluorobenzoate (57)



Pyridine (1.30 equiv, 0.53 mL, 6.50 mmol), DMAP (0.10 equiv, 61 mg, 0.50 mmol) and pentafluorobenzoyl chloride (1.30 equiv, 0.94 mL, 6.50 mmol) were added to the solution of (1*S*)-2-iodo-3-methylcyclopent-2-en-1-ol (**56**) (1.12 g, 5.0 mmol) in dry Et_2O (30 mL) at 25 °C. The resulting suspension was stirred at 25 °C for 3 h. The reaction mixture was poured into a saturated NH_4Cl solution (20 mL), extracted with Et_2O (3 x 20 mL). The combined organic phase was washed with brine and dried over Na_2SO_4 anhydrous. The crude product was purified by column chromatography (silica gel, 5% Et_2O:pentane) to afford the product (*S*)-**57** as a pale yellow solid (1.78 g, 85% yield).

HPLC (Chiralcel OD-H; heptane:*i*-PrOH = 95:5, 0.5 mL/min): t_R/min = 10.402 (major), 11.204 (minor); 97% *ee*.
mp = 38.8-40.4 °C
$[\alpha]_D^{20}$ –6.8 (c 0.5, CH_2Cl_2)
^{1}H NMR ($CDCl_3$, 600 MHz): δ = 5.98-5.89 (m, 1H), 2.60-2.41 (m, 2H), 2.37-2-24 (m, 1H), 2.06-1.93 (m, 1H), 1.86-1.78 (m, 3H) ppm.
^{13}C NMR ($CDCl_3$, 150 MHz): δ = 159.1, 154.0, 147.3, 144.0, 141.8, 139.8, 136.4, 108.9, 89.2, 88.5, 35.7, 30.7, 19.7 ppm.
IR (film): 1723 (s), 1650 (m), 1493 (s), 1322 (s), 986 (s) cm^{-1}.
MS (EI, 70 eV), *m/z* (%): 291 (43), 205 (15), 195 (100), 168 (10), 117 (7), 79 (38).
$C_{13}H_8F_5IO_2$ Anal. Calcd.: C 37.35, H 1.93
Found: C 37.29, H 1.98

(5*S*)-1-Iodo-5-methyl-5-pentylcyclopentene (58)

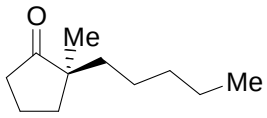


A flame-dried round bottom flask equipped with a magnetic stirring bar, an argon inlet and a rubber septum was charged with a CuCN·2LiCl solution (1.0 M in THF, 0.60 mL, 0.60 mmol, 1.20 equiv) and cooled to 0 °C (ice-bath). A dipentylzinc solution (5.60 M in THF, 0.21 mL, 1.20 mmol, 2.40 equiv) was added dropwise, and the reaction mixture was stirred at 0 °C for 10 min. The ice-bath was removed and a THF (1 mL) solution of (1*S*)-2-iodo-3-methyl-cyclopenten-1-yl 2,3,4,5,6-pentafluorobenzoate (**57**) (96% *ee*, 209 mg, 0.50 mmol, 1.0 equiv) was added dropwise. The reaction mixture was stirred at 25 °C for 4 h. A saturated aqueous NH_4Cl solution (20 mL) was added followed by 25% aqueous NH_3 solution (1 mL). The reaction mixture was stirred at 25 °C until the copper salts had dissolved then extracted with

Et_2O (3 x 20 mL). The combined organic phase was washed with brine and dried over Na_2SO_4 anhydrous. Evaporation of the solvents and the purification by column chromatography (silica gel, pentane) afforded the cyclopentenyl iodide (*S*)-**58** as a colourless oil (129 mg, 93% yield).
GC (Chirasil-Dex CB, 25 mm x 0.25 mm); conditions: 60 °C (1 min), ramp of 20 °C/ min to 160 °C; t_R(min) = 7.057 (major), 7.151 (minor); 95% *ee*.

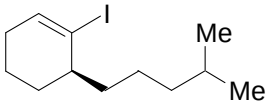
$[\alpha]_D^{20}$ +6.2 (c 0.26, CH_2Cl_2)
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 5.95 (t, *J* = 2.54 Hz, 1H), 2.32-2.12 (m, 2H), 1.90-1.78 (m, 1H), 1.66-1.54 (m, 1H), 1.32-1.04 (m, 8H), 0.91 (s, 3H), 0.82 (t, *J* = 6.91 Hz, 3H) ppm.
^{13}C NMR ($CDCl_3$, 75 MHz): δ = 138.3, 111.0, 52.5, 40.6, 33.6, 32.8, 32.3, 27.6, 24.4, 23.0, 14.5 ppm.
IR (film): 2954 (s), 2925 (s), 2849 (s), 1738 (m), 1455 (m), 1374 (m), 1217 (m) cm^{-1}.
MS (EI, 70 eV), *m/z* (%): 278 (M^+, 16), 207 (100), 192 (2), 151 (3), 91 (3), 80 (77).
$C_{11}H_{19}I$ HRMS (EI): Calcd.: 278.0531
Found: 278.0544

(2*S*)-2-Methyl-2-pentylcyclopentanone (59)



Prepared according to TP 8 from (5*S*)-1-iodo-5-methyl-5-pentylcyclopentene (**58**) (217 mg, 0.78 mmol, 1.0 equiv), THF (6.2 mL), *t*-BuLi (1.88 M in pentane, 0.83 mL, 1.56 mmol, 2.0 equiv), $B(OMe)_3$ (neat, 0.22 mL, 1.95 mmol, 2.50 equiv) and a suspension of $NaBO_3 \cdot 4H_2O$ (1.20 g, 7.80 mmol, 10.0 equiv) in H_2O (9.4 mL). After purification by column chromatography (silica gel, 10% Et_2O:pentane), the ketone (*S*)-**59** was obtained as a colourless oil (92 mg, 70% yield, 95% *ee*).
GC (Chirasil-Dex CB, 25 mm x 0.25 mm); conditions: 60 °C (1 min), ramp of 5 °C/ min to 160 °C; t_R (min) = 14.223 (minor), 14.336 (major).
$[\alpha]_D^{20}$ +53 (c 0.24, CH_2Cl_2)
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.28-2.02 (m, 2H), 1.72 (m, 3H), 1.70-1.58 (m, 1H), 1.40-1.00 (m, 8H), 0.92 (s, 3H), 0.80 (t, *J* = 6.97 Hz, 3H) ppm.
^{13}C NMR ($CDCl_3$, 75 MHz): δ = 224.3, 48.7, 38.1, 37.0, 36.0, 32.8, 24.3, 22.9, 22.2, 19.1, 14.4 ppm.
IR (film): 2958 (s), 2931 (s), 2860 (m), 1738 (s), 1461 (m), 1161 (w) cm^{-1}.
MS (EI, 70 eV), *m/z* (%): 99 (5), 98 (100), 83 (5), 69 (7), 56 (26).
$C_{11}H_{20}O$ HRMS (EI): Calcd.: 168.1514
Found: 168.1516

(6*S*)-1-Iodo-6-(4-methylpentyl)cyclohexene (60)

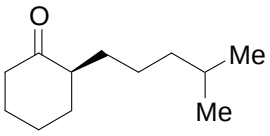


Prepared according to TP 5 using (1*S*)-2-iodocyclohex-2-en-1-yl 2,3,4,5,6-pentafluorobenzoate ((*S*)-**45**) (98% *ee*, 418 mg, 1.0 mmol), NMP (1.1 mL), (4-methyl)pentylzinc iodide (1.68 M in THF, 1.90 mL, 2.0 mmol, 2.0 equiv) and a CuCN·2LiCl solution (1.0 M in THF, 2.0 mL, 2.0 mmol, 2.0 equiv). The resulting mixture was slowly warmed up to 25 °C and stirred for 15 h.

Purification by column chromatography (silica gel, pentane) afforded the cyclohexenyl iodide (*S*)-**60** as a colourless oil (257 mg, 88% yield, 96% *ee*).

GC (Chirasil-Dex CB, 25 mm x 0.25 mm); conditions: 40 °C (1 min), ramp of 20 °C/ min to 150 °C; t_R(min) = 11.954 (major), 12.167 (minor).
$[\alpha]_D^{20}$ +3.2 (c 0.5, CH_2Cl_2)
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 6.30 (dt, *J* = 1.55, 3.6 Hz, 1H), 2.26-2.15 (m, 1H), 2.02-1.93 (m, 2H), 1.81-1.40 (m, 5H), 1.40-1.05 (m, 6H), 0.86-0.78 (m, 6H) ppm.
^{13}C NMR ($CDCl_3$, 75 MHz): δ = 138.7, 107.7, 45.3, 39.3, 35.3, 30.0, 28.5, 28.3, 24.9, 23.1, 22.9, 18.9 ppm.
IR (film): 2930 (s), 2858 (m), 1462 (w), 1384 (w), 1366 (w), 964 (w) cm^{-1}.
MS (EI, 70 eV), *m/z* (%): 292 (M^+, 32), 208 (30), 165 (8), 149 (2), 123 (7), 109 (61), 95 (54), 81 (100), 67 (42), 55 (20).
$C_{12}H_{21}I$ HRMS (EI): Calcd.: 292.0688
Found: 292.0705

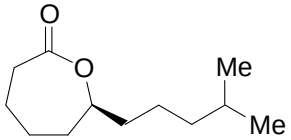
(2*R*)-2-(4-Methylpentyl)cyclohexanone (61)



Prepared according to TP 7 from (6*S*)-1-iodo-6-(4-methylpentyl)cyclohexene (**60**) (247 mg, 0.85 mmol), THF (7 mL), *t*-BuLi (1.60 M in pentane, 1.06 mL, 2.0 equiv), $(TMSO)_2$ (neat, 0.27 mL, 1.28 mmol, 1.50 equiv). The resulting silyl enol ether in THF (3.5 mL) was treated with a HF·pyridine complex (70%) (0.04 mL, 0.85 mmol) in dry pyridine (0.7 mL). After purification by column chromatography (silica gel, 10% Et_2O:pentane), the ketone (*R*)-**61** was obtained as a colourless oil (138 mg, 89% yield, 95% *ee*).

GC (Chirasil-Dex CB, 25 mm x 0.25 mm); conditions: 40 °C (1 min), ramp of 3 °C/ min to 150 °C; t_R (min) = 31.815 (major), 32.077 (minor).
$[\alpha]_D^{20}$ +18 (c 3.75, Et_2O)
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.33-2.08 (m, 3H), 2.07-1.83 (m, 2H), 1.82-0.97 (m, 11H), 0.76 (d, *J* = 6.52 Hz, 6H) ppm.
^{13}C NMR ($CDCl_3$, 75 MHz): δ = 214.0, 51.2, 42.3, 39.4, 34.2, 30.0, 28.4, 28.2, 25.3, 25.2, 22.99, 22.94 ppm.
IR (film): 2932 (s), 2864 (m), 1712 (s), 1449 (w), 1366 (w), 1124 (w) cm^{-1}.
MS (EI, 70 eV), *m/z* (%): 182 (M^+, 3), 149 (1), 121 (1), 111 (9), 98 (100), 83 (16), 70 (11), 55 (16).
$C_{12}H_{22}O$ HRMS (EI): Calcd.: 182.1671
Found: 182.1679

(7*R*)-7-(4-Methylpentyl)oxepan-2-one (10-methyl-6-undecanolide; 62)

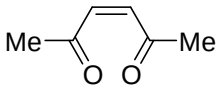


m-CPBA (70%, 200 mg, 1.16 mmol, 2.0 equiv) was added to a solution of (2*R*)-2-(4-methylpentyl)cyclohexanone (**61**; 106 mg, 0.58 mmol) in CH_2Cl_2 (3 mL) at 0 °C. The reaction mixture was stirred at 25 °C for 18 h, and then was poured into an aqueous Na_2SO_3 solution (1 M), extracted with CH_2Cl_2 (3 x 25 mL). The combined organic phase was washed with a saturated $NaHCO_3$, brine and dried over anhydrous $MgSO_4$. Evaporation of the solvents and the purification by column chromatography (silica gel, 50% Et_2O:pentane) afforded the lactone (*R*)-**62** as a colourless oil (105 mg, 91% yield, 95% *ee*).

GC (Chirasil-Dex CB, 25 mm x 0.25 mm); conditions: 40 °C (1 min), ramp of 20 °C/ min to 160 °C; t_R (min) = 12.806 (major), 13.094 (minor).
$[\alpha]_D^{20}$ –1.5 (c 3.2, Et_2O) [Lit.[78] $[\alpha]_D^{25}$ -1.2 (c 3.2, Et_2O)]
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 4.08-3.97 (br, s, 1H), 2.50-2.35 (m, 2H), 1.80-1.63 (m, 3H), 1.55-1.20 (m, 7H), 1.19-1.08 (m, 1H), 1.01-0.90 (m, 2H), 0.66 (d, *J* = 6.4 Hz, 6H) ppm.
^{13}C NMR ($CDCl_3$, 75 MHz): δ = 177.3, 82.1, 40.2, 38.2, 36.5, 36.1, 29.9, 29.4, 24.8, 24.6, 24.11, 24.06 ppm.
IR (film): 2936 (s), 2867 (m), 1731 (s), 1448 (m), 1281 (m), 1256 (m), 1176 (m), 1014 (m) cm^{-1}.
MS (EI, 70 ev), *m/z* (%): 198 (M^+, 1), 180 (1), 165 (2), 155 (4), 137 (4), 125 (5), 113 (43), 95 (8), 85 (100), 67 (3), 55 (30).
$C_{12}H_{22}O_2$ HRMS (EI): Calcd.: 198.1620
Found: 198.1620

5. Formal total synthesis of (+)-estrone via asymmetric allylic substitution

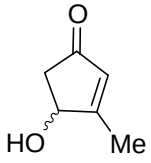
cis-Hex-3-ene-2,5-dione (73)



A solution of magnesium methylperphthalate (MMPP) (12.4 g, 25.0 mmol, 0.50 equiv) in H_2O (100 mL) was added dropwise to a solution of 2,5-dimethylfuran (**72**) (5.33 mL, 50.0 mmol) in abs. EtOH (200 mL) at 25 °C. The reaction mixture was stirred at 25 °C for 12 h and then was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic phase was washed with a saturated aqueous $NaHCO_3$ solution, brine and dried over $MgSO_4$ anhydrous. After evaporation of the solvents, the obtained *cis*-hex-3-ene-2,5-dione (**73**) was used in the next step without further purification. The crude product was identified by the NMR analysis and mass spectroscopy.
The data were in agreement with those reported.[100]

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 6.25 (s, 2H), 2.22 (s, 6H) ppm.
^{13}C NMR ($CDCl_3$, 75 MHz): δ = 200.9 (2 carbons), 136.1 (2 carbons), 30.1 (2 carbons) ppm.
MS (EI, 70 eV), *m/z* (%): 112 (M^+, 15), 97 (100), 69 (36).

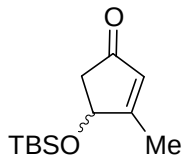
4-Hydroxy-3-methylcyclopent-2-en-1-one (*rac*-74)



The crude product of *cis*-3-hexene-2,5-dione (**73**) was slowly added over 2 h to a solution of 1% aqueous Na_2CO_3 (50 mL) which was heated at reflux. The reaction mixture was heated at reflux for 3 h. After cooling to 25 °C, the mixture was neutralized with 2 M HCl, extracted with EtOAc (3 x 50 mL). The combined organic phase was washed with brine and dried over Na_2SO_4 anhydrous. Removal of the solvents afforded the crude 4-hydroxy-3-methylcyclopent-2-en-1-one (*rac*-**74**) as a brown oil, which was used in the next step without further purification. An analytical sample was obtained by column chromatography (silica gel, Et_2O).
The data were in agreement with those reported.[100]

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 5.92-5.86 (m, 1H), 4.76-4.67 (br, s, 1H), 2.90-2.72 (br, s, 1H), 2.72 (dd, *J* = 6.19, 18.36 Hz, 1H), 2.25 (dd, *J* = 2.65, 18.36 Hz, 1H), 2.10 (br, s, 3H) ppm.
^{13}C NMR ($CDCl_3$, 75 MHz): δ = 206.2, 177.8, 131.8, 73.0, 45.7, 16.2 ppm.
IR (neat): 3394 (br), 1683 (s), 1624 (m), 1379 (w), 1294 (w), 1194 (w), 1077 (w) cm^{-1}.
MS (EI, 70 eV), *m/z* (%): 112 (M^+, 100), 97 (34), 84 (33), 69 (69), 55 (20).

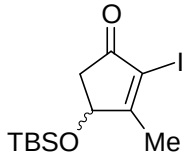
4-[*tert*-Butyl(dimethyl)silyl]oxy-3-methylcyclopent-2-en-1-one (*rac*-75)



Imidazole (3.40 g, 50.0 mmol) was added to a solution of the crude product of 4-hydroxy-3-methylcyclopent-2-en-1-one (*rac*-**74**) obtained as described above in DMF (60 mL) followed by gradually adding TBDMSCl (7.54 g, 50.0 mmol) at 25 °C. The reaction mixture was stirred at 25 °C for 12 h, then was poured into ice-cooled water, extracted with Et_2O (3 x 50 mL). The combined organic phase was washed with brine and dried over $MgSO_4$ anhydrous. Purification by column chromatography (silica gel, 25% Et_2O:pentane, 0.3% Et_3N) afforded 4-[*tert*-butyl(dimethyl)silyl]oxy-3-methylcyclopent-2-en-1-one (*rac*-**75**) as a brown oil (3.39 g, 30% yield, over 3 steps starting from **72**).

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 5.86-5.80 (m, 1H), 4.66-4.59 (m, 1H), 2.62 (dd, *J* = 5.97, 17.91 Hz, 1H), 2.18 (dd, *J* = 2.88, 17.91 Hz, 1H), 2.05-1.95 (m, 3H), 0.82 (s, 9H), 0.05 (s, 3H), 0.02 (s, 3H) ppm.
^{13}C NMR ($CDCl_3$, 75 MHz): δ = 205.6, 177.9, 131.3, 73.3, 46.3, 26.0 (3 carbons), 18.4, 16.3, -4.2, -4.6 ppm.
IR (neat): 2956 (m), 2930 (m), 2858 (m), 1721 (s), 1630 (m), 1253 (m), 1094 (s), 839 (s) cm^{-1}.
MS (EI, 70 eV), *m/z* (%): 211 (3), 169 (100), 127 (26), 95 (43), 75 (24).
$C_{12}H_{22}O_2Si$ HRMS (EI): Calcd.: 226.1389
Found: 226.1402

4-{[*tert*-Butyl(dimethyl)silyl]oxy}-2-iodo-3-methylcyclopent-2-en-1-one (*rac*-76)



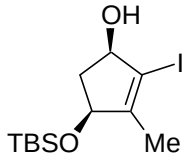
I_2 (1.50 equiv, 4.76 g, 18.8 mmol) and PDC (0.30 equiv, 1.41 g, 3.75 mmol) were added to the solution of 4-{[*tert*-butyl(dimethyl)silyl]oxy}-3-methylcyclopent-2-en-1-one (*rac*-**75**) (2.75 g, 12.2 mmol) in dry CH_2Cl_2 (100 mL). The reaction flask was covered with an aluminium foil and the reaction mixture was stirred at 25 °C for 22 h. The progress of the reaction was followed by GC- or TLC-analysis. Additional I_2 (1.0 equiv, 3.10 mg, 12.2 mmol) was added and the reaction mixture was stirred for additional 24 h. The reaction mixture was filtered and the residue was washed with pentane. The combined organic phase was washed with H_2O, a saturated $Na_2S_2O_3$ solution, brine and dried over $MgSO_4$ anhydrous. After purification by column chromatography (silica gel, 25% Et_2O:pentane, 0.3% Et_3N), the product *rac*-**76** was obtained as a yellow solid (3.31 g, 77% yield).

mp = 57.8-59.4 °C
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 4.70-4.60 (m, 1H), 2.75 (dd, *J* = 6.08, 17.91 Hz, 1H), 2.26 (dd, *J* = 2.43, 17.91 Hz, 1H), 2.04 (s, 3H), 0.76 (s, 9H), 0.00 (s, 3H), -0.03 (s, 3H) ppm.
^{13}C NMR ($CDCl_3$, 75 MHz): δ = 199.4, 179.8, 105.1, 73.9, 44.1, 26.0 (3 carbons), 19.3, 18.4, -4.2, -4.6 ppm.
IR (film): 2953 (m), 2930 (m), 1705 (s), 1615 (m), 1253 (m), 1088 (m), 886 (m), 840 (m) cm^{-1}.
MS (EI, 70 eV), *m/z* (%): 352 (M^+, 1), 337 (2), 295 (100), 253 (46), 221 (21), 168 (18), 75 (49).
$C_{12}H_{21}IO_2Si$ HRMS (EI): Calcd.: 352.0356
Found: 352.0350

The asymmetric reduction of *rac*-76

A flame-dried round bottom flask equipped with a magnetic stirring bar, an argon inlet and a rubber septum was charged with (*S*)-diphenylprolinol (60 mg, 0.23 mmol, 5 mol%) and THF (4.3 mL). $B(OMe)_3$ (27 μL, 0.23 mmol, 5 mol%) was added to the reaction mixture, and then it was stirred at 25 °C for 1 h. The borane-*N*,*N*-diethylaniline complex (0.83 mL, 4.66 mmol) was added dropwise followed by the slow addition of a solution of 4-{[*tert*-butyl(dimethyl)silyl]oxy}-3-methylcyclopent-2-en-1-one (*rac*-**76**) (1.64 g, 4.66 mmol) in THF (4.3 mL) over 30 min. The reaction mixture was stirred at 25 °C for 1.5 h then was carefully quenched with MeOH (2.1 mL). The solvents were evaporated under reduced pressure. The residue oil was partitioned between H_2O and Et_2O. The organic phase was collected and the aqueous phase was further extracted with Et_2O (3 x 25 mL). The combined organic phase was washed with 7% Na_2CO_3 solution, brine and dried over Na_2SO_4 anhydrous. After removal of the solvents, the crude product obtained as the mixture of the diastereoisomers was purified by column chromatography (silica gel, 20% Et_2O:pentane) to give the alcohols **77a** and **77b** in 94% total yield.

(1*R*,4*S*)-4-{[*tert*-Butyl(dimethyl)silyl]oxy}-2-iodo-3-methylcyclopent-2-en-1-ol (77a)



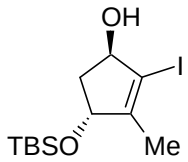
The product was obtained in pure form as a white solid (750 mg, 46% yield, 84% *ee*).

mp = 94.3-95.6 °C

HPLC (Chiralcel OD, heptane:*i*-PrOH = 99:1, 0.4 mL/min); t_R (min) = 30.63 (minor), 36.43 (major).
$[\alpha]_D^{20}$ +2 (c 0.3, CH_2Cl_2)
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 4.40-4.29 (m, 2H), 2.68 (dt, *J* = 7.19, 13.33 Hz, 1H), 1.98-1.80 (br, s, 1H), 1.71 (s, 3H), 1.62 (dt, *J* = 5.20, 13.33 Hz, 1H), 0.80 (s, 9H), 0.00 (s, 3H), -0.01 (s, 3H) ppm.
^{13}C NMR ($CDCl_3$, 75 MHz): δ = 150.5, 104.1, 78.8, 76.5, 43.8, 26.1 (3 carbons), 18.5, 16.9, -4.1, -4.5 ppm.
IR (neat): 3435 (s), 1254 (m), 1112 (m), 1066 (s), 994 (s), 866 (s), 836 (s), 783 (s) cm^{-1}.
MS (EI, 70 eV), *m/z* (%): 297 (32), 279 (5), 170 (17), 95 (5), 75 (100).

$C_{12}H_{23}IO_2Si$	HRMS (EI):	Calcd.: 353.0434 $[M-H]^+$
		Found: 353.0444 $[M-H]^+$
$C_{12}H_{23}IO_2Si$	Anal.	Calcd.: C 40.68, H 6.54
		Found: C 40.75, H 6.53

(1*R*,4*R*)-4-{[*tert*-Butyl(dimethyl)silyl]oxy}-2-iodo-3-methylcyclopent-2-en-1-ol (77b)

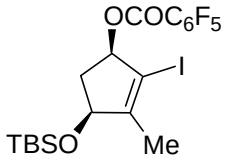


The product was obtained in pure form as a white solid (800 mg, 49% yield, 99% *ee*).

mp = 75.4-76.5 °C
HPLC (Chiralcel OD, heptane:*i*-PrOH = 95:5, 0.5 mL/min); t_R (min) = 10.21 (major).
$[\alpha]_D^{20}$ +36 (c 0.3, CH_2Cl_2)
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 4.71-4.60 (m, 2H), 2.20 (ddd, *J* = 2.27, 6.75, 13.95 Hz, 1H), 1.99 (ddd, *J* = 4.28, 7.02, 13.95 Hz, 1H), 1.78 (br, s, 1H), 1.70 (s, 3H), 0.80 (s, 9H), 0.00 (s, 3H), -0.01 (s, 3H) ppm.
^{13}C NMR ($CDCl_3$, 75 MHz): δ = 151.8, 103.1, 81.0, 77.1, 43.6, 26.1 (3 carbons), 18.5, 16.9, -4.2, -4.5 ppm.
IR (neat): 3292 (s), 1249 (m), 1068 (s), 1049 (s), 887 (s), 843 (s), 773 (s) cm^{-1}.
MS (EI, 70 eV), *m/z* (%): 354 (M^+, 1), 297 (56), 279 (16), 205 (10), 170 (38), 96 (9), 75 (100).

$C_{12}H_{23}IO_2Si$	HRMS (EI):	Calcd.: 354.0512
		Found: 354.0515

(1*R*,4*S*)-4-{[*tert*-Butyl(dimethyl)silyl]oxy}-2-iodo-3-methylcyclopent-2-en-1-yl 2,3,4,5,6-pentafluorobenzoate (78a)

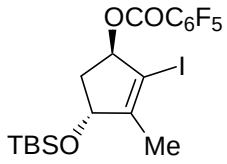


Pyridine (1.30 equiv, 0.30 mL, 3.67 mmol), DMAP (0.10 equiv, 34 mg, 0.28 mmol) and pentafluorobenzoyl chloride (1.30 equiv, 0.53 mL, 3.67 mmol) were added to the solution of (1*R*,4*S*)-4-{[*tert*-butyl(dimethyl)silyl]oxy}-2-iodo-3-methylcyclopent-2-en-1-ol (**77a**) (1.0 g, 2.82 mmol) in dry Et_2O (17 mL) at 25 °C. The resulting suspension was stirred at 25 °C for 2 h, and then was poured into a saturated NH_4Cl solution. The mixture was extracted with Et_2O (3 x 25 mL). The combined organic phase was washed with a saturated $NaHCO_3$ solution,

brine and dried over $MgSO_4$ anhydrous. Purification by column chromatography (silica gel, 10% CH_2Cl_2:pentane) afforded the product **78a** as a white solid (1.41 g, 91% yield, 81% *ee*).

mp = 40.9-42.8 °C
HPLC (Chiralcel OD, heptane:*i*-PrOH = 99:1, 0.5 mL/min); t_R (min) = 8.93 (minor), 12.47 (major).
$[\alpha]_D^{20}$ –2 (c 0.3, CH_2Cl_2)
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 5.71-5.66 (m, 1H), 4.44-4.37 (m, 1H), 2.90 (dt, *J* = 7.30, 13.71 Hz, 1H), 1.80-1.69 (m, 4H), 0.79 (s, 9H), 0.00 (s, 3H), -0.02 (s, 3H) ppm.
^{13}C NMR ($CDCl_3$, 75 MHz): δ = 159.0, 154.5, 147.7, 141.6, 139.8, 136.4, 134.9, 108.5, 94.1, 82.7, 76.2, 41.7, 26.1 (3 carbons), 18.4, 17.0, -4.2, -4.5 ppm.
IR (neat): 1740 (s), 1497 (s), 1354 (m), 1323 (m), 1225 (s), 1085 (s), 990 (s), 882 (s), 836 (s), 777 (s) cm^{-1}.
MS (EI, 70 eV), *m/z* (%): 491 (3), 269 (100), 195 (15), 168 (10), 75 (14).
$C_{19}H_{22}F_5IO_3Si$ Anal. Calcd.: C 41.62, H 4.04
Found: C 41.63, H 4.39

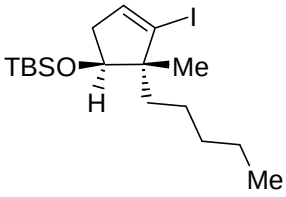
(1*R*,4*R*)-4-{[*tert*-Butyl(dimethyl)silyl]oxy}-2-iodo-3-methylcyclopent-2-en-1-yl 2,3,4,5,6-pentafluorobenzoate (78b)



Pyridine (1.30 equiv, 0.53 mL, 6.50 mmol), DMAP (0.10 equiv, 73 mg, 0.50 mmol) and pentafluorobenzoyl chloride (1.30 equiv, 0.94 mL, 6.50 mmol) were added to the solution of (1*R*,4*R*)-4-{[*tert*-butyl(dimethyl)silyl]oxy}-2-iodo-3-methylcyclopent-2-en-1-ol (**77b**) (1.77 g, 5.0 mmol) in dry Et_2O (34 mL) at 25 °C. The resulting suspension was stirred at 25 °C for 2 h, and then was poured into a saturated NH_4Cl solution. The mixture was extracted with Et_2O (3 x 25 mL). The combined organic phase was washed with a saturated $NaHCO_3$ solution, brine and dried over $MgSO_4$ anhydrous. Purification by column chromatography (silica gel, 10% CH_2Cl_2:pentane) afforded the product **78b** as a white solid (2.47 g, 90% yield, 99% *ee*).

mp = 56.3-57.4 °C
HPLC (Chiralcel OD-H, heptane:*i*-PrOH = 99:1, 0.4 mL/min); t_R (min) = 12.82 (major).
$[\alpha]_D^{20}$ +34 (c 0.3, CH_2Cl_2)
^{1}H NMR ($CDCl_3$, 600 MHz): 5.92 (m, 1H), 4.77-4.71 (m, 1H), 2.30 (ddd, *J* = 1.67, 6.91, 14.40 Hz, 1H), 2.17 (ddd, *J* = 4.50, 6.91, 14.40 Hz, 1H), 2.06 (s, 3H), 0.79 (s, 9H), 0.00 (s, 3H), -0.02 (s, 3H) ppm.
^{13}C NMR ($CDCl_3$, 150 MHz): δ = 159.2, 157.1, 146.5, 144.5, 142.7, 139.0, 137.2, 108.6, 93.0, 86.0, 76.6, 42.0, 26.1 (3 carbons), 18.5, 17.0, -4.2, -4.5 ppm.
IR (neat): 1739 (s), 1498 (s), 1354 (m), 1323 (s), 1225 (s), 1084 (s), 990 (s), 882 (s), 836 (s), 777 (s) cm^{-1}.
MS (EI, 70 eV), *m/z* (%): 491 (3), 473 (4), 421 (2), 336 (31), 279 (16), 195 (46), 168 (38), 75 (100).
$C_{19}H_{22}F_5IO_3Si$ Anal. Calcd.: C 41.62, H 4.04
Found: C 41.67, H 4.25

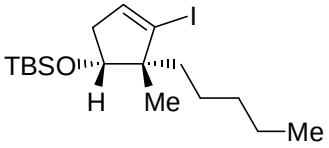
(1*S*,2*R*)-*tert*-Butyl[(3-iodo-2-methyl-2-pentylcyclopent-3-en-1-yl)oxy]dimethylsilane (79a)



A flame-dried round bottom flask equipped with a magnetic stirring bar, an argon inlet and a rubber septum was charged with a CuCN·2LiCl solution (1.0 M in THF, 0.75 mL, 0.75 mmol, 1.50 equiv). The solution was cooled to 0 °C in an ice bath, and then dipentylzinc (5.60 M in THF, 0.21 mL, 1.20 mmol, 2.40 equiv) was added. The reaction mixture was stirred at 0 °C for 10 min. The ice bath was removed then the solution of (1*R*,4*S*)-4-{[*tert*-butyl(dimethyl)silyl]oxy}-2-iodo-3-methylcyclopent-2-en-1-yl 2,3,4,5,6-pentafluorobenzoate (**78a**) (274 mg, 0.50 mmol) in THF (1 mL) was added dropwise at 25 °C. The reaction mixture was stirred at 25 °C for 12 h, and then was poured into a saturated NH_4Cl solution (contained 25 % of aqueous NH_3). The mixture was extracted with Et_2O (3 x 25 mL). The combined organic phase was washed with brine and dried over $MgSO_4$ anhydrous. After purification by column chromatography (silica gel, pentane), the product **79a** was obtained as a colourless oil (110 mg, 54% yield, 81% *ee*).

GC (Chirasil-Dex CB, 25 mm x 0.25 mm); conditions: 60 °C (1 min), ramp of 5 °C/min to 140 °C (20 min), ramp of 1 °C/min to 160 °C (30 min); t_R (min) = 42.322 (minor), 42.777 (major).
$[\alpha]_D^{20}$ +0.71 (c 0.28, CH_2Cl_2)
^{1}H NMR ($CDCl_3$, 300 MHz): 5.96 (t, *J* = 2.53 Hz, 1H), 4.17 (t, *J* = 6.82 Hz, 1H), 2.43 (ddd, *J* = 2.53, 6.82, 15.6 Hz, 1H), 2.14 (ddd, *J* = 2.53, 6.82, 15.6 Hz, 1H), 1.36-1.08 (m, 8H), 0.88-0.78 (m, 15H), -0.001 (s, 3H), -0.012 (s, 3H) ppm.
^{13}C NMR ($CDCl_3$, 75 MHz): 135.5, 109.6, 72.9, 54.8, 42.3, 38.7, 32.9, 26.1 (3 carbons), 24.2, 23.0, 19.8, 18.4, 14.5, -4.0, -4.6 ppm.
IR (neat): 2927 (m), 1250 (m), 1115 (s), 864 (s), 834 (s), 773 (s) cm^{-1}.
MS (EI, 70 eV), *m/z* (%): 408 (M^+, 1), 393 (3), 351 (100), 281 (70), 211 (6), 75 (69).
$C_{17}H_{33}IOSi$ HRMS (EI): Calcd.: 408.1345
Found: 408.1307

(1*R*,2*R*)-*tert*-Butyl[(3-iodo-2-methyl-2-pentylcyclopent-3-en-1-yl)oxy]dimethylsilane (79b)

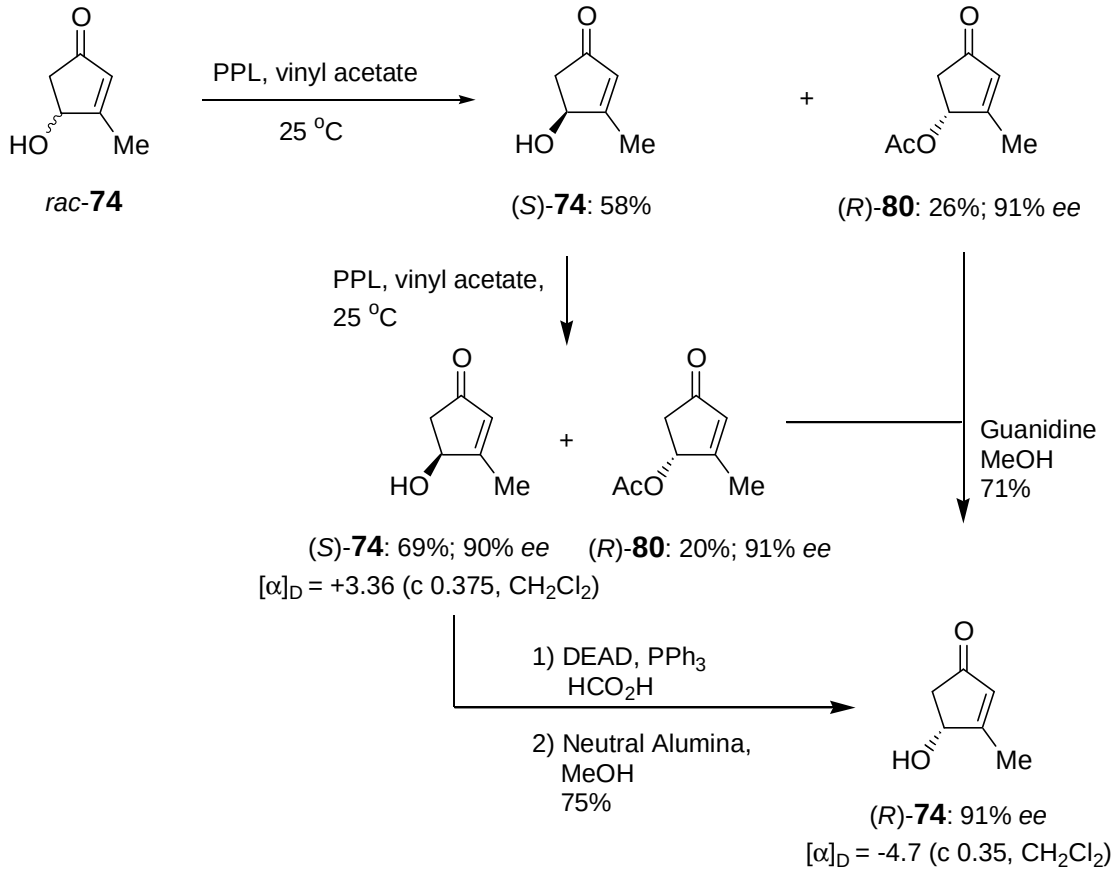


A flame-dried round bottom flask equipped with a magnetic stirring bar, an argon inlet and a rubber septum was charged with a CuCN·2LiCl solution (1.0 M in THF, 0.75 mL, 0.75 mmol, 1.50 equiv). The solution was cooled to 0 °C in an ice bath and then dipentylzinc (5.60 M in THF, 0.21 mL, 1.20 mmol, 2.40 equiv) was added. The reaction mixture was stirred at 0 °C for 10 min. The ice bath was removed then the solution of (1*R*,4*R*)-4-{[*tert*-butyl(dimethyl)silyl]oxy}-2-iodo-3-methylcyclopent-2-en-1-yl 2,3,4,5,6-pentafluorobenzoate (**78b**) (274 mg, 0.50 mmol) in THF (1 mL) was added dropwise at 25 °C. The reaction mixture was stirred at 25 °C for 12 h, then was poured into a saturated NH_4Cl solution (contained 25 % of aqueous NH_3). The mixture was extracted with Et_2O (3 x 25 mL). The combined organic phase was washed with brine and dried over $MgSO_4$ anhydrous. After

purification by column chromatography (silica gel, pentane), the product **79b** was obtained as a colourless oil (138 mg, 68% yield, 99% *ee*).

GC (Chirasil-Dex CB, 25 mm x 0.25 mm); conditions: 60 °C (1 min), ramp of 5 °C/min to 140 °C (20 min), ramp of 1 °C/min to 160 °C (30 min); t_R (min) = 39.628 (major).
$[\alpha]_D^{20}$ +1.9 (c 0.32, CH_2Cl_2)
^{1}H NMR ($CDCl_3$, 300 MHz): 6.02 (dd, *J* = 2.10, 2.64 Hz, 1H), 4.04 (t, *J* = 7.80 Hz), 2.39 (ddd, *J* = 2.64, 7.80, 15.68 Hz, 1H), 2.14 (ddd, *J* = 2.10, 7.80, 15.68 Hz, 1H), 1.50-1.02 (m, 8H), 0.92 (s, 3H), 0.86-0.76 (m, 12H), -0.009 (s, 3H), -0.032 (s, 3H) ppm.
^{13}C NMR ($CDCl_3$, 75 MHz): 135.8, 108.9, 73.5, 54.5, 43.4, 35.9, 33.2, 28.0, 26.1 (3 carbons), 24.5, 23.0, 18.3, 14.5, -4.2, -4.6 ppm.
IR (neat): 1462 (w), 1256 (m), 1112 (s), 862 (s), 835 (s), 809 (m), 773 (s) cm^{-1}.
MS (EI, 70 eV), *m/z* (%): 393 (2), 351 (84), 281 (100), 211 (8), 184 (5), 149 (6), 73 (24).
$C_{17}H_{33}IOSi$ HRMS (EI): Calcd.: 407.1267 $[M-H]^+$
Found: 407.1277 $[M-H]^+$

Enzymatic resolution of 4-hydroxy-3-methylcyclopent-2-enone (*rac*-74) via porcine pancreatic lipase (PPL) in vinyl acetate.



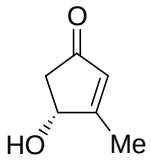
A mixture of 4-hydroxy-3-methylcyclopent-2-enone (*rac*-**74**) (1.21 g, 10.8 mmol) and porcine pancreatic lipase (PPL; 1.21 g) in vinyl acetate (30 mL) was stirred at 25 °C. The separation of the alcohol *rac*-**74** was not possible under a variety of conditions by HPLC or capillary GC. Therefore the course of the reaction (the conversion and the enantiomeric excess) was monitored from the corresponding acetate (**80**) by using HPLC (chiracel OJ column, *i*-PrOH:heptane, 10:90, flow rate 0.5 mL/min). An additional portion of PPL (1.2 g)

was added after stirring for 4 days (14% conversion, 100% *ee* of the resulting acetate (*R*)-**80**), and the reaction mixture was stirred for additional 5 days. The crude mixture was then filtered. The residue was washed with CH_2Cl_2. The combined filtrate was concentrated to give the crude product which was purified by column chromatography (silica gel, Et_2O) to give the acetate (*R*)-**80** (437 mg, 26% yield, 91% *ee*) and the unreacted alcohol (*S*)-**74** (706 mg, 6.3 mmol, 58% recovered). The unreacted alcohol was again submitted to enzymatic resolution conditions as described above. Purification by column chromatography (silica gel, Et_2O) gave the additional acetate (*R*)-**80** as a brown oil (194 mg, 20% yield, 91% *ee*) and the unreacted alcohol (*S*)-**74** (487 mg, 90% *ee* (determined for the corresponding acetate)), which could be inverted into the desired (*R*)-**74** by using the Mitsunobu reaction (see below).

Deacetylation of (1*R*)-2-methyl-4-oxo-2-cyclopenten-1-yl acetate (80)

A stock solution of guanidine (0.5 M in methanol) was prepared by adding sodium (350 mg, 15.0 mmol) to ice-cooled methanol (30 mL) under an argon atmosphere. When all the sodium had reacted, guanidine carbonate (2.77 g, 15.0 mmol) was added. The resulting solution was stirred at 25 ^oC for 30 min, and then the mixture was allowed to settle out the precipitated salts.

A flamed-dried round bottom flask was charged with (1*R*)-2-methyl-4-oxo-2-cyclopenten-1-yl acetate ((*R*)-**80**) (420 mg, 2.73 mmol) in abs. methanol (3 mL) under an argon atmosphere. The reaction mixture was cooled to 0 ^oC and the solution of 0.5 M guanidine in methanol prepared as described above was added dropwise. The reaction mixture was stirred below 15 ^oC for 5 min. The completion of the reaction was checked by TLC (Et_2O). Glacial acetic acid (0.17 mL) was then added to the reaction mixture to neutralize the guanidine. The reaction mixture was stirred for 5 min, and then the solvent was evaporated at reduced pressure to give a thick slurry. The residue was partitioned between water (100 mL) and toluene-EtOAc (1:1, 100 mL). The aqueous layer was neutralized by 2 M HCl and further extracted with EtOAc. The combined organic layer was washed with H_2O, brine and dried over Na_2SO_4. After removal of the solvents, the obtained crude product was purified by column chromatography (Et_2O) to give (4*R*)-4-hydroxy-2-iodo-3-methyl-2-cyclopenten-1-one [(*R*)-**74**; 217 mg, 71%, 91% *ee* (determined for the corresponding acetate (*R*)-**80**)].



91% *ee*

$[\alpha]_D^{20}$ –4.7 (c 0.35, CH_2Cl_2)

HPLC (Determined for the corresponding acetate (*R*)-**80**) (Chiralcel OJ, heptane:*i*-PrOH = 90:10, 0.5 mL/min); t_R (min) = 25.118 (major), 30.043 (minor); 91% *ee*.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 5.92-5.86 (m, 1H), 4.76-4.67 (br, s, 1H), 2.90-2.72 (br, s, 1H), 2.72 (dd, *J* = 6.19, 18.36 Hz, 1H), 2.25 (dd, *J* = 2.65, 18.36 Hz, 1H), 2.10 (br, s, 3H) ppm.

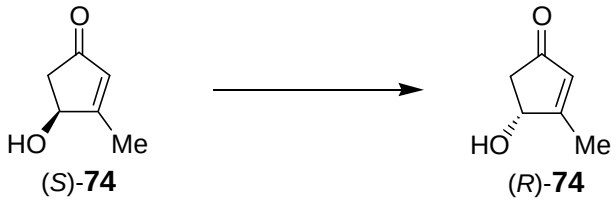
^{13}C NMR ($CDCl_3$, 75 MHz): δ = 206.2, 177.8, 131.8, 73.0, 45.7, 16.2 ppm.

IR (neat): 3394 (br), 1683 (s), 1624 (m), 1379 (w), 1294 (w), 1194 (w), 1077 (w) cm^{-1}.

MS (EI, 70 eV), *m/z* (%): 112 (M^+, 100), 97 (34), 84 (33), 69 (69), 55 (20).

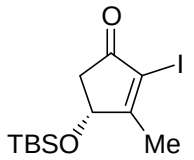
$C_6H_8O_2$ HRMS (EI): Calcd.: 112.0524
Found: 112.0517

Mitsunobu inversion of (4*S*)-4-hydroxy-2-iodo-3-methylcyclopent-2-en-1-one ((*S*)-74)



Formic acid (0.23 mL, 6.0 mmol) was added dropwise to a mixture of (4*S*)-4-hydroxy-2-iodo-3-methylcyclopent-2-en-1-one ((*S*)-**74**) (336 mg, 3.0 mmol) and PPh_3 (1.57 g, 6.0 mmol) in THF (10 mL) under an argon atmosphere. The reaction mixture was cooled to 10 °C (ice bath), and was maintained below 15 °C while DEAD (1.10 mL, 6.0 mmol) was added dropwise. The reaction mixture was warmed to 25 °C and stirred for 12 h. The solvents were evaporated at reduced pressure and the residue was dissolved in *tert*-butyl methyl ether (TBME; 20 mL). To the reaction mixture was slowly added hexane (40 mL). The solution was stirred for 20 min at 25 °C and then was filtered. The residue was washed with 1:1 TBME:hexane (2 x 100 mL). The combined filtrate was concentrated to give an oil, which was further dissolved in abs. methanol (30 mL). To the solution was added gradually neutral alumina (20.0 g). The reaction mixture was stirred at 25 °C for 5 h to saponified the formate ester intermediate. The mixture was filtered through a glass-fritted funnel, and the residue was washed with methanol (3 x 100 mL). After removal of the solvents, the resulting crude product was purified by column chromatography (Et_2O) to give (4*R*)-4-hydroxy-2-iodo-3-methylcyclopent-2-en-1-one ((*R*)-**74**) as a brown oil (252 mg, 75% yield, 91% *ee* (determined for the corresponding acetate)).

(4*R*)-4-{[*tert*-Butyl(dimethyl)silyl]oxy}-2-iodo-3-methylcyclopent-2-en-1-one ((*R*)-76)

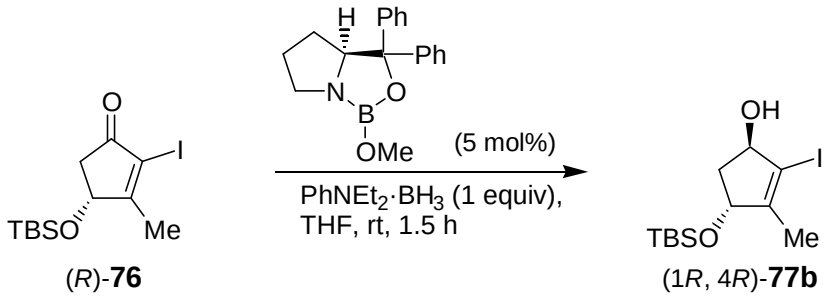


Imidazole (2.13 g, 31.4 mmol, 1.50 equiv) was added to a solution of (4*R*)-4-hydroxy-3-methylcyclopent-2-en-1-one ((*R*)-**74**) (2.34 g, 20.9 mmol) in DMF (50 mL) followed by gradually adding TBDMSCl (4.73 g, 31.4 mmol, 1.50 equiv) at 25 °C. The reaction mixture was stirred at 25 °C for 12 h. The reaction mixture was poured into ice-cooled water, and was extracted with Et_2O (3 x 50 mL). The combined organic phase was washed with brine and dried over $MgSO_4$. The crude product which was obtained as a brown oil was used in the next step without purification.

I_2 (1.50 equiv, 8.0 g, 31.4 mmol) and PDC (0.30 equiv, 2.36 g, 6.27 mmol) were added to the solution of the crude (4*R*)-4-{[*tert*-butyl(dimethyl)silyl]oxy}-3-methylcyclopent-2-en-1-one obtained as described above in dry CH_2Cl_2 (180 mL). The reaction mixture was stirred at 25 °C for 24 h. Additional I_2 (1.0 equiv, 5.30 g, 20.9 mmol) was added and the reaction mixture was stirred for additional 24 h. The mixture was filtered and the residue was washed with pentane. The combined organic layer was washed with H_2O, a saturated $Na_2S_2O_3$ solution, brine and dried over $MgSO_4$. After purification by column chromatography (silica gel, 25% Et_2O:pentane, 0.3% Et_3N), the product **(*R*)-76** was obtained as a yellow solid (5.37 g, 73% yield).

The data were in agreement with *rac*-**76**.

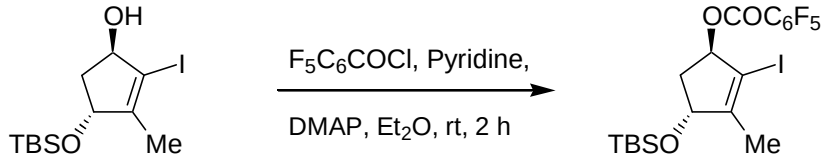
(1*R*,4*R*)-4-{[*tert*-Butyl(dimethyl)silyl]oxy}-2-iodo-3-methylcyclopent-2-en-1-ol (77b)



(*R*)-**76** (1*R*, 4*R*)-**77b**

A flame-dried round bottom flask equipped with a magnetic stirring bar, an argon inlet and a rubber septum was charged with (*S*)-diphenylprolinol (193 mg, 0.76 mmol, 5 mol%) and THF (16 mL). $B(OMe)_3$ (90 μL, 0.76 mmol, 5 mol%) was added to the solution, and the reaction mixture was stirred at 25 °C for 1 h. The borane-*N*,*N*-diethylaniline complex (2.71 mL, 15.3 mmol) was added dropwise followed by the slow addition of a solution of (4*R*)-4-{[*tert*-butyl(dimethyl)silyl]oxy}-3-methylcyclopent-2-en-1-one ((*R*)-**76**) (5.37 g, 15.3 mmol) in THF (16 mL) over 1 h. The reaction mixture was stirred at 25 °C for 1.5 h, then was carefully quenched with MeOH (7 mL). The solvents were evaporated under reduced pressure. The residue oil was partitioned between H_2O and Et_2O. The organic phase was collected and the aqueous phase was further extracted with Et_2O (3 x 50 mL). The combined organic phase was washed with 7% Na_2CO_3 solution, brine and dried over Na_2SO_4. The solvents were evaporated affording the crude product which was purified by column chromatography (silica gel, 20% Et_2O:pentane) to give the pure allylic alcohol (1*R*, 4*R*)-**77b** as a major product in 95% yield (5.13 g, 99% *ee*). The separable minor product, diastereoisomer (1*R*, 4*S*)-**77a**, was obtained in less than 5% yield.

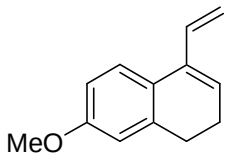
(1*R*,4*R*)-4-{[*tert*-Butyl(dimethyl)silyl]oxy}-2-iodo-3-methylcyclopent-2-en-1-yl 2,3,4,5,6-pentafluorobenzoate (78b)



(1*R*, 4*R*)-**77b** (1*R*, 4*R*)-**78b**

Pyridine (1.30 equiv, 1.52 mL, 18.8 mmol), DMAP (0.10 equiv, 177 mg, 1.45 mmol) and pentafluorobenzoyl chloride (1.30 equiv, 2.71 mL, 18.8 mmol) were added to the solution of the allylic alcohol (1*R*, 4*R*)-**77b** (5.13 g, 14.5 mmol) in dry Et_2O (85 mL) at 25 °C. The resulting suspension was stirred at 25 °C for 2 h, and then was poured into a saturated NH_4Cl solution. The mixture was extracted with Et_2O (3 x 50 mL). The combined organic phase was washed with a saturated $NaHCO_3$ solution, brine and dried over $MgSO_4$. Purification by column chromatography (silica gel, 10% CH_2Cl_2:pentane) afforded the product (1*R*, 4*R*)-**78b** as a white solid (7.23 g, 91% yield, 99% *ee*).

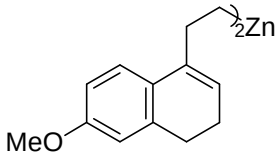
7-Methoxy-4-vinyl-1,2-dihydronaphthalene (Dane's diene; 81)



A solution of 6-methoxytetralone (6.34 g, 36.0 mmol) in THF (36 mL) was added to a solution of vinylmagnesium bromide (1.60 M in THF, 1.20 equiv, 25.0 mL) over 30 min. The reaction mixture was heated at reflux for 1 h. The reaction mixture was cooled in ice bath and a saturated NH_4Cl solution was added. The layers were separated, and the aqueous layer was extracted with Et_2O (3 x 50 mol). The etheral phases were combined, washed with brine, dried over Na_2SO_4. The solvents were evaporated to give the resulting allylic alcohol as a brown oil.
Quinoline (0.5 equiv, 2.25 mL) and a crystal of iodine were added to a solution of the crude allylic alcohol obtained as described above in dry benzene (135 mL). The reaction flask was fitted with a Dean-Stark apparatus, and the reaction mixture was heated at reflux under a nitrogen atmosphere until the theoretical amount of water had been removed. The reaction mixture was cooled, washed with a saturated $NaHCO_3$ solution, brine and dried over $MgSO_4$. Purification by column chromatography (silica gel: 25% Et_2O:pentane) gave 7-methoxy-4-vinyl-1,2-dihydronaphthalene (Dane's diene; **81**) in 5.54 g (83% yield).
The data were in agreement with those reported.[110]

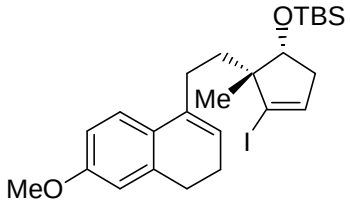
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.19 (d, *J* = 8.85 Hz, 1H), 6.69-6.60 (m, 2H), 6.58-6.45 (m, 1H), 5.98 (dt, *J* = 0.89, 4.87 Hz, 1H), 5.43 (dd, *J* = 1.77, 17.36 HZ, 1H), 5.09 (dd, *J* = 1.77, 10.84 Hz, 1H), 3.72 (s, 3H), 2.65 (t, *J* = 7.80 Hz, 2H), 2.27-2.14 (m, 2H) ppm.
^{13}C NMR ($CDCl_3$, 75 MHz): δ = 159.0, 138.9, 136.6, 136.1, 127.6, 125.4, 124.5, 115.3, 114.2, 111.2, 55.6, 29.1, 23.6 ppm.

Di[2-(6-methoxy-3,4-dihydro-1-naphthalenyl)ethyl]zinc (71)



a) Hydroboration step: A flame-dried Schlenk flask equipped with a magnetic stirring bar, an argon inlet and a rubber septum was charged with Dane's diene (**81**) (3.56 g, 19.1 mmol) and cooled to 0 °C in an ice bath. Diethylborane (Et_2BH; 1.0 equiv, 4.92 mL) which was prepared by mixing $BH_3 \cdot Me_2S$ (1.64 mL) and Et_3B (3.28 mL) in ratio 1:2 was added dropwise. The reaction mixture was stirred at 0 °C for 3 h. The volatiles were evaporated under high vacuum (0.1 mmHg) at 0 °C affording the crude hydroboration product.
b) Boron-Zinc exchange step: The organoborane prepared above was placed under an argon atmosphere, and then Et_2Zn (2.0 equiv, 4.11 mL) was added at 0 °C. The reaction mixture was warmed to 25 °C and stirred for 16 h. The excess of Et_2Zn and Et_3B which was formed were evaporated under high vacuum (0.1 mmHg) at 25 °C. The resulting dialkylzinc was dissolved in toluene (5 mL) and stirred for 10 min then was evaporated under high vacuum. The process (addition of toluene (5 mL), then pumping off) was repeated 2 times to ensure the removal of residual Et_2Zn. The resulting dialkylzinc was dissolved in THF (5 mL) and titrated yielding the dialkylzinc **71** as a solution in THF.

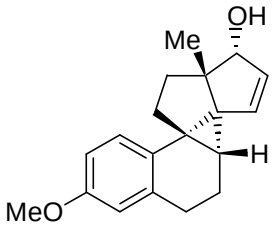
(1*R*, 2*R*)-*tert*-Butyl({3-iodo-2-[2-(6-methoxy-3,4-dihydronaphthalen-1-yl)ethyl]-2-methyl-cyclopent-3-en-1-yl}oxy)dimethylsilane (82)



A flame-dried round bottom flask equipped with a magnetic stirring bar, an argon inlet and a rubber septum was charged with a CuCN·2LiCl solution (1.0 M in THF, 2.40 mL, 2.40 mmol, 2.40 equiv). The solution was cooled to 0 °C in an ice bath, and then the dialkylzinc **71** (2.40 M in THF, 1.0 mL, 2.40 mmol, 2.40 equiv) was added. The reaction mixture was stirred at 0 °C for 30 min. The ice bath was removed then the solution of (1*R*, 4*R*)-**78b** (548 mg, 1.0 mmol) in THF (2 mL) was added dropwise at 25 °C. The reaction mixture was stirred at 25 °C. The complete consumption of the starting material was checked by TLC. The reaction mixture was poured into a saturated NH_4Cl solution (contained 25 % of aqueous NH_3), extracted with Et_2O (3 x 25 mL). The combined organic phase was washed with brine and dried over $MgSO_4$. After purification by column chromatography (silica gel, 5% CH_2Cl_2:pentane), the product (1*R*, 2*R*)-**82** was obtained as a colourless oil (346 mg, 66% yield).

HPLC (Determined for the resulting alcohol) (Chiralcel OJ, heptane:*i*-PrOH = 85:15, 0.5 mL/min); t_R (min) = 16.134 (minor), 18.919 (major), 97% *ee*.
$[\alpha]_D^{20}$ –10.4 (c 0.365, Et_2O)
^{1}H NMR (for the resulting alcohol) (C_6D_6, 400 MHz): δ = 7.31 (d, *J* = 8.38 Hz, 1H), 6.53 (dd, *J* = 2.61, 8.38 Hz, 1H), 6.47 (d, *J* = 2.61 Hz, 1H), 5.55-5.52 (m, 1H), 5.52-5.48 (m, 1H), 3.46-3.39 (m, 1H), 3.11 (s, 3H), 2.46-2.35 (m, 1H), 2.35-2.23 (m, 3H), 1.88 (ddd, *J* = 2.81, 7.70, 16.00 Hz, 1H), 1.84-1.76 (m, 2H), 1.69 (ddd, *J* = 2.22, 6.10, 16.00 Hz, 1H), 1.53-1.36 (m, 2H), 0.87 (br, s, 1H), 0.62 (s, 3H) ppm.
^{13}C NMR (for the resulting alcohol) (C_6D_6, 100 MHz): δ = 158.9, 138.7, 137.6, 135.7, 128.4, 124.8, 122.3, 114.2, 111.3, 108.6, 76.7, 54.6, 54.4, 42.4, 35.3, 29.2, 28.7, 26.1, 23.4 ppm.
IR (neat): 2927 (m), 1606 (w), 1499 (w), 1249 (s), 1114 (s), 861 (s), 835 (s), 774 (s) cm^{-1}.
MS (EI, 70 eV), *m/z* (%): 522 (4), 465 (4), 397 (26), 265 (27), 187 (100), 73 (43).
$C_{25}H_{37}IO_2Si$ HRMS (EI): Calcd.: 522.1451 $[M-H_2]^+$
Found: 522.1428 $[M-H_2]^+$

(6b*R*,8a*S*,9*R*,11a*S*,11b*R*)-4-Methoxy-8a-methyl-1,7,8,8a,9,11b-hexahydro-2*H*-pentaleno-[6a',1':3,1]cyclopropa[1,2-*a*]naphthalen-9-ol (85)

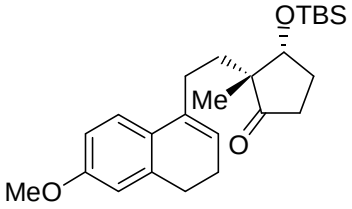


A flame-dried round bottom flask equipped with a magnetic stirring bar, an argon inlet and a rubber septum was charged with the cycloalkenyl iodide (1*R*, 2*R*)-**82** (173 mg, 0.33 mmol) and THF (20 mL). Ph_3P (26 mg, 0.10 mmol, 0.30 equiv), Ag_2CO_3 (100 mg, 0.36 mmol, 1.10

equiv) and $Pd(OAc)_2$ (11 mg, 0.05 mmol, 0.15 equiv) were added to the reaction mixture. The resulting suspension was stirred at 25 °C for 15 min, and then was heated at 65 °C for 16 h. A black suspension resulted after 10-20 min at 65 °C. After GC-analysis of a filtered aliquot showed that the reaction had proceeded to the completion, the suspension was cooled to 25 °C and filtered through a plug of silica gel (Et_2O), and the filtrate was concentrated to give the crude Heck product as a yellow oil. This sample was dissolved in THF (3.3 mL), and a TBAF solution (1.0 M in THF, 1.0 mL) was added at 0 °C. The reaction mixture was stirred at 25 °C for 16 h and quenched with a saturated NH_4Cl solution. The mixture was extracted with Et_2O (3 x 25 mL). The combined organic phase was washed with brine and dried over Na_2SO_4. The crude product was purified by column chromatography (silica gel, 40% Et_2O:pentane) to provide the product **85** as a colourless oil (53 mg, 57% yield).
The product decomposes slowly in a chloroform solution.

^{1}H NMR (C_6D_6, 400 MHz): δ = 7.26 (d, *J* = 9.39 Hz, 1H), 6.67-6.63 (m, 2H), 5.60 (dd, *J* = 2.35, 5.87 Hz, 1H), 5.48 (d, *J* = 5.87 Hz, 1H), 3.89 (br, s, 1H), 3.31 (s, 3H), 2.75-2.63 (m, 1H), 2.61-2.50 (m, 1H, 2.31-2.21 (m, 1H), 2.13-2.03 (m, 1H), 1.96-1.85 (m, 2H), 1.66-1.55 (m, 1H), 1.42 (dd, *J* = 5.09, 7.04 Hz, 1H), 1.09-0.97 (m, 1H), 0.85 (s, 3H), 0.79 (br, s, 1H) ppm.
^{13}C NMR (C_6D_6, 100 MHz): δ = 157.7, 138.0, 134.9, 132.5, 129.6, 128.4, 114.2, 112.1, 81.9, 57.5, 55.3, 54.6, 37.0, 35.1, 30.3, 29.2, 25.1, 23.1, 22.2 ppm.
IR (neat): 3386 (br), 2930 (m), 1725 (m), 1606 (m), 1497 (m), 1454 (m), 1243 (s), 1111 (s), 1034 (s), 811 (s), 734 (s) cm^{-1}.
MS (EI, 70 eV), *m/z* (%): 282 (M^+, 7), 264 (100), 249 (57), 234 (16), 221 (10), 202 (17), 189 (12), 178 (12), 165 (16), 152 (9), 141 (7), 128 (12), 115 (15), 101 (7), 91 (11).
$C_{19}H_{22}O_2$ HRMS (EI): Calcd.: 282.1620
Found: 282.1628

(2*R*,3*R*)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-2-[2-(6-methoxy-3,4-dihydronaphthalen-1-yl)-ethyl]-2-methylcyclopentanone (87)

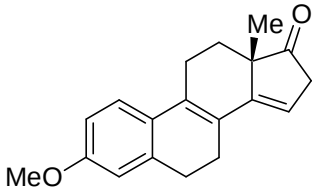


A flame-dried round bottom flask equipped with a magnetic stirring bar, an argon inlet and a rubber septum was charged with the cycloalkenyl iodide **82** (131 mg, 0.25 mmol) and THF (2 mL). The reaction mixture was cooled to –78 °C, and then *t*-BuLi (1.53 M in pentane, 0.50 mmol, 0.33 mL) was added dropwise. The reaction mixture was stirred at –78 °C for 30 min, and then $B(OMe)_3$ (neat, 70 µL, 0.63 mmol) was added dropwise. The reaction mixture was stirred at temperatures from –78 °C to 25 °C for 24 h, then a suspension of $NaBO_3 \cdot 4H_2O$ (385 mg, 2.50 mmol) in H_2O (3 mL) was added at 25 °C. After stirring at 25 °C for 24 h, the reaction mixture was poured into water, extracted with Et_2O (3 x 25 mL). The combined organic phase was washed with brine and dried over $MgSO_4$. The solvents were evaporated and the crude product was purified by column chromatography (silica gel, 10% Et_2O:pentane, 0.1% Et_3N) to yield the ketone (2*R*, 3*R*)-**87** as a colourless oil (46 mg, 45% yield).

$[\alpha]_D^{20}$ +4.2 (c 0.29, CH_2Cl_2)
^{1}H NMR (C_6D_6, 300 MHz): δ = 7.68 (d, *J* = 8.82 Hz, 1H), 6.75 (dd, *J* = 2.65, 8.82 Hz, 1H), 6.57 (d, *J* = 2.65 Hz, 1H), 6.15-6.05 (m, 1H), 3.80 (t, *J* = 5.29 Hz, 1H), 3.34 (s, 3H), 2.60-2.49

(m, 4H), 2.49-2.35 (m, 2H), 2.30-2.15 (m, 1H), 1.98-1.82 (m, 1H), 1.75-1.57 (m, 4H), 0.92 (s, 3H), 0.90 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H) ppm.
^{13}C NMR (C_6D_6, 75 MHz): δ = 221.85, 163.01, 142.72, 140.11, 133.59, 129.32, 121.64, 117.51, 116.81, 82.33, 58.61, 57.80, 38.22, 34.98, 33.71, 32.50, 30.93, 29.80 (3 carbons), 27.50, 23.89, 22.05, –0.38, –0.90 ppm.
IR (neat): 2929 (m), 1739 (s), 1606 (m), 1496 (m), 1463 (m), 1255 (s), 1157 (m), 1110 (m), 1039 (m), 836 (s), 776 (s) cm^{-1}.
MS (EI, 70 eV), *m/z* (%): 414 (M^+, 8), 187 (100), 174 (2), 161 (2), 146 (2), 73 (2).
$C_{25}H_{38}O_3Si$ HRMS (EI): Calcd.: 414.2590
Found: 414.2571

3-Methoxyestra-1(10),2,4,8,14-pentaen-17-one (Torgov diene) (67)



A flame-dried round bottom flask equipped with a magnetic stirring bar, an argon inlet and a rubber septum was charged with the ketone (2*R*, 3*R*)-**87** (40 mg, 0.10 mmol), dry benzene (10 mL) and anhydrous *p*-TsOH (114 mg). The reaction mixture was stirred at 25 °C for 12 h then was diluted with Et_2O, washed with 5% Na_2CO_3, and dried over $MgSO_4$.
The crude product was dissolved in THF (1 mL) and cooled to 0 °C. A TBAF solution (1.0 M in THF, 0.2 mL) was added to the reaction mixture. The reaction mixture was stirred at 25 °C for 16 h then was poured into a saturated NH_4Cl solution, extracted with Et_2O (3 x 10 mL). The combined organic phase was washed with brine and dried over Na_2SO_4.
The crude alcohol was dissolved in Et_2O (4 mL) and CH_2Cl_2 (12 mL). The reaction mixture was cooled to 0 °C. To the mixture were added *Celite* (77 mg) and CrO_3 (30 mg). The reaction mixture was stirred at 25 °C for 12 h. The resulting suspension was filtered and washed with Et_2O. The solvents were evaporated. The crude product was purified by column chromatography (silica gel, 20% Et_2O:pentane) affording the Torgov diene (**67**) as a yellow solid (17 mg, 61% yield).

mp = 141-144 °C (Lit.: **mp** = 144-145 °C)[96, 99]
HPLC (Chiralcel OJ, heptane:*i*-PrOH = 80:20, 0.5 mL/min); t_R (min) = 19.896 (major), 38.345 (major); 99% *ee*.
$[\alpha]_D^{20}$ = –95.6 (c 0.50, $CHCl_3$) (Lit.: $[\alpha]_D^{20}$ = –102.6 (c 0.904, $CHCl_3$)[96, 99]
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.24 (d, *J* = 8.22 Hz, 1H), 6.76-6.70 (m, 2H), 5.85 (t, *J* = 2.54 Hz, 1H), 3.80 (s, 3H), 3.30 (d, *J* = 23.48 Hz, 1H), 2.92 (dd, *J* = 3.13, 23.48 Hz, 1H), 2.82-2.75 (m, 2H), 2.68-2.54 (m, 3H), 2.35-2.24 (m, 1H), 2.06-1.99 (m, 1H), 1.63-1.53 (m, 1H), 1.13 (s, 3H) ppm.
^{13}C NMR ($CDCl_3$, 100 MHz): δ = 220.18, 158.91, 147.15, 138.40, 130.09, 128.83, 125.55, 124.35, 114.89, 113.86, 111.38, 55.50, 49.27, 42.17, 28.67, 27.57, 23.18, 22.98, 20.81 ppm.
IR (neat): 1735 (s), 1425 (m), 1250 (s), 1139 (s), 1037 (s), 816 (s), 792 (s) cm^{-1}.
MS (EI, 70 eV), *m/z* (%): 280 (M^+, 91), 252 (100), 237 (30), 223 (10), 165 (8).
$C_{19}H_{20}O_2$ HRMS (EI): Calcd.: 280.1463
Found: 280.1454

6. Abbreviations

Ac	acetyl
br	broad
t-Bu	*tert*-butyl
cat.	catalytic
c-Hex	cyclohexyl
^{o} C	degree celcius
d	doublet
δ	chemical shift
DEAD	diethyl azodicarboxylate
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethylsulfoxide
dppf	1,1´-bisdiphenylphosphinoferrocene
dba	dibenzylideneacetone
ee	enantiomeric excess
equiv.	equivalent
Et	ethyl
EtOAc	ethyl acetate
EI	electron ionization
FG	functional group
GC	gas chromatography
h	hour
HPLC	high-pressure liquid chromatography
HRMS	high resolution mass spectroscopy
Hz	herz
i-Pr	isopropyl
IR	infrared spectroscopy
J	coupling constant
LG	leaving group
m	multiplet
M	molar
Me	methyl
min.	minute
mp.	melting point
MMPP	magnesium methylperphtalate
MS	mass spectroscopy
M^{+}	molecular ion peak
mmol	millimole
NMP	*N*-methyl-pyrrolidinone
NMR	nuclear magnetic resonance
Nu	nucleophile
PDC	pyridinium dichlorochromate
Pent	pentyl
PG	protecting group
Ph	phenyl
py	pyridine
q	quartet
quant.	quantitative
rac	racemic

s	singlet
t	triplet
THF	tetrahydrofuran
TLC	thin layer chromatography
TMSCl	chlorotrimethylsilane
TP	typical procedure
t_R	retention time

Curriculum vitae

Name: Darunee Soorukram
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Education Background

06/2003-present: **Ph.D. student** at the Ludwig-Maximilians-University, Munich, Germany under the guidance of Prof. Dr. Paul Knochel
Thesis title: "Copper(I)-Mediated Regio- and Stereoselective Allylic Substitution Reactions and Their Applications to Natural Product Syntheses"

2000-2003: **Master of Science** (Organic Chemistry) at Mahidol University, Bangkok, Thailand under the guidance of Prof. Dr. Manat Pohmakotr
Thesis title: "Reactions of Vicinal Dianion of Chiral Succinic Acid Derivatives"
Scholarships:
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1996-1999: **Bachelor of Science** (Chemistry) at Khon Kaen University, Thailand
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Publications

[1] Pohmakotr, M.; Soorukram, D.; Tuchinda, P.; Prabpai, S.; Kongsaeree, P.; Reutrakul, V., "Highly diastereoselective alkylation of vicinal dianions of chiral succinic acid derivatives: a new general strategy to (*R*)-β-arylmethyl-γ-butyrolactones" *Tetrahedron Lett*. **2004**, *45*, 4315-4318.

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[5] Soorukram, D.; Knochel, P., "A Practical Synthesis of Optically Active Chiral Ketones in High Enantiomeric Excess" *Synthesis (accepted)*.

[6] Soorukram, D.; Knochel, P., "Enantioselective Synthesis of (+)-Estrone" (*manuscript submitted for publication*).

[7] Soorukram, D.; Metzger, A.; Knochel, P., "Copper-Mediated Stereoselective Allylic Substitution Reactions" (*manuscript in preparation*).

Oral communication and poster presentations

[1] Soorukram, D.; Knochel, P.; "Stereoselective Allylic Substitutions of Functionalized Zinc Organometallic" Poster at OMCOS13, 17 -21 July, 2005, Geneva, Switzerland
[2] 9. International SFB-Symposium, 10-11 October, 2005, Aachen, Germany
[3] "Formal Total Synthesis of (+)-Estrone via Asymmetric Allylic Substitution" Oral presentation, 2006, Ludwig-Maximilians-Universität, Munich, Germany
[4] Soorukram, D.; Knochel, P.; "Copper Catalyzed Preparation of Ketones bearing an α-Stereogenic Center" Poster at 1st European Chemistry Congress, 27-31 August, 2006, Budapest, Hungary

Languages

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English	Fluent written and spoken
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