Natural Product Synthesis

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A Convergent and Stereoselective Synthesis of the Glycolipid Components Phthioceranic Acid and Hydroxyphthioceranic Acid**

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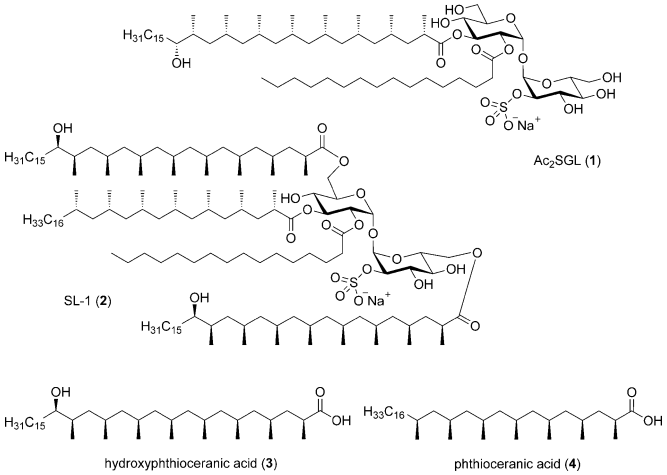
Approximately one-third of the world population, primarily in developing nations, is infected with the pathogenic germ *Mycobacterium tuberculosis*, the causative agent of tuberculosis and annually more than 1.4 million people die from this disease.[1] Tremendous effort is being invested in the search for new and effective antibiotics to combat acute and dangerous life-threatening infections. However, just as important are further studies towards a better understanding of the underlying molecular-biological processes, ideally giving rise to an effective vaccine in the long term.[2]

One approach towards this goal takes advantage of the special structure of the cell wall of *M. tuberculosis*, which consists in part of glycolipids with long-chain fatty acids.[3] Two prominent representatives of this substance class are the sulfoglycolipids Ac_2SGL (**1**) and SL-1 (**2**), featuring a 2-sulfated trehalose as a central carbohydrate, which is acylated two or four times, respectively (Scheme 1). In addition to palmitinic acid, the polymethylated C_{32} and C_{30} fatty acids hydroxyphthioceranic acid (**3**) and phthioceranic acid (**4**) were also found in these rather uncommon glycolipids.[4] Studies revealed that at least **1**, possibly **2** as well, is a potentional antigen for a specific immune response towards *M. tuberculosis*. It was shown to stimulate T-cells for the production of γ-interferon for discovering and killing cells that are infected with *M. tuberculosis*.[5] The special methyl substitution in **3** and **4** as well as its relative position in the trehalose core regulates the specific identification of Ac_2SGL-specific T-cells. At least two methyl substituents are necessary for successful stimulation. Based upon this knowledge, sulfoglycolipids like **1** and **2** have been proposed as promising components of a possible vaccine against *M. tuberculosis*.

The main challenge for chemists pursuing a total synthesis of **1** or **2** is the stereoselective preparation of the polydeoxypropionates **3** and **4**. Pioneering work in this area was accomplished by the group of Minnaard and Feringa, who not only reported the first synthesis of **3** and **4**, but additionally synthesized the complete sulfoglycolipid Ac_2SGL (**1**).[6]



Scheme 1. Sulfoglycolipids Ac_2SGL (**1**) and SL-1 (**2**) and the polydeoxypropionates hydroxyphthioceranic acid (**3**) and phthioceranic acid (**4**).

In general, polydeoxypropionates are important structural motifs found in many natural products with completely different biological activities and origins.[7] Numerous efficient synthetic strategies have been developed for their highly selective formation.[8] As a general feature all these methods share a linear-iterative principle: one deoxypropionate unit after the other is typically attached to the growing alkyl chain in the carbon–carbon bond-forming event. For the conversion of the product of the previous cycle into the substrate for the next cycle additional transformations have to be performed, however, which affect the overall yield, efficiency, and atom-economy of the processes, in particular for long-chain polydeoxypropionates. The sole exception in this respect is the methodology of Micalizio et al.,[9] who reported the synthesis of smaller polydeoxypropionates through a convergent alkyne/allylic alcohol cross-coupling with subsequent substrate-controlled asymmetric hydrogenation.

We herein report the first convergent, conceptually novel synthesis of the two glycolipid components hydroxyphthioceranic acid (**3**) and phthioceranic acid (**4**), which is based on our recently developed, noniterative strategy for the stereochemically flexible construction of trideoxypropionates **6** (Scheme 2).[10] This methodology relies on a highly stereoselective and high-yielding three-step reaction sequence comprising an oxy-Cope rearrangement of aldol product **5**,

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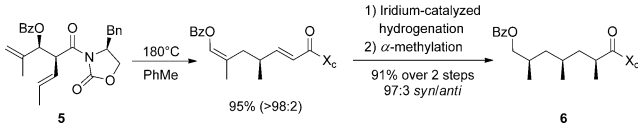
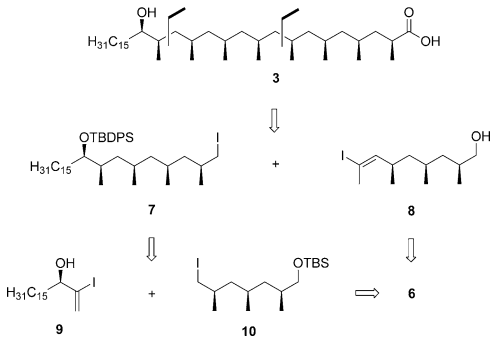


Scheme 2. Stereoselective synthesis of trideoxypropionates **6**.[10] X_c = chiral auxiliary.

hydrogenation of the enol ester, and auxiliary-controlled enolate methylation.

Our synthesis of hydroxyphthioceranic acid (**3**) is based on the convergent assembly of three building blocks **8**–**10** of similar size and complexity. It was planned to link them through two cross-coupling reactions with subsequent stereoselective hydrogenations to afford the complete carbon framework of **3** (Scheme 3). Both **8** and **10** should be

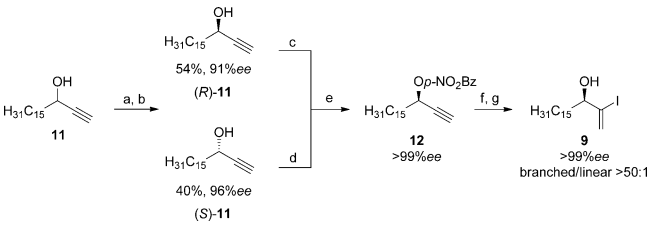


Scheme 3. Strategy for the convergent synthesis of hydroxyphthioceranic acid (**3**). TBDPS = *tert*-butyldiphenylsilyl, TBS = *tert*-butyldimethylsilyl.

accessible from trideoxypropionate **6** in only a few steps. As the starting point of the synthesis a Suzuki–Miyaura reaction[11] of iodo-substituted allylic alcohol **9** and trideoxypropionate **10** was envisioned. We expected the subsequent hydrogenation of the *exo*-methylene group to be stereoselective and substrate-controlled such that the C_9–C_{32} fragment **7** would be obtained with the correct absolute configuration. Finally, **7** was to be coupled with vinyl iodide **8** in a second Suzuki–Miyaura reaction to link the remaining C_1–C_8 fragment.

For the synthesis of the enantiomerically pure iodo-substituted allylic alcohol **9** an enzymatic kinetic resolution[12] of the readily available propargylic alcohol **11** proved to be particularly practical, selective, and efficient (Scheme 4). With the commercially available Novozym 435 both enantiomers of **11** could be obtained in very good overall yield and optical purity.

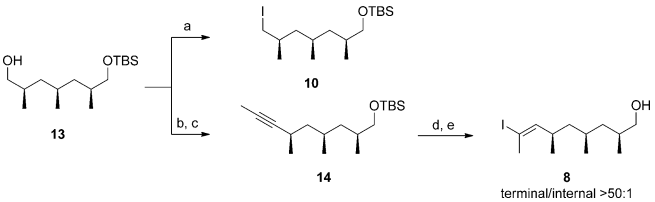
Mitsunobu inversion of the *S* enantiomer with *p*-nitrobenzoic acid and DIAD, as well as esterification of the *R* enantiomer with *p*-NO_2BzCl afforded the common ester **12** which was recrystallized to enantiomerically pure form (> 99 % *ee*) with a total yield of 69 % starting from **11**. This sequence was easily accomplished on a multigram scale and routinely afforded 10–20 g amounts of the desired product. Regioselective, substrate-controlled hydrozirconation of the



Scheme 4. a) CAL-B, vinyl acetate, hexane, RT; b) acetyl *S* enantiomer, NaOH, MeOH/H_2O, reflux; c) *p*-NO_2BzCl, pyridine, CH_2Cl_2, 0 °C, 96 %; d) *p*-NO_2BzOH, PPh_3, diisopropyl azodicarboxylate (DIAD), THF, 0 °C to RT, 84 %; e) recrystallization from hexane, 73 %; f) NaOH, MeOH/H_2O, reflux, 94 %; g) 1. MeLi, THF, −20 °C to RT; [Cp_2ZrHCl]/$ZnCl_2$, THF, 40 °C; 2. I_2, THF, 0 °C, 70 %.

free propargylic alcohol (*R*)-**11** was accomplished according to the protocol of Ready and Zhang[13] with the assistance of a [Cp_2ZrHCl]/$ZnCl_2$ complex. After subsequent iodination the branched vinyl iodide **9** was obtained in 70 % yield and with > 99 % *ee*, without observation of the linear regioisomer.

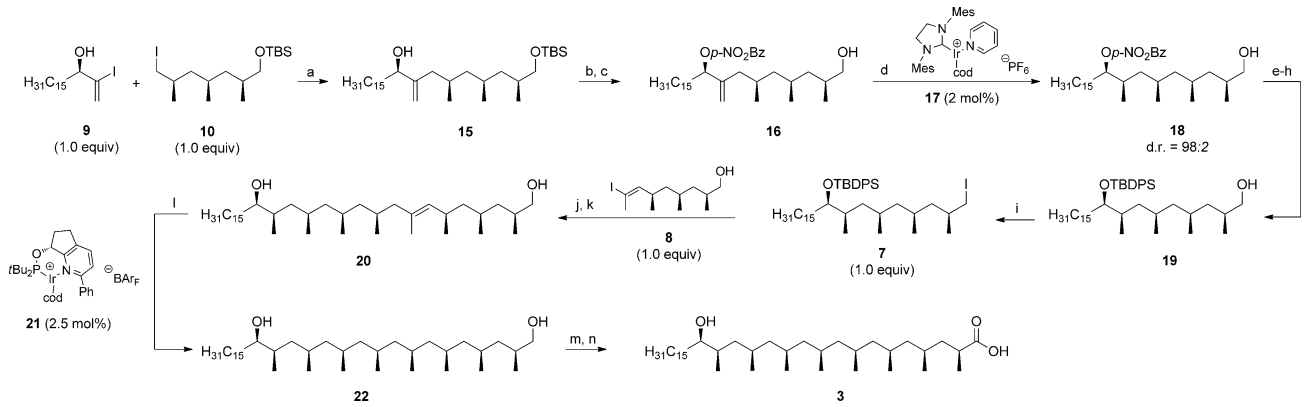
The two building blocks **8** and **10** were accessible from the common intermediate **13**[10b] in only a few steps (Scheme 5). Simple iodination gave **10** almost quantitatively. A second



Scheme 5. a) PPh_3, imidazole, I_2, Et_2O/CH_3CN, 0 °C, 98 %; b) 1. 1-hydroxy-1,2-benziodoxol-3(1H)-one 1-oxide (IBX), DMSO/THF, RT; 2. Bestmann–Ohira reagent, NaOMe, THF, −78 °C; then aldehyde, THF, −78 °C to 0 °C, 88 % over 2 steps; c) 1. *n*BuLi, THF, −78 °C; 2. MeI, dimethylhexahydro-2-pyrimidinone (DMPU), −78 °C to RT, 97 %; d) 1. [Cp_2ZrHCl], THF, RT; 2. I_2, THF, RT; 86 %; e) tetrabutylammonium fluoride (TBAF), THF, RT, 98 %.

equivalent of **13** was elongated by one C_2 unit: the internal alkyne **14** was obtained as a single regioisomer in 85 % yield over a sequence of four steps comprising an IBX oxidation, alkynylation with the Bestmann–Ohira reagent,[14] methylation, and hydrozirconation/iodination with the Schwartz reagent. Cleavage of the TBS group finally afforded the second building block **8** for the following Suzuki—Miyaura reaction.

According to conditions developed by Marshall and Lee for similar palladium-catalyzed sp^2–sp^3 cross-coupling reactions,[15] iodide **10** was converted into a reactive alkyllithium–boranate complex through halogen–metal exchange with *t*BuLi and reaction with *B*-OMe-9-BBN.[16] Treatment of this complex with equimolar amounts of vinyl iodide **9** gave rise to the allylic alcohol **15** in 79 % yield under very mild conditions (Scheme 6). Initial efforts to hydrogenate the free allylic alcohol **15**[17] were accompanied by an isomerization to the ketone and resulted only in low selectivity. Thus, **15** was first converted into ester alcohol **16**, whose hydrogenation



Scheme 6. a) 1. **10**, *t*BuLi, Et_2O, −78 °C, then *B*-OMe-9-borabicyclo[3.3.1]nonane (*B*-OMe-9-BBN), THF, −78 °C to RT; *ii:* **9**, K_3PO_4, 5 mol% $[PdCl_2(dppf)]\cdot CH_2Cl_2$, DMF, RT, 79%; dppf = 1,1′-bis(diphenylphosphanyl)ferrocene; b) *p*-NO_2BzCl, CH_2Cl_2, pyridine, 0 °C, 97%; c) tetrabutylammonium tribromide ($TBABr_3$), MeOH, RT, 97%; d) 2 mol% **17**, H_2 (90 bar), CH_2Cl_2, RT, 98%; e) TBSCl, imidazole, 4-dimethylaminopyridine (DMAP), CH_2Cl_2, RT, 99%; f) MeOH, K_2CO_3, 60 °C, 94%; g) TBDPSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 98%; h) $TBABr_3$, MeOH/THF, RT, 99%; i) PPh_3, imidazole, I_2, Et_2O/CH_3CN, RT, 99%; j) 1. *t*BuLi, Et_2O, −78 °C, then *B*-OMe-9-BBN, THF, −78 °C to RT; 2. **8**, K_3PO_4, 5 mol% $[PdCl_2(dppf)]\cdot CH_2Cl_2$, DMF, RT, 85%; k) TBAF, THF, RT, 94%; l) 2.5 mol% **21**, H_2 (60 bar), CH_2Cl_2, RT, 99%; m) $NaHCO_3$, KBr, NaOCl, 2,2,6,6-tetramethylpiperidin-*N*-oxyl (TEMPO) (5 mol%), CH_2Cl_2, 0 °C, 93%; n) *t*BuOH/H_2O/isoprene, $NaClO_2$, NaH_2PO_4, RT, 88%.

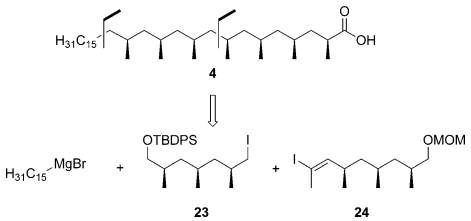
instantly succeeded with the Crabtree catalyst (as BAr_F^- salt) with a diastereoselectivity of 95:5 in favor of the *syn* isomer of **18**. We then turned to the further optimized iridium catalyst ($[Ir(cod)(SIMes)(Pyr)]^+PF_6^-$) (**17**; cod = cyclooctadiene, SIMes = 1,3-dimesitylimidazolin-2-ylidene)[18] carrying an N-heterocyclic carbene (NHC) ligand instead of the PCy_3 ligand. With this catalyst the diastereoselectivity increased to 98:2 *syn*/*anti* and the catalyst loading required for full conversion could be lowered to 2 mol%. The relative configuration of **18** was determined by two-dimensional NMR spectroscopy according to the method of Breit et al. (see the Supporting Information).[19]

In order to facilitate the second Suzuki–Miyaura cross-coupling the base-sensitive *p*-nitrobenzoyl group was exchanged for a TBDPS group in **19** which was further converted into iodide **7**. Under the same conditions, which had been proven successfully above, the sp^2–sp^3 cross-coupling of alkyl iodide **7** and vinyl iodide **8** delivered the product in 85% yield. Once again, an excess of one of the substrates was not necessary and after cleavage of the silyl ether, alkene **20** was obtained in very good yield and as a single stereoisomer.

In order to establish the last stereogenic center in the carbon backbone of the natural product, the trisubstituted alkene **20** needed to be hydrogenated with full stereochemical control. For this purpose we intended to use our experience in the enantioselective hydrogenations of unfunctionalized, trisubstituted alkenes with chiral iridium pyridyl phosphinite complexes.[20,21] In the event, alkene **20** was hydrogenated with the assistance of the chiral iridium complex **21** (2.5 mol%) to afford the all-*syn*-configured alkane **22** with complete diastereoselectivity and excellent yield in direct analogy to γ-tocotrienyl acetate.[21] Again, the relative configuration of **22** was assigned with the method of Breit[19] and was in agreement with the observed asymmetric induction in hydrogenations of structurally similar, trisubstituted alkenes.[20b–d] Final oxidation of hydroxyphthioceranol (**22**) in a two-step process consisting of TEMPO and Pinnick oxidation furnished hydroxyphthioceranic acid (**3**) in 82% yield. Thus, the natural product was produced in 23 steps along the longest linear route and 25% overall yield (starting with the *N*-acylated Evans auxilary) and on a practical half-gram-scale.

For the synthesis of phthioceranic acid (**4**) we pursued a slightly modified strategy because this natural product has both one hydroxy group and one deoxypropionate unit less than **3**. At the same time we intended to demonstrate the flexibility of our strategy. The key step for the assembly of the polydeoxypropionate backbone of **4** should be the sp^2–sp^3 Suzuki–Miyaura cross-coupling of building blocks **23** and **24** with subsequent hydrogenation, reactions that had served so well in the synthesis of hydroxyphthioceranic acid (Scheme 7). The terminal vinyl iodide **24** is identical to building block **8** used in the synthesis of **3** except for the MOM group. Alkyl iodide **23** differs from the coupling partner **10** employed in the previous synthesis in terms of the exchanged functional groups at the termini. This was done since it seemed easier now to first join building blocks **23** and **24** and complete the polydeoxypropionate fragment of the natural product before attaching the long, lipophilic alkyl chain in a copper-catalyzed Grignard reaction.

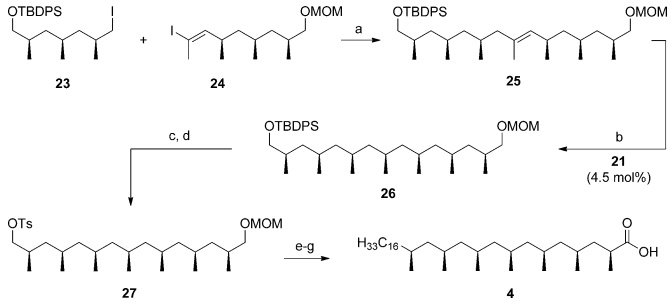
Owing to the bifunctional character of trideoxypropionate **6** as starting material this strategic change posed no problems and the envisioned synthesis worked smoothly. Both building blocks **23** and **24** were synthesized in very good overall yields



Scheme 7. Strategy for the convergent synthesis of phthioceranic acid (**4**). MOM = methoxymethyl.

according to the strategy described above for building blocks **8** and **10** (for details see the Supporting Information).

The Suzuki–Miyaura-reaction of alkyl iodide **23** and vinyl iodide **24** was accomplished as described above and furnished alkene **25** in excellent yield (Scheme 8). In the second key step alkene **25** was hydrogenated to give alkane **26** in high yield and 92:8 *syn*/*anti* diastereoselectivity employing 4.5 mol% of the chiral iridium catalyst **21**. Small amounts of



Scheme 8. a) 1. **23**, *t*BuLi, Et_2O, −78 °C, then *B*-OMe-9-BBN, THF, −78 °C to RT; 2. **24**, K_3PO_4, 5 mol% $[PdCl_2(dppf)]\cdot CH_2Cl_2$, DMF, RT, 92%; b) 4.5 mol% **21**, H_2 (85 bar), CH_2Cl_2, RT, 94% (92:8 d.r.); c) TBAF, THF, RT, 95%; d) TsCl, CH_2Cl_2/pyridine, DMAP, RT, 92%; e) $C_{15}H_{31}MgBr$, 8 mol% Li_2CuCl_4, Et_2O, RT, 76%; f) $(CH_2Cl)_2$/MeOH, cat. HCl, 70 °C, 96%; g) $RuCl_3$, $NaIO_4$, CH_3CN/CCl_4, 85%.

the minor diastereomer were easily separated in the following reaction steps by column chromatography. Finally, **26** was converted into tosylate **27** and the C_{15} alkyl chain was introduced through a copper-catalyzed Grignard addition with the third building block. MOM deprotection and oxidation of the primary alcohol to the carboxylic acid[6a] completed the synthesis of phthioceranic acid (**4**) with a total yield of 21% over the longest linear route of 19 steps.

In conclusion, we have developed the first convergent total syntheses of the glycolipid components hydroxyphthioceranic acid (**3**) and phthioceranic acid (**4**) providing these natural products with high efficiency and stereoselectivity and in preparatively useful amounts. Key steps of our strategy are two palladium-catalyzed Suzuki–Miyaura reactions to couple three single building blocks, respectively, with subsequent catalyst-controlled and highly diastereoselective hydrogenations. The trideoxypropionate **6** employed as the starting material in our syntheses is easily accessible on large scale through a sequence of an oxy-Cope rearrangement, hydrogenation, and enolate methylation which establish most of the stereogenic centers in the products **3** and **4**. We believe that our conceptually novel strategy not only provides an efficient, selective, and rapid access towards the target compounds, but also holds great potential for the synthesis of other natural products especially those with very long polydeoxypropionate chains.

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[1] W. H. Organization, *Global Tuberculosis Report* **2012**.
[2] M. J. Bannon, *Arch. Dis. Child.* **1999**, *80*, 80–83.
[3] a) D. E. Minnikin, L. Kremer, L. G. Dover, G. S. Besra, *Chem. Biol.* **2002**, *9*, 545–553; b) M. Jackson, G. Stadthagen, B. Gicquel, *Tuberculosis* **2007**, *87*, 78–86.
[4] M. B. Goren, O. Brokl, B. C. Das, E. Lederer, *Biochemistry* **1971**, *10*, 72–81.
[5] J. Guiard, A. Collmann, L. F. Garcia-Alles, L. Mourey, T. Brando, L. Mori, M. Gilleron, J. Prandi, G. De Libero, G. Puzo, *J. Immunol.* **2009**, *182*, 7030–7037.
[6] a) B. ter Horst, B. L. Feringa, A. J. Minnaard, *Org. Lett.* **2007**, *9*, 3013–3015; b) D. Geerdink, B. ter Horst, M. Lepore, L. Mori, G. Puzo, A. K. H. Hirsch, M. Gilleron, G. De Libero, A. J. Minnaard, *Chem. Sci.* **2013**, *4*, 709–716; for a synthesis of a SL-1 (**2**)-analogue see: c) C. D. Leigh, C. R. Bertozzi, *J. Org. Chem.* **2008**, *73*, 1008–1017.
[7] a) S. Omura, H. Tanaka in *Antibiotics: Chemistry, Biology and Practice* (Ed.: S. Omura), Academic Press, New York, **1984**, pp. 351–404; b) L. Katz, *Chem. Rev.* **1997**, *97*, 2557–2576.
[8] For excellent review articles see: a) S. Hanessian, S. Giroux, V. Mascitti, *Synthesis* **2006**, 1057–1076; b) B. ter Horst, B. L. Feringa, A. J. Minnaard, *Chem. Commun.* **2010**, *46*, 2535–2547; for a selection of recent reports see e.g.: c) B. Breit, C. Herber, *Angew. Chem.* **2004**, *116*, 3878–3880; *Angew. Chem. Int. Ed.* **2004**, *43*, 3790–3792; d) T. Sugimura, Y. Sato, C. Y. Im, T. Okuyama, *Org. Lett.* **2004**, *6*, 4439–4442; e) R. Des Mazery, M. Pullez, F. Lopez, S. R. Harutyunyan, A. J. Minnard, B. L. Feringa, *J. Am. Chem. Soc.* **2005**, *127*, 9966–9967; f) T. Novak, Z. Tan, B. Liang, E. Negishi, *J. Am. Chem. Soc.* **2005**, *127*, 2838–2839; g) C. Herber, B. Breit, *Angew. Chem.* **2005**, *117*, 5401–5403; *Angew. Chem. Int. Ed.* **2005**, *44*, 5267–5269; h) B. Liang, T. Novak, Z. Tan, E. Negishi, *J. Am. Chem. Soc.* **2006**, *128*, 2770–2771; i) B. ter Horst, B. L. Feringa, A. J. Minnaard, *Chem. Commun.* **2007**, 489–491; j) J. Zhou, K. Burgess, *Angew. Chem.* **2007**, *119*, 1147–1149; *Angew. Chem. Int. Ed.* **2007**, *46*, 1129–1131; k) J. Zhou, Y. Zhu, K. Burgess, *Org. Lett.* **2007**, *9*, 1391–1393; l) J. Zhou, J. W. Ogle, Y. Fan, V. Banphavichit, Y. Zhu, K. Burgess, *Chem. Eur. J.* **2007**, *13*, 7162–7170; m) M. J. Cook, T. Rovis, *J. Am. Chem. Soc.* **2007**, *129*, 9302–9303; n) T.-K. Lum, S. Y. Wang, T.-P. Loh, *Org. Lett.* **2008**, *10*, 761–764; o) G. Zhu, B. Liang, E. Negishi, *Org. Lett.* **2008**, *10*, 1099–1101; p) G. J. Brand, C. Studte, B. Breit, *Org. Lett.* **2009**, *11*, 4668–4670; q) Y. Schmidt, B. Breit, *Org. Lett.* **2009**, *11*, 4767–4769.
[9] a) P. S. Diez, G. C. Micalizio, *Angew. Chem.* **2012**, *124*, 5242–5246; *Angew. Chem. Int. Ed.* **2012**, *51*, 5152–5156.
[10] a) C. F. Weise, M. Pischl, A. Pfaltz, C. Schneider, *Chem. Commun.* **2011**, *47*, 3248–3250; b) C. F. Weise, M. C. Pischl, A. Pfaltz, C. Schneider, *J. Org. Chem.* **2012**, *77*, 1477–1488.
[11] Reviews: a) N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457–2483; b) S. R. Chemler, D. Trauner, S. J. Danishefsky, *Angew. Chem.* **2001**, *113*, 4676–4701; *Angew. Chem. Int. Ed.* **2001**, *40*, 4544–4568.
[12] C. Raminelli, J. V. Comasseto, L. H. Andrade, A. L. M. Porto, *Tetrahedron: Asymmetry* **2004**, *15*, 3117–3122.
[13] D. Zhang, J. M. Ready, *J. Am. Chem. Soc.* **2007**, *129*, 12088–12089.
[14] S. Müller, B. Liepold, G. J. Roth, H. J. Bestmann, *Synlett* **1996**, 521–522.
[15] a) J. A. Marshall, B. A. Johns, *J. Org. Chem.* **1998**, *63*, 7885–7892; b) Y. Yuan, H. Men, C. Lee, *J. Am. Chem. Soc.* **2004**, *126*, 14720–14721.
[16] K. B. Bahnck, S. D. Rychnovsky, *J. Am. Chem. Soc.* **2008**, *130*, 13177–13181.
[17] a) D. A. Evans, M. M. Morrissey, *J. Am. Chem. Soc.* **1984**, *106*, 3866–3868; b) D. A. Evans, M. M. Morrissey, R. L. Dow, *Tetrahedron Lett.* **1985**, *26*, 6005–6008.

[18] a) H. M. Lee, T. Jiang, E. D. Stevens, S. P. Nolan, *Organometallics* **2001**, *20*, 1255 – 1258; b) L. D. Vázquez-Serrano, B. T. Owens, J. M. Buriak, *Chem. Commun.* **2002**, 2518 – 2519.

[19] a) Y. Schmidt, B. Breit, *Org. Lett.* **2010**, *12*, 2218 – 2221b) Y. Schmidt, K. Lehr, L. Colas, B. Breit, *Chem. Eur. J.* **2012**, *18*, 7071 – 7081.

[20] a) S. Kaiser, S. P. Smidt, A. Pfaltz, *Angew. Chem.* **2006**, *118*, 5318 – 5321; *Angew. Chem. Int. Ed.* **2006**, *45*, 5194 – 5197; b) S. Bell, B. Wüstenberg, S. Kaiser, F. Menges, T. Netscher, A. Pfaltz, *Science* **2006**, *311*, 642 – 644; c) A. Wang, B. Wüstenberg, A. Pfaltz, *Angew. Chem.* **2008**, *120*, 2330 – 2332; *Angew. Chem. Int. Ed.* **2008**, *47*, 2298 – 2300; d) see Ref. [8m–o] additionally; for applications in total syntheses see: e) G. G. Bianco, H. M. C. Ferraz, A. M. Costa, L. V. Costa-Lotufo, C. Pessoa, M. O. de Moraes, M. G. Schrems, A. Pfaltz, L. F. Silva, *J. Org. Chem.* **2009**, *74*, 2561 – 2566; f) T. Yoshinari, K. Ohmori, M. G. Schrems, A. Pfaltz, K. Suzuki, *Angew. Chem.* **2010**, *122*, 893 – 897; *Angew. Chem. Int. Ed.* **2010**, *49*, 881 – 885; g) H. J. Jessen, A. Schumacher, F. Schmid, A. Pfaltz, K. Gademann, *Org. Lett.* **2011**, *13*, 4368 – 4370.

[21] Reviews on asymmetric hydrogenations with iridium complexes: a) S. J. Roseblade, A. Pfaltz, *Acc. Chem. Res.* **2007**, *40*, 1402 – 1411; b) T. L. Church, P. G. Andersson, *Coord. Chem. Rev.* **2008**, *252*, 513 – 531; c) D. H. Woodmansee, A. Pfaltz, *Top. Organomet. Chem.* **2011**, *34*, 31 – 76; d) D. H. Woodmansee, A. Pfaltz, *Chem. Commun.* **2011**, *47*, 7912 – 7916; e) A. Cadu, P. G. Andersson, *J. Organomet. Chem.* **2012**, *714*, 3 – 11; f) Y. Zhu, K. Burgess, *Acc. Chem. Res.* **2012**, *45*, 1623 – 1636.

