Asymmetric Hydrogenation

DOI: 10.1002/anie.201307903

Catalytic Asymmetric Hydrogenation of α-CF_3- or β-CF_3-Substituted Acrylic Acids using Rhodium(I) Complexes with a Combination of Chiral and Achiral Ligands**

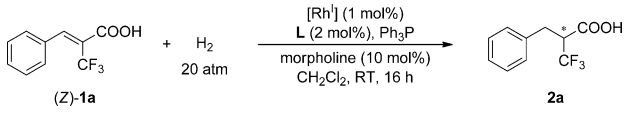
*Kaiwu Dong, Yang Li, Zheng Wang, and Kuiling Ding**

Dedicated to Professor Manfred T. Reetz on the occasion of his 70th birthday

The introduction of trifluoromethyl (CF_3) groups into organic molecules can substantially modify the lipophilicity, metabolic stability, and bioavailability of the biologically interesting molecules, and thus has attracted much attention from synthetic chemists over recent years.[1,2] Optically active carboxylic acids with CF_3 substituents are versatile chiral building blocks for the synthesis of pharmaceuticals, agrochemicals, natural products and fragrances.[3] Accordingly, the development of methodologies for the enantioselective construction of trifluoromethylated carboxylic acid derivatives is highly desirable and has become an important research area.[2] However, the catalytic asymmetric synthesis of optically active α-CF_3- or β-CF_3-substituted propanoic acid derivatives is less explored, with α-trifluoromethylation of some specific carbonyl compounds[4] and conjugate addition of β-trifluoromethylated acrylic acid derivatives being among the few documented examples.[5] In this context, asymmetric hydrogenation (AH) of α- or β-trifluoromethylated acrylic acid derivatives, one of the most straightforward and environmentally benign approaches, still remains a big challenge,[6,7] probably because of the highly electron-withdrawing nature of the CF_3 group in the olefinic substrates, despite the fact that numerous chiral catalysts have been successfully developed for the AH of various nonfluoro-substituted acrylic acids. Even though a few Ru^{II} or Rh^{I} complexes with chiral bisphosphine ligands catalyze the hydrogenation of some specific α-CF_3- or β-CF_3-substituted acrylic acids, the procedures are usually associated with only a single substrate.[6,7] Herein, we report a highly enantioselective AH of a broad range of α-CF_3- or β-CF_3-substituted acrylic acids, using a Rh^{I} complex generated in situ with a mixture of a chiral secondary phosphine oxide (SPO) and an achiral triarylphosphine ligand, as the catalyst.

The research project was inspired by the excellent performance of chiral SPO molecules as preligands in Rh^{I}-catalyzed AHs of a variety of olefinic substrates.[8] The feasibility of using Rh^{I}/SPO-type catalysts in AHs of CF_3-substituted acrylic acid derivatives was first investigated by screening several SPO ligands (**L1**–**L6**) with α-CF_3-substituted cinnamic acid ((*Z*)-**1a**) as a model substrate (Table 1).

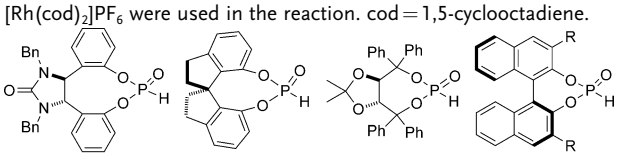
Table 1: Effect of PPh_3 on the Rh^{I}-catalyzed asymmetric hydrogenation of (*Z*)-**1a** in the presence of SPO preligands **L1**–**L6**.[a]



(*Z*)-**1a** → **2a**

Entry	L ([mol%])	Ph_3P [mol%]	Conv. [%][b]	*ee* [%][c]
1	(*S*,*S*)-**L1** (2)	1	30	37 (*S*)
2	(*R*)-**L2** (2)	1	44	58 (*R*)
3	(*R*,*R*)-**L3** (2)	1	95	23 (*S*)
4	(*S*)-**L4** (2)	1	74	11 (*R*)
5	(*S*)-**L5** (2)	1	80	84 (*R*)
6	(*S*)-**L6** (2)	1	82	92 (*R*)
7[d]	(*S*)-**L6** (2)	1	> 99	98 (*R*)

[a] Reaction conditions: 1 mol% $[Rh(cod)_2]BF_4$, [**1a**] = 0.1 M. [b] Determined by ^{19}F NMR spectroscopy. [c] Determined by HPLC on a chiral stationary phase after **2a** was transformed to its corresponding methyl ester with CH_2N_2. The absolute configurations were assigned by comparison of their optical rotations with reported values (see the Supporting Information). [d] The solvent mixture $CHCl_3/H_2O$ (4/1) and $[Rh(cod)_2]PF_6$ were used in the reaction. cod = 1,5-cyclooctadiene.



(*S*,*S*)-**L1** (*R*)-**L2** (*R*,*R*)-**L3** (*S*)-**L4** R = H; (*S*)-**L5** R = Me; (*S*)-**L6** R = Et

As shown in Table S1 in the Supporting Information, only very poor conversions (16 h, < 15%) were obtained under the initially tested conditions, indicating that the complexes generated with Rh^{I} and these SPO ligands are not adequately active for catalysis. Gratifyingly, when we investigated the reaction using Rh^{I} complexes with SPO/PPh_3[9] monodentate ligand mixtures,[10–16] the addition of achiral PPh_3 had a profound influence on the catalysis, as evidenced by the substantial improvement in the catalytic performance (30–95% conversions, 11–92% *ee*, Table 1, entries 1–6). Such a dramatic change in catalytic behavior upon addition of Ph_3P can be attributed to an active Rh^{I} species, coordinated

[*] K. Dong, Y. Li, Dr. Z. Wang, Prof. Dr. K. Ding
State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences
345 Lingling Road, Shanghai 200032 (P. R. China)
E-mail: kding@mail.sioc.ac.cn

[**] We thank the financial support of this work from the Major Basic Research Development Program of China (grant no.2010CB833300), the NSFC (grant nos. 91127041, 21121062, and 21232009), the Chinese Academy of Sciences, and the Science and Technology Commission of Shanghai Municipality.

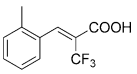
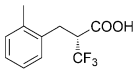
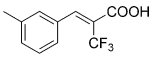
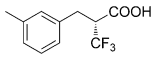
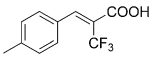
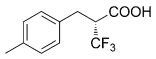
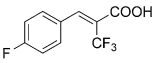
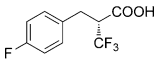
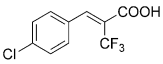
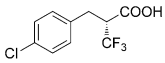
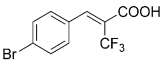
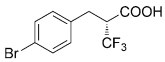
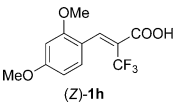
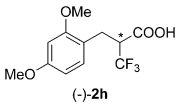
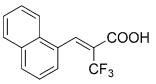
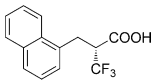
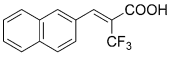
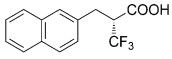
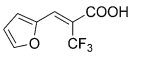
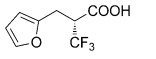
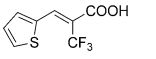
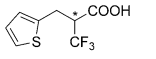
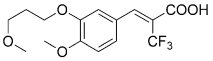
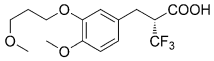
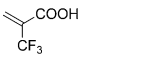
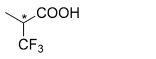
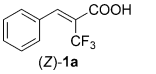
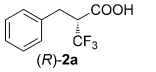
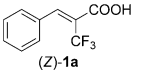
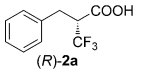
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201307903.

simultaneously with a chiral SPO and an achiral Ph_3P.[9] The screening of achiral triarylphosphine ligands, the change of the Rh^I source, and the variation of the molar ratios of SPO/PPh_3 resulted in the optimized reaction conditions including $CHCl_3$/water (4:1) as solvent mixture at 20 atm of H_2 in the presence of morpholine (0.1 equiv), with the catalyst generated in situ from $[Rh(cod)_2]PF_6$/(*S*)-**L6**/PPh_3 (1:2:1, 1 mol% Rh loading; see the Supporting Information). Under these conditions, full conversion was achieved with 98% *ee* of the corresponding product (*R*)-**2a** (Table 1, entry 7). It should be noted that the addition of water seems to be critical in order to achieve high activity and selectivity. Although the exact underlying reason is not clear yet, we speculate that water helps to break down the $[Rh^I(SPO)_2]$-type complex (e.g., by cleaving the H bond between two SPO ligands),[8,17] thus facilitating the formation of the Rh^I species with both ligands ($[Rh^I(SPO)(Ph_3P)]$), which is responsible for the catalysis.

With the optimal catalyst $[Rh(cod)_2]PF_6$/(*S*)-**L6**/PPh_3 (1:2:1, 1 mol% Rh^I) in hand, we subsequently investigated its use in the reaction of α-CF_3-substituted substrates with various β substituents under the optimized reaction conditions. AHs of α-CF_3-substituted acrylic acid derivatives **1b**–**1n** proceeded smoothly to give the corresponding α-CF_3-substituted propanoic acid derivatives **2b**–**2n** with excellent enantioselectivities (95–99% *ee*; Table 2). It is remarkable that this catalyst system tolerates both electronic and steric modifications of the substituent on the β-aryl rings of the acrylic acids (Table 2, entries 1–9), even though a higher H_2 pressure and longer reaction time are required for sterically hindered substrates ((*Z*)-**1b**, (*Z*)-**1h**, and (*Z*)-**1i**; entries 1, 7, and 8). The AHs of α-CF_3-substituted substrates with β-heteroaryl groups, such as furan-2-yl ((*Z*)-**1k**) or 2-thien-2-yl ((*Z*)-**1l**), were also successful, affording the corresponding propanoic acid derivatives (*R*)-**2k** and (−)-**2l**, respectively, with 97% *ee* (Table 2, entries 10 and 11). The protocol was also successfully applied to the hydrogenation of **1m**, affording an excellent *ee* value (97%) of **2m**, which has much structural resemblance to an important intermediate[3a] of the synthesis of the blood-pressure-lowering drug aliskiren (Table 2, entry 12). Moreover, the hydrogenation of **1n**, a prototype α-CF_3-substituted acrylic acid without a β substituent, afforded the α-CF_3-substituted propanoic acid **2n** with 96% *ee* (Table 2, entry 13). Finally, with a slight modification of the reaction conditions, the catalyst loadings in the hydrogenation of (*Z*)-**1a** could be decreased to 0.1–0.01 mol% (Table 2, entries 14 and 15), still giving the product with 93% *ee*, albeit with only 70% conversion of substrate in the latter case (entry 15).

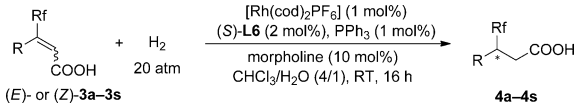
Encouraged by these results, we sought to extend the $[Rh(cod)_2]PF_6$/(*S*)-**L6**/PPh_3 catalyst system to the AH of β-CF_3-substituted acrylic acid derivatives. The reactions were performed under the conditions optimized for (*Z*)-**1a** (Table 3). The catalyst system proved to be quite versatile for this type of substrate, leading to complete the conversion of all tested substrates and affording the corresponding products with excellent *ee* values (92–>99%; Table 3, entries 1–20). For the substrates with an aryl ring at the β position, the electronic nature of the aryl substituent(s) had no obvious effect on the reaction (Table 3, entries 8–12).

Table 2: Rh^I-catalyzed asymmetric hydrogenation of α-CF_3-substituted acrylic acids **1a**–**1n**.[a]

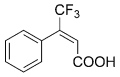
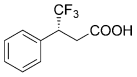
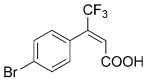
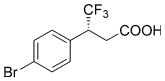
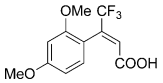
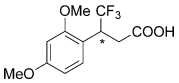
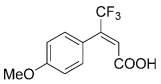
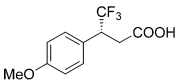
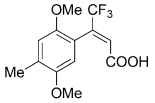
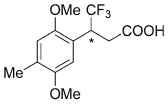
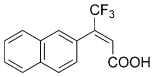
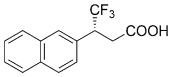
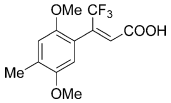
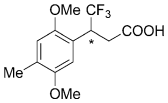
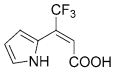
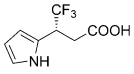
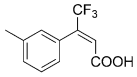
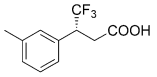
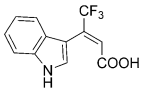
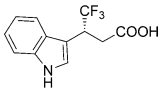
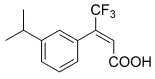
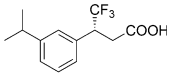
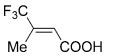
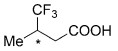
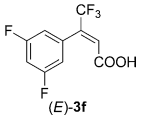
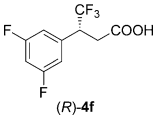
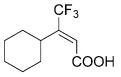
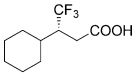
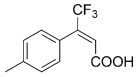
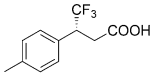
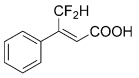
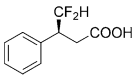
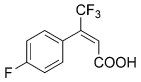
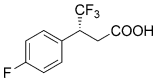
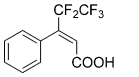
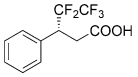
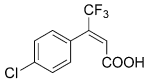
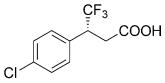
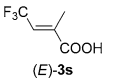
Entry	Substrate	Product	*ee* [%]
1[b]	 (*Z*)-**1b**	 (*R*)-**2b**	98 (*R*)
2	 (*Z*)-**1c**	 (*R*)-**2c**	97 (*R*)
3	 (*Z*)-**1d**	 (*R*)-**2d**	95 (*R*)
4	 (*Z*)-**1e**	 (*R*)-**2e**	97 (*R*)
5	 (*Z*)-**1f**	 (*R*)-**2f**	96 (*R*)
6	 (*Z*)-**1g**	 (*R*)-**2g**	97 (*R*)
7[b]	 (*Z*)-**1h**	 (-)-**2h**	97[f]
8[b]	 (*Z*)-**1i**	 (*R*)-**2i**	99 (*R*)
9	 (*Z*)-**1j**	 (*R*)-**2j**	97 (*R*)
10	 (*Z*)-**1k**	 (*R*)-**2k**	97 (*R*)
11	 (*Z*)-**1l**	 (-)-**2l**	97[f]
12	 (*Z*)-**1m**	 (*R*)-**2m**	97 (*R*)
13[c]	 **1n**	 **2n**	96[f]
14[d]	 (*Z*)-**1a**	 (*R*)-**2a**	93 (*R*)
15[e]	 (*Z*)-**1a**	 (*R*)-**2a**	93 (*R*)

[a] Reaction conditions: [**1**] = 0.10 M. All conversions were higher than 99%, as determined by ^{19}F NMR spectroscopy, unless otherwise noted. The *ee* values were determined by HPLC on a chiral stationary phase after the acids were transformed to their corresponding methyl esters with CH_2N_2, and the absolute configurations of the products were deduced by comparison of their Cotton effects with that of (*R*)-(−)-**2a** in the CD spectra (see the Supporting Information). [b] 50 atm H_2, 24 h. [c] *ee* values were determined by GC on a chiral stationary phase without prior esterification. [d] 0.1 mol% of [Rh^I], 50 atm H_2, *i*PrOH/H_2O (4/1), 24 h. [e] 0.01 mol% of [Rh^I], 50 atm H_2, *i*PrOH/H_2O (4/1), 48 h, 70% conversion of (*Z*)-**1a** was achieved. [f] The absolute configuration was not assigned.

Table 3: Rh^{I}-catalyzed asymmetric hydrogenation of β-CF_3-substituted acrylic acids **3a–s**.[a]



(*E*)- or (*Z*)-**3a–3s** → **4a–4s**

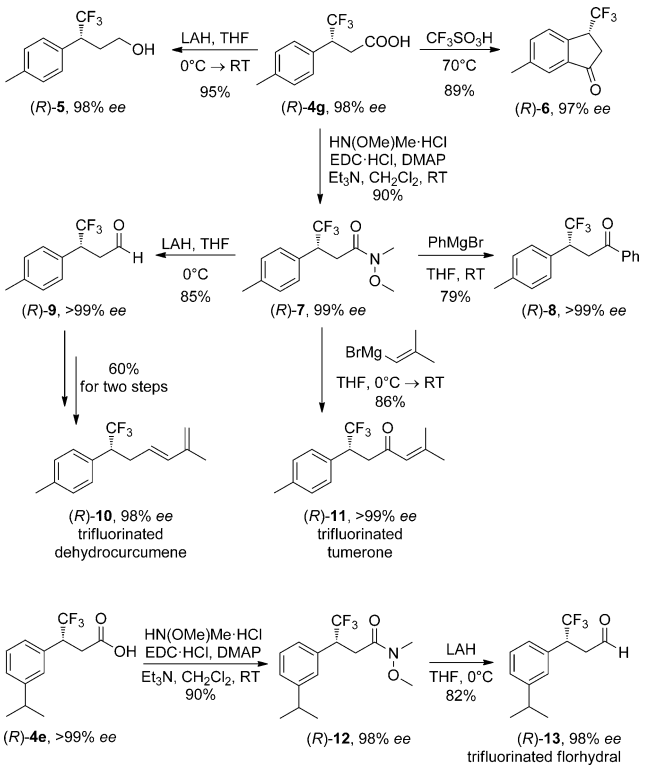
Entry	Substrate	Product	*Ee* [%]	Entry	Substrate	Product	*Ee* [%]
1	 (*E*)-**3a**	 (*R*)-**4a**	99 (*R*)	11	 (*E*)-**3j**	 (*R*)-**4j**	97 (*R*)
2[b]	 (*E*)-**3b**	 (-)-**4b**	>99[e]	12	 (*E*)-**3k**	 (*R*)-**4k**	>99 (*R*)
3[b,c]	 (*E*)-**3c**	 (-)-**4c**	>99[e]	13	 (*E*)-**3l**	 (*R*)-**4l**	98 (*R*)
4[b,c]	 (*Z*)-**3c**	 (+)-**4c**	94[e]	14[b]	 (*E*)-**3m**	 (*R*)-**4m**	>99 (*R*)
5	 (*E*)-**3d**	 (*R*)-**4d**	>99 (*R*)	15	 (*E*)-**3n**	 (*R*)-**4n**	99 (*R*)
6	 (*E*)-**3e**	 (*R*)-**4e**	>99 (*R*)	16[d]	 (*E*)-**3o**	 **4o**	90[e]
7	 (*E*)-**3f**	 (*R*)-**4f**	>99 (*R*)	17	 (*E*)-**3p**	 (*R*)-**4p**	>99 (*R*)
8	 (*E*)-**3g**	 (*R*)-**4g**	98 (*R*)	18	 (*Z*)-**3q**	 (*S*)-**4q**	97 (*S*)
9	 (*E*)-**3h**	 (*R*)-**4h**	>99 (*R*)	19	 (*E*)-**3r**	 (*R*)-**4r**	>99 (*R*)
10	 (*E*)-**3i**	 (*R*)-**4i**	97 (*R*)	20[d]	 (*E*)-**3s**	**4s**	92[e]

[a] Reaction conditions: [**3**] = 0.10 M. All conversions were higher than 99%, as determined by ^{19}F NMR spectroscopy. The *ee* values were determined by HPLC on a chiral stationary phase after the acids were transformed to their corresponding methyl esters with CH_2N_2, and the absolute configurations of the products were deduced by comparison of their Cotton effects with that of (*R*)-(−)-**4f** in the CD spectra (see the Supporting Information). [b] 50 atm H_2, 24 h. [c] 2 mol% catalyst. [d] The *ee* values were determined directly by GC on a chiral stationary phase. [e] The absolute configuration was not assigned.

However, the sterically more crowded substrates required higher hydrogen pressure (50 atm), a longer reaction time (24 h), and/or a higher catalyst loading (2 mol%) for complete conversions (Table 3, entries 2–4). Remarkably, AHs of *E* or *Z* isomers of **3c** gave the products (−)-**4c** or (+)-**4c**, respectively, with the same level of enantioselectivity (94% *ee*), but the opposite sense of asymmetric induction (Table 3, entry 3 vs. entry 4), suggesting a directing effect of carboxy group.[9,18] The AH of analogous substrates containing pyrrol-2-yl or indol-3-yl at the β position of acrylic acid proceeded with excellent enantiocontrol to give the corresponding hydrogenated products (*R*)-**4m** or (*R*)-**4n**, respectively, in more than 99% *ee* (Table 3, entries 14 and 15). The catalyst system also worked very well for β-alkyl-β-CF_3-substituted acrylic acid derivatives (*E*)-**3o** and (*E*)-**3p** (Table 3, entries 16 and 17), as well as β-difluoromethyl- and pentafluoroethyl-substituted cinnamic acids ((*Z*)-**3q** and (*E*)-**3r**; Table 3, entries 18 and 19), to afford full conversion of the substrates with excellent enantioselectivities. Furthermore, the AH of (*E*)-**3s**, a β-CF_3-substituted acrylic acid with

an α-methyl substituent, provided the corresponding product with 92% *ee* (Table 3, entry 20). It should be noted that some of the obtained hydrogenation products are highly valuable chiral synthons or bioactive molecules. For example, (*R*)-**4f** (>99% *ee*) is the key intermediate in the synthesis of an inhibitor of β-amyloid production,[6c] while (*R*)-**4m** (>99% *ee*) has been used as a key intermediate for the synthesis of a biologically interesting heliotridane analogue.[5a] Compound (*R*)-**4n** (>99% *ee*) itself is a plant growth regulator (TFIBA),[5b] while (*S*)-**4o**[19] and **4s**[19c,20] are well-known intermediates for pharmacologically active compounds that contain a trifluoromethyl group, such as amino acid antagonists or inhibitors.

Apart from the useful hydrogenation products **4f**, **4m**, **4n**, and **4o** mentioned above, the synthetic utility of the present procedure was further demonstrated with a series of transformations of (*R*)-**4g** into the corresponding alcohol **5**, cycloketone **6**,[21] and Weinreb amide **7** without any loss of enantiopurity (Scheme 1; for details, see the Supporting Information). As a synthetically versatile intermediate, the



Scheme 1. Transformation of hydrogenation products to optically active CF_3-substituted synthons and bioactive molecules. DMAP = 4-dimethylaminopyridine, EDC = 3-(3-dimethylaminopropyl)-1-ethylcarbodiimide, LAH = lithium aluminum hydride.

Weinreb amide **7** was further transformed into a variety of useful chiral products (**8**–**11**), including trifluorinated natural products,[3b] such as dehydrocurcumene **10** and tumerone **11**. Finally, (*R*)-**4e** was transformed into a trifluorinated analogue of florhydral through a two-step sequence without significant loss of optical purity.

In summary, a Rh^I catalyst containing a simple chiral SPO ligand (*S*)-**L6** and an achiral Ph_3P ligand was developed for highly efficient asymmetric hydrogenations of various α-CF_3- or β-CF_3-substituted acrylic acids with excellent enantioselectivities. This catalyst system provides a straightforward approach to diverse optically active α-CF_3- or β-CF_3-substituted propanoic acid derivatives with biological importance. The resultant products were readily transformed to a variety of optically active CF_3-substituted synthons and bioactive molecules.

Received: September 8, 2013
Published online: November 8, 2013

Keywords: acrylic acids · asymmetric catalysis · hydrogenation · rhodium · secondary phosphine oxides

[1] a) W. K. Hagmann, *J. Med. Chem.* **2008**, *51*, 4359; b) *Fluorine in Medicinal Chemistry and Chemical Biology* (Ed.: I. Ojima), Wiley-Blackwell, Chichester, **2009**; c) K. Müller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881; d) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320.

[2] For reviews, see: a) T. Furuya, A. S. Kamlet, T. Ritter, *Nature* **2011**, *473*, 470; b) J. Nie, H.-C. Guo, D. Cahard, J.-A. Ma, *Chem. Rev.* **2011**, *111*, 455; c) F. L. Qing, *Chin. J. Org. Chem.* **2012**, *32*, 815; d) A. Studer, *Angew. Chem.* **2012**, *124*, 9082; *Angew. Chem. Int. Ed.* **2012**, *51*, 8950; e) Z. He, Y. Huang, F. Verpoort, *Acta Chim. Sin.* **2013**, *71*, 700; f) T. Liang, C. N. Neumann, T. Ritter, *Angew. Chem.* **2013**, *125*, 8372; *Angew. Chem. Int. Ed.* **2013**, *52*, 8214.

[3] For reviews, see: a) W. Tang, X. Zhang, *Chem. Rev.* **2003**, *103*, 3029; b) J.-H. Xie, Q.-L. Zhou, *Acta Chim. Sin.* **2012**, *70*, 1427; c) S. Khumsubdee, K. Burgess, *ACS Catal.* **2013**, *3*, 237; for recent examples, see: d) S. Li, S.-F. Zhu, C.-M. Zhang, S. Song, Q.-L. Zhou, *J. Am. Chem. Soc.* **2008**, *130*, 8584, and references therein; e) J.-Q. Li, X. Quan, P. G. Andersson, *Chem. Eur. J.* **2012**, *18*, 10609.

[4] a) D. A. Nagib, M. E. Scott, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2009**, *131*, 10875; b) A. E. Allen, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2010**, *132*, 4986; c) Q. H. Deng, H. Wadepohl, L. H. Gade, *J. Am. Chem. Soc.* **2012**, *134*, 10769.

[5] a) Y. Huang, E. Tokunaga, S. Suzuki, M. Shiro, N. Shibata, *Org. Lett.* **2010**, *12*, 1136; b) L. Wen, Q. Shen, X. Wan, L. Lu, *J. Org. Chem.* **2011**, *76*, 2282; c) A. Morigaki, T. Tanaka, T. Miyabe, T. Ishihara, T. Konno, *Org. Biomol. Chem.* **2013**, *11*, 586.

[6] a) X. Zhang, T. Uemura, K. Matsumura, N. Sayo, H. Kumobayashi, H. Takaya, *Synlett* **1994**, 501; b) T. Uemura, X. Zhang, K. Matsumura, N. Sayo, H. Kumobayashi, T. Ohta, K. Nozaki, H. Takaya, *J. Org. Chem.* **1996**, *61*, 5510; c) A. Alimardanov, A. Nikitenko, T. J. Connolly, G. Feigelson, A. W. Chan, Z. Ding, M. Ghosh, X. Shi, J. Ren, E. Hansen, R. Farr, M. MacEwan, S. Tadayon, D. M. Springer, A. F. Kreft, D. M. Ho, J. R. Potoski, *Org. Process Res. Dev.* **2009**, *13*, 1161; d) L. Qiu, Y. M. Li, F. Y. Kwong, W. Y. Yu, Q. H. Fan, A. S. C. Chan, *Adv. Synth. Catal.* **2007**, *349*, 517; for a heterogeneous AH, see: e) G. Szőllősi, T. Varga, K. Felföldi, S. Cserényi, M. Bartók, *Catal. Commun.* **2008**, *9*, 421.

[7] K. Iseki, Y. Kuroki, T. Nagai, Y. Kobayashi, *Chem. Pharm. Bull.* **1996**, *44*, 477. See also Ref. [6e].

[8] a) M. T. Reetz, T. Sell, R. Goddard, *Chimia* **2003**, *57*, 290; b) X. Jiang, A. J. Minnaard, B. Hessen, B. L. Feringa, A. L. L. Duchateau, J. G. O. Andrien, J. A. F. Boogers, J. G. de Vries, *Org. Lett.* **2003**, *5*, 1503; c) X. Jiang, M. van den Berg, A. J. Minnaard, B. L. Feringa, J. G. de Vries, *Tetrahedron: Asymmetry*

2004, *15*, 2223; d) H. Landert, F. Spindler, A. Wyss, H.-U. Blaser, B. Pugin, Y. Ribourduoille, B. Gschwend, B. Ramalingam, A. Pfaltz, *Angew. Chem.* **2010**, *122*, 7025; *Angew. Chem. Int. Ed.* **2010**, *49*, 6873; e) K. Dong, Z. Wang, K. Ding, *J. Am. Chem. Soc.* **2012**, *134*, 12474; for a highlight on asymmetric catalysis with chiral SPO preligands, see: f) N. V. Dubrovina, A. Börner, *Angew. Chem.* **2004**, *116*, 6007; *Angew. Chem. Int. Ed.* **2004**, *43*, 5883.

[9] We recently reported the use of the mixed-ligand strategy in Rh^{I}-catalyzed AHs of β,β-diarylacrylic acids, see: Y. Li, K. Dong, Z. Wang, K. Ding, *Angew. Chem.* **2013**, *125*, 6880; *Angew. Chem. Int. Ed.* **2013**, *52*, 6748.

[10] For a review, see: a) M. T. Reetz, *Angew. Chem.* **2008**, *120*, 2592; *Angew. Chem. Int. Ed.* **2008**, *47*, 2556; b) S. Piovesana, D. M. Scarpino Schietroma, M. Bella, *Angew. Chem.* **2011**, *123*, 6340; *Angew. Chem. Int. Ed.* **2011**, *50*, 6216.

[11] For leading examples, see: a) M. T. Reetz, G. Mehler, *Tetrahedron Lett.* **2003**, *44*, 4593; b) M. T. Reetz, T. Sell, A. Meiswinkel, G. Mehler, *Angew. Chem.* **2003**, *115*, 814; *Angew. Chem. Int. Ed.* **2003**, *42*, 790; c) M. T. Reetz, X. Li, *Angew. Chem.* **2005**, *117*, 3019; *Angew. Chem. Int. Ed.* **2005**, *44*, 2959; d) M. T. Reetz, Y. Fu, A. Meiswinkel, *Angew. Chem.* **2006**, *118*, 1440; *Angew. Chem. Int. Ed.* **2006**, *45*, 1412; e) M. T. Reetz, O. Bondarev, *Angew. Chem.* **2008**, *120*, 4607; *Angew. Chem. Int. Ed.* **2007**, *46*, 4523.

[12] For leading examples, see: a) D. Peña, A. J. Minnaard, J. A. F. Boogers, A. H. M. de Vries, J. G. de Vries, B. L. Feringa, *Org. Biomol. Chem.* **2003**, *1*, 1087; b) R. Hoen, J. A. F. Booger, H. Bernsmann, A. J. Minnaard, A. Meetsma, T. D. Tiemersma-Wegman, A. H. M. de Vries, J. G. de Vries, B. L. Feringa, *Angew. Chem.* **2005**, *117*, 4281; *Angew. Chem. Int. Ed.* **2005**, *44*, 4209; c) J. G. de Vries, L. Lefort, *Chem. Eur. J.* **2006**, *12*, 4722; d) J. A. F. Boogers, U. Felfer, M. Kotthaus, L. Lefort, G. Steinbauer, A. H. M. de Vries, J. D. de Vries, *Org. Process Res. Dev.* **2007**, *11*, 585.

[13] a) C. Monti, C. Gennari, U. Piarulli, *Tetrahedron Lett.* **2004**, *45*, 6859; b) C. Monti, C. Gennari, U. Piarulli, J. G. de Vries, A. H. M. de Vries, L. Lefort, *Chem. Eur. J.* **2005**, *11*, 6701; c) L. Pignataro, B. Lynikaite, R. Colombo, S. Carboni, M. Krupicka, U. Piarulli, C. Gennari, *Chem. Commun.* **2009**, 3539; d) L. Pignataro, B. Lynikaite, J. Cvengros, M. Marchini, U. Piarulli, C. Gennari, *Eur. J. Org. Chem.* **2009**, 2539.

[14] a) M. Weis, C. Waloch, W. Seiche, B. Breit, *J. Am. Chem. Soc.* **2006**, *128*, 4188; b) A. C. Laungani, J. M. Slattery, I. Krossing, B. Breit, *Chem. Eur. J.* **2008**, *14*, 4488; c) J. Wieland, B. Breit, *Nat. Chem.* **2010**, *2*, 832.

[15] a) M. Kuil, P. E. Goudriaan, P. W. N. M. van Leeuwen, J. N. H. Reek, *Chem. Commun.* **2006**, 4679; b) X.-B. Jiang, L. Lefort, P. E. Goudriaan, A. H. M. de Vries, P. W. N. M. van Leeuwen, J. G. de Vries, J. N. H. Reek, *Angew. Chem.* **2006**, *118*, 1245; *Angew. Chem. Int. Ed.* **2006**, *45*, 1223; c) X.-B. Jiang, P. W. N. M. van Leeuwen, J. N. H. Reek, *Chem. Commun.* **2007**, 2287; d) F. W. Patureau, M. Kuil, A. J. Sandee, J. N. H. Reek, *Angew. Chem.* **2008**, *120*, 3224; *Angew. Chem. Int. Ed.* **2008**, *47*, 3180; e) P.-A. R. Breuil, F. W. Patureau, J. N. H. Reek, *Angew. Chem.* **2009**, *121*, 2196; *Angew. Chem. Int. Ed.* **2009**, *48*, 2162.

[16] D. J. Frank, A. Franzke, A. Pfaltz, *Chem. Eur. J.* **2013**, *19*, 2405.

[17] A Rh^{I} complex with two molecules of (*S*,*S*)-**L6** has been isolated and characterized (see Figure S5 in the Supporting Information), but showed very low activity (< 5% conv.) in the catalysis under analogous experimental conditions.

[18] For examples of carboxy-directed AH, see: a) S. Song, S.-F. Zhu, Y.-B. Yu, Q.-L. Zhou, *Angew. Chem.* **2013**, *125*, 1596; *Angew. Chem. Int. Ed.* **2013**, *52*, 1556; b) T. Besset, R. Gramage-Doria, J. N. H. Reek, *Angew. Chem.* **2013**, *125*, 8957; *Angew. Chem. Int. Ed.* **2013**, *52*, 8795.

[19] a) D. F. Loncrini, H. M. Walborsky, *J. Med. Chem.* **1964**, *7*, 369; b) W. F. Hoffman, A. W. Alberts, P. S. Anderson, J. S. Chen, R. L. Smith, A. K. Willard, *J. Med. Chem.* **1986**, *29*, 849; c) R. T. Jacobs, P. R. Bernstein, L. A. Cronk, E. P. Vacek, L. F. Newcomb, D. Aharony, C. K. Buckner, E. J. Kusner, *J. Med. Chem.* **1994**, *37*, 1282.

[20] a) A. Décor, C. Grand-Maître, O. Hucke, J. O'Meara, C. Kuhn, L. Constantineau-Forget, C. Brochu, E. Malenfant, M. Bertrand-Laperle, J. Bordeleau, E. Ghiro, M. Pesant, G. Fazal, V. Gorys, M. Little, C. Boucher, S. Bordeleau, P. Turcotte, T. Guo, M. Garneau, C. Spickler, A. Gauthier, *Bioorg. Med. Chem. Lett.* **2013**, *23*, 3841; b) Y. Leblanc, P. Roy, Z. Wang, C. S. Li, N. Chauret, D. A. Nicoll-Griffith, J. M. Silva, Y. Aubin, J. A. Yergey, C. C. Chan, D. Riendeau, C. Brideau, R. Gordon, L. Xu, J. Webb, D. M. Viscoc, P. Prasit, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3317.

[21] a) G. K. Surya Prakash, F. Paknia, H. Vaghoo, G. Rasul, T. Mathew, G. A. Olah, *J. Org. Chem.* **2010**, *75*, 2219; b) G. K. Surya Prakash, F. Paknia, A. Narayanan, G. Rasul, T. Mathew, G. A. Olah, *J. Fluorine Chem.* **2012**, *143*, 292.

