

Palladium-Catalyzed Asymmetric Hydrogenation of α -Acyloxy-1-arylethanones**

Jianzhong Chen, Delong Liu, Nicholas Butt, Chao Li, Dongyang Fan, Yangang Liu, and Wanbin Zhang*

α -Acyloxy-1-arylethanols, especially those possessing chiral centers, are a class of useful structural motifs commonly found in natural products and drug candidates.^[1] They can serve as important intermediates for the preparation of many bioactive and medicinal molecules (Figure 1).^[2] However, little

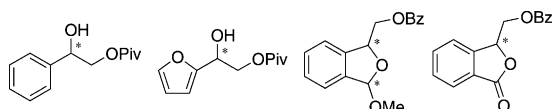


Figure 1. Chiral α -acyloxy-1-arylethanols. Bz = benzoyl, Piv = pivaloyl.

attention has been focused on their synthesis and the general approaches to prepare them often involve the selective acylation of the corresponding chiral diol species.^[3] Strategies to directly obtain the chiral α -acyloxy-1-arylethanols from α -acyloxy-1-arylethanones are relatively unknown. The initial study on the asymmetric reduction of α -acyloxy ketones was achieved in 1985 by utilizing the mixed reducing agent of a chiral diamine and SnCl_2 .^[4] Although moderate yields and good enantioselectivities were obtained, 3 equivalents of the reducing agent were required. Santaniello and co-workers, Fujisawa and co-workers, and Ema et al. reported asymmetric reductions of prochiral α -acyloxy ketones, using either baker's yeast or similar enzymes, with excellent enantioselectivity but moderate regioselectivity.^[5] Kambourakis and co-workers developed an efficient ketoreductase-catalyzed asymmetric synthesis of chiral α -acyloxy-1-alkylethanols.^[6] These enzyme regulated asymmetric syntheses require harsh reaction conditions, often have limited substrate scope, and

often involve the migration of the acyl group by hydrolysis. The asymmetric transfer hydrogenation of α -acyloxy-1-arylethanones has also been accomplished but with low yield and enantioselectivity or limited substrate scope.^[7] To the best of our knowledge, a strategy using transition-metal-catalyzed asymmetric hydrogenation of α -acyloxy-1-arylethanones remains unexplored, despite it being one of the most powerful methods for preparing chiral compounds.

Enantioselective hydrogenation reactions are of great interest to the chemistry community because of their atom efficiency and minimal environmental impact.^[8] In particular, palladium-catalyzed hydrogenations have gained increasing interest, however the use of palladium catalysis in the asymmetric hydrogenation of carbonyl compounds is relatively unexplored and requires high catalyst loadings (usually S/C = 50), the specific use of TFE as a solvent, and has limited substrate scope.^[9,10] Herein we present an efficient palladium-catalyzed asymmetric hydrogenation of a variety of α -acyloxy-1-arylethanones substrates for the preparation of chiral α -acyloxy-1-arylethanols.

We first carried out the asymmetric hydrogenation of 2-oxo-2-phenylethyl benzoate (**1aa**) using a catalytic system of $\text{Pd}(\text{OCOCF}_3)_2$ (2.0 mol %) and C_{10} -BridgePHOS (**L1**, 2.4 mol %), a novel chiral diphosphine ligand we recently developed,^[10c,h] under 30 bar H_2 at room temperature in TFE. As shown in Table 1, the reaction barely proceeded when using C_{10} -BridgePHOS (entry 1). Thus, commonly used axially chiral diphosphine ligands (*R*)-binap (**L2**) and (*R*)-SegPHOS (**L3**) were screened, and provided similar results (entries 2 and 3). Finally, (*R*)-3,5-di-*t*Bu-4-MeO-SegPHOS (**L4**; (*R*)-DTBM-SegPHOS), which possesses a high electron density and steric bulk, was examined. To our delight, almost quantitative conversion was obtained with moderate enantioselectivity (71 % *ee*, entry 4).

Using **L4** as the chiral ligand, our attention turned to the effect the acyl group on **1a** had on the reaction. A broad range of substrates (**1a**) having different acyloxy groups (R^1) were investigated (Table 2). Aromatic groups were first examined and up to 71 % *ee* was obtained with Ph as a substituent (entry 1). Both electron-withdrawing and electron-donating groups at different positions of the aromatic ring delivered somewhat poor enantioselectivity (entries 2–6). Aliphatic groups were then examined. A methyl group could provide quantitative conversion but low enantioselectivity (entry 7). Increasing the steric hindrance of R^1 increased the enantioselectivity. A *t*Bu group, possessing the greatest steric bulk, gave the highest *ee* value (76 % *ee*, entries 7–11). Thus the bulky aliphatic *t*Bu group was selected for subsequent reactions.

[*] J. Chen, Dr. N. Butt, Prof. W. Zhang
School of Chemistry and Chemical Engineering
Shanghai Jiao Tong University
800 Dongchuan Road, Shanghai 200240 (China)
E-mail: wanbin@sjtu.edu.cn
Homepage: <http://wanbin.sjtu.edu.cn>

Prof. D. Liu, C. Li, D. Fan, Prof. Y. Liu, Prof. W. Zhang
School of Pharmacy, Shanghai Jiao Tong University
800 Dongchuan Road, Shanghai 200240 (China)

[**] This work was partly supported by the National Nature Science Foundation of China (No. 21172143, 21172145 and 21232004), Science and Technology Commission of Shanghai Municipality (No. 09JC1407800), Nippon Chemical Industrial Co. Ltd, Shanghai Jiao Tong University (SJTU), and the Instrumental Analysis Center of SJTU. We thank Prof. Tsuneo Imamoto and Dr. Masashi Sugiya for helpful discussions.

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.201306231>.

Table 1: The effect of ligand on the reaction.^[a]

$\text{Ph-C(=O)-CH}_2\text{-O-C(=O)-Ph} \xrightarrow[\text{TFE, RT, H}_2 \text{ (30 bar), 24 h}]{\text{Pd(OCOCF}_3)_2 / \text{L}^*} \text{Ph-CH(OH)-CH}_2\text{-O-C(=O)-Ph}$ 1aa 2aa s/c = 50				
Entry	Ligand	Conv. [%] ^[b]	<i>ee</i> [%] ^[c,d]	
1	L1	< 5	—	
2	L2	< 5	—	
3	L3	< 5	—	
4	L4	> 99	71	

[a] Reaction conditions: **1aa** (0.1 mmol), Pd(OCOCF₃)₂ (2.0 mol %), ligands (2.4 mol %), TFE (1 mL), RT, 24 h. [b] Determined by ¹H NMR analysis. [c] Determined by HPLC analysis on a chiral stationary phase. [d] The absolute configuration of product was determined as *R* by comparison of the specific rotations with the literature data.^[7a] TFE = 2,2,2-trifluoroethanol.

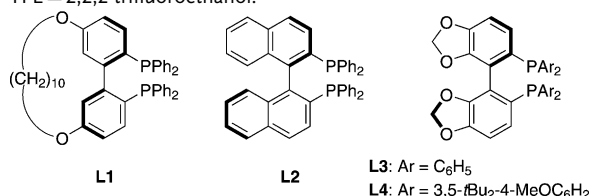


Table 2: The effect of R¹ group on the reaction.^[a]

$\text{Ph-C(=O)-CH}_2\text{-O-C(=O)-R}^1 \xrightarrow[\text{TFE, RT, H}_2 \text{ (30 bar), 24 h}]{\text{Pd(OCOCF}_3)_2 / \text{L4}} \text{Ph-CH(OH)-CH}_2\text{-O-C(=O)-R}^1$ 1a 2a s/c = 50				
Entry	R ¹	2a	Conv. [%] ^[b]	<i>ee</i> [%] ^[c,d]
1	Ph	2aa	> 99	71
2	2-ClC ₆ H ₄	2ab	> 99	59
3	2-MeOC ₆ H ₄	2ac	> 99	62
4	3-MeOC ₆ H ₄	2ad	> 99	70
5	4-MeOC ₆ H ₄	2ae	> 99	67
6	1-naphthyl	2af	> 99	58
7	Me	2ag	> 99	32
8	Et	2ah	> 99	39
9	Cy	2ai	> 99	44
10	<i>i</i> Pr	2aj	> 99	51
11	<i>t</i> Bu	2ak	> 99	76

[a] Reaction conditions: **1a** (0.1 mmol), Pd(OCOCF₃)₂ (2.0 mol %), **L4** (2.4 mol %), TFE (1 mL), RT, 24 h. [b] Determined by ¹H NMR analysis. [c] Determined by HPLC analysis on a chiral stationary phase. [d] The absolute configuration of product was determined as *R* by comparison with **2aa**.

Solvent had an obvious effect on the reaction outcome with the substrate **1ak** (Table 3). Compared with the initial result in TFE, both MeOH and EtOH gave full conversions and better enantioselectivities (entries 1–3). However, a by-product also appeared, thus resulting in a lower yield. Only 27% conversion was obtained with *i*PrOH as the solvent (entry 4). The use of the aprotic solvent CH₂Cl₂ provided the desired product exclusively with good enantiomeric excess (entry 5). Other low-polarity solvents, such as DME and toluene, were used but reactivity was poor (entries 6 and 7). Considering both CH₂Cl₂ and EtOH showed promising results, these two were chosen to examine the effect of pressure and temperature on the reaction.

Table 3: Optimization of the reaction conditions.^[a]

$\text{Ph-C(=O)-CH}_2\text{-O-C(=O)-}^i\text{Bu} \xrightarrow[\text{solvent, RT, H}_2 \text{ (bar), 24 h}]{\text{Pd(OCOCF}_3)_2 / \text{L4}} \text{Ph-CH(OH)-CH}_2\text{-O-C(=O)-}^i\text{Bu}$ 1ak 2ak s/c = 50					
Entry	Solvent (v/v)	H ₂ (bar)	Conv. [%] ^[b]	<i>ee</i> [%] ^[c]	By-product [%] ^[d]
1	TFE	30	> 99	76	0
2	MeOH	30	> 99	87	11
3	EtOH	30	> 99	88	13
4	<i>i</i> PrOH	30	27	88	8
5	CH ₂ Cl ₂	30	> 99	88	0
6	DME	30	< 5	—	—
7	toluene	30	< 5	—	—
8	CH ₂ Cl ₂	60	> 99	89	0
9	EtOH	60	> 99	89	17
10	CH ₂ Cl ₂	10	> 99	87	0
11	EtOH	10	> 99	86	10
12 ^[e]	EtOH	30	> 99	93	8
13 ^[e]	CH ₂ Cl ₂	30	< 5	—	—
14 ^[f]	EtOH	30	51	93	10
15 ^[e]	EtOH/CH ₂ Cl ₂ (10:1)	30	< 5	—	—
16 ^[e]	EtOH/TFE (10:1)	30	> 99	92	3
17 ^[e]	EtOH/TFE (20:1)	30	> 99	92	5
18 ^[e]	EtOH/TFE (8:1)	30	> 99	92	2
19 ^[e]	EtOH/TFE (4:1)	30	> 99	92	< 1
20 ^[g]	EtOH/TFE (4:1)	30	> 99	92	< 1
21 ^[h]	EtOH/TFE (4:1)	30	> 99	92	< 1

[a] Reaction conditions: **1ak** (0.1 mmol), Pd(OCOCF₃)₂ (2.0 mol %), **L4** (2.4 mol %), solvent (1 mL), RT, 24 h. [b] Determined by ¹H NMR analysis. [c] Determined by HPLC analysis on a chiral stationary phase. [d] The by-product was determined to be acetophenone by ¹H NMR analysis. [e] At 0 °C. [f] At –10 °C. [g] S/C = 2000, (0.66 g **1ak**), 3 days. [h] S/C = 5000, (1.66 g **1ak**), 5 days. DME = dimethoxyethane.

Increasing H₂ pressure from 30 to 60 bar in both CH₂Cl₂ and EtOH resulted in a slight increase in enantiomeric excess (Table 3, entries 8 and 9). Similarly, a slight decrease in enantiomeric excess was observed by reducing the H₂ pressure from 30 to 10 bar (entries 10 and 11). Unlike the effects of H₂ pressure, reaction temperature had a significant effect on the asymmetric catalysis. Decreasing the reaction temperature to 0 °C under 30 bar H₂, provided the desired product with 93% *ee* in EtOH, while only a trace amount of product was obtained in CH₂Cl₂ (entries 12 and 13). Further lowering the temperature to –10 °C in EtOH also gave excellent enantioselectivity, but a significant decrease in reaction activity was observed (entry 14).

Although excellent enantioselectivity was obtained by using EtOH as the solvent, a by-product was always produced. Therefore, a mixed solvent system was examined by addition of either CH₂Cl₂ or TFE to EtOH. The reaction was unsuccessful in a mixed solvent system of EtOH/CH₂Cl₂ (10:1) at 0 °C (Table 3, entry 15). To our delight, when CH₂Cl₂ was replaced by TFE, the reaction proceeded smoothly with excellent enantioselectivity and formation of the by-product was significantly suppressed (entry 16). The ratio of TFE in the mixed solvent affects the production of the by-product. A higher ratio of TFE decreased the formation of the by-product, as well as the enantioselectivity of the desired product (entries 16–19). Taking into account these results,

a mixed solvent system (EtOH/TFE, ratio 4:1) was considered suitable for the reaction (entry 19).

To examine the efficiency of our current catalytic system, the hydrogenation of **1ak** was tested with a relatively low catalyst loading (S/C = 2000 and 5000; Table 3, entries 20 and 21). To our delight, the reaction proceeded smoothly with quantitative conversion of the substrate and 92 % *ee*, albeit with a long reaction time. The example represents by far the lowest catalyst loading for the palladium-catalyzed asymmetric hydrogenation.^[11]

Finally, substrate scope was explored based on the optimized reaction conditions (Table 4). The influence of the electronic and steric effects of the substituents on the aromatic ring were first examined. Substrates with a substituent

Table 4: Asymmetric hydrogenation of α -acyloxy-1-arylethanones.^[a]

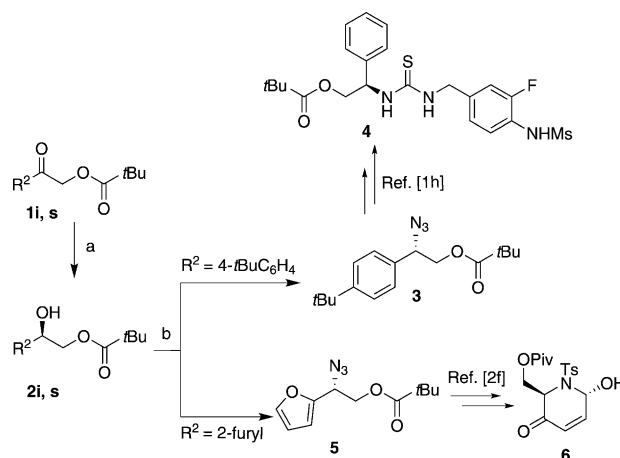
$\begin{array}{c} \text{R}^2 \\ \\ \text{O} \\ \\ \text{R}^2-\text{C}-\text{O}-\text{C}(=\text{O})-\text{tBu} \\ \text{1} \end{array} \xrightarrow[\text{EtOH/TFE (4:1), s/c = 50}]{\text{Pd}(\text{OCOCF}_3)_2 / \text{L4}, 0^\circ\text{C}, \text{H}_2 (30 \text{ bar}), 24 \text{ h}} \begin{array}{c} \text{OH} \\ \\ \text{R}^2-\text{C}-\text{O}-\text{C}(=\text{O})-\text{tBu} \\ \text{2} \end{array}$				
Entry	R ²	2	Conv. [%] ^[b]	<i>ee</i> [%] ^[c,d]
1	Ph	2ak	> 99	92
2	2-MeOC ₆ H ₄	2b	> 99	86
3	3-MeOC ₆ H ₄	2c	> 99	92
4	4-MeOC ₆ H ₄	2d	> 99	96
5	2-ClC ₆ H ₄	2e	> 99	83
6	3-ClC ₆ H ₄	2f	> 99	90
7	4-ClC ₆ H ₄	2g	> 99	94
8	4-MeC ₆ H ₄	2h	> 99	92
9	4- <i>t</i> BuC ₆ H ₄	2i	> 99	96
10	4-PhC ₆ H ₄	2j	> 99	96
11	4-HOC ₆ H ₄	2k	> 99	94
12	4-EtOC ₆ H ₄	2l	> 99	96
13	4-BrC ₆ H ₄	2m	> 99 ^[e]	94
14	4-FC ₆ H ₄	2n	> 99	94
15	4-CF ₃ C ₆ H ₄	2o	> 99	90
16	3,4-OCH ₂ OC ₆ H ₃	2p	> 99	95
17	3,4-(MeO) ₂ C ₆ H ₃	2q	> 99	96
18 ^[e]	2-naphthyl	2r	> 99	93
19	2-furyl	2s	> 99	97
20 ^[f]	2-thienyl	2t	37	95

[a] Reaction conditions: **1** (0.1 mmol), Pd(OCOCF₃)₂ (2.0 mol %), **L4** (2.4 mol %), EtOH/TFE (4/1, 1 mL), 0 °C, 24 h. [b] Determined by ¹H NMR analysis with less than 1 % by-product. [c] Determined by HPLC analysis on a chiral stationary phase. [d] The absolute configuration of products was deduced as *R* by comparison with **2aa**. [e] 48 h. [f] 72 h.

ent at the 4-position gave the best results for both electron-donating and electron-withdrawing species (entries 1–7). Therefore, a series of substrates with a substituents at the 4-position were examined and all gave excellent results (entries 8–15). 3,4-Disubstituted α -acyloxy ketones were also subjected to the hydrogenation. The reaction proceeded smoothly and gave the desired products in quantitative conversion and excellent *ee* values (entries 16 and 17). When the phenyl ring was replaced by either a naphthalene, furan, or thiophene ring, excellent enantioselectivities (up to 97 % *ee*) were also observed, albeit with a low reaction activity for the thiophene species (entries 18–20).

The reduced products **2** have the potential to participate in a variety of transformations. An illustration is provided by

transforming **2i** into its corresponding O-acyl thiourea species (**4**), a novel and promising analgesic and antiinflammatory agent (Scheme 1).^[1h] The compound **2i** was prepared from the α -acyloxy-1-arylethanone **1i** with quantitative conversion and



Scheme 1. Reagents and conditions: a) **L4** (2.4 mol %) and Pd-(OCOCF₃)₂ (2.0 mol %), H₂ (30 bar), EtOH/TFE (> 99 % conversions and 96 %, 97 % *ee*); b) DPPA, DBU, toluene (71 % and 77 % yield, 95 % and 92 % *ee* for **3** and **5**, respectively). DBU = 1,8-diazabicyclo-[5.4.0]undec-7-ene, DPPA = diphenylphosphoryl azide.

96 % *ee* (Table 4, entry 9). The azide species **3** was prepared from **2i** in 71 % yield and 95 % *ee*, and then converted into **4** according to a literature procedure.^[1h] Similarly, the chiral 1,6-dihydro-2*H*-pyridin-3-one **6** (an intermediate which can be used to prepare chiral pyridine-3-ones and pyridines species) was prepared from the intermediate **2s** via **5** (Scheme 1).^[2f]

X-ray crystallography studies confirmed the absolute configuration of the products. X-ray crystal analysis of **2i** showed that the aforementioned product could be assigned with the *R* configuration,^[12] which is consistent with that of previously reported results.^[7a]

To conclude, we have developed the first efficient palladium-catalyzed asymmetric hydrogenation of α -acyloxy-1-arylethanones, thus providing the hydrogenated products in up to quantitative conversions and excellent enantioselectivities (up to 97 % *ee*). This procedure utilizes the lowest reported catalyst loadings (S/C = 5000) for the palladium-catalyzed hydrogenation. The absolute configuration of the products was confirmed to be in accordance with reported results and further confirmed by X-ray crystallography studies. The hydrogenated products could subsequently be transformed into natural products and drug candidates. This simple and convenient methodology is suitable for the synthesis of a wide range of chiral α -acyloxy-1-arylethanols, important intermediates for the preparation of many kinds of drug candidates.

Received: July 17, 2013

Published online: September 13, 2013

Keywords: homogeneous catalysis · hydrogenation · palladium · reduction · synthetic methods

- [1] a) E. Lipka, M.-P. Vaccher, C. Vaccher, C. Len, *Bioorg. Med. Chem. Lett.* **2005**, 15, 501; b) D. F. Ewing, V. Glacon, C. Len, G. Mackenzie, *New J. Chem.* **2005**, 29, 1461; c) W. Fenical, P. R. Jensen, *Nat. Chem. Biol.* **2006**, 2, 666; d) K. C. Nicolaou, M. O. Frederick, A. Burtuloso, R. M. Denton, F. Rivas, K. P. R. Cole, R. Aversa, R. Gibe, T. Umezawa, T. Suzuki, *J. Am. Chem. Soc.* **2008**, 130, 7466; e) K. C. Nicolaou, Y. Tang, J. Wang, *Angew. Chem.* **2009**, 121, 3501; *Angew. Chem. Int. Ed.* **2009**, 48, 3449; f) K. C. Nicolaou, J. Wang, Y. Tang, L. Botta, *J. Am. Chem. Soc.* **2010**, 132, 11350; g) J. Luo, H. Wang, X. Han, L.-W. Xu, J. Kwiatkowski, K.-W. Huang, Y. Lu, *Angew. Chem.* **2011**, 123, 1901; *Angew. Chem. Int. Ed.* **2011**, 50, 1861; h) R. S. Bhondwe, D. W. Kang, M. S. Kim, H. S. Kim, S. G. Park, K. Son, S. Choi, K. A. L. Kuhs, V. A. Pavlyukovets, L. V. Pearce, P. M. Blumberg, J. Lee, *Bioorg. Med. Chem. Lett.* **2012**, 22, 3656.
- [2] a) H. P. Märki, Y. Cramer, R. Eigenmann, A. Krasso, H. Ramuz, K. Bernauer, M. Goodman, K. L. Melmon, *Helv. Chim. Acta* **1988**, 71, 320; b) K. Mori, H. Takaishi, *Tetrahedron* **1989**, 45, 1639; c) M. H. Haukaas, G. A. O'Doherty, *Org. Lett.* **2002**, 4, 1771; d) M. Inoue, S. Hatano, M. Kodama, T. Sasaki, T. Kikuchi, M. Hiram, *Org. Lett.* **2004**, 6, 3833; e) K. Ogawa, Y. Koyama, I. Ohashi, I. Sato, M. Hiram, *Chem. Commun.* **2008**, 6327; f) I. Husain, M. Saquib, V. Bajpai, B. Kumar, A. K. Shaw, *J. Org. Chem.* **2011**, 76, 8930.
- [3] a) D. F. Ewing, N. Fahmi, G. Mackenzie, A. Pranzo, *Nucleosides Nucleotides* **1999**, 18, 559; b) F. Iwasaki, T. Maki, W. Nakashima, O. Onomura, Y. Matsumura, *Org. Lett.* **1999**, 1, 969; c) D. F. Ewing, N. E. Fahmi, C. Len, G. Mackenzie, A. Pranzo, *J. Chem. Soc. Perkin Trans. 1* **2000**, 3561; d) Z. L. Wei, G. Q. Lin, Z. Y. Li, *Bioorg. Med. Chem.* **2000**, 8, 1129; e) D. F. Ewing, C. Len, G. Mackenzie, J. P. Petit, G. Ronco, P. Villa, *J. Pharm. Pharmacol.* **2001**, 53, 945; f) D. F. Ewing, V. Glacon, G. Mackenzie, C. Len, *Tetrahedron Lett.* **2002**, 43, 989; g) J. Lub, M. P. Ezquerro, B. Malo, *Mol. Cryst. Liq. Cryst.* **2006**, 457, 161; h) W. Muramatsu, J. M. William, O. Onomura, *J. Org. Chem.* **2012**, 77, 754.
- [4] T. Mukaiyama, K. Tomimori, T. Oriyama, *Chem. Lett.* **1985**, 1359.
- [5] a) A. Manzocchi, A. Fiechi, E. Santaniello, *J. Org. Chem.* **1988**, 53, 4405; b) R. Hayakawa, M. Shimizu, T. Fujisawa, *Tetrahedron: Asymmetry* **1997**, 8, 3201; c) T. Ema, Y. Sugiyama, M. Fukumoto, H. Moriya, J.-N. Cui, T. Sakai, M. Utaka, *J. Org. Chem.* **1998**, 63, 4996; d) T. Ema, H. Moriya, T. Kofukuda, T. Ishida, K. Maehara, M. Utaka, T. Sakai, *J. Org. Chem.* **2001**, 66, 8682; e) T. Ema, H. Yagasaki, N. Okita, K. Nishikawa, T. Korenaga, T. Sakai, *Tetrahedron: Asymmetry* **2005**, 16, 1075; f) T. Ema, H. Yagasaki, N. Okita, M. Takeda, T. Sakai, *Tetrahedron* **2006**, 62, 6143.
- [6] I. A. Kaluzna, J. D. Rozzell, S. Kambourakis, *Tetrahedron: Asymmetry* **2005**, 16, 3682.
- [7] a) J. A. Kenny, M. J. Palmer, A. R. C. Smith, T. Walsgrove, M. Wills, *Synlett* **1999**, 1615; b) M. Wills, M. Palmer, A. Smith, J. Kenny, T. Walsgrove, *Molecules* **2000**, 5, 4.
- [8] For reviews, see: a) R. Noyori, *Asymmetric Catalysis in Organic Synthesis*, Wiley, New York, **1993**; b) R. Noyori, T. Ohkuma, *Angew. Chem.* **2001**, 113, 40; *Angew. Chem. Int. Ed.* **2001**, 40, 40; c) X. Cui, K. Burgess, *Chem. Rev.* **2005**, 105, 3272; d) F. Glorius, *Org. Biomol. Chem.* **2005**, 3, 4171; e) W. S. Knowles, *Angew. Chem.* **2002**, 114, 2096; *Angew. Chem. Int. Ed.* **2002**, 41, 1998; f) W. Tang, X. Zhang, *Chem. Rev.* **2003**, 103, 3029; g) *Handbook of Homogeneous Hydrogenation* (Eds.: J. G. de Vries, C. J. Elsevier), Wiley-VCH, Weinheim, **2007**; h) G. Shang, W. Li, X. Zhang in *Catalytic Asymmetric Synthesis*, 3rd ed. (Ed.: I. Ojima), Wiley, Hoboken, **2010**, pp. 343–436; i) J.-H. Xie, S.-F. Zhu, Q.-L. Zhou, *Chem. Rev.* **2011**, 111, 1713; j) T. Imamoto in *Hydrogenation*, (Ed.: I. Karamé), Intech, Rijeka, **2012**, chap. 1, pp. 3–30; For very recent papers, see: k) T. Imamoto, K. Tamura, Z. Zhang, Y. Horiuchi, M. Sugiya, K. Yoshida, A. Yanagisawa, I. D. Gridnev, *J. Am. Chem. Soc.* **2012**, 134, 1754; l) C. Liu, J.-H. Xie, Y.-L. Li, J.-Q. Chen, Q.-L. Zhou, *Angew. Chem.* **2013**, 125, 621; *Angew. Chem. Int. Ed.* **2013**, 52, 593; m) S. Song, S.-F. Zhu, Y.-B. Yu, Q.-L. Zhou, *Angew. Chem.* **2013**, 125, 1596; *Angew. Chem. Int. Ed.* **2013**, 52, 1556; n) A. Iimuro, K. Yamaji, S. Kandula, T. Nagano, Y. Kita, K. Mashima, *Angew. Chem.* **2013**, 125, 2100; *Angew. Chem. Int. Ed.* **2013**, 52, 2046; o) Y. Liu, W. Zhang, *Angew. Chem.* **2013**, 125, 2259; *Angew. Chem. Int. Ed.* **2013**, 52, 2203; p) Z.-S. Ye, R.-N. Guo, X.-F. Cai, M.-W. Chen, L. Shi, Y.-G. Zhou, *Angew. Chem.* **2013**, 125, 3773; *Angew. Chem. Int. Ed.* **2013**, 52, 3685; q) G. Liu, X. Liu, Z. Cai, G. Jiao, G. Xu, W. Tang, *Angew. Chem.* **2013**, 125, 4329; *Angew. Chem. Int. Ed.* **2013**, 52, 4235; r) C. Kohrt, W. Baumann, A. Spannenberg, H.-J. Drexler, I. D. Gridnev, D. Heller, *Chem. Eur. J.* **2013**, 19, 7443; s) T. Wang, F. Chen, J. Qin, Y.-M. He, Q.-H. Fan, *Angew. Chem.* **2013**, 125, 7313; *Angew. Chem. Int. Ed.* **2013**, 52, 7172; t) A. Schumacher, M. Bernasconi, A. Pfaltz, *Angew. Chem.* **2013**, 125, 7570; *Angew. Chem. Int. Ed.* **2013**, 52, 7422; u) Y. Liu, H. Du, *J. Am. Chem. Soc.* **2013**, 135, 6810; v) D. Zhao, B. Beiring, F. Glorius, *Angew. Chem.* **2013**, 125, 8612; *Angew. Chem. Int. Ed.* **2013**, 52, 8454; w) T.-L. Liu, C.-J. Wang, X. Zhang, *Angew. Chem.* **2013**, 125, 8574; *Angew. Chem. Int. Ed.* **2013**, 52, 8416; x) X.-H. Yang, J.-H. Xie, W.-P. Liu, Q.-L. Zhou, *Angew. Chem.* **2013**, 125, 7987; *Angew. Chem. Int. Ed.* **2013**, 52, 7833; y) W. Chen, F. Spindler, B. Pugin, U. Nettekoven, *Angew. Chem.* **2013**, 125, 8814; *Angew. Chem. Int. Ed.* **2013**, 52, 8652; z) T. Yamamura, H. Nakatsuka, S. Tanaka, M. Kitamura, *Angew. Chem.* **2013**, 125, 9483; *Angew. Chem. Int. Ed.* **2013**, 52, 9313; aa) N. Ortega, D.-T. D. Tang, S. Urban, D. Zhao, F. Glorius, *Angew. Chem.* **2013**, 125, 9678; *Angew. Chem. Int. Ed.* **2013**, 52, 9500.
- [9] For reviews, see: a) Y.-G. Zhou, *Acc. Chem. Res.* **2007**, 40, 1357; b) D.-S. Wang, Q.-A. Chen, S.-M. Lu, Y.-G. Zhou, *Chem. Rev.* **2012**, 112, 2557; c) Q.-A. Chen, Z.-S. Ye, Y. Duan, Y.-G. Zhou, *Chem. Soc. Rev.* **2013**, 42, 497; For selected papers, see: d) H. Abe, H. Amii, K. Uneyama, *Org. Lett.* **2001**, 3, 313; e) D. Drago, P. S. Pregosin, *Organometallics* **2002**, 21, 1208; f) A. Suzuki, M. Mae, H. Amii, K. Uneyama, *J. Org. Chem.* **2004**, 69, 5132; g) Q. Yang, G. Shang, W. Gao, J. Deng, X. Zhang, *Angew. Chem.* **2006**, 118, 3916; *Angew. Chem. Int. Ed.* **2006**, 45, 3832; h) Y.-Q. Wang, S.-M. Lu, Y.-G. Zhou, *J. Org. Chem.* **2007**, 72, 3729; i) Y.-Q. Wang, C.-B. Yu, D.-W. Wang, X.-B. Wang, Y.-G. Zhou, *Org. Lett.* **2008**, 10, 2071; j) C.-B. Yu, D.-W. Wang, Y.-G. Zhou, *J. Org. Chem.* **2009**, 74, 5633; k) A. Arnanz, C. González-Arellano, A. Juan, G. Villaverde, A. Corma, M. Iglesias, F. Sánchez, *Chem. Commun.* **2010**, 46, 3001; l) M. Boronat, A. Corma, C. González-Arellano, M. Iglesias, F. Sánchez, *Organometallics* **2010**, 29, 134; m) D.-S. Wang, Q.-A. Chen, W. Li, C.-B. Yu, Y.-G. Zhou, X. Zhang, *J. Am. Chem. Soc.* **2010**, 132, 8909; n) M.-W. Chen, Y. Duan, Q.-A. Chen, D.-S. Wang, C.-B. Yu, Y.-G. Zhou, *Org. Lett.* **2010**, 12, 5075; o) D.-S. Wang, D.-W. Wang, Y.-G. Zhou, *Synlett* **2011**, 947; p) X.-Y. Zhou, M. Bao, Y.-G. Zhou, *Adv. Synth. Catal.* **2011**, 353, 84; q) Y. Duan, M.-W. Chen, Z.-S. Ye, D.-S. Wang, Q.-A. Chen, Y.-G. Zhou, *Chem. Eur. J.* **2011**, 17, 7193; r) D.-S. Wang, J. Tang, Y.-G. Zhou, M.-W. Chen, C.-B. Yu, Y. Duan, G.-F. Jiang, *Chem. Sci.* **2011**, 2, 803; s) D.-S. Wang, Z.-S. Ye, Q.-A. Chen, Y.-G. Zhou, C.-B. Yu, H.-J. Fan, Y. Duan, *J. Am. Chem. Soc.* **2011**, 133, 8866; t) C.-B. Yu, K. Gao, D.-S. Wang, L. Shi, Y.-G. Zhou, *Chem. Commun.* **2011**, 47, 5052; u) C.-B. Yu, K. Gao, Q.-A. Chen, M.-W. Chen, Y.-G. Zhou, *Tetrahedron Lett.* **2012**, 53, 2560; v) Y. Duan, M.-W. Chen, Q.-A. Chen, C.-B. Yu, Y.-G. Zhou, *Org. Biomol. Chem.* **2012**, 10, 1235; w) N. S. Goulioukina, I. A. Shergold, G. N. Bondarenko, M. M. Ilyin, V. A. Davankov, I. P. Beletskaya, *Adv. Synth. Catal.* **2012**, 354, 2727.
- [10] a) M. D. Jones, R. Raja, J. M. Thomas, B. F. G. Johnson, D. W. Lewis, J. Rouzard, K. D. M. Harris, *Angew. Chem.* **2003**, 115, 4462; *Angew. Chem. Int. Ed.* **2003**, 42, 4326; b) R. Raja, J. M.

Thomas, M. D. Jones, B. F. G. Johnson, D. E. W. Vaughan, *J. Am. Chem. Soc.* **2003**, *125*, 14982; c) Y.-Q. Wang, S.-M. Lu, Y.-G. Zhou, *Org. Lett.* **2005**, *7*, 3235; d) N. S. Goulioukina, G. N. Bondarenko, A. V. Bogdanov, K. N. Gavrilov, I. P. Beletskaya, *Eur. J. Org. Chem.* **2009**, 510; e) C. Wang, G. Yang, J. Zhuang, W. Zhang, *Tetrahedron Lett.* **2010**, *51*, 2044; f) B. Teng, J. Zheng, H. Huang, P. Huang, *Chin. J. Chem.* **2011**, *29*, 1312; g) X.-Y. Zhou, D.-S. Wang, M. Bao, Y.-G. Zhou, *Tetrahedron Lett.* **2011**, *52*, 2826; h) C. Li, J. Chen, G. Fu, D. Liu, Y. Liu, W. Zhang, *Tetrahedron* **2013**, *69*, 6839.

- [11] To the best of our knowledge, the ratio of S/C was 50:1 for most cases of palladium-catalyzed asymmetric hydrogenation and only one example of higher S/C ratio (1000:1) was reported.^[9c,k,l]
- [12] CCDC 943698 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. The single-crystal structure could be found in the Supporting Information.