

SpinPhox/Iridium(I)-Catalyzed Asymmetric Hydrogenation of Cyclic α -Alkylidene Carbonyl Compounds**

Xu Liu, Zhaobin Han, Zheng Wang, and Kuiling Ding*

Dedicated to Professor Chengye Yuan on the occasion of his 90th birthday

Abstract: Optically active medium-sized cyclic carbonyl compounds bearing an α -chiral carbon center are of interest in pharmaceutical sciences and asymmetric synthesis. Herein, SpinPhox/Ir^I catalysts have been demonstrated to be highly enantioselective in the asymmetric hydrogenation of the C=C bonds in the exocyclic α,β -unsaturated cyclic carbonyls, including a broad range of α -alkylidene lactams, unsaturated cyclic ketones, and lactones. It is noteworthy that the procedure can be successfully used in the asymmetric hydrogenation of the challenging α -alkylidenelactam substrates with six- or seven-membered rings, thus affording the corresponding optically active carbonyl compounds with an α -chiral carbon center in generally excellent enantiomeric excesses (up to 98% ee). Synthetic utility of the protocol has also been demonstrated in the asymmetric synthesis of the anti-inflammatory drug loxoprofen and its analogue, as well as biologically important ϵ -aminocaproic acid derivatives.

Optically active medium-sized cyclic carbonyl compounds bearing an α -chiral carbon center are recurring structural motifs in pharmaceutical sciences and versatile chiral building blocks in asymmetric synthesis (Figure 1).^[1] An attractive synthetic route to these compounds would be the catalytic asymmetric hydrogenation (AH) of the C=C bonds in the exocyclic α,β -unsaturated cyclic carbonyls, by virtue of the high efficiency, atom-economy, and cost-effectiveness of the methodology. While a great number of chiral catalysts have been developed over the years for AH of various acyclic and endocyclic unsaturated carbonyl compounds,^[2] documented examples which are especially effective for the AH of the exocyclic C=C bonds of α -alkylidene lactams,^[3] lactones,^[4] and/or cyclic ketones^[5] are still quite rare. The difficulty associated with this type of substrate in asymmetric hydrogenation is probably due to the exocyclic nature of the C=C bond which may hamper substrate bonding to the metal center, and has been assumed to be a key factor in achieving

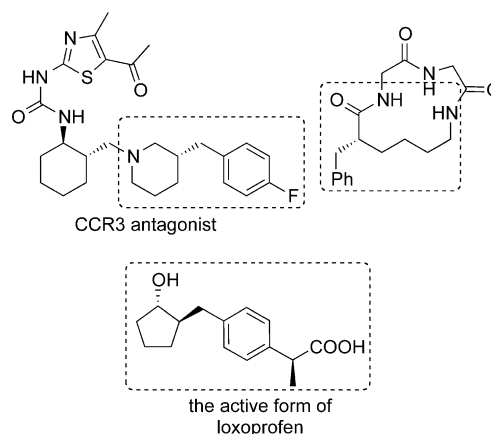


Figure 1. Examples of biologically active molecules derived from medium-sized cyclic carbonyl compounds.

high activity and good stereocontrol in the rhodium- or ruthenium-catalyzed AH.^[6] The iridium complexes of chiral P,N ligands are particularly noteworthy in overcoming these limitations,^[7] and demonstrated excellent enantioselectivities in the AH of a wide range of largely unfunctionalized olefins,^[8] including olefins with weakly coordinating groups^[9] and tetrasubstituted olefins.^[10] In this context, a few excellent iridium catalysts have been developed recently for AH of C=C bonds in α,β -unsaturated carbonyl compounds as well, as exemplified by the independent pioneering studies of the groups of Bolm, Hou, and Zhou.^[11] Nevertheless, challenges still remain in the AH of exocyclic α,β -unsaturated cyclic carbonyls with regard to the limited substrate scope, and the enantioselectivities are often strongly dependent on the ring size of the substrates in the AH of α -alkylidene lactams and lactones,^[3–5] as indicated by BiphPhox/Ir^I catalysts (Figure 2).^[12] We previously reported a class of chiral iridium(I) complexes, SpinPhox/Ir^I (Figure 2), with spiro P,N ligands^[13] for efficient AH of ketimines, α,β -unsaturated carboxylic acids, and Weinreb amides, as well as α,α' -bis(2-

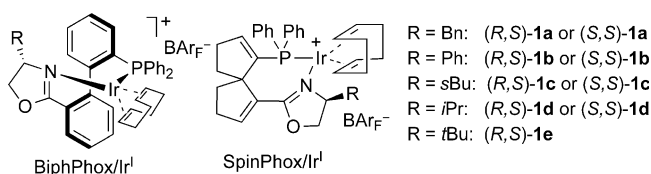


Figure 2. BiphPhox/Ir^I and SpinPhox/Ir^I catalysts.

[*] X. Liu, Dr. Z. Han, 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

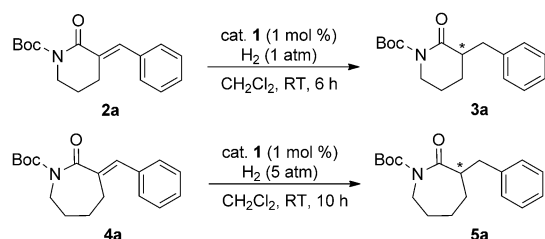
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hydroxyarylidene)ketones.^[14] Herein, we communicate the successful application of SpinPhox/Ir^I catalysts in the AH of the challenging six- and seven-membered α -alkylidene carbonyls with a focus on the lactam derivatives. The synthetic utility of the protocol is also showcased in the asymmetric synthesis of the nonsteroidal anti-inflammatory drug loxoprofen and an ϵ -aminocaproic acid derivative.

To test the viability of the catalysis, a preliminary screening of the SpinPhox/Ir^I complexes (*R,S*)-**1a–e** and (*S,S*)-**1a–d**,^[12a] and of the reaction conditions were performed using AH of (*E*)-3-benzylidenepiperidin-2-one, and its *N*-benzyl-, *N*-phenyl-, *N*-methyl-, or *N*-Boc-protected derivatives as the model reactions (see Table S2 in the Supporting Information). It turns out that the *N*-Boc-protected derivative **2a** appears to be optimal in terms of the reactivity and enantioselectivity (up to 93% *ee*). The AH of **2a** was performed under an ambient pressure of H₂ at room temperature in CH₂Cl₂ for 6 hours in the presence of 1 mol % of different SpinPhox/Ir^I complexes. As shown in Table 1, the catalysts (*R,S*)-**1c** and (*S,S*)-**1c**, bearing a (*S*)-*s*Bu group on the oxazoline moiety, turned out to be favorable for the enantiocontrol of the reaction, thus affording the piperidone **3a** with an *ee* value much higher than that of their counterparts (entries 3 and 8). It is also noteworthy that both (*R,S*)-**1c** and (*S,S*)-**1c** gave **3a** in excellent optical purity but as opposite enantiomers, thus indicating that the spirochirality of the ligand controls the sense of asymmetric induction in the catalysis.

Table 1: Iridium(I) catalysts for AH of the *N*-Boc-protected **2a** and (*E*)-3-benzylidenepiperidin-2-one (**4a**).^[a]



Entry	Subs.	Cat.	Conv. [%] ^[b]	<i>ee</i> [%] ^[c]
1	2a	(<i>R,S</i>)- 1a	75	77 (<i>S</i>)
2	2a	(<i>R,S</i>)- 1b	> 99	19 (<i>S</i>)
3	2a	(<i>R,S</i>)- 1c	60	91 (<i>S</i>)
4	2a	(<i>R,S</i>)- 1d	54	70 (<i>S</i>)
5	2a	(<i>R,S</i>)- 1e	40	6 (<i>S</i>)
6	2a	(<i>S,S</i>)- 1a	28	73 (<i>R</i>)
7	2a	(<i>S,S</i>)- 1b	> 99	37 (<i>R</i>)
8	2a	(<i>S,S</i>)- 1c	> 99	93 (<i>R</i>)
9	2a	(<i>S,S</i>)- 1d	70	70 (<i>R</i>)
10	4a	(<i>S,S</i>)- 1c	86	31 (<i>R</i>)
11	4a	(<i>R,S</i>)- 1c	> 99	97 (<i>S</i>)
12	4a	(<i>R,S</i>)- 1a	> 99	77 (<i>S</i>)
13	4a	(<i>R,S</i>)- 1b	> 99	89 (<i>S</i>)
14	4a	(<i>R,S</i>)- 1d	> 99	94 (<i>S</i>)
15	4a	(<i>R,S</i>)- 1e	> 99	95 (<i>S</i>)

[a] Unless otherwise noted, all reactions were conducted under 1 or 5 atm of H₂ at 25 °C for 6 or 10 h with [**2a**] and [**4a**] = 0.1 M and [**1**] = 1 mm (1 mol %). [b] Determined by ¹H NMR spectroscopy. [c] The *ee* values were determined by HPLC analysis on a chiral stationary phase, and the absolute configurations were determined according to the method specified in footnote [c] of Table 2. Boc = *tert*-butoxycarbonyl.

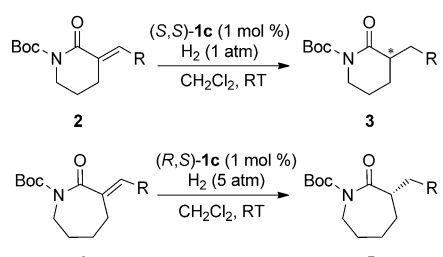
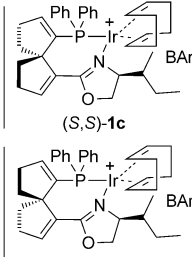
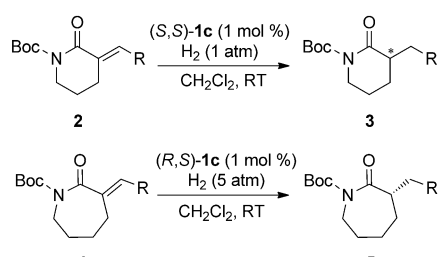
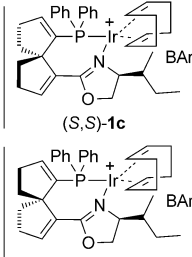
Encouraged by the excellent preliminary results attained in the hydrogenation of the six-membered substrate **2a** with **1c**, we extended this catalyst system to the hydrogenation 3-alkylidene caprolactams, a class of seven-membered exocyclic α,β -unsaturated lactams which have almost been neglected in AH studies.^[15] A quick survey with (*E*)-3-benzylidene azepin-2-one (**4a**) as the model substrate revealed that (*R,S*)-**1c** is the chirality-matched catalyst (Table 1, entry 11 versus 10). Other (*R,S*) isomers of the catalysts **1a,b** and **1d,e** only showed inferior results to those of (*R,S*)-**1c** (entries 12–15).

The optimized catalyst, (*S,S*)-**1c**, was subsequently used in the AH of various *N*-Boc-protected (*E*)-3-alkylidenepiperidin-2-ones (**2b–p**; Table 2). The reactions were conducted at room temperature under 1 atm of H₂ in the presence of 1 mol % of (*S,S*)-**1c**, and the results are summarized in the left column of Table 2. Except for the substrate **2d**, having a sterically demanding *ortho*-tolyl group (entry 4), the reactions of 3-alkylidene-2-piperidones having an aryl substituent were generally successful and afforded high *ee* values (89–95%) for substrates with a *para*- (**2b**, and **2e–i**), *meta*- (**2c,2j**, and **2k**), or disubstituted phenyl ring (**2l**), irrespective of the electron-donating or electron-withdrawing nature of the substituent (entries 3–12). Furthermore, the substrates with heteroaryl substituents (**2m–o**) were also hydrogenated in quantitative conversions with excellent enantioselectivities (entries 13–15). Unfortunately, the AH of piperidone substrates containing an aliphatic group (**2p**) was less successful, with a somewhat lower *ee* value being attained at an elevated catalyst loading (entries 16).

The hydrogenation of a range of *N*-Boc-protected alkylidenecaprolactams having various aryl substituents was further carried out with (*R,S*)-**1c** as the catalyst under the optimized reaction conditions mentioned above, and the results are shown in the right column of Table 2. All the reactions proceeded smoothly at room temperature under 5 atm of H₂ to afford the corresponding chiral caprolactams **5a–q** with full conversion of the substrates and excellent *ee* values (95–98%; entries 1–17). For these substrates, it appears that the reactions are quite general and less influenced by the electronic nature or the steric bulk of the aryl substituents in the substrates.

Having established the applicability of SpinPhox/Ir^I catalysts in the hydrogenation of six- and seven-membered cyclic amides with α -alkylidene substituents, we further examined their adaptability in AH of some other medium-sized cyclic α,β -unsaturated carbonyls. As shown in Table 3, a variety of lactones, ketones, and lactams with an exocyclic C=C bond (**6a–g**) have also been hydrogenated smoothly with high enantioselectivity under 5 atm of H₂ by suitable choice of the iridium(I) catalyst, (*S,S*)-**1c** or (*R,S*)-**1b** (1 mol %). The catalyst (*S,S*)-**1c** was found to be highly enantioselective for the reaction of the six-membered-ring lactone **6a** and ketones **6b,c**, as well as seven-membered-ring ketone **6d**, having an α -benzylidene substituent, to give the corresponding hydrogenation products **7a–d** in excellent *ee* values (entries 1–4). All these facts further attest to the versatility of the present catalyst system, although the catalyst (*R,S*)-**1b** only showed moderate to good enantioselectivities (81–83%) in the AH of substrates **6e–g** having five-membered rings (entries 5–7).

Table 2: AH of the N-Boc-protected **2a–p** and **4a–q** catalyzed by iridium(I) catalysts (*(S,S)*-**1c** and (*(R,S)*-**1c**, respectively.^[a]

						
						
Entry	R	Conv. [%] ^[b]	ee [%] ^[c]	R	Conv. [%] ^[b]	ee [%] ^[c]
1	Ph (2a)	> 99	93 (<i>R</i>)	Ph (4a)	> 99	97 (<i>S</i>)
2	4-MeC ₆ H ₄ (2b)	> 99	91 (<i>R</i>)	4-MeC ₆ H ₄ (4b)	> 99	98 (<i>S</i>)
3	3-MeC ₆ H ₄ (2c)	> 99	91 (<i>R</i>)	3-MeC ₆ H ₄ (4c)	> 99	97 (<i>S</i>)
4 ^[d]	2-MeC ₆ H ₄ (2d)	50	73 (<i>R</i>)	2-MeC ₆ H ₄ (4d)	> 99 ^[d]	98 (<i>S</i>)
5	4-MeOC ₆ H ₄ (2e)	> 99	89 (<i>R</i>)	4-MeOC ₆ H ₄ (4e)	> 99	98 (<i>S</i>)
6	4-ClC ₆ H ₄ (2f)	> 99	93 (<i>R</i>)	4-ClC ₆ H ₄ (4f)	> 99	95 (<i>S</i>)
7	4-BrC ₆ H ₄ (2g)	> 99	93 (<i>R</i>)	4-BrC ₆ H ₄ (4g)	> 99	98 (<i>S</i>)
8	4-FC ₆ H ₄ (2h)	> 99	93 (<i>R</i>)	4-FC ₆ H ₄ (4h)	> 99	97 (<i>S</i>)
9	4-CF ₃ C ₆ H ₄ (2i)	> 99	95 (<i>R</i>)	4-CF ₃ C ₆ H ₄ (4i)	> 99	98 (<i>S</i>)
10	3-CF ₃ C ₆ H ₄ (2j)	> 99	95 (<i>R</i>)	3-CF ₃ C ₆ H ₄ (4j)	> 99	98 (<i>S</i>)
11	3-ClC ₆ H ₄ (2k)	> 99	94 (<i>R</i>)	3-ClC ₆ H ₄ (4k)	> 99	97 (<i>S</i>)
12	3,4-Cl ₂ C ₆ H ₃ (2l)	> 99	95 (<i>R</i>)	3,4-Cl ₂ C ₆ H ₃ (4l)	> 99	98 (<i>S</i>)
13 ^[e]	3-furyl (2m)	> 99	93 (+)	3-FC ₆ H ₄ (4m)	> 99	97 (<i>S</i>)
14 ^[e]	2-furyl (2n)	> 99	96 (+)	2-furyl (4n)	> 99	97 (+)
15 ^[e]	2-thienyl (2o)	> 99	93 (+)	2-thienyl (4o)	> 99	96 (+)
16 ^[e]	cyclohexyl (2p)	79	79 (+)	2-FC ₆ H ₄ (4p)	> 99	98 (<i>S</i>)
17				3-PhOC ₆ H ₄ (4q)	> 99	98 (<i>S</i>)

[a] Unless otherwise noted, the reactions were performed with 0.15 mmol of **2a–p** and **4a–q** in CH₂Cl₂ (1.5 mL) in the presence of 1 mol % of (*(S,S)*)-**1c** and (*(R,S)*)-**1c** at RT, respectively. [b] Determined by ¹H NMR spectroscopy. [c] Determined by HPLC on a chiral stationary phase. The absolute configurations of **3g** and **5g** were determined by X-ray crystallographic analyses, while those of the other hydrogenation products were assigned by comparison of their CD spectra with that of **3g** or **5g**, respectively. [d] 2 mol % of (*(S,S)*)-**1c** was used with a reaction time of 10 h. [e] 5 mol % of (*(S,S)*)-**1c** was used with reaction time of 24 h.

On the basis of the the crystal structure information of the SpinPhox/Ir^I complexes (*(R,S)*- and (*(S,S)*)-**1**^[14e] and the observed asymmetric induction in the catalysis, as well as the related mechanism reported by Andersson,^[16] a plausible asymmetric induction model is proposed for the present

Table 3: AH of exocyclic α,β-unsaturated ketones, lactams, and lactones catalyzed by the iridium(I) complexes **1**.^[a]

 6a-i $\xrightarrow[\text{H}_2 \text{ (5 atm), CH}_2\text{Cl}_2, \text{RT, 10 h}]{\text{1 (1 mol \%)}}$ 7a-i $n = 0, 1, 2$ $x = \text{CH}_2, \text{O, or N-Bn}$				
Entry	Substrate	Catalyst	Conv. [%] ^[b]	ee [%] ^[c]
1	 6a	(<i>S,S</i>)- 1 c	> 99	92 (<i>S</i>)
2	 6b	(<i>S,S</i>)- 1 c	> 99	97 (<i>R</i>)
3	 6c	(<i>S,S</i>)- 1 c	> 99	93 (<i>R</i>)
4	 6d	(<i>R,S</i>)- 1 c	> 99	96 (<i>S</i>)
5	 6e	(<i>R,S</i>)- 1 b	> 99	83 (–)
6	 6f	(<i>R,S</i>)- 1 b	> 99	83 (–)
7	 6g	(<i>R,S</i>)- 1 b	> 99	81 (<i>S</i>)

[a] Reaction conditions: 0.15 mmol of **6a–g**, CH₂Cl₂ (1.5 mL), *P*(H₂) = 5 atm, 1 mol % of iridium(I) complex **1**, RT, 10 h. [b] Determined by ¹H NMR spectroscopy. [c] Determined by HPLC analysis on a chiral stationary phase. The absolute configurations were assigned by comparing their specific rotations with the literature reported values.

catalytic system. As shown in Figure 3, the hydrogen bonding between the lactam carbonyl moieties and the upper Ir–H probably has significant impact on the approach of the C=C double bond to the iridium center during the catalysis. The opposite asymmetric induction observed in AH of **2a** using (*(R,S)*)-**1c** and (*(S,S)*)-**1c** (Table 1) can be rationalized on the basis of this model, thus indicating the critical role of the spirochirality in the ligand for the control of asymmetric induction, even though the chirality of the oxazoline moiety might influence the level of enantioselectivity as well.

To illustrate the synthetic application of the present methodology, the enantioenriched caprolactams (*(S)*)-**5a** and (*(S)*)-**5b** (Table 2) were readily hydrolyzed to the corresponding chiral aminocaproic acids without loss of optical purity, which are homologues of ε-aminocaproic acid (a marketed enzyme inhibitor used to treat certain bleeding disorders)^[17] and bioisosteres of lysine (Scheme 1A). The synthetic application of this protocol was further demonstrated in the asymmetric synthesis of loxoprofen (**10a**), a nonsteroidal

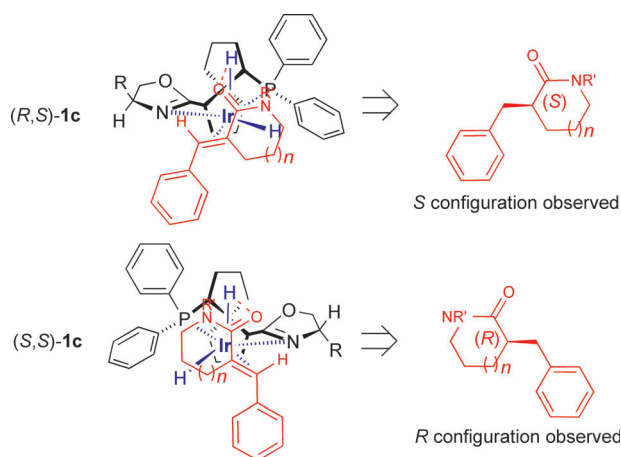
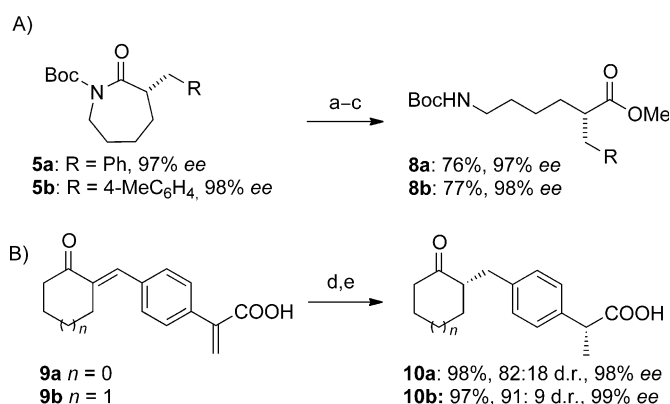


Figure 3. A plausible asymmetric induction model for SpinPhox/Ir^I-catalyzed AH of α-alkylidene lactams.



Scheme 1. A) Transformation of the optically active caprolactams **5a** and **5b** into the corresponding ε-aminocaproic acid derivatives: a) 30% aq HCl, 100°C, 2 h; b) MeOH, H₂SO₄ (cat), 60°C, 2 h; c) (Boc)₂O, Et₃N, CH₂Cl₂, RT, 2 h. B) Asymmetric synthesis of loxoprofen (**10a**) and its analogue **10b** by a two-step hydrogenation of **9a,b** using a single catalyst (*R,S*)-**1b**: d) (*R,S*)-**1b** (1 mol%), 30 atm H₂, Et₃N (1 equiv), CH₂Cl₂, RT, 12 h; e) (*R,S*)-**1b** (1–2 mol%), 30 atm H₂, CH₂Cl₂, RT, 12 h.

anti-inflammatory drug with medicinal significance and research interests (Scheme 1b).^[18] A two-step AH of the acrylic and alkylidene C=C bonds in the (*E*)-2-[4-[(2-oxocycloalkylidene)methyl]phenyl]acrylic acids **9a,b** by using a (*R,S*)-**1b**, afforded (1'*S*, 2*R*)-loxoprofen (**10a**; 98% *ee*, 82:18 d.r.) and its analogue **10b** (99% *ee*, 91:9 d.r.) in excellent enantio- and diastereoselectivities (for details see the Supporting Information).

In summary, we have disclosed that SpinPhox/Ir^I-catalysts are highly efficient and versatile in enantioselective hydrogenation of a broad spectrum of exocyclic α,β-unsaturated carbonyl compounds with particular merits in addressing the challenging α-alkylidenelactam substrates with six- or seven-membered rings, thus affording the corresponding optically active carbonyl compounds with an α-chiral carbon center in excellent enantiomeric excesses (up to 98% *ee*). Synthetic utility of the present protocol has also been demonstrated in

the asymmetric synthesis of the anti-inflammatory drug loxoprofen and its analogue, as well as biologically important ε-aminocaproic acid derivatives.

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- [1] a) G.-Q. Lin, Y.-M. Li, A. S. C. Chan, *Principles and Applications of Asymmetric Synthesis*, Wiley-Interscience, New York, **2001**, pp. 71–134, and references therein; b) P. M. Weintraub, J. S. Sabol, J. M. Kane, D. R. Borchering, *Tetrahedron* **2003**, *59*, 2953; c) A. Padwa, S. R. Harring, M. A. I. Semones, *J. Org. Chem.* **1998**, *63*, 44; d) R. S. Meissner, J. J. Perkins, L. T. Duong, G. D. Hartman, W. F. Hoffman, J. R. Huff, N. C. Ihle, C. Leu, R. M. Nagy, A. Naylor-Olsen, G. A. Rodan, S. B. Rodan, D. B. Whitman, G. A. Wesolowski, M. E. Duggan, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 25, and references therein; e) T.-Y. Yue, D. D. McLeod, K. B. Albertson, S. R. Beck, J. Deerberg, J. M. Fortunak, W. A. Nugent, L. A. Radesca, L. Tang, C. D. Xiang, *Org. Process Res. Dev.* **2006**, *10*, 262; f) P. A. Procopiou, K. Biggadike, A. F. English, R. M. Farrell, G. N. Hagger, A. P. Hancock, M. V. Haase, W. R. Irving, M. A. Snowden, Y. E. Solanke, C. J. Tralau-Stewart, S. E. Walton, J. A. Wood, *J. Med. Chem.* **2001**, *44*, 602; g) H. T. Balaydin, M. Sentürk, A. Menzek, *Bioorg. Med. Chem. Lett.* **2012**, *22*, 1352.
- [2] For comprehensive reviews, see: a) R. Noyori, *Asymmetric Catalysis in Organic Synthesis*, Wiley, New York, **1993**; b) *Comprehensive Asymmetric Catalysis I–III* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**; c) *Catalytic Asymmetric Synthesis*, 3rd ed. (Ed.: I. Ojima), Wiley, Hoboken, **2010**; d) *Handbook of Homogeneous Hydrogenation*, Vol. 2 (Eds.: J. G. de Vries, C. J. Elsevier), Wiley-VCH, Weinheim, **2007**, part IV.
- [3] a) J. Y. L. Chung, D. Zhao, D. L. Hughes, L. M. McNamara, E. J. J. Grabowski, P. J. Reider, *Tetrahedron Lett.* **1995**, *36*, 7379; b) T. Y. Yue, W. A. Nugent, *J. Am. Chem. Soc.* **2002**, *124*, 13692; c) F.-T. Tian, D.-M. Yao, Y.-Y. Liu, F. Xie, W.-B. Zhang, *Adv. Synth. Catal.* **2010**, *352*, 1841; d) Y.-Y. Liu, D.-M. Yao, K. Li, F.-T. Tian, F. Xie, W.-B. Zhang, *Tetrahedron* **2011**, *67*, 8445; e) Y.-Y. Liu, W.-B. Zhang, *Angew. Chem.* **2013**, *125*, 2259; *Angew. Chem. Int. Ed.* **2013**, *52*, 2203.
- [4] a) T. Ohta, T. Miyake, N. Seido, H. Kumabayashi, H. Takaya, *J. Org. Chem.* **1995**, *60*, 357, and references therein; b) J. Q. Li, X. Quan, P. G. Andersson, *Chem. Eur. J.* **2012**, *18*, 10609; c) D. H. Woodmansee, M.-A. Mueller, L. Troendlin, E. Hoermann, A. Pfaltz, *Chem. Eur. J.* **2012**, *18*, 13780. See also ref. 3c.
- [5] a) C. Thorey, F. Henin, J. Muzart, *Tetrahedron: Asymmetry* **1996**, *7*, 975; b) T. Yamamoto, M. Ogura, A. Amano, K. Adachi, T. Hagiwara, T. Kanisawa, *Tetrahedron Lett.* **2002**, *43*, 9081; c) G. Fogassy, A. Tungler, A. Lévai, *J. Mol. Catal. A* **2003**, *192*, 189; d) F. Maurer, V. Huch, A. Ullrich, U. Kazmaier, *J. Org. Chem.* **2012**, *77*, 5139.
- [6] a) W. S. Knowles, *Acc. Chem. Res.* **1983**, *16*, 106; b) A. S. C. Chan, J. J. Pluth, J. Halpern, *J. Am. Chem. Soc.* **1980**, *102*, 5952; c) J.-H. Xie, Q.-L. Zhou, *Acta Chim. Sin.* **2012**, *70*, 1427.
- [7] For reviews, see: a) X. Cui, K. Burgess, *Chem. Rev.* **2005**, *105*, 3272; b) K. Källström, I. Munslowand, P. G. Andersson, *Chem. Eur. J.* **2006**, *12*, 3194; c) S. J. Roseblade, A. Pfaltz, *Acc. Chem. Res.* **2007**, *40*, 1402; d) T. L. Church, P. G. Andersson, *Coord. Chem. Rev.* **2008**, *252*, 513; e) D. H. Woodmansee, A. Pfaltz, *Chem. Commun.* **2011**, *47*, 7912.

- [8] a) J. Blankenstein, A. Pfaltz, *Angew. Chem.* **2001**, *113*, 4577; *Angew. Chem. Int. Ed.* **2001**, *40*, 4445, and references therein; b) W. J. Tang, W. M. Wang, X. M. Zhang, *Angew. Chem.* **2003**, *115*, 973; *Angew. Chem. Int. Ed.* **2003**, *42*, 943; c) S. Bell, B. Wustenberg, S. Kaiser, F. Menges, T. Netscher, A. Pfaltz, *Science* **2006**, *311*, 642; d) M. Engman, J. S. Diesen, A. Paptchikhine, P. G. Andersson, *J. Am. Chem. Soc.* **2007**, *129*, 4536; e) M. Dieguez, J. Mazuela, O. Pamies, J. J. Verendel, P. G. Andersson, *J. Am. Chem. Soc.* **2008**, *130*, 7208; f) J. Zhao, K. Burgess, *J. Am. Chem. Soc.* **2009**, *131*, 13236.
- [9] a) P. Cheruku, J. Diesen, P. G. Andersson, *J. Am. Chem. Soc.* **2008**, *130*, 5595; b) P. Cheruku, A. Paptchikhine, T. L. Church, P. G. Andersson, *J. Am. Chem. Soc.* **2009**, *131*, 8285.
- [10] M. G. Schrems, E. Neumann, A. Pfaltz, *Angew. Chem.* **2007**, *119*, 8422; *Angew. Chem. Int. Ed.* **2007**, *46*, 8274.
- [11] a) S. M. Lu, C. Bolm, *Angew. Chem.* **2008**, *120*, 9052; *Angew. Chem. Int. Ed.* **2008**, *47*, 8920; b) W.-J. Lu, Y.-W. Chen, X.-L. Hou, *Angew. Chem.* **2008**, *120*, 10287; *Angew. Chem. Int. Ed.* **2008**, *47*, 10133; c) S. Li, S.-F. Zhu, C.-M. Zhang, S. Song, Q.-L. Zhou, *J. Am. Chem. Soc.* **2008**, *130*, 8584; d) W.-J. Lu, X.-L. Hou, *Adv. Synth. Catal.* **2009**, *351*, 1224.
- [12] Although the BiphPhox/Ir^I catalysts developed by the group of Zhang were particularly enantioselective in AH of five-membered exocyclic α,β -unsaturated carbonyl compounds, the catalysts only showed moderate enantioselectivities for the reaction of substrates having a six- or seven-membered ring. See Ref. [3c–e].
- [13] a) *Privileged Chiral Ligands and Catalysts*; (Ed.: Q.-L. Zhou), Wiley-VCH, Weinheim, **2011**; For a leading reference, see: b) A. S. C. Chan, W. Hu, C.-C. Pai, C.-P. Lau, Y. Jiang, A. Mi, M. Yan, J. Sun, R. Lou, J. Deng, *J. Am. Chem. Soc.* **1997**, *119*, 9570; For reviews, see: c) J.-H. Xie, Q.-L. Zhou, *Acc. Chem. Res.* **2008**, *41*, 581; d) K. Ding, Z. Han, Z. Wang, *Chem. Asian J.* **2009**, *4*, 32; e) G. B. Bajracharya, M. A. Arai, P. S. Koranne, T. Suzuki, S. Takizawa, H. Sasai, *Bull. Chem. Soc. Jpn.* **2009**, *82*, 285.
- [14] a) Z. Han, Z. Wang, X. Zhang, K. Ding, *Angew. Chem.* **2009**, *121*, 5449; *Angew. Chem. Int. Ed.* **2009**, *48*, 5345; b) Y. Zhang, Z. Han, F. Li, K. Ding, A. Zhang, *Chem. Commun.* **2010**, *46*, 156; c) Z. Han, Z. Wang, K. Ding, *Adv. Synth. Catal.* **2011**, *353*, 1584; d) X. Wang, Z. Han, Z. Wang, K. Ding, *Angew. Chem.* **2012**, *124*, 960; *Angew. Chem. Int. Ed.* **2012**, *51*, 936; e) J. Shang, Z. Han, Y. Li, Z. Wang, K. Ding, *Chem. Commun.* **2012**, *48*, 5172; f) X. Wang, P. Guo, X. Wang, Z. Wang, K. Ding, *Adv. Synth. Catal.* **2013**, *355*, 2900.
- [15] There was only one example so far concerning the AH of a single 3-alkylenecaprolactam substrate with a moderate *ee* value (75%). See Ref. [3b].
- [16] T. L. Church, T. Rasmussen, P. G. Andersson, *Organometallics* **2010**, *29*, 6769.
- [17] a) C. Van Aelbrouck, L. Englberger, D. Faraoni, *Recent Pat. Cardiovasc. Drug Discovery* **2012**, *7*, 175; b) M. MacDonald, D. V. Velde, J. Aubé, *Org. Lett.* **2000**, *2*, 1653.
- [18] a) S. Naruto, A. Terada, *Chem. Pharm. Bull.* **1983**, *31*, 4286; b) T. Mandai, T. Yamakawa, *Synlett* **2000**, *6*, 862; c) T. Hyodo, Y. Kiyotsuka, Y. Kobayashi, *Org. Lett.* **2009**, *11*, 1103; d) J.-B. Xie, J.-H. Xie, X.-Y. Liu, W.-L. Kong, S. Li, Q.-L. Zhou, *J. Am. Chem. Soc.* **2010**, *132*, 4538; e) N. Yamakawa, S. Suemasu, T. Ishihara, T. Asano, T. Mizushima, Y. Okamoto, K.-I. Tanaka, K. Miyata, M. Otsuka, *J. Med. Chem.* **2012**, *55*, 5143, and references therein.