

# Enantioselective Hydrogenation of Acyclic Aromatic *N*-Aryl Imines Catalyzed by an Iridium Complex of (*S,S*)-1,2-Bis(*tert*-butylmethylphosphino)ethane

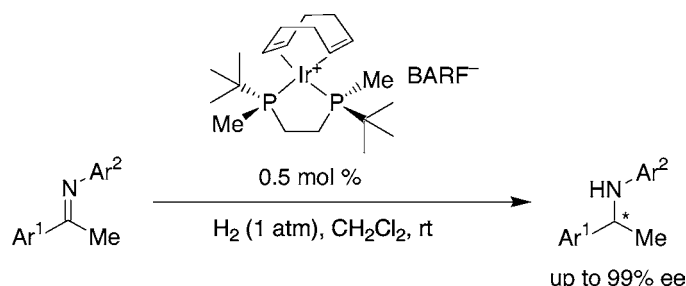
Tsuneo Imamoto,\* Noriyuki Iwadate, and Kazuhiro Yoshida

Department of Chemistry, Faculty of Science,  
Chiba University, Yayoi-cho, Inage-ku, Chiba 263-8522, Japan

imamoto@faculty.chiba-u.jp

Received March 6, 2006

## ABSTRACT



An iridium(I) complex of (*S,S*)-1,2-bis(*tert*-butylmethylphosphino)ethane with tetrakis(3,5-bis(trifluoromethyl)phenyl)borate as the counterion catalyzes the hydrogenation of acyclic aromatic *N*-aryl imines under 1 atm of hydrogen pressure at room temperature to give the corresponding optically active secondary amines with up to 99% ee.

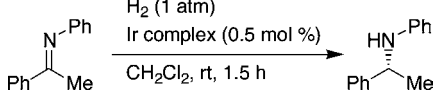
Optically active secondary amines are useful intermediates in the synthesis of biologically active compounds. Therefore, the development of efficient methods for their preparation is synthetically important. Among the methods for the preparation of optically active amines, the enantioselective hydrogenation of C=N double bonds using chiral transition-metal complexes as catalysts is one of the most useful.<sup>1</sup> Especially, iridium complexes with phosphine-based chiral auxiliaries were proved to exhibit high to excellent enantioselectivities in the hydrogenation of imines.<sup>2,3</sup> For example, the Ir–f–binaphane complexes developed by Xiao and Zhang were used in the hydrogenation of acyclic imines to afford the corresponding secondary amines with excellent

enantiomeric excesses of up to 99.6%.<sup>21</sup> However, most of the reported methods require high hydrogen pressures (5–100 atm) to complete the reactions, and to our knowledge, only a few reactions have been tested under an atmospheric pressure of hydrogen.<sup>20,u</sup> Herein, we report a new catalyst system that promotes the asymmetric hydrogenation of acyclic aromatic *N*-aryl imines under 1 atm of hydrogen pressure at room temperature.

Our initial attempt at the hydrogenation was carried out with the combination of several Ir(I) salts and (*S*)-BINAP. The activities of the catalyst systems were tested in the hydrogenation of *N*-(1-phenylethylidene)aniline as the model substrate with 0.5 mol % of the iridium catalyst in dichloromethane. The results are summarized in Table 1.

No reduction occurred when a neutral iridium complex was employed (entry 1). The cationic complexes with the BF<sub>4</sub><sup>-</sup>, TfO<sup>-</sup>, or PF<sub>6</sub><sup>-</sup> counterion were not effective at all under the conditions employed (entries 2–4). In sharp contrast, the complex possessing tetrakis(3,5-bis(trifluoromethyl)phenyl)borate as the counterion was effective (entry 5).

(1) For representative reviews, see: (a) Blaser, H.-U.; Spindler, F. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 1, Chapter 6.2, pp 247–265. (b) Okuma, T.; Noyori, R. In *Comprehensive Asymmetric Catalysis, Suppl. J*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 2004; Vol. 1, Chapter 6.2, pp 43–53. (c) Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029–3069.

**Table 1.** Effects of Counterions


entry	Ir complex	yield (%) <sup>a</sup>	ee (%)
1	[IrCl(cod)] <sub>2</sub> /( <i>S,S</i> )-BINAP	0	
2	[Ir( <i>S,S</i> )-binap(cod)][BF <sub>4</sub> ]	0	
3	[Ir( <i>S,S</i> )-binap(cod)][OTf]	0	
4	[Ir( <i>S,S</i> )-binap(cod)][PF <sub>6</sub> ]	0	
5	[Ir( <i>S,S</i> )-binap(cod)][BARF]	93	16

<sup>a</sup> Isolated yield.

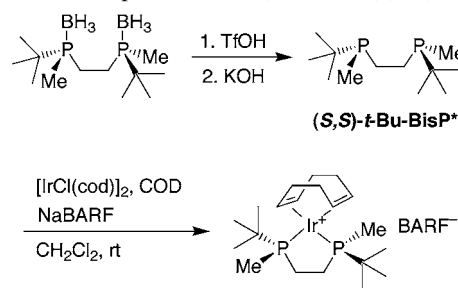
ethylphenyl)borate ([BARF]<sup>-</sup>)<sup>4</sup> remarkably promoted the reduction even under 1 atm of hydrogen pressure to give the product in 93% yield after 1.5 h, albeit with low ee (16%) of the product (entry 5). Although the pronounced rate acceleration effect of BARF as the counterion was observed in many reactions including Ir-catalyzed hydrogenation reactions,<sup>2m,p,r,u,w,5</sup> we were surprised to obtain this result.

(2) (a) Spindler, F.; Pugin, B.; Blaser, H.-U. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 558–559. (b) Ng Cheong, Y.; Osborn, J. A. *J. Am. Chem. Soc.* **1990**, *112*, 9400–9401. (c) Tani, K.; Onouchi, J.; Yamagata, T.; Kataoka, Y. *Chem. Lett.* **1995**, 955–956. (d) Morimoto, T.; Achiwa, K. *Tetrahedron: Asymmetry* **1995**, *6*, 2661–2664. (e) Togni, A. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1475–1477. (f) Sablong, R.; Osborn, J. A. *Tetrahedron: Asymmetry* **1996**, *7*, 3059–3062. (g) Sablong, R.; Osborn, J. A. *Tetrahedron Lett.* **1996**, *37*, 4937–4940. (h) Schnider, P.; Koch, G.; Prétôt, R.; Wang, G.; Bohnen, F. M.; Krüger, C.; Pfaltz, A. *Chem.–Eur. J.* **1997**, *3*, 887–892. (i) Zhu, G.; Zhang, X. *Tetrahedron: Asymmetry* **1998**, *9*, 2415–2418. (j) Kainz, S.; Brinkmann, A.; Leitner, W.; Pfaltz, A. *J. Am. Chem. Soc.* **1999**, *121*, 6421–6429. (k) Margalef-Català, R.; Claver, C.; Salagre, P.; Fernández, E. *Tetrahedron: Asymmetry* **2000**, *11*, 1469–1476. (l) Xiao, D.; Zhang, X. *Angew. Chem., Int. Ed.* **2001**, *40*, 3425–3428. (m) Blaser, H.-U.; Buser, H.-P.; Häusel, R.; Jalett, H.-P.; Spindler, F. *J. Organomet. Chem.* **2001**, *621*, 34–38. (n) Pugin, B.; Landert, H.; Spindler, F.; Blaser, H.-U. *Adv. Synth. Catal.* **2002**, *344*, 974–979. (o) Jiang, X.; Minnaad, A. J.; Hessen, B.; Feringa, B. L.; Duchateau, A. L. L.; Andrien, J. G. O.; Boogers, J. A. F.; de Vries, J. G. *Org. Lett.* **2003**, *5*, 1503–1506. (p) Cozzi, P. G.; Menges, F.; Kaiser, S. *Synlett* **2003**, 833–836. (q) Guiu, E.; Muñoz, B.; Castellón, S.; Claver, C. *Adv. Synth. Catal.* **2003**, *345*, 169–171. (r) Solinas, M.; Pfaltz, A.; Cozzi, P. G.; Leitner, W. *J. Am. Chem. Soc.* **2004**, *126*, 16142–16147. (s) Dorta, R.; Brogini, D.; Stoop, R.; Rügger, H.; Spindler, F.; Togni, A. *Chem.–Eur. J.* **2004**, *10*, 267–278. (t) Maire, P.; Deblon, S.; Breher, F.; Geier, J.; Böhrer, C.; Rügger, H.; Schönberg, H.; Grützmacher, H. *Chem.–Eur. J.* **2004**, *10*, 4198–4205. (u) Blanc, C.; Agbossou-Niedercorn, F.; Nowogrocki, G. *Tetrahedron: Asymmetry* **2004**, *15*, 2159–2163. (v) Liu, D.; Li, W.; Zhang, X. *Tetrahedron: Asymmetry* **2004**, *15*, 2181–2184. (w) Trifonova, A.; Diesen, J. S.; Chapman, C. J.; Andersson, P. G. *Org. Lett.* **2004**, *6*, 3825–3827. (x) Ezhova, M. B.; Patrick, B. O.; James, B. R.; Waller, F. J.; Ford, M. E. *J. Mol. Catal. A: Chem.* **2004**, *224*, 71–79. (y) Vargas, S.; Rubio, M.; Suárez, A.; Pizzano, A. *Tetrahedron Lett.* **2005**, *46*, 2049–2052. (z) Moessner, C.; Bolm, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 7564–7567.

(3) Other examples of asymmetric hydrogenation of imines catalyzed by Ti, Ru, Rh, or Pd. (a) Willoughby, C. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1992**, *114*, 7562–7564. (b) Willoughby, C. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 11703–11714. (c) Uematsu, N.; Fujii, A.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 4916–4917. (d) Vedejs, E.; Trapencieris, P.; Suna, E. *J. Org. Chem.* **1999**, *64*, 6724–6729. (e) Cogley, C. J.; Henschke, J. P. *Adv. Synth. Catal.* **2003**, *345*, 195–201. (f) Kang, G.-J.; Cullen, W. R.; Fryzuk, M. D.; James, B. R.; Kutney, J. P. *J. Chem. Soc., Chem. Commun.* **1988**, 1466–1467. (g) Bakos, J.; Orosz, A.; Heil, B.; Laghmari, M.; Lhoste, P.; Sinou, D. *J. Chem. Soc., Chem. Commun.* **1991**, 1684–1685. (h) Buriak, J. M.; Osborn, J. A. *Organometallics* **1996**, *15*, 3161–3169. (i) Tararov, V. I.; Kadyrov, R.; Riermeier, T. H.; Holz, J.; Börner, A. *Tetrahedron: Asymmetry* **1999**, *10*, 4009–4015. (j) Tararov, V. I.; Börner, A. *Synlett* **2005**, 203–211. (k) Abe, H.; Amii, H.; Uneyama, K. *Org. Lett.* **2001**, *3*, 313–315.

This was because a previously reported hydrogenation of the same substrate under 1 atm of hydrogen pressure using a chiral Ir complex with BARF required a relatively high catalyst loading (2 mol %) and a long reaction time (4 h) to give a moderate yield (39%) of the product.<sup>2u</sup>

Encouraged by this result, we prepared an iridium(I) complex of (*S,S*)-1,2-bis(*tert*-butylmethylphosphino)ethane ((*S,S*)-*t*-Bu-BisP\*) bearing BARF as the counterion because the phosphine ligand was proved to show pronounced efficiency in the rhodium-catalyzed hydrogenation of dehydroamino acids and related substrates,<sup>6</sup> and we envisioned that the ligand could also be successfully used in the iridium-catalyzed asymmetric hydrogenation of imines. The preparative route to the desired complex [Ir(*S,S*)-*t*-Bu-BisP\*)(cod)]-[BARF] is shown in Scheme 1. In this preparation, we used

**Scheme 1.** Preparation of [Ir(*t*-Bu-BisP\*)(cod)][BARF]

the air-stable borane complex of (*S,S*)-1,2-bis(*tert*-butylmethylphosphino)ethane as the starting material. The enantiomerically pure borane complex prepared according to the literature was subjected to deboronation by reaction with trifluoromethanesulfonic acid in toluene, followed by treatment with potassium hydroxide to give diphosphine ligand (*S,S*)-*t*-Bu-BisP\*.<sup>7,8</sup> The ligand was immediately reacted with [IrCl(cod)]<sub>2</sub> in the presence of cyclooctadiene, and the

(4) (a) Brookhart, M.; Grant, B.; Vople, J. A. *Organometallics* **1992**, *11*, 3920–3922. (b) Hughes, R. P.; Lindner, D. C.; Rheingold, A. L.; Yap, G. P. A. *Inorg. Chem.* **1997**, *36*, 1726–1727. (c) Reger, D. L.; Wright, T. D.; Little, C. A.; Lamba, J. J. S.; Smith, M. D. *Inorg. Chem.* **2001**, *40*, 3810–3814.

(5) For hydrogenations of alkenes catalyzed by iridium complexes containing BARF, see: (a) Lightfoot, A.; Schnider, P.; Pfaltz, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 2897–2899. (b) Blackmond, D. G.; Lightfoot, A.; Pfaltz, A.; Posner, T.; Schnider, P.; Zimmermann, N. *Chirality* **2000**, *12*, 442–449. (c) Powell, M. T.; Hou, D.-R.; Perry, M. C.; Cui, X.; Burgess, K. *J. Am. Chem. Soc.* **2001**, *123*, 8878–8879. (d) Blankenstein, J.; Pfaltz, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4445–4447. (e) Tang, W.; Wang, W.; Zhang, X. *Angew. Chem., Int. Ed.* **2003**, *42*, 943–946. (f) Schenkel, L. B.; Ellman, J. A. *J. Org. Chem.* **2004**, *69*, 1800–1802. (g) Källström, K.; Hedberg, C.; Brandt, P.; Bayer, A.; Andersson, P. G. *J. Am. Chem. Soc.* **2004**, *126*, 14308–14309. (h) Smidt, S. P.; Zimmermann, N.; Studer, M.; Pfaltz, A. *Chem.–Eur. J.* **2004**, *10*, 4685–4693. (i) Cui, X.; Burgess, K. *Chem. Rev.* **2005**, *105*, 3272–3296.

(6) (a) Imamoto, T.; Watanabe, J.; Wada, Y.; Masuda, H.; Yamada, H.; Tsuruta, H.; Matsukawa, S.; Yamaguchi, K. *J. Am. Chem. Soc.* **1998**, *120*, 1635–1636. (b) Gridnev, I. D.; Yamanoi, Y.; Higashi, N.; Tsuruta, H.; Yasutake, M.; Imamoto, T. *Adv. Synth. Catal.* **2001**, *343*, 118–136.

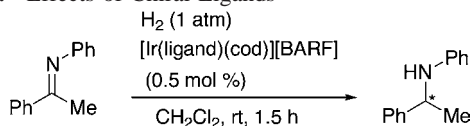
(7) For the preparation of (*S,S*)-*t*-Bu-BisP\*, see: ref 6 and: Crépy, K. V. L.; Imamoto, T.; Seidel, G.; Fürstner, A. *Org. Synth.* **2005**, *82*, 22–29.

(8) For the preparation of (*R,R*)-*t*-Bu-BisP\*, see: Crépy, K. V. L.; Imamoto, T. *Tetrahedron Lett.* **2002**, *43*, 7735–7737.

resulting iridium complex was treated with NaBARF in dichloromethane to give the desired complex as a brown powder.

The enantioinductive ability of this chiral iridium complex was tested in the hydrogenation of the model substrate *N*-(1-phenylethylidene)aniline under 1 atm of hydrogen pressure. The result is summarized in Table 2, together with the results

**Table 2.** Effects of Chiral Ligands



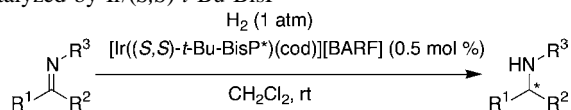
entry	ligand	yield (%) <sup>a</sup>	ee (%)
1	( <i>S</i> )-BINAP	93	16
2	( <i>R</i> )-Ph-PHOX <sup>b</sup>	97	49
3	( <i>R</i> )- <i>i</i> -Pr-PHOX <sup>c</sup>	94	84
4	( <i>S,S</i> )- <i>t</i> -Bu-BisP* <sup>e</sup>	91	86

<sup>a</sup> Isolated yield. <sup>b</sup> (*R*)-2-(2-(Diphenylphosphino)phenyl)-4-phenyl-4,5-dihydrooxazole. <sup>c</sup> (*R*)-2-(2-(Diphenylphosphino)phenyl)-4-(1-methylethyl)-4,5-dihydrooxazole.

obtained by the use of the iridium complexes of (*S*)-BINAP, (*R*)-Ph-PHOX, and (*R*)-*i*-Pr-PHOX. In all cases, the reactions proceeded rapidly to afford the product in high yields, and among these ligands, (*R*)-*i*-Pr-PHOX and (*S,S*)-*t*-Bu-BisP\* exhibited high enantioselection ability (entries 3 and 4).

On the basis of these results, we examined the applicability of [Ir((*S,S*)-*t*-Bu-BisP\*)(cod)][BARF] to other acyclic *N*-aryl imines. The results are presented in Table 3. All reactions

**Table 3.** Enantioselective Hydrogenation of Acyclic Imines Catalyzed by Ir/((*S,S*)-*t*-Bu-BisP\*)

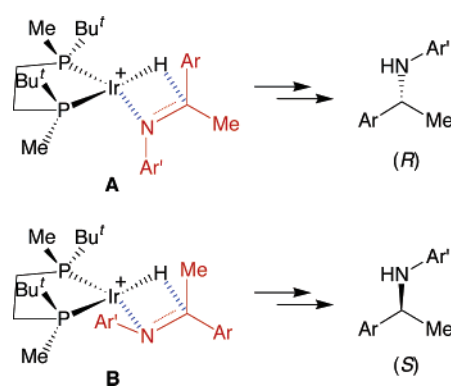


entry	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	time (h)	yield (%) <sup>a</sup>	ee (%) <sup>b</sup> (config)
1	Ph	Me	Ph	1.5	91	86 ( <i>R</i> ) <sup>c</sup>
2	4-MeOC <sub>6</sub> H <sub>4</sub>	Me	Ph	2	98	69 (+) <sup>d</sup>
3	4-FC <sub>6</sub> H <sub>4</sub>	Me	Ph	1.5	92	84 (-) <sup>d</sup>
4	Ph	Me	4-MeOC <sub>6</sub> H <sub>4</sub>	2	93	86 ( <i>R</i> ) <sup>c</sup>
5	Ph	Me	4-FC <sub>6</sub> H <sub>4</sub>	12	99	84 (-) <sup>d</sup>
6	Ph	Me	4-ClC <sub>6</sub> H <sub>4</sub>	12	99	83 (+) <sup>d</sup>
7	Ph	Me	4-CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	12	95	99 (-) <sup>d</sup>
8	Ph	Me	3,5-(CF <sub>3</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	12	97	90 (-) <sup>d</sup>
9	4-MeOC <sub>6</sub> H <sub>4</sub>	Me	4-MeOC <sub>6</sub> H <sub>4</sub>	2	98	83 (+) <sup>d</sup>
10	Ph	CF <sub>3</sub>	Ph	12	0	
11	<i>t</i> -Bu	Me	Ph	12	0	

<sup>a</sup> Isolated yield. <sup>b</sup> Enantiomeric excesses were determined by HPLC using a chiral column. See Supporting Information. <sup>c</sup> Absolute configurations were determined by comparison with the reported analytical data.<sup>2h,10</sup> <sup>d</sup> Absolute configurations were not determined.

were carried out in dichloromethane under 1 atm of hydrogen pressure with a catalyst loading of 0.5 mol %. The reactions of *N*-(1-arylethylidene)aniline proceeded rapidly to give the corresponding products in high yields (entries 1–3), and the substrate R<sup>1</sup> = *p*-methoxyphenyl afforded relatively low enantioselectivity (69%) (entry 2). Except for the reactions of the imine derivatives of aniline and *p*-methoxyaniline, the reactions of acetophenone-based *N*-aryl imines required a long time (entries 5–8). It is noted that the highest enantioselectivity (99%) was achieved when the imine derivative of 4-trifluoromethylaniline was used (entry 7).<sup>9</sup> On the other hand, attempted hydrogenations of *N*-(2,2,2-trifluoro-1-phenylethylidene)aniline and *N*-(1,2,2-trimethylpropylidene)aniline under the same conditions resulted in complete recovery of the starting materials (entries 10 and 11).

It is interesting to consider the enantioselection mechanism of this asymmetric hydrogenation of imines. Although the stereochemical outcome of the examined reactions is not clear in most cases, the two reactions (entries 1 and 4) provided the same sense of enantioselection. Thus, dihydrogen added to the C=N double bonds from the *Si* face to give *R*-configuration products. On the other hand, the mechanism underlying the Ir-catalyzed asymmetric hydrogenation of alkenes and imines has been extensively investigated,<sup>2b,5i,11</sup> and experimental findings and theoretical calculations strongly suggest that the enantioselection is determined at the migratory insertion step. Although the detailed catalytic cycle of the present asymmetric hydrogenation has not yet been elucidated, the stereochemical outcome can be explained in terms of both steric and electronic factors. Thus, we assume that the reaction proceeds through a four-membered transition state; namely, the C=N function interacts with the Ir–H bond trans to the Ir–P bond. Two transition states, **A** and **B** (Figure 1), are possible, in which



**Figure 1.** Possible transition states leading to secondary amines.

**A** is more preferable than **B** because there is a large steric repulsion between the *N*-aryl group (Ar') and the *tert*-butyl group on the phosphorus atom in **B**. It is generally known that unsymmetric imines exist mostly as anti isomers, and hence, the reaction via transition state **A** eventually leads to secondary amines with the *R* configuration.

In conclusion, we found that iridium(I)–phosphine complexes with a BARF counterion exhibited exceedingly high catalytic activity in the hydrogenation of imines. Indeed, in the presence of 0.5 mol % of the catalysts, the hydrogenations were completed under 1 atm of hydrogen pressure in dichloromethane at room temperature. High to excellent

enantioselectivities of up to 99% were achieved by the use of [Ir(*S,S*)-*t*-Bu-BisP\*](cod)][BARF] as the catalyst.

**Acknowledgment.** This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Sciences, Sports and Culture, Japan.

**Supporting Information Available:** Experimental procedures and spectroscopic data of new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL060546B

---

(9) During the preparation of this manuscript, Dervisi et al. reported that *N*-aryl imines were hydrogenated under 1 atm hydrogen pressure at room temperature. The hydrogenation in the presence of [Ir(ddppm)(cod)]PF<sub>6</sub> (0.5–1 mol %) for 9–24 h afforded the corresponding secondary amines with up to 94% ee. Dervisi, A.; Carcedo, C.; Ooi, L. *Adv. Synth. Catal.* **2006**, *348*, 175–183.

(10) Chi, Y.; Zhou, Y.-G.; Zhang, X. *J. Org. Chem.* **2003**, *68*, 4120–4122.

(11) (a) Cooper, A. C.; Streib, W. E.; Eisenstein, O.; Caulton, K. G. *J. Am. Chem. Soc.* **1997**, *119*, 9069–9070. (b) Kimmich, B. F. M.; Somsook, E.; Landis, C. R. *J. Am. Chem. Soc.* **1998**, *120*, 10115–10125. (c) Brandt, P.; Hedberg, C.; Andersson, P. G. *Chem.–Eur. J.* **2003**, *9*, 339–347. (d) Mazet, C.; Smidt, S. P.; Meuwly, M.; Pfaltz, A. *J. Am. Chem. Soc.* **2004**,

---

*126*, 14176–14181. (e) Dietiker, R.; Chen, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 5513–5516. (f) Fan, Y.; Cui, X.; Burgess, K.; Hall, M. B. *J. Am. Chem. Soc.* **2004**, *126*, 16688–16689. (g) Dorta, R.; Brogini, D.; Kissner, R.; Togni, A. *Chem.–Eur. J.* **2004**, *10*, 4546–4555.