Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 15 (2004) 2159–2163

Efficient enantioselective hydrogenation of arylimines using aminophosphine-oxazoline iridium catalysts

Catherine Blanc,[a] Francine Agbossou-Niedercorn[a,*] and Guy Nowogrocki[b]

[a]*Laboratoire de Catalyse de Lille, UMR CNRS 8010, ENSCL, BP 108, 59652 Villeneuve d'Ascq Cedex, France*
[b]*Laboratoire de Cristallographie et Physicochimie du Solide, UMR CNRS 8012, ENSCL, BP 108, 59652 Villeneuve d'Ascq Cedex, France*

Received 21 April 2004; accepted 6 May 2004
Available online 11 June 2004

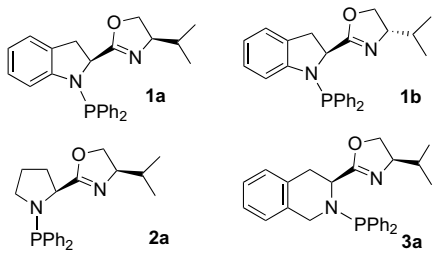
Abstract—The preparation and characterization of cationic iridium complexes bearing chiral aminophosphine-oxazoline auxiliaries of general formula [Ir(COD)L*]X [X: PF_6 and $B(Ar^F)_4$] is reported. These complexes have been applied to the asymmetric hydrogenation of two imines: *N*-(phenylethylidene)aniline **S1** and *N*-(phenylethylidene)benzylamine **S2** providing the corresponding chiral amines in up to 90% and 82% ee, respectively.

1. Introduction

The highly enantioselective hydrogenation of C=C and C=O bonds has been accomplished frequently in the presence of rhodium and ruthenium catalysts.[1] Conversely, the hydrogenation of imines is often less effective using identical or closely related catalysts.[2,3] Yet, the reduction of C=N bonds represents an important process for obtaining enantiomerically pure amines. In fact, chiral amines are often important functionalities in biologically active compounds and they are produced for industrial purposes.[4,5] The largest scale industrial enantioselective catalytic process involves an imine hydrogenation reaction. The produced amine is the precursor to the chiral herbicide (1*S*)-Metolachlor.[6]

Among the significant successes met in the area of enantioselective reduction of imines, Buchwald et al. have developed an *ansa*-titanocene catalyst for a highly effective hydrogenation of cyclic ketimines (up to 98% ee).[7] On the other hand, as mentioned above, several transition metal catalysts of group VIII have also been applied more or less successfully to the hydrogenation of imines[2] but iridium complexes bearing phosphorus based chiral auxiliaries appeared more appropriate for that transformation.[6,8] Xiao and Zhang were able, for example, to reach very high enantioselectivities (up to >99% ee) in the hydrogenation of acyclic imines catalyzed by Ir-f-Binaphthane complexes.[9] On the other side, the potential of bitopic ligands of the *P*,*N* type has been demonstrated in a multitude of enantioselective catalytic reactions.[1a] Particularly, the phosphine-oxazolines (phox ligands) developed initially by Pfaltz, Williams and Helmchen[10] have been applied successfully in many different processes,[11] and induced also high enantioselectivities in the hydrogenation of imines.[12] As a representative example, *N*-(phenylethylidene)aniline and related imines are hydrogenated in the presence of the mentioned catalysts with up to 89% ee.[12a]

We have already reported on the synthesis of a class of *P*,*N* ligands, the aminophosphine-oxazolines (Scheme 1).[13] These auxiliaries are readily prepared from two optically active aminoacids. One is providing the chiral



Scheme 1.

* Corresponding author. Tel.: +33-03-20-43-49-27; fax: +33-03-20-43-65-85; e-mail: francine.agbossou@ensc-lille.fr

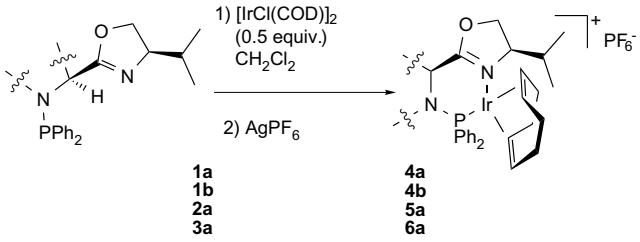
0957-4166/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2004.05.015

oxazoline unit and the second one the chiral aminophosphine end. Three aminoacids have been selected to prepare these ligands that is D-indoline-2-carboxylic acid (for ligands **1a** and **1b**), D-proline (for **2a**), and 1,2,3,4-D-tetrahydroisoquinoline-3-carboxylic acid (for **3a**). These ligands appeared to be very efficient in both the asymmetric allylic alkylation[13] and the conjugate addition to enones.[14]

Here, we report on the preparation of cationic iridium(I) complexes bearing aminophosphine-oxazolines and on their use in the asymmetric hydrogenation of imines.

2. Results and discussion

The cationic iridium complexes **4a**, **4b**, **5a**, and **6a** are easily prepared, in separate experiments, through reaction of 2 equiv of ligands **1a**, **1b**, **2a**, and **3a** with 1 equiv of $[Ir(COD)Cl]_2$ in CH_2Cl_2 at reflux for 3 h followed by the exchange of the chloride, which is performed in the presence of $AgPF_6$ at room temperature. After filtration of the resulting mixture, the expected complexes are isolated in high yields (Scheme 2).[15]



1a **1b** **2a** **3a** → **4a** **4b** **5a** **6a**

Scheme 2.

We also prepared complex **7a** where the PF_6 anion has been replaced with $B(Ar^F)_4$[16] through reaction of the intermediate complex toward **4a** with sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate instead of $AgPF_6$ in a biphasic system (Scheme 3).[15] The crystal structure of **7a** has been determined by X-ray diffraction (Fig. 1).[17]

Complex **7a** presents characteristics quite similar to those of other iridium complexes reported in the literature even though small differences are observed.[12a,18] The complex presents a square-planar as coordination geometry of the iridium atom. The P–Ir–N angle is slightly larger than in the analogous PHOX ligand[19] (88.0(7)° vs 85.6(1)°). The bond distances between iridium and the two heteroatoms [Ir–N, 2.04(2) vs 2.106(3) Å; Ir–P, 2.251(7) vs 2.3009(12) Å] are quite close. Compared to other closely related complexes and because of the higher flexibility of ligand **1a**, there is a deviation of the chelate ring from planarity and a twist-boat conformation is observed in **7a**. The phenyl rings are placed in pseudoequatorial and pseudoaxial positions, as is often encountered in other diphenylphophane complexes.[12a]

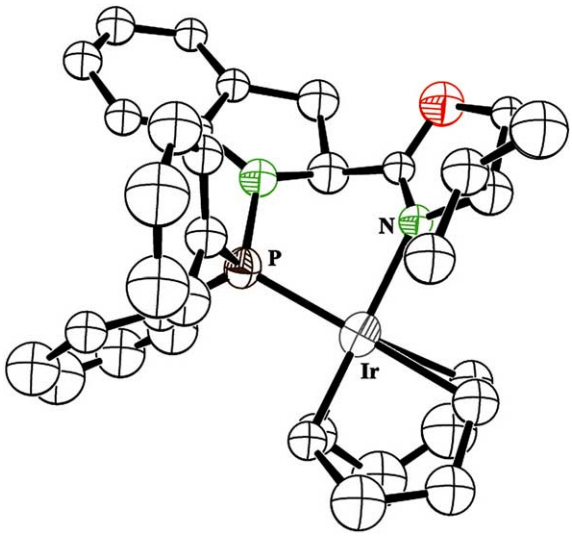
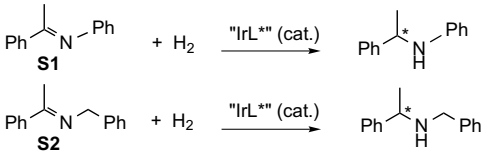


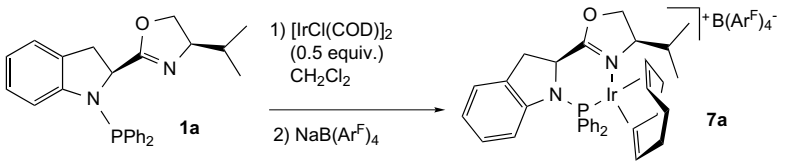
Figure 1. Crystal structure of **7a**. The H atom and PF_6 are omitted for clarity.

These iridium complexes were next applied in the enantioselective hydrogenation of two imines, that is *N*-(phenylethylidene)aniline **S1**, and *N*-(phenylethylidene)benzylamine **S2** (Scheme 4).[20] The hydrogenation results are reported in Table 1. Hydrogenation carried out on **S1** in the presence of the original PHOX auxiliary[19] is also reported for comparison.



Scheme 4.

The initial hydrogenation experiments have been carried out on **S1** at room temperature and under 50 bar of hydrogen for 12 h in dry degassed CH_2Cl_2 in the presence



Scheme 3.

Table 1. Asymmetric hydrogenation of **S1** and **S2**[a]

Entry	Substrate	Ligand	Complex	P_{H2} (bar)	Temp (°C)	S/Ir	Conv. (%)[b]	Ee (%) (Config.)[c]
1	**S1**	**1a**	**4a**	50	25	50	98	80 (*S*)
2		**1b**	**4b**	50	25	80	83	14 (*R*)
3		**2a**	**5a**	50	25	50	100	72 (*S*)
4		**3a**	**6a**	50	25	50	94	68 (*S*)
5[d]		**PHOX**	[e]	50	25	50	36	68 (*S*)
6		**1a**	[f]	50	25	50	14	nd[g]
7		**3a**	[g]	50	25	30	<5	nd
8		**1a**	**4a**	50	0	50	100	84 (*S*)
9		**2a**	**5a**	50	0	30	82	85 (*S*)
10		**1a**	**4a**	20	25	50	100	86 (*S*)
11		**1a**	**4a**	5	25	50	100	81 (*S*)
12		**2a**	**5a**	20	25	50	100	73 (*S*)
13		**3a**	**6a**	30	25	30	91	72 (*S*)
14		**1a**	**7a**	50	25	50	91	83 (*S*)
15[h]		**1a**	**7a**	1	25	50	39	87 (*S*)
16		**1a**	**7a**	50	0	50	100	89 (*S*)
17		**1a**	**7a**	20	25	50	100	90 (*S*)
18	**S2**	**1a**	**4a**	50	25	50	100	81 (*S*)
19		**2a**	**5a**	50	25	50	100	62 (*S*)
20		**3a**	**6a**	50	25	50	100	60 (*S*)
21		**1a**	**7a**	50	25	50	100	82 (*S*)

[a] The hydrogenations were carried out during 12 h in freshly distilled CH_2Cl_2 in the conditions mentioned in the table following the general procedure given in Ref. 20.

[b] Conversions were determined by GC and ^1H NMR.

[c] Ee were determined by HPLC using a Chiralcel OD column (hexane/isopropanol: 90/10; 1 mL min^{-1}).

[d] Reaction time of 2 h.

[e] $[Ir(COD)(PHOX)]PF_6$ prepared as complex **4a** from $[IrCl(COD)]_2$ and commercially available (*S*)-2-(2-diphenylphosphanyl-phenyl)-4-isopropyl-4,5-dihydro-oxazole.

[f] The catalyst was prepared in situ by reacting $[IrCI(COD)]_2$ and **1a** in toluene.

[g] Tetra(terbutyl)ammonium iodide was added (10 mol%) to the reaction mixture containing $[IrCl(COD)]_2$ and ligand **3a**.

[h] Reaction time of 4 h.

of **4a** and **4b**. We found that **4a**, which is bearing ligand **1a** with a (*R*) configuration on the oxazoline ring and (*S*) on the aminophosphine residue, induced a higher selectivity (80% ee, entry 1) than its diastereomeric complex **4b** carrying a ligand with a (*S*) configuration on the oxazoline unit (14% ee, entry 2). In addition, the antipode amines are obtained with these two chiral auxiliaries. This clearly points out the great impact of the stereogenic center of the oxazoline unit on the selectivity of the reaction. A further variation of the selectivity is expected while investigating the substituent effect on the stereogenic center. Generally, high conversions and good to high enantioselectivities (over 68% ee) are obtained under 50 bar of H_2 at room temperature. The PHOX auxiliary is providing an enantioselectivity identical to that induced by ligand **3a** (68% ee) (entries 4 and 5). As already noticed for the other catalytic reactions (asymmetric allylic alkylation and conjugate addition to enones), the more rigid ligands **1a** and **2a** are leading to the best results in terms of enantioselectivity.[13,14]

We next varied the catalytic conditions. For example, while performing the hydrogenation of **S1** with the neutral precursor $[IrCl\{\mathbf{1a}\}]_2$ prepared in situ in toluene through reaction of $[IrCl(COD)]_2$ with **1a**, the reaction became very slow (entry 6). On the other side, when terbutylammonium iodide was added to the catalytic mixture (entry 7) containing the neutral precatalyst obtained from a reaction between $[IrCl(COD)]_2$ with ligand **3a**, the process slowed down significantly (conversion <5%, entry 7). This is not surprising as the resulting neutral iridium iodide species $[IrI\{\mathbf{1a}\}]_2$ is expected to exhibit properties close to those of the neutral complex $[IrCl\{\mathbf{1a}\}]_2$ (entry 6). Also, the beneficial effect of iodine on the hydrogenation of imines has been reported when neutral catalysts are involved.[9] In our case, the addition of iodine to a catalytic mixture containing $[IrCl\{\mathbf{1a}\}]_2$ is providing a catalyst inducing less than 5% ee during the hydrogenation of **S1**. The temperature and the hydrogen pressure have an influence on the efficiency of the process. Indeed, while lowering the temperature to 0 °C, the selectivity increased for **4a** ($\Delta ee = 4\%$, entries 1 and 8) and for **5a** ($\Delta ee = 12.5\%$, entries 2 and 9). On the other side, reducing the hydrogen pressure from 50 to 30 or further to 20 bar led to an increase of the selectivity. For example, for **4a**, a 6% ee increase was obtained (entries 1 and 10). A similar enhancement was observed for **6a** ($\Delta ee = 4\%$, entries 4 and 13). Lowering further the hydrogen pressure became detrimental (entry 11). The effect of the counterion of the iridium cationic complex has been reported in the case of the hydrogenation of tetrasubstituted alkenes.[21] Thus replacing PF_6 by $B(Ar^F)_4$ enhances generally the selectivity of the reaction. An identical enhancement of the selectivity has been obtained while using complex **7a** instead of **4a** ($\Delta ee = 4\%$, entries 17 vs 10). Thus, the adjustment of the catalytic conditions led to 90% ee as the best result (entry 17).

Substrate **S2** (*N*-(phenylethylidene)benzylamine) was also hydrogenated efficiently in the presence of the cationic iridium precatalysts but with a slightly lower selectivity than **S1**, that is from 62% to 82% ee (entries 18–21). For this substrate **S2**, again complexes **4a** and **7a**, which are bearing the more rigid and more sterically demanding ligand of the series, **1a**, are providing the best results.

3. Conclusion

In conclusion, we have demonstrated that cationic iridium complexes with chiral aminophosphine-oxazolines are efficient catalysts for the enantioselective hydrogenation of imines. The complexes are readily accessible and air-stable. In the hydrogenation of *N*-(phenylethylidene)aniline **S1**, up to 90% ee could be reached. The hydrogenation of substrate **S2** provided the corresponding amine with up to 82% ee. These chiral inductions compare very well to the best results obtained with phosphine-oxazolines on the same substrates. The substrate scope for imine hydrogenation as well as applications of this family of ligands to other asymmetric transformations are under investigation in our laboratory.

Acknowledgements

We thank CNRS and MEN (grant to C.B.) for financial support.

References and notes

1. (a) *Catalytic Asymmetric Synthesis*; Ojima, I., Ed., 2nd ed.; Wiley-VCH: New York, 2000; (b) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; (c) Noyori, R.; Ohkuma, T. *Angew. Chem., Int. Ed.* **2001**, *40*, 40; (d) Blaser, H. U.; Malan, C.; Pugin, B.; Spindler, F.; Steiner, H.; Sterder, M. *Adv. Synth. Catal.* **2003**, *345*, 103.
2. (a) Bakos, J.; Tóth, I.; Heil, B.; Markó, I. *J. Organomet. Chem.* **1985**, *279*, 23; (b) Becalski, A. G.; Cullen, W. R.; Fryzuk, M. D.; James, B. R.; Kang, G.-J.; Rettig, S. J. *Inorg. Chem.* **1991**, *30*, 5002; (c) Bakos, J.; Orosz, A.; Heil, B.; Laghmari, M.; Lhoste, P.; Sinou, D. *J. Chem. Soc., Chem. Commun.* **1991**, 1684; (d) Amrami, Y.; Leconte, L.; Sinou, D.; Bakos, J.; Toth, I.; Heil, B. *Organometallics* **1989**, *8*, 542; (e) Lensink, C.; de Vries, J. G. *Tetrahedron: Asymmetry* **1992**, *3*, 235; (f) Tararov, V. I.; Kadyrov, R.; Riermeier, T. H.; Holz, J.; Börner, A. *Tetrahedron: Asymmetry* **1999**, *10*, 4009; (g) Sablong, R.; Osborn, J. A. *Tetrahedron Lett.* **1996**, *37*, 4937.
3. For transfer hydrogenation of imines, see: (a) Uematsu, N.; Fujii, A.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 4916; (b) Mao, J.; Baker, D. C. *Org. Lett.* **1999**, *1*, 841; (c) Vedejs, E.; Trapencieris, P.; Suna, E. *J. Org. Chem.* **1999**, *64*, 6724.
4. Imwinkelried, R. *Chimia* **1997**, *51*, 300.
5. (a) Breuer, M.; Ditrich, K.; Habicher, T.; Hauer, B.; Keßeler, M.; Stürmer, R.; Zelinski, T. *Angew. Chem., Int. Ed.* **2004**, *43*, 788; (b) Spindler, F.; Blaser, H.-U. In *Transition Metals for Organic Synthesis*; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, 1998; Vol. 2, p 69.
6. (a) Togni, A. *Angew. Chem., Int. Ed.* **1996**, *35*, 1475; (b) Spindler, F.; Blaser, H. U. *Enantiomer* **1999**, *4*, 557; (c) Blaser, H.-U.; Brieden, W.; Pugin, B.; Spindler, F.; Studer, M.; Togni, A. *Top. Catal.* **2002**, *19*, 3.
7. (a) Willoughby, C. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1992**, *114*, 7562; (b) Willoughby, C. A.; Buchwald, S. L. *J. Org. Chem.* **1993**, *58*, 7627; (c) Willoughby, C. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 8952; (d) Willoughby, C. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 11703.
8. (a) Chan, Y. N. C.; Osborn, J. A. *J. Am. Chem. Soc.* **1990**, *112*, 9400; (b) Spindler, F.; Pugin, B.; Blaser, H. U. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 558; (c) Morimoto, T.; Nakajima, N.; Achiwa, K. *Synlett* **1995**, 748; (d) Tani, K.; Onouchi, J.; Yamagata, Y.; Kataoka, Y. *Chem. Lett.* **1995**, 955; (e) Satoh, K.; Inenaga, M.; Kanai, K. *Tetrahedron: Asymmetry* **1998**, *9*, 2657; (f) Cahill, J. P.; Lightfoot, A. P.; Goddard, R.; Rust, J.; Guiry, P. J. *Tetrahedron: Asymmetry* **1998**, *9*, 4307; (g) Broger, E. A.; Burkart, W.; Hennig, M.; Scalone, M.; Schmid, R. *Tetrahedron: Asymmetry* **1998**, *9*, 4043; (h) Guiu, E.; Muñoz, B.; Castillón, S.; Claver, C. *Adv. Synth. Catal.* **2003**, *345*, 169.
9. Xiao, D.; Zhang, X. *Angew. Chem., Int. Ed.* **2001**, *40*, 3425.
10. (a) Von Matt, P.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 566; (b) Dawson, G. J.; Frost, C. G.; Williams, J. M. J. *Tetrahedron Lett.* **1993**, *34*, 3194; (c) Sprinz, J.; Helmchen, G. *Tetrahedron Lett.* **1993**, *34*, 1769.
11. Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336.
12. (a) Schnider, P.; Koch, G.; Prétôt, R.; Wang, G.; Bohnen, F. M.; Krüger, C.; Pfaltz, A. *Chem. Eur. J.* **1997**, *3*, 887; (b) Kainz, S.; Brikmann, A.; Leitner, W.; Pfaltz, A. *J. Am. Chem. Soc.* **1999**, *121*, 6421; (c) Pfaltz, A. *Chimia* **2001**, *55*, 708; (d) Cozzi, P. G.; Menges, F.; Kaiser, S. *Synlett* **2003**, 833.
13. Blanc, C.; Hannedouche, J.; Agbossou-Niedercorn, F. *Tetrahedron Lett.* **2003**, *44*, 6469.
14. Blanc, C.; Agbossou-Niedercorn, F. *Tetrahedron: Asymmetry* **2004**, *15*, 757.
15. Iridium complexes ^{31}P NMR (121 MHz, CD_2Cl_2, δ ppm): **4a**: 51.0 (s); **4b**: 51.0 (s); **5a**: 51.3 (s); **6a**: 51.0 (s); **7a**: 51.3 (s). **7a**: ^{1}H NMR (300 MHz, CD_2Cl_2): δ 0.21 (d, $J = 6.6$ Hz, 3H); 0.73 (d, $J = 7.1$ Hz, 3H); 0.92 (m, 2H); 1.28 (m, 3H); 1.58 (m, 2H); 1.84 (m, 1H); 2.13 (m, 2H); 2.48 (m, 4H); 3.00 (m, 1H); 3.38 (m, 1H); 3.70 (m, 2H); 4.08 (m, 1H); 4.36 (m, 1H); 4.58 (dd, $J = 4.9$ and 9.5 Hz, 1H); 4.67 (t, $J = 9.8$ Hz, 1H); 4.98 (m, 1H); 5.18 (m, 1H); 5.73 (m, 1H); 5.82 (d, $J = 7.8$ Hz, 1H); 6.73 (t, $J = 7.8$ Hz, 1H); 6.85 (m, 1H); 7.23 (d, $J = 6.8$ Hz, 1H); 7.34–7.45 (m, 8H); 7.82 (m, 3H).
16. Nishida, H.; Takada, N.; Yoshimura, M.; Sonoda, T.; Kobayashi, H. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2600; For reviews on 'noncoordinating' ions, see: (a) Strauss, S. H. *Chem. Rev.* **1993**, *93*, 927; (b) Krossing, I.; Raabe, I. *Angew. Chem., Int. Ed.* **2004**, *43*, 2066.
17. Burnett, M. N.; Johnson, C. K. ORTEP-III: Oak Ridge Thermal Ellipsoid Plot Program for Crystal Structure Illustrations, Oak Ridge National Laboratory Report ORNL-6895, 1996. CCDC number 238864.
18. Menges, F.; Pfaltz, A. *Adv. Synth. Catal.* **2002**, *344*, 40.
19. PHOX auxiliary used: commercially available (*S*)-2-(2-diphenylphosphanyl-phenyl)-4-isopropyl-4,5-dihydro-oxazole.
20. General procedure for the iridium-catalyzed hydrogenation of imines: A glass flask equipped with a magnetic stir bar was charged with *N*-(phenylethylidene)aniline **S1** (70 mg, 0.35 mmol) and placed in a stainless-steel

autoclave (50 mL). The autoclave was purged with N_2. Under nitrogen, precatalyst **4a** (6 mg, 0.007 mmol) was dissolved in freshly distilled and degassed methylene chloride (5 mL) and transferred via cannula to the autoclave. Then, the autoclave was pressurized with H_2 (50 bar) and stirred overnight at room temperature. After depressurization and evaporation of the solvent, the resulting slurry was filtered through a short pad of silica gel. The hydrogenated product (*S*)-*N*-phenyl-1-phenylethylamine was isolated in 96% yield (68 mg). The enantiomeric excess was determined by HPLC using a Chiralcel OD column (*i*-PrOH/hexane: 90/10; flow rate: 1 mL/min; detection UV at 254 nm; $t_R(S) = 9.6$ min, $t_R(R) = 11.3$ min).

21. Lightfoot, A.; Schider, P.; Pfaltz, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 2897.