Tetrahedron Letters 49 (2008) 7290–7293

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Access to chiral tertiary amines via the iridium-catalyzed asymmetric hydrogenation of enamines

Pradeep Cheruku, Tamara L. Church, Anna Trifonova, Thomas Wartmann, Pher G. Andersson *

Department of Biochemistry and Organic Chemistry, Uppsala University, Box 576, S751-23 Uppsala, Sweden

ARTICLE INFO

Article history:
Received 8 September 2008
Revised 29 September 2008
Accepted 8 October 2008
Available online 14 October 2008

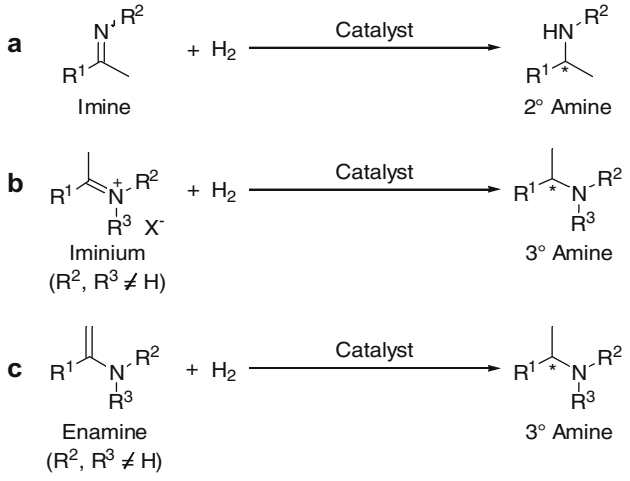
Keywords:
Asymmetric catalysis
Hydrogenation
Enamines
Chiral tertiary amines

ABSTRACT

The asymmetric hydrogenation of *N*,*N*-dialkyl and *N*-alkyl-*N*-aryl enamines to chiral tertiary amines was studied. All the N,P-ligated iridium complexes investigated were active catalysts for the reaction, but only those with bicycle-supported oxazoline-phosphine ligands gave reasonable stereoinduction. The best catalyst produced a range of chiral tertiary amines in up to 87% ee.

The prevalence of chiral trialkyl and dialkylaryl tertiary amines can hardly be overstated. They are present in myriad natural products, including Cinchona, tetrahydroisoquinoline, and tetrahydro-β-carboline alkaloids. They are also used as enantioselective organocatalysts[1] and as ligands for asymmetric transition metal catalysts.[2] Chiral tertiary amines have been synthesized by several methods; however, the discovery and development of routes to this class of compounds are ongoing. Turner and co-workers recently developed a chemoenzymatic system for the dynamic kinetic resolution of cyclic tertiary amines.[3] Hartwig and co-workers have reported the iridium-catalyzed, enantioselective allylic amination of allyl acetates,[4] carbonates[4] and alcohols[5] to produce chiral tertiary amines in good or high yields and high ee values. Asymmetric allylic amination has since been accomplished with other palladium[6] and iridium[7] catalysts, though each was applied to make only one or two tertiary amines. The copper-catalyzed addition of terminal alkynes to isoquinoline iminium ions has been shown to yield N-alkylated (i.e., tertiary) isoquinolines with chirality in the 1 position.[8]

Catalytic enantioselective hydrogenation is currently a major source of chiral materials, and can be envisioned as a route to chiral tertiary amines. Considerable progress has been made in the enantioselective hydrogenation of imines, which can produce chiral secondary amines very selectively (Scheme 1a).[9] Though tertiary amines cannot be produced by imine hydrogenation, they are accessible from the hydrogenation of iminium salts (Scheme 1b) and enamines (Scheme 1c). In 2001, Magee and Norton reported the direct asymmetric hydrogenation of two iminium salts to tertiary amines with modest ee values;[10] in 2006, Zhu, Deng, and co-workers used asymmetric transfer hydrogenation to convert two iminium ions to tertiary amines very stereoselectively.[11] The latter method has been applied to the synthesis of some naturally occurring alkaloids.[12] The asymmetric hydrogenation of enamines has also been achieved. In the earliest report, Lee and Buchwald used a titanocene catalyst to hydrogenate a range of enamines to chiral tertiary amines with high ee values.[13] Though



Scheme 1. Asymmetric hydrogenation as a route to chiral amines.

* Corresponding author. Tel.: +46 18 471 3801; fax: +46 18 471 3818.
E-mail address: pher.andersson@biorg.uu.se (P. G. Andersson).

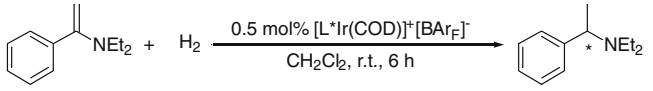
0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.10.035

5 mol % of catalyst was required, good yields were obtained. The rhodium-catalyzed asymmetric hydrogenations of β-amino-α,β-unsaturated esters and amides have also been reported, and can be very stereoselective.[14] However, only primary and secondary amines have been synthesized this way; in one case, evidence suggests that the reaction is actually a hydrogenation of the imine tautomer of the substrate.[14c] Rhodium catalysts have also been applied to the asymmetric hydrogenation of enamines without additional coordinating groups. Börner and co-workers published the hydrogenation of this type of enamine to tertiary amines in up to 72% ee,[15] whereas Zhou and co-workers obtained better enantioselectivities using a rhodium catalyst in combination with iodine and acetic acid.[16] Kalck et al. recently described the asymmetric hydrogenation of enamines by rhodium and iridium catalysts in an ionic liquid; a wide range of ee values were reported.[17]

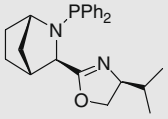
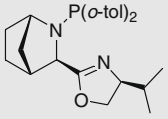
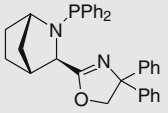
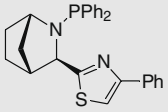
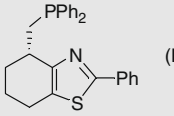
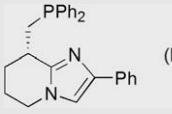
The successes reported in the asymmetric hydrogenation of enamines suggest that it is a viable route to chiral tertiary amines, and the reaction is especially attractive considering the straightforward substrate synthesis.[18] However, very few asymmetric enamine hydrogenations have been demonstrated. The promise showed by this reaction, coupled with the need for further development in the synthesis of chiral tertiary amines, led us to pursue enamines as substrates in our iridium-catalyzed hydrogenation studies. Iridium complexes with chiral N,P or N,C ligands have been used extensively in the asymmetric hydrogenation of imines[9] and of largely unfunctionalized olefins[19,20] and have recently been applied to the asymmetric hydrogenation of olefins with weakly coordinating or non-coordinating functional groups[21] such as vinyl fluorides,[22] vinyl silanes,[23] vinyl phosphonates[24] and enol phosphinate esters.[25] Especially relevant to enamine reduction are the recent asymmetric hydrogenations of their oxygen analogues, enol ethers,[20f,26] and of heteroaromatic rings.[27] Lewis bases are known to inhibit olefin hydrogenation by N,P-ligated iridium complexes,[28] so the amine functionalities in both the starting material and product pose potential threats to iridium-catalyzed enamine hydrogenation. However, such catalysts are active for the hydrogenation of imines to secondary amines, so we were hopeful that they could also produce tertiary amines through hydrogenation.

We began by testing several of our chiral iridium complexes, which have known activity for asymmetric olefin hydrogenation,[22a,29,30] in the reduction of a prochiral enamine (Table 1). We chose α-(diethylamino)styrene, **1**, as the substrate for these initial reactions. The amine functionality of **1** did not inactivate the catalysts tested; in fact, all the catalysts converted **1** completely to the desired tertiary amine, α-(diethylamino) ethylbenzene, after 6 h under 50 bar H_2 at room temperature.[31,32] The structurally similar thiazole-phosphine and imidazole-phosphine ligands **E** and **F** (entries 5 and 6) produced active catalysts for enamine reduction, but imparted little or no stereoselectivity. Bicycle-based oxazoline-phosphine ligands **A**–**C** (entries 1–3) produced catalysts that combined hydrogenation activity with much better stereoselectivity. Among these three catalysts, the substituent(s) at the 4 position of the oxazoline ring appeared to impact stereodiscrimination of the catalyst less than the phosphine substituents did. Two catalysts whose ligands differed only in the oxazoline moiety (**A** and **C**, entries 1 and 3) hydrogenated **1** with identical ee values, whereas changing the $-PPh_2$ group of **A** to the $-P(o\text{-tol})_2$ group in **B** produced a sizeable increase in ee for the same reaction (84% vs 64%, entries 2 and 1, respectively). Nevertheless, the oxazoline group clearly played an important role in stereoselectivity, as a bicycle-based thiazole-phosphine ligand (**D**, entry 4) produced a catalyst that completely hydrogenated **1** to a racemic mixture of tertiary amine products. Overall, $[(\mathbf{B})Ir(COD)]^+[BAr_F]^-$ was the most stereoselective catalyst for the hydrogenation of the test enamine, and was therefore used in further studies of this reaction.

Table 1
Screening of N,P ligands in the asymmetric hydrogenation of α-(diethylamino)-styrene, **1**, by $[(L^*)Ir(COD)]^+[BAr_F]^-$



1, 0.1 M 50 bar

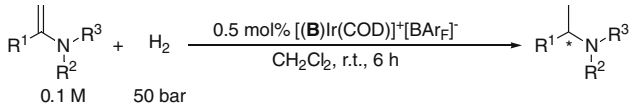
Entry	L*	Conv.[a] (%)	ee[b] (%)
1	 (**A**)	>99	64 (+)
2	 (**B**)	>99	84 (+)
3	 (**C**)	>99	64 (+)
4	 (**D**)	>99	0
5	 (**E**)	>99	14
6	 (**F**)	>99	0

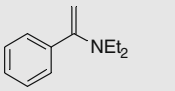
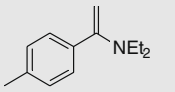
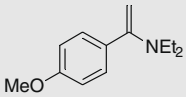
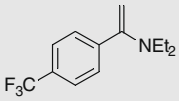
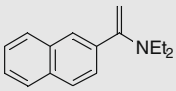
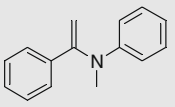
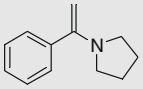
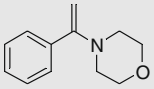
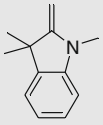
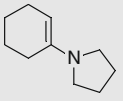
[a] Conversion to α-(diethylamino)ethylbenzene, as determined by ^1H NMR.
[b] ee of amine product, determined by ^1H NMR after reaction with (*R*)-*O*-mandelic acid.

Most of the enamines examined in this study were synthesized from the corresponding ketones and secondary amines using White and Weingarten's $TiCl_4$-mediated method[33] and were purified by distillation.[34] The substrate scope of enamine hydrogenation by $[(\mathbf{B})Ir(COD)]^+[BAr_F]^-$ was evaluated using the same conditions applied to the reduction of **1**: 0.5 mol % catalyst and 50 bar H_2 at room temperature for 6 h (Table 2). This was sufficient to convert most enamines to the desired tertiary amine, though a range of enantioselectivities were obtained. For example, replacing the phenyl group of **1** with a 4-tolyl group (entry 2) produced a small increase in stereoselectivity, returning the corresponding amine in 87% ee. The related substrate **3**, which has a more electron-donating 4-methoxy group, however, was reduced in only 64% ee (entry 3). Improved stereoselectivity was observed in the hydrogenation of the electron-poor 4-trimethylfluoro derivative **4** (77% ee; entry 4), though this reaction was still slightly less selective than the reduction of **1**. The 2-naphthyl-substituted enamine **5** was also hydrogenated in a moderate 64% ee (entry 5).

At first, the nature of the amine group appeared to have much less impact on the reaction than that of the aryl group, as α-(methylphenylamino)styrene (**6**, entry 6) was reduced in similar ee to the dialkylamino substrate **1** (79% vs 84%). The reaction proved more difficult when the amino group was cyclic (entries 7 and

Table 2
The hydrogenation of various enamines using the catalyst $[(\mathbf{B})Ir(COD)]^+[BArF]^-$



Entry	Substrate	Conv.[a] (%)	ee[b] (%)
1	 **(1)**	>99	84 (+)
2	 **(2)**	>99	87
3	 **(3)**	>99	64
4	 **(4)**	>99	77
5	 **(5)**	>99	64
6	 **(6)**	>99	79 (+)
7	 **(7)**	66	33 (*R*)[c]
8	 **(8)**	75	30
9	 **(9)**	>99	20
10	 **(10)**	>99	n.a.[d]

[a] Conversion to product tertiary amine, as determined by ^{1}H NMR.
[b] ee of amine product, determined by ^{1}H NMR after reaction with (*R*)-*O*-mandelic acid.
[c] Determined based on comparison of the ^{1}H NMR spectrum of the (*R*)-*O*-mandelic acid adduct with the literature value.[13]
[d] Not applicable.

8). α-(1-Pyrrolidino)styrene (**7**) was 66% hydrogenated after 6 h, but in only 33% ee (entry 7). This result was particularly notable because **7** can be thought of as a cyclic version of **1**; apparently, the restricted flexibility conferred by the five-membered ring had a large effect on the hydrogenation reaction. The same behavior was observed in the reduction of α-(4-morpholino)styrene (**8**), which was hydrogenated to 75% conversion and in 30% ee after 6 h (entry 8). A longer reaction time did not improve this result; a very similar conversion was obtained even when the reaction was run for 36 h. Fischer base (**9**, entry 9), a cyclic amine with an exocyclic double bond, was completely hydrogenated, though the product was formed in only 20% ee. Finally, $[(\mathbf{B})Ir(COD)]^+[BAr_F]^-$ completely reduced **10**, which contains a trisubstituted olefin (entry 10). Though the hydrogenation of this substrate yields an achiral product, we were encouraged by the ability of the catalyst to reduce enamines bearing trisubstituted olefins, as this will certainly be important in the future development of asymmetric enamine hydrogenation. Based on the sensitivity of the conversion to subtle changes on the enamine, in particular amongst the cyclic substrates, we speculate that the tertiary amine products can inhibit the catalyst if they are sufficiently basic and unhindered. This would explain why an *N*,*N*-diethylamine-functionalized enamine such as **1** is hydrogenated to completion despite the fact that the pyrrolidine derivative **7**, which has a more exposed electron pair, is not. (The fact that the conversion of **8** to amine reached a plateau suggests that it is the product, rather than the starting material, that poisons the catalyst.) The other pyrrolidine-containing substrate, **10**, was hydrogenated to completion; in this case, the more hindered amine produced in the reduction of the trisubstituted olefin may be less capable of inhibiting the catalyst. Enamines **6** and **9**, despite bearing small methyl groups on the nitrogen, are also fully hydrogenated, perhaps because they form dialkyl aryl amines, which are less basic than trialkyl amines.

Several complexes of the form $[(L^*)Ir(COD)]^+[BAr_F]^-$ are active catalysts for the hydrogenation of *N*,*N*-dialkyl and *N*-alkyl-*N*-aryl enamines to tertiary amines. When $L^* = \mathbf{B}$, a bicycle-supported phosphine-oxazoline ligand, the catalyst produces chiral tertiary amines in up to 87% ee. In most cases, 0.5 mol % of catalyst was sufficient to completely reduce the substrate after 6 h at room temperature, though a few interesting cases of lower catalyst activity were observed. The asymmetric reductions of nine enamines are reported. Future work on this topic will focus on understanding the subtle effect of enamine structure on catalyst activity, improving stereoselectivity, and extending the reaction to include enamines with trisubstituted double bonds.

Acknowledgments

The authors are grateful to Ms. P. Kaukoranta, Mr. A. Paptchikhine, and Dr. J. S. Diesen for providing catalyst samples, and to The Swedish Research Council (VR; Contract 2006-3611) for funding. T.W. is grateful to the ERASMUS-Programme, and T.L.C. is grateful to Wenner-Gren Stiftelserna for a postdoctoral fellowship.

References and notes

1. Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713.
2. (a) Kizirian, J.-C. *Chem. Rev.* **2008**, *108*, 140; (b) Masson, G.; Housseman, C.; Zhu, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 4614.
3. (a) Bailey, K. R.; Ellis, A. J.; Reiss, R.; Snape, T. J.; Turner, N. J. *Chem. Commun.* **2007**, 3640; (b) Dunsmore, C.; Carr, R.; Fleming, T.; Turner, N. *J. Am. Chem. Soc.* **2006**, *128*, 2224.
4. Ohmura, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 15164.
5. Yamashita, Y.; Gopalarathnam, A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 7508.
6. (a) Watson, I. D. G.; Yudin, A. K. *J. Am. Chem. Soc.* **2005**, *127*, 17516; (b) Nemoto, T.; Matsuda, T.; Akimoto, Y.; Fukuyama, T.; Hamada, Y. *Org. Lett.* **2005**, *7*, 4447; (c) Faller, J. W.; Wilt, J. C. *Org. Lett.* **2005**, *7*, 633; (d) Watson, I. D. G.; Styler, S. A.; Yudin, A. K. *J. Am. Chem. Soc.* **2004**, *126*, 5086.
7. (a) Nemoto, T.; Sakamoto, T.; Matsumoto, T.; Hamada, Y. *Tetrahedron Lett.* **2006**, *47*, 8737; (b) Leitner, A.; Shekhar, S.; Pouy, M. J.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 15506; (c) Welter, C.; Koch, O.; Lipowsky, G.; Helmchen, G. *Chem. Commun.* **2004**, 896; (d) Kiener, C.; Shu, C.; Incarvito, C.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 14272.
8. Taylor, A. M.; Schreiber, S. L. *Org. Lett.* **2006**, *8*, 143.
9. (a) Spindler, F.; Blaser, H.-U. In *Handbook of Homogeneous Hydrogenation*; de Vries, J., Elsevier, C. J., Eds.; Wiley-VCH Verlag GmbH & Co.: Weinheim, 2007; Vol. 3, (b) Blaser, H.-U.; Spindler, F. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999, Vol. 1.
10. Magee, M. P.; Norton, J. R. *J. Am. Chem. Soc.* **2001**, *123*, 1778.
11. Wu, J.; Wang, F.; Ma, Y.; Cui, X.; Cun, L.; Zhu, J.; Deng, J.; Yu, B. *Chem. Commun.* **2006**, 1766.
12. (a) Szawkało, J.; Czarnocki, S. J.; Zawadzka, A.; Wojtasiewicz, K.; Leniewski, A.; Maurin, J. K.; Czarnocki, Z.; Drabowicz, J. *Tetrahedron: Asymmetry* **2007**, *18*, 406; (b) Szawkało, J.; Zawadzka, A.; Wojtasiewicz, K.; Leniewski, A.; Drabowicz, J.; Czarnocki, Z. *Tetrahedron: Asymmetry* **2005**, *16*, 3619.

13. Lee, N. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 5985.
14. (a) Kubryk, M.; Hansen, K. B. *Tetrahedron: Asymmetry* **2006**, *17*, 205; (b) Dai, Q.; Yang, W.; Zhang, X. *Org. Lett.* **2005**, *7*, 5343; (c) Hsiao, Y.; Rivera, N. R.; Rosner, T.; Krska, S. W.; Njolito, E.; Wang, F.; Sun, Y.; Armstrong, J. D., III; Grabowski, E. J. J.; Tillyer, R. D.; Spindler, F.; Malan, C. *J. Am. Chem. Soc.* **2004**, *126*, 9918.
15. Tararov, V. I.; Kadyrov, R.; Riermeier, T. H.; Holz, J.; Börner, A. *Tetrahedron Lett.* **2000**, *41*, 2351.
16. Hou, G.-H.; Xie, J.-H.; Wang, L.-X.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2006**, *128*, 11774.
17. Kalck, P.; Urrutigoity, M.; Bachelier, A.; Preti, M.; Riviere, P. Fr. Pat. Appl.,2008, 2910471; *Chem. Abstr.*, **2008**, *149*, 106863.
18. For some enamine syntheses, see: Whitesell, J. K. In *Comprehensive Organic Synthesis*; Winterfeldt, E., Ed.; Trost, B. M.; Fleming, I., Series Eds.; Pergamon: Oxford, 1991; Vol. 6.
19. For initial reports, see: (a) Schnider, P.; Koch, G.; Prétôt, R.; Wang, G.; Bohnen, F. M.; Krüger, C.; Pfaltz, A. *Chem.-Eur. J.* **1997**, *3*, 887; (b) Lightfoot, A.; Schnider, P.; Pfaltz, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 2897.
20. For overviews of asymmetric iridium-catalyzed olefin hydrogenation, see: (a) Roseblade, S. J.; Pfaltz, A. *Acc. Chem. Res.* **2007**, *40*, 1402; (b) Roseblade, S. J.; Pfaltz, A. *C. R. Chim.* **2007**, *10*, 178; (c) Pfaltz, A.; Bell, S. In *Handbook of Homogeneous Hydrogenation*; de Vries, J., Elsevier, C. J., Eds.; Wiley-VCH Verlag GmbH & Co.: Weinheim, 2007, Vol. 3; (d) Källström, K.; Munslow, I.; Andersson, P. G. *Chem.-Eur. J.* **2006**, *12*, 3194; (e) Cui, X.; Burgess, K. *Chem. Rev.* **2005**, *105*, 3272; (f) Valla, C.; Pfaltz, A. *Chim. Oggi.* **2004**, *22*, 4; (g) Pfaltz, A.; Drury, W. J., III. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5723; (h) Pfaltz, A.; Blankenstein, J.; Hilgraf, R.; Hörmann, E.; McIntyre, S.; Menges, F.; Schönleber, M.; Smidt, S. P.; Wüstenberg, B.; Zimmermann, N. *Adv. Synth. Catal.* **2003**, *345*, 33.
21. Church, T. L.; Andersson, P. G. *Coord. Chem. Rev.* **2008**, *252*, 513.
22. (a) Kaukoranta, P.; Engman, M.; Hedberg, C.; Bergquist, J.; Andersson, P. G. *Adv. Synth. Catal.* **2008**, *350*, 1168; (b) Engman, M.; Diesen, J. S.; Paptchikhine, A.; Andersson, P. G. *J. Am. Chem. Soc.* **2007**, *129*, 4536.
23. Källström, K.; Munslow, I. J.; Hedberg, C.; Andersson, P. G. *Adv. Synth. Catal.* **2006**, *348*, 2575.
24. Goulioukina, N. S.; Dolgina, T. M.; Bondarenko, G. N.; Beletskaya, I. P.; Ilyin, M. M.; Davankov, V. A.; Pfaltz, A. *Tetrahedron: Asymmetry* **2003**, *14*, 1397.
25. (a) Cheruku, P.; Diesen, J.; Andersson, P. G. *J. Am. Chem. Soc.* **2008**, *130*, 5595; (b) Cheruku, P.; Gohil, S.; Andersson, P. G. *Org. Lett.* **2007**, *9*, 1659.
26. (a) Zhu, Y.; Burgess, K. *Adv. Synth. Catal.* **2008**, *350*, 979; (b) Roseblade, S. J.; Pfaltz, A. *Acc. Chem. Res.* **2007**, *40*, 1402.
27. Zhou, Y.-G. *Acc. Chem. Res.* **2007**, *40*, 1357.
28. Crabtree, R. *Acc. Chem. Res.* **1979**, *12*, 331.
29. (a) Hedberg, C.; Källström, K.; Brandt, P.; Hansen, L. K.; Andersson, P. G. *J. Am. Chem. Soc.* **2006**, *128*, 2995; (b) Trifonova, A.; Diesen, J. S.; Andersson, P. G. *Chem.-Eur. J.* **2006**, *12*, 2318; (c) Trifonova, A.; Diesen, J. S.; Chapman, C. J.; Andersson, P. G. *Org. Lett.* **2004**, *6*, 3825; (d) Källström, K.; Hedberg, C.; Brandt, P.; Bayer, A.; Andersson, P. G. *J. Am. Chem. Soc.* **2004**, *126*, 14308.
30. The synthesis of catalyst $[(\mathbf{D})\mathrm{Ir(COD)}]^{+}[\mathrm{BAr_F}]^{-}$ will be reported separately. Paptchikhine, A.; Cheruku, P.; Andersson, P. G., in preparation.
31. *General procedure for enamine hydrogenation*: A vial was charged with substrate (0.2 mmol) and Ir complex (0.5 mol %). Dry CH_2Cl_2 (2 mL) was added and the vial was placed in a steel bomb. The bomb was purged three times with hydrogen, then filled to 50 bar with H_2 gas. After stirring for 6 h at room temperature, the pressure was released and the solvent was removed in vacuo. The crude product was chromatographed (EtOAc/pentane) to remove catalyst residues before conversions and ee values were determined.
32. Of course, we are unable to rule out the possibility that the catalysis was slowed by competitive binding of the enamines or tertiary amines to the metal.
33. White, W. A.; Weingarten, H. *J. Org. Chem.* **1967**, *32*, 213.
34. 2,3-Dihydro-1,3,3-trimethyl-2-methylene-1*H*-indole (Table 2, entry 9) and 1-(1-cyclohexen-1-yl)pyrrolidine (Table 2, entry 10) were purchased from Aldrich and used as received.