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Highly Flexible Synthesis of Chiral Azacycles via Iridium-Catalyzed Hydrogenation

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Saturated, chiral nitrogen-containing heterocycles are common motifs in medicinal compounds and natural products such as alkaloids, and their preparation by asymmetric catalysis has seen intensive study over the past 20 years.[1] Transition-metal-catalyzed hydrogenation, one of the most powerful, efficient and well-established methods for preparing enantiomerically enriched compounds, has been used.[2] In fact, the most common strategy to access chiral nitrogen heterocycles is via the hydrogenation of heteroaromatic compounds such as quinolines, isoquinolines, quinoxalines, pyridines, and pyrroles.[3]

The metal-catalyzed asymmetric hydrogenation of cyclic imines has also been achieved,[4] most often in the presence of an aromatic substituent. Naturally, this reaction can give chirality α to the nitrogen atom only.

Enamide hydrogenation has been used but is usually dependent on functionalization at nitrogen.[5] Since Buchwald's first report,[6] several groups have hydrogenated unfunctionalized enamines,[2b,7] though few have yielded high selectivity. Zhou and co-workers[8] reported the direct hydrogenation of cyclic N,N-dialkyl enamines.

Two successful asymmetric hydrogenations of cyclic alkenes in which the double bond is distant from nitrogen and in the same ring have been reported. Szöllösi and co-workers[9] used a cinchona-modified Pd/Al_2O_3 catalyst to reduce an α,β-unsaturated carboxylic acid with moderate selectivity. Zhang and co-workers[10] hydrogenated a protected *N*-acyl-functionalized 2,5-dihydropyrrole with high selectivity.

Since iridium-based hydrogenation catalysts $[(L)Ir(COD)]^+[BAr_F]^-$ (COD = 1,4-cyclooctadiene, $[BAr_F]^- = [(3,5\text{-}(F_3C)_2\text{-}C_6H_3)_4B]^-$) do not require coordinating groups to direct the stereoselectivity,[11] we imagined that they may be well-suited for the hydrogenation of heterocyclic olefins in which the heteroatom is remote from the olefin, such as substrate **2**. Additionally, as iridium catalysts are not coordinated by the N group, any protecting group can be chosen and later removed, thus leaving room for further synthetic modifications.

Herein we report the use of iridium-catalyzed asymmetric hydrogenations that produce five-, six-, and seven-membered azacycles with good to excellent enantioselectivities. We synthesized a range of tosyl-protected aminodienes **1** from the corresponding amidoalkenes and allyl bromides (Scheme 1). Ring-closing metathesis using Grubbs' second-generation catalyst[12] produced 1,2,3,6-tetrahydropyridines **2** in good yields.

We screened six-membered, N-tosyl-protected azacyclic alkenes bearing methyl or phenyl substituents against our catalyst library (Table 1).[13] Catalysts with the structurally similar ligands **A**−**D** gave high selectivity for the phenyl-substituted olefin, whereas the ligand with a bicyclic backbone, **E**, performed better for the methyl-substituted olefin. Ligand **D** (Table 1, entry 4) produced a less reactive catalyst.

Scheme 1. Synthesis of Precursors **2**

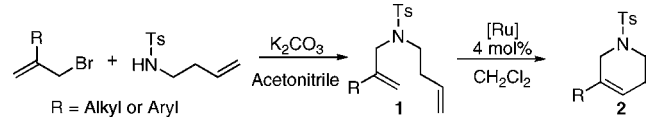
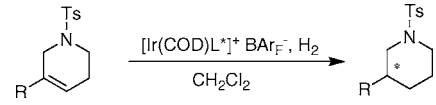
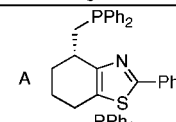
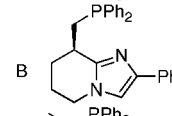
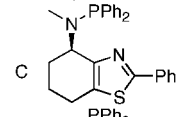
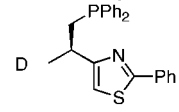
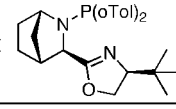


Table 1. Screening of Catalysts for Asymmetric Hydrogenation of **2**[a]



Entry	Ligand	R	conv[b] (%)	*ee*[c] (%)
1	A 	Ph	>99	>99 (+)
		Me	65	85 (+)
2	B 	Ph	>99	91 (-)
		Me	>99	91 (-)
3	C 	Ph	81	97 (-)
		Me	97	70 (-)
4	D 	Ph	27	>99 (-)
		Me	43	84 (-)
5	E 	Ph	95	57 (-)
		Me	>99	97 (-)

[a] Reaction conditions: 0.5 mol % catalyst, 50 bar H_2, 15 h, room temperature. [b] Determined by ^1H NMR spectroscopy. [c] Determined by chiral HPLC.

These results encouraged us to evaluate a range of substrates bearing different aliphatic or aromatic substituents using catalysts based on ligands **A** and **E** (Table 2). We found that the catalyst derived from ligand **E** tolerated several CH_2X derivatives while retaining selectivity (Table 2, entries 1−4). Excellent selectivity and high activity were obtained for substrates with electron-rich substituents (entries 5−9) using $[(\mathbf{A})Ir(COD)]^+[BAr_F]^-$, whereas lower selectivity was obtained for those with electron-poor aryl groups (entries 10, 12, and 14). However, these substrates could be reduced faster and more enantioselectively using $[(\mathbf{B})Ir(COD)]^+[BAr_F]^-$.

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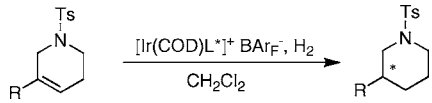
Table 2. Asymmetric Hydrogenation of Six-Membered N-Heterocyclic Olefins[a]

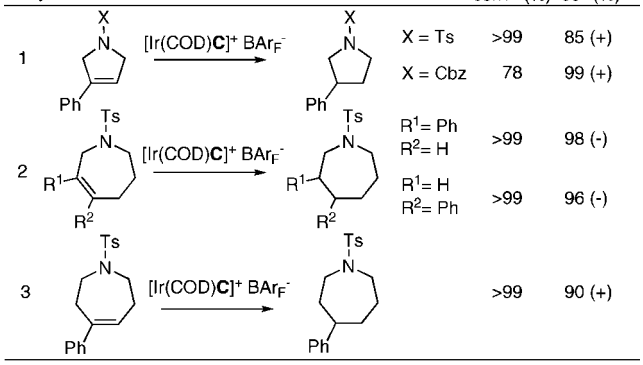


Entry	R	Ligand	conv[b] (%)	ee[c] (%)
1	Me	E	>99	97 (−)
2	Bu	E	>99	81 (−)
3	Bn	E	97	92 (−)
4	CH_2OH	E	>99	97 (−)
5	C_6H_5	A	>99	>99 (+)
6	4-MeC_6H_4	A	>99	>99 (+)
7	3-MeC_6H_4	A	97	97 (+)
8	4-$MeOC_6H_4$	A	>99	99 (+)
9	3-$MeOC_6H_4$	A	60	98 (+)
10	4-$F_3CC_6H_4$	A	19	87 (+)
11	4-$F_3CC_6H_4$	B	74	96 (−)
12	4-ClC_6H_4	A	57	87 (+)
13	4-ClC_6H_4	B	94	98 (−)
14	4-BrC_6H_4	A	68	94 (+)
15	4-BrC_6H_4	B	92	98 (−)

[a−c]See the corresponding footnotes in Table 1.

The method was also applicable to five- and seven-membered heterocyclic alkenes (Table 3). The best catalyst for these hydrogenations was [(**C**)Ir(COD)]$^+$[BAr_F]$^-$. Changing the protecting group from Ts to Cbz slightly improved the selectivity for the five-membered cyclic alkene (entry 1).

Table 3. Asymmetric Hydrogenation of Five- and Seven-Membered N-Heterocyclic Olefins[a]

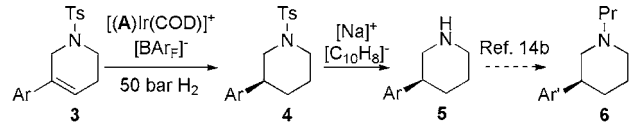


[a−c]See the corresponding footnotes in Table 1.

To demonstrate the utility of this type of hydrogenation, we applied it to the synthesis of 3-PPP (Preclamol, **6**; Scheme 2). 3-PPP is the first selective D2-like dopamine autoreceptor agonist and has been known since the 1980s.[14] Several related 3-phenylpiperidines show dopaminergic activity[15] and have proven useful in the treatment of various central nervous system disorders.[16] We started with compound **3** bearing an electron-rich aryl substituent. Thus, catalyst [(**A**)Ir(COD)]$^+$[BAr_F]$^-$ (1 mol %, 20 h) was used and gave compound **4** in 93% yield and >99% *ee* after recrystallization from Et_2O. The *ee* before recrystallization was 98% (Table 2, entry 9). Deprotection of the amine with sodium naphthalenide gave compound **5** in 85% yield. Compound **5** can be elaborated to 3-PPP by N-alkylation and removal of the methyl group.[14b]

In conclusion, we have developed a method for the synthesis of chiral pyrrolidines, piperidines, and azepanes using N,P-ligated iridium catalysts. The selectivity ranged from good to excellent.

Scheme 2. Synthesis of the 3-PPP Precursor **5** via Asymmetric Hydrogenation of Heterocyclic Olefin **3**



Ar = 3-MeO-C_6H_4-, Ar' = 3-HO-C_6H_4-

The ease of substrate preparation, high yield, and selectivity of this reaction make it useful for the synthesis of medicinal compounds and natural products, as demonstrated for **5**, the precursor to 3-PPP. We are currently investigating asymmetric hydrogenation of other heterocyclic alkenes.

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Supporting Information Available: Experimental details, separation methods, and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Buffat, M. G. P. *Tetrahedron* **2004**, *60*, 1701. (b) Farina, V.; Reeves, J. T.; Senanayake, C. H.; Song, J. J. *Chem. Rev.* **2006**, *106*, 2734.
(2) (a) Lennon, I. C.; Moran, P. H. *Curr. Opin. Drug Discovery Dev.* **2003**, *6*, 855. (b) Church, T. L.; Andersson, P. G. In *Chiral Amine Synthesis: Methods, Developments and Applications*; Nugent, T. C., Ed.; Wiley-VCH: Weinheim, Germany, 2010; p 179.
(3) (a) Zhou, Y.-G. *Acc. Chem. Res.* **2007**, *40*, 1357. (b) Glorius, F. *Org. Biomol. Chem.* **2005**, *3*, 4171. (c) Kuwano, R. *Heterocycles* **2008**, *76*, 909.
(4) (a) Blaser, H.-U.; Spindler, F. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 1, p 247. (b) Claver, C.; Fernández, E. In *Modern Reduction Methods*; Andersson, P. G., Munslow, I. J., Eds.; Wiley-VCH: Weinheim, Germany, 2008; p 237. (c) Ohkuma, T.; Noyori, R. In *Comprehensive Asymmetric Catalysis, Supplement 1*; Springer: Berlin, 2004; Vol. 1, p 43. (d) Brunel, J. M. *Recent Res. Dev. Org. Chem.* **2003**, *7*, 155.
(5) (a) Morimoto, T.; Nakajima, N.; Achiwa, K. *Tetrahedron: Asymmetry* **1995**, *6*, 75. (b) Lei, A.; Chen, M.; He, M.; Zhang, X. *Eur. J. Org. Chem.* **2006**, 4343.
(6) Lee, N. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 5985.
(7) (a) Blaser, H. U.; Hönig, H.; Studer, M.; Wedemeyer-Exl, C. *J. Mol. Catal. A: Chem.* **1999**, *139*, 253. (b) Nugent, T. C.; El-Shazly, M. *Adv. Synth. Catal.* **2010**, *352*, 753.
(8) Hou, G.-H.; Xie, J.-H.; Yan, P.-C.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2009**, *131*, 1366.
(9) Szollosi, G.; Szori, K.; Bartók, M. *J. Catal.* **2008**, *256*, 349.
(10) Tang, W.; Wu, S.; Zhang, X. *J. Am. Chem. Soc.* **2003**, *125*, 9570.
(11) (a) Church, T. L.; Andersson, P. G. *Coord. Chem. Rev.* **2008**, *252*, 513. (b) Roseblade, S. J.; Pfaltz, A. *Acc. Chem. Res.* **2007**, *40*, 1402. (c) Källström, K.; Munslow, I.; Andersson, P. G. *Chem.—Eur. J.* **2006**, *12*, 3194. (d) Cui, X.; Burgess, K. *Chem. Rev.* **2005**, *105*, 3272.
(12) (a) Grubbs, R. H. *Tetrahedron* **2004**, *60*, 7117. (b) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199.
(13) (a) Kaukoranta, P.; Engman, M.; Hedberg, C.; Bergquist, J.; Andersson, P. G. *Adv. Synth. Catal.* **2008**, *350*, 1168. (b) Hedberg, C.; Källström, K.; Brandt, P.; Hansen, L. K.; Andersson, P. G. *J. Am. Chem. Soc.* **2006**, *128*, 2995. (c) Engman, M.; Diesen, J. S.; Paptchikhine, A.; Andersson, P. G. *J. Am. Chem. Soc.* **2007**, *129*, 4536. (d) Cheruku, P.; Paptchikhine, A.; Ali, M.; Neudörfl, J.-M.; Andersson, P. G. *Org. Biomol. Chem.* **2008**, *6*, 366. (e) Trifonova, A.; Diesen, J. S.; Andersson, P. G. *Chem.—Eur. J.* **2006**, *12*, 2318.
(14) (a) Liljefors, T.; Wikström, H. *J. Med. Chem.* **1986**, *29*, 1896. (b) Wikström, H.; Sanchez, D.; Lindberg, P.; Hacksell, U.; Arvidsson, L. E.; Johnsson, A. M.; Thorberg, S. O.; Nilsson, J. L. G.; Svensson, K. *J. Med. Chem.* **1984**, *27*, 1030.
(15) (a) Hansson, L. O.; Waters, N.; Holm, S.; Sonesson, C. *J. Med. Chem.* **1995**, *38*, 3121. (b) Macchia, M.; Cervetto, L.; Demontis, G. C.; Longoni, B.; Minutolo, F.; Orlandini, E.; Ortore, G.; Papi, C.; Sbrana, A.; Macchia, B. *J. Med. Chem.* **2003**, *46*, 161.
(16) (a) Ehrich, E.; Mundel, T. (Alkermes Controlled Therapeutics, Cambridge, MA). PCT Appl. WO2005089486, 2005; *Chem. Abstr.* **2005**, *143*, 319178. (b) Solvay Pharmaceuticals B.V., The Netherlands. Eur. Pat. Appl. 1336406, 2002; *Chem. Abstr.* **2003**, *139*, 173826.

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