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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**

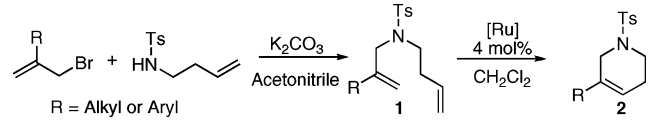
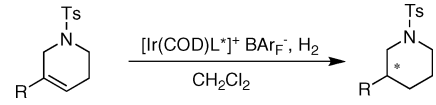


Table 1. Screening of Catalysts for Asymmetric Hydrogenation of **2**[a]



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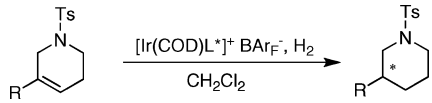
Table 2. Asymmetric Hydrogenation of Six-Membered N-Heterocyclic Olefins[a]

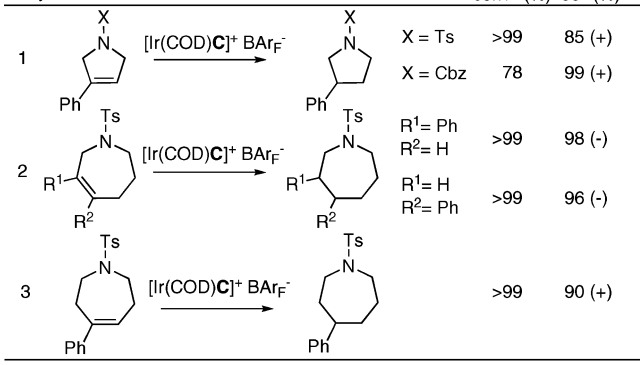


Entry	R	Ligand	conv[b] (%)	ee[c] (%)
1	Me	E	>99	97 (−)
2	Bu	E	>99	81 (−)
3	Bn	E	97	92 (−)
4	CH_2OH	E	>99	97 (−)
5	C_6H_5	A	>99	>99 (+)
6	4-MeC_6H_4	A	>99	>99 (+)
7	3-MeC_6H_4	A	97	97 (+)
8	4-$MeOC_6H_4$	A	>99	99 (+)
9	3-$MeOC_6H_4$	A	60	98 (+)
10	4-$F_3CC_6H_4$	A	19	87 (+)
11	4-$F_3CC_6H_4$	B	74	96 (−)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

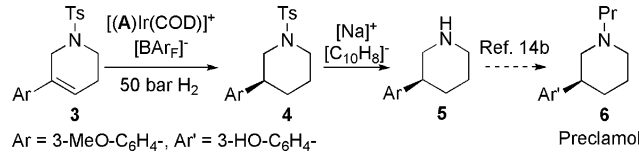


[a−c]See the corresponding footnotes in Table 1.

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.

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