CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.200802576

Iridium-Catalyzed Asymmetric Hydrogenation of Unfunctionalized Enamines

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Optically active amines are present in many natural products prompting the development of numerous different strategies and methodologies to access these compounds. Our group, among others, has already reported the synthesis of enantioenriched secondary amines via catalytic asymmetric hydrogenation of imines using cationic iridium complexes with chiral N,P ligands.[1] In seeking to broaden the utility of this class of catalysts, we studied the asymmetric hydrogenation of unfunctionalized enamines as a route to optically active tertiary amines. In contrast with the well known hydrogenation of enamides or other functionalized enamines,[2] there are only few examples of successful asymmetric hydrogenations of unfunctionalized enamines: Buchwald and Lee employed an *ansa*-titanocene complex that gave high enantioselectivities with various (1-arylvinyl)-amines, although relatively high catalyst loadings (typically 5 mol%) were required.[3] Börner and co-workers, with a rhodium–diphosphine catalyst, obtained moderate enantiomeric excesses with a cyclic and an acyclic vinylamine,[4] and more recently, the group of Zhou achieved enantioselectivities of 87 to >99% *ee* in the hydrogenation of 1-(1,2-diarylvinyl)pyrrolidines by using a rhodium catalyst derived from a spiro phosphonite ligand.[5] Here we report the application of cationic iridium catalysts with chiral oxazoline- or pyridine-based N,P ligands for the asymmetric hydrogenation of various unfunctionalized enamines.[6]

Initial studies were performed with enamines having a terminal double bond. Thus, *N*-methyl-*N*-phenyl- (**1a**) and *N*-methyl-*N*-benzyl-(1-phenylvinyl)amine (**1d**) were hydrogenated by using a range of iridium complexes under 50 bar of H_2 in CH_2Cl_2 for 2 h. A brief catalyst screening revealed a pronounced difference in behavior between the two substrates; hydrogenation of **1a** proceeded well using Ir-phox complexes such as **3**, whereas Ir-threphox complexes such as **4** gave poor results, especially in terms of enantioselectivity, while the reverse behavior was observed for **1b**. Thus, after an exhaustive screening of catalysts and reaction conditions for the two enamines (see Supporting Information for details), two optimized methods were established, one for *N*-aryl- and and one for *N*-benzyl-substituted enamines (Table 1). Method A, which involves the use of 1 mol% of phox catalyst **3**, under 10 or 50 bar of hydrogen pressure (depending on the substrate) in CH_2Cl_2, gave high conversion and *ee* values of 90–91% for enamines **1a–c** (Table 1, entries 1–4). While the substituents at the *N*-phenyl group had essentially no effect on the enantioselectivity, the *para*-methoxy group in derivative **1b** reduced the reactivity such that 50 bar of hydrogen pressure were necessary to obtain full conversion (Table 1, compare entries 2 and 3). Method B, which involves the use of 0.5 mol% of commercially available threphox complex **4**[7] under 10 or 50 bar of hydrogen pressure in CH_2Cl_2 or TBME, gave poor results with this class of enamine, but was more effective for the asymmetric hydrogenation of enamines with a benzyl-substituted nitrogen atom (Table 1, entries 5–10). Amine **2d** was obtained with full conversion and high enantioselectivity, comparable to the *ee* reported by Buchwald and Lee[3] for this substrate, using either CH_2Cl_2 or TBME as solvent (Table 1, entries 5 and 6). The presence of *para* substituents at the phenyl ring attached to the double bond had a negative effect on both reactivity and enantioselectivity. Although full conversion could be obtained at 50 bar of H_2 pressure, enantioselectivities were only moderate (Table 1, entries 7–10). The hydrogenation of enamines **1e** and **1f** was found to be very sensitive to the choice of solvent. While enamine **1e** gave higher conversion and better enantioselectivity in TBME than in CH_2Cl_2, the opposite trend was observed for enamine **1f**.

The furyl-substituted enamine **1g** proved to be much less reactive than the phenyl-substituted analogue. It was necessary to raise the reaction temperature to 0°C to achieve full conversion and the *ee* did not exceed 50% (Table 1,

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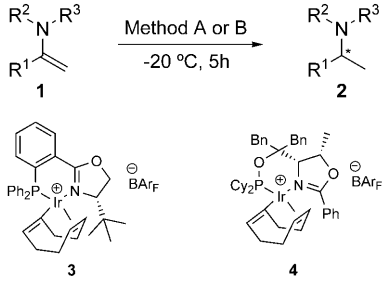
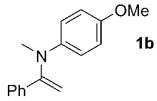
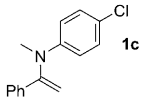
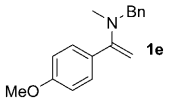
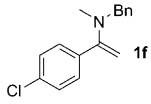
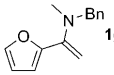
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.200802576.

Table 1. Asymmetric hydrogenation of enamines **1a–j**.



Method A : Catalyst **3** (1 mol%), 10 or 50 bar H_2, CH_2Cl_2
Method B : Catalyst **4** (0.5 mol%), 10 bar H_2, CH_2Cl_2 or TBME

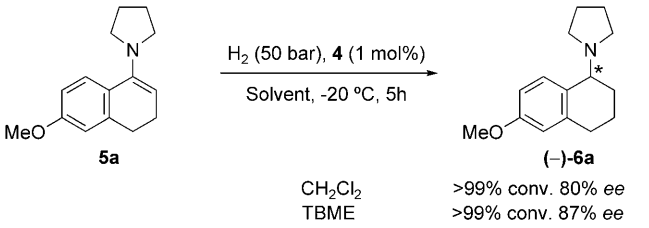
Entry	Enamine	Method A Conv. [%][b]	Method A *ee* [%][c]	Method B Conv. [%][b]	Method B *ee* [%][c]
1	 **1a**	98	91 (+)	51	13(+)
2	 **1b**	70	87 (+)	43	20(+)
3		>99 (50 bar)	90 (+)	>99 (50 bar)	17(+)
4	 **1c**	>99	90.5 (+)	55	55(+)
5	 **1d**	>99	78 (+)	>99	92(−)
6		–	–	>99[d]	92.5(−)
7	 **1e**	>99 (50 bar)	56 (+)	73	65(−)
8		–	–	93 (50 bar)	74(−)[d]
9	 **1f**	88	27 (+)	62	76(−)
10		98 (50 bar)	19 (+)	>99 (50 bar)	75(−)
11	 **1g**	>99[e]	7 (+)	98[e]	50(−)
12	 **1h**	>99	44 (*S*)	>99	8(*R*)
13	 **1i**	>99	18 (+)	>99	54(−)
14	 **1j**	53 (50 bar)	21[f]	26 (50 bar)	n.d.[g]

[a] Reactions were carried out under 10 bar hydrogen pressure, in CH_2Cl_2, and at −20 °C unless otherwise specified. [b] Determined by GC analysis after removal of the catalyst (see Supporting Information for details). [c] Determined by HPLC analysis on a Daicel Chiralcel OJ column (see supporting information for details). [d] TBME was used as solvent. [e] The reaction was carried out at 0 °C. [f] Determined by ^{1}H NMR analysis of the diasteromers resulting from addition of (*R*)- or (*S*)-*O*-methylmandelic acid (see Supporting Information for details). [g] Not determined.

entry 11). Enamines bearing alkyl substituents on the nitrogen afforded low enantioselectivities with both methods, although full conversions were obtained under 50 bar of hydrogen pressure (Table 1, entries 12 and 13). Hydrogenation of the *tert*-butyl-substituted enamine **1f** was slow and unselective (Table 1, entry 14). At room temperature the reaction went to completion but led to racemic product.

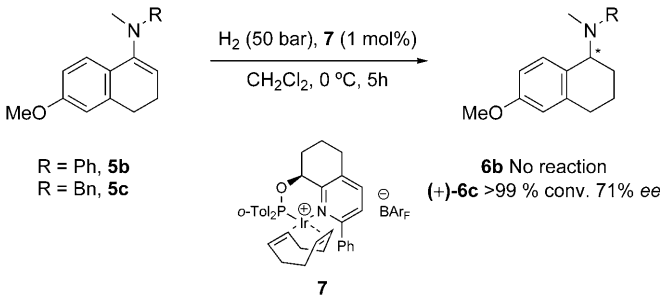
The results show that iridium complexes **3** and **4** are active catalysts for the hydrogenation of enamines giving full conversion with catalyst loadings of 0.5–1 mol%. The enantiomeric excesses strongly depend on the substitution pattern at the C=C bond and the nitrogen atom. A *N*-aryl or *N*-benzyl group seems to have a benficial effect on the enantioselectivity. With enamines **1a–d** the *ee* values were comparable to those reported for the hydrogenation of analogous enamines using titanocene catalysts.[2] While titanocene catalysts have been successfully applied to a broader range of enamines than catalysts **3** and **4**, iridium complexes are more active, which allows substantially lower catalyst loadings.

Once the ability of iridium-P,N complexes for the asymmetric hydrogenation of unfunctionalized enamines with a terminal double bond was demonstrated, 1,2-disubstituted enamines were the next objective. First, cyclic substrates, such as **5a**, were examined. The hydrogenation of enamines of this type has not been reported yet. After an extensive catalyst screening and optimization of the reaction conditions (see Supporting Information for details), the threphox catalyst **4** was found to provide the best results under conditions similar to those of Method B, but with 50 bar of hydrogen pressure and 1 mol% catalyst loading (Scheme 1). In this case, TBME proved to be the solvent of choice giving up to 87% *ee*, whereas the *ee* in CH_2Cl_2 was only 80%.



Scheme 1. Asymmetric hydrogenation of cyclic enamines with catalyst **4**.

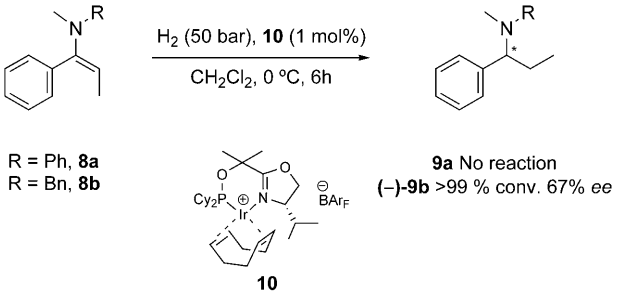
When imines **5b** and **5c** (see Scheme 2) were subjected to these conditions, low (<10%) or no conversion was obtained, respectively. Therefore, the temperature was raised



Scheme 2. Asymmetric hydrogenation of cyclic enamines with catalyst **7**.

to 25 °C, resulting in full conversion and 59 % *ee* for enamine **5c** when the reaction was carried out in TBME, but again no reaction was observed with **5b**. Therefore, other catalysts were examined (see Supporting Information for details). Complex **7** derived from a pyridine–phosphinite ligand, that had previously shown exceptionally high reactivity in the hydrogention of furans,[8] proved to be the most reactive catalyst in this case. With 1 mol % of catalyst **7** under 50 bar hydrogen pressure at 0 °C in CH_2Cl_2, enamine **5c** was fully hydrogenated with 71 % *ee* (Scheme 2). Attempts to increase the enantioselectivity by decreasing the temperature to −20 °C were unsuccessful. Although the enantioselectivity raised to 76 %, the conversion dropped to 47 %. Unfortunately, all attempts to hydrogenate enamine **5b**, using various catalysts and reaction conditions failed.

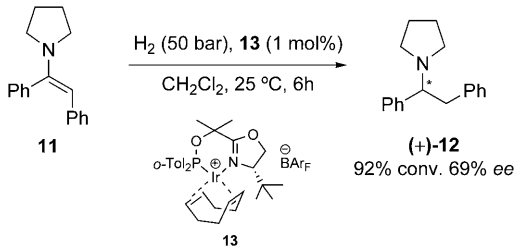
We next tested analogous acyclic enamines using **8a** and **8b** as substrates, the latter isolated as a 95:5 *E*/*Z* mixture. Since the results obtained with catalyst **7** were unsatisfactory, additional catalysts were screened (see Supporting Information for details). Among them, complex **10** was identified as the most effective catalyst for the asymmetric hydrogenation of substrate **8b**. At 0 °C and 1 mol % catalyst loading under 50 bar of hydrogen pressure it gave the corresponding amine **9b** with full conversion and 67 % *ee* (Scheme 3). At



Scheme 3. Asymmetric hydrogenation of acyclic enamines with catalyst **10**.

−20 °C the reaction still went to completion but disappointingly, the enantioselectivity did not improve. As observed for the cyclic enamine **5b** the *N*-phenyl derivative **8a** did not react under these conditions. With the more reactive pyridine-based catalysts of type **7**, partial hydrogenation was observed at room temperature but the enantioselectivity was low.

The pyrrolidine enamine **11** was also tested (Scheme 4). The asymmetric hydrogenation of this substrate has been previously reported by Zhou and co-workers, who obtained full conversion and enantioselectivities of up to 87 % *ee* using 2 mol % of a rhodium spiro-phosphonite complex, and 2 mol % of iodine and 20 mol % of acetic acid as additives.[5] Again complex **7** proved to be the most active catalyst, giving full conversion even at −20 °C, although with poor enantioselectivity (up to 41 % *ee*; see Supporting Information for details). Better results were obtained with the oxazoline–phosphinite complex **13**, which afforded amine **12**



Scheme 4. Asymmetric hydrogenation of acyclic enamine **11**.

with high conversion and 69 % *ee* in CH_2Cl_2 at room temperature under 50 bar hydrogen pressure (Scheme 4).

In summary, we have found that cationic iridium complexes with chiral oxazoline- or pyridine-based N,P ligands are active catalysts for the asymmetric hydrogenation of enamines. The best results were obtained with (1-phenylvinyl)-amines bearing a phenyl or benzyl substituent on the nitrogen atom, which were hydrogenated with enantiomeric excesses of >90 %. Enantioselectivities in the hydrogenation of cyclic and acyclic 1,2-disubstituted enamines were lower. Nevertheless, the cyclic enamine **6a** was converted to the saturated amine with 87 % *ee*. With the exception of (1,2-diarylvinyl)amines **11** the asymmetric hydrogenation of disubstituted enamines of this type has not been reported before. These results show that iridium complexes with chiral N,P ligands[9] are useful catalysts for the asymmetric hydrogenation of enamines that broaden the scope of this transformation.

Experimental Section

General procedure for the iridium-catalyzed asymmetric hydrogenation of enamines: A solution of the enamine (0.2 mmol) and the iridium complex (1 mol % or 0.5 mol %) in dry dichloromethane or TBME (1 mL) under inert atmosphere was placed in an autoclave, which was sealed and placed in cooling bath for one hour at the appropriate temperature. After this time, the autoclave was purged with hydrogen, pressurized to the desired hydrogen pressure, and stirred at the corresponding temperature for the indicated time. Then, the solvent was evaporated and the catalyst removed by filtration through a short silica gel column (3×1 cm) with a 1:1 mixture of pentane and diethyl ether as eluent, giving the amine product as a pure compound after evaporation of the solvent. For amines which still contained impurities after filtration, an extractive acidic workup was carried out to obtain the pure compounds.

For catalyst screening, reactions were performed on a 0.1 mmol scale.

See Supporting Information for details and analytical data of compounds.

Acknowledgements

A. Baeza would like to thank the Spanish Ministerio de Educación, Ciencia y Deporte (MECD) and Fundación Española para la Ciencia y la Tecnología (FECYT) for a Postdoctoral fellowship. Support of this work by the Swiss National Science Foundation and the Federal Commission for Technology and Innovation (KTI) is gratefully acknowledged.

Keywords: amines · asymmetric catalysis · asymmetric hydrogenation · enamines · iridium

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Received: December 8, 2008
Published online: January 28, 2009

