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Highly Efficient Iridium-Catalyzed Asymmetric Hydrogenation of Unprotected β-Enamine Esters

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Abstract: A highly efficient and enantioselective hydrogenation of unprotected β-enamine esters catalyzed by Ir-(*S*,*S*)-f-Binaphane complex has been developed. This methodology provides straightforward access to free β-amino acids in high yields with excellent enantioselectivities up to 97% ee and high reactivities (TON > 5000).

Enantiopure β-amino acids and their derivatives are ubiquitous important structural motifs in important natural products and pharmaceuticals.[1] In life sciences, extensive existence and applications of chiral β-amino acids have been found in biologically active peptides. Chiral β-amino acids are also widely used as key intermediates or chiral building blocks in the synthesis of small-molecule pharmaceuticals,[2] such as (*S*)-dapoxetine,[3] which is used for the treatment of a variety of disorders as depression, bulimia or anxiety, and some antiretroviral agents, (*S*)-maraviroc,[4] compound **1** and **2** (Figure 1).[5,6]

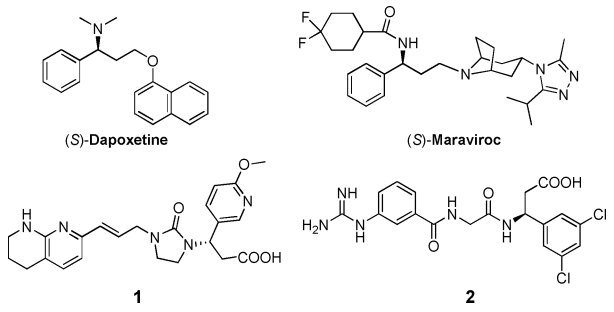
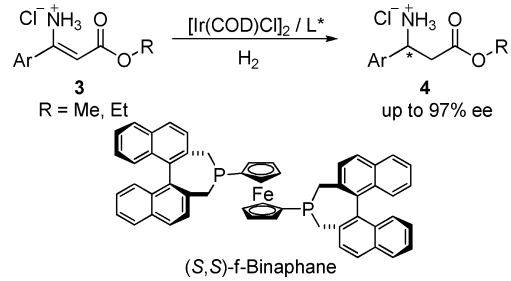


Figure 1

Due to its significance in chemical synthesis, many approaches have been developed for the enantioselective synthesis of chiral β-amino acids.[7] Although catalytic asymmetric hydrogenation could be a successful methodology for the preparation chiral α-amino acids in industry,[8] its application for large-scale synthesis of enantiopure β-amino acids has been largely limited by the indispensable involvement of *N*-acyl in current/most hydrogenation approaches. The chelating assistance of the *N*-protecting group plays a crucial role in achieving high reactivity and enantioselectivity.[9] To avoid the redundancy of introduction and removal of the acyl group, developing a generally applicable and highly efficient catalyst system for direct hydrogenation of unprotected enamine esters would be an ideal solution to access free enantiopure β-amino acids. However, only few related works were reported. In 2004, Merck and Solvias groups reported the first example of catalytic asymmetric hydrogenation of unprotected β-enamine esters and amides by using Rh-Josiphos complexes with excellent enantioselectivity.[10] One drawback of this method is really low turnovers (<1000) due to product inhibition. Later, Ru catalysts were also reported to catalyze asymmetric hydrogenation of unprotected β-enamine esters with high ee's by the Takasago group.[11] More recently, both of these methodologies have been successfully applied to the synthesis of Sitagliptin, achieving excellent enantioselectivities.[7d,12] Inspired by these encouraging results and our recent work on the asymmetric hydrogenation of unprotected N−H imines,[13] we decided to tackle the asymmetric hydrogenation of this class of challenging substrates. Herein we report the first example of Ir-catalyzed asymmetric hydrogenation of unprotected β-enamine esters affording free β-amino esters with excellent enantioselectivities (up to 97% ee) and high reactivities (TON > 5000) (Scheme 1).[14]

Scheme 1



Considering the fact that the primary beta amine ester products in this transformation could have a strong inhibitory effect on the catalyst,[15] and also the fact that the products are unstable with ester substrates in some solvent,[7a] we chose β-enamine hydrochloride esters as the substrates for our study. Our initial evaluation began with hydrogenation of β-enamine hydrochloride ester **3a** as the model substrate with a series of catalysts. Few promising results were obtained using Rh-phosphine catalysts. A number of Ir-phosphine complexes were also screened (Table 1, entries 1−11). We were gratified to find that (*S*,*S*)-f-Binaphane ligand was able to achieve excellent enantioselectivity as well as full conversion (entry 3). Other types of bidentate diphosphine ligands, such as TangPhos, Me-DuPhos, BINAP, ^{t}Bu-Josiphos, and monodentate phosphorus ligands, such as Monophos, NMe-NBn-Monophos, showed either significantly lower enantioselectivities or reactivities (entries 1−2 and 4−11). Interestingly, the solvent played a key role in this Ir-f-Binaphane catalyst system. Low conversions were observed in CH_2Cl_2, THF, or toluene (entries 14−16). Only moderate enatioselectivities were obtained in MeOH and EtOH, although full conversions were achieved (entries 12−13). However, consistent with the asymmetric hydrogenation of N−H imines,[13] we discovered that a mixture solvent of MeOH/CH_2Cl_2 could provide the best ee's and high reactivities. By adjusting the solvent ratio to MeOH/CH_2Cl_2 = 2:1, 97% ee was obtained under the optimized

conditions (entry 20). Examination of the hydrogen pressure effect revealed that insufficient H_2 pressure could result in incomplete conversion albeit without any enantioselectivity loss (entry 21).

Table 1. Asymmetric Hydrogenation of **3a** (Ar = Phenyl, R = Et)[a]

entry	ligand	solvent	conv (%)[b]	ee (%)[c]
1	(*S*,*S*,*R*,*R*)-TangPhos	MeOH/CH_2Cl_2 (2:1)	>99	46
2	(*S*,*R*)-DuanPhos	MeOH/CH_2Cl_2 (2:1)	>99	37
3	**(*S*,*S*)-f-Binaphane**	**MeOH/CH_2Cl_2 (2:1)**	**>99**	**97**
4	(*R*)-Me-DuPhos	MeOH/CH_2Cl_2 (2:1)	60	6
5	(*R*)-BINAP	MeOH/CH_2Cl_2 (2:1)	>99	14
6	(*R*)-SEGPHOS	MeOH/CH_2Cl_2 (2:1)	>99	29
7	(*S*)-PhanePhos	MeOH/CH_2Cl_2 (2:1)	23	35
8	(*R*,*S*)-^{t}Bu-JosiPhos	MeOH/CH_2Cl_2 (2:1)	78	19
9	(*S*)-NMe-NBn-MonoPhos	MeOH/CH_2Cl_2 (2:1)	98	20
10	(*R*)-MonoPhos	MeOH/CH_2Cl_2 (2:1)	74	3
11	(*S*,*RR*)-MonoPhos-PE	MeOH/CH_2Cl_2 (2:1)	96	12
12	(*S*,*S*)-f-Binaphane	MeOH	>99	75
13	(*S*,*S*)-f-Binaphane	EtOH	>99	4
14	(*S*,*S*)-f-Binaphane	CH_2Cl_2	10	41
15	(*S*,*S*)-f-Binaphane	Toluene	5	33
16	(*S*,*S*)-f-Binaphane	THF	14	89
17	(*S*,*S*)-f-Binaphane	MeOH/CH_2Cl_2 (1:1)	>99	87
18	(*S*,*S*)-f-Binaphane	MeOH/CH_2Cl_2 (3:1)	>99	94
19	(*S*,*S*)-f-Binaphane	MeOH/THF (2:1)	>99	94
20[d]	(*S*,*S*)-f-Binaphane	MeOH/CH_2Cl_2 (2:1)	>99	97
21[e]	(*S*,*S*)-f-Binaphane	MeOH/CH_2Cl_2 (2:1)	69	97

[a] Reaction conditions: [Ir(COD)Cl]$_2$/phosphine/substrate = 0.5:1.0:100, ligand/metal = 1:1, rt, 100 atm of H_2, 12 h. [b] Determined by GC analysis. [c] Determined by chiral GC analysis of the corresponding acetamides (see Supporting Information). [d] 50 atm of H_2. [e] 20 atm of H_2.

Encouraged by the promising result in the hydrogenation of substrate **3a**, a variety of β-enamine hydrochloride esters were examined using the Ir-f-Binaphane catalyst system (Table 2). The R group in the ester moiety had no obvious influence on the reactivity and enantioselectivity of this reaction (entries 1−2). The electronic property of substituents on the aryl ring of the substrate had very little effect on the enantiomeric excess of the product. Substrates bearing electron-donating or electron-withdrawing substituents on the aromatic ring were all smoothly hydrogenated to the corresponding products with high enatioselectivities, 92−97% ee (entries 3−9). The substrate with a substituent at the *ortho* position (**3j**) and with a 1-naphthyl group (**3l**) resulted in diminished ee values possibly due to the steric hindrance (entries 10−11). Both the 2-naphthyl substrate **3m** and 2-thienyl **3k** afforded products in 94 and 95% ee, respectively (entries 12−13).

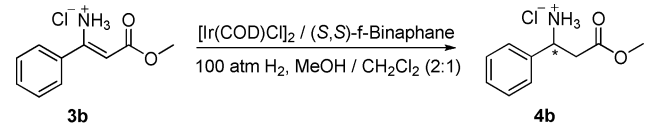
Table 2. Asymmetric Hydrogenation of Enamine Esters **3**[a]

entry	Ar	R	product	ee (%)[b,c]
1	C_6H_5 (**3a**)	Et	**4a**	97 (*S*)
2	C_6H_5 (**3b**)	Me	**4b**	96 (*S*)
3	4-MeC_6H_4 (**3c**)	Me	**4c**	95 (*S*)
4	4-MeOC_6H_4 (**3d**)	Me	**4d**	94 (*S*)
5	4-FC_6H_4 (**3e**)	Me	**4e**	95 (*S*)
6	4-ClC_6H_4 (**3f**)	Me	**4f**	96 (*S*)
7	4-BrC_6H_4 (**3g**)	Me	**4g**	97 (*S*)
8	3-MeC_6H_4 (**3h**)	Me	**4h**	92 (−)
9	3-ClC_6H_4 (**3i**)	Me	**4i**	94 (−)
10	2-MeC_6H_4 (**3j**)	Me	**4j**	84 (*S*)
11	1-naphthyl (**3l**)	Me	**4l**	90 (*S*)
12	2-naphthyl (**3m**)	Me	**4m**	92 (*S*)
13	2-thienyl (**3k**)	Me	**4k**	95 (*S*)

[a] Reaction conditions: [Ir(COD)Cl]$_2$/(*S*,*S*)-f-Binaphane/substrate = 0.5:1.0:100, 50 atm of H_2, rt, 12 h, >99% conversion, isolated yields >90%. [b] Determined by chiral GC analysis of the corresponding acetamides (see Supporting Information). [c] Absolute configurations were determined by comparison with the retention times to reported data.

To explore the potential application of the Ir-(*S*,*S*)-f-Binaphane catalyst system in the practical synthesis of chiral β-amino acids, we further studied the reactivity and the turnover number (TON) limit of the hydrogenation of **3b** (Scheme 2). The transformation was completed with 0.1 mol % catalyst (TON = 1000) at rt and even with as low as 0.02 mol % catalyst (TON = 5000) at 40 °C. Only very slight erosions of ee were observed. Furthermore, when the substrate to catalyst ratio (S/C) was furthered increased to 10 000 (0.01 mol % catalyst), the excellent enantioselectivity still remained unchanged. To our best knowledge, this is the highest turnover for asymmetric hydrogenation of unprotected β-enamine esters to date. The high reactivity suggested that the hydrogenation possibly proceeded via a "nonchelate" mechanism, without Ir/nitrogen interaction. Aminium salt loss of the coordination ability compared to the amine counterpart could also minimize or avoid the product inhibition.[15]

Scheme 2



3b **4b**

r.t., S/C = 1, 000 >99% conv. 95% ee
40 °C, S/C = 5, 000 >99% conv. 94% ee
40 °C, S/C = 10, 000 87% conv. 94% ee

In conclusion, we have developed a highly efficient and highly enantioselective hydrogenation of unprotected β-enamine esters catalyzed by the Ir-(*S*,*S*)-f-Binaphane complex, which provides efficient access to enantiomerically enriched β-amino acids without use of a protecting group. This method could be potentially useful for the practical preparation of chiral drug intermediates. Further studies are underway and will be reported in due course.

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Supporting Information Available: Complete ref 5, experimental procedures, the characterizations of substrates and products, and the analysis of enantioselectivities of hydrogenation products. This material is available free of charge via the Internet at http://pubs.acs.org.

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