Iridium(I)-Catalyzed Asymmetric Hydrogenation of Prochiral Imines; Protic Amines as Catalyst Improvers

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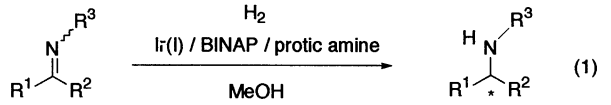
A catalytic system, Ir(I)-BINAP-protic amine, was found to be effective for asymmetric hydrogenation of imines and the highest enantioselectivity of 90% ee has been attained for the hydrogenation of the cyclic imine, 2-phenyl-3,4,5,6-tetrahydropyridine.

Catalytic asymmetric hydrogenation of prochiral alkenes and ketones has been extensively studied.[1] On the contrary, relatively few reports on enantioselective hydrogenation of C=N double bonds with homogeneous catalysts in successfully high optical yields are available.[2-4] Among them several Ir-chiral diphosphine systems have been reported as fairly efficient catalytic systems for hydrogenation of imines.[4] In these Ir(I) and Ir(III) catalytic systems an iodide ion is indispensable as a component of the efficient catalyst. We report herein that the new iridium catalyst system without iodide ions, which is prepared *in situ* from $[Ir(cod)Cl]_2$ and BINAP [BINAP = 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl] or tolBINAP [tolBINAP = 2,2'-bis{di(*p*-tolyl)-phosphino}-1,1'-binaphthyl] in the presence of a small amount of a protic amine,[5] is effective for the hydrogenation of prochiral imines to the corresponding amines with good catalytic activity as well as enantioselectivity (eq 1).



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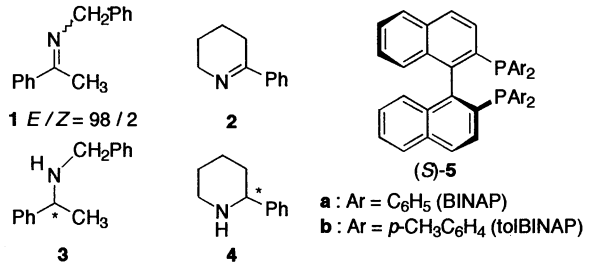


Table 1 summarizes the results of the asymmetric hydrogenation of imines with Ir(I)-BINAPs systems. For hydrogenation of *N*-(α-methylbenzylidene)benzylamine **1**, we have found that an Ir(I)-tolBINAP-benzylamine system is the most effective among examined and 70% ee has been attained in the reaction carried out in methanol with 60 kg/cm^2 of H_2 at 20 °C. The catalyst system without benzylamine was far less effective and the enantioselectivity decreased to only 23% ee. Besides benzylamine other primary amines such as butylamine or aniline were also effective. Secondary amine, *N*-methylbenzylamine, was effective but tertiary amine, *N*,*N*-dimethylbenzylamine, was not effective. In this hydrogenation the chirality of the added amine, (*S*)- or (*R*)-α-methylbenzylamine, did not affect the enantioselection. Different from so far reported asymmetric catalysts comprised of Ir-chiral diphosphine systems,[4] iodide ions added as KI or Bu_4NI did not affect the present catalytic system.

Table 1. Asymmetric hydrogenation of imines catalyzed by Ir(I)-BINAP-amine systems [a]

Run	Imine	Ligand	Additive[b]	Convn.[c] %	Amine % ee[d,e]
1	**1**	(*S*)-**5b**	none	100	23 (*R*)
2	**1**	(*R*)-**5a**	$PhCH_2NH_2$	100	66 (*S*)
3	**1**	(*S*)-**5b**	$PhCH_2NH_2$	100	70 (*R*)
4	**1**	(*S*)-**5b**	$^nBuNH_2$	100	70 (*R*)
5	**1**	(*S*)-**5b**	$PhNH_2$	100	68 (*R*)
6	**1**	(*S*)-**5b**	$PhCH_2NH(CH_3)$	98	63 (*R*)
7	**1**	(*S*)-**5b**	$PhCH_2N(CH_3)_2$	100	28 (*R*)
8	**1**	(*S*)-**5b**	(*S*)-$PhCH(CH_3)NH_2$	100	67 (*R*)
9	**1**	(*S*)-**5b**	(*R*)-$PhCH(CH_3)NH_2$	100	67 (*R*)
10	**2**	(*S*)-**5b**	none	63	39 (*R*)
11	**2**	(*S*)-**5a**	$PhCH_2NH_2$	100	80 (*R*)
12	**2**	(*R*)-**5a**	$PhCH_2NH_2$	100	87 (*S*)
13	**2**	(*S*)-**5b**	$PhCH_2NH_2$	100	90 (*R*)

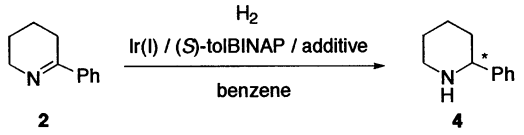
[a] Reaction conditions: $[Ir(cod)Cl]_2$ / BINAP or tolBINAP = 1 / 2.1, [imine] / [Ir] = 100 / 1, [imine] = 1 M, $p(H_2)$ = 60 kg / cm^2, reaction temperature = 20 °C, reaction time = 18 h. All hydrogenations were performed in methanol in a stainless steel autoclave. [b] [Additve] / [Ir] = 5 / 1. [c] Conversion was determined by GLC using a Shimadzu capillary column, CBP1-M25-025. [d] Enantiomeric excesses were determined by HPLC using a DAICEL CHIRALCEL OD (eluent: Hexane / ^{i}PrOH = 199 / 1). [e] Absolute configurations were determined from optical rotations.[2]

The cyclic imine, 2-phenyl-3,4,5,6-tetrahydropyridine **2**, in which the geometry of the C=N double bond is fixed to *E*-configuration, was found to be a more suitable substrate and the highest enantioselectivity of 90% ee has been attained. In order to get information about the influence of the geometry of the C=N double bond on the enantioselectivity, we have examined the relation between the enantioselectivity of the product amine and the geometry of the starting imine. When the hydrogenation of the acyclic imine **1** (*E* / *Z* = 92 / 8) was stopped at 1 h after applying the hydrogen pressure, the (*R*)-amine **3** obtained in 60% conversion showed 67% ee and the recovered imine showed the same *E* / *Z* ratio to that of the starting imine. It is not clear at moment whether the rates of the hydrogenation for the *E*- and the *Z*-imine are the same or rapid isomerization is present between the *E*- and the *Z*-imine in this catalytic system.

The effect of the added protic amine was characteristic of the Ir(I)-BINAP system. For example, the hydrogenation of the imine **1** with an Ir(I)-(*R,R*)-DIOP-benzylamine system [DIOP = 2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino) butane] afforded the (*S*)-amine **3** in only 14% ee with 97% conversion. When $[Rh(cod)Cl]_2$ was employed instead of $[Ir(cod)Cl]_2$ the hydrogenation of the imine **1** scarcely proceeded.[6]

The hydrogenation of imine **2** with Ir(I)-(*S*)-tolBINAP in benzene afforded the opposite enantiomer, the (*S*)-amine **4**, in high enantioselectivity but the catalytic activity was low (Table 2). Different from the reaction in methanol, addition of a small amount of benzylamine retarded the reaction considerably. Interestingly, in benzene addition of a small amount of alcohol such as methanol or ethanol enhanced the catalytic activity without impairing the enantioselectivity.

Table 2. Asymmetric hydrogenation of imine **2** in benzene [a]



2 **4**

Run	Additive[b]	Convn./%	% ee
1	none	46	89 (*S*)
2	$PhCH_2NH_2$	3	—
3	CH_3OH	66	89 (*S*)
4	C_2H_5OH	58	91 (*S*)

[a] Reaction conditions: see Table 1.
[b] [Additve] / [Ir] = 5 / 1.

Typical experimental procedure is as follows. A Schlenk flask was charged with 2-phenyl-3,4,5,6-tetrahydropyridine **2** (0.44 g, 2.87 mmol), $[Ir(cod)Cl]_2$ (9.3 mg, 0.0138 mmol), (*S*)-tolBINAP (19.4 mg, 0.0286 mmol) and a solution of $PhCH_2NH_2$ (15 mg, 0.138 mmol) in methanol (2.2 mL) under argon and the reaction mixture was stirred at 25 °C for 1 h.[7] The resulting red solution was transferred by stainless steel cannula to a dry, argon-filled autoclave. Hydrogen was introduced into the autoclave until the pressure gauge indicates 20 kg/cm^2. The pressure is carefully released to 1 kg/cm^2. This procedure is repeated three times, and finally hydrogen was pressurized to 60 kg/cm^2. The reaction mixture was stirred at 20 °C for 18 h. The solvent was removed *in vacuo* and the residue was distilled by Kugelrohr apparatus to give (*R*)-2-phenylpiperidine **4** (0.35 g, 100% conversion, 80% isolated yield, 90% ee). The yield was determined by GC and ^1H NMR.

The effect of the added protic amine and incubation were also observed for the hydrogenation of the imine **1** with cationic iridium species prepared *in situ* from $[Ir(cod)Cl]_2$ and $AgPF_6$ in the presence of tolBINAP. For example, (*R*)-amine **3** was obtained in 56% ee and 100% conversion with an Ir(I)-(*S*)-tolBINAP-$AgPF_6$-$PhCH_2NH_2$ system. Without incubation both the enantioselectivity and the catalytic activity for the hydrogenation of the imine **1** decreased (23% ee and 48% conversion). Without the added benzylamine the hydrogenation of the imine **1** gave the corresponding amine in 98% conversion but in at most 5% ee.

We are now investigating about the role of the added amine in an Ir(I)-BINAP catalytic system. This research was supported by the Grant-in-Aid for Scientific Research from the Ministry of Education, Science, and Culture, Japan (#05234217, 06455012).

References and Notes

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6 The (*R*)-amine **3** was obtained in 3% yield and 10% ee with Rh(I)-(*R*)-BINAP-$PhCH_2NH_2$.

7 The incubation of the catalyst system was needed to attain the high and reproducible enantioselectivity. For example, when the reaction mixture was pressurized without incubation at room temperature the enantioselectivity of the hydrogenation of the imine **2** decreased to 39% ee.