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Additive effects in Ir–BICP catalyzed asymmetric hydrogenation of imines

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Abstract

Remarkable additive effects of imides and 1,3-indandione were found in an iridium–BICP catalyzed asymmetric hydrogenation of imines. The highest enantioselectivity of 95% ee has been obtained for the hydrogenation of 2,3,3-trimethylindolenine catalyzed by an Ir–BICP catalyst.

Asymmetric hydrogenation of C=N bonds is an attractive method for the synthesis of chiral amines.[1] In contrast to numerous highly enantioselective catalytic systems for hydrogenation of C=C bonds, hydrogenations of prochiral imines only give modest enantiomeric excesses with most catalyst systems.[1] A highly enantioselective hydrogenation catalyst was reported by Buchwald's group using a chiral titanocene system, albeit with low turnovers.[2] High enantioselectivity was achieved by Rh-catalyzed hydrogenation of functionalized imines by a DuPont research group.[3] A more recent approach by Noyori et al. uses Ru–chiral diamine complexes as effective catalysts for the enantioselective transfer hydrogenation of imines with triethylammonium formate.[4] Extremely high activity has been observed for the asymmetric reduction of imines using a chiral ferrocenyldiphosphine–iridium catalyst.[5] However, achieving high activity and enantioselectivity as well as broad substrate scope still represent a challenge in this important research area. Furthermore, the effect of various additives in this type of reaction is not well understood. Herein, we report our studies on the additive effects (Table 1) of an iridium-catalyzed asymmetric hydrogenation of imines using BICP (**1**)[6] as the chiral ligand.

2,3,3-Trimethylindolenine was chosen as a model substrate. It is generally accepted that neutral metal [Rh(I) or Ir(I)] complexes usually show higher enantioselectivity than the corresponding cationic species, and that iodide ions can prevent the deactivation of the iridium catalyst.[1,5] In our initial study, the asymmetric hydrogenation of imine **2** was carried out under 1000 psi H_2 with an Ir(I) complex catalyst prepared in situ from $[Ir(COD)Cl]_2$ and (*R*,*R*)-BICP (molar ratio: imine/Ir/BICP=100/1/1.2). Interestingly, we have found that using iodide as an additive in a mixture of MeOH and benzene (1:1) gave both low conversion and enantioselectivity (entries 1 and 2). Protic amines, documented as

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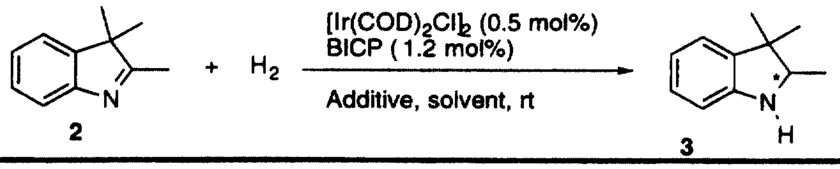
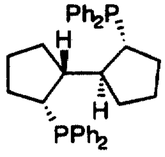
Table 1
Asymmetric hydrogenation of 2,3,3-trimethylindolenine catalyzed by an Ir(I)–BICP complex[a]



Entry	solvent	additive (% mol)	pressure (psi)	time (h)	conversion (%)[b]	ee (%)[b]
1	C_6H_6-MeOH	n-Bu_4NI (2)	1050	72	2.1	34.5 (+)[c]
2	C_6H_6-MeOH	BiI_3 (0.65)	1050	72	55.0	27.0 (+)
3	MeOH	(*R*)-α-methylbenzylamine (5)	1050	72	3.3	8.5 (+)
4	MeOH	(*S*)-α-methylbenzylamine (5)	1050	72	1.4	11.4 (+)
5	toluene	phthalimide (2)	1000	72	92.0	75.1 (+)
6	toluene	phthalimide (4)	1000	65	97.8	92.2 (+)
7	toluene	phthalimide (6)	1000	65	100	92.2 (+)
8	toluene	phthalimide (8)	1000	65	100	91.4 (+)
9	toluene	phthalimide (16)	1000	65	98.7	88.1 (+)
10	toluene	none	1000	96	100	78.1 (+)
11	DMF	phthalimide (4)	1000	65	98.1	18.7 (+)
12	C_6H_6-MeOH	phthalimide (4)	1000	100	26.1	14.4 (-)
13	CH_2Cl_2	phthalimide (4)	1000	100	100	93.9 (+)
14[d]	CH_2Cl_2	phthalimide (4)	1000	100	100	95.1 (+)
15	toluene	succinimide (4)	1000	65	99.2	88.3 (+)
16	toluene	hydanton (4)	1000	65	100	90.1 (+)
17	toluene	2,3-Naphthalene-dicarboximide (4)	1000	70	100	91.7 (+)
18	toluene	4,5-dichlorophthalimide (4)	1000	70	100	91.8 (+)
19	toluene	*N*-Me-phthalimide (4)	1000	65	100	90.0 (+)
20	toluene	*N*-K-phthalimide (4)	1000	68	71.8	37.0 (+)
21	toluene	*N*-Br-phthalimide (4)	1000	70	100	31.8 (+)
22	toluene	phthalic anhydride (4)	1000	68	100	83.4 (+)
23	toluene	1,3-indandione (4)	1000	96	100	90.2 (+)

a. Reaction conditions: $[Ir(COD)Cl]_2$: (*R*, *R*)-BICP : imine = 1 : 2.4 : 200, [imine] = 0.15 M; b. Determined by GC using a Supelco β-DEX-225 column; c. Optical rotation was taken in $CHCl_3$; d. This reaction was carried out at 0 °C.

effective promoters in an Ir–BINAP catalytic system,[7] also did not work well in our system (entries 3 and 4). We therefore focused our attention on other additives for the hydrogenation reaction. Inspired by Achiwa's work[8] showing that imides can improve both the catalytic activity and enantioselectivity of bisphosphine–iridium(I) catalyzed hydrogenation of certain imines, we found that phthalimide has a dramatic effect on the enantioselectivity of our Ir–BICP catalytic system for the hydrogenation of trimethylindolenine. In the presence of phthalimide (4 mol%), imine **2** was hydrogenated smoothly with 92.2% ee in toluene using an iridium catalyst generated in situ from $[Ir(COD)Cl]_2$ and (*R*,*R*)-BICP (**1**) (entry 6). A control experiment showed that phthalimide is an important additive (entry 10). Systematic



(*R*, *R*)-BICP (1)

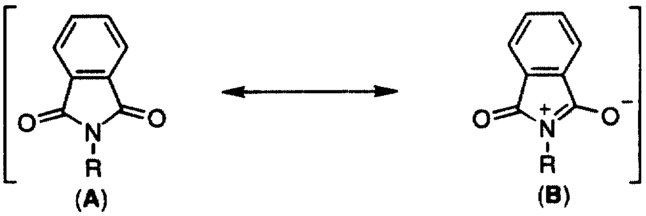
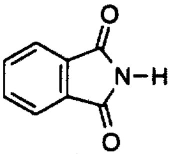


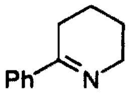
Fig. 1. Canonical forms of imide

studies show that the presence of 4 mol% of phthalimide gave the optimal results (entries 5–10). A strong solvent effect was observed in this catalytic system. While polar solvents such as alcohol or DMF gave poor results (entries 11 and 12), toluene and CH_2Cl_2 were found to be preferred solvents for this catalytic system (entries 6 and 13).

The best enantioselectivity (95.1% ee) with complete conversion for the hydrogenation of imine **2** was found when the reaction was carried out at 0°C in CH_2Cl_2 (entry 14). Various imides such as succinimide, hydantion, 2,3-naphthalenedicarboximide and 4,5-dichlorophthalimide can be used as additives (4 mol%) to improve the enantioselectivity of Ir–BICP catalyzed hydrogenation of 2,3,3-trimethylindolenine (**2**) (entries 15–18).



Phthalimide



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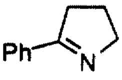

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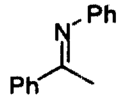

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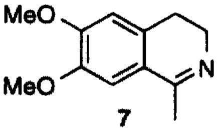

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Colquhoun and co-workers have reported that imidato ligands, derived from imides $[(RCO)_2N^-]$, behave like pseudo-halogens in terms of their σ-acceptor and π-donor properties.[9] To investigate whether an ionic Ir–N bond accounts for the additive effect of phthalimide, we replaced phthalimide with *N*-methyl phthalimide. Surprisingly, the hydrogenation still went smoothly and gave similar enantioselectivity as found with phthalimide (entry 19). However, using potassium phthalimide as the additive, the reaction not only gave low enantioselectivity but also low conversion (entry 20). These results indicate that the additive effect of phthalimide does not stem from an Ir–N bonded complex. One possible explanation for the observed results is that the canonical form of phthamide involving a C–O single bond may coordinate to the Ir complex. Introduction of electron withdrawing groups adjacent to the N atom will disfavor the canonical form **B** in Fig. 1. Indeed, when *N*-bromophthalimide was used as an additive, much lower enantioselectivity was observed (entry 21). Furthermore, phthalic anhydride had almost no effect on the enantioselectivity for this reaction (entry 22). On the other hand, 1,3-indandione can form a more stable enol form through keto–enol tautomerism. The presence of this additive increased the enantioselectivity of the hydrogenation of imine **2** (entry 23). Based on these results, we speculate that those canonical forms in imides and 1,3-indandione have significant contributions to the dramatic additive effect in the Ir-catalyzed hydrogenation of imines.

The additive effect of imides found in this study and the enantioselectivity are very sensitive to the substrate structure. When other cyclic and non-cyclic imines were used as substrates, the Ir–BICP catalyst did not give the same high enantioselectivity as found for 2,3,3-trimethylindolenine. In the presence of phthalimide (4 mol%), the following enantiomeric excesses were obtained for different substrates: **4** (64.7% ee, 100% conversion); **5** (56.3% ee, 12.8% conversion); **6** (13.7% ee, 68.2% conversion); **7** (4.0% ee, 94.6% conversion). Further study showed that different imines needed other additives to achieve optimal results. For example, imine **7** can be hydrogenated in 41.3% ee with high conversion in methanol using benzylamine (5 mol%) as the additive. In certain cases, addition of acids such as HOAc, or H_2SO_4 can improve the reactivity of the hydrogenation, but the enantioselectivity did not change significantly. It is clear that Ir-catalyzed hydrogenation of imines is a complicated catalytic system and a good understanding of this process is presently not available.

In conclusion, remarkable additive effects of imides and 1,3-indandione were found in an iridium–BICP complex catalyzed asymmetric hydrogenation of imines. A mechanistic rationale for the additive effect is proposed. Further investigations on developing more efficient catalysts for this type of reaction are in progress.

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