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Asymmetric iridium-catalyzed hydrogenation of 2-methylindole using phosphite ligands

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ABSTRACT

The iridium-catalyzed asymmetric hydrogenation of 2-methylindole using monodentate phosphites and amidophosphites as ligands was examined. The use of iodine as the additive resulted in increased enantioselectivity and conversion in the iridium-catalyzed hydrogenation of 2-methylindole. Full conversion and up to 80% ee were obtained with a catalyst based on a phosphite ligand.

Chiral indolines are important structural motifs which are used commonly in the chemical and pharmaceutical industries.[1,2] Different methods have been developed to obtain such molecules in an enantioselective manner, however, only a few catalytic methods have been reported, most based on enzymatic or nonenzymatic kinetic resolutions.[3] Asymmetric hydrogenation of indoles is the most straightforward and powerful approach to make chiral indolines in terms of simplicity and atom efficiency.[4] Kuwano and Ito developed the first highly effective hydrogenation of a series of *N*-protected indoles by application of rhodium or ruthenium complexes.[5] Feringa and co-workers reported the Rh-catalyzed hydrogenation of 2-substituted *N*-protected indoles with moderate enantioselectivity.[6] In 2010, the Pfaltz group revealed Ir/N,P-catalyzed hydrogenation of *N*-protected indoles with high ee but low reactivity,[7] whereas Zhang and Wang reported the asymmetric hydrogenation of *N*-unprotected indoles using Pd-catalysts containing chiral phosphine ligands and camphorsulfonic acid as the activator.[8,9] It should be noted that monodentate phosphites and phosphoramidites have been shown to be excellent and sometimes superior alternatives to phosphine ligands, in terms of enantioselectivity, simplicity of synthesis, and ease of structural variation.[10–12] Herein, we report on the application of phosphite-type ligands in the iridium-catalyzed asymmetric hydrogenation of 2-methylindole using different Ir-precursors, solvents, and additives.

Readily available chiral phosphite-type ligands **L1**–**L4** (Fig. 1), all prepared from (*S*)-BINOL, were screened in the asymmetric

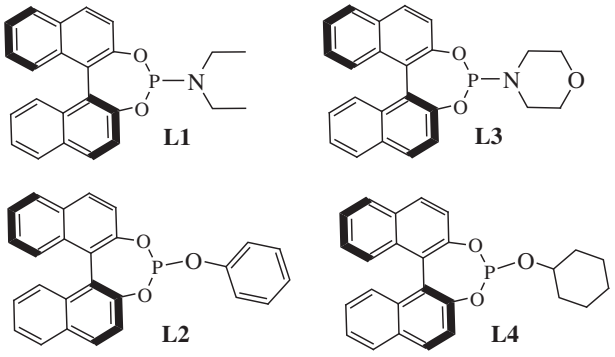
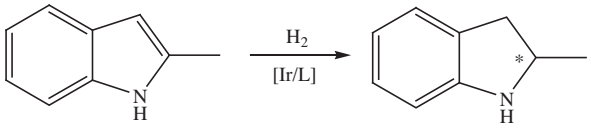


Figure 1. Phosphite ligands.



Scheme 1. Ir-catalyzed asymmetric hydrogenation of 2-methylindole using phosphite ligands.

hydrogenation of 2-methylindole (**1**) (Scheme 1) in EtOH using a catalyst prepared in situ from $[Ir(COD)Cl]_2$ (0.5 mol %) and the corresponding chiral ligand. After 12 h, a moderate conversion was obtained with monodentate ligand **L4** only at 35 atm of hydrogen pressure and 50 °C (Table 1, entries 1–4).

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Table 1
Ir-catalyzed asymmetric hydrogenation of 2-methylindole

Entry	Catalyst[a]	Solvent	Additive	Temp (°C)	Time (h)	Conversion (%)	ee (%)
1	$[Ir(COD)Cl]_2$/4**L1**	EtOH	—	50	12	0	—
2	$[Ir(COD)Cl]_2$/4**L2**	EtOH	—	50	12	0	—
3	$[Ir(COD)Cl]_2$/4**L3**	EtOH	—	50	12	0	—
4	$[Ir(COD)Cl]_2$/4**L4**	EtOH	—	50	12	34	11 (*S*)
5	$[Ir(COD)Cl]_2$/4**L1**	EtOH	I_2[b]	50	12	5	0
6	$[Ir(COD)Cl]_2$/4**L2**	EtOH	I_2[b]	50	12	65	47 (*S*)
7	$[Ir(COD)Cl]_2$/4**L3**	EtOH	I_2[b]	50	12	48	6 (*S*)
8	$[Ir(COD)Cl]_2$/4**L4**	EtOH	I_2[b]	50	12	51	43 (*S*)
9	$[Ir(COD)_2]$BARF/**L1**	EtOH	—	50	12	4	—
10	$[Ir(COD)_2]$BARF/**L2**	EtOH	—	50	12	3	—
11	$[Ir(COD)_2]$BARF/**L3**	EtOH	—	50	12	5	—
12	$[Ir(COD)_2]$BARF/**L4**	EtOH	—	50	12	7	—
13	$[Ir(COD)_2]$BARF/**L1**	EtOH	I_2[b]	50	12	62	48 (*S*)
14	$[Ir(COD)_2]$BARF/**L2**	EtOH	I_2[b]	50	12	62	55 (*S*)
15	$[Ir(COD)_2]$BARF/**L3**	EtOH	I_2[b]	50	12	72	72 (*S*)
16	$[Ir(COD)_2]$BARF/**L4**	EtOH	I_2[b]	50	12	100	**80** (*S*)
17	$[Ir(COD)_2]$BARF/**L4**	CF_3CH_2OH	I_2[b]	50	12	15	50 (*S*)
18	$[Ir(COD)_2]$BARF/**L4**	MeOH	I_2[b]	50	12	85	62 (*S*)
19	$[Ir(COD)_2]$BARF/**L4**	*i*-PrOH	I_2[b]	50	12	22	10 (*S*)
20	$[Ir(COD)_2]$BARF/**L4**	THF	I_2[b]	50	12	77	40 (*S*)
21	$[Ir(COD)_2]$BARF/**L4**	EtOH	I_2[b]	20	24	17	60 (*S*)

[a] 1 mol % of catalyst.
[b] 10 mol % of iodine.

Considering the remarkable impact of the additive on the catalytic activity and enantioselectivity in the asymmetric hydrogenation of heterocyclic compounds,[13] we next examined the effect of an additive. The addition of iodine (10 mol %) had a positive effect on the conversion and enantioselectivity (Table 1, entries 5–8). It should be noted that the best results were obtained with the use of phosphite ligands **L2** and **L4**. We also examined the hydrogenation of 2-methylindole using ligands **L1**–**L4** and $[Ir(COD)_2]$BARF as a cationic iridium precursor. Unfortunately, very low conversion was obtained in all cases without addition of iodine (Table 1, entries 9–12). However, addition of iodine significantly increased the conversion and also gave moderate to good enantioselectivities (Table 1, entries 13–16). A limited solvent screen showed that EtOH was the solvent of choice compared to CF_3CH_2OH, MeOH, *i*-PrOH, and THF (Table 1, entries 16–20). To evaluate the effect of temperature and try to increase the enantioselectivity, the temperature was reduced from 50 °C to 20 °C. In this case, incomplete conversion of **1** was observed over 24 h, and a lower enantioselectivity was obtained compared to hydrogenation at 50 °C using phosphite **L4** (Table 1, entries 16 and 21).

In summary, we have demonstrated that high enantioselectivity (up to 80% ee) in the Ir-catalyzed hydrogenation of 2-methylindole can be achieved using easily accessible monodentate phosphite-type ligands. We found that the use of iodine as the additive gave increased enantioselectivity and conversion in the Ir-catalyzed hydrogenation of 2-methylindole. Moreover, solvent screening showed that EtOH was the solvent of choice. Further studies on extending this method to other *N*-unsubstituted prochiral indoles are in progress.

Ligands **L1**–**L4**,[14–16] $[Ir(COD)Cl]_2$,[17] $[Ir(COD)_2]$BARF[18] (BARF = {tetrakis[3,5-bis(trifluoromethyl)phenyl]borate} were prepared as published.

Hydrogenation procedure

The hydrogenation experiments were carried out in a 10 mL stainless-steel high-pressure reactor. The reactor was charged in open air with dimeric $[Ir(COD)Cl]_2$ (2 mg, 0.003 mmol) or $[Ir(COD)_2]$BARF (7 mg, 0.006 mmol), ligand (0.012 mmol) and CH_2Cl_2 (0.4 mL). After stirring at room temperature for 5 min, in several cases (see Table 1) an additive (0.06 mmol) was placed in the reactor and the solution was stirred for an additional 10 min, before removing the solvent in vacuo. 2-Methylindole (0.6 mmol) and the solvent (2 mL) were added to the catalyst and the reactor was pressurized with hydrogen (35 atm). Hydrogenation was performed at 20 °C or 50 °C for the indicated period of time. After stirring, the vessel was depressurized, and the catalyst was removed via a short silica gel (0.06–0.2 mm, 60 Å, 1 cm^3) column using CH_2Cl_2 as the eluent (1 mL). The filtrate was concentrated in vacuo. The extent of conversion of 2-methylindole was determined according to ^1H NMR spectroscopy. The enantioselectivity of the hydrogenation reactions was determined by chiral HPLC according to a literature procedure (Chiralcel OD-H, 250 × 4.6 mm column, 95:5:0.2 hexane/*i*-PrOH/Et_3N, 1 mL/min, 254 nm).[8]

References and notes

1. Gueritte, F.; Fahy, J. In *Anti-cancer Agents from Natural Products*; Cragg, G. M., Kingston, D. G. I., Newman, D. J., Eds.; CRC Press: Boca Raton, 2005.
2. *Modern Alkaloids*; Fattorusso, E., Taglialatela-Scafati, O., Eds.; Wiley-VCH: Weinheim, 2008.
3. Anas, S.; Kagan, H. B. *Tetrahedron: Asymmetry* **2009**, *20*, 2193.
4. Zhou, Y.-G. *Acc. Chem. Res.* **2007**, *40*, 1357.
5. Kuwano, R.; Sato, K.; Kurokawa, T.; Karube, D.; Ito, Y. *J. Am. Chem. Soc.* **2000**, *122*, 7614.
6. Mrsic, N.; Jerphagnon, T.; Minnaard, A. J.; Feringa, B. L.; de Vries, J. G. *Tetrahedron: Asymmetry* **2010**, *21*, 7.
7. Baeza, A.; Pfaltz, A. *Chem. Eur. J.* **2010**, *16*, 2036.
8. Wang, D.-S.; Chen, Q.-A.; Li, W.; Yu, C.-B.; Zhou, Y.-G.; Zhang, X. *J. Am. Chem. Soc.* **2010**, *132*, 8909.
9. Li, C.; Chen, J.; Fu, G.; Liu, D.; Liu, Y.; Zhang, W. *Tetrahedron* **2013**, *69*, 6839.
10. van Leeuwen, P.; Kamer, P.; Claver, C.; Pamies, O.; Dieguez, M. *Chem. Rev.* **2011**, *111*, 2077.
11. Lyubimov, S. E.; Kalinin, V. N.; Tyutyunov, A. A.; Olshevskaya, V. A.; Dutikova, Y. V.; Cheong, C. S.; Petrovskii, P. V.; Safronov, A. S.; Davankov, V. A. *Chirality* **2009**, *21*, 2.
12. Lyubimov, S. E.; Davankov, V. A.; Said-Galiev, E. E.; Khokhlov, A. R. *Catal. Commun.* **2008**, *9*, 1851.
13. Wang, D.-S.; Chen, Q.-A.; Lu, S.-M.; Zhou, Y.-G. *Chem. Rev.* **2012**, *112*, 2557.
14. Bernsmann, H.; van den Berg, M.; Hoen, R.; Minnaard, A.; Mehler, G.; Reetz, M.; De Vries, J.; Feringa, B. *J. Org. Chem.* **2005**, *70*, 943.
15. Sole, C.; Bonet, A.; de Vries, A. H. M.; de Vries, J. G.; Lefort, L.; Gulyas, H.; Fernandes, E. *Organometallics* **2012**, *31*, 7855.
16. Pignataro, L.; Lynikaite, B.; Colombo, R.; Carboni, S.; Krupička, M.; Piarulli, U.; Gennari, C. *Chem. Commun.* **2009**, 3539.
17. Herde, J. L.; Lambert, J. C.; Senoff, C. V.; Cushing, M. A. In *Inorganic Syntheses*; Parshall, G. W., Ed.; Hoboken: John Wiley, 2007; Vol. 15, pp 18–20.
18. Semeniuchenko, V.; Khilya, V.; Groth, U. *Synlett* **2009**, 271.