EFFICIENT ASYMMETRIC HYDROGENATION OF IMINES CATALYZED BY A NEUTRAL IRIDIUM(I) COMPLEX OF (4*R*,5*R*)-MOD-DIOP[1)]

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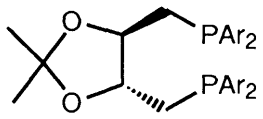
A neutral iridium(I) complex of (4*R*,5*R*)-MOD-DIOP (**1b**) was found to be an efficient catalyst for the asymmetric hydrogenation of imines, *N*-(α-methylbenzylidene)benzylamine (**4**) and 2,3,3-trimethylindolenine (**6**), in the presence of tetrabutylammonium iodide. A high enantioselectivity with up to 81.4% ee was achieved.

KEYWORDS catalytic asymmetric hydrogenation; imine; iridium(I) complex; chiral bisphosphine ligand; optically active amine; chiral column

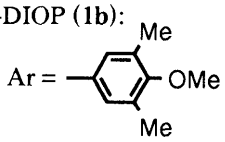
Numerous methods for the syntheses of optically active amines have already been developed. Most of them are based on procedures using a stoichiometric amount of chiral reagents such as chiral reducing agents, resolving agents, and natural resources. On the other hand, much progress in the use of homogeneous catalytic reactions has produced many efficient catalysts composed of transition metals and chiral ligands for the asymmetric hydrogenation of functionalized olefins and ketones.[2)] We have already developed several efficient bisphosphine ligands, including BPPMs,[3)] BCPMs,[4)] modified DIOPs,[5)] and BIMOPs[6)] for rhodium(I) or ruthenium(II) catalyzed asymmetric hydrogenation of some olefins and ketones such as itaconic acids, *N*-acyldehydroamino acids, ketopantolactone, amino ketones, and keto esters.[7)] However, only a few efficient catalysts of chiral rhodium(I) or iridium(I) complexes have appeared in the literature regarding the catalytic asymmetric hydrogenation of imines to form chiral amines;[8)] very few bisphosphine ligands, such as BDPP,[8a)] sulfonated BDPP,[8b)] Cycphos,[8c)] and Duphos,[8d)] are known to be efficient as rhodium(I) or iridium(I) complex catalysts.

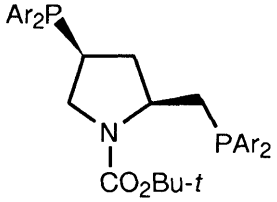
We report herein the catalytic asymmetric hydrogenation of representative ketimines using a neutral iridium(I) complex of a modified DIOP, (4*R*,5*R*)-MOD-DIOP (**1b**),[5b)] in comparison with the complexes of original DIOP (**1a**) and several other bisphosphine ligands.



(4*R*,5*R*)-DIOP (**1a**): Ar = Ph

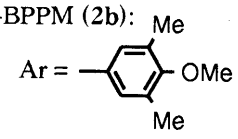
(4*R*,5*R*)-MOD-DIOP (**1b**):

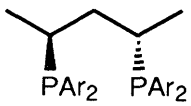




(2*S*,4*S*)-BPPM (**2a**): Ar = Ph

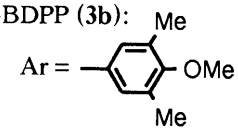
(2*S*,4*S*)-MOD-BPPM (**2b**):





(2*S*,4*S*)-BDPP (**3a**): Ar = Ph

(2*S*,4*S*)-MOD-BDPP (**3b**):



First, we carried out the asymmetric hydrogenation of *N*-(α-methylbenzylidene)benzylamine (**4**), a representative ketimine, with a neutral rhodium(I) complex of (4*R*,5*R*)-DIOP (**1a**) in a mixed solvent of benzene and methanol in the presence of tetrabutylammonium iodide under an initial hydrogen pressure of 100 atm (Entry 1 in Table I). Although the reaction proceeded completely in 48 h, the product (**5**) was almost racemic. Therefore, we next carried out the asymmetric hydrogenation using a neutral iridium(I) complex. A preliminary asymmetric hydrogenation was carried out with the ketimine (**4**) in a mixed solvent of benzene and methanol under an initial hydrogen pressure of 100 atm in the presence of 1 mol% of an iridium(I) complex prepared just prior to use, by mixing chloro(1,5-cyclooctadiene)iridium(I) dimer, (4*R*,5*R*)-DIOP (**1a**), and tetrabutylammonium iodide in a molar ratio of 1:2.4:4 (Entry 2). The conversion was 100% after 72 h, and the enantiomeric excess (ee) was 22.4% (*S*). The conversion was determined by gas chromatography (GC) with a column of PEG 20M, and the ee was measured by high performance liquid chromatography (HPLC) with a chiral column, Chiralcel OJ. The absolute configuration was determined according to the sign of its optical rotation. In order to investigate the effect of the substituents of DIOP on the enantioselectivity, the hydrogenation was carried out by using (4*R*,5*R*)-MOD-DIOP (**1b**) instead of DIOP (**1a**) under similar reaction conditions (Entry 3). The enantiomeric excess was considerably increased, to 45.5% ee. Contrary to our expectations, the iridium(I) complexes of BPPM (**2a**) and MOD-BPPM (**2b**)[3)] were far less effective for the

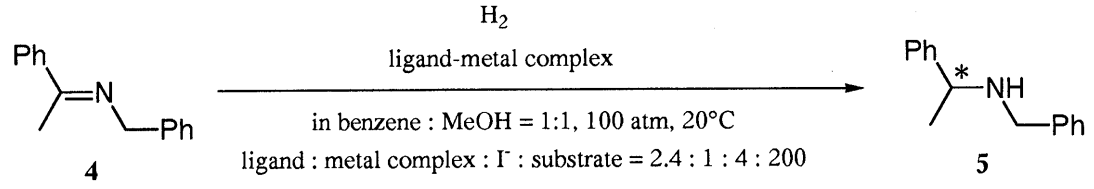


Table I. Catalytic Asymmetric Hydrogenation of *N*-(α-Methylbenzylidene)benzylamine (**4**)[a]

Entry	Ligand	Metal complex	Time (h)	Convn.[b] (%)	ee[c] (%)
1	(4*R*,5*R*)-DIOP (**1a**)	$[Rh(COD)Cl]_2$	48	100.0	~ 0
2		$[Ir(COD)Cl]_2$	72	100.0	22.4 (*S*)
3	(4*R*,5*R*)-MOD-DIOP (**1b**)	$[Ir(COD)Cl]_2$	48	73.6	**45.5** (*S*)
4	(2*S*,4*S*)-BDPP (**3a**)	$[Ir(COD)Cl]_2$	48	100.0	12.3 (*R*)
5	(2*S*,4*S*)-MOD-BDPP (**3b**)	$[Ir(COD)Cl]_2$	48	100.0	30.5 (*R*)

a) All hydrogenations were carried out with 0.5 mmol of substrate (**4**), 2.5×10^{-3} mmol of metal complex, 6.0×10^{-3} mmol of ligand, and 1.0×10^{-2} mmol of tetrabutylammonium iodide in 2.5 ml of solvent (benzene/MeOH = 1:1) at 20°C under an initial hydrogen pressure of 100 atm.

b) Determined by GC analysis using a column packed with PEG 20M Chromosorb W (AW-DMCS).

c) Determined by HPLC analysis with a chiral column of Chiralcel OJ (Daicel) employing hexane/isopropyl alcohol (200:1) as the solvent system. The absolute configuration was determined on the basis of the optical rotation value of (*R*)-*N*-benzyl-1-phenylethylamine, $[\alpha]_D^{20}$+56.2° (*c* 1.071, EtOH) [K.Park, *J. Prakt. Chem.*, **86**, 287 (1912)].

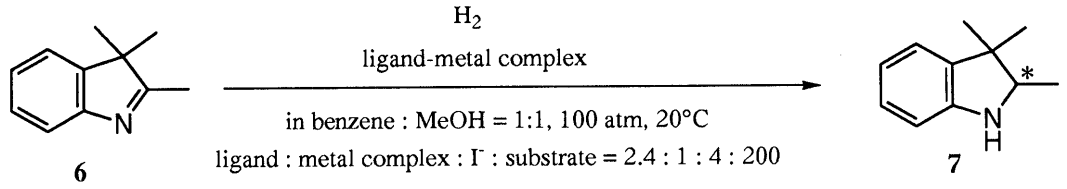


Table II. Catalytic Asymmetric Hydrogenation of 2,3,3-Trimethylindolenine (**6**)[a]

Entry	Ligand	Metal complex	Convn.[b] (%)	ee[c] (%)
1	(4*R*,5*R*)-DIOP (**1a**)	$[Rh(COD)Cl]_2$	95.3	~ 0
2		$[Ir(COD)Cl]_2$	100.0	66.2 (+)
3	(4*R*,5*R*)-MOD-DIOP (**1b**)	$[Rh(COD)Cl]_2$	60.4	~ 0
4		$[Ir(COD)Cl]_2$	100.0	**81.4** (+)

a) All hydrogenations were carried out with 0.5 mmol of substrate (**6**), 2.5×10^{-3} mmol of metal complex, 6.0×10^{-3} mmol of ligand, and 1.0×10^{-2} mmol of tetrabutylammonium iodide in 2.5 ml of solvent (benzene/MeOH = 1:1) at 20°C for 48 h under an initial hydrogen pressure of 100 atm.

b) Determined by GC analysis using a column packed with PEG 20M Chromosorb W (AW-DMCS).

c) Determined by HPLC analysis of the *N*-acetyl derivative of **7** with a chiral column of Chiralcel OJ (Daicel) employing hexane/isopropyl alcohol (300:1) as the solvent system.

asymmetric hydrogenation. The iridium(I) complexes of BDPP (**3a**) and MOD-BDPP (**3b**)[9] were also less effective under our conditions, although the conversions were 100% and MOD-BDPP (**3b**) was better than BDPP (**3a**) (Entries 4 and 5).

In order to evaluate the capability of MOD-DIOP (**1b**) in the iridium(I)-catalyzed asymmetric hydrogenation of ketimines, 2,3,3-trimethylindolenine (**6**) was chosen as a representative cyclic imine. When asymmetric hydrogenation was carried out with the neutral rhodium(I) complex of DIOP (**1a**) or MOD-DIOP (**1b**) under the same reaction conditions described above, the reaction proceeded well, but the enantiomeric excess was almost 0% (Entries 1 and 3 in Table II). On the other hand, the iridium(I) complex of (4*R*,5*R*)-DIOP (**1a**) was very effective for the asymmetric hydrogenation of **6**, resulting in 100% conversion and 66.2% ee (Entry 2), which were determined by GC and HPLC, respectively. The absolute configuration of product (**7**) was not determined. When the iridium(I) complex of (4*R*,5*R*)-MOD-DIOP (**1b**) was used as the catalyst under the same reaction conditions, a remarkably high enantiomeric excess (81.4% ee) was attained with 100% conversion (Entry 4).

Thus, a modified DIOP, MOD-DIOP (**1b**), was revealed to be an efficient ligand in the asymmetric hydrogenation of ketimines using the neutral iridium(I) complex as the catalyst; in particular with the cyclic ketimine 2,3,3-trimethylindolenine (**6**), a high enantiomeric excess of up to 81.4% ee was attained. We demonstrated here that the introduction of both *p*-methoxy and *m*,*m*'-dimethyl groups into the phenyl groups of bisphosphine ligands is capable of improving the enantioselectivity of their iridium(I) complex catalysts. These experimental findings potentially offer *1*) a strategy for the development of much more efficient catalysts for the asymmetric hydrogenation of ketimines, and *2*) a practical synthetic method for optically active amines, including physiologically active compounds.

Further investigations on developing more efficient catalysts for the asymmetric hydrogenation of various ketimines are in progress.

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