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Highly Efficient and Enantioselective Iridium-Catalyzed Asymmetric Hydrogenation of *N*-Arylimines

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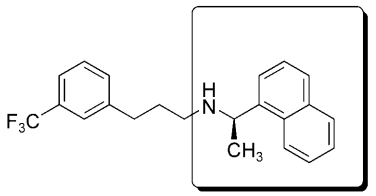
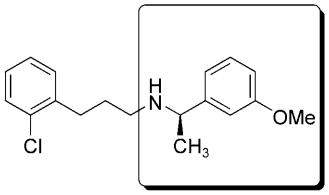
Abstract: A catalytic method employing the cationic iridium-(S_c,R_p)-DuanPhos [(1*R*,1′*R*,2S,2′S)-2,2′-di-*tert*-butyl-2,2′,3,3′-tetrahydro-1*H*,1′*H*-1,1′-biisophosphindole] complex and BARF {tetrakis[3,5-bis(trifluoromethyl)phenyl]borate} counterion effectively catalyzes the enantioselective hydrogenation of acyclic *N*-arylimines with high turnover numbers (up to 10,000 TON) and excellent enantioselectivities (up to 98% *ee*), achieving the practical synthesis of chiral secondary amines.

Keywords: asymmetric catalysis; enantioselectivity; hydrogenation; imines; iridium



Cinacalcet



NPS *R*-568

Figure 1. Structures of Cinacalcet and NPS *R*-568.

Enantiomerically pure amines and their derivatives are of great significance in pharmaceutical, biological and synthetic chemistry.[1] The importance of chiral amines such as those serving as key moieties in drugs or drug candidates, for example, Cinacalcet,[2] and NPS *R*-568[3] (Figure 1), drives chemists to develop efficient synthetic methodologies for approaching them. The groups of List,[4] MacMillan,[5] and Xiao[6] have recently made a major progress in direct asymmetric reductive aminations by employing a chiral organocatalyst or a combination of transition metal catalyst and Brønsted acid to access chiral amines. Kadyrov and Börner also reported on transition metal-catalyzed asymmetric reductive aminations providing chiral amines.[7] However, the catalytic asymmetric hydrogenation of imines is still a powerful method to afford the amine product enantiomerically due to its high efficiency, low catalyst loading and atom economy.[8a]

The asymmetric reduction of imines remains a challenge in modern synthesis, in contrast to the significant progress made in the catalytic asymmetric hydrogenation of ketones and olefins over the last few decades.[1b,8] A number of chiral transition metal complexes, such as Ti, Rh, Ru, and Ir complexes, have been investigated and exhibited promising results in the asymmetric hydrogenation of imines.[9] Buchwald and co-workers developed a highly effective chiral titanocene catalyst for the hydrogenation of cyclic imines.[9a] On the other hand, chiral Ir complexes have shown more potential recently for the reduction of acyclic imines. Imamoto reported the asymmetric hydrogenation of acyclic imines using Ir-bisP* complexes with high enantioselectivities.[9h] Ir-P,N ligand complexes that the catalyzed asymmetric hydrogenation of acyclic *N*-arylketimines have been reported by Zhou et al.[9i] and Knochel et al.[9j] Xiao et al. demonstrated the catalytic capability of Cp*Ir(III)-diamine for the reduction of a wide variety of imines.[9k] More recently, Feringa and de Vries reported the use of Ir-monodentate phosphoramidites in imine hydrogenations.[10] However, the high catalyst loading (0.5–

1 mol%) remains an obstacle to the practical application of these methodologies. The only successful example of the asymmetric hydrogenation of imines in industrial synthesis is the application of neutral iridium complex $[Ir(cod)Cl]_2$ and XyliPhos in the production of the herbicide (*S*)-metolachlor, achieving turnover number (TON) up to 10^6 and 80% *ee*.[11a] The low TON problem in most systems may possibly be attributed to the inhibitory effect of the amine product on the catalysts,[12] and to the possible formation of undesired polymeric Ir clusters.[9i,,11] We envision that introducing a highly electron-donating and highly sterically hindered bisphospholane ligand exerting a strong *trans* effect could minimize binding of the amine product to the catalyst and inhibit the formation of Ir clusters. Thus we envisioned that the series of electron-donating, rigid and sterically hindered ligands developed in our research group, such as TangPhos,[13] DuanPhos,[14] Binapine,[15] could be excellent candidates for Ir-bisphosphine complex-catalyzed imine hydrogenations (Figure 2). Herein, we report a highly efficient asymmetric hydrogenation of acyclic *N*-arylimines catalyzed by the Ir-DuanPhos complex with excellent enantioselectivities (up to 98% *ee* and TONs up to 10,000).

Our initial study began with *N*-(1-phenylethylidene)aniline (**1a**) as the model substrate and a brief screening of Ir precursors and different chiral phosphorus ligand (Table 1). First, we investigated the performance of TangPhos in combination with different Ir salts. Under 50 atm H_2, the neutral iridium chloride complex and the cationic complex with BF_4^- counterion gave incomplete conversion and only moderate *ee* (entries 1 and 2). Meanwhile, the imine substrate was fully converted to the corresponding amine product with 73% *ee* in the presence of BARF {tetrakis[3,5-bis(trifluoromethyl)phenyl]borate} counterion (entry 3). These results are consistent with the reported acceleration effect of BARF in Ir-catalyzed hydrogenation reactions.[16] Subsequently, the effect of solvents was investigated in an effort to attain higher enantioselectivities (entries 3–8). Dichloromethane was the only solvent that gave both good *ee* values and complete conversions during the screening. Furthermore, Ir complexes of different chiral phosphorus ligands were prepared and tested (Table 1). The hydrogenation with Ir-(*R*,*R*)-DuPhos or Ir-(*S*,*S*)-f-Binaphane proceeded smoothly with high conversions; however, the enantioselectivities are only comparable to or lower than that of Ir-TangPhos (entries 10–12). To our delight, the best result was obtained with the Ir-(S_p,R_c)-DuanPhos with 93% *ee* and > 99% conversions (entry 15). The hydrogen pressure showed no obvious effect on the activity or enantioselectivity. Even under 5 atm H_2, the reaction reached completion within 3 h, and the *ee* remained the same under the milder conditions (entry 16). In comparison, an Ir complex of the less electron-donating and less sterichindered BINAP ligand gave lower enantioselectivities (entry 14).

To explore the efficiency and the applicability of this Ir-DuanPhos catalyst, the hydrogenation of a series of substituted *N*-arylimines was studied under the optimized conditions. Asymmetric hydrogenation was performed using 0.1 mol% catalyst loading (Table 2). Full conversions (> 99%) were observed for all substrates, with excellent *ee* values ranging from 89% to 98%. The electronic properties of the substituents comprising the R^1 and R^2 group of the imine have limited effect on the yields or the enantioselectivities. As shown in Table 2, the introduction of an electron-donating group on the R phenyl ring slightly decreased the enantioselectivity (entries 2 and 3); an electron-withdrawing substituent on the R′ phenyl also affords slightly lower *ee* values (entries 11 and 12). Notably, 98% *ee* was achieved with the presence of the more sterically hindered 2-naphthyl group in the imine substrate (entry 8).

To explore the potential of the Ir-catalyzed asymmetric hydrogenation of imines as a practical means to synthesize chiral amines, the catalyst loading was further decreased to 0.02 mol% and 0.01 mol% (TON = 5,000 and 10,000). The model imine substrate **1a** was smoothly hydrogenated with full conversion, and over 92% *ee* can still be retained under the mild reaction conditions [5 atm H_2, rrom temperature; Eq.(1)]. To the best of our knowledge, this result represents the highest reactivity (TON) in the asymmet-

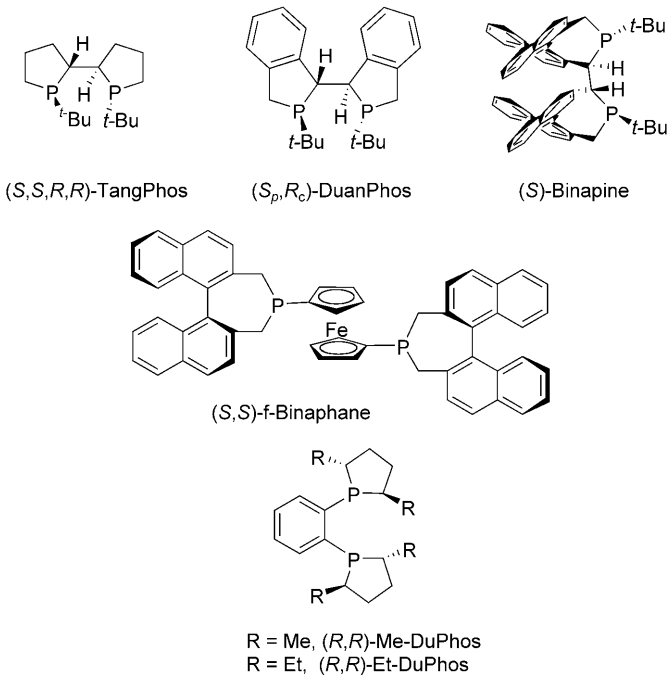
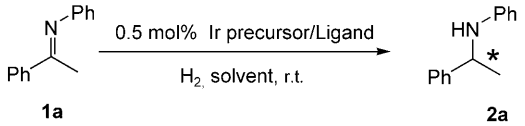


Figure 2. Structures of ligands for asymmetric hydrogenation.

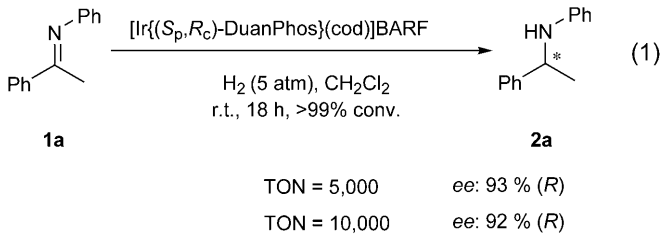
Table 1. Ir-catalyzed asymmetric hydrogenation of *N*-arylimine **1a**.[a]



1a **2a**

Entry	Ir precursor	Ligand	Solvent	Conv. [%][b]	*ee* [%] (config.)[c]
1	$[Ir(cod)Cl]_2$	(*S*,*S*,*R*,*R*)-TangPhos	CH_2Cl_2	89	62 (*R*)
2	$Ir(cod)_2BF_4$	(*S*,*S*,*R*,*R*)-TangPhos	CH_2Cl_2	93	63 (*R*)
3	$Ir(cod)_2BARF$	(*S*,*S*,*R*,*R*)-TangPhos	CH_2Cl_2	> 99	73 (*R*)
4	$Ir(cod)_2BARF$	(*S*,*S*,*R*,*R*)-TangPhos	THF	> 99	4 (*R*)
5	$Ir(cod)_2BARF$	(*S*,*S*,*R*,*R*)-TangPhos	Ethyl acetate	> 99	7 (*R*)
6	$Ir(cod)_2BARF$	(*S*,*S*,*R*,*R*)-TangPhos	IPA	67	16 (*S*)
7	$Ir(cod)_2BARF$	(*S*,*S*,*R*,*R*)-TangPhos	Methanol	92	15 (*S*)
8	$Ir(cod)_2BARF$	(*S*,*S*,*R*,*R*)-TangPhos	Ethyl ether	90	23 (*R*)
9	$Ir(cod)_2BARF$	(*S*)-Binapine	CH_2Cl_2	5	37 (*S*)
10	$Ir(cod)_2BARF$	(*S*,*S*)-f-Binaphane	CH_2Cl_2	>99	74 (*R*)
11	$Ir(cod)_2BARF$	(*R*,*R*)-Me-DuPhos	CH_2Cl_2	>99	49 (*S*)
12	$Ir(cod)_2BARF$	(*R*,*R*)-Et-DuPhos	CH_2Cl_2	>99	67 (*S*)
13	$Ir(cod)_2BARF$	(*R*,*S*)-CyPF-*t*-Bu-Josiphos	CH_2Cl_2	>99	48 (*S*)
14	$Ir(cod)_2BARF$	(*R*)-BINAP	CH_2Cl_2	>99	14 (*S*)
15	$Ir(cod)_2BARF$	(S_p,R_c)-DuanPhos	CH_2Cl_2	>99	93 (*R*)
16[d]	$Ir(cod)_2BARF$	(S_p,R_c)-DuanPhos	CH_2Cl_2	>99	93 (*R*)

[a] The reactions were carried out with 0.1 mmol of substrate in 2 mL of solvent in the presence of 0.5 mol% of Ir catalyst for 20 h under an initial hydrogen pressure of 50 atm.
[b] The conversions were determined by GC.
[c] The enantiomeric excesses were determined by chiral HPLC or GC. The absolute configuration was determined by comparison of the retention times and sign of the optical rotation with the reported data (see Supporting Information).
[d] Initial H_2 5 atm, reaction time 3 h, room temperature.



1a **2a** (1)

TON = 5,000 *ee*: 93 % (*R*)
TON = 10,000 *ee*: 92 % (*R*)

ric hydrogenation of imines using chiral cationic iridium catalysts. Also, this hydrogenation proceeded under ambient hydrogen pressure (1 atm) within 3 h (0.05 mol% catalyst loading, >99% conversion). No obvious *ee* value erosion of the hydrogenation was observed. Some methoxy-substituted *N*-aryl groups such as the 4-methoxyphenyl in **2j** could be easily removed by CAN (cerium ammonium nitrate) to obtain the corresponding primary amines without affecting the *ee* values.[17]

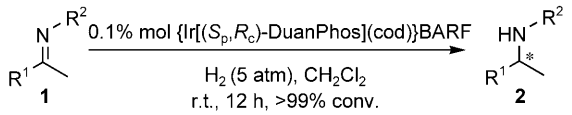
In conclusion, high enantiomeric excesses were obtained in the asymmetric hydrogenation of various *N*-arylimines catalyzed by an Ir complex containing the highly rigid electron-donation P-chiral bisphospholane ligand, DuanPhos, with high yields. High turnover numbers for *N*-arylimine substrates were achieved under mild conditions. Further studies of screening catalysts and application of these catalysts towards other types of imine substrates are currently ongoing and will be reported in due course.

Experimental Section

General Remarks

All reactions and manipulations were performed in the nitrogen-filled glovebox or under nitrogen using standard Schlenk techniques unless otherwise noted. Column chromatography was performed using Sorbent silica gel 60 Å (230–450 mesh). ^{31}P NMR spectral data were recorded on Varian VNMRS 400 MHz, VNMRS 500 MHz and Bruker 400 MHz spectrometers. Chemical shifts are reported in ppm. Enantiomeric excess values were determined by chiral GC on

Table 2. Ir-catalyzed asymmetric hydrogenation of *N*-aryl-imines.[a]



Entry	R^1	R^2	Product	*ee* [%][b]	Config.
1	C_6H_5	C_6H_5	**2a**	93	(*R*)
2	4-Me-C_6H_4	C_6H_5	**2b**	90	(+)
3	4-MeO-C_6H_4	C_6H_5	**2c**	90	(+)
4	4-F-C_6H_4	C_6H_5	**2d**	93	(–)
5	4-Cl-C_6H_4	C_6H_5	**2e**	92	(+)
6	4-Br-C_6H_4	C_6H_5	**2f**	92	(+)
7	3-Cl-C_6H_4	C_6H_5	**2g**	93	(–)
8	2-naphthyl	C_6H_5	**2h**	98	(+)
9	C_6H_5	4-Me-C_6H_4	**2i**	92	(+)
10	C_6H_5	4-MeO-C_6H_4	**2j**	93	(–)
11	C_6H_5	4-F-C_6H_4	**2k**	89	(–)
12	C_6H_5	4-Cl-C_6H_4	**2l**	90	(+)

[a] *Reaction conditions:* 0.1 mmol of substrate in 2 mL of CH_2Cl_2, 0.1 mol% of Ir catalyst, room temperature, 12 h, 5 atm H_2 pressure.

[b] The enantiomeric excesses were determined by chiral HPLC or GC.

Agilent 7890 GC equipment and chiral HPLC on Agilent 1200 Series equipment.

General Procedure for Asymmetric Hydrogenation

In the nitrogen-filled glovebox, the solid complex {Ir-[(S_p,R_c)-DuanPhos](cod)}BARF (3.1 mg, 0.002 mmol) was dissolved in degassed CH_2Cl_2 (10 mL) and equally divided into 20 vials. To each vial, imine substrate (0.1 mmol, S/C = 1000) was then added to the catalyst solution and 1.5 mL degassed CH_2Cl_2 were added to each of the vials. The resulting solution was transferred to an autoclave, which was charged with 5 atm of H_2. The hydrogenation was performed at room temperature for 12 h and the hydrogen was released carefully. The solvent was then evaporated and the residue was purified by column chromatography to give the corresponding hydrogenation product, which was then analyzed directly by chiral GC (Gamma Dex 225 or Beta Dex 390) or HPLC (Chiralcel OD-H) to determine the enantiomeric excess.

Acknowledgements

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