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Highly Enantioselective Reductive Amination of Simple Aryl Ketones Catalyzed by Ir−f-Binaphane in the Presence of Titanium(IV) Isopropoxide and Iodine

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Abstract: Using an Ir−f-Binaphane complex as the catalyst, complete conversions and high enantioselectivies (up to 96% ee) were achieved in the asymmetric reductive amination of aryl ketones in the presence of $Ti(O^iPr)_4$ and I_2. A simple and efficient method of synthesizing chiral primary amines has been realized.

The paramount significance of chiral amines in pharmaceutical and agrochemical substances drives the development of efficient catalytic asymmetric methods for their formation. Most of the past studies in this field have focused on the enantioselective reduction of C−N double bonds. In contrast to the high enantioselectivities observed in asymmetric reduction of both alkenes and ketones,[1] only limited success has been achieved in the enantioselective hydrogenation of imines.[2] Among them, a variety of chiral Ti,[3] Ir,[4] Rh,[5] Ru,[6] and Pd[7] complexes have been investigated as catalysts for the reduction of imines. Without isolating and purifying the imines, the asymmetric reductive amination of ketones or aldehydes with amines is a simple and practical method for the preparation of chiral amines. However, it has not received adequate attention. Only two preliminary studies have been reported. The first example of asymmetric reductive amination was reported by Blaser et al. Using the Ir−Xyliphos complex, they found that methoxyacetone reacted with 2-methyl-5-ethylaniline to yield an enriched chiral amine as a precursor of an important grass herbicide, with complete conversion and 78% ee (10^4 turnovers).[8a] Borner et al. developed a Rh-chiral diphosphine catalyst for asymmetric reductive amination of α-keto acid derivatives, and enantiomerically enriched *N*-benzyl α-amino acid was obtained in 59% yield and 38% ee. However, the corresponding α-hydroxy acid was also generated.[8b]

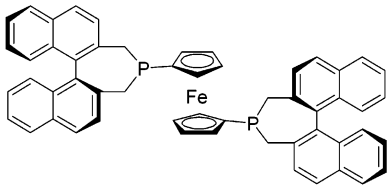

FIGURE 1. (*S*,*S*)-f-Binaphane.

Recently, we have developed a chiral ligand, f-Binaphane (Figure 1), that has shown excellent reactivities and enantioselectivities for Ir-catalyzed asymmetric hydrogenation of acyclic imines (up to 99% ee).[4a] Importantly, we found that ketones cannot be hydrogenated by Ir complexes under the same conditions. As part of our ongoing studies on asymmetric hydrogenation of imines, we used the Ir−f-Binaphane catalytic system to explore the asymmetric reductive amination reaction. In the presence of $Ti(O^iPr)_4$ and I_2, high enantioselectivity and activity have been achieved for asymmetric reductive amination of aryl ketones using a Ir−f-Binaphane catalyst. Our preliminary results pave a new way to produce chiral amines.

In our experiments, we chose acetophenone **1a** as a test substrate for asymmetric reductive amination. We have screened various arylamines (aniline, benzylamine, 2,6-dimethylaniline, *o*-anisidine, *m*-anisidine, *p*-anisidine) and solvents (DCM, toluene, THF, methanol, 2-propanol) to search for the optimal conditions. The best result was obtained with respect to yield and enantioselectivity of chiral amine **2a** (93% yield, 91% ee; yield of imine **3a** is 2%, Table 1, entry 5), when *p*-anisidine and dichlo-

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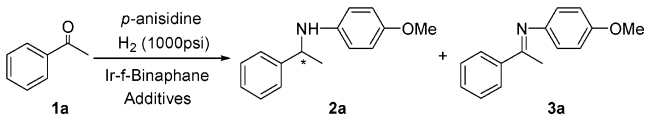
TABLE 1. Additive Effect in Asymmetric Reductive Amination of Acetophenone with *p*-Anisidine[a]



entry	additive	yield of **3a** (%)	chiral amine **2a** yield (%)	chiral amine **2a** ee (%)[b]
1	10% I_2, 2.0 equiv of $Ti(O^iPr)_4$	<1	>99	94
2	10% I_2, 1.5 equiv of $Ti(O^iPr)_4$	<1	>99	94
3	10% I_2, 1.0 equiv of $Ti(O^iPr)_4$	<1	>99	91
4	10% I_2, 0.5 equiv of $Ti(O^iPr)_4$	<1	>99	89
5	10% I_2	2	93	91
6	1.5 equiv of $Ti(O^iPr)_4$	no reaction detected		

[a] Reaction conditions: 1.2 equiv of *p*-anisidine, 1 mol % of Ir−(*S*,*S*)-f-Binaphane complex generated in situ from $[Ir(COD)Cl]_2$ and f-Binaphane in DCM, H_2 (1000 psi), DCM, rt, 10 h. [b] Absolute configurations were determined as *R*-(+) by the sign of optical rotation.

romethane were used. This result led to the following conclusion: the Ir−f-Binaphane catalytic system is highly active and enantioselective for imine reduction. However, the formation of the imine is the limiting step in achieving complete conversion for asymmetric reductive amination.

Studies on the effect of additives are important to achieve high reactivities and enantioselectivities in asymmetric catalysis.[9] We have investigated the additive effect for the formation of imines and asymmetric reduction of imines and the results are summarized in Table 1. In addition to 10% I_2 as an additive, we used either $Ti(O^iPr)_4$, 4 Å MS, $MgSO_4$, or TsOH to accelerate the formation of imines. In our experiments, $Ti(O^iPr)_4$ was found to be a efficient accelerant for asymmetric reductive amination, as the others did not have an obviously positive effect. The yield of chiral amine **2a** increased from 93% (entry 5) to >99% (entry 2), and the enantioselectivity improved slightly (entries 2 and 5, 91 to 94% ee). When the amount of $Ti(O^iPr)_4$ decreased from 1.5 equiv to 0.5 equiv, the yield of chiral amine **2a** did not change, while the enantioselectivity dropped from 94 to 89% ee (entries 2−4). However, more $Ti(O^iPr)_4$ did not have any improvement on enantioselectivity (Table 1, entriy 1). Using the Ir−f-Binaphane complex as a catalyst and 10% I_2 as an additive, chiral amine **2a** was also obtained through the hydrogenation of the corresponding imine, *N*-(1-phenylidene)-4′-methoxyaniline, with the same enantioselectivity (94% ee) under the same reaction conditions;[4a] when 10% I_2 and 1.5 equiv of $Ti(O^iPr)_4$ were employed as additives for this imine reduction reaction, the enantioselectivity did not change. So, we believe that $Ti(O^iPr)_4$ does not have any effect on the enantioselectivity of hydrogenation of imines. We also found that iodine plays a very important role in the Ir−f-Binaphane catalytic system. In the presence of $Ti(O^iPr)_4$, or $Ti(O^iPr)_4$ with tetrabutylamonium iodide or acetic acid, no reaction occurs (entry 6). On the basis of these findings, we propose the mechanism in Scheme 1. In the presence of Lewis acid, imines were formed through an equilibrium from an intermediate, aminoalcoholatitanium(IV) complex **4**. In the presence of I_2, the resulting imine was hydrogenated by an Ir−f-Binaphane complex to yield chiral amines.[10] A similar intermediate **4** was reported by Bhattacharyya et al. in another reductive amination reaction.[11]

SCHEME 1. The Proposed Mechanism of Asymmetric Reductive Amination in the Presence of $Ti(O^iPr)_4$, and I_2

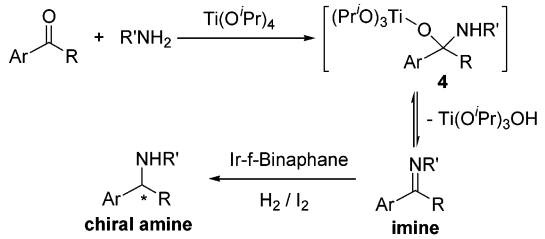
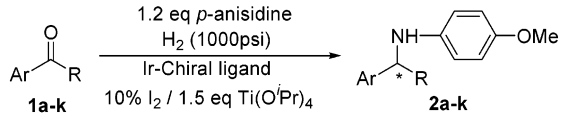


TABLE 2. Asymmetric Reductive Amination of Various Aryl Ketones with *p*-Anisidine[a]



entry	substrate	Ar	R	ee (%)	confign
1	**1a**[b]	Ph	Me	94	*R*-(+)[e]
2	**1b**[b]	Ph	Et	85	(+)[f]
3	**1c**[b]	Ph	^{n}Bu	79	*R*-(+)[e]
4	**1d**[b]	2-Me-C_6H_4	Me	44	(+)[f]
5	**1e**[b]	3-Me-C_6H_4	Me	89	(+)[f]
6	**1f**[b]	4-Me-C_6H_4	Me	96	(+)[f]
7	**1g**[b]	4-OMe-C_6H_4	Me	95	(+)[f]
8	**1h**[b]	4-F-C_6H_4	Me	93	(−)[f]
9	**1i**[b]	4-Cl-C_6H_4	Me	92	(+)[f]
10	**1j**[b]	4-Br-C_6H_4	Me	94	(+)[f]
11	**1k**[b]	2-furan	Me	92	(+)[f]
12	**1a**[c]	Ph	Me	16	*S*-(−)[e]
13	**1a**[d]	Ph	Me	25	*S*-(−)[e]

[a] Reaction conditions: 1 mol % of Ir−chiral ligand complex generated in situ from $[Ir(COD)Cl]_2$ and chiral ligand in DCM, H_2 (1000 psi), DCM, 10% I_2, 1.5 equiv of $Ti(O^iPr)_4$, rt, 10 h. The yields are >99%. [b] Chiral ligand: (*S*,*S*)-f-Binaphane. [c] Chiral ligand: (*R*)-BINAP. [d] Chiral ligand: (*R*)-MeO-BIPHEP. [e] Absolute configurations were determined by the sign of optical rotation. [f] Absolute configurations were not determined.

Under the optimized conditions, a series of aryl ketones **1a**−**k** were explored (Table 2), and the yields of the corresponding chiral amines **2a**−**k** are higher than 99%. The simplest aryl ketone **1a** was reductively aminated with 94% ee with use of an Ir−f-Binaphane complex as the catalyst (entry 1). This result is superior to ee values obtained with other phosphine ligands (entry 12, 16% ee with (*R*)-BINAP, entry 13, 25% ee with (*R*)-BIPHEP). When the alkyl group of ketones (*R*) was changed from Me to Et and then ^{n}Bu, the ee value dropped from 94 to 85 and then 79%, respectively (entries 1−3). We also examined electronic effects of substrate with a series of substituted acetophenones (entries 4−10). An electron-donating para substituent on acetophenones was found to give higher enantioselectivities (entry 6, 96% ee). High enantioselectivity was also achieved on reductive ami-

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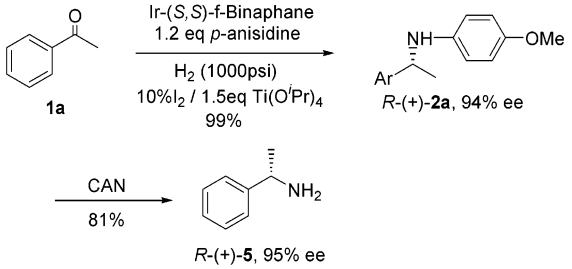
SCHEME 2. Simple and Efficient Synthesis of a Chiral Primary Amine



nation of a heterocyclic ketone (entry 11, 92% ee). Unfortunately, the Ir−f-Binaphane catalytic system did not work for the asymmetric reductive amination of alkyl ketones.

It is noteworthy that the *N*-*p*-methoxyphenyl group on the chiral amine **2** can be easily removed by oxidation with CAN (cerium ammonium nitrate).[12] On the basis of this strategy, the chiral primary amine **5** was synthesized from acetophenone through a two-step asymmetric reductive amination synthesis (Scheme 2).

In conclusion, the Ir−f-Binaphane complex shows high activities and enantioselectivities (up to 96% ee) for asymmetric reductive amination of aryl ketones in the presence of $Ti(O^iPr)_4$ and I_2. A simple and efficient method of preparation of chiral primary amines from aryl ketones was developed. Future work will focus on exploring the substrate scope and investigation of the reaction mechanism.

Experiment Section

Typical Procedure for Asymmetric Reductive Amination (2a). In a glovebox that was filled with N_2 were dissolved acetophenone (60 mg, 0.5 mmol), *p*-anisidine (74 mg, 0.6 mmol), titanium(IV) isopropoxide (213 mg, 0.75 mmol), and iodine (13 mg, 0.05 mmol) in 2 mL of DCM. The Ir−(*S*,*S*)-f-Binaphane complex was made in situ by mixing $[Ir(COD)Cl]_2$ (1.7 mg, 0.0025 mmol) and (*S*,*S*)-f-Binaphane (4.4 mg, 0.0055 mmol) in 3 mL of DCM. The mixture was stirred for 30 min and transferred to the substrate solution. This reaction solution was transferred to a Parr bomb. The reductive amination was performed at room temperature under 1000 psi of hydrogen for 12 h. After the reaction was finished, hydrogen was released carefully and the reaction mixture was passed through a silica gel plug eluted with EtOAc/hexane 6:1. Solvent was removed under vacuum to yield chiral amine **2a** as a yellow oil (113 mg, >99% yield). *R*-(+)-4-Methoxy-*N*-(1-phenylethyl) aniline **2a**: $[\alpha]^{25}_D$ +7.0° (*c* 2, $CHCl_3$); ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.44 (3H, d, J = 6.72 Hz), 3.63 (3H, s), 3.74 (1H, br), 4.37 (1H, q, J = 6.67 Hz), 6.42−6.45 (2H, m), 6.63−6.68 (2H, m), 7.17−7.20 (1H, m), 7.25−7.33 (4H, m) ppm; ^{13}C NMR (90.6 MHz, $CDCl_3$) δ 25.3, 54.5, 55.9, 114.8, 115.0, 126.1, 127.0, 128.8, 141.8, 145.7, 152.1 ppm; HRMS (ADCI) calcd for $C_{15}H_{18}NO$ $[M + H]^+$ 228.1388, found 228.1424; 94% ee by HPLC (Chiralcel OD, hexane:2-propanol 97:3, 1.0 mL/min, *R* isomer t_1 = 11.8 min, *S* isomer t_2 = 13.2 min).

Procedure for Oxidation Deprotection of Chiral Amine 2a. The chiral amine *R*-(+)-4-methoxy-*N*-(1-phenylethyl) aniline **2a** (85 mg, 0.395 mmol, 93.3% ee) was dissolved into a mixture of MeOH/H_2O (20 mL, 4:1); after the reaction solution was cooled to 0 °C, CAN (cerium ammonium nitrate) (866 mg, 1.58 mmol) was added in one portion and the resulting reaction system was stirred for 6 h at the same temperature. Water was added and the solution was washed with CH_2Cl_2. The aqueous solution was made alkaline by adding 1 N NaOH, and then extracted with ethyl acetate. The combined organic solution was washed with brine and dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified through silica gel column chromatography, eluted with ethyl acetate, to afford the chiral primary amine, *R*-(+)-α-methyl-benzylamine **5** as a yellow oil (39 mg, 81.3% yield). $[\alpha]^{25}_D$ +29.9° (*c* 1, $CHCl_3$); ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.55 (3H, d, J = 6.59 Hz), 1.63 (2H, br), 4.27 (1H, q, J = 6.57 Hz), 7.39−7.42 (1H, m), 7.47−7.53 (4H, m) ppm; ^{13}C NMR (90.6 MHz, $CDCl_3$) δ 25.6, 51.1, 125.5, 126.6, 128.3, 147.7 ppm; 95% ee by GC after protection with acetic anhydride (Chiralselect 1000, dimension 30 m × 0.25 mm, column temperature 160 °C, carrier gas He (1 mL/min), *S*-isomer t_1 = 18.7 min, *R*-isomer t_2 = 19.7 min).

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Supporting Information Available: Experimental procedures and compound characterization data for compounds **2a**−**k** and **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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