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Phosphoric Acid-Catalyzed Enantioselective Transfer Hydrogenation of *N*-Aryl-*ortho*-Hydroxybenzophenone Ketimines

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Abstract: The first enantioselective chiral phosphoric acid-catalyzed transfer hydrogenation of *N*-aryl-*ortho*-hydroxybenzophenone ketimines using a Hantzsch ester as hydrogen source was developed to afford, after removal of the *N*-aryl group, the corresponding chiral diarylmethylamines in high yields and enantioselectivities.

Keywords: diarylmethylamines; Hantzsch esters; *ortho*-hydroxybenzophenone ketimine; organocatalysis; phosphoric acids; transfer hydrogenation

Chiral diarylmethylamines are important synthetic intermediates and are substructures of many medicinally relevant compounds.[1] Methodologies for their asymmetric syntheses have relied upon the chiral auxiliary-based addition of arylmetallic reagents to C=N bonds,[2] or metal-catalyzed enantioselective addition of arylstannanes, aryltitaniums, and arylboron reagents to *N*-sulfonyl-, *N*-sulfamoyl-, and *N*-*tert*-butylsulfinylimines.[3]

The enantioselective reduction of diaryl ketimines[4] would provide another convenient way for the preparation of chiral non-racemic diarylmethylamines. In 2010, Zhang and Gosselin et al. reported the asymmetric hydrogenation of diarylimines in the presence of an iridium-monodentate phosphine complex under high pressure (up to 1500 psi). To the best of our knowledge, this is the only example known to date.[5]

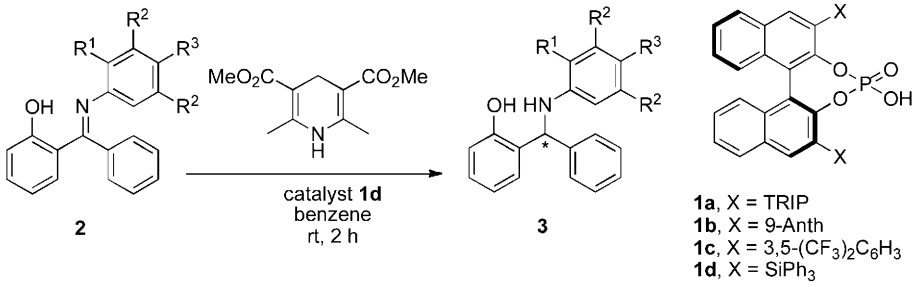
The chiral Brønsted acid-catalyzed reduction of ketimines has become an important alternative for the metal-catalyzed process. Examples of the organocatalytic enantioselective reduction of *N*-protected aryl alkyl ketimines using a Hantzsch ester as reducing agent have been reported.[6,7,8,9] However, the metal-free variants of the asymmetric hydrogenation of substituted diarylketimines remain unknown.

We recently reported a highly enantioselective chiral phosphoric acid-catalyzed reduction of *ortho*-hydroxyaryl alkyl N–H ketimines using a Hantzsch ester as hydrogen source.[10] Herein we describe the first chiral phosphoric acid-catalyzed transfer hydrogenation of *N*-aryl-*ortho*-hydroxybenzophenone ketimines using a Hantzsch ester as hydrogen source.[11]

The *N*-PMP protected *ortho*-hydroxybenzophenone ketimine **2** was initially chosen as a substrate for the screening of (*S*)-binol-derived phosphoric acid catalysts **1**[12] using Hantzsch dimethyl ester as reducing agent. As can be seen, performing the reduction at room temperature in benzene afforded the corresponding amine **3** with complete conversion within 2 h (entries 1–4, Table 1). Among the four phosphoric acids tested, only **1d** afforded **3** with reasonable enantioselectivity (*ee* 63%) (entry 4). A low conversion rate was observed in acetonitrile under otherwise identical conditions. Performing the same reaction in other solvents (1,2-dichloroethane, diethyl ether) afforded amine **3** with complete conversion but lower enantioselectivity (data not shown).

Reasoning that the steric and electronic environment at the ketimine nitrogen might modify the interaction of the catalyst, the ketimine substrate and the Hantzsch ester, the reduction of diarylimines with different *N*-aryl groups was next examined. The imines derived from *ortho*-substituted anilines (entries 5 and 6) were reduced to amines with negligible enantioselectivity. The nature of *para* substituent of anilines did

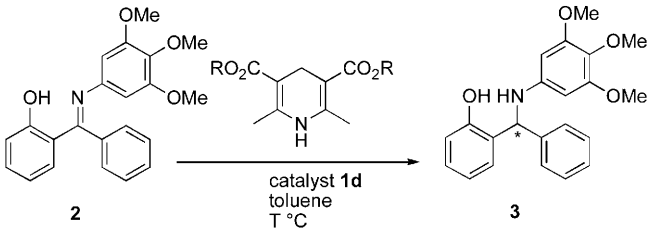
Table 1. Survey of catalysts and *N*-protecting groups.[a]



Entry	Catalyst	R^1	R^2	R^3	*ee*[b] [%]
1	**1a**	H	H	MeO	8
2	**1b**	H	H	MeO	10
3	**1c**	H	H	MeO	0
4	**1d**	H	H	MeO	**63**
5	**1d**	MeO	H	H	10
6	**1d**	MeO	H	MeO	4
7	**1d**	H	H	H	62
8	**1d**	H	H	*i*-Pr	64
9	**1d**	H	MeO	MeO	**76**

[a] *Reaction conditions:* imine (**2**) (0.125 mmol), Hantzsch dimethyl ester (0.165 mmol), catalyst (0.0125 mmol) in benzene (5 mL) for 2 h.
[b] Determined by chiral HPLC analysis.

Table 2. Survey of Hantzsch esters.[a]



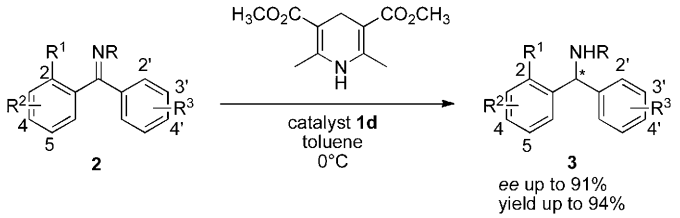
Entry	R	Temperature [°C]	*ee* [%][b]
1	Me	r.t.[c]	76
2	Et	r.t.[c]	76
3	*t*-Bu	r.t.[c]	64
4	Me	0[d]	**89**

[a] *Reaction conditions:* imine (**2a**) (0.125 mmol), Hantzsch ester (0.165 mmol), catalyst **1d** (0.0125 mmol) in toluene (5 mL).
[b] Determined by chiral HPLC analysis.
[c] 2 h.
[d] 16 h.

not influence the enantioselectivity of the process as *N*-Ph and *N*-4-*i*-Pr-C_6H_4 imines were reduced to amines with a similar enantioselectivity as that observed for the *N*-PMP imine (entries 4, 7 and 8). However, the presence of *meta*-substituents in the *N*-aryl group influenced considerably the enantioselectivities. Indeed, the *N*-(3,4,5-trimethoxyphenyl)imine was reduced to the corresponding amine with 76% *ee* (entry 9). A similar result was obtained when toluene was used as solvent.

The Hantzsch ester was next screened using the 3,4,5-trimethoxyphenyl (TMP)-derived imine as substrate (Table 2). Using the hindered Hantzsch di-*tert*-butyl ester as hydrogen source led to reduced enantioselectivity as compared to its dimethyl and diethyl counterparts. (entry 3 *vs.* 1 and 2). Finally, when the reaction was carried out at 0 °C using the Hantzsch dimethyl ester as hydrogen source, a remarkable *ee* enhancement was observed leading to the amine in ex-

Table 3. Chiral phosphoric acid-catalyzed transfer hydrogenation of *N*-aryl-*ortho*-hydroxybenzophenone ketimines **2**.[a]



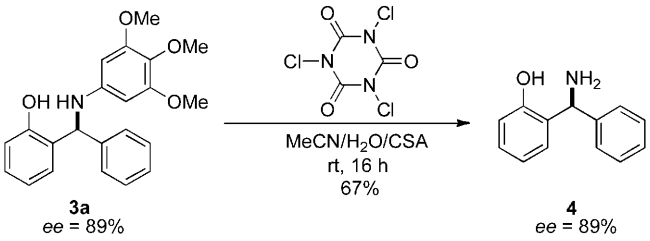
Entry	Imine	R	R^1	R^2	R^3	Yield [%][b]	*ee*[c] [%]
1	**2a**	TMP	OH	H	H	89	89
2	**2b**	TMP	OH	H	4′-Me	74	85
3	**2c**	TMP	OH	H	4′-Ph	93	88
4	**2d**	TMP	OH	H	4′-Br	94	88
5	**2e**	TMP	OH	H	4′-NO_2	74	91
6	**2f**	TMP	OH	H	3′-Me	90	84
7	**2g**	TMP	OH	H	3′-MeO	74	81
8	**2h**	TMP	OH	H	3′-NO_2	82	88
9	**2i**	TMP	OH	5-Me	H	76	84
10	**2j**	TMP	OH	5-OMe	H	81	80
11	**2k**	TMP	OH	4-Me	H	80	80
12	**2l**	TMP	OH	4-Me	4′-Cl	93	89
13	**2m**	PMP	H	H	H	0	–
14	**2n**	PMP	Me	H	H	0	–
15	**2o**	PMP	Cl	H	H	0	–

[a] *Reaction conditions:* imine (**2**) (0.125 mmol), Hantzsch dimethyl ester (0.165 mmol), catalyst (0.0125 mmol) in toluene (5 mL) for 16 h at 0 °C for imines **2a–l**, for 72 h at room temperature for imines **2m–o**.
[b] After column chromatography.
[c] Determined by chiral HPLC analysis.

cellent isolated yield (89%) and enantioselectivity (89%, entry 4).

Under optimized conditions [Hantzsch dimethyl ester (1.3 equiv.), **1d** (0.1 equiv.), toluene, 0 °C, 16 h], the scope of this reduction was next explored with a variety of differently substituted *N*-TMP-*ortho*-hydroxybenzophenone ketimines. As shown in Table 3, ketimines with different electron-withdrawing and electron-donating groups in different positions of both aromatic rings were reduced to the corresponding *N*-TMP-diarylmethylamines with good to excellent yields (74–94%) and enantioselectivity 80–91% *ee*). Functional groups (OMe, Cl, Br, NO_2) are well tolerated. The pivotal role of the *ortho*-hydroxy group is readily seen since substrates lacking this function were inert under the established conditions (entries 13–15). It is thus interesting to note that the presence of the *ortho*-hydroxy group not only accelerated the reduction, but also allowed efficient differentiation of the two sterically similar aryl groups.

Finally, the trimethoxyphenyl group can be removed using trichloroisocyanuric acid[13a] as oxidizing agent in wet acidic acetonitrile at room temperature (Scheme 1). The unprotected aminophenol **4** was obtained in moderate yield with unchanged enantiomeric purity. Attempts with cerium ammonium nitrate[13b] failed to produce the desired product. The absolute configuration of amine was determined to be "*S*" by comparison of the sign of the optical rotation of **4** with that reported in the literature.[14]



Scheme 1. Removal of the trimethoxyphenyl group.

The *N*-aryl-*ortho*-hydroxybenzophenone ketimines used in this study were synthesized in good to excellent yields by simply heating *ortho*-hydroxyacetophenones and anilines under solventless conditions. These ketimines existed as unique *E*-isomers as evidenced by the downfield shift of the phenol group due to the intramolecular H-bond (δ_{OH} = 13.6–14.7 ppm in $CDCl_3$). As the presence of the *ortho*-hydroxy moiety is essential for both the reactivity and enantioselectivity of the present transformation, we postulated that the reduction may proceed *via* a transition state **A**

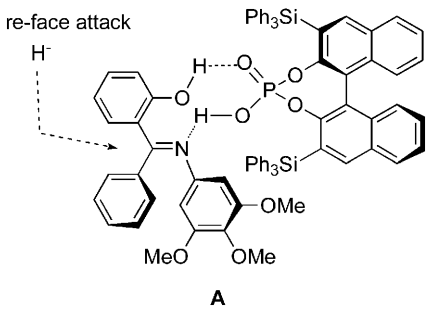


Figure 1. Proposed transition state.

whereby phosphoric acid acted as a bifunctional catalyst to form hydrogen bonds with both the imine and the hydroxy groups of the substrate.[10,15] Approach of the nucleophile from the less hindered *re*-face of the imine would then give the observed (*S*)-*N*-aryldiarylmethylamine (Figure 1). Alternatively, the phosphate oxygen could form an additional H-bond with the NH group of the Hantzsch ester leading to a ternary complex. Delivering the hydride in a pseudo-intramolecular fashion would then afford the same observed enantiomer.[16]

In summary, we have described an unprecedented chiral phosphoric acid-catalyzed enantioselective reduction of *N*-aryl-*ortho*-hydroxybenzophenone ketimines using a Hantzsch ester as hydrogen source. This transformation provided an attractive alternative to optically active *ortho*-hydroxydiarylmethylamines. The presence of the *ortho*-hydroxy group offered a handle for further *ortho*-functionalization.[17] In addition, the *ortho*-hydroxy group is readily removed under standard procedures.[17] Thus amines **3** could be considered as useful platforms to other chiral *ortho*-substituted or unsubstituted diarylmethylamines. Further investigations of the reaction mechanism and the extension of the reaction scope are currently on going in our laboratory.

Experimental Section

General Procedure for Enantioselective Reduction of Imines 2a–l

A 10-mL tube equipped with a magnetic stir bar was charged with imine (0.125 mmol, 1.0 equiv.), Hantzsch dimethyl ester (37 mg, 0.165 mmol, 1.3 equiv.) and catalyst **1d** (10.8 mg, 10 mol%). The tube was closed with a rubber septum, flushed with argon, and cooled in an ice bath. Dried toluene (5 mL) was introduced and the resulting solution was stirred at 0 °C for 16 h. The crude product was directly purified by silica gel column chromatography (first with heptane/AcOEt 10/1 and then with toluene/AcOEt 7/1) to yield the desired *N*-aryldiarylmethylamine as a white powder.

Procedure for Removal of the 3,4,5-Trimethoxyphenyl Group from Amine 3a

To a solution of **3a** (183 mg, 0.5 mmol) in MeCN (8 mL) and H_2O (0.5 mL) were added trichloroisocyanuric acid (58 mg, 0.25 mmol) and camphorsulfonic acid (116 mg, 0.5 mmol). The mixture was stirred for 16 h at room temperature and then partitioned in CH_2Cl_2 (100 mL) and a saturated aqueous solution of $NaHCO_3$ (20 mL). The organic layer was separated, dried ($MgSO_4$), and concentrated. The residue was purified by silica gel column chromatography to afford **4** as a white solid; yield: 67.0 mg (67%).

Acknowledgements

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