ORGANIC LETTERS

2010
Vol. 12, No. 20
4705−4707

Chiral Phosphoric Acid-Catalyzed Enantioselective Transfer Hydrogenation of *ortho*-Hydroxyaryl Alkyl N−H Ketimines

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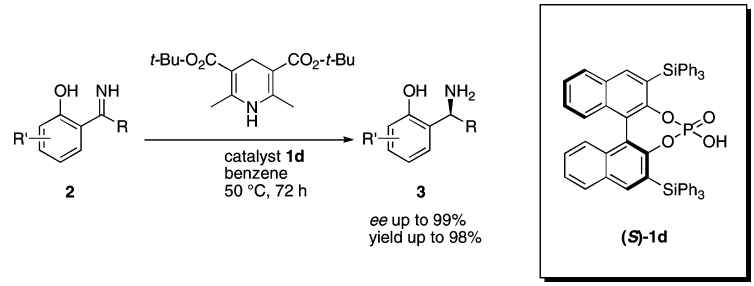
Received September 2, 2010

ABSTRACT



The first enantioselective chiral phosphoric acid-catalyzed transfer hydrogenation of *unprotected ortho*-hydroxyaryl alkyl N−H ketimines using Hantszch di-*tert*-butyl ester as a reductant is reported. A variety of *ortho*-hydroxybenzylamines were obtained in good to excellent yields and enantiomeric excesses.

Enantiomerically pure *ortho*-hydroxybenzylamines are an important class of chiral ligands for transition metal mediated and catalyzed processes[1] and have been used as chiral auxiliaries in asymmetric synthesis.[2] In addition, they are useful chiral building blocks for syntheses of natural products and many pharmacologically active compounds.[3] This family of aminophenols is generally obtained by enzymatic[4] or chemical resolution[5] of racemics or by diastereoselective alkylation/reduction of imines.[1b,2c,5,6] Although enantioselective reduction of N-protected enamides, enamines, and imines is well developed,[7−10] only very few reports have dealt with the reduction of N−H imines.[8] Very recently, Zhang and Gosselin et al. reported an iridium-catalyzed asymmetric hydrogenation of the hydrochloride salt of N−H imines at high pressure leading directly to α-chiral primary amines in good to excellent ee's.[8c,d]

Since the pioneering work of Terada and Akiyama, the chiral binol-derived phosphoric acids have found wide applications in the development of catalytic enantioselective transformations,[10,11] including the enantioselective reduction of N-

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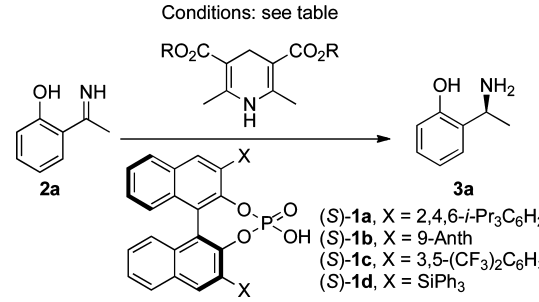
10.1021/ol102043x
Published on Web 09/21/2010

protected imines.[12] We report herein the first examples of enantioselective transfer hydrogenation of *unprotected ortho*-hydroxyaryl alkyl N−H ketimines using chiral phosphoric acid as a catalyst and Hantzsch ester as the hydrogen source.

The *ortho*-hydroxyaryl alkyl N−H ketimines are synthesized in quantitative yields by simply mixing *ortho*-hydroxyaryl alkyl ketone with ammonia in methanol at room temperature.[13] All *ortho*-hydroxyaryl alkyl ketimines were quite stable at room temperature and existed as one single *E*-isomer due to the presence of an intramolecular H-bond ($\delta_{OH} = 14.3-16.3$ ppm). Using **2a** as a test substrate, the survey of reaction conditions varying the solvents, the temperature, the structure of phosphoric acids, and Hantzsch esters is shown in Table 1. The hindered 3,3′-bis(triphenylsilyl)-substituted phosphoric acid (*S*)-**1d** turned out to be the most effective in terms of chirality transfer, and benzene was a better reaction medium than other solvents screened (Et_2O, $CHCl_3$, CH_3CN, PhMe, entries 5−8). The reaction temperature also played an important role. At room temperature, the reaction went extremely slow (entry 9), while at temperature higher than 60 °C, the reduction proceeded with reduced enantioselectivity. A slight improvement of enantioselectivity was observed when the Hantzsch di-*tert*-butyl ester was used instead of diethyl ester (entry 11 vs 4). Overall, the optimal conditions consisted of performing the reduction of **2a** in benzene in the presence of chiral phosphoric acid **1d** (0.1 equiv) and Hantzsch di-*tert*-butyl ester (1.3 equiv) at 50 °C. Under these conditions, amine **3a** was isolated in 94% yield with 92% ee (cf. Table 2).[14]

Having established optimal conditions, we next examined the scope of this reaction by varying the nature of R and R′ substituents in imines **2** (Table 2). A variety of *ortho*-hydroxyaryl alkyl N−H ketimines having a substituent at the

Table 1. Survey of Reaction Conditions for the Enantioselective Transfer Hydrogenation of Imine **2a**[a]



entry	cat.	R	solvent	t (°C)	convn (%)[b]	ee (%)[c]
1	**1a**	Et	PhH	60	100	20
2	**1b**	Et	PhH	60	100	54
3	**1c**	Et	PhH	60	100	60
4	**1d**	Et	PhH	60	100	**89**
5	**1d**	Et	Et_2O[d]	60	<5	-
6	**1d**	Et	$CHCl_3$	60	100	71
7	**1d**	Et	CH_3CN	60	100	74
8	**1d**	Et	PhMe	60	100	83
9	**1d**	Et	PhH	rt	<5	-
10	**1d**	Me	PhH	60	100	87
11	**1d**	*t*-Bu	PhH	60	100	**90**
12	**1d**	*t*-Bu	PhH	50	100	**92**

[a] Reaction conditions: imine (**2a**) (0.5 mmol), Hantzsch ester (0.65 mmol), catalyst (**1**) (0.05 mmol) in solvent (5 mL). [b] Determined by ^{1}H NMR analysis. [c] Determined by chiral HPLC analysis of the corresponding acetamide. [d] The reaction was performed in a sealed tube.

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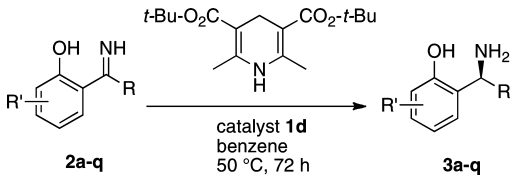
Table 2. Substrate Scope of Chiral Phosphoric Acid Catalyzed Transfer Hydrogenation of *ortho*-Hydroxyaryl Alkyl N−H Ketimines **2**[a]



2a-q 3a-q

entry	amine	R	R′	yield (%)[b]	ee (%)[c]
1	**3a**	Me	H	94	92
2	**3b**	Me	3-Me	56	97
3	**3c**	Me	4-F	91	89
4	**3d**	Me	4-Me	93	96
5	**3e**	Me	4-OMe	68	94
6	**3f**	Me	4-NO_2	88	96
7	**3g**	Me	5-Me	86	91
8	**3h**	Me	5-*t*-Bu	70	90
9	**3i**	Me	5-Br	97	90
10	**3j**	Me	5-OMe	85	87
11	**3k**	Me	5-NO_2	77	92
12	**3l**	Me	6-OEt	56	99
13	**3m**	Et	H	86	89
14	**3n**	*n*-Pr	H	98	89
15	**3o**	*n*-hexyl	H	81	89
16	**3p**	*i*-Pr	H	98	81

[a] Reaction conditions: imine (**2**) (0.5 mmol), Hantzsch di-*tert*-butyl ester (0.65 mmol), and catalyst (0.05 mmol) in benzene (5 mL) for 72 h. [b] Yields after chromatography. [c] Determined by chiral HPLC analysis of the corresponding acetamide or propanamide.

3, 4, 5, and 6 position of the aromatic ring were readily reduced to afford the corresponding amines. The presence of either an electron-withdrawing (F, Br, NO_2) or an electron-donating group (Me, OMe) at C-3, C-4, and C-5 of the aromatic ring did not affect significantly the enantioselectivity. On the other hand, an excellent enantioselectivity was observed in the reduction of **2l** having an ethoxy group at C-6 leading to the corresponding amine (**3l**) with up to 99% ee (entry 12).

Previously, only N−Ar imines derived from acetophenone were used as substrates in phosphoric acid-catalyzed transfer hydrogenation,[10a−c] and a computational model was advanced to account for the observed selective reduction of aryl methyl ketimines.[10c] It was thus remarkable to observe that, in our case, other *ortho*-hydroxyaryl alkyl N−H ketimines (R = Et, *n*-Pr, *n*-hexyl, *i*-Pr) can also be reduced efficiently to provide the corresponding amines (**3m**−**3p**, entries 13−16, Table 2) in high yields and ee's.

The absolute configuration of amine **3** was determined to be "*S*" by comparison of the sign of its optical rotation with that of the known amines (see the Supporting Information for details). A control experiment indicated that reduction of imine **2a** did not take place in the absence of phosphoric acid. In the proton NMR spectrum of **2a** (C_6D_6), the phenolic OH appeared at $\delta = 15.6$ ppm indicating the presence of a strong intramolecular H-bond between the phenolic O−H and the imine nitrogen. Upon addition of 1.0 equiv of phosphoric acid (**1d**), the resonance of this OH moved to higher field (aromatic region). This experiment indicated that phosphoric acid (**1d**) is capable of breaking this intramolecular H-bond and activating the imine via, most probably, the formation of an intermolecular H-bond with the imine nitrogen. Consequently, we assumed that the reaction may proceed via a transition state **A** (Figure 1), wherein the phosphoric acid formed H-bonds with both the hydroxyl and the imine functions of **2**.[15] The hydride transfer would then occur from the *re* face of the imines to deliver the amines with the observed (*S*) configuration.

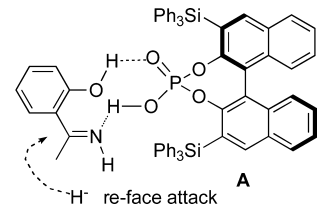


Figure 1. Plausible transition state.

In summary, we have developed the first highly enantioselective chiral phosphoric acid-catalyzed reduction of bench-stable *unprotected ortho*-hydroxyaryl alkyl N−H ketimines using Hantzsch ester as a hydrogen source. The reaction is applicable to a wide range of substrates with different electronic and steric properties. While *ortho*-hydroxybenzylamines are interesting compounds in their own right, the presence of a hydroxy group offered a valuable opportunity for further modification on the *ortho*-position.[16] Further investigation of the reaction mechanism and application of the methodology to the synthesis of bioactive compounds is currently ongoing in our laboratory.

Acknowledgment. Financial support from CNRS and ICSN is gratefully acknowledged.

Supporting Information Available: Experimental procedures, product characterization, ee measurement, and copies of the ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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