Asymmetric Catalysis

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A Powerful Brønsted Acid Catalyst for the Organocatalytic Asymmetric Transfer Hydrogenation of Imines**

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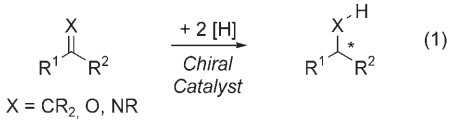
The catalytic hydrogenation of alkenes, ketones, and imines is arguably one of the most important transformations in chemistry. Powerful asymmetric versions have been realized that require metal catalysts or the use of a stoichiometric amount of metal hydrides [Eq. (1)].[1]



(1)

Although effective and industrially relevant catalytic asymmetric hydrogenations and transfer hydrogenations of olefins and ketones have been developed, the corresponding imine reductions, although potentially highly useful for the synthesis of enantiomerically pure amines, are less advanced.[2] Living organisms employ organic dihydropyridine cofactors such as nicotinamide adenine dinucleotide (NADH) in combination with enzyme catalysts for the reduction of imines.[3] Chemical transition metal catalyzed asymmetric imine reductions have also been developed,[4] and are used, in at least one case, on an industrial scale.[5] However, with the exception of interesting Lewis base catalyzed asymmetric imine hydrosilylations,[6] organocatalytic and metal-free variants were not known. Recently, we and MacMillan and co-workers developed an asymmetric transfer hydrogenation of α,β-unsaturated aldehydes catalyzed by a chiral ammonium salt by using Hantzsch esters as a biomimetic hydrogen source.[7] Rueping et al.[8] very recently reported the development of a novel and elegant approach using Hantzsch esters as the reducing reagent for the catalytic asymmetric reduction of imines using a chiral Brønsted acid catalyst previously developed by Akiyama et al.[9,10] We now report parallel and independent studies from our laboratory

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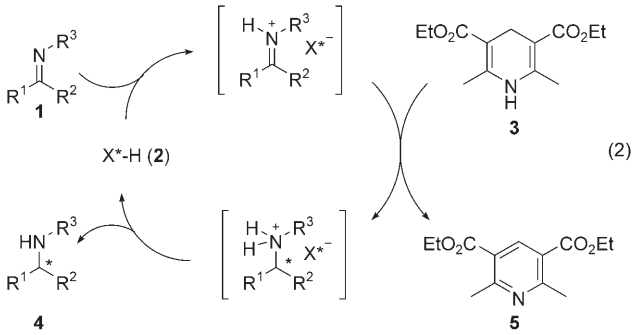
on the same reaction that resulted in the development of a significantly improved new catalyst for the highly efficient and enantioselective transfer hydrogenation of ketimines catalyzed by Brønsted acids.[11]

In pioneering studies, the research groups of Akiyama[10] and Terada[11] recently introduced relatively strong chiral phosphoric acid catalysts for asymmetric addition reactions to aldimines as a new strategy for organic catalysis.[12,13] Inspired by these studies, and the recent observation that imines are reduced with Hantzsch esters in the presence of achiral Lewis or Brønsted acid catalysts,[14] we envisioned a catalytic cycle which is initiated by protonation of ketimine **1** from a chiral Brønsted acid catalyst **2** [Eq. (2)]. The resulting iminium ion pair, which may be stabilized by hydrogen bonding, is chiral and its reaction with the Hantzsch dihydropyridine **3** could give an enantiomerically enriched amine **4** and pyridine **5**.



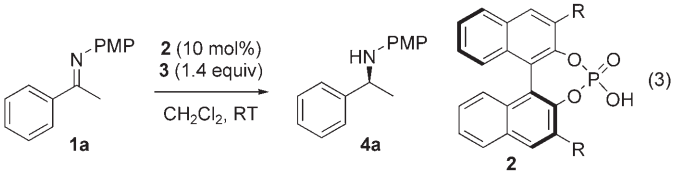
(2)

With this idea in mind, we synthesized and screened a variety of chiral phosphoric acid catalysts for the reduction of imine **1a** in the presence of Hantzsch ester **3** [Eq. (3), Table 1].[15]

Although the commercially available phosphoric acid **2a** clearly showed turnover, the enantioselectivity was low (entry 1). Increasing the steric bulk of the catalyst by adding aromatic substituents at the 3,3′-positions of the binaphthol core significantly increased the enatioselectivity but generally reduced the turnover (entries 2–9). The highest *ee* value (81%) was achieved with the new sterically congested phosphoric acid catalyst **2i**. Although the yield of **4a** was low (10% after 20 h), the only remaining material was the starting imine **1a**.

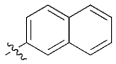
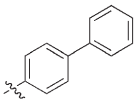
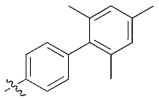
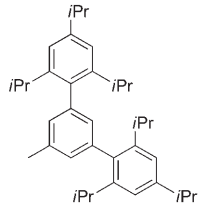
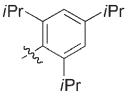
After further optimization of the reaction, which included changing the solvent from dichloromethane to toluene, increasing the temperature from RT to 35°C, and lowering the catalyst loading from 10 mol% to only 1 mol%, the *ee* value of the product **4a** could be further improved to 88% and with an excellent yield of 96% [Table 2, entry 1]. These conditions have been applied to several substituted aromatic ketimines **1a–j** and one aliphatic imine **1k** with good to excellent results [Eq. (4), Table 2].

Remarkably high yields were achieved in all cases, while the *ee* values were generally very good (80–93%). The highest yield was achieved with *p*-methyl-substituted imine **1f**, which provided amine **4f** in 98% yield (entry 6). *o*-Methyl-substituted imine **1h** gave the highest enantioselectivity and furnished amine **4h** with 93% *ee* (entry 8). Functional



(3)

Table 1: Catalyst screening for the asymmetric transfer hydrogenation of imine **1a**.

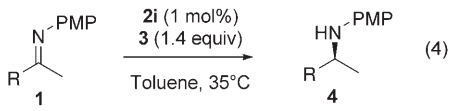
Entry	R		Conversion [%] (*t*)	*ee* [%]
1	H	**2a**	58 (6 h)	6
2		**2b**	59 (17 h)	40
3		**2c**	34 (17 h)	44
4		**2d**	80 (17 h)	51
5		**2e**	10 (20 h)	32
6		**2f**	7 (20 h)	30
7		**2g**	28 (17 h)	65
8		**2h**	4 (22 h)	n.d.[a]
9		**2i**	10 (20 h)	81

[a] n.d. = not determined.

groups (-NO_2, -F, -CN, -OMe) are tolerated well, although the full scope of the reaction has yet to be established. Remarkably, even an aliphatic imine (**1k**) could be used to give amine **4k** with high enantioselectivity (90% *ee*).

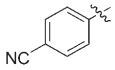
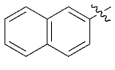
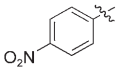
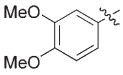
A similar study by Rueping's research group using Akiyama's phosphoric acid catalyst appeared during the preparation of this manuscript.[8,10b] However, our reaction times are generally shorter (42–71 h versus 72 h), our temperature is lower (35°C versus 60°C), our yields (80–98% versus 46–91%) and *ee* values (80–93% versus 68–84%) are higher, and most importantly our catalyst loading is much lower (1 mol% versus 20 mol%). Moreover, we can also reduce aliphatic ketimines highly enantioselectively while Rueping et al. only provided aromatic examples.

Imine generation and its reduction can also be performed in situ in the presence of molecular sieves. The *ee*-conserving

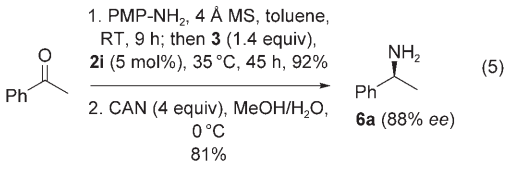


(4)

Table 2: Preliminary substrate scope of the asymmetric transfer hydrogenation of imines.

Entry	R		*t* [h]	Yield [%]	*ee* [%]
1		**a**	45	96	88
2		**b**	42	87	80
3		**c**	42	85	84
4		**d**	45	95	85
5		**e**	42	96	80
6		**f**	42	98	88
7		**g**	45	84	89
8		**h**	71	91	93
9		**i**	45	92	80
10		**j**	71	88	92
11		**k**	60	80	90

oxidative removal of the *p*-methoxyphenyl (PMP) group to give amine **6a** is well established [Eq. (5); CAN = cerium(IV) ammonium nitrate].[4i]



(5)

In summary we have developed an efficient organocatalytic asymmetric ketimine reduction using chiral phosphoric acid derivative **2i** in the presence of the commercially available Hantzsch ester **3**. Remarkable features of our process include a) its high yields and enantioselectivities, b) its scope, including both aliphatic and aromatic amines, c) its simplicity and practicability (in situ generation and reduction of imines), and d) the remarkably low catalyst loading, which so far is unprecedented in asymmetric Brønsted acid catalysis. Further extension of this methodology is ongoing and will be reported shortly.

Experimental Section

General procedure for the asymmetric transfer hydrogenation reaction**:** A mixture of imine **1** (0.4 mmol), Hantzsch ester **3** (142 mg, 0.56 mmol, 1.4 equiv), and phosphoric acid **2i** (3 mg, 0.004 mmol) in toluene (4 mL) was stirred at 35 °C in an argon atmosphere for 42–71 h. The solvent was evaporated at reduced pressure and the products were isolated by flash chromatography (SiO_2, ethyl acetate/hexane) to give pure amines **4**. The *ee* values were determined by using established HPLC techniques with chiral stationary phases.

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