Towards a Practical Brønsted Acid Catalyzed and Hantzsch Ester Mediated Asymmetric Reductive Amination of Ketones with Benzylamine

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Abstract: We report the use of benzylamine as the amine component in Hantzsch ester mediated and chiral Brønsted acid catalyzed enantioselective reductive aminations of ketones. The method is noteworthy because the benzyl group is easily removable, and amine product purification is achieved through Hantzsch ester oxidation product removal via basic hydrolysis.

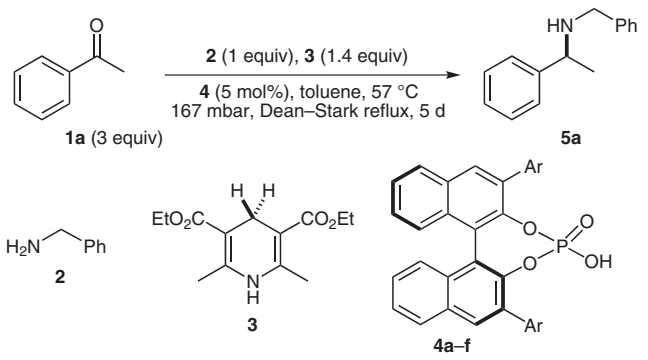
Key words: benzylamine, Hantzsch ester, reductive amination, organocatalysis, chiral amines, Brønsted acids

The catalytic asymmetric reductive amination of carbonyl compounds is not only an attractive strategy for carbon–nitrogen bond-forming fragment couplings but potentially also a powerful approach to chiral primary amines.[1] Recently, we have developed a Brønsted acid catalyzed asymmetric reductive amination of ketones using Hantzsch esters as hydride source, and 3,3′-bis(2,4,6-triisopropylphenyl)-1,1′-binaphthyl-2,2′-diyl hydrogen phosphate (TRIP) as Brønsted acid organocatalyst.[2–4] Both Rueping et al.[3a] and MacMillan et al.[3b] developed alternative variants and additional applications of these methodologies have appeared.[3,5] Despite these advances, however, such catalytic asymmetric reductive aminations have been limited to aromatic amines, in particular *p*-anisidine. While the so-introduced *p*-methoxyphenyl group (PMP) can be easily removed under oxidative conditions to release the corresponding primary amine, *p*-anisidine is toxic, and the protecting group removal conditions are rather challenging for large-scale and industrial applications.[6,7] A possibly attractive alternative would be to use benzylamine, which introduces an easily removable benzyl protecting group. Here we report progress towards the realization of this goal with a chiral Brønsted acid catalyzed and Hantzsch ester mediated enantioselective reductive amination of ketones using benzylamine as the amine component.

In initial optimization studies, we found the use of ketone **1** (3 equiv), benzylamine **2** (1 equiv), Hantzsch ester **3** (1.4 equiv), and toluene as the solvent to furnish the desired product **5** upon treatment with a chiral acid catalyst. We have synthesized and screened chiral phosphoric acid catalysts **4a–f** for the enantioselective reductive amination of acetophenone (**1a**, Table 1). From this survey the phenanthrene- and anthracene-substituted phosphoric acids **4e** and **4f** emerged as the best catalysts. The highest enantioselectivities were obtained with the 9-anthryl-substituted phosphoric acid **4f**, which provided amine product **5a** in 94:6 er.

The efficient removal of water formed during the reaction is important. While we have initially used molecular sieves for this purpose, we later found that azeotropic removal using a Dean–Stark trap under refluxing conditions at reduced pressure (57 °C, 167 mbar) is quite effective and practical as well.

Table 1 Catalyst Screening[a]



Entry	Ar	4	Conv. (%)[b]	er[c]
1	Ph	**4a**	99	79:21
2	4-biphenyl	**4b**	97	85:15
3	2,4,6-(*i*-Pr)$_3$C$_6$H$_2$	**4c**	95	63:37
4	3,5-(F$_3$C)$_2$C$_6$H$_3$	**4d**	98	84:16
5	9-phenanthryl	**4e**	99	91:9
6	9-anthryl	**4f**	99	94:6

[a] Conditions: 0.5 mmol scale.
[b] From GC analysis.
[c] From chiral HPLC analysis (see the Supporting Information).

With catalyst **4f** we also examined other ketone substrates for the enantioselective reductive amination with benzylamine under optimized reaction conditions. As shown in (Table 2), aromatic as well as aliphatic ketone substrates can be successfully used (entries 1–4). Under preparative conditions, acetophenone gave the corresponding amine product **5a** in high yield (96%) and enantioselectivity (94:6 er).[8] Subjecting other ketones to the reductive ami-

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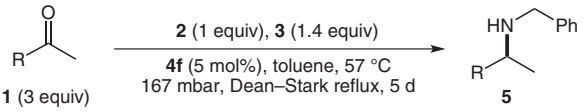
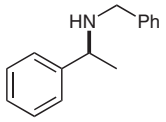
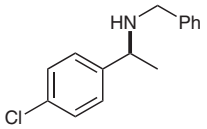
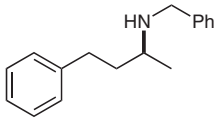
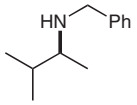
nation conditions generally gave the corresponding products in lower enantioselectivity. For example, 4-chloro acetophenone gave amine **5b** in 85:15 er. Also, while aliphatic ketone substrates can be reductively aminated with benzylamine, the enantiomeric ratios are once again lower (entries 3 and 4).

Another general problem of Hantzsch ester mediated imine reductions and reductive aminations is that in addition to the desired amine product, the corresponding Hantzsch pyridine is produced and can be difficult to separate.

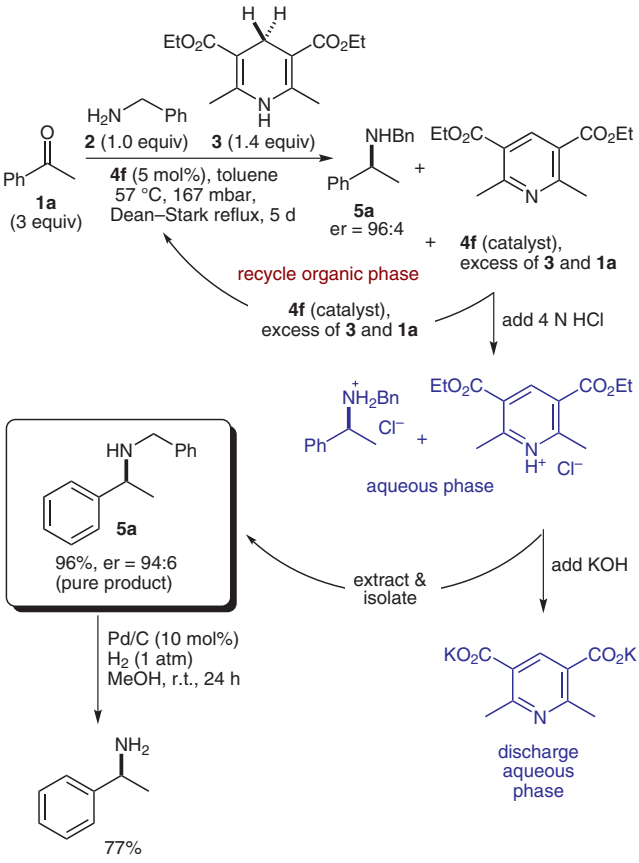
Table 2 Preliminary Substrate Scope[a]



Entry	5	Product	Yield (%)[b]	er[c]
1	**5a**		96	94:6
2	**5b**		89	85:15
3	**5c**		81	63:37
4[d]	**5d**		59	73:27

[a] Conditions: 0.5 mmol scale.
[b] Isolated yield.
[c] From chiral HPLC analysis (see the Supporting Information).
[d] Reaction time 7 d.

To further improve the practicality of our method, we have therefore investigated the workup and purification procedure towards an effective removal of this byproduct. This was finally achieved in the following way (Scheme 1): After completion of the reaction, the mixture was treated with 4 N HCl, which removes both the amine product **5a** and the Hantzsch pyridine into the aqueous phase by hydrochloride salt formation. In contrast, catalyst **4f** as well as excess ketone and Hantzsch ester remains in the organic layer. Neutralizing the aqueous layer with solid potassium hydroxide (KOH) and then adding more KOH (8 equiv), results in the hydrolysis of the ester groups of the Hantzsch pyridine to furnish the corresponding water-soluble potassium carboxylate. Extraction with ethyl acetate provides the pure chiral amine product **5a** in 96% yield with the same enantiomeric ratio (94:6). Under these optimized reaction conditions, it is possible to recycle the catalyst and excess ketone and Hantzsch ester. In the first recycle of the catalyst, and after re-adding the reagents, the reaction goes to completion after five days to provide the product in 93% yield while maintaining the same enantiomeric ratio (94:6). As expected, debenzylation of product **5** can be easily be performed via a simple hydrogenolysis (H_2, Pd/C). This unoptimized step furnished the desired product in 77% yield.



Scheme 1 Production purification and isolation by acid/base workup.

In summary, we demonstrate the use of benzylamine as the amine component in the asymmetric Brønsted acid catalyzed enantioselective reductive amination of ketones using the Hantzsch ester as hydrogen source. Notable advantages of the present method include (1) its simplicity and practicability, (2) product purification via removal of Hantzsch pyridine by hydrolysis, and (3) the successful recycle of the catalyst and excess of ketone and Hantzsch ester without affecting the enantioselectivity. Despite these advancements, further improvements on the scope, enantioselectivity, and reactivity of this transformation are clearly needed but also expected.

General Procedure for the Phosphoric Acid Catalyzed Reductive Amination of Ketones

In a typical experiment a mixture of ketone **1** (1.5 mmol, 3.0 equiv), benzylamine (**2**, 0.5 mmol, 1.0 equiv, 0.055 mL), Hantzsch ester **3** (0.7 mmol, 1.4 equiv, 0177 g), and phosphoric acid **4f** (5 mol%, 0.025 mmol, 0.0175 g) in toluene (15 mL) were stirred at 57 °C

under Dean–Stark refluxing conditions at reduced pressure (167 mbar) for 5–7 d. The solvent was removed under reduced pressure and purification of the crude by column chromatography on silica gel afforded the pure amine **5**. The er values were determined by using established HPLC techniques with chiral stationary phases.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(8) The absolute configuration of amine **5a** was established via comparing the HPLC chromatogram with authentic sample of (*S*)-**5a**.

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