

# A One-Pot Process for the Enantioselective Synthesis of Amines via Reductive Amination under Transfer Hydrogenation Conditions

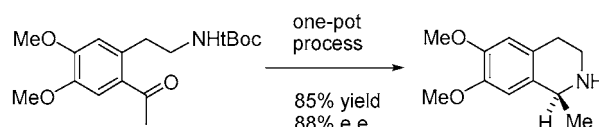
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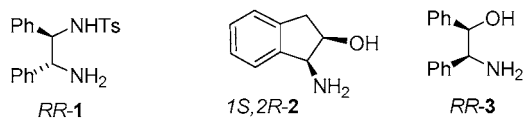
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## ABSTRACT



Cyclic amines may be prepared via a sequence of deprotection followed by intramolecular reductive amination of *t*-Boc-protected amino ketones under asymmetric transfer hydrogenation conditions. In cases where the corresponding imine reaction proceeds with high enantioselectivity, this is reflected in the one-step process.

Asymmetric transfer hydrogenation has recently emerged as an excellent method for the enantioselective reduction of ketones to alcohols.<sup>1</sup> Although a long-established method for ketone reduction, the significant recent increase in interest in this method has been largely due to the introduction by Noyori of several new ruthenium(II)-based catalysts.<sup>2</sup> In particular, the monotosylated diamine TsDPEN **1** (Figure 1)



**Figure 1.** Structures of ligands used for asymmetric transfer hydrogenation.

has been adopted as one of the optimal ligands for this process, particularly when used in formic acid/triethylamine, which acts both as the solvent and the hydrogen source.<sup>2,3</sup>

The Ru(II)/TsDPEN system also works well for the reduction of C=N double bonds. However, this variation has been significantly less developed. Noyori has reported that several amines, most particularly tetrahydroisoquinolines, can be prepared by this method in high yield and enantioselectivity.<sup>4</sup> Vedejs et al. have since extended their work.<sup>5</sup> Baker and Mao have also described the analogous use of Rh(III)/

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(3) (a) Palmer, M.; Walsgrove, T.; Wills, M. *J. Org. Chem.* **1997**, *62*, 5226. (b) Nordin, S. J. M.; Roth, P.; Tarnai, T.; Alonso, D. A.; Brandt, P.; Andersson, P. G. *Chem. Eur. J.* **2001**, *7*, 1431. (c) Everaere, K.; Mortreux, A.; Bulliard, M.; Brussee, J.; van der Gen, A.; Nowogrocki, G.; Carpentier, J. F. *Eur. J. Org. Chem.* **2001**, 275. (d) Hennig, M.; Püntener, K.; Scalone, M. *Tetrahedron: Asymmetry* **2000**, *11*, 1849. (e) Blacker, A. J.; Mellor, B. J. (Avecia/Zeneca), WO 98/42643 A1, 1998.

(4) Uematsu, N.; Fujii, A.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 4916.

(5) Vedejs, E.; Trapencieris, P.; Suna, E. *J. Org. Chem.* **1999**, *64*, 6724.

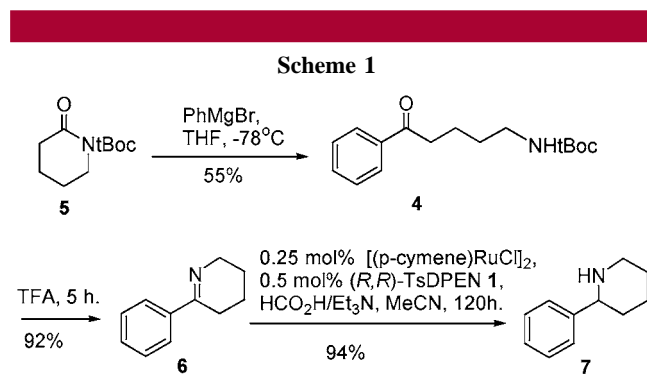
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Cp\* catalysts.<sup>6</sup> It is noteworthy that C=N reduction requires TsDPEN/Ru reagents in formic acid/triethylamine with an organic cosolvent such as acetonitrile, dichloromethane, or DMF. In contrast the popular combination of Ru(II) with amino alcohol ligands such as **2** and **3** (Figure 1) is incompatible with formic acid and therefore not suitable for imine reduction.

In the applications described above, the imine was prepared and isolated prior to the key reduction step. We reasoned that the synthetic potential of the method might be further increased if it was possible to perform the imine formation and reduction in one synthetic step, i.e., through a reductive amination process. This would be particularly useful for the synthesis of cyclic amines through an intramolecular cyclization process. Furthermore, given that the formic acid/triethylamine (5:2 molar ratio) reductions are typically carried out at ca. pH 5, we reasoned that this would be compatible with the reductive amination process.<sup>7</sup>

Toward this end, we identified the *t*-Boc-protected amino ketone **4** as a convenient system for our initial studies. The use of *t*-Boc is significant because, as well as being a commonly used protecting group, it may be removed under acidic conditions not dissimilar to those employed for the formic acid/triethylamine transfer hydrogenation reaction. Ketone **4** is a known compound and was prepared in one step from the *t*-Boc-protected  $\delta$ -lactam **5** following a literature precedent (Scheme 1).<sup>8</sup> To assess whether the imine



derived from **4** was convenient for transfer hydrogenation, we first removed the *t*-Boc group with TFA to give an amine, which cyclized readily to **6** under the reaction conditions (92% isolated yield). The reduction of **6** to amine **7** was achieved through the use of reported Ru(II)/TsDPEN conditions (with acetonitrile cosolvent) in 94% isolated yield, although the product was essentially racemic (Scheme 1). The method for the determination of ee is described later in this paper.

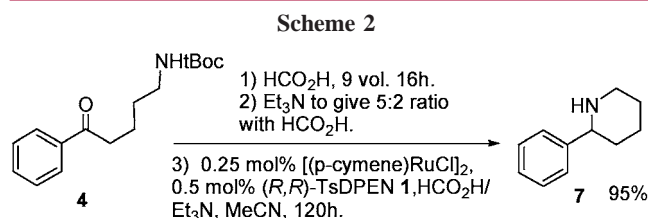
Although the reduction had proceeded without any selectivity, we reasoned that **4** still represented a good test

(6) (a) Mao, J. Baker, D. C. *Org. Lett.* **1999**, *1*, 841. (b) Meuzelaar, G. J.; van Vliet, M. C. A.; Maat, L.; Sheldon, R. A. *Eur. J. Org. Chem.* **1999**, 2315. (c) Ahn, K. H.; Ham, C.; Kim, S.-K.; Cho, C.-W. *J. Org. Chem.* **1997**, *62*, 7047.

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substrate for the reaction under study, as the yield was high. Our first attempt at effecting a one-pot deprotection/cyclization/reduction sequence under transfer hydrogenation conditions did, however, result in failure. Analysis of the reaction mixture revealed that *t*-Boc deprotection had been unsuccessful, presumably because the pH of the solution was too high for this process. In view of this we believed that we might have more success if we first performed the deprotection/cyclization sequence under more strongly acidic conditions and then adjusted the reaction mixture later for the transfer hydrogenation process. After a short series of tests we found that the use of 9 volumes of formic acid was sufficient to promote full *t*-Boc removal after 16 h, resulting in formation of imine **6**. The reaction was then repeated, but after the time required to remove the *t*-Boc group, sufficient triethylamine was added to generate a 5:2 formic acid/triethylamine mixture to which the Ru(II)/TsDPEN catalyst was added. Anhydrous acetonitrile was also added to reproduce the conditions reported as being essential for imine reduction.<sup>4</sup> The deprotection and reduction events could all be conveniently monitored by NMR analysis, which revealed essentially full reduction to **7** after 24 h at 28 °C (Scheme 2).<sup>9</sup> To our knowledge this represents the first report



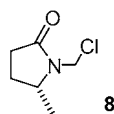
of a reductive alkylation of amines under Ru(II)/TsDPEN conditions. Although the yield was good, the product was again essentially racemic.

Determination of the ee of the product **7** proved difficult, no success being achieved with either chiral HPLC (OD column) or europium shift reagents. We were successful, however, when we employed the pyrrolidine reagent **8** to derivatize the amine (Figure 2).<sup>10</sup> Displacement of the chlorine atom from the chloromethyl position results in formation of two diastereoisomers in which the methyl doublet conveniently indicated the ratio of enantiomers.

Despite the low enantioselectivity observed in the reduction, we were encouraged by the high conversion. To confirm

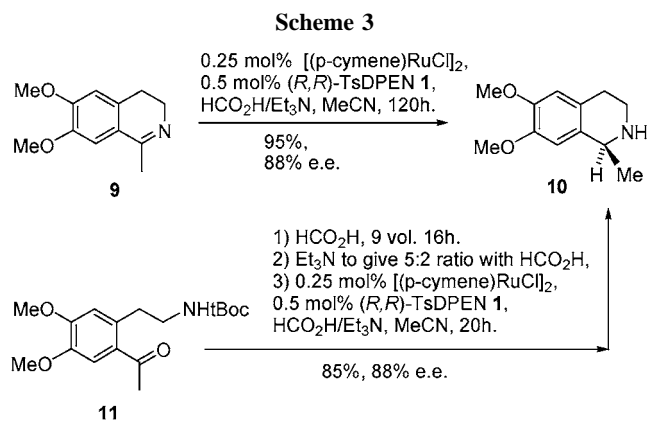
(9) **Typical Procedure.** *t*-Boc-amino-ketone (0.2 g) was stirred in freshly distilled formic acid (1.8 mL) for 16 h. The flask was then sealed and cooled to 0°C; triethylamine (3 mL) was added cautiously with vigorous shaking until all gas had been reabsorbed. In a separate flask a mixture of (*p*-cymene) ruthenium(II) chloride dimer (0.25 mol %) and (*1R,2R*)-TsDPEN (0.5 mol %), triethylamine (1 drop), and anhydrous acetonitrile (1 mL) were stirred at 28 °C for 40 min. The catalyst solution was transferred to the formic acid/triethylamine solution, and the mixture was stirred at 28°C until complete by NMR. The mixture was made basic (pH 9–10) with saturated Na<sub>2</sub>CO<sub>3</sub> solution and extracted with DCM (3 × 25 mL). The combined organics were dried (MgSO<sub>4</sub>) and filtered, and the solvent removed under reduced pressure. The residue was purified by flash column chromatography (10–15% v/v ethyl acetate/hexane on silica pretreated with Et<sub>3</sub>N) to afford the amine.

(10) Smith, M. B.; Bembofsky, B. T.; Son, Y. C. *J. Org. Chem.* **1994**, *59*, 1719.



**Figure 2.** NMR derivatizing agent for ee determination.

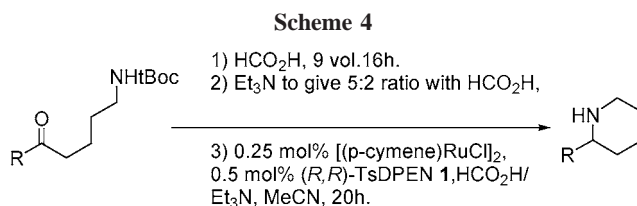
that the low selectivity was not the result of our modified conditions, we repeated the reduction on **9**, a substrate that has been reported to give a product of high enantioselectivity under normal asymmetric transfer hydrogenation conditions. Compound **9** was prepared following a literature method and was successfully reduced to amine **10** in 95% yield and 88% ee using TsDPEN in formic acid/triethylamine with acetonitrile as cosolvent (Scheme 3).<sup>4</sup> For the comparative one-



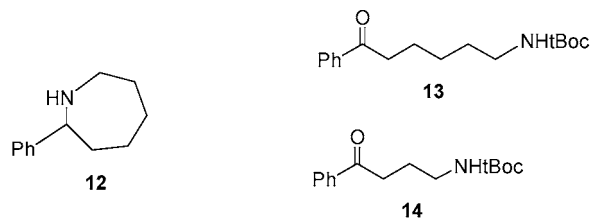
pot cyclization/reduction the *t*-Boc-protected material **11** was used as the substrate. Using the protocol described previously, the product **10** was formed in 85% yield and 88% ee, comparable to the result from the direct imine reduction (Scheme 3). This method represents a viable practical alternative to reduction of the preformed imine **9**; it was pleasing to see that the results were not significantly deteriorated using the alternative method. We therefore conclude that **6** is a poor substrate with regard to enantioselectivity in this particular application.

To test the generality of the one-pot method we also investigated the preparation of the cyclic amines from a series of compounds (Scheme 4), the results of which are illustrated in Table 1. In the majority of cases examined the conversions were excellent, although the products were essentially racemic. It was also possible to form the seven-membered ring product **12** from **13** in only 12% yield (racemic); however, attempts to form the five-membered heterocyclic product from **14** failed.

The reason for the loss of stereocontrol in the cyclization of **4**, under conditions where **10** is formed in high ee, is unclear. Unlike the ketone reduction process, the asymmetric transfer hydrogenation of imines is less well understood. One pattern that does appear to emerge, however, is that the



See Table 1

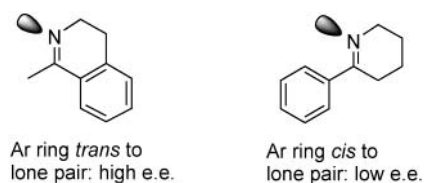


introduction of an aromatic ring on the side of the imine bearing the lone pair is detrimental to enantioselectivity, which suggests some sort of steric clash between this group

**Table 1.** One-Pot Deprotection/Cyclization/Asymmetric Transfer Hydrogenation of  $\delta$ -*t*-Boc Amino Ketones

R	yield, %
<i>o</i> -(MeO) <sub>6</sub> H <sub>4</sub>	78
<i>n</i> -(MeO) <sub>6</sub> H <sub>4</sub>	96
<i>p</i> -(MeO) <sub>6</sub> H <sub>4</sub>	94
<i>p</i> (CF <sub>3</sub> ) <sub>6</sub> H <sub>4</sub>	99
<i>m</i> -(CF <sub>3</sub> ) <sub>6</sub> H <sub>4</sub>	98
2-thiophene	20
<i>c</i> -C <sub>6</sub> H <sub>11</sub>	98

and a group in the catalyst. An aromatic ring on the side of the imine *opposite* the nitrogen lone pair, by contrast, appears to be essential for high selectivity (Figure 3).



**Figure 3.** Relationship of aromatic ring position to extent of enantioselectivity in reduction.

By analogy with the ketone reduction, it may be the case that this ring is able to engage in a  $\pi$ -stabilizing interaction with the  $\eta^6$ -ring on the catalyst.<sup>11</sup>

This analysis is supported by the original observation by Noyori that the reduction of the derivative of **9** bearing a

(11) Yamakawa, M.; Yamada, I.; Noyori, R. *Angew. Chem., Int. Ed.* **2001**, *40*, 2818.

phenyl ring in place of the exocyclic methyl group gives a product of some 10% lower ee.<sup>4</sup>

In conclusion, we have demonstrated that the synthesis of cyclic amines may be achieved under modified conditions of asymmetric transfer hydrogenation and that in cases where the intermediate imines are known to give products of high ee, this is reproduced in our process. We are currently examining the extension of this methodology to further substrates, including acyclic imines.

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Swansea EPSRC MS service for MS analysis of certain compounds. We wish to acknowledge the use of the EPSRC's Chemical Database Service at Daresbury.<sup>12</sup>

**Supporting Information Available:** Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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