Chiral Phosphoric Acid-Catalyzed Asymmetric Transfer Hydrogenation of Quinolin-3-amines

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ABSTRACT: A chiral phosphoric acid catalyzed asymmetric transfer hydrogenation of aromatic amines, quinolin-3-amines, was successfully developed with up to 99% ee. To supplement our previous work on the Ir-catalyzed asymmetric hydrogenation of 2-alkyl substituted quinolin-3-amines, a number of 2-aryl substituted substrates were reduced to provide a series of valuable chiral exocyclic amines with high diastereo- and enantioselectivities.

Optically active exocyclic amines exist as key structural elements in many biologically active molecules including natural and unnatural products.1 In addition, they are useful intermediates for organic synthesis and serve as chiral catalysts in various asymmetric transformations. Due to the simplicity and atom efficiency, asymmetric catalytic reduction of exocyclic enamines, imines, and aromatic amines represents a significant approach to these compounds.2 Compared to the various successful examples of the asymmetric hydrogenation of exocyclic enamines and imines,1,3 little attention has been paid to the asymmetric hydrogenation of aromatic amines due to their high stability of aromaticity and strong coordinating ability. However, catalytic asymmetric hydrogenation of other heteroarenes has been well documented.4–10

Very recently, we reported the first asymmetric hydrogenation of aromatic amines, 2-alkyl substituted quinolin-3-amines, giving the chiral exocyclic amines in excellent yields, with high diastereo- and enantioselectivities.11 However, for the 2-aryl substituted substrate, only a moderate ee value was obtained. In consideration of the successful application of chiral phosphoric acids (CPA) in the asymmetric transfer hydrogenation of C=C, C=N, and C=O double bonds and heteroaromatic compounds with Hantzsch esters (HEH)12–14 as the hydrogen source, we envision that quinolin-3-amines could also be enantioselectively reduced using this catalyst system (Scheme 1). As a part of our sustained efforts in the asymmetric hydrogenation of aromatic compounds,1a,b,c,d and also as a supplement to our previous work,11 herein, we report an efficient CPA-catalyzed transfer hydrogenation of 2-aryl substituted quinolin-3-amines with excellent diastereo- and enantioselectivities.

Initially, 2-phenylquinolin-3-amine was selected as the model substrate. The original experiment was conducted in 1,4-dioxane by using CPA (S)-3a as the catalyst and HEH 2a as the hydrogen source. Unfortunately, no reaction was observed.

Scheme 1. Asymmetric Reduction of Quinolin-3-amines

Scheme 2. Evaluation of Protecting Group of Quinolin-3-amines

(Scheme 2). Then, the effect of the N-protecting groups of 2-phenylquinolin-3-amine on the reactivity and enantioselectivity was investigated. Several protecting groups were introduced to the amino group, and to our delight, the desired products could be obtained for both the tert-butoxycarbonyl group (Boc) and p-toluenesulfonyl group (Ts) protected substrates while the phthaloyl group (Phth) failed to promote the reaction. The Ts group protected substrate 4-methyl-N-(2-phenylquinolin-3-...
yl)benzenesulfonamide (1a) gave better enantioselectivity (47% ee).

Encouraged by those promising results, our further studies moved to explore the asymmetric transfer hydrogenation of 1a. The first survey of the reaction medium showed that the mixed solvent of 1,4-dioxane and CH₂Cl₂ with a ratio of 2/1 gave the best result in terms of both yield and enantioselectivity (96% yield, 54% ee; entry 7, Table 1). Next, various commercially available CPAs were tested (entries 8–12, Table 1). The highest enantioselectivity of 95% ee was achieved with the sterically demanding catalyst (S)-3f (entry 12, Table 1), and the results indicated that 2a was still the best choice.

To determine the substrate generality and limitations of this strategy, a series of 2-aryl substituted quinolin-3-amines were subjected to asymmetric transfer hydrogenation under the optimized conditions, and the results are summarized in Table 2. All the 2-aryl substituted substrates were smoothly converted to the corresponding products in high yields with high ee values regardless of the electronic properties of the C2 substituted aromatic ring. Notably, the best enantioselectivity was obtained for the substrate 1e with a 4-methoxy group on the phenyl ring (99% ee; entry 5, Table 2). The hydrogenation of 6-fluoro substituted substrate 1k gave the corresponding product 4k in 94% yield with a moderate 73% ee (entry 11, Table 2). This method was also successfully applied to the 2-(3-pyridinyl) substituted substrate 1l with 97% ee (entry 12, Table 2).

The 2-alkyl substituted substrate, N-(2-butyloquinolin-3-yl)-4-methylbenzenesulfonylamide (1m), could also be completely transformed under the standard reaction conditions. The desired product 4m was obtained with moderate enantio- and diastereoselectivity (Scheme 3).

Based on the previous study on the mechanism of hydrogenation and transfer hydrogenation of quinolines, the asymmetric transfer hydrogenation might proceed through two different paths (Scheme 5). In path a, the partial reductive intermediate A isomerizes to exocyclic imine B; in path b, A isomerizes to endocyclic imine C. To differentiate the two paths, an isotopic labeling experiment was carried out with CH₃Cl₂/CD₃OD (3:1) as the solvent (Scheme 6). ¹H NMR analysis of the product showed that the deuterium atom was taken up to the C3-position with 80% incorporation, and deuterium at the C2-position was not observed, which suggested that the
reaction mainly proceeded via the endocyclic imine intermediate C (path b), and a dynamic kinetic resolution process was involved.

In conclusion, we have developed a chiral phosphoric acid catalyzed asymmetric transfer hydrogenation of aromatic amines, quinolin-3-amines, with up to 99% ee. To supplement the reaction mainly proceeds via the endocyclic imine intermediate, and a dynamic kinetic resolution process is involved. Further work will be devoted to the synthetic application of the developed strategy.

ASSOCIATED CONTENT

Supporting Information
Experimental details and full 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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Notes
The authors declare no competing financial interest.

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