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

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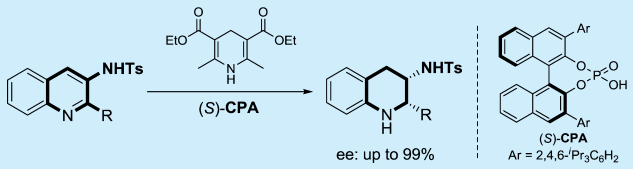
Supporting Information

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.

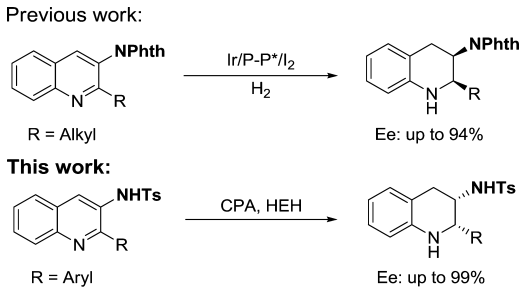


Optically active exocyclic amines exist as key structural elements in many biologically active molecules including natural and unnatural products.[1] In addition, they are useful intermediates for organic synthesis and serve as chiral catalysts in various asymmetric transformations. Due to the simplicity 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,[4a,b,f] 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.

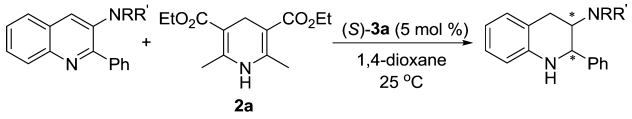
Initially, 2-phenylquinolin-3-amine was selected as the model substrate. The original experiment was conducted in 1,4-dioxane by using CPA (*S*)-**3a** as the catalyst and HEH **2a** as the hydrogen source. Unfortunately, no reaction was observed

Scheme 1. Asymmetric Reduction of Quinolin-3-amines



(Scheme 2). Then, the effect of the *N*-protecting groups of 2-phenylquinolin-3-amine on the reactivity and enantioselectivity

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



NRR'	NH_2	NPhth	NHBoc	**NHTs (1a)**
yield (%)	<5	<5	70	**89**
ee (%)	N/A	N/A	42	**47**

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-

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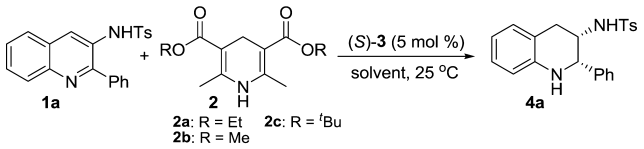
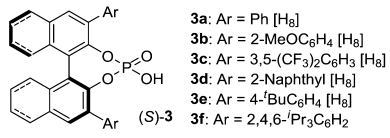
yl)benzenesulfonamide (**1a**) gave better enantioselectivity (47% ee).

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 CH_2Cl_2 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

Table 1. Evaluation of Reaction Parameters[a]





entry	solvent	2	3	yield (%)[b]	ee (%)[c]
1	1,4-dioxane (D)	**2a**	**3a**	89	47
2	PhMe	**2a**	**3a**	94	2
3	THF	**2a**	**3a**	60	23
4	CH_2Cl_2	**2a**	**3a**	91	6
5	D/CH_2Cl_2 (1:2)	**2a**	**3a**	99	43
6	D/CH_2Cl_2 (1:1)	**2a**	**3a**	98	49
7	D/CH_2Cl_2 (2:1)	**2a**	**3a**	96	54
8	D/CH_2Cl_2 (2:1)	**2a**	**3b**	98	28
9	D/CH_2Cl_2 (2:1)	**2a**	**3c**	87	10
10	D/CH_2Cl_2 (2:1)	**2a**	**3d**	98	46
11	D/CH_2Cl_2 (2:1)	**2a**	**3e**	91	64
12	**D/CH_2Cl_2 (2:1)**	**2a**	**3f**	**94**	**95**
13	D/CH_2Cl_2 (2:1)	**2b**	**3f**	94	95
14	D/CH_2Cl_2 (2:1)	**2c**	**3f**	28	77

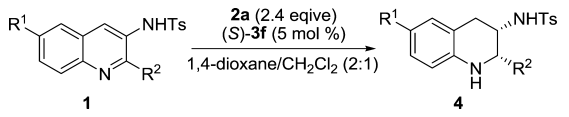
[a]Conditions: **1a** (0.125 mmol), **2** (0.300 mmol, 2.4 equiv), (*S*)-**3** (5 mol %), solvent (3.0 mL), 25 °C, 12−24 h. [b]Isolated yield based on **1a**. [c]Determined by chiral HPLC analysis.

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). Finally, several common HEHs were also evaluated (entries 13−14, 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-butylquinolin-3-yl)-4-methylbenzenesulfonamide (**1m**), could also be completely transformed under the standard reaction conditions. The

Table 2. Asymmetric Transfer Hydrogenation of Quinolin-3-amines 1[a]

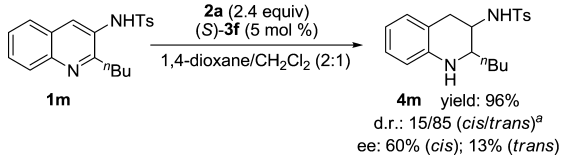


entry	R	Ar	yield (%)[b]	ee (%)[c]
1	H	C_6H_5	94 (**4a**)	95 (*S*,*S*)[d]
2	H	3-MeC_6H_4	96 (**4b**)	97 (−)
3	H	4-MeC_6H_4	98 (**4c**)	91 (−)
4	H	4-^{t}BuC_6H_4	93 (**4d**)	94 (−)
5	H	4-MeOC_6H_4	96 (**4e**)	99 (−)
6	H	4-ClC_6H_4	97 (**4f**)	95 (−)
7	H	4-BrC_6H_4	99 (**4g**)	96 (−)
8	H	4-FC_6H_3	93 (**4h**)	98 (−)
9	H	4-$CF_3C_6H_4$	99 (**4i**)	98 (−)
10	H	2-naphthyl	91 (**4j**)	83 (−)
11	F	C_6H_5	94 (**4k**)	73 (−)
12[e]	H	3-pyridinyl	70 (**4l**)	97 (−)

[a]Conditions: **1** (0.125 mmol), **2a** (0.300 mmol, 2.4 equiv) in 1,4-dioxane/CH_2Cl_2 (2:1, 3.0 mL), CPA (*S*)-**3f** (5 mol %), 25 °C, 24 h. [b]Isolated yield based on **1**. [c]Determined by chiral HPLC analysis. [d]The absolute configuration of **3a** was determined to be *cis*-(*S*,*S*) by comparison of the ^{1}H NMR, HPLC, and optical rotation with data reported by ref 14i. [e]50 °C.

desired product **4m** was obtained with moderate enantio- and diastereoselectivity (Scheme 3).

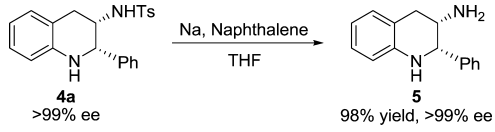
Scheme 3. Asymmetric Transfer Hydrogenation of 2-Butyl Substituted Substrate 1m



[a]The relative configuration was determined by comparison of the ^{1}H NMR with data reported by ref 11.

It should be noted that the Ts group could be easily removed by the treatment of sodium/naphthalene without loss of optical purity in high yield (Scheme 4).

Scheme 4. Removal of the Tosyl Group in 4a



Based on the previous study on the mechanism of hydrogenation and transfer hydrogenation of quinolines,[15] 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** isomerize to endocyclic imine **C**. To differentiate the two paths, an isotopic labeling experiment was carried out with CH_2Cl_2/CD_3OD (3:1) as the solvent (Scheme 6). ^{1}H 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

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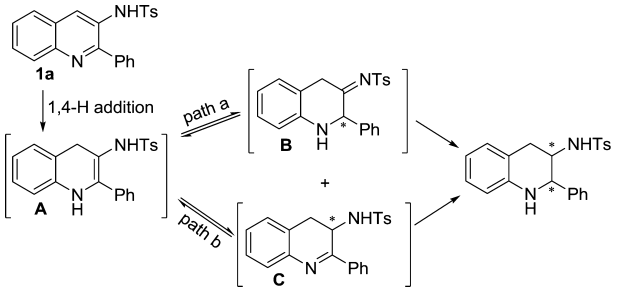
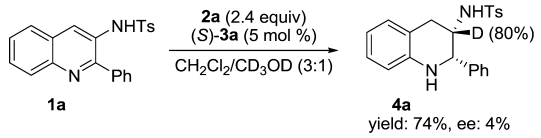
Scheme 5. Two Possible Paths for the Asymmetric Transfer Hydrogenation



Scheme 6. Isotopic Labeling Experiment



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 our previous work on 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 yields and enantioselectivities. Preliminary mechanistic studies indicate that the reaction mainly proceeds *via* an 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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