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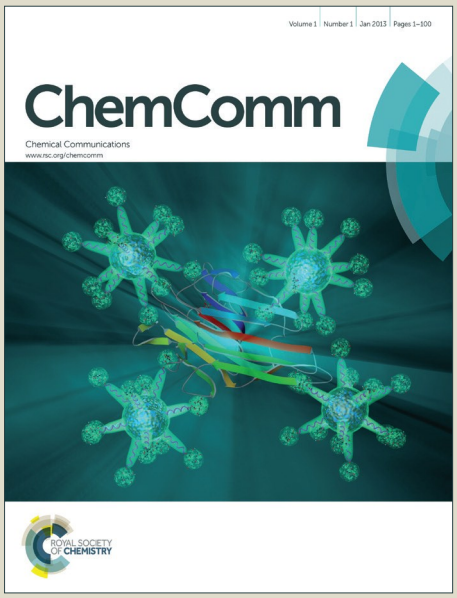

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ARTICLE

Chiral Phosphoric Acid Catalyzed Oxidative Kinetic Resolution of Cyclic Secondary Amine Derivatives including Tetrahydroquinolines by Hydrogen Transfer to Imines

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A chiral Brønsted acid catalyzed dehydrogenative kinetic resolution of tetrahydroquinoline derivatives, which are representative cyclic secondary amines, based on their hydrogen transfer to aromatic imines was efficiently achieved with high enantioselectivities. This hydrogen transfer of tetrahydroquinolines to imines was not driven by their aromatization to quinolines. This dehydrogenative kinetic resolution could be also applied to the asymmetric synthesis of various benzofused heterocycles containing secondary amine cores.

Enantiomerically pure amines are key components of pharmaceuticals and agrochemicals.[1] Thus, the development of new strategies for the enantioselective construction of carbon-nitrogen skeletons has captured the attention of synthetic organic chemists.[2] The kinetic resolution of racemic starting materials using either chemical reagents or biotechnological approaches is one of the most important methods to afford chiral compounds.[3]

The 2-substituted tetrahydroquinoline structure is often found in a variety of natural and biologically active compounds. Many research groups have recently reported the asymmetric synthesis of tetrahydroquinoline derivatives based on the enantioselective hydrogenation using transition-metal catalysts with high-pressure molecular hydrogen[6] or the organocatalyzed transfer hydrogenation using Hantzsch ester.[7] Nevertheless, there are few reports of the catalytic synthesis of tetrahydroquinolines in a highly enantioselective manner based on kinetic resolution.[8] As an initial work, Krasnov *et al.* reported the kinetic resolution of 2-methyltetrahydroquinoline based on an acylation reaction using a chiral acylating reagent,[8a] in which use of more than half amount of the chiral reagent was required. More recently, although the Toste group has elegantly developed a chiral phosphoric acid catalyzed synthesis of 2-substituted tetrahydroquinoline derivatives by the dehydrogenative deracemization of racemic tetrahydroquinolines, the use of excess amounts oxidant and hydrogen donor was needed, and this method was limited to 2-aryl-substituted tetrahydroquinolines.[8c] Clearly, there is a great demand for the development of a catalytic kinetic resolution of tetrahydroquinolines having a wide substrate scope.

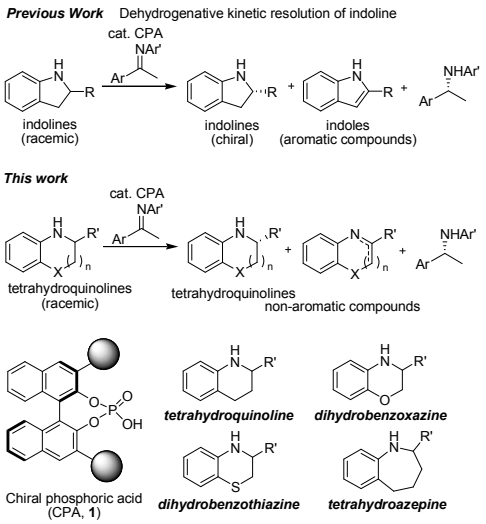

Figure 1 Concept of this work and target compounds for this OKR

We have recently developed a chiral phosphoric acid[9] catalyzed oxidative kinetic resolution of 2-substituted indoline derivatives based on the hydrogen transfer to imines,[10] wherein one hydrogen molecule was transferred to imine to afford amine accompanied by the formation of indole. This hydrogen transfer would be strongly driven by the aromatization of indoline to indole. In contrast, the dehydrogenation of one hydrogen molecule of tetrahydroquinolines gives dihydroquinolines, which are not aromatic compounds. The dehydrogenation reaction of tetrahydroquinolines is thus expected to be more difficult in terms of thermodynamic stability. We hypothesized that the amine in the products has lower hydrogen donating ability to

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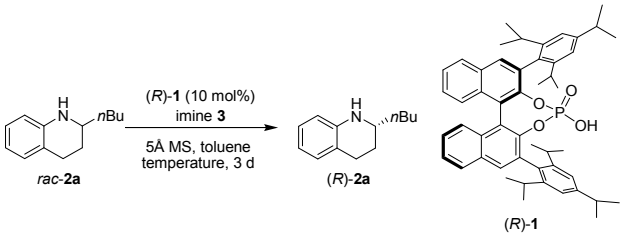
cyclic ketimine and the equilibrium would be biased to the products. To achieve the dehydrogenative kinetic resolution, we should be able to access various chiral heterocycles that show promising functions in medicinal chemistry. We wish to report herein the chiral phosphoric acid catalyzed asymmetric hydrogen transfer reaction of tetrahydroquinolines and cyclic amines employing imines as hydrogen acceptors, which would be a good example of an efficient OKR of secondary amine.

Table 1 Examination of reaction conditions

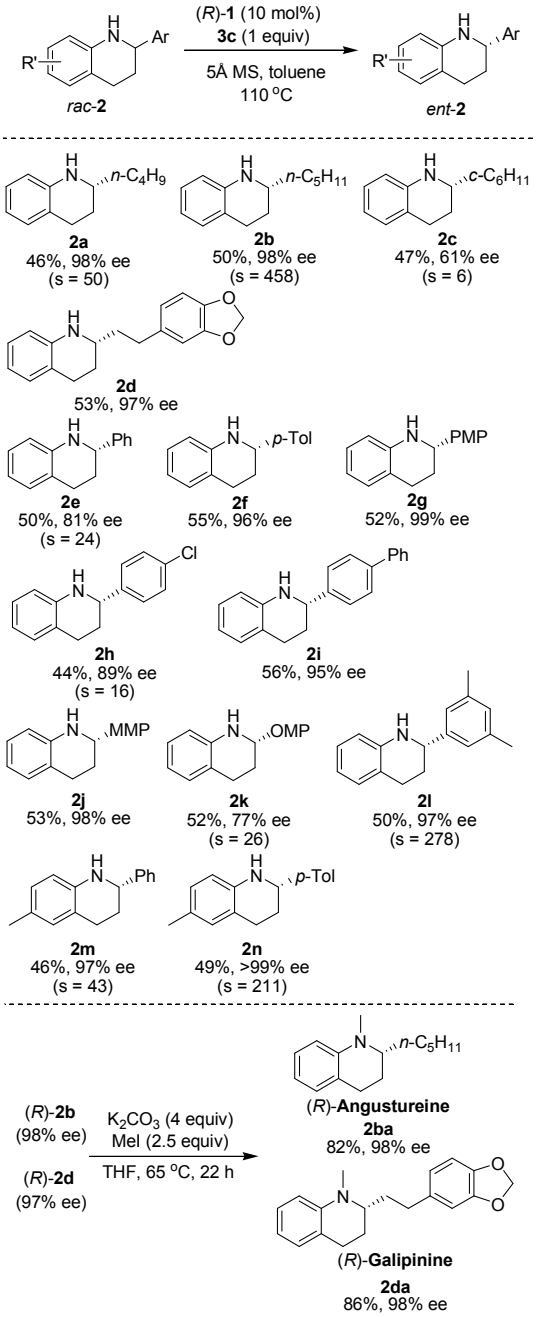


Entry	Imine (1 equiv)	T/°C	Yield[a]/%	Ee[b]/% ee
1	 **3a**	50	53	24
2	 **3b**	50	85	24
3	**3b**	110	57	77
4	 **3c**	110	46	98

[a] Isolated yields. [b] Enantiomer ratios were determined by HPLC analysis on a chiral stationary phase. PMP = *p*-methoxyphenyl, TMP = 3,4,5-trimethoxyphenyl.

As an initial examination, we treated racemic 2-butyltetrahydroquinoline **2a** with 1.0 equiv of *N*-PMP aldimine **3a** in the presence of a catalytic amount of phosphoric acid (*R*)-**1**[11] and molecular sieves 5Å (5Å MS) at 50 °C (Table 1, entry 1). Transfer hydrogenation from **2a** to **3a** proceeded to furnish (*R*)-**2a** in 53% yield with 24% ee. Use of ketimine **3b** improved the selectivity with lower conversion (entry 2). Raising the reaction temperature resulted in high conversion and good ee (entry 3). Use of ketimine **3c** bearing a 3,4,5-trimethoxyphenyl group on nitrogen further improved ee of **2a** to 98%, and amine **4c** was obtained in 63% yield with 93% ee.[12]

Scheme 2 Substrate scope of CPA-catalyzed OKR of tetrahydroquinolines and derivatization[a,b]



[a] Isolated yields. [b] Enantiomer ratios were determined by HPLC analysis on a chiral stationary phase. Tol = tolyl, PMP = *p*-methoxyphenyl, MMP = *m*-methoxyphenyl, OMP = *o*-methoxyphenyl.

Next, we explored the scope of the CPA-catalyzed oxidative kinetic resolution of a range of tetrahydroquinoline derivatives under the optimum reaction conditions (Scheme 2). Although tetrahydroquinolines bearing pentyl (**2b**) or arylethyl (**2d**) group proved to be suitable substrates, the substitution of cyclohexyl group at 2-position gave inferior results. For substrates having various aryl groups at 2-position, phenyl group (**2e**) and electron-donating (**2f** and **2g**) or –withdrawing

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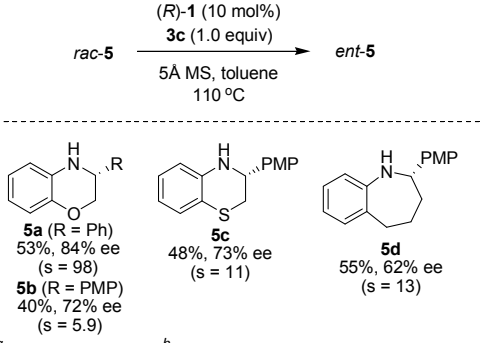
(**2h** and **2i**) substitution at *p*-position of the aromatic ring at 2-position had marginal effects, and high enantioselectivities were obtained with efficient conversions. The *m*- , *o*-, and 3,5-substitutions of the aromatic ring were also effective for enantiocontrol (**2j**-**2l**). In addition, we examined tetrahydroquinoline substrates having a substituent on their aromatic rings. Substrates **2m** and **2n** having a methyl group at 6-position were also suitable for this OKR, and excellent enantiomeric excesses were realized with good conversion. Products (*R*)-**2b** and (*R*)-**2d** were efficiently transformed into methylated natural products, (*R*)-angustureine ((*R*)-**2ba**) and (*R*)-galipinine ((*R*)-**2da**) without loss of optical purity.

As an extension of this work, we investigated OKR of other cyclic secondary amines (Scheme 3). When the reaction was performed under the same optimum conditions using 2-phenyldihydrooxazine[13] **5a**, the product was isolated in 53% yield with 84% ee. **5b** bearing a *para*-methoxy group at 2-position and dihydrothiazine[13] **5c** also participated in this OKR. Next, tetrahydrodiazepine **5d**, which has a seven-membered cyclic secondary amine structure, could be used for this OKR albeit with lower conversion. It should be noted that the present OKR is the few example of the catalytic synthesis of chiral tetrahydroazepines.[14]

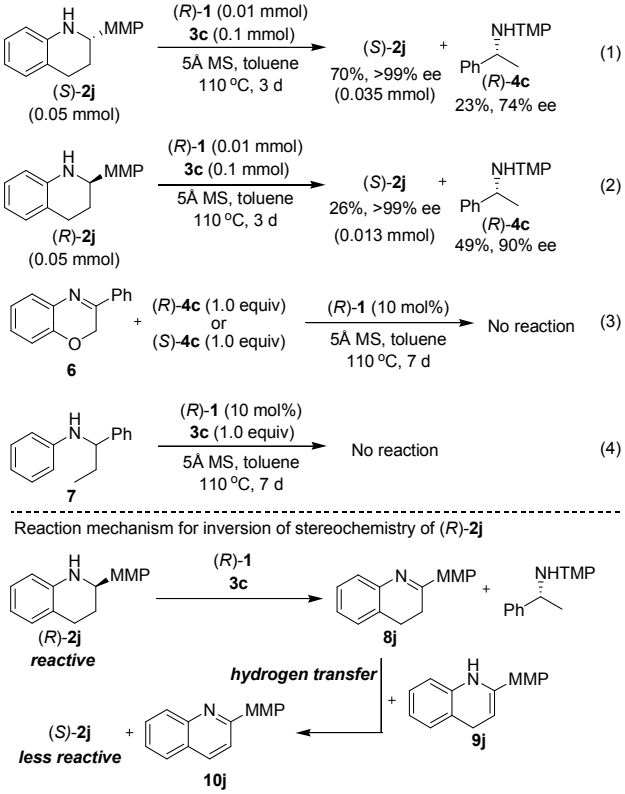
Scheme 3 Substrate scope of CPA-catalyzed OKR of cyclic secondary amines



[a] Isolated yields. [b] Enantiomer ratios were determined by HPLC analysis on a chiral stationary phase. PMP = *p*-methoxyphenyl.

To gain further insight of the reaction mechanism of this OKR process, we compared the reactivity of both enantiomers of tetrahydroquinoline **2j** by means of (*R*)-**1**. Remarkable difference of the hydrogen donating ability was observed between the enantiomers of **2j**. Whereas (*S*)-**2j** underwent hydrogen transfer slowly to give **4c** in 23% with 74% ee,[15] accompanied by the recovery of (*S*)-**2j** in 70% (Scheme 4, Eq 1), (*R*)-**2j** reacted smoothly with **3c** to give (*S*)-**2j** and (*R*)-**4c** in 26%, >99% ee, and 49%, 90% ee, respectively (Eq 2). Quite interestingly, inversion of the stereochemistry of **2j** was observed, which could be explained by considering that dihydroquinoline **8j** was hydrogenated by the isomerized **9j** to give (*S*)-**2j**, resulting in the inversion of the stereochemistry of **2j**.[16] Next, we examined the reverse reaction of *ent*-**4c** with **6** (Eq 3).[17] Neither of the enantiomers of **4c** furnished the reduction product of **6**, which clearly indicated that the hydrogen transfer reaction would not exist between the dihydroquinoline and **4c** in this kinetic resolution. These results suggest that although transfer hydrogenation of (*S*)-isomer was slow, (*R*)-isomer rapidly underwent transfer hydrogenation with ketimine to furnish **8j** and **9j**. Subsequet reduction of **8j** proceeded highly enantioselective manner to give (*S*)-**2j** as a single enantiomer. Interestingly, extremely low conversion was observed when we examined kinetic resolution of acyclic secondary amine **7**, which clearly shows that the cyclic structure of secondary amine is also important for this hydrogen transfer reaction to ketimines.

Scheme 4 Probing the reaction mechanism



In conclusion, we have developed highly efficient OKR of a series of 2-substituted cyclic secondary amine derivatives, involving asymmetric transfer hydrogenation in high yields with high to excellent enantioselectivities. This method features an efficient dehydrogenative kinetic resolution catalyzed by chiral phosphoric acid based on asymmetric hydrogen transfer to ketimine derivative.

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