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Facile Construction of Three Contiguous Stereogenic Centers *via* Dynamic Kinetic Resolution in Asymmetric Transfer Hydrogenation of Quinolines

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An efficient and facile route to chiral tetrahydroquinolines with three contiguous stereogenic centers *via* dynamic kinetic resolution process has been successfully developed by using chiral phosphoric acid as catalyst and Hantzsch ester as the hydrogen source with up to 89% ee.

The compounds with multiple stereocenters are widely found in the natural products and biologically active compounds. To achieve these complex compounds through conventional stepwise processes is normally a difficult task. Thus, it is of great importance to develop an effective method for the preparation of chiral compounds with multiple contiguous stereocenters. Dynamic kinetic resolution (DKR) is a powerful strategy for accessing single enantiomer with a 100% theoretical yield from the racemic substrates.[1] In the past decades, DKR has been widely employed in the transformation of racemic alcohols, amines,[2] ketones, α-substituted β-ketoesters,[3] 2,3-disubs-tituted quinolines, indoles and 3,4-disubstituted isoquinolines.[4] In most cases, one or two stereogenic centers generated, and only a few protocols for the synthesis of chiral compounds with three/multiple stereocenters in one step were reported (Scheme 1).[5] Very recently, a highly efficient asymmetric hydrogenation of racemic α,α'-disubstituted ketones to generate chiral alcohols with three conti-guous stereocenters through DKR was reported by Zhou's group,[5b] this process effectively construct of complex compounds with multiple contiguous stereocenters. Therefore, high enantiocontrol method for construction of three contiguous stereogenic centers *via* a DKR process is very significant.

1,2,3,4-Tetrahydroquinolines are important structural units in a number of natural alkaloids, medicinal chemistry and material sciences.[6] Since our group developed highly enantioselective chiral iridium-catalyzed hydrogenation of quinoline derivatives,[7a] a series of efficient methods to access enantiopure tetrahydroquinolines involving iridium,[7] ruthenium[8] and rhodium[9] catalyzed hydro-genation and organocatalyzed transfer hydrogenation[10] have been documented.[11] These products obtained generally contain one or two stereogenic centers. In 2008, Rueping and Zhou groups[4a-d] reported highly enantioselective hydrogenation/transfer hydrogenation of 2,3-disubstituted quinolines by DKR, giving the chiral 2,3-disubstituted 1,2,3,4-tetrahydroquinolins with two contiguous stereogenic centers (Scheme 2). Based on these progresses, we conceived that the

construction of three contiguous stereogenic centers[12] by DKR might be realized *via* asymmetric reduction of quinolines, with the driving force of exocyclic and endocyclic enamine/imine isomerization. Herein, we report a highly enantioselective transfer hydrogenation of 2,3-disubstituted quinolines through DKR to obtain chiral 1,2,3,4-tetrahydroquinolines with three contiguous stereogenic centers.
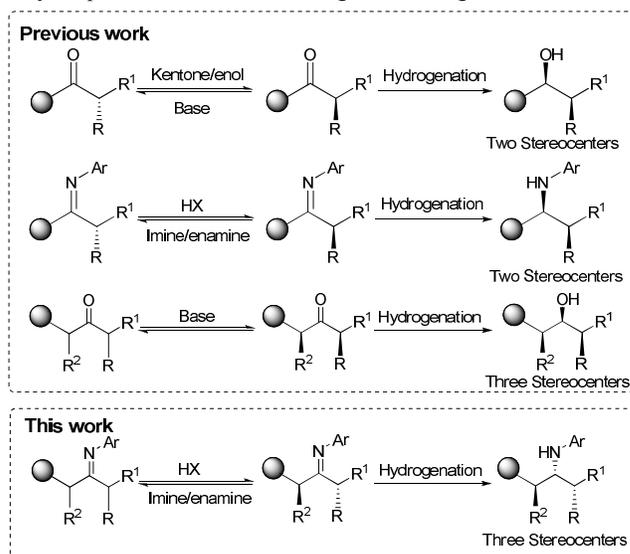

Scheme 1. General Strategy of Asymmetric Hydrogenation of Ketones, Imines, Heteroarenes *via* DKR
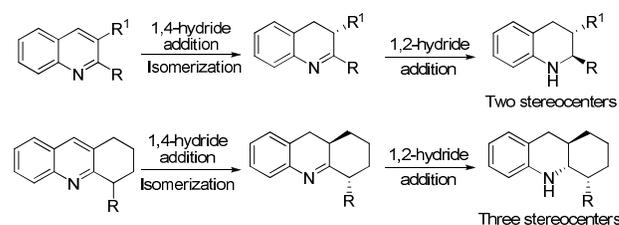
Scheme 2. Asymmetric Hydrogenation of 2,3-Disubstituted Quinolines

To test this hypothesis, we synthesized the 4-methyl-1,2,3,4-tetrahydroacridine **1a** and submitted it to transfer hydrogenation conditions with (S)-Binol-derived chiral phosphoric acid **3a** as the catalyst and diethyl Hantzsch ester (HEH) **4a** as the hydrogen source.[13] To our delight, the desired product **2a** was obtained in 88% yield, 54% ee and 14:1 dr (**2a:2a'** and no other diastereoisomers were detected) (Entry 1, Table 1). Subsequently, a variety of solvents were investigated. The reduction reaction was performed smoothly in all tested solvents, and 1,4-dioxane was the most suitable choice.

**Table 1.** The Effect of Solvents on Reactivity and Selectivity[a]
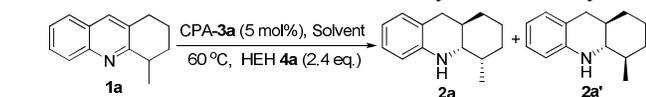
Entry	Solvent	Yield (%)[b]	Ee (%)[c]	Dr (2a:2a')[d]
1	Benzene	88	54	14:1
2	Toluene	96	57	17:1
3	THF	96	60	11:1
4	1,4-Dioxane	96	63	17:1
5	CHCl₃	72	43	8:1
6	p-Xylene	99	59	17:1

[a] Quinoline **1a** (0.125 mmol), CPA-**3a** (0.00625 mmol), Hantzsch esters **4a** (0.30 mmol), solvents (3.0 mL), 60 °C, 24 h. [b] Isolated yields. [c] Determined by HPLC. [d] The dr value was determined by ¹H NMR.

Further examinations were focused on some commercially available chiral phosphoric acids. The excellent selectivity was obtained with 3,3'-phenyl-substituted Binol-phosphoric acid **3a** (Entry 1, Table 2), providing the product in 63% ee, 17:1 dr and 96% yield. When reaction temperature was decreased to 25 °C, the enantioselectivity was further improved and good yield was retained (Entry 7, Table 2). Since Hantzsch esters usually played a vital role in the transfer hydrogenation reactions, the effect of different Hantzsch esters on the reactivity and enantioselectivity was investigated (Entries 8-13, Table 2), and **4g** gave the highest enantioselectivity and moderate yield. Fortunately, when catalyst **3a** was replaced by **3f**, the highest selectivity and excellent yield could be obtained (Entry 14, Table 2). Therefore, the optimal conditions were established as phosphoric acid **3f** (5 mol%), Hantzsch ester **4g** (2.4 equiv), 1,4-Dioxane, 25 °C.

Table 2. Optimization of Transfer Hydrogenation Reaction[a]
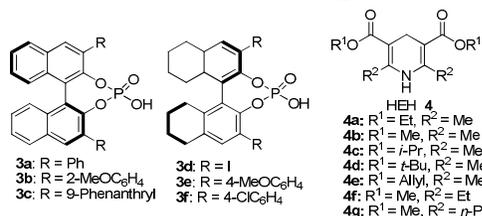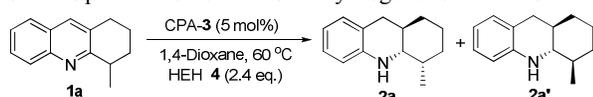
Entry	CPA	R¹	R²	Yield (%)[b]	Ee (%)[c]	Dr (2a:2a')[d]
1	**3a**	Et (**4a**)	Me	96	63	17:1
2	**3b**	Et (**4a**)	Me	96	57	11:1
3	**3c**	Et (**4a**)	Me	88	7	11:1
4	**3d**	Et (**4a**)	Me	76	57	14:1
5	**3e**	Et (**4a**)	Me	99	50	19:1
6	**3f**	Et (**4a**)	Me	96	60	17:1
7[e]	**3a**	Et (**4a**)	Me	96	66	>20:1
8[e]	**3a**	Me (**4b**)	Me	92	73	>20:1
9[e]	**3a**	i-Pr (**4c**)	Me	76	63	>20:1
10[e]	**3a**	t-Bu (**4d**)	Me	72	49	>20:1
11[e]	**3a**	Allyl (**4e**)	Me	84	70	>20:1
12[e]	**3a**	Me (**4f**)	Et	84	77	>20:1
13[e]	**3a**	Me (**4g**)	n-Pr	80	81	>20:1
14[e]	**3f**	Me (**4g**)	n-Pr	99	82	>20:1

[a] Quinoline **1** (0.125 mmol), CPA-**3** (0.00625 mmol), Hantzsch esters **4** (0.30 mol), 1,4-Dioxane (3.0 mL), 60 °C, 24 h. [b] Isolated yields. [c] Determined by HPLC. [d] The dr value was determined by ¹H NMR. [e] 25 °C, 24 h.

With the optimal reaction conditions in hand, our attention was turned to investigate the scope of various substituted quinolines, and these results were summarized in Table 3. It was noteworthy that the substrates with different aliphatic substituents at the 4-position worked well with good yields, 82-88% ee and diastereoselectivities (**2a-2f**). Among these results, substrates bearing methoxy and fluoro-substituent on the phenyl ring (**1g** and **1h**) afforded the highest ee value. In addition, the substrate **1i** with phenyl substituent at the 4-position was also a suitable reaction partner when the reaction temperature was raised to 60 °C and **3a** was used as catalyst, moderate 46% ee and 5/1 dr was obtained.

Table 3. Chiral Phosphoric Acid Catalytic Asymmetric Transfer Hydrogenation of **1**[a]

2a	2b	2c
Yield: 99%	Yield: 91%	Yield: 84%
Ee: 82%, dr: >20:1	Ee: 88%, dr: >20:1	Ee: 84%, dr: >20:1
2d	2e	2f
Yield: 71%	Yield: 82%	Yield: 85%
Ee: 85%, dr: >20:1	Ee: 89%, dr: >20:1	Ee: 67%, dr: >20:1
2g	2h	2i[b]
Yield: 60%	Yield: 97%	Yield: 49%
Ee: 87%,dr: >20:1	Ee: 88%, dr: >20:1	Ee: 46%, dr: 5:1

[a] Quinolines **1** (0.125 mmol), CPA-**3f** (0.00625 mmol), Hantzsch esters **4g** (0.30 mol), 1,4-Dioxane (3.0 mL), 25 °C, 24 h. Isolated yields. The dr values were determined by ¹H NMR and ee values were determined by chiral HPLC analysis. [b] **1i** (0.125 mmol), CPA-**3a** (0.00625 mmol), Hantzsch esters **4g** (0.30 mol), 1,4-Dioxane (3.0 mL), 60 °C, 24 h.
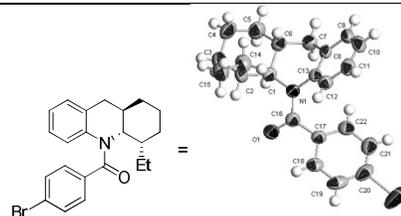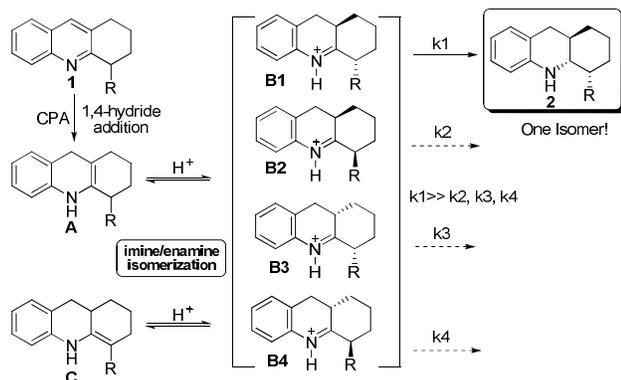

Figure 1. X-ray Crystal Structure of Compound **5b**.

The absolute configuration of transfer hydrogenation product **2b** was determined by X-ray diffraction analysis of the corresponding *N*-4-bromobenzoyl derivative **5b** recrystallized from mixture solvent dichloromethane/*n*-hexane (Figure 1).[14]

Scheme 3. Proposed Reaction Pathway for the Asymmetric Transfer Hydrogenation *via* DKR

Based on the above experimental results and stereochemistry of the products, a plausible reaction pathway is depicted in Scheme 3. Firstly, the substrate interacts with the chiral phosphate acid to give intermediary chiral ion pair.[10] Then the partial reductive intermediate **A** is formed by 1,4-H addition, followed by Brønsted acid-catalyzed isomerization to produce iminium **B**, with four stereoisomers. Subsequently, a highly diastereoselective 1,2-hydride addition give the desired product **2** (Scheme 4). The excellent diastereo- and enantioselectivity achieved in this transfer hydrogenation are attributed to the rapid Brønsted acid-catalyzed isomerization among intermediates **A**, **B** and **C** (Scheme 3).
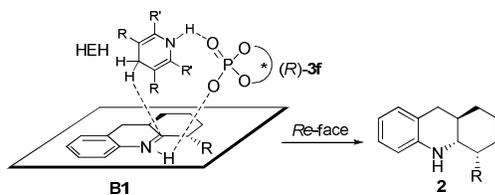
Scheme 4 Proposed Transition State Model for the Asymmetric Transfer Hydrogenation

Conclusions

In summary, we have successfully developed an asymmetric transfer hydrogenation of quinolines, providing an efficient convenient route to synthesize tetrahydroquinoline derivatives with three contiguous stereogenic centers through dynamic kinetic resolution. Rapid Brønsted acid-catalyzed enamine/imine isomerization is the driving force. Further study on applying dynamic kinetic resolution strategy for asymmetric synthesis of optically active compounds is in progress.

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14 CCDC 994490 contains the supplementary crystallographic data for this paper. These can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.