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 a 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 enantiomers with a 100% theoretical yield from the racemic substrates. In the past decades, DKR has been widely employed in the transformation of racemic alcohols, amines, ketones, α-substituted β-ketoesters, 2,3-disubstituted quinolines, indoles and 3,4-disubstituted isoquinolines. 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). Very recently, a highly efficient asymmetric hydrogenation of racemic α,α'-disubstituted ketones to generate chiral alcohols with three contiguous stereocenters through DKR was reported by Zhou’s group, this process was used to effectively construct complex compounds with multiple contiguous stereocenters. Therefore, a 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 materials science. Since our group developed highly enantioselective chiral iridium-catalyzed hydrogenation of quinoline derivatives, a series of efficient methods to access enantiopure tetrahydroquinolines involving iridium, ruthenium and rhodium catalyzed hydrogenation and organocatalyzed transfer hydrogenation have been documented. These products obtained generally contain one or two stereogenic centers. In 2008, Rueping and Zhou groups reported highly enantioselective hydrogenation/transfer hydrogenation of 2,3-disubstituted quinolines by DKR, giving the chiral 2,3-disubstituted 1,2,3,4-tetrahydroquinolines with two contiguous stereogenic centers (Scheme 2). Based on the progress, we conceived that the construction of three contiguous stereogenic centers 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.

To test this hypothesis, we synthesized the 4-methyl-1,2,3,4-tetrahydroacridine 1a and subjected 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. 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.

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 the 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 and 25 °C.

With the optimal reaction conditions in hand, our attention was turned to investigate the scope of various substituted quinolines, and these results are 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-substituents on the phenyl ring (1g and 1h) afforded the highest ee value. In addition, substrate 1i with a 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 were obtained.
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 (Fig. 1).\(^{14}\)

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 an 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 diastereoselectivity achieved in this transfer hydrogenation are attributed to the rapid Brønsted acid-catalyzed isomerization among intermediates A, B and C (Scheme 3).

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 a dynamic kinetic resolution strategy for asymmetric synthesis of optically active compounds is in progress.

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Notes and references


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