Asymmetric Catalysis

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Highly Enantioselective Direct Synthesis of Endocyclic Vicinal Diamines through Chiral Ru(diamine)-Catalyzed Hydrogenation of 2,2′-Bisquinoline Derivatives

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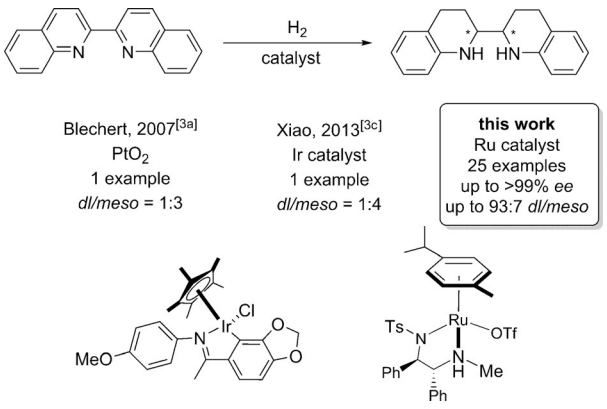
Abstract: *An asymmetric hydrogenation of 2,2′-bisquinoline and bisquinoxaline derivatives, catalyzed by chiral cationic ruthenium diamine complexes, was developed. A broad range of chiral endocyclic vicinal diamines were obtained in high yields with excellent diastereo- and enantioselectivity (up to 93:7 dl/meso and > 99 % ee). These chiral diamines could be easily transformed into a new class of chiral N-heterocyclic carbenes (NHCs), which are important but difficult to access.*

Over the past decades, the chemistry of chiral vicinal diamines and their derivatives has attracted a great deal of interest because they are key substructures in biologically active natural products, pharmaceuticals, and chiral catalysts.[1] To date, a number of chiral vicinal diamines have been reported and successfully used as metal ligands or organocatalysts in asymmetric catalysis.[1c–l] In the pursuit of more efficient chiral catalysts, the design and synthesis of rigid chiral cyclic diamines is one of the frequently used strategies in asymmetric catalysis. Although many efficient methods have been developed for the preparation of chiral vicinal diamines,[1c–e,2] the practical synthesis of enantiomerically pure endocyclic vicinal diamines, such as 2,2′-bis(1,2,3,4-tetrahydroquinoline),[3] 1,1′-bis(1,2,3,4-tetrahydroisoquinoline),[4] bisindoline, bisisoindoline,[5] and 2,2′-bispiperidine[4f,6] derivatives is still a serious challenge. To the best of our knowledge, the direct catalytic enantioselective synthesis of such rigid diamines has not yet been achieved.

Transition-metal-catalyzed asymmetric hydrogenation (AH) has been established as one of the most powerful tools for the preparation of a wide range of enantiomerically pure compounds in organic synthesis.[7] In particular, the AH of heteroaromatic compounds has recently been an important topic in asymmetric catalysis.[8,9] A number of N-containing heteroaromatic substrates, including quinolines,[9a–e] quinoxalines,[9f–i] isoquinolines,[9j–m] indoles,[9n–q] pyrroles,[9r,s] pyridines,[9t–v] indolizidines,[9w] pyrimidines,[9x] phenanthrolines,[10a,b] and naphthyridines,[10c,d] have been successfully hydrogenated with excellent enantioselectivity. Expectedly, direct asymmetric reduction of the readily available aromatic bisheterocycles (e.g., 2,2′-bisquinolines) is undoubtedly the most convenient strategy for obtaining chiral rigid endocyclic diamines. However, asymmetric reduction of such bisheterocyclic compounds, particularly adjacent bisheteroaromatic substrates, has been less exploited and remains a challenging task. In comparison with the most studied monoheterocyles, many kinds of bisheterocycles are known to coordinate more strongly to transition metals[11] and thus inhibit catalysis. In addition, it is more challenging to realize high diastereo- and enantioselectivity. To date, only few examples have been reported,[3a,c,4b,f,6b,10] and most of them involve heterogeneous catalysis to give racemic products.[3a,4b,f] For example, only two reports concerning the reduction of 2,2′-bisquinoline could be found. In 2007, Blechert et al. reported the hydrogenation of 2,2′-bisquinoline by using PtO_2 as the heterogeneous catalyst.[3a] Most recently, Xiao et al. demonstrated the first homogeneous hydrogenation of 2,2′-bisquinoline catalyzed by a cyclometallated Ir complex.[3c] In both cases, however, the *meso* isomer was obtained as the main product (Scheme 1).

Most recently, we found that the Ru complexes of chiral vicinal diamines, which are often used as catalysts for asymmetric transfer hydrogenation,[1h,i,12] are highly efficient in the AH of N-containing heteroaromatic compounds and give excellent enantioselectivity.[9b,c,10b–d] For example, a wide range of quinolines, including 2-aryl quinolines, could be effectively hydrogenated with high reactivity and enantioselectivity.[9c] In particular, this catalytic system has been demonstrated to be highly effective in the AH of challenging 1,10-phenanthrolines.[10b] Inspired by these results and given the importance of chiral endocyclic vicinal diamines, we



Scheme 1. Hydrogenation of 2,2′-bisquinoline.

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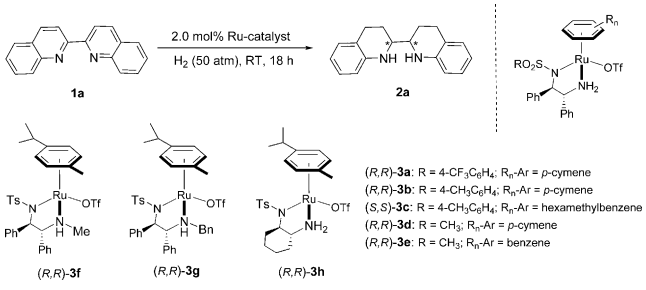
attempted to apply this kind of cationic Ru(diamine) catalyst to the AH of bisquinoline and bisquinoxaline derivatives.

In our initial study, the commercially available 2,2′-bisquinoline (**1a**) was chosen as the model substrate. Pleasingly, the reaction proceeded smoothly under 50 atm of H_2 at 20 °C in methanol to give the desired product in 80% conversion with a 70:30 *dl*/*meso* ratio and >99% *ee* (Table 1, entry 1). To optimize the reaction conditions, the

Table 1: Optimization of reaction conditions for the AH of bisquinoline **1a**.[a]

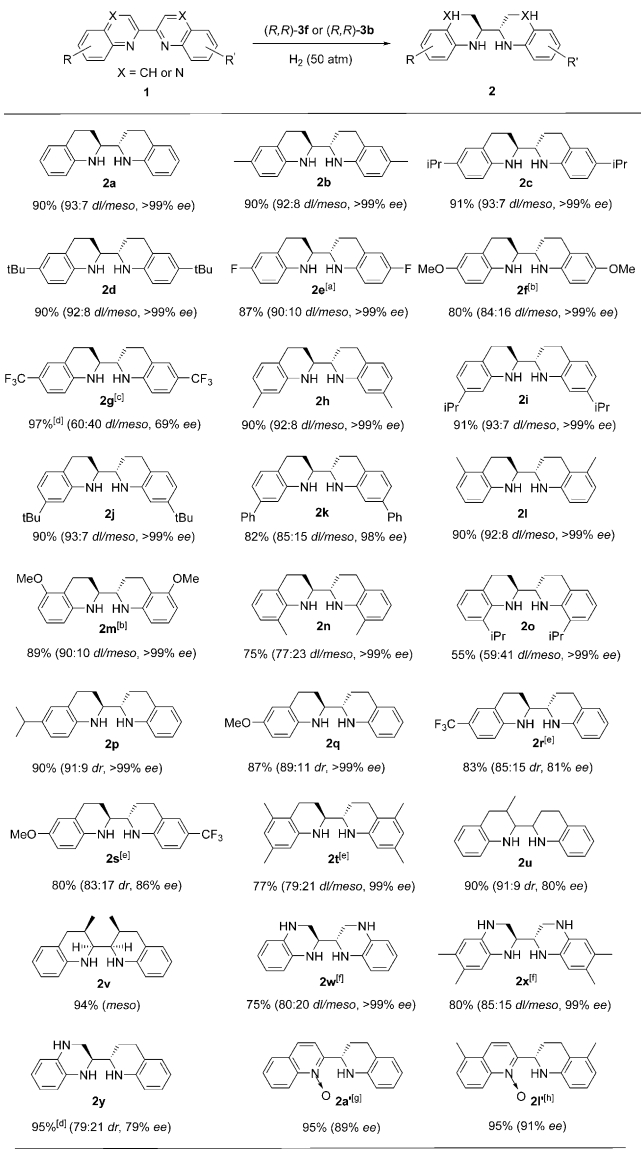


Entry	Solvent	Catalyst	Conv. [%][b]	*dl*/*meso*[b]	*ee* [%][c]
1	MeOH	(*R*,*R*)-**3a**	80	70:30	>99
2	*i*PrOH	(*R*,*R*)-**3a**	>95	90:10	>99
3	*i*PrOH	(*R*,*R*)-**3b**	>95	90:10	>99
4	*i*PrOH	(*S*,*S*)-**3c**	70	86:14	>99
5	*i*PrOH	(*R*,*R*)-**3d**	95	89:11	99
6	*i*PrOH	(*R*,*R*)-**3e**	>95	70:30	90
7	***i*PrOH**	**(*R*,*R*)-3 f**	**>95**	**93:7**	**>99**
8	*i*PrOH	(*R*,*R*)-**3g**	>95	90:10	>99
9	*i*PrOH	(*R*,*R*)-**3h**	87	65:35	>99

[a] Reaction conditions: Substrate **1a** (0.1 mmol, 25.8 mg) in solvent (1.0 mL), Ru catalyst (2.0 mol%), H_2 (50 atm), stirred at RT for 18 h. [b] The conversions and ratio of *dl*/*meso* were determined by ^{1}H NMR spectroscopy of the crude reaction mixtures. [c] The enantiomeric excesses were determined by HPLC with an AD-H chiral-phase column.

effect of solvent, hydrogen pressure, reaction temperature, and catalyst on the AH of **1a** was investigated. The results are shown in Table 1 and Tables S1, S2 of the Supporting Information. Notably, the hydrogenation proceeded well in several organic solvents with good diastereoselectivity and excellent enantioselectivity, and isopropanol was found to give the best result (entry 2). Moreover, the enantioselectivity was insensitive to hydrogen pressure and temperature, while low reactivity and diastereoselectivity were observed under low pressure (Table S2, entry 5). Then, various Ru complexes were further tested, and (*R*,*R*)-**3f** turned out to be optimal (entry 7).

Under the optimized reaction conditions, a variety of 2,2′-bisquinoline derivatives were investigated. As shown in Scheme 2, all these reactions proceeded smoothly to produce the desired diamines with unprecedented enantioselectivity in most cases. It was found that the hydrogenation was insensitive to steric hindrance from alkyl side chain at the 6,6′-, 7,7′-, or 5,5′-positions of 2,2′-bisquinoline. However, introduction of alkyl groups into the 8,8′-positions of 2,2′-bisquinoline (**1n** and **1o**) resulted in a prominent decrease in diastereoselectivity. In addition, unsymmetric 2,2′-bisquinolines (**1p**–**s**) and disubstituted 2,2′-bisquinoline (**1t**) could also



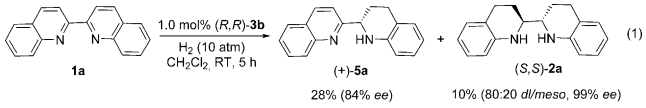
Scheme 2. Scope of the AH of 2,2′-bisquinoline and 2,2′-bisquinoxaline derivatives. General conditions: Substrate (0.1 mmol) in *i*PrOH (1.0 mL), (*R*,*R*)-**3f** (2.0 mol%), H_2 (50 atm), stirred at RT for 18 h. Yields of isolated product are given. The *ee* values were determined by HPLC with a chiral stationary phase. [a] Stirred for 36 h. [b] Stirred at 50 °C for 24 h. [c] Stirred at 50 °C for 48 h. [d] Total yield of reduced products. [e] (*R*,*R*)-**3f** (5.0 mol%) in 1,2-dichloroethane (2.0 mL), stirred at 50 °C for 48 h. [f] (*R*,*R*)-**3f** (3.0 mol%) in dichloromethane. [g] (*R*,*R*)-**3b** (1.0 mol%), 2 h. [h] (*R*,*R*)-**3b** (2.0 mol%), 10 h.

be hydrogenated with good to excellent enantioselectivity. Notably, substrate **1f**, which bears methoxy groups at the 6,6′-positions, showed markedly low reactivity and diastereoselectivity, and substrates bearing CF_3 (**1g**, **1r**, and **1s**) resulted in low reactivity, diastereoselectivity, and enantioselectivity. Interestingly, hydrogenation of substrates bearing methyl groups at the 3,3′-positions (**1u** and **1v**) proceeded smoothly to give the chiral product with fairly good enantioselectivity and *meso* product, respectively.

Furthermore, it is desirable to apply this catalytic system to other bisheterocycles. We demonstrated this through the AH of more challenging 2,2′-biquinoxalines (**1w**, **1x**). After

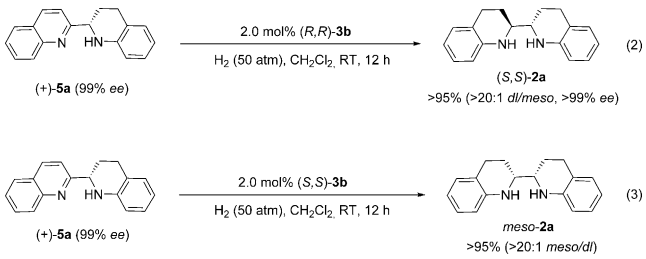
screening of the reaction conditions, (Table S3), both substrates could be reduced smoothly with good diastereoselectivity and excellent enantioselectivity. Notably, the unsymmetric 2-(quinolin-2-yl)quinoxaline (**1y**) could also be hydrogenated, albeit with much low enantioselectivity. In addition, hydrogenation of 2,2′-bisquinoline N-oxides (**1a′**, **1l′**) proceeded smoothly. Only the quinoline ring was reduced, with quite good enantioselectivity, and could be easily transformed to 1,2,3,4-tetrahydro-2,2′-bisquinolines (Scheme S3 in the Supporting Information).

To gain more information on the catalytic process, bisquinoline **1a** was hydrogenated with 1.0 mol% (*R*,*R*)-**3b** in CH_2Cl_2 under low hydrogen pressure. After 5 hours, 41% conversion was observed, and the partially reduced product (**5a**) was obtained in 28% yield with 84% *ee* [Eq. (1)]. This result indicates that the two quinoline rings are hydrogenated



(1)

step sequentially and the first quinoline ring is reduced faster than the second one. Then, the reaction intermediate (+)-**5a** (99% *ee* after recrystallization) was hydrogenated by using both enantiomers of catalyst **3b**. In both cases, full conversion was observed, and (*S*,*S*)-**2a** and *meso*-**2a** were obtained as the sole products, respectively [Eq. (2) and (3)]. This result

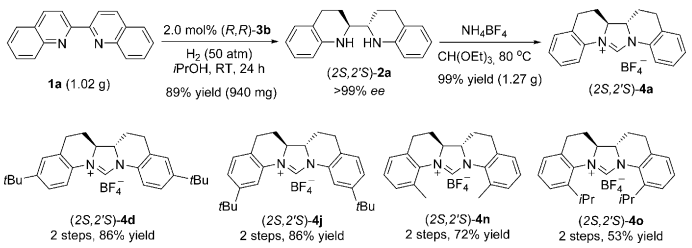


(2)

(3)

suggests that the generation of the second chiral center is completely controlled by the chirality of catalyst, and the diastereoselectivity was unusually high (>20:1). In addition, the absolute configuration of **2a** was determined to be 2*S*,2*S*′ based on single-crystal X-ray analysis of *N*-tosyl-1,1′,2,2′,3,3′,4,4′-octahydro-2,2′-biquinoline (Scheme S1).[13] Based on this result and our previous studies on the AH of quinoline, a cyclic 10-membered transition state for the AH of **1a** is proposed, and the enantioselectivity originates from the CH–π attraction between the η^6-arene ligand in the Ru complex and the fused phenyl ring (Figure S1 in the Supporting Information).

To demonstrate the potential of this new method, these chiral vicinal diamines were employed for the preparation of chiral benzimidazolium salts, a precursor of chiral NHC ligands. As shown in Scheme 3, AH of **1a** was carried out on a gram scale to give (2*S*,2′*S*)-**2a** in 89% yield of isolated



Scheme 3. Synthesis of chiral benzimidazolium tetrafluoroborates.

product with >99% *ee*. Subsequent treatment of (2*S*,2′*S*)-**2a** with triethyl orthoformate and NH_4BF_4 provided the key benzimidazolium tetrafluoroborate (2*S*,2′*S*)-**4a** in quantitative yield, providing a facile and practical approach to a new class of rigid NHC ligands, which might be useful for asymmetric catalysis.[3a,b,4f–h,14] Similarly, several other benzimidazolium salts were synthesized in good yields.

In conclusion, we have developed a highly efficient AH of 2,2′-bisquinoline and 2,2′-bisquinoxaline derivatives that makes use of chiral cationic ruthenium diamine catalysts and proceeds with very good diastereoselectivity and an unprecedented level of enantioselectivity. This new method thus provides a practical and facile approach to the synthesis of optically pure chiral endocyclic vicinal diamines, which can be used as chiral ligands for developing new catalysts. In particular, these chiral vicinal diamines can be easily derived to give a new class of chiral NHC ligands, which are difficult to access through other methods. We believe that this study will stimulate future work on applications of these new chiral vicinal diamines and NHC ligands in asymmetric catalysis.

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Keywords: 2,2′-bisquinolines · asymmetric catalysis · homogeneous catalysis · hydrogenation · vicinal diamines

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