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Highly Enantioselective SPINOL-Derived Phosphoric Acid Catalyzed Transfer Hydrogenation of Diverse C=N-Containing Heterocycles

Yiliang Zhang,[a] Rong Zhao,[a] Robert Li-Yuan Bao,[a] and Lei Shi*[a]

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A highly efficient and enantioselective hydrogenation of diversely substituted C=N-containing heterocyclic compounds such as 3-aryl-1,4-benzoxazines and 2-arylquinolines was experimentally explored by using 1,1′-spirobiindane-7,7′-diol-derived chiral phosphoric acids as the catalyst. This method provides straightforward access to the corresponding tetrahydroquinolines and dihydro-2*H*-1,4-benzothiazines in high yields (85–99 %) with excellent enantioselectivities (91–99 %). The attractive features of this procedure, which include mild reaction conditions, operational simplicity, relatively low catalyst loading (1 mol-%), and high levels of enantioselectivities, make it a useful approach for the practical synthesis of optically active nitrogen-containing aromatic heterocycles.

Introduction

Chiral nitrogen-containing aromatic heterocycles are important targets in synthetic organic chemistry. One of the effective methods for their preparation is the asymmetric transfer hydrogenation of the corresponding C=N-containing heterocyclic compounds. In the past few decades, many researchers have specifically concentrated on the hydrogenation of C=N-containing heterocyclic compounds, the corresponding products of which are the substructures or building blocks of many naturally occurring alkaloids and active pharmaceutical ingredients.[1] More noticeably, a great deal of effort has been devoted to the development of stereoselective methods for the manufacture of highly enantioenriched tetrahydroquinolines and dihydro-2*H*-1,4-benzoxazines (Figure 1).[2] Despite significant progress in this field, the asymmetric hydrogenation of C=N-containing heterocyclic compounds is still a promising research direction in the domain of organic synthesis and methodology.

With respect to asymmetric hydrogenation of quinoline and benzoxazine derivatives, although many highly enantioselective processes catalyzed by transition-metal complexes based on Ir,[3] Rh,[4] Ru,[5] and Pd[6] have been reported, most of the papers fail to give satisfactory results for 2-aryl- or heteroaryl-substituted quinolines and 3-aryl-1,4-benzoxazines. In particular, the groups of Zhou,[7] Beller,[8] Pa-

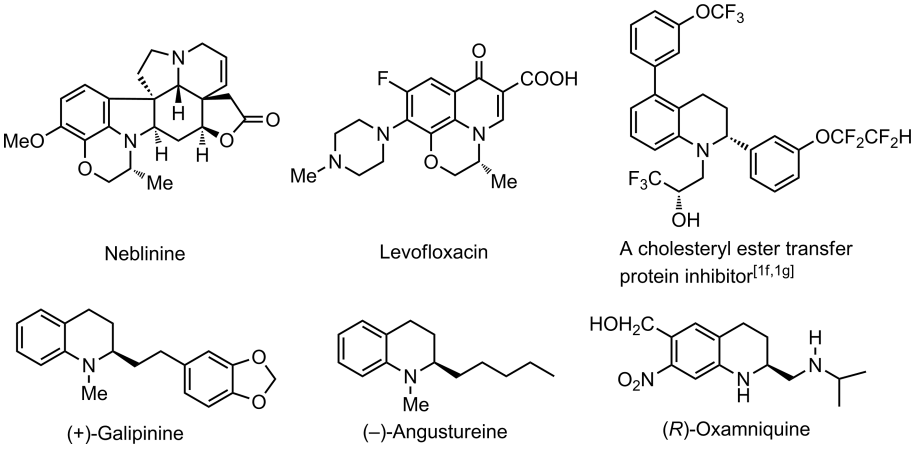

Figure 1. Natural molecules and drugs containing a chiral 1,4-benzoxazine or quinoline scaffold.

[a] Institute of Organic Chemistry, The Academy of Fundamental and Interdisciplinary Sciences, Harbin Institute of Technology, Harbin 150080, P. R. China
E-mail: lshi@hit.edu.cn
http://homepage.hit.edu.cn/pages/shilei

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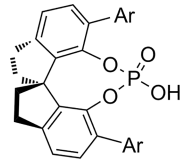
til,[9] and Gong[10] successfully utilized metal/Brønsted acid binary catalytic systems[11] in asymmetric hydrogenation reactions to afford 2-aryltetrahydroquinolines and 3-aryl-dihydro-2*H*-1,4-benzo-xazines in good yields with good enantioselectivities.

Small organic molecules have recently been shown to be highly efficient and selective chiral catalysts for the enantioselective reduction of C=N bonds by using an organic hydride source.[12] On the one hand, for asymmetric reduction of 1,4-benzoxazine derivatives, the combined research groups of Wang and Sun[13] and Zhang[14] independently implemented the targeted transformations by using trichlorosilane as the reducing agent and a Lewis base as the catalyst; this afforded good levels of enantioselectivities. Significant contributions to this topic have been disclosed by the groups of Rueping,[15] Antilla,[16] Thomas,[17] Blechert,[17,18] and Schmidt,[18] who found the combination of chiral phosphoric acids based on the 1,1′-binaphthalene-2,2′-diol (BINOL) skeleton and Hantzsch ester proved useful for the highly enantioselective reduction of 1,4-benzoxazines. On the other hand, for the enantioselective hydrogenation of quinoline derivatives, the first asymmetric organocatalytic transfer hydrogenation of 2-substituted quinolines was described by Rueping in 2006 in a system with a Hantzsch ester as the hydride donor and 3,3′-disubstituted binaphthyl–phosphoric acids.[19] Later on, Du[20] demonstrated the use of chiral phosphoric acid catalysts based on the bis-BINOL scaffold for the reduction of 2-substituted quinolines, in which high enantioselectivities up to 98%*ee* were achieved with a practical catalyst loading as low as 0.2 mol-%. Subsequently, the groups of Toste,[21] Zhou,[22] Bousquet,[23] and Pélinski[23] reported the use of BINOL-based phosphoric acids as catalysts in the asymmetric organocatalytic hydrogenation of a range of quinoline derivatives with good enantioselectivities. Almost at the same time, the groups of Betzer and Marinetti,[24] Guinchard and Voituriez,[25] and Zhang[26] individually investigated the potential and efficiency of other organocatalysts to promote the analogous reactions with Hantzsch ester as the stoichiometric hydride source, and in some cases,[24,25] moderate enantioselectivities were observed. Clearly, each of these aforementioned approaches has its own virtues, but each suffers from a limited substrate scope, especially if 2-aryl or heteroaryl-substituted quinolines and 3-aryl-1,4-benzoxazines are employed as the reactants in the asymmetric hydrogenation (see Schemes S1 and S2, Supporting Information).

Despite the fact that a number of chiral BINOL-based phosphoric acids are known and have been used in the field of organocatalysis over the past decade,[27] the search for novel and efficient chiral phosphoric acids is still required to satisfy the new needs of mankind for chiral compounds. Recently, a relatively new class of chiral phosphoric acids with a 1,1′-spirobiindane-7,7′-diol (SPINOL) scaffold was developed and investigated by different research groups with remarkable results.[28] To overcome the limited substrate scope, we decided to apply the chiral SPINOL-derived phosphoric acid catalyst system (Figure 2) in the asymmetric transfer hydrogenation of 2-aryl- and heteroaryl-substituted quinolines and 3-aryl-1,4-benzoxazines. To the best of our knowledge, there have been no reports concerning the use of chiral SPINOL-derived phosphoric acid catalysts in asymmetric transfer hydrogenation of quinolines and 1,4-benzoxazines.[29]



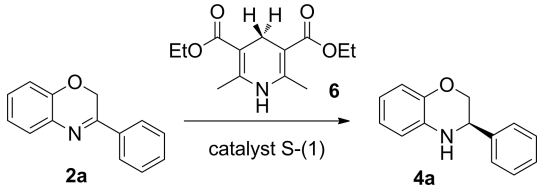
1a: Ar = 3,5-$(CF_3)_2$-C_6H_3
1b: Ar = 1-naphthyl
1c: Ar = 2-naphthyl
1d: Ar = 9-anthracenyl
1e: Ar = 4-*tert*-butylphenyl
1f: Ar = 4-chlorophenyl
1g: Ar = 4-nitrophenyl

Figure 2. Chiral SPINOL-derived phosphoric acids.

Results and Discussion

We started our research by analyzing the reactivity and selectivity in the asymmetric hydrogenation of 1,4-benzoxazine (**2a**) by using Hantzsch ester as the stoichiometric hydride source in the presence of a catalytic amount of SPINOL-derived phosphoric acid catalyst **1** (10 mol-%) at 60 °C. As can be seen in Table 1, 9-anthracenyl-substituted SPINOL-derived phosphoric acid catalyst **1d** performed exceptionally well in the model reaction; it provided expected

Table 1. Optimization of the reaction conditions.[a]



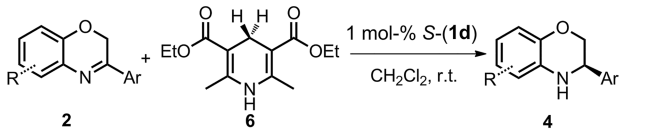
Entry	Catalyst	Solvent[b]	Yield [%][c]	*ee* [%][d]
1	(*S*)-**1a**	THF	57	8
2	(*S*)-**1b**	THF	98	93
3	(*S*)-**1c**	THF	97	70
4	(*S*)-**1d**	THF	97	97
5	(*S*)-**1e**	THF	86	37
6	(*S*)-**1f**	THF	67	45
7	(*S*)-**1g**	THF	92	69
8[e]	(*S*)-**1d**	THF	98	97
9[f]	(*S*)-**1d**	THF	97	97
10[f,g]	(*S*)-**1d**	CH_2Cl_2	95	98
11[f,g]	(*S*)-**1d**	$CHCl_3$	94	95
12[f,g]	(*S*)-**1d**	CCl_4	65	97
13[f]	(*S*)-**1d**	benzene	95	98
14[f]	(*S*)-**1d**	toluene	89	96
15[f,g]	(*S*)-**1d**	MTBE	90	95
16[f–h]	(*S*)-**1d**	CH_2Cl_2	0	–
17[f,g,i]	(*S*)-**1d**	CH_2Cl_2	70	47

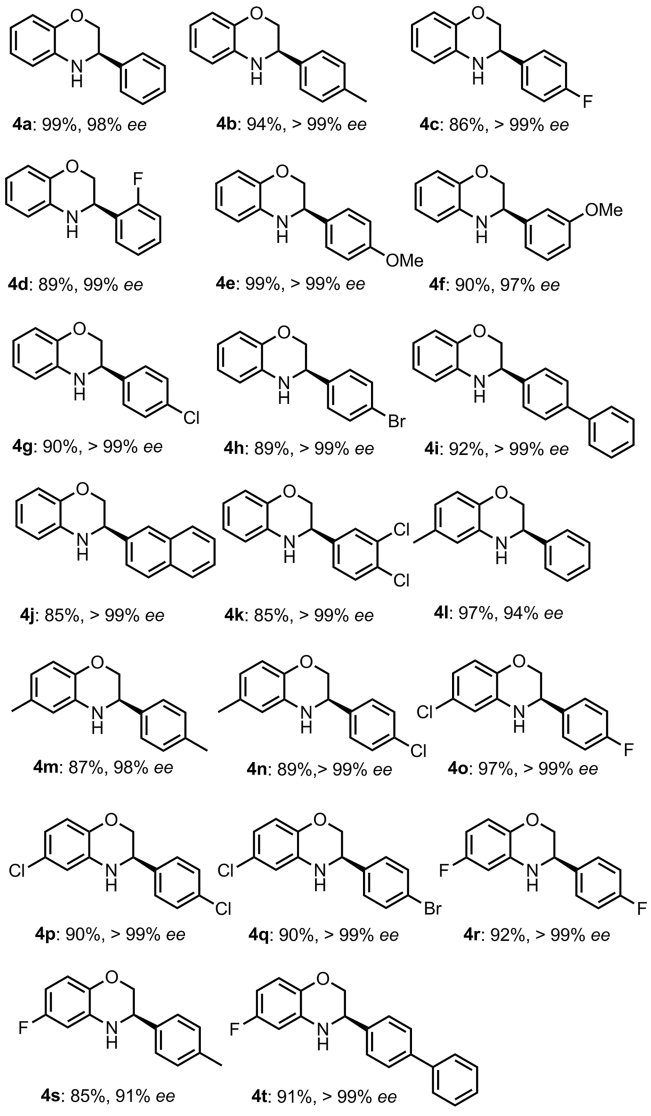
[a] Reaction conditions: **2a** (0.1 mmol), **6** (1.3 equiv.), and **1** (10 mol-%) at 60 °C. [b] MTBE = methyl *tert*-butyl ether. [c] Yield of isolated product after column chromatography. [d] Determined by HPLC analysis by using a Chiralcel OD-H column. [e] Catalyst: 5 mol-%. [f] Catalyst: 1 mol-%. [g] At room temperature. [h] Trichlorosilane was used as the hydride donor. [i] 2-Naphthylbenzothiazoline was used as the hydride donor.

3-phenyl-dihydro-2*H*-benzoxazine **4a** in 97% yield with 97%*ee* (Table 1, entry 4). Notably, the catalyst loading was reduced from 10 to 1 mol-% without any loss in the yield or enantioselectivity (Table 1, entries 8 and 9). Having identified catalyst **1d** as our optimal catalyst, an extensive screen of the solvent was undertaken (Table 1, entries 10–15). The enantioselectivity of the reaction sometimes depended on the solvent polarity, and excellent enantioselectivities up to 98% were achieved in both dichloromethane and benzene. It would be more convenient to use dichloromethane as the solvent at room temperature for the asymmetric hydrogenation of 1,4-benzoxazine derivatives instead of benzene at 60 °C. Other organohydride donors such as trichlorosilane and 2-naphthylbenzothiazoline were also examined to replace Hantzsch ester; however, unsatisfactory result were obtained, in that no product was formed (Table 1, entry 16) or only a moderate yield and low enantioselectivity were obtained (Table 1, entry 17).

With the optimized reaction conditions established, substituted 1,4-benzoxazines **2a**–**t** were used to investigate the reaction scope; the results are summarized in Table 2. Various substituents on the phenyl ring of 3-substituted 1,4-benzoxazines did not have any detrimental effect on either the yields or the enantioselectivities. Both electron-donating groups (e.g., Me and OMe; see **2b**, **2e**, and **2f**) and electron-withdrawing groups (e.g., F, Cl, and Br; see **2c**, **2d**, **2g**, **2h**, and **2k**) on the phenyl ring of the 3-substituted 1,4-benzoxazines were tolerated in this protocol. The corresponding dihydro-2*H*-1,4-benzoxazines were furnished in good yields with excellent enantioselectivities. Next, we examined the influence of different substituents in the 6-position of the 1,4-benzoxazines towards the enantioselectivity. The introduction of electron-donating or electron-withdrawing sub-

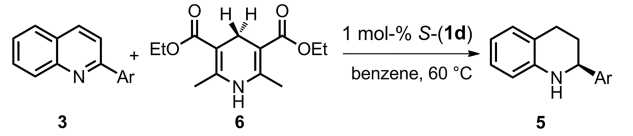
Table 2. Substrate scope of the transfer hydrogenation of 1,4-benzoxazines.[a]

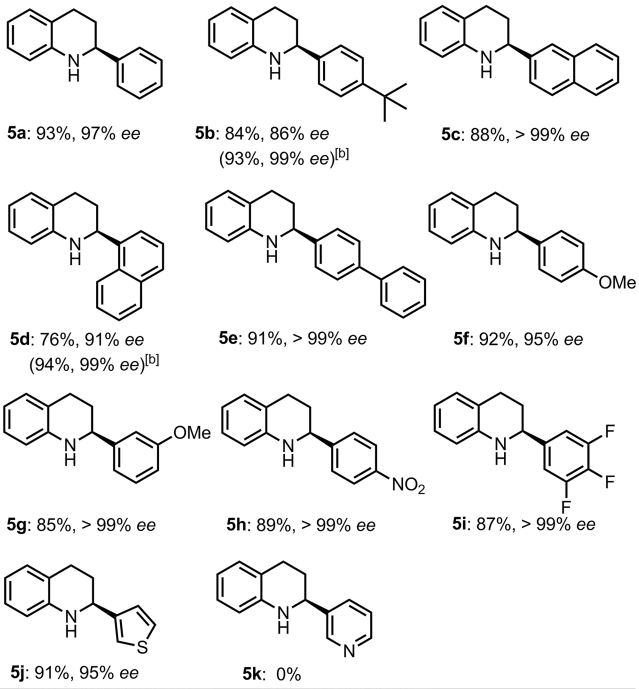




[a] The reaction was performed on a 0.1 mmol scale under a nitrogen atmosphere in CH_2Cl_2 at r.t. for 24 h; the ratio of **2**/**6** was 1:1.25, yields of the isolated products are given, and the *ee* values were determined by HPLC.

Table 3. Substrate scope of the transfer hydrogenation of quinolines.[a]

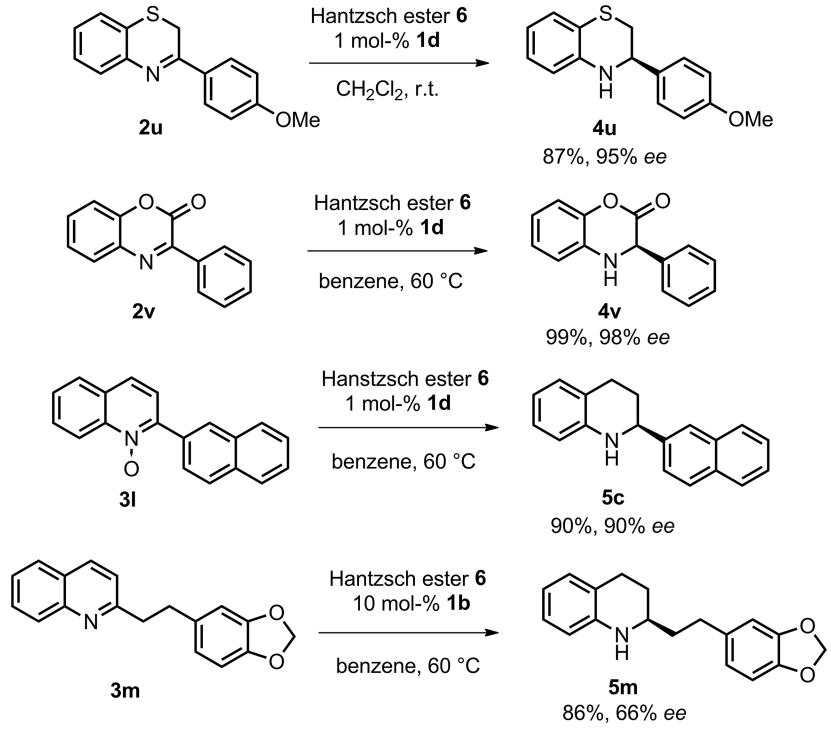




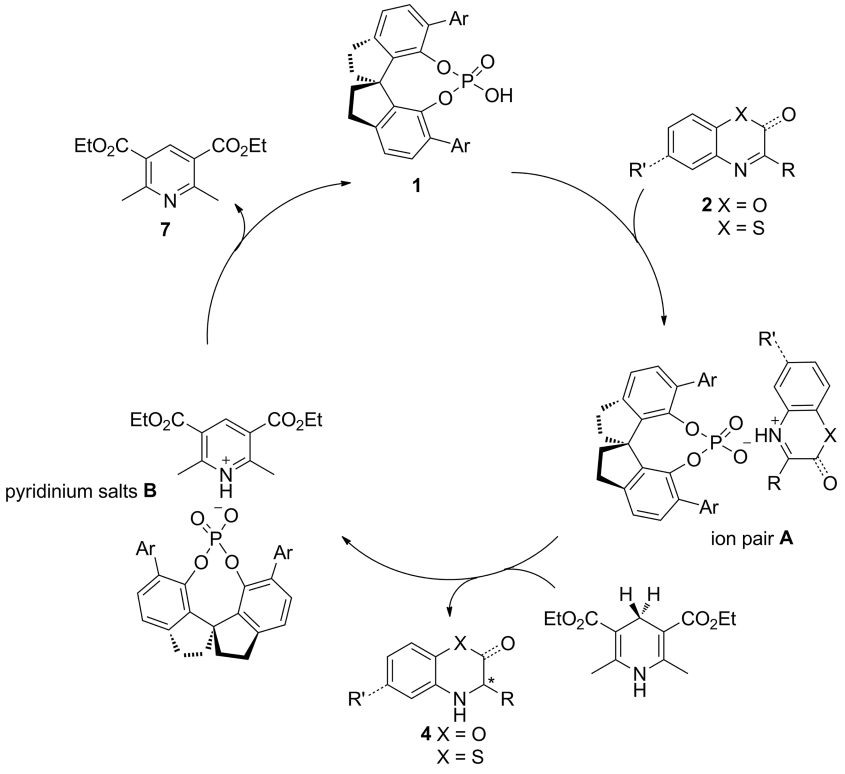
[a] Unless indicated otherwise, the reaction was performed on a 0.1 mmol scale under a nitrogen atmosphere in benzene at 60 °C for 24 h; the ratio of **3**:**6** was 1:2.5, yields of the isolated product are given, and the *ee* values were determined by HPLC. [b] Reactions of **3b** and **3d** were catalyzed by 1 mol-% **1b**.

stituents in the 6-position had no definite effect on the *ee* values.

Asymmetric transfer hydrogenation of 2-arylquinolines **3** was subsequently explored, and the results are listed in Table 3. Considering the significant similarity in the chemical structures of 2-arylquinolines **3** and 3-aryl-1,4-benzoxazines **2**, catalyst **1d** (1 mol-%) was used as the preferred organocatalyst in the enantioselective reduction of 2-arylquinolines **3**. However, the corresponding hydrogenation reactions were conducted in the nonpolar solvent benzene



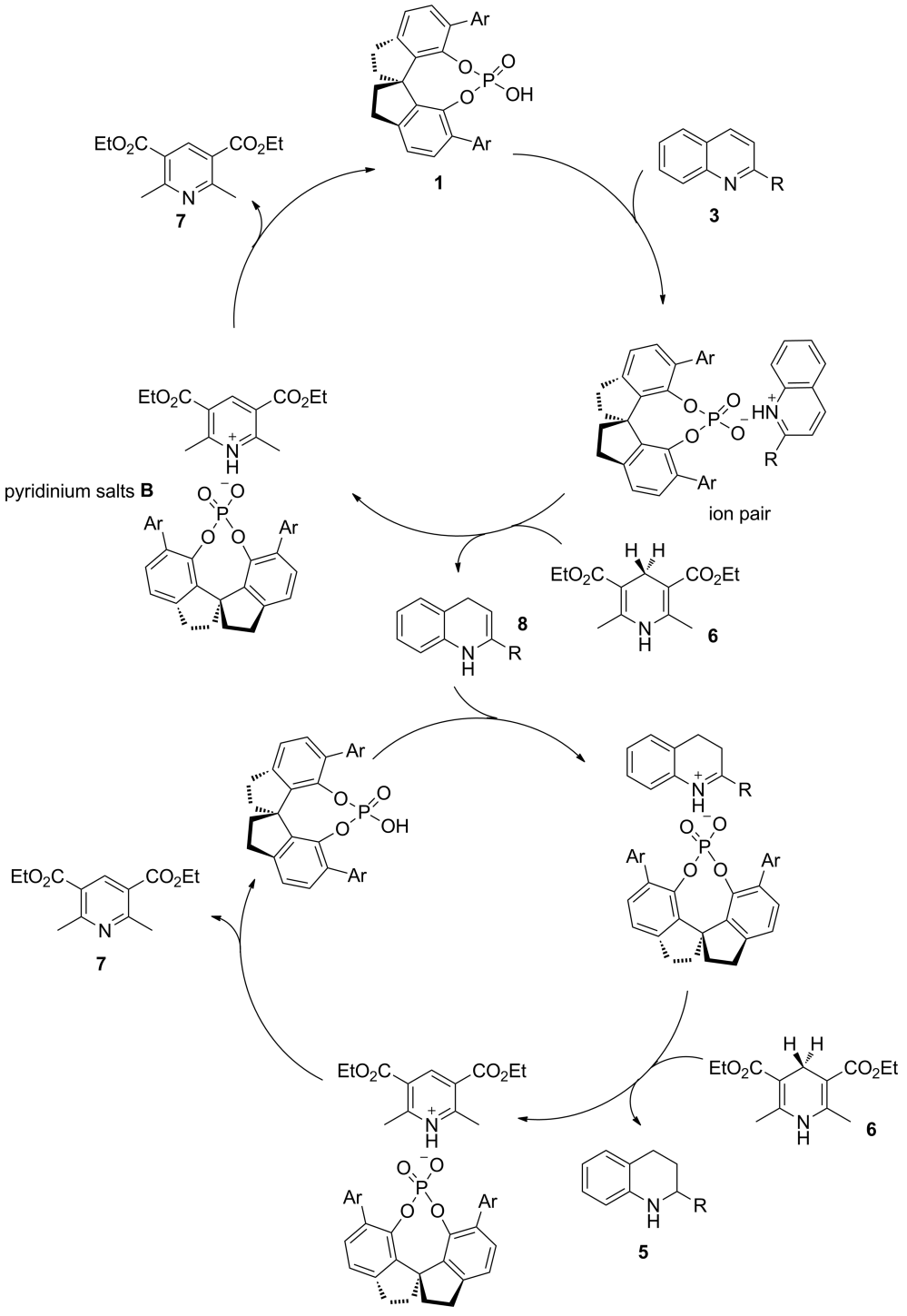
Scheme 1. Substrate scope of other transfer hydrogenation reactions.



Scheme 2. Proposed catalytic cycle for the SPINOL-derived chiral phosphoric acid catalyzed hydrogenation of 3-aryl-1,4-benzoxazines **2**.

at 60 °C, owing to poor solubility of quinolines in chlorinated solvents. Pleasingly, the reduction of 2-arylquinolines **3** proceeded with similar enantiocontrol, and differently substituted 2-aryltetrahydroquinolines **5** bearing either electron-donating groups (e.g., *t*Bu and OMe; see **5b**, **5f**, and **5g**) or electron-withdrawing groups (e.g., NO_2 and F; see **5h** and **5i**) on the phenyl ring were isolated in good yields with excellent enantioselectivities. For the cases in which relatively low enantioselectivities were obtained (i.e., **3b** and **3d**), modification of the substituents in the SPINOL-derived phosphoric acid catalyst from 9-anthracenyl groups to less bulky 1-naphthyl groups significantly improved the enantioselectivities to 99%*ee*, and this occurred together with a clear increase in reactivity. Notably, the hydrogenation reaction of 2-(2-pyridine)quinoline (**3k**) did not occur under our optimized reaction conditions.

With the successful achievement of the asymmetric hydrogenation of 2-arylquinolines and 3-aryl-1,4-benzox-



Scheme 3. Proposed catalytic cycle for the SPINOL-derived chiral phosphoric acid catalyzed hydrogenation of 2-arylquinolines **3**.

azines, we further examined the performance of chiral SPINOL-derived phosphoric acid catalysts in the enantioselective reduction of other analogous C=N-containing heterocyclic compounds, and the results are presented in Scheme 1. The reduction of 3-(4-methoxyphenyl)-2*H*-1,4-benzthiazine (**2u**) and 3-phenyl-2*H*-1,4-benzoxazin-2-one (**2v**) proceeded with similar enantiocontrol, and good enantioselectivities of 95 and 98% were obtained, respectively. Moreover, upon using 2-(naphthalen-2-yl) quinoline 1-oxide (**3l**) as the starting material, a slightly diminished enantioselectivity of 90% was observed. Last, but not least, we attempted to apply our SPINOL-derived phosphoric acid catalyst system to the synthesis of the biologically active tetrahydroquinoline alkaloid galipinine. Unfortunately, the asymmetric transfer hydrogenation of corresponding quinoline **3m** only gave rise to moderate enantioselectivity by using Hantzsch ester as the hydride donor and a loading as high as 10 mol-% of the 1-naphthyl-substituted SPINOL-derived phosphoric acid as the catalyst. Furthermore, some Lewis acids[30] and Brønsted acids[31] were employed as additives (see Table S1, Supporting Information), but they did not help to enhance the enantioselectivities.

On the basis of previous reports,[3c,7a,15a,19a,22] possible mechanisms for the asymmetric hydrogenation of 2-arylquinolines and 3-aryl-1,4-benzoxazines are depicted in Schemes 2 and 3. The asymmetric hydrogenation of 1,4-benzoxazines (Scheme 2) begins with the protonation of cyclic imine **2** by SPINOL-derived chiral phosphoric acid **1**, which results in the formation of chiral iminium/phosphate ion pair **A**. Subsequently, hydride transfer from Hantzsch 1,4-dihydropyridines gives rise to corresponding dihydro-2*H*-1,4-benzothiazines **4** and pyridinium salts **B**, which further undergoes proton transfer to regenerate SPINOL-derived chiral phosphoric acid **1** for the catalytic cycle and affords Hantzsch pyridine **7**. In this sequence, SPINOL-derived chiral phosphoric acid **1** might behave as a Lewis base/Brønsted acid bifunctional catalyst by engaging in a hydrogen bond with cyclic imine **2** and in another hydrogen bond with the N–H bond of Hantzsch ester **6**. Similarly, enantioselective reduction of 2-arylquinolines (Scheme 3) involves a cascade transfer hydrogenation, including 1,4-hydride addition to form enamine intermediate **8**, enamine–imine isomerization by protonation, subsequent 1,2-hydride addition to furnish expected tetrahydroquinolines **5**, and final proton transfer to regenerate chiral catalyst **1**.

Conclusions

In summary, we successfully developed a highly efficient SPINOL-derived chiral phosphoric acid catalyzed transfer hydrogenation of various aryl-substituted 1,4-benzoxazines and quinolines. The chiral phosphoric acids based on the 1,1′-spirobiindane-7,7′-diol framework were found to be highly effective to access the corresponding dihydro-2*H*-1,4-benzoxazines and tetrahydroquinolines in good yields with excellent enantioselectivities. To the best of our knowledge, the present study is by far the best in the asymmetric hydrogenation of 2-arylquinolines and 3-aryl-1,4-benzoxazines reported to date. The mild reaction conditions of this asymmetric transfer hydrogenation of C=N-containing heterocycles, its operational simplicity, and the relatively low catalyst loading (1 mol-%) make this transformation one of the most convenient and general methods for the preparation of optically active tetrahydroquinolines and dihydro-2*H*-1,4-benzothiazines, which are important structural units present in many biologically active alkaloids and pharmaceutical intermediates.

Experimental Section

General Method: All reactions were monitored by TLC and visualized by UV lamp (254/365 nm). Column chromatography was performed by using 230–400 mesh silica gel. ^{1}H NMR and ^{13}C NMR spectra were recorded with a Bruker AV-400 or Bruker AV-600 spectrometer in $CDCl_3$ or [D_6]DMSO. HRMS (ESI) was recorded by using an Agilent 6520 accurate-Mass Q-TOF LC–MS system (1200–6520/Agilent). Optical rotations were measured with an Anton Paar MCP 500 Polarimeter in a 1 dm cell. Melting points were measured in open capillaries. The enantiomeric excesses were determined by HPLC analysis by using a Waters 2695 Series instrument (column Daicel Co. CHIRALCEL OD-H; eluent: hexane/2-propanol). The chiral HPLC methods were calibrated with the corresponding racemic mixtures. Chemical yields refer to pure isolated substances. Unless otherwise noted, commercially available compounds were used as provided without further purification. Solvents for chromatography were technical grade. The reaction solvents, CH_2Cl_2 and benzene, were used without purification.

General Procedure for the Transfer Hydrogenation of Benzoxazines: A 10 mL Schlenk tube was charged with the 3-aryl-1,4-benzoxazine (0.1 mmol, 1 equiv.), Hantzsch ester (32 mg, 0.125 mmol, 1.25 equiv.), catalyst (1 mol-%), and CH_2Cl_2 (1 mL). The resulting mixture was stirred at room temperature for 24 h. The solvent was removed under reduced pressure, and purification of the crude product by column chromatography on silica gel (petroleum ether/ethyl acetate) afforded the pure product.

General Procedure for the Transfer Hydrogenation of Quinolines: A 10 mL Schlenk tube was charged with the 2-arylquinoline (0.1 mmol, 1 equiv.), Hantzsch ester (64 mg, 0.25 mmol, 2.5 equiv.), catalyst (1 mol-%), and benzene (1 mL). The resulting mixture was stirred at 60 °C for 24 h. The solvent was removed under reduced pressure, and purification of the crude product by column chromatography on silica gel (petroleum ether/ethyl acetate) afforded the pure product.

Acknowledgments

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