Asymmetric Catalysis

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# The Development of Double Axially Chiral Phosphoric Acids and Their Catalytic Transfer Hydrogenation of Quinolines**

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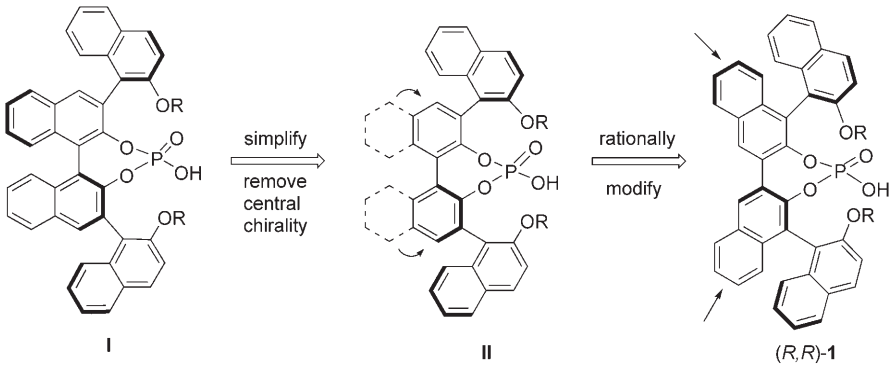
The design of novel chiral catalysts for asymmetric synthesis is an active field of modern organic chemistry.[1] Chiral phosphoric acid catalysts, pioneered by Akiyama et al. and Terada and co-workers,[2] have been recently applied to a wide range of asymmetric organic transformations.[3] Brønsted acids are used in these asymmetric reactions, mainly to protonate the electrophile, which is thereby activated and ready for attack by a corresponding nucleophile. To our knowledge, the previously reported chiral phosphoric acid catalysts are based on a limited number of backbone scaffolds, namely 3,3′-substituted binol (1,1′-bi-2-naphthyl),[4] 3,3′-substituted $H_8$-binol,[5] taddol ($\alpha,\alpha,\alpha',\alpha'$-tetraaryl-2,2-dimethyl-1,3-dioxolan-4,5-dimethanol),[6] vanol (3,3′-diphenyl-[2,2′-binaphthalene]-1,1′-diol), and vapol (2,2′-diphenyl-[3,3′-biphenanthrene]-4,4′-diol).[7] The development of new chiral phosphoric acids with tunable backbones and the expansion of their application to other useful asymmetric organic transformations is still a great challenge for chemists. Herein, the design, synthesis, and application of novel double axially chiral phosphoric acid catalysts are reported.

The rationale for our design of new chiral phosphoric acid catalysts originated from the observation that substitutents at the 3,3′-positions of binol are very important for achieving high selectivity. The use of 3,3′-nonsubstituted binol phosphate as a catalyst always gave low or even no enantioselectivity.[4b, c] We assumed that if the substitutents at the 3,3′-positions of binol phosphate **I** possess a stable double axial chirality, then better performance in organocatalysis may be achieved compared to the mono axially chiral phosphoric acid catalysts based on the same scaffold. For the synthesis of the new catalyst, we removed the middle axial chirality of **I** to give the simplified compound **II**. Then for convenience, we further rationally modified **II** to obtain compound (*R*,*R*)-**1** (Scheme 1) as the target catalysts. (*R*,*R*)-**1** has double axial chirality and can be recognized as a "dimeric" form of (*R*)-alkoxy-binol phosphate. (*R*,*R*)-**1** has a larger chiral pocket than those of previously developed phosphoric acid catalysts.




***Scheme 1.*** Rational design of new double axially chiral phosphoric acids.

The requisite chiral phosphoric acid catalysts (*R*,*R*)-**1a–d** were conveniently synthesized from MOM-protected alkoxy (*R*)-binol **2** in a five-step sequence as illustrated in Scheme 2.[8] MOM-monoprotected alkoxy (*R*)-binol **2** was iodonated to afford **3**, and then coupled with the corresponding mono boric acid intermediate **4** to give the bis-binol derivatives **5** in 79–92% yield. Cleavage of the MOM groups afforded the corresponding alkoxy-substituted bis-binol **6** in 88–94% yield. The double axially chiral phosphoric acid catalysts **1a–d** were obtained after treatment with $POCl_3$, and subsequent hydrolysis (93–96% yield).

The catalytic efficiency of our chiral phosphoric acid catalysts was examined for the asymmetric transfer hydrogenation of quinolines. Although a variety of chiral Rh, Ru, and Ir complexes have been demonstrated to be highly efficient and enantioselective in the hydrogenation of prochiral olefins, ketones, and imines, most of these catalysts failed to give satisfactory results in the asymmetric hydrogenation of heteroaromatic compounds.[9] A few successful examples of the asymmetric hydrogenation of quinolines have recently been reported.[10] Chiral phosphoric acids as organocatalysts can provide excellent enantioselectivities in the transfer hydrogenation of imines, quinolines, and α-imino esters.[4a–f] Rueping et al.[10b] reported the asymmetric transfer

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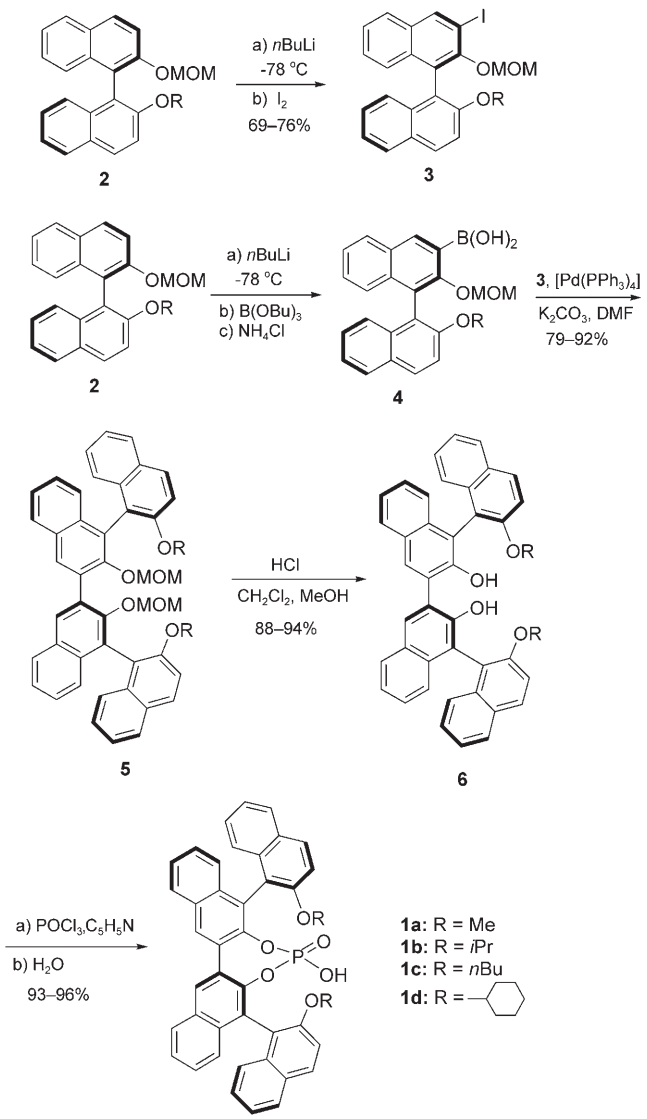
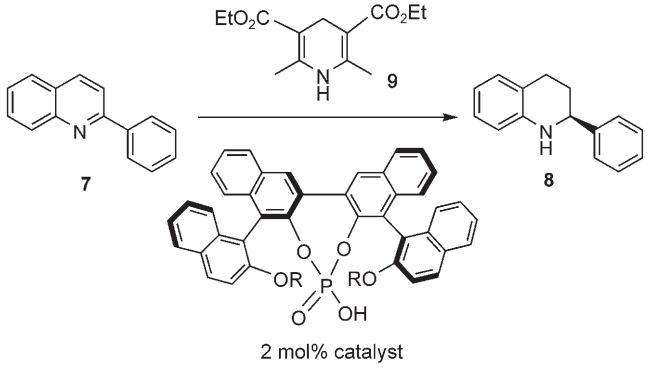



***Scheme 2.*** Synthesis of new double axially chiral phosphoric acids. MOM = methoxymethyl.

hydrogenation of quinolines using 3,3′-bis(9-phenanthryl)-binol phosphate. A variety of 2-aryl-substituted tetrahydroquinolines were synthesized with excellent enantioselectivities (> 99 % *ee*), but 2-alkyl-substituted tetrahydroquinolines had lower enantioselectivities (87–91 % *ee*). Herein, we report that a low catalyst loading (0.2 mol %) is sufficient in the asymmetric transfer hydrogenation of quinolines when catalyzed by our chiral phosphoric acid catalysts **1**. By using this new catalyst we obtain excellent enantioselectivities of up to 98 % *ee* for 2-aryl- and 2-alkyl-substituted quinolines.

With the new Brønsted acids (**1a**–**1d**) in hand, we first investigated which chiral phosphoric acid would be most effective for the catalyzed transfer hydrogenation of quinolines (Table 1). When the phosphoric acid catalysts were present at 2 mol % in toluene at 35 °C, both **1a** and **1c** could catalyze the hydrogen transfer with good enantioselectivities (70 and 85 % *ee*, respectively). Whereas **1b** and **1d** showed improved catalytic properties for the same reaction (93 and

***Table 1:*** Screening of the new phosphoric acid catalysts.[a]




| Entry | Catalyst | R | Yield [%] | *ee* [%][b] |
|---|---|---|---|---|
| 1 | **1a** | Me | 98 | 70 |
| 2 | **1b** | *i*Pr | > 99 | 93 |
| 3 | **1c** | *n*Bu | > 99 | 85 |
| 4 | **1d** | cyclohexanyl | > 99 | 95 |

[a] Reaction conditions: **7** (0.1 mmol), **9** (2.4 equiv), and **1** (2 mol %) in toluene (3 mL) at 35 °C for 20 h. [b] Determined by HPLC on a chiral stationary phase using a Chiracel-OD-H column.

95 % *ee*, respectively). The higher enantioselectivity is probably due to the increased steric effects of **1d**. It is interesting to note that the enantioselectivity was slightly improved from 95 to 96 % *ee* when the loading of catalyst **1d** was varied from 2 to 0.2 mol %.

The influence of the solvent on the catalyzed transfer hydrogenation of 2-phenylquinoline was examined in $CH_2Cl_2$, $CHCl_3$, benzene, toluene, and $Et_2O$ (Table 2); in all cases excellent enantioselectivities (94–96 % *ee*) were obtained. The hydrogenation of 2-butylquinoline resulted in excellent enantioselectivity (93 % *ee*) when the reaction was conducted in $Et_2O$. A slight increase in the enantioselectivity (from 93 to 94 % *ee*) was observed when Hantzsch ester **10** was used.

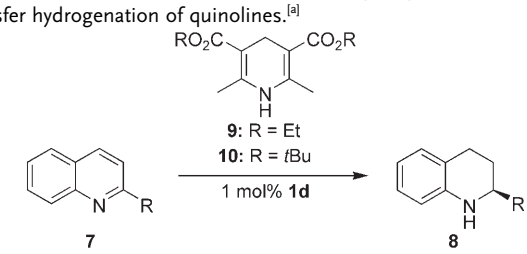
The scope of the Brønsted acid catalyzed transfer hydrogenation was further explored by testing a wide range of 2-substituted quinolines under the optimized reaction conditions (namely, 2.4 equiv **10** and either 0.2 or 1 mol % **1d** in $Et_2O$ at 35 °C for 20 h). High enantioselectivities and good yields for a series of tetrahydroquinolines were observed (Table 3). In the transfer hydrogenation of 2-aryl-substituted quinolines, our catalyst loading (0.2 mol %) was lower than that reported by Rueping et al. (2 mol %).[10b] In the same reaction for 2-alkyl-substituted quinolines, our new chiral phosphoric catalyst **1d** gave higher enantioselectivity (up to 95 % *ee*) than the previously reported method (up to 91 % *ee*).[10b]

The reduction of 2,3-disubstituted quinolines **11a**–**c** were also examined under the optimized reaction conditions using **1d** (1 mol %). The tetrahydroquinolines **12a**–**c** were obtained in high yields with excellent diastereoselectivities (up to > 20:1) and high enantioselectivities (up to 92 % *ee*; Table 4). Interestingly, **12a** was obtained in the *cis* configuration, while **12b** and **12c** had *trans* configurations. A rational mechanism for this transformation is not clear at present.

In summary, we have synthesized a series of novel chiral phosphoric acid catalysts based on the bis-binol scaffold. In

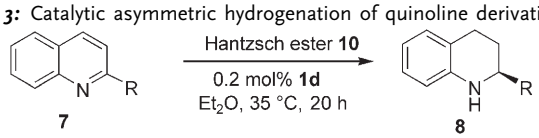
***Table 2:*** Influence of the solvents on the new phosphoric acid catalyzed transfer hydrogenation of quinolines.[a]

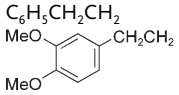
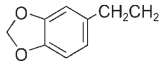



| Entry | Solvent | R = Ph | | R = *n*Bu | |
|---|---|---|---|---|---|
| | | yield [%] | *ee* [%][b] | yield [%] | *ee* [%][b] |
| 1 | $CCl_4$ | 92 | 80 | 85 | 8 |
| 2 | $CH_2Cl_2$ | 98 | 95 | 98 | 85 |
| 3 | $CHCl_3$ | 97 | 94 | 97 | 65 |
| 4 | benzene | >99 | 96 | >99 | 82 |
| 5 | toluene | >99 | 96 | 98 | 85 |
| 6 | THF | 88 | 92 | 91 | 80 |
| 7 | $Et_2O$ | >99 | 96 | >99 | 93 |
| 8 | dioxane | 95 | 88 | 48 | 16 |
| 9 | $Et_2O$ | >99 | 96[c] | >99 | 94[c] |

[a] Reaction conditions: **7** (0.1 mmol), **9** (2.4 equiv), and **1d** (1 mol%) in solvent (3 mL) at 35 °C for 20 h. [b] Determined by HPLC on a chiral stationary phase using a Chiracel-OD-H column. [c] Using Hantzsch ester **10** (2.4 equiv).

***Table 3:*** Catalytic asymmetric hydrogenation of quinoline derivatives.[a]

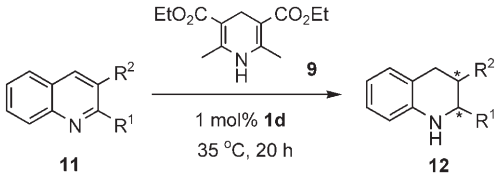


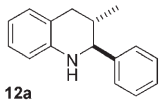
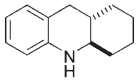
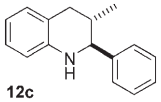

| Entry | R | Product | Yield [%] | *ee* [%][b] | Config[d] |
|---|---|---|---|---|---|
| 1 | $C_6H_5$ | **8a** | >99 | 96 | *S* |
| 2 | 4-$BrC_6H_4$ | **8b** | >99 | 97 | *S* |
| 3 | 4-$ClC_6H_4$ | **8c** | 96 | 98 | *S* |
| 4 | 4-$FC_6H_4$ | **8d** | >99 | 97 | *S* |
| 5 | 4-$CH_3C_6H_4$ | **8e** | >99 | 94 | *S* |
| 6 | 2-$CH_3C_6H_4$ | **8f** | 52[c] | 86 | *S* |
| 7 | 4-$CH_3OC_6H_4$ | **8g** | >99 | 95 | *S* |
| 8 | 2-naphthyl | **8h** | >99 | 97 | *S* |
| 9 | 4-$CF_3C_6H_4$ | **8i** | >99 | 98 | *S* |
| 10 | 1,1′-biphenyl-4-yl | **8j** | >99 | 97 | *S* |
| 11 | $CH_3$ | **8k** | >99[c] | 88 | *R* |
| 12 | $CH_3CH_2CH_2$ | **8l** | >99[c] | 94 | *R* |
| 13 | $CH_3(CH_2)_2CH_2$ | **8m** | >99[c] | 94 | *R* |
| 14 | $CH_3(CH_2)_3CH_2$ | **8n** | >99[c] | 92 | *R* |
| 15 | cyclohexyl | **8o** | >99[c] | 90 | *R* |
| 16 | $C_6H_5CH_2CH_2$ | **8p** | >99[c] | 93 | *R* |
| 17 |  | **8q** | >99[c] | 90 | *R* |
| 18 |  | **8r** | >99[c] | 95 | *R* |

[a] Reaction conditions: **7** (0.1 mmol), **10** (2.4 equiv), and **1d** (0.2 mol%) at 35 °C in $Et_2O$ (3 mL) for 20 h. [b] Determined by HPLC on a chiral stationary phase using a Chiracel-OD-H column. [c] Using **1d** (1 mol%) at 35 °C for 12 h. [d] Determined by comparison of the optical rotation sign with literature data or by analogy.

comparison to the chiral phosphoric acids based on the 3,3′-substituted binol scaffold, our catalysts show higher efficiency in the asymmetric transfer hydrogenation of 2-aryl- and 2-alkyl-substituted quinolines. Low catalyst loadings (0.2–1 mol%) was sufficient to afford tetrahydroquinoline derivatives with excellent enantioselectivities (up to 98% *ee*) and yields. Furthermore, 2,3-disubstituted quinolines were also hydrogenated with excellent diastereoselectivities and high enantioselectivities (up to 92% *ee*). Further exploration of this new type of Brønsted acid in other asymmetric transformations is currently underway within our research group.

***Table 4:*** Catalytic asymmetric hydrogenation of 2,3-disubstituted quinolines.[a]




| Entry | Product | Yield [%] | d.r.[b] | *ee* [%][c] |
|---|---|---|---|---|
| 1 |  **12a** | >99 | >20:1 (*cis*/*trans*) | 82 |
| 2 |  **12b** | >99 | >20:1 (*trans*/*cis*) | 92 |
| 3 |  **12c** | 93 | 94:6 (*trans*/*cis*) | 91 |

[a] Reaction conditions: **11** (0.1 mmol), **9** (2.4 equiv), and **1d** (1 mol%) in $Et_2O$ (3 mL) at 35 °C for 12 h. [b] Determined by $^1H$ NMR spectroscopy. [c] Determined by HPLC on a chiral stationary phase using a Chiracel-OD-H column.

## *Experimental Section*

Representative example of the asymmetric hydrogenation of quinolines. The quinoline **7a** (0.1 mmol), catalyst **1d** (0.2 mol%), Hantzsch dihydropyridine **10** (0.24 mmol), and $Et_2O$ (3 mL) were added to a vial and the mixture was exposed to an argon atmosphere. The resulting yellow solution was stirred at 35 °C for 20 h. The solvent was evaporated in vacuo, and the crude product was purified by column chromatography on silica gel to afford the (*S*)-2-phenyl-1,2,3,4-tetrahydroquinoline (**8a**) in quantitative yield (>99%). $^1H$ NMR (300 MHz, $CDCl_3$): $\delta = 1.88$–$2.11$ (m, 2H), 2.69 (dt, $J = 16.2$, 4.8 Hz, 1H), 2.82–2.91 (m, 1H), 3.95 (s, 1H), 4.37 (dd, $J = 9.3$, 3.3 Hz, 1H), 6.48 (d, $J = 7.5$ Hz, 1H), 6.62 (td, $J = 7.5$, 0.9 Hz, 1H), 6.95–7.00 (m, 2H), 7.24–7.37 ppm (m, 5H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta = 26.3$, 30.9, 56.1, 113.9, 117.0, 120.7, 126.4, 126.8, 127.3, 128.5, 129.2, 144.6, 144.7 ppm; $[\alpha]_D^{20} = -34.8\ deg\,cm^3\,g^{-1}\,dm^{-1}$ ($c = 0.011\ g\,cm^{-3}$, $CHCl_3$, 96% *ee*). The *ee* value of the product was determined by HPLC on a chiral stationary phase (Chiracel-OD-H; hexanes:*i*PrOH 95:5 at $0.6\ mL\,min^{-1}$), major isomer: $t_r = 16.31$ min, minor isomer: $t_r = 21.04$ min. Lit.[10b] $[\alpha]_D^{RT} = -37.7\ deg\,cm^3\,g^{-1}\,dm^{-1}$ ($c = 0.011\ g\,cm^{-3}$, $CHCl_3$, 97% *ee*).

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**Keywords:** asymmetric synthesis · Brønsted acid · hydrogenation · organocatalysis · tetrahydroquinolines

  

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