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Enantioselective Metal-Free Hydrogenations of Disubstituted Quinolines

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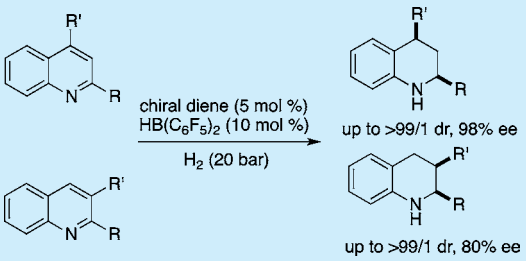
Supporting Information

ABSTRACT: A metal-free hydrogenation of 2,4-disubstituted quinolines was realized for the first time using chiral diene derived borane catalysts to furnish the corresponding tetrahydroquinolines in 75−98% yields with 95/5−99/1 dr's and 86−98% ee's. This catalytic system was also effective for 2,3-disubstituted quinolines to give moderate to good ee's.



The asymmetric hydrogenation of heteroarenes provides an extremely powerful and straightforward approach for the synthesis of optically active saturated heterocycles.[1] Quinolines are one class of the most often studied substrates due to the fact that the resulting tetrahydroquinoline derivatives are very useful building blocks for the synthesis of natural products and biologically interesting compounds.[2] Since the first example of highly enantioselective hydrogenation of 2-subsituted quinolines was reported in 2003 by Zhou and co-workers (Figure 1),[3]

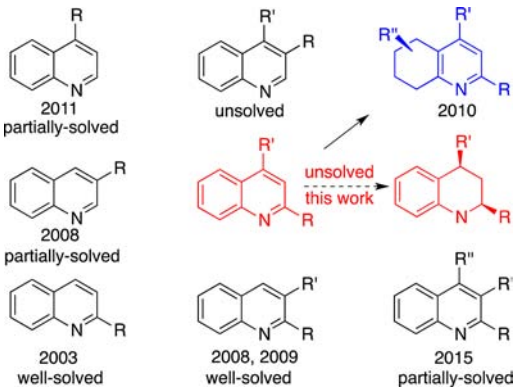


Figure 1. Asymmetric hydrogenations or transfer hydrogenations of quinolines.

numerous chiral transition-metal catalysts and organocatalysts have been successfully developed for this transformation.[4,5] For 3- or 4-substituted quinolines, however, only very limited examples have been reported. In 2008, Rueping and co-workers described a chiral Brønsted acid catalyzed asymmetric transfer hydrogenation of 3-subsitutued quinolines using Hantzsch ester as hydrogen source to give up to 86% ee (Figure 1).[6] Soon after, the same group reported such a transformation of 4-substituted quinolines to afford the corresponding products with up to 91% ee (Figure 1).[7] Notably, the asymmetric hydrogenation of polysubstituted quinolines is of great interest due to its ability to concurrently construct at least two stereogenic centers. For 2,3-disubstituted quinolines, various catalytic hydrogenation and transfer hydrogenation systems have been developed (Figure 1).[8] Glorius and co-workers reported an interesting carbocyclic ring hydrogenation for chiral 2,4-disubstituted quinolines in 2010 (Figure 1).[9] Very recently, our group described a highly enantioselective metal-free hydrogenation of 2,3,4-trisubstituted quinolines (Figure 1).[10] However, the asymmetric hydrogenation of 2,4- and 3,4-disubstituted quinolines still remains as an unsolved problem.

Rapid growth has been witnessed in the metal-free hydrogenation accompanied by the recently emerging chemistry of frustrated Lewis pairs (FLPs).[11,12] Significantly, promising advances have been achieved for the FLP-catalyzed asymmetric hydrogenation.[13] Quinolines were also reported to be suitable substrates for the FLP catalysis.[14] In 2011, Repo and co-workers reported an asymmetric hydrogenation of 2-phenylquinoline with 37% ee.[15] Recently, our group accomplished various highly enantioselective hydrogenations utilizing chiral borane catalysts derived in situ from chiral dienes or diynes.[16,17] In particular, a wide range of 2,3,4-trisubstituted quinolines were smoothly hydrogenated for the first time with high *cis*-selectivities and enantioselectivies.[10] Herein, we report our preliminary efforts on the metal-free asymmetric hydrogenation of 2,4-disubstituted quinolines as well as 2,3-disubstituted quinolines.

We initially chose the optimal reaction conditions for the asymmetric hydrogenation of 2,3,4-triphenylquinoline (**1**) to examine the transformation of 2,4-diphenylquinoline (**4a**) (Scheme 1).[10] Under the catalysis of chiral borane derived in situ from chiral diene **3a**, the desired tetrahydroquinoline **5a**

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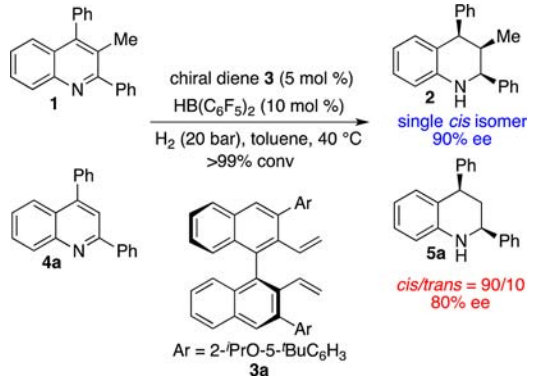
Scheme 1. Controlled Experiments on the Hydrogenation of Quinolines 1 and 4a



was obtained with 90/10 dr and 80% ee. The diminished stereoselectivities of compound **5a** compared with **2** are likely attributed to the less steric hindrance of quinoline **4a** than that of quinoline **1**. Further decreasing the temperature from 40 to 25 °C gave 83% ee with an identical dr (Figure 2). Under these

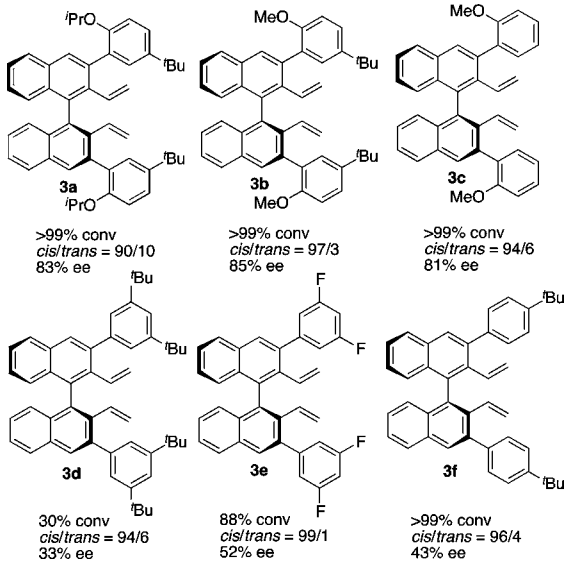


Figure 2. Representative chiral dienes for asymmetric hydrogenations of quinoline **4a**.

reaction conditions, various chiral dienes **3b–f** were next studied for this hydrogenation (Figure 2). With the change of isopropoxy group to methoxy group, chiral diene **3b** gave a much better diastereoselectivity. Chiral **3c** gave comparable results with **3b**. When chiral **3d** was used, a drastic drop of reactivity and ee was observed. Chiral dienes **3e** and **3f** were also effective for this transformation to afford high diastereoselectivities but moderate ee's.

To further improve the enantioselectivity, the reaction conditions including temperature, concentration, and solvents were subsequently optimized. Lowering the temperature to 15 °C can give a 90% ee (Table 1, entry 2). A slightly higher ee was obtained at 0 °C but with only a 37% conversion (Table 1, entry 3). The change of concentration had little impact on this reaction (Table 1, entries 4 and 5). When the catalyst loading was reduced to 5 mol %, a very low conversion was obtained but without loss of diastereoselectivity and enantioselectivity (Table 1, entry 6). Solvents influenced this hydrogenation

Table 1. Optimization of Reaction Conditions[a]

entry	solvent	temp (°C)	conv[b] (%)	cis/trans[c]	ee[c] (%)
1	toluene	25	>99	97/3	85
2	toluene	15	98	97/3	90
3	toluene	0	37	98/2	92
4[d]	toluene	15	>99	97/3	88
5[e]	toluene	15	93	97/3	90
6[f]	toluene	15	19	97/3	91
7	CH_2Cl_2	15	67	97/3	73
8	mesitylene	15	81	96/4	78
9	Et_2O	15	trace		
10	*n*-hexane	15	75	95/5	81

[a]All reactions were carried out with quinoline **4a** (0.10 mmol), chiral diene **3b** (0.005 mmol), $HB(C_6F_5)_2$ (0.01 mmol), and H_2 (20 bar) in solvent (0.2 mL) for 24 h unless otherwise noted. [b]Determined by crude ^1H NMR. [c]Determined by chiral HPLC. [d]0.1 mL of toluene was used. [e]1.0 mL of toluene was used. [f]5 mol % of catalyst was used.

largely, and toluene proved to be the better one (Table 1, entries 2 and 7–10).

2,4-Disubstituted quinolines **4a–y** were next subjected to the asymmetric hydrogenation using chiral diene **3b** under the optimal reaction conditions. It was found that all these reactions proceeded well to give the corresponding tetrahydroquinolines **5a–y** in 75–98% yields with 95/5–99/1 dr's and 86–98% ee's (Table 2, entries 1–25). Both electron-rich and electron-poor aryl substituents at the 2- and 4-positions of quinolines were well tolerant to give high levels of diastereoselectivities and enantioselectivities (Table 2, entries 1–14, 18–22). Notably, furan, thiophene, and alkene substituents were well tolerable to the hydrogenation condition using the FLP catalysis (Table 2, entries 15–17, 23). The asymmetric hydrogenation of quinoline **4w** containing a cyclohexenyl substituent at the 4-position furnished the desired product **5w** in 93% yield with 98/2 dr and 86% ee (Table 2, entry 23). Moreover, quinolines **4x,y** bearing substituents at the 6-position were also effective for this hydrogenation. However, alkyl substituents at 2- or 4-position of quinolines only gave low to moderate ee's at present. The absolute configuration of tetrahydroquinoline **5c** was determined to be 2*S*,4*R* by its X-ray structure (Figure 3).

The current catalytic system can also be applied to the asymmetric hydrogenation of 2,3-disubstituted quinolines. It was found that 2,3-disubstituted quinolines were more reactive and more sensitive to the reaction concentration than 2,4-disubstituted quinolines. As shown in Table 3, the asymmetric hydrogenation of various 2,3-disubstituted quinolines **6a–o** in toluene (0.1 M) at 0 °C went smoothly to give the corresponding products **7a–o** in 74–99% yields with >95/5–99/1 dr's and 45–80% ee's (entries 1–15). The relatively lower ee indicated that the substituents on the 4-positions of quinolines were beneficial to the acquirement of high enantioselectivities.[10]

In summary, with the use of chiral borane catalysts derived in situ from chiral dienes, a highly enantioselective hydrogenation of 2,4-disubstituted quinolines was accomplished for the first time to furnish a wide range of tetrahydroquinoline derivatives in 75–98% yields with 95/5–99/1 dr's and 86–98% ee's. Moreover, this catalytic system was also effective for the asymmetric hydrogenation of 2,3-disubstituted quinolines to afford high levels of yields and dr's with moderate to good ee's.

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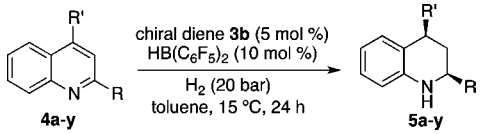
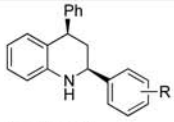
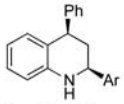
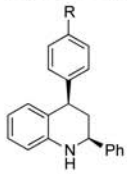
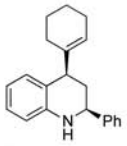
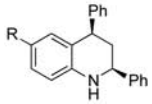
Table 2. Asymmetric Hydrogenation of 2,4-Disubstituted Quinolines 4[a]



entry	product (5)	yield (%)[b]	*cis*/*trans*[c]	ee (%)[c]
				
1	**5a**: R = H	91	97/3	91
2	**5b**: R = 2-Cl	98	>99/1	97
3	**5c**: R = 2-Br	86	99/1	97
4	**5d**: R = 3-Cl	92	98/2	90
5	**5e**: R = 3-Br	89	99/1	91
6	**5f**: R = 3-Me	87	98/2	91
7	**5g**: R = 3-OMe	93	98/2	94
8	**5h**: R = 4-Cl	91	98/2	91
9	**5i**: R = 4-Br	86	99/1	96
10	**5j**: R = 4-CF_3	75	95/5	87
11	**5k**: R = 4-Me	95	98/2	95
12	**5l**: R = 4-Ph	94	98/2	94
13	**5m**: R = 3,4-Me_2	89	98/2	94
				
14	**5n**: Ar = 2-naphthyl	90	98/2	96
15	**5o**: Ar = 2-furyl	80	98/2	87
16	**5p**: Ar = 2-thienyl	93	98/2	89
17	**5q**: Ar = 3-thienyl	88	99/1	90
				
18	**5r**: R = F	89	96/4	96
19	**5s**: R = Cl	97	98/2	95
20	**5t**: X = Br	86	99/1	94
21	**5u**: X = Me	90	98/2	90
22	**5v**: X = OMe	92	98/2	91
				
23	**5w**	93	98/2	86
				
24	**5x**: X = Me	94	98/2	98
25	**5y**: X = Cl	84	96/4	94

[a]All reactions were carried out with quinolines **4** (0.40 mmol), $HB(C_6F_5)_2$ (0.04 mmol), chiral diene **3b** (0.02 mmol), and H_2 (20 bar) in toluene (0.8 mL) at 15 °C for 24 h. [b]Isolated yield. [c]Determined by chiral HPLC.

Further efforts to expand the substrate scope and explore novel metal-free hydrogenations are underway in our laboratory.

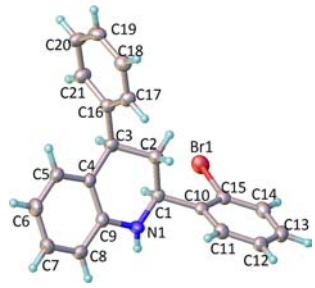
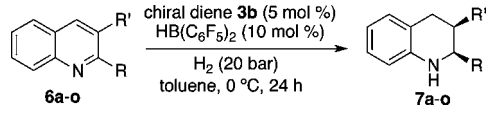
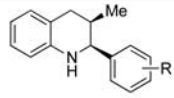
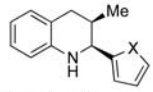
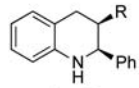


Figure 3. X-ray structure of compound (2*S*,4*R*)-**5c**.

Table 3. Asymmetric Hydrogenation of 2,3-Disubstituted Quinolines 6[a]



entry	product (7)	yield (%)[b]	*cis*/*trans*[c]	ee (%)[c]
				
1	**7a**: R = H	91	>99/1	69
2	**7b**: R = 3-Cl	99	>95/5	72
3	**7c**: R = 3-Br	99	>99/1	66
4	**7d**: R = 3-CF_3	90	>99/1	65
5	**7e**: R = 3-Me	98	>95/5	73
6	**7f**: R = 4-Cl	87	>99/1	74
7	**7g**: R = 4-Br	97	>99/1	77
8	**7h**: R = 4-CF_3	92	>99/1	70
9	**7i**: R = 4-Me	94	>99/1	69
10	**7j**: R = 4-OMe	96	>99/1	65
				
11	**7k**: X = O	94	>99/1	45
12	**7l**: X = S	96	>99/1	56
				
13	**7m**: R = Et	91	>99/1	80
14	**7n**: R = *n*-Pr	95	>99/1	80
15	**7o**: R = *n*-hex	74	>99/1	80

[a]All reactions were carried out with quinolines **6** (0.40 mmol), $HB(C_6F_5)_2$ (0.04 mmol), chiral diene **3b** (0.02 mmol), and H_2 (20 bar) in toluene (4.0 mL) at 0 °C for 24 h. [b]Isolated yield. [c]Determined by chiral HPLC.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03307.

Procedure for the metal-free asymmetric hydrogenation of disubstituted quinolines, characterization of products, and data for the determination of enantiomeric excesses along with the NMR spectra (PDF)

X-ray data for **5c** (CIF)

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Notes

The authors declare no competing financial interest.

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