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Cis-Selective and Highly Enantioselective Hydrogenation of 2,3,4-Trisubstituted Quinolines

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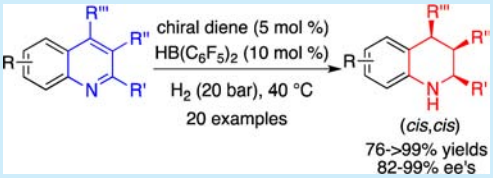
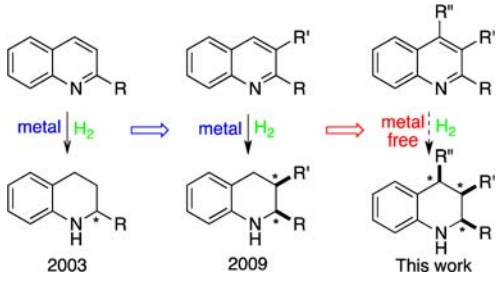
Supporting Information

ABSTRACT: A highly enantioselective *cis*-hydrogenation of 2,3,4-trisubstituted quinolines has been realized for the first time using chiral borane catalysts generated in situ from chiral dienes. A variety of tetrahydroquinoline derivatives containing three contiguous stereogenic centers were obtained in 76−99% yields with 82−99% ee's.

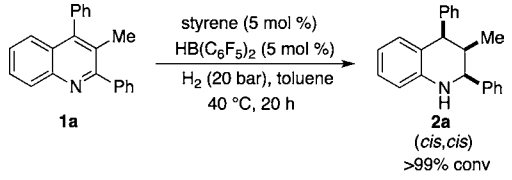


The catalytic asymmetric hydrogenation of quinolines represents one of the most efficient accesses to optically active tetrahydroquinoline derivatives, which are very important building blocks for the synthesis of natural products and biologically active compounds.[1,2] In 2003, Zhou and co-workers reported the first asymmetric hydrogenation of 2-substituted quinolines using a chiral iridium catalyst to give tetrahydroquinolines with up to 96% ee (Scheme 1).[3] Following this seminal work, a variety of transition-metal catalytic systems have been rapidly developed.[4,5] Notably, in contrast to the intensive studies on 2-substituted quinolines, the asymmetric hydrogenation of 2,3-disubstituted quinolines seems to be more challenging, and only several examples have been reported.[6,7] For example, in 2009, Zhou and co-workers described an Ir-catalyzed enantioselective hydrogenation of 2,3-disubstituted quinolines with up to 86% ee.[6a] In 2011, Fan and co-workers reported a Ru-catalyzed asymmetric reaction with up to 98% ee.[6b] Despite these advances, there still are some unsolved quinoline substrates for the asymmetric hydrogenation with H_2, such as 4-substituted quinolines.[8] Glorius and co-workers reported a two-step heterogeneous hydrogenation of chiral 2,4-disubstituted quinolines to give decahydroquinolines, in which the carbocyclic instead of the heterocyclic ring was hydrogenated first.[9] However, for the even more difficult 2,3,4-trisubstituted quinolines, the asymmetric hydrogenation has not been reported yet. The challenges are likely to lie in how to overcome the bulky steric hindrance and construct the three

Scheme 1. Asymmetric Hydrogenation of Quinolines with H_2



Scheme 2. Hydrogenation of 2,3,4-Trisubstituted Quinoline 1a



Scheme 3. Evaluation of Chiral Dienes for Asymmetric Hydrogenation of 2,3,4-Trisubstituted Quinoline 1a

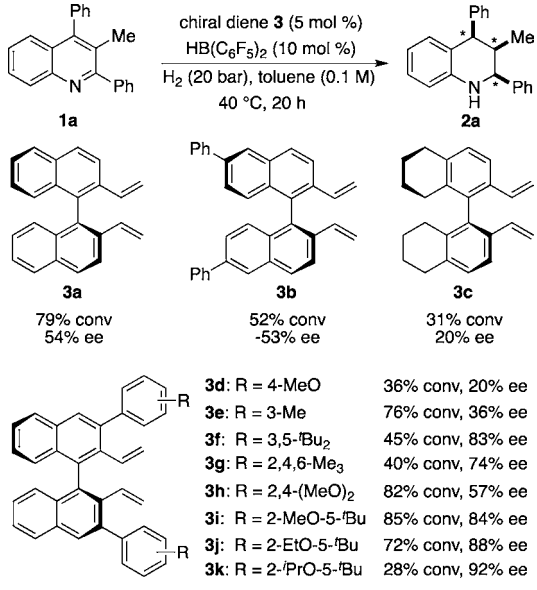


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Table 1. Optimization of Reaction Conditions for Asymmetric Hydrogenation of 2,3,4-Trisubstituted Quinoline 1a[a]

entry	diene 3	solvent	concn (M)	conv[b] (%)	ee[c] (%)
1	**3i**	toluene	0.1	85	84
2	**3i**	CH_2Cl_2	0.1	30	92
3	**3i**	*n*-hexane	0.1	71	67
4	**3i**	Et_2O	0.1	trace	
5	**3i**	mesitylene	0.1	72	83
6	**3i**	toluene	0.5	>99	84
7	**3i**	CH_2Cl_2	0.5	>99	80
8	**3k**	toluene	0.1	28	92
9	**3k**	toluene	0.5	>99	90
10	**3k**	toluene	1.0	82	90
11	**3k**	CH_2Cl_2	0.5	40	90
12[d]	**3k**	toluene	0.5	15	90

[a]All reactions were carried out with 2,3,4-trisubstituted quinoline **1a** (0.10 mmol), chiral diene **3** (0.005 mmol), $HB(C_6F_5)_2$ (0.01 mmol), and H_2 (20 bar) at 40 °C for 20 h unless other noted. [b]Determined by crude ^1H NMR. [c]Determined by chiral HPLC. [d]5 mol % of borane was used.

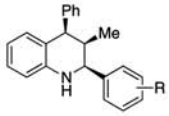
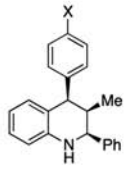
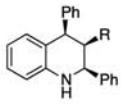
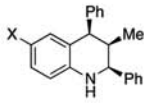
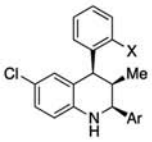
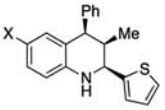
contiguous stereogenic centers with high levels of stereo- and enantioselectivity.

The metal-free hydrogenation with molecular H_2 enters a new era due to the rapid growth of frustrated Lewis pair (FLP) chemistry.[10] A wide range of unsaturated compounds have been hydrogenated using stoichiometric or catalytic amount of FLP catalysts.[11] Recently, some significant advances have also been made for the catalytic asymmetric hydrogenation using chiral substrates or chiral FLP catalysts.[12−14] 2-Substituted quinolines proved to be suitable substrates for the metal-free hydrogenation.[15] In particular, in 2011, Repo and co-workers reported an asymmetric hydrogenation of 2-phenylquinoline using chiral *ansa*-ammonium borate to give the product with 37% ee.[13e] Our group has been exploring highly enantioselective hydrogenation of unsaturated compounds, especially some unsolved substrates. Recently, we successfully realized the asymmetric hydrogenation of imines, silyl enol ethers, and 2,3-disubstituted quinoxalines using in situ generated borane catalysts by the hydroboration of chiral dienes or diynes with Piers' borane.[16−18] On the basis of these previous works, our catalytic system is expected to have a good chance to solve the challenging hydrogenation of 2,3,4-trisubstituted quinolines. Herein, we report our preliminary efforts on this subject.

Initially, an in situ generated achiral borane by hydroboration of styrene (5 mol %) with Piers' borane $HB(C_6F_5)_2$ (5 mol %) was subjected to the hydrogenation of 3-methyl-2,4-diphenylquinoline (**1a**) under H_2 (20 bar) in toluene at 40 °C for 20 h (Scheme 2). We were pleased to find that this reaction proceeded smoothly to give the desired product **2a** in a quantitative conversion. Significantly, this hydrogenation was a highly stereoselective reaction to furnish a single *cis*,*cis*-isomer. This interesting result indicates that it is possible to realize the asymmetric reaction using a chiral borane catalyst.

A variety of chiral dienes **3** were therefore examined for the asymmetric hydrogenation of 2,3,4-trisubstituted quinoline **1a**. As shown in Scheme 3, all of these chiral dienes were effective for this reaction to give *cis*,*cis*-tetrahydroquinoline **2a**. A simple chiral diene **3a** derived from (*S*)-BINOL gave a good conversion with 54% ee, while 6,6′-Ph_2BINOL-derived diene **3b** led a converse absolute configuration. H_8-BINOL-derived

Table 2. Metal-Free Asymmetric Hydrogenation of Quinolines[a]

entry	product (**2**)	yield (%)[b]	ee (%)[c]
			
1	**2a**: R = H	90	90
2	**2b**: R = 4-MeO	92	84
3	**2c**: R = 4-Me	>99	92
4	**2d**: R = 4-Cl	83	84
5	**2e**: R = 3-Me	92	93
6	**2f**: R = 3-Cl	82	82
7	**2g**: R = 3-Br	76	85
8	**2h**: R = 3-CF_3	83	90
			
9	**2i**: X = F	86	93
10	**2j**: X = Cl	88	91
11	**2k**: X = Br	94	82
			
12[d]	**2l**: R = Et	91	93
13[e]	**2m**: R = *n*-C_6H_{13}	86	89
			
14	**2n**: R = Cl	87	93
15	**2o**: R = Br	97	92
			
16	**2p**: X = F, Ar = Ph	81	91
17	**2q**: X = Cl, Ar = Ph	91	92
18	**2r**: X = H, Ar = 4-tol	89	97
			
19	**2s**: X = H	78	96
20	**2t**: X = Br	84	99

[a]All reactions were carried out with quinolines **1** (0.40 mmol), $HB(C_6F_5)_2$ (0.04 mmol), chiral diene **3k** (0.02 mmol), and H_2 (20 bar) in toluene (0.8 mL) at 40 °C for 20 h. [b]Isolated yield. [c]Determined by chiral HPLC. [d]Contained 9% stereoisomers determined by GC−MS. [e]Contained 15% stereoisomers determined by GC−MS.

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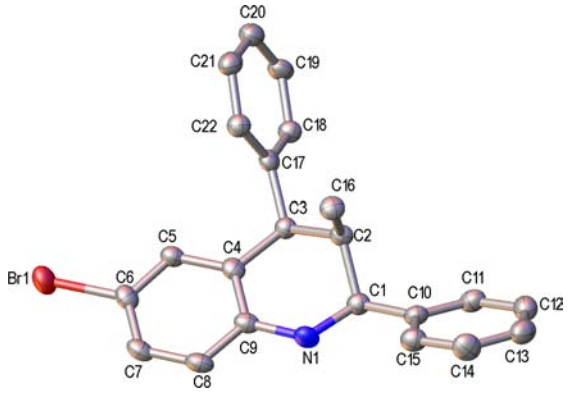

Figure 1. X-ray structure of compound (2*S*,3*R*,4*R*)-**2o**.

diene **3c** resulted in a low conversion and ee. It was found that the 3,3′-substituents on the binaphthyl framework (**3d**−**k**) had a large impact on both reactivity and enantioselectivity. Chiral diene **3i** gave 85% conversion with 84% ee. When chiral diene **3k** was used, 92% ee was obtained but only with a very low conversion.

The reaction conditions were next optimized to further improve the reactivity and enantioselectivity. Solvents had an obvious influence on this hydrogenation (Table 1, entries 1−6). CH_2Cl_2 gave a better ee but a lower conversion (Table 1, entry 2). Increasing the concentration from 0.1 to 0.5 M resulted in a quantitative conversion without loss of enantioselectivity (Table 1, entry 1 vs 6). Notably, this improvement was more significant when chiral **3k** was used (Table 1, entries 8 vs 9), and a quantitative conversion with 90% ee was obtained. Further increasing the concentration to 1.0 M gave only 82% conversion due to the incomplete dissolution of substrate (Table 1, entry 10). Reducing the catalyst loading to 5 mol % diminished the reactivity largely (Table 1, entry 12).

The metal-free asymmetric hydrogenation of a broad range of 2,3,4-trisubstituted quinolines **1** was investigated under the optimal reaction conditions. As shown in Table 2, all these reactions went efficiently to afford the desired products **2a**−**t** in 76% yields with 82−99% ee's. Various aryl substituents at the 2- or 4-positions of quinolines were well tolerant for this reaction (Table 2, entries 1−11). When quinolines bearing an ethyl or *n*-hexanyl group at the 3-position were used as substrates, products **2l,m** were obtained in high yields with 92−93% ee's (Table 2, entries 12 and 13). However, a small amount of stereoisomers was observed in these two cases. 2,3,4,6-Tetrasubstituted quinolines were also suitable substrates for this reaction to furnish tetrahydroquinolines **2n**−**r** in 81−97% yields with 91−97% ee's (Table 1, entries 14−18). The hydrogenation of quinolines containing a thiophene-yl group at the 2-position gave up to 99% ee (Table 2, entries 19 and 20). The absolute configuration of compound **2o** was determined to be 2*S*,3*R*,4*R* by its X-ray structure (Figure 1).

In summary, a highly enantioselective metal-free hydrogenation of 2,3,4-trisubstituted quinolines was successfully realized for the first time using a chiral borane catalyst generated in situ from chiral dienes. A wide range of tetrahydroquinolines containing three contiguous stereogenic centers were obtained in 76% yields with 82−99% ee's. Significantly, in most cases, only *cis*,*cis*-isomers were afforded. The current work exhibits some unique advantages of FLP catalysts on the bulky polysubstituted substrates, which may be helpful to solve some other challenging substrates in the field of hydrogenation.

■ ASSOCIATED CONTENT

Supporting Information

Procedure for the metal-free asymmetric hydrogenation of 2,3,4-trisubstituted quinolines, characterization of quinolines and products, a CIF file for the single crystal, and data for the determination of enantiomeric excesses along with the NMR spectra. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01240.

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Notes

The authors declare no competing financial interest.

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