Asymmetric Hydrogenation of Phenanthridines with Chiral Boranes

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Abstract

The asymmetric hydrogenation of N-heteroarenes provides an efficient method for the synthesis of optically active cyclic secondary amines. In this paper, we described an asymmetric hydrogenation of phenanthridines using a chiral mono-alkene-derived borane. A variety of dihydrophenanthridines were furnished in high yields with up to 93% ee. The current catalytic system was very sensitive for the steric hindrance of phenanthridines. Bulky substituents at one phenyl group of phenanthridines were required to obtain the high enantioselectivity. But large substituents adjacent to the C=N bonds would diminish the reactivity sharply.

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Asymmetric Hydrogenation of Phenanthridines with Chiral Boranes

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Keywords

Asymmetric hydrogenation | N-Heteroarenes | Phenanthridines | Frustrated Lewis pairs | Chiral boranes

Comprehensive Summary

The asymmetric hydrogenation of N-heteroarenes provides an efficient method for the synthesis of optically active cyclic sec

Background and Originality Content

Optical active 5,6-dihydrophenanthridines are important functional moieties widely presented in natural products and biologically active molecules.[1] Despite numerous reported methods, there are only limited asymmetric catalytic approaches for their synthesis have been disclosed.[2] In 2015, Lautens and co-workers described a Pd-catalyzed asymmetric homocoupling reaction of *o* -bromobenzylamines, giving 5,6-dihydrophenanthridins with up to 99% ee.[3a] Recently, Liu reported an iron-catalyzed dehydrogenative kinetic resolution of 5,6-dihydrophenanthridines.[3b] Notably, the asymmetric hydrogenation of phenanthridines stands as an atomic economy and straightforward route to access optically active 5,6-dihydrophenanthridines. A significant progress has been achieved in recent years. In 2017, Fan and co-workers disclosed a Ru-catalyzed

asymmetric hydrogenation of phenanthridines, delivering the corresponding products in excellent yields with 75–92% ee's (Scheme 1).[4a] One year later, Zhou and co-workers reported an Ir-catalyzed asymmetric hydrogenation of phenanthridines with high enantioselectivities (Scheme 1).[4b]However, to the best of our knowledge, the metal-free asymmetric hydrogenation of phenanthridines has rarely been reported.

Scheme 1 Asymmetric hydrogenation of phenanthridines

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Frustrated Lewis pairs (FLPs) has become one type of non-metallic catalysts for the catalytic hydrogenation since their seminal discovery in 2006.[5,6] Especially, the FLP-catalyzed asymmetric hydrogenation has witnessed a rapid growth over the past 15 years.[7] A wide range of unsaturated compounds containing C=N, C=O, and C=C bonds have proven to be valuable substrates for this metal-free reaction.[8] Interestingly, FLPs exhibit some unique catalytic activity and selectivity during the hydrogenation of N-heteroarenes, such as quinolines[9] and quinoxalines.[10] Strangely, phenanthridines have seldom been employed as substrates for the FLP-catalyzed hydrogenation. Herein, we wish to report our efforts on the metal-free asymmetric hydrogenation of phenanthridines with chiral boranes (Scheme 1).

Results and Discussion

Initially, we subjected 6-methylphenanthridine (**1a**) into the asymmetric hydrogenation with the use of chiral borane derived from chiral diene **3a** (Scheme 2). A 48% conversion was observed but only led to a racemic product, which might be attributed to the small steric hindrance and the little difference between the two sides of the N-ring. When a *tert* -butyl substituent was introduced at 3-position of phenanthridine (**1b**), the conversion was improved to 83% along with a 11% ee. Furthermore, when **1c** was employed as a substrate, the desired product **4c** was obtained in 83% conversion with 16% ee.

Scheme 2 Initial studies on the asymmetric hydrogenation of phenanthridines

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With **1c** as substrate, several chiral dienes were subsequently evaluated for the asymmetric hydrogenation at 40 °C (Scheme 3). Chiral diene **3b** exhibited high reactivity, but resulted in a very low ee (Scheme 3). When a bulkier chiral diene **3c** was utilized, the ee could be reached to 71%. Moreover, chiral dienes **3d** and**3e** derived boranes could also promote this reaction efficiently, but only yielded moderate ee's.

Scheme 3 The screen of chiral dienes

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To further improve the enantioselectivity, a variety of more readily available chiral monoenes **5** were also examined (Figure 1). In comparison to chiral diene **3c** , chiral monoene **5a** gave a little higher conversion. The substituents at the 3,3'-position of binaphthyl framework (**5b** -**e**) were found to influence the enantioselectivity obviously, but could not afford better results. When chiral monoene **5f** bearing two different substituents at the 3,3'-position of the chiral framework was utilized, the desired product **4a** was obtained in 91% conversion with 65% ee. The chiral framework had an impact on both reactivity and enantioselectivity. H_8-BINOL-derived chiral monoene**5g** gave a similar result with **5a** . While 1,1'-spirobiindane chiral framework (**5h**) yielded a slightly higher ee with a little drop of conversion.

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Figure 1 The screen of chiral monoenes

With the optimal chiral monoene **5a** in hand, various reaction conditions were further optimized. When the reaction temperature was lowered from 40 °C to 30 °C, the conversion was diminished dramatically from 99% to 54% with a little improved ee value (Table 1, entries 1 vs 2). Further increasing the reaction concentration could enhance the reactivity (Table 1, entry 3). Several solvents were also examined for this reaction, and benzene proved to be the optimal choice (Table 1, entries 3-9). Subsequent adjustments of temperature or concentration did not afford better results (Table 1, entries 10 and 11). When the reaction was shortened to 16 h, a quantitative conversion was also obtained along with 80% ee (Table 1, entry 12).

Table 1 Optimization of the Reaction Conditions[a] .

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Entry	Solvent	Temp. (°C)	Conv. (%)[b]	ee. (%)[c]
1[d]	toluene	40	99	74
2[d]	toluene	30	54	78
3	toluene	30	95	78
4	C_6H_5F	30	99	77
5	C_6H_5Cl	30	99	74
6	CH_2Cl_2	30	99	74
7	hexane	30	88	68
8	Et_2O	30	99	77
9	benzene	30	99	80
10	benzene	20	42	82
11[e]	benzene	20	69	82
12[f]	benzene	30	99	80

[a] All reactions were carried out with**1c** (0.1 mmol), $HB(C_6F_5)_2$ **2**(0.01 mmol), chiral alkene **5a** (0.01 mmol), and H_2 (40 bar) in solvent (0.5 mL) at 30 °C for 24 h.[b] Determined by crude ^{1}H NMR.[c] Determined by chiral HPLC.[d] With 1.0 mL solvent.[e] With 0.2 mL solvent.[f] For 16 h.

Under optimal conditions, the scope of substrates for the asymmetric hydrogenation was investigated. As illustrated in Scheme 4, a variety of electron-donating and withdrawing substituents on the phenyl motif were well tolerated for this reaction, delivering the desired dihydrophenanthridines **4c-r** in 81-96% yields with 57-93% ee's. Notably, a fluorine substituent at the 3-position of phenanthridine (**1o**) led to the corresponding product**4o** a promising 93% ee. The absolute configuration of compound**4o** was designed as *R* according to its X-ray structure analysis.[11] The absolute configuration of other analogs was tentatively assigned accordingly. When the substitution at the 6-position of phenanthridine was replaced with an ethyl group (**1s**), product **4s** was yielded with 78% ee. Furthermore, when methyl groups were used instead of *tert* -butyl groups at the 7- and 9- positions (**1t**), a decreased 23% ee was obtained. While, changing with phenyl groups, the desired product**4u** was obtained in a 94% yield and 83% ee were obtained. Unfortunately, bulky phenanthridines **1v** -**x** were still inert substrates for the current catalytic system. Further efforts on the utilization of chiral products **4** as chiral hydrogen sources for the transfer hydrogenation of various unsaturated compounds failed, which may be attributed to the bulky steric hindrances of them.

Scheme 4 Asymmetric hydrogenation of phenanthridines

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Conclusions

In summary, a metal-free asymmetric hydrogenation of 6-substituted phenanthridines was achieved by using chiral monoene derived borane catalyst. a variety of dihydrophenanthridines were obtained in 81-96% yields with up to 93% ee. The obvious difference between the two sides of the N-ring was required to give reasonable reactivity and enantioselectivity. However, the bulky substituents at the 6-position would inhibit the reaction. Further efforts on searching for more effective chiral catalyst and expanding their application in asymmetric reactions are underway in our laboratory.

Experimental

Typical procedure for the asymmetric hydrogenation of phenanthridine 1c : To a glass test tube (10 mL) in a nitrogen atmosphere glovebox, $HB(C_6F_5)_2$ (**2**) (13.8 mg, 0.04 mmol), chiral alkene **5a** (28.0 mg, 0.04 mmol), and dry toluene (2.0 mL) were added. The resulting mixture was stirred at room temperature for 5 min, followed by the addition of phenanthridine **1c** (122.2mg, 0.4 mmol). Then the tube was moved to a stainless-steel autoclave, and the autoclave was purged three times with H_2 and the final pressure of H_2 was adjusted to 40 bar. The reaction was stirred at 40 °C for 16 h. The solvent was removed under reduced pressure, and the crude residue was purified by flash chromatography on silica with petroleum ether/ethyl acetate (20/1) to afford dihydrophenanthridine **4c** as a white solid (112.2 mg, 91% yield, 80% ee).

Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.2023xxxxx.

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Asymmetric Hydrogenation of Phenanthridines with Chiral boranes Guangyu Cui, Xiangqing Feng,* and Haifeng
A metal-free asymmetric hydrogenation of phenanthridines was successfully accomplished by using a chiral monoene-derived