

Highly Enantioselective Hydrosilylation of Ketones Catalyzed by a Chiral Oxazaborolidinium Ion

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Supporting Information

ABSTRACT: A highly enantioselective hydrosilylation of ketones was developed for the synthesis of a variety of chiral secondary alcohols. In the presence of a chiral oxazaborolidinium ion (COBI) catalyst, the reaction proceeded with good yields (up to 99%) with excellent enantioselectivities (up to 99% ee).

C hiral secondary alcohols are useful building blocks for the synthesis of natural products and pharmaceuticals.¹ The enantioselective reduction of prochiral ketones, such as asymmetric hydrogenation,² hydroboration,³ and hydrosilylation,⁴ is one of the most efficient synthetic methods to produce chiral alcohols. Among them, asymmetric hydrosilylation of ketones has emerged as an attractive synthetic method to afford chiral secondary alcohols due to the mild conditions and operational simplicity. Transition-metal-catalyzed asymmetric hydrosilylations of ketones based on noble metals such as Rh, Co, and Ir are well established.⁵ Recently, due to the high cost and toxicity of the noble metals, many efforts have been devoted to the development of environmentally friendly coin metal catalysts, such as Fe, Zn, and Cu complexes, for asymmetric hydrosilylations of ketones.⁶

Another main type of hydrosilylation is the Piers metal-free hydrosilylation reaction.⁷ In 1996, the Piers group developed a fascinating $B(C_6F_5)_3$ -catalyzed hydrosilylation of carbonyl compounds.8 A peculiar mechanism9 of this reaction is that Si-H bonds are activated by boron Lewis acid which attracts the interest of organic chemists and is a fast-growing field.¹⁰ However, the asymmetric version of Piers type hydrosilylation is still in the early stages of development. The first asymmetric Piers hydrosilylation was reported by Oestreich and co-workers in 2008.9e They used a chiral silane for hydrosilylation of acetophenone and obtained chiral alcohol with 38% ee. Several examples of asymmetric hydrosilylation of imines^{10e,j} were reported, while reports regarding carbonyl compounds are somewhat rare. To the best of our knowledge, only two examples of highly enantioselective, boron-catalyzed hydrosilvlation of carbonyl compounds exist. In 2016, Du and coworkers reported enantioselective hydrosilylation of 1,2dicarbonyl compounds by using an in situ generated frustrated Lewis pair (FLP) catalyst system (Figure 1, eq 1).^{11a} Unfortunately, this catalytic system was not effective in acetophenone hydrosilylation (42% ee).^{11a} The Oestreich group reported asymmetric hydrosilylation of acetophenones by using the 3,3'-disubstituted binaphthyl backbone of a borane





Figure 1. (1) Asymmetic hydrosilylation of 1,2-dicarbonyl compounds catalyzed by FLP. (2) Asymmetric hydrosilylation with acetophenones.(3) Asymmetic hydrosilylation of ketones with COBI catalyst.

catalyst without the assistance of an additional Lewis base (Figure 1, eq 2).^{11b} However, only for acetophenone and halogen or ester substituted derivatives, ee values for the resulting secondary alcohols of >93% were obtained. A limited substrate scope, low yields, and enantioselectivities have necessitated the development of new catalytic, enantioselective methods.

Recently, our group reported highly enantioselective carbonyl addition reactions catalyzed by chiral oxazaborolidinium ion $(COBI)^{12}$ as a Lewis acid catalyst. Especially, enantioselective cyanosilylation of ketones^{12f} was successfully developed, and

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there is substantial evidence for the formation of a complex between COBI and ketones. We anticipated that COBI would be a suitable Lewis acid catalyst for the enantioselective hydrosilylation of ketones and an alternative to the powerful Corey–Bakshi–Shibata (CBS) reduction.^{3,12a} The borane reagents for CBS reduction have disadvantages such as stability, high volatility, flammability, and a significant decrease of enantioselectivity by impurities.^{3a} Herein, we describe the successful development of the catalytic, enantioselective hydrosilylation reaction of ketones by using a boron Lewis acid catalyst to obtain highly optically active secondary alcohols.

Initially, an asymmetric hydrosilylation reaction between dimethylphenylsilane and acetophenone was examined in the presence of 20 mol % of COBI catalyst 1 activated by triflic acid. The reaction was carried out at room temperature in toluene and quenched with MeOH/K₂CO₃ (saturated) after completion of the reaction. First, we screened the catalyst structure and found that the catalyst system with a 3,5-dimethylphenyl Ar substituent and 2-methoxyphenyl R substituent, activated by triflic acid, gave the best result in 89% yield, 98% ee (Table 1, entries 1–6). When the COBI

Table 1. Optimization of the Asymmetric Hydrosilylation of Acetophenone a



^{*a*}The reaction of silanes (1.38 mmol) with acetophenone (0.46 mmol) was performed in the presence of **1** (20 mol %), in 0.46 mL of solvent at room temperature. ^{*b*}Isolated yield of **3a**. ^{*c*}The *ee* of **3a** was determined by chiral HPLC.

catalyst was activated by triflic imide, dimethylphenylsilane did not react with acetophenone (entry 4). It is probable that the role of the triflate ion is to activate the Si atom by anionic coordination to give a pentacoordinate Si in which the Si–H bond is weakened.^{13,14} In the COBI catalyst system, the 2methoxyphenyl substituent of boron appeared to be superior to the pentafluorophenyl substituent (Table 1, entries 5 and 6).^{7,9d,11a,b} Additional studies focused on the changes of hydrosilanes. Bulkier diphenyl-substituted hydrosilanes had a low reactivity (entries 7–8). On the other hand, trihydrogensubstituted phenylsilane had the highest reactivity, completing the reaction in 20 min (entry 9). However, dimethylphenylsilane showed the best result in terms of yield and enantioselectivity (entries 5-9).

With the optimized reaction conditions for the catalytic asymmetric hydrosilylation reaction in hand, we evaluated this method with a range of substituted acetophenones (Table 2).

Table 2. Asymmetric Hydrosilylation of Various Acetophenones^a

| PhMe ₂ SiH | + | O cat. 1e (20 mol %) MeOH/K ₂ CO ₃ | | | ŌН |
|-----------------------|----|---|----------|------------------------|---------------------|
| | | Ar CH ₃ rt, t | oluene | 2 h | Ar CH ₃ |
| | | | | | 2 |
| entry | 2 | Ar | time (h) | yield (%) ^b | ee (%) ^c |
| 1 | 2a | Ph | 6 | 89 | 98 |
| 2 | 2b | $4-MeC_6H_4$ | 13 | 94 | 96 |
| 3 | 2c | 4-MeOC ₆ H ₄ | 40 | 53 | 88 |
| 4 ^{<i>d</i>} | 2d | $4-BrC_6H_4$ | 3 | 97 | 99 |
| 5 | 2e | 4-ClC ₆ H ₄ | 3 | 98 | 99 |
| 6 | 2f | $4-CF_3C_6H_4$ | 2 | 89 | 90 |
| 7 | 2g | $4-CNC_6H_4$ | 2 | 93 | 96 |
| 8 ^e | 2h | $4-NO_2C_6H_4$ | 2 | 99 | 99 |
| 9 | 2i | $2 - MeC_6H_4$ | 4 | 95 | 85 |
| 10 | 2j | 2-ClC ₆ H ₄ | 13 | 98 | 99 |
| 11 | 2k | 1-naph | 1 | 99 | 96 |
| 12 | 21 | 2-naph | 17 | 99 | 97 |
| 13 | 2m | 2-furyl | 13 | 65 | 94 |
| 14 | 2n | 2-thienyl | 1 | 86 | 92 |
| | | | | | |

^{*a*}The reaction of dimethylphenylsilane (1.38 mmol) with acetophenones (0.46 mmol) was performed in the presence of **1e** (20 mol %), in 0.46 mL of toluene at room temperature. ^{*b*}Isolated yield of **3**. ^{*c*}The *ee* of **3** was determined by chiral HPLC. ^{*d*}1.8 mmol of 4′-bromoacetophenone was used. ^{*e*}10 mol % of catalyst **1e** was used.

Regardless of the electronic properties of substituents on the acetophenones, highly optically active secondary alcohols 2 were obtained (Table 2, entries 2–9). However, strong electron-donating methoxy substituted acetophenone resulted in a moderate yield of product (entry 3). This catalytic system was also successfully applied to reactions of various aromatic ketones such as naphthyl, furyl, and thienyl (entries 11-14).

Encouraged by the good results exhibited in Table 2, we applied this catalytic asymmetric hydrosilylation method to reactions of a range of ketones. Since the 4-bromo group in the product of entry 4 in Table 2 is easily replaced by a large variety of other substituents using Pd(0) catalysis, 4-bromophenyl alkyl ketones were selected as the reactants. As summarized in Scheme 1, the reactions produced the corresponding chiral secondary alcohols 2 in good yields and high enantioselectivities. It is notable that this method was successfully applied to the dialkyl ketone substrates to generate chiral secondary alcohols 2t and 2u. Interestingly, pyruvic aldehyde dimethyl acetal gave the deoxygenated^{7a,15} product 2u in high yield.

While the Piers type borohydride mechanism⁹ cannot be ruled out, the observed stereochemistry for the catalytic hydrosilylation reaction using COBI catalyst **1e** can be rationalized using the transition state model shown in Figure 2. The mode of coordination of acetophenone to **1e** is the same as has been previously observed in enantioselective cyanosilylation.^{12f} In the pretransition-state assembly **3**, shown in Figure 2, the acetophenone group is situated above the *m*-xylyl group, which effectively shields the *re* face (back) from attack by the dimethylphenylsilane, which is activated by the triflate anion. Additionally, a $\pi - \pi$ interaction¹⁶ between the aryl ring of the

Scheme 1. Asymmetric Hydrosilylation of Various Ketones^a



^{*a*}The reaction of dimethylphenylsilane (1.38 mmol) with ketones (0.46 mmol) was performed in the presence of 1e (20 mol %), in 0.46 mL of toluene at room temperature. ^{*b*}Isolated yield of 2. ^{*c*}The *ee* of 2 was determined by chiral HPLC and GC. ^{*d*}4'-Bromophenacyl bromide was used as starting material. ^{*e*}Reaction time is 36 h. ^{*f*}Yield was measured by GC. ^{*g*}Pyruvic aldehyde dimethyl acetal was used as



Figure 2. Transition state model for the asymmetric hydrosilylation of acetophenone catalyzed by 1e.

acetophenone with the dimethylphenylsilane aryl group holds the two aryl rings together. Nucleophilic addition of the dimethylphenylsilane from the *si* face (front) of the acetophenone leads to intermediate **4**. After deprotection of the silyl group, chiral secondary alcohol **2a** was obtained as the major enantiomer. Comparisons of the optical rotation data with literature values confirmed the absolute (R) stereochemistry of products.

We have presented the first boron-catalyzed asymmetric hydrosilylation that gives rise to ee values greater than 90% for a broad range of aryl alkyl ketones. This mild and enantioselective reaction provides access to a variety of chiral secondary alcohols in good yields as well as high to excellent enantioselectivities. The absolute configuration of the major product was the same as that predicted by the transition-state model in Figure 2. Further investigations concerning the mechanism of this reaction as well as the extension of the scope are in progress in our laboratory.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.or-glett.7b03076.

Experimental procedures, full analytical data (PDF)

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Notes

The authors declare no competing financial interest.

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