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Asymmetric 1,2-Reduction of Enones with Potassium Borohydride Catalyzed by Chiral *N,N′*-Dioxide–Scandium(III) Complexes

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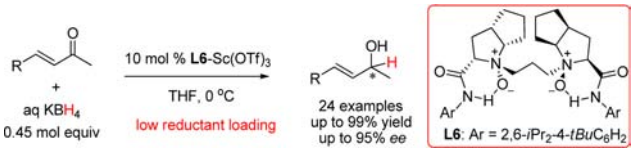
ABSTRACT



The first catalytic enantioselective 1,2-reduction of enones with 0.45 mol equiv potassium borohydride solution catalyzed by a chiral *N,N′*-dioxide–Sc(III) complex catalyst was accomplished under mild reaction conditions. A number of optically active allylic alcohols were obtained in good to excellent enantioselectivities (up to 95% ee) with nearly quantitative yields.

The enantioselective reduction of prochiral ketones provides the most efficient access to optically active secondary alcohols. It has been successfully achieved with a wide variety of reducing agents.[1] Alkali metal borohydrides are valuable and commonly used reducing agents in organic chemistry.[2] They take advantage of safety with regards to use, storage and handling, commercial availability, and cheapness, as well as efficiency for reducing different functional groups with chemo-, regio-, and diastereoselectivities.[3] Modification of metal borohydrides with chiral amino alcohols,[4] monosaccharide derivatives,[3b,5] and carboxylic acids[6] was explored to realize asymmetric reduction. However, stoichiometric amounts of chiral ligands and reductant were required with varying degrees of enantioselectivity.[7] The use of a chiral cobalt hydride (Co–H) species for the reduction of chromanone derivatives, which was generated from optically (β-oxoaldiminato)cobalt(II) complexes and $NaBH_4$, was reported by Mukaiyama and co-workers.[8,9] Zhao′s group developed a polymer-supported

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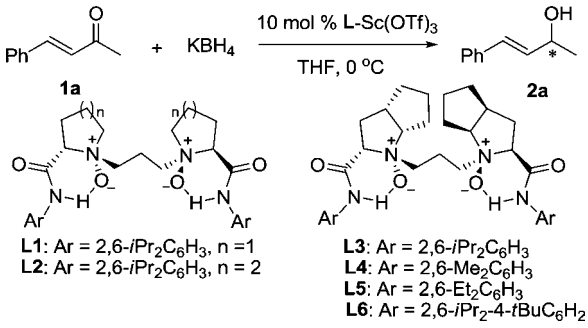
chiral sulfonamide catalyst for the asymmetric reduction of ketones by treating $NaBH_4$ with Me_3SiCl or $BF_3 \cdot OEt_2$ to generate diborane.[10] Nonetheless, the utilization of simple chiral Lewis acid complexes for asymmetric metal borohydride reduction has not been reported. The studies are handicapped probably due to the low solubility of metal borohydrides in an aprotic solvent and background reaction.[3a] Therefore, the development of a highly efficient and wet-tolerant chiral catalyst is desirable.

Chiral allylic alcohols are key structural subunits of numerous natural and unnatural products with a wide range of biological activities.[11] The enantioselective 1,2-reduction of α,β-unsaturated ketones is one of the most efficient strategies for their construction.[12] However, it is generally complicated by competing 1,2 and 1,4 processes.[13] Chemoselective 1,2-reduction of α-enones with $NaBH_4$ in combination with lanthanoid chlorides was reported early in 1978.[14] Nonetheless, the catalytic asymmetric version has not been realized yet.[15] Herein, we reported the first catalytic enantioselective reduction of prochiral enones and ketones by employing potassium borohydride (KBH_4) as the reducing agent. In the presence of a chiral *N,N′*-dioxide−scandium(III) complex catalyst,[16] the reaction performed well with 0.45 mol equiv of KBH_4 aqueous solution under mild reaction conditions.

Table 1. Optimization of the Reaction Conditions[a]



entry	ligand	additive[b]	yield (%)[c]	ee (%)[d]
1	**L1**		41	40
2	**L2**		58	48
3	**L3**		75	67
4	**L4**		55	33
5	**L5**		70	48
6	**L3**	H_2O	99	74
7	**L3**	CH_3OH	64	55
8	**L3**	EtOH	49	52
9	**L3**	*i*PrOH	67	60
10[e]	**L3**		99	80
11[e]	**L6**		99	90
12[e,f]	**L6**		80	85
13[e,g]	**L6**		99	89
14[e,h]	**L6**		68	82
15[e,i]	**L6**		99	89
16[e,j]	**L6**		99	77

[a] Unless otherwise noted, all reactions were performed with ligand (10 mol %), $Sc(OTf)_3$ (10 mol %), **1a** (0.10 mmol), KBH_4 solid (0.12 mmol) in THF (1.2 mL) at 0 °C for 2 h. [b] 20 μL additives were added. [c] Isolated yield. [d] Determined by HPLC analysis (Chiralcel IB). [e] 22.5 μL of 2 mol/L KBH_4 aqueous solution were used (0.045 mmol of KBH_4) at 0 °C for 1.5 h. [f] 15.0 μL of 2 mol/L aq KBH_4 (0.030 mmol of KBH_4). [g] 30.0 μL of 2 mol/L aq KBH_4 (0.060 mmol of KBH_4). [h] The reaction was performed at 35 °C. [i] The reaction was performed at −20 °C. [j] 22.5 μL of 2 mol/L $NaBH_4$ aqueous solution were used (0.045 mmol of $NaBH_4$).

In the initial study, (*E*)-4-phenylbut-3-en-2-one **1a** and KBH_4 were chosen as the substrate and reductant, respectively. The reaction was performed in THF at 0 °C with 10 mol % of chiral *N,N′*-dioxide−scandium(III) complexes, generating allylic alcohol **2a** as the sole product (Table 1). The structure of the ligand was optimized first. As for the amino acid backbone, L-ramipril derived *N,N′*-dioxide **L3** was superior to both **L1** (derived from L-proline) and **L2** (derived from L-pipecolic acid) (Table 1, entry 3 vs entries 1 and 2). Meanwhile, steric hindrance of the amide moiety of the ligand played a key role in promoting the enantioselectivity of the reaction (Table 1, entry 3 vs entries 4 and 5). An array of protic additives (Table 1, entries 6−9) were surveyed to distinguish which one(s) may exert steric and electronic influences upon the reactivity of the substituted complex ion from metal borohydride.[14b,17] Interestingly, when a small amount of water was added, the reduction rate was dramatically

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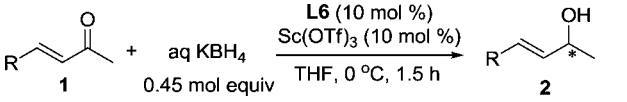
accelerated with a complete conversion. And the ee value was increased to 74% (Table 1, entry 6). Other protic additives, such as CH_3OH, EtOH, and *i*PrOH, which were commonly used as solvents in the reduction with $NaBH_4$, delivered the products with poor results (Table 1, entries 7−9). These results prompted us to investigate the optimal reaction conditions in the presence of water. To our delight, when the aqueous solution of KBH_4 was used instead of the use of a solid reductant and water additive separatively, the reaction performed in a homogeneous catalyst system. The loading of KBH_4 could be decreased to 0.45 mol equiv, and the chiral allylic alcohol was obtained in excellent yield with 80% ee (Table 1, entry 10). Remarkably, when the highly sterically demanding ligand **L6** was employed, 90% ee and 99% yield were achieved (Table 1, entry 11 vs 10). Further screening of the amount of reductant and reaction temperature resulted in no better outcomes (Table 1, entries 12−15). When the $NaBH_4$ aqueous solution was used, the enantioselectivity slightly decreased (Table 1, entry 16).

The utility of this reducing system was further explored with the reduction of structurally different α,β-unsaturated ketones by using 0.45 mol equiv of KBH_4 aqueous solution (Table 1, entry 11). Such asymmetric 1,2-reductions were also efficient to provide the corresponding chiral allylic alcohols **2** in excellent yields and good to excellent enantioselectivities within 1.5 h (Table 2). The electron-withdrawing groups on the aromatic ring of enones **1h**−**1k** led to some loss of enantioselectivity due to the competition of the background reaction (Table 2, entries 1−7 vs 8−11). The disubstituted α,β-unsaturated ketones with electron-donating groups were also good substrates and afford the chiral allylic alcohols in 90−94% ee (Table 2, entries 12−14). The substrate with a β-cinnamyl group still gave an excellent yield with 90% ee (Table 2, entry 15). It was noteworthy that the reaction could also be extended to fused-ring and heteroaromatic enones, affording the products in excellent yields with 85%−90% ee (Table 2, entries 16−18). Moreover, when β-ionone was used, the allylic alcohol **2s**, which could be used for spices in food and cosmetics,[18] was formed exclusively in 90% ee (Table 2, entry 19).

Next, the catalytic system was expanded to the reduction of saturated ketones under the defined conditions (Scheme 1). By prolonging the reaction time to 8 h, the chiral secondary alcohol products were isolated in moderate to good enantioselectivities with quantitative yields. Indan-1-one **1v** incorporating a five-membered ring was a suitable substrate for the reaction, delivering the product **2v** with 86% ee.

To show the synthetic utility of the catalyst system, the reduction of (*E*)-4-phenylbut-3-en-2-one **1a** was expanded to a gram scale. As shown in Scheme 2, the product could be isolated in 99% yield with 89% ee. After a simple recrystallization, the enantioselectivity increased to 99% ee with a 75% yield. Notably, the allylic alcohol **2a** could be easily transformed into the epoxy alcohol **3a**, which is a valuable and versatile intermediate in organic synthesis.[19] Furthermore, hydrogenation of **2a** smoothly generated

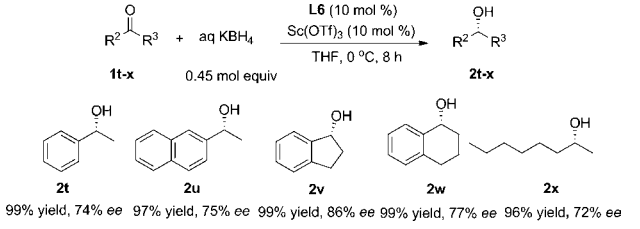
Table 2. Substrate Scope of the Asymmetric Reduction of Enone[a]



entry	R	product	yield (%)[b]	ee (%)[c]
1	Ph	**2a**	99	90 (*R*)
2	3-MeC_6H_4	**2b**	99	90 (*R*)
3	2-$MeOC_6H_4$	**2c**	99	95 (*R*)
4	3-$MeOC_6H_4$	**2d**	99	90 (*R*)
5	4-$MeOC_6H_4$	**2e**	99	90 (*R*)
6	4-PhC_6H_4	**2f**	99	88
7	4-$BnOC_6H_4$	**2g**	99	94 (*R*)
8	4-FC_6H_4	**2h**	99	88 (*R*)
9	4-ClC_6H_4	**2i**	99	86 (*R*)
10	4-BrC_6H_4	**2j**	99	85 (*R*)
11	3-$CF_3C_6H_4$	**2k**	99	81 (*R*)
12		**2l**	99	94
13		**2m**	99	93
14		**2n**	99	90 (*R*)
15		**2o**	99	90
16	2-naphthyl	**2p**	99	90
17	2-furyl	**2q**	99	90
18[d]		**2r**	90	85
19[d]		**2s**	97	90

[a] Unless otherwise noted, all reactions were performed with the ligand **L6** (10 mol %), $Sc(OTf)_3$ (10 mol %), enones **1** (0.1 mmol), 22.5 μL of 2 mol/L KBH_4 aqueous solution in THF (1.2 mL) at 0 °C for 1.5 h. [b] Isolated yield. [c] Determined by HPLC analysis. The absolute configuration was determined by comparison with the reported optical rotation or CD spectra with **3a** (see the Supporting Information). [d] Reaction time was 5 h.

Scheme 1. Scope of Saturated Ketones in the Catalytic Asymmetric Reduction Reaction



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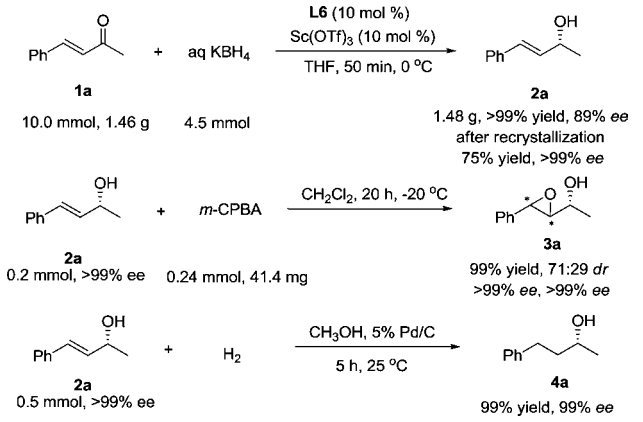
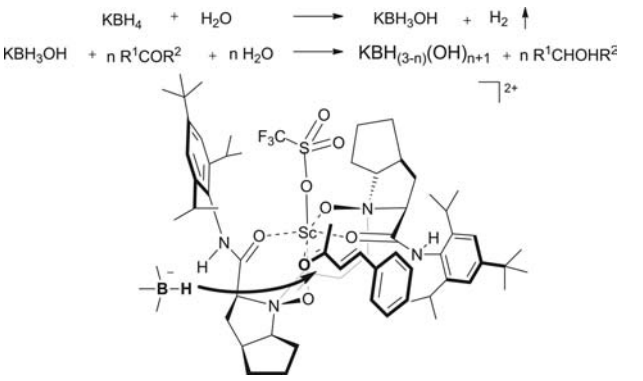
Scheme 2. Synthetic Utility of the Catalyst System



Scheme 3. Proposed Mechanism of the Catalytic Asymmetric 1,2-Reduction of (*E*)-4-Phenylbut-3-en-2-one **1a**



4-phenyl-butan-2-ol **4a** in excellent yield (99%) without any loss of enantioselectivity, which is an important intermediate for the synthesis of antitumor compounds.[20]

We next try to shed light on the function of H_2O in this catalytic asymmetric reduction. First, direct proof of the critical reductant species in the reaction mixture was confirmed by HRMS spectra experiments.[21] The spectrum of the sample by treating KBH_4 with H_2O revealed ions at m/z 92.9890 (MS ES+) and 68.9915 (MS ES−), which corresponded to $[KBH_3OH + Na^+]$ and KBH_3O^-. It suggested that the initial reducing species was KBH_3OH, generated from the reaction of KBH_4 and H_2O (Scheme 3). The comparative experiments verified the hydrogen source of the reduction. The use of 0.45 and 0.30 mol equiv of KBH_4 gave 99% and 80% isolated yields, respectively (Table 1, entries 11 and 12). Deuterium labeling experiments were performed to elucidate the source of the hydrogen atom of the products.[21] These results indicated that the reductant could provide no less than 2 equiv of hydrogen ions for the reaction in this case. The monosubstituted species BH_3OR^- (R = alkoxy or H) was found to be more reactive than BH_4^- (Table 1, entry 10 vs 3).[14b,17,22] The presence of water could also benefit proton transfer to accelerate the catalytic cycle. Additionally, the existence of water enhanced the solubility of the reductant and the reaction could be carried out in a homogeneous system.

In light of the sluggish reaction rate of enone **1a** at 0 °C without the scandium complex catalyst, the activation of enone was crucial for the initiation of the reaction. On the basis of the experimental results and the structure of the Sc^{III}–*N,N*′-dioxide complex,[16a] a possible catalytic process was proposed in Scheme 3. The enone coordinated with the **L6**–$Sc(OTf)_3$ catalyst form the intermediate. The *Re* face of activated enone **1a** was shielded by the rear bulky amide moiety of the ligand. Subsequently, the H^- ion of the reducing species attacked from the *Si* face of carbonyl group, followed by a quick protonation of the oxygen ion with water to generate the desired product (*R*)-**2a**.

In summary, we have developed the first catalytic enantioselective 1,2-reduction of enones and ketones employing 0.45 mol equiv KBH_4 as the reductant catalyzed by a *N,N*′-dioxide–scandium(III) complex under mild reaction conditions. A number of optically active allylic alcohols were obtained in good to excellent enantioselectivities (up to 95% ee) and quantitative yields within a short reaction time. The catalytic system features a convenient operation, a low amount of the reductant, and air and moisture tolerance. Further studies of the application of the catalyst to other reduction reactions are underway.

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Supporting Information Available. Experimental procedures, spectral and analytical data for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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(21) For details, see the Supporting Information.

(22) The use of alcohols is unfavorable for both the yield and the enantioselectivity. The species generated from alcohol and KBH_4 is varied which is less reactive for the reduction. Additionally, the interaction between the substrate and metal center might be intervened by preferential binding of alcohols.