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To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.202100856

Link to VoR: https://doi.org/10.1002/ejoc.202100856

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European Journal of Organic Chemistry 10.1002/ejoc.202100856

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COMMUNICATION

Cobalt-Catalyzed Asymmetric 1, 4-Reduction of *β,β*-Dialkyl *α,β*-Unsaturated Esters with PMHS

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A cobalt-catalyzed asymmetric reduction of *β,β*-dialkyl *α,β*-unsaturated esters with PMHS was reported to deliver the corresponding esters containing a chiral trialkyl carbon center at *β*-position with up to 97% yield and 98% *ee*. The chiral tridentate ligand oxazoline iminopyridine OIP could perform well for the asymmetric reduction instead of chiral bidentate ligands. This operationally simple protocol shows a broad scope of substrates using one equivalent of readily available PMHS as a cheap and easy-to-handle reductive reagent.

Introduction

The compounds containing chiral trialkyl carbon center are essential constituents of pharmaceuticals and natural products, and also play an important role in organic synthesis (Figure 1).[1] There are several useful methods for the construction of chiral trialkyl carbon centers, including asymmetric addition,[2] cross-coupling,[3] hydrogenation,[4] reduction,[5] and so on.[6] During the last few decades, the asymmetric hydrogenation or reductions of *α,β*-unsaturated acids or esters enabled by some noble metals such as ruthenium catalysts with chiral diphosphine ligands,[7] rhodium catalysts with chiral phosphorus or nitrogen containing ligands,[8] and iridium catalysts with chiral P,O- and P,N-ligands[9] have been successfully documented (Scheme 1a). The 3d metals have been gradually paid increasing attention due to earth-abundance.[10] The asymmetric hydrogenation is an ideal strategy in industry. However, the use of high-pressure hydrogen brings safely hazard in the laboratory. Compared to asymmetric hydrogenation, asymmetric reduction is more operationally simple in the laboratory.

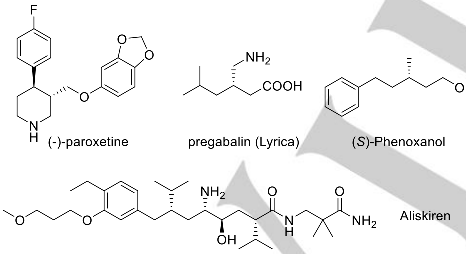
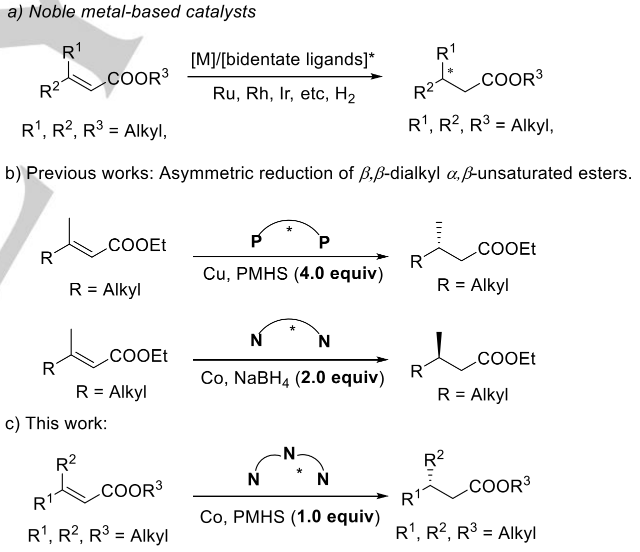


Figure 1. Potential synthetic applications of the asymmetric hydrogenation reduction of *β,β*-dialkyl *α,β*-unsaturated esters.

The asymmetric reduction of *β,β*-dialkyl *α,β*-unsaturated esters are generally required for good results. In 1999, Buchwald et al. found the copper with chiral diphosphine ligands could catalyze the asymmetric reduction with four equivalents of polymethylhydrosiloxane (PMHS) typically to afford the corresponding products with 80-92% *ee*.[11] Later, Lipshutz et al. explored another chiral diphosphine ligands (SEGPHOS and JOSIPHOS) could also be suitable for copper-catalyzed asymmetric reduction of *β,β*-dialkyl *α,β*-unsaturated esters with two equivalents of PMHS.[12] In 1989, Pfaltz et al. first reported a highly effective cobalt catalysts with chiral bidentate N,N-ligands for the asymmetric reduction of *β,β*-dialkyl *α,β*-unsaturated esters with two equivalents of sodium borohydrides to afford chiral products with up to 97% yield and 96% *ee* (Scheme 1b).[13] However, over stoichiometric amounts of reductive reagents have been used, and these systems suffer from limited by the stability and modification site of the catalyst, the practical application of these reactions is limited. Theoretically, when the 1,4-reductions with hydrosilane or hydroborane occur, only one equivalent of hydrosilane or hydroborane is needed to form the silyl enols or boronic enols as the intermediates. Herein, we reported a tridentate ligand-promoted cobalt-catalyzed[14] asymmetric reduction of *β,β*-dialkyl *α,β*-unsaturated esters with one equivalent of PMHS under mild conditions (Scheme 1c).

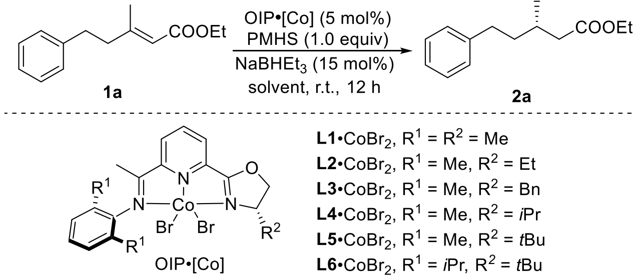
Scheme 1. Asymmetric 1, 4-reduction of *β,β*-dialkyl *α,β*-unsaturated esters.



Results and Discussion

We initiated our study on the reaction of ethyl (*E*)-3-methyl-5-phenylpent-2-enoate **1a** as a model substrate and PMHS as a hydrogen source. The reaction of **1a** in the presence of 5 mol% of **L1**·$CoBr_2$[15] and 15 mol% of $NaBHEt_3$ as an activator in a solution of THF at room temperature could afford the desired product **2a** in 95% conversion with 87% *ee* (entry 1, Table 1). With the increased steric hindrance of the group on oxazoline (Et, Bn, *i*Pr, and *t*Bu), yields of **2a** were changed slightly; however, enantioselectivities were increased from 87% to 96% (entries 2–6). When the more sterically hindered 2, 6-diisopropyl-aniline-derived ligand **L6** was used, the conversion and enantioselectivities of **2a** showed decrease to a certain degree. When diethyl ether, 1, 4-dioxane, and toluene were used as solvents, no better results were obtained (entries 7–9).

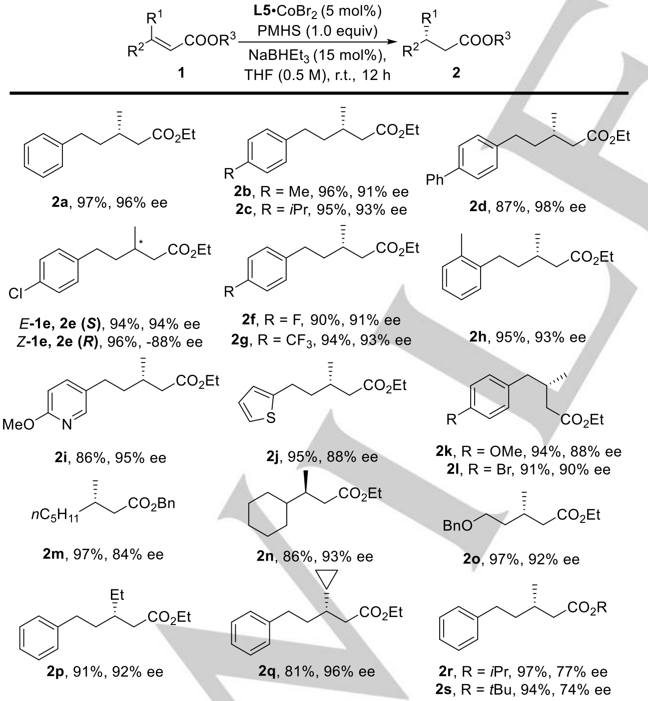
Table 1. Optimizations[a].



entry	OIP•[Co]	solvent`	conv.[b] (%)	*ee*[c] (%)
1	**L1**•CoBr$_2$	THF	95	87
2	**L2**•CoBr$_2$	THF	99	87
3	**L3**•CoBr$_2$	THF	95	88
4	**L4**•CoBr$_2$	THF	99	92
5	**L5**•CoBr$_2$	THF	>99	96
6	**L6**•CoBr$_2$	THF	72	90
7	**L5**•CoBr$_2$	Et$_2$O	99	95
8	**L5**•CoBr$_2$	1,4-dioxane	74	95
9	**L5**•CoBr$_2$	toluene	72	87
10 [d]	**L5**•CoBr$_2$	THF	>99	92

[a] The reaction was conducted using **1a** (0.25 mmol) in solvent (0.5 mL) under N$_2$ for 12 h; [b] Determined by ^{1}H NMR. [c] Determined by HPLC analysis. [d] 2 mol% of precatalyst was used.

Scheme 2. Substrate Scope[a]



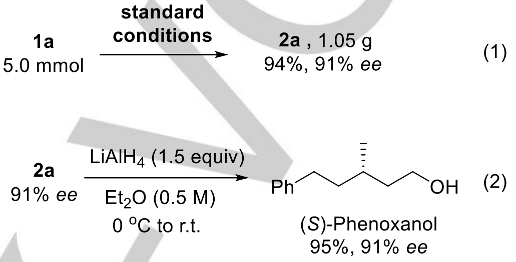
[a] Reaction conditions: **1** (0.25 mmol), **L5**•CoBr$_2$ (5 mol%), PMHS (1.0 equiv), and NaBHEt$_3$ (15 mol%), THF (0.5 M) at r.t. under N$_2$ for 12 h; isolated yield and *ee* values were determined by Chiral HPLC.

When the catalyst loading was decreased to 2 mol%, **2a** could also be obtained in >99% conversion with 92% *ee* (entry 10).

With the optimized reaction conditions in hand, the substrate scope has been explored in Scheme 2. The absolute configuration of the products was established by comparison of its optical rotation with previous reports.[12] The reactions of substrates bearing electron-donating group could afford **2b** and **2c** in 95–96% yields with 91–93% *ee*, respectively. Substrates bearing electron-withdrawing group on the phenyl group were also suitable for the reaction to give the products **2d**-**2g** in 87–94% yields with 91–98% *ee*. The asymmetric reduction of (*Z*)-**1e** was examined to give (*R*)-**2e** with -88% *ee*. Furthermore, heterocycles, such as pyridine and thiophene, could be tolerated this transformation. The influence of different carbon chain length of *α,β*-unsaturated esters was studied to afford **2k**, **2l**, and **2m** in 91–97% yields with 84–90% *ee*. The (*E*)-2-cyclohexylhept-2-en-4-one (**1n**) could participate well to afford **2n** in 86% yield with 93% *ee*. Substrate with ether was also converted to the corresponding product **2o** in 97% yield with 92% *ee*. When the steric hindrance of the alkyl chain was increased, **2p** and **2q** were obtained in 91% and 81% yield with 92% and 96% *ee*, respectively. The method also works efficiently for substrates bearing sterically bulky esters to furnish the chiral products **2r** and **2s** in 97% and 94% isolated yield, albeit with a slightly lower ee (77% and 74% ee).

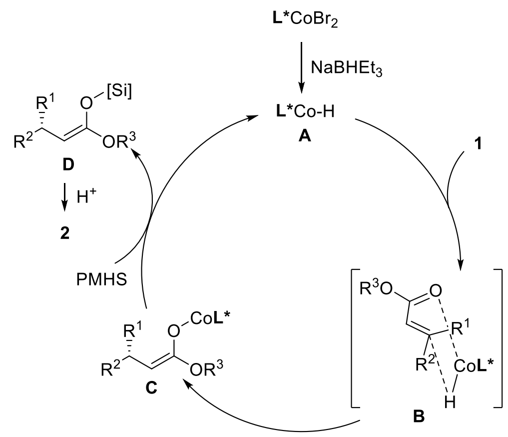
A gram-scale reaction of **1a** was carried out to afford the **2a** in 94% yield with 91% *ee*. **2a** could be easily derivatized to phenoxanol which is a rose fragrance widely used in fragrance compound and household toiletries (Scheme 3).[16]

Scheme 3. Gram-Scale Reaction and Synthetic Application.



Based on the previously reported literatures,[11] a plausible mechanism was proposed in Scheme 4. First, the precatalyst OIP•CoBr$_2$ could be reduced by NaBHEt$_3$ to form cobalt hydride species A. Then the *β,β*-dialkyl *α,β*-unsaturated ester could coordinate with species A followed by the insertion into a Co–H bond to generate species C via a possible six-membered ring intermediate B. Due to the lack of formation of six-membered ring intermediate, the reaction of unsaturated lactones afforded chiral lactones with lower *ee*. The cobalt enolate species C could react with PMHS via σ-bond metathesis to afford a silyl enolate D and regenerate the cobalt hydride species. Subsequently, the desired product was obtained by the hydrolysis of D in the quenching step.

Scheme 4. Proposed Mechanism.



Conclusion

In conclusion, we reported a cobalt-catalyzed asymmetric reduction of *β,β*-dialkyl *α,β*-unsaturated esters to access the corresponding esters containing a chiral carbon trialkyl center at *β*-position with up to 97% yield and 98% *ee*. The tridentate ligand with small imine group was found as a suitable chiral ligand for this transformation. The readily available PMHS, as a cheap, safe, and easy-to-handle hydrogen source, has been used with one equivalent as a reductive reagent.[17] Further studies on earth-abundant transition metal-catalyzed asymmetric reduction reactions will be continuing undergoing.

Acknowledgements

Financial support was provided by NSFC (21922107 and 21772171), Zhejiang Provincial Natural Science Foundation of China (LR19B020001), Center of Chemistry for Frontier Technologies, and Key Laboratory of Organosilicon Chemistry and Material Technology of Ministry of Education, Hangzhou Normal University (KFJJ2020001).

Conflict of Interest

The authors declare no conflict of interest.

Keywords: Cobalt-catalyzed •; Asymmetric hydrosilylation • Tridentate ligand • α,β-Unsaturated esters • Chiral trialkyl carbon center

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10.1002/ejoc.202100856

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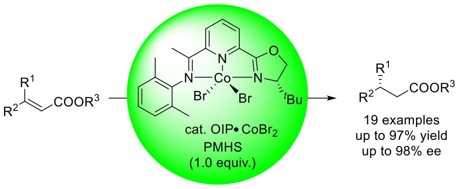

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