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Selective Asymmetric Hydrogenation of Four-Membered *Exo*-α,β-Unsaturated Cyclobutanones Using RuPHOX−Ru as a Catalyst

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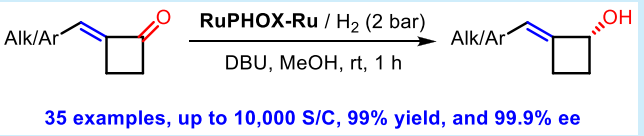
Supporting Information

ABSTRACT: The selective asymmetric hydrogenation of four-membered *exo*-α,β-unsaturated cyclobutanones has been achieved for the first time using RuPHOX-Ru as a catalyst, providing four-membered *exo*-cyclic chiral allylic alcohols in high yields and with up to 99.9% ee. The reaction could be performed on a gram scale with a relatively low catalyst loading (up to 10000 S/C), and the resulting products can be transformed to several biologically active molecules.



Asymmetric hydrogenation catalyzed by chiral metal complexes is one of the most efficient methods for the preparation of chiral compounds because of their high atom economy, environmental friendliness, and operational simplicity.[1] The selective hydrogenation of a C═C, C═O, and other double bonds present in one substrate is undoubtedly a huge challenge because they are generally reduced under similar reaction conditions.

Chiral allylic alcohols are recurring structural motifs in natural products and versatile building blocks in organic synthesis.[2] One of the most popular methods for accessing such backbones is the selective asymmetric hydrogenation of α,β-unsaturated ketones.[3] In particular, the selective asymmetric hydrogenation of α,β-unsaturated cyclic ketones has remained a long-standing topic of interest.[4,6] Much effort has been focused on the selective hydrogenation of endocyclic α,β-unsaturated ketones with excellent results being obtained.[4] Only a handful of groups have recently disclosed chiral Ir complex catalyzed asymmetric hydrogenations of exocyclic α,β-unsaturated ketones.[5,6] Among them, the selective asymmetric hydrogenation of C═C double bonds is easy to achieve.[5] However, only two cases have been reported for the selective asymmetric hydrogenation of C═O double bonds of five-membered or larger α,β-unsaturated cyclic ketones—one by Zhou et al.[6a] and the other by our group.[6b] Nevertheless, the selective asymmetric hydrogenation of four-membered *exo*-α,β-unsaturated cyclobutanones is yet to be explored.

Four-membered exocyclic chiral allylic alcohols are important skeletons in numerous bioactive compounds and pharmaceuticals[7] and important intermediates in organic synthesis (Figure 1).[8] Just recently, we have realized the Ir-catalyzed selective asymmetric hydrogenation of the C═C double bond of *exo*-α,β-unsaturated four-membered cyclobutanones (Scheme 1).[9] We envisaged that the asymmetric hydrogenation of the C═O double bond of the above cyclobutanone substrates could also be achieved via selection of an appropriate chiral catalyst.

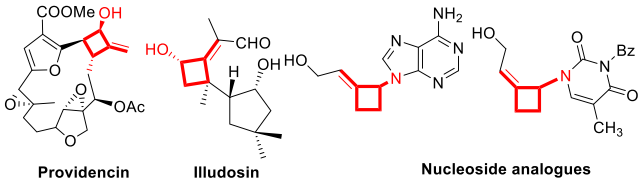
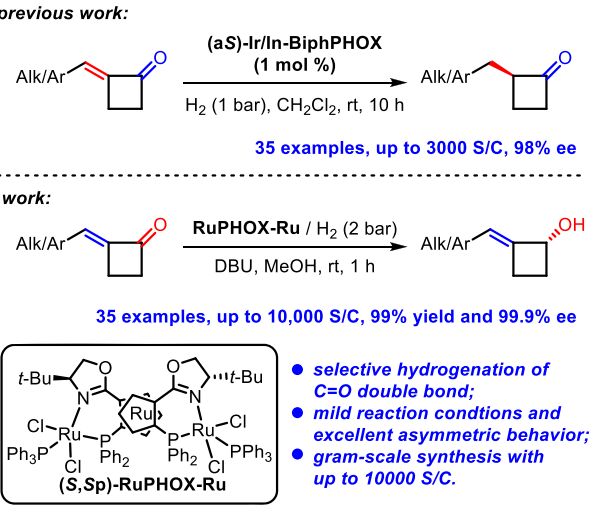


Figure 1. Bioactive compounds bearing chiral four-membered exocyclic allylic alcohols and their derivatives.

Scheme 1. Asymmetric Hydrogenation of *Exo*-α,β-Unsaturated Four-Membered Cyclobutanones



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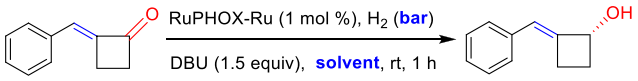
We have previously developed a readily accessible chiral ruthenocenyl P,P,N,N-ligand, RuPHOX, which has shown promising asymmetric catalytic behavior in several asymmetric reactions.[10] In particular, its Ru complex, RuPHOX−Ru, has been successfully applied in the asymmetric hydrogenation of many types of substrates containing C═C and/or C═O double bonds.[11] Herein, we disclose an efficient and mild RuPHOX−Ru-catalyzed selective asymmetric hydrogenation of the C═O double bond of four-membered *exo*-α,β-unsaturated cyclobutanones.

Initially, the RuPHOX-Ru-catalyzed asymmetric hydrogenation of (*E*)-2-benzylidenecyclobutan-1-one (**1a**) was carried out under hydrogen pressure (20 bar) with DBU as a base in different solvents at room temperature over 1 h.[12] As shown in Table 1, MeOH was first used as a solvent with the

Table 1. Screening of Solvent and Hydrogen Pressure[a]



1a **2a**

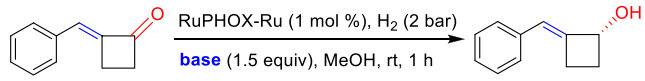
entry	solvent	H_2 (bar)	conv[b] (%)	ee[c] (%)
1	MeOH	20	>99	90
2	EtOH	20	>99	81
3	*i*-PrOH	20	>99	53
4	CF_3CH_2OH	20	7	3
5	DCM	20	>99	21
6	1,4-dioxane	20	>99	19
7	acetone	20	>99	63
8	THF	20	>99	6
9	DME	20	>99	39
10	MeOH	50	>99	88
11	MeOH	6	>99	94
12	MeOH	2	>99	94
13	MeOH	balloon	46	73

[a]Reaction conditions: **1a** (0.30 mmol), (*S*,*Sp*)-RuPHOX-Ru (1.0 mol %) and DBU (1.5 equiv) in a suitable solvent (2 mL) under a certain hydrogen pressure at rt for 1 h. [b]Determined by ^{1}H NMR. [c]Determined by chiral HPLC analysis of **2a** using an OD-H column. The absolute configuration of **2a** was determined from a single crystal and is shown in the SI.

desired product, (*E*)-2-benzylidenecyclobutan-1-ol (**2a**), being obtained in quantitative conversion and 90% ee (entry 1). The use of EtOH provided the same conversion but a lower enantioselectivity than that of MeOH (entry 2). When *i*-PrOH was used as a solvent, the ee decreased sharply (entry 3). However, only 7% conversion was obtained when the reaction was conducted in CF_3CH_2OH (entry 4). As a comparison, aprotic solvents, such as DCM and THF, were used, and both provided the desired product **2a** in full conversions but with unsatisfactory enantioselectivities (entries 5−9). Next, the asymmetric hydrogenation was carried out in MeOH under different hydrogen pressures. When the reaction was conducted under hydrogen pressure (50 bar), a similar conversion was observed, but the ee was reduced slightly (entry 10). To our delight, the enantioselectivity was improved when the reactions were carried out under a relatively low hydrogen pressure (entries 11 and 12, 94% ee under either 6 or 2 bar). However, only 46% conversion and 73% ee were observed when the reaction was carried out using only a hydrogen balloon (entry 13).

Subsequently, the impact of different bases on the reaction was examined in MeOH under hydrogen pressure (2 bar) (Table 2). First, commonly used sodium-containing bases and

Table 2. Screening of Base[a]



1a **2a**

entry	base	conv[b] (%)	ee[c] (%)
1	NaOH	>99	82
2	Na_2CO_3	>99	85
3	$NaHCO_3$	>99	84
4	CH_3COONa	13	25
5	CH_3CH_2ONa	>99	87
6	*t*-BuONa	>99	87
7	Et_3N	>99	84
8	DIPEA	>99	88
9	morpholine	>99	81
10	TMEDA	>99	83
11	DBU	>99	94
12[d]	DBU	>99	93
13[e]	DBU	>99	89

[a]Reaction conditions: **1a** (0.30 mmol), (*S*,*Sp*)-RuPHOX-Ru (1.0 mol %), and base (1.5 equiv) in MeOH (2 mL) under hydrogen pressure (2 bar) at rt for 1 h. [b]Determined by ^{1}H NMR. [c]Determined by chiral HPLC analysis of **2a** using an OD-H column. The absolute configuration of **2a** was determined by single-crystal X-ray diffraction. [d]2.0 equiv. [e]1.0 equiv.

salts were screened (entries 1−6). The most promising results were obtained when CH_3CH_2ONa and *t*-BuONa were used as bases (entries 5 and 6). Then several organic bases were also examined with the desired product being obtained in full conversion and with good to excellent enantioselectivities (entries 7−11). DBU was found to be the best base (entry 11). Finally, the amount of DBU was examined in the reaction. It was found that the desired product could be obtained in full conversion but with a slight variation in enantioselectivity at higher and lower base loadings (entries 12 and 13, 2.0 and 1.0 equiv). Therefore, subsequent reactions were carried out using DBU (1.5 equiv) as a base in MeOH under hydrogen pressure (2 bar) at room temperature for 1 h.

With the optimized reaction conditions in hand, substrates **1** bearing different substituted aryl rings were then investigated (Scheme 2). First, **1** with different substituents at the 2-position of the aryl rings were examined, and the desired products were obtained in high yields with up to 93% ee (**2b**−**e**). Electron-donating and electron-withdrawing substituents on the phenyl ring of the substrate had no effect on the reactivity but a slight effect on the enantioselectivity of the products. Substrates with electron-donating groups located at the 2-position provided higher enantioselectivities than that of substrates with election-withdrawing groups (**2d** and **2e** versus **2b** and **2c**). A similar phenomenon was observed when the substituents were present at the 3- or 4-position of the phenyl ring (**2f** to **2aa**). Furthermore, substitution at the 4-position of the phenyl ring led to an obvious increase in the enantioselectivity (**2k** to **2aa**), in which the substrate bearing a 4-OMe group afforded the highest ee (**2w**, > 99.9%). Additionally, two naphthalene substrates also provided their corresponding products in high yields and with moderate to

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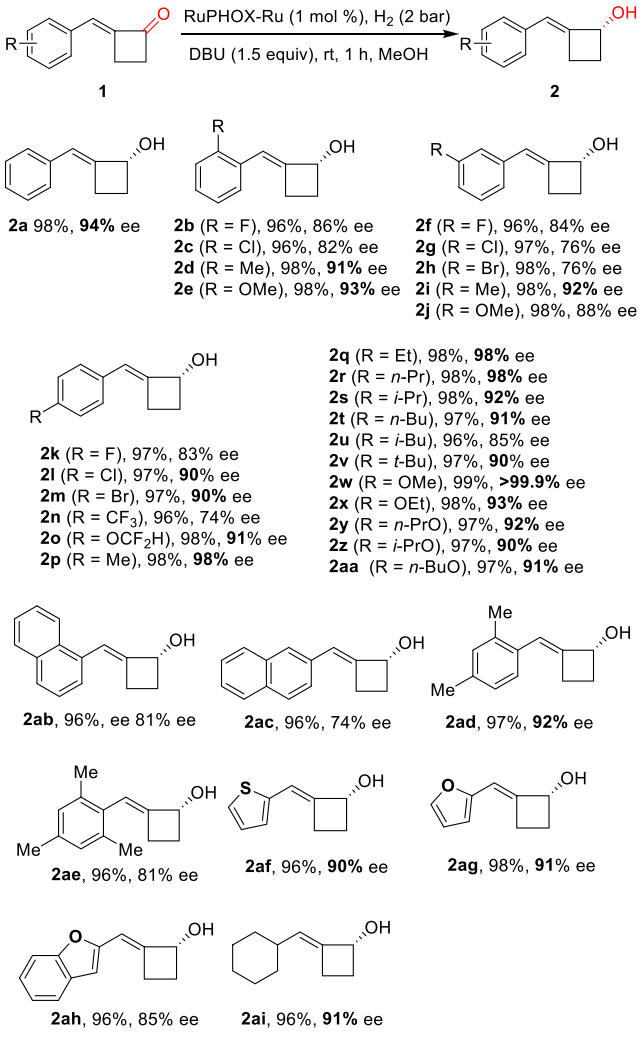
Scheme 2. Substrate Scope of Asymmetric Hydrogenation[a]

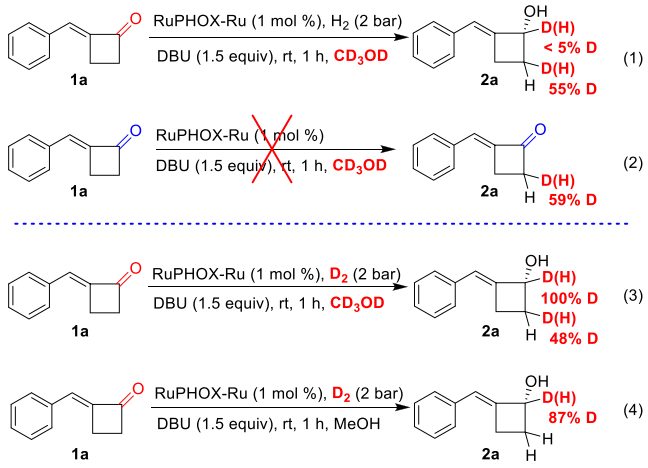


[a]Reaction conditions: **1** (0.30 mmol), (*S*,*Sp*)-RuPHOX-Ru (1 mol %), DBU (1.5 equiv) in MeOH (3 mL) under 2 bar hydrogen pressure at rt for 1 h. Isolated yields. ee's were determined by chiral HPLC analysis of **2** using an OD-H, OJ-H, or AD-H column. The absolute configurations of **2** were determined according to **2a**.

good enantioselectivities (**2ab** and **2ac**). Pleasingly, this catalytic asymmetric hydrogenation system is also amenable to substrates bearing two or three groups on the phenyl ring (**2ad** and **2ae**), of which the hydrogenation products were obtained in quantitative yields and with up to 92% ee. Excellent catalytic behaviors were also observed for heterocyclic substrates (**2af** to **2ah**). The aryl substituent can be replaced by an aliphatic ring, such as a cyclohexyl group, with the desired product being prepared in quantitative yield and up to 91% ee (**2ai**).

To gain a better understanding of the reaction mechanism, deuterium-labeling experiments using D_2 and/or CD_3OD were conducted.[13] When the reaction was performed in CD_3OD and H_2, more than 95% H was incorporated at the α-position of the hydroxyl group (Scheme 3, eq 1). When the above reaction was carried out in the absence of H_2 or D_2, no product was observed (eq 2). The results show that the reaction proceeds via reduction by H_2 rather than the solvent MeOH. However, approximately 50% H at the α-position was deuterated when the reaction was carried out in CD_3OD,

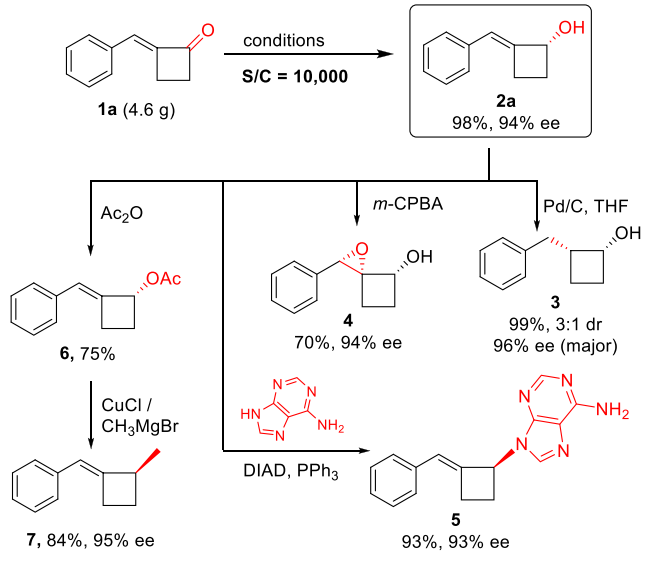
Scheme 3. Deuterium-Labeling Experiments



suggesting the presence of a keto−enol tautomerization eqilibrium during the reaction (eqs 1−3).[14] It was found that no deuteration of the α-position H atom was observed when the reaction was carried out with D_2 in MeOH, illustrating the reaction process proceeds via an asymmetric hydrogenation of the C═O double bond of the ketone rather than the C═C double bond of the enol equivalent (eq 4).

To examine the efficiency of the catalyst system, a gram-scale hydrogenation of **1a** (4.60 g) was carried out with a low catalyst loading of 0.01 mol % (S/C = 10000) with modified reaction conditions under 30 bar H_2 at room temperature over 72 h (Scheme 4). The desired product **2a** in which the C═O

Scheme 4. Gram-Scale Synthesis of 2a and Its Transformation



double bond was hydrogenated was obtained in 98% yield and with 94% ee. Then the C═C double bond of **2a** could be further reduced using Pd/C as a catalyst in THF, affording the corresponding **3** in quantitative yield, 3:1 dr and 96% ee. The results reveal that the C═O and C═C double bonds can be hydrogenated sequentially by controlling the reaction conditions. Combined with our previous work,[9] we can selectively hydrogenate the C═O or C═C double bonds of four-membered *exo*-α,β-unsaturated cyclobutanones. The two

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different double bonds can also be reduced successively if needed.

The C=C double bond could also be oxidized by *m*-CPBA to give the corresponding epoxidation product **4** in 70% yield without any loss in enantioselectivity.[15] Furthermore, the transformation could be performed at the hydroxyl group, and **2a** could be transformed to **5**, with opposite configuration, via a Mitsunobu reaction.[8] The hydroxyl group of **2a** could also be acetylated by Ac_2O easily to give **6**, which was then treated with CH_3MgBr, providing the alkylated product **7** in high yield and 95% ee (Scheme 4).[16]

In summary, we have developed an efficient RuPHOX−Ru-catalyzed selective asymmetric hydrogenation of four-membered *exo*-α,β-unsaturated cyclobutanones. The reduced products were obtained in almost quantitative yields and up to 99.9% ee under mild reaction conditions. The reaction could be performed on a gram scale with a relatively low catalyst loading (up to 10000 S/C), and the resulting product can be transformed to several biologically active compounds. Combined with our previous work, we can selectively hydrogenate the C=O or C=C double bonds of four-membered *exo*-α,β-unsaturated cyclobutanones. The two different double bonds can also be reduced successively if required.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01514.

Experimental procedures and spectral data for all new compounds (PDF)

Accession Codes

CCDC 1899684 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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