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Asymmetric transfer hydrogenation of cycloalkyl vinyl ketones to allylic alcohols catalyzed by ruthenium amido complexes†

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A chemoselective 1,2-reduction of cycloalkyl vinyl ketones *via* asymmetric transfer hydrogenation is described. The reduction proceeded smoothly with a chiral diamine ruthenium complex as a catalyst and a HCOOH–NEt_3 azeotrope as both a hydrogen source and solvent under mild conditions. A wide range of 1-cycloalkyl chiral allylic alcohols were obtained in good yields and up to 87% ee. It was found that the alkyl group plays an important role in the enantioselectivity.

Chiral allylic alcohols are privileged structural subunits of various natural products, as well as valuable building blocks for a wide range of biologically active molecules, such as pharmaceuticals and agrochemicals (Fig. 1).[1] Thus, much attention has been paid on developing efficient methods to prepare these compounds.[2] Among which, the transition-metal catalyzed asymmetric hydrogenation of the carbonyl group of enones is a direct method to produce chiral allylic alcohols.[3] In 1995, a breakthrough in this field was realized with chiral ruthenium/diphosphine/diamine complexes as catalysts, giving the chiral allylic alcohols in up to 98% ee.[4] Since then, these types of catalysts have been widely used in the asymmetric hydrogenation of a variety of cyclic and acyclic enones including simple aryl vinyl ketones and alkyl vinyl ketones to give the corresponding chiral allylic alcohols.[5] In addition, borohydride reagents were also applied in the enantioselective 1,2-reduction of enones, such as chiral oxazaborolidine catalyzed reduction (Corey–Bakshi–Shibata reduction)[6] and the metal borohydride reduction catalyzed by chiral Lewis acid complexes.[7] Lately, novel chiral metal hydrides like CuH[8] and NiH[9] were also developed for the 1,2-reduction of enones. Although great progress has been achieved in the enantioselective 1,2-reduction of enones, several drawbacks and challenges still exist. For example, air-sensitive and expensive chiral phosphine ligands were necessary for the formation of metal complex catalysts. Moreover, the substrates were limited to simple aryl vinyl ketones and alkyl vinyl ketones. Thus, the synthesis of 1-cycloalkyl chiral allylic alcohols, important intermediates of pharmaceuticals and natural products, is almost undeveloped.[9,10] Therefore, it is highly desirable to develop a simple and inexpensive catalytic system for the 1,2-reduction of cycloalkyl vinyl ketones under mild conditions to access 1-cycloalkyl chiral allylic alcohols.

Asymmetric transfer hydrogenation (ATH) is attractive as an alternative to hydrogenation due to convenient operation and avoidance of H_2 gas and pressure vessels.[11] Ever since the chiral diamine ruthenium complex, a famous catalyst for ATH, has been discovered by Noyori,[12] a large number of chiral diamine-derived Ru, Rh, and Ir complexes have been developed for the ATH of simple aryl ketones and diaryl ketones.[13] However, little attention has been focused on the ATH of enones.[14] Notably, the chiral diamine ruthenium complex is highly chemoselective for the ATH of the C=O functional group and tolerance of the alkene.[3a,15] To continue our research interest in the asymmetric synthesis of chiral alcohols,[16] we report a chemoselective ATH of cycloalkyl vinyl

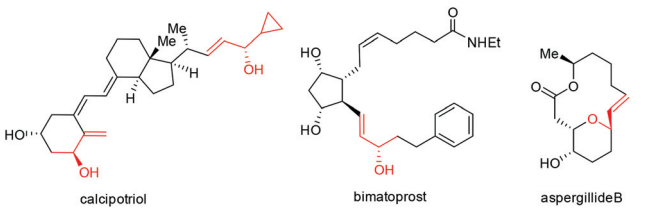

Fig. 1 Representative pharmaceuticals and natural products containing chiral allylic alcohols.

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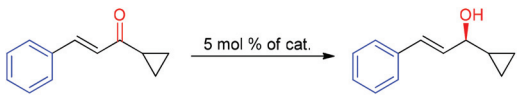
ketones with a chiral diamine ruthenium complex as a catalyst and a HCOOH–NEt_3 azeotrope as a hydrogen source under mild conditions, giving a variety of 1-cycloalkyl chiral allylic alcohols in good yields and high enantioselectivities.

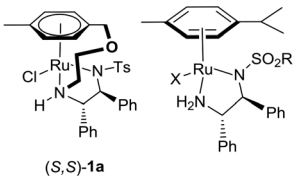
Our investigation was started with the ATH of (*E*)-1-cyclopropyl-3-phenylprop-2-en-1-one (**2a**) as a model reaction. To our delight, when the bifunctional oxo-tethered ruthenium complex (*S*,*S*)-**1a** was used as a catalyst with HCOOH–TEA (molar ratio F/T = 5/2) as a hydrogen source and solvent, the reaction performed exclusively to give the target product **3a** in 71% yield and 60% ee (Table 1, entry 1). Notably, the olefin moiety of **2a** remained intact. A survey of different chiral monosulfonyl diamine ruthenium complexes **1b–1i** indicated that (*S*,*S*)-**1d** was the best choice with respect to the yields and enantioselectivities (Table 1, entries 2–9, entry 4; 90% yield, 81% ee). It was reported that the counteranion effect of these kinds of catalysts plays an important role in the reactivity and enantioselectivity.[17] Therefore, the anion effect of ruthenium complexes was also evaluated with catalysts (*S*,*S*)-**1j** and (*S*,*S*)-**1k**, but no positive effect was observed (Table 1, entries 10 and 11). Kelkar and coworkers reported that both reactivity and enantioselectivity of the ATH of imines were improved by varying the molar ratio of F/T from 5/2 to 1.1/1.[18] Then, the reaction was attempted with an acidic mixture of F/T (molar ratio F/T = 1.1/1) as a hydrogen source and solvent; however, a lower yield and ee value were observed (Table 1, entry 12). Next, the reaction was conducted with HCOONa as a hydrogen source in an aqueous medium, such as H_2O/MeOH (v/v = 1 : 1), H_2O/DMF (v/v = 1 : 1), H_2O/TFE (v/v = 1 : 1), and H_2O/*i*-PrOH (v/v = 1 : 1), but inferior results were obtained in comparison with the F/T system (Table 1, entries 13–16). Finally, the optimized reaction conditions were set as: 5 mol% of (*S*,*S*)-**1d**, F/T (5 : 2) as a hydrogen source and solvent, 40 °C, and 24 h (Table 1, entry 4).

As shown in Scheme 1, a variety of styryl cyclopropyl ketones **2a–2w** were efficiently hydrogenated to give the corresponding chiral allylic alcohols with good yields and high enantioselectivities under the optimized reaction conditions. In general, it was found that the substrates bearing a substitu-

Table 1 Optimization of the reaction conditions[a]

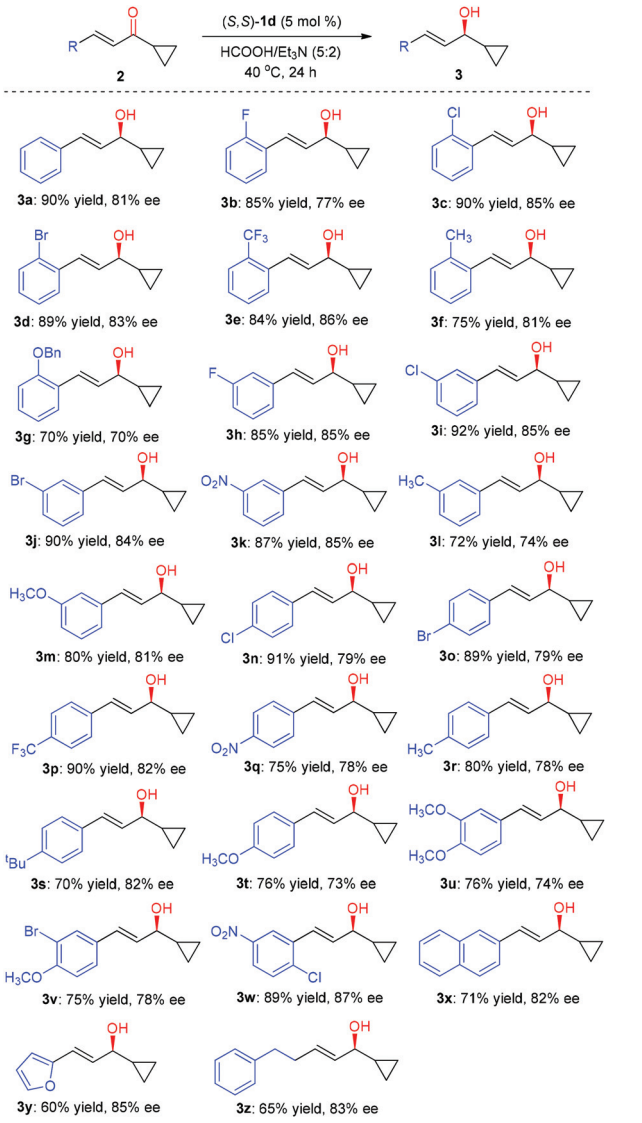


Entry	Cat.	[H] source[b]	Solvent (v/v)	Yield (%)	ee (%)
1	(*S*,*S*)-**1a**	F : T (5 : 2)	—	71	60
2	(*S*,*S*)-**1b**	F : T (5 : 2)	—	57	61
3	(*S*,*S*)-**1c**	F : T (5 : 2)	—	49	53
4	(*S*,*S*)-**1d**	F : T (5 : 2)	—	90	81
5	(*S*,*S*)-**1e**	F : T (5 : 2)	—	65	77
6	(*S*,*S*)-**1f**	F : T (5 : 2)	—	68	79
7	(*S*,*S*)-**1g**	F : T (5 : 2)	—	70	77
8	(*S*,*S*)-**1h**	F : T (5 : 2)	—	69	73
9	(*S*,*S*)-**1i**	F : T (5 : 2)	—	75	79
10	(*S*,*S*)-**1j**	F : T (5 : 2)	—	62	77
11	(*S*,*S*)-**1k**	F : T (5 : 2)	—	65	79
12	(*S*,*S*)-**1d**	F : T (1.1 : 1)		76	80
13	(*S*,*S*)-**1d**	HCOONa	H_2O/MeOH (1 : 1)	45	25
14	(*S*,*S*)-**1d**	HCOONa	H_2O/DMF (1 : 1)	53	47
15[c]	(*S*,*S*)-**1d**	HCOONa	H_2O/TFE (1 : 1)	62	18
16	(*S*,*S*)-**1d**	HCOONa	H_2O/*i*-PrOH (1 : 1)	52	39



(*S*,*S*)-**1b**: R = CH_3, X = Cl
(*S*,*S*)-**1c**: R = 4-$CH_3C_6H_4$, X = Cl
(*S*,*S*)-**1d**: R = 4-$CF_3C_6H_4$, X = Cl
(*S*,*S*)-**1e**: R = 4-$NO_2C_6H_4$, X = Cl
(*S*,*S*)-**1f**: R = 4-$CF_3OC_6H_4$, X = Cl
(*S*,*S*)-**1g**: R = 3,5-$CF_3C_6H_3$, X = Cl
(*S*,*S*)-**1h**: R = 3,4,5-FC_6H_2, X = Cl
(*S*,*S*)-**1i**: R = C_6F_5, X = Cl
(*S*,*S*)-**1j**: R = 4-$CF_3C_6H_4$, X = OTf
(*S*,*S*)-**1k**: R = 4-$CF_3C_6H_4$, X = BF_4

[a] Reaction conditions: **2a** (0.2 mmol), 5 mol% catalyst, 40 °C, 24 h, 1.0 mL of solvent, isolated yield, the ee values were determined by HPLC analysis. [b] The data in the brackets are the molar ratio. [c] TFE : CF_3CH_2OH.



Scheme 1 Substrate scope. Reaction conditions: Cyclopropyl vinyl ketone **2** (0.2 mmol), (*S*,*S*)-**1d** (5 mol%), F/T (1.0 mL, molar ratio = 5 : 2), 40 °C, 24 h; isolated yield; the ee values were determined by HPLC analysis.

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ent at the *ortho*- or *meta*-position on the phenyl ring gave relatively higher ee than the *para*-substituted ones due to the steric effect. For example, both products **3c** and **3i** have 85% ee, but product **3n** has only 79% ee. In addition, substrates bearing an electron-deficient phenyl ring (**2b–2e**; **2h–2k**; **2n–2q**) gave slightly higher ee than the electron-rich ones (**2f**, **2g**; **2l**, **2m**; **2r–2t**). Notably, substrate **2u** with two CH_3O groups on the phenyl ring gave only 74% ee. In contrast, up to 87% ee was obtained for substrate **2w** bearing two electron-withdrawing groups, NO_2 and Cl, on the phenyl ring. Furthermore, when the R group of substrate **2** was switched to naphthyl and furyl, the corresponding chiral allylic alcohols **3x** and **3y** were obtained in 82% and 85% ee, respectively. Most importantly, in addition to the arylvinyl cyclopropyl ketones, the alkylvinyl cyclopropyl ketone **2z** was also applicable to this ATH, giving the chiral allylic alcohol **3z** in 83% ee (Fig. 2).[19]

To further demonstrate the important role of cyclopropyl in the enantioselectivity, substrates with a larger cycloalkyl like **2aa** and **2ab** were also investigated. As shown in Scheme 2, product **3aa** bearing a cyclobutyl was obtained with 67% ee. In sharp contrast, a racemate of cyclohexylated product **3ab** was observed. Interestingly, when the cyclopropyl was replaced by isopropyl, the ee value was decreased from 81% to 39%. Moreover, the substrate containing a *tert*-butyl gave product **3ad** in a comparable ee value to **3a**. However, if the cyclopropyl was replaced by ethyl, the racemic product **3ae** was obtained.

In summary, we have developed an exclusively chemoselective asymmetric transfer hydrogenation of cycloalkyl vinyl ketones to prepare 1-cycloalkyl chiral allylic alcohols. The reduction was conducted with a chiral diamine ruthenium complex as a catalyst and a HCOOH–NEt_3 azeotrope as both a hydrogen source and solvent under mild conditions. The studies revealed that the alkyl group plays an important role in the enantioselectivity.

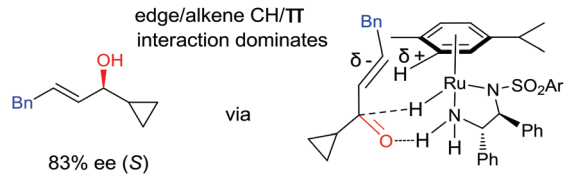
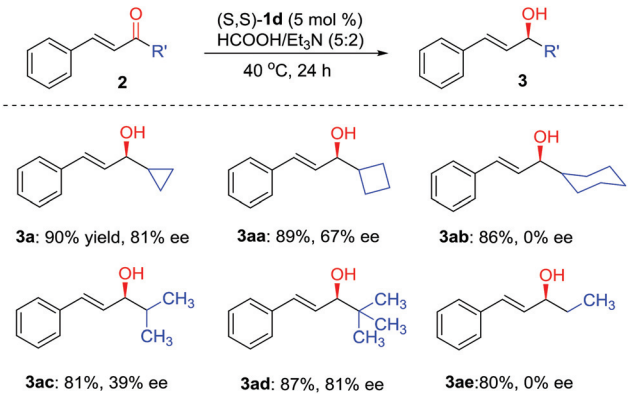


Fig. 2 A mode of ATH of cyclopropyl vinyl ketone.



Scheme 2 The effect of the alkyl group on the enantioselectivity. Reaction conditions: Styryl alkyl ketone **2** (0.2 mmol), (*S*,*S*)-**1d** (5 mol%), F/T (1.0 mL, molar ratio = 5 : 2), 40 °C, 24 h; isolated yield; the ee values were determined by HPLC analysis.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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19 The absolute configuration of **3z** was assigned as *S* by comparison of the sign of optical rotation and HPLC analysis with ref. 9.