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Rhodium-Catalyzed Enantioselective Isomerization of Secondary Allylic Alcohols

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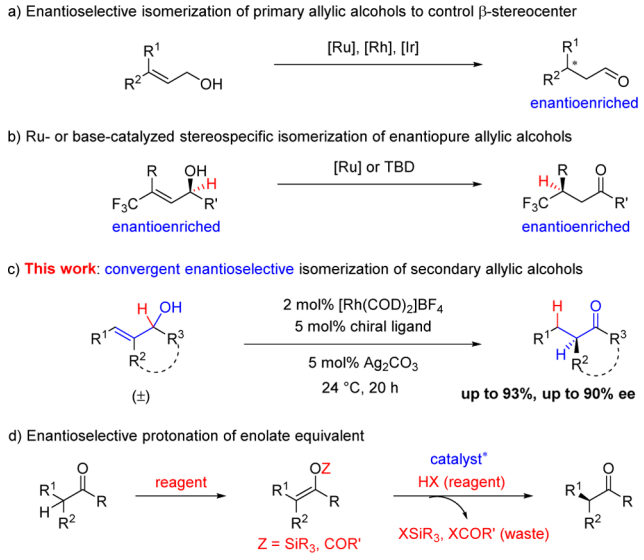
Supporting Information

ABSTRACT: The first catalytic enantioselective isomerization of secondary allylic alcohols to access ketones with a α-tertiary stereocenter is presented. The racemic allylic alcohol substrates can be converted to the enantioenriched ketone products in a stereoconvergent fashion. The use of commercially available catalysts and mild reaction conditions makes this an attractive method in stereoselective synthesis.

The catalytic isomerization of allylic alcohols to the corresponding carbonyl compounds is an extensively explored transformation in organic synthesis. This process has the significant advantage of converting readily available allylic alcohols to versatile carbonyls in an economical, redox-neutral fashion.[1] Following some pioneering work in this field,[2] various transition-metal complexes based on rhodium,[3] ruthenium,[4] iridium,[5] palladium,[6] iron[7] and others[8] have been successfully developed for the efficient redox isomerization. For the development of catalytic enantioselective variant of this process,[9] great advancement has been achieved for the isomerization of β-substituted primary allylic alcohols from the pioneering work of the Fu group, the Mazet group and others (Scheme 1a).[10] As to the corresponding secondary allylic alcohols, only kinetic resolution of racemic alcohols[11] or stereospecific isomerization of enantioenriched substrates to β-substituted ketones (Scheme 1b)[12] was reported in recent years. Herein we report a Rh-catalyzed stereoconvergent isomerization of secondary allylic alcohols, and in particular, the first enantioselective redox-neutral synthesis of ketones with a α-tertiary stereocenter (Scheme 1c).

Scheme 1. Catalytic Enantioselective Isomerization of Allylic Alcohols



Our group has focused on the development of catalytic enantioselective redox-neutral transformations such as amination of alcohols through borrowing hydrogen methodology.[13] In connection with that, we became interested in the stereoconvergent isomerization of racemic secondary allylic alcohols to access ketones with a α-tertiary stereocenter, a process that requires no external reagent and is completely atom economical. Such a seemingly straightforward transformation, however, possesses significant challenges. In fact, enantioselective protonation has long been recognized as a difficult task in asymmetric synthesis.[14,15] The use of preformed enolate equivalents and a bulky external proton source are typically necessary to achieve good level of stereoselectivity, which, on the other hand, inevitably leads to much waste generation (Scheme 1d). Achieving enantioselectivity in the isomerization of allylic alcohols will be more challenging as modification on the substrate or proton donor structure is not possible. A delicate choice of base is also important, which is required to promote an efficient proton shuffle but should not racemize the tertiary stereocenter in the product. A catalytic loading of base will be ideal for the overall economy of the process.

We chose allylic alcohol **1a** as our model substrate, and optimization was carried out to realize the isomerization under mild conditions to achieve any stereoselectivity. Extensive screening of various metal catalysts including iridium, ruthenium and rhodium complexes proved that the use of cationic $[Rh(COD)_2]BF_4$ led to the most efficient isomerization reaction, which could be carried out at ambient temperature to deliver ketone **2a** in high yield and good enantioselectivity (entry 1, Table 1). Test of other anions on the rhodium complex led to no improvement at all (results not shown). Although further focused screening of analogous SegPhos ligands proved ineffective (such as entry 2), the screening of more diverse bisphosphine ligands identified (*R*)-BINAP as the optimal choice (entry 4 vs entries 3, 5−7). The use of other types of ligand such as *P*,*N*-ligands and MonoPhos, on the other hand, turned out to be completely ineffective. The

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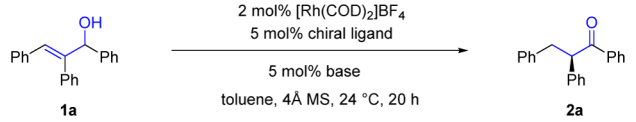
Table 1. Optimization of Isomerization of 1a[a]



entry	ligand	base	yield (%)[b]	ee (%)[c]
1	(*R*)-SegPhos	Ag_2CO_3	82	80
2	(*R*)-DTBM-SegPhos	Ag_2CO_3	35	12
3	(*S*)-DifluorPhos	Ag_2CO_3	50	−70
4	(*R*)-BINAP	Ag_2CO_3	90	84
5	(*R*)-T-BINAP	Ag_2CO_3	85	84
6	(*R*)-DM-BINAP	Ag_2CO_3	86	82
7	(*R*)-H_8-BINAP	Ag_2CO_3	86	76
8	(*R*)-BINAP	none	<5	
9	(*R*)-BINAP	Li_2CO_3	85	80
10	(*R*)-BINAP	Et_3N	83	70
11	(*R*)-BINAP	pyridine	49	76
12	(*R*)-BINAP	DBU	35	<2
13	(*R*)-BINAP	KO*t*-Bu	90	<2

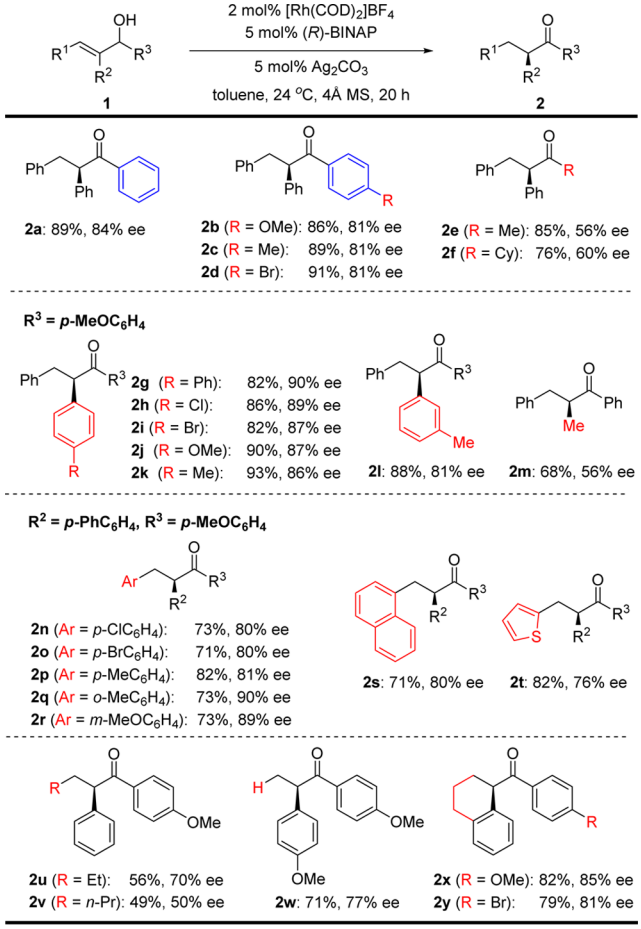
[a]The reaction was carried out with 0.2 mmol **1a**, 2 mol % $[Rh(COD)_2]BF_4$, 5 mol % chiral ligand, 5 mol % base and 50 mg 4 Å MS in 1 mL of solvent. [b]Isolated yield. [c]Determined by chiral HPLC analysis.

screening of various reaction parameters including solvents, concentration, temperature, etc. led to no improvement either. It is interesting to note that a catalytic amount of base proved effective (entry 8), which likely functions as the proton shuffle in this reaction. The identity of base was also examined at different stages of optimization. Weak bases such as carbonates or amines delivered the product in good enantioselectivity (entries 9−11), with silver carbonate still being the optimal choice. In the presence of these weak bases, no racemization of **2a** was observed. In contrast, the use of strong bases such as DBU or KO*t*-Bu produced **2a** in a racemic form, which could be partially due to product racemization (entries 12−13).

With the optimal conditions in hand, the scope of this catalytic enantioselective isomerization was examined. For all substrates, the same set of reaction conditions was adopted. As shown in Scheme 2, a range of racemic acyclic secondary allylic alcohols bearing aryl substituents underwent isomerization smoothly to deliver the ketone products in high yields and good to high levels of enantioselectivity. The electronic variation on the substrates were well-tolerated and the products were formed with essentially the same level of efficiency and selectivity (**2b**, **2d** vs **2a**; **2i** vs **2j**, etc.). Heterocyclic substituents could be tolerated as well (**2t**). The incorporation of alkyl substituents at R^1, R^2 and R^3 positions, however, led to reduced enantioselectivity in general (**2e**−**2f**, **2m** and **2u**−**2v**). A 1,1,-disubstituted allylic alcohol was also examined, which led to the formation of **2w** in good yield and selectivity (77% ee). In addition, bicyclic ketone products such as **2x** and **2y** could also be accessed in good ee of 81−85% using this system.

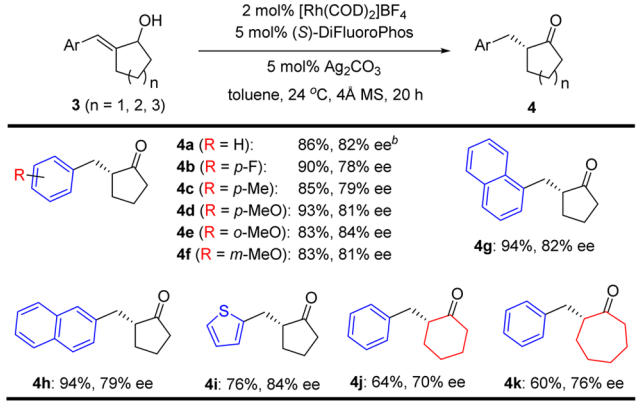
This catalytic system could also be applied to the enantio selective isomerization of a range of cyclic allylic alcohols (Scheme 3). For the isomerization of this series of substrates, the use of DifluorPhos was identified to be superior to BINAP. For the model reaction of **3a**, the corresponding cyclic ketone **4a** was obtained in a good ee of 82%. In addition, a range of aryl-substituted five-membered allylic alcohols could undergo isomerization to yield the corresponding cyclopentanones in high yields and good to high enantioselectivities (**4b**−**4h**).

Scheme 2. Catalytic Enantioselective Isomerization of Acyclic Allylic Alcohols[a]



[a]See Table 1 and Supporting Information for details.

Scheme 3. Catalytic Enantioselective Isomerization of Cyclic Allylic Alcohols[a,b]



[a]See Table 1 and Supporting Information for details. [b](*R*)-BINAP was used and 90% yield, −76% ee was obtained for **4a**.

Thiophene-substituted **4i** was also obtained in a good ee of 84%. In addition, this method is not limited to the preparation of cyclopentanones. Enantioenriched cyclohexanone **4j** and cycloheptanone **4k** were also produced by this catalytic system. Overall, this simple catalytic system using commercially available catalysts and a simple procedure proved to be highly

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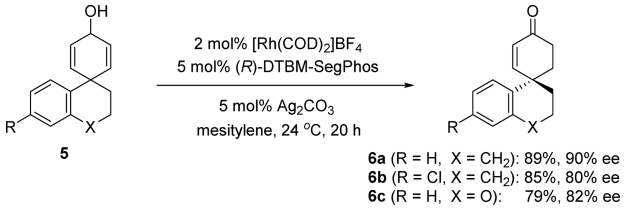
efficient for the conversion of a wide range of racemic secondary allylic alcohols to enantioenriched ketones bearing a α-tertiary stereocenter.

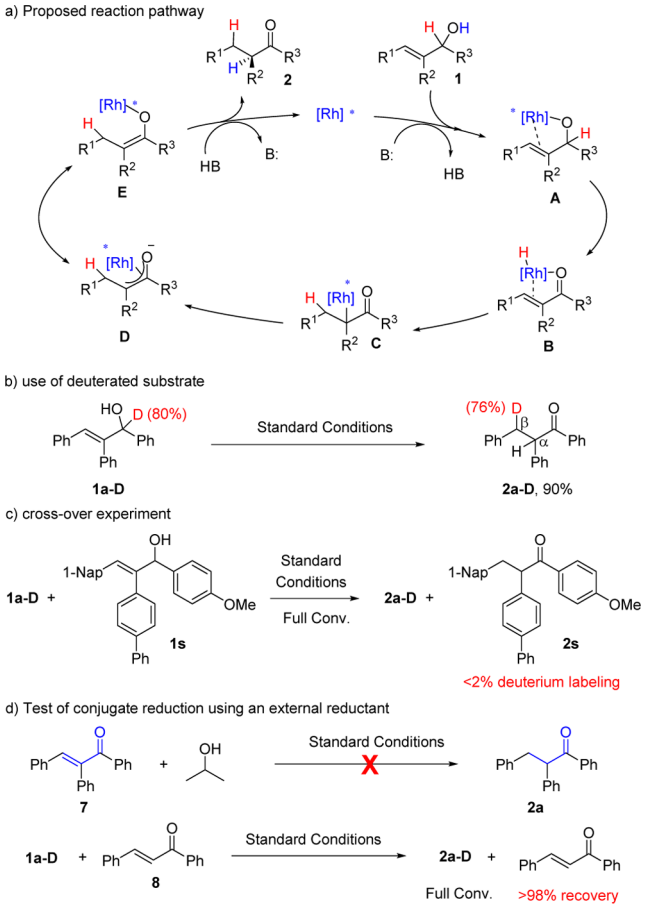
As a further demonstration of the scope of this method, this catalytic system can be extended to the control of γ-stereocenter to ketones. As shown in Scheme 4, stereoconvergent desymmetrization of bis-allylic alcohols **5** was achieved under similar conditions to deliver spirocyclic enones **6** in good to high ee.[16] This catalytic system, therefore, is capable of controlling the selectivity in the isomerization step as well.

Scheme 4. Enantioselective Isomerization To Access Ketones with a γ-Stereocenter



The proposed reaction pathway is shown in Scheme 5a. Under basic conditions, the generally accepted mechanism for allylic alcohol isomerization is through an alcohol dehydrogenation-conjugate reduction sequence.[1] Thus, substrate **1** presumably gets deprotonated and forms the corresponding rhodium alkoxide intermediate **A**. β-Hydride elimination produces intermediate **B**. A formal conjugate reduction of the enone then yields the η-1 rhodium complex **C**, which should tautomerize through the η-3 tatutomer **D** to the key rhodium enolate **E**. Protonation of **E** then produces the product and regenerates the rhodium catalyst. It is postulated that the stereoconvergence in this catalytic system is realized by a nonselective formation of **B** (possibly through dehydrogenation). The chiral rhodium complex then promotes either enantioselective conjugate reduction to form **6** or enantioselective protonation to generate **2** and **4** in an overall stereoconvergent fashion.

Scheme 5. Mechanistic Insights



To shed some light on this reaction pathway, deuterium-labeled substrate **1a-D** was subjected to the standard reaction conditions (Scheme 5b). As expected, a clean deuterium labeling on the β-carbon took place and no scrambling of deuterium to the α-carbon was observed by ^{1}H as well as ^{2}H NMR. When a crossover experiment using **1a-D** and **1r** were carried out, only **2a-D** and **2s** were observed as the products, suggesting that the isomerization is an intramolecular process (Scheme 5c). This conclusion was further supported by the attempted transfer hydrogenation of enone **7** using isopropyl alcohol or the reaction of **1a-D** in the presence of enone **8** (Scheme 5d). In both cases, the proposed [Rh−H] intermediate failed to react in an intermolecular fashion.

In conclusion, we have developed the first general catalytic enantioselective redox isomerization of secondary allylic alcohols to deliver ketones with a α- or γ-stereocenter. By employing commercially available catalysts and a simple procedure, a range of allylic alcohols could be isomerized in a stereoconvergent fashion with high yields and good to high level of enantioselectivity. Current efforts in our laboratory are focused on the development of other enantioselective redox isomerization processes.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b01096.

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

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Notes

The authors declare no competing financial interest.

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