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Enantioselective Cyclopropanation/[1,5]-Hydrogen Shift to Access Rauhut−Currier Product

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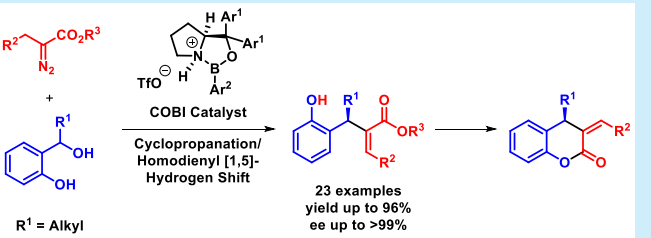
ABSTRACT: A Michael addition initiated cyclopropanation/[1,5]-hydrogen shift has been developed for the enantioselective synthesis of Rauhut−Currier products. The reaction of α-alkyl diazoesters and in situ generated *o*-quinone methides proceeds in the presence of chiral oxazaborolidinium ion, providing *Z*-stereocontrolled Rauhut−Currier products in high yields (up to 96%) with excellent *Z*/*E* selectivities (>20:1) and enantioselectivities (up to >99% ee). The synthetic utility was illustrated by conversion of the product to 3,4-dihydrocoumarins with two adjacent chiral stereocenters.



Enantioenriched α-methylene carbonyl derivatives possessing a chiral center at the β′-position, Rauhut−Currier (RC) products, are valuable building blocks for the synthesis of biologically active molecules and natural products due to their multifunctional composition.[1] These derivatives can be prepared by an asymmetric intermolecular RC reaction (Scheme 1A). Despite recent advances in this area,[2] asymmetric synthesis of β-substituted RC products such as β-substituted RC ketones or esters has not been successful by general RC catalysis, and to the best of our knowledge, only one example of highly enantioselective synthesis of (*E*)-β-

Scheme 1. Synthesis of β-Substituted Rauhut−Currier Products and [1,5]-Hydrogen Shift of Acylalkylcyclopropane

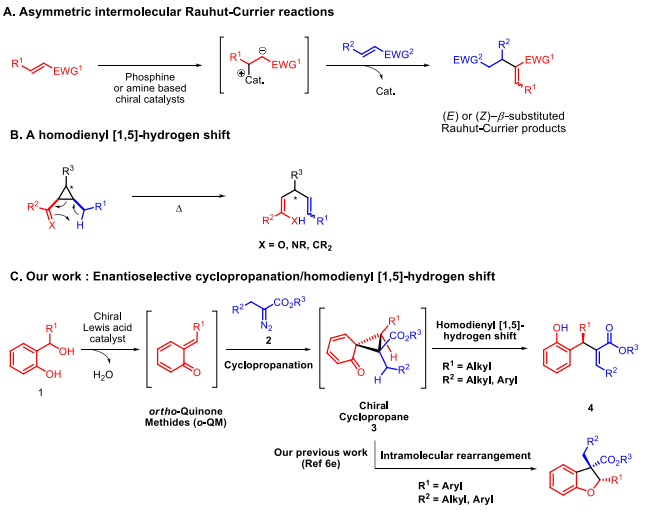
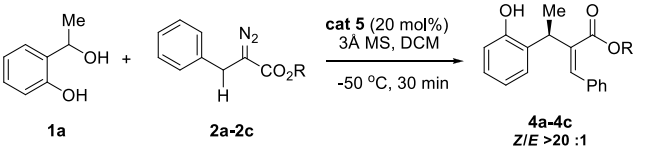
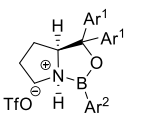


Table 1. Optimization of the Asymmetric Synthesis of Rauhut−Currier Products[a]





5a: Ar¹ = Ar² =phenyl
5b: Ar¹ = 3,5-dimethylphenyl, Ar² = phenyl
5c: Ar¹ = 3,5-dimethylphenyl, Ar² = 2-methylphenyl

entry	catalyst	4	R	yield (%)	ee (%)
1	**5a**	**4a**	*t*-butyl	79	97
2[c]	**5b**	**4a**	*t*-butyl	95	>99
3	**5c**	**4a**	*t*-butyl	87	97
4	**5b**	**4b**	Me	63	95
5	**5b**	**4c**	Et	75	95
6[b]	**5b**	**4a**	*t*-butyl		

[a]Reaction of 2-(1-hydroxymethyl)phenols **1a** (0.2 mmol) with α-benzyl diazoester **2** (0.4 mmol) were performed in the presence of catalyst **5** and 3 Å molecular sieves (100 mg) in 2.0 mL of solvent at −50 °C for 30 min. All yields refer to isolated products. The ee values were determined by chiral HPLC. [b]The reaction was performed in the absence of molecular sieves. [c]1 mmol scale reaction was also performed to give **4a** in 90% yield with >99% ee. DCM = dichloromethane.

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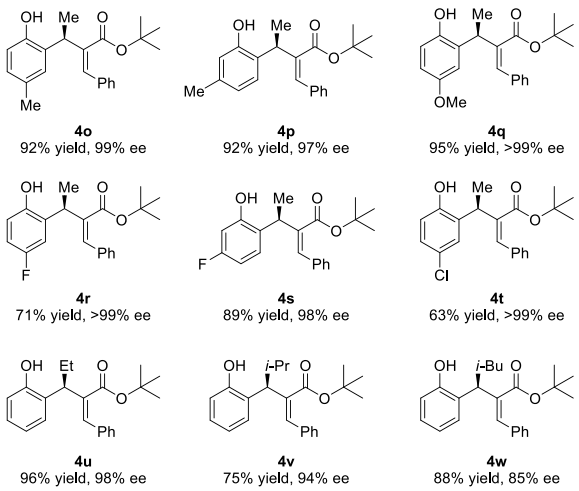
Table 2. Enantioselective Formation of Rauhut–Currier Products with Various α-Alkyl Diazoesters[a]

entry	4	R	yield (%)	ee (%)
1	**4d**	4-MePh	73	>99
2	**4e**	2-MePh	91	98
3	**4f**	4-OMePh	91	>99
4	**4g**	4-BrPh	86	99
5	**4h**	4-CF_3Ph	93	98
6	**4i**	2-Nap	85	>99
7	**4j**	1-Nap	88	98
8	**4k**	Me	76	>99
9	**4l**	Pen	88	>99
10	**4m**	*i*-Pr	93	>99
11	**4n**	vinyl	91	>99

[a]Reaction of 2-(1-hydroxymethyl)phenols **1a** (0.2 mmol) with α-benzyl diazoester **2** (0.4 mmol) was performed in the presence of catalyst **5b** and 3 Å molecular sieves (100 mg) in 2.0 mL of solvent at −50 °C for 30 min. All yields refer to isolated products. The ee values were determined by chiral HPLC. DCM = dichloromethane.

Scheme 2. Enantioselective Formation of Rauhut–Currier Products with Various 2-(1-Hydroxyalkyl)phenols.[a]



[a]Reaction of 2-(1-hydroxyalkyl)phenols **1** (0.2 mmol) with α-benzyl diazoester **2a** (0.4 mmol) were performed in the presence of catalyst **5b** and 3 Å molecular sieves (100 mg) in 2.0 mL of solvent at −50 °C for 30 min. All yields refer to isolated products. The ee values were determined by chiral HPLC. DCM = dichloromethane.

substituted RC products has been reported.[3a] A regioselective conjugate addition of silyl-dienol ethers and subsequent isomerization with a chiral bifunctional organocatalyst afforded highly enantioenriched (*E*)-β-substituted RC products. Consequently, the development of new highly enantioselective *E*/

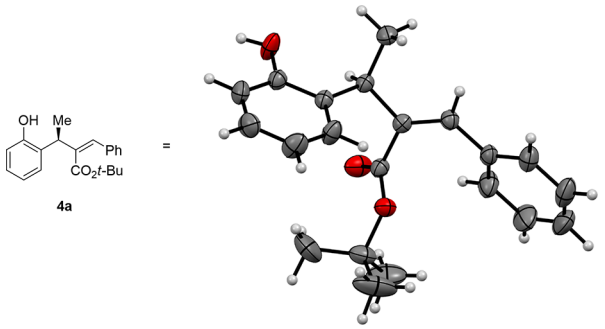
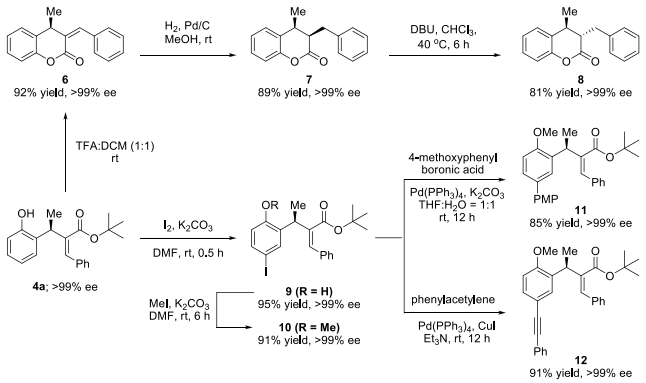


Figure 1. ORTEP view of **4a**. Displacement ellipsoids are drawn at the 50% probability level.

Scheme 3. Synthetic Transformation of Rauhut–Currier Products



Z-stereocontrolled methods[3b] to access β-substituted RC products is highly desirable.

Homodienyl [1,5]-hydrogen shift[4] is a hydrogen transfer reaction through a cyclopropane with an appended vinyl,[5] carbonyl, or imine group[4b] instead of the diene system in the general [1,5]-hydrogen shift (Scheme 1B). Although it has been known for decades, an asymmetric version of this reaction has not been reported to date. Recently, our group has developed highly enantioselective catalytic Michael-initiated cyclopropanations and tandem reactions[6] with α-diazoesters using chiral oxazaborolidinium ion (COBI)[7] as a Lewis acid catalyst. We envisioned that the reaction of *o*-hydroxyphenyl alcohol **1** as a precursor of *o*-quinone methides[8] (*o*-QM) (R^1 = alkyl) and α-alkyl diazoesters **2** would generate chiral cyclopropane **3**, which is ideally substituted for subsequent [1,5]-hydrogen shift to provide highly functionalized RC products **4** (Scheme 1C). Herein, we report the first example of a catalytic enantioselective synthesis of RC products through tandem Michael-initiated cyclopropanation/[1,5]-hydrogen shift starting from 2-(1-hydroxyalkyl)phenols **1** and α-alkyl diazoesters **2**.

In connection with our hypothesis, *o*-hydroxyphenyl ethanol **1a** and *tert*-butyl-2-diazo-3-phenylpropanoate **2a** were considered as model substrates for optimization of the asymmetric cyclopropanation/[1,5]-hydrogen shift (Table 1). Study of the reaction between *tert*-butyl diazoester **2a** having β-hydrogens and *o*-QM generated from **1a** in the presence of chiral oxazaborolidiniumion catalysts **5a** as Lewis acid afforded only (*Z*)-β-phenyl-substituted RC product **4a** in 79% yield with high enantioselectivity (97%) (entry 1). While studying the substituents effect of catalyst **5**, we sought to change the aryl groups (Ar^1 and Ar^2) of the catalyst and discovered that **5b**

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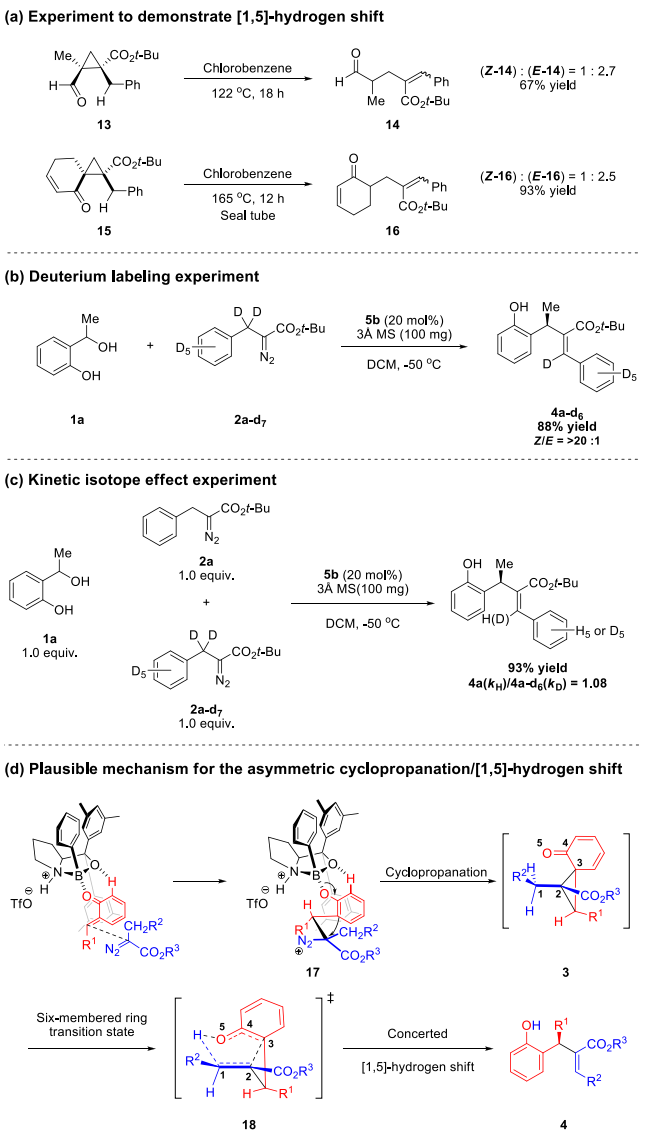
Scheme 4. (a) Model Experiment. (b) Deuterium Experiment. (c) Kinetic Isotope Effect Experiment. (d) Pretransition State and Plausible Mechanism for Asymmetric Synthesis of Rauhut−Currier Products



gave the best yield (95%) with excellent enantioselectivity (>99%) (entries 2 and 3). Modifications of ester functionality of **2a** (−CO_2Me, −CO_2Et instead of −CO_2*t*-Bu) gave decreased yields and enantioselectivities of RC products **4b** and **4c** (entries 4 and 5). Failure of the reaction to afford **4a** in the absence of molecular sieves is indicative of deactivation of COBI catalyst by eliminated water from **1a** (entry 6).[6e]

Initially, we evaluated the scope of various diazo compounds using the optimized conditions for this catalytic enantioselective cyclopropanation/[1,5]-hydrogen shift for the synthesis of RC products (Table 2). Electronic variations on the *β*-aryl ring of the *α*-alkyl diazoesters had no significant impact on their reactivity with *o*-QM to deliver enantioenriched RC products (entries 1−5). For example, reactions of diazo compounds with electron-donating (−Me, −OMe) or -withdrawing groups (−Br, −CF_3) on the *β*-aryl ring proceeded smoothly with *o*-QM from **1a** to afford (*Z*)-olefinic products (**4d**−**4h**). *α*-Methyl diazoesters substituted with a 1- or 2-naphthyl group in the *β*-position afforded highly enantioenriched RC products **4i** and **4j** in high yields. Remarkably, reactions of various *β*-alkyl-substituted diazo esters, such as methyl, *n*-pentyl, *i*-propyl, and vinyl groups, resulted in high yields and excellent enantioselectivities (>99%) (**4k**−**4n**).

Next, we turned our attention to deploying various *o*-QMs with **2a** for enantioselective synthesis of RC products. As illustrated in Scheme 2, reactions of in situ generated *o*-QMs possessing electron-donating (−Me, −OMe) or electron-withdrawing (−F, −Cl) groups proceeded well under the optimized reaction conditions to afford the desired RC products **4o**−**4t** in good to high yields with excellent enantioselectivity (up to >99%). The effect of *para*-halogen substituents on the phenolic −OH was significant in the reaction leading to decreased yields of the desired RC products (**4r** and **4t**). This anomaly may be associated with weak coordination of phenol **1** to COBI **5b** from an electron-withdrawing effect of *para*-halogens. For different alkyl substituents at R^1,[9] the reactions proceeded in high yield with high stereoselectivities (**4u**−**4w**). For the aryl substituents at R^1, 2-aryl-2,3-dihydrobenzofurans are formed via an intramolecular rearrangement of donor−acceptor cyclopropane intermediate (Scheme 1C).[6e] The absolute configuration of **4a** was unambiguously determined by X-ray crystallographic analysis (Figure 1); the configurations of all other products **4** were assigned accordingly.

Since the resulting RC products are composed of multifunctional groups, we demonstrated their synthetic utility by several modifications as illustrated in Scheme 3. Acid-mediated intramolecular transesterification[10] of **4a** afforded coumarin derivative **6**. The exocyclic double bond in **6** was selectively hydrogenated on a solid support[11] to create an additional chiral center affording *cis*-3,4-dihydrocoumarin **7** as a single diastereomer (>99% ee). Base-promoted C2-epimerization[12] furnished *trans*-3,4-dihydrocoumarin **8** in 81% yield without a loss of optical purity (>99% ee). Since dihydrocoumarin scaffolds are found in a wide range of natural products and synthetic compounds that show diverse biological and pharmacological activities,[13] the development of stereoselective synthetic methods for their preparation has attracted considerable attention.[11,12,14]

Electrophilic aromatic substitution enabled installation of iodine at the *para* position of phenol **4a** to give **9** in 95% yield. Protection of the phenolic −OH with methyl iodide furnished **10**, which was then subjected to coupling reactions with arylboronic acid[15] and phenylacetylene.[16] Palladium-catalyzed cross-coupling resulted in addition of 4-methoxyphenyl (PMP) and phenylacetylene groups to afford **11** and **12** in 85% and 91%, respectively. All these transformations proceeded well without any loss of optical purity (>99%).

To acquire a better understanding of this [1,5]-hydrogen shift, *cis*-cyclopropanes[17] **13** and **15**, which have a similar structure to intermediate **3**, were prepared according to the known procedure[18] and subjected to thermal rearrangement conditions in chlorobenzene (Scheme 4a). The [1,5]-hydrogen shift of *cis*-cyclopropanes was corroborated by the obtained RC products **14** and **16** in 67% and 93% yield, respectively.

For further mechanistic insight, deuterium labeling and kinetic isotope experiments (Scheme 4b,c) were conducted, which provided the following two facts: (a) conversion of the *β*-sp^3-carbon of diazoester **2a** to *β*-sp^2-carbon of product **4a** occurs during the reaction and (b) the k_H/k_D of 1.08 illustrates the [1,5]-hydrogen shift is not a rate-determining step. Based on these results and the absolute configuration of **4a**, we

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propose a plausible mechanism as follows. In the pretransition state (Scheme 4d),[6e] α-alkyl diazoester approached the β-methide carbon atom of the *o*-QM with the ester group positioned away from the carbonyl group of the quinone moiety because of dipole−dipole interaction between the two carbonyl groups. Release of catalyst followed by intramolecular ring-closure forms the highly ordered asymmetric cyclopropane **3**. We assume hydrogen at C_1 migrates to carbonyl oxygen in a concerted manner via six-membered ring transition state **18**. In order for the olefinic product to be (*Z*)-selective, the transition state requires a *cis* relation between the ester group (CO_2R^3) at C_2 and R^2. Substituent R^2 at C_1 is situated in an equatorial position where one of two methylene hydrogens can effectively overlap with the reacting C_4═O π-bond and breaking C_2-C_3 σ-bond.[4c] This conformational preference in the TS leaves substituent R^2 and esters on the same side of the C═C double bond in the final products **4**. The driving force for such a [1,5]-hydrogen shift is restoration of aromaticity.

In summary, the first example of highly enantiocontrolled catalytic formation of (*Z*)-β-substituted Rauhut−Currier products has been developed. This tandem cyclopropanation/[1,5]-hydrogen shift provides highly functionalized Rauhut−Currier products in a single step with excellent enantioselectivity. The synthetic utility of this product was demonstrated by transformation to 3,4-dihydrocoumarins with two chiral stereocenters. We believe that the developed method provides an alternative route to access chiral Rauhut−Currier products. Detailed mechanistic studies and applications to bioactive molecules are currently under investigation in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03937.

General information, experimental procedures, single-crystal data analysis, characterization of products, and full analytical data with spectra (PDF)

Accession Codes

CCDC 1989604 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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(17) The *cis* geometry means the carbonyl and benzyl group are directed *cis* to each other in the cyclopropane.

(18) For the preparation of cyclopropane **13** and **15**, see ref 6b and supporting materials.

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