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Rh(III)-Catalyzed C−H Activation-Initiated Directed Cyclopropanation of Allylic Alcohols

Erik J. T. Phipps and Tomislav Rovis*

Department of Chemistry, Columbia University, New York, New York 10027, United States

Supporting Information

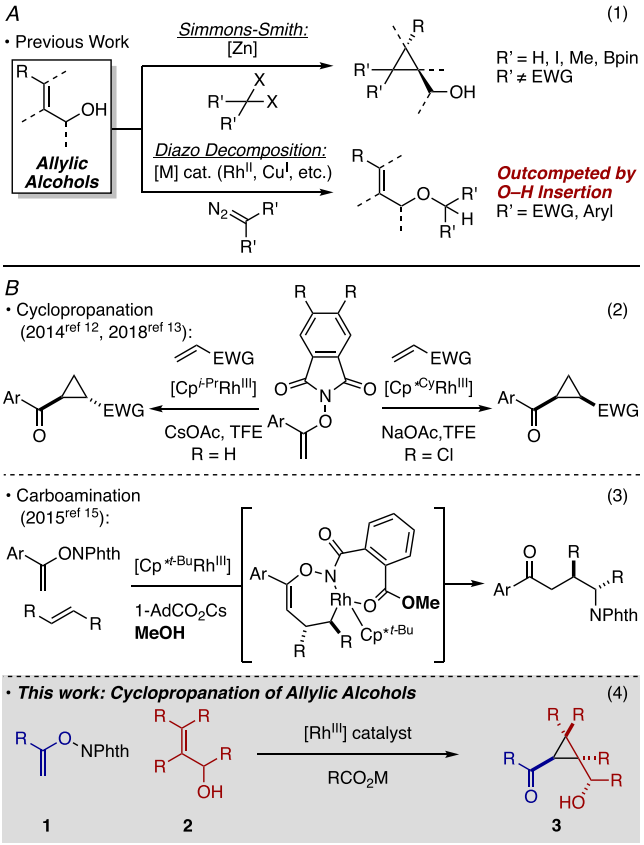
ABSTRACT: We have developed a Rh(III)-catalyzed diastereoselective [2+1] annulation onto allylic alcohols initiated by alkenyl C−H activation of *N*-enoxyphthalimides to furnish substituted cyclopropyl-ketones. Notably, the traceless oxyphthalimide handle serves three functions: directing C−H activation, oxidation of Rh(III), and, collectively with the allylic alcohol, in directing cyclopropanation to control diastereoselectivity. Allylic alcohols are shown to be highly reactive olefin coupling partners leading to a directed diastereoselective cyclopropanation reaction, providing products not accessible by other routes.

Biological and synthetic targets containing cyclopropane units have intrigued organic chemists for years as a result of their unique properties and the synthetic challenges.[1] A number of powerful methods have been developed for the stereoselective synthesis of cyclopropane motifs.[2] These methods largely share a common approach of an alkene that undergoes a [2+1] annulation with carbenes, metal carbenes, or metal-carbenoid species. In particular, allylic alcohols have been exploited as coupling partners in cyclopropanation reactions for their leverageable, pendent hydroxyl group. Ultimately, this handle provides regio- and diastereoselective cyclopropanations.

Two methods have emerged as preferred techniques for the cyclopropanation of alkenes: Simmons−Smith type reactions and catalyzed diazo decompositions (Scheme 1). The Simmons−Smith approach features stoichiometric zinc reagents to aid both the formation and transfer of carbenoid species from simple methylene sources. Similarly, metal-catalyzed diazo decomposition is a broadly powerful reactivity manifold for the cyclopropanation of alkenes, with Rh,[3] Ru,[4] Pd,[5] Cu,[6] Co,[7] and Fe[8] catalysts utilized for their carbenoid formation and transfer capabilities. Notably, both modes of reactivity have also been rendered asymmetric when using prochiral alkenes.[9]

With regards to allylic alcohols, notable shortcomings have arisen in the two established methods outlined above. While Simmons−Smith reactivity is regio- and diastereoselective, it is largely limited to methylenation:[10] substituted methylene transfer remains underdeveloped. Metal-catalyzed diazo decomposition fails with allylic alcohols as conversion to cyclopropanes is low yielding due to competitive O−H insertion.[11]

Scheme 1. Directed Cyclopropanations and Precedent Involving *N*-Enoxyphthalimides



We have previously reported that *N*-enoxyphthalimides are a unique one-carbon component for the cyclopropanation of activated alkenes.[12] Furthermore, tuning the cyclopentadienyl (Cp) ligand on the Rh^{III} catalyst delivers either *cis*- or *trans*-disubstituted cyclopropanes stereoselectively.[13,14] In a complementary approach, we found that exchanging trifluoroethanol (TFE) solvent for methanol (MeOH) and again tuning the Cp ligand on the Rh catalyst, activated alkenes undergo *syn*-1,2-carboamination.[15] This chemodivergence is hypothesized to originate from MeOH participating as a nucleophile to open the phthalimide ring that allows the *N*-enoxyphthalimide to act as a bidentate ligand throughout catalysis. On the basis of these findings, we sought to expand the scope of our reported

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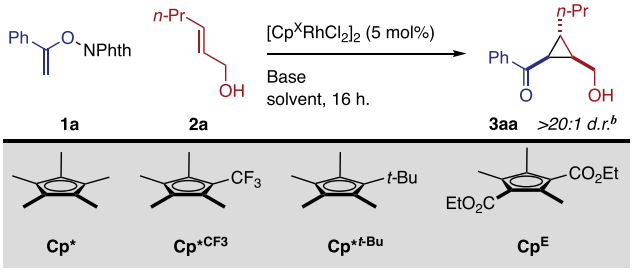
cyclopropanation toward unactivated alkenes. Herein, we report that allylic alcohols undergo directed diastereoselective cyclopropanation using this approach.

Initial investigations began with phenyl-*N*-enoxyphthalimide **1a** and *trans*-2-hexen-1-ol **2a** in the presence of various Rh(III) catalysts in TFE at room temperature delivering cyclopropane **3aa** in moderate yield but high diastereoselectivities (Table 1, entries 1–4). A solvent (entries 5 and 6) and base screen revealed that KOPiv in TFE is optimal, providing 64% yield and >20:1 *d.r.* for the desired product (entry 7). Furthermore, we discovered that reducing the reaction temperature to 0 °C leads to the desired cyclopropane in 81% yield while preserving excellent diastereoselectivity (entry 8).

Table 1. Reaction Optimization[a]



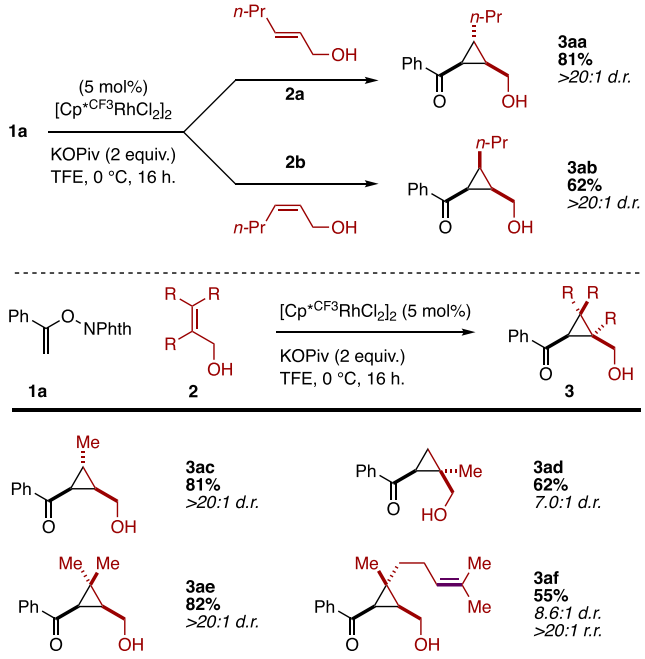
Entry	Cp^X	Base	Solvent	Yield **3aa**[c]
1	Cp*	KOAc	TFE	24%
2	Cp^{*CF3}	KOAc	TFE	50%
3	$Cp^{*t\text{-}Bu}$	KOAc	TFE	22%
4	Cp^{E}	KOAc	TFE	45%
5	Cp^{*CF3}	KOAc	MeOH	36%
6	Cp^{*CF3}	KOAc	THF	29%
7	Cp^{*CF3}	KOPiv	TFE	64%
8[d]	Cp^{*CF3}	KOPiv	TFE	81%[e]

[a]Conditions: **1a** (1 equiv), **2a** (1.2 equiv), Base (2 equiv), $[Cp^XRhCl_2]_2$ (5 mol %), in solvent (0.2M) at 21 °C for 16 h. [b]Determined by the ^{1}H NMR of the unpurified reaction mixture [c]Yields determined by ^{1}H NMR. [d]Reactions carried out at 0 °C instead of 21 °C. [e]Isolated yield.

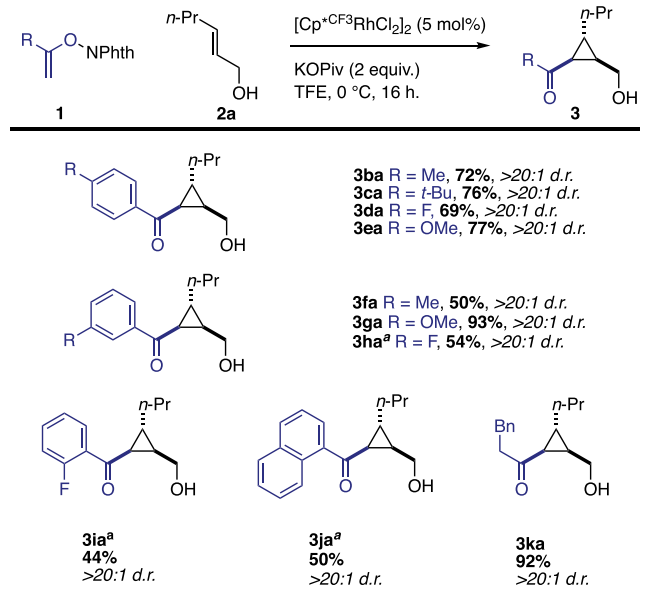
We next examined if the diastereoselectivity of the trisubstituted cyclopropane product was directly correlated with initial alkene geometry (Scheme 2). Both *trans*- and *cis*-1,2-disubstituted primary allylic alcohols provide the desired cyclopropanes **3aa** and **3ab** in good yield—81% and 62%, respectively, and >20:1 *d.r.*, implicating a stereospecific transformation with respect to the alkene. Similar to the parent allylic alcohol, we found crotyl alcohol gives cyclopropane **3ac** in excellent diastereoselectivity and 81% yield. Methallyl alcohol gives cyclopropane **3ad** in 62% yield with 7.0:1 *d.r.* while prenyl alcohol furnishes **3ae** in 82% yield and >20:1 *d.r.* To showcase the regio-preference of our cyclopropanation protocol, **1a** was subjected to substrate **2f** (geraniol) bearing a tethered trisubstituted alkene as a potential competitive site for cyclopropanation. Gratifyingly, cyclopropane **3af** was generated in 55% yield with good diastereoselectivity and excellent regioselectivity.

With optimized conditions in hand, we examined the scope of this reaction (Scheme 3). Varying *para*- (**3ba**–**3ea**) and *meta*- (**3fa**–**3ha**) arene substitution on the enoxyphthalimide is tolerated, with each substrate displaying >20:1 diastereoselectivity. *ortho*-Fluorine containing enoxyphthalimide delivers cyclopropane **3ia** in 44% yield. An alkyl substituted

Scheme 2. Selectivity of Cyclopropanation



Scheme 3. *N*-Enoxyphthalimide Scope



[a]Low conversion at 0 °C, isolated yield at 21 °C

N-enoxyphthalimide[16] is also a competent substrate, affording cyclopropane **3ka** in 92% yield.

Next, a range of suitable allylic alcohols for the cyclopropanation reaction was explored (Scheme 4). Notably, chiral allylic alcohol substrates provide additional complexity leading to the potential of four different stereoisomers. In the event, these reactions deliver the corresponding cyclopropanes **3ag**-**3ai** with varying levels of diastereoselectivity depending on the substituent size, from vinyl (73%, 2.5:1 *d.r.*, major to Σ minor), to methyl (69%, 7.1:1 *d.r.*) and phenyl (62%, >20:1 *d.r.*). Using *trans*-1,2-disubstituted secondary allylic alcohols, we observed single diastereomers of cyclopropanes **3aj**–**3al** in outstanding yields. Finally, we sought to assess the directing ability of cyclic allylic alcohols. When cyclohexenol **2m** is subjected to the

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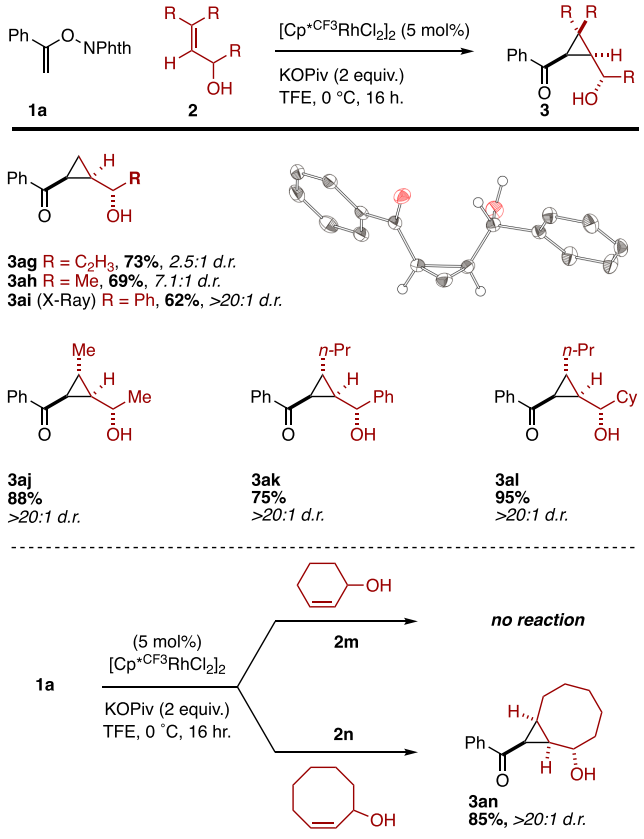
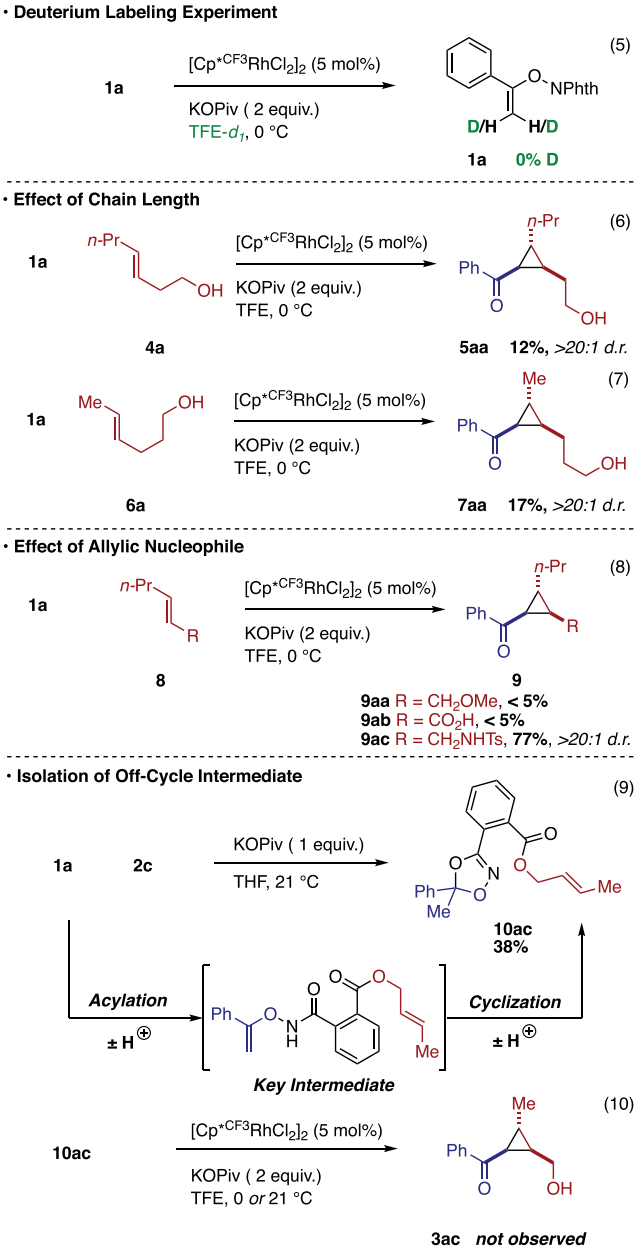
Scheme 4. Allylic Alcohol Scope



Scheme 5. Mechanistic Experiments



reaction conditions, no cyclopropane is observed. However, with cyclooctenol **2n**, cyclopropane **3an** is afforded in excellent yield and diastereoselectivity. On the basis of previous Simmons–Smith cyclopropanations that explore directing effects of cyclic systems,[17] we hypothesize that the larger ring accommodates the correct C–O bond angle for the cyclopropanation to occur, affording the same relative stereochemistry as observed with acyclic allylic alcohols.

To investigate the mechanism of this cyclopropanation reaction (Scheme 5), we subjected **1a** to the reaction conditions in the absence of alkene with TFE-d_1 solvent and observed no deuteration of the alkenyl protons suggesting that the C–H activation is irreversible. Homoallylic alcohol **4a** gives cyclopropane **5aa** in only 12% yield indicating the chain length from the oxygen atom to the olefin is of great importance. Similarly, *bis*-homoallylic alcohol **6a** gives cyclopropane **7aa** in only 17% yield. Allylic ether **8a** is a poor substrate with only trace **9aa** observed indicating the presence of an unhindered hydroxyl-group is necessary for the reaction to take place. Allylic carboxylic acid **8b** gives cyclopropane **9ab** in trace yield. Interestingly, protected allylic amine **8c** gives cyclopropane **9ac** in 77% yield and 9.5:1 *d.r.* indicating the importance of the strength of the pendent nucleophile. In another experiment, we set out to detect potential reactivity between **1a** and **2c** in the absence of Rh catalyst and were surprised to observe the formation of dioxazoline **10ac** in 38% yield with 1 equiv of KOPiv in THF at room temperature. We speculate this occurs via opening of the phthalimide ring and acylation of the allylic alcohol (eq 8). Subjecting dioxazoline **10ac** to the cyclopropanation reaction conditions did not afford cyclopropane, suggesting that dioxazoline **10ac** is an off-cycle product.

On the basis of these experiments, we propose the following mechanism (Scheme 6). First, **2** undergoes acylation with **1** that gives intermediate **I**. Maintaining the reaction temperature at 0 °C inhibits cyclization of **10ac**, which is instead intercepted by the active Rh(III) catalyst **II**. Intermediate **I** undergoes irreversible C–H activation via concerted metalation-deprotonation that gives rhodacycle **III**. At this stage, we hypothesize the formation of intermediate **IV** by cleavage of the N–O bond and formation of a Rh-carbene. Due to the prior acylation of the allylic alcohol, intermediate **V** is formed via the [2+1] annulation where the Rh-carbene is delivered across the alkene and on the same face as the pendent oxygen atom in stereoselective fashion. Protodemetalation and subsequent phthalimide ring closure releases the product and turns the catalyst over.

In summary, we have developed a directed diastereoselective cyclopropanation protocol for the [2+1] annulation of *N*-enoxyphthalimides and allylic alcohols. The diastereoselectivity

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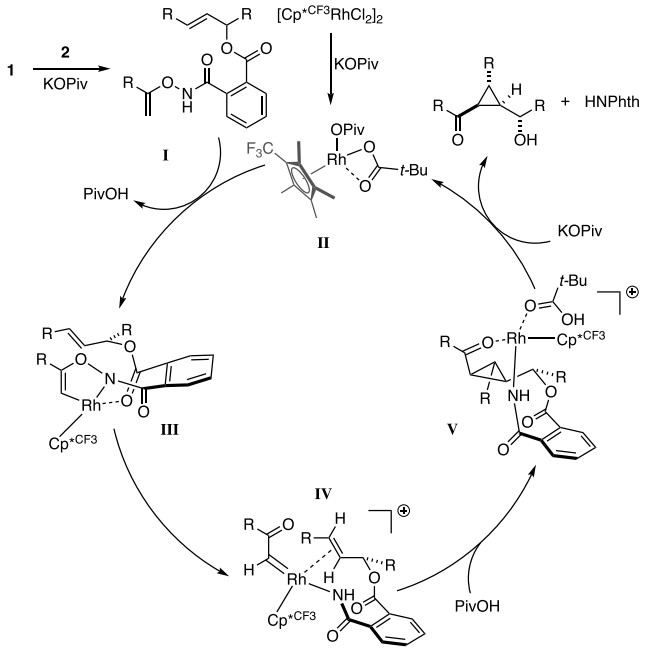
Scheme 6. Proposed Catalytic Cycle



of the reaction is speculated to arise from an intermediate generated by a ring-opening acylation of the allylic alcohol. Generation of a Rh-carbenoid leads to intramolecular cyclopropanation in excellent yield and diastereoselectivity.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.9b02156.

Experimental descriptions, analytical data, and NMR spectra (PDF)

Data for $C_{17}H_{16}O_2$ (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*tr2504@columbia.edu

ORCID

Tomislav Rovis: 0000-0001-6287-8669

Notes

The authors declare no competing financial interest.

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