Stereoselective Hydroxyallylation of Cyclopropenes with Cyclopropanols via NHC Catalysis of Transient Organozinc Species

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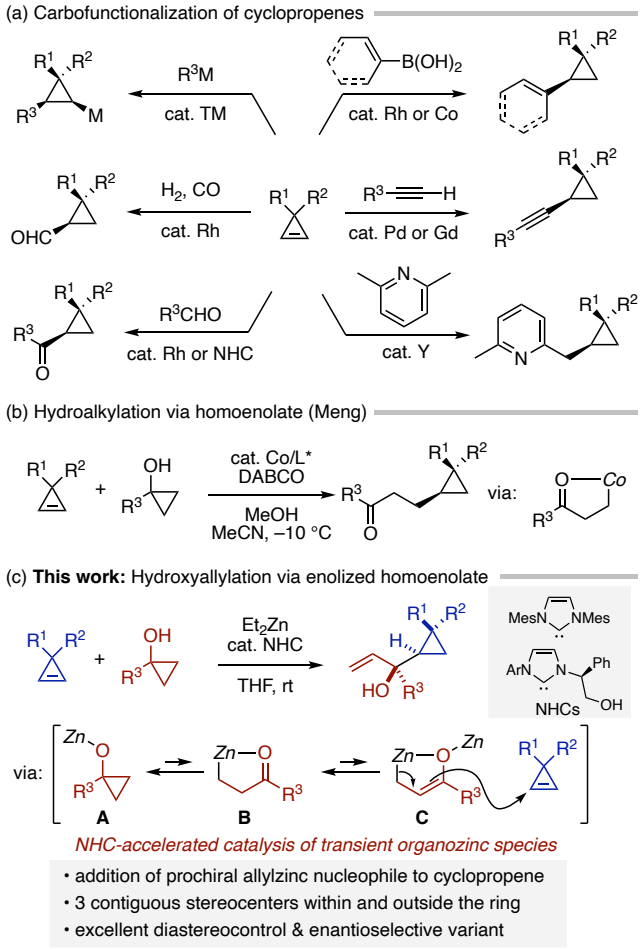
ABSTRACT: A stereoselective hydroxyallylation reaction of cyclopropenes with cyclopropanols is achieved under zinc-mediated conditions, affording densely functionalized cyclopropanes with excellent diastereocontrol over three contiguous stereocenters within and outside the cyclopropane ring. A racemic variant of the reaction is synergistically promoted by catalytic N-heterocyclic carbene (NHC) and organic base (DBU), whereas chiral amino alcohol-derived bifunctional NHC enables a catalytic enantioselective variant. Mechanistically, the reaction features transient generation of enolized zinc homoenolate via ring-opening of zinc cyclopropoxide and enolization of the resulting homoenolate, followed by its addition to the cyclopropene as a prochiral allylzinc nucleophile.

Cyclopropanes represent important structural elements in medicinal chemistry and drug design[1] and serve as versatile building blocks in synthetic chemistry.[2] Consequently, the efficient and selective preparation of densely functionalized cyclopropanes has continued to attract the interest of the synthetic chemistry community. Besides the well-established methods for de novo construction of cyclopropane rings, such as cyclopropanation using carbenoids, the installation of functional groups to preexisting three-membered ring, the addition reaction to the C=C bond of cyclopropene in particular, represents an actively pursued approach to functionalized cyclopropanes.[3] Thus, a wide variety of catalytic stereoselective carbo- and heterofunctionalization reactions of cyclopropenes have been developed over the last two decades. As for carbofunctionalization, representative examples include transition metal-catalyzed carbometalation using main group organometallic reagents,[4] Rh- or Co-catalyzed hydroarylation/vinylation using organoboronic acids,[5] Rh-catalyzed hydroformylation,[6] Rh- or NHC-catalyzed hydroacylation,[7] Gd- or Pd-catalyzed hydroalkynylation using terminal alkynes,[8] Y-catalyzed hydroalkylation using 2-methylazaarenes,[9] and Co-catalyzed hydroalkylation using cyclopropanols (Scheme 1a and 1b).[10] When performed on unsymmerical 3,3-disubstituted cyclopropenes, these transformations allow for diastereo- and enantiocontrol of vicinal stereocenters of the cyclopropane ring. For carbometalation, cyclopropanes with all three chiral carbons can even be constructed in a stereoselective fashion through the electrophilic trapping of the cyclopropylmetal intermediate. However, to our knowledge, carbofunctionalization of cyclopropenes with a prochiral nucleophile that generates an additional stereogenic center outside the cyclopropane ring remains unknown.

Among the aforementioned carbofunctionalization reactions of cyclopropenes, the Co-catalyzed hydroalkylation using a cyclopropanol, reported by Meng and coworkers, is unique in that it enables the introduction of synthetically useful γ-oxoalkyl groups from readily accessible and stable cyclopropanols (Scheme 1b).[10] Mechanistically, this transformation is believed to involve a cobalt homoenolate,[11,12] which is generated through the ring-opening of a cobalt cyclopropoxide. Herein, we disclose a distinct reaction of the same reactants under zinc-mediated conditions, which provides a hydroxyallylated cyclopropane through the intermediacy of enolized zinc homoenolate as a prochiral nucleophile (Scheme 1c).[13] Mediated by Et_2Zn and assisted by catalytic N-heterocyclic carbene (NHC), the reaction proceeds with perfect diastereocontrol over three contiguous stereocenters, including one outside the cyclopropane ring. Furthermore, an enantioselective variant of this transformation was achieved using a chiral amino alcohol-derived bifunctional NHC.

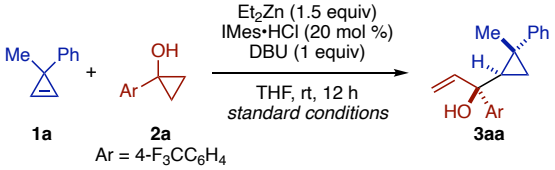
Scheme 1. Stereoselective Carbofunctionalization of Cyclopropenes



Recently, our group has demonstrated multifaceted reaction modes of zinc homoenolate **B** generated in equilibrium through the ring-opening of zinc cyclopropoxide **A** (Scheme 1c). Thus, besides its reactivity as a β-carbonyl alkylzinc nucleophile,[14,15] enolization of the zinc homoenolate gives rise to a new species, enolized homoenolate **C**. Depending on the electrophilic reaction partner, the latter species behaves as a β-zincio enolate[13a-c] or a γ-oxyallylzinc species,[13d] thereby opening new reaction spaces for readily accessible cyclopropanols.[16] Given the capability of a preformed allylzinc reagent to undergo allylzincation of cyclopropenes,[17] we hypothesized that the reaction of cyclopropene with cyclopropoxide **A** would converge to hydroxyallylated cyclopropane via enolized homoenolate **C**.

The present study commenced with a survey of a model reaction between 3-methyl-3-phenylcyclopropene (**1a**) and 1-(4-(trifluoromethyl)phenyl)cyclopropanol (**2a**; Table 1). Extensive screening experiments led us to identify a reaction system comprised of Et_2Zn (1.5 equiv), IMes•HCl (20 mol %), and DBU (1 equiv) that promotes the hydroxyallylation in THF at room temperature to afford the cyclopropane **3aa** in 91% yield as a single diastereomer (entry 1). The relative stereochemistry was assigned on the basis of X-ray crystallographic analysis of one of the derivatives of the present hydroxyallylation products (vide infra). A synergistic effect of the NHC ligand and the base was suggested from control experiments omitting either, which resulted in a significant decrease in the yield of **3aa** (entries 2 and 3). Furthermore, no reaction was observed when Et_2Zn alone was used (entry 4). The importance of IMes•HCl was further corroborated by the diminished reactivity using other ligands such as IPr•HCl, bpy, and TMEDA (entries 5–7). DBU proved to be the optimal base; the use of other bases such as DABCO made the reaction sluggish (entry 8).

Table 1. Zinc-Mediated Hydroxyallylation of Cyclopropene



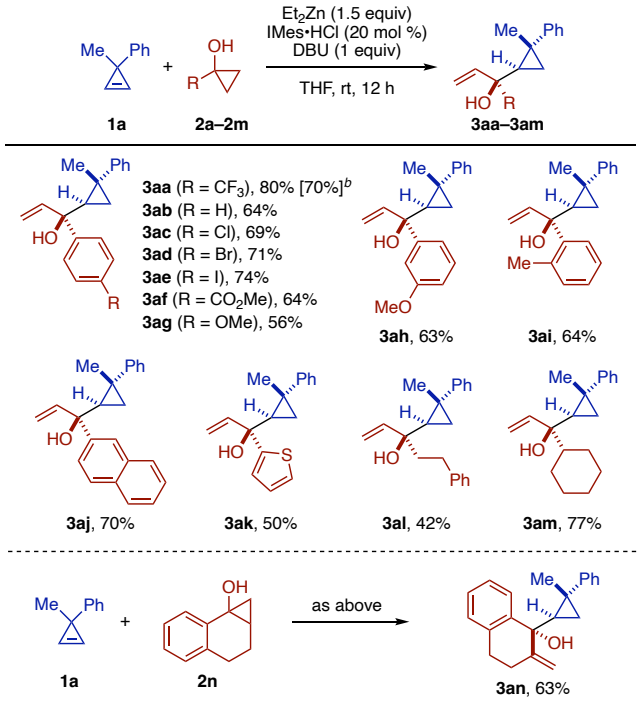
entry	deviation from standard conditions	yield (%)[b]
1	none	91
2	w/o IMes•HCl	53
3	w/o DBU	41
4	w/o IMes•HCl and DBU	0
5	IPr•HCl instead of IMes•HCl	64
6	bpy instead of IMes•HCl	17
7	TMEDA instead of IMes•HCl	22
8	DABCO instead of DBU	61

[a]The reaction was performed using 0.15 mmol of **1a** and 0.10 mmol of **2a** at the concentration of 0.20 M. [b]Determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as an internal standard.

With the optimal reaction conditions in hand, we explored the scope of the present hydroxyallylation. First, a variety of cyclopropanols were subjected to the reaction with **1a** (Scheme 2). 1-Arylcyclopropanols containing various *para*-substituents such as trifluoromethyl, halogen (Cl, Br, I), ester, and methoxy groups participated in the hydroxyallylation to afford the corresponding products **3aa**–**3ag** in 56–80% yields with virtually perfect diastereocontrol (>20:1 dr). The preparation of **3aa** and **3ab** could be performed on a 1 mmol scale in 70% yield. The reaction was found to become somewhat sluggish with electron-donating methoxy group. Substitution at the *meta*- and the *ortho*-position could also be well tolerated (see **3ah** and **3ai**). 2-Naphthyl- and 2-thienylcyclopropanols participated in the reaction to give the corresponding products **3aj** and **3ak**, respectively. 1-Alkylcyclopropanols were also amenable to the hydroxyallylation, affording the desired products **3al** and **3am** again as single diastereomers. Furthermore, the reaction between **1a** and bicyclic cyclopropanol **2n** furnished the adduct **3an** in a diastereoselective fashion.

Scheme 2. Hydroxyallylation of 1a with Various Cyclopropanols[a]

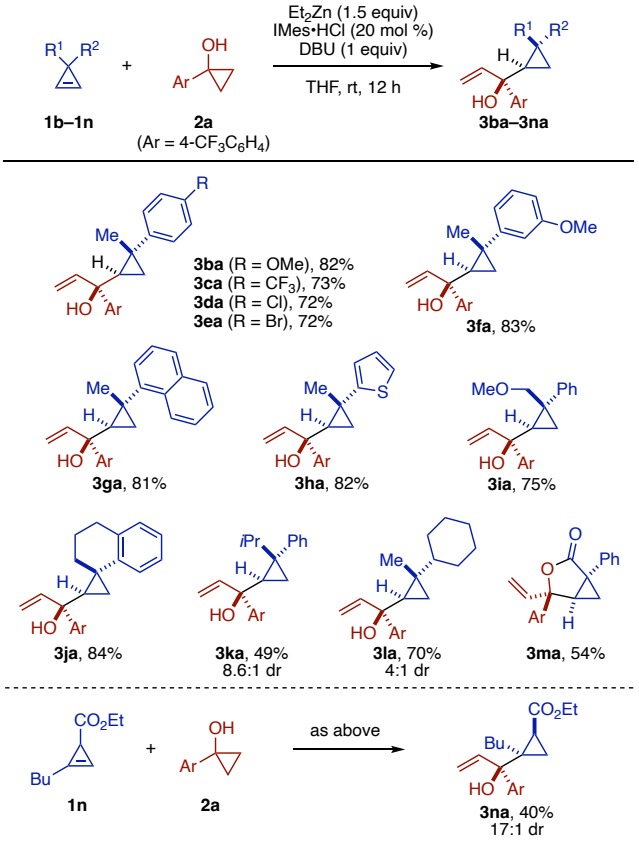
https://doi.org/10.26434/chemrxiv-2023-hch07 **ORCID:** https://orcid.org/0000-0002-8997-3268



[a]The reaction was performed on a 0.1 mmol scale. [b]The yield of a 1 mmol scale reaction is shown in the brackets.

We next explored the scope of cyclopropenes for the present hydroxyallylation using **2a** as the reaction partner (Scheme 3). A variety of 3-aryl-3-methylcyclopropenes participated in the hydroxyallylation to afford the products **3ba**–**3ha** in 72–83% yields as single diastereomers (>20:1 dr). 3-Phenyl-3-methoxymethylcyclopropene and spirobicyclic cyclopropene underwent the hydroxyallylation with perfect diastereocontrol, affording the adducts **3ia** and **3ja**, respectively, in good yields. On the other hand, the reaction of 3-phenyl-3-isopropylcyclopropene was accompanied by a detectable amount of minor diastereomer (**3ka**, 8.6:1 dr), likely due to deteriorated facial selectivity with respect to the cyclopropene C=C bond. A diminished diastereoselectivity was also observed with 3-cyclohexyl-3-methylcyclopropene (**3la**, 4:1 dr). The reaction of 3-phenyl-3-ethoxycarbonylcyclopropene afforded a bicyclic lactone derivative **3ma** through in situ lactonization of the initially formed hydroxyallylation product. 1-Butyl-3-ethoxycarbonylcyclopropene **1n** also took part in the hydroxyallylation with **2a**, where the adduct **3na** featuring vicinal tetrasubstituted carbons was obtained in a regio- and diastereoselective fashion.

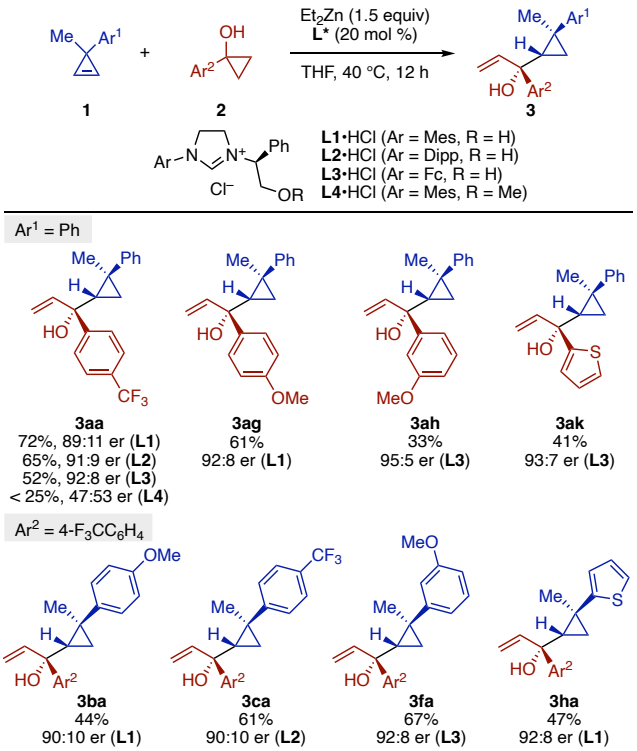
Scheme 3. Hydroxyallylation of Various Cyclopropenes with 1a[a]



[a]The reaction was performed on a 0.1 mmol scale. R' = Me unless otherwise noted.

Given the ability of NHC to accelerate the present hydroxyallylation, we became interested in the feasibility of its enantioselective variant using a chiral NHC. Upon screening several chiral NHCs, we were pleased to find that L-phenylglycinol-derived NHC preligands **L1**•HCl–**L3**•HCl (20 mol %) promoted the model reaction between **1a** and **2a** at 40 °C, affording **3aa** in 52–72% yields with good enantiomeric ratios (ers) of 89:11 to 92:8 (Scheme 4). The free hydroxy moiety of these ligands proved crucial, as the methyl ether analogue **L4**•HCl slowed the reaction and failed to induce enantioselectivity (see Table S1 for additional results of ligand screening). The background reaction in the absence of NHC was also sluggish (10% yield by ^{1}H NMR), demonstrating ligand-accelerated catalysis with the bifunctional ligands **L1**–**L3**. Using these ligands, the enantioselective hydroxyallylation proved feasible across a series of 1-arylcyclopropanol and 3-methyl-3-arylcyclopropenes, displaying enantioselectivities up to 95:5 er. The absolute configuration of the product was determined by conversion of **3aa** into a known chiral compound and comparison of its optical rotation with the literature data (vide infra).

Scheme 4. Enantioselective Hydroxyallylation[a]



[a]The reaction was performed on a 0.1 mmol scale. The enantiomeric ratio was determined by HPLC using chiral stationary phase. Mes = 2,4,6-trimethylphenyl; Dipp = 2,6-diisopropylphenyl; Fc = ferrocenyl.

We performed a series of experiments to shed light on mechanistic aspects of the present reaction. First, the reaction between **1a** and tetradeuterated cyclopropanol **2b**-d_4 under the standard conditions afforded the product **3ab**-d_4 in 44% yield, where the cyclopropyl position *syn* to the hydroxyallyl group was substantially deuterated (69% D; Figure 1a).[18] This observation supports the intermediacy of a cyclopropylzinc species formed through a *syn*-allylzincation process as well as its in situ protonation prior to quenching, where the proton mainly originates from the methylene groups of **2b**-d_4. In agreement with this observation, no deuterium incorporation was observed when the model reaction between **1a** and **2a** was quenched by D_2O. Second, to probe the influence of the NHC and the base on the ring-opening and enolization processes of zinc cyclopropoxide (i.e., the equilibrium among **A**–**C** in Scheme 1c), enantioenriched cyclopropanol **2n** (88:12 er) was treated with Et_2Zn in the absence or presence of these additives (Figure 1b). Without additive, the reaction (12 h) returned the majority of unreacted **2n** with no change in the er. By contrast, the addition of IMes•HCl (20 mol %) resulted in the complete decomposition of **2n** to 2-methyltetralone (**4**) within 3 h. DBU (1 equiv) also promoted the decomposition of **2n** to **4** along with a subtle decrease in the er of **2n** (82:18). The chiral NHC **L1** was also found to accelerate the decomposition of **2n**, interestingly with apparent kinetic resolution (99:1 er for the recovered **2n**). These and additional control experiments on this system (see Table S2 and Scheme S1), along with the reported reactivity of zinc cyclopropoxide and homoenolate,[14] suggest that NHC and DBU are particularly crucial in promoting the enolization process to generate the putative intermediate **C**, which would be rather slow in their absence. Finally, the enantiomeric excess (ee) of **L1** was found to be linearly correlated with the ee of the hydroxyallylation product (Figure 1c). The lack of nonlinear effects suggests that only one molecule of NHC is involved in the enantiodetermining hydroxyallylation step. In this respect, we speculate that NHC coordinates to the allylzinc moiety rather than the zinc enolate moiety of enolized homoenolate, so that it can increase the nucleophilicity of the former moiety.[19]

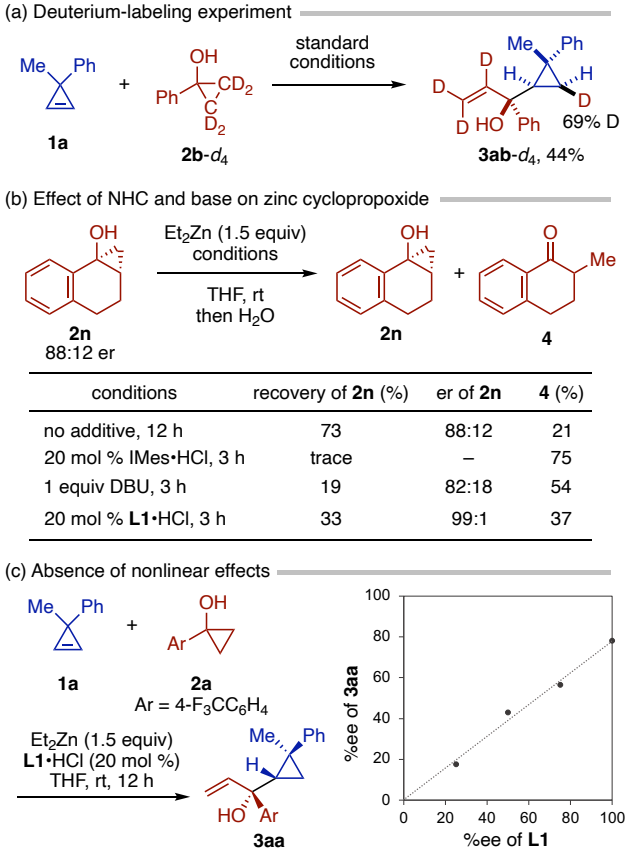
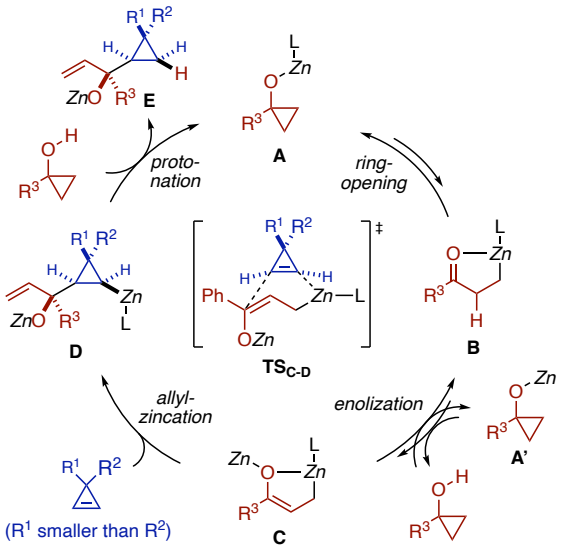


Figure 1. Mechanistic experiments. (a) Reaction of deuterium-labeled cyclopropanol. (b) Effect of NHC and base on the decomposition of zinc cyclopropoxide. (c) Examination of nonlinear effects in the reaction using chiral NHC **L1**.

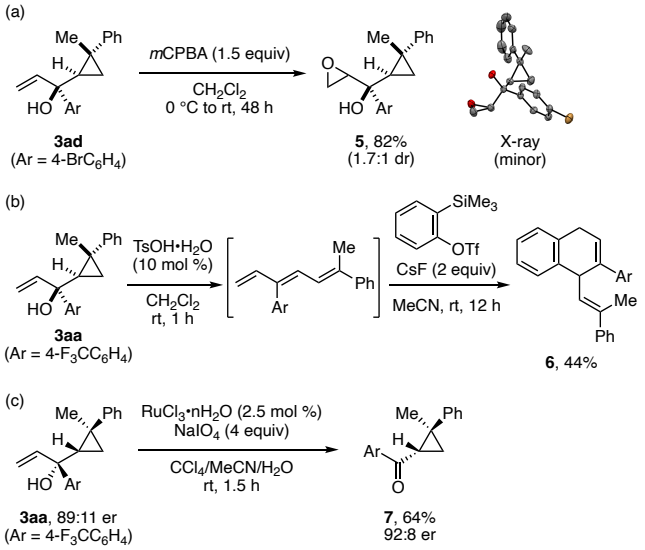
We propose a formal catalytic cycle illustrated in Scheme 5 for the present hydroxyallylation. Ring-opening of NHC-bound zinc cyclopropoxide **A** generates homoenolate **B** in equilibrium. Homoenolate **B** is then enolized with the aid of an appropriate base such as NHC-free cyclopropoxide **A'**, product alkoxide **E**, or externally added DBU. The resulting enolized homoenolate **C** undergoes allylation to cyclopropene. The observed diastereoselectivity can be explained by a half-chair-like transition state $\mathbf{TS_{C\text{-}D}}$, where the cyclopropene exposes its less hindered olefinic face toward the allylzinc nucleophile and points its quaternary carbon vertex away from the ZnO moiety of the enolized homoenolate.[17] Finally, the cyclopropylzinc species **D** would be protonated by the transiently regenerated cyclopropanol (or another proton shuttle) to furnish the product alkoxide **E** and regenerates the NHC-bound cyclopropoxide **A**.

Scheme 5. Proposed Formal Catalytic Cycle



Scheme 6 shows selected transformations of the hydroxyallylated cyclopropanes. Epoxidation of the terminal olefin moiety of **3ad** afforded a diastereomeric mixture (1.7:1) of the epoxide **5** in 82% yield (Scheme 6a). The structure of the minor diastereomer was unambiguously determined by X-ray crystallographic analysis, thus confirming the relative configuration of the three contiguous stereocenters. Exposure of **3aa** to catalytic TsOH•H_2O caused dehydrative C–C bond cleavage of the cyclopropylcarbinol moiety (Scheme 6b).[20] The resulting triene intermediate was allowed to react with benzyne, affording the product **6** arising from [4+2] cycloaddition on the less hindered diene moiety. $RuCl_3$/$NaIO_4$-mediated reaction of enantioenriched **3aa** resulted in the oxidative cleavage of the allylic alcohol moiety to give the acylcyclopropane **7** with stereochemical integrity, for which the absolute configuration was determined by comparison with the literature data.[7b]

Scheme 6. Product Transformations



In summary, we have developed a zinc-mediated stereoselective hydroxyallylation reaction of cyclopropenes using cyclopropanols, affording densely functionalized cyclopropane derivatives with excellent control over three contiguous stereocenters. Mechanistically, the reaction features the generation of enolized homoenolate through the ring-opening of zinc cyclopropoxide, enolization of the resulting homoenolate, and allylzincation of the cyclopropene with this transient prochiral nucleophile. The racemic variant of the reaction is synergistically promoted by an NHC ligand (IMes) and an organic base (DBU), whereas a chiral NHC/hydroxy bifunctional ligand enables catalytic and enantioselective conversion of zinc cyclopropoxide into the hydroxyallylation product. It is worth noting that the present reaction represents a rare example of catalytic enantioselective C–C bond formation involving NHC-supported organozinc species.[19,21,22] Further exploration of ligand-enabled transformations of homoenolates and enolized homoenolates is currently underway.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data for all the new products (PDF).

Accession Codes

CCDC 2314511 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 CB1, 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interests.

ACKNOWLEDGMENT

This work was supported by JSPS KAKENHI (Grant No. 20K23375 (N.Y.), 22K14687 (K.K.), and 22K05254 (A.M.)), Takeda Science Foundation (N.Y.), Astellas Foundation for Research on Metabolic Disorders (N.Y.), Research Support Project for Life Science and Drug Discovery (Basis for Supporting Innovative Drug Discovery and Life Science Research (BINDS)) from AMED (Grant No. JP22ama121040 (N.Y.)), the Takahashi Industrial and Economic Research Foundation (K.K.), the NOVARTIS Foundation (Japan) for the Promotion of Science (K.K.), and the Research Foundation for Pharmaceutical Sciences (K.K.). We thank Dr. Yoshiya Sekiguchi for his preliminary experiments on this work. Professors Hidetoshi Tokuyama and Hirofumi Ueda (Tohoku University) are gratefully acknowledged for the access to a polarimeter.

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