Zinc-Catalyzed β-Allylation of Cyclopropanols via Enolized Homoenolate

Yoshiya Sekiguchi[†] and Naohiko Yoshikai[†,‡,*]

[†]Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, Singapore 637371, Singapore

[‡]Graduate School of Pharmaceutical Sciences, Tohoku University, 6-3 Aoba, Aramaki, Aoba-ku, Sendai 980-8578, Japan

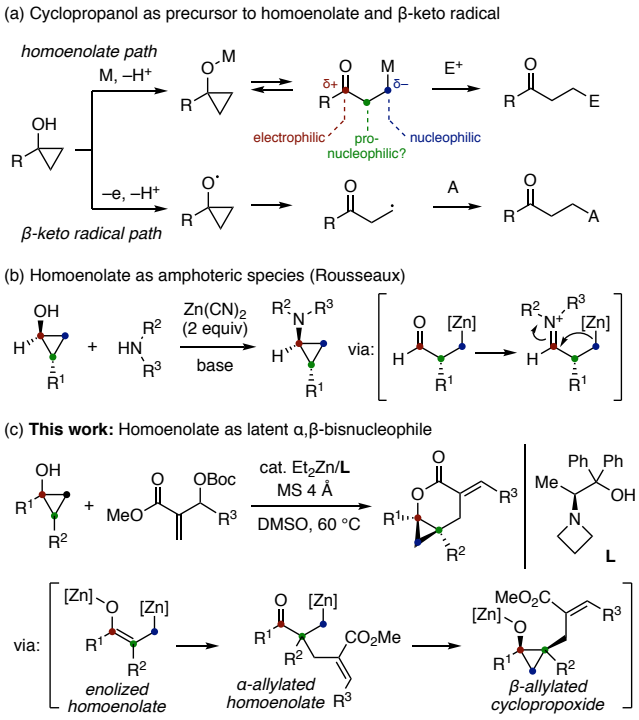
Supporting Information Placeholder

ABSTRACT: We report herein a zinc-catalyzed β-allylation of cyclopropanols with Morita–Baylis–Hillman (MBH) carbonates with retention of the cyclopropane ring. The reaction is promoted by a zinc aminoalkoxide catalyst generated from Et_2Zn and a β-aminoalcohol, affording cyclopropyl-fused α-alkylidene-δ-valerolactone derivatives in moderate to good yields. A bicyclic 1,2-disubstituted cyclopropanols undergoes allylation at the sterically more hindered β-position. This observation, together with other mechanistic experiments, suggest that the present reaction does not proceed via direct β-C–H cleavage of the cyclopropanol, but rather involves zinc homoenolate and its enolization to generate a key bis-nucleophilic species. α-Allylation of this "enolized homoenolate" with MBH carbonate would be followed by regeneration of the cyclopropane ring and irreversible lactonization. A sequence of the present reaction and known cyclopropanol transformation provides an opportunity to transform a simple cyclopropanol into α,β- or β,β-difunctionalized ketones.

The cyclopropane ring has attracted the attention of synthetic chemists over decades for its high strain-driven reactivity as well as for its presence in many biologically active substances.[1] Among all cyclopropanes, cyclopropanols represent unique three-carbon synthons in synthetic methodology development and total synthesis.[2] They have been extensively explored as precursors to homoenolates and β-keto radicals, which serve as intermediates of orthogonal reactivity for the synthesis of β-functionalized ketones (Scheme 1a). The former species are typically generated via ring-opening tautomerization of metal cyclopropoxide, while formation of the latter involves one-electron oxidation to cyclopropoxy radical or its equivalent followed by facile ring opening. Because of the high propensity of cyclopropanols toward these and other ring opening modes, it is difficult to install a new functional group into existing cyclopropanols without rapture of the three-membered ring. This marks a sharp contrast with the extensive development of C–H activation of other types of cyclopropanes containing directing groups.[3]

While metal homoenolate has been predominantly used as precursor to β-functionalized ketones, it is intrinsically amphoteric species that has nucleophilic β-carbon and electrophilic carbonyl group (Scheme 1a). This amphoteric nature has recently been exploited on several occasions.[4] A particularly notable example in this context is the zinc-mediated conversion of cyclopropanol to cyclopropylamine by Rousseaux, which elegantly utilized the electrophilicity of the aldehyde allowing the condensation with secondary amine and the nucleophilicity of the carbon–zinc bond allowing the ring closure (Scheme 1b).[5] Inspired by this and other precedents on zinc homoenolate[6] and prompted by our own work on catalytic generation of zinc homoenolate,[7] we wondered if it would be possible to enolize the zinc homoenolate, thus rendering the α-carbon nucleophilic (see Scheme 1a). Electrophilic trapping of the resulting bis-nucleophilic, enolized homoenolate at the α-position, followed by ring closure of the homoenolate, would furnish a β-functionalized cyclopropanol. Along with this hypothesis, we have discovered a zinc-catalyzed β-allylation of a cyclopropanol with a Morita–Baylis–Hillman carbonate *with retention* of the cyclopropyl ring, which is reported herein (Scheme 1c). A catalyst generated from Et_2Zn and a β-amino alcohol promotes allylation of the β-position and subsequent lactonization to afford cyclopropyl-fused α-alkylidene-δ-valerolactones in moderate to good yields, which overall represents the first example of direct C–H functionalization of a cyclopropanol. Mechanistic experiments have proved consistent with the proposed reaction pathway involving α-functionalization of the enolized homoenolate.

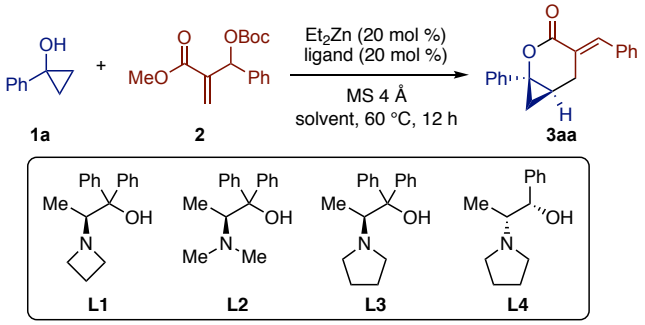
Scheme 1. Cyclopropanols as Three-Carbon Synthons



To realize our hypothetical ring-opening/α-functionalization/ring-closure functionalization of cyclopropanol in a catalytic manner, two major requirements, among others, should be satisfied. First, the electrophile should not be directly intercepted by the initially generated zinc homoenolate, but has to wait it to enolize for the desired α-functionalization. Second, even if the α-functionalization and subsequent ring closure were feasible, the thus-formed cyclopropanol product should not take part in the homoenolate chemistry again, which might lead to multiple substitution or ring-opening decomposition. Retrospectively, MBH carbonate appears to meet these requirements because it lacks reactivity toward organozinc reagents and because its ester moiety allows lactonization with the cyclopropanol, thus irreversibly affording the unreactive product.

Table 1 shows a part of the optimization of the reaction between 1-phenylcyclopropanol (**1a**) and MBH carbonate (**2a**) derived from methyl acrylate and benzaldehyde. A catalytic system comprised of Et_2Zn (20 mol %), alanine-derived amino alcohol **L1** (20 mol %), and molecular sieves (MS) 4 Å promoted the reaction in DMSO at 60 °C to afford [4.1.0]-bicyclic lactone **3aa** in 49% yield (entry 1). The reaction became sluggish in less polar and less coordinating solvents such as THF and toluene (entries 2 and 3). Omission of either MS 4 Å or **L1** led to a diminished yield of **3aa** (entries 4 and 5). Amino alcohols other than **L1** were as ineffective as the ligand-free system, except that the structurally similar **L3** displayed a comparable performance (entries 6–8). Note that these and other chiral amino alcohols tested induced only modest enantioselectivity (up to 18% ee; see Table S1). Finally, the yield of **3aa** could be improved to 74% with excess **1a** (1.5 equiv), reduced catalyst loadings (10 mol % Et_2Zn and 15 mol % **L1**), and prolonged reaction time (24 h; entries 9 and 10).

Table 1. Zinc-Catalyzed Addition of 1-Phenylcyclopropanol (1a) to Chalcone (2a)[a]



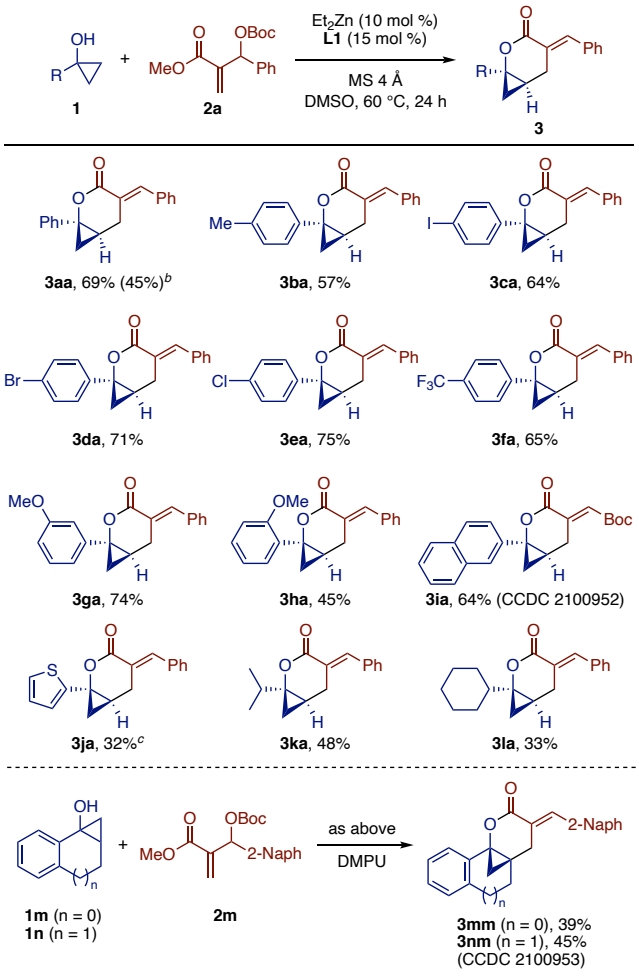
entry	ligand	solvent	yield (%)[b]
1	**L1**	DMSO	49
2	**L1**	THF	12
3	**L1**	toluene	9
4[c]	**L1**	DMSO	13
5	–	DMSO	22
6	**L2**	DMSO	32
7	**L3**	DMSO	44
8	**L4**	DMSO	20
9[d]	**L1**	DMSO	63
10[d,e]	**L1**	DMSO	74

[a]The reaction was performed using 0.10 mmol each of **1a** and **2a** in 0.9 mL solvent (0.11 M). [b]Determined by GC using mesitylene as an internal standard. [c]4 Å MS was omitted. [d]0.15 mmol of **1a** and 0.10 mmol of **2a** were used. [e]10 mol % of Et_2Zn and 15 mol % of **L1** were used. The reaction was performed for 24 h.

With the optimized catalytic system (Table 1, entry 10) in hand, we explored the scope of the present allylation. First, a variety of cyclopropanols were subjected to the reaction with **2a** (Scheme 2). A series of 1-arylcyclopropanols participated in the allylation to afford the corresponding lactones **3aa**–**3ja** in moderate to good yields, with tolerance to methyl, iodo, bromo, chloro, and trifluoromethyl groups. Methoxy groups on the *meta* (**3ga**) and the *ortho* (**3ha**) positions were also tolerated. The reaction of **1a** could be performed on a 5 mmol scale, albeit in a moderate yield (45%). 1-(2-Naphthyl)- and 1-(2-thienyl)cyclopropanols also afforded the desired products **3ia** and **3ja**, respectively. The molecular structure of the former was unambiguously confirmed by X-ray crystallographic analysis. The latter was difficult to purify by flash chromatography and thus was obtained by recrystallization in modest yield (32%). 1-Alkylcyclopropanols bearing secondary alkyl groups also reacted with **2a** to afford the corresponding products **3ka** and **3la** in moderate yields, while the reaction of 1-

pentylcyclopropanol was complex and failed to give the desired product. Interestingly, bicyclic cyclopropanols **1m** and **1n** underwent allylation with MBH carbonate **2m** at the more hindered β-position to afford methano-bridged polycyclic lactones **3mm** and **3nm**, respectively, in moderate yields. The structure of the latter was confirmed by X-ray crystallographic analysis. Given these results, it appeared less likely that the present reaction proceeded through direct cleavage of the β-C–H bond (vide infra).

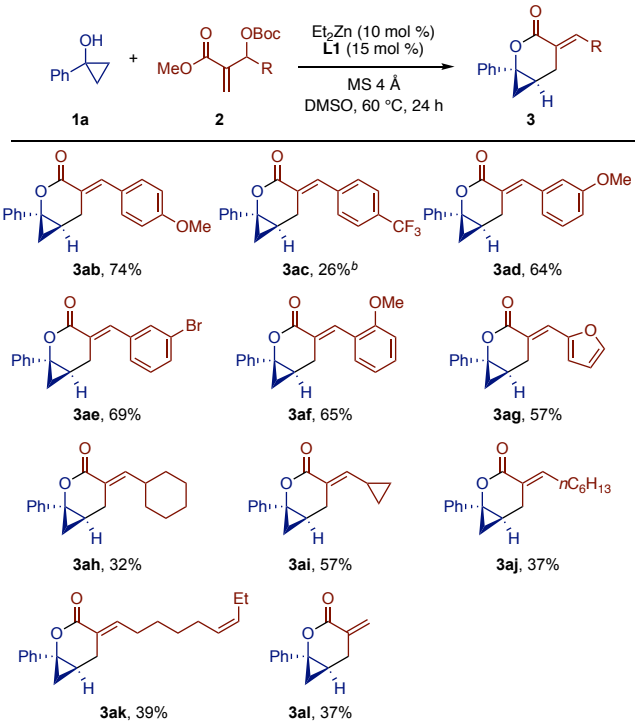
Scheme 2. β-Allylation of Various Cyclopropanols with MBH Carbonate 2a[a]



[a]The reaction was performed on a 0.3 mmol scale under the conditions in Table 1, entry 10. [b]The yield of a 5 mmol scale reaction is shown in the parentheses. [c]The product was isolated by recrystallization. The yield was based on the obtained crystals.

We next explored the addition of **1a** to various MBH carbonates (Scheme 3). A series of MBH carbonates derived from (hetero)aryl aldehydes proved to be good substrates, affording the corresponding bicyclic lactones **3ab**–**3ag** in moderate to good yields. Those derived from aliphatic aldehydes were also tolerated to furnish the products **3ah**–**3ak**, albeit in somewhat lower yields. The formaldehyde-derived MBH carbonate **2l** also took part in the reaction to give the desired product **3al**. It should be mentioned that change of the methyl ester moiety of the MBH carbonate to cyclohexyl or *tert*-butyl ester led to diminished yields (see Table S1).

Scheme 3. Allylation of Cyclopropanol 1a with Various MBH Carbonates[a]



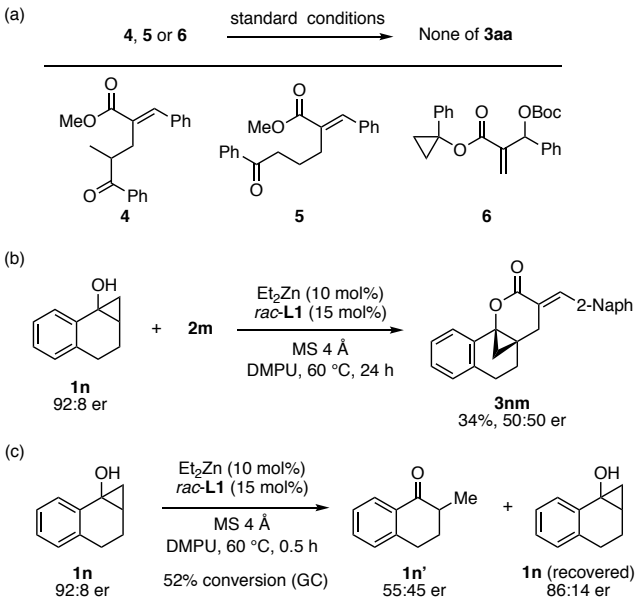
[a]The reaction was performed on a 0.3 mmol scale under the conditions in Table 1, entry 10. [b]The product was isolated by recrystallization. The yield was based on the obtained crystals.

To gain insight into the mechanism, we performed a series of control experiments. Firstly, we synthesized compounds **4**, **5**, and **6** to probe the possibility of mechanisms involving either of them as the intermediate (Scheme 4a). The compound **4** corresponds to the product of α-allylation of propiophenone with the MBH carbonate **2a**, which is a byproduct (12%) actually obtained in the reaction between **1a** and **2a**. Another isomer **5** is the product of the ring-opening allylation of **1a** with **2a** via homoenolate, which was prepared by our recently developed nickel-catalyzed reaction.[8] Cyclopropyl ester **6** was also synthesized to examine the possibility of an ester exchange between **1a** and **2a** prior to allylation. In fact, none of **4**–**6** gave rise to even a trace amount of the lactone **3aa**. The failure of **4** and **5** excludes the possibility of β-deprotonation and cyclization of the resulting homoenolate to cyclopropoxide, which was unsurprising in light of the low acidity of the β-position. Meanwhile, the lack of reactivity of **6** ruled out a pathway involving ester-directed β-deprotonation of the cyclopropane ring.

Next, we used an enantioenriched sample (92:8 er) of the cyclopropanol **1n**, which was prepared by kinetic

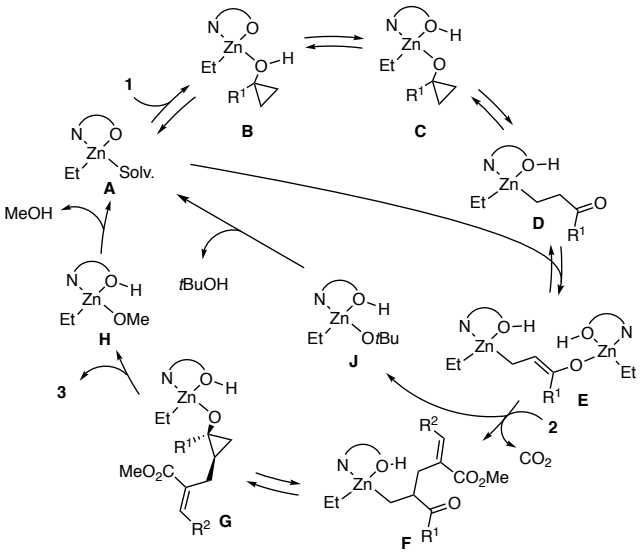
resolution using Et_2Zn/**L4** catalyst (see the SI for detail) to probe the stereochemical integrity during the reaction. The reaction of enantioenriched **1n** with **2m** using racemic **L1** afforded a racemic mixture of the product **3nm** in 34% yield (Scheme 4b). This excludes the possibility of direct β-allylation of **1n** and indicates that the stereochemical information of **1n** is lost through ring-opening formation of zinc homoenolate and its enolization (vide infra). Exposure of **1n** to the reaction conditions in the absence of MBH carbonate resulted in conversion (52% in 0.5 h) into its ketone isomer **1n'** as a near racemic mixture (55:45 er) as well as recovery of **1n** with a partially decreased enantiomeric ratio (84:16 er; Scheme 4c). While the former observation may be attributable not only to the enolization of homoenolate but also to that of the ketone **1n'** itself, the latter appears to reflect the reversibility of the ring-opening and the homoenolate enolization.

Scheme 4. Control Experiments



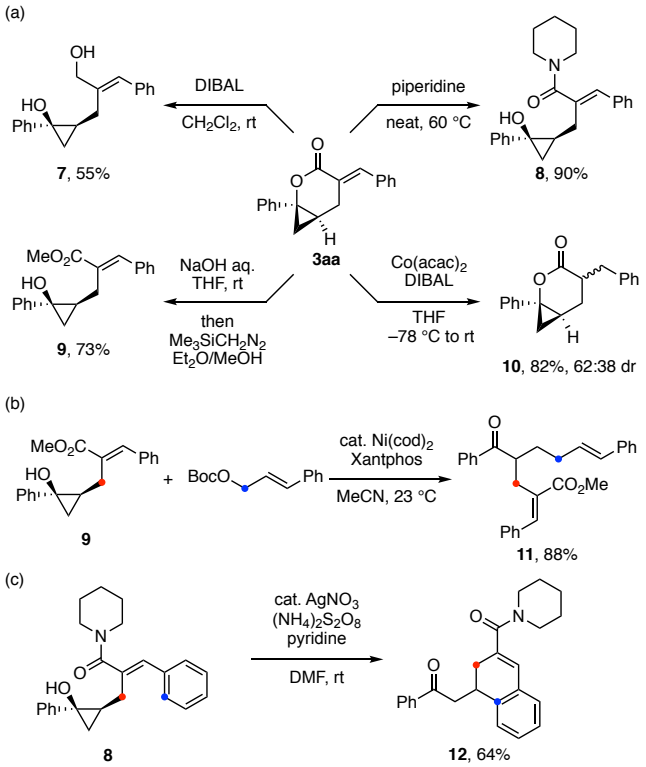
On the basis of the above experiments and previous studies on organozinc/β-amino alcohol systems including ours,[7,9] we propose a catalytic cycle in Scheme 5. Et_2Zn and **L1** would afford ethylzinc aminoalkoxide **A**, which would exist in equilibrium with alkoxide-bridged dimer (not shown). Coordination of cyclopropanol **1** to **A** would give the intermediate **B**, followed by deprotonation of the cyclopropyl OH with the internal aminoalkoxide base to generate the cyclopropoxide species **C**. Homoenolate **D**, formed by ring-opening of **C**, would be deprotonated by another molecule of **A** to generate the "enolized homoenolate" **E**.[10] Interception of **E** with MBH carbonate **2** would afford α-allylated homoenolate **F** along with ethylzinc *tert*-butoxide **J**, which would regenerate **A** by releasing *t*BuOH. Reconstruction of the cyclopropane ring from **F** would be followed by intramolecular transesterification of the cyclopropoxide **G** to afford **3** and ethylzinc methoxide **H**, which would release MeOH and regenerate **A**. The cyclopropane reconstruction might also take place to generate the *trans* isomer of **G** in a reversible manner, but the overall reaction would be driven by the transesterification of **G**.

Scheme 5. Possible Catalytic Cycle



Selected transformations of the product **3aa** are shown in Scheme 6a. Reduction of the lactone moiety by DIBAL provided the diol **7**. Treatment with piperidine afforded the cyclopropanol **8** bearing amide moiety in an excellent yield. Basic hydrolysis and subsequent treatment with trimethylsilyldiazomethane furnished the methyl ester **9**. Note that the compound **9** was not observed in the β-allylation, pointing to facile transesterification under the reaction conditions. The 1,4-reduction was achieved by DIBAL in the presence of a stoichiometric amount of $Co(acac)_2$ to afford the lactone **10** as a mixture of separable diastereomers. Furthermore, the β-functionalized cyclopropanols obtained above could be further exploited as precursors to homoenolate or β-keto radical. Thus, the nickel-catalyzed reaction of **9** with cinnamyl carbonate[8] afforded the α,β-difunctionalized ketone **11** in good yield (Scheme 6b). Meanwhile, treatment of **8** with catalytic $AgNO_3$ and ammonium persulfate[11] resulted in β-scission of the more substituted C–C bond and oxidative radical cyclization onto the nearby benzene ring to give the β,β-difunctionalized ketone, that is, dihydronaphthalene derivative **12** (Scheme 6c).

Scheme 6. Product Transformations



In summary, we have developed a zinc-catalyzed β-allylation of cyclopropanols with MBH carbonate without rapture of the cyclopropane ring. The reaction features a ring-opening/α-allylation/ring-closure mechanism involving enolized homoenolate as the key intermediate. The modest electrophilicity of MBH carbonate as well as its ester functionality has allowed this novel reactivity pattern feasible under catalytic conditions, affording cyclopropane-fused α-alkylidene-δ-valerolactone derivatives in moderate to good yields. The mechanistic experiments are consistent with the indirect, roundabout mechanism for the ring functionalization. The small but finite asymmetric induction observed holds promise for the development of an enantioselective variant. While interconversion between homoenolate and enolate represents a common and important process in N-heterocyclic carbene catalysis,[12] the present reaction represents a rare example of related process in the chemistry of metal homoenolates. Further exploration of metal homoenolate as a latent α,β-bisnucleophilic species is ongoing in our laboratory.

ASSOCIATED CONTENT

Supporting Information

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

Accession Codes

CCDC 2100952-2100953 contain 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.

AUTHOR INFORMATION

Corresponding Author

*naohiko.yoshikai.c5@tohoku.ac.jp

Notes

The authors declare no competing financial interests.

ACKNOWLEDGMENT

This work was supported by the Ministry of Education (Singapore) and Nanyang Technological University (MOE2016-T2-2-043 and RG101/19). We thank Dr. Yongxin Li (Nanyang Technological University) for his assistance with the X-ray crystallographic analysis.

REFERENCES

(1) (a) Dian, L.; Marek, I. Asymmetric Preparation of Polysubstituted Cyclopropanes Based on Direct Functionalization of Achiral Three-Membered Carbocycles. *Chem. Rev.* **2018**, *118*, 8415-8434. (b) Fumagalli, G.; Stanton, S.; Bower, J. F. Recent Methodologies That Exploit C-C Single-Bond Cleavage of Strained Ring Systems by Transition Metal Complexes. *Chem. Rev.* **2017**, *117*, 9404-9432. (c) Schneider, T. F.; Kaschel, J.; Werz, D. B. A New Golden Age for Donor-Acceptor Cyclopropanes. *Angew. Chem. Int. Ed.* **2014**, *53*, 5504-5523. (d) Rubin, M.; Rubina, M.; Gevorgyan, V. Transition Metal Chemistry of Cyclopropenes and Cyclopropanes. *Chem. Rev.* **2007**, *107*, 3117-3179.

(2) (a) McDonald, T. R.; Mills, L. R.; West, M. S.; Rousseaux, S. A. L. Selective Carbon-Carbon Bond Cleavage of Cyclopropanols. *Chem. Rev.* **2021**, *121*, 3-79. (b) Cai, X.; Liang, W.; Dai, M. Total Syntheses via Cyclopropanols. *Tetrahedron* **2019**, *75*, 193-208. (c) Nikolaev, A.; Orellana, A. Transition-Metal-Catalyzed C–C and C–X Bond-Forming Reactions Using Cyclopropanols. *Synthesis* **2016**, *48*, 1741-1768. (d) Sekiguchi, Y.; Yoshikai, N. Metal-Catalyzed Transformations of Cyclopropanols via Homoenolates. *Bull. Chem. Soc. Jpn.* **2021**, *94*, 265-280.

(3) Sustac Roman, D.; Charette, A. B. In *C-H Bond Activation and Catalytic Functionalization II*; Dixneuf, P. H., Doucet, H., Eds.; Springer: 2016, p 91-113.

(4) (a) Yang, J.; Shen, Y.; Lim, Y. J.; Yoshikai, N. Divergent Ring-Opening Coupling between Cyclopropanols and Alkynes under Cobalt Catalysis. *Chem. Sci.* **2018**, *9*, 6928-6934. (b) Yang, J.; Sun, Q.; Yoshikai, N. Cobalt-Catalyzed Regio-and Diastereoselective Formal [3+ 2] Cycloaddition between Cyclopropanols and Allenes. *ACS Catal.* **2019**, *9*, 1973-1978. (c) Davis, D. C.; Walker, K. L.; Hu, C.; Zare, R. N.; Waymouth, R. M.; Dai, M. Catalytic Carbonylative Spirolactonization of Hydroxycyclopropanol. *J. Am. Chem. Soc.* **2016**, *138*, 10693-10699. (d) Cai, X.; Liang, W.; Liu, M.; Li, X.; Dai, M. Catalytic Hydroxycyclopropanol Ring-Opening Carbonylative Lactonization to Fused Bicyclic Lactones. *J. Am. Chem. Soc.* **2020**, *142*, 13677-13682.

(5) (a) Mills, L. R.; Barrera Arbelaez, L. M.; Rousseaux, S. A. L. Electrophilic Zinc Homoenolates: Synthesis of Cyclopropylamines from Cyclopropanols and Amines. *J. Am. Chem. Soc.* **2017**, *139*, 11357-11360. (b) West, M. S.; Lills, L. R.; McDonald, T. R.; Lee, J. B.; Ensan, D.; Rousseaux, S. A. L. Synthesis of trans-2-Substituted Cyclopropylamines from α-Chloroaldehydes. *Org. Lett.* **2019**, *21*, 8409-8413.

(6) (a) Nakamura, E.; Aoki, S.; Sekiya, K.; Oshino, H.; Kuwajima, I. Carbon-Carbon Bond-Forming Reactions of Zinc Homoenolate of Esters. A Novel Three-Carbon Nucleophile with General Synthetic Utility. *J. Am. Chem. Soc.* **1987**, *109*, 8056-8066. (b) Das, P. P.;

Belmore, K.; Cha, J. K. S_N2' Alkylation of Cyclopropanols via Homoenolates. *Angew. Chem. Int. Ed.* **2012**, *51*, 9517-9520.

(7) Sekiguchi, Y.; Yoshikai, N. Enantioselective Conjugate Addition of Catalytically Generated Zinc Homoenolate. *J. Am. Chem. Soc.* **2021**, *143*, 4775-4781.

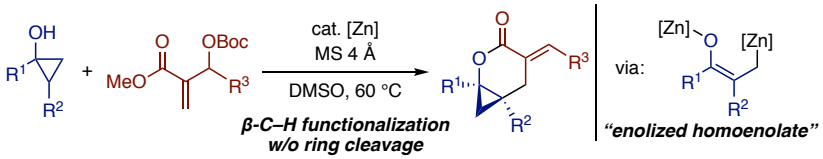
(8) Sekiguchi, Y.; Lee, Y. Y.; Yoshikai, N. Nickel-Catalyzed Ring-Opening Allylation of Cyclopropanols via Homoenolate. *Org. Lett.* **2021**, DOI: 10.1021/acs.orglett.1c02072.

(9) (a) Noyori, R.; Suga, S.; Oka, H.; Kitamura, M. Self and Nonself Recognition of Chiral Catalysts: The Origin of Nonlinear Effects in the Amino-Alcohol Catalyzed Asymmetric Addition of Diorganozincs to Aldehydes. *Chem. Rec.* **2001**, *1*, 85-100. (b) Frantz, D. E.; Fassler, R.; Tomooka, C. S.; Carreira, E. M. The Discovery of Novel Reactivity in the Development of C-C Bond-Forming Reactions: In Situ Generation of Zinc Acetylides with Zn(II)/R_3N. *Acc. Chem. Res.* **2000**, *33*, 373-381.

(10) Huang, W.; Meng, F. Cobalt-Catalyzed Diastereo- and Enantioselective Hydroalkylation of Cyclopropenes with Cobalt Homoenolates. *Angew. Chem. Int. Ed.* **2021**, *60*, 2694-2698.

(11) Chiba, S.; Cao, Z.; El Biary, S. A. A.; Narasaka, K. Generation of β-Keto Radicals from Cyclopropanols Catalyzed by $AgNO_3$. *Chem. Lett.* **2006**, *35*, 18-19.

(12) (a) Enders, D.; Niemeier, O.; Henseler, A. Organocatalysis by N-Heterocyclic, Carbenes. *Chem. Rev.* **2007**, *107*, 5606-5655. (b) Marion, N.; Diez-Gonzalez, S.; Nolan, S. P. N-Heterocyclic Carbenes as Organocatalysts. *Angew. Chem. Int. Ed.* **2007**, *46*, 2988-3000. (c) Hopkinson, M. N.; Richter, C.; Schedler, M.; Glorius, F. An Overview of N-Heterocyclic Carbenes. *Nature* **2014**, *510*, 485-496. (d) Mahatthananchai, J.; Bode, J. W. On the Mechanism of N-Heterocyclic Carbene-Catalyzed Reactions Involving Acyl Azoliums. *Acc. Chem. Res.* **2014**, *47*, 696-707. (e) Flanigan, D. M.; Romanov-Michailidis, F.; White, N. A.; Rovis, T. Organocatalytic Reactions Enabled by N-Heterocyclic Carbenes. *Chem. Rev.* **2015**, *115*, 9307-9387.


OH
R1
R2
+
MeO
O
OBoc
R3
cat. [Zn]
MS 4 Å
DMSO, 60 °C
β-C–H functionalization
w/o ring cleavage
O
O
R1
R2
R3
via:
[Zn]
O
[Zn]
R1
R2
"enolized homoenolate"