Zinc-Catalyzed β-Allylation of Cyclopropanols via Enolized Homoenolate

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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 Et₂Zn 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 homoenolate6 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 Et₂Zn 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
Finally, modest enantioselectivity and other chiral amino alcohols diminished yield of (between irreversibly affording allows lactonization with the cyclopropanol which might le if the initially generated electrophile should not be directly intercepted by the requirements functionalization and subsequent 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 homoenoate, 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 homoenoate 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 Et₂Zn (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 % Et₂Zn 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)

| entry | ligand | solvent | yield (%) |
|-------|--------|---------|-----------|
| 1     | L₁     | DMSO    | 49        |
| 2     | L₁     | THF     | 12        |
| 3     | L₁     | toluene | 9         |
| 4a    | L₁     | DMSO    | 13        |
| 5     | –      | DMSO    | 22        |
| 6     | L₂     | DMSO    | 32        |
| 7     | L₃     | DMSO    | 44        |
| 8     | L₄     | DMSO    | 20        |
| 9d    | L₁     | DMSO    | 63        |
| 10d   | L₁     | DMSO    | 74        |

*The reaction was performed using 0.10 mmol each of 1a and 2a in 0.9 mL solvent (0.11 M). Determined by GC using mesitylene as an internal standard. 4 Å MS was omitted. 0.15 mmol of 1a and 0.10 mmol of 2a were used. 10 mol % of Et₂Zn 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 3nn, 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 CYCLOPROANOLS WITH MBH CARBONATE 2a

The reaction was performed on a 0.3 mmol scale under the conditions in Table 1, entry 10. 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

The reaction was performed on a 0.3 mmol scale under the conditions in Table 1, entry 10. 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 homoenoate, which was prepared by our recently developed nickel-catalyzed reaction. 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 homoenoate 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 Et₂Zn/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**

(a) 4, 5 or 6 standard conditions — None of 3aa

(b) 1n + 2m

- Et₂Zn (10 mol%) rac-L1 (15 mol%)
- MS 4 Å DMPU, 60 °C, 24 h
- 3nm
- 34%, 50:50 er

(c) 1n

- Et₂Zn (10 mol%) rac-L1 (15 mol%)
- MS 4 Å DMPU, 60 °C, 0.5 h
- 1n′ 55:45 er
- 1n (recovered) 86:14 er

On the basis of the experiments and previous studies on organozinc/β-amino alcohol systems including ours,⁷ ⁹ we propose a catalytic cycle in Scheme 5. Et₂Zn 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 βBuOH. Reconstruction of the cyclopropane ring from F would be followed by intramolecular transesterification of the cyclopropoxide G to afford 3 and ethylzine 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 carbonate¹¹ afforded the α,β-difunctionalized ketone 11 in good yield (Scheme 6b). Meanwhile, treatment of 8 with catalytic AgNO₃ and ammonium persulfate¹¹ 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-alkyldene-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, 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.

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Notes

The authors declare no competing financial interests.

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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) Funmagalli, 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.; Georgyv, V. Transition Metal Chemistry of Cyclopropanes and Cyclopropanols. 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-Catalysed 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 Regioand 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 Carboxylative Spirolactonization of Hydroxyxycyclopropanol. J. Am. Chem. Soc. 2016, 138, 10693-10699. (d) Cai, X.; Liang, W.; Liu, M.; Li, X.; Dai, M. Catalytic Hydroxyxycyclopropanol Ring-Opening Carboxylative 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. 2’ 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.1e02072.

(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. Rev. 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)/R2N. 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 AgNO3. Chem. Lett. 2006, 35, 18-19.

(12) (a) Enders, D.; Niemeier, O.; Henseler, A. Organocatalysis by N-Heterocyclic Carbene. Chem. Rev. 2007, 107, 5606-5655. (b) Marion, N.; Diez-Gonzalez, S.; Nolan, S. P. N-Heterocyclic Carbene 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.
β-C–H functionalization w/o ring cleavage via: "enolized homoenolate"