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Lewis Acid Mediated Reactions of 1-Cyclopropyl-2-arylethanones with Allenic Esters: A Facile Synthetic Protocol for the Preparation of Dihydrofuro[2,3-*h*]chromen-2-one Derivatives

Min Shi,* Xiang-Ying Tang, and Yong-Hua Yang

State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, China
mshi@mail.sioc.ac.cn

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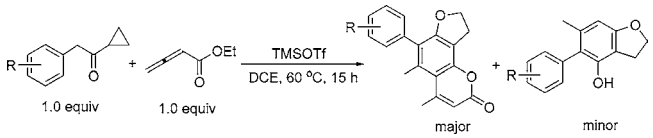
ABSTRACT



TMSOTf-mediated reactions of 1-cyclopropyl-2-arylethanones with allenic esters afford a novel method for the synthesis of dihydrofuro[2,3-*h*]chromen-2-one derivatives in moderate to good yields. This process is a sequential reaction involving a nucleophilic ring-opening reaction of the cyclopropane by H_2O, two intermolecular aldol-type reactions and one intramolecular aldol-type reaction, a cyclic transesterification, dehydration, and aromatization mediated by Lewis acid.

Cyclopropane-containing compounds, as versatile building blocks in organic synthesis, have been well understood.[1] The ring-opening reactions of cyclopropyl ketones are synthetically useful reactions that have been studied extensively. Previously, we reported $SnCl_4$-mediated reactions of cyclopropyl alkyl ketones with α-ketoesters to afford a novel method for the synthesis of 1,6-dioxa-spiro[4.4]non-3-en-2-ones with high stereoselectivities in moderate to good yields.[2] In this paper, we wish to report Lewis acid mediated reactions of 1-cyclopropyl-2-arylethanones with allenic esters for the construction of dihydrofuro[2,3-*h*]chromen-2-one skeletons.

Initial studies were aimed at finding the optimal reaction conditions for the Lewis acid mediated reaction. Using 1-cyclopropyl-2-arylethanone **1a** as the substrate, we examined the reaction of **1a** (1.0 equiv) with ethyl 2,3-butadienoate (2.0 equiv) in the presence of a variety of Lewis acids. The results are summarized in Table 1. Using TMSOTf (1.0 equiv) as the catalyst in 1,2-dichloroethane (DCE) with 5.4 μL of water (1.0 equiv) at 60 °C, 4,5-dimethyl-6-phenyl-8,9-dihydrofuro[2,3-*h*]chromen-2-one **2a**, which was unam-

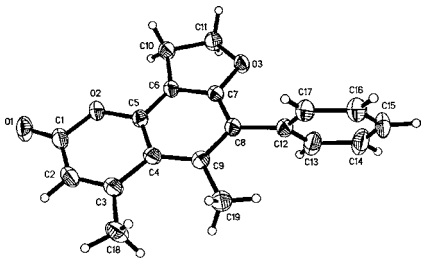


Figure 1. X-ray crystal structure of **2a**.

(1) (a) Reissig, H.-U.; Zimmer, R. *Chem. Rev.* **2003**, *103*, 1151. (b) Paquette, L. A. *Chem. Rev.* **1986**, *86*, 733. (c) Wong, H. N. C.; Hon, M.-Y.; Tse, C.-W.; Yip, Y.-C.; Tanko, J.; Hudlicky, T. *Chem. Rev.* **1989**, *89*, 165. (d) de Meijere, A.; Wessjohann, L. *Synlett* **1990**, 20. (e) Kulinkovich, O. G. *Russ. Chem. Rev.* **1993**, *62*, 839. (f) Kulinkovich, O. G. *Pol. J. Chem.* **1997**, 849. (g) Wenkert, E. *Acc. Chem. Res.* **1980**, *13*, 27. (h) Wenkert, E. *Heterocycles* **1980**, *14*, 1703. (i) Seebach, D. *Angew. Chem.* **1979**, *91*, 259; *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 239. (j) Gnad, F.; Reiser, O. *Chem. Rev.* **2003**, *103*, 1603.

(2) Yang, Y.-H.; Shi, M. *Org. Lett.* **2006**, *8*, 1709−1712.

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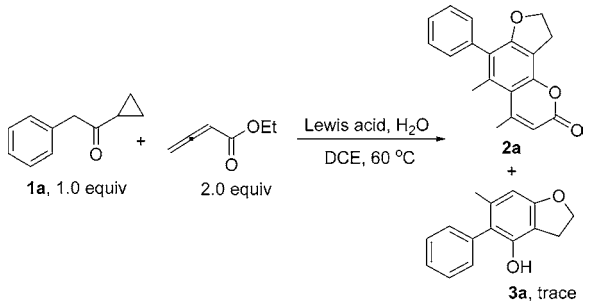
Table 1. Lewis Acid Mediated Reactions of 1-Cyclopropyl-2-arylethanone **1a** with Ethyl 2,3-Butadienoate



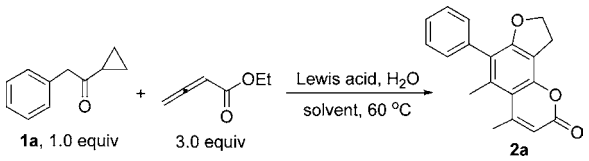
entry	Lewis acid (equiv)	water (μL)	time (h)	yield (%)[a]
1	TMSOTf (1.0)	5.4	15	57
2	BF_3·Et_2O (1.0)	5.4	24	trace
3	Yb(OTf)$_3$ (1.0)	5.4	15	0
4	Sc(OTf)$_3$ (1.0)	5.4	15	0
5	La(OTf)$_3$ (1.0)	5.4	15	0
6	Zr(OTf)$_4$ (1.0)	5.4	15	17
7	Cu(OTf)$_2$ (1.0)	5.4	15	12
8	Sn(OTf)$_2$ (1.0)	5.4	15	trace
9	TfOH (1.0)	5.4	15	42
10	$TiCl_4$ (1.0)	5.4	15	0
11	TfOH (0.1)	5.4	15	22
12	TMSOTf (1.0)	10.8	15	46
13	TMSOTf (1.0)	16.2	15	29
14	TMSOTf (1.0)	0	15	41
15	$TiCl_4$ (1.0)/TfOH (0.1)	0	15	11
16	TMSOTf (1.0)/TfOH (1.0)	0	15	52
17	TMSOTf (1.0)/Et_3N (1.0)	0	15	0
18	TMSOTf (1.0)/OEt_2 (1.0)	0	15	40

[a] Isolated yields.

biguously determined by X-ray diffraction (Figure 1),[3] was formed in 57% yield along with a trace amount of 2,3-dihydrobenzofuran-4-ol derivative **3a** (Table 1, entry 1). The examination of various Lewis acids and the Brønsted acid (TfOH) revealed that TMSOTf is the best one for the reaction under identical conditions (Table 1, entries 2−11). Increasing the amount of water did not improve the yield of **2a** (Table 1, entries 12 and 13). In the absence of water, **2a** was obtained in 41% yield, suggesting that addition of extra water is required in this reaction (Table 1, entry 14). The mixed catalysts of $TiCl_4$ (0.1 equiv)/TfOH (0.1 equiv) and TMSOTf (1.0 equiv)/TfOH (1.0 equiv) produced **2a** in 11 and 52% yields, respectively (Table 1, entries 15 and 16).[4] Lewis basic additives of Et_3N and Et_2O (1.0 equiv) gave **2a** in 0 and 41% yield (Table 1, entries 17 and 18).[5]

Next, we attempted to further optimize the reaction conditions by changing the ratios of **1a** and ethyl 2,3-butadienoate and the solvents using TMSOTf as a promoter. The results of **1a** (1.0 equiv) with ethyl 2,3-butadienoate (3.0 equiv) are shown in Table 2 in the presence of TMSOTf or

Table 2. Further Optimization of the Reaction Conditions with **1a** (1.0 equiv) and Ethyl 2,3-Butadienoate (3.0 equiv)

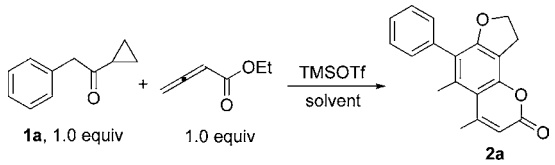


entry	Lewis acid (equiv)	solvent	time (h)	yield (%)[a]
1	TMSOTf (1.0)	DCE	15	48
2	TMSOTf (1.0)/TfOH (1.0)	DCE	15	51
3	TfOH (1.0)/BF_3·Et_2O (1.0)	DCE	15	27
4	TfOH (1.0)/Zr(OTf)$_4$ (1.0)	DCE	15	18
5	TMSOTf (1.0)/Et_3N (1.5)	DCE	10	N.R.
6	TMSOTf	CH_3CN	48	trace
7	TMSOTf	hexane	72	trace
8	TMSOTf	THF	48	N.R.
9	TMSOTf	toulene	15	46

[a] Isolated yields.

mixed catalysts. We found that the yield of **2a** could not be improved under similar conditions (Table 2, entries 1−5). Other solvents such as acetonitrile, hexane, THF, or toluene did not benefit the formation of **2a** either (Table 2, entries 6−9). However, we found that in the reaction of **1a** (1.0 equiv) with ethyl 2,3-butadienoate (1.0 equiv) the yield of **2a** could be obtained in 63% yield in toluene at 110 °C and in 70% yield in DCE at 60 °C, respectively (Table 3, entries

Table 3. Further Optimization of the Reaction Conditions with **1a** (1.0 equiv) and Ethyl 2,3-Butadienoate (1.0 equiv)



entry	solvent	temp (°C)	time (h)	yield (%)[a]
1	toulene	110	10	63
2	chlorobenzene	120	2	45
3	DCE	60	15	70[b]

[a] Isolated yields. [b] Using **1a** (2.0 equiv) and ethyl 2,3-butadienoate (1.0 equiv) under identical conditions, **2a** was obtained in 70% yield as well.

1 and 3). In all the above cases described in Tables 1−3, **3a** was observed in trace.

With these optimized reaction conditions in hand, we next turned our interest to the reaction generality. A variety of 1-cyclopropyl-2-arylethanones **1** were examined under these optimal conditions. As for 1-cyclopropyl-2-arylethanones **1b−e** and **1h−l** having an electron-withdrawing group or a moderately electron-donating group on the benzene ring, the corresponding dihydrofuro[2,3-*h*]chromen-2-one derivatives **2b−e** and **2h−l** were obtained in moderate to good yields

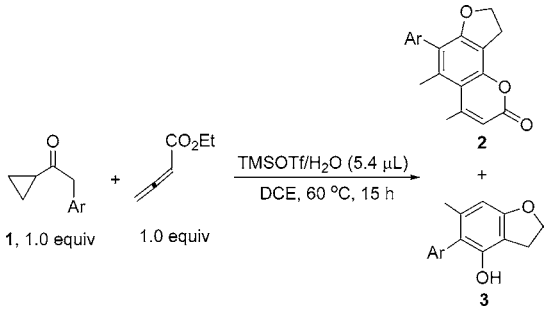
(3) A synergistic combination of Lewis acids has been reported. Myers, E. L.; Butts, C. P.; Aggarwal, V. K. *Chem. Commun.* **2006**, 4434−4436.

(4) The crystal data of **2a** have been deposited in CCDC with number 609488. Empirical formula, $C_{20}H_{17}ClO_3$; formula weight, 340.79; crystal size, 0.506 × 0.328 × 0.137; crystal color/habit, colorless/prismatic; crystal system, triclinic; lattice type, primitive; lattice parameters, a = 6.8783(12) Å, b = 10.2073(18) Å, c = 12.061(2) Å, α = 74.717(3)°, β = 80.936(4)°, γ = 82.909(3)°, V = 803.7(2) Å^3; space group, P-1; Z = 2; D_{calcd} = 1.408 g/cm^3; F_{000} = 356; R1 = 0.0855, wR2 = 0.2556. Diffractometer: Rigaku AFC7R.

(5) A Lewis base can activate a Lewis acid: (a) Jesen, W. B. *The Lewis Acid−Base Concepts*; Wiley-Interscience: New York, 1980; pp 136−137. (b) Denmark, S. E.; Wynn, T. *J. Am. Chem. Soc.* **2001**, *123*, 6199.

along with 2,3-dihydrobenzofuran-4-ol derivatives **3b**−**e** and **3h**−**l** in trace or 10−25% yields (Table 4, entries 1−4 and 7−11). For 1-cyclopropyl-2-arylethanone **1f** bearing a strongly electron-donating methoxy group on the benzene ring at the *para*-position, the reaction proceeded smoothly to afford the corresponding dihydrofuro[2,3-*h*]chromen-2-one derivative **2f** in 85% yield along with **3f** in 9% yield (Table 4, entry 5). As for a strongly electron-donating methoxy group on the benzene ring at the *ortho*-position, the corresponding dihydrofuro[2,3-*h*]chromen-2-one derivative **2g** was formed in 42% yield (Table 4, entry 6). Moreover, the structure of **3i** has been confirmed by X-ray diffraction.[6]

Table 4. Reactions of Various 1-Cyclopropyl-2-arylethanones (1.0 equiv) with Ethyl Buta-2,3-dienoate (1.0 equiv) Mediated by TMSOTf (1.0 equiv)[a]



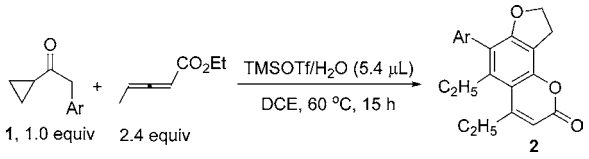
		yield/%[b]	
entry	Ar	**2**	**3**
1	**1b**, *p*-ClC_6H_4	**2b**, 65	**3b**, 10
2	**1c**, *p*-BrC_6H_4	**2c**, 68	**3c**, 10
3	**1d**, *p*-MeC_6H_4	**2d**, 50	**3d**, 17
4	**1e**, *o*-MeC_6H_4	**2e**, 44	**3e**, trace
5	**1f**, *p*-$MeOC_6H_4$	**2f**, 85	**3f**, 9
6	**1g**, *o*-$MeOC_6H_4$	**2g**, 42	**3g**, trace
7	**1h**, *m*-FC_6H_4	**2h**, 45	**3h**, 22
8	**1i**, *p*,*m*-$Cl_2C_6H_3$	**2i**, 54	**3i**, 25
9	**1j**, *o*-BrC_6H_4	**2j**, 37	**3j**, 15
10	**1k**, *m*-BrC_6H_4	**2k**, 52	**3k**, 15
11	**1l**, *m*-MeC_6H_4	**2l**, 60	**3l**, trace

[a] All reactions were performed with **1** (0.6 mmol) and ethyl buta-2,3-dienoate (0.6 mmol). [b] Isolated yields.

Using ethyl penta-2,3-dienoate (2.4 equiv) in this reaction, the corresponding dihydrofuro[2,3-*h*]chromen-2-one derivatives **2m**−**p** were obtained in moderate yields without the formation of 2,3-dihydrobenzofuran-4-ol derivatives (Table 5, entries 1−4).[7]

A plausible mechanism for the formation of **2** and **3** is outlined in Scheme 1 using **1b** as a model. Initially, the reaction of **1b** with water generates 1-(4-chlorophenyl)-5-hydroxypentan-2-one intermediate **A**.[8] The aldol reaction of

Table 5. Reactions of Various Cyclopropyl Benzyl Ketones **1** (1.0 equiv) with Ethyl Penta-2,3-dienoate (2.4 equiv) Mediated by TMSOTf (1.0 equiv) and Water (5.4 μL, 1.0 equiv)[a]

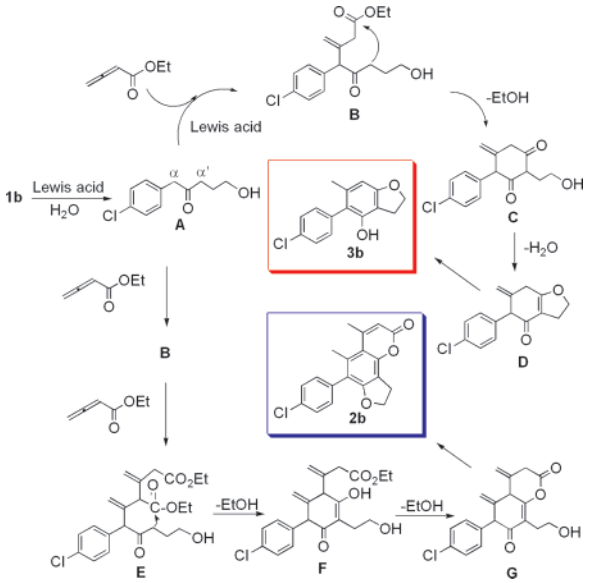


		yield/%[b]
entry	Ar	**2**
1	**1a**, C_6H_5	**2m**, 45
2	**1b**, *p*-ClC_6H_4	**2n**, 47
3	**1c**, *p*-BrC_6H_4	**2o**, 44
4	**1d**, *p*-MeC_6H_4	**2p**, 30

[a] All reactions were performed with **1** (0.3 mmol) and ethyl penta-2,3-dienoate (0.72 mmol). [b] Isolated yields.

intermediate **A** from the C_α-position with ethyl 2,3-butadienoate at the electron-deficient middle carbon atom in the presence of Lewis acid produces intermediate **B**. The subsequent intramolecular aldol reaction from the $C_{\alpha'}$-position affords intermediate **C**. Intramolecular cyclization

Scheme 1. Plausible Reaction Mechanism



and dehydration produce intermediate **D**. After aromatization, product **3b** can be formed. On the other hand, when the intermediate **B** is formed, it gives intermediate **E** via the aldol reaction with another molecule of ethyl 2,3-butadienoate. The subsequent intramolecular aldol reaction from the $C_{\alpha'}$-position and enolization afford intermediate **F**. Intramolecular cyclic transesterification gives intermediate **G**, which produces product **2b** via intramolecular cyclization, dehydration, and aromatization (Scheme 1).

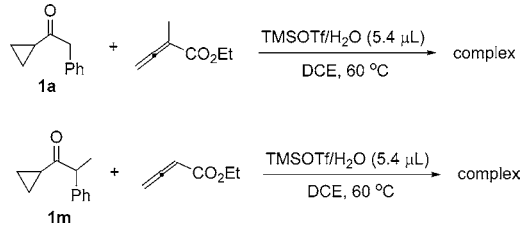
(6) See the Supporting Information. The crystal data of **3i** have been deposited in CCDC with number 651059. Empirical formula, $C_{15}H_{12}O_2Cl_2$; formula weight, 295.15; crystal size, 0.408 × 0.377 × 0.189; crystal color/habit, colorless/prismatic; crystal system, triclinic; lattice type, primitive; lattice parameters, a = 7.5450(8) Å, b = 12.3334(13) Å, c = 15.3243(16) Å, α = 77.685(2)°, β = 80.438(2)°, γ = 74.498(2)°, V = 1333.5(2) Å^3; space group, P-1; Z = 4; D_{calcd} = 1.470 g/cm^3; F_{000} = 608; R1 = 0.0513, wR2 = 0.1270. Diffractometer: Rigaku AFC7R.

(7) We found that in this case 1.0 equiv of cyclopropyl benzyl ketone **1** with 2.4 equiv of ethyl penta-2,3-dienoate gave the best result.

(8) Our previous control experiment showed that 1-aryl-5-hydroxypentan-2-one is the intermediate in the reaction of Lewis acid catalyzed reactions of cyclopropyl alkyl ketones with α-ketoesters. Please see ref 2.

To clarify the reaction mechanism, several control experiments were carried out under the standard conditions (Scheme 2). We found that in the reaction of 1-cyclopropyl-2-phenylethanone **1a** with ethyl 2-methylbuta-2,3-dienoate as well as 1-cyclopropyl-2-phenyl-propan-1-one **1m** with ethyl buta-2,3-dienoate complex product mixtures were formed without the formation of products **2** and **3**, suggesting that sterically bulky groups in 1-cyclopropyl-2-arylethanone and allenic ester can block out intramolecular aldol reaction. It should be emphasized here that, for aliphatic monoactivated cyclopropanes, the reaction gave complex product mixtures, and none of such identified products could be isolated.

Scheme 2. Control Experiments



Interestingly, we found that, by using 1-cyclopropyl-2-(3-methoxyphenyl)ethanone **1n** as a substrate under the standard conditions, 2-methoxy-5-methyl-9,10-dihydro-8*H*-7-oxa-cyclohepta[*b*]naphthalen-6-one **3n** was formed in 43% yield (Scheme 3), which was unambiguously determined by X-ray diffraction (Figure 2).[9] A plausible mechanism has also been outlined in Scheme 3. The ring-opening reaction of **1n** with water catalyzed by TMSOTf produces intermediate **H**, which gives zwitterionic intermediate **I** via a Friedel−Crafts reaction. Intramolecular aldol reaction affords zwitterionic intermediate **J**, which produces intermediate **K** via an intramolecular proton transfer. Intramolecular cyclic transesterification and dehydration produce intermediate **L**. The subsequent aromatization furnishes the final product **3n**.

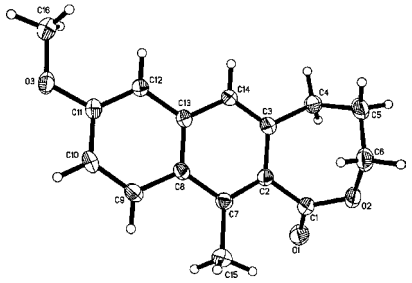
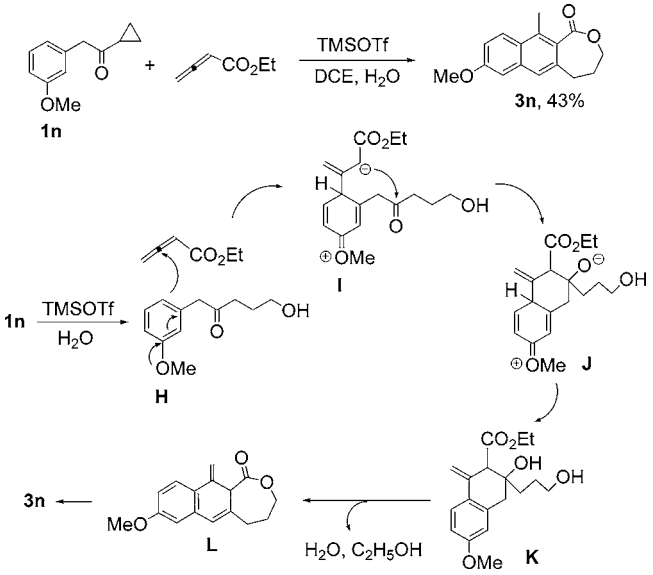


Figure 2. X-ray crystal structure of **3n**.

Scheme 3. TMSOTf-Mediated Reaction of 1-Cyclopropyl-2-(3-methoxyphenyl)ethanone **1n** with Ethyl Buta-2,3-dienoate



In conclusion, we have found a reaction process involving the sequential ring-opening reaction of cyclopropyl alkyl ketones by H_2O, followed by two intermolecular aldol-type reactions with allenic esters and one intramolecular aldol-type reaction, and a cyclic transesterification along with a dehydration and aromatization mediated by Lewis acids, which affords an efficient synthetic protocol for the preparation of dihydrofuro[2,3-*h*]chromen-2-one derivatives.[10] Further work directed at elucidation of the detailed mechanisms of this process and the application of it to the synthesis of dihydrofuro[2,3-*h*]chromen-2-one-containing natural products is currently in progress.

Acknowledgment. We thank the Shanghai Municipal Committee of Science and Technology (04JC14083, 06XD14005), the Chinese Academy of Sciences (KGCX2-210-01), and the National Natural Science Foundation of China for financial support (20472096, 203900502, 20672127, and 20732058).

Supporting Information Available: The spectroscopic data (^{1}H, ^{13}C spectroscopic data), HRMS of the compounds shown in Tables 1−5 and Schemes 2 and 3, the X-ray crystal structures of compounds **2a**, **3i**, and **3n**, along with the detailed description of experimental procedures are included. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) The crystal data of **3n** have been deposited in CCDC with number 649305. Empirical formula, $C_{16}H_{16}O_3$; formula weight, 256.29; crystal size, 0.412 × 0.301 × 0.097; crystal color/habit, colorless/prismatic; crystal system, orthorhombic; lattice type, primitive; lattice parameters, a = 7.1088(10) Å, b = 8.1024(11) Å, c = 22.341(3) Å, α = 90°, β = 90°, γ = 90°, V = 1286.8(3) Å^3; space group, P2(1)2(1)2(1); Z = 4; D_{calcd} = 1.323 g/cm^3; F_{000} = 544; R1 = 0.0399, wR2 = 0.0852. Diffractometer: Rigaku AFC7R.

(10) General Reaction Procedure: 1-cyclopropyl-2-phenylethanone **1a** (48 mg, 0.3 mmol), ethyl buta-2,3-dienoate (67.2 mg, 0.6 mmol), water (5.4 μL, 0.3 mmol), TMSOTf (108 μL, 0.6 mmol), and CH_2Cl_2 (3.0 mL) were added into a Schlenk tube. The reaction mixture was stirred at 60 °C for 15 h. The solvent was removed under reduced pressure, and then the residue was purified by flash column chromatography.