A New Preparation of Cyclopropanone Hemiketals by Reductive Coupling of Terminal Olefins with Ethylene Carbonate

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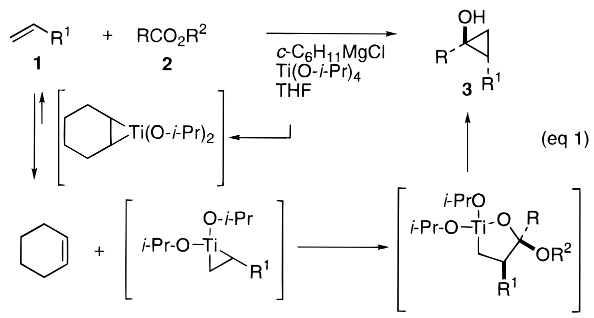
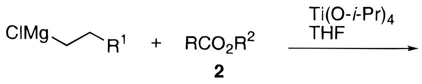
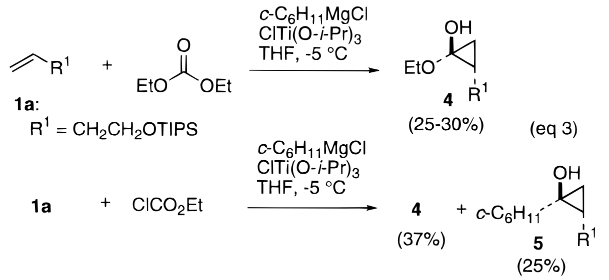
Since cyclopropanone was first implicated as the key reaction intermediate in the Favorskii rearrangement, this small-ring compound has attracted considerable attention from theoretical and synthetic chemists.[2] A few notable examples notwithstanding,[3] cyclopropanones are usually not isolated in a pure state because of their extreme instability. They are known to readily suffer polymerization, nucleophilic attack, or ring-opening. In the presence of an alcohol, for example, they undergo facile formation of the corresponding hemiketals, which can be viewed as convenient synthetic equivalents of the parent cyclopropanone functionality.[4,5] Only a handful of methods exist for the preparation of these synthetically useful cyclopropanone hemiketals.[6] Herein we report a new, general synthetic method for cyclopropanone hemiketals by utilizing Ti(II)-mediated coupling of monosubstituted olefins with ethylene carbonate.



(eq 1)



(eq 2)



(eq 3)

Our approach evolved from the previously reported facile preparation of cyclopropanols **3** by reductive coupling of terminal olefins **1** with alkyl carboxylates **2** (eq 1).[7] This new hydroxycyclopropanation, in turn, stemmed from the original Kulinkovich procedure (eq 2).[8,9] We reasoned that an analogous application of our new hydroxycyclopropanation to the use of a carbonate in lieu of an alkyl carboxylate might provide an expeditious synthesis of cyclopropanone hemiketals. When cyclohexylmagnesium chloride (5 equiv) was slowly (during 30−60 min) added at −5 °C to a THF solution of olefin **1a** (1.0−1.5 equiv), diethyl carbonate (1.0 equiv), and $\mathrm{ClTi(O}\text{-}i\text{-}\mathrm{Pr)_3}$ or $\mathrm{Ti(O}\text{-}i\text{-}\mathrm{Pr)_4}$ (1.0 equiv), the desired cyclopropanone hemiketal **4** was indeed isolated, albeit in poor (25−30%) yield [based on the consumed (27%) starting material], along with unidentified byproducts (eq 3).[10a] Interestingly, substitution of ethyl chloroformate for diethyl carbonate also afforded the hemiketal **4** (37% yield) and the cyclopropanol **5** (25% yield) (based on 36% consumption of the olefin **1a**); the latter product must be derived from ethyl cyclohexanecarboxylate, which was generated in situ. Despite considerable experimentation, both reactions proved to be recalcitrant toward optimization. When cyclopentylmagnesium chloride was employed, both reactions resulted in even poorer yield.[11]

Subsequently, a reliable reaction protocol was found by use of ethylene carbonate. Under otherwise identical reaction conditions, the intermolecular reductive coupling of the olefin **1a** and ethylene carbonate took place smoothly at 0 °C to give the cyclopropanone hemiketal **6a**,**b** in 47% isolated yield as a 2:1 diastereomeric mixture (eq 4).[10b] Similarly, use of propylene 1,3-carbonate also afforded the corresponding hemiketal **6c** in 53% isolated yield and as a single diastereomer.[10b] In contrast to hydroxycyclopropanations of alkyl carboxylates,[7a] these hemiketal-forming reactions were found to be sensitive to the reaction temperature as outlined in eq 4, where 0 °C was found to be the optimum temperature. Additional

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(1) (a) Department of Chemistry, University of Alabama, Tuscaloosa, AL 35487. (b) Department of Chemical Technology, Seoul National University, Seoul, Korea.

(2) For general reviews, see: (a) Turro, N. J. *Acc. Chem. Res.* **1969**, *2*, 25. (b) Wasserman, H. H.; Clark, G. M.; Turley, P. C. *Top. Curr. Chem.* **1974**, *47*, 73. (c) Wasserman, H. H.; Berdahl, D. R.; Lu, T.-J. In *The Chemistry of the Cyclopropyl Group*; Rappoport, Z., Ed.; Wiley: Chichester, 1987; Chapter 23.

(3) The bulky *tert*-butyl-disubstituted cyclopropanes are shown to be stable at room temperature: (a) Pazos, J. F.; Greene, F. D. *J. Am. Chem. Soc.* **1967**, *89*, 1030. (b) Crandall, J. K.; Machleder, W. H. *J. Am. Chem. Soc.* **1968**, *90*, 7347. (c) Camp, R. L.; Greene, F. D. *J. Am. Chem. Soc.* **1968**, *90*, 7349.

(4) Salaün, J. *Chem. Rev.* **1983**, *83*, 619.

(5) 1-Siloxy-1-alkoxycyclopropanes have been utilized as the homoenolate anion precursors: Kuwajima, I.; Nakamura, E. *Top. Curr. Chem.* **1990**, *155*, 1.

(6) Among these methods are addition of diazoalkanes to ketenes in the presence of an alcohol, acyloin-type cyclization of 3-chloropropanoate, and the Simmons−Smith cyclopropanation of ketene trimethylsilyl ketals.

(7) (a) Lee, J.; Kim, H.; Cha, J. K. *J. Am. Chem. Soc.* **1996**, *118*, 4198. See also: (b) Lee, J.; Kang, C. H.; Kim, H.; Cha, J. K. *J. Am. Chem. Soc.* **1996**, *118*, 291. (c) Lee, J.; Kim, H.; Cha, J. K. *J. Am. Chem. Soc.* **1995**, *117*, 9919.

(8) (a) Kulinkovich, O. G.; Sviridov, S. V.; Vasilevskii, D. A.; Pritytskaya, T. S. *Zh. Org. Khim.* **1989**, *25*, 2244. (b) Kulinkovich, O. G.; Sviridov, S. V.; Vasilevskii, D. A.; Savchenko, A. I.; Pritytskaya, T. S. *Zh. Org. Khim.* **1991**, *27*, 294. (c) Kulinkovich, O. G.; Sviridov, S. V.; Vasilevskii, D. A. *Synthesis* **1991**, 234. (d) Kulinkovich, O. G.; Vasilevskii, D. A.; Savchenko, A. I.; Sviridov, S. V. *Zh. Org. Khim.* **1991**, *27*, 1428. (e) For use of tributyl vanadate, see: Kulinkovich, O. G.; Sorokin, V. L.; Kel'in, A. V. *Zh. Org. Khim.* **1993**, *29*, 66.

(9) (a) de Meijere, A.; Kozhushkov, S. I.; Spaeth, T.; Zefirov, N. S. *J. Org. Chem.* **1993**, *58*, 502. (b) See also: Chaplinski, V.; de Meijere, A. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 413.

(10) (a) The product **4** was obtained as a single diastereomer, and the indicated stereochemical assignment was made on the basis of difference NOE measurements. (b) The stereochemistry of the products **6a**−**c** was assigned on the basis of difference NOE measurements; NOEs from the cyclopropane ring protons, including the −O*H* proton, provided a reliable guide to their stereochemical assignment. (c) Hemiketals **7**−**10** were obtained as a 4:1−5:1 mixture of the β-H and α-H diastereomers.

(11) More recently, we discovered that use of cyclopentylmagnesium chloride (rather than cyclohexylmagnesium chloride) provides uniformly higher yields of cyclopropanols from alkyl carboxylates: Lee, J.; Cha, J. K. Unpublished results.

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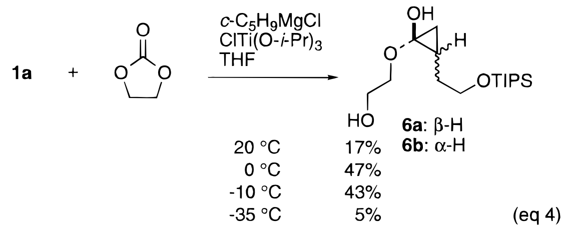
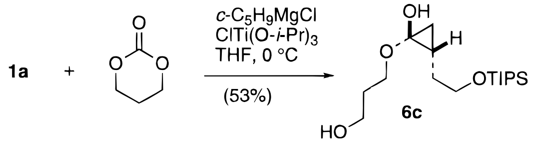
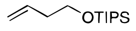
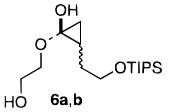
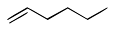
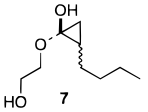
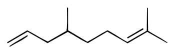
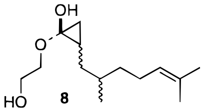
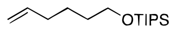
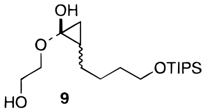
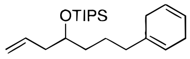
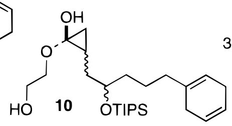


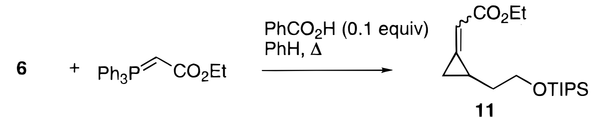
(eq 4)



examples are summarized in Table 1.[12] This transformation appears to be general and would be compatible with the presence of other functional groups in the olefin partner. These hemiketals **6**−**10** bearing a β-hydroxyethoxy substituent appear to be considerably less stable than the counterparts containing an ethoxy moiety (i.e., **4**). For additional characterization, the hemiketal **6a**,**b** was converted in 56% yield to the cyclopropylidene ester **11** by treatment with (carbethoxymethylene)triphenylphosphorane in the presence of benzoic acid.[13,14]

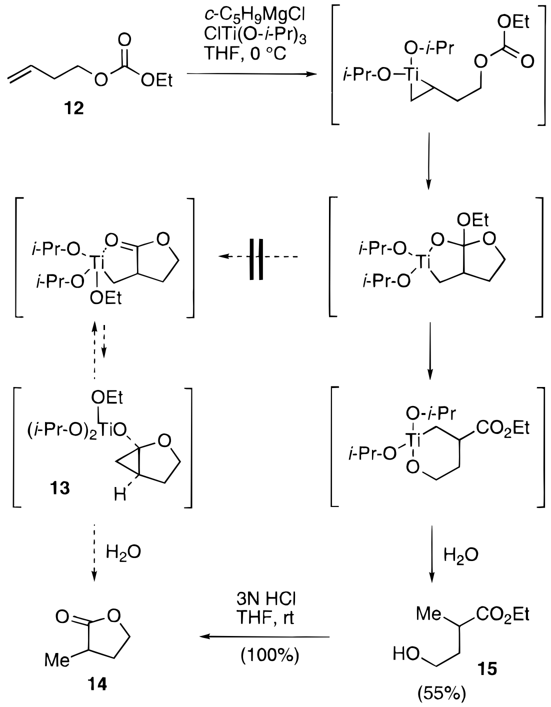
Table 1. Coupling of Olefins 1a−e with Ethylene Carbonate[10c]

Olefin	Product	Yield
 **1a**	 **6a**,**b**	47%
 **1b**	 **7**	47%
 **1c**	 **8**	53%
 **1d**	 **9**	41%
 **1e**	 **10**	37%



11
(56%)

The intramolecular process employing ethyl 3-butenylcarbonate (**12**) did not give rise to the highly strained cyclic hemiketal **13**, which would be expected to rapidly undergo Favorskii-type ring opening to afford γ-lactone **14**.[15] Instead, treatment of **12** with cyclopentylmagnesium chloride (2.2 equiv) at 0 °C in the presence of ClTi(O-*i*-Pr)$_3$ (1.0 equiv) produced ethyl 4-hydroxy-2-methylbutanoate (**15**) in 55% yield.[15b] A slightly higher (64%) yield was obtained when the reaction was performed at −40 °C.



In summary, we have developed a new, general method for the synthesis of cyclopropanone hemiketals by utilizing reductive coupling of terminal olefins with ethylene carbonate. While reaction yields are moderate, a broad range of functional groups can be conveniently introduced into the otherwise inaccessible target compounds. Other salient features include the ease of operation and the ready availability of inexpensive reagents. Further synthetic and mechanistic studies are currently in progress.

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Supporting Information Available: Characterization/spectral data (14 pages).

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[12] A representative experimental procedure is given below: to a solution of ethylene carbonate (0.24 g, 2.73 mmol) and 1-(triisopropylsiloxy)-3-butene (**1a**) (0.21 g, 0.91 mmol) in 10 mL of THF was added ClTi(O-*i*-Pr)$_3$ (0.9 mL of 1.0 M solution in hexane, 1.0 equiv). Commercially available cyclopentylmagnesium chloride (2.7 mL of 2.0 M solution in ether) was added at 0 °C over a period of 30 min (syringe pump). The reaction mixture was then stirred for an additional 1 h and poured into water (15 mL). The organic layer was separated, and the aqueous layer was extracted with ether (3 × 10 mL). The combined extracts were washed with brine (10 mL) and dried over MgSO$_4$. Filtration and evaporation *in vacuo* gave the crude product. Purification by column chromatography on silica gel afforded 0.14 g (47%) of hemiketal **6a**,**b** as a 2:1 diastereomeric mixture (a colorless oil).

[13] Cf. (a) Osborne, N. F. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1435. (b) Rüchardt, C.; Eichler, S.; Panse, P. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 619.

[14] A tandem application of our cyclopropanation protocol and Wittig olefination thus provides a new, convenient synthetic method for alkylidenecyclopropanes.

[15] (a) Very recently, Sato and co-workers reported the identical reaction of **12**, in which the γ-lactone **14** was obtained in 92% yield with use of *i*-PrMgCl at −40 °C: Okamoto, S.; Kasatkin, A.; Zubaidha, P. K.; Sato, F. *J. Am. Chem. Soc.* **1996**, *118*, 2208. Under Sato's reaction conditions, we believe the actual product was also ester **15**, which underwent facile lactonization during workup with 3 N HCl. (b) Indeed, in our hands, the experimental procedure of Sato gave 70% of **15** and 4% of **14**, when the reaction was quenched with addition of water in lieu of 3 N HCl. Moreover, treatment of **15** with 3 N HCl at room temperature gave the lactone **14** in quantitative yield.