A New Variant of the Kulinkovich Hydroxycyclopropanation. Reductive Coupling of Carboxylic Esters with Terminal Olefins

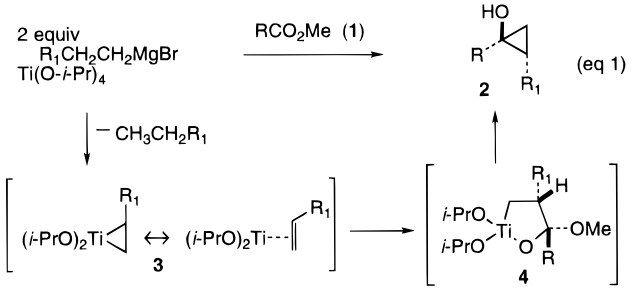
Jinhwa Lee, Heejin Kim, and Jin Kun Cha*

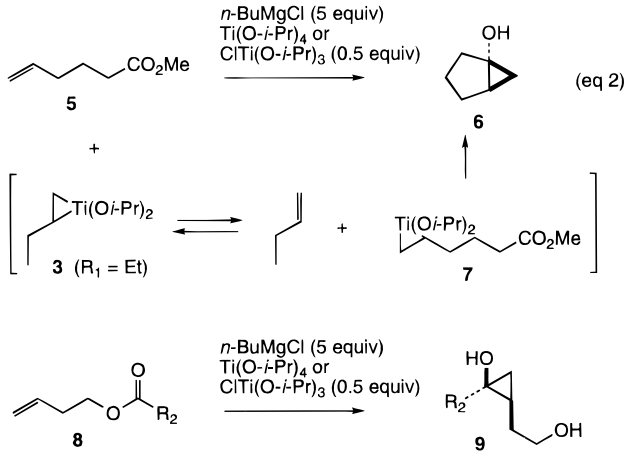
Department of Chemistry, University of Alabama Tuscaloosa, Alabama 35487

Received December 11, 1995

Cyclopropanols are valuable synthetic intermediates because of their facile, selective ring-opening reactions to afford intermediates synthetically useful for subsequent structural elaboration.[1] Recently, Kulinkovich reported a diastereoselective hydroxycyclopropanation, which involves treatment of a carboxylic ester with an excess (3 equiv) of Grignard reagent at −78 to 0 °C in the presence of Ti(O-*i*-Pr)$_4$ (cat or 1 equiv), affording *cis*-1,2-dialkylcyclopropan-1-ol in good yield (eq 1).[2,3] An enantioselective version was achieved by Corey by use of TADDOL.[4] We have successfully implemented the Kulinkovich hydroxycyclopropanation in the stereocontrolled construction of seven- or eight-membered carbocycles by its tandem application with the oxy-Cope rearrangement.[5] The major shortcoming of the original Kulinkovich procedure lies in the requirement of at least 2 equiv of the Grignard reagent, since 1 equiv of the reagent is sacrificed as the corresponding hydrocarbon ($R_1CH_2CH_3$) during the formation of the putative titanacyclopropane intermediate **3**. While acceptable for commercially available Grignard reagents, such loss is too inefficient and costly, particularly for synthetically prepared, valuable Grignard reagents. Herein we report an efficient solution by utilizing Ti(O-*i*-Pr)$_4$-mediated reductive coupling of carboxylic esters with monosubstituted olefins.

By intercepting the titanacyclopropane intermediate **3** by ligand exchange with a monosubstituted alkene (**5** + **3** → **7** + 1-butene), we and the Sato group have independently developed an intramolecular hydroxycyclopropanation.[6,7] Thus, treatment of *ω*-vinyl carboxylate **5** with a suitable Grignard reagent (*n*-BuMgCl or *i*-PrMgBr) in the presence of Ti(O-*i*-Pr)$_4$ (eq 2) afforded the bicyclopropanol **6**. Similarly, esters of *ω*-buten-1-ol **8** gave *trans*-1,2-dialkylcyclopropanols **9**; this stereochemical outcome complements the *cis*-stereochemistry of an intermolecular Kulinkovich reaction. We have also investigated the scope and limitations, particularly in regard to the requisite steric accessibility of the olefin moiety, of the intramolecular hydroxycyclopropanations: only monosubstituted olefinic esters are amenable to cyclization. Neither di- nor multisubstituted alkenes afford the cyclized products, but only an intermolecular hydroxycyclopropanation (i.e., derived from the Grignard reagent) takes place.





Identical application of the olefin exchange tactic to an intermolecular process results in a mixture of products, e.g., **1** + **10** → **11** + **12**. This complication of competing ligand exchanges which arises by action of *n*-BuMgCl, however, is circumvented by employing cyclohexylmagnesium chloride. We believe that use of the latter Grignard reagent allows the equilibrium for the ligand exchange step to be shifted to favor the desired titanacyclopropane intermediate **14**, since the formation of a disubstituted olefin (cyclohexene) provides the key to shifting equilibrium.[8] Consequently, the intermolecular reductive coupling of carboxylic esters and monosubstituted olefins proceeds cleanly at room temperature and in good yield.[9] Table 1 summarizes the hydroxycyclopropanations of ethyl acetate with several olefins, and additional examples involving other esters are included in Table 2.

Several aspects exemplified by Tables 1 and 2 deserve further comment. First, the presence of other functional groups (such as di-and trisubstituted olefins, bromo and siloxy substituents) in the olefin partner is well tolerated. When 1,7-octadiene (**26**) was employed, monocyclopropanol **27** and dicyclopropanol **28** were obtained in 49% and 10% yield (Table 1, entry 7), respectively. No 1,6-diene cyclization product mediated by a titanium complex was found in an appreciable (<5%) amount.[10] Second, a double bond may also be present in the ester partner (Table 2, entries 4 - 8). Third, both *γ*- and *δ*-lactones can be utilized to afford 1,2-*cis*-disubstituted cyclopropan-1-ols (entries 9, 10).[11] Lastly, norbornene was found to be amenable, most likely due to ring strain, to our hydroxycyclopropanation protocol (Table 1, entry 8).

(1) For general reviews, see: (a) Gibson, D. H.; DePuy, C. H. *Chem. Rev.* **1974**, *74*, 605. (b) Salaün, J. *Top. Curr. Chem.* **1988**, *144*, 1.

(2) (a) Kulinkovich, O. G.; Sviridov, S. V.; Vasilevskii, D. A.; Prityts kaya, T. S. *Zh. Org. Khim.* **1989**, *25*, 2244. (b) Kulinkovich, O. G.; Sviridov, S. V.; Vasilevskii, D. A.; Savchenko, A. I.; Prityts kaya, 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.

(3) de Meijere, A.; Kozhushkov, S. I.; Spaeth, T.; Zefirov, N. S. *J. Org. Chem.* **1993**, *58*, 502.

(4) Corey, E. J.; Rao, S. A.; Noe, M. C. *J. Am. Chem. Soc.* **1994**, *116*, 9345.

(5) Lee, J.; Kim, H.; Cha, J. K. *J. Am. Chem. Soc.* **1995**, *117*, 9919.

(6) Lee, J.; Kang, C. H.; Kim, H.; Cha, J. K. *J. Am. Chem. Soc.* **1996**, *118*, 291.

(7) (a) Kasatkin, A.; Sato, F. *Tetrahedron Lett.* **1995**, *36*, 6079. (b) See also: Kasatkin, A.; Nakagawa, T.; Okamoto, S.; Sato, F. *J. Am. Chem. Soc.* **1995**, *117*, 3881.

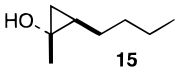
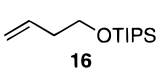
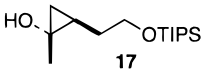
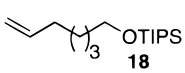
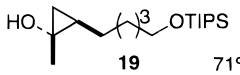
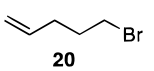
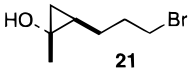
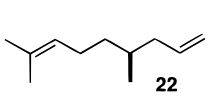
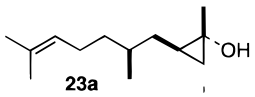
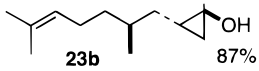
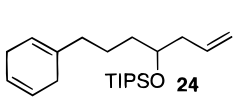
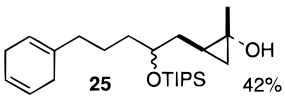
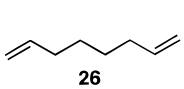
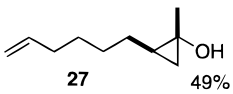
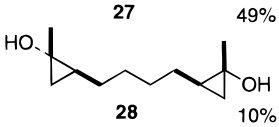
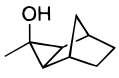
(8) (a) As pointed out by a referee, the product composition under Curtin-Hammett conditions, which are applicable to our hydroxycyclopropanation protocol, is related both to the relative amounts of two titanacyclopropane intermediates **13** and **14** and to their relative reactivity. (b) When ester **1** was treated with cyclohexylmagnesium chloride−ClTi(O-*i*-Pr)$_3$ alone (i.e., in the absence of olefin **10** under otherwise identical conditions), only an intractable reaction mixture was obtained, and no cyclopropanol was found. (c) With the sole exception of norbonene (**29**), use of disubstituted alkenes failed to furnish the cyclopropanol products. (d) Treatment of olefin **10** with ClTi(O-*i*-Pr)$_3$ and the cyclohexyl Grignard reagent, followed by subsequent addition of ester **1**, failed to give cyclopropanol **12**. This control experiment is indicative of the transient nature of **13** and **14** at room temperature. On the other hand, attempts to examine these putative titanacyclopropane intermediates at low temperature have been thwarted by the limiting temperature requirement of ≥ −5 °C in the initial formation of **13** from cyclohexylmagnesium chloride and ClTi(O-*i*-Pr)$_3$.

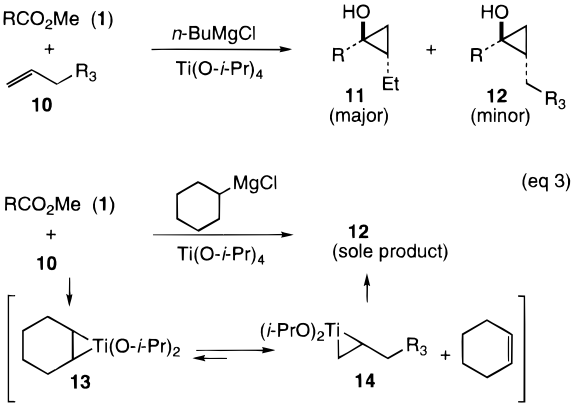
(9) A typical experimental procedure involves a slow (over 1 h period) addition of a commercially available solution of cyclohexylmagnesium chloride (4.5 equiv) to a THF solution of an ester (1.0 equiv), an olefin (1.5 equiv), and Ti(O-*i*-Pr)$_4$[ClTi(O-*i*-Pr)$_3$] (1.0 equiv).

(10) Cf.: Urabe, H.; Hata, T.; Sato, F. *Tetrahedron Lett.* **1995**, *36*, 4261.

S0002-7863(95)04147-3 CCC: $12.00

Table 1. Hydrocyclopropanation of Ethyl Acetate

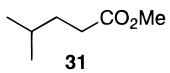
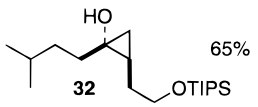
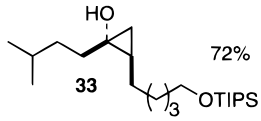
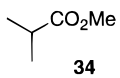
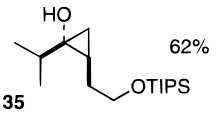
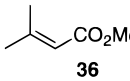
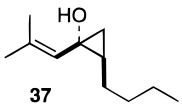
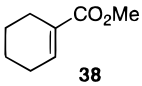
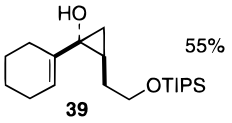
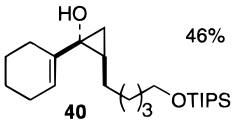
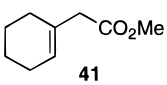
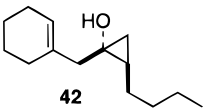
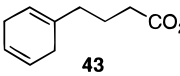
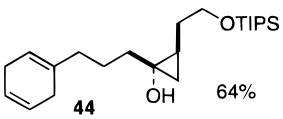
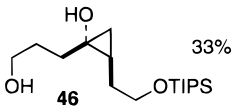
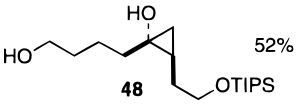
entry	ester	olefin	products	yield
1	EtOAc	1-hexene	 **15**	95%
2		 **16**	 **17**	75%
3		 **18**	 **19**	71%
4		 **20**	 **21**	64%
5		 **22**	 **23a**	
			 **23b**	87%
6		 **24**	 **25**	42%
7		 **26**	 **27**	49%
			 **28**	10%
8		 **29**	 **30**	37%



In summary, we believe that this key variant represents a significant improvement over the original Kulinkovich procedure: loss of a valuable Grignard reagent as the corresponding alkane is circumvented by utilizing commerically available cyclohexylmagnesium chloride. Since the preparation of the alkyl halide precursors to the Grignard reagent is precluded by employing an olefin, this new modification also provides an environmentally more friendly route to synthetically useful, functionalized cyclopropanols. Other salient features include the ease of operation and the ready availability of inexpensive reagents. Further mechanistic and synthetic studies are currently in progress.

(11) Stereochemistry was unequivocally established by difference NOE measurements.

Table 2

entry	ester	olefin	products	yield
1	 **31**	**16**	 **32**	65%
2	**31**	**18**	 **33**	72%
3	 **34**	**16**	 **35**	62%
4	 **36**	1-hexene	 **37**	37%
5	 **38**	**16**	 **39**	55%
6	**38**	**18**	 **40**	46%
7	 **41**	1-hexene	 **42**	56%
8	 **43**	**16**	 **44**	64%
9	 **45**	**16**	 **46**	33%
10	 **47**	**16**	 **48**	52%

Acknowledgment. This paper is dedicated to Professor Michael P. Cava on the occasion of his 70th birthday. We are grateful to the National Institutes of Health (GM35956) for generous financial support and a Research Career Development Award (to J.K.C.; GM00575). J.L. thanks The University of Alabama for a graduate fellowship. We are also indebted to Dr. Ken Belmore for the difference NOE measurement of **46** and **48** and to Mr. Brian J. Nobes (Pharmacology, Vanderbilt University) for accurate mass measurement.

Supporting Information Available: Representative experimental procedure and characterization/spectral data (36 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

JA954147F