Intramolecular Hydroxycyclopropanation of ω-Vinyl Carboxylic Esters

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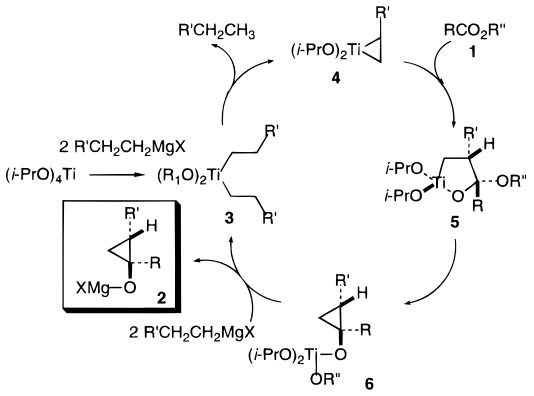
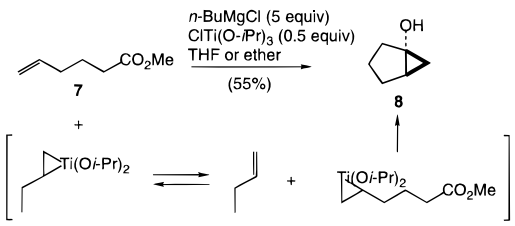
Reactions of Grignard reagents in the presence of transition metals have found numerous synthetic applications in organic chemistry. Recently, use of organotitanium and zirconium compounds has resulted in the design and development of new stereoselective carbon−carbon bond-forming reactions.[1−3] As part of our research program in cyclopropane-mediated natural product synthesis, we became interested in the Kulinkovich hydroxycyclopropanation (**1** → **2**), 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)$_4$ (1 equiv), affording *cis*-1,2-dialkylcyclopropan-1-ols in good yields (Scheme 1).[4−7] Herein we report an intramolecular version of the Kulinkovich hydroxycyclopropanation, which entails treatment of ω-vinyl carboxylates with *n*-BuMgCl in the presence of Ti(O*i*-Pr)$_4$ or ClTi(O*i*-Pr)$_3$.

As summarized in Scheme 1, the Kulinkovich hydroxycyclopropanation under stoichiometric or catalytic conditions is likely to involve the formal "double alkylation" of the titanacyclopropane intermediate **4**, which is formed by the reaction of Ti(O*i*-Pr)$_4$ [or ClTi(O*i*-Pr)$_3$] and a Grignard reagent (2 equiv), accompanied by elimination of the corresponding alkane (R′CH$_2$CH$_3$). We speculated that the putative intermediate **4** might undergo reversible exchange with a suitable alkene.[8,9] When the alkene moiety is tethered to a carboxylic ester, an intramolecular hydroxycyclopropanation of the newly generated

Scheme 1. Kulinkovich Hydroxycyclopropanation



intermediate would be expected to ensue. Indeed, treatment of methyl 5-hexenoate (**7**) with 3 or 5 equiv of *n*-BuMgCl in the presence of 0.5 equiv of ClTi(O*i*-Pr)$_3$ at room temperature afforded cyclopropanol **8** in 48% or 55% (isolated) yield, respectively (eq 1).[10] We believe that the actual yield is



(1)

considerably higher (judging from TLC), since loss occurred during isolation due to volatility of the product. When the identical reaction was carried out at −78 °C, only a complex mixture of unidentified products was obtained. Considerably lower yield was obtained by use of EtMgBr in place of *n*-BuMgCl. Both ether and THF were found to be suitable as solvents.

Additional results, obtained under our standard reaction conditions (5 equiv of *n*-BuMgCl, 0.5 equiv of ClTi(O-*i*Pr)$_3$, ether, room temperature), are summarized in Table 1. The identical application to a homologue, **9**, afforded smoothly the bicyclic cyclopropanol **10**. A precipitous decrease in yield was observed for the intramolecular hydroxycyclopropanation of **11** to afford bicyclo[5.1.0]octan-1-ol (**12**) in 11% yield. Not surprisingly, further extensions to methyl 8-nonenoate (**13**) and methyl 4-pentenoate (**15**) failed to produce the corresponding bicyclic cyclopropanols **14** and **16**, respectively.

In general, the intramolecular hydroxycyclopropanations appear to be relatively little influenced by the presence of substituents in the chain (entries 6−13), with the exception of allylic substituents (entries 8 and 9). For example, reaction of **25** gave a 7:2 mixture of the cyclopropanols **26a** and **26b** in 58% yield, and their stereochemistry was firmly established by NOE experiments. The cyclic substrate **27** also afforded two products, **28a**,**b**, in good yield but with poor (2:1) diastereoselectivity. A considerably lower yield was found for the epimer **29**, presumably due to strain associated with *trans*-ring junction. Reaction of **21**, which contains an alkoxy group at the allylic position, gave the cyclopropanol **22** as a single isomer in only 14% yield (entry 8). Poor yield can be ascribed to the competing elimination of the adjacent TIPSO group in the titanacyclopropane intermediate.[8] Moreover, the importance of

(1) For recent reviews in this area, see: (a) Reetz, M. T. In *Organometallics in Synthesis*; Schlosser, M., Ed.; Wiley: New York, 1994; Chapter 3. (b) Weidmann, B.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 31. (c) Sato, F. *J. Organomet. Chem.* **1985**, *285*, 53. (d) Dzhemilev, U. M.; Vostrikova, O. S.; Tolstikov, G. A. *J. Organomet. Chem.* **1986**, *304*, 17. (e) Buchwald, S. L.; Nielsen, R. B. *Chem. Rev.* **1988**, *88*, 1047. (f) Negishi, E.; Takahashi, T. *Acc. Chem. Res.* **1994**, *27*, 124.

(2) One of the earliest examples is a facile reduction of esters by catalytic Cp_2TiCl_2 and stoichiometric *i*-PrMgBr. (a) Sato, F.; Jinbo, T.; Sato, M. *Tetrahedron Lett.* **1980**, *21*, 2175. (b) Barr, K. J.; Berk, S. C.; Buchwald, S. L. *J. Org. Chem.* **1994**, *59*, 4323 and references cited therein.

(3) See, *inter alia*: (a) Buchwald, S. L.; Watson, B. T.; Huffman, J. C. *J. Am. Chem. Soc.* **1987**, *109*, 2544. (b) RajanBabu, T. V.; Nugent, W. A.; Taber, D. F.; Fagan, P. J. *J. Am. Chem. Soc.* **1988**, *110*, 7128. (c) Lund, E. C.; Livinghouse, T. *J. Org. Chem.* **1989**, *54*, 4487. (d) Takahashi, T.; Seki, T.; Nitto, Y.; Saburi, M.; Rousset, C. J.; Negishi, E. *J. Am. Chem. Soc.* **1991**, *113*, 6266. (e) Knight, K. S.; Waymouth, R. M. *J. Am. Chem. Soc.* **1991**, *113*, 6268. (f) Hoveyda, A. H.; Xu, Z.; Morken, J. P.; Houri, A. F. *J. Am. Chem. Soc.* **1991**, *113*, 8950. (g) Negishi, E. (guest editor). *Tetrahedron* **1995**, *51*, 4255−4281.

(4) (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.

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

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

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

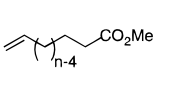
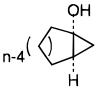
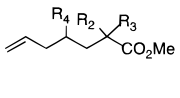
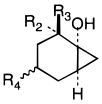
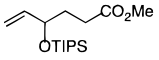
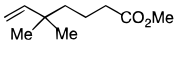
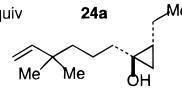
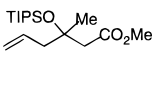
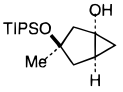
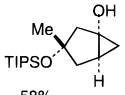
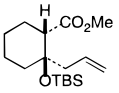
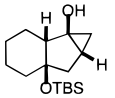
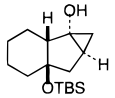
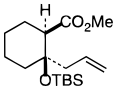
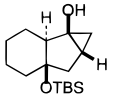
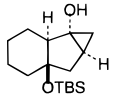
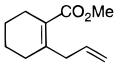
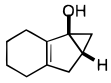
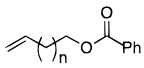
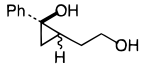
(8) Such olefin exchange has been invoked in the generation of allyltitanium compounds by treatment of allyl halides or alcohols with a mixture of Ti(O*i*-Pr)$_4$ (or "Cp_2Zr") and 2 equiv of *i*-PrMgBr: Kasatkin, A.; Nakagawa, T.; Okamoto, S.; Sato, F. *J. Am. Chem. Soc.* **1995**, *117*, 3881. See also: Ito, H.; Taguchi, T.; Hanzawa, Y. *Tetrahedron Lett.* **1992**, *33*, 1295.

(9) Subsequent to submission of our manuscript, Sato and Kasatkin reported a stereoselective synthesis of *trans*-1,2-disubstituted cyclopropanols from esters of 3-butenols (cf. entries 14 and 15, Table 1) under similar reaction conditions: Kasatkin, A.; Sato, F. *Tetrahedron Lett.* **1995**, *36*, 6079.

(10) Some bicyclo[*n*.1.0]-1-alkanols were previously prepared by Simmons−Smith cyclopropanation of trimethylsilyl cycloalkenyl ethers, followed by hydrolysis under mild conditions: (a) Murai, S.; Aya, T.; Sonoda, N. *J. Org. Chem.* **1973**, *38*, 4354. (b) Rubottom, G. M.; Lopez, M. I. *J. Org. Chem.* **1973**, *38*, 2097.

0002-7863/96/1518-0291$12.00/0

Table 1. Intramolecular Kulinkovich Hydroxycyclopropanations[a]

entry	substrate	Grignard[b]	products	yield, % (isomer ratio)
1	 **7**: n = 5	5 equiv 3 equiv	 **8**: n = 5	55% 48%
2	**9**: n = 6	5 equiv 3 equiv	**10**: n = 6	62% 55%
3	**11**: n = 7	5 equiv	**12**: n = 7	11%[c]
4	**13**: n = 8	5 equiv	**14**: n = 8	0%
5	**15**: n = 4	5 equiv	**16**: n = 4	0%
6	 **17**: R_2 = OTIPS, R_3 = R_4 = H	5 equiv	 **18**: R_2 = OTIPS, R_3 = R_4 = H	76% (2 : 1)
7	**19**: R_2 = R_3 = Me, R_4 = OTIPS	5 equiv	**20**: R_2 = R_3 = Me, R_4 = OTIPS	75% (1 : 1)
8	 **21**	5 equiv	 **22**	14% (1 : 0)
9	 **23**	5 equiv	 **24a**  **24b**	0% 61%
10	 **25**	5 equiv	 **26a**  **26b**	58% (7 : 2)
11	 **27**	5 equiv	 **28a**  **28b**	70% (2 : 1)
12	 **29**	5 equiv	 **30a**  **30b**	42% (3 : 2)
13	 **31**	5 equiv	 **32**	0%
14	 n = 1 **33**	5 equiv	 **34a**: α-H **34b**: β-H	78% (7 : 1)
15	n = 2 **35**	5 equiv	**36a**: α-H **36b**: β-H	15%

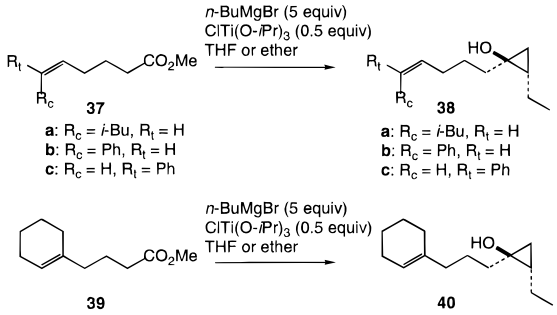
[a] Conditions: ester (1 equiv), $ClTi(O\textit{i}\text{-}Pr)_3$ (0.5 equiv), *n*-BuMgCl (5 equiv, otherwise noted), ether, room temperature, 1−2 h. [b] A commercially available ethereal solution of *n*-BuMgCl was used. [c] The pure product was not obtained due to the presence of unidentified byproducts.

steric accessibility of the olefin during the olefin exchange step was well illustrated in the reaction of **23**: only the corresponding intermolecular product **24b** was obtained in 61% yield (entry 9). In contrast, the same substituents were well tolerated at the α position of the ester functionality (entries 6 and 7).

Esters of ω-alken-1-ols, especially 3-buten-1-ols, appear to be amenable to the intramolecular hydroxycyclopropanation as well.[9] Thus, reaction of benzoate **33** gave a 7:1 mixture of the cyclopropanols **34a**,**b** in 78% yield, the stereochemistry of which was firmly established by NOE studies. The relative stereochemistry of the alkyl and phenyl substituents of the major product **34a** was *trans*. This stereochemical preference, although not exceptionally high, complements the exclusive *cis* stereochemistry of an intermolecular Kulinkovich cyclopropanation. A further extension to a homologue, **35**, suffered from poor yield, which is in marked contrast to the trend involving esters **7** and **9** (entries 1 and 2).[11,12]

Subsequently, an apparent shortcoming of this procedure was uncovered, in that only esters with monosubstituted olefins are amenable to the intramolecular hydroxycyclopropanation under the present reaction conditions. Neither di- nor trisubstituted alkenes gave the cyclized products; only an intermolecular hydroxycyclopropanation was found to take place in good yield.

In summary, we have developed an intramolecular hydroxycyclopropanation of ω-vinyl esters which should be of synthetic



utility in carbocyclic ring construction. The salient features include the ease of operation, the ready availability of inexpensive reagents, and the formation of the cyclopropanol functionality which is suitable for further elaboration. Moreover, our reaction protocol serves to corroborate the intermediacy of a titanacyclopropane in the Kulinkovich hydroxycyclopropanation. Further mechanistic and synthetic studies are in progress.

Acknowledgment. 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). We thank Dr. Ken Belmore for the difference NOE measurements of **20** and **22**.

Supporting Information Available: Representative experimental procedure and spectral data (21 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.

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(11) Application of our hydroxycyclopropanation protocol to γ-lactones having an ω-vinyl-substituted tether failed to provide the corresponding ring-enlarged cyclopropanols.

(12) Cf.: Reductive cyclization of δ-enones or δ-ynones by $Cp_2Ti(PMe_3)_2$ has been shown to afford titanacycles in good yield: (a) Hewlett, D. F.; Whitby, R. J. *J. Chem. Soc., Chem. Commun*. **1990**, 1684. (b) Kablaoui, N. M.; Buchwald, S. L. *J. Am. Chem. Soc*. **1995**, *117*, 6785. (c) Crowe, W. E.; Rachita, M. J. *J. Am. Chem. Soc*. **1995**, *117*, 6787.