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Low-Valent Titanium-Mediated Cyclopropanation of Vinylogous Esters

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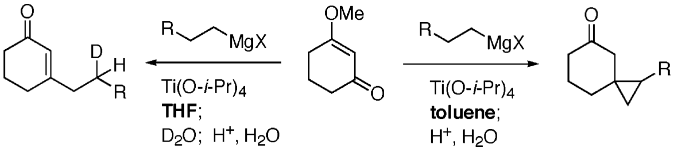
ABSTRACT



Inter- and intramolecular titanium-mediated cyclopropanation reactions of vinylogous esters are reported. Comparison between the Kulinkovich cyclopropanation of esters and vinylogous esters provides mechanistic insight regarding reaction variables such as reaction temperature, solvents, and a Lewis acid additive.

Cyclopropanes have long spurred a spate of synthetic and mechanistic studies due to their unique reactivity.[1] In 1989, Kulinkovich and co-workers developed an efficient cyclopropanation of esters by convenient generation of low-valent titanium species.[2,3] The Kulinkovich reaction has also been applied to other carboxylic acid derivatives to provide ready access to heteroatom-substituted cyclopropanes.[4−6] These cyclopropanation reactions build on the presumed intermediacy of the key dialkoxytitanacyclopropane or titanium(II)−alkene complex that is generated in situ from a Grignard reagent (Scheme 1).[7−9] We herein report cyclopropanation of vinylogous esters, along with comparison with that of carboxylic esters.

Slow addition of *n*-butylmagnesium bromide (excess; as a ~1.5 M solution in ether) to a solution of 3-methoxy-2-cyclohexen-1-one (**1**) and Ti(O-*i*-Pr)$_4$ (1.1 equiv) in ether at room temperature cleanly gave cyclopropane **3a** as a ~2:1 diastereomeric mixture in 60−66% yield (entry 2 in Scheme 2). The reaction mixture was treated with water (or D$_2$O), followed by mild aqueous acid, to ensure complete hydrolysis of the enol ether functionality (e.g., **2**) to the corresponding ketone (e.g., **3**) so as to avoid complications due to partial conversion during silica gel column chromatography.[10] When the reaction was carried out at 0 °C, a mixture of **3a** (34%) and **4a** (25%) was obtained (entry 3). The product ratio was also dependent on solvents: a mixture of **3a** (15−20%) and **4a** (35−40%) was isolated in THF (entry 4). When THF

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(1) (a) de Meijere, A. *Chem. Rev.* **2003**, *103*, 931 and accompanying reviews. (b) Kulinkovich, O. G. *Chem. Rev.* **2003**, *103*, 2597.

(2) (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.; Sorokin, V. L.; Kel'in, A. V. *Zh. Org. Khim.* **1993**, *29*, 66. (d) Kulinkovich, O. G.; Savchenko, A. I.; Sviridov, S. V.; Vasilevskii, D. A. *Mendeleev Commun.* **1993**, 230.

(3) (a) Kulinkovich, O. G.; de Meijere, A. *Chem. Rev.* **2000**, *100*, 2789. (b) Sato, F.; Urabe, H.; Okamoto, S. *Chem. Rev.* **2000**, *100*, 2835.

(4) Chaplinski, V.; de Meijere, A. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 413.

(5) (a) Lee, J.; Kang, C. H.; Kim, H.; Cha, J. K. *J. Am. Chem. Soc.* **1996**, *118*, 291. (b) Lee, J.; Kim, H.; Cha, J. K. *J. Am. Chem. Soc.* **1996**, *118*, 4198. (c) Lee, J.; Kim, Y. G.; Bae, J.; Cha, J. K. *J. Org. Chem.* **1996**, *61*, 4878. (d) Lee, J.; Ha, J. D.; Cha, J. K. *J. Am. Chem. Soc.* **1997**, *119*, 8127. (e) Sung, M. J.; Lee, C.-W.; Cha, J. K. *Synlett* **1999**, 561.

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(7) Wu, Y.-D.; Yu, Z.-X. *J. Am. Chem Soc.* **2001**, *123*, 5777.

(8) Casey, C. P.; Strotman, N. A. *J. Am. Chem. Soc.* **2004**, *126*, 1699.

(9) Although titanium complexes are best described as six-coordinate octahedral species, for convenience they are shown as tetrahedral intermediates devoid of coordinating solvents.

(10) (a) Actual isolated yields after column chromatography are given, but loss occurred during purification due to the volatility of the products. Cf. (b) **3b**: Sonoda, A.; Moritani, I.; Miki, J.; Tsuji, T. *Tetrahedron Lett.* **1969**, 3187.

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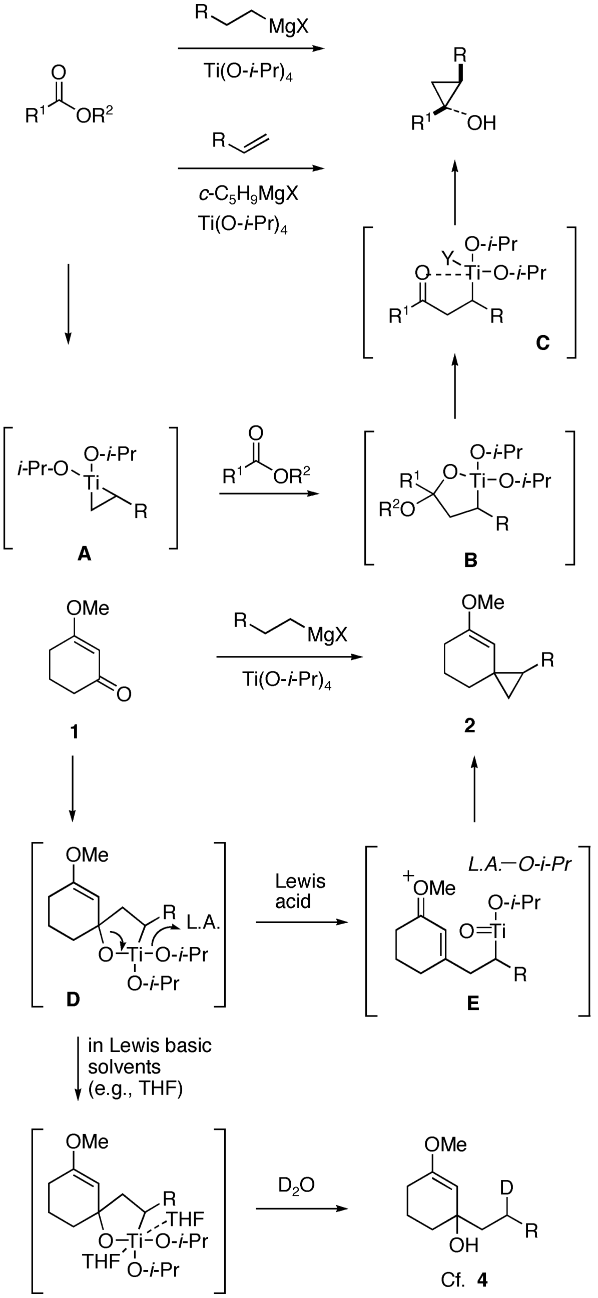
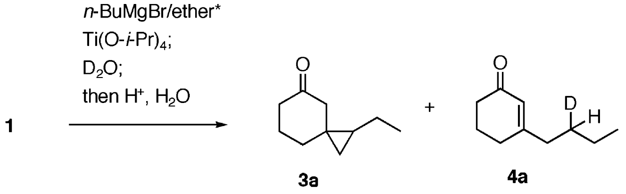
Scheme 1



Scheme 2



3a + **4a**

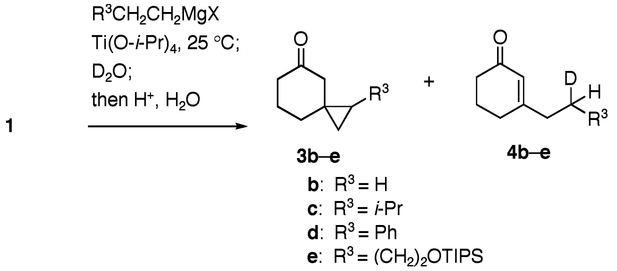
entry	solvent	temp	products		(isolated yield)
1	toluene	25 °C	77%	+	0%
2	ether	25 °C	66%	+	0%
3	ether	0 °C	34%	+	25%
4	THF	25 °C	15-20%	+	35-40%
5	*n*-BuMgBr/THF*;THF	25 °C	0%	+	49%

was used in generating the Grignard reagent and also as the reaction solvent, **4a** was the sole product (entry 5). Exclusive formation of **3a** (77%) was observed in toluene (entry 1).

Similarly, other Grignard reagents such as ethyl, isoamyl, 2-phenethyl, and 4-triisopropylsiloxybutylmagnesium chlorides or bromides afforded the corresponding cyclopropanes **3b**−**e** in comparable yields (entries 1−7 in Scheme 3). Again, low (~2:1) diastereoselectivity was observed for **3c**−**e**. With 4-triisopropylsiloxybutylmagnesium chloride in ether, a small amount of **4e** (7%) was isolated, along with the major product **3e** (45%) (entry 4). Additionally, the product ratio of **3e** to **4e** appeared to be affected by the reaction time (entry 4 vs 5), which was suggestive of a common pathway leading to **3e** and **4e**. When the Grignard reagent generated in a THF solution was added to a solution of **1** and Ti(O-*i*-Pr)$_4$ in ether, a dramatic reversal in the ratio of **3e** to **4e** was found (entry 6) in parallel with the above-mentioned solvent effects noted for **3a**−**4a**. The unexpected solvent effects could be overridden by addition of a Lewis acid (2 equiv) (entry 7; also vide infra).

Coupling of **1** and a terminal olefin under the typical olefin exchange modification procedure (employing cyclopentyl or cyclohexyl Grignard reagents)[5] surprisingly failed to produce appreciable amounts of the desired coupling products **3** or **4**. The reductive dimerization product of the terminal olefin employed was isolated in low yields from a complex crude reaction mixture. This unexpected yet striking difference in the Kulinkovich cyclopropanation reaction of esters and vinylogous esters might be attributed in part to a subtle difference in their relative reactivity toward the presumed titanacyclopropane intermediate derived from the cyclopentyl Grignard reagent vis-à-vis the requisite olefin exchange process.[9,11] Although elucidation of mechanistic implications must await further studies, a satisfactory solution to this

Scheme 3



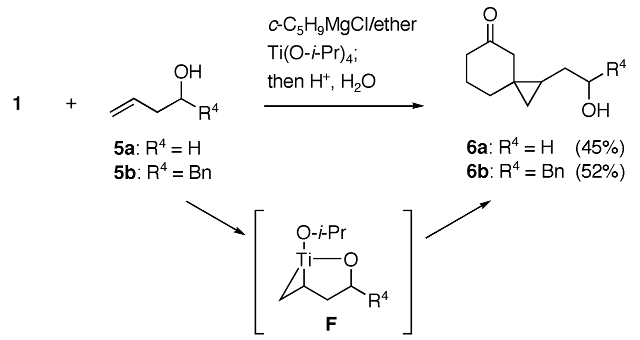
3b–e + **4b–e**

b: $R^3 = H$
c: $R^3 = i\text{-Pr}$
d: $R^3 = Ph$
e: $R^3 = (CH_2)_2OTIPS$

entry	solvent	R=R^{3}CH$_2$CH$_2$;	products (isolated yield)		
1	ether	**b:** ethyl	46%	+	0%
2	ether	**c**: isoamyl	54%	+	0%
3	ether	**d**: 2-phenethyl	43%	+	0%
4	ether (2 h)	**e**: TIPSO(CH$_2$)$_4$	45%	+	7%
5	ether (12 h)	"	50%	+	3%
6	THF/ether	"	5%	+	42%
7	THF/ether; BF$_3$.Et$_2$O added	"	50%	+	0%

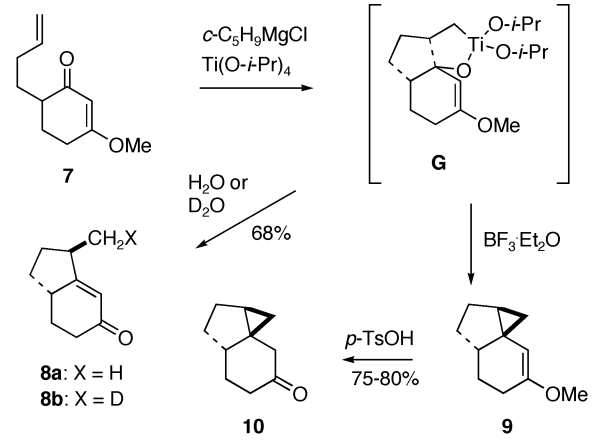
unexpected difficulty was found in the use of a homoallylic alcohol: on the basis of our previous hydroxycyclopropanation of **5a**,**b**,[12] the intermediate **F** is presumably involved, where an internal hydroxy group helps to increase the rate of olefin exchange to afford the desired cyclopropane **6a**,**b** in 45 and 52% yields (Scheme 4).

Scheme 4



Cyclization of **7** also took place smoothly to provide **8a** in 68% yield (Scheme 5).[13] The intermediacy of the titanaoxacyclopentane **G** was gleaned from the deuterium labeling experiment (i.e., formation of **8b**). Addition of $BF_3 \cdot Et_2O$ (2−5 equiv) prior to aqueous workup resulted in clean cyclopropanation to deliver **10** in 75−80% yield (upon exposure to p-$TsOH \cdot H_2O$ to ensure complete hydrolysis of the enol ether **9**). Because of the additional strain associated with a substituted tricyclic cyclopropane, a Lewis acid was required to induce ring closure of **G** even when ether was employed as the reaction solvent.

Scheme 5



A plausible mechanism involves addition to the vinylogous ester of the postulated titanacyclopropane intermediate, generated from the Grignard reagent and Ti(O-i-Pr)$_4$, to afford **D**, as indicated in Scheme 1. Subsequent rearrangement of **D** to **2** likely entails a delocalized oxonium ion **E**, formation of which would in turn be facilitated by an electrophilic titanate, followed by facile ring closure. Thus, noncoordinating solvents such as toluene are best for the cyclopropanation. On the other hand, formation of **E** would be hindered by use of Lewis basic solvents (e.g., THF) or low reaction temperatures (e.g., entries 2 vs 3 and 4 vs 5 in Scheme 2). Analogous observations for the competing production of **3e** and **4e** in Scheme 3 can be attributed to internal chelation by a siloxy or benzyloxymethoxy[14] group to the titanium, whereas subsequent addition of a Lewis acid promotes cyclopropanation (entries 6 and 7).

It is informative to compare **D** → **E** → **2** with the respective processes in the original Kulinkovich reaction of esters, i.e., **B** → **C** → the cyclopropanol product (Scheme 1): in contrast to the former rearrangement, the latter would be promoted by a nucleophilic titanate involving either the migration of an alkoxy group or the formation of an ate complex (by addition of an external alkoxy group or excess Grignard reagent). Therefore, no significant solvent effects were observed for the Kulinkovich cyclopropanation of esters.

On a final note, the isolation and characterization of **4a**−**e** provides additional evidence that it is the less substituted Ti−C bond of the presumed titanacyclopropane or π-complex intermediate that first adds to the carbonyl group (i.e., **1** → **D**), as well as in related coupling reactions of imides[5d] and ketones.[15,16]

In summary, we have developed inter- and intramolecular titanium-mediated cyclopropanation reactions of vinylogous esters.[17] Synthetically useful cyclopropanes can be readily introduced at otherwise inaccessible sites. More importantly, the comparison study between the Kulinkovich cyclopropanation of esters and vinylogous esters provides mechanistic insight regarding these reactions: the unusual effects exerted

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[11] In most cases, the original Kulinkovich cyclopropanation procedure and the olefin exchange modification can be utilized interchangeably with only small differences in yields. Rare exceptions include cyclopropanation of benzoates and nitriles: (a) Lee, J.; Cha, Unpublished results. See also: (b) Gensini, M.; Kozhushkov, S. I.; Yufit, D. S.; Howard, J. A. K.; Es-Sayed, M.; de Meijere, A. *Eur. J. Org. Chem.* **2002**, 2499. (c) Footnote 16 in ref 6f.

[12] (a) Quan, L. G.; Kim, S.-H.; Lee, J. C.; Cha, J. K. *Angew. Chem., Int. Ed.* **2002**, *41*, 2160. See also: (b) Savchenko, A. I.; Kulinkovich, O. G. *Zh. Org. Khim.* **1997**, *33*, 913. (c) Isakov, V. E.; Kulinkovich, O. G. *Synlett* **2003**, 967.

[13] Both diastereomers of **8a** were previously prepared by a different method: Kakiuchi, K.; Ue, M.; Tsukahara, H.; Shimizu, T.; Miyao, T.; Tobe, Y.; Odaira, Y.; Yasuda, M.; Shima, K. *J. Am. Chem. Soc.* **1989**, *111*, 3707. Unfortunately, the close similarity in ^1H and ^{13}C NMR chemical shifts reported for these diastereomers precluded unequivocal differentiation of the two possible diastereomers. The stereochemistry of **8a** is tentatively assigned on the basis of the requisite geometry for cyclization.

[14] Coupling reaction of **1** and benzyloxymethoxybutylmagnesium chloride was comparable to that with the corresponding triisopropylsiloxybutyl Grignard reagent leading to **3e** and/or **4e**.

[15] Morlender-Vais, N.; Solodovnikova, N.; Marek, I. *J. Chem. Soc., Chem. Commun.* **2000**, 1849.

[16] Coupling of zirconocene−alkene complexes with aldehydes is also known to occur at the less substituted metal−C bond, and this regiochemistry is opposite to that with alkenes: Takahashi, T.; Suzuki, N.; Hasegawa, M.; Nitto, Y.; Aoyagi, K.; Saburi, M. *Chem. Lett.* **1992**, 331. This interesting dichotomy might be attributed to kinetic control of the coupling with a carbonyl functionality due to the well-known oxophilicity of titanium or zirconium, whereas the corresponding coupling with an alkene would be subject to thermodynamic control.

[17] Cyclopropanation of vinylogous amides also proceeds cleanly under similar conditions: Feng, W.; Cha, J. K. Unpublished results.

by reaction temperature, solvents, and a Lewis acid additive have been rationalized. Further mechanistic and synthetic studies are currently in progress.

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Supporting Information Available: Representative experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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