Pergamon

Tetrahedron Letters 42 (2001) 4991–4994

TETRAHEDRON LETTERS

Titanium-mediated diastereoselective formation of (*E*)-2-alkyl-1-ethenylcyclopropanols from β-haloesters

Isabelle Sylvestre, Jean Ollivier and Jacques Salaün*

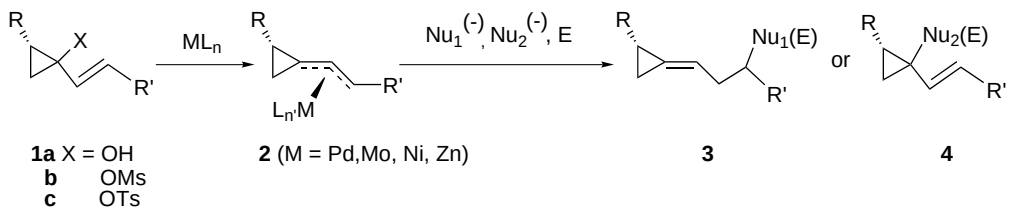
Laboratoire des Carbocycles, UMR 8615, Institut de Chimie Moléculaire d'Orsay Bât. 420, Université de Paris-Sud, 91405 Orsay, France

Received 7 March 2001; revised 26 March 2001; accepted 29 May 2001

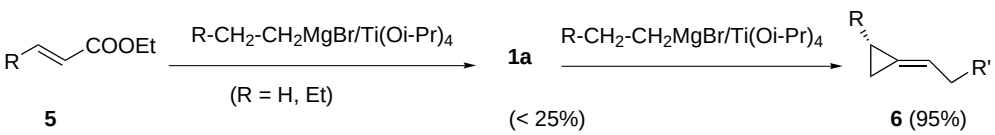
Abstract—The titanium(IV)-mediated cyclopropanation of ethyl β-chloropropionate by Grignard reagents and in situ tosylation, followed by base-induced dehydrochlorination provided diastereoselectivity pure (*E*)-2-alkyl-1-ethenyl-1-(tosyloxy)cyclopropanes, suitable precursors of 1,1-ethyleneallylmetal species of significant synthetic potential.

It is notorious and well-documented that functionalized cyclopropanes provide building blocks of unprecedented synthetic potential.[1] Particularly, the derivatives of 1-ethenylcyclopropanols **1a**, which can undergo either selective acid, base or thermally-induced $C_3 \rightarrow C_{4-8}$ ring expansions,[2] or fluoride-ion-induced $C_3 \rightarrow C_{10,15,20}$ ring enlargements.[3] Moreover, the corresponding sulfonic esters **1b**,**c** (mesylates, tosylates) of these allylic alcohols **1a** form significant π- or σ-1,1-ethyleneallylmetal complexes **2** (M = Pd, Mo, Ni, Zn, …), which undergo regio- and diastereoselective substitutions either by soft nucleophiles $Nu_1^{(-)}$, (e.g. enolates) to provide alkylidenecyclopropanes **3** or by hard nucleophiles $Nu_2^{(-)}$ (e.g. organometallic, hydride reagents) to lead to (1-alkenyl)cyclopropanes **4**[5] (Scheme 1). On the other hand, substitution by electrophiles E (e.g. aldehydes, ketones) provides **3**, exclusively; but, this regioselectivity can be reversed by silyl substituent effect (R′ = $SiMe_3$).[5] Various useful synthetic applications of the amazing organometallic complexes **2** have been recently reported.[6]

The 1-(1-alkenyl)cyclopropanols **1a** (R = H; R′ = H, aryl, alkyl) were previously available either from the cyclopropanone hemiacetal,[7] or from the 1-hydroxycyclopropanecarboxylic acid;[8] while their 2-methyl substituted chiral derivatives **1a** (R = Me) were obtained diastereo- (de >80–100%) and enantiomerically pure (ee



Scheme 1.



Scheme 2.

Keywords: titanium-mediated cyclopropanations; sulfonic esters; dehydrohalogenation; (*E*)-2-alkyl-1-ethenylcyclopropanols.
* Corresponding author. Fax: +33-1-69-15-62-78; e-mail: jasalaun@icmo.u-psud.fr

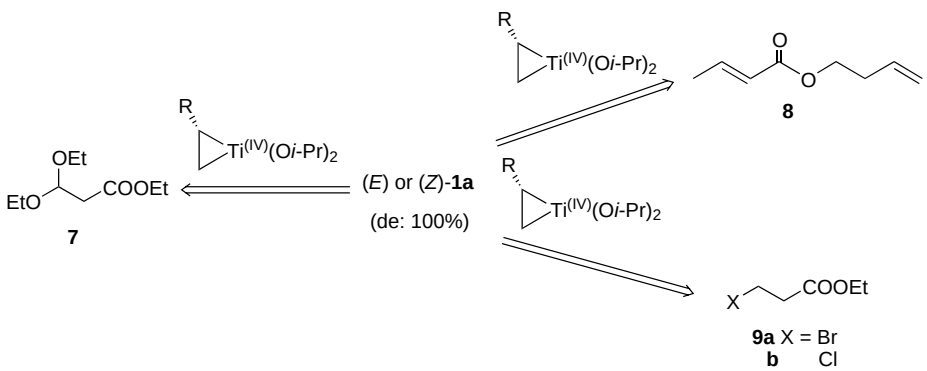
0040-4039/01/$ - see front matter
PII: S0040-4039(01)00900-5

>95–99%) from the suitable asymmetric cyclopropanone hemiacetals[6c] or α-hydroxyacids.[9] A new and attractive method for the ready preparation of cyclopropanols was based on the titanium(IV)-mediated reaction of alkylcarboxylates with Grignard reagents.[10] However, α,β-unsaturated esters **5** provided the expected 1-vinylcyclopropanols **1a** in rather low yields ($\leq$25%)[11] because, as recently observed allylic alcohols such as **1a** underwent further reductive elimination (or alkylation) of the hydroxy group.[12] Thus for instance, upon reaction with the EtMgBr/Ti(O*i*-Pr)$_4$ reagent the 1-styrylcyclopropanol **1a** (R = H; R′ = Ph) gave the (2-phenylethylidene)cyclopropane **6** in 95% yield[13] (Scheme 2). Nevertheless, this embarrassing problem was overcome by means of the titanium(IV)-mediated cyclopropanation of ethyl 3,3-diethoxypropionate **7**, followed by a modified Knoevenagel condensation of malonic acid under microwave irradiation,[14] and by the titanium-mediated cyclopropanation of homoallylic conjugated esters **8**,[11] which provided diastereochemically pure 2-substituted (R = Et, $HOCH_2$-CH_2-) (*E*)- and (*Z*)-1-(1-alkenyl) cyclopropanols, respectively (Scheme 3). Then, the palladium(0)-catalyzed azidation of the corresponding sulfonated esters **1b**,**c**, which occurred with complete retention of configuration, allowed for instance, the diastereoselective synthesis of (*E*)-[14] and (*Z*)-2,3-aminocyclopropanecarboxylic acids[11] of biological importance.[15] We report herein our attempts to form **1a**–**c**, alternatively from the titanium(IV)-mediated cyclopropanation of β-haloesters such as **9a**,**b** followed by base-induced dehydrohalogenation.

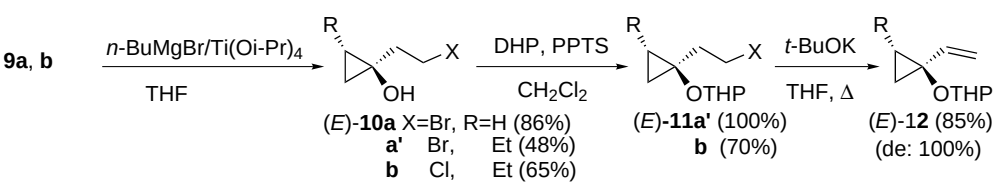
While reaction of ethyl 3-bromopropionate **9a** (X = Br) with 2 equiv. of EtMgBr in the presence of 0.5 equiv. of Ti(O*i*-Pr)$_4$ gave the 1-(2-bromoethyl)cyclopropanol **10a** (X = Br; R = H) in 86% yield,[16] on the other hand, reaction of **9a** with 2.5 equiv. of *n*-BuMgBr and 0.2 equiv. of Ti(O*i*-Pr)$_4$ in THF at room temperature, led to the (*E*)-1-(2-bromoethyl)-2-ethylcyclopropanol **10a**′ (X = Br; R = Et) in only 48% yield. However, better yield was obtained under these conditions from the β-chloroester **9b** (X = Cl), likely due to a reduced steric hindrance, which provided the (*E*)-1-(2-chloroethyl)-2-ethylcyclopropanol **10b** (X = Cl; R = Et) in 65% yield (de: 100%)[17] (Scheme 4).

Cyclopropanols were considered as homoenols which readily underwent electrophilic and anionic ring opening;[1a] therefore, base-induced dehydrohalogenation of **10a**,**b**, required previous *O*-protection. Thus, treatment of 1-(2-haloethyl)cyclopropanols **10a**′,**b** with 2,3-dihydropyran (DHP, PPTS, CH_2Cl_2)[18] at room temperature for 24 h gave the tetrahydropyranyl ethers (*E*)-**11a**′,**b** in 100 and 70% yield, respectively. Then, upon treatment with 2 equiv. of potassium *t*-butoxide in THF at reflux for 12 h (*E*)-**11a**′,**b** underwent dehydrohalogenation to produced the expected (*E*)-1-ethenyl-2-ethyl-1-tetrahydropyranyloxycyclopropane **12** in 72 and 85% yields, respectively. Otherwise direct, base-induced dehydrohalogenation of cyclopropanols (*E*)-**10a**′,**b** led to tarry material. As previously reported,[8] (*E*)-**12** can then undergo deprotection of the THP group by means of ethanol in the presence of PPTS.[18]

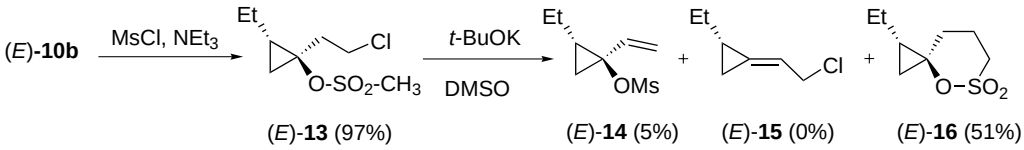
On the other hand, mesylation of (*E*)-**10b** (1.25 equiv. of MsCl, 3 equiv. of NEt_3) in diethyl ether at 0°C followed by stirring at room temperature for 5 h, produced the mesylate (*E*)-**13** in 97% yield. However, base-induced eliminations of hydrogen chloride or of methanesulfonic acid from (*E*)-**13** (2 equiv. of *t*-BuOK, 25 equiv. of DMSO in benzene at room temperature for 16 h), which were expected to give as previously reported,[19] the regiomeric allylic mesylate (*E*)-**14** or chloride (*E*)-**15**, potent precursors of the 1,1-ethylene-allylmetal complexes **2**,[4] failed; in fact, besides (*E*)-**14** (5%) was obtained as major product the spirocyclopropylsulfonate (*E*)-**16** (51%) (Scheme 5), likely arising from the base-induced deprotonation of the mesyloxy methyl followed by chloride substitution and cyclization.[20]



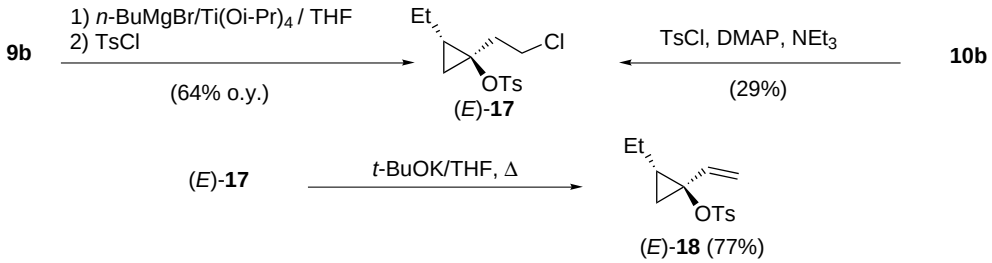
Scheme 3.



Scheme 4.



Scheme 5.



Scheme 6.

Otherwise, one-pot titanium(IV)-mediated cyclopropanation of the β-chloroester **9b** by 2.5 equiv. of *n*-BuMgBr and 0.2 equiv. of Ti(O*i*-Pr)$_4$, followed by the addition in situ of 2.5 equiv. of tosylchloride as work-up (therefore without any hydrolysis) provided directly the (*E*)-1-(2-chloroethyl)-2-ethyl-1-tosyloxycyclopropane **17** in 64% overall yield. Comparatively, tosylation under classical conditions of isolated (*E*)-**10b** (1 equiv. of DMAP, 1.1 equiv. of NEt_3) in dichloro methane at room temperature for 13 h, gave (*E*)-**17** in only 29% yield (19% overall yield from **9b**).[21] Finally, base-induced dehydrochlorination of (*E*)-**17** by 2 equiv. of *t*-BuOK in THF at reflux for 12 h led to the required (*E*)-1-ethenyl-2-ethyl-1-(tosyloxy)cyclopropane **18** in 77% yield (Scheme 6), therefore in 50% overall yield from the cheap commercially available ethyl β-chloropropionate **9b**. Preliminary studies on the asymmetric cyclopropanation of **9b** (2.5 equiv. of *n*-BuMgBr, 0.2 equiv. of Ti(O*i*-Pr)$_4$), in the presence of 0.4 equiv. of TADDOL as titanium chiral ligand,[22] provided the cyclopropanol (*E*)-**10b**, with 76:24 enantioselectivity.[23]

In conclusion, complementary to the titanium(IV)-mediated cyclopropanation of the ethyl 3,3-diethoxypropionate **7**,[14] and of the homoallylic ester **8**,[11] the reaction of the β-chloroester **9b** with the *n*-BuMgBr/Ti(O*i*-Pr)$_4$ reagent, followed by in situ tosylation and base-induced dehydrochlorination can furnish readily 2-alkyl-1-ethenylcyclopropanol derivatives such as (*E*)-**18**, efficient precursors of the astonishing useful 1,1-ethyleneallylmetal complexes **2**.[6] Applications of this new strategy to asymmetric substrates is under current investigation.

References

1. (a) Salaün, J. In *The Chemistry of the Cyclopropyl Group*; Rappoport, Z., Ed. Rearrangements Involving the Cyclopropyl Group; Wiley: New York, 1987; pp. 809–878; (b) *Carbocyclic Three- and Four-membered Ring Systems in Methods of Organic Chemistry*; Houben-Weyl; de Meijere, A., Ed.; 1997; Vol. E 17a–f and references cited therein.
2. Salaün, J. *Top. Curr. Chem.* **1988**, *144*, 1–71.
3. (a) Schnaubelt, J.; Ullmann, A.; Reissig, H.-U. *Synlett* **1995**, 1223–1225; (b) Ulmann, A.; Reissig, H.-U.; Rademacher, O. *Eur. J. Org. Chem.* **1998**, 2541–2549.
4. (a) Stolle, A.; Ollivier, J.; Piras, P. P.; Salaün, J.; de Meijere, A. *J. Am. Chem. Soc.* **1992**, *114*, 4051–4067; (b) Ollivier, J.; Dorizon, P.; Piras, P. P.; de Meijere, A.; Salaün, J. *Inorg. Chim. Acta* **1994**, *222*, 37–49; (c) Salaün, J. *Russ. J. Org. Chem.* **1997**, *33*, 742–780.
5. Ollivier, J.; Girard, N.; Salaün, J. *Synlett* **1999**, 1539–1542.
6. (a) Chevtchouk, T.; Ollivier, J.; Salaün, J. *Tetrahedron: Asymmetry* **1997**, *8*, 1005–1009 and 1011–1014; (b) Stolle, A.; Becker, H.; Salaün, J.; de Meijere, A. *Tetrahedron Lett.* **1994**, *35*, 3517–3520 and 3521–3524; (c) Atlan, V.; Racouchot, S.; Rubin, M.; Bremer, C.; Ollivier, J.; de Meijere, A.; Salaün, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1131–1135; (d) Estieu, K.; Paugam, R.; Ollivier, J.; Salaün, J.; Cordero, F. M.; Goti, A.; Brandi, A. *J. Org. Chem.* **1997**, *62*, 8276–8277; (e) Ferrara, M.; Cordero, F. M.; Goti, A.; Brandi, A.; Estieu, K.; Paugam, R.; Ollivier, J.; Salaün, J. *J. Chem. Eur.* **1999**, 2725–2739; (f) Pisaneschi, F.; Cordero, F. M.; Goti, A.; Paugam, R.; Ollivier, J.; Brandi, A.; Salaün, J. *Tetrahedron: Asymmetry* **2000**, *11*, 897–909; (g) Cordero, F. M.; Pisaneschi, F.; Goti, A.; Ollivier, J.; Salaün, J.; Brandi, A. *J. Am. Chem. Soc.* **2000**, *122*, 8075–8076.
7. Salaün, J. *Chem. Rev.* **1983**, *83*, 619–632 and references cited therein.
8. Salaün, J.; Almirantis, Y. *Tetrahedron* **1983**, *39*, 2421–2428.
9. Salaün, J. *Chem. Rev.* **1989**, *89*, 1247–1270 and references cited therein.
10. For a recent review see: Kulinkovitch, O. G.; de Meijere, A. *Chem. Rev.* **2000**, *100*, 2789–2834 and references cited therein.
11. Racouchot, S.; Ollivier, J.; Salaün, J. *Synlett* **2000**, 1729–1732.

12. Epstein, O. L.; Savchenko, A. I.; Pritytskaya, T. S.; Kulinkovich, O. G. Proceedings of the conference: *Organometallic Chemistry on the Eve of the 21 Century*; Moscow, May 19–23, 1998.
13. Kozyrkov, Y.; Pukin, A.; Kulinkovich, O. G.; Ollivier, J.; Salaün, J., unpublished results.
14. Kozyrkov, Y.; Pukin, A.; Kulinkovich, O. G.; Ollivier, J.; Salaün, J. *Tetrahedron Lett*. **2000**, *41*, 6399–6402.
15. (a) Salaün, J.; Baird, M. S. *Curr. Med. Chem*. **1995**, *2*, 511–542; (b) Salaün, J. *Top. Curr. Chem*. **2000**, *207*, 1–67.
16. Sviridov, S. V.; Vali Vasilevskii, D. A.; Kulinkovich, O. G. *Zh. Org. Khim*. **1991**, *27*, 1431–1433; *J. Org. Chem. USRR* (Engl. Transl.) **1991**, *27*, 1251–1253.
17. The configuration of the cyclopropanol (*E*)-**10b** has been assigned on the basis of 2D-NOESY experiments: IR neat 3340, 2962, 2932; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.20 (dd, $J=6$ and 6 Hz, 1H), 0.80–1.30 (m, 5H), 1.45 (q, $J=6.70$ Hz, 2H), 1.95 (dt, $J=14.3$ and 7.3 Hz, 1H), 2.20 (dt, $J=14.3$ and 6.9 Hz, 1H), 3.80 (dd, $J=6$ and 6 Hz, 2H); ^{13}C NMR (66 MHz, $CDCl_3$) δ 13.7, 19.2, 22.8, 27.3, 37.1, 42, 57.4; MS *m*/*z* (EI), 149 (M^+, 12), 147 (M^+, 44), 119 (11), 93 (35), 91 (100), 75 (12), 63 (65), 57 (48); 43 (75); 41 (30); HRMS (M+Na) found:171.0552; required for $C_7H_{13}NaOCl$ 171.0553.
18. Miyashita, N.; Yoshikoshi, A.; Grieco, P. A. *J. Org. Chem*. **1977**, *42*, 3772–3774.
19. Salaün, J.; Bennani, F.; Compain, J. C.; Fadel, A.; Ollivier, J. *J. Org. Chem*. **1980**, *45*, 4129–4135.
20. For the base-induced ring opening of a cyclopropylmesylate related to **12**, see: Ref. 11.
21. For comparable noteworthy yield improvements in the direct tosylation, i.e. resulting from the one-pot successive Grignard reagent and tosyl chloride additions, see Ref. 6c.
22. Corey, E. J.; Rao, S. A.; Noe, M. C. *J. Am. Chem. Soc*. **1994**, *116*, 9345–9346.
23. Determined by gas chromatography on a chiral capillary column (Cydex B).