ORGANIC LETTERS

2000
Vol. 2, No. 25
4079−4081

Novel Carbon–Carbon Bond Formation Reaction of Methoxyallene Oxide Promoted by TiI_4

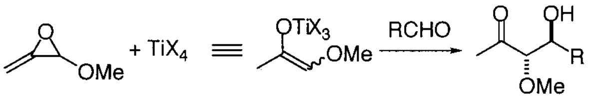
Ryuuichirou Hayakawa and Makoto Shimizu*

Department of Chemistry for Materials, Mie University, Tsu, Mie 514-8507, Japan

mshimizu@chem.mie-u.ac.jp

Received October 12, 2000

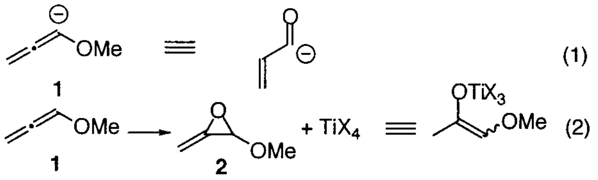
ABSTRACT



Methoxyallene oxide was readily prepared in situ by epoxidation of methoxyallene with 3-chloroperbenzoic acid, and the subsequent reaction with aldehydes or acetals was promoted by titanium tetraiodide and additives to give 2,3-dialkoxy- or 3-hydroxy-2-methoxy ketones in good yields.

Although methoxyallene **1**[1] has been widely used as an acyl anion equivalent of acrolein (Scheme 1, eq 1),[2] the epoxidation of allene derivatives usually gave various decomposed products.[3] There are only limited examples in which epoxidation of allenes is successfully carried out. For example, it has been reported that the allene possessing a bulky substituent such as a *tert*-butyl group is epoxidized using peracid to give a cyclopropanone derivative.[4] Bis-epoxidation of allenes has also been reported to give hydoxyketones.[5] The intramolecular cyclization to cyclopentenone is carried out via epoxidation of 1,2,4-triene derivatives.[6] However, its intermolecular version appears to be difficult due to the instability of allene oxides.

Scheme 1



We have now found the first intermolecular carbon−carbon bond formation of methoxyallene oxide **2** derived from methoxyallene **1**, where the methoxyallene oxide plays the role of an equivalent of the enolate of methoxyacetone on treatment with titanium(IV) iodide (Scheme 1, eq 2). The epoxidation of methoxyallene **1** was regioselectively carried out at the electron-rich carbon−carbon double bond with *m*-CPBA to give the methoxyallene oxide **2**. The reaction of methoxyallene oxide **2** with acetals or aldehydes proceeded to give the aldols possessing a methoxy group at the α-position to the carbonyl group[7] with complete regioselectivity and high diastereoselectivity. The results of the reaction with acetals are summarized in Table 1.[8]

The reaction of methoxyallene oxide **2** was not reproducible using commercially available *m*-CPBA, and therefore, purified *m*-CPBA was used.[9] The reaction with benzaldehyde dimethyl acetal in the absence of acid gave 1,2-dimethoxy-1-phenylbutan-3-one in moderate yield with complete regioselectivity (entry 1).[10] Other metal iodides such as magne-

---

[1] Hoff, S.; Brandsma, L.; Arens, J. F. *Recl. Trav. Chim. Pays-Bas* **1968**, *87*, 916−924.

[2] Tius, M. A. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; John Wiley & Sons: Chichester, 1995; Vol. 5, pp 3316−3320.

[3] Crandall, J. K.; Machleder, W. H. *J. Am. Chem. Soc.* **1968**, *90*, 7292−7295. Crandall, J. K.; Machleder, W. H.; Thomas, M. J. *J. Am. Chem. Soc.* **1968**, *90*, 7346−7347.

[4] Crandall, J. K.; Machleder, W. H. *J. Am. Chem. Soc.* **1968**, *90*, 7347−7349. Camp, R. L.; Greene, F. D. *J. Am. Chem. Soc.* **1968**, *90*, 7349.

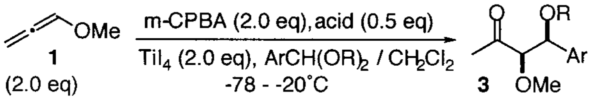
[5] Marshall, J. A.; Tang, Y. *J. Org. Chem.* **1994**, *59*, 1457−1464

[6] Grimaldi, J.; Bertrand, M. *Tetrahedron Lett.* **1969**, 3269−3272

[7] Paquette, L. A.; O'Neil, S. V.; Guillo, N.; Zeng, Q.; Young, D. G. *Synlett* **1999**, 1857−1866.

10.1021/ol006729u CCC: $19.00

Table 1. Reaction of Methoxyallenoxide with Acetals[a]

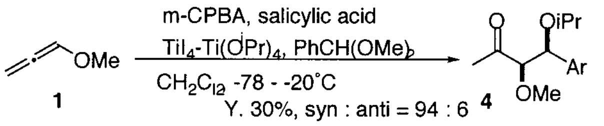


entry	Ar	R	additional acid	yield/%[b]	*syn*:*anti*[c]
1	Ph	Me	none	63	76:24
2	Ph	Me	3-chlorobenzoic acid	56	75:25
3	Ph	Me	acetic acid	68	68:32
4	Ph	Me	chloroacetic acid	75	74:26
5	Ph	Me	salicylic acid	81	72:28
6	Ph	Et	salicylic acid	69	76:24
7	4-ClC_6H_4	Me	salicylic acid	65	76:24
8	4-Tol	Me	salicylic acid	66	78:22

[a] Reaction conditions; see ref 8. [b] Isolated yield. [c] Determined by ^1H NMR. Representative peaks (Ar = Ph, R = Me): *syn* δ 3.64 (J = 3.63 Hz) and 4.51 (J = 3.63), *anti* 3.74 (J = 6.59) and 4.34 (J = 6.59). For more details, see Supporting Information.

sium iodide, aluminum iodide, or other titanium halides could not efficiently promote the reaction.[7] The use of commercially available *m*-CPBA sometimes gave the aldol adducts in higher yields. The difference in the yields is due to the presence of 3-chlorobenzoic acid or water as an impurity in *m*-CPBA. Therefore, the addition of various carboxylic acids was investigated. The addition of chloroacetic acid improved the yield up to 75% (entry 4). The best result was obtained using salicylic acid as an additive (entry 5). The ethyl ether was obtained in the reaction with diethyl acetal (entry 6). The reaction with the acetal possessing an electron-withdrawing or -donating group proceeded with similar efficiency. The reaction with benzaldehyde dimethyl acetal using a mixture of titanium tetraiodide and titanium tetraisopropoxide (1:1) was investigated to improve the stereoselectivities in the reaction with acetals (Scheme 2).

Scheme 2

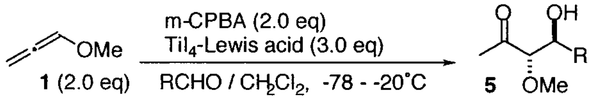


The isopropyl ether **4** was obtained, and the dimethyl ether was not detected in the reaction, which suggests that elimination and addition of alcohol would be involved under the reaction conditions. However, the adduct was not obtained in the reaction with aliphatic aldehyde dimethyl acetal.

The addition reaction with aldehyde was next investigated in order to increase the selectivity and reactivity, and the results are summarized in Table 2.

Diastereoselectivity was not observed using titanium tetraiodide (entry 1), whereas the use of Lewis acid as an additive improved the diastereoselectivity.[11] Moderate *syn*-selectivity was observed in the presence of boron trifluoride etherate (entry 3). When titanium tetrachloride was added, *anti*-adduct was obtained as a major product (entries 4−6). High *anti*-selectivity was achieved using a mixture of TiI_4−$TiCl_4$ (1:3). However, as the amount of $TiCl_4$ used was increased, the product yield decreased. The best result was

Table 2. Reaction of Methoxyallenoxide with Aldehydes[a]



entry	R	TiI_4-Lewis acid	yield/%[b]	*anti*:*syn*[c]
1	Ph	TiI_4	57	51:49
2	Ph	TiI_4−BF_3•OEt_2 (2:1)	57	44:56
3[d]	Ph	TiI_4−BF_3•OEt_2 (2:1)	17	27:73
4	Ph	TiI_4−$TiCl_4$ (3:1)	65	71:29
5	Ph	TiI_4−$TiCl_4$ (1:1)	57	79:21
6	Ph	TiI_4−$TiCl_4$ (1:3)	42	89:21
7	Ph	TiI_4−Ti(O*i*-Pr)$_4$ (3:1)	42	84:16
8	Ph	TiI_4−Ti(O*i*-Pr)$_4$ (1:1)	72	90:10
9	Ph	TiI_4−Ti(O*i*-Pr)$_4$ (1:3)	22	88:12
10	4-$MeOC_6H_4$	TiI_4−Ti(O*i*-Pr)$_4$ (1:1)	61	75:25
11	4-BrC_6H_4	TiI_4−Ti(O*i*-Pr)$_4$ (1:1)	72	95:5
12	4-ClC_6H_4	TiI_4−Ti(O*i*-Pr)$_4$ (1:1)	78	94:6
13	4-FC_6H_4	TiI_4−Ti(O*i*-Pr)$_4$ (1:1)	71	96:4
14	4-$NO_2C_6H_4$	TiI_4−Ti(O*i*-Pr)$_4$ (1:1)	73	94:6
15	2,6-$Cl_2C_6H_3$	TiI_4−Ti(O*i*-Pr)$_4$ (1:1)	71	94:6
16	C_6F_5	TiI_4−Ti(O*i*-Pr)$_4$ (1:1)	74	95:5
17	(*E*)-PhCH=CH	TiI_4−Ti(O*i*-Pr)$_4$ (1:1)	64	82:18
18	$PhCH_2CH_2$	TiI_4−Ti(O*i*-Pr)$_4$ (1:1)	59	63:37
19	*c*-Hex	TiI_4−Ti(O*i*-Pr)$_4$ (1:1)	71	89:11[e]
20	*t*-Bu	TiI_4−Ti(O*i*-Pr)$_4$ (1:1)	53	77:23[e]

[a] Reaction conditions: see ref 11. [b] Isolated yield. [c] Determined by HPLC. [d] The reaction temperature was −78 to −70 °C. [e] Determined by ^1H NMR. Representative peaks (R = *c*-Hex), *syn* δ 2.22 and 3.44, *anti* 2.24 and 3.40; (R = *t*-Bu), *syn* δ 2.46 (J = 9.57 Hz) and 3.42, *anti* 1.99 (J = 6.33) and 3.31. For more details, see Supporting Information.

---

(8) Titanium tetraiodide was purified by sublimation (180 °C/0.8 mmHg). **Typical procedure:** To a suspension of *m*-CPBA (0.72 mmol) and salicylic acid (0.18 mmol) in CH_2Cl_2 (1.5 mL) was added a solution of methoxyallene (0.72 mmol) in CH_2Cl_2 (1.0 mL) at 0 °C under an argon atmosphere. After 30 min of stirring, the mixture was transferred to a mixture of TiI_4 (400 mg, 0.72 mmol)[6] and the acetal (0.36 mmol) in CH_2Cl_2 (2.0 mL) with the aid of CH_2Cl_2 (1.5 mL). After being stirred at −78 to −20 °C, the reaction was quenched with saturated aqueous $NaHCO_3$, aqueous 5% $NaHSO_3$, and triethylamine. The mixture was filtered through a Celite pad. The layers were separated and extracted with ethyl acetate (10 mL × 3). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ and brine and then dried over anhydrous Na_2SO_4. Purification by preparative TLC on silica gel gave the adduct.

(9) Schwartz, N. N.; Blumbergs, J. H. *J. Org. Chem.* **1964**, *29*, 1976−1979.

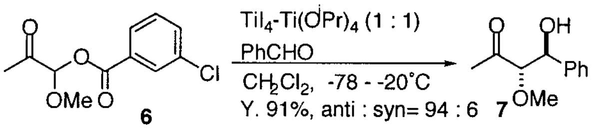
(10) Other adduct such as 1,4-dimethoxy-1-phenylbutan-3-one could not be detected.

(11) **Typical procedure for the reaction of aldehydes:** To a suspension of *m*-CPBA (0.72 mmol) in CH_2Cl_2 (0.5 mL) was added a solution of methoxyallene (0.72 mmol) in CH_2Cl_2 (1.0 mL) at 0 °C under an argon atmosphere, and the resulting mixture was stirred at 0 °C for 30 min. To a solution of TiI_4 (0.54 mmol) in CH_2Cl_2 (1.0 mL) was added a solution of Ti(O*i*-Pr)$_4$ (1.0 M in CH_2Cl_2) at 0 °C. The resulting solution was stirred at ambient temperature for 10 min, and to it was added a solution of aldehyde (0.36 mmol) in CH_2Cl_2 (1.0 mL) at −78 °C. The suspension of the epoxidation reaction mixture was transferred to the resulting mixture of TiX_4 and aldehyde with the aid of CH_2Cl_2 (1.5 mL). The reaction mixture was stirred and worked up as in the case with acetals.

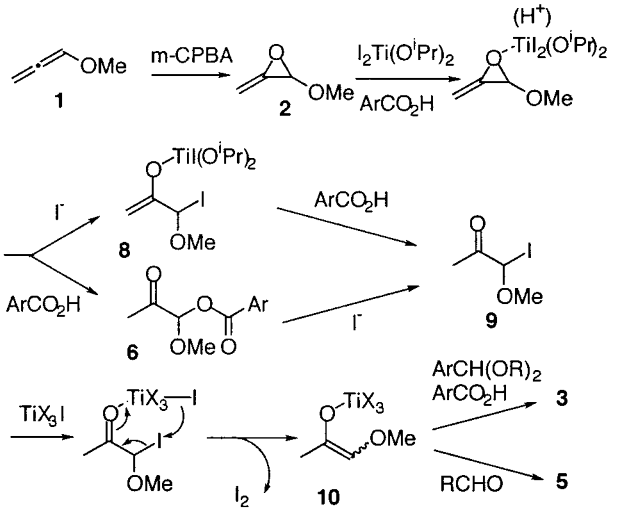
obtained using TiI_4−Ti(O*i*-Pr)$_4$ (1:1) (entry 8).[12] The solubility and the bulkiness of the isopropyl group of the resulting reactive species, TiI_2(O*i*-Pr)$_2$, are thought to be responsible for the observed high yield and *anti*-selectivity. Under the optimized conditions, the reaction of methoxyallenoxide with various aldehydes was investigated. Moderate yield and selectivity were observed in the reaction of 4-methoxybenzaldehyde (entry 10). In this case retro-aldol reaction caused the lower yield and selectivity, since this adduct readily underwent retro-aldol reaction even upon purification on silica gel TLC.[13] The reactions with aldehydes possessing electron-withdrawing substituents gave the adducts with high selectivities in high yields, in which the use of 4-fluorobenzaldehyde gave the best result (entry 13). The reaction with aliphatic aldehyde was also carried out with *anti*-selectivity.

The hemiacetal **6** was isolated as a byproduct in the present reaction, suggesting that it would be one of the intermediates. The subsequent reaction of **6** with benzaldehyde under the influence of TiI_4−Ti(O*i*-Pr)$_4$ gave the adduct **7** in high yield with high selectivity (Scheme 3). We propose a plausible reaction mechanism as shown in Scheme 4. The titanium enolate **8** would be formed via ring-opening reaction of methoxyallene oxide **2** with diiododiisopropoxytitanium derived from TiI_4 and Ti(O*i*-Pr)$_4$ and undergoes protonation with 3-chlorobenzoic acid to give iodo ketone **9**. The iodo ketone **9** would also be formed by displacement of the benzoyloxy group of **6** with iodide anion. The iodo ketone **9** would be in turn regioselectively transformed into the titanium enolate **10** via reduction of the iodine with the iodide anion,[14] and the subsequent reaction with aldehyde gives the adduct in a regioselective manner. Although arguments on the stereochemical outcome need more experimental supports, the formation of (*Z*)-enolate with TiI_4 and that of the (*E*)-counterpart with TiI_4/Ti(O*i*-Pr)$_4$ followed by a cyclic transition state appear to explain the observed *syn*- and *anti*-selectivity, respectively.[15]

Scheme 3



Scheme 4



In conclusion, we have shown a novel regio- and stereoselective carbon−carbon bond formation reaction utilizing methoxyallene oxide **2**. The mechanism of the present reaction is intriguing, where the reductive formation of the titanium enolate from α-iodo ketone was efficiently carried out using titanium(IV) iodide at low temperature.[14] Although the formation of the enolate of methoxyacetone in a regioselective manner was reported,[16] the present approach also offers a convenient alternative. Various alkoxy-substituted aldols, useful synthetic synthons, may be synthesized utilizing the present reaction, since alkoxyallenes are readily available from propargyl ethers.

Acknowledgment. This work was supported by a Grant-in Aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture of the Japanese Government.

Supporting Information Available: Experimental procedures and product characterization for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL006729U

---

[12] The color of the titanium solution turned from brown to green at 0 °C. Stirring at ambient temperature turned the color of the solution to red-brown.

[13] The buffered silica gel was used for the purification. The buffered silica gel was prepared by suspending 93 g of silica gel (Merck 60F_{254}) in 230 mL of phosphate buffer solution (pH 7.0) for 2 h and dried.

[14] Tsuritani, T.; Ito, S.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **2000**, *65*, 5066−5068. Maeda, K.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **1998**, *63*, 4558−4560. Liu, M. Z.; Guo, Z. W.; Hui, Y. Z. *Youji Huaxue* **1997**, *17*, 319−323. Borah, H. N.; Boruah, R. C.; Sandhu, J. S. *J. Chem. Soc., Chem. Commun.* **1991**, 154−155.

[15] Reviews: Paterson, I.; Goodmanm J. M.; Lister, M. A.; Schumann, R. C.; McClure, C. K.; Norcross, R. D. *Tetrahedron* **1990**, *46*, 4663−4684. Mukaiyama, T. *Org. React.* **1982**, *28*, 203−331. Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1−115. Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, Chapter 2.

[16] Poirier, J.-M.; Hennequin, L.; Fomani, M. *Bull. Soc. Chim. Fr.* **1986**, 436−448.