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Lewis Acid-Promoted Addition of Methylenecyclopropanes to Aldehydes and Ketones[1]

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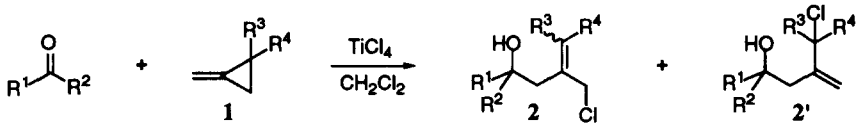
Abstract: In the presence of $TiCl_4$, methylenecyclopropane (**1a**) easily reacted with aliphatic aldehydes to give the β-(chloromethyl)allylated products **2** in good yields along with a small amount of the methylenetetrahydrofurans **3**. The reaction with chiral α- and β-alkoxy aldehydes proceeded with high levels of chelation control. © 1997 Elsevier Science Ltd.

Methylenecyclopropanes (MCPs) exhibit unique reactivities originated from the highly strained structure (E_s = 171 kJ mol^{-1}),[2] and they can be easily prepared and functionalized by various methods.[3] Therefore, they have been frequently used for organic synthesis, particularly, carbon-carbon bond formation.[4-7] The transition metal-catalyzed [3+2] cycloaddition of MCPs to carbon-carbon multiple bonds has been known to be an efficient method for the construction of five-membered carbocycles.[4] Recently, the radical addition to MCPs followed by rearrangement of the resulting cyclopropylmethyl radical has been extensively studied for the synthesis of cyclopentanes and more complex polycyclic compounds.[5] However, little work has been carried out on carbon-carbon bond formation utilizing the nucleophilic addition of MCPs to carbon electrophiles.[6,7] We report herein that the Prins-type reaction[8] of MCPs **1** with carbonyl compounds activated by a Lewis acid proceeds with ring cleavage to provide the allylated products **2** and **2'**. (eq. 1)



(eq. 1)

Initially, we examined the reaction of the parent MCP (**1a**: R^3, R^4 = H)[3a] with 3-phenylpropanal using several kinds of Lewis acid. The $TiCl_4$-mediated reaction of **1a** at -78 °C gave the homoallyl alcohol **2a**[9] in 72% yield along with a small amount of the cycloadduct **3a**. (entry 1 in Table 1) Other Lewis acids such as $SnCl_4$, BCl_3, and $AlCl_3$ were less effective for the allylation compared with $TiCl_4$. The use of BF_3•OEt_2 and TMSOTf for the selective formation of **3a** only gave a complex mixture of products.

Next, we carried out the $TiCl_4$-mediated addition of **1a** with various aldehydes as shown in Table 1. Aliphatic aldehydes such as heptanal, cyclohexanecarbaldehyde, and 3-cyclohexenecarbaldehyde smoothly reacted with **1a** to afford the corresponding homoallyl alcohols **2b-d** in good yields. (entries 2-4) Since isobutyraldehyde and pivalaldehyde were not as reactive as the above three aldehydes, elevated temperature and/or longer reaction time were required to obtain acceptable yields. (entries 5, 6) On the other hand, aromatic and α,β-unsaturated aldehydes (R^1 = Ph, *p*-$MeOC_6H_4$, 2-furyl, (*E*)-CH_3CH=CH, (*E*)-PhCH=CH, R^2 = H) except for *p*-nitrobenzaldehyde were insensitive to **1a** even at rt. (entry 7) A similar tendency was

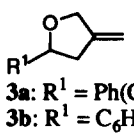
observed in the allylation of ketones with **1a**. Aliphatic ketones such as 3-pentanone and cyclohexanone underwent the allylation with **1a** (entries 8, 9), however, the use of acetophenone did not lead to the adduct.

We further examined the applicability of methylenecyclopropanes to the present reaction. Although the MCP **1b**[3b] bearing an alkyl group on the cyclopropane ring reacted with 3-phenylpropanal activated by $TiCl_4$ to give the allylated products **2j** and **2'j** as a mixture of stereoisomers, **1b** was much less reactive than **1a** (entry 10). No adducts were obtained in the reactions of phenyl- and *gem*-dimethyl-substituted MCPs (**1**: R^3 = Ph, R^4 = H and R^3, R^4 = Me)[3b] even at rt. Interestingly, the bicyclic MCP **7**[3b] easily added to aliphatic aldehydes without cleavage of the cyclopropane ring to give the γ-chlorohydrins **8** as a single stereoisomer.[10] (eq. 2) Introduction of a trimethylsilyl group on the cyclopropane ring dramatically increased the reactivity of MCP. The addition of the MCP **1c**[3c] to 3-phenylpropanal was completed within 10 min to give the allylated products **2k** and **2'k** along with the 2:1 adduct **4**. (entry 11) The diol **4** would be formed by the reaction of the allylsilane **5** with 3-phenylpropanal.[11] The high reactivity of **1c** can be attributed to the electronic effect of the silyl group on the *exo*-methylene carbon. Indeed, its δ ^{13}C value in **1c** is about 3 ppm more upfield than that in **1a**. This observation clearly indicates that **1c** has a higher nucleophilicity than **1a**. In this reaction, the formation of the ordinary allylsilane-type reaction product **6** was not observed. This is probably reasonable in view of the thermodynamical instability of **6**.

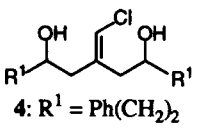
Table 1. $TiCl_4$-mediated addition of methylenecyclopropanes **1** to carbonyl compounds[a]

Entry	Carbonyl Compounds R^1	Carbonyl Compounds R^2	MCPs R^3 (R^4 = H)	Conditions	Products	Yield / % 2 + 2' (2 : 2')	Yield / % 3 or 4[b]
1	$Ph(CH_2)_2$	H	H (**1a**)	- 78 °C, 2 h	**2a** + **3a**	72	5
2	C_6H_{13}	H	H	- 78 °C, 2 h	**2b** + **3b**	73	7
3	*c*-C_6H_{11}[c]	H	H	- 78 °C, 2 h	**2c**	86	–
4	*c*-C_6H_9[d]	H	H	- 78 °C, 50 min	**2d**	82[e]	–
5	*i*-Pr	H	H	- 40 °C, 2.5 h	**2e**	75	–
6	*t*-Bu	H	H	0 °C, 24 h	**2f**	49	–
7	*p*-$O_2NC_6H_4$	H	H	- 78 °C, 2 h → rt, 2 h	**2g**	20	–
8	Et	Et	H	0 °C, 14 h	**2h**	5	–
9	$(CH_2)_5$		H	0 °C, 14 h	**2i**	61	–
10	$Ph(CH_2)_2$	H	C_8H_{17} (**1b**)	- 78 °C, 2 h	**2j** + **2'j**	18 (73 : 27)	–
11	$Ph(CH_2)_2$	H	$SiMe_3$ (**1c**)	- 78 °C, 10 min	**2k** + **2'k** + **4**	73 (43 : 57)	6

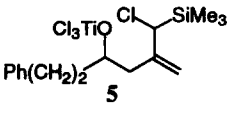
[a]The reactions in entries 1-7, 10, and 11 were performed with **1** (1.3 mmol), a carbonyl compound (1.0 mmol), and $TiCl_4$ (1.0 mmol) in CH_2Cl_2 (5 ml) under N_2. In entries 8 and 9, increased amounts of **1** (3.0 mmol) and $TiCl_4$ (1.5 mmol) were employed. [b]The structures of **3** and **4** are shown below. [c]Cyclohexyl. [d]3-Cyclohexenyl. [e]A 66:34 diastereomeric mixture.



3a: $R^1 = Ph(CH_2)_2$
3b: $R^1 = C_6H_{13}$



4: $R^1 = Ph(CH_2)_2$



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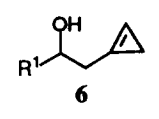

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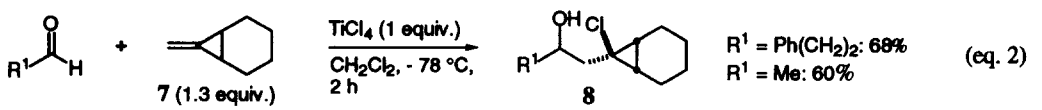
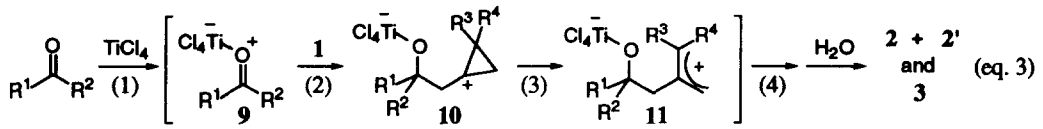


7 (1.3 equiv.)

8

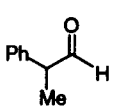
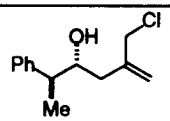
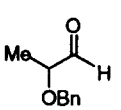
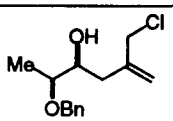
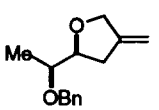
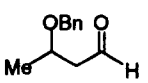
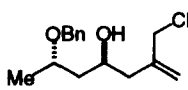
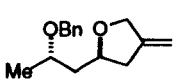
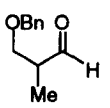
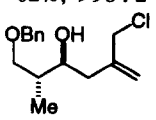
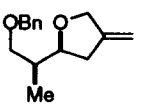
(eq. 2)

A plausible mechanism for the present allylation is as follows (eq. 3): (1) coordination of a carbonyl compound to $TiCl_4$ forms the complex **9**, (2) **9** is subjected to nucleophilic addition of **1**, (3) the formed cyclopropyl cation **10** isomerized to the π-allyl cation **11**,[12] and (4) nucleophilic attack of the ligands bound to titanium gives the homoallyl alcohols **2**, **2'**, and the 3-methylenetetrahydrofuran **3**. The low reactivity of α,β-unsaturated and aromatic carbonyl compounds can be attributed to delocalization of the positive charge on the carbonyl carbon of **9**, which would reduce the electrophilicity of **9** to prevent the reaction with **1**.[13]

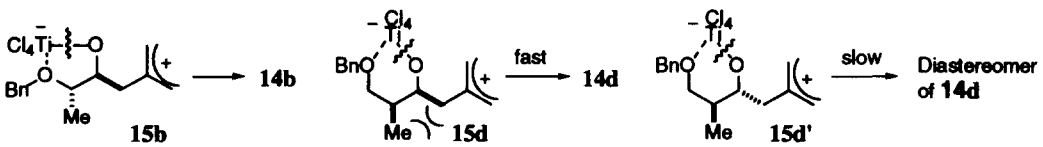


In order to investigate the diastereoselectivity of the present reaction, **1a** and four chiral aldehydes **12a-d** were employed. (Table 2) Contrary to our expectations, the reaction of 2-phenylpropanal afforded the anti-Cram product as the major isomer. This result is a sharp contrast to the stereochemical outcome in the $TiCl_4$-mediated allylation of **12a** with allylsilanes.[14,15] Allylation of the chiral α- and β-benzyloxy aldehydes **12b-d** with **1a** as well as that with allylsilanes exhibited high levels of chelation control.[14,16] The increased amount of the [3+2] cycloadduct **14b** is probably because the strained five-membered chelation ring in the intermediate **15b** induces cleavage of the Ti-O bond. In the reaction of **12d**, the major isomers **13d** and **14d** were different from each other in relative configuration. This result supports that the cyclization of **15d** to **14d** is faster than that of **15d'** to the diastereomer of **14d**. The fast cyclization may come from the steric repulsion between the substituents on the chelation ring in **15d**.

Table 2. $TiCl_4$-mediated addition of methylenecyclopropane (**1a**) to chiral aldehydes (**12**)[a]

Aldehyde	Product (major isomer) Yield, Diastereomeric Ratio		Aldehyde	Product (major isomer) Yield, Diastereomeric Ratio	
 **12a**	 **13a** 71%, 63 : 37		 **12b**	 **13b** 62%, >98 : 2	 **14b** 14%, >98 : 2
 **12c**	 **13c** 68%, 96 : 4	 **14c** trace	 **12d**	 **13d** 60%, 87 : 13	 **14d** 5%, 87 : 13

[a]Reaction conditions: **1a** (3.0 mmol), **12** (1.0 mmol), and $TiCl_4$ (1.5 mmol) in CH_2Cl_2 (5 mL) at -78 °C for 2 h.



In conclusion, we have disclosed the reactivity of MCPs to carbonyl compounds activated by a Lewis acid and developed a new type of allylation of carbonyl compounds. The $TiCl_4$-mediated addition of **1a** is an

efficient method for the synthesis of the homoallyl alcohols **2**, **2'**, and **13**, which are synthetic intermediates of pharmaceutically important α-methylene-γ-lactones.[9] We are now investigating on the Lewis acid-promoted [3+2] cycloaddition of **1a** to carbonyl compounds, and the results will be reported in due course.

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