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Lewis acid-catalyzed novel [3+2] cycloaddition of methylenecyclopropanes with activated aldehydes or ketones☆

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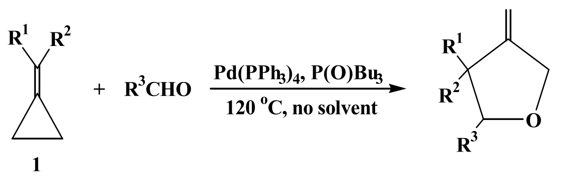
Abstract—Methylenecyclopropanes react with activated aldehydes or ketones in the presence of various Lewis acids to give the corresponding [3+2] cycloaddition products having tetrahydrofuran (THF) skeleton in good yields and in some cases with high stereoselectivity. © 2003 Elsevier Science Ltd. All rights reserved.

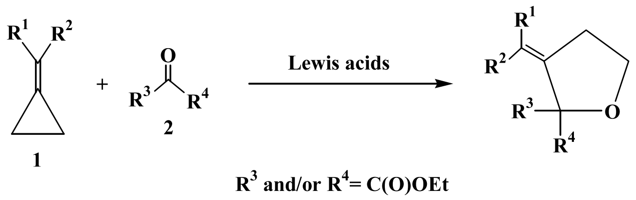
Methylenecyclopropanes (MCPs) **1** are highly strained but readily accessible molecules that have served as useful building blocks in organic synthesis.[1] Strain in organic molecules often correlates with increased reactivity because its relief provides a potent thermodynamic driving force. Thus, it comes as no surprise that MCPs undergo a variety of ring-opening and cycloaddition reactions. Since numerous methodologies have been developed for the construction of MCPs,[1] they have now emerged as versatile tools in organic synthesis.[1] [3+2] Cycloaddition of MCPs to carbon–carbon or carbon–heteroatom multiple bonds, under catalysis by such transition metals as Pd and Ni, has been extensively studied. For example, MCPs have been found to react with carbon–carbon multiple bonds,[2] carbon dioxide,[3] aldehydes,[4] and imines[5] in the presence of Pd catalysts to give [3+2] cycloaddition products (Scheme 1). The mechanism of these reactions are very similar to that of the reaction of trimethylene methane precursors with multiple bonds in the presence of Pd catalysts to give five-membered rings.[6] However, these reactions usually require severe reaction conditions such as high temperature (120°C) and/or prolonged reaction time (3 days), which limited their use in organic synthesis.

Recently, examples of Lewis acid-catalyzed reactions of MCPs with alcoholic or aromatic amino nucleophiles and aldehydes or ketones under milder conditions have been disclosed.[7] In this communication, we wish to describe a new and conceptually novel [3+2] approach to tetrahydrofuran skeletons **3** by the reaction of MCPs with activated ketones such as diethyl ketomalonate (**2a**) and ethyl glyoxylate (**2b**) in the presence of Lewis acids (Scheme 2). The novelty of the present work is the unusual regioselectivity observed and the [3+2] cycloaddition products reported in this paper have never been disclosed before. In most cases, this reaction can complete even at room temperature.

The Lewis acids played a critical role in this reaction. Various Lewis acids have been tested for the reaction of



Scheme 1. Pd(0)-catalyzed cycloaddition of MCPs with aldehydes.



Scheme 2. Lewis acid-catalyzed cycloaddition of MCPs with activated aldehydes and ketones.

Keywords: methylenecyclopropane; [3+2] cycloaddition; Lewis acids; activated ketones and aldehydes.

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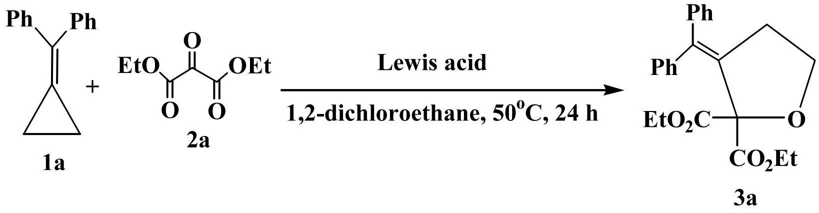
diphenylmethylenecyclopropane (**1a**) with ketomalonate (**2a**) (Table 1). The reaction proceeded smoothly in 1,2-dichloroethane (DCE) at 50°C in the presence of Lewis acids such as $Sn(OTf)_2$, $Yb(OTf)_3$ or $BF_3{\cdot}Et_2O$ (Table 1, entries 1–3), but $Zn(OTf)_2$ and $Cu(OTf)_2$ gave very poor results under the same conditions (Table 1, entries 4 and 5). In addition, we also found that the reaction proceeded very well in dichloromethane and DCE, but THF, DMF, 1,4-dioxane or CH_3CN gave no cycloaddition product. Table 2 summarizes the results of the reactions of various MCPs with **2a** and **2b**. The substituents on the phenyl ring of MCPs have significant effect on the ease of the reaction (Table 2, entries 1–4). The reaction of **1a** with **2a** proceeded with greater ease than of **1b** with **2a**, and that of **1d** with **2a** proceeded with greater ease than that of **1a** with **2a**. Based on these results, we can conclude that electron-withdrawing groups (such as -Cl) can hinder the reaction and that electron-donating groups (such as -OMe) facilitate it under the same conditions.

The structure of **3a** was confirmed by X-ray diffraction (Fig. 1).[8] The stereochemistry of the double bond in **3e**,**f** was established by NOE effects. The yields of the reactions of MCPs with **2b** were not high. This may be due to the fact that **2b** can be easily polymerized and/or oxidized to the corresponding acid by air even if the reaction is carried out under nitrogen atmosphere. MCPs can then react with the acid to give ring-opening products in the presence of Lewis acid. A plausible

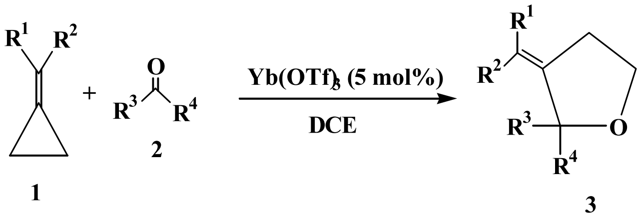
Table 1. The effect of Lewis acid on the cycloaddition



Entry	Lewis acid	Yield (%)[a]
1	$Yb(OTf)_3$	84
2	$Sn(OTf)_2$	47
3	$BF_3{\cdot}Et_2O$	71
4	$Cu(OTf)_2$	11
5	$Zn(OTf)_2$	Trace
6	None	No reaction

[a] Isolated yields.

Table 2. Reactions of MCPs with **2a** and **2b**



Entry[a]	R_1/R_2	R_3/R_4	Time (h)/temp. (°C)	Isolated yield (%) (*E*/*Z*)
1	C_6H_5/C_6H_5, **1a**	CO_2Et/CO_2Et, **2a**	24/40	**3a**, 84
2	C_6H_5/p-ClC_6H_4, **1b**	**2a**	48/70	**3b**, 51 (1:1)
3	p-MeC_6H_4/p-MeC_6H_4, **1c**	**2a**	18/40	**3c**, 86
4	p-$MeOC_6H_4/p$-$MeOC_6H_4$, **1d**	**2a**	2/rt	**3d**, 75
5	p-$MeOC_6H_4$/H, **1e**	**2a**	24/rt	**3e**, 48 (11:1)
6	m-$C_6H_5OC_6H_4$/H, **1f**	**2a**	24/rt	**3f**, 56 (6.1:1)
7	p-ClC_6H_4/C_6H_5, **1g**	**2a**	24/70	**3g**, 65 (1:1)
8	p-ClC_6H_4/p-ClC_6H_4, **1h**	**2a**	24/90	**3h**, 54
9	**1a**	CO_2Et/H, **2b**	48/rt	**3i**, 48
10	**1c**	**2b**	48/rt	**3j**, 52
11	**1d**	**2b**	2/rt	**3k**, 54

[a] All reactions were carried out with MCPs **1a**–**h** (0.5 mmol) and **2** (0.6 mmol) in the presence of $Yb(OTf)_3$ (5 mol%) using 1,2-dichloroethane (DCE) as solvent.

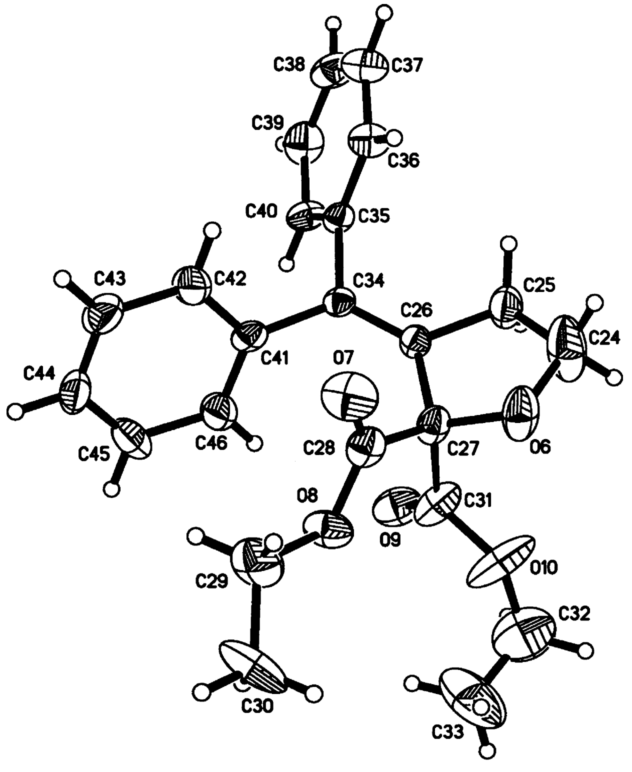


Figure 1. The ORTEP draw of **3a**.

mechanism for this novel cycloaddition reaction of MCPs is shown in Scheme 3. We believe this novel cycloaddition involves a stepwise process like the Lewis acid-catalyzed [2+2] cycloadditions of ketenes with aldehydes rather than a concerted one.[9] The rearrangement of the carbon cation **4** to **5** is the key step of this reaction.[10]

In conclusion, the type of transformation reported here by us has not been known before. The present atom-economical [3+2] cycloaddition is potentially useful for the construction of biologically important tetrahydrofuran skeletons.[11] This Lewis acid-catalyzed cyclization is an important transformation for heterocycle synthesis of five-membered ring systems. Efforts are underway to elucidate the mechanistic details of this reaction and to examine its scope and limitations.

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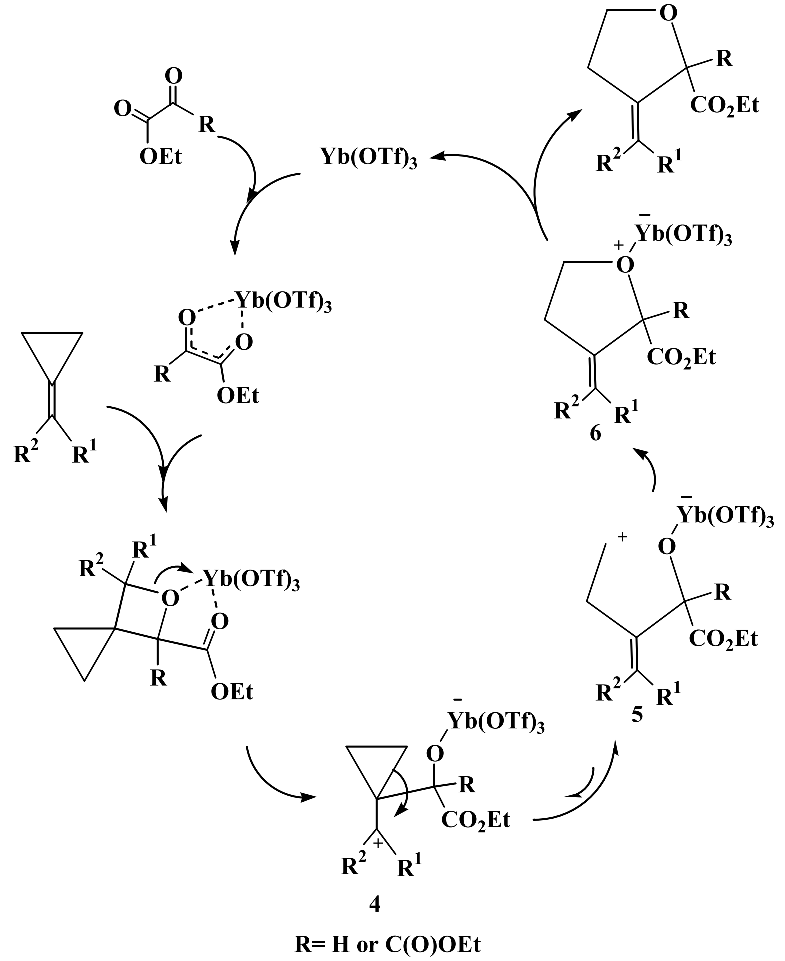

R= H or C(O)OEt

Scheme 3. Proposed mechanism for Lewis acid-catalyzed cycloaddition of MCPs to activated carbonyl compounds.

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11. *Typical procedure for the cycloaddtion of MCPs with an activated ketone*: Under an argon atmosphere, MCP **1a** (103 mg, 0.5 mmol), Yb(OTf)$_3$ (0.0025 mmol) and activated ketone **2a** (104 mg, 0.6 mmol) were dissolved in 1.5 mL DCE. The reaction mixture was heated to 50°C and stirred for 24 h. Concentration of reaction mixture and purification of product by silica gel chromatography (hexane/ethyl acetate = 10/1 as an eluent) afforded adduct **3a** in 84% yield as a colorless solid. Mp 78–79°C; IR (neat): ν 2980, 2885, 1760, 1731, 1597, 1491, 1236, 1084 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$, TMS): δ 1.12 (t, J = 6.7 Hz, 6H), 2.73 (t, J = 7.3 Hz, 2H), 3.82–3.90 (m, 2H), 4.00–4.10 (m, 4H), 7.18–7.32 (m, 10H); ^{13}C NMR (75 MHz, CDCl$_3$, TMS): δ 13.85, 33.17, 61.98, 68.27, 87.18, 127.14, 127.74, 128.05, 128.47, 129.28, 135.60, 139.80, 140.14, 140.15, 143.05, 168.26; MS (EI): m/z 308 (M$^+$), 234, 206, 191, 166. Anal. calcd for $C_{23}H_{24}O_5$: C, 72.61; H, 6.36. Found: C, 72.60; H, 6.51%.