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Lewis acid-mediated addition of silylated methylenecyclopropane to aldehydes—synthesis of tetrahydrofuran derivatives

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Abstract—Lewis acid-mediated intermolecular addition of silylated methylenecyclopropane to aldehydes provides a novel route to tetrahydrofuran derivatives.

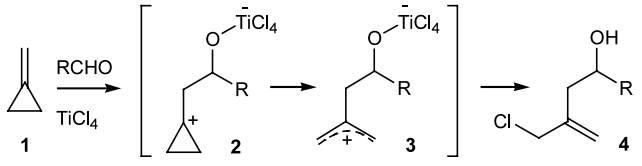
Methylenecyclopropane **1**, with its highly strained ring and reactive exocyclic double bond, has long attracted interest as a synthetic intermediate,[1] and methylenecyclopropane derivatives have consequently been extensively used in synthesis, for example in [3+2] cycloaddition reactions catalysed by transition metals,[2] in radical based annulation reactions[3] and in radical cyclisation reactions.[4] A new aspect of methylene cyclopropane chemistry was recently revealed by Hosomi et al. who showed that methylenecyclopropane could be coupled with aldehydes using Lewis acids such as $TiCl_4$.[5] In this process, activation of an aldehyde with $TiCl_4$ leads to intermolecular nucleophilic attack of the double bond of the methylenecyclopropane to give a cyclopropyl cation **2** which opens to give π-allyl cation intermediate **3**, which in turn is quenched by a chloride anion to give alkenols **4** in good yield (Scheme 1).

We have subsequently shown that analogous intramolecular reactions, e.g. of **5**, provide an efficient route to cycloalkenols **7** (Scheme 2).[6]

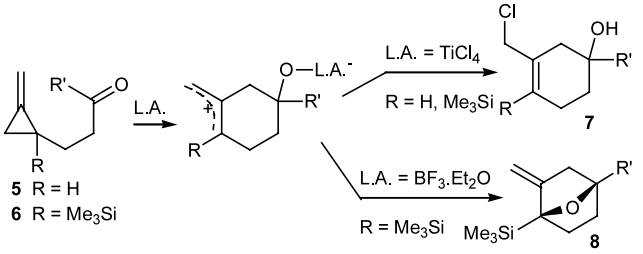
Furthermore, we have found that incorporation of a silyl substituent leads to increased reactivity of the methylenecyclopropane, such that cyclisations, e.g. of **6**, can be mediated with milder Lewis acids, such as $BF_3{\cdot}Et_2O$.[7] This in turn allows the intermediate allyl cation to be trapped intramolecularly by the alkoxide, leading to bicyclic **8**.

The enhanced reactivity of the silylated methylenecyclopropanes encouraged us to investigate the intermolecular addition of silylated methylenecyclopropanes to aldehydes,[8] which might lead directly to tetrahydrofuran products (in effect a [3+2] cycloaddition process[9]). Herein we describe our preliminary investigations into such cyclisations.

Treatment of methylenecyclopropane with a strong base followed by a trialkylsilyl chloride provides a convenient route to silylated methylenecyclopropane.[10] Methylenecyclopropyl(trimethyl)silane, however, is too volatile to be conveniently handled, so we used methylenecyclopropyl(trisisopropyl)silane **9**.



Scheme 1.



Scheme 2.

Keywords: methylenecyclopropane; Lewis acid; tetrahydrofuran.

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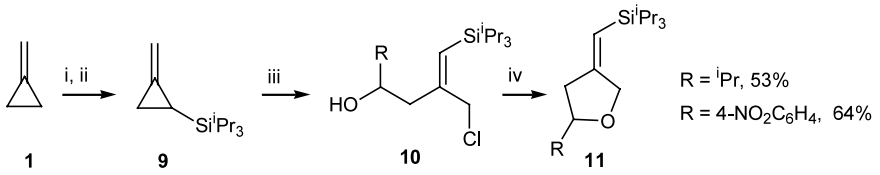


Scheme 3. *Reagents and conditions*: (i) BuLi, THF, −78°C; (ii) $^{i}Pr_3SiCl$, 0°C; (iii) RCHO, $TiCl_4$, −78°C; (iv) NaH, THF, 25°C.

Reaction of **9** with 2-methylpropanal or 4-nitrobenzaldehyde using $TiCl_4$, in CH_2Cl_2, led to the anticipated chloroalkenols **10** in reasonable yields (Scheme 3). The chloroalkenols could be converted to the corresponding tetrahydrofurans **11** by treatment with NaH in essentially quantitative yield.[11]

Reaction of **9** with 2-methylpropanal or 4-nitrobenzaldehyde using $BF_3{\cdot}Et_2O$, however, led to a mixture of products (Scheme 4) which included the anticipated tetrahydrofuran **11**, but also the furofurans **12** and **13** as a mixture of diastereoisomers[11] (Table 1).

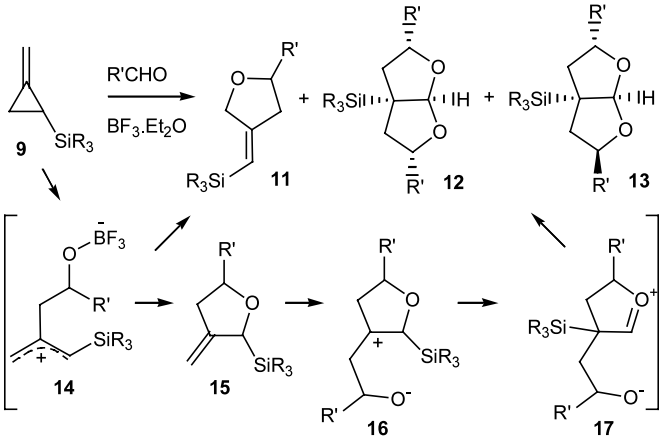
The unexpected formation of **12** and **13** can be readily rationalised. Addition of methylenecyclopropyl(trisisopropyl)silane **9** to the aldehyde is followed by rearrangement to the allyl cation intermediate **14**, which can be trapped by the alkoxide to give either tetrahydrofuran **11** or the regioisomer **15**. Whereas the relatively stable vinylsilane **11** is subsequently isolated, the allylsilane **15** reacts with a further equivalent of the aldehyde to give **16**. A 1,2-silyl shift,[12] presumably encouraged by formation of the relatively stable oxonium ion **17** then allows the cationic intermediate to be trapped by the second alkoxide to give the observed furofurans.

The reaction was also carried out using methylenecyclopropyl(*tert*butyldiphenyl)silane with 4-nitrobenzaldehyde, and the change of silyl group increased the amount of **11** relative to **15**, as well as dramatically affecting the stereoselectivity of the subsequent reaction of **15** so that furofuran **13** was obtained as a single diastereoisomer.

Reaction of **9** with benzaldehyde, again using $BF_3{\cdot}Et_2O$, led again to the anticipated tetrahydrofuran **18** in reasonable yield, but now accompanied by the naphthalene derivative **19** in 21% yield (Scheme 5).

The formation of naphthalene **19** presumably arises from trapping of the intermediate allyl cation by the phenyl and subsequent aromatisation of the newly formed ring. In the expectation that this latter pathway might be enhanced with a more electron rich aromatic aldehyde, the reaction was carried out using 3-methoxybenzaldehyde, but lower yields were obtained with little evidence for a change in selectivity.

In conclusion, we have found that silylated methylenecyclopropanes react with aldehydes mediated by $BF_3{\cdot}Et_2O$ to give simple tetrahydrofurans as well as furofurans or naphthalene derivatives. The formation of furofurans proceeds by a novel cascade sequence involving two equivalents of aldehyde. Opportunities to control the selectivity of these novel reactions by varying the silyl substituent and alternative Lewis acids are being explored in our laboratories.

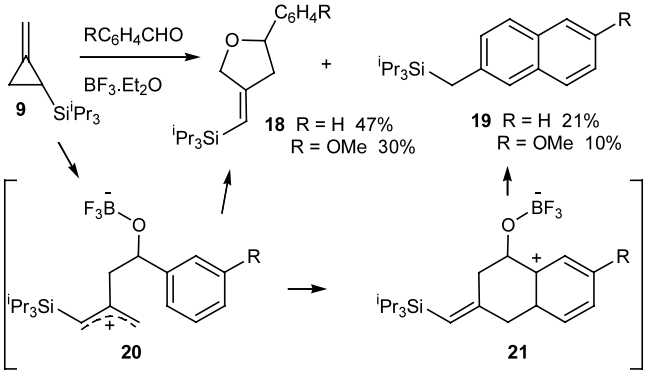


Scheme 4.

Table 1. Conditions and yields for reaction of **9** with various aldehydes (Scheme 4)

R_3	R′	Conditions	Yields		
			11	**12**	**13**
$^{i}Pr_3$	^{i}Pr	0°C→rt	30	14	15[a]
$^{i}Pr_3$	4-$NO_2C_6H_4$	−78°C→rt	32	18	8[a]
$^{i}Pr_3$	^{i}Pr	0°C→rt	41	14	28[b]
$^{i}Pr_3$	4-$NO_2C_6H_4$	−78°C→rt	44	29	16[b]
$Ph_2{}^{t}Bu$	4-$NO_2C_6H_4$	−78°C→rt	33	0	20[b]

[a] Using 1 equiv. aldehyde. Yield is based on **9**.
[b] Using 2 equiv. aldehyde. Yield is based on **9**.



Scheme 5.

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