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Efficient one-pot ring-opening/aldol reactions using (cyclopropyl)methylstannanes

Bernard Leroy*

Université catholique de Louvain, Département de Chimie, Unité de Chimie organique et médicinale, Pl. Pasteur 1, 1348 Louvain-la-Neuve, Belgium

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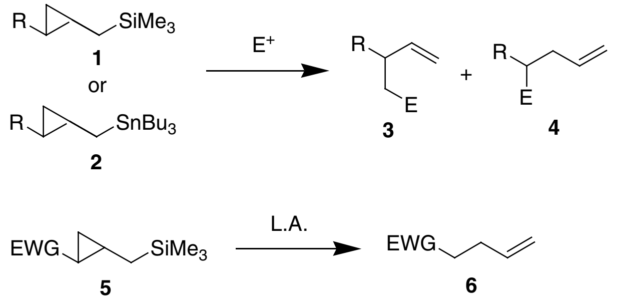
Abstract—(Cyclopropyl)methylstannanes, substituted with an electron-withdrawing group, have been found to be effective homoallylating reagents of aldehydes and ketones. The reaction proceeds by Lewis-acid catalyzed ring opening, followed by an aldol condensation of the resulting enolate, providing homoallylation products in excellent yields. The diastereoselectivity of the process was found to be highly dependent upon the temperature and the solvent, the reaction giving mainly *anti* adducts at −78 °C and *syn* compounds at 0 °C.

Allylation reactions of electrophiles such as carbonyl compounds with allylsilanes and allylstannanes have become, over the years, one of the most reliable methods for carbon–carbon bond formation.[1] However, the analogous transformation using (cyclopropane)methylsilanes **1** or -stannanes **2** to achieve homoallylation has been far less studied (Scheme 1). This relative disinterest is due to the lack of reactivity of these derivatives compared to their allyl counterparts, the limited number of electrophiles suitable for this coupling, as well as the difficulty in controlling the regiochemistry of the process with substituted cyclopropanes.[2]



Scheme 1.

The ring opening of (cyclopropyl)methylsilanes is known to be easy and highly regioselective when the ring is substituted with a group able to stabilize a negative charge, such as an electron-withdrawing substituent.[3] However, few attempts have been made to use compounds such as **5** for one-pot ring-opening and subsequent condensation with electrophiles, which would correspond to a formal homoallylation process.[4] Recently, trimethylsilylmethyl cyclopropyl ketones, such as **7**, have been found to undergo smooth ring opening to afford the corresponding enolates, which reacts with aldehydes and ketones to afford aldol products.[5]

We became interested in applying this methodology to the corresponding cyclopropanes substituted with an ester function instead of a ketone derivative. Much to our surprise, we observed that, in contrast to ketone **7**, which underwent rapid and quantitative ring opening in the presence of boron trifluoride, ester **9** was completely unreactive under similar conditions (Scheme 2). The use of various other Lewis acids, Brønsted acids or treatment of **9** with fluoride anion never afforded any traces of the ring-opened product **10**.

In order to circumvent the lack of reactivity of silane **9**, we turned our attention to the use of (cyclopropyl)methyl stannanes such as **12**. This derivative, as well as the other esters **13** and **14**, are easily prepared by rhodium-catalysed cyclopropanation of allyltributyltin with various diazo esters (Scheme 3).[6] The cyclopropanated

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* Tel.: +32 10 47 29 19; fax: +32 10 47 27 88; e-mail: leroy@chim.ucl.ac.be

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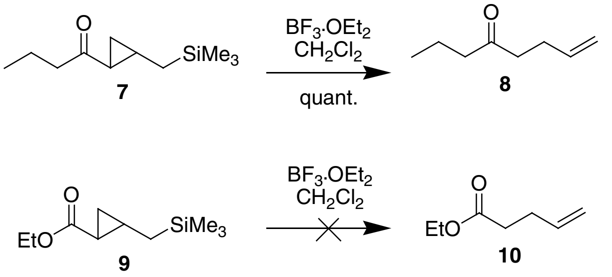
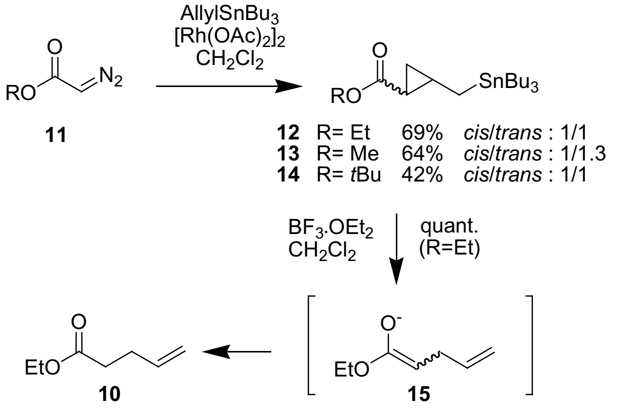


Scheme 2.



Scheme 3.

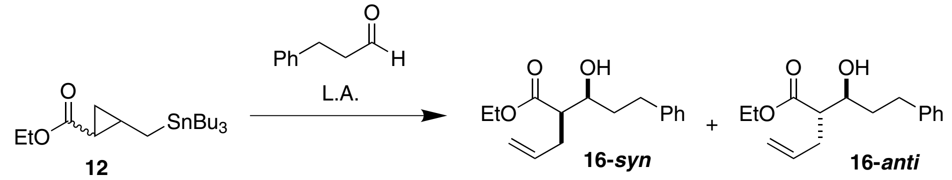
products are usually obtained as a 1/1 mixture of *cis* and *trans* isomers, which are rather difficult to separate by standard chromatographic techniques, and therefore were used as a mixture for subsequent reactions. We were delighted to find that, upon treatment with boron trifluoride, **12** underwent smooth and quantitative ring opening to afford pentenoate **10**, presumably *via* an intermediate equivalent to the enolate **15**.

Having demonstrated that the ring opening of **12** was an efficient process, we next turned our attention to the trapping of the in situ generated enolate by a carbonyl derivative. For preliminary studies, the ring-opening reaction was performed in the presence of dihydrocinnamaldehyde, to afford aldol product **16** as a mixture of *syn* and *anti* isomers. The most significant results are summarized in Table 1.

Moderate yields were initially obtained with $BF_3·OEt_2$ (entries 1–5) and $TiCl_2(O\text{-}i\text{-}Pr)_2$ (entries 6–7), which gave generally **16**-*syn* as the major product. An interesting change in the diastereoselectivity was observed with $SnCl_4$ and Et_2AlCl (entries 9–12). Finally, $TiCl_4$ was found to be the most efficient Lewis acid for this transformation. The diastereoselectivity is affected by the solvent (entries 13–14), the amount of Lewis acid (entry 15) and the temperature. In diethyl ether, **16**-*anti* was the major product when the reaction was carried on at −78 °C (entry 16). However, **16**-*syn* became predominant when working at 0 °C (entry 17).[7]

The influence of the geometry of the cyclopropane on the diastereoselectivity of the final adduct was then investigated. Pure *cis* or *trans* cyclopropanes **12** were engaged in a tandem ring-opening/condensation reaction,

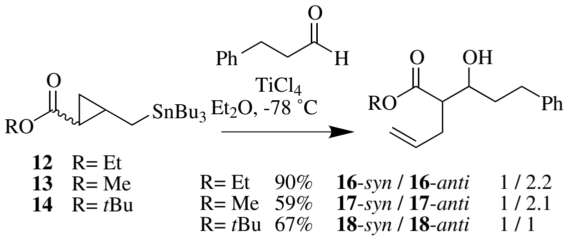
Table 1. Optimization of the one-pot ring-opening/aldol reaction



Entry	Lewis acid	Solvent	Temperature (°C)	Yield[a] (%)	**16**-*syn*:**16**-*anti*[b]
1	$BF_3·OEt_2$ (1 equiv)	CH_2Cl_2	−78	Traces	—
2	$BF_3·OEt_2$ (2 equiv)	CH_2Cl_2	−78	43	1/1
3	$BF_3·OEt_2$ (2 equiv)	Et_2O	−78	56	1.5/1
4	$BF_3·OEt_2$ (2 equiv)	THF	−78	Traces	—
5	$BF_3·OEt_2$ (2 equiv)	Benzene	0	62	2.3/1
6	$TiCl_2(O\text{-}i\text{-}Pr)_2$ (2 equiv)	CH_2Cl_2	−78	33	1.5/1
7	$TiCl_2(O\text{-}i\text{-}Pr)_2$ (2 equiv)	Et_2O	−78	42	1.2/1
8	$SnCl_4$ (2 equiv)	CH_2Cl_2	−78	10	1.2/1
9	$SnCl_4$ (2 equiv)	Et_2O	−78	27	1/3.4
10	Et_2AlCl (2 equiv)	CH_2Cl_2	−78	75	1/1.8
11	Et_2AlCl (2 equiv)	Et_2O	−78	68	1/1.8
12	Et_2AlCl (2 equiv)	Benzene	0	57	1/1.2
13	$TiCl_4$ (2 equiv)	CH_2Cl_2	−78	47	2.1/1
14	$TiCl_4$ (2 equiv)	Benzene	0	68	2.3/1
15	$TiCl_4$ (1 equiv)	Et_2O	−78	54	1.7/1
16	**$TiCl_4$ (2 equiv)**	**Et_2O**	**−78**	**90**	**1/2.2**
17	**$TiCl_4$ (2 equiv)**	**Et_2O**	**0**	**73**	**3.2/1**

[a] All yields refer to pure, isolated product. All the reactions were complete after 2 h at the given temperature.

[b] Determined by NMR analysis of the crude reaction mixture.

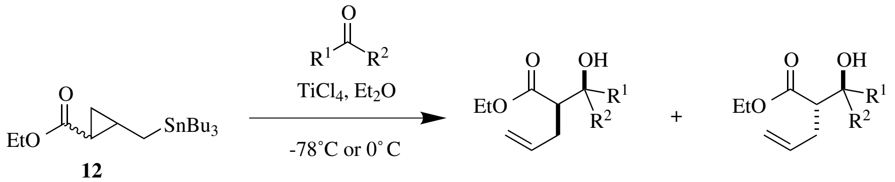


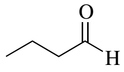
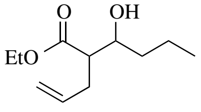
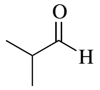
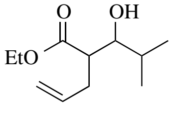
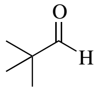
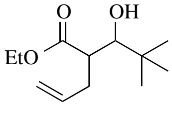
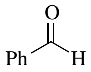
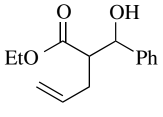
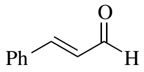
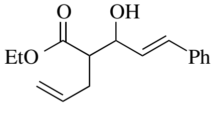
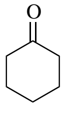
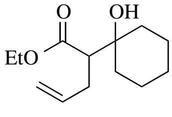
Scheme 4.

using $BF_3 \cdot OEt_2$ or $TiCl_4$ as Lewis acid. In both cases, the aldol products were obtained in the same diastereoisomeric ratio as observed when a mixture of cyclopropanes was used. The influence of the nature of the ester group was also examined. Methyl ester **13** gave results similar to the ethyl ester **12**, but no selectivity was observed with a more hindered ester such as **14** (Scheme 4).

With an efficient method for one-pot ring-opening/aldol condensation of (cyclopropyl)methylstannane **12** in hand, we applied this strategy to other carbonyl electrophiles. As described in Table 2, the reaction proved to be very efficient in most cases, giving aldol products in excellent yields. Substrates such as primary, secondary or tertiary aliphatic aldehydes (entries 1–3), aromatic and unsaturated aldehydes (entries 4–5) and ketones (entry 6) are tolerated for this transformation.[8] As in the case of dihydrocinnamaldehyde, an important effect of the temperature on the diastereoselectivity was

Table 2. Scope of the one-pot ring-opening/aldol reaction



Entry	Electrophile	Product	Yield[a] (−78 °C, %)	*syn*/*anti* (−78 °C)	Yield[a] (0 °C, %)	*syn*/*anti*[b] (0 °C)
1		 **19**	94	1/1.6	99	4/1
2		 **20**	81	1.9/1	96	2.9/1
3		 **21**	95	1.5/1	89	1.1/1
4		 **22**	95	1/1.5	96	1.7/1
5		 **23**	71	1/1.9	48	>20/1
6		 **24**			99	—

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[a] All yields refer to pure, isolated product. All the reactions were complete after 2 h at the temperature given.

[b] Determined by NMR analysis of the crude reaction mixture.

observed for primary aliphatic, aromatic and unsaturated aldehydes, which gave mostly *anti* products when the reaction was performed at low temperature and *syn* products at 0 °C. In the case of cinnamaldehyde, the *syn* product **23** was effectively the only isomer observed, even if the yield was lower than usual, probably due to partial degradation of the product. In contrast, secondary and tertiary aliphatic aldehydes gave, under all conditions, the *syn* compounds as the major adducts.

In summary, we have developed an efficient and versatile method for formal homallylation of aldehydes and ketones. By controlling simple parameters such as the temperature and the solvent, an easy access to both diastereomers of the substituted aldol adducts has been delineated. We are currently working on the application of this methodology to the synthesis of related natural products, as well as on the improvement of the stereoselectivity of the reaction. These results will be reported in due course.

Acknowledgements

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References and notes

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7. (a) The diastereoisomeric relationship for all aldol products was assigned by comparison with literature NMR data when available. The frequency of the resonance for the hydrogen vicinal to the hydroxyl group is consistently higher for the *syn* isomer than for the *anti* one. Marcantoni, E.; Alessandrini, S.; Malavolta, M.; Bartoli, G.; Bellucci, M. C.; Sambri, L.; Dalpozzo, R. *J. Org. Chem.* **1999**, *64*, 1986; (b) Curran, D. P.; Ramamoorthy, P. S. *Tetrahedron* **1993**, *49*, 4841; (c) Fráter, G.; Müller, U.; Günther, W. *Tetrahedron* **1984**, *40*, 1269.
8. *Typical experimental procedure*: Preparation of **16**: to a solution of (cyclopropyl)methylstannane **12** (100 mg, 0.239 mmol) and dihydrocinnamaldehyde (38.5 mg, 0.287 mmol) in dry diethyl ether (5 mL) at −78 °C was added $TiCl_4$ (479 μL, 0.479 mmol, 1 M solution in dichloromethane). The reaction mixture was stirred at −78 °C for 2 h, then allowed to warm to rt. The solution was diluted with dichloromethane (20 mL) and quenched with saturated $NaHCO_3$ (20 mL). The aqueous layer was separated and extracted with dichloromethane (2 × 20 mL). The combined organic layers were dried ($MgSO_4$) and evaporated in vacuo. The residue was purified by column chromatography (silica gel, petroleum ether–diethyl ether, 2:1) to give **16** (mixture, *syn*/*anti* 1/2.2) as a colourless oil (57 mg, 90%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.15–7.31 (5H, m), 5.66–5.84 (1H, m), 4.98–5.11 (2H, m), 4.09–4.21 (2H, m), 3.85 (1H*syn*, dq, $J = 9.1$, 4.8 Hz), 3.71 (1H*anti*, hept, $J = 4.3$ Hz), 2.33–2.92 (6H, m), 1.69–1.84 (2H, m), 1.25 (3H, t, $J = 7.2$ Hz). IR (film) 3470, 3026, 2932, 1729, 1642, 1181, 1030. MS (CI) *m*/*z* : 263.1 (M+H$^+$, 65), 244.9 (85), 217.0 (30), 198.9 (55), 171.0 (100).