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Donor cyclopropanes in synthesis: utilising silylmethylcyclopropanes to prepare 2,5-disubstituted tetrahydrofurans

Jonathan Dunn, Majid Motevalli, Adrian P. Dobbs *

School of Biological and Chemical Sciences, Queen Mary University of London, Mile End Road, London E1 4NS, UK

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ABSTRACT

The use of donor-only silylmethylcyclopropanes in the Lewis acid promoted reaction with aldehydes to generate 2,5-disubstituted tetrahydrofurans is described. The diastereoselectivity obtained in the product is very dependent upon the temperature of the reaction.

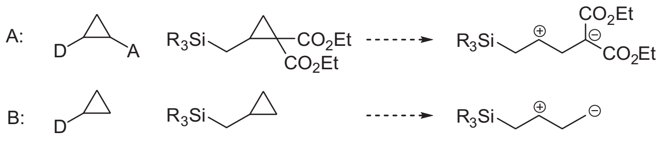
The use of donor–acceptor (D–A) cyclopropanes in synthesis is well documented,[1,2] and more recently, acceptor-cyclopropanes have also been utilised in a number of transformations.[2] Herein, we report one of the first applications of donor cyclopropanes—silylmethylcyclopropanes—in the synthesis of substituted tetrahydrofurans.

The use of silylmethylcyclopropanes as part of D–A cyclopropanes has been widely reported, where the silicon group aids stabilisation of a β-carbocation, via the β-effect, while an anion stabilising group—most frequently a carbonyl or dicarbonyl function—is used to stabilise a carbanion (Scheme 1A).[3–7] Recent studies have suggested that the role of this group, frequently malonate, may be more subtle, including complexation of the Lewis acid between the 1,3-dicarbonyl groups.[8] However, very little has been reported on the use of donor-only cyclopropanes (Scheme 1B), where there is no anion stabilising group.[9] As part of our ongoing interest in the use of silyl groups to stabilise cationic intermediates,[10–12] herein we report the use of acceptor-free silylmethylcyclopropanes in [3+2] cycloaddition reactions.

Attempts to form the prerequisite silylmethylcyclopropanes by reaction of cyclopropylmagnesium bromide with either chloro- or iodomethylsilanes were unsuccessful, as was the ‘reverse’ reaction of a Grignard reagent derived from a chloromethylsilane with bromocyclopropane. It should be noted that a very recent publication suggests that this transformation is possible when using an organolithium species.[13] In our approach, however, a wide variety of allylsilanes could be prepared from allylmagnesium bromide with a chlorosilane. These then readily underwent Simmons–Smith or related reactions to give the desired silylmethylcyclopropanes (Table 1).

The cyclopropanes were then employed in [3+2] cycloaddition reactions. There has only been one previous report attempting these, with no published experimental details.[9] Therefore, it was considered important to define the scope of the reaction, both in terms of reaction partner for the donor and also optimising the reaction conditions. A range of aromatic and aliphatic aldehydes were reacted with each of the silylmethylcyclopropanes prepared, in the presence of a Lewis acid (either $TiCl_4$, $SnCl_4$, $BF_3{\cdot}OEt_2$ or $InCl_3$) at either −78 °C, room temperature or reflux, but all failed to give any tetrahydrofuran product. One feature of these reactions was that the silylmethylcyclopropane was never recovered, but often a mixture of the chlorosilane **1**, the hydroxysilane **2** or the disiloxane **3** were obtained. When using tin tetrachloride as the Lewis acid, the homoallylstannane **4**[14] was often obtained in high yields if an aqueous work-up was avoided (Scheme 2).

To improve the likelihood that the silylmethylcyclopropane would react with the aldehyde rather than the Lewis acid, more reactive aldehydes—glyoxals—were investigated. Again, initial trials employing phenyl glyoxal with phenyldimethylsilylmethylcyclopropane failed to give any tetrahydrofuran. However, Yadav[3]



Scheme 1. (A) Donor–acceptor and (B) donor-cyclopropanes.

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* Corresponding author.
E-mail address: a.dobbs@qmul.ac.uk (A.P. Dobbs).

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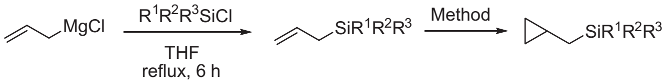
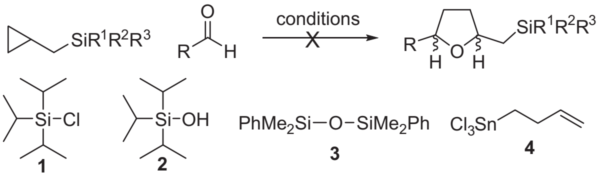
Table 1
Preparation of silylmethylcyclopropanes



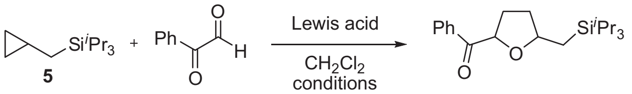
R^1	R^2	R^3	% Yield allylsilane	Cyclopropanation method[a]	% Yield
Et	Et	Et	90	Simmons–Smith	42
^{n}Bu	^{n}Bu	^{n}Bu	88	Simmons–Smith	65
^{i}Pr	^{i}Pr	^{i}Pr	81	Simmons–Smith	77
				Yamamoto	56
Me	Ph	Ph	59	Simmons–Smith	71
^{t}Bu	Ph	Ph	92	Simmons–Smith	86
Me	Me	Ph	86	Simmons–Smith	82
				Furukawa	61
				Yamamoto	63

[a] Simmons–Smith: copper chloride (5 equiv)/Zn powder (5 equiv), CH_2I_2 (2 equiv), Et_2O, reflux, 24 h; Yamamoto: $AlMe_3$ (2 equiv), CH_2I_2 (2 equiv), CH_2Cl_2, r.t., 2 h; Furukawa: $ZnEt_2$ (5 equiv), CH_2I_2 (5 equiv), CH_2Cl_2, r.t., 6 h.



Scheme 2. Attempted [3+2] cycloadditions to give 2,5-disubstituted tetrahydrofurans.

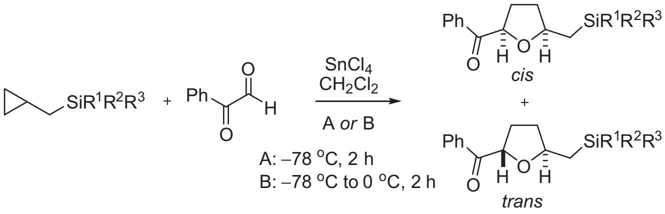
Table 2
Lewis acid screening for the reaction of phenyl glyoxal with triisopropylsilylmethylcyclopropane



Lewis acid	Conditions[a]	% Yield THF	% Recovered **5**
$SnCl_4$	−78 °C, 3 h	81	0
$SnBr_4$	−78 °C, 5 h	37	42
$AlCl_3$	−78 °C, 4 h	9	20
$TiCl_4$	−78 °C, 3 h	1	11
$ZnBr_2$	Reflux 48 h	15	0
	0 °C—reflux, 6 d, DCE	12	14
$ZnBr_2$ (2 equiv)	Reflux 96 h	63	0
$ZnCl_2$	0 °C—Reflux, 6 d	31	24
	0 °C—Reflux, 6 d, DCE	34	47
ZnI_2	0 °C—Reflux, 6 d, DCE	2	6

[a] All reactions performed in the ratio cyclopropane (1 equiv):Lewis acid (1.1 equiv):aldehyde (1.5 equiv).

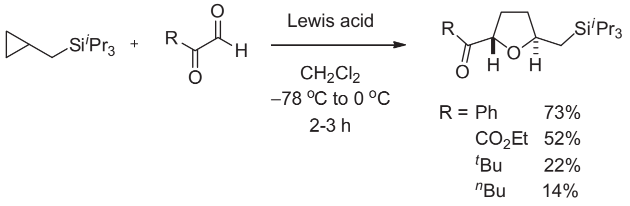
Table 3
Effect of the size of the silyl substituents and temperature on product distribution



R^1	R^2	R^3	Conditions[a]	% Yield	Ratio *cis*:*trans*
^{i}Pr	^{i}Pr	^{i}Pr	A	81	2:1
			B	85[b]	*trans*
Me	Me	Ph	A	53	2:1
			B	71[b]	*trans*
Me	Ph	Ph	A	50	2:1
			B	48	1:3
^{t}Bu	Ph	Ph	A	66	2:1
			B	72	1:1
^{n}Bu	^{n}Bu	^{n}Bu	A	43	1:1
			B	26	1:5
Et	Et	Et	A	21	2:1
			B	53	1:10

[a] All reactions performed in the ratio cyclopropane (1 equiv):Lewis acid (1.1 equiv):aldehyde (1.5 equiv). Conditions A: −78 °C, 2 h; Conditions B: −78 °C–0 °C, 2–3 h.

[b] Reaction performed in the ratio cyclopropane (1 equiv):Lewis acid (0.7 equiv):aldehyde (1.5 equiv).



Scheme 3. Preparation of silylmethylcyclopropanes.

has proposed that the best method to prevent nucleophilic attack at silicon during reactions is to incorporate bulky substituents on the silicon, the *tert*-butyldiphenylsilyl group in their case. Reaction of *tert*-butyldiphenylsilylmethylcyclopropane with freshly distilled phenyl glyoxal and tin tetrachloride in dichloromethane at −78 °C gave a moderate 31% yield of a 2,5-disubstituted tetrahydrofuran. This was our starting point for optimisation studies. It was found that the similarly bulky triisopropylsilyl group could also be successfully employed in the cycloaddition reaction, and the products were easier to purify by chromatography. First, a range of Lewis acids was screened for the reaction of triisopropylsilylmethylcyclopropane (**5**) with phenyl glyoxal (Table 2).

Optimum conditions were found to be combining the $SnCl_4$ and phenyl glyoxal in CH_2Cl_2 at −78 °C, followed by dropwise addition of the cyclopropane via syringe pump at 24 ml/h; rapid addition led to homoallylstannane formation. It was also found that the more dilute the reaction, the higher the yield of THF, with 0.06 M (with respect to the cyclopropane) being optimal. Many Lewis acids were re-screened, and it was found that both tin and zinc halides were efficient at promoting the reaction but that most other Lewis acids were very poor at promotion. The effect of temperature on the reaction was intriguing. During the optimisation reactions, when the reaction was run at temperatures below 0 °C, two compounds were always obtained which were inseparable by column chromatography. The compounds had the same molecular mass (but slightly different retention times by GCMS), R_f values and similar NMR signals, that is, the same number of carbon environments and a duplication of proton signals. The compounds were assigned as diastereoisomers of the THF arising from the *cis*/*trans* relative stereochemical substitution patterns across the oxygen in the ring. It was found that performing the reaction at 0 °C gave the *trans* stereoisomer exclusively, and this could be isolated and characterised. However, when the reaction was performed at −78 °C and also quenched at −78 °C, a mixture of diastereomers was obtained, but with the *cis*-isomer being the major (but never exclusive) one. Assignments of stereochemistry were initially based upon NOE observations.

Therefore we returned to investigate the combination of the effect of the size of the silyl group together with the observed temperature effect (Table 3).

Many other aldehydes were reacted employing the optimised reaction conditions, mostly with those bearing electron-withdraw-