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Reaction of 2-silylmethylcyclopropyl ketones with in situ oxirane-derived aldehydes and formation of 2-hydroxymethyl tetrahydrofurans

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ABSTRACT

The enolates formed from Lewis acid treatment of (2-trimethylsilylmethyl)cyclopropyl alkyl and aryl ketones reacted with aldehydes formed in situ from alkoxy-, aryl- and vinyl-substituted oxiranes to generate aldol products in good yields. Selected aldol products were conveniently transformed into highly substituted tetrahydrofurans under oxidative conditions.

The ring strain present in a three-membered ring makes it a useful synthon in organic synthesis. Vicinal placement of a donor and an acceptor group on the ring provides dual activation that renders the cleavage of the in-between σ_{C-C} bond feasible under mild Lewis acid conditions. A silylmethyl group acts as a donor group for the β-effect of silicon.[1] We have previously reported reactions of enolates generated from the ring cleavage of 2-trimethylsilylmethylcyclopropyl alkyl/aryl ketones with aldehydes, ketones and imines to deliver aldol and iminoaldol products that were subsequently transformed into tetrahydofurans and pyrrolidines, respectively, under oxidative conditions.[2]

As an extension of this protocol, we envisioned reactions of 2-trimethylsilylmethylcyclopropyl ketones with aldehydes formed in situ from oxiranes to generate aldols in a single step. Application of oxiranes as in situ precursors to aldehydes appeared appealing because (a) generation of oxiranes from alkenes is simple and (b) alkenes bearing diverse substituents are readily available by following literature methods.[3] We report herein the construction of tetrahydrofuran skeleton through the addition of a cyclopropane-derived enolate to an in situ oxirane-derived aldehyde followed by ring closure under oxidative conditions. The resultant 2-hydroxymethyltetrahydrofuran constitutes a common structural feature present in acetogenins that have desirable biological properties such as antineoplastic and immunosuppressive activities.[4]

The rearrangement of oxiranes to aldehydes in the presence of Lewis acids is known.[5] We commenced our studies with the screening of Lewis acids for the reaction of an isomeric mixture of **1a** with the oxirane **2a** (Ar = C_6H_5, R = CH_2OBn). $TiCl_4$ (1.2 equiv, CH_2Cl_2, −78 °C), Et_2AlCl (1.2 equiv, CH_2Cl_2, −30 °C), $LiClO_4$ in CH_3NO_2 (3 equiv, 0.25 M, 25 °C), $ZnCl_2$ (1.5 equiv, CH_2Cl_2, 25 °C), $InCl_3$ (1.2 equiv, CH_2Cl_2, 25 °C), $SnCl_4$ (1.2 equiv, CH_2Cl_2, −78 °C), $Yb(OTf)_3$ (5 mol %, CH_2Cl_2, 25 °C) and $Zn(OTf)_2$ (5 mol %, CH_2Cl_2, 0→25 °C) were unsatisfactory. These reactions were either complicated, leading to the formation of several products, or did not occur at all. In some instances, the cyclopropane had simply transformed into 3-butenyl phenyl ketone, **4**, and the oxirane had rearranged to α-benzyloxymethyl-α-phenylacetaldehyde, **5**, quantitatively.

The use of $BF_3{\cdot}OEt2$ (1.5 equiv, CH_2Cl_2, −30 °C, 1 h) generated the desired product **3a** as a 1:1.2 diastereomeric mixture in 40% overall yield based on the cyclopropyl ketone used. All the cyclopropyl ketone had reacted; the balance material was transformed into 3-butenyl phenyl ketone. All the oxirane had also reacted. However, the above carbonyl product **5** was not isolated. It is likely that **5** had polymerized under the acidic condition of the reaction. Intense very polar spots were indeed visible on TLC.

An experiment with additional suspended K_2CO_3 (2 equiv) furnished the product repeatedly in slightly improved yield (45–48%).[6,7] Though the diastereomeric ratio had improved to 3:1 with $Sc(OTf)_3$ (5 mol %, CH_2Cl_2, 25 °C, 45 min), the overall yield based on the cyclopropane reactant had reduced considerably to 21% due probably to the predominant transformation of the enolate into 3-butenyl phenyl ketone. Though the reversal in diastereoselectivity is interesting, we do not have an explanation for this observation at present. We considered examining other reactions with the $BF_3{\cdot}OEt_2$–K_2CO_3 combination to assess the generality of the protocol.

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The results are collected in Table 1. A comparison of the results in entries *a*–*e* suggests that an electron-withdrawing group on the oxirane ring has little effect on the overall success of the reaction. Electron-withdrawing substituents on the aryl ring also do not have a noticeable effect on the overall success of the reaction (entries *k*–*n*); the only exception was the *p*-nitro substituent (entry *o*) that retarded the reaction completely.

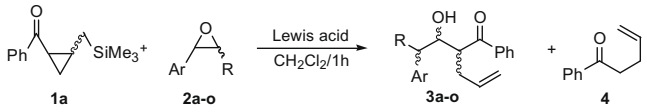
Separate reactions of cis-**1a** and trans-**1a** with **2a** were carried out to estimate the relative reactivities. Both the reactions were completed in one hour and each furnished the same 1:1.2 diastereomeric mixture of the corresponding aldol products. This suggests competitive enolate generation from both the diastereomers preceding the reaction with the in situ-formed aldehyde. The relative stereostructure of the major diastereomer of **3l** as shown at entry 6 in Table 2 was ascertained by single-crystal X-ray structure analysis.

We next replaced the aryl substituent with a vinyl group and studied the oxiranes **2p** and **2q** (Scheme 1). The reactions proceeded well and diastereomeric mixtures of the desired products **3p** (dr = 1:10:8:2.6)[8] and **3q** (the dr could not be ascertained because neither the diastereomeric ^{1}H signals could be discerned nor the diastereomers could be separated) were obtained in 45% and 60% overall yields, respectively. From the reaction of **2p**, the double bond-isomer **6p** was also isolated in 10% yield. Such a product was not formed from the reaction of **2q**. Instead, a small amount of **7q** was formed in 8% yield by S_N2' cleavage of the oxirane. A vinyl group, therefore, acts as an attractive alternative to an aryl group on the oxirane ring that raises the synthetic utility of the present protocol.

The reaction of a diastereomeric mixture of **1b** (cis/trans = 1:1.3) with styrene oxide **2b** for 1 h furnished an inseparable 1.2:1 diastereomeric mixture[9] of the desired product **8b** in 70% yield based on the reacted cyclopropane substrate (Scheme 2). The unreacted cyclopropane substrate (recovered in 36% yield) was discovered to be trans-**1b**, indicating that the trans-isomer had reacted slower than the cis-isomer. The species equivalent to **4**, that is, 3-butenyl *t*-butyl ketone was not formed.

The result of the reaction of an inseparable diastereomeric mixture of **1c** (cis/trans = 1:1.7) with **2b** was similar to that of **1b**; cis-**1c** reacted faster than trans-**1c** and generated an inseparable 1:5

Table 1
Reactions of **1a** with different oxiranes **2a**–**o** in the presence of $BF_3{\cdot}OEt_2$–K_2CO_3 at −30 °C.



1a **2a-o** **3a-o** **4**

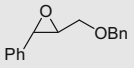
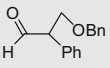
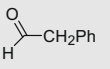
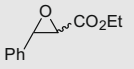
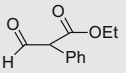
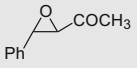
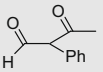
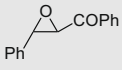
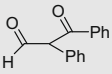
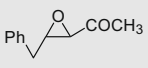
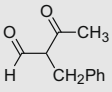
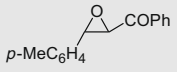
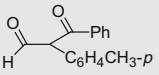
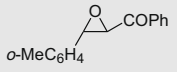
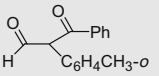
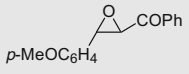
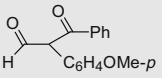
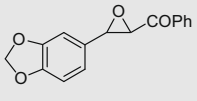
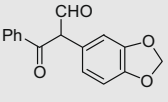
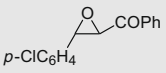
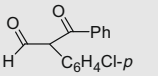
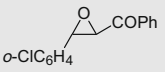
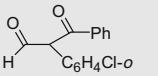
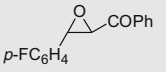
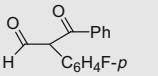
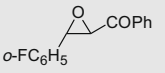
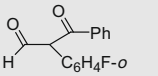
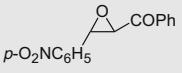
Entry	Oxirane	Reacting aldehyde	Yield of **3**[a] (%)	**3**'s dr[b]
a			45	1:1.2
b			47	1:1
c			36	4:1
d			41	1:1:1:1
e			38	2:7:1
f			NR	
g			73	2:11:1
h			71	2.3:1[c]
i			56	1:4
j			61	4 diastereomers

Table 1 (*continued*)

Entry	Oxirane	Reacting aldehyde	Yield of **3**[a] (%)	**3**'s dr[b]
k			61	8:4:1
l			60	8:1:1
m			58	4:1:5:1[c]
n			56	1:2.6:2.6[d]
o		No reaction		

[a] Isolated overall yield.
[b] Diastereomers were separated by radial chromatography over E-Merck silica gel PF_{254} using mixtures of hexanes and EtOAc as the eluent. The ratios shown are in the order of the polarity characteristics, the least polar diastereomer appears first and the most polar diastereomer appears last.
[c] The stereostructure of the acetate of the major diastereomer was determined by single-crystal X-ray structure analysis. However, this diastereomer was not subjected to oxidative cyclization.
[d] The diastereomeric ratio was estimated from ^{1}H integrals of the isomeric mixture because they were inseparable.