Acknowledgment. We thank Dr. H. Bull of Merck Sharp and Dohme Laboratories for a sample of ACE used in the early phases of this research and for the gift of *N*-(3-phenyl-1-carboxylpropyl)-L-lysyl-L-proline. The support of this research by NIH Grant AM 32539 is gratefully acknowledged.

A Method for the Generation of Electronegatively Substituted Cyclopropyl Anions under Preparatively Useful Conditions. Aldol Condensation with Carbonyl Partners[1]

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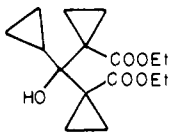
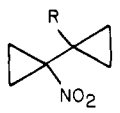
Received June 29, 1984

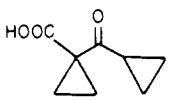
Despite the intrinsically greater acidity of protons attached to three-membered rings,[2] cyclopropanes carrying carbonyl, nitro, and sulfonyl groups exhibit markedly decreased equilibrium acidities relative to suitable acyclic congeners.[3,4] This is because proton abstraction is accompanied by formation of an exocyclic π-bond in order to maximize charge delocalization. The increase in p character with resultant development of planarity leads to a sharp enhancement of ring strain[5] and heightened chemical reactivity. The consequences are dramatic. For example, all attempts to deprotonate ethyl cyclopropanecarboxylate have led to formation of the trimeric self-condensation product **1**.[6,7]



1



2a, R = NO_2
b, R = NO

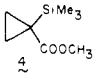
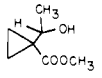
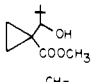
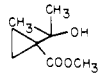
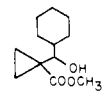
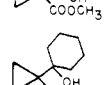
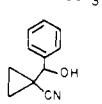
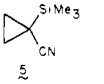
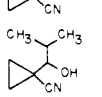
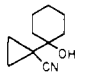
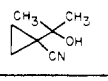


3

Nitrocyclopropane leads spontaneously in the presence of strong base to **2a** and **2b**.[7,8] The dianion of cyclopropanecarboxylic acid is capable of reaction with select reactive electrophiles.[9-11] Near 50 °C, however, dimerization occurs rapidly to deliver **3**.[11]

As a consequence, simple electronegatively substituted cyclopropanes have not been available for use as basic building blocks in organic synthesis. Although bulky substituents appended to the three-membered ring[12,13] or bonded to the carbonyl group[14] are known to retard the proclivity for dimerization, steric inhibition complicates the question of synthetic utility. We can now report that fluoride ion induced desilylation of simple α-(trimethylsilyl)-substituted cyclopropane derivatives combines a convenient method of carbanion generation with a means for efficient electrophile capture. Since aldol condensations of cyclopropyl anions have not been previously reported,[15] this utilitarian C-C bond-forming process is highlighted here.

Table I. Desilylation-Aldol Condensation of 4 and 5

substrate	fluoride source	carbonyl reagent	mol equiv	product		yield, %
	TBAF	$CH_3C(=O)H$	5.0		**6**	90
4	TBAF	$(CH_3)_3CC(=O)H$	5.0		**7**	51
	TBAF	$CH_3C(=O)CH_3$	5.0		**8**	68
	TBAF		1.2			27
	TBAF		2.2		**9**	49
	TBAF		1.2			45
	TBAF		2.0		**10**	42
	TBAF		2.4			47
	BTAF		3.0			83
5	CsF		2.6		**11**	66[a]
	TBAF	$(CH_3)_2CHC(=O)H$	2.2			13
	BTAF		2.0		**12**	60
	CsF		3.0			47[b]
	TBAF		1.5			43
	BTAF		2.6		**13**	43
	BTAF	$CH_3C(=O)CH_3$	4.3		**14**	55

[a] This composite yield includes 7% of isolated **11** and 59% of its *O*-(trimethylsilyl) derivatives. [b] 23% of **12** and 24% of 12-$OSiMe_3$.

Slow addition (2-3 h) of methyl 1-(trimethylsilyl)cyclopropanecarboxylate (**4**)[9] to cold (0 °C) tetrahydrofuran solutions containing dry tetra-*n*-butylammonium fluoride (TBAF, 1.5-2.5 equiv) and the selected aldehyde or ketone led to rapid reaction. After 30 min at 0 °C, workup afforded the respective β-hydroxy esters **6-10**, which were readily purified by chromatography (column or gas phase) without evidence of retroaldol fragmentation. Comparable handling of nitrile **5**[16] proved equally satisfactory (Table I). All new compounds were characterized spectroscopically and by combustion analysis.

Because of the stringent need for dry TBAF and the recognized difficulties in achieving this end result without partial degradation,[17] the effect of the fluoride ion source was briefly examined. Although the more stable benzyltrimethylammonium fluoride (BTAF)[18] is not as soluble in THF at this temperature, its presence served in several instances to improve substantially the yield of

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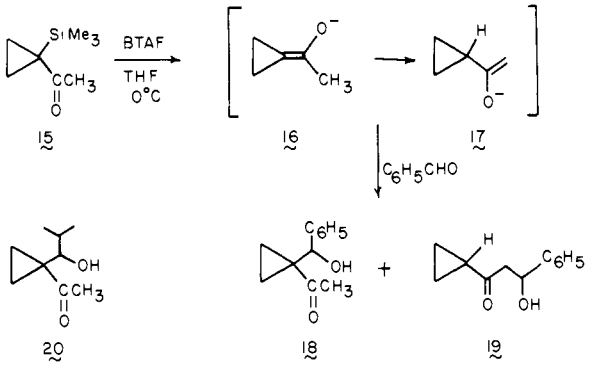
the condensation product. With cesium fluoride as catalyst, the aldol products were found to be accompanied by appreciable quantities of their $OSiMe_3$ derivatives. Such trimethylsilyl group transfers were limited to this fluoride ion source.

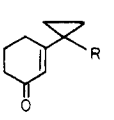
One advantage offered by the lower molecular weight carbonyl reagents is their volatility. Thus, they could be initially introduced in multiple molar equivalents and the excess subsequently removed during solvent evaporation. Self-condensation was not troublesome.

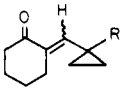
The reaction of ketone **15** with aldehydes in the presence of BTAF was next examined. In this instance, initially formed enolate ion **16** could experience prototropic shift to give **17** prior to electrophilic capture. In the presence of 2.4 equiv of benzaldehyde, **18** proved to be the major (and on occasion the sole) product (58–63% isolated). The amounts of **19** produced were



widely variable ranging from 0% to 19%. Thus, proton transfer is not a serious side reaction. In a single experiment involving isobutyraldehyde, **20** was the only aldol product isolated (27%). No effort was made in either case to recover the volatile cyclopropyl methyl ketone.

The serviceable behavior of **15** prompted study of the more extended systems **21**[19] and **25**.[16] Although the enolates obtained by desilylation (BTAF) of these substrates are certain to be less reactive due to enhanced charge delocalization, they entered usefully into aldol condensation. For example, the conversion of **21** to **22** proceeded in 73% yield. An increase in steric bulk as with isobutyraldehyde led to a lower yield of aldol (**23**, 27%); the protonated product **24** (70%) was dominant. Under the same conditions, **25** was transformed in the presence of benzaldehyde





21, R = $SiMe_3$
22, R = $CH(OH)C_6H_5$
23, R = $CH(OH)CH(CH_3)_2$
24, R = H

25, R = $SiMe_3$
26, R = $CH(OH)C_6H_5$

to **26** (45%). The high regiospecificity of these alkylations is noteworthy.

The yields described herein have not been maximized. Nonetheless, in situ removal of an α-$SiMe_3$ group from an electronegatively substituted three-membered ring is seen to be operationally well suited to preparative cyclopropyl carbanion generation. This protocol offers considerable flexibility for basing new synthetic strategies on these intermediates. Understandably, success will be improved if the electrophilic partner is relatively inert toward direct reaction with F^- at 0 °C for short time periods.

Acknowledgment. We gratefully acknowledge support of this work by the National Science Foundation.

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Cyclization of (1-Methyl-5-hexenyl)sodium in Ethers

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Received July 13, 1984

Reactions of 1-methyl-5-hexenyl chloride and bromide in ethers with sodium naphthalene and sodium mirrors at room temperature and 0 °C give large amounts of *cis*- and *trans*-1,2-dimethylcyclopentanes. Table I gives results for sodium naphthalene at room temperature.

1-Methyl-5-hexenyl radicals are intermediates (Scheme I),[1] and their cyclization is well-known,[9] but many of our cis/trans ratios are much lower than 3.8, the value for radical cyclization.[10,11] For sodium-mirror reaction, the cis/trans ratio ranges as low as 0.32. This suggests that 1-methyl-5-hexenylsodium also cyclizes, with a trans preference, giving [(2-methylcyclopentyl)methyl]sodiums. Cyclizations of other 1-methyl-5-hexenyl metallics are known, and most of them show a strong trans preference.[12]

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(10) The reaction of 1-methyl-5-hexenyl bromide with tributyltin hydride in DME, promoted by AIBN under fluorescent lighting at room temperature, gives 1,2-dimethylcyclopentanes with a cis/trans ratio of 3.8. The literature gives similarly determined values of about 2.7 for reactions near 70 °C.[9a,c]

(11) Conceivably, our ratios could be even lower than indicated, making the contrast with radical cyclization even *more* pronounced. Methylcyclohexane is lumped with *cis*-1,2-dimethylcyclopentane in Table I. At present, we assume that it is negligible, since five-membered-ring 1-methyl-5-hexenyl cyclizations are overwhelmingly favored for both radicals and anions.[9,12]

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