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Allylation of Donor–Acceptor Cyclopropanes

Ming Yu and Brian L. Pagenkopf*

Department of Chemistry and Biochemistry, The University of Texas at Austin, Austin, Texas 78712

pagenkopf@mail.utexas.edu

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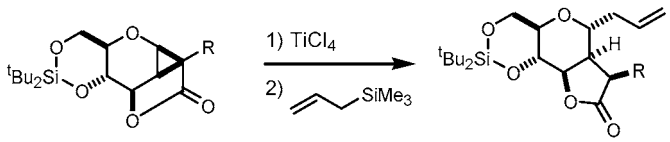
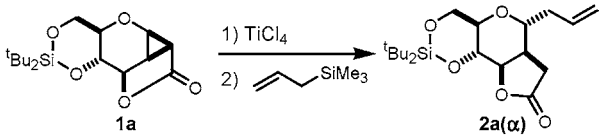
ABSTRACT



Direct allylation of glycal-derived donor–acceptor cyclopropanes has been achieved with $TiCl_4$ activation followed by addition of allyltrimethylsilane. The α diastereomer is the major product, with selectivities ranging from 3:1 to 10:1 and yields around 80%.

A wide variety of nucleophiles and electrophiles are known to react with glycal-derived cyclopropanes,[1] which has made them valuable synthetic intermediates for preparing C(2)-branched sugars.[2,3] Despite the considerable development of this area, it is surprising that a method for the direct allylation of donor−acceptor (DA) cyclopropanes has not been forthcoming. Kemmit and Bambal pioneered the conjugate addition of allyl silanes to electrophilic cyclopropanes,[4] and more recently, Sugita et al. reported a Lewis acid promoted cycloaddition reaction between DA-cyclopropanes and allyltrimethylsilanes.[5] Reiser described elegant cyclopropane allylations that proceed via a traditional Sakurai reaction followed by rearrangement.[6] Recently, we reported intramolecular glycal cyclopropanations[7] and showed that these new DA-cyclopropanes can be channeled through new reactivity manifolds.[8,9] In this paper, we describe stereoselective allylations of dihydropyran-derived DA cyclopropanes with allylsilanes and stannanes (Scheme 1).

Scheme 1



A wealth of information is known about the allylation of glycosyl donors,[10] and this work prompted us to test whether activation of donor−acceptor cyclopropane **1a** with a suitable Lewis acid would generate an oxo-carbenium ion or other compatible glycosyl donor.[11] Toward this end, several Lewis acids were investigated, and $TiCl_4$ (1.7 equiv) was found to

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(4) Bambal, R.; Kemmett, R. D. W. *J. Chem. Soc., Chem. Commun.* **1988**, 734−735.

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(9) For other reactions, see: (a) Yu, M.; Pagenkopf, B. L. *Tetrahedron* **2003**, *59*, 2765−2771. (b) Yu, M.; Pagenkopf, B. L. *J. Org. Chem.* **2002**, *67*, 4553−4558.

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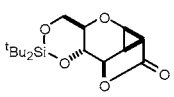
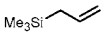
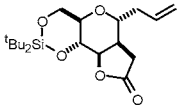
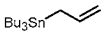
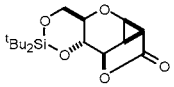
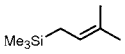
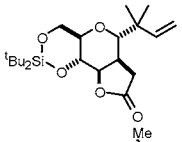
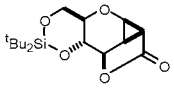
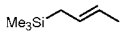
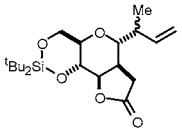
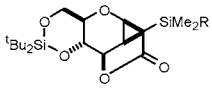
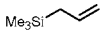
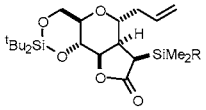
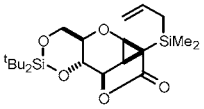
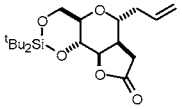
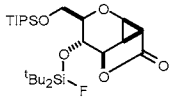
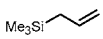
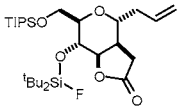
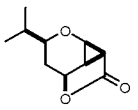
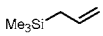
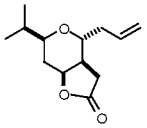
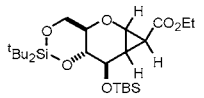
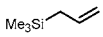
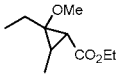
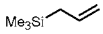
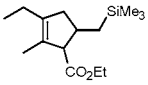
be superior to $BF_3{\cdot}OEt_2$, Me_3SiOTf, $SnCl_4$, $Sc(OTf)_3$, $ZrCl_4$ or Et_2AlCl for activating **1a** to allylation. Addition of $TiCl_4$ to a CH_2Cl_2 or Et_2O solution of **1a** resulted in complete conversion to a more polar species (TLC) after 1.5 h.[9a] Subsequent addition of allyltrimethylsilane lead to formation of **2a** (Table 1, entry 1) in 79% yield as a 4:1 mixture of α

Table 1. Allyl Additions to DA-Cyclopropanes[a]

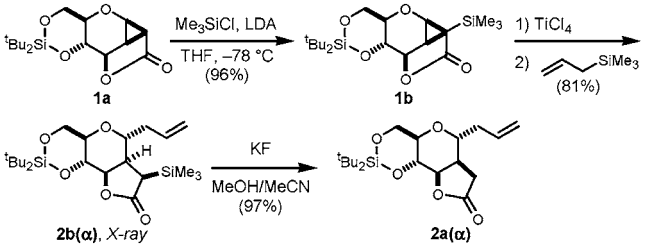
entry	substrate	allylation reagent	products	yield ratio
1				79% 4:1
2	"		"	87%, 7:1
3				78% 10:1
4[b]				79%
				
5[c]	R = Me		R = Me	81%, 8:1
6	R = vinyl		R = vinyl	79%, 8:1
7		no exogenous silane		77% 3:1
8				78% 5:1
9				72% 5:1
10			-	-
11[d]				85%

[a] CH_2Cl_2 solvent, isolated yields. [b] 1:1 mixture of diastereomers at the allylic position. [c] Structure assignment of **2b(α)** from X-ray crystallography. [d] Inseparable mixture.

to β diastereomers. Curiously, *the order of addition proved critical for this transformation*: decomposition occurred when $TiCl_4$ was added to a premixed solution containing both cyclopropane and allylsilane.

Allyltributylstannane also works in this reaction (entry 2), but we chose to focus on silanes. The more hindered prenylsilane gave the addition product in 78% yield with 10:1 dr. Crotylation resulted in exclusive formation of the α-isomer, but without stereocontrol at the allylic methyl position (entry 4). Diastereoselectivity for the allylation was improved by increasing nonbonded interactions on the β-face of the lactone by temporary silylation (entries 5 and 6; Scheme 2). The stereochemical assignment of the major

Scheme 2



diastereomer in entry 5 was confirmed by single-crystal X-ray analysis,[12] and subsequent desilylation with KF in MeOH/MeCN gave **2a(α)** (97%).

The possibility of increasing the ratio of the minor β-diastereomer through an intramolecular allylation was investigated in entry 7, but the change in diastereomeric ratio was minimal (3:1 vs 4:1). Conformationally restrictive cyclic protective groups for the C(4) and C(6) hydroxyl groups were proven unnecessary by reactions in entries 8 and 9. A variety of enantiomerically pure dihydropyrans are available from hetero-Diels−Alder cycloadditions,[13] and entry 9 confirms that cyclopropanes derived from these synthetically important substrates participate efficiently in the allylation reaction.

In contrast, attempted allylation of substrates prepared by intermolecular cyclopropanation resulted in decomposition (entry 10) or formation of formal [3 + 2] cycloaddition products (entry 11) as observed by others.[5]

Acknowledgment. We thank the Robert A. Welch Foundation, the Texas Advanced Research Program 003658-0455-2001, the DOD Prostate Cancer Research Program DAMD17-01-1-0109, and the donors of the American Chemical Society Petroleum Research Fund for partial financial support of this research. We are grateful to Vincent Lynch for determination of the X-ray structure. M.Y. thanks the Dorothy B. Banks Charitable Trust Fund for a graduate scholarship.

Supporting Information Available: X-ray structure data, CIF file for **2b(α)**, detailed experimental procedures, and characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) See the Supporting Information.

(13) Bednarski, M. D.; Lyssikatos, J. P. In *Comprehensive Organic Synthesis*; Trost, B. M., Heathcock, C. H., Eds.; Pergamon: New York, 1991; Vol. 2, pp 661−706.