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An "Anti-Baldwin" 3-*Exo-Dig* Cyclization: Preparation of Vinylidene Cyclopropanes from Electron-Poor Alkenes

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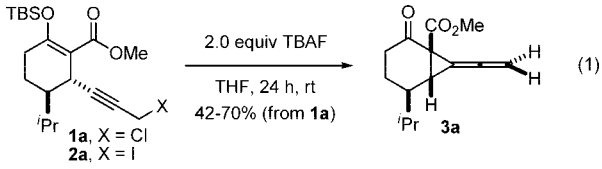
Baldwin's rules are routinely used as a first round of analysis to predict the propensity of cyclization for a given system.[1] Although exceptions are not uncommon,[2] these stereoelectronic guidelines continue to occupy a prominent and useful role in synthetic planning. We report in this Communication a rare example of the 3-*exo-dig* cyclization mode as a method to prepare vinylidene cyclopropanes from electron-poor alkenes. To our knowledge, only isolated examples of 3-*exo-dig* reactions have been reported in the literature, with all involving nucleophilic attack of a heteroatom onto a pendant alkyne.[3]

Vinylidene cyclopropanes (VCPs) can be prepared from electron-rich alkenes using carbenes derived from propargylic halides[4a,b] or dibromocyclopropanes[4c] and have been utilized as valuable intermediates in organic synthesis.[5] Electron-deficient alkenes are unable to undergo this reaction, because of the electrophilic nature of the carbene. In the course of a recent synthetic study we had cause to seek an efficient preparation of these allenes (e.g., **3a**) and considered that 1,3-dicarbonyls and their enolic congeners (e.g., **1a**) might undergo S_N2' cyclization with a pendant propargyl halide, a process predicted to be disfavored under Baldwin's rules.

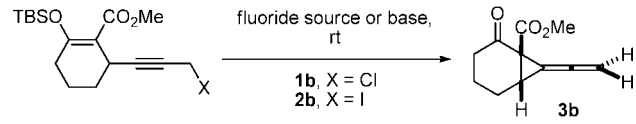


(1)

Initial investigations revealed that silyl enol ether **1a** did undergo 3-*exo-dig* cyclization in the presence of an excess of TBAF, albeit in variable yields (eq 1).[6] In an attempt to expand the scope of this transformation, we were surprised to find silyl enol ether **1b**, which lacks the 4-isopropyl substituent, was considerably more resistant to cyclization with TBAF in THF, yielding only 13% of **3b** (Table 1, entry 1). Seeking improvement, a number of weak bases and fluoride sources were examined. Best results were obtained using carbonates and phosphates in conjunction with a noncoordinating cation. DMF was found to be the optimal solvent, as the use of other polar aprotic solvents resulted in diminished yields.

Unfortunately, exposure of **1c** and **1d** to Cs_2CO_3 in DMF led to only trace quantities of bicycles **3c** and **3d**, respectively (Scheme 1). In need of more active substrates, we probed the identity of the propargylic leaving group. Iodide/chloride exchange was facile using the Finkelstein reaction.[7] For the cyclization of **2b**, weak, noncoordinating bases in DMF were again effective, with reaction times being significantly shorter than with **1b** (Table 1, entries 5−10). Fluoride sources were the most effective promoters. The best reagent/solvent combinations were TBAF in THF or MeCN and TBAT in DMF or MeCN; however, TBAF in THF was chosen for further experiments for the combination of efficiency and rapid reaction rate that these conditions engendered.

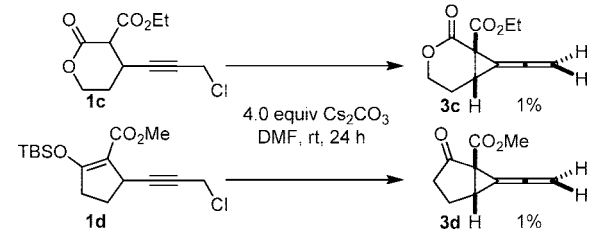
Table 1. Screen of 3-*Exodig* Cyclization Reaction Variables[a]



entry	substrate	reagent[b]	time (h)	solvent	yield (%)[c]
1	**1b**	TBAF	22	THF	13
2	**1b**	Cs_2CO_3	22	DMF	35
3	**1b**	Cs_2CO_3	22	MeCN	33[d]
4	**1b**	K_2CO_3/18-c-6	23	DMF	43
5	**2b**	TBAF	0.1	THF	78[d]
6	**2b**	TBAF	0.5	MeCN	77
7	**2b**	TBAT	3	MeCN	77
8	**2b**	TBAT	2	DMF	82
9	**2b**	Cs_2CO_3	2.5	DMF	59
10	**2b**	K_2CO_3/18-c-6	5	DMF	46

[a] Conditions: Silyl enol ether **1b** and **2b** (1.0 equiv) and reagent (3.0 equiv) in solvent (0.03 M) at room temperature. [b] 18-c-6 = 1,4,7,10,13,16-hexaoxacyclooctadecane. TBAF = tetrabutylammonium fluoride. TBAT = tetrabutylammonium triphenyldifluorosilicate. TASF = tris(dimethylamino)sulfonium difluorotrimethylsilicate. [c] Yield determined by GLC analysis against an internal standard. [d] Yield determined by isolation.

Scheme 1. Attempted Cyclization of Propargyl Chlorides



Using the propargylic iodides,[8] a variety of VCPs could be prepared from the corresponding silyl enol ethers in fair to excellent yields in 5 min (Scheme 2). Our structural assignment of these products as VCPs was confirmed by an X-ray crystallographic study of the 2,4-dinitrophenylhydrazone derived from **3b**.[9] Unexpectedly, replacement of the keto ester moiety with a lactone ester or keto nitrile attenuated the efficiency of the cyclization (**3c** and **3f**). We were initially unable to prepare products from secondary or tertiary halides, because of difficulty in preparing the substrate iodides. Fortunately, a secondary chloride and tertiary bromide were successfully cyclized with TBAF although the reactions were more sluggish, requiring 9 and 0.75 h, respectively. We believe these hindered halides are less prone to intermolecular side-reactions than the primary halides, leading to efficient intramolecular cyclization.

A slight modification of the reaction conditions was required to extend this methodology to acyclic systems. Only 8% of **3i** was formed when TBAF was added to a solution of the corresponding iodide in THF, with oligomers being the main byproducts. We

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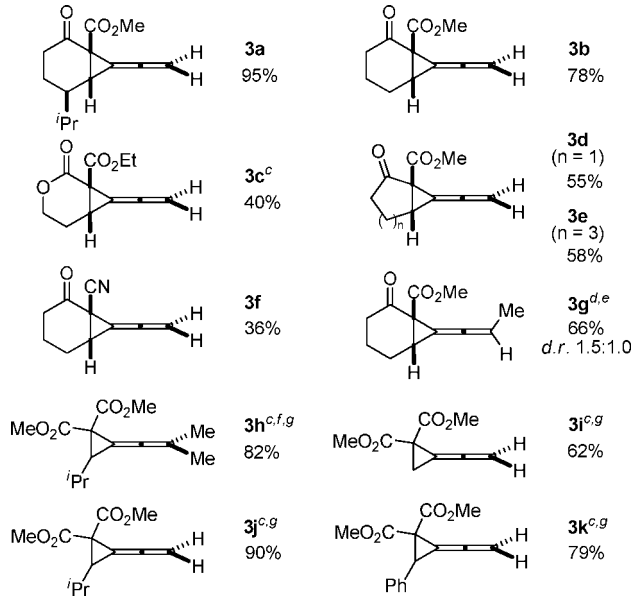
Scheme 2. Scope of the 3-*Exo-Dig* Cyclization of Propargyl Halides[a,b]



[a] Conditions: Silyl enol ether propargyl iodide (1.0 equiv) and TBAF (1.2 equiv) in THF (0.05 M) at room temperature unless otherwise noted. [b] Values represent isolated yields (average of at least two experiments). [c] Substrate for cyclization was the unsilylated diester. [d] TBAF (2.0 equiv). [e] Propargyl chloride was used. [f] Propargyl bromide was used. [g] Syringe pump addition (0.04 mmol/min) of diester **2** to TBAF (2.0 equiv) in THF (0.07 M).

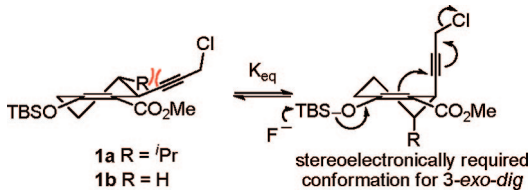


Figure 1. Conformational analysis of cyclization.

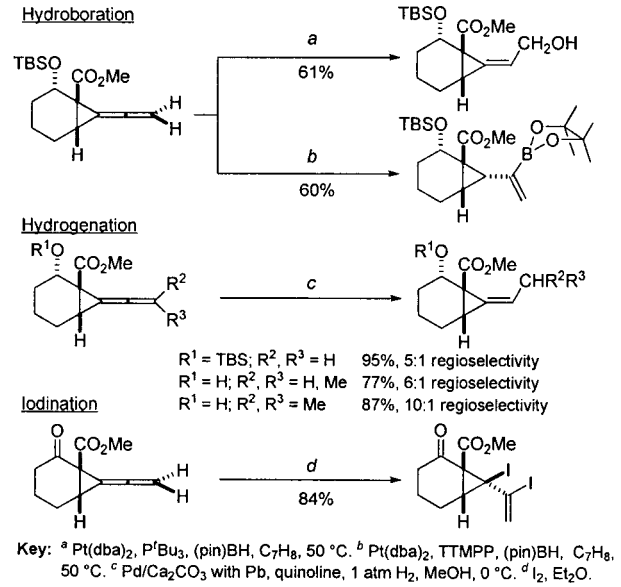
reasoned that intermolecular substitution was dominant without the conformational constraints found in the cyclic systems that orient the alkyne in the reactive conformation. The use of high dilution conditions was predicted to disfavor intermolecular alkylation and select for the desired intramolecular cyclization. Because of the fast cyclization rate, we were able to use syringe pump addition of the iodide to a solution of TBAF in THF over 40 min. The volume of THF was kept at a manageable level while still operating under low substrate concentrations ($[R-I]_t \approx 10^{-4}$ M). The linear substrates cyclized in good yields using this procedure.

The efficiency with which **1a** undergoes cyclization relative to **1b** can be explained through analysis of the competing half-chair conformations (Figure 1). K_{eq} is expected to be larger for **1a** than **1b** as a consequence of an unfavorable *gauche* interaction in the diequatorial conformation. This results in a higher concentration of the reactive diaxial conformation.

Preliminary experiments show that these VCPs can undergo selective addition reactions such as hydroboration, hydrogenation, and iodination (Scheme 3). It was necessary to reduce the ketone when using metal-catalyzed processes to prevent ring opening of the cyclopropane via β-carbon elimination.

In conclusion, we have described simple and efficient 3-*exo-dig* cyclizations of propargylic halides possessing a suitably placed active methine. The prior dearth of reactions for accessing the

Scheme 3. Further Transformations of VCP Products



Key: [a] $Pt(dba)_2$, P^tBu_3, (pin)BH, C_7H_8, 50 °C. [b] $Pt(dba)_2$, TTMPP, (pin)BH, C_7H_8, 50 °C. [c] Pd/Ca_2CO_3 with Pb, quinoline, 1 atm H_2, MeOH, 0 °C. [d] I_2, Et_2O.

product VCPs from electron-poor alkenes has limited any study of their synthetic utility which, in light of the unique display of reactive functionality, could be substantial.

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Supporting Information Available: Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) Enolsilane substrates were prepared by TBSOTf-promoted conjugate addition of alkynyltrimethylaluminates to enones. Diester substrates were prepared either by alkylation of dimethyl malonate or the conjugate addition of alkynyldiethylalanes to Knoevenagel condensation products. Full preparative details are given in the Supporting Information.

(9) CCDC 671491 contains the supplementary crystallographic data for this compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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