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Cyclopentannulation of Conjugated Enones Using a Vinyldiazomethane-Based Reagent

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Supporting Information

ABSTRACT: Herein, we describe a two-step method for the cyclopentannulation of conjugated enones using methyl 3-(*tert*-butyldimethylsilyloxy)-2-diazo-3-butenoate (**1**) as a bifunctional reagent. The enol silane and stabilized diazoalkane functionalities are exploited independently in sequential Mukaiyama−Michael and diastereoselective α,α'-diketone coupling. Di-, tri-, and tetrasubstituted enones are amenable to annulation under this protocol. Overall, this chemistry is an effective surrogate for a substituted "acetone 1,3-dipole".

The stereo- and regiocontrolled synthesis of substituted cyclopentanones is an enduring research problem, especially in connection with natural product synthesis[1] (see Figure 1A for a small selection of cyclopentanoid natural products). A variety of creative methods for both cyclization and annulations have been developed. 3C + 2C annulations, wherein an electron-deficient alkene serves as a 2C component, have been particularly popular as the requisite conjugated enone-containing starting materials are readily obtained and are versatile synthetic intermediates. Single and multistep procedures have been developed, and in some instances, general reagent classes have been devised for the synthesis of cyclopentanoids.[1] Here, we describe the use of methyl 3-(*tert*-butyldimethylsiloxy)-2-diazo-3-butenoate,[2] represented by formula **1** in Scheme 1B, as a bifunctional reagent for two-step annulation, wherein the enol silane bonds first to the electrophilic β-carbon of a conjugated enone[3] and then the diazo group participates in Cu(I)-catalyzed formal α,α'-diketone coupling. Though this approach requires two separate steps, it (i) can be applied to various conjugated enones, (ii) gives ready access to structures where an acetone unit has been added in a 1,2-fashion across an electron deficient alkene (equivalent to an "acetone-1,3-dipole"), and (iii) provides annulation products not easily obtained by established methods.

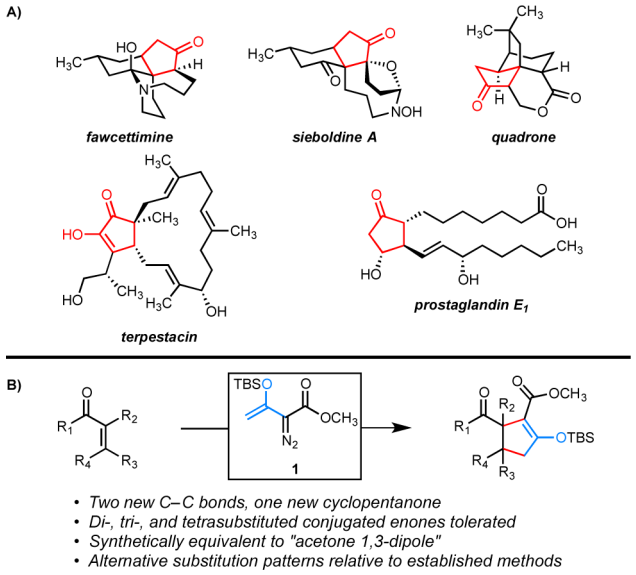
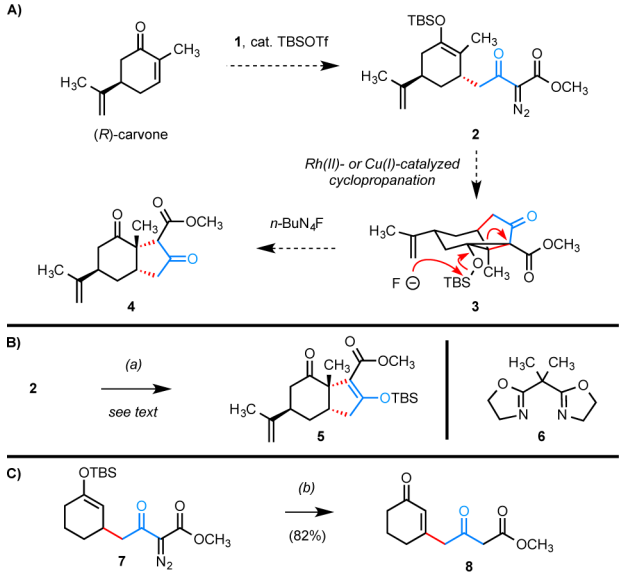


Figure 1. (A) Cyclopentanone-bearing natural products; (B) concept for two-step cyclopentannulation.

Scheme 1. Annulation in Detail[a]



[a]Conditions and notes: (a) $(CuOTf)_2$·PhH (10 mol %), ligand **6** (22 mol %), toluene, 55 °C, 2 h; (b) $[Rh(OAc)_2]_2$ (2 mol %), CH_2Cl_2, rt, 1.5 h.

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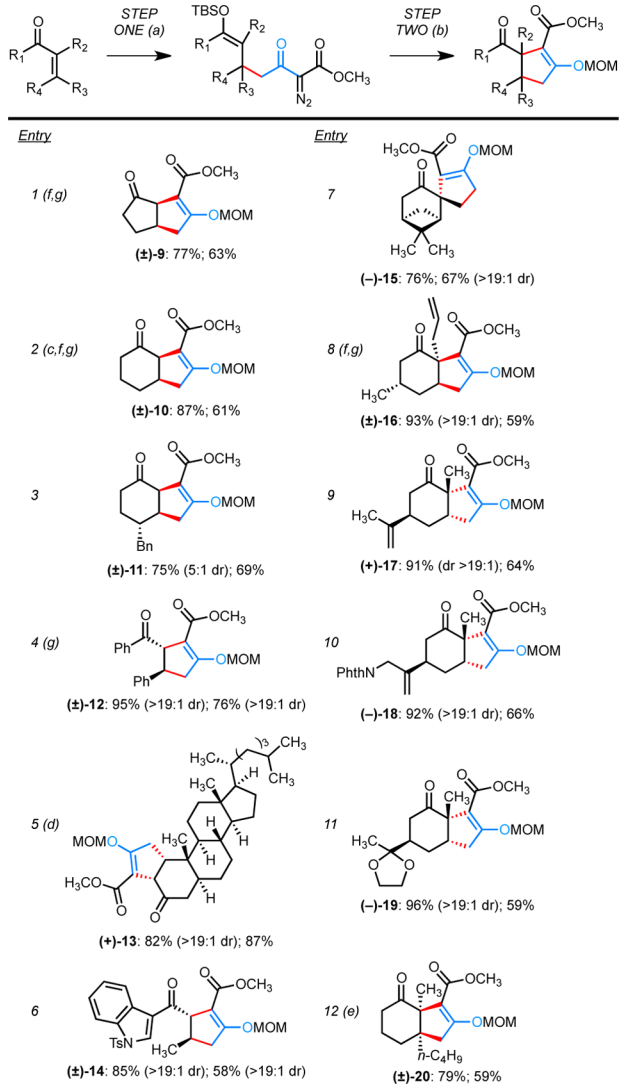
methane (TMM) cycloaddition,[4] Danheiser's Lewis acid mediated allenylsilane cycloaddition,[5] Boger's thermally induced cyclopropene ketal cycloaddition,[6] Lu's phosphine-catalyzed union of electron-deficient alkenes with 2,3-butadienoates or 2-butynoates,[7] and low valent transition metal-catalyzed processes.[1c] Despite the existence of these powerful methodologies, alternative approaches, many requiring more than one step, continue to appear in the chemical literature.[8]

As part of a recent study, we needed a method that would formally append acetone across a conjugated enone. We further required that if a substituted, unsymmetrical acetone fragment were used, the extra group would be proximal to the former enone α-carbon rather than the β-carbon (as occurs with several of the aforementioned methods). Conceptually, these requirements could be met using methyl 3-(*tert*-butyldimethylsiloxy)-2-diazo-3-butenoate (**1**). Recently, Doyle reported that reagent **1** undergoes Mukaiyama−Michael addition reactions to conjugated enones under Zn(II)-catalysis, producing functionalized diazoacetates.[3] However, the interaction of the resultant enol silane and stabilized diazoalkane functionalities was not explored.[9] We questioned whether an intermediate like **2** (potentially derived from Mukaiyama−Michael addition of **1** to (*R*)-carvone; see Scheme 1A) might undergo intramolecular, chemo-, and regioselective cyclopropanation, to generate general structure **3**, prior to deliberate fluoride-induced fragmentation of the electronically biased oxycyclopropane,[10] ultimately giving β-ketoester **4**. After initial experimentation and optimization, we found that compound **2** was converted directly to unsaturated ester **5** when treated with 10 mol % $(CuOTf)_2$·PhH and 22 mol % bis(oxazoline) **6** (see Scheme 1B; an isolated yield for **5** was not recorded, see below).[11] The use of ligated Cu(I) is essential since without **6** complex reaction mixtures result arising from other reaction pathways. For example, as shown in Scheme 1C, conjugate addition product **7**, derived from cyclohexenone and **1**, underwent an internal hydrogen transfer when treated with otherwise "ligand-free" Cu(I) or $Rh(OAc)_2$.[12]

In performing the first step of the overall annulation, we replaced the $Zn(OTf)_2$ catalyst that Doyle employed with *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf).[13] In addition to slightly improving convenience (especially since the preparation of **1** requires TBSOTf), this change permitted the use substrates bearing suitably protected heteroatom functionality (see entries 6, 10, and 11 in Table 1). Moreover, conjugated enones with sterically demanding γ- and δ-substitution (see entires 3, 5, and 8−11) underwent addition. For these experiments, the observed diastereoselectivity ranged from 5:1 to >19:1.

During preliminary studies of the annulation, we observed that the crude reaction mixtures contained β-siloxy-α,β-unsaturated esters (similar to **5**), yet these proved unstable to common chromatographic methods, including the use of Florisil.[14] This complicated characterization efforts as multiple species, all bearing the desired constitution, were present after the loss of the trialkylsilyl group. Thus, the silyl ethers were deliberately cleaved upon workup using *n*-Bu_4NF and the resulting crude material was treated with excess chloromethyl methyl ether and excess di-*iso*-propylethylamine to generate stable methoxymethyl ethers. We highlight that this measure was taken solely to aid in characterization, and that the annulation certainly does not require this process. Also, we note that yields for the second step of this process comprise the deprotection/reprotection events, indicating that the yields listed are minimums for annulation and are likely higher than indicated.

Table 1. Reaction Scope (h,i,j)[a]



[a]Conditions and notes: (a) **1** (1.2 equiv), TBSOTf (20 mol %), 0 °C; (b) (i) $(CuOTf)_2$·PhH (12.5 mol %), ligand **6** (27.5 mol %), toluene, 55 °C; *n*-Bu_4NF (1.3 equiv), 0 °C; (ii) MOMCl (3 equiv), *i*-Pr_2EtN (5 equiv), CH_2Cl_2, rt; (c) **1** (1.1 equiv) used; (d) **1** (2.0 equiv) used; (e) **1** (1.4 equiv) used; (f) TBSOTf (10 mol %) used; (g) $(CuOTf)_2$·PhH (10 mol %), ligand **6** (22 mol %) used; (h) for all cyclic enones, only the cis ring fusion was observed after annulation; (i) Mukaiyama−Michael reaction times vary from 30 min to 20 h, specific values given in Supporting Information; (j) annulation reaction times vary from 25 min to 6 h, specific values given in Supporting Information.

The second step of annulation proceeds unremarkably. Generally, substrates that are competent Michael acceptors in the first step are well suited for the Cu(I)-catalyzed cyclization. One type of exception noted is that substrates bearing an aryl group at either the α- or β-carbon of the conjugated enone are not amenable to the second step of the annulation, ostensibly because the intermediate Cu(I)-carbenoid may react with the arene though Buchner-type cyclopropanation and/or related processes.[15] Cyclic 5- and 6-membered enones furnish no detectable levels of the *trans*-diastereomer, while acyclic 1,2-disubstituted enones give *trans*-3,4-disubstituted cyclopenta-

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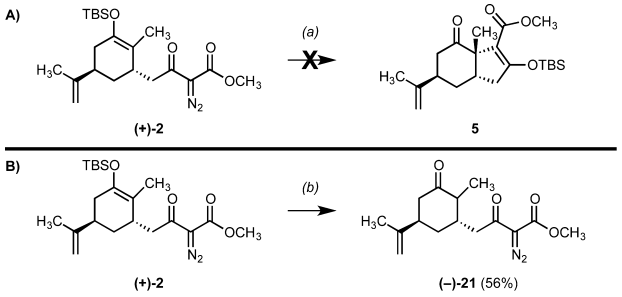
nones. Entry 12 is noteworthy in that it *demonstrates that vicinal, all-carbon quaternary stereocenters may be created by this process.*[16] Finally, it is worth mentioning that the second step scales well as entry 9 may be conducted on a gram scale with only slight decrease in yield (61%; see Supporting Information for details).

Experiments were conducted to clarify the nature of the cyclization process. For instance, purely thermal treatment of (+)-**2** (toluene, reflux, 40 h) in an attempt to induce a dipolar cycloaddition of the diazoacetate fragment with the enol silyl ether does not furnish compound **5**, the observed immediate product of annulation prior to deprotection/protection (Scheme 2).[17] Also, treatment of compound (+)-**2** with BF_3·OEt_2 in nitromethane, conditions reported by Mander[18] to be effective for cyclizing γ,δ-unsaturated α-diazoketones, provided only silyl ether hydrolysis product (−)-**21**, casting uncertainty over a Lewis acid catalyzed process.

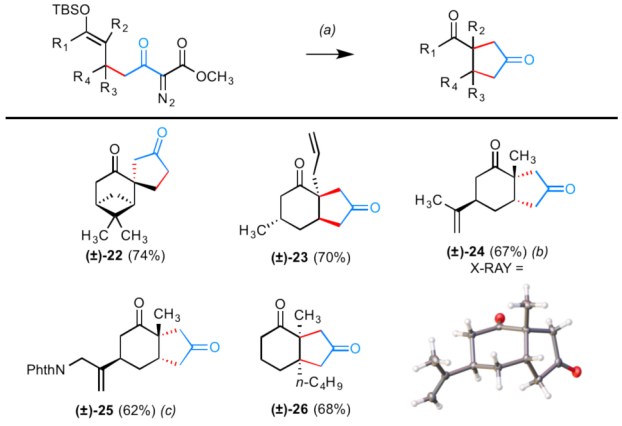
Scheme 2. Selected Control Experiments[a]



[a]Conditions and notes: (a) Toluene, reflux, 40 h; (b) BF_3·OEt_2, CH_3NO_2, −10 to 0 °C, 21 h.

Finally, we note that removal of the methoxycarbonyl group gives facile access to products of formal dipolar cycloaddition of a molecule of acetone across a conjugated enone. As shown in Table 2, diverting the crude reaction mixtures of the Cu(I)-catalyzed annulation to heating in wet DMSO or DMF instead of deprotection-protection brought about removal of the ester group altogether via an acyl ketene-based hydrolysis−decarboxylation mechanism.[19] Again, the observed yields are those of the sequences beginning with the purified Mukaiyama−Michael addition adducts. Such a sequence complements other annulations yet does not require oxidative cleavage of an alkene to give a carbonyl, a fact that could prove useful in the synthesis of polyfunctional molecules containing multiple alkenes or other easily oxidized functional groups.[20]

Table 2. Decarboxylative Annulation with 1[a]



[a]Conditions and notes: (a) $(CuOTf)_2$·PhH (12.5 mol %), ligand **6** (27.5 mol %), toluene (0.05 M), 55 °C; aqueous workup; wet DMSO, 100−125 °C, 1−2 h (specific values given in Supporting Information); (b) $(CuOTf)_2$·PhH (15 mol %), ligand **6** (33 mol %) used; (c) DMF, 140 °C, 1.5 h, for decarboxylation.

In conclusion, we have devised and developed a cyclopentannulation sequence dependent on the bifunctional reactivity of reagent **1**. The two-step process is applicable to differentially substituted α,β-unsaturated enones, which are readily obtained and are very common synthetic intermediates. Additionally, products not easily obtained by other means are made available using this approach, and optional methoxycarbonyl group removal gives products of a formal cycloaddition of acetone. Given the sheer number of cyclopentanoid natural products, the use of reagent **1** in complex molecule synthesis endeavors seems promising. Such studies are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

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

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Notes

The authors declare no competing financial interest.

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