Annulation

DOI: 10.1002/ange.200501579

Stereoselective Synthesis of Highly Substituted Cyclopentenones through [4+1] Annulations of Trialkylsilyl Vinyl Ketenes with α-Benzotriazolyl Organolithium Compounds**

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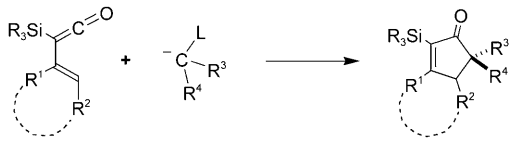
Cyclopentenones serve as valuable synthetic building blocks and are themselves key features in the structure of a number of prostaglandins[1] and other bioactive natural products. Popular strategies for the construction of this important ring system include the intramolecular aldol reaction, the Nazarov cyclization,[2] the Rautenstrauch rearrangement,[3] and the Pauson–Khand reaction.[4,5] Only a few general [4+1] routes to five-membered carbocycles have been reported to date, one example being the method we developed based on anion-accelerated vinylcyclopropane rearrangements.[6,7] Recently, studies by us[8] and others[9] have led to several new [4+1] approaches to the synthesis of the 2-cyclopentenone ring system. Herein, we report a new variant of our stereocontrolled [4+1] annulation strategy that provides especially efficient access to highly substituted and functionalized cyclopentenones.

As outlined in Scheme 1, our [4+1] annulation strategy is based on the reaction of nucleophilic species with leaving groups ("carbenoid reagents") with trialkylsilyl vinyl ketenes

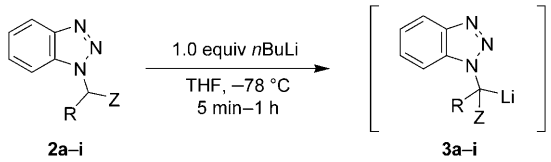


1a: R = *i*Pr, $R^1 = R^2 = CH_3$
1b: R = *i*Pr, $R^1 = R^2 = (CH_2)_4$
1c: R = Et, $R^1 = R^2 = CH_3$

Scheme 1. Strategy for [4+1] annulation. L = leaving group.

("TAS vinyl ketenes").[8] The utility of vinyl ketenes as versatile intermediates in organic synthesis is now well established.[10] However, vinyl ketenes are rarely isolable species and in most applications are generated as transient intermediates which are trapped in situ in [2+2] cycloadditions. Silyl substituents have the ability to suppress the usual propensity of vinyl ketenes to undergo dimerization and [2+2] cycloaddition reactions, thus opening up new opportunities for useful synthetic transformations. For example, TAS vinyl ketenes participate as electron-rich diene components in Diels–Alder and hetero-Diels–Alder reactions leading to cyclohexenones, phenols, and oxygen and nitrogen heterocycles.[11] In the case of reactions with carbenoid reagents, addition initially furnishes dienolate intermediates, which are believed to undergo ionization and subsequent 4π electrocyclization to generate cyclopentenone rings (see below). TAS vinyl ketenes are readily available through several routes, including the photochemical Wolff rearrangement of α′-silyl-α′-diazo-α,β-unsaturated ketones used for the preparation of **1a–c** in this study.[11a]

The goal of the current investigation was to extend the scope of this [4+1] annulation strategy to include the synthesis of cyclopentenones with a much broader range of substituents at the C5 position. A variety of carbenoid reagents were screened with the aim of identifying new classes of molecules that are competent in the desired transformation and are more readily available than the diazo compounds, sulfur ylides, and stable carbenes previously employed.[8] Among the several classes of compounds examined to date, α-benzotriazolyl organolithium compounds of type **3** were best able to meet our requirements (Scheme 2). Extensive research by Katritzky and co-workers over the past two decades has demonstrated the utility of *N*-substituted benzotriazoles as valuable intermediates for organic synthesis.[12] Benzotriazoles of type **2** bearing a wide range of



2a–i **3a–i**

a: Z = N(CO$_2$*t*Bu)(Bn), R = H
b: Z = OEt, R = C(H)=CH$_2$
c: Z = OEt, R = C≡CCH$_3$
d: Z = SPh, R = H
e: Z = OMe, R = H
f: Z = 9-carbazolyl, R = H
g: Z = 4-MeOC$_6$H$_4$, R = H
h: Z = OPh, R = CH$_3$
i: Z = SPh, R = CH$_3$

Scheme 2. Preparation of α-benzotriazolyl organolithium compounds. Benzotriazoles **2b** and **2d–f** are commercially available, and the details for the preparation of **2a**, **2c**, and **2g–i** are given in the Supporting Information.

substituents are either commercially available or readily prepared in one or two steps from inexpensive starting materials and undergo metalation with *n*-butyllithium at −78 °C to provide access to α-benzotriazolyl organolithium derivatives of type **3**. The ability of benzotriazole to function as a leaving group is also well documented and has been exploited by Katritzky and co-workers in the context of numerous useful synthetic transformations.[12]

The reaction of the benzotriazolyl carbamate **2a** with TAS vinyl ketene **1a** was examined to investigate the feasibility of the proposed [4+1] annulation (Scheme 3). Benzotriazole **2a**

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[**] We thank the National Institutes of Health (GM 28273) and Merck Research Laboratories for generous financial support.

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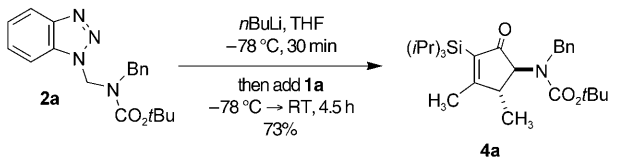
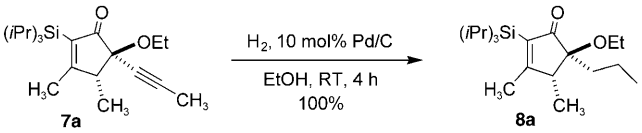


Scheme 3. Demonstration of the feasibility of the [4+1] annulation. Bn = benzyl.

was prepared in 70% overall yield as previously described by Katritzky and co-workers[13] through protection of benzylamine as its *tert*-butyloxycarbonyl (Boc) derivative and reaction of the crude carbamate with one equivalent of benzotriazole and one equivalent of paraformaldehyde in the presence of catalytic *para*-toluenesulfonic acid (toluene, reflux). Metalation of **2a** with *n*BuLi produced the expected organolithium species, which was found to add smoothly to vinyl ketene **1a** at −78 °C in the desired fashion. Upon warming to room temperature, the resulting dienolate intermediate lost the benzotriazole moiety and cyclopentenone **4a** formed in good yield and with greater than 96% selectivity for the *trans*-substituted isomer.

Tables 1 and 2 delineate the scope of the [4+1] annulation. In some cases, the desired cyclopentenone begins to appear at low temperature during the addition of the organolithium reagent, and formation of the five-membered-ring product is completed simply by warming to room temperature (Table 1). This protocol proved effective for annulations that involve carbenoid reagents with strong electron-donor substituents such as amine derivatives (entries 1 and 2) and the combination of an alkoxy moiety and a vinyl or alkynyl group (entries 3 and 4). Each of these reactions was observed to proceed with a preference for the formation of the cyclopentenone with the heteroatom substituent at C5 *trans* to the substituent at C4. This preference is particularly high with small R^3 groups, such as hydrogen or alkynyl moieties. The latter case is synthetically significant, as the products of such reactions (e.g., **7a**) undergo hydrogenation (Scheme 4) to furnish 5-alkyl-substituted cyclopentenones that cannot be produced directly under such mild conditions or with such high stereoselectivity (see below).

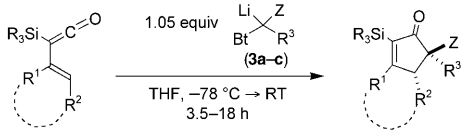


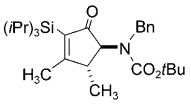
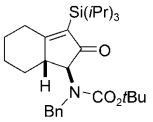
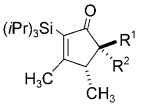
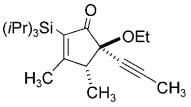
Scheme 4. Preparation of 5-alkyl-substituted cyclopentenones.

Attempted annulation with α-benzotriazolyllithium reagents **3d–i** under similar conditions did not lead to the desired cyclopentenones. Control experiments that employed benzotriazole **3d** confirmed that addition to TAS vinyl ketene **1a** proceeds smoothly at −78 °C in the expected manner, but cyclization of the resulting dienolate intermediate does not then occur. We therefore turned to the use of Lewis acids to promote the crucial ionization of the benzotriazole group required for five-membered-ring formation. Extensive screening studies identified $ZnBr_2$ as particularly effective for the desired transformation.[14] Although no reaction is observed upon addition of one equivalent of $ZnBr_2$ to the dienolate solution, efficient cyclization takes place when two or more equivalents of the Lewis acid are added at −78 °C and the reaction mixture is allowed to warm to room temperature. Under these conditions, the desired [4+1] annulation can be achieved with a variety of carbenoid reagents that bear a single heteroatom substituent such as SPh or OMe (Table 2). Cyclopentenone formation is even observed with the aryl-substituted benzotriazole **3g**, although in this case elevated temperatures are required to complete the cyclization.

A notable feature of these [4+1] annulations is the high level of stereoselectivity observed in most of the reactions. Control experiments established that the stereochemical outcome of these [4+1] annulations is not a consequence of thermodynamic control. Specifically, equilibration experiments yielded mixtures of *trans*- and *cis*-substituted cyclopentenones with ratios significantly different from those obtained in the annulation.[15] Thus, it appears likely that the stereochemical course of the [4+1] annulation reflects a mechanism-based kinetic preference for the observed products.

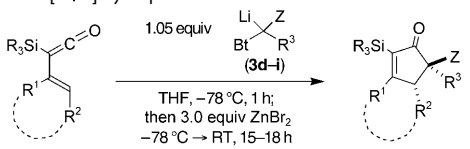
Table 1: [4+1] Cyclopentenone annulations.[a]

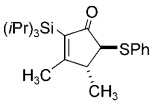
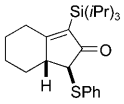
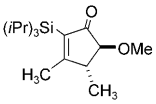
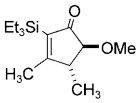
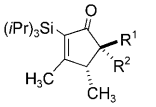
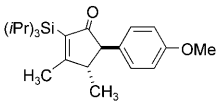
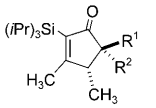
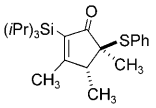


Entry	Ketene	Carbenoid reagent	Product		Yield [%][b] (*trans*/*cis*)[c]
1	**1a**	**3a**		**4a**	73 (≥96:4)
2	**1b**	**3a**		**5a**	67 (≥99:1)
3[d]	**1a**	**3b**		**6a,b**	70 (76:24)
4	**1a**	**3c**		**7a**	54 (97:3)

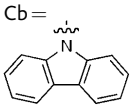
[a] Only the major diastereomer is shown for cases in which d.r. ≥ 96:4; Bt = benzotriazolyl. [b] Yields of isolated product purified by column chromatography. [c] Ratios determined by ^{1}H NMR spectroscopic analysis. [d] **6a**: R^1 = OEt, R^2 = –CH=CH_2; **6b**: R^1 = –CH=CH_2, R^2 = OEt.

Table 2: Lewis acid promoted [4+1] cyclopentenone annulations.[a]



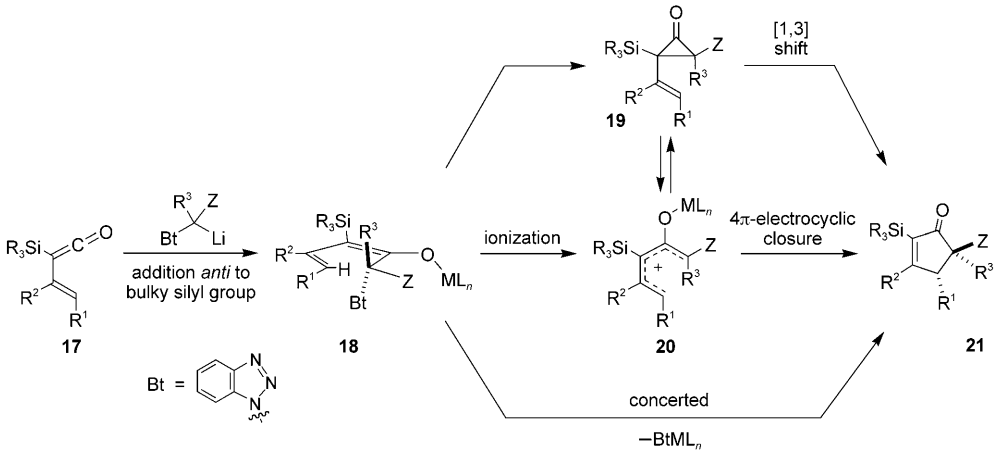
Entry	Ketene	Carbenoid reagent	Product		Yield [%][b] (*trans*/*cis*)[c]
1	**1a**	**3d**		**9a**	69–74 (98:2)
2	**1b**	**3d**		**10a**	75 (98:2)
3	**1a**	**3e**		**11a**	68–82 (≥99:1)
4	**1c**	**3e**		**12a**	67–70 (≥99:1)
5[d]	**1a**	**3f**		**13a,b**	85 (74:26)
6	**1a**	**3g**		**14a**	34[e] (≥99:1)
7[f]	**1a**	**3h**		**15a,b**	65 (77:23)
8	**1a**	**3i**		**16a**	64 (97:3)

[a] Only the major diastereomer is shown for cases in which d.r. ≥ 97:3. [b] Yields of isolated product purified by column chromatography. [c] Ratios determined by ^{1}H NMR spectroscopic analysis. [d] **13a**: R^1 = Cb, R^2 = H; **13b**: R^1 = H, R^2 = Cb. [e] Reaction mixture was allowed to warm to RT over 10 h and then heated at reflux for an additional 4 h. [f] **15a**: R^1 = OPh, R^2 = CH_3; **15b**: R^1 = CH_3, R^2 = OPh. Cb =



Scheme 5 outlines several alternative pathways to account for the mechanism of the [4+1] annulation. Addition of the carbenoid reagent to the vinyl ketene is predicted to be highly stereoselective because of the shielding effect of the bulky trialkylsilyl group and should result in the formation of the *Z*-enolate **18**. Direct formation of the five-membered-ring product could then result from a concerted process in which ring closure is concomitant with leaving-group departure. An alternative pathway involves ionization to produce oxidopentadienylic cation **20**,[16] which should then undergo rapid conrotatory 4π-electrocyclic closure[17] to generate the cyclopentenone product.[18] Finally, the involvement of cyclopropanone intermediates of type **19** cannot be excluded, particularly in view of the finding that simple silyl ketenes react with diazomethane and trimethylsilyldiazomethane to form mono- and bis(silyl)cyclopropanones.[19]

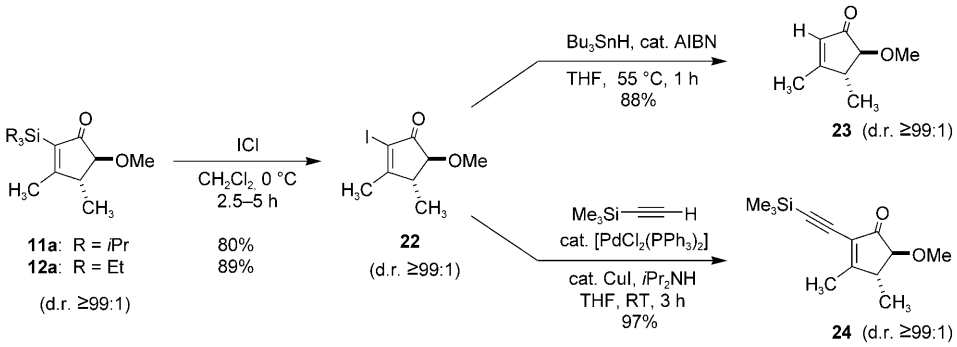
The stereochemical outcome of the [4+1] annulations that we investigated previously[8] is consistent with a mechanism that involves stereospecific conrotatory electrocyclic closure of a 2-oxidopentadienylic cation. In those prior cases, we suggested that ionization of the dienolate intermediate occurs to generate a cation in which the single C1 substituent is *cis* to the oxy anion to minimize nonbonded interactions. A similar mechanism can account for the reactions reported herein, provided that one assumes that ionization leads to the isomer of intermediate **20** shown in Scheme 5 because of an associative interaction between the heteroatom Z and the metal (M = Zn or Li) in **18** and/or **20**. Alternatively, if cyclization of **18** involves a concerted process, then the stereochemical outcome could reflect a preference for the mode of conrotation from **18** that rotates the leaving group *anti*



Scheme 5. Possible mechanistic pathways for the [4+1] annulation. M = metal center, L = ligand.

to the incipient σ bond and which proceeds via the transition state in which the donor heteroatom occupies an "outside" position ("torquoselectivity").[20]

The vinyl silane moiety incorporated in the [4+1] annulation products provides a useful handle for further synthetic transformations. Of particular interest to us was their conversion into vinyl halides, as a number of naturally occurring 2-halocyclopentenones have recently been found to exhibit potent antitumor activity.[1] In addition, the utility of 2-haloenones in a variety of transition-metal-catalyzed coupling reactions is well documented. With these ends in mind, we investigated the transformations outlined in Scheme 6 to lay



Scheme 6. Useful synthetic transformations of [4+1] annulation products. AIBN = azobisisobutyronitrile.

the groundwork for future applications of this annulation methodology. Conversion of α-silyl cyclopentenone annulation products **11a** and **12a** into iodoenone **22** proceeded smoothly by using a modification of the method of Alimardanov and Negishi.[21] Reduction of **22** with nBu$_3$SnH then afforded **23**, and Sonogashira coupling proceeded smoothly to furnish **24** with no detectable epimerization or double-bond migration in either case.

Further studies are underway aimed at the development of asymmetric variants of the annulation reaction and its application in the synthesis of natural products.

Received: May 10, 2005
Published online: August 5, 2005

Keywords: annulation · azoles · cyclopentenones · electrocyclic reactions · ketenes

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[14] Other Lewis acids that promote the desired reaction in good yield include $BF_3{\cdot}OEt_2$, $AlCl_3$, $Cu(OTf)_2$, $TiCl_4$, and $SnCl_4$.
[15] For example, exposure of **9a** to KOtBu in THF (RT, 19 h) afforded a 91:9 mixture of **9a** and the corresponding *cis* isomer, and similar reaction of **11a** produced a 62:38 mixture of *trans*- and *cis*-substituted cyclopentenones; exposure of **12a** to methanesulfonic acid (MeOH, RT, 32 h) afforded a 70:30 mixture of *trans*/*cis* isomers.
[16] Depending on the reaction conditions, this intermediate may be a free zwitterionic species or could still be associated with the metal center.
[17] Pentadienyl cation electrocyclic ring closures are involved in the mechanism of the Nazarov cyclization; for reviews, see: reference [2a] and S. E. Denmark in *Comprehensive Organic Synthesis*, *Vol. 5* (Eds.: B. M. Trost, I. Fleming), Pergamon, Oxford, **1991**, p. 751.
[18] For the formation of cyclopentenones through the base-induced cyclization of α′-chloro-β′,γ′-unsaturated ketone enolate and enamine derivatives, see: J. Mathew, *J. Org. Chem.* **1991**, *56*, 713. Although it was proposed that these cyclizations proceed by an "intramolecular abnormal S_N2'" mechanism, we believe these reactions more likely involve the cyclization of an oxidopentadienylic cation analogous to **20**. For a related transformation which involves a benzotriazolyl moiety in place of chloride as the leaving group, see: A. R. Katritzky, G. Zhang, J. Jiang, *J. Org. Chem.* **1995**, *60*, 7605.
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