Cycloadditions

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Synthesis of Cyclopentenones from Cyclopropanes and Silyl Ynol Ethers**

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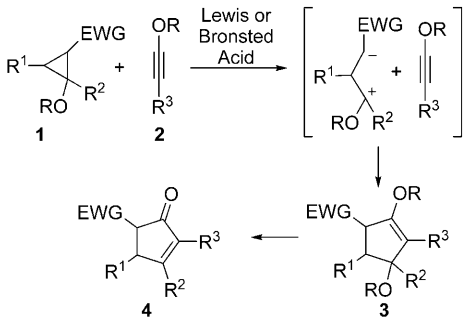
Five-membered carbocyclic rings appear in all classes of organic materials including pharmaceutical agents, polymers, natural products, and catalysts. Accordingly, their preparation has challenged synthetic chemists since the inception of the field.[1] In this regard, [3+2] cycloadditions—both concerted and stepwise—represent convergent strategies for the formation of the cyclopentane nucleus.[2] Dipolar cycloadditions, in particular, have proven especially successful for this construction. Of the various all-carbon dipolar synthons available, donor–acceptor cyclopropanes (**1**) have proven especially versatile.[3] In the presence of Lewis acids, donor–acceptor cyclopropanes undergo ring-opening to yield 1,3-zwitterions. Pursuing a general interest in the reactivity of electron-rich alkynes,[4] we envisioned a cycloaddition between such intermediates and ynol ethers (**2**, Scheme 1). In analogy to Diels–Alder reactions involving the diene



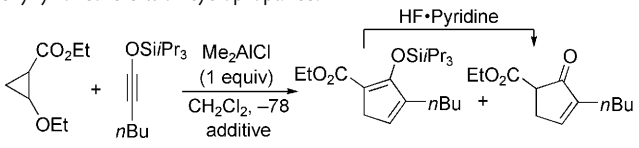
Scheme 1. Cycloaddition of ynol ethers with 1,3-zwitterions derived from the opening of donor–acceptor cyclopropanes. EWG = electron-withdrawing group.

developed by Danishefsky,[5] we postulated that the intermediate vinylogous acetal **3** might decompose to give cyclopentenone **4** during the reaction. While donor–acceptor cyclopropanes have been shown to combine with indoles,[6] enol ethers,[7] and aryl acetylenes,[8] a condensation with ynol derivatives has not been documented. Indeed, these alkynes have hardly been explored in the context of [3+2] cycloadditions.[9]

Exploratory studies examined the reaction of cyclopropane **1a** ($R^1 = R^2 = H$) with ynol ether **2a** ($R^3 = n$Bu), which is prepared in a single step from *n*-hexyne.[10] Several Bronsted and Lewis acids, including Me_3SiOTf ($Tf = SO_2CF_3$), $HN(Tf)_2$, and BBr_3, promoted the formation of cyclopentadiene **5aa** and cyclopentenone **4aa** in moderate yield. However, despite substantial efforts to optimize the reaction conditions we were unable to develop a protocol that returned the cycloadducts in synthetically useful yields. Our early experiments suggested similarly mediocre performance with Me_2AlCl; therefore, when we reinvestigated the use of this Lewis acid several months after our initial experiments we were surprised to find that it promoted the cycloaddition cleanly and rapidly.[11] Our hope that the increase in yield reflected improved technique was quickly dispelled when we found substantial differences in reactivity between aged and freshly opened bottles of reagent.

Reactions involving Me_2AlCl from freshly opened bottles required more than 24 h to go to completion (Table 1, entry 1). Under otherwise identical conditions, reagent drawn from bottles aged for several months displayed markedly superior reactivity (Table 1, entry 2). Reasoning that this observation could be accounted for by evaporation (solutions of Me_2AlCl in hexanes were used), adventitious air, or water, we performed a series of control experiments. Modest changes to the charge of Me_2AlCl had little effect on

Table 1: Effects of additives on the aluminum(III)-mediated reaction of silyl ynol ethers with cyclopropanes.[a]



Entry	Me_2AlCl[b]	Additive	*t* [h]	Yield [%][c]
1	freshly opened	none	28	74
2	aged[d]	none	6	76
3	freshly opened	H_2O (10 mol%)	24	64
4	freshly opened	air[e]	5	77
5	freshly opened	MeOH (1 equiv)	3	70
6	aged[d]	air[e]	5	74

[a] 0.33 M in **2**. Reactions were carried out on a 0.5 mmol scale. [b] 1 M solution in hexanes. [c] Yield of isolated compound **4aa**. [d] Opened several months prior to use. [e] Dry air (20 mL) was bubbled through the reaction mixture at 23 °C.

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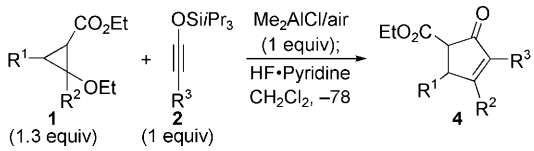
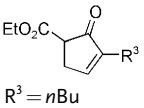
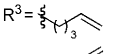
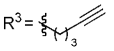
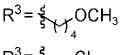
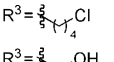
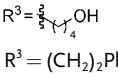
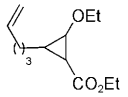
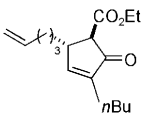
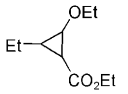
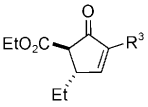
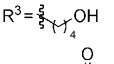
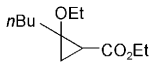
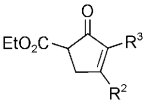
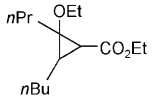
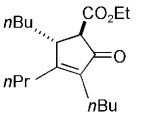
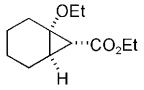
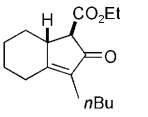
the rate of the reaction (results not shown), and small amounts of water (Table 1, entry 3) had no effect. In contrast, when dry air was bubbled through solutions containing the Lewis acid we could recapitulate the phenomenon observed with aged bottles of reagent and isolate **4aa** in good yield (Table 1, entry 4).[12]

Under optimized reaction conditions, air was bubbled through a solution of Me_2AlCl (1 equiv) at room temperature. Then at −78 °C, cyclopropane (1.3 equiv) and ynol ether (1 equiv) were added, and the mixture was stirred until the reaction was complete (2–24 h). Subsequently, HF·pyridine was added, and after an aqueous workup, the residue was purified by column chromatography to give cyclopentenone **4**. In this way, a series of substituted donor–acceptor cyclopropanes were combined with a range of ynol ethers to yield enones in generally good yields (Table 2). Silyl ynol ethers bearing olefins, alkynes, ethers, halides, and aromatic rings all functioned effectively in the transformation (Table 2, entries 1–12). Unfortunately, the ynol derived from phenyl acetylene was a poor substrate (Table 2, entry 13). Both cis- and trans-disubstituted cyclopropanes appear to behave identically (Table 2, entries 1 and 2). Likewise, substitution at C3 (Table 2, entries 14–16), C1 (Table 2, entry 17), or both (Table 2, entries 18 and 19) are accommodated in the cycloaddition. Thus, tri-, tetra-, and even penta-substituted cyclopentenones can be formed in good yields and in a convergent manner. When two stereocenters were generated in the reaction (Table 2, entries 14–16, 18, and 19), we observed greater than 10:1 diastereoselectivity favoring the more stable *trans* isomer. Furthermore, both partners in the cycloaddition can be accessed in a single operation from readily available materials.

The ^{1}H NMR spectra of anaerobic solutions of Me_2AlCl revealed one singlet at $\delta = -0.31$ ppm ($CDCl_3$). After oxygenation, the same solution displays two upfield singlets at $\delta = -0.39$ and -0.43 ppm and two downfield resonances which are suggestive of a methoxide group ($\delta = 3.87$ and 3.85 ppm). We interpret these signals as arising from (MeO)AlMeCl, the product of aerobic oxidation of one methyl–aluminum bond. The two sets of signals (ca. 1:2 ratio) likely correspond to diastereomeric cyclic trimers.[13] Indeed, addition of 1 equivalent of methanol to Me_2AlCl yielded a substance with substantially the same spectrum, and the reagent thus produced is a better Lewis acid for the cycloaddition than Me_2AlCl (Table 1, entry 5). Interestingly, while the major products formed upon addition of either methanol or air to Me_2AlCl are the same, the reaction resulting from the addition of methanol is noticeably messier: an unidentified precipitate is formed, and the ^{1}H NMR spectrum of the filtrate indicates several minor products. Perhaps as a consequence, the cycloadditions carried out using this reagent are lower yielding and generate more side products. Thus, aerobic oxidation of dialkyl alanes constitutes a clean and efficient method to generate a strong but selective Lewis acid. Finally, it is important to note that we observe no difference in reactivity between the (MeO)AlMeCl generated from freshly opened versus aged bottles of Me_2AlCl (Table 1, compare entries 4 and 6).

Table 2: Synthesis of cyclopentenes from silyl enol ethers and cyclopropanes.[a]



Entry	Cyclopropane	Ynol Ether (**2**)	Product (**4**)	Yield [%][b]
1	*cis*-**1a**	**2a**	 $R^3 = n$Bu	77
2	*trans*-**1a**	**2a**	$R^3 = n$Bu	75
3	*cis*-**1a**	**2b**		67
4	*cis*-**1a**	**2c**		71
5	*cis*-**1a**	**2d**		72
6	*cis*-**1a**	**2e**		72
7	*cis*-**1a**	**2f**[c]		79
8	*cis*-**1a**	**2g**	$R^3 = (CH_2)_2$Ph	54
9	*cis*-**1a**	**2h**	$R^3 = CH_2$-(*c*Pent)	82
10	*cis*-**1a**	**2i**	$R^3 = c$Hex	76
11	*cis*-**1a**	**2j**	$R^3 = CH_2OBn$	72
12	*cis*-**1a**	**2k**	$R^3 = (CH_2)_2OBn$	54
13	*cis*-**1a**	**2l**	$R^3 = $Ph	24
14	 **1b**[d]	**2a**		70
15	 **1c**[e]	**2a**	 $R^3 = n$Bu	76
16	**1c**[e]	**2f**[c]		81
17	 **1d**[d,f]	**2a**	 $R^2 = R^3 = n$Bu	63
18	 **1e**[d]	**2a**		46[g]
19	 **1f**[d]	**2a**		79[g]

[a] Reactions were carried out on a 1.0 mmol scale. Dry air (40 mL) was bubbled through A solution of Me_2AlCl at 23 °C prior to use (*c*Hex = cyclohexyl, *c*Pent = cyclopentyl). See the Supporting Information for complete experimental details. [b] Yield of isolated product. [c] The ynolate **2f** used was bis(*i*Pr)$_3$Si-ether. [d] Single unassigned diastereomer. [e] Mixture of diastereomers. [f] **1d** (2.5 equiv). [g] d.r. > 20:1.

With respect to the utility of the methodology described here, comparisons to two standard syntheses of cyclopentenones are appropriate. This cycloaddition is more direct than

the Nazarov cyclization, and in contrast to that cyclization, yields a single olefin positional isomer.[14] Likewise, while the Pauson–Khand reaction is generally limited to intramolecular cyclizations, the reactivity described above functions efficiently in an intermolecular context.[15]

While (MeO)AlMeCl has been characterized previously, it has found infrequent use as a Lewis acid.[16] In the present transformation, this species appears strong enough to activate the cyclopropane towards ring-opening and to mediate the decomposition of the vinylogous acetal (**3**); fortunately it is mild enough to coexist with the ynol ether and the cyclopentenone. Whether this favorable reactivity profile extends to other classes of cycloadditions and, more broadly, to other Lewis acid promoted reactions remains the subject of future investigations.

Experimental Section

A dried test tube was charged with anhydrous dichloromethane (1 mL) and Me_2AlCl (0.5 mL of a 1M solution in hexanes, 1 equiv). Dry air (20 mL) was bubbled through the solution at room temperature. The resulting solution then was cooled to −78 °C before cyclopropane (0.65 mmol, 1.3 equiv) and silyl ynol ether (0.5 mmol, 1 equiv) were added sequentially. The reaction mixture was stirred at −78 °C and upon completion (as evident by TLC), the reaction was quenched by adding 30% HF·pyridine solution (0.5 mL). After stirring at −78 °C for 5 min, the mixture was diluted with diethyl ether and water. The aqueous layer was washed with 30 mL diethyl ether and the combined organic extracts were washed with brine (50 mL), dried over anhydrous $MgSO_4$, concentrated in vacuo and the resulting residue was purified by column chromatography on silica gel to afford the product.

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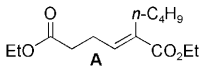
[11] $MeAlCl_2$: **4aa** in 34% yield; MAO (methylaluminoxane): 11% yield; Et_2AlCl: 53% yield; Me_3Al, $AlCl_3$, and $(EtO)_3Al$: traces.

[12] Additional notes: a) The isolation of minor quantities of **A** from the reaction mixture indicates that the cycloaddition is stepwise; b) lower yields were obtained with *tert*-butyl-diphenylsilyl ethers while *tert*-butyl-dimethylsilyl ethers could not be prepared in satisfactory yields; c) similar yields are observed in dicholoethane while substantially reduced yields were observed in chloroform and no reaction occured in diethyl ether or THF.



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