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Ambiphilic Allenyl Enolates: Reactions With Electrophiles

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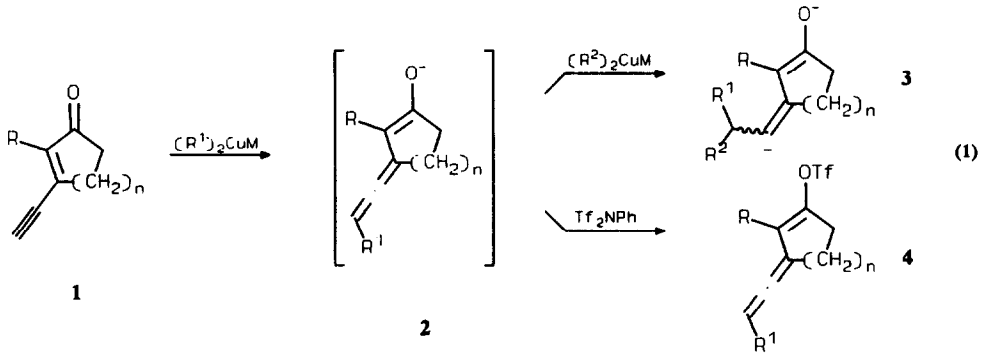
Abstract: **Allenyl enolates generated from 1,6 additions of organocopper reagents to 3-ethynyl-2-cycloalkenones act as ambident α,γ-nucleophiles. The γ:α ratio of products is a function of carbon hybridization, steric environment, and cycloalkenone ring size; typically, γ-products predominate.**

The ambident nature of dienolate nucleophiles has made them attractive targets for research and exploitation in organic chemistry.[1] Typically, conjugated dienolates and their analogs undergo selective α-alkylation under kinetic control;[2] O-silylation of such dienolates to give silyl dienol ethers provides two-step access to regioselective γ-alkylation.[3] General access to direct, regioselective α- or γ-alkylation of dienolates by control of reaction conditions remains a problem in organic synthesis.[4] For this reason, the extension of the 1,4 addition--enolate trapping strategy of use in total synthesis[5] to dienolate intermediates generated from 1,6 addition reactions of dienones and dienoates has remained relatively unexploited.[6]

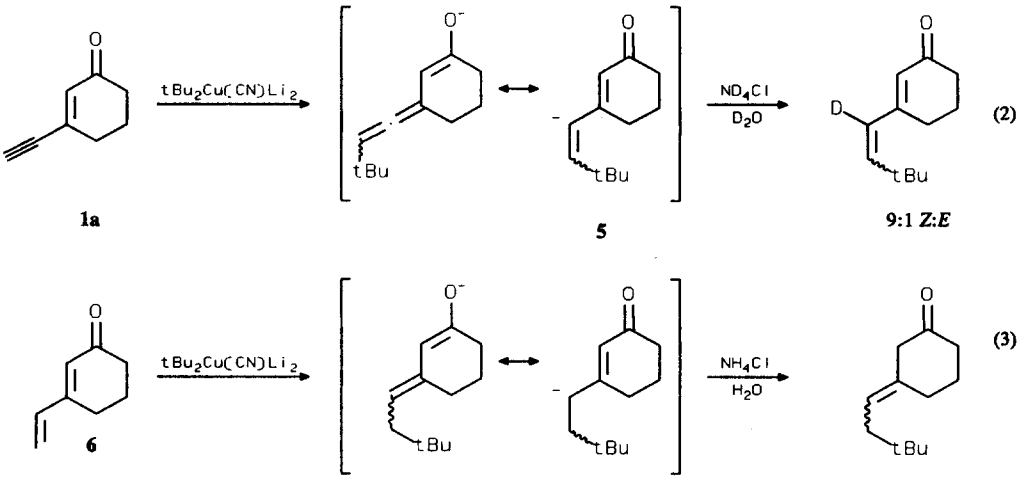
Recently, we reported[7a] that enynones **1** undergo facile, high-yield 1,6 addition reactions of various nucleophiles to provide allenyl enolate intermediates, **2** (Eq 1). These intermediates are ambiphiles, reacting as electrophiles with selected nucleophiles to give dianionic intermediates **3**,[7b] and reacting as nucleophiles with appropriate electrophiles to give adducts such as dienol triflates **4**. We report here our preliminary studies of the nucleophilic behavior of ambiphiles **2**.[7c]



(1)

While it was expected that reaction of these intermediates with C-selective electrophiles would give normal α-alkylation, deuterium labelling studies of enynone **1a** indicated nearly exclusive γ-nucleophilicity (Eq. 2).[7a] The decisive role of the sp-hybridized γ carbon in relative localization of dienolate negative charge via contribution of resonance structure **5** became clear when compared to the results from analogous dienone **6**, which underwent nearly exclusive α-protonation (Eq 3).

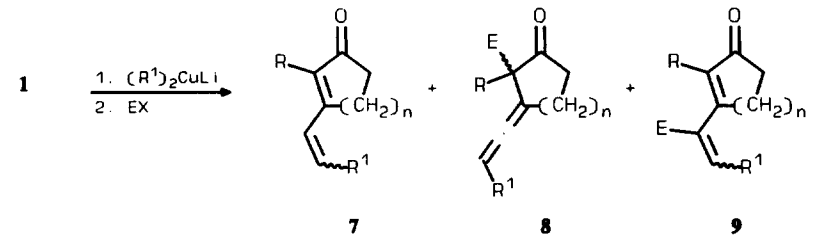
Regioselectivity during attack of electrophiles was found to be a function of electrophile, in addition to inherent relative



charge localization in the allenyl enolates. Similar γ-nucleophilicity was observed when enynones **1** derived from cyclohexenone were submitted to 1,6 addition of an organocopper reagent, followed by quenching with the highly reactive electrophile tolualdehyde at -78°C (Eq 4 and Table, entries 6 and 9). When the less reactive electrophile iodomethane was used, little reaction occurred at -78°C, paralleling the well-documented relative nucleophilic inertness of enolates derived from organocopper-mediated conjugate additions.[5] With the addition of HMPA and warming to -20°C, partitioning of the allenyl enolate was observed (entries 4, 5, and 8). 3-Ethynyl-2-cyclohexenone gave mostly α-methylation, favoring it over γ-methylation in a 3:1 ratio. When the α carbon was substituted with either a methyl group or a phenylthio group, γ-methylation became more competitive: giving α:γ methylation ratios of 1.2:1 and 1:1.5, respectively. These observations can be rationalized by invoking straightforward steroelectronic control arguments. Partitioning between the inherently less nucleophilic α and more nucleophilic γ carbons is biased by steric inhibition to attack of the electrophile. As the size of the substiuent on the α carbon becomes larger, α-attack becomes increasingly difficult relative to γ-attack; thus, no sustitution on the α carbon results in the largest amount of α methylation. Stereoelectronic control during attack of the electrophile is seen not only in the alkylation partitioning ratio, but also in the general *Z*-stereopreference of the products formed from γ-attack itself. Thus, as in the case of protonation,[7a] γ-alkylation proceeds from the lesser hindered face of the γ carbon of allenyl enolate **2**, resulting in net *anti*-addition of nucleophile and electrophile across the triple bond of the initial enynone substrate.

When acetyl chloride was used as electrophile (entry 7) under conditions typically favoring C-alkylation of enolates,[8] the only acylated product observed was that resulting from α-acylation. This result reinforces the difficulty of predicting the outcome of acylation reactions of enolates, which are highly substrate-dependent.[8]

When enynones **1** derived from cyclopentenone were submitted to 1,6 addition of an organocopper reagent, followed by quenching with an electrophile, a dramatic ring size effect could be observed. Use of tolualdehyde or iodomethane as electrophile under reaction conditions comparable to those experiments previously described resulted only in γ-alkylation; α-alkylated adducts were present in only small or trace amounts. Such an apparent enhancement in the γ-nucleophilicity as ring size is reduced from six to five carbons can be rationalized along the lines of previously proposed[1d,9] conformational preferences of cyclic dienols and dienolates. Allenyl enolate intermediate **2a** (Figure) arising from 1,6 addition of cyanodimethylcopperdilithium to 3-ethynyl-2-methyl-2-cyclopentenone provides a mixed hybridization state dienolate with all conjugated atoms lying in approximately the same plane (dihedral angle $\Theta \simeq 180°$). Charge thus is fully delocalized; attack of the electrophile is highly biased toward the



7 8 9 (4)

Table. 1,6 Addition–Dienolate Trapping of 3-Alkynyl-2-cycloalkenones.

	1				Products, % (*Z*:*E*)		
Entry	R	n	R^1	EX	7	8	9
1	CH_3	1	CH_3	CH_3I			64 (2.3:1)
2	CH_3	1	CH_3	pTolCHO			86 (1:27)
3	CH_3	1	t-C_4H_9	pTolCHO			94[a]
4	H	2	t-C_4H_9	CH_3I	42 (R=CH_3) (1:1)	20	20[b]
5	CH_3	2	CH_3	CH_3I		50	40 (1:3)
6	CH_3	2	t-C_4H_9	pTolCHO			95 (1:1)
7	CH_3	2	t-C_4H_9	AcCl		43	
8	PhS	2	CH_3	CH_3I[c]		21	29 (2.5:1)
9	PhS	2	CH_3	pTolCHO			27[b]

a. Facile equilibration of *Z* and *E* isomers observed. b. Undetermined mixture of isomers.
c. 30 equivalents used.

2a 2b

Figure. Newman projections of intermediates 2a and 2b.

γ carbon by stereoelectronic control factors and the γ:α alkylation ratio observed is large. Allenyl enolate **2b** arising from 1,6 addition of cyanodimethylcopperdilithium to 3-ethynyl-2-methyl-2-cyclohexenone, on the other hand, may provide a mixed hybridization state dienolate with a less planar system of conjugated atoms (dihedral angle $\Phi \simeq 162°$). In such a case charge is more delocalized, causing the relative charge densities at the α and γ carbons to be more similar. Stereoelectronic control factors now bias attack of the electrophile at the γ carbon less, and as a consequence, the observed γ:α alkylation ratio is smaller.

In summary, ambiphilic allenyl enolates **2** generated from 1,6 addition of organocopper reagents exhibit pronounced γ-nucleophilicity. The ratio of γ:α adducts is a function of inherent nucleophilic differences between the sp-hybridized γ and sp^2-hybridized α carbons of **2**, and differential steric hinderance to attack of electrophiles. Superimposed upon these factors is the effect of ring size, which may inhibit charge delocalization by reducing planarity of the conjugated dienolate system. Clearly, it should be possible to bias these allenyl enolates to react as exclusive α nucleophiles through proper selection of a small, electron-withdrawing α-substituent; these efforts are underway and will be reported in due course.

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