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Ambiphilic Allenyl Enolates

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Contents

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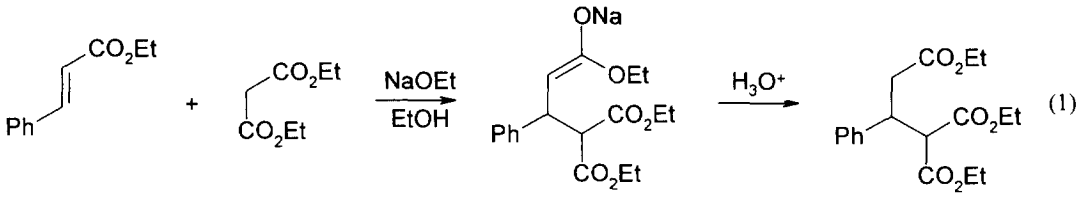
1. INTRODUCTION

1.1 *Nucleophilic 1,4 addition*

Nucleophilic 1,4 addition to electrophilic, unsaturated systems has been a cornerstone carbon-carbon bond-forming reaction of the twentieth century.[1] Discovered by Komnenos and Claisen[2,3] in 1883, the scope and broadly applicable nature of the reaction was investigated by Michael.[4] Well-known now as conjugate or Michael addition,[5,6] the process (e.g. eq 1[4]) is well-described as a base-catalyzed vinylogous aldol condensation: generally, a stabilized enolate acting as an α carbon nucleophile (conjugate donor) attacks the electron deficient β carbon of an α,β-unsaturated ketone or ester (conjugate acceptor), leading to the product or conjugate enolate. Subsequent protonation and tautomerization leads to the conjugate adduct, a 1,5-dicarbonyl compound. Historically run in



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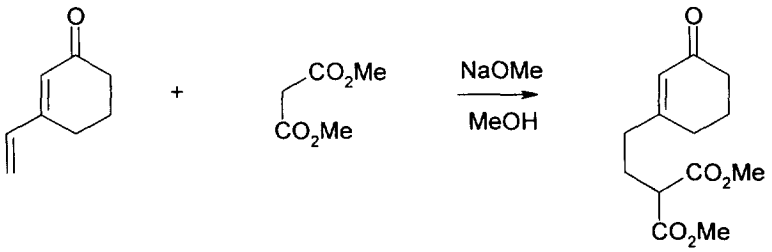
protic solvents to minimize competition of the conjugate enolate with conjugate donor for acceptor, heteronucleophiles and other stabilized carbon nucleophiles may be used. Regardless, the reaction is observed to be reversible, and chemical yields usually are in the range of 50 - 70%. The advent of modern organocopper chemistry,[7] which allows the use of nonstabilized carbon nucleophiles,[1,8-10] and advances in organosilicon[11] and organotin[12,13] chemistry, providing access to these valuable heteronucleophiles, have established 1,4 addition as a powerful and efficient method for chemical bond construction. Applications of 1,4 addition to multibond-forming reactions, such as annulations[14-16] and tandem dialkylations,[17,18] provide convergent access to complex natural products.[8,19,20]

1.2 *Extended nucleophilic addition: 1,6 and 1,8 addition*

On the other hand, *extended* conjugate addition reactions to polyunsaturated carbonyl compounds have been much less extensively exploited in organic synthesis.[21] Early observations of 1,6 additions of ethyl acetoacetate to sorbate esters[22] have been followed by other reports of exclusive 1,6 addition,[21,23,24] 1,4 and 1,6 addition of nucleophile to conjugate acceptor,[25] and exclusive 1,4 addition in extended conjugated systems.[19,26] A representative 1,6 addition of dimethyl malonate to 3-vinyl-2-cyclohexenone[27] is shown in eq 2. Exceptionally rare 1,8 additions (e.g. eq 3[28]) have infrequently found synthetic utility.[29]



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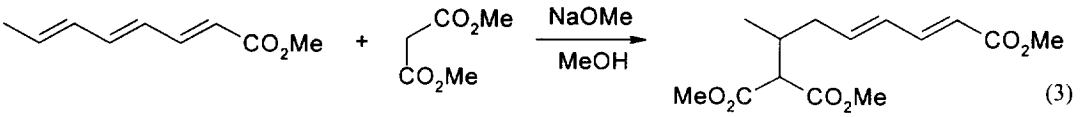

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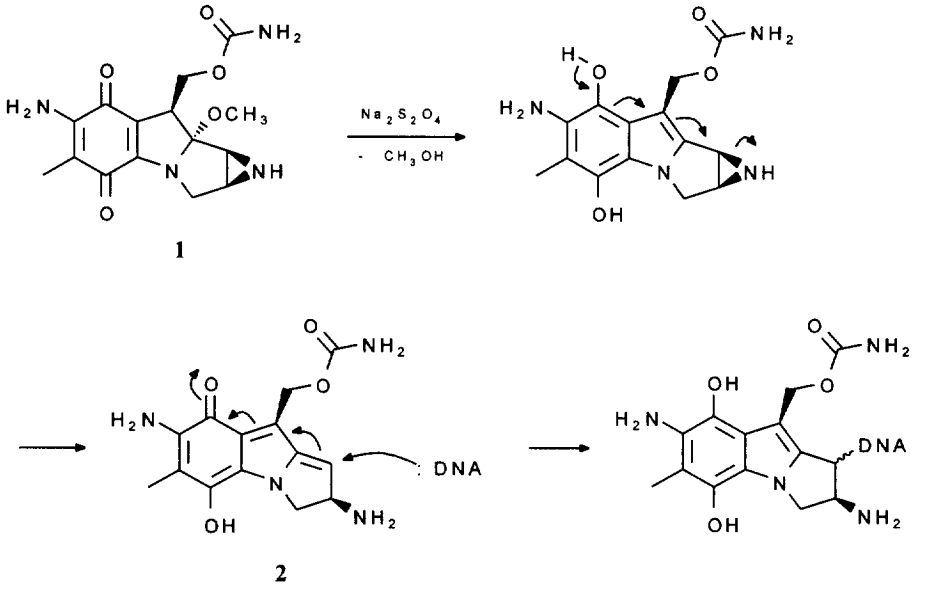
1.3 *1,6 and 1,8 additions involving natural products*

Many natural product antibiotics contain polyunsaturated carbonyl functional groups. Recently, a number have been discovered to exert their antibiotic activity by way of extended conjugate addition reactions. The antibacterial properties of structurally simple but highly reactive γ-methylene-γ-butenolide are almost certainly due to its nature as a conjugate acceptor.[30] The prototypical bioreductive alkylation agent Mitomycin C (**1**, Scheme 1) is presumed to alkylate DNA *in vitro* via 1,6 addition to a quinone methide intermediate (**2**).[31] It has been suggested that the antitumor agent illudin S (**3**) and its derivatives[32] may be activated by a similar bioreductive process, as may the antibiotic azinomycin[33] (**4**).



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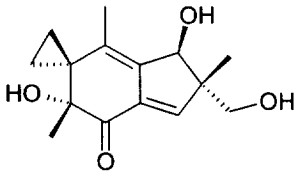
Scheme 1. Alkylation of DNA by Mitomycin C.



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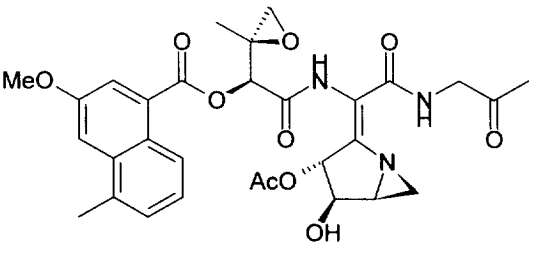

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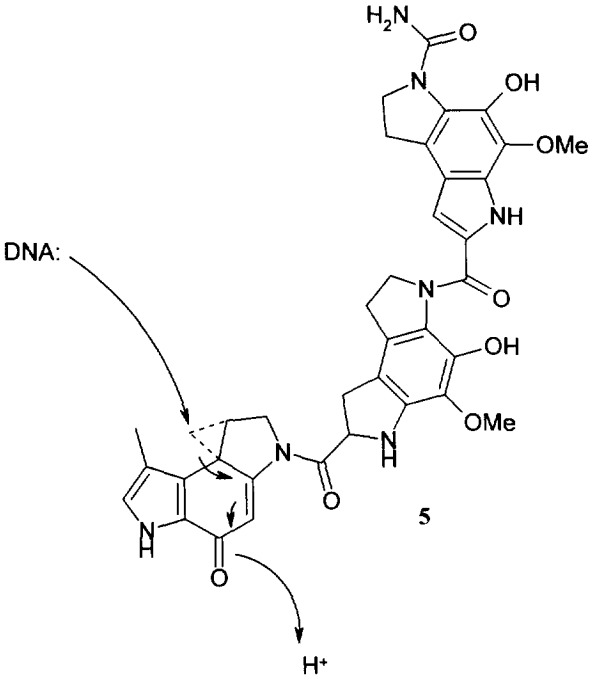
1.3.1 *CC-1065 and the duocarmycins.* A surprising degree of structural variety can be found in these natural product conjugate acceptor classes: formal all sp^2- hybridized polyunsaturated carbonyl moieties can be replaced with almost fantastic conjugate acceptor motifs. DNA alkylation agent CC-1065 (**5**, Scheme 2), the duocarmycins, and many of their biologically active structural analogs share a formally sp^2- and sp^3-hybridized conjugated cyclopropylenone moiety which undergoes 1,6 addition of nucleophilic residues on DNA.[34] A similar motif can be found in the DNA alkylating agent ptaquiloside (**6**);[35] recently, highly cyclopropanated, fungicidal metabolites of stearic acid , U-106305 and FR-900848 (**7**) have been isolated and synthesized.[36] Interestingly, the simplest model studies[37,38] of this functional group as a conjugate acceptor indicate exclusive 1,4-not 1,6-addition (eq 4[37]).



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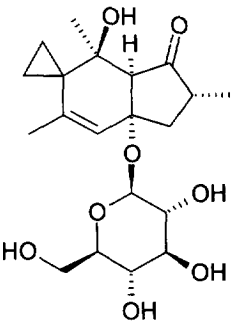
Scheme 2. Alkylation of DNA by CC-1065.



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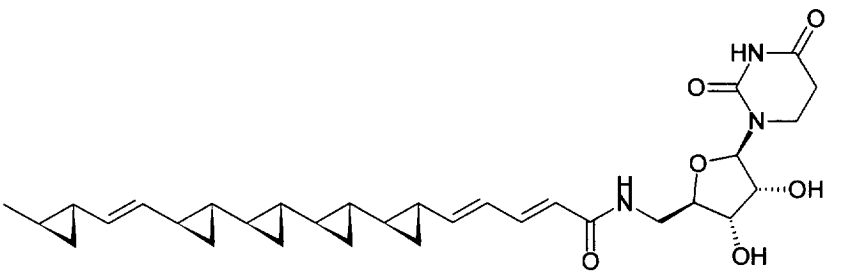

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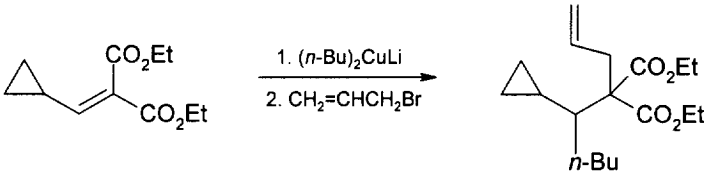
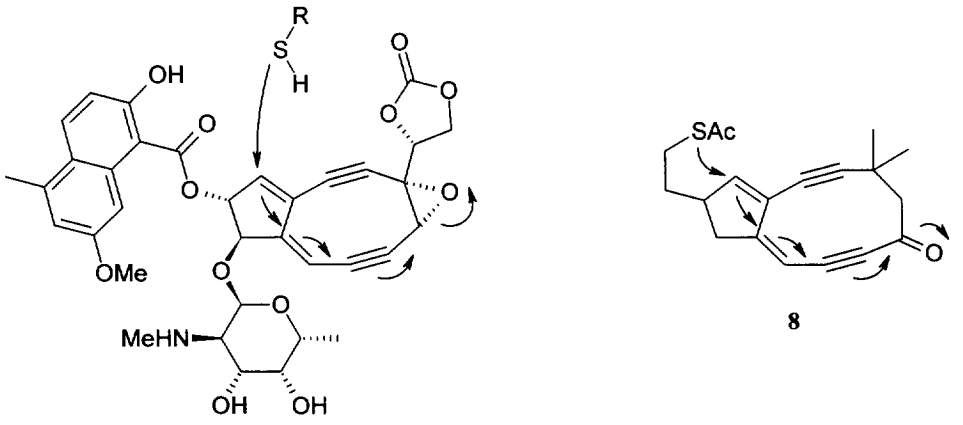


(4)

98%

1.3.2 *Endiyne antibiotics*. Similarly, the widely studied endyine antibiotics[39] share formally *sp*- and sp^2-hybridized conjugated enyne moieties essential for Bergman cyclization to provide diradical intermediates which ultimately cause DNA double strand scission. One of these antibiotics, neocarzinostatin chromophore, is triggered to undergo Bergman cyclization following a 1,8 epoxide opening (Scheme 3);[40] numerous models of this ring system, including cyclodec-4-en-2,7-diynone **8**,[41] behave similarly.[42] It has been suggested that an alternative triggering reaction of dynemicin may also involve a 1,6 addition.[43,44] Again, referring to simple model studies, various outcomes are reported: early results of conjugate additions to 3-hexen-5-yn-2-one indicate a thermodynamic preference for 1,6 addition (eq 5).[45] On the other hand, nitrile **9**[46] and ester **10**[47] are found to undergo exclusive 1,4 and 1,6 additions of organocopper reagents, respectively, while reductive epoxide opening of **11** is highly dependent upon alkyne substitution (eq 6).[48]



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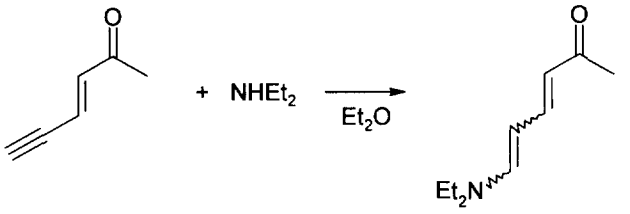
Scheme 3. Thiol Addition to Neocarzinostatin.



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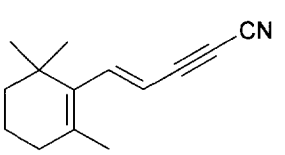

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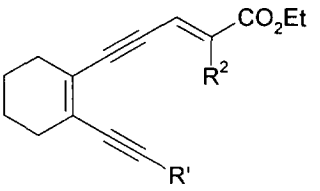

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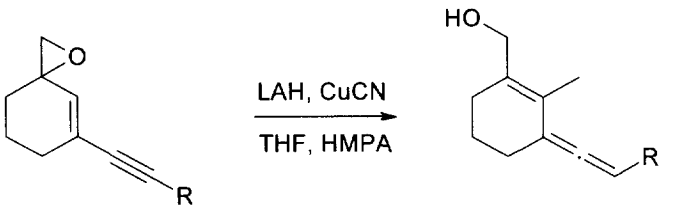

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R = $CH_2OCH_2OCH_3$ quant.
R = Ph decomp.

The potential wide-ranging utility of extended conjugate additions to mixed hybridization state, polyunsaturated carbonyl substrates suggests an examination of reaction scope, regioselectivity, parameters, and mechanism would be valuable for development of these variants of the Michael reaction. Concentrating on conjugated alkenynones and alkenynoates, this review highlights current contributions to this development effort.

2. 1,6 ADDITIONS TO ALKENYNONES AND ALKENYNOATES

2.1 *Alkenynone and alkenynoate synthesis*

A variety of methods can be used to prepare conjugated β-alkynyl alkenones, alkenals, and alkenoates, including thermal rearrangements,[49] 1,4 addition–eliminations,[50] palladium-catalyzed cross-coupling reactions,[51,52] and organocopper-mediated substitutions of iodoalkynes.[53] Among these methods, 1,2 addition–elimination reactions of protected 1,3-diketones,[54-57] Horner-Wittig olefinations of propiolaldehyde derivatives,[52,58] and palladium-catalyzed condensations of alkynes with propiolates or alkynones give the most rapid access to the desired conjugate acceptors from readily available starting materials. 3-Ethynyl-2-cycloalkenones **12**, for example,

are easily prepared from the reaction of an alkynylmetal reagent with monoenol ethers of 1,3-cycloalkanediones, followed by aqueous acidic workup (eq 7 and Table 1).[54] Yields vary but the reaction sequence is relatively general, tolerating various alkynylmetals and cycloalkanediones. It does not succeed when poorly nucleophilic alkynylmetals are used. Rather, competing enolate formation of the cycloalkanedione monoenol ether results in aldol--dehydration products. Additionally, if very bulky α′ substituents are present in the enol ether starting material, addition of the alkynylmetal to the carbonyl group can be difficult or impossible (e.g. **12i**).

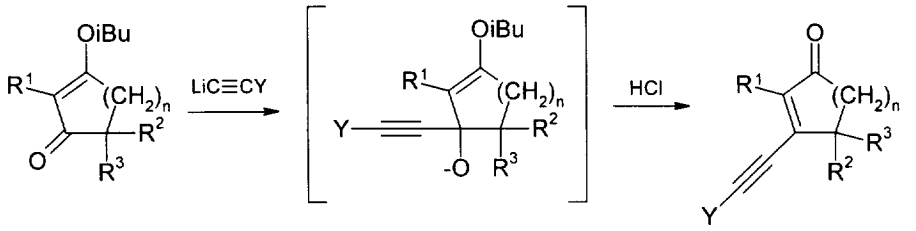

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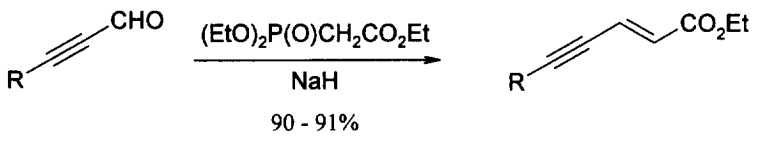
Table 1. Alkenynone Synthesis via eq 7.

	n	R^1	R^2	R^3	Y	Yield, %
12a	1	Me	H	H	H	56
12b	1	Me	H	H	CH_2=C(Me)–	30
12c	1	Me	H	H	HC≡C–	28
12d	2	Me	H	H	H	71
12e	2	H	H	H	H	43
12f	2	H	H	H	TMS	82
12g	2	Me	H	H	Ph	63
12h	2	Me	Me	Me	H	28
12i	2	Me	*t*-Bu	H	H	NR

Horner-Wittig olefination also proves to be very versatile: 2-alkynals, prepared from the reaction of the corresponding acetylide with DMF,[59] react with Horner ylides derived from commercially available trialkyl phosphonoacetates and dialkyl acetylmethylphosphonates to provide the desired adducts in high yields and stereochemical purities[60] (e.g. eq 8[52]). Use of trialkyl 4-phosphonocrotonates allows extension of the method to alka-2,4-dien-6-ynoates. Finally, regio- and stereospecific palladium-catalyzed cross-coupling of two alkynes provides a general route to a wide variety of 3-substituted alk-2-en-4-ynyl ketones, esters, and sulfones[61,62] (eq 9 and Table 2[63]). The method is most efficient when hindered, strongly basic triarylphosphine ligands such as tris(2,6-dimethoxyphenyl)phosphine (TDMPP) or tris(2,4,6-trimethoxyphenyl)phosphine (TTMPP) are used. The starting ketones and esters are readily available from the corresponding acetylides and alkyl chloroformates or acyl chlorides.[64] In the case of ketone **13e**, small amounts of (*E*)-**13e** (8%) and heterotrimer **14** (10%) also form.



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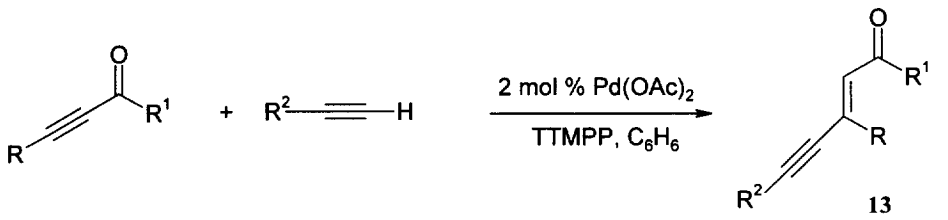
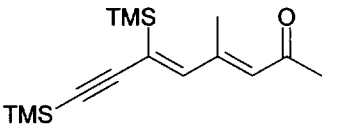


(9)

Table 2. Alkenynone and Alkenynoate Synthesis via eq 9.

	R	R^1	R^2	Yield, %
13a	*n*-Pr	OBn	TMS	90%
13b	Me	OMe	TMS	95%
13c	Me	OBn	TMS	99%
13d	*n*-Pr	OMe	TMS	90%
13e	Me	Me	TMS	70%
13f	Me	Me	CH_2=C(Me)-	74%



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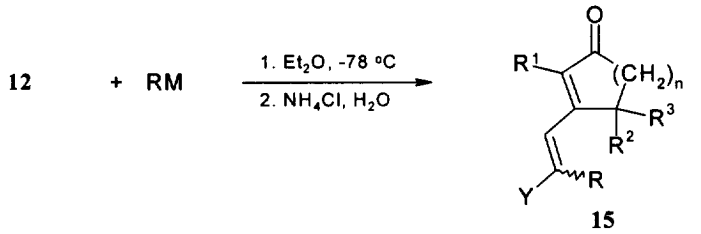
2.2 *Organocopper-mediated 1,6 additions*

Both alkenynones and alkenynoates undergo facile, virtually regiospecific additions of organocopper reagents. Generally, the conjugated ketones undergo addition more rapidly than the corresponding esters, especially when geometrically constrained, as are cycloalkenynones **12** (eq 10). Table 3 summarizes organocopper addition studies[53] of compounds **12** and indicates that: (1) the nucleophilic reagent invariably attacks the distal *sp* hybridized carbon of the conjugated system. After protic quench, dienones **15** result; (2) the reaction is insenitive to ring size, substitution patterns on the ring, and substitution of the distal carbon of the alkyne moiety; and (3) there is a distinct stereopreference for formation of (*Z*)-**15**. Moreover, it is apparent that the larger the alkyl group appended, the greater the (*Z*) stereodiscrimination. This last observation contrasts with the use of the

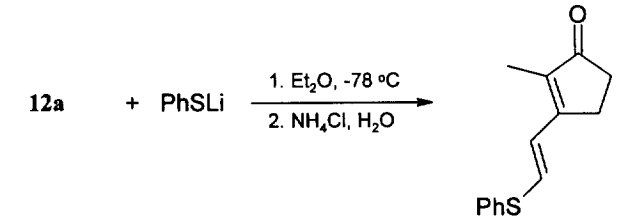
heteronucleophile PhSLi, which also adds to **12a** without complication, but provides an (*E*) adduct after protic quench (eq 11).[65]



15 (10)

Table 3. Synthesis of Dienones **15** via eq 10.

	RM	R	Yield, %	Ratio, (*Z*) : (*E*)
12a	$(Me)_2Cu(CN)Li_2$	Me	91	2.5 : 1
12e	$(Me)_2Cu(CN)Li_2$	Me	75	1.2 : 1
12g	$(Me)_2Cu(CN)Li_2$	Me	89	2.5 : 1
12h	$(Me)_2Cu(CN)Li_2$	Me	75	6 : 1
12i	$(Me)_2Cu(CN)Li_2$	Me	86	all (*Z*)
12a	$(Et)_2Cu(CN)(MgBr)_2$	Et	77	3 : 1
12a	$(i\text{-}Pr)_2Cu(CN)(MgCl)_2$	*I*-Pr	87	4 : 1
12g	$(i\text{-}Pr)_2Cu(CN)(MgCl)_2$	*I*-Pr	81	6 : 1
12g	$(n\text{-}Bu)_2Cu(CN)Li_2$	*n*-Bu	81	7 : 1
12a	$(t\text{-}Bu)_2Cu(CN)Li_2$	*t*-Bu	93	34 : 1
12e	$(t\text{-}Bu)_2Cu(CN)Li_2$	*t*-Bu	83	9 : 1
2g	$(t\text{-}Bu)_2Cu(CN)Li_2$	*t*-Bu	89	35 : 1
12a	$(Ph)_2Cu(CN)Li_2$	Ph	88	6 : 1
12g	$(Ph)_2Cu(CN)Li_2$	Ph	81	all (*Z*)
12i	$(Ph)_2Cu(CN)Li_2$	Ph	78	all (*Z*)
12a	$(CH_2{=}CH)_2Cu(CN)Li_2$	$CH_2{=}CH–$	83	5 : 1
12g	$(CH_2{=}CH)_2Cu(CN)Li_2$	$CH_2{=}CH–$	82	3 : 1
12i	$[p\text{-}(n\text{-}C_{12}H_{25})Ph]_2Cu(CN)Li_2$	$p\text{-}(n\text{-}C_{12}H_{25})Ph$	59	all (*Z*)



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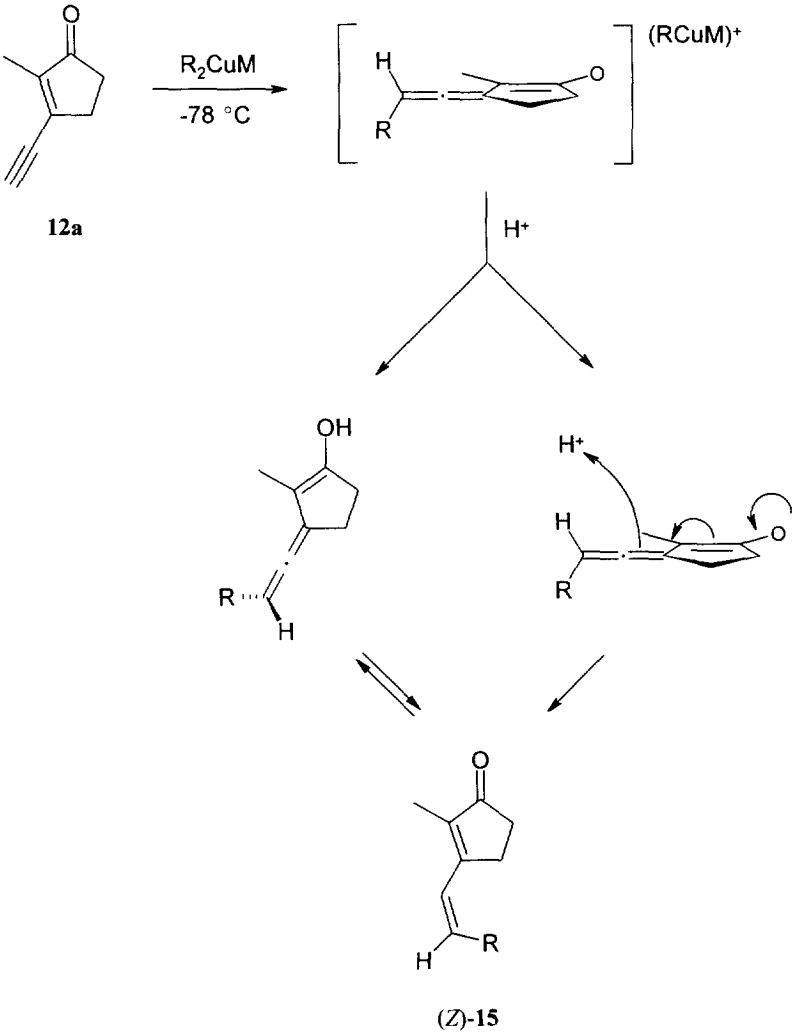
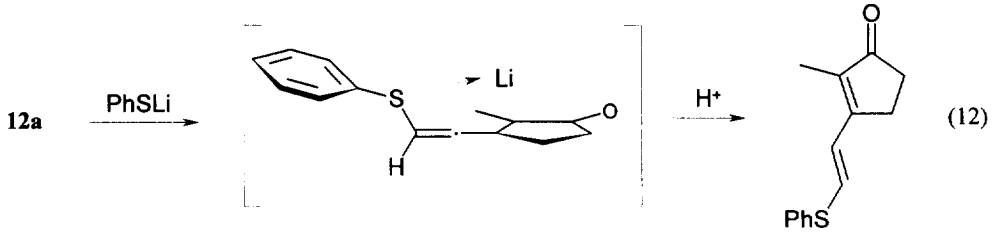
Taken together, these data strongly suggest adduct formation via a 1,6 addition of organocopper reagents, with the intermediacy of an allenyl enolate (e.g. Scheme 4). Subsequent to π-complex formation of the cuprate with the double bond proximal to the carbonyl group and either intramolecular rearrangement leading to alkylation, intermolecular rearragement leading to alkylation, or direct attack leading to alkylation,[66] a delocalized, conjugated allenyl enolate intermedate forms. When protonated, this allenyl enolate may protonate at oxygen to produce an allenyl enol; tautomerization then leads to the thermodynamically preferred[67,68] dienone. Alternatively, the enolate may protonate at the *sp*-hybridized allenic carbon directly. Regardless, tautomerization of the enol or direct protonation of the enolate should prefer to occur from the face opposite that of the bulkier alkyl substituent of the distal allene carbon, causing (*Z*) adducts to predominate.



(*Z*)-**15**

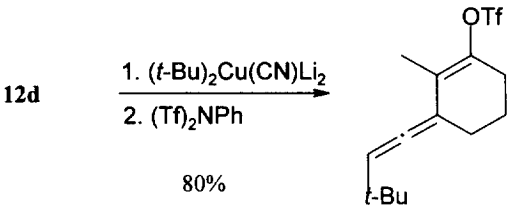
Scheme 4. 1,6-Addition of Organocopper Reagents to Alkenynones.

In agreement with the stereochemical outcome of the reaction, the bulkier the substituent that is appended, the greater the stereodiscrimination that results. It is not, however, essential that the stereodirecting substituent be the one appended by the organocopper reagent: in the case where substrate **12g** with a phenyl group at its distal *sp*-hybridized carbon is reacted with $(Me)_2Cu(CN)Li_2$, the 1,6 (*Z*) adduct still forms in 89% diastereomeric excess (Table 3, entry 4). The unique preference for (*E*) adduct formation using lithium thiophenoxide as nucleophile suggests the β-coordinating potential of the phenylthio group[69,70] may be sufficient to ensure *syn* protonation of the allenyl enolate (eq 12).



(12)

Observation and trapping of the requisite allenyl enolate intermediate confirms the experimental description of these reactions as 1,6 additions: when **12a** is reacted with $Me_2Cu(CN)Li_2$ at -78 °C, the carbonyl and both alkynyl carbon resonances of the ^{13}C NMR spectrum are found to disappear, with concomitant observation of four new sp^2-hybridized carbon and one *sp*-hybridized central allene carbon resonances.[54] Even more convincing is the isolation of allenyl enol triflates when N-phenyltriflimide is added subsequent to organocopper additions to alkenynone **12d** (eq 13). Such triflates are useful as allenyl enolate equivalents,[71] and can be exploited in any of the reactions of vinyl triflates.[72] Other ketones have been found to undergo 1,6 additions of organocopper reagents, including the 3-hexen-5-yn-2-one derivatives **16**.[52,73]



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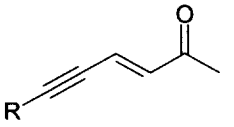
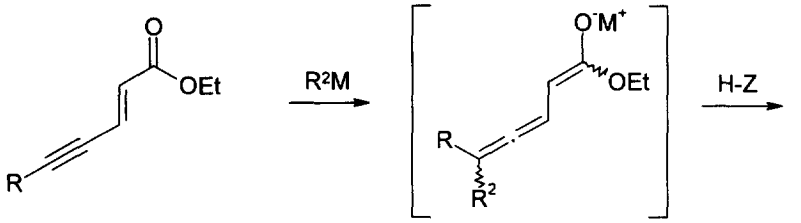


16a R = Ph
16b R = $(CH_3)_2C{=}CHCH_2CH_2$
16c R = *t*-Bu

16

Slower-reacting alkenynoates require higher temperatures (-20 - 0 °C, depending upon the identity of the organocopper species) for efficient 1,6 additions (eq 14 and Table 4).[52,62,73] Yields of 1,6 adducts are good and wide variation in substrate structure is possible. Sterically demanding esters (Table 4, entry 7), α,β-unsaturated analogs of which would not successfully undergo classical 1,4 additions of cuprates, provide routes to sterically

shielded allenes; ester **10**,[47] lactone **20**,[62] and dioxanone **21**[62,74] all provide 1,6 adducts as major products. 1,6 Additions of organolithium reagents are found to be particularly effective when 3-5 mol % of trimeric 2-(N,N-dimethylaminomethyl)phenylthiocopper(I)[75] is used as catalyst.[62]



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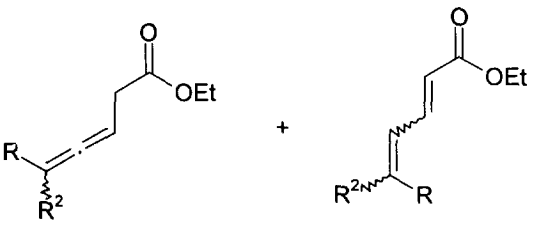
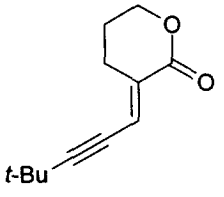
(14)



18 **19**

Table 4. Synthesis of Allenes and Dienes via eq 14.

	R	R^2M	R^2	H-Z	Yield **18**, %	Yield **19**, %
17a	Ph	$(Me)_2CuLi$	Me	2 N H_2SO_4	79	--
17b	*n*-Bu	$(Me)_2CuLi$	Me	2 N H_2SO_4	76	8
17b	*n*-Bu	$(Me)_2CuLi$	Me	*t*-$BuCO_2H$	71	--
17a	Ph	$(n\text{-Bu})_2Cu(CN)Li_2$	*n*-Bu	2 N H_2SO_4	49	12
17a	Ph	$(n\text{-Bu})_2Cu(CN)Li_2$	*n*-Bu	*t*-$BuCO_2H$	70	--
17b	*n*-Bu	$(Ph)_2CuLi$	Ph	2 N H_2SO_4	62	--
17a	Ph	$(t\text{-Bu})_2Cu(CN)Li_2$	*t*-Bu	2 N H_2SO_4	81	--
17c	*t*-Bu	$(t\text{-Bu})_2Cu(CN)Li_2$	*t*-Bu	2 N H_2SO_4	91	--



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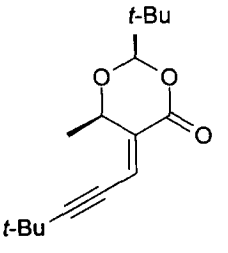


21

In a reaction not observed with other alkenynoates, *benzyl* ester (*E*)- **13g** undergoes an anomalous reduction[76] when reacted with methylcopper reagents (eq 15 and Table 5).[77] Deuterium labeling studies suggest the intermediacy of a dianionic species, **25**, perhaps formed via reductive elimination of a progenitor δ-copper(III)–allenyl enolate. The extent of reduction is influenced by the addition of ligating adjuvants to the cuprate: Lewis acidic TMSCl[78] promotes 1,6 addition, whereas Lewis basic $(n\text{-Bu})_3P$[79] promotes conjugate reduction. Moreover, the choice of organocopper reagent is important if reduction is to be observed. For instance, the use of $(Ph)_2Cu(CN)Li_2$ as nucleophile provides only 1,6 addition products. Finally, the isolation of isomerized starting material supports initial, reversible formation of a copper–π complex.[66]

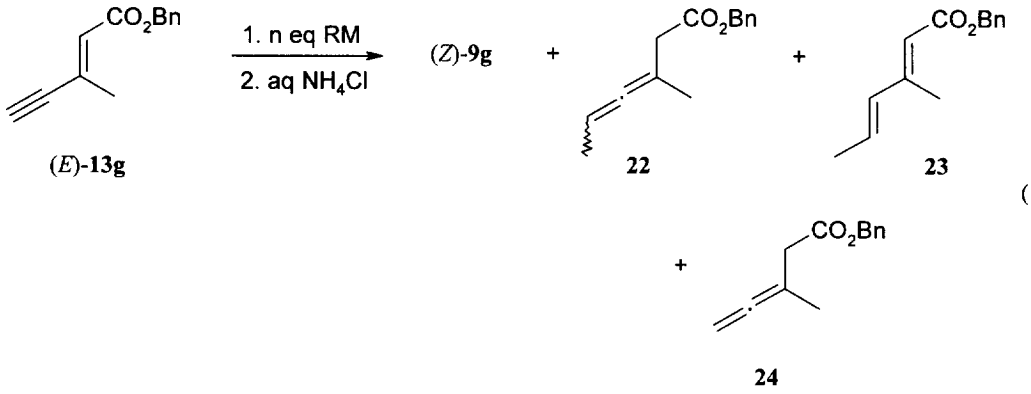
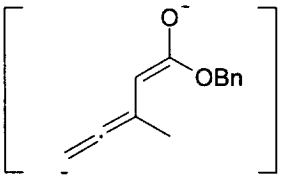


Table 5. Reactions of (*E*)-**13g** (eq 15).

			Yield, %		
RM	n	(*Z*)-**13g**	**22**	**23**	**24**
$(n\text{-Bu})_2Cu(CN)Li_2$	1.2	28	13		
$(Me)_2Cu(CN)Li_2 \cdot TMSCl$	5.0	20		60	
$(Me)_2CuLi \cdot P(n\text{-Bu})_3$	5.0	20			64
$(Ph)_2Cu(CN)Li_2$	5.0		41		

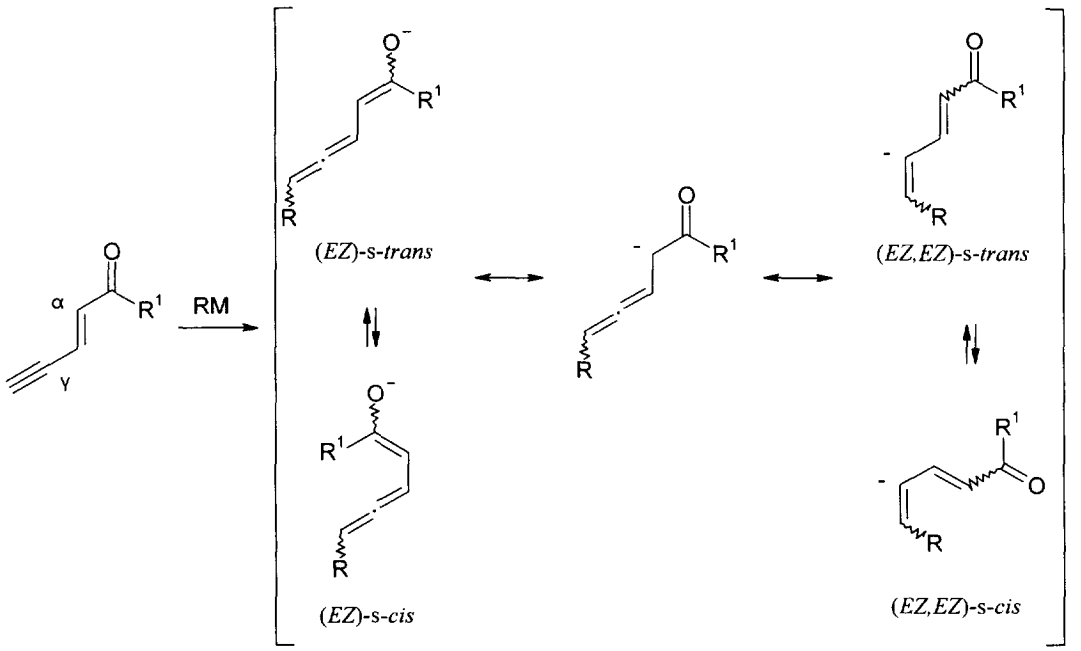


25

3. REACTION OF ALLENYL ENOLATES WITH ELECTROPHILES

3.1 *The ambident nature of allenyl enolates*

Allenyl enolates can be described as classic, ambident, delocalized anions: negative charge may be associated with the oxygen, α-carbon, or γ-carbon atoms (Scheme 5). As O anions, they may adopt (*E*) or (*Z*) enolate geometries; either may prefer an s-*trans* or s-*cis* enallene conformation. Similar considerations apply for the γ-C anion isomers. The stereogenic allene moiety consequently is epimerizable, which may reduce or eliminate any inherent stereofacial bias during reactions with electrophiles. Analogy would strongly suggest that allenyl enolates have nucleophilic properties and conformational preferences similar to those of dienolates, which typically undergo kinetically controlled reactions as α-C nucleophiles or O nucleophiles in the presence of soft or hard electrophiles, respectively.[80-82] In fact, the formally mixed hybridization state of allenyl enolates leads to unique and unanticipated regio- and stereoselectivities in reactions with electrophiles.

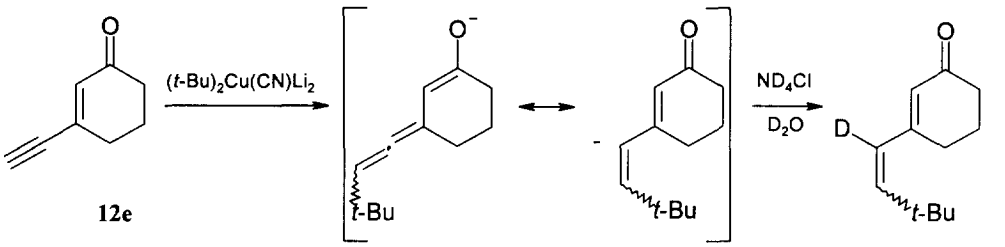


Scheme 5. O-, α-, andγ-Allenyl Enolate Resonance Isomers.

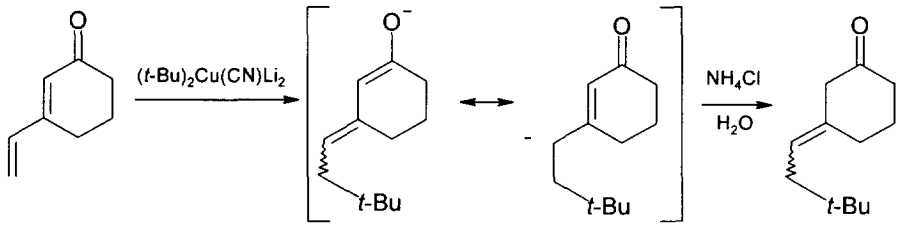
3.2 *Hydrogen electrophiles*

Using the conformationally locked (*E*)-s-*trans* allenyl enolate derived from addition of $(t\text{-Bu})_2\text{Cu(CN)Li}_2$ to ethynylcyclohexenone **12e**, deuterium quenching studies indicate regiospecific γdeuteration with no detectable α incorporation of label (eq 16). In contrast, the dienolate derived from 3-ethenyl-2-cyclohexenone is regiospecifically α deuterated, either directly or via enol-keto tautomerization (eq 17).[54,82,83] Thus, (*E*)-s-*trans* allenyl enolates formed from 1,6 additions of organocopper reagents to cycloalkenones **12** are nucleophilically reactive only at their *sp*-hybridized γ carbons in the presence of a proton source. As previously discussed,

protonation of the γ carbon occurs from the less sterically shielded face, reliably leading to an excess of (*Z*) adduct **15**.

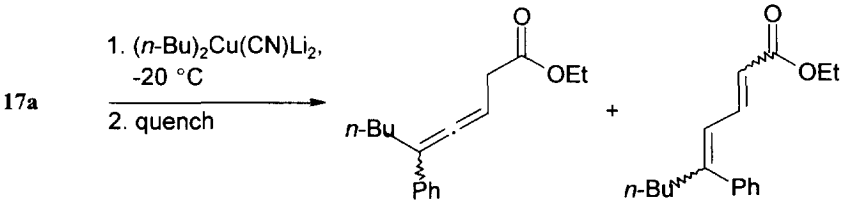


(16)



(17)

Conformationally labile acyclic allenyl enolates are more challenging: regioselectivity of protonation varies according to both structure of the allenyl enolate and proton donor reagent. Although NMR studies[66,81,84] of the 1,6 addition of $(t\text{-Bu})_2Cu(CN)Li_2$ to (*E*)-ethyl 6,6-dimethyl-2-hepten-4-ynoate in THF might predict formation of the corresponding *(E)*-s-*trans* allenyl enolate, in fact the (*Z*)-s-*trans* isomer forms predominantly.[85] Otherwise, this and similarly derived enolates appear to be well-described as O-bound metal enolates. When alkenynoates are used as substrates, there is a marked influence of the effective size, relative Lewis hardness, and acidity of the protonating agent on regioselectivity.[81] The 1,6 adduct enolate of ester **17a**, when quenched with excess 2 N H_2SO_4 at 25 °C, provides a mixture of α- and γ-protonated products. When the quench is performed at -80 °C using ca. 2 equiv. of pivalic acid followed by warming to room temperature, however, γ-protonation is strongly disfavored and only the α-protonated allenyl ester is found to form (eq 18).[52] When alkenynones are used as substrates, far less regioselectivity in protonation is observed regardless of quenching method. This may be due to the greater thermodynamic acidity of ketones relative to esters, enhancing equilibration to the conjugated dienone adduct via the progenitor enol.



(18)

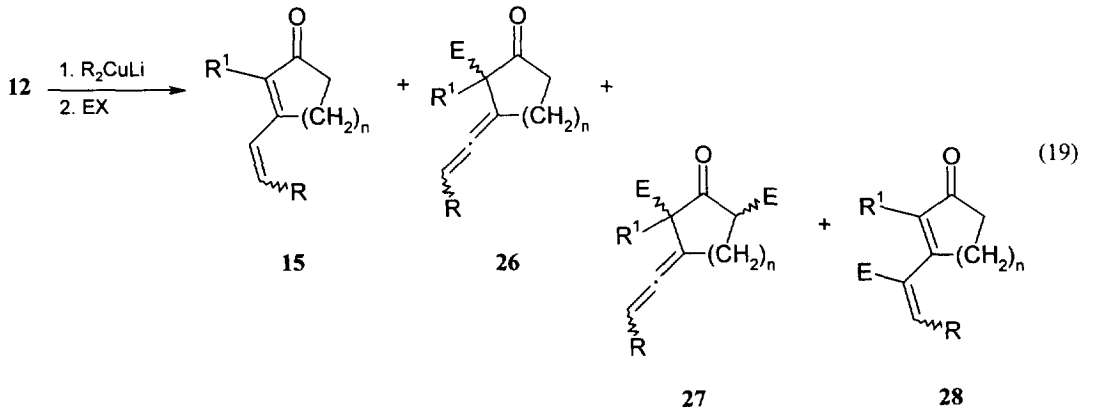
2 N H_2SO_4, 25 °C:	61%	4 : 1
pivalic acid, -80 °C:	70%	>99 : 1

3.3 *Carbon electrophiles*

Alkylations of enolates derived from conjugate additions of organocopper reagents can be difficult. The enolate appears to be relatively unreactive, and only excellent electrophiles, such as methyl iodide, allyl bromide, benzyl bromide, or carbonyl substrates normally provide efficient alkylation. Adjuvant, transmetallation, and enolate equivalent strategies can be employed to overcome this limitation.[7,8,17,20]

3.3.1 *Alkyl halides*. The regioselectivity of methylations of allenyl enolates derived from cycloalkenones **12** is determined by steric interactions that develop during a presumably late transition state. Ring size, ring substituents, and the bulkiness of the group appended during 1,6 addition are observed to exert influences (eq 19 and Table 6).[82,86] Addition of Me_2CuLi to cyclopentenone **12a** followed by MeI quench provides only γ,δ-dimethylated adducts, whereas the corresponding reaction of cyclohexenone **12d** provides a nearly 1:1 ratio of α,δ- and γ,δ-dimethylation. In the case of a five-membered ring, developing pseudo 1,3-diaxial interactions make α-methylation of the allenyl enolate unfavorable and the less sterically demanding γ-methylation dominates. In the six-membered ring, gauche and eclipsing interactions which develop during γ-methylation become approximately equivalent in energy to the pseudo 1,3-diaxial interactions devloped during α-methylation and a mixture of products is formed. The size of the α substituent therefore should be important, but only if it is conformationally significant. For this reason, the α:γ methylation ratio is similar for substrates **12d** and **12j**. Steric control as exhibited by ring size is reiterated when bulkier $(t\text{-Bu})_2CuLi$ is added to the alkenynones. The relative contribution of gauche and eclipsing interactions to hindering γ-methylation is enhanced in both five- and six-membered rings, so that α-methylation becomes more competitive, as indicated both by the increased α:γ methylation ratio for **12d** and the appearance of overmethylated adducts for **12a** and **12d**. Finally, when no α substituent is present as in substrate **12e**, α-methylation is clearly preferred in order to mitigate any guache interactions between the *t*-Bu and C4 methylene substituents of the ring which develop during γ-methylation.

Methylations of acyclic allenyl ester enolates are unsuccessful when MeI or BnBr are used as quenching agents; however, the very reactive electrophile MeOTf provides α-methylated adducts exclusively.[81,87] In these cases, regiochemistry is entirely insensitive to the steric environment of the allene moiety (eq 20). On the other hand, when allyl or propargyl bromide is used to quench the allenyl enolate, exclusive γ-alkylation is observed, and there is considerable sensitivity to the steric environment of the allene moiety during the reaction (eq 21).

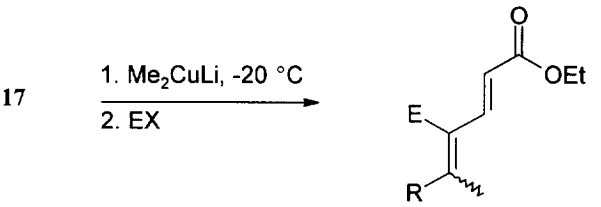


(19)

Table 6. 1,6 Addition–Enolate Trapping of **12** with MeI (eq 19).

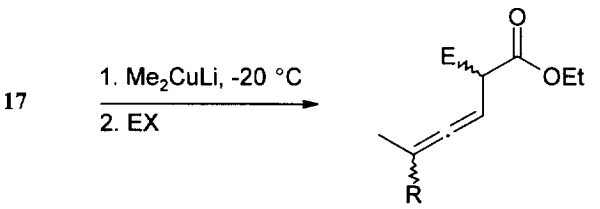
					Products, % (*Z* : *E*)			
	R^1	n	R	EX	**15**	**26**	**27**	**28**
12a	Me	1	Me	MeI				64 (2.3:1)
12a	Me	1	*t*-Bu	MeI			9[a]	34
12d	Me	2	Me	MeI		50		40 (1:3)
12e	H	2	*t*-Bu	MeI	42 (R^1=Me) (1:1)	20		20
12d	Me	2	*t*-Bu	MeI		51	20	29 (1:>99)
12j	PhS	2	Me	MeI		21		29 (2.5:1)

a. 2,2,5,5-tetramethyl adduct.



(20)

R = *n*-Bu, EX = CH_2=$CHCH_2Br$: 60%, 1:1 (*Z*:*E*)
R = *t*-Bu, EX = CH_2=$CHCH_2Br$: 80%, >99:1 (*Z*:*E*)



(21)

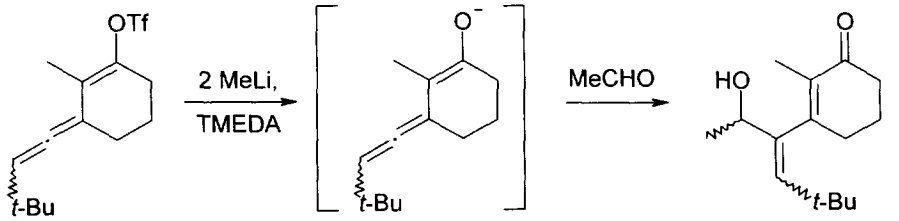
R = *n*-Bu, EX = MeOTf: 71%
R = *t*-Bu, EX = MeOTf: 51%

3.3.2 *Aldehydes, ketones, and acyl halides.* Although reversible, aldol-type enolate alkylations are facile compared to those using alkyl halides as eletrophiles. When *p*-tolualdehyde replaces MeI in eq 19, γ-aldol adducts are formed exclusively (Table 7).[82,88] Again, a strong preference for anti-addition of nucleophile and electrophile is observed. This stereochemical outcome often is obscured by the rapid equilibration of the stereoisomeric adducts, however. As seen before, the allenyl enolate intermediates appear to react as simple, O-bound metal enolates: when lithium enolate **29** is generated from its corresponding enol triflate and allowed to react with acetaldehyde, only the γ-aldol adduct is isolated (eq 22).[71] This compares very favorably with 1,6 addition of $Me_2Cu(CN)Li_2$ to **12d**, followed by addition of acetaldehyde, to result in a mixture of stereoismoeric γ-aldol adducts in 86% yield.[86]

Table 7. 1,6 Addition–Enolate Trapping of **12** with *p*-Tolualdehyde (eq 19).

	R^1	n	R	EX	**28**, % (*Z*:*E*)
12a	Me	1	Me	*p*-TolCHO	86 (1:27)
12a	Me	1	*t*-Bu	*p*-TolCHO	94[a]
12d	Me	2	*t*-Bu	*p*-TolCHO	95 (1:1)
12j	PhS	2	Me	*p*-TolCHO	27[a]

a. Facile equilibration of (*Z*) and (*E*) isomers.

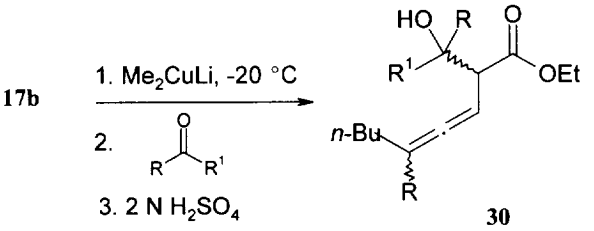


29 80%

(22)

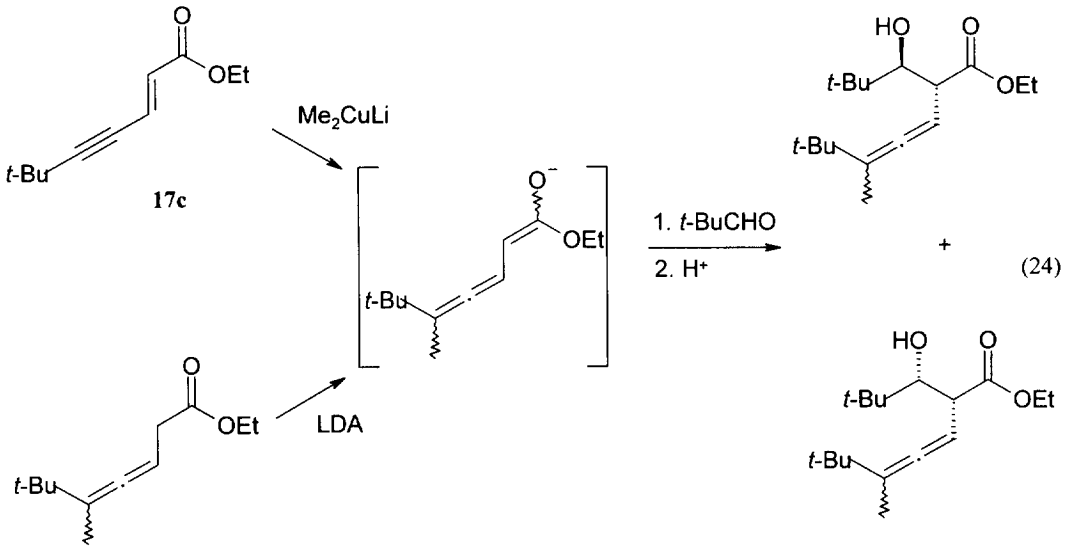
Strongly contrasting with the γ-selectivity of these conformationally restricted, cyclic allenyl enolates, acyclic allenyl ester enolates provide only α-aldol adducts **30** when reacted with benzaldehyde, pivalaldehyde, acryladehyde, or acetone (e.g. eq 23).[81] A study of the stereochemistry of this regiospecfic aldol condensation[85] indicates that the (*Z*)-s-*trans* allenyl enolates formed from 1,6 addition of copper reagents to (*RS,E*)-ethyl 6,6-dimethyl-2-hepten-4-ynoate in ether procede with moderate simple diastereoselectivity[89] via a non-Zimmerman-Traxler transisition state to provide anti adducts. Diastereofacial bias, however, is low. If the corresponding (*E*)-s-*trans* allenyl enolate is prepared from (*RS*)-ethyl 5,6,6-trimethyl-3,4-heptadienoate and LDA, syn adducts are isolated. Transmetalation of the (*E*)-enolate with $MgBr_2 \cdot Et_2O$ reverses simple diastereoselectivity, and

diastereofacial selection away from the bulkier *t*-Bu group of the allene moiety is enhanced (eq 24).



(23)

R = H, R^1 = Ph:	79%
R = H, R^1 = CH_2=CH:	53%
R = Me, R^1 = Me:	71%

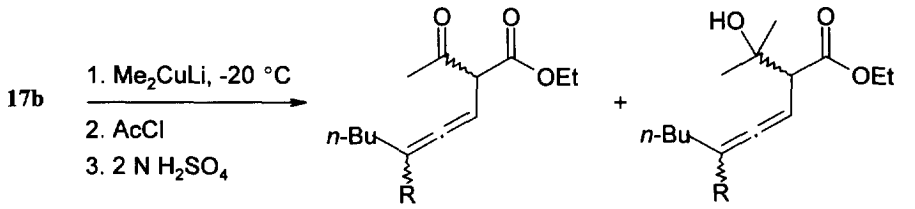


(24)

Allenyl enolate formation	anti : syn
1,6 addition of Me_2CuLi	6.7 : 1
LDA	1 : 1.9
LDA + $MgBr_2 \cdot Et_2O$	5.2 : 1

Like the γ-selectivity of cyclic allenyl enolates, the α-selectivity of these acyclic allenyl enolates is not mediated or particularly influenced by the presence of copper(I): when the lithium enolate of 6-methyl-4,5-decadien-2-one is generated from its corresponding trimethylsilyl enol ether[81,90] and allowed to react with allyl bromide, only the α-allyl adduct is isolated.

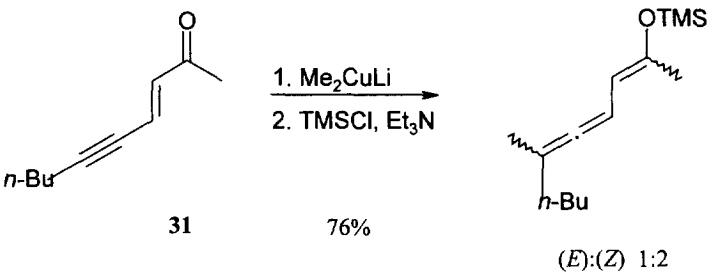
The outcomes of enolate acylations can be difficult to predict.[91] When AcCl is used to quench allenyl enolates, both cyclic and acyclic substrates yield only α-adducts;[81,82] β-diketones and β-keto esters are isolated. In the latter case, subsequent reaction of the adducts with excess organocopper reagent present in the reaction mixture leads to coproduction of acetone-aldol adducts (eq 25).[81]



(25)

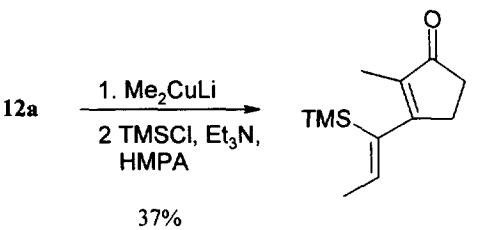
3.4 *Heteroatom electrophiles*

3.4.1 *Silyl halides, tin halides, and triflating reagents.* Only the hardest of electophiles–silyl halides and triflating reagents–appear to react at the oxygen atom of allenyl enolates. As implied above, the allenyl enolate from 1,6 addition of Me_2CuLi to ketone **31** can be trapped using TMSCl[52,92] (eq 26);[81] there is a preference for formation of the (*Z*) enol ether. On the other hand, a similar reaction of cyclopentenone derivative **12a** leads to a γ-trimethylsilyl adduct as the only silicon-containing product (eq 27);[86,93] the unique (*Z*) stereochemistry of this adduct may indicate alternative syn 1,2-carbometallation when reaction conditions for 1,6 addition are modified with TMSCl. Similarly, the softer electrophile $(n\text{-Bu})_3SnCl$[94] also provides only γ-adducts.[86]



31 76% (*E*):(*Z*) 1:2

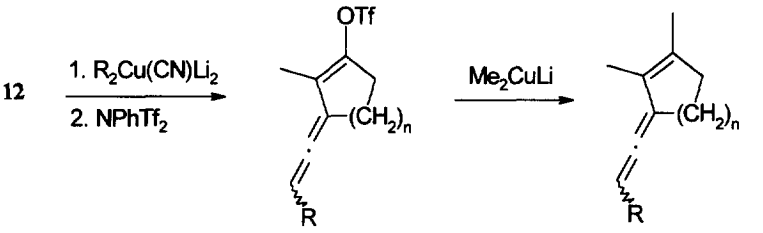
(26)



37%

(27)

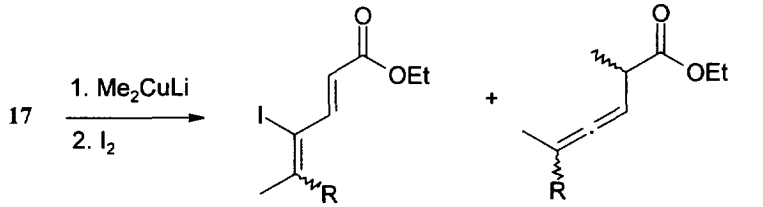
Very synthetically useful allenyl enol triflates[95] (e.g. eq 22) can be prepared in an analogous manner, using N-phenyltriflimide as electrophile. The acyclic enol triflate analogous to the silyl enol ether of eq 26 is, like many enol triflates, extremely sensitive to hydroysis. Those derived from the 3-ethynyl-2-cycloalkenone series, on the other hand, are more stable: they can be isolated chromatographically and stored neat temporarily or as hexane solutions for more prolonged periods. The reactivity of these triflates is similar to that of simple vinyl triflates (eq 28).[54]



(28)

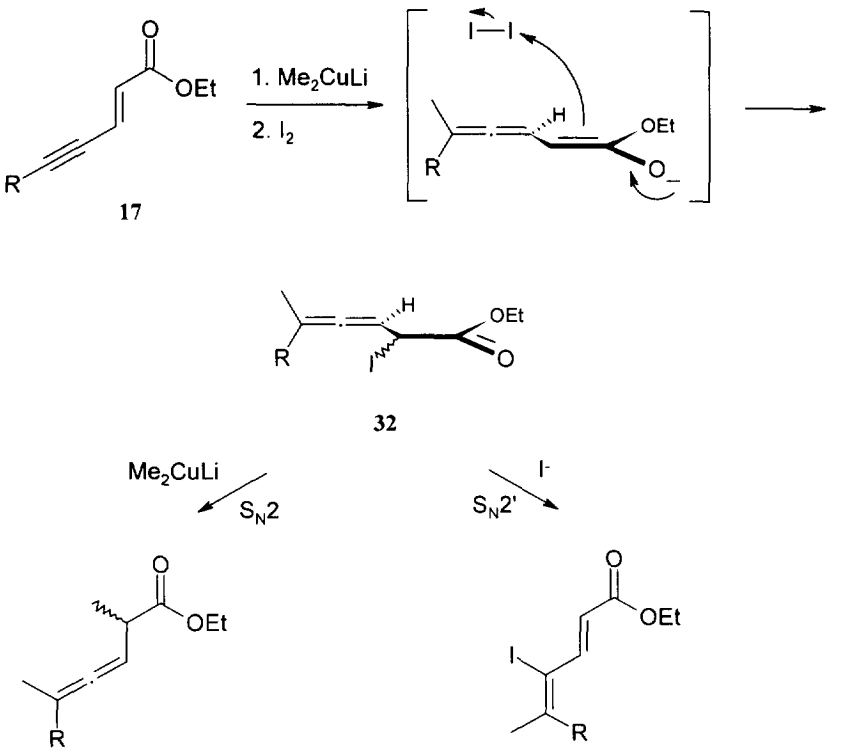
n = 1, R = *t*-Bu:	78%	
n = 2, R = Me:	85%	
n = 2, R = *n*-Bu:	79%	n = 2, R = *n*-Bu: 82%
n = 2, R = Ph:	50%	

3.4.2 *Halogens.* Iodine and bromine are quite soft electrophiles. When reacted with allenyl enolates derived from esters **17**, it is reasonable to anticipate a high α-selectivity. It is surprising at first glance, then, to discover that no α-iodo adducts are isolated when the allenyl enolate generated from 1,6 addition of Me_2CuLi to either **17b** or **17c** is quenched with I_2 (eq 29).[96] A reasonable mechanistic hypothesis for the observed products can be formulated based upon the following observations: (1) the ratio of γ-iodo and α-methyl adducts changes to favor the latter when a larger excess of Me_2CuLi is used or when the ligating agent $(n\text{-Bu})_3P$ is used; (2) no γ-iodo adduct forms with substrate **17c**, where R=*t*-Bu; and (3) when ester **17b** is reacted with Me_2CuLi prepared from CuI and is quenched with either Br_2, O_2, or $CuCl_2$, the γ-iodo adduct still forms. It is likely therefore that 1,6 addition–iodination does result in formation of a reactive, allyic α-iodo adduct (**32**, Scheme 6). This adduct suffers substitution of the α-iodo group by the excess Me_2CuLi present in the reaction, which is competitive with S_N2' reaction with nucleophilic iodide,[97] present as the initial counterion of the copper(I) salt used to prepare the cuprate, or formed during α-iodination using I_2. Steric hindrance to this latter substitution will be caused by bulky R groups on the allene, making direct substitution more favorable.



(29)

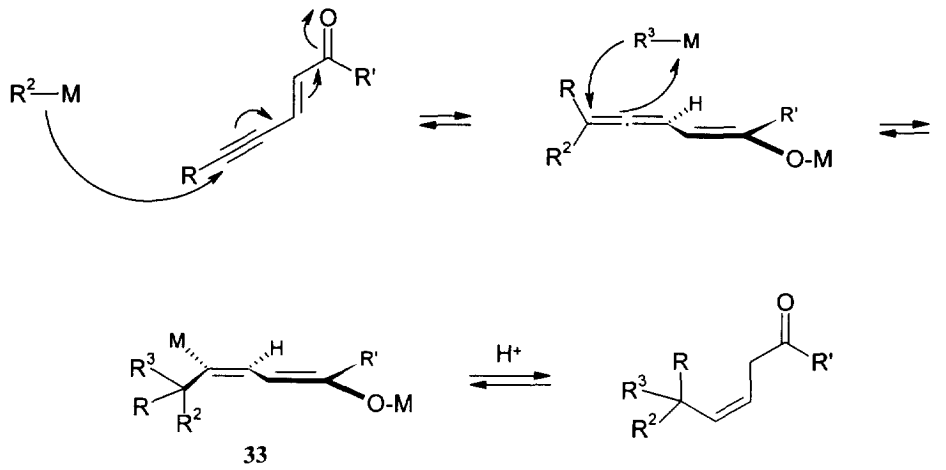
17b:	48% (2*E*,4*Z*):(2*E*,4*E*) 5:1	7%
17c:	---	70%



Scheme 6. Me_2CuLi 1,6 Addition–Iodination Reactions of **17**.

4. REACTION OF ALLENYL ENOLATES WITH NUCLEOPHILES

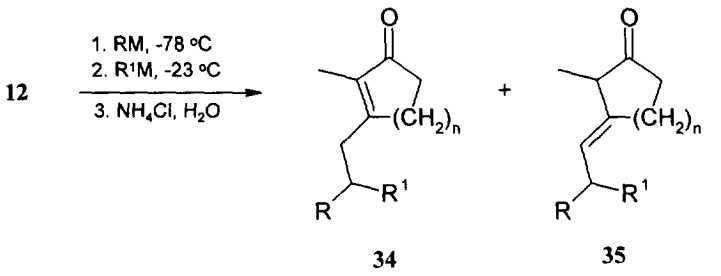
A cursory glance at the structural formula of an allenyl enolate is sufficient to imply the ambident nucleophilic character of these intermediates. Their Lewis structural resonance isomers suggest, and experiment confirms, that these vinylogous enolates may react as O, α-C, or γ-C nucelophiles in reactions with electrophiles. As allenes, however, these species also may exhibit *electrophilic* character. For example, allenes are known to undergo carbo- and silacuprations.[98,99] Moreover, the observed regioselectivity of these reactions indicates that addition of an organocopper reagent can be predicted to occur at the less substituted sp^2-hybridized carbon of an allene and distal to any electron donating group. The enolate moiety of an allenyl enolate certainly qualifies as an electron donating substituent with respect to the allene group; thus, it is not unreasonable to hypothesize a tandem 1,6 addition–5,6 addition sequence, which would result in a dianion adduct, **33** (Scheme 7). This dianion would have its formal negative charges in a favorable, orthogonal orientation, constituting a vinylog of known α-lithioenolates.[100]



33

Scheme 7. *gem*-Dialkylation via 1,6–5,6 Double Addition.

3-Ethynyl-2-cycloalkenones **12** are observed to undergo this tandem geminal double addition[86,101] (eq 30 and Table 8). While the initial 1,6 addition is facile, ocurring rapidly at -78 °C, the subsequent 5,6 addition is not observed unless the reaction is warmed to at least -30 °C. This temperature difference allows two different organocuprates to be added in sequence. Alternatively, a mixed homocuprate capable of transferring both[102] of its alkyl ligands can be used. Given the presence of RCu(CN)Li in the reaction milieu from initial 1,6 addition, the second nucleophile undergoing 5,6 addition need not be an organocopper reagent *per se*, as long as it is capable of forming a heterocuprate *in situ* at a rate competitive to that of addition. The order of addition, however, can influence the efficiency of the process: when possible, initial 1,6 addition of the smaller of the substituents to be appended minimizes steric interactions during subsequent 5,6 addition. NOE difference spectroscopy confirms that the double addition is (*E*) stereospecific,[86] although there is rapid isomerization of (*E*)-**35** to conjugated **34** when n=1. Allenyl enolates derived from cyclohexenone **12d** are considerably less reactive as electrophiles compared to those derived from cyclopentone **12a**. As in reactions of electrophiles with these allenyl enolates, in reactions with nucleophiles steric interactions developing in a presumably late transition state leading to the dianion determine the facility of reaction. Gauche interactions between the ethylidene and C4 methylene groups in the s-*trans* intermediate conformation and between the α-methyl and ethylidene groups in the alternative s-*cis* intermediate conformation together are considerably greater in the six-membered analog, retarding its formation. This effect is reiterated when the tandem, one-pot reaction is compared to functionally equivalent, two-pot sequential 1,6 addition. For instance, in side-by-side experiments, ketone **12a** can be reacted with $Me_2Cu(CN)Li_2$ according to eq 10 and 1,6 adduct **15a** (76%) isolated, then the adduct in turn reacted with $Ph_2Cu(CN)Li_2$ to provide **34** (R=Me, R^1=Ph, n=1) in 70% yield, for an overall two-step effective yield of 53% from **12a**. If the order of addition of Ph and Me substitutents is reversed, the overall yield decreases to 18%. Using the one-pot tandem reaction (entries 4 and 5, Table 8) of eq 30 provides the same overall yields. However, when two Me groups are added to ketone **12d** using the two-pot, sequential method, overall yield (step one, 80%; step two, 52%) of **35** (R,R1=Me, n=2) is 42%. The one-pot tandem reaction (entry 8, Table 8) provides the double addition adduct in 11% yield.



(30)

Table 8. Tandem Nucleophilic 1,6–5,6 Additions via eq 30.

	RM	R¹M	n	R	R¹	Yield, % 34	35
12a	$(Me)_2Cu(CN)Li_2$	$(Me)_2Cu(CN)Li_2$	1	Me	Me	50	
12a	$(Me)_2Cu(CN)Li_2$	$(PhMe_2Si)_2Cu(CN)Li_2$	1	Me	$PhMe_2Si$	42	
12a	$PhMe_2SiCu(CN)MeLi_2$		1	Me	$PhMe_2Si$	60	
12a	$PhCu(CN)MeLi_2$		1	Me	Ph	53	
12a	$(Ph)_2Cu(CN)Li_2$	MeLi	1	Ph	Me	20	
12a	$(Me)_2Cu(CN)Li_2$	PhLi	1	Me	Ph	38	
12a	$PhMe_2SiCu(CN)MeLi_2$	$PhMe_2SiLi$	1	Me	$PhMe_2Si$	21	
12d	$(Me)_2Cu(CN)Li_2$	$(Me)_2Cu(CN)Li_2$	2	Me	Me		11
12d	$(Me)_2Cu(CN)Li_2$	$(PhMe_2Si)_2Cu(CN)Li_2$	2	Me	$PhMe_2Si$		37
12d	$PhCu(CN)MeLi_2$		2	Me	Ph		7

5. CONCLUSION

Alkenynones and alkenynoates are functionally rich molecules that offer good potential for exploitation by the synthetic chemist using proven, reliable carbon-carbon bond-forming reactions. Ultimate reagent-derived regioselection for any mode of nucleophilic addition–1,2- 1,4- or 1,6–should provide routes for rapid elaboration of mixed hybridization state, conjugated systems.[87,103] In particular, the ambiphilic allenyl enolate products of 1,6 additions provide many unique features for synthetic exploitation: enantiodifferentiating conjugate addition[104] may lead to enantiomerically enriched allenes; conformational direction[105] of allenyl enolate reactions with electrophiles may allow effective regio- and stereochemical control elements to be designed into the original susbstrate, while reactions with nucleophiles suggest a host of convergent methods for new quaternary carbon syntheses, annulation, and bicycloannulation.[106]

6. ACKNOWLEDGEMENTS

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63. Representative procedure: A solution of 1.31 g (10.5 mmol) of methyl 2-hexynoate, 1.80 g (11.9 mmol) trimethylsilylethyne, and 30 mL of dry C_6H_6 was stirred under Ar as 45.8 mg (0.19 mmol) of $Pd(OAc)_2$ and 96.0 mg (0.19 mmol) of TTMPP were added sequentially. The reaction was stirred at room temperature for 16 h, after which time TLC (silica, 24:1 hexanes:Et_2O) indicated nearly complete reaction. Evaporation of the C_6H_6 by rotary evaporation was followed by flash chromatography to provide 2.12 g (90%) of ester **9d**: IR (thin film) 2960 (s), 2140 (w), 1720 (s), 1610 (s), 1150 (s), 860 (s), 760 (m) cm^{-1}; ^1H NMR δ 6.05 (t, 1H, *J*=0.6 Hz), 3.68 (s, 3H), 2.69 (t, 3H, *J*=8.5 Hz), 1.53 (m, 2H), 0.91 (t, 3H, *J*=6.8 Hz) 0.18 (s, 9H); MS (*m/z*) 224 (23), 209 (100), 193 (28), 151 (50), 120 (70), 105 (93), 89 (76), 73 (77). A sample was prepared for combustion analysis by desilylation using a suspension of KF in wet Et_2O with $Bn(Bu)_4NCl$ as a phase

transfer catalyst, followed by MPLC (silica, 40:1 hexanes:Et_2O): Anal. calcd for $C_9H_{12}O_2$: C, 71.03; H, 7.95. Found C, 70.91; H, 7.94.

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93. Representative procedure: A dry, Ar-purged 25 mL round bottom flask was charged with 40.8 mg (0.45 mmol) of CuCN and 3 mL Et_2O. Stirring was begun as the suspension was cooled to 0 °C and 720 μL (0.90 mmol) of a 1.25 M solution of MeLi in Et_2O added dropwise. Cooling to -78 °C was follwed by dropwsie addition of 35.8 mg (0.30 mmol) of **8a** in 2 mL Et_2O. After 1.5 h, the supernatant of a centrifuged mixture of 212 μL (5.0 mmol) TMSCl, 220 μL Et_3N, and 1 mL HMPA was added all at once. The reaction was left to stir overnight as it slowly warmed to room temperature. Dilution with 40 mL of hexanes was follwed by pouring the flask contents into 0 °C aq. satd. $NaHCO_3$. Extraction, separation, and washing of the organic phase once with 0 °C aq. satd. $NaHCO_3$ was followed by drying (Na_2SO_4); filtration and evaporation of the solvents gave the crude product, the IR spectrum of which contained no allene band. Preparative TLC (3:1 hexanes:Et_2O) gave 12.6 mg (37%) of a mixture of (*E*)- and (*Z*)-2-methyl-3-(1-methylpropenyl)-2-cyclopentenone and 23.1 mg (37%) of (*Z*)-2-methyl-3-(1-trimethylsilylpropenyl)-2-cyclopentenone. ^1H NMR δ 5.92 (q, 1H, *J*=6.2 Hz), 2.45 (br s, 4H), 1.56 (d, 3H, *J*=6.2 Hz), 1.54 (t, 3H, *J*=1.4 Hz), 0.08 (s, 9H). NOE difference spectroscopy established both regiochemistry and stereochemistry of silylation: upon irradiation of the δ 0.08 singlet, a substantial enhancement of the δ 1.56 doublet was observed.
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Martin Hulce received his B.S. in chemistry from Butler University in Indianapolis, Indiana in 1978. Graduate studies with Gary H. Posner at the Johns Hopkins University in Baltimore, Maryland led to M.A. and Ph.D. degrees in organic chemistry in 1980 and 1983, respectively. After two years as a research chemist in the Agricultural Chemicals Department of E.I. du Pont de Nemours and Co., Inc., in Wilmington, Delaware, he joined the faculty of the University of Maryland, Baltimore County, as an Assistant Professor of Chemistry and Biochemistry. In 1991, he joined the faculty of Creighton University, in Omaha, Nebraska, where he is an Associate Professor of Chemistry and Director of the Laboratory for Metaloorganic Chemistry. He is a recent recipient of the Robert F. Kennedy Memorial Student Award for Teaching Achievement.