Cumulenes

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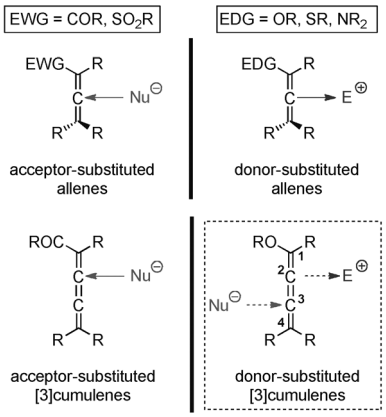
Ambivalent Reactivity Modes of β-Chlorovinyl Ketones: Electrophilic Lithium [3]Cumulenolates from Soft Vinyl Enolization Strategy**

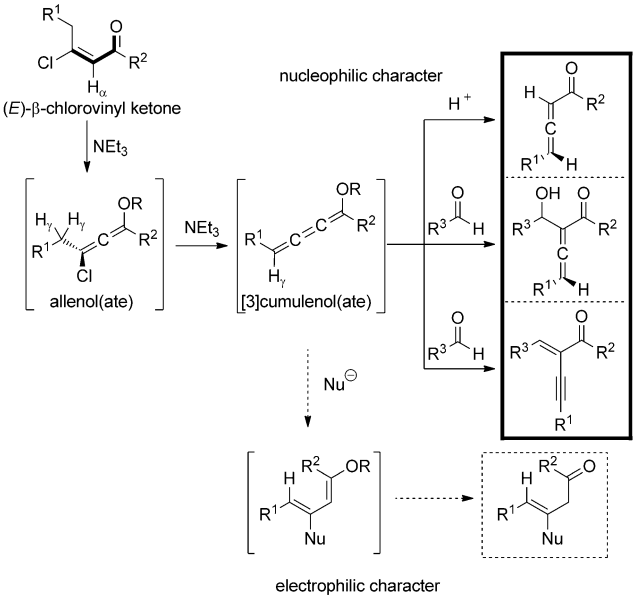
*Hun Young Kim, Edward Oscar Rooney, Raymond Phillip Meury, and Kyungsoo Oh**

The orthogonal arrangement of cumulated double bonds has attracted a great deal of attention from the scientific community since the first allene was prepared by Burton and von Pechmann in 1887.[1] The selection of substituents having a different electronic nature allows the ambivalent reactivity of allenes towards nucleophilic as well as electrophilic reagents with controlled regio- and stereoselectivity.[2,3] Thus, donor/acceptor-substituted allenes have emerged among the most versatile synthetic building blocks in the development of novel carbon–carbon bond-forming reactions (Scheme 1). In contrast, the reactivity behavior of [n]cumulene derivatives, compounds with three or more consecutive double bonds, has not been fully explored because of the difficulty associated with their preparation other than tetrasubstituted [3]cumulene derivatives.[4] While a limited number of acyl-substituted [3]cumulene derivatives are known to be stable[5] and subsequently utilized in the enyne cycloaddition,[6] palladium-catalyzed arylation,[7] Lewis acid catalyzed Diels–Alder reactions,[8] phosphine-[9] and silver-catalyzed [3+2] cycloaddition reactions,[10] the synthesis as well as synthetic utility of donor-substituted [3]cumulene derivatives have yet to be established.[11]



Scheme 1. Known and proposed reactivity patterns of functionalized allenes and [3]cumulenes.

Recently, we reported a facile α-vinyl enolization pathway of (*E*)-β-chlorovinyl ketones in which transient oxy-substituted [3]cumulene derivatives [i.e., cumulenol(ate)s] were postulated as nucleophilic species, reacting either with a protic source[12] or aldehydes[13] (Scheme 2). Drawn by the possibility of investigating the ambivalent reactivity modes of donor-substituted [3]cumulene derivatives, we envisioned a reaction of in situ generated [3]cumulene derivatives with nucleophiles. Herein, we report an electrophilic reactivity mode of oxy-substituted [3]cumulene derivatives in the syntheses of vinyl allenones and 3-methylenepyrrolidines with excellent stereoselectivities.



Scheme 2. Ambivalent reactivity modes of in situ generated oxy-substituted [3]cumulenes.

During the course of our investigation into the nucleophilicity of β-chlorovinyl ketones, we observed the formation of the aldol product **2a** as well as the vinyl allenone **3a** under the influence of lithium salts (Table 1).[13] While **3a** was obtained with a low yield of 15%, we were particularly encouraged by the fact that **3a**, a trisubstituted alkene, was formed stereoselectively. To optimize the formation of **3a**, we

[*] Dr. H. Y. Kim, E. O. Rooney, R. P. Meury, Prof. Dr. K. Oh
Department of Chemistry and Chemical Biology, Indiana University Purdue University Indianapolis (IUPUI)
Indianapolis, IN 46202 (USA)
E-mail: ohk@iupui.edu
Homepage: http://chem.iupui.edu/people/kyungsoo-oh

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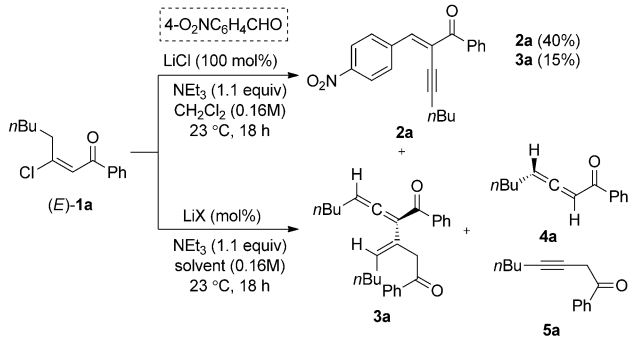
Table 1: Optimization of the vinyl allenone formation.[a]



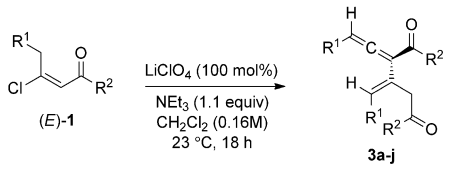
Entry	LiX (mol%)	Solvent	Yield [%][b]
1	LiCl (100)	CH_2Cl_2	20
2	LiBr (100)	CH_2Cl_2	10
3	LiOTf (100)	CH_2Cl_2	0
4	$LiClO_4$ (100)	CH_2Cl_2	65
5	$LiClO_4$ (100)	CH_3CN	50
6	$LiClO_4$ (100)	Et_2O	50
7	$LiClO_4$ (100)	THF	20
8	$LiClO_4$ (100)	$PhCH_3$	0
9[c]	$LiClO_4$ (100)	CH_2Cl_2	0
10	$LiClO_4$ (20)	CH_2Cl_2	5
11[d]	$LiClO_4$ (100)	CH_2Cl_2	n.r.
12	[e]	CH_2Cl_2	0

[a] Reaction conditions: (*E*)-**1a** (1.0 mmol), NEt_3 (1.1 mmol), LiX (1.0 mmol) in solvent (0.16 M) at 23 °C. [b] Yield of **3a** isolated after column chromatography (the remaining molecular mass balance accounts for a 2:1 mixture of **4a** and **5a**. [c] Reaction at −15 °C. [d] Reaction without NEt_3. [e] Reaction without lithium salt. n.r. = no reaction of (*E*)-**1a**. THF = tetrahydrofuran.

screened a number of different lithium sources and reaction parameters in the absence of an aldehyde. Upon treating (*E*)-**1a** with stoichiometric amounts of both NEt_3 and $LiClO_4$ at ambient temperature, the stereoselective formation of **3a** was obtained in 65% yield (entry 4). The use of other lithium salts was less satisfactory in promoting the vinyl allenone formation (entries 1–3), and the NEt_3-promoted elimination of (*E*)-**1a** predominated to give a mixture of allenyl and propargyl ketones (**4a**/**5a** = 2:1). Additional control experiments showed that while the stereoselective formation of **3a** could be effected in some coordinating solvents (entries 5–7), the employment of a lower reaction temperature (entry 9) as well as a catalytic amount of $LiClO_4$ (entry 10) primarily led to the formation of allenyl and propargyl ketones in greater than 90%.

The scope of vinyl allenone formation from (*E*)-β-chlorovinyl ketones was evaluated under the optimized reaction conditions (Table 2). The reaction was readily applicable to a range of aryl ketones. In general, full and clean reaction conversions were observed within 18 hours at ambient temperature without any isolable by-products, although the yields of the isolated products ranged between 61–78%.[14] The electronic and steric nature of aryl substituents of (*E*)-**1** showed little effect on the reaction outcome (entries 1–7). The subjection of (*E*)-**1h** and (*E*)-**1i**, having a functional group such as a halide (entry 8) and an ester (entry 9), respectively, also demonstrated the mild nature of

Table 2: Scope of the vinyl allenone formation.[a]

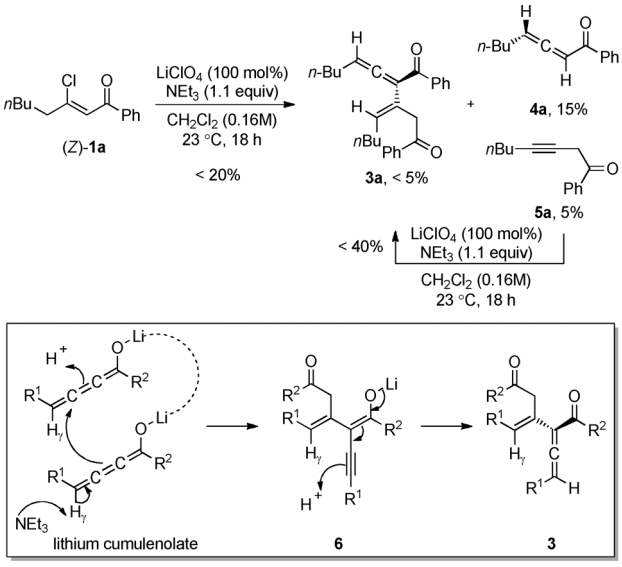


Entry	R^1	R^2	Yield [%][b]
1	*n*Bu	C_6H_4	**3a**: 65
2	$(CH_2)_8CH_3$	C_6H_4	**3b**: 68
3	*n*Bu	2-naphthyl	**3c**: 71
4	*n*Bu	3-MeC_6H_4	**3d**: 78
5	*n*Bu	4-MeC_6H_4	**3e**: 61
6	*n*Bu	4-$OMeC_6H_4$	**3f**: 72
7	*n*Bu	4-BrC_6H_4	**3g**: 70
8	$(CH_2)_3Cl$	C_6H_4	**3h**: 74
9	$(CH_2)_2CO_2Me$	C_6H_4	**3i**: 70
10	*n*Bu	Et	**3j**: 0[c]

[a] Reaction conditions: (*E*)-**1** (1.0 mmol), NEt_3 (1.1 mmol), $LiClO_4$ (1.0 mmol) in CH_2Cl_2 (0.16 M) at 23 °C. [b] Yield of **3** isolated after column chromatography. [c] A 5:1 mixture of allenyl and propargyl ketones was isolated in 68% yield.

our reaction conditions. However, no vinyl allenone was observed from (*E*)-**1j**; it only resulted in the formation of elimination products (entry 10).

To gain insights into the formation of the vinyl allenones, we performed additional control experiments using stereodefined β-chlorovinyl ketones as well as allenyl and propargyl ketones (Scheme 3). First, under the optimized reaction conditions, the reaction of (*Z*)-**1a** showed the formation of **3a** in less than 5% conversion along with 20% of the elimination products **4a** and **5a**, whereas the reaction of (*E*)-**1a** led to the exclusive formation of **3a** in greater than 95%. These results were very comparable to the rates of α-vinyl enolization of (*Z*)-**1a** and (*E*)-**1a** in the absence of a stoichiometric amount of $LiClO_4$,[12] thus suggesting little effect of the



Scheme 3. Proposed reaction mechanism for lithium-promoted vinyl allenone formation.

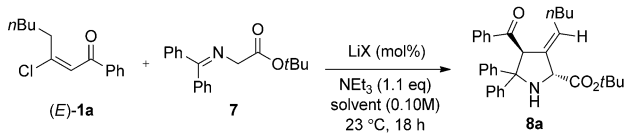
lithium salts for the NEt_3-promoted α-vinyl enolization. The different aptitudes of α-vinyl enolization between stereodefined β-chlorovinyl ketones are believed to be due to the planar *s-cis* conformation for (*Z*)-**1a** and the nonplanar *s-cis* conformation for (*E*)-**1a**. In addition, the preferential formation of the unconjugated propargyl ketone **5a** rather than its conjugated counterpart, alkynyl ketone, provides strong evidence for the α-vinyl enolization pathway of (*E*)-**1**.[12] Next, the formation of **3a** from **4a** and **5a** was examined. While the stereoselective formation of **3a** was observed upon subjecting a 2:1 mixture of **4a** and **5a** under our optimized reaction conditions, the inefficient formation of **3a** persisted under varied reaction conditions such as longer reaction time, higher reaction temperature, and varied amounts of $LiClO_4$ and NEt_3. Taken together, these observations lead us to conclude that while the direct α-vinyl enolization pathway of allenyl ketones to lithium cumulenolates is feasible, the process is not efficient under our reaction conditions.[15] Thus, the major pathway to vinyl allenones from (*E*)-**1a** should involve the lithium cumulenolates derived from the direct α-vinyl enolization pathway of (*E*)-**1a**. Based on our data, we propose a possible mechanism for the lithium-promoted vinyl allenone formation from (*E*)-β-chlorovinyl ketones which involves a vinylogous conjugate addition reaction of the [3]cumulenolates with subsequent alkyne–allene isomerization (**6**→**3**). The high stereoselectivity of a pendant alkene moiety in vinyl allenones suggests a closed transition state rather than an open transition state.[16]

The electrophilic behavior of lithium cumulenolates in our vinyl allenone formation is remarkable considering the fact that the titanium cumulenolates[13] and lithium cumulenolates[17] previously behaved as nucleophilic species. This unique reactivity of lithium cumulenolates can be favorably compared to the electrophilic behavior of allenyl ketones under Lewis acid catalysis.[18] Motivated by the observed electrophilic reactivity mode of lithium cumulenolates, we investigated intermolecular C–C bond formations between (*E*)-β-chlorovinyl ketones and nucleophilic species. Thus, upon subjecting a mixture of (*E*)-**1a** and the ketimine ester **7**[19] under stoichiometric amounts of both NEt_3 and lithium salts at ambient temperature, the stereoselective formation of the 3-methylenepyrrolidine **8a** was observed (Table 3). Our optimization efforts resulted in the single diastereomeric form of **8a** in greater than 95% yield in the presence of a catalytic amount of LiBr using CH_3CN as an optimal solvent (entry 8). Additional control experiments of the reaction also showed that the formation of **8a** could not be effected in the absence of either LiBr or NEt_3 (entries 9 and 10).

The scope of the 3-methylenepyrrolidine formation from the reaction of (*E*)-β-chlorovinyl ketones and a ketimine ester in the presence of lithium salts is illustrated in Table 4. The reaction was readily applicable to a range of aryl and alkyl ketones with excellent yields (87–99%). The electronic and steric nature of (*E*)-**1** showed little effect on the reaction (entries 1–8), and the reaction tolerated functional groups such as halide (entry 9), ester (entry 10), and phthalimide (entry 11).

While the stereoselective formation of **8** raises an interesting mechanistic issue between the concerted and the stepwise [3+2] cycloaddition pathways,[20] we were pleased to observe several conjugate addition products **9** which could be converted into **8** under the reaction conditions (Scheme 4).[21] Thus, it is likely that the formation of **8** is a stepwise process by the conjugate addition reaction of the ketimine ester **7** with lithium cumulenolates and susbsequent intramolecular Mannich-type cyclization.[22] In addition, the γ,γ-disubstituted-β-chlorovinyl ketone (*E*)-**1l** was also transformed into a formal [3+2] addition product in a one-pot fashion to give **8l** in 78% yield.[23] Our preliminary study also revealed the synthetic potential of the vinyl allenones **3** in the intermolecular Diels–Alder reaction, where highly functionalized cyclohexene derivatives **11** with a stereodefined exocyclic double bond had been stereoselectively constructed under mild reaction conditions.[24]

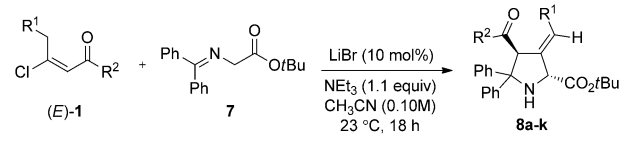
Table 3: Optimization of the 3-methylenepyrrolidine formation.[a]



Entry	LiX (mol%)	Solvent	Yield [%][b]
1	$LiClO_4$ (100)	CH_2Cl_2	0
2	LiOTf (100)	CH_2Cl_2	12
3	LiBr (100)	CH_2Cl_2	15
4	LiBr (100)	CH_3CN	95
5	LiBr (100)	Et_2O	50
6	LiBr (100)	THF	94
7	LiBr (100)	$PhCH_3$	36
8	LiBr (10)	CH_3CN	95
9[c]	–	CH_3CN	0
10[d]	LiBr (10)	CH_3CN	n.r.

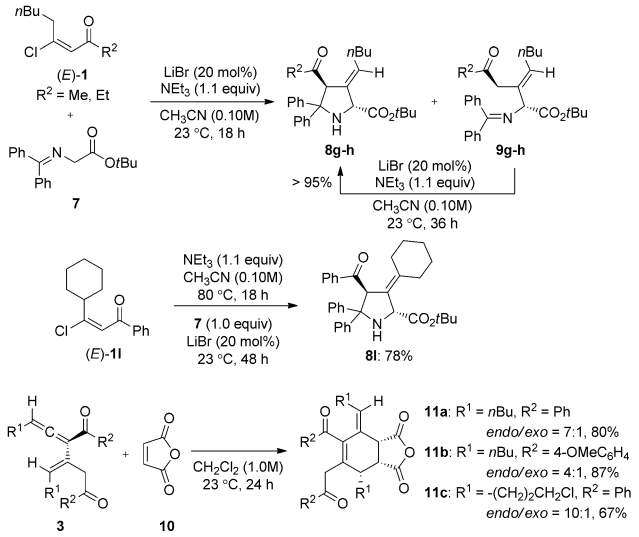
[a] Reaction conditions: (*E*)-**1a** (1.5 mmol), **7** (1.0 mmol), NEt_3 (1.1 mmol), LiX in solvents (0.10 M) at 23 °C. [b] Yield of **8a** isolated after column chromatography. [c] Reaction without lithium salt. [d] Reaction without NEt_3.

Table 4: Scope of the 3-methylenepyrrolidine formation.[a]



Entry	R^1	R^2	Yield [%][b]
1	*n*Bu	C_6H_4	**8a**: 95
2	*n*Bu	2-naphthyl	**8b**: 95
3	*n*Bu	4-MeC_6H_4	**8c**: 95
4	*n*Bu	4-$OMeC_6H_4$	**8d**: 95
5	*n*Bu	4-BrC_6H_4	**8e**: 95
6	*n*Bu	4-$NO_2C_6H_4$	**8f**: 97[c]
7[d]	*n*Bu	Me	**8g**: 93
8[d]	*n*Bu	Et	**8h**: 95
9	$(CH_2)_3Cl$	C_6H_4	**8i**: 87
10	$(CH_2)_2CO_2Me$	C_6H_4	**8j**: 99
11	phthalyl	C_6H_4	**8k**: 95

[a] Reaction conditions: (*E*)-**1a** (1.5 mmol), **7** (1.0 mmol), NEt_3 (1.1 mmol), LiBr (0.1 mmol) in CH_3CN (0.10 M) at 23 °C. [b] Yield of **8** isolated after column chromatography. [c] No purification. [d] Reaction using 20 mol% of LiBr in 36 h.



Scheme 4. Mechanistic rationale and synthetic application of vinyl allenones.

In summary, we have uncovered the electrophilic reactivity mode of oxy-substituted [3]cumulene derivatives, accessible by a soft vinyl enolization of (*E*)-β-chlorovinyl ketones. Complementary to the previously disclosed nucleophilic reactivity mode of (*E*)-β-chlorovinyl ketones,[13] the newly discovered electrophilic mode highlights the unique ambivalent nature of (*E*)-β-chlorovinyl ketones in the presence of different Lewis acids. While the reactivity modes of allenes are primarily controlled by donor and acceptor substituents, the reactivity modes of oxy-substituted [3]cumulenes can be modulated using different Lewis acids. Thus, the electrophilic reactivity of oxy-substituted [3]cumulenes presented herein readily allows stereoselective vinyl allenone formation in the presence of $LiClO_4$, whereas nucleophilic reagents, ketimine esters, attack the C3-position to provide formal [3+2] cycloaddition products in the presence of LiBr. We are currently extending the ambivalent reactivity of oxy-substituted [3]cumulenes to other C–C bond-forming reactions, and these results will be the subject of future publications.

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[14] In our previous deuterium-labeling studies, we observed that about 10% of the (*E*)-β-chlorovinyl ketones was decomposed by NEt_3 (1.1 equiv), displacing the β-chlorine atom of (*E*)-**1** through a conjugate addition/elimination process.[12]
[15] To further investigate the electrophilic species in the vinyl allenone formation, we subjected (*E*)- and (*Z*)-β-chloro-β-phenylvinyl ketones as well as different allenyl ketones and propargyl ketones in the reaction of (*E*)-**1**. While the formation of **3a** was observed in low yields (10–50%), we did not observe the formation of cross-products. We thank one of referees for suggesting the additional experiments.
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[21] In fact, most substrates in Table 4 can provide a mixture of the conjugate addition and cyclized products in varying degrees when the reaction is stopped early or employs (*E*)-**1** as a limiting reagent. Although the mixtures are not separable on column chromatography, the crude reaction mixture can be subjected to the intramolecular Mannich-type cyclization to give only cyclized products under basic conditions.[20c] For the NMR

spectra of the crude reaction mixtures obtained under unoptimized reaction conditions, see Supporting Information.

[22] While the subjection of a mixture of allenyl and propargyl ketones, instead of (*E*)-**1**, under our optimized reaction conditions leads to the formation of **8**, the yields of the isolated products remain low (40–60%) despite the use of a large excess of starting materials (3–10 equiv), and is due to the decomposition of the starting materials.

[23] The α-vinyl enolization of (*E*)-**11** to the corresponding [3]cumulenol requires a higher reaction temperature of 80°C.[12] The reaction mode of (*E*)-**11** should closely resemble a stepwise [3+2] cycloaddition of allenyl ketone under Lewis acid catalysis. Indeed, the reaction of isolated allenyl ketone from (*E*)-**11** displayed a similar reactivity pattern requiring a long reaction time, but no decomposition of starting material was observed.

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