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COMMUNICATION

Selectivity between an Alder-Ene Reaction and a [2+2] Cycloaddition in the Intramolecular Reactions of Allene-Tethered Arynes

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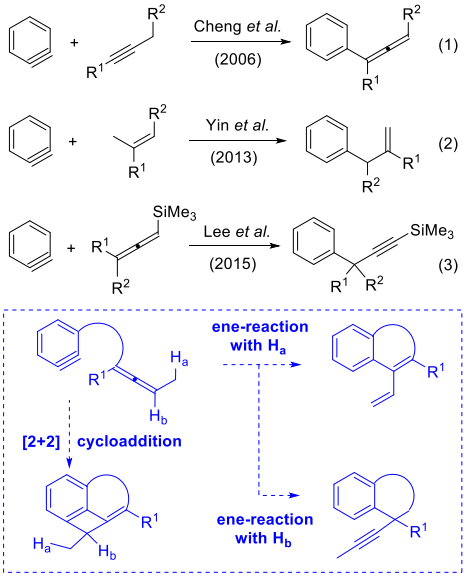
Substituent-dependent reactivity and selectivity in the intramolecular reactions of arynes tethered with an allene is described. With a 1,3-disubstituted allene moiety, an Alder-ene reaction of an allenic C–H bond is preferred over a [2 + 2] cycloaddition, whereas a [2+2] cycloaddition of the terminal π-bond of the allene is preferred with a 1,1-disubstituted allene. With a 1,1,3-trisubstituted allene-tethered aryne, an Alder-ene reaction with an allylic C–H bond is preferred over a [2 + 2] cycloaddition.

A wide variety of electron-deficient π-systems have been employed as an ene-acceptor either in thermal or Lewis acid-catalyzed conditions.[1] Due to the electrophilic nature of benzyne species,[2] they can behave as an efficient ene-acceptor[3] to react with ene-donors containing π-systems such as alkynes, alkenes, and allenes (Scheme 1). In 2006, Cheng reported intermolecular Alder-ene reactions between benzyne and terminal and internal alkynes (Eq 1),[4] and the corresponding reaction with alkenes was also reported by Yin in 2013 (Eq 2),[5] which was further extended to alkenes containing a polar functional group[6] by employing arynes generated from tetraynes via hexadehydro Diels-Alder reaction.[7] Recently, Lee and coworkers also explored the Alder ene reaction between benzyne and silylallenes (Eq 3).[8]

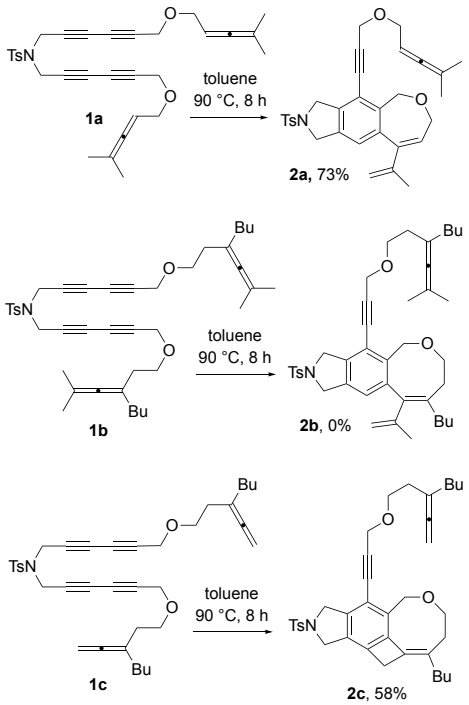
In 2011, Lautens and coworkers reported intramolecular Alder-ene reactions of arynes generated via a strong based-mediated elimination with aryl bromides.[9] Recently, Hoye[10] and Lee[11] reported the intramolecular Alder-ene reactions of arynes generated from tri- and tetraynes under thermal conditions. At this juncture, we want to further explore the scope and selectivity of the intramolecular Alder-ene reactions by accommodating an allene as the ene-donor (Eq 4).[12] The main concern in this intramolecular reaction would be the Alder-ene selectivity between the allylic and allenic C–H bonds, which is expected to mainly depend on the substituent pattern of the allene moiety. In this communication, we describe the reactivity and selectivity trend of intramolecular Alder-ene reactions that also compete with [2+2] cycloaddition of the terminal π-system of the allene.[13]



Scheme 1. Alder-ene reactions of arynes

First, we examined the Alder-ene reaction by using symmetrical tetraynes **1a–1c** (Scheme 2). The reaction of tetrayne **1a** that contains a three-atom tether with a *gem*-dimethylated allene[14] moiety (toluene, 90 °C, 8 h) afforded 7-membered ring Alder-ene product **2a** in 73% yield. On the other hand, tetrayne **1b** containing a four-atom tether with a tetrasubstituted allene moiety did not provide either Type-I or Type-II ene reaction product, instead decomposition of **1b** was observed. Under the identical conditions, however, substrate **1c** containing a terminal allene moiety afforded only the [2 + 2] cycloadduct engaging the terminal π-bond of the allene[15] to generate **2c** in 58% yield, and Alder-ene product was not observed.

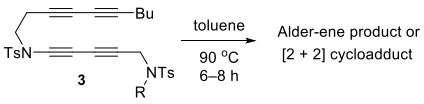
‡Electronic Supplementary Information (ESI) available. For detailed experimental procedure· ^{1}H and ^{13}C spectra see DOI: 10.1039/x0xx00000x

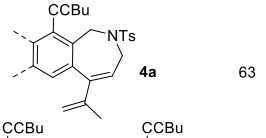
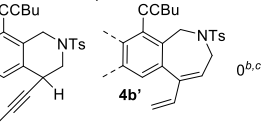
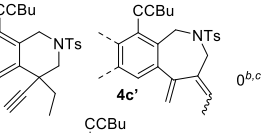
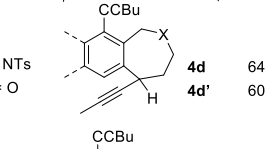
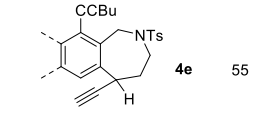
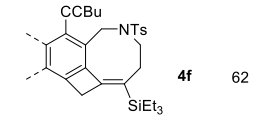
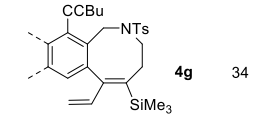
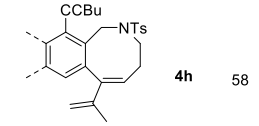


Scheme 2. Reactions of symmetrical tetraynes tethered with an allene moiety.

On the basis of the drastic change of the reaction modes depending on the substituent pattern in allenes, we further explored the general trend of the reactivity of unsymmetrical tetraynes **3a–3h** that contain structurally different allene moieties (Table 1). As expected, tetrayne **3a** bearing a three-atom tether with a *gem*-dimethyl allene moiety exclusively formed 7-membered Alder-ene product **4a** in 63% yield (entry 1). In stark contrast, tetrayne **3b** containing a 1,3-disubtituted allene[16] moiety results in decomposition of the starting material and neither Alder-ene product **4b** nor **4b'** of the allenic or allylic C–H bond was observed (entry 2). Substrate **3c** containing a 1,1-disubstituted terminal allene also decomposed without providing either Type-I or Type-II ene product **4c** or **4c'** (entry 3). Surprisingly, however, substrates **3d** and **3d'** containing a 1,3-disubtituted allene with an extra methylene exclusively engaged in the Alder-ene reaction with an allenic C–H bond[8] to afford **4d** and **4d'** in 64 and 60% yield, respectively (entries 4 and 5), and the Type-1 ene product of the corresponding allylic C–H bond was not observed. The reaction of the mono-substituted allene in **3e** induced the Type-I ene reaction of an allenic C–H bond to provide a terminal alkyne-containing product **4e** in 55% yield (entry 6). Substrate **3f** containing a 1,1-disubstituted terminal allene, which is identical with **3e** but containing a triethylsilyl group at the internal position of the allene

Table 1. Reactions of ynamide-tethered tetraynes tethered to different allene moieties



Entries	R	Product	Yield (%)[a]
1	**3a**	 **4a**	63
2	**3b**	 **4b** **4b'**	0[b,c]
3	**3c**	 **4c** **4c'**	0[b,c]
4	**3d**, X = NTs	 **4d**	64
5	**3d'**, X = O	**4d'**	60
6	**3e**	 **4e**	55
7	**3f**	 **4f**	62
8	**3g**	 **4g**	34
9	**3h**	 **4h**	58

[a]Isolated Yield. [b]Decomposition of starting material.
[c]Decomposition of starting material in toluene at 55 °C with 5 mol% of $AgSbF_6$.

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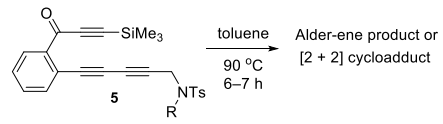
afford [2 + 2] cycloadduct **4f** in 62% yield and no Alder-ene product was observed (entry 7). Both substrates **3g** and **3h** containing a 1,1,3- or 1,3,3-trisubstituted allene[17] moiety, respectively, afforded the corresponding Type-I Alder-ene products **4g** and **4h** in 34 and 58% yield, respectively (entries 4 and 5).

These examples suggest that the preference for the formation of different modes of Alder-ene or [2 + 2] cycloaddition depends subtly on the substituents on the allene moiety and the length of the tether between the allene and the aryne. In general, Alder-ene reaction of an allylic C–H bond is most favorable with trisubstituted allenes (entries 1, 8 and 9) whereas that of an allenic C–H bond becomes more favorable with monosubstituted and 1,3-disubstitued allenes (entries 4–6). Alternatively, 1,1-disubstituted terminal allene induces [2 + 2] cycloaddition over an Alder-ene reaction (entry 7).

Next, we explored the reactivity of arynes generated from triynes **5a–5f** containing different allene moieties (Table 2). The reaction of triynes **5a** and **5b** bearing a *gem*-dimethyl-containing trisubstituted allene or a 1,3-disubstituted allene moiety led to only decomposition without generating the expected 7-membered ring Type-I Alder-ene product **6a** and **6b** (entries 1 and 2). On the other hand, triynes **5c** with a longer tether bearing a 1,3-disubstituted allene moiety provided Type-I ene product **6c** in 72% yield, where only an allenic C–H bond participated in the reaction (entry 3). As expected, substrate **5d** bearing a *gem*-dimethyl-containing trisubstituted allene provided an 8-membered ring Type-I Alder-ene product **6d** in 50% yield (entry 4). It is quite surprising to find that **5e** containing a 1,1-disubstituted terminal allene moiety did not participate in the expected [2+2] cycloaddition between the allene and aryne, instead the toluene moiety of NTs group participated in a Diels-Alder reaction to generate benzobarrelene[18] **6e**, where the allene moiety remains intact (entry 5). The preference of a Diels-Alder reaction is further demonstrated with triyne **5f** devoid of the allene moiety, which provided benzobarrelene **6f** in 58% yield (entry 6). Despite the identical allene moieties in tetraynes **3f** and triynes **5e**, their reaction outcomes are quite different, which strongly suggests that the reactivity of the putative aryne intermediates are intricately affected by multiple factors including the substituents on the aryne core moiety. In comparison, a *gem*-dimethyl allene-containing propiolated triynes **5g** exclusively provided Alder-ene reaction product **6g** in marginal yields (entry 7). The formation of product **6g** suggests that the hexadehydro Diels-Alder reaction of **5g** require higher activation barrier than the Alder-ene reaction between the alkyne moiety and the tethered allene segment. It was assumed that the low yield from this reaction is the consequence of the instability of the propiolate ester functionality at the elevated temperature. Indeed, when 1,3-diynyl propargyl alcohol **5h** was subjected to the identical conditions, the corresponding Alder-ene product **6h** was obtained in 62% yield (entry 8).

Having recognized the significant impact of the structure of the tether, alkynes and allene moiety, we employed various substrates that contain a 1,3-diyne (**7a–7f**) and monoynes (**7ga–7gd**) tethered with differently substituted allene moieties to further explore the selectivity between the Alder-ene and a [2+2] cycloaddition (Table 3). Upon heating (150 °C, toluene, 12 h), all 1,3-diyne-tethered allenes **7a–7f** provided [2 + 2] cycloadducts **8a–8f** in good yields (entries 1–6), whereas monoynes **7ga–7gd** only led to decomposition under the identical conditions (entries 7–10) and none of the expected [2 + 2] cycloadducts **8ga–8gd** were observed.

Table 2. Reactivity of benzene-tethered triynes containing different allene moieties



Entries	R	Product	Yield (%)[a]
1	**5a**	**6a**	0[b,c]
2	**5b**	**6b**	0[b,c]
3	**5c**	**6c**	72
4	**5d**	**6d**	50
5	**5e**	**6e**	34
6	**5f**	**6f**	58
7	**5g**, R =	**6g**	32[d]
8	**5h**, R = H	**6h**	

[a]Isolated yield. [b]Decomposition of starting material. [c]Decomposition of starting material in toluene at 55 °C with 5 mol% of $AgSbF_6$. [d]Reaction at 150 °C for 12 h.

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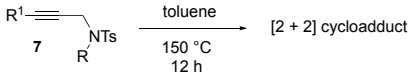
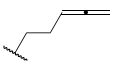
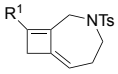
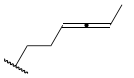
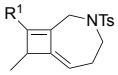
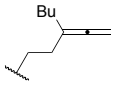
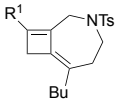
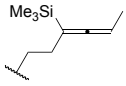
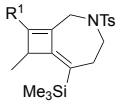
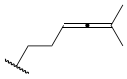
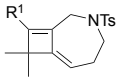
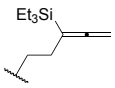
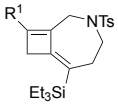
Table 3. Reactivity of sulfoamide-tethered alkyne containing different allene moieties

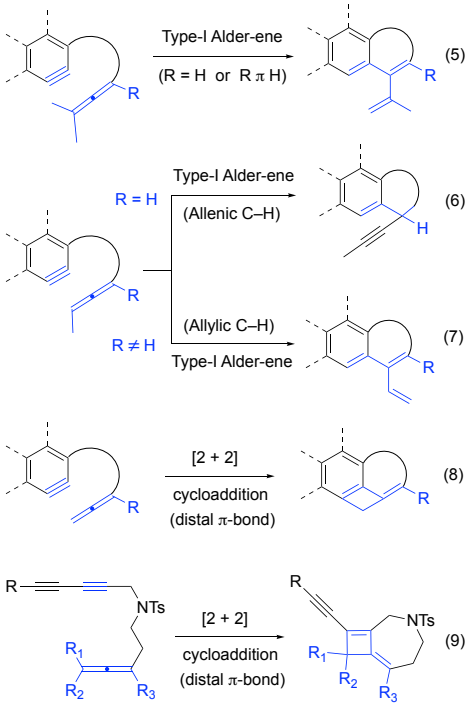


Entries	R	Product	Yield (%)[a]
1			82
	7a, R^1 = $CCSiEt_3$	**8a**	
2			85
	7b, R^1 = $CCSiEt_3$	**8b**	
3			80
	7c, R^1 = $CCSiEt_3$	**8c**	
4			78
	7d, R^1 = $CCSiEt_3$	**8d**	
5			65
	7e, R^1 = $CCSiEt_3$	**8e**	
			
6	**7f,** R^1 = $CCSiEt_3$	**8f**	78
7	**7ga,** R^1 = H	**8ga**	0[b]
8	**7gb,** R^1 = Br	**8gb**	0[b]
9	**7gc,** R^1 = Bu	**8gc**	0[b]
10	**7gd,** R^1 = Ph	**8gd**	0[b]

[a]Isolated yield. [b]Decomposition of starting material

It is worthy to note the activating role of the extra alkynyl substituent at the terminal position of the alkyne in these [2 + 2] cycloadditions.[19]

In summary, we have systematically investigated the intramolecular reaction between allenes and arynes by employing allene-tethered tetraynes and triynes as the aryne precursors. From the data accumulated in Scheme 2 and Tables 1–3, a general reactivity and selectivity trend has emerged (Scheme 3). Allenes containing *gem*-dimethyl group at the distal carbon exclusively participate in the Type-I ene reaction regardless of the substituent at the proximal carbon (Eq 5). 1,3-Disubstituted allene favorably participate in the Alder-ene reaction with an allenic C–H bond (Eq 6), whereas 1,1,3-trisubstituted allene prefers to generate the Alder-ene with an allylic–H bond (Eq 7). The reaction between a 1,1-disubstituted terminal allene and an aryne favor for a [2+2] cycloaddition (Eq 8). On the other hand, the reaction between 1,3-diyne and an allene moiety provide [2+2] cycloaddition product irrespective of the substituent pattern of the allene (Eq 9). This general reactivity trend would be a useful guide for further investigation of aryne chemistry involving allene counterparts.



Scheme 3. A general trend of selectivity in the intramolecular reaction of allenes with an aryne

Acknowledgment

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Notes and references

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