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Alder-Ene Reactions of Arynes

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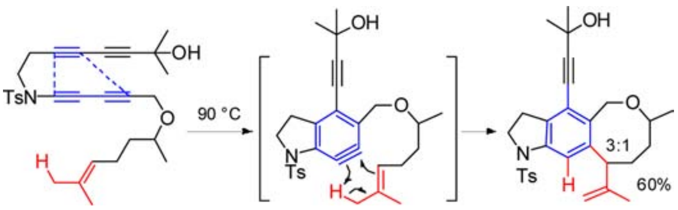
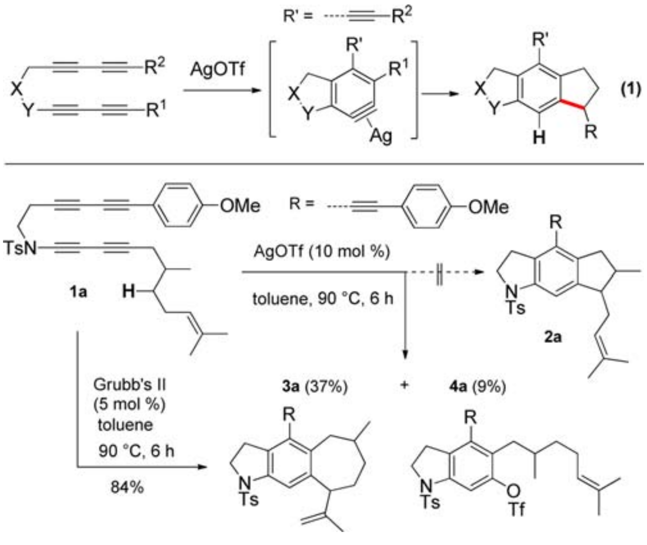
ABSTRACT



Efficient Alder-ene reactions of various arynes generated directly from bis-1,3-diynes are described. The reactivity of ene donors with different tethers was examined under thermal and metal-catalyzed conditions, which indicates that both the formation of aryne intermediates and their ene reactions are less sensitive to the catalyst than to the structural features of the substrates.

During the past decade, the chemistry of arynes has witnessed explosive resurgence[1] probably because of the availability of a relatively convenient method for their generation starting from 1-trimethylsilyl-2-aryl triflate under mild conditions.[2] Due to the low-lying of LUMO level relative to typical alkynes caused by distortion of the bond angles of the alkyne moiety,[3] arynes are highly reactive species that behave as an electrophilic reagent toward a variety of electron-rich species. Recently, we took advantage of the electrophilic nature of arynes for an effective alkane C–H bond functionalization and fluorination via their in situ generation directly from acyclic alkyne precursors[4] under silver-catalyzed condition (eq 1 in Scheme 1). While expanding the scope of this C–H functionalization reaction with various substrates, we examined the reactivity of bis-1,3-diyne substrate **1a** that contains an alkene moiety tethered to the 1,3-diyne subunit with a relatively long tether (Scheme 1). Under the typical conditions for C–H functionalization, however, the expected product **2a** was not formed, but only Alder-ene reaction product **3a** and triflate adduct **4a** were isolated in 37 and 9% yields, respectively. When the catalyst was changed to a Grubbs second-generation ruthenium complex, Alder-ene product **3a** was isolated in 84% yield as the sole product. With these initial observations, we decided

Scheme 1. Initial Unexpected Observations



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[1] (a) Reviews: (a) Dyke, A. M.; Hester, A. J.; Lloyd-Jones, G. C. *Synthesis* **2006**, 4093. (b) Sanz, R. *Org. Prep. Proced. Int.* **2008**, *40*, 215. (c) Chen, Y.; Larock, R. C. In *Modern Arylation Methods*; Akermann, L., Ed.; Wiley-VCH: Weinheim, Germany, 2009; pp 401–473. (d) Kitamura, T. *Aust. J. Chem.* **2010**, *63*, 987. (e) Tadross, P. M.; Stoltz, B. M. *Chem. Rev.* **2012**, *112*, 3550. (f) Gampe, C. M.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2012**, *51*, 3766. (g) Wu, C.; Shi, F. *Asian J. Org. Chem.* **2013**, *2*, 116.

[2] Himeshima, Y.; Sonoda, T.; Kobayashi, H. *Chem. Lett.* **1983**, 1211.

[3] Rodan, N. G.; Domelsmith, L. N.; Houk, K. N. *Tetrahedron Lett.* **1979**, *20*, 3237.

[4] For preliminary results, see: (a) Yun, S. Y.; Wang, K.-P.; Lee, N.-K.; Mamidipalli, P.; Lee, D. *J. Am. Chem. Soc.* **2013**, DOI: 10.1021/ja400477r. (b) Wang, K.-P.; Yun, S. Y.; Lee, D. *Abstracts of Papers*; 244th American Chemical Society Meeting, Philadelphia, PA; Washington, DC, 2012, ORGN 355.

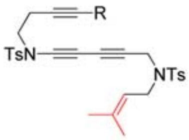
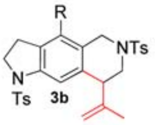
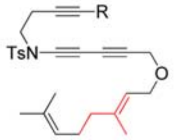
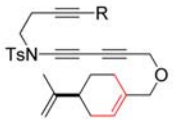
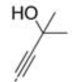
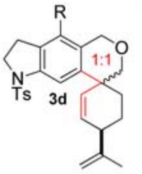
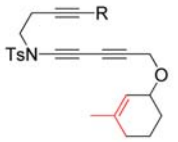
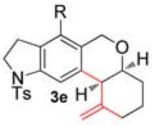
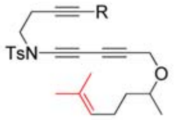
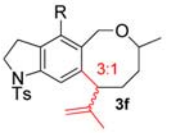
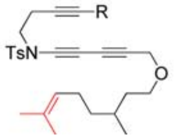
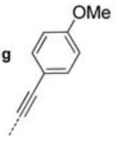
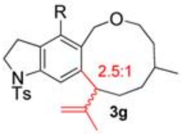
10.1021/ol4005905

to examine the relative reactivity of arynes toward C–H insertion vs Alder-ene reaction[5] with diverse bis-1,3-diyne substrates containing a tethered alkene moiety, and herein we report the general reaction profiles of the Alder-ene reaction of arynes[6] formed directly from bis-1,3-diynes.

First, we examined the Alder-ene reactions of unsymmetrical ynamide[7]-based substrates **1b**–**g** under different conditions with or without added silver triflate or Grubbs ruthenium complex (Table 1).[8] Substrates **1b** and **1c** that contain an ene donor prenyl or genranyl group tethered via either nitrogen or oxygen showed similar behavior to yield the expected cyclization products **3b** and **3c** (entries 1 and 2). Cyclic alkenes with different substituent patterns in substrates **1d** and **1e** did not affect the efficiency of the ene reaction, affording **3d** and **3e** in 90 and 94% yield, where the former is a mixture of diastereomers (1.3:1) but the latter is a single diastereomer (entries 3 and 4). Notably, the tertiary alcohol did not interfere with the ene reaction although potentially it can react with another aryne intermediate in an intermolecular manner. The effect of the tether sizes between the ene donor and the incipient aryne moiety was examined with substrates **1f** and **1g**. Surprisingly, their ene reactions to form 8- and 10-membered ring products **3f** and **3g** were still the major reaction pathway, providing **3f** and **3g** in 60 and 59% yields, respectively, as mixtures of diastereomers (entries 5 and 6). To the best of our knowledge, forming medium-sized rings via Alder-ene reaction with arynes is unprecedented.

The two different modes of initial cyclization to the respective aryne intermediates and their subsequent ene reaction are expected to be affected by the position of heteroatom (NTs) in the tether. The heteroatom effect in the tether was examined with substrates **1h**–**1j** (Scheme 2). Compared to the efficient ene reaction of **1h** to generate **3h** in 80% yield, that of **1i** and **1j** provided **3i** in only 49% yield and none of **3j**. This significant discrepancy can be explained by the mode selectivity of the hexadehydro Diels–Alder reaction[6l,9] in the first step. From **1h**, only a single aryne intermediate **I-1** was assumed to be generated, which then underwent a facile ene reaction to deliver **3h**, whereas from **1i** two intermediates **I-2** and **I-3** were generated where the former underwent ene reaction like **I-1** to afford **3h**, but the latter polymerized. Similarly, substrate **1j** led selectively to the formation of a wrong regioisomeric aryne intermediate **I-4**, which then polymerized, yielding no Alder-ene product. This conclusion is further supported by another reaction with **1k**, which also can undergo two different modes of initial aryne formation, but the

Table 1. Silver-Catalyzed and Thermal Ene Reaction of Putative Aryne Intermediates

entry	substrate	R	conditions[a]	product	yield (%)[b]
1	 **1b**		A		93
2	 **1c**		A B		65 73
3	 **1d**		B		90
4	 **1e**		B		94
5	 **1f**		B		60
6	 **1g**		B		59

[a] Conditions: **A**. AgOTf (5 mol %), toluene 90 °C, 6 h; **B**. Toluene 90 °C, 6 h. [b] Isolated yield after SiO$_2$ chromatography.

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(5) For a review on transition metal-catalyzed Alder ene reactions: (a) Trost, B. M.; Frederiksen, M. U.; Rudd, M. T. *Angew. Chem., Int. Ed.* **2005**, *44*, 6630. For general reviews on ene reactions: (b) Snider, B. B. *Acc. Chem. Res.* **1980**, *13*, 426. (c) Oppolzer, W. *Angew. Chem.* **1984**, *96*, 840. (d) Baird, M. S. *Top. Curr. Chem.* **1988**, 144. (e) Mikami, K.; Shimizu, M. *Chem. Rev.* **1992**, *92*, 1021. (f) Dias, L. C. *Curr. Org. Chem.* **2000**, *4*, 305.

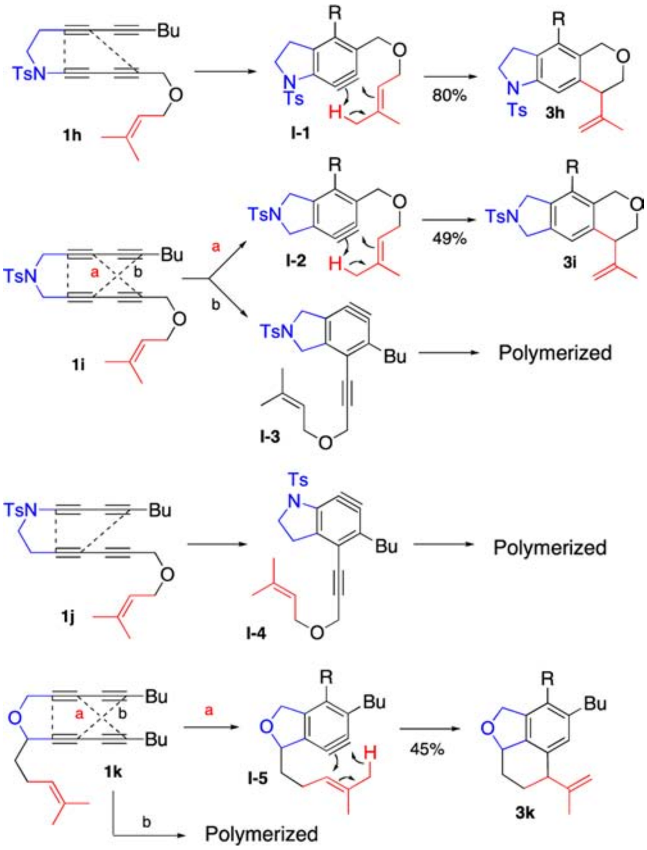
(6) Previous reports on the Alder-ene reactions with arynes: (a) Tabushi, I.; Okazaki, K.; Oda, R. *Tetrahedron* **1969**, *25*, 4401. (b) Ahlgren, G.; Akermark, B. *Tetrahedron Lett.* **1970**, *11*, 3047. (c) Wasserman, H. H.; Solodar, A. J.; Keller, L. S. *Tetrahedron Lett.* **1968**, *9*, 5597. (d) Friedman, L.; Osiewicz, R. J.; Rabideau, P. W. *Tetrahedron Lett.* **1968**, *9*, 5735. (e) Garsky, V.; Koster, D. F.; Arnold, R. T. *J. Am. Chem. Soc.* **1974**, *96*, 4207. (f) Wasserman, H. H.; Keller, L. S. *Tetrahedron Lett.* **1974**, *15*, 4355. (g) Crews, P.; Beard, J. *J. Org. Chem.* **1973**, *38*, 522. (g) Nakayama, J.; Yoshimura, K. *Tetrahedron Lett.* **1994**, *35*, 2709. (h) Aly, A. A.; Mohamed, N. K.; Hassan, A. A.; Mourad, A.-F. E. *Tetrahedron* **1999**, *55*, 1111. (i) Aly, A. A.; Shaker, R. M. *Tetrahedron Lett.* **2005**, *46*, 2679. (j) Candito, D. A.; Panteleev, J.; Lautens, M. *J. Am. Chem. Soc.* **2011**, *133*, 14200. (k) Candito, D. A.; Dobrovolsky, D.; Lautens, M. *J. Am. Chem. Soc.* **2012**, *134*, 15572. (l) Hoye, T. R.; Baire, B.; Niu, D.; Willoughby, P. H.; Woods, B. P. *Nature* **2012**, *490*, 208.

(7) A review on ynamide, see: (a) DeKorver, K. A.; Li, H.; Lohse, A. G.; Hayashi, R.; Lu, Z.; Zhang, Y.; Hsung, R. P. *Chem. Rev.* **2010**, *110*, 5064. (b) Evano, G.; Coste, A.; Jouvin, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 2840.

(8) A comparative study of the ene reaction with and without Grubbs catalyst indicates that the overall transformation does not require any metal catalyst, although the reaction rate with the catalyst seems to be slightly higher. See Supporting Information for details.

(9) (a) Meyerson, S.; Fields, E. K. *Tetrahedron Lett.* **1967**, *8*, 571. (b) Miyawaki, K.; Suzuki, R.; Kawano, T.; Ueda, I. *Tetrahedron Lett.* **1997**, *38*, 3943. (c) Bradley, A. Z.; Johnson, R. P. *J. Am. Chem. Soc.* **1997**, *119*, 9917. (d) Kociolek, M. G.; Johnson, R. P. *Tetrahedron Lett.* **1999**, *40*, 4141. (e) Kimura, H.; Torikai, K.; Miyawaki, K.; Ueda, I. *Chem. Lett.* **2008**, *37*, 662. (f) Tsui, J. A.; Sterenberg, B. T. *Organometallics* **2009**, *28*, 4906. (g) Ajaz, A.; Bradley, A. Z.; Burrell, R. C.; Li, W. H. H.; Daoust, K. J.; Bovee, L. B.; DiRico, K. J.; Johnson, R. P. *J. Org. Chem.* **2011**, *76*, 9320. (h) For a review on dehydro Diels–Alder reaction, see: Wessig, P.; Müller, G. *Chem. Rev.* **2008**, *108*, 2051.

Scheme 2. Mode Selectivity of Aryne Formation and Their Fates in Thermal Conditions (toluene, 90 °C, 6 h)



intermediate **I-5** generated via **Path-a** could undergo an Alder-ene reaction to deliver the final product **3k** in 45% yield. The other half of the material in **Path-b** was lost via polymerization.

Next, the ene reaction behaviors of symmetrical substrates **1l**–**s** were examined under the same respective conditions (Table 2). The geranyl- and neryl-substituted substrates **1l** and **1m** provided products **3l** and **3m** (entries 1 and 2). Similar to **3c** (entry 3 in Table 1), **3l** was obtained as a mixture of *E*/*Z*-isomers (2:1), but **3m** was isolated as a single isomer. As elegantly proposed by Lautens and coworkers,[6j,k] this contrasting outcome is the consequence of selective participation of the allylic C–H bonds on the carbon trans to the tether connecting the alkene to the incipient aryne moiety. Tetra-substituted cyclic alkene-tethered substrate **1n** afforded quantitatively a single regio- and stereoisomeric product **3n** that contains a newly formed all-carbon quaternary center (entry 3). Substrates **1o** and **1p** containing a tethered prenyl group as the ene donor yielded **3o** and **3p** in 95 and 70% yields, respectively (entries 4 and 5). It was expected that the *gem*-dimethyl group in **1p** would facilitate the ring closure,[10] but the heteroatom tether as in **1o** seems to have a greater beneficial effect. In line with this assumption, the *gem*-diester moiety in **1q** did show somewhat different reactivity compared to the corresponding heteroatom-tethered substrates, providing ene product **3q** in 87% yield but only at 120 °C rather than 90 °C under otherwise identical conditions (entry 6). Substrate **1r** containing a cyclic trisubstituted alkene connected to the 1,3-diyne moiety via an all-carbon tether afforded a tetracyclic product **3r** in 74% yield (entry 7). The relatively diminished yield for **3r** compared to that of **3n**/**3o** seems to be caused not only

Table 2. Alder-Ene Reactions of Arynes Generated from Symmetrical Substrates with and without Silver Catalyst

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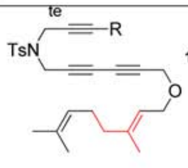
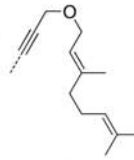
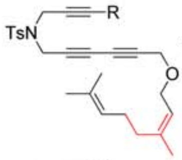
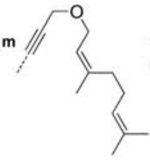
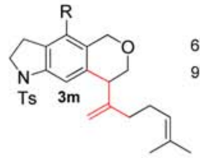
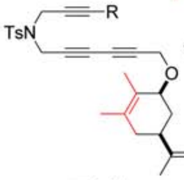
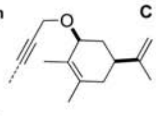
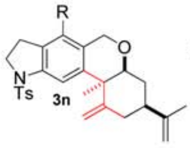
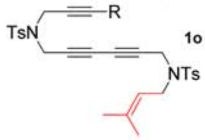
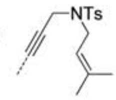
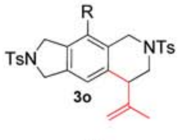
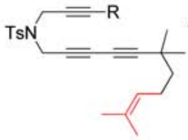
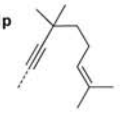
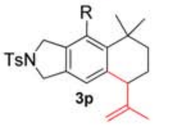
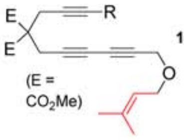
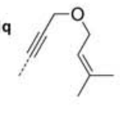
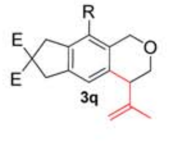
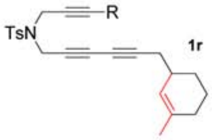
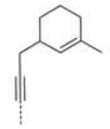
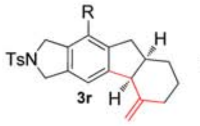
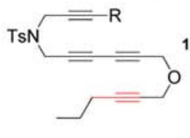
1	 1l		A C	 3l	87 75
2	 1m		A C	 3m	67 97
3	 1n		C	 3n	98
4	 1o		B	 3o	95
5	 1p		A C	 3p	62 70
6	 1q		C	 3q	87[c]
7	 1r		B	 3r	74
8	 1s		A C D	 3s	56 54 73

[a] Conditions: **A**. AgOTf (5 mol %), toluene, 90 °C, 6 h. **B**. Grubbs second-generation complex (5 mol %), toluene, 90 °C, 6 h. **C**. Toluene, 90 °C, 6 h. **D**. CH_3CN, 90 °C, 6 h. [b] Isolated yield after SiO_2 chromatography. [c] At 120 °C for 6 h in toluene.

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(10) Review on the *gem*-dialkyl effect: Jung, M. E.; Piizzi, G. *Chem. Rev.* **2005**, *105*, 1735.

by the formation of the incipient 5-membered ring instead of a 6-membered ring during the ene cyclization, but also by the all-carbon tether instead of NTs- or oxygen-based tether.[4b,11] Finally, substrate **1s** containing an alkyne[12] instead of an alkene as the ene donor could also undergo ene reaction to deliver allene **3s** but in only marginal yield in toluene with AgOTf catalyst or without the catalyst in 56 and 54% yield, respectively (entry 8). However, the yield of a thermal reaction was significantly improved up to 73% in CH_3CN.

In conclusion, we have developed an efficient intramolecular ene reaction of aryne intermediates that were generated directly from the corresponding acyclic alkyne building blocks. Among various reactivities of arynes, the ene reaction was demonstrated to be one of the most favorable reactions if suitable alkene ene donors are tethered to the incipient aryne moiety. The tether size that connects the ene donor to the 1,3-diyne moiety and substituent patterns on the alkene significantly affects the efficiency of the ring-closing ene process, but more importantly the heteroatom in the tether connecting the two 1,3-diynes or the alkene and the 1,3-diyne seem to have greatest impact on the reactivity of various substrates.

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Supporting Information Available. Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) During the hydrovinylative cyclization of bis-1,3-diynes, it was noticed that different heteroatoms in the tether confer profound impact on their reactivity, see: Yun, S. Y.; Wang, K.-P.; Kim, M.; Lee, D. *J. Am. Chem. Soc.* **2012**, *134*, 10783. Under these reaction conditions, NTs-containing bis-1,3-diynes did not readily participate in the hydrovinylative cyclization; instead they underwent hexadehydro Diels–Alder reaction to form arynes. An account of the aryne formation and their trapping with halogenated hydrocarbons will be described elsewhere.

(12) For examples of intermolecular ene reactions between arynes and terminal alkynes, see: Jayanth, T. T.; Jeganmohan, M.; Cheng, M.-J.; Chu, S.-Y.; Cheng, C.-H. *J. Am. Chem. Soc.* **2006**, *128*, 2232.

The authors declare no competing financial interest.