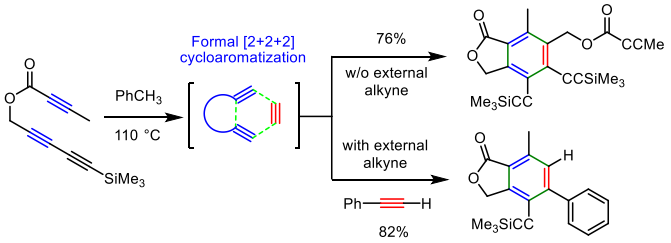
Selectivity in the Formal [2 + 2 + 2] Cycloaromatization of Enyne-Allenes Generated by the Alder-Ene Reaction from Triynes

Duy-Viet Vo, Yanshu Luo, Yuanzhi Xia*, and Daesung Lee*

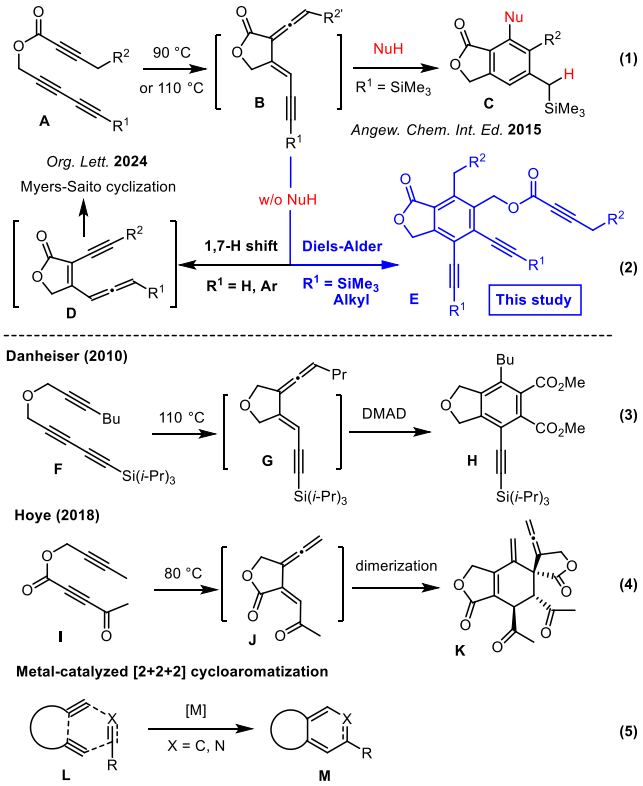
ABSTRACT: 1,3-Diynyl propiolates undergo the Alder-ene reaction to generate enyne-allenes, which participate in the Diels-Alder reaction to provide products of a formal [2 + 2 + 2] cycloaromatization of three alkynes. Without an external alkyne, the enyne-allene reacts with one of the alkyne moieties of the 1,3-diynyl propiolate, whereas external alkynes can be used to trap the enyne-allene to provide various arene products. The substituents on the dienophile alkynes have a profound impact on their reactivity. In this Diels-Alder reaction, 1,3-diynes display higher reactivity than monoynes, an excess amount (4–5 equiv) of external monoynes needs to be employed thus to get good product selectivity.



The arene skeleton is ubiquitous in natural products, pharmaceuticals, and functional molecules. Thus, numerous synthetic methods for their construction relying on the transition metal-catalyzed trimerization of alkynes have been reported.[1] The thermal [4 + 2] cycloaddition of 1,3-diyne and alkyne, the so-called hexadehydro Diels-Alder (HDDA) reaction, is a versatile method for synthesizing heteroatom-functionalize arenes.[2,3] While exploring HDDA reactions, we discovered a novel benzannulation reaction of an ester-tethered 1,3,8-triyne **A** (Scheme 1). Initially, we expected heating **A** would induce an HDDA reaction to form a benzyne intermediate, but the Alder-ene reaction[4-6] is more favorable to generate enyne-allene **B**. In the presence of nucleophiles, **B** could be trapped to yield **C** (eq 1).[7] If the 1,3-diyne moiety of **B** is terminal (R^1 = H) or aryl-substituted R^1 = aryl), **B** undergoes a formal 1,7-H shift to form an alternative enyne-allene **D**, which participates in the Myers-Saito cyclization[7,8] to provide final products via a diradical or zwitterionic intermediate. In contrast, if the substituent R^1 is a silyl or an alkyl group, a completely different reactivity of enyne-allene **B** was revealed. Upon heating **A** at 110 °C in toluene in the absence of nucleophiles, clean conversion of **A** occurred to give product **E**, which is the consequence of the Diels-Alder reaction between enyne-allene **B** and **A** (eq 2).

Danheiser reported a similar transformation whereby triyne **F** generates arene product **H** via enyne-allene **G** (eq 3).[9] In this reaction, electron-deficient external dienophiles were employed, and the dimerization product of type **E** was not observed.[10] In a related reaction, Hoye observed that the enallene **J** generated from **I** participated in a Diels-Alder dimerization to provide **K** (eq 4).[11] These reactions can be considered as a thermal equivalent of the metal-catalyzed reaction of the diyne **L** with external alkyne or alkene to generate the cycloaddition products **M**.

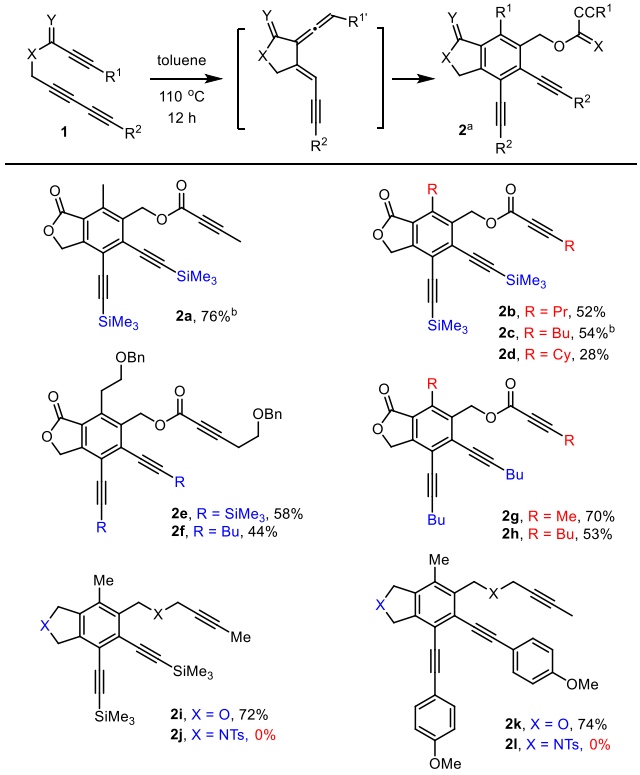
Scheme 1. Various reactivities of ene-allenes



Considering the favorable reactivity of enyne-allene **B** for a thermal cycloaddition, we explored its reactivity for a unique Diels-Alder reaction with the substrate **A**, and diverse external alkynes with steric and electronic variations factors to examine the scope and detailed mechanism for this reactivity. Herein, we report the reactivity and selectivity of the Diels-Alder reactions of triyne-based propiolate derivatives.

We commenced our exploration with 1,3-diynyl tetrolate **1a** in toluene under reflux, which led to the formation of dimer **2a** in 76% yield (Table 1). Changing the methyl group to bulkier groups such as propyl (**1b**), butyl (**1c**), and cyclohexyl (**1d**) groups decreased the yield of the corresponding products, yielding **2b** (52%), **2c** (54%), and **2d** (28%), respectively. Especially when a branched alkyl substituent at the propargylic carbon (**1d**), the yield of dimerization product (**2d**) drastically decreased. Substrates containing a benzyloxy group on the propiolate and a trimethylsilyl or butyl substituent on the 1,3-diyne moiety provided products **2e** (58%) and **2f** (44%) in moderate yields. Substrates with a butyl substituent on the 1,3-diyne moiety and a methyl (**1g**) or butyl (**1h**) group generated products **2g** (70%) and **2h** (53%). These results indicate that the bulky substituent on the allene moiety hinders the Diels-Alder reaction, lowering the efficiency of the reaction. On the other hand, substrates with a bulky trimethylsilyl group on the 1,3-diyne gave higher yields than those with a butyl group (**2e** vs. **2f** and **2g** vs. **2h**). Triynes containing an ether- or an *NTs*-tether displayed contrasting behaviors. The ether-tethered triynes containing trimethylsilyl (**1i**) or a 4-methoxyphenyl group (**1k**) provided good yields of products **2h** (72%) and **2k** (74%).[12] In contrast, the corresponding *NTs*-tethered triynes (**1j** and **1l**) did not give products **2j** and **2l** under identical conditions, and only the decomposition of the starting materials was observed. We surmise that this is the consequence of the steric interaction between the dienophile's propargylic NTs group and the enyne-allene moiety in the Diels-Alder transition state.[13]

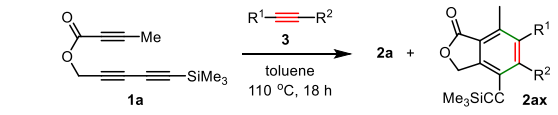
Table 1. Diels-Alder Dimerization of 1,3-diynyl propiolate derivatives via Alder-ene reaction



[a] Isolated yield. [b] The structures of dimers **2a** and **2c** were confirmed by the synthesis procedure provided in the Supporting information.

To gain further insight into the chemo- and regioselectivity of this Diels-Alder reaction, we explore the reactions of internal and terminal diynes (Table 2). The reaction of **1a** with sterically well-differentiated 1,3-diyne **3a** provided product **2aa** with a 72% yield (entry 1). Also, 1,3-diyne **3b**, which contains sterically less differentiated hydroxymethyl and butyl groups, provided high selectivity of single product **2ab** in 73% yield (entry 2). In contrast, the reaction of 1,3-diyne **3c** containing 4-methoxyphenyl group formed only dimer **2a** (69%) (entry 3). The reason for this lower dienophilicity of **3c** compared to **3a** and **3b** is not apparent. To compare the dienophilicity of 1,3-diyne and monoyne, triyne **3d** was employed, which provided a 1:2 mixture of **2a** and **2ad** with a 72% yield (entry 4). The reaction of monosubstituted 1,3-diyne **3e** selectively engaged the terminal alkyne moiety to provide **2ae** along with **2a** (90%, 4:1) (entry 6). This result indicates that the sterically less hindered terminal alkyne is more reactive than the internal alkyne of the 1,3-diynes. The higher reactivity of 1,3-diyne was further confirmed by a skipped diyne **3f**, which gave a 4:1 mixture (75%) of **2a** and **2af** even with 4 equivalents of **3f** (entry 6). The reaction of alkynes containing a branched propargylic alcohol **3g** gave only **2a** (entry 7), whereas the reaction with ketone **3h** led to the decomposition of the starting material (entry 8).

Table 2. Diels-Alder reaction of 1,3-diynyl tetrolate with external diynes



entry	alkyne (**3**)	product	yield (%)[a]
1	**a**, R = $SiMe_3$ (1.0 eq)	**2aa**	72
2	**b**, R = Bu (1.0 eq)	**2ab**	73
3	**c**, R = Ph-4-OMe (1.0 eq)	**2a**	69
4	**d** (1.0 eq)	**2a** + **2ad** (1:2)	72
5	**e** (1.0 eq)[b]	**2a** + **2ae** (1:4)	90
6	**f** (4.0 eq)	**2a** + **2af** (4:1)	75
7	**g**, X = H, OH (3 eq)	**2a** only	
8	**h**, X = O (5 eq)	decomposition	

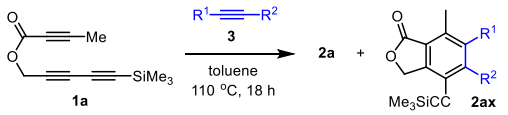
[a] Isolated yield.

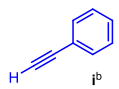
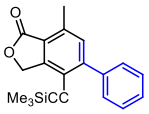
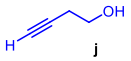
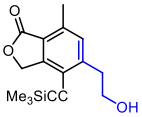
Considering the reactivity and selectivity trend of the Diels-Alder reaction between enyne-allenes and 1,3-diynes, we further examined the reaction profile of terminal and internal mono-ynes (Table 3). Because mono-ynes are less reactive than 1,3-diynes, the reactions employing lower stoichiometry of mono-ynes[14] generated a mixture of **2a** and the cross-Diels-Alder products. Thus, the reactions were carried out with super-stoichiometric amounts (up to 5

equivalents) of dienophile alkynes. The reaction of **1a** with phenylacetylene (**3i**) and 3-butyn-1-ol (**3j**) provided products **2ai** and **2aj** in 82% and 44% yields (entries 1 and 2). With trimethylsilyl acetylene (**3k**), a mixture of **2a:2ak** (70%) was obtained in a 1:1 ratio (entry 3). Similarly, the reaction of 2-methylbut-3-yne-2-ol (**3l**) gave **2a**:**2al** (82%) with a 1:1 ratio (entry 4). In contrast, the reaction with *t*-butyl acetylene (**3m**) provided only **2a** without any product of **3m** incorporation (entry 7). On the other hand, the reactions with propargylic alcohols **3n–3p**, with an internal alkyne moiety, regardless of the steric difference, provided only **2a**. Based on these observations, we concluded that, for mono-ynes, only the terminal alkynes could participate in the Diels-Alder reactions with enyne-allenes to generate the corresponding arene products. In addition, the reactivity of terminal alkynes depends differentially on the substituent's steric factor, so adjusting their stoichiometry can control the product distribution.

To gain insight into the selectivity of various Diels-Alder reaction manifolds, we conducted DFT calculations focusing on the reactivity of enyne-allene **IN1-1a** (generated from **1a** via the Alder ene reaction through **TS0-1a** with a barrier of 28.7 kcal/mol) (Scheme 2). Concerning the chemo- and regioselectivity of the Diels-Alder reaction of enyne-allene **IN1-1a**, we posit that the steric and electronic effects of the substituents on the diene and dienophile play a crucial role. We considered 3 alkyne dienophile components that interact with the enyne-allene **IN1-1a**, leading to 6 different transition states (**TS1–TS6**).[15] Among the three alkyne moieties in **1a**, the sterically least hindered C1–C2 alkyne most favorably participated in the reaction via **TS1-1a** (24.1 kcal/mol). Other transition states **TS2–TS6** involving C3–C4 and C5–C6 alkynes lead to the other isomers, including **2a-a** and **2a-b**, which have at least 2.4 kcal/mol higher energies than **TS1-1a**; thus, these isomers were not obtained.[16] The cycloaddition for the formation of **IN2-1a** is highly exergonic by 50.5 kcal/mol. Calculations showed that the aromatization of **IN2-1a** by a 1,5-H shift could be realized if a three-water cluster as in **TS7-1** is involved as a proton shuttle.[17,18]

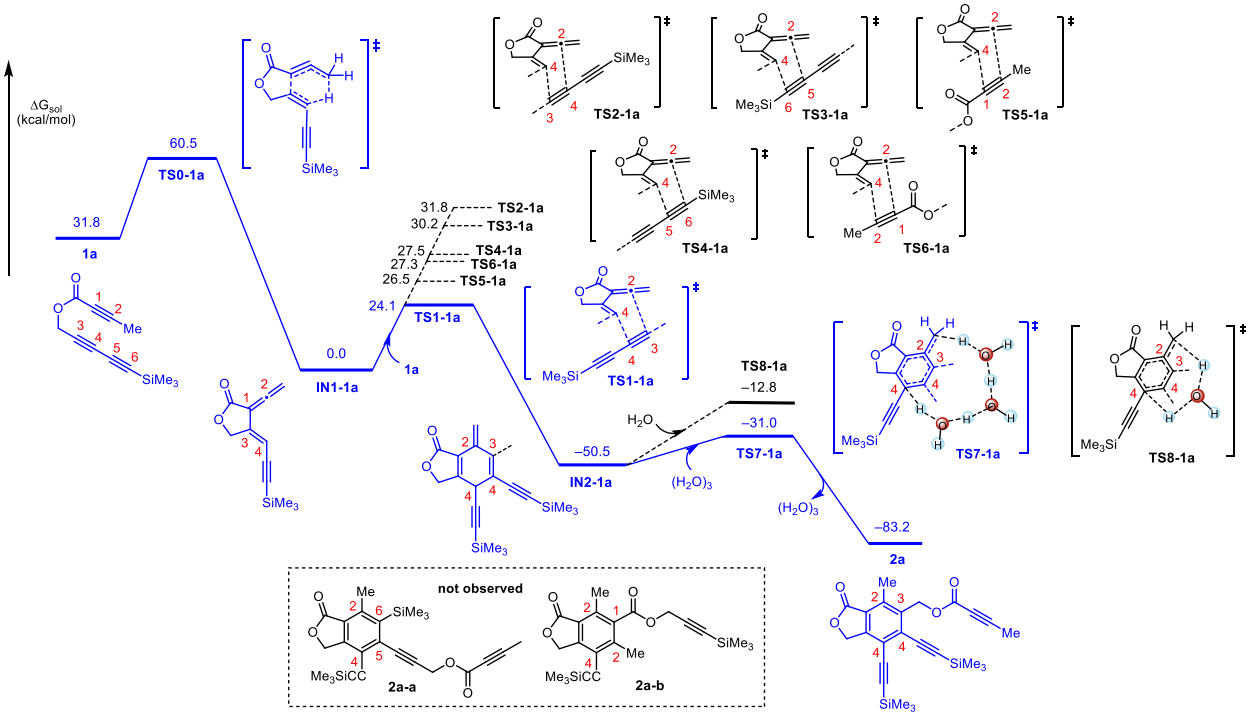
Table 3. Diels-Alder reactions of 1,3-diynyl tetrolate with external monoynes



entry	alkyne (**3**) (5 equiv)	product	yield (%)[a]
1	 **i**[b]	 **2ai**	82
2	 **j**	 **2aj**	44[c]
3	 **k**, R = TMS	 **2a:2ak** = 1:1	70
4	**l**, R = CMe_2OH	**2a:2al** = 1:1	82
5	**m**, R = *t*-Bu	**2a** only	–
6	 **n**, R = TMS	**2a** only	
7	**o**, R = Bpin	**2a** only	–
8	**p**, R = Bu	**2a** only	

[a]Isolated yield. [b]4 equivalents were employed. [c]Contaminated with a trace amount of regioisomer (9:1).

Scheme 2. DFT calculations for chemoselectivity and regioselectivity in the Diels-Alder reaction of enyne-allene **IN1-1a** (Optimization: B3LYP/6-31G(d); Solvation: M06/6-311+G(d,p))



In conclusion, we discovered new Diels-Alder heterodimerization of the enyne-allenes generated via the Alder-ene reaction of ester-tethered triynes. This dimerization process could be diverted by employing external alkynes to generate cross-Diels-Alder reaction products. In terms of the reactivity of alkyne dienophiles, terminal 1,3-diyne is more reactive than internal 1,3-diyne, which is more reactive than monoyne. In general, the reactivity of alkynes toward the enyne-allene counterpart critically depends on steric factors. However, the electronic effect of the substituent cannot be neglected. For example, the 1,3-diyne containing a 4-methoxyphenyl group (**3c**) is significantly less reactive than the corresponding 1,3-diynes substituted with trimethylsilyl (**3a**) or butyl (**3b**) group, this reactivity difference should result from an electronic rather than steric effect. These sequential bond-forming processes to generate the arene products can be considered formal [2+2+2] cycloaromatization, a thermal counterpart of the transition metal-catalyzed process.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

This material is available free of charge at http://pubs.acs.org

General information, Experimental details, Characterization data of substrates and products, References, 1H&13C NMR, nOe, HMQC, HMBC spectra, Computational details.

Accession codes

AUTHOR INFORMATION

Corresponding Author

*__Daesung Lee__ – Department of Chemistry, University of Illinois Chicago, 845 W. Taylor St., Chicago, Illinois 60607 (USA); orcid.org/0000-0003-3958-5475; Email: dsunglee@uic.edu

Yuanzhi Xia – College of Chemistry and Materials Engineering, Wenzhou University, 325035 Wenzhou, Zhejiang Province (P. R. China), orcid.org/0000-0003-2459-3296; Email: xiayz04@mails.ucas.ac.cn

Authors

Duy-Viet Vo – Department of Chemistry, University of Illinois Chicago, 845 W. Taylor St., Chicago, Illinois 60607 (USA), orcid.org/0000-0002-9268-6358.

Yanshu Luo – College of Chemistry and Materials Engineering, Wenzhou University, 325035 Wenzhou, Zhejiang Province (P. R. China)

Notes

The authors declare no competing financial interests.

ACKNOWLEDGMENT

We are grateful to NSF (CHE-2055055) and NSFC for financial support (21873074) for financial support. The Mass Spectrometry Laboratory at UIUC is acknowledged.

REFERENCES

(1) (a) Kotha, S.; Brahmachary, E.; Lahiri, K. Transition Metal Catalyzed [2+2+2] Cycloaddition and Application in Organic Synthesis. *European J. Org. Chem.* **2005**, 4741–4767. (b) Domínguez, G.; Pérez-Castells, J. Recent Advances in [2+2+2] Cycloaddition Reactions. *Chem. Soc. Rev.* **2011**, *40*, 3430. (c) Roglans, A.; Pla-Quintana, A.; Solà, M. Mechanistic Studies of Transition-Metal-Catalyzed [2 + 2 + 2] Cycloaddition Reactions. *Chem. Rev.* **2021**, *121*, 1894–1979.

(2) (a) Miyawaki, K.; Suzuki, R.; Kawano, T.; Ueda, I. Cycloaromatization of a Non-Conjugated Polyenyne System: Synthesis of 5H-Benzo[d]Fluoreno[3,2-b]Pyrans via Diradicals Generated from 1-[2-4-(2-alkoxymethylphenyl)butan-1,3-diynyl]Phenylpentan-2,4-Diyn-1-Ols and Trapping Evidence for the 1,2-Didehydrobenzene Diradical. *Tetrahedron Lett.* **1997**, *38*, 3943–3946. (b) Hoye, T. R.; Baire, B.; Niu, D.; Willoughby, P. H.; Woods, B. P. The Hexadehydro-Diels–Alder Reaction. *Nature* **2012**, *490*, 208–212. (c) Karmakar, R.; Ghorai, S.; Xia, Y.; Lee, D. Synthesis of Phenolic Compounds by Trapping Arynes with a Hydroxy Surrogate. *Molecules* **2015**, *20*, 15862–15880. (d) Karmakar, R.; Mamidipalli, P.; Salzman, R. M.; Hong, S.; Yun, S. Y.; Guo, W.; Xia, Y.; Lee, D. Benzannulation of Triynes Initiated by an Alder-Ene Reaction and Subsequent Trifluoromethylthiolate Addition. *Org. Lett.* **2016**, *18*, 3530–3533. (e) Meng, X.; Lv, S.; Cheng, D.; Hu, Q.; Ma, J.; Liu, B.; Hu, Y. Fused Multifunctionalized Chromenes from Tetraynes and α,β-unsaturated Aldehydes. *Chem. Eur. J.* **2017**, *23*, 6264–6271. (f) Karmakar, R.; Le, A.; Xie, P.; Xia, Y.; Lee, D. Reactivity of Arynes for Arene Dearomatization. *Org. Lett.* **2018**, *20*, 4168–4172. (g) Ghorai, S.; Lin, Y.; Xia, Y.; Wink, D. J.; Lee, D. Silver-Catalyzed Annulation of Arynes with Nitriles for Synthesis of Structurally Diverse Quinazolines. *Org. Lett.* **2020**, *22*, 626–630. Review: (h) Fluegel, L. L.; Hoye, T. R. Hexadehydro-Diels–Alder Reaction: Benzyne Generation via Cycloisomerization of Tethered Triynes. *Chem. Rev.* **2021**, *121*, 2413–2444.

(3) Mechanistic and theoretical studies of HDDA reaction: (a) Ajaz, A.; Bradley, A. Z.; Burrell, R. C.; Li, W. H. H.; Daoust, K. J.; Bovee, L. B.; DiRico, K. J.; Johnson, R. P. Concerted vs Stepwise Mechanisms in Dehydro-Diels–Alder Reactions. *J. Org. Chem.* **2011**, *76*, 9320–9328. (b) Willoughby, P. H.; Niu, D.; Wang, T.; Haj, M. K.; Cramer, C. J.; Hoye, T. R. Mechanism of the Reactions of Alcohols with *o*-Benzynes. *J. Am. Chem. Soc.* **2014**, *136*, 13657–13665. (c) Liang, Y.; Hong, X.; Yu, P.; Houk, K. N. Why Alkynyl Substituents Dramatically Accelerate Hexadehydro-Diels–Alder (HDDA) Reactions: Stepwise Mechanisms of HDDA Cycloadditions. *Org. Lett.* **2014**, *16*, 5702–5705. (d) Wang, T.; Niu, D.; Hoye, T. R. The Hexadehydro-Diels–Alder Cycloisomerization Reaction Proceeds by a Stepwise Mechanism. *J. Am. Chem. Soc.* **2016**, *138*, 7832–7835.

(4) For general reviews on ene reactions: (a) Hoffmann, H. M. R. The Ene Reaction. *Angew. Chem., Int. Ed.* **1969**, *8*, 556–577. (b) Mikami, K.; Shimizu, M. Asymmetric Ene Reactions in Organic Synthesis. *Chem. Rev.* **1992**, *92*, 1021–105. For a review on transition metal-catalyzed Alder-ene reactions: (c) Trost, B. M.; Frederiksen, M. U.; Rudd, M. T. Ruthenium-catalyzed Reactions—A Treasure Trove of Atom-economic Transformations. *Angew. Chem. Int. Ed.* **2005**, *44*, 6630–6666.

(5) Alder-ene reaction of allenes: (a) Dai, S.-H.; Dolbier, W. R., Jr. Allene-Perfluorocyclobutanone Ene Reaction. Kinetic

Isotope Effects. *J. Am. Chem. Soc.* **1972**, *94*, 3953–3954. (b) Brummond, K. M.; Chen, H.; Sill, P.; You, L. A Rhodium(I)-Catalyzed Formal Allenic Alder Ene Reaction for the Rapid and Stereoselective Assembly of Cross-Conjugated Trienes. *J. Am. Chem. Soc.* **2002**, *124*, 15186–15187. (c) Cheong, P. H.-Y.; Morganelli, P.; Luzung, M. R.; Houk, K. N.; Toste, F. D. Gold-Catalyzed Cycloisomerization of 1,5-Allenynes via Dual Activation of an Ene Reaction. *J. Am. Chem. Soc.* **2008**, *130*, 4517–4526. (d) Sabbasani, V. R.; Huang, G.; Xia, Y.; Lee, D. Facile Alder-Ene Reactions of Silylallenes Involving an Allenic C(Sp^2)–H Bond. *Chem. Eur. J.* **2015**, *21*, 17210–17214.

(6) Alder-ene reactions of arynes: (a) Tabushi, I.; Okazaki, K.; Oda, R. Relative Reactivities of Substituted Olefins toward Benzyne. *Tetrahedron* **1969**, *25*, 4401–4407. (b) Garsky, V.; Koster, D. F.; Arnold, R. T. Studies of the Stereochemistry and Mechanism of the Ene Reaction Using Specifically Deuterated Pinenes. *J. Am. Chem. Soc.* **1974**, *96*, 4207–4210. (c) 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. Ene Reaction of Arynes with Alkynes. *J. Am. Chem. Soc.* **2006**, *128*, 2232–2233. (d) Candito, D. A.; Panteleev, J.; Lautens, M. Intramolecular Aryne–Ene Reaction: Synthetic and Mechanistic Studies. *J. Am. Chem. Soc.* **2011**, *133*, 14200–14203. (e) Karmakar, R.; Mamidipalli, P.; Yun, S. Y.; Lee, D. Alder-Ene Reactions of Arynes. *Org. Lett.* **2013**, *15*, 1938–1941. (f) Gupta, S.; Xie, P.; Xia, Y.; Lee, D. Reactivity and Selectivity in the Intermolecular Alder–Ene Reactions of Arynes with Functionalized Alkenes. *Org. Lett.* **2017**, *19*, 5162–5165. (g) Gupta, S.; Lin, Y.; Xia, Y.; Wink, D. J.; Lee, D. Alder-Ene Reactions Driven by High Steric Strain and Bond Angle Distortion to Form Benzocyclobutenes. *Chem. Sci.* **2019**, *10*, 2212–2217. (h) Jones, C. R.; Yang, Y. The Aryne Ene Reaction. *Synthesis* **2022**, *54*, 5042–5054.

(7) (a) Karmakar, R.; Yun, S. Y.; Chen, J.; Xia, Y.; Lee, D. Benzannulation of Triynes to Generate Functionalized Arenes by Spontaneous Incorporation of Nucleophiles. *Angew. Chem. Int. Ed.* **2015**, *54*, 6582–6586. (b) Vo, D.-V.; Su, S.; Karmakar, R.; Lee, D. Reactivity of Enyne-Allenes Generated via an Alder-Ene Reaction. *Org. Lett.* **2024**, *26*, 1299–1303.

(8) (a) Myers, A. G.; Dragovich, P. S.; Kuo, E. Y. Studies on the Thermal Generation and Reactivity of a Class of (.Sigma.,.Pi.)-1,4-Biradicals. *J. Am. Chem. Soc.* **1992**, *114*, 9369–9386. (b) Musch, P. W.; Remenyi, C.; Helten, H.; Engels, B. On the Regioselectivity of the Cyclization of Enyne–Ketenes: A Computational Investigation and Comparison with the Myers-Saito and Schmittel Reaction. *J. Am. Chem. Soc.* **2002**, *124*, 1823–1828. (c) Cremeens, M. E.; Hughes, T. S.; Carpenter, B. K. Mechanistic Studies on the Cyclization of (*Z*)-1,2,4-Heptatrien-6-Yne in Methanol: A Possible Nonadiabatic Thermal Reaction. *J. Am. Chem. Soc.* **2005**, *127*, 6652–6661. (d) Pedroli, C.; Ravelli, D.; Protti, S.; Albini, A.; Fagnoni, M. Singlet vs Triplet Reactivity of Photogenerated α,*n*-Didehydrotoluenes. *J. Org. Chem.* **2017**, *82*, 6592–6603. (e) Wenthold, P. G.; Winter, A. H. Nucleophilic Addition to Singlet Diradicals: Heterosymmetric Diradicals. *J. Org. Chem.* **2018**, *83*, 12397–12403.

(9) Related thermal cyclizations: (a) Saaby, S.; Baxendale, I. R.; Ley, S. V. Non-Metal-Catalysed Intramolecular Alkyne Cyclotrimerization Reactions Promoted by Focussed Microwave Heating in Batch and Flow Modes. *Org. Biomol. Chem.* **2005**, *3*, 3365. (b) Sakai, T.; Danheiser, R. L. Cyano Diels–Alder and Cyano Ene Reactions. Applications in a Formal [2 + 2 + 2] Cycloaddition Strategy for the Synthesis of Pyridines. *J. Am. Chem. Soc.* **2010**, *132*, 13203–13205. (c) Robinson, J. M.; Sakai, T.; Okano, K.; Kitawaki, T.; Danheiser, R. L. Formal [2 + 2 + 2] Cycloaddition Strategy Based on an Intramolecular Propargylic Ene Reaction/Diels–Alder Cycloaddition Cascade. *J. Am. Chem. Soc.* **2010**, *132*, 11039–11041. (d) Li, X.; Xu, J. Theoretical Insights into the Metal-Free and Formal [2 + 2 + 2] Cycloaddition Strategy via Intramolecular Cascade Propargylic Ene/Diels–Alder Reactions with Tautomerization. *Org. Biomol. Chem.* **2011**, *9*, 5997. (e) Lan, Y.; Danheiser, R. L.; Houk, K. N. Why Nature Eschews the Concerted [2 + 2 + 2] Cycloaddition of a Nonconjugated Cyanodiyne. Computational Study of a Pyridine Synthesis Involving an Ene–Diels–Alder–Bimolecular Hydrogen-Transfer Mechanism. *J. Org. Chem.* **2012**, *77*, 1533–1538.

(10) In the absence of external alkenes, the enyne-allene **G** undergoes Diels-Alder dimerization. See the supporting information (page S27) of ref 9b.

(11) Wang, Y.; Hoye, T. R. Isomerizations of Propargyl 3-Acylpropiolates via Reactive Allenes. *Org. Lett.* **2018**, *20*, 4425–4429.

(12) A structurally similar ether-tethered triyne containing a butyl group and triisopropylsilyl group led to the formation of Diels-Alder dimer of the corresponding enyne-allene intermediate. See ref 9b (page S27).

(13) To confirm this hypothesis, **1l** was heated at 110 °C in toluene in the presence of phenylacetylene (5 equiv), and the putative enyne-allene intermediate could be trapped to generate Diels-Alder product **2l′** in 83% yield (5:1 regioisomeric ratio). This information is included in the Supporting Information (page S-6).

(14) All the dienophiles Danheiser reported are electron-deficient alkenes and alkynes in intermolecular reactions.

(15) Relative solvation-free energies in toluene were calculated at the (SMD)M06/6-311+G(d,p)//B3LYP/6-31G* level. For more details on the calculation data, see the supporting information.

(16) The more favorable reactivity of 1,3-diyne over monoyne and the regioselectivity in the Diels-Alder reaction with a structurally related cyclic 1,3-diynes has been demonstrated: Zou, J.; Qiu, Z.-C.; Yu, Q.-Q.; Wu, J.-M.; Wang, Y.-H.; Shi, K.-D.; Li, Y.-F. Discovery of a Potent Antiosteoporotic Drug Molecular Scaffold Derived from Angelica sinensis and Its Bioinspired Total Synthesis. *ACS Cent. Sci.* **2024**, *10*, 628–636.

(17) (a) Xia, Y.; Liang, Y.; Chen, Y.; Wang, M.; Jiao, L.; Huang, F.; Liu, S.; Li, Y.; Yu, Z.-X. An Unexpected Role of a Trace Amount of Water in Catalyzing Proton Transfer in Phosphine-Catalyzed (3 + 2) Cycloaddition of Allenoates and Alkenes. *J. Am. Chem. Soc.* **2007**, *129*, 3470–3471. (b) Shi, F.-Q.; Li, X.; Xia, Y.; Zhang, L.; Yu, Z.-X. DFT Study of the Mechanisms of in Water Au(I)-Catalyzed Tandem [3,3]-Rearrangement/Nazarov Reaction/[1,2]-Hydrogen Shift of Enynyl Acetates: A Proton-Transport Catalysis Strategy in the Water-Catalyzed [1,2]-Hydrogen Shift. *J. Am. Chem. Soc.* **2007**, *129*, 15503–15512.

(18) The 1,5-H shift with the assistance of one water molecule has a much higher barrier (37.7 kcal/mol).