

ORGANIC CHEMISTRY

FRONTIERS

RESEARCH ARTICLE

View Article Online
View Journal | View IssueCite this: *Org. Chem. Front.*, 2026, **13**, 1977Diels–Alder dimerization of ene-allenes and enyne-allenes generated *via* the propargylic Alder–ene reaction of diynes and triynesKumudi J. W. Rajapaksa,^a Duy-Viet Vo,^b Wu Tong Tong,^b Yanshu Luo,^b Eunhye Lee,^a Yuanzhi Xia^b and Daesung Lee^b

Efficient Diels–Alder dimerizations of ene-allenes and enyne-allenes to generate highly functionalized spirocycles and the DFT studies of their *exo/endo* mode and stereoselectivity are described. The ene-allenes and enyne-allenes are generated *in situ* *via* the propargylic Alder–ene reaction of alkyne ene-donors tethered to ene-acceptor alkynes or 1,3-diynes. The chemo-, regio-, and stereo-selectivities of the dimerization depend on the tether structure and the substituents on the ene-donors and acceptors, while the solvent plays a crucial role in the [1,5]-H shift of the dimers.

Received 20th October 2025,
Accepted 3rd February 2026

DOI: 10.1039/d5qo01454a

rsc.li/frontiers-organic

Introduction

The alkyne trimerization^{1,2} *via* the Alder–ene reaction^{3–5} of triynes of different connectivity efficiently generates various arene products.⁶ Ley and coworkers observed that triyne **A1** generated **C1** under microwave conditions (Scheme 1, eqn (1)).⁷ A diradical mechanism was proposed for this reaction, but convincing evidence for the involvement of ene-allene intermediate **B1** was obtained by Danheiser and coworkers.^{3a} The propargyl ene reaction of triyne **A2** to generate enyne-allene **B2**, followed by an intermolecular Diels–Alder reaction with electron-deficient alkyne, afforded arene product **C2** (eqn (2)). We discovered that an ester-tethered 1,3,8-triyne **A3** prefers to undergo an Alder–ene reaction over the hexadehydro Diels–Alder reaction.^{8,9} The reactivity of enyne-allene **B3-1** crucially depends on the substituent R¹ on the enyne moiety and reaction conditions. If R¹ is a silyl group, the enyne-allene of **B3-1** favorably undergoes conjugate addition with MeOH or AcOH to give product **D3** (eqn (3)).^{10,11} In the absence of nucleophiles, **B3-1** revealed two distinct reactivities (eqn (4)). If R¹ is a silyl group, the enyne-allene moiety participates in a Diels–Alder reaction with a sterically less hindered alkyne of the 1,3-diyne of **A3** to give arene product **C3**.¹² On the other hand, if R¹ is terminal (R¹ = H) or an aryl group, product **E3** was obtained¹³ *via* a sequence of formal 1,7-H shift to generate alternative enyne-allene **B3-2**,¹⁴ Myers–Saito cyclization,¹⁵ followed by 1,5-H transfer-induced cyclization.¹⁶ We further

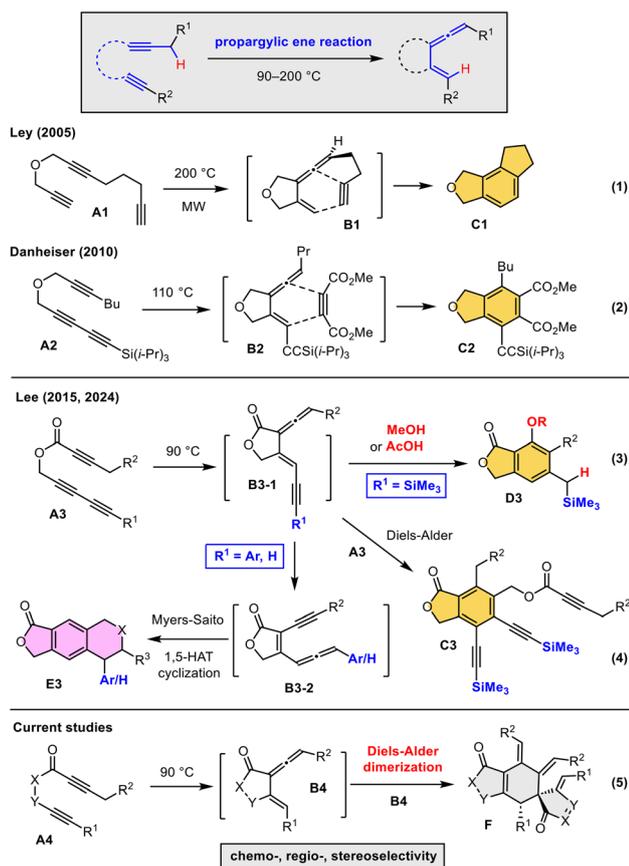
explored the reactivity of enyne-allene **B4** generated from **A4** containing different tethers, where X–Y is an arene, ester, and amide functionality. In the absence of nucleophiles, the enyne-allenes **B4** preferentially participate in Diels–Alder homo-dimerization to provide a spirocyclic product **F** with good chemo-, regio-, and stereo-selectivities.¹⁷ Herein, we report the reactivity profiles and the DFT studies for the observed stereoselectivities of these Diels–Alder homo-dimerization reactions.

Results and discussion

We commenced our exploration with the diyne ketone **1a** (Table 1), which, upon heating in toluene at 70 °C, led to the formation of the dimer **2a** in 68% yield (entry 1). The structural identity of **2a** was established by spectroscopic evidence and further confirmed by single-crystal X-ray diffraction analysis.¹⁸ At higher temperatures (entries 2 and 3) or in different solvents (THF and dichloroethane), the yield of **2a** was not improved (entries 4 and 5). However, when the solvent was changed to CH₃CN, a different product was obtained, which was identified as double bond isomerized desilylation product **2a'** (entries 6 and 7). The Lewis acid-catalyzed reaction in toluene also afforded product **2a'** but with reduced yields (entries 8 and 9).

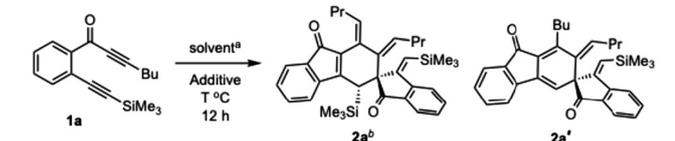
With the optimized conditions, other substrates containing different combinations of substituents R¹ and R on both alkynes were explored (Table 2). Replacing the SiMe₃ group with a phenyl group in **1b** provided **2b** in 47% yield as a mixture of diastereomers (dr = 3 : 1) (entry 2). However, substrate **1c** and **1d** containing a butyl group or proton in R posi-

^aDepartment of Chemistry, University of Illinois Chicago, 845 W. Taylor St., Chicago, Illinois 60607, USA. E-mail: dsunglee@uic.edu^bCollege of Chemistry and Materials Engineering, Wenzhou University, 325035 Wenzhou, Zhejiang, P. R. China



Scheme 1 Various cycloadditions of enyne-allenes generated by the propargyl Alder-ene reaction.

Table 1 Optimization of the Diels-Alder homo-dimerization of an ene-allene generated from diyne **1a**

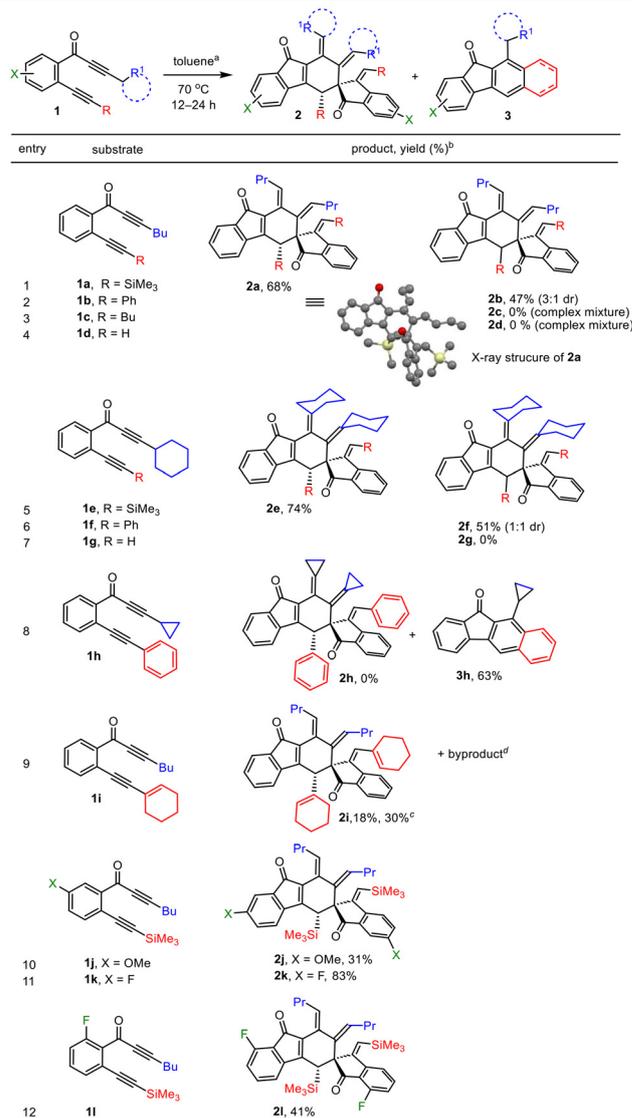


Entry	Solvent	Additive	T (°C)	2a (%)	2a' ^c (%)
1	Toluene	None	70	68	— ^d
2	Toluene	None	90	56	—
3	Toluene	None	110	65	—
4	THF	None	70	54	—
5	ClCH ₂ CH ₂ Cl	None	70	51	—
6	CH ₃ CN	None	70	— ^e	44
7	CH ₃ CN	None	90	—	71
8	Toluene	AgSbF ₆ (15 mol%)	95	—	44
9	Toluene	AgSbF ₆ (15 mol%)	70	—	66

^a Condition: undistilled solvents. ^b The stereochemistry is assigned based on X-ray data. ^c Isolated yield. ^d 2a' was not observed. ^e 2a was not observed.

tion did not give any identifiable product (entries 3 and 4). A similar reactivity trend was observed with a cyclohexyl-containing substrates **1e–1g**, giving highest yield with silyl group

Table 2 Substituent effect on the Alder-ene and Diels-Alder homo-dimerization reactions



^a Undistilled. ^b Isolated yield. ^c Grubbs II (10 mol%) in CHCl₃ at 70 °C. ^d In addition to **2i**, a byproduct was obtained in 26% yield. The characterization data of this byproduct is a Diels-Alder adduct corresponding to **3h**, even though good quality NMRs could not be obtained.

(74%), slightly lower yield with a phenyl group (51%), but no identifiable product with a terminal alkyne (entries 5–7). Similar to **2b**, **2f** was generated as a mixture of diastereomers (dr = 1:1) of the stereogenic carbon centers not the double bond geometry. This assignment is based on the analogy to the confirmed structure of **2a**. The cyclopropyl group in substrate **1h** completely changes the reaction manifold from the propargylic Alder-ene to a Diels-Alder reaction, generating **3h** (63%) without **2h** (entry 8). The reactivity difference between **1f** and **1h** results should be the consequence of the lower tendency of the cyclopropyl group to participate in the propargylic ene reaction due to the increased ring strain of the cyclopropyl-



idene intermediate. The reactivity of cyclohexenyl alkyne-containing **1i** was examined and **2i** (18%) was generated in low yield (entry 9). The yield of **2i** was increased to 30% under metal-catalyzed conditions. The substituent on the aromatic linker has a significant impact on the reactivity; thus, an electron-donating OMe-containing **1j** gave **2j** in 31%, whereas fluorine-containing **1k** provided **2k** in 83% yield (entries 10 and 11). These results indicate that the electron-donating methoxy group lowers the reactivity of the alkyne as an enophile at the *para*-position. In contrast, **1l** containing fluorine-substituent at the *meta*-position to the alkyne gave **2l** in reduced yield (41%) (entry 12).

To gain insight into the reactivity and selectivity (chemo, regio, stereo) for these reactions, we carried out DFT-based theoretical calculations (Fig. 1).¹⁹ The Gibbs free energy (ΔG) profile of the reaction of **1a** is shown in Fig. 1A. The Alder-ene reaction of **1a** proceeds through **TS1-1a** to generate enallene **IN1-1a**, the ΔG of which is 25.6 kcal mol⁻¹ lower than starting **1a**. For the reactivity of ene-allene **IN1-1a**, two different modes of Diels-Alder reaction are compared: homo-dimerization and the Diels-Alder reaction with an alkyne dienophile. Among these, the lowest barrier (**TS1-1a**/18.0 kcal mol⁻¹) is associated with the homo-dimerization pathway leading to diradical **IN2-1a**, which cyclizes *via* a lower-barrier transition state **TS-IN2-1a**

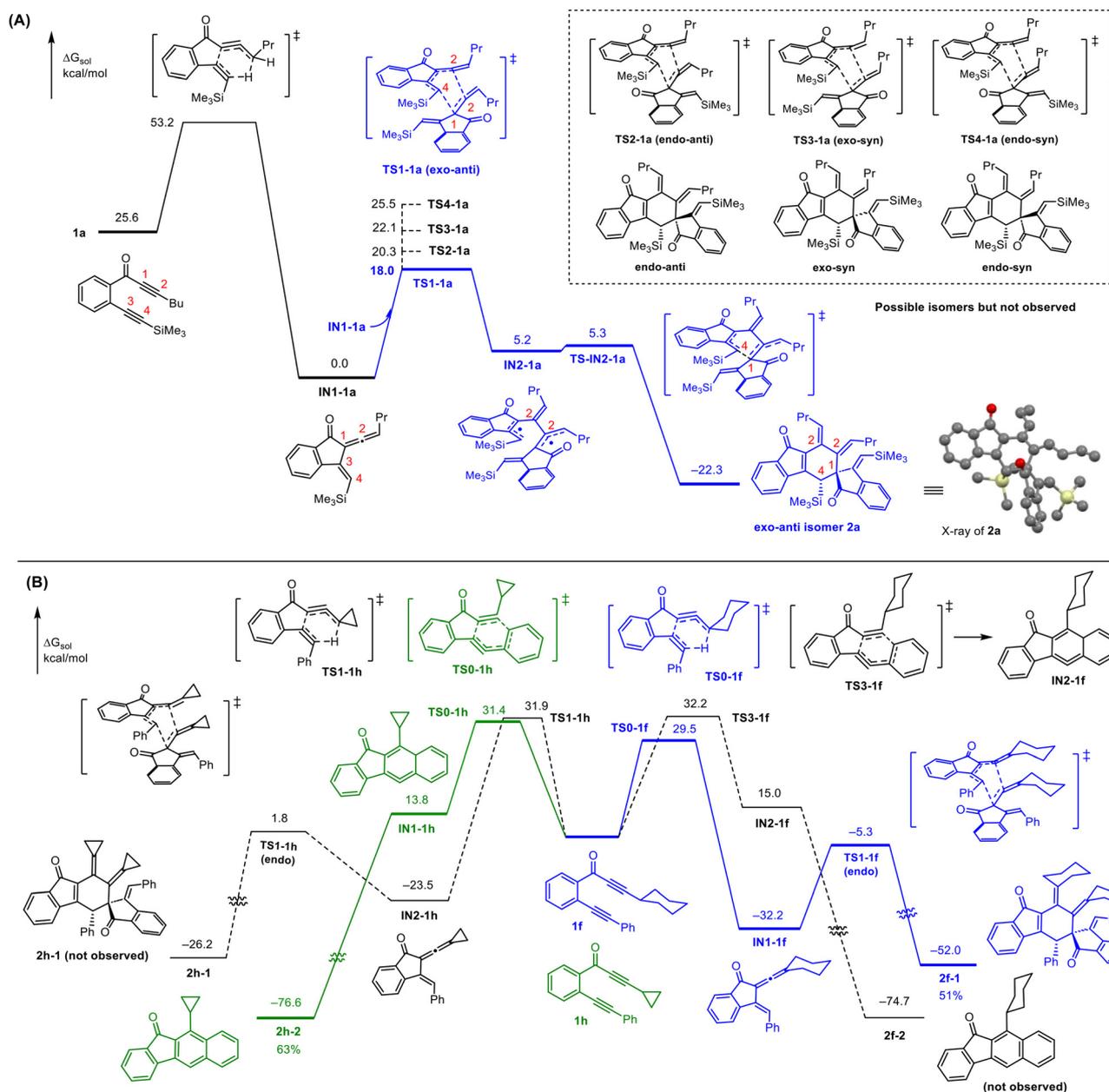


Fig. 1 (A) DFT calculations for chemo-, regio-, and stereo-selectivity in the Diels-Alder reaction of ene-allene **IN1-1a**, and (B) mode selectivity of alkynyl ketones **1f/1h** (optimization: B3LYP/6-31G(d); solvation: M06/6-311+G(d,p)).



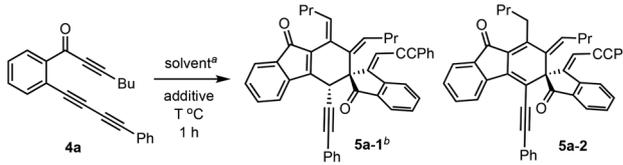
1a, leading to the observed product **2a** (*exo-anti*). The modes of homo-dimerization for the other diastereomers (*endo-anti/endo-syn/endo-syn*) proceed through higher barriers (**TS2-1a**/20.3 kcal mol⁻¹, **TS3-1a**/22.1 kcal mol⁻¹, **TS4-1a**/25.5 kcal mol⁻¹). Even the lowest barrier (**TS5-1a**/21.9 kcal mol⁻¹) of the Diels–Alder pathway between **IN1-1a** and an alkyne moiety leading to diradical **IN3-1a** (19.4 kcal mol⁻¹) has a higher transition state energy by 3.9 kcal mol⁻¹; thus, products *via* this pathway were not observed.

Next, we calculated the energy landscapes of the competing Alder–ene and Diels–Alder reactions of **1f** and **1h** (Fig. 1B). The Alder–ene reaction of **1f** proceeds through **TS0-1f** (29.5 kcal mol⁻¹) to generate intermediate **IN1-1f**, which undergoes homo-dimerization through **TS1-1f** (26.9 kcal mol⁻¹, relative to **IN1-1f**) to generate **2f-1** (51% yield). On the other hand, the Diels–Alder transition state **TS3-1f** (32.2 kcal mol⁻¹) has 2.7 kcal mol⁻¹ higher barrier than the Alder–ene pathway; thus, product **2f-2** was not observed. It should be noted that in our DFT calculations, intermediate **IN1-1f** was treated as an isolated single molecule. However, in the actual reaction, the low concentration of **IN1-1f** species is expected to further increase the effective activation barrier for the homo-dimerization transition state. Nevertheless, the DFT results indicate that the homo-dimerization pathway remains kinetically favored, in agreement with the experimental observations. In contrast, the cyclopropyl-containing substrate **1h** favors a Diels–Alder reaction to generate product **2h-2** *via* **TS0-1h** (31.4 kcal mol⁻¹) and intermediate **IN1-1h** (13.8 kcal mol⁻¹). Even though the calculated transition state energy for the Alder–ene reaction (**TS1-1h**/31.9 kcal mol⁻¹) to form enallene intermediate **IN2-1h** is slightly higher than that of the Diels–Alder reaction (31.4 kcal mol⁻¹), the homo-dimerization product **2h-1** was not experimentally observed.

With the reactivity trend of the diyne ketones observed in the experiment and theoretical calculations, we further explored the reactions of triynones, which are expected to be more reactive toward the Alder–ene reaction due to the additional conjugated alkyne (Table 3). Heating triynone **4a** in toluene at 90 °C provided a Diels–Alder dimer in 34% yield (entry 1). However, we noticed that the characteristic spectroscopic feature of this compound is similar yet different from that of the expected product **5a-1**. After careful examination of the spectral data, we concluded that it is **5a-2**, which is derived from **5a-1** *via* a 1,5-H shift. In a different solvent or at a higher temperature, **5a-2** was obtained in lower yields (entries 2 and 3). Interestingly, when the reaction was carried out in chloroform, it delivered **5a-1** in a lower yield (28%). But at a lower temperature (70 °C) in chloroform, the yield of **5a-1** was increased to 45% (entries 4 and 5). The metal-catalyzed conditions in either toluene or chloroform also induced 1,5-H shift; thus, **5a-2** was obtained exclusively in moderate yields (entries 6 and 7).

To better understand the effect of the 1,3-diyne moiety on the reactivity of triynone **4a** and the alkyne substituent on **5a-1**, we calculated the energy landscape of the reaction (Fig. 2). As expected, the barrier for the Alder–ene reaction of

Table 3 Solvent-dependent 1,5-H shift in the Diels–Alder homo-dimerization of the enyne-allene generated from **4a**



Entry	Solvent	Additive	T (°C)	5a-1 ^c (%)	5a-2 ^c (%)
1	Toluene	None	90	— ^d	34
2	THF	None	90	—	24
3	CH ₃ CN	None	90	—	15
4	CHCl ₃	None	90	28	— ^e
5	CHCl ₃	None	70	45	—
6	CHCl ₃	G-II (10 mol%)	90	— ^d	31
7	Toluene	AgSbF ₆ (15 mol%)	90	—	37

^a Undistilled solvents. ^b The stereochemistry is tentatively assigned based on the analogy to **2a** and DFT calculation data in Fig. 2. ^c Isolated yield. ^d **5a-1** was not observed. ^e **5a-2** was not observed.

4a (23.1 kcal mol⁻¹) is lower than **1a** (27.6 kcal mol⁻¹), **1f** (29.5 kcal mol⁻¹), and **1h** (31.9 kcal mol⁻¹). Like Me₃Si-containing **IN1-1a**, which prefers an *exo*-transition state, enyne-allene **IN1-4a** favors the *exo*-transition state (**exo-TS1**) by 1.1 kcal mol⁻¹ compared to the corresponding *endo*-transition state (**endo-TS1**), generating **exo-5a-1**. While the reaction of **IN1-1a** proceeds through a diradical mechanism, **IN1-4a** participates in a concerted [4 + 2] cycloaddition, which is assumed to be the consequence of the smaller alkyne moiety that does not cause a severe steric interaction in the *exo*-transition state. On the other hand, the reaction of **IN1-4a** through **endo-TS1** forms a diradical intermediate **IN2-4a**, which selectively produces **endo-5a-1**. In an alternative Diels–Alder reaction between **IN1-4a** and an alkyne moiety of **4a**, the energy of **TS3-IN1** (25.6 kcal mol⁻¹) has at least 7.3 kcal mol⁻¹ higher than **exo-TS1**; thus, the Diels–Alder product **IN5-4a** was not observed. The conversion of **exo-5a-1** to the **5a-2** is highly exergonic, but the [1,5]-H shift *via* **exo-TS2** has a relatively high kinetic barrier (23.7 kcal mol⁻¹). The participation of three molecules of water to form the organized transition state **exo-TS2** is required to be located on the energy surface.²⁰

Based on the observed solvent effect on the [1,5]-H shift and reaction efficiency, we further examined the reaction profile of triynones containing a variety of substituents on the alkynyl ketone and 1,3-diyne moiety (Table 4). When subjected to the optimized conditions (CHCl₃, 70 °C), triynones **4b** containing a triisopropyl group produced **5b** in 42% (dr = 1.5 : 1) yield, and the corresponding dimethylsilyloxymethyl-substituted product **5c** was obtained in 59% (dr = 2 : 1) yield. We observed that **5b** and **5c** underwent 1,5-H shift if exposed to basic Al₂O₃. Triynones containing a cyclohexyl-substituted alkynyl ketone showed a similar trend to produce homo-dimerization products. The triynone **4d** containing a phenyl group gave **5d** in 68% yield. As expected, when having an electron-donating *para*-methoxy group lowered the yield of **5e** (58%),



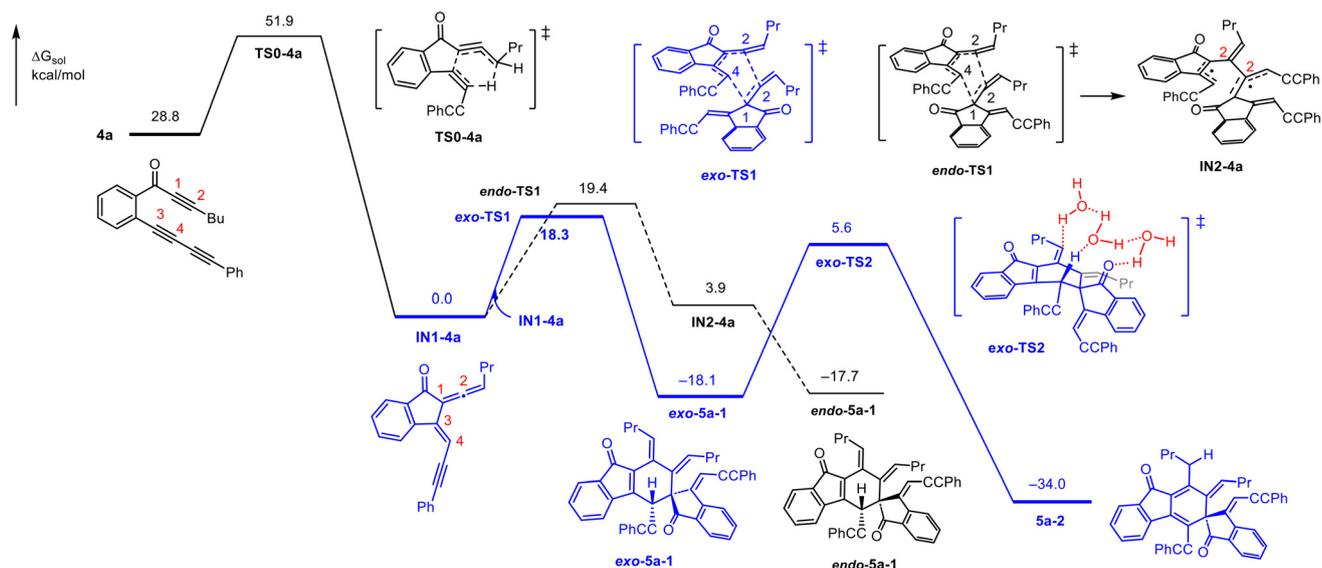
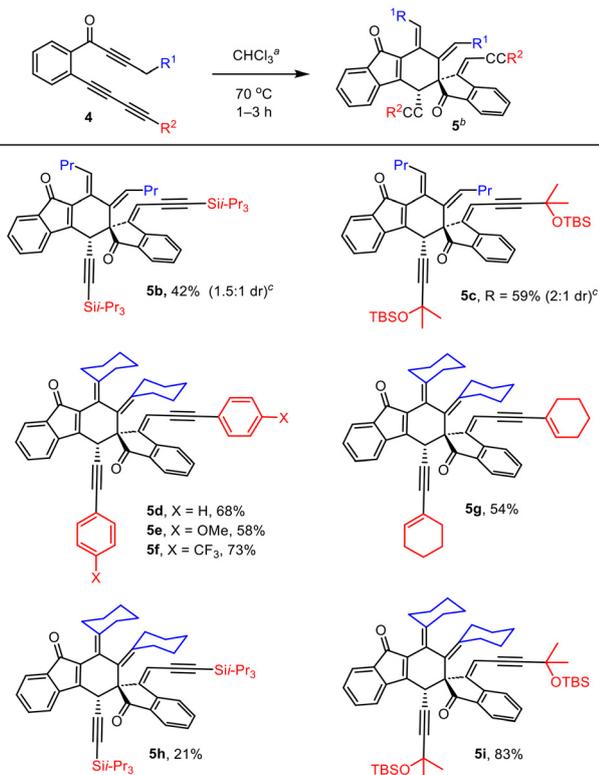


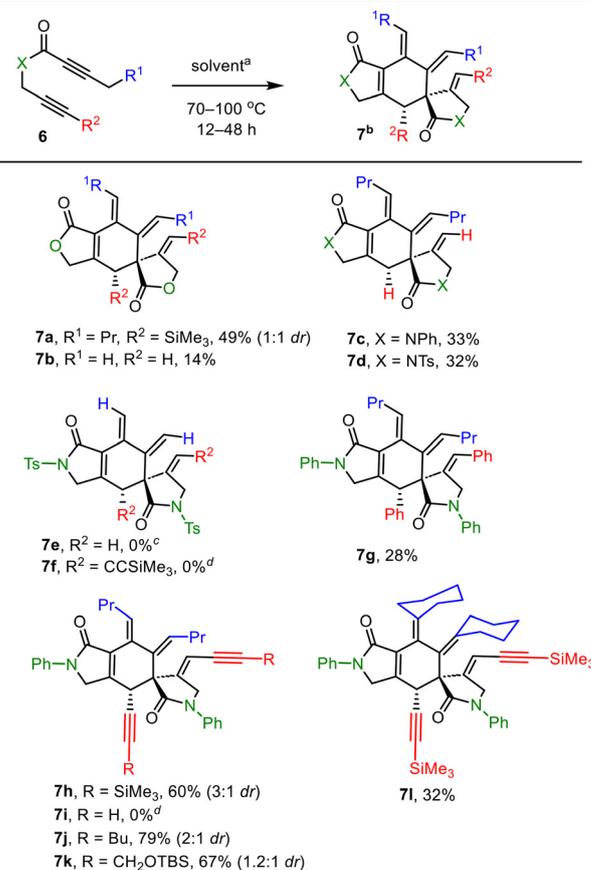
Fig. 2 DFT calculations for chemoselectivity and regioselectivity in the Diels–Alder reaction of enyne-allene **IN1-4a** and 1,5-H shift (optimization: B3LYP/6-31G(d); solvation: M06/6-311+G(d,p)).

Table 4 The Diels–Alder homo-dimerization of enyne-allenes generated from triynones



^a Undistilled. ^b Isolated yield. ^c On basic Al₂O₃, the product undergoes [1,5]-H shift.

Table 5 Exploration of homo-dimerization of ene-allenes and enyne-allenes generated from ester- and amide-tethered diynes and triynes



^a Undistilled solvents; toluene was used for **6a–6e**, **6g**, chloroform was used for **6f**, **6h–6l**. ^b Isolated yield. ^c Starting material was recovered. ^d Complex mixture.



while the electron-withdrawing trifluoromethyl group increased the yield of **5f** (73%). Similarly, the corresponding cyclohexenyl-, triisopropyl-, and dimethylsilyloxymethyl-substituted products **5g** (54%), **5h** (21%) and **5i** (83%) were obtained. The reason for the significantly lower yield of **5h** is not clear.

Next, we examined the reactions of ester- and amide-tethered substrates (Table 5). The reaction of ester-tethered diyne with a trimethylsilyl substituent (**6a**, $R^2 = \text{SiMe}_3$) gave product **7a** (49%, dr = 1 : 1), whereas the corresponding substrate with a terminal alkyne (**6b**, $R^2 = \text{H}$) gave **7b** in much lower yield (14%). The amide-tethered substrates with a terminal alkyne (**6c** and **6d**, $R^2 = \text{H}$) produced **7c** (33%) and **7d** (32%) in marginal yields. Products **7e** and **7f** containing methylidenes derived from substrates containing a propynyl group (**6e** and **6f**, $R^1 = \text{H}$) could not be obtained; **6e** was recovered, whereas **6f** decomposed. We assume that the lower yields or lack of formation of products (**7b**, **7e**, and **7f**) containing sterically unhindered methylene moieties is due to their instability. For the reaction of the substrate containing a phenyl-substituted alkyne (**6g**, $R^2 = \text{Ph}$), an intramolecular tetrahydro Diels–Alder reaction competes with the Alder–ene reaction to form the ene-allene intermediate, thus **7g** (28%) was obtained in low yield. The reaction of amide-tethered triynes containing a diyne moiety with a trimethylsilyl, butyl, and silyloxymethyl substituent provided **7h** (60%), **7j** (79%), and **7k** (67%) as a mixture of diastereomers. However, the corresponding cyclohexyl-containing triyne gave **7l** (32%) as a single isomer. As an exception, the terminal alkyne-containing product **7i** could not be obtained, most likely due to the instability of the terminal 1,3-diyne moiety in the starting material **6i**.

Conclusions

In conclusion, we explored tandem Alder–ene reaction to form ene-allene and enyne-allene intermediates followed by their Diels–Alder homo-dimerization to generate highly functionalized novel spirocyclic compounds under thermal conditions. The reaction profiles of a wide variety of aryl-, ester-, and amide-tethered alkynones were examined. The tether and the substituents have a profound impact on the chemo-, regio- and stereoselectivities, and the yield of the products. The solvent-dependent double bond migration *via* a formal 1,5-H shift of aryl-tethered dimers yields structural variation to the spirocyclic molecules. DFT-based theoretical calculations were carried out to gain insight into the observed experimental results.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data that supports the findings of this study are available in the supplementary information (SI). Supplementary infor-

mation is available. See DOI: <https://doi.org/10.1039/d5qo01454a>.

CCDC 2494308 (**2a**) contains the supplementary crystallographic data for this paper.¹⁸

Acknowledgements

We are grateful to NSF (CHE-2055055, D. L.) for financial support. Acknowledgment is made to the Donors of the American Chemical Society Petroleum Research Fund under New Directions Grant 65576-ND1. NSFC is acknowledged for financial support (21873074, 21572163, 22308263). We thank Dr Binh Khanh Mai (The University of Pittsburgh) for helpful advice on DFT calculation. The Mass Spectrometry Laboratory at UIUC is acknowledged.

References

- Reviews on metal-catalyzed alkyne trimerizations: (a) S. Saito and Y. Yamamoto, Recent Advances in the Transition-Metal-Catalyzed Regioselective Approaches to Polysubstituted Benzene Derivatives, *Chem. Rev.*, 2000, **100**, 2901; (b) N. E. Shore, in *Comprehensive Organic Synthesis*, ed. B. M. Trost and I. Fleming, Pergamon, Oxford, 1991, ch. 9.4, vol. 5, pp. 1129–1162; (c) D. B. Grotjahn, in *Comprehensive Organometallic Chemistry II*, ed. L. S. Hegeudus, E. W. Abel, F. G. A. Stone and G. Wilkinson, Pergamon, Oxford, 1995, ch. 7.3, vol. 12, pp. 741–770; (d) N. Agenet, O. Bjuisine, F. Slowinski, V. Gandon, C. Aubert and M. Malacria, Cotrimerizations of Acetylenic Compounds, *Org. React.*, 2007, **68**, 1; (e) S. Kotha, E. Brahmachary and K. Lahiri, Transition Metal Catalyzed [2+2+2] Cycloaddition and Application in Organic Synthesis, *Eur. J. Org. Chem.*, 2005, 4741; (f) P. R. Chopade and J. Louie, [2+2+2] Cycloaddition Reactions Catalyzed by Transition Metal Complexes, *Adv. Synth. Catal.*, 2006, **348**, 2307; (g) B. R. Galan and T. Rovis, Beyond Reppe: Building Substituted Arenes by [2+2+2] Cycloadditions of Alkynes, *Angew. Chem., Int. Ed.*, 2009, **48**, 2830; (h) K. Tanaka, Cationic Rhodium(I)/BINAP-Type Bisphosphine Complexes: Versatile New Catalysts for Highly Chemo-, Regio-, and Enantioselective [2+2+2] Cycloadditions, *Synlett*, 2007, 1977.
- Thermal alkyne trimerizations: (a) V. Breitkopf, H. Hopf, F.-G. Klärner, B. Witulski and B. Zimny, The effect of pressure on the trimerization and Diels–Alder reaction of cyanoacetylene. Synthesis and reactivity of 2,3,5-tricyanobicyclo[2.2.0]hexa-2,5-diene (“tricyano Dewar benzene”), *Liebigs Ann.*, 1995, **100**, 613; (b) M. G. Kociolek and R. P. Johnson, Intramolecular thermal cyclotrimerization of an acyclic triyne: An uncatalyzed process, *Tetrahedron Lett.*, 1999, **40**, 4141; (c) D. Rodríguez, L. Castedo, D. Domínguez and C. Saa, Synthesis of the benzo[b]fluorene core of the kinamycins by cycloaromatization of non-conjugated ben-



- zotriynes, *Tetrahedron Lett.*, 1999, **40**, 7701; (d) S. Taniguchi, T. Yokoi, A. Izuoka, M. M. Matsushita and T. Sugawara, Noncatalytic, solvent-free thermal formation of cyclic trimers using 1,6-bis(acyloxymethyl)hexa-2,4-diyne derivatives, *Tetrahedron Lett.*, 2004, **45**, 2671.
- 3 (a) J. M. Robinson, T. Sakai, K. Okano, T. Kitawaki and R. L. Danheiser, Formal [2+2+2] Cycloaddition Strategy Based on an Intramolecular Propargylic Ene Reaction/Diels–Alder Cycloaddition Cascade, *J. Am. Chem. Soc.*, 2010, **132**, 11039; (b) T. Sakai and R. L. Danheiser, 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; (c) X. Li and J. Xu, 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; (d) Y. Lan, R. L. Danheiser and K. N. Houk, 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; For a review of Diels–Alder reactions of vinylallenes, see: (e) M. Murakami and T. Matsuda, Cycloadditions of Allenes, in *Modern Allene Chemistry*, ed. N. Krause and A. S. K. Hashmi, Wiley-VCH, Weinheim, 2004, vol. 2, pp. 727–815.
- 4 For general reviews on ene reactions: (a) H. M. R. Hoffmann, The Ene Reaction, *Angew. Chem., Int. Ed. Engl.*, 1969, **8**, 556; (b) B. B. Snider, Lewis-Acid-Catalyzed Ene Reactions, *Acc. Chem. Res.*, 1980, **13**, 426; (c) K. Mikami and M. Shimizu, *Chem. Rev.*, 1992, **92**, 1021; (d) L. C. Dias, Asymmetric Ene Reactions in Organic Synthesis, *Curr. Org. Chem.*, 2000, **4**, 30; (e) W. Adam and O. Krebs, The Nitroso Ene Reaction: A Regioselective and Stereoselective Allylic Nitrogen Functionalization of Mechanistic Delight and Synthetic Potential, *Chem. Rev.*, 2003, **103**, 4131; (f) T. J. J. Müller, Recent Advances in Ene Reactions with Carbon Enophiles, *Adv. Synth. Catal.*, 2025, **367**, e70122; (g) B. Megha, P. Chandrakanta and S. C. Pan, Organocatalytic Asymmetric Ene Reactions, *Asian J. Org. Chem.*, 2021, **10**, 2440–2453; For a review on transition metal-catalyzed Alder–ene reactions: (h) B. M. Trost, M. U. Frederiksen and M. T. Rudd, Ruthenium-Catalyzed Reactions—A Treasure Trove of Atom-Economic Transformations, *Angew. Chem., Int. Ed.*, 2005, **44**, 6630.
- 5 Alder–ene reaction of allenes: (a) S.-H. Dal and W. R. Dolber Jr, Allene-Perfluorocyclobutanone Ene Reaction. Kinetic Isotope Effects, *J. Am. Chem. Soc.*, 1972, **94**, 3953; (b) C. B. Lee and D. R. Taylor, Ene reactions of allenes. Part 3. Reactions of electron-deficient azo-compounds with acyclic allenes and alkenes, *J. Chem. Soc., Perkin Trans. 1*, 1977, 1463–1468; (c) K. M. Brummond, H. Chen, P. Sill and L. You, 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; (d) P. H.-Y. Cheong, P. Morganelli, M. R. Luzung, K. N. Houk and F. D. Toste, Gold-Catalyzed Cycloisomerization of 1,5-Allenynes via Dual Activation of an Ene Reaction, *J. Am. Chem. Soc.*, 2008, **130**, 4517; (e) L. M. Joyce, M. A. Drew, A. J. Tague, T. Thaima, A. Gouranourimi, A. Afriafard, S. G. Pyne and C. J. T. Hyland, A Rare Alder–ene Cycloisomerization of 1,6-Allenynes, *Chem. – Eur. J.*, 2022, **28**, e2202104022; (f) V. R. Sabbasani, G. Huang, Y. Xia and D. Lee, Facile Alder–Ene Reactions of Silyllallenes Involving an Allenic C(sp²)-H Bond, *Chem. – Eur. J.*, 2015, **21**, 17210; (g) T. Arif, C. Borie, M. Jean, N. Vanthuyne, M. P. Bertrand, D. Siri and M. Nechab, Organocopper triggered cyclization of conjugated dienyne via tandem SN 2'/Alder–ene reaction, *Org. Chem. Front.*, 2018, **5**, 769; (h) C. Borie, N. Vanthuyne, M. P. Bertrand, D. Siri and M. Nechab, Palladium Tandem Catalysis in the Atropodistereoselective Synthesis of Indenes Bearing Central and Axial Chirality, *ACS Catal.*, 2016, **6**, 1559; (i) Z. Y. Zheng, L. Deiana, D. Posevins, A. A. Rafi, K. H. Zhang, M. J. Johansson, C. W. Tai, A. Cordova and J. E. Bäckvall, Efficient Heterogeneous Copper-Catalyzed Alder–Ene Reaction of Allenynamides to Pyrrolines, *ACS Catal.*, 2022, **12**, 1791–1796.
- 6 Alder–ene reactions of arynes: (a) I. Tabushi, K. Okazaki and R. Oda, Relative reactivities of substituted olefins toward benzyne, *Tetrahedron*, 1969, **25**, 4401; (b) G. Ahlgren and B. Akermark, The addition of benzyne to 1, 2-dideuteriocyclohexene, *Tetrahedron Lett.*, 1970, **11**, 3047; (c) V. Garsky, D. F. Koster and R. T. Arnold, Studies of the Stereochemistry and Mechanism of the Ene Reaction Using Specifically Deuterated Pinenes, *J. Am. Chem. Soc.*, 1974, **96**, 4207; J. Nakayama and K. Yoshimura, A general synthesis of aromatic compounds carrying two neopentyl groups on adjacent positions, *Tetrahedron Lett.*, 1994, **35**, 2709; (d) A. A. Aly, N. K. Mohamed, A. A. Hassan and A.-F. E. Mourad, Reaction of diimines and benzyne, *Tetrahedron*, 1999, **55**, 1111; (e) A. A. Aly and R. M. Shaker, 5-Benzyl-1H-tetrazols from the reaction of 1-aryl-5-methyl-1H-tetrazoles with 1,2-dehydrobenzene, *Tetrahedron Lett.*, 2005, **46**, 2679; (f) R. Karmakar, P. Mamidipalli, S. Y. Yun and D. Lee, Alder–Ene Reactions of Arynes, *Org. Lett.*, 2013, **15**, 1938; (g) S. Gupta, P. Xie, Y. Xia and D. Lee, Reactivity and Selectivity in the Intermolecular Alder–Ene Reactions of Arynes with Functionalized Alkenes, *Org. Lett.*, 2017, **19**, 5162; (h) S. Gupta, P. Xie, Y. Xia and D. Lee, Reactivity of arynes toward functionalized alkenes: intermolecular Alder–ene vs. addition reactions, *Org. Chem. Front.*, 2018, **5**, 2208; (i) S. Gupta, Y. Lin, Y. Xia, J. D. Wink and D. Lee, Alder–ene reactions driven by high steric strain and bond angle distortion to form benzocyclobutenes, *Chem. Sci.*, 2019, **10**, 2212; (j) T. Ballav, S. Barman and V. Ganesh, Aryne Alder–Ene Reaction Enables Arylation of Conformationally Locked Styrenes, *Org. Lett.*, 2025, **27**, 4107–4111; Examples of intermolecular ene reactions between arynes and terminal alkynes, see: (k) T. T. Jayanth, M. Jeganmohan, M. J. Cheng, S. Y. Chu and C. H. Cheng,



- Ene reaction of arynes with alkynes, *J. Am. Chem. Soc.*, 2006, **128**, 2232; (l) H. H. Wasserman, A. J. Solodar and L. S. Keller, On the stereochemistry of benzyne addition to cis- and trans-propenyl ethers and acetates, *Tetrahedron Lett.*, 1968, **9**, 5597; (m) L. Friedman, R. J. Osiewicz and P. W. Rabideau, The course of addition of benzyne to cis- and trans-acetoxy- and methoxypropene, *Tetrahedron Lett.*, 1968, **9**, 5735; (n) H. H. Wasserman and L. S. Keller, Steric effects in the ene reaction.: The reaction of benzyne with cis- and trans-2-methylbut-1-en-1-yl acetates, *Tetrahedron Lett.*, 1974, **15**, 4355; (o) P. Crews and J. J. Beard, Cycloadditions of benzyne with cyclic olefins. Competition between 2+4, ene, and 2+2 reaction pathways, *J. Org. Chem.*, 1973, **38**, 522; (p) D. A. Candito, J. Panteleev and M. Lautens, Intramolecular Aryne-Ene Reaction: Synthetic and Mechanistic Studies, *J. Am. Chem. Soc.*, 2011, **133**, 14200; (q) D. A. Candito, D. Dobrovolsky and M. Lautens, Development of an intramolecular aryne ene reaction and application to the formal synthesis of (\pm)-crinine, *J. Am. Chem. Soc.*, 2012, **134**, 15572–15580; (r) Y. Yang and C. R. Jones, The aryne ene reaction, *Synthesis*, 2022, 5042; (s) R. Karmakar, N. K. Lee, E. L. Perera and D. Lee, Alder-ene reactions of arynes to form medium-sized and macrocyclic frameworks of sizes up to a 46-membered ring, *Chem. Commun.*, 2024, **60**, 13947.
- 7 S. Saaby, I. R. Baxendale and S. V. Ley, Non-metal-catalysed intramolecular alkyne cyclotrimerization reactions promoted by focussed microwave heating in batch and flow modes, *Org. Biomol. Chem.*, 2005, **3**, 3365.
- 8 Hexahydro Diels–Alder reactions: (a) A. Z. Bradley and R. P. Johnson, Thermolysis of 1, 3, 8-nonatriyne: evidence for intramolecular [2+4] cycloaromatization to a benzyne intermediate, *J. Am. Chem. Soc.*, 1997, **119**, 9917; (b) K. Miyawaki, R. Suzuki, T. Kawano and I. Ueda, 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; (c) T. R. Hoye, B. Baire, D. Niu, P. H. Willoughby and B. P. Woods, The hexahydro-Diels–Alder reaction, *Nature*, 2012, **490**, 208; (d) S. Y. Yun, K. P. Wang, N. K. Lee, P. Mamidipalli and D. Lee, Alkane C–H Insertion by Aryne Intermediates with a Silver Catalyst, *J. Am. Chem. Soc.*, 2013, **135**, 4668–4671; (e) R. Karmakar, S. Ghorai, Y. Xia and D. Lee, Synthesis of Phenolic Compounds by Trapping Arynes with a Hydroxy Surrogate, *Molecules*, 2015, **20**, 15862; (f) T. Wang and T. R. Hoye, Hexahydro-Diels–Alder (HDDA)-Enabled Carbazolyne Chemistry: Single Step, de Novo Construction of the Pyranocarbazole Core of Alkaloids of the *Murraya koenigii* (Curry Tree) Family, *J. Am. Chem. Soc.*, 2016, **138**, 13870; (g) R. Karmakar, P. Mamidipalli, R. M. Salzman, S. Hong, S. Y. Yun, Y. Xia and D. Lee, Benzannulation of triynes initiated by an alder-ene reaction and subsequent trifluoromethylthiolate addition, *Org. Lett.*, 2016, **18**, 3530; (h) S. P. Ross and T. R. Hoye, Reactions of hexahydro-Diels–Alder benzynes with structurally complex multifunctional natural products, *Nat. Chem.*, 2017, **9**, 523; (i) Q. Hu, L. Li, F. Yin, H. Zhang, Y. Hu, B. Liu and Y. Hu, Fused multifunctionalized isoindole-1, 3-diones via the coupled oxidation of imidazoles and tetraynes, *RSC Adv.*, 2017, **7**, 49810; (j) X. Meng, S. Lv, D. Cheng, Q. Hu, J. Ma, B. Liu and Y. Hu, Fused Multifunctionalized Chromenes from Tetraynes and α , β -Unsaturated Aldehydes, *Chem. – Eur. J.*, 2017, **23**, 6264; (k) Y. Hu, J. Ma, L. Li, Q. Hu, S. Lv, B. Liu and S. Wang, Fused multifunctionalized dibenzoselenophenes from tetraynes, *Chem. Commun.*, 2017, **53**, 1542; (l) R. Karmakar, A. Le, P. Xie, Y. Xia and D. Lee, Reactivity of arynes for arene dearomatization, *Org. Lett.*, 2018, 4168; (m) S. Ghorai, Y. Lin, Y. Xia, J. D. Wink and D. Lee, Silver-Catalyzed Annulation of Arynes with Nitriles for Synthesis of Structurally Diverse Quinazolines, *Org. Lett.*, 2020, **22**, 626; Reviews: (n) O. J. Diamond and T. B. Marder, Methodology and applications of the hexahydro-Diels–Alder (HDDA) reaction, *Org. Chem. Front.*, 2017, **4**, 891; (o) L. L. Fluegel and T. R. Hoye, Hexahydro-Diels–Alder reaction: Benzyne generation via cycloisomerization of tethered triynes, *Chem. Rev.*, 2021, **121**, 2413.
- 9 Mechanistic and theoretical studies of HDDA reaction: (a) P. H. Willoughby, D. Niu, T. Wang, M. K. Haj, C. J. Cramer and T. R. Hoye, Mechanism of the Reactions of Alcohols with o-Benzynes, *J. Am. Chem. Soc.*, 2014, **136**, 13657; (b) B. Baire, T. Wang and T. R. Hoye, Tactics for probing aryne reactivity: mechanistic studies of silicon-oxygen bond cleavage during the trapping of (HDDA-generated) benzynes by silyl ethers, *Chem. Sci.*, 2014, **5**, 545; (c) Y. Liang, X. Hong, P. Yu and K. N. Houk, Why alkynyl substituents dramatically accelerate hexahydro-Diels–Alder (HDDA) reactions: Stepwise mechanisms of HDDA cycloadditions, *Org. Lett.*, 2014, **16**, 5702; (d) D. J. Marell, L. R. Furan, B. P. Woods, X. Lei, A. J. Bendelsmith, C. J. Cramer, T. R. Hoye and K. T. Kuwata, Mechanism of the intramolecular hexahydro-Diels–Alder reaction, *J. Org. Chem.*, 2015, **80**, 11744; (e) T. Wang, D. Niu and T. R. Hoye, The hexahydro-Diels–Alder cycloisomerization reaction proceeds by a stepwise mechanism, *J. Am. Chem. Soc.*, 2016, **138**, 7832; (f) A. Ajaz, A. Z. Bradley, R. C. Burrell, W. H. H. Li, K. J. Daoust, L. B. Bovee, K. J. DiRico and R. P. Johnson, Concerted vs stepwise mechanisms in dehydro-Diels–Alder reactions, *J. Org. Chem.*, 2011, **76**, 9320.
- 10 R. Karmakar, S. Y. Yun, Y. Chen, Y. Xia and D. Lee, Benzannulation of triynes to generate functionalized arenes by spontaneous incorporation of nucleophiles, *Angew. Chem., Int. Ed.*, 2015, **54**, 6582.
- 11 If the R¹ substituent is an aromatic group, the nucleophile trapping occurs with the opposite mode selectivity (the OR is on the benzylic position and H is on the arene ring).
- 12 D.-V. Vo, T. Wu, Y. Luo, Y. Xia and D. Lee, Selectivity in the Formal [2 + 2 + 2] Cycloaromatization of Enyne–Allenes



- Generated by the Alder-ene Reaction from Triynes, *Org. Lett.*, 2024, **26**, 7778.
- 13 D.-V. Vo, S. Su, R. Karmakar and D. Lee, Reactivity of Enyne-Allenenes Generated via an Alder-Ene Reaction, *Org. Lett.*, 2024, **26**, 1299.
- 14 A formal 1,7-H shift enyne-allenes; M. Zhang, H. Lu, B. Li, H. Ma, W. Wang, X. Cheng, Y. Ding and A. Hu, Experimental and Computational Study on the Intramolecular Hydrogen Atom Transfer Reactions of Maleimide-Based Eneidyne After Cycloaromatization, *J. Org. Chem.*, 2021, **86**, 1549.
- 15 (a) A. G. Myers and P. J. Proteau, Evidence for spontaneous, low-temperature biradical formation from a highly reactive neocarzinostatin chromophore-thiol conjugate, *J. Am. Chem. Soc.*, 1989, **111**, 1146; (b) A. G. Myers, E. Y. Kuo and N. S. Finney, Thermal generation of α , 3-dehydrotoluene from (Z)-1, 2, 4-heptatrien-6-yne, *J. Am. Chem. Soc.*, 1989, **111**, 8057; (c) R. Nakata, H. Yamada, E. Okazaki and I. Saito, Biradical formation from acyclic conjugated enyne-allene system related to neocarzinostatin and esperamicin-calicheamicin, *Tetrahedron Lett.*, 1989, **30**, 4995; (d) A. G. Myers, S. P. Aryedson and R. W. Lee, A new and unusual pathway for the reaction of neocarzinostatin chromophore with thiols. Revised structure of the protein-directed thiol adduct, *J. Am. Chem. Soc.*, 1996, **118**, 4725; (e) P. W. Murphy, C. Remenyi, H. Helten and B. Engles, 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; (f) L. Feng, D. Kumar, D. M. Birney and S. M. Kerwin, α , 5-Didehydro-3-picoline Diradicals from Skipped Azaenediynes: Computational and Trapping Studies of an Aza-Myers- Saito Cyclization, *Org. Lett.*, 2004, **6**, 2059; (g) A. G. Myers, P. S. Dragovich and E. Y. Kuo, Studies on the Thermal Generation and Reactivity of a Class of (σ,π) -1,4-Biradicals, *J. Am. Chem. Soc.*, 1992, **114**, 9369; (h) A. G. Myers and C. A. Parrish, DNA cleavage by an α , 3-dehydrotoluene precursor conjugated to a minor groove binding element, *Bioconjugate Chem.*, 1996, **7**, 322; (i) M. E. Cremeens, T. S. Hughes and B. K. Carpenter, 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; (j) C. Pedroli, D. Ravelli, S. Protti, A. Albini and M. Fagnoni, Singlet vs Triplet Reactivity of Photogenerated α ,n-Didehydrotoluenes, *J. Org. Chem.*, 2017, **82**, 6592; (k) P. G. Wenthold and A. H. Winter, Nucleophilic Addition to Singlet Diradicals: Heterosymmetric Diradicals, *J. Org. Chem.*, 2018, **83**, 12397.
- 16 Examples of 1,5-H transfer cyclization reactions: (a) K. K. Wang, H.-R. Zhang and J. L. Petersen, Thermolysis of Benzoenyne-Allenenes to Form Biradicals and Subsequent Intramolecular Trapping with a Tetraaryllallene To Generate Two Triarylmethyl Radical Centers, *J. Org. Chem.*, 1999, **64**, 1650; (b) I. Suzuki, M. Wakayama, A. Shigenaga, H. Nemoto and M. Shibuya, Synthesis of enediyne model compounds producing toluene diradicals possessing a highly radical character via enyne-allene intermediates, *Tetrahedron Lett.*, 2000, **41**, 10019; (c) M. Nechab, D. Campolo, J. Maury, P. Perfetti, N. Vanthuyne, D. Siri and M. P. Bertrand, Memory of chirality in cascade rearrangements of enediynes, *J. Am. Chem. Soc.*, 2010, **132**, 14742; (d) A. Gaudel-Siri, D. Campolo, S. Mondal, M. Nechab, D. Siri and M. P. Bertrand, Theoretical study to explain how chirality is stored and evolves throughout the radical cascade rearrangement of enyne-allenes, *J. Org. Chem.*, 2014, **79**, 9086; (e) A. Rana, E. M. Cinar, D. Samanta and M. Schmittel, Solving the puzzling competition of the thermal C²-C⁶ vs Myers-Saito cyclization of enyne-carbodiimides, *J. Org. Chem.*, 2016, **12**, 43; A perspective on HAT processes: (f) S. Sarkar, K. P. S. Cheung and V. Gevorgyan, C-H functionalization reactions enabled by hydrogen atom transfer to carbon-centered radicals, *Chem. Sci.*, 2020, **11**, 12974.
- 17 A related Diels-Alder dimerization of ene-allene; Y. Wang and T. R. Hoye, Isomerizations of Propargyl 3-Acylpropiolates via Reactive Allenes, *Org. Lett.*, 2018, **20**, 4425.
- 18 The crystallographic data for **2a**, CCDC 2494308: Experimental Crystal Structure Determination, 2026, DOI: [10.5517/ccdc.csd.cc2pqjki](https://doi.org/10.5517/ccdc.csd.cc2pqjki).
- 19 For the computational details, see the SI.
- 20 Even with two water molecules, an appropriate transition state could not be located on the energy surface.

