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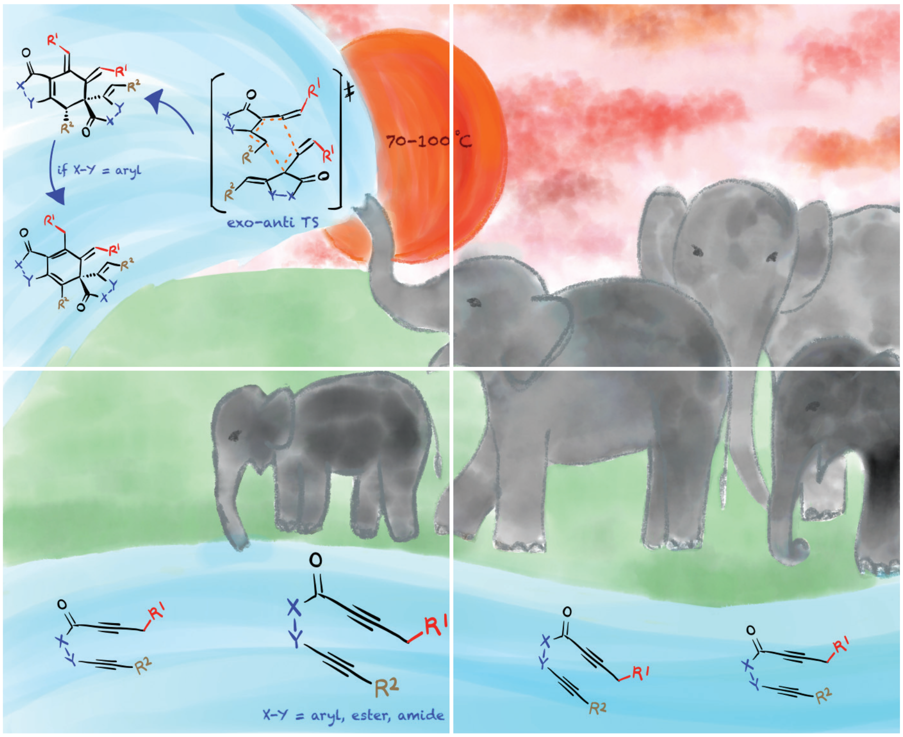

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Diels–Alder dimerization of ene-allenes and enyne-allenes generated *via* the propargylic Alder–ene reaction of diynes and triynes

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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.

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 R^1 on the enyne moiety and reaction conditions. If R^1 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 R^1 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 R^1 is terminal (R^1 = H) or an aryl group, product **E3** was obtained[13] *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 diynyl 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 CH_3CN, 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 R^1 and R on both alkynes were explored (Table 2). Replacing the $SiMe_3$ 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-

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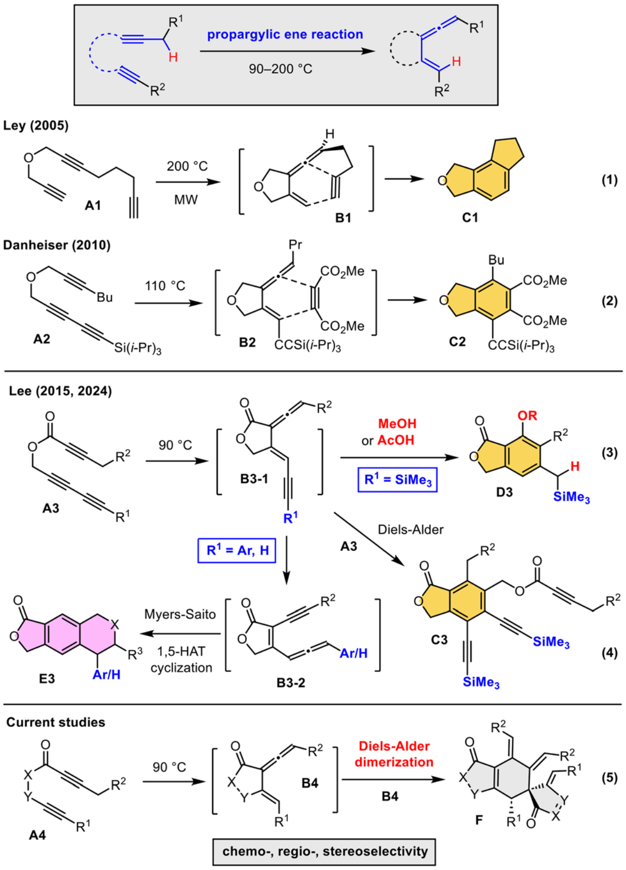
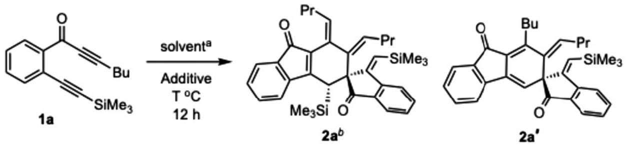


Scheme 1 Various cycloadditions of enyne-allenes generated by the propargyl Alder–ene reaction.

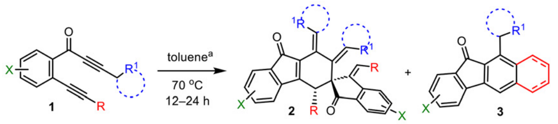
Table 1 Optimization of the Diels–Alder homo-dimerization of an ene-allene generated from diynone **1a**

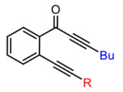
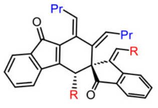
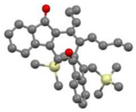
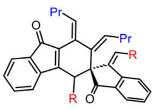
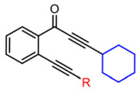
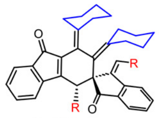
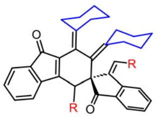
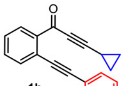
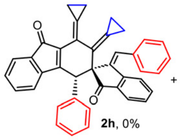
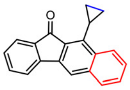
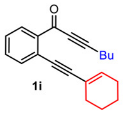
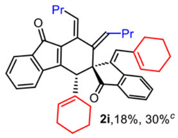
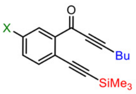
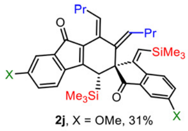
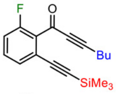
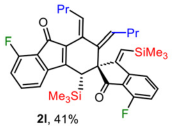


Entry	Solvent	Additive	T (°C)	**2a** (%)	**2a′** [c] (%)
1	Toluene	None	70	68	—[d]
2	Toluene	None	90	56	—
3	Toluene	None	110	65	—
4	THF	None	70	54	—
5	$ClCH_2CH_2Cl$	None	70	51	—
6	CH_3CN	None	70	—[e]	44
7	CH_3CN	None	90	—	71
8	Toluene	$AgSbF_6$ (15 mol%)	95	—	44
9	Toluene	$AgSbF_6$ (15 mol%)	70	—	66

[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.

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



entry	substrate	product, yield (%)[b]
1 2 3 4	 **1a**, R = $SiMe_3$ **1b**, R = Ph **1c**, R = Bu **1d**, R = H	 **2a**, 68% ≡  X-ray strucure of **2a**  **2b**, 47% (3:1 dr) **2c**, 0% (complex mixture) **2d**, 0 % (complex mixture)
5 6 7	 **1e**, R = $SiMe_3$ **1f**, R = Ph **1g**, R = H	 **2e**, 74%  **2f**, 51% (1:1 dr) **2g**, 0%
8	 **1h**	 **2h**, 0% +  **3h**, 63%
9	 **1i**	 **2i**,18%, 30%[c] + byproduct[d]
10 11	 **1j**, X = OMe **1k**, X = F	 **2j**, X = OMe, 31% **2k**, X = F, 83%
12	 **1l**	 **2l**, 41%

[a] Undistilled. [b] Isolated yield. [c] Grubbs II (10 mol%) in $CHCl_3$ 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.

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 (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 cyclopropylidene 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 **TS-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-**

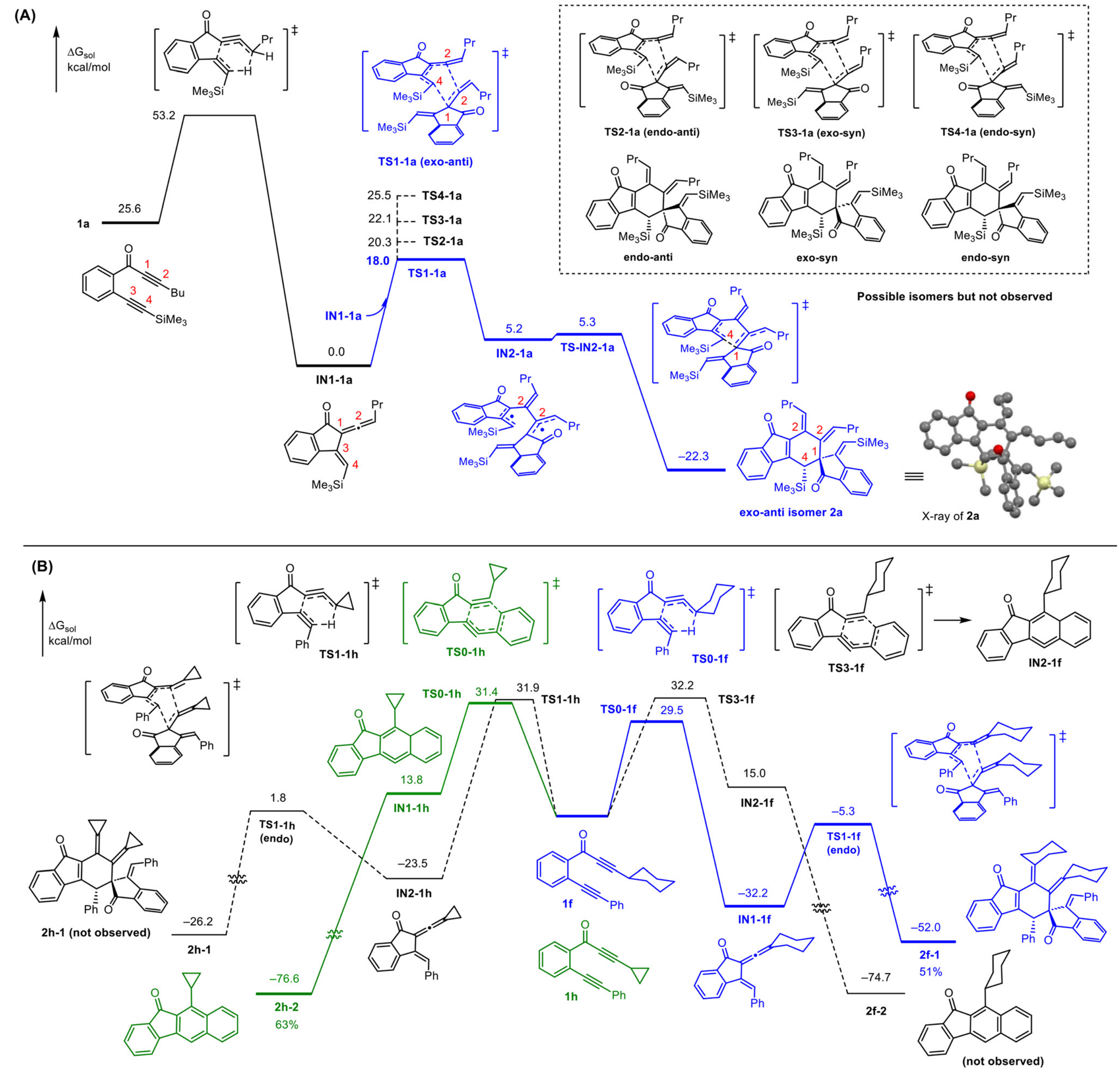


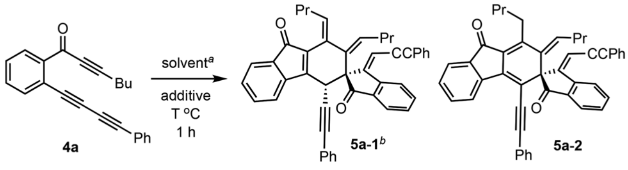
Fig. 1 (A) DFT calculations for chemo-, regio-, and stereo-selectivity in the Diels–Alder reaction of ene-allene **IN1-1a**, and (B) mode selectivity of alkynyl ketones **1f**/**1h** (optimization: B3LYP/6-31G(d); solvation: M06/6-311+G(d,p)).

1a, leading to the observed product **2a** (***exo-anti***). The modes of homo-dimerization for the other diastereomers (***endo-anti***/***exo-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 diynyl 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).

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_3CN	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.

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 **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 Me_3Si-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 ($CHCl_3$, 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 Al_2O_3. 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%),

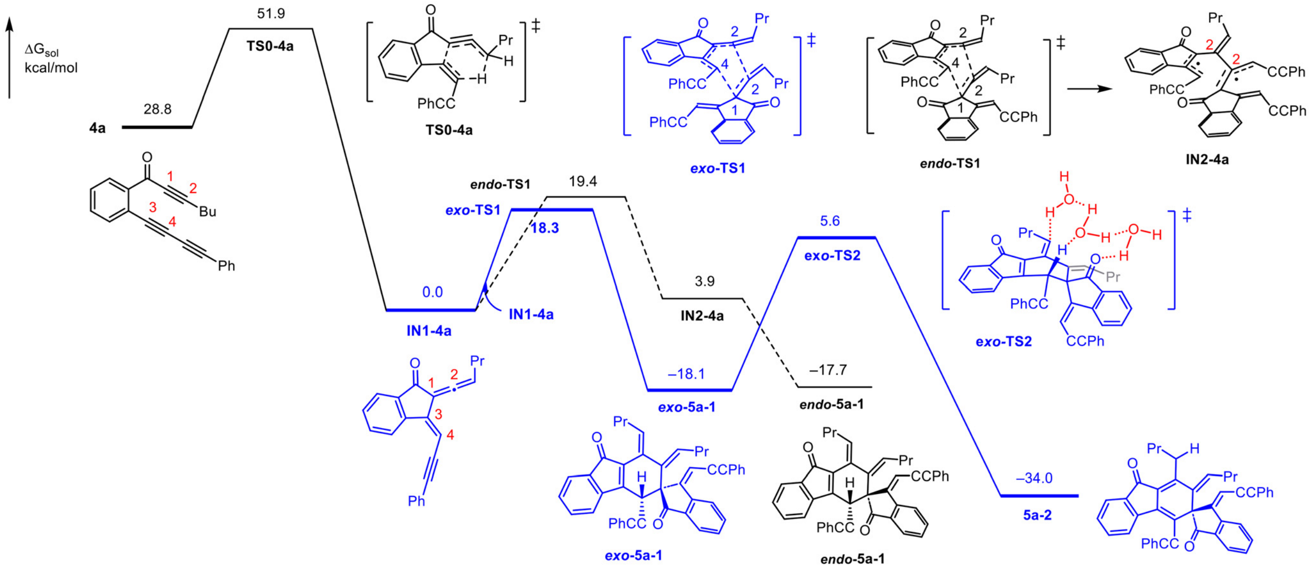
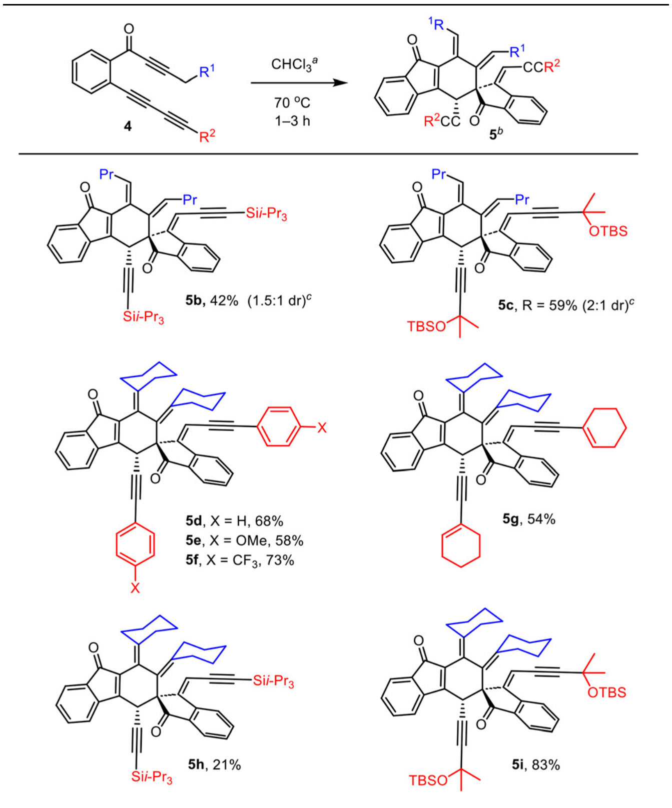


Fig. 2 DFT calculations for chemoselectivity and regioselectivity in the Diels–Alder reaction of enyne-allene **IN1-4a** and 1,5-H shift (optimization: B3LYP/6-31G(d); solvation: M06/6-311+G(d,p)).

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



5b, 42% (1.5:1 dr)[c]

5c, R = 59% (2:1 dr)[c]

5d, X = H, 68%
5e, X = OMe, 58%
5f, X = CF_3, 73%

5g, 54%

5h, 21%

5i, 83%

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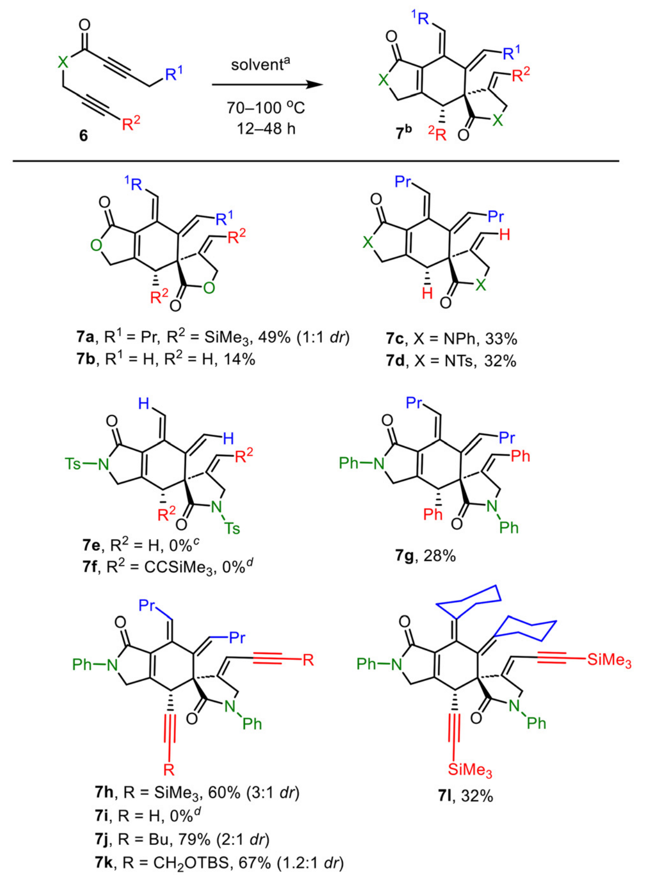
[a] Undistilled. [b] Isolated yield. [c] On basic Al_2O_3, the product undergoes [1,5]-H shift.

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



7a, R^1 = Pr, R^2 = $SiMe_3$, 49% (1:1 *dr*)
7b, R^1 = H, R^2 = H, 14%

7c, X = NPh, 33%
7d, X = NTs, 32%

7e, R^2 = H, 0%[c]
7f, R^2 = $CCSiMe_3$, 0%[d]

7g, 28%

7h, R = $SiMe_3$, 60% (3:1 *dr*)
7i, R = H, 0%[d]
7j, R = Bu, 79% (2:1 *dr*)
7k, R = CH_2OTBS, 67% (1.2:1 *dr*)

7l, 32%

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[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 = $SiMe_3$) gave product **7a** (49%, dr = 1 : 1), whereas the corresponding substrate with a terminal alkyne (**6b**, R^2 = H) gave **7b** in much lower yield (14%). The amide-tethered substrates with a terminal alkyne (**6c** and **6d**, R^2 = 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 = 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 methylidene moieties is due to their instability. For the reaction of the substrate containing a phenyl-substituted alkyne (**6g**, R^2 = Ph), an intramolecular tetradehydro 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 information is available. See DOI: https://doi.org/10.1039/d5qo01454a.

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

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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.