Formal [2 + 2 + 2] Cycloaddition Strategy Based on an Intramolecular Propargylic Ene Reaction/Diels−Alder Cycloaddition Cascade

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Abstract: A formal, metal-free, [2 + 2 + 2] cycloaddition strategy is described based on a cascade of two pericyclic processes. The first step involves an intramolecular propargylic ene reaction of a 1,6-diyne to generate a vinylallene, which then reacts in an inter- or intramolecular Diels−Alder reaction with an alkenyl or alkynyl dienophile. Reactions involving unsymmetrical alkenyl and alkynyl dienophiles proceed with good to excellent regioselectivity, and the diastereoselectivity in the Diels−Alder step is also high, with endo cycloadducts produced as the exclusive products of the reaction. In the case of alkynyl dienophiles, [4 + 2] cycloaddition initially generates an isotoluene-type intermediate that isomerizes to the isolated aromatic product upon exposure to a catalytic amount of DBU at room temperature. The mechanism of several earlier fully intramolecular related transformations have been shown to involve an analogous process rather than the diradical-mediated pathways proposed previously.

[2 + 2 + 2] Cycloadditions provide rapid access to polysubstituted six-membered rings. The most prominent variant of this powerful strategy is the transition-metal-catalyzed process in which three alkynes combine to form benzenoid aromatic products.[1] Although the fully intramolecular metal-catalyzed cotrimerization is generally an efficient process, the bimolecular variant involving the reaction of an α,ω-diyne with a third acetylene suffers from several limitations. Often a large excess of the third alkyne must be employed due to its competitive trimerization, and reactions in which the third alkyne is unsymmetrical frequently proceed with poor regioselectivity.[2]

Herein we describe a formal, metal-free, bimolecular [2 + 2 + 2] cycloaddition strategy based on a cascade of two pericyclic processes (Scheme 1). The first step involves an intramolecular propargylic ene-type reaction of a 1,6-diyne to generate a vinylallene of type **2**. The vinylallene is necessarily in an s-cis conformation, rendering it highly reactive in the second step, an inter- or

**Scheme 1.** Propargylic Ene Reaction/Diels−Alder Cycloaddition Cascade
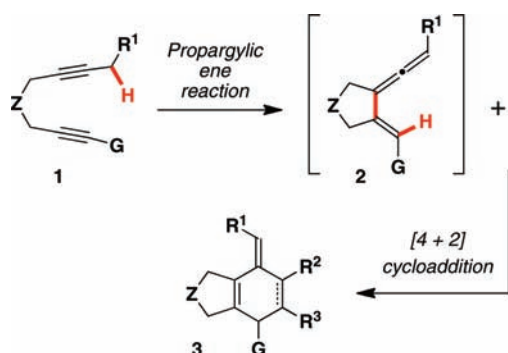
intramolecular Diels−Alder reaction with an alkenyl or alkynyl dienophile.[3] The efficacy of the propargylic-type ene reaction in this sequence is noteworthy. Although the intramolecular ene reaction is a well established process,[4] very few examples have been reported involving propargylic rather than allylic hydrogen atoms.[5,6] Overall, this two-stage pericyclic cascade sequence provides rapid access to highly functionalized alkylidenecyclohexane derivatives. When alkynes are employed as dienophiles, the initial products are isotoluene derivatives[7] that are easily isomerized to aromatic products upon exposure to base.

Scheme 2 presents representative examples of the formal [2 + 2 + 2] cycloaddition involving *N*-methylmaleimide as a dienophile and illustrating the effect of variations in the 1,6-diyne tether on the facility of the propargylic ene reaction.[8] Good yields are obtained using only 1 equiv of the dienophile, in contrast to most cases of the metal-catalyzed bimolecular [2 + 2 + 2] process. Products are obtained as predominantly *Z* isomers, as expected for cycloadditions in which bond formation to the central carbon of the allene moiety occurs preferentially trans to the R[1] substituent on the terminal carbon of the allene (Scheme 1).[9] In the case of these ene reactions involving unactivated alkynes as enophiles, efficient reaction generally requires temperatures in the range

Scheme 2. Formal [2 + 2 + 2] Cycloadditions with *N*-Methylmaleimide as Dienophile
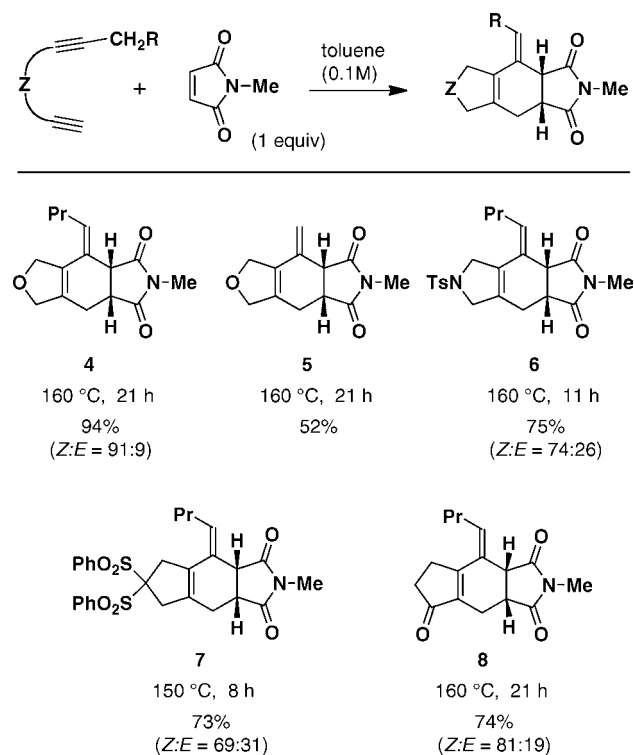
**Table 1.** Formal [2 + 2 + 2] Cycloadditions with Alkenyl Dienophiles
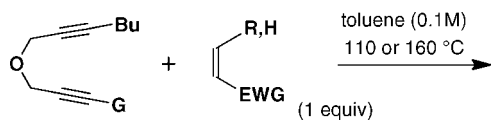
entry	G	dienophile	major product	yield (%)[a]
1	H **9** 160 °C, 21 h		**10**	72[b,c]
2	CO₂Me **11** 160 °C, 1 h		**12**	93[d,e]
3	Ph **13** 160 °C, 12 h		**14**	65[f]
4	CO₂Me **11** reflux, 19 h		**15**	57[f]
5	C≡CSi(i-Pr)₃ **16** reflux, 21 h		**17**	68[g]
6	C≡CSi(i-Pr)₃ **16** reflux, 21 h		**18**	63[h]

[a] Isolated yield of products purified by chromatography. [b] Mixture of Z and E isomers (86:14). [c] The regioisomeric Diels–Alder product was isolated in 11% yield. [d] Reaction at reflux for 21 h gave **12** in 68% yield. [e] Mixture of Z and E isomers (92:8). [f] Mixture of Z and E isomers (93:7). [g] Mixture of Z and E isomers (90:10). [h] Mixture of Z and E isomers (81:19).

150−160 °C.[10] Thermolysis in the absence of dienophiles leads to the formation of vinylallene dimers which are obtained as complex mixtures of regio- and stereoisomers.[11]

Further examples demonstrating the scope of the bimolecular version of this formal [2 + 2 + 2] cycloaddition strategy are shown in Tables 1 and 2. As expected, propargylic ene reactions involving diynes bearing electron-withdrawing groups proceed under milder conditions and in these cases the tandem ene reaction/Diels–Alder cascade can be carried out in refluxing toluene (Table 1, entries 2 and 4−6, Table 2, entry 3). In reactions involving MVK, methyl

acrylate, and butynone, yields are slightly improved by carrying out the tandem process in the presence of small amounts of BHT as a radical inhibitor. No competition from [4 + 2] arenyne[12] or "ynone"[13] type cycloadditions was observed in cases with G = Ph or CO₂Me (Table 1, entries 2−4). Reactions involving unsymmetrical alkenyl and alkynyl dienophiles proceed smoothly with good to excellent regioselectivity in the Diels–Alder step as observed previously for cycloadditions of vinylallenes.[3] Diastereoselectivity in the Diels–Alder step is also high, and endo cycloadducts are observed as the exclusive products of the reaction (Table 1, entries 2−6).[14] Finally, in the case of alkynyl dienophiles (Table 2), [4 + 2] cycloaddition initially generates an isotoluene-type intermediate that isomerizes to the isolated aromatic product upon exposure to a catalytic amount of DBU at room temperature.

Table 2. Formal [2 + 2 + 2] Cycloadditions with Alkynyl Dienophiles
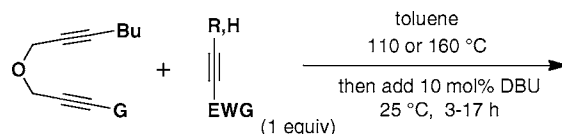
| entry	G	dienophile	major product	yield (%)[a]
1	H **9** 160 °C, 21 h		**19**	75
2	H **9** 160 °C, 21 h		**20**	40[b]
3	C≡CSi(i-Pr)₃ **16** reflux, 21 h		**21**	81

[a] Isolated yield of products purified by chromatography. [b] The regioisomeric Diels–Alder product was isolated in 6% yield.

Fully intramolecular "cyclotrimerizations" of triynes constitute one of the most useful variants of the transition-metal-catalyzed process, providing efficient access to angularly fused polycyclic systems. Several examples of purely *thermal* [2 + 2 + 2] cycloadditions of triynes have been reported prior to our work. Notably, in 1999 Kociolek and Johnson reported that the gas phase thermolysis of 1,6,11-dodecatriyne at 500−600 °C and 0.01 Torr affords a hexahydroindacene [2 + 2 + 2] cycloadduct together with derived dehydrogenation products in 35% combined yield.[15] Johnson proposed a stepwise mechanism to account for this process in which bond formation initially occurs between two alkynes to generate a 1,4-diradical which is then trapped by the third alkyne to directly produce an aromatic ring. An analogous diradical mechanism was proposed by Parsons et al. to account for an interesting cyclization of enediynes discovered in their laboratory.[16] More recently, Ley and co-workers have reported the cyclotrimerization of triyne **22** carried out in DMF either by heating at 200

°C or by using focused microwave heating.[17] Ley et al. reported the isolation of an intermediate that they identified as **27**, leading to the proposal of the mechanism outlined in Scheme 3 involving several unusual strained and reactive intermediates.

We have repeated the thermolysis of **22** and obtained unequivocal evidence that the intermediate formed in this reaction is not **27**, but rather the isomeric triene **28**[18] (Scheme 4), the product expected if the reaction proceeds via a sequential propargylic ene/[4 + 2] cycloaddition cascade mechanism rather than the pathway proposed by Ley and co-workers as outlined in Scheme 3. In addition, we have also found that cyclotrimerization of the related substrate **30** leads to the formation of diene **31** (the product predicted by our pericyclic cascade mechanism), rather than the isomeric diene **32** reported by Ley et al. as the product of this reaction (Scheme 5).[17]

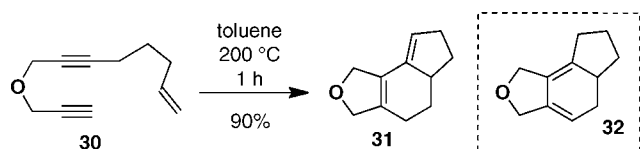**Scheme 3.** Mechanism Proposed (Ref 17) for Thermal Cyclo-trimerization of **22**
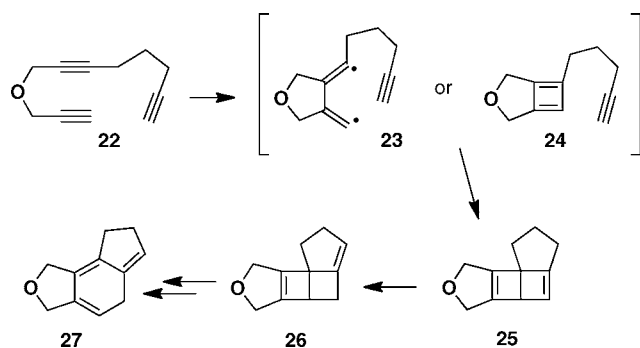
Scheme 4. Cyclotrimerization of Triyne **22**
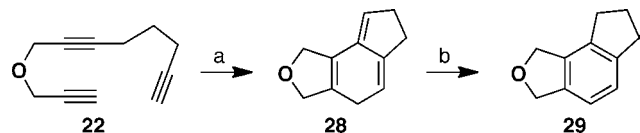
[a] Conditions: (a) 160 °C, 14 h, toluene. (b) Add 0.1 equiv of TsOH-H2O, 60 °C, 3 h; 56% total overall yield after reduction of indene byproduct (H2, Pd/C, MeOH, rt).

Scheme 5. Cyclotrimerization of **30**

In summary, this study establishes the utility of a bimolecular propargylic ene reaction/Diels–Alder cascade as a method for achieving formal, thermal [2 + 2 + 2] cycloadditions leading to functionalized polycyclic compounds. The mechanisms of several earlier fully intramolecular related transformations appear to involve an analogous pericyclic cascade process rather than the diradical-mediated pathways proposed previously. Further studies are underway in our laboratory aimed at developing additional syntheti-cally useful variants of this [2 + 2 + 2] strategy.

Supporting Information Available: Experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) As our study neared completion, Roglans et al. reported three related examples of a fully intramolecular propargylic ene/intramolecular Diels–Alder process involving 15-membered macrocyclic triaza triynes and enediynes: González, I.; Pla-Quintana, A.; Roglans, A.; Dachs, A.; Solà, M.; Parella, T.; Farjas, J.; Roura, P.; Lloveras, V.; Vidal-Gancedo, J. *Chem. Commun.* **2010**, *46*, 2944.

(7) For the synthesis and thermal behavior of *p*-isotoluene, see: Gajewski, J. J.; Gortva, A. M. *J. Am. Chem. Soc.* **1982**, *104*, 334, and references cited therein.

(8) For full details on the synthesis of the 1,6-diyne cycloaddition substrates, see the Supporting Information.

(9) *E/Z* stereochemistry was assigned by differential nOe experiments. See Supporting Information for details.

(10) Attempts to extend the intramolecular propargylic ene reaction to 1,7-diynes were not successful. Unreacted starting material was recovered after prolonged heating at 200 °C (see Supporting Information for further details). Note that in contrast to intramolecular ene reactions of 1,6-dienes, similar reactions involving 1,7-dienes require higher temperatures and proceed in low yield.[4]

(11) For the isolation and characterization of products generated by dimerization of the vinylallene produced by thermolysis of **16**, see the Supporting Information.

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