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Highly Selective Diels-Alder Reactions of Directly Connected Enyne Dienophiles

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Abstract: The paper describes the course of cycloadditions of Diels−Alder dienophiles containing linked enyne sites, each substituted with activating groups. Consistently, it was found that in the enyne cases the Diels−Alder reaction occurred specifically at the acetylenic center. Furthermore, it was found that the regiochemical sense of the cycloaddition was apparently determined by the remote activating group bound to the olefinic site. This remote acrylyl group totally dominated the course of the cycloaddition, relative to the activating group bound directly on the acetylene site. Explanations for these findings at the computational level are provided. The computations also rationalize the strong preference for cycloaddition to occur at the acetylene linkage and encompass the otherwise surprising regiochemical dominance by the remote ester on the olefinic site. The high selectivities available through such reactions provide important new opportunities in the synthesis of orsenillate type substructures that are found in a variety of natural products of contemporary interest.

Introduction

Since its discovery in 1928, the Diels−Alder reaction has emerged as one of the most powerful and versatile methods available for the construction of six-membered rings.[1] This reaction typically involves a cycloaddition between a 1,3-diene and an alkene-based dienophile. For uncatalyzed normal electron demand Diels−Alder reactions to work well in the absence of the benefits of intramolecularity, it is necessary for the dienophilic double bond to be activated by an electron-withdrawing group capable of resonance with the olefinic site. Rather less attention has been given to the development of synthetically viable Diels−Alder variants in which a similarly activated alkyne serves as the dienophilic coupling partner. Of course, the parent alkynes bearing two activating groups (cf. acetylenedicarboxylate esters) are well-known to be reactive dienophiles. In the research reported herein, primary attention is focused on alkyne dienophiles that are activated by only a single ester.

Earlier, our laboratory had attempted to exploit Diels−Alder cycloaddition reactions between monoactivated acetylenic dienophiles (cf. β-alkylated propiolic esters) and a variety of dienes, with the goal of producing benzoate esters. However, in sharp contrast to the situation with parent acetylenedicarboxylates, uncatalyzed Diels−Alder reactions of monoactivated acetylenic dienophiles bearing nonactivating substitution at the other acetylenic carbon have been found to be particularly slow.[2] The problem of a highly concise orsenillate synthesis, which was our goal, was partly ameliorated by the discovery of a more reactive acetylenic Diels−Alder variant, i.e., an “ynolide” as the dienophile (Scheme 1, eq 1). The ynolide concept has been successfully applied to the total syntheses of cycloproparadicicol and aigialomycin D.[3] Cycloadditions of allene-activated dienophiles with activated dienes were also examined as possible solutions to the problem, but the utility of the type of construction implied in eq 2 is undercut by the unexpectedly poor regioselectivity observed in the cycloaddition step (Scheme 1).[4]

With various long-term total synthesis designs in mind, we wondered about the relative dienophilicities of acetylenic (ynoate) and ethylenic (enoate) dienophiles activated by identical groups. We first studied a directly connected enyne system wherein the olefinic and acetylenic dienophile sites would carry identical activating groups, A_o (olefin activating group) and A_a (acetylene activating group), respectively (cf. **2**). In Scheme 2, our expectations at the outset of the study are spelled out. At

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(1) (a) Diels, O; Alder, K. *Justus Liebigs Ann. Chem.* **1928**, *460*, 98. (b) Alder, K.; Rickert, H. F. *Justus Liebigs Ann. Chem.* **1936**, *524*, 180.

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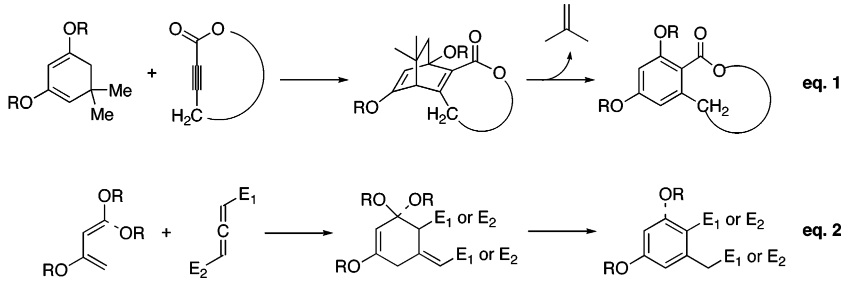
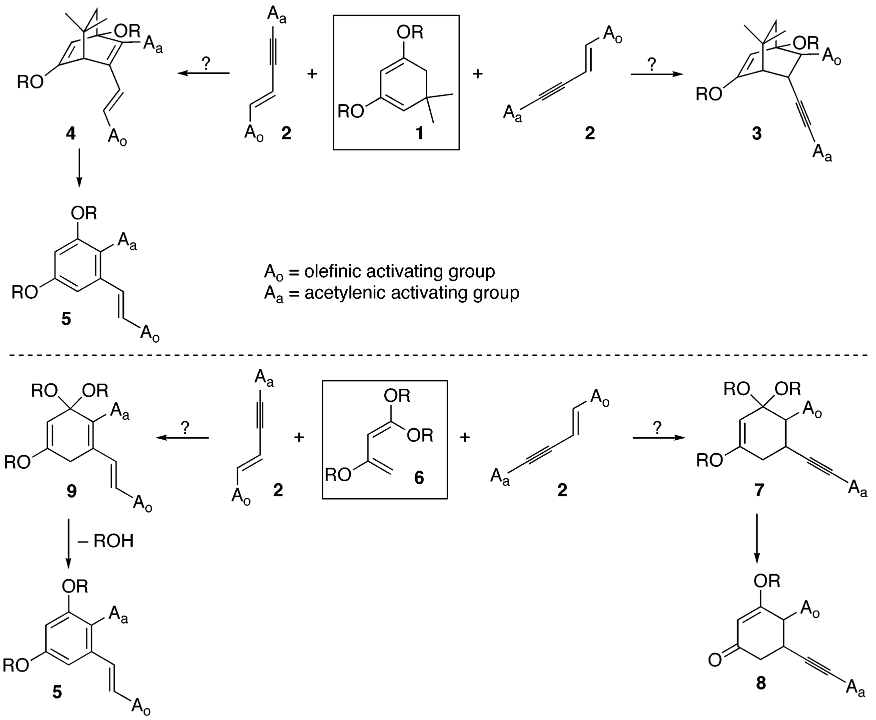
Scheme 1. Possible Syntheses of Aromatic Rings from Diels−Alder Reactions



Scheme 2



that time, the question of inherent chemoselectivity of "ene" vs "yne" potential dienophilic sites had not been well aired in the literature,[5] and we had no solid basis to prognosticate as to this matter. Specifically, we hoped to investigate two diene types, **1** and **6**, with respect to this question. With either of these probe dienes, it was expected that, if the cycloaddition step were to occur at the acetylenic dienophile site, an aromatic product would ensue. In the case of diene type **1**, cycloaddition followed by fragmentation of isobutylene would lead directly to the orsenillate type product **5**. By contrast, if cycloaddition was to occur at the olefinic center, producing an intermediate of the type **3**, retro-Diels−Alder fragmentation of isobutylene could well be more problematic, since the coordinated bond breaking steps (synchronous or sequential) would not directly accomplish aromatization.

Related issues apply to the use of acyclic diene type **6**. Reaction at the ynoate site would be expected to yield **9**. Following expected de-alcoholysis (i.e., elimination of ROH), the orsenillate **5** would be produced. Alternatively, cycloaddition at the enoate site would lead to **7**. The way in which **7** would unravel was less clear. The formation of **8** as a primary product from **7** would certainly find ample precedent.[2a] However, various competing prototypically related courses would be open to this enolizable, vinylogous, β-dicarbonyl system. It will have been noted that, in drafting the prospectus summary shown in Scheme 2, we were operating under the tacit assumption that the immediate activating group on each of the potentially dienophilic linkages would control the regiochemical course of reaction of its adjoining site. Actually, there was no data base to support this expectation.

The issue of the relative reactivity of olefinic and acetylenic dienophiles bearing an identical activating group had been taken up with separate substrates.[7−12] In our case, the two unsaturated

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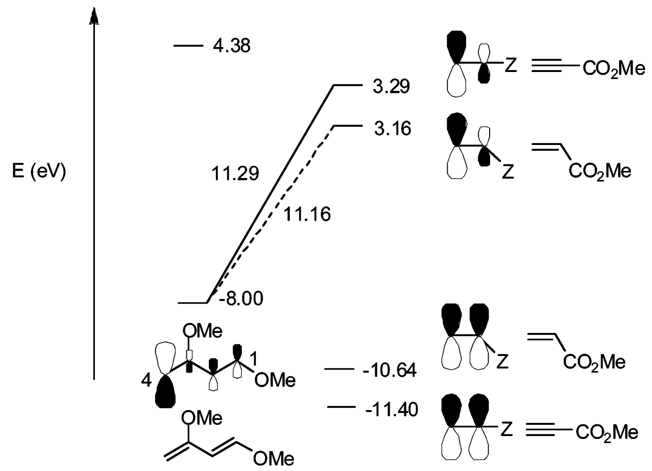


Figure 1. Frontier molecular orbitals for the reactions of dimethoxybutadiene (DMB) with methyl acrylate and methyl propiolate.

sites ("o" and "a") would be directly linked. We here note that Kocienski et al. have reported that the reaction of an enyne, activated by a single ester substituent on the alkyne moiety, with a Danishefsky-type diene afforded the product formed from addition to the double bond in about 40% yield.[5a] Two other minor products were also formed from addition to the triple bond, in yields of only about 9% each. Nevertheless, in light of the massive body of Diels−Alder driven research,[6] the question we were implicitly asking, i.e., that of the chemoselectivity of reaction of a conjugated enyne, wherein each linkage is equipped with an identical terminal activating group, had not otherwise been posed in the literature.

Our reading of Sauer's elegant investigations of Diels−Alder reactions of symmetrical dienes, such as cyclopentadiene and 9,10-dimethylanthracene, with alkynes and alkenes suggested that, at least in these cases, alkenes are usually more reactive than alkynes in Diels−Alder reactions.[7] Konovalov and coworkers demonstrated that with symmetrical cyclopentadienones as the dienic components, alkynes are more reactive than alkenes when the accepting characteristics of the diene increases.[8] In general, it seems that, with symmetrical dienes, disubstituted alkenes are somewhat more reactive than similarly substituted alkynes.[9−11]

These trends are well accommodated by frontier molecular orbital (FMO) theory,[12] which teaches that reactions having small $HOMO_{diene}-LUMO_{dienophile}$ gaps manifest faster rates. Thus, regiochemistry of the Diels−Alder reaction is controlled by the better overlap of the diene HOMO and dienophile LUMO orbitals, both of which have coefficients controlled by the substituent locations.[12d,e]

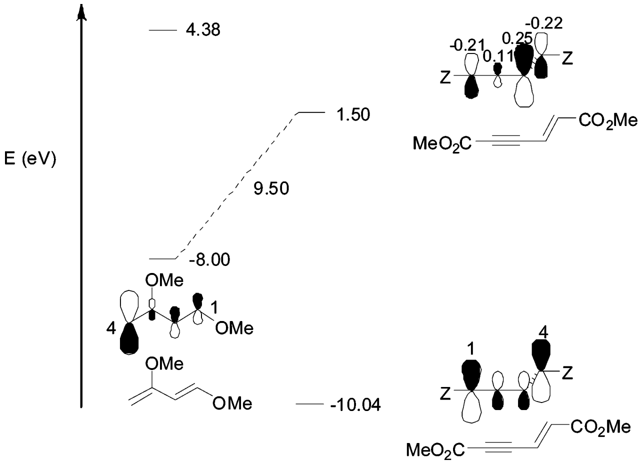
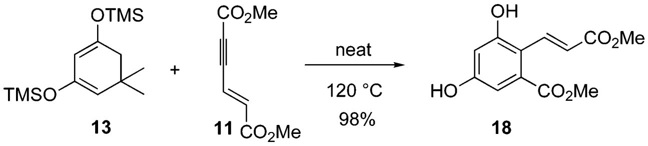


Figure 2. Frontier molecular orbitals for the reaction of dimethoxybutadiene (DMB) with dimethyl-hex-2-en-4-ynedioate. Orbital coefficients are shown above the LUMO orbital of the dienophile.

Scheme 3. Diels−Alder Reaction of Cyclic Diene **13** with the Enyne Dienophile, **11**



The FMO interactions in the reactions of 1,3-dimethoxybutadiene (DMB) with the dienophiles, methyl acrylate and methyl propiolate, are shown pictorially in Figure 1. HF (Hartree−Fock) energies for the frontier orbitals of the diene and dienophile components are shown; p-orbitals are sized in proportion to the coefficient of the atomic orbitals in the molecular orbitals.

The LUMO energy of methyl acrylate (3.16 eV) is lower than that of methyl propiolate (3.29 eV). As a result, the $HOMO_{diene}-LUMO_{dienophile}$ gap for the reaction involving methyl acrylate (11.16 eV) is smaller than that for the corresponding reaction involving methyl propiolate (11.29 eV). The regiochemical outcome of each reaction is controlled by the overlap of the largest lobes, on C_4 of the diene and on the β-carbon of the dienophile.

Similarly, FMO theory can also, in principle, be used to predict the selectivities of Diels−Alder reactions involving enynes. Figure 2 shows FMO interactions in the cycloaddition reaction of DMB with the diactivated enyne, dimethyl-hex-2-en-4-ynedioate. The $HOMO_{diene}-LUMO_{enyne}$ gap is smallest, and both the chemoselectivity and regiochemistry of the reaction should be controlled by overlap of C_4 of the diene with C_3 of the dienophile. Thus, strictly on the basis of FMO considerations, in keeping with the analogy to monoactivated dienophiles described above, it would be predicted that reaction will occur at the ene of the enyne, with the expectation that the directly connected ester substituent will control the regiochemical outcome (cf. Scheme 2).

A number of deficiencies of FMO theory have been identified since the development of the theory, mainly due to the lack of quantitative significance of FMO interactions.[13,14] In connection with these early findings, empirical findings as well as higher

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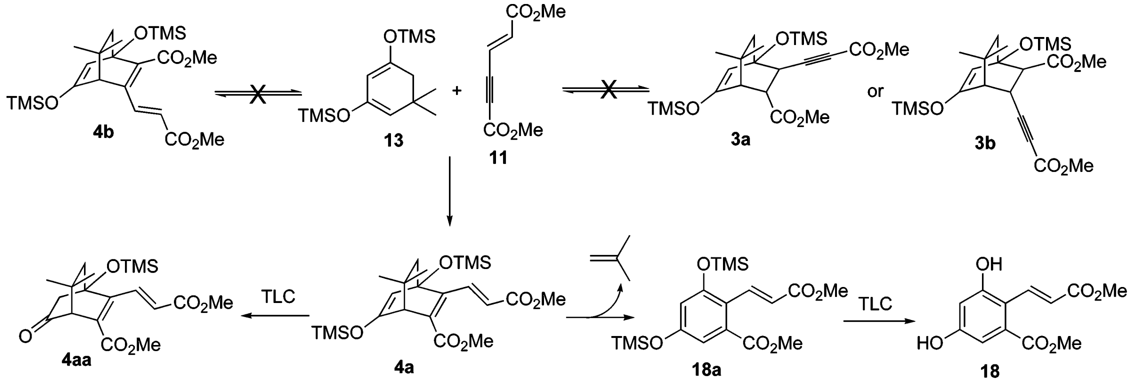
Scheme 4



level theoretical analyses have shown that FMO interactions alone can fail to predict the relative reactivities of alkenes and alkynes in Diels−Alder reactions.[15] The necessity to go beyond FMO theory to explain the relative reactivities of alkenes and alkynes in nucleophilic additions was noted some time ago.[16] Because of the nucleophilic character of the dienes to be employed in our projected synthetic ventures, the alkyne might be expected to be more reactive than the alkene. As shown in an early theoretical treatment, nucleophilic (“one-bond”) dienes may exhibit differing reactivity patterns relative to “two-bond” dienes such as cyclopentadiene and 9,10-dimethylanthracene.[17] In connection with these findings, Singleton and co-workers have recently noted the shortcomings of FMO theory in and of itself to predict the regiochemical sense of Diels−Alder cycloaddition reactions.[18]

As will be seen via the empirical results described herein, remarkably efficient and selective syntheses of conjugated arenes were accomplished via Diels−Alder reactions involving enyne dienophiles. In our case, exclusive attack on the yne is observed, and stereoselectivity is controlled by the remote vinyl ester substituent. Theoretical explorations prompted by these results have provided explanations of these phenomena as well as new insights into structural factors which impact upon the stability of transition states of Diels−Alder reactions.

Results and Discussion

Diels−Alder Cycloadditions of Enynes. 2-Hexen-4-ynedioic acid dimethyl ester, **11**, easily synthesized via the dimerization of methyl propiolate,[19] was coheated with dimedone-derived diene **13** at 120 °C for 12 h.[20] Of four possible products which might have been anticipated from this reaction, only the styrenyl ester, **18**, was observed (98% yield) (Scheme 3). The structure assigned to **18** was confirmed through a crystal structure of its bismethylated derivative (i.e., the corresponding resorcinol dimethyl ether). Clearly, the diene had reacted with the triple bond of **11**. However, surprisingly to us at the time, *the remote vinyl ester had totally dictated the regioselectivity of the reaction even in the presence of the attached ester*, in contrast to the expectation, shown in Scheme 2.

It was necessary to establish whether product **18** arises from a strong kinetic preference, or whether it reflects a subsequent transformation (via retro Diels−Alder reaction followed by a Diels−Alder reaction in the observed sense). Put differently, we wondered whether or not **18** actually reflects a thermodynamic sink of the various Diels−Alder, retro Diels−Alder, and aromatization progressions (Scheme 4). This matter was studied with careful monitoring of the course of the events by proton NMR spectroscopy.

As shown in Figure 3, cycloaddition happened slowly at room temperature (15% conversion after 24 h). At a slightly higher temperature (50 °C) the cycloaddition was faster (58% conversion after 24 h). The fragmentation of isobutylene leading to aromatic product occurred very slowly at approximately 80 °C wherein trace quantities of **18a** could be detected. Aromatization was completed at approximately 120 °C in approximately 12 h, giving **18a** as the only product. Its bis-desilylated derivative, **18**, was obtained after preparative TLC purification. We emphasize that *during this whole monitoring exercise, there appeared no other observable intermediates. We conclude that under our conditions, **18** is arising under strictly kinetic control.* This conclusion is further confirmed by the isolation and characterization **4aa** from silyl enol ether **4a**.

This result prompted further exploration. Accordingly, four other dienes (**14**,[21] **15**, **16**,[4] and **17**[22]) were prepared and studied. Each was subjected to thermolysis with enyne **11**. Diels−Alder adducts (**18**−**21**) were obtained in good to excellent yields (Table 1). In each case, the cycloadduct was the product of addition of the diene to the triple bond of the enyne. The regioselectivity of each transformation was apparently solely dictated by the activating group on the vinyl moiety. In fact, only one product was also observed arising from reaction of **11** with cyclohexadiene (**15**), which lacks additional “nucleophilic” activation. We do note, however, that, in the case of **15**, the yield of the cycloaddition reaction with **11** was notably lower than that with the “nucleophilic” dienes.

In an effort to gain a further grasp of the governing issues, we next explored reactions between diene **13** and four other enyne *bis*-dienophiles (Table 2). Two adducts were obtained when the ester group on the alkene moiety was deleted and a bromine was inserted on the dienophile (cf. **24**). We also

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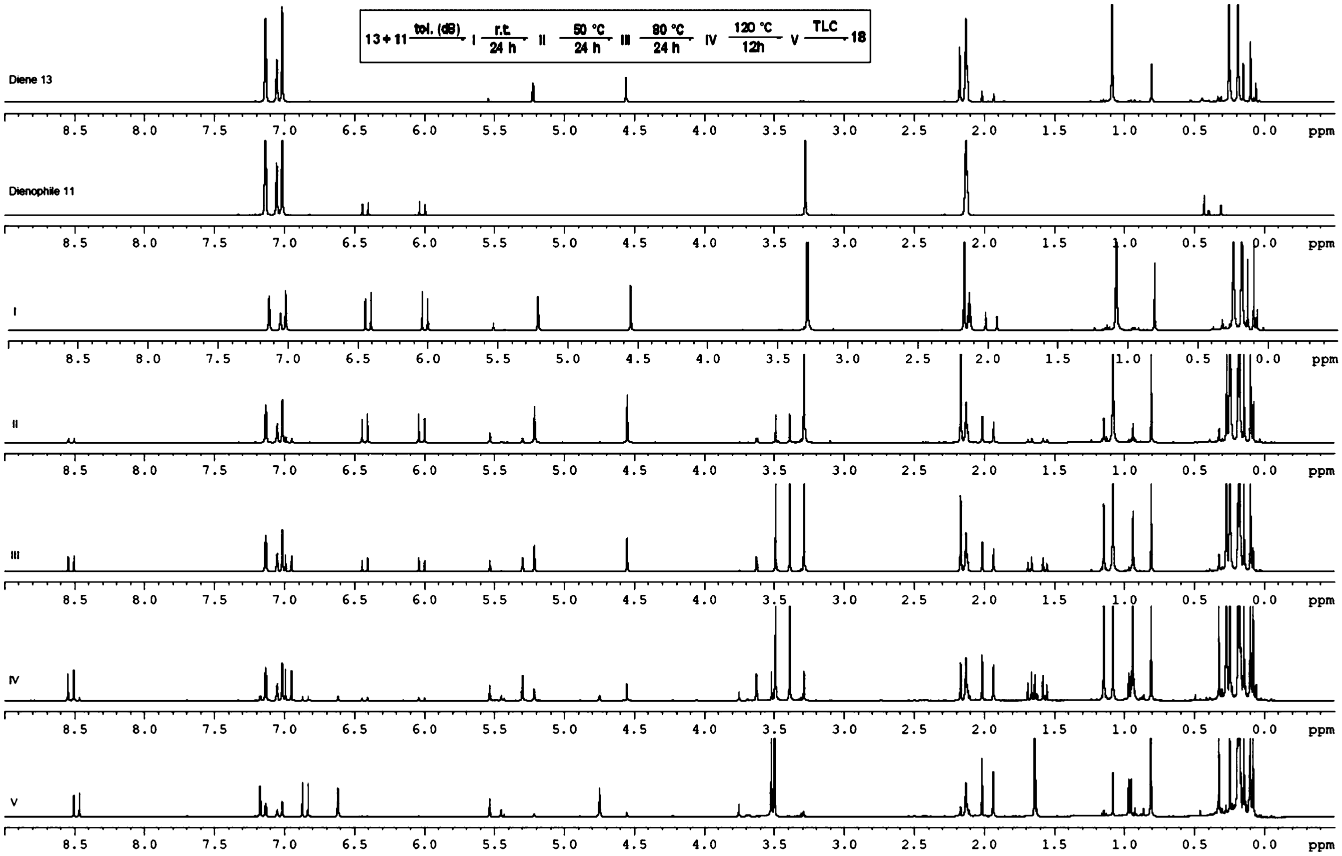

Figure 3. Diels−Alder reaction of diene **13** and dienophile **11** at different temperatures. Dienophile **11** (1.0 equiv, 6.5 mg) and diene **13** (1.2 equiv, 13.2 mg) were dissolved in 1 mL of toluene (d_8) in an NMR tube. The temperature was elevated from rt to 120 °C. Proton NMR was taken every 12 h.

examined the case of dienophile **25**,[23] which carries an olefinic *gem*-dimethyl group. Even in these cases, the major product of each cycloaddition reaction had been formed under the apparent control of the vinyl moiety, though yields of the Diels−Alder reaction were somewhat reduced. Remarkably, despite the similarity of these cycloadditions to those first investigated by Kocienski et al., the chemoselectivity of the reaction proceeded only by addition to the triple bond of the monoactivated enynes. These issues will be explored in the theoretical section.

Application of the chemistry to reactions with the enyne, methyl pent-4-en-2-ynoate (see **22**, $R_1 = CO_2Me$, R_2, $R_3 = H$) was attempted. However, this dienophile is unstable, even below the temperatures required for cycloaddition. By contrast, cycloaddition reactions of the more stable **26** and **27** (available via one-flask tandem manganese dioxide oxidation/Horner−Wadsworth−Emmons olefination)[24] with **13** at 160 °C did afford adducts **32** and **33**, respectively, in excellent yields and with complete selectivity. It will be noted that the reaction of **13** with **27** points the way to an efficient synthesis of biaryl compounds.

The unexpected sense of regiocontrol observed in the Diels−Alder reactions of the enyne-dienophiles described above led us to speculate on the regiochemical outcome of Diels−Alder reactions of dienophiles possessing β,β'-connected *bis*-dienyl ester functionality (cf. **35**) (Scheme 5). Furthermore, with this type of dienophile, it would be possible to investigate issues of product stereochemistry when the olefin undergoes the cycloaddition. We were also interested to learn which dienophile substituent (ester or vinyl ester) would dictate the stereochemical outcome of the Diels−Alder reaction in the *bis*-enophile case.

In the event, treatment of *bis*-dienophile **35**[25] with diene **40** led to a 1:1 mixture of *endo*/*exo* type cycloadducts (Scheme 6). Since the ene linkages of **35** are both *E*, each Diels−Alder adduct per force contains one *endo* and one *exo* group. For purposes of this discussion, we define the "*endo* product" as the one in which the apparent regiocontrolling (i.e., "ortho") group emerges *endo*. If there is a dichotomy between the regio- and stereo-determinants, we classify this as the "*exo* product." In both cases presented below, a single regioisomer was observed, as shown. The use of the more reactive Rawal diene (**44**)[26] provided Diels−Alder adducts with the same sense of regioselectivity and with an improved diastereomeric ratio (*endo*(**45**)/*exo*(**46**) = 4:1). The observed sense of regiochemistry is consistent with the regioselectivities obtained in our previously described enynyl−dienophile cases, where cycloaddition had occurred at the ynoate site.

By contrast, reaction of Rawal's diene (**44**)[26] with enyne **11** at room temperature provided a single regioisomeric product in moderate yield (Scheme 7). Reaction of diene **40** in refluxing benzene yielded a similar result. Once again, the regiochemistry was controlled by the vinyl ester moiety. Neither of these dienes produced adducts resulting from reaction across the enoate sector. These phenomena were reproduced by computations. In

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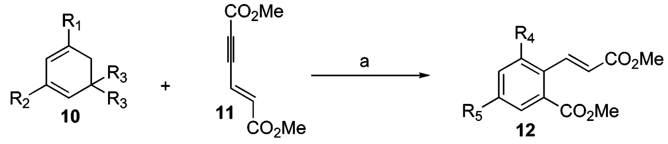
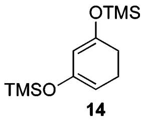
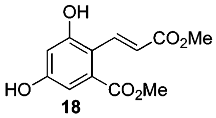
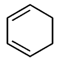
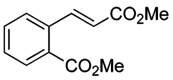
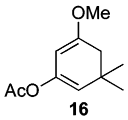
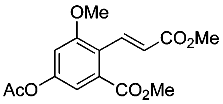
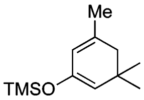
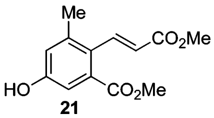
Table 1. Diels−Alder Reactions of Cyclic Dienes with the Enyne Dienophile, **11**



Entry^a	Diene	Product	Yield^b
1	 **14**	 **18**	98%
2	 **15**	 **19**	65%
3	 **16**	 **20**	96%
4	 **17**	 **21**	98%

^{a} The mixture of diene (2.5 equiv) and dienophile (1.0 equiv) were heated at 120 °C for 12 to 36 h. ^{b} Isolated yields after silica gel chromatography.

this context, a new phenomenon controlling the chemoselectivity and regioselectivity observed in these reactions was found (vide infra).

Theoretical Studies. In order to determine the chemo- and regioselectivities in these reactions, the transition states for many of the systems that had been explored experimentally were also studied computationally. Lowest energy conformations of transition states are reported in each case. The transition states for the reactions were obtained using density functional theory, which has been found to give geometries and energies of transition states in accord with experimental measures such as kinetic isotope effects and reaction rates. In the case at hand, the calculations give excellent agreement with experiment and also led to the discovery of a phenomenon that causes acetylenes activated by two electron-releasing groups to be more reactive toward nucleophilic dienes, or nucleophiles in general, than ethylenes activated by two electron-withdrawing groups.

Computational Methods. Geometry optimizations for all reactants and transition structures were performed using the B3LYP[27,28] density functional theory (DFT) method as implemented in the Gaussian 03[29] suite of programs, with the 6-31G(d) basis set.

Transition States of Enyne Cycloadditions. The activation enthalpies for formation of the four possible adducts resulting from addition of 5,5-dimethyl-1,3-dimethoxycyclohexa-1,3-diene, **49**, the dimethoxy analogue of dienes **13** and **16**, to the triple bond (**TS1**, **TS2**) or the double bond (**TS3**, **TS4**) of **11** are shown in Table 3. The vinyl ester controlled yne Diels−Alder adduct is formed from **TS1** which has an activation enthalpy of 14 kcal/mol ($\Delta G^{\ddagger} = 27$ kcal/mol). The ester-controlled yne Diels−Alder adduct is formed from **TS2** and has an activation enthalpy of 20 kcal/mol ($\Delta G^{\ddagger} = 33$ kcal/mol). Both intermediates, formed from reactions involving the enyne triple bond, extrude isobutylene through a retro-Diels−Alder reaction to form styrenyl products.

The reaction enthalpies of −33 and −31 kcal/mol ($\Delta G_{\text{int}} =$ −18 and −17 kcal/mol) for formation of the vinyl ester controlled and ester controlled intermediates, respectively, indicate that these cycloadducts might be experimentally observable under short reaction times. With reference to the intermediates, the free energy of activation for isobutylene loss from the vinyl ester controlled DA adduct is 27 kcal/mol; this is approximately equal to the initial cycloaddition step. In contrast, the free energy of activation for isobutylene loss from the ester controlled DA adduct is 28 kcal/mol, which is about 5 kcal/mol less than the corresponding cycloaddition step.

The activation enthalpies for formation of adducts resulting from addition of the diene to the enyne double bond are both equal to 23 kcal/mol; these are 9 kcal/mol greater than the activation barrier for **TS1**, involving vinyl ester controlled addition to the triple bond of the enyne. The reaction enthalpies for these reactions are about −10 kcal/mol; these cycloadducts are about 21 kcal/mol less stable than those produced from addition to the triple bond. What is more, the reaction free energies of these reactions are about +5 kcal/mol, which

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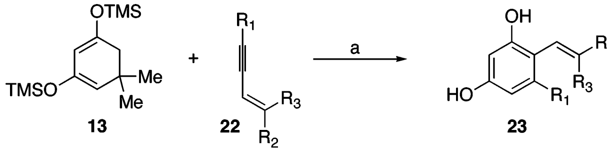
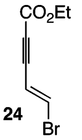
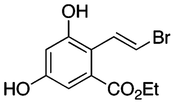
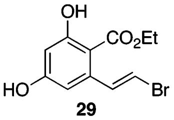
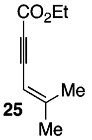
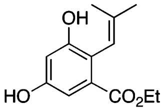
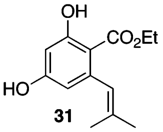
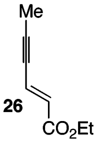
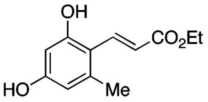
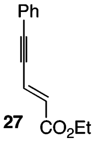
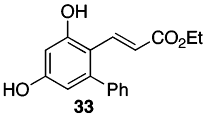
(27) (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.(c) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 1372.

(28) (a) Stephens, P. J.; Devlin, F. J.; Chabalowski, C. F.; Frisch, M. J. *J. Phys. Chem.* **1994**, *98*, 11623. (b) Stephens, P. J.; Devlin, F. J.; Ashvar, C. S.; Bak, K. L.; Taylor, P. R.; Frisch, M. J. *ACS Symp. Ser.* **1996**, *629*, 105. (c) Hehre, W. J.; Radom, L.; Schleyer, P. V.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; Wiley: New York, 1986.

(29) Frisch, M. J., et al. *Gaussian 03*, revision C.02; Gaussian, Inc.: Wallingford, CT, 2004.

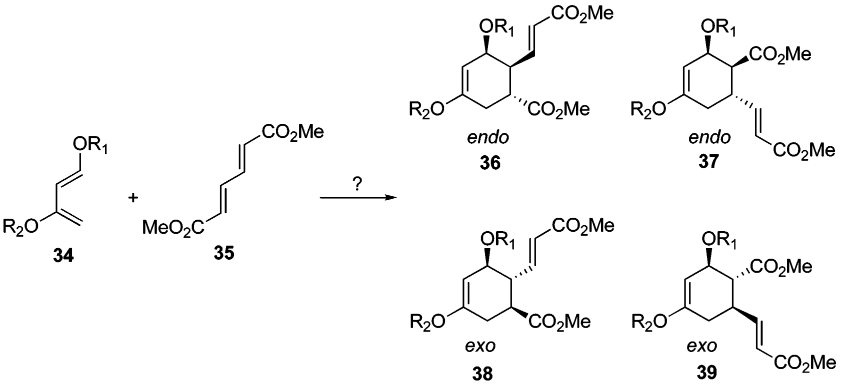
Table 2. Diels−Alder Reactions of Cyclic Dienes with Enyne Dienophiles



Entry[a]	Dienophile	Product(s)		Temp (°C)	Yield[b]
1	 **24**	 **28** (major)	 **29**	120	62% (3:1)
2	 **25**	 **30** (major)	 **31**	210	73% (5:2)
3	 **26**	 **32**		160	98%
4	 **27**	 **33**		160	92%

[a] The mixture of diene (2.5 equiv) and dienophile (1.0 equiv) were heated at the designated temperature for 12−36 h. [b] Isolated yield after silica gel chromatography.

Scheme 5[a]



[a] Note: *Endo* and *exo* are defined here based on the relationship between the regio-directing group and the inside proton of the diene. Thus, a *trans* relationship between these moieties would be considered *endo* and a *cis* relationship is considered *exo.*

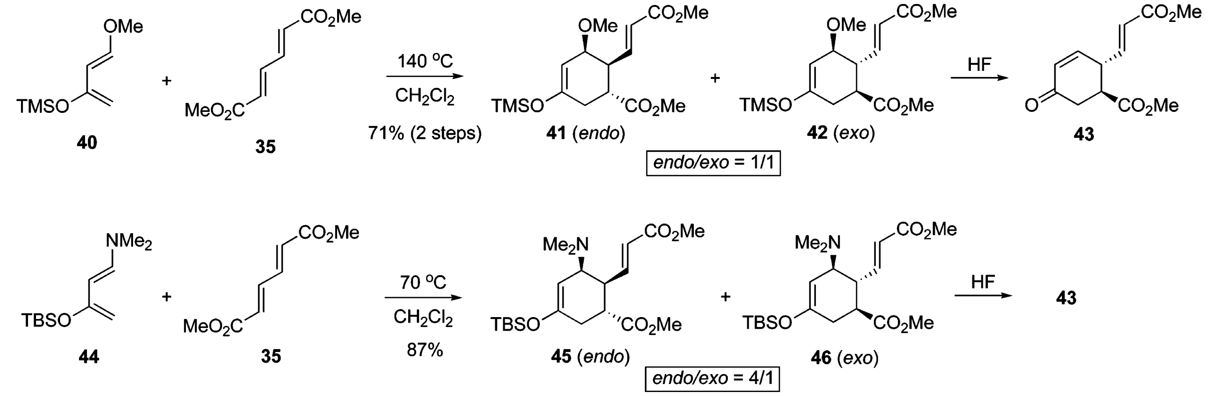
indicates that the equilibrium of the reaction is shifted toward reactants. Therefore, in comparison to the fast, irreversible cycloadditions of dienes with the triple bonds of diactivated enynes, cycloaddition involving the double bond is slow and reversible.

Overall, these results are in agreement with the experimental results for Diels−Alder reactions of diester-substituted enynes outlined above: kinetics and thermodynamics favor the addition of dienes to the triple bonds of diester-substituted enynes over addition to double bonds. In addition, they suggest that the regioselectivity is controlled by the vinyl ester, not the ester group, which is also in agreement with experiment.

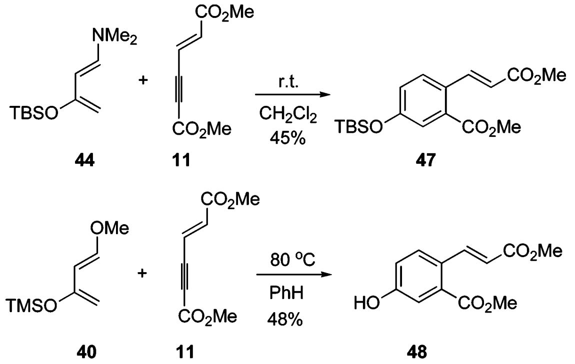
The barriers for these cycloadditions are rationalized by the transition structures for each of these cycloadditions, which show the contributions of the ester and vinyl ester moieties. Four transition structures corresponding to both diene $C{\equiv}C_{\text{enyne}}$ (**TS1**, **TS2**) and both diene $C{=}C_{\text{enyne}}$ (**TS3**, **TS4**) cycloadditions are shown in Figure 4. Like the methyl acrylate and methyl propiolate cycloadditions, these transition structures are all highly asynchronous, with the difference between partial bonds ranging from 0.8 to 1.3 Å.[30]

The p-orbitals of the ester and vinyl ester substituents are orthogonal in the transition structures for diene $C{\equiv}C_{\text{enyne}}$ cycloadditions. Because of this arrangement of substituents in

Scheme 6



Scheme 7



TS1 and **TS2**, the partial negative charge that develops in the rather zwitterionic transition states (a charge transfer from diene to dienophile is 0.3e in **TS1)** can be stabilized by both substituents at once. However, in reactions involving the double bond (**TS3**, **TS4**), the partial negative charge can be stabilized mostly by the β substituent only. Highly asymmetric transition structures such as these were first discovered by Domingo et al.[31] and later investigated by Morokuma et al.[9] and Singleton and co-workers[10] for related cycloadditions of diactivated alkynes.

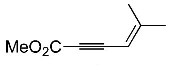
Regioselectivity in Enyne Cycloadditions. In highly asynchronous **TS1**, the acrylate group is in a position to stabilize the negative charge directly, while the immediately bound ester can do so only indirectly. It is clearly advantageous for the acrylate to be able to stabilize the developing anion.

To model the effect of the ester and vinyl ester substituents on the regioselectivities of these reactions, we have performed calculations on the isodesmic reactions of the vinyl anion with methyl acrylate and methyl-2,4-pentadienoate to form ethylene and the ester and vinyl ester stabilized vinyl anions (Figure 5). The isodesmic reaction preserves the number and type of bonds on each side of the equation. This model provides a measure of stabilization of a fully formed vinyl anion when the group is directly conjugated with the carbanion (direct stabilization), or when there is what we call indirect stabilization. These equations measure the stabilization of a vinyl anion by the substituents. The relevance to the cycloadditions is that, in the transition states in Figure 4, the highly nucleophilic diene is forming a bond to one terminus of the acetylene, and there is considerable vinyl anion character built up at the other terminus. The isodesmic equations assess how the substituents would stabilize the vinyl anion were it to be fully formed as an intermediate in these cycloadditions.

Returning to the stabilizations assessed in Figure 5, the direct stabilization of the vinyl anion is largest. An ester provides 32 kcal/mol stabilization, and an acrylate group gives an even larger 48 kcal/mol. The amazing fact is that indirect stabilization by the ester or the acrylate is also very large, 21 and 27 kcal/mol. In a resonance picture, indirect stabilization can be thought of as the stabilization of the carbene resonance form of the vinyl anion:

B3LYP predicts that the vinyl anion is stabilized by −32 kcal/mol by direct interaction with the ester group and by −21 kcal/mol from indirect interaction with the ester group. In contrast, the acrylate directly stabilizes the negative charge by −48 kcal/mol and indirectly by −27 kcal/mol; these acrylate stabilization energies are 16 and 6 kcal/mol, respectively, greater than the stabilization energies obtained with the ester substituent.

The preference for the formation of the vinyl ester controlled adduct in the reactions of **11** with dienes is primarily the result of an electronic effect, in which the negative charge that develops at the transition state is best stabilized by the combination of direct conjugation to the vinyl ester substituent and indirect stabilization by the ester group. This indirect stabilization is a new aspect of cycloaddition reactivity that will have important effects on the relative reactivities of alkenes and alkynes.



50

Reactions of Monoactivated Enynes. Two examples of cycloadditions involving monoester-substituted enynes are

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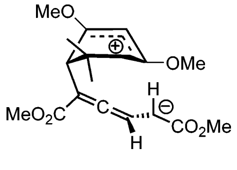
(30) IRC calculations performed on the transition state for the formation of the vinyl ester-controlled adduct uncovered the zwitterionic intermediate ($S^2 = 0$) shown below, corresponding to the adduct formed from nucleophilic addition of the diene. The energy of this intermediate is 12.5 kcal/mol, which is 1.5 kcal/mol lower than the transition state. However, the ring-closing transition structure proceeding from this intermediate could not be found, most likely because of the near-zero activation barrier for conversion of this zwitterions to product.



(31) (a) Domingo, L. R.; Jones, R. A.; Picher, M. T.; Sepúlveda-Arques, J. *Tetrahedron* **1995**, *51*, 8739. (b) Domingo, L. R.; Arnó, M.; Andrés, J. *Tetrahedron Lett.* **1996**, *37*, 7573. (c) Domingo, L. R.; Picher, M. T.; Aurell, M. J. *J. Phys. Chem. A* **1999**, *103*, 11425.

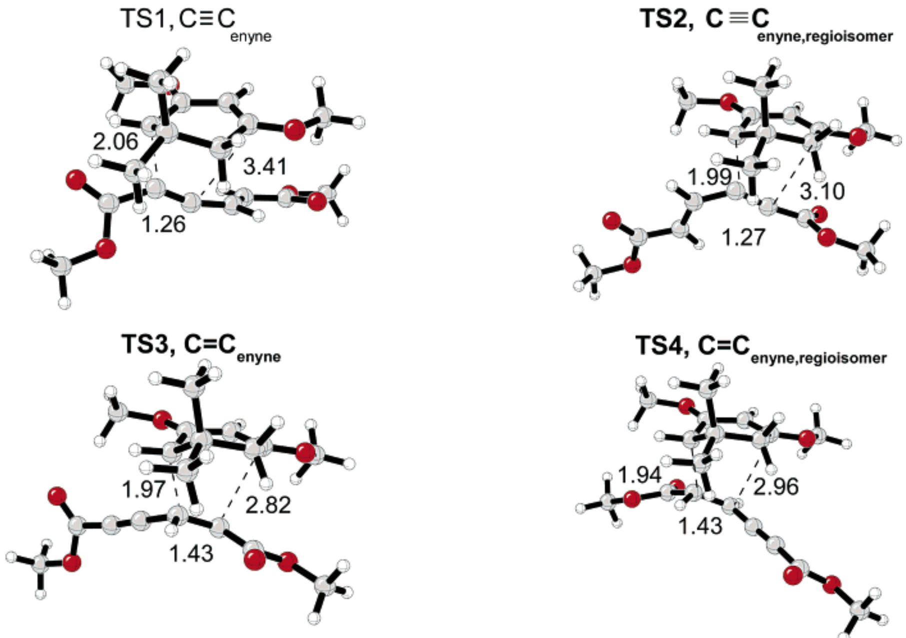
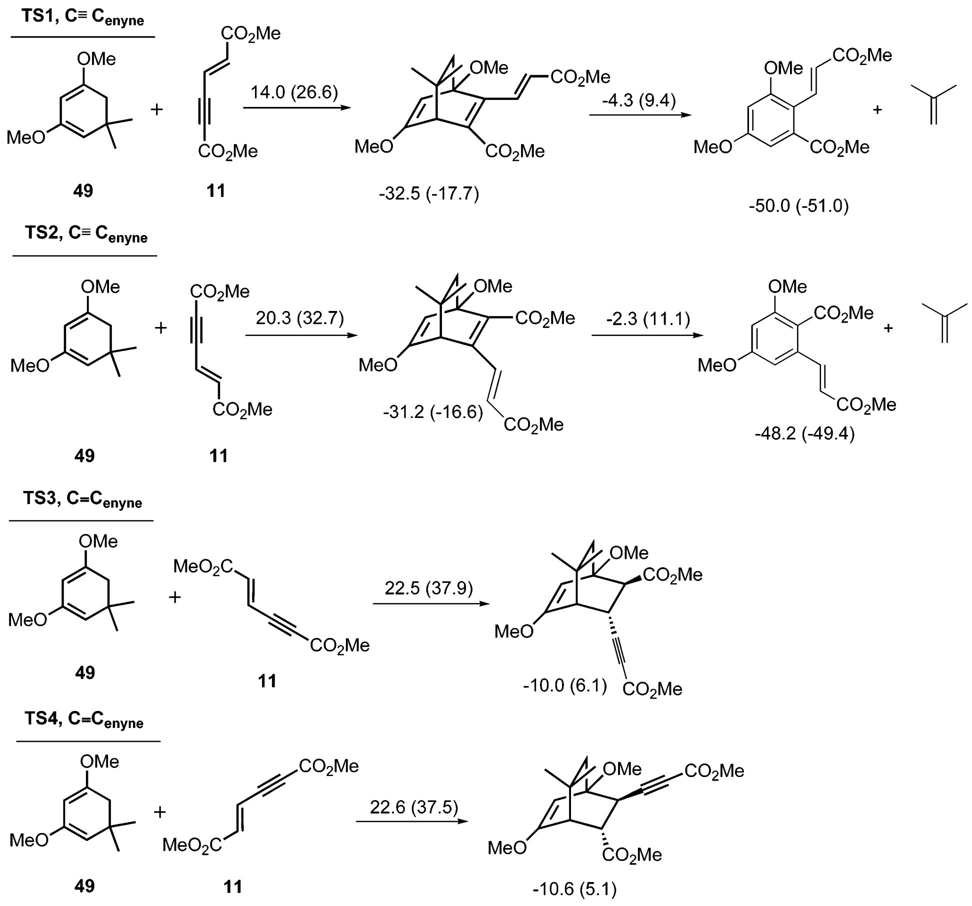


Figure 4. B3LYP transition structures for the four modes of cycloaddition of **49** with enyne **11**. Forming bond distances are in angstroms.

Table 3. B3LYP Relative Enthalpies of Transition States (above Arrows) and Products of Diels−Alder Reactions of **49** with Enyne **11** (Free Energies of Transition States and Products Are Shown in Parentheses)



represented by eqs 1 and 2 in Table 2. As shown, addition to the double bond does not occur. Notably, however, both enynes react to give vinyl-controlled adducts (cf. **28** and **30**) in an ~3:1 preference over ester-controlled adducts (cf. **29** and **31**).

Geometries and energies for model reactions have been computed in an attempt to understand the observed chemo- and regioselectivities. Relative energies for the reaction of one of enyne, **50**, a model for enyne **25** used in experimental studies,

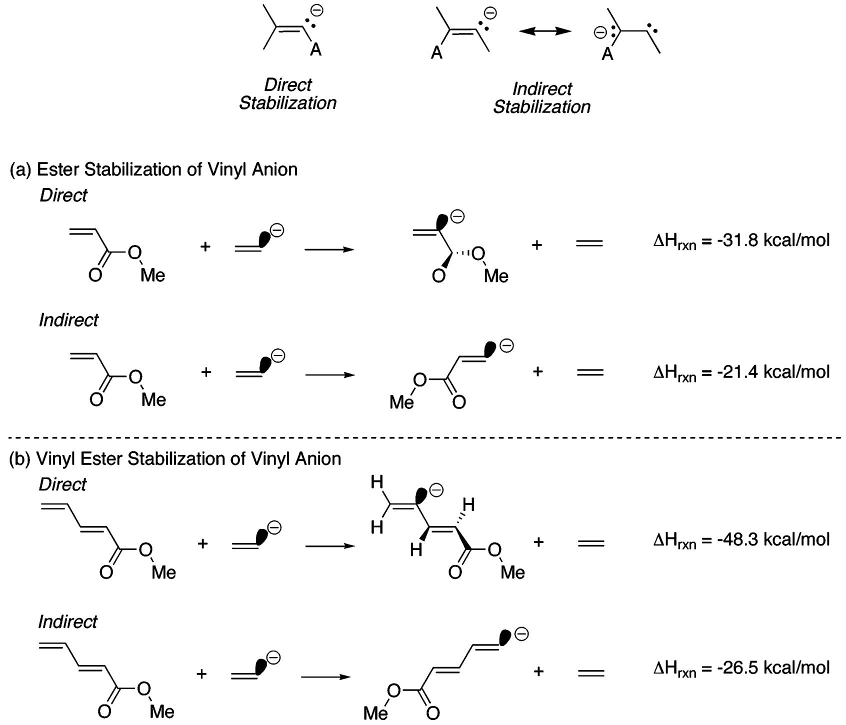
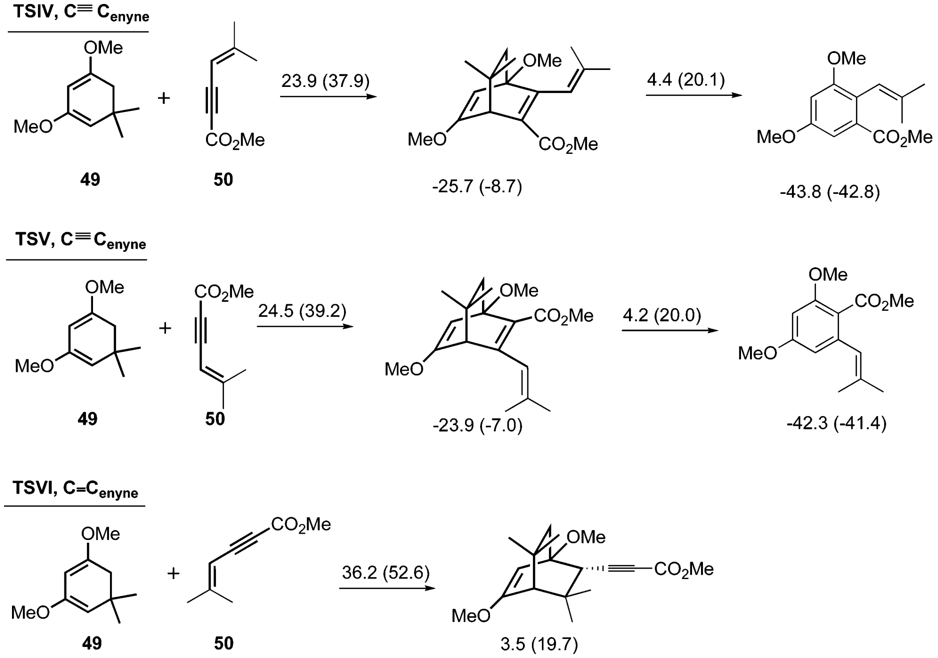


Figure 5. B3LYP stabilization energies (kcal/mol) by ester and acrylate substituents from isodesmic reactions of methyl acrylate and methyl-2,4-pentadienoate with the vinyl anion. Direct and indirect stabilization is assessed.

Table 4. B3LYP Relative Enthalpies of Transition States (above Arrows) and Products of Diels−Alder Reactions of **49** with Enyne **50** (Free Energies of Transition States and Products Are Shown in Parentheses)



with **49** are shown in Table 4; transition state geometries and relative energies are also shown in Figure 6. Enynes **24** and **25** are similar enough that conclusions derived from the study of one of these reactants should be readily applicable to the other.

The activation enthalpies for vinyl-controlled and ester-controlled cycloadditions to the triple bond of the enyne are 24 and 25 kcal/mol, respectively. These are about 12 kcal/mol smaller than the activation enthalpy for addition to the double bond of the enyne (36 kcal/mol). These results are similar to the predicted preference for vinyl-controlled addition to the triple bond of diactivated enynes; more significantly, the final products observed in experiment result from cycloadditions of the diene with the triple bond of monoactivated enynes.

The reaction enthalpies for formation of the yne, vinyl-controlled and yne, ester-controlled adducts are −26 and −24 kcal/mol, respectively; these are about 30 kcal/mol more stable than the reaction enthalpy for formation of the ene-controlled cycloadduct (+4 kcal/mol). Moreover, cycloaddition of the diene

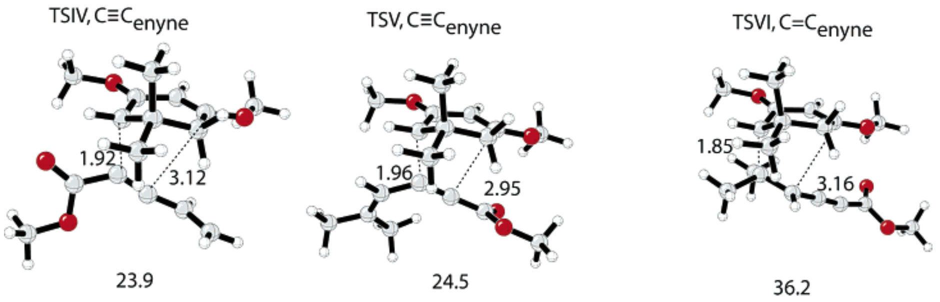
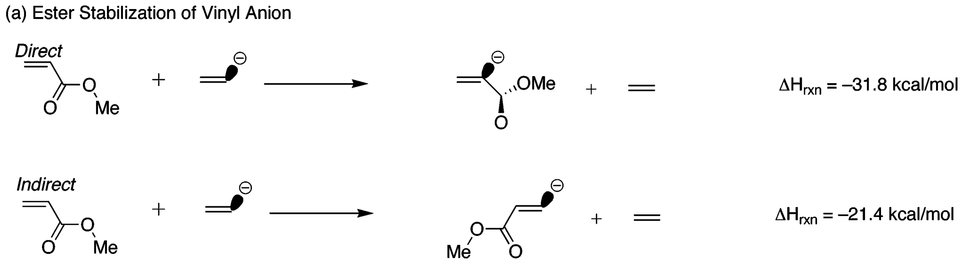


Figure 6. B3LYP transition state geometries and activation enthalpies, in kcal/mol, for the reaction of methyl pent-4-en-2-ynoate, **50**, with **49**.


(a) Ester Stabilization of Vinyl Anion

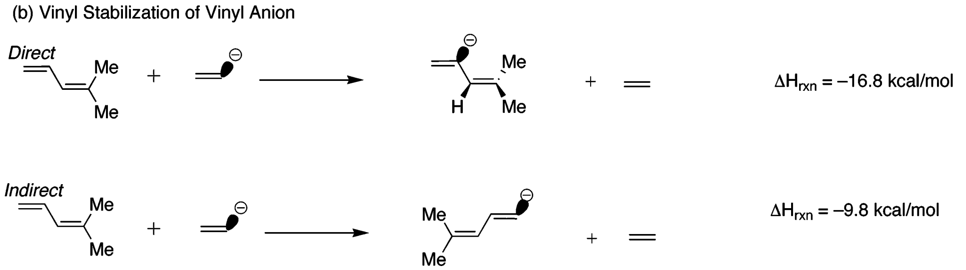
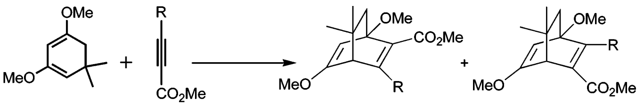

(b) Vinyl Stabilization of Vinyl Anion

Figure 7. B3LYP reaction enthalpies, in kcal/mol, for the isodesmic reactions of methyl acrylate and *trans*-1,3-butadiene with the vinyl anion forming the directly, and indirectly, stabilized vinyl anions and ethylene.

Table 5. B3LYP Activation Enthalpies for Diels–Alder Reactions **49** with Substituted Propiolates to Give Ester-Controlled (**I**) and Non-Ester-Controlled (**II**) Diels–Alder Adducts



49 **I** **II**

	$\Delta H^{\ddagger}$	
R	I	II
H	16.0	24.8
Me	22.7	27.3
CH=CMe$_2$	24.5	23.9

with the double bond of the monoactivated enyne is very endergonic (+20 kcal/mol), more so than for reactions involving addition to the double bond of the diactivated enyne. Presumably, the large endergonicity of the reactions involving these monoactivated enynes is the result of significant reactant stabilization by the gem-dimethyl substituents on the vinyl moiety. With reference to the norbornadiene intermediates, extrusion of isobutylene requires about 30 and 28 kcal/mol (+4.4 and +4.2 kcal/mol with reference to the enyne and diene reactants) for formation of the vinyl-controlled and ester-controlled adducts, respectively. The formation of the styrenyl final products is exothermic by about −43 kcal/mol.

These results suggest that while the thermodynamics greatly favor formation of the stable norbornadiene cycloadducts over unstable norbornene adducts, kinetics control the course of the reaction. Therefore, initial fast cycloaddition of the diene with the triple bond of the enyne results in the formation of stable norbornadiene cycloadducts, which subsequently extrude isobutylene to form the styrenyl final products.

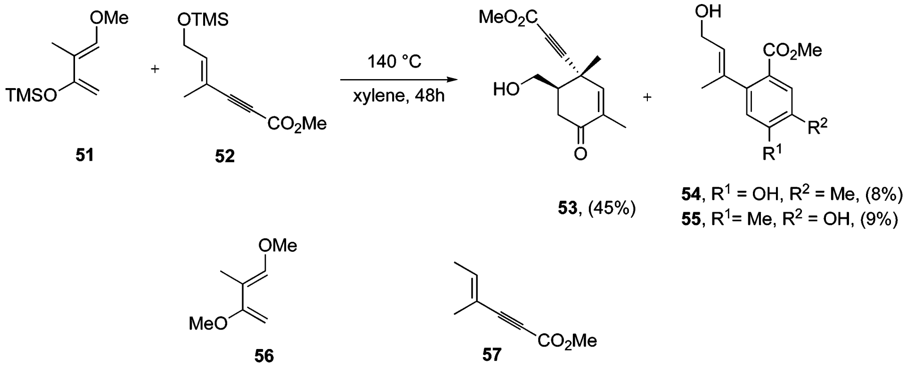
The product differentiation arises in the initial rate-determining cycloaddition step. The predicted 1 kcal/mol preference for formation of the vinyl-controlled over the ester-controlled regioisomer in this model system is consistent with the 5:2 regioisomeric ratio of styrenyl products obtained in experimental studies. To account for this preference we have evaluated the ability of the vinyl and ester groups to stabilize the negative charges that develop in these transition states.

Figure 7 depicts the energies of anion stabilization by butylene and ester groups. Thus, direct interaction of the butylene group with the negative charge is preferable to indirect interaction. The ester group stabilizes the anion more than the vinyl group does, both in a direct (15 kcal/mol) and indirect (12 kcal/mol) sense, through interaction with the negative charge; the opposite was true for the vinyl ester substituent.

If these substituent effects were additive, then the ester-controlled adducts would be expected to be formed preferentially in the cases of dienophiles **26** and **27**. However, both experimental results and transition state calculations indicate that the vinyl controlled adduct is formed in preference to the ester-controlled adduct.

The influence of steric repulsion in the transition states for the reaction of **49** with **50** was evaluated by comparison with

Scheme 8



analogous reactions involving methyl propiolate and methyl butynoate. The expectation is that replacement of the terminal acetylenic hydrogen atom of methyl propiolate with a methyl group or a butylene group will increase the activation enthalpy for formation of the ester-controlled adducts, presumably due to steric repulsion in the transition state. This is indeed the case. B3LYP activation enthalpies for the formation of ester-controlled (**I**) and non-ester-controlled (**II**) adducts of these reactions are shown in Table 5. The activation enthalpy for formation of the ester-controlled reaction of **49** with methyl propiolate ($R = H$) is 16 kcal/mol. In comparison, the activation enthalpies for the reactions involving methyl butynoate ($R = Me$) and **50** ($R =$ butylene) are 23 and 24 kcal/mol, respectively. The approximately 7 kcal/mol increase in the activation enthalpies for these reactions in comparison with the reaction involving methyl propiolate is evidently due to steric repulsion between the olefinic proton of the diene and the methyl and butylene groups of both dienophiles.

The activation enthalpy for the formation of the non-ester-controlled adducts of methyl propiolate and methyl butynoate are 25 and 27 kcal/mol, respectively. By contrast, the activation enthalpy for the formation of the vinyl-controlled adduct of **50** is only 24 kcal/mol. These differences are consistent with the inability of the terminal hydrogen atom and methyl group of methyl propiolate and methyl butynoate, respectively, to stabilize the negative charge that develops at the transition state of these reactions. As discussed in relation to Figure 7, the butylene group is, in fact, able to stabilize the developing negative charge appreciably.

These results signify that, while the transition states for formation of ester-controlled adducts from reactions involving monoactivated enynes are stabilized by interaction of the developing negative charge with the ester group, steric repulsion from the butylene group overwhelms this interaction. These combined effects result in the formation of vinyl-controlled adducts from transition states which are stabilized by direct interaction of the vinyl group and indirect interaction of the ester group with the developing vinyl anion.

Finally, to complement these findings we have also investigated the cycloaddition reactions first reported by Kocienski, shown in Scheme 8, involving addition of an activated diene with a monoactivated enyne, in which the ene, propargyl ester controlled adduct, **53**, is produced in preference to either of the isomers resulting from addition to the triple bond (**54** and **55**). Substrates **56** and **57** were used to model the substrates used in experimental studies.

Indeed, calculations support the experimental results reported by Kocienski. The formation of the ene-propargyl ester cycloadduct is favored over formation of the yne, vinyl controlled cycloadduct, but by only 0.2 kcal/mol ($\Delta H^{\ddagger} = 21.5$ and 21.7 kcal/mol, respectively). This suggests that both adducts should be formed in almost equal amounts, whereas the experiment gives an ~1.3 kcal/mol lower activation enthalpy for formation of the ene, propargyl ester controlled cycloadduct. The transition state corresponding to formation of the yne, ester controlled cycloadduct could not be located, presumably because of the steric interactions between the methyl group on the *cis*-dimethyl vinyl substituents and the incoming diene.

The reaction enthalpies for formation of the intermediates resulting from addition to the triple bond are about -40 kcal/mol; these are more exothermic reactions than reactions with the double bond (-18 kcal/mol). Significantly, ene-controlled reactions are *exergonic* by -1 kcal/mol, in contrast to reactions involving **24** and **25**, which are *endergonic* by as much as $+20$ kcal/mol. The exothermicity of this variant of the reaction reported by Kocienski et al. is due to the absence of significant steric strain in the monocyclic product. Although calculations do not fully account for the large kinetic preference for formation of ene-controlled cycloadducts, they bolster the notion that these cycloadducts, once formed, are thermodynamically stable.

Conclusions

In summary, we have described highly efficient chemo- and regioselective Diels–Alder reactions for the syntheses of polysubstituted aromatic compounds and biaryl compounds from unsymmetrical dienes and enynes in good to excellent yield. A dienophile based on a β,β'-connected dienyl ester was also explored and gave adducts with the same sense of regioselectivity. Theoretical considerations of these reactions account for experimentally observed chemoselectivities and regioselectivities. The importance of indirect stabilization was discovered; this causes a deactivated alkyne to be substantially more reactive than a deactivated alkene in cycloadditions with strongly asymmetric nucleophilic dienes. The consequences of this effect in other cycloadditions are being actively explored.

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Supporting Information Available: Experimental procedures, data on new compounds, and B3LYP coordinates and energies of reactants, transition structures, intermediates, and products. This material is available free of charge via the Internet at http://pubs.acs.org.

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