

Facile, Regioselective [4 + 2] Cycloaddition Involving 1-Aryl-4-phenyl-1-azadienes and Allenic Esters: An Efficient Route to Novel Substituted 1-Aryl-4-phenyl-1,4-dihydropyridines

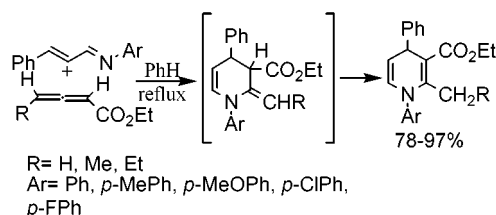
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ABSTRACT



1-Aryl-4-phenyl-1-azadienes undergo facile, regioselective [4 + 2] cycloaddition to the C2,C3 π -bond of allenic esters in refluxing benzene, and the formed adducts undergo a 1,3-H shift to afford novel 2-alkyl-1-aryl-3-ethoxycarbonyl-4-phenyl-1,4-dihydropyridines (78–97%). However, when the reaction is carried at room temperature, besides the [4 + 2] addition, the [2 + 2] mode of addition involving C=N of azadiene and C3,C4 π -bond of allenic esters also intervenes. The resulting *N*-aryl-2-ethoxy-carbonyl-methylidene-4-styrylazetidines (17–28%) undergo reorganization on silica gel to afford 2-cyclohexen-1-ones.

As compared to extensive preparative, mechanistic and theoretical investigations on Diels–Alder reaction, the hetero-Diels–Alder processes have attracted relatively less attention despite comparable synthetic utility. However, in the past couple of decades, a considerable amount of work has been reported in the field of hetero-Diels–Alder methodology, with definite advancements in theoretical understanding and synthetic utilization.¹ Among the heterodienes, the 1-azadienes have been reported to be sluggish as

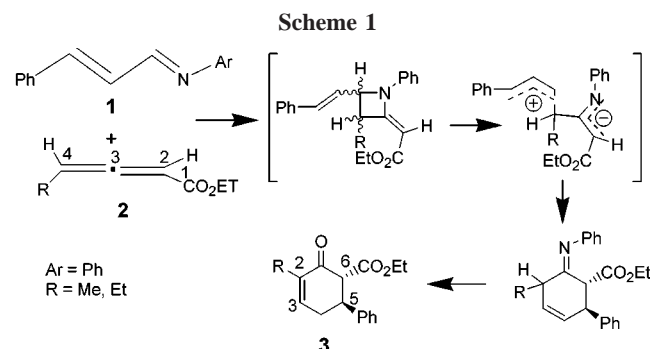
dienes in hetero-Diels–Alder reactions, and their 4 π participation is marred by, inter alia, competing [2 + 2]

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(1) (a) Boger, D. L.; Weinreb, S. M. In *Hetero Diels–Alder Methodology in Organic Synthesis*; Academic Press Inc.: San Diego, 1987; Chapter 9, p 239. (b) Boger, D. L. *Tetrahedron* **1983**, 39, 2869. (c) Barulenga, J.; Tomas, M. *Adv. Heterocycl. Chem.* **1993**, 57, 1. (d) Behforouz, M.; Ahamadian, M. *Tetrahedron* **2000**, 56, 5259. (e) Boger, D. L.; Patel, M.

Progress in Heterocyclic Chemistry; Suschitzky, H., Scaiven, E. F. V., Eds.; Pergamon Press: London, 1989; Vol. 1, p 30. (f) McCarrick, M. A.; Wu, Y. D.; Houk, K. N. *J. Org. Chem.* **1993**, 58, 3330. (g) Sisti, N. J.; Motorina, I. A.; Dau, M. E. T. H.; Riche, C.; Fowler, F. W.; Grierson, D. S. *J. Org. Chem.* **1996**, 61, 3715. (h) Motorina, I. A.; Grierson, D. S. *Tetrahedron Lett.* **1999**, 40, 721. (i) Mogen, J.; Jorgensen, K. A. *J. Chem. Soc., PerkinTrans. 2* **1997**, 1183. (j) Sylvie, P.; Masure, D.; Halle, J.-C.; Chaquin, P. *J. Org. Chem.* **1997**, 62, 8687. (k) Boger, D.; Schaum, R. P.; Garbaccia, R. M. *J. Org. Chem.* **1998**, 63, 6329. (l) Stainhagen, H.; Corey, E. J. *Angew. Chem., Int. Ed.* **1999**, 38, 1928. (m) Wijnen, J. W.; Zavarise, S.; Engberts, J. B. F. N.; Charton, M. *J. Org. Chem.* **1996**, 61, 2001. (n) Fabian, W. M. F.; Janoschek, R. *J. Am. Chem. Soc.* **1997**, 119, 4253. (o) Graven, A.; Johannsen, M.; Jorgenson, K. A. *Chem. Commun.* **1996**, 2373. (p) Cuerva, J. M.; Cardenas, D. J.; Echavarren, A. M. *Chem. Commun.* **1999**, 1721. (q) Augusti, R.; Gozzo, F. C.; Moraes, L. A. B.; Sparrapan, R.; Eberlin, M. N. *J. Org. Chem.* **1998**, 63, 4889. (r) Hedegus, L. S.; Montgomery, J.; Narukawa, Y.; Snustad, O. C. *J. Am. Chem. Soc.* **1991**, 113, 5784.

additions.^{1a,b} Various strategies that have been devised^{1a–h,2} to ensure their 4π participation include the introduction of electron-withdrawing substituent(s) on azadienes so as to improve their frontier orbital complementarity for inverse electron demand Diels–Alder reaction. It has been reported³ that reaction of 1-aza-1,4-diphenyl-1,3-butadiene (**1**, Ar = Ph) and allenic esters (**2**) leads to formation of cyclohexenones (**3**) in low yield (25–30%); the latter are postulated to be derived from (2 + 2) cycloadducts (Scheme 1), though

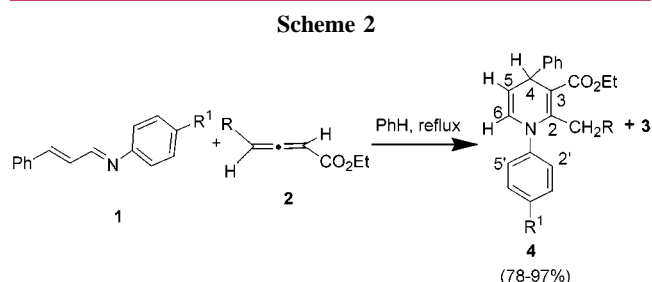


no such proposed intermediate had been isolated and/or characterized, and no other reaction product has been reported.

Taking cognizance of a recent report on cycloadditions of cyclic and acyclic dienes with ketenes, wherein interconvertibility of initially formed (4 + 2), and (2 + 2) cycloadducts has been described,⁴ we decided to reinvestigate the above azadiene–allenic ester cycloadditions with the aim of establishing the mechanism of the reported³ cyclohexenone formation and to develop a protocol for 4π participation of azadienes in reactions with allenic esters. The latter was of particular interest for development of a simple route to novel substituted 1,4-dihydropyridines, which are highly sought on account of both their diverse biological activities and synthetic applications.^{1g,p,2,5}

Initially, the reactions were carried out by heating equivalent amounts of azadiene (**1**) and allenic ester (**2**) in dry

refluxing benzene, with strict exclusion of moisture. Contrary to the earlier report,³ this led to almost exclusive formation of 2-alkyl-1-aryl-3-ethoxycarbonyl-4-phenyl-1,4-dihydropyridines (**4**). Apparently, these dihydropyridines are derived from an initial (4 + 2) cycloaddition followed by a 1,3-hydrogen shift. The earlier reported³ cyclohexenones (**3**) were detected in trace amount only in some cases, and it was observed that the rate of the reaction decreased with increasing size of the 4-alkyl substituent on the allenic esters (Scheme 2, Table 1).



The dihydropyridines have been characterized by detailed spectroscopic analysis, microanalytical data, and comparison of the spectroscopic data with the reported data for related system.⁶ In their IR spectra these molecules displayed a band due to ester carbonyl at $\sim 1690\text{ cm}^{-1}$, indicating an extensively conjugated ester carbonyl, which was reminiscent of the IR band of ester carbonyl in Hantzsch esters. In its proton NMR spectrum compound **4f** displayed, besides resonances in the aromatic region, a doublet at δ 5.99, which was coupled to a double doublet at δ 4.88; the latter was coupled to a doublet at δ 4.58. These resonances have been assigned, respectively, to C6–H, C5–H, and C4–H (compare ref 6). The assigned structures (**4a–h**) are also corroborated by the ^{13}C NMR spectral data.

Table 1. Reactions of Azadiene (**1**) and Allenic Esters (**2**) in Refluxing Benzene

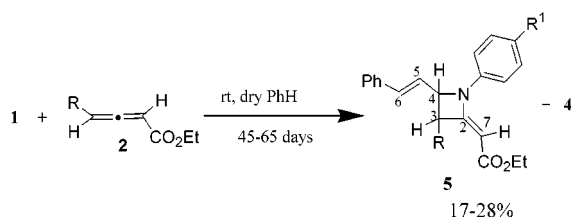
no.	R	R ¹	reaction time (h)	4 (% yield) ^a
1	H	H	58	4a (96)
2	Me	H	70	4b (85)
3	Et	H	80	4c (79)
4	H	Me	57	4d (95)
5	Me	Me	65	4e (88)
6	H	OMe	55	4f (97)
7	Me	OMe	68	4g (92)
8	Et	OMe	80	4h (85)
9	H	Cl	55	4i (94)
10	Me	Cl	65	4j (89)
11	Et	Cl	85	4k (78)
12	H	F	55	4l (97)
13	Me	F	65	4m (90)
14	Et	F	85	4n (85)

^a Yield refers to isolated pure product.

- (2) (a) Boger, D. L.; Corbett, W. C.; Wiggins, J. M. *J. Org. Chem.* **1990**, 55, 2999. (b) Teng, M.; Fowler, W. *Tetrahedron Lett.* **1989**, 30, 2481. (c) Teng, M.; Fowler, W. *J. Org. Chem.* **1990**, 55, 5646. (e) Boger, D. L.; Nakahara, S. *J. Org. Chem.* **1991**, 56, 880. (f) Boger, D. L.; Curran, T. T. *J. Org. Chem.* **1990**, 55, 5439. (g) Boger, D. L.; Corbett, W. L.; Curran, T. T.; Kasper, A. M. *J. Am. Chem. Soc.* **1991**, 113, 1713. (3) Gandhi, R. P.; Ishar, M. P. S.; Wali, A. *Tetrahedron Lett.* **1987**, 6679. (4) Machiguchi, T.; Hasegawa, T.; Ishiwata, A.; Terashima, S.; Yamabe, S.; Minato, T. *J. Am. Chem. Soc.* **1999**, 121, 4771. (5) (a) Eisner, U.; Kuthan, J. *Chem. Rev.* **1972**, 72, 1. (b) Stout, D. M.; Meyers, A. I. *Chem. Rev.* **1982**, 82, 223. (c) Calzoli, L.; Gaggelli, E.; Maccotta, A.; Valensin, G. *J. Chem. Soc., Perkin Trans. 2* **1997**, 363 and references therein. (d) Straub, A.; Goehert, A. *Angew. Chem., Int. Ed. Engl.* **1996**, 35, 2662. (e) Zhao, B.; Zhu, X.; Lu, Y.; Xia, C. Z.; Chang, J. P. *Tetrahedron Lett.* **2000**, 41, 257. (f) Vadecea, Y.; Suaraz, M.; Morales, A.; Rodriguez, E.; Ochoa, E.; Gonzalaz, L.; Martin, N.; Quinterio, M.; Seorane, C.; Soto, J. L. *J. Chem. Soc., Perkin Trans. 1* **1996**, 947. (g) Breitenbucher, J. G.; Figliozzi, G. *Tetrahedron Lett.* **2000**, 41, 4311 and references therein. (h) Bossert, F.; Meyer, H.; Wehinger, E. *Angew. Chem., Int. Ed. Engl.* **1981**, 20, 762. (i) Lavilla, R.; Coll, O.; Kumar, R.; Bosch, J. *J. Org. Chem.* **1998**, 63, 2728 and references therein. (j) Wenkert, E. *Pure Appl. Chem.* **1981**, 53, 1271. (k) Bosch, J.; Bennasar, M.-L. *Synlett* **1995**, 587. (l) Levecher, V.; Benoit, R.; Duflos, J.; Dupas, G.; Boutguignon, J.; Queguiner, G. *Tetrahedron* **1991**, 47, 429.

As almost exclusively the (4 + 2) mode of cycloaddition was obtained under these conditions, and in the light of recent report on formation of (2 + 2) adducts on reacting ketenes with cyclic/acyclic dienes at room temperature,⁴ we attempted the reactions of azadienes with allenic esters by stirring at ambient temperature. Our goal was the isolation of the (2 + 2) adduct and investigation of its transformation to cyclohexenones (3). Equimolar solutions of azadiene (1) and allenic esters (2) in dry benzene were stirred at room temperature for 45–65 days. The ¹H NMR spectrum of the crude sample obtained after evaporation of the solvent showed the presence of considerable amounts of (2 + 2) cycloadducts (5, Scheme 3) in addition to the dihydropyri-

Scheme 3



dines (4); the relative ratios of 4 and 5 determined from ¹H NMR of crude reaction products are given in Table 2 along with reaction times.

Table 2. Reactions of Azadiene (1) and Allenic Ester (2) at Room Temperature

no.	R ¹	R	reaction time (days)	4/5 product ratio ^a	5 (% yield) ^b
1	Me	Me	62	2.5/1.0	5a (27)
2	Cl	Me	52	2.3/1.0	5b (28)
3	Cl	Et	45	1.9/1.0	5c (28)
4	Cl	H	49	4.0/1.0	5d (17)
5	H	Me	60	2.2/1.0	5e (26)
6	OMe	Me	65	2.8/1.0	5f (25)

^a Ratio measured from the ¹H NMR spectra of crude reaction products.

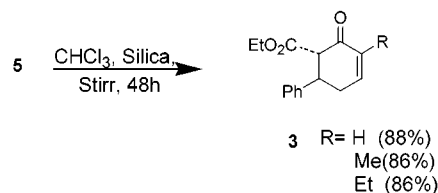
^b Yield refers to the isolated pure adducts (5) and amount of cyclohexenones (3) formed.

The (2 + 2) cycloadducts were isolated by flash column chromatography and characterized spectroscopically. In its ¹H NMR, 5a (R = Me) revealed a 1H double doublet at δ 6.35 (C5–H), a 1H split singlet at δ 5.34 (C7–H), a double doublet at δ 4.56 (1H, *J* = 7.56, 2.44 Hz, C4–H), a quartet at δ 4.15 (2H, –CO₂CH₂), another split quartet at δ 3.41 (C3–H), and a doublet at δ 1.59 (3H, C3–CH₃); some of these ¹H NMR spectral assignments were aided by comparison of the spectral data reported for (2 + 2) cycloadducts of

1-azadienes with ketenes.^{1g,7} The *trans*-arrangement around the C3–C4 bond is based on the low value of ³*J*_{3,4} (~2.5 Hz),^{7c} and the obtained spectral data indicates single geometry at the exocyclic double bond. However, the assigned geometry is tentative, based mainly on nonobservance of NOE for C1'–H on irradiating C3–Me resonance in 5a.

To confirm the formation of cyclohexenones through (2 + 2) adduct, the isolated (2 + 2) adducts (5) were stirred with silica gel, in chloroform, for 2 days at which time most of the (2 + 2) adduct were converted to cyclohexenones (3, Scheme 4); the latter were separated by column chromatography and identified spectroscopically.³

Scheme 4



Mechanistic aspects of the reported observations are far from clear. In keeping with the mechanistic proposals for reactions of 1-azadienes/imines with ketenes^{1g,7a,b,8} and reported detection of zwitterionic intermediates in additions to allenes⁹ and in view of the fact that allenic esters are related to ketenes, it is often tempting³ to consider the formation of both (2 + 2) and (2 + 4) adducts through a common zwitterionic intermediate, B (Scheme 5). However, the involvement of a common zwitterionic intermediate (B),¹⁰ though in consonance with the obtained single geometric arrangement around the exocyclic double bond in 5 as well orientation of the azadiene moiety in adducts, fails to explain the differential π -bond selectivity of the two modes of addition and the complete stereoselectivity of (2 + 2) mode of addition, i.e., *trans*-arrangement around the C3–C4 bond in azetidines (5). Heating 5 in refluxing benzene for extended

(7) (a) Brady, W. T.; Shieh, C. H. *J. Org. Chem.* **1983**, *48*, 2499. (b) Arrastia, I.; Arrieta, A.; Ugalde, J. M.; Cossio, F. P.; Lecea, B. *Tetrahedron Lett.* **1994**, *35*, 7825. (c) Gaudemer, A. In *Stereochemistry*; Kagan, H. B., Ed.; Georg Thieme: Stuttgart, 1977; Vol 1, pp 44–136.

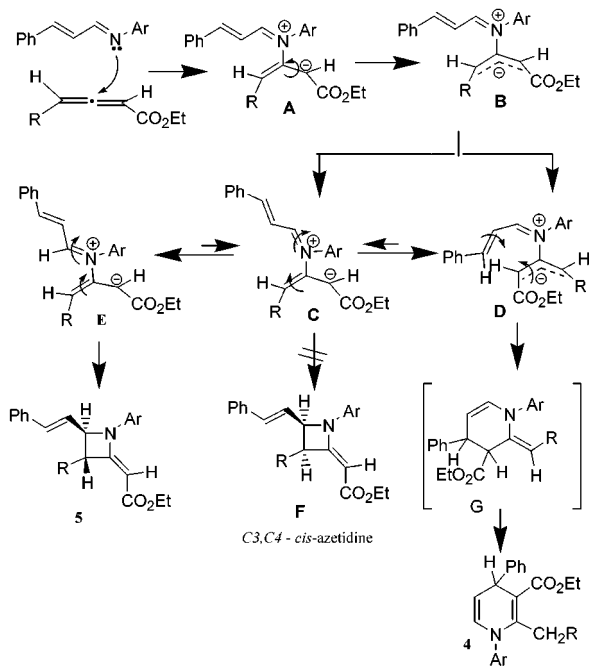
(8) (a) Lecea, B.; Arrastia, I.; Arrieta, A.; Roa, G.; Lopez, X.; Arriortua, M. I.; Ugalde, J. M.; Cossio, F. P. *J. Org. Chem.* **1996**, *61*, 3070. (b) Arrieta, A.; Cossio, F. P.; Lecea, B. *J. Org. Chem.* **1999**, *64*, 1831. (c) Lopez, R.; Sordo, T. L.; Sordo, J. A.; Gonzalez, J. *J. Org. Chem.* **1993**, *58*, 7036. (d) Sordo, J. A.; Gonzalez, J.; Sordo, T. *J. Am. Chem. Soc.* **1992**, *114*, 6249. (e) Cossio, F. P.; Ugalde, J. M.; Lopez, X.; Lecea, B.; Palomo, C. *J. Am. Chem. Soc.* **1993**, *115*, 995. (f) Lecea, B.; Arrastia, I.; Rao, G.; Lopez, X.; Arriortua, M.; Ugalde, J. M.; Cossio, F. P. *J. Org. Chem.* **1996**, *61*, 3070. (g) Pacansky, J.; Chang, J. S.; Brown, D. W.; Schwarz, W. *J. Org. Chem.* **1982**, *47*, 2333. (h) Moore, H. W.; Hughes, G. *Tetrahedron Lett.* **1982**, *23*, 4003.

(9) Gompper, R. G.; Lach, D. *Angew Chem., Int. Ed. Engl.* **1970**, *10*, 70.

(10) The formation of zwitterionic intermediate B shall involve the interaction of a nitrogen lone pair of electrons with the LUMO of the C2–C3- π bond at the central allenic carbon; the azadiene shall approach from the side opposite to substituent R on the allenic moiety. In the intermediate B, substituents on the allenic moiety are kept away from the azadiene component, and reported low-energy *anti*-arrangement around C=N (Anteuys, N.; Bruyn, A. De.; Sandhu, J. S. *J. Magn. Reson.* **1972**, *8*, 7) has been maintained.

(6) (a) Alberola, A.; Gonzalez, A. M.; Gonzalez, B.; Laguna, M. A.; Fulido, F. J. *Tetrahedron Lett.* **1986**, *27*, 2027. (b) Saunders, M.; Gold, E. H. *J. Org. Chem.* **1962**, *27*, 1439. (c) Eynde, J. J. V.; Delfosse, F.; Mayence, A.; Haverbeke, Y. V. *Tetrahedron* **1995**, *51*, 6511.

Scheme 5



periods led to their slow deterioration, and not a trace of dihydropyridine (**4**) was detected at any stage, thereby indicating the complete irreversibility of azetidine formation or at least that of **5**, under the reaction conditions. Therefore, the major mode of transformation has to be the cyclization in **D** leading to **G**, followed by 1,3-H shift in **G** to afford **4**; such facile 1,3-H shifts are preceded in allene chemistry.¹¹

Alternatively, the obtained C2–C3 π -bond selectivity for the (4 + 2) mode of addition is consistent with a concerted cycloaddition through a HOMO-diene–LUMO-dienophile interaction; therefore, only the electron-deficient C2–C3 π bond of allenic esters is involved. Involvement of such electron-neutral 1-azadienes in HOMO-diene controlled hetero-Diels–Alder reactions with electron-deficient dienophiles is anticipated.^{1a–h,2,12} It may be mentioned here that geometric outcome at the exocyclic double bond and the stereochemistry of addition (at C3) in (4 + 2) adducts, which could have provided useful information, is lost due to H-shift leading to **4**.

The formation of azetidines can also be rationalized as a concerted ($\pi_s^2 + \pi_s^2 + \pi_s^2$) process; though such a mechanism for observed facile (2 + 2) additions of allene was proposed^{13a} and latter discarded in favor of a diradical mechanism,^{13b} many of the recently obtained results have been rationalized in terms of such a concerted mechanism.^{14,15}

(11) Hayakawa, K.; Nishiyama, H.; Kanematsu, K. *J. Org. Chem.* **1985**, 50, 512.

(12) (a) Dau, M. E. T. H.; Flament, J.-P.; Lefour, J.-M.; Riche, C.; Grierson, D. S. *Tetrahedron Lett.* **1992**, 33, 2343. (b) Boger, D. L.; Kasper, A. M. *J. Am. Chem. Soc.* **1989**, 111, 1517. (c) Trione, C.; Toledo, L. M.; Kuduk, S. D.; Fowler, F. W.; Grierson, D. S. *J. Org. Chem.* **1993**, 58, 2075. (d) Greoigre, P. J.; Mellor, J. M.; Merriman, G. D. *Tetrahedron* **1995**, 51, 6115. (e) Jurisc, B. S.; Zdravkovski, Z. *J. Org. Chem.* **1995**, 61, 3163.

(13) (a) Pasto, D. J. *J. Am. Chem. Soc.* **1979**, 101, 37. (b) Pasto, D. J. *Tetrahedron* **1984**, 40, 2805.

The involved orbital interactions are depicted in **H** (Figure 1). A HOMO–C3–C4 π bond and LUMOs of C=N, and

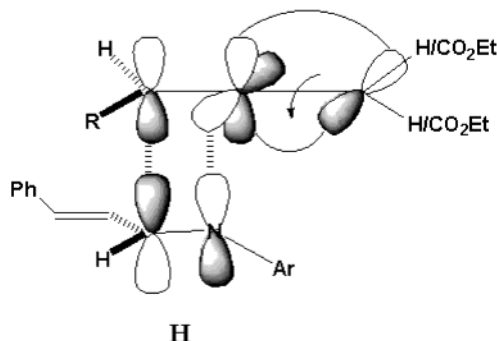


Figure 1.

C2–C3 π bond interaction may be the reason for the observed involvement of only the relatively electron-rich π bond of allenic esters in this mode of cycloaddition. The obtaining of relatively higher yields of (2 + 2) adducts from allenic esters bearing electron-donating alkyl substituents at C4 supports such a contention. It may be mentioned here that similar divergent π -bond selectivities for formation of (4 + 2) and (2 + 2) addition products from reaction of electron-rich siloxy-dienes with allenic esters have been recently reported.¹⁶

Though the mechanistic details of the reported transformations need further probing, the facile 4 π participation of 1-azadienes, leading to valuable 1,4-diaryl-1,4-dihydropyridines, in very high yields is of significant synthetic value.¹⁷ The investigations have also led to the isolation of azetidines (**5**), and their reorganization to cyclohexenones (**3**) has been established.

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Supporting Information Available: Experimental procedures and full characterization of compound **4a–n**, **5a–f** and **3a**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(14) (a) Horino, Y.; Kimura, M.; Wakamiya, Y.; Okajima, T.; Tamaru, Y.; *Angew. Chem., Int. Ed.* **1999**, 38, 121. (b) Kimura, M.; Horino, Y.; Wakamiya, Y.; Okajima, T.; Tamaru, Y. *J. Am. Chem. Soc.* **1997**, 119, 10869. (c) Kimura, M.; Wakamiya, Y.; Tamaru, Y. *Tetrahedron Lett.* **1997**, 38, 3963.

(15) Regiochemistry for both modes of addition, when considered as concerted processes, is in consonance with atomic orbital coefficients in the frontier molecular orbitals of both reactants.^{1g,13b}

(16) Jung, M. E.; Nishimura, N. *J. Am. Chem. Soc.* **1999**, 121, 3529.

(17) This approach is all the more important in the light of reported low reactivity of 1-azadienes towards acetylenic dienophiles.^{1a,b}