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An Unexpectedly Mild Thermal Alder−Ene-Type Cyclization of Enallenes

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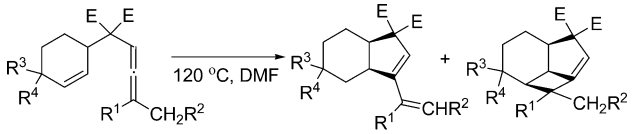


1 (E = CO_2Me) major **2** minor **3**

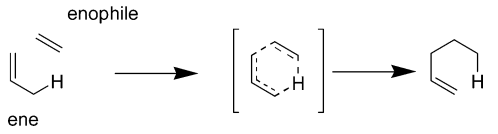
1a, **2a**, **3a**: R^1 = Me, R^2 = H, R^3 = H, R^4 = H
1b, **2b**, **3b**: R^1 = Me, R^2 = Me, R^3 = H, R^4 = H
1c, **2c**: R^1, CH_2R^2 = -$(CH_2)_5$-, R^3 = H, R^4 = H
1d, **2d**, **3d**: R^1 = Me, R^2 = H, R^3 = Me, R^4 = Me

A mild, thermal Alder−ene reaction of enallenes has been developed. The allenic double bond acts as the "ene" and generates a carbon−carbon bond to an unactivated olefinic "enophile" in DMF at 120 °C to give [*n*.3.0] bicyclic systems (n = 3−5) in good yields. Except for a minor [2 + 2] cycloaddition byproduct, the reaction proceeded with complete atom economy, as there is no requirement of a catalyst or additional reactants, and no waste products are formed in the process.

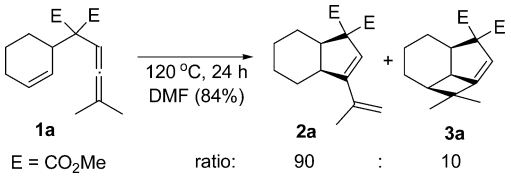
A major part of organic synthesis is the construction of the carbon skeleton of a desired target molecule. It is therefore important that the carbon−carbon bond-forming step occurs with a high degree of chemo-, regio-, as well as stereoselectivity, preferably under mild reaction conditions. It is also desirable that the reaction takes place with a high degree of atom economy. One reaction that stands up to these demands is the Diels−Alder reaction, which has been widely used as a key step in total synthesis. In contrast to the many applications found for Diels−Alder reactions, the closely related Alder−ene reaction has received much less attention in organic chemistry, despite the fact that this thermal reaction of readily available alkenes (enophiles) with an olefin possessing an allylic hydrogen (enes) is a very attractive way of creating carbon−carbon bonds (Scheme 1).

One of the major drawbacks of the Alder−ene reaction is the much higher activation energy required, compared to the analogous Diels−Alder reaction. Therefore, Alder−ene reactions typically occur at high temperatures, often resulting in low yields and poor selectivity, which limits their synthetic applications.[1] However, as for the dienophile in Diels−Alder reactions, activation of the enophile by electron-withdrawing groups and/or by the presence of a Lewis acid catalyst decreases the activation barrier to such an extent that the ene reaction becomes synthetically useful.[2]

SCHEME 1



SCHEME 2



Unactivated olefins are, in general, very poor enophiles and require a drastic increase in temperature to be able to undergo an Alder−ene reaction. Alder−ene reactions between an allene and an alkene are not well-documented, and only a few such reactions have been reported. These reactions are performed at very high temperatures, and in most cases with the [2 + 2] cycloaddition product as a byproduct.[3] In contrast with the thermal Alder−ene reaction, [2 + 2] cycloaddition reactions between an allene and an alkene are well-documented and constitute a powerful method for the synthesis of methylenecyclobutane derivatives.[4]

During our studies on the scope and limitation of the palladium-catalyzed carbocyclization reactions of enallenes[5] and allenic allylic acyloxylates,[6] we found that in the absence of palladium(0) an Alder−ene reaction occurred. In this case, one of the allenic double bonds acts as the "ene" and generates a carbon−carbon bond to the unactivated olefinic "enophile", in DMF at 120 °C, to give a fused ring system (Scheme 2). This reaction proceeds with high stereo- and regioselectivity, with

(1) (a) Hoffmann, H. M. R. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 556. (b) Oppolzer, W.; Snieckus, V. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 478.

(2) (a) Snider, B. B. *Acc. Chem. Res.* **1980**, *13*, 426. (b) Mikami, K.; Shimizu, M. *Chem. Rev.* **1992**, *92*, 1021.

(3) (a) Huntsman, W. D.; Li, Y. J.; Giannamore, V. P. *Isr. J. Chem.* **1985**, *26*, 88. (b) Chia, H.-A.; Kirk, B. E.; Taylor, D. R. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1209. (c) Kirk, B. E.; Taylor, D. R. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1844. (d) Bertrand, M.; Cavallin, B.; Roumestant, M. L.; Sylvestre-Panthet, P. *Isr. J. Chem.* **1985**, *26*, 95. (e) Lee, C. B.; Taylor, D. R. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1463. (f) Taylor, D. R.; Wright, D. B. *J. Chem. Soc., Perkin Trans. 1* **1973**, 956. (g) Brummond, K. M.; Chen, D. *Org. Lett.* **2005**, *7*, 3473.

(4) (a) Ohno, H.; Mizutani, T.; Kadoh, Y.; Miyamura, K.; Tanaka, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 5113. (b) Ma, S. *Chem. Rev.* **2005**, *105*, 2829. (c) Aben, R. W. M.; Braverman, S.; Scheeren, H. W. *Eur. J. Org. Chem.* **2003**, 894. (d) Dauben, W. G.; Rocco, V. P.; Shapiro, G. *J. Org. Chem.* **1985**, *50*, 3155. (e) Hansen, T. V.; Skattebol, L.; Stenstrom, Y. *Tetrahedron* **2003**, *59*, 3461. (f) Hayakawa, K.; Aso, K.; Shiro, M.; Kanematsu, K. *J. Am. Chem. Soc.* **1989**, *111*, 5312. (g) Narasaka, K.; Hayashi, Y.; Shimadzu, H.; Niihata, S. *J. Am. Chem. Soc.* **1992**, *114*, 8869. (h) Padwa, A.; Lipka, H.; Watterson, S. H.; Murphree, S. S. *J. Org. Chem.* **2003**, *68*, 6238. (i) Padwa, A.; Meske, M.; Murphree, S. S.; Watterson, S. H.; Ni, Z. *J. Am. Chem. Soc.* **1995**, *117*, 7071. (j) Skatteboel, L.; Stenstroem, Y. *Tetrahedron Lett.* **1983**, *24*, 3021. (k) Snider, B. B.; Ron, E. *J. Org. Chem.* **1986**, *51*, 3643. (l) Yoshida, M.; Hidaka, Y.; Nawata, Y.; Rudzinski, J. M.; Osawa, E.; Kanematsu, K. *J. Am. Chem. Soc.* **1988**, *110*, 1232.

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(6) Franzén, J.; Löfstedt, J.; Falk, J.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **2003**, *125*, 14140.

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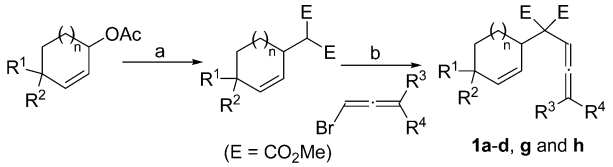
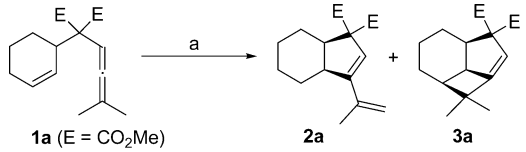
SCHEME 3



1a: n = 1, $R^1 = R^2 = H$, $R^3 = R^4 = Me$
1b: n = 1, $R^1 = R^2 = H$, $R^3 = Me$ $R^4 = Et$
1c: n = 1, $R^1 = R^2 = H$, $R^3 = R^4 = -(CH_2)_5-$
1d: n = 1, $R^1 = R^2 = Me$, $R^3 = R^4 = Me$
1g: n = 2, $R^1 = R^2 = H$, $R^3 = R^4 = Me$
1h: n = 0, $R^1 = R^2 = H$, $R^3 = R^4 = Me$

TABLE 1. Thermal Cyclization of *cis*-1a under Different Reaction Conditions



entry	solvent	*T* (°C)	time (h)	ratio **2a**/**3a**	conv[b] (%)
1[c]	CH_3CN	160	1	83:17	100
2[c]	neat	160	1	n.d.	100 (+ byproducts)
3	CH_3CN	110	15	78:22	50
4	DCE	110	15	77:23	65
5	AcOH	110	15	n.d.	65 (+ byproducts)
6	DMF	110	15	82:18	70
7	toluene	110	15	83:17	60
8	ionic liquid[d]	110	15	80:20	50
9	water	110	15	n.d.	10
10	**DMF**	**120**	**24**	**90:10**	**100**

[a] Enallene **1a** was dissolved in the specific solvent (10 mL/mmol) and heated to the indicated temperature. [b] Conversion was determined by ^1H NMR. [c] Microwave heating. [d] Ionic liquid: 1-butyl-3-methylimidazolium tetrafluoroborate ((BMIm)BF_4).

the Alder−ene product as the major product and a [2 + 2] cycloaddition product[4a] as a minor byproduct. Except for the minor byproduct, the reaction proceeds with complete atom economy because there is no requirement of additional reactants or catalyst and no other waste products are formed in the process.

The required starting materials **1** were readily obtained from the corresponding allylic acetates (Scheme 3). A Pd(0)-catalyzed allylic substitution of the acetate with sodium dimethyl malonate, followed by reaction with sodium hydride and the corresponding bromoallene, furnished enallenes **1a**−**d** in good yields.[5,7]

With the requisite substrates in hand, we started to investigate suitable reaction conditions for the thermal cyclization reaction (see Table 1). Starting with microwave heating of **1a** in CH_3CN at 160 °C for 1 h resulted in formation of the major product **2a** and the minor byproduct **3a** in a ratio of 83:17, in an isolated yield of 80% (Table 1, entry 1). The reaction was tried without solvent, and enallene **1a** was heated at 160 °C neat for 24 h, which resulted in a cyclization to give **2a** together with a mixture of unidentified products, most likely polymerized material (entry 2). The ene reaction was found to work at lower reaction temperature as well. After 15 h at 110 °C in CH_3CN, 50% of **1a** was converted to **2a** and **3a** in a 78:22 ratio (entry 3). Various solvents were investigated for the reaction of **1a**, and it was found that there is only a minor solvent effect for the reaction (except for water), as the conversion and ratio between **2a** and **3a** is not considerably affected. Since DMF gave a somewhat higher conversion (70%) after 15 h at 110 °C, compared to the other solvents, it was selected as the solvent (entry 6). The reaction temperature was increased to 120 °C, and full conversion to produce **2a** and **3a** was obtained after 24 h, in an improved ratio **2a**/**3a** of 90:10 and an isolated total yield of 84% (Table 2, entry 1).

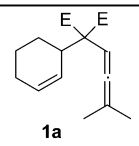
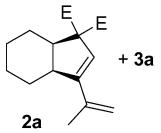
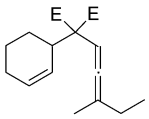
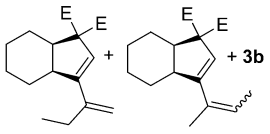
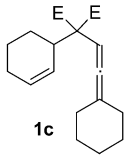
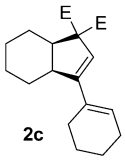
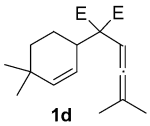
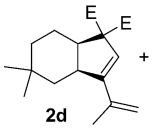
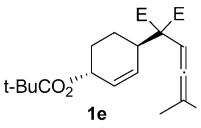
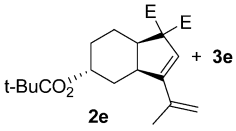
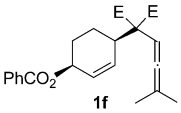
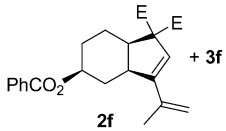
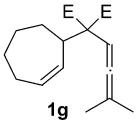
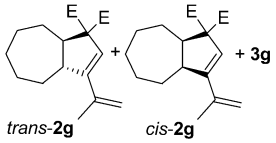
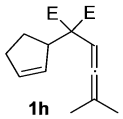
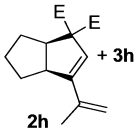
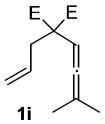
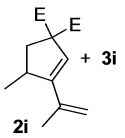
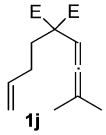
The optimized reaction conditions (Table 1, entry 10) were employed on a number of different allene-substituted cyclohexene derivatives **1b**−**f** (in DMF at 120 °C) to give *cis*-**2b**−**f** together with the minor **3b**−**f** [2 + 2]-byproduct in good yields (Table 2, entries 2−6). Note that **1c** gave **2c** as the sole product, without the [2 + 2] cycloaddition byproduct (entry 3) (Figure 1). It was found that two methyl groups in the allylic position of the enophile (**1d**, entry 4) increased the reaction time noticeably, from 24 h to 4.5 days. This is probably due to the more electron-rich enophile. The steric hindrance of the two methyl groups may also contribute to the increased reaction time. Despite the increased reaction time, **2d** + **3d** were obtained in a ratio of 95:5 and in high yield (86%). When the enophile instead was substituted with a *t*-$BuCO_2^-$ or $PhCO_2^-$ group in the allylic position, the reaction time for full conversion was 24 h (entries 5 and 6), which is the same reaction time as for the nonsubstituted enophiles. Thus, the reaction of substrate *trans*-**1e** at 120 °C for 24 h gave **2e** + **3e** in a ratio of 90:10 in a total yield of 82% (entry 5). Substrate *cis*-**1f** gave **2f** + **3f** in a ratio of 81:19 in 72% total yield after 24 h at 120 °C (entry 6). It does seem to make a slight difference whether the substituent is positioned *cis* or *trans* to the allene substituent, as the *cis* derivative decreased the chemoselectivity and yield to some extent. The dependence of the substrate ring size on the outcome of the cyclization was investigated (entries 7 and 8). In contrast to the six-membered ring substrates **1a**−**f**, which all gave the *cis*-fused ring systems with high stereoselectivity, the seven-membered ring analogue (**1g**) cyclized to give *trans*-**2g** and *cis*-**2g** in a ratio of 70:30, together with a small amount of the **3g** [2 + 2] cycloaddition product (ratio **2g**/**3g** was 95:5), in a total yield of 81% (entry 7).[8] Cyclization of the five-membered ring analogue (**1h**) under the optimized reaction conditions resulted in a somewhat less chemoselective reaction, and **2h** + **3h** were obtained in a ratio of 65:35 in a total yield of 77% (entry 8). When the reaction was applied on an acyclic substrate the yield dropped considerably. Enallene **1i** was heated at 120 °C for 72 h to give **2i** + **3i** in an 85:15 ratio and 35% total yield (entry 9). The residue was unidentified byproducts. In an attempt to create a cyclohexene derivative instead of a cyclopentene derivative, substrate **1j** was synthesized. Unfortunately, **1j** (entry 10) gave no thermal Alder−ene reaction, and the starting material could be recovered after 24 h at 120 °C.

To be able to make a comparison between allenes and olefins acting as the "ene" part in a thermal Alder−ene reaction, substrate **4** was prepared. Applying the optimized reaction conditions to **4** did not result in any reaction, and the starting material was recovered (Scheme 4). This indicates that the allene is essential for the reaction to occur under these relatively mild reaction conditions.

(7) The acyclic substrate **1i** was synthesized from an acyclic allylic acetate. For synthesis of enallene substrates **1e** and **1f**, see ref 6.

(8) The stereochemistry of *trans*-**2g** and *cis*-**2g** was assigned by NOE measurements.

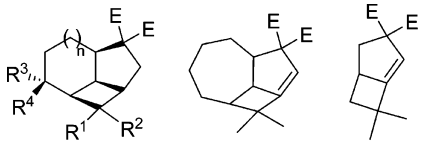
TABLE 2. Thermal Cyclization of Enallenes 1[a]

Entry	Substrate	Product	Time (h)	Ratio **2/3**[b,c]	Yield (%)[d]
1	 **1a**	 + **3a** **2a**	24	90:10	84
2	 **1b**	 **2b** 62 : **2b'** 38	36	80:20	87
3	 **1c**	 **2c**	24	100:0	88
4	 **1d**	 + **3d** **2d**	108	95:5	86
5	 t-BuCO$_2$ **1e**	 + **3e** t-BuCO$_2$ **2e**	24	90:10	82
6	 PhCO$_2$ **1f**	 + **3f** PhCO$_2$ **2f**	24	81:19	72
7	 **1g**	 *trans*-**2g** 70 : *cis*-**2g** 30	72	95:5	81
8	 **1h**	 + **3h** **2h**	24	65:35	77
9	 **1i**	 + **3i** **2i**	72	85:15	35
10	 **1j**	-	24	-	-

[a] E = CO_2Me. Unless otherwise noted, **1** was dissolved in DMF and heated at 120 °C for the indicated number of hours. [b] For the structure of **3**, see Figure 1. [c] The ratio between **2** and **3** was determined by ^1H NMR integration. [d] Isolated yields after flash chromatography.

Products **2** obtained in the thermal Alder−ene cyclization contain a conjugated diene unit, which could undergo further transformations, for example, a Diels−Alder reaction.[9] The synthetic utility of compounds **2** were demonstrated by the reaction of the mixture **2a** + **3a** (ratio 90:10) with maleic anhydride in refluxing toluene to give product **5**, which could be isolated as a single diastereoisomer, in excellent yield (Scheme 5), without contamination of **3a**. This provides a simple, direct route to more complex polycyclic systems. The stereochemistry of **5** was assigned by its X-ray crystal structure (see the Supporting Information).

In conclusion, we have developed a novel and mild thermal Alder−ene cyclization of readily available enallenes. The reaction conditions employed in this protocol (120 °C in DMF,

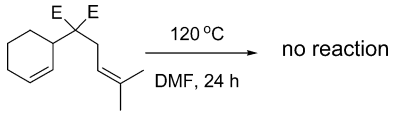


3a-f and **3h** **3g** **3i**

3a: n = 1, $R^1 = R^2$ = Me, $R^3 = R^4$ = H
3b: n = 1, R^1, R^2 = Me, Ethyl, $R^3 = R^4$ = H
3c: n = 1, $R^1 = R^2$ = -$(CH_2)_5$-, $R^3 = R^4$ = H
3d: n = 1, $R^1 = R^2$ = Me, $R^3 = R^4$ = Me
3e: n = 1, $R^1 = R^2$ = Me, R^3 = *t*-$BuCO_2$, R^4 = H
3f: n = 1, $R^1 = R^2$ = Me, R^3 = H, R^4 = $PhCO_2$
3h: n = 0, $R^1 = R^2$ = Me, R^3 = H, R^4 = H

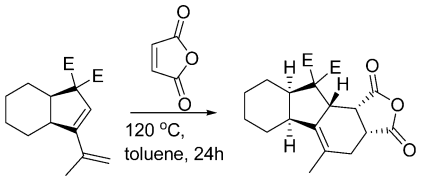
FIGURE 1. The [2 + 2] cycloaddition byproducts (E = CO_2Me).

SCHEME 4. Attempted Alder−Ene Reaction of 4



4 (E = CO_2Me)

SCHEME 5



2a (E =CO_2Me) **5** (93%)

for 24 h) are much milder compared to Alder−ene reactions with simple double bonds, which require much higher temperatures.

Experimental Section

General Procedure for the Preparation of 2. Compounds 2a and 3a. A solution of **1a** (0.139 g, 0.5 mmol**)** in DMF (3 mL) was heated to 120 °C for 24 h. Water (10 mL) was added, and the aqueous layer was extracted with Et_2O (4 × 20 mL). The combined organic phases were washed with water (3 × 10 mL) and dried (Na_2SO_4), and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (pentane/Et_2O 6:1) to give 0.117 g (84%) of **2a** and **3a** in a ratio of 90:10. Pure samples of **2a** and **3a** were obtained by preparative HPLC. **2a:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.67 (s, 1H), 5.05 (br s, 2H), 3.73 (s, 3H), 3.72 (s, 3H), 3.10 (td, J = 7.0, 4.3, 1H), 2.92 (m, 1H), 1.93 (s, 3H), 1.97−1.83 (m, 2H), 1.63 (dddd, J = 18.4, 11.3, 6.7, 4.9, 1H), 1.49 (m, 2H), 1.24 (m, 2H), 1.04 (m, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.0, 171.3, 153.4, 138.4, 123.9, 115.1, 67.8, 52.8, 52.6, 44.1, 43.1, 28.4, 24.3, 23.8, 22.5, 21.1. **3a:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.43 (d, J = 2.6 Hz, 1H), 3.72 (s, 3H), 3.67 (s, 3H), 3.38 (ddd, J = 9.3, 7.0, 2.6 Hz, 1H), 3.31 (td, J = 7.5, 5.1 Hz, 1H), 2.16 (td, J = 8.2, 5.0 Hz, 1H), 1.67−1.42 (m, 4H), 1.27 (s, 3H), 1.13 (s, 3H), 1.06 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.5, 170.8, 161.9, 114.9, 73.5, 52.5, 52.1, 48.0, 46.9, 44.3, 40.7, 26.8, 25.2, 23.6, 21.9, 19.9.

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Supporting Information Available: Experimental procedures and characterization data for compounds **2b**−**i**, **3h**, **4**, and **5** and CIF file for compound **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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