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Lewis Acid Catalyzed Diels−Alder Reactions of 1,2-Naphthoquinones

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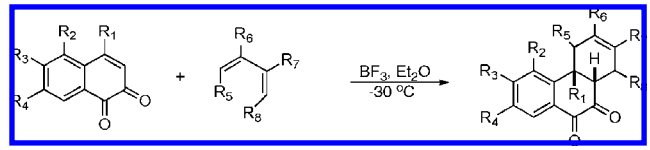
ABSTRACT

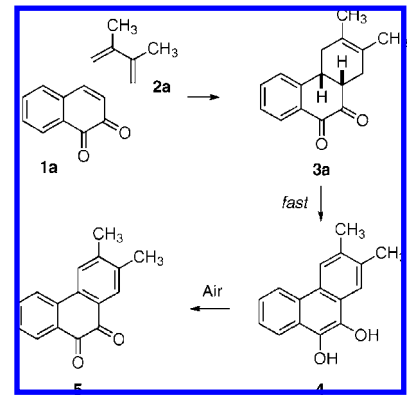


The use of BF_3·OEt_2 catalysis in Diels−Alder reactions of 3,4-unsubstituted 1,2-naphthoquinones provides direct access to *cis*-tetrahydrophenanthrene derivatives in good to excellent yields (66−99%) without rapid adduct aromatization commonly associated with corresponding thermal processes.

Since its discovery, the Diels−Alder reaction has been intensively studied, due to its utility in synthesis, tolerance of diverse functionalities, and structural breadth of reaction partners.[1] However, one class of potential dienophiles that has so far proven to be problematic are 3,4-unsubstituted 1,2-naphthoquinones.[2] Indeed Fieser and Seligman observed that "1,2-naphthoquinone ... gives with dienes reaction mixtures of a most unpromising nature."[2a] The challenge lies in finding conditions that promote cycloaddition without subsequent aromatization (Scheme 1).[3] We report here on a solution to this problem through the use of Lewis acid catalysis.

Lewis acid activation of dienophiles is now an established and important tool in Diels−Alder chemistry.[4] However, no studies on such activation with 1,2-naphthoquinones have appeared.[5] Thus we began by screening a number of Lewis acids for their ability to promote the cycloaddition of 2,3-dimethylbutadiene and 1,2-naphthoquinone (Table 1). Significantly this revealed that the nonchelating Lewis acid BF_3·OEt_2 in CH_2Cl_2 at −30 °C produced the desired tetrahydrophenanthrene derivative **3a**, without aromatization

Scheme 1. Diels−Alder Addition of 2,3-Dimethyl-1,3-butadiene and 1,2-Naphthoquinone



(1) (a) For a recent review of Diels−Alder cycloadditions and total synthesis, see: Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassiliko-giannakis, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 1668. (b) For a recent example of Diels−Alder additions of substituted 1,2-naphthoquinones employed to access the steroid core, see: Gelman, D. M.; Mayes, P. A.; Mulder, R.; Perlmutter, P. *Tetrahedron: Asymmetry* **2006**, *17*, 3341.

(2) (a) Fieser, L. F.; Seligman, A. M. *J. Am. Chem. Soc.* **1934**, *56*, 2690. (b) Fieser, L. F.; Dunn, J. T. *J. Am. Chem. Soc.* **1937**, *59*, 1016. (c) Fieser, L. F.; Dunn, J. T. *J. Am. Chem. Soc.* **1937**, *59*, 1018.

(3) (a) Ansell, M. F.; Murray, R. A. *Chem. Commun.* **1969**, 1111. (b) Paquette, J.; Brassard, P. *Can. J. Chem.* **1989**, *67*, 1354.

(4) Yates, P.; Eaton, P. *J. Am. Chem. Soc.* **1960**, *82*, 4436.

(5) For a report on Lewis acid activation on the conjugate addition to 1,2-naphthoquinones, see: Naruta, Y. *J. Am. Chem. Soc.* **1980**, *102*, 3774. For an example of BF_3·OEt_2 activation of a Diels−Alder reaction with a 1,4-naphthoquinone dienophile see: Motoyoshiya, J.; Masue, Y.; Iwayama, G.; Yoshioka, S.; Nishii, Y.; Aoyama, H. *Synthesis* **2004**, 2099.

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Scheme 2. BF_3-Catalyzed Diels−Alder Cycloadditions of Dienes **2a−c** to 1,2-Naphthoquinones **1a−d**

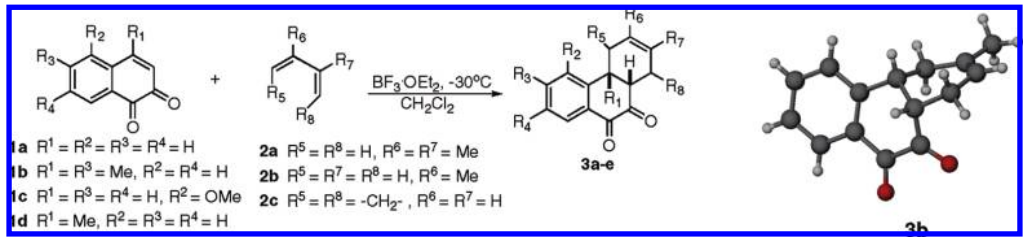


Table 1. Lewis Acid Screen for Diels−Alder Addition of **1a** to **2a**

entry	Lewis acid	mol %	temp (°C)	time (h)	conversion	products[a]
1	$BF_3{\cdot}OEt_2$	100	−30	1	100	**3**
2	$BF_3{\cdot}OEt_2$	10	−30	1.5	100	**3**
3	$AlCl_3$	100	−10	3	100	*c*
4	$AlCl_3$	100	−70	2.5	100	**4**[b]
5	$TiCl_4$	10	−30	1	0	
6	$Ti(O^iPr)_4$	100	0	3	15	**4**[b]
7	$Sc(OTf)_3$	10	0	2	100	**4**[b]
8	$Sc(OTf)_3$	10	−70	2	7	**3**

[a] Product ratios determined by comparison of product peaks in ^1H NMR spectrum to 1,2-naphthoquinone peaks. [b] Only aromatized adduct **4** observed. [c] Conversion of starting material; however, adducts **3a**, **4**, or **5** were not observed.

(to **4** and/or **5**). In addition $BF_3{\cdot}OEt_2$ proved superior in performance compared to chelating metals (entries 3−8, Table 1).[6]

The scope of this activation was tested with substituted 1,2-naphthoquinones **1a−d**[7] and dienes **2a−c** (Table 2). Most reactions proceeded to completion, and products were isolated in good to excellent yields. The adduct **3a** was accessed for the first time (i.e. without aromatization to **4**) in 99% yield (entry 1).[3] Addition of **1a** to isoprene (**2b**) also gave smooth conversion to adduct **3b** (entry 2). This adduct proved to be crystalline and X-ray crystallographic analysis confirmed its structure (Scheme 2).[8,9] Entry 3 is particularly noteworthy as the corresponding thermal process is known.[10] Thus, at room temperature the reaction was reported to take 1 week producing adduct **3c** in 15% yield. The corresponding $BF_3{\cdot}OEt_2$-catalyzed process produced **3c** in 95% yield under our standardized conditions. The protocol was then extended to substituted dienophiles **1b** and **1c** in their reaction with **2a** to yield the corresponding adducts **3d** and **3e** in 99% and 63% yields, respectively (entries 4 and 5).

Table 2. Results for Lewis Acid Catalyzed Diels−Alder Cycloaddition of 1,2-Naphthoquinones

entry	dienophile	diene	product	yield (%)
1	**1a**	**2a**	**3a**	99
2	**1a**	**2b**	**3b**	66
3	**1a**	**2c**	**3c**	95
4	**1b**	**2a**	**3d**	99
5	**1c**	**2a**	**3e**	63
6	**1d**	**2a**	**6**	95

In the case of 4-methyl-1,2-naphthoquinone (**1d**, entry 6, Table 2) tetracycle **6** was unexpectedly formed in essentially quantitative yield (Scheme 3). The structure was confirmed by X-ray crystallography. This result sits in stark contrast to that obtained in Gates' morphine synthesis where the Diels−Alder adduct of 4-cyanomethyl-1,2-naphthoquinone

(6) The isolated adducts were sufficiently stable for analysis but readily aromatized when stored at ambient temperature. Even when stored under inert atmosphere at −20 °C (freezer), the aromatized product appeared after several days.

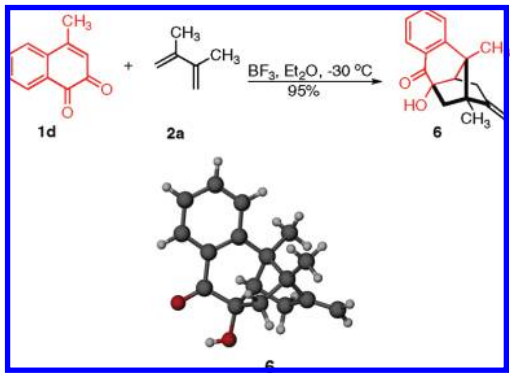
(7) Synthesised according to: Gelman, D. M.; Perlmutter, P. *Tetrahedron Lett.* **2009**, *50*, 39.

(8) **General procedure for the Diels−Alder cycloaddition.** $BF_3{\cdot}OEt_2$ (0.1 equiv) was added to a solution of 1,2-naphthoquinone **1** (1 equiv) in CH_2Cl_2 (0.18 M) at −78 °C. After 10 mins diene **2** (2 equiv) was added dropwise. The reaction was allowed to warm to −30 °C and monitored by TLC. When starting materials had been consumed the reaction was cooled to −78 °C and brine (equal volume to CH_2Cl_2) was added slowly. The reaction was allowed to warm to rt, and the contents were extracted with hexanes. The combined organics were then dried (Na_2SO_4) and filtered, and excess solvent was removed in vacuo to yield tetrahydrophenanthrene **3** without need for further purification. For some substrates crystallization could be achieved from a mixture of CH_2Cl_2/hexanes at −5 °C overnight.

(9) For other X-ray crystal structures of *cis*-tetrahydrophenanthrenes, prepared by other means, see: (a) Bruyere, D.; Bouyssi, D.; Balme, G. *Tetrahedron* **2004**, *60*, 4007. (b) Duthaler, R. O.; Mathies, P.; Petter, W.; Heuberger, C.; Scherrer, V. *Helv. Chim. Acta* **1984**, *67*, 1217. (c) Lin, Z.; Chen, J.; Valenta, Z. *Tetrahedron Lett.* **1997**, *38*, 3863. (d) Pattenden, G; Blake, A. J.; Reddy, L. K.; Stoker, D. A. *Synlett* **2006**, *18*, 3073.

(10) Friedrichsen, W.; Kallweit, I.; Schmidt, R. *Liebigs Ann. Chem.* **1977**, 116.

Scheme 3. Reaction of Quinone **1d** with Diene **2a**



and butadiene was obtained in high yields under Brönsted acid conditions.[11] Norbornane **6** has some structural similarity with lumitetracycline, a photochemical product of doxycycline.[12] Mechanistic studies to determine the similarity of these two processes are currently underway and will be disclosed in due course.

In conclusion, routine access to *cis*-tetrahydrophenanthrenes is now available through BF_3-catalyzed Diels−Alder additions of 1,2-naphthoquinones to 1,3-dienes at low temperatures. Under these new conditions the problems that have been commonly associated with corresponding thermal additions, namely, adduct aromatization, are completely avoided.

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Supporting Information Available: Experimental procedures and CIF files. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) (a) Drexel, R. E.; Olack, G.; Jones, C.; Chumurny, G. N.; Santini, R.; Morrison, H. *J. Org. Chem.* **1990**, *55*, 2471. (b) Barton, D. H. R.; Ley, S. V.; Meguro, K.; Williams, D. J. *J. Chem. Soc., Chem. Commun.* **1977**, 790.