J. Org. Chem. **1997,** *62,* 8274−8275

Communications

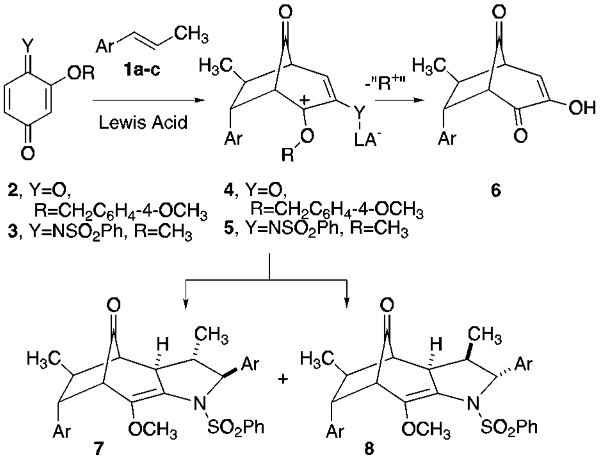
Tandem 5 + 2/3 + 2 and 5 + 2/3 + 3 Cycloaddition Reactions

Thomas A. Engler,* Cynthia M. Scheibe, and Rajesh Iyengar

Department of Chemistry, University of Kansas, Lawrence, Kansas 66045

Received August 28, 1997

Tandem reactions are of considerable current interest because they rapidly assemble products with molecular complexity significantly greater than starting materials.[1,2] Their value is amplified if they also selectively create multiple stereogenic centers. While developing new Lewis acid-promoted reactions of styrenyl systems **1** with 2-alkoxy-1,4-benzoquinones,[3,4] we found that the initially formed alkoxy carbocation **4** could be intercepted via displacement of the arylmethyl group (R), stereoselectively providing bicyclo[3.2.1]octenyl-adduct **6**.[5] Herein we report that intermediates similar to **4** can also be intercepted via a second cycloaddition process generating products in which three rings and up to eight stereogenic centers result from starting components with only one ring and a double bond as the sole sources of stereochemistry. These novel tandem cycloadditions significantly extend the synthetic potential of Lewis acid-promoted quinone−alkene reactions.



For **1**, **7/8**: **a**, Ar=C_6H_5; **b**, Ar=C_6H_4-2-CH_3; **c**, Ar=C_6H_4-4-Cl

Initial experiments on BF_3-promoted reactions of quinone monoimide **3** with 1 equiv of (*E*)-propenylbenzene (**1a**) indicated the formation of a 2:1 adduct in modest yield (8%) for which structure **7a** was proposed. Manipulation of stoichiometry (>2 equiv of **1a**) and temperature (−20 °C)[6] resulted in good yields of **7a** accompanied by lesser amounts of a stereoisomeric product **8a**. The generality of the process was demonstrated with several propenylbenzenes (Table 1). In reactions of **1c**, yet a third 2:1 adduct **9** was isolated, albeit in low yield. The structures of products **7a** and **9** were firmly established by single-crystal X-ray analysis, and that of **8a** was determined by comparison of $^1H-^1H$ NOE data from it with that from **7a**; structures of **7b**/**c** and **8b**/**c** were assigned by spectral comparison. These products apparently result from reaction of an initially formed 5 + 2 cycloadduct **5** with a second propenylbenzene followed by either carbon−nitrogen bond formation (path a) or carbon−carbon bond formation (path b).[7]

---

* To whom correspondence should be addressed. Phone: (913)785−4670. FAX: (913)785-5396. E-mail: tengler@caco3.chem.ukans.edu.

[1] For reviews and summaries of various processes, see (a) Ho, T.-L. *Tandem Organic Reactions*; Wiley-Interscience: New York; 1992. (b) Ho, T.-L. *Tactics of Organic Synthesis*; Wiley-Interscience: New York; 1994. (c) Hudlicky, T. *Chem. Rev. (Washington, D.C.)* **1996**, *96*, 3−30. (d) Tietze, L. F. *Chem. Rev. (Washington, D.C.)* **1996**, *96*, 115−136. (e) Denmark, S. E.; Thorarensen, A. *Chem. Rev. (Washington, D.C.)* **1996**, *96*, 137−165. (f) Winkler, J. D. *Chem. Rev. (Washington, D.C.)* **1996**, *96*, 167−176. (g) Ryu, I.; Sonoda, N.; Curran, D. P. *Chem. Rev. (Washington, D.C.)* **1996**, *96*, 177−194. (h) Parsons, P. J.; Penkett, C. S.; Shell, A. J. *Chem. Rev. (Washington, D.C.)* **1996**, *96*, 195−206. (i) Wang, K. K. *Chem. Rev. (Washington, D.C.)* **1996**, *96*, 207−222. (j) Padwa, A.; Weingarten, M. D. *Chem. Rev. (Washington, D.C.)* **1996**, *96*, 223−269. (k) Harvey, D. F.; Sigano, D. M. *Chem. Rev. (Washington, D.C.)* **1996**, *96*, 271−288. (l) Malacria, M. *Chem. Rev. (Washington, D.C.)* **1996**, *96*, 289−306. (m) Molander, G. A.; Harris, C. R. *Chem. Rev. (Washington, D.C.)* **1996**, *96*, 307−338. (n) Snider, B. B. *Chem. Rev. (Washington, D.C.)* **1996**, *96*, 339−363. (o) Negishi, E.-i.; Copéret, C.; Ma, S.; Liou, S.-Y.; Liu, F. *Chem. Rev. (Washington, D.C.)* **1996**, *96*, 365−393. (p) Heumann, A.; Réglier, M. *Tetrahedron* **1996**, *52*, 9289−9346. (q) Bunce, R. A. *Tetrahedron* **1995**, *51*, 13103−13159. (r) Posner, G. H. *Chem. Rev. (Washington, D.C.)* **1986**, *86*, 831−844. (s) Skrydstrup, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 345−347.

[2] For selected representative recent reports of specific processes, with references to extensive literature, see (a) Nakamura, E.; Kubota, K.; Sakata, G. *J. Am. Chem. Soc.* **1997**, *119*, 5457−5458. (b) Grigg, R.; Rasul, R.; Savic, V. *Tetrahedron Lett.* **1997**, *38*, 1825−1828. (c) Grigg, R.; Loganathan, V.; Sridharan, V. *Tetrahedron Lett.* **1996**, *37*, 3399−3402. (d) Yamada, H.; Aoyagi, S.; Kibayashi, C. *Tetrahedron Lett.* **1997**, *38*, 3027−3030. (e) Markó, I. E.; Mekhalfia, A.; Murphy, F.; Bayston, D. J.; Bailey, M.; Janousek, Z.; Dolan, S. *Pure Appl. Chem.* **1997**, *69*, 565−570. (f) Fillery, S. F.; Gordon, G. J.; Luker, T.; Whitby, R. J. *Pure Appl. Chem.* **1997**, *69*, 633−638. (g) Fish, P. V.; Johnson, W. S. *J. Org. Chem.* **1994**, *59*, 2324−2335. (h) Fish, P. V.; Johnson, W. S.; Jones, G. S.; Tham, F. S.; Kullnig, R. K. *J. Org. Chem.* **1994**, *59*, 6150−6152. (i) Lautens, M.; Fillion, E. *J. Org. Chem.* **1997**, *62*, 4418−4427. (j) Organ, M. G.; Winkle, D. D.; Huffmann, J. *J. Org. Chem.* **1997**, *62*, 5254−5266. (k) Paquette, L. A.; Kuo, L. H.; Doyon, J. *J. Am. Chem. Soc.* **1997**, *119*, 3038−3047. (l) Davies, H. M. L.; Ahmed, G.; Churchill, M. R. *J. Am. Chem. Soc.* **1996**, *118*, 10774−10782. (m) Pearson, W. H.; Mi, Y. *Tetrahedron Lett.* **1997**, *38*, 5441−5444.

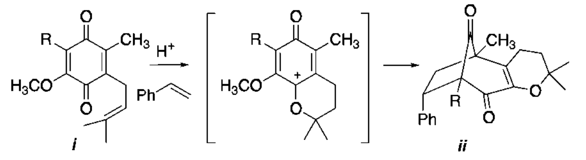
[3] (a) Engler, T. A.; Combrink, K. D.; Letavic, M. A.; Lynch, K. O., Jr.; Ray, J. E. *J. Org. Chem.* **1994**, *59*, 6567−6587. (b) Engler, T. A.; Wei, D.; Letavic, M. A.; Combrink, K. D.; Reddy, J. P. *J. Org. Chem.* **1994**, *59*, 6588−6599.

[4] 5 + 2 Cycloadducts are also found in reactions of quinone mono- and bis-imides: (a) Engler, T. A.; Meduna, S. P.; LaTessa, K. O.; Chai, W. *J. Org. Chem.* **1996**, *61*, 8598−8603. (b) Engler, T. A.; Chai, W.; LaTessa, K. O. *J. Org. Chem.* **1996**, *61*, 9297−9308.

[5] For 5 + 2 cycloadditions of carbocations formed in quinone monoketal solvolysis or phenol oxidation, see (a) Büchi, G.; Mak, C.-P. *J. Am. Chem. Soc.* **1977**, *99*, 8073−8075. (b) Büchi, G.; Chu, P.-S. *J. Org. Chem.* **1978**, *43*, 3717−3719. (c) Mak, C.-P.; Büchi, G. *J. Org. Chem.* **1981**, *46*, 1−3. (d) Mortlock, S. V.; Seckington, J. K.; Thomas, E. J. *J. Chem. Soc., Perkin Trans 1* **1988**, 2305−2307. (e) Angle, S. R.; Turnbull, K. D. *J. Org. Chem.* **1993**, *58*, 5360−5369. (f) Gates, B. D.; Dalidowicz, P.; Tebben, A.; Wang, S.; Swenton, J. S. *J. Org. Chem.* **1992**, *57*, 2135−2143. (g) Yamamura, S.; Shizuri, Y.; Shigemori, H.; Okuno, Y.; Ohkubo, M. *Tetrahedron* **1991**, *47*, 635−644. (h) Grieco, P. A.; Walker, J. K. *Tetrahedron* **1997**, *53*, 8975−8996. (i) Collins, J. L.; Grieco, P. A., Walker, J. K. *Tetrahedron Lett.* **1997**, *38*, 1321−1324. An analogous process is the perezone to pipitzol rearrangement, see (j) Joseph-Nathan, P.; Santillan, R. L. In *Studies in Natrural Product Chemistry*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam; 1989; Vol. 5, pp 763−813.

[6] At higher temperatures the 5 + 2 adduct collapses to a 2-aryl-2,3-dihydrobenzofuran (51%), as is found in benzoquinone reactions.[3,4]

[7] Intramolecular carbocation activation of quinones to intermolecular cycloaddition has been reported; e.g. **i** to **ii**, see Mamont, P. *Bull. Soc. Chim. Fr.* **1970**, 1557−1564.

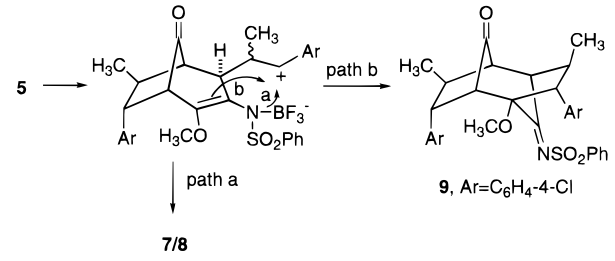


S0022-3263(97)01601-0 CCC: $14.00

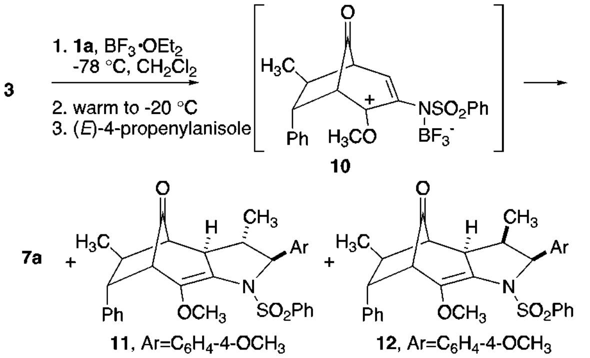
Table 1. BF_3•OEt_2-Promoted Reactions of Monoimide 3 with Propenylbenzenes 1[a]

	time (h)	products (% yield)
1a	1	**7a** (58), **8a** (16)
1b	0.3	**7b** (51), **8b** (14)[b]
1c	17	**7c** (24), **8c** (20), **9** (13)

[a] Conducted by adding BF_3•OEt_2 to a solution of **1** and **3** in CH_2Cl_2 at −20 °C. [b] 2-Aryl-7-methoxy-3-methyl-5-(*N*-benzenesulfonylamino)-2,3-dihydrobenzofuran (28%) was also found.[6]

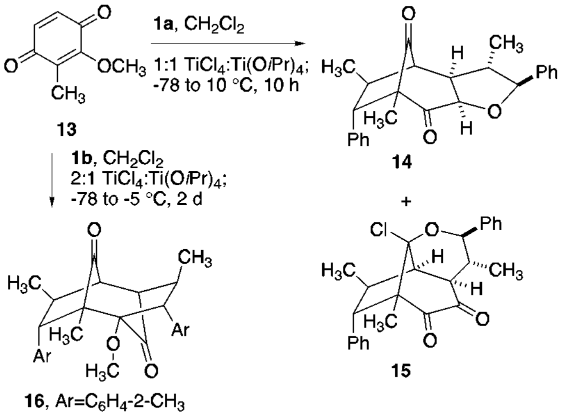


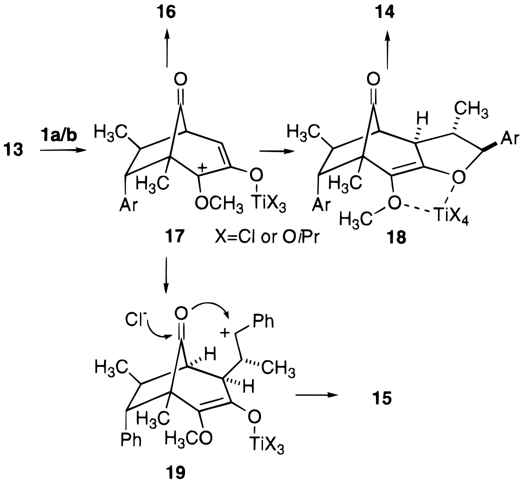
Products from tandem addition of two different propenylbenzenes can also be generated. For example, addition of BF_3•OEt_2 to a 1:1 mixture of **1a** and monoimide **3** in CH_2Cl_2 at −78 °C, followed by warming to −20 °C and addition of (*E*)-4-propenylanisole, afforded **7a** (10%) accompanied by hybrid tandem adducts **11** and **12** in 15 and 22% yields, respectively. The structure of **11** was again established by single-crystal X-ray analysis, and comparison of $^1H-^1H$ NOE from both **11** and **12** allowed stereochemical assignment of the latter. Evidently, the (*E*)-4-propenylanisole traps carbocation **10** formed in an initial cycloaddition.



Tandem cycloadducts are also generated in reactions of quinones, although not as efficiently, and different propenylbenzenes produce different types of products. For example, reactions of quinone **13** with 2 equiv or more of **1a** promoted by a 1:1 mixture of $TiCl_4$:$Ti(OiPr)_4$ gave **14** and **15** in 28% and 12% yields, respectively. Reactions of **1b** with **13** were more sluggish, requiring a 2:1 mixture of $TiCl_4$:$Ti(OiPr)_4$ as the promoter, and gave adduct **16** (22%). The structures of **14** and **16** were established by single-crystal X-ray analysis, and that of **15** is assigned from NMR, IR, and mass spectral data.[8]

Mechanistically, the formation of **14** and **16** parallels that of **7** and **9**, respectively, with the additional step that derives **14**, intermediate **18** undergoes dealkylation under the reaction conditions or hydrolysis upon workup. A possible route to **15** involves the addition of the second propenylbenzene to **17** to produce cation **19** in addition to that leading to **18**. We reason that intermediate **19** undergoes addition of chloride ion, C−O bond formation, oxidation,[9] and demethylation (not necessarily in that order).





Previous research has established the stereoselectivity of 5 + 2 cycloadditions between alkoxyquinones and styrenes.[3] Herein, the stereochemical details of the second cycloaddition, e.g. **5** to **7**−**9**, remain to be established; however, initial results reveal that these remarkable tandem cycloadditions are reasonably stereoselective and result in the formation of up to eight new stereogenic centers. These results raise the synthetic potential of quinone−alkene reactions to new heights, particularly since they can be orchestrated such that the alkenyl component involved in the second cycloaddition can be different from the one involved in the initial 5 + 2 cycloaddition.

Acknowledgment. This work was supported financially by the National Science Foundation (OSR-955223) and the KU General Research Fund. We thank Dr. Martha Morton for help with NMR experiments and Mr. Lawrence Seib for X-ray structure determinations.

Supporting Information Available: Full physical and spectral data (mp, $^1H/^{13}C$ NMR, IR, mass and HRMS, and/or CHN) for all new compounds, explanation of the structural assignment for **15**, copies of NMR spectra for compounds with HRMS data, summaries of data from ^1H-^1H NOE, HMQC and HMBC experiments, and ORTEP drawings[10] for **7a**, **9**, **11**, **14**, and **16** (33 pages).

JO971601K

---

(8) X-ray quality crystals of **15** have not yet been obtained. Data from $^1H-^1H$ NOE, COSY, HMQC, and HMBC spectra and a discussion of this structure assignment are included in the Supporting Information.

(9) The oxidant may be the Ti(IV)-complexed quinone.[3a] For reports of Ti(IV)-oxidation of electron-rich alkenes, see (a) Inaba, S.-i.; Ojima, I. *Tetrahedron Lett.* **1977**, 2009−2012. (b) Reetz, M. T.; Schwellnus, K.; Hubner, F.; Massa, W.; Schmidt, R. E. *Chem. Ber.* **1983**, *116*, 3708−3724. (c) Jacobsen, E. J.; Totten, G. E.; Wenke, G.; Karydas, A. C.; Rhodes, Y. E. *Synth. Commun.* **1985**, *15*, 301−306.

(10) The authors have deposited atomic coordinates for structures **7a**, **9**, **11**, **14**, and **16** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, CB2 1EZ, U.K.