

LEWIS ACID-CATALYZED DIELS-ALDER REACTIONS OF PERI-HYDROXYLATED NAPHTHOQUINONES:

A REGIOCHEMICAL DIVERGENCE

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The ability of Lewis acids to enhance regioselectivity in Diels Alder reactions between unsymmetrical dienes and dienophiles is well documented.^{1,2} In practice, selection of the specific Lewis acid employed in any particular reaction is usually based on the unscientific but eminently pragmatic approach of trial and error. It is generally assumed, however, that all Lewis acids which promote regioselectivity in a given reaction will enhance the formation of the same regioisomer. We now report that in the case of some peri-hydroxylated naphthoquinones, such an assumption is entirely unwarranted. For at least in the reactions which we have investigated, either regioisomer can be obtained with a high degree of selectivity, depending on the particular Lewis acid employed. This observation may well have fruitful

Table 1^a

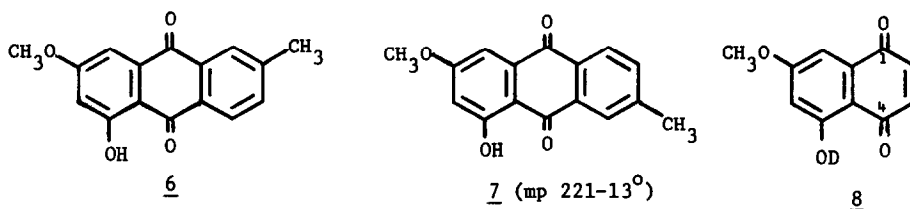
				Equivs. ^b of Catalyst	Rxn. Temp.
<p><u>1</u>⁴ + <u>2</u>^{3b} $\xrightarrow{\text{MgI}_2^c}$</p>	25°	40%	60%	none	25°
		35	65	0.05	~20+0°
		≤5	≥95	0.5	~20+0°
<p><u>3</u>⁴ + <u>2</u> $\xrightarrow{\text{BF}_3 \cdot \text{Et}_2\text{O}}$</p>	25°	45	55	none	25°
		55	45	0.05	~20+0°
		≥95	≤5	0.4	~20°
		≥95	≤5	2	25°

a) All reactions were conducted in ether using excess diene. The yield of adduct(s) is 70~90% (unoptimized).^b In 4 and 5 R=H or CH₃ depending on which naphthoquinone (1 or 3) was used.

b) based on quinone. c) prepared in anhydrous ether from Mg and I₂. d) see footnote 5.

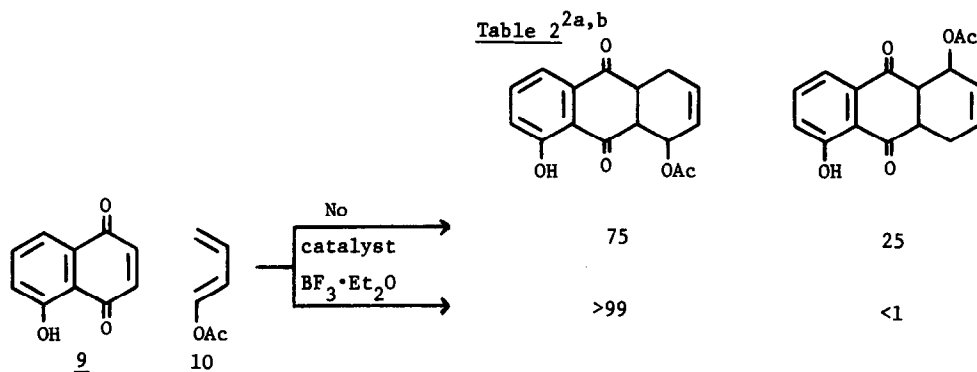
application in quinone chemistry, but at the same time it suggests that the exercise of a modicum of caution in the assignment of regiochemistry to adducts from Lewis-acid-catalyzed Diels Alder reactions is perhaps generally advisable.

The results of our initial studies, which were conducted primarily in the context of developing a regiospecific route to Altersolanol B (see accompanying paper), and with the particular objective of overcoming the unsatisfactory outcome of the uncatalyzed reaction between 1 and 2, are given in Table 1. These results indicate that regiochemistry is a function of both the specific Lewis acid catalyst and its concentration (reaction temperature may also be important^{2b,7}). The regiochemistry of the adduct(s) was determined by conversion⁸ to 6 and/or 7 and analysis by NMR using an authentic⁹ sample of 6 for direct comparison.*



In a parallel study, the consequences of replacing the peri-hydroxy group with a peri-deuteroxy group (1 vs 8) were briefly explored in order to probe the possible regiochemical impact of a deuterium isotope effect on the hydrogen bonding interaction^{3a,b} between the peri-OH group and the C-4 carbonyl in 1. Within experimental error no difference in regiochemistry was detected in the reactions of 1 and 8 with 2 (reactions conducted at 25° in EtOH and EtOD, respectively; the adducts were characterized as a ~4:6 ratio of 6:7).

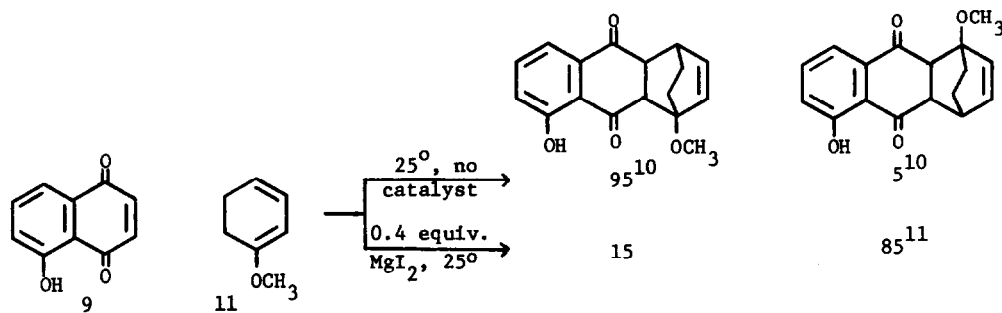
The results described in Table 1 for the BF₃·Et₂O- and B(OAc)₃-catalyzed reactions are those anticipated by analogy to the findings of Trost, Stork and co-workers^{2a,b} for the reaction of 9 and 10 (Table 2). Thus, the MgI₂-promoted outcome in Table 1 would appear



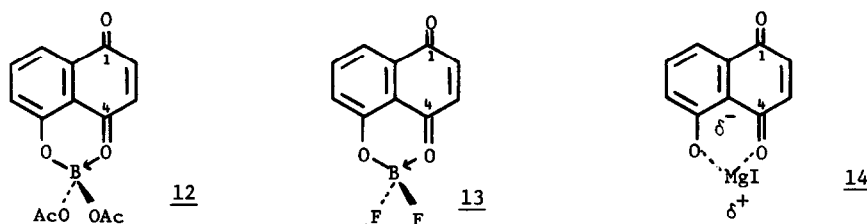
*Anthraquinone 6 was isolated from Alternaria Porri by Stoessl⁹ and named "Pigment I". For reasons most evident in the framework of a synthesis of Altersolanol B, the regioisomer of 6, viz 7, has come to be known as Pigment minus I. The 60 MHz NMR spectra of 6⁹ and 7 are very similar, but the two compounds can be differentiated by the position of the resonance due to the peri-OH protons [sharp singlets (in CDCl₃) at δ 12.90 for 6, and δ 12.87 for 7 (assignment confirmed by peak enhancement with authentic 6)].

anomalous. In view of this disparity, it was of interest to determine whether the effect observed for MgI_2 was unique to the substrates employed or was a portent of a more general phenomenon. As a preliminary step in the investigation of this question, the effect of MgI_2 on the reaction of 9 and 11 has been examined also (Table 3). Here, too, MgI_2 leads to a regiochemical outcome which is the reverse of what might otherwise² have been anticipated.

Table 3



At present it is not possible to provide a complete rationale for the results described above. We would suggest, however, that at least in the case of $B(OAc)_3$ and $BF_3 \cdot Et_2O$, the *peri*-hydroxyl group plays a crucial directional role and that the structures of the Lewis acid "complexes" involved in the reactions reported above differ substantially from those more commonly proposed for dienophiles which lack a second available ligating group (i.e., the *peri*-hydroxyl group). In particular, it is well established^{12a} that many *peri*-hydroxyquinones react readily with $B(OAc)_3$ to give compounds with structures analogous to 12. The electron withdrawing impact of the interaction between the electron deficient boron and the oxygen of the C-4 carbonyl could account for the observed regiochemical outcome by an extension of our



earlier hypothesis.³ A similar structure (13) and rationale might apply in the case of $BF_3 \cdot Et_2O$. Less precedent for structure 13 is available, but it is known that enolized β -diketones (which 1, 3 and 9 may be viewed as) react with BF_3 to give products akin to 13.^{12b}

The situation with the MgI_2 results is less clear. Extension of our earlier hypothesis³ would suggest that if the MgI_2 "complex" has a structure such as 14, where the electron density at the C-4 carbonyl is greater than that at the C-1 carbonyl (due to the greater polarization of the O-Mg bond), the regiochemical results observed could be accommodated. Such an hypothesis would seem to require^{3b} that the MgI_2 -catalyzed reactions proceed slower than the uncatalyzed reactions. In some cases,¹³ however, rate acceleration is observed. Further speculations on the exact role of the MgI_2 , although not lacking, would appear premature at this time.

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References and Notes

- For a review see V.M. Andreev and L.K. Andreeva in B.A. Kazanskii, I.L. Knunyants, M.M. Shemyakin and N.N. Melnikov (Eds.), "Organic Compounds: Reactions and Methods", Vol. 21,IFI/Plenum, New York, 1973, pp. 41-91.
- For recent applications of Lewis acid catalysis to Diels Alder reactions of quinones see, *inter alia*, a) B.M. Trost, J. Ippen and W.C. Vladuchick, *J. Am. Chem. Soc.*, **99**, 8116 (1977); b) G. Stork and A.A. Hagedorn, III, *ibid.*, **100**, 3609 (1978); c) Z. Stojanac, R.A. Dickinson, N. Stojanac, R. Woznow and Z. Valenta, *Can. J. Chem.*, **53**, 616 (1975).
- The outcome of the uncatalyzed reaction provides an index of the relative importance of the conflicting effects of hydrogen bonding and electron donation on regiochemistry: c.f., a) T.R. Kelly, J.W. Gillard, R.N. Goerner, Jr. and J.M. Lyding, *J. Am. Chem. Soc.*, **99**, 5513 (1977) and b) T.R. Kelly, *Tetrahedron Letters*, 1387 (1978).
- For the preparation of 3 see J.F. Garden and R.H. Thompson, *J. Chem. Soc.*, 2483 (1957). In our experience 3 is very sensitive to acid and base and is best stored as an ether solution in the freezer. Selective methylation of 3 (Ag₂O, CH₃I, CH₂Cl₂) gives 1, which is similarly unstable.
- B(OAc)₃ was prepared⁶ by heating boric acid in excess acetic anhydride and collecting the crystals which separated upon cooling. It is generally less corrosive toward substrates than BF₃·Et₂O. The utility of B(OAc)₃ as a Diels Alder catalyst was first demonstrated, in a related context, by Dr. Judith M. Lyding, whom we thank for helpful discussions and a gift of B(OAc)₃.
- a) See H. Steinberg, "Organoboron Chemistry", Vol. 1, John Wiley and Sons, New York, 1964, p. 394 and references therein. b) For a recent application of boron acetates to another facet of Diels Alder chemistry, see A.M. Birch, A.J. H. Mercer, A.M. Chippendale and K.W. Greenhalgh, *J.C.S. Chem. Comm.*, 745 (1977).
- Substitution of isoprene for diene 2 results in ~50:50 mixtures of 4/5-type adducts, even when carried out in the presence of MgI₂ (1 equivalent) or B(OAc)₃ (2 equivalents). Thus, it would appear that the presence of a strongly polarizing substituent on the diene contributes substantially to the regiochemical outcome.
- The crude adducts were oxidized [after methylation (CH₃I/Ag₂O) in the case of adducts of 3] by treatment with base and air.³ Appropriate precautions were taken to avoid "loss" of a regioisomer.
- A. Stoessl, *Can. J. Chem.*, **47**, 767 (1969).
- These results are in essential agreement with those previously reported: A.J. Birch and V.H. Powell, *Tetrahedron Letters*, 3467 (1970); V.H. Powell, *ibid.*, 3463 (1970).
- No attempt was made to optimize the regiochemical outcome of the reaction. The structure of the major adduct was confirmed by degradation (see ref. 3a, footnote 16) to the monomethyl ether of 1,5-dihydroxyanthraquinone and comparison with an authentic sample. The monomethyl ethers of 1,5- and 1,8-dihydroxyanthraquinone are clearly distinguishable by the position of the pmr resonance (in CDCl₃) of the *peri*-OH protons (1,5 isomer: δ 12.48; 1,8 isomer: δ 12.90).
- a) ref. 6a, Chapter 8. b) ref. 6a, pp. 524-5.
- Apart from one exception (*vide infra*) use of B(OAc)₃, BF₃·Et₂O and MgI₂ (including the reactions with isoprene - see footnote 7) was attended by rate acceleration. The one exception is the MgI₂-catalyzed reaction of 9 and 11 described in the text [conducted in ~1:1 Et₂O/THF (because the MgI₂-9 complex is poorly soluble in ether)], which was slightly slower than the uncatalyzed reaction between 9 and 11 (also conducted in THF/Et₂O at 25° for comparison purposes). The significance of this observation remains to be determined.

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