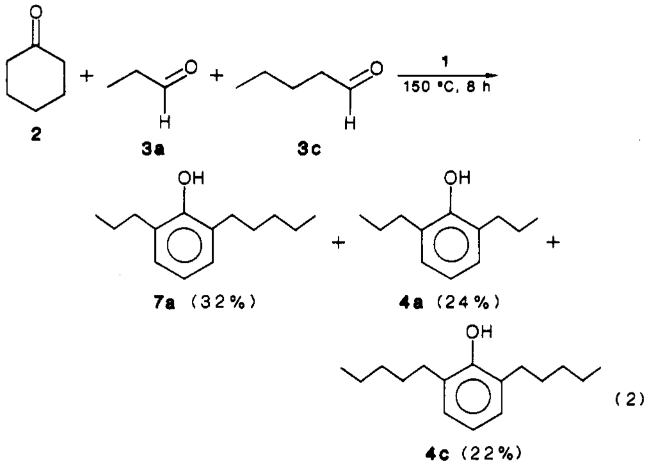
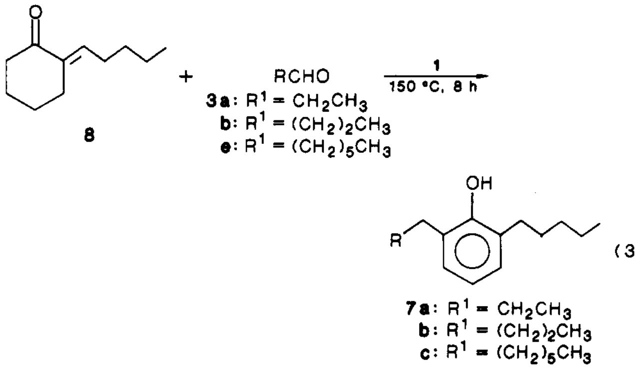
stage probably because of the stability of the resulting conjugated alkylidene compounds.

The preparation of unsymmetrical 2,6-dialkylphenols substituted by different alkyl substituents may further enhance the utility of the present method. Thus, **2a** was allowed to react with a equimolar mixture of different kinds of aldehydes, **3a** and **3c**. As expected, 2-pentyl-6-propylphenol (**7a**) was formed in 32% yield together with symmetrical phenols, **4a** (24%) and **4c** (22%) (eq 2).



(2)

This problem was solved by employing a two-step sequence involving the reaction between 2-alkylidenecycloalkanones and aldehydes. The reaction of 2-pentylidenecyclohexanone (**8**), prepared in advance by Cp_2ZrH_2-catalyzed cross-condensation of **2a** with **3c**,[9] with aldehydes **3** in the presence of **1** afforded unsymmetrical phenols (**7**) in good yields. 2-Pentyl-6-propylphenol (**7a**), 2-butyl-6-pentylphenol (**7b**), and 2-heptyl-6-pentylphenol (**7c**) were synthesized from the reaction with **3a**, **3b**, and **3e**, respectively, in high yields (eq 3).



(3)

Although the detailed mechanism remains unclear, it is probable that the present cross-aromatization proceeds via continuous three steps: (i) double aldol condensation of **2** with **3** to give 2,6-dialkylidenecyclohexanone, (ii) isomerization of an exo-cyclic double bond to an endo-cyclic one, and (iii) aromatization to **4**. These processes fully conform to the driving force of the formation of thermodynamically favored products.

In conclusion, this efficient synthesis of a wide variety of substituted phenols offers great synthetic versatility.

Registry No. **1**, 1291-32-3; **2a**, 108-94-1; **2b**, 589-92-4; **2c**, 98-53-3; **2d**, 591-24-2; **3a**, 123-38-6; **3b**, 123-72-8; **3c**, 110-62-3; **3d**, 66-25-1; **3e**, 111-71-7; **3f**, 124-13-0; **3g**, 78-84-2; **3h**, 590-86-3; **3i**, 96-17-3; **3j**, 630-19-3; **3k**, 104-55-2; **3l**, 98-01-1; **4a**, 6626-32-0; **4b**, 62083-20-9; **4c**, 116374-97-1; **4d**, 91069-45-3; **4e**, 116374-98-2; **4f**, 3307-31-1; **4g**, 52348-51-3; **4h**, 116374-99-3; **4i**, 54116-67-5; **4j**, 81216-68-4; **4k**, 116375-00-9; **4l**, 116375-01-0; **4m**, 116405-66-4; **5**, 116375-02-1; **6**, 62085-75-0; **7a**, 116375-03-2; **7b**, 116375-04-3; **7c**, 116375-05-4; **8**, 25677-40-1; Cp_2TiCl_2, 1271-19-8; Cp_2HfCl_2, 12116-66-4; Cp_2ZrH_2, 37342-98-6; $Cp_2Zr(O\text{-}^iPr)_2$, 78091-18-6; $Cp_2Zr(H)Cl$, 37342-97-5.

Supplementary Material Available: General experimental procedures and spectral data for metallocene complexes, **4a–m**, **5–8** (8 pages). Ordering information is given on any current masthead page.

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Comparative Analysis via Secondary Deuterium Isotope Effects of Transition State Structural Features Associated with Cycloadditions to Norbornadiene$[2_\pi + 2_\pi + 2_\pi]$ and Quadricyclane-$[2_\sigma + 2_\sigma + 2_\pi]$

Summary: Quadricyclane-*1-d* and norbornadiene-*2-d* undergo cycloaddition to 2π addends of differing reactivity to give products wherein the distribution of deuterium is commensurate with the operation of concerted processes but with asynchronous capture of the attacking reagent.

Sir: Whereas the valence isomeric ring systems described by norbornadiene (N) and quadricyclane (Q)[2] present a similar steric profile to attacking reagents, they differ appreciably in having sets of frontier orbitals of inverse symmetry.[3] Adherence by N and Q to orbital symmetry restrictions consequently allows for operation of contrasting types of cycloaddition chemistry. While experimental documentation of the orbital-correlated processes abound,[4,5] the homo-Diels–Alder reactivity exhibited by N is not commonly found in other bridged dienes[6] because

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(1) Postdoctoral fellowship awardee of the Deutsche Forschungsgemeinschaft, 1985–1986.

(2) (a) Dauben, W. G.; Cargill, R. L. *Tetrahedron* **1961**, *15*, 197. (b) Hammond, G. S.; Turro, N. J.; Fischer, A. *J. Am. Chem. Soc.* **1961**, *83*, 4674. (c) Hammond, G. S.; Wyatt, P.; DeBoer, C. D.; Turro, N. J. *Ibid.* **1964**, *86*, 2532.

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(4) Norbornadienes: (a) Ullman, E. F. *Chem. Ind. (London)* **1958**, 1173. (b) Blomquist, A. T.; Meinwald, Y. C. *J. Am. Chem. soc.* **1959**, *81*, 667. (c) Hall, H. K. *j. Org. Chem.* **1960**, *25*, 42. (d) Davies, D. I. *J. Chem. Soc.* **1960**, 3669. (e) Cookson, R. C.; Dance, J.; Hudec, J. *Ibid.* **1964**, 5416. (f) Nickon, A.; Kwasnik, H. R.; Mathew, C. T.; Swartz, T. D.; Williams, R. O.; DiGiorgio, J. B. *J. Org. Chem.* **1978**, *43*, 3904. (g) Jenner, G.; Papadopoulos, M. *Tetrahedron Lett.* **1982**, *23*, 4333. (h) De Lucchi, O.; Lucchini, V.; Pasquato, L.; Modena, G. *J. Org. Chem.* **1984**, *49*, 596. (i) Adam, W.; De Lucchi, O.; Pasquato, L.; Will, B. *Chem. Ber.* **1987**, *120*, 531.

(5) Quadricyclanes: (a) Smith, C. D. *J. Am. Chem. Soc.* **1966**, *88*, 4273. (b) Martin, H.-D.; Kagabu, S.; Schiwek, H.-J. *Tetrahedron Lett.* **1975**, 3311. (c) Burrage, M. E.; Cookson, R. C.; Gupte, S. S.; Stevens, I. D. R. *J. Chem. Soc. Perkin Trans. 2* **1975**, 1325. (d) Olsen, H. *J. Am. Chem. Soc.* **1982**, *104*, 6836. (e) De Lucchi, O.; Modena, G. *J. Chem. Soc., Chem. Commun.* **1982**, 914; *Phosphorus Sulfur* **1983**, *14*, 229. (f) De Lucchi, O.; Lucchini, V.; Pasquato, L.; Zamai, M.; Modena, G. *Gazz. Chim. Ital.* **1984**, *114*, 293. (g) Weissman, S. A.; Baxter, S. G. *Tetrahedron Lett.* **1987**, *28*, 603.

(6) (a) Fickes, G. N.; Metz, T. E. *J. Org. Chem.* **1978**, *43*, 4057. (b) Yamaguchi, R.; Ban, M.; Kawanisi, M.; Ōsawa, E.; Jaime, C.; Buda, A. B.; Katsumata, S. *J. Am. Chem. Soc.* **1984**, *106*, 1512.

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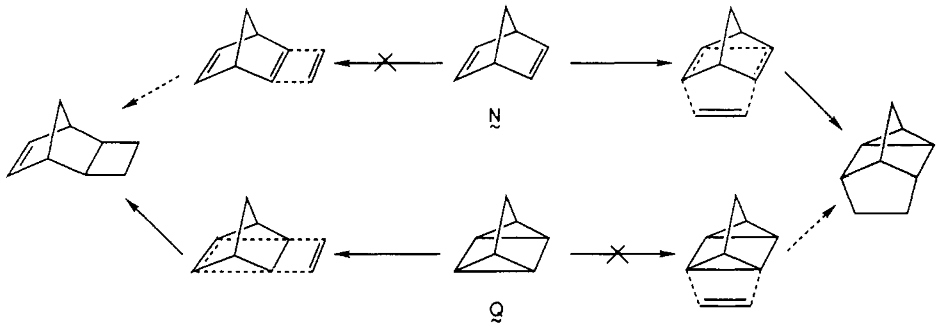
Scheme I



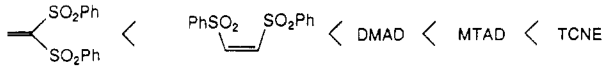
of the strong dependency on through-space interaction[7] and spatial proximity of its π bonds[8] (see Scheme I).

Particularly striking about the pair of allowed reactions is their stereospecificity and exceptional proclivity for Alder-like endo selectivity.[9]

For these reasons, these thermal reactions have been widely interpreted as proceeding via concerted six-electron transition states, provided that addend polarity does not induce zwitterion formation.[10]

In an attempt to garner additional insight into the transition states of these unusual reactions, we have undertaken the determination of secondary deuterium isotope effects. The expectation was that the intrinsic power of this mechanistic tool[11] would provide reliable insight into the symmetry characteristics (synchronous or asynchronous) of the activated complexes, and critical indication as to whether covalent bonding occurs concertedly. To this end, Q was metalated at C-1 with *n*-BuLi in TMEDA, and quenched with D_2O.[12] Subsequent isomerization of Q-*1-d* with iodine in toluene or $[Rh(CO)_2Cl]_2$ in CH_2Cl_2 afforded N-*2-d*.[13] The extent of d_1 substitution was 80% (by mass spectral analysis: 20% d_0, 0% d_2).

The five addends selected encompass a significant (qualitative) reactivity range that increases in the following order:



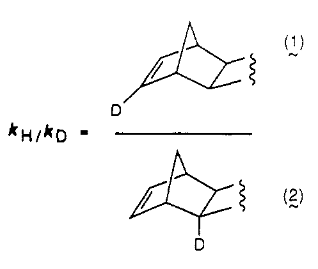
All of these reagents cycloadd in the predescribed manner to N and Q with the exception of DMAD, whose reaction with N was catalyzed by $RuH_2[PPh_3]_4$ to deliver the same [2 + 2] adduct as formed from Q.[14] Following chromatographic purification, each sample was subjected directly to ^2H NMR analysis.

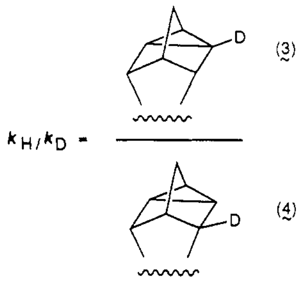
Table I. Deuterium Isotope Effects (k_H/k_D's) Determined for 1–4

addend	from Q-*1-d*	from N-*2-d*
DMAD[a]	0.884 ± 0.007	0.884 ± 0.012[e]
MTAD[b]	0.943 ± 0.018	0.945 ± 0.025
TCNE[c]	0.950 ± 0.022	0.941 ± 0.020
1,2-BPSE[d]	0.940 ± 0.012	0.941 ± 0.010

[a] Dimethyl acetylenedicarboxylate. [b] *N*-Methyltriazolinedione. [c] Tetracyanoethylene. [d] *cis*-1,2-Bis(phenylsulfonyl)ethylene. [e] Catalysis by $RuH_2(PPh_3)_4$ to deliver 1 and 2.

Determination of the deuterium isotope effects, defined as one of the product ratios shown, was accomplished by careful integration of the respective ^2H NMR signals recorded at 46 or 77 MHz. The adducts stemming from 1,1-bis(phenylsulfonyl)ethylene are nonsymmetric and are discussed separately below. Especially striking is the identify of the isotope effects manifested by either hydrocarbon toward the same reagent (Table I). Interestingly, the order of magnitude witnessed for DMAD (~ 12%) is approximately double that generated by the other three. The limitations set by addend symmetry restrict mechanistic analysis to the direction and magnitude of these k_H/k_D values. The observed partition factors are





consistent with those changes in hybridization that take effect while proceeding from the Q and N ground states to the respective transition states.[15,16] For Q, the options at carbon are to proceed from original $sp^{2.1}$ status in either the sp^2 (1) or $sp^{2.7}$ (2) direction. Where N is concerned, the π bonds are disrupted and the trigonal carbons are necessarily forced to adopt either cyclopropyl or tetrahedral geometry. The inverse nature of the isotope effect in both series is uniquely consistent with increasing p

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(9) (a) Tabushi, I.; Yamamura, K.; Yoshida, Z. *J. Am. Chem. Soc.* **1972**, *94*, 787. (b) Kobuke, Y.; Sugimoto, T.; Furukawa, J.; Fueno, T. *Ibid.* **1972**, *94*, 3633. (c) Tabushi, I.; Yamamura, K.; Yoshida, Z.; Togashi, A. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 2922. (d) Consult ref 4h for a sterically driven exception.

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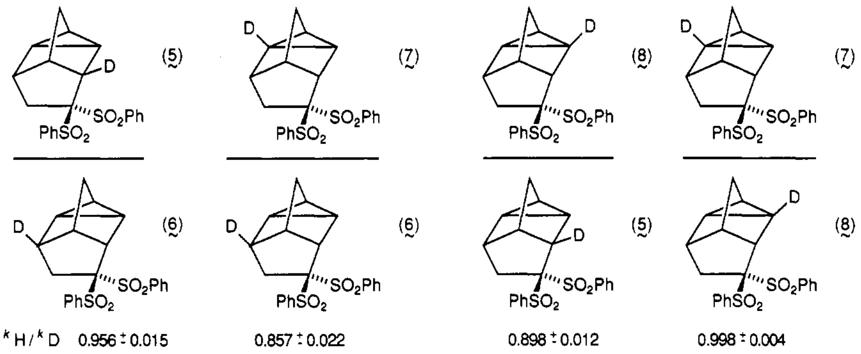

character at the sight of bond formation. The magnitude of the k_H/k_D values reflects the adoption of early transition states where substantive hybridization changes have not yet materialized. For the reaction of DMAD with Q-*1-d*, further progress along the reaction profile is manifested. The kinetic isotope effect for the DMAD/N-*2-d* cycloaddition must be interpreted with greater caution. Since the process is catalyzed, and passaged through a metallacycle has been suggested, the identity of the k_H/k_D's for the matched reactions is perhaps fortuitous. The possibility does exist, of course, that the degree of bond formation for both processes is similar in the respective transition states.

More mechanistically informative yet is the reaction between N and 1,1-bis(phenylsulfonyl)ethylene where four isotope effects are now made available. The **5**/**6** ratio agrees in direction with preferred bond formation to the more electropositive carbon of the addend.[17] The isotopic fractionation seen here indicates that while the cycloaddition is not synchronous, it is concerted. Product distributions **7**/**6** and **8**/**5** reveal a sizeable preference for deuterium incorporation on the proximal five- rather than the distal three-membered ring. This is because the hybridization changes required for cyclopropane construction are much less than those associated with the incipient cyclopentyl centers.[18] In fact, no preference is seen for placement of D at either of the possible $sp^{2.1}$ sites (**7**/**8** is essentially unity).[19]

The deuterium isotope effects realized from both symmetrical and unsymmetrical addends are consistent with the operation of nonsynchronous, concerted bonding schemes within relatively early transition states. Thus, the $[2_\pi + 2_\pi + 2_\pi]$ reactions of N and $[2_\sigma + 2_\sigma + 2_\pi]$ cycloadditions to Q share similar mechanistic characteristics; moreover, their features compare closely to those observed for the Diels–Alder reaction.[20] Therefore, in the absence of any piece of experimental evidence adduceable as support for a noncerted mechanism, the two processes studied here should be viewed as proceeding in one step, unless exceptionally strong polarization within the addend intervenes.[10]

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[17] This phenomenon is extensively precedented. For examples, consult: (a) Brown, P.; Cookson, R. C. *Tetrahedron* **1965**, *21*, 1993. (b) Holder, R. W.; Graf, N. A.; Duesler, E.; Moss, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 2929.

[18] Wolfsberg has suggested that the α-D effect is perhaps more accurately correlated with the changes in the H–C–X bending frequencies, which are very sensitive to the extent of C–X bond making or breaking.[11] We do not exclude this point of emphasis in our claims.

[19] The isotope effects for the addition of 1,1-bis(phenylsulfonyl)ethylene to Q-*1-d* were indeterminable due to an inseparable low-level impurity that exhibited ^{2}H-NMR absorptions that coincidentally overlapped with certain of those arising from the cycloadduct.

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Regioselective Azide Opening of 2,3-Epoxy Alcohols by $[Ti(O\text{-}i\text{-}Pr)_2(N_3)_2]$: Synthesis of α-Amino Acids

Summary: Treatment of 2,3-epoxy alcohols with $[Ti(O\text{-}i\text{-}Pr)_2(N_3)_2]$ affords the corresponding 3-azido 1,2-diols, which are readily transformed in two steps to the α-amino acids.

Sir: We have recently reported a mild procedure for the regioselective nucleophilic ring opening of 2,3-epoxy alcohols mediated by $Ti(O\text{-}i\text{-}Pr)_4$.[1] Enhanced rate and C-3 selectivity were observed in the ring opening of *trans*-epoxy alcohol **1** in the presence of the metal alkoxide (Scheme I). In the course of that study, we found that $[Ti(O\text{-}i\text{-}Pr)_2(N_3)_2]$ is a safe,[2] mild reagent for azide ring opening of 2,3-epoxy alcohols (Scheme I).[3,4] This reagent had been previously reported to catalyze the opening of isolated epoxides by Me_3SiN_3.[5]

The $[Ti(O\text{-}i\text{-}Pr)_2(N_3)_2]$ reagent was routinely prepared on a multigram scale according to the procedure published by Choukroun and Gervais.[6] In a typical experiment, a solution of the epoxy alcohol (1.0 mmol) in 5 mL of dry benzene was added to a suspension of $[Ti(O\text{-}i\text{-}Pr)_2(N_3)_2]$[7,8]

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[1] Caron, M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1557.

[2] $[Ti(O\text{-}i\text{-}Pr)_2(N_3)_2]$ was tested for shock sensitivity by striking a small amount with a hammer; no evidence of decomposition was found. Thermal stability analysis was performed by accelerated rate calorimetry. This material shows a relatively vigorous exotherm starting at 126 °C, which appears to become a detonation at 160 °C. Extrapolation indicates that the same behavior should be expected after 48 h at 97 °C, 30 min at 123 °C, and 30 s at 144 °C (Dr. P. Conrad, Eli Lilly and Co., private communication). It should be noted however, that $[Ti(O\text{-}i\text{-}Pr)_2(N_3)_2]$ has been refluxed overnight in xylenes (137–144 °C) without incident.

[3] Another excellent metal-mediated opening of 2,3-epoxy alcohols was recently reported, see: Maruoka, K.; Sano, H.; Yamamoto, H. *Chem. Lett.* **1985**, 599.

[4] Recently, a C-3 selective azide reagent consisting of NaN_3 supported on a calcium zeolite was reported: Onaka, M.; Sugita, K.; Izumi, Y. *Chem. Lett.* **1986**, 1327.

[5] (a) Blandy, C.; Choukroun, R.; Gervais, D. *Tetrahedron Lett.* **1983**, *24*, 4189. (b) Sinou, D.; Emziane, M. *Tetrahedron Lett.* **1986**, *27*, 4423.

[6] Choukroun, R.; Gervais, D. *J. Chem. Soc., Dalton Trans.* **1980**, 1800.

[7] We usually handle $[Ti(O\text{-}i\text{-}Pr)_2(N_3)_2]$ under an inert atmosphere (glovebag), although no adverse effects on the yield or selectivity were seen on the few occasions when the reagent was handled quickly in air.

0022-3263/88/1953-5185$01.50/0