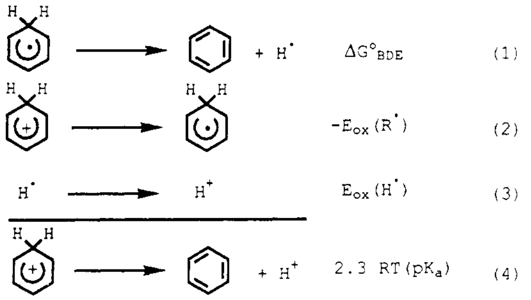
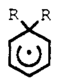


the pK_a's of three arenium ions in acetonitrile. The data allow us to assess the relevance of the thermodynamic data measured in strongly acidic media to reactions in organic solvents.

Using a technique that is described elsewhere,[9] we have determined half-wave potentials for the electrochemical oxidation and reduction of three dihydroarenyl radicals (**1**–**3a**) as well as those for the respective *gem*-dimethyl-substituted derivatives (**1**–**3b**) (Table I).[10] Combining these data with values for eqs 1[11] and 3[5] gives an estimate of the acidities (eq 4) of the arenium ions in acetonitrile.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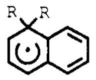
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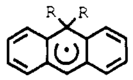
3

(a) R = H
(b) R = Me

A relatively large cathodic shift was observed in the oxidation potentials of the radicals **1a** (340 mV) and **2a** (270 mV) as compared to the respective *gem*-dimethylated derivatives (**1b** and **2b**). There was essentially no effect on the oxidation of **3a** compared to **3b** nor on the reductions of **1**–**3a** versus the respective *gem*-dimethyl analogues. The cathodic shifts on the oxidations of **1** and **2** (undoubtedly a kinetic effect associated with the rapid loss of a proton from the carbocation generated at the electrode) preclude the use of these data for eq 2 since they will not have thermodynamic significance (i.e. $E_{1/2} \neq E^\circ$).

Table II. Acidities of Carbocations at 300 K[a]

carbocation	ΔG°_4 (kcal mol^{-1})	pK_a(MeCN)[b]	pK_a(HF)[c]
1a$^+$	-33.0	-24.0	-9.3
2a$^+$	-27	-19.7[d]	-4.2
3a$^+$	-12.6	-9.1	3.2

[a] Calculated from eqs 1–4. [b] pK_a = $\Delta G^\circ_4/2.303RT$; the uncertainty in these values is ±2. [c] Measured in liquid HF, corrected for symmetry, ref 2a,b. [d] The uncertainty in this value is ±3.

The ^{13}C NMR spectra of **1**–**3a**$^+$ at low temperature in SO_2ClF[4a] suggest that benzannelation of **1a**$^+$ does not significantly increase the delocalization of the charge (in fact, it tends to localize the positive charge). The similarity of the oxidation potentials of **1**–**3b** is consistent with this conclusion and we have, therefore, used these potentials in the thermochemical calculations.

The pK_a's derived using eqs 1–4 are given in Table II. The loss of a proton from **1a**$^+$ or **2a**$^+$ is much more exoergonic than proton loss from **3a**$^+$, a result that is consistent with the magnitude of the observed cathodic shifts. Our ΔpK_a data also agree surprisingly well with the ΔpK_a's measured in liquid HF[3a,b] (Table II), suggesting that the relative thermodynamic data obtained in the strongly acidic media correctly describe thermodynamic differences in organic solvents.

The absence of a solvent effect on the relative pK_a's is remarkable since it implies that the there is a constant difference between the Gibbs solvation energies of the ions in the two media. A similar effect has been observed for the formation of cumyl and diarylmethyl carbocations in a number of solvents.[13,14] The small effects may simply be related to the relatively small Gibbs solvation energy of the delocalized ions (ca. -40 kcal mol^{-1})[9] compared to the proton (-258 kcal mol^{-1}).[5] In the present case, the change in solvation properties of the proton may account for much of the constant difference between the two sets of data.

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[7] Nicholas, A. M. de P.; Arnold, D. R. *Can. J. Chem.* **1982**, *60*, 2165.

[8] Parker, V. D.; Tilset, M. *J. Am. Chem. Soc.* **1988**, *110*, 1649.

[9] Basically, this technique uses modulated photolysis for the generation of radicals with phase-sensitive electrochemical detection. Wayner, D. D. M.; McPhee, D. J.; Griller, D. *J. Am. Chem. Soc.* **1988**, *110*, 132.

[10] Radicals were generated by hydrogen atom abstraction from the appropriate dihydroaromatic compound using *tert*-butoxyl radical. 1,4-Cyclohexadiene and 9,10-dihydronaphthalene were commercially available. All other compounds were prepared by literature procedures. Radical **3b** was generated by hydrogen atom abstraction with *tert*-butoxyl radical from 1,1-dimethyl-1,2-dihdyronaphthalene. In this case two anodic waves were observed, at $E_{1/2}$ = 0.3 V and at $E_{1/2}$ = 0.8 V. We have assumed that these waves correspond to the oxidation of the abstraction product and addition product, respectively.

[11] Gibbs bond energies for **1**–**3a** are 17.1 ± 2, 23.0 ± 3, and 35.2 ± 2 kcal mol^{-1}, respectively. These values were derived from literature data[5,12] and by assuming that the entropy of the hydrocarbon and radical cancel ($T\Delta S$ = 8 kcal mol^{-1}). The value for **2a** was based on an estimate of ΔH°_f (**2a**) using the MMX force field. This approach gave Gibbs bond energy values for **1a** and **3a** that were within 1 kcal mol^{-1} of the experimental values.

[12] (a) Lias, S. G.; Bartmess, J. E.; Leibman, J. G.; Holmes, J. L.; Levin, R. D.; Mallard, W. G. *J. Phys. Chem. Ref. Data* **1988**, *17*, supplement 1. (b) Burkey, T. J.; Majewski, M.; Griller, D. *J. Am. Chem. Soc.* **1986**, *108*, 2218.

[13] Sim, B. A.; Milne, P. H.; Griller, D.; Wayner, D. D. M. *J. Am. Chem. Soc.* In press.

[14] Wolf, J. F.; Harch, P. G.; Taft, R. W. *J. Am. Chem. Soc.* **1975**, *97*, 2904.

Synthesis of Dihydro-1*H*-indenes via a Formal 3 + 2 Cycloaddition of *p*-Quinone Methides and Styrenes

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Received January 30, 1990

Summary: The synthesis of dihydro-1*H*-indenes via the formal 3 + 2 cycloaddition of an electron-rich alkene and a *p*-quinone methide is reported.

During the course of studies on the chemistry of *p*-quinone methides we have discovered a facile synthesis of dihydro-1*H*-indenes via a formal 3 + 2 cycloaddition.[1]

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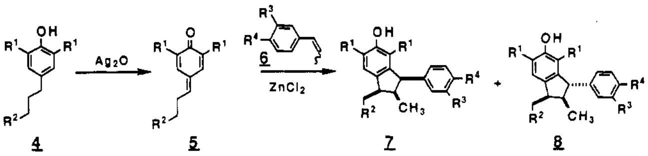
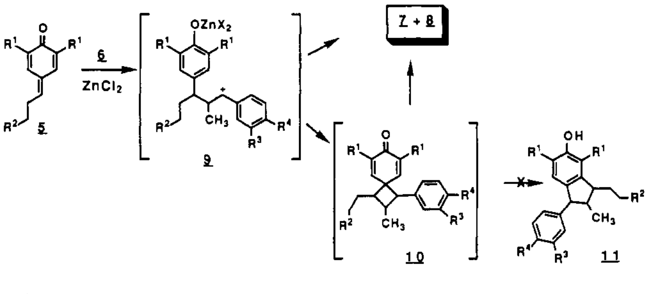
Table I. $ZnCl_2$-Mediated Reaction of Styrenes and *p*-Quinone Methides[6]



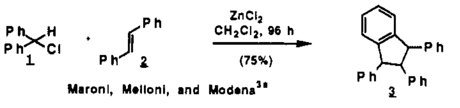
entry	phenol	R^1	R^2	quinone method	styrene $(Z/E)^a$	R^3	R^4	yield (%)	products (ratio)
1	**4a**	OCH_3	H	**5a**	**6a** (1>:99)	H	H	67	**7e**/**8e** (1:17)^b
2	**4a**	OCH_3	H	**5a**	**6b** (13:1)	H	OH	96	**7f**/**8f** (1:1)^d
3	**4a**	OCH_3	H	**5a**	**6c** (11:1)	OCH_3	OH	51	**7g**/**8g** (1:1)^d
4	**4b**	CH_3	Ph	**5b**	**6b** (13:1)	H	OH	71	**7h**/**8h** (2.2:1)^c
5	**4b**	CH_3	Ph	**5b**	**6c** (11:1)	OCH_3	OH	54	**7i**/**8i** (3:1)^d
6	**4a**	OCH_3	H	**5a**	**6d** (10:1)	H	OCH_3	79	**7j**/**8j** (1:1)^b
7	**4a**	OCH_3	H	**5a**	**6d** (1:99)	H	OCH_3	81	**7j**/**8j** (1:43)^{b,c}

^{a} Ratio determined by capillary GC. ^{b} Ratio determined by ^{1}H NMR. ^{c} Ratio determined by HPLC. ^{d} Inseparable mixture.

Scheme I. Proposed Mechanisms for 3 + 2 Cycloaddition



This process is mechanistically related to the acid-mediated dimerization of styrenes, a well-documented reaction, that normally affords dihydro-1*H*-indenes in moderate to low yields.[2] Marcuzzi, Melloni, and Modena have reported the reaction of phenyl-substituted alkynes and alkenes with diphenylmethyl cations to afford dihydro-1*H*-indenes.[3] For example, treatment of chloride 1 with styrene 2 in the presence of zinc(II) chloride afforded adduct 3 in good yield (eq 1).[3a]



(1)

We report here the stereoselective synthesis of dihydro-1*H*-indenes in a single step from a *p*-quinone methide and an electron-rich alkene in the presence of a Lewis acid. Table I shows several examples of this reaction using styrenes as the activated alkene.[4] The quinone methides were prepared by Ag_2O oxidation[5] of the corresponding phenols.[6]

The success of this formal 3 + 2 cycloaddition, which is believed to be a stepwise reaction, relies on the selective activation of a quinone methide in the presence of a styrene. This is easily achieved by taking advantage of the facile complexation of a Lewis acid with the basic carbonyl oxygen of the quinone methide.[7] Attack on the quinone methide–Lewis acid complex by the styrene is believed to afford benzylic cation **9** (Scheme I). Cation **9** can then be captured by the newly formed aromatic ring in two different ways: electrophilic aromatic substitution meta to the phenol to directly afford the observed products or, alternatively, **9** might be attacked by the aryl ring in the ipso position to afford cyclohexadienone **10**, which could then undergo bond migration to afford either diastereomers **7** and **8** and/or regioisomer **11**. Since the migratory aptitude of a benzylic carbon can be similar to that of a secondary alkyl carbon,[8] all three products might be observed if **10** were an intermediate. The formation of **10** is not likely due to the known difficulty for the formation of spiro[3.5]nonadienones by this type of reaction,[9] but it cannot be ruled out as an intermediate. The regio- and stereochemical assignments for the adducts follow directly from the ^{1}H NMR coupling constants and difference NOE experiments.[10,11]

Excellent stereocontrol at two of the three stereogenic centers is observed in these examples. Thus, only two of the four possible racemic diastereomers are formed in the reaction. Little or no stereochemical control at the third, bis-benzylic stereocenter is seen in the case of (*Z*)-styrenes (*Z*)-**6b** and (*Z*)-**6c**; however, (*E*)-styrenes (*E*)-**6a** and (*E*)-**6d** afford the trans-cis diastereomer **8**, where the alkene geometry is retained with ≥17:1 selectivity. In entry 1 (Table I), the assignment of the minor component as **7e** is based on the similar TLC and ^{1}H NMR characteristics of the compound.[12] In the case of entry 7 (Table I) the minor

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[1] Arnaiz, D. O. Unpublished results from this laboratory. For previous work from our laboratory on the chemistry of quinone methides, see: (a) Angle, S. R.; Turnbull, K. D. *J. Am. Chem. Soc.* **1989**, *111*, 1136. (b) Angle, S. R.; Louie, M. S.; Mattson, H. L.; Yang, W. *Tetrahedron Lett.* **1989**, *30*, 1193.

[2] For leading references, see: (a) MacMillan, J.; Martin, I. L.; Morris, D. J. *Tetrahedron* **1969**, *25*, 905. (b) Higashimura, T.; Hiza, M. *J. Polym. Sci. Polym. Chem. Ed.* **1981**, *19*, 1957.

[3] (a) Marcuzzi, F.; Melloni, G.; Modena, G. *J. Org. Chem.* **1979**, *44*, 3022. (b) Marcuzzi, F.; Melloni, G. *J. Chem. Res.* (*S*) **1979**, 184. (c) Marcuzzi, F.; Melloni, G. *Tetrahedron Lett.* **1975**, 2771, 2869. For related work, see: (d) Mayr, H.; Bäuml, E. *Tetrahedron Lett.* **1984**, *25*, 1984. (e) Mayr, H.; Pock, R. *Chem. Ber.* **1986**, *119*, 2473.

[4] In cases where an inseparable mixture of 7 and 8 was obtained the assignment of ^{1}H NMR spectra and coupling constants was made on chromatography fractions enriched in one of the diastereomers in conjunction with ^{1}H NMR decoupling experiments.

[5] Dyall, L. K.; Winstein, S. *J. Am. Chem. Soc.* **1972**, *94*, 2196. See also ref 1a.

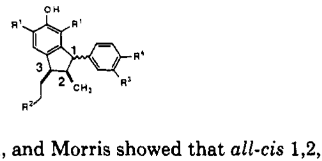
[6] All new compounds were characterized by ^{1}H NMR, ^{13}C NMR, IR, MS, and HRMS and/or elemental analysis data except for **5a**, which was unstable to handling and characterized only by ^{1}H NMR (see supplementary material for spectral data).

[7] Cf.: Wagner, H.-U.; Gompper, R. "Quinone Methides" in *The Chemistry of the Quinonoid Compounds*; Patai, S., Ed.; John Wiley and Sons: New York, 1974; pp 1145–1178.

[8] Hedeya, A. E.; Winstein, S. *J. Am. Chem. Soc.* **1967**, *89*, 1661.

[9] (a) Murphy, W. S.; Wattanasin, S. *Chem. Soc. Rev.* **1983**, 213. (b) le Noble, W. J.; Gabrielsen, B. *Tetrahedron Lett.* **1970**, 45. (c) Dorling, S.; Harley-Mason, J. *Chem. Ind.* **1959**, 1551.

[10] NOE experiments for dihydro-1*H*-indene **8e** [^{1}H NMR (300 MHz, $CDCl_3$)]: Irradiation of the aryl methine resonance at δ 6.58 caused a 3.8% enhancement for the adjacent methoxy resonance at δ 3.45, a 15% enhancement for the H(3) resonance at δ 3.00, and a 26% enhancement for the resonance corresponding to the exocyclic methylene attached to C(3) at δ 1.59. Irradiation of the exocyclic methylene resonance at δ 1.59 caused a 14% enhancement for the methine H(1) resonance at δ 4.00, a 6.5% enhancement for the aryl methine resonance at δ 6.58, and a positive enhancement for both aliphatic methyl groups at δ 1.00 and 0.95. No enhancement to the H(2) methine hydrogen resonance at δ 2.46 was observed. NOE experiments for **7j** [^{1}H NMR (300 MHz, C_6D_6)]: Irradiation of the aryl methine signal at δ 6.36 caused 44.8% enhancement of the methoxy resonance at δ 3.26, a 39.4% enhancement of the H(3) methine signal at δ 2.55 and a 25.2% enhancement of the methylene signal at δ 1.79–1.58. Irradiation of H(1) methine signal at δ 3.78 caused a 14.3% enhancement of the methoxy signal at δ 3.35, a 35.4% enhancement of the H(3) methine signal at δ 2.55, and a 2.8% enhancement of the methylene signal at δ 1.79–1.58.

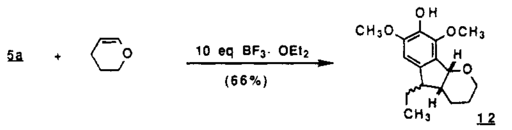


[11] MacMillan, Martin, and Morris showed that *all-cis* 1,2,3-trisubstituted dihydro-1*H*-indenes show characteristic values for *J*[H(1)–H(2)] and *J*[H(2)–H(3)] of approximately 7.0 Hz for each pair.[2a] Compounds 7 show nearly identical values for these same coupling constants and have been assigned as having this same *all-cis* orientation.

diastereomer was identical with **7j** produced from the reaction of quinone methide **5a** with the (*Z*)-**6d** in entry 6.[6] The origin of the stereochemical control is currently under investigation and will be discussed in a full account of this work.

It is worth noting that in entries 3 and 5 (Table I) styrene **6c**, a bidentate Lewis base (*o*-methoxyphenol), afforded a lower yield of adducts than styrene **6b** (entries 2 and 4), which is a monodentate Lewis base (phenol). The low yield may be due to competitive styrene polymerization initiated by complexation of the *o*-methoxyphenol of **6c** with the Lewis acid.[13]

In theory, this reaction should not be limited to styrenes, any alkene with a substituent capable of stabilizing a positive charge might participate in the cycloaddition. To test this idea, a solution of dihydropyran and quinone methide **5a** was treated with $BF_3 \cdot OEt_2$ to afford a 66% yield of hexahydroindeno[1,2-*b*]pyran **12** as a 1:1 mixture of diastereomers (eq 2). The diastereomers were separated by HPLC and the stereo- and regiochemical assignments were confirmed by NOE experiments.



(2)

We anticipate this process to be a general reaction and are currently exploring its scope and utility in the synthesis of natural products.

Acknowledgment. This research was supported by a grant from the National Institutes of Health (GM 39354). We thank Mr. Ron New and Dr. Richard Kondrat for mass spectra and Professor David Hart of The Ohio State University for a helpful discussion.

Supplementary Material Available: General procedures for quinone methide formation and the formal cycloaddition, spectral data used for the characterization of **5b**, **7**, and **8**, and a summary of key NOE experiments for **7j**, **8j**, and **12** (8 pages). Ordering information is given on any current masthead page.

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[12] Diastereomer **7e** was not available since the reaction of (*Z*)-**6a** with quinone methide **5a** afforded adduct **7e** as an inseparable mixture of several compounds in 13% yield.

[13] To support this notion considerable low R_f material was seen in the TLC of the crude reaction mixtures and intractable material, insoluble in CH_2Cl_2, was obtained. In addition, simple ethenylstyrenes failed to afford adducts; only styrene polymerization was observed in these cases.

Directed Nitrile Oxide Cycloaddition Reactions. The Use of Hydrogen Bonding To Direct Regio- and Stereochemistry in Nitrile Oxide Cycloadditions with Cyclopentenylamides

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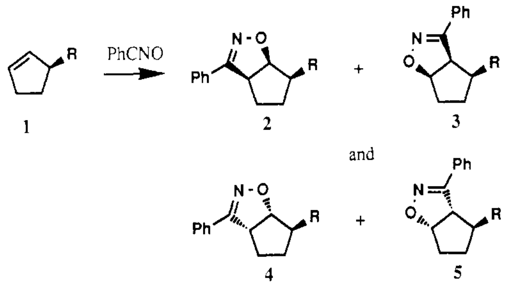
Received March 23, 1990

Summary: 2° amides derived from cyclopentenylamine direct the regio- and stereochemistry of cycloaddition reactions with benzonitrile oxide and 2,2-dimethylpropane nitrile oxide by hydrogen bonding.

Lewis acids can effect the rates of organic reactions—and hence dictate chemo-, regio-, and stereoselectivity—either by altering the electronic structure of one of the reactants (for example, the Diels–Alder reaction[2]) or by serving as templates to bring the reactants together (for example, the directed epoxidation of allylic alcohols[3]). Although analogous in many respects to Diels–Alder reactions, many 1,3-dipolar cycloaddition reactions do not benefit from the addition of Lewis acids, perhaps because 1,3-dipoles are often better Lewis bases than the acceptors with which they react.[4] However, the Lewis basicity of a 1,3-dipole might be used to advantage in a reaction in which a Lewis acid functions as a template to bring a dipole and a dipolarophile together in a proper orientation for cycloaddition (Figure 1).[5] A proton is the simplest Lewis acid, and indeed there is good evidence that an allylic hydroxy

Table I. Cycloaddition of PhCNO with 3-Substituted Cyclopentenes



substr	R	solvent	ratio 2:3:4:5 2	3	4	5	ref
1a	Me	Et_2O	3	1	63	33	6a
1b	NMe_2	Et_2O	7	0	23	70	6a
1c	OMe	Et_2O	3	4	22	71	6a
1d	OAc	Et_2O	5	3	15	77	6a
1e	OH	Et_2O	30	5	12	53	6a
1e	OH	PhH	50	nd[a]	17	33	
1f	NHCOPh	PhH	90	nd	nd	10	

[a] nd = not determined. Small amounts (<5%) could have gone undetected.

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[1] Dreyfus Teacher Scholar, 1986–91; National Institutes of Health Career Development Awardee, 1987–92.

[2] Leading references: (a) Paquette, L. A. In *Asymmetric Synthesis*, Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, pp 456–478. (b) Helmchen, G.; Karge, R.; Weetman, J. In *Modern Synthetic Methods*; Scheffold, R., Ed.; Springer-Verlag: Berlin, 1986; Vol. 4, pp 261–306. (c) Loncharich, R. J.; Schwartz, T. R.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 14.

[3] Henbest epoxidation: Berti, G. *Top Stereochem.* **1973**, *7*, 93. Sharpless asymmetric epoxidation: Sharpless, K. B. *Janssen Chem. Acta* **1988**, *6*, 3.

[4] (a) For example, many BF_3–nitrone complexes are stable solids: LeBel, N. A.; Balasubramanian, N. *Tetrahedron Lett.* **1985**, *26*, 4331. (b) For effects of Lewis acids on nitrile oxide cycloadditions, see: Morrocchi, S.; Ricca, A.; Velo, L. *Tetrahedron Lett.* **1967**, 331. Grundmann, C.; Richter, R. *Tetrahedron Lett.* **1968**, 963. Plumet, J.; Escobar, G.; Manzano, C.; Arjona, O.; Carrupt, P.-A.; Vogel, P. *Heterocycles* **1986**, *24*, 1535. Curran, D. P.; Kim, B. H.; Piyasena, H. P.; Loncharich, R. J.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 2137.

[5] For a recent example where $Ti(O\text{-}i\text{-}Pr)_3Cl$ is proposed to alter the regioselectivity of an azomethine imine cycloaddition by a template effect, see: Barr, D. A.; Grigg, R.; Sridharan, V. *Tetrahedron Lett.* **1989**, *30*, 4727.

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