Communication

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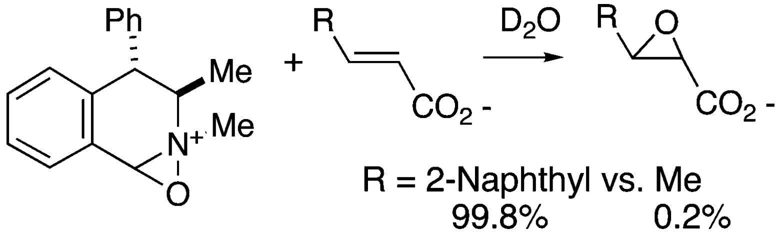

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Oxaziridinium Salts as Hydrophobic Epoxidation Reagents: Remarkable Hydrophobically-Directed Selectivity in Olefin Epoxidation

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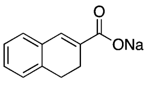
Recently we reported that use of the hydrophobic effect in the reductions of ketones permits a dramatic increase in selectivity for ketones located in a hydrophobic environment when a hydrophobic borohydride is employed and the reaction medium is changed from organic to aqueous.[1] The face−face packing of the hydrophobic units on the borohydride and the ketone in the transition state of reduction minimizes the water-accessible hydrocarbon surface area, leading to the observed relative rate acceleration.[1b,2]

We hoped that hydrophobic oxidizing reagents could also be developed. Herein we report the ability of hydrophobic oxaziridinium salts to effect relative rate increases in the selective epoxidation of hydrophobic olefins that are an order of magnitude greater than the largest increases observed in hydride reductions.[1] Using substoichiometric hydrophobic iminium salts and oxone as a co-oxidant, we further show that these selective epoxidations can be made catalytic. In addition, we demonstrate the importance of accurate transition-state models in the development of hydrophobic reagents.

We considered perbenzoic acids, aryl ketone-derived dioxiranes, and aryl oxaziridinium salts. Each class has a hydrophobic aryl group theoretically capable of packing with a hydrophobic unit on a substrate. However, computer models for perbenzoic acid oxidation predict a spiro, highly synchronous transition state where the hydrophobic phenyl ring assumes a position from which it is incapable of packing on the hydrophobic unit of the olefin (Figure 1).[3] By contrast, the calculations predict a synchronous transition state for dioxirane or oxaziridinium cation epoxidation in which a hydrophobic group would be located in a position conducive to packing with the hydrophobic unit of the olefin during epoxidation (Figure 1).[3,4]

On the basis of the model of the transition state for perbenzoic acid epoxidation shown in Figure 1, no change in selectivity for the epoxidation of the hydrophobic olefin should be observed when the hydrophobicity of the peracid is varied. To test this, peracids magnesium monoperoxyphthalate (MMPP), sodium perfluoromonoperoxyphthalate (PFPP), and peracetic acid (PAA) were employed in competition reactions of derivatives of cinnamic acid with crotonic acid in $NaHCO_3/D_2O$. MMPP contains a hydrophobic phenyl ring, PFPP contains a significantly more hydrophobic[5] perfluorinated phenyl ring, and PAA contains no hydrophobic substituent. The results in Table 1 show that there is *no* preference for the hydrophobic olefin to form product **1** when MMPP or PFPP are used relative to simple peracetic acid, PAA.



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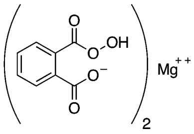
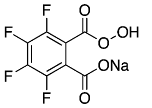
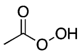


MMPP



PFPP



PAA

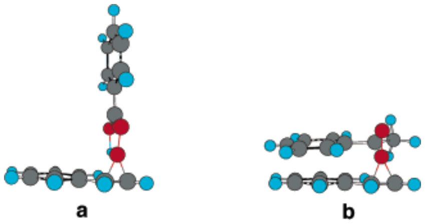
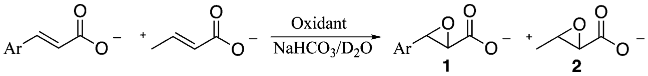


Figure 1. Transition-state models of the epoxidation of styrene with (a) perbenzoic acid and (b) the dioxirane derived from acetophenone.

Table 1. Ratio of Epoxide Products (1:2) Formed in the Competition Reactions of Crotonic Acid and Derivatives of Cinnamic Acids with Peracids of Different Hydrophobicity ($\Delta\Delta G^{\ddagger}$ (kcal/mol) for Each Reaction Is in Parentheses)[a,b]

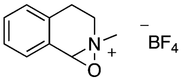


Ar	MMPP	PFPP	PAA
Ph	44:56 (0.16)	44:56 (0.16)	75:25 (−0.65)
p-CF_3Ph	16:84 (0.98)	18:82 (0.88)	35:65 (0.37)
2-naph	47:53 (0.07)	50:50 (0.00)	72:28 (−0.56)
3	93.3:6.7 (−1.56)	92.9:7.1 (−1.53)	93.2:6.8 (−1.55)

[a] Competition reactions were carried to ca. 5% epoxidation of the olefins at room temperature and analyzed directly by HNMR (substrate concentrations ranged from 5 to 300 mM; see Supporting Information for specific concentrations). [b] Integer ratios are within an error ±1%; other ratios are within an error of ±0.2% in at least duplicate runs.

When non-hydrophobic PAA is used, selectivity for all hydrophobic olefins except fused **3** actually increases, which is contrary to expectations if hydrophobic direction were involved. This increase in selectivity results from the low steric bulk of PAA. When MMPP and PFPP are employed, repulsion likely exists between the rotating hydrophobic unit of the olefin and the aryl ring of the peracid. This repulsion is removed when nonbulky PAA is used or when rotation of the hydrophobic unit of the olefin is prevented through a ring fusion as with **3**. Thus, in agreement with models, there is no facilitating hydrophobic interaction in the transition states of these peracid epoxidations.

The results were very different in epoxidations with isolable oxaziridinium reagents,[6] selected for evaluation as likely hydrophobically accelerated epoxidation reagents. Previously reported oxaziridiniums **6** and **7** were employed in these experiments. The rigid hydrophobic backbone structure and the orientation of the oxygen atom in a pseudoaxial position[6c] suggested that a significant



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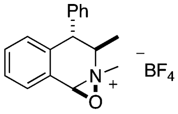

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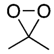
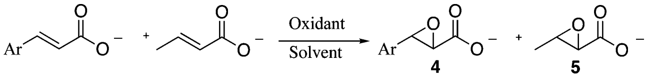


DMDO

10.1021/ja053660i CCC: $30.25 © 2005 American Chemical Society

Table 2. Ratio of Epoxide Products (4:5) Formed in the Competition Reactions of Crotonic Acid and Derivatives of Cinnamic Acids with Dioxirane and Oxaziridinium Epoxidizing Reagents under Different Conditions ($\Delta\Delta G^\ddagger$ (kcal/mol) for Each Reaction Is in Parentheses)[a,b]



Ar	solvent	DMDO	oxaz. **6**	oxaz. **7**
Ph	D$_2$O	61:39 (−0.27)	96.5:3.5 (−1.97)	98.1:1.9 (−2.34)
Ph	1:1 (v:v) *i*PrOD: D$_2$O	59:41 (−0.22)	88:12 (−1.18)	91.8:8.2 (−1.43)
p-CF$_3$Ph	D$_2$O	22:78 (0.75)	84:16 (−0.98)	92.7:7.3 (−1.51)
p-CF$_3$Ph	1:1(v:v) *i*PrOD: D$_2$O	22:78 (0.75)	54:46 (−0.10)	69:31 (−0.47)
2-naph	D$_2$O	68:32 (−0.45)	98.7:1.3 (−2.57)	99.8:0.2 (−3.68)
2-naph	1:1(v:v) *i*PrOD: D$_2$O	66:32 (−0.39)	95.9:4.1 (−1.87)	98.1:1.9 (−2.34)
3	D$_2$O	90.5:9.5 (−1.34)	99.7:0.3 (−3.44)	99.9+:0.1 (−4.10)
3	1:1 (v:v) *i*PrOD: D$_2$O	90:10 (−1.30)	98.9:1.1 (−2.67)	99.4:0.6 (−3.03)

[a] Competition reactions were carried to ca. 5% epoxidation of the olefins at room temperature in the solvent with NaHCO$_3$ and analyzed directly by HNMR (substrate concentrations ranged from 5 to 300 mM; see Supporting Information for specific concentrations). [b] Integer ratios are within an error ±1%; other ratios are within an error of ±0.2% in at least duplicate runs.

hydrophobic binding interaction was likely in the transition state of epoxidation. Because dioxirane epoxidation exhibits a nearly identical transition-state geometry to that for oxaziridinium epoxidation,[3,4] we considered dimethyl dioxirane (DMDO) a reasonable non-hydrophobic control for the hydrophobic oxaziridiniums.

The results of the competition reactions with oxaziridium salts **6** and **7** and DMDO (Table 2) show a very large increase in selectivity for the hydrophobic olefin when **6** or **7** is used in place of DMDO in an aqueous medium. This selectivity increases directly with the hydrophobicity of the olefin. In the competition reaction of a 2-naphthyl olefin and a methyl olefin, a change in $\Delta\Delta G^\ddagger$ of 3.23 kcal favoring epoxidation of the 2-naphthyl olefin was observed (but minimal chirality) when oxaziridinium **7** was employed in place of DMDO. This corresponds to a 240-fold relative rate increase for epoxidation of the 2-naphthyl olefin, the largest change in selectivity we have observed in a hydrophobically accelerated atom-transfer reaction.

When a 1:1 ratio of D$_2$O:*i*PrOD was used as the solvent for the competition reactions, little or no change is observed for reactions involving DMDO. By contrast, with hydrophobic oxaziridinium reagents, ca. 1 kcal of binding energy is consistently lost (Table 2) as a result of the alcohol-induced damping of the hydrophobic effect, and the rates of reactions are much slower. Even so, significant selectivity is still present, indicating that a completely aqueous solution is not required. Thus for water insoluble substrates our demonstrated selectivities in mixed solvents, reflecting more than just hydrophobic binding forces, could be useful.

Extensive oxidation of substrate carboxylate groups (but not un-ionized carboxylic groups) compete with olefin epoxidation in the mixed solvent, while very little is observed in D$_2$O.[7]

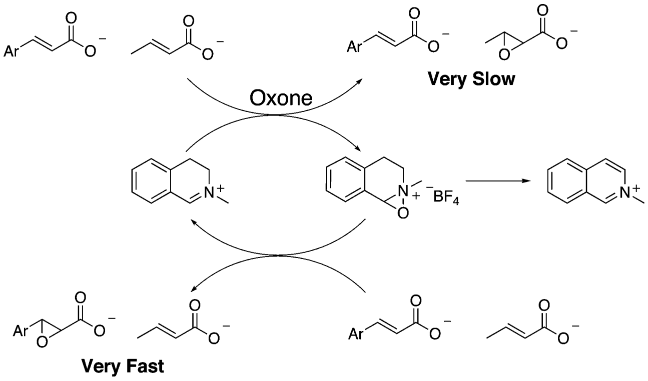


Figure 2. Catalytic cycle using hydrophobic iminium salts.

The oxaziridinium epoxidations have been made catalytic through the use of the associated iminium salts with oxone as a stoichiometric co-oxidant (Figure 2).[8] These iminium-catalyzed epoxidations successfully reproduce the selectivities observed in the noncatalytic epoxidations of Table 2. Five to ten turnovers of the iminium catalyst are consistently achieved in these reactions. The turnover number is dependent upon the pH at which the reactions are conducted, as decomposition of the oxaziridium to an isoquinolinium species occurs more rapidly in more alkaline conditions (see Supporting Information). While oxone can act as an epoxidizing agent when not in the presence of a catalyst, this background process is very slow compared to the rate of hydrophobic epoxidation.

We have shown previously that hydrophobically induced substrate selectivity in borohydride reductions can be translated into regioselective reactions in a diketone.[1] Thus, we expect that our selective oxygen-atom transfers will also be regioselective, and perhaps stereoselective, in polyenes.

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Supporting Information Available: NMR and mass spectra, procedures for the synthesis of previously unreported compounds, and procedures for competition experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Biscoe, M. R.; Breslow, R. *J. Am. Chem. Soc.* **2003**, *125*, 12718−12719. (b) Biscoe, M. R.; Uyeda, C.; Breslow, R. *Org. Lett.* **2004**, *6*, 4331−4334.
(2) (a) Breslow, R. *Acc. Chem. Res.* **1991**, *24*, 159−164. (b) Blokzijl, W,; Engberts, J. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1545−1579. (c) Otto, S.; Engberts, J. *Org. Biomol. Chem.* **2003**, 1, 2809−2820.
(3) Houk, K. N.; Liu, J.; DeMello, N. C.; Condroski, K. R. *J. Am. Chem. Soc.* **1997**, *119*, 10147−10152.
(4) Washington, I.; Houk, K. N. *J. Am. Chem. Soc.* **2000**, *122*, 2948−2949.
(5) Sheppard, W. A.; Sheetz, C. M. *Organic Fluorine Chemistry*; W. A. Benjamin, Inc.: New York, 1969.
(6) (a) Milliet, P.; Picot, A.; Lusinchi, X. *Tetrahedron Lett.* **1976**, *19*, 1573−1576. (b) Milliet, P.; Picot, A.; Lusinchi, X. *Tetrahedron* **1981**, *37*, 4201−4208. (c) Bohe, L.; Hanquet, G.; Lusinchi, M.; Lusinchi, X. *Tetrahedron Lett.* **1993**, *34*, 7271−7274.
(7) Hanquet, G.; Lusinchi, X.; Milliet, P. *Tetrahedron* **1993**, *49*, 423−438.
(8) (a) Aggarwal, V. K.; Wang, M. F. *Chem. Commun.* **1996**, 191−192. (b) Page, P. C. B.; Rassias, G. A.; Bethell, D.; Schilling, M. B. *J. Org. Chem.* **1998**, *63*, 2774−2777. (c) Minakata, S.; Takemiya, A.; Nakamura, K.; Ryu, I.; Komatsu, M. *Synlett* **2000**, *12*, 1810−1812.

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