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A SUPPORTED EPOXIDATION CATALYST FOR NUCLEOPHILIC OLEFINS

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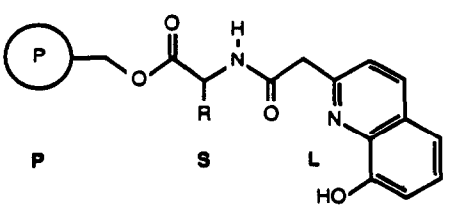
Summary: A polystyrene-supported peptide-linked epoxidation catalyst is described and its utility for the discovery of new epoxidants is discussed.

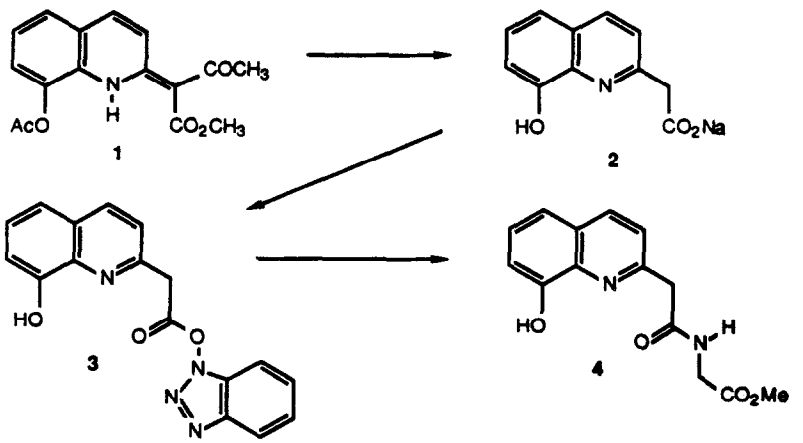
How do chemists develop new reagents when little is known of the actual transition state structures and energies which are involved? One answer is they develop a hypothetical, mechanistic model of the reaction to be used and then design specific reagents using the model as a guide. Another answer is that they prepare and test a large number of candidates. The former approach is the one most commonly described and is usually described as rational reagent design. The second approach is, presumably then, irrational or at least less rational. But is it so? The results to be expected from the 'rational' approach can be only as good as the guiding model is realistic. For many objectives, there would seem to be too little known for a strictly objective design approach to be used and, in those cases, the most rational approach is to couple mechanistic designs with an efficient synthesis of many candidates and a rapid screening protocol. We describe such an approach as semirational and outline in this Letter an application directed toward new methodology for asymmetric epoxidation.

The highly enantioselective epoxidation of allylic alcohols developed by Sharpless and coworkers several years ago is one of the most effective methods yet devised for the introduction of chirality into complex molecules.[1] To aid in the discovery of related enantioselective methods for isolated olefins, we have developed a supported epoxidation catalyst which allows for the efficient synthesis and screening of candidate reagents. The catalyst is shown below and consists of a polymer support (**P**) which is connected to a variable spacer arm (**S**, ultimately the source of chirality) and a ligand (**L**) for a transition metal epoxidant.[2] Ligand **L** was selected because it may be readily linked to a polymer-bound primary or secondary amine and since it anchors the spacers (**S**) to be tested for chiral induction near to the metal binding site. As we will show, **P** and **S** can be a polystyrene resin with bound peptide which is prepared directly by the Merrifield method. Such a catalyst readily allows for the investigation of many peptidic **S**'s either by conventional methodology or by newer methods based on simultaneous multiple peptide synthesis.[3]

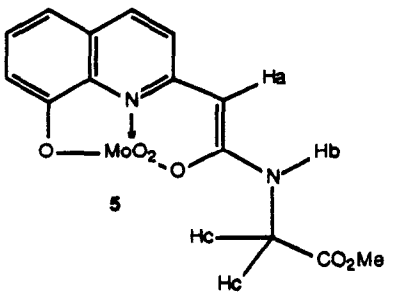


P **S** **L**

Synthesis of the ligand fragment (**L**) is summarized below. Thus 8-hydroxyquinoline N-oxide with methyl acetoacetate and acetic anhydride gave **1** in 66% yield by analogy with the results of Iwao and Kuraishi.[4] Deacylation (CH_3ONa, CH_3OH) and saponification (NaOH, CH_3OH-H_2O) gave the acid salt **2** in 92% yield. While the acid itself could not be handled without decarboxylation, the salt **2** could be stored without decomposition.



To establish that the 8-hydroxyquinoline acetic acid ligand could be used as part of an effective epoxidation catalyst, **2** was converted to the N-hydroxybenzotriazole (HOBT) activated ester **3** with 1,1'-bis(benzotriazolyl)oxalate in DMF according to the method of Ogura[5] and coupled with methyl glycine hydrochloride (Et_3N, DMF) to give the complete ligand **4** (85%). Next, treatment of **4** with $MoO_2(acac)_2$ in MeOH (6 hrs, 25° C) gave a stable, microcrystalline molybdenum complex (mp = 168 °C, decomp) in 91% yield. We assigned the structure of this material as **5** based on the following evidence. First, CI(methane) MS showed M+1 peaks at 397, 399, 400, 401, 402, 403, 404 and 405 m/e with no indication of dimeric species or other attached ligands. The IR (KBr) contained strong bands at 938 and 908 cm^{-1} which are characteristic of the asymmetric and symmetric stretches of a MoO_2 subunit.[6] Finally, the ^1H NMR shows an olefinic proton at 4.72 ppm (assigned as H_a) and an exchangeable proton on 8.58 ppm (H_b) which is coupled to a two proton doublet at 4.14 ppm (J=6 Hz, H_c). While one additional ligand to molybdenum would be expected, we have been unable to detect its presence. No peaks corresponding to acetylacetone or methanol could be seen in the d_6-acetone NMR spectrum of **5**.



Chemically, **5** does epoxidize isolated olefins at 2 mole% levels with tBuOOH in CH_2Cl_2 as will be summarized below.

While catalyst **5** carries out olefin epoxidations effectively, we were more interested in obtaining a polymer bound analog which could be prepared from peptides which were attached to the Merrifield resin upon which they were synthesized. With the HOBT ester **3** and a polystyrene-bound peptide amine, preparation of such a material was easy. Thus polystyrene-supported BOC glycine (1.0 mmol/g loading) was deprotected (a. TFA, CH_2Cl_2; b. iPr_2NEt, CH_2Cl_2) and then treated with freshly prepared **3** (DMF) and finally with $MoO_2(acac)_2$ (CH_2Cl_2, 24 hrs). After washing (CH_2Cl_2, 5 x 2 min), the polystyrene-supported glycine-linked complex (**6**) was ready for use as an epoxidation catalyst. Successful coupling of the ligand to the resin was demonstrated by its detachment from the solid support as the methyl ester (**4**) using MeOH/Et_3N.

Olefin Epoxidations with 2 Mole% Homogeneous (**5**) and Polystyrene-Supported (**6**) Molybdenum Catalysts.

Olefin	Catalyst	Temp °C	Time Hrs	Yield[a] %	Conversion[b] %	Stereoselect[c]
1-Nonene	**5**	80	12	-	80[f]	-
	6	80	72	76	80	-
Cyclooctene	**5**	25	24	-	92	-
	6	25	24	73	61	-
4-iPr-1-Me-cyclohexene	**5**	25	36	-	95	3:7 cis:trans[d]
	6	25	48	100	100	3:7 cis:trans
Tetramethyl ethylene	**5**	25	24	-	88	
	6	25	24	79	84	
2-Cyclohex-en-1-ol	**5**	25	6	-	89	25:1 cis:trans[e]
	6	25	12	60	83	22:1 cis:trans
E-3-heptene	**5**	80	6	-	98	E-epoxide only
	6	80	6	96	100	E-epoxide only
Z-3-heptene	**5**	80	12	-	89	Z-epoxide only
	6	80	12	73	87	Z-epoxide only

a. Yield by capillary VPC using an internal standard; b. Percentage of epoxide in the product by capillary VPC; c. Stereoselectivity by VPC with calibration by authentic materials; d. mCPBA gave 1:1 cis:trans and $MoO_2(acac)_2$/tBuOOH gave 2:1 cis:trans (cis = cis isopropyl, methyl);[7] e. $VO(acac)_2$/tBuOOH gave 50:1 and perbenzoic acid gave 12:1;[8] f. By NMR.

As summarized in the table above, both catalysts (**5** and **6**) give smooth epoxidization of a variety of olefin types at concentrations of 0.25-0.50 M in methylene chloride using 1.5 equivalents of t-butylhydroperoxide as the oxidant. Yields in the table were determined by VPC and in the case of the polymer-bound catalyst **6** were calibrated against an internal

standard. To test for decomposition of catalyst **6**, we reused one sample of catalyst (2 mole%) to successively epoxidize four batches of tetramethylethylene and observed no reduction in the yield of the product epoxide in the series of experiments. Finally, we confirmed that catalyst **6** utilized the hydroxyquinoline ligand for binding the epoxidant molybdenum by showing that polymer-bound glycine alone did not yield an active epoxidant upon treatment with $MoO_2(acac)_2$ and tBuOOH.

In conclusion, we have developed an effective epoxidation catalyst which is conveniently prepared from readily available polystyrene-supported peptidic amines. Such peptides may be prepared by conventional solid phase methodology and converted directly to active epoxidants without the necessity for their isolation or even their removal from the support upon which they are synthesized. We have further found that only 2 mg of the catalytic resin is necessary to epoxidize olefins like 1-methylcyclohexene and to analyze the enantiomeric purity of the product by chiral capillary VPC.[9] With the recent advent of methods for the simultaneous synthesis of many different peptides,[3] it is now possible to examine large numbers of different epoxidants in a short period of time. Thus the catalyst described provides the key element in a scheme by which we may rapidly prepare and screen many new catalytic epoxidants for asymmetric induction. Related semirational approaches to reagent discovery may be devised for a variety of chemical reactions and we believe that in many instances such methods provide the best way to find novel molecules having desirable properties.[10]

Notes and References.

1) T. Katsuki and K.B. Sharpless, *J. Am. Chem. Soc.*, 102, 5974 (1980).
2) For previous work on supported epoxidation catalysts see: G.L. Linden and M.F. Farona, *J. Catalysis*, 48, 284 (1977); S. Bhaduri, A. Ghosh and H. Khwaja, *J. Chem. Soc., Dalton.*, 447 (1981); S. Colonna, H. Molinari, S. Banfi, S. Julia, J. Masana and A. Alvarez, *Tetrahedron*, 39, 1635 (1983); N. Kobayashi, *British Polymer Journal*, 16, 205 (1984); T. Yokayama, M. Nishizawa, T. Kimura and T.M. Suzuki, *Bull. Chem. Soc. Japan*, 58, 3271 (1985); K. Zhang, G.S. Kumar and D.C. Neckers, *J. Polymer Sci.*, 23, 1213 (1985).
3) E.g. H.M. Geysen, R.H. Meloen and S.J. Barteling, *Proc. Natl. Acad. Sci. USA*, 81, 3998 (1984); R.A. Houghten, *Proc. Natl. Acad. Sci. USA.*, 82, 5131 (1985); R.A. Houghten, S.T. DeGraw, M.K. Bray, S.R. Hoffmann and N.D. Frizzell, *BioTechniques*, 4, 522 (1986).
4) M. Iwao and T. Kuraishi, *J. Heterocyclic Chem.*, 15, 1425 (1978).
5) K. Takeda, I. Sawada, A. Suzuki and H. Ogura, *Tetrahedron Lett.*, 24, 4451 (1983); K. Takeda, K. Tsuboyama, K. Yamaguchi and H. Ogura, *J. Org. Chem.*, 50, 273 (1985).
6) R.J. Butcher, H.P. Gunz, R.G.A.R. Maclagan, H.K.J. Powell, C.J. Wilkins and Y.S. Hian, *J. Chem. Soc., Dalton*, 1223 (1975).
7) Cf. V.P. Yur'ev, I.A. Gailyunas, L.V. Spirikhin and G.A. Tolstikov, *Zhurnal Obshchei Khimii*, 45, 2312 (1975).
8) K.B. Sharpless and R.C. Michaelson, *J. Am. Chem. Soc.*, 95, 6136 (1973).
9) V. Schurig, *Angew. Chem. Int. Ed. Engl.*, 23, 747 (1984).
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