Functionalized Iminium Salt Systems for Catalytic Asymmetric Epoxidation

Philip C. Bulman Page,* Gerasimos A. Rassias, David Barros, Adel Ardakani, Benjamin Buckley, Donald Bethell,† Timothy A. D. Smith, and Alexandra M. Z. Slawin‡

Department of Chemistry, Loughborough University, Loughborough, Leicestershire LE11 3TU, England, Robert Robinson Laboratories, Department of Chemistry, University of Liverpool, Oxford Street, Liverpool L69 3BX, England, and Department of Chemistry, University of St. Andrews, St. Andrews, Scotland

p.c.b.page@lboro.ac.uk

Received March 8, 2001

A range of dihydroisoquinolinium salts containing alcohol, ether, and acetal functionalities in the nitrogen substituent has been prepared and tested as asymmetric epoxidation catalysts, providing ee's of up to ca. 60%.

Introduction

Nonracemic epoxides are important and highly versatile building blocks in asymmetric synthesis,[1] and the epoxide functionality is itself a part of the structure of many natural products and biologically active compounds.[2] Despite the development over the past few years of several methods for asymmetric epoxidation, access to chiral epoxides with high ee remains an important objective, perhaps because no single method is appropriate for all epoxide structures. Approaches to chiral epoxides from carbonyl compounds are known,[3] but epoxidation of alkenes remains the usual route. Nonracemic chiral peracids are of limited value for asymmetric epoxidation,[4] and an asymmetric version of the related Payne procedure, driven by hydrogen peroxide, has provided high ee's only when using as mediator a nitrile derived from a chiral helicene.[5]

The greatest impact in the construction of nonracemic chiral epoxides has been made with the introduction of catalytic systems. The best-known catalytic process is that of Sharpless for the epoxidation of allylic alcohols, usually with greater than 90% ee.[6] Chiral complexes of transition metals with salen ligands[7] have been developed by Jacobsen,[8] Katsuki, and others as catalysts for asymmetric epoxidation, although again the reaction is not universally applicable; for example, trisubstituted and arylalkenes tend to give higher ee's than tetrasubstituted[9] and acyclic *E*-alkenes.[10,11] More seriously, the reaction is not stereospecific, particularly in the case of aryl alkene substrates, a result of bond rotation in a reaction intermediate. Addition of cinchona alkaloid-derived salts allows the generation of trans epoxides as the major products from *Z*-alkene substrates.[12]

Asymmetric epoxidation of α,β-unsaturated ketones can be achieved using the Julià−Colonna procedure, which employs alkaline hydrogen peroxide and a chiral polypeptide, typically polyleucine. The reaction is most successful for chalcone substrates.[13]

Chiral dioxiranes can be very effective reagents for asymmetric epoxidation.[14,15] Over the last 5 years, independent work by Yang, Armstrong, and Shi has identified enantiomerically pure chiral ketones whose derived di-

† University of Liverpool.
‡ University of St. Andrews.

(1) Sharpless, K. B. *Aldrichim. Acta* **1983**, *16*, 67. Gorzynski Smith, J. *Synthesis* **1984**, 629. Behrens C. H.; Katsuki, T. *Coord. Chem. Rev.* **1995**, *140*, 189.

(2) See, for example: Paquette, L. A.; Gao, Z.; Ni, Z.; Smith, G. F. *J. Am. Chem. Soc.* **1998**, *120*, 2543. Amano, S.; Ogawa, N.; Ohtsuka, M.; Chida, N. *Tetrahedron* **1999**, *55*, 2205.

(3) Julienne, K.; Metzner, P. *J. Org. Chem.* **1998**, *63*, 4532.

(4) Ewins, R. C.; Henbest, H. B.; McKervey, M. A. *J. Chem. Soc., Chem. Commun.* **1967**, 1085. Pirkle, W, H.; Rinaldi, P. L. *J. Org. Chem.* **1977**, *42*, 2080. Montanari, F. J. *J Chem. Soc., Chem. Commun.* **1969**, 135. (b) Bowman, R. M.; Collins, J. F.; Grundon, M. F. *J. Chem. Soc., Perkin Trans. 1* **1973**, 626. Bowman, R. M.; Collins, J. F.; Grundon, M. F. *J Chem. Soc., Chem. Commun.* **1967**, 1131. Morrison, J. D.; Mosher, H. S. *Asymmetric Organic Reactions*; American Chemical Society: Washinghton, DC, 1971; p 336.

(5) Hassine, B.; Gorsane, M.; Geerts-Evrard, F.; Pecher, J.; Martin, R. H.; Castelet, D. *Bull. Soc. Chim. Belg.* **1986**, *95*, 547. Hassine, B.; Gorsane, M.; Pecher, J.; Martin, R. H. *Bull. Soc. Chim. Belg.* **1986**, *95*, 557.

(6) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974. Hanson, R. M.; Sharpless, K. B. *J. Org. Chem.* **1986**, *51*, 1922. Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.

(7) Cesarotti, E.; Pasini, A.; Ugo, R. J. *J. Chem. Soc., Dalton Trans.* **1981**, 2147. Nakajima, K.; Kojima, M.; Fujita, J. *Chem. Lett.* **1986**, 1483.

(8) Chang, S.; Lee, N. H.; Jacobsen, E. N. *J. Org. Chem.* **1993**, *58*, 6939 and references therein.

(9) Brandes, B. D.; Jacobsen, E. N. *Tetrahedron Lett.* **1995**, *36*, 5123.

(10) Sakaki, H.; Irie, R.; Katsuki, T. *Synlett* **1993**, 300.

(11) Brandes, B. D.; Jacobsen, E. N. *J. Org. Chem.* **1994**, *59*, 4378.

(12) Chang, S.; Galvin, J. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1994**, *116*, 6937.

(13) Julià, S.; Masana, J.; Vega, J. C. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 929. Julià, S.; Guixer, J.; Masana, J.; Rocas, J.; Colonna, S.; Annunziata, R.; Molinari, J. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1317. Colonna, S.; Molinari, H.; Banfi, S.; Julià, S.; Masana, J.; Alverez, A. *Tetrahedron* **1983**, *39*, 1635. Banfi, S.; Colonna, S.; Molinari, H.; Julià, S.; Guixer, J. *Tetrahedron* **1984**, *40*, 5207. Bezuidenhoudt, B. C. B.; Swanepoel, A.; Augustyn, J. A. N.; Ferreira, D. *Tetrahedron Lett.* **1987**, *28*, 4857. Itsuno, S.; Sakakura, M.; Ito, K. *J. Org. Chem.* **1990**, *55*, 6047. Baures, P. W.; Eggleston, D. S.; Flisak, J. R.; Gombatz, K. J.; Lantos, I.; Mendelson, W.; Remich, J. J. *Tetrahedron Lett.* **1990**, *31*, 6501. Fliasak, J. R.; Gombatz, K. J.; Holmes, M. M.; Jarmas, A. A.; Lantos, I.; Mendelson, W. G.; Novack, V. J.; Remich, J. J.; Snyder, L. *J. Org. Chem.* **1993**, *58*, 6247. Bentley, P. A.; Bergeron, S.; Cappi, M. W.; Hibbs, D. E.; Hursthouse, M. B.; Nugent, T. C.; Pulido, R.; Roberts, S. M.; Wu, L. E. *J. Chem. Soc., Chem. Commun.* **1997**, 739.

(14) Denmark, S. E.; Wu, Z. *J. Org. Chem.* **1998**, *63*, 2810. Denmark, S. E.; Wu, Z. *Synlett* **1999**, 847. Denmark, S. E.; Forbes, D. C.; Hays, D. S.; De Pue, J. S.; Wilde, R. G. *J. Org. Chem.*, **1995**, *60*, 1391.

(15) Curci, R.; Fiorentino, M.; Serio, M. R. *J Chem. Soc., Chem. Commun.* **1984**, 155. Brown, D. S.; Marples, B. A.; Smith, P.; Walton, L. *Tetrahedron* **1995**, *51*, 3587.

10.1021/jo010258n CCC: $20.00 © 2001 American Chemical Society
Published on Web 09/14/2001

oxiranes are among the best asymmetric epoxidizing agents. In the presence of alkaline Oxone (Caroate), Yang's C_2-symmetric ketone,[16] Armstrong's chiral α-fluoro ketone,[17] and particularly Shi's fructose-derived chiral ketone catalyze the asymmetric epoxidation of a wide variety of alkenes, including allylic and homoallylic alcohols and ethers, with good to excellent enantioselectivities.[18]

Oxaziridines such as those of Davis,[19] and related systems,[20] are excellent reagents for the asymmetric oxidation of sulfides to sulfoxides but are much less successful with less potent nucleophilic substrates such as alkenes. Oxaziridinium salts, first reported in 1976 by Lusinchi,[21] are, however, extremely reactive for oxygen transfer to nucleophilic substrates, including sulfides and alkenes.[22,23] They have been prepared both by quaternization of the corresponding oxaziridines and by peracid oxidation of iminium salts. Dihydroisoquinolinium salts **1** (R = R′ = H) catalyze the epoxidation of simple olefins in the presence of Oxone as the stoicheiometric oxidant, the corresponding racemic oxaziridinium salts **2** (R = R′ = H) being presumed to be the active oxidants.[24] The first enantiomerically pure oxaziridinium salt **2** (R = Ph, R′ = Me; X = BF_4^-) was prepared by quaternization of an oxaziridine derived from a chiral imine, prepared in turn in four steps from norephedrine,[25] and was shown to induce asymmetric epoxidation of alkenes. Furthermore, the corresponding iminium salt **1** (R = Ph, R′ = Me; X = BF_4^-) was shown to catalyze epoxidation using Oxone; ee's of up to ca. 40% have been obtained. Complete retention of stereochemistry is observed, suggesting a single-step oxygen-transfer process. A binaphthalene-derived iminium salt has been reported to catalyze asymmetric epoxidation of simple alkenes under similar conditions,[26] providing, for example, 1-phenylcyclohexene oxide with 71% ee and *trans*-stilbene oxide with 31% ee. Armstrong and others have shown that even acyclic iminium salts can mediate epoxidation by Oxone.[27]

We have previously described our approach to a new type of cyclic chiral iminium salt containing the asymmetric centers in an exocyclic substituent at nitrogen, and these iminium salts have been successfully employed in the catalytic asymmetric epoxidation of simple alkenes, giving ee's of up to ca. 40% (obtained using the isopinocampheyl-derived catalyst **3** as its tetraphenylborate salt).[28] A complicating feature of these processes is that two diastereoisomeric oxaziridinium salts may be formed by attack of oxidant at the *Si* or *Re* face of the iminium species (illustrated below in Scheme 2). Each might deliver the oxygen atom to either of the prochiral faces of the alkene substrate with a different degree of enantiocontrol, and they may be in competition for the alkene substrate. On the basis that the presence of polar units within the chiral exocyclic substituent might help to control the diastereofacial selectivity of attack of the iminium unit by persulfate and/or the diastereofacial selectivity of approach of the alkene substrate to the reactive oxidizing intermediate, we have prepared and tested a number of catalysts from chiral amino alcohol, amino diol, amino ether, and amino acetal precursors. Herein, we describe the preparation and use as catalysts of a range of iminium salts functionalized at the nitrogen atom and prepared from amino alcohols, aminoethers, and aminoacetals, to investigate if the additional functionality could be used to control the stereochemistry of formation of the active oxygen transfer intermediate and hence improve epoxide ee's.

Results and Discussion

Catalyst Preparation. We reasoned that attachment of the controlling asymmetric centers to the iminium nitrogen atom (e.g., on exocyclic carbon atoms) would bring those centers nearer to the site of the reaction and might therefore be expected to lead to higher ee's.

We prepare our catalysts through condensation of enantiomerically pure chiral primary amines with 2-(2-bromoethyl)benzaldehyde **4**[29] as shown in Scheme 1. This approach has the great advantage that asymmetric

(16) Yang, D.; Yip, Y.-C.; Tang, M.-W.; Wong, M.-K.; Zheng, J.-H.; Cheung, K.-K. *J. Am. Chem. Soc.* **1996**, *118*, 491. Yang, D.; Wang, X. C.; Wong, M.-K.; Yip, Y.-C.; Tang, M.-W. *J. Am. Chem. Soc.* **1996**, *118*, 11311. Yang, D.; Wong, M. K.; Yip, Y. P.; Wang, X. C.; Tang, M. W.; Zheng, J. H.; Cheung, K. K. *J. Am. Chem. Soc.* **1998**, *120*, 5943. Yang, D.; Yip, Y.-C.; Chen, J.; Cheung, K.-K. *J. Am. Chem. Soc.* **1998**, *120*, 7659.

(17) Armstrong, A.; Hayter, B. R. *J. Chem. Soc., Chem. Commun.* **1998**, 621.

(18) Tu, Y.; Wang, Z.-X.; Shi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 9806. Wang, Z.-X.; Tu, Y.; Frohn, M.; Shi, Y. *J. Org. Chem.* **1997**, *62*, 2328. Wang, Z.-X.; Shi, Y. *J. Org. Chem.* **1997**, 62, 8622. Wang, Z.-X.; Shi, Y. *J. Org. Chem.* **1998**, *63*, 3099. Zhu, Y.; Tu, Y.; Yu, H.; Shi, Y. *Tetrahedron Lett.* **1998**, *39*, 7819. Cao, G. A.; Wang, Z.-X.; Tu, Y.; Shi, Y. *Tetrahedron Lett.* **1998**, *39*, 4425. Frohn, M.; Wang, Z.-X.; Shi, Y. *J. Org. Chem.* **1998**, *63*, 6425. Frohn, M.; Dalkiewicz, M.; Tu, Y.; Wang, Z.-X.; Shi, Y. *J. Org. Chem.* **1998**, *63*, 2948.

(19) Davis, F. A.; Harakal, M. E.; Awad, S. B. *J. Am. Chem. Soc.* **1983**, *105*, 3123. Davis, F. A.; Hague, M. S. *J. Org. Chem.* **1986**, *51*, 4083. Davis, F. A.; Chattopadhyay, S. *Tetrahedron Lett.* **1986**, *27*, 5079. Davis, F. A.; Towson, J. C.; Weismiller, M. C.; Lal, S.; Caroll, P. J. *J. Am. Chem. Soc.* **1988**, *110*, 8477. Davis, F. A.; Lal, S. G. *J. Org. Chem.* **1988**, *53*, 5004. Davis, F. A.; Sheppard, A. C. *Tetrahedron* **1989**, *45*, 5703. Davis, F. A.; Thimma Reddy, R.; Weismiller, M. C. *J. Am. Chem. Soc.* **1989**, *111*, 5964. Towson, J. C.; Weismiller, M. C.; Lal, S. G.; Sheppard, A. C.; Davis, F. A. *Org. Synth.* **1990**, *69*, 158. Davis, F. A.; Thimma Reddy, R.; McCauley, J. P., Jr.; Przeslawski, R. M.; Harakal, M. E.; Carroll, P. J. *J. Org. Chem.* **1991**, *56*, 809. Davis, F. A.; Kumar, A.; Chen, B.-C. *J. Org. Chem.* **1991**, *56*, 1143. Davis, F. A.; Weismiller, M. C.; Murphy, C. K.; Thimma Reddy, R.; Chen, B.-C. *J. Org. Chem.* **1992**, *57*, 7274. Davis, F. A.; Thimma Reddy, R.; Han, W.; Carroll, P. J. *J. Am. Chem. Soc.* **1992**, *114*, 1428. Davis, F. A.; Thimma Reddy, R.; Han, W.; Reddy, R. E. *Pure Appl. Chem.* **1993**, *65*, 633. Chen, B.-C.; Murphy, C. K.; Kumar, A.; Thimma Reddy, R.; Clark, C.; Zhou, P.; Lewis, B. M.; Gala, D.; Mergelsberg, I.; Scherer, D.; Buckley, J.; DiBenedetto, D.; Davis, F. A. *Org. Synth.* **1995**, *73*, 159. Davis, F. A.; Reddy, R. E.; Kasu, P. V. N.; Portonovo, P. S.; Carroll, P. J. *J. Org. Chem.* **1997**, *62*, 3625.

(20) Page, P. C. B.; Heer, J. P.; Bethell, D.; Collington, E. W.; Andrews, D. M. *Tetrahedron*: *Asymmetry* **1995**, *6*, 2911. Page, P. C. B.; Heer, J. P.; Bethell, D.; Collington, E. W.; Andrews, D. M. *Synlett* **1995**, 773. Rebek, J., Jr.; McCready, R. *J. Am. Chem. Soc.* **1980**, *102*, 5602. Nanjo, K.; Suzuki, K.; Sekiya, M. *Chem. Lett.* **1978**, 1143. Rebek, J., Jr.; Wolf, S.; Mossman, A. *J. Org. Chem.* **1978**, *43*, 180. Page, P. C. B.; Heer, J. P.; Bethell, D.; Collington, E. W.; Andrews, D. M. *Tetrahedron Lett.* **1994**, *35*, 9629.

(21) Milliet, P.; Picot, A.; Lusinchi, X. *Tetrahedron Lett.* **1976**, 1573. Milliet, P.; Picot, A.; Lusinchi, X. *Tetrahedron Lett.* **1976**, 1577.

(22) Hanquet, G.; Lusinchi, X.; Milliet, P. *Tetrahedron Lett.* **1987**, *28*, 6061.

(23) Hanquet, G.; Lusinchi, X.; Milliet, P. *Tetrahedron Lett.* **1988**, *29*, 3941.

(24) Hanquet, G.; Lusinchi, X.; Milliet, P. *C. R. Hebd. Seances Acad. Sci.* **1991**, *313*, *S11*, 625. Lusinchi, X.; Hanquet, G. *Tetrahedron* **1997**, *53*, 13727.

(25) Bohé, L.; Hanquet, G.; Lusinchi, M.; Lusinchi, X. *Tetrahedron Lett.* **1993**, *34*, 7271. Bohé, L.; Lusinchi, M.; Lusinchi, X. *Tetrahedron* **1999**, *55*, 141.

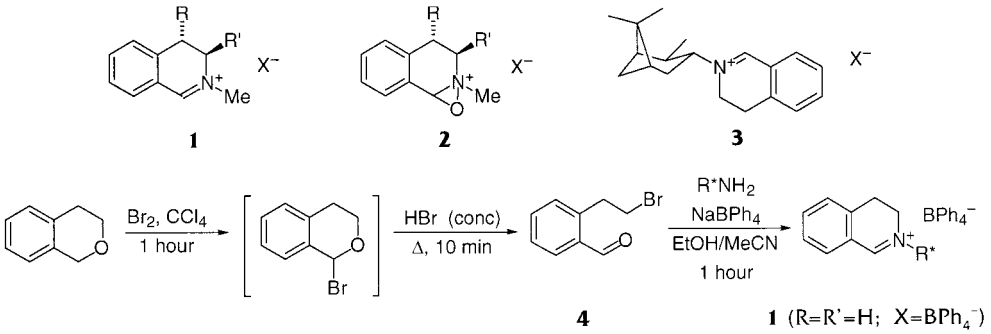
(26) Aggarwal, V. K.; Wang, M. F. *J. Chem. Soc., Chem. Commun.* **1996**, 191.

(27) Armstrong, A.; Ahmed, G.; Garnett, I.; Gioacolou, K. *Synlett* **1997**, 1075. Armstrong, A.; Draffan, A. G. *Synlett* **1998**, 646. Armstrong, A.; Ahmed, G.; Garnett, I.; Gioacolou, K.; Wailes, J. S. *Tetrahedron* **1999**, *55*, 2341. Minakata, S.; Takemiya, A.; Nakamura, K.; Ryu, I.; Komatsu, M. *Synlett* **2000**, 1810.

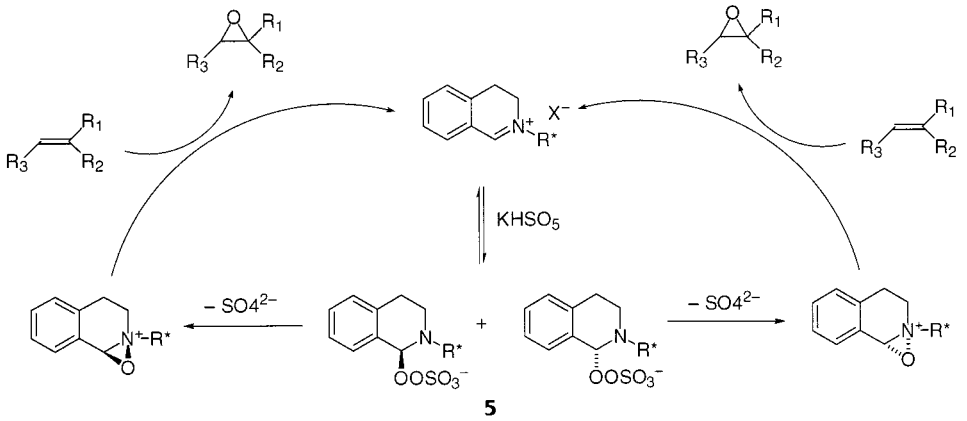
(28) Page, P. C. B.; Rassias, G. A.; Barros, D.; Bethell, D.; Schilling, M. B. *J. Chem. Soc, Perkin Trans. 1* **2000**, 3325.

(29) Rieche, A.; Schmitz, E. *Chem. Ber.* **1956**, *89*, 1257.

Scheme 1



Scheme 2



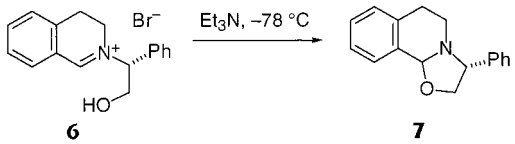
catalysts may be derived rapidly from a wide variety of readily available chiral primary amines. Cyclocondensation directly with the appropriate amine takes place, generally at room temperature, to give the iminium salts **1** in good yields. We have found the tetraphenylborate salts, readily prepared by the addition of sodium tetraphenylborate to the cyclocondensation reaction, to be the most crystalline and most easily handled. The synthesis of the catalysts is rapid, inexpensive, involves simple synthetic steps, does not require chromatography, and is easily scaled up. We have prepared catalysts on scales of up to 70 g without any difficulties.

Our standard conditions for the epoxidation reactions, optimized for 1-phenylcyclohexene as substrate, comprise typically 5 or 10 mol % of the dihydroisoquinolinium salt, 2 equiv of Oxone, and 4 equiv of sodium carbonate in water−acetonitrile (1:1) at 0 °C. Blank reactions carried out in parallel under the same conditions, in the presence of Oxone, but without catalyst, gave no reaction over up to 8 h when 4 equiv of sodium carbonate was present.

We have postulated a catalytic cycle for an oxaziridinium ion as the oxidative intermediate (Scheme 2). The first stage is (probably reversible) nucleophilic attack of persulfate on the iminium salt to give an initial adduct **5**, uncharged at nitrogen. Irreversible expulsion of sulfate follows to give the oxaziridinium species, a reaction which we believe to be the rate-determining step under our reaction conditions. Oxygen may then be transferred to a substrate in a subsequent fast step.

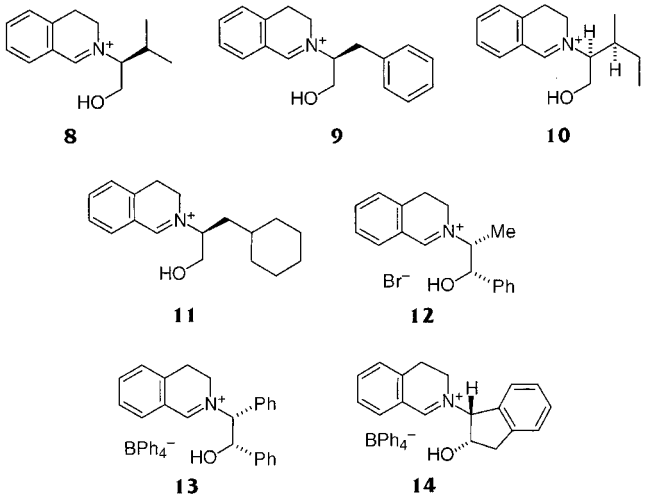
Catalysts from Chiral 1,2-Amino Alcohol Precursors Containing a Primary Hydroxyl Group. Chiral 1,2-amino alcohols containing a primary hydroxyl group are readily derived by reduction of α-amino acids. 2-(2-Bromoethyl)benzaldehyde reacts with such amino alcohols in the same manner as with the simple amines to furnish the desired dihydroisoquinolinium salts. Dihydroisoquinolinium species **8**−**11** were prepared as their tetraphenylborate salts, derived from *S*-valinol, *S*-phenyl alaninol, (2*S*,3*S*)-isoleucinol, and *S*-2-cyclohexylmethyl-2-aminoethanol, respectively. Dihydroisoquinolinium salts containing a pendant hydroxyl group such as **6** have been reported to undergo base-induced ring closure to form the corresponding oxazolidines **7** with high diastereoselectivity and yields (Scheme 3).[30] Under the reaction conditions used for their preparation, ^{1}H NMR spectroscopy indicated that no such cyclization had taken place.

Scheme 3



All of these derivatives produced almost racemic 1-phenylcyclohexene oxide when catalytic amounts of the salts were used in the epoxidation procedure under our standard conditions. An interesting feature of the reactions is that they proceed much more slowly than those catalyzed by mediators that lack the pendant hydroxyl group. For example, with iminium salt **3**, at 0.5 mol % catalyst loading, complete epoxidation of 1-phenylcyclohexene is observed within 1 h, but more than 2 mol % of catalysts **8**−**11** is required in order to achieve the same effect. We believe this to be due to the existence of an equilibrium between the ring-open iminium salt (active) and ring-closed oxazolidine (inactive) forms of the catalysts under the slightly alkaline reaction conditions.

(30) Yamato, M.; Hashigaki, K.; Ishikawa, S.; Qais, N. *Tetrahedron Lett.* **1988**, *29*, 6949. Yamato, M.; Hashigaki, K.; Ishikawa, S.; Qais, N. *Tetrahedron* **1990**, *46*, 5909. Schneider, W.; Müller, B. *Arch. Pharm. Chem.* **1961**, 645.



Catalysts from Chiral 1,2-Amino Alcohol Precursors Containing a Secondary Hydroxyl Group. Dihydroisoquinolinium species derived from chiral 1,2-amino alcohols containing a secondary hydroxyl group are also formed readily using our method, and we prepared three such salts **12**−**14**. Interestingly, the bromide salt of the norephedrine derivative **12** precipitated directly from the reaction medium, no anion exchange being required to produce crystalline material.

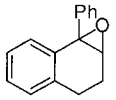
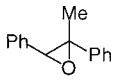
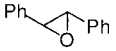
We were pleased to observe improved ee's on testing of these derivatives as epoxidation catalysts, suggesting that the presence of a secondary hydroxylic center may help to impart greater enantioselectivity at the oxygen transfer step than does a primary center at this position in the catalyst structure, perhaps suggesting that a substituent at this position may help to control the approach of the alkene substrate.

For example, the (1*S*,2*R*)-norephedrine derivative **12** catalyzed the epoxidation of 1-phenylcyclohexene with 30% ee. Using the related catalyst derived from (1*S*,2*R*)-2-amino-1,2-diphenylethanol **13**, 1-phenylcyclohexene oxide was obtained in similar yield and 24% ee. In comparison, the (1*R*,2*S*)-aminoindanol derivative **14** imparted lower asymmetric induction (<14% ee), and in addition, deteriorated during the process, the reaction ceasing completely after 2 h (<40% conversion). Table 1 shows some of the results obtained with the norephedrine-derived dihydroisoquinolinium salt **12** with other aryl alkene substrates, under our usual reaction conditions.

The improved ee's observed, however, come at the expense of the catalyst activity: At least 5 mol % of catalyst is required for the complete epoxidation of 1-phenylcyclohexene in 1 h, compared with 2 mol % of catalysts which contain a primary hydroxyl group, and ca. 0.3 mol % of catalysts containing simple alkyl groups. It is possible that the position of the equilibrium between the ring-open and ring-closed forms is less favorable in these cases, reducing the availability of the iminium form.

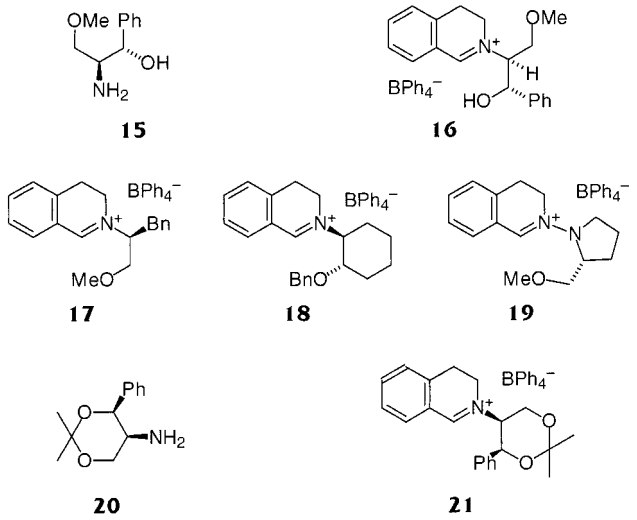
The dihydroisoquinolinium salt derived from 1,1-diphenyl-2-aminopropanol, which contains a tertiary hydroxyl group, could not be prepared. Examination of the crude reaction product showed complete absence of the signals expected for the iminium proton (ca. 8.5−9.1 ppm) and the iminium bond (1650 cm^{-1}) and perhaps suggests a preference of such systems to exist entirely in the oxazolidine form, although we were unable to isolate the material.

Table 1. Catalytic Asymmetric Epoxidation Using Catalyst 12[a]

epoxide	ee/%; configuration	isolated yield/%
	33 (+) -	61
	30 (+)-(R,R)	64
	20 (+)-(R,R)	57
	12 (+)-(R,R)	45

[a] Conditions: Oxone (2 equiv), sodium carbonate (4 equiv), water/acetonitrile (1:2), 0 °C, 10 mol % catalyst **12** unless otherwise stated.

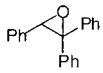
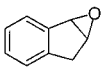
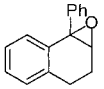
Catalysts from Amino Ether Precursors. We were not able to prepare catalysts from amino diols, but (1*S*,2*S*)-2-amino-3-methoxy-1-phenylpropanol **15**, which is structurally related to norephedrine and contains a primary alcohol protected as its methyl ether as well as a secondary alcohol, did furnish the derived dihydroisoquinolinium tetraphenylborate **16**, albeit in low yield. However, compound **16** exhibited negligible catalytic activity, again perhaps because of equilibrium with the ring-closed oxazolidine form resulting from the presence of the hydroxyl group.



Accordingly, we prepared a number of dihydroisoquinolinium salts **17**−**19** from simpler amino ethers.

The first catalyst of this type, **17**, prepared from *S*-phenylalaninol methyl ether, indeed proved to be much more active than the related derivative of the parent amino alcohol, but poor enantioselectivity was imparted in the epoxidation of 1-phenylcyclohexene (<7% ee). Catalyst **18**, prepared from (1*S*,2*S*)-2-benzyloxycyclohexylamine, has the substantially larger benzyl group attached to the oxygen atom, which itself is sited at an asymmetric carbon atom. Again, 1-phenylcyclohexene oxide was isolated from an epoxidation reaction using this catalyst in good yield but with less than 5% ee. These experiments perhaps suggest that the size of the ether

Table 2. Catalytic Asymmetric Epoxidation Using Catalysts 3 and 21

catalyst	3		21	
epoxide	yield/%	(ee); configuration	yield/%	(ee); configuration
	68	(8)-(+)-(*R*)	64	(20)-(+)-(*R*)
	72	(15)-(+)-(1*R*,2*R*)	52	(52)-(−)-(1*S*,2*S*)
	43	(5)-(+)-(*S*)	54	(59)-(+)-(*S*)
	68	(40)-(+)-(1*R*,2*R*) †	55	(41)-(−)-(1*S*,2*S*)
	34	(3)-(+)-(1*S*,2*R*)	52	(17)-(+)-(1*S*,2*R*)
	73	(20)-(−)-(1*S*,2*R*)	64	(49)-(−)-(1*S*,2*R*)

[a] Conditions: Oxone (2 equiv), sodium carbonate (4 equiv), water/acetonitrile (1:1), 0 °C, 5 mol % catalyst **21** unless otherwise stated. [b] 10 mol % catalyst.

substituent in such catalysts is not particularly important for asymmetric induction during oxygen transfer to the alkene.

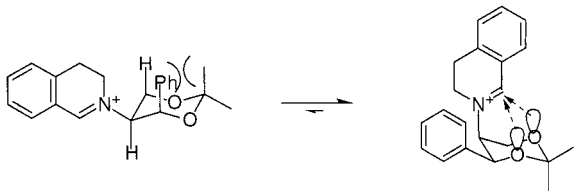
The third amino ether tested was the chiral hydrazine derived from *R*-prolinol methyl ether (RAMP).[31] Here, in the case of the iminium salt **19**, interaction between the ethereal oxygen atom and the iminium carbon atom would produce a six-membered ring rather than five as in catalysts **17** and **18**. The hydrazonium salt **19**, however, proved to be inactive as a catalyst for asymmetric epoxidation under a variety of conditions, perhaps due to decreased electrophilicity in the iminium bond resulting from the adjacent nitrogen atom.

A Catalyst from an Amino Acetal Precursor. Protection of the diol moiety of (1*S*,2*S*)-2-amino-1-phenylpropane-1,3-diol as the acetonide provides a primary amine containing an acetal unit within the structure. This compound, 5-amino-2,2-dimethyl-4-phenyl-1,3-dioxane **20**,[32] reacted smoothly with 2-(2-bromoethyl)-benzaldehyde under our usual conditions to furnish the corresponding dihydroisoquinolinium tetraphenylborate salt **21** in greater than 75% yield.

Iminium salt **21** was tested in the catalytic asymmetric epoxidation of several alkenes at 0 °C, and a comparison of the results with those obtained using the isopinocampheylamine-derived catalyst **3** is presented in Table 2. These results indicate that catalyst **21** in general induces much higher enantioselectivity in the asymmetric epoxidation than others we have discovered to date, providing in some cases dramatic improvements in ee over catalyst **3**.[28]

A feature of this compound is the syn relationship between the nitrogen heterocycle and the phenyl group. This implies that either the phenyl or the dihydroisoquinolinium group must be axial if the dioxane retains a chair conformation as in **22** or **23** (Scheme 4). Despite

Scheme 4



23 **22**

the similar size of the two substituents, ^{1}H NMR spectroscopy suggests the presence of only one conformer at ambient temperature: First, all the proton signals are sharp and the coupling constants corresponding to each of the protons of the 1,3-dioxane ring are consistent with a chair conformation, in accord with previous reports of substituted 2,2-dimethyl-1,3-dioxane rings.[33] Second, in the ^{13}C NMR spectrum, the geminal methyl groups appear at 17.98 and 28.68 ppm (axial and equatorial respectively); this is also consistent with a chair conformation.[34] Conformer **22** would be expected to be the thermodynamically favored one as a result of reduced 1,3-diaxial interactions.

It is tempting to propose a stabilizing interaction between the electron cloud associated with the oxygen atom lone pairs and the electron-depleted carbon atom of the iminium unit, as shown in **22**. One could envisage a bonding interaction between the p orbital on the carbon atom of the iminium unit and the in-phase combination of the axial lone pair sp^3 orbitals on the two oxygen atoms. This suggestion is supported by single-crystal X-ray analysis. It is interesting that the X-ray analysis does not indicate a twist-boat conformation.

The relative success of the dioxane-derived catalyst may stem partly from the high conformational rigidity, perhaps a result of the stereoelectronic effects discussed above. The strong preference of similar systems such as **24** to exist in such a conformation has been documented both experimentally and theoretically.[35] In conformer **22**,

24

the phenyl substituent may hinder the attack of the oxidant at that side of the iminium bond, rendering the opposite side more accessible. This arrangement is thus likely to produce a preponderance of one of the two possible diastereoisomeric oxaziridinium intermediates (Scheme 5), and enantiocontrol would then result solely from the process of oxygen transfer to the substrate.

This high conformational rigidity is absent from the dihydroisoquinolinium salt **3** derived from isopinocampheylamine. Consequently, in that case rotation around the bond between the nitrogen atom and the chiral unit may result in both diastereotopic faces of the iminium moiety becoming susceptible to attack by the oxidant, and the two diastereoisomeric oxaziridinium salts so formed

(31) Enders, D.; Eichenauer, H. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 549.

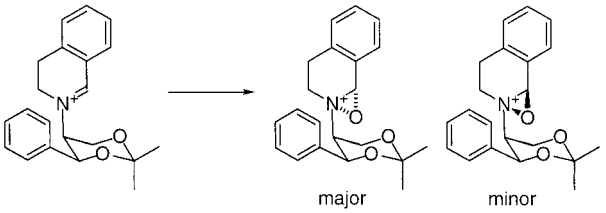
(32) Nordin, I. C.; Thomas, J. A. *Tetrahedron Lett.* **1984**, *25*, 5723.

(33) Dondoni, A.; Perrone, D.; Merino, P. *J. Chem. Soc., Chem. Commun.* **1991**, 1313.

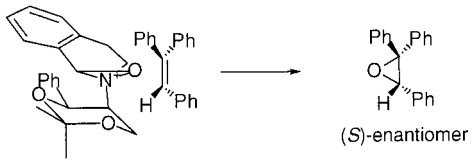
(34) Evans, D. A.; Rieger, D. L.; Gage, J. R. *Tetrahedron Lett.* **1990**, *31*, 7099. Ohfune, Y.; Nishio, H. *Tetrahedron Lett.* **1984**, *25*, 4133.

(35) Alonso, J. L.; Wilson, E. B. *J. Am. Chem. Soc.* **1980**, *102*, 1125. Baggett, N.; Bukhari, M. A.; Foster, A. B.; Lehmann, J.; Webber, J. M. *J. Chem. Soc.* **1963**, 4157.

Scheme 5



Scheme 6



may be very different in their potential for asymmetric induction in the epoxidation process.

Transition-State Considerations. Two transition states have been proposed for the epoxidation of alkenes by dioxiranes and oxaziridines, the spiro and the planar. A possible transition state, constructed according to the spiro model, for the epoxidation of triphenylethylene by the acetal catalyst is shown in Scheme 6. Assuming an oxaziridinium intermediate, in the spiro transition state the alkene approaches the oxaziridinium moiety in such a way that the axis of the carbon−carbon double bond is perpendicular to the carbon−nitrogen bond axis. In the planar transition state, the two components approach one another in such a way that these axes are parallel to one another and in the same plane. The spiro transition state is now generally accepted as the mechanism in operation during both dioxirane- and oxaziridine-mediated epoxidation.[19,21] It is also supported by recent theoretical and computational studies.[36]

Conclusion

We have discovered an acetal-containing iminium salt epoxidation catalyst, a member of a new family of iminium salts that contain additional functional groups, which provides up to ca. 60% ee in the epoxidation of simple alkenes. This selectivity may stem partially from internal stabilization of the positive charge by the adjacent oxygen atom, which increases the conformational and rotational rigidity of the molecule.

Experimental Section

2-(2-Bromoethyl)benzaldehyde 4. Bromine (60 g, 0.37 mol) was added slowly to an ice-cooled solution of isochroman (50 g, 0.37 mol) in carbon tetrachloride (200 mL) over a period of 10 min, with stirring. After the exothermic reaction subsided, the cooling bath was removed and the dark brown solution heated under reflux until the reaction mixture became pale yellow and liberation of HBr fumes ceased (ca. 1.5 h). The solution was allowed to attain ambient temperature and the solvent removed under reduced pressure. To the yellow oil obtained (1-bromoisochroman), aqueous hydrobromic acid (48%, 75 mL) was added and the reaction mixture heated under reflux. After 10−15 min, the solution was allowed to cool and extracted with diethyl ether (4 × 50 mL). The combined organic extracts were washed with water (2 × 30 mL) and aqueous sodium bicarbonate and dried over magnesium sulfate. Evaporation of the solvent under reduced pressure furnished crude 2-(2-bromoethyl)benzaldehyde as an orange oil ca. 85−90% pure (67.5 g, 65%). Analytically pure samples could be obtained by distillation under reduced pressure; chromatography is not recommended. Both the crude and the distilled compound can be used in the synthesis of dihydroisoquinolinium salts: ν_{max}/cm^{-1} (neat) 2742, 1697, 1600, 1575, 1260, 1193, 755; δ_H ($CDCl_3$, 400 MHz) 3.54−3.63 (4 H, m), 7.33 (1 H, d, J = 8.0 Hz), 7.48 (1 H, t, J = 7.5 Hz), 7.54 (1 H, t, J = 7.9 Hz), 7.80 (1 H, d, J = 7.6 Hz), 10.14 (1 H, s); δ_C (62.50 MHz) 33.17 (CH_2), 36.70 (CH_2), 128.10 (CH), 132.51 (CH), 134.14 (CH) 134.33 (quat), 134.88 (CH), 140.95 (quat), 193.33 (CH); m/z 211; calcd for C_9H_9BrO 211.98373; found 211.98370.

General Procedure for the Synthesis of Dihydroisoquinolinium Salts from 2-(2-Bromoethyl)benzaldehyde and Primary Amines. A solution of the amine in ethanol (10 mL per 1 g of amine, 1 equiv) was added dropwise to 2-(2-bromoethyl) benzaldehyde (1.8 equiv; 1.2 equiv if distilled material is used) at 0 °C. The reaction mixture was stirred for a few hours or overnight while ambient temperature was attained. Sodium tetraphenylborate or other anion-exchanging salt (1.10 equiv) in the minimum amount of acetonitrile was added in one portion to the reaction mixture, and after the mixture was stirred for 5 min the organic solvents were removed under reduced pressure. Ethanol was added to the residue, followed by water. The resulting solid was collected by filtation and washed with additional ethanol followed by diethyl ether. If no solid materialized after the addition of water the suspension was allowed to settle, the ethanol/water phase was decanted off, and the gummy residue was macerated in hot ethanol.

General Procedure for the Catalytic Asymmetric Epoxidation of Simple Alkenes Mediated by Iminium Salts. Oxone (2 equiv) was added to an ice-cooled solution of sodium carbonate (4 equiv) in water (12 mL per 1.20 g of sodium carbonate) with vigorous stirring, and the resulting foaming suspension was left to stir for 5 min until the effervescence subsided. The iminium salt (5−10 mol % with respect to the substrate) was then added as a solution in acetonitrile (7 mL per 100 mg of catalyst), followed by the alkene substrate (1 equiv), in solid form or as a solution in acetonitrile (5 mL). The suspension was stirred at 0 °C until the substrate was completely consumed as indicated by TLC analysis, or overnight. The reaction mixture was diluted with water until most of the inorganics dissolved and extracted four times with diethyl ether. The organic extracts were washed with water and brine and dried over sodium sulfate. Filtration and evaporation of the solvents provided the crude epoxides, which are ca. 90% pure. Analytically pure epoxides can be obtained by chromatography on a short column of silica gel, eluting initially with light petroleum to remove nonpolar impurities and/or unreacted parent alkene, followed by light petroleum/ethyl acetate (95:5) to afford the epoxides.

Acknowledgment. This investigation has enjoyed the support of the Leverhulme Trust, the EPSRC, and Loughborough University.

Supporting Information Available: Full experimental data; X-ray picture of catalyst **21**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO010258N

(36) Bach, R. D.; Andres, J. L.; Su, M.-D.; McDouall, J. J. *J. Am. Chem. Soc.* **1993**, *115*, 5768. Houk, K. N.; Liu, J.; DeMello, N. C.; Condroski, K. R. *J. Am. Chem. Soc.* **1997**, *119*, 10147. Houk, K.; Washington, Y. *J. Am. Chem. Soc.* **2000**, *122*, 2948.