COVER FEATURE

Professor Varinder K. Aggarwal*

Recipient of one of the 1998 RSC Corday–Morgan prizes

Career

Varinder Aggarwal graduated from Cambridge University with a first class honours degree in Natural Sciences in 1983. He remained at Cambridge and obtained his PhD with Stuart Warren in 1986, working on acyclic stereochemical control using sulfur rearrangements. He then obtained a Harkness Fellowship and worked with Gilbert Stork at Columbia University in New York, on ribonucleic acid synthesis. In 1988 he was appointed to a lectureship at the University of Bath before moving to Sheffield University in 1991, where he was promoted to Reader in 1995 and to Professor in 1997. In September 2000 he will move to the Chair of Synthetic Chemistry at Bristol University.

His research interests span organometallic chemistry, asymmetric catalysis and the total synthesis of natural products. In the area of catalysis, his group has developed catalytic, asymmetric processes for the preparation of epoxides, aziridines and cyclopropanes, developed novel catalysts and processes for alkene epoxidation, and developed improved conditions for the Baylis–Hillman reaction.

He has received a number of awards including the Zeneca award (1996), Pfizer awards (1996, 1998), Glaxo Wellcome award (1996), the RSC Hickinbottom award and fellowship (1997), a Nuffield Fellowship (1997), the Novartis Lectureship (1999), the Liebigs Lectureship of the German Chemical Society (1999) and one of the RSC Corday–Morgan prizes (1998).

Research

I have always been interested in asymmetric synthesis and at the start of my academic career I began by investigating the applications of C_2 symmetric sulfoxides as potential chiral control elements. Even though this auxiliary-based approach to asymmetric synthesis was somewhat dated, there were few general auxiliaries for chiral acyl anion and chiral ketene equivalents. We therefore investigated the use of sulfoxides as potential

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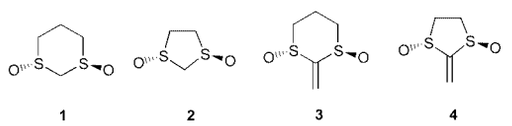
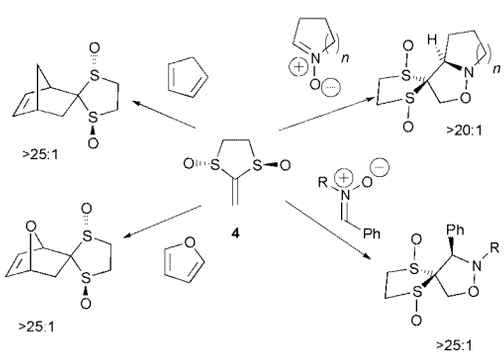


chiral auxiliaries and this turned out to be a very fruitful program of research. We developed simple, high yielding and highly enantioselective routes to the chiral sulfoxides **1**–**4**.[1–3] In anion reactions, sulfoxide **1** was superior to **2**, giving high yields and high diastereocontrol with aromatic aldehydes.[4,5] The adducts were easily converted into α-hydroxyacids and a range of acid derivatives (esters, amides, and acids) and ketones without racemisation.[6,7] In cycloaddition chemistry (Diels–Alder and nitrone), sulfoxide **4** was superior to **3**, providing adducts again with high diastereocontrol (usually >95 : 5) (Scheme 1).[2,3,8] The dithiolane moiety could then be converted into a



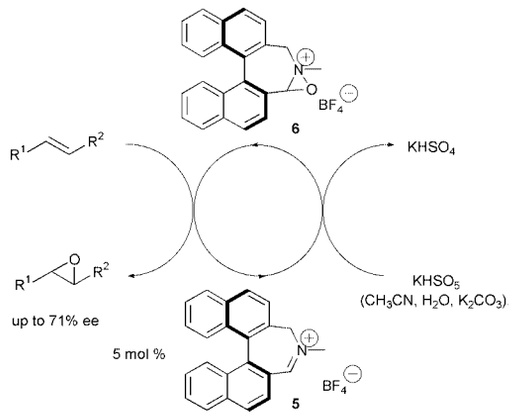
Scheme 1

carbonyl group in two steps. Alkenyl substituted analogues of **3** also underwent highly diastereoselective epoxidation reactions and the resulting epoxides could be opened by amine nucleophiles to generate α-amino amides.[9] This provided a versatile route to amino acid derivatives.

In the area of catalysis we have focused on the synthesis of epoxides from alkenes and from carbonyl compounds. For alkene epoxidation we have discovered that the binaphthyl derived iminium salt **5** gives good yields and moderate enantioselectivities (Scheme 2).[10] This process offers a significant advantage over the related ketone mediated process in giving faster rates and allowing lower catalyst loadings. Recently we have discovered that amines are able to catalyse the epoxidation of alkenes using oxone as the oxidant.[11] This observation may lead to a useful process for epoxidation and this unusual form of catalysis may even lead to the development of other new reactions.

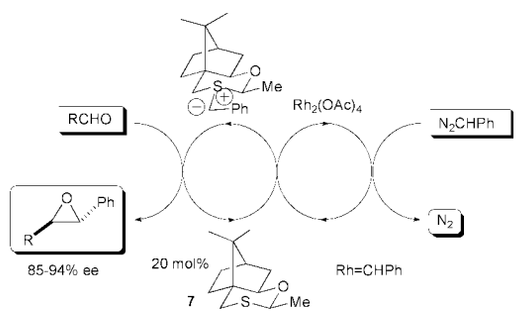
In the process for making epoxides from carbonyl compounds we sought to convert the stoichiometric sulfur ylide reaction into a catalytic process. As sulfur ylides react with carbonyl compounds to give epoxides and return sulfide, all we had to do to convert the reaction into a catalytic process was to find suitably mild conditions under which the sulfide could be converted back into the ylide. This was achieved using the reaction of diazo compounds with sulfides. The alternative method of ylide formation by alkylation of the sulfide and treatment with base is extremely slow especially with catalytic

DOI: 10.1039/b001932l



Scheme 2

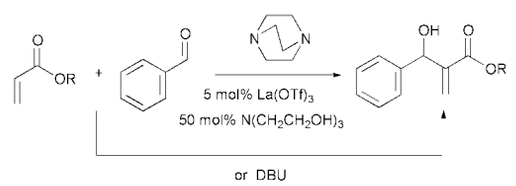
quantities of sulfides. Using chiral sulfides, readily derived from camphor in two steps, high enantioselectivity was obtained for a range of carbonyl compounds (Scheme 3).[12–14]



Scheme 3

The catalytic process for epoxidation was also applied to aziridination [15] and cyclopropanation [16] and in each case high enantioselectivity was obtained. A more user-friendly process has also been developed for epoxidation, aziridination and cyclopropanation in which the diazo compound does not have to be handled but is generated *in situ*. This work, together with a new class of highly effective sulfides for use in this process, will be reported shortly.

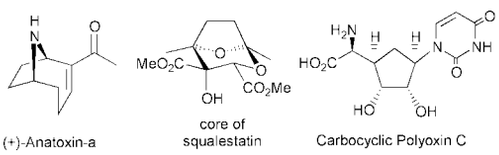
Another interesting area that we have worked on is the Baylis–Hillman reaction. However, the reaction is slow, limited in scope and when we embarked on our work, there were no practical catalytic asymmetric versions of this process.[17] We therefore set out to find conditions which enhanced the rate of the reaction as this would broaden its scope and following this study we could begin to embark on enantioselective Baylis–Hillman reactions. We have achieved enhanced rates in a number of ways: through the discovery of metal and ligand accelerated catalysis (up to 40 fold increase in rate);[18,19] through the discovery that DBU is an even better catalyst than the current best catalyst (up to 50 fold increase in rate) [20] (Scheme 4)



Scheme 4

and through the use of formamide as an additive (up to 50 fold increase in rate).[21] Under our new optimum conditions reactions which took 28 days can now be completed in less than 24 hours and chiral catalysts based on quinine, which gave essentially no product under ambient conditions, now give measurable amounts of product. However, we still have some way to go to achieve our ultimate goal in this reaction.

Finally, we have embarked on the asymmetric synthesis of biologically active compounds and have developed short enantioselective routes to anatoxin-a,[22] the core of squalestatin,[23] the carbocyclic analogue of polyoxin C,[24] a formal synthesis of pyripyropene A [25] and we are currently working on the total synthesis of griseolic acid, avenaciolide and subglutinol in addition to other smaller targets. In each of these syntheses we have used either methodology that we have developed or new strategies that have not been used previously with the particular class of molecule.



Acknowledgements

First and foremost, I wish to thank my research group, past and present, for their practical and intellectual contributions to our research programs, their hard work and dedication, and for creating such a genial atmosphere in which to work. I also wish to thank my wife and family for reminding me (without ever saying it!) that there is more to life than chemistry!

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