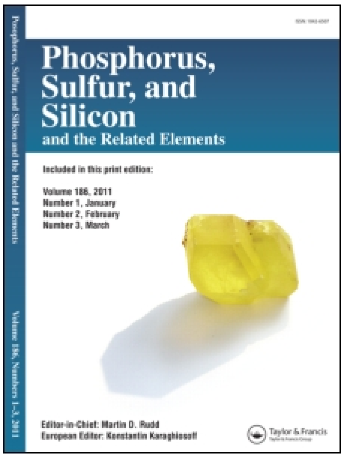

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Varinder K. Aggarwal[a]; Hesham Abdel-rahman[a]; Alison Thompson[a]; Beverley Mattison[a]; Ray V. H. Jones[b]
[a] Department of Chemistry, University of Sheffield, Sheffield, UK [b] Process Technology Department, Zeneca FCMO, Stirlingshire, UK

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A NOVEL CATALYTIC CYCLE FOR THE SYNTHESIS OF EPOXIDES USING SULFUR YLIDES, AND APPLICATION TO THE SYNTHESIS OF CYCLOPROPANES AND AZIRIDINES .

Varinder K. Aggarwal,[a*] Hesham Abdel-Rahman,[a] Alison Thompson,[a] Beverley Mattison,[a] Ray V. H. Jones,[b]

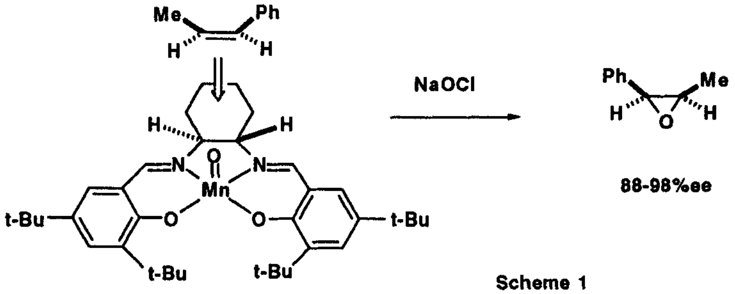
a Department of Chemistry, University of Sheffield, Sheffield S3 7HF, UK.
b Zeneca FCMO, Process Technology Department, Earls Road, Grangemouth, Stirlingshire FK3 8XG, UK.

Abstract We have developed a new catalytic cycle for the synthesis of epoxides from carbonyl compounds and diazocompounds. These reactions are mediated by catalytic quantities of rhodium acetate (0.01 eq.) and dimethyl sulfide (0.2 eq.). In this catalytic cycle, phenyl diazomethane is decomposed by rhodium acetate to give a metallocarbene and this reacts with the sulfide to give a sulfur ylide which in turn reacts with the aldehyde to give an epoxide and returns the sulfide back into the catalytic cycle. The use of catalytic amounts of chiral sulfides gives non-racemic epoxides. It has been found that other diazocompounds can be used in the catalytic cycle e.g. N,N-diethyl diazoacetamide. In addition, it has been found that substitution of aldehydes for enones furnishes cyclopropanes, and substitution with imines gives aziridines. For the preparation of terminal epoxides, diazomethane could not be used instead of phenyl diazomethane. Instead, it was discovered that terminal epoxides could be prepared using diethyl zinc, chloroiodomethane, dimethyl sulfide and an aldehyde. A second catalytic cycle for epoxidation has therefore been developed.

Key Words catalytic, asymmetric synthesis, sulfur ylide, epoxide, aziridine, cyclopropane, rhodium acetate, Simmons Smith.

Introduction

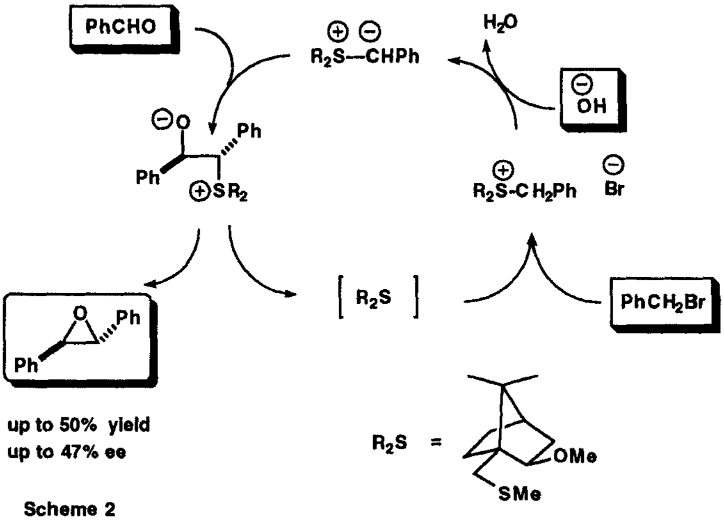
The asymmetric synthesis of epoxides from unfunctionalised alkenes is a difficult problem but a breakthrough has recently been reported by Jacobsen (Scheme 1).[1,2] In his system, chiral manganese salen complexes efficiently oxidise alkenes to give epoxides in good yield and high enantiomeric excess. However high enantioselectivities



Scheme 1

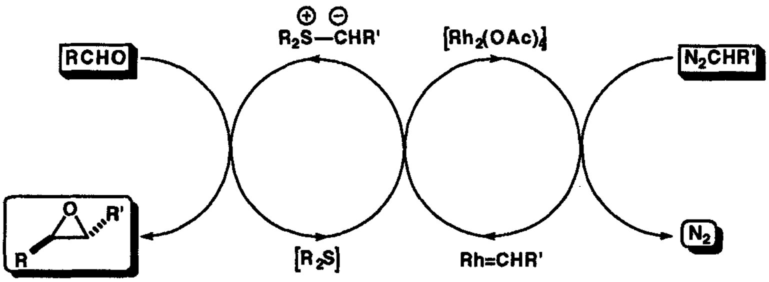
in the oxidation process are only obtained from a limited range of alkenes; those that are *cis* disubstituted and directly bonded to π-systems give good enantioselectivities.[3,4]

For *cis* disubstituted alkenes in which the two substituents become increasingly similar, it becomes increasingly difficult for a chiral oxidant to distinguish the enantiotopic faces and only low enantioselectivities would result. A potential solution to this specific problem and the more general problem of preparing non-racemic epoxides is to prepare epoxides from chiral sulfur ylides and carbonyl compounds.[5] Indeed, there are already several examples of the use of chiral sulfur ylides for the synthesis of epoxides.[6-10] The question we posed was how to develop a catalytic asymmetric cycle for this process. Furukawa has shown that a catalytic cycle for asymmetric epoxidation from carbonyl compounds can be set up using a mixture of sulfide, alkyl halide, base and aldehyde (Scheme 2).[6] However, the yields and enantioselectivities are low, only limited turnover is obtained and as Furukawa comments himself, 'there are some disadvantages' to his system.



Scheme 2

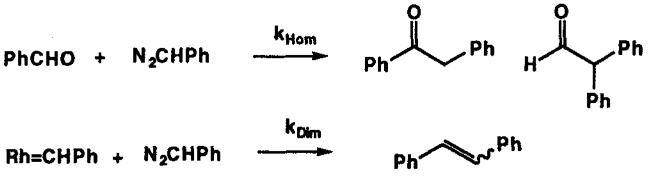
We asked ourselves whether sulfur ylide formation could be executed by decomposition of diazocompounds in the presence of metal salts and whether this reaction could be conducted in the presence of an aldehyde. Such a process would allow turnover of sulfides in the cycle (Scheme 3). Allylic sulfides have been converted to allylic sulfur ylides by this method and the products used in [2,3] sigmatropic rearrangements.[11-13]



Scheme 3

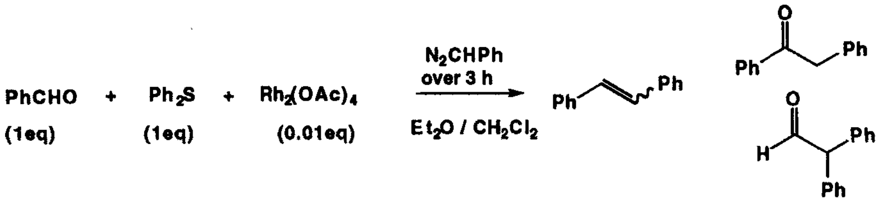
Results

Several potential problems with Scheme 3 were immediately apparent. Diazo compounds react directly with aldehydes to give homologated products[14-16] and a particular problem associated with phenyl diazomethane is its ready dimerisation in the presence of rhodium acetate (Scheme 4).[17,18] To minimise these potential side reactions we needed to keep the concentration of phenyl diazomethane low and this was achieved by slow addition.



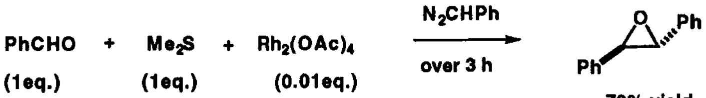
Scheme 4

In our preliminary experiments we used benzaldehyde, diphenyl sulfide, rhodium acetate and phenyl diazomethane (equation 1) but the main product isolated was stilbene with only traces of homologated products. The trace amounts of homologated products showed that the direct reaction of phenyl diazomethane with aldehydes was not a serious problem in the cycle. However, the formation of large amounts of stilbene showed that the metallocarbene reacted faster with phenyl diazomethane than with diphenyl sulfide.



Eq. 1

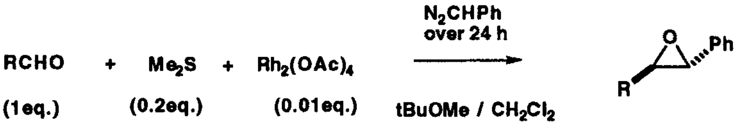
To enhance the rate of reaction between the metallocarbene and sulfide, we required a more nucleophilic sulfide and so changed from diphenyl sulfide to dimethyl sulfide. Under these conditions, no stilbene was formed, only epoxide. The reaction worked for both aromatic and aliphatic aldehydes. Reactions with aliphatic aldehydes usually gave mixtures of *trans* and *cis* epoxides whilst aromatic aldehydes gave the *trans* epoxide predominantly.



70% yield

	(trans:cis)
p-NO$_2$C$_6$H$_4$CHO	62% (100:0)
C$_6$H$_{11}$CHO	66% (79:21)
C$_5$H$_{11}$CHO	55% (56:44)

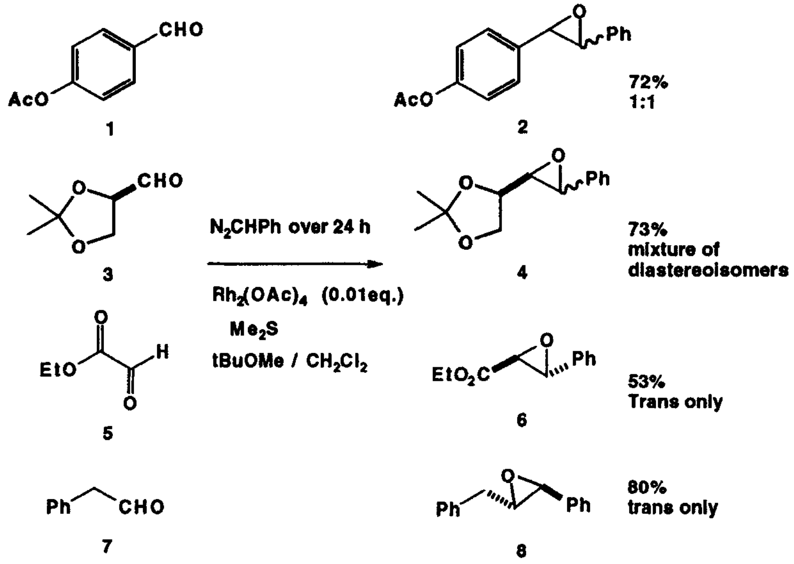
Attempts to use catalytic amounts of sulfides were initially unsuccessful. Reduced amounts of sulfides gave reduced amounts of epoxides and this indicated that the sulfide was being held up in the catalytic cycle from either a slow rate of reaction between the semi-stabilised ylide and the aldehyde or slow rate of decomposition of the betaine to give the aldehyde. In order to give the reaction more time to go to completion, we added the phenyl diazomethane over 24 hours instead of 3 hours and now good yields of epoxides were obtained with just 0.2 equivalents of dimethyl sulfide. Again both aliphatic and aromatic aldehydes worked well. We have therefore achieved catalytic



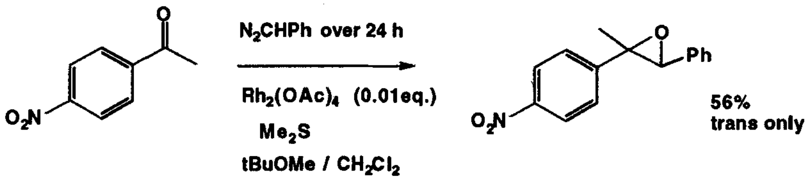
PhCHO	74% (88:12)
p-NO$_2$C$_6$H$_4$CHO	89% (100:0)
C$_6$H$_{11}$CHO	51% (79:21)
C$_5$H$_{11}$CHO	45% (56:44)

sulfur ylide chemistry.[19]

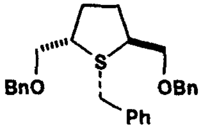
An additional advantage of our catalytic cycle is that the epoxidation process is being conducted under neutral conditions and this allows us to carry out chemistry not possible with current technology. The sensitive aldehydes (**1, 3, 5, 7**) work well in the catalytic cycle.



p-Acetoxy benzaldehyde **1** gave a 72% yield of epoxide **2**. Under traditional sulfur ylide chemistry, the sensitive acetoxy group would have been hydrolysed. Chiral aldehyde **3** gave epoxide **4** as a mixture of diastereoisomers but without racemisation. Glyoxylates are sensitive compounds but were effective substrates in our catalytic cycle giving epoxide **6** in good yield. Phenyl acetaldehyde **7**, an aldehyde particularly prone to enolisation, gave a good yield of the corresponding epoxide **8**. Evidently, the series of chemical reactions occurring in our catalytic cycle are tolerant of many functional groups. Reactions with ketones at room temperature are limited to reactive ketones due to the low nucleophilicity of the sulfur ylide we have used. p-Nitroacetophenone works well but at room temperature acetophenone did not give any epoxide.

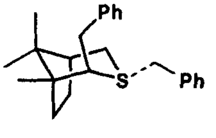


Having achieved catalytic sulfur ylide chemistry we sought to introduce asymmetry into the cycle. There are numerous examples of the use of chiral sulfonium salts for asymmetric epoxidation[5] and some of them (**9**,[7] **10**,[8] **11**,[9,10] **12**[8]) are shown below with yields and enantioselectivities for reactions of their corresponding benzyl sulfonium salts with benzaldehyde. Sulfide **10** gives the highest enantioselectivity and was therefore selected for inclusion in the catalytic cycle. This was prepared according to the method of Durst.[8] In the process of preparing **10**, some of the intermediate **12** was retained for testing in the catalytic cycle. Both sulfides had been used by Durst for asymmetric epoxidation.



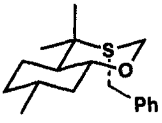
9

53%, 60%ee



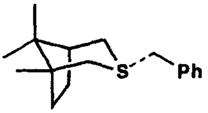
10

38%, >96%ee



11

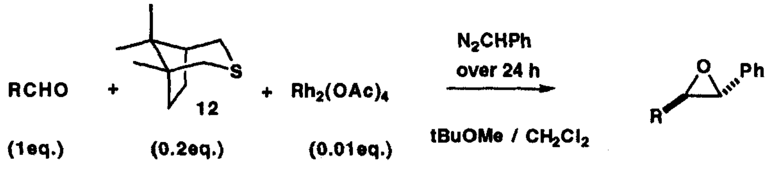
80%, 72%ee



12

39%, 15%ee

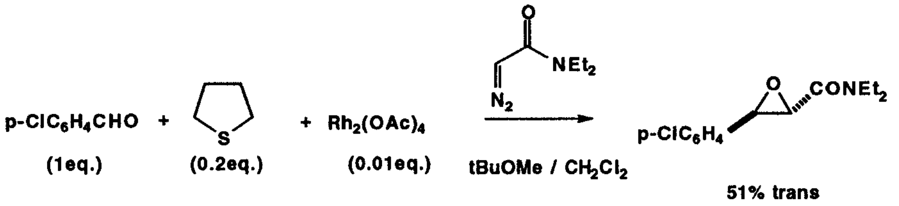
Using only catalytic quantities of **12**, we obtained significantly higher yields of epoxides with similar levels of enantioselectivity to that reported by Durst using traditional sulfur ylide chemistry (equation 2).[19] However, use of the sterically more hindered sulfide **10** led only to stilbene. This indicated that the reaction between the rhodium carbene and the sulfide is very sensitive to sterics and further work is under way to solve this problem of reactivity. Nevertheless we have demonstrated a process for catalytic asymmetric epoxidation.



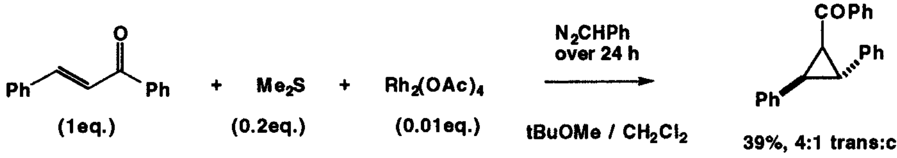
Eq. 2

PhCHO	58% (86:14) 11%ee
p-ClC$_6$H$_4$CHO	62% (82:18) 11%ee

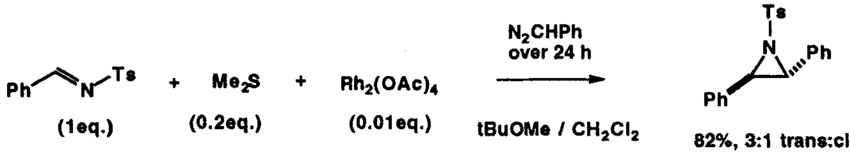
We have probed the scope of this reaction. Variation in the structure of the diazocompound has been investigated. Substitution of phenyl diazomethane by diazomethane was unsuccessful presumably because metal catalysed dimerisation competed too effectively. Substitution of phenyl diazomethane by ethyl diazoacetate would not work because the intermediate sulfur ylide is too stabilised and does not react with simple aldehydes.[20] Substitution of phenyl diazomethane by N,N-diethyl diazoacetamide was successful and epoxy amides were obtained by this method. It is known that sulfur ylides stabilised by amide groups do react with aldehydes.[21,22]



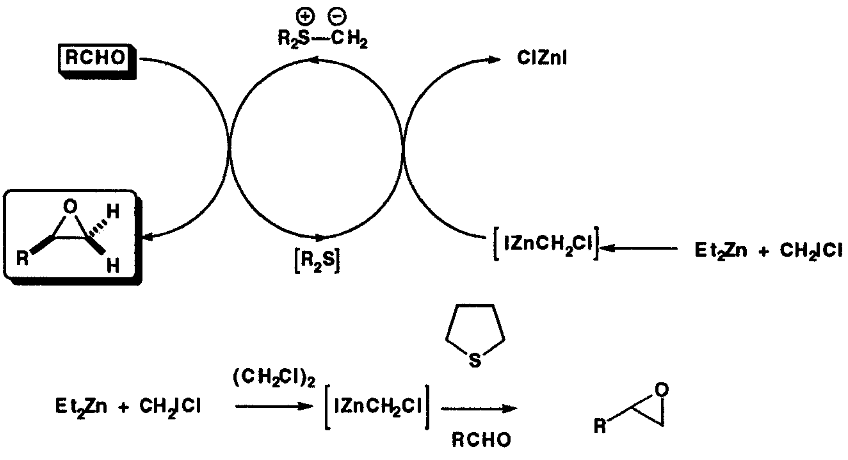
It is known that stabilised sulfur ylides react with enones to give cyclopropanes[23] and we were interested to determine whether the catalytic cycle could be applied to cyclopropanations. We replaced the aldehyde for an enone and were very gratified to find that it did and moderate yields of the corresponding cyclopropane were obtained with only catalytic amounts of sulfides. We are currently working on the use of chiral sulfides in this catalytic cycle. Such cyclopropanation reactions are noteworthy in that they complement existing processes. Asymmetric cyclopropanations have been conducted on electron donating alkenes;[24] none have been conducted on electron deficient alkenes. Our cyclopropanation reactions only work on electron deficient alkenes.



Finally, we have investigated the use of our catalytic cycle for the synthesis of aziridines. There are several reports on the reaction between sulfur ylides and imines to give aziridines and in general electron withdrawing groups are required on the imine nitrogen to achieve good results.[25-27] Nevertheless, often mediocre yields of products are obtained, presumably because the reactions are often conducted in the presence of aqueous base and competing hydrolysis of the imine occurs. As our catalytic cycle operates under neutral conditions we were optimistic that it would give higher yields of aziridines. We replaced benzaldehyde with the corresponding tosylimine, carried out the catalytic cycle as described previously and obtained high yields of the corresponding aziridines as a mixture of *cis* and *trans* isomers. Even with catalytic amounts of sulfides high yields of the product aziridines were obtained.



In the work described so far, we have discovered a novel catalytic cycle for epoxidation, cyclopropanation, and aziridination but the chemistry is limited by the class of diazocompounds that will give sulfur ylides. Phenyl diazocompounds, and diazoacetamides worked well but diazomethane did not. We have addressed this problem. Diazocompounds in conjunction with metal catalysts are used for cyclopropanation and we have found that the same system can also be used for sulfur ylide formation. In considering alternative methods for formation of the sulfur ylides we considered the use of alternative methods in cyclopropanation and were attracted by the Simmons Smith reaction.[28] We took diethyl zinc, chloroiodomethane, dimethyl sulfide and an aldehyde and obtained epoxides in very high yield. This chemistry was applied to a range of aldehydes and high yields of terminal epoxides were obtained in each case



R	yield
Ph	92%
$pNO_2C_6H_4$	95%
$pClC_6H_4$	65%
cyclo-C_6H_{11}	60%

Scheme 5

(Scheme 5). This method is potentially even more versatile than the former method due to the greater availability of the carbene precursors. Furthermore, the zinc chemistry complements the diazo chemistry as diazoacetamides are stable organic compounds whereas 1,1-diiodoacetamides are much less stable and diazoalkanes are not suitable for ylide formation whereas diiodoalkanes are.

Conclusion

A novel catalytic cycle for asymmetric epoxidation has been developed using catalytic amounts of a chiral sulfide and rhodium acetate, and stoichiometric amounts of an aldehyde and diazocompound. Key to the success of this catalytic cycle is slow addition of the diazocompound to the reaction mixture to allow turnover of the sulfide and to avoid competitive side reactions, and the use of unhindered, nucleophilic sulfides. The catalytic cycle can be extended to the synthesis of cyclopropanes and aziridines by substituting the aldehyde for an enone or imine. For the preparation of terminal epoxides, diazomethane could not be used. Instead, it was discovered that terminal epoxides could be prepared using diethyl zinc, chloroiodomethane, dimethyl sulfide and an aldehyde. A second catalytic cycle for epoxidation has therefore been developed.

Acknowledgements We thank ZENECA FCMO, DTI (Department of Trade and Industry), and EPSRC (Engineering and Physical Sciences Research Council) for post-doctoral support (HAR) through the LINK- asymmetric synthesis program, ZENECA FCMO and Sheffield University for a PhD studentship (AT) and Sheffield University (BM) for a one year studentship.

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