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# Novel Catalytic Cycle for the Synthesis of Epoxides from Aldehydes and Sulfur Ylides Mediated by Catalytic Quantities of Sulfides and $Rh_2(OAc)_4$

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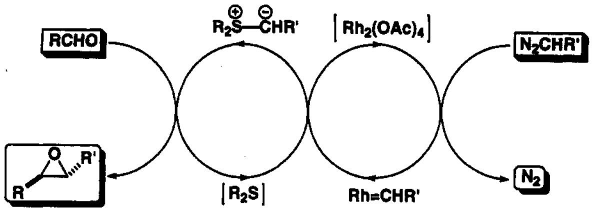
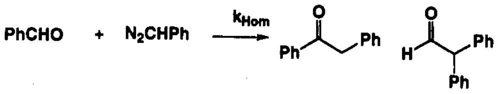
Over 30 years have passed since sulfur ylides were first reported to react with aldehydes and ketones to furnish epoxides.[1] Since then this reaction has found widespread use not only in epoxide synthesis[2] but also in the preparation of cyclopropanes[3] and to a lesser extent in the synthesis of aziridines.[4] In attempts to prepare nonracemic epoxides, reactions of homochiral sulfur ylides with carbonyl compounds have been studied and good enantioselectivities are beginning to emerge.[5] Invariably stoichiometric amounts of the homochiral sulfide precursor are required.[6] This is because this process of epoxidation involves two steps: firstly alkylation of a sulfide and isolation of the sulfonium salt, followed in a second step by treatment with base in the presence of a carbonyl compound. We are attempting to develop a catalytic cycle for the preparation of epoxides using only catalytic quantities of sulfides. Realizing that the slowest step in the above process for epoxidation is probably the rate of alkylation of the sulfide, we have sought other methods for sulfur ylide generation. One possibility is to react sulfides with diazo compounds in the presence of appropriate metal catalysts, and this method offers several advantages.[7] Firstly, the conventional two-step sequence for ylide formation is reduced to one step, and secondly, the reaction occurs under neutral conditions. The metal-catalyzed decomposition of diazo compounds in the presence of sulfides has often been used to prepare unsaturated sulfur ylides, which can then undergo [2,3] sigmatropic rearrangements.[8] This method has never been used to generate sulfur ylides in the presence of carbonyl compounds. Our aim was to try to develop a catalytic cycle in which sulfides were reacted with diazo compounds to give sulfur ylides, which then reacted with carbonyl compounds to give epoxides. The regenerated sulfide may then continue the process as shown in Scheme 1. In this paper we report our success in achieving this catalytic process.

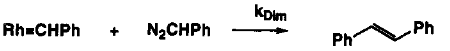
**Scheme 1**



We were aware that careful consideration would have to be given to the reaction conditions used to avoid potential competitive side reactions from mixing together an aldehyde, a sulfide, $Rh_2(OAc)_4$, and a diazo compound. For example, diazo compounds are well-known to react with carbonyl compounds directly to give homologated products[9] (eq 1), and diazo compounds are known to dimerize in the presence of metal salts[10] (eq 2). To minimize the extent of these potential side reactions we needed to maintain a low concentration of the diazo compound, and this can be achieved by slow addition.



(1)



(2)

Due to its greater stability[11] compared to alkyldiazo compounds we chose to work with $PhCHN_2$ and to use initially diphenyl sulfide (a nonvolatile sulfide) and benzaldehyde in the catalytic cycle. Thus, $PhCHN_2$ was added, over 3 h, to a solution of the above reagents, but the only product isolated was stilbene. This showed that reaction of the intermediate metallocarbene with $PhCHN_2$ ($k_{Dim}$) was faster than reaction of the metallocarbene with the sulfide. To improve the rate of the latter reaction we required a more nucleophilic sulfide.[12] We therefore repeated the above reaction using dimethyl sulfide in place of diphenyl

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(6) In one exceptional case, Furukawa (ref 5a) has carried out the whole process in one pot using 0.5 equiv of sulfide in the presence of an alkyl halide, base, and aldehyde to give epoxides. However, the yields of the product epoxides obtained are very low, and he acknowledges that his method is not a good one for the preparation of epoxides.

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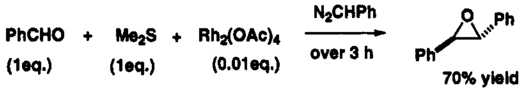
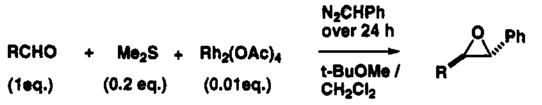
sulfide (eq 3), and this time stilbene oxide was obtained in good yield. Other aromatic and aliphatic aldehydes also worked well, giving good yields of epoxides. Reactions with aliphatic aldehydes gave mixtures of *trans*- and *cis*-epoxides. These results showed for the first time that under our carefully chosen conditions epoxides could be formed from diazo compounds and aldehydes with minimal interference from alternative potential side reactions. Without $Rh_2(OAc)_4$ only homologated products were obtained, showing that ylide formation required metal catalysis.



(3)

| R | Yield (trans:cis) |
|---|---|
| p-$NO_2C_6H_4CHO$ | 62% (100:0) |
| $C_6H_{11}CHO$ | 66% (56:44) |
| $C_5H_{11}CHO$ | 55% (79:21) |

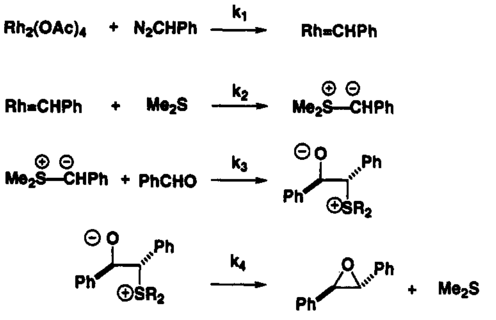
Attempts to use catalytic quantities of dimethyl sulfide (0.2 molar equiv) gave reduced yields of epoxides together with stilbene and homologated products. Reasoning that the sulfide was being "held up" in the catalytic cycle at either the sulfur ylide stage (slow $k_3$, eq 7) or at the betaine stage (slow $k_4$, eq 8), we decided to add the diazo compound over 24 h. Under these conditions[13] good yields of epoxides were obtained for both aromatic and aliphatic aldehydes (eq 4).



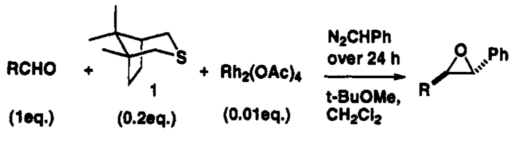
(4)

| R | Yield (trans:cis) |
|---|---|
| Ph | 74% (88:12) |
| p-$ClC_6H_4$ | 76% (80:20) |
| p-$NO_2C_6H_4$ | 89% (100:0) |
| $C_6H_{11}$ | 51% (56:44) |
| $C_5H_{11}$ | 45% (79:21) |

The success of our catalytic cycle relies on the reactions represented in eqs 5–8 occurring at a significantly faster rate than the potential side reactions represented in eq 1 and 2. Having achieved the major goal of obtaining turnover in epoxide formation, we turned our attention to the use of homochiral sulfides in the catalytic cycle. We decided to prepare sulfide **1**,[5c] a compound which Durst had converted to the sulfonium salt and reacted with benzaldehyde under basic conditions to furnish nonracemic epoxides.[14] Using *only 0.2 equiv* of the homochiral sulfide **1** in our catalytic cycle (eq 9), higher yields of the epoxides were obtained compared to the standard stoichiometric sulfur ylide process[14] and with similar levels of enantioselectivity.[14,5c]



(5)
(6)
(7)
(8)



(9)

| | | | |
|---|---|---|---|
| PhCHO | 58% | (86:14) | 11%ee |
| p-$ClC_6H_4CHO$ | 62% | (82:18) | 11%ee |

In summary, this communication describes the first *catalytic cycle for the synthesis of nonracemic epoxides from carbonyl compounds* and carbenoids using *catalytic quantities of sulfides and catalytic quantities of $Rh_2(OAc)_4$* and operating under *neutral conditions*. We are currently exploring the use of other homochiral sulfides for use in the catalytic cycle.

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(12) Trost has also observed that diaryl sulfides are significantly less nucleophilic than dialkyl sulfides: Trost, B. M.; Bogdanowicz, M. J. *J. Am. Chem. Soc.* **1973**, *95*, 5298.

(13) The diazo compound (1 μmol) was added in *t*-BuOMe rather than $Et_2O$ to avoid problems with solvent evaporation. The following general procedure was used in all of the reactions: To a stirred solution of dimethyl sulfide (0.2 mmol), rhodium(II) acetate (0.01 mmol), and the aldehyde (1 mmol) in dichloromethane (4 mL) was added a solution of phenyldiazomethane (2 mmol in 6 mL of *tert*-butyl methyl ether) at room temperature over a period of 24 h *via* a syringe pump. After the addition was complete, the solvent was removed *in vacuo* and the residue was chromatographed on flash silica using dichloromethane/petroleum ether (60–80 °C) (2:3) as eluent.

(14) Sulfide **1** was converted to the benzylsulfonium salt and reacted with benzaldehyde (see ref 5c) under the standard stoichiometric sulfur ylide conditions, giving *trans*-stilbene oxide (39% yield, 15% ee) and *cis*-stilbene oxide (15% yield) (see ref 5c). Yields are for the reaction of the sulfonium salt with the aldehyde and do not include the yields obtained in sulfonium salt formation. We have found that alkylation of sulfides with silver salts and halides can be a capricious reaction. The different *trans*:*cis* ratios observed in Durst's work and our own are probably due to the different reaction conditions employed. From further studies of our own we have found that benzylsulfonium ylides react reversibly with aromatic aldehydes but that the extent of reversibility is solvent dependent.