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A Novel Procedure for the Synthesis of Epoxides: Application of Simmons−Smith Reagents toward Epoxidation

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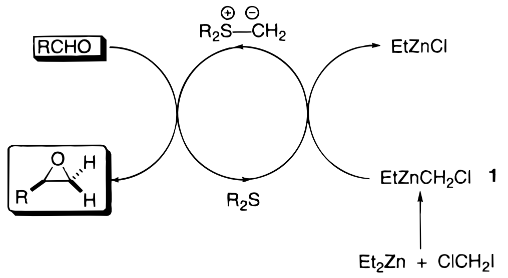
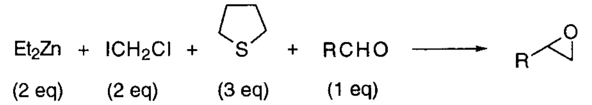
The Simmons−Smith reaction[1] and recent modifications[2] thereof has emerged as a powerful method for the diastereo-[3] and enantioselective cyclopropanation of alkenes.[4] In view of their effectiveness as cyclopropanating agents, it was surprising that Simmons−Smith reagents had not been exploited further in organic synthesis.[5] Motivated by this, and by our interest in catalytic asymmetric epoxidation,[6,7] we initiated a program focused toward the use of Simmons−Smith reagents for the synthesis of epoxides, and in this paper we report our success in achieving this goal (Scheme 1).

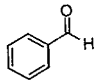
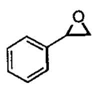
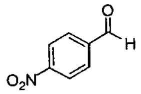
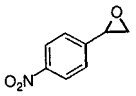
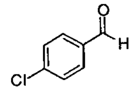
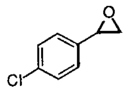
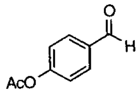
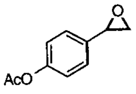
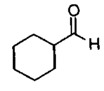
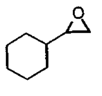
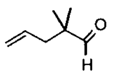
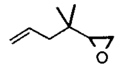
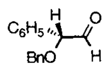
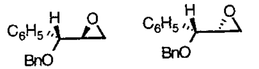
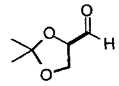
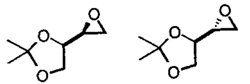
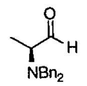
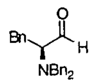
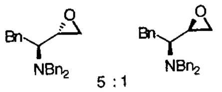
Scheme 1. Application of Organozinc Reagents toward Epoxidation



We were intrigued by the possibility that Simmons−Smith reagents could react with sulfides to generate ylides (Scheme 1).[8,9] These zinc-derived sulfur ylides could then be used to generate epoxides from aldehydes and might offer a more attractive alternative to the more traditional routes to sulfur ylides, in terms of enhanced chemoselectivity, stereoselectivity and milder reaction conditions. A major concern, however, was whether the sensitive epoxides would be compatibile with the reaction conditions, in particular, whether they would survive in the presence of EtZnCl, a potential Lewis acid.

Table 1. Organozinc-Mediated Epoxidation Reactions of Aldehydes



Entry	Substrate	Product(s)[a]	% Yield[b]
1			74
2			95
3			65
4			58
5			60
6			70
7		 2 : 1	72
8		 1 : 1	71
9		 5 : 1	85
10		 5 : 1	84

[a] Product ratios are based on analysis by gas chromatography and/or ^{1}H NMR. [b] Yields refer to isolated products.

Initially, we decided to investigate the reaction of zinc carbenoids derived from Et_2Zn and $ClCH_2I$ (e.g., $EtZnCH_2Cl$ **1**, Scheme 1) with sulfides. Such species are implied intermediates in the generation of active zinc carbenoids by the Furukawa protocol[3] and have been the subject of recent structural investigation.[10] We treated an aldehyde with Et_2Zn, $ClCH_2I$ (this is higher yielding than CH_2I_2[11]), and tetrahydrothiophene and were pleased to obtain epoxide in high yield (Table 1).[12] Aromatic and aliphatic aldehydes worked well, and the reaction even tolerated

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unsaturated aldehydes (entry 6) without undergoing cyclopropanation. This indicated that reaction of the zinc carbenoid with the sulfide was much more rapid than reaction with the alkene. α-Alkoxy (entries 7 and 8) and α-amino aldehydes (entries 9 and 10) also reacted smoothly, giving epoxides but as mixtures of diastereoisomers. In all cases, the diastereoselectivity was similar to that observed in reactions of trimethylsulfonium ylide with the aldehydes.[13] However, in no case was any racemization detected, whereas it has been reported that in the case of the aldehyde derived from phenylalanine substantial racemization occurs in the ylide epoxidation process.[14] The epoxide derived from phenylalanine (entry 10) is extremely important as it is a key intermediate in the syntheses of many HIV protease inhibitors.[14,15] The mild conditions reported here makes this method competitive with other literature methods.

In summary, we have developed a novel application of organozinc reagents toward the epoxidation of carbonyl compounds *via* the intermediacy of sulfur ylides. Ongoing studies include the design and synthesis of chiral sulfides for asymmetric epoxidation.

Acknowledgment. We thank Hesham Abdel Rahman for carrying out preliminary studies and the Engineering and Physical Sciences Research Council (EPSRC) for support.

Supporting Information Available: Experimental procedures, spectral data and methods for determination of enantiomeric excess of epoxides derived from chiral aldehydes (5 pages).

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(11) For comparative studies of the two reagents in cyclopropanation see: Denmark, S. E.; Edwards, J. P. *J. Org. Chem.* **1991**, *56*, 6974.

(12) Sample experimental details (Table 1, entry 1): **Styrene Oxide.** To a solution of diethyl zinc (1.82 mL of a 1.1 M solution in toluene, 2.0 mmol) in 1,2-dichloroethane (6 mL) was added chloroiodomethane (0.14 mL, 2.0 mmol) at −15 °C, under an atmosphere of nitrogen. The reaction mixture was stirred for 15 min before the addition of tetrahydrothiophene (0.26 mL, 3.0 mmol) and benzaldehyde (0.10 mL, 1.0 mmol). The reaction mixture was allowed to warm to ambient temperature and then stirred for 48 h. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with NH_4Cl (5 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by column chromatography (eluant: 10% EtOAc/Petrol) to afford *styrene oxide* as a colorless oil (78 mg, 74%): δ_H ($CDCl_3$) (250 MHz) 7.25 (5H, m), 3.85 (1H, dd $J =$ 4.5 Hz, 3.0 Hz, C*H*OCH$_2$), 3.30 (1H, dd, $J = 5.0$ Hz, 4.5 Hz, C*H*$_2$O), 2.85 (1H, dd, $J = 5.0$ Hz, 3.0 Hz, C*H*$_2$O).

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(14) Ng, J. S.; Przybyla, C. A.; Liu, C.; Yen, J. C.; Muellner, F. W.; Weyker, C. L. *Tetrahedron* **1995**, *51*, 6397. The α-alkoxy aldehyde (entry 7) is even more prone to racemization than the α-amino aldehyde (entry 10) but again none was detected.

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