Homochiral Group Transfer in Organic Synthesis *via* α-Diazocarbonyl Intermediates

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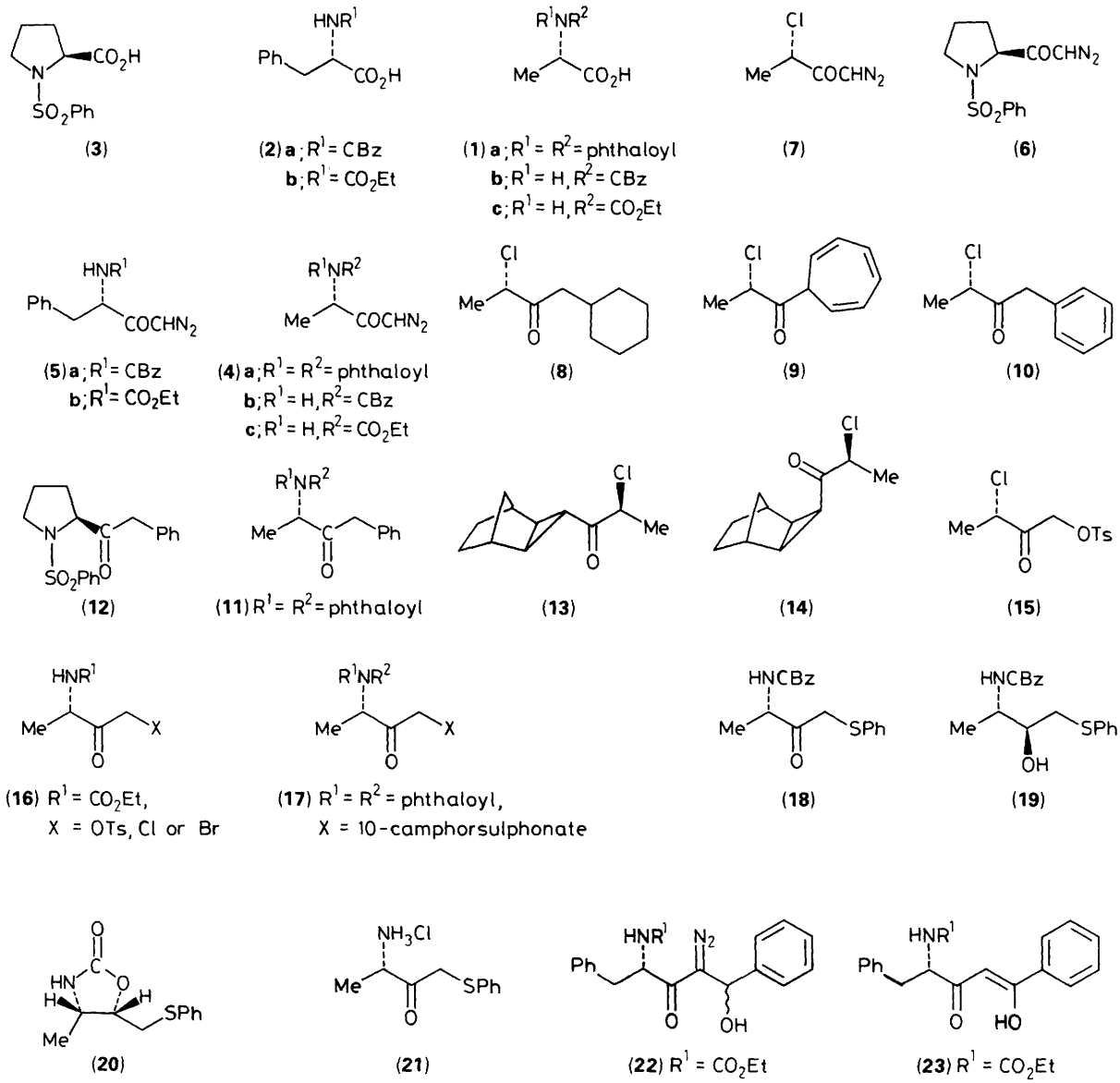
Optically active diazoketones derived from *N*-protected amino acids and (*S*)-2-chloropropionic acid have been used as homochiral group transfer reagents in the synthesis of various optically active α-functionalised ketones and related compounds.

In principle it should be possible to transfer a homochiral group to a substrate *via* diazoketone formation and decomposition using any of the many characteristic versions[1] of the latter such as cyclopropanation, C–H insertion, electrophilic aromatic substitution, aromatic cycloaddition, and αα-substitution. The recent report[2] of the use of a diazoketone derived from (*R*)-lactic acid to transfer a homochiral group to dibenzylphosphate prompts us to describe several new examples of the application of this group transfer technique to the synthesis of potentially useful homochiral molecules.



CBz = $PhCH_2OC(:O)$; Ts = $OSO_2C_6H_4Me$

Natural amino acids offer a ready entry into the homochiral diazoketone series. *N*-Protected L-alanine, L-phenylalanine, and L-proline (**1**)—(**3**) were prepared by standard procedures and transformed into diazoketones (**4**)—(**6**), respectively, in good yields *via* acyl chloride or mixed anhydride formation followed by exposure to ethereal diazomethane. In another series, (*S*)-(2)-chloropropionic acid was similarly transformed into diazoketone (**7**). NMR studies employing chiral shift reagents confirmed that diazoketone formation was racemization free. Metal catalysed and stoicheiometric modes of decomposition of these diazoketones were examined in the following areas.

(i) C–H insertion. Treatment of cyclohexane with (**7**) in the presence of a catalytic amount of rhodium(II) mandelate[3] led to smooth C–H insertion furnishing chloroketone (**8**) (60% yield), $[\alpha]_D^{20}$ −54.2° (*c* 7.00, CH_2Cl_2).

(ii) Aromatic cycloaddition. Diazoketone (**7**) reacted with benzene also under rhodium(II) catalysis yielding the unstable cycloheptatriene (**9**) which re-aromatised to benzyl chloroketone (**10**) (59%), $[\alpha]_D^{20}$ −18.2° (*c* 3.8, CH_2Cl_2), on standing or on brief exposure to trifluoroacetic acid. In a similar fashion, the alanine and proline derived diazoketones (**4a**) and (**6**) reacted catalytically with benzene to afford cycloheptatrienyl adducts which were readily rearranged into benzyl ketones (**11**) (55%), m.p. 89—91 °C, $[\alpha]_D^{20}$ −28.6° (*c* 10.0, CH_2Cl_2), and (**12**) (31%), m.p. 111—114 °C, $[\alpha]_D^{20}$ −152.1° (*c* 0.7, CH_2Cl_2), respectively.

(iii) Cyclopropanation. Several alkenes were successfully cyclopropanated with diazoketone (**7**) under rhodium(II) mandelate catalysis, the formation of chromatographically separable adducts, *exo-anti*-cyclopropane (**13**) (14%), $[\alpha]_D^{20}$ −25.0° (*c* 9.5, CH_2Cl_2), and *exo-syn*-cyclopropane (**14**) (36%), $[\alpha]_D^{20}$ −17.3 (*c* 4.8, CH_2Cl_2), from norbornene providing a typical example. We presumed at the inception of this study that rhodium(II) catalysed decomposition of diazoketones of type (**4**)—(**7**) would not compromise their homochirality and this could be confirmed by NMR chiral shift studies on the product (**11**) of the reaction of (**4a**), and of its racemate, with benzene.

(iv) αα-Substitution. This fourth process, in which nitrogen

is replaced by a new functional group, represents a particularly useful mode of diazoketone decomposition, offering a route to a variety of optically active α-functionalised ketones. For example, treatment of diazoketone (**7**) with toluene-*p*-sulphonic acid (1 equiv.) in diethyl ether at 20 °C furnished tosylate (**15**), m.p. 45.5—46.5 °C, $[\alpha]_D^{20}$ −43.1° (*c* 8.2, CH_2Cl_2). In the amino ketone series, treatment of diazoketone (**4c**) with toluene-*p*-sulphonic, hydrochloric, or hydrobromic acid produced the appropriate α-functionalised ketone (**16**). The absence of racemization in these reactions was inferred from the fact that reaction of diazoketone (**4a**) with (+)-camphorsulphonic acid gave a single diastereoisomeric sulphonate (**17**), whereas use of the (±)-diazoketone furnished a 50:50 mixture of diastereoisomers. αα-Substitution with thiophenol was also possible, though in this case rhodium(II) catalysis was required, a representative example being the conversion of diazoketone (**4b**) into α-(phenylthio)ketone (**18**), $[\alpha]_D^{20}$ −2.9(*c* 14, CH_2Cl_2) in 85% yield. Ketone (**18**) provides access to other homochiral intermediates. For example, reduction with baker's yeast furnished a single alcohol (**19**) (74%), m.p. 93 °C, $[\alpha]_D^{20}$ +3.6 (*c* 4.7, CH_2Cl_2) [$NaBH_4$ reduction afforded (**19**) and its epimer in a 70:30 ratio] whose stereochemistry was established by NMR analysis of the oxazolidone (**20**) produced on treatment with sodium hydroxide. Deprotection of (**18**) with hydrochloric acid yielded the crystalline aminoketone hydrochloride (**21**), m.p. 130—132 °C, $[\alpha]_D^{20}$ −5.95° (3.8, MeOH).

(v) β-Diketone formation. A final example illustrates the formation of a lithiated diazoketone and its conversion into an optically active β-dicarbonyl compound. Treatment of a mixture (1:4 molar ratio) of diazoketone (**5b**) and benzaldehyde in tetrahydrofuran at −100 °C with lithium di-isopropylamide (LDA) furnished a separable mixture of two diazoketols (**22**) (79%) which were readily rearranged by rhodium(II) acetate catalysis[4] into the same diketone (**23**) (69%), $[\alpha]_D^{20}$ −35.1° (*c* 10.6, $CHCl_3$).

We thank Glaxo Group Research Ltd. for a research studentship (to M. B. O'S.) and Dr. Peter Myers for valuable discussions. We are indebted to A. H. Marks and Co. Ltd. for the generous gift of (*R*)- and (*S*)-2-chloropropionic acid.

Received, 24th October 1989; Com. 9/04575I

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1 For a comprehensive survey of these reactions, see G. Maas, *Top. Curr. Chem.*, 1987, **137**, 75, and references therein.
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