

Asymmetric Synthesis of Substituted Chromanones *via* C–H Insertion Reactions of α -Diazoketones Catalysed by Homochiral Rhodium(II) Carboxylates

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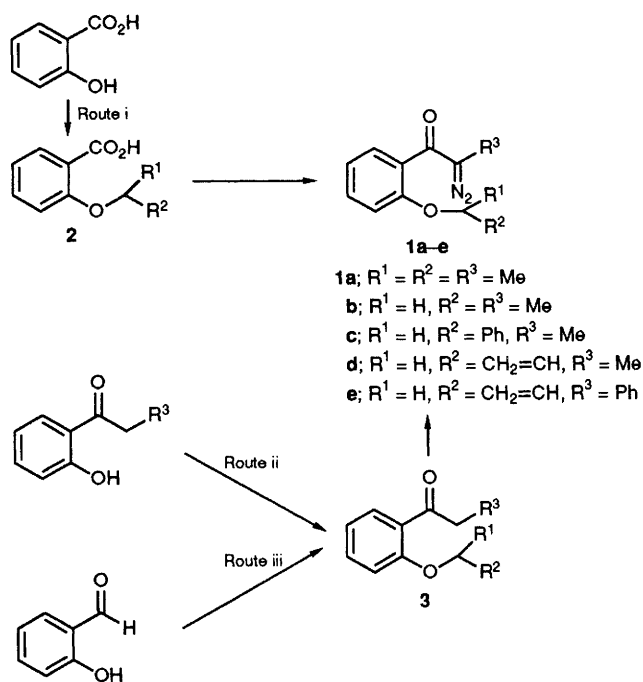
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High levels of regio-, stereo- and enantio-selectivity are achieved in the asymmetric synthesis of six-membered oxygen heterocycles *via* intramolecular C–H insertion reactions of α -diazoketones catalysed by chiral rhodium(II) carboxylates.

Of particular importance in catalytic synthesis employing diazocarbonyl intermediates are intramolecular processes involving cyclopropanation, C–H insertion and N–H insertion.^{1,2} Intramolecular N–H insertion has been applied very successfully to five-membered ring closures leading to carbapenems.² Carbocycle formation *via* C–H insertion shows a strong preference for five-membered rather than six-membered rings.^{2,3} In favourable cases asymmetric synthesis is observed when homochiral catalysts are used to decompose the α -diazocarbonyl precursors, notably high levels of enantioselection having been observed in γ -lactone formation *via* C–H insertion⁴ and in cyclopropanation.^{5–8} We now report the first examples of C–H insertion reactions leading to six-membered oxygen heterocycles from simple diazoketones and demonstrate that high levels of enantioselectivity can be obtained through the use of a homochiral rhodium(II) carboxylate catalyst.

Diazoketones **1a–e** were prepared from *ortho*-substituted phenols *via* the routes summarised in Scheme 1. In route i salicylic acid was alkylated on both oxygen groups with the appropriate alkyl bromide and potassium carbonate in acetone. Alkaline hydrolysis afforded the acid **2** which was then transformed into **1b,c** (overall yield for the four stages 50 and 35%, respectively) *via* acyl chloride formation followed by exposure to ethereal diazoethane. Route ii was used to convert *ortho*-hydroxypropiophenone into the *o*-alkyl derivatives **3** which were then transformed into diazoketones **1a** (29% yield) and **1d** (48% yield) *via* diazo transfer using mesyl azide. Salicylaldehyde served as the starting material for route iii, sequential alkylation with allyl bromide, addition of benzyl magnesium bromide and oxidation to ketone followed by diazo transfer, again with mesyl azide, to afford diazoketone **1e** (25% yield based on salicylaldehyde).

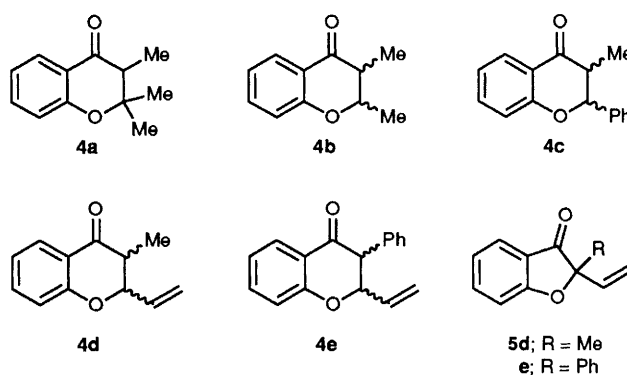
Decomposition of diazoketones **1a–e** was studied in di-



Scheme 1

chloromethane at 0, 20 and 40 °C using 1–2% by mass of rhodium(II) mandelate, rhodium(II) *N*-benzenesulfonyl-L-proline⁹ and Doyle's Rh^{III}-MEPY. [MEPY = methyl (*S*)-(–)-2-pyrrolidone-5-carboxylate].⁴ Exposure of **1a** to the proline catalyst at 0 °C furnished chromanone **4a** quantitatively, $[\alpha]_{\text{D}}^{15} +32.4$ (*c* 4.51, CH₂Cl₂), and subsequent studies established that the proline catalyst produced the highest enantioselectivities of the three catalysts studied. NMR chiral studies employing Eu(hfc)₃ {tris[(heptafluoropropylhydroxymethylene)camphorato]europium(III)} revealed that the enantiomer excess (e.e.) of **4a** was 70%. Cyclisation of ketones **1b** and **c** was conducted at 40 °C and was found to proceed quantitatively producing chromanones **4b** and **c**, respectively, in which the *cis*-isomer predominated to the extent of 75–80%. This *cis* isomers had e.e. values of 82 and 62%, respectively.

In a related series consisting of diazoketones **1d** and **e**, in which the ortho substituent bore an allyl group, cyclisation proceeded quantitatively and led predominately to the C–H insertion products **4d** and **e** (>90% from NMR spectroscopy)



along with some sigmatropic rearrangement leading to benzo-furanones **5d** and **e** (<10% from NMR spectroscopy). With rhodium(II) proline as the catalyst the former process predominated (*ca.* 97%) furnishing *cis* disubstituted chromanones (92%) of **4d** and 95% of **4e** ratio from NMR studies) with e.e. values of 79% in the case of **4d** and 45% in the case of **4e**. In conclusion, this study shows that catalysed C–H insertion reactions of ketocarbenoids can be extended easily to the construction of several chromanones, with in some instances, good levels of enantioselectivity.

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