Unprecedented catalytic enantioselective trapping of arene oxides with dialkylzinc reagents†

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Received (in Cambridge, UK) 24th September 2001, Accepted 30th October 2001
First published as an Advance Article on the web 15th November 2001

The first catalytic enantioselective trapping of symmetrical and racemic arene oxides with organometallic reagents is reported.

Arene oxide has been subjected to several studies since the demonstration that this class of compounds is formed from aromatic hydrocarbons by the microsomal enzyme fraction from mammalian liver.1 Much interest, therefore, has been generated concerning the solution chemistry of arene oxide. The nucelophilic utilities in these studies were in most cases heteronucleophiles such as water, alcohols, thiols and amines.2 There are only few reports dealing with ring-opening reactions of arene oxides carried out with organometallic reagents.2,3,4 Moreover, none of these procedures employing organometallic reagents are catalytic or enantioselective.

We herein report an unprecedented catalytic and enantioselective desymmetrization of symmetrical arene oxides 1a,b with hard alkylmetal, and a new, highly enantioselective RKR starting from the racemic arene oxide 8 (Schemes 1, 2 and 3).

Benzene oxide (1a) and indan-8,9-oxide (1b) were examined as symmetrical arene-oxide substrates (Schemes 1 and 2). Benzene oxide is known to exist in equilibrium with its tautomeric valence structure, the oxepin 1a’. This compound exists mainly as oxepin at room temperature, even if the oxide component 1a determines the reactions of the system with most agents.5

Table 1 Enantioselective trapping-ring-opening of benzene oxide 1a with R2Zn

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<tr>
<th>Entry</th>
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<th>Yield (%)</th>
<th>ee (%)</th>
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<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>Me</td>
<td>69:31</td>
<td>85</td>
<td>93</td>
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<tr>
<td>2</td>
<td>1a</td>
<td>Et</td>
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Conditions: all reactions were run in accordance with the typical procedure (see ref. 8). Yields are determined on the basis of weight.1 H NMR and GC analysis of the crude reaction mixture.5 Determined by GC on CSP.

Epoxide 1a was allowed to react at −78 °C (1 h, 95% conversion) with Me2Zn (1.5 equiv.) in the presence of a catalytic amount of Cu(OtBu)2 (0.015 equiv.) and the chiral ligand (R,R,R)-2 (0.030 equiv.) to give a crude reaction mixture consisting of the not previously synthesized regioisomeric dienols (15,6S)-3a (α-adduct) and 5a (γ-adduct) (entry 1, Table 1).6 The reaction with Et2Zn gave a slightly different result, with a predominance of the achiral γ-adduct 6a (entry 2, Table 1).7 The substituted enantioenriched dihydroaromatic α-adducts (15,6S)-3a (93% ee) and (15,6S)-4a (64% ee) were obtained with a complete anti-stereoselectivity.10

Indian 8-oxide (1b), containing a tetrasubstituted epoxide is known to exist only in the oxide form. The copper-phosphoramidite catalyzed allylic alkylation, pointing to reductive elimination as the regio- and stereo-determining step of the addition reaction.8,9 In this work we report an unprecedented catalytic and enantioselective desymmetrization of symmetrical arene oxides 1a,b with hard alkylmetal, and a new, highly enantioselective RKR starting from the racemic arene oxide 8 (Schemes 1, 2 and 3).

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equiv.) proceeded very cleanly to afford a 66:34 mixture of regioisomeric dihydronaphthols 9 (α-adduct) and 10 (α-adduct), the latter with a remarkable enantiopurity (>98% ee) (Scheme 3). On the other hand, the addition of Et2Zn to racemic 

In summary, the present work describes an unprecedented catalytic and enantioselective trapping of symmetrical and racemic arene oxides. This method offers a new route to enantioenriched dihydroaromatic alcohols, not easily accessible by means of other synthetic methods. An examination of the regiochemical outcome indicated that a 1,6-addition mode may be operative in a biased system such as indan 8,9-oxide for this particular kind of allylic alkylation.

We gratefully acknowledge funding by the MURST (Rome), the University of Pisa, and Merck (2000 ADP Chemistry Award to P. C.).

Notes and references
8 Typical procedure: a solution of Cu(OTf)2 (5.8 mg, 0.015 mmol) and 2 (16.2 mg, 0.03 mmol) in anhydrous toluene (2 ml) was stirred at room temperature for 40 min. The colorless solution was cooled to −78°C and subsequently added with a solution of arene oxide (1.0 mmol) and 1.5 mmol of R2Zn (solution in toluene). The reaction was followed by GC analysis and quenched with saturated aqueous NH4Cl (see the Supporting Information for further details). The conjugate γ-adducts 5a and 6a were obtained only in a mixture with regioisomeric α-adducts 3a and 4a. In our hands, it was not possible to isolate in a pure state the achiral γ-adducts 5a and 6a, or some simple derivatives of theirs, probably due to a rapid aromatization process.
9 The anti-stereochemistry of Sα was demonstrated by comparison with the product obtained by the addition of MeLi to benzene oxide 1a, a reaction that is known to proceed with syn-stereochemistry. 10 It is worthy of mention that all the corresponding “blank reactions”, performed on epoxides 1a,b and 8 in the same reaction conditions but in the absence of the chiral ligand (R,R,R)-2, afforded the corresponding rearranged phenols as the main product (phenol from 1a, 4-indanol from 1b, and 1-naphthol from 8).
12 The interconversion between the regioisomeric (α-allyl)copper(II) complexes of type 7A–C could be reasonably explained also by the intervention of suprafacial 1,3-shifts.
13 All the attempted analyses of the enantiopurity of alcohol 9 both by HPLC- and GC-CCSPs gave extensive decomposition of the compound. The absolute configuration of compound (1R,2R)-10 was demonstrated by a single crystal X-ray analysis after derivatization of the enantiomer (1S,2R)–10 with a chiral auxiliary derived from 4,5-dichlorophthalic acid and (1S,2R,R)-2,10-camphorsulfonic. Details of the procedure will be reported separately in a forthcoming paper.