Unprecedented catalytic enantioselective trapping of arene oxides with dialkylzinc reagents†

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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 nucleophiles utilized 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 oxide carried out with organometallic reagents.2,3

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 from each substrate enantiomer with a high ee. The RKR, a single chiral catalyst induces the formation of a distinct regioisomer from each substrate enantiomer with a high ee. The reaction with Et2Zn gave a slightly different result, with a predominance of the achiral α-oxidation (entry 1, Table 1).8 The reaction with Et2Zn gave a slightly different result, with a predominance of the achiral α-oxidation (entry 1, Table 1).8 The substituted enantiocentenedihydroaromatic α-adducts (15,65)-3a (93% ee) and (15,65)-4a (64% ee) were obtained with a complete anti-stereoselectivity.10

Indane-8,9-oxide (1b), containing a tetrasubstituted epoxide is known to exist only in the oxide form. The copper-phosphoramidite catalyzed addition of R2Zn at –78 °C to 1b (3 h, 95% conversion) gave a ca. 80:20 mixture of the corresponding α- and γ-adducts 3b:5b (R = Me) and 4b:6b (R = Et) (Scheme 2).11

It is remarkable that the α-adducts 3b (≥95% ee) and 4b exclusively derive from an anti-stereoselective 1,6-addition pathway (and therefore more appropriately called ε-adducts, Scheme 2). This unexpected regiochemical behavior could be of interest to gain further insight into the interconversion between the regioisomeric (α-allyl)coppper complex of type 7A–C that are formed during the oxidative step.15 Considering the conjugate nature of the starting epoxide, this interconversion between the regioisomeric (α-allyl)coppper complex of type 7A–C probably occurs by means of an intermediate delocalized (α-allyl)coppper complex species of type 7D.15 In this biad framework the attack at the tertiary carbon terminus of 7D to give 7B is not favourable for steric reasons, while the attack at the secondary terminus of 7D to give the (α-allyl)coppper complex 7C could be highly favoured. The subsequent rate limiting reductive elimination step on 7C affords the ε-adducts 3b,4b,15 (1,6-addition products), as observed.

Naphthalene 1,2-oxide (8) seems to exist only in the oxide form and it is very prone to spontaneous epoxide ring-opening and aromatization. Despite its extreme chemical reactivity, the addition of Et2Zn (1.5 equiv.) to racemic 8 in the presence of Cu(OtF)2 (0.015 equiv.) and chiral ligand (R,R,R)-2 (0.030

Scheme 1

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate R</th>
<th>Ratio α:γ</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>Me</td>
<td>69:31</td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td>1a</td>
<td>Et</td>
<td>38:62</td>
<td>88</td>
</tr>
</tbody>
</table>

†Electronic supplementary information (ESI) available: experimental details. See http://www.rsc.org/suppdata/cc/b1/b108541g/
equiv.) proceeded very cleanly to afford a 66:34 mixture of regioisomeric dihydroaromatic alcohols 9 (γ-adduct) and 10 (α-adduct), the latter with a remarkable enantioselectivity (>98% ee) (Scheme 3). On the other hand, the addition of Et₂Zn to racemic 8 catalyzed by a copper complex with the racemic ligand (S,S,S)(R,R,R)-2 afforded with almost complete (>96%) regioselectivity the racemic γ-adduct 9. A complete examination of these results clearly indicates that also arene oxide rac-8 exhibits a complementary enantiomer-dependent regioselectivity typical of a RRR process, in which the α-adduct 10 is obtained from the less reactive enantiomer (1S,2R)-8 of the racemic substrate, while the γ-adduct derives from the more reactive (1R,2S)-8.

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.

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Notes and references
8. Typical procedure: a solution of Cu(OTf)₂ (5.8 mg, 0.015 mmol) and 2 (10.2 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 additioned with a solution of arene oxide (1.0 mmol) in toluene (0.5 ml) 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).
9. 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.
10. The anti-stereochemistry of 3a 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-stereoselectivity.
11. 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).
13. The interconversion between the regioisomeric (α-allyl)copper(n) complexes of type 7A–C could be reasonably explained also by the intervention of suprafacial 1,3-shifts.
14. All the attempted analyses of the enantiopurity of alcohol 9 both by HPLC- and GC-6Ss gave extensive decomposition of the compound. The absolute configuration of compound (1R,2S)-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)−(−)−2,10-camphorsultam. Details of the procedure will be reported separately in a forthcoming paper.