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Unprecedented catalytic enantioselective trapping of arene oxides with dialkylzinc reagents†

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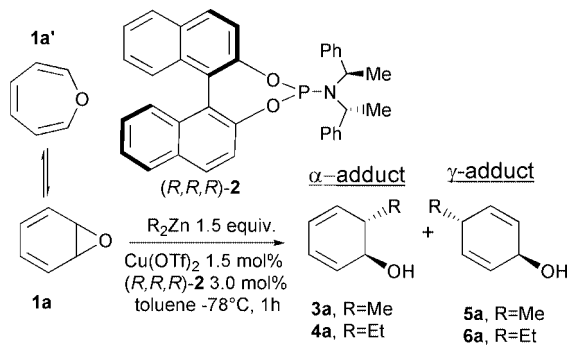
The first catalytic enantioselective trapping of symmetrical and racemic arene oxides with organometallic reagents is reported.

Arene oxide has been subjected to several studies since the demonstration that this class of compounds is formed from aromatic hydrocarbons by the microsomial 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.[2a,3] Moreover, none of these procedures employing organometallic reagents are catalytic or enantioselective.

We have recently reported a new kinetic resolution of cyclic vinyl oxiranes,[4] a desymmetrization of symmetrical methylidene cycloalkene oxides[5] and a new catalytic regiodivergent kinetic resolution (RKR)[6] based on dialkylzinc reagents and chiral copper complexes of phosporamidite ligands.[7] In the RKR, a single chiral catalyst induces the formation of a distinct regioisomer from each substrate enantiomer with a high ee. The procedure was useful to gain insight into the reaction mechanism of this particular kind of copper-catalyzed allylic alkylation, pointing to reductive elimination as the regio- and stereodetermining step of the addition reaction.

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.[3]



Scheme 1

† Electronic supplementary information (ESI) available: experimental details. See http://www.rsc.org/suppdata/cc/b1/b108541g/

Table 1 Enantioselective trapping-ring-opening of benzene oxide **1a** with R_2Zn[a]

Entry	Substrate	R	Ratio α:γ	Yield (%)[b]	ee (%)[c]
1	**1a**	Me	69:31	85	93
2	**1a**	Et	38:62	88	64

[a] *Conditions*: all reactions were run in accordance with the typical procedure (see ref. 8).[b] Yields are determined on the basis of weight, ^{1}H NMR and GC analysis of the crude reaction mixture.[c] Determined by GC on CSP.

Epoxide **1a** was allowed to react at −78 °C (1 h, 95% conversion) with Me_2Zn (1.5 equiv.) in the presence of a catalytic amount of $Cu(OTf)_2$ (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 (1*S*,6*S*)-**3a** (α-adduct) and **5a** (γ-adduct) (entry 1, Table 1).[8] The reaction with Et_2Zn gave a slightly different result, with a predominance of the achiral γ-adduct **6a** (entry 2, Table 1).[9] The substituted enantioenriched dihydroaromatic α-adducts (1*S*,6*S*)-**3a** (93% ee) and (1*S*,6*S*)-**4a** (64% ee) were obtained with a complete *anti* stereoselectivity.[10]

Indan 8,9-oxide (**1b**), containing a tetrasubstituted epoxide is known to exist only in the oxide form. The copper-phosphoramidite catalyzed addition of R_2Zn 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 (σ-allyl)copper(III) complexes of type **7A–C** that are formed during the oxidative step.[12] Considering the conjugate nature of the starting epoxide, this interconversion between the regioisomeric (σ-allyl)copper(III) complexes of type **7A–C** probably occurs by means of an intermediate delocalized (π-allyl)copper(III) species of type **7D**.[13] In this biased framework the attack at the tertiary carbon terminus atom of **7D** to give **7B** is not favourable for steric reasons, while the attack at the secondary terminus of **7D** to give the (σ-allyl)copper(III) complex **7C** could be highly favoured. The subsequent rate limiting reductive elimination step on **7C** affords the ε-adducts **3b,4b** (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 Et_2Zn (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

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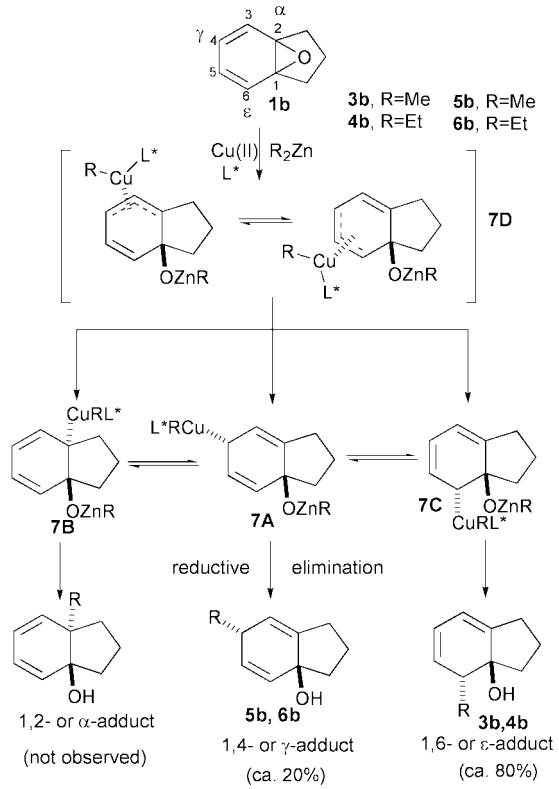
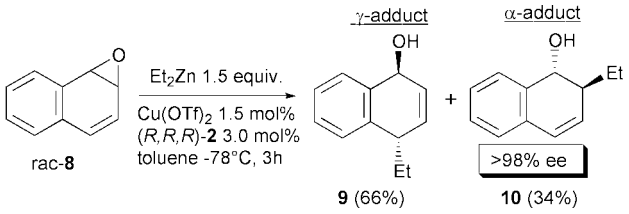


Scheme 2

equiv.) proceeded very cleanly to afford a 66:34 mixture of regioisomeric dihydronaphthols **9** (γ-adduct) and **10** (α-adduct), the latter with a remarkable enantioselectivity (>98% ee) (Scheme 3).[11,14] On the other hand, the addition of Et_2Zn 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 RKR process, in which the α-adduct **10** is obtained from the less reactive enantiomer (1*S*,2*R*)-**8** of the racemic substrate, while the γ-adduct derives from the more reactive (1*R*,2*S*)-**8**.[6,14]



Scheme 3

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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7 For an overview of phosphoramidite in catalytic asymmetric conjugate addition, see: B. L. Feringa, *Acc. Chem. Res.*, 2000, **33**, 346.

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 additioned with a solution of arene oxide (1.0 mmol) in toluene (0.5 ml) and 1.5 mmol of R_2Zn (solution in toluene). The reaction was followed by GC analysis and quenched with saturated aqueous NH_4Cl (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[2a].

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**).

12 For very recent experimental evidence supporting the intervention of Cu(III) intermediates, see: A. S. E. Karlström and J.-E. Bäckwall, *Chem. Eur. J.,* 2001, **7**, 1981 and references therein. Even if not indicated in Scheme 2 for the sake of simplicity, the copper(III) complexes **7A–D** are probably cationic species with OTf^- as a possible counterion.

13 The interconversion between the regioisomeric (σ-allyl)copper(III) 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-CSPs gave extensive decomposition of the compound. The absolute configuration of compound (1*R*,2*S*)-**10** was demonstrated by a single crystal X-ray analysis after derivatization of the enantiomer (1*S*,2*R*)-**10** with a chiral auxiliary derived from 4,5-dichlorophthalic acid and (1*S*,2*R*,4*R*)-(−)-2,10-camphorsultam. Details of the procedure will be reported separately in a forthcoming paper.