Enantioselective *ortho*-Hydroxyalkylation of Phenols promoted by Chiral Alkoxyaluminium Chlorides

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The asymmetric *ortho*-specific hydroxyalkylation of phenols with trichloroacetaldehyde in the presence of chiral alkoxyaluminium chlorides gives rise to optically active 2-(2,2,2-trichloro-1-hydroxyethyl)phenols, with good optical yields.

In a series of papers[1] we have described highly regioselective syntheses of *ortho*-substituted phenols using the reaction of non-transition metal phenolates with electrophilic compounds and we have assumed that chelate intermediates, involving both the metal phenolate and the reactant, provide regioselectivity by virtue of the proximity of the phenolic *ortho*-carbon to the electrophilic reaction centre.[2]

If such chelates are involved in the key step of the reaction, then stereoselective reactions could take place when suitable chiral auxiliaries are located at the metal centre. We have now obtained evidence for considerable enantiocontrol in hydroxyalkylation of phenols (**1**) with trichloroacetaldehyde (**2**)† by using chiral alkoxy(ethyl)aluminium chloride promoters (**3**)[4] (Scheme 1).

In a typical asymmetric reaction, a solution of phenoxy(menthoxy)aluminium chloride [**5**; X = H, R* = (−)-menthyl] (10 mmol) [prepared *in situ* from phenol (**1**; X = H) (10 mmol), (−)-menthol‡ (10 mmol), and diethylaluminium chloride (10 mmol)] and trichloroacetaldehyde (**2**) (10 mmol) in toluene (50 ml) was stirred at 25 °C for 24 h. Water was added, and the mixture was extracted with diethyl ether. Following silica gel chromatography (−)-2-(2,2,2-trichloro-1-hydroxyethyl)phenol (**4a**)§ (96%) was isolated as a colourless solid, m.p. 72—73 °C, $[\alpha]_{546}^{25}$ −35.9° (*c* 1.5, ethanol), corresponding to *ca.* 33% enantiomeric excess (e.e.).

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† A procedure for the synthesis of racemic 2-(2,2,2-trichloro-1-hydroxyethyl)phenols from aluminium phenolates and trichloroacetaldehyde has been reported (ref. 3).

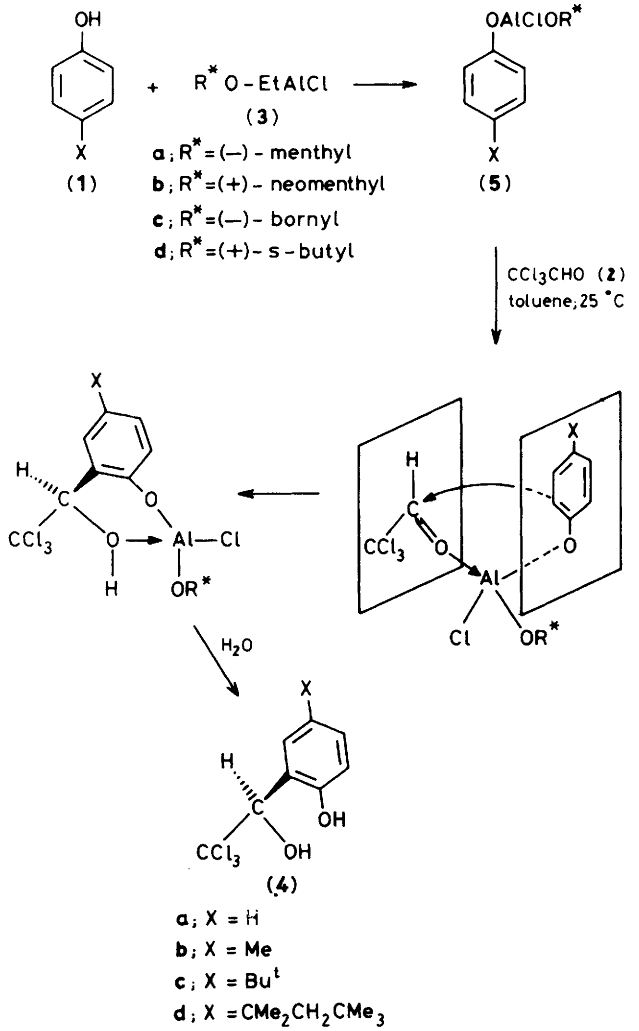
‡ The chiral alcohols in this study (commercially available) were: (−)-menthol, $[\alpha]_D^{20}$ −49°; (+)-neomenthol, $[\alpha]_D^{20}$ +20°; (−)-borneol, $[\alpha]_D^{20}$ −19°, (+)-butan-2-ol, $[\alpha]_D^{20}$ +13.5°.

§ The structures of the isolated products (**4a**—**d**) were confirmed by direct comparison with the corresponding racemic samples prepared by the method reported in ref. 3.

Table 1. Asymmetric hydroxyalkylation of phenols (**1**) in toluene with trichloroacetaldehyde (**2**) in the presence of R*OAlEtCl (**3**).[a]

Entry	X	Chiral promoter	Product	Yield [b] (%)	M.p. /°C	$[\alpha]_{546}$/° [c]	C.d.[d] $[\theta]$	E.e.[e] (%)
1	H	(**3a**)	(**4a**)	96	72—73	−35.9	−3441	32.7
2	Me	(**3a**)	(**4b**)	97	145—146	−37.9	−3400	49.5
3	Bu^t	(**3a**)	(**4c**)	98	109—110	−30.8	−3486	41.3
4	Oct[f]	(**3a**)	(**4d**)	95	110—111	−20.6	−2120	33.0
5	Me	(**3b**)	(**4b**)	75		+4.3	+410	6.2
6	Me	(**3c**)	(**4b**)	60		−1.2	−240	1.7
7	Me	(**3d**)	(**4b**)	70		0.0		0.0
8	Me	(**3a**)[g]	(**4b**)	85		−18.3	−1649	23.0
9	Me	(**3a**)[h]	(**4b**)	51		−7.1	−658	8.8
10	Me	(**3a**)[i]	(**4b**)	82		−22.5	−1970	29.0

[a] Conditions (unless otherwise stated): 25 ± 1 °C, 24 h; (**1**):(**3**) mole ratio, 1 : 1. [b] The yields quoted refer to chromatographically isolated products. [c] 25 ± 0.5 °C (*c* 1.5 in EtOH). [d] Circular dichroism (c.d.) of a 2×10^{-3} M solution in ethanol at 25 ± 0.5 °C [λ_{max} (**4a**) 279, (**4b**) 288, (**4c**) 285, (**4d**) 289 nm]. [e] The optical yields were determined by 270 MHz ^{1}H n.m.r. using tris[3-(heptafluoropropylhydroxymethylene)-(−)-camphorato]europium(III). [f] Oct = 1,1,3,3-tetramethylbutyl. [g] (**1**):(**3**) mole ratio, 1 : 0.5. [h] (**1**):(**3**) mole ratio, 1 : 0.2. [i] At 0 °C.



Scheme 1. Proposed reaction pathway (attack at chloral *re*-face depicted).

The phenol substituent and the chiral auxiliary in the chloroaluminium promoter (**3**) were varied as shown in Table 1.

Using (−)-menthoxy(ethyl)aluminium chloride (**3a**) (entries 1 to 4) all tested phenols gave rise to laevorotatory carbinols (**4a—d**) with 33—50% optical yields and ≥95% chemical yields. The reaction is slightly sensitive to the substituent bulkiness, but the requirements of the chiral alkoxy-moiety in (**3**) play a more important role. In contrast to the efficiency of the (−)-menthol catalyst (**3a**), the other alkoxides employed, *viz.* (+)-neomenthoxy- (**3b**), (−)-borneoxy- (**3c**), and (+)-s-butoxy-(ethyl)aluminium chloride (**3d**) (entries 5 to 7), gave inferior or no enantioselection. It is noteworthy, however, that the use of the (+)-neomenthol promoter (**3b**) resulted in production of dextrorotatory (**4b**) with the opposite absolute configuration to that of the usual product, (−)-(**4b**).

High yield and good enantioselectivity were always attained with the reagent prepared using a 1 : 1 ratio of (**1**) to (**3**), whereas use of the reagent made with less than the stoicheiometric ratio (entries 8 and 9) resulted in disappointingly low chemical and optical yields. Furthermore, decreasing the reaction temperature from 25 to 0 °C (entry 10) resulted in a slightly reduced optical yield.

The stereochemical behaviour of this *ortho*-specific alkylation of phenols with a prochiral carbonyl compound, promoted by chiral alkoxyaluminium chlorides, appears to be a general phenomenon. Initial experiments utilizing other aldehydes and α-ketoesters as hydroxyalkylating reactants show similar trends. We are currently testing other chiral metal alkoxides (*e.g.* Ti, Zn, and Mg).

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