Asymmetric Synthesis of the Enantiomers of the Diarylcarbinol (1*R*)- and (1*S*)-1-(1-Hydroxyphenylmethyl)-2-hydroxybenzene

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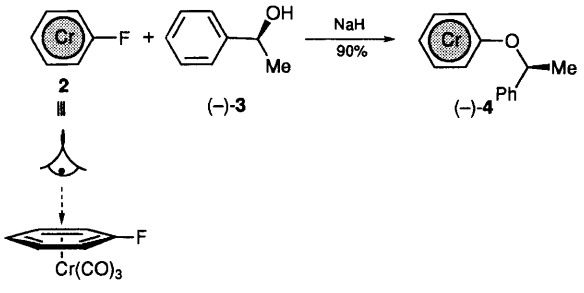
(1*S*)-1-Phenethyl(phenyl chromium tricarbonyl) ether (−)-**4** undergoes completely stereoselective *ortho*-deprotonation with the thus formed carbanion being converted by the complementary sequences, benzoylation/hydride reduction and formylation/PhMgBr addition, to generate after decomplexation and deprotection the homochiral diarylcarbinols (−)-(1*R*)- and (+)-(1*S*)-1-(1-hydroxyphenylmethyl)-2-hydroxybenzene **1**, respectively.

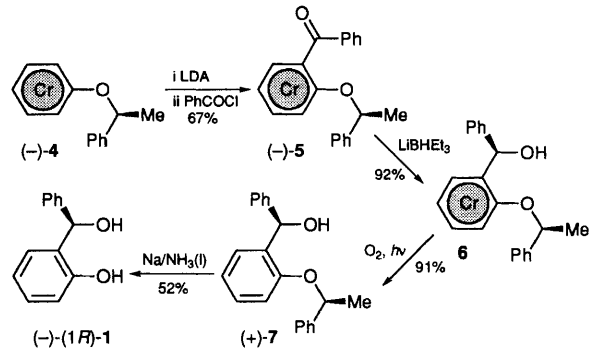
Attachment of a chromium tricarbonyl unit to an arene changes its chemical characteristics:[1] The ring proton acidities are enhanced and the complexed arene becomes susceptible to nucleophilic attack.[2] Furthermore 1,2-differentially substituted arene chromium tricarbonyl complexes are chiral and such complexes have been resolved by a variety of methods including the separation of diastereoisomers[3] and kinetic resolutions.[4] In this area, attention has recently been focused on the asymmetric synthesis of arene chromium tricarbonyl complexes *via* the diastereoselective *ortho*-substitution of a phenyl chromium tricarbonyl moiety attached to a chiral auxiliary,[5] and the *ortho*-deprotonation of an acetal derived from benzaldehyde chromium tricarbonyl by a homochiral lithium amide base.[6] We report herein a new auxiliary, derived from 1-phenethanol, for the diastereoselective *ortho*-lithiation of a complexed phenyl ring, which results in the highest diastereoselectivities to date, and its use in the asymmetric synthesis of the homochiral diarylcarbinols (1*R*)- and (1*S*)-1-(1-hydroxyphenylmethyl)-2-hydroxybenzene **1**. Diarylcarbinols are an important class of compounds[7] difficult to obtain in homochiral form by other methods.

The auxiliary 1-phenethyl was introduced *via* an *ipso*-substitution reaction between tricarbonyl (fluorobenzene) chromium **2** and phenethanol **3**. Treatment of **2** with the sodium salt of (−)-(1*S*)-1-phenethanol **3**, resulted in the formation of (1*S*)-1-phenethyl(phenyl chromium tricarbonyl) ether (−)-**4** {$[\alpha]_D^{24}$ −304.9 (*c* 0.30, CH_2Cl_2)} as a yellow crystalline material. The diastereotopic nature of the *ortho* protons in (−)-**4** was evidenced by their chemical shifts at δ_H 4.86 and 5.27.

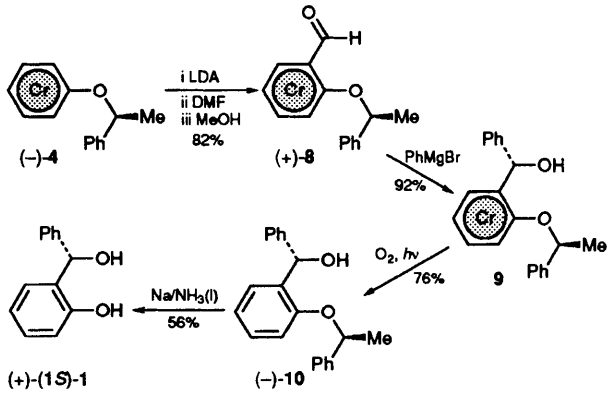


Deprotonation of (−)-**4** with lithium diisopropylamide (LDA, 1.5 equiv., −78 °C, THF) followed by quenching of the resultant anion with benzoyl chloride (5 equiv.) gave the red crystalline complex (−)-**5** {$[\alpha]_D^{25}$ −200.0 (*c* 0.26, CH_2Cl_2)} as a single diastereoisomer. ^{1}H NMR spectroscopic analysis of crude product **5** before purification was consistent with completely regio- and diastereo-selective deprotonation of **4** by LDA.

It has been established previously that *ortho*-substituted aldehydes and ketones undergo highly stereoselective addition reactions with nucleophiles approaching the unhindered face of the carbonyl, *anti* to the chromium tricarbonyl moiety, in the *anti* C=O to *ortho*-substituent, conformation.[4a,8] Thus superhydride® reduction (3.0 equiv., −78 °C, THF) of (−)-**5** gave the diarylcarbinol complex **6** completely stereoselectively. In the racemic series an X-ray crystal structure analysis established the relative configurations within (±)-**6** while the absolute configuration of **6** is assigned unambiguously from that of the starting (1*S*)-1-phenethanol. All attempts at removing the auxiliary while retaining the chromium tricarbonyl unit failed [H_2, 8 atm., Pd–C and Na/NH_3(l)] and therefore removal of the chromium tricarbonyl unit preceded removal of the auxiliary. Decomplexation (O_2, *hν*, Et_2O), generated (+)-**7** {$[\alpha]_D^{25}$ +153.6 (*c* = 0.13, CH_2Cl_2)} and removal of the auxiliary [Na/NH_3(l), −78C, 52%] gave (−)-1-[(1*R*)-1-hydroxyphenylmethyl]-2-hydroxybenzene **1** {$[\alpha]_D^{25}$ −35.13 (*c* 0.60, CH_2Cl_2)} which was confirmed to be homochiral (>98% ee) by ^{1}H NMR spectroscopic analysis upon comparison with authentic racemic (±)-**1** using (−)-(1*R*)-1-(9-anthryl)-2,2,2-trifluoroethanol as the chiral shift reagent.



Synthesis of (+)-(1*S*)-1-(1-hydroxyphenylmethyl)-2-hydroxybenzene **1** was then pursued, while still retaining (−)-(1*S*)-1-phenethanol as the source of the chiral auxiliary, *via* the complexed aldehyde (+)-**8**. Thus lithiation of (−)-**4** was carried out as before but quenched by the addition of dimethylformamide (DMF, 5.0 equiv.) to give (+)-**8** {$[\alpha]_D^{24}$ +641.7 (*c* 0.76, CH_2Cl_2)} as a single diastereoisomer. Addition of PhMgBr (4.0 equiv., −78 °C, THF) to the aldehyde complex (+)-**8** proceded completely stereoselectively to give the secondary alcohol **9** (92%), the epimer of **6**, as a single diastereoisomer, *vide supra*. Removal of the chromium tricarbonyl unit generated (−)-**10** {$[\alpha]_D^{25}$ −225.7 (*c* 0.21, CH_2Cl_2)} the epimer of (+)-**7** while subsequent removal of the



auxiliary, as before, gave homochiral (>98% ee) (+)-(1*S*)-**1** {$[\alpha]_D^{26}$ +36.1 (*c* 1.22, CH_2Cl_2)}.

Finally, deprotonation of **4** with LDA and quenching with benzaldehyde generated a 1:2 mixture of **6** and **9** indicating little selectivity in the formation of the benzylic stereogenic centre in this direct process.

In conclusion, the *O*-phenethyl chiral auxiliary in the complex **4** induces a completely stereoselective *ortho*-deprotonation reaction with LDA. The thus derived ketone **5** and aldehyde **8** undergo completely stereoselective hydride and Grignard additions respectively to generate, in a complementary fashion, following decomplexation and deprotection the homochiral diarylcarbinols (1*R*)- and (1*S*)-1-(1-hydroxyphenylmethyl)-2-hydroxybenzene **1**, respectively.

We thank the SERC for an earmarked studentship to W. E. H.

Received, 3rd November 1994; Com. 4/06729K

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