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Preliminary communication

Asymmetric synthesis of *R*-α-methyl-*o*-methoxybenzyl methyl ether via the diastereoselective functionalisation of (+)-(*o*-methoxybenzyl methyl ether)chromium tricarbonyl

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Abstract

α-Methylation of (+)-(*o*-methoxybenzyl methyl ether)$Cr(CO)_3$ occurs completely stereoselectively to yield, after decomplexation, homochiral *R*-α-methyl-*o*-methoxybenzyl methyl ether.

Deprotonations of (benzyl alkyl ether)$Cr(CO)_3$ complexes with butyllithium occur exclusively at the α-position to generate the corresponding lithio derivatives. These have been shown to react with a variety of electrophiles to give the α-alkylated complexes, with complete suppression of the Wittig rearrangement [1].

(Benzyl methyl ether)$Cr(CO)_3$ has enantiotopic α-protons, and so α-alkylation will give rise to a racemic mixture. However, if an *ortho* substituent is present, the two benzylic protons are rendered diastereotopic. Thus, deprotonation with a strong base followed by electrophilic quench could give rise to diastereoisomers. Of particular interest is (*o*-methoxybenzyl methyl ether)$Cr(CO)_3$, since in this complex deprotonation with strong bases could occur in the positions *ortho* to either substituent or at one of the two diastereotopic benzylic sites. Furthermore, if selective benzylic metallation was observed, opposing mechanisms involving either steric or chelation control could be suggested to account for any observed diastereoselectivity [2,3].

Treatment of a tetrahydrofuran solution of *o*-methoxybenzyl alcohol **1** with potassium hydride followed by methyl iodide gave *o*-methoxybenzyl methyl ether **2**. Thermolysis of chromium hexacarbonyl with arene **2** in a refluxing mixture of dibutyl ether/tetrahydrofuran (10/1), generated the corresponding chromium tricarbonyl complex **3** in good yield.

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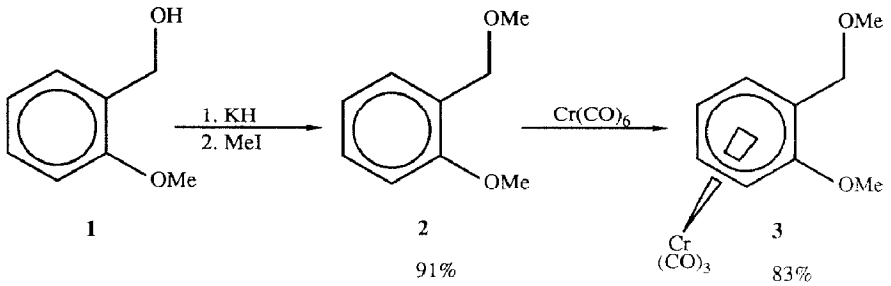
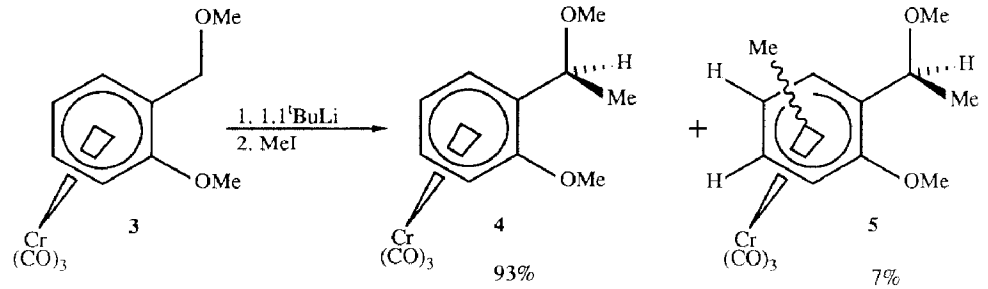
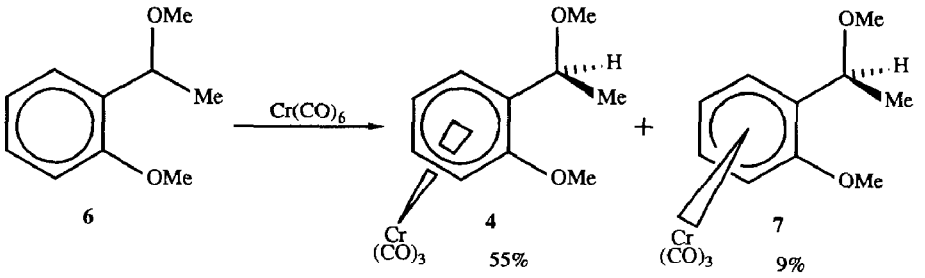


Metallation of complex **3** with 1.1 equivalents of t-butyllithium (−78°C, 2 h) in tetrahydrofuran solution gave, on addition of methyl iodide (−78°C, 2 h), a 13/1 mixture of a single monomethylated and a single dimethylated derivative **4** and **5** in quantitative yield. The ^{1}H NMR spectrum of complex **5** contained a multiplet splitting pattern characteristic of the three contiguous protons of a 1,2,3-trisubstituted arene confirming that the second methylation had occurred in a position *ortho* to one of the substituents. Fractional recrystallisation of the mixture gave complex **4** exclusively. The relative configuration within **4** was assigned as *RR*(*SS*) by a single crystal X-ray structure analysis [4]. The stereochemistry of product **4** is consistent with *exo* methylation of the configurationally stable [5] carbanion formed by the exclusive removal of the *exo* benzylic proton from conformations in which the benzyl methoxyl group lies *anti* to the *ortho* substituent. This rules out any cyclic lithium chelated intermediate.

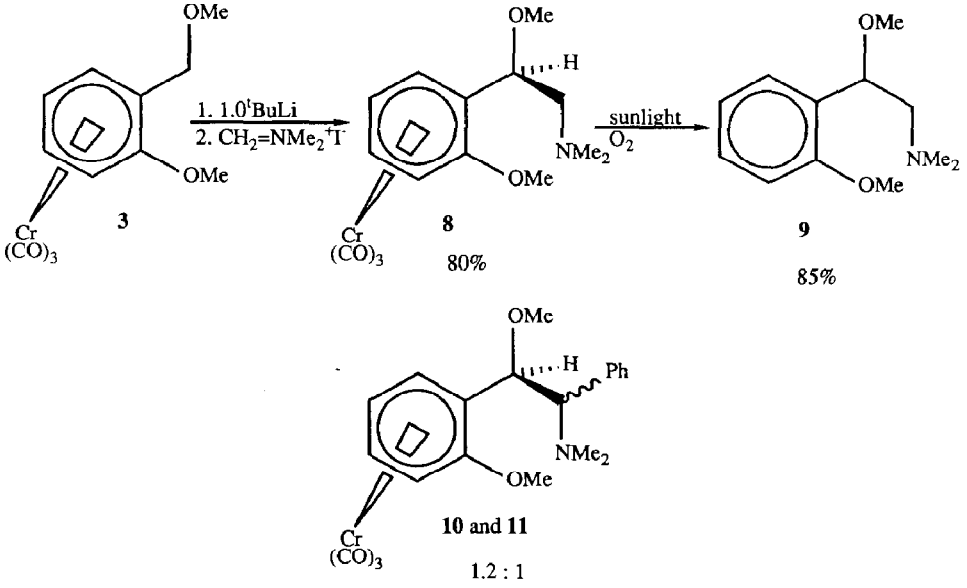


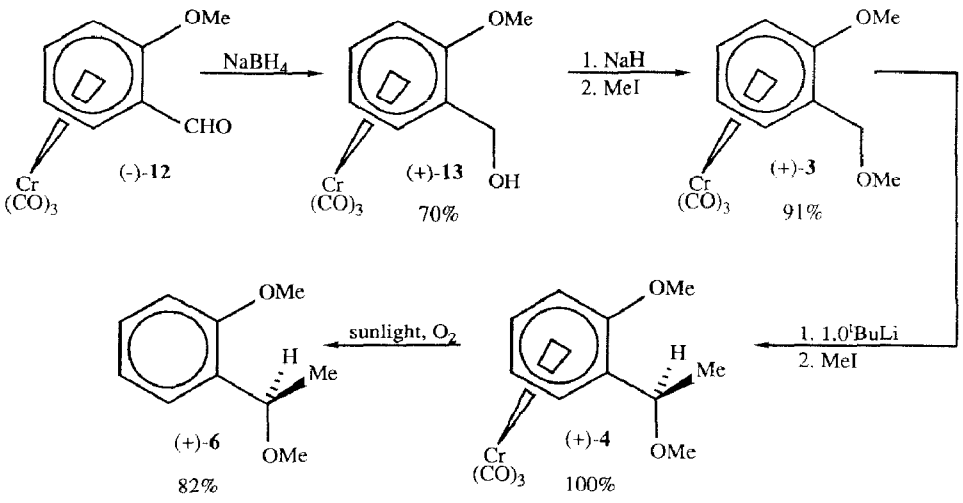
Decomplexation of **4** occurred on exposure of a diethyl ether solution to air and sunlight, to give the free racemic arene **6** in good yield. Complexation of the ether **6** with chromium hexacarbonyl gave a 6.5/1 mixture of the *RR*(*SS*) and *RS*(*SR*) diastereoisomers **4** and **7**, respectively, in good overall yield; the ^{1}H NMR spectrum of the major isomer being identical to that of diastereoisomerically pure **4** prepared above. The complexation of arenes possessing benzylic oxygen substituents has been shown to proceed via chelation of a lone pair of electrons on the oxygen substituent with the incoming metal unit. In the case of compound **6**, the two faces of the arene are diastereotopic, thus complexation can generate two possible diastereoisomers. The stereoselectivity observed is consistent with chelation of the benzylic oxygen function to the incoming metal unit in preferred conformations which put the benzylic proton rather than the methyl group *syn* to the *ortho* methoxyl substituent [6].



Treatment of a tetrahydrofuran solution of complex **3** (−78°C, 2 h) with strictly 1 equivalent t-butyllithium followed by addition of Eschenmoser's salt ($CH_2{=}NMe_2{}^+I^-$) gave exclusively the dimethylaminomethylated product **8**, with complete control of the α-stereochemistry. Thus the dimethylated product **5** must arise either via double deprotonation of the starting material with the excess of alkyllithium reagent or via two sequential deprotonation/methylation reactions; it does not arise because of any loss of regioselectivity in the initial deprotonation. Decomplexation of **8** in air and sunlight gave the free phenethanolamine derivative **9** in good yield. Repetition of the above alkylation reaction, but with *N*,*N*-dimethylbenzylideneammonium iodide as the electrophile, gave a 1.2/1 mixture of diastereoisomers **10** and **11**. Whilst the reaction was completely stereoselective at the α-centre, virtually no stereocontrol at the β-centre was observed.

Sequential reduction and *O*-methylation of the readily available homochiral (*o*-anisaldehyde)$Cr(CO)_3$ (**12**) [7,8] allows the trivial synthesis of homochiral **3**. Repeating the above diastereoselective alkylation on homochiral material therefore permits the asymmetric synthesis of chiral α-substituted benzyl methyl ethers. Thus treatment of (−)-(*o*-anisaldehyde)$Cr(CO)_3$ ((−)-**12**) {$[\alpha]_D^{25}$ −1044° (*c* 0.06 $CHCl_3$) lit. [7,8] $[\alpha]_D$ −1020° (*c* 0.09 $CHCl_3$)} in a mixture of tetrahydrofuran and methanol at 20°C with sodium borohydride gave a good yield of (+)-(*o*-methoxybenzyl alcohol)$Cr(CO)_3$ ((+)-**13**) {$[\alpha]_D^{22}$ +237° (*c* 1.04 $CHCl_3$)}. Treatment of a





tetrahydrofuran solution of (+)-**13** with sodium hydride followed by methyl iodide at 20 °C gave homochiral (+)-**3** in good yield {$[\alpha]_D^{22}$ +200° (*c* 1.26 $CHCl_3$)}. Addition of exactly 1 equiv. of t-butyllithium to (+)-**3** in tetrahydrofuran (−78 °C, 2 h) followed by methyl iodide (−78 °C, 2 h) gave a quantitative yield of (+)-**4** {$[\alpha]_D^{22}$ +220° (*c* 0.80 $CHCl_3$)}. Decomplexation of (+)-**4** occurred on exposure of a diethyl ether solution to air and sunlight to give, following filtration, evaporation of the solvent and vacuum distillation, (+)-**6** {$[\alpha]_D^{23}$ +109° (*c* 1.19 $CHCl_3$)}, which must be homochiral owing to the stereochemical integrity of its precursors.

Since the absolute configuration of (−)-(*o*-anisaldehyde)$Cr(CO)_3$ ((−)-**12**) is known [8,9], and since the stereochemistry of the key deprotonation step above has been unambiguously established, it follows that the absolute configuration of (+)-**6** can be assigned as *R*.

All new compounds were fully characterised and gave correct elemental microanalyses.

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