Chiral base-mediated benzylic functionalisation of (alkyl benzyl ether)tricarbonylchromium(0) complexes

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Asymmetric functionalisation of the benzylic methylene group in tricarbonylchromium(0) complexes of alkyl benzyl ethers [(PhCH$_2$OR)(CO)$_3$Cr^0] is achieved in high yield (86–96%) and high enantiomeric excess (ee) (97 to ≥99%) using chiral base methodology.

Asymmetric functionalisation of a methylene group is a strategically simple and attractive approach to asymmetric synthesis. Implementation of this strategy has now been achieved for several systems using methods which formally involve an asymmetric deprotonation with a chiral base followed by a stereoselective electrophilic quench. Using this approach highly enantioselective functionalisations of methylene groups in ketones,[1] alkyl carbamates[2] and *N*-Boc pyrrolidines[3] have been achieved, and moderately enantioselective functionalisations of methylene groups in *N*-Boc-*N*-methylbenzylamine,[4] benzyl dialkyl phosphates[5] and (*S*)-alkylthiocarbamates[6] have been noted. In view of current interest in this area and the recent interest in the use of chiral bases to discriminate between enantiotopic aryl hydrogens in a range of tricarbonyl(arene)chromium(0) complexes[7] and between enantiotopic benzylic hydrogens in tricarbonyl (phthalan)chromium(0),[8] we report herein a highly enantioselective chiral base-mediated functionalisation of the benzylic methylene groups of tricarbonylchromium(0) complexes of alkyl benzyl ethers.

In contrast to its uncomplexed counterpart,[9] the benzylic carbanion derived from (benzyl methyl ether)tricarbonylchromium(0) **1** is completely stable with respect to the Wittig rearrangement and has been effectively quenched with a range of electrophiles.[10] Furthermore, stereoselective alkylation of the benzylic position in (*o*-methoxybenzyl methyl ether)tricarbonylchromium(0) is proposed to proceed *via* a benzylic anion which is rendered configurationally stable by electronic and steric interactions with the tricarbonylchromium(0) unit.[11] Thus (benzyl methyl ether)tricarbonylchromium(0) **1** appeared to be an interesting and viable candidate for asymmetric methylene group functionalisation provided that asymmetric deprotonation of **1** could be realised.

(Benzyl methyl ether)tricarbonylchromium(0) **1** was synthesised by converting benzyl alcohol into (benzyl alcohol) tricarbonylchromium(0) (69%) followed by treatment with acidic methanol (89%).[10] In an initial exploratory experiment, the established chiral base **7** was used to deprotonate **1** and diphenyl disulfide was used to quench the reaction. Workup gave the novel† α-(phenylsulfenyl)benzyl methyl ether complex **3** in 52% yield. The product of this reaction was readily analysed by chiral HPLC and its ee was found to be a moderate 22% (Table 1, entry 1). The next base to be employed was the recently introduced C_2-symmetric vicinal diamide **8**.[12] In this case the reaction of complex **1** to give the α-phenylsulfenyl derivative **3** proceeded in 86% yield and, to our delight, the ee of the product was found to be 97% (Table 1, entry 2).

In order to probe this highly enantioselective process further, the reaction between (benzyl methyl ether)tricarbonylchromium(0) **1** and chiral base **8** was next quenched with iodomethane. This gave the α-methylbenzyl methyl ether complex **4** in 96% yield and 97% ee (Table 1, entry 3).‡ Comparison of the $[\alpha]_D$ of this material with literature data[13]

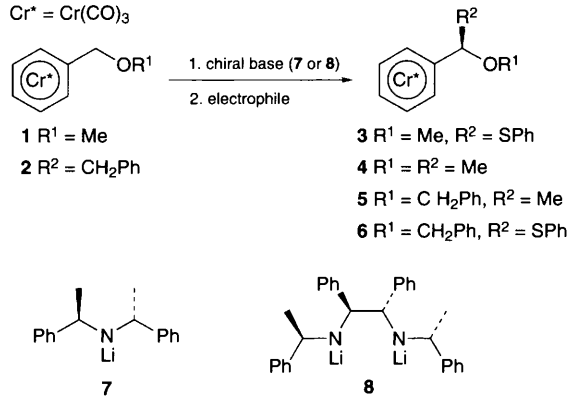
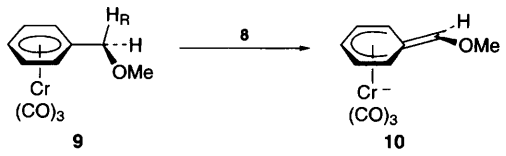


Table 1 Deprotonation/electrophilic quench reactions of (alkyl benzyl ether)tricarbonylchromium(0) complexes using chiral bases[a]

Entry	Substrate	Chiral base	Electrophile	Product	Yield (%)	Ee (%)[b]	$[\alpha]_D$[c]
1	**1**	**7**	PhSSPh	**3**	52	22	+17
2	**1**	**8**	PhSSPh	**3**	86	97	−79[d]
3	**1**	**8**	MeI	**4**	96	97	+54
4	**2**	**8**	MeI	**5**	89	≥99	+4.5
5	**2**	**8**	PhSSPh	**6**	95	99	−186

[a] The experimental procedure for the conversion of **1** to **4** using chiral base **8** is typical: A solution of the chiral dilithium amide **8** was prepared by treatment of the corresponding diamine (0.180 g, 0.43 mmol) in THF (5 cm^3) at −78 °C with BuLi (1.6 mol dm^{-3} in hexanes; 0.54 cm^3, 0.86 mmol). The solution was allowed to warm to room temperature with stirring, and then recooled to −78 °C. To the resulting pink solution was added a solution of LiCl (0.017 g, 0.40 mmol) in THF (5 cm^3) *via* a cannula. To this was added complex **1** (0.100 g, 0.39 mmol) in THF (5 cm^3) *via* a cannula over approximately 2 min. The yellow–orange solution was stirred at −78 °C for a further 20 min, MeOH (1 cm^3) was added, the solution warmed to room temp. and the solvents removed *in vacuo*. The residue was subjected to flash chromatography [SiO_2; diethyl ether : petroleum ether (40–60 °C), 1 : 4] to give complex **4** as a bright yellow solid (0.101 g, 96%). [b] Ees measured by HPLC (Chiralcel OD-H). [c] All values measured within 24.5–26.5 °C in CH_2Cl_2 (c = 1). [d] $[\alpha]_D$ measured on a recrystallised sample of ee ≥99.5%.



revealed that the absolute configuration of **4** was *R*. Although definition of the precise nature of this asymmetric process requires much more experimentation, the stereochemical outcome of this reaction may be rationalised by invoking removal of the pro-*R* hydrogen from the conformation which places it antiperiplanar to chromium (**9**) and reasoning that the resultant stable anion **10** is alkylated on its *exo* face.§

In order to probe whether the high enantioselectivity observed with complex **1** and base **8** is maintained when the uncomplexed ether substituent is altered, (dibenzyl ether)tricarbonylchromium(0) **2** was synthesised by $NaH/PhCH_2Br$ treatment of (benzyl alcohol)tricarbonylchromium(0) (81% yield). Reaction of **2** with base **8** followed by an iodomethane quench gave the known[10] α-methylbenzyl benzyl ether complex **5** in 89% yield and ≥99% ee (Table 1, entry 4), whilst quenching with diphenyldisulfide gave the novel complex **6** in 95% yield and 99% ee (Table 1, entry 5). Thus this initial probe suggests that the source of the enantiocontrol in this reaction is relatively insensitive to the steric properties of the uncomplexed ether substituent.

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Footnotes

† The novel complexes **3** and **6** gave satisfactory microanalytical and spectroscopic (IR, ^1H NMR, ^{13}C NMR, *m/z*) data.

‡ A control reaction on uncomplexed α-methylbenzyl methyl ether was also performed at this stage. This led only to the reisolation of starting material.

§ The stereochemical assignments of products **3**, **5** and **6** are currently based on the assumption that they are formed in an analogous manner to **4**.

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