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 [(PhCH₂OR)(CO)₃Cr⁰] is achieved in high yield (86–96%) and high enantiomeric excess (ee) (97 to \geq 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 carbamates² and N-Boc pyrrolidines3 have been achieved, and moderately enantioselective functionalisations of methylene groups in N-Boc-N-methylbenzylamine,⁴ benzyl dialkyl phosphates⁵ and (S)-alkylthiocarbamates⁶ 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) complexes⁷ 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 data¹³



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 cm³) at -78 °C with BuLi (1.6 mol dm⁻³ in hexanes; 0.54 cm³, 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 cm³) *via* a cannula. To this was added complex 1 (0.100 g, 0.39 mmol) in THF (5 cm³) *via* a cannula over approximately 2 min. The yellow–orange solution was subjected to flash chromatography [SiO₂; 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 CH₂Cl₂ (*c* = 1). ^{*d*} [α]_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/PhCH₂Br treatment of (benzyl alcohol)tricarbonylchromium(0) (81% yield). Reaction of 2 with base 8 followed by an iodomethane quench gave the known¹⁰ α -methylbenzyl benzyl ether complex 5 in 89% yield and \geq 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.

M. H. S. gratefully acknowledges a CASE award from The Associated Octel Company Limited.

Footnotes

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

 \ddagger 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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Received, 19th January 1996; Com. 6/00443A