Stereocontrolled conversion of secondary benzyl ether tricarbonylchromium(0) complexes into tertiary benzyl ether complexes

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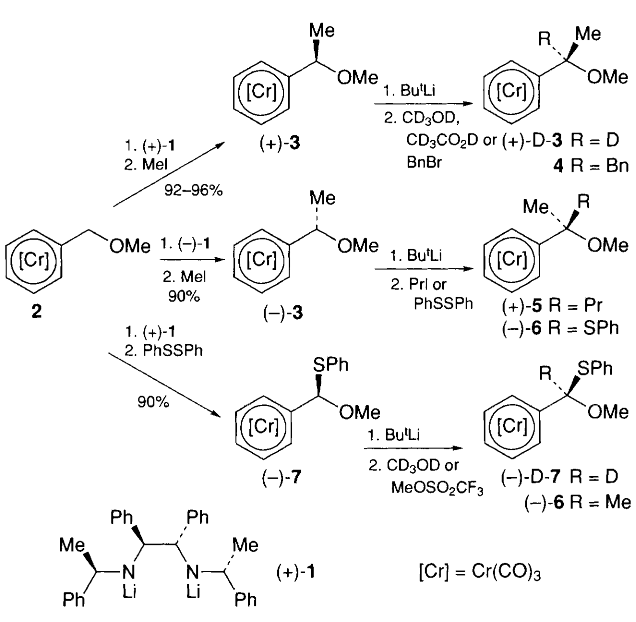
Deprotonation of enantiomerically enriched secondary benzyl ether tricarbonylchromium(0) complexes (96–99% ee) with *tert*-butyllithium followed by quenching with a range of electrophiles gives tertiary benzyl ether tricarbonylchromium(0) complexes of high enantiomeric purity (92–98.5% ee) in good yield (65–94%) with overall retention of configuration.

We recently discovered that the benzylic methylene groups in tricarbonylchromium(0) complexes of alkyl benzyl ethers may be functionalised asymmetrically in excellent yield and high enantiomeric excess by chiral base methodology.[1] In a typical example, reaction of the chiral base (+)-**1**[2] with the benzyl methyl ether complex **2**[3] followed by an iodomethane quench gave the secondary benzyl ether complex (+)-**3** in 96% yield and 97% ee. In view of current interest in the stereospecific conversion of secondary *O*-benzyl carbamates into tertiary *O*-benzyl carbamates,[4] a reaction which forms the basis of the most promising approach to optically active tertiary benzylic alcohols to date,[4a] we decided to probe whether or not optically active complexes of secondary benzyl ethers such as (+)-**3** could be converted into optically active complexes of tertiary benzyl ethers by a deprotonation–electrophilic quench sequence. The results of our studies are communicated herein.

Complex **2**, which is derived from benzyl alcohol in two straightforward steps,[3] was converted to complex (+)-**3** using the chiral base (+)-**1** (Scheme 1). Complex (+)-**3** (98.5% ee and *R* configuration†) was deprotonated with *tert*-butylithium in THF at −78 °C, and after 90 min at this temperature the anion was quenched with CD_3OD (Table, entry 1). Work-up gave a 90% yield of complex (+)-D-**3** (91% D incorporation) which HPLC analysis revealed had an ee of 98.5% and was also of *R* configuration. Thus the deprotonation–quench sequence had clearly proceeded with overall retention of configuration, presumably *via* a configurationally stable anion.

Early studies on the *sec*-butyllithium-promoted deprotonation of *N*,*N*-diisopropyl carbamate derivatives of secondary alcohols revealed that reprotonation of these systems with methanol led to the return of the starting material with retention of configuration whilst reprotonation with acetic acid led to material of inverted configuration.[4c] Quenching the anion of complex (+)-**3** with CD_3CO_2D, however, gave product (+)-D-**3** in which the stereochemical configuration had been retained (Table 1, entry 2), suggesting that in the case of the anion of complex (+)-**3**, in contrast to the carbamate system, the two different quench processes follow the same mechanistic pathway.

Having ascertained that the lithium anion of (+)-**3** is configurationally stable at −78 °C, our attention turned to



Scheme 1

Table 1 Conversion of secondary benzyl ether tricarbonylchromium(0) complexes into tertiary benzyl ether complexes[a]

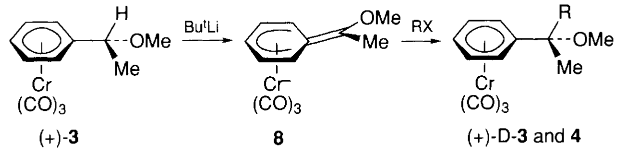
Entry	Substrate	Substrate ee (%)[b]	Electrophile	Product	Product yield (%)	Product ee (%)[b]	Product $[\alpha]_D$[c]
1	(+)-**3**	98.5 ± 0.5	CD_3OD	D-**3**	90[d]	98.5 ± 0.5	+52
2	(+)-**3**	96	CD_3CO_2D	D-**3**	94[e]	96	+50
3	(+)-**3**	96	BnBr	**4**	87	95	−5[f]
4	(−)-**3**	96	PrI	**5**	65	95 ± 5[g]	+11
5	(−)-**3**	96	PhSSPh	**6**	65	98 ± 2	−114
6	(−)-**7**	99	CD_3OD	D-**7**	86[h]	97	−68
7	(−)-**7**	98	$MeOSO_2CF_3$	**6**	92	92	−92
8	(−)-**10**	99	EtI	**11**	84	96 ± 2	−73

[a] The experimental procedure for the conversion of (+)-**3** to **4** is typical: BuᵗLi (1.7 M in pentane; 0.65 cm^3, 1.1 mmol) was added to a solution of (+)-**3** (272 mg, 1.00 mmol) in THF (10 cm^3) at −78 °C. The solution was stirred at −78 °C for 30 min and then BnBr (0.15 cm^3, 1.2 mmol) was added. The solution was stirred at −78 °C for a further 3 h, after which time MeOH (1 cm^3) was added. The solution was allowed to warm to room temperature and the solvents removed *in vacuo*. The residue was subjected to flash chromatography [SiO_2; diethyl ether–light petroleum (40–60 °C), 1 : 4] to give complex **4** as a bright yellow solid (0.314 g, 87%). [b] Ees measured by HPLC (Chiralcel OD-H) unless stated otherwise; accuracy ±1% unless stated otherwise. [c] All values measured within the range 24.5–27.5 °C in CH_2Cl_2 (*c* 0.5–1). [d] 91% D incorporation. [e] 93% D incorporation. [f] Measured at 436 nm. [g] Ee determined by oxidative decomplexation of (+)-**5** and comparison of $[\alpha]_D$ of ligand with a literature value (ref. 6). [h] 90% D incorporation.

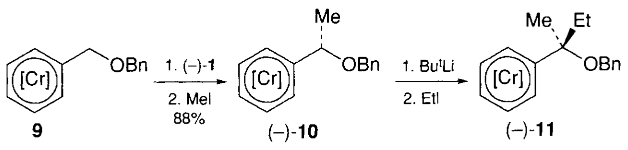
synthetically more interesting electrophiles. Whilst deprotonation of (±)-**3** followed by quenching with iodomethane and chlorotrimethylsilane has been shown to proceed in 93 and 53% yield, respectively, indicating that the formation of carbon–carbon and carbon–heteroatom bonds in this system is chemically feasible,[5] the stereochemical consequences and the synthetic scope of this type of process needed to be determined. Thus, complex (+)-**3** was deprotonated and quenched with benzyl bromide. Work-up led to the isolation of the novel complex **4**[‡] of essentially the same enantiomeric purity as its precursor in 87% yield (Table 1, entry 3), and an X-ray crystallographic analysis of this product[§] revealed that its absolute configuration was *S*. Thus, in contrast with deprotonation–alkylation of secondary *O*-benzyl carbamates, which proceeds with inversion of configuration,[4a] the deprotonation–alkylation of (+)-**3** proceeds with overall retention of configuration.

The overall retention of configuration observed in the deprotonation–quench sequences performed on complex (+)-**3** may be rationalised as follows. Removal of the benzylic proton of (+)-**3** from a conformation that places it antiperiplanar to the tricarbonylchromium(0) unit gives the chromium-centred and configurationally-locked anion **8** (Scheme 2). The incoming electrophile then approaches the sterically less-hindered *exo* face of the complex to give the observed products (+)-D-**3** and **4**.

In a preliminary probe of the synthetic scope of the reaction, several other electrophiles and complexes were examined. Deprotonation of complex **2** with chiral base (−)-**1** followed by quenching with iodomethane gave complex (−)-**3**. Subsequent deprotonation of (−)-**3** with *tert*-butyllithium and quenching with iodopropane or diphenyl disulfide gave the novel complexes (+)-**5** and (−)-**6**[¶] respectively in good yield and high enantiomeric excess (Table 1, entries 4 and 5). The absolute stereochemistry of (+)-**5** was confirmed as *R* by oxidative removal of the tricarbonylchromium(0) unit and comparison of the $[\alpha]_D$ of the ligand with that of a sample made by an independent route.[6] Deprotonation of complex **2** with chiral base (+)-**1** and quenching with diphenyl disulfide gave the thioacetal (−)-**7**. Whilst deprotonation of this complex with *tert*-butyllithium followed by a CD_3OD quench proceeded in high yield and with retention of stereochemistry (Table 1, entry 6), quenching with iodomethane failed to give any methylated product. Changing the electrophile to $MeSO_2CF_3$, however, led to the successful alkylation of (−)-**7**. Finally, deprotonation of the tricarbonylchromium(0) complex of dibenzyl ether **9** with chiral base (−)-**1** and quenching with iodomethane gave the secondary benzylic ether complex (−)-**10** (Scheme 3). Deprotonation of (−)-**10** with *tert*-butyllithium and quenching with iodoethane gave the novel tertiary benzylic ether complex (−)-**11**[¶] in 84% yield and 96% ee.



Scheme 2



Scheme 3

M. H. S. and P. C. V. P. gratefully acknowledge CASE awards from The Associated Octel Company Limited and Zeneca Pharmaceuticals respectively.

Footnotes

[†] The absolute configuration of (+)-**3** was determined previously (ref. 1) by comparison of its $[\alpha]_D$ value with a literature value.

[‡] The novel complexes **4**, **5**, **6** and **11** gave satisfactory microanalytical and spectroscopic (IR, ^1H NMR, ^{13}C NMR, *m/z*) data.

[§] Details of this analysis will be published in the full account of this study.

[¶] The stereochemical assignments of products (−)-**6** and (−)-**11** are based on the assumption that they are formed in an analogous manner to (+)-D-**3**, **4**, (+)-**5** and (−)-D-**7** *i.e.* with overall retention of configuration.

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Received, 9th August 1996; Com. 6/05558C