COMMUNICATION

Chiral base-mediated asymmetric functionalisation of tricarbonylchromium(0) complexes of benzyl sulfides

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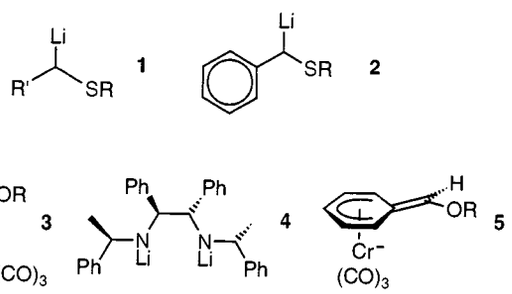
Chiral base-mediated asymmetric functionalisation of tricarbonylchromium(0) complexes of benzyl sulfides gives, after crystallisation, products of high enantiomeric purity (92–99% ee) in acceptable yield (51–76%); an intriguing reversal of stereoselectivity with respect to the analogous oxygen systems is noted.

The configurational instability of α-sulfur substituted alkyllithium compounds **1**[1] and benzyllithium compounds **2**[2] is well documented and attempts to use these species in asymmetric synthesis have met with little success to date. Indeed, the first examples of enantiomerically enriched α-sulfur substituted alkyllithium compounds, whose chirality is determined solely by the stereogenic carbon centre, were prepared only very recently. Thus, generation of the α-sulfur substituted alkyllithiums **1** (R′ = Me, Pr, Pr^i; R = CON$\overline{\text{CMe}_2\text{OCH}_2\text{CMe}_2}$) by deprotonation of their conjugate acids with Bu^{s}Li–(−)-sparteine and subsequent quenching with carbon dioxide or chlorotrimethylsilane gave products in 77–95% yield and 40–60% ee.[1]



We recently discovered that the benzylic methylene group in tricarbonylchromium(0) complexes of alkyl benzyl ethers **3** may be asymmetrically functionalised in high yield (86–96%) and high enantiomeric excess (97–99%) by deprotonation with the chiral base **4** followed by an electrophilic quench.[3] The success of this approach is partially attributed to the configurational stability of the intermediate anion to which structure **5** presumably makes a significant contribution.

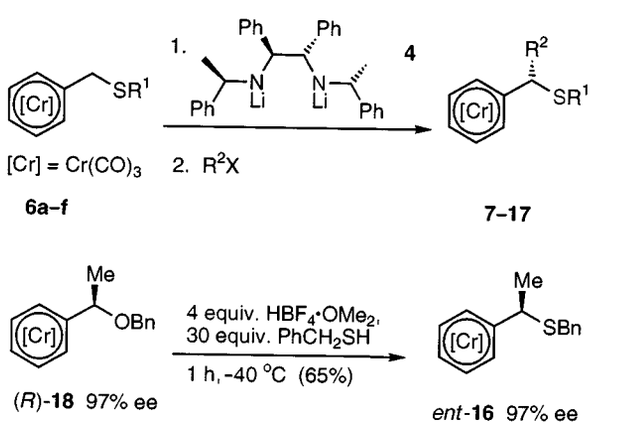
In view of (i) the recognised instability of α-sulfur substituted lithium compounds, and (ii) the emerging potential of chiral sulfides as ligands in asymmetric synthesis,[4] we were intrigued to discover whether or not the anions of tricarbonylchromium(0) complexes of alkyl/aryl benzyl sulfides **6** would be sufficiently configurationally stable to undergo bond-forming reactions and produce enantiomerically enriched products. The results of our studies are described herein.

The novel complexes **6a**,**b**,**d–f**† and the known complex **6c**[5] were prepared from the readily accessible tricarbonylchromium(0) complex of benzyl alcohol[6] in good yield (72–90%) by treatment with the appropriate thiol in the presence of HBF_4·OMe_2.[5]

The reactivity of complex **6a** (R = Ph) was examined initially. Thus reaction of **6a** first with the chiral base **4** at −78 °C for 6 h and then with iodomethane at −78 °C for a further 2 h led to clean benzylic methylation and the isolation of the novel complex **7** (R^1 = Ph; R^2 = Me) in 94% yield (Table 1, entry 1). Product **7** was readily analysed by chiral HPLC‡ and its ee was found to be a very encouraging 63%.§

In order to determine the effect of changing the sulfide substituent R^1 from an aryl group to an alkyl group, complex **6b** (R^1 = Me) was examined next. Reaction of this complex with the chiral base **4** for 1 h at −78 °C followed by quenching for 1 h at −78 °C with benzyl bromide, 2-(bromomethyl)naphthalene and chlorotrimethylsilane gave novel products **8**–**10** respectively in good yield (62–93%) and significantly increased ee (88–89%) (Table 1, entries 2–4).

The effect of increasing the steric bulk of the sulfide substituent R^1 on the enantioselectivity of the reaction was subsequently explored by reacting complexes **6c** (R^1 = Et), **6d** (R^1 = Pr^i) and **6e** (R^1 = Bu^t) with chiral base **4** and a range of electrophiles. The reactions of **6c** (R^1 = Et) gave good yields (72–88%) of the known product **11**[8] and the novel products **12**–**13** in slightly diminished ee (78–82%) (Table 1, entries 5–7). In contrast, complexes **6d** (R^1 = Pr^i) and **6e** (R^1 = Bu^t) were relatively unreactive and gave products **14** and **15** in very poor ee (18 and 20% respectively) when quenched with iodomethane and 2-(bromomethyl)naphthalene respectively (Table 1, entries 8 and 9).



† The novel complexes **6a**,**b**,**d–f**, **7**–**10** and **12**–**17** gave satisfactory microanalytical and spectroscopic (IR, ^{1}H NMR, ^{13}C NMR, MS) data.

‡ Racemic products for HPLC analysis were generated by Bu^{t}Li deprotonation–electrophilic quench of the appropriate substrate.

§ In contrast, reaction of (1,3-dihydroisobenzothiophene)tricarbonylchromium(0) with a chiral amide base has been reported to give racemic products.[7]

Table 1 Deprotonation–electrophilic quench reactions of complexes **6a–f** using chiral base **4**[a]

							Before crystallisation		After crystallisation		
Entry	Substrate	R^1	R^2X	Product	R^1	R^2	Yield (%)	Ee (%)[b]	Yield (%)	Ee (%)[b]	$[\alpha]_D$[c]
1	**6a**	Ph	MeI	**7**	Ph	Me	94[d]	63	—	—	—
2	**6b**	Me	$PhCH_2Br$	**8**	Me	CH_2Ph	91	88	71	92	+114
3	**6b**	Me	$C_{11}H_9Br$	**9**	Me	$C_{11}H_9$	93	88	76	94	+161
4	**6b**	Me	Me_3SiCl	**10**	Me	$SiMe_3$	62	89	—	—	—
5	**6c**	Et	$PhCH_2Br$	**11**	Et	CH_2Ph	75	78	65	97	+87
6	**6c**	Et	$C_{11}H_9Br$	**12**	Et	$C_{11}H_9$	88	80	60	90	+120
7	**6c**	Et	Me_3SiCl	**13**	Et	$SiMe_3$	72	82	51	99	−101
8	**6d**	Pr^i	MeI	**14**	Pr^i	Me	94[e]	18	—	—	—
9	**6e**	Bu^t	$C_{11}H_9Br$	**15**	Bu^t	$C_{11}H_9$	45[f]	20	—	—	—
10	**6f**	CH_2Ph	MeI	**16**	CH_2Ph	Me	84	91	—	—	—
11	**6f**	CH_2Ph	$C_{11}H_9Br$	**17**	CH_2Ph	$C_{11}H_9$	83	91	51	98	+156

[a] The experimental procedure for the conversion of **6b** to **9** (Entry 3) is typical: A solution of the chiral dilithium amide **4** was prepared by treatment of the corresponding diamine (0.185 g, 0.44 mmol) in THF (5 cm^3) at −78 °C with BuLi (1.6 mol dm^{-3} in hexanes; 0.55 cm^3, 0.88 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 **6b** (0.110 g, 0.40 mmol) in THF (5 cm^3) *via* a cannula over approximately 2 min. The yellow–orange solution was stirred at −78 °C for 1 h and then 2-(bromomethyl)naphthalene (0.265 g, 1.20 mmol) was added. The yellow solution was stirred at −78 °C for a further 1 h, MeOH (2 cm^3) was added, the solution warmed to room temperature and the solvents removed *in vacuo*. Flash chromatography of the residue [Al_2O_3 (grade II); diethyl ether–petroleum ether (40–60 °C), 1:9] gave complex **9** as a bright yellow solid (0.154 g, 93%) of ee 88%. Recrystallisation from diethyl ether–petroleum ether (40–60 °C) gave fine yellow crystals (0.125 g, 76%) of ee 94%. [b] Ees measured by HPLC (Chiralcel OD-H); accuracy ±1%. [c] All values measured within the range 22–29 °C in CH_2Cl_2 (*c* 1). [d] Reaction carried out at −78 °C for 6 h with base and then 2 h with electrophile. [e] Reaction carried out at −78 °C for 6 h with base and then 2 h with electrophile—product contaminated with 9% starting material. [f] Reaction carried out at −78 °C for 6 h with base and then 2 h with electrophile—unreacted starting material was also recovered.

Although complex **6b** was emerging as the most attractive substrate for asymmetric functionalisation of benzyl sulfides, the volatility of methanethiol, used in the synthesis of **6b**, prompted a search for an alternative R^1 substituent. Thus complex **6f** ($R^1 = CH_2Ph$) was synthesised and reacted with chiral base **4**. Quenching with iodomethane and 2-(bromomethyl)-naphthalene gave products **16** and **17** in good yield (83–84%) and with ees essentially equivalent to those obtained when R^1 = Me (91%) (Table 1, entries 10–11).

Complexes **8**, **9**, **11**–**13** and **17** were crystallised, leading to samples of good enantiomeric purity (92–99% ee) in acceptable yield (51–76%) (Table 1, entries 2, 3, 5–7, 11). An X-ray crystallographic analysis of complex **13** (99% ee)¶ revealed, to our surprise, that it was the opposite enantiomer to the one we had predicted based on our results obtained with the analogous ethers.[3,9] In order to probe this change in stereochemical outcome further, the ether complex (*R*)-**18**[3] (97% ee) was reacted with benzyl thiol in the presence of $HBF_4{\cdot}OMe_2$. Work-up gave complex **16** in 65% yield and HPLC analysis of this material revealed that it was the opposite enantiomer to that obtained by the deprotonation–quench route. As acid catalysed substitutions of this type are known to proceed with retention of configuration,[10] this result is stereochemically consistent with the X-ray crystallographic analysis of **13**. It thus appears that deprotonation of tricarbonylchromium(0) complexes of benzyl sulfides with the chiral base **4** proceeds in the opposite stereochemical sense to deprotonation of the corresponding ethers. An investigation into the origin of this intriguing stereochemical reversal is currently underway.

¶ Details of this analysis will be published in the full account of this study.

Acknowledgements

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