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Use of a bis-lithium amide base in asymmetric metallation of tricarbonyl(η^6-1,3-dihydroisobenzothiophene)chromium(0)

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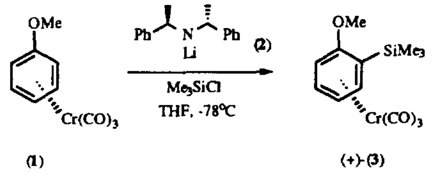
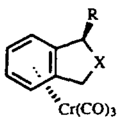
Abstract

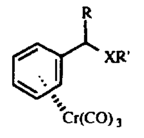
Enantiomerically enriched tricarbonyl(η^6-arene)chromium complexes derived from tricarbonyl(η^6-1,3-dihydroisobenzothiophene)chromium(0) can be obtained in up to 95% ee by means of an enantioselective metallation reaction using the bis-lithium amide base **8**. © 1998 Elsevier Science Ltd. All rights reserved.

In previous reports we have described the use of an asymmetric metallation approach for the synthesis of enantiomerically enriched tricarbonyl(η^6-arene)chromium complexes, e.g. the conversion of anisole complex **1** into the *ortho*-silylated derivative **3** by chiral lithium amide base **2**.[1–3]

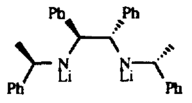




(4) X = O
(5) X = S



(6) X = O
(7) X = S



(8)

Whilst the chiral base **2** has proved very valuable in this type of reaction, and also provided products **4** in reasonable enantiomeric excess, it gave very poor results in reactions leading to sulfur analogues **5** and in benzylic metallations described by Gibson and co-workers leading to **6** and **7**.[4,5] In these latter cases high selectivity was achieved by use of the bis-lithium amide base **8**, which we then showed to give excellent selectivity in reactions leading to **4**.[6] Here we demonstrate that the use of this chiral

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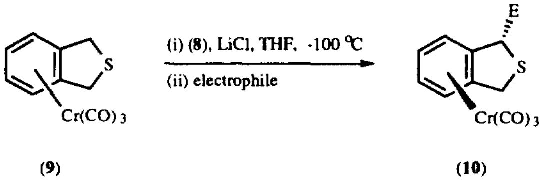
Table 1
Substitution of complex **9** via metallation



electrophile	MeI	EtI	BnBr	Ph_2CO	Me_3SiCl	allylBr	$ArCH_2Br$[a]
(**10**) yield (%)	95	91	70	88	95	75	89
(**10**) ee (%)[b]	94	87[c]	n.d.[d]	95	89	n.d.[d]	95

a - $ArCH_2Br$ = 2-(bromomethyl)naphthalene.

b - Determined by HPLC - see footnote 10.

c - Warming to -78 °C to facilitate alkylation may account for slightly lower ee.

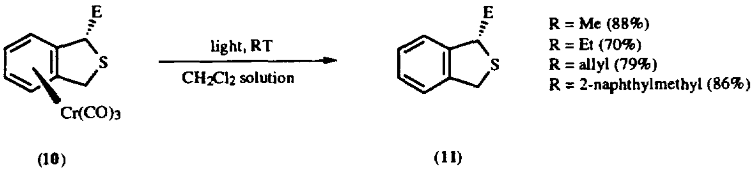
d - Not determined (ee assay not readily established).

base also provides dramatic improvements to the hitherto poor selectivity in the synthesis of sulfur-containing complexes **5**, allowing easy access to enantiomerically pure complexes and the corresponding free sulfides.

As mentioned above, the substitution reactions of complex **9** mediated by chiral base **2** proceeded in only about 5% enantiomeric excess (ee). In these reactions LiCl was included, since without this additive no products were observed. We next examined analogous reactions employing bis-amide **8**, Table 1.[7]

Again, it proved essential to include LiCl in the reaction mixture, or very low yields of product were obtained.[8] The results demonstrate the superiority of base **8** over base **2** in this type of application (under otherwise identical conditions), very high levels of enantioselectivity being observed in all cases.[9] The absolute stereochemistry of the products is based on an X-ray structure determination carried out on the methylated product **10** (E=Me) following recrystallisation.[10] The sense of asymmetric induction is as expected from our previous work on the corresponding isobenzofuran series (synthesis of **4**), the bis-amide **8** giving opposite selectivity to the simpler amide **2** (both prepared from (*R*)-phenylethylamine). Interestingly, Gibson and co-workers observed a swap-over in the sense of absolute stereochemical outcome in the synthesis of sulfur derivatives **7** compared with the ethers **6**, using base **8**.[4,5] This unexpected observation is not duplicated in our results, presumably due to the additional conformational constraint imposed by incorporating the heteroatom into a ring structure.

In most cases the highly enantiomerically enriched complexes **10** obtained could be efficiently recrystallised to provide material of ≥99% ee.[11] These products could then be de-metallated by exposure to light, to provide the corresponding enantiomerically pure sulfides **11**.



In conclusion, these results serve to highlight the usefulness of bis-lithium amide **8** for certain chiral base reactions in which base **2** gives poor selectivity.[12] In addition, a new route to potentially useful enantiomerically pure sulfides has been established.

Acknowledgements

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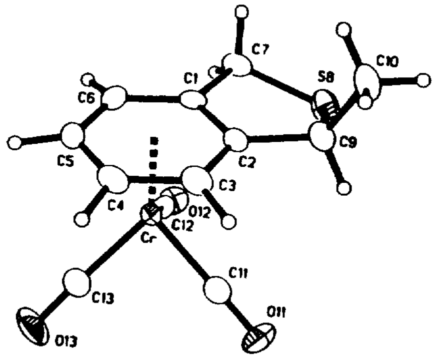
6. Synthesis of diamine corresponding to **8**, see Bambridge, K.; Begley, M. J.; Simpkins, N. S. *Tetrahedron Lett.* **1994**, *35*, 3391.
7. Typical experimental procedure: A solution of the bis-lithium amide **8** was prepared by addition of ^{n}BuLi (0.50 ml of a 1.6 M solution in hexanes, 0.81 mmol) dropwise to a solution of the chiral diamine (0.17 g, 0.40 mmol) in THF (10 ml) at −78°C under an atmosphere of nitrogen. The solution was briefly warmed to room temperature and then cooled to −100°C before addition of a solution of LiCl (8 mg) in THF (5 ml) via cannula. To this mixture was added a solution of complex **9** (0.10 g, 0.37 mmol) in THF (5 ml) dropwise via cannula, and the resulting red coloured solution stirred at −100°C for a further 1 h. After this time MeI (0.12 ml, 1.84 mmol) was added, and after a further 1 h at −100°C the reaction was quenched by addition of MeOH (1 ml). The cooling bath was then removed and the mixture allowed to warm to room temperature before removal of the solvent under reduced pressure. Flash column chromatography of the residue on silica gel (EtOAc:light petroleum ether) then gave the product complex (**10** E=Me) as a yellow solid, 0.10g (95%), m.p. 118°C; (found: C, 50.63; H, 3.53. $C_{12}H_{10}O_3SCr$ requires C, 50.35; H, 3.52%); ν_{max}/cm^{-1} ($CHCl_3$) 1971 and 1897; δ_H (250 MHz; $CDCl_3$) 1.59 (3H, d, *J* 7, CH_3), 3.86 (1H, d, *J* 14, SCH_2), 4.24 (1H, d, *J* 14, SCH_2), 4.34 (1H, q, *J* 7, SCH), 5.26 (2H, d, *J* 3, ArH) and 5.42–5.48 (2H, m, ArH); δ_C (68 MHz; $CDCl_3$) 26.4 (CH_3), 35.8 (CH_2), 47.6 (CH), 89.7 (ArCH), 90.3 (ArCH), 91.4 (ArCH), 91.6 (ArCH), 111.0 (ArC), 116.6 (ArC) and 232.8 (CO); *m/z* (EI) 286 (M^+, 24%) and 202 [$(M{-}3CO)^+$, 100%], (found: M^+, 285.9764. $C_{12}H_{10}O_3SCr$ requires M, 285.9756).
8. Reactions conducted using **8** in the absence of LiCl gave little or no product, indicating that the presence of salt greatly facilitates the rate of metallation. Small amounts of chiral products from such reactions did however show similar ee levels to those from 'added salt' reactions, indicating that LiCl does not seem to enhance the level of base enantioselectivity in these reactions. In some cases the use of more than *ca.* 0.5 equivalents of LiCl in combination with base **8** lead to substantial amounts of double alkylation.
9. Reaction with acetone also gave product in high enantiomeric excess (*ca.* 99%) but in a much reduced yield (20%), presumably due to enolisation problems.
10. The configuration shown is based on the collection of low temperature data, including Friedel equivalents, and by refinement of a Flack parameter [value −0.02(2)], see Flack, H. D. *Acta Crystallogr., Sect. A* **1983**, *39*, 876.

*Structure of **10** (E = Me)*



11. Enantiomerically pure compounds **10** ($\geq$99% ee) with the following substituents were obtained in the indicated yields by recrystallisation from ^{i}PrOH: R=Me (89%); R=Me$_3$Si (85%); R=2-naphthylmethyl (76%). In the case of **10** (R=PhC(OH)Ph) the solvent used was Et$_2$O:petroleum ether. Enantiomeric excess values were determined by HPLC using a Chiralcel OD column (detection at 256 nm) and ^{i}PrOH (3–5%)-hexane as eluent.
12. For other examples of the use of chiral bis-lithium amides, see (a) Newcombe, N. J.; Simpkins, N. S. *J. Chem. Soc., Chem. Commun.*, **1995**, 831. (b) Tierney, J. P.; Alexakis, A.; Mangeney, P. *Tetrahedron: Asymmetry* **1997**, *8*, 1019.