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Asymmetric deprotonation—substitution of arenetricarbonylchromium(0) complexes: substituent controlled lithiation with the butyllithium–sparteine system

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Abstract

Attempted enantioselective deprotonation of fluorobenzenetricarbonylchromium(0) with ca. 1 equivalent of butyllithium/(−)-sparteine in ether–hexane at −78°C followed by a chlorotrimethylsilane quench gave the racemic *ortho*-substituted product. Analogous enantioselective deprotonation of anisoletricarbonylchromium(0), followed by electrophilic quench, gave the 1-(*R*p)-substituted complexes in up to 77% yield with 27% e.e., but with methoxymethoxybenzenetricarbonylchromium(0), (4-triisopropylsilyloxymethyl)methoxymethoxybenzenetricarbonylchromium(0) and (*N*-*t*-butoxycarbonylaniline)tricarbonylchromium(0), the 1-(*S*p)-products were formed in up to 58% yield with 92% e.e. The results are explained in terms of coordinative and non-coordinative enantioselective lithiation.

1. Introduction

In recent years, arenetricarbonylchromium(0) complexes have gained a significant place in the range of organic synthetic protocols applied to aromatic and heteroaromatic compound synthesis.[1,2] The electron withdrawing ability of the metal moiety has been exploited in the synthesis of multifunctional aromatic rings by nucleophilic addition/oxidation,[3–7] by directed lithiations[8–11] and by benzylic functionalisation.[12,13]

The enantioselective deprotonation of prochiral complexes using asymmetric directed lithiation methodology provides a potentially efficient route to non-racemic chiral complexes for use in asymmetric synthesis. Enantiomerically pure complexes were first generated by the use of

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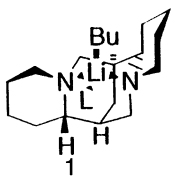
chiral auxiliaries[14] or, in particular cases, by dynamic kinetic resolution,[15,16] but more recently asymmetric deprotonation by chiral bases has been used. This access to chiral complexes has been achieved by a number of groups with either chiral lithium amide base or alkyllithium/chiral ligand reagents. Among the former, Simpkins has made notable progress,[17] but the use of amide bases is constrained by the reversibility of the deprotonation process and/or the rapid racemisation of the initially formed chiral complex. More stereochemically robust is the series of complexes of alkyllithiums with chiral ligands used principally by Uemura,[18] Kündig[19,20] and Schmaltz.[21] We report here our own observations on the butyllithium/(−)-sparteine system **1**, which have revealed unexpected complexities in the control mechanisms of the deprotonation process.

Directed lithiation results from a combination of two effects,[22] labilisation of the protons adjacent to the directing group and coordination of the incoming base by the directing group as in **2**, a and b, respectively.



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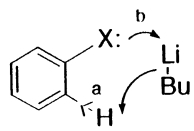
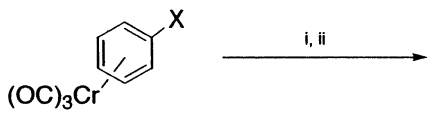


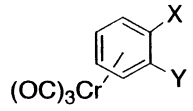
2

Extensive studies by ourselves[10] and others[22,23] have established that one of the consequences of the attachment of the tricarbonylchromium unit is that, although the acidity of the ring protons (effect a) is enhanced by complexation, the coordinating ability of heteroatoms conjugated to the complexed arene (effect b) is reduced. This is critical to a base system such as butyllithium/(−)-sparteine which operates most effectively under coordinating conditions[24] and although, for example, a fluorine substituent is the most powerful *ortho*-proton activating group known in functionalised benzene complexes,[10] without coordination of the incoming base, enantioselectivity may not be optimal. A key feature of this study was therefore to identify the best readily accessible directing group for enantioselective deprotonation.

We have previously described details for the regioselective lithiation in functionalised arene complexes,[25] but it was now necessary to establish precise protocols for effective enantioselective lithiation. Preliminary experiments established a reaction protocol (Scheme 1) of adding butyllithium (*n*- or *sec*- 1.1–1.5 equiv.) in hexanes to a solution of rigorously dried (−)-sparteine (3.0–3.5 equiv.) in dry degassed ether and allowing the mixture to equilibrate at −78°C for 30 min before adding the complex (1 equiv.) in dry degassed ether (to produce hexane:ether ca.



3a, X = F
3b, X = OMe
3c, X = CH_2OMe
3d, X = OMOM
3e, X = NHBoc



4a, X = F, Y = $SiMe_3$
4b, X = OMe, Y = $SiMe_3$
4c, X = OMe, Y = CONHCHMeNpth
4d, X = OMOM, Y = $SiMe_3$
4e, X = OMOM, Y = CONHCHMePh
4f, X = OMOM, Y = CH_2OH
4g, X = NHBoc, Y = $SiMe_3$
4h, X = CH_2OMe, Y = CH_2OH

Scheme 1. Reagents: i. BuLi/(−)sparteine, −78°C, hexane–Et_2O; ii. quench Y, −78°C→rt

4:1). Deprotonation was allowed to proceed for 1–4 h at this temperature before the quench (5 equiv.) was added and the mixture allowed to warm to room temperature over ≥ 3 h. Routine work up (see Experimental) gave the products which were analysed by chiral HPLC on Chiracel OD-H and by optical rotation. Deviation from this protocol, particularly with respect to reactant ratios and times, could produce widely varying stereochemical results, which will be addressed later. Key enantiopure products were structurally defined by single-crystal X-ray structure determination. For consistency, the planar chiralities (*R*p)- or (*S*p)- are quoted with the directing group as the reference point.

2. Results and discussion

The chiral HPLC columns available to us were not always effective in enantiomer separation and in such cases, an enantiomerically pure isocyanate quench, (*R*)- or (*S*)-1-phenylethyl isocyanate or (*R*)- or (*S*)-1-(1-naphthyl)ethyl isocyanate was used. Separation of the diastereoisomeric products and again, analysis by single-crystal X-ray structure determination established the stereochemical consequences of the lithiations. In order to eliminate (or otherwise) the possibility of diastereoselectivity in the chiral quenching process distorting the result, each run was repeated with the antipodal quench and the product ratios compared.

With these protocols in place, the lithiations could be assessed and the results are given in Table 1. Starting with the powerfully activating, but non-coordinating fluorobenzene complex **3a**, lithiation as above (run 1) with a chlorotrimethylsilane quench gave a racemic product **4a**. The combination of the high proton acidity and the lack of coordination of the base together with the small and therefore spacially undemanding directing group was completely ineffective in enantioselection.

The anisole complex **3b** contains an ether oxygen atom conjugated to the electron withdrawing chromium unit which significantly reduces the donor power of the oxygen atom. This ether group is therefore weakly coordinating although still strongly activating of the *ortho*-protons. Asymmetric deprotonation as above with the chlorotrimethylsilane quench (run 2) gave a product **4b** of $[\alpha]_D^{24}$ −52, which could not be resolved by our chiral HPLC columns, but which from published data[17] represents a 27% e.e. of the (*R*p)-enantiomer.

To confirm this and provide a more definitive assessment of the enantioselection, the commercially available chiral quenches, (*R*)- and (*S*)-α-methyl-1-naphthylisocyanate, were used (runs 3, 4) and these proved to be most effective at a slightly elevated temperature (–42°C). The diastereoisomeric products **4c** were readily separable by flash chromatography and the structure of the minor isomer from the (*R*)-isocyanate quench was determined by X-ray analysis (Fig. 1) to be **4c**.

The X-ray analysis of (*S*p,*R*)-**4c** showed the complex to have *S* planar chirality (Fig. 1) and confirmed the (*R*) configuration at the naphthyl stereogenic centre [C(10), crystallographic numbering]. Both the methoxy and amide groups retain a near co-planar relationship with respect to the aryl ring; the torsional twist about the C(1)–C(7) bond is only ca. 8° and that about the C(2)–O(22) linkage is ca. 7°. This geometry is probably a consequence of a sterically enforced *syn* relationship between the amide nitrogen N(9) and the methoxy oxygen O(22), and the presence of an intramolecular N–H···O hydrogen bond. The naphthalene ring is rotated steeply out of this plane, the C(7)–N(9)–C(10)–C(11) torsion angle being ca. 75°.

Table 1
Enantioselective deprotonation of arenetricarbonylchromium(0) complexes with BuLi/(−)-sparteine

No.	Substrate ligand	Method	BuLi	Sparteine (equiv.)	Electrophile	Quench temp. (°C)	Product[a]	(Planar chirality) and substituent Y	Yield (%)	$[\alpha]_D^{24}$	E.e. (%) of lithiation	Selectivity
1	PhF	A	*sec*	1.5	Me_3SiCl	−78	**4a**	2-$SiMe_3$	73	0[b]	0	–
2	PhOMe	A	*sec*	1.5	Me_3SiCl	−78	**4b**	2-$SiMe_3$	77	−52[c]	27	*R*
3	PhOMe	A	*sec*	1.5	(*R*)-1-NpthCHMeNCO	−42	**4c**	(*R*p)-2-CONH-C^{R}HMeNpth	27	+171[b]	17[d]	*R*
								(*S*p)-2-CONH-C^{R}HMeNpth	19	+30[b]		
4	PhOMe	A	*sec*	1.5	(*S*)-1-NpthCHMeNCO	−42	**4c**	(*S*p)-2-CONH-C^{S}HMeNpth	19	−166[b]		
								(*R*p)-2-CONH-C^{S}HMeNpth	33	−38[b]	27[d]	*R*
5	$PhCH_2OMe$	A	*sec*	1.5	Me_3SiCl	−78	**5**[a]	α-$SiMe_3$	68	0[b]	0	–
6	PhOMOM	A	*n*	1.5	Me_3SiCl	−78	**4d**	2-$SiMe_3$	60	+237[b]	56	*S*
7	PhOMOM	A	*sec*	1.5	(*R*)-PhCHMeNCO	−42	**4e**	(*S*p)-2-CONH-C^{R}HMePh	69	+86[b]	72[d]	*S*
								(*R*p)-2-CONH-C^{R}HMePh	11	−131[b]		
8	PhOMOM	A	*sec*	1.5	(*S*)-PhCHMeNCO	−42	**4e**	(*R*p)-2-CONH-C^{S}HMePh	2	−98[b]		
								(*S*p)-2-CONH-C^{S}HMePh	19	+138[b]	81[d]	*S*
9	PhOMOM	C	*n*	3.5	$(CH_2O)_n$	−78	**4f**	2-CH_2OH	58	+247[e]	92	*S*
10	4-TIPSOCH_2-$C_6H_4OCH_3$	B	*n*	3.0	DMF	−78	**7a**	2-CHO	54[f]	+57[c]	12	*R*
11	4-TIPSOCH_2-$C_6H_4OCH_2OMe$	A	*n*	3.0	Me_3SiCl	−78	**7b**	2-$SiMe_3$	45	+76[e]	58	*S*
12	4-TIPSOCH_2-$C_6H_4OCH_2$-OMe	A	*n*	3.0	Me_3SiOTf	−78	**7b**	2-$SiMe_3$	63	+33[b]	30	*S*
13	4-TIPSOCH_2-$C_6H_4OCH_2OMe$	B	*n*	3.5	DMF	−78	**7c**	2-CHO	86	−294[b]	40	*S*
14	4-TIPSOCH_2-$C_6H_4OCH_2OMe$	B	*n*	3.0	Ph_2CO	−78	**7d**	2-CH(OH)Ph_2	75	+18[b]	40	*S*

Table 1 (*Continued*)

No.	Substrate ligand	Method	BuLi	Sparteine (equiv.)	Electrophile	Quench temp. (°C)	Product[a]	(Planar chirality) and substituent Y	Yield (%)	$[\alpha]_D^{24}$	E.e. (%) of lithiation	Selectivity
15	4-TIPSOCH$_2$-C$_6$H$_4$OCH$_2$-CH$_2$OCH$_3$	B	*n*	3.0	DMF	−78	**7e**	2-CHO	50[g]	−247[b]	15	*S*
16	4-TIPSOCH$_2$-C$_6$H$_4$OCH$_2$-OCH$_2$CH$_3$	B	*n*	3.0	DMF	−78	**7f**	2-CHO	83	−525[c]	32	*S*
17	4-TIPSOCH$_2$-C$_6$H$_4$OMEM[h]	B	*n*	3.0	DMF	−78	**7g**	2-CHO	98	−106[b]	16	*S*
18	PhNHBoc	A	*sec*[i]	6.0	Me$_3$SiCl	−78	**4g**	2-SiMe$_3$	26	+45[b,j]	47	*S*

[a] These products characterised in racemic form in Ref. 25 or Ref. 26 (for run 5).
[b] $c=0.2$ in $CHCl_3$.
[c] $c=0.3$ in DCM.
[d] Assuming no diastereoselectivity in the quenching process.
[e] $c=0.8$ in DCM.
[f] 34% of racemic metasubstituted product 3-CHO isolated (see Ref. 25 for characterisation).
[g] 28% of racemic metasubstituted product 3-CHO isolated (see Ref. 25 for characterisation).
[h] MEM = $CH_2OCH_2CH_2OMe$.
[i] 3 equiv. of BuLi used.
[j] Rotations measured at 27°C.

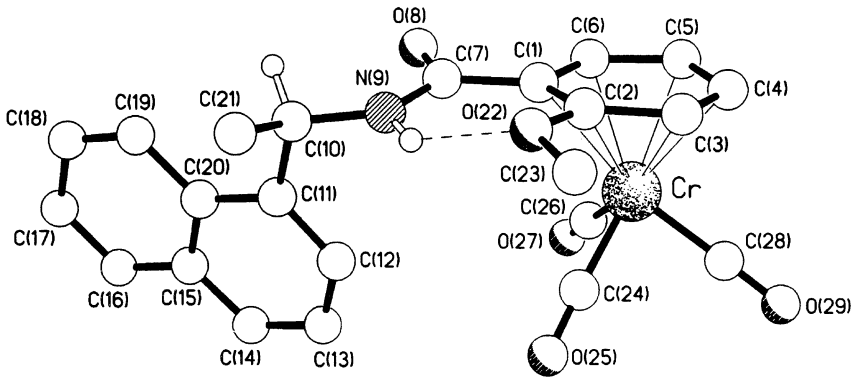


Figure 1. The molecular structure of (*S*p,*R*)-**4c**, the N···O,H···O distances (Å) and N–H···O angle (°) are 2.68, 1.96 and 136

This confirmed the (*R*p)-isomer as the predominant enantiomer but the e.e. was only 17% as assessed by isolated material. The converse check on the enantioselectivity by the use of the enantiomeric (*S*)-isocyanate (run 4) gave (*R*p,*S*)-**4c** as the major product (27% e.e.) again confirming the initial deprotonation to be (*R*)-selective. However, the e.e. values for the deprotonations were low and a more strongly coordinating directing group was necessary.

We turned next to the benzyl methyl ether complex **3c** because the ether oxygen atom is suitably situated for coordination of the incoming base, but there is no significant activation of the α-protons by the methoxymethyl group and this would be a test of the effectiveness of the coordinative element of enantioselection. However, with no ring proton activation, the acidity of the benzylic protons proved to be too great[12,13,26] and no ring lithiation could be detected. A chlorotrimethylsilane quench (run 5) gave only the racemic α-silylated product **5**.

To incorporate both of the features of directed lithiation, we chose the phenol methoxymethyl (MOM) ether complex **3d**. Lithiation as above with a chlorosilane quench (run 6) gave a 60% yield of the product **4d** of 56% e.e. The enantiomers were identified and the sense of the enantioselectivity confirmed by quenching the lithiated intermediate with (*R*)- and (*S*)-α-methyl-1-phenylisocyanates (runs 7, 8), analogous to the naphthyl isocyanate use above, to give the (*S*p,*R*)-**4e** (69% isolated yield) and the (*S*p,*S*)-**4e** (19% isolated yield) as the respective major isomers, as determined by X-ray analysis of the minor (*R*p,*R*)-product of the former (Fig. 2). The relative geometries of the two side chains in compound (*R*p,*R*)-**4e** are very similar to those seen in the (*S*p,*R*)-**4c** above, there being only small torsional twists about the C(2)–C(11) and C(1)–O(7) bonds (ca. 9 and 14°, respectively) and a stabilising N–H···O hydrogen bond between them. The C(11)–N(12)–C(13)–C(20) torsion angle is ca. 77°. The OCH_2OMe group has *gauche* geometries about the O(7)–C(8) and C(8)–O(9) bonds. The packing of the molecules is similar to that seen for (*S*p,*R*)-**4c** with the formation of C–H···π linked helical chains. The use of the minor isomer (*R*p,*R*)-**4e** for X-ray analysis was determined simply by the greater ease of production of suitable crystals for this diastereomer. The e.e. values for lithiation, as assessed by isolated material, were 72 and 85%, respectively, assuming no diastereoselection in the quenching process.

Subsequently, after a very considerable optimisation programme, a paraformaldehyde quench (run 9) was shown to give a 58% yield of the enantiomeric hydroxymethyl products **4f**, which were separated by HPLC to establish a 92% e.e. X-Ray analysis of the major product (Fig. 3) confirmed the (*S*)-selectivity of the initial lithiation process.

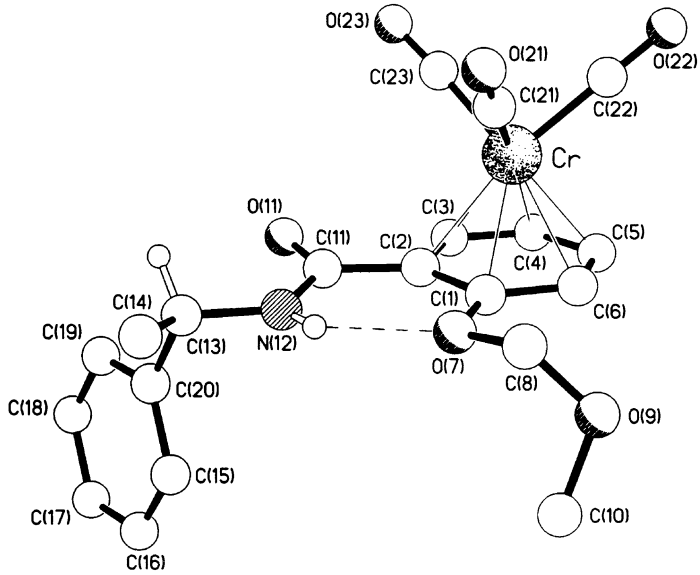


Figure 2. The molecular structure of (*R*p,*R*)-**4e**, the N···O,H···O distances (Å) and N–H···O angle (°) are 2.73, 2.03 and 134. For the enantiomer, (*S*p,*S*)-**4e** [C(13)-*S*], the equivalent parameters are 2.72, 2.05 and 131

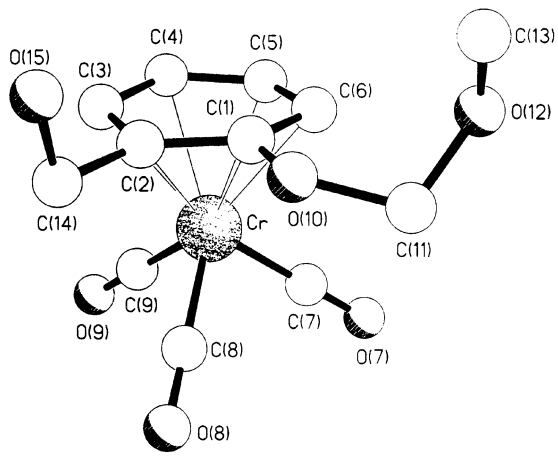
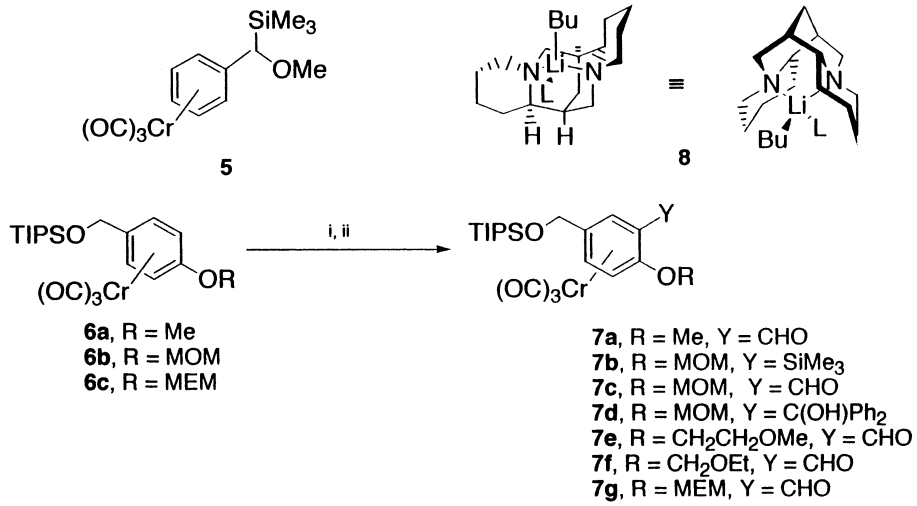


Figure 3. The molecular structure of one of the four independent molecules in the crystals of (*S*p)-**4f**

Compound (*S*p)-**4f** was found to crystallise with four independent molecules (**A**–**D**) in the asymmetric unit, all of which have an (*S*)-planar chirality, but different relative conformations for their OMe and OCH_2OMe groups. The conformations are characterised by the presence of different combinations of *gauche* and *anti* geometries associated with the C(1)–C(2)–C(14)–C(15) and C(1)–O(10)–C(11)–C(12) chains. In the four independent molecules the conformations of these chains are (+*g*, +*g*), (*a*, +*g*), (+*g*, −*g*) and (*a*, −*g*) for **A** to **D**, respectively. The molecule with the (+*g*, +*g*) conformation is illustrated in Fig. 3; the torsional twists about the C(11)–O(12) bond in the four molecules are +*g*, +*g*, −*g* and −*g* for **A** to **D**, respectively. Each molecule is linked to an independent neighbour by an O–H···O hydrogen bond between the hydroxy group O(15) in one molecule and its counterpart in the next, and so on (i.e. **A** to **B** to **C** to **D**). Each

set of four hydrogen bonded independent molecules is hydrogen bonded to its symmetry related neighbour to form a helical chain (i.e. –**A**–**B**–**C**–**D**–**A**–**B**–**C**–**D**–); the O···O distances are in the range 2.74–2.81 Å with H···O distances between 1.90 and 2.24 Å.

The lithiation/quench process was therefore extended to the 4-triisopropylsilyloxymethyl analogues **6** (Scheme 2 and Table 1, runs 10–17) which, under the optimised conditions, produced the 2-substituted (*S*p)-products **7** in 45–86% yield, but the e.e. was lower at 15–58%. Extension of the coordinating arm to the MEM (2-methoxyethoxymethoxy-) group gave an excellent 98% yield, but a low 16% e.e., a result attributable to the added bulk of the directing group.[25] Finally, the Boc-aniline complex **3e** was converted to the 2-silylated product **4g** in 26% yield and 47% e.e. again with the (*S*)-selectivity but with poor enantioselectivity.



Scheme 2. Reagents: i. BuLi/(–)sparteine, –78°C, hexane–Et_2O; ii. quench Y, –78°C→rt

With MOM–ether established as the preferred directing group we examined the effect of some alternative chiral ligand–organolithium base combinations on these and other ethers. The results are given in Table 2.

The use of the C_2-symmetric (–)-α-isosparteine–butyllithium combination **8**[24] under otherwise identical conditions, together with a DMF quench (entry 1), gave the formylated product in 66% yield, but only 16% e.e. ($[\alpha]_D^{24}$ +115, $c=0.2$ in $CHCl_3$) compared with 86 and 40%, respectively, for the (–)-sparteine mediated process. Remarkably, the major isomer was the (*R*)-enantiomer. Other ligands tested were (+)-(1*R*,2*R*)-1,2-dimethoxy-1,2-diphenylethane (entries 2, 3 and 4) and (1*R*,2*R*)-*trans*-1,2-bis(dimethylamino)cyclohexane (entry 5), the latter in toluene as solvent to maximise ligand base coordination, but in no case did the alternative ligand exceed the better yield/e.e. combinations observed with (–)-sparteine–butyllithium.

The results for the MOM–ether and the Boc–amine complexes represent a complete reversal of the selectivity observed for the anisole complex. A reasonable explanation for this reversal is the operation of non-coordination or coordination control of the approach of the chiral base complex. The weak or non-coordination by phenolic oxygen atom of the anisole complex referred to above would result in approach from of the bulky sparteine–lithium moiety *anti* to the methoxy group. Conversely, the coordination of the base complex by the remote oxygen of the MOM or BocNH groups would result in approach of the sparteine–lithium moiety *syn* to the directing group thereby reversing the local spatial selectivity of the base.

Table 2
Effect of chiral ligand variation on asymmetric deprotonation

No.	Substrate	Chiral ligand	Method[a]	Conditions	Quench	Yield (%)	E.e. (%)	Configuration
1	**6**, R = CH_2OMe	(−)-α-Isosparteine	B	−78°C/hexane–Et_2O	DMF	66 (87)[b]	16 (42)[b]	*R* (*S*)
2	**6**, R = Me	(+)-(1*R*,2*R*)-1,2-Dimethoxy-1,2-diphenylethane	D	−78°C/toluene	DMF	51	19	*R*
3	**6**, R = CH_2OMe	(+)-(1*R*,2*R*)-1,2-Dimethoxy-1,2-diphenylethane	D	−78°C/toluene	DMF	76 (67)	10 (41)	*R* (*S*)
4	**6**, R = MEM	(+)-(1*R*,2*R*)-1,2-Dimethoxy-1,2-diphenylethane	D	−78°C/toluene	DMF	70	33	*R*
5	**3**, X = CH_2OMe	(1*R*,2*R*)-*trans*-1,2-bis(dimethylamino)cyclohexane	A	−79°C/hexane–Et_2O	$(CH_2O)_n$	10	7	*R*

[a] See Experimental for details.
[b] Reference data for (−)-sparteine under the same conditions.

In principle, this allows access to either enantiomer of the chiral chromium complexes but the e.e. values for the methoxy-controlled (*R*)-lithiations (20–30%) were not of practical use. However, the MOM-directed (*S*)-lithiations, optimised at 92% e.e. and 58% yield (Table 1, run 9) create the opportunity for application to enantioselective synthesis and subsequent papers will report both this and an alternative access to the (*R*)-enantiomeric series.

3. Experimental

General reagents and conditions were as previously described.[25] (−)-Sparteine was distilled from calcium hydride. Optical rotations were measured using a 1 dm path length (c given as g/100 mL) on a Perkin–Elmer 141 polarimeter in $CHCl_3$. Analytical HPLC was performed on a Gilson HPLC (Gilson UV–Vis detector) or a Unicam Crystal 200 (Unicam UV–Vis detector) instrument—enantiomer analysis was performed using Chiralcel OD-H and AS columns (Diacel Chemical Industries, Ltd.).

For consistency, the complexed aryl carbon attached to the directing group is designated as C-1 throughout and is the reference point for the assignment of planar chirality.

3.1. General procedure for the stereoselective deprotonation of arenetricarbonylchromium(0)

3.1.1. Method A

A solution of (−)-sparteine or (1*R*,2*R*)-*trans*-1,2-bis(dimethylamino)cyclohexane as appropriate (1.5–3.0 equiv.) in deoxygenated ether (8 mL) at −78°C was treated with the alkyllithium (1.5 mmol, 1.5 equiv.) and the solution left to stir for 30 min at −78°C. A solution of the substrate complex (1 mmol, 1 equiv.) in ether (2 mL) was added and the resultant solution left to stir for a further 4 h at −78°C. The electrophile (5 mmol, 5 equiv.) was added, either at −78 or at −42°C. and the solution allowed to warm slowly to rt overnight. The product mixture was washed twice with water and once with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Flash column chromatography furnished the functionalised complex. The results are presented in Table 1 which includes specific rotations for products previously fully characterised in racemic form.[25] Data for diastereomers **4c** and **4e,** for which full characterisation has not been previously reported, are as follows.

*(1*R*p,1′*R*)-η*^{6}*-{2-[1-(1-Naphthyl)ethylamido]anisole}tricarbonylchromium(0)* (R*p*,R)-***4c*** the major product from anisole complex **3b**, on lithiation as above and quenching with (*R*)-1-(1-naphthyl)ethyl isocyanate, isolated as bright orange crystals (27%) from DCM/hexane, $[\alpha]_D^{24}$ +171 (*c* 0.2 in $CHCl_3$) mp 57–59°C (found: C, 63.10; H, 4.88; N, 2.90. $C_{23}H_{19}CrNO_5$ requires C, 62.59; H, 4.34; N, 3.17%); ν_{max} (Nujol)/cm^{-1} 2930m, 1966vs, 1885vs, 1656m, 1525 and 1460; δ_H (270 MHz; $CDCl_3$) 8.21–7.43 (7H, m, Npth), 7.68 (1H, brd, N*H*), 6.58 (1H, dd, J_1 1.49 Hz, J_2 6.43 Hz, ArC(3)*H*), 6.04 (1H, quint, *J* 6.93 Hz, C^R*H*), 5.68 (1H, dt, J_1 1.49 Hz, J_2 6.43 Hz, ArC(5)*H*), 5.02–4.97 (2H, m, ArC(4,6)*H*), 3.73 (3H, s, OMe) and 1.76 (3H, d, *J* 6.68 Hz, Me); δ_C (75 MHz) 162.2 (*C*=O), 141.5 (Ar*C*(1)-O), 138.6 (Npth*C*(1′)-CH), 134.1, 130.9 (Npth*C*(5,10)), 128.9, 128.3, 126.5, 125.8, 125.4, 123.5, 122.7 (Npth*C*H), 96.8, 94.8 (Ar*C*H), 85.3 (Ar*C*(2)-C=O), 85.0, 73.1 (Ar*C*H), 56.4 (OMe), 46.1 (*C*^{R}H) and 21.5 (Me); *m*/*z* (CI) 459 (M^++NH_4), 442 (M^++H), 306 (442–$Cr(CO)_3$) and 151 (306–CH(Me)Npth). Found: M^+ 442.0752; $C_{23}H_{20}CrNO_5$ requires 442.0747.

*(1*S*p,1′*R*)-η*^{6}*-{2-[1-(1-Naphthyl)ethylamido]anisole}tricarbonylchromium(0) (*S*p,R*)-**4c*** was the minor product from anisole complex **3b** on lithiation as above and quenching with (*R*)-1-(1-naphthyl)ethyl isocyanate, isolated as orange crystals (19%), $[\alpha]_D^{24}$ +30 (*c* 0.2 in $CHCl_3$), mp 165–174°C (found: C, 62.44; H, 4.09; N, 3.15. $C_{23}H_{19}CrNO_5$ requires: C, 62.59; H, 4.34; N, 3.17%); ν_{max} (Nujol)/cm^{-1} 2923m, 1966vs, 1881vs, 1657m, 1524 and 1456; δ_H (270 MHz; $CDCl_3$) 8.11–7.43 (8H, m, Npth, N*H*), 6.58 (1H, dd, J_1 1.24 Hz, J_2 6.43 Hz, ArC(3)*H*), 5.99 (1H, quint, *J* 6.93 Hz, C^R*H*), 5.67 (1H, ddd, J_1 1.49 Hz, J_2 6.18 Hz, J_3 7.67 Hz, ArC(5)*H*), 5.30–4.93 (2H, m, ArC(4,6)*H*), 3.75 (3H, s, OMe) and 1.73 (3H, d, *J* 6.68 Hz, Me); δ_C (75 MHz) 162.3 (*C*=O), 141.74 (Ar*C*(1)-O), 138.3 (Npth*C*(1′)-C^{R}H), 134.1, 131.0 (Npth*C*(5,10)), 128.8, 128.3, 126.6, 125.8, 125.2, 123.4, 122.2 (Npth*C*H), 97.0, 94.9 (Ar*C*H), 85.5 (Ar*C*(2)-C=O), 84.5, 72.7 (Ar*C*H), 56.4 (OMe), 46.1 (*C*^{R}H) and 21.2 (Me); *m*/*z* (CI) 459 (M^++NH_4), 442 (M^++H), 306 (M^+–$Cr(CO)_3$) and 276 (306–OMe+H). Found: M^+ 442.0739; $C_{23}H_{20}CrNO_5$ requires: 442.0747.

*Crystal data for (*S*p,*R*)-**4c***: $C_{23}H_{19}NO_5Cr$, $M=441.4$, orthorhombic, space group $P2_12_12_1$ (no. 19), $a=10.767(1)$, $b=12.623(2)$, $c=15.303(2)$ Å, $V=2079.8(4)$ Å^3, $Z=4$, $D_c=1.410$ g cm^{-3}, μ(Mo-Kα)=5.84 cm^{-1}, $T=293$ K, yellow prisms; 2091 independent measured reflections, F^2 refinement, $R_1=0.046$, $wR_2=0.096$, 1492 independent observed reflections [$|F_o|>4\sigma(|F_o|)$, $2\theta\leq 50°$], 276 parameters. The absolute chirality of *S*p,*R*-**4c** was determined by a combination of *R*-factor tests [$R_1^+=0.0460$, $R_1^-=0.0516$] and by use of the Flack parameter [$x^+=-0.06(5)$]. CCDC 155404.

*(1*R*p,1′*S*)-η*^{6}*-{2-[1-(1-Naphthyl)ethylamido]anisole}tricarbonylchromium(0) (*R*p,S*)-**4c*** was the major product from anisole complex **3b** on lithiation as above and quenching with (*S*)-1-(1-naphthyl)ethyl isocyanate, isolated in 33% yield, $[\alpha]_D^{24}$ −38 (*c* 0.2 in $CHCl_3$), spectroscopically as the enantiomer above.

*(1*S*p,1′*S*)-η*^{6}*-{2-[1-(1-Naphthyl)ethylamido]anisole}tricarbonylchromium(0) (*S*p,S*)-**4c*** was the minor product from anisole complex **3b** on lithiation as above and quenching with (*S*)-1-(1-naphthyl)ethyl isocyanate, isolated in 19% yield, $[\alpha]_D^{24}$ −166 (*c* 0.2 in $CHCl_3$), spectroscopically as the enantiomer above.

*(1*S*p,1′*R*)-η*^{6}*-[2-(1-Phenylethylamido)methoxymethoxybenzene]tricarbonylchromium(0) (*S*p,R*)-**4e*** was the major product from methoxymethoxybenzene complex **3d** on lithiation as above and quenching with (*R*)-1-phenylethyl isocyanate, isolated as bright orange crystals from DCM/hexane (69%); $[\alpha]_D^{24}$ +86 (*c* 0.2 in $CHCl_3$); mp 73–75°C (found: C, 57.59; H, 4.89; N, 3.38. $C_{20}H_{19}CrNO_6$ requires C, 57.01; H, 4.55; N, 3.32%); ν_{max} (Nujol)/cm^{-1} 3415w, 1968vs, 1885, 1659, 1525m and 1452m; δ_H (270 MHz; $CDCl_3$) 7.59 (1H, brd, *J* 7.08 Hz, N*H*), 7.39–7.27 (5H, m, Ph), 6.52 (1H, dd, J_1 1.35 Hz, J_2 6.54 Hz, ArC(3)*H*), 5.68 (1H, dt, J_1 1.38 Hz, J_2 6.15 Hz, ArC(5)*H*), 5.33 (1H, dd, J_1 1.0 Hz, J_2 6.8 Hz, ArC(6)*H*), 5.32–5.20 (1H, m, C^R*H*), 5.22 (1H, d, *J* 6.8 Hz, O-CH_2-O), 5.17 (1H, d, *J* 6.75 Hz, O-CH_2-O), 5.00 (1H, t, *J* 6.48 Hz, ArC(4)*H*), 3.52 (3H, s, OMe) and 1.58 (3H, d, *J* 6.90, Me); δ_C (75 MHz) 162.5 (*C*=O), 143.1 (Ar*C*(1)-O), 139.5 (Ph*C*-CH), 128.8, 127.3, 125.8 (Ph*C*H), 96.6, 96.3, 95.3 (Ar*C*H), 85.8 (Ar*C*-C=O), 85.2 (Ar*C*H), 76.8 (O-*C*H_2-O), 57.7 (OMe), 49.5 (Ph-*C*^{R}H) and 22.3 (Me); *m*/*z*(EI) 337 (M^+–$(CO)_3$), 292 (337–CH_2OMe), 240 (292–Cr), 120 (240–NHCH(Me)Ph) and 105 (CH(Me)Ph). Found: M^+ 421.0611; $C_{20}H_{19}CrNO_6$ requires: 421.0617.

*(1*R*p,1′*R*)-η*^{6}*-[2-(1-Phenylethylamido)methoxymethoxybenzene]tricarbonylchromium(0) (*R*p,R*)-**4e*** was the minor product from methoxymethoxybenzene complex **3d** on lithiation as above and quenching with (*R*)-1-phenylethyl isocyanate, isolated as bright orange crystals (11%) from

DCM/hexane, $[\alpha]_D^{24}$– 131 (*c* 0.8 in $CHCl_3$); mp 143–146°C (found: C, 56.79; H, 4.75; N, 3.26. $C_{20}H_{19}CrNO_6$ requires: C, 57.01; H, 4.55; N, 3.32%); ν_{max} (Nujol)/cm^{-1} 3400m, 1965vs, 1885 and 1656; δ_H (270 MHz; $CDCl_3$) 7.55 (1H, brd, *J* 6.75 Hz, N*H*), 7.43–7.22 (5H, m, Ph), 6.48 (1H, dd, J_1 1.48 Hz, J_2 6.43 Hz, ArC(3)*H*), 5.63 (1H, ddd, J_1 1.49 Hz, J_2 5.94 Hz, J_3 6.80 Hz, ArC(5)*H*), 5.32 (1H, dd, J_1 0.87 Hz, J_2 6.80 Hz, ArC(6)*H*), 5.3–5.2 (1H, m, C^RH), 5.23 (1H, d, *J* 6.68 Hz, O-CH_2-O), 5.11 (1H, d, *J* 6.68 Hz, O-CH_2-O), 5.00 (1H, dt, J_1 0.74 Hz, J_2 6.31 Hz, ArC(4)*H*), 3.48 (3H, s, OMe) and 1.57 (3H, d, *J* 4.45, Me); δ_C (75 MHz) 162.4 (*C*=O), 143.3 (Ar*C*(1)-O), 139.1 (Ph*C*-C^RH), 128.8, 127.5, 126.0 (Ph*C*H), 96.3, 96.2, 95.0 (Ar*C*H), 86.0 (Ar*C*-C=O), 85.5 (Ar*C*H), 77.1 (O-*C*H_2-O), 57.6 (OMe), 49.7 (Ph-*C*^RH) and 22.2 (Me); *m*/*z*(EI) 421 (M^+), 365 (M^+–CO), 337 (M^+–$(CO)_3$), 292 (337–CH_2OMe), 240 (292–Cr) and 120 (240–NHCHPh(Me). Found: M^+ 421.0613; $C_{20}H_{19}CrNO_6$ requires: 421.0617.

Crystal data for R*p*,R-***4e*** $C_{20}H_{19}NO_6Cr$, M=421.4, orthorhombic, space group $P2_12_12_1$ (no. 19), a=11.758(5), b=11.816(6), c=14.090(5) Å, V=1958(1) Å^3, Z=4, D_c=1.430 g cm^{-3}, μ(Mo-Kα)=6.20 cm^{-1}, T=293 K, yellow blocks; 1968 independent measured reflections, F^2 refinement, R_1=0.036, wR_2=0.086, 1651 independent observed reflections [$|F_o|>4\sigma(|F_o|)$, $2\theta \leq 50°$], 245 parameters. The absolute chirality of *R*p,*R*-**4e** was determined by a combination of *R*-factor tests [R_1^+=0.0363, R_1^-=0.0406] and by use of the Flack parameter [x^+=+0.09(4), x^-=+0.91(4)]. CCDC 155405.

*(1*S*p,1′*S*)-η*^{6}*-[2-(1-Phenylethylamido)methoxymethoxybenzene]tricarbonylchromium(0)* (S*p*,S)-***4e*** was the major product from methoxymethoxybenzene complex **3d** on lithiation as above and quenching with (*S*)-1-phenylethyl isocyanate, isolated as bright orange crystals from DCM/hexane (19%), $[\alpha]_D^{24}$ +138 (*c* 0.8 in $CHCl_3$); spectroscopically as the enantiomer above.

The crystal structure of (*S*p,*S*)-**4e** was essentially identical, but antipodal, to that of (*R*p,*R*)-**4e**. *Crystal data for (*S*p,S)-**4e***: $C_{20}H_{19}NO_6Cr$, M=421.4, orthorhombic, space group $P2_12_12_1$ (no. 19), a=11.752(5), b=11.808(5), c=14.094(7) Å, V=1956(1) Å^3, Z=4, D_c=1.431 g cm^{-3}, μ(Mo-Kα)=6.21 cm^{-1}, T=293 K, yellow cubes; 1970 independent measured reflections, F^2 refinement, R_1=0.039, wR_2=0.086, 1577 independent observed reflections [$|F_o|>4\sigma(|F_o|)$, $2\theta \leq 50°$], 245 parameters. The absolute chirality of *(Sp,S)-**4e*** was determined by a combination of *R*-factor tests [R_1^+=0.0390, R_1^-=0.0444] and by use of the Flack parameter [x^+=–0.09(5), x^-=+1.09(5)]. CCDC 155406.

*(1*R*p,1′*S*)-η*^{6}*-[2-(1-Phenylethylamido)methoxymethoxybenzene]tricarbonylchromium(0)* (R*p*,S)-***4e*** was the minor product from methoxymethoxybenzene complex **3d**, on lithiation as above and quenching with (*S*)-1-phenylethyl isocyanate, isolated in 2% yield, $[\alpha]_D^{24}$ –98 (*c* 0.2 in $CHCl_3$), spectroscopically as the enantiomer above.

3.1.2. Method B

A solution of the complex in a mixture of deoxygenated ether–cyclohexane (3:1) (4 mL) at –78°C was added to a solution of the sparteine isomer (3 equiv.) and *n*-BuLi (1.1 equiv.) in a mixture of ether–cyclohexane (3:1) (12 mL) at –78°C. The resultant solution was allowed to stir for a further 1 h, then quenched with a suitable electrophile (1–5 equiv.) which was dissolved in a mixture of ether–cyclohexane at –78°C and allowed to warm up slowly to rt over 2 days. After work-up, the organic layer was washed twice with water and once with brine, dried ($MgSO_4$) and concentrated under reduced pressure. FCC furnished the desired functionalised complex. The results are presented in Table 1 which includes specific rotations for products previously fully characterised in racemic form.[25]

3.1.3. Method C

A solution of (−)-sparteine (3.7 equiv., 0.31 mL, 1.369 mmol) in a deoxygenated mixture of ether (3 mL) and hexane (0.5 mL) at −78°C was treated with *n*-butyllithium (1.35 equiv., 0.50 mmol) and the solution stirred for 30 min at −78°C. A solution of η^6-(methoxymethoxybenzene)tricarbonylchromium(0) **3d** (1 equiv., 0.1 g, 0.37 mmol) in ether (1 mL) was added and the resultant solution stirred for further 4 h at −78°C. Paraformaldehyde (5 equiv., 55 mg, 1.85 mmol) was added and the solution was allowed to warm up to −10°C over 3 h. The reaction was then worked up as described in Method A to give (1-*S*p)-η^6-[2-(hydroxymethyl)methoxymethoxybenzene]tricarbonyl chromium(0), (*S*p)-**4f**, as the major product in 58% yield and of 92% e.e. Spectroscopically this was as previously described.[25]

*Crystal data for (Sp)-**4f***: $C_{12}H_{12}O_6Cr$, $M=304.2$, orthorhombic, space group $P2_12_12_1$ (no. 19), $a=13.190(1)$, $b=14.490(1)$, $c=28.047(3)$ Å, $V=5360.4(9)$ Å^3, $Z=16$ (there are four crystallographically independent molecules in the asymmetric unit), $D_c=1.508$ g cm^{-3}, μ(Cu-Kα)=72.3 cm^{-1}, $T=293$ K, yellow platelike needles; 4702 independent measured reflections, F^2 refinement, $R_1=0.063$, $wR_2=0.145$, 3240 independent observed absorption corrected reflections [$|F_o|>4\sigma(|F_o|)$, $2\theta\leq124°$], 702 parameters. The absolute chirality of (*S*p)-**4f** was determined by a combination of *R*-factor tests [$R_1^+=0.0629$, $R_1^-=0.0914$] and by use of the Flack parameter [$x^+=-0.01(2)$, $x^-=+1.01(2)$]. CCDC 155407.

3.1.4. Method D

A solution of the complex (1 equiv.) in deoxygenated toluene was added to a solution of (+)-(1*R*,2*R*)-1,2-dimethoxy-1,2-diphenylethane (2 equiv.) and *n*-BuLi (1.1 equiv.) in toluene at −78°C. The resultant solution was allowed to stir for a further hour, then quenched with DMF (1–5 equiv.) and allowed to warm up slowly to rt over 2 days. After work-up with 1 M HCl (10 mL) the organic layer was washed twice with water (10 mL) and once with brine (10 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure and the products purified by FCC. The results are shown in Table 2.

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