Dilithiation of arenetricarbonylchromium(0) complexes with enantioselective quench: application to chiral biaryl synthesis

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Received (in Cambridge, UK) 28th September 2001, Accepted 29th October 2001
First published as an Advance Article on the web 27th November 2001

Dilithiation of methoxymethoxyarenetricarbonylchromium complexes with 2.5 equiv. of butyllithium and 6 equiv. of (−)-sparteine followed by enantioselective electrophilic quench gave the planar chiral (*R*)-complexes in up to 95% ee. This technique was applied to the synthesis of the chromium complexes of biaryl analogues **7** of actinoidinic acid.

Introduction

Enantioselective lithiation with butyllithium–(−)-sparteine **1** (Fig. 1), first introduced by Nozaki *et al.*,[1] and extensively

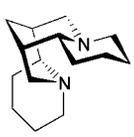

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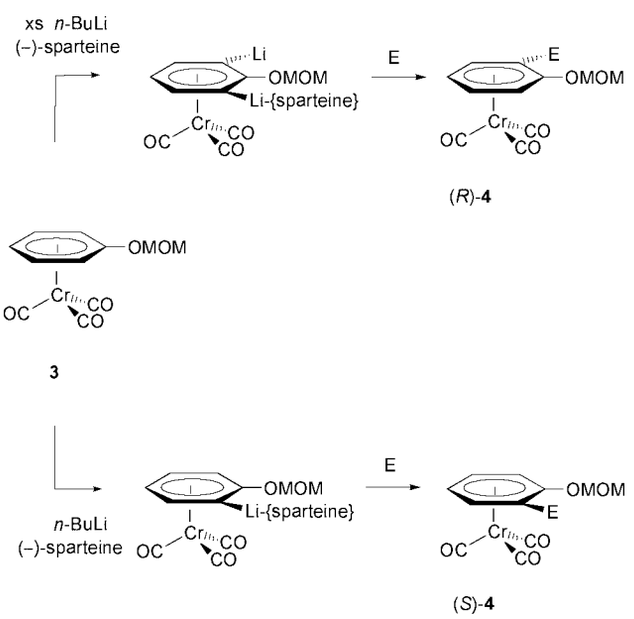
Fig. 1

developed by Hoppe and co-workers,[2–5] is widely used in synthesis. As applied to arenetricarbonylchromium(0) complexes by Uemura *et al.*,[6] who have used a wider range of chiral ligands, this method opens a direct route to planar chiral metal complexes which have found, in recent years, a significant place in organic synthesis.[7] Recently described methods for producing these complexes in enantiopure form include resolution of a racemate,[8,9] diastereoselective complexation,[10,11] and diastereoselective[12] and enantioselective deprotonation[6,13–16] but all but the latter are indirect and cumbersome in comparison with that method.

Recently, we published our investigations into the enantioselective deprotonation, with the (−)-sparteine–butyllithium system, of arenetricarbonylchromium(0) complexes with coordinating functional groups,[17] and its application to *ent*-actinoidinic acid, *ent*-**5**, synthesis.[18] For a synthesis of the natural antipode, **5**, (+)-sparteine would be required and although it can be prepared,[19] it is not currently commercially available. This prompted us to investigate the possibility of obtaining either enantiomer of planar chiral arenetricarbonylchromium(0) complexes with (−)-sparteine as the sole stereodirector.

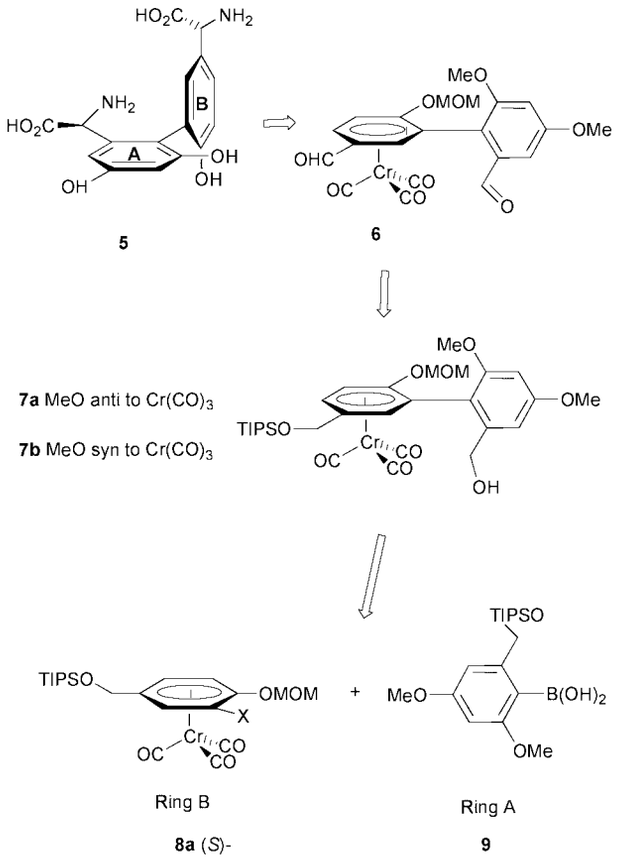
Examples of the generation of both senses of stereoinduction with (−)-sparteine are rare. It has been achieved *via* the use of different electrophiles,[20] solvents[21] or coordinating substituents in the substrate[17,22] and there is one example of enantioselective deprotonation of arenetricarbonylchromium(0) complexes with amide bases, where a change from external to internal quench conditions led to an excess of the opposite enantiomer[23] in a process different to that described here. Davies *et al.* have demonstrated that either diastereomer of a monosubstituted chiral sulfoxide benzenetricarbonylchromium complex was accessible *via* lithiation or dilithiation protocols.[24] In this case the stereocontrol derived from the sulfoxide group on the substrate but we sought to apply the concept to the (−)-sparteine–butyllithium–arenetricarbonylchromium system where the stereocontrol would derive from the reagent. This aspect of this investigation has been reported in preliminary form and is expressed in Scheme 1.[25]



Scheme 1

In addition, as a part of our programme of synthesis of actinoidinic acid **5** (Scheme 2),[18] the biaryl diamino acid unit in vancomycin **2**[26,27] (Fig. 2), and the stereoisomers of **5**, we sought to apply the method to the preparation of the isomers of the chiral precursors **7** of this substance derivable from an **8**–**9** coupling process.

DOI: 10.1039/b108807f



Scheme 2

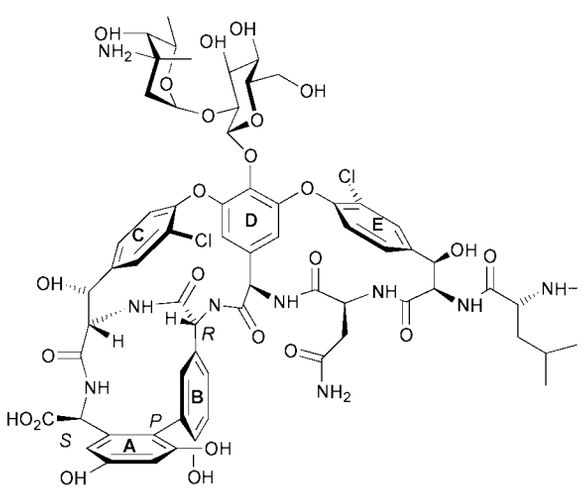


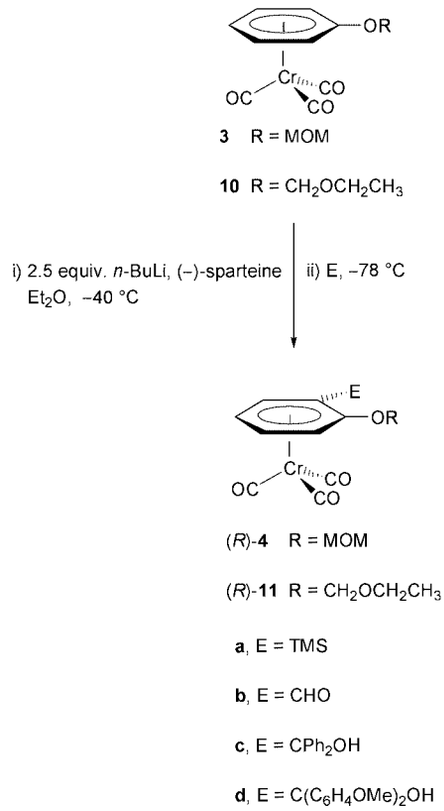
Fig. 2

Results and discussion

Asymmetric quenching of dilithiated arenetricarbonylchromium(0) complexes

In Scheme 1 the mono- and dilithiations of methoxymethoxybenzenetricarbonylchromium(0) complex **3** are shown. Complex **3** had been shown to be a particularly good substrate for enantioselective monolithiation to generate the (*S*)-enantiomers[17] but for this study, the system was optimised for dilithiation.

Thus it was found necessary to raise the temperature to −40 °C for 1 h for sufficient dilithiation and the protocol developed was to premix the excess base–sparteine at −78 °C for 30 min, add the substrate and warm the mixture to −40 °C for 1 h. The mixture was then recooled to −78 °C and the anions so generated were quenched with a range of electrophiles (Scheme 3). The results are shown in Table 1.



Scheme 3

In all cases, except for Run 1, complex **3** gave good ee's and the absolute stereochemistry of the predominant enantiomers of compounds **4b**, **4c** and **4d** was determined as (*R*) by X-ray analysis (Figs. 3–5). In **4b** the three carbonyl groups are oriented

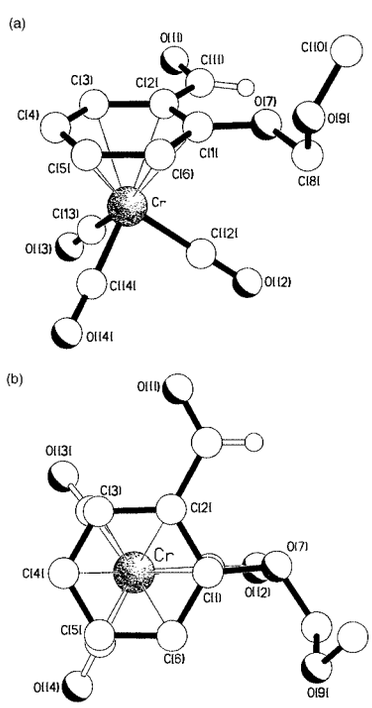


Fig. 3

so as to eclipse the C(1), C(3) and C(5) positions of the aryl ring (Fig. 3a,b), and C(8) of the OMOM lies close to the aromatic ring plane [torsional twist about C(1)–O(7) of *ca.* 6°]; the Cr–C(aryl) distances are in the range 2.198(5) to 2.263(5) Å.

Table 1 (*R*)-Selectivity by dilithiation: asymmetric quench of aryl ether complexes **3**, **10** and **12**

	Substrate	Quench	Product	Yield (%)	Ee (%)[a]	$[\alpha]_D^{24}$
1	**3**	TMSCl	(*R*)-**4a**	27	52	−216[b]
2	**3**	DMF	(*R*)-**4b**	30	95	1002[c]
3	**3**	Benzophenone	(*R*)-**4c**	30[d]	97	—
4	**3**	4,4′-Dimethoxybenzophenone	(*R*)-**4d**	17	94	−38[a]
5	**10**	DMF	(*R*)-**11b**	37	13	36[c]
6	**10**	Benzophenone	(*R*)-**11c**	46	68	−103[b]
7	**10**	4,4′-Dimethoxybenzophenone	(*R*)-**11d**	37	36	−28[b]
8	**12**	DMF	**8b**, X = CHO	60	46	350
9	**12**	C_2Cl_6	**8b**, X = Cl	65	40	−48
10	**12**	$BrCF_2CF_2Br$	**8b**, X = Br	60	30	−29

[a] Ee determined by HPLC (Chiracel OD-H column); yield and $[\alpha]_D$ are those of non-recrystallised material. [b] $c = 0.3$. [c] $c = 0.15$. [d] Not separable from starting material, yield determined by HPLC (Chiracel OD-H column).

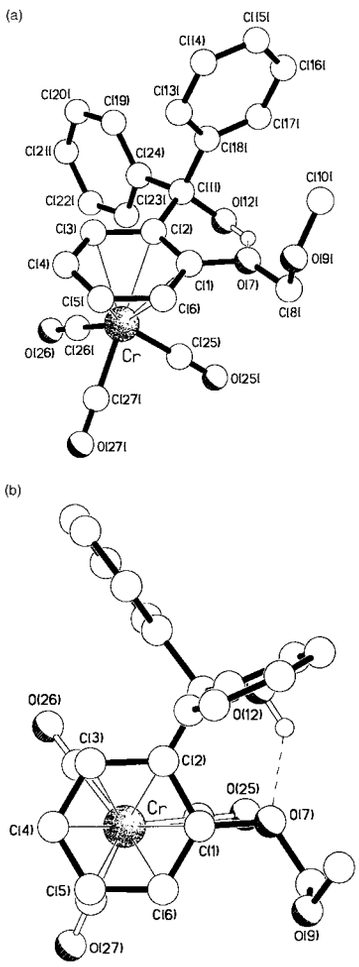


Fig. 4

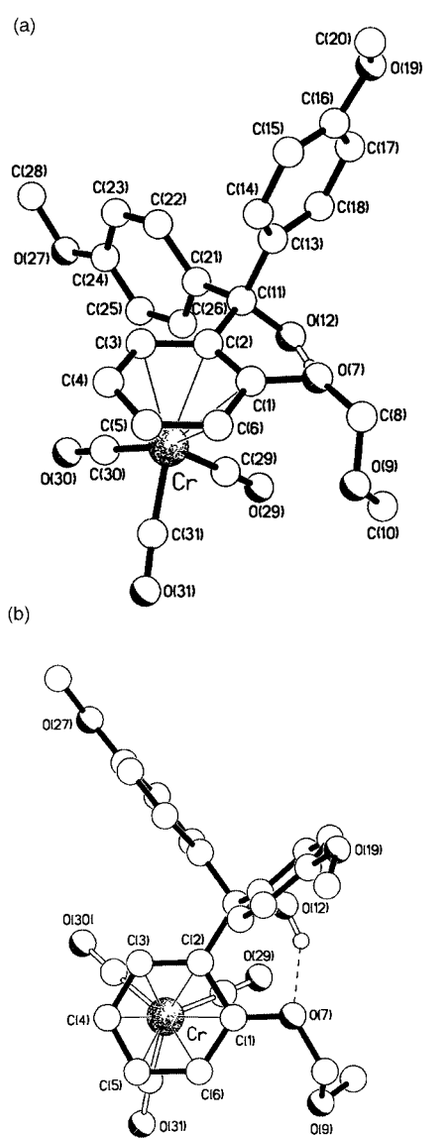


Fig. 5

Complex **4c** also has the same eclipsing geometry of the three carbonyl groups, and an equivalent 6° twist about the C(1)–O(7) bond to the OMOM substituent (Fig. 4a,b); the Cr–C(aryl) bond lengths range between 2.194(3) and 2.266(3) Å. In this latter structure the orientation of the CPh_2OH moiety is to some extent controlled by an intramolecular hydrogen bond between the OH group and O(7) of the OMOM sidearm. The presence of *para*-methoxy groups on the two phenyl rings results in a change in the overall conformation of the molecule with **4d** having its three carbonyl groups rotated *ca.* 20° [in the direction of C(2)] from an eclipsed geometry with the coordinated aryl ring (Fig. 5); C(8) again lies essential coplanar with the aryl ring [C(1)–O(7) of torsional twist of *ca.* 3°]. There is an analogous intramolecular hydrogen bond between the hydroxy group and the OMOM substituent. In the structures of both **4b** and **4c** the terminal OMe group of the OMOM moiety is oriented "above" the plane of the coordinated aryl ring whereas in **4d** it lies on the same side as the chromium centre.

In order to probe the effect of increasing spacial bulk, analogous dilithiations were carried out with the ethoxymethoxyphenol complex **10** and the results, shown in Table 1 (Runs 5–7), demonstrate that the larger end group has a deleterious effect on the selectivity with the ee reduced to low (13% from Run 5, *cf.* 95% from Run 2) to moderate (68% from Run 6 *cf.* 97% from Run 3). In a presumably congested trans-

ition state for lithiation or quenching, the bulk of the directing group is clearly critical.

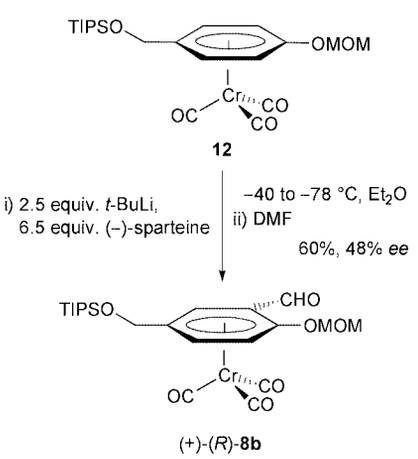
The origin of the enantioselectivities has been discussed previously.[17,25] Here it is sufficient to emphasise that the stereoselection in the dilithiated species is presumed to involve an enantioselective quench of the sparteine complexed intermediate with a preferential attack at the more reactive/less stabilised *pro*-*R*-lithio-centre. The lithio-centres are sufficiently well differentiated to produce up to 97% ee in the (*R*)-product.

This explanation requires the presence of dilithiated material and this was established by a deuteriation study. Firstly, complex **3**, in ether, was added at −78 °C to a solution of 3 equiv. (−)-sparteine and 2 equiv. *n*-BuLi in ether and the reaction quenched with D_2O after 10 min. After this brief treatment, the presence of both mono- and dideuteriated products in a ratio of 100 : 36, determined by HRMS, was observed. This showed that the first lithiation took place rapidly but also that the second lithiation was already evident.

In further experiments, reaction for 4 h at −40 °C and for 8 h at −40 °C, in the latter case with 3 equiv. *n*-BuLi, both gave a mono : di ratio of only 100 : 65. It was considered that a lack of solubility of the monolithio species was affecting further lithiation and the last experiment was repeated with the addition of THF after mixing the reactants, sufficient to produce an almost homogeneous solution and as a result, the mono- to dilithio ratio changed to 74 : 100. Multiple lithiation has already been reported by Gibson *et al.*[28] with the weaker amide bases, but we could detect no trideuterio species from these reactions.

Evidence on the ease of proton transfer between mono- and non-lithiated complexes, a process which could complicate our observations, is conflicting[14] but under our conditions this is not observed.[29,30] However, it may be expected that a dilithiated species will deprotonate the non-lithiated complex **3**. To check this, 1 equiv. of complex **3**, dissolved in ether, was partially dilithiated with a solution of 3 equiv. (−)-sparteine and 2 equiv. *n*-BuLi in ether at −78 °C as before and after 10 min, the mixture was further treated with 1 equiv. of complex **3** in ether. The solution was left to stir for 4 h at −78 °C then quenched with D_2O. The high resolution mass spectrum showed only complex **3** and monodeuteriated complex in a ratio of 20 : 100 indicating that the dilithiated material generated was monoprotonated by proton transfer from **3**.

When the optimised conditions were applied to η^6-[4-(triisopropylsiloxymethyl)(methoxymethoxy)benzene]tricarbonylchromium(0) **12** (Scheme 4) with a DMF quench, complex



Scheme 4

8[17,31] was obtained in 67% yield but as predominantly **8a**, the (*S*)-isomer in 10% ee, $[\alpha]_D^{24}$ −50 (*c* = 0.2, $CHCl_3$). Since this is the product of enantioselective lithiation and is indicative of poor dilithiation, *t*-BuLi base was used and resulted in 60% yield of predominantly (+)-(*R*)-**8b** with an ee of 46%, $[\alpha]_D^{24}$ +350 (*c* = 0.2, $CHCl_3$). Premixing of the (−)-sparteine and the *t*-BuLi was not necessary, since addition of *t*-BuLi to a solution of complex **12** and (−)-sparteine in ether gave the same result.

By manipulation of the degree of lithiation of the system we have thus obtained both enantiomers of functionalised arenechromium complexes derived from prochiral complexes **3**, **10** and **12** and in the case of complex **3** in excellent ee, though in only moderate yield for the (*R*)-series. This control of the stereoselection was achieved by using the same stereogenic ligand, (−)-sparteine, but switching the key step between enantioselective deprotonation and enantioselective electrophilic quench.

Cross-coupling of the ring B complexes

The first objective in the preparation of actinoidinic acid isomers **5** was the preparation of the antipodes of the biaryls **7a** or **b** *via* complexed ring B precursors **8a/b**. Scheme 2 shows the retro-synthesis of actinoidinic acid in which the complexes **7** could be formed directly through the coupling of ring A and B synthons **9** and **8** respectively. Diastereoselective cross-coupling with arenetricarbonylchromium(0) complexes has been reported by Kamikawa and Uemura,[32] and ourselves[33] and we confirmed that, in a Suzuki coupling with these complexes, the larger of the *ortho*-groups of the attacking arylboronic acid will be *syn* to the chromium fragment in the biaryl product as indicated in structure **7a**.

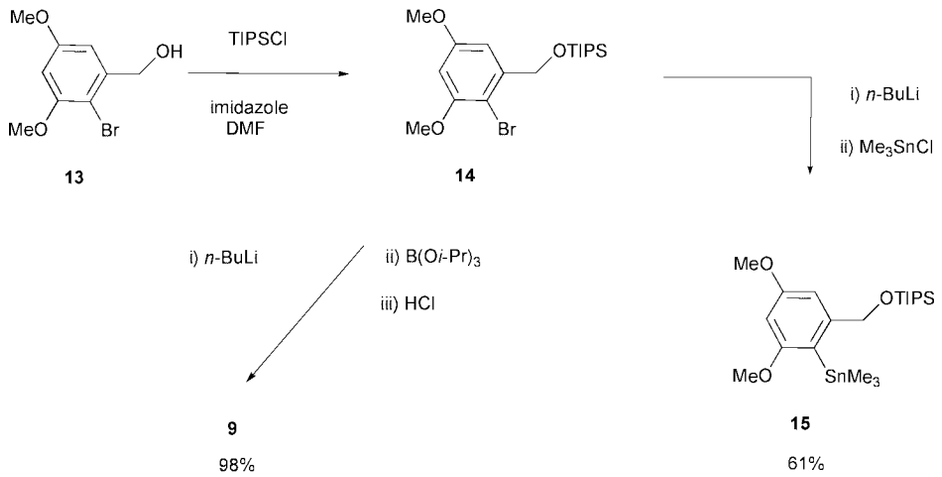
Firstly, the ring B analogues **8**, with X = Br, Cl, were prepared by applying the enantioselective quench technique described above for the (*R*)-series for X = I[31] or with the monodeprotonation technique[17] for the (*S*)-series and in each case, quenching with 1,2-dibromo-1,1,2,2-tetrafluoroethane or hexachloroethane. The results are shown in Table 1 (Runs 8–11).

Analogues of ring A were first prepared and their efficacy in the coupling reaction investigated. Alcohol **13**[34] was protected with a bulky triisopropylsilyl (TIPS) group (Scheme 5) since this should interact strongly with the tricarbonylchromium(0) unit during coupling and it was hoped that this effect would increase the diastereoselectivity of the process. The product **14** was then transformed into the corresponding trimethylstannane **15** by a lithiation–stannylation sequence. The electron rich stannane **15** proved to be too unstable for purification by chromatography. Even when basic alumina was used as the stationary phase considerable protolysis was observed and recrystallisation was the only practical purification technique.

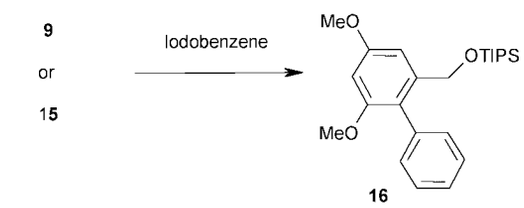
Coupling of stannane **15**, under standard Stille conditions,[35] with iodobenzene in DMA at 90 °C overnight, with tetrakis-(triphenylphosphine)palladium(0) as catalyst, led to a disappointing yield of 16% of the desired coupled product **16** (Scheme 6, Method A). However, the presence of this coupled product did indicate that it was possible to couple this sterically hindered ring A analogue and we explored other methodologies.

The boronic acid **9** was prepared from **14** *via* lithiation and quenching with B(O*i*-Pr)$_3$ to give a crude yield of 98% (Scheme 5). Suzuki coupling of **9** with iodobenzene in DME overnight at room temperature increased the yield of **16** to 56% when CsF was used as base and $Pd_2(dba)_3$ as the source of palladium (Scheme 6, Method B). By using coupling conditions optimised for highly hindered boronic acids[36] it was possible to increase the yield further to 89%. (Scheme 6, Method C).

Alternatively, a less hindered analogue of ring A, the cyclic boronic acid **18**, was prepared by a modification of the method reported by Nicolaou *et al.* (Scheme 7).[37,38] Thus **13**[34] was protected with a THP group in a yield of 98%. The product, (±)-**17**, was then dissolved in THF, lithiated with *n*-BuLi and quenched with B(O*i*-Pr)$_3$. Work-up with 2 M HCl deprotected the alcohol and gave directly the cyclic boronic acid **18**. After recrystallisation from water, the boronic acid was isolated in 72% yield. The overall yield from **13** was 70%.



Scheme 5

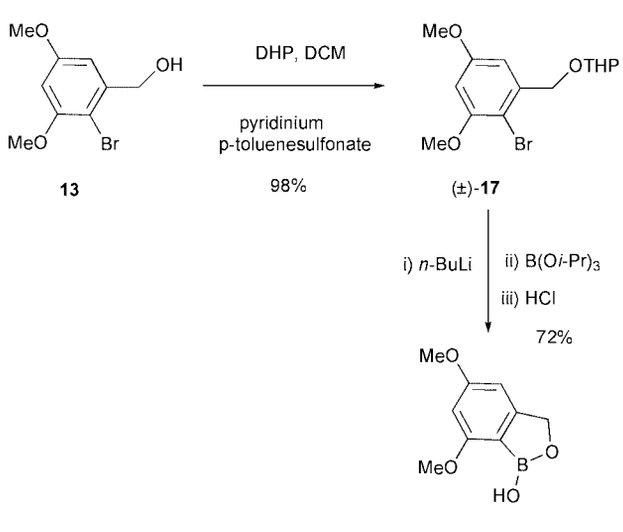


Method A: **15**, $Pd(PPh_3)_4$, DMA, 90 °C, 16 h, 16%

Method B: **9**, $Pd_2(dba)_3$, CsF, DME, 16 h, 56%

Method C: **9**, $Pd(PPh_3)_4$, NaOH, DME/H_2O, 90 °C, 4 h, 89%

Scheme 6



Scheme 7

Cyclic boronic acids of this type have received little investigation, so for unambiguous characterisation, the X-ray structure of **18** (Fig. 6) was determined. The structure clearly shows a planar boron centre [sum of angles at B(1) is 360°] with a relatively short B–C bond length of 1.548(2) Å. Recently, a group published an X-ray structure of 1-hydroxy-1,3-dihydro-2,1-benzoxaborole.[39] The researchers compared their X-ray structure with *ab initio* molecular orbital calculations, which predicted the planar structure at the boron centre and the relatively short B–C bond. Although **18** forms a hydrogen-bonded dimeric structure very similar to that observed in the structure of 1-hydroxy-1,3-dihydro-2,1-benzoxaborole, the pattern of bonding within the oxaborole ring matches much

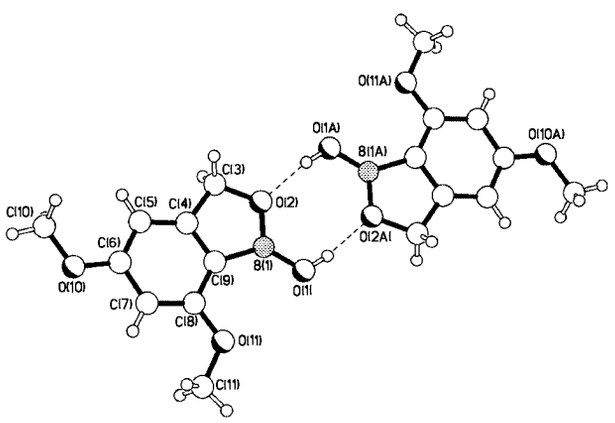
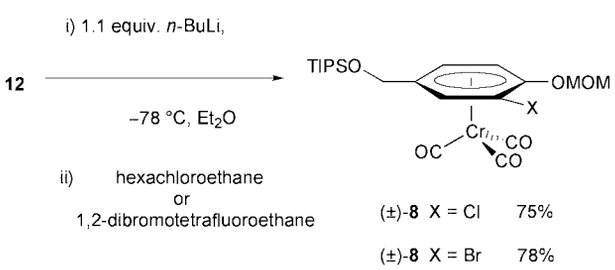


Fig. 6

more closely that observed in the structure of 3-ethyl-1-hydroxy-3-(4-hydroxybenzoyl)-1,3-dihydro-2,1-benzoxaborole.[40]

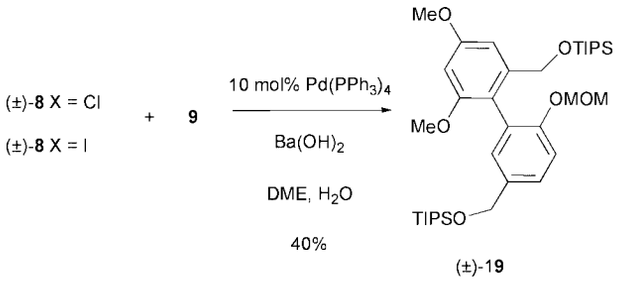
Having ring A analogues and the halogenated ring B complexes to hand (Scheme 8),[31] the diastereoselective coupling



Scheme 8

could now be addressed. Early attempts failed, but application of the optimised conditions from the model couplings to the reaction of **9** with the iodo complex (±)-**8**, X = I, in DME–water with 10 mol% $Pd(PPh_3)_4$ as catalyst and barium hydroxide, led to the decomplexed coupled product (±)-**19** in 40% yield (Scheme 9). Isolation of the decomplexed coupled product (±)-**19** rather than the complexed product is only a set-back if the decomplexation took place before the coupling reaction, resulting in the loss of any stereocontrol.

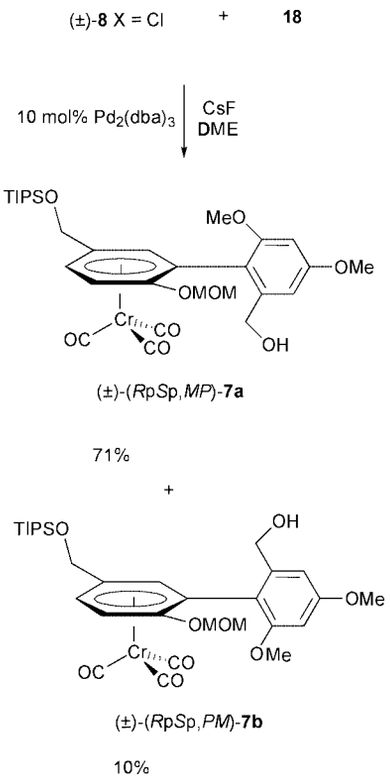
Therefore the chloro complex (±)-**8**, X = Cl, was coupled with **9** under the same conditions but again a 40% yield of the decomplexed coupled product (±)-**19** was obtained (Scheme 9). This demonstrated that the decomplexation must have occurred after coupling, since uncomplexed electron rich chloroarenes do not couple under these conditions.[41] It was possible to separate the two enantiomers of (±)-**19** by HPLC on a chiral OD-H



Scheme 9

column and therefore a monitoring system for the reaction in the enantiopure series was established.

However, since the formation of the amino acid functions in actinoidinic acid would require an asymmetric Strecker reaction,[18] it was necessary to have the chromium present to exert the required axial stereocontrol[42] and a coupling process which retained the chromium was sought. Coupling of cyclic boronic acid **18** with halo complexes (±)-**8**, X = Cl, Br or I, using the conditions reported by Nicolaou *et al.*[37] [20 mol% $Pd(PPh_3)_4$, Na_2CO_3, toluene–methanol–water, 4 h reflux], gave only 33, 40 or 20% yields respectively of the decomplexed coupled product. Use of the conditions reported by Kamikawa and Uemura[32] (MeOH–H_2O, 10 mol% $Pd(PPh_3)_4$, Na_2CO_3, 30 min reflux) with the boronic acid **18** and the iodo or bromo complexes (±)-**8**, X = I, Br, led, in both cases, to protolysis of the C–halide bonds. However, the room temperature coupling of the chloro complex (±)-**8**, X = Cl, with boronic acid **18** in DME using $Pd_2(dba)_3$ catalyst and caesium fluoride base gave the diastereomeric complexes (±)-**7a** and (±)-**7b** in 71 and 10% yield respectively (Scheme 10).



Scheme 10

These results established a key step for an actinoidinic acid synthesis using Suzuki coupling. To establish the axial stereochemistry of the products, an X-ray structural analysis was carried out on the major isomer (Fig. 7). As expected, and in accordance with the earlier results,[32] this showed the major isomer to be (±)-**7a**, with the slightly bulkier *ortho*-CH_2OH group of the uncomplexed ring *syn* to the tricarbonyl-

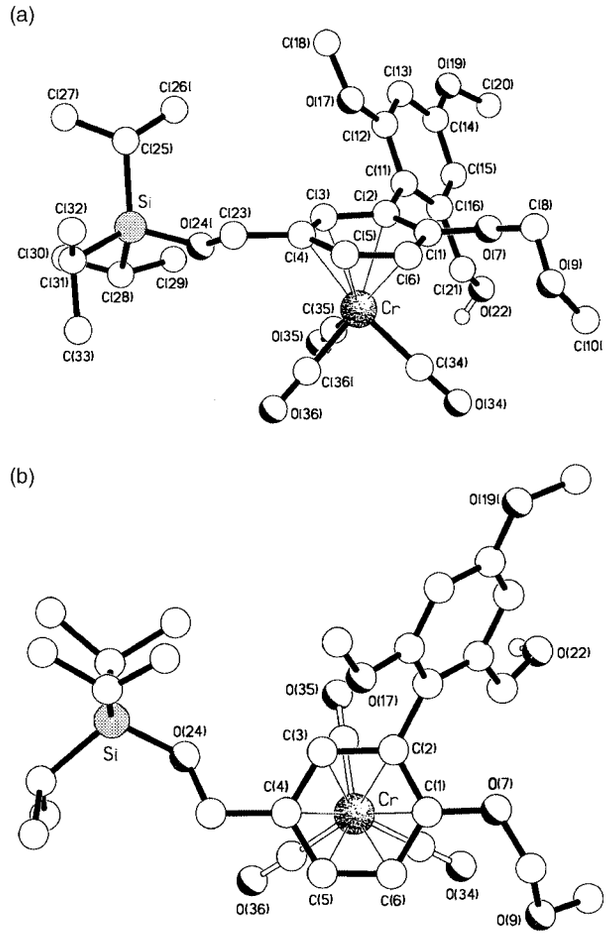
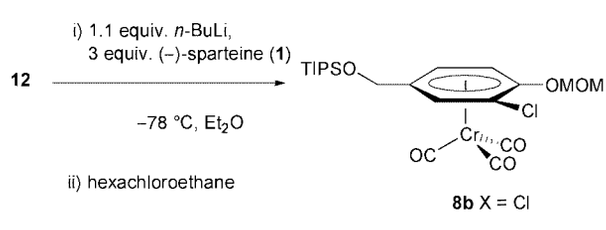


Fig. 7

chromium(0) unit (Fig. 7), its associated benzene ring being rotated *ca.* 60° out of the plane of the coordinated aryl ring. This orientation, however, is not accompanied by any hydrogen bonding interaction involving the terminal OH group. In this structure the three carbonyl groups are rotated by *ca.* 25° [in the direction of C(6)] from an eclipsed geometry. The Cr–C(aryl) distances are in the range 2.194(4) to 2.291(4) Å. As in **4d** the terminal OMe group of the OMOM ligand lies on the same side of the aryl ring as the chromium centre, but C(8) lies slightly above, the torsional twist about C(1)–O(7) being *ca.* 21°.

NMR analysis confirmed a previous observation[42] that the protons *syn* to the $Cr(CO)_3$ unit in are shifted to a lower field than the *anti* protons. The methoxy group protons of (±)-**7a** occur at 3.66 ppm and the methylhydroxy group protons appear, as a multiplet, at 4.97 ppm, whereas in (±)-**7b**, these resonances appear at 3.86 and 4.47 ppm respectively.

In enantioselective mode at higher concentration **12** was deprotonated with 1.1 equiv. of *n*-BuLi in the presence of 3 equiv. of (−)-sparteine at −78 °C (Scheme 11). After 1 h the

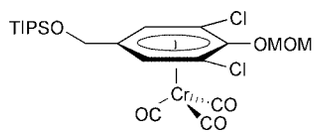


Scheme 11

reaction was quenched with hexachloroethane and allowed to warm up overnight to −10 °C. (+)-(*S*)-Isomer **8a**, X = Cl, was isolated in 95% yield with $[a]_D^{24}$ +16 (*c* = 1.0, $CHCl_3$).

It was not possible to determine the ee directly from **8a**, X = Cl, therefore it was coupled directly with the cyclic boronic acid **18**, as depicted in Scheme 10, but at higher concentration. The major diastereomer (+)-(S_p,*P*)-**7a**, $[\alpha]_D^{24}$ +10 (*c* = 0.5, $CHCl_3$) was shown by chiral HPLC (column OD-H) to have an ee of 20%.

Applying the dilithiation protocol to **12** with 6.5 equiv. of (−)-sparteine and 2.5 equiv. of *t*-BuLi at −40 °C for 3 h, gave, in addition to the disubstituted complex η^6-[2,6-dichloro-4-(triisopropylsiloxymethyl)(methoxymethoxy)benzene]tricarbonylchromium(0) (**20**) (Fig. 8) 21% yield), the desired (−)-(*R*)-



20

Fig. 8

8b, X = Cl, in 65% yield, $[\alpha]_D^{24}$ −48 (*c* = 1.0, $CHCl_3$). Again, the ee was determined by HPLC analysis of the major diastereomer (−)-(R_p,*M*)-**7a** [40% ee, $[\alpha]_D^{24}$ −28 (c = 0.5, $CHCl_3$)] from the coupling with **18**.

For the bromo analogue, complex **12** was treated again with (−)-sparteine (6.5 equiv.) and 2.2 equiv. of *t*-BuLi as before, followed by a 1,2-dibromotetrafluoroethane quench. The disubstituted product was not observed but the complex (−)-(*R*)-**8b**, X = Br, was obtained in 60% yield, $[\alpha]_D^{24}$ −29 (*c* = 2.3, $CHCl_3$). The ee was determined, as before, by coupling (−)-(*R*)-**8b**, X = Br, with boronic acid **18** under the same conditions as for the chloro analogue (60% yield, 7 : 1 diastereomeric ratio) to give (−)-(R_p,*M*)-**7a**, $[\alpha]_D^{24}$ −21 (*c* = 0.5, $CHCl_3$) with an ee of 30% (by HPLC analysis).

We have, therefore, prepared both antipodes of the intermediate **7a** in enantio-enriched form from chloroarene complexes *via* coupling under mild conditions by using one ligand, (−)-sparteine, as the stereocontroller, although only in moderate ee. Of further benefit, boronic acid **18**, a valuable synthon for cross-coupling chemistry, was prepared in high yield and purity.

Experimental

Reactions with complexes and butyllithium and work-ups, extractions, drying and FCC (flash column chromatography) of complexes were carried out under nitrogen and were performed using standard Schlenk line techniques.[43] Tetrahydrofuran, cyclohexane, DME and diethyl ether were distilled from sodium benzophenone ketyl. Dioxane and toluene were distilled from sodium. (−)-Sparteine was distilled from calcium hydride and stored over KOH. D_2O, anhydrous DMF and anhydrous DMA were obtained from Aldrich Chemical Co. and, after deoxygenation, used without further purification. Caesium fluoride, $Pd(PPh_3)_4$, $Pd_2(dba)_3$, hexachloroethane and dibromotetrafluoroethane were obtained from Lancaster Synthesis Ltd and used without further purification. η^6-(Methoxymethoxybenzene)tricarbonylchromium(0) **3**,[31] η^6-(ethoxymethoxybenzene)tricarbonylchromium(0) **10**,[31] η^6-(4-triisopropylsiloxymethyl-1-methoxymethoxybenzene)tricarbonylchromium(0) **12**,[31] 2-bromo-3,5-dimethoxybenzyl alcohol **13**[34] and (±)-η^6-(2-iodo-4-triisopropylsiloxymethyl-1-methoxymethoxybenzene)-tricarbonylchromium(0) **8**, X = I,[31] were prepared according to literature procedures.

Unless otherwise stated, the butyllithium used was a nominal 2.5 M in hexanes and the precise concentration was determined by titration against diphenylacetic acid.[44] *tert*-Butyllithium was a nominal 1.7 M in hexane. Flash column chromatography[45] was performed on Sorbisil C-60. All reactions except those with alkyllithiums were monitored by TLC with Merck silica gel 60 F_{254} plates.

Elemental analyses were carried out by Mr Stephen Boyer, SACS, University of North London, and are reported as the average of two runs. Optical rotations were measured using a 1 dm path length (*c* given as g per 100 mL) on a Perkin–Elmer 141 polarimeter, if not otherwise stated, in $CHCl_3$ and are reported in units of 10^{-1} deg cm^2 g^{-1}. Infrared spectra were recorded on a Perkin–Elmer RX FT-IR System and a Perkin–Elmer 1710 FTIR instrument. NMR spectra were performed, if not otherwise stated, in $CDCl_3$ at ambient temperature on a JEOL GSX 270 (270 MHz ^{1}H and 68 MHz ^{13}C) spectrometer. Mass spectra were recorded on VG Micromass 7070E and AutoSpec-Q spectrometers. Analytical HPLC was performed on a Gilson HPLC (Gilson UV–VIS detector). Enantiomer analysis was performed using Chiracel OD-H (15 cm) column (Diacel Chemical Industries, Ltd.). Melting points were taken on a Kofler hot stage apparatus and are uncorrected.

The carbon attached to the directing group has been labelled ArC(1).

Dilithiation: (*R*)-selective functionalisation of compounds 3, 10 and 12

Typical procedure. To a solution of distilled (−)-sparteine (3.65–5.00 equiv.) in deoxygenated diethyl ether (6 mL) at −78 °C was added *n*-BuLi (or *t*-BuLi for **12**) (1.6 M in hexanes, 2.5 equiv.) and the solution was stirred at −78 °C for 30 min. A solution of η^6-(alkoxymethoxybenzene)tricarbonylchromium(0) complex (**3**, **10** or **12**) (1 equiv.) in deoxygenated diethyl ether (3 mL) was added and the resultant solution stirred for 1 h at −40 °C then recooled to −78 °C. Thereafter, the solution was quenched with a suitable electrophile and stirred for an indicated period of time. After work up with 2 M HCl, the organic layer was washed with distilled water (2 × 10 mL) and brine (2 × 10 mL), dried ($MgSO_4$) and the solvent removed under reduced pressure. The product was then purified using flash column chromatography and analysed by HPLC on Chiracel OD-H. For yields ee and optical rotations see Table 1. For spectral data on the series **3** and **10** and **8b**, X = CHO, see ref. 31.

Crystal data for 4b.† $C_{12}H_{10}O_6Cr$, *M* = 302.2, monoclinic, $P2_1$ (no. 4), *a* = 6.681(1), *b* = 13.750(2), *c* = 7.411(1) Å, *β* = 106.18(1)°, *V* = 653.9(1) Å^3, *Z* = 2, D_c = 1.535 g cm^{-3}, μ(Mo-Kα) = 0.89 mm^{-1}, *T* = 293 K, orange blocks; 1559 independent measured reflections, F^2 refinement, R_1 = 0.040, wR_2 = 0.090, 1367 independent observed absorption corrected reflections [$|F_o| > 4\sigma(|F_o|)$, $2\theta \leq 55°$], 173 parameters. *R*-factor and Flack tests gave R_1^+ = 0.0396, R_1^- = 0.0405 and x^+ = +0.26(10), x^- = +0.74(10), *i.e.* only a relatively weak indication of the absolute chirality.

Crystal data for 4c.† $C_{24}H_{20}O_6Cr$, *M* = 456.4, orthorhombic, $P2_12_12_1$ (no. 19), *a* = 10.822(1), *b* = 11.509(2), *c* = 17.707(2) Å, *V* = 2205.5(6) Å^3, *Z* = 4, D_c = 1.375 g cm^{-3}, μ(Mo-Kα) = 0.56 mm^{-1}, *T* = 293 K, yellow prisms; 3866 independent measured reflections, F^2 refinement, R_1 = 0.038, wR_2 = 0.090, 3525 independent observed absorption corrected reflections [$|F_o| > 4\sigma(|F_o|)$, $2\theta \leq 50°$], 261 parameters. The chirality of **4c** was determined by a combination of *R*-factor tests [R_1^+ = 0.0383, R_1^- = 0.0459] and x^+ = +0.02(2), x^- = +0.98(2)] based on a full set of Friedel opposites.

Crystal data for 4d.† $C_{26}H_{24}O_8Cr$, *M* = 516.5, trigonal, $P3_1$ (no. 144), *a* = 12.536(2), *c* = 13.273(2) Å, *V* = 1806.3(4) Å^3, *Z* = 3, D_c = 1.424 g cm^{-3}, μ(Cu-Kα) = 4.33 mm^{-1}, *T* = 293 K, orange

† CCDC reference numbers 172233–172237. See http://www.rsc.org/suppdata/p1/b1/b108807f/ for crystallographic files in .cif or other electronic format.

rhombs; 2052 independent measured reflections, F^2 refinement, $R_1 = 0.088$, $wR_2 = 0.125$, 1033 independent observed absorption corrected reflections [$|F_o| > 4\sigma(|F_o|)$, $2\theta \leq 128°$], 321 parameters. The chirality of **4d** was determined by a combination of *R*-factor tests [$R_1^+ = 0.0879$, $R_1^- = 0.0992$] and by use of the Flack parameter [$x^+ = +0.01(4)$, $x^- = +0.99(4)$].

Deuteriation studies with lithiated complex 3

(i) Complex **3** (75 mg, 0.27 mmol) was dissolved in ether (1.5 mL) and added at −78 °C to a solution of (−)-sparteine (3 equiv., 0.38 mL, 0.81 mmol) and *n*-BuLi (2 equiv.) in ether (3 mL) followed, after 10 min, by a D_2O quench (0.5 mL). After warm-up, the ether phase was separated and dried (Na_2SO_4). The solution was filtered through a pad of silica gel and evaporated. The MS analysis (EI) of the residue found: *m*/*z* M^+(D) 274.9988. $C_{11}H_9DO_5Cr$ requires: 274.9996. M^+(2D) 276.0025. $C_{11}H_8D_2O_5Cr$ requires: 276.0059, ratio 100 : 36.

(ii) The reaction was repeated as described above except that after addition the temperature was raised to −40 °C and the deprotonation time was changed to 4 h. *m*/*z* (EI) found: M^+(D) 274.9995. $C_{11}H_9DO_5Cr$ requires: 274.9996. M^+(2D) 276.0056. $C_{11}H_8D_2O_5Cr$ requires: 276.0059, ratio 100 : 65.

(iii) The reaction was repeated as described above except that 3 equiv. *n*-BuLi were used and after addition, the temperature was raised to −40 °C and the deprotonation time was changed to 8 h. *m*/*z* (EI) found: M^+(D) 274.9991. $C_{11}H_9DO_5Cr$ requires: 274.9996. M^+(2D) 276.0040. $C_{11}H_8D_2O_5Cr$ requires: 276.0059, ratio 100 : 65.

(iv) The reaction was repeated as described above except that 3 equiv. *n*-BuLi were used and after addition THF (3 mL) was added and the temperature was raised to −40 °C. The deprotonation time was changed to 8 h. *m*/*z* (EI) found: M^+(D) 274.9994. $C_{11}H_9DO_5Cr$ requires: 274.9996. M^+(2D) 276.0040. $C_{11}H_8D_2O_5Cr$ requires: 276.0047, ratio 74 : 100.

(v) Complex **3** (75 mg, 0.27 mmol) was dissolved in ether (1.5 mL) and added at −78 °C to a solution of (−)-sparteine (3 equiv., 0.38 mL, 0.81 mmol) and *n*-BuLi (2 equiv.) in ether (3 mL) followed by addition of complex **3** (75 mg, 0.27 mmol) in ether (1.5 mL) after 10 min. The solution was left to stir for 4 h at −78 °C and was quenched with D_2O (0.5 mL). *m*/*z* (EI) found: M^+ 273.9921. $C_{11}H_{10}O_5Cr$ requires: 273.9933. M^+(D) 274.9989. $C_{11}H_8D_2O_5Cr$ requires: 274.9996, ratio 20 : 100.

(+)-η⁶-[2-Formyl-4-(triisopropylsiloxymethyl)methoxymethoxybenzene]tricarbonylchromium(0) 8b, X = CHO, *via* dilithiation with *t*-BuLi

η⁶-[4-(Triisopropylsiloxymethyl)methoxymethoxybenzene]tricarbonylchromium(0) **12** (300 mg, 0.65 mmol) was dissolved in ether (1 mL) and added to a solution of *t*-BuLi (2.5 equiv.) and (−)-sparteine (6.5 equiv.) in ether (6 mL) at −78 °C. After addition the solution was stirred at −40 °C for 1 h, recooled to −78 °C and quenched overnight with DMF (1.75 equiv., 0.09 mL, 1.13 mmol) dissolved in ether (0.5 mL). The reaction was worked-up with water (10 mL). FCC (eluant: 20% ether–hexane) furnished the title complex (+)-**8b**, X = CHO, as a bright orange crystalline solid (194 mg, 0.40 mmol, 60%, 46% ee), $[a]_D = +350$ (*c* = 0.2, $CHCl_3$ at 25 °C). HPLC (OD-H column): detector 320 nm, flow: 0.5 mL min^{-1}, 0.5% isopropyl alcohol (ISP) in hexane, major enantiomer 18 min, minor 19.2 min. For spectral data of the product see ref. 31.

2-Bromo-3,5-dimethoxy-1-triisopropylsiloxymethylbenzene 14

A solution of 2-bromo-3,5-dimethoxybenzyl alcohol **13** (6.40 g, 25.9 mmol), imidazole (5.30 g, 77.7 mmol) and triisopropylsilyl chloride (6.65 mL, 31.1 mmol) in DMF (25 mL) was stirred at rt for 16 h. Ether (150 mL) was added, repeatedly washed with water (5 × 50 mL) and dried ($MgSO_4$). Concentration under reduced pressure followed by FCC (eluant: 10% ether–hexane) gave the *title compound* **14** as a white crystalline solid (9.70 g, 24.1 mmol, 93%), mp 33–34 °C (Found: C, 53.82; H, 7.52%. $C_{18}H_{31}O_3SiBr$ requires: C, 53.59; H, 7.75%). ν_{max}(KBr)/cm^{-1} 3084w, 2942s, 2865s, 1583s, 1458s, 1338s, 1220s, 1157s, 1074s, 882s, 804s, 684s, 665s, 646s, 574m, 458m. δ_H (270 MHz) 6.92 (1 H, d, *J* 3.0 Hz, ArC(6)*H*), 6.39 (1 H, d, *J* 3.0 Hz, ArC(4)*H*), 4.79 (2 H, s, Ar–CH_2), 3.85 (3 H, s, Ar(3/5)–O*Me*), 3.80 (3 H, s, Ar(3/5)–O*Me*), 1.23–1.01 (21 H, m, *TIPS*); δ_C (68 MHz) 159.9 (Ar*C*(3/5)–OMe), 156.1 (Ar*C*(3/5)–OMe), 142.8 (Ar*C*(1)–CH_2), 103.3 (Ar*C*(6)H), 100.5 (Ar*C*(2)–Br), 98.2 (Ar*C*(4)H), 65.1 (Ar–*C*H_2), 56.3 (ArC(3/5)–O*Me*), 55.5 (ArC(3/5)–O*Me*), 18.1 (TIPS-*Me*), and 12.1 (Si–*C*H). *m*/*z* (CI) 420 ($M^+ + NH_4$, 33%), 403 ($M^+ + H$, 98), 376 (420 − C_3H_8, 74), 359 ($M^+ - C_3H_7$, 87), 246 (403 − TIPS), 68), 231 (246 − O + H, 100), 135 (42), 73 (78), 61 (88). Found: $M^+ + H$ 403.1305. $C_{18}H_{32}O_3Si^{79}Br$ requires: 403.1304.

3,5-Dimethoxy-2-trimethylstannanyl-1-triisopropylsiloxymethylbenzene 15

To a solution of 2-bromo-3,5-dimethoxy-1-triisopropylsiloxymethylbenzene **14** (5 g, 12.4 mmol) in THF (45 mL) at −78 °C was added *n*-BuLi (2.4 M, 10 mL, 24.4 mmol) and the solution was left to stir for 1 h. Chlorotrimethyltin (12.4 g, 62 mmol) dissolved in THF (10 mL) was added slowly and the solution was allowed to warm up to rt overnight. The THF was removed *in vacuo* and replaced with ether (100 mL). The ether phase was washed with saturated KF solution (2 × 50 mL) and with water (2 × 50 mL). The ether was removed and recrystallisation (hexane–ether) of the residue gave the *title compound* **15** as a white crystalline solid. (3.73 g, 7.64 mmol, 61%), mp 33°C (Found: C, 51.42; H, 8.70. $C_{21}H_{40}O_3SiSn$ requires: C, 51.51; H, 8.45%). ν_{max}(KBr)/cm^{-1} 3105w, 3073w, 2942s, 2865s, 1587s, 1467s, 1310s, 1151s, 1071s, 808s, 691s, 523m. δ_H (270 MHz) 6.91 (1 H, d, *J* 2.5 Hz, ArC(6)*H*), 6.30 (1 H, d, *J* 2.2 Hz, ArC(4)*H*), 4.75 (2 H, s, Ar–CH_2–O), 3.80 (3 H, s, Ar(3/5)–O*Me*), 3.75 (3 H, s, Ar(3/5)–O*Me*), 1.14–1.04 (21 H, m, *TIPS*), 0.25 (9 H, with Sn satellites, Sn(*Me*)$_3$); δ_C (68 MHz) 164.8 (Ar*C*(3/5)–OMe), 162.0 (Ar*C*(3/5)–OMe), 151.0 (Ar*C*(1)–CH_2), 134.8 (Ar*C*(2)–Sn), 103.0 (Ar*C*(6)H), 96.0 (Ar*C*(4)H), 66.8 (Ar–*C*H_2–O), 55.4 (Ar*C*(3/5)–O*Me*), 55.2 (Ar*C*(3/5)–O*Me*), 18.1 (TIPS-*Me*), 12.1 (Si–*C*H), −6.4 (Sn*Me*$_3$). *m*/*z* (FAB$^+$) 487 (M^+ − H, 9%), 473 (M^+ − Me, 100), 443 ($M^+ - 3 \times$ Me, 15), 315 (443 − Sn, 21), 165 (50). Found: M^+ − Me 473.1542. $C_{20}H_{37}O_3Si^{120}Sn$ requires: 473.1534.

2,4-Dimethoxy-6-triisopropylsiloxymethylphenylboronic acid 9

To a solution of 2-bromo-3,5-dimethoxy-1-triisopropylsiloxymethylbenzene **14** (5 g, 12.5 mmol) in THF (60 mL) at −78 °C was added *n*-BuLi (2.2 M, 7 mL, 15 mmol) and the solution left to stir for 1 h. Triisopropoxyborane (4.33 mL, 18.8 mmol) was added slowly and the solution was allowed to warm up to rt overnight. 1 M HCl (10 mL) was added and left to stir for 30 min. THF was removed *in vacuo* and replaced with ether (100 mL). The ether phase was washed with water (50 mL) and brine (50 mL) and dried ($MgSO_4$). The ether was removed and a *white solid* of **9** remained (4.51 g, 12.25 mmol, 98%). ν_{max}(KBr)/cm^{-1} 3344br, 2943s, 2865s, 1602s, 1460s, 1305s, 1155s, 1063s, 882s, 809s, 687s, 501m. The boronic acid was too unstable for microanalysis and was used without further purification.

4,6-Dimethoxy-2-triisopropylsiloxymethylbiphenyl 16

Method A. A solution of 3,5-dimethoxy-2-trimethylstannanyl-1-triisopropylsiloxymethylbenzene **15** (0.3 g, 0.61 mmol), iodobenzene (0.018 mL, 1.62 mmol) and $Pd(PPh_3)_4$ (10 mol%, 0.070 g, 0.061 mmol) in deoxygenated DMA (6 mL) was stirred at 90 °C for 16 h. Water (15 mL) was added and the solution extracted with ether (3 × 15 mL). The combined organic layers were washed with water (15 mL) and brine (15 mL) and dried ($MgSO_4$). Concentration *in vacuo* followed by FCC (eluant: 5% ether–hexane) gave the *title product* **16** as a

white solid (0.04 g, 0.09 mmol, 16%), mp 66–67 °C (Found: C, 72.20; H, 9.16. $C_{24}H_{36}O_3Si$ requires: C, 71.95; H, 9.06%). ν_{max}(KBr)/cm^{-1} 3309w, 2941s, 2864s, 1605s, 1465s, 1331s, 1198s, 1157s, 1051s, 842s, 774s, 704m, 691m. δ_H (270 MHz) 7.41–7.13 (5 H, m, Ph), 6.93 (1 H, d, *J* 2.5 Hz, Ar(3)*H*), 6.44 (1 H, d, *J* 2.5 Hz, Ar(5)*H*), 4.45 (2 H, s, Ar–CH_2–O), 3.85 (3 H, s, Ar(4/6)–O*Me*), 3.67 (3 H, s, Ar(4/6)–O*Me*), 1.10–0.91 (21 H, m, *TIPS*); δ_C (68 MHz) 160.3 (Ar*C*(4/6)–OMe), 157.1 (Ar*C*(4/6)–OMe), 141.2 (Ar*C*(2)–CH_2), 136.8 (Ph*C*(1′)–ArC(1)), 130.2 (Ph*C*(3′,5′)H), 128.1 (Ph*C*(2′,6′)H), 126.9 (Ph*C*(4′)H), 112.1 (Ar(1)*C*–Ph), 102.3 (Ar*C*(3)H), 97.3 (Ar*C*(5)H), 63.1 (Ar–*C*H_2), 55.8 (ArC(4/6)–O*Me*), 55.3 (ArC(4/6)–O*Me*), 18.1 (TIPS-*Me*), 12.0 (Si–*C*H). *m*/*z* (EI) 400 (M^+, 4%), 357 (400 − ^{i}Pr, 11), 295 (357 − 2 × OMe, 10), 281 (357 − Ph + H, 100), 151 (M^+ − TIPSO − Ph + H, 88), 77 (Ph, 43). Found: M^+ 400.2441. $C_{24}H_{36}O_3Si$ requires: 400.2434.

Method B. A solution of 2,4-dimethoxy-6-triisopropylsiloxymethylphenylboronic acid **9** (0.3 g, 0.81 mmol), iodobenzene (0.018 mL, 1.62 mmol), caesium fluoride (0.245 g, 1.62 mmol) and $Pd_2(dba)_3$ (5 mol%, 0.041 g, 0.041 mmol) in deoxygenated DME (5 mL) was stirred at rt for 16 h. Ether (25 mL) was added and the solution was washed with 10% NaOH (15 mL), water (15 mL) and brine (15 mL) and dried ($MgSO_4$). Concentration *in vacuo* followed by FCC (eluant: 5% ether–hexane) gave the *title product* **16** as a white solid (0.184 g, 0.46 mmol, 56%). For spectral data see Method A.

Method C. A solution of 2,4-dimethoxy-6-triisopropylsiloxymethylphenylboronic acid (**15**) (0.3 g, 0.81 mmol), iodobenzene (0.018 mL, 1.62 mmol), sodium hydroxide (0.046 g, 1.14 mmol) and $Pd(PPh_3)_4$ (10 mol%, 0.094 g, 0.081 mmol) in deoxygenated DME–water (6 mL–1 mL) was stirred under reflux for 8 h. Water (15 mL) was added and the solution extracted with ether (3 × 15 mL). The combined organic layers were washed with 10% NaOH (15 mL), water (15 mL) and brine (15 mL) and dried ($MgSO_4$). Concentration *in vacuo* followed by FCC (eluant: 5% ether–hexane) gave the *title product* **16** as a white solid (0.290 g, 0.72 mmol, 89%). For spectral data see Method A.

(±)-1-Bromo-2,4-dimethoxy-6-tetrahydropyranyloxymethylbenzene 17

A solution of 2-bromo-3,5-dimethoxybenzyl alcohol **13** (2 g, 8.1 mmol), pyridinium toluene-*p*-sulfonate (1 g, 3.8 mmol) and dihydro-4*H*-pyran (7.14 mL, 79.1 mmol) in DCM (100 mL) was stirred at rt for 16 h. DCM (250 mL) was added, repeatedly washed with water (5 × 50 mL) and dried ($MgSO_4$). Concentration under reduced pressure followed by FCC (eluant: 10% ether–hexane) gave the *title compound* (±)-**17** as a white solid (2.62 g, 7.9 mmol, 98%), mp 42–43 °C (Found: C, 50.95; H, 5.93. $C_{14}H_{19}O_4Br$ requires: C, 50.77; H, 5.78%). ν_{max}(KBr)/cm^{-1} 3017w, 2955s, 2878m, 1600m, 1580s, 1456s, 1327s, 1202m, 1058s, 1034s, 976s, 904m, 850s. δ_H (270 MHz) 6.69 (1 H, d, *J* 2.2 Hz, ArC(6)*H*), 6.37 (1 H, d, *J* 2.7 Hz, ArC(4)*H*), 4.89–4.50 (3 H, m, Ar–CH_2–O, O–C*H*–O), 3.82 (3 H, d, *J* 3.0 Hz, Ar(3/5)–O*Me*), 3.77 (3 H, d, *J* 2.7 Hz, Ar(3/5)–O*Me*), 3.54–3.38 (2 H, m, O–CH_2), 1.92–0.83 (6 H, m, pyran-ring); δ_C (68 MHz) 159.8 (Ar*C*(3/5)–OMe), 156.5 (Ar*C*(3/5)–OMe), 139.8 (Ar*C*(1)–CH_2), 105.1 (Ar*C*(6)H), 102.5 (Ar*C*(2)–Br), 98.5 (Ar*C*(4)H, O–*C*H–O), 68.7 (Ar–*C*H_2–O), 62.3 (O–*C*H_2), 56.3 (ArC(3/5)–O*Me*), 55.5 (ArC(3/5)–O*Me*), 30.6 (*C*(3′)H_2), 25.5 (*C*(5′)H_2), 19.4 (*C*(4′)H_2). *m*/*z* (EI) 330 (M^+, 11%), 246 (M^+ − THP, 5), 230 (246 − O, 100), 199 (230 − OMe, 4), 151 (230 − Br, 81), 135 (33), 85 (39). Found: M^+ 330.0475. $C_{14}H_{19}O_4{}^{79}Br$ requires: 330.0467.

5,7-Dimethoxy-1,3-dihydro-2,1-benzoxaborol-1-ol 18

To a solution of 1-bromo-2,4-dimethoxy-6-tetrahydropyranyloxymethylbenzene **17** (2.5 g, 7.6 mmol) in THF (60 mL) at −78 °C was added *n*-BuLi (2.2 M, 4.2 mL, 9.12 mmol) and the solution was left to stir for 1 h. Triisopropoxyborane (2.63 mL, 11.4 mmol) was added slowly and the solution was allowed to warm up to rt overnight. 2 M HCl (10 mL) was added and the mixture was left to stir for 4 h. THF was removed *in vacuo* and replaced with ether (100 mL). The ether phase was washed with water (50 mL) and brine (50 mL). The ether was removed and the remaining white solid was recrystallised from water to give the title compound **18** as bright white crystals. (1.05 g, 5.5 mmol 72%), mp 121–123 °C (Found: C, 55.75; H, 5.87. $C_9H_{11}O_4Br$ requires: C, 55.72; H, 5.72%). ν_{max}(KBr)/cm^{-1} 3333br, 3007m, 2944m, 2875w, 2832w, 1600s, 1464s, 1417s, 1331s, 1212s, 1153, 1077s, 973s, 832s, 761s, 646m, 529m. δ_H (270 MHz) 6.41 (1 H, d, *J* 1.2 Hz, ArC(4)*H*), 6.30 (1 H, d, *J* 1.2 Hz, ArC(6)*H*), 5.67 (1 H, s, OH), 4.98 (2 H, s, Ar–CH_2–O), 3.83 (3 H, s, Ar(5/7)–O*Me*), 3.81 (3 H, s, Ar(5/7)–O*Me*); δ_C (68 MHz) 165.0 (Ar*C*(5/7)–OMe), 163.2 (Ar*C*(5/7)–OMe), 157.8 (Ar*C*–CH_2), 104.6 (d, $^1J_{C-B}$ 13.0 Hz, Ar*C*–B), 97.6 (Ar*C*(4)H), 98.2 (Ar*C*(6)H), 71.1 (Ar–*C*H_2–O), 55.6 (ArC(5/7)–O*Me*), 55.4 (ArC(5/7)–O*Me*). *m*/*z*(EI) 194 (M^+, 100%), 179 (M^+ − Me, 16), 163 (M^+ − OMe, 30), 152 (31), 135 (12), 121 (28). Found: M^+ 194.0748. $C_9H_{11}O_4B$ requires: 194.0750.

Crystal data for 18.† $C_9H_{11}BO_4$, M = 194.0, triclinic, $P\bar{1}$ (no. 2), a = 5.666(2), b = 8.465(1), c = 10.467(1) Å, α = 109.35(1), β = 98.65(1), γ = 95.75(1)°, V = 462.2(2) Å^3, Z = 2, D_c = 1.394 g cm^{-3}, μ(Cu-Kα) = 0.90 mm^{-1}, T = 293 K, clear plates; 1493 independent measured reflections, F^2 refinement, R_1 = 0.043, wR_2 = 0.115, 1356 independent observed reflections [$|F_o| > 4\sigma(|F_o|)$ $2\theta \leq 128°$], 132 parameters.

General procedure for the regiocontrolled deprotonation of arenetricarbonylchromium(0) complexes

n-Butyllithium (1.1 equiv.) was added to a solution of the complex (1 equiv.) in deoxygenated THF (15 mL) or ether (20 mL) at −78 °C, under nitrogen. The resultant solution was allowed to stir for a further 1–2 h at that temperature and was then quenched with a suitable electrophile (0.9–5 equiv.) and allowed to warm slowly to room temperature over a period of 3–15 h. The solvent was removed *in vacuo* and replaced with ether (20 mL) or ethyl acetate (20 mL) as necessary. Unless otherwise stated, the reaction was worked up with 1 M HCl (5 mL), and the organic phase was washed with water (2 × 20 mL) and brine (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure. FCC and/or recrystallisation as appropriate gave the desired functionalised complex. So prepared were the following complexes.

(±)-η^6-(2-Chloro-4-triisopropylsiloxymethyl-1-methoxymethoxybenzene)tricarbonylchromium(0) (±)-8, X = Cl

From η^6-(4-triisopropylsiloxymethyl-1-methoxymethoxybenzene)tricarbonylchromium(0) **12** (1 g, 2.17 mmol) in ether (50 mL), with an overnight quench with a solution of hexachloroethane (2.5 equiv., 1.3 g, 5.40 mmol) in ether (4 mL). The reaction was worked-up with 1 M HCl (20 mL). FCC (eluant: 1% ether–hexane) and recrystallisation (ether–hexane) gave the *title complex* (±)-**8**, X = Cl, as a bright yellow crystalline solid (0.697 g, 1.41 mmol, 75%), mp 50–52 °C (Found: C, 51.18; H, 6.18. $C_{21}H_{31}CrO_6SiCl$ requires: C, 50.95; H, 6.31%). ν_{max}(KBr)/cm^{-1} 3102w, 2945s, 2863s, 1970vs, 1896vs, 1452s, 1128s, 973s, 664s. δ_H (270 MHz) 5.77 (1 H, d, *J* 1.7 Hz, ArC(3)*H*), 5.59 (1 H, d, *J* 6.7 Hz, ArC(6)*H*), 5.31 (1 H, dd, *J* 6.7, 1.73 Hz, ArC(5)*H*), 5.18 (1 H, d, *J* 7.2 Hz, O–CH_2–O), 5.11 (1 H, d, *J* 7.2 Hz, O–CH_2–O), 4.51 (1 H, d, *J* 12.9 Hz, Ar–CH_2), 4.46 (1 H, d, *J* 12.9 Hz, Ar–CH_2), 3.54 (3 H, s, O*Me*), 1.22–0.87 (21 H, m, *TIPS*); δ_C (68 MHz) 233.2 (*C*O), 132.4 (Ar*C*(1)–O), 105.2 (Ar*C*(4)–CH_2), 96.7 (Ar*C*(3)H), 92.2 (O–*C*H_2–O), 88.5 (Ar*C*(5)H), 80.6 (Ar*C*(2)–Cl), 79.2 (Ar*C*(6)H), 62.7 (Ar–*C*H_2),

57.2 (O*Me*), 18.0 (TIPS-*Me*), 11.9 (Si–*C*H). *m*/*z* (FAB^+) 494 (M^+, 37%), 451 ($M^+ - CH_3CHCH_3$, 12), 438 ($M^+ - 2 \times CO$, 6), 410 ($M^+ - 3 \times CO$, 65), 367 (42), 59 (36), 52 (Cr, 26). Found: M^+ 494.0997. $C_{21}H_{13}CrO_6SiCl$ requires: 494.0984.

(±)-η⁶-(2-Bromo-4-triisopropylsiloxymethyl-1-methoxymethoxybenzene)tricarbonylchromium(0) (±)-8, X = Br

From η⁶-(4-triisopropylsiloxymethyl-1-methoxymethoxybenzene)tricarbonylchromium(0) **12** (1 g, 2.17 mmol) in ether (30 mL) with a 1,2-dibromotetrafluoroethane (1.3 equiv., 0.34 mL, 2.82 mmol) overnight quench. The reaction was worked-up with 1 M HCl (20 mL). FCC (eluant: 1% ether–hexane) and recrystallisation (ether–hexane) gave the *title complex* (±)-**8**, X = Br, as a bright yellow oil (0.985 g, 1.82 mmol, 78%), solidifying to mp 34–37 °C. ν_{max}(KBr)/cm^{-1} 3079w, 2943m, 2864m, 1970vs, 1890vs, 1469m, 1084s, 970s, 620s. δ_H (270 MHz) 5.87 (1 H, d, *J* 1.5 Hz, ArC(3)*H*), 5.55 (1 H, d, *J* 6.9 Hz, ArC(6)*H*), 5.38 (1 H, dd, *J* 1.5, 6.9 Hz, ArC(5)*H*), 5.19 (1 H, d, *J* 6.9 Hz, O–CH_2–O), 5.13 (1 H, d, *J* 6.9 Hz, O–CH_2–O), 4.49 (1 H, d, *J* 12.6 Hz, Ar–CH_2), 4.43 (1 H, d, *J* 12.6 Hz, Ar–CH_2), 3.53 (3 H, s, O*Me*), 1.29–1.04 (21 H, m, *TIPS*); δ_C (68 MHz) 232.2 (*C*O), 136.0 (Ar*C*(1)–O), 106.7 (Ar*C*(4)–CH_2), 96.6 (Ar*C*(3)H), 95.2 (O–*C*H_2–O), 89.5 (Ar*C*(5)H), 80.2 (Ar*C*(2)–Br), 78.7 (Ar*C*(6)H), 62.7 (Ar–*C*H_2), 57.2 (O*Me*), 18.0 (TIPS-*Me*), 11.9 (Si–*C*H). *m*/*z* (FAB^+) 538 (M^+, 13%), 495 ($M^+ - CH_3CHCH_3$, 15), 482 ($M^+ - 2 \times CO$, 1), 454 ($M^+ - 3 \times CO$, 23), 411 (22), 376 (17), 151 (27), 52 (Cr, 27). Found: M^+ 538.0481. $C_{21}H_{31}CrO_6Si^{79}Br$ requires: 538.0478.

(+)-(*S*)-η⁶-(2-Chloro-4-triisopropylsiloxymethyl-1-methoxymethoxybenzene)tricarbonylchromium(0) 8a, X = Cl

A solution of η⁶-(4-triisopropylsiloxymethyl-1-methoxymethoxybenzene)tricarbonylchromium(0) **12** (2.0 g, 4.3 mmol) in ether (4 mL) at −78 °C was added to a solution of (−)-sparteine (3 equiv.) and *n*-BuLi (1.1 equiv.) in ether (12 mL) at −78 °C. The resultant solution was allowed to stir for a further 1 h and then quenched with hexachloroethane (2 equiv., 2.1 g, 8.6 mmol) dissolved in ether (4 mL) at −78 °C. The reaction was allowed to warm up to −10 °C overnight. After work-up with water (10 mL), the organic layer was washed twice with water and once with brine, dried ($MgSO_4$) and concentrated under reduced pressure. FCC (eluant: 10% ether–hexane) gave the *title complex* **8a**, X = Cl, as a bright orange crystalline solid (2.03 g, 0.4.1 mmol, 95%, 20% ee, $[\alpha]_D^{24}$ +16 (*c* = 1.0)). The ee was determined for the *complex* (+)-(S_p,*P*)-**7a**, prepared from (+)-**8a** and boronic acid **18**. (+)-(S_p,*P*)-**7a** (20% ee, $[\alpha]_D^{24}$ +10 (*c* = 0.5), HPLC (OD-H): detector 320 nm, flow: 0.5 mL min^{-1}, 4% ISP in hexane, minor enantiomer 15.5 min, major 17.7 min).

(−)-(*R*)-η⁶-(2-Chloro-4-triisopropylsiloxymethyl-1-methoxymethoxybenzene)tricarbonylchromium(0) 8b, X = Cl, *via* dilithiation with *t*-BuLi

η⁶-(4-Triisopropylsiloxymethyl-1-methoxymethoxybenzene)tricarbonylchromium(0) **12** (2.0 g, 4.34 mmol) and (−)-sparteine (6.5 equiv., 6.7 mL, 0.28 mmol) were dissolved in ether (40 mL) at −78 °C. *t*-BuLi (2.5 equiv.) was added slowly and the solution was left to stir for 15 min. After addition the solution was stirred at −40 °C for 3 h, recooled to −78 °C and stirred for a further hour and quenched overnight at −78 °C with C_2Cl_6 (1.5 equiv., 1.54 g, 6.51 mmol) dissolved in ether (16 mL). The reaction was worked-up with 1 M HCl (10 mL) at −78 °C. FCC (eluant: 5% ether–hexane) gave the *complex* η⁶-(2,6-dichloro-4-triisopropylsiloxymethyl-1-methoxymethoxybenzene)tricarbonylchromium(0) **20** as a yellow solid (470 mg, 0.91 mmol, 21%), mp 42–43 °C (Found: C, 47.83; H, 5.65. $C_{21}H_{30}CrO_6SiCl_2$ requires: C, 47.64; H, 5.71%). ν_{max}(KBr)/cm^{-1} 3092w, 2947s, 2866s, 1978vs, 1916vs, 1888vs, 1422m, 1122s, 904m, 813m, 618s. δ_H (270 MHz) 5.31 (2 H, s, ArC(3,5)*H*), 5.14 (2 H, s, O–CH_2–O), 4.62 (2 H, s, Ar–CH_2), 3.67 (3 H, s, O*Me*), 1.23–0.87 (21 H, m, *TIPS*); δ_C (68 MHz) 230.7 (*C*O), 127.1 (Ar*C*(1)–O), 109.6 (Ar*C*(4)–CH_2), 109.3 (Ar*C*(2,6)–Cl), 103.5 (O–*C*H_2–O), 85.8 (Ar*C*(3,5)H), 62.4 (Ar–*C*H_2), 58.4 (O*Me*), 18.0 (TIPS-*Me*), 11.9 (Si–*C*H). *m*/*z* (FAB^+) 528 (M^+, 16%), 485 (6), 444 ($M^+ - 3 \times CO$, 61), 401 (26), 357 (11), 52 (Cr, 21). Found: M^+ 528.0613. $C_{21}H_{30}CrO_6SiCl_2$ requires: 528.05938.

Further elution gave the *title complex* (−)-(*R*)-**8b**, X = Cl, as a bright yellow solid (1.4 g, 2.82 mmol, 65%, 40% ee, $[\alpha]_D^{24}$ −48 (*c* = 1.0)). The ee was determined by coupling the product with boronic acid **18** to give the *complex* (−)-(R_p,*M*)-**7a** which was shown to be 40% ee, $[\alpha]_D^{24}$ −28 (*c* = 0.5) by HPLC on Chiracel OD-H: detector 320 nm, flow: 0.5 mL min^{-1}, 4% ISP in hexane, major enantiomer 15.5 min, minor 17.7 min.

(−)-(*R*)-η⁶-(2-Bromo-4-triisopropylsiloxymethyl-1-methoxymethoxybenzene)tricarbonylchromium(0) 8b, X = Br, *via* dilithiation with *t*-BuLi

η⁶-(4-Triisopropylsiloxymethyl-1-methoxymethoxybenzene)tricarbonylchromium(0) **12** (2.0 g, 4.34 mmol) and (−)-sparteine (6.5 equiv., 6.7 mL, 0.28 mmol) were dissolved in ether (40 mL) at −78 °C. *t*-BuLi (2.2 equiv.) was added slowly and the solution was left to stir for 15 min. After addition the solution was stirred at −40 °C for 2 h recooled to −78 °C and stirred for a further hour and quenched overnight at −78 °C with $C_2Br_2F_4$ (1.0 equiv., 0.52 mL, 4.34 mmol) dissolved in ether (16 mL). The reaction was worked-up with 1 M HCl (10 mL) at −78 °C. FCC (eluant: 5% ether–hexane) gave the *title complex* (−)-(*R*)-**8b** as a bright yellow solid (1.4 g, 2.82 mmol, 60%, 30% ee, $[\alpha]_D^{24}$ −29 (*c* = 2.3)). The ee was determined as above for **8b**, X = Cl, by conversion to (−)-(R_p,*M*)-**7a** of 30% ee, $[\alpha]_D^{24}$ −21 (*c* = 0.5). HPLC (Chiracel OD-H): detector 320 nm, flow: 0.5 mL min^{-1}, 4% ISP in hexane, major enantiomer 15.5 min, minor 17.7 min.

(±)-4,6-Dimethoxy-2′-methoxymethoxy-2,5′-bis(triisopropylsilyloxymethyl)biphenyl 19

A solution of complex (±)-**8**, X = Cl (0.3 g, 0.61 mmol), boronic acid **9** (0.25 g, 0.67 mmol), barium hydroxide (0.046 g, 1.14 mmol) and $Pd(PPh_3)_4$ (10 mol%, 0.094 g, 0.081 mmol) in deoxygenated DME–water (6 mL–1 mL) was stirred under reflux for 4 h. Water (15 mL) was added and the solution extracted with ether (3 × 15 mL). The combined organic layers were washed with 10% NaOH (15 mL), water (15 mL) and brine (15 mL) and dried ($MgSO_4$). Concentration *in vacuo* followed by FCC (eluant: 10% ether–hexane) gave the decomplexed *biphenyl* (±)-**19** as a colourless oil (0.160 g, 0.24 mmol, 40%). ν_{max}(neat)/cm^{-1} 2941s, 2865s, 1606s, 1462s, 1078s, 1016s, 882s, 808s, 680s. δ_H (270 MHz) 7.26 (1 H, d, *J* 8.2 Hz, Ar(4′)*H*), 7.13 (1 H, d, *J* 7.4 Hz, Ar(3′)*H*), 7.00 (1 H, s, Ar(6′)*H*), 6.95 (1 H, s, Ar(3)*H*), 6.42 (1 H, s, Ar(5)*H*), 4.96 (2 H, s, OCH_2O), 4.75 (2 H, s, Ar–CH_2), 4.46 (2 H, s, Ar–CH_2), 3.84 (3 H, s, O*Me*), 3.65 (3 H, s, O*Me*), 3.29 (3 H, s, OCH$_2$O*Me*), 1.40–0.81 (42 H, m, 2 × TIPS); δ_C (68 MHz) 160.1 (Ar*C*–OMe), 157.8 (Ar*C*–OMe), 154.1 (Ar*C*(2′)–OMOM), 142.5 (Ar*C*–CH_2), 135.1 (Ar*C*–CH_2), 129.6 (ArC(4′/6′)H), 126.4 (ArC(4′/6′)H), 125.8 (Ar*C*(1′)–Ar), 117.3 (ArC(3′)H), 115.5 (Ar*C*(1)–Ar), 101.8 (ArC(3)H), 97.1 (ArC(5)H), 95.1 (O–*C*H_2–O), 64.8.1 (Ar–*C*H_2), 62.9 (Ar–*C*H_2), 55.7 (OCH$_2$O*Me*, O*Me*), 55.2 (O*Me*), 18.2 (TIPS-*Me*), 18.1 (TIPS-*Me*), 12.1 (Si–*C*H), 12.0 (Si–*C*H). *m*/*z* (CI) 664 ($M^+ + NH_4$, 11%), 647 (M^+ + H, 6), 473 (M^+ − OTIPS, 33), 429 (473 − CH_2OMe + H, 5), 385 (12), 255 (429 − OTIPS − H, 100). Found: M^+ 646.4071. $C_{36}H_{62}O_6Si_2$ requires: 626.4085.

Synthesis of diastereomers η⁶-[2-(4,6-dimethoxy-2-hydroxymethylphenyl)-4-triisopropylsiloxymethyl-1-methoxymethoxybenzene]tricarbonylchromium(0) 7a and 7b

(i) The racemic diastereomers (±)-(R_pS_p,*MP*)-7a and (±)-(R_pS_p,*PM*)-7b. A solution of complex (±)-**8**, X = Cl (0.2 g, 0.40 mmol), boronic acid **18** (0.086 g, 0.89 mmol), caesium fluoride

(0.134 g, 0.89 mmol) and $Pd_2(dba)_3$ (10 mol%, 0.042 g, 0.04 mmol) in deoxygenated DME was stirred at rt for 16 h. Ether (50 mL) was added and the solution was washed with 10% NaOH (15 mL), water (15 mL) and brine (15 mL) and dried ($MgSO_4$). Concentration *in vacuo* followed by FCC (eluant: 70% ether–hexane) gave the *biaryl complexes* (±)-(R_pS_p,*MP*)-**7a** as a yellow crystalline solid (0.178 g, 0.28 mmol, 71%), mp 110–112 °C (Found: C, 57.62; H, 6.83. $C_{30}H_{42}O_9SiCr$ requires: C, 57.49; H, 6.75%). ν_{max}(KBr)/cm^{-1} 2941s, 2863s, 1954vs, 1884vs, 1865vs, 1606s, 1460s, 1156s, 628s. δ_H (270 MHz) 6.87 (1 H, d, *J* 2.5 Hz, Ar(3′)*H*), 6.44 (1 H, d, *J* 2.5 Hz, Ar(5′)*H*), 5.75 (1 H, d, *J* 6.7 Hz, Ar(5)*H*), 5.73 (1 H, s, Ar(3)*H*), 5.58 (1 H, d, *J* 6.7 Hz, Ar(6)*H*), 5.01–4.92 (4 H, m, CH_2–OH, O–CH_2–O), 4.44 (2 H, s, Ar–CH_2), 3.86 (3 H, s, ArC(4′/6′)–O*Me*), 3.66 (3 H, s, ArC(4′/6′)–O*Me*), 3.37 (3 H, s, OCH_2OMe), 2.06 (1 H, t, *J* 5.94 Hz, OH), 1.25–0.9 (21 H, m, TIPS); δ_C (68 MHz) 233.6 (*C*O), 161.2 (Ar*C*(4′/6′)–OMe), 159.2 (Ar*C*(4′/6′)–OMe), 142.2 (Ar*C*(1)–OMOM), 138.7 (Ar*C*(2′)), 113.0 (Ar*C*(1′)–Ar), 104.3 (Ar*C*(3′)H), 103.9 (Ar*C*(4)–CH_2), 99.6 (Ar*C*(5′)H), 98.1 Ar*C*(3)H, 95.8 (O–*C*H_2–O), 95.3 (Ar*C*(2)–Ar), 93.5 (Ar*C*(5)H), 78.8 (ArC(6)H), 63.2 (Ar–*C*H_2–O), 62.6 (Ar–*C*H_2–O), 56.9 (ArC(4′/6′)–OMe), 55.8 (ArC(4′/6′)–OMe), 55.4 (OCH_2OMe), 18.1 (TIPS-*Me*), 12.0 (Si–*C*H). *m*/*z* (FAB$^+$) 626 (M^+, 6%), 542 (M^+ − 3 × CO, 85), 525 (542 − OH, 7), 497 (11), 469 (M^+ − TIPS, 16), 453 (M^+ − TIPSO, 11), 369 (542 − TIPSO, 11), 308 (41), 255 (M^+ − TIPSO − $Cr(CO)_3$ − MOM − OH, 100). Found: M^+ 626.2016. $C_{30}H_{42}CrO_9Si$ requires: 626.2003.

Crystal data for (±)-7a†. $C_{30}H_{42}O_9SiCr$, M = 626.7, triclinic, $P\bar{1}$ (no. 2), a = 8.352(1), b = 10.142(1), c = 20.393(2) Å, α = 91.13(1), β = 91.21(1), γ = 110.57(1)°, V = 1616.1(4) Å^3, Z = 2, D_c = 1.288 g cm^{-3}, μ(Cu-Kα) = 3.68 mm^{-1}, T = 293 K, yellow platy needles; 4429 independent measured reflections, F^2 refinement, R_1 = 0.058, wR_2 = 0.142, 3284 independent observed absorption corrected reflections [$|F_o| > 4\sigma(|F_o|)$, $2\theta \leq 120$ °], 403 parameters.

Further elution gave the *diastereomeric complexes* (±)-(R_pS_p,*PM*)-**7b** as a yellow crystalline solid (0.025 g, 0.04 mmol, 10%), mp 123–124 °C. ν_{max}(KBr)/cm^{-1} 3452w, 2942m, 2865m, 1959vs, 1882vs, 1604s, 1462s, 1157s, 628m. δ_H (270 MHz) 6.73 (1 H, d, *J* 2.5 Hz, Ar(3′)*H*), 6.49 (1 H, d, *J* 2.5 Hz, Ar(5′)*H*), 5.56 (1 H, dd, *J* 1.7, 6.7 Hz, Ar(5)*H*), 5.61 (1 H, d, *J* 1.5 Hz, Ar(3)*H*), 5.39 (1 H, d, *J* 6.7 Hz, Ar(6)*H*), 5.08 (1 H, d, *J* 6.9 Hz, O–CH_2–O), 4.87 (1 H, d, *J* 6.9 Hz, O–CH_2–O), 4.55–4.38 (2 H, m, Ar–CH_2–OH), 4.45 (2 H, s, Ar–CH_2), 3.89 (3 H, s, ArC(4′/6′)–O*Me*), 3.86 (3 H, s, ArC(4′/6′)–O*Me*), 3.34 (3 H, s, OCH_2OMe), 1.78 (1 H, t, *J* 5.94 Hz, OH), 1.18–1.3 (21 H, m, TIPS); δ_C (68 MHz) 233.6 (*C*O), 161.1 (Ar*C*(4′/6′)–OMe), 157.8 (Ar*C*(4′/6′)–OMe), 143.1 (Ar*C*(1)–OMOM), 139.5 (Ar*C*(2′)–CH_2), 112.1 (Ar*C*(1′)–Ar), 104.6 (Ar*C*(4)–CH_2), 104.4 (Ar*C*(3′)H), 103.6 (Ar*C*(2)–Ar), 98.1 (Ar*C*(5′,3)H), 96.2 (O–*C*H_2–O), 93.0 (Ar*C*(5)H), 76.9 (ArC(6)H), 63.7 (ArC(4,2′)–*C*H_2–O), 56.9 (ArC(4′,6′)–OMe), 55.4 (OCH_2OMe, ArC(4′/6′)–OMe), 18.1 (TIPS-*Me*), 12.0 (Si–*C*H). *m*/*z*(FAB$^+$) 626 (M^+), 542 (M^+ − 3 × CO), 497, 469, 368 (542 − OTIPS − H), 308, 293, 255, 52 (Cr). Found: M^+ 626.2012. $C_{30}H_{42}CrO_9Si$ requires: 626.2003.

(ii) Non-racemic (R_p)-diastereomers (−)-(R_p,*M*)-7a and (−)-(R_p,*P*)-7b. These compounds were similarly prepared from (−)-**8b** (40% ee) to give a products of 40% ee, $[\alpha]_D^{24}$ −28 (c = 0.5) and $[\alpha]_D^{24}$ −29 (c = 0.2) respectively.

(iii) Non-racemic (S_p)-diastereomers (+)-(S_p,*P*)-7a and (+)-(S_p,*M*)-7b. These compounds were similarly prepared from (+)-**8a** (20% ee) to give products of 20% ee, $[\alpha]_D^{24}$ +10 (c = 0.5) and $[\alpha]_D^{24}$ = + 10 (c = 0.2) respectively.

Coupling using boronic acid 9 with complex (−)-(*R*)-η^6-(2-bromo-4-triisopropylsiloxymethyl-1-methoxymethoxybenzene)tricarbonylchromium(0) 8b, X = Br

(−)-(*R*)-η^6-(2-Bromo-4-triisopropylsiloxymethyl-1-methoxymethoxybenzene)tricarbonylchromium(0) **8b**, X = Br (100 mg, (0.185 mmol, 30% ee), was coupled with **9** as above to give (−)-(R_p,*M*)-**7a** (60%, 70 mg, 0.11 mmol), $[\alpha]_D^{24}$ −21 (c = 0.5) 30% ee, and the diastereomer (−)-(R_p,*P*)-**7b** (8%, 9 mg, 0.015 mmol) 30% ee, $[\alpha]_D^{24}$ −20 (c = 0.2).

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