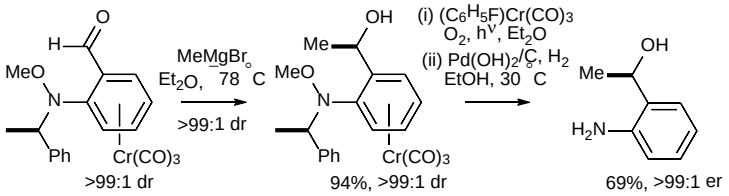
Asymmetric synthesis of secondary benzylic alcohols via arene chromium tricarbonyl complexes

M. Rute G. da Costa,[a] M. João M. Curto,[a] Stephen G. Davies,*[,b] Fátima C. Teixeira[a,b] and James E. Thomson[b]

[a] *Laboratório Nacional de Energia e Geologia, I.P., Estrada do Paço do Lumiar, 22, 1649-038 Lisboa, Portugal*

[b] *Department of Chemistry, Chemistry Research Laboratory, University of Oxford, Mansfield Road, Oxford, OX1 3TA, U.K.*

E-mail: steve.davies@chem.ox.ac.uk



Asymmetric synthesis of secondary benzylic alcohols via arene chromium tricarbonyl complexes

M. Rute G. da Costa,[a] M. João M. Curto,[a] Stephen G. Davies,*[,b] Fátima C. Teixeira[a,b] and James E. Thomson[b]

[a] *Laboratório Nacional de Energia e Geologia, I.P., Estrada do Paço do Lumiar, 22, 1649-038 Lisboa, Portugal*

[b] *Department of Chemistry, Chemistry Research Laboratory, University of Oxford, Mansfield Road, Oxford, OX1 3TA, U.K.*

E-mail: steve.davies@chem.ox.ac.uk

Abstract

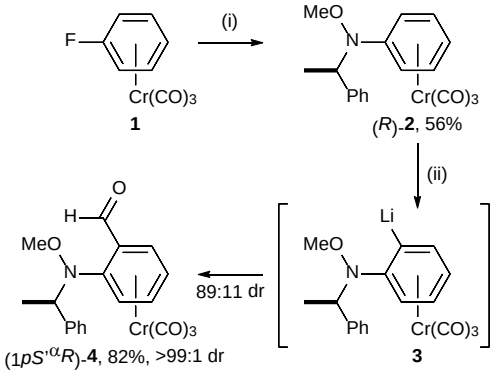
(Aryl aldehyde)- and (aryl ketone)-chromium tricarbonyl complexes *ortho*-substituted with the chiral auxiliary *O*-methyl-*N*-(α-methylbenzyl)hydroxylamine undergo diastereoselective addition of Grignard reagents and Super-Hydride®, respectively, to give the corresponding secondary alcohols in high diastereoisomeric purity. These compounds may be easily decomplexed and deprotected to give the corresponding enantiopure amino alcohols.

Key words: arene chromium tricarbonyl; secondary alcohols, asymmetric synthesis; hydroxylamines

1. Introduction

Compounds bearing optically active secondary alcohols are an important group of molecules, being present in many natural products and biologically active compounds, and also as intermediates in the synthesis of other organic functionalities.[1,2] Over the years, there have been a number of studies on the synthesis of non-racemic secondary alcohols from achiral carbonyl compounds via asymmetric induction.[3] The two major methods for the enantioselective synthesis of non-racemic secondary alcohols are the enantioselective nucleophilic addition to aldehydes and the enantioselective reduction of unsymmetrical ketones.[1,3,4] In these cases, a chiral reducing agent or catalyst interacts with a prochiral substrate. Stereoselective nucleophilic additions to *ortho*-substituted (aryl aldehyde)- and (aryl ketone)-chromium tricarbonyl complexes have been achieved with achiral reducing agents, because the carbonyl group is already in a chiral environment. Usually, these nucleophilic additions occur with very high diastereoselectivities, as a result of attack on the carbonyl group from the uncomplexed face of the arene, since the chromium tricarbonyl unit sterically

blocks the other face of the carbonyl group. The conformation of the carbonyl, which could have the oxygen *anti* or *syn* to the *ortho*-substituent, can be predicted on the basis of known effects such as steric hindrance, dipolar repulsion or hydrogen bonding, leading to the preferred diastereoisomer upon nucleophilic addition.[5] We have recently reported the synthesis of (aryl aldehyde)- and (aryl ketone)-chromium tricarbonyl complexes *ortho*-substituted with the chiral auxiliary *O*-methyl-*N*-(α-methylbenzyl)hydroxylamine.[6] For example, enantiomerically pure complex (1*pS*,α*R*)-**4** was prepared upon deprotonation of (*R*)-*O*-methyl-*N*-(α-methylbenzyl)hydroxylamine with BuLi followed by addition of the resultant lithium amide to (η^6-fluorobenzene)tricarbonylchromium(0) **1**, which gave (*R*)-**2** in 56% yield. Subsequently, a solution of (*R*)-**2** in Et_2O at –78 °C was treated with *t*-BuLi to effect diastereoselective *ortho*-deprotonation to give lithiated aryl anion **3**, which was reacted with ethyl formate to give *ortho*-formyl substituted complex (1*pS*,α*R*)-**4** in 82% yield as a single diastereoisomer (>99:1 dr) after chromatographic purification (Scheme 1). Unfortunately, reaction of lithiated aryl anion **3** with aldehydes gave relatively poor diastereoselectivity (~60:40 dr) upon formation of the new benzylic stereogenic centre, and this low diasteroselectivity can be explained by the absence of steric or electronic control elements. We have observed similarly low diastereoselectivity,[5f,g,j] when the anion derived from (*S*)-[(α-methylbenzyloxy)benzene]tricarbonylchromium(0) and the anion derived from [diphenyl sulfoxide]tricarbonylchromium(0) were reacted with benzaldehyde to afford ~65:35 mixtures of the corresponding benzylic alcohols.



Scheme 1. *Reagents and conditions:* (i) (*R*)-*O*-methyl-*N*-(α-methylbenzyl)hydroxylamine, BuLi, THF, –78 °C to rt, 16 h; (ii) *t*-BuLi, Et_2O, –78 °C, 2 h then HCO_2Et, –78 °C to rt, 16 h.

It was envisaged that the addition of an organometallic reagent to the carbonyl group within *ortho*-substituted (aryl aldehyde)-chromium tricarbonyl complex **4** may be a selective alternative procedure to create a benzylic stereogenic centre, and that reduction of the corresponding *ortho*-substituted (aryl ketone)-chromium tricarbonyl complexes **7** (R′ ≠ H) with hydride reagents may also provide complementary

diastereoselectivity. By comparison with the X-ray crystal structure for the corresponding *ortho*-methyl substituted complex,[6] it was anticipated that *ortho*-formyl substituted complex **4** and *ortho*-acyl substituted complexes **7** would adopt conformations **5** and **8** in which (i) the nitrogen atom is pyramidalised and its lone pair is approximately in the same plane as the complexed arene ring, whilst pointing towards the *ortho*-acyl substituent to minimise 1,3-allylic strain; (ii) the methoxy group (as opposed to the bulky α-methylbenzyl fragment) projects towards the chromium tricarbonyl moiety; and (iii) the conformation with respect to rotation about the N–C(α) bond is staggered and the C(α)–*H* atom is placed in between the arene ring and methoxy substituent. The *ortho*-acyl fragment can then be expected to adopt a conformation where the carbonyl group lies in the plane of the complexed aryl ring and is *anti* to the chiral auxiliary due to minimisation of dipolar repulsion. In each case, the nucleophiles would then be expected to approach complexes **5** and **8** *anti* to the bulky chromium tricarbonyl moiety, giving rise to the epimeric adducts **6** and **9**, respectively (Figure 1).

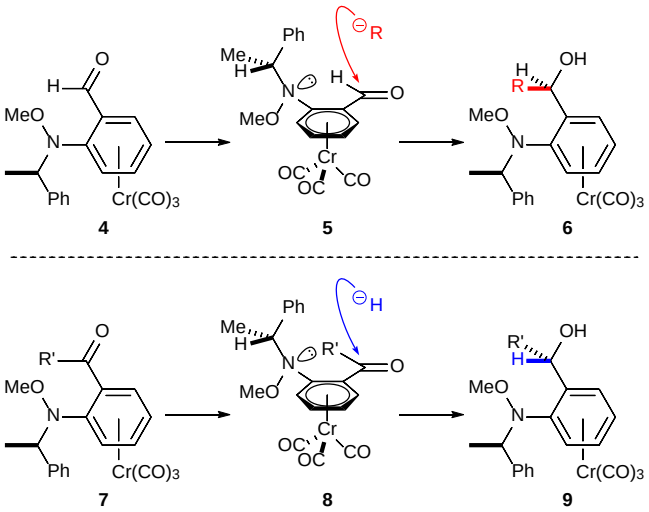


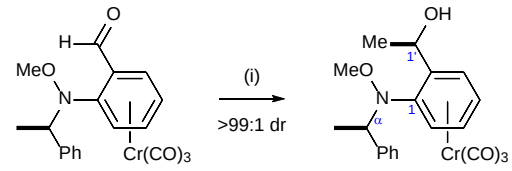
Figure 1. Proposed strategy to create benzylic stereogenic centres.

2. Results and discussion

2.1. Nucleophilic additions to (aryl aldehyde)- and (aryl ketone)-chromium tricarbonyl complexes

Our initial investigations were optimised on a racemic model system. *ortho*-Substituted aldehyde complex (1*pRS*,α*SR*)-**4** was prepared as a single diastereoisomer (>99:1 dr), following our previously reported procedure,[6] upon deprotonation of (*RS*)-**2** with *t*-BuLi followed by reaction of the resultant carbanion with ethyl formate. MeMgBr was subsequently added dropwise to a solution of (1*pRS*,α*SR*)-**4** in Et_2O at –78 °C, which induced a change in the red colour of the solution to yellow. The ^{1}H NMR spectrum of the crude reaction mixture showed the presence of a single product (>99:1 dr), and purification via

recrystallisation gave **10** in 81% yield and >99:1 dr (Scheme 2). The relative (1*pRS*,1'*SR*,α*SR*)-configuration[7] within **10** was unambiguously determined by single crystal X-ray diffraction analysis (Figure 2). Within the solid state structure of **10**, the *O*-methyl-*N*-(α-methylbenzyl)hydroxylamino chiral auxiliary adopts a conformation in complete accordance with our predictions: the α-methylbenzyl group is *anti* to the bulky chromium tricarbonyl unit and the nitrogen of the hydroxylamine is pyramidalised with the lone pair pointing towards the *ortho*-substituent to minimise 1,3-allylic strain, forcing the nitrogen atom to adopt an (*S*)-configuration; an intramolecular O–H···N hydrogen-bond is also present between the hydroxyl group and the nitrogen atom.



(1*pRS*,1'*SR*)-**4**, >99:1 dr **10**, 81%, >99:1 dr

Scheme 2. *Reagents and conditions:* (i) MeMgBr, Et_2O –78 °C, 30 min.

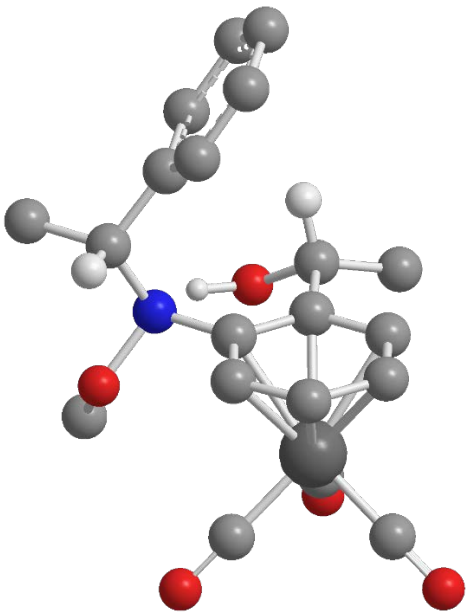
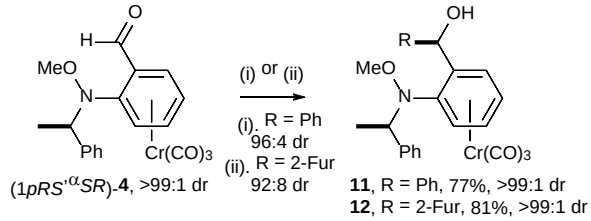


Figure 2. X-ray crystal structure of (1*pRS*,1'*SR*,α*SR*)-**10**.

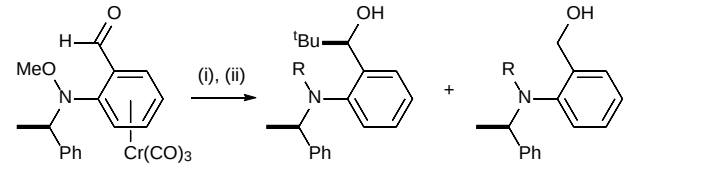
PhMgBr was added dropwise to a solution of (1*pRS*,α*SR*)-**4** in Et_2O at –78 °C, which again induced a change in colour from red to yellow, to give **11** (R = Ph) in 96:4 dr. Recrystallisation of the crude reaction mixture (*n*-hexane/Et_2O) afforded **11** as a single diastereoisomer (>99:1 dr) in 77% yield. The reaction was repeated using 2-furyllithium (which was synthesised in situ by deprotonation of furan with BuLi/TMEDA), which gave **12** (R = 2-Fur) in 92:8 dr. In this case, purification of the crude reaction mixture via flash column chromatography gave **12** in 81% yield and >99:1 dr (Scheme 3). The stereochemical outcomes of these

reactions were assigned by analogy to the corresponding reaction using MeMgBr as the nucleophile, for which the relative configuration of the product **10** had been unambiguously assigned.



Scheme 3. *Reagents and conditions:* (i) PhMgBr, Et_2O, –78 °C, 30 min; (ii) 2-furyllithium, Et_2O, –78 °C, 30 min. [2-Fur = 2-furyl].

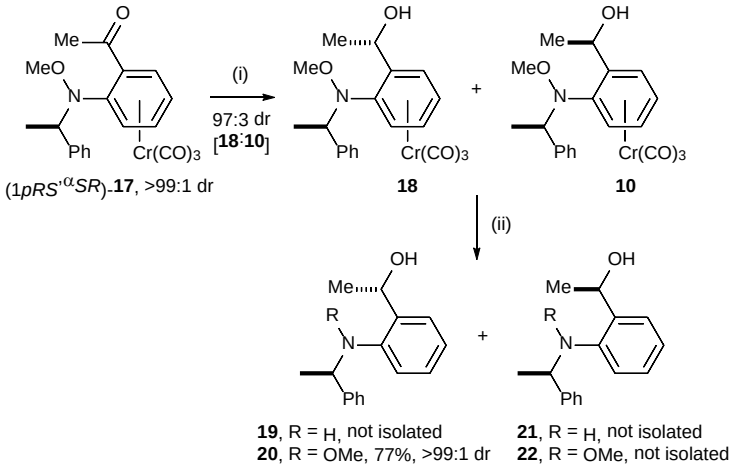
In a similar manner, the nucleophilic addition to (1*pRS*,α*SR*)-**4** with *t*-BuMgCl was attempted, although the diastereoselectivity could not be determined in this case because the ^{1}H NMR spectrum of the crude reaction mixture was very broad and it was impossible to discern the peaks due to major and minor diastereoisomers. Purification via flash column chromatography promoted partial decomplexation during the elution, giving only **16** in 25% isolated yield; the formation of **16** in this case is consistent with reduction[8] of the aldehyde functionality by the Grignard reagent. Repetition of the reaction followed by immediate decomplexation of the crude reaction mixture (by exposing it to air and sunlight for 24 h as a solution in Et_2O) gave a 60:9:31 mixture of **13** (95:5 dr), **14** (95:5 dr) and **16**, respectively. Purification via flash column chromatography gave **13** in 32% yield and >99:1 dr, and **16** in 29% yield (Scheme 4). The relative configurations of **13** and **14** were again assigned by analogy to the corresponding reaction using MeMgBr.



Scheme 4. *Reagents and conditions:* (i) *t*-BuMgCl, Et_2O, –78 °C, 30 min; (ii) O_2, hν, Et_2O, rt, 24 h.

The epimeric secondary alcohols with the opposite configuration at the benzylic position were next targeted by reduction of the corresponding (aryl ketone)-chromium tricarbonyl complexes. Reduction of (1*pRS*,α*SR*)-**17**[6] with Super-Hydride® gave a complex mixture of products which was found to undergo rapid decomplexation in solution. Due to the instability of the products, the crude reaction mixture was decomplexed as before, by exposing it to air and sunlight as a solution in Et_2O. In this case, ^{1}H NMR spectroscopic analysis of the crude reaction mixture after decomplexation revealed the presence of a 19:78:3 mixture of **19**, **20** and **22**, respectively, corresponding to a diastereoselectivity of 97:3 dr [(**19**+**20**):(**21**+**22**)]

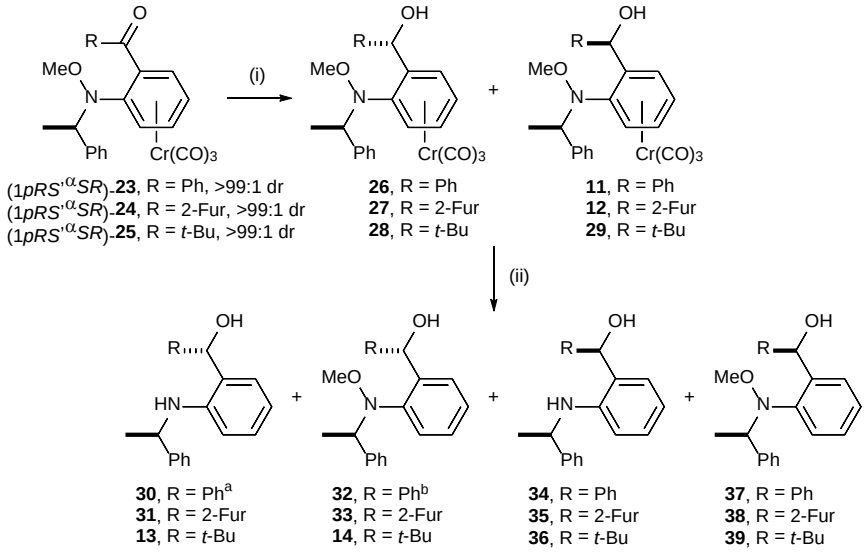
upon formation of the intermediate complexes **18** and **10**. Purification via flash column chromatography gave **20** as a single diastereoisomer (>99:1 dr) in 77% isolated yield (Scheme 5). The relative configurations within the decomplexed amino alcohols **19**–**22** were established upon decomplexation of authentic samples of the epimeric complexes **18** and **10**.



Scheme 5. *Reagents and conditions:* (i) $LiBHEt_3$, Et_2O, –78 °C, 30 min; (ii) O_2, hν, Et_2O, rt, 24 h.

Similarly, reduction of (1*pRS*,α*SR*)-**23** (R = Ph) with Super-Hydride® in THF at –78 °C gave **26** in 98:2 dr. As complex **26** was not sufficiently stable to be isolated (unlike its epimer **11**) it was decomplexed prior to attempting purification. After decomplexation and purification via flash column chromatography **30** and **32** were isolated in 9 and 76% yield, respectively, as single diastereoisomers (>99:1 dr) in each case. The reduction of the ketone complexes (1*pRS*,α*SR*)-**24** (R = 2-Fur)[6] and (1*pRS*,α*SR*)-**25** (R = *t*-Bu)[6] with Super-Hydride® were also performed under the same conditions. As before, the adducts were found to be unstable with respect to decomplexation and so the reaction diastereoselectivities were determined only after complete decomplexation had been achieved. For the reduction of complex **24** (R = 2-Fur), ^{1}H NMR spectroscopic analysis of the crude decomplexed mixture revealed a 15:10:45:30 mixture of **31**, **33**, **35** and **38**, respectively, corresponding to a diastereoselectivity of 25:75 dr [(**31**+**33**):(**35**+**38**)] upon formation of the intermediate complexes **27** and **12**; it was not possible to separate the diastereoisomers via flash column chromatography in this case. Likewise, for the reduction of complex **25** (R = *t*-Bu), only compounds **13** and **36** were produced in a 25:75 diastereoisomeric ratio; as before, all attempts to separate these epimers by flash column chromatography failed (Scheme 6). Comparison of the ^{1}H NMR spectra of these samples with those of authentic samples, which were prepared upon addition of either 2-furyllithium or *t*-BuMgCl to *ortho*-substituted aldehyde complex (1*pRS*,α*SR*)-**4** followed by decomplexation, established the identity of the major diastereoisomer in each case. The reduction of (aryl ketone)-chromium tricarbonyl complexes **24**

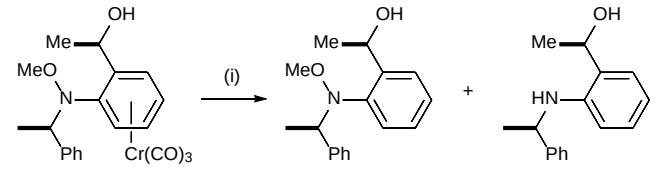
(R = 2-Fur) and **25** (R = *t*-Bu) proved to be less selective than the other reactions investigated and in fact proceeded with the opposite sense of diastereoselectivity. Interestingly, complexes **24** (R = 2-Fur) and **25** (R = *t*-Bu) are yellow whereas all the other *ortho*-formyl and *ortho*-acyl complexes investigated are red, which is indicative of the carbonyl group being in conjugation with the complexed aryl ring. The opposite stereochemical outcomes upon reduction of **24** (R = 2-Fur) and **25** (R = *t*-Bu) could therefore be explained if the carbonyl groups within **24** (R = 2-Fur) and **25** (R = *t*-Bu) do not lie in the same plane as the complexed aromatic ring.



Scheme 6. *Reagents and conditions:* (i) $LiBHEt_3$, Et_2O, –78 °C, 30 min; (ii) O_2, hν, Et_2O, rt, 24 h. [[a] isolated in 9% yield and >99:1 dr; [b] isolated in 76% yield and >99:1 dr; 2-Fur = 2-furyl].

2.2. Optimising the deprotection procedures

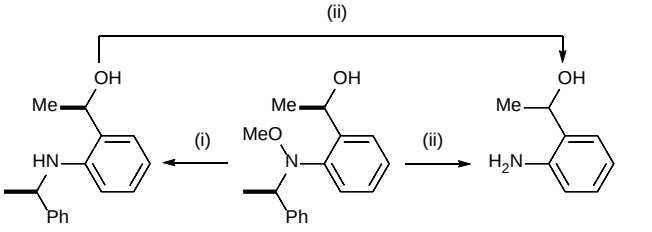
Decomplexation of (1*pRS*,1'*SR*,α*SR*)-**10** was achieved by exposing it to air and sunlight for 24 h as a solution in Et_2O. ^1H NMR spectroscopic analysis of the crude reaction mixture indicated the presence of a 10:90 mixture of **22** and **21**, respectively. The crude reaction mixture was purified via flash column chromatography and **21** was isolated in 70% yield and >99:1 dr. The decomplexation procedure was repeated using iodine as oxidant, which gave an 85:15 mixture of **22** and **21**, respectively. Purification by flash column chromatography afforded **22** in 67% yield and **21** in 9% yield, as single diastereoisomers (>99:1 dr) in each case. The reaction was also repeated by exposing a solution of **10** and (fluorobenzene)tricarbonylchromium(0) **1** (3.0 equiv) in Et_2O to air and sunshine for 5 days, as it was shown that the addition of (fluorobenzene)tricarbonylchromium(0) **1** promoted complete N–O bond cleavage under these conditions. Following purification of the crude reaction mixture, **21** was isolated in 93% yield and >99:1 dr (Scheme 7).



(1*pRS*,1′*SR*,α*SR*)-**10**, >99:1 dr **22**, >99:1 dr (ii). 67% **21**, >99:1 dr (i). 70%, (ii). 9%, (iii). 93%

Scheme 7. *Reagents and conditions:* (i) O_2, hν, Et_2O, rt, 24 h; (ii) I_2, THF, 0 °C, 3 h; (iii) (fluorobenzene)$Cr(CO)_3$ **1**, O_2, hν, Et_2O, 5 days.

With a procedure for removal of the chromium tricarbonyl fragment having already been achieved without compromising the stereochemical integrity of the newly formed benzylic stereogenic centre, our attention turned to removal of the auxiliary. Some procedures exist for removal of the benzylic bond of the auxiliary by treatment with sodium and liquid ammonia[9] or by hydrogenolysis.[10] The use of sodium in ammonia[9] for the deprotection of (1′*RS*,α*RS*)-**22** gave only N–O bond cleavage, giving (1′*RS*,α*RS*)-**21** in quantitative yield with none of the desired product (*RS*)-**40** being formed. Various attempts at the hydrogenolysis of (1′*RS*,α*RS*)-**22** were evaluated with the optimal conditions being the hydrogenolysis of (1′*RS*,α*RS*)-**22** in the presence of $Pd(OH)_2$/C in EtOH at 30 °C, which gave (*RS*)-1-(2-aminophenyl)ethanol (*RS*)-**40** in 75% yield after purification via preparative TLC. Hydrogenolytic deprotection of secondary amine (1′*RS*,α*RS*)-**21** under the same conditions gave (*RS*)-**40** in 77% isolated yield (Scheme 8).

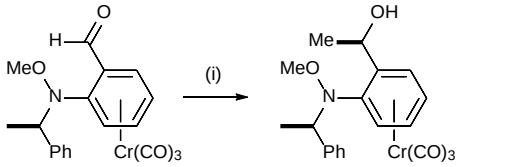


(1′*RS*,α*RS*)-**21** quant, >99:1 dr (1′*RS*,α*RS*)-**22** >99:1 dr (*RS*)-**40**, 75% (from **22**) 77% (from **21**)

Scheme 8. *Reagents and conditions:* (i) Na, NH_3, EtOH, THF, –78 °C, 20 min; (ii) $Pd(OH)_2$/C, H_2 (5 atm), EtOH, 30 °C, 48 h.

2.3. Synthesis of enantiopure (*R*)-1-(2-aminophenyl)ethanol

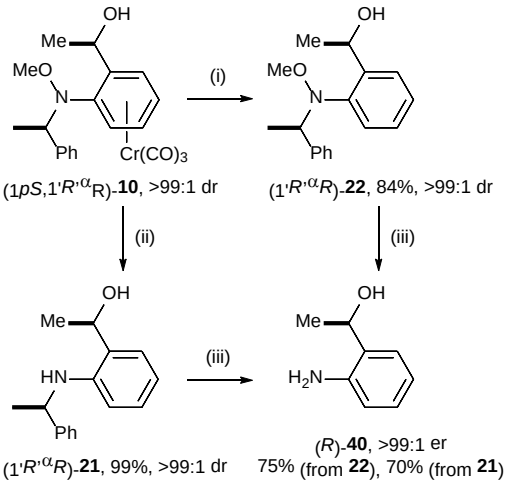
With this methodology established and optimized for the preparation of racemic complexes, it was extended to enantiomerically pure complex (1*pS*,α*R*)-**4**, which was prepared as previously reported.[6] A solution of complex (1*pS*,α*R*)-**4** in Et_2O at –78 °C was treated with MeMgBr to give (1*pS*,1′*R*,α*R*)-**10** as a single diastereoisomer (>99:1 dr). Purification of the crude reaction mixture via recrystallisation afforded (1*pS*,1′*R*,α*R*)-**10** in 94% yield and >99:1 dr (Scheme 9). The ^1H and ^{13}C NMR spectroscopic data for this enantiopure sample were identical to those of the authentic racemic sample (1*pRS*,1′*SR*,α*SR*)-**10** prepared previously.



(1*pS*,1′*R*,α_R)-**4**, >99:1 dr (1*pS*,1′*R*,α_R)-**10**, 94%, >99:1 dr

Scheme 9. *Reagents and conditions:* (i) MeMgBr, Et_2O, –78 °C, 30 min.

Subsequent decomplexation of (1*pS*,1′*R*,α*R*)-**10** was performed under the conditions optimised for the racemic series of compounds. A solution of (1*pS*,1′*R*,α*R*)-**10** in Et_2O was treated with excess I_2 for 3.5 h, and purification of the crude reaction mixture via flash column chromatography allowed isolation of (1′*R*,α*R*)-**22** in 84% yield and >99:1 dr. Alternatively, the decomplexation procedure was repeated by exposing a solution of (1*pS*,1′*R*,α*R*)-**10** and (fluorobenzene)tricarbonylchromium(0) **1** in Et_2O to air and sunshine for 4 days, and after purification via flash column chromatography (1′*R*,α*R*)-**21** was isolated in 99% yield and >99:1 dr. Hydrogenolysis of both (1′*R*,α*R*)-**22** and (1′*R*,α*R*)-**21** in the presence of $Pd(OH)_2/C$ at 30 °C under a pressure of 5 atm of H_2 gave, after purification via flash column chromatography, (*R*)-1-(2-aminophenyl)ethanol (*R*)-**40** in 75 and 70% yield, respectively. In each case, the NMR spectra of (1′*R*,α*R*)-**21**, (1′*R*,α*R*)-**22** and (*R*)-**40** were identical to the authentic racemic samples,[11,12] and (*R*)-**40** {$[\alpha]_D^{23}$ –6.0 (*c* 0.1 in MeOH); lit.[13] for (*S*)-**40**: $[\alpha]_D^{23}$ +4.5 (*c* 16.2 in MeOH)} was assessed to be >99:1 er as determined by ^{1}H NMR spectroscopic analysis in the presence of the chiral solvating agent (*R*)-1-(9-anthryl)-2,2,2-trifluoroethanol[14] and comparison with an authentic racemic standard (Scheme 10).



(1′*R*,α_R)-**10**, >99:1 dr (1′*R*,α_R)-**21**, 99%, >99:1 dr

Scheme 10. *Reagents and conditions:* (i) I_2, THF, 0 °C, 3 h; (ii) (fluorobenzene)$Cr(CO)_3$ **1**, O_2, hν, Et_2O; (iii) $Pd(OH)_2/C$, H_2 (5 atm), EtOH, 30 °C, 48 h.

3. Conclusions

The use of *O*-methyl-*N*-(α-methylbenzyl)hydroxylamine as a chiral auxiliary in arene tricarbonyl chromium complexes has been shown to be efficient for the stereoselective synthesis of diastereomerically pure

secondary alcohols. Diastereoselective addition of Grignard reagents and Super-Hydride® to (aryl aldehyde)- and (aryl ketone)-chromium tricarbonyl complexes, respectively, *ortho*-substituted with the chiral auxiliary, proceed with complementary diastereoselectivity to give both epimers at the benzylic position. The stereochemical outcomes of these processes are consistent with nucleophilic addition to the *exo* face of the carbonyl in the *anti*-conformation. The decomplexation of the resultant amino alcohol complexes was investigated and complementary procedures have been identified, which proceed without disruption of the new alcohol bearing stereogenic centre. Application of this methodology to an enantiopure target gave (*R*)-1-(2-aminophenyl)ethanol in 65% overall yield and >99:1 er.

4. Experimental

4.1. General Experimental

All reactions involving air sensitive reagents and organometallic complexes, as well as their purifications, were performed under an atmosphere of dry nitrogen and all solvents were degassed before use. All solvents were distilled under a nitrogen atmosphere. Et_2O and THF were distilled from Na/benzophenone ketyl. Reagents were used as purchased and when necessary were purified according to standard procedures.[15] BuLi and *t*-BuLi were used as solutions in hexanes and titrated against diphenylacetic acid immediately before use. Flash column chromatography was performed on silica gel (Kieselgel 60, 230-400 Mesh). Melting points were determined on a Reichert Thermovar or on a Gallenkamp melting point apparatus and are uncorrected. Optical rotations were measured using a Perkin-Elmer 241 polarimeter with a thermally water-jacketed 10 cm cell. Concentrations (*c*) are given in g/100 mL and specific rotation values are given in units of 10^{-1} deg cm^2g^{-1}. Infrared spectra were recorded using a Perkin-Elmer 172SX Fourier Transform or a Perkin-Elmer 781 spectrometer. ^1H NMR spectra were recorded at 200 MHz on a Varian Gemini 200 or a Bruker AC 200, at 300 MHz on a General Electrical QE-300, and at 500 MHz on a Bruker AMX 500. ^{13}C NMR spectra were recorded at 50 MHz on a Bruker AC 200 and at 125 MHz on a Bruker AMX 500. NMR spectra were recorded in $CDCl_3$, using tetramethylsilane (δ_H 0.00 ppm) or residual chloroform (δ_H 7.26 ppm; δ_C 77.0 ppm) as internal standards. Chemical shifts (δ) are reported in ppm and coupling constants (*J*) in Hz. Since some hydroxylamine complexes were found to be unstable with respect to decomplexation, it was not possible to record their ^{13}C NMR spectra. Mass spectra (*m/z*) were recorded on a Kratos 25 RF, a VG MicromassLab ZAB 1F, a VG MassLab 20-250 or an APCI Plataform spectrometer. High resolution mass

spectra (HRMS) were obtained on a VG AutoSpect instrument. Elemental analyses were performed on a Carlo Erba 1106 elemental analyser.

4.2. General procedure 1: reaction of aryl aldehyde complex 4 with organometallic reagents

The requisite organometallic reagent (2.0 equiv) was added dropwise to a stirred solution of aryl aldehyde complex **4** (1.0 equiv) in Et_2O at –78 °C and the resultant mixture was stirred at –78 °C for 30 min. MeOH (0.5 mL) was then added and the reaction mixture was allowed to warm to rt, then concentrated in vacuo. The residue was dissolved in Et_2O and the resultant solution was filtered through a plug of alumina (eluent Et_2O) and concentrated in vacuo.

4.3. General procedure 2: reaction of aryl ketone complexes with Super-Hydride®

Super-Hydride® (2.0 equiv) was added dropwise to a stirred solution of the requisite aryl ketone complex (1.0 equiv) in Et_2O at –78 °C and the resultant mixture was stirred at –78 °C for 30 min. MeOH (0.5 mL) was then added added and the reaction mixture was allowed to warm to rt, then concentrated in vacuo. The residue was dissolved in Et_2O and the resultant solution was filtered through a plug of alumina (eluent Et_2O) and concentrated in vacuo.

4.4. (1*pRS*,1'*SR*,α*SR*)-{1-[*O*-Methyl-*N*-(α-methylbenzyl)hydroxylamino]-2-(1'-hydroxyethyl)benzene}tricarbonylchromium(0) (1*pRS*,1'*SR*,α*SR*)-10

MeMgBr (0.08 mL, 3.0 M in Et_2O, 0.250 mmol) was added to a stirred solution of (1*pRS*,α*SR*)-**4** (49 mg, 0.125 mmol, >99:1 dr) in Et_2O (5 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 30 min, according to *general procedure 1*, to give (1*pRS*,1'*SR*,α*SR*)-**10** in >99:1 dr. Purification via recrystallisation (40–60 °C petrol/Et_2O) gave (1*pRS*,1'*SR*,α*SR*)-**10** as a yellow crystalline solid (41 mg, 81%, >99:1 dr); $C_{20}H_{21}CrNO_5$ requires C, 59.0; H, 5.2; N, 3.4%; found: C, 59.0; H, 5.1; N, 3.3%; mp 90 °C (dec.); ν_{max} (KBr) 3400 (O–H), 3091, 3032 (C–H, Ar), 2980, 2936 (C–H), 1963, 1882 (C≡O), 1605, 1520, 1496, 1453 (C=C); δ_H (500 MHz, $CDCl_3$) 1.49 (3H, d, *J* 6.7, C(α)*Me*), 1.52 (3H, d, *J* 6.2, C(2')H_3), 3.33 (3H, s, O*Me*), 3.46 (1H, s, O*H*), 4.16 (1H, q, *J* 6.7, C(α)*H*), 5.03 (1H, br q, *J* 6.2, C(1')*H*), 5.33–5.37 (3H, m, *Ar*), 5.78 (1H, d, *J* 6.2, *Ar*), 7.29–7.45 (5H, m, *Ph*); *m/z* (ESI^+) 408 ($[M+H]^+$, 100%).

4.4.1. X-ray crystal structure determination for (1*pRS*,1'*SR*,α*SR*)-10

$C_{20}H_{21}CrNO_5$, *M* = 407.39, monoclinic, *a* = 12.468(1) Å, *b* = 9.137(2) Å, *c* = 18.232(2) Å, β = 109.92(1)°, *V* = 1952.7(5) Å^3, space group *P* $2_1/c$, Z = 4, μ = 51.53 cm^{-1}. Colourless prism, crystal dimensions 0.19 × 0.29 × 0.74 mm.

Enraf-Nonius MACH3 diffractometer, ω-2θ scan mode with the ω scan width = 1.03 + 0.33tanθ, ω scan speed 2.2–10.1° min^{-1}, graphite-monochromated Cu/Kα radiation (λ = 1.54180 Å), 3060 reflections were measured ($2 < \theta < 60$, 0, h, 0, k; –1.1), 2702 unique, giving 1993 with $I > 3.0\sigma(I)$.

Direct Methods, full-matrix least-squares refinement with all non-hydrogen atoms in anisotropic approximation. All hydrogen atoms were located in the difference Fourier maps and included in the final refinement with fixed positional and thermal parameters [only atom H(4) attached to O(4) was refined isotropically]. Chebychev weighting scheme[16] with parameters 25.6, –14.5 and 17.0 was applied. Corrections for Lorenz and polarisation effects as well as empirical absorption correction based on azimuthal scan data[17] were applied. Final R and R' values are 0.046 and 0.053. All crystallographic calculations were carried out using the CRYSTALS[18] program package on PC/AT-486. Neutral atom scattering factors were taken from the usual sources.[19]

Crystallographic data (excluding structure factors) for (1*pRS*,1'*SR*,α*SR*)-**10** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 1853734. Copies of these data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

4.5. (1*pRS*,1'*SR*,α*SR*)-{1-[*O*-Methyl-*N*-(α-methylbenzyl)hydroxylamino]-2-(phenylhydroxymethyl)benzene}tricarbonylchromium(0) (1*pRS*,1'*SR*,α*SR*)-11

PhMgBr (0.26 mL, 3.0 M in Et_2O, 0.77 mmol) was added to a stirred solution of (1*pRS*,α*SR*)-**4** (150 mg, 0.38 mmol, >99:1 dr) in Et_2O (20 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 40 min, according to *general procedure 1*, to give (1*pRS*,1'*SR*,α*SR*)-**11** in 96:4 dr. Purification via recrystallisation (*n*-hexane/Et_2O) gave (1*pRS*,1'*SR*,α*SR*)-**11** as a yellow crystalline solid (139 mg, 77%, >99:1 dr); $C_{25}H_{23}CrNO_5$ requires C, 64.0; H, 4.9; N, 3.0%; found: C, 64.2; H, 4.9; N, 2.9%; mp 93 °C (dec.); ν_{max} (KBr) 3359 (O–H), 3092, 3067, 3030 (C–H, Ar), 2983, 2937, 2820 (C–H), 1960, 1904, 1893 (C≡O), 1604, 1497, 1455, 1423 (C=C); δ_H (300 MHz, $CDCl_3$) 1.37 (3H, d, *J* 6.9, C(α)*Me*), 3.35 (3H, s, O*Me*), 3.93 (1H, q, *J* 6.9, C(α)*H*), 4.00 (1H, s, O*H*), 5.08 (1H, d, *J* 6.3, *Ar*), 5.29 (1H, app t, *J* 6.0, *Ar*), 5.38 (1H, app t, *J* 6.0,

Ar), 5.82 (1H, d, *J* 6.3, *Ar*), 5.88 (1H, s, C(1')*H*), 7.30–7.42 (10H, m, *Ph*); *m/z* (FAB$^+$) 469 ([M]$^+$, 10%), 452 ([M–OH]$^+$, 1), 353 ([M–$C_4H_4O_4$]$^+$, 62), 336 ([M–$C_4H_5O_5$]$^+$, 20), 275 ([M–$C_{10}H_{10}O_4$]$^+$, 100], 247 ([M–$C_{11}H_{10}O_5$]$^+$, 18), 195 ([M–$C_{11}H_{10}CrO_5$]$^+$, 4).

4.6. (1*pRS*,1'*SR*,α*SR*)-{1-[*O*-Methyl-*N*-(α-methylbenzyl)hydroxylamino]-2-(2''-furylhydroxymethyl)benzene}tricarbonylchromium(0) (1*pRS*,1'*SR*,α*SR*)-12

BuLi (0.35 mL, 1.4 M in hexanes, 0.492 mmol) was added dropwise to a stirred solution of furan (40 µL, 0.49 mmol) and TMEDA (0.10 mL, 0.74 mmol) in Et_2O (5 mL) at –20 °C. The reaction mixture was stirred at –20 °C for 2 h, then cooled to –78 °C and added dropwise to a solution of (1*pRS*,α*SR*)-**4** (45 mg, 0.11 mmol, >99:1 dr) in Et_2O (5 mL) at –78 °C. The resultant mixture was stirred at –78 °C for 30 min, according to *general procedure 1*, to give (1*pRS*,1'*SR*,α*SR*)-**12** in 92:8 dr. Purification via flash column chromatography (eluent 40–60 °C petrol/Et_2O, 9:1), followed by recrystallisation (*n*-hexane/Et_2O) gave (1*pRS*,1'*SR*,α*SR*)-**12** as a yellow crystalline solid (47 mg, 81%, >99:1 dr); $C_{23}H_{21}CrNO_6$ requires C, 60.1; H, 4.6; N, 3.05%; found: C, 60.3; H, 4.8; N, 2.95%; mp 85 °C (dec.); ν_{max} (KBr) 3448 (O–H), 3081, 3032 (C–H, Ar), 2984, 2937, 2809 (C–H), 1977, 1885, 1865 (C≡O), 1603, 1518, 1498, 1451, 1435 (C=C); δ_H (300 MHz, $CDCl_3$) 1.27 (3H, d, *J* 6.6, C(α)*Me*), 2.99 (1H, d, *J* 2.4, O*H*), 3.23 (3H, s, O*Me*), 3.80 (1H, q, *J* 6.6, C(α)*H*), 5.37–5.41 (2H, m, *Ar*), 5.58 (1H, dd, *J* 5.7, 1.5, *Ar*), 5.80 (1H, dd, *J* 5.7, 1.2, *Ar*), 6.14 (1H, d, *J* 2.4, C(1')*H*), 6.29 (1H, d, *J* 3.0, C(3")*H*), 6.35 (1H, dd, *J* 2.7, 1.5, C(4")*H*), 7.33 (5H, m, *Ph*), 7.47 (1H, app s, C(5")*H*); *m/z* (FAB) 459 ([M]$^+$, 11%), 442 ([M–OH]$^+$, 4), 343 ([M–$C_4H_4O_4$]$^+$, 94), 326 ([M–$C_4H_5O_5$]$^+$, 13), 275 ([M–$C_8H_8O_5$]$^+$, 100), 247 (([M–$C_9H_8O_6$]$^+$, 12), 195 ([M–$C_9H_8CrO_5$]$^+$, 10).

4.7. (1'*RS*,α*RS*)-1'-[2-*N*-(α-Methylbenzyl)aminophenyl]-2',2'-dimethylpropan-1'-ol (1'*RS*,α*RS*)-13 and (*RS*)-{2-[*O*-methyl-*N*-(α-methylbenzyl)hydroxylamino]phenyl}methanol (*RS*)-16

t-BuMgCl (0.13 mL, 2.0 M in Et_2O, 0.27 mmol) was added to a stirred solution of (1*pRS*,α*SR*)-**4** (52 mg, 0.133 mmol, >99:1 dr) in Et_2O (5 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 2 h, according to *general procedure 1*. The crude reaction mixture was dissolved in Et_2O (10 mL) and the resultant mixture was exposed to air and sunlight for 24 h to give a 60:9:31 mixture of **13** (95:5 dr), **14** (95:5 dr) and **16**, respectively. Purification via flash column chromatography (eluent 40–60 °C petrol/Et_2O, 9:1), followed by recrystallisation (40–60 °C petrol/Et_2O) gave (1'*RS*,α*RS*)-**13** (12 mg, 32%, >99:1 dr) and (*RS*)-**16** as white crystalline solids (10 mg, 29%).

Data for (1'*RS*,α*RS*)-**13**: $C_{19}H_{25}NO$ requires C, 80.5; H, 8.9; N, 4.9%; found: C, 80.5; H, 8.8; N, 5.0%.; mp 78 °C; ν_{max} (KBr) 3405 (N–H and O–H), 2956, 2868 (C–H), 1604, 1584, 1511, 1451 (C=C); δ_H (500 MHz, $CDCl_3$) 1.07 (9H, s, C*Me*$_3$), 1.54 (3H, d, *J* 6.8, C(α)*Me*), 2.18 (1H, br s, N*H*), 4.47 (1H, q, *J* 6.8, C(α)*H*), 4.56 (1H, s, C(1')*H*), 5.51 (1H, br s, O*H*), 6.39 (1H, d, *J* 8.2, C(6)*H*), 6.58 (1H, app dt, *J* 7.4, 1.0, C(4)*H*), 6.98 (1H, app dt, *J* 7.5, 1.6, C(5)*H*), 7.01 (1H, d, *J* 7.6, C(3)*H*), 7.22–7.25 (1H, m, *Ph*), 7.31–7.37 (4H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 25.3 (C(α)*Me*), 26.8 (C*Me*$_3$), 37.5 (*C*Me$_3$), 53.4 (*C*(α)), 83.0 (*C*(1')), 112.3, 115.3 (*C*(4), *C*(6)), 124.0 (*C*(2)), 125.7, 126.7, 128.1, 128.6, 129.9 (*C*(3), *C*(5), *o*,*m*,*p*-*Ph*), 145.8, 145.9 (*C*(1), *i*-*Ph*); *m/z* (ESI^+) 284 ($[M+H]^+$, 100%).

Data for (*RS*)-**16**: mp 75 °C; ν_{max} (KBr) 3370 (O–H), 3062, 3031 (C–H, Ar), 2978, 2934, 2891, 2808 (C–H), 1601, 1583, 1494, 1452 (C=C); δ_H (500 MHz, $CDCl_3$) 1.41 (3H, d, *J* 6.8, C(α)*Me*), 3.34 (3H, s, O*Me*), 4.02 (1H, br t, *J* 5.6, O*H*), 4.24 (1H, q, *J* 6.8, C(α)*H*), 4.75 (1H, dd, *J* 13.3, 5.6, C*H*$_A$H$_B$OH), 4.86 (1H, dd, *J* 13.3, 5.0, CH$_A$*H*$_B$OH), 7.17–7.36 (8H, m, *Ar*, *Ph*), 7.43 (1H, d, *J* 8.1, *Ar*, *Ph*); δ_C (125 MHz, $CDCl_3$) 17.8 (C(α)*Me*), 60.4 (*C*(α)), 63.9 (*C*H$_2$OH), 67.2 (O*Me*), 123.4, 126.5, 127.4, 127.6, 128.1 (*C*(3), *C*(4), *C*(5), *C*(6), *o*,*m*,*p*-*Ph*), 135.8 (*C*(2)), 141.4, 147.5 (*C*(1), *i*-*Ph*); *m/z* (CI^+) 258 ($[M+H]^+$, 6%), 228 ($[M+H–CH_2O]^+$, 12), 108 ($[C_7H_8O]^+$, 100), 105 ($[PhCHCH_3]^+$, 78); HRMS (CI^+) $C_{16}H_{20}NO_2^+$ ($[M+H]^+$) requires 258.1489; found 258.1494.

4.8. (1'*RS*,α*SR*)-1'-{2-[*O*-Methyl-*N*-(α-methylbenzyl)hydroxylamino]phenyl}ethanol (1'*RS*,α*SR*)-20

Super-Hydride® (0.24 mL, 1.0 M in THF, 0.24 mmol) was added to a stirred solution of (1*pRS*,α*SR*)-**17** (48 mg, 0.119 mmol, >99:1 dr) in Et_2O (5 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 30 min, according to *general procedure 2*. The crude reaction mixture was dissolved in Et_2O (10 mL) and the resultant solution was exposed to air for 19 hours on a cloudy day to give a 19:78:3 mixture of **19**, **20** and **22**, respectively. Purification via flash column chromatography (eluent 40–60 °C petrol/Et_2O, 9:1) gave (1'*RS*,α*SR*)-**20** as a white crystalline solid (25 mg, 77%, >99:1 dr); $C_{17}H_{21}NO_2$ requires C, 75.25; H, 7.8; N, 5.2%; found: C, 75.2; H, 7.8; N, 5.2%; mp 82 °C; ν_{max} (film) 3608–3403 (O–H), 3063, 3031 (C–H, Ar), 2976, 2933, 2892, 2808 (C–H), 1601, 1482, 1452 (C=C); δ_H (500 MHz, $CDCl_3$) 1.42 (3H, d, *J* 6.8, C(α)*Me*), 1.53 (3H, d, *J* 6.5, C(2')*H*$_3$), 3.36 (3H, s, O*Me*), 3.72 (1H, br s, O*H*), 4.23 (1H, q, *J* 6.8, C(α)*H*), 5.39 (1H, dq, *J* 6.5, 2.4, C(1')*H*), 7.20–7.43 (9H, m, *Ar*, *Ph*); δ_C (125 MHz, $CDCl_3$) 19.0 (C(α)*Me*), 23.8 (*C*(2')), 60.3 (*C*(α)), 66.0 (O*Me*), 67.8 (*C*(1')), 123.6, 125.6, 127.0, 127.4, 127.9, 128.0, 128.2 (*C*(3), *C*(4), *C*(5), *C*(6),

o,m,p-Ph), 141.0, 141.5, 146.6 (*C*(1), *C*(2), *i-Ph*); *m/z* (CI^+) 272 ($[M+H]^+$, 8%), 241 ($[M+H–CH_3O]^+$, 16), 240 ($[M–CH_3O]^+$, 37), 226 ($[M+H–C_2H_6O]^+$, 34), 224 ($[M+H–C_2H_7O_2]^+$, 100), 105 ($[PhCHCH_3]^+$, 64).

Data for **19**: ν_{max} (KBr) 3391 (O–H, N–H), 3062, 3027 (C–H, Ar), 2975, 2927, 2869 (C–H), 1607, 1587, 1515, 1505, 1494, 1455 (C=C); δ_H (300 MHz, $CDCl_3$) 1.54 (3H, d, *J* 6.6, C(α)*Me*), 1.69 (3H, d, *J* 6.6, C(2')H_3), 4.49 (1H, q, *J* 6.6, C(α)*H*), 5.00 (1H, q, *J* 6.6, C(1')*H*), 6.39 (1H, d, *J* 8.1, C(6)*H*), 6.59 (1H, app dt, *J* 7.2, 0.9, C(4)*H*), 6.99 (1H, app dt, *J* 7.8, 1.5, C(5)*H*), 7.05 (1H, dd, *J* 7.2, 0.9, C(3)*H*), 7.18–7.39 (5H, m, *Ph*); δ_C (75 MHz, $CDCl_3$) 21.3 (C(α)*Me*), 25.3 (*C*(2')), 53.1 (*C*(α)), 70.7 (*C*(1')), 112.3 (*C*(6)), 116.2 (*C*(4)), 127.2 (*C*(2)), 125.7, 126.4, 126.7, 128.5, 128.6 (*C*(3), *C*(5) *o,m,p-Ph*), 145.5, 145.7 (*C*(1), *i-Ph*); *m/z* (CI^+) 242 ($[M+H]^+$, 7%), 224 ($[M–OH]^+$, 10), 105 ($[PhCHCH_3]^+$, 100); HRMS (CI^+) $C_{16}H_{20}NO^+$ ($[M+H]^+$) requires 242.1539; found 242.1533.

4.9. (1'*RS*,α*SR*)-Phenyl[2-*N*-(α-methylbenzyl)aminophenyl]methanol (1'*RS*,α*SR*)-30 and (1'*RS*,α*SR*)-Phenyl{2-[*O*-methyl-*N*-(α-methylbenzyl)hydroxylamino]phenyl}methanol (1'*RS*,α*SR*)-32

Step 1: Super-Hydride® (0.21 mL, 1.0 M in THF, 0.21 mmol) was added to a stirred solution of (1*pRS*,α*SR*)-**23** (50 mg, 0.11 mmol, >99:1 dr) in Et_2O (5 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 30 min, according to *general procedure 2*, to give **26** in 98:2 dr. Data for **26**: δ_H (300 MHz, $CDCl_3$) 1.37 (3H, d, *J* 6.6, C(α)*Me*), 3.30 (3H, s, O*Me*), 4.30 (1H, q, *J* 6.6, C(α)*H*), 4.45 (1H, d, *J* 6.6, O*H*), 5.20 (1H, dd, *J* 6.0, 1.2, *Ar*), 5.29 (1H, app t, *J* 6.0, *Ar*), 5.38 (1H, app dt, *J* 6.0, 1.2, *Ar*), 5.77 (1H, d, *J* 6.6, *Ar*), 5.86 (1H, d, *J* 6.3, C(1')*H*), 7.28–7.37 (6H, m, *Ph*), 7.43 (2H, t, *J* 7.5 *Ph*), 7.61 (2H, d, *J* 7.5, *Ph*).

Step 2: The crude reaction mixture from the previous step was dissolved in Et_2O (10 mL) and the resultant solution was exposed to air and light for 2 cloudy days. Purification via flash column chromatography (eluent 40–60 °C petrol/Et_2O, 9:1) gave (1'*RS*,α*SR*)-**30** as a white crystalline solid (3 mg, 9%) and (1'*RS*,α*SR*)-**32** as a colourless oil (27 mg, 76%).

Data for (1'*RS*,α*SR*)-**32**: $C_{22}H_{23}NO_2$ requires C, 79.25; H, 6.95; N, 4.2%; found: C, 79.0; H, 6.9; N, 4.0%; ν_{max} (film) 3401 (O–H), 3063, 3030 (C–H, Ar), 2978, 2933, 2893, 2810 (C–H), 1601, 1583, 1494, 1452 (C=C); δ_H (200 MHz, $CDCl_3$) 1.38 (3H, d, *J* 6.8, C(α)*Me*), 3.35 (3H, s, O*Me*), 4.14 (1H, q, *J* 6.8, C(α)*H*), 4.46 (1H, br s, O*H*), 6.28 (1H, s, C(1')*H*), 7.06–7.21 (2H, m, *Ar*, *Ph*), 7.25–7.49 (12H, m, *Ar*, *Ph*); δ_C (50 MHz, $CDCl_3$) 18.1 (C(α)*Me*), 60.4 (*C*(α)), 67.3 (O*Me*), 72.9 (*C*(1')), 123.8, 126.7, 127.1, 127.4, 127.9,

128.1, 128.1, 128.3 (*C*(3), *C*(4), *C*(5), *C*(6), *o,m,p-Ph*), 138.8 (*C*(2)), 141.4, 143.6, 147.2 (*C*(1), *i-Ph*); *m/z* (ESI^+) 334 ($[M+H]^+$, 100%).

Data for (1'*RS*,α*SR*)-**30**: $C_{21}H_{21}NO$ requires C, 83.1; H, 7.0; N, 4.6%; found: C, 83.1; H, 6.95; N, 4.7%; mp 85–86 °C; ν_{max} (KBr) 3347 (O–H and N–H), 3082, 3060, 3025 (C–H)Ar, 2986, 2935, 2860 (C–H), 1606, 1588, 1511, 1494, 1467, 1453 (C=C); δ_H (500 MHz, $CDCl_3$) 1.39 (3H, d, *J* 6.7, C(α)*Me*), 2.51 (1H, br s, N*H*), 4.45 (1H, q, *J* 6.7, C(α)*H*), 5.05 (1H, br s, O*H*), 5.94 (1H, s, C(1')*H*), 6.38 (1H, d, *J* 8.1, C(6)*H*), 6.63 (1H, app dt, *J* 7.4, 1.0, C(4)*H*), 6.93–6.94 (2H, m, *Ph*), 7.04 (1H, app dt, *J* 7.7, 1.6, C(5)*H*), 7.08 (1H, dd, *J* 7.5, 1.6, C(3)*H*), 7.13–7.46 (8H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 25.1 (C(α)*Me*), 52.5 (*C*(α)), 76.0 (*C*(1')), 112.5 (*C*(6)), 116.1 (*C*(4)), 126.3 (*C*(2)), 125.6, 126.3, 126.6, 127.4, 128.3, 128.4, 128.9, 129.1 (*C*(3), *C*(5), *o,m,p-Ph*), 141.9, 145.1, 145.1 (*C*(1), *i-Ph*); *m/z* (CI^+) 304 ($[M+H]^+$, 62%), 286 ($[M–OH]^+$, 100), 105 ($[PhCHCH_3]^+$, 61).

4.10. Reaction of (1*pRS*,α*SR*)-24 with Super-Hydride® followed by decomplexation

Super-Hydride® (0.53 mL, 1.0 M in THF, 0.526 mmol) was added to a stirred solution of (1*pRS*,α*SR*)-**24** (120 mg, 0.263 mmol, >99:1 dr) in Et_2O (15 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 30 min, according to *general procedure 2*. The crude reaction mixture was dissolved in Et_2O (20 mL) and the resultant mixture was exposed to air and light for 24 h to give an inseparable 15:10:45:30 mixture of **31**, **33**, **35** and **38**, respectively. Data for **31**: δ_H (500 MHz, $CDCl_3$) 1.48 (3H, d, *J* 6.7, C(α)*Me*), 4.50 (1H, q, *J* 6.7, C(α)*H*), 5.94 (1H, s, O*H*), 6.30–7.47 (13H, m, C(1')*H*, *Ar*, *Ph*). Data for **33**: δ_H (500 MHz, $CDCl_3$) 1.34 (3H, d, *J* 6.9, C(α)*Me*), 3.33 (3H, s, O*Me*), 4.16 (1H, q, *J* 6.9, C(α)*H*), 6.18–7.47 (13H, m, C(1')*H*, *Ar*, *Ph*).

4.11. Reaction of complex (1*pRS*,α*SR*)-25 with Super-Hydride® followed by decomplexation

Super-Hydride® (0.22 mL, 1.0 M in THF, 0.22 mmol) was added to a stirred solution of (1*pRS*,α*SR*)-**25** (50 mg, 0.112 mmol, >99:1 dr) in Et_2O (5 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 18 h, according to *general procedure 2*. The crude reaction mixture was dissolved in Et_2O (10 mL) and the resultant mixture was exposed to air and light for 19 h to give an inseparable 25:75 mixture of **13** and **36**, respectively. Data for **13**: δ_H (500 MHz, $CDCl_3$) 1.09 (9H, s, C*Me*$_3$), 1.54 (3H, d, *J* 6.8, C(α)*Me*), 2.14 (1H, br s, N*H*), 4.42 (1H, q, *J* 6.8, C(α)*H*), 4.59 (1H, s, C(1')*H*), 5.50 (1H, br s, O*H*), 6.39 (1H, d, *J* 8.2, *Ar*), 6.58

(1H, app dt, *J* 7.4, 1.0, *Ar*), 6.98 (1H, app dt, *J* 7.0, 1.7, *Ar*), 7.02 (1H, dd, *J* 7.5, 1.4, *Ar*), 7.21–7.26 (1H, m, *Ph*), 7.31–7.41 (4H, m, *Ph*).

4.12. (1'*RS*,α*RS*)-1'-[2-*N*-(α-Methylbenzyl)aminophenyl]ethanol 21 and (1'*RS*,α*RS*)-1'-{2-[*O*-methyl-*N*-(α-methylbenzyl)hydroxylamino]phenyl}ethanol 22

Method A: A solution of (1*pRS*,1'*SR*,α*SR*)-**10** (32 mg, 0.079 mmol, >99:1 dr) in Et_2O (10 mL) was exposed to air and sunlight for 24 h to give a 10:90 mixture of **22** and amine **21**, respectively. Purification via flash column chromatography (eluent 40–60 °C petrol/Et_2O, 9:1) gave (1'*RS*,α*RS*)-**21** as a colourless oil (13.3 mg, 70%, >99:1 dr); ν_{max} (KBr) 3392 (O–H and N–H), 3025 (C–H, Ar), 2970, 2927 (C–H), 1605, 1586, 1514, 1451 (C=C); δ_H (200 MHz, $CDCl_3$) 1.56 (3H, d, *J* 6.7, C(α)*Me*), 1.68 (3H, d, *J* 6.6, C(2')H_3), 4.55 (1H, q, *J* 6.7, C(α)*H*), 5.03 (1H, q, *J* 6.6, C(1')*H*), 6.43 (1H, d, *J* 8.2, C(6)*H*), 6.62 (1H, app dt, *J* 7.3, 0.9, C(4)*H*), 6.98–7.11 (2H, m, C(3)*H*, C(5)*H*), 7.18–7.39 (5H, m, *Ph*); δ_C (50 MHz, $CDCl_3$) 21.5 (C(α)*Me*), 25.2 (*C*(2')), 52.9 (*C*(α)), 69.8 (*C*(1')), 112.3 (*C*(6)), 116.2 (*C*(4)), 127.2 (*C*(2)), 125.8, 126.1, 126.7, 128.6, 128.7 (*C*(3), *C*(5), *o,m,p-Ph*), 145.4, 145.7 (*C*(1), *i-Ph*); *m/z* (CI^+) 242 ($[M+H]^+$, 39%), 224 ($[M–OH]^+$, 100), 223 ($[M–H_2O]^+$, 16), 208 ($M–CH_5O]^+$, 28), 105 ($[PhCHCH_3]^+$, 69); HRMS (CI^+) $C_{16}H_{20}NO^+$ ($[M+H]^+$) requires 242.1539; found 242.1543.

Method B: A solution of I_2 (65 mg, 0.26 mmol) in THF (10 mL) was added to a stirred solution of (1*pRS*,1'*SR*,α*SR*)-**10** (52 mg, 0.13 mmol, >99:1 dr) in THF (10 mL) at 0 °C. The reaction mixture was stirred at rt for 4 h then concentrated in vacuo. The residue was extracted with Et_2O (3 × 30 mL) and the combined organic extracts were washed sequentially with satd aq $Na_2S_2O_5$ (3 × 35 mL), satd aq $NaHCO_3$ (3 × 35 mL) and brine (3 × 35 mL), then dried and concentrated in vacuo. Purification by preparative TLC (eluent 40–60 °C petrol/Et_2O, 9:1) gave (1'*RS*,α*RS*)-**22** as a white crystalline solid (23 mg, 67%) and (1'*RS*,α*RS*)-**21** as a colourless oil (2.7 mg, 9%).

Data for compound **22**: $C_{17}H_{21}NO_2$ requires C, 75.25; H, 7.8; N, 5.2%; found: C, 75.6; H, 7.9; N, 4.8%; mp 115–116 °C; ν_{max} (film) 3360 (O–H), 3029 (C–H, Ar), 2981, 2968, 2940, 2929, 2855, 2806 (C–H), 1602, 1584, 1491, 1461, 1451 (C=C); δ_H (300 MHz, $CDCl_3$) 1.38 (3H, d, *J* 6.9, C(α)*Me*), 1.56 (3H, d, *J* 6.6, C(2')H_3, 3.30 (3H, s, O*Me*), 4.24 (1H, q, *J* 6.9, C(α)*H*), 4.35 (1H, br s, O*H*), 5.34 (1H, q, *J* 6.6, C(1')*H*), 7.20–7.45 (9H, m, *Ar*, *Ph*); δ_C (75 MHz, $CDCl_3$) 17.9 (C(α)*Me*), 24.1 (*C*(2')), 60.3 (*C*(α)), 66.6 (O*Me*), 67.2 (*C*(1')), 123.7, 125.7, 126.8, 127.4, 127.8, 128.1, 128.1 (*C*(3), *C*(4), *C*(5), *C*(6), *o,m,p-Ph*), 140.6, 141.7, 146.5 (*C*(1), *C*(2), *i-Ph*); *m/z* (ESI^+) 272 ($[M+H]^+$, 100%).

Method C: A solution of (1*pRS*,1'*SR*,α*SR*)-**10** (104 mg, 0.255 mmol, >99:1 dr) and (fluorobenzene)tricarbonylchromium(0) **1** (178 mg, 0.765 mmol) in Et_2O (20 mL) was exposed to air and sunlight for 5 days. Purification via flash column chromatography (eluent 40–60 °C petrol/Et_2O, 9:1) gave (1'*RS*,α*RS*)-**21** as a colourless oil (57.7 mg, 93%).

Method D: NH_3 (2 mL) was condensed at –78 °C and subsequently dried by addition of sodium until the solution remained deep blue. The resultant mixture was carefully warmed and the dried ammonia was recondensed at –78 °C. EtOH (0.1 mL) was added, followed by sodium (7 mg, 0.30 mmol) and the resultant mixture was stirred at –78 °C for 15 min. A solution of (1'*RS*,α*RS*)-**22** (44 mg, 0.16 mmol, >99:1 dr) in THF (0.4 mL) was then added and the resultant mixture was stirred at –78 °C for 10 min, which caused decolourisation. Two further portions of sodium (2 × 7.5 mg) were added until the solution remained blue. After 10 min, analysis by TLC showed no evidence of starting material. NH_4Cl was added and the reaction mixture was allowed to warm to rt, then concentrated in vacuo. The residue was dissolved in CH_2Cl_2 and the resultant solution was filtered and concentrated in vacuo to afford (1'*RS*,α*RS*)-**21** as a pale yellow oil (39 mg, quant).

4.13. (*RS*)-1-(2-Aminophenyl)ethanol (*RS*)-40[11,12]

Method A: 20% $Pd(OH)_2/C$ (5 mg, 20% w/w) was added to a solution of (1'*RS*,α*RS*)-**22** (25 mg, 0.092 mmol) in EtOH (5 mL) and the resultant mixture was vigorously stirred at 30 °C for 48 h under H_2 (5 atm). The reaction mixture was then filtered through a plug of Celite® (eluent EtOAc) and concentrated in vacuo. Purification by preparative TLC (petroleum ether/Et_2O, 1:1) gave (*RS*)-**40** as a white crystalline solid (9.4 mg, 75%); mp (54–56 °C); {lit.[11b] mp 58 °C}; δ_H (300 MHz, $CDCl_3$) 1.59 (3H, d, *J* 6.6, C(2´)*H*$_3$), 4.92 (1H, q, *J* 6.6, C(1´)*H*), 6.65–6.75 (2H, m, C(4)*H* and C(6)*H*) 7.07–7.09 (2H, m, C(3)*H* and C(5)*H*).

Method B: 20% $Pd(OH)_2/C$ (5 mg, 20% w/w) was added to a solution of (1'*RS*,α*RS*)-**21** (26 mg, 0.108 mmol, >99:1 dr) in EtOH (5 mL) and the resultant mixture was vigorously stirred at 30 °C for 48 h under H_2 (5 atm). The reaction mixture was then filtered through a plug of Celite® (eluent EtOAc) and concentrated in vacuo. Purification by preparative TLC (petroleum ether/Et_2O, 1:1) gave (*RS*)-**40** as a white crystalline solid (11.4 mg, 77%).

4.14. (1*pS*,1′*R*,α*R*)-{1-[*O*-Methyl-*N*-(α-methylbenzyl)hydroxylamino]-2-(1'-hydroxyethyl)benzene}tricarbonylchromium(0) (1*pS*,1′*R*,α*R*)-10

MeMgBr (0.33 mL, 3.0 M in Et_2O, 1.00 mmol) was added to a stirred solution of (1*pS*,α*R*)-**4** (130 mg, 0.332 mmol, >99:1 dr, >99:1 er) in Et_2O (15 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 10 min, according to *General Procedure 1*, to give (1*pS*,1'*R*,α*R*)-**10** in >99:1 dr. Purification via recrystallisation (40–60 °C petrol/Et_2O) gave (1*pS*,1'*R*,α*R*)-**10** as a yellow crystalline solid (126 mg, 94%, >99:1 dr); mp 90 °C (dec.); $[\alpha]_D^{23}$ –28.4 (*c* 0.63 in $CHCl_3$).

4.15. (1'*R*,α*R*)-1'-{2-[*O*-methyl-*N*-(α-methylbenzyl)hydroxylamino]phenyl}ethanol (1'*R*,α*R*)-22

A solution of I_2 (67 mg, 0.26 mmol) in THF (10 mL) was added to a stirred solution of (1*pS*,1′*R*,α*R*)-**10** (54 mg, 0.132 mmol, >99:1 dr) in THF (10 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 3.5 h then concentrated in vacuo. The residue was extracted with Et_2O (3 × 30 mL) and the combined organic extracts were washed with satd aq $Na_2S_2O_5$ (50 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 40–60 °C petrol/Et_2O, 9:1) gave (1′*R*,α*R*)-**22** as a white crystalline solid (30 mg, 84%, >99:1 dr); mp 138–139 °C; $[\alpha]_D^{23}$ +98.7 (*c* 0.45 in $CHCl_3$).

4.16. (1'*R*,α*R*)-1'-[2-*N*-(α-Methylbenzyl)aminophenyl]ethanol (1'*R*,α*R*)-21

A solution of (1*pS*,1′*R*,α*R*)-**10** (73 mg, 0.18 mmol, >99:1 dr) and (fluorobenzene)tricarbonylchromium(0) **1** (125 mg, 0.538 mmol) in Et_2O (20 mL) was exposed to air and sunlight for 4 days. Purification via flash column chromatography (eluent 40–60 °C petrol/Et_2O, 9:1) gave (α*R*,1′*R*)-**21** as a colourless oil (43 mg, 99%, >99:1 dr); $[\alpha]_D^{23}$ –96.0 (*c* 1.17 in $CHCl_3$).

4.17. (*R*)-1-(2-Aminophenyl)ethanol (*R*)-40[13,20]

*Method A (from **22**)*: 20% $Pd(OH)_2/C$ (4 mg, 20% w/w) was added to a solution of (1′*R*,α*R*)-**22** (20 mg, 0.074 mmol, >99:1 dr) in EtOH (5 mL) and the resultant mixture was stirred vigorously at 30 °C for 24 h under H_2 (5 atm). The reaction mixture was then filtered through a plug of Celite® (eluent EtOAc) and concentrated in vacuo. Purification via flash column chromatography (eluent 40–60 °C petrol/Et_2O, 1:1) gave (*R*)-**40** as a white crystalline solid (7.6 mg, 75%, >99:1 er); mp 50–52 °C; {lit.[13] mp 49–54 °C}; $[\alpha]_D^{23}$ –6.0 (*c* 0.1 in MeOH); {lit.[13] for (*S*)-**40**: $[\alpha]_D^{23}$ +4.5 (*c* 16.2 in MeOH)}.

*Method B (from **21**)*: 20% $Pd(OH)_2/C$ (8 mg, 20% w/w) was added to a solution of (1′*R*,α*R*)-**21** (40 mg, 0.166 mmol) in EtOH (5 mL) and the resultant mixture was stirred vigorously at 30 °C for 24 h under H_2 (5 atm). The reaction mixture was then filtered through a plug of Celite® (eluent EtOAc) and concentrated in vacuo. Purification via flash column chromatography (eluent 40–60 °C petrol/Et_2O, 1:1) gave (*R*)-**40** as a white crystalline solid (16 mg, 70%, >99:1 er).

Acknowledgements

We thank Fundação para a Ciência e a Tecnologia (Programa Praxis XXI) for provision of funding (to F.C.T., Praxis XXI BD/5433/95 JNICT). We also thank Dr. A. N. Chernega, and the Oxford Chemical Crystallography Service for X-ray crystal structure determination and the use of their diffractometers.

References and notes

[1] Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833.

[2] Spino, C.; Mayers, N.; Desfossés, H. *Tetrahedron Lett.* **1996**, *37*, 6503.

[3] Solladié, G. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: London, 1983, Vol. 2, pp 157–199.

[4] (a) Nógrádi, M. *Stereoselective Synthesis*, VCH: New York, 1986; pp 105–193; (b) Noyori, R.; Kitamura, M. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 49; (c) Pu, L. *Tetrahedron* **2003**, *59*, 9873; (d) Collados, J. F.; Solà, R.; Harutyunyan, S. R.; Maciá, B. *ACS Catal.* **2016**, *6*, 1952; (e) Veguillas, M.; Solà, R.; Shaw, L.; Maciá, B. *Eur. J. Org. Chem.* **2016**, 1788.

[5] (a) Davies, S. G.; McCarthy, T. D. In *Comprehensive Organometallic Chemistry II*; Abel, E. W.; Stone, F. G. A.; Wilkinson, G., Eds.; Pergamon: Oxford, 1995; Vol. 12, pp 1039–1070; (b) Solladié-Cavallo, A. *Polyhedron* **1985**, *4*, 901; (c) Roques, B. P. *J. Organomet. Chem.* **1977**, *136*, 33; (d) Solladié-Cavallo, A. In *Advances in Metal-Organic Chemistry*; Liebeskind, L. S., Ed.; JAI Press: Greenwich, 1989; Vol. 1, pp 99–133; (f) Coote, S. J.; Davies, S. G.; Goodfellow, C. L.; Sutton, K. H.; Middlemiss, D.; Naylor, A. *Tetrahedron: Asymmetry* **1991**, *1*, 817; (g) Davies, S. G.; Goodfellow, C. L. *Synlett* **1989**, 59; (h) Davies, S. G.; Goodfellow, C. L. *J. Chem. Soc., Perkin Trans. 1* **1990**, 393; (i) Davies, S. G.; Hume, W. E. *J. Chem. Soc., Chem. Commun.* **1995**, 251; (j) Davies, S. G.; Hume, W. E.; Roberts, P. M.; Thomson, J. E. *Tetrahedron* **2010**, *66*, 8076; (k) Uemura, M.; Miyake, R.; Nakayama, K.; Shiro, M.; Hayashi, Y. *J. Org. Chem.* **1993**, *58*, 1238; (l) Koide, H.; Uemura, M. *Tetrahedron Lett.* **1999**, *40*, 3443.

[6] da Costa, M. R. G.; Curto, M. J. M.; Davies, S. G.; Teixeira, F. C.; Thomson, J. E. *Tetrahedron* **2017**, *73*, 5411.

[7] For a description of the application of the Cahn-Ingold-Prelong notation of absolute stereochemistry within molecules possessing planar chiralaty, such as arene chromium tricarbonyl complexes, see: Schögl, K. *Top. Stereochem.* **1967**, *1*, 39. The stereochemical descriptor of the arene chromium tricarbonyl fragment is specified at the centre of highest priority, C(1).

[8] Jenkins, P. R. *Organometallic Reagents in Synthesis*; Oxford Chemistry Primers, Oxford University Press: Oxford, 1992; Vol. 3.

[9] Davies, S. G.; Hedgecock, C. J. R.; McKenna, J. M. *Tetrahedron: Asymmetry* **1995**, *6*, 2507.

[10] (a) Davies, S. G.; Ichihara, O. *Tetrahedron: Asymmetry* **1991**, *2*, 183; (b) Davies, S. G.; Garrido, N. M.; Ichihara, O.; Walters, I. A. S. *J. Chem. Soc., Chem. Commun.* **1993**, 1153; (c) Davies, S. G.; Fenwick, D. R. *J. Chem. Soc., Chem. Commun.* **1995**, 1109.

[11] Fleming, I.; Loreto, M. A.; Wallace, I. H. M.; Michael, J. P. *J. Chem. Soc., Perkin Trans. 1* **1986**, 349; (b) Kagi, R.I.; Johnson, B. L. *Aust. J. Chem.* **1975**, *28*, 2275.

[12] Nieminen, T. E. A.; Hase, T. A. *Tetrahedron Lett.* **1987**, *28*, 4725.

[13] Nagai, U.; Shishido, T.; Chida, R.; Mitsuhashi, M. *Tetrahedron* **1965**, *21*, 1701.

[14] Parker, D. *Chem. Rev.* **1991**, *91*, 1441.

[15] Perrin, D. D.; Armarego, W. L. F.; Perrin, D. R. *Purification of Laboratory Chemicals*; 2nd Edn; Pergamon Press: Oxford, 1980.

[16] Rollet, J. S. *Computing Methods in Crystallography*, Pergamon Press: Oxford, 1965.

[17] North, A. C. T.; Philips, D. C.; Mathews, F. S. *Acta Crystallogr., Sect. A.* **1968**, *24*, 351.

[18] Watkin, D. J.; Carruthers, J. R.; Betteridge, P. W. *CRYSTALS User Guide*, Chemical Crystallography Laboratory, University of Oxford, UK, 1985.

[19] *International Tables for Crystallography*, Kynoch Press: Birmingham, UK; 1974, Vol. 4.

[20] (a); (b) Moller, E. R.; Jorgensen, K. A. *J. Org. Chem.* **1996**, *61*, 5770.