DOI: 10.1002/ejoc.200900007

Synthesis of Enantioenriched Secondary and Tertiary Alcohols via Tricarbonylchromium(0) Complexes of Benzyl Allyl Ethers

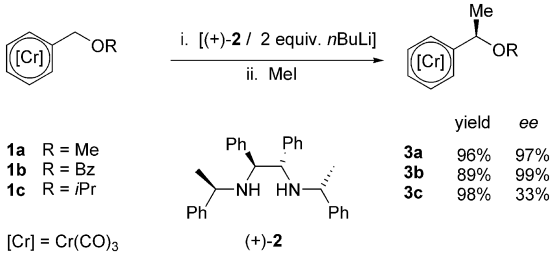
Keren Abecassis,[a] Susan E. Gibson,*[a] and Mar Martin-Fontecha[a]

Keywords: Alcohols / Allylic compounds / Chiral base / Chromium / Enantioselectivity / Alkylation

Allyl ethers of the tricarbonylchromium(0) complexes of benzylic alcohols undergo highly enantioselective benzylic functionalisation using a chiral base/electrophilic quench sequence; the allyl group is readily removed to reveal a hydroxy group as demonstrated in the syntheses of enantioenriched imidazole alcohols, a triol and a tertiary alcohol.

Introduction

Some time ago, we demonstrated that tricarbonylchromium(0) complexes of benzyl ethers **1** react with the chiral diamide derived from butyllithium/chiral diamine **2** and an electrophile, e.g. iodomethane, to give chiral ether complexes such as **3**. The reactions typically gave very good yields of products, and the products were generated in high enantiomeric excess when the substrate was a methyl ether (like **1a**), or benzyl ether (like **1b**). Poorer enantiomeric excesses were obtained with some other substrates, e.g. the isopropyl ether **1c** (Scheme 1).[1]



Scheme 1. Asymmetric functionalisation of tricarbonylchromium(0) ether complexes.

As a consequence of the high enantioselectivity observed with methyl ethers, subsequent applications of this chemistry, such as our recent syntheses of the tris-pyridine ligand **4**,[2] and dendrimers with either a homochiral or a heterochiral relationship between their layers such as the heterochiral dendrimer **5**[3] (Figure 1) have been based predominantly on methyl ethers.

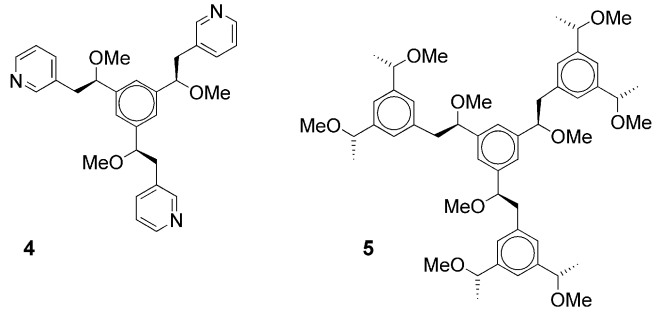


Figure 1. Examples of molecules made using chiral base chemistry.

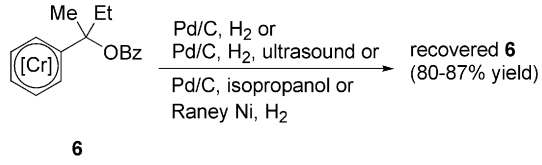
In order to expand the scope of the chemistry, it would be useful to be able to convert the ether functional group into an alcohol. For example, conversion of the ethers in dendrimer **5** and its homochiral partner into alcohols would enable us to explore and compare the effect of hydrogen bonding on the conformational equilibria of the two dendrimers. In order to effect the desired functional group transformation, it was necessary to i. identify an ether that can be readily converted to an alcohol and that also undergoes the deprotonation/alkylation reaction depicted in Scheme 1, ii. ascertain that the selectivity of the reaction is maintained with the new ether, and iii. demonstrate that the selected ether can be converted into the corresponding alcohol without loss of enantiopurity at the newly formed stereocenter. A study which led to the identification of an appropriate ether, and the application of the resulting protecting-group chemistry in the synthesis of enantioenriched alcohols is described herein.

Results and Discussion

Given that benzyl ether substrates such as **1b** undergo the deprotonation/electrophilic quench sequence to give alkylated products in good yield and enantiomeric excess, we

[a] Department of Chemistry, Imperial College London, South Kensington Campus, London SW7 2AZ, UK
Fax: +44-207-594-5804
E-mail: s.gibson@imperial.ac.uk
Supporting information for this article is available on the WWW under http://www.eurjoc.org or from the author.

carried out a study some time ago on complex **6**, formed by a double alkylation of **1b**,[4] to determine whether or not its benzyl ether could be removed under hydrogenation conditions to give an alcohol. Four sets of conditions were investigated, but all led to the recovery of starting material in between 80 and 87% yield (Scheme 2), an outcome which may reflect the degree of steric crowding around the benzyl group of **6**.[5]



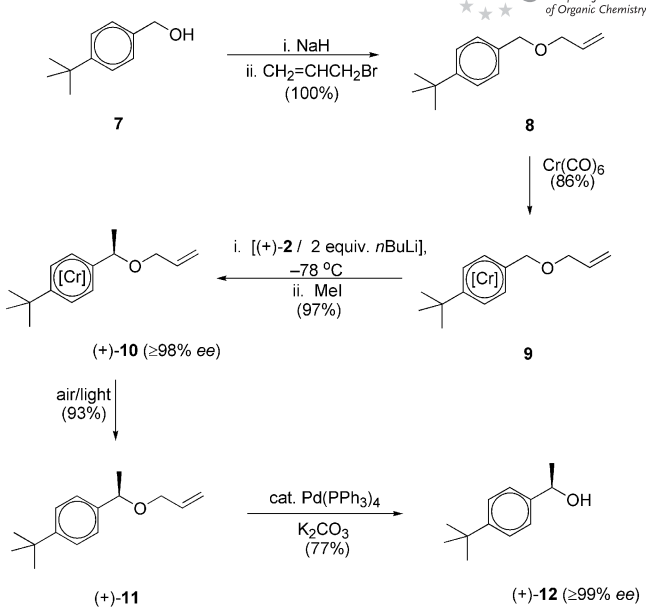
Scheme 2. An early attempt to convert a benzyl ether to its alcohol.

At the outset of this current study, we considered the use of a *p*-methoxyphenyl ether, predicting that this group would also give good yields and enantioselectivities, and that it would be amenable to removal using methods such as ceric ammonium nitrate or DDQ.[6] The use of an ether group containing an aromatic ring was eventually dismissed, however, as the aromatic ring would dictate that the protecting group must be introduced after the chromium complex had been formed, in order to avoid an undesirable competition between relatively similar aromatic rings during the complexation step. In light of the above, we elected to test whether or not an allyl ether would enable us to extend our chiral base chemistry to the synthesis of enantiopure alcohols.

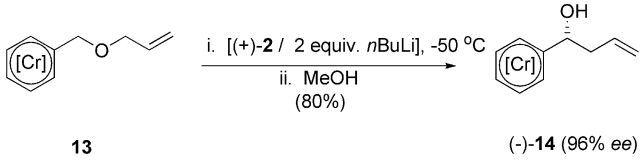
To prepare a suitable model substrate, 4-*tert*-butylbenzyl alcohol **7**, was treated with sodium hydride followed by allyl bromide to give the novel allyl ether **8**, and this was treated with hexacarbonylchromium(0) to give its tricarbonylchromium(0) complex **9**, as a yellow solid (Scheme 3). To deprotonate ether **9**, diamine (+)-**2** was treated with *n*-butyllithium, and complex **9** was added to the resulting deep red solution at –78 °C. After the addition of iodomethane at –78 °C and work-up, a yellow oil was obtained that was identified as the methylated complex (+)-**10** on the basis of its elemental analysis, IR, ^{1}H NMR, ^{13}C NMR and mass spectra. In order to establish the stereoisomeric composition of (+)-**10**, the reaction was repeated using diamine (–)-**2**. Analysis of both products by chiral HPLC revealed that **10** had been formed in each case in ≥ 98% *ee*, thus establishing that allyl ethers do indeed support an enantioselective alkylation reaction.

It is interesting to contrast this result with the outcome of the reaction between the benzyl allyl ether complex **13**, and the chiral base derived from (+)-**2** at –50 °C, followed by a methanol quench.[7] Presumably as a result of the slightly higher reaction temperature, this led to an enantioselective [2,3]-Wittig rearrangement that generated alcohol (–)-**14** (Scheme 4).

The tricarbonylchromium(0) unit was subsequently removed from the samples of (+)- and (–)-**10** by air/light oxidation to give the ethers (+)- and (–)-**11**, respectively. After



Scheme 3. Use of an allyl ether leads to high selectivities for methylation and the protecting group is readily removed without loss of enantioselectivity [(+) series depicted here].



Scheme 4. Deprotonation at a higher temperature (–50 °C rather than –78 °C) leads to a Wittig rearrangement.[7]

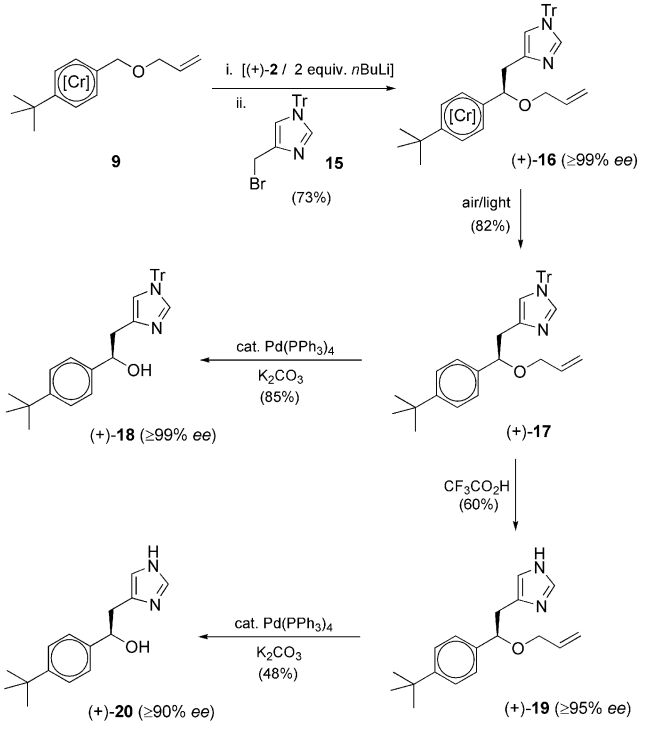
some experimentation, deprotection of samples of (+)- and (–)-**11** to give (+)- and (–)-**12**, respectively was achieved by dissolving the allyl ether in methanol, adding 5 mol-% tetrakis(triphenylphosphane)palladium(0) followed by 3 equiv. of potassium carbonate, and heating under reflux for 48 h. The product mixture was then neutralised with acid, taking care to stop at pH 7 to avoid racemisation. Analysis of both products by chiral HPLC revealed that **12** had been formed in each case in ≥ 98% *ee*, and that the deprotection step had proceeded without loss of enantiopurity.

Having established that the protection of benzyl alcohol **7** as an allyl ether was compatible with the chiral base reaction in terms of yield and enantioselectivity and that the allyl group could be removed without loss of enantiopurity, in the case of the electrophile iodomethane, we proceeded to challenge the system with i) a more complex electrophile, ii) the triple functionalisation of a triol, and iii) the synthesis of a tertiary alcohol.

Synthesis of Enantiopure Imidazole Alcohols

Initially we examined the introduction of a functionalised electrophile. Imidazoles derived from the amino acid histidine are common ligands for metals found in biological systems e.g. for iron in cytochrome *c* peroxidase[8] and zinc

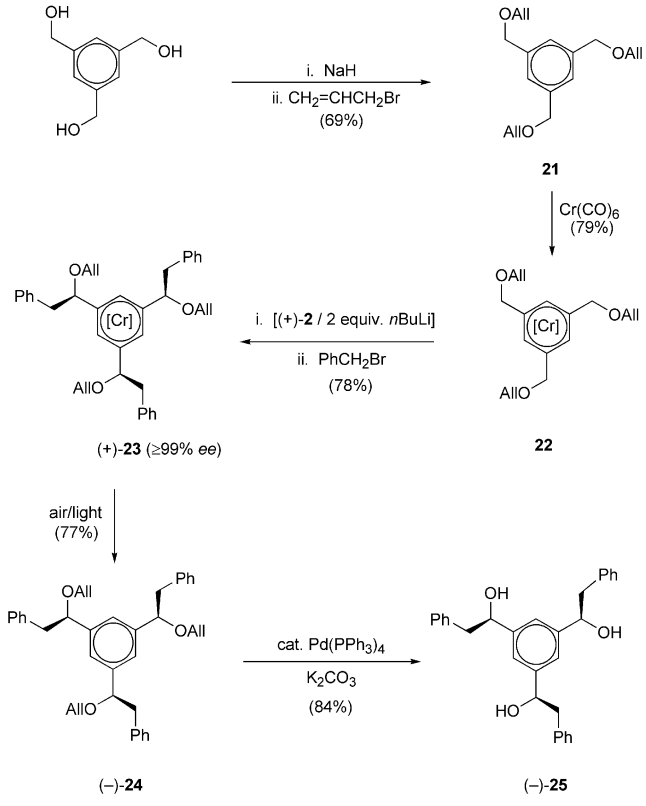
in carbonic anhydrase and matrix metalloproteinases,[9] and it was thus of interest to us to determine whether or not we could generate chiral molecules containing both an imidazole and an alcohol, with a view to exploring their metal-binding properties and potential applications in catalysis. The electrophile to be tested, 4-bromomethyl-1-trityl-1*H*-imidazole (**15**) was synthesised from the corresponding alcohol[10] using *N*-bromosuccinimide/triphenylphosphane in 84% yield. Electrophile **15** proved difficult to handle due to its pronounced instability in solution, but after some experimentation it was found that using it freshly prepared and adding it as a suspension in THF led to a satisfactory reaction with allyl ether complex **9** and the formation of the protected imidazole alcohol (+)-**16** in good yield (Scheme 5). Synthesis of (–)-**16** and HPLC analysis revealed that the enantiomeric excess of both (+)-**16** and (–)-**16** was ≥ 99%. Removal of the chromium unit from **16** proceeded smoothly to give **17** from which point two deprotection paths were followed. Application of the palladium-catalysed deallylation protocol developed above for chiral allyl ether **11** (Scheme 3) gave the imidazole alcohol **18**, in which one of the imidazole nitrogen atoms remained protected, whilst acid-catalysed removal of the trityl group from **17** followed by deallylation gave the completely deprotected imidazole alcohol **20** via **19**. HPLC analysis revealed that both (+)- and (–)-**18** had been generated in high enantiomeric excess (≥ 99%). HPLC analysis of (+)- and (–)-**19**, and (+)- and (–)-**20** proved more difficult and whilst peaks for the minor enantiomers were not observed in all cases, the quality of the data only allowed us to define their enantiopurities as ≥ 95% and ≥ 90%, respectively.



Scheme 5. Synthesis of two imidazole alcohols.

Synthesis of an Enantiopure Triol

In order to test whether or not the allyl protecting group strategy could be used to satisfactorily generate more than one chiral alcohol in a substrate using the chiral base approach, the triol, 1,3,5-tris(hydroxymethyl)benzene,[2b] was subjected to allyl ether formation, alkylation, and deprotection (Scheme 6). Allylation of the triol to give the tris ether **21**, and subsequent formation of its chromium tricarbonyl complex **22** proceeded without incident. Deprotonation of **22** using chiral bases (+)- and (–)-**2** and quenching with benzyl bromide gave (+)-**23** and (–)-**23** in 78 and 91% yield, respectively, and ≥ 99% *ee* as determined by HPLC. The chromium tricarbonyl group was removed from both enantiomers to give the two separate chiral ethers **24**, and it was gratifying to find that the ethers could be deprotected using the same palladium-based protocol described above to give the chiral triols (–)- and (+)-**25** in 84% and 80% yield, respectively. Although it was impossible to identify HPLC conditions that gave a satisfactory separation of the enantiomers of **25**, careful inspection of their ^1H and ^{13}C NMR spectra in $CDCl_3$ and C_6D_6 failed to reveal any evidence for the presence of diastereoisomers of **25** i.e. compounds that would be expected to be present had epimerisation taken place. It is therefore reasonable to assume that the enantiopurity of the enantiomers of **25** is the same as that of the enantiomers of **23**.



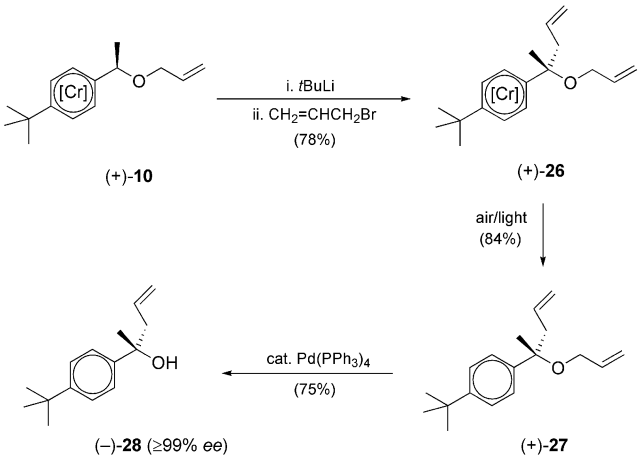
Scheme 6. Synthesis of an enantiopure triol.

The successful use of the allyl protecting group in the synthesis of a chiral triol paves the way for the synthesis of analogues of **5** in which i) all of the ether groups are re-

placed by alcohols, or ii) the three "inner ethers" or the six "outer ethers" are selectively replaced by alcohols, thus enabling us to study the effect of several different hydrogen bonding arrays on the conformational equilibria of these dendrimers. Furthermore, conversion of the three hydroxy groups of **25** into phosphites should provide an interesting set of ligands, given the widespread use of phosphites in for example, rhodium-,[11] and copper[12]-catalysed asymmetric synthesis.

Synthesis of an Enantiopure Tertiary Alcohol

Methods for the synthesis of enantiopure tertiary alcohols are limited compared to those available for the synthesis of enantiopure secondary alcohols. This may be attributed in part to the difficulties associated with developing conditions for the selective addition of nucleophiles to ketones compared to aldehydes,[13] and also to the steric demands of tertiary alcohols and their derivatives which have rendered them a challenge to methods based on enzymatic kinetic resolutions.[14] The synthesis of an enantiopure tertiary alcohol thus seemed an excellent challenge for the chiral base/allyl protecting group chemistry. Allylation of (+)- and (–)-**10**, using methodology developed previously that was shown to proceed with retention of configuration,[4] gave (+)- and (–)-**26** in good yield (Scheme 7). Removal of the chromium from both of the enantiomers gave the enantiomers of **27**, which were subjected to the allyl deprotection protocol followed by a careful work-up. To our delight, HPLC analysis of the enantiomers of **28** revealed that these tertiary alcohols had been generated in ≥ 99% *ee*.



Scheme 7. Synthesis of an enantiopure tertiary alcohol.

Conclusions

Allyl ethers of the tricarbonylchromium(0) complexes of benzylic alcohols have been shown to undergo highly stereoselective functionalisation at their benzylic positions using a chiral base/electrophilic quench reaction sequence. The resulting chiral ethers are readily deprotected without loss of enantiopurity using catalytic amounts of tetrakis(triphenylphosphane)palladium(0). Successful application of the protocol to the synthesis of imidazole alcohols, a triol, and a tertiary alcohol indicates that the allyl protecting group chemistry described herein is robust and versatile.

Experimental Section

General: All reactions and manipulations involving organometallic compounds were performed under dry nitrogen, using standard vacuum line Schlenk techniques.[15] Reactions and operations involving the use of (arene)tricarbonylchromium(0) complexes were protected from light. Tetrahydrofuran was distilled from sodium benzophenone ketyl and used immediately. Dichloromethane was distilled from calcium hydride. The concentration of *n*-butyllithium was determined by titration against diphenylacetic acid in tetrahydrofuran.[16] The diamines (+)- and (–)-**2**[17] were prepared according to literature procedures. All other chemicals were used as purchased from commercial sources. Thin-layer chromatography (TLC) was performed on Merck silica gel glass plates 60 (F254), using UV light (254 nm) as visualizing agent and/or vanillin, ninhydrin, or potassium permanganate as developing agents. Flash column chromatography was performed using BDH silica gel (particle size 33–70 μm). Melting points were recorded with a Sanyo Gallenkamp melting point apparatus in open capillaries and are uncorrected. Optical rotations were recorded with an AA 10 polarimeter from Index Instruments or with a Perkin–Elmer 241 polarimeter using a 1-dm path length; concentrations are given as g/100 mL. IR spectra were recorded with Perkin–Elmer Spectrum RX and 100 FT-IR spectrometers. NMR spectra were recorded at room temperature with Bruker AV 400 instrument in $CDCl_3$, unless otherwise stated. Chemical shifts are reported in ppm. Mass spectra were recorded with Micromass Platform II and Micromass AutoSpec-Q instruments by the mass spectrometry service at Imperial College London. Elemental analyses were performed by the London Metropolitan University microanalytical service. Analytical HPLC was performed using a Unicam Crystal 200 pump, a Unicam 100 UV/Vis detector and a Daicel Chiralcel OD-H column (25 × 0.46 cm).

Typical Procedure for the Synthesis of Allyl Ethers

1-Allyloxymethyl-4-*tert*-butylbenzene (8): 4-*tert*-Butylbenzyl alcohol (**7**, 2.65 mL, 15 mmol) was added to a suspension of sodium hydride (60% dispersion in mineral oil; 717 mg, 17.9 mmol, previously washed with hexane) in dry THF (50 mL) and the mixture was stirred for 1 h at 0 °C before allyl bromide (2.6 mL, 30 mmol) was added in one portion and stirring continued for a further 16 h at room temperature. After this time, methanol (1 mL) was added and the solvent was removed in vacuo. The resulting crude product was filtered through a long silica gel column, eluted with 200 mL of hexane/diethyl ether, 80:20, and then 200 mL of hexane/diethyl ether, 70:30. After removal of the solvents, ether **8** was obtained as a colourless oil (3.06 g, 100%). R_f = 0.39 (SiO_2; hexane/diethyl ether, 98:2). IR ($CHCl_3$): $\tilde{\nu}$ = 1647 (m, $\nu_{C=C}$), 1267 (s, ν_{C-O}), 1086 (s, ν_{C-O}). ^{1}H NMR (400 MHz): δ = 1.32 [s, 9 H, $C(CH_3)_3$], 4.03 (d, J = 5.5 Hz, 2 H, $OCH_2CH=CH_2$), 4.50 (s, 2 H, OCH_2Ar), 5.20 (d, J = 10.5 Hz, 1 H, $CH=CH_{cis}H$), 5.31 (d, J = 17 Hz, 1 H, $CH=CH_{trans}H$), 5.96 (ddt, J = 17, 10.5, 5.5 Hz, 1 H, $CH=CH_2$), 7.29 (d, J = 8.5 Hz, 2 H, $C_{Ar}H \times 2$), 7.38 (d, J = 8.5 Hz, 2 H, $C_{Ar}H \times 2$) ppm. ^{13}C NMR (100 MHz): δ = 31.4 [$C(CH_3)_3$], 34.6 [$C(CH_3)_3$], 71.2 ($OCH_2CH=CH_2$), 72.0 (OCH_2C_{Ar}), 117.1 ($CH=CH_2$), 125.4, 127.7 ($C_{Ar}H \times 4$), 134.9 ($CH=CH_2$), 135.3 ($C_{Ar}CH_2$),

150.6 [$C_{Ar}C(CH_3)_3$] ppm. MS (EI): *m/z* (%) = 204 (16) [M^+], 189 (72) [$M^+ - CH_3$], 162 (29) [$M^+ - 3CH_3 + 3$ H], 148 (41) [$M^+ - C(CH_3)_3 + H$], 147 (100) [$M^+ - C(CH_3)_3$], 57 (94) [$C(CH_3)_3^+$]. $C_{14}H_{20}O$ (204.15): calcd. C 82.30, H 9.87; found C 82.21, H 9.80.

Typical Procedure for the Synthesis of an (Arene)tricarbonylchromium(0) Complex

(1-Allyloxymethyl-4-*tert*-butylbenzene)tricarbonylchromium(0) (9): Allyl ether **8** (2.68 g, 13.1 mmol) and hexacarbonylchromium(0) (3.20 g, 14.5 mmol) were added to dry di-*n*-butyl ether (130 mL) and THF (15 mL) and the mixture was degassed 10 times and shielded from ambient light. The reaction mixture was heated under reflux for 24 h at 135 °C and then cooled to room temperature. The solvents were removed under reduced pressure and the crude mixture was purified by flash column chromatography (SiO_2; hexane/diethyl ether, 100:0 → 90:10) to yield complex **9** (3.82 g, 86%) as a yellow solid; m.p. 39–40 °C. R_f = 0.20 (SiO_2; hexane/diethyl ether, 90:10). IR ($CHCl_3$): $\tilde{\nu}$ = 1966 (s, ν_{CO}), 1891 (s, ν_{CO}). ^{1}H NMR (400 MHz): δ = 1.28 [s, 9 H, $C(CH_3)_3$], 4.11 (d, J = 5.5 Hz, 2 H, $OCH_2CH{=}CH_2$), 4.23 (s, 2 H, OCH_2Ar), 5.22–5.30 (m, 3 H, $CH{=}CH_{cis}$ and $C_{Cr}H \times 2$), 5.33 (d, J = 17 Hz, 1 H, $CH{=}CH_{trans}$), 5.56 (d, J = 7 Hz, 2 H, $C_{Cr}H \times 2$), 5.93 (ddt, J = 17, 10.5, 5.5 Hz, 1 H, $CH{=}CH_2$) ppm. ^{13}C NMR (100 MHz): δ = 31.2 [$C(CH_3)_3$], 34.0 [$C(CH_3)_3$], 70.2 ($OCH_2CH{=}CH_2$), 72.2 (OCH_2C_{Cr}), 90.6, 92.5 ($C_{Cr}H \times 4$), 108.0 ($C_{Cr}CH_2$), 118.0 ($CH{=}CH_2$), 121.9 [$C_{Cr}C(CH_3)_3$], 134.0 ($CH{=}CH_2$), 233.4 ($C{\equiv}O \times 3$) ppm. MS (CI): *m/z* (%) = 358 (83) [M + NH_4^+], 341 (100) [M + H^+], 285 (17) [M + H^+ – 2 CO], 284 (38) [M^+ – 2 CO], 283 (97) [M – 2 CO – H^+]. $C_{17}H_{20}CrO_4$ (340.08): calcd. C 59.99, H 5.92; found C 60.04, H 5.94.

Typical Procedure for Benzylic Enantioselective Alkylation

(+)-(*R*)-[4-[2-(Allyloxy)-2-(4-*tert*-butylphenyl)ethyl]-1-trityl-1*H*-imidazole]tricarbonylchromium(0) [(+)-16]: *n*-Butyllithium (0.6 mL, 2.5 M in hexane, 1.5 mmol) was added dropwise to a stirred solution of diamine (+)-**2** (313 mg, 0.74 mmol) in THF (7 mL) at –78 °C. The solution was warmed to room temperature over a period of 30 min. The resulting deep red solution was then recooled to –78 °C. A solution of heat-gun-dried lithium chloride (32 mg, 0.74 mmol) in THF (6 mL) was added through a cannula and the reaction mixture was stirred for a further 5 min before a precooled solution (–78 °C) of complex **9** (230 mg, 0.68 mmol) in THF (7 mL) was added dropwise through a cannula. The reaction was stirred at –78 °C for 45 min before a solution of compound **15** (653 mg, 1.9 mmol) in THF was added through a cannula. Stirring was continued for a further 2 h at –78 °C and then the reaction mixture was quenched with methanol (2 mL) and the solvents were removed in vacuo to give a yellow solid. Purification of the crude product by flash column chromatography (SiO_2; hexane/ethyl acetate, 80:20 → 60:40) yielded complex **16** (327 mg, 73%) as a yellow solid; m.p. 60–61 °C. R_f = 0.31 (SiO_2; hexane/ethyl acetate, 70:30). Enantiometric excess was determined by HPLC analysis (Chiralcel OD-H, *n*-hexane/*i*PrOH, 90:10, 1.0 mL/min, 330 nm); (*R*)-enantiomer t_r = 10.6 min (major); (*S*)-enantiomer t_r = 24.0 min (minor): ≥ 99% *ee*. $[\alpha]_D^{20}$ = +22 (*c* = 1.03, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 1959 (s, ν_{CO}), 1877 (s, ν_{CO}). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.30 [s, 9 H, $C(CH_3)_3$], 2.92 (dd, J = 14.5, 5.0 Hz, 1 H, CH_2-imid), 2.99 (dd, J = 14.5, 5.0 Hz, 1 H, CH_2-imid), 4.02 (dd, J = 12.5, 5.5 Hz, 1 H, OCH_2), 4.27 (dd, J = 12.5, 5.0 Hz, 1 H, OCH_2), 4.47 (apparent t, J = 5.5 Hz, 1 H, OCH), 5.13–5.15 (m, 2 H, $CH{=}CH_{cis}$ and $C_{Cr}H$), 5.25 (d, J = 17.5 Hz, 1 H, $CH{=}CH_{trans}$), 5.35 (d, J = 7.0 Hz, 1 H, $C_{Cr}H$), 5.42 (d, J = 6.5 Hz, 1 H, $C_{Cr}H$), 5.55 (d, J = 6.5 Hz, 1 H, $C_{Cr}H$), 5.82 (dddd, J = 17.5, 10.5, 5.5, 5.0 Hz, 1H $CH{=}CH_2$), 6.64 (s, 1 H, 5-H imid), 7.14–7.16 (m, 6 H, $C_{Ar}H \times 6$), 7.36–7.37 (m, 9 H, $C_{Ar}H \times 9$), 7.44 (s, 1 H, 2-H imid) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 31.0 [$C(CH_3)_3$], 33.9 [$C(CH_3)_3$], 37.9 (CH_2-imid), 71.7 (OCH_2), 75.2 [$C(C_6H_5)_3$], 78.1 (OCH), 90.0 ($C_{Cr}H$), 90.4 ($C_{Cr}H$), 90.5 ($C_{Cr}H \times 2$), 112.2 [$C_{Cr}CH(CH_2$imid)-OAllyl], 117.1 ($CH_2{=}CH$), 119.8 (5-CH imid), 123.5 [$C_{Cr}C(CH_3)_3$], 128.1 [$C_{Ar(trityl)}H \times 6$], 129.7 [$C_{Ar(trityl)}H \times 9$], 134.4 ($CH_2{=}CH$), 136.6 (4-C imid), 138.1 (2-CH imid), 142.3 [$C_{Ar(trityl)} \times 3$], 233.6 ($C{\equiv}O \times 3$) ppm. MS (EI): *m/z* (%) = 578 (12) [M^+ – 3 CO], 536 (31) [M^+ – 3 CO – $CH_2CH{=}CH_2$], 526 (10) [M^+ – $Cr(CO)_3$], 283 (93) [M^+ – $Cr(CO)_3$ – $CH_2CH{=}CH_2$], 243 (100) [CPh_3^+]. $C_{40}H_{38}CrN_2O_4$ (662.74): calcd. C 72.49, H 5.78, N 4.23; found C 72.45, H 5.70, N 4.14.

(–)-(*S*)-[4-[2-(Allyloxy)-2-(4-*tert*-butylphenyl)ethyl]-1-trityl-1*H*-imidazole]tricarbonylchromium(0) [(–)-16]: Complex (–)-**16** was prepared from complex **9** (230 mg, 0.68 mmol), diamine (–)-**2** (284 mg, 0.68 mmol) and bromide **15** (660 mg, 2.0 mmol), following the procedure described for complex (+)-**16**. 69% yield, yellow solid; *ee* ≥ 99%. $[\alpha]_D^{20}$ = –23 (*c* = 1.35, $CHCl_3$). All other analytical data were identical to those obtained for (+)-**16**.

Typical Procedure for Oxidative Decomplexation

(+)-(*R*)-4-[2-(Allyloxy)-2-(4-*tert*-butylphenyl)ethyl]-1-trityl-1*H*-imidazole [(+)-17]: Complex (+)-**16** (310 mg, 0.47 mmol) was dissolved in diethyl ether (50 mL) and was left standing for 48 h by the window. The solvent of the resulting brown suspension was evaporated under reduced pressure and the residue was purified by flash column chromatography (SiO_2; hexane/ethyl acetate, 90:10 → 70:30) to afford compound (+)-**17** as a white solid (201 mg, 82%); m.p. 57–58 °C. R_f = 0.32 (SiO_2; hexane/ethyl acetate, 70:30). $[\alpha]_D^{20}$ = +18 (*c* = 1.30, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 1130 (m, ν_{C-O}), 1086 (m, ν_{C-O}). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.33 [s, 9 H, $C(CH_3)_3$], 2.87 (dd, J = 14.5, 6.0 Hz, 1 H, CH_2-imid), 3.10 (dd, J = 14.5, 8.0 Hz, 1 H, CH_2-imid), 3.75 (dd, J = 12.5, 5.5 Hz, 1 H, OCH_2), 3.91 (dd, J = 12.5, 5.0 Hz, 1 H, OCH_2), 4.63 (apparent t, J = 7.0 Hz, 1 H, OCH), 5.09 (d, J = 10.5 Hz, 1 H, $CH{=}CH_{cis}$), 5.16 (d, J = 17.5 Hz, 1 H, $CH{=}CH_{trans}$), 5.80 (dddd, J = 17.5, 10.5, 5.5, 5.0 Hz, 1 H, $CH{=}CH_2$), 6.49 (s, 1 H, 5-H imid), 7.10–7.12 [m, 6 H, $C_{Ar(trityl)}H \times 6$], 7.22 (d, J = 8.0 Hz, 2 H, $C_{Ar}H \times 2$), 7.29–7.37 [m, 12 H, $C_{Ar(trityl)}H \times 9$, $C_{Ar}H \times 2$ and 2-H imid] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 31.4 [$C(CH_3)_3$], 34.5 [$C(CH_3)_3$], 37.5 (CH_2-imid), 69.7 (OCH_2), 75.1 [$C(C_6H_5)_3$], 80.8 (OCH), 116.5 ($CH_2{=}CH$), 119.6 (5-CH imid), 125.1 ($C_{Ar}H \times 2$), 126.4 ($C_{Ar}H \times 2$), 127.9 [$C_{Ar(trityl)}H \times 9$], 129.8 [$C_{Ar(trityl)}H \times 6$], 135.0 ($CH_2{=}CH$), 137.8 [$C_{Ar}CH(CH_2$imid)OAllyl and 2-CH imid], 139.0 (4-C imid), 142.5 [$C_{Ar(trityl)} \times 3$], 150.1 [$C_{Ar}C(CH_3)_3$] ppm. MS (EI): *m/z* (%) = 526 (8) [M^+], 485 (34) [M^+ – $CH_2CH{=}CH_2$], 283 (13) [M^+ – CPh_3], 243 (100) [CPh_3^+]. $C_{37}H_{38}N_2O$ (526.71): calcd. C 84.37, H 7.27, N 5.38; found C 84.45, H 7.18, N 5.38.

(–)-(*S*)-4-[2-(Allyloxy)-2-(4-*tert*-butylphenyl)ethyl]-1-trityl-1*H*-imidazole [(–)-17]: Compound (–)-**17** was prepared from complex (–)-**16** (220 mg, 0.42 mmol) following the procedure described for imidazole (+)-**17**. 79% yield, white solid. $[\alpha]_D^{20}$ = –19 (*c* = 1.60, $CHCl_3$). All other analytical data were identical to those obtained for (+)-**17**.

Typical Procedure for Deallylation

(+)-(*R*)-1-(–4-*tert*-Butylphenyl)-2-(1-trityl-1*H*-imidazol-4-yl)ethanol [(+)-18]: $Pd(PPh_3)_4$ (14 mg, 0.013 mmol) was added to a stirred solution of allyl protected alcohol (+)-**17** (130 mg, 0.25 mmol) in anhydrous methanol (5 mL) under nitrogen. The slightly yellow solution was stirred for 5 min, and K_2CO_3 (104 mg, 0.75 mmol) was added. The reaction mixture was refluxed for 24 h and once at room temperature, was neutralised with 1 M HCl and extracted with

dichloromethane (3 × 25 mL). The combined organic layers were washed with brine, dried with Na_2SO_4 and evaporated under reduce pressure. Purification by flash column chromatography (SiO_2; hexane/ethyl acetate, 70:30 → 50:50) gave compound (+)-**18** as a white solid (103 mg, 85%); m.p. 180–181 °C. R_f = 0.22 (SiO_2; hexane/ethyl acetate, 70:30). Enantiometric excess was determined by HPLC analysis (Chiralcel OD-H, *n*-hexane/*i*PrOH, 97:3, 0.75 mL/min, 220 nm); (*S*)-enantiomer t_r = 54.4 min (minor); (*R*)-enantiomer t_r = 60.4 min (major): ≥ 99% *ee*. $[a]_D^{20}$ = +9 (*c* = 1.35, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3250 (υ_{OH}). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.33 [s, 9 H, $C(CH_3)_3$], 2.00 (br. s, 1 H, OH), 2.89 (dd, *J* = 14.5, 8.5 Hz, 1 H, C*H*$_2$-imid), 2.97 (dd, *J* = 14.5, 3.5 Hz, 1 H, C*H*$_2$-imid), 5.00 (dd, *J* = 8.5, 3.5 Hz, 1 H, C*H*OH), 6.55 (s, 1 H, 5-H imid), 7.12–7.14 [m, 6 H, $C_{Ar(trityl)}H \times 6$], 7.28–7.37 [m, 13 H, $C_{Ar(trityl)}H \times 9$ and $C_{Ar}H \times 4$], 7.43 (s, 1 H, 2-H imid) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 31.4 [$C(CH_3)_3$], 34.5 [$C(CH_3)_3$], 37.0 (*C*H$_2$-imid), 73.6 (CHOH), 75.3 [$C(C_6H_5)_3$], 118.9 (5-CH imid), 125.1 ($C_{Ar}H \times 2$), 125.6 ($C_{Ar}H \times 2$), 128.1 [$C_{Ar(trityl)}H \times 9$], 129.8 [$C_{Ar(trityl)}H \times 6$], 138.3 [$C_{Ar}CH(CH_2imid)OH$], 138.5 (2-CH imid), 141.2 (4-C imid), 142.3 [$C_{Ar(trityl)} \times 3$], 149.9 [$C_{Ar}C(CH_3)_3$] ppm. MS (EI): *m*/*z* (%) = 486 (22) [M^+], 467 (4) [$M^+ - H_2O$], 243 (100) [CPh_3^+]. $C_{34}H_{34}N_2O$ (486.65): calcd. C 83.91, H 7.04, N 5.76; found C 83.89, H 6.95, N 5.64.

(–)-(*S*)-1-(4-*tert*-Butylphenyl)-2-(1-trityl-1*H*-imidazol-4-yl)ethanol [(–)-18]: Compound (–)-**18** was prepared from allyl-protected alcohol (–)-**17** (205 mg, 0.39 mmol) following the procedure described for compound (+)-**18**. 71% yield, white solid; *ee* ≥ 99%. $[a]_D^{20}$ = –10 (*c* = 1.00, $CHCl_3$). All other analytical data were identical to those obtained for (+)-**18**.

Supporting Information (see also the footnote on the first page of this article): Full experimental details and analytical data.

Acknowledgments

Financial support for a post-doctoral stipend from the Spanish Ministerio de Educación y Ciencia (MEC) (to M. M.-F) and a studentship from the Engineering and Physical Sciences Research Council (EPSRC) (to K. A.) is gratefully acknowledged.

[1] a) E. L. M. Cowton, S. E. Gibson, M. J. Schneider, M. H. Smith, *Chem. Commun.* **1996**, 839–840; b) M. Rudd, Ph. D. Thesis, Imperial College London, **2006**.
[2] a) M. P. Castaldi, S. E. Gibson, M. Rudd, A. J. P. White, *Angew. Chem. Int. Ed.* **2005**, *44*, 3432–3435; b) M. P. Castaldi, S. E. Gibson, M. Rudd, A. J. P. White, *Chem. Eur. J.* **2006**, *12*, 138–148.
[3] a) A. R. E. Brewer, A. F. Drake, S. E. Gibson, J. T. Rendell, *Org. Lett.* **2007**, *9*, 3487–3490; b) A. R. E. Brewer, A. F. Drake, S. E. Gibson, J. T. Rendell, *Tetrahedron* **2008**, *64*, 6615–6627.
[4] S. E. Gibson, P. C. V. Potter, M. H. Smith, *Chem. Commun.* **1996**, 2757–2758.
[5] P. C. V. Potter, Ph. D. Thesis, Imperial College London, **1996**.
[6] a) R. Johansson, B. Samuelsson, *J. Chem. Soc., Perkin Trans. 1* **1984**, 2371–2374; b) K. C. Nicolaou, W. E. Brenzovich, P. G. Bulger, T. M. Francis, *Org. Biomol. Chem.* **2006**, *4*, 2119–2157.
[7] S. E. Gibson, P. Ham, G. R. Jefferson, *Chem. Commun.* **1998**, 123–124.
[8] J. Hirst, S. K. Wilcox, P. A. Williams, J. Blankenship, D. E. McRee, D. B. Goodin, *Biochemistry* **2001**, *40*, 1265–1273.
[9] G. Parkin, *Chem. Rev.* **2004**, *104*, 699–767.
[10] R. Millet, J. Domarkas, R. Houssin, P. Gilleron, J.-F. Goossens, P. Chavatte, C. Logé, N. Pommery, J. Pommery, J.-P. Hénichart, *J. Med. Chem.* **2004**, *47*, 6812–6820.
[11] M. T. Reetz, *Angew. Chem. Int. Ed.* **2008**, *47*, 2556–2588.
[12] A. Alexakis, J. Burton, J. Vastra, C. Benhaim, X. Fournioux, A. van den Heuvel, J.-M. Levêque, F. Mazé, S. Rosset, *Eur. J. Org. Chem.* **2000**, 4011–4027.
[13] C. Garcia, V. S. Martin, *Curr. Org. Chem.* **2006**, *10*, 1849–1889.
[14] a) R. Kourist, S. Bartsch, U. T. Bornscheuer, *Adv. Synth. Catal.* **2007**, *349*, 1393–1398; b) M. M. Elenkov, H. W. Hoeffken, L. Tang, B. Hauer, D. B. Janssen, *Adv. Synth. Catal.* **2007**, *349*, 2279–2285.
[15] D. F. Shriver, M. A. Drezdzon, *The Manipulation of Air Sensitive Compounds*, Wiley, Chichester, **1986**.
[16] W. G. Kofron, L. M. Baclawski, *J. Org. Chem.* **1976**, *41*, 1879–1880.
[17] V. Rodeschini, N. S. Simpkins, F. Zhang, *Org. Synth.* **2007**, *84*, 306–316.

Received: January 6, 2009
Published Online: February 18, 2009

