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Trading *N* and *O*. Part 3: Synthesis of 1,2,3,4-tetrahydroisoquinolines from α-hydroxy-β-amino esters

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ABSTRACT

A range of enantiopure 1,2,3,4-tetrahydroisoquinolines have been prepared directly from α-hydroxy-β-amino esters. Activation of the α-hydroxy group upon treatment with Tf_2O and 2,6-di-*tert*-butyl-4-methylpyridine promotes aziridinium formation, which is then followed by rupture of the C(3)–N bond and Friedel–Crafts alkylation-type cyclisation of an *N*-benzyl moiety onto the resultant benzylic carbenium ion. The nature of the *N*-protecting group was varied and it was found that superior yields were obtained for reactions employing two benzylic groups. In the cases where two different *N*-benzyl groups were used, the regioselectivity resulting from competitive cyclisation of either *N*-benzyl group was addressed by the introduction of a *p*-trifluoromethyl group on one of the *N*-benzyl moieties, which retarded the rate of cyclisation via this electron poor aryl ring. This methodology was employed in the asymmetric synthesis of a range of enantiopure 1,2,3,4-tetrahydroisoquinolines, which were isolated in good yields as single diastereoisomers.

1. Introduction

The tetrahydroisoquinoline (or, more formally, 1,2,3,4-tetrahydroisoquinoline)[1] motif **1** is highly prevalent in many alkaloids and potential therapeutic agents, which often exhibit significant biological activity.[2] For example, (−)-(*S*)-cherylline **2**, which was isolated from plants from the Amaryllidaceae family, and (±)-nomifensine **3** are representative examples of 4-aryl tetrahydroisoquinolines which are known to have central nervous system activity. (±)-Nomifensine **3** is a monoamine reuptake inhibitor with unique dual activity at the norepinephrine and dopamine transporters.[3] Its maleate salt was marketed as an anti-depressant in the 1970s (Merital)[4] and has also been used in the treatment of ADHD;[3] it shows enantioselective pharmacological activity with the (*S*)-enantiomer being the eutomer.[5] (−)-Lycorine **4**, another alkaloid from the Amaryllidaceae family,[6] is a potent anti-cancer agent[7] known for its anti-proliferative properties as well as being an inhibitor of protein synthesis in eukaryotic cells (Fig. 1).[8] Classic synthetic methods to access tetrahydroisoquinoline molecular scaffolds include the Bischler–Napieralski synthesis[9] and Pictet–Spengler reaction,[10] but substantial efforts into the development of new methods for tetrahydroisoquinoline formation have been reported in recent years, including C–H activation strategies,[11] acid-catalysed cyclisations[12] and Lewis acid promoted Friedel–Crafts type reactions,[13] amongst others.[14]

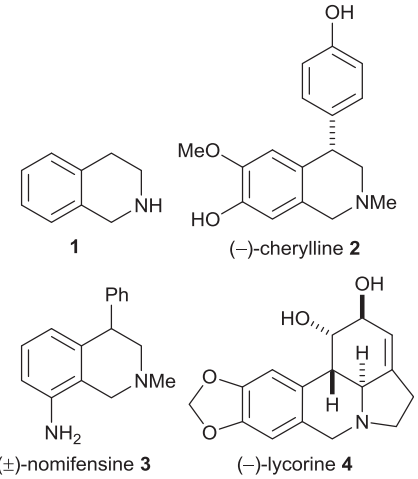

Fig. 1. The tetrahydroisoquinoline motif **1** and examples of biologically active tetrahydroisoquinolines **2**–**4**.

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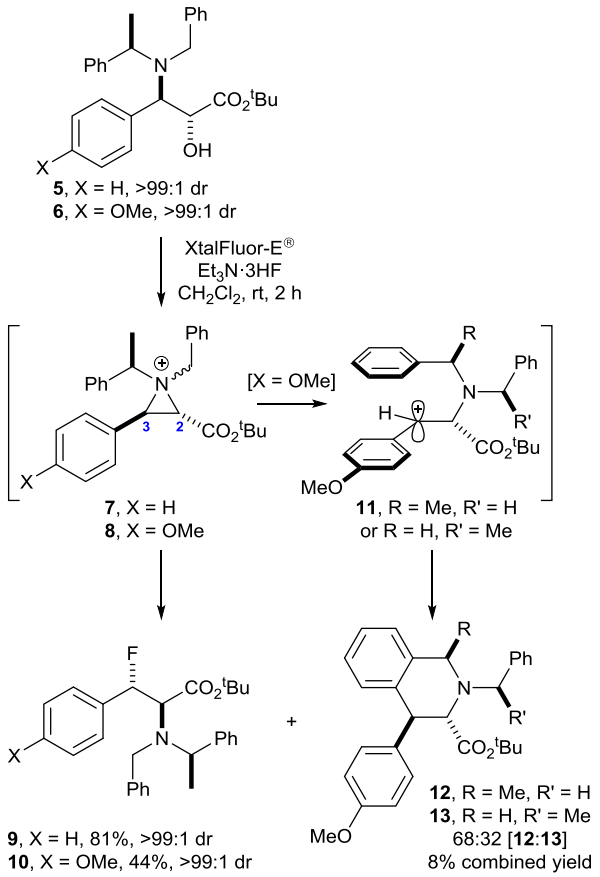
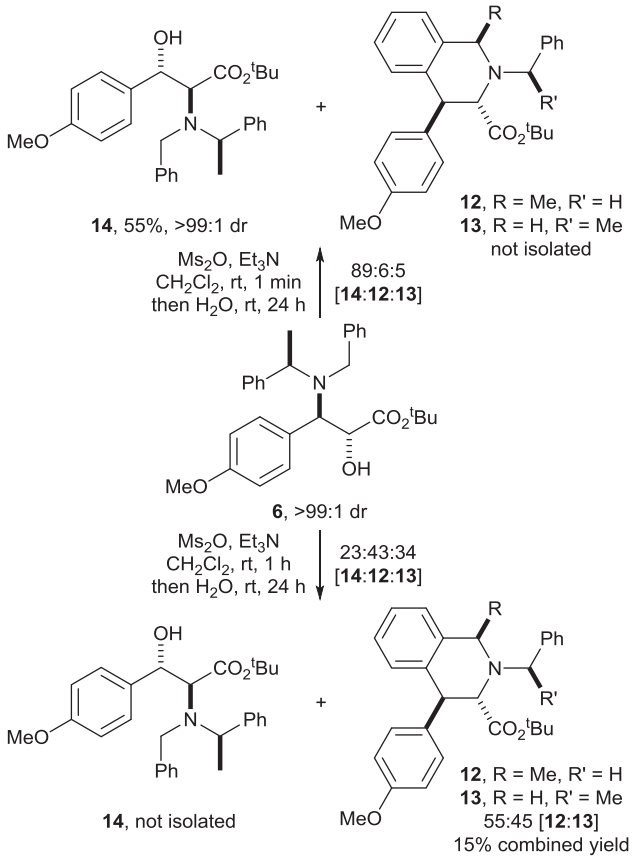
0040-4020/

As part of our previous studies into the asymmetric synthesis of substituted *anti*-β-fluorophenylalanines,[15] we developed a reaction for the rearrangement and deoxofluorination of α-hydroxy-β-amino esters. For example, treatment of **5** with XtalFluor-E® and $Et_3N{\cdot}HF$ promoted formation of the corresponding aziridinium ion **7**, which then underwent regioselective ring-opening at the C(3)-position with fluoride to give β-fluoro-α-amino ester **9** in 81% yield and >99:1 dr. However, application of this protocol to the *p*-methoxy bearing analogue **6** resulted in the formation of an 80:12:8 mixture of β-fluoro-α-amino ester **10** and the regioisomeric tetrahydroisoquinolines **12** (>99:1 dr) and **13** (>99:1 dr), respectively, from which **10** was isolated in 44% yield and >99:1 dr, and a 68:32 mixture of **12** and **13** was isolated in 8% combined yield (Scheme 1). In the latter case, the regioisomeric mixture of tetrahydroisoquinolines **12** and **13** is presumably formed as a result of rupture of the C(3)–N bond within aziridinium intermediate **8** to give the corresponding benzylic carbenium ion **11** (which is assisted by the presence of the electron donating *p*-methoxy group), followed by competitive Friedel–Crafts alkylation-type cyclisation via either the *N*-α-methylbenzyl or *N*-benzyl groups, respectively.



Scheme 1.

In a related study concerning the synthesis of β-hydroxy-α-amino acids from α-hydroxy-β-amino esters (which also proceeds via the intermediacy of the corresponding aziridinium ions),[16] we observed that treatment of α-hydroxy-β-amino ester **6** with Ms_2O followed by the addition of H_2O after 1 min gave an 89:6:5 mixture of β-hydroxy-α-amino ester **14** and tetrahydroisoquinolines **12** and **13**, respectively, from which only **14** was isolated in 55% yield and >99:1 dr. However, treatment of **6** with Ms_2O followed by the addition of H_2O after 1 h gave a 23:43:34 mixture of **14**, **12** and **13**, respectively, from which only a 55:45 mixture of **12** and **13** was isolated in 15% combined yield (Scheme 2). Herein, we report our attempts to optimise these procedures for the selective formation of tetrahydroisoquinolines and develop a general asymmetric protocol for the synthesis of enantiopure tetrahydroisoquinolines from α-hydroxy-β-amino esters.

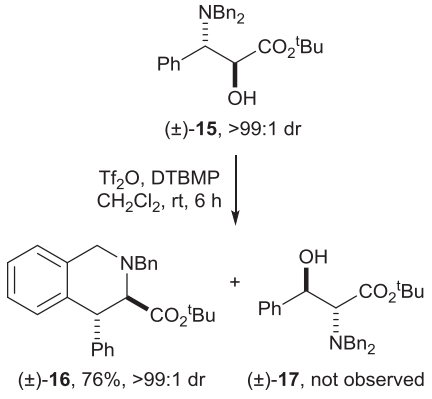


Scheme 2.

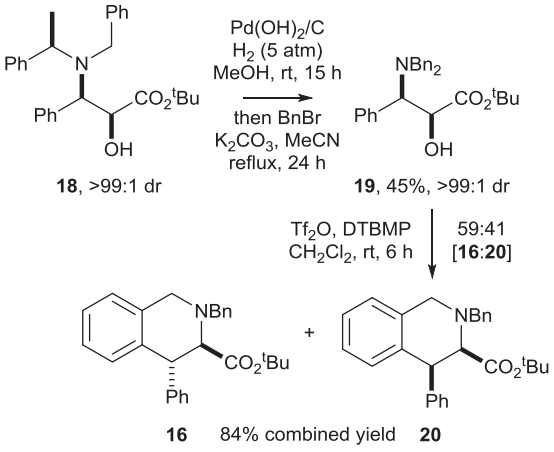
2. Results and discussion

2.1. Preliminary studies

Our initial studies towards the development of an efficient protocol for the preparation of tetrahydroisoquinolines were conducted using *N*,*N*-dibenzyl substituted *anti*-α-hydroxy-β-amino esters, as cyclisation of either *N*-benzyl group would lead to the same product and avoid mixtures of regioisomers being formed. Reaction of the known racemic *N*,*N*-dibenzyl substituted α-hydroxy-β-amino ester *anti*-**15**[16] with 3.0 equiv of Tf_2O in the presence of 6.0 equiv of Et_3N gave a complex mixture of products from which only tetrahydroisoquinoline **16** was isolated in 37% yield and >99:1 dr. 2,6-Di-*tert*-butyl-4-methylpyridine (DTBMP) was employed next, as this base is often used alongside Tf_2O,[17] and in polymerisation reactions as its steric bulk prevents it from reacting with carbocationic intermediates.[18] Reaction of **15** with 3.0 equiv of Tf_2O and 6.0 equiv of DTBMP enabled the isolation of **16** in 58% yield and >99:1 dr. However, optimised conditions were found by decreasing the equivalents of Tf_2O and DTBMP to 1.5 and 3.0, respectively; this resulted in the exclusive formation of **16** as a single diastereoisomer (>99:1 dr), which was isolated in 76% yield (Scheme 3). The relative *anti*-configuration within **16** was initially established by ^1H NMR $^3J_{3,4}$ coupling constant analysis[19] ($^3J_{3,4}$=3.0 Hz) and this assignment was then confirmed unambiguously via single crystal X-ray diffraction analysis (Fig. 2).[20]



Scheme 3.



Scheme 4.

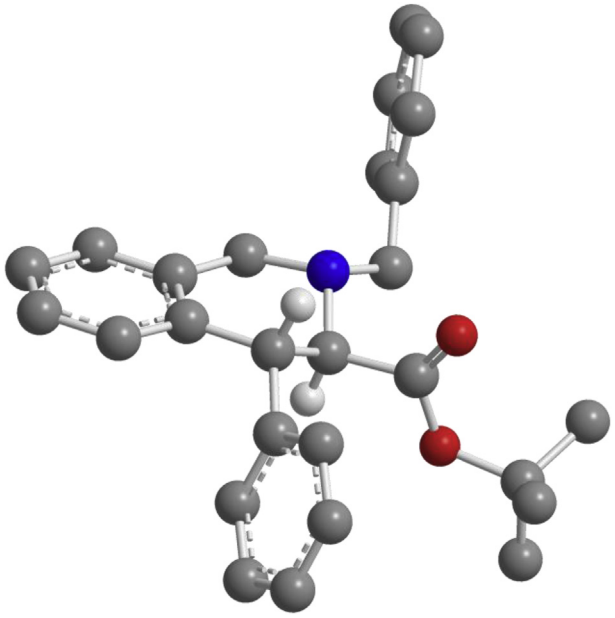


Fig. 2. X-ray crystal structure of (*RS*,*RS*)-**16** (selected H atoms are omitted for clarity).

A sample of the epimeric α-hydroxy-β-amino ester, *syn*-**19**, was prepared from the known α-hydroxy-β-amino ester (2*S*,3*R*,α*R*)-**18**[21] via hydrogenolysis and chemoselective N-benzylation, which gave an enantiopure sample of *syn*-**19** in 45% yield (from **18**) and >99:1 dr.[22] Reaction of *syn*-**19** with Tf_2O and DTBMP (i.e., under the optimised conditions for the formation of tetrahydroisoquinoline *anti*-**16** from *anti*-**15**) gave a 59:41 mixture of *anti*-**16** and *syn*-**20**, respectively, which were isolated in 84% combined yield (Scheme 4). The relative configuration within *syn*-**20** was assigned based on the diagnostic value of the ^{1}H NMR ^3J coupling constant observed between the C(3)*H* and C(4)*H* protons ($^3J_{3,4}$=6.1 Hz).[19]

The results of both of these reactions are consistent with our proposed mechanism for tetrahydroisoquinoline formation. Upon activation of the hydroxyl group within α-hydroxy-β-amino ester *anti*-**15**, aziridinium *anti*-**21** is formed [with inversion of configuration at C(2)]; subsequent rupture of the C(3)–N bond generates the corresponding benzylic carbenium ion **23** in conformation **23A**, which undergoes rapid ring-closure [with retention of configuration at C(3)] to give *anti*-tetrahydroisoquinoline **16** as a single diastereoisomer. For *syn*-**19**, however, treatment with Tf_2O results in the formation of aziridinium *syn*-**22**. In this case, rupture of the C(3)–N bond gives the corresponding benzylic carbenium ion in conformation **23B**, which is presumably higher in energy than **23A** as the phenyl and ester substituents experience unfavourable steric interactions. Collapse of conformer **23B** to give *syn*-tetrahydroisoquinoline **20** would be accompanied by an increase in steric strain, so ring-closure in this case is presumably slower than ring-closure of conformer **23A**. This allows rotation around the C(2)–C(3) bond to occur at a competitive rate, alleviating the steric strain and producing conformer **23A**, for which trapping with an *N*-benzyl group is fast. Thus, a 59:41 mixture of *anti*-**16** and *syn*-**20**, respectively, is formed upon reaction of *syn*-**19**. Upon reaction of *anti*-**15**, cyclisation of **23A** presumably occurs faster than C(2)–C(3) bond rotation and high diastereoselectivity is therefore observed in this case (Fig. 3).

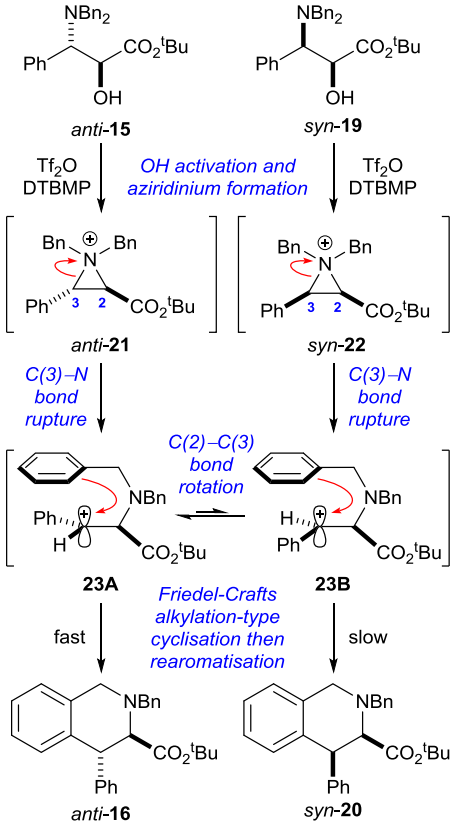
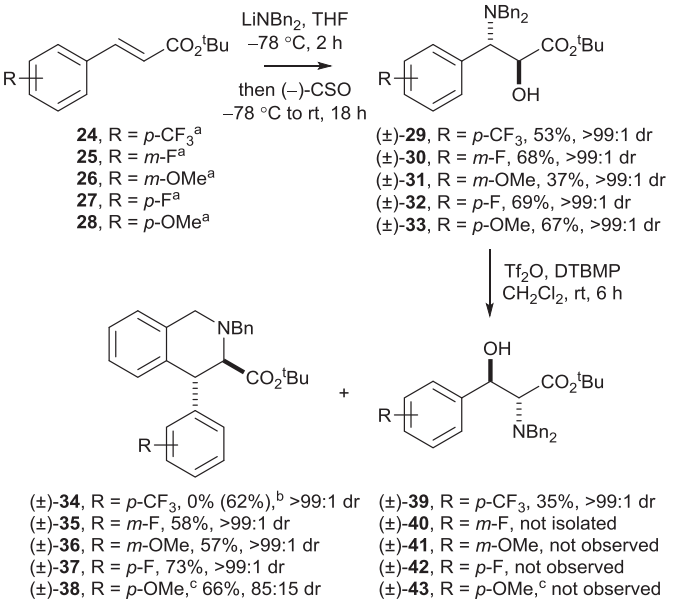


Fig. 3. Proposed mechanism for tetrahydroisoquinoline formation.

The substrate scope of this methodology was investigated next. The substituents around the C(3)-aryl ring were varied in order to evaluate their impact on the cyclisation reaction, and to see if these results corroborate our proposed mechanism. α-Hydroxy-β-amino esters **29**–**33** were prepared in 37–69% yield and >99:1 dr in each case upon conjugate addition of lithium *N*,*N*-dibenzylamide to α,β-unsaturated esters **24**–**28**,[23] followed by oxidation of the intermediate lithium (*Z*)-β-amino enolates[24] with (−)-camphorsulfonyloxaziridine [(−)-CSO] according to our standard aminohydroxylation procedure.[25–27] The relative *anti*-configurations within α-hydroxy-β-amino esters **29**–**33** were established upon inspection of the diagnostic values of their ^{1}H NMR ^3J coupling constants ($^3J_{2,3}$=3.0–4.4 Hz).[28] Furthermore, in the case of the *m*-methoxy substituted α-hydroxy-β-amino ester **31**, this assignment was confirmed unambiguously via single crystal X-ray diffraction analysis (Fig. 4).[20] Upon application of the conditions for tetrahydroisoquinoline formation (i.e., treatment with Tf_2O and DTBMP at rt for 6 h), reaction of α-hydroxy-β-amino esters **31** (R=*m*-OMe) and **32** (R=*p*-F) promoted full conversion to tetrahydroisoquinolines **36** and **37**, respectively, which were isolated in 57 and 73% yield, and >99:1 dr in both cases. It was found that increasing the electron withdrawing ability of the substituent on the C(3)-aryl ring also resulted in formation of a β-hydroxy-α-amino ester: reaction of **30** (R=*m*-F) under the standard reaction conditions gave a 73:27 mixture of tetrahydroisoquinoline **35** and β-hydroxy-α-amino ester **40**, from which **35** was isolated in 58% yield and >99:1 dr. For α-hydroxy-β-amino ester **29** (R=*p*-CF_3), full conversion to β-hydroxy-α-amino ester **39** was observed, and **39** was isolated in 35% yield and >99:1 dr after purification. The relative *anti*-configuration within **39** was tentatively assigned by ^{1}H NMR ^3J coupling constant analysis ($^3J_{2,3}$=9.4 Hz),[29] and by analogy to the stereochemical outcome observed in related systems.[16] However, upon heating the reaction of **29** (R=*p*-CF_3) at 40 °C for 6 h an 80:20 mixture of tetrahydroisoquinoline **34** and β-hydroxy-α-amino ester **39** was recovered, from which **34** was isolated in 62% yield and >99:1 dr. Increasing the electron density of the C(3)-aryl ring caused a reduction in diastereoselectivity, with the reaction of **33** (R=*p*-OMe) with Tf_2O and DTBMP at rt for 6 h giving tetrahydroisoquinoline **38** in 75:25 dr. Cooling the reaction mixture to −20 °C and reducing the reaction time to 2.5 h gave **38** in 85:15 dr, and 66% isolated yield and 85:15 dr after chromatographic purification (Scheme 5). In all cases, the ^{1}H NMR $^3J_{3,4}$ coupling constants observed for the major tetrahydroisoquinoline products **34**–**38** were diagnostic[19] of their relative *anti*-configurations ($^3J_{3,4}$=2.3–3.3 Hz).



Scheme 5. [a>99:1 dr [(*E*):(*Z*)]; [b]Yield in parentheses corresponds to the reaction that was heated at 40 °C for 6 h; [c]The reaction mixture was cooled to −20 °C for 2.5 h].

These findings are again consistent with our proposed reaction mechanism. Both the formation of β-hydroxy-α-amino esters when an electron withdrawing substituent is present on the C(3)-aryl ring, and the formation of diastereoisomeric mixtures of tetrahydroisoquinolines for substrates incorporating a highly electron donating substituent, are consistent with reaction via a carbenium intermediate. If an electron withdrawing group is present then rupture of the C(3)–N bond to give the corresponding benzylic carbenium ion may be disfavoured, and the aziridinium intermediate may instead be preferentially opened by either adventitious water or upon aqueous work-up, to give a β-hydroxy-α-amino ester. As good conversion to tetrahydroisoquinoline products can be achieved upon heating the reaction mixture to 40 °C in these cases, this would be consistent with enabling the energetic barrier for rupture of the C(3)–N bond to be overcome. The reduction in diastereoselectivity observed when a strongly electron donating group is present is consistent with the rate of C(2)–C(3) bond rotation becoming competitive with the rate of ring-closure due to the increased stabilisation of the benzylic carbenium ion.

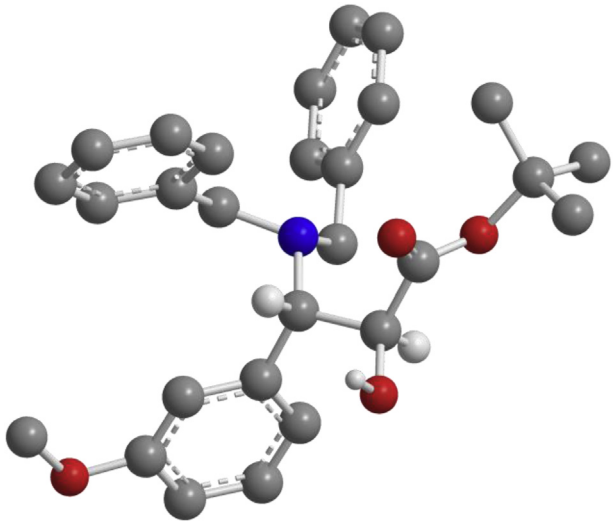


Fig. 4. X-ray crystal structure of (*RS*,*RS*)-**31** (selected H atoms are omitted for clarity).

2.2. Further mechanistic considerations

It was envisaged that ring-closure onto the carbenium ion **44** could proceed via either: (i) cyclisation via the *ipso*-carbon, to give a [6,5]-spirocyclic intermediate **45**, followed by a 1,2-alkyl shift and rearomatisation; or (ii) direct cyclisation via the *ortho*-carbon to give a [6,6]-bicyclic intermediate followed by rearomatisation (Fig. 5).

These mechanisms were investigated by replacing the *N*,*N*-dibenzylamino fragment with either an *N*,*N*-bis(*p*-methoxybenzyl)-amino or an *N*,*N*-bis(*m*-methoxybenzyl)amino substituent. Substrates **47** and **49** were selected as model systems for these investigations due to the relative neutrality[30] of the C(3)-aryl substituent, and the additional possibility of analysing the crude reaction mixtures by ^{19}F NMR spectroscopy. α-Hydroxy-β-amino ester **47** was prepared in 70% yield and >99:1 dr upon conjugate addition of lithium *N*,*N*-bis(*p*-methoxybenzyl)amide to α,β-unsaturated ester **27** followed by oxidation of the intermediate lithium (*Z*)-β-amino enolate[24] with (−)-CSO. The same tandem conjugate addition/enolate oxidation procedure was attempted for the synthesis of **49** although this only gave returned starting material.

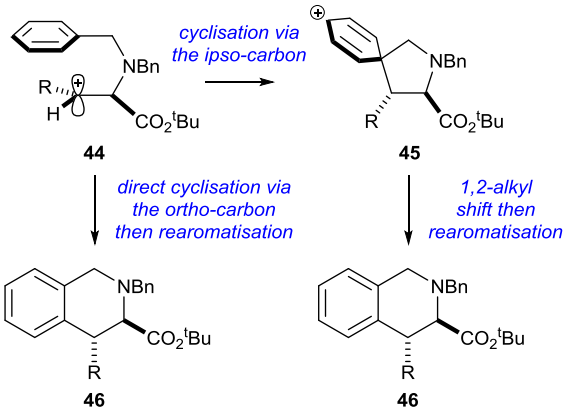
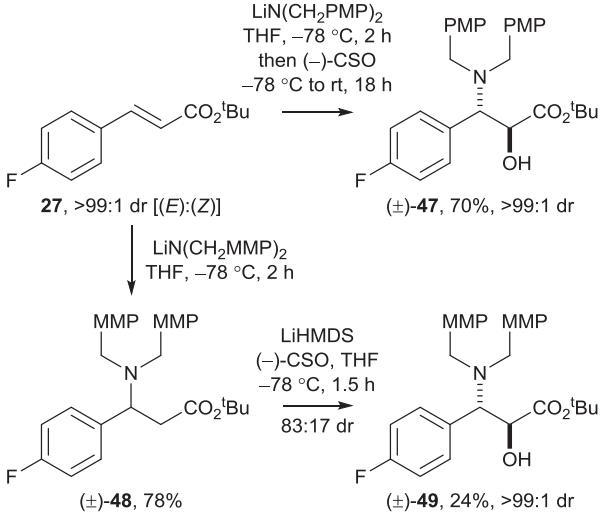


Fig. 5. Possible mechanisms for cyclisation to give tetrahydroisoquinolines. [R=aryl].

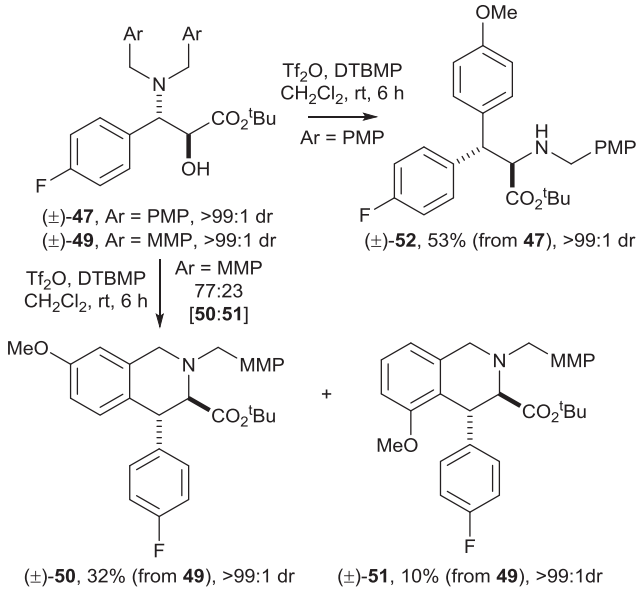
A stepwise conjugate addition/enolate oxidation protocol was therefore adopted for the synthesis of **49**: conjugate addition of lithium *N*,*N*-bis(*m*-methoxybenzyl)amide to **27**, followed by treatment with saturated aqueous NH_4Cl, gave **48** in 78% yield. Deprotonation of **48** followed by oxidation of the resultant lithium (*E*)-β-amino enolate[24] with (−)-CSO gave α-hydroxy-β-amino ester **49** in 24% yield and >99:1 dr (Scheme 6). The relative *anti*-configurations within **47** and **49** were assigned from the diagnostic values of the ^{1}H NMR $^3J_{2,3}$ coupling constants ($^3J_{2,3}$=3.9 and 3.8 Hz, respectively).[28]



Scheme 6. [PMP=*p*-methoxyphenyl; MMP=*m*-methoxyphenyl].

Treatment of **49** (Ar=MMP) with Tf_2O and DTBMP in CH_2Cl_2 at rt for 6 h gave a 77:23 mixture of two regioisomeric tetrahydroisoquinolines **50** and **51**, which were separated by flash column chromatography and isolated as single diastereoisomers in 32 and 10% yield, respectively. The relative *anti*-configurations within **50** and **51** were assigned by analogy to those within **16** and **34**–**38**, and these assignments were supported by ^{1}H NMR $^3J_{3,4}$ coupling constant analyses ($^3J_{3,4}$=2.8 and 1.7 Hz for **50** and **51**, respectively).[19] Treatment of **47** did not result in the formation of any tetrahydroisoquinoline products but instead gave β,β-diaryl-α-amino ester **52**, which was isolated in 53% yield and >99:1 dr (Scheme 7).

The formation of β,β-diaryl-α-amino ester **52** is consistent with cyclisation of benzylic carbenium ion **54** via the *ipso*-carbon (as would be expected from the well-established *ortho*/*para*-directing effect of the methoxy substituent) to form spirocyclic intermediate **55**, followed by fragmentation[31] and hydrolysis of the resultant



Scheme 7. [PMP=*p*-methoxyphenyl; MMP=*m*-methoxyphenyl].

iminium intermediate **56** to give **52** (Fig. 6). The relative (*RS*,*SR*)-configuration within **52** was therefore tentatively assigned based on this mechanistic rationale. When **49** was reacted to form the regiomeric tetrahydroisoquinolines **50** and **51**, however, the cyclisation must go via a [6,6]-bicyclic intermediate: the corresponding spirocyclic intermediate would be expected to be less stable than **55** (due to the absence of the mesomerically electron-donating *p*-methoxy group) and therefore undergo fragmentation more readily than **55**, although a β,β-diaryl-α-amino ester was not observed in this case. This outcome is also consistent with the well-established *ortho*/*para*-directing effect of the methoxy substituent. In the absence of β,β-diaryl-α-amino esters derived from the *N*,*N*-dibenzyl substituted analogues **15** and **29**–**33**, direct cyclisation to give a [6,6]-bicyclic intermediate would be a consistent mechanistic pathway, although the alternative pathway via a spirocyclic intermediate cannot be completely excluded.

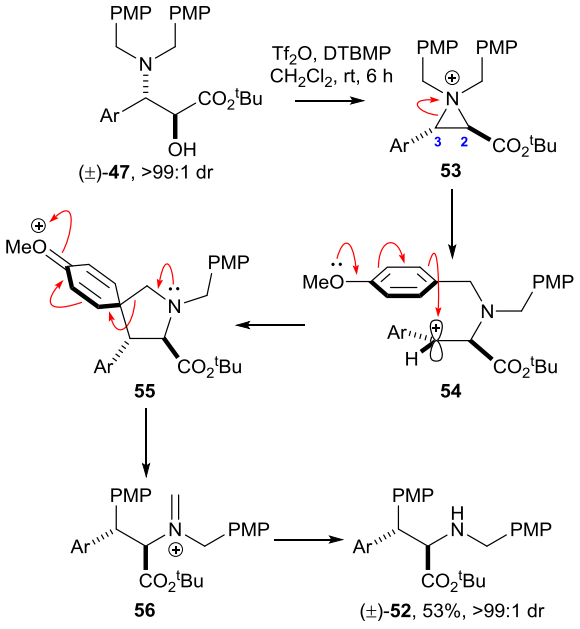
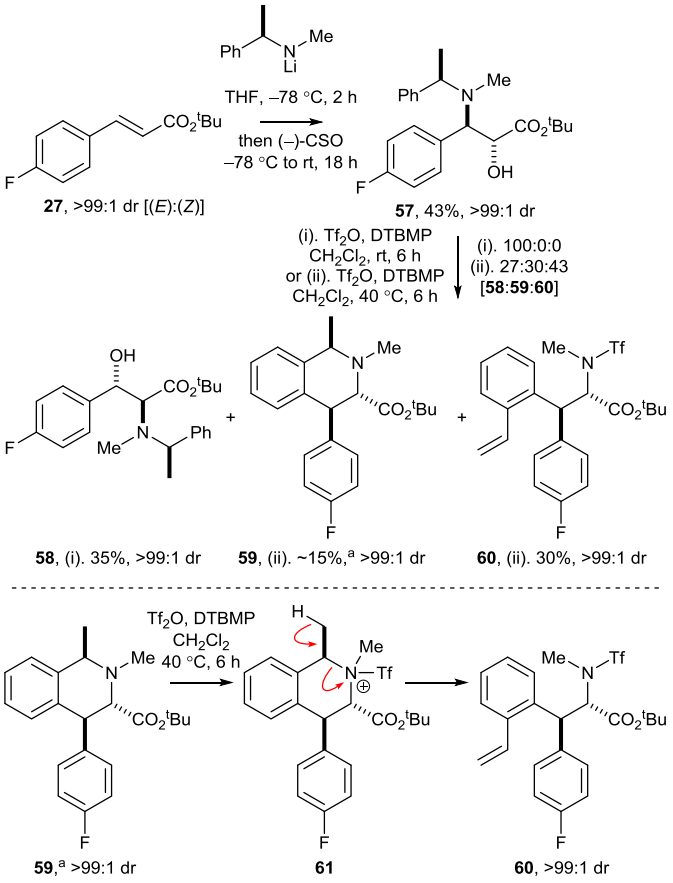


Fig. 6. Proposed mechanism for the formation of β,β-diaryl-α-amino ester **52**. [PMP=*p*-methoxyphenyl; Ar=*p*-fluorophenyl].

2.3. Asymmetric synthesis of 1-methyl-3-(*tert*-butoxycarbonyl)-4-aryl-tetrahydroisoquinolines

With an optimised procedure for the one-pot, diastereoselective synthesis of tetrahydroisoquinolines derived from racemic *N*,*N*-dibenzyl substituted α-hydroxy-β-amino esters developed, attention was turned next towards applying this methodology in the synthesis of enantiopure tetrahydroisoquinolines. As competitive cyclisation of both the *N*-α-methylbenzyl and *N*-benzyl groups was previously observed upon reaction of enantiopure α-hydroxy-β-amino ester **6**[15] (leading to mixtures of regioisomeric tetrahydroisoquinolines **12** and **13**), an alternative protecting group strategy was required such that only one of the groups on nitrogen would be able to participate in the cyclisation step. Thus, both the *N*-methyl substituted α-hydroxy-β-amino ester **57** and the *N*-allyl analogue **62** were initially evaluated in the tetrahydroisoquinoline forming reaction manifold. α-Hydroxy-β-amino ester **57** was prepared in 43% yield and >99:1 dr upon conjugate addition of lithium (*R*)-*N*-methyl-*N*-(α-methylbenzyl)amide[32] to α,β-unsaturated ester **27** followed by oxidation of the intermediate lithium (*Z*)-β-amino enolate[24] with (−)-CSO. The configurations of the newly formed C(2) and C(3) stereogenic centres within **57** were assigned by reference to our transition state mnemonic[33] for the conjugate addition reaction and by analogy to the many other examples of this aminohydroxylation already reported.[26] Treatment of **57** with Tf_2O and DTBMP in CH_2Cl_2 at rt for 6 h (i.e., the standard conditions for tetrahydroisoquinoline formation) gave β-hydroxy-α-amino ester **58** exclusively, and after purification **58** was isolated in 35% yield and >99:1 dr. However, heating the reaction mixture at 40 °C for 6 h gave a 27:30:43 mixture of **58**, tetrahydroisoquinoline **59** and styrene **60**, respectively, from which a 97:3 mixture of **59** and **60** was isolated in ~15% yield, and **60** was isolated in 30% yield, as single diastereoisomers in each case (Scheme 8). The relative *anti*-configuration within **58** was tentatively assigned by ^{1}H NMR ^3J coupling constant analysis ($^3J_{2,3}$=8.7 Hz),[29] and by analogy to the stereochemical outcome observed in related systems.[16] The configuration of **59** was assigned by analogy to the stereochemical outcome observed for the tetrahydroisoquinolines derived from all other *N*,*N*-dibenzyl protected substrates investigated. The structure of **60** was initially determined by ^{1}H, ^{13}C and ^{19}F NMR spectroscopic analyses and its relative configuration, as well as its structure, was then established unambiguously by single crystal X-ray diffraction analysis (Fig. 7).[20] Furthermore, the absolute (*S*,*S*)-configuration within **60** was assigned following the determination of a Flack *x* parameter[34] of −0.010(14) for the structure of **60**. The formation of β-hydroxy-α-amino ester **58** and tetrahydroisoquinoline **59** is consistent with rearrangement of **57** via an aziridinium intermediate. It was proposed that, in turn, styrene **60** was derived from tetrahydroisoquinoline **59** via a sequence of N-triflation to give ammonium species **61** and subsequent elimination. In support of this mechanistic hypothesis, the 97:3 mixture of **59** and **60**, respectively, was resubjected to the reaction conditions and full conversion to styrene **60** was observed; this outcome therefore also supports both the stereochemical assignment of tetrahydroisoquinoline **59** and our proposed mechanistic rationale for tetrahydroisoquinoline formation. Further attempted reaction optimisation by reducing the number of equivalents of Tf_2O and DTBMP was unsuccessful, resulting instead in the formation of complex mixtures of products.

The corresponding *N*-allyl substituted α-hydroxy-β-amino ester **62** was prepared in 78% yield and >99:1 dr upon conjugate addition of lithium (*R*)-*N*-allyl-*N*-(α-methylbenzyl)amide[35] to α,β-unsaturated ester **27** followed by oxidation of the intermediate lithium (*Z*)-β-amino enolate[24] with (−)-CSO. The configurations of the newly formed C(2) and C(3) stereogenic centres within **62** were again assigned by reference to our transition state mnemonic[33] for the conjugate addition reaction and by analogy to the many other examples of this aminohydroxylation already reported.[26] Treatment of **62** with Tf_2O and DTBMP in CH_2Cl_2 at rt for 6 h (i.e., the standard conditions for tetrahydroisoquinoline formation) promoted full conversion to tetrahydroisoquinoline **63** as a single diastereoisomer (>99:1 dr); following chromatographic purification of the crude reaction mixture, **63** was isolated in 31% yield and >99:1 dr (Scheme 9). The relative *anti*-configuration within **63**



Scheme 8. [a97:3 mixture of **59** and **60**, respectively].

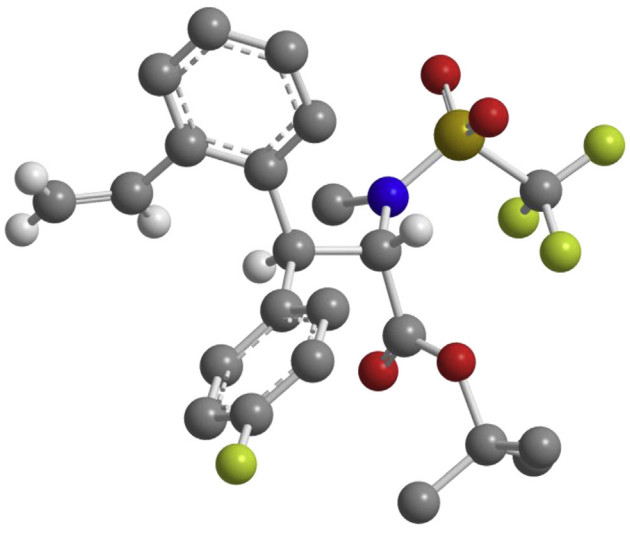
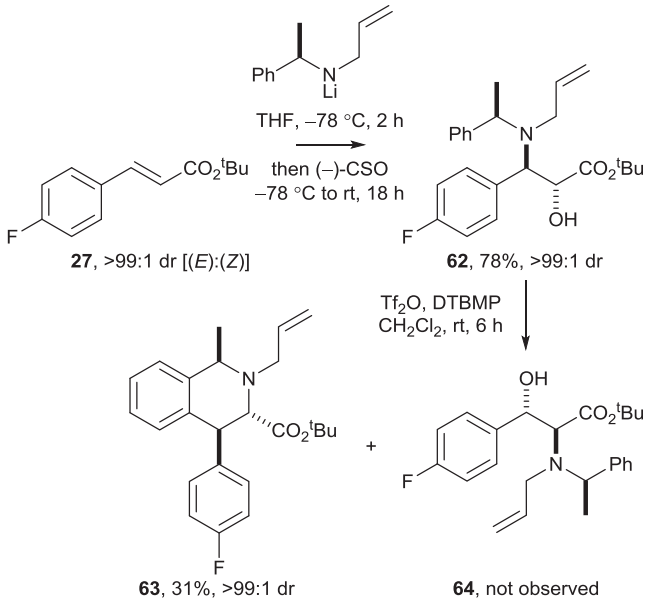
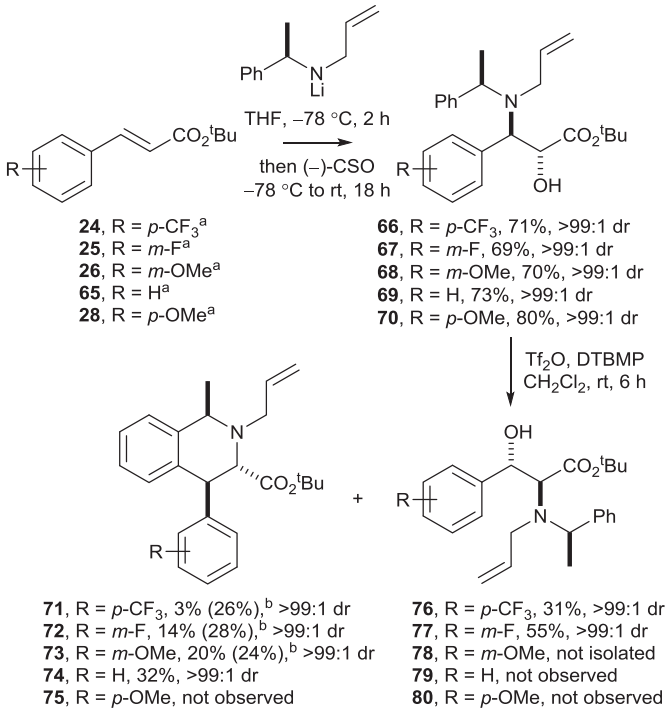


Fig. 7. X-ray crystal structure of (*S*,*S*)-**60** (selected H atoms are omitted for clarity).



Scheme 9.



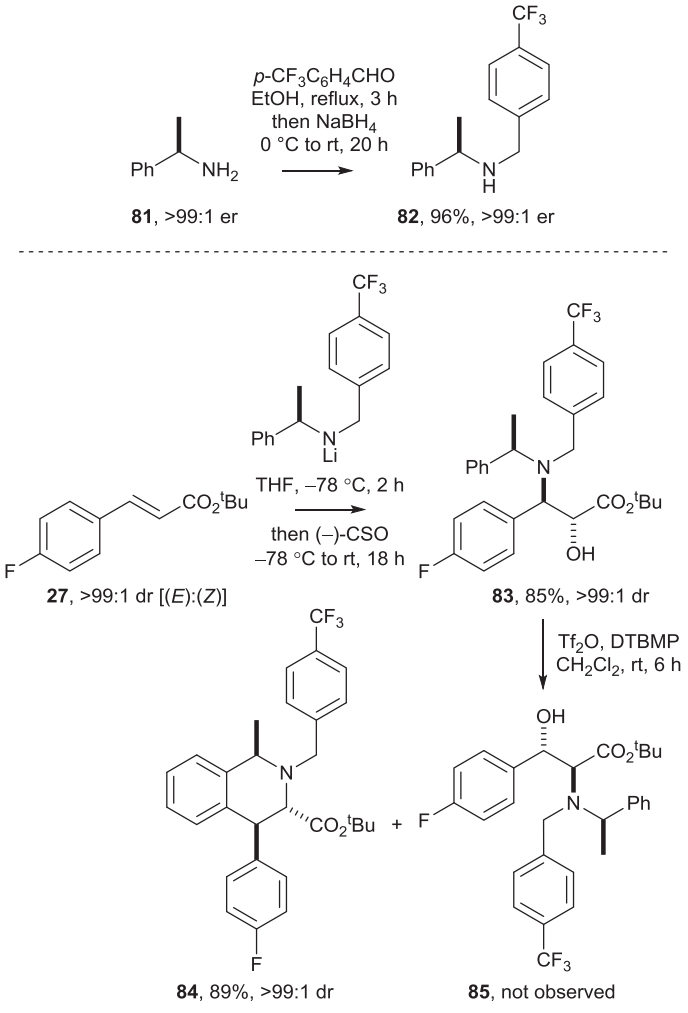
Scheme 10. [a>99:1 dr [(*E*):(*Z*)]; bYields in parentheses correspond to reactions that were heated at 40 °C for 24 h].

($^3J_{3,4}$=4.4 Hz) was assigned by ^{1}H NMR ^3J coupling constant analysis.[19]

The substrate scope of this *N*-allyl substituted series of compounds was next established in the tetrahydroisoquinoline formation reaction manifold. α-Hydroxy-β-amino esters **66**–**70**[36] were prepared in 69–80% yield and >99:1 dr in each case upon conjugate addition of lithium (*R*)-*N*-allyl-*N*-(α-methylbenzyl)amide[35] to α,β-unsaturated esters **24**–**26**, **65** and **28**, followed by oxidation of the intermediate lithium (*Z*)-β-amino enolates[24] with (−)-CSO according to our standard aminohydroxylation procedure.[25–27] The relative *anti*-configurations within **66**–**68** and **70** were assigned by reference to our transition state mnemonic[33] for the conjugate addition reaction and by analogy to the well-established outcome of this aminohydroxylation process, and these assignments were supported by ^{1}H NMR $^3J_{2,3}$ coupling constant analyses ($^3J_{2,3}$=3.5–3.8 Hz).[28] Subjection of **66** (R=*p*-CF_3) and **67** (R=*m*-F) to the reaction conditions gave 96:4 and 80:20 mixtures of the corresponding β-hydroxy-α-amino esters **76** and **77**, and tetrahydroisoquinolines **71** and **72**, respectively, from which **76** and **77** were isolated as single diastereoisomers in 31 and 55% yield; tetrahydroisoquinolines **71** and **72** were also isolated in 3 and 14% yield, respectively, and >99:1 dr in each case. Subjection of **68** (R=*m*-OMe) to the reaction conditions gave a 67:34 mixture of tetrahydroisoquinoline **73** and β-hydroxy-α-amino ester **78**, respectively, whereas reaction of the known α-hydroxy-β-amino ester **69**[15,36] (R=H) gave tetrahydroisoquinoline **74** exclusively. After chromatographic purification of the crude reaction mixtures, **73** and **74** were isolated in 20 and 32% yield, respectively, and in >99:1 dr in both cases. Upon reaction of **70** (R=*p*-OMe) with Tf_2O and DTBMP in CH_2Cl_2 at −20 °C for 2.5 h, a complex mixture was produced, which did not contain any species consistent with either **75** or **80**. Attempts to optimise this reaction to promote formation of the corresponding tetrahydroisoquinoline **75** from **70** were unsuccessful, resulting in complex mixtures in all cases. For the reactions where β-hydroxy-α-amino esters were formed, heating the reactions of **66**, **67** and **68** at 40 °C for 24 h increased conversion to the corresponding tetrahydroisoquinolines **71**, **72** and **73**, which were isolated as single diastereoisomers (>99:1 dr) in increased yields of 26, 28 and 24%, respectively (Scheme 10). ^{1}H NMR ^3J coupling constant analyses were used to assign the relative *anti*-configurations within β-hydroxy-α-amino esters **76** ($^3J_{2,3}$=8.8 Hz) and **77** ($^3J_{2,3}$=8.4 Hz),[29] and tetrahydroisoquinolines **71**–**74** ($^3J_{3,4}$=3.9–4.5 Hz).[19]

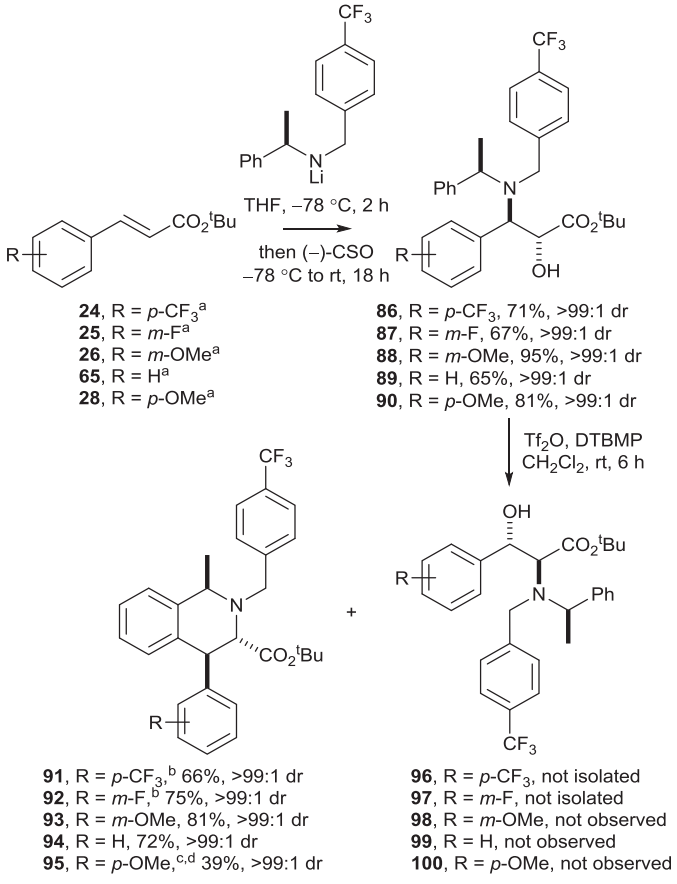
A change in the nature of the non-participating *N*-protecting group clearly influences the reaction outcome and, in the case of these *N*-methyl and *N*-allyl substrates, is detrimental to the formation of the corresponding tetrahydroisoquinolines. As higher yields, greater substrate scope and cleaner conversion to tetrahydroisoquinoline products were observed when both protecting groups on nitrogen were benzylic, investigations focussed next on trying to bias the cyclisation of one benzyl group over the other. Increasing the electron density of the aryl ring of one of the *N*-benzyl groups (e.g., upon the introduction of a *p*-methoxy group) was expected to promote the formation of the corresponding β,β-diaryl-α-amino ester (vide supra), and in any case this approach would be inherently limited to syntheses of C(6)-methoxy substituted tetrahydroisoquinolines, even if it could be deployed successfully. Instead, it was envisaged that regioselective cyclisation may be achieved by adding an electron withdrawing group to the aryl ring of one of the benzyl groups, thus retarding the rate of cyclisation via the electron poor aryl ring in favour of cyclisation via the unsubstituted benzyl group. Furthermore, it was envisaged that by tuning the electron density of the two different *N*-benzyl groups in this way the α-methylbenzyl chiral auxiliary may either be incorporated into the tetrahydroisoquinoline scaffold [to generate stereodefined C(1)-methyl substituted tetrahydroisoquinolines] or not [to generate C(1)-unsubstituted tetrahydroisoquinolines], as desired. α-Hydroxy-β-amino ester **83** (which incorporates a *p*-CF_3 group on the aryl ring of the *N*-benzyl group), was therefore synthesised and subjected to the conditions for tetrahydroisoquinoline formation. The requisite enantiopure amine (*R*)-**82** was prepared in 96% yield and >99:1 er via reductive alkylation of (*R*)-α-methylbenzylamine **81** (>99:1 er) with *p*-(trifluoromethyl)benzaldehyde.[37] Conjugate addition of the lithium amide reagent derived from deprotonation of (*R*)-**82** with BuLi to α,β-unsaturated ester **27**, followed by in situ oxidation of the intermediate lithium (*Z*)-β-amino enolate[24] with (−)-CSO, gave **83** in 85% isolated yield and >99:1 dr. The relative *anti*-configuration within **83** was assigned by

reference to our transition state mnemonic[33] for the conjugate addition reaction and by analogy to the established stereochemical outcome of this aminohydroxylation process,[38] and this assignment was supported by ^{1}H NMR $^3J_{2,3}$ coupling constant analysis ($^3J_{2,3}$=3.1 Hz).[28] Reaction of α-hydroxy-β-amino ester **83** with Tf_2O and DTBMP gave *N*-*p*-(trifluoromethyl)benzyl substituted tetrahydroisoquinoline **84** exclusively and, following chromatographic purification **84** was isolated in 72% yield and >99:1 dr (Scheme 11). The relative *anti*-configuration within **84** ($^3J_{3,4}$=3.6 Hz) was assigned by ^{1}H NMR ^3J coupling constant analysis,[19] and the regioselectivity of this transformation was confidently assigned by ^{1}H–^{13}C NMR HMBC analysis. When compared with the corresponding *N*-allyl analogue **63**, the yield of tetrahydroisoquinoline **84** is far superior. In this case, the *N*-(α-methylbenzyl) chiral auxiliary is retained in the tetrahydroisoquinoline product, making this an efficient route to stereodefined C(1)-methyl substituted tetrahydroisoquinolines.



Scheme 11.

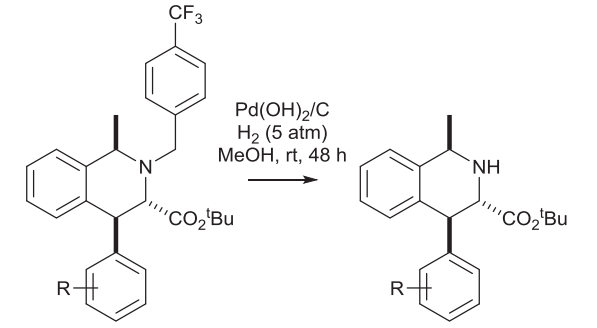
The conditions for tetrahydroisoquinoline formation were next applied to the range of substituted α-hydroxy-β-amino esters **86**–**90**. Conjugate addition of the lithium amide reagent derived from deprotonation of (*R*)-**82** with BuLi to α,β-unsaturated esters **24**–**26**, **65** and **28** with in situ oxidation of the intermediate lithium (*Z*)-β-amino enolates[21] with (−)-CSO, gave α-hydroxy-β-amino esters **86**–**90** in 67–95% yield and >99:1 dr in each case. The configurations within **86**–**90** were again assigned by reference to our transition state mnemonic[33] for the conjugate addition reaction and by analogy to the established stereochemical outcome of this aminohydroxylation process,[25–27] and this assignment was supported by ^{1}H NMR $^3J_{2,3}$ coupling constant analyses ($^3J_{2,3}$=2.7–3.0 Hz).[28] Upon reaction of α-hydroxy-β-amino esters **86** (R=*p*-CF_3) and **87** (R=*m*-F) with Tf_2O and DTBMP, it was necessary to heat the reaction mixture at 40 °C for 6 h to achieve full conversion: reaction of **86** (R=*p*-CF_3) gave a 93:7 mixture of tetrahydroisoquinoline **91** and β-hydroxy-α-amino ester **96**, respectively, from which **91** was isolated in 66% yield and >99:1 dr. For **87** (R=*m*-F) a 96:4 mixture of tetrahydroisoquinoline **92** and β-hydroxy-α-amino ester **97** was recovered, from which **92** was isolated in 75% yield and >99:1 dr. α-Hydroxy-β-amino esters **88** (R=*m*-OMe) and **89** (R=H) were found to react cleanly under standard reaction conditions (i.e., at rt for 6 h) to give full conversion to tetrahydroisoquinolines **93** and **94**, respectively, which were isolated in 81 and 72% yield and in >99:1 dr in both cases. However, for α-hydroxy-β-amino ester **90** (R=*p*-OMe) a reduction in diastereoselectivity was again observed. Reaction of **90** with Tf_2O and DTBMP at −20 °C for 2.5 h gave an 80:20 mixture of **95** and **101**, respectively, from which **95** was isolated in 39% yield and >99:1 dr (Scheme 12). The regiochemistries of **91**–**95** and **101** were assigned via ^{1}H–^{13}C NMR HMBC analyses, and ^{1}H NMR ^3J coupling constant analyses were used to assign the relative configurations within the major 3,4-*anti*-diastereoisomers **91**–**95** ($^3J_{3,4}$=3.2–3.8 Hz) and 3,4-*syn*-**101** ($^3J_{3,4}$=5.5 Hz).[19]



Scheme 12. [[a]>99:1 dr [(*E*):(*Z*)]; [b]The reaction mixture was heated at 40 °C for 6 h; [c]The reaction mixture was cooled to −20 °C for 2.5 h; [d]the minor (1*R*,3*S*,4*R*)-diastereoisomer **101** was also isolated in 13% yield and >99:1 dr].

Studies into the hydrogenolytic removal of the *N*(2)-[*p*-(trifluoromethyl)benzyl] protecting group within tetrahydroisoquinolines **84** and **91**–**95** were undertaken next. Reaction of **94** (R=H) under H_2 (5 atm) in the presence of Pearlman's catalyst [$Pd(OH)_2$/C] at rt for 48 h gave **105** in 59% yield and >99:1 dr. Deprotection of **93** (R=*m*-OMe) and **95** (R=*p*-OMe) under identical

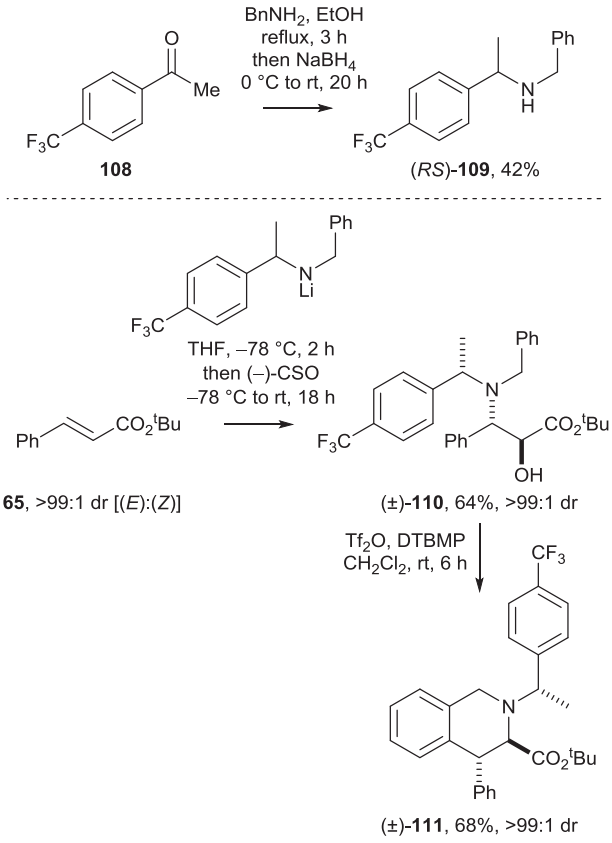
conditions gave **104** and **107**, respectively, in 74 and 61% yield. However, when **84** (R=*p*-F) was reacted under this optimised protocol, N-debenzylation was accompanied by complete defluorination. Reducing the catalyst loading from 40 to 25% w/w gave 69% conversion to **106** after 48 h, with full conversion to **106** being observed after 5 days; **106** was then isolated in 72% yield and >99:1 dr after chromatographic purification of the crude reaction mixture. Deprotection of the remaining fluorinated tetrahydroisoquinolines **91** and **92** using this alternative protocol gave **102** and **103** in 43 and 37% yield, respectively (Scheme 13).



91, R = *p*-CF_3, >99:1 dr
92, R = *m*-F, >99:1 dr
93, R = *m*-OMe, >99:1 dr
94, R = H, >99:1 dr
84, R = *p*-F, >99:1 dr
95, R = *p*-OMe, >99:1 dr

102, R = *p*-CF_3,[a] 43%, >99:1 dr
103, R = *m*-F,[a] 37%, >99:1 dr
104, R = *m*-OMe, 74%, >99:1 dr
105, R = H, 59%, >99:1 dr
106, R = *p*-F,[a] 72%, >99:1 dr
107, R = *p*-OMe, 61%, >99:1 dr

Scheme 13. [[a]Reaction time of 5 days].



Scheme 14.

2.4. Asymmetric synthesis of 3-(*tert*-butoxycarbonyl)-4-aryltetrahydroisoquinolines

The synthesis of *N*(2)-[α-methyl-*p*-(trifluoromethyl)benzyl] substituted tetrahydroisoquinolines was conducted in the racemic series in the first instance. The requisite secondary amine (*RS*)-**109** was synthesised by the reductive alkylation of benzylamine with *p*-(trifluoromethyl)acetophenone **108**, which gave (*RS*)-**109** in 42% yield. Subsequent conjugate addition of the lithium amide reagent derived from deprotonation of (*RS*)-**109** with BuLi to *tert*-butyl cinnamate **65**, with in situ oxidation of the intermediate lithium (*Z*)-β-amino enolate[24] with (−)-CSO, gave (±)-**110** in 64% yield and in >99:1 dr. The relative configuration within (±)-**110** was assigned by reference to our transition state mnemonic[33] for the conjugate addition reaction and by analogy to the established stereochemical outcome of this aminohydroxylation process,[25–27] and this assignment was supported by ^{1}H NMR $^3J_{2,3}$ coupling constant analysis ($^3J_{2,3}$=3.1 Hz).[26] Reaction of (±)-**110** with Tf_2O and DTBMP at rt for 6 h promoted full conversion to (±)-**111**, which was isolated in 68% yield and >99:1 dr after chromatographic purification (Scheme 14). The regiochemistry of (±)-**111** was assigned via ^{1}H–^{13}C NMR HMBC analysis and the relative 3,4-*anti*-configuration within (±)-**111** was initially assigned based on ^{1}H NMR ^3J coupling constant analysis ($^3J_{3,4}$=1.6 Hz),[19] and the relative (3*RS*,4*RS*,α*SR*)-configuration of **111** was subsequently confirmed by single crystal X-ray diffraction analysis (Fig. 8).[20] Complete regioselectivity was again observed in the cyclisation step as a result of exclusive cyclisation via the unsubstituted phenyl ring.

Investigations into an effective strategy to deprotect the *N*(2)-[α-methyl-*p*-(trifluoromethyl)benzyl] group within (±)-**111** were undertaken next. In the first instance **111** was reacted under standard hydrogenolysis conditions: stirring **111** under H_2 pressure (5 atm) in the presence of $Pd(OH)_2/C$ (25% w/w) at rt for 48 h, gave a 55:20:22:3 mixture of starting material **111**, α-amino ester **112** [which presumably results from hydrogenolytic cleavage of the C(1)–N(2) bond within **111**], tetrahydroisoquinoline **113** and

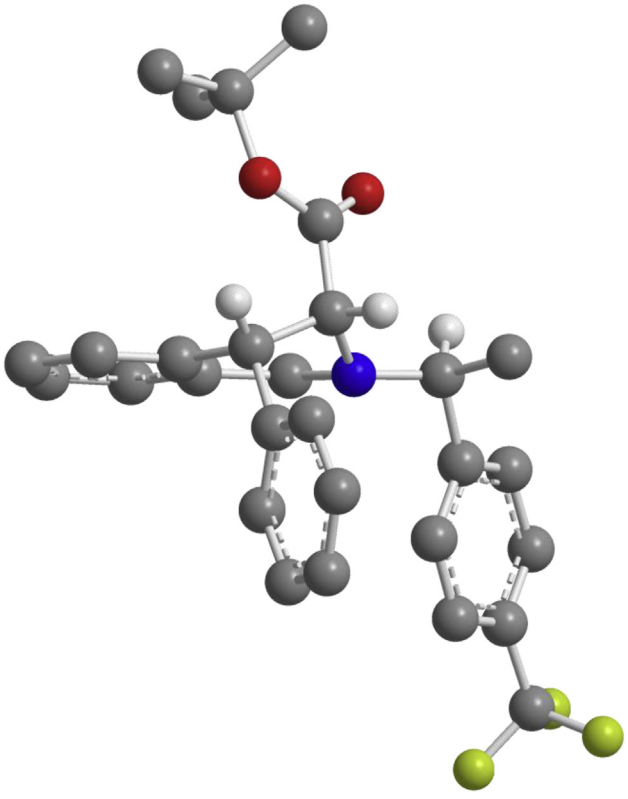
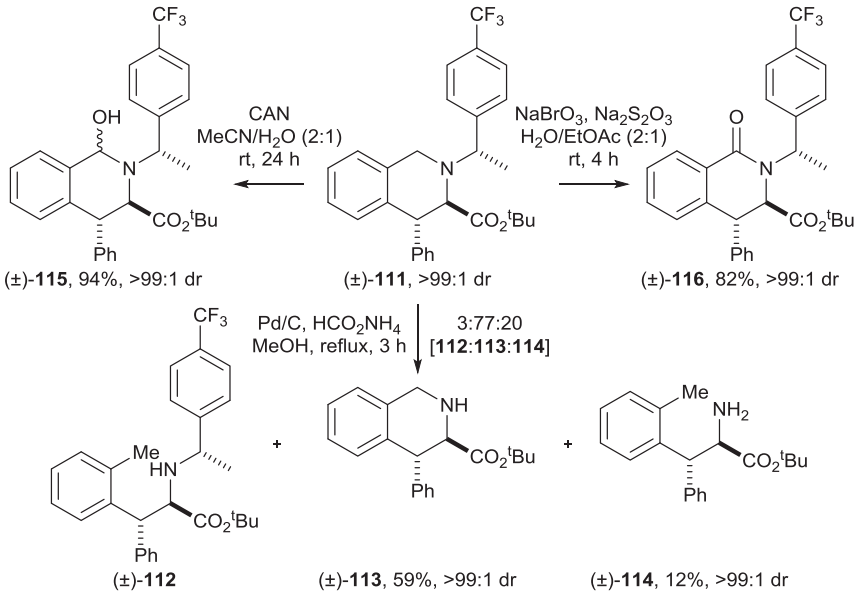


Fig. 8. X-ray crystal structure of (3*RS*,4*RS*,α*SR*)-**111** (selected H atoms are omitted for clarity).

α-amino ester **114**, respectively. Increasing the catalyst loading to 40% w/w resulted in a 60:40 mixture of **113** and **114**, respectively. Investigations into alternative debenzylation strategies were undertaken next, in the hope that a protocol may be found that would favour removal of the *N*(2)-[α-methyl-*p*-(trifluoromethyl)benzyl] group over cleavage of the C(1)–N(2) bond. However, treatment of **111** with Na in NH_3 at −78 °C for 30 min gave returned starting material. Reaction of **111** with $NaBrO_3$ and $Na_2S_2O_4$ resulted in oxidation at the C(1) position, giving **116** in 82% yield.[39] Similarly, treatment of **111** with CAN[40,41] gave **115** as a single diastereoisomer [of unknown configuration at C(1)] in 94% yield. Reduction of **111** under transfer hydrogenolysis conditions (i.e., treatment with HCO_2NH_4 in the presence of Pd/C for 8 h) gave a 3:70:27 mixture of **112**, **113** and **114**, respectively. Further optimisation revealed that 3 h was sufficient to achieve full conversion, giving a 3:77:20 mixture of **112**, **113** and **114**, respectively, from which **113** was isolated in 59% yield and >99:1 dr (Scheme 15).



Scheme 15.

With a selective cyclisation pathway identified, and subsequent deprotection optimised, work could begin on the corresponding enantiopure system. The resolution of α-methyl-*p*-(trifluoromethyl)benzylamino **117** was first conducted according to a known procedure.[42] Racemic α-methyl-*p*-(trifluoromethyl)benzylamine (*RS*)-**117** was synthesised via the reductive amination of *p*-(trifluoromethyl)acetophenone **108**, which gave (*RS*)-**117** in 68% yield.[43] Subsequent coupling of (*RS*)-**117** with (*R*)-*O*-acetylmandelic acid gave a 50:50 mixture of enantiopure diastereoisomers **118** and **119**, which were separated by column chromatography and isolated in 33 and 36% yield, respectively, as single diastereoisomers (>99:1 dr). The relative configuration within **118** was established by single crystal X-ray diffraction analysis (Fig. 9),[20] and the determination of a Flack *x* parameter[34] of 0.09(12) for the structure of **118** confirmed the assigned absolute (*R*,*R*)-configuration of **118**; this analysis therefore also established the absolute (2*R*,α*S*)-configuration of **119**. With diastereoisomerically pure samples of **118** and **119** in hand, subsequent hydrolysis was required to liberate the corresponding enantiomerically pure amines (*R*)-**117** and (*S*)-**117**. Heating a solution of **118** in HBr at reflux for 24 h was found to effectively cleave the amide bond, but purification of (*R*)-**117** by an acid/base extraction protocol gave (*R*)-**117** in only 38% yield; comparison of the specific rotation of this sample of (*R*)-**117** {$[\alpha]_D^{20}$ +22.0 (*c* 1.0 in MeOH)} with the literature value {lit.[44] $[\alpha]_D^{20}$ +20.0 (*c* 1.0 in MeOH)} showed excellent agreement. Attempts to improve the isolated yield of either (*R*)-**117** or (*S*)-**117** were not successful. However, it was found that subjection of the crude reaction mixtures of (*R*)-**117** or (*S*)-**117** to reductive alkylation with benzaldehyde, in the presence of 1.0 equiv of K_2CO_3, gave (*R*)-**109** or (*S*)-**109** in 48 and 63% yield (from **118** or **119**), respectively, and>99:1 er[45] in each case (Scheme 16).

With samples of both antipodes of *N*-benzyl-*N*-[α-methyl-*p*-(trifluoromethyl)benzyl]amine **109** in hand, work towards the synthesis of the corresponding enantiopure *N*(2)-[α-methyl-*p*-(trifluoromethyl)benzyl] substituted tetrahydroisoquinoline **111** was undertaken. Conjugate addition of the lithium amide reagent derived from deprotonation of (*S*)-**109** with BuLi to *tert*-butyl cinnamate **65**, with in situ oxidation of the intermediate lithium (*Z*)-β-amino enolate[24] with (+)-CSO, gave α-hydroxy-β-amino ester

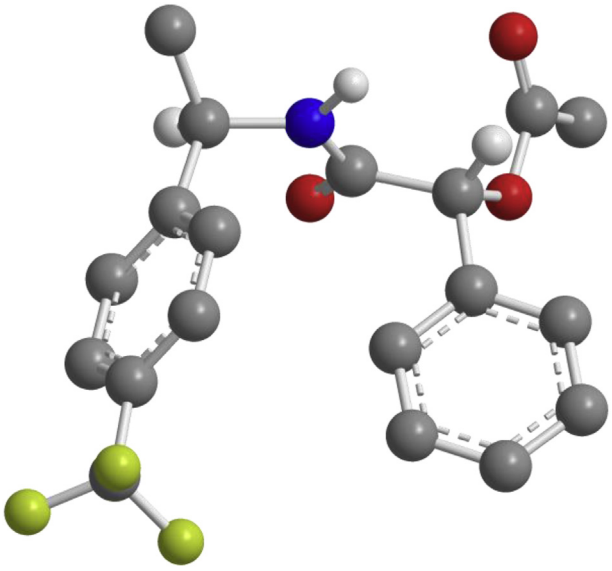
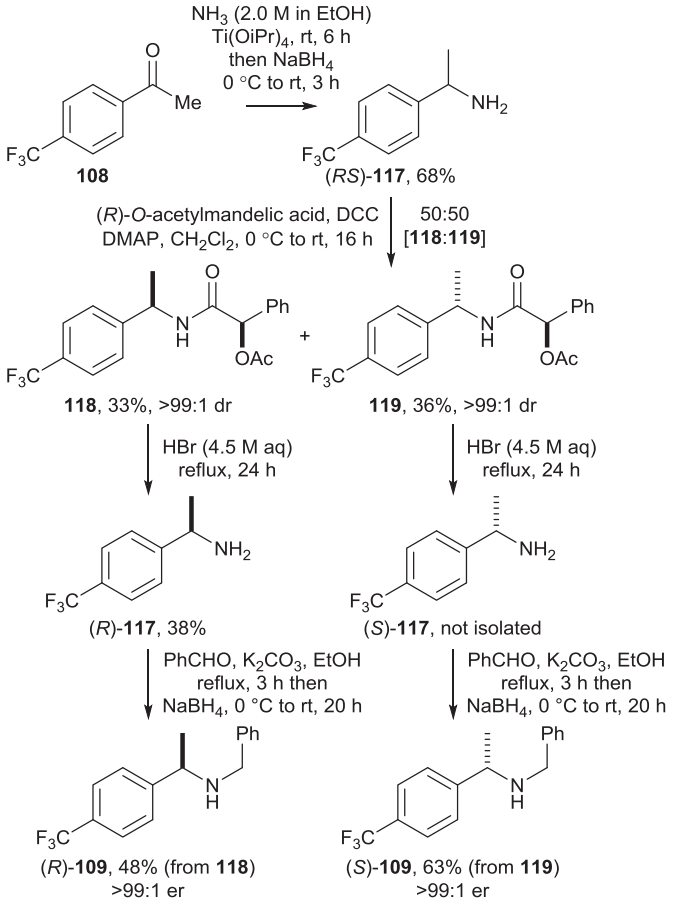
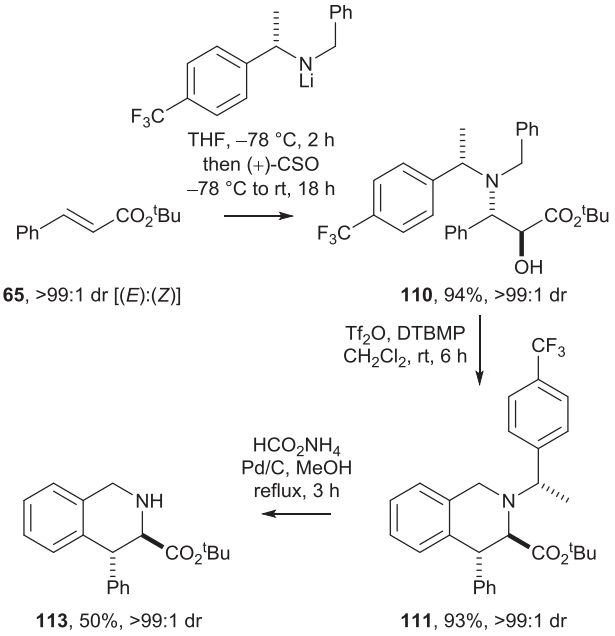


Fig. 9. X-ray crystal structure of (*R*,*R*)-**118** (selected H atoms are omitted for clarity).



Scheme 16.



Scheme 17.

(*S*,*S*,*S*)-**110** in 94% yield and >99:1 dr. Subsequent treatment of (*S*,*S*,*S*)-**110** with Tf_2O and DTBMP gave tetrahydroisoquinoline (3*R*,4*R*,α*S*)-**111** as the sole product, which was isolated in 93% yield and >99:1 dr. Application of the previously optimised deprotection conditions to (3*R*,4*R*,α*S*)-**111** gave a 9:74:17 mixture of **112**, **113** and **114**, respectively, from which (*R*,*R*)-**113** was isolated in 50% yield and >99:1 dr (Scheme 17). All ^1H and ^{13}C NMR spectroscopic data for these species were entirely consistent with the racemic samples prepared previously (vide supra).

3. Conclusion

In conclusion, a general protocol for the synthesis of a range of 3,4-disubstituted and 1,3,4-trisubstituted 1,2,3,4-tetrahydroisoquinolines directly from α-hydroxy-β-amino esters has been developed. Treatment of a β-aryl substituted α-hydroxy-β-amino ester with Tf_2O and 2,6-di-*tert*-butyl-4-methylpyridine promoted activation of the α-hydroxy group and aziridinium formation [with inversion of configuration at C(2)], which was followed by rupture of the C(3)–N bond and rapid Friedel–Crafts alkylation-type cyclisation of an *N*-benzyl moiety onto the resultant benzylic carbenium ion [with retention of configuration at C(3)]. The nature of the *N*-protecting group was varied and it was found that superior yields were obtained for reactions employing two benzylic groups on nitrogen. In the cases where two different *N*-benzyl groups were used, the issue of regioselectivity resulting from the competitive cyclisation via either *N*-benzyl group was addressed by the introduction of a *p*-trifluoromethyl group on one of the *N*-benzyl moieties; this retarded the rate of cyclisation via the electron poor aryl ring to such an extent that complete regioselectivity was observed upon formation of the corresponding 1,2,3,4-tetrahydroisoquinoline resulting from exclusive cyclisation via the other unsubstituted *N*-benzyl group. This methodology was employed in the asymmetric synthesis of a range of enantiopure 3,4-*anti*-3-(*tert*-butoxycarbonyl)-4-aryl-1,2,3,4-tetrahydroisoquinolines, which were isolated in good yields as single diastereoisomers.

4. Experimental

4.1. General experimental

Reactions involving organometallic or other moisture-sensitive reagents were carried out under a nitrogen or argon atmosphere using standard vacuum line techniques and glassware that was flame dried and cooled under nitrogen before use. BuLi was purchased (as a solution in hexanes) and titrated against diphenylacetic acid before use. Solvents were dried according to the procedure outlined by Grubbs and co-workers.[46] Water was purified by an Elix® UV-10 system. All other reagents were used as supplied (analytical or HPLC grade) without prior purification. Organic layers were dried over $MgSO_4$ or $NaSO_4$. Thin layer chromatography was performed on aluminium plates coated with 60 F_{254} silica. Plates were visualised using UV light (254 nm), iodine, 1% aq $KMnO_4$, or 10% ethanolic phosphomolybdic acid. Flash column chromatography was performed on Kieselgel 60 silica.

Melting points were recorded on a Gallenkamp Hot Stage apparatus. Optical rotations were recorded on a Perkin–Elmer 241 polarimeter with a water-jacketed 10 cm cell. Specific rotations are reported in 10^{-1} deg cm^2 g^{-1} and concentrations in g/100 mL. IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer using an ATR module. Selected characteristic peaks are reported in cm^{-1}. NMR spectra were recorded on Bruker Avance spectrometers in the deuterated solvent stated. Spectra were recorded at rt. The field was locked by external referencing to the relevant deuteron resonance. ^1H–^1H COSY, ^1H–^{13}C HMQC, and ^1H–^{13}C HMBC analyses were used to establish atom connectivity. Low-resolution mass spectra were recorded on either a VG MassLab 20–250 or a Micromass Platform 1 spectrometer. Accurate mass measurements were run on either a Bruker MicroTOF internally calibrated with polyalanine, or a Micromass GCT instrument fitted with

a Scientific Glass Instruments BPX5 column (15 m×0.25 mm) using amyl acetate as a lock mass.

4.2. General procedure I: aminohydroxylation of α,β-unsaturated esters

BuLi (1.55 equiv) was added dropwise to a stirred solution of the requisite amine (1.60 equiv) in THF at −78 °C and the resultant mixture was stirred at −78 °C for 30 min. A solution of the requisite α,β-unsaturated ester (1.0 equiv) in THF at −78 °C was then added dropwise via cannula and the resultant mixture was stirred at −78 °C for 2 h (−)-CSO (1.6 equiv) was then added and the reaction mixture was allowed to warm to rt then stirred at rt for 18 h. Satd aq NH_4Cl was added and the reaction mixture was stirred at rt for 5 min, then concentrated in vacuo. The residue was partitioned between CH_2Cl_2 and 10% aq citric acid, and the aqueous layer was extracted with three portions of CH_2Cl_2. The combined organic extracts were washed sequentially with satd aq $NaHCO_3$ and brine, then dried and concentrated in vacuo. The residue was then triturated with cold Et_2O and filtered. The resultant solution was then dried and concentrated in vacuo.

4.3. General procedure II: tetrahydroisoquinoline formation

Tf_2O (1.5 equiv) was added to a stirred solution of the requisite α-hydroxy-β-amino ester (1.0 equiv) and DTBMP (3.0 equiv) in CH_2Cl_2 at 0 or −20 °C. The resultant mixture was stirred at the stated temperature for the time stated, then H_2O was added and the aqueous layer was extracted with portions of CH_2Cl_2. The combined organic extracts were then dried and concentrated in vacuo. The residue was dissolved in Et_2O and the resultant solution was filtered, then dried and concentrated in vacuo.

4.4. General procedure III: N-deprotection of *N*(2)-[*p*-(trifluoromethyl)benzyl] substituted tetrahydroisoquinolines

$Pd(OH)_2/C$ (either 25 or 40% w/w, as stated) was added to a degassed solution of the requisite terahydroisoquinoline (1.0 equiv) in MeOH and the resultant mixture was placed under H_2 (5 atm) and stirred at rt for either 48 h or 5 days, as stated. The reaction mixture was filtered through Celite® (eluent MeOH) and concentrated in vacuo.

4.5. (*RS*,*RS*)-*N*(2)-Benzyl-3-(*tert*-butoxycarbonyl)-4-phenyl-1,2,3,4-tetrahydroisoquinoline 16

Following *general procedure II*, Tf_2O (181 μL, 1.08 mmol) was reacted with **15**[16] (300 mg, 0.719 mmol, >99:1 dr) and DTBMP (443 mg, 2.16 mmol) in CH_2Cl_2 (9 mL) at rt for 6 h. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 20:1) gave **16** as a pale yellow solid (219 mg, 76%, >99:1 dr); mp 68–70.5 °C; ν_{max} (ATR) 1723 (C=O); δ_H (500 MHz, $CDCl_3$) 1.38 (9H, s, C*Me*$_3$), 3.58 (1H, d, *J* 3.0, C(3)*H*), 3.86 (1H, d, *J* 13.4, NC*H*$_A$H$_B$Ph), 3.92 (1H, d, *J* 15.0, C(1)*H*$_A$), 3.96 (1H, d, *J* 13.4, NCH$_A$*H*$_B$Ph), 4.06 (1H, d, *J* 15.0, C(1)*H*$_B$), 4.50 (1H, d, *J* 3.0, C(4)*H*), 6.90–7.42 (14H, m, *Ar*, *Ph*); δ_C (125 MHz, $CDCl_3$) 28.2 (C*Me*$_3$), 47.9 (*C*(4)), 51.0 (*C*(1)), 59.5 (NCH_2Ph), 67.0 (*C*(3)), 81.3 (*C*Me$_3$), 126.0, 126.1, 126.2, 126.3 (*C*(5), *C*(6), *C*(7), *C*(8)), 126.9, 127.8, 128.1, 128.6, 129.1, 129.7 (*o*,*m*,*p*-*Ph*), 134.7 (*C*(8a)), 135.2 (*C*(4a)), 138.6, 144.7 (*i*-*Ph*), 171.4 (CO_2^tBu); *m*/*z* (ESI^+) 400 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{27}H_{30}NO_2^+$ ($[M+H]^+$) requires 400.2271; found 400.2273.

4.6. *tert*-Butyl (2*S*,3*R*)-2-hydroxy-3-(*N*,*N*-dibenzylamino)-3-phenylpropanoate 19

Step 1: $Pd(OH)_2/C$ (35 mg, 25% w/w) was added to a degassed solution of **18**[21] (139 mg, 0.32 mmol, >99:1 dr) in MeOH (5 mL) and the resultant mixture was stirred under H_2 (5 atm) at rt for 15 h. The reaction mixture was then filtered through Celite® (eluent MeOH) and concentrated in vacuo to give *tert*-butyl (2*S*,3*R*)-2-hydroxy-3-amino-3-phenylpropanoate as a colourless oil (77 mg, quant, >99:1 dr); $[\alpha]_D^{20}$ +11.4 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3363, 3298 (N–H), 3165 (O–H), 3086, 3063, 3030, 3003, 2978, 2932 (C–H), 1727 (C=O); δ_H (400 MHz, $CDCl_3$) 1.41 (9H, s, C*Me*$_3$), 2.59 (3H, br s, N*H*$_2$, O*H*), 4.15–4.20 (2H, m, C(2)*H*, C(3)*H*), 7.21–7.41 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 27.9 (C*Me*$_3$), 58.5, 75.3 (*C*(2), *C*(3)), 82.5 (*C*Me$_3$), 127.0, 127.5, 128.4 (*o*,*m*,*p*-*Ph*), 142.2 (*i*-*Ph*), 172.6 (*C*(1)); *m*/*z* (ESI^+) 260 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{13}H_{19}NNaO_3^+$ ($[M+Na]^+$) requires 260.1257; found 260.1250.

Step 2: BnBr (0.10 mL, 0.84 mmol) and K_2CO_3 (290 mg, 2.1 mmol) were added to a stirred solution of *tert*-butyl (2*S*,3*R*)-2-hydroxy-3-amino-3-phenylpropanoate (100 mg, 0.42 mmol) in MeCN (2.5 mL) and the resultant mixture was heated at reflux for 24 h. The reaction mixture was then allowed to cool to rt and filtered. The filter cake was washed with EtOAc (3 mL), then the combined organic washings were concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 10:1) gave **19** as a colourless oil (78 mg, 45%, >99:1 dr); ν_{max} (ATR) 3464 (O–H), 1724 (C=O); $[\alpha]_D^{20}$ −32.4 (*c* 1.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.00 (9H, s, C*Me*$_3$), 308 (2H, d, *J* 13.4, N(C*H*$_A$H$_B$Ph)$_2$), 3.81 (1H, d, *J* 9.8, C(3)*H*), 3.91 (2H, d, *J* 13.4, N(CH$_A$*H*$_B$Ph)$_2$), 4.14 (1H, br s, O*H*), 4.55 (1H, d, *J* 9.8, C(2)*H*), 7.15–7.39 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 27.5 (C*Me*$_3$), 53.8 (N(*C*H$_2$Ph)$_2$), 65.6 (*C*(3)), 70.4 (*C*(2)), 81.3 (*C*Me$_3$), 127.4, 128.1, 128.3, 128.7, 129.1, 130.5 (*o*,*m*,*p*-*Ph*), 133.1, 138.5 (*i*-*Ph*), 171.3 (*C*(1)); *m*/*z* (ESI^+) 418 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{27}H_{32}NO_3^+$ ($[M+H]^+$) requires 418.2377; found 418.2374.

4.7. (*RS*,*SR*)-*N*(2)-Benzyl-3-(*tert*-butoxycarbonyl)-4-phenyl-1,2,3,4-tetrahydroisoquinoline 20

Following *general procedure II*, Tf_2O (15 μL, 90 μmol) was reacted with **19** (25 mg, 60 μmol, >99:1 dr) and DTBMP (36 mg, 0.18 mmol) in CH_2Cl_2 (0.6 mL) at rt for 6 h. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 20:1) gave a 59:41 mixture of **16** and **20**, respectively, as a pale yellow oil (20 mg, 84%). Data for **20**: δ_H (500 MHz, $CDCl_3$) 1.21 (9H, s, C*Me*$_3$), 3.77 (1H, d, *J* 13.4, NC*H*$_A$H$_B$Ph), 3.79 (1H, d, *J* 6.1, C(3)*H*), 3.85 (1H, d, *J* 15.3, C(1)*H*$_A$), 3.86 (1H, d, *J* 13.4, NCH$_A$*H*$_B$Ph), 4.16 (1H, d, *J* 15.3, C(1)*H*$_B$), 4.57 (1H, d, *J* 6.1, C(4)*H*), 6.95–7.48 (14H, m, *Ar*, *Ph*); δ_C (125 MHz, $CDCl_3$) 28.0 (C*Me*$_3$), 48.2 (*C*(4)), 52.0 (*C*(1)), 60.0 (NCH_2Ph), 66.6 (*C*(3)), 80.9 (*C*Me$_3$), 125.8, 125.8, 125.9 (*C*(6), *C*(7), *C*(8)), 126.9, 127.2 (*p*-*Ph*), 127.9, 128.0, 128.3, 128.4 (*o*,*m*-*Ph*), 129.0 (*C*(5)), 135.0, 138.3, 140.3, 140.6 (*C*(4a), *C*(8a), *i*-*Ph*), 169.2 (CO_2^tBu).

4.8. *tert*-Butyl (*RS*,*RS*)-2-hydroxy-3-(*N*,*N*-dibenzylamino)-3-[4′-(trifluoromethyl)phenyl]propanoate 29

Following *general procedure I*, BuLi (2.2 M in hexanes, 2.58 mL, 5.67 mmol) and *N*,*N*-dibenzylamine (1.12 mL, 5.85 mmol) were reacted with **24** (1.00 g, 3.66 mmol, >99:1 dr) and (−)-CSO (1.43 g, 6.22 mmol) in THF (20 mL). Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O 5:1) gave **29** as yellow solid (930 mg, 53%, >99:1 dr); mp 84–87 °C; ν_{max} (ATR) 3479 (O–H), 1723 (C=O); δ_H (700 MHz, $CDCl_3$) 1.30 (9H, s, C*Me*$_3$), 2.94 (1H, br s, O*H*), 3.52 (2H, d, *J* 14.0, N(C*H*$_A$H$_B$Ph)$_2$), 3.97 (2H, d, *J* 14.0,

N(CH$_A$H$_B$Ph)$_2$), 4.20 (1H, d, *J* 3.0, C(3)*H*), 4.81 (1H, app s, C(2)*H*), 7.23–7.28 (2H, m, *Ph*), 7.31–7.35 (4H, m, *Ph*), 7.37–7.40 (4H, m, *Ph*), 7.50–7.54 (2H, m, C(2′)*H*, C(6′)*H*), 7.58–7.62 (2H, m, C(3′)*H*, C(5′)*H*); δ_C (175 MHz, $CDCl_3$) 27.7 (*C*Me$_3$), 54.8 (N(*C*H$_2$Ph)$_2$), 63.7 (*C*(3)), 71.9 (*C*(2)), 83.0 (*C*Me$_3$), 124.2 (q, *J* 272.1, *C*F$_3$), 124.8 (q, *J* 3.8, *C*(3′), *C*(5′)), 127.1 (*p-Ph*), 128.3, 128.7 (*o,m-Ph*), 129.7 (q, *J* 32.4, *C*(4′)), 130.1 (*C*(2′), *C*(6′)), 139.5 (*i-Ph*), 140.5 (*C*(1′)), 172.9 (*C*(1)); δ_F (377 MHz, $CDCl_3$) −62.5 (C*F*$_3$); *m/z* (ESI$^+$) 486 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{30}F_3NNaO_3^+$ ([M+Na]$^+$) requires 508.2070; found 508.2073.

4.9. *tert*-Butyl (*RS*,*RS*)-2-hydroxy-3-(*N*,*N*-dibenzylamino)-3-(3′-fluorophenyl)propanoate 30

Following *general procedure I*, BuLi (2.2 M in hexanes, 4.76 mL, 10.5 mmol) and *N*,*N*-dibenzylamine (2.07 mL, 10.8 mmol) were reacted with **25** (1.50 g, 6.75 mmol, >99:1 dr) and (−)-CSO (2.63 g, 11.5 mmol) in THF (42 mL). Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 5:1) gave **30** as a white solid (2.00 g, 68%, >99:1 dr); mp 77–80 °C; ν_{max} (ATR) 3487 (O–H), 2979 (C–H), 1724 (C=O); δ_H (500 MHz, $CDCl_3$) 1.30 (9H, s, C*Me*$_3$), 2.93 (1H, br s, O*H*), 3.51 (2H, d, *J* 14.0, N(C*H*$_A$H$_B$Ph)$_2$), 3.98 (2H, d, *J* 14.0, N(CH$_A$*H*$_B$Ph)$_2$), 4.12 (1H, d, *J* 3.9, C(3)*H*), 4.77 (1H, d, *J* 3.9, C(2)*H*), 6.97–7.42 (14H, m, *Ar*, *Ph*); δ_C (125 MHz, $CDCl_3$) 27.7 (*C*Me$_3$), 54.8 (N(*C*H$_2$Ph)$_2$), 63.7 (*C*(3)), 72.3 (*C*(2)), 82.9 (*C*Me$_3$), 114.4 (d, *J* 21.0, *Ar*), 116.8 (d, *J* 21.9, *Ar*), 125.5 (d, *J* 2.9, *C*(6′)), 127.0, 128.2, 128.8 (*o,m,p-Ph*), 129.3 (d, *J* 7.6, *C*(5′)), 138.8 (d, *J* 6.7, *C*(1′)), 139.5 (*i-Ph*), 162.5 (d, *J* 245.1, *C*(3′)), 172.8 (*C*(1)); δ_F (377 MHz, $CDCl_3$) −113.2 (C(3′)*F*); *m/z* (ESI$^+$) 436 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{27}H_{31}FNO_3^+$ ([M+H]$^+$) requires 436.2282; found 436.2279.

4.10. *tert*-Butyl (*RS*,*RS*)-2-hydroxy-3-(*N*,*N*-dibenzylamino)-3-(3′-methoxyphenyl)propanoate 31

Following *general procedure I*, BuLi (2.2 M in hexanes, 4.51 mL, 9.93 mmol) and *N*,*N*-dibenzylamine (1.97 mL, 10.25 mmol) were reacted with **26** (1.50 g, 6.41 mmol, >99:1 dr) and (−)-CSO (2.50 g, 10.9 mmol) in THF (40 mL). Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 5:1) gave **31** as a pale yellow solid (1.05 g, 37%, >99:1 dr); mp 112–115 °C; ν_{max} (ATR) 3487 (O–H), 1724 (C=O); δ_H (500 MHz, $CDCl_3$) 1.33 (9H, s, C*Me*$_3$), 3.50 (2H, d, *J* 14.0, N(C*H*$_A$H$_B$Ph)$_2$), 3.81 (3H, s, O*Me*), 3.99 (2H, d, *J* 14.0, N(CH$_A$*H*$_B$Ph)$_2$), 4.11 (1H, d, *J* 4.4, C(3)*H*), 4.77 (1H, d, *J* 4.4, C(2)*H*), 6.83–7.44 (14H, m, *Ar*, *Ph*); δ_C (125 MHz, $CDCl_3$) 27.8 (*C*Me$_3$), 54.8 (N(*C*H$_2$Ph)$_2$), 55.1 (O*Me*), 64.4 (*C*(3)), 72.5 (*C*(2)), 82.6 (*C*Me$_3$), 112.8 (*C*(4′)), 115.7 (*C*(2′)), 122.2 (*C*(6′)), 126.8 (*C*(5′)), 128.2, 128.8, 128.9 (*o,m,p-Ph*), 137.4 (*C*(1′)), 139.7 (*i-Ph*), 159.4 (*C*(3′)), 172.9 (*C*(1)); *m/z* (ESI$^+$) 448 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{34}NO_4^+$ ([M+H]$^+$) requires 448.2482; found 448.2485.

4.11. *tert*-Butyl (*RS*,*RS*)-2-hydroxy-3-(*N*,*N*-dibenzylamino)-3-(4′-fluorophenyl)propanoate 32

Following *general procedure I*, BuLi (2.2 M in hexanes, 3.17 mL, 6.98 mmol) and *N*,*N*-dibenzylamine (1.38 mL, 7.20 mmol) were reacted with **27** (1.00 g, 4.50 mmol, >99:1 dr) and (−)-CSO (1.76 g, 7.65 mmol) in THF (28 mL). Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 8:1) gave **32** as a white solid (1.35 g, 69%, >99:1 dr); mp 113–116 °C; ν_{max} (ATR) 3483 (O–H), 2978 (C–H), 1723 (C=O); δ_H (700 MHz, $CDCl_3$) 1.29 (9H, s, C*Me*$_3$), 2.92 (1H, br s, O*H*), 3.48 (2H, d, *J* 14.0, N(C*H*$_A$H$_B$Ph)$_2$), 3.98 (2H, d, *J* 14.0, N(CH$_A$*H*$_B$Ph)$_2$), 4.12 (1H, d, *J* 3.9, C(3)*H*), 4.78 (1H, app s, C(2)*H*), 7.03 (2H, app t, *J* 8.7, *Ar*, *Ph*), 7.23–7.40 (12H, m, *Ar*, *Ph*); δ_C (175 MHz, $CDCl_3$) 27.7 (*C*Me$_3$), 54.8 (N(*C*H$_2$Ph)$_2$), 63.5 (*C*(3)), 72.5 (*C*(2)), 82.7 (*C*Me$_3$), 114.8 (d, *J* 21.0, *C*(3′), *C*(5′)), 126.9, 128.2, 128.8 (*o,m,p-Ph*), 131.5 (d, *J* 7.6, *C*(2′), *C*(6′)), 131.8 (d, *J* 3.2, *C*(1′)), 139.7 (*i-Ph*), 162.2 (d, *J* 246.1, *C*(4′)), 172.9 (*C*(1)); δ_F (377 MHz, $CDCl_3$) −114.9 (C(4′)*F*); *m/z* (ESI$^+$) 436 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{27}H_{31}FNO_3^+$ ([M+H]$^+$) requires 436.2282; found 436.2286.

4.12. *tert*-Butyl (*RS*,*RS*)-2-hydroxy-3-(*N*,*N*-dibenzylamino)-3-(4′-methoxyphenyl)propanoate 33

Following *general procedure I*, BuLi (2.2 M in hexanes, 4.51 mL, 9.93 mmol) and *N*,*N*-dibenzylamine (1.97 mL, 10.3 mmol) were reacted with **28** (1.50 g, 6.41 mmol, >99:1 dr) and (−)-CSO (2.50 g, 10.9 mmol) in THF (40 mL). Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 5:1) gave **33** as a white solid (1.93 g, 67%, >99:1 dr); mp 100–103 °C; ν_{max} (ATR) 3483 (O–H), 1724 (C=O); δ_H (500 MHz, $CDCl_3$) 1.31 (9H, s, C*Me*$_3$), 3.44 (2H, d, *J* 14.0, N(C*H*$_A$H$_B$Ph)$_2$), 3.82 (3H, s, O*Me*), 3.98 (2H, d, *J* 14.0, N(CH$_A$*H*$_B$Ph)$_2$), 4.07 (1H, d, *J* 4.4, C(3)*H*), 4.75 (1H, d, *J* 4.4, C(2)*H*), 6.89 (2H, d, *J* 8.7, C(3′)*H*, C(5′)*H*), 7.21–7.42 (12H, m, *Ar*, *Ph*); δ_C (125 MHz, $CDCl_3$) 27.7 (*C*Me$_3$), 54.8 (N(*C*H$_2$Ph)$_2$), 55.2 (O*Me*), 63.8 (*C*(3)), 72.9 (*C*(2)), 82.5 (*C*Me$_3$), 113.3 (*C*(3′), *C*(5′)), 126.8, 127.7, 128.1, 128.8 (*C*(2′), *C*(6′), *o,m,p-Ph*), 131.1 (*C*(1′)), 139.8 (*i-Ph*), 158.9 (*C*(4′)), 173.0 (*C*(1)); *m/z* (ESI$^+$) 448 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{34}NO_4^+$ ([M+H]$^+$) requires 448.2482; found 448.2481.

4.13. (*RS*,*RS*)-*N*(2)-Benzyl-3-(*tert*-butoxycarbonyl)-4-[4′-(trifluoromethyl)phenyl]-1,2,3,4-tetrahydroisoquinoline 34

Following *general procedure II*, Tf_2O (0.10 mL, 0.618 mmol) was reacted with **29** (200 mg, 0.412 mmol, >99:1 dr) and DTBMP (254 mg, 1.24 mmol) in CH_2Cl_2 (5.2 mL) at 40 °C for 6 h, which gave an 80:20 mixture of **34** and **39**, respectively. Purification by flash column chromatography (eluent 30–40 °C petrol/Et_2O, 20:1) gave **34** as a colourless viscous oil (120 mg, 62%, >99:1 dr); ν_{max} (ATR) 1724 (C=O); δ_H (400 MHz, $CDCl_3$) 1.39 (9H, s, C*Me*$_3$), 3.52 (1H, d, *J* 2.3, C(3)*H*), 3.86–3.96 (2H, m, NC*H*$_2$Ph), 3.98 (1H, d, *J* 15.9, C(1)*H*$_A$), 4.12 (1H, d, *J* 15.9, C(1)*H*$_B$), 4.56 (1H, app s, C(4)*H*), 6.91–7.00 (3H, m, C(5)*H*, *Ar*), 7.07–7.25 (8H, m, *Ar*), 7.51 (2H, d, *J* 8.1, C(3′)*H*, C(5′)*H*); δ_C (100 MHz, $CDCl_3$) 28.2 (*C*Me$_3$), 47.4 (*C*(4)), 50.9 (*C*(1)), 59.3 (NC*H*$_2$Ph), 65.7 (*C*(3)), 81.6 (*C*Me$_3$), 124.3 (q, *J* 271.8, *C*F$_3$), 124.7 (q, *J* 3.7, *C*(3′), *C*(5′)), 126.2, 126.5, 126.5, 127.0, 128.1 (*Ar*), 128.5 (q, *J* 210.2, *C*(4′)), 128.6, 129.4 (*Ar*), 129.6 (*C*(5)), 134.1 (*C*(4a)), 134.8 (*C*(8a)), 138.2 (*i-Ph*), 148.9 (*C*(1′)), 170.9 (*C*O$_2^t$Bu); δ_F (472 MHz, $CDCl_3$) −62.3 (C*F*$_3$); *m/z* (ESI$^+$) 468 ([M+H]$^+$, 100%), HRMS (ESI$^+$) $C_{28}H_{29}F_3NO_2^+$ ([M+H]$^+$) requires 468.2145; found 468.2130.

4.14. (*RS*,*RS*)-*N*(2)-Benzyl-3-(*tert*-butoxycarbonyl)-4-(3′-fluorophenyl)-1,2,3,4-tetrahydroisoquinoline 35

Following *general procedure II*, Tf_2O (60 μL, 0.35 mmol) was reacted with **30** (100 mg, 0.23 mmol, >99:1 dr) and DTBMP (142 mg, 0.69 mmol) in CH_2Cl_2 (2.9 mL) at rt for 6 h, which gave a 77:23 mixture of **35** and **40**, respectively. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 10:1) gave **35** as a yellow oil (56 mg, 58%, >99:1 dr); ν_{max} (ATR) 2976 (C–H), 1723 (C=O); δ_H (500 MHz, $CDCl_3$) 1.39 (9H, s, C*Me*$_3$), 3.56 (1H, d, *J* 2.5, C(3)*H*), 3.90 (1H, d, *J* 13.4, NC*H*$_A$H$_B$Ph), 3.96 (1H, d, *J* 15.6, C(1)*H*$_A$), 3.97 (1H, d, *J* 13.4, NCH$_A$*H*$_B$Ph), 4.08 (1H, d, *J* 15.6, C(1)*H*$_B$), 4.49 (1H, d, *J* 2.5, C(4)*H*), 6.84–7.26 (13H, m, *Ar*, *Ph*); δ_C (125 MHz, $CDCl_3$) 28.2 (*C*Me$_3$), 47.4 (*C*(4)), 50.9 (*C*(1)), 59.5 (NC*H*$_2$Ph), 66.3 (*C*(3)), 81.5 (*C*Me$_3$), 113.1 (d, *J* 21.0, *Ar*), 116.2 (d, *J* 21.9, *Ar*), 124.6 (d, *J* 1.9, *C*(6′)), 126.2, 126.4, 127.0, 128.1, 128.1, 128.7, (*C*(6), *C*(7), *C*(8), *o,m,p-Ph*), 129.1 (d, *J* 8.6, *C*(5′)), 129.7 (*C*(5)), 134.4 (*C*(4a)), 134.7 (*C*(8a)), 138.4 (*i-Ph*), 147.4 (d, *J* 6.7, *C*(1′)), 162.6 (d, *J* 245.1, *C*(3′)), 171.0 (*C*O$_2^t$Bu); δ_F (377 MHz, $CDCl_3$) −114.3 (C(3′)*F*); *m/z* (ESI$^+$) 418 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{27}H_{29}FNO_2^+$ ([M+H]$^+$) requires 418.2177; found 418.2174.

4.15. (*RS*,*RS*)-*N*(2)-Benzyl-3-(*tert*-butoxycarbonyl)-4-(3′-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline 36

Following *general procedure II*, Tf_2O (60 μL, 0.34 mmol) was reacted with **31** (100 mg, 0.22 mmol, >99:1 dr) and DTBMP (138 mg, 0.67 mmol) in CH_2Cl_2 (2.6 mL) at rt for 6 h. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 10:1) gave **36** as a pale yellow oil (54 mg, 57%, >99:1 dr); ν_{max} (ATR) 2976 (C–H), 2931 (C–H), 1723 (C=O); δ_H (500 MHz, $CDCl_3$) 1.39 (9H, s, CMe_3), 3.61 (1H, d, *J* 3.1, C(3)*H*), 3.76 (3H, s, O*Me*), 3.88 (1H, d, *J* 13.6, NC$H_A$$H_B$Ph), 3.92 (1H, d, *J* 15.6, C(1)H_A), 3.96 (1H, d, *J* 13.6, NCH$_A$$H_B$Ph), 4.05 (1H, d, *J* 15.6, C(1)H_B), 4.48 (1H, d, *J* 3.1, C(4)*H*), 6.71–6.81 (3H, m, *Ar*), 6.99 (10H, m, *Ar*, *Ph*); δ_C (125 MHz, $CDCl_3$) 28.2 (CMe_3), 47.8 (*C*(4)), 50.9 (*C*(1)), 55.1 (O*Me*), 59.6 (NCH_2Ph), 67.0 (*C*(3)), 81.3 (CMe_3), 111.6 (*C*(4′)), 115.1 (*C*(2′)), 121.7 (*C*(6′)), 126.0 (*C*(8)), 126.1, 126.2, 128.7, 135.0 (*C*(6), *C*(7), *C*(5′), *p-Ph*), 126.9 (*C*(5)), 128.1, 128.7 (*o*,*m-Ph*), 129.7 (*C*(1′)), 134.6 (*C*(4a)), 138.7 (*i-Ph*), 146.3 (*C*(8a)), 159.3 (*C*(3′)), 171.4 (*C*O_2^{t}Bu); *m/z* (ESI$^+$) 430 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{32}NO_3^+$ ([M+H]$^+$) requires 430.2377; found 430.2381.

4.16. (*RS*,*RS*)-*N*(2)-Benzyl-3-(*tert*-butoxycarbonyl)-4-(4′-fluorophenyl)-1,2,3,4-tetrahydroisoquinoline 37

Following *general procedure II*, Tf_2O (0.12 mL, 0.69 mmol) was reacted with **32** (200 mg, 0.46 mmol, >99:1 dr) and DTBMP (283 mg, 1.38 mmol) in CH_2Cl_2 (2.9 mL) at rt for 6 h. Purification by flash column chromatography (eluent 30–40 °C/Et_2O 20:1) gave **37** as a colourless viscous oil (139 mg, 73%, >99:1 dr); ν_{max} (ATR) 2977 (C–H), 1724 (C=O); δ_H (500 MHz, $CDCl_3$) 1.38 (9H, s, CMe_3), 3.51 (1H, d, *J* 2.9, C(3)*H*), 3.87 (1H, d, *J* 13.4, NC$H_A$$H_B$Ph), 3.93 (1H, d, *J* 15.6, C(1)H_A), 3.96 (1H, d, *J* 13.4, NCH$_A$$H_B$Ph), 4.07 (1H, d, *J* 15.6, C(1)H_B), 4.48 (1H, d, *J* 2.9, C(4)*H*), 6.93–6.98 (3H, m, C(3′)*H*, C(5′)*H*, *Ar*), 7.03–7.08 (3H, m, *Ar*, *Ph*), 7.08–7.13 (3H, m, C(2′)*H*, C(6′)*H*, *Ar*, *Ph*), 7.15 (1H, dd, *J* 7.5, 1.2, *Ar*), 7.17–7.21 (3H, m, *Ar*, *Ph*); δ_C (125 MHz, $CDCl_3$) 28.2 (CMe_3), 47.0 (*C*(4)), 51.0 (*C*(1)), 59.5 (NCH_2Ph), 66.7 (*C*(3)), 81.4 (CMe_3), 114.5 (d, *J* 21.0, *C*(3′), *C*(5′)), 126.1, 126.2, 126.3, 127.0, 129.6 (*C*(5), *C*(6), *C*(7), *C*(8), *p-Ph*), 128.1, 128.7 (*o*,*m-Ph*), 130.5 (d, *J* 7.6, *C*(2′), *C*(6′)), 134.6 (*C*(8a)), 135.0 (*C*(4a)), 138.5 (*i-Ph*), 140.5 (d, *J* 2.9, *C*(1′)), 161.6 (d, *J* 244.1, *C*(4′)), 171.2 (*C*O_2^{t}Bu); δ_F (377 MHz, $CDCl_3$) −117.2 (C(4′)*F*); *m/z* (ESI$^+$) 418 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{27}H_{29}FNO_2^+$ ([M+H]$^+$) requires 418.2177; found 418.2181.

4.17. (*RS*,*RS*)-*N*(2)-Benzyl-3-(*tert*-butoxycarbonyl)-4-(4′-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline 38

Method A: Following *general procedure II*, Tf_2O (60 μL, 0.34 mmol) was reacted **33** (100 mg, 0.22 mmol, >99:1 dr) and DTBMP (138 mg, 0.67 mmol) in CH_2Cl_2 (2.6 mL) at rt for 6 h, which gave **38** in 75:25 dr. Purification via flash column chromatography (30–40 °C petrol/Et_2O, 20:1) gave **38** as a pale brown viscous oil (32 mg, 34%, 75:25 dr); ν_{max} (ATR) 2976 (C–H), 2930 (C–H), 2835 (C–H), 1723 (C=O); δ_H (500 MHz, $CDCl_3$) 1.38 (9H, s, CMe_3), 3.55 (1H, d, *J* 3.3, C(3)*H*), 3.82 (3H, s, O*Me*), 3.86 (1H, d, *J* 13.5, NC$H_A$$H_B$Ph), 3.90 (1H, d, *J* 15.6, C(1)H_A), 3.96 (1H, d, *J* 13.5, NCH$_A$$H_B$Ph), 4.04 (1H, d, *J* 15.6, C(1)H_B), 4.45 (1H, d, *J* 3.3, C(4)*H*), 6.81–6.85 (2H, m, C(3′)*H*, C(5′)*H*), 6.97–7.16 (11H, m, C(5)*H*, C(6)*H*, C(7)*H*, C(8)*H*, C(2′)*H*, C(6′)*H*, *Ph*); δ_C (125 MHz, $CDCl_3$) 28.2 (CMe_3), 47.1 (*C*(4)), 51.0 (*C*(1)), 55.3 (O*Me*), 59.6 (NCH_2Ph), 67.3 (*C*(3)), 81.2 (CMe_3), 113.2 (*C*(3′), *C*(5′)), 126.0, 126.9, 129.6 (*C*(6), *C*(7), *p-Ph*), 126.2 (*C*(8)), 128.1, 128.7 (*o*,*m-Ph*), 130.1 (*C*(2′), *C*(6′)), 131.5 (*C*(5)), 134.5 (*C*(8a)), 135.6 (*C*(4a)), 137.0 (*C*(1′)), 138.7 (*i-Ph*), 158.2 (*C*(4′)), 171.4 (*C*O_2^{t}Bu); *m/z* (ESI$^+$) 430 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{32}NO_3^+$ ([M+H]$^+$) requires 430.2377; found 430.2385.

Method B: Following *general procedure II*, Tf_2O (60 μL, 0.34 mmol) was reacted **33** (100 mg, 0.22 mmol) and DTBMP (138 mg, 0.67 mmol) in CH_2Cl_2 (2.6 mL) at −20 °C for 2.5 h, which gave **38** in 85:15 dr. Purification via flash column chromatography (30–40 °C petrol/Et_2O, 10:1) gave **38** as a pale brown viscous oil (64 mg, 66%, 85:15 dr).

4.18. *tert*-Butyl (*RS*,*RS*)-2-(*N*,*N*-dibenzylamino)-3-hydroxy-3-[4′-(trifluoromethyl)phenyl]propanoate 39

Following *general procedure II*, Tf_2O (30 μL, 0.16 mmol) was reacted with **29** (50 mg, 0.10 mmol, >99:1 dr) and DTBMP (63 mg, 0.31 mmol) in CH_2Cl_2 (1.5 mL) at rt for 6 h. Purification by flash column chromatography (eluent 30–40 °C petrol/EtOAc, 10:1) gave **39** as a colourless viscous oil (18 mg, 35%, >99:1 dr); ν_{max} (ATR) 3448 (O–H), 1722 (C=O); δ_H (500 MHz, $CDCl_3$) 1.66 (9H, s, CMe_3), 2.97 (1H, d, *J* 3.8, O*H*), 3.48 (1H, d, *J* 9.4, C(2)*H*), 3.51 (2H, d, *J* 13.9, N(C$H_A$$H_B$Ph)$_2$), 3.90 (2H, d, *J* 13.9, N(CH$_A$$H_B$Ph)$_2$), 5.03 (1H, dd, *J* 9.4, 3.8, C(3)*H*), 6.95–7.00 (4H, m, *Ph*), 7.15–7.23 (8H, m, C(2′)*H*, C(6′)*H*, *Ph*), 7.51 (2H, d, *J* 8.0, C(3′)*H*, C(5′)*H*); δ_C (125 MHz, $CDCl_3$) 28.6 (CMe_3), 55.2 (N(CH_2Ph)$_2$), 66.6 (*C*(2)), 72.3 (*C*(3)), 82.7 (CMe_3), 124.3 (q, *J* 272.8, CF_3), 124.9 (q, *J* 2.9, *C*(3′), *C*(5′)), 127.2, 128.0 (*o*,*m*,*p-Ph*), 128.2 (*C*(2′), *C*(6′)), 128.8 (*o*,*m*,*p-Ph*), 129.9 (q, *J* 32.0, *C*(4′)), 138.2 (*i-Ph*), 144.9 (*C*(1′)), 171.7 (*C*O_2^{t}Bu); δ_F (472 MHz, $CDCl_3$) −62.4 (CF_3); *m/z* (ESI$^+$) 486 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{31}F_3NO_3^+$ ([M+H]$^+$) requires 486.2251; found 486.2236.

4.19. *tert*-Butyl (*RS*,*RS*)-2-hydroxy-3-[*N*,*N*-bis(4″-methoxybenzyl)amino]-3-(4′-fluorophenyl)propanoate 47

Following *general procedure I*, BuLi (2.2 M in hexanes, 3.17 mL, 6.98 mmol) and *N*,*N*-bis(*p*-methoxybenzyl)amine (1.85 g, 7.20 mmol) were reacted with **27** (1.00 g, 4.50 mmol, >99:1 dr) and (−)-CSO (1.76 g, 7.65 mmol) in THF (26 mL). Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 3:1) gave **47** as a pale yellow solid (1.56 g, 70%, >99:1 dr); mp 100–102 °C; ν_{max} (ATR) 3487 (O–H), 1725 (C=O); δ_H (500 MHz, $CDCl_3$) 1.31 (9H, s, CMe_3), 2.88 (1H, br s, O*H*), 3.39 (2H, d, *J* 13.8, N(C$H_A$$H_B$Ar)$_2$), 3.80 (6H, s, 2×O*Me*), 3.86 (2H, d, *J* 13.8, N(CH$_A$$H_B$Ar)$_2$), 4.09 (1H, d, *J* 3.9, C(3)*H*), 4.74 (1H, d, *J* 3.9, C(2)*H*), 6.86 (4H, d, *J* 8.7, *Ar*), 7.02 (2H, t, *J* 8.7, C(2′)*H*, C(6′)*H*), 7.17 (2H, app s, *Ar*), 7.24–7.28 (4H, m, *Ar*); δ_C (125 MHz, $CDCl_3$) 27.8 (CMe_3), 53.8 (N(CH_2Ar)$_2$), 55.3 (2×O*Me*), 63.5 (*C*(3)), 72.3 (*C*(2)), 82.7 (CMe_3), 113.5 (*C*(3″), *C*(5″)), 114.8 (d, *J* 21.0, *C*(2′), *C*(6′)), 129.8 (*C*(2″), *C*(6″)), 131.4 (d, *J* 7.6, *C*(3′), *C*(5′)) 131.7 (C(1″)), 132.0 (d, *J* 3.8, *C*(1′)), 158.6 (C(4″)), 162.2 (d, *J* 246.1, *C*(4′)), 172.9 (*C*(1)); δ_F (377 MHz, $CDCl_3$) −115.0 (C(4′)*F*), *m/z* (ESI$^+$) 496 ([M+H]$^+$, 100%), HRMS (ESI$^+$) $C_{29}H_{35}FNO_5^+$ ([M+H]$^+$) requires 496.2494; found 496.2500.

4.20. *tert*-Butyl (*RS*)-3-[*N*,*N*-bis(3″-methoxybenzyl)amino]-3-(4′-fluorophenyl)propanoate 48

BuLi (2.2 M in hexanes, 1.58 mL, 3.49 mmol) was added dropwise to a stirred solution of *N*,*N*-bis(*m*-methoxybenzyl)amine (926 mg, 3.60 mmol) in THF (7.5 mL) at −78 °C and the resultant mixture was stirred at −78 °C for 30 min. A solution of **27** (500 mg, 2.25 mmol, >99:1 dr) in THF (7.5 mL) at −78 °C was added dropwise via cannula and the resultant mixture was stirred at −78 °C for 2 h. Satd aq NH_4Cl (5 mL) was added and the resultant mixture was left to warm to rt then concentrated in vacuo. The residue was partitioned between CH_2Cl_2 (50 mL) and 10% aq citric acid (30 mL), and the aqueous layer was extracted with CH_2Cl_2 (3×30 mL). The combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (30 mL) and brine (30 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 10:1) gave **48** as a pale yellow viscous oil (840 mg, 78%); ν_{max} (ATR) 2976 (C–H), 2835 (C–H), 1726 (C=O); δ_H (500 MHz, $CDCl_3$) 1.32 (9H, s, CMe_3), 2.71 (1H, dd, *J* 14.6, 9.3,

C(2)H_A), 2.96 (1H, dd, *J* 14.6, 6.3, C(2)H_B), 3.29 (2H, d, *J* 13.8, N(C$H_A$$H_B$Ar)$_2$), 3.66 (2H, d, *J* 13.8, N(CH$_A$$H_B$Ar)$_2$), 3.80 (6H, s, 2×O*Me*), 4.28 (1H, dd, *J* 9.3, 6.3, C(3)*H*), 6.75–6.80 (2H, m, *Ar*), 6.92–6.95 (4H, m, *Ar*), 7.02–7.08 (2H, m, C(3′)*H*, C(5′)*H*), 7.19–7.29 (4H, m, C(2′)*H*, C(6′)*H*, *Ar*); δ_C (125 MHz, $CDCl_3$) 27.9 (C*Me*$_3$), 37.1 (*C*(2)), 53.9 (N(*C*H$_2$Ar)$_2$), 55.1 (2×O*Me*), 58.7 (*C*(3)), 80.6 (*C*Me$_3$), 112.3, 114.3, 121.1 (*Ar*), 114.8 (d, *J* 21.0, *C*(3′), *C*(5′)), 129.2 (*Ar*), 130.1 (d, *J* 7.6, *C*(2′), *C*(6′)), 134.4 (d, *J* 2.9, *C*(1′)), 141.3, 159.6 (*Ar*), 162.0 (d, *J* 246.1, *C*(4′)), 170.8 (*C*(1)); δ_F (377 MHz, $CDCl_3$) −40.1 (C(4′)*F*); *m/z* (ESI$^+$) 480 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{29}H_{35}FNO_4^+$ ([M+H]$^+$) requires 480.2545; found 480.2545.

4.21. *tert*-Butyl (*RS*,*RS*)-2-hydroxy-3-[*N*,*N*-bis(3″-methoxybenzyl)amino]-3-(4′-fluorophenyl)propanoate 49

LiHMDS (1.0 M in THF, 1.25 mL, 1.25 mmol) was added to a stirred solution of **48** (400 mg, 0.834 mmol, >99:1 dr) in THF (4.2 mL) at 0 °C and the resultant mixture was stirred at 0 °C for 30 min. The reaction mixture was then cooled to −78 °C and (−)-CSO (383 mg, 1.67 mmol) was added. The reaction mixture was stirred at −78 °C for 1.5 h then allowed to warm to rt. NH_4Cl (5 mL) was then added and the reaction mixture was concentrated in vacuo. The residue was partitioned between CH_2Cl_2 (50 mL) and H_2O (30 mL), and the aqueous layer was extracted with CH_2Cl_2 (3×30 mL). The combined organic extracts were then dried and concentrated in vacuo. The residue was then triturated with cold Et_2O (100 mL) and filtered. The resultant solution was then dried and concentrated in vacuo, which gave **49** in 83:17 dr. Purification via flash column chromatography (toluene/Et_2O, 15:1) gave **49** as colourless oil (98 mg, 24%, >99:1 dr); ν_{max} (ATR) 3483 (O–H), 1723 (C=O); δ_H (500 MHz, $CDCl_3$) 1.28 (9H, s, C*Me*$_3$), 2.94 (1H, d, *J* 4.3, O*H*), 3.47 (2H, d, *J* 14.0, N(C$H_A$$H_B$Ar)$_2$), 3.81 (6H, s, 2×O*Me*), 3.96 (2H, d, *J* 14.0, N(CH$_A$*H*-$_B$Ar)$_2$), 4.14 (1H, d, *J* 3.8, C(3)*H*), 4.77 (1H, app d, *J* 3.8, C(2)*H*), 6.77–6.81 (2H, m, *Ar*), 6.95–6.99 (4H, m, *Ar*), 7.00–7.05 (2H, m, C(3′)*H*, C(5′)*H*), 7.21–7.26 (2H, m, *Ar*), 7.35–7.40 (2H, m, C(2′)*H*, C(6′)*H*); δ_C (125 MHz, $CDCl_3$) 27.7 (C*Me*$_3$), 54.8 (N(*C*H$_2$Ar)$_2$), 55.1 (2×O*Me*), 63.7 (*C*(3)), 72.6 (*C*(2)), 82.8 (*C*Me$_3$), 112.2, 114.3, 121.0 (*Ar*), 114.8 (d, *J* 21.0, *C*(3′), *C*(5′)), 129.2 (*Ar*), 131.5 (d, *J* 7.6, *C*(2′), *C*(6′)), 131.9 (d, *J* 3.8, *C*(1′)), 141.4, 159.7 (*Ar*), 162.2 (d, *J* 246.1, *C*(4′)), 172.8 (*C*(1)); δ_F (377 MHz, $CDCl_3$) −114.9 (C(4′)*F*); *m/z* (ESI$^+$) 496 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{29}H_{35}FNO_5^+$ ([M+H]$^+$) requires 496.2494; found 496.2486.

4.22. (*RS*,*RS*)-*N*(2)-(3″-Methoxybenzyl)-3-(*tert*-butoxycarbonyl)-4-(4′-fluorophenyl)-7-methoxy-1,2,3,4-tetrahydroisoquinoline 50 and (*RS*,*RS*)-*N*(2)-(3″-methoxybenzyl)-3-(*tert*-butoxycarbonyl)-4-(4′-fluorophenyl)-5-methoxy-1,2,3,4-tetrahydroisoquinoline 51

Following *general procedure II*, Tf_2O (30 μL, 0.20 mmol) was reacted with **49** (65 mg, 0.13 mmol, >99:1 dr) and DTBMP (81 mg, 0.39 mmol) in CH_2Cl_2 (1.65 mL) at rt for 6 h, which gave a 77:23 mixture of **50** and **51**, respectively. Purification via flash column chromatography (30–40 °C petrol/Et_2O, 10:1) gave **50** as a colourless oil (21.3 mg, 32%, >99:1 dr); ν_{max} (ATR) 2933 (C–H), 2836 (C–H), 1725 (C=O); δ_H (500 MHz, $CDCl_3$) 1.40 (9H, s, C*Me*$_3$), 3.53 (1H, d, *J* 2.8, C(3)*H*), 3.69 (3H, s, C(3″)O*Me*), 3.77 (3H, s, C(7)O*Me*), 3.83 (1H, d, *J* 13.5, NC$H_A$$H_B$Ar), 3.91 (1H, d, *J* 15.7, C(1)H_A), 3.93 (1H, d, *J* 13.5, NCH$_A$$H_B$Ar), 4.05 (1H, d, *J* 15.7, C(1)H_B), 4.43 (1H, d, *J* 2.8, C(4)*H*), 6.59 (1H, d, *J* 2.5, C(8)*H*), 6.63–6.71 (3H, m, C(6)*H*, C(2″)*H*, C(6″)*H*), 6.75 (1H, dd, *J* 8.2, 2.2, C(4″)*H*), 6.88 (1H, d, *J* 8.5, C(5)*H*), 6.92–6.97 (2H, m, C(3′)*H*, C(5′)*H*), 7.09–7.13 (3H, m, C(2′)*H*, C(6′)*H*, C(5″)*H*); δ_C (125 MHz, $CDCl_3$) 28.2 (C*Me*$_3$), 46.4 (*C*(4)), 51.1 (*C*(1)), 55.0 (C(3″)O*Me*), 55.1 (C(7)O*Me*). 59.6 (NCH$_2$Ar), 66.9 (*C*(3)), 81.4 (*C*Me$_3$), 110.3 (*C*(8)), 112.9 (*C*(6)), 113.1 (*C*(4″)), 113.7 (*C*(2″)), 114.5 (d, *J* 21.0, *C*(3′), *C*(5′)), 121.0 (*C*(6″)), 127.1 (*C*(4a)), 129.0 (*C*(5″)), 130.4 (d, *J* 8.6, *C*(2′), *C*(6′)), 130.6 (*C*(5)), 135.8 (*C*(8a)), 140.2 (*C*(1″)), 140.9 (d, *J* 3.8, *C*(1′)), 157.9 (*C*(7)), 159.6 (*C*(3″)), 161.5 (d, *J* 244.1, *C*(4′)), 171.3 (*C*O$_2$^{t}Bu); δ_F (377 MHz, $CDCl_3$) −117.3 (C(4′)*F*); *m/z* (ESI$^+$) 478 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{29}H_{33}FNO_4^+$ ([M+H]$^+$) requires 478.2388; found 478.2381. Further elution gave **51** as a colourless oil (7 mg, 10%, >99:1 dr); ν_{max} (ATR) 2918 (C–H), 1724 (C=O); δ_H (500 MHz, $CDCl_3$) 1.38 (9H, s, C*Me*$_3$), 3.52 (1H, d, *J* 1.7, C(3)*H*), 3.63 (3H, s, C(5)O*Me*), 3.67 (3H, s, C(3″)O*Me*), 3.87 (1H, d, *J* 13.4, NC$H_A$$H_B$Ar), 3.92 (1H, d, *J* 13.4, NCH$_A$$H_B$Ar), 3.98 (1H, d, *J* 15.8, C(1)H_A), 4.06 (1H, d, *J* 15.8, C(1)H_B), 4.65 (1H, app s, C(4)*H*), 6.58–6.65 (3H, m, C(6)*H*, C(2″)*H*, C(6″)*H*), 6.68–6.74 (2H, m, C(8)*H*, *Ar*), 6.88–6.93 (2H, m, C(3′)*H*, C(5′)*H*), 7.06–7.18 (4H, m, C(7)*H*, C(2′)*H*, C(6′)*H*, *Ar*); δ_C (125 MHz, $CDCl_3$) 28.2 (C*Me*$_3$), 41.5 (*C*(4)), 50.4 (*C*(1)), 55.0 (C(3″)O*Me*), 55.4 (C(5)O*Me*), 59.2 (NCH$_2$Ar), 65.9 (*C*(3)), 81.2 (*C*Me$_3$), 107.8 (*C*(6)), 112.9, 129.0 (*C*(4″), *C*(5″)), 113.6 (*C*(2″)), 114.1 (d, *J* 21.0, *C*(3′), *C*(5′)), 118.3 (*C*(8)), 120.9 (*C*(6″)), 123.7 (*C*(4a)), 127.0 (*C*(7)), 130.0 (d, *J* 7.6, *C*(2′), *C*(6′)), 136.1 (*C*(8a)), 140.4 (*C*(1″)), 140.5 (d, *J* 2.9, *C*(1′)), 157.2 (*C*(5)), 159.6 (*C*(3″)), 161.3 (d, *J* 243.2, *C*(4′)), 171.4 (*C*O$_2$^{t}Bu); δ_F (377 MHz, $CDCl_3$) −118.0 (C(4′)*F*); *m/z* (ESI$^+$) 478 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{29}H_{33}FNO_4^+$ ([M+H]$^+$) requires 478.2388; found 478.2381.

4.23. *tert*-Butyl (*RS*,*SR*)-2-[*N*-(4‴-methoxybenzyl)amino]-3-(4″-methoxyphenyl)-3-(4′-fluorophenyl)propanoate 52

Following *general procedure II*, Tf_2O (50 μL, 0.30 mmol) was reacted with **47** (100 mg, 0.20 mmol, >99:1 dr) and DTBMP (124 mg, 0.61 mmol) in CH_2Cl_2 (2.5 mL) at rt for 6 h. Purification via flash column chromatography (eluent petrol 30–40 °C/Et_2O, 3:1) gave **52** as a white solid (50 mg, 53%, >99:1 dr); mp 85–86 °C; ν_{max} (ATR) 3320 (N–H), 1723 (C=O); δ_H (500 MHz, $CDCl_3$) 1.25 (1H, s, C*Me*$_3$), 1.75 (1H, br s, N*H*), 3.55 (1H, d, *J* 13.1, NC$H_A$$H_B$Ar), 3.75–3.81 (5H, m, NCH$_A$$H_B$Ar, C(2)*H*, O*Me*), 3.82 (3H, s, O*Me*), 4.08 (1H, d, *J* 9.6, C(3)*H*), 6.78–6.94 (6H, m, *Ar*), 7.08 (4H, m, *Ar*), 7.21–7.25 (2H, m, *Ar*); δ_C (125 MHz, $CDCl_3$) 27.8 (C*Me*$_3$), 51.4 (NCH$_2$Ar), 53.1 (*C*(3)), 55.2, 55.3 (2×O*Me*), 64.6 (*C*(2)), 81.1 (*C*Me$_3$), 113.6, 113.8 (*C*(3″), *C*(5″), *C*(3‴), *C*(5‴)), 114.9 (d, *J* 21.0, *C*(3′), *C*(5′)), 129.3, 129.7 (*C*(2″), *C*(6″), *C*(2‴), *C*(6‴)), 130.0 (d, *J* 8.6, *C*(2′), *C*(6′)), 131.6, 133.1 (*C*(1″), *C*(1‴)), 137.8 (d, *J* 2.9, *C*(1′)), 158.3, 158.7 (*C*(4″), *C*(4‴)), 161.6 (d, *J* 245.1, *C*(4′)), 173.3 (*C*(1)); δ_F (377 MHz, $CDCl_3$) −116.6 (C(4′)*F*); *m/z* (ESI$^+$) 466 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{33}FNO_4^+$ ([M+H]$^+$) requires 466.2388; found 466.2375.

4.24. *tert*-Butyl (*R*,*R*,*R*)-2-hydroxy-3-[*N*-methyl-*N*-(α-methylbenzyl)amino]-3-(4′-fluorophenyl)propanoate 57

Following *general procedure I*, BuLi (2.2 M in hexanes, 3.17 mL, 6.98 mmol) and (*R*)-*N*-methyl-*N*-(α-methylbenzyl)amine[32] (970 mg, 7.20 mmol, >99:1 er) were reacted with **27** (1.00 g, 4.50 mmol, >99:1 dr) and (−)-CSO (1.76 g, 7.65 mmol) in THF (26 mL). Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 3:1) gave **57** as a pale yellow solid (729 mg, 43%, >99:1 dr); mp 81–84 °C; $[\alpha]_D^{20}$ +59.0 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3492 (O–H), 2977 (C–H), 1726 (C=O); δ_H (500 MHz, $CDCl_3$) 1.30 (3H, d, *J* 6.8, C(α)*Me*), 1.32 (9H, s, C*Me*$_3$), 2.24 (3H, s, N*Me*), 3.77 (1H, q, *J* 6.8, C(α)*H*), 3.98 (1H, d, *J* 3.9, C(3)*H*), 4.65 (1H, d, *J* 3.9, C(2)*H*), 6.99–7.05 (2H, m, C(3′)*H*, C(5′)*H*), 7.20–7.25 (1H, m, *p*-*Ph*), 7.28–7.39 (4H, m, *o*,*m*-*Ph*), 7.46–7.51 (2H, m, C(2′)*H*, C(6′)*H*); δ_C (125 MHz, $CDCl_3$) 11.7 (C(α)*Me*), 27.9 (C*Me*$_3$), 33.0 (N*Me*), 56.8 (*C*(α)), 67.2 (*C*(3)), 71.0 (*C*(2)), 82.5 (*C*Me$_3$), 115.0 (d, *J* 21.0, *C*(3′), *C*(5′)), 126.7 (*p*-*Ph*), 127.5, 128.1 (*o*,*m*-*Ph*), 131.0 (d, *J* 7.6, *C*(2′), *C*(6′)), 133.0 (d, *J* 3.8, *C*(1′)), 143.7 (*i*-*Ph*), 162.4 (d, *J* 246.1, *C*(4′)), 171.7 (*C*(1)); δ_F (377 MHz, $CDCl_3$) −114.3 (C(4′)*F*); *m/z* (ESI$^+$) 374 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{22}H_{29}FNO_3^+$ ([M+H]$^+$) requires 374.2126; found 374.2125.

4.25. *tert*-Butyl (2*S*,3*S*,α*R*)-2-[*N*-methyl-*N*-(α-methylbenzyl)-amino]-3-hydroxy-3-(4′-fluorophenyl)propanoate 58

Following *general procedure II*, Tf_2O (70 μL, 0.40 mmol) was reacted with **57** (100 mg, 0.27 mmol, >99:1 dr) and DTBMP (165 mg, 0.80 mmol) in CH_2Cl_2 (3.4 mL) at rt for 6 h. Purification by flash column chromatography (eluent 30–40 °C petrol/Et_2O, 5:1) gave **58** as a pale brown oil (35 mg, 35%, >99:1 dr); $[\alpha]_D^{20}$ −52.1 (*c* 0.3 in $CHCl_3$); ν_{max} (ATR) 3469 (O—H), 2976 (C—H), 1723 (C=O); δ_H (500 MHz, $CDCl_3$) 1.12 (3H, d, *J* 6.6, C(α)*Me*), 1.54 (9H, s, C*Me*$_3$), 2.11 (3H, s, N*Me*), 3.38 (1H, br s, O*H*), 3.67 (1H, q, *J* 6.6, C(α)*H*), 3.70 (1H, d, *J* 8.7, C(2)*H*), 5.00 (1H, d, *J* 8.7, C(3)*H*), 6.86 (2H, d, *J* 6.0, C(3′)*H*, C(5′)*H*), 7.04–7.40 (7H, m, C(2′)*H*, C(6′)*H*, *Ph*); δ_C (125 MHz, $CDCl_3$) 20.5 (C(α)*Me*), 28.4 (C*Me*$_3$), 35.5 (N*Me*), 62.9 (*C*(α)), 67.5 (*C*(2)), 71.9 (*C*(3)), 82.2 (*C*Me$_3$), 114.7 (d, *J* 21.3, *C*(3′), *C*(5′)), 126.7, 127.0, 128.1 (*o*,*m*,*p*-*Ph*), 128.6 (d, *J* 8.3, *C*(2′), *C*(6′)), 137.4 (d, *J* 2.8, *C*(1′)), 145.6 (*i*-*Ph*), 162.3 (d, *J* 246.0, *C*(4′)), 172.5 (*C*(1)); δ_F (377 MHz, $CDCl_3$) −115.2 (C(4′)*F*); *m*/*z* (ESI$^+$) 396 ([M+Na]$^+$, 16%), 374 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{22}H_{28}FNNaO_3^+$ ([M+Na]$^+$) requires 396.1945; found 396.1947.

4.26. (1*R*,3*S*,4*S*)-1,*N*(2)-Dimethyl-3-(*tert*-butoxycarbonyl)-4-(4′-fluorophenyl)-1,2,3,4-tetrahydroisoquinoline 59 and *tert*-butyl (*S*,*S*)-2-(*N*-methyl-*N*-trifylamino)-3-(4′-fluorophenyl)-3-(2″-vinylphenyl)propanoate 60

Following *general procedure II*, Tf_2O (70 μL, 0.40 mmol) was reacted with **57** (100 mg, 0.27 mmol, >99:1 dr) and DTBMP (165 mg, 0.80 mmol) in CH_2Cl_2 (3.4 mL) at 40 °C for 6 h, which gave a 27:30:43 mixture of **58**, **59** and **60**, respectively. Purification by flash column chromatography (eluent 30–40 °C petrol/Et_2O, 8:1) gave **60** as a white solid (39 mg, 30%, >99:1 dr); mp 107–108 °C; $[\alpha]_D^{20}$ +12.5 (*c* 0.3 in $CHCl_3$); ν_{max} (ATR) 2982 (C—H), 2933 (C—H), 1732 (C=O), 1605 (C=C); δ_H (700 MHz, $CDCl_3$) 1.16 (9H, s, C*Me*$_3$), 2.96 (3H, s, N*Me*), 4.72 (1H, d, *J* 12.1, C(3)*H*), 5.15 (1H, d, *J* 12.1, C(2)*H*), 5.39 (1H, app d, *J* 11.0, CH=CH$_A$H$_B$), 5.56 (1H, app d, *J* 17.1, CH=CH$_A$H$_B$), 6.97 (2H, t, *J* 8.5, *Ar*), 7.07 (1H, dd, *J* 17.1, 11.0, C*H*=CH$_A$H$_B$), 7.24–7.61 (6H, m, *Ar*); δ_C (175 MHz, $CDCl_3$) 27.4 (C*Me*$_3$), 31.4 (N*Me*), 46.0 (*C*(3)), 62.6 (*C*(2)), 83.0 (*C*Me$_3$), 115.6 (d, *J* 20.4, *C*(3′), *C*(5′)), 118.4 (CH=*C*H$_2$), 119.7 (q, *J* 323.4, *C*F$_3$), 126.5, 127.8, 127.9, 128.5 (*C*(3″), *C*(4″), *C*(5″), *C*(6″)), 130.8 (d, *J* 7.6, *C*(2′), *C*(6′)), 133.7 (d, *J* 3.8, *C*(1′)), 134.2 (*C*(1″)), 135.0 (*C*H=CH$_2$), 137.4 (*C*(2″)), 162.1 (d, *J* 246.7, *C*(4′)), 168.6 (*C*(1)); δ_F (377 MHz, $CDCl_3$) −114.6 (C(4′)*F*), −75.1 (C*F*$_3$); *m*/*z* (FI$^+$) 487 ([M]$^+$, 100%); HRMS (FI$^+$) $C_{23}H_{25}F_4NO_4S^+$ ([M]$^+$) requires 487.1435; found 487.1302. Further elution gave a 97:3 mixture of **59** and **60**, respectively, as a brown oil (14 mg, ~15%). Data for **59**: δ_H (500 MHz, $CDCl_3$) 1.31 (9H, s, C*Me*$_3$), 1.47 (3H, d, *J* 5.5, C(α)*Me*), 2.53 (3H, s, N*Me*), 3.63–3.73 (1H, m, C(3)*H*), 4.11 (1H, d, *J* 5.5, C(α)*H*), 4.38–4.44 (1H, m, C(4)*H*), 6.68 (1H, d, *J* 7.6, *Ar*), 6.93–6.99 (2H, m, C(3′)*H*, C(5′)*H*), 7.06–7.11 (1H, m, *Ar*), 7.12–7.21 (4H, m, C(2′)*H*, C(6′)*H*, *Ar*); δ_C (500 MHz, $CDCl_3$) 21.2 (C(1)*Me*), 27.9 (C*Me*$_3$), 40.2 (N*Me*), 46.3 (*C*(4)), 57.5 (*C*(1)), 67.8 (*C*(3)), 81.3 (*C*Me$_3$), 114.9 (d, *J* 21.0, C(3′)*H*, C(5′)*H*), 126.1, 126.5, 126.7, 129.4 (*C*(5), *C*(6), *C*(7), *C*(8)), 130.6 (d, *J* 8.6, *C*(2′), *C*(6′)), 134.3 (*C*(8a)), 139.5 (*C*(4a)), 140.1 (*C*(1′)), 161.5 (d, *J* 244.1, *C*(4′)), 171.5 (*C*O$_2$^{t}Bu); δ_F (377 MHz, $CDCl_3$) −116.9 (C(4′)*F*); *m*/*z* (ESI$^+$) 356 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{22}H_{27}FNO_2^+$ ([M+H]$^+$) requires 356.2020; found 356.2025.

4.27. *tert*-Butyl (*R*,*R*,*R*)-2-hydroxy-3-[*N*-allyl-*N*-(α-methylbenzyl)amino]-3-(4′-fluorophenyl)propanoate 62

Following *general procedure I*, BuLi (2.2 M in hexanes, 9.52 mL, 20.9 mmol) and (*R*)-*N*-allyl-*N*-(α-methylbenzyl)amine[35] (3.48 g, 21.6 mmol, >99:1 er) were reacted with **27** (3.00 g, 13.5 mmol, >99:1 dr) and (−)-CSO (5.27 g, 23.0 mmol) in THF (80 mL). Purification via flash column chromatography (30–40 °C petrol/Et_2O, 5:1) gave **62** as a pale yellow viscous oil (4.18 g, 78%, >99:1 dr); $[\alpha]_D^{20}$ +2.0 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3495 (O—H), 2978 (C—H), 1722 (C=O), 1603 (C=C); δ_H (700 MHz, $CDCl_3$) 1.21 (3H, d, *J* 6.8, C(α)*Me*), 1.29 (9H, s, C*Me*$_3$), 2.89–3.05 (1H, br s, O*H*), 3.25 (1H, dd, *J* 15.7, 7.2, CH$_A$H$_B$CH=CH$_2$), 3.45 (1H, dd, *J* 15.7, 4.9, CH$_A$H$_B$CH=CH$_2$), 4.10 (1H, q, *J* 6.8, C(α)*H*), 4.21 (1H, d, *J* 3.2, C(3)*H*), 4.51 (1H, d, *J* 3.2, C(2)*H*), 5.03 (1H, app d, *J* 10.2, CH$_2$CH=CH$_A$H$_B$), 5.11 (1H, app d, *J* 17.2, CH$_2$CH=CH$_A$H$_B$), 5.83–5.91 (1H, m, CH$_2$C*H*=CH$_2$), 7.01 (2H, app t, *J* 8.6, C(3′)*H*, C(5′)*H*), 7.22–7.48 (7H, m, C(2′)*H*, C(6′)*H*, *Ph*); δ_C (175 MHz, $CDCl_3$) 13.9 (C(α)*Me*), 27.8 (C*Me*$_3$), 50.5 (*C*H$_2$CH=CH$_2$), 56.6 (*C*(α)), 65.0 (*C*(3)), 72.3 (*C*(2)), 82.4 (*C*Me$_3$), 114.9 (d, *J* 21.6, *C*(3′), *C*(5′)), 115.7 (CH$_2$CH=*C*H$_2$), 126.7, 127.7, 128.1 (*o*,*m*,*p*-*Ph*), 131.2 (d, *J* 8.3, *C*(2′), *C*(6′)), 133.7 (d, *J* 2.5, *C*(1′)), 138.8 (CH$_2$*C*H=CH$_2$), 144.1 (*i*-*Ph*), 162.3 (d, *J* 246.7, *C*(4′)), 172.0 (*C*(1)); δ_F (377 MHz, $CDCl_3$) −114.6 (C(4″)*F*); *m*/*z* (ESI$^+$) 400 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{24}H_{31}FNO_3^+$ ([M+H]$^+$) requires 400.2282; found 400.2290.

4.28. (1*R*,3*S*,4*S*)-1-Methyl-*N*(2)-allyl-3-(*tert*-butoxycarbonyl)-4-(4′-fluorophenyl)-1,2,3,4-tetrahydroisoquinoline 63

Following *general procedure II*, Tf_2O (0.13 mL, 0.75 mmol) was reacted with **62** (200 mg, 0.50 mmol, >99:1 dr) and DTBMP (310 mg, 1.0 mmol) in CH_2Cl_2 (6.3 mL) at rt for 6 h. Purification by flash column chromatography (eluent 30–40 °C/Et_2O, 10:1) gave **63** as a brown viscous oil (20 mg, 31%, >99:1 dr); $[\alpha]_D^{20}$ +19.0 (*c* 0.5 in $CHCl_3$); ν_{max} (ATR) 1729 (C=O), 1604 (C=C); δ_H (500 MHz, $CDCl_3$) 1.27 (9H, s, C*Me*$_3$), 1.41 (3H, d, *J* 6.5, C(1)*Me*), 3.33–3.43 (2H, m, *C*H$_2$CH=CH$_2$), 3.84 (1H, d, *J* 4.4, C(3)*H*), 4.27 (1H, q, *J* 6.5, C(1)*H*), 4.43 (1H, d, *J* 4.4, C(4)*H*), 4.91–4.99 (2H, m, CH$_2$CH=C*H*$_2$), 5.55–5.65 (1H, m, CH$_2$C*H*=CH$_2$), 6.91–7.23 (8H, m, *Ar*); δ_C (125 MHz, $CDCl_3$) 22.7 (C(1)*Me*), 27.9 (C*Me*$_3$), 46.7 (*C*(4)), 53.9 (*C*H$_2$CH=CH$_2$), 55.4 (*C*(1)), 64.8 (*C*(3)), 81.1 (*C*Me$_3$), 114.6 (d, *J* 21.0, *C*(3′), *C*(5′)), 116.4 (CH$_2$CH=*C*H$_2$), 126.1, 126.7, 127.0, 129.5 (*C*(5), *C*(6), *C*(7), *C*(8)), 130.3 (d, *J* 7.6, *C*(2′), *C*(6′)), 134.1 (*C*(4a)), 136.4 (CH$_2$*C*H=CH$_2$), 139.6 (d, *J* 1.9, *C*(1′)), 140.7 (*C*(8a)), 161.4 (d, *J* 244.1, *C*(4′)) 172.0 (*C*O$_2$^{t}Bu); δ_F (472 MHz, $CDCl_3$) −117.2 (C(4′)*F*); *m*/*z* (ESI$^+$) 382 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{24}H_{29}FNO_2^+$ ([M+H]$^+$) requires 382.2177; found 382.2180.

4.29. *tert*-Butyl (*R*,*R*,*R*)-2-hydroxy-3-[*N*-allyl-*N*-(α-methylbenzyl)amino]-3-[4′-(trifluoromethyl)phenyl]propanoate 66

Following *general procedure I*, BuLi (2.2 M in hexanes, 2.59 mL, 6.97 mmol) and (*R*)-*N*-allyl-*N*-(α-methylbenzyl)amine[35] (948 mg, 5.88 mmol, >99:1 er) were reacted with **24** (1.00 g, 3.68 mmol, >99:1 dr) and (−)-CSO (1.43 g, 6.25 mmol) in THF (20 mL). Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 10:1) gave **66** as a pale yellow viscous oil (1.17 g, 71%, >99:1 dr); $[\alpha]_D^{20}$+2.1 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3485 (O—H), 2978 (C—H), 1723 (C=O), 1619 (C=C); δ_H (500 MHz, $CDCl_3$) 1.23 (3H, d, *J* 6.8, C(α)*Me*), 1.30 (9H, s, C*Me*$_3$), 2.95 (1H, br s, O*H*), 3.30 (1H, dd, *J* 15.7, 7.0, CH$_A$H$_B$CH=CH$_2$), 3.45–3.52 (1H, m, CH$_A$H$_B$CH=CH$_2$), 4.10 (1H, q, *J* 6.8, C(α)*H*), 4.30 (1H, d, *J* 3.5, C(3)*H*), 4.52 (1H, d, *J* 3.5, C(2)*H*), 5.06 (1H, dd, *J* 10.2, 1.4, CH$_2$CH=CH$_A$H$_B$), 5.14 (1H, dd, *J* 17.2, 1.4, CH$_2$CH=CH$_A$H$_B$), 5.85–5.94 (1H, m, CH$_2$C*H*=CH$_2$), 7.22–7.61 (9H, m, *Ar*, *Ph*); δ_C (125 MHz, $CDCl_3$) 14.3 (C(α)*Me*), 27.5 (C*Me*$_3$), 50.7 (*C*H$_2$CH=CH$_2$), 57.0 (*C*(α)), 65.1 (*C*(3)), 72.1 (*C*(2)), 82.7 (*C*Me$_3$), 116.0 (CH$_2$CH=*C*H$_2$), 124.2 (q, *J* 271.8, *C*F$_3$), 124.9 (q, *J* 3.8, *C*(3′), *C*(5′)), 126.8, 127.7, 128.2 (*o*,*m*,*p*-*Ph*), 129.8 (q, *J* 32.4, *C*(4′)), 129.8 (*C*(2′), *C*(6′)), 138.7 (CH$_2$*C*H=CH$_2$), 142.4 (*C*(1′)), 143.8 (*i*-*Ph*), 172.0 (*C*(1)); δ_F (472 MHz, $CDCl_3$) −62.5 (C*F*$_3$); *m*/*z* (ESI$^+$) 450 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{25}H_{31}F_3NO_3^+$ ([M+H]$^+$) requires 450.2251; found 450.2249.

4.30. *tert*-Butyl (*R*,*R*,*R*)-2-hydroxy-3-[*N*-allyl-*N*-(α-methylbenzyl)amino]-3-(3′-fluorophenyl)propanoate 67

Following *general procedure I*, BuLi (2.2 M in hexanes, 9.52 mL, 20.9 mmol) and (*R*)-*N*-allyl-*N*-(α-methylbenzyl)amine[35] (3.48 g, 21.6 mmol, >99:1 er) were reacted with **25** (3.00 g, 13.5 mmol, >99:1 dr) and (−)-CSO (5.27 g, 23.0 mmol) in THF (80 mL). Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 5:1) gave **67** as pale yellow viscous oil (3.74 g, 69%, >99:1 dr); $[\alpha]_D^{20}$ +0.3 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3479 (O–H), 2975 (C–H), 1724 (C=O), 1588 (C=C); δ_H (500 MHz, $CDCl_3$) 1.23 (3H, d, *J* 6.9, C(α)*Me*), 1.31 (9H, s, C*Me*$_3$), 2.95 (1H, br s, O*H*), 3.28 (1H, dd, *J* 15.7, 7.0, C*H*$_A$H$_B$CH=CH$_2$), 3.44–3.52 (1H, m, CH$_A$*H*$_B$CH=CH$_2$), 4.13 (1H, q, *J* 6.9, C(α)*H*), 4.22 (1H, d, *J* 3.5, C(3)*H*), 4.49 (1H, d, *J* 3.5, C(2)*H*), 5.05 (1H, dd, *J* 10.2, 1.7, CH$_2$CH=C*H*$_A$H$_B$), 5.13 (1H, dd, *J* 17.3, 1.7, CH$_2$CH=CH$_A$*H*$_B$), 5.84–5.94 (1H, m, CH$_2$*C*H=CH$_2$), 6.94–7.48 (9H, m, *Ar*, *Ph*); δ_C (125 MHz, $CDCl_3$) 14.1 (C(α)*Me*), 27.8 (C*Me*$_3$), 50.6 (*C*H$_2$CH=CH$_2$), 56.8 (*C*(α)), 65.1 (*C*(3)), 72.3 (*C*(2)), 82.6 (*C*Me$_3$), 114.5 (d, *J* 21.0, *C*(2′)), 115.8 (CH$_2$CH=*C*H$_2$), 116.5 (d, *J* 21.0, *C*(4′)), 125.1 (d, *J* 2.9, *C*(6′)), 126.7, 127.7, 128.1 (*o*,*m*,*p*-*Ph*), 129.4 (d, *J* 7.6, *C*(5′)), 138.7 (CH$_2$*C*H=CH$_2$), 140.7 (d, *J* 6.7, *C*(1′)), 144.0 (*i*-*Ph*), 162.5 (d, *J* 245.1, *C*(3′)), 172.0 (*C*(1)); δ_F (472 MHz, $CDCl_3$) −113.3 (C(3″)*F*); *m*/*z* (ESI$^+$) 400 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{24}H_{31}FNO_3^+$ ([M+H]$^+$) requires 400.2282; found 400.2291.

4.31. *tert*-Butyl (*R*,*R*,*R*)-2-hydroxy-3-[*N*-allyl-*N*-(α-methylbenzyl)amino]-3-(3′-methoxyphenyl)propanoate 68

Following *general procedure I*, BuLi (2.2 M in hexanes, 9.03 mL, 19.9 mmol) and (*R*)-*N*-allyl-*N*-(α-methylbenzyl)amine[35] (3.30 g, 20.5 mmol, >99:1 er) were reacted with **26** (3.00 g, 12.8 mmol, >99:1 dr) and (−)-CSO (4.99 g, 21.8 mmol) in THF (80 mL). Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 3:1) gave **68** as a pale yellow viscous oil (3.69 g, 70%, >99:1 dr); $[\alpha]_D^{20}$ +3.0 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3486 (O–H), 2976 (C–H), 1723 (C=O), 1599 (C=C); δ_H (500 MHz, $CDCl_3$) 1.23 (3H, d, *J* 7.0, C(α)*Me*), 1.32 (9H, s, C*Me*$_3$), 3.27 (1H, dd, *J* 15.6, 7.1, C*H*$_A$H$_B$CH=CH$_2$), 3.43–3.52 (1H, m, CH$_A$*H*$_B$CH=CH$_2$), 3.80 (3H, s, O*Me*), 4.14 (1H, q, *J* 7.0, C(α)*H*), 4.21 (1H, d, *J* 3.8, C(3)*H*), 4.51 (1H, d, *J* 3.8, C(2)*H*), 5.04 (1H, dd, *J* 10.1, 1.4, CH$_2$CH=C*H*$_A$H$_B$), 5.13 (1H, dd, *J* 17.3, 1.4, CH$_2$CH=CH$_A$*H*$_B$), 5.86–5.95 (1H, m CH$_2$*C*H=CH$_2$), 6.82 (1H, dd, *J* 8.2, 2.5, C(4′)*H*), 7.02–7.07 (2H, m, C(2′)*H*, C(6′)*H*) 7.20–7.25 (2H, m, *p*-*Ph*, C(5′)*H*), 7.32 (2H, app t, *J* 7.6, *m*-*Ph*), 7.46 (2H, d, *J* 7.4, *o*-*Ph*); δ_C (125 MHz, $CDCl_3$) 13.9 (C(α)*Me*), 27.8 (C*Me*$_3$), 50.6 (*C*H$_2$CH=CH$_2$), 55.2 (O*Me*), 56.6 (*C*(α)), 65.8 (*C*(3)), 72.4 (*C*(2)), 82.2 (*C*Me$_3$), 113.0 (*C*(4′)), 115.3, 121.9 (*C*(2′), *C*(6′)), 115.6 (CH$_2$CH=*C*H$_2$), 126.6, 129.0 (*C*(5′), *p*-*Ph*), 127.7, 128.0 (*o*,*m*-*Ph*), 138.9 (CH$_2$*C*H=CH$_2$), 139.5 (*C*(1′)), 144.2 (*i*-*Ph*), 159.3 (*C*(3′)), 172.4 (*C*(1)); *m*/*z* (ESI$^+$) 412 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{25}H_{34}NO_4^+$ ([M+H]$^+$) requires 412.2482; found 412.2483.

4.32. *tert*-Butyl (*R*,*R*,*R*)-2-hydroxy-3-[*N*-allyl-*N*-(α-methylbenzyl)amino]-3-phenylpropanoate 69

Following *general procedure I*, BuLi (2.3 M in hexanes, 4.95 mL, 11.4 mmol) and (*R*)-*N*-allyl-*N*-(α-methylbenzyl)amine[35] (1.89 g, 11.8 mmol, >99:1 er) were reacted with **65** (1.50 g, 7.34 mmol, >99:1 dr) and (−)-CSO (2.86 g, 12.5 mmol) in THF (60 mL). Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 10:1) gave **69** as a pale yellow oil (2.03 g, 73%, >99:1 dr);[36] $[\alpha]_D^{20}$ +4.5 (*c* 1.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.18 (3H, d, *J* 6.8, C(α)*Me*), 1.26 (9H, s, C*Me*$_3$), 2.96 (1H, br s, O*H*), 3.23 (1H, dd, *J* 15.6, 7.2, C*H*$_A$H$_B$CH=CH$_2$), 3.44 (1H, dd, *J* 15.6, 5.3, CH$_A$*H*$_B$CH=CH$_2$), 4.11 (1H, q, *J* 6.8, C(α)*H*), 4.21 (1H, d, *J* 3.4, C(3)*H*), 4.51 (1H, d, *J*, 3.4, C(2)*H*), 5.01 (1H, dd, *J* 10.2, 1.3, CH$_2$CH=C*H*$_A$H$_B$), 5.10 (1H, dd, *J* 17.2, 1.3, CH$_2$CH=CH$_A$*H*$_B$), 5.87 (1H, dddd, *J* 17,2, 10.2, 7.2, 5.3, CH$_2$*C*H=CH$_2$), 7.16–7.50 (10H, m, *Ph*).

4.33. *tert*-Butyl (*R*,*R*,*R*)-2-hydroxy-3-[*N*-allyl-*N*-(α-methylbenzyl)amino]-3-(4′-methoxyphenyl)propanoate 70

Following *general procedure I*, BuLi (2.2 M in hexanes, 4.51 mL, 9.93 mmol) and (*R*)-*N*-allyl-*N*-(α-methylbenzyl)amine[35] (1.65 g, 10.3 mmol, >99:1 er) were reacted with **28** (1.50 g, 6.41 mmol, >99:1 dr) and (−)-CSO (2.50 g, 10.9 mmol) in THF (36 mL). Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 5:1) gave **70** as a pale yellow oil (2.10 g, 80%, >99:1 dr); $[\alpha]_D^{20}$+16.8 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3490 (O–H), 2975 (C–H), 1724 (C=O), 1610 (C=C); δ_H (500 MHz, $CDCl_3$) 1.20 (3H, d, *J* 6.8, C(α)*Me*), 1.30 (9H, s, C*Me*$_3$), 3.02 (1H, br s, O*H*), 3.22 (1H, dd, *J* 15.6, 7.2, C*H*$_A$H$_B$CH=CH$_2$), 3.44 (1H, dd, *J* 15.6, 5.4, CH$_A$*H*$_B$CH=CH$_2$), 3.79 (3H, s, O*Me*), 4.11 (1H, q, *J* 6.8, C(α)*H*), 4.17 (1H, d, *J* 3.8, C(3)*H*), 4.50 (1H, d, *J* 3.8, C(2)*H*), 5.02 (1H, dd, *J* 10.2, 1.4, CH$_2$CH=C*H*$_A$H$_B$), 5.11 (1H, dd, *J* 17.2, 1.4, CH$_2$CH=CH$_A$*H*$_B$), 5.82–5.92 (1H, m, CH$_2$*C*H=CH$_2$), 6.82–7.46 (9H, m, *Ar*, *Ph*); δ_C (125 MHz, $CDCl_3$) 13.6 (C(α)*Me*), 27.8 (C*Me*$_3$), 50.6 (*C*H$_2$CH=CH$_2$), 55.1 (O*Me*), 56.4 (*C*(α)), 65.4 (C(3)), 72.5 (*C*(2)), 82.1 (*C*Me$_3$), 113.4 (*C*(3′), *C*(5′)), 115.6 (CH$_2$CH=*C*H$_2$), 126.6 (*p*-*Ph*), 127.8, 128.0 (*o*,*m*-*Ph*), 129.8 (*C*(1′)) 130.7 (*C*(2′), *C*(6′)), 138.9 (CH$_2$*C*H=CH$_2$), 144.3 (*i*-*Ph*), 159.0 (*C*(4′)), 172.2 (*C*(1)); *m*/*z* (ESI$^+$) 412 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{25}H_{34}NO_4^+$ ([M+H]$^+$) requires 412.2482; found 412.2478.

4.34. (1*R*,3*S*,4*S*)-1-Methyl-*N*(2)-allyl-3-(*tert*-butoxycarbonyl)-4-[4′-(trifluoromethyl)phenyl]-1,2,3,4-tetrahydroisoquinoline 71

Following *general procedure II*, Tf_2O (0.12 mL, 0.67 mmol) was reacted with **66** (200 mg, 0.45 mmol, >99:1 dr) and DTBMP (270 mg, 1.3 mmol) in CH_2Cl_2 (5.6 mL) at 40 °C for 24 h, which gave an 82:18 mixture of **71** and **76**, respectively. Purification by flash column chromatography (eluent 30–40 °C petrol/Et_2O, 15:1) gave **71** as a yellow oil (50 mg, 26%, >99:1 dr); $[\alpha]_D^{20}$ −12.9 (*c* 0.5 in $CHCl_3$); ν_{max} (ATR) 1727 (C=O), 1618 (C=C); δ_H (500 MHz, $CDCl_3$) 1.28 (9H, s, C*Me*$_3$), 1.42 (3H, d, *J* 6.6, C(1)*Me*), 3.38–3.41 (2H, m, C*H*$_2$CH=CH$_2$), 3.90 (1H, d, *J* 3.9, C(3)*H*), 4.30 (1H, q, *J* 6.6, C(1)*H*), 4.52 (1H, d, *J* 3.9, C(4)*H*), 4.90–4.99 (2H, m, CH$_2$CH=C*H*$_2$), 5.51–5.61 (1H, m, CH$_2$*C*H=CH$_2$), 6.93–6.96 (1H, m, C(5)*H*), 7.10–7.15 (1H, m, C(6)*H*), 7.17–7.20 (1H, m, C(7)*H*), 7.23–7.32 (3H, m, C(8)*H*, C(2′)*H*, C(6′)*H*), 7.50–7.55 (2H, m, C(3′)*H*, C(5′)*H*); δ_C (125 MHz, $CDCl_3$) 22.8 (C(1)*Me*), 27.9 (C*Me*$_3$), 47.4 (*C*(4)), 54.0 (*C*H$_2$CH=CH$_2$), 55.4 (*C*(1)), 64.5 (*C*(3)), 81.2 (*C*Me$_3$), 116.6 (CH$_2$CH=*C*H$_2$), 124.3 (q, *J* 271.8, *C*F$_3$), 124.8 (q, *J* 3.8, *C*(3′), *C*(5′)), 126.1 (*C*(6)), 127.0 (*C*(8)), 127.1 (*C*(7)), 128.4 (q, *J* 32.5, *C*(4′)), 129.2 (*C*(2′), *C*(6′)), 129.6 (*C*(5)), 133.2 (*C*(4a)), 136.1 (CH$_2$*C*H=CH$_2$), 140.9 (*C*(8a)), 148.1 (*C*(1′)), 171.8 (*C*O$_2$ ^{t}Bu); δ_F (472 MHz, $CDCl_3$) −62.3 (C*F*$_3$); *m*/*z* (ESI$^+$) 432 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{25}H_{29}F_3NO_2^+$ ([M+H]$^+$) requires 432.2145; found 432.2133.

4.35. (1*R*,3*S*,4*S*)-1-Methyl-*N*(2)-allyl-3-(*tert*-butoxycarbonyl)-4-(3′-fluorophenyl)-1,2,3,4-tetrahydroisoquinoline 72

Following *general procedure II*, Tf_2O (130 μL, 0.75 mmol) was reacted with **67** (200 mg, 0.50 mmol, >99:1 dr) and DTBMP (310 mg, 1.50 mmol) in CH_2Cl_2 (6.3 mL) at 40 °C for 24 h. Purification by flash column chromatography (eluent 30–40 °C petrol/Et_2O, 20:1) gave **72** as a pale yellow oil (53 mg, 28%, >99:1 dr); $[\alpha]_D^{20}$ +85.2 (*c* 0.3 in $CHCl_3$); ν_{max} (ATR) 1728 (C=O), 1615 (C=C); δ_H (500 MHz, $CDCl_3$) 1.28 (9H, s, C*Me*$_3$), 1.41 (3H, d, *J* 6.6, C(1)*Me*), 3.37–3.41 (2H, m, C*H*$_2$CH=CH$_2$), 3.88 (1H, d, *J* 4.3, C(3)*H*), 4.27 (1H, q, *J* 6.6, C(1)*H*), 4.45 (1H, d, *J* 4.3, C(4)*H*), 4.93–4.99 (2H, m, CH$_2$CH=C*H*$_2$), 5.56–5.65 (1H, m, CH$_2$*C*H=CH$_2$), 6.84–6.92 (2H, m, C(2′)*H*, C(4′)*H*), 6.94–7.00 (2H, m, C(6)*H*, C(6′)*H*), 7.09–7.14 (1H, m,

C(5)*H*), 7.15–7.18 (1H, m, C(8)*H*), 7.20–7.26 (2H, m, C(7)*H*, C(5′)*H*); δ_C (125 MHz, $CDCl_3$) 22.8 (C(1)*Me*), 27.9 (C*Me*$_3$), 47.2 (*C*(4)), 54.0 (*C*H$_2$CH=CH$_2$), 55.4 (*C*(1)), 64.5 (*C*(3)), 81.1 (*C*Me$_3$), 113.0 (d, *J* 21.0, *Ar*), 115.9 (d, *J* 21.9, *Ar*), 116.5 (CH$_2$CH=*C*H$_2$), 124.5 (d, *J* 2.9, *C*(6′)), 126.0 (*C*(5)), 126.8 (*C*(7)), 127.0 (*C*(8)), 129.2 (d, *J* 8.6, *C*(5′)), 129.6 (*C*(6)), 133.5 (*C*(8a)), 136.3 (CH$_2$*C*H=CH$_2$), 140.8 (*C*(4a)), 146.7 (d, *J* 6.7, *C*(1′)), 162.6 (d, *J* 245.1, *C*(3′)), 171.9 (*C*O$_2$^{t}Bu); δ_F (472 MHz, $CDCl_3$) −114.0 (C(3′)*F*); *m/z* (ESI$^+$) 382 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{24}H_{29}FNO_2^+$ ([M+H]$^+$) requires 382.2177; found 382.2173.

4.36. (1*R*,3*S*,4*S*)-1-Methyl-*N*(2)-allyl-3-(*tert*-butoxycarbonyl)-4-(3′-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline 73

Method A: Following *general procedure II*, Tf_2O (60 μL, 0.37 mmol) was reacted with **68** (100 mg, 0.24 mmol, >99:1 dr) and DTBMP (150 mg, 0.73 mmol) in CH_2Cl_2 (3.1 mL) at rt for 6 h, which gave a 66:34 mixture of **73** and **78**, respectively. Purification by flash column chromatography (eluent 30–40 °C petrol/Et_2O, 20:1) gave **73** as a brown oil (20 mg, 20%, >99:1 dr); $[\alpha]_D^{20}$ +76.1 (*c* 0.4 in $CHCl_3$); ν_{max} (ATR) 1728 (C=O), 1599 (C=C); δ_H (500 MHz, $CDCl_3$) 1.28 (9H, s, C*Me*$_3$), 1.43 (3H, d, *J* 6.5, C(1)*Me*), 3.37–3.42 (2H, m, C*H*$_2$CH=CH$_2$), 3.76 (3H, s, O*Me*), 3.91 (1H, d, *J* 4.5, C(3)*H*), 4.27 (1H, q, *J* 6.5, C(1)*H*), 4.42 (1H, d, *J* 4.5, C(4)*H*), 4.95–5.01 (2H, m, CH$_2$CH=C*H*$_2$), 5.60–5.69 (1H, m, CH$_2$C*H*=CH$_2$), 6.73–6.80 (3H, m, *Ar*), 6.95–7.00 (1H, m, C(5)*H*), 7.07–7.13 (4H, m, C(6)*H*, C(7)*H*, C(8)*H*, *Ar*); δ_C (125 MHz, $CDCl_3$) 22.7 (C(1)*Me*), 27.9 (C*Me*$_3$), 47.4 (*C*(4)), 54.0 (*C*H$_2$CH=CH$_2$), 55.1 (O*Me*), 55.4 (*C*(1)), 64.7 (*C*(3)), 80.9 (*C*Me$_3$), 111.5, 114.9, 121.5 (*Ar*), 116.4 (CH$_2$CH=*C*H$_2$), 125.9, 128.8 (*C*(7), *Ar*), 126.5 (*C*(6)), 126.9 (*C*(8)), 129.6 (*C*(5)), 134.1 (*C*(4a)), 136.4 (CH$_2$CH=CH$_2$), 140.6 (*C*(8a)), 145.6 (*C*(1′)), 159.2 (*C*(3′)), 172.2 (*C*O$_2$^{t}Bu); *m/z* (ESI$^+$) 394 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{25}H_{32}NO_3^+$ ([M+H]$^+$) requires 394.2377; found 394.2372.

Method B: Following *general procedure II*, Tf_2O (0.12 mL, 0.73 mmol) was reacted with **68** (200 mg, 0.486 mmol, >99:1 dr) and DTBMP (300 mg, 1.46 mmol) in CH_2Cl_2 (3.15 mL) at 40 °C for 24 h. Purification by flash column chromatography (eluent 30–40 °C petrol/Et_2O, 15:1) gave **73** as a pale yellow oil (45 mg, 24%, >99:1 dr).

4.37. (1*R*,3*S*,4*S*)-1-Methyl-*N*(2)-allyl-3-(*tert*-butoxycarbonyl)-4-phenyl-1,2,3,4-tetrahydroisoquinoline 74

Following *general procedure II*, Tf_2O (53 μL, 0.31 mmol) was reacted with **69** (100 mg, 0.26 mmol, >99:1 dr) and DTBMP (129 mg, 0.63 mmol) in CH_2Cl_2 (3.3 mL) at rt for 6 h. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 20:1) gave **74** as a pale red oil (30 mg, 32%, >99:1 dr); ν_{max} (ATR) 1728 (C=O), 1149 (C=C); $[\alpha]_D^{20}$ +80.0 (*c* 0.5 in $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 1.28 (9H, s, C*Me*$_3$), 1.43 (3H, d, *J* 6.6, C(1)*Me*), 3.33–3.39 (1H, m, C*H*$_A$H$_B$CH=CH$_2$), 3.43 (1H, dd, *J* 14.8, 6.9, CH$_A$*H*$_B$CH=CH$_2$), 3.91 (1H, d, *J* 4.5, C(3)*H*), 4.28 (1H, q, *J* 6.6, C(1)*H*), 4.64 (1H, d, *J* 4.5, C(4)*H*), 4.91–4.98 (2H, m, CH$_2$CH=C*H*$_2$), 5.63 (1H, dddd, *J* 17.0, 10.7, 6.9, 5.0, CH$_2$C*H*=CH$_2$), 6.96–7.29 (9H, m, *Ar*, *Ph*); δ_C (125 MHz, $CDCl_3$) 22.6 (C(1)*Me*), 27.9 (C*Me*$_3$), 47.3 (*C*(4)), 53.9 (*C*H$_2$CH=CH$_2$), 55.4 (*C*(1)), 64.8 (*C*(3)), 80.9 (*C*Me$_3$), 116.3 (CH$_2$CH=*C*H$_2$), 125.9 (*C*(8)), 126.2, 126.5 (*C*(6), *C*(7)), 126.9 (*p-Ph*), 127.9, 129.0 (*o*,*m-Ph*), 129.6 (*C*(5)), 134.3 (*C*(4a)), 136.3 (CH$_2$*C*H=CH$_2$), 140.7 (*C*(8a)), 143.8 (*i-Ph*), 172.1 (*C*O$_2$^{t}Bu); *m/z* (ESI$^+$) 364 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{24}H_{31}NO_2^+$ ([M+H]$^+$) requires 364.2271; found 364.2276.

4.38. *tert*-Butyl (2*S*,3*S*,α*R*)-2-[*N*-allyl-*N*-(α-methylbenzyl)-amino]-3-hydroxy-3-[4′-(trifluoromethyl)phenyl]propanoate 76

Following *general procedure II*, Tf_2O (70 μL, 0.43 mmol) was reacted with **66** (128 mg, 0.29 mmol, >99:1 dr) and DTBMP (180 mg, 0.86 mmol) in CH_2Cl_2 (3.6 mL) at rt for 6 h, which gave a 4:96 mixture of **71** and **76**, respectively. Purification by flash column chromatography (30–40 °C petrol/Et_2O, 10:1) gave **71** as a yellow oil (4 mg, 3%, >99:1 dr). Further elution gave **76** as a colourless oil (39 mg, 31%, >99:1 dr); $[\alpha]_D^{20}$ +83.0 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3447 (O–H), 2978 (C–H), 1723 (C=O), 1620 (C=C); δ_H (500 MHz, $CDCl_3$) 1.29 (3H, d, *J* 6.9, C(α)*Me*), 1.55 (9H, s, C*Me*$_3$), 3.35 (1H, dd, *J* 14.9, 8.1, C*H*$_A$H$_B$CH=CH$_2$), 3.41–3.53 (1H, m, CH$_A$*H*$_B$CH=CH$_2$), 3.54 (1H, d, *J* 8.8, C(2)*H*), 4.03 (1H, q, *J* 6.9, C(α)*H*), 4.91 (1H, d, *J* 8.8, C(3)*H*), 5.09 (1H, app d, *J* 10.1, CH$_2$CH=C*H*$_A$H$_B$), 5.14 (1H, dd, *J* 16.7, 1.0, CH$_2$CH=CH$_A$*H*$_B$), 5.61–5.67 (1H, m, CH$_2$C*H*=CH$_2$), 6.85 (2H, d, *J* 7.3, C(2′)*H*, C(6′)*H*), 7.07–7.22 (5H, m, *Ph*), 7.47 (2H, d, *J* 8.2, C(3′)*H*, C(5′)*H*); δ_C (125 MHz, $CDCl_3$) 14.9 (C(α)*Me*), 28.1 (C*Me*$_3$), 51.4 (*C*H$_2$CH=CH$_2$), 57.2 (*C*(α)), 65.3 (*C*(2)), 73.2 (*C*(3)), 82.0 (*C*Me$_3$), 117.2 (CH$_2$CH=*C*H$_2$), 124.2 (q, *J* 271.8, *C*F$_3$), 124.7 (q, *J* 3.8, *C*(3′), *C*(5′)), 126.6, 127.4, 127.6 (*o*,*m*,*p-Ph*), 127.9 (*C*(2′), *C*(6′)), 129.6 (q, *J* 32.4, *C*(4′)), 137.2 (CH$_2$*C*H=CH$_2$), 143.2 (*i-Ph*), 145.6 (*C*(1′)), 173.1 (*C*(1)); δ_F (377 MHz, $CDCl_3$) −62.4 (C*F*$_3$); *m/z* (ESI$^+$) 450 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{25}H_{30}F_3NNaO_3^+$ ([M+Na]$^+$) requires 472.2070; found 472.2078.

4.39. *tert*-Butyl (2*S*,3*S*,α*R*)-2-[*N*-allyl-*N*-(α-methylbenzyl) amino]-3-hydroxy-3-(3′-fluorophenyl)propanoate 77

Following *general procedure II*, Tf_2O (60 μL, 0.38 mmol) was reacted with **67** (100 mg, 0.25 mmol, >99:1 dr) and DTBMP (154 mg, 0.75 mmol) in CH_2Cl_2 (3.2 mL) at rt for 6 h, which gave a 20:80 mixture of **72** and **77**, respectively. Purification by flash column chromatography (eluent 30–40 °C petrol/Et_2O, 8:1) gave **72** as a pale yellow oil (13 mg, 14%, >99:1 dr). Further elution gave **77** as a viscous yellow oil (55 mg, 55%, >99:1 dr); $[\alpha]_D^{20}$ −37.7 (*c* 1.2 in $CHCl_3$); ν_{max} (ATR) 3479 (O–H), 2977 (C–H), 1723 (C=O), 1592 (C=C); δ_H (500 MHz, $CDCl_3$) 1.30 (3H, d, *J* 6.8, C(α)*Me*), 1.54 (9H, s, C*Me*$_3$), 3.35 (1H, dd, *J* 14.8, 7.9, C*H*$_A$H$_B$CH=CH$_2$), 3.44–3.51 (1H, m, CH$_A$*H*$_B$CH=CH$_2$), 3.54 (1H, d, *J* 8.4, C(2)*H*), 4.06 (1H, q, *J* 6.8, C(α)*H*), 4.88 (1H, d, *J* 8.4, C(3)*H*), 5.07 (1H, dd, *J* 10.1, 1.2, CH$_2$CH=C*H*$_A$H$_B$), 5.12 (1H, dd, *J* 17.3, 1.2, CH$_2$CH=CH$_A$*H*$_B$), 5.61–5.61 (1H, m, CH$_2$C*H*=CH$_2$), 6.79–7.24 (9H, m, *Ar*, *Ph*); δ_C (125 MHz, $CDCl_3$) 15.2 (C(α)*Me*), 28.1 (C*Me*$_3$), 51.4 (*C*H$_2$CH=CH$_2$), 57.5 (*C*(α)), 65.4 (*C*(2)), 73.2 (*C*(3)), 81.9 (*C*Me$_3$), 114.0 (d, *J* 21.9, *Ar*), 114.3 (d, *J* 21.0, *Ar*), 117.0 (CH$_2$CH=*C*H$_2$), 122.9 (d, *J* 2.9, *C*(6′)), 126.7, 127.7, 128.0, (*o*,*m*,*p-Ph*), 129.2 (d, *J* 7.6, *C*(5′)), 137.4 (CH$_2$*C*H=CH$_2$), 143.5 (*i-Ph*), 144.2 (d, *J* 7.6, *C*(1′)), 162.6 (d, *J* 245.1, *C*(3′)), 173.1 (*C*(1)); δ_F (472 MHz, $CDCl_3$) −113.7 (C(3′)*F*); *m/z* (ESI$^+$) 400 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{24}H_{31}FNO_3^+$ ([M+H]$^+$) requires 400.2282; found 400.2292.

4.40. (*R*)-*N*-[4-(Trifluoromethyl)benzyl]-*N*-(α-methylbenzyl) amine 82

p-(Trifluoromethyl)benzaldehyde (8.62 g, 49.5 mmol) was added to a stirred solution of (*R*)-α-methylbenzylamine **81** (6.00 mL, 47.2 mmol, >99:1 er) in EtOH (30 mL) and the resultant solution was heated at reflux for 3 h. The reaction mixture was allowed to cool to rt, then cooled to 0 °C. $NaBH_4$ (1.78 g, 47.2 mmol) was added portionwise (maintaining a reaction temperature below 15 °C), and the resultant suspension was stirred at rt for 20 h. The reaction mixture was then concentrated in vacuo and the residue was partitioned between CH_2Cl_2 (500 mL) and H_2O (500 mL). The aqueous layer was extracted with CH_2Cl_2 (2×200 mL) and the combined organic extracts were then dried and concentrated in vacuo to give **82** as a yellow oil (12.6 g, 96%, >99:1 er);[37] ν_{max} (ATR) 3467 (N–H), 1325 (C–F); $[\alpha]_D^{20}$ +39.4 (*c* 1.0 in $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 1.30 (3H, d, *J* 6.6, C(α)*Me*), 1.55 (1H, br s, N*H*), 3.57 (1H, d, *J* 13.7, NC*H*$_A$H$_B$Ar), 3.62 (1H, d, *J* 13.7, NCH$_A$*H*$_B$Ar), 3.71 (1H, q, *J* 6.6, C(α)*H*), 7.16–7.29 (5H, m, *Ph*), 7.32 (2H, d, *J* 8.0, C(2)*H*, C(6)*H*), 7.48 (2H, d, *J* 8.0, C(3)*H*, C(5)*H*); δ_C (125 MHz, $CDCl_3$) 24.5 (C(α)*Me*), 51.1 (NCH$_2$Ar), 57.6 (*C*(α)), 124.3 (q, *J* 271.8, *C*F$_3$), 125.3 (q, *J* 3.8, *C*(3),

C(5)), 126.7 (*m*-*Ph*), 127.1 (*p*-*Ph*), 128.3 (*o*-*Ph*), 128.6 (*C*(2), *C*(6)), 129.1 (q, *J* 32,4, *C*(4)), 144.8 (*C*(1)), 145.3 (*i*-*Ph*); δ_F (377 MHz, $CDCl_3$) −62.3 (C*F*$_3$); *m*/*z* (ESI$^+$) 280 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{16}H_{17}F_3N^+$ ([M+H]$^+$) requires 280.1308; found 280.1303.

4.41. *tert*-Butyl (*R*,*R*,*R*)-2-hydroxy-3-{*N*-[4″-(trifluoromethyl)-benzyl]-*N*-(α-methylbenzyl)amino}-3-(4′-fluorophenyl)propanoate 83

Following *general procedure I*, BuLi (2.2 M in hexanes, 1.59 mL, 3.50 mmol) and (*R*)-**82** (1.00 g, 3.60 mmol, >99:1 er) were reacted with **27** (500 mg, 2.25 mmol, >99:1 dr) and (−)-CSO (877 mg, 3.83 mmol) in THF (18 mL). Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 5:1) gave **83** as a pale yellow oil (985 mg, 85%, >99:1 dr); ν_{max} (ATR) 3490 (O–H), 1724 (C=O), 1325 (C–F); $[\alpha]_D^{20}$ −25.6 (*c* 1.0 in $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 1.23–1.26 (3H, d, *J* 6.9, C(α)*Me*), 1.24 (9H, s, C*Me*$_3$), 2.94 (1H, br s, O*H*), 4.05 (1H, d, *J* 15.6, NC*H*$_A$H$_B$Ar), 4.18 (1H, d, *J* 15.6, NCH$_A$*H*$_B$Ar), 4.23 (1H, q, *J* 6.9, C(α)*H*) 4.25 (1H, d, *J* 3.1, C(3)*H*), 4.48–4.51 (1H, m, C(2)*H*), 6.00–7.56 (13H, m, *Ar*, *Ph*); δ_C (125 MHz, $CDCl_3$) 15.8 (C(α)*Me*), 27.6 (C*Me*$_3$), 51.7 (NCH$_2$Ar), 58.3 (*C*(α)), 64.0 (*C*(3)), 72.8 (*C*(2)), 82.6 (*C*Me$_3$), 114.9 (d, *J* 21.0, *C*(3′), *C*(5′)), 124.3 (q, *J* 271.8, C*F*$_3$), 125.0 (q, *J* 3.8, *C*(3″), *C*(5″)), 127.1 (*p*-*Ph*), 127.9 (*C*(2″), *C*(6″)), 127.8, 128.3 (*o*,*m*-*Ph*), 129.7 (q, *J* 32.4, *C*(4″)), 132.4 (d, *J* 7.6, *C*(2′), *C*(6′)), 135.0 (*C*(1′)), 144.7 (*i*-*Ph*), 147.5 (*C*(1″)), 163.1 (d, *J* 247.0, *C*(4′)), 173.2 (*C*(1)); δ_F (377 MHz, $CDCl_3$) −62.2 (C*F*$_3$), −114.5 (C(4′)*F*); *m*/*z* (ESI$^+$) 540 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{29}H_{31}F_4NNaO_3^+$ ([M+Na]$^+$) requires 540.2132; found 540.2124.

4.42. (1*R*,3*S*,4*S*)-1-Methyl-*N*(2)-[4″-(trifluoromethyl)benzyl]-3-(*tert*-butoxycarbonyl)-4-(4′-fluorophenyl)-1,2,3,4-tetrahydroisoquinoline 84

Following *general procedure II*, Tf_2O (98 μL, 0.58 mmol) was reacted with **83** (200 mg, 0.386 mmol, >99:1 dr) and DTBMP (238 mg, 1.16 mmol) in CH_2Cl_2 (5.5 mL) at rt for 6 h. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 30:1) gave **84** as a red oil (171 mg, 89%, >99:1 dr); ν_{max} (ATR) 1726 (C=O), 1325 (C–F); $[\alpha]_D^{20}$ +10.9 (*c* 1.0 in $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 1.30 (9H, s, C*Me*$_3$), 1.48 (3H, d, *J* 6.5, C(1)*Me*), 3.65 (1H, d, *J* 3.6, C(3)*H*), 4.01 (1H, d, *J* 15.4, NC*H*$_A$H$_B$Ar), 4.05 (1H, d, *J* 15.4, NCH$_A$*H*$_B$Ar), 4.40 (1H, q, *J* 6.5, C(1)*H*), 4.51 (1H, d, *J* 3.6, C(4)*H*), 6.75–7.04 (7H, m, *Ar*), 7.15–7.30 (3H, m, *Ar*), 7.36 (2H, d, *J* 8.3, C(3″)*H*, C(5″)*H*); δ_C (125 MHz, $CDCl_3$) 23.3 (C(1)*Me*), 27.9 (C*Me*$_3$), 47.9, (*C*(4)), 54.8 (NCH$_2$Ar), 55.8 (*C*(1)), 65.1 (*C*(3)), 81.4 (*C*Me$_3$), 114.5 (d, *J* 21.9, *C*(3′), *C*(5′)), 124.2 (q, *J* 271.8, C*F*$_3$), 124.9 (q, *J* 3.8, *C*(3″), *C*(5″)), 126.2 (*C*(8)), 127.0, 127.1 (*C*(6), *C*(7)), 128.0 (*C*(2″), *C*(6″)), 129.0 (q, *J* 32.4, *C*(4″)), 129.7 (*C*(5)), 130.3 (d, *J* 7.6, *C*(2′), *C*(6′)), 133.4 (*C*(4a)), 139.5 (d, *J* 2.9, *C*(1′)), 140.6 (*C*(8a)), 144.2 (*C*(1″)), 161.5 (d, *J* 245.1, *C*(4′)), 171.5 (*C*O$_2$^{t}Bu); δ_F (377 MHz, $CDCl_3$) −117.1 (C(4′)*F*), −62.3 (C*F*$_3$); *m*/*z* (ESI$^+$) 500 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{29}H_{30}F_4NO_2^+$ ([M+H]$^+$) requires 500.2207; found 500.2195.

4.43. *tert*-Butyl (*R*,*R*,*R*)-2-hydroxy-3-{*N*-[4″-(trifluoromethyl)-benzyl]-*N*-(α-methylbenzyl)amino}-3-[4′-(trifluoromethyl)-phenyl]propanoate 86

Following *general procedure I*, BuLi (2.2 M in hexanes, 1.30 mL, 2.86 mmol) and (*R*)-**82** (821 mg, 2.94 mmol, >99:1 er) were reacted with **24** (500 mg, 1.84 mmol, >99:1 dr) and (−)-CSO (717 mg, 3.13 mmol) in THF (15 mL). Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 7:1) gave **86** as a pale yellow oil (737 mg, 71%, >99:1 dr); ν_{max} (ATR) 3481 (O–H), 1724 (C=O), 1325 (C–F); $[\alpha]_D^{20}$ −31.2 (*c* 1.0 in $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 1.26 (9H, s, C*Me*$_3$), 1.26 (3H, d, *J* 6.9, C(α)*Me*), 2.97 (1H, br s, O*H*), 4.09 (1H, d, *J* 15.8, NC*H*$_A$H$_B$Ar), 4.22 (1H, d, *J* 15.8, NCH$_A$*H*$_B$Ar), 4.22 (1H, q, *J* 6.9, C(α)*H*), 4.35 (1H, d, *J* 2.7, C(3)*H*), 4.48–4.53 (1H, m, C(2)*H*), 7.26–7.64 (13H, m, *Ar*, *Ph*); δ_C (125 MHz, $CDCl_3$) 16.1 (C(α)*Me*), 27.7 (C*Me*$_3$), 51.9 (NCH$_2$Ar), 58.5 (*C*(α)), 64.3 (*C*(3)), 72.7 (*C*(2)), 83.0 (*C*Me$_3$), 124.0, 124.3 (2×q, *J* 271.8, 2×C*F*$_3$), 124.9, 125.1 (2×q, *J* 3.5, *C*(3′), *C*(5′), *C*(3″), *C*(5″)), 127.3 (*p*-*Ph*), 127.8, 130.0 (*o*,*m*-*Ph*), 128.0 (*C*(2″), *C*(6″)), 128.4 (*C*(2′), *C*(6′)), 128.9, 129.8 (2×q, *J* 32.5, *C*(4′), *C*(4″)), 142.5 (*C*(1′)), 143.4 (*i*-*Ph*), 146.2 (*C*(1″)), 172.2 (*C*(1)); δ_F (377 MHz, $CDCl_3$) −62.3, −62.5 (2×C*F*$_3$); *m*/*z* (ESI$^+$) 568 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{30}H_{32}F_6NO_3^+$ ([M+H]$^+$) requires 568.2281; found 568.2274.

4.44. *tert*-Butyl (*R*,*R*,*R*)-2-hydroxy-3-{*N*-[4″-(trifluoromethyl)-benzyl]-*N*-(α-methylbenzyl)amino}-3-(3′-fluorophenyl)propanoate 87

Following *general procedure I*, BuLi (2.2 M in hexanes, 1.59 mL, 3.50 mmol) and (*R*)-**82** (1.00 g, 3.60 mmol, >99:1 er) were reacted with **25** (500 mg, 2.25 mmol, >99:1 dr) and (−)-CSO (877 mg, 3.83 mmol) in THF (18 mL). Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 7:1) gave **87** as a pale yellow oil (775 mg, 67%, >99:1 dr); ν_{max} (ATR) 3482 (O–H), 1724 (C=O), 1325 (C–F); $[\alpha]_D^{20}$ −30.9 (*c* 1.0 in $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 1.22 (3H, d, *J* 6.9, C(α)*Me*), 1.24 (9H, s, C*Me*$_3$), 2.94 (1H, br s, O*H*), 4.05 (1H, d, *J* 15.6, NC*H*$_A$H$_B$Ar), 4.17–4.25 (3H, m, NCH$_A$*H*$_B$Ar, C(α)*H*, C(3)*H*), 4.46 (1H, app s, C(2)*H*), 6.95–7.55 (13H, m, *Ar*, *Ph*); δ_C (125 MHz, $CDCl_3$) 15.8 (C(α)*Me*), 27.7 (C*Me*$_3$), 51.9 (NCH$_2$Ar), 58.3 (*C*(α)), 64.2 (*C*(3)), 72.9 (*C*(2)), 82.9 (*C*Me$_3$), 114.6 (d, *J* 21.0, *C*(4′)), 116.7 (d, *J* 21.9, *C*(2′)), 124.2 (q, *J* 271.8, C*F*$_3$), 125.1 (q, *J* 3.8, *C*(3″), *C*(5″)), 125.4 (*C*(6′)), 127.9 (*C*(2″), *C*(6″)), 127.2 (*p*-*Ph*), 128.1, 128.3 (*o*,*m*-*Ph*), 128.8 (q, *J* 32.4, *C*(4″)), 129.5 (d, *J* 8.6, *C*(5′)), 140.8 (d, *J* 4.8, *C*(1′)), 143.6 (*i*-*Ph*), 146.3 (*C*(1″)), 162.6 (d, *J* 246.1, *C*(3′)), 172.4 (*C*(1)); δ_F (377 MHz, $CDCl_3$) −62.2 (C*F*$_3$), −113.1 (C(3′)*F*); *m*/*z* (ESI$^+$) 518 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{29}H_{32}F_4NO_3^+$ ([M+H]$^+$) requires 518.2313; found 518.2305.

4.45. *tert*-Butyl (*R*,*R*,*R*)-2-hydroxy-3-{*N*-[4″-(trifluoromethyl)-benzyl]-*N*-(α-methylbenzyl)amino}-3-(3′-methoxyphenyl)-propanoate 88

Following *general procedure I*, BuLi (2.2 M in hexanes, 1.41 mL, 3.10 mmol) and (*R*)-**82** (954 mg, 3.41 mmol, >99:1 er) were reacted with **26** (500 mg, 2.00 mmol, >99:1 dr) and (−)-CSO (779 mg, 3.40 mmol) in THF (16 mL). Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 5:1) gave **88** as a pale yellow oil (1.01 g, 95%, >99:1 dr); ν_{max} (ATR) 3487 (O–H), 1725 (C=O), 1325 (C–F); $[\alpha]_D^{20}$ −29.0 (*c* 1.0 in $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 1.21–1.27 (3H, d, *J* 6.9, C(α)*Me*), 1.24 (9H, s, C*Me*$_3$), 2.91 (1H, br s, O*H*), 3.79 (3H, s, O*Me*), 4.04 (1H, d, *J* 15.6, NC*H*$_A$H$_B$Ar), 4.17 (1H, d, *J* 15.6, NCH$_A$*H*$_B$Ar), 4.21 (1H, d, *J* 2.9, C(3)*H*), 4.24 (1H, q, *J* 6.9, C(α)*H*), 4.42–4.45 (1H, m, C(2)*H*), 6.82 (1H, d, *J* 8.2, C(4′)*H*), 7.00–7.08 (2H, m, C(2″)*H*, C(6″)*H*), 7.20–7.54 (10H, m, *Ar*, *Ph*); δ_C (125 MHz, $CDCl_3$) 15.7 (C(α)*Me*), 27.7 (C*Me*$_3$), 51.9 (NCH$_2$Ar), 55.2 (O*Me*), 58.2 (*C*(α)), 64.9 (*C*(3)), 73.0 (*C*(2)), 82.6 (*C*Me$_3$), 112.8 (*C*(4′)), 115.8 (*C*(2′)), 122.2 (*C*(6′)), 124.5 (q, *J* 271.8, C*F*$_3$), 125.0 (q, *J* 3.5, *C*(3″), *C*(5″)), 127.1 (*p*-*Ph*), 127.9 (*C*(2″), *C*(6″)), 128.1, 128.2 (*o*,*m*-*Ph*), 128.7 (q, *J* 32.1, *C*(4″)), 129.0 (*C*(5′)), 139.6 (*C*(1′)), 143.8 (*i*-*Ph*), 146.6 (*C*(1″)), 159.3 (*C*(3′)), 172.4 (*C*(1)); δ_F (377 MHz, $CDCl_3$) −62.2 (C*F*$_3$); *m*/*z* (ESI$^+$) 530 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{30}H_{35}F_3NO_4^+$ ([M+H]$^+$) requires 530.2513; found 530.2507.

4.46. *tert*-Butyl (*R*,*R*,*R*)-2-hydroxy-3-{*N*-[4′-(trifluoromethyl)-benzyl]-*N*-(α-methylbenzyl)amino}-3-phenylpropanoate 89

Following *general procedure I*, BuLi (2.2 M in hexanes, 3.45 mL, 7.59 mmol) and (*R*)-**82** (2.19 g, 7.83 mmol, >99:1 er) were reacted with **65** (1.00 g, 4.90 mmol, >99:1 dr) and (−)-CSO (1.91 g,

4.90 mmol) in THF (40 mL). Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 5:1) gave **89** as a colourless oil (1.59 g, 65%, >99:1 dr); ν_{max} (ATR) 3494 (O–H), 1724 (C=O), 1325 (C–F); $[\alpha]_D^{20}$ −25.6 (*c* 1.0 in $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 1.20 (9H, s, CMe_3), 1.21 (3H, d, *J* 6.9, C(α)*Me*), 2.79 (1H, br s, O*H*), 4.02 (1H, d, *J* 15.6, NCH_AH_BAr), 4.17 (1H, d, *J* 15.6, NCH$_A$$H_B$Ar), 4.21 (1H, q, *J* 6.9, C(α)*H*), 4.22 (1H, d, *J* 3.0, C(3)*H*), 4.45 (1H, d, *J* 3.0, C(2)*H*), 7.24–7.52 (14H, m, *Ar*, *Ph*); δ_C (125 MHz, $CDCl_3$) 15.5 (C(α)*Me*), 27.7 (CMe_3), 51.9 (NCH_2Ar), 58.2 (*C*(α)), 65.1 (*C*(3)), 73.1 (*C*(2)), 82.5 (*C*Me$_3$), 124.3 (q, *J* 271.8, *C*F$_3$), 125.0 (q, *J* 3.0, *C*(3′), *C*(5′)), 127.9 (*C*(2′), *C*(6′)), 127.1, 127.7 (*p*-*Ph*), 128.0, 128.1, 128.2, 129.8 (*o*,*m*-*Ph*), 128.7 (q, *J* 32.0, *C*(4′)), 138.1, 143.9 (*i*-*Ph*), 146.6 (*C*(1′)), 172.4 (*C*(1)); δ_F (377 MHz, $CDCl_3$) −62.2 (CF_3); *m*/*z* (ESI$^+$) 500 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{29}H_{33}F_3NO_3^+$ ([M+H]$^+$) requires 500.2407; found 500.2401.

4.47. *tert*-Butyl (*R*,*R*,*R*)-2-hydroxy-3-{*N*-[4″-(trifluoromethyl)-benzyl]-*N*-(α-methylbenzyl)amino}-3-(4′-methoxyphenyl)-propanoate 90

Following *general procedure I*, BuLi (2.2 M in hexanes, 1.41 mL, 3.10 mmol) and (*R*)-**82** (954 mg, 3.41 mmol, >99:1 er) were reacted with **28** (500 mg, 2.00 mmol, >99:1 dr) and (−)-CSO (779 mg, 3.40 mmol) in THF (16 mL). Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 5:1) gave **90** as a pale yellow oil (859 mg, 81%, >99:1 dr); ν_{max} (ATR) 3486 (O–H), 1724 (C=O), 1325 (C–F); $[\alpha]_D^{20}$ −26.7 (*c* 1.0 in $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 1.20–1.23 (3H, d, *J* 6.6, C(α)*Me*), 1.22 (9H, s, CMe_3), 2.88 (1H, br s, O*H*), 3.79 (3H, s, O*Me*), 3.98 (1H, d, *J* 15.6, NCH_AH_BAr), 4.14 (1H, d, *J* 15.6, NCH$_A$$H_B$Ar), 4.15–4.17 (1H, m, C(3)*H*), 4.20 (1H, q, *J* 6.6, C(α)*H*), 4.42–4.45 (1H, m, C(2)*H*), 6.83 (2H, d, *J* 8.2, C(3′)*H*, C(5′)*H*), 7.23–7.42 (7H, m, *Ar*, *Ph*), 7.64 (2H, d, *J* 7.4, *o*-*Ph*), 7.50 (2H, d, *J* 7.7, C(2″)*H*, C(6″)*H*); δ_C (125 MHz, $CDCl_3$) 15.5 (C(α)*Me*), 27.7 (CMe_3), 51.8 (NCH_2Ar), 55.2 (O*Me*), 58.1 (*C*(α)), 64.6 (*C*(3)), 73.2 (*C*(2)), 82.4 (*C*Me$_3$), 113.4 (*C*(3′), *C*(5′)), 124.4 (q, *J* 271.8, *C*F$_3$), 125.0 (q, *J* 3.8, *C*(3″), *C*(5″)), 127.0 (*p*-*Ph*), 127.9 (*C*(2″), *C*(6″)), 128.1, 128.2 (*o*,*m*-*Ph*), 128.6 (q, *J* 32.4, *C*(4″)), 130.0 (*C*(1′)), 130.9 (*C*(2′), *C*(6′)), 144.0 (*i*-*Ph*), 146.7 (*C*(1″)), 159.0 (*C*(4′)), 172.4 (*C*(1)); δ_F (377 MHz, $CDCl_3$) −62.2 (CF_3); *m*/*z* (ESI$^+$) 530 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{30}H_{35}F_3NO_4^+$ ([M+H]$^+$) requires 530.2513; found 530.2504.

4.48. (1*R*,3*S*,4*S*)-1-Methyl-*N*(2)-[4″-(trifluoromethyl)benzyl]-3-(*tert*-butoxycarbonyl)-4-[4′-(trifluoromethyl)phenyl]-1,2,3,4-tetrahydroisoquinoline 91

Following *general procedure II*, Tf_2O (89 μL, 0.53 mmol) was reacted with **86** (200 mg, 0.352 mmol, >99:1 dr) and DTBMP (217 mg, 1.06 mmol) in CH_2Cl_2 (5 mL) at 40 °C for 6 h, which gave a 93:7 mixture of **91** and **96**, respectively. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 30:1) gave **91** as a red oil (127 mg, 66%, >99:1 dr); ν_{max} (ATR) 1726 (C=O), 1326 (C–F); $[\alpha]_D^{20}$ +14.4 (*c* 1.0 in $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 1.27 (9H, s, CMe_3), 1.46 (3H, d, *J* 6.5, C(1)*Me*), 3.60 (1H, d, *J* 3.2, C(3)*H*), 3.98 (2H, app s, NCH_2Ar), 4.41 (1H, q, *J* 6.5, C(1)*H*), 4.55 (1H, d, *J* 3.2, C(4)*H*), 6.85 (2H, d, *J* 8.0, C(2″)*H*, C(6″)*H*), 6.99 (1H, d, *J* 7.6, C(5)*H*), 7.12 (2H, d, *J* 8.1, C(2′)*H*, C(6′)*H*), 7.14–7.31 (5H, m, *Ar*), 7.49 (2H, d, *J* 8.1, C(3′)*H*, C(5′)*H*); δ_C (125 MHz, $CDCl_3$) 23.3 (C(1)*Me*), 27.9 (CMe_3), 47.7 (*C*(4)), 54.7 (NCH_2Ar), 55.7 (*C*(1)), 65.0 (*C*(3)), 81.6 (*C*Me$_3$), 124.3 (q, *J* 271.8, C(4″)*C*F$_3$), 124.4 (q, *J* 271.8, C(4′)*C*F$_3$), 124.7 (q, *J* 3.8, *C*(3′), *C*(5′)), 124.8 (q, *J* 3.8, *C*(3″), *C*(5″)), 126.4 (*C*(8)), 127.2 (*C*(6)), 127.3 (*C*(7)), 128.0 (*C*(2″), *C*(6″)), 128.6 (q, *J* 32.4, *C*(4′)), 128.9 (q, *J* 32.4, *C*(4″)), 129.2 (*C*(2′), *C*(6′)), 129.7 (*C*(5)), 132.6 (*C*(4a)), 140.8 (*C*(8a)), 144.0 (*C*(1″)), 148.0 (*C*(1′)), 171.2 (*C*O$_2$^{t}Bu); δ_F (377 MHz, $CDCl_3$) −62.5, −62.3 (2×CF_3); *m*/*z* (ESI$^+$) 550 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{30}H_{36}F_6NO_2^+$ ([M+H]$^+$) requires 550.2175; found 550.2166.

4.49. (1*R*,3*S*,4*S*)-1-Methyl-*N*(2)-[4″-(trifluoromethyl)benzyl]-3-(*tert*-butoxycarbonyl)-4-(3′-fluorophenyl)-1,2,3,4-tetrahydroisoquinoline 92

Following *general procedure II*, Tf_2O (98 μL, 0.58 mmol) was reacted with **87** (200 mg, 0.386 mmol, >99:1 dr) and DTBMP (238 mg, 1.16 mmol) in CH_2Cl_2 (5.5 mL) at 40 °C for 6 h, which gave a 96:4 mixture of **92** and **97**, respectively. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 30:1) gave **92** as a red oil (145 mg, 75%, >99:1 dr); ν_{max} (ATR) 1726 (C=O), 1325 (C–F); $[\alpha]_D^{20}$ +10.2 (*c* 1.0 in $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 1.29 (9H, s, CMe_3), 1.47 (3H, d, *J* 6.5, C(1)*Me*), 3.67 (1H, d, *J* 3.4, C(3)*H*), 4.03 (2H, app t, *J* 17.7, NCH_2Ar), 4.41 (1H, q, *J* 6.5, C(1)*H*), 4.51 (1H, d, *J* 3.4, C(4)*H*), 6.71–6.76 (1H, m, C(2′)*H*), 6.85 (1H, d, *J* 7.7, C(6′)*H*), 6.95–6.99 (3H, m, *Ar*), 7.02 (1H, d, *J* 7.4, C(5)*H*), 7.16–7.31 (4H, m, *Ar*), 7.38 (2H, d, *J* 8.0, C(3″)*H*, C(5″)*H*); δ_C (125 MHz, $CDCl_3$) 23.3 (C(1)*Me*), 27.9 (CMe_3), 47.5, (*C*(4)), 54.8 (NCH_2Ar), 55.8 (*C*(1)), 64.9 (*C*(3)), 81.4 (*C*Me$_3$), 113.0 (d, *J* 21.9, *C*(4′)), 116.0 (d, *J* 21.0, *C*(2′)), 124.2 (q, *J* 271.8, *C*F$_3$), 124.5 (d, *J* 2.9, *C*(6′)), 124.9 (q, *J* 3.8, *C*(3″), *C*(5″)), 126.3 (*C*(8)), 127.1, 127.1 (*C*(6), *C*(7)), 128.0 (*C*(2″), *C*(6″)), 128.9 (q, *J* 32.4, *C*(4″)), 129.2 (d, *J* 7.6, *C*(5′)), 129.7 (*C*(5)), 132.9 (*C*(4a)), 140.7 (*C*(8a)), 144.2 (*C*(1″)), 146.5 (d, *J* 6.7, *C*(1′)), 162.6 (d, *J* 246.1, *C*(3′)), 171.4 (*C*O$_2$^{t}Bu); δ_F (377 MHz, $CDCl_3$) −113.9 (C(3′)*F*), −62.3 (CF_3); *m*/*z* (ESI$^+$) 500 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{29}H_{30}F_4NO_2^+$ ([M+H]$^+$) requires 500.2207; found 500.2195.

4.50. (1*R*,3*S*,4*S*)-1-Methyl-*N*(2)-[4″-(trifluoromethyl)benzyl]-3-(*tert*-butoxycarbonyl)-4-(3′-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline 93

Following *general procedure II*, Tf_2O (95 μL, 0.57 mmol) was reacted with **88** (200 mg, 0.378 mmol, >99:1 dr) and DTBMP (233 mg, 1.13 mmol) in CH_2Cl_2 (5.4 mL) at rt for 6 h. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 30:1) gave **93** as a red oil (156 mg, 81%, >99:1 dr); ν_{max} (ATR) 1725 (C=O), 1325 (C–F); $[\alpha]_D^{20}$ +2.4 (*c* 1.0 in $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 1.30 (9H, s, CMe_3), 1.48 (3H, d, *J* 6.5, C(1)*Me*), 3.70 (1H, d, *J* 3.4, C(3)*H*), 3.72 (3H, s, O*Me*), 4.02 (1H, d, *J* 15.7, NCH_AH_BAr), 4.06 (1H, d, *J* 15.7, NCH$_A$$H_B$Ar), 4.42 (1H, q, *J* 6.5, C(1)*H*), 4.51 (1H, d, *J* 3.4, C(4)*H*), 6.59–6.69 (1H, m, C(2′)*H*), 6.64 (1H, d, *J* 7.6, C(6′)*H*), 6.82–6.86 (1H, m, C(4′)*H*), 6.96 (2H, d, *J* 8.0, C(2″)*H*, C(6″)*H*), 7.06 (1H, d, *J* 7.6, C(5)*H*), 7.15–7.30 (4H, m, C(6)*H*, C(7)*H*, C(8)*H*, C(5′)*H*), 7.34 (2H, d, *J* 8.0, C(3″)*H*, C(5″)*H*); δ_C (125 MHz, $CDCl_3$) 23.3 (C(1)*Me*), 27.9 (CMe_3), 47.9, (*C*(4)), 54.8 (NCH_2Ar), 55.0 (O*Me*), 55.8 (*C*(1)), 65.2 (*C*(3)), 81.2 (*C*Me$_3$), 111.5 (*C*(4′)), 114.7 (*C*(2′)), 121.5 (*C*(6′)), 124.3 (q, *J* 271.8, *C*F$_3$), 124.8 (q, *J* 3.8, *C*(3″), *C*(5″)), 126.1 (*C*(8)), 126.9, 126.9 (*C*(6), *C*(7)), 128.1 (*C*(2″), *C*(6″)), 128.7 (*C*(5′)), 128.7 (q, *J* 32.4, *C*(4″)), 129.8 (*C*(5)), 133.3 (*C*(4a)), 140.8 (*C*(8a)), 144.4 (*C*(1″)), 145.4 (*C*(1′)), 159.3 (*C*(3′)), 171.7 (*C*O$_2$^{t}Bu); δ_F (377 MHz, $CDCl_3$) −62.3 (CF_3); *m*/*z* (ESI$^+$) 512 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{30}H_{33}F_3NO_3^+$ ([M+H]$^+$) requires 512.2407; found 512.2397.

4.51. (1*R*,3*S*,4*S*)-1-Methyl-*N*(2)-[4′-(trifluoromethyl)benzyl]-3-(*tert*-butoxycarbonyl)-4-phenyl-1,2,3,4-tetrahydroisoquinoline 94

Following *general procedure II*, Tf_2O (150 μL, 0.90 mmol) was reacted with **89** (300 mg, 0.60 mmol, >99:1 dr) and DTBMP (370 mg, 1.80 mmol) in CH_2Cl_2 (8 mL) at rt for 6 h. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 20:1) gave **94** as a pale yellow oil (208 mg, 72%, >99:1 dr); ν_{max} (ATR) 1724 (C=O), 1323 (C–F); $[\alpha]_D^{20}$ +6.2 (*c* 1.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.26 (9H, s, CMe_3), 1.44 (3H, d, *J* 6.4, C(1)*Me*), 3.67 (1H, d, *J* 3.5, C(3)*H*), 3.97 (1H, d, *J* 15.8, NCH_AH_BAr), 4.03 (1H, d, *J* 15.8, NCH$_A$$H_B$Ar), 4.38 (1H, q, *J* 6.4, C(1)*H*), 4.51 (1H, d, *J* 3.5, C(4)*H*), 6.88 (2H, d, *J* 8.1, C(2′)*H*, C(6′)*H*), 6.99–7.06 (3H, m, *Ar*, *Ph*), 7.12–7.31 (8H, m, *Ar*, *Ph*);

δ_C (125 MHz, $CDCl_3$) 23.3 (C(1)*Me*), 27.9 (C*Me*$_3$), 47.8, (*C*(4)), 55.0 (NCH_2Ar), 55.9 (*C*(1)), 65.4 (*C*(3)), 81.2 (*C*Me$_3$), 124.3 (q, *J* 272.8, *C*F_3), 124.9 (q, *J* 3.8, *C*(3′), *C*(5′)), 126.1 (*p-Ph*), 126.2 (*C*(8)), 126.8, 127.0 (*C*(6), *C*(7)), 127.9, 127.9 (*C*(2′), *C*(6′), *m-Ph*), 128.7 (q, *J* 32.4, *C*(4′)), 129.0 (*o-Ph*), 129.8 (*C*(5)), 133.5 (*C*(4a)), 140.8 (*C*(8a)), 143.8 (*i-Ph*), 144.4 (*C*(1′)), 171.7 (*C*O_2^{t}Bu); δ_F (377 MHz, $CDCl_3$) −62.2 (CF_3); *m*/*z* (ESI$^+$) 482 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{29}H_{31}F_3NO_2^+$ ([M+H]$^+$) requires 482.2301; found 482.2290.

4.52. (1*R*,3*S*,4*S*)-1-Methyl-*N*(2)-[4″-(trifluoromethyl)benzyl]-3-(*tert*-butoxycarbonyl)-4-(4′-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline 95

Following *general procedure II*, Tf_2O (74 μL, 0.44 mmol) was reacted with **90** (155 mg, 0.293 mmol, >99:1 dr) and DTBMP (180 mg, 0.88 mmol) in CH_2Cl_2 (4.2 mL) at −20 °C for 2.5 h, which gave an 80:20 mixture of **95** and **101**, respectively. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 20:1) gave **95** as a red oil (59 mg, 39%, >99:1 dr); ν_{max} (ATR) 1726 (C=O), 1325 (C–F); $[\alpha]_D^{20}$ +31.3 (*c* 0.3 in $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 1.27 (9H, s, C*Me*$_3$), 1.45 (3H, d, *J* 6.5, C(1)*Me*), 3.64 (1H, d, *J* 3.8, C(3)*H*), 3.84 (3H, s, O*Me*), 3.98 (1H, d, *J* 15.7, NCH_AH$_B$Ar), 4.03 (1H, d, *J* 15.7, NCH$_A$*H*$_B$Ar), 4.36 (1H, q, *J* 6.5, C(1)*H*), 4.45 (1H, d, *J* 3.8, C(4)*H*), 6.79–6.99 (6H, m, *Ar*), 7.01 (1H, d, *J* 7.4, C(5)*H*), 7.13–7.27 (3H, m, *Ar*), 7.32 (2H, d, *J* 8.0, C(3″)*H*, C(5″)*H*); δ_C (125 MHz, $CDCl_3$) 23.3 (C(1)*Me*), 27.9 (C*Me*$_3$), 46.8, (*C*(4)), 54.8 (NCH_2Ar), 55.3 (O*Me*), 55.8 (*C*(1)), 65.3 (*C*(3)), 81.2 (*C*Me$_3$), 113.2 (*C*(3′), *C*(5′)), 124.3 (q, *J* 271.8, *C*F_3), 124.8 (q, *J* 3.8, *C*(3″), *C*(5″)), 126.1 (*C*(8)), 126.7, 126.9 (*C*(6), *C*(7)), 128.0 (*C*(2″), *C*(6″)), 128.7 (q, *J* 32.4, *C*(4″)), 129.7 (*C*(5)), 130.0 (*C*(2′), *C*(6′)), 134.0 (*C*(4a)), 135.9 (*C*(1′)), 140.6 (*C*(8a)), 144.4 (*C*(1″)), 158.1 (*C*(4′)), 171.8 (*C*O_2^{t}Bu); δ_F (377 MHz, $CDCl_3$) −62.3 (CF_3); *m*/*z* (ESI$^+$) 512 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{30}H_{33}F_3NO_3^+$ ([M+H]$^+$) requires 512.2407; found 512.2405. Further elution gave (1*R*,3*S*,4*R*)-**101** as a pale red oil (20 mg, 13%, >99:1 dr); ν_{max} (ATR) 1726 (C=O), 1325 (C–F); $[\alpha]_D^{20}$ −28.6 (*c* 0.5 in $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 1.26 (9H, s, C*Me*$_3$), 1.54 (3H, d, *J* 6.3, C(1)*Me*), 3.59 (1H, d, *J* 5.5, C(3)*H*), 3.64 (1H, d, *J* 14.8, NCH_AH$_B$Ar), 3.79 (3H, s, O*Me*), 4.18 (1H, d, *J* 14.8, NCH$_A$*H*$_B$Ar), 4.32 (1H, q, *J* 6.3, C(1)*H*), 4.46 (1H, d, *J* 5.5, C(4)*H*), 6.80 (2H, d, *J* 8.7, C(3′)*H*, C(5′)*H*), 6.91 (1H, d, *J* 7.7, C(5)*H*), 7.04–7.11 (3H, m, *Ar*), 7.17–7.23 (2H, m, *Ar*), 7.54 (2H, d, *J* 8.2, C(3″)*H*, C(5″)*H*), 7.60 (2H, d, *J* 8.2, C(2″)*H*, C(6″)*H*); δ_C (125 MHz, $CDCl_3$) 23.3 (C(1)*Me*), 28.1 (C*Me*$_3$), 47.8, (*C*(4)), 55.1 (NCH_2Ar), 55.2 (O*Me*), 55.8 (*C*(1)), 64.2 (*C*(3)), 81.0 (*C*Me$_3$), 113.5 (*C*(3′), *C*(5′)), 124.3 (q, *J* 271.8, *C*F_3), 125.3 (q, *J* 3.8, *C*(3″), *C*(5″)), 125.3 (*C*(8)), 126.0, 126.1 (*C*(6), *C*(7)), 127.8 (*C*(5)), 128.6 (*C*(2″), *C*(6″)), 129.3 (q, *J* 31.5, *C*(4″)), 131.3 (*C*(2′), *C*(6′)), 131.9 (*C*(1′)), 134.5 (*C*(4a)), 140.7 (*C*(8a)), 143.9 (*C*(1″)), 158.6 (*C*(4′)), 170.4 (*C*O_2^{t}Bu); δ_F (377 MHz, $CDCl_3$) −62.3 (CF_3); *m*/*z* (ESI$^+$) 512 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{30}H_{33}F_3NO_3^+$ ([M+H]$^+$) requires 512.2407; found 512.2404.

4.53. (1*R*,3*S*,4*S*)-1-Methyl-3-(*tert*-butoxycarbonyl)-4-[4′-(trifluoromethyl)phenyl]-1,2,3,4-tetrahydroisoquinoline 102

Following *general procedure III*, Pd(OH)$_2$/C (26 mg, 25% w/w) was reacted with **91** (105 mg, 0.19 mmol, >99:1 dr) in MeOH (1 mL) for 5 days. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 2:1, 1% Et_3N) gave **102** as a colourless oil (32 mg, 43%, >99:1 dr); ν_{max} (ATR) 3322 (N–H), 1729 (C=O), 1369 (C–F); $[\alpha]_D^{20}$ +44.4 (*c* 0.5 in $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 1.31 (9H, s, C*Me*$_3$), 1.56 (3H, d, *J* 6.8, C(1)*Me*), 1.98 (1H, br s, N*H*), 3.81 (1H, d, *J* 6.3, C(3)*H*), 4.38 (1H, q, *J* 6.8, C(1)*H*), 4.39 (1H, d, *J* 6.3, C(4)*H*), 6.81 (1H, d, *J* 7.7, C(5)*H*), 7.07–7.11 (1H, m, *Ar*), 7.17–7.23 (2H, m, *Ar*), 7.31 (2H, d, *J* 8.1, C(3′)*H*, C(5′)*H*), 7.57 (2H, d, *J* 8.1, C(2′)*H*, C(6′)*H*); δ_C (125 MHz, $CDCl_3$) 23.8 (C(1)*Me*), 27.8 (C*Me*$_3$), 47.4 (*C*(4)), 49.3 (*C*(1)), 60.3 (*C*(3)), 81.6 (*C*Me$_3$), 124.3 (q, *J* 271.8, *C*F_3), 125.2 (q, *J* 3.8, *C*(3′), *C*(5′)), 126.1 (*C*(8)), 126.5, 126.7 (*C*(6), *C*(7)), 128.9 (q, *J* 32.4, *C*(4′)), 129.6 (*C*(2′), *C*(6′)), 129.8 (*C*(5)), 134.9 (*C*(4a)), 139.8 (*C*(8a)), 148.0 (*C*(1′)), 171.8 (*C*O_2^{t}Bu); δ_F (377 MHz, $CDCl_3$) −62.4 (CF_3); *m*/*z* (ESI$^+$) 392 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{22}H_{25}F_3NO_2^+$ ([M+H]$^+$) requires 392.1832; found 392.1831.

4.54. (1*R*,3*S*,4*S*)-1-Methyl-3-(*tert*-butoxycarbonyl)-4-(3′-fluorophenyl)-1,2,3,4-tetrahydroisoquinoline 103

Following *general procedure III*, Pd(OH)$_2$/C (50 mg, 25% w/w) was reacted with **92** (200 mg, 0.40 mmol, >99:1 dr) in MeOH (1 mL) for 5 days. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 2:1, 1% Et_3N) gave **103** as a colourless oil (51 mg, 37%, >99:1 dr); ν_{max} (ATR) 3402 (N–H), 1725 (C=O), 1152 (C–F); $[\alpha]_D^{20}$ +79.1 (*c* 1.0 in $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 1.32 (9H, s, C*Me*$_3$), 1.55 (3H, d, *J* 6.6, C(1)*Me*), 2.03 (1H, br s, N*H*), 3.82 (1H, d, *J* 6.6, C(3)*H*), 4.30 (1H, d, *J* 6.6, C(4)*H*), 4.36 (1H, q, *J* 6.6, C(1)*H*), 6.85 (1H, d, *J* 7.7, C(5)*H*), 6.87–6.91 (1H, m, C(2′)*H*), 6.92–6.97 (1H, m, C(4′)*H*), 6.98 (1H, d, *J* 7.7, C(6′)*H*), 7.07–7.11 (1H, m, *Ar*), 7.15–7.22 (2H, m, *Ar*), 7.24–7.30 (1H, m, C(5′)*H*); δ_C (125 MHz, $CDCl_3$) 23.8 (C(1)*Me*), 27.8 (C*Me*$_3$), 47.4 (*C*(4)), 49.4 (*C*(1)), 60.3 (*C*(3)), 81.4 (*C*Me$_3$), 113.0 (d, *J* 21.0, *C*(4′)), 116.2 (d, *J* 21.9, *C*(2′)), 124.9 (d, *J* 2.9, *C*(6′)), 126.0 (*C*(8)), 126.4, 126.6 (*C*(6), *C*(7)), 129.7 (d, *J* 8.6, *C*(5′)), 129.8 (*C*(5)), 132.2 (*C*(4a)), 139.8 (*C*(8a)), 146.3 (d, *J* 6.7, *C*(1′)), 162.9 (d, *J* 246.1, *C*(3′)), 171.9 (*C*O_2^{t}Bu); δ_F (377 MHz, $CDCl_3$) −113.4 (C(3′)*F*); *m*/*z* (ESI$^+$) 342 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{21}H_{25}FNO_2^+$ ([M+H]$^+$) requires 342.1864; found 342.1862.

4.55. (1*R*,3*S*,4*S*)-1-Methyl-3-(*tert*-butoxycarbonyl)-4-(3′-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline 104

Following *general procedure III*, Pd(OH)$_2$/C (40 mg, 40% w/w) was reacted with **93** (100 mg, 0.20 mmol, >99:1 dr) in MeOH (1 mL) for 48 h. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 2:1, 1% Et_3N) gave **104** as a colourless oil (51 mg, 74%, >99:1 dr); ν_{max} (ATR) 3405 (N–H), 1725 (C=O); $[\alpha]_D^{20}$ +67.9 (*c* 1.0 in $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 1.31 (9H, s, C*Me*$_3$), 1.55 (3H, d, *J* 6.8, C(1)*Me*), 1.95 (1H, br s, N*H*), 3.77 (3H, s, O*Me*), 3.85 (1H, d, *J* 6.7, C(3)*H*), 4.26 (1H, d, *J* 6.7, C(4)*H*), 4.36 (1H, q, *J* 6.8, C(1)*H*), 6.70–6.81 (3H, m, C(2′)*H*, C(4′)*H*, C(6′)*H*), 6.88 (1H, d, *J* 7.7, C(5)*H*), 7.04–7.10 (1H, m, *Ar*), 7.13–7.25 (3H, m, *Ar*); δ_C (125 MHz, $CDCl_3$) 23.9 (C(1)*Me*), 27.8 (C*Me*$_3$), 47.8 (*C*(4)), 49.5 (*C*(1)), 55.1 (O*Me*), 60.3 (*C*(3)), 81.2 (*C*Me$_3$), 111.7 (*C*(4′)), 115.4 (*C*(2′)), 121.7 (*C*(6′)), 125.9 (*C*(8)), 126.3, 126.4 (*C*(6), *C*(7)), 129.3 (*C*(5′)), 129.8 (*C*(5)), 135.8 (*C*(4a)), 139.8 (*C*(8a)), 145.1 (*C*(1′)), 159.5 (*C*(3′)), 172.1 (*C*O_2^{t}Bu); *m*/*z* (ESI$^+$) 354 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{22}H_{28}NO_3^+$ ([M+H]$^+$) requires 354.2064; found 354.2062.

4.56. (1*R*,3*S*,4*S*)-1-Methyl-3-(*tert*-butoxycarbonyl)-4-phenyl-1,2,3,4-tetrahydroisoquinoline 105

Following *general procedure III*, Pd(OH)$_2$/C (35 mg, 40% w/w) was reacted with **94** (139 mg, 0.29 mmol, >99:1 dr) in MeOH (1 mL) for 48 h. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 2:1, 1% Et_3N) gave **105** as a pale yellow oil (55 mg, 59%, >99:1 dr); ν_{max} (ATR) 3290 (O–H), 1724 (C=O); $[\alpha]_D^{20}$ +87.7 (*c* 1.0 in $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 1.30 (9H, s, C*Me*$_3$), 1.57 (3H, d, *J* 6.8, C(1)*Me*), 2.01 (1H, br s, N*H*), 3.85 (1H, d, *J* 7.1, C(3)*H*), 4.28 (1H, d, *J* 7.1, C(4)*H*), 4.37 (1H, q, *J* 6.8, C(1)*H*), 6.85 (1H, d, *J* 7.7, C(5)*H*), 7.05–7.10 (1H, m, *Ar*), 7.13–7.34 (7H, m, *Ar*, *Ph*); δ_C (125 MHz, $CDCl_3$) 23.9 (C(1)*Me*), 27.8 (C*Me*$_3$), 47.9 (*C*(4)), 49.6 (*C*(1)), 60.3 (*C*(3)), 81.2 (*C*Me$_3$), 125.9 (*C*(8)), 126.3, 126.3 (*C*(6), *C*(7)), 126.6 (*p-Ph*), 128.3, 129.3 (*o*,*m-Ph*), 129.8 (*C*(5)), 136.1 (*C*(4a)), 139.9 (*C*(8a)), 143.4 (*i-Ph*), 172.1 (*C*O_2^{t}Bu); *m*/*z* (ESI$^+$) 324 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{21}H_{26}NO_2^+$ ([M+H]$^+$) requires 324.1958; found 324.1956.

4.57. (1*R*,3*S*,4*S*)-1-Methyl-3-(*tert*-butoxycarbonyl)-4-(4′-fluorophenyl)-1,2,3,4-tetrahydroisoquinoline 106

Following *general procedure III*, Pd(OH)$_2$/C (29 mg, 25% w/w) was reacted with **84** (115 mg, 0.23 mmol, >99:1 dr) in MeOH (1 mL) for 5 days. Purification via flash column chromatography (eluent 30–40 °C petrol/Et$_2$O, 2:1, 1% Et$_3$N) gave **106** as a colourless oil (57 mg, 72%, >99:1 dr); ν_{max} (ATR) 3394 (N–H), 1726 (C=O), 1151 (C–F); $[\alpha]_D^{20}$ +55.3 (*c* 1.0 in CHCl$_3$); δ_H (500 MHz, CDCl$_3$) 1.31 (9H, s, C*Me*$_3$), 1.55 (3H, d, *J* 6.8, C(1)*Me*), 1.95 (1H, br s, N*H*), 3.79 (1H, d, *J* 6.8, C(3)*H*), 4.28 (1H, d, *J* 6.8, C(4)*H*), 4.35 (1H, q, *J* 6.8, C(1)*H*), 6.82 (1H, d, *J* 7.7, C(5)*H*), 6.97–7.02 (2H, m, C(3′)*H*, C(5′)*H*), 7.06–7.10 (1H, m, *Ar*), 7.11–7.21 (4H, m, *Ar*); δ_C (125 MHz, CDCl$_3$) 23.9 (C(1)*Me*), 27.9 (C*Me*$_3$), 47.0 (*C*(4)), 49.5 (*C*(1)), 60.4 (*C*(3)), 81.4 (*C*Me$_3$), 115.1 (d, *J* 21.0, *C*(3′), *C*(5′)), 126.0 (*C*(8)), 126.4, 126.4 (*C*(6), *C*(7)), 129.7 (*C*(5)), 130.7 (d, *J* 7.6, *C*(2′), *C*(6′)), 135.9 (*C*(4a)), 139.3 (d, *J* 3.8, *C*(1′)), 139.8 (*C*(8a)), 161.8 (d, *J* 244.1, *C*(4′)), 172.1 (*C*O$_2$^{t}Bu); δ_F (377 MHz, CDCl$_3$) −116.4 (C(4′)*F*); *m*/*z* (ESI$^+$) 342 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{21}H_{25}FNO_2^+$ ([M+H]$^+$) requires 342.1864; found 342.1865.

4.58. (1*R*,3*S*,4*S*)-1-Methyl-3-(*tert*-butoxycarbonyl)-4-(4′-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline 107

Following *general procedure III*, Pd(OH)$_2$/C (24 mg, 40% w/w) was reacted with **95** (60 mg, 0.12 mmol, >99:1 dr) in MeOH (1 mL) for 48 h. Purification via flash column chromatography (eluent 30–40 °C petrol/Et$_2$O, 2:1, 1% Et$_3$N) gave **107** as a colourless oil (25 mg, 61%, >99:1 dr); ν_{max} (ATR) 3378 (N–H), 1725 (C=O); $[\alpha]_D^{20}$ +72.0 (*c* 1.0 in CHCl$_3$); δ_H (500 MHz, CDCl$_3$) 1.31 (9H, s, C*Me*$_3$), 1.56 (3H, d, *J* 6.9, C(1)*Me*), 3.88 (3H, s, O*Me*), 3.81 (1H, d, *J* 7.1, C(3)*H*), 4.24 (1H, d, *J* 7.1, C(4)*H*), 4.38 (1H, q, *J* 6.9, C(1)*H*), 6.83–6.87 (3H, m, C(5)*H*, C(3′)*H*, C(5′)*H*), 7.05–7.10 (3H, m, *Ar*), 7.13–7.20 (2H, m, *Ar*); δ_C (125 MHz, CDCl$_3$) 23.8 (C(1)*Me*), 27.8 (C*Me*$_3$), 47.0 (*C*(4)), 49.6 (*C*(1)), 55.2 (O*Me*), 60.4 (*C*(3)), 81.3 (*C*Me$_3$), 113.7 (*C*(3′), *C*(5′)), 125.9 (*C*(8)), 126.3, 126.3 (*C*(6), *C*(7)), 129.8 (*C*(5)), 130.2 (*C*(2′), *C*(6′)), 135.4 (*C*(4a)), 136.3 (*C*(1′)), 139.7 (*C*(8a)), 158.3 (*C*(4′)), 172.1 (*C*O$_2$^{t}Bu); *m*/*z* (ESI$^+$) 354 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{22}H_{28}NO_3^+$ ([M+H]$^+$) requires 354.2064; found 354.2064.

4.59. (*RS*)-*N*-Benzyl-*N*-[α-methyl-4-(trifluoromethyl)benzyl]-amine (*RS*)-109

p-(Trifluoromethyl)acetophenone **108** (2.00 g, 10.6 mmol) was added to a stirred solution of benzylamine (1.10 mL, 10.1 mmol) in EtOH (6.5 mL) and the resultant mixture was heated at reflux for 3 h. The reaction mixture was allowed to cool to rt, then cooled to 0 °C. NaBH$_4$ (382 mg, 10.1 mmol) was added portionwise (maintaining the reaction temperature below 15 °C), and the resultant mixture was stirred at rt for 20 h. The reaction mixture was then concentrated in vacuo and the residue was partitioned CH$_2$Cl$_2$ (10 mL) and H$_2$O (10 mL). The aqueous layer was extracted with CH$_2$Cl$_2$ (2×8 mL) and the combined organic extracts were then dried and concentrated in vacuo to give (*RS*)-**109** as a pale yellow oil (1.25 g, 42%); ν_{max} (ATR) 3321 (N–H), 1323 (C–F); δ_H (400 MHz, CDCl$_3$) 1.35 (3H, d, *J* 6.6, C(α)*Me*), 1.70 (1H, br s, N*H*), 3.56 (1H, d, *J* 13.2, NC*H*$_A$H$_B$Ph), 3.63 (1H, d, *J* 13.2, NCH$_A$*H*$_B$Ph), 3.87 (1H, q, *J* 6.6, C(α)*H*), 6.20–7.34 (5H, m, *Ph*), 7.48 (2H, d, *J* 7.8, C(2)*H*, C(6)*H*), 7.59 (2H, d, *J* 7.8, C(3)*H*, C(5)*H*); δ_C (100 MHz, CDCl$_3$) 24.2 (C(α)*Me*), 51.3 (NCH$_2$Ph), 56.9 (*C*(α)), 124.0 (q, *J* 271.8, *C*F$_3$), 125.1 (q, *J* 4.0, *C*(3), *C*(5)), 126.7 (*p*-*Ph*), 126.7 (*C*(2), *C*(6)), 127.7, 128.1 (*o*,*m*-*Ph*), 128.9 (q, *J* 31.8, *C*(4)), 139.9, 149.4 (*i*-*Ph*, *C*(1)); δ_F (377 MHz, CDCl$_3$) −62.2 (C*F*$_3$); *m*/*z* (ESI$^+$) 280 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{16}H_{17}F_3N^+$ ([M+H]$^+$) requires 280.1308; found 280.1305.

4.60. *tert*-Butyl (*RS*,*RS*,*RS*)-2-hydroxy-3-{*N*-benzyl-*N*-[α-methyl-4′-(trifluoromethyl)benzyl]amino}-3-phenylpropanoate (*RS*,*RS*,*RS*)-110

Following *general procedure I*, BuLi (2.2 M in hexanes, 3.45 mL, 7.60 mmol) and (*RS*)-**109** (2.19 g, 7.84 mmol) were reacted with **65** (1.00 g, 4.90 mmol) and (−)-CSO (1.91 g, 8.33 mmol) in THF (40 mL). Purification via flash column chromatography (eluent 30–40 °C petrol/Et$_2$O, 5:1) gave (*RS*,*RS*,*RS*)-**110** as a colourless oil (1.08 g, 64%, >99:1 dr); ν_{max} (ATR) 3491 (O–H), 1722 (C=O), 1325 (C–F); δ_H (400 MHz, CDCl$_3$) 1.16 (3H, d, *J* 6.9, C(α)*Me*), 1.18 (9H, s, C*Me*$_3$), 2.83 (1H, d, *J* 4.7, O*H*), 3.85 (1H, d, *J* 14.7, NC*H*$_A$H$_B$Ph), 4.14 (1H, d, *J* 3.1, C(3)*H*), 4.15 (1H, d, *J* 14.7, NCH$_A$*H*$_B$Ph), 4.32 (1H, q, *J* 6.9, C(α)*H*), 4.43 (1H, dd, *J* 4.7, 3.1, C(2)*H*), 7.19–7.35 (8H, m, *Ph*), 7.44–7.48 (2H, m, *Ph*), 7.59 (2H, d, *J* 8.8, C(3′)*H*, C(5′)*H*), 7.63 (2H, d, *J* 8.8, C(2′)*H*, C(6′)*H*); δ_C (100 MHz, CDCl$_3$) 14.0 (C(α)*Me*), 27.6 (C*Me*$_3$), 52.2 (NCH$_2$Ph), 56.8 (*C*(α)), 64.8 (*C*(3)), 74.1 (*C*(2)), 82.4 (*C*Me$_3$), 124.3 (q, *J* 271.8, *C*F$_3$), 124.9 (q, *J* 4.0, *C*(3′), *C*(5′)), 126.8, 127.7 (*p*-*Ph*), 128.1, 128.1, 128.3, 129.8 (*o*,*m*-*Ph*), 128.2 (*C*(2′), *C*(6′)), 129.0 (q, *J*, 32.6, *C*(4′)), 137.9, 141.2, 148.7 (*C*(1′), *i*-*Ph*), 171.2 (*C*(1)); δ_F (377 MHz, CDCl$_3$) −62.3 (C*F*$_3$); *m*/*z* (ESI$^+$) 500 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{29}H_{33}F_3NO_3^+$ ([M+H]$^+$) requires 500.2407; found 500.2403.

4.61. (3*RS*,4*RS*,α*SR*)-*N*(2)-[α-Methyl-4′-(trifluoromethyl)-benzyl]-3-(*tert*-butoxycarbonyl)-4-phenyl-1,2,3,4-tetrahydroisoquinoline (3*RS*,4*RS*,α*SR*)-111

Following *general procedure II*, Tf$_2$O (250 μL, 1.50 mmol) was reacted with (*RS*,*RS*,*RS*)-**110** (500 mg, 1.00 mmol, >99:1 dr) and DTBMP (610 mg, 3.0 mmol) in CH$_2$Cl$_2$ (15 mL) rt for 6 h. Purification via flash column chromatography (eluent 30–40 °C petrol/Et$_2$O, 30:1) gave (3*RS*,4*RS*,α*SR*)-**111** as a white solid (328 mg, 68%, >99:1 dr); mp 123–125 °C; ν_{max} (ATR) 1724 (C=O), 1324 (C–F); δ_H (500 MHz, CDCl$_3$) 1.15 (3H, d, *J* 6.8, C(α)*Me*), 1.38 (9H, s, C*Me*$_3$), 3.71 (1H, d, *J* 15.8, C(1)*H*$_A$), 3.91 (1H, d, *J* 15.8, C(1)*H*$_B$), 4.03 (1H, q, *J* 6.8, C(α)*H*), 4.08 (1H, d, *J* 1.6, C(3)*H*), 4.62 (1H, d, *J* 1.6, C(4)*H*), 6.96 (1H, d, *J* 7.1, C(8)*H*), 7.04 (1H, d, *J* 7.3, C(5)*H*), 7.08–7.16 (2H, m, C(6)*H*, C(7)*H*), 7.16 (2H, d, *J* 7.1, *Ph*), 7.24 (2H, d, *J* 8.2, C(2′)*H*, C(6′)*H*), 7.25–7.35 (3H, m, *Ph*), 7.48 (2H, d, *J* 8.2, C(3′)*H*, C(5′)*H*); δ_C (125 MHz, CDCl$_3$) 21.0 (C(α)*Me*), 28.1 (C*Me*$_3$), 47.9, (*C*(4)), 49.9 (*C*(1)), 61.8 (*C*(α)), 62.7 (*C*(3)), 81.4 (*C*Me$_3$), 124.3 (q, *J* 262.3, *C*F$_3$), 125.3 (q, *J* 3.8, *C*(3′), *C*(5′)), 126.0 (*C*(8)), 126.2, 126.2 (*C*(6), *C*(7)), 126.3 (*p*-*Ph*), 127.3 (*C*(2′), *C*(6′)), 127.9, 128.9 (*o*,*m*-*Ph*), 129.0 (q, *J* 32.4, *C*(4′)), 129.7 (*C*(5)), 134.6 (*C*(4a)), 134.9 (*C*(8a)), 145.1 (*i*-*Ph*), 150.6 (*C*(1′)), 170.8 (*C*O$_2$^{t}Bu); δ_F (377 MHz, CDCl$_3$) −62.3 (C*F*$_3$); *m*/*z* (ESI$^+$) 482 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{29}H_{31}F_3NO_2^+$ ([M+H]$^+$) requires 482.2301; found 482.2287.

4.62. *tert*-Butyl (2*RS*,3*RS*,α*SR*)-2-{*N*-[α-methyl-4″-(trifluoromethyl)benzyl]amino}-3-(2′-methylphenyl)-3-phenylpropanoate (2*RS*,3*RS*,α*SR*)-112, (*RS*,*RS*)-3-(*tert*-butoxycarbonyl)-4-phenyl-1,2,3,4-tetrahydroisoquinoline (*RS*,*RS*)-113 and *tert*-butyl (*RS*,*RS*)-2-amino-3-(2′-methylphenyl)-3-phenylpropanoate (*RS*,*RS*)-114

Pd/C (100 mg, 100% w/w) and HCO$_2$NH$_4$ (132 mg, 3.28 mmol) were added to a stirred, degassed solution of (3*RS*,4*RS*,α*SR*)-**111** (100 mg, 0.328 mmol, >99:1 dr) in MeOH (4.6 mL) at rt and the resultant mixture was stirred at rt for 5 min, then heated at reflux for 3 h. The reaction mixture was then allowed to cool to rt, filtered through Celite® (eluent MeOH), and concentrated in vacuo to give a 3:77:20 mixture of (2*RS*,3*RS*,α*SR*)-**112**, (*RS*,*RS*)-**113** and (*RS*,*RS*)-**114**, respectively. Purification via flash column chromatography (eluent 30–40 °C petrol/acetone, 10:1) gave (*RS*,*RS*)-**114** as a pale yellow solid (12 mg, 12%, >99:1 dr); mp 57.5–59 °C; ν_{max} (ATR) 1735 (C=O); δ_H (500 MHz, CDCl$_3$) 1.16 (9H, s, C*Me*$_3$), 2.00–2.10 (2H, br s, N*H*$_2$),

2.32 (3H, s, C(2′)*Me*), 4.15 (1H, d, *J* 9.9, C(2)*H*), 4.33 (1H, d, *J* 9.9, C(3)*H*), 7.14 (2H, d, *J* 3.9, *Ph*), 7.16–7.28 (6H, m, *Ar*, *Ph*), 7.59 (1H, d, *J* 7.7, *Ar*); δ_C (125 MHz, $CDCl_3$) 28.7 (C*Me*$_3$), 31.9 (C(2′)*Me*), 52.7 (*C*(3)), 59.6 (*C*(2)), 81.1 (*C*Me$_3$), 125.0 (*p*-*Ph*), 126.3 (*C*(6′)), 126.6, 126.6 (*C*(4′), *C*(5′)), 128.3 (*m*-*Ph*), 129.0 (*o*-*Ph*), 131.0 (*C*(3′)), 137.4 (*C*(2′)), 139.3 (*C*(1′)), 140.4 (*i*-*Ph*), 173.3 (*C*(1)); *m*/*z* (ESI$^+$) 312 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{20}H_{26}NO_2^+$ ([M+H]$^+$) requires 312.1958; found 312.1960. Further elution gave (*RS*,*RS*)-**113** as a pale yellow solid (38 mg, 59%, >99:1 dr); mp 111.5–113 °C; ν_{max} (ATR) 1727 (C=O); δ_H (500 MHz, $CDCl_3$) 1.26 (9H, s, C*Me*$_3$), 1.78 (1H, br s, N*H*), 3.71 (1H, d, *J* 9.0, C(3)*H*), 4.16–4.26 (3H, m, C(1)H_2, C(4)*H*), 6.82 (1H, d, *J* 7.7, C(5)*H*), 7.04–7.09 (2H, m, *Ar*, *Ph*), 7.13–7.18 (3H, m, *Ar*, *Ph*), 7.22–7.33 (3H, m, *Ar*, *Ph*); δ_C (125 MHz, $CDCl_3$) 27.7 (C*Me*$_3$), 47.1 (*C*(1)), 48.3, (*C*(4)), 64.2 (*C*(3)), 81.3 (*C*Me$_3$), 125.5 (*C*(8)), 126.3, 126.4, 126.8 (*C*(6), *C*(7), *p*-*Ph*), 128.4 (*m*-*Ph*), 129.4 (*o*-*Ph*), 129.8 (*C*(5)), 135.0 (*C*(8a)), 137.3 (*C*(4a)), 142.6 (*i*-*Ph*), 171.9 (*C*O$_2$^{t}Bu); *m*/*z* (ESI$^+$) 310 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{20}H_{24}NO_2^+$ ([M+H]$^+$) requires 310.1802; found 310.1801. Data for (2*RS*,3*RS*,α*SR*)-**112**: δ_H (500 MHz, $CDCl_3$) 0.97 (9H, s, C*Me*$_3$), 1.21 (3H, d, *J* 6.6, C(α)*Me*), 1.89 (1H, br s, N*H*), 2.28 (3H, s, C(2′)*Me*), 3.60 (1H, q, *J* 6.6, C(α)*H*), 3.92 (1H, d, *J* 9.9, C(2)*H*), 4.36 (1H, d, *J* 9.9, C(3)*H*), 7.06–7.62 (13H, m, *Ar*, *Ph*); δ_C (125 MHz, $CDCl_3$) 20.0 (C(2′)*Me*), 23.5 (C(α)*Me*), 27.4 (C*Me*$_3$), 50.6 (*C*(3)), 57.7 (*C*(α)), 64.9 (*C*(2)), 80.9 (*C*Me$_3$), 124.2 (q, *J* 271.8, *C*F$_3$), 125.2 (q, *J* 3.8, *C*(3″), *C*(5″)), 125.9 (*p*-*Ph*), 126.4 (*C*(6′)), 126.5, 126.5 (*C*(4′), *C*(5′)), 127.2, 128.2 (*m*-*Ph*, *C*(2″), *C*(6″)), 129.4 (*o*-*Ph*), 129.2 (q, *J* 32.4, *C*(4″)), 130.7 (*C*(3′)), 137.2 (*C*(2′)), 139.4 (*C*(1′)), 140.0 (*i*-*Ph*), 149.8 (*C*(1″)), 173.3 (*C*(1)).

4.63. (1*RS**,3*RS*,4*RS*,α*SR*)-1-Hydroxy-*N*(2)-[α-methyl-4′-(trifluoromethyl)benzyl]-3-(*tert*-butoxycarbonyl)-4-phenyl-1,2,3,4-tetrahydroisoquinoline 115

CAN (205 mg, 0.347 mmol) was added to a stirred solution of (3*RS*,4*RS*,α*SR*)-**111** (30 mg, 62 μmol, >99:1 dr) in MeCN/H_2O (2:1, 0.6 mL) and the resultant solution was stirred at rt for 24 h. Satd aq $NaHCO_3$ (0.5 mL) was added and the resultant mixture was stirred at rt for 10 min, then extracted with Et_2O (3×2 mL). The combined organic extracts were then dried and concentrated in vacuo to give (1*RS**,3*RS*,4*RS*,α*SR*)-**115** as a yellow oil (29 mg, 94%, >99:1 dr); ν_{max} (ATR) 3642 (O–H), 1713 (C=O); δ_H (500 MHz, $CDCl_3$) 1.34 (3H, d, *J* 6.9, C(α)*Me*), 1.41 (9H, s, C*Me*$_3$), 3.94 (1H, d, *J* 1.3, C(3)*H*), 4.37 (1H, app s, C(4)*H*), 4.56 (1H, q, *J* 6.9, C(α)*H*), 4.85 (1H, d, *J* 11.0, O*H*), 5.39 (1H, d, *J* 11.0, C(1)*H*), 6.80 (2H, d, *J* 6.6, *o*-*Ph*), 6.95–7.02 (3H, m, C(2′)-*H*, C(6′)*H*, *p*-*Ph*), 7.12–7.33 (7H, m, *Ar*, *m*-*Ph*), 7.60 (1H, d, *J* 7.7, C(5)*H*); δ_C (125 MHz, $CDCl_3$) 19.4 (C(α)*Me*), 27.9 (C*Me*$_3$), 48.3 (*C*(4)), 56.9 (*C*(α)), 61.4 (*C*(3)), 79.9 (*C*(1)), 82.3 (*C*Me$_3$), 124.2 (q, *J* 271.8, *C*F$_3$), 124.7 (q, *J* 3.8, *C*(3′), *C*(5′)), 126.6, 127.3 (*Ar*), 127.4 (*C*(2′), *C*(6′)), 128.0 (*o*-*Ph*), 128.1 (*Ar*), 128.1 (*m*-*Ph*), 128.7 (q, *J* 32.4, *C*(4′)), 128.8 (*p*-*Ph*), 128.8 (*C*(5)), 132.2 (*C*(4a)), 138.2 (*C*(8a)), 143.7 (*i*-*Ph*), 147.7 (*C*(1′)), 175.8 (*C*O$_2$^{t}Bu); *m*/*z* (ESI$^+$) 480 ([M–OH]$^+$, 100%); HRMS (ESI$^+$) $C_{29}H_{29}F_3NO_2^+$ ([M–OH]$^+$) requires 480.2145; found 480.2143.

4.64. (3*RS*,4*RS*,α*SR*)-1-Oxo-*N*(2)-[α-methyl-4′-(trifluoromethyl)benzyl]-3-(*tert*-butoxycarbonyl)-4-phenyl-1,2,3,4-tetrahydroisoquinoline 116

A solution of $NaBrO_3$ (56 mg, 0.37 mmol) in H_2O (1.25 mL) was added to a stirred solution of (3*RS*,4*RS*,α*SR*)-**111** (60 mg, 0.13 mmol, >99:1 dr) in EtOAc (1.6 mL) at rt and the resultant mixture was stirred at rt for 10 min. A solution of $Na_2S_2O_4$ (54 mg, 0.37 mmol) in H_2O (2.3 mL) was added dropwise at rt over 5 min and the resultant mixture was stirred at rt for 4 h. EtOAc (4 mL) was then added and the resultant mixture was washed with satd aq $Na_2S_2O_3$ (4 mL). The aqueous layer was extracted with EtOAc (2×3 mL) and the combined organic extracts were washed with brine (5 mL), then dried and concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (5 mL) and the resultant solution was washed with 1.0 M aq HCl (3×4 mL). The combined aqueous layers were concentrated in vacuo to give (3*RS*,4*RS*,α*SR*)-**116** as a yellow oil (49 mg, 82%, >99:1 dr); ν_{max} (ATR) 1726, 1653 (C=O); δ_H (500 MHz, $CDCl_3$) 1.24 (9H, s, C*Me*$_3$), 1.47 (3H, d, *J* 7.2, C(α)*Me*), 3.89 (1H, d, *J* 1.9, C(3)*H*), 4.41–4.44 (1H, m, C(4)*H*), 6.14 (1H, q, *J* 7.2, C(α)*H*), 6.57 (2H, d, *J* 7.6, *o*-*Ph*), 6.86 (2H, d, *J* 8.0, C(2′)*H*, C(6′)*H*), 6.98 (2H, app t, *J* 7.7, *m*-*Ph*), 7.04–7.14 (4H, m, *Ar*, *Ph*), 7.44–7.51 (2H, m, *Ar*, *Ph*), 8.26–8.29 (1H, m, C(8)*H*); δ_C (125 MHz, $CDCl_3$) 14.9 (C(α)*Me*), 27.5 (C*Me*$_3$), 46.8 (*C*(4)), 50.2 (*C*(α)), 61.6 (*C*(3)), 82.7 (*C*Me$_3$), 124.0 (q, *J* 271.8, *C*F$_3$), 124.9 (q, *J* 3.8, *C*(3′), *C*(5′)), 127.1 (*p*-*Ph*), 127.3 (*C*(2′), *C*(6′)), 127.6 (*o*-*Ph*), 128.0 (*C*(8)), 128.1, 128.8 (*C*(6), *C*(7)), 128.4 (*m*-*Ph*), 128.9 (q, *J* 32.4, *C*(4′)), 130.8 (*C*(8a)), 132.3 (*C*(5)), 135.3 (*C*(4a)), 139.8 (*i*-*Ph*), 142.9 (*C*(1′)), 164.2 (*C*(1)), 170.5 (*C*O$_2$^{t}Bu); *m*/*z* (FI$^+$) 495 ([M]$^+$, 100%).[47]

4.65. (*RS*)-*N*-[α-Methyl-4-(trifluoromethyl)benzyl]amine (*RS*)-117

Ti(O^{i}Pr)$_4$ (31.5 mL, 106 mmol) was added to (*p*-trifluoromethyl) acetophenone **108** (10.0 g, 53.1 mmol) in NH_3 (2.0 M in EtOH, 133 mL) and the resultant mixture was stirred at rt for 6 h. $NaBH_4$ (3.01 g, 79.7 mmol) was added at 0 °C, and the resultant suspension was stirred at rt for 3 h, then poured into 2.0 M aq NH_4OH (200 mL). The resultant suspension was filtered (eluent EtOAc) and the aqueous layer was extracted with EtOAc (2×80 mL). The combined organic extracts were extracted with 1.0 M aq HCl (3×50 mL) and the combined aqueous extracts were washed with EtOAc (3×30 mL), treated with 2.0 M aq NaOH until pH>8 was observed, then extracted with EtOAc (4×50 mL). The combined organic extracts were washed with brine (200 mL), then dried and concentrated in vacuo to give (*RS*)-**117** as a pale yellow oil (6.84 g, 68%);[43] δ_H (400 MHz, $CDCl_3$) 1.40 (3H, d, *J* 6.6, C(α)*Me*), 1.59 (2H, br s, NH_2), 4.20 (1H, q, *J* 6.6, C(α)*H*), 7.48 (2H, d, *J* 7.8, C(2)*H*, C(6)*H*), 7.59 (2H, d, *J* 7.8, C(3)*H*, C(5)*H*).

4.66. (*R*)-*N*-[α-Methyl-4′-(trifluoromethyl)benzyl] (*R*)-2-acetoxy-2-phenylethanamide 118 and (*S*)-*N*-[α-methyl-4′-(trifluoromethyl)benzyl] (*R*)-2-acetoxy-2-phenylethanamide 119

DCC (2.35 g, 12.1 mmol) and DMAP (50 mg) were added to a stirred solution of (*RS*)-**117** (2.29 g, 12.1 mmol) and (*R*)-*O*-acetylmandelic acid (2.35 g, 12.1 mmol, >99:1 er) in CH_2Cl_2 (60 mL) at 0 °C and the resultant mixture was stirred at rt for 16 h. The reaction mixture was filtered and the filtrate was washed sequentially with 1.0 M aq HCl (40 mL), satd aq $NaHCO_3$ (40 mL) and brine (40 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 2:1, 1% Et_3N) gave **119** as a white solid (1.58 g, 36%, >99:1 dr); mp 132.5–133.5 °C; ν_{max} (ATR) 3292 (N–H), 1742, 1662 (C=O), 1327 (C–F); $[\alpha]_D^{20}$ −153.0 (*c* 1.0 in MeOH); δ_H (500 MHz, $CDCl_3$) 1.40 (3H, d, *J* 7.0, C(α)*Me*), 2.13 (3H, s, CO*Me*), 4.87 (1H, br s, N*H*), 5.00 (1H, q, *J* 7.0, C(α)*H*), 5.94 (1H, s, C(2)*H*), 7.33–7.39 (3H, m, C(2′)*H*, C(6′)*H*, *Ph*), 7.48–7.53 (4H, m, *Ph*), 7.58 (2H, d, *J* 8.2, C(3′)*H*, C(5′)*H*); δ_C (125 MHz, $CDCl_3$) 20.8 (CO*Me*), 22.1 (C(α)*Me*), 50.0 (*C*(α)), 77.2 (*C*(2)), 125.9 (q, *J* 269.9, *C*F$_3$), 126.4 (q, *J* 3.8, *C*(3′), *C*(5′)), 127.9 (*C*(2′), *C*(6′)), 128.7 (*o*-*Ph*), 129.8 (*m*-*Ph*), 130.2 (*p*-*Ph*), 130.3 (q, *J* 31.5, *C*(4′)), 136.8 (*i*-*Ph*), 149.5 (*C*(1′)), 171.0 (*C*(1)), 172.1 (*C*OMe); δ_F (377 MHz, $CDCl_3$) −63.9 (*C*F$_3$); *m*/*z* (ESI$^+$) 388 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{19}H_{18}F_3NNaO_3^+$ ([M+Na]$^+$) requires 388.1131; found 388.1122. Further elution gave **118** as a white solid (1.46 g, 33%, >99:1 dr); mp 118–120 °C; ν_{max} (ATR) 3291 (N–H), 1744, 1663 (C=O), 1327 (C–F); $[\alpha]_D^{20}$ −17.0 (*c* 1.0 in MeOH); δ_H (500 MHz, $CDCl_3$) 1.47 (3H, d, *J* 7.0, C(α)*Me*), 2.15 (3H, s, CO*Me*), 4.87 (1H, br s, N*H*), 5.06 (1H, q, *J* 7.0, C(α)*H*), 5.94 (1H, s, C(2)*H*), 7.24 (2H, d, *J* 8.4, C(2′)*H*, C(6′)*H*), 7.34–7.38 (3H, m, *Ph*), 7.44–7.49 (4H, m, C(3′)*H*, C(5′)*H*, *Ph*); δ_C (125 MHz, $CDCl_3$) 20.8 (CO*Me*), 22.0 (C(α)*Me*), 50.0 (*C*(α)), 77.1

(*C*(2)), 125.7 (q, *J* 270.8, *C*F$_3$), 126.4 (q, *J* 3.8, *C*(3′), *C*(5′)), 127.6 (*C*(2′), *C*(6′)), 128.8 (*o*-*Ph*), 129.8 (*m*-*Ph*), 130.2 (*p*-*Ph*), 130.3 (q, *J* 32.4, *C*(4′)), 136.7 (*i*-*Ph*), 149.5 (*C*(1′)), 170.9 (*C*(1)), 172.1 (*C*OMe); δ_F (377 MHz, $CDCl_3$) −63.7 (C*F*$_3$); *m*/*z* (ESI$^+$) 388 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{19}H_{18}F_3NNaO_3^+$ ([M+Na]$^+$) requires 388.1131; found 388.1120. A 57:43 mixture of **118** and **119**, respectively, was also recovered as a white solid (812 mg, 18%).

4.67. (*R*)-*N*-[α-Methyl-4-(trifluoromethyl)benzyl]amine (*R*)-117

A solution of **118** (100 mg, 0.27 mmol, >99:1 dr) in 4.5 M aq HBr (2 mL) was heated at reflux for 24 h, then allowed to cool to rt and concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (3 mL), and the resultant solution was extracted with 1.0 M aq HCl (4×3 mL). The combined aqueous extracts were treated with 2.0 M NaOH until pH>8 was observed, and the resultant mixture was extracted with CH_2Cl_2 (4×5 mL). The combined organic extracts were then dried and concentrated in vacuo to give (*R*)-**117** as a pale yellow oil (20 mg, 38%); $[\alpha]_D^{20}$ +22.0 (*c* 1.0 in MeOH); {lit.[44] $[\alpha]_D^{20}$ +20.0 (*c* 1.0 in MeOH)}.

4.68. (*R*)-*N*-Benzyl-*N*-[α-methyl-4-(trifluoromethyl)benzyl] amine (*R*)-109

A solution of **118** (1.52 g, 4.15 mmol, >99:1 dr) in 4.5 M aq HBr (10 mL) was heated at reflux for 24 h, then allowed to cool to rt and concentrated in vacuo. The residue was dissolved in EtOH (26 mL), then PhCHO (461 μL, 4.56 mmol) and K_2CO_3 (630 mg, 4.56 mmol) were added to the resultant solution. The resultant mixture was heated at reflux for 3 h, allowed to cool to rt, and then cooled further to 0 °C. $NaBH_4$ (157 mg, 4.15 mmol) was added and the reaction mixture was stirred at rt for 20 h, then concentrated in vacuo. The residue was partitioned between CH_2Cl_2 (20 mL) and H_2O (20 mL). The aqueous layer was extracted with CH_2Cl_2 (2×10 mL) and the combined organic extracts were dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 3:1, 1% Et_3N) gave (*R*)-**109** as a pale yellow oil (554 mg, 48% from **118**, >99:1 er);[45] $[\alpha]_D^{20}$ +47.8 (*c* 1.0 in MeOH).

4.69. (*S*)-*N*-Benzyl-*N*-[α-methyl-4-(trifluoromethyl)benzyl] amine (*S*)-109

A solution of **119** (1.58 g, 4.33 mmol, >99:1 dr) in 4.5 M aq HBr (10 mL) was heated at reflux for 24 h, then allowed to cool to rt and concentrated in vacuo. The residue was dissolved in EtOH (27 mL), then PhCHO (481 μL, 4.76 mmol) and K_2CO_3 (598 mg, 4.37 mmol) were added to the resultant solution. The resultant mixture was heated at reflux for 3 h, allowed to cool to rt, and then cooled further to 0 °C. $NaBH_4$ (163 mg, 4.33 mmol) was added and the reaction mixture was stirred at rt for 20 h, then concentrated in vacuo. The residue was partitioned between CH_2Cl_2 (20 mL) and H_2O (20 mL). The aqueous layer was extracted with CH_2Cl_2 (2×10 mL) and the combined organic extracts were dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 3:1, 1% Et_3N) gave (*S*)-**109** as a pale yellow oil (756 mg, 63% from **119**, >99:1 er);[45] $[\alpha]_D^{20}$ −45.7 (*c* 1.0 in MeOH).

4.70. *tert*-Butyl (*S*,*S*,*S*)-2-hydroxy-3-{*N*-benzyl-*N*-[α-methyl-4′-(trifluoromethyl)benzyl]amino}-3-phenylpropanoate (*S*,*S*,*S*)-110

Following *general procedure I*, BuLi (2.2 M in hexanes, 1.20 mL, 2.65 mmol) and (*S*)-**109** (718 mg, 2.57 mmol, >99:1 er) were reacted with **65** (350 mg, 1.71 mmol, >99:1 dr) and (+)-CSO (667 mg, 8.33 mmol) in THF (14 mL). Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 5:1) gave (*S*,*S*,*S*)-**110** as a colourless oil (800 mg, 94%, >99:1 dr); $[\alpha]_D^{20}$ +27.8 (*c* 1.0 in $CHCl_3$).

4.71. (3*R*,4*R*,α*S*)-*N*(2)-[α-Methyl-4′-(trifluoromethyl)benzyl]-3-(*tert*-butoxycarbonyl)-4-phenyl-1,2,3,4-tetrahydroisoquinoline (3*R*,4*R*,α*S*)-111

Following *general procedure II*, Tf_2O (252 μL, 1.50 mmol) was reacted with (*S*,*S*,*S*)-**110** (500 mg, 1.00 mmol, >99:1 dr) and DTBMP (620 mg, 3.0 mmol) in CH_2Cl_2 (15 mL) at rt for 6 h. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 30:1) gave (3*R*,4*R*,α*S*)-**111** as a white solid (449 mg, 93%, >99:1 dr); mp 95–97.5 °C; $[\alpha]_D^{20}$ +6.8 (*c* 1.0 in $CHCl_3$).

4.72. (*R*,*R*)-3-(*tert*-Butoxycarbonyl)-4-phenyl-1,2,3,4-tetrahydroisoquinoline (*R*,*R*)-113

Pd/C (100 mg, 100% w/w) and HCO_2NH_4 (132 mg, 3.28 mmol) were added to a stirred, degassed solution of (3*R*,4*R*,α*S*)-**111** (100 mg, 0.33 mmol, >99:1 dr) in MeOH (4.6 mL) and the resultant mixture was stirred at rt for 5 min, then heated at reflux for 3 h. The reaction mixture was then allowed to cool to rt, filtered through Celite® (eluent MeOH) and concentrated in vacuo to give a 9:74:17 mixture of (2*R*,3*R*,α*S*)-**112**, (*R*,*R*)-**113** and (*R*,*R*)-**114**, respectively. Purification via flash column chromatography (eluent 30–40 °C petrol/acetone, 10:1) gave (*R*,*R*)-**113** as a pale yellow solid (34 mg, 50%, >99:1 dr); mp 78.5–81 °C; $[\alpha]_D^{20}$ −30.8 (*c* 1.0 in $CHCl_3$).

Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2016.03.008.

References and notes

1. The term “tetrahydroisoquinoline” is used throughout this manuscript to mean “1,2,3,4-tetrahydroisoquinoline”.
2. (a) Scott, J. D.; Willams, R. M. *Chem. Rev.* **2002**, *102*, 1669; (b) Bru, C.; Guillou, C. *Tetrahedron* **2006**, *62*, 9043; (c) Avendano, C.; de la Cuesta, E. *Chem.—Eur. J.* **2010**, *16*, 9722; (d) Chen, C.-K.; Lin, F.-H.; Tseng, L.-H.; Jiang, C.-L.; Lee, S.-S. *J. Nat. Prod.* **2011**, *74*, 411.
3. Pechulis, A. D.; Beck, J. P.; Curry, M. A.; Wolf, M. A.; Harms, A. E.; Xi, N.; Opalka, C.; Sweet, M. P.; Yang, Z.; Vellekoop, A. S.; Klos, A. M.; Crocker, P. J.; Hassler, C.; Laws, M.; Kitchen, D. B.; Smith, M. A.; Olson, R. E.; Liu, S.; Molino, B. F. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 7219.
4. British Medical Association; British National Formulatory, **1982**.
5. Kunstmann, R.; Gerhards, H.; Kruse, H.; Leven, M.; Paulus, E. F.; Schacht, U.; Schmitt, K.; Witte, P. U. *J. Med. Chem.* **1987**, *30*, 798.
6. Evidente, A.; Kornienko, A. *Phytochem. Rev.* **2009**, *8*, 449.
7. Wang, P.; Yuan, H.-H.; Zhang, X.; Li, Y.-P.; Shang, L.-Q.; Yin, Z. *Molecules* **2014**, *19*, 2469.
8. Nair, J. J.; Rárová, L.; Strnad, M.; Bastida, J.; van Staden, J. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 6195.
9. (a) Bischler, A.; Napieralski, B. *Ber. Dtsch. Chem. Ges.* **1893**, *26*, 1903. See also: (b) Grunewald, G. L.; Sall, D. J.; Monn, J. A. *J. Med. Chem.* **1988**, *31*, 433; (c) Uematsu, N.; Fujii, A.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 4916; (d) Al-Hiari, Y. M.; Bennett, S. J.; Davies, R. J.; Khalaf, A. I.; Waigh, R. D.; Worsley, A. J.; Cox, B. *J. Heterocycl. Chem.* **2005**, *42*, 647.
10. (a) Pictet, A.; Spengler, T. *Ber. Dtsch. Chem. Ges.* **1911**, *44*, 2030. See also: (b) Stöckigt, J. *Phytochemistry* **1979**, *18*, 965; (c) Yokoyama, A.; Ohwada, T.; Shudo, K. *J. Org. Chem.* **1999**, *64*, 611; (d) Gremmen, C.; Wanner, M. J.; Koomen, G.-J. *Tetrahedron Lett.* **2001**, *42*, 8885; (e) Bonamore, A.; Barba, M.; Botta, B.; Boffi, A.; Macone, A. *Molecules* **2010**, *15*, 2070; (f) Pesnot, T.; Gershater, M. C.; Ward, J. M.; Hailes, H. C. *Chem. Commun.* **2011**, 3242.
11. (a) Rakshit, S.; Grohmann, C.; Besset, T.; Glorius, F. *J. Am. Chem. Soc.* **2011**, *133*, 2350; (b) Ye, B.; Carmer, N. *Science* **2012**, *338*, 504.
12. (a) Brozda, D.; Koroniak, L.; Rozwadowska, M. D. *Tetrahedron: Asymmetry* **2000**, *11*, 3017; (b) Saitoh, T.; Shikiya, K.; Hariguchi, Y.; Sano, T. *Chem. Pharm. Bull.* **2003**, *51*, 667; (c) Malhotra, R.; Chakrabarti, S.; Ghosh, A.; Ghosh, R.; Dey, T. K.; Dutta, S.; Dutta, S.; Roy, S.; Basu, S.; Hujra, S. *Tetrahedron: Asymmetry* **2013**, *24*, 278; (d) Pan, L.; Chen, R.; Dongshun, N.; Xia, L.; Chen, X. *Synlett* **2013**, 241.
13. (a) Chandrasekhar, S.; Mohanty, P. K.; Harikishan, K.; Sasmal, P. K. *Org. Lett.* **1999**, *1*, 877; (b) Weber, K.; Kuklinski, S.; Gmeiner, P. *Org. Lett.* **2000**, *2*, 647; (c) Chandrasekhar, S.; Reddy, N. R.; Reddy, M. V.; Jagannadh, B.; Nagaraju, A.; Ravi

Sankar, A.; Kunwar, A. *Tetrahedron Lett.* **2002**, *43*, 1885; (d) Concellón, J. M.; Tuya, P.; del Solar, V.; García-Granda, S.; Díaz, M. R. *Org. Lett.* **2009**, *11*, 3750; (e) Coote, S. J.; Davies, S. G.; Fletcher, A. M.; Roberts, P. M.; Thomson, J. E. *Chem.—Asian J.* **2010**, *5*, 589; (f) Catak, S.; D'hooghe, M.; De Kimpe, N.; Waroquier, M.; Van-Speybroek, V. *J. Org. Chem.* **2010**, *75*, 885; (g) Liebert, C.; Brinks, M. K.; Capucci, A. G.; Fleming, M. J.; Lautens, M. *Org. Lett.* **2011**, *13*, 3000; (h) Wang, S.; Chai, Z.; Zhou, S.; Wang, S.; Zhu, X.; Wei, Y. *Org. Lett.* **2013**, *15*, 2628; (i) Chong, H.-S.; Chen, Y. *Org. Lett.* **2013**, *15*, 5912; (j) Min, J.-Y.; Kim, G. *J. Org. Chem.* **2014**, *79*, 1444; (k) Tummanapalli, S.; Muthuraman, P.; Vangapandu, D. N.; Majumder, S. *Tetrahedron Lett.* **2014**, *55*, 6787.

14. (a) Teichert, J. F.; Fañanás-Mastral, M.; Feringa, B. L. *Angew. Chem., Int. Ed.* **2011**, *50*, 688; (b) Candito, D. A.; Dobrovolkyy, D.; Lautens, M. *J. Am. Chem. Soc.* **2012**, *132*, 15572; (c) Lui, Q.; Wu, Y.; Chen, P.; Liu, G. *Org. Lett.* **2013**, *15*, 6210; (d) Zotova, M.; Vorobyeva, D.; Dixneuf, P.; Bruneau, C.; Osipov, S. *Synlett* **2013**, 1517; (e) Chong, H.-S.; Sun, X.; Chen, Y.; Wang, M. *Tetrahedron Lett.* **2015**, *56*, 946.
15. Davies, S. G.; Fletcher, A. M.; Frost, A. B.; Roberts, P. M.; Thomson, J. E. *Org. Lett.* **2015**, *17*, 2254.
16. Davies, S. G.; Fletcher, A. M.; Frost, A. B.; Roberts, P. M.; Thomson, J. E. *Tetrahedron* **2014**, *70*, 5849.
17. Anderson, A. G.; Stang, P. J. *J. Org. Chem.* **1976**, *41*, 3034.
18. Dembinski, A.; Yagci, Y.; Schnabel, W. *Polymer* **1993**, *34*, 3738.
19. For *anti*-tetrahydroisoquinolines ^{1}H NMR $^{3}J_{3,4}$ coupling constants of 1.5–4.0 Hz are usually observed whereas values of 5.5–6.0 Hz are indicative of *syn*-tetrahydroisoquinolines; see: (a) Chen, W.; Cui, J.; Zhu, Y.; Hu, X.; Mo, W. *J. Org. Chem.* **2012**, *77*, 1585; (b) Hammad, S. F.; Smith, F. T. *J. Heterocycl. Chem.* **2013**, *50*, 114. See also: Ref. 12a.
20. Crystallographic data (excluding structure factors) for the structures of **16**, **60**, (±)-**111** and **118** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 1439612–1439616, respectively.
21. Davies, S. G.; Fletcher, A. M.; Frost, A. B.; Lee, J. A.; Roberts, P. M.; Thomson, J. E. *Tetrahedron* **2013**, *69*, 8885.
22. Attempted epimerisation of *anti*-**16** via our usual oxidation/diastereoselective reduction protocol produced a 55:45 mixture of *anti*-**16** and *syn*-**19**, respectively. For highly diastereoselective examples of this procedure, see: (a) Davies, S. G.; Fletcher, A. M.; Foster, E. M.; Lee, J. A.; Roberts, P. M.; Thomson, J. E. *J. Org. Chem.* **2013**, *78*, 2500; (b) Brambilla, M.; Davies, S. G.; Fletcher, A. M.; Hao, L.; Lv, L.; Roberts, P. M.; Thomson, J. E. *Tetrahedron* **2014**, *70*, 3491; (c) Davies, S. G.; Foster, E. M.; Lee, J. A.; Roberts, P. M.; Thomson, J. E. *J. Org. Chem.* **2014**, *79*, 9686. See also: Ref. 21.
23. α,β-Unsaturated esters **24**–**28** were synthesised in 25–55% yield and >99:1 dr [(*E*):(*Z*)] following a modified Wadsworth-Emmons procedure; see: Claridge, T. D. W.; Davies, S. G.; Lee, J. A.; Nicholson, R. L.; Roberts, P. M.; Russell, A. J.; Smith, A. D.; Toms, S. M. *Org. Lett.* **2008**, *10*, 5437.
24. Davies, S. G.; Foster, E. M.; McIntosh, C. R.; Roberts, P. M.; Rosser, T. E.; Smith, A. D.; Thomson, J. E. *Tetrahedron: Asymmetry* **2011**, *22*, 1035.
25. (a) Bunnage, M. E.; Davies, S. G.; Goodwin, C. J. *Synlett* **1993**, 731; (b) Bunnage, M. E.; Chernega, A. N.; Davies, S. G.; Goodwin, C. J. *J. Chem. Soc. Perkin Trans. 1* **1994**, 2373; (c) Bunnage, M. E.; Davies, S. G.; Goodwin, C. J. *J. Chem. Soc. Perkin Trans. 1* **1994**, 2385; (d) Bunnage, M. E.; Davies, S. G.; Goodwin, C. J.; Ichihara, O. *Tetrahedron* **1994**, *50*, 3975; (e) Bunnage, M. E.; Burke, A. J.; Davies, S. G.; Millican, N. L.; Nicholson, R. L.; Roberts, P. M.; Smith, A. D. *Org. Biomol. Chem.* **2003**, *1*, 3708.
26. For reviews of this methodology, see: (a) Davies, S. G.; Price, P. D.; Smith, A. D. *Tetrahedron: Asymmetry* **2005**, *16*, 2833; (b) Davies, S. G.; Fletcher, A. M.; Roberts, P. M.; Thomson, J. E. *Tetrahedron: Asymmetry* **2012**, *23*, 1111.
27. For further applications of our aminohydroxylation procedure, see: (a) Abraham, E.; Candela-Lena, J. I.; Davies, S. G.; Georgiou, M.; Nicholson, R. L.; Roberts, P. M.; Russell, A. J.; Sánchez-Fernández, E. M.; Smith, A. D.; Thomson, J. E. *Tetrahedron: Asymmetry* **2007**, *18*, 2510; (b) Abraham, E.; Davies, S. G.; Millican, N. L.; Nicholson, R. L.; Roberts, P. M.; Smith, A. D. *Org. Biomol. Chem.* **2008**, *6*, 1655; (c) Abraham, E.; Brock, E. A.; Candela-Lena, J. I.; Davies, S. G.; Georgiou, M.; Nicholson, R. L.; Perkins, J. H.; Roberts, P. M.; Russell, A. J.; Sánchez-Fernández, E. M.; Scott, P. M.; Smith, A. D.; Thomson, J. E. *Org. Biomol. Chem.* **2008**, *6*, 1665; (d) Davies, S. G.; Nicholson, R. L.; Price, P. D.; Roberts, P. M.; Russell, A. J.; Savory, E. D.; Smith, A. D.; Thomson, J. E. *Tetrahedron: Asymmetry* **2009**, *20*, 758; (e) Csatayová, K.; Davies, S. G.; Lee, J. A.; Roberts, P. M.; Russell, A. J.; Thomson, J. E.; Wilson, D. L. *Org. Lett.* **2011**, *13*, 2606; (f) Brock, E. A.; Davies, S. G.; Lee, J. A.; Roberts, P. M.; Thomson, J. E. *Org. Lett.* **2011**, *13*, 1594; (g) Davies, S. G.; Figuccia, A. L. A.; Fletcher, A. M.; Roberts, P. M.; Thomson, J. E. *Org. Lett.* **2013**, *15*, 2042; (h) Davies, S. G.; Fletcher, A. M.; Foster, E. M.; Lee, J. A.; Roberts, P. M.; Thomson, J. E.; Waul, M. A. *Tetrahedron* **2014**, *70*, 7106; (i) Davies, S. G.; Figuccia, A. L. A.; Fletcher, A. M.; Roberts, P. M.; Thomson, J. E. *Tetrahedron* **2014**, *70*, 3601; (j) Csatayová, K.; Davies, S. G.; Fletcher, A. M.; Ford, J. G.; Klauber, D. J.; Roberts, P. M.; Thomson, J. E. *J. Org. Chem.* **2014**, *79*, 10932; (k) Csatayová, K.; Davies, S. G.; Fletcher, A. M.; Ford, J. G.; Klauber, D. J.; Roberts, P. M.; Thomson, J. E. *Tetrahedron* **2015**, *71*, 7170. See also: Refs. 16, 21, 22a–c.
28. For *anti*-α-hydroxy-β-amino esters ^{1}H NMR $^{3}J_{2,3}$ coupling constants of ~4.0 Hz are usually observed whereas values of ~10.0 Hz are indicative of *syn*-α-hydroxy-β-amino esters; see: Refs. 16, 22a–c.
29. For *anti*-β-hydroxy-α-amino esters ^{1}H NMR $^{3}J_{2,3}$ coupling constants of ~8.0 Hz are usually observed whereas values of ~9.5 Hz are indicative of *syn*-β-hydroxy-α-amino esters; see: Refs. 16, 21.
30. Brown, H. C.; Okamoto, Y. *J. Am. Chem. Soc.* **1958**, *80*, 4979.
31. For similar Friedel–Crafts alkylation/fragmentation processes, see: (a) Yokosaka, T.; Nemoto, T.; Hamada, Y. *Chem. Commun.* **2012**, 5431; (b) Yokosaka, T.; Nemoto, T.; Hamada, Y. *Tetrahedron Lett.* **2013**, *54*, 1562; (c) Yokosaka, T.; Shiga, N.; Nemoto, T.; Hamada, Y. *J. Org. Chem.* **2014**, *79*, 3866.
32. (a) Davies, S. G.; Smyth, G. D. *Tetrahedron: Asymmetry* **1996**, *7*, 1001; (b) Garrido, N. M.; Díez, D.; Domínguez, S. H.; García, M.; Sánchez, M. R.; Davies, S. G. *Tetrahedron: Asymmetry* **2006**, *17*, 2183; (c) Chernega, A.; Davies, S. G.; Elend, D. L.; Smethurst, C. A. P.; Roberts, P. M.; Smith, A. D.; Smyth, G. D. *Tetrahedron* **2007**, *63*, 7036; (d) Davies, S. G.; Garner, A. C.; Goddard, E. C.; Kruchinin, D.; Roberts, P. M.; Smith, A. D.; Rodríguez-Solla, H.; Thomson, J. E.; Toms, S. M. *Org. Biomol. Chem.* **2007**, *5*, 1961; (e) Davies, S. G.; Russell, A. J.; Sheppard, R. L.; Smith, A. D.; Thomson, J. E. *Org. Biomol. Chem.* **2007**, *5*, 3190.
33. Costello, J. F.; Davies, S. G.; Ichihara, O. *Tetrahedron: Asymmetry* **1994**, *5*, 1999.
34. (a) Flack, H. D. *Acta Crystallogr. Sect. A* **1983**, *39*, 876; (b) Flack, H. D.; Bernardinelli, G. *J. Appl. Crystallogr.* **2000**, *33*, 1143.
35. (a) Davies, S. G.; Fenwick, D. R. *J. Chem. Soc., Chem. Commun.* **1995**, *109*; (b) Davies, S. G.; Fenwick, D. R.; Ichihara, O. *Tetrahedron: Asymmetry* **1997**, *8*, 3387; (c) Chippindale, A. M.; Davies, S. G.; Iwamoto, K.; Parkin, R. M.; Smethurst, C. A. P.; Smith, A. D.; Rodríguez-Solla, H. *Tetrahedron* **2003**, *59*, 3253; (d) Davies, S. G.; Haggitt, J. R.; Ichihara, O.; Kelly, R. J.; Leech, M. A.; Price Mortimer, A. J.; Roberts, P. M.; Smith, A. D. *Org. Biomol. Chem.* **2004**, *2*, 2630; (e) Davies, S. G.; Garner, A. C.; Nicholson, R. L.; Osborne, J.; Roberts, P. M.; Savory, E. D.; Smith, A. D.; Thomson, J. E. *Org. Biomol. Chem.* **2009**, *7*, 2604; (f) Davies, S. G.; Fletcher, A. M.; Roberts, P. M.; Smith, A. D. *Tetrahedron* **2009**, *65*, 10192; (g) Davies, S. G.; Fletcher, A. M.; Lee, J. A.; Lorkin, T. J. A.; Roberts, P. M.; Thomson, J. E. *Tetrahedron* **2013**, *69*, 9779.
36. α-Hydroxy-β-amino ester **69** (R=H) has been prepared previously; see: Davies, S. G.; Polywka, M. E. C.; Fenwick, D. R.; Reed, F. *PCT Int. Appl.* **1995** WO 9518134. See also: Refs. 15, 35a.
37. Amine (*R*)-**82** was assessed to be >99:1 er by ^{1}H NMR spectroscopic analysis in the presence of (*R*)-*O*-acteylmandelic acid (at rt in $CDCl_3$), and comparison with an authentic racemic sample.
38. Davies, S. G.; Garrido, N. M.; Kruchinin, D.; Ichihara, O.; Kotchie, L. J.; Price, P. D.; Price Mortimer, A. J.; Russell, A. J.; Smith, A. D. *Tetrahedron: Asymmetry* **2006**, *17*, 1793.
39. For applications of this procedure in debenzylation processes, see: Corr, M. J.; O'Hagan, D. *J. Fluor. Chem.* **2013**, *155*, 72 See also: Ref. 15.
40. Bull, S. D.; Davies, S. G.; Fenton, G.; Mulvaney, A. W.; Prasad, R. S.; Smith, A. D. *J. Chem. Soc. Perkin Trans. 1* **2000**, 3765.
41. For applications of this procedure in *N*-debenzylation processes, see: (a) Cailleau, T.; Cooke, J. W. B.; Davies, S. G.; Ling, K. B.; Naylor, A.; Nicholson, R. L.; Price, P. D.; Roberts, P. M.; Russell, A. J.; Smith, A. D.; Thomson, J. E. *Org. Biomol. Chem.* **2007**, *5*, 3922; (b) Davies, S. G.; Fletcher, A. M.; Hughes, D. G.; Lee, J. A.; Price, P. D.; Roberts, P. M.; Russell, A. J.; Smith, A. D.; Thomson, J. E.; Williams, O. M. H. *Tetrahedron* **2011**, *67*, 9975; (c) Davies, S. G.; Lee, J. A.; Roberts, P. M.; Shah, R. S.; Thomson, J. E. *Chem. Commun.* **2012**, 9236; (d) Davies, S. G.; Roberts, P. M.; Shah, R. S.; Thomson, J. E. *Tetrahedron Lett.* **2013**, *54*, 6423.
42. Gomtsyan, A.; Bayburt, E. K.; Keddy, R.; Turner, S. C.; Jinkerson, T. K.; Didomenico, S.; Perner, R. J.; Koenig, J. R.; Drizin, I.; McDonald, H. A.; Surowy, C. S.; Honore, P.; Mikusa, J.; Marsh, K. C.; Wetter, J. M.; Faltynek, C. R.; Lee, C.-H. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3894.
43. Miriyala, B.; Bhattacharyya, S.; Williamson, J. S. *Tetrahedron* **2004**, *60*, 1463.
44. Guijarro, D.; Pablo, O.; Yus, M. *J. Org. Chem.* **2010**, *75*, 5265.
45. Amines (*R*)-**109** and (*S*)-**109** were assessed to be >99:1 er by ^{1}H NMR spectroscopic analysis in the presence of (*R*)-*O*-acteylmandelic acid (at rt in $CDCl_3$), and comparison with an authentic racemic sample.
46. Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. *J. Organometallics* **1996**, *15*, 1518.
47. Attempted analysis of **116** by high resolution mass spectrometry (FI^{+}) failed to produce satisfactory data.