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Enantiospecific Stereodivergent Synthesis of *trans*- and *cis*-*N*(2),3-Dimethyl-4-phenyl-1,2,3,4-tetrahydroisoquinolines

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Dedicated to the 150th anniversary of Japan–UK diplomatic relations

Abstract: The acid-promoted cyclizations of a range of *N*-benzylethanolamines (derived from pseudoephedrine or ephedrine) give the corresponding *trans*-*N*(2),3-dimethyl-4-phenyl-1,2,3,4-tetrahydroisoquinolines with high levels of diastereoselectivity and in good yields of isolated product. The cyclizations of the corresponding chromium tricarbonyl complexes are rendered completely stereoselective. Acid-promoted cyclization of *N*-(3′,4′-dimethoxybenzyl)ephedrine and its chromium tricarbonyl complex occur with complementary diastereoselectivities to give *trans*- and *cis*-*N*(2),3-dimethyl-4-phenyl-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline, respectively, in >99:1 d.r. The latter is consistent with a "double inversion" mechanism, which involves neighboring group participation by the chromium tricarbonyl moiety followed by rearomatization to give the corresponding *cis*-tetrahydroisoquinoline with overall retention of configuration.

Keywords: chromium · cyclization · ephedrine · pseudoephedrine · tetrahydroisoquinoline

Introduction

4-Aryl-1,2,3,4-tetrahydroisoquinolines[1] are widespread in nature and display potent pharmacological activity. For example, nomifensine **1** is a powerful inhibitor of the uptake of monamine neurotransmitters and has been marketed as a drug under the trade name Merital for the treatment of depression.[2] More importantly, this compound displays enantioselective pharmacological activity, with the (*S*)-enantiomer being the eutomer.[3] As a result of the biological significance of 4-aryltetrahydroisoquinolines, there has been much interest in their synthesis.[3,4] Biogenetically it is thought that tetrahydroisoquinoline alkaloids are derived from acyclic precursors. For example, the alkaloids (*S*)-latifine **3**[5] and (*S*)-cherylline **4**[6] are believed to be derived from the same acyclic precursor **2** (Figure 1). In general, therefore, a biomimetic[7] synthetic route for the construction of 4-aryltetrahydroisoquinolines is the cyclization of an appropriately substituted *N*-benzyl-1-arylethanolamine;[8] for instance, the acid-promoted cyclization of *N*-benzyl-1-

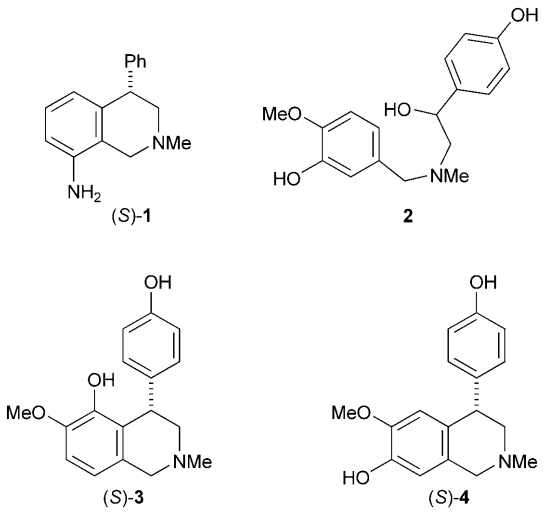

Figure 1. Biologically active tetrahydroisoquinolines (*S*)-nomifensine **1**, (*S*)-latifine **3** and (*S*)-cherylline **4**.

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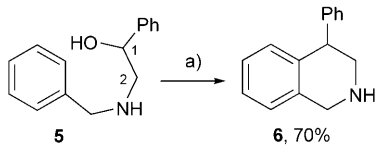
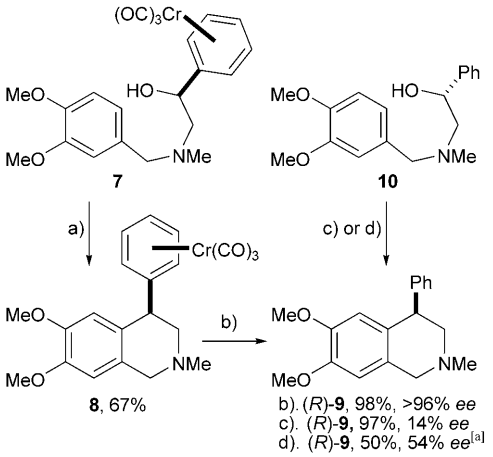
phenylethanolamine **5** is known to give the corresponding 4-phenyltetrahydroisoquinoline **6** in good yield (Scheme 1).[9]



Scheme 1. Reagents and conditions: a) TFA/H_2SO_4 (1:1), CH_2Cl_2, reflux, 30 min.

This synthetic strategy has been widely employed for the preparation of 4-aryltetrahydroisoquinolines functionalized in both aromatic rings, the ring closure being facilitated by the presence of electron-releasing substituents on the *N*-benzyl group and retarded with electron-withdrawing substituents. Despite being widely available, enantiopure *N*-benzyl-1-arylethanolamines have not been previously utilized for the formation of 4-aryltetrahydroisoquinolines through an acid-catalysed cyclization procedure.[10] If the mechanism of such a process were to proceed via a free benzylic carbocation (S_N1) for a substrate such as **5** (with only one stereogenic center at the benzylic position) then all stereochemical information would be lost giving rise to a racemic product. If, however, the *N*-benzyl substituent participates via an intramolecular S_N2-type displacement, the stereochemical integrity would be maintained giving a product with inversion of configuration. The enantiomeric excess of the 4-aryltetrahydroisoquinoline produced as a consequence of the acid-promoted cyclization of an enantiopure *N*-benzyl-1-arylethanolamine will reflect the relative importance of these two competing mechanistic pathways, with any enantiomeric excess arising as a consequence of the latter reaction manifold. As part of our ongoing research program concerning the utility of arene chromium tricarbonyl complexes in synthesis,[11–14] we have previously reported the enantiospecific synthesis of (*R*)-2-methyl-4-phenyl-6,7-dimethoxytetrahydroisoquinoline **9** from (*S*)-1-phenyl-2-(*N*-methylamino)ethanol (halostachine) derivatives **7** and **10**.[13] In the case where the substrate is complexed to a chromium tricarbonyl moiety, the acid-mediated cyclization of **7** was found to proceed with complete retention of configuration to give **9** in >96% *ee* (after oxidative decomplexation), consistent with a "double inversion" mechanism using neighbouring group participation of the chromium tricarbonyl moiety. However, in the absence of the chromium tricarbonyl functionality the cyclization of **10** proceeds with appreciable levels of racemization, even at low temperature (Scheme 2).

To date, there appear to be few reports assessing the levels of diastereoselectivity observed during acid-mediated cyclization reactions of 1,2-disubstituted precursors for the preparation of 3-substituted-4-aryltetrahydroisoquinolines.[15,16] A single account of work in this area concluded that insufficient resolution by ^{1}H NMR spectroscopy precluded an assessment of the reaction diastereoselectivity.[17]



Scheme 2. Reagents and conditions: a) $HBF_4{\cdot}OMe_2$, CH_2Cl_2, −20 °C, 72 h; b) O_2, Et_2O, *hv*, 48 h; c) TFA/H_2SO_4 (1:1), CH_2Cl_2, reflux, 30 min; d) $HBF_4{\cdot}OMe_2$, CH_2Cl_2, −20 °C, 69 h. [a] The reaction only proceeded to 50% conversion.

We therefore proposed to investigate acid-promoted diastereoselective cyclization reactions and also to exploit arene chromium tricarbonyl chemistry for the control of stereochemistry in the constuction of the new C(4)-stereogenic center within the tetrahydroisoquinoline scaffold. In the case of an *N*-3,4-dimethoxybenzyl substituted precursor, such as the halostachine derivatives **7** and **10**, either of the mesomerically electron-donating methoxy substituents may facilitate the cyclization reaction (either through an S_N1 or S_N2-type mechanism): under the influence of the *para*-methoxy group the cyclization step may proceed via a five-membered ring spirocyclic intermediate **12**, followed by dienone-phenol-type rearrangement to give the corresponding six-membered ring intermediate **13**, whilst the influence of the *meta*-methoxy group may effect cyclization to **13** directly. Subsequent loss of a proton would give rise to the observed 3,4-disubstituted tetrahydroisoquinoline **14** (Figure 2).[18]

To probe the mechanism and substrate scope of this reaction manifold we proposed to investigate the acid-mediated

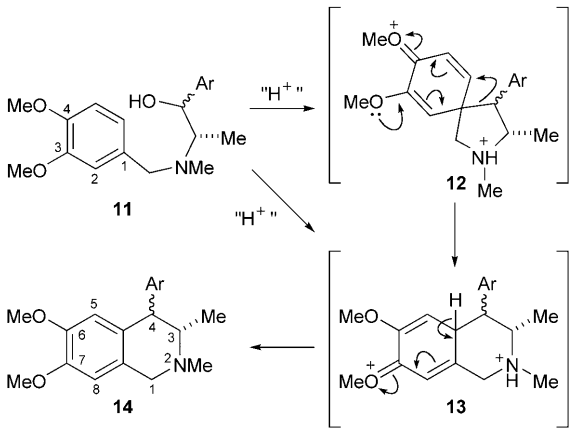


Figure 2. Cyclization of **11** via potential intermediates **12** and **13**.

cyclizations of (1*R*,2*S*)-ephedrine and (1*R*,2*R*)-pseudoephedrine derivatives **15** and **16** and the corresponding chromium tricarbonyl complexes **17** and **18**, respectively (Figure 3). Part of this work has been communicated previously.[14]

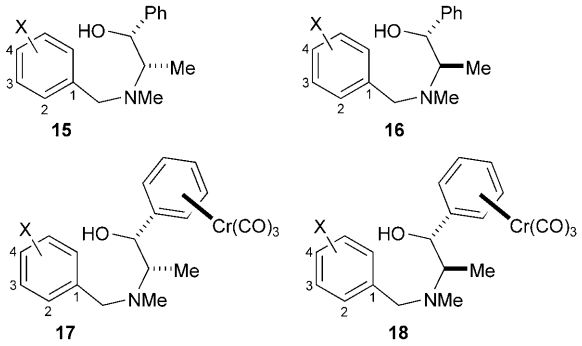


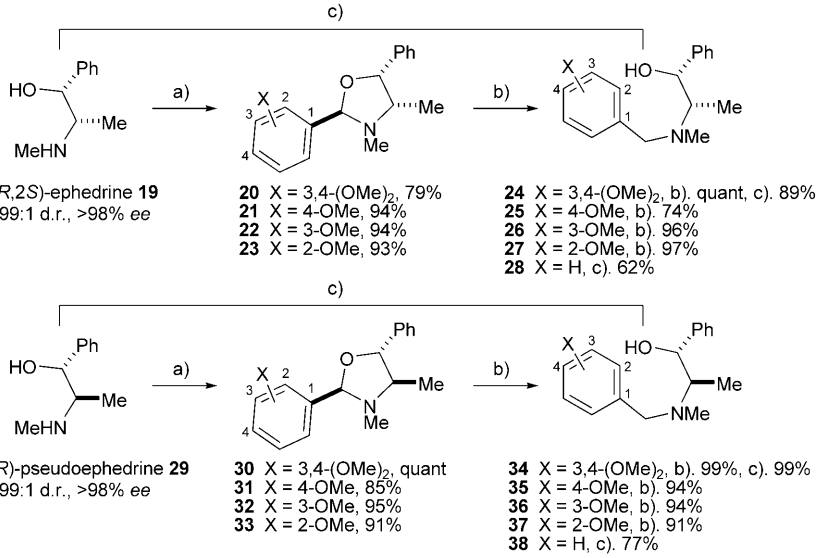
Figure 3. Ephedrine and pseudoephedrine derived cyclization precursors **15–18**. [X = 3,4-$(OMe)_2$, 4-OMe, 3-OMe, 2-OMe, H].

Results and Discussion

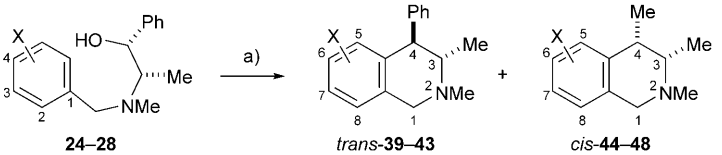
Cyclization of Uncomplexed Substrates

Cyclization precursors **24–28** and **34–38** were prepared in good yield from either (1*R*,2*S*)-ephedrine **19** or (1*R*,2*R*)-pseudoephedrine **29** by either direct alkylation or condensation with the requisite aryl aldehyde followed by reduction of the corresponding oxazolidine derivatives **20–23** and **30–33**. In each case, the configuration of the newly generated C(2)-stereogenic center within oxazolidines **20–23** and **30–33** was tentatively assigned based on minimization of 1,3-steric interactions within the five-membered ring. Of diagnostic relevance, the ^{1}H NMR spectra of all of the (1*R*,2*S*)-ephedrine derived substrates **24–28** displayed characteristic coupling constants of 4.1–5.0 Hz between the two stereogenic protons, compared with 9.7–9.8 Hz for the diastereoisomeric (1*R*,2*R*)-pseudoephedrine derivatives **34–38** (Scheme 3).

Exposure of the (1*R*,2*S*)-ephedrine derived substrates **24–28** to a 1:1 mixture of TFA and H_2SO_4 in CH_2Cl_2 at reflux gave the corresponding *trans*-tetrahydroisoquinolones **39–43** in ≥93:7 d.r. (Scheme 4). The *trans*-configurations within the major diastereoisomers **39–43** were established by ^{1}H NMR ^3J coupling constant analyses which showed characteristic coupling constants of 8.0–8.5 Hz between the C(3)*H* and C(4)*H* protons;[19] the minor components were therefore assigned as the corresponding *cis*-diastereoisomers **44–48** which displayed diagnostic ^{1}H NMR ^3J coupling constants of 4.4–4.6 Hz between the C(3)*H* and C(4)*H* protons, although the coupling constants of these minor components could not be determined in some cases.[19] ^{1}H NMR NOE difference analyses of **41** and **46** confirmed this assignment: for *trans*-**41** irradiation of C(4)*H* showed a small enhancement of 4.0% to the adjacent C(3)*H* proton, whereas for *cis*-**46** irradiation of the C(4)*H* proton gave a much larger enhancement of 8.5% to the C(3)*H* proton. Furthermore, the relative *trans*-configuration within **42** was unambiguously established by X-ray crystallographic analysis, with the (3*S*,4*R*)-absolute configuration assigned from the known [(1*R*,2*S*)-ephedrine **19** derived] (*S*)-configuration of the C(3)-stereogenic center (Figure 4).



Scheme 3. Reagents and conditions: a) ArCHO, TsOH, C_6H_6, reflux, 14 h; b) $LiAlH_4$, THF, reflux, 20 h; c) $ArCH_2Br$, K_2CO_3, MeCN, reflux, 3 h. [All compounds were isolated in >99:1 d.r.].



	d.r. (*trans*/*cis*)	Products (*trans*/*cis*)	*trans* yield (%)	*trans* $^3J_{3,4}$ (Hz)	*cis* yield (%)	*cis* $^3J_{3,4}$ (Hz)
24 X = 3,4-$(OMe)_2$	>99:1	**39**:**44** X = 6,7-$(OMe)_2$	74[a]	8.0	–	4.4
25 X = 4-OMe	97:3	**40**:**45** X = 6-OMe	92[a]	8.4	–	–
26 X = 3-OMe	93:7	**41**:**46** X = 7-OMe	56[a]	8.5	2[a]	4.6
27 X = 2-OMe	>99:1	**42**:**47** X = 8-OMe	57[a]	8.0	–	–
28 X = H	97:3	**43**:**48** X = H	97[b]	8.3	–	4.5

Scheme 4. Reagents and conditions: a) TFA/H_2SO_4 (1:1), CH_2Cl_2, reflux, 30 min. [a] Isolated in >99:1 d.r. [b] Combined yield for 97:3 mixture of **43**:**48**.

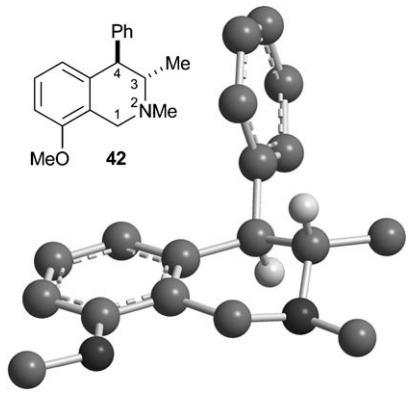
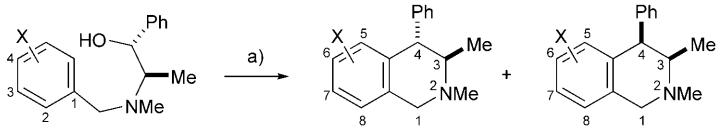


Figure 4. Chem3D representation of the single crystal X-ray structure of (3*S*,4*R*)-**42** (some H atoms have been omitted for clarity).

Analogous cyclization of the (1*R*,2*R*)-pseudoephedrine derived substrates **34–38** also produced *trans*-tetrahydroisoquinolines **39–43** as the major diastereoisomers (Scheme 5), but in the opposite enantiomeric series, which would be expected given the known configurations of the C(2)-stereogenic centers within (1*R*,2*S*)-ephedrine and (1*R*,2*R*)-pseudoephedrine. The samples of **39–43** isolated from the cyclizations of (1*R*,2*R*)-pseudoephedrine derived substrates **34–38** displayed equal and opposite specific rotations to those isolated upon cyclization of the (1*R*,2*S*)-ephedrine derived substrates **24–28**.



34–38 *trans*-**39–43** *cis*-**44–48**

		d.r. (*trans*/*cis*)	Products (*trans*/*cis*)		*trans* yield (%)	*trans* $^3J_{3,4}$ (Hz)	*cis* yield (%)	*cis* $^3J_{3,4}$ (Hz)
34	X = 3,4-(OMe)$_2$	88:12	**39**:**44**	X = 6,7-(OMe)$_2$	79[a]	8.5	–	4.4
35	X = 4-OMe	93:7	**40**:**45**	X = 6-OMe	92	8.4	–	–
36	X = 3-OMe	87:13	**41**:**46**	X = 7-OMe	41	8.5	4[b]	4.6
37	X = 2-OMe	>99:1	**42**:**47**	X = 8-OMe	91	8.0	–	–
38	X = H	94:6	**43**:**48**	X = H	quant[b]	8.3	–	4.5

Scheme 5. Reagents and conditions: a) TFA/H_2SO_4 (1:1), CH_2Cl_2, reflux, 30 min. [All compounds were isolated in > 99:1 d.r.]; [a] Combined yield for 88:12 mixture of **39**:**44**. [b] Combined yield for 94:6 mixture of **43**:**48**.

In all cases, substrates **24–28** and **34–38** underwent preferential cyclization to give the *trans*-tetrahydroisoquinolines **39–43** in ≥87:13 d.r., and the high-yielding conversion of both the *N*-benzyl-substituted precursors **28** and **38** implies that the presence of a methoxy substituent is not a prerequisite for cyclization. It is reasonable to assume that the ring closures are irreversible, since the diastereoisomeric ratios observed in the cyclizations of the (1*R*,2*S*)-ephedrine derived precursors **24–28** are different to those observed upon cyclization of the corresponding (1*R*,2*R*)-pseudoephedrine derived substrates **34–38**. For instance, in the cyclizations of the 3,4-dimethoxybenzyl substituted precursors, **39** was obtained in >99:1 d.r. from cyclization of (1*R*,2*S*)-**24**, whereas an 88:12 mixture of **39**:**44** was obtained from identical treatment of (1*R*,2*R*)-**34**. The stereochemical outcome observed in the cyclization of the (1*R*,2*R*)-pseudoephedrine derived substrates **34–38** is inconsistent with an S_N2-type pathway, but may be rationalized by invoking a stereoselective S_N1 process. Thus, a likely general reaction mechanism for the acid-mediated cyclizations of **34–38** may therefore be proposed: initial protonation of the tertiary amine gives the corresponding quaternary ammonium salt (thus preventing aziridinium ion formation); protonation of the hydroxyl functionality renders it a good leaving group, and ionization results in the formation of a benzylic carbocation. The faces of the planar carbocationic intermediate are rendered diastereotopic by virtue of the adjacent stereogenic center, and the internal nucleophile may discriminate between them exclusively in favour of forming the *trans*-diastereoisomer, since the transition state leading to a *trans*-tetrahydroisoquinoline will be of a considerably lower energy than that leading to the corresponding *cis*-tetrahydroisoquinoline, owing to the developing steric interactions between the C(4)-phenyl and C(3)-methyl groups in the latter case. As *trans*-tetrahydroisoquinolines **39–43** are formed as the major product from cyclization of all the (1*R*,2*S*)-epehdrine derived substrates **24–28** this does not allow prediction as to the relative importance of either a direct S_N2-type or stereoselective S_N1 mechanistic pathway in these cases.

For the *N*-monomethoxybenzyl substituted compounds, higher levels of stereocontrol are observed in the *para*-methoxy and *ortho*-methoxy substituted cases **25**, **27**, **35** and **37** relative to the *meta*-methoxy substituted analouges **26** and **36**. This higher stereocontrol may be accounted for by invoking a mechanism that proceeds under the influence of the *ortho*- or *para*-methoxy substituents via a spirocyclic five-membered ring intermediate for which steric compression is more pronounced than in the corresponding six-membered ring intermediates formed under the influence of the *meta*-methoxy group. Assuming that spirocyclic intermediates feature in the cyclization process there is the possibility for the formation of regioisomeric products through migration of either of the two alkyl groups upon subsequent dienone-phenol rearrangement. Given these cyclization reactions give exclusive formation of single regioisomers, a possible mechanistic rationale is that migration of the group bearing the phenyl substituent is favoured owing to its greater migratory aptitude; this interpretation seems reasonable, as the migrating group must be able to stabilize a developing positive charge, a role that the *N*-methylamino group is unable to perform, since the nitrogen atom is presumably protonated under the acidic reaction conditions (Figure 5).

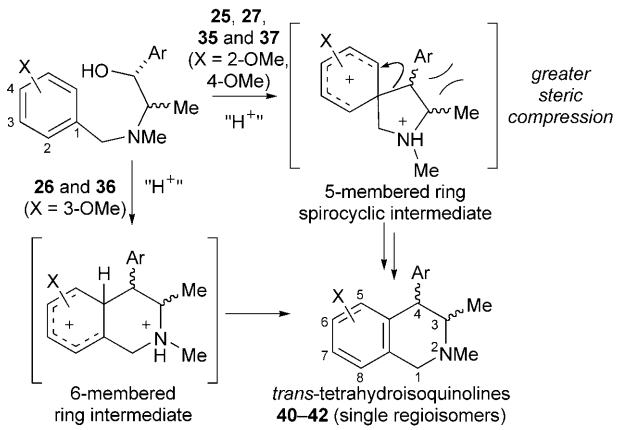
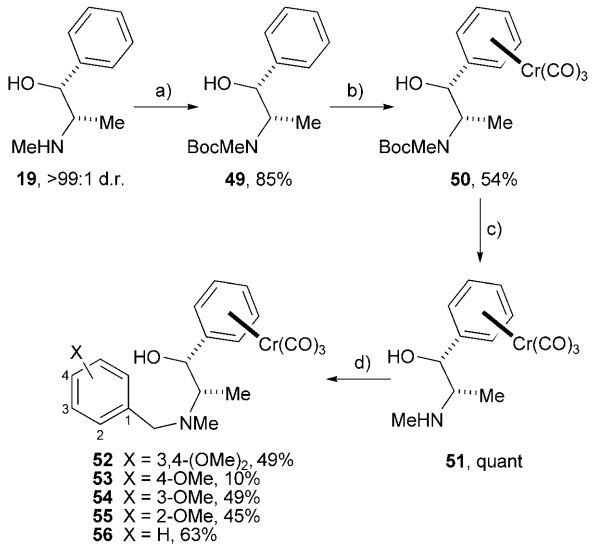


Figure 5. Stereoselective cyclization and regioselective rearrangement.

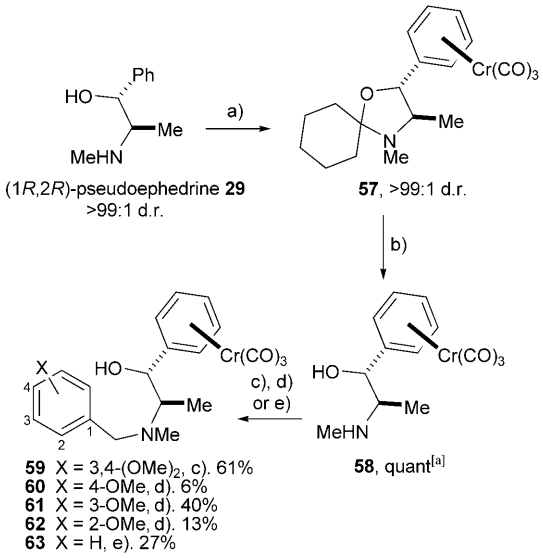
Cyclization of Chromium Tricarbonyl Complexes

The corresponding chromium tricarbonyl complexes of substrates **24**–**28** and **34**–**38** were next prepared. [(1*R*,2*S*)-Ephedrine]$Cr(CO)_3$ **51**, derived from (1*R*,2*S*)-ephedrine **19**, was prepared by reaction of *N*-Boc protected (1*R*,2*S*)-ephedrine **49** with $Cr(CO)_6$ to give **50** in 54% yield (Scheme 6). Subsequent *N*-Boc deprotection was accomplished upon exposure to neat formic acid giving **51** in quantitative yield. The *N*-3,4-dimethoxybenzyl substituted complex **52** was obtained upon alkylation of **51** with 3,4-dimethoxybenzyl bromide in the presence of K_2CO_3. The ^1H NMR spectrum of the product revealed a three proton aromatic multiplet at $\delta_H = 6.69$–6.79 ppm and a five proton aromatic multiplet at $\delta_H = 5.21$–5.55 ppm, clearly indicating that the chromium tricarbonyl unit was co-ordinated to the phenyl ring and that no migration to the more electron rich dimethoxy substituted aromatic ring had occurred. The remaining (1*R*,2*S*)-ephedrine derived chromium tricarbonyl complexes **53**–**56** were readily prepared by a directly analogous procedure involving alkylation of **51** with the appropriately substituted benzyl bromide. In each case no migration of the chromium tricarbonyl moiety was observed.



Scheme 6. Reagents and conditions: a) Boc_2O, Et_3N, CH_2Cl_2, RT, 60 h; b) $Cr(CO)_6$, Bu_2O/THF (10:1), reflux, 48 h; c) HCO_2H, RT, 4.5 h; d) $ArCH_2Br$, K_2CO_3, MeCN, reflux, 3 h. [All compounds isolated in >99:1 d.r.].

[(1*R*,2*R*)-Pseudoephedrine]$Cr(CO)_3$ **58** was prepared by hydrolysis of oxazolidine complex **57** in the presence of TsOH (≈1.0 equiv) and conc aq HCl at reflux for 15 h, which gave a mixture of **58** and cyclohexanone (Scheme 7).

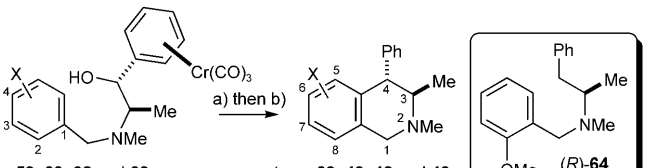


Scheme 7. Reagents and conditions: a) cyclohexanone, C_6H_6, reflux, 22 h then $Cr(CO)_6$, Bu_2O, THF, reflux, 48 h; b) TsOH, HCl (conc aq), THF/H_2O (2:1), RT, 15 h; c) $ArCH_2Br$, K_2CO_3, MeCN, reflux, 3 h; d) ArCHO, TsOH, CH_2Cl_2, 4 Å MS then $NaBH_4$, MeOH, RT, 15 h; e) BnBr, $NaHCO_3$, NaI, EtOH, RT, 63 h. [All compounds were isolated in >99:1 d.r.]. [a] Mixture with cyclohexanaone.

This mixture was immediately treated with 3,4-dimethoxybenzyl bromide to give complex (1*R*,2*R*)-**59** in 61% isolated yield over the two steps. The ^1H NMR spectrum of the crude reaction mixture again indicated that the chromium tricarbonyl unit had not undergone migration to the more electron rich aromatic ring. The corresponding *N*-methoxybenzyl substituted (1*R*,2*R*)-pseudoephedrine derived complexes **60**–**62** were synthesised by condensation of [(1*R*,2*R*)-pseudoephedrine]$Cr(CO)_3$ **58** with the requisite regioisomer of methoxybenzaldehyde and subsequent reduction of the resultant oxazolidine complexes with $NaBH_4$, and the *N*-benzyl substituted complex **63** was prepared through the benzylation of complex **58** with BnBr in the presence of a catalytic quantity of NaI; no migration of the chromium tricarbonyl moiety was observed in any case.

In each case, yellow solutions of the cyclization precursor complexes **52**–**56** and **59**–**63** in CH_2Cl_2 at −20 °C were treated with 1.0 equiv of HBF_4, but only starting material was returned. Further optimization revealed that excess acid is required to promote a reaction; the fact that these substrates

require more than one equivalent of acid is consistent with the hypothesis that the first equivalent of acid protonates the tertiary amine and excess acid is then required to achieve further reaction. Upon treatment of 3,4-dimethoxybenzyl substituted **59** with acid, the reaction mixture turned deep purple (indicative of benzylic carbocation formation) and within 24 h the colour of the solution had reverted to yellow. After work-up a single product was obtained, which was tentatively assigned as the corresponding *trans*-tetrahydroisoquinolone complex. This assignment was confirmed by subsequent oxidative decomplexation, which liberated *trans*-**39** (Scheme 8); the specific rotation of the product was



59, **60**, **62** and **63** — *trans*-**39**, **40**, **42** and **43**

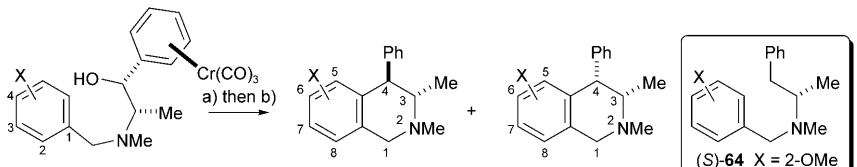
	d.r. (*trans*/*cis*)		*trans* product	yield (%)
59 X = 3,4-(OMe)$_2$	>99:1	**39** X = 6,7-(OMe)$_2$		95
60 X = 4-OMe	>99:1	**40** X = 6-OMe		94
62 X = 2-OMe	>99:1	**42** X = 8-OMe[a]		9
63 X = H	>99:1	**43** X = H		28

Scheme 8. Reagents and conditions: a) $HBF_4{\cdot}OMe_2$, CH_2Cl_2, 0 °C, 2 h; b) O_2, Et_2O, *hν*, 24 h. [All compounds isolated in >99:1 d.r.]. [a] 50:50 ratio of **42**:**64**.

both equal and opposite to that of the product prepared from cyclization of the uncomplexed epimeric analogue **24** derived from (1*R*,2*S*)-ephedrine **19**. Acid-mediated cyclization of C(4′)-methoxy substituted complex **60** gave a single tetrahydroisoquinoline complex, with oxidative decomplexation giving *trans*-**40** in 94% yield and >99:1 d.r. Attempted acid-mediated cyclization of **62** afforded a 50:50 mixture of *trans*-**42** and (*R*)-**64**, contaminated with small amounts of unidentified impurities after decomplexation. Recrystallization of the mixture afforded **42** in 9% yield and >99:1 d.r. The identity of (*R*)-**64** was confirmed by independent chemical synthesis: an authentic sample of (*RS*)-**64** was prepared in 96% yield by alkylation of (*RS*)-*N*-methylamphetamine with 2-methoxybenzylbromide. The formation of (*R*)-**64** in this system is consistent with reduction occurring as a consequence of a disproportionation reaction, whereby the secondary alcohol serves as the reducing agent.[20] In this case a phenyl ketone complex would be generated which presumably polymerizes under the strongly acidic reaction conditions. Cyclization of the *N*-benzyl substituted (1*R*,2*S*)-ephedrine derivative **63**, followed by decomplexation gave *trans*-**43** along with uncomplexed starting material (1*R*,2*R*)-**38** in a ratio of 87:13, respectively. Purification of the crude reaction mixture by flash column chromatography enabled the isolation of *trans*-**43** in 28% yield and >99:1 d.r.

Acid-mediated cyclization of the *N*-3,4-dimethoxybenzyl- and *N*-monomethoxybenzyl substituted (1*R*,2*S*)-ephedrine derived complexes **52**, **53**, and **55** afforded the desired *N*(2),3-dimethyl-4-phenyltetrahydroisoquinolines after decomplexation: treatment of a solution of 3,4-dimethoxybenzyl substituted **52** in CH_2Cl_2 at −20 °C with excess HBF_4 gave rise to a single product which was tentatively assigned as the corresponding *cis*-tetrahydroisoquinoline complex in >99:1 d.r.[21] Subsequent decomplexation confirmed this assignment with the liberation of *cis*-tetrahydroisoquinoline (3*S*,4*S*)-**44** (which displayed a diagnostic ^3J coupling constant of 4.4 Hz between the C(3)*H* and C(4)*H* protons) which was isolated in 75% yield (over the two steps) and >99:1 d.r., confirming that the cyclization of **52** had occurred with complete retention of configuration at the benzylic stereogenic center. Analogous treatment of C(4′)-methoxy substituted **53** with excess HBF_4 at −20 °C gave a single tetrahydroisoquinoline complex, with subsequent oxidative decomplexation giving *trans*-**40** as a single diastereoisomer (>99:1 d.r.) in 78% yield over the 2 steps. Cyclization of C(2′)-methoxy substituted **55**, followed by decomplexation, gave a 63:37 mixture of (3*S*,4*R*)-**42** and (*S*)-**64**, respectively. Recrystallization of the mixture enabled isolation of **42** in 50% yield and >99:1 d.r. In the case of (1*R*,2*S*)-ephedrine derived *N*-benzyl substituted complex **56**, attemped cyclization was found to give (*S*)-**65** as the only isolable product after decomplexation (Scheme 9).

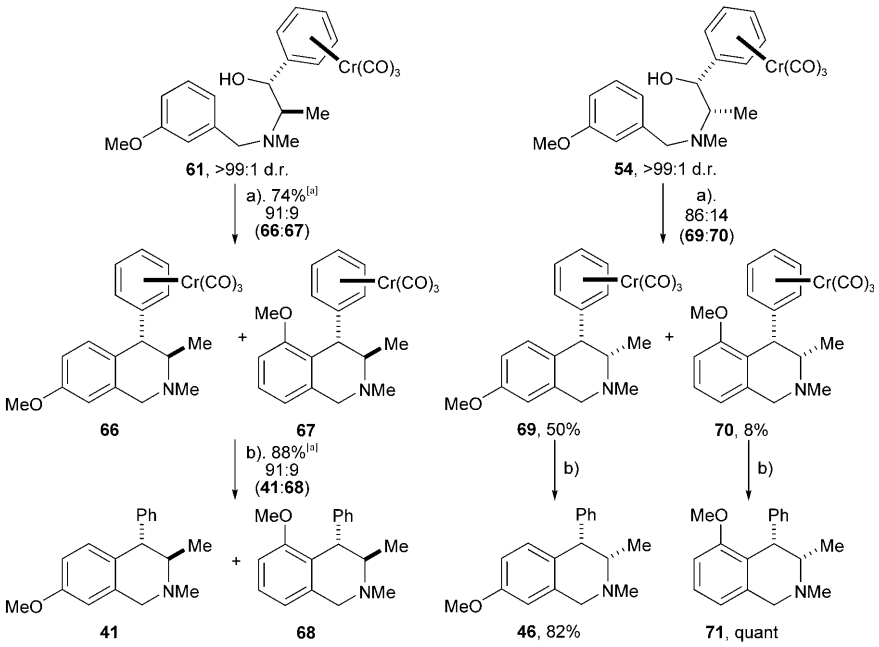
Analogous cyclization of C(3′)-methoxy substituted precursors (1*R*,2*S*)-**54** and (1*R*,2*R*)-**61** also proceeded with extremely high levels of diastereoselectivity, although in these cases mixtures of regioisomers were formed (Scheme 10). Cyclization of (1*R*,2*R*)-pseudoephedrine derived complex **61** gave an inseparable 91:9 mixture of complexes **66** and **67**, which, after decomplexation, gave an inseparable 91:9 mixture of *trans*-**41** and another *trans*-tetrahydroisoquinoline, which was tentatively assigned as the 5-methoxy substituted regioisomer **68**, in 65% combined yield over the two steps. Cyclization of the (1*R*,2*S*)-ephedrine derived complex **54** produced a separable 86:14 mixture of regioisomeric tetra-



52, **53**, **55** and **56** — *trans*-**39**, **40**, **42** and **43** — *cis*-**44**, **45**, **47** and **48**

	d.r. (*trans*/*cis*)		Products (*trans*/*cis*)	*trans* yield (%)	*trans* $^3J_{3,4}$ (Hz)	*cis* yield (%)	*cis* $^3J_{3,4}$ (Hz)
52 X = 3,4-(OMe)$_2$	1:>99	**39**:**44**	X = 6,7-(OMe)$_2$	–	–	75	4.4
53 X = 4-OMe	>99:1	**40**:**45**	X = 6-OMe	78	8.4	–	–
55 X = 2-OMe	>99:1	**42**:**47**	X = 8-OMe[a]	50	8.0	–	–
56 X = H	–	**43**:**48**	X = H	–	–	–	–

Scheme 9. Reagents and conditions: a) $HBF_4{\cdot}OMe_2$, CH_2Cl_2, 0 °C, 2 h; b) O_2, Et_2O, *hν*, 24 h. [All compounds were isolated in >99:1 d.r.]. [a] 63:37 ratio of **42**:**64**.



Scheme 10. Reagents and conditions: a) $HBF_4{\cdot}OMe_2$, CH_2Cl_2, −20 °C, 46 h; b) O_2, Et_2O, *hv*, 24 h. [All compounds were isolated in > 99:1 d.r.]. [a] Combined yield.

hydroisoquinoline complexes **69** and **70**, which were isolated in 50 and 8% yield, respectively, and in > 99:1 d.r. in both cases. Subsequent oxidative decomplexation confirmed the *cis*-configuration within complexes **69** and **70**, giving *cis*-**46** ($J_{3,4}$ = 4.6 Hz) in 82% yield upon decomplexation of *cis*-**69**, and *cis*-**71** ($J_{3,4}$ = 3.8 Hz) in quantitative yield after decomplexation of *cis*-**70**.

The cyclizations of complexes **52–55** and **59–63** are rendered completely stereoselective (> 99:1 d.r.) upon co-ordination of the substrates to chromium tricarbonyl, owing to the stereocontrolling influence of the transition metal fragment. Cyclization of the (1*R*,2*R*)-pseudoephedrine derived complexes **59–63** proceeded with retention of configuration to give the corresponding *trans*-tetrahydroisoquinolines after decomplexation. In the case of the *N*-3,4-dimethoxybenzyl- and *N*-3-methoxybenzyl (1*R*,2*S*)-ephedrine derived complexes **52** and **54**, respectively, the cyclization reactions also proceeded with retention of configuration to give the corresponding *cis*-tetrahydroisoquinolines after decomplexation. The stereochemical outcomes of these reactions, as well as the increased rates of cyclization versus the uncomplexed substrates, are consistent with a "double inversion" mechanism involving neighbouring group participation by the chromium tricarbonyl moiety during the ionization of the protonated hydroxyl group, which occurs with initial inversion of configuration. Subsequent intramolecular trapping of the resultant carbocation must occur from the unhindered *exo* face, again with inversion, to account for the overall retention of configuration. In contrast, cyclization of the *N*-4-methoxybenzyl and *N*-2-methoxybenzyl substituted (1*R*,2*S*)-ephedrine derived complexes **53** and **55**, respectively, proceeded with complete inversion of configuration. These data suggest that the cyclization reactions of the (1*R*,2*S*)-ephedrine derived complexes **52–55** must proceed under the influence of the methoxy groups. Ring closure of *N*-3-methoxybenzyl substituted **54** occurs under the influence of the *meta*-methoxy group to give the six-membered ring intermediate **73** directly (Figure 6), whilst cyclization of the *N*-4-methoxybenzyl and *N*-2-methoxybenzyl substituted complexes **53** and **55** under the influence of the *para*- and *ortho*-methoxy groups, respectively, would orientate the β-methyl group and arene chromium tricarbonyl unit *cis* within the corresponding five-membered ring spirocyclic intermediates **78**. The greater steric compression associated with *cis*-five-membered spirocyclic intermediates **78** (relative to *cis*-**73**) may manifest itself in a transition state of sufficiently high energy as to prevent cyclization, and thereby prolongs the lifetime of the benzylic carbocations **74**. A lower energy reaction pathway would result from intramolecular trapping of the epimerized benzylic carbocations **75** from the unhindered *exo* face to give the *trans*-configured spirocyclic intermediates **76**, with subsequent rearrangement and loss of a proton accounting for the observed *trans*-tetrahydroisoquinoline products **40** and **42** (Figure 7). For the *N*-3,4-dimethoxybenzyl substituted complex (1*R*,2*S*)-**52** the cyclization presumably proceeds under the influence of the *meta*-methoxy group to give six-membered ring intermediate **73** directly, leading to the *cis*-product **44**, for which steric compression in the transition state is less severe than the corresponding spirocyclic intermediate **78** formed from cyclization under the influence of the *para*-methoxy substituent.

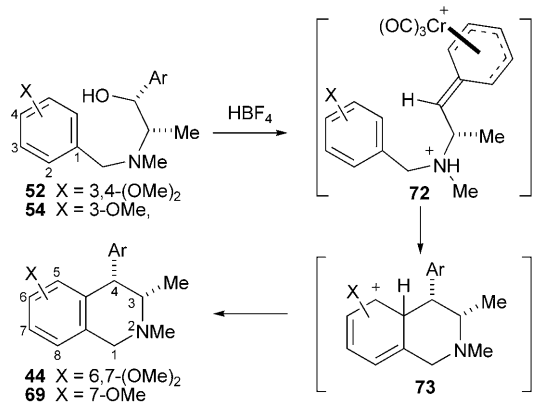


Figure 6. Cyclization with retention of configuration. [Ar = Ph·Cr(CO)$_3$].

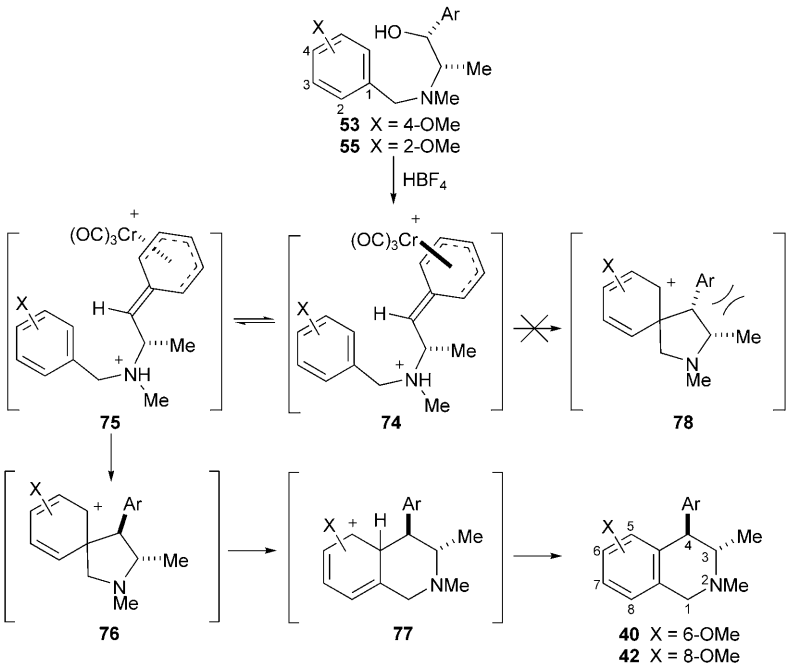


Figure 7. Cyclization with inversion of configuration. [Ar = Ph·Cr(CO)$_3$].

Conclusions

In conclusion, the acid-mediated cyclization of a range of differentially substituted *N*-benzylethanolamines [derived from (1*R*,2*S*)-ephedrine and (1*R*,2*R*)-pseudoephedrine] proceed to give preferential formation of the *trans*-*N*(2),3-dimethyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline products. The diastereoselectivities observed during these cyclizations may be accounted for by the presence of methoxy substituents around the aromatic ring and their influence upon the cyclization reaction. The cyclization reactions are rendered completely diastereostereoselective upon co-ordination of the precursors to a chromium tricarbonyl unit, proceeding through a neighboring group participation mechanism with overall retention of configuration, except where steric crowding prohibits the formation of a *cis*-1,2-disubstituted spirocyclic intermediate; in this case epimerization of the benzylic carbocation and complete inversion of configuration is observed. The acid-mediated cyclizations of (1*R*,2*S*)-*N*-(3′,4′-dimethoxybenzyl)ephedrine and the corresponding chromium tricarbonyl complex are complementary, with the former giving *trans*-(3*S*,4*R*)-*N*(2),3-dimethyl-4-phenyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline upon exposure to acid, and the latter affording the corresponding *cis*-(3*S*,4*S*)-diastereoisomer, after decomplexation.

Experimental Section

General Experimental

All reactions involving organometallic or other moisture-sensitive reagents were carried out under a nitrogen or argon atmosphere by using standard vacuum line techniques and glassware that was flame dried and cooled under nitrogen before use. Solvents were dried according to the procedure outlined by Grubbs and co-workers.[22] Water was purified by a Millipore Elix UV-10 system. All other solvents were used as supplied (analytical or HPLC grade) without prior purification. Organic layers were dried over $MgSO_4$. Thin layer chromatography was performed on aluminium plates coated with 60 F_{254} silica. Plates were visualized by using UV light (254 nm), iodine, 1% aq $KMnO_4$, or 10% ethanolic phosphomolybdic acid. Flash column chromatography was performed on Kieselgel 60 silica.

Elemental analyses were recorded by the microanalysis service of the Inorganic Chemistry Laboratory, University of Oxford, UK. Melting points were recorded by using a Gallenkamp Hot Stage apparatus and are uncorrected. 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 by using a Bruker Tensor 27 FT-IR spectrometer as either a thin film on NaCl plates (film) or a KBr disc (KBr), as stated. Selected characteristic peaks are reported in cm^{-1}. NMR spectra were recorded by using Bruker Avance spectrometers in the deuterated solvent stated. The field was locked by external referencing to the relevant deuteron resonance. Low-resolution mass spectra were recorded by using either a VG MassLab 20–250 or a Micromass Platform 1 spectrometer. Accurate mass measurements were run by using either a Bruker MicroTOF, which was 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.

General Procedure 1: Alkylation

A solution of the amino alcohol (1.0 equiv) and the appropriately substituted benzylbromide (1.0 equiv) in the specified solvent was heated at reflux in the presence of K_2CO_3 (2.0–3.0 equiv) for 3 h. The solution was then concentrated in vacuo and water was added. The organic layer was separated and the aqueaous layer was extracted with either CH_2Cl_2 or Et_2O. The combined organic extracts were then dried, filtered and concentrated in vacuo.

General Procedure 2: Reductive Amination

A solution of the amino alcohol (1.0 equiv) and the appropriately substituted benzaldehyde (1.0 equiv) in C_6H_6 was treated with a catalytic quantity of TsOH and the resultant mixture was heated at reflux under Dean–Stark conditions for 10–20 h. The reaction mixture was then concentrated in vacuo and water was added. The organic layer was separated and the aqueous layer was extracted with either Et_2O or CH_2Cl_2. The combined organic extracts were then dried, filtered and concentrated in vacuo to give the corresponding oxazolidine. A portion of this material (1.0 equiv) was dissolved in THF and $LiAlH_4$ (≈1.2 equiv) was cautiously added. The resultant mixture was heated at reflux for 20–30 h then allowed to cool to RT. The reaction mixture was then cooled to 0 °C and water and NaOH (15% aq) were sequentially added. The precipitated aluminium salts were removed by filtration and filtrate was concentrated in vacuo.

General Procedure 3: Cyclization of Uncomplexed Substrates

A solution of the amino alcohol (1.0 equiv) in CH_2Cl_2 was treated with H_2SO_4 and TFA (1:1, excess) producing a red/purple solution. The mixture was heated at reflux for the specified period of time and then quenched with aqueous base (either NaOH or K_2CO_3). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were washed with water, then dried, filtered, and concentrated in vacuo.

General Procedure 4: Cyclization of Chromium Tricarbonyl Complexes

A solution of the amino alcohol complex (1.0 equiv) in CH_2Cl_2 at −78 °C was treated with $HBF_4{\cdot}OMe_2$ (excess) and the resultant solution was stirred at −78 °C for 1 h. The reaction mixture was then allowed to warm to −20 °C and was quenched by the addition of aqueous base (either NaOH or K_2CO_3). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were then filtered through a short plug of Al_2O_3 (eluent CH_2Cl_2) and the filtrate was concentrated in vacuo.

General Procedure 5: Decomplexation

A solution of the relevant complex in Et_2O (10 mg mL^{-1}) was allowed to stand in air and sunlight until the yellow solution became colourless (approx. 24–48 h). The precipitated chromium residues were removed by filtering the solution through a short plug of celite and the filtrate was concentrated in vacuo.

(1*R*,2*S*)-1-Phenyl-2-[*N*-methyl-*N*-(3′,4′-dimethoxybenzyl)amino]propan-1-ol (**24**):

Method A: (1*R*,2*S*)-Ephedrine **19** (1.01 g, 6.11 mmol) was reacted with freshly distilled 3,4-dimethoxybenzylbromide (1.41 g, 6.10 mmol) in MeCN (100 mL) according to *general procedure 1* for 4 h to give **24**, as a colourless oil (1.71 g, 89 %, >99:1 d.r.). Purification of an aliquot by means of reduced pressure distillation (5 mbar) gave an analytically pure sample of **24**; $[\alpha]_D^{20} = -30.4$ ($c = 0.5$ in $CHCl_3$); IR (film): $\tilde{\nu}_{max} = 3019$, 1515, 723 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.02$ (3H, d, $J = 6.8$ Hz, C(2)CH_3), 2.18 (3H, s, NCH_3), 2.96 (1H, qd, $J = 6.8$, 5.3 Hz, C(2)*H*), 3.55 (2H, app d, $J = 2.4$ Hz, NCH_2), 3.83 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 4.85 (1H, d, $J = 5.3$ Hz, C(1)*H*), 6.74–7.35 ppm (8H, m, *Ph*, *Ar*); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 9.7$, 38.2, 55.8, 55.9, 58.9, 63.2, 74.1, 110.9, 111.7, 120.7, 126.3, 126.9, 128.0, 132.1, 142.80, 148.0, 149.0 ppm; MS (CI): *m*/*z*: 316 ([*M*+H]$^+$, 100 %); elemental analysis: calcd (%) for $C_{19}H_{25}NO_3$: C 72.35, H 8.0, N 4.4; found: C 72.0, H 8.4, N 4.4.

Method B: (1*R*,2*S*)-Ephedrine **19** (5.00 g, 30.3 mmol) and 3,4-dimethoxybenzaldehyde (5.00 g, 30.1 mmol) in C_6H_6 (80 mL) were reacted according to *general procedure 2* for 23 h to give **20** (93:7 d.r. crude) as, after purification by means of recrystallization (CH_2Cl_2/hexane), a white solid (7.49 g, 79 %, >99:1 d.r.); m.p.: 93 °C; $[\alpha]_D^{20} = -48.6$ ($c = 1.9$ in $CHCl_3$); IR (KBr disc): $\tilde{\nu}_{max} = 3010$, 1517 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta_H = 0.81$ (3H, d, $J = 6.4$ Hz, C(4)CH_3), 2.19 (3H, s, NCH_3), 2.97 (1H, dq, $J = 8.1$, 6.4 Hz, C(4)*H*), 3.91 (3H, s, OCH_3), 3.95 (3H, s, OCH_3), 4.66 (1H, s, C(2)*H*), 5.13 (1H, d, $J = 8.2$ Hz, C(5)*H*), 6.90–7.47 ppm (8H, m, *Ph*, *Ar*); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 14.8$, 35.6, 55.8, 55.8, 63.8, 82.3, 98.8, 110.9, 121.2, 127.8, 127.9, 128.0, 128.1, 128.2, 130.9, 140.2, 149.3, 149.9 ppm; MS (CI): *m*/*z*: 312 ([*M*+H]$^+$, 100 %); elemental analysis: calcd (%) for $C_{19}H_{23}NO_3$: C 72.8; H 7.4; N 4.5; found: C 72.9; H 7.6; N 4.4. A portion of this material (1.95 g, 6.22 mmol) was reduced with $LiAlH_4$ (354 mg, 9.33 mmol) to furnish **24** as a colourless oil (1.96 g, quant., >99:1 d.r.).

(1*R*,2*S*)-1-Phenyl-2-[*N*-methyl-*N*-(4′-methoxybenzyl)amino]propan-1-ol (**25**): A mixture of (1*R*,2*S*)-ephedrine **19** (5.00 g, 30.3 mmol) and 4-methoxybenzaldehyde (4.12 g, 30.3 mmol) in C_6H_6 (150 mL) was reacted according to *general procedure 2* to give (2*S*,4*S*,5*R*)-2-(4′-methoxyphenyl)-*N*(3),4-dimethyl-5-phenyloxazolidine **21** as a white solid (8.09 g, 94 %, >99:1 d.r.). Purification of an aliquot by means of recrystallization (Et_2O/hexane) gave an analytically pure sample of **21**;[23] m.p.: 85–86 °C; $[\alpha]_D^{20} = -55.2$ ($c = 1.5$ in $CHCl_3$); $[\alpha]_D^{20} = -38.9$ ($c = 1.9$ in C_6H_6); IR (KBr disc): $\tilde{\nu}_{max} = 3010$, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.80$ (3H, d, $J = 6.5$ Hz, C(4)CH_3), 2.18 (3H, s, NCH_3), 2.96 (1H, dq, $J = 8.3$, 6.5 Hz, C(4)*H*), 3.85 (3H, s, OCH_3), 4.67 (1H, s, C(2)*H*), 5.14 (1H, d, $J = 8.3$ Hz, C(5)*H*), 6.96–7.61 ppm (9H, m, *Ph*, *Ar*); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 14.9$, 35.6, 55.3, 63.9, 82.3, 98.6, 114.0, 127.7, 128.0, 128.2, 129.8, 130.4, 140.2, 160.6 ppm; MS (CI): *m*/*z*: 284 ([*M*+H]$^+$, 100 %). A portion of this material (2.68 g, 9.44 mmol) was reduced with $LiAlH_4$ (430 mg, 11.3 mmol) to furnish **25** as a colourless oil that solidified on standing (2.00 g, 74 %). Purification of an aliquot by means of recrystallization (Et_2O/hexane) gave an analytically pure sample of **25**; m.p.: 50–52 °C (Et_2O/hexane); $[\alpha]_D^{20} = -33.4$ (c 1.0 in $CHCl_3$); IR (KBr disc): $\tilde{\nu}_{max} = 3400$, 3010, 1514, 702; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.00$ (3H, d, $J = 6.8$ Hz, C(2)CH_3), 2.19 (3H, s, NCH_3), 2.93 (1H, qd, $J = 6.8$, 5.0 Hz, C(2)*H*), 3.55 (1H, d, $J = 13.2$ Hz, NCH_A), 3.59 (1H, d, $J = 13.2$ Hz, NCH_B), 3.82 (3H, s, OCH_3), 4.88 (1H, d, $J = 5.0$ Hz, C(1)*H*), 6.86–7.41 ppm (9H, m, *Ph*, *Ar*); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 9.7$, 38.3, 55.2, 58.5, 63.2, 73.7, 113.8, 126.4, 127.1, 128.2, 130.0, 131.7, 143.0, 158.9 ppm; MS (CI): *m*/*z*: 286 ([*M*+H]$^+$, 100 %); elemental analysis: cacld (%) for $C_{18}H_{23}NO_2$: C 75.8, H 8.1, N 4.9; found: C 75.9, H 8.4, N 5.0.

(1*R*,2*S*)-1-Phenyl-2-[*N*-methyl-*N*-(3′-methoxybenzyl)amino]propan-1-ol (**26**): A mixture of (1*R*,2*S*)-ephedrine **19** (10.0 g, 60.5 mmol) and 3-methoxybenzaldehyde (8.24 g, 60.5 mmol) in C_6H_6 (100 mL) was reacted according to *general procedure 2* to give (2*R*,4*S*,5*R*)-2-(3′-methoxyphenyl)-*N*(3),4-dimethyl-5-phenyloxazolidine **22** as a pale yellow oil (16.1 g, 94 %). Purification of an aliquot by means of reduced pressure distillation (160–172 °C, 0.06 mm Hg) gave an analytically pure sample of **22**; $[\alpha]_D^{20} = -49.1$ ($c = 1.1$ in $CHCl_3$); IR (film): $\tilde{\nu}_{max} = 3010$, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.80$ (3H, d, $J = 6.4$ Hz, C(4)CH_3), 2.21 (3H, s, NCH_3), 2.98 (1H, dq, $J = 8.2$, 6.4 Hz, C(4)*H*), 3.86 (3H, s, OCH_3), 4.69 (1H, s, C(2)*H*), 5.15 (1H, d, $J = 8.2$ Hz, C(5)*H*), 6.89–7.47 ppm (9H, m, *Ph*, *Ar*); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 14.8$, 35.7, 55.2, 63.9, 82.5, 98.7, 113.6, 115.0, 120.9, 128.0, 128.2, 128.5, 129.5, 129.7, 140.0, 160.0 ppm; MS (CI): *m*/*z*: 284 ([*M*+H]$^+$, 100 %); elemental analysis: calcd (%) for $C_{18}H_{21}NO_2$: C 76.3; H 7.5; N 4.9; found: C 76.5; H 7.8; N 4.8. A portion of this material (5.00 g, 17.6 mmol) was reduced with $LiAlH_4$ (800 mg, 21.1 mmol) to furnish **26** as a colourless oil (4.86 g, 96 %). Purification of an aliquot by means of flash column chromatography (eluent Et_2O) gave an analytically pure sample of **26**; $[\alpha]_D^{20} = -28.4$ ($c = 1.0$ in $CHCl_3$); IR (film): $\tilde{\nu}_{max} = 3420$, 3010, 703; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.01$ (3H, d, $J = 6.8$ Hz, C(2)CH_3), 2.21 (3H, s, NCH_3), 2.95 (1H, qd, $J = 6.8$, 5.0 Hz, C(2)*H*), 3.32 (1H, br s, O*H*), 3.59 (1H, d, $J = 13.5$ Hz, NCH_A), 3.61 (1H, d, $J = 13.5$ Hz, NCH_B), 3.79 (3H, s, OCH_3), 4.88 (1H, d, $J = 5.0$ Hz, C(1)*H*), 6.78–7.36 ppm (9H, m, *Ph*, *Ar*); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 9.7$, 38.6, 55.1, 59.0, 63.4, 73.8, 112.6, 114.1, 121.1, 126.4, 127.1, 128.2, 129.4, 141.4, 142.8, 159.9 ppm; MS (CI): *m*/*z*: 286 ([*M*+H]$^+$, 100 %); elemental analysis: calcd (%) for $C_{18}H_{23}NO_2$: C 75.8, H 8.1, N 4.9; found: C 75.9, H 8.4, N 4.9.

(1*R*,2*S*)-1-Phenyl-2-[*N*-methyl-*N*-(2′-methoxybenzyl)amino]propan-1-ol (**27**): A mixture of (1*R*,2*S*)-ephedrine **19** (8.00 g, 48.4 mmol) and 2-methoxybenzaldehyde (6.59 g, 48.4 mmol) in C_6H_6 (100 mL) was reacted according to *general procedure 2* to furnish (2*R*,4*S*,5*R*)-2-(2′-methoxyphenyl)-*N*(3),4-dimethyl-5-phenyloxazolidine **23** as a white solid (12.7 g, 93 %, >99:1 d.r.). Purification of an aliquot by means of recrystallization (Et_2O/hexane) gave an analytically pure sample of **23**; m.p.: 100–101 °C (Et_2O/hexane); $[\alpha]_D^{20} = -75.1$ ($c = 1.3$ in $CHCl_3$); IR (KBr disc): $\tilde{\nu}_{max} =$ 3010, 1496, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.83$ (3H, d, $J =$ 6.4 Hz, C(4)CH_3), 2.26 (3H, s, NCH_3), 3.04 (1H, dq J 7.7, 6.4, C(4)*H*), 3.90 (3H, s, OCH_3), 5.21 (1H, app d, $J = 8.1$ Hz, C(4)*H*), 5.31 (1H, s, C(2)*H*), 6.95–7.97 ppm (9H, m, *Ph*, *Ar*); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 14.8$, 36.0, 55.6, 63.8, 82.7, 91.8, 110.9, 121.0, 126.1, 127.6, 127.9, 128.2, 128.6, 130.1, 140.3, 159.1 ppm; MS (CI): *m*/*z*: 284 ([*M*+H]$^+$, 100 %); elemental analysis: calcd (%) for $C_{18}H_{21}NO_2$: C 76.3, H 7.5, N 4.9; found: C 76.6, H 7.6, N 4.75. A portion of this material (4.71 g, 16.6 mmol) was reduced with $LiAlH_4$ (800 mg, 21.1 mmol) to furnish **27** as a white powder (4.62 g, 97 %, >99:1 d.r.). Purification of an aliquot by means of recrystallization (Et_2O/hexane) gave an analytically pure sample of **27**; m.p.: 88 °C (Et_2O/hexane); $[\alpha]_D^{20} = -64.8$ ($c = 0.9$ in $CHCl_3$); IR (KBr disc): $\tilde{\nu}_{max} = 3420$, 3005, 1495, 704 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ 0.97 (3H, d, $J = 6.9$ Hz, C(2)CH_3), 2.15 (3H, s, NCH_3), 2.95 (1H, qd, $J =$ 6.9, 4.1 Hz, C(2)*H*), 3.59 (1H, d, $J = 13.1$ Hz, NCH_A), 3.84 (1H, d, $J =$ 13.1 Hz, NCH_B), 3.90 (3H, s, OCH_3), 4.25 (1H, br s, O*H*), 4.97 (1H, d,

J=4.1 Hz, C(1)H), 6.91–7.39 ppm (9H, m, *Ph*, *Ar*); ^{13}C NMR (100 MHz, $CDCl_3$): δ=9.9, 38.7, 54.8, 55.2, 64.0, 73.7, 110.6, 120.4, 126.4, 126.9, 127.1, 127.6, 128.5, 131.0, 142.5, 158.1 ppm; MS (CI): m/z: 286 ([M+H]$^+$, 100%); elemental analysis: calcd (%) for $C_{18}H_{23}NO_2$: C 75.8, H 8.1, N 4.9; found: C 76.0, H 8.4, N 4.6.

(1*R*,2*S*)-1-Phenyl-2-(*N*-methyl-*N*-benzylamino)propan-1-ol (**28**): A mixture of (1*R*,2*S*)-ephedrine **19** (8.00 g, 48.4 mmol) and BnBr (5.40 mL, 45.4 mmol) in MeCN (50 mL) was reacted according to *general procedure 1* to furnish, after recrystallization (Et_2O/hexane) **28** as a white solid (7.66 g, 62%, >99:1 d.r.); m.p.: 45–46 °C (Et_2O/hexane) (49–51 °C)[24]; $[\alpha]_D^{20}=-29.7$ (c=1.5 in $CHCl_3$) {$[\alpha]_D^{20}=-29.5$ (c=2.35 in $CHCl_3$)}[24]; ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.00 (3H, d, J=6.8 Hz, C(2)CH_3), 2.20 (3H, s, NCH_3), 2.94 (1H, qd, J=6.8, 4.9 Hz, C(2)H), 3.46 (1H, br s, OH), 3.61 (1H, d, J=13.5 Hz, NCH_A), 3.64 (1H, d, J=13.5 Hz, NCH_B), 4.89 (1H, d, J=4.9 Hz, C(1)H), 7.24–7.35 ppm (10H, m, *Ph*); ^{13}C NMR (100 MHz, $CDCl_3$): δ=9.7, 38.6, 59.1, 63.5, 73.7, 126.4, 127.1, 127.5, 127.8, 128.5, 129.2, 139.7, 142.9 ppm; MS (CI): m/z: 256 ([M+H]$^+$, 100%).

(1*R*,2*R*)-1-Phenyl-2-[*N*-methyl-*N*-(3′,4′-dimethoxybenzyl)amino]propan-1-ol (**34**):

Method A: (1*R*,2*R*)-Pseudoephedrine **29** (1.37 g, 8.29 mmol) was reacted with freshly distilled 3,4-dimethoxybenzylbromide (1.92 g, 8.31 mmol) in MeCN (100 mL) according to *general procedure 1* for 5 h to give **34** as a white solid (2.60 g, 99%, >99:1 d.r.). Purification of an aliquot by means of recrystallization (Et_2O/hexane) gave an analytically pure sample of **34**; m.p.: 77–78 °C (Et_2O/hexane);$[\alpha]_D^{20}=-131$ (c=1.0 in $CHCl_3$); IR (KBr disc): $\tilde{\nu}_{max}$=3340, 3010, 704 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.81 (3H, d, J=6.6 Hz, C(2)CH_3), 2.25 (3H, s, NCH_3), 2.76 (1H, dq, J=9.7, 6.6 Hz, C(2)H), 3.45 (1H, d, J=12.9 Hz, NCH_A), 3.72 (1H, d, J=12.9 Hz, NCH_B), 3.90 (3H, s, OCH_3), 3.92 (3H, s, OCH_3), 4.33 (1H, d, J=9.7 Hz, C(1)H), 6.82–7.34 ppm (8H, m, *Ph*, *Ar*); ^{13}C NMR (100 MHz, $CDCl_3$): δ=7.1, 35.6, 55.8, 57.8, 64.4, 74.7, 111.0, 111.8, 121.0, 127.3, 127.4, 127.6, 128.1, 131.2, 141.9, 148.3, 149.1 ppm; MS (CI): m/z: 316 ([M+H]$^+$, 100%); elemental analysis: calcd (%) for $C_{19}H_{25}NO_3$; C 72.35, H 8.0, N 4.4; found: C 72.6, H 8.2, N 4.3.

Method B: (1*R*,2*R*)-Pseudoephedrine **29** (9.12 g, 55.2 mmol) and 3,4-dimethoxybenzaldehyde (9.17 g, 55.2 mmol) in C_6H_6 (100 mL) were reacted according to *general procedure 2* for 14 h to give, after purification by means of recrystallization (pentane/Et_2O), (2*R*,4*R*,5*R*)-2-(3′,4′-dimethoxyphenyl)-*N*(3),4-dimethyl-5-phenyloxazolidine **30** as a white solid (17.3 g, quant., >99:1 d.r.); m.p.: 54–56 °C; $[\alpha]_D^{20}=-47.1$ (c=1.0 in $CHCl_3$); IR (KBr disc): $\tilde{\nu}_{max}$=3008, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.25 (3H, d, J=6.0 Hz, C(4)CH_3), 2.22 (3H, s, NCH_3), 2.54 (1H, dq, J=8.7, 6.0 Hz, C(4)H), 3.90 (3H, s, OCH_3), 3.95 (3H, s, OCH_3), 4.76 (1H, d, J=8.7 Hz, C(5)H), 4.91 (1H, s, C(2)H), 6.86–7.45 ppm (8H, m, *Ph*, *Ar*); ^{13}C NMR (100 MHz, $CDCl_3$): δ=14.2, 35.1, 55.8, 68.8, 86.3, 99.6, 110.4, 110.6, 120.9, 126.8, 127.1, 128.5, 128.6, 132.0, 140.7, 149.4, 149.9 ppm; MS (CI): m/z: 314 ([M+H]$^+$, 100%); elemental analysis: calcd (%) for $C_{19}H_{23}NO_3$: C 72.8; H 7.4; N 4.5; found: C 72.9; H 7.6; N 4.4. A portion of this material (3.59 g, 11.5 mmol) in MeOH (40 mL) was reduced with $NaBH_4$ (1.00 g, 26.4 mmol) according to *general procedure 2* to give **34** as a colourless oil (3.60 g, 99%, >99:1 d.r.).

(1*R*,2*R*)-1-Phenyl-2-[*N*-methyl-*N*-(4′-methoxybenzyl)amino]propan-1-ol (**35**): A mixture of (1*R*,2*R*)-pseudoephedrine **29** (5.00 g, 30.3 mmol) and 4-methoxybenzaldehyde (4.12 g, 30.3 mmol) in C_6H_6 (150 mL) was reacted according to *general procedure 2* to give (2*R*,4*R*,5*R*)-2-(4′-methoxyphenyl)-*N*(3),4-dimethyl-5-phenyloxazolidine **31** as an oil that solidified on standing (7.32 g, 85%). Purification of an aliquot by means of recrystallization (Et_2O/hexane) gave an analytically pure sample of **31**; m.p.: 65 °C (Et_2O/hexane); $[\alpha]_D^{20}=-51.0$ (c=2.2 in $CHCl_3$); IR (KBr disc): $\tilde{\nu}_{max}$=3010, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.26 (3H, d, J=6.1 Hz, C(4)CH_3), 2.22 (3H, s, NCH_3), 2.55 (1H, dq, J=8.7, 6.1 Hz, C(4)H), 3.83 (3H, s, OCH_3), 4.78 (1H, d, J=8.7 Hz, C(5)H), 4.94 (1H, s, C(2)H), 6.95–7.53 ppm (9H, m, *Ph*, *Ar*); ^{13}C NMR (100 MHz, $CDCl_3$): δ=14.3, 35.0, 55.3, 68.8, 86.4, 99.4, 113.9, 126.8, 128.0, 128.5, 129.4, 131.8, 140.8, 160.5 ppm; MS (CI): m/z: 284 ([M+H]$^+$, 100%); elemental analysis: calcd (%) for $C_{18}H_{21}NO_2$: C 76.3, H 7.5, N 4.9; found: C 76.2, H 7.8, N 4.9. A portion of this material (2.50 g, 8.80 mmol) was reduced with $LiAlH_4$ (400 mg, 10.5 mmol) to give **35** as a colourless oil (4.77 g, 94%); $[\alpha]_D^{20}=-125$ (c=0.8 in $CHCl_3$); IR (film): $\tilde{\nu}_{max}$=3340, 3010, 703 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.81 (3H, d, J=6.7 Hz, C(2)CH_3), 2.23 (3H, s, NCH_3), 2.76 (1H, dq, J=9.8, 6.7 Hz, C(2)H), 3.46 (1H, d, J=12.8 Hz, NCH_A), 3.70 (1H, d, J=12.8 Hz, NCH_B), 3.83 (3H, s, OCH_3), 4.33 (1H, d, J=9.8 Hz, C(1)H), 6.90–7.35 ppm (9H, m, *Ph*, *Ar*); ^{13}C NMR (100 MHz, $CDCl_3$): δ=7.1, 35.4, 55.2, 57.6, 64.5, 74.7, 113.9, 127.5, 127.8, 128.3, 130.2, 130.9, 142.2, 159.1 ppm; MS (CI): m/z: 286 ([M+H]$^+$, 100%); elemental analysis: calcd (%) for $C_{18}H_{23}NO_2$: C 75.8, H 8.1, N 4.9; found: C 75.6, H 8.5, N 5.0.

(1*R*,2*R*)-1-Phenyl-2-[*N*-methyl-*N*-(3′-methoxybenzyl)amino]propan-1-ol (**36**): A mixture of (1*R*,2*R*)-pseudoephedrine **29** (10.0 g, 60.5 mmol) and 3-methoxybenzaldehyde (8.24 g, 60.5 mmol) in C_6H_6 (100 mL) was reacted according to *general procedure 2* to give (2*R*,4*R*,5*R*)-2-(3′-methoxyphenyl)-*N*(3),4-dimethyl-5-phenyloxazolidine **32** as a colourless oil (16.3 g, 95%). Purification of an aliquot by means of reduced pressure distillation (b.p.: 152–160 °C, 0.06 mm Hg) gave an analytically pure sample of **32** that solidified up on standing; m.p.: 58 °C; $[\alpha]_D^{20}=-44.0$ (c=1.0 in $CHCl_3$); IR (KBr disc): $\tilde{\nu}_{max}$=3010, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.25 (3H, d, J=6.0 Hz, C(4)CH_3), 2.25 (3H, s, NCH_3), 2.58 (1H, dq, J=8.8, 6.0 Hz, C(4)H), 3.86 (3H, s, OCH_3), 4.78 (1H, d, J=8.8 Hz, C(5)H), 4.95 (1H, s, C(2)H), 6.90–7.46 ppm (9H, m, *Ph*, *Ar*); ^{13}C NMR (100 MHz, $CDCl_3$): δ=14.2, 35.2, 55.2, 68.8, 86.6, 99.5, 113.1, 115.1, 120.6, 126.9, 127.9, 128.6, 129.5, 140.6, 141.3, 160.0 ppm; MS (CI): m/z: 284 ([M+H]$^+$, 100%); elemental analysis: calcd (%) for $C_{18}H_{21}NO_2$: C 76.3, H 7.5, N 4.9; found: C 76.1, H 7.6, N 4.8. A portion of this material (5.03 g, 17.7 mmol) was reduced with $LiAlH_4$ (800 mg, 21.1 mmol) to furnish **36** as a colourless oil (4.77 g, 94%). Purification of an aliquot by means of flash column chromatography (eluent Et_2O) gave an analytically pure sample of **36**; $[\alpha]_D^{20}=-121$ (c=1.0 in $CHCl_3$); IR (film): $\tilde{\nu}_{max}$=3350, 3010, 1496, 702 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.81 (3H, d, J=6.7 Hz, C(2)CH_3), 2.25 (3H, s, NCH_3), 2.76 (1H, dq, J=9.7, 6.7 Hz, C(2)H), 3.49 (1H, d, J=13.0 Hz, NCH_A), 3.73 (1H, d, J=13.0 Hz, NCH_B), 3.83 (3H, s, OCH_3), 4.32 (1H, d, J=9.7 Hz, C(1)H), 5.17 (1H, br s, OH), 6.82–7.35 ppm (9H, m, *Ph*, *Ar*); ^{13}C NMR (100 MHz, $CDCl_3$): δ=7.1, 35.7, 55.2, 58.2, 64.9, 74.8, 112.9, 114.4, 121.4, 127.5, 127.9, 128.4, 129.6, 140.5, 142.1, 160.0 ppm; MS (CI): m/z: 286 ([M+H]$^+$, 100%); elemental analysis: calcd (%) for $C_{18}H_{23}NO_2$: C 75.8, H 8.1, N 4.9; found: C 75.6, H, 8.2, N 4.45.

(1*R*,2*R*)-1-Phenyl-2-[*N*-methyl-*N*-(2′-methoxybenzyl)amino]propan-1-ol (**37**): A mixture of (1*R*,2*R*)-pseudoephedrine **29** (8.00 g, 48.4 mmol) and 2-methoxybenzaldehyde (6.59 g, 48.4 mmol) in C_6H_6 (100 mL) was reacted according to *general procedure 2* to give, after purification by means of reduced pressure distillation (180 °C, 0.06 mm Hg), (2*R*,4*R*,5*R*)-2-(2′-methoxyphenyl)-*N*(3),4-dimethyl-5-phenyloxazolidine **33** as a colourless oil (12.5 g, 91%, >99:1 d.r.); $[\alpha]_D^{20}=-4.84$ (c=1.0 in $CHCl_3$); IR (film): $\tilde{\nu}_{max}$=3010, 1495, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.24 (3H, d, J=6.1 Hz, C(4)CH_3), 2.26 (3H, s, NCH_3), 2.58 (1H, dq, J=8.7, 6.1 Hz, C(4)H), 3.87 (3H, s, OCH_3), 4.75 (1H, d, J=8.7 Hz, C(5)H), 5.58 (1H, s, C(2)H), 6.90–7.76 ppm (9H, m, *Ph*, *Ar*); ^{13}C NMR (100 MHz, $CDCl_3$): δ=14.2, 35.3, 55.6, 69.0, 86.3, 92.4, 110.8, 121.1, 126.9, 127.0, 127.8, 128.3, 128.5, 129.9, 140.9, 158.6 ppm; MS (CI): m/z: 284 ([M+H]$^+$, 100%); elemental analysis: calcd (%) for $C_{18}H_{21}NO_2$: C 76.3, H 7.5, N 4.9; found: C 76.6, H 7.5, N 4.8. A portion of this material (5.03 g, 17.7 mmol) was reduced with $LiAlH_4$ (800 mg, 21.1 mmol) to give **37** as a white solid (4.62 g, 91%). Purification of an aliquot by means of recrystallization (Et_2O/hexane) gave an analytically pure sample of **37**; m.p.: 62–65 °C (Et_2O/hexane); $[\alpha]_D^{20}=-120$ (c=1.3 in $CHCl_3$); IR (film): $\tilde{\nu}_{max}$=3360, 3010, 1496, 702 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.82 (3H, d, J=6.7 Hz, C(2)CH_3), 2.23 (3H, s, NCH_3), 2.77 (1H, dq, J=9.7, 6.7 Hz, C(2)H), 3.47 (1H, d, J=12.7 Hz, NCH_A), 3.81 (1H, d, J=12.7 Hz, NCH_B), 3.88 (3H, s, OCH_3), 4.34 (1H, d, J=9.7 Hz, C(1)H), 5.37 (1H, br s, OH), 6.90–7.37 ppm (9H, m, *Ph*, *Ar*); ^{13}C NMR (100 MHz, $CDCl_3$): δ=7.3, 36.3, 52.8, 55.1, 65.5, 75.0, 110.5, 120.3, 127.0, 127.6, 127.7, 128.3, 128.8, 131.0, 142.5, 158.3 ppm; MS (CI): m/z: 286 ([M+H]$^+$, 100%); elemental analysis: calcd (%) for $C_{18}H_{23}NO_2$: C 75.8, H 8.1, N 4.9; found: C 76.0, H 8.4, N 4.95.

(1*R*,2*R*)-1-Phenyl-2-(*N*-benzyl-*N*-methylamino)propan-1-ol (**38**): A mixture of (1*R*,2*R*)-pseudoephedrine **29** (6.00 g, 36.3 mmol) and BnBr

(4.30 mL, 36.2 mmol) in MeCN (50 mL) was reacted according to *general procedure 1* to give, after recrystallization (CH_2Cl_2/hexane), **38** as a white solid (7.18 g, 77%, >99:1 d.r.); m.p.: 57–58°C; $[\alpha]_D^{20}=-125$ ($c=1.5$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=0.82$ (3H, d, $J=6.6$ Hz, C(2)CH_3), 2.24 (3H, s, NCH_3), 2.76 (1H, dq, $J=9.7$, 6.6 Hz, C(2)H), 3.52 (1H, d, $J=12.9$ Hz, NCH_A), 3.76 (1H, d, $J=12.9$ Hz, NCH_B), 4.33 (1H, d, $J=9.7$ Hz, C(1)H), 5.24 (1H, br s, OH), 7.26–7.38 ppm (10H, m, *Ph*); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=7.2$, 35.7, 58.2, 64.9, 74.8, 127.6, 127.9, 128.1, 128.4, 128.7, 129.2, 138.9, 142.3 ppm; MS (CI): *m/z*: 256 ($[M+H]^+$, 100%).

(3*S*,4*R*)-*N*(2),3-Dimethyl-4-phenyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline [(3*S*,4*R*)-**39**]: A solution of **24** (685 mg, 2.17 mmol) in CH_2Cl_2 (12 mL) was reacted according to *general procedure 3* at 40°C for 30 min to give **39** (>99:1 d.r. crude) as a brown oil (480 mg, 74%, >99:1 d.r.). Purification of an aliquot by means of reduced pressure distillation (5 mbar) gave an analytically pure sample of **39**; $[\alpha]_D^{20}=-13.7$ ($c=1.3$ in $CHCl_3$); IR (film): $\tilde{\nu}_{max}=3010$, 1514, 705 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.09$ (3H, d, $J=6.4$ Hz, C(3)CH_3), 2.44 (3H, s, NCH_3), 2.73 (1H, dq, $J=8.0$, 6.4 Hz, C(3)H), 3.60 (3H, s, OCH_3), 3.75 (1H, d, $J=8.0$ Hz, C(4)H), 3.81 (2H, br s, C(1)H_2), 3.86 (3H, s, OCH_3), 6.19 (1H, s, *Ar*), 6.56 (1H, s, *Ar*), 7.12–7.32 ppm (5H, m, *Ph*); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=16.0$, 40.7, 51.7, 55.8 (2C), 57.0, 62.4, 108.5, 112.6, 126.2, 128.1, 128.6, 129.4, 129.6, 145.1, 147.4, 147.6 ppm; MS (CI): *m/z*: 297 ($[M]^+$, 100%); HRMS (CI$^+$) $C_{19}H_{23}NO_3^+$ ($[M]^+$) requires 297.1723; found 297.1728.

(3*S*,4*R*)-*N*(2),3-Dimethyl-4-phenyl-6-methoxy-1,2,3,4-tetrahydroisoquinoline [(3*S*,4*R*)-**40**]: A solution of **25** (1.18 g, 4.12 mmol) in CH_2Cl_2 (50 mL) was reacted according to *general procedure 3* at 40°C for 1 h to give **40** (97:3 d.r. crude) as a white solid (1.05 g, 92%, >99:1 d.r.). Purification of the residue by means of recrystallization (Et_2O/hexane) gave **40** as a white crystalline solid; m.p.: 75–76°C (Et_2O/hexane); $[\alpha]_D^{20}=-3.82$ ($c=0.8$ in $CHCl_3$); IR (KBr disc): $\tilde{\nu}_{max}=1505$, 703 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.08$ (3H, d, $J=6.4$ Hz, C(3)CH_3), 2.43 (3H, s, NCH_3), 2.73 (1H, dq, $J=8.4$, 6.4 Hz, C(3)H), 3.62 (3H, s, OCH_3), 3.77 (1H, d, $J=8.4$ Hz, C(4)H), 3.80 (2H, br s, C(1)H_2), 6.27 (1H, d, $J=2.7$ Hz, C(5)H), 6.70 (1H, dd, $J=8.4$, 2.7 Hz, C(7)H), 7.00 (1H, d, $J=8.4$ Hz, C(8)H), 7.13–7.32 ppm (5H, m, *Ph*); ^{13}C NMR (100 MHz, C_6D_6): $\delta=14.4$, 41.1, 52.7, 54.1, 55.6, 61.9, 112.7, 114.6, 126.3, 127.0, 127.3, 127.8, 129.6, 138.8, 145.8, 158.7 ppm; MS (CI): *m/z*: 268 ($[M+H]^+$, 100%); elemental analysis: calcd (%) for $C_{18}H_{21}NO$: C 80.9, H 7.9, N 5.2; found: C 81.0, H 8.05, N 5.2.

(3*S*,4*R*)- and (3*S*,4*S*)-*N*(2),3-Dimethyl-4-phenyl-7-methoxy-1,2,3,4-tetrahydroisoquinoline [(3*S*,4*R*)-**41**] and [(3*S*,4*S*)-**46**]: A solution of **26** (2.24 g, 7.85 mmol) in CH_2Cl_2 (25 mL) was reacted according to *general procedure 3* at 40°C for 1.5 h to give **41** (93:7 d.r. crude) as a pale brown oil. Purification of the residue by means of flash column chromatography (eluent Et_2O) gave **41** which was recrystallized (Et_2O/hexane) to give **41** as a white solid (1.18 g, 56%); m.p.: 121.5°C; $[\alpha]_D^{20}=+133$ ($c=0.05$ in $CHCl_3$); IR (KBr disc): $\tilde{\nu}_{max}=3010$, 1504, 702 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.08$ (3H, d, $J=6.4$ Hz, C(3)CH_3), 2.44 (3H, s, NCH_3), 2.74 (1H, dq, $J=8.5$, 6.4 Hz, C(3)H), 3.76 (1H, d, $J=8.5$ Hz, C(4)H), 3.77 (3H, s, OCH_3), 3.84 (2H, br s, C(1)H_2), 6.61–7.32 ppm (8H, m, *Ph*, *Ar*); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=16.3$, 40.8, 51.5, 55.1, 57.9, 62.6, 110.4, 112.9, 126.5, 127.1, 128.5, 129.7, 131.1, 135.7, 145.6, 157.8 ppm; MS (CI): *m/z*: 267 ($[M]^+$, 100%); elemental analysis: calcd (%) for $C_{18}H_{21}NO$: C 80.9, H 7.9, N 5.2; found: C 80.7, H 8.3, N 5.1. Further elution gave **46** as a colourless oil that solidified on standing (42 mg, 2%); m.p.: 41–42°C; $[\alpha]_D^{20}=-45.4$ ($c=0.7$ in $CHCl_3$); IR (KBr disc): $\tilde{\nu}_{max}=3018$, 1504, 704; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=0.84$ (3H, d, $J=6.6$ Hz, C(3)CH_3), 2.39 (3H, s, NCH_3), 2.86 (1H, qd, $J=6.6$, 4.6 Hz, C(3)H), 3.78 (3H, s, OCH_3), 3.53 (1H, d, $J=15.5$ Hz, C(1)H_A), 3.95 (1H, d, $J=15.5$ Hz, C(1)H_B), 4.05 (1H, d, $J=4.6$ Hz, C(4)H), 6.62–7.29 ppm (8H, m, *Ph*, *Ar*); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=14.3$, 42.2, 50.4, 55.1, 57.1, 59.2, 110.4, 112.8, 126.2, 130.1, 130.6, 130.9, 131.1, 136.0, 143.3, 157.8 ppm; MS (CI): *m/z*: 267 ($[M]^+$, 100%); elemental analysis: calcd (%) for $C_{18}H_{21}NO$: C 80.9, H 7.9, N 5.2; found: C 81.1, H 8.3, N 5.15.

(3*S*,4*R*)-*N*(2),3-Dimethyl-4-phenyl-8-methoxy-1,2,3,4-tetrahydroisoquinoline [(3*S*,4*R*)-**42**]: A solution of **27** (500 mg, 1.75 mmol) in CH_2Cl_2 (25 mL) was cyclized according to *general procedure 3* at 40°C for 2.5 h to give **42** (>99:1 d.r. crude) as a pale yellow solid (269 mg, 57%, >99:1 d.r.). Purification of an aliquot by means of recrystallization (Et_2O/hexane) gave an analytically pure sample of **42**; m.p.: 114–116°C (Et_2O/hexane); $[\alpha]_D^{20}=-64.5$ ($c=0.5$ in $CHCl_3$); IR (KBr disc): $\tilde{\nu}_{max}=3005$, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.07$ (3H, d, $J=6.4$ Hz, C(3)CH_3), 2.47 (3H, s, NCH_3), 2.73 (1H, dq, $J=8.0$, 6.4 Hz, C(3)H), 3.81 (1H, d, $J=8.0$ Hz, C(4)H), 3.85 (3H, s, OCH_3), 3.63 (1H, d, $J=16.3$ Hz, C(1)H_A), 3.98 (1H, d, $J=16.3$ Hz, C(1)H_B), 6.36–7.31 ppm (8H, m, *Ph*, *Ar*); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=15.8$, 41.3, 52.3, 52.1, 55.2, 61.7, 106.9, 122.2, 123.7, 126.4, 126.6, 128.3, 129.7, 139.2, 145.4, 155.7 ppm; MS (CI): *m/z*: 268 ($[M+H]^+$, 100%); elemental analysis: calcd (%) for $C_{18}H_{21}NO$: C 80.9, H 7.9, N 5.2; found: C 81.2, H 7.75, N 5.0.

(3*S*,4*R*)- and (3*S*,4*S*)-*N*(2),3-Dimethyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline [(3*S*,4*R*)-**43**] and [(3*S*,4*S*)-**48**]: A solution of **28** (2.00 g, 7.83 mmol) in CH_2Cl_2 (50 mL) was reacted according to *general procedure 3* at 40°C for 5 h to give a 97:3 mixture of **43** and **48** respectively. Purification of the residue by means of flash column chromatography (eluent Et_2O) gave a 97:3 mixture of **43** and **48** as a white solid (1.80 g, 97%). Data for **43**: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.09$ (3H, d, $J=6.3$ Hz, C(3)CH_3), 2.45 (3H, s, NCH_3), 2.75 (1H, dq, $J=8.3$, 6.3 Hz, C(3)H), 3.85 (1H, d, $J=8.3$ Hz, C(4)H), 3.86 (2H, m, C(1)H_2), 6.73–7.33 ppm (9H, m, *Ph*, *Ar*). Data for mixture: MS (CI): *m/z*: 237 ($[M]^+$, 100%); elemental analysis: calcd (%) for $C_{17}H_{19}N$: C 86.0, H 8.1, N 5.9; found: C 85.7, H 8.2, N 6.3. Subsequent recrystallization (Et_2O/hexane) of an aliquot enabled the isolation of a diastereoisomerically pure sample of **48**; m.p.: 102–103°C (Et_2O/hexane); $[\alpha]_D^{20}=+160$ ($c=0.2$ in $CHCl_3$); IR (film): $\tilde{\nu}_{max}=3005$, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=0.86$ (3H, d, $J=6.6$ Hz, C(3)CH_3), 2.40 (3H, s, NCH_3), 2.88 (1H, dq, $J=6.6$, 4.5 Hz, C(3)H), 3.56 (1H, d, $J=15.5$ Hz, C(1)H_A), 3.99 (1H, d, $J=15.5$ Hz, C(1)H_B), 4.10 (1H, d, $J=4.5$ Hz, C(4)H), 6.95–7.28 ppm (9H, m, *Ph*, *Ar*); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=16.3$, 41.1, 52.3, 57.8, 62.6, 125.9, 126.0, 126.5, 127.1, 128.4, 129.8, 130.0, 134.6, 138.1, 145.3; MS (CI): *m/z*: 237 ($[M]^+$, 100%); HRMS (CI$^+$) $C_{17}H_{19}N^+$ ($[M]^+$) requires 237.1517; found 237.1519; elemental analysis: calcd (%) for $C_{17}H_{19}N$: C 86.0, H 8.1, N 5.9; found: C 86.35, H 8.1, N 5.9.

(3*R*,4*S*)-*N*(2),3-Dimethyl-4-phenyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline [(3*R*,4*S*)-**39**]: A solution of **34** (641 mg, 2.03 mmol) in CH_2Cl_2 (11.0 mL) was cyclized according to *general procedure 3* for 30 min at 40°C to give an 88:12 mixture of **39** and **44** respectively. Purification of the residue by using flash column chromatography (eluent Et_2O) gave an inseparable 88:12 mixture of **39** and **44** as a colourless oil (480 mg, 79%); MS (CI): *m/z*: 298 ($[M+H]^+$, 100%).

(3*R*,4*S*)-*N*(2),3-Dimethyl-4-phenyl-6-methoxy-1,2,3,4-tetrahydroisoquinoline [(3*R*,4*S*)-**40**]: A solution of **35** (810 mg, 2.84 mmol) in CH_2Cl_2 (50 mL) was cyclized according to *general procedure 3* at 40°C for 1 h to give **40** (93:7 d.r. crude) as a pale-yellow oil (750 mg, 92%). Purification of the residue by means of flash column chromatography (eluent Et_2O) and subsequent recrystallization (Et_2O/hexane) gave **40** as a white crystalline solid (>99:1 d.r.); m.p.: 75°C; $[\alpha]_D^{20}=+4.25$ ($c=0.5$ in $CHCl_3$); MS (CI): *m/z*: 267 ($[M]^+$, 100%); elemental analysis: calcd (%) for $C_{18}H_{21}NO$: C 80.9, H 7.9, N 5.2; found: C 80.8, H 8.2, N 5.0.

(3*R*,4*S*)- and (3*R*,4*R*)-*N*(2),3-Dimethyl-4-phenyl-7-methoxy-1,2,3,4-tetrahydroisoquinoline [(3*R*,4*S*)-**41**] and [(3*R*,4*R*)-**46**]: A solution of **36** (1.69 g, 5.92 mmol) in CH_2Cl_2 (50 mL) was cyclized according to *general procedure 3* at 40°C for 1.75 h to give a 87:13 mixture of **41** and **46**, respectively, as a red oil. Purification of the residue by means of flash column chromatography (eluent Et_2O) enabled isolation of the minor component which was recrystallized (Et_2O/hexane) to give **46** as a white solid (32 mg, 4%, >99:1 d.r.); m.p.: 121–122°C; $[\alpha]_D^{20}=-145$ ($c=0.05$ $CHCl_3$); MS (CI): *m/z*: 267 ($[M]^+$, 100%); elemental analysis: calcd (%) for $C_{18}H_{21}NO$: C 80.9, H 7.9, N 5.2; found: C 80.6, H 8.3, N 5.0. Further elution gave **41** as a colourless oil that solidified on standing (649 mg, 41%, >99:1 d.r.); m.p.: 41–42°C; $[\alpha]_D^{20}=+44.9$ ($c=0.9$ in $CHCl_3$); MS (CI): *m/z*: 267 ($[M]^+$, 100%); elemental analysis: calcd (%) for $C_{18}H_{21}NO$: C 80.9, H 7.9, N 5.2; found: C 81.2, H 8.3, N 5.1.

(3*R*,4*S*)-*N*(2),3-Dimethyl-4-phenyl-8-methoxy-1,2,3,4-tetrahydroisoquinoline [(3*R*,4*S*)-**42**]: A solution of **37** (1.85 g, 6.47 mmol) in CH_2Cl_2 (50 mL)

was reacted according to *general procedure 3* at 40 °C for 5 h to give **42** (99:1 d.r. crude) as a pale yellow solid. Purification of the residue by means of recrystallization (Et_2O/hexane) furnished **42** as a white crystalline solid (1.57 g, 91 %, >99:1 d.r.); m.p.: 114–116 °C (Et_2O/hexane); $[\alpha]_D^{20} = +65.5$ ($c = 1.1$ in $CHCl_3$); MS (CI): *m/z*: 268 ($[M+H]^+$, 100 %); elemental analysis: calcd (%) for $C_{18}H_{21}NO$: C 80.9, H 7.9, N 5.2; found: C 80.6, H 8.2, N 5.5.

X-ray Crystal Structure Determination of [(3R,4S)-42]

Data were collected by using an Enraf–Nonius CAD4-F 4-circle diffractometer with graphite monochromated $Cu_{K\alpha}$ radiation using standard procedures at 190 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealized positions. The structure was refined using CRYSTALS.[25]

X-ray crystal structure data for [(3*R*,4*S*)-**42**] [$C_{18}H_{21}NO$]: $M = 267.37$, orthorhombic, space group $P2_12_12_1$; $a = 5.978(2)$, $b = 9.257(1)$, $c = 26.799(4)$ Å; $V = 1482.9(6)$ Å^3, $Z = 4$, $\mu = 0.062$ mm^{-1}, colourless block, crystal dimensions $= 0.4 \times 0.6 \times 0.8$ mm^3. A total of 1804 unique reflections were measured for $5 < \theta < 27$ and 1645 reflections were used in the refinement. The final parameters were $wR_2 = 0.091$ and $R_1 = 0.075$ [$I > 3.0\sigma(I)$]. CCDC 746820 [(3*R*,4*S*)-**42**] contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre at www.ccdc.cam.ac.uk/data_request/cif

(3*R*,4*S*)- and (3*R*,4*R*)-*N*(2),3-Dimethyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline [(3*R*,4*S*)-**43**] and [(3*R*,4*R*)-**48**]: A solution of **38** (2.40 g, 9.40 mmol) in CH_2Cl_2 (50 mL) was cyclized according to *general procedure 3* at 40 °C for 3.25 h to give a 94:6 mixture of **43** and **48**, respectively. Purification by means of flash column chromatography (eluent Et_2O) gave an inseparable 94:6 mixture of **43** and **48** as a colourless oil (2.23 g, quant); IR (film): $\tilde{\nu}_{max} = 3005$, 1485, 700 cm^{-1}; MS (CI): *m/z*: 237 ($[M]^+$, 100 %); elemental analysis: calcd (%) for $C_{17}H_{19}N$: C 86.0; H 8.1; N 5.9; found: C 85.7; H 8.2; N 6.3.

(1*R*,2*S*)-1-Phenyl-2-[*N*-methyl-*N*-(*tert*-butoxycarbonyl)amino]propan-1-ol (**49**): A solution of (1*R*,2*S*)-ephedrine **19** (20.0 g, 121 mmol) in CH_2Cl_2 (400 mL) at 0 °C was treated with Boc_2O (33.7 g, 139 mmol) and NEt_3 (16.8 mL, 121 mmol) and the resultant solution was left to stand at 20 °C for 60 h. Saturated aqueous citric acid (500 mL) was then added to the reaction mixture, and the organic phase was separated and washed sequentially with sat aq $NaHCO_3$ (500 mL), water (500 mL) and brine (500 mL) then dried, filtered and concentrated in vacuo. Purification of the residue by means of reduced pressure distillation (160 °C, 0.06 mm Hg) gave **49** as a colourless oil (27.3 g, 85 %, >99:1 d.r.); $[\alpha]_D^{20} = -26.8$ ($c = 1.9$ in $CHCl_3$); IR (film): $\tilde{\nu}_{max} = 3420$, 3008, 1675, 703 cm^{-1}; ^{1}H NMR (400 MHz, [D_6]DMSO, 360 K): $\delta = 1.17$ (3H, d, $J = 6.9$ Hz, C(2)CH_3), 1.30 (9H, s, C(CH_3)$_3$), 2.64 (3H, s, NCH_3), 4.06 (1H, app quin, $J = 7.0$ Hz, C(2)*H*), 4.57 (1H, dd, $J = 7.0$, 5.0 Hz, C(1)*H*), 5.17 (1H, d, $J = 5.0$ Hz, O*H*), 7.18–7.34 ppm (5H, m, *Ph*); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 12.8$, 28.2, 31.8, 58.1, 76.7, 79.7, 126.4, 127.6, 128.2, 142.3, 142.4 ppm; MS (CI): *m/z*: 266 ($[M+H]^+$, 100 %); elemental analysis: calcd (%) for $C_{15}H_{23}NO_3$: C 67.9, H 8.7, N 5.3; found: C 68.2, H 9.0, N 5.2.

{(1*R*,2*S*)-1-Phenyl-2-[*N*-methyl-*N*-(*tert*-butoxycarbonyl)amino]propan-1-ol}tricarbonylchromium(0) (**50**): A deoxygenated mixture of **49** (20.1 g, 75.8 mmol) and $Cr(CO)_6$ (16.7 g, 75.9 mmol) in Bu_2O (400 mL) and THF (40 mL) was heated at reflux under a nitrogen atmosphere for 48 h.[26] The resultant mixture was allowed to cool to RT, filtered and concentrated in vacuo. Purification of the residue by means of recrystallization (CH_2Cl_2/hexane) gave **50** as a yellow powder (16.5 g, 54 %, >99:1 d.r.); m.p.: 84 °C; $[\alpha]_D^{20} = -36.2$ ($c = 0.1$ in $CHCl_3$); IR (KBr disc): $\tilde{\nu}_{max} = 1965$, 1885, 1668 cm^{-1}; ^{1}H NMR (400 MHz, [D_6]DMSO, 360 K): $\delta = 1.17$ (3H, d, $J = 6.9$ Hz, C(2)CH_3) 1.34 (9H, s, C(CH_3)$_3$), 2.72 (3H, s, NCH_3), 3.93 (1H, app q, $J = 6.9$ Hz, C(2)*H*), 4.21 (1H, app t, $J = 6.9$ Hz, C(1)*H*), 5.47–5.77 ppm (5H, m, *Ar*Cr(CO)$_3$); MS (CI): *m/z*: 402 ($[M+H]^+$, 100 %); elemental analysis: calcd (%) for $C_{18}H_{23}CrNO_6$: C 53.9, H 5.8, N 3.5; found: C 54.2, H 6.0, N 3.2.

[(1*R*,2*S*)-1-Phenyl-2-(*N*-methylamino)propan-1-ol]tricarbonylchromium(0) (**51**): A solution of **50** (439 mg, 1.09 mmol) in HCO_2H (98–100 %, 15 mL) at RT was left to stand for 4.5 h concentrated in vacuo. The residue was treated with 2.0 M aq NaOH and the aqueous layer was extracted with Et_2O (10 mL). The combined organic extracts were concentrated in vacuo to give **51** as a yellow solid (330 mg, quant, >99:1 d.r.). Purification of an aliquot by means of recrystallization (Et_2O/hexane) gave an analytically pure sample of **51**; m.p.: 92–97 °C (dec); $[\alpha]_D^{20} = -33.0$ ($c = 0.2$ in $CHCl_3$); IR (KBr disc): $\tilde{\nu}_{max} = 1970$, 1885 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.93$ (3H, d, $J = 6.5$ Hz, C(2)CH_3), 2.48 (3H, s, NCH_3), 2.72 (1H, qd, $J = 6.5$, 3.4 Hz, C(2)*H*), 4.46 (1H, d, $J = 3.4$ Hz, C(1)*H*), 5.16–5.66 ppm (5H, m, *Ar*Cr(CO)$_3$); MS (CI): *m/z*: 302 ($[M+H]^+$, 100 %); elemental analysis: calcd (%) for $C_{13}H_{15}CrNO_4$: C 51.8, H 5.0, N 4.65; found: C 51.9, H 5.0, N 4.7.

{(1*R*,2*S*)-1-Phenyl-2-[*N*-methyl-*N*-(3′,4′-dimethoxybenzyl)amino]propan-1-ol}tricarbonylchromium(0) (**52**): A mixture of **51** (991 mg, 3.29 mmol) and freshly distilled 3,4-dimethoxybenzylbromide (760 mg, 3.29 mmol) in MeCN (40 mL) was reacted according to *general procedure 1* for 3 h to give **52** as a yellow oil. Purification of the residue by means of flash coloumn chromatography (eluent Et_2O) furnished **52** as a yellow oil (727 mg, 49 %, >99:1 d.r.); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.11$ (3H, d, $J = 6.7$ Hz, C(2)CH_3) 2.23 (3H, s, NCH_3), 2.78 (1H, qd, $J = 6.7$, 6.2 Hz, C(2)*H*), 3.45 (1H, d, $J = 13.2$ Hz, NCH_A), 3.51 (1H, d, $J = 13.2$ Hz, NCH_B), 3.85 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 4.38 (1H, d, $J = 6.2$ Hz, C(1)*H*), 5.21–5.55 (5H, m, *Ar*Cr(CO)$_3$), 6.69–6.79 ppm (3H, m, *Ar*); MS (CI): *m/z*: 452 ($[M+H]^+$, 100 %).

{(1*R*,2*S*)-1-Phenyl-2-[*N*-methyl-*N*-(4′-methoxybenzyl)amino]propan-1-ol}tricarbonylchromium(0) (**53**): A mixture of **51** (330 mg, 1.09 mmol) and freshly distilled 4-methoxybenzylbromide (220 mg, 1.09 mmol) in CH_2Cl_2 (30 mL) was reacted according to *general procedure 1* at RT for 28 h to give **53** as a yellow oil. Purification of the residue by means of flash column chromatography (Al_2O_3 grade V, petroleum ether/Et_2O, 1:1) furnished **53** as a yellow oil (47 mg, 10 %, >99:1 d.r.); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.10$ (3H, d, $J = 6.7$ Hz, C(2)CH_3), 2.22 (3H, s, NCH_3), 2.78 (1H, qd, $J = 6.7$, 6.4 Hz, C(2)*H*), 3.50 (1H, d, $J = 13.2$ Hz, NCH_A), 3.55 (1H, d, $J = 13.2$ Hz, NCH_B), 3.81 (3H, s, OCH_3), 4.35 (1H, d, $J = 6.4$ Hz, C(1)*H*), 5.22–5.54 (5H, m, *Ar*Cr(CO)$_3$), 6.79–7.07 ppm (4H, m, *Ar*); MS (CI): *m/z*: 422 ($[M+H]^+$, 100 %).

{(1*R*,2*S*)-1-Phenyl-2-[*N*-methyl-*N*-(3′-methoxybenzyl)amino]propan-1-ol}tricarbonylchromium(0) (**54**): A mixture of **51** (620 mg, 2.06 mmol) and freshly distilled 3-methoxybenzylbromide (500 mg, 2.49 mmol) in EtOH (10 mL) was reacted according to *general procedure 1* in the presence of $NaHCO_3$ (260 mg, 3.09 mmol) and a catalytic quantity of NaI at RT for 19.5 h to give a yellow oil. Purification of the residue by means of flash column chromatography (Al_2O_3 grade V, gradient elution petroleum ether/Et_2O) gave **54** as a yellow oil (427 mg, 49 %, >99:1 d.r.); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.12$ (3H, d, $J = 6.7$ Hz, C(2)CH_3), 2.24 (3H, s, NCH_3), 2.73 (1H, d, $J = 3.0$ Hz, O*H*), 2.78 (1H, app quin, $J = 6.7$ Hz, C(2)*H*), 3.53 (1H, d, $J = 13.5$ Hz, NCH_A), 3.58 (1H, d, $J = 13.5$ Hz, NCH_B), 3.80 (3H, s, OCH_3), 4.35 (1H, dd, $J = 6.7$ Hz, 3.0, C(1)*H*), 5.22–5.54 (5H, m, *Ar*Cr(CO)$_3$), 6.70–7.21 ppm (4H, m, *Ar*); MS (CI): *m/z*: 422 ($[M+H]^+$, 100 %).

{(1*R*,2*S*)-1-Phenyl-2-[*N*-methyl-*N*-(2′-methoxybenzyl)amino]propan-1-ol}tricarbonylchromium(0) (**55**): A mixture of **51** (176 mg, 0.58 mmol) and freshly distilled 2-methoxybenzylbromide (127 mg, 0.63 mmol) in EtOH (5 mL) was reacted according to *general procedure 1* in the presence of $NaHCO_3$ (67 mg, 0.80 mmol) and a catalytic quantity of NaI at RT for 63 h to furnish **55** as a yellow oil (111 mg, 45 %, >99:1 d.r.). Crystallization of an aliquot (Et_2O/hexane) gave an analytically pure sample of **55**; $[\alpha]_D^{22} = +28.8$ (c 0.1 in $CHCl_3$); IR (film): $\tilde{\nu}_{max} = 1965$, 1885 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.07$ (3H, d, $J = 6.8$ Hz, C(2)CH_3), 2.19 (3H, s, NCH_3), 2.83 (1H, qd, $J = 6.8$, 5.4 Hz, C(2)*H*), 3.65 (1H, d, $J = 3.3$ Hz, O*H*), 3.57 (1H, d, $J = 13.2$ Hz, NCH_A), 3.69 (1H, d, $J = 13.2$ Hz, NCH_B), 3.87 (3H, s, OCH_3), 4.49 (1H, br s, C(1)*H*), 5.18–5.60 (5H, m, *Ar*Cr(CO)$_3$), 6.88–7.29 ppm (4H, m, *Ar*); MS (CI): *m/z*: 421 ($[M]^+$, 100 %); elemental analysis: calcd (%) for $C_{21}H_{23}CrNO_5$: C 59.85, H 5.5, N 3.3; found: C 59.65, H 5.6, N 3.1.

[(1*R*,2*S*)-1-Phenyl-2-(*N*-methyl-*N*-benzylamino)propan-1-ol]tricarbonylchromium(0) (**56**): A mixture of [(ephedrine)Cr(CO)$_3$] (**51**) (792 mg, 2.63 mmol) and BnBr (0.35 mL, 2.94 mmol) in EtOH (10 mL) was react-

ed according to *general procedure 1* in the presence of $NaHCO_3$ (331 mg, 3.94 mmol) and a catalytic quantity of NaI at RT for 68 h to give **56** as a yellow oil (653 mg, 63 %, >99:1 d.r.); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.12 (3H, d, J = 6.7 Hz, C(2)CH_3), 2.24 (3H, s, NCH_3), 2.78 (1H, app quin, J = 6.7 Hz, C(2)H), 3.56 (1H, d, J = 13.5 Hz, NCH_A), 3.61 (1H, d, J = 13.5 Hz, NCH_B), 4.36 (1H, d, J = 6.7 Hz, C(1)H), 5.22–5.53 (5H, m, *Ar*Cr(CO)$_3$), 7.12–7.40 ppm (5H, m, *Ph*).

[(4*S*,5*R*)-2-Cyclohexyl-*N*(3)-4-dimethyl-5-phenyloxazolidine]tricarbonylchromium(0) (**57**): A mixture of (1*R*,2*S*)-ephedrine **29** (10.0 g, 60.5 mmol) and cyclohexanone (10.0 mL, 96.5 mmol) in C_6H_6 (100 mL) was heated at reflux in a Dean–Stark apparatus for 22 h. The reaction mixture was then concentrated in vacuo and the residue was distilled under reduced pressure (166 °C, 0.06 mm Hg) to give (4*S*,5*R*)-2-cyclohexyl-*N*(3),4-dimethyl-5-phenyloxazolidine as a colourless oil that solidified on standing (13.6 g, 91 %); m.p.: 72–73 °C (m.p.: 77–78 °C[28]); $[\alpha]_D^{20}$ = +9.53 (c = 1.2 in $CHCl_3$) {$[\alpha]_D^{20}$ = +8.0 (c = 1.0 in $CHCl_3$)[27]}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.63 (3H, d, J = 6.4 Hz, C(4)CH_3) 1.75–1.13 (10H, m, (CH_2)$_5$), 2.30 (3H, s, NCH_3), 3.25 (1H, dq, J = 8.0, 6.4 Hz, C(4)H), 5.07 (1H, d, J = 8.0 Hz, C(5)H), 7.34–7.22 ppm (5H, m, *Ph*). A deoxygenated solution of this material (3.00 g, 12.2 mmol) and $Cr(CO)_6$ (3.00 g, 13.6 mmol) in Bu_2O (50 mL) and THF (4 mL) was heated at reflux under a nitrogen atmosphere for 48 h.[26] The resultant mixture was allowed to cool to RT, filtered and concentrated in vacuo. Purification of the residue by means of recrystallization (CH_2Cl_2/hexane) gave **57** as a yellow solid (1.98 g, 42 %); m.p.: 107 °C (CH_2Cl_2/hexane); $[\alpha]_D^{20}$ = +156 (c = 0.3 in $CHCl_3$); IR (KBr disc): $\tilde{\nu}_{max}$ = 1973, 1890 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.83 (3H, d, J = 6.4 Hz, C(4)CH_3), 1.89–1.09 (10H, m, (CH_2)$_5$), 2.26 (3H, s, NCH_3), 3.20 (1H, dq, J = 8.0, 6.4 Hz, C(4)H), 4.57 (1H, d, J = 8.0 Hz, C(5)H), 5.57–5.13 ppm (5H, m, *Ar*); MS (CI): m/z: 381 ([M]$^+$, 100 %); elemental analysis: calcd (%) for $C_{19}H_{23}CrNO_4$: C 59.8, H 6.1, N 3.7; found: C 59.55, H 6.2, N 3.8.

[(1*R*,2*R*)-1-Phenyl-2-(*N*-methylamino)propan-1-ol]tricarbonylchromium(0) (**58**): A solution of **57** (302 mg, 0.79 mmol) and TsOH (103 mg, 0.54 mmol) in THF (10 mL) and water (5 mL) was treated with HCl (conc aq, 1 mL) and the resultant mixture was heated at reflux for 15 h. The reaction mixture was then allowed to cool to RT then basified with 2.0 M aq NaOH (20 mL), the solvent evaporated and the aqueous phase was extracted with Et_2O (20 mL). The combined organic extracts were dried, filtered, and concentrated in vacuo to give **58** (238 mg, quant).

{(1*R*,2*R*)-1-Phenyl-2-[*N*-methyl-*N*-(3′,4′-dimethoxybenzyl)amino]propan-1-ol}tricarbonylchromium(0) (**59**): A mixture of **58** [freshly prepared from **57**] (260 mg, 0.54 mmol) and freshly distilled 3,4-dimethoxybenzylbromide (128 mg, 0.55 mmol) in MeCN (40 mL) was reacted according to *general procedure 1* for 3 h to give a yellow oil. Purification of the residue by means of flash column chromatography (Al_2O_3 grade V, eluent Et_2O) gave **59** as a yellow solid (149 mg, 61 %, >99:1 d.r.). Purification of an aliquot by means of recrystallization (CH_2Cl_2/hexane) gave an analytically pure sample of **59**; m.p.: 124–128 °C (CH_2Cl_2/hexane); $[\alpha]_D^{20}$ = +83.7 (c = 0.1 in $CHCl_3$); IR (KBr disc): $\tilde{\nu}_{max}$ = 1975, 1885 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.00 (3H, d, J = 6.7 Hz, C(2)CH_3), 2.21 (3H, s, NCH_3), 2.58 (1H, dq, J = 9.0, 6.7 Hz, C(2)H), 3.44 (2H, d, J = 12.8 Hz, NCH_A), 3.67 (1H, d, J = 12.8 Hz, NCH_B), 3.89 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 3.97 (1H, d, J = 9.0 Hz, C(1)H), 5.14 (1H, br s, OH), 5.22–5.52 (5H, m, *Ar*Cr(CO)$_3$), 6.82–6.84 ppm (3H, m, *Ar*); MS (CI): m/z: 452 ([M+H]$^+$, 100 %); elemental analysis: calcd (%) for $C_{22}H_{25}CrNO_6$: C 58.5, H 5.6, N 3.1; found: C 58.5, H 5.8, N 3.0.

{(1*R*,2*R*)-1-Phenyl-2-[*N*-methyl-*N*-(4′-methoxybenzyl)amino]propan-1-ol}tricarbonylchromium(0) (**60**): A mixture of **58** [freshly prepared from **57**] (1.09 g, 2.85 mmol) and 4-methoxybenzaldehyde (700 mg, 5.14 mmol) in CH_2Cl_2 (20 mL) was reacted according to *general procedure 2* to furnish the corresponding oxazolidine as a yellow oil after purification by flash column chromatography (Al_2O_3 grade V, eluent Et_2O). This material was reduced with $NaBH_4$ (108 mg, 2.85 mmol) to give, after purification by means of recrystallization (CH_2Cl_2/hexane), **60** as a yellow solid (72 mg, 6 %, >99:1 d.r.); m.p.: 154–155 °C (CH_2Cl_2/hexane); $[\alpha]_D^{22}$ = +91.6 (c = 0.1 in $CHCl_3$); IR (KBr disc): $\tilde{\nu}_{max}$ = 3010, 1975, 1890 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.99 (3H, d, J = 6.6 Hz, C(2)CH_3), 2.19 (3H, s, NCH_3), 2.58 (1H, dq, J = 9.6, 6.6 Hz, C(2)H), 3.43 (1H, d, J = 12.8 Hz, NCH_A), 3.65 (1H, d, J = 12.8 Hz, NCH_B), 3.82 (3H, s, OCH_3), 3.90 (1H, d, J = 9.6 Hz, C(1)H), 5.14 (1H, br s, OH), 5.21–5.53 (5H, m, *Ar*Cr(CO)$_3$), 6.86–7.24 ppm (4H, m, *Ar*); MS (CI): m/z: 422 ([M+H]$^+$, 100 %); elemental analysis: calcd (%) for $C_{21}H_{23}CrNO_5$: C 59.85, H 5.5, N 3.3; found: C 60.0, H 5.8, N 3.2.

{(1*R*,2*R*)-1-Phenyl-2-[*N*-methyl-*N*-(3′-methoxybenzyl)amino]propan-1-ol}tricarbonylchromium(0) (**61**): A mixture of **58** [freshly prepared from **57**] (510 mg, 1.34 mmol) and 3-methoxybenzaldehyde (190 mg, 1.40 mmol) in CH_2Cl_2 (25 mL) was reacted according to *general procedure 2* to give the corresponding oxazolidine as a yellow oil (332 mg, 59 %). This material was reduced with $NaBH_3CN$ (84 mg, 1.34 mmol) to give **61** as a yellow solid (60 mg, 40 %, >99:1 d.r.). Purification of an aliquot by means of recrystallization (CH_2Cl_2/hexane) gave an analytically pure sample of **61** as a yellow crystalline solid; m.p.: 118–119 °C (CH_2Cl_2/hexane); $[\alpha]_D^{22}$ = +82.2 (c = 0.1 in $CHCl_3$); IR (KBr disc): $\tilde{\nu}_{max}$ = 3020, 1972, 1890 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.01 (3H, d, J = 6.6 Hz, C(2)CH_3), 2.22 (3H, s, NCH_3), 2.59 (1H, dq, J = 9.5, 6.6 Hz, C(2)H), 3.48 (1H, d, J = 13.0 Hz, NCH_A), 3.69 (1H, d, J = 13.0 Hz, NCH_B), 3.83 (3H, s, OCH_3), 3.92 (1H, d, J = 9.5 Hz, C(1)H), 5.08 (1H, br s, OH), 5.22–5.54 (5H, m, *Ar*Cr(CO)$_3$), 6.81–7.29 ppm (4H, m, *Ar*); MS (CI): m/z: 422 ([M+H]$^+$, 100 %); elemental analysis: calcd (%) for $C_{21}H_{23}CrNO_5$: C 59.85, H 5.5, N 3.3; found: C 59.6, H 5.6, N 3.3.

{(1*R*,2*R*)-1-Phenyl-2-[*N*-methyl-*N*-(2′-methoxybenzyl)amino]propan-1-ol}tricarbonylchromium(0) (**62**): A mixture of **58** [freshly prepared from **57**] (146 mg, 0.38 mmol) and 2-methoxybenzaldehyde (60 mg, 0.44 mmol) in CH_2Cl_2 (5 mL) was reacted according to *general procedure 2* to give the corresponding oxazolidine as a yellow oil. Without further purification, this material was reduced with $NaBH_4$ (15 mg, 0.38 mmol) to give, after purification by means of recrystallization (CH_2Cl_2/hexane), **62** as a yellow solid (21 mg, 13 %, >99:1 d.r.); m.p.: 124–125 °C (CH_2Cl_2/hexane); $[\alpha]_D^{22}$ = +68.2 (c = 0.05 in $CHCl_3$); IR (KBr disc): $\tilde{\nu}_{max}$ = 3020, 1970, 1895 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.02 (3H, d, J = 6.7 Hz, C(2)CH_3), 2.19 (3H, s, NCH_3), 2.58 (1H, dq, J = 9.5, 6.7 Hz, C(2)H), 3.44 (1H, d, J = 12.6 Hz, NCH_A), 3.75 (1H, d, J = 12.6 Hz, NCH_B), 3.87 (3H, s, OCH_3), 3.93 (1H, d, J = 9.5 Hz, C(1)H), 5.21–5.55 (5H, m, *Ar*Cr(CO)$_3$), 6.89–7.32 ppm (4H, m, *Ar*); MS (CI): m/z: 422 ([M+H]$^+$, 100 %); HRMS (CI$^+$) $C_{19}H_{23}CrNO_3^+$ ([M-C_2O_2]$^+$) requires 365.1078; found 365.1077.

[(1*R*,2*R*)-1-Phenyl-2-(*N*-methyl-*N*-benzylamino)propan-1-ol]tricarbonylchromium(0) (**63**): A mixture of **58** [freshly prepared **57**] (146 mg, 0.38 mmol) and BnBr (50 μL, 0.42 mmol) in EtOH (10 mL) was reacted according to *general procedure 1* in the presence of $NaHCO_3$ (50 mg, 0.60 mmol) and a catalytic quantity of NaI at RT for 71 h. Purification of the residue by means of recrystallization (CH_2Cl_2/hexane) gave **63** as a yellow solid (40 mg, 27 %, >99:1 d.r.); m.p.: 159 °C (CH_2Cl_2/hexane); $[\alpha]_D^{22}$ = +80.0 (c = 0.1 in $CHCl_3$); IR (film): $\tilde{\nu}_{max}$ = 3020, 1972, 1895 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.01 (3H, d, J = 6.7 Hz, C(2)CH_3), 2.21 (3H, s, NCH_3), 2.59 (1H, dq, J = 9.5, 6.7 Hz, C(2)H), 3.50 (1H, d, J = 12.9 Hz, NCH_A), 3.72 (1H, d, J = 12.9 Hz, NCH_B), 3.92 (1H, d, J = 9.5 Hz, C(1)H), 5.12 (1H, br s, OH), 5.22–5.53 (5H, m, *Ar*Cr(CO)$_3$), 7.29–7.38 ppm (5H, m, *Ph*); MS (CI): m/z: 392 ([M+H]$^+$, 100 %); elemental analysis: calcd (%) for $C_{20}H_{21}CrNO_4$: C 61.4, H 5.4; found: C 61.25, H 5.5.

(3*R*,4*S*)-*N*(2),3-Dimethyl-4-phenyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**39**): A solution of **59** (100 mg, 0.22 mmol) in CH_2Cl_2 (15 mL) was reacted according to *general procedure 4* at 0 °C for 2 h to give a yellow oil (>99:1 d.r. crude). Purification of the residue by means of flash column chromatography (Al_2O_3 grade V, eluent CH_2Cl_2) gave [(3*R*,4*S*)-*N*(2),3-dimethyl-4-phenyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline]tricarbonylchromium(0) as a yellow oil (99 mg, quant, >99:1 d.r.); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.01 (3H, d, J = 6.5 Hz, C(3)CH_3) 2.34 (3H, s, NCH_3), 3.12 (1H, q, J = 6.5 Hz, C(3)H), 3.44 (1H, app s, C(4)H), 3.44 (1H, d, J = 15.6 Hz, C(1)H_A), 3.70 (1H, d, J = 15.6 Hz, C(1)H_B), 3.88 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 4.87–5.71 (5H, m, *Ar*Cr(CO)$_3$), 6.56 (1H, s, C(5)H), 6.91 ppm (1H, s, C(8)H); MS (CI): m/z: 434 ([M+H]$^+$, 100 %). This material was decomplexed according to *general procedure 5* to give **39** as a colourless oil (64 mg, 95 % for 2 steps, >99:1 d.r.); $[\alpha]_D^{20}$ = +13.8 (c = 0.2 in $CHCl_3$); MS (CI): m/z: 297

([*M*]$^+$, 100%); HRMS (CI$^+$) $C_{19}H_{23}NO_2^+$ ([*M*]$^+$) requires 297.1723; found 297.1728.

(3*R*,4*S*)-*N*(2),3-Dimethyl-4-phenyl-6-methoxy-1,2,3,4-tetrahydroisoquinoline (**40**): A solution of **60** (44 mg, 0.10 mmol) in CH_2Cl_2 (10 mL) was cyclized according to *general procedure 4* at −20 °C for 24 h to give [(3*R*,4*S*)-*N*(2),3-dimethyl-4-phenyl-6-methoxy-1,2,3,4-tetrahydroisoquinoline]-tricarbonylchromium(0) as a yellow oil (40 mg, 95%, >99:1 d.r.). This material (40 mg, 0.10 mmol) was decomplexed according to *general procedure 5* to give, after purification by means of recrystallization (Et_2O/hexane), **40** as a white solid (25 mg, 94%, >99:1 d.r.); m.p.: 75 °C (Et_2O/hexane); $[\alpha]_D^{20}$ = +4.3 (*c* = 0.4 in $CHCl_3$).

(3*R*,4*S*)-*N*(2),3-Dimethyl-4-phenyl-8-methoxy-1,2,3,4-tetrahydroisoquinoline (**42**): A solution of **62** (44 mg, 0.10 mmol) in CH_2Cl_2 (10 mL) was cyclized according to *general procedure 4* at −20 °C for 24 h to give [(3*R*,4*S*)-*N*(2),3-dimethyl-4-phenyl-8-methoxy-1,2,3,4-tetrahydroisoquinoline]-tricarbonylchromium(0) as a yellow oil. This material (40 mg, 0.10 mmol) was decomplexed according to *general procedure 5* to give, after purification by means of recrystallization (Et_2O/hexane), **40** as a white solid (4 mg, 9%, >99:1 d.r.); m.p.: 114–116 °C (Et_2O/hexane); $[\alpha]_D^{20}$ = +63 (*c* = 1.0 in $CHCl_3$).

(*RS*)-*N*-Methyl-*N*-(2′-methoxybenzyl)-1-phenyl-propan-2-amine (**64**): (*RS*)-*N*-(Methyl)amphetamine hydrochloride (1.77 g, 9.54 mmol) was dissolved in excess 2.0 M aq NaOH and the resultant solution was extracted with CH_2Cl_2 (3×50 mL). The combined organic extracts were dried, filtered and concentrated in vacuo to give (*RS*)-*N*-(methyl)amphetamine as a colourless oil (1.41 g, 99%). A mixture of this material and freshly distilled 2-methoxybenzylbromide (1.92 g, 9.54 mmol) in MeCN (50 mL) was reacted according to *general procedure 1* to give (*RS*)-**64** as a pale yellow oil (2.45 g, 96%). Purification of an aliquot by means of reduced pressure bulb-to-bulb distillation (b.p.: ≈180 °C, 0.06 mm Hg) gave an analytically pure sample of (*RS*)-**64**; IR (film): $\tilde{\nu}_{max}$ = 3010, 1492, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.04 (3H, d, *J* = 6.5 Hz, C(3)H_3), 2.32 (3H, s, NCH_3), 2.50–3.12 (3H, m, C(1)H_2, C(2)*H*), 3.64 (1H, d, *J* = 14.1 Hz, NCH_A), 3.67 (1H, d, *J* = 14.1 Hz, NCH_B), 3.85 (3H, s, OCH_3), 6.86–7.34 ppm (9H, m, *Ph*, *Ar*); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0, 37.5, 39.4, 50.9, 55.3, 60.6, 110.3, 120.4, 125.8, 127.8, 128.2, 128.3, 129.4, 130.3, 141.2, 157.9 ppm; MS (CI): *m*/*z*: 270 ([*M*+H]$^+$, 100%); elemental analysis: calcd (%) for $C_{18}H_{23}NO$: C 80.3, H 8.6, N 5.2; found: C 80.2, H 8.8, N 5.1.

(3*R*,4*S*)-*N*(2),3-Dimethyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline (**43**): A solution of **63** (29 mg, 0.07 mmol) in CH_2Cl_2 (6 mL) was reacted according to *general procedure 4* at −20 °C for 24.5 h, followed by decomplexation according to *general procedure 5* to give **43** as a yellow oil (18 mg, 89% from **63** in 2 steps). Purification of the residue by means of flash column chromatography (eluent Et_2O) gave **43** as a colourless oil (6 mg, 28%, >99:1 d.r.); $[\alpha]_D^{20}$ = +47 (*c* = 0.1 in $CHCl_3$).

(3*S*,4*S*)-*N*(2),3-Dimethyl-4-phenyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**44**): A solution of **52** (61 mg, 0.14 mmol) in CH_2Cl_2 (5 mL) was cyclized according to *general procedure 4* at −20 °C for 43 h to give (crude >99:1 d.r.), after purification by flash column chromatography (Al_2O_3 grade V, eluent Et_2O), [(3*S*,4*S*)-*N*(2),3-dimethyl-4-phenyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline]tricarbonyl-chromium(0) as a yellow solid (48 mg, 82%, >99:1 d.r.). Further purification of an aliquot by means of recrystallization (CH_2Cl_2/hexane) gave an analytically pure sample (>99:1 d.r.); $[\alpha]_D^{20}$ = +173 (*c* = 0.2 in $CHCl_3$); IR (film): $\tilde{\nu}_{max}$ = 1965, 1885 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.06 (3H, d, *J* = 6.8 Hz, C(3)CH_3), 2.28 (3H, s, NCH_3), 2.76 (1H, qd, *J* = 6.8, 3.2 Hz, C(3)*H*), 3.46 (1H, d, *J* = 3.2 Hz, C(4)*H*), 3.87 (3H, s, OCH_3), 3.93 (3H, s, OCH_3), 3.40 (1H, d, *J* = 15.2 Hz, C(1)H_A), 3.94 (1H, d, *J* = 15.2 Hz, C(1)H_B), 5.06–5.63 (5H, m, *Ar*Cr(CO)$_3$), 6.52 ppm (2H, s, C(5)*H*), 7.03 (2H, s, C(8)*H*); MS (CI): *m*/*z*: 434 ([*M*+H]$^+$, 100%); elemental analysis: calcd (%) for $C_{22}H_{23}CrNO_5$: C 61.0, H 5.35, N 3.2; found: C 61.0, H 5.6, N 3.5. This material (48 mg, 0.11 mmol) was decomplexed according to *general procedure 5* to give **44** as a white powder (30 mg, 92%, >99:1 d.r.); $[\alpha]_D^{20}$ = +108 (*c* = 0.1 in $CHCl_3$); m.p.: 93–94 °C (CH_2Cl_2/hexane); IR (KBr disc): $\tilde{\nu}_{max}$ = 3010, 1520, 705 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.83 (3H, d, *J* = 6.6 Hz, C(3)CH_3), 2.38 (3H, s, NCH_3), 2.85 (1H, dq, *J* = 6.6, 4.4 Hz, C(3)*H*), 3.68 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 3.48 (1H, d, *J* = 15.1 Hz, C(1)H_A), 3.91 (1H, d, *J* = 15.1 Hz, C(1)H_B), 4.02 (1H, d, *J* = 4.4 Hz, C(4)*H*), 6.42 (1H, s, C(5)*H*), 6.57 (2H, s, C(8)*H*), 7.17–7.29 ppm (5H, m, *Ph*); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.4, 42.3, 50.8, 55.9, 56.6, 59.2, 108.6, 112.4, 126.1, 126.9, 127.6, 128.2, 129.5, 130.4, 142.8, 147.5, 147.6 ppm; MS (CI): *m*/*z*: 297 ([*M*]$^+$, 100%); HRMS (CI$^+$) $C_{19}H_{23}NO_2^+$ ([*M*]$^+$) requires 297.1723; found 297.1728.

(3*S*,4*R*)-2,3-Dimethyl-4-phenyl-6-methoxy-1,2,3,4-tetrahydroisoquinoline (**40**): A solution of **53** (47 mg, 0.11 mmol) in CH_2Cl_2 (15 mL) was cyclized according to *general procedure 4* at −20 °C for 46 h to give [(3*S*,4*R*)-2,3-dimethyl-4-phenyl-6-methoxy-1,2,3,4-tetrahydroisoquinoline]-tricarbonylchromium(0) as a yellow solid (42 mg, 93%, >99:1 d.r.); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.00 (3H, d, *J* = 6.7 Hz, C(3)CH_3), 2.37 (3H, s, NCH_3), 3.17 (1H, app q, *J* = 6.7 Hz, C(3)*H*), 3.45 (1H, app s, C(4)*H*), 3.46 (1H, d, *J* = 15.5 Hz, C(1)H_A), 3.73 (1H, d, *J* = 15.5 Hz, C(1)H_B), 3.83 (3H, s, OCH_3), 4.94–5.83 (5H, m, *Ar*Cr(CO)$_3$), 6.81 (1H, dd, *J* = 8.5, 2.6 Hz, C(7)*H*), 6.92 (1H, d, *J* = 2.5 Hz, C(5)*H*), 7.00 ppm (1H, d, *J* = 8.5 Hz, C(8)*H*); MS (CI): *m*/*z*: 403 ([*M*]$^+$, 100%); HRMS (CI$^+$) $C_{21}H_{21}CrNO_4^+$ ([*M*]$^+$) requires 403.0876; found 403.0880. This material (42 mg, 0.10 mmol) was decomplexed according to *general procedure 5* to furnish, after purification by means of recrystallization (Et_2O/hexane), **40** as a white solid (23 mg, 84%, >99:1 d.r.); m.p.: 75 °C (Et_2O/hexane); $[\alpha]_D^{20}$ = −3.9 (*c* = 0.5 in $CHCl_3$).

(3*S*,4*R*)-*N*(2),3-Dimethyl-4-phenyl-8-methoxy-1,2,3,4-tetrahydroisoquinoline (**42**) and (*S*)-*N*-methyl-*N*-(2′-methoxybenzyl)-1-phenyl-propan-2-amine (**64**): A solution of **55** (66 mg, 0.16 mmol) in CH_2Cl_2 (20 mL) was reacted according to *general procedure 4* at −20 °C for 36 h, followed by decomplexation according to *general procedure 5* gave a 63:37 mixture of **42** and **64** as a yellow oil (38 mg, 90% from **55** in 2 steps). Purification of the residue by means of recrystallization (Et_2O/hexane) gave an analytically pure sample of **42** (21 mg, 50%, >99:1 d.r.); m.p.: 115 °C; $[\alpha]_D^{20}$ = −66.4 (*c* = 0.1 in $CHCl_3$). The mother liquor was concentrated in vacuo and the residue was purified by flash column chromatography (eluent Et_2O) to give **64** as a colourless oil (17 mg, 31%).

(*S*)-*N*-methyl-*N*-benzyl-1-phenyl-propan-2-amine (**65**): A solution of **56** (319 mg, 0.82 mmol) in CH_2Cl_2 (20 mL) was treated according to *general procedure 4* at −20 °C for 48 h, followed by decomplexation according to *general procedure 5* to give **65** as a colourless oil (78 mg, 40% from **56** in 2 steps); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.04 (3H, d, *J* = 6.5 Hz, C(3)H_3), 2.28 (3H, s, NCH_3), 2.39–3.10 (3H, m, C(1)H_2, C(2)*H*), 3.62 (2H, br s, NCH_2), 7.11–7.44 ppm (10H, m, *Ph*); MS (CI): *m*/*z*: 240 ([*M*+H]$^+$, 100%).

(3*R*,4*S*)-*N*(2),3-Dimethyl-4-phenyl-7-methoxy-1,2,3,4-tetrahydroisoquinoline (**41**) and (3*R*,4*S*)-*N*(2),3-dimethyl-4-phenyl-5-methoxy-1,2,3,4-tetrahydroisoquinoline] (**68**): A solution of **61** (51 mg, 0.12 mmol) in CH_2Cl_2 (5 mL) was reacted according to *general procedure 4* at −20 °C for 42 h to give an inseparable 91:9 mixture of **66** and **67** as a yellow oil (40 mg, 74%). This material (36 mg, 0.09 mmol) was decomplexed according to *general procedure 5* to give an inseparable 91:9 mixture of **41** and **68** (21 mg, 88%). Data for **68**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.00 (3H, d, *J* = 6.6 Hz, C(3)CH_3), 2.38 (3H, s, NCH_3), 3.21 (1H, q, *J* = 6.5 Hz, C(3)*H*), 3.42 (1H, s, C(4)*H*), 3.50 (1H, d, *J* = 16.2 Hz, C(1)H_A), 3.74 (1H, d, *J* = 16.2 Hz, C(1)H_B), 3.80 (3H, s, OCH_3), 4.95–5.86 (5H, m, *Ar*Cr(CO)$_3$), 6.61 (1H, d, *J* = 2.7 Hz, C(8)*H*), 6.82 (1H, dd, *J* = 8.5, 2.7 Hz, C(6)*H*), 7.27 ppm (1H, d, *J* = 8.5 Hz, C(5)*H*); MS (CI): *m*/*z*: 404 ([*M*+H]$^+$, 100%).

(3*S*,4*S*)-*N*(2),3-Dimethyl-4-phenyl-7-methoxy-1,2,3,4-tetrahydroisoquinoline (**46**) and (3*S*,4*S*)-*N*(2),3-dimethyl-4-phenyl-5-methoxy-1,2,3,4-tetrahydroisoquinoline (**71**): A solution of **54** (427 mg, 1.01 mmol) in CH_2Cl_2 (25 mL) was reacted according to *general procedure 4* at −20 °C for 142 h to give an 86:14 mixture of regioisomeric *cis*-tetrahydroisoquinolines as a yellow oil. Purification of the residue by means of flash column chromatography (Al_2O_3 grade V, petroleum ether/Et_2O, 8:1) gave [(3*S*,4*S*)-*N*(2),3-dimethyl-4-phenyl-5-methoxy-1,2,3,4-tetrahydroisoquinoline]tricarbonylchromium(0) as yellow oil (32 mg, 8%, >99:1 d.r.); $[\alpha]_D^{20}$ = +9.4 (*c* = 0.1 in $CHCl_3$); IR (film): $\tilde{\nu}_{max}$ = 1966, 1890 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.01 (3H, d, *J* = 6.7 Hz, C(3)CH_3), 2.25 (3H, s, NCH_3), 2.61 (1H, qd, *J* = 6.7, 2.6 Hz, C(3)*H*), 3.67 (1H, d, *J* = 2.6 Hz, C(4)*H*), 3.89 (3H, s, OCH_3), 3.43 (1H, d, *J* = 16.0 Hz, C(1)H_A), 4.11 (1H, d, *J* =

16.0 Hz, C(1)H_B), 4.89–5.73 (5H, m, *Ar*Cr(CO)$_3$), 6.70–6.77 (2H, m, C(6)*H*, C(8)*H*), 7.21 ppm (1H, app t, $J=7.9$ Hz, C(7)*H*); MS (CI): *m/z*: 403 ([*M*]$^+$, 100%); elemental analysis: calcd (%) for $C_{21}H_{21}CrNO_4$: C 62.5, H 5.25, N 3.5; found: C 62.6, H 5.3, N 3.2. Further elution gave [(3*S*,4*S*)-*N*(2),3-dimethyl-4-phenyl-7-methoxy-1,2,3,4-tetrahydroisoquinoline]tricarbonylchromium(0) as a yellow oil (205 mg, 50%, >99:1 d.r.); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.07$ (3H, d, $J=6.8$ Hz, C(3)CH_3), 2.28 (3H, s, NCH_3), 2.76 (1H, dq, $J=6.8$, 3.3 Hz, C(3)*H*), 3.50 (1H, d, $J=3.3$ Hz, C(4)*H*), 3.80 (3H, s, OCH_3), 3.44 (1H, d, $J=15.7$ Hz, C(1)H_A), 3.98 (1H, d, $J=15.7$ Hz, C(1)H_B), 5.02–5.63 (5H, m, *Ar*Cr(CO)$_3$), 6.58 (1H, d, $J=2.6$ Hz, C(8)*H*), 6.84 (1H, dd, $J=8.6$, 2.6 Hz, C(6)*H*), 7.42 ppm (1H, d, $J=8.6$ Hz, C(5)*H*); MS (CI): *m/z*: 403 ([*M*]$^+$, 100%); HRMS (CI$^+$) $C_{21}H_{21}CrNO_4^+$ ([*M*]$^+$) requires 403.0876; found 403.0880. [(3*S*,4*S*)-*N*(2),3-dimethyl-4-phenyl-7-methoxy-1,2,3,4-tetrahydroisoquinoline]tricarbonylchromium(0) (205 mg, 0.51 mmol) was decomplexed according to *general procedure 5* to give, after purification by means of recrystallization (Et_2O/hexane), **46** as a white powder (112 mg, 82%, >99:1 d.r.); m.p.: 122 °C (Et_2O/hexane); $[\alpha]_D^{20}=+144$ ($c=0.1$ in $CHCl_3$). [(3*S*,4*S*)-*N*(2),3-Dimethyl-4-phenyl-7-methoxy-1,2,3,4-tetrahydroisoquinoline]tricarbonylchromium(0) (30 mg, 0.08 mmol) was decomplexed according to *general procedure 5* to give **71** as a white powder (20 mg, quant., >99:1 d.r.). Purification of an aliquot by means of recrystallization (Et_2O/hexane) afforded an analytically pure sample of **71**; m.p.: 151–152 °C (Et_2O/hexane); $[\alpha]_D^{20}=+232$ ($c=0.1$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=0.88$ (3H, d, $J=6.6$ Hz, C(3)CH_3), 2.29 (3H, s, NCH_3), 2.62 (1H, dq, $J=6.6$, 3.8 Hz, C(3)*H*), 3.55 (3H, s, OCH_3), 3.98 (1H, d, $J=3.8$ Hz, C(4)*H*), 3.45 (1H, d, $J=15.5$ Hz, C(1)H_A), 4.09 (1H, d, $J=15.5$ Hz, C(1)H_B), 6.57–7.28 ppm (8H, m, *Ph*, *Ar*); MS (CI): *m/z*: 267 ([*M*]$^+$, 100%); elemental analysis: calcd (%) for $C_{18}H_{21}NO$: C 80.9, H 7.9, N 5.2; found: C 80.8, H 8.1, N 5.0.

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[19] ^{1}H NMR ^3J coupling constants are diagnostic in these systems, see: S. J. Coote, S. G. Davies, K. H. Sutton, *J. Chem. Soc. Perkin Trans. 1* **1988**, 1481; W. H. Pirkle, C. W. Boeder, *J. Org. Chem.* **1977**, *42*, 3697. Given that enantiopure samples of (1*R*,2*S*)-ephedrine **19** and (1*R*,2*R*)-pseudoephedrine **29** were used (>98% *ee*), and the configuration at the C(2)-stereogenic centers is not affected by the cyclization reaction, all the tetrahydroisoquinolines isolated in this manuscript are also enantiopure.
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