# Stereodivergent Addition of Allylmetal Reagents to Imines Derived from (*R*)-2,3-Di-*O*-benzylglyceraldehyde by Appropriate Selection of Metal and Double Stereodifferentiation

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*Dedicated to Prof. Domingo Gonzalez, University of Zaragoza, on the occasion of his retirement*

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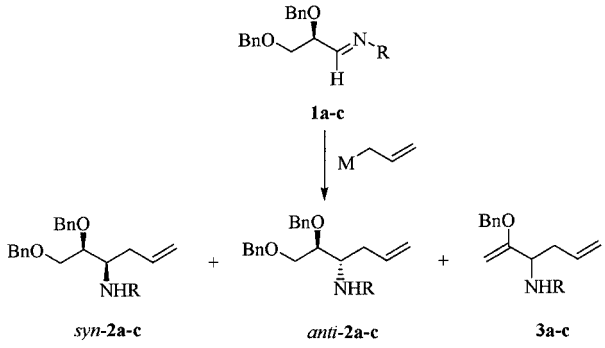
The addition of allylmetal reagents to *N*-benzylimines derived from (*R*)-2,3-di-*O*-benzylglyceraldehyde has been achieved with high yields and diastereoselectivities. Homoallylamine **2a** of *syn* configuration is obtained preferentially with allylmagnesium bromide, whereas homoallylamine **2a** of *anti* configuration is obtained as the major reaction product with allyl-9-borabicyclo[3.3.1]nonane. Appropriate combinations of the allylmetal reagent and imines derived from (*R*)-2,3-di-*O*-benzylglyceraldehyde and (*S*)- or (*R*)-1-phenylethylamine afforded *syn* or *anti* homoallylamines with total stereocontrol through double stereodifferentiation processes.



## Introduction

The reaction between allylic organometallic compounds and imines provides a potentially valuable route to homoallylic amines, which are important building blocks[1] due to the various possible transformations of the C=C double bond of the allylic moiety. Allylmetal reagents are generally more reactive than nonstabilised organometallic compounds, and a variety of metals has been successfully employed in C=N addition reactions.[2] Organometallic addition to imines possessing an α-chiral centre has recently started to attract the attention of organic chemists,[3] and, in particular, the stereoselectivity achieved in the addition of allylmetal reagents has proved to be highly dependent on the nature of the metal and the structure of the imine.[4]

We have recently reported on the addition of methyl-, benzyl-, phenyl-, and vinylmagnesium halides to *N*-benzylimines derived from conveniently protected (*R*)-glyceraldehyde.[5] 3-Amino-1,2-diol derivatives are versatile synthetic intermediates,[6] and we have used them in the asymmetric synthesis of several classes of amino acids[5] and related biologically active molecules such as the anti-HIV agent Palinavir.[7] In this paper we report the results obtained in diastereoselective allylation of *N*-benzylimines derived from (*R*)-2,3-di-*O*-benzylglyceraldehyde. The reaction affords homoallylamines of either *syn* or *anti* configuration, depending on the allylmetal reagent, as shown in Scheme 1.




**a:** R = $CH_2C_6H_5$; **b:** R = (*S*)-$CH(CH_3)C_6H_5$; **c:** R = (*R*)-$CH(CH_3)C_6H_5$

Scheme 1. Stereoselective addition of allylmetal reagents to imines **1a-c**

## Results and Discussion

Chiral imine **1a** was readily obtainable from (*R*)-2,3-di-*O*-benzylglyceraldehyde and benzylamine,[5a] and the allylation of this compound in diethyl ether at low temperature with excesses of different allylmetal reagents was investigated.

Treatment of imine **1a** with allylmagnesium chloride, allylcopper and allylstannane reagents afforded the desired

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homoallylamine **2a** in moderate chemical yield and with low or negligible diastereoselectivity (entries 1, 4 and 5). The use of allylmagnesium bromide (entries 2 and 3) gave slight improvements in both yield and diastereoselectivity, with the *syn*-3-amino-1,2-diol derivative **2a** being obtained preferentially under chelation control.[8] The best results (yield 65%, *syn*/*anti* = 75:25) were obtained when imine **1a** was added to allylmagnesium bromide (entry 3). On the other hand, the use of allylcerium (entry 6) and allyl-9-borabicyclononane (allyl-BBN, entry 7), switched the stereochemical course of the reaction and the non-chelation product **2a** with the *anti* relative configuration was obtained predominantly, with allyl-BBN giving the best results (yield 70%, *syn*/*anti* = 18:82).

Barbier-type allylation[9] with allyl bromide and magnesium or zinc powder combinations (entries 8 and 9) did not proceed below ambient temperature. However, the allylation products were obtained at room temperature in low yields and with diastereoselectivities that depended on the metal. With magnesium and allyl bromide, for example, homoallylamine **2a** of *syn* configuration was obtained preferentially, whereas homoallylamine **2a** of *anti* configuration was the major compound on using the allyl bromide-zinc powder combination. All results are summarised in Table 1.

In order to achieve complete diastereoselectivity in the nucleophilic addition of allylmetal reagents to imines derived from (*R*)-glyceraldehyde, a double stereodifferentiation strategy was investigated. In this approach, imines **1b** and **1c** were prepared from (*R*)-2,3-di-*O*-benzylglyceraldehyde and (*S*)- or (*R*)-1-phenylethylamine, respectively,[5a] and their reactivity with allylmagnesium bromide and allyl-BBN was assessed (entries 10−13).

The stereochemical course of these reactions was mainly controlled by the α-alkoxy chiral centre in the carbonyl moiety (1,2-asymmetric induction) and the metal (magnesium or boron), while the chiral centre in the amine moiety (1,3-asymmetric induction) modulated the diastereoselectivity of the process either upwards (matched pair) or downwards (mismatched pair).

Therefore, 1,2-asymmetric induction does not completely override the influence of the nitrogen auxiliary (1,3-asymmetric induction), as reported by Yamamoto et al.[4b] for similar imines derived from (*S*)-lactaldehyde. Treatment of **1b** ($S^{\#}$, *S* imine) with allylmagnesium bromide produced *syn*-3-amino-1,2-diol derivative **2b** with complete stereocontrol (entry 10), whereas treatment of **1c** ($S^{\#}$, *R* imine) with allyl-BBN exclusively produced the *anti* 3-amino-1,2-diol derivative **2c** (entry 13). Therefore, the $S^{\#}$, *S* combination was a matched pair for the chelation product, while the $S^{\#}$, *R* combination was a matched pair for the non-chelation product. ($^{\#}$ Nomenclature of the α-alkoxy chiral center in the carbonyl moiety changes from *R* for the aldehyde to *S* for the imine).

Many of the reaction conditions tested (entries 1−3, 5, 6, 8−11) gave the corresponding amines **2a−c** together with variable, but small, amounts of by-products that were isolated (yield 6−12%) and fully characterised as olefins **3a−c** by their analytical and spectroscopic data (Scheme 1). The formation of these by-products is the result of an elimination/nucleophilic addition process that, in such a strongly basic medium, competes with the single nucleophilic addition.

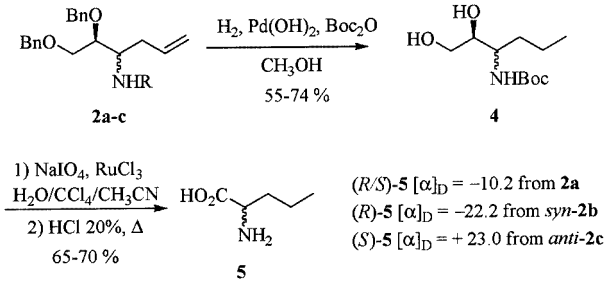
The assignment of the absolute configurations at the newly formed stereogenic carbons in the allylation reactions was performed by conversion of the resulting compounds − **2a** (*syn*/*anti* 75:25), *syn*-**2b** and *anti*-**2c** − into known norvaline according to reported procedures for similar transformations,[5c,11] as shown in Scheme 2.

Conversion of homoallylamines into the corresponding *syn* or *anti* *N*-Boc-aminodiol **4** was conveniently performed

Table 1. Stereoselective addition of allylmetal reagents to imines **1a−c**

| Entry | Imine | Allyl-M | Product | Yield (%)[a] | *syn*/*anti*[b] |
|---|---|---|---|---|---|
| 1 | **1a** | Allyl-MgCl[c] | **2a** | 60 | 47:53 |
| 2 | **1a** | Allyl-MgBr[c] | **2a** | 65 | 60:40 |
| 3 | **1a** | Allyl-MgBr[d] | **2a** | 65 | 75:25 |
| 4 | **1a** | $(Allyl)_2Cu(CN)Li_2$, $BF_3{\cdot}OEt_2$[e] | **2a** | 50 | 43:57 |
| 5 | **1a** | Allyl-$SnBu_3$, $BF_3{\cdot}OEt_2$ [f] | **2a** | 48 | 58:42 |
| 6 | **1a** | Allyl-$CeCl_2$[d] [g] | **2a** | 65 | 33:67 |
| 7 | **1a** | Allyl-BBN[h] | **2a** | 70 | 18:82 |
| 8 | **1a** | Allyl-Br, Mg[i] | **2a** | 31 | 83:17 |
| 9 | **1a** | Allyl-Br, Zn[i] | **2a** | 42 | 26:74 |
| 10 | **1b** | Allyl-MgBr[d] | **2b** | 65 | 98:2 |
| 11 | **1c** | Allyl-MgBr[d] | **2c** | 65 | 65:35 |
| 12 | **1b** | Allyl-BBN[h] | **2b** | 25 | 50:50 |
| 13 | **1c** | Allyl-BBN[h] | **2c** | 70 | 2:98 |

[a] Isolated yield for **2** after chromatography on silica gel. [b] Ratio determined by $^1H$ NMR analysis of the crude reaction mixture. [c] The reaction was carried out in dry diethyl ether by addition of the allylmetal reagent (2.1 equiv.) to imine **1a** at −30 °C under Ar. The reaction mixture was then stirred at room temperature for 12 h. [d] The reaction was carried out in dry diethyl ether by addition of the corresponding imine **1a−c** to allylmagnesium bromide (2.1 equiv.) at −30 °C under Ar. The reaction mixture was then stirred at room temperature for 12 h. [e] The reaction was carried out according to ref. 10. [f] $BF_3{\cdot}OEt_2$ (1 equiv.) was added to the imine **1a** before addition of the allylmetal reagent at −78 °C.[g] Prepared in situ from Allyl-MgBr and $CeCl_3$. [h] The reaction was carried out at −78 °C in dry diethyl ether by addition of the imine **1a−c** to allyl-BBN. [i] Barbier procedure: imine **1a** was added to a mixture of the allyl bromide (1.1 equiv.) and the metal (1.2 equiv.) in dry THF at room temperature. The reaction mixture was stirred for 2 days.




Scheme 2. Determination of the absolute configuration of the addition adducts by conversion into norvaline.

by hydrogenolysis in methanol at atmospheric pressure, with $Pd(OH)_2$ on charcoal as a catalyst and in the presence of $(Boc)_2O$. This method proved suitable except when *syn*-**2b** was the starting material. In this case an increase in the hydrogen pressure to 50 atm was required to achieve hydrogenation. Subsequent treatment of compound **4** with an excess of sodium periodate in the presence of ruthenium trichloride,[12] followed by acid hydrolysis, gave norvaline **5** of *R* or *S* configuration depending on the nature of the starting compound. The obtained compounds were compared with a sample of enantiomerically pure (*S*)-norvaline {ref.[13] $[\alpha]_D^{28} = +24.0$ ($c$ = 10, 5 N HCl)} in order to perform unambiguous assignment of configuration.

The stereochemical integrity of (*R*)- and (*S*)-norvaline obtained from *syn*-**2b** or *anti*-**2c**, respectively, was confirmed by preparation of the Mosher amides[14] of the corresponding methyl esters (MeOH, $SOCl_2$). Analysis of $^1H$ and $^{19}F$ NMR spectra showed that, in contrast with the splitting observed for *rac*-**5**, only one set of signals, corresponding to a single enantiomer, was observed in each case. Thus, the enantiomeric purity for the compounds analysed was >98:2, demonstrating that racemisation had not occurred to any appreciable extent during the nucleophilic allylation of imines **2**.

To explain the excellent stereoselectivity observed in the allylation reaction between imines **1b** and allylmagnesium bromide, we postulate that *N*-benzylimine **1b** chelates the magnesium atom of the allylmagnesium reagent to form a five-membered ring (α-chelate) in which the *N*-1-phenylethyl group is situated in a conformation in which 1,3-allylic strain[15] is minimised. At the same time, a six-membered, chair-like transition state containing the imine and allylic moieties is formed (Figure 1). In the chelated complex **A**, the benzyloxymethyl group in the (*R*)-glyceraldehyde moiety and the phenyl group in the chiral amine would effectively block the *si*-face of the *E*-imine[16] and the allylmagnesium reagent would approach the *re*-face. As a result, only the *syn* diastereomer would be formed. This model is in accordance with that proposed by Jäger et al. to explain the stereochemical course of the addition of Grignard reagents to related imines.[17] Other conformations obtained by rotation around the N−C bond[18] can also be successfully invoked to explain the 1,3-asymmetric induction: an example is a Felkin−Anh-type model[19] in which the stereodifferentiation is a consequence of the bulkiness of the phenyl group occupying the orthogonal position. The stereochemical course of the allylation reaction between allyl-BBN and imine **1c** can be explained by considering the transition state **B** in Figure 1. Allylboron reagents are non-chelating species, so the boron atom exclusively coordinates to the imine nitrogen. In this intermediate, the α-C−OBn bond in the glyceraldehyde moiety is orientated perpendicular to the imine group, in accordance with the Felkin−Anh postulate, and the *N*-1-phenylethyl group is positioned in a conformation in which the 1,3-allylic strain is minimised. The attack of the allyl reagent at the less hindered *si*-face of the imine, through a six-membered ring transition state, accounts for the exclusive formation of the *anti* diastereomer.

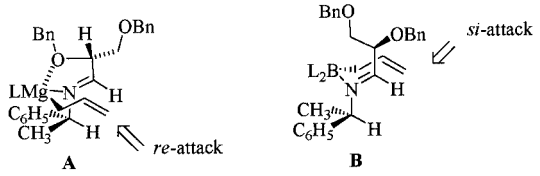



Figure 1. Chelation-controlled and non-chelation-controlled addition of allylic organometallic compounds to imines **2b** and **2c**

## Conclusion

In summary, we have shown that *syn* and *anti* diastereoisomers of homoallylamine **2a** can be obtained preferentially from the same starting compound, *N*-benzylimine **1a**, by choosing the appropriate allylmetal reagent. A double stereodifferentiation process that involves treatment of imines derived from (*S*)- or (*R*)-1-phenylethylamine, **1b** or **1c**, with allylmagnesium bromide or allyl-BBN, provides enantiopure *syn* or *anti* 3-amino-1,2-diol derivatives **2b** and **2c**, respectively, with total diastereoselectivity. These highly functionalised compounds, each possessing a homoallylamine moiety, are valuable key building blocks for the preparation of a wide variety of biologically active compounds. In particular, our interest is focussed on asymmetric synthesis of amino acids, and research into this area is underway and will be reported in due course.

## Experimental Section

**General Remarks:** Diethyl ether was distilled from sodium benzophenone ketyl. Whenever possible the reactions were monitored by TLC. TLC was performed on precoated silica gel polyester plates and products were viewed by use of UV light (254 nm) and anisaldehyde/sulfuric acid/ethanol (2:1:100). Column chromatography was performed on silica gel (Kieselgel 60). Chemicals for reactions were used as purchased from Aldrich. Compounds **1a−c** were prepared from (*S*)-2,3-di-*O*-benzylglyceraldehyde according to our previously described procedure for **1a**.[5a] Melting points were determined in open capillaries with a Büchi capillary melting point apparatus and are not corrected. NMR spectra were recorded on Varian Unity-300 or Bruker ARX 300 instruments operating at 300 MHz for $^1H$ NMR, 75 MHz for $^{13}C$ NMR and 282 MHz for $^{19}F$ NMR. Chemical shifts (δ) are reported in parts per million and

the coupling constants (*J*) in Hertz. The following abbreviations are used: s, singlet; d, doublet; t, triplet; m, multiplet; br. s, broad singlet; bd, broad doublet; dd, doublet of doublets. The $^1$H NMR and $^{13}$C NMR spectra of *N*-Boc-protected compounds were not conclusive at room temperature, due to the presence of a dynamic equilibrium between rotamers caused by the restricted rotation of the nitrogen-carbon bond of the urethane group. In order to overcome this problem, NMR spectra of these compounds were acquired at 60 °C. Optical rotations were measured on a Perkin−Elmer 241-C polarimeter at 20 °C with concentrations given in g/100 mL. High-resolution Mass Spectra (HRMS) were recorded on a VG-autospec instrument. Elemental analyses were performed with a Perkin−Elmer 200 C,H,N,S elemental analyser.

**{(*R*)-1-[(*S*)-1,2-Bis(benzyloxy)ethyl]but-3-enyl}[(*S*)-1-phenylethyl]-amine (*syn*-2b):** A solution of the chiral imine **1b** (373 mg, 1 mmol) in dry diethyl ether (5 mL) was added dropwise at −30 °C under argon to a stirred solution of allylmagnesium bromide in diethyl ether (1 M, 2.1 mL, 2.1 mmol), further diluted with dry diethyl ether (10 mL). After stirring for 12 h at room temperature, the reaction mixture was poured into saturated aqueous $NH_4Cl$ (10 mL), the organic phase was separated, and the water layer was extracted with diethyl ether (2 × 20 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated to give an oily residue. Purification of the residue by flash chromatography with diethyl ether/hexane (1:4) afforded 270 mg (65%) of compound *syn*-**2b** as a colourless oil. $[\alpha]_D^{20} = -29.5$ (*c* = 1 in $CHCl_3$). $^1$H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 1.28 (d, *J* = 6.6 Hz, 3 H), 1.51 (br. s, 1 H), 2.27−2.32 (m, 2 H), 2.49−2.55 (m, 1 H), 3.52−3.58 (m, 1 H), 3.58 (dd, *J* = 9.6, *J* = 4.5 Hz, 1 H), 3.70 (dd, *J* = 9.6, *J* = 6 Hz, 1 H), 3.88 (q, *J* = 6.6 Hz, 1 H), 4.40 (s, 2 H), 4.49 (d, *J* = 11.7 Hz, 1 H), 4.73 (d, *J* = 11.7 Hz, 1 H), 4.92−4.99 (m, 2 H), 5.61−5.73 (m, 1 H), 7.22−7.35 (m, 15 H) ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 25.2, 35.0, 55.2, 55.7, 71.9, 73.0, 73.3, 79.3, 116.7, 126.8, 127.0, 127.4, 127.6, 127.8, 128.2, 136.1, 138.4, 138.9, 145.9 ppm. HRMS (FAB) for $C_{28}H_{34}NO_2$ [M + H$^+$]: calcd. 416.2589; found 416.2593.

**{(*S*)-1-[(*S*)-1,2-Bis(benzyloxy)ethyl]but-3-enyl}[(*R*)-1-phenylethyl]-amine (*anti*-2c):** A solution of allyl-9-BBN (2.1 mmol) was prepared from a solution of 9-BBN in THF (0.5 M, 4.2 mL, 2.1 mmol), methanol (67.2 mg, 2.1 mmol) and a solution of allyl bromide in diethyl ether (1 M, 2.1 mL, 2.1 mmol). The solution of allyl-9-BBN was slowly added at −78 °C under Ar to a solution of the imine **1c** (373 mg, 1 mmol) in dry diethyl ether (10 mL). After stirring for 5 h the reaction mixture was quenched at −78 °C with HCl (10 M, 5 mL) and stirred for an additional 5 days at room temperature. The organic phase was separated and the water layer was extracted with diethyl ether. The water layer was adjusted to pH = 11 with 10% NaOH and further extracted with diethyl ether (2 × 20 mL). The combined organic layers were dried over dry $MgSO_4$, filtered and concentrated to give an oily residue. Purification of the residue by flash chromatography with diethyl ether/hexane (1:4) afforded 291 mg (70%) of compound *anti*-**2c** as a colourless oil. $[\alpha]_D^{20} = +5.2$ (*c* = 1 in $CHCl_3$). $^1$H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 1.28 (d, *J* = 6.6 Hz, 3 H), 1.62 (br. s, 1 H), 2.21−2.42 (m, 2 H), 2.67−2.72 (m, 1 H), 3.46−3.52 (m, 1 H), 3.56 (dd, *J* = 10.3, *J* = 5.9 Hz, 1 H), 3.72 (dd, *J* = 10.3, *J* = 3.3 Hz, 1 H), 3.85 (q, *J* = 6.6 Hz, 1 H), 4.44 (d, *J* = 12.2 Hz, 1 H), 4.44 (d, *J* = 11.7 Hz, 1 H), 4.51 (d, *J* = 12.2 Hz, 1 H), 4.61 (d, *J* = 11.7 Hz, 1 H), 5.01−5.07 (m, 2 H), 5.69−5.81 (m, 1 H), 7.19−7.36 (m, 15 H) ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 24.6, 34.1, 55.1, 55.2, 70.9, 72.3, 73.2, 79.8, 117.3, 126.8, 126.9, 127.4, 127.5, 127.6, 127.7, 128.2, 128.3, 135.5, 138.4, 138.8, 145.9 ppm. HRMS (FAB) for $C_{28}H_{34}NO_2$ [M + H$^+$]: calcd. 416.2589; found 416.2596.

**(2*S*,3*R*)-3-*tert*-Butoxycarbonylamino-1,2-hexanediol (*syn*-4):** Homoallylamine *syn*-**2b** (415 mg, 1 mmol) was dissolved in methanol (15 mL). $Pd(OH)_2$/C (20%, 150 mg) and di-*tert*-butyl dicarbonate (655 mg, 3 mmol) were then successively added to the solution. The mixture was stirred under $H_2$ at 50 atm for 5 days at room temperature and then filtered, and the solvent was evaporated in vacuo. The residue was purified by flash chromatography with diethyl ether/hexane (1:1) to give 175 mg (75%) of *N*-Boc-aminodiol *syn*-**4** as a white solid. M.p. 63 °C (ref.[20] for the enantiomer, m.p. 62−63 °C). $[\alpha]_D^{20} = -12.0$ (*c* = 1 in $CHCl_3$). $^1$H NMR ($CDCl_3$, 300 MHz, 60 °C): δ = 0.92 (t, *J* = 7.5 Hz, 3 H), 1.45 (s, 9 H), 1.45−1.54 (m, 4 H), 2.31 (br. s, 2 H), 3.50−3.60 (m, 2 H), 3.65−3.72 (m, 2 H), 4.59 (bd, 1 H) ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz, 60 °C): δ = 13.8, 19.4, 28.5, 34.4, 51.5, 64.1, 73.6, 79.9, 157.1 ppm.

**(2*S*,3*S*)-3-*tert*-Butoxycarbonylamino-1,2-hexanediol (*anti*-4):** Homoallylamine *anti*-**2c** (415 mg, 1 mmol) was dissolved in methanol (15 mL). $Pd(OH)_2$/C (20%, 150 mg) and di-*tert*-butyl dicarbonate (655 mg, 3 mmol) were then successively added to the solution. The mixture was shaken under $H_2$ at 1 atm at room temperature for 5 days and filtered, and the solvent was evaporated in vacuo. The residue was purified by flash chromatography with diethyl ether/hexane (1:1) to give 130 mg (55%) of *N*-Boc-aminodiol *anti*-**4** as a white solid. M.p. 90 °C (ref.,[20] m.p. 90−91 °C). $[\alpha]_D^{20} = +9.3$ (*c* = 1 in $CHCl_3$). $^1$H NMR ($CDCl_3$, 300 MHz, 60 °C): δ = 0.92 (t, *J* = 7.2 Hz, 3 H), 1.43 (s, 9 H), 1.35−1.44 (m, 2 H), 1.49−1.57 (m, 2 H), 2.35 (br. s, 1 H), 2.78 (br. s, 1 H), 3.47−3.55 (m, 2 H), 3.58−3.68 (m, 2 H), 4.61 (bd, 1 H) ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz, 60 °C): δ = 13.8, 19.4, 28.4, 34.4, 51.5, 64.1, 73.6, 79.9, 157.1 ppm.

**Typical Procedure for Norvaline Synthesis:** Small portions of $NaIO_4$ (850 mg, 4 mmol) were added to a stirred solution of the corresponding *syn* or *anti* *N*-Boc-aminodiol **4** (233 mg, 1 mmol) in acetonitrile/carbon tetrachloride/water (2:2:3, 20 mL). The mixture was vigorously stirred for 5 min after completion of the addition and was then treated with $RuCl_3{\cdot}H_2O$ (9.2 mg, 0.04 mmol). Stirring was continued for an additional 2 h. Dichloromethane (25 mL) was added and the mixture was extracted with aqueous $NaHCO_3$ (1 M). The aqueous solution was washed with diethyl ether, cooled to 0 °C, carefully acidified with saturated aqueous $KHSO_4$ and extracted with diethyl ether (3 × 30 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The residue was dissolved in THF (5 mL) and hydrolysed by heating under reflux in hydrochloric acid (3 N) for 12 h. The reaction mixture was diluted with THF (5 mL), washed with diethyl ether (3 × 30 mL) and evaporated to give the (*R*)- or (*S*)-norvaline hydrochloride, from which the free amino acid was isolated by ion-exchange chromatography (Dowex 50 W × 8, H$^+$) as a white solid.

**(*R*)-Norvaline (*R*)-5:** (82 mg, 70% yield), m.p. >300 °C, $[\alpha]_D^{20}$ = −22.2 (*c* = 10 in 5 N HCl); {ref.[13] $[\alpha]_D^{20} = -24.0$ (*c* = 10 in 5 N HCl)}. $^1$H NMR ($D_2O$, 300 MHz, 25 °C): δ = 0.85 (t, *J* = 7.5 Hz, 3 H), 1.27−1.34 (m, 2 H), 1.69−1.78 (m, 2 H), 3.63 (t, *J* = 7.5 Hz, 1 H) ppm. $^{13}$C NMR ($D_2O$, 75 MHz, 25 °C): δ = 12.7, 17.6, 32.6, 54.4, 175.1 ppm.

**(*S*)-Norvaline (*S*)-5:** (76 mg, 65% yield), m.p. >300 °C, $[\alpha]_D^{20}$ = +23.0 (*c* = 10 in 5 N HCl) {ref.,[13] $[\alpha]_D^{20} = +24.0$ (*c* = 10 in 5 N HCl)}. $^1$H NMR ($D_2O$, 300 MHz, 25 °C): δ = 0.81 (t, *J* = 7.5 Hz, 3 H), 1.19−1.29 (m, 2 H), 1.65−1.74 (m, 2 H), 3.60 (t, *J* = 7.5 Hz, 1 H) ppm. $^{13}$C NMR ($D_2O$, 75 MHz, 25 °C): δ = 12.9, 17.8, 32.5, 54.6, 175.1 ppm.

**Typical Procedure for the Preparation of Norvaline Methyl Ester (*S*)-MTPA Amides:** Thionyl chloride (47.6 mg, 0.4 mmol) was ad-

ded dropwise at 0 °C to a stirred solution of the corresponding (*R*)- or (*S*)-norvaline **5** (19.9 mg, 0.17 mmol) in dry methanol (6 mL). The reaction mixture was stirred under reflux conditions for 60 h and then concentrated under reduced pressure to afford crude (*R*)- or (*S*)-norvaline methyl ester hydrochloride, which was used as such in the next step. (*R*)-Methoxy(trifluoromethyl)phenylacetyl chloride (MTPA-Cl) (50.5 mg, 0.2 mmol) and diisopropylethylamine (32.2 mg, 0.25 mmol) were added to a stirred solution of the (*R*)- or (*S*)-norvaline methyl ester hydrochloride in dry dichloromethane (1 mL) under an argon atmosphere. The mixture was stirred at room temperature for 48 h. The reaction mixture was quenched with aqueous $NH_4Cl$ (1 M, 10 mL) and extracted with diethyl ether (3 × 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo to afford the corresponding MTPA amides. Note: One must bear in mind that, due to the standard rules of nomenclature the (*S*)-MPTA amides and the (*R*)-MPTA chloride have an identical absolute configuration

**(*R*)-Norvaline Methyl Ester (*S*)-MTPA Amide:** $^1$H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 0.93 (t, *J* = 7.2 Hz, 3 H), 1.29−1.45 (m, 2 H), 1.57−1.65 (m, 1 H), 1.77−1.97 (m, 1 H), 3.72 (s, 3 H), 4.56−4.66 (m, 1 H), 7.62 (bd, 1 H), 7.33−7.46 (m, 3 H), 7.50−7.56 (m, 2 H) ppm. $^{19}$F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = −69.56 ppm.

**(*S*)-Norvaline Methyl Ester (*S*)-MTPA Amide:** $^1$H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 0.85 (t, *J* = 7.2 Hz, 3 H), 1.14−1.29 (m, 2 H), 1.51−1.69 (m, 1 H), 1.71−1.85 (m, 1 H), 3.74 (s, 3 H), 4.60−4.70 (m, 1 H), 7.04 (bd, 1 H), 7.34−7.48 (m, 3 H), 7.50−7.63 (m, 2 H) ppm. $^{19}$F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = −69.18 ppm.

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