

A general protocol to afford enantioenriched linear homoprenylic amines†

Irene Bosque, Francisco Foubelo and Jose C. Gonzalez-Gomez*

Departamento de Química Orgánica, Facultad de Ciencias and Instituto de Síntesis Orgánica (ISO), Universidad de Alicante, Apdo. 99, 03080 Alicante, Spain. E-mail: josecarlos.gonzalez@ua.es

†Electronic Supplementary Information (ESI) available: Copies of ^1H and ^{13}C NMR spectra for all reported compounds, HPLC chromatograms and details for the determination of absolute configuration of selected examples. Crystal data file for compound *ent-2b* (CCDC 953178) is also provided.

ABSTRACT: The reaction of a readily obtained chiral branched homoprenylammonium salt with a range of aldehydes, including aliphatic substrates, affords the corresponding linear isomers in good yields and enantioselectivities.

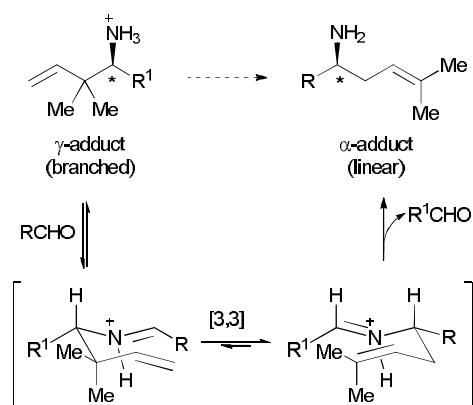
Introduction

Allylation of imines is one of the most valuable tools to build enantioenriched homoallylic amines, using either catalytic¹ or non-catalytic² methods. In addition to the challenge posed by the stereoselection, regioselectivity is a very important issue in allylation reactions. Generally, γ -substituted allylic reagents furnish the corresponding branched products (γ -adducts) with high selectivity. In particular, very few examples of α -regioselective prenylation of imines have been reported. The first useful protocol was reported by H. Yamamoto in 1996 and consists in the addition of *in-situ* generated prenyl barium reagent to imines at 0 °C.³ Although this elegant procedure showed excellent levels of regioselectivity in the examples examined, it has some practical limitations related to the formation and manipulation of activated (Rieke) barium under anhydrous conditions. In the past two decades very little progress has been made in this area. Recently it was reported that prenylhafnium reagent, formed from prenylSnBu₃/HfCl₄, adds to imines in propionitrile with excellent α -selectivity.⁴ More recently, it was found that prenyl zinc reagent in combination with 1,3-dimethyl-2-imidazolidinone at 120 °C can also be used for the α -addition to imines.⁵ Furthermore, the cross-coupling of imines with 2-methyl-3-buten-2-ol, mediated by an *in-situ* formed low-valent titanium reagent, has also been successfully used.⁶ Very recently, the linear prenylation of imines has also been accomplished under transfer hydrogenation conditions.⁷ Surprisingly, to our best knowledge, only one example of α -prenylation of

imines with moderate enantioselectivity (80:20 er) has been reported to date.³ Enantioenriched homoprenyl amines have been recently prepared by α -deprotonation of amines with n-BuLi/(-)-sparteine, to give a chiral organolithium that was quenched with prenyl bromide. This method has been successfully applied to N-Boc pyrrolidine and benzylamines.⁸

Homoprenylsulfonamides have been extensively used for the synthesis of pyrrolidines through 5-endo-trig cyclizations promoted by triflic acid⁹ or iodine.¹⁰ Furthermore, the utility of homoprenyl amine derivatives as building blocks of bioactive natural compounds has also been illustrated under cationic¹¹ or radical¹² conditions. Given that the protocols available for α -regioselective prenylation of imines remain scarce, the synthetic applications of the corresponding linear amines are still underexploited. In this context we decided to develop an alternative method that allows access to a variety of enantioenriched linear homoprenylamines from an easily available chiral substrate.

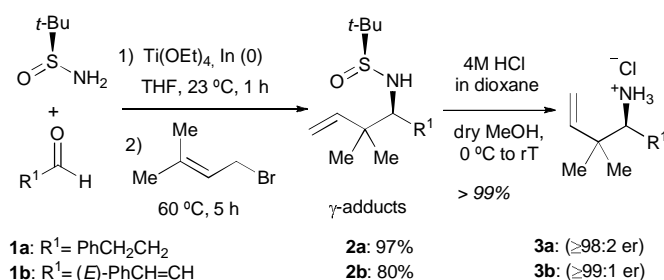
Our approach is based on the precedented 2-azonia-Cope rearrangement of chiral iminiums derived from branched homoallylic primary amines. This strategy was first employed by using a derivative of (1*R*)-camphorquinone as a chiral template¹³ and more recently in catalytic methods that use chiral Brønsted acids as ligands for the asymmetric induction via a chiral ion-pair.¹⁴ To our surprise, this approach has never been used as a general method to generate homoprenylic amines.¹⁵ We reasoned that chiral γ -adducts, easily available from the addition of prenyl organometallic reagents to imine derivatives, could act as convenient aminoprenyl donors to other aldehydes. In our approach, the geminal methyl groups are expected to sterically promote the rearrangement to an iminium ion with an internal more stable double bond (Scheme 1). In this model it is assumed that the (*E*)-iminium intermediate rearranges through a closed chair-like transition state in which the bulkier substituent (R^1) is placed in equatorial position. The fact that this favored transition state involves two gauche interactions of the R^1 group with the geminal methyl groups anticipated a more challenger enantioselection than in other related transfer aminoallylations.



Scheme 1. Working model for enantioselective transfer aminoprenylation of aldehydes.

Results and discussion

To prepare the chiral donors we used the indium mediated one-pot protocol recently developed in our research group for the diastereoselective aminoallylation of aldehydes.¹⁶ The corresponding branched homoprenylic sulfonamides were obtained with high γ -regio and stereoselectivity. After conventional acidic deprotection, the corresponding enantioenriched¹⁷ amine hydrochlorides **3a** and **3b** were obtained in quantitative yield. (Scheme 2).



Scheme 2. Enantioenriched homoprenyl amine donors.

Initially, we screened both aminoprenyl chiral donors using 3-phenylpropanal as acceptor. The conditions chosen were very simple. The corresponding γ -adduct **2** was *in-situ* deprotected and after removal of all volatile compounds under vacuum, a solution of 3-phenylpropanal (1.2 equiv) in the appropriate solvent was added to the chiral donor **3** and submitted to the reaction conditions indicated in Table 1. While the best yield in the sigmatropic rearrangement at 25 °C was obtained in CH₂Cl₂ with the donor **3a** (entry 1), the best enantioselectivity was obtained using the donor derived from cinnamaldehyde (**3b**, entry 2). In the latter case, it was necessary to quench the reaction mixture with HONH₂·AcOH in MeOH,¹³ probably due to the better stability of the conjugate iminium formed after the rearrangement. We were encouraged by the

result obtained with **3b** because this donor was obtained enantiomerically pure in excellent yield, and the absolute configuration of its enantiomer (*ent*-**2b**) was ascertained by X-ray crystal diffraction analysis (see ESI). More importantly, this result proved that compound **3b** could act as chiral aminoprenyl transfer agent to different aldehydes. In order to avoid the quenching with HONH₂·AcOH, it was examined the addition of 5 equivalents of H₂O to the reaction mixture but only starting **3b** was recovered (entry 3). The reaction was found to proceed with similar enantioselectivity in toluene but in lower yield (entry 4). When the reaction was run at 40 °C, the same enantioselectivity was obtained for **4a** but in a shorter reaction time (12 h, entry 5). We examined the addition of different molecular sieves to the reaction mixture (entries 6-8), however we observed slightly lower yields and enantioselectivities in all cases. More importantly, we also demonstrate that the reaction proceeded in good yield in the presence of substoichiometric amounts of camphorsulfonic acid (entries 9, 10). Unfortunately, the enantioselectivities obtained with both enantiomeric chiral Brønsted acids were lower than with the hydrochloride **3b**.

Table 1. Screening of different reaction conditions.

Entry	3	Conditions ^a	t (h)	Yield ^b	er ^c
1	3a	CH ₂ Cl ₂ , 25 °C	24	80% ^d	83:17
2	3b	CH ₂ Cl ₂ , 25 °C	24	65%	88:12
3	3b	CH ₂ Cl ₂ , ^d 25 °C	24	0	-
4	3b	Toluene, 25 °C	24	50%	88:12
5	3b	CH₂Cl₂, 40 °C	12	78%	88:12
6	3b	CH ₂ Cl ₂ , 40 °C, 3Å MS	12	70%	82:18
7	3b	CH ₂ Cl ₂ , 40 °C, 4Å MS	12	74%	82:18
8	3b	CH ₂ Cl ₂ , 40 °C, 5Å MS	12	71%	86:14
9	3b^e	CH ₂ Cl ₂ , 40 °C, (+)-CSA	12	70%	82:18
10	3b^e	CH ₂ Cl ₂ , 40 °C, (-)-CSA	12	74%	82:18

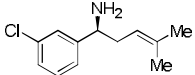
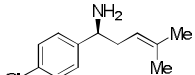
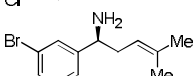
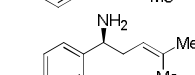
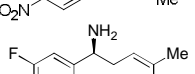
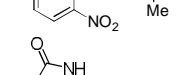
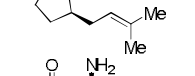
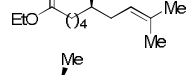
^a Unless otherwise specified, all reactions were run in dry solvents and quenched with HONH₂·HCl in MeOH at 40 °C. ^b Isolated yield. ^c Determined by HPLC analysis of benzoyl derivative. ^d 5 equiv of H₂O were added. ^e Free amine of **3b** and 10 mol% of CSA was used.

Having found a simple and reliable set of conditions for the enantioselective aminoprenylation of aldehydes we set about determining the scope and limitations. A range of aldehydes was examined, affording the results shown in Table 2. Given that enolizable aliphatic aldehydes would furnish iminium ions which are in equilibrium with their enamines, these substrates are more challengers. We were pleased to find that

this subclass of aldehydes (Table 2, entries 1-5) were suitable substrates for this protocol, affording the corresponding linear homoprenylic amines in good yields and moderate to good enantioselectivities. Interestingly the use of the chiral (*S*)-citronellal resulted in a match (entry 5) and mismatched (entry 4) combination with the chiral donor (*ent*-**3b** or **3b**, respectively) that impacted both, the isolated yield and the enantioselectivity. A limitation to this protocol was encountered with benzaldehyde, which gave very little conversion to isolate a pure product. However, cinnamaldehyde (entry 6) and aromatic aldehydes with diverse electron-withdrawing substituents (entries 7-12) furnished the corresponding enantioenriched products ($\geq 89:11$ er) in decent yields. Importantly, our protocol tolerates various functional groups -including nitro, halogens, alkenes and alkoxycarbonyl groups- in the reactive aldehyde. We thus decided to take advantage of this chemoselectivity. When 3-methoxycarbonyl-propanal was used in our standard protocol, the corresponding γ -lactam was directly obtained (entry 13). However, the use of 5-ethoxycarbonyl pentanal lead to the formation of the corresponding acyclic aminoprenyl derivative in excellent yield (entry 14). More interestingly, when 6-oxoheptanal was used, the aminoprenylation was followed by intramolecular iminium formation. Upon reduction with NaCNBH₃, the corresponding *cis*-2,7-azepane derivative **4o** was obtained in reasonable overall yield and good enantioselectivity (entry 15).

Table 2. Substrate scope.

Entry	Product	4	Yield ^a	er ^b /dr
1 ^c		4a	78 %	88:12 er
2		4b	70 %	89:11 er
3		4c	65 %	82:18 er
4 ^d		4d	63 %	81:19 dr ^e
5 ^{d,f}		4e	75 %	93:7 dr ^e
6		4f	80 %	89:11 er
7		4g	52 %	92:8 er

8		4h	45 %	89:11 er
9 ^c		4i	30%	89:11 er
10		4j	50 %	89:11 er
11		4k	83 %	90:10 er
12		4l	60 %	94:6 er
13 ^c		4m	75 %	88:12 er
14 ^c		4n	87 %	85:15 er
15 ^{c,g}		4o	37 %	86:14 er

[a] Isolated yields after column chromatography. [b] Determined by HPLC analysis (CHIRALCEL OD-H). [c] The enantiomer was also obtained from *ent*-**3b** with the same selectivity. [d] (*S*)-citronellal with 98:2 er was used. [e] Determined by ¹³C-NMR analysis. [f] *ent*-**3b** was used as chiral donor. [g] NaCNBH₃ was used to quench the reaction.

The assignment of the absolute configuration of the major enantiomer of amine **4a** was performed by ¹H-NMR analysis of its (*R*)-MPA amide, with and without Ba(ClO₄)₂. As described by the group of Riguera, the addition of Ba²⁺ to the NMR sample of **4a** should facilitate the formation of a chelate.¹⁸ This equilibrium shift from an *antiperiplanar* to a *synperiplanar* conformation leads to an increase shielding of the vinylic and methyl signals by the phenyl group of the MPA auxiliary (Figure 1). The same analysis was performed to revealed the absolute configuration of the major enantiomers of **4b** and **4k** (see ESI for details). Importantly, the inversion of the configuration at the stereogenic center from donor (*S*)-**3b** to the major enantiomer of **4** is predicted by our working model (Scheme 1).

both enantiomeric forms of the chiral donor are obtained from commercially available starting materials after only two synthetic operations. To the best of our knowledge, this represents the most general and easy to reproduce protocol that gives access to these highly versatile building blocks. Therefore, we hope that this methodology may find wide applications in synthetic organic chemistry.

Experimental

General Remarks:

(*R*_s)-*N*-*tert*-Butylsulfinyl amine and its enantiomer were a gift of Medalchemy (> 99% ee by chiral HPLC on a Chiracel AS column, n-Hexane/*i*-PrOH 90:10, 1 mL/min, λ =222 nm). TLCs were performed on silica gel 60 F₂₅₄, using aluminum plates and visualized with phosphomolybdic acid (PMA) or ninhydrine stain. Flash chromatographies were carried out on handpacked columns of silica gel 60 (230- 400 mesh). Melting points are uncorrected. Optical rotations were measured using a polarimeter with a thermally jacketted 5 cm cell at approximately 20 °C and concentrations (c) are given in g/100 mL. Infrared analyses were performed with a spectrophotometer equipped with an ATR component; wavenumbers are given in cm⁻¹. GC analyses were obtained with an HP-5 column (30 m × 0.25 mm, i.d. × 0.25 μm) and an EI (70 eV) detector; the temperature program was as follows: hold at 60 °C for 3 min, ramp from 60 to 270 °C at 15 °C/min, hold at 270 °C for 10 min. Mass spectra (EI) were obtained at 70 eV; and fragment ions in m/z with relative intensities (%) in parentheses. HRMS analyses were also carried out in the electron impact mode (EI) at 70 eV using a quadrupole mass analyzer or in the electrospray ionization mode (ES⁺) using a TOF analyzer. ¹H NMR spectra were recorded at 300 or 400 MHz, using CDCl₃ or CD₃CN as the solvent and TMS as internal Standard (0.00 ppm); the data is being reported as (s = singlet, d = doublet, t = triplet, m = multiplet or unresolved, br = broad signal, coupling constant(s) in Hz, integration). ¹³C NMR spectra were recorded with ¹H-decoupling at 101 MHz using the solvent signal as reference (77.16 ppm for CDCl₃). DEPT-135 experiments were performed to assign CH, CH₂ and CH₃.

General procedure for the synthesis of the simple chiral donors **2a**,²¹ **2b** and *ent*-**2b**

To a dry flask were added (*R*_S)-*N*-*tert*-butylsulfinyl amine (605 mg, 5.00 mmol) followed by indium powder (713 mg, 6.25 mmol), and the mixture was evacuated and left under Ar atmosphere. Then a solution of the corresponding cinnamaldehyde (726 mg, 5.5 mmol) in dry THF (10 mL) was added, followed by Ti(OEt)₄ (2.3 mL, 10.00 mmol) and the reaction mixture was stirred under Ar for 1 h at 23 °C. At this time, 3,3-dimethylallyl bromide (873 μL, 7.5 mmol) was added and the reaction mixture was heated to 60 °C for 3 h. The mixture was allowed to reach room temperature and was carefully added over a stirring mixture of 4:1 EtOAc/brine (50 mL). The resulted white suspension was filtered through a short pad of Celite, washed with EtOAc and organics were concentrated *in vacuo*. The resulted suspension was diluted in 4:1 EtOAc/Hexane (50 mL) and filtered again through Celite. Organics were concentrated and the residue (92:8 dr according ¹H NMR) was purified by column chromatography (8:2 Hexane/EtOAc).

(*S*_S,1*E*,3*S*)-*N*-*tert*-Butylsulfinyl-4,4-dimethyl-1-phenylhexa-1,5-dien-3-amine (2b)

Compound **2b** was obtained according to the general procedure as a white solid (1.218 g, 80%, 99:1 dr according ¹H NMR): mp 94.0 – 95.1 °C. Diastomeric excess was determined by HPLC of the corresponding benzamide (99:1 er by chiral HPLC on a Chiracel ODH column, n-Hexane/*i*-PrOH 95:5, 1 mL/min, λ=220 nm): major enantiomer *t*_R = 16.3 min, minor enantiomer *t*_R = 21.1 min. [α]²⁰_D +163.4 (*c* 1.10, CHCl₃). *R*_f = 0.21 (7:3 Hexane/EtOAc). IR: ν_{max}/ cm⁻¹ 3289, 3057, 2958, 2924, 1637, 1364, 1337, 1184, 1059, 996, 984, 912. ¹H NMR (300 MHz, CDCl₃) δ 7.43 – 7.27 (m, 5H), 6.63 (d, *J* = 15.9 Hz, 1H), 5.96 (dd, *J* = 15.9, 8.8 Hz, 1H), 5.85 (dd, *J* = 17.4, 10.8 Hz, 1H), 5.19 (dd, *J* = 10.7, 1.0 Hz, 1H), 5.13 (dd, *J* = 17.5, 1.1 Hz, 1H), 3.71 (d, *J* = 8.9 Hz, 1H), 3.59 (br s, 1H), 1.19 (s, 9H), 1.07 (s, 3H), 1.06 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 145.9 (CH), 136.8 (C), 135.3 (CH), 128.7 (CH), 127.9 (CH), 126.7 (CH), 126.4 (CH), 114.6 (CH₂), 63.3 (CH), 55.7 (C), 41.7 (C), 26.3 (CH₃), 22.9 (CH₃), 19.7 (CH₃). GC *t*_R = 16.28 min. LRMS (EI) *m/z* (%) 249 (M⁺, 2), 230 (10), 180 (10), 179 (95), 131 (14), 130 (100), 117 (13), 116 (98), 115 (41), 103 (12), 91 (12), 77 (17), 55 (10). HRMS (EI) calcd for C₁₈H₂₇NOS – C₄H₈ 249.1109, found 249.1227.

The minor compound ((*S*_S,1*E*,3*R*)-**2b**) was also isolated from the reaction described above as a white solid (106 mg, 7%): mp 45.1 – 46.8 °C. [α]²⁰_D +4.0 (*c* 1.06, CHCl₃). *R*_f = 0.34 (7:3 Hexane/EtOAc). IR ν_{max}/ cm⁻¹ 3288, 3057, 2957, 2925, 1637, 1366, 1337,

1183, 1059, 996, 985, 912. ¹H NMR (400 MHz, CDCl₃) δ 7.44 – 7.27 (m, 4H), 7.25 – 7.16 (m, 1H), 6.62 (d, *J* = 15.8 Hz, 1H), 6.20 (dd, *J* = 15.8, 8.3 Hz, 1H), 5.86 (dd, *J* = 17.4, 10.8 Hz, 1H), 5.14 (dd, *J* = 10.8, 1.3 Hz, 1H), 5.08 (dd, *J* = 17.4, 1.3 Hz, 1H), 3.61 (t, *J* = 8.6 Hz, 1H), 3.30 (d, *J* = 9.0 Hz, 1H), 1.22 (s, 9H), 1.11 (s, 3H), 1.07 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 144.4 (CH), 136.9 (C), 133.3 (CH), 128.8 (CH), 128.6 (CH), 127.8 (CH), 126.8 (CH), 114.2 (CH₂), 67.9 (CH), 56.8 (C), 41.9 (C), 24.6 (CH₃), 24.5 (CH₃), 22.9 (CH₃). GC t_R = 16.89 min. LRMS (EI) *m/z* (%) 249 (M⁺, 2), 230 (10), 180 (10), 179 (95), 131 (14), 130 (100), 117 (13), 116 (98), 115 (35), 103 (12), 91 (13), 77 (17), 55(10). HRMS (EI) calcd for C₁₈H₂₇NOS – C₄H₈ 249.1109, found 249.1112.

(*R*_S,1*E*,3*R*)-*N*-*tert*-Butylsulfinyl-4,4-dimethyl-1-phenylhexa-1,5-dien-3-amine (*ent*-2b**)**

Compound *ent*-**2b** was obtained according to the general procedure in similar yield with identical spectroscopic and physical data, except for [α]_D²⁰ –162.6 (*c* 1.01, CHCl₃). In this case (*S*_S)-*N*-*tert*-Butylsulfinyl amine was used.

The minor compound ((*R*_S,1*E*,3*S*)-**2b**) was also isolated from the reaction described above as a white foam. The spectroscopic and physical data was identical to ((*S*_S,1*E*,3*R*)-**2b**), except for [α]_D²⁰ –4.5 (*c* 0.96, CHCl₃).

General procedure for the synthesis of the rearranged amines 4a – 4l, 4n and lactam 4m

To a solution of **2b** [(*S*_S,1*E*,3*S*)-**2b**] (92 mg, 0.3 mmol) in dry MeOH (3.7 mL) at 0 °C was carefully added a solution of HCl in 1,4-dioxane (4M, 1.2 mmol, 300 μL). The reaction mixture was stirred for 1 h while reaching the room temperature. After removal of the solvent and volatiles under reduced pressure (*t*-BuSO₂Me), the corresponding hydrochloride **3b** was obtained as a white solid. To a solution of crude hydrochloride **3b** in dry CH₂Cl₂ (2 mL) was added the corresponding aldehyde (0.36 mmol), and the reaction was stirred at 40 °C for 12 h. The reaction was quenched with a solution of HONH₂·AcOH in MeOH (0.5 M, 1.4 mL).¹³ The reaction mixture was diluted with EtOAc (5 mL) and NaOH (2 M, 5 mL), and after phase separation, the aqueous phase was extracted with EtOAc (3 x 5 mL). Organics were washed with NaOH (2 M, 5 mL) followed by brine (5 mL), dried over MgSO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (gradient from 97:3

CH₂Cl₂/MeOH to 90:10:0.05 CH₂Cl₂/MeOH/20% NH₄OH) to provide the desired amines **4a** – **4l** and **4n**. For the lactam **4m**, column chromatography was carried out with 1:3 Hexane/EtOAc. The enantiomers of some arranged products (*ent-4a*, *ent-4m*, and *ent-4n*) were prepared following the same procedure but starting from donor *ent-2b*.

(R)-6-Methyl-1-phenyl-5-hepten-3-amine (4a)

Following the general procedure from 3-Phenylpropanal, compound **4a** was obtained as a yellow oil after column chromatography (48 mg, 0.234 mmol, 78%): Enantiomeric excess was determined by HPLC of the corresponding benzamide (88:12 er on a Chiracel ODH column, n-Hexane/i-PrOH 95:5, 1 mL/min, $\lambda=220$ nm): major enantiomer $t_R = 30.4$ min, minor enantiomer $t_R = 23.9$ min. $[\alpha]_D^{20} -6.2$ (*c* 0.70, CHCl₃). $R_f = 0.28$ (9:1 CH₂Cl₂/MeOH). IR $\nu_{\max}/\text{cm}^{-1}$ 3360, 3292, 3026, 2963, 2915, 2855, 1496, 1453, 1376, 745, 698. ¹H NMR (400 MHz, CDCl₃) δ 7.32 – 7.27 (m, 2H), 7.23 – 7.14 (m, 3H), 5.13 (ddd, *J* = 8.2, 2.7, 1.3 Hz, 1H), 2.84 (ddd, *J* = 12.8, 7.5, 5.3 Hz, 1H), 2.76 (ddd, *J* = 13.8, 10.3, 5.8 Hz, 2H), 2.65 (ddd, *J* = 13.7, 10.1, 6.2 Hz, 2H), 2.19 (dt, *J* = 12.3, 6.1 Hz, 1H), 2.15 – 2.05 (m, 1H), 1.85 – 1.75 (m, 1H), 1.72 (s, 3H), 1.70 – 1.65 (m, 1H), 1.63 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 142.2 (C), 134.7 (C), 128.5 (CH), 128.5 (CH), 125.9 (CH), 120.7 (CH), 51.6 (CH), 38.6 (CH₂), 35.9 (CH₂), 32.7 (CH₂), 26.0 (CH₃), 18.2 (CH₃). GC $t_R = 12.36$ min. LRMS (EI) *m/z* (%) 203 (M⁺, 0.1), 202 (0.3), 135 (10), 134 (100), 117 (33), 91 (89), 65 (10). HRMS (EI) calcd for C₁₄H₂₁N 203.1674, found 203.1726.

(S)-6-Methyl-1-phenyl-5-hepten-3-amine (ent-4a)

Following the general procedure from 3-Phenylpropanal, compound *ent-4a* was obtained with identical spectroscopic and physical data as compound **4a** except for $[\alpha]_D^{20} +6.5$ (*c* 0.75, CHCl₃). In this case *ent-2b* was used as chiral donor.

(R)-2-Methyl-2-tridecen-5-amine (4b)

Following the general procedure from *n*-decanal, compound **4b** was obtained as a yellow oil after column chromatography (47 mg, 0.210 mmol, 70%): Enantiomeric excess was determined by HPLC of the corresponding (R)-MPA derivative (89:11 er, see ESI). $[\alpha]_D^{20} -5.3$ (*c* 0.95, CHCl₃). $R_f = 0.37$ (9:1 CH₂Cl₂/MeOH). IR $\nu_{\max}/\text{cm}^{-1}$ 3360, 3292, 2957, 2922, 2852, 1619, 1572, 815, 721 cm⁻¹. ¹H NMR (400 MHz, CDCl₃)

δ 5.15 (ddd, $J = 8.1, 2.6, 1.3$ Hz, 1H), 2.75 (br s, 1H), 2.20 – 1.87 (m, 4H), 1.73 (s, 3H), 1.63 (s, 3H), 1.49 – 1.35 (m, 2H), 1.34 – 1.20 (m, 14H), 0.88 (t, $J = 6.8$ Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 134.2 (C), 121.4 (CH), 51.9 (CH), 37.4 (CH_2), 36.4 (CH_2), 32.1 (CH_2), 29.9 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.5 (CH_2), 26.4 (CH_2), 26.1 (CH_3), 22.8 (CH_2), 18.2 (CH_3), 14.3 (CH_3). GC $t_{\text{R}} = 12.54$ min. LRMS (EI) m/z (%) 225 (M^+ , 0.1), 224 (0.3), 157 (13), 156 (100), 81 (5), 69 (6), 56 (10). HRMS (EI) calcd for $\text{C}_{15}\text{H}_{31}\text{N}$ 225.2457, found 225.2469.

(S)-1-Cyclohexyl-4-methyl-3-penten-1-amine (4c)

Following the general procedure from Cyclohexylcarbaldehyde, compound **4c** was obtained as a yellow oil after column chromatography (35 mg, 0.195 mmol, 65%): Enantiomeric excess was determined by HPLC of the corresponding benzamide (82:18 er on a Chiracel ODH column, n-Hexane/i-PrOH 95:5, 0.5 mL/min, $\lambda=220$ nm): major enantiomer $t_{\text{R}} = 20.8$ min, minor enantiomer $t_{\text{R}} = 18.5$ min. $[\alpha]_{\text{D}}^{20} -5.1$ (c 0.85, CH_2Cl_2). $R_{\text{f}} = 0.20$ (9:1 $\text{CH}_2\text{Cl}_2/\text{MeOH}$). IR $\nu_{\text{max}}/\text{cm}^{-1}$ 3370, 3292, 2921, 2851, 1448, 1376, 890, 817. ^1H NMR (400 MHz, CDCl_3) δ 5.15 (t, $J = 7.3$ Hz, 1H), 2.65 – 2.49 (m, 1H), 2.28 – 2.10 (m, 1H), 2.10 – 1.91 (m, 2H), 1.77 (br d, $J = 11.3$ Hz, 3H), 1.73 (s, 3H), 1.68 (br s, 2H), 1.63 (s, 3H), 1.38 – 0.91 (m, 7H). ^{13}C NMR (101 MHz, CDCl_3) δ 134.1 (C), 121.9 (CH), 56.7 (CH), 43.1 (CH), 33.1 (CH_2), 29.9 (CH_2), 28.4 (CH_2), 26.8 (CH_2), 26.7 (CH_2), 26.5 (CH_2), 26.1 (CH_3), 18.2 (CH_3). GC $t_{\text{R}} = 10.73$ min. LRMS (EI) m/z (%) 181 (M^+ , 0.1), 180 (0.3), 113 (8), 112 (100), 98 (9), 95 (37), 81 (12), 67 (6), 55 (6). HRMS (EI) calcd for $\text{C}_{12}\text{H}_{23}\text{N}$ 181.1830, found 181.1841.

(5R,7S)-2,7,11-Trimethyldodeca-2,10-dien-5-amine (4d)

Following the general procedure from (*S*)-Citronellal, compound **4d** was obtained as a yellow oil after column chromatography (42 mg, 0.189 mmol, 63%): Diastereomeric excess was determined by comparing the ^{13}C NMR spectra of both diastereoisomers **4d** and **4e** (82:18 dr, see ESI). $[\alpha]_{\text{D}}^{20} +5.0$ (c 1.07, CHCl_3). $R_{\text{f}} = 0.29$ (9:1 $\text{CH}_2\text{Cl}_2/\text{MeOH}$). IR $\nu_{\text{max}}/\text{cm}^{-1}$ 3350, 2963, 2913, 2859, 1727, 1668, 1450, 1376, 828, 750. ^1H NMR (300 MHz, CDCl_3) δ 5.19 – 5.06 (m, 2H), 2.87 (tt, $J = 9.6, 5.0$ Hz, 1H), 2.35 – 1.90 (m, 6H), 1.73 (d, $J = 0.6$ Hz, 3H), 1.68 (d, $J = 1.0$ Hz, 3H), 1.64 (s, 3H), 1.60 (s, 3H), 1.43 – 1.09 (m, 5H), 0.89 (d, $J = 6.6$ Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 134.4 (C), 131.3 (C), 124.9 (CH), 121.2 (CH), 49.4 (CH), 44.7 (CH_2), 37.9 (CH_2), 36.9 (CH_2), 29.4 (CH),

26.1 (CH₃), 25.9 (CH₃), 25.6 (CH₂), 19.3 (CH₃), 18.2 (CH₃), 17.8 (CH₃). GC t_R = 12.04 min. LRMS (EI) m/z (%) 203 (M⁺, 0.1), 155 (12), 154 (100), 137 (19), 112 (6), 98 (7), 96 (5), 95 (38), 82 (89), 70 (13), 69 (39), 67 (10). HRMS (EI) calcd for C₁₅H₂₉N 223.2300, found 223.2279.

(5*S*,7*S*)-2,7,11-Trimethyldodeca-2,10-dien-5-amine (4e)

Following the general procedure from (*S*)-Citronellal, but using *ent*-**2b** as chiral donor, compound **4e** was obtained as a yellow oil after column chromatography (50 mg, 0.224 mmol, 75%): Diastereomeric excess was determined by comparing the ¹³C NMR spectra of both diastereoisomers **4d** and **4e** (93:7 dr, see ESI) $[\alpha]_D^{20} +10.6$ (c 0.80, CH₂Cl₂). $R_f = 0.27$ (9:1 CH₂Cl₂/MeOH). IR ν_{max}/cm^{-1} 3351, 2963, 2913, 2848, 1727, 1668, 1450, 1376, 829, 754. ¹H NMR (300 MHz, CDCl₃) δ 5.19 – 5.06 (m, 2H), 2.88 (dt, $J = 12.0, 7.4$ Hz, 1H), 2.26 (br s, 2H), 2.19 – 2.09 (m, 1H), 2.06 – 1.90 (m, 3H), 1.73 (d, $J = 0.6$ Hz, 3H), 1.68 (d, $J = 1.0$ Hz, 3H), 1.64 (s, 3H), 1.60 (s, 3H), 1.58 – 1.51 (m, 1H), 1.44 – 1.30 (m, 2H), 1.27 – 1.07 (m, 2H), 0.91 (d, $J = 6.6$ Hz, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 134.5 (C), 131.4 (C), 124.9 (CH), 121.1 (CH), 49.6 (CH), 44.9 (CH₂), 36.9 (CH₂), 36.0 (CH₂), 29.5 (CH), 26.1 (CH₃), 25.9 (CH₃), 25.4 (CH₂), 20.3 (CH₃), 18.2 (CH₃), 17.8 (CH₃). GC t_R = 12.16 min. LRMS (EI) m/z (%) 223 (M⁺, 0.1), 155 (12), 154 (100), 137 (19), 112 (6), 98 (7), 95 (38), 82 (9), 81 (89), 70 (13), 69 (39), 67 (10). HRMS (EI) calcd for C₁₅H₂₉N 223.2300, found 223.2283.

(*E,S*)-6-Methyl-1-phenylhepta-1,5-dien-3-amine (4f)

Following the general procedure from Cinnamaldehyde, compound **4f** was obtained as a yellow oil after column chromatography (48 mg, 0.240 mmol, 80%): Enantiomeric excess was determined by HPLC of the corresponding benzamide (89:11 er on a Chiracel ODH column, n-Hexane/*i*-PrOH 95:5, 1 mL/min, $\lambda=220$ nm): major enantiomer $t_R = 37.7$ min, minor enantiomer $t_R = 42.0$ min. $[\alpha]_D^{20} -8.5$ (c 0.92, CH₂Cl₂). $R_f = 0.15$ (9:1 CH₂Cl₂/MeOH). IR ν_{max}/cm^{-1} 3370, 3301, 2917, 2859, 1448, 1376, 812. ¹H NMR (400 MHz, CDCl₃) δ 7.42 – 7.29 (m, 4H), 7.24 – 7.17 (m, 1H), 6.51 (d, $J = 15.9$ Hz, 1H), 6.21 (dd, $J = 15.9, 6.8$ Hz, 1H), 5.30 – 5.05 (m, 1H), 3.53 (q, $J = 6.7$ Hz, 1H), 2.24 (t, $J = 7.0$ Hz, 2H), 1.92 (br s, 2H), 1.73 (s, 3H), 1.65 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 137.3 (C), 134.8 (CH), 134.3 (C), 129.1 (CH), 128.7 (CH), 127.4 (CH), 126.4 (CH), 120.5 (CH), 54.3 (CH), 36.6 (CH₂), 26.1 (CH₃), 18.2 (CH₃). GC t_R = 13.09

min. LRMS (EI) m/z (%) 201 (M^+ , 0.1), 133 (11), 132 (100), 130 (9), 117 (8), 115 (31). HRMS (EI) calcd for $C_{14}H_{19}N$ 201.1517, found 201.1538.

(S)-1-(2-Chlorophenyl)-4-methyl-3-penten-1-amine (4g)

Following the general procedure from 2-Chlorobenzaldehyde, compound **4g** was obtained as a yellow oil after column chromatography (32 mg, 0.156 mmol, 52%): Enantiomeric excess was determined by HPLC of the corresponding benzamide (92:8 er on a Chiracel ODH column, n-Hexane/*i*-PrOH 95:5, 1 mL/min, $\lambda=220$ nm): major enantiomer $t_R = 18.4$ min, minor enantiomer $t_R = 14.9$ min. $[\alpha]_D^{20} -69.8$ (c 1.50, $CHCl_3$). $R_f = 0.50$ (9:1 $CH_2Cl_2/MeOH$). IR ν_{max}/cm^{-1} 3370, 3282, 3060, 2967, 2913, 2853, 1668, 1439, 1035, 854, 694. 1H NMR (300 MHz, $CDCl_3$) δ 7.53 (dd, $J = 7.7, 1.6$ Hz, 1H), 7.33 (dd, $J = 7.8, 1.4$ Hz, 1H), 7.29 – 7.24 (m, 1H), 7.19 – 7.13 (m, 1H), 5.17 (tdd, $J = 6.7, 2.8, 1.4$ Hz, 1H), 4.42 (dd, $J = 8.3, 4.8$ Hz, 1H), 2.44 (dt, $J = 11.6, 5.7$ Hz, 1H), 2.36 – 2.19 (m, 1H), 1.72 (d, $J = 0.7$ Hz, 3H), 1.62 (br s, 2H), 1.61 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.4 (C), 135.0 (C), 133.0 (C), 129.6 (CH), 127.9 (CH), 127.4 (CH), 127.1 (CH), 120.8 (CH), 52.4 (CH), 36.4 (CH_2), 26.0 (CH_3), 18.1 (CH_3). GC $t_R = 11.89$ min. LRMS (EI) m/z (%) 209 (0.1, M^+), 142 (34), 141 (9), 140 (100), 115 (8), 113 (5, 78 (3, 77 (13). Anal. Calc'd for $C_{12}H_{16}ClN$: C 68.73, H 7.69, N 6.68. Found: C 68.99, H 7.52, N 6.58.

(S)-1-(3-Chlorophenyl)-4-methyl-3-penten-1-amine (4h)

Following the general procedure from 3-Chlorobenzaldehyde, compound **4h** was obtained as a yellow oil after column chromatography (27 mg, 0.129 mmol, 45%): Enantiomeric excess was determined by HPLC of the corresponding benzamide (89:11 er on a Chiracel ODH column, n-Hexane/*i*-PrOH 95:5, 1 mL/min, $\lambda=220$ nm): major enantiomer $t_R = 29.5$ min, minor enantiomer $t_R = 18.9$ min. $[\alpha]_D^{20} -30.2$ (c 0.87, $CHCl_3$). $R_f = 0.34$ (9:1 $CH_2Cl_2/MeOH$). IR ν_{max}/cm^{-1} 3370, 3281, 2968, 2913, 1596, 1573, 1432, 784, 697. 1H NMR (300 MHz, $CDCl_3$) δ 7.36 (t, $J = 1.7$ Hz, 1H), 7.26 – 7.16 (m, 3H), 5.19 – 4.97 (m, 1H), 3.92 (t, $J = 6.7$ Hz, 1H), 2.32 (t, $J = 7.0$ Hz, 2H), 1.88 (d, $J = 3.6$ Hz, 1H), 1.71 (d, $J = 1.0$ Hz, 3H), 1.64 (br s, 1H), 1.59 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.5 (C), 135.1 (C), 134.3 (C), 129.7 (CH), 127.1 (CH), 126.8 (CH), 124.8 (CH), 120.6 (CH), 56.0 (CH), 38.5 (CH_2), 26.0 (CH_3), 18.1 (CH_3). GC $t_R = 12.24$ min.

LRMS (EI) m/z (%) 206 (1), 142 (32), 141 (9), 140 (100), 138 (3), 77 (13). HRMS (ES⁺) calcd for C₁₂H₁₇ClN 210.1050, found 210.1044.

(S)-1-(4-Chlorophenyl)-4-methyl-3-penten-1-amine (4i)

Following the general procedure from 4-Chlorobenzaldehyde, compound **4i** was obtained as a yellow oil after column chromatography (18 mg, 0.09 mmol, 30%): Enantiomeric excess was determined by HPLC of the corresponding benzamide (89:11 er on a Chiracel ODH column, n-Hexane/i-PrOH 95:5, 1 mL/min, $\lambda=220$ nm): major enantiomer $t_R = 32.8$ min, minor enantiomer $t_R = 21.4$ min. $[\alpha]_D^{20} -25.5$ (c 1.50, CHCl₃). $R_f = 0.33$ (9:1 CH₂Cl₂/MeOH). IR ν_{max}/cm^{-1} 3375, 3286, 2968, 2912, 1859, 1668, 1489, 1089, 1013, 822. ¹H NMR (300 MHz, CDCl₃) δ 7.30 (s, 4H), 5.10 (tt, $J = 7.3, 1.4$ Hz, 1H), 3.95 (t, $J = 7.0$ Hz, 1H), 2.32 (t, $J = 7.1$ Hz, 2H), 1.72 (d, $J = 0.9$ Hz, 3H), 1.62 (br s, 2H), 1.60 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 144.7 (C), 135.0 (C), 132.5 (C), 128.5 (CH), 127.9 (CH), 120.7 (CH), 55.8 (CH), 38.5 (CH₂), 26.0 (CH₃), 18.1 (CH₃). GC $t_R = 12.18$ min. LRMS (EI) m/z (%) 143 (9), 142 (34), 141 (28), 140 (100), 138 (8), 115 (8), 113 (21), 78 (6), 77 (36). HRMS (EI) calcd for C₁₂H₁₆ClN 209.0971, found 209.1251.

(S)-1-(3-Bromophenyl)-4-methyl-3-penten-1-amine (4j)

Following the general procedure from 3-Bromobenzaldehyde, compound **4j** was obtained as a yellow oil after column chromatography (37 mg, 0.146 mmol, 50%): Enantiomeric excess was determined by HPLC of the corresponding benzamide (89:11 er on a Chiracel ODH column, n-Hexane/i-PrOH 95:5, 1 mL/min, $\lambda=220$ nm): major enantiomer $t_R = 31.8$ min, minor enantiomer $t_R = 20.8$ min. $[\alpha]_D^{20} -22.6$ (c 1.20, CHCl₃). $R_f = 0.33$ (9:1 CH₂Cl₂/MeOH). IR ν_{max}/cm^{-1} 3370, 3301, 2966, 2912, 1593, 1567, 1427, 1068, 782. ¹H NMR (300 MHz, CDCl₃) δ 7.51 (t, $J = 1.7$ Hz, 1H), 7.39 – 7.33 (m, 1H), 7.29 – 7.23 (m, 1H), 7.18 (t, $J = 7.7$ Hz, 1H), 5.09 (tdd, $J = 6.0, 2.8, 1.4$ Hz, 1H), 3.91 (t, $J = 6.7$ Hz, 1H), 2.32 (t, $J = 7.0$ Hz, 2H), 1.72 (br s, 2H), 1.70 (d, $J = 0.9$ Hz, 3H), 1.58 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 148.7 (C), 135.1 (C), 130.1 (C), 130.0 (CH), 129.7 (CH), 125.2 (CH), 122.6 (CH), 120.6 (CH), 55.9 (CH), 38.4 (CH₂), 26.0 (CH₃), 18.1 (CH₃). GC $t_R = 12.87$ min. LRMS (EI) m/z (%) 254 (0.1), 187 (12), 186 (98), 185 (13), 184 (100), 182 (2), 157 (7), 104 (9), 77 (13). HRMS (ES⁺) calcd for C₁₂H₁₇BrN 254.0544, found 254.0548.

(S)-1-(4-Nitrophenyl)-4-methyl-3-penten-1-amine (4k)

Following the general procedure from 4-Nitrobenzaldehyde, compound **4k** was obtained as a yellow oil after column chromatography (55 mg, 0.250 mmol, 83%): Enantiomeric excess was determined by HPLC of the corresponding benzamide (90:10 er on a Chiracel ODH column, n-Hexane/i-PrOH 90:10, 1 mL/min, $\lambda=220$ nm): major enantiomer $t_R = 36.5$ min, minor enantiomer $t_R = 30.1$ min. $[\alpha]_D^{20} -21.7$ (c 1.10, CHCl_3). $R_f = 0.36$ (9:1 $\text{CH}_2\text{Cl}_2/\text{MeOH}$). IR $\nu_{\text{max}}/\text{cm}^{-1}$ 3376, 2971, 2911, 2848, 1597, 1507, 1342, 856, 751, 701. ^1H NMR (300 MHz, CDCl_3) δ 8.19 (dd, $J = 8.8, 2.1$ Hz, 2H), 7.54 (dd, $J = 8.6, 2.1$ Hz, 2H), 5.08 (tt, $J = 7.4, 1.4$ Hz, 1H), 4.08 (t, $J = 6.7$ Hz, 1H), 2.34 (t, $J = 7.1$ Hz, 2H), 1.71 (d, $J = 0.7$ Hz, 3H), 1.64 (br s, 2H), 1.57 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 153.8 (C), 147.0 (C), 135.8 (C), 127.4 (CH), 127.4 (CH), 123.7 (CH), 123.7 (CH), 119.9 (CH), 55.9 (CH), 38.5 (CH_2), 26.0 (CH_3), 18.1 (CH_3). GC $t_R = 14.37$ min. LRMS (EI) m/z (%) 152 (9), 151 (100), 121 (4), 105 (31), 104 (13), 93 (5), 78 (5), 77 (6). HRMS (EI) calcd for $\text{C}_{12}\text{H}_{16}\text{N}_2\text{O}_2$ 220.1212, found 220.1202.

(S)-1-(5-Fluoro-2-nitrophenyl)-4-methyl-3-penten-1-amine (4l)

Following the general procedure from 5-Fluoro-2-nitrobenzaldehyde, compound **4l** was obtained as a yellow oil after column chromatography (42 mg, 0.176 mmol, 60%): Enantiomeric excess was determined by HPLC of the corresponding benzamide (94:6 er on a Chiracel ODH column, n-Hexane/i-PrOH 95:5, 1 mL/min, $\lambda=220$ nm): major enantiomer $t_R = 37.8$ min, minor enantiomer $t_R = 28.0$ min. $[\alpha]_D^{20} -89.8$ (c 0.75, CHCl_3). $R_f = 0.53$ (9:1 $\text{CH}_2\text{Cl}_2/\text{MeOH}$). IR $\nu_{\text{max}}/\text{cm}^{-1}$ 3390, 3302, 2970, 2916, 2849, 1584, 1512, 1352, 851, 757, 704. ^1H NMR (400 MHz, CDCl_3) δ 7.88 (dd, $J = 9.0, 5.1$ Hz, 1H), 7.59 (dd, $J = 9.9, 2.8$ Hz, 1H), 7.03 (ddd, $J = 9.0, 7.1, 2.8$ Hz, 1H), 5.13 (tt, $J = 6.6, 2.7, 1.3$ Hz, 1H), 4.59 (ddd, $J = 8.2, 4.8, 1.6$ Hz, 1H), 2.47 – 2.36 (m, 1H), 2.34 – 2.23 (m, 1H), 1.72 (s, 3H), 1.60 (br s, 5H). ^{13}C NMR (101 MHz, CDCl_3) δ 165.1 (d, $J = 255.3$ Hz, C), 145.3 (d, $J = 8.0$ Hz, C), 145.2 (C), 136.1 (C), 127.1 (d, $J = 9.5$ Hz, CH), 120.0 (CH), 115.5 (d, $J = 24.4$ Hz, CH), 114.7 (d, $J = 24.4$ Hz, CH), 50.7 (CH), 37.5 (CH_2), 26.0 (CH_3), 18.1 (CH_3). GC $t_R = 13.04$ min. LRMS (EI) m/z (%) 170 (9), 169 (100), 152 (3), 123 (17), 122 (17), 122 (23), 69 (4). HRMS (EI) calcd for $\text{C}_{12}\text{H}_{16}\text{N}_2\text{O}_2\text{F}$ 239.1196, found 239.1197.

(R)-5-Prenyl-2-pyrrolidinone (4m)

Following the general procedure from Methyl 4-oxobutanoate,²² compound **4m** was obtained as a yellow oil after column chromatography (35 mg, 0.225 mmol, 75%): Enantiomeric excess was directly determined by HPLC of the lactam (88:12 er on a Chiracel ODH column, n-Hexane/i-PrOH 90:10, 1 mL/min, $\lambda=220$ nm): major enantiomer $t_R = 8.1$ min, minor enantiomer $t_R = 9.5$ min. $[\alpha]_D^{20} -14.5$ (c 0.90, CHCl_3). $R_f = 0.20$ (1:3 Hexane:EtOAc). IR $\nu_{\text{max}}/\text{cm}^{-1}$ 3210, 3100, 2969, 2915, 1689, 1440, 1424, 1343, 856. ^1H NMR (300 MHz, CDCl_3) δ 6.05 (br s, 1H), 5.09 (tdd, $J = 6.9, 2.8, 1.4$ Hz, 1H), 3.65 (p, $J = 6.6$ Hz, 1H), 2.38 – 2.29 (m, 2H), 2.28 – 2.14 (m, 3H), 1.82 – 1.74 (m, 1H), 1.72 (s, 3H), 1.63 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 178.1 (C), 135.5 (C), 119.3 (CH), 54.7 (CH), 35.3 (CH_2), 30.3 (CH_2), 26.9 (CH_2), 26.0 (CH_3), 18.1 (CH_3). GC $t_R = 11.30$ min. LRMS (EI) m/z (%) 153 (M^+ , 2), 85 (5), 84 (100), 69 (2), 56 (6), 55 (3). HRMS (ES^+) calcd for $\text{C}_9\text{H}_{16}\text{NO}$ 154.1232, found 154.1231.

(S)-5-Prenyl-2-pyrrolidinone (ent-4m)

Following the general procedure from Methyl 4-oxobutanoate, compound *ent-4m* was obtained with identical spectroscopic and physical data as compound **4m** except for $[\alpha]_D^{20} +14.1$ (c 0.95, CHCl_3). In this case *ent-2b* was used as chiral donor.

(R)-Ethyl 6-amino-9-methyl-8-decenoate (4n)

Following the general procedure from Ethyl 6-oxohexanoate,²³ but in a larger scale (1.45 mmol of donor **2b**), compound **4n** was obtained as a yellow oil after column chromatography (286 mg, 1.261 mmol, 87%): Enantiomeric excess was determined by HPLC of the corresponding benzamide (85:15 er on a Chiracel ODH column, n-Hexane/i-PrOH 95:5, 1 mL/min, $\lambda=220$ nm): major enantiomer $t_R = 20.5$ min, minor enantiomer $t_R = 30.1$ min. $[\alpha]_D^{20} -5.3$ (c 1.20, CHCl_3). $R_f = 0.30$ (1:3 Hexane:EtOAc). IR $\nu_{\text{max}}/\text{cm}^{-1}$ 3439, 3370, 2972, 2928, 2860, 1733, 1248, 1179, 851, 722. ^1H NMR (300 MHz, CDCl_3) δ 5.13 (dd, $J = 7.9, 6.9$ Hz, 1H), 4.12 (q, $J = 7.1$ Hz, 2H), 2.77 (br s, 1H), 2.31 (t, $J = 7.4$ Hz, 2H), 2.23 (br s, 2H), 2.18 – 1.94 (m, 2H), 1.73 (s, 3H), 1.70 – 1.65 (m, 1H), 1.63 (s, 3H), 1.62 – 1.54 (m, $J = 13.0$ Hz, 1H), 1.55 – 1.40 (m, 2H), 1.40 – 1.30 (m, 2H), 1.26 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 173.8 (C), 134.5 (C), 121.1 (CH), 60.3 (CH_2), 51.7 (CH), 36.8 (CH_2), 36.3 (CH_2), 34.4 (CH_2), 26.03 (CH_3), 25.9 (CH_2), 25.1 (CH_2), 18.2 (CH_3), 14.4 (CH_3). GC $t_R = 12.46$ min. LRMS (EI)

m/z (%) 227 (M^+ , 0.1), 182 (9), 159 (9), 158 (100), 140 (13), 113 (8), 112 (72), 84 (17), 81 (12), 69 (27), 67 (17), 56 (23). Anal. Calc'd for $C_{13}H_{25}NO_2$: C 68.68, H 11.08, N 6.16. Found: C 68.30, H 10.71, N 5.79.

(S)-Ethyl 6-amino-9-methyl-8-decenoate (*ent-4n*)

Following the general procedure from Ethyl 6-oxohexanoate, compound *ent-4n* was obtained with identical spectroscopic and physical data as compound **4n** except for $[\alpha]_D^{20} +5.5$ (c 0.95, $CHCl_3$). In this case *ent-2b* was used as chiral donor.

(2R,7R)-2-Methyl-7-prenylazepane (4o**)**

Following the general procedure from 6-Oxoheptanal.²⁴ However, instead of adding $HONH_2 \cdot AcOH$ to the arranged mixture, $NaBH_3CN$ (1.8 mmol, 114 mg) was added and the reaction was stirred for 12 h at room temperature. Then, the reaction mixture was diluted with EtOAc (5mL) and NaOH (2 M, 5 mL), and extracted with EtOAc (3 x 5mL), washed with NaOH (2 M, 5 mL) and brine (5 mL). Organics were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (gradient from 97:3 $CH_2Cl_2/MeOH$ to 90:10:0.05 $CH_2Cl_2/MeOH/20\% NH_4OH$) to provide the desired free amine **4o** as a yellow oil (20 mg, 0.110 mmol, 37%): Enantiomeric excess was determined by HPLC of the corresponding benzamide (86:14 er on a Chiracel ODH column, n-Hexane/*i*-PrOH 98:2, 1 mL/min, $\lambda=220$ nm): major enantiomer $t_R = 17.0$ min, minor enantiomer $t_R = 20.8$ min. $[\alpha]_D^{20} -1.5$ (c 1.10, $CHCl_3$). $R_f = 0.37$ (9:1 $CH_2Cl_2/MeOH$). IR ν_{max}/cm^{-1} 3311, 2962, 2924, 2855, 1678, 1450, 1375, 751. 1H NMR (300 MHz, $CDCl_3$) δ 5.15 – 5.04 (m, 1H), 2.82 (dq, $J = 9.6, 6.4, 3.3$ Hz, 1H), 2.67 (ddd, $J = 10.0, 7.2, 3.2$ Hz, 1H), 2.24 – 2.02 (m, 2H), 1.78 – 1.73 (m, 2H), 1.72 (d, $J = 0.9$ Hz, 3H), 1.71 – 1.64 (m, 3H), 1.62 (s, 3H), 1.61 – 1.50 (m, 2H), 1.49 – 1.36 (m, 2H), 1.14 (d, $J = 6.4$ Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.4 (C), 121.5 (CH), 59.7 (CH), 55.2 (CH), 38.0 (CH_2), 35.9 (CH_2), 35.7 (CH_2), 25.8 (CH_3), 25.3 (CH_2), 25.0 (CH_2), 23.6 (CH_3), 18.0 (CH_3). GC $t_R = 9.19$ min. LRMS (EI) m/z (%) 181 (M^+ , 1), 113 (8), 112 (100), 95 (10), 82 (5), 69 (7), 56 (6). HRMS (ES^+) calcd for $C_{12}H_{24}N$ 182.1909, found 182.1906.

(2S,7S)-2-Methyl-7-prenylazepane (*ent-4o*)

Following the general procedure from 6-Oxoheptanal, compound *ent*-**4o** was obtained with identical spectroscopic and physical data as compound **4o** except for $[\alpha]_{\text{D}}^{20} +1.8$ (*c* 0.95, CHCl₃). In this case *ent*-**2b** was used as chiral donor.

General procedure for the synthesis of pyrrolidines **5a** and **5n**.

To a solution of free amine **4a** or **4n** (1.17 mmol) in CH₂Cl₂ (11 mL) at 0 °C, were added Et₃N (248 μL, 1.75 mmol) and *p*-nitrobenzenesulfonyl chloride (310 mg, 1.40 mmol). The solution was allowed to warm to 25 °C and stirred over 12 h. The reaction was quenched with HCl (1M), and after phase separation, the organic layer was washed with NaOH (1M), followed by water and brine. Evaporation of the solvent under vacuum gave crude **4a**-Ns or **4n**-Ns, which were purified by column chromatography (9:1 Hexane/EtOAc) and totally characterized (see physical and spectroscopical data of the *p*-nosylate derivatives below). At this point, trifluoromethanesulfonic acid (19 μL, 0.2 mmol) was added to a solution of **4a**-Ns or **4n**-Ns in dry toluene (70 mL) and the reaction mixture was stirred at 0 °C for 1 h. After concentration under reduced pressure, the residue was purified by column chromatography (9:1 Hexane/EtOAc) to provide the desired pyrrolidines **5a** or **5n**.

(*R*)-*p*-Nosylate of **4a** (**4a**-Ns)

Compound **4a**-Ns was obtained according to the general procedure as a white solid (392 mg, 1.01 mmol, 86%): mp 72.8 – 75.2 °C. $[\alpha]_{\text{D}}^{20} -8.6$ (*c* 0.95, CHCl₃). $R_f = 0.15$ (9:1 Hexane/EtOAc). IR $\nu_{\text{max}}/\text{cm}^{-1}$ 3289, 3027, 2926, 2859, 1605, 1528, 1347, 1308, 1161, 1092, 852, 735. ¹H NMR (300 MHz, CDCl₃) δ 8.31 (d, *J* = 9.0 Hz, 2H), 7.98 (d, *J* = 8.9 Hz, 2H), 7.29 – 7.27 (m, 1H), 7.25 – 7.23 (m, 1H), 7.23 – 7.16 (m, 1H), 7.09 – 7.05 (m, 2H), 4.84 (ddd, *J* = 7.5, 4.4, 1.3 Hz, 1H), 4.56 (br s, 1H), 3.41 – 3.26 (m, 1H), 2.67 – 2.50 (m, 2H), 2.18 (dt, *J* = 13.6, 6.7 Hz, 1H), 2.13 – 2.05 (m, 1H), 1.88 – 1.78 (m, 1H), 1.73 (ddt, *J* = 14.0, 9.3, 7.0 Hz, 1H), 1.61 (d, *J* = 0.6 Hz, 3H), 1.51 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 150.0 (C), 147.0 (C), 141.0 (C), 136.5 (C), 128.7 (CH), 128.4 (CH), 128.4 (CH), 126.3 (CH), 124.4 (CH), 118.2 (CH), 54.4 (CH), 36.6 (CH₂), 33.4 (CH₂), 31.9 (CH₂), 26.1 (CH₃), 18.1 (CH₃). GC $t_R = 24.32$ min. LRMS (EI) *m/z* (%) 320 (4), 319 (22), 289 (4), 156 (10), 132 (5), 122 (5), 118 (10), 117 (100), 92 (12), 91 (93), 77 (4), 65 (5). HRMS (ES⁺) calcd for C₂₀H₂₅N₂O₄S 389.1535, found 389.1539.

(R)-*p*-Nosylate of 4n (4n-Ns)

Compound **4n-Ns** was obtained according to the general procedure as a yellow wax (420 mg, 1.02 mmol, 88%): $[\alpha]_D^{20} +6.0$ (*c* 0.95, CHCl₃). $R_f = 0.28$ (8:2 Hexane/EtOAc). IR $\nu_{\max}/\text{cm}^{-1}$ 3280, 2931, 2863, 1730, 1529, 1348, 1307, 1160, 1091, 853, 735. ¹H NMR (300 MHz, CDCl₃) δ 8.35 (d, *J* = 9.0 Hz, 2H), 8.04 (d, *J* = 9.0 Hz, 2H), 4.83 (ddd, *J* = 7.5, 6.1, 1.4 Hz, 1H), 4.54 (d, *J* = 8.4 Hz, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 3.38 – 3.23 (m, 1H), 2.22 (t, *J* = 7.4 Hz, 2H), 2.18 – 1.94 (m, 2H), 1.60 (s, 3H), 1.55 (d, *J* = 7.5 Hz, 2H), 1.50 (s, 3H), 1.49 – 1.28 (m, 3H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.22 – 1.13 (m, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 173.6 (C), 150.1 (C), 147.3 (C), 136.2 (C), 128.4 (CH), 124.4 (CH), 118.4 (CH), 60.5 (CH₂), 54.8 (CH), 34.8 (CH₂), 34.1 (CH₂), 33.6 (CH₂), 26.0 (CH₃), 25.2 (CH₂), 24.7 (CH₂), 18.1 (CH₃), 14.4 (CH₃). GC $t_R = 25.88$ min. LRMS (EI) *m/z* (%) 344 (6), 343 (36), 313 (8), 299 (9), 298 (16), 297 (100), 281 (9), 269 (11), 207 (24), 186 (6), 157 (5), 156 (17), 122 (13), 95 (28), 69 (71). HRMS (ES⁺) calcd for C₁₉H₂₉N₂O₆S 413.1746, found 413.1732.

(R)-2,2-dimethyl-5-phenethyl-1-(*p*-nosyl)pyrrolidine (5a)

Compound **5a** was obtained according to the general procedure as a white solid (361 mg, 0.93 mmol, 93%): mp 86.8 – 89.5 °C. $[\alpha]_D^{20} -59.4$ (*c* 0.95, CHCl₃). $R_f = 0.30$ (9:1 Hexane/EtOAc). IR $\nu_{\max}/\text{cm}^{-1}$ 2959, 29223, 2859, 1525, 1455, 1342, 1151, 855, 738. ¹H NMR (300 MHz, CDCl₃) δ 8.20 (d, *J* = 8.8 Hz, 2H), 7.76 (d, *J* = 8.8 Hz, 2H), 7.36 – 7.30 (m, 2H), 7.30 – 7.26 (m, 0.7H), 7.26 – 7.23 (m, 0.3H), 7.21 – 7.14 (m, 2H), 3.68 – 3.57 (m, 1H), 2.72 (ddd, *J* = 13.4, 8.5, 4.6 Hz, 1H), 2.50 (dt, *J* = 13.9, 8.4 Hz, 1H), 2.33 – 2.22 (m, 1H), 2.07 – 1.93 (m, 1H), 1.85 – 1.69 (m, 4H), 1.60 (s, 3H), 1.31 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 149.6 (C), 147.6 (C), 141.0 (C), 128.8 (CH), 128.7 (CH), 128.7 (CH), 126.3 (CH), 124.1 (CH), 67.1 (C), 61.4 (CH), 40.6 (CH₂), 36.6 (CH₂), 32.9 (CH₂), 31.5 (CH₃), 27.1 (CH₂), 26.6 (CH₃). GC $t_R = 24.01$ min. LRMS (EI) *m/z* (%) 373 (5), 15 (100), 253 (5), 156 (5), 122 (12), 117 (6), 105 (5), 98 (14), 97 (8), 96 (6), 91 (25), 83 (6), 82 (17), 81 (82), 65 (4). HRMS (ES⁺) calcd for C₂₀H₂₅N₂O₄S 389.1535, found 389.1538.

(R)-Ethyl 5-(5,5-dimethyl-1-(*p*-nosyl)pyrrolidin-2-yl)pentanoate (5n)

Compound **5n** was obtained according to the general procedure as a yellow oil (380 mg, 0.92 mmol, 93%): $[\alpha]_D^{20} -29.3$ (*c* 0.95, CHCl₃). $R_f = 0.40$ (8:2 Hexane/EtOAc). IR $\nu_{\max}/$

cm⁻¹ 3110, 2970, 2939, 2869, 1731, 1528, 1462, 1347, 1305, 1152, 1092, 854, 736. ¹H NMR (300 MHz, CDCl₃) δ 8.33 (d, *J* = 9.0 Hz, 2H), 8.05 (d, *J* = 9.1 Hz, 2H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.80 (ddd, *J* = 9.4, 6.6, 2.9 Hz, 1H), 2.29 (t, *J* = 7.4 Hz, 2H), 2.07 – 1.59 (m, 7H), 1.58 (s, 3H), 1.57 – 1.42 (m, 2H), 1.36 – 1.32 (m, 1H), 1.31 (s, 3H), 1.26 (t, *J* = 7.1 Hz, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 173.6 (C), 149.7 (C), 148.7 (C), 128.5 (CH), 124.2 (CH), 66.7 (C), 62.9 (CH), 60.4 (CH₂), 40.7 (CH₂), 35.4 (CH₂), 34.2 (CH₂), 31.3 (CH₃), 27.3 (CH₂), 27.0 (CH₃), 26.2 (CH₂), 24.8 (CH₂), 14.4 (CH₃). GC t_R = 26.48 min. LRMS (EI) *m/z* (%) 367 (10), 285 (5), 284 (15), 283 (100), 253 (3), 226 (33), 97 (5), 82 (9), 81 (42). HRMS (ES⁺) calcd for C₁₉H₂₉N₂O₆S 413.1746, found 413.1740.

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