

Ring Expansions of 2-Alkenylazetidinium Salts – a New Route to Pyrrolidines and Azepanes

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Series of enantiomerically pure 3-alkenylpyrrolidines, substituted azepanes and stereodefined aminoalkenes were synthesized from 2-alkenylazetidinium trifluoromethanesulfonate salts. The high chemoselectivity of these reactions was found to be strongly dependent both on the nature of the base involved in the process (PhLi or KHMDS) and on the relative *cis* or *trans* stereochemistry of the intermediate ammonium ylide. When the ylide and the adjacent alkene are

trans, a [1,2] sigmatropic shift occurs exclusively, producing a pyrrolidine with high levels of regioselectivity. On the other hand, clean conversion into 4,5-dehydroazepanes through a [2,3] sigmatropic shift is observed when these two groups are in a *cis* relationship.

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Introduction

Thanks to the growing number of available methods for the generation of ammonium ylides, the Stevens rearrangement is clearly emerging as a powerful synthetic tool:^[1] recent examples of the application of this rearrangement to the synthesis of natural products include the synthesis of complex alkaloids such as desoxycodein-D,^[2] epilupinine,^[3] tuniforcidine and platynecine.^[4] Despite extensive mechanistic investigations,^[5] however, there is still a need to understand and predict both the regioselectivity and the diastereoselectivity of this reaction, especially in order to plan its use in a total synthesis. In this context, four-membered-ring azetidines (more specifically as their ammonium derivatives) have only been rarely used as substrates for this rearrangement,^[6] in spite of the important ring strain in this heterocycle, which could be useful as an efficient driving force for the ring expansion involved in the process.^[7] As part of our continuing interest in the chemistry of azetidines,^[8] we recently reported the ring expansion of enantiomerically pure 2-alkenylazetidinium salts **1** in Stevens rearrangements^[9] to give 3-alkenylpyrrolidines **2** with total regioselectivity and modest to good diastereoselectivity. In this article we offer a full account on this work, which defines the stereochemical requirements needed in 2-alkenylazetidinium salts **1** to drive the reaction selectively either towards the production of pyrrolidines **2**, through Stevens rearrangements, or towards azepanes **3**, through a [2,3] sigmatropic shift/ring expansion methodology (Figure 1).

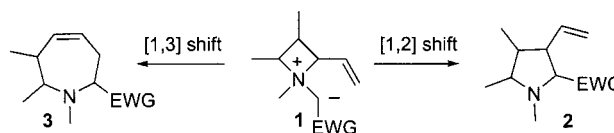


Figure 1. Rearrangements of 2-alkenylazetidinium salts.

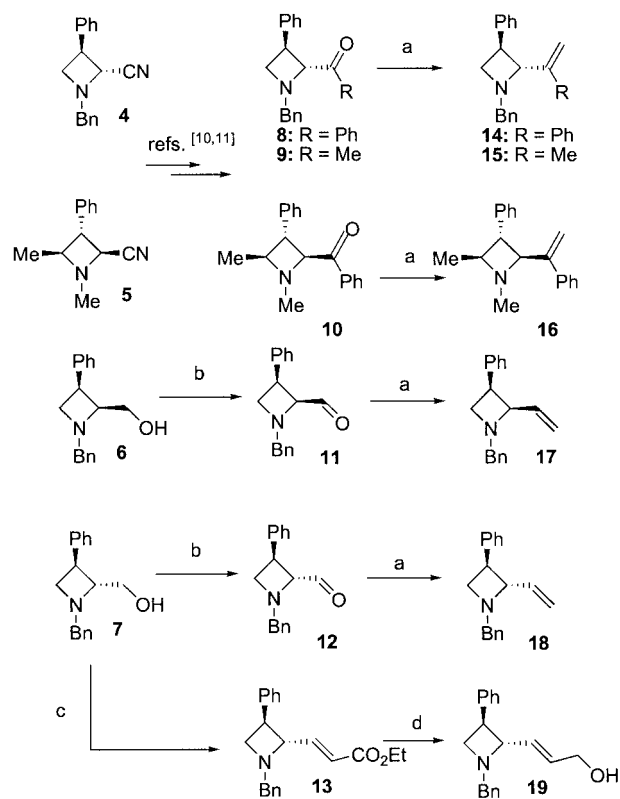
Results

Synthesis of 2-Alkenylazetidines

The starting materials required for this study, the 2-alkenylazetidines **13–19** with different substitution patterns both on the heterocycle and on the alkene moiety (Scheme 1), were all prepared in good yields from the corresponding 2-cyanoazetidines **4–5**.^[10] The key step for the alkene formation involves a Wittig olefination performed either on ketones **8–10** or on aldehydes **11–12** to afford 2-alkenylazetidines **13–18**.

The ketones were prepared by addition of organolithium reagents to nitrile moieties as described previously,^[11] whereas aldehydes **11** and **12** were produced by Swern oxidation of the corresponding primary alcohols **6** and **7**, respectively.^[12] Gratifyingly, these aldehydes were produced without any detectable epimerization, even though α -amino aldehydes are known to have low configurational stabilities;^[13] this notable stability is attributed to the presence of the four-membered ring, which most certainly disfavors the formation of an intermediate exocyclic enol.^[14] Unsaturated (*E*)-ester **13** was stereoselectively prepared from **7** in a one-pot, two-step Swern oxidation/Wittig olefination sequence, with subsequent reduction of **13** with DIBALH

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Scheme 1. a) Trimethylphosphonium iodide, BuLi, -78°C , THF, 79% (**14**), 84% (**15**), 86% (**16**), 62% from **6** (**17**), 62% from **7** (**18**). b) Swern oxidation. c) Swern oxidation, then $(\text{C}_6\text{H}_5)_3\text{PCH}=\text{CHCO}_2\text{Et}$, 84%. d) DIBALH, THF, -78°C , quant.

giving allylic alcohol **19**. As a note, a hindered ketone (**8**; $\text{R} = t\text{Bu}$) failed to give the corresponding alkene upon trial Wittig olefination (Scheme 1).

Synthesis of 2-Alkenylazetidinium Salts

Those enantiomerically pure 2-alkenylazetidines with various representative substitution patterns were next treated with MeOTf or $\text{TfOCH}_2\text{CO}_2\text{Et}$ to give the corresponding azetidinium triflates. This allowed for the isolation of compounds **20–30** in excellent yields and with high diastereoselectivity ($de > 95\%$), except in the case of **23** ($de = 12\%$; Figure 2). The relative stereochemistry in these salts was determined by a NOESY experiment performed on **21**.

The high stereoselectivity observed during the formation of the trifluoromethanesulfonate salts, which proved to be crucial for their further rearrangement, can be explained by simply considering the four different conformers and interconverters of the azetidine ring (A–D) depicted in Figure 3. Among these, conformer C (all substituents in pseudoequatorial positions) appears to be the most stable and, furthermore, the lone pair of the nitrogen atom is sterically not hindered by the substituents and so is especially readily available to react with an electrophile. The observed selectivity can therefore be explained by the favoured alkylation of this conformer. In the particular case of compound **17**, a similar conformational analysis does not clearly show one conformer as more stable than the others, which may account for the low selectivity observed in the synthesis of **23**.

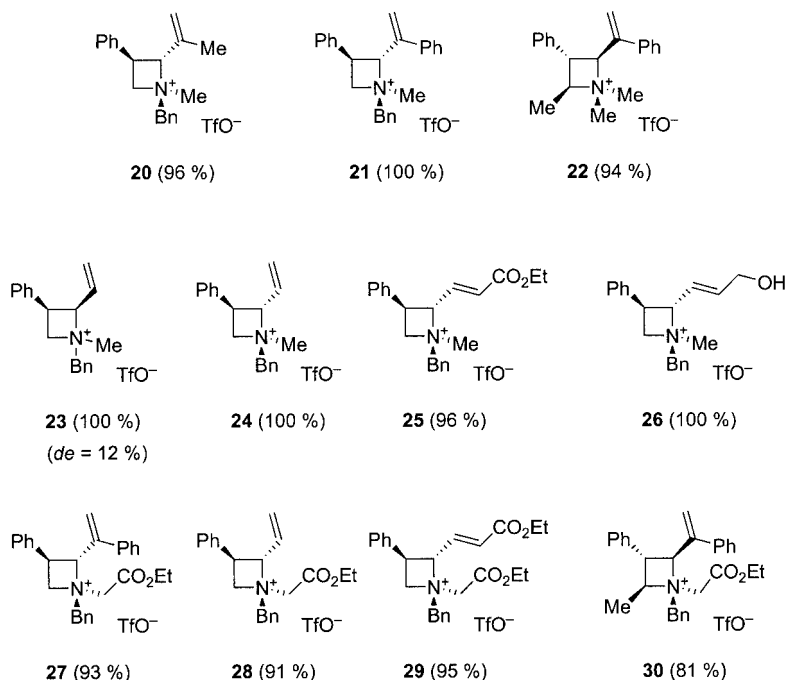
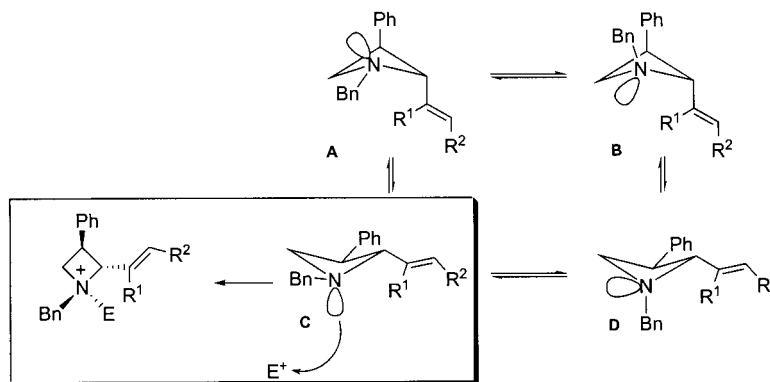


Figure 2. Prepared azetidinium trifluoromethanesulfonate salts.

Figure 3. Conformational analysis for 2,3-*trans*-azetidines.

With a set of representative azetidinium triflates at hand, we next focused on the reactivity of the ylides obtained after treatment with a strong base.

Stevens Rearrangements of 2-Alkenylazetidinium Salts

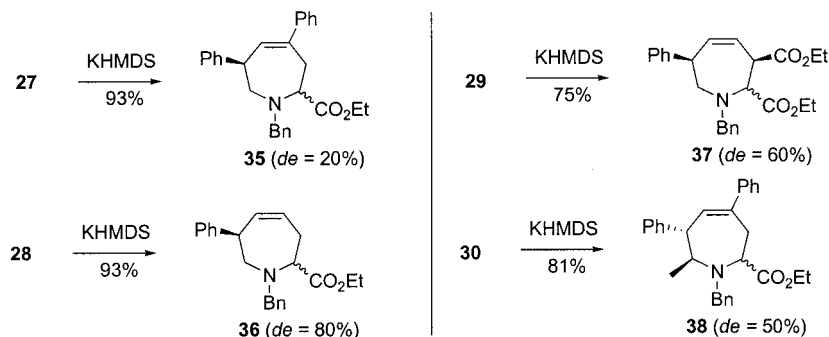
In order to perform the Stevens rearrangements, compounds **20**, **21** and **23–26**, all possessing methyl and benzyl groups on the nitrogen atom, were treated with KHMDS in THF at -78°C . Under these conditions, the 3-alkenylpyrrolidines **31–34** were cleanly produced with complete regioselectivity and moderate diastereoselectivity at C-2 (Table 1). The azetidinium salts **23** and **25**, however, failed to produce the desired pyrrolidines and gave complex mixtures of inseparable compounds.

[1,3] Shifts of Ylides Derived from 2-Alkenylazetidinium Salts

We next addressed the reactivity of azetidinium ions **27–30**, bearing ethoxycarbonylmethyl and benzyl groups – both groups susceptible to participation in rearrangement processes – on the nitrogen atom. Compounds **27–30** were therefore treated with KHMDS at -78°C as previously, and in this case we were pleased to observe that a completely different mechanistic pathway prevailed, since azepanes **35–38** were now produced in high yields and with variable diastereoselectivity at C-2 (Scheme 2). Interestingly, the crude reaction mixtures were systematically very clean, with no products resulting from Stevens rearrangements being detectable. The formation of seven-membered rings can be explained in terms of a [2,3] shift of the ylide generated after

Table 1. Stevens rearrangement of azetidinium ylides.

Substrate	Conditions	Product	Yield [%]	de [%]
20	KHMDS	31 (R = Ph, R' = H)	69	8
21	KHMDS	32 (R = Me, R' = H)	94	72
24	KHMDS	33 (R = H, R' = H)	83	6
26	KHMDS	34 (R = Ph, R' = CH ₂ OH)	72	12



Scheme 2. Formation of azepanes from azetidinium trifluoromethanesulfonate salts.

selective deprotonation α to the ester groups. Epimeric mixtures were in most cases difficult to separate by flash chromatography, but a pure sample of the major epimer **35a** could be obtained, allowing for its structure to be secured by X-ray crystallography^[15] (Figure 4), whilst the absolute configuration of the C-3 stereocenter in compound **37** was tentatively assigned on the basis of mechanistic considerations (vide infra).

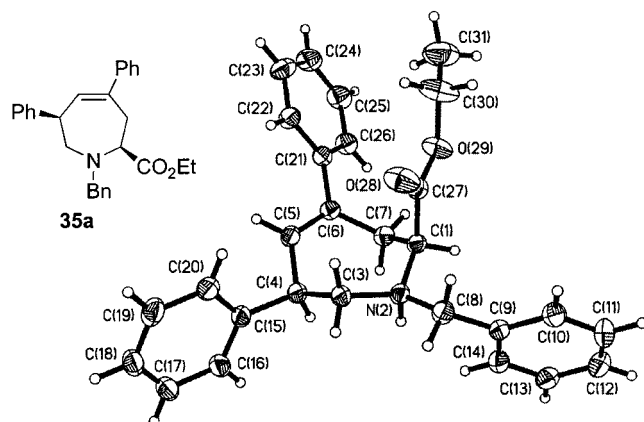


Figure 4. ORTEP view of azepane **35** (major 2,6-*cis* diastereoisomer).

Discussion

The dramatically different behaviour of the different azetidinium ylides, giving rise to the formation either of pyrrolidines or of azepanes, clearly depends on the relative configuration of the starting ylide (i.e., the relative stereochemistry between the ylide and the alkene group). On the one hand, the anions are generated at the benzylic positions of the quaternary amines when starting from azetidinium salts **20–21** and **24–26**, which means that these anions are in *trans* relationships with the adjacent alkenes: the two reacting centres for [2,3] shifts to produce azepanes are too far away from each other and so [1,2] shifts (Stevens rearrangements) occur exclusively, resulting in the selective formation of pyrrolidines. When, on the other hand, the anions are generated from azetidinium salts **27–30**, selective deprotonation occurs α to the ester moieties and the ylides now have *cis* relationships with the adjacent alkenes, so the two reacting centres involved in the [2,3] shift can efficiently overlap and this pathway now occurs exclusively.^[16] With regard to the configurations of the C-3 stereocenters in the pyrrolidines, these were deduced from the well-established fact^[17] that the migration during the Stevens rearrangement process occurs with retention of configuration. In the case of azepane **37** the absolute configuration at C-3 in the azepane is only tentatively assigned since we were not able to grow suitable crystals of one epimer and NOE experiments were inconclusive, so the assignment of the configuration is the result only of an examination of the possible transition states for the production of **37** (depicted in Figure 5).

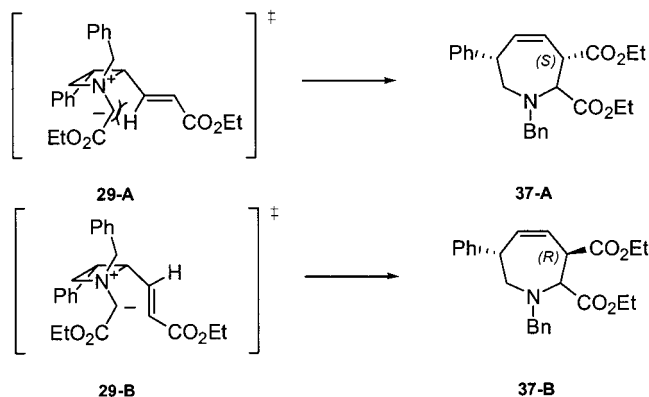


Figure 5. Possible transition states for the [2,3] shift in the ylide derived from **29**.

In the ylide derived from alkenylazetididine **29**, the alkene can adopt either an extended conformation (**29-A**) or a folded conformation (**29-B**). In the latter case, in which there is efficient overlap of the reacting centres, the *Si* face of the alkene can be attacked by the ylide without any steric congestion, which results in the formation of **37-B**, while in **29-A** overlapping of the reacting centres clearly brings about a severe steric interaction that probably disfavours the formation of **37-A** (Figure 5). The C-2 epimeric mixtures obtained in all these reactions are probably the results of unselective removal of the diastereotopic protons in the starting ammonium salts, resulting in (*Z*) and (*E*) mixtures of intermediate ylides. Finally, the complex mixtures obtained from **23** (epimeric mixture of ammonium salts) can be easily explained since both [1,2] or [2,3] shifts can occur, depending on the configuration of the starting ammonium. Moreover, the ammonium salt **25**, which also gives a complex mixture when treated with a base, might be deprotonated in a competitive manner at C-2 of the azetidinium ring, due to the presence of the vinylogous ester moiety: this would allow an epimerization at this stereocenter^[18] that would ultimately result in the two possible rearrangements.

In order to analyse the parameters governing the rearrangement processes further, we finally briefly studied the influence of the base used to promote the reactions, and eventually found that its nature was of great importance. On switching from KHMDS to phenyllithium, a base commonly used in similar reactions,^[7] different results were obtained depending on the starting azetidinium salt: while a Stevens rearrangement still occurred in the case of **26** (69% yield, 8% *de*), extensive degradation was observed in the case of substrates **20** and **24** and a surprising outcome was obtained with **21**, with S_N2' addition of the organolithium reagent occurring on the alkene, resulting in an opening of the azetidine to give alkene **39** with high (*E*) selectivity (Table 2, Entry 1): clearly, the S_N2' process is more rapid than the ylide formation in this isolated case. Similar behaviour was also noted with *n*-butyl or *tert*-butyllithium (Table 2, Entries 2 and 3), but in the latter case the stereoselectivity dropped. Azetidinium salt **22**, bearing a similar alkenyl side chain, behaved similarly with organolithium reagents (Table 2, Entries 4 and 5).

Table 2. S_N2' opening of azetidinium salts by organolithium reagents.

21, 22		RLi	Product	Yield [%]	(E)/(Z)
1	21	PhLi	39: R ¹ = Bn, R ² = H, R ³ = $\rightarrow$ Ph	80	>98:2
2	21	<i>n</i> BuLi	40: R ¹ = Bn, R ² = H, R ³ = $\rightarrow$ Ph	62	>98:2
3	21	<i>t</i> BuLi	41: R ¹ = Bn, R ² = H, R ³ = $\rightarrow$ Ph	quant.	65:35
4	22	PhLi	42: R ¹ = Me, R ² = $\rightarrow$ Me, R ³ = $\rightarrow$ Ph	58	>98:2
5	22	<i>n</i> BuLi	43: R ¹ = Me, R ² = $\rightarrow$ Me, R ³ = $\rightarrow$ Ph	62	65:35

This reaction was quite unexpected, since ammonium salts and amines have only seldom been reported to act as leaving groups in S_N2' reactions with organometallic reagents. As a matter of fact, such reactions are restricted to particular cases in which the functioning of the nitrogen atom as a leaving group is favoured by strain release, such as in 2-vinyl-^[19a] or 2-ethynyl-*N*-tosylaziridines.^[19b] This is indeed also the case with our strained, cyclic substrates and to the best of our knowledge represents the first example of ammonium ions acting as leaving groups in S_N2' processes involving organometallic nucleophiles.^[20] Interestingly, alkenes **39–43** are produced stereoselectively, and the exclusive (or major) isomer was in each case shown to have an (*E*) configuration by NOE experiments performed on **39** and **41**. This stereochemistry involves the reactive conformation of the double bond in the starting azetidinium ions being a folded one (Figure 6), as in the case of the formation of azepanes (Figure 5). We were not able to determine whether this reaction occurs through a *syn* or an *anti* mechanism, however, since it was restricted to this particular alkene substituted by a phenyl group. This last point, though, does give some insights into the mechanism of this reaction, which probably involves the creation of a transient partial negative charge – which would be stabilized by the aromatic ring – on the alkenyl carbon atom.

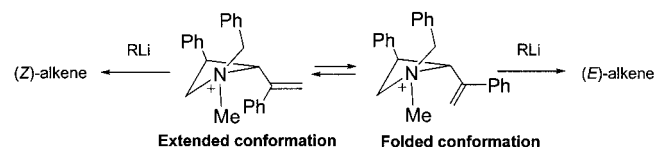


Figure 6. Organolithium reagents preferably react on the folded conformation of the alkene.

In conclusion, we have shown that efficient ring expansions, selectively leading either to pyrrolidines or to azepanes through [1,2] or [2,3] sigmatropic shifts, respectively, can be performed from 2-alkenylazetidinium salts. The sizes of the cyclic products obtained after rearrangement were shown to be dependent on the relative stereochemistry of the intermediate ylides. Furthermore, we have for the first time discovered an S_N2' reaction involving an organolithium reagent and an ammonium ion acting as a leaving group. This work reports an original route to azepane alkaloids, which are of high interest in view of their diverse biological activities,^[21] and gives further insights

into the underrated chemistry of functionalized azetidines, for which efficient asymmetric syntheses have emerged.^[22]

Experimental Section

General Comments: ¹H and ¹³C NMR spectra were recorded with a Bruker Avance 300 spectrometer at 300 and 75 MHz, respectively; chemical shifts are reported in ppm from TMS. Optical rotations were determined with a Perkin–Elmer 141 instrument. All the reactions were carried out under argon. Column chromatography was performed on silica gel (230–400 mesh) with various mixtures of diethyl ether (Et₂O), ethyl acetate (AcOEt), petroleum ether (PE) and cyclohexane (CyH). TLC was performed on Merck Kieselgel 60 F₂₅₄ plates. Melting points are uncorrected. THF and diethyl ether were distilled from sodium/benzophenone ketyl, and dichloromethane was distilled from calcium hydride. The mention of “usual workup” means: (i) decantation of the organic layer, (ii) extraction of the aqueous layer with diethyl ether, (iii) drying of the combined organic phases with MgSO₄, and (iv) solvent evaporation under reduced pressure. The compositions of the stereoisomeric mixtures were determined by NMR analysis on the crude products before any purification.

General Procedure for the Preparation of 2-Alkenylazetidines 14–18

Through Wittig Olefination of 2-Oxoazetidines: A solution of *n*-butyllithium (1.6 M in hexanes, 0.87 mL, 1.4 mmol) was added dropwise at 0 °C to a suspension of methyltriphenylphosphonium iodide (606 mg, 1.5 mmol) in dry THF (5 mL). After the mixture had been kept at 0 °C for 10 min, a solution of the required 2-oxoazetidine (1 mmol) in THF (2 mL) was added dropwise. After stirring at room temp. for 1 h, the reaction mixture was hydrolysed by addition of water. Usual workup (water/diethyl ether) provided a residue that was purified by flash chromatography.

(2*R*,3*R*)-1-Benzyl-3-phenyl-2-(1-phenylvinyl)azetidine (14): This compound was purified by flash chromatography (Et₂O/PE, 2:98, 5:95, 10:90, 20:80), yield: 79%, oil. [α]_D²⁰ = +59 (*c* = 1, CH₂Cl₂). ¹H NMR (CDCl₃): δ = 7.41–7.12 (m, 15 H, Ph), 5.66–5.65 (m, 1 H, HHC=), 5.42 (d, *J* = 2.0 Hz, 1 H, HHC=), 4.11 (d, *J* = 7.9 Hz, 1 H, 2-H), 4.00 (A part of AB system, *J* = 13.1 Hz, 1 H, NCHHPh), 3.70 (t, *J* = 7.2 Hz, 1 H, 3-H), 3.53–3.43 (m, 2 H, 4-H, NCHHPh), 3.07 (dd, *J* = 6.8 and 8.9 Hz, 1 H, 4'-H) ppm. ¹³C NMR: δ = 148.9 (C-q), 141.2, 139.9, 138.4 (C-*ipso* Ph), 128.9–126.6 (CHPh), 114.1 (CH₂), 76.0 (C-2), 62.1 (C-5), 57.6 (C-4), 45.2 (C-3) ppm. MS (ESI, pos.): *m/z* = 348.1 [M + Na]⁺, 326.1 [M + H]⁺.

(2*R*,3*R*)-1-Benzyl-2-isopropenyl-3-phenylazetidine (15): This compound was purified by flash chromatography (Et₂O/PE, 2:8), yield: 84%, oil. [α]_D²⁰ = –27 (*c* = 0.15, CH₂Cl₂). ¹H NMR (CDCl₃): δ = 7.40–7.20 (m, 10 H, Ph), 5.06 (s, 1 H, HHC=C), 4.85 (s, 1 H, HHC=), 3.91 (A part of AB system, *J* = 13.1 Hz, 1 H, NCHHPh), 3.70–3.63 (m, 2 H, 2-H, 4-H), 3.56–3.43 (m, 2 H, 3-H, NCHHPh), 2.97 (dd, *J* = 6.8 and 8.8 Hz, 1 H, 4'-H), 1.76 (s, 3 H, Me) ppm. ¹³C NMR: δ = 139.2 (C-q), 134.9, 134.0 (C-*ipso* Ph), 133.2, 131.4, 130.1, 129.5, 128.8, 127.6, 127.1 (CHPh), 124.2 (CH₂), 80.3 (C-2), 67.5 (CH₂), 63.8 (C-4), 44.7 (C-3), 36.7 (CH₃) ppm. MS (ESI, pos.): *m/z* = 286.1 [M + Na]⁺, 264.1 [M + H]⁺.

(2*S*,3*S*,4*S*)-1,6-Dimethyl-3-phenyl-2-(1-phenylvinyl)azetidine (16): This compound was purified by flash chromatography (Et₂O/PE, 10:90, 20:80, 50:50), *R*_f = 0.80 (Et₂O/PE, 1:1), yield: 86%, oil. [α]_D²⁰ = +13 (*c* = 1, CH₂Cl₂). ¹H NMR (CDCl₃): δ = 7.30–7.13 (m, 10 H, Ph), 5.54 (s, 1 H, HHC=), 5.40 (d, *J* = 0.3 Hz, 1 H, HHC=), 3.75 (dd, *J* = 0.9 and 7.7 Hz, 1 H, 2-H), 3.12–2.92 (m, 2 H, 4-H, 3-H), 2.41 (s, 3 H, NMe), 1.28 (d, *J* = 5.7 Hz, 3 H, Me) ppm.

^{13}C NMR: δ = 149.3 (C-q), 140.7, 140.2 (C-*ipso* Ph), 128.4–126.6 (CHPh), 113.8 (CH₂), 74.7 (C-2), 67.0 (C-4), 53.6 (C-3), 42.8 (CH₃), 20.3 (CH₃) ppm. MS (ESI, pos.): m/z = 286.1 [M+Na]⁺, 264.1 [M+H]⁺. C₂₄H₂₃N (325.45): calcd. C 88.57, H 7.12, N 4.30; found C 88.43, H 6.98, N 4.44.

Through Wittig Olefination of 2-Formylazetidines. First Step – Swern Oxidation: Oxalyl chloride (0.13 mL, 1.5 mmol) was added dropwise at -78°C to a solution of dry DMSO (0.12 mL, 1.7 mmol) in dichloromethane (6 mL). After the mixture had been stirred at -78°C for 20 min, a solution of the required 2-hydroxymethylazetidine (1 mmol) in dichloromethane (2 mL) was added dropwise, and after the mixture had additionally been stirred at -60°C for 0.5 h, triethylamine (0.52 mL, 3.7 mmol) was added dropwise. The temperature was slowly (1 h) raised to ca. -15°C and water was added. Usual workup (water/dichloromethane) gave the aldehyde, which was used crude in the olefination step. **Second Step – Wittig Olefination:** The following compounds were obtained by the described general procedure, starting either with the 2-oxoazetidine or with the crude 2-formylazetidine.

(2R,3R)-1-Benzyl-3-phenyl-2-vinylazetidine (17): This compound was purified by flash chromatography (Et₂O/PE, 2:98, 5:95), R_f = 0.77 (Et₂O/PE, 3:7), yield: 62%, oil. $[\alpha]_D^{20}$ = -10 (c = 0.7, CH₂Cl₂). ^1H NMR (CDCl₃): δ = 7.63–7.59 (m, 2 H, Ph), 7.55–7.33 (m, 8 H, Ph), 5.69–5.57 (m, 1 H, CH=CH₂), 5.32 (ddd, J = 1.2, 2.3 and 17.3 Hz, 1 H, CH=CHH), 5.07 (ddd, J = 0.77, 2.3 and 10.2 Hz, 1 H, CH=CHH), 4.13 (t, J = 7.3 Hz, 1 H, 2-H), 4.05 (A part of AB system, J = 13.5 Hz, 1 H, NCHHPh), 3.73 (td, J = 2.5 and 7.9 Hz, 1 H, 3-H), 3.62–3.57 (m, 2 H, 4-H, NCHHPh), 3.42 (t, J = 7.5 Hz, 1 H, 4'-H) ppm. ^{13}C NMR: δ = 140.6, 138.6 (C-*ipso* Ph), 136.7 (CH), 128.9, 128.6, 128.3, 128.2, 126.9, 126.4 (CHPh), 117.1 (CH₂), 71.3 (C-2), 61.3 (CH₂), 57.4 (C-4), 41.6 (C-3) ppm. MS (IC, NH₃): m/z = 250 [M+H]⁺.

(2S,3R)-1-Benzyl-3-phenyl-2-vinylazetidine (18): This compound was purified by flash chromatography (Et₂O/PE, 15:85), R_f = 0.38 (Et₂O/PE, 3:7), yield: 62%, oil. $[\alpha]_D^{20}$ = $+60$ (c = 0.6, CH₂Cl₂). ^1H NMR (CDCl₃): δ = 7.39–7.23 (m, 10 H, Ph), 6.09–5.98 (m, 1 H, CH=CH₂), 5.26 (ddd, J = 0.96, 1.74 and 17.2 Hz, 1 H, CH=CHH), 5.13 (ddd, J = 0.77, 1.93 and 10.2 Hz, 1 H, CH=CHH), 3.89 (A part of AB system, J = 12.7 Hz, 1 H, NCHHPh), 3.73 (q, J = 6.8 Hz, 1 H, 4-H), 3.66 (d, J = 7.5 Hz, 1 H, 2-H), 3.58 (t, J = 8.5 Hz, 1 H, 3-H), 3.55 (B part of AB system, J = 12.7 Hz, 1 H, NCHHPh), 3.07 (dd, J = 8.9 and 9.1 Hz, 1 H, 4'-H) ppm. ^{13}C NMR: δ = 141.2 (C-*ipso* Ph), 139.2 (CH), 138.1 (C-*ipso* Ph), 129.1, 128.5, 128.4, 127.2, 127.1, 126.6 (CHPh), 116.4 (CH₂), 75.5 (C-2), 62.2 (C-5), 57.9 (C-4), 43.4 (C-3) ppm. MS (IC, NH₃): m/z = 250 [M+H]⁺. HRMS: m/z calcd. for C₁₈H₂₀N [M+H]⁺ 250.1590; found 250.1585.

Ethyl 3-[(2S,3R)-1-Benzyl-3-phenylazetid-2-yl]acrylate (13): Oxalyl chloride (0.15 mL, 1.7 mmol) was added dropwise at -78°C to a solution of dry DMSO (0.14 mL, 1.9 mmol) in dichloromethane (8 mL). After the mixture had been stirred at -78°C for 20 min, a solution of the 2-(hydroxymethyl)azetidine **7** (289 mg, 1.14 mmol) in dichloromethane (3 mL) was added dropwise. After the mixture had additionally been stirred at -60°C for 0.5 h, triethylamine (0.60 mL, 4.2 mmol) was added dropwise, followed after 10 min by a solution of Ph₃P=CHCO₂Et (760 mg, 2.2 mmol) in dichloromethane (3 mL). The reaction mixture was allowed to slowly (1 h) reach room temp. and stirred for an additional hour and water was added. Usual workup (water/dichloromethane) gave an oil that was purified by flash chromatography (AcOEt/CyH, 10:90, 25:75). The title compound was obtained as an oil (239 mg, 84%), R_f = 0.63 (AcOEt/CyH, 1:1). $[\alpha]_D^{20}$ = -14 (c = 1.3, CH₂Cl₂). ^1H NMR

(CDCl₃): δ = 7.18–7.02 (m, 10 H, Ph), 6.86 (dd, J = 5.8 and 15.6 Hz, 1 H, CH=CHCO₂Et), 5.87 (dd, J = 1.35 and 15.6 Hz, 1 H, CH=CHCO₂Et), 4.03 (q, J = 7.1 Hz, 2 H, CH₂O), 3.69 (A part of AB system, J = 12.7 Hz, 1 H, NCHHPh), 3.63 (dd, J = 0.96 and 6.0 Hz, 1 H, 2-H), 3.55 (td, J = 0.6 and 7.5 Hz, 1 H, 4-H), 3.41–3.28 (m, 2 H, 3-H, NCHHPh), 2.91 (dd, J = 6.5 and 9.1 Hz, 1 H, 4'-H), 1.27 (t, J = 7.0 Hz, 3 H, Me) ppm. ^{13}C NMR: δ = 166.6 (CO), 147.7 (CH), 140.4, 137.7 (C-*ipso* Ph), 129.0, 128.6, 128.5, 127.4, 127.2, 127.0 (CHPh), 121.6 (CH), 72.9 (C-2), 62.2 (CH₂), 60.5 (CH₂), 57.9 (C-4), 43.8 (C-3), 14.4 (Me) ppm. MS (ESI, pos.): m/z = 344.1 [M+Na]⁺, 322.1 [M+H]⁺. HRMS: m/z calcd. for C₂₁H₂₄NO₂ [M+H]⁺ 322.1800; found 322.1802.

(2E)-3-[(2S,3R)-1-Benzyl-3-phenylazetid-2-yl]prop-2-en-1-ol (19): A solution of DIBALH in toluene (1.2 mL, 1.22 mmol) was added at -78°C to a solution of the above ester **13** (157 mg, 0.49 mmol) in THF (8 mL). The reaction mixture was gradually (1.5 h) warmed to -20°C with stirring and was hydrolyzed at this temperature by addition of an aqueous saturated solution of NH₄Cl (3 mL). Usual workup (water/diethyl ether) gave an oil that was used as such for the next step (137 mg, quant.). R_f = 0.46 (CH₂Cl₂/MeOH, 9:1). $[\alpha]_D^{20}$ = $+19$ (c = 1.1, CH₂Cl₂). ^1H NMR (CDCl₃): δ = 7.26–7.09 (m, 10 H, Ph), 5.79–5.61 (m, 2 H, CH=CH), 3.98 (d, J = 5.0 Hz, 2 H, CH₂O), 3.72 (A part of AB system, J = 12.7 Hz, 1 H, NCHHPh), 3.65–3.55 (m, 2 H, 2-H, 4-H), 3.50–3.36 (m, 2 H, 3-H, NCHHPh), 2.94 (dd, J = 6.6 and 9.1 Hz, 1 H, 4'-H), 1.89 (br. s, 1 H, OH) ppm. ^{13}C NMR: δ = 141.1, 137.9 (C-*ipso* Ph), 132.5, 131.6, 129.3, 128.5, 128.4, 128.3, 127.2, 127.1, 126.7, 125.4 (CHPh), 74.4 (C-2), 63.1 (CH₂O), 62.3 (NCH₂), 58.0 (C-4), 43.5 (C-3) ppm. MS (ESI, pos.): m/z = 302.1 [M+Na]⁺, 280.1 [M+H]⁺. HRMS: m/z calcd. for C₁₉H₂₁NO₂ [M+H]⁺ 280.1696; found 280.1683.

General Procedure for the Preparation of 2-Alkenylazetidinium Trifluoromethanesulfonates 20–30: Methyl trifluoromethanesulfonate (0.225 mL, 2 mmol) or ethyl trifluoromethylsulfonyloxyacetate (472 mg, 2.0 mmol) was added dropwise at 0°C to a solution of the azetidine (1 mmol) in dichloromethane (5 mL). The mixture was stirred at room temp. for 1 h and the solvent was then evaporated under reduced pressure. The residue was washed with small quantities of dry diethyl ether and then dried under vacuum.

(2R,3R)-1-Benzyl-2-(1-methylvinyl)-3-phenylazetidinium Trifluoromethanesulfonate (20): Yield: 96%, white solid; m.p. 142°C . $[\alpha]_D^{20}$ = $+43$ (c = 0.3, CH₂Cl₂). ^1H NMR ([D₆]acetone): δ = 7.72–7.68 (m, 2 H, Ph), 7.46–7.39 (m, 3 H, Ph), 7.28–7.16 (m, 5 H, Ph), 5.59 (s, 1 H, C=CHH), 5.52 (d, J = 1.6 Hz, 1 H, C=CHH), 5.40–5.32 (m, 1 H, 4-H), 5.04 (A part of AB system, J = 12.9 Hz, 1 H, NCHHPh), 4.72 (B part of AB system, J = 12.9 Hz, 1 H, NCHHPh), 4.71–4.59 (m, 2 H, 2-H, 4'-H), 4.12–4.0 (m, 1 H, 3-H), 3.07 (s, 3 H, NMe), 1.95 (s, 3 H, Me) ppm. ^{13}C NMR: δ = 141.2 (C-*ipso* Ph), 139.2 (CH), 138.1 (C-*ipso* Ph), 129.1, 128.5, 128.4, 127.2, 127.1, 126.6 (CHPh), 116.4 (CH₂), 75.5 (C-2), 62.2 (CH₃), 57.9 (C-4), 43.4 (C-3) ppm. MS (ESI, pos.): m/z = 278.1 [M – OTf]⁺.

(2R,3R)-1-Benzyl-3-phenyl-2-(1-phenylvinyl)azetidinium Trifluoromethanesulfonate (21): Yield: quant; oil. $[\alpha]_D^{20}$ = $+90$ (c = 1, acetone). ^1H NMR ([D₆]acetone): δ = 7.50–7.21 (m, 15 H, Ph), 5.96–5.83 (m, 3 H, 2-H, C=CH₂), 4.75–4.51 (m, 3 H, 3-H, 4-H, CHHPh), 3.89–3.82 (m, 2 H, 4'-H, CHHPh), 2.94 (s, 3 H, Me) ppm. ^{13}C NMR: δ = 139.2, 137.7, 134.6, 132.2 (C-*ipso* Ph, C-7), 130.9, 129.6, 129.4, 128.7, 127.7, 127.4, 125.6 (CHPh), 80.6 (C-2), 67.9 (CH₂), 64.5 (C-4), 43.6 (Me), 37.6 (C-3) ppm. MS (ESI, pos.): 340.2 [M – OTf]⁺. C₂₆H₂₆F₃NO₃S (489.55): calcd. C 63.79, H 5.35, N 2.86; found C 63.62, H 5.54, N 2.72.

(2S,3S,4S)-1,1,4-Trimethyl-3-phenyl-2-(1-phenylvinyl)azetidinium Trifluoromethanesulfonate (22): Yield: 94%; white solid; m.p. 182 °C. $[\alpha]_D^{20} = +54$ ($c = 0.4$, CH₂Cl₂). ¹H NMR ([D₆]acetone): $\delta = 7.76$ – 7.64 (m, 4 H, Ph), 7.54 – 7.33 (m, 6 H, Ph), 6.17 (d, $J = 10.5$ Hz, 1 H, 2-H), 5.93 (s, 2 H, C=CH₂), 4.95 – 4.80 (m, 1 H, 4-H), 4.58 (t, $J = 10.5$ Hz, 1 H, 3-H), 3.24 (s, 3 H, NMe), 2.96 (s, 3 H, NMe), 1.67 (d, $J = 6.6$ Hz, 3 H, Me) ppm. ¹³C NMR: $\delta = 140.0$, 138.7 (C-*ipso* Ph), 135.6 (C-q), 130.1 – 128.0 (CHPh), 124.4 (CH₂), 79.9 , 76.9 (C-5, C-6), 53.0 (C-2), 45.9 (C-4), 40.0 (C-3), 12.8 (CH₃) ppm. MS (ESI, pos.): $m/z = 277.1$ [M – OTf]⁺. C₂₁H₂₄F₃NO₃S (427.48): calcd. C 59.00, H 5.66, N 3.28; found C 59.29, H 5.72, N 3.36.

(2R,3R)-1-Benzyl-1-methyl-3-phenyl-2-vinylazetidinium Trifluoromethanesulfonate (23): Yield: quant; oil; mixture of stereoisomers. ¹H NMR ([D₆]acetone): $\delta = 7.86$ – 7.82 (m, 2 H, Ph), 7.77 – 7.74 (m, 3 H, Ph), 7.63 – 7.51 (m, 5 H, Ph), 7.48 – 7.32 (m, 10 H, Ph), 6.37 (td, $J = 10.2$ and 17.0 Hz, 1 H, CH=CH₂), 5.97 – 5.79 (m, 3 H), 5.71 (dd, $J = 1.4$ Hz, 1 H), 5.65 (d, $J = 1.4$ Hz, 1 H), 5.61 – 5.50 (m, 4 H), 5.22 – 5.15 (m, 1 H), 5.07 (s, 2 H), 5.0 – 4.90 (m, 2 H), 4.84 (A part of AB system, $J = 12.9$ Hz, 1 H, CHHPh), 4.47 – 4.39 (m, 1 H), 4.36 (B part of AB system, $J = 12.9$ Hz, 1 H, CHHPh), 3.49 (s, 3 H, Me for major isomer), 3.07 (s, 3 H, Me for minor isomer) ppm.

(2S,3R)-1-Benzyl-1-methyl-3-phenyl-2-vinylazetidinium Trifluoromethanesulfonate (24): Yield: quant; oil. $[\alpha]_D^{20} = -13$ ($c = 0.4$, acetone). ¹H NMR ([D₆]acetone): $\delta = 7.55$ – 7.41 (m, 5 H, Ph), 7.31 – 7.23 (m, 3 H, Ph), 7.12 – 7.09 (m, 2 H, Ph), 5.98 – 5.86 (m, 1 H, CH=CH₂), 5.62 (d, $J = 3.7$ Hz, 1 H, CH=CHH), 5.57 (d, $J = 3.5$ Hz, 1 H, CH=CHH), 5.16 (t, $J = 7.1$ Hz, 1 H, 2-H), 4.70 (A part of AB system, $J = 13.1$ Hz, 1 H, NCHHPh), 4.62 (B part of AB system, $J = 13.1$ Hz, 1 H, NCHHPh), 4.47 (t, $J = 8.7$ Hz, 1 H, 4-H), 4.37 – 4.31 (m, 1 H, 3-H), 4.28 – 4.22 (m, 1 H, 4'-H), 3.12 (s, 3 H, NMe) ppm. ¹³C NMR: $\delta = 135.0$ (C-*ipso* Ph), 132.5 , 130.9 , 129.7 , 129.3 , 128.5 (CHPh), 128.3 (CH), 127.7 (CH₂), 127.3 , 126.9 (CHPh), 79.4 (C-2), 67.4 (CH₂), 65.9 (C-4), 44.0 (C-5), 38.2 (C-3) ppm. MS (ESI, pos.): $m/z = 264.1$ [M – OTf]⁺.

(2S,3R)-1-Benzyl-2-(3-hydroxy-1-propenyl)-1-methyl-3-phenylazetidinium Trifluoromethanesulfonate (26): Yield: quant; oil. $[\alpha]_D^{20} = -18$ ($c = 0.8$, acetone). ¹H NMR ([D₆]acetone): $\delta = 7.68$ – 7.64 (m, 2 H, Ph), 7.45 – 7.38 (m, 3 H, Ph), 7.29 – 7.17 (m, 5 H, Ph), 6.35 (tdd, $J = 0.8$, 3.7 and 15.5 Hz, 1 H, CH=CH), 5.96 (tdd, $J = 1.9$, 7.9 and 15.5 Hz, 1 H, CH=CH), 5.45 (t, $J = 9.8$ Hz, 1 H, 2-H), 4.83 (A part of AB system, $J = 13.1$ Hz, 1 H, NCHHPh), 4.75 (B part of AB system, $J = 13.1$ Hz, 1 H, NCHHPh), 4.69 (t, $J = 10.2$ Hz, 1 H, 4-H), 4.51 (qd, $J = 10.2$ and 1.7 Hz, 1 H, 3-H), 4.29 (dd, $J = 8.5$ and 9.4 Hz, 1 H, 4'-H), 4.03 – 4.01 (m, 2 H, CH₂O), 3.09 (s, 3 H, NMe) ppm. ¹³C NMR: $\delta = 146.7$ (CH), 136.9 (C-*ipso* Ph), 133.1 (CHPh), 131.3 (C-*ipso* Ph), 130.1 , 129.7 , 129.4 , 128.9 , 128.2 (CHPh), 118.4 (CH), 81.6 (C-2), 68.1 (CH₂), 66.6 (C-4), 61.7 (CH₂), 43.6 (Me), 39.7 (C-3) ppm. MS (ESI, pos.): $m/z = 294.1$ [M – OTf]⁺.

(2R,3R)-1-Benzyl-1-[(ethoxycarbonyl)methyl]-3-phenyl-2-(1-phenylvinyl)azetidinium Trifluoromethanesulfonate (27): Yield: 93%; white solid; m.p. 57 °C. $[\alpha]_D^{20} = +7$ ($c = 0.5$, acetone). ¹H NMR ([D₆]acetone): $\delta = 7.69$ – 7.22 (m, 13 H, Ph), 6.90 – 6.86 (m, 2 H, Ph), 6.40 (s, 1 H, C=CHH), 5.99 (s, 1 H, C=CHH), 5.65 (d, $J = 10.8$ Hz, 1 H, 2-H), 5.34 (A part of AB system, $J = 17.1$ Hz, 1 H, CHHCO), 5.05 (q, $J = 10.2$ Hz, 1 H, 3-H), 4.83 (t, $J = 10.5$ Hz, 1 H, 4-H), 4.70 (A' part of A'B' system, $J = 12.9$ Hz, 1 H, NCHHPh), 4.43 – 4.28 (m, 3 H, 4'-H, CH₂O), 3.86 (B' part of A'B' system, $J = 13.2$ Hz, 1 H, NCHHPh), 3.73 (B part of AB system, $J = 17.1$ Hz, 1 H, CHHCO), 1.39 (t, $J = 7.1$ Hz, 3 H, Me) ppm. ¹³C NMR: $\delta =$

165.1 (CO), 138.7 , 137.5 , 135.1 , 132.7 , 131.4 , 129.9 , 129.7 , 129.6 , 129.4 , 129.1 (C-*ipso* Ph, CHPh, C=CH₂), 128.6 (C=CH₂), 127.4 , 127.3 (CHPh), 81.0 (C-2), 65.0 (CH₂), 63.2 , 62.8 (C-4, CH₂), 54.8 (CH₂O), 36.6 (C-3), 13.9 (Me) ppm. MS (IC, NH₃, pos.): $m/z = 412$ [M – OTf]⁺.

(2S,3R)-1-Benzyl-1-[(ethoxycarbonyl)methyl]-3-phenyl-2-vinylazetidinium Trifluoromethanesulfonate (28): Yield: 91%; oil. $[\alpha]_D^{20} = -30$ ($c = 1.7$, acetone). ¹H NMR ([D₆]acetone): $\delta = 7.59$ – 7.46 (m, 5 H, Ph), 7.28 – 7.22 (m, 3 H, Ph), 7.10 – 7.07 (m, 2 H, Ph), 6.02 – 5.91 (m, 1 H, CH=CH₂), 5.70 (d, $J = 17.1$ Hz, 1 H, CH=CHH), 5.60 (d, $J = 10.4$ Hz, 1 H, CH=CHH), 5.38 (dd, $J = 6.8$ and 9.8 Hz, 1 H, 2-H), 4.98 (A part of AB system, $J = 13.3$ Hz, 1 H, NCHHPh), 4.87 – 4.76 (m, 3 H, 4-H, NCHHPh, CHHCO), 4.65 (q, $J = 9.4$ Hz, 1 H, 3-H), 4.44 (t, $J = 10.0$ Hz, 1 H, 4'-H), 4.25 – 4.35 (m, 2 H, CH₂O), 3.88 (B' part of A'B' system, $J = 17.3$ Hz, 1 H, CHHCO), 1.32 (t, $J = 7.1$ Hz, 3 H, Me) ppm. ¹³C NMR: $\delta = 165.3$ (CO), 135.1 , 132.5 (C-*ipso* Ph), 131.3 (CH=CH₂), 129.9 , 129.3 (CHPh), 129.1 (CH=CH₂), 128.5 , 127.7 , 127.3 , 126.4 (CHPh), 81.7 (C-2), 65.4 , 65.2 (C-4, C-5), 63.1 (NCH₂), 53.7 (OCH₂), 37.2 (C-3), 13.9 (Me) ppm. MS (ESI, pos.): $m/z = 336.1$ [M – OTf]⁺. C₂₃H₂₆F₃NO₅S (485.52): calcd. C 56.90, H 5.40, N 2.88; found C 57.02, H 5.42, N 2.92.

(2S,3R)-1-Benzyl-1-[(ethoxycarbonyl)methyl]-2-[2-(ethoxycarbonylvinyl)-3-phenylazetidinium Trifluoromethanesulfonate (29): Yield: 95%; oil. $[\alpha]_D^{20} = -74$ ($c = 0.3$, acetone). ¹H NMR ([D₆]acetone): $\delta = 7.78$ – 7.74 (m, 2 H, Ph), 7.64 – 7.56 (m, 3 H, Ph), 7.43 – 7.30 (m, 5 H, Ph), 7.03 (dd, $J = 7.1$ and 15.8 Hz, 1 H, CH=CH), 6.47 (dd, $J = 1.2$ and 15.6 Hz, 1 H, CH=CH), 6.03 (td, $J = 1.2$ and 8.1 Hz, 1 H, 2-H), 5.34 (A part of AB system, $J = 13.3$ Hz, 1 H, NCHHPh), 5.19 (B part of AB system, $J = 13.3$ Hz, 1 H, NCHHPh), 5.09 – 4.82 (m, 4 H, 3-H, 4-H, CH₂CO), 4.43 – 4.26 (m, 3 H, 4'-H, OCH₂), 4.16 (q, $J = 7.1$ Hz, 2 H, OCH₂), 1.34 (t, $J = 7.1$ Hz, 3 H, Me), 1.23 (t, $J = 7.1$ Hz, 3 H, Me) ppm. ¹³C NMR: $\delta = 165.9$, 164.7 (CO), 135.9 (CH), 134.5 , 133.3 (C-*ipso* Ph), 132.4 – 128.2 (CHPh, CH), 80.5 (C-2), 66.9 , 66.7 (CH₂), 63.5 , 61.6 (OCH₂), 54.2 (C-4), 38.5 (C-3), 14.3 , 14.1 (Me) ppm. MS (ESI, pos.): $m/z = 408.3$ [M – OTf]⁺.

(2S,3S,4S)-1-Benzyl-1-[(ethoxycarbonyl)methyl]-4-methyl-3-phenyl-2-(1-phenylvinyl)azetidinium Trifluoromethanesulfonate (30): Yield: 81%; white solid. $[\alpha]_D^{20} = -19$ ($c = 0.7$, acetone). ¹H NMR ([D₆]acetone): $\delta = 7.68$ – 7.34 (m, 15 H, Ph), 6.45 (s, 1 H, C=CHH), 6.26 (s, 1 H, C=CHH), 6.24 (d, $J = 11.2$ Hz, 1 H, 2-H), 5.62 (A part of AB system, $J = 12.7$ Hz, 1 H, NCHHPh), 5.39 (B part of AB system, $J = 12.7$ Hz, 1 H, NCHHPh), 4.89 – 4.69 (m, 3 H, 3-H, 4-H, CHHCO), 4.25 – 4.21 (m, 2 H, OCH₂), 4.16 (B' part of A'B' system, $J = 17.3$ Hz, 1 H, CHHCO), 1.39 (d, $J = 6.6$ Hz, 3 H, Me), 1.30 (t, $J = 7.1$ Hz, 3 H, Me) ppm. ¹³C NMR: $\delta = 166.1$ (CO), 142.4 (C-q), 139.1 , 138.7 , 136.1 (C-*ipso* Ph), 134.8 – 127.3 (CHPh), 120.4 (CH₂), 81.1 (C-2), 66.0 , 65.7 (CH₂), 63.3 (CH₂O), 58.4 (C-4), 46.1 (C-3), 14.5 (Me), 14.2 (Me) ppm. MS (ESI, pos.): $m/z = 426.3$ [M – OTf]⁺.

General Procedure for the Ring Expansions Starting from 2-Alkenylazetidinium Trifluoromethanesulfonates: A solution of KHMDS (0.5 M in toluene, 2.4 mL, 1.2 mmol) was added dropwise at -78 °C to a solution of 2-alkenylazetidinium salt (1 mmol) in THF (6 mL). The temperature was slowly (1.5 h) raised to -30 °C and the mixture was hydrolyzed at this temperature by addition of a saturated aqueous solution of NH₄Cl (5 mL). Usual workup gave an oil that was purified by flash chromatography.

(2R,3S,4R)- and (2S,3S,4R)-1-Methyl-2,4-diphenyl-3-(1-phenylvinyl)pyrrolidine (31): This compound was purified by preparative TLC (Et₂O/PE, 6:4), inseparable mixture of two isomers at C-2 in

a 54:46 ratio; yield: 68%, oil. The following data are characteristic of the major isomer. R_f = 0.67 (Et₂O/PE, 4:6). ¹H NMR (CDCl₃): δ = 7.55–6.82 (m, 15 H, Ph), 5.19 (s, 1 H, C=CHH), 5.14 (s, 1 H, C=CHH), 3.92 (d, J = 8.1 Hz, 1 H, 2-H), 3.70–3.39 (m, 3 H, 4-H, 5-H, 5'-H), 3.06 (t, J = 9.4 Hz, 1 H, 3-H), 2.58 (s, 3 H, NMe) ppm. ¹³C NMR: δ = 147.3 (C-q), 143.0, 142.2, 141.6 (C-*ipso* Ph), 129.5–126.3 (CHPh), 115.6 (CH₂), 74.3 (C-2), 63.7 (C-5), 55.1 (C-3), 49.9 (C-4), 40.7 (Me) ppm. MS (ESI, pos.): m/z = 340.1 [M + H]⁺.

(2R,3S,4R)- and (2S,3S,4R)-3-Isopropenyl-1-methyl-2,4-diphenylpyrrolidine (32): This compound was purified by flash chromatography (Et₂O/PE, 2:98, 5:95, 10:90), mixture of two isomers at C-2 in a 86:14 ratio; overall yield: 94%, oil. Isolated major isomer: R_f = 0.71 (Et₂O/PE, 3:7). $[a]_D^{20}$ = –16 (c = 0.6, CH₂Cl₂). ¹H NMR (CDCl₃): δ = 7.35–7.09 (m, 10 H, Ph), 4.64–4.56 (m, 1 H, C=CHH), 4.55–4.53 (m, 1 H, C=CHH), 3.65 (d, J = 10.2 Hz, 1 H, 2-H), 3.56–3.42 (m, 2 H, 4-H, 5-H), 3.11 (t, J = 9.2 Hz, 1 H, 3-H), 2.49 (td, J = 0.96 and 8.5 Hz, 1 H, 5'-H), 2.24 (s, 3 H, NMe), 1.13 (s, 3 H, Me) ppm. ¹³C NMR: δ = 144.3, 142.6 (C-*ipso* Ph), 140.6 (C-q), 129.0, 128.6, 128.5, 128.4, 127.9, 127.7, 127.6, 127.5, 127.4, 126.8 (CHPh), 113.9 (CH₂), 74.4 (C-2), 64.0 (C-5), 59.3 (C-3), 47.0 (C-4), 41.2 (Me), 22.4 (Me) ppm. MS (ESI, pos.): m/z = 300.1 [M + Na]⁺, 278.1 [M + H]⁺. C₂₀H₂₃N (277.4): calcd. C 86.59, H 8.36, N 5.05; found C 86.47, H 8.25, N 4.92. Isolated minor isomer: R_f = 0.57 (Et₂O/PE, 3:7). $[a]_D^{20}$ = –22 (c = 0.3, CH₂Cl₂). ¹H NMR (CDCl₃): δ = 7.46–7.23 (m, 10 H, Ph), 4.74 (s, 1 H, C=CHH), 4.65 (s, 1 H, C=CHH), 3.76 (d, J = 10.1 Hz, 1 H, 2-H), 3.66–3.52 (m, 2 H, 4-H, 5-H), 3.21 (t, J = 9.6 Hz, 1 H, 3-H), 2.69–2.56 (m, 1 H, 5'-H), 2.34 (s, 3 H, NMe), 1.23 (s, 3 H, Me) ppm. ¹³C NMR: δ = 144.3, 142.6 (C-*ipso* Ph), 140.7 (C-q), 129.0, 128.6, 128.5, 128.4, 127.9, 127.7, 127.6, 127.5, 127.4, 126.5 (CHPh), 113.1 (CH), 76.2 (C-2), 64.1 (C-5), 59.3 (C-3), 47.6 (C-4), 40.8 (NMe), 20.5 (Me) ppm. MS (ESI, pos.): m/z = 300.1 [M + Na]⁺, 278.1 [M + H]⁺.

(2R,3S,4R)- and (2S,3S,4R)-1-Methyl-2,4-diphenyl-3-vinylpyrrolidine (33): This compound was purified by flash chromatography (Et₂O/PE, 5:95, 10:90, 15:85), mixture of two isomers at C-2 in a 53:47 ratio; overall yield: 83%, oil. Isolated major isomer: R_f = 0.78 (Et₂O/PE, 3:7). $[a]_D^{20}$ = +27 (c = 0.1, CH₂Cl₂). ¹H NMR (CDCl₃): δ = 7.44–7.21 (m, 10 H, Ph), 5.37 (td, J = 9.8 and 16.8 Hz, 1 H, CH=CH₂), 4.66–4.58 (m, 2 H, CH=CH₂), 3.71 (d, J = 9.6 Hz, 1 H, 2-H), 3.55 (dd, J = 6.7 and 8.9 Hz, 1 H, 5-H), 3.28 (td, J = 6.8 and 10.6 Hz, 1 H, 4-H), 3.05 (q, J = 9.1 Hz, 1 H, 3-H), 2.63 (dd, J = 9.1 and 10.4 Hz, 1 H, 5'-H), 2.34 (s, 3 H, NMe) ppm. ¹³C NMR: δ = 142.2 (C-*ipso* Ph), 139.3 (CH), 128.6, 128.4, 128.0, 127.8, 127.4, 126.8, 126.4 (CHPh), 114.9 (CH₂), 74.9 (C-2), 64.1 (C-5), 56.8 (C-3), 50.1 (C-4), 40.9 (C-6) ppm. MS (ESI, pos.): m/z = 286.1 [M + Na]⁺, 264.1 [M + H]⁺. HRMS: m/z calcd. for C₁₉H₂₂N [M + H]⁺ 264.1747; found 264.1758. Isolated minor isomer: R_f = 0.77 (Et₂O/PE, 3:7). $[a]_D^{20}$ = –63 (c = 0.3, CH₂Cl₂). ¹H NMR (CDCl₃): δ = 7.46–7.19 (m, 10 H, Ph), 5.89–5.71 (m, 1 H, CH=CH₂), 4.90 (dd, J = 1.4 and 10.2 Hz, 1 H, CH=CHH), 4.67 (dd, J = 0.66 and 17 Hz, 1 H, CH=CHH), 3.41 (dd, J = 3.3 and 9.8 Hz, 1 H, 5-H), 3.22–3.12 (m, 1 H, 4-H), 3.07 (d, J = 9.4 Hz, 1 H, 2-H), 2.91 (t, J = 9.6 Hz, 1 H, 5'-H), 2.70 (q, J = 8.3 Hz, 1 H, 3-H), 2.22 (s, 3 H, NMe) ppm. ¹³C NMR: δ = 146.2, 141.0 (C-*ipso* Ph), 138.0 (C-q), 128.6, 128.4, 128.3, 128.1, 127.6, 127.4, 126.2 (CHPh), 116.3 (CH₂), 78.1 (C-2), 63.7 (C-5), 63.5 (C-3), 48.9 (C-4), 40.8 (C-6) ppm. MS (ESI, pos.): m/z = 286.1 [M + Na]⁺, 264.1 [M + H]⁺.

3-[(2R,3S,4R)- and (2S,3S,4R)-1-Methyl-2,4-diphenylpyrrolidin-3-yl]prop-2-en-1-ol (34): For this compound, 2.2 equiv. of KHMDS was used. This compound was purified by flash chromatography (Et₂O/PE, 5:95, 10:90, 15:85), mixture of two isomers at C-2 in a

58:42 ratio; overall yield: 72%, oil. Isolated major isomer: R_f = 0.65 (Et₂O/PE, 9:1). $[a]_D^{20}$ = –53 (c = 0.3, CH₂Cl₂). ¹H NMR (CDCl₃): δ = 7.33–7.07 (m, 10 H, Ph), 5.55 (tdd, J = 1.6, 8.1 and 15.4 Hz, 1 H, CH=CH), 5.14 (tdd, J = 0.96, 5.6 and 15.4 Hz, 1 H, CH=CH), 3.84 (dd, J = 0.96 and 5.6 Hz, 2 H, CH₂O), 3.27 (dd, J = 3.3 and 9.6 Hz, 1 H, 5-H), 3.07–3.00 (m, 1 H, 4-H), 2.95 (d, J = 9.5 Hz, 1 H, 2-H), 2.79 (t, J = 9.6 Hz, 1 H, 5'-H), 2.62 (q, J = 8.1 Hz, 1 H, 3-H), 2.09 (s, 3 H, NMe) ppm. ¹³C NMR: δ = 145.9 (CH), 140.8 (CH), 131.4, 131.0 (C-*ipso* Ph), 128.6, 128.4, 128.2, 128.1, 127.6, 127.5, 126.3 (CHPh), 78.2 (C-2), 63.7 (C-5), 63.3 (CH₂O), 61.6 (C-3), 49.1 (C-4), 40.7 (C-6) ppm. MS (ESI, pos.): m/z = 294.1 [M + H]⁺. C₂₀H₂₃NO (293.4): calcd. C 81.87, H 7.90, N 4.77; found C 81.74, H 7.83, N 4.89. Isolated minor isomer: R_f = 0.55 (Et₂O/PE, 9:1). $[a]_D^{20}$ = –34 (c = 0.6, CH₂Cl₂). ¹H NMR (CDCl₃): δ = 7.26–7.08 (m, 10 H, Ph), 5.19–5.04 (m, 2 H, CH=CH), 3.62–3.57 (m, 32 H, CH₂O, 2-H), 3.44 (dd, J = 6.7 and 9.1 Hz, 1 H, 5-H), 3.17 (td, J = 7.5 and 10.5 Hz, 1 H, 4-H), 2.95 (q, J = 8.5 Hz, 1 H, 3-H), 2.50 (dd, J = 9.1 and 10.4 Hz, 1 H, 5'-H), 2.22 (s, 3 H, NMe) ppm. ¹³C NMR: δ = 142.3 (CH), 140.2 (CH), 134.5, 130.1 (C-*ipso* Ph), 128.7, 128.5, 128.1, 127.8, 127.0, 126.6 (CHPh), 75.3 (C-2), 64.3 (C-5), 63.2 (CH₂O), 55.2 (C-3), 50.3 (C-4), 40.9 (NMe) ppm. MS (ESI, pos.): m/z = 294.1 [M + H]⁺.

Ethyl (2R,6R)- and (2S,6R)-1-Benzyl-4,6-diphenyl-2,3,6,7-tetrahydro-1H-azepane-2-carboxylate (35): This compound was purified by flash chromatography (Et₂O/PE, 5:95, 10:90, 15:85), mixture of two isomers at C-2 in a 60:40 ratio; overall yield: 93%, oil. Isolated major isomer: R_f = 0.56 (Et₂O/PE, 3:7). $[a]_D^{20}$ = +6 (c = 0.4, CH₂Cl₂). ¹H NMR (CDCl₃): δ = 7.41–7.20 (m, 15 H, Ph), 6.04 (d, J = 4.1 Hz, 1 H, 5-H), 4.19 (q, J = 7.1 Hz, 2 H, CH₂O), 4.09 (t, J = 4.0 Hz, 1 H, 2-H), 3.95–3.82 (m, 3 H, 6-H, NCH₂Ph), 3.26–3.08 (m, 4 H, 3-H, 3'-H, 7-H, 7'-H), 1.22 (t, J = 7.1 Hz, 3 H, Me) ppm. ¹³C NMR: δ = 173.9 (CO), 144.7, 144.3, 138.9 (C-*ipso* Ph, C-4), 133.4 (C-5), 128.9–126.2 (CHPh), 64.3 (C-2), 60.8 (CH₂O), 59.4 (NCH₂), 57.2 (C-3), 46.3 (C-6), 32.1 (C-7), 14.3 (Me) ppm. MS (IC, NH₃): m/z = 412 [M + H]⁺. Minor isomer (not isolated pure): R_f = 0.55 (Et₂O/PE, 3:7). ¹H NMR (CDCl₃): δ = 7.33–7.11 (m, 15 H, Ph), 6.04 (d, J = 4.1 Hz, 1 H, 5-H), 5.56–3.88 (m, 5 H, 2-H, NCH₂, CH₂O), 3.73 (dd, J = 2.7 and 8.7 Hz, 1 H, 6-H), 3.57 (dd, J = 10.8 and 11 Hz, 1 H, 3-H), 3.26 (ddd, J = 1.35, 8.7, 15.6 Hz, 1 H, 7-H), 2.99 (dd, J = 2.5 and 15.6 Hz, 1 H, 7'-H), 2.74 (dd, J = 2.7 and 13.7 Hz, 1 H, 3'-H), 0.99 (t, J = 7.1 Hz, 3 H, Me) ppm. ¹³C NMR: δ = 173.2 (CO), 144.9, 144.0, 139.4, 139.0 (C-*ipso* Ph, C-4), 134.5 (C-5), 128.8–126.1 (CHPh), 63.0 (C-2), 60.4 (CH₂O and CH₂N), 55.1 (C-3), 46.1 (C-6), 34.6 (C-7), 14.1 (Me) ppm. HRMS: m/z calcd. for C₂₈H₃₀NO₂ [M + H]⁺ 412.2271; found 412.2270.

Ethyl (2R,6R)- and (2S,6R)-1-Benzyl-6-phenyl-2,3,6,7-tetrahydro-1H-azepane-2-carboxylate (36): This compound was purified by flash chromatography (Et₂O/PE, 5:95, 10:90, 15:85), mixture of two isomers at C-2 in a 90:10 ratio; overall yield: 99%, oil. Major isomer (not isolated pure): R_f = 0.55 (Et₂O/PE, 3:7). ¹H NMR (CDCl₃): δ = 7.40–7.15 (m, 10 H, Ph), 5.81–5.74 (m, 2 H, 4-H, 5-H), 4.21 (q, J = 7.1 Hz, 2 H, CH₂O), 3.98–3.94 (m, 1 H, 6-H), 3.84–3.81 (m, 2 H, NCH₂Ph), 3.13–2.97 (m, 2 H, 7-H, 7'-H), 2.85–2.73 (m, 2 H, 3-H, 3'-H), 1.31 (t, J = 7.1 Hz, 3 H, Me) ppm. ¹³C NMR: δ = 173.7 (CO), 144.1, 139.0 (C-*ipso* Ph), 135.0, 128.8, 128.6, 128.4, 128.2, 127.9, 127.6, 127.0, 126.9, 126.3 (CHPh, CH=CH), 65.3 (C-2), 60.7 (CH₂O), 57.7 (C-7), 56.4 (CH₂N), 46.4 (C-6), 28.9 (C-3), 14.3 (Me) ppm. MS (IC, NH₃): m/z = 336 [M + H]⁺. HRMS: m/z calcd. for C₂₂H₂₆NO₂ [M + H]⁺ 336.1958; found 336.1941.

Diethyl (2R,3R,6R)- and (2S,3R,6R)-1-Benzyl-6-phenyl-2,3,6,7-tetrahydro-1H-azepane-2,3-dicarboxylate (37): This compound was

purified by flash chromatography (Et₂O/PE, 5:95, 10:90, 15:85), mixture of two isomers at C-2 in a 80:20 ratio; overall yield: 75%, oil. Major isomer (not isolated pure): R_f = 0.80 (Et₂O/PE, 4:6). ¹H NMR (CDCl₃): δ = 7.33–6.99 (m, 10 H, Ph), 5.80–5.64 (m, 2 H, 4-H, 5-H), 4.20–4.06 (m, 6 H, 2-H, 3-H, 2 × CH₂O), 4.05–3.97 (m, 1 H, NCHHPh), 3.84–3.83 (m, 2 H, 6-H, NCHHPh), 2.97 (dd, J = 5 and 14 Hz, 1 H, 7-H), 2.83 (dd, J = 10.4 and 14 Hz, 1 H, 7'-H), 1.24–1.16 (m, 6 H, 2 × Me) ppm. ¹³C NMR: δ = 173.0, 172.6 (CO), 143.6, 138.9 (C-*ipso* Ph), 135.5, 128.8, 128.6, 128.5, 128.4, 128.1, 127.9, 127.4, 127.2, 127.1, 126.6, 125.2 (CHPh, C-4, C-5), 66.7 (C-2), 61.3, 61.2 (2 × CH₂O), 57.8 (C-7), 55.3 (NCH₂Ph), 47.4 (C-3), 45.6 (C-6), 14.3, 14.2 (2 × Me) ppm. MS (ESI, pos.): m/z = 430.3 [M + Na]⁺. HRMS: m/z calcd. for C₂₅H₃₀NO₄ [M + H]⁺ 408.2169; found 408.2200.

Ethyl (2R,6S,7S)- and (2S,6S,7S)-1-Benzyl-4,6-diphenyl-2,3,6,7-tetrahydro-1H-azepane-2-carboxylate (38): This compound was purified by flash chromatography (Et₂O/PE, 5:95, 10:90, 15:85), mixture of two isomers at C-2 in a 75:25 ratio; overall yield: 81%, oil. Major isomer (not isolated pure): R_f = 0.77 (Et₂O/PE, 4:6). ¹H NMR (CDCl₃): δ = 7.34–7.01 (m, 15 H, Ph), 5.86 (d, J = 5.2 Hz, 1 H, 5-H), 4.23 (A part of AB system, J = 14.8 Hz, 1 H, NCHHPh), 4.00–3.70 (m, 6 H, 2-H, 3-H, 6-H, NCHHPh, CH₂O), 3.54–3.41 (m, 1 H, 7-H), 2.79 (dd, J = 4.8 and 15.2 Hz, 1 H, 3'-H), 1.11–1.03 (m, 6 H, 2 × Me) ppm. ¹³C NMR: δ = 174.5 (CO), 144.6, 143.2, 141.1, 135.8, 132.4, 128.7, 128.5, 128.4, 128.2, 126.9, 126.8, 126.7, 126.3 (C-*ipso* Ph, CHPh, C-4, C-5), 62.3 (C-2), 60.4 (CH₂O), 56.7 (C-7), 54.5 (NCH₂Ph), 53.4 (C-3), 33.1 (C-6), 19.8 (Me), 14.3 (Me) ppm. MS (ESI, pos.): m/z = 448.1 [M + Na]⁺. HRMS: m/z calcd. for C₂₁H₃₂NO₂ [M + H]⁺ 426.2428; found 426.2242.

General Procedure for the Opening of 2-Alkenylazetidinium Trifluoromethanesulfonates with Organolithium Reagents. Synthesis of Alkenes 39–43: A solution of the required organolithium reagent was added dropwise at –78 °C to a solution of the trifluoromethanesulfonate azetidinium salt (1 mmol) in dry THF (6 mL). The temperature was gradually (1.5 h) raised to –30 °C and the mixture was hydrolysed at this temperature by addition of a saturated aqueous solution of NH₄Cl (5 mL). Usual workup gave an oil that was purified by flash chromatography.

(Benzyl)(methyl)[(2R,3E)-2,4,5-triphenylpent-3-enyl]amine (39): This compound was purified by flash chromatography (Et₂O/PE, 2:98, 5:95, 10:90), yield: 80%, R_f = 0.63 (Et₂O/PE, 3:7). $[a]_D^{20}$ = –97 (c = 0.7, CH₂Cl₂). ¹H NMR (CDCl₃): δ = 7.49–7.13 (m, 20 H, Ph), 6.20 (d, J = 9.4 Hz, 1 H, 3-H), 4.04–3.91 (m, 3 H, 2-H, 5-H), 3.55 (s, 2 H, NCH₂Ph), 2.76 (d, J = 7.7 Hz, 2 H, 1-H), 2.25 (s, 3 H, NMe) ppm. ¹³C NMR: δ = 143.9, 143.1, 140.0, 137.9, 136.2 (C-*ipso* Ph, C-4), 133.7 (C-3), 129.1–125.9 (CHPh), 64.3 (C-1), 62.7 (NCH₂Ph), 43.7 (C-2), 42.9 (NMe), 36.2 (C-5) ppm. MS (ESI, pos.): m/z = 418.2 [M + H]⁺. C₃₁H₃₁N (417.6): calcd. C 89.16, H 7.48, N 3.35; found C 90.22, H 7.39, N 3.48.

(Benzyl)[(2R,3E)-2,4-diphenylnon-3-enyl](methyl)amine (40): This compound was purified by preparative TLC (Et₂O/PE, 4:6), yield: 62%, oil: R_f = 0.76 (Et₂O/PE, 4:6). $[a]_D^{20}$ = +22 (c = 1.5, CH₂Cl₂). ¹H NMR (CDCl₃): δ = 7.42–7.24 (m, 15 H, Ph), 5.88 (d, J = 9.0 Hz, 1 H, 3-H), 4.04 (q, J = 7.7 Hz, 1 H, 2-H), 3.62 (s, 2 H, NCH₂Ph), 2.78 (dd, J = 2.9 and 7.0 Hz, 2 H, 1-H, 1'-H), 2.57–2.53 (m, 2 H, 5-H), 2.34 (s, 3 H, NMe), 1.33–1.26 (m, 6 H, 6-H, 7-H, 8-H), 0.85 (t, J = 7.1 Hz, 3 H, Me) ppm. ¹³C NMR: δ = 144.2, 143.1, 140.9, 138.4 (C-*ipso* Ph, C-4), 139.0 (C-3), 131.0–126.1 (CHPh), 64.1 (C-1), 62.4 (NCH₂Ph), 43.1 (C-2), 42.6 (NMe), 30.2 (C-5), 31.0, 29.7, 28.2 (C-6, C-7, C-8), 13.0 (Me) ppm. MS (ESI, pos.): m/z = 398.2 [M + H]⁺.

(Benzyl)[(2R,3E)- and (2R,3Z)-6,6-dimethyl-2,4-diphenylhept-3-enyl](methyl)amine (41): This compound was purified by flash chromatography (Et₂O/PE, 10:90), yield: quant.; oil; 35:65 mixture of (Z) and (E) isomers; R_f = 0.71 (Et₂O/PE, 3:7). Major isolated isomer: $[a]_D^{20}$ = –17 (c = 0.3, CH₂Cl₂). ¹H NMR (CDCl₃): δ = 7.34–7.16 (m, 15 H, Ph), 5.78 (d, J = 9.7 Hz, 1 H, 3-H), 3.95 (q, J = 7.7 Hz, 1 H, 2-H), 3.57 (A part of AB system, J = 13.1 Hz, 1 H, NCHHPh), 3.47 (B part of AB system, J = 13.1 Hz, 1 H, NCHHPh), 2.81–2.58 (m, 2 H, 1-H, 1'-H), 2.54 (s, 2 H, 5-H, 5'-H), 2.26 (s, 3 H, NMe), 0.76 (s, 9 H, *t*Bu) ppm. ¹³C NMR: δ = 146.1, 146.0, 139.9, 136.2 (C-*ipso* Ph, C-4), 134.6 (C-3), 129.0–126.2 (CHPh), 64.4 (C-1), 62.7 (C-8), 43.8 (C-2), 42.9 (NMe), 32.8 (C-5), 31.2 (C-q), 30.8 (*t*Bu) ppm. MS (ESI, pos.): m/z = 420.2 [M + Na]⁺, 398.2 [M + H]⁺. HRMS: m/z calcd. for C₂₉H₃₆N [M + H]⁺ 398.2842; found 398.2855.

Dimethyl[(1S,2S,3E)-1-methyl-2,4,5-triphenylpent-3-enyl]amine (42): This compound was purified by flash chromatography (Et₂O/PE, 30:70, 100:0), yield: 58%, oil; R_f = 0.61 (Et₂O). $[a]_D^{20}$ = –167 (c = 0.5, CH₂Cl₂). ¹H NMR (CDCl₃): δ = 7.41–7.03 (m, 15 H, Ph), 6.51 (d, J = 9.0 Hz, 1 H, 3-H), 3.88 (s, 2 H, 5-H), 3.54 (t, J = 9.4 Hz, 1 H, 2-H), 3.08–2.93 (m, 1 H, 1-H), 2.26 (s, 6 H, NMe₂), 0.72 (d, J = 6.6 Hz, 3 H, Me) ppm. ¹³C NMR: δ = 144.4, 143.2, 139.9, 136.3 (C-*ipso* Ph, C-4), 135.1 (C-3), 128.6–125.7 (CHPh), 64.9 (C-1), 50.0 (C-2), 40.7 (2 × NMe), 35.9 (C-5), 9.3 (Me) ppm. MS (ESI, pos.): m/z = 356.1 [M + H]⁺. C₂₆H₂₉N (355.5): calcd. C 87.84, H 8.22, N 3.94; found C 87.75, H 8.16, N 3.91.

Dimethyl[(1S,2S,3E)- and (1S,2S,3Z)-1-methyl-2,4-diphenylnon-3-enyl]amine (43): This compound was purified by flash chromatography (Et₂O/PE, 3:7), yield: 62%, oil; 35:65 mixture of (Z) and (E) isomers; R_f = 0.75 (Et₂O). Major isolated isomer: $[a]_D^{20}$ = +51 (c = 1, CH₂Cl₂). ¹H NMR (CDCl₃): δ = 7.38–7.00 (m, 10 H, Ph), 6.12 (d, J = 9.0 Hz, 1 H, 3-H), 3.57 (t, J = 9.4 Hz, 1 H, 2-H), 3.03–2.88 (m, 1 H, 1-H), 2.47–2.43 (m, 2 H, 5-H), 2.29 (s, 6 H, NMe₂), 1.28–1.16 (m, 6 H, 6-H, 7-H, 8-H), 0.79–0.73 (m, 6 H, 2 × Me) ppm. ¹³C NMR: δ = 146.0, 143.5, 139.5 (C-*ipso* Ph, C-4), 132.2 (C-3), 128.5, 128.4, 128.1, 126.7, 126.5, 126.1 (CHPh), 64.7 (C-1), 49.8 (C-2), 40.6 (2 × NMe), 32.2 (C-5), 30.2, 28.0, 22.6 (C-6, C-7, C-8), 14.1 (Me), 9.6 (Me) ppm. MS (ESI, pos.): m/z = 335.2 [M + H]⁺.

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