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A convenient synthesis of racemic and optically active 1-aza-1,3-dienes derived from γ-amino esters: reduction to α,β-unsaturated and saturated γ-amino acid derivatives

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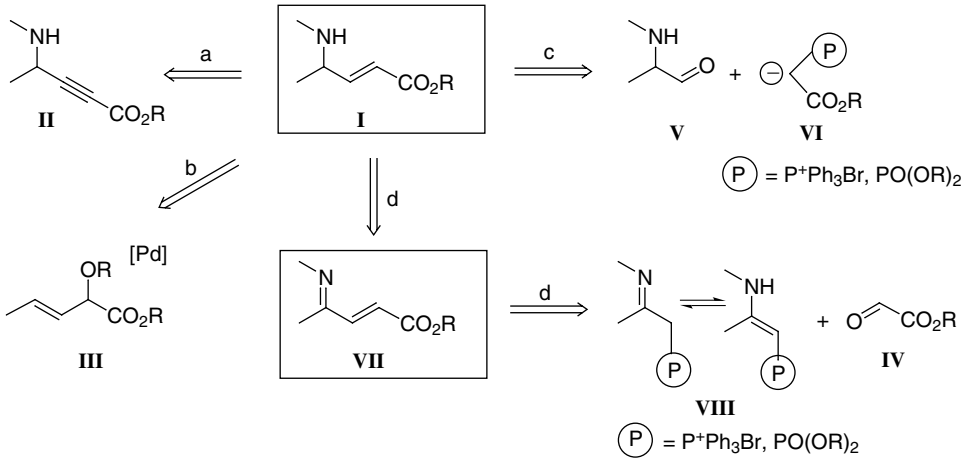
Abstract—A simple synthesis of racemic and optically active 1-azadienes derived from γ-amino esters by olefination reaction of alkyl glyoxylates and functionalized phosphonium salts or phosphine oxides is reported. Selective reduction of these 1-azadienes with hydrides yields (*E*)-γ-amino-α,β-unsaturated esters. A simple procedure for the preparation of saturated γ-amino acids and γ-amino esters from the previously synthesized vinylogous amino esters is also described. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

Azadienes have become a useful tool for the preparation of a large variety of structures such as six-membered rings[1–3] and metal-complexes[4] among others; in the last decade, some new methods of generating azadienes have been found increasing the scope of these approaches.[1–3] Furthermore, there is an increasing demand for the synthesis of γ-amino acid derivatives not only due to their biological activity,[5] but also because they constitute the units to form peptides with helical secondary structures.[6a,b] Thus, the γ-aminobutyric acid (GABA) is a major neurotransmitter known to prevent epilepsy,[5] various GABA-analogues are enzyme inhibitors[6c] and γ-aminoacids are also present in the structure of natural products with antitumor activity like *Hapalosin*,[7a–c] *Dolastatin*[7d] and *Caliculins*.[7e,f] Likewise, allylamines represent an important class of compounds because of their physiological properties as chemotherapeutic agents,[8a–d] enzyme inhibitors,[8e] and because of their usefulness as building blocks in organic synthesis and their presence in several natural products.[8f] Within allylamine derivatives, special interest has focused in the last decade on amino acid derivatives with an (*E*)-ethenyl unit inserted between the carbonyl carbon and C_α (vinylogous amino



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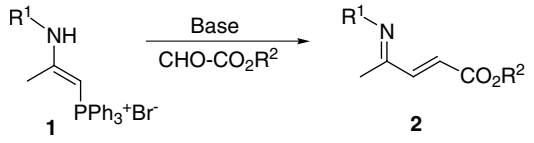
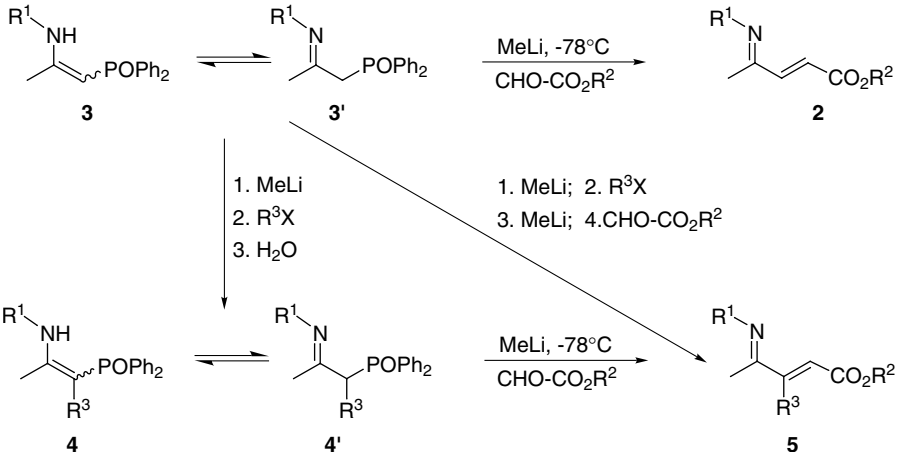


Scheme 2. Preparation of azadienes **2**.

acids) not only as constituents of vinylogous polypeptides[9a] or foldamers,[9b] but also as key intermediates[10a] in the preparation of biologically active enzyme inhibitors,[10b] polyoxamic acid[10c] as well as of acyclic[10d,e] and cyclic derivatives.[10f–i] Despite the growing interest in these compounds, the development of a methodology directed towards the synthesis of vinylogous amino esters (**I**) is still an active area of research in synthetic organic chemistry and three synthetic strategies have been developed for their preparation, involving γ-amino-α,β-alkynoates (**II**) (Ru-catalyzed coupling of alkenes[11a] or reduction[6c,11b]) (Scheme 1, route a), Palladium-catalyzed substitution of allylic carbonate[11c] (**III**) (Scheme 1, route b), and by olefination reaction using phosphorus ylides[10f] or phosphonates[10a,g–i,12] (**VI**) with carbonyl compounds (**V**) (Scheme 1, route c).

In connection with our interest in the chemistry of azadienes derived from β-amino acids[13a,b] and aminophosphonates,[13c] and in the use of β-functionalized phosphorus derivatives as building blocks in synthetic strategies,[14] we have used β-functionalized enamines derived from phosphonium salts and phosphine oxides as homologation reagents for the conversion of carbonyl derivatives into allylamines,[15] with the introduction of two additional carbon atoms in the resulting chain. Here, we aim to extend this methodology to the synthesis of racemic and optically active 1-azadienes and (*E*)-allylamines containing an ester group in the γ-position as well as to explore the synthetic use of such derivatives in the preparation of γ-aminoacids and γ-aminoesters. Retrosynthetically, we envisaged obtaining vinylogous amino acid derivatives (**I**) by selective reduction of the carbon–nitrogen double bond of 1-aza-1,3-dienes (**VII**) obtained by an olefination reaction of β-enamino phosphorus compounds (**VIII**) or their synthetic equivalent:



Scheme 3. Synthesis of the C-α-alkylated phosphine oxides **4** and azadienes **2** and **5**.

Table 1. 1-Azadienes **2**,**5** obtained

Entry	S.M	**2**,**5**[a]	R^1	R^2	R^3	Method	Yield (%)
1	**1a**	**2a**	$CH(Ph)_2$	Et	–	A	91
2	**1b**	**2b**	*p*-MePh	Et	–	B	81
3	**1c**	**2c**	*p*-MeOPh	Et	–	A	83[b]
4	**1d**	**2d**	Ph–CH–CH_3(±)	Me	–	A	–[b]
5	**1e**	**2e**	Ph–CH–CH_3(R)	Et	–	A	81
6	**1f**	**2f**	Ph–CH–CH_3(*S*)	Me	–	A	69
7	**3a**	**2b**	*p*-MePh	Et	–	C	67[b]
8	**3f**	**2e**	Ph–CH–CH_3(*R*)	Et	–	C	74
9	**4d**	**5b**	*p*-MePh	Et	Al	B	65
10	**4c**	**5d**	*p*-MeOPh	Et	Me	B	60
11	**4a**	**5e**	$CH(Ph)_2$	Et	Me	B	70
12	**4b**	**5f**	Ph–CH–CH_3(±)	Et	Me	B	70
13	**3a**[c]	**5a**	*p*-MePh	Et	Me	A	68
14	**3a**[c]	**5c**	*p*-MePh	Et	Bz	A	60
15	**3e**[c]	**5g**	Ph–CH–CH_3(*S*)	Et	Me	A	71
16	**3f**[c]	**5h**	Ph–CH–CH_3(*R*)	Et	Me	A	80

[a] β-Enamino phosphonium salts **1** or β-enamino phospine oxides **3**,**3′**,**4**,**4′** used for the preparation of either **2** or **5**.
[b] Product **2** not isolated or purified and used directly for the next step.
[c] 'One pot' reaction from **3**,**3′**.

tautomeric imino compounds, with alkyl glyoxylates (**IV**) (Scheme 1, route d).

2. Results and discussion

2.1. Preparation of 1-azadienes derived from γ-amino esters 2 and 5 from β-enamino phosphonium salts 1 and β-enamino-3 or β-imino phosphine oxides 3′

The β-functionalized phosphonium salts **1** and phosphine oxides **3** or **3′** were prepared according to literature procedures.[15] As shown in Schemes 2 and 3, their olefination reaction with alkyl glyoxylates and the respective formation of 1-azadienes **2** and **5** were easily accomplished in two different fashions. Thus, the synthesis of the azadienes **2**, derived from γ-amino esters (Table 1, entries 1–6), was carried out from phosphonium salts **1** by means of simple deprotonation with base[†] followed by the addition of ethyl glyoxylate (methyl glyoxylate in entries 4 and 6, Table 1) and stirring at room temperature for 24 h; in these conditions, the expected *N*-aliphatic and *N*-aromatic 1-azadienes **2** were obtained (Scheme 2) after aqueous work-up and chromatography with SiO_2 in high yields (Table 1, 67–91%). This olefination reaction is not restricted to phosphonium salts **1** and can be extended to the corresponding β-enamino- or β-imino phospine oxides **3** or **3′** when MeLi in THF at −78°C was used for the deprotonation, giving 1-azadienes **2** in good yields (Table 1, entries 7 and 8).

Following an analogous methodology, the 3-substituted-1-azadienes **5** were prepared from C_α alkylated phosphine oxides **4** or **4′**. Metalloenamines are especially useful for the carbon–carbon bond formation. In our case, moreover, the presence of a stabilizing group such as phosphine oxide in the β-position could control the deprotonation affording a considerable control of the regiochemistry. Thus, the metallation of β-enamino- and/or β-imino phospine oxides **3** or **3′** with MeLi in THF at −78°C followed by addition of alkyl halides and aqueous work-up afforded C_α alkylated phosphine oxides **4** or **4′**. These compounds are isolated as β-imino phosphine oxides **4′** in the case of *N*-aryl derivatives (Table 2, entries 3 and 4) while a mixture of (*Z*)- and (*E*)-enamines **4** and β-imino phosphine oxides **4′** are obtained from *N*-alkyl phosphine oxides **3** or **3′** (Table 2, entries 1 and 2), although for our subsequent purposes, the separation of the enamines and imines is not necessary. Wittig–Horner olefination reaction of these phosphine oxides **4** or **4′** with ethyl glyoxylate led to the formation of 3-substituted 1-azadienes **5** (Table 1, entries 9–12). C_α alkylated 1-azadienes **5** can be prepared stepwise from the corresponding phosphine oxides **3** or **3′** by deprotonation with MeLi in THF at −78°C followed by alkylation with methyl iodide (Table 1, entries 13, 15 and 16) or benzyl bromide (entry 14); the in situ deprotonation of the intermediate formed and subsequent addition of ethyl glyoxolate and stirring at room temperature for 24 h afforded the expected 1-azadienes **5** derived from γ-amino esters.

Table 2. Alkylated β-enamino phosphine oxides **4/4′** obtained

Entry	**4**,**4′**[a]	R^1	R^3	Yield (%)
1	**4a**[b]	$CH(Ph)_2$	Me	80
2	**4b**[b]	Ph–CH–CH_3(±)	Me	85
3	**4′c**[c]	*p*-MeOPh	Me	75
4	**4′d**[c]	*p*-MePh	Al	83

[a] Products **4/4′** prepared from the corresponding β-enamino phosphine oxides **3**,**3′**.
[b] Obtained as ∽1:1 mixtures of *E*/*Z* enamines/β-imino phosphine oxides **4/4′**.
[c] Obtained as β-imino phosphine oxides **4′**.

[†] When methyllithium was used as base, the metallation was performed in THF at −78°C, but a weaker base such as potassium carbonate (THF) would suffice, probably owing to the partially stabilized nature of the conjugated phosphorus ylides generated. The use of this base requires no special precautions.

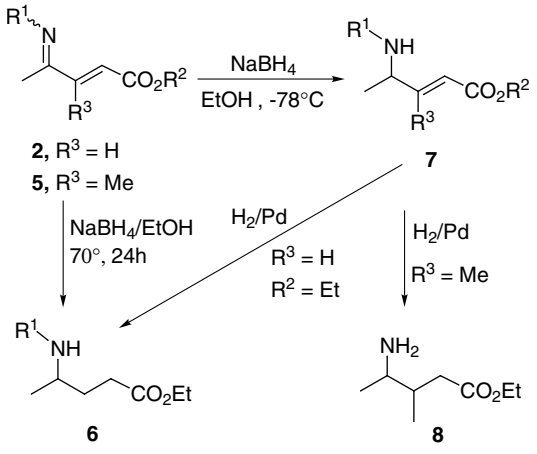
Compounds **2** and **5** were characterized on the basis of their spectroscopic data. Thus the ^1H NMR spectra of products **2** display a typical doublet in the range 5.9–6.2 ppm corresponding to the olefinic proton (C*H*–CO_2Et) with a typical *trans* coupling constant ($^3J_{H-H}$=15–16 Hz) whereas the signal of the other olefinic proton appears at 6.6–6.9 ppm as a doublet ($^3J_{H-H}$=15–16 Hz) and usually overlapped with the aromatic region. Conversely, products **5** display a single signal belonging to the olefinic proton in the range 6.1–6.3 ppm as a singlet. Also the ^{13}C NMR spectra of products **2** and **5** display very characteristics signals for the C=N (in the range of 140–160 ppm) and for the C=O (160–170 ppm); the signals corresponding to the olefinic carbons appear often overlapped in the aromatic region.

Functionalized 1-azadienes may be an important family of products not only for their use as precursors of γ-aminoacids and allylamines but also because they have become a useful tool for the preparation of heterocyclic compounds;[1,2] hence it is of special interest that azadienes **2** and **5** are stable to air and moisture, and can be purified, isolated and stored several hours. It is also noteworthy that the described reaction is compatible with the introduction of chiral substituents (Table 1, entries 4, 5, 6, 8, 12, 15 and 16) and in general with functional groups that can be removed under treatment in adequate conditions.[16]

2.2. Reductions of the 1-azadienes 2 and 5 with $NaBH_4$: synthesis of γ-amino esters 6

Reduction of both the C=C and the imino C=N double bonds of 1-aza-1,3-butadienes can be achieved when these derivatives are treated with sodium borohydride. Reduction of the previously prepared racemic and optically active 1-azadienes **2** with $NaBH_4$ in EtOH at 70°C for 24 h led to the formation of simple γ-amino esters **6a**,**b** (Scheme 4). From a preparative point of view, it is of interest that the synthesis of the γ-amino esters **6a**,**b** does not require the isolation and purification of the 1-azadienes **2**. Thus, the γ-amino esters **6** can be obtained by a 'one pot' synthesis from phosphonium salts **1**. This olefination reaction is followed by evaporation of the solvent and reduction with the hydride.

Spectroscopic data support the structure of compounds **6**. The ^1H NMR spectra of products **6** are characteristic for the disappearance of the olefinic signals in the range



6a. R^1 = (+)-CH-MePh (61% from **2e**, 92% from **7d**)
6b. R^1 = Tolyl (71% from **2b**)

Scheme 4. Synthesis of the γ-amino esters **6** and **8**.

5.5–7 ppm; these products display a multiplet at 2.2–2.5 corresponding to the CH_2 bonded to the ethoxycarbonyl group. Also, the ^{13}C NMR spectra of products **6** show the presence of a new signal at 48–50 ppm belonging to the C–N bond and the absence of the typical signal for the C=N (in the range 140–160 ppm).

2.3. Selective reductions of the imino group of 1-azadienes 2 and 5: synthesis of (*E*)-γ-amino-α,β-unsaturated esters 7

A variety of reducing agents, such as hydrogen in the presence of metal catalysts,[17,18] simple or modified hydrides[17,19] have been developed for the conversion of the imine group into amines. But, hydrogenation is not compatible with compounds containing a double bond and several other reducible functional groups. In this context, reductive amination of carbonyl compounds with sodium triacetoxyborohydride[20a] and with silica gel and zinc borohydride[20b] including some specific examples of α,β-unsaturated carbonyl derivatives has been recently reported, but as far as we know, no example of reduction of imines containing a carboxyl ester group (conjugated amino acrylic esters) has been described. In addition, competitive 1,2 and 1,4-addition reactions of nucleophiles to imines derived from α,β-unsaturated carbonyl derivatives have been observed.[21]

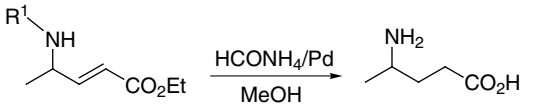
The preparation of the α,β-ethylenic γ-amino esters **7** was accomplished using different methodologies. Thus, the method A (see Section 3) involves the reduction of the racemic and optically active 1-azadienes **2** and **5** with $NaBH_4$ in EtOH at −78°C for 24 h to give vinylogous amino esters **7** in good yields (Table 3, entries 1, 3, 5, 8, 10 and 11). The synthesis of the vinylogous amino esters **7** does not require the isolation and purification of the 1-azadienes and they can also be obtained in a 'one pot' synthesis from phosphonium salts **1** and phosphine oxides **3** or **3′**. The olefination reaction of these substrates with alkyl glyoxylates is followed by the evaporation of the solvent and the reaction mixture was directly reduced with $NaBH(OAc)_3$ in CH_3CN at 0°C (method B, Table 3, entries 2, 4, 6, 7 and 9). As shown in Table 3, the yield and the ratio of the two diastereoisomers obtained for racemic or optically active derivatives R^1=(*S*), (*R*)-CHMePh is affected by the conditions of solvent, temperature and reagent used. The use of milder conditions (method A) resulted in a considerable increase of the diastereoisomeric excess (70–76% vs 52–60%).

Compounds **7** were also characterized on the basis of their spectroscopic data. Thus the ^1H NMR spectra of products **7a–f** (R^3=H) display an olefinic system similar to the one described for the starting azadienes **2** with a double doublet ($^3J_{H-H}$=4–5 Hz and 15–16 Hz) in the range 6.6–6.8 ppm and usually overlapped in the aromatic region, corresponding to the β-olefinic proton. Analogously, β-substituted γ-amino esters **7g–i** displayed a single singlet at 5.7 ppm for the α-olefinic proton. Another characteristic feature of the ^1H NMR spectra of products **7** is the presence of a new complex signal (typically at 3.0–3.2 ppm) corresponding to CH_3–C*H*–NHR. Since products **2** and **7a–f** showed coupling constants of 15–16 Hz for the olefinic protons, we have assumed an *E* stereochemistry for all the azadienes and allylamines described in this manuscript; this assignment was confirmed by the presence of a NOE effect (4%) between the olefinic proton and the Ph–C*H*–N in **7g–i**. All the diastereomeric excesses were calculated by the relative integrals of the corresponding pairs of proton signals for the two isomers in their ^1H NMR spectra. It is of remarkable

Table 3. Secondary α,β-enthylenic γ-aminoesters **7** obtained

Entry	7	R^1	R^2	R^3	Method[a]	Yield (%)	de (%)	$[\alpha]_D^{20}$ (deg.)[a,b]
1	**7a**	*p*-MeOPh	Et	H	A	75	–	–
2	**7a**	*p*-MeOPh	Et	H	B	62[c]	–	–
3	**7b**	$CH(Ph)_2$	Et	H	A	68	–	–
4	**7c**	Ph–CH–CH_3(±)	Et	H	B	68[c]	52	–
5	**7d**	Ph–CH–CH_3(*R*)	Et	H	A	81	72	+144.3
6	**7d**	Ph–CH–CH_3(*R*)	Et	H	B	75[c]	56	+116.9
7	**7e**	Ph–CH–CH_3(*S*)	Et	H	B	80[c]	52	−107.8
8	**7f**	Ph–CH–CH_3(*S*)	Me	H	A	68	70	−135.2
9	**7g**	Ph–CH–CH_3(±)	Et	Me	B	75[d]	60	–
10	**7h**	Ph–CH–CH_3(*S*)	Et	Me	A	69	76	−143.1
11	**7i**	Ph–CH–CH_3(*R*)	Et	Me	A	58	74	+128.1

[a] See Section 3 for details.
[b] For the obtained mixtures.
[c] Yields calculated from the corresponding phosphonium salts **1** or **1′**.
[d] Yield calculated from the corresponding phosphine oxides **3** or **3′**.



7d, R^1 = (+)-(*R*)-CHMePh **9a** $[\alpha]^{25}_D = +14°$

7e, R^1 = (-)-(*S*)-CHMePh **9b** $[\alpha]^{25}_D = -6°$

Scheme 5. Preparation of the γ-aminobutyric acid (GABA) **9**.

interest that the use of optically active 1-azadienes and the adequate use of the experimental condition allowed us to prepare enantiomerically enriched vinylogous amino esters with high de. The elucidation of the absolute configuration of the synthesized α,β-unsaturated γ-amino esters was performed by transformation of products **7** into the known amino acids **9** (see Section 2.4).

2.4. Preparation of γ-aminoesters 8 and γ-aminoacids 9 from α,β-ethylenic γ-amino esters 7

As shown in Schemes 4 and 5, vinylogous amino esters **7** can be easily converted into their corresponding γ-amino esters **8** and γ-amino acids **9** by catalytic hydrogenation in different conditions. The synthesis of a γ-amino ester **6a** was accomplished by reduction of the corresponding α,β-unsaturated γ-amino ester **7d**. Treatment of C_α unsubstituted (R^3=H) optically active unsaturated γ-amino ester **7d** with H_2/Pd(C) in EtOH for 24 h afforded diastereoselectively the γ-amino ester **6a** in very high yield (92%, Scheme 4). However, the treatment in the same conditions (and even in shorter periods: 3 h) of the C_α substituted (R^3=CH_3) vinylogous amino esters **7h** did not afford the expected secondary aminoester but, only the *N*-unsubstituted γ-amino ester **8** was obtained quantitatively as a mixture of isomers; the catalytic *cis*-hydrogenation occurs in this case from both faces of the double bond.[22]

Transformation to carboxylic acid was achieved by the treatment of enantiomerically enriched vinylogous amino esters **7d** (R^1=(+)-(*R*)-CHMePh) and **7e** (R^1=(−)-(*S*)-CHMePh) with H_2 (generated in situ by heating HCO_2NH_4/Pd(C) in MeOH) and afforded γ-amino acids **9a** (from **7d**) and **9b** (from **7e**) in almost quantitative yields. The specificic rotation of both products was then measured and compared with the literature data; the values obtained for **9a** and **b** were +14 and −6° (in $CHCl_3$), respectively, whereas the literature reports a specific rotation of +12° (in H_2O) for the (*R*)-4-aminopentanoic acid;[23] thereby we can assign now that the stereochemistry of the chiral center in **9a** is the (*R*) acid and consequently the absolute configuration of the allylamine **7d** is (*R*,*R*); conversely, the configuration of the chiral center in **9b** must be (*S*) and the absolute configuration of **7e** (*S*,*S*).

In conclusion, we describe a new strategy for a simple and general method to synthesize a broad range of racemic and optically active 1-azadienes **2** and **5** derived from γ-amino esters, and vinylogous amino esters **7** from easily available starting materials and under mild reactions conditions. Moreover, γ-amino α,β-ethylenic esters **7** were successfully used as precursors for the preparation of saturated γ-amino esters **6**,**8** and γ-amino acids **9**. Compounds with these substructures of γ-amino acids could be very useful in the synthesis of biologically active derivatives with interest in medicinal chemistry.[5–10]

3. Experimental

3.1. General

Chemicals were purchased from Aldrich Chemical Company. Solvents for extraction and chromatography were technical grade. All solvents used in reactions were freshly distilled from appropriate drying agents before use. All other reagents were recrystallized or distilled as necessary. All reactions were performed under an atmosphere of dry nitrogen. Analytical TLC was performed with Merck silica gel 60 F_{254} plates. Visualization was accomplished by UV. Flash chromatography was carried out using Merck silica gel 60 (230–400 mesh ASTM). Melting points were determined with a Electrothermal IA9100 Digital Melting Point Apparatus and are uncorrected. ^{1}H (300 MHz), ^{13}C (75 MHz) and ^{31}P NMR (120 MHz) spectra were recorded on a Varian VXR 300 MHz spectrometer using $CHCl_3$ solutions with TMS as an internal reference for ^{1}H and ^{13}C NMR spectra and phosphoric acid (85%) for ^{31}P NMR spectra. Coupling constants (*J*) are reported in Hz. Low-resolution mass spectra (MS) were obtained at 50–70 eV by electron impact (EIMS) on a Hewlett Packard 5971 or 5973 spectrometer. Data are reported in the form *m*/*z* (intensity relative to base=100). Infrared spectra (IR) were taken on a Nicolet IRFT Magna 550 spectrometer, and were obtained as solids in KBr or as neat oils. Peaks are reported in cm^{-1}. Elemental analyses were performed in a LECO CHNS-932 apparatus. β-enamino phosphonium salts **1** and **1′** and β-enamino phosphine oxides **3** and **3′** were synthesized according to literature procedures.[15] Compounds **1b**,**e**,**f**,**3a**,**d**–**f**,**9a** and **b** are known.[15]

3.1.1. (*E*)-Triphenyl-(2-diphenylmethylaminoprop-1-enyl)phosphonium bromide (1a). The general procedure for the synthesis of β-enamino phosphonium salts **1** and **1′** has been described in the literature.[15] 2.4 g (85%) of **1a** as a solid. Mp>230–231°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.62 (s, 1H), 7.04–7.74 (m, 25H), 5.66 (s, 1H), 3.74 (d, 1H, $^2J_{PH}$=13.5 Hz), 1.98 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.0 (d, $^2J_{PC}$=14.0 Hz), 122.4–139.8 (C-arom), 63.4, 59.2 (d, $^1J_{PC}$=121.9 Hz), 22.6 (d, $^3J_{PC}$=5.1 Hz); ^{31}P NMR (120 MHz, $CDCl_3$) δ 15.8; IR (KBr) 3191, 3019, 1520, 1122 cm^{-1}; MS (70 eV) 483 (M^+−HBr, 100). Anal calcd for $C_{34}H_{31}BrNP$: C, 72.34; H, 5.54; N, 2.48. Found: C, 72.51; H, 5.47; N, 2.60.

3.1.2. (*E*)-Triphenyl(2-*p*-methoxyphenylaminoprop-1-enyl)phosphonium bromide (1c). 2.09 g (83%) of **1c** as a solid. Mp 279–280°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.4 (s, 1H), 6.82–7.85 (m, 19H), 4.28 (d, 1H, $^2J_{PH}$=14.1 Hz), 3.75 (s, 3H), 2.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.5 (d, $^2J_{PC}$=14.1 Hz), 114.1–157.2 (C-arom), 56.7 (d, $^1J_{PC}$=118.8 Hz), 55.1, 21.8; ^{31}P NMR (120 MHz, $CDCl_3$) δ 16.9; IR (KBr) 3138, 2985, 1514, 1242, 1103 cm^{-1}; MS (70 eV) 423 (M^+−HBr, 27). Anal calcd for $C_{28}H_{27}BrNOP$: C, 66.67; H, 5.40; N, 2.78. Found: C, 66.78; H, 5.47; N, 2.70.

3.1.3. (*E*)-Triphenyl[2-(1-(±)-(*R*) and (*S*)-phenylethyl) aminoprop-1-enyl] phosphonium bromide (1d). 2.26 g (90%) of **1d** as a solid. Mp 224–225°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.16 (s, 1H), 7.15–7.64 (m, 20H), 4.49 (s, 1H), 3.44 (d, 1H, $^2J_{PH}$=14.1 Hz), 1.90 (s, 3H), 1.73 (d, 3H, $^3J_{HH}$=6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.3 (d, $^2J_{PC}$=13.6 Hz), 122.1–143.0 (C-arom), 57.7 (d, $^1J_{PC}$=121.4 Hz), 54.7, 23.2, 21.4 (d, $^3J_{PC}$=5.0 Hz); ^{31}P NMR (120 MHz, $CDCl_3$) δ 15.4; IR (KBr) 3490, 3178, 1546, 1454, 1116 cm^{-1}; MS (70 eV) 422 (M^++1−HBr, 100). Anal calcd for $C_{29}H_{29}BrNP$: C, 69.33; H, 5.82; N, 2.79. Found: C, 69.47; H, 5.67; N, 2.65.

3.2. General procedures for the synthesis of azadienes 2

Method A. To a −78°C suspension of β-enamino phosphonium salt **1** (3 mmol) in THF (25 mL) was added MeLi (1.6 M, 3 mmol). The mixture was allowed to stir at this temperature for 1 h and a solution of freshly distilled ethylglyoxylate (methylglyoxylate in entries 4 and 6, Table 1) (3 mmol) in THF (5 mL) was then added at the same temperature. The mixture was allowed to reach slowly room temperature and stirred for additional 24 h. Finally, the mixture was concentrated, diluted with CH_2Cl_2 (50 mL), washed with H_2O (2×10 mL), dried over $MgSO_4$, filtered through a short SiO_2 column (using EtOAc/Hexane as the eluent) and concentrated under vacuum yielding the expected azadienes **2** as sticky oils.

Method B: To a 0°C suspension of β-enamino phosphonium salt **1** (5 mmol) in THF (20 mL) was added K_2CO_3 (0.69 mg, 5 mmol). The resulting mixture was stirred for 1 h and then ethyl glyoxylate (5 mmol) was added dropwise; the suspension was then stirred at room temperature for 1 day and afterwards washed with H_2O (3×20 mL), extracted with CH_2Cl_2 (3×50 mL), and dried over $MgSO_4$. Finally, the solvent was evaporated under vacuum and the resulting residue chromatographed with a SiO_2 column affording the azadienes **2**.

Method C. The same methodology as described in method A was applied for the preparation of the azadienes **2** using as starting material the β-enamino phosphine oxides **3** or **3′**.

3.2.1. Ethyl 4-(diphenylmethyl)imino-2-pentenoate (2a). Prepared from **1a** following method A; 930 mg (81%) of **2a** as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.0–7.6 (m, 11H), 6.2 (d, 1H, $^3J_{HH}$=16.3 Hz), 5.68 (s, 1H), 4.1 (q, 2H, $^3J_{HH}$=7.1 Hz), 1.90 (s, 3H), 1.16 (t, 3H, $^3J_{HH}$=7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.8, 163.6, 147.0–124.4 (C-arom), 68.4, 60.3, 14.3, 13.8; IR (neat) 3058, 1716, 1473, 1183; MS (70 eV) 277 (M^+−30, 90). Anal calcd for $C_{20}H_{21}NO_2$: C, 78.15; H, 6.89; N, 4.56. Found: C, 78.42; H, 6.95; N, 4.71.

3.2.2. Ethyl 4-(*p*-methylphenyl)imino-2-pentenoate (2b). Prepared from **1b** following method B; 930 mg (81%) of **2b** as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.07 (d, 1H, $^3J_{HH}$=16.1 Hz), 6.56–7.06 (m, 4H), 6.35 (d, 1H, $^3J_{HH}$=16.1 Hz), 4.19 (m, 2H), 2.26 (s, 3H), 1.92 (s, 3H), 1.19–1.23 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.0, 164.6, 119.1–147.7 (C-arom), 60.8, 20.7, 15.9, 14.1; IR (neat) 2979, 1730, 1542, 1185 cm^{-1}; MS (70 eV) 231 (M^+, 30). Anal calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.96; H, 7.42; N, 5.92.

3.2.3. Ethyl 4-[1-(+)-(*R*)-phenylethyl]imino-2-pentenoate (2e). Prepared from **1e** following method A; 750 mg (81%) of **2e** as a yellow oil. $[\alpha]_D^{25}$=−28 (CH_2Cl_2, *c* 0.75). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.1–7.8 (m, 6H), 6.20 (d, 1H, $^3J_{HH}$=16.2 Hz), 4.70 (q, 1H, $^3J_{HH}$=6.6 Hz), 4.1 (q, 2H, $^3J_{HH}$=7.1 Hz), 1.94 (s, 3H), 1.39 (d, 3H, $^3J_{HH}$=6.6 Hz), 1.16 (t, 3H, $^3J_{HH}$=7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7, 162.6, 131.8–123.8 (C-arom), 60.3, 51.7, 24.4, 16.1,14.0; IR (neat) 2980, 1730, 1550, 1032 cm^{-1}; MS (70 eV) 245 (M^+, 80). Anal calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.12; H, 7.92; N, 5.79

3.2.4. Methyl 4-[1-(−)-(*S*)-phenylethyl]imino-2-pentenoate (2f). Prepared from **1f** following method A; 930 mg (81%) of **2f** as a yellow oil. $[\alpha]_D^{25}$=+26 (CH_2Cl_2, *c* 0.9). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.1–7.6 (m, 6H), 6.21 (d, 1H, $^3J_{HH}$=16.3 Hz), 4.68 (q, 1H, $^3J_{HH}$=6.6 Hz), 3.69 (s, 3H), 1.94 (s, 3H), 1.42 (d, 3H, $^3J_{HH}$=6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7, 162.6, 131.8–123.8 (C-arom), 60.3, 51.7, 24.4, 14.0; IR (neat) 2980, 1731, 1542, 1023 cm^{-1}; MS (70 eV) 231 (M^+−15, 80). Anal calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.96; H, 7.42; N, 5.92.

3.2.5. 2-*N*-(*p*-Methoxyphenyl)aminopropyldiphenylphosphine oxide (3b). 1.65 g (91%) of **3b** as a dark oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.66–7.83 (m, 14H), 3.67 (s, 3H), 3.53 (d, 2H, $^2J_{PH}$=14.7 Hz, *syn*), 3.52 (d, 2H, $^2J_{PH}$=14.4 Hz, *anti*), 2.26 (s, 3H, *syn*), 1.93 (s, 3H, *anti*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.7, 152.2, 113.8–139.8 (C-arom), 55.5, 55.2, 47.8 (d, $^1J_{PC}$=55.9 Hz), 45.0 (d, $^1J_{PC}$=61.4 Hz), 32.6, 21.5; ^{31}P NMR (120 MHz) 29.4, 26.5; IR (KBr) 3221, 3020, 1581, 1191 cm^{-1}; MS (70 eV) 363 (M^+, 100). Anal calcd for $C_{22}H_{22}NO_2P$: C, 72.71; H, 6.10; N, 3.85. Found: C, 72.49; H, 6.27; N, 4.07.

3.2.6. 2-*N*-(Diphenylmethyl)aminopropyldiphenylphosphine oxide (3c). 1.7 g (80%) of **3c** as a solid. Mp 143–145°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.40 (s, 1H), 7.06–7.81 (m, 20H), 5.51 and 5.53 (s, 1H), 4.64 (s, 1H), 4.29 (d, $^2J_{PH}$=17.1 Hz), 4.13 (d, $^2J_{PH}$=22.8 Hz), 3.4–3.6 (m), 2.4 (s, 3H), 1.97 and 2.10 (s, 3H, *E* and *Z*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.5, 156.9, 126.4–143.7 (C-arom), 83.1 (d, $^1J_{PC}$=126.4 Hz), 77.7 (d, $^1J_{PC}$=114.6 Hz), 62.1, 61.5, 21.8 (d, $^3J_{PC}$=15.1 Hz), 20.1 (d, $^3J_{PC}$=6.0 Hz); ^{31}P NMR (120 MHz) 29.3, 23.6; IR (KBr) 3217, 3025, 1588, 1533, 1176 cm^{-1}; MS (70 eV) 423 (M^+, 35). Anal calcd for $C_{28}H_{26}NOP$: C, 79.41; H, 6.19; N, 3.31. Found: C, 79.51; H, 6.23; N, 3.20.

3.3. General procedure for the synthesis of C-α-alkylated phospine oxides (4)

To a −78°C suspension of β-enamino phosphine oxide **3**,**3′** (5 mmol) in THF (25 mL) was added MeLi (1.6 M, 5 mmol). The mixture was allowed to stir at this temperature for 1 h and MeI (Table 2, entries 1, 2 and 3) or allyl bromide (entry 4) (5 mmol) was then added. The mixture was then allowed to slowly reach room temperature and stirred for

additional 24 h; afterwards, the reaction mixture was washed with H_2O (20 mL), extracted with CH_2Cl_2 (3×50 mL), the solvent was evaporated under reduced pressure and the resulting residue crystallized from Et_2O affording the expected C-α-alkylated phospine oxides **4** as yellowish solids.

3.3.1. (*Z*) and (*E*)-1-Methyl-2-*N*-(diphenylmethylamino)-prop-1-enyldiphenylphosphine oxide (4a). Prepared from **3c**; 1.75 g (80%) of **4a** as a yellowish solid. Mp 58–60°C ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.90–7.77 (m, 20H), 5.40 (s, 1H), 3.82 (m, 1H, *syn*), 3.68 (m, 1H, *anti*), 2.19 (s, 3H, *syn*), 1.93 (s, 3H, *anti*), 1.37 (dd, 3H, $^3J_{HH}$=7.3 Hz, $^3J_{PH}$=16.2 Hz, *anti*), 1.20 (dd, 3H, $^3J_{HH}$=7.2 Hz, $^3J_{PH}$=15.9 Hz, *anti*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.0, 132.2–126.5 (C-arom), 67.7, 51.0 (d, $^1J_{PC}$=57.4 Hz), 48.0 (d, $^1J_{PC}$=63.5 Hz), 17.0, 12.0, 11.3; ^{31}P NMR (120 MHz, $CDCl_3$) δ 32.2 and 30.2; IR (KBr) 3057, 2943, 1448, 1192 cm^{-1}; MS (70 eV) 437 (M^+, 27). Anal calcd for $C_{29}H_{28}NOP$: C, 79.61; H, 6.45; N, 3.20. Found: C, 79.76; H, 6.50; N, 3.26.

3.3.2. (*Z*) and (*E*)-1-Methyl-2-*N*-(1-(±)-(*R*) and (*S*)-phenylethylamino)prop-1-enyldiphenylphosphine oxide (4b). 1.59 g (85%) of **4b** as a yellowish liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.89–7.88 (m, 15H), 4.41 (q, 1H, $^3J_{HH}$=6.6 Hz), 3.58 and 3.68 (m, 1H), 1.89 and 1.92 (s, 3H), 1.36 (m, 3H), 0.97 (d, 3H, $^3J_{HH}$=6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6, 166.0, 142.9–125.4 (C-arom), 58.8, 47.8 (d, $^1J_{PC}$=65.6 Hz), 23.8, 23.4, 16.3, 16.0, 11.8, 11.1. ^{31}P NMR (120 MHz, $CDCl_3$) δ 32.7 and 32.5; IR (neat) 3061, 2937, 1443, 1198 cm^{-1}; MS (70 eV) 375 (M^+, 35). Anal calcd for $C_{24}H_{26}NOP$: C, 76.78; H, 6.98; N, 3.73. Found: C, 76.96; H, 6.99; N, 3.75.

3.3.3. 1-Methyl-2-*N*-(*p*-methoxyphenylimino)propyldiphenylphosphine oxide (4′c). 1.41 g (75%) of **4′c** as a yellowish liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.70–7.99 (m, 14H), 3.95 (s, 1H), 3.75 (s, 3H), 2.23 (s, 3H), 1.37 (dd, 3H, $^3J_{HH}$=7.2 Hz, $^3J_{PH}$=16.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9, 132.5–114.2 (C-arom), 55.7, 50.1 (d, $^1J_{PC}$=57.9 Hz), 31.0, 11.4; ^{31}P NMR (120 MHz, $CDCl_3$) δ 31.9; IR (KBr) 3030, 1618, 1430 cm^{-1}; MS (70 eV) 377 (M^+, 61). Anal calcd for $C_{23}H_{24}NO_2P$: C, 73.19; H, 6.41; N, 3.71. Found: C, 72.95; H, 6.64; N, 3.98.

3.3.4. (*E*)-1-(2-propenyl)-2-*N*-(*p*-methylphenylimino)-propyldiphenylphosphine oxide (4′d). 1.41 g (75%) of **4′d** as a yellowish solid. Mp 121–123°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41–7.92 (m, 10H), 6.91–6.03 (m, 4H), 5.71 (m, 1H), 5.04 (m, 2H), 3.65 (m, 1H), 2.90–2.41 (m, 2H), 2.19 (s, 3H), 1.77 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.3 (d, $^2J_{PC}$=3.5 Hz), 147.7–128.7 (C-arom), 118.6, 116.3, 52.6 (d, $^1J_{PC}$=61.4 Hz), 30.0, 20.6, 18.7; ^{31}P NMR (120 MHz, $CDCl_3$) δ 30.7; IR (KBr) 3052, 1642, 1441, 1192 cm^{-1}; MS (70 eV) 387 (M^+, 43). Anal calcd for $C_{25}H_{26}NOP$: C, 77.50; H, 6.76; N, 3.62. Found: C, 77.59; H, 6.63; N, 3.55.

3.4. General procedures for the synthesis of azadienes 5

Method A. To a −78°C suspension of β-enamino phosphine oxide **3**,**3′** (5 mmol) in THF (25 mL) was added MeLi (1.6 M, 5 mmol). The mixture was allowed to stir at this temperature for 1 h and MeI (Table 1, entries 10–13, 15 and 16), allyl bromide (entry 9) or benzyl bromide (entry 14) (5 mmol) were then added. The mixture was then allowed to slowly reach room temperature and stirred for additional 24 h. Afterwards, the mixture was cooled again to −78°C and MeLi (1.6 M, 5 mmol) was added; after 1 h of stirring at the same temperature, a solution of freshly distilled ethyl glyoxylate (5 mmol) in THF (5 mL) was added; the resulting mixture was then allowed to reach room temperature and stirred for additional 12 h. Finally, the resulting crude was evaporated, diluted with CH_2Cl_2 (50 mL), washed with H_2O (2×10 mL), dried over $MgSO_4$, and chromatographed (SiO_2, hexane/EtOAc: 2:1) yielding the expected azadienes **5** as sticky oils.

Method B. To a −78°C solution of the C-α-alkylated phospine oxides **4** (5 mmol) was added MeLi (1.6 M, 5 mmol); after 1 h of stirring at the same temperature, a solution of freshly distilled ethyl glyoxylate (5 mmol) in THF (5 mL) was added; the resulting mixture was then allowed to reach room temperature and stirred for additional 12 h. Finally, the resulting crude was evaporated, diluted with CH_2Cl_2 (50 mL), washed with H_2O (2×10 mL), dried over $MgSO_4$, and chromatographed (SiO_2, hexane/EtOAc: 2:1) yielding the expected azadienes **5** as sticky oils.

3.4.1. Ethyl 3-methyl-4-(4-methylphenyl)imino-2-pentenoate (5a). Prepared from **3a** following method A; 830 mg (68%) of **5a** as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.30–7.20 (m, 4H), 6.31 (s, 1H), 4.18 (q, 2H, $^3J_{HH}$=7.2 Hz), 2.72 (s, 3H), 2.37 (s, 3H), 1.94 (s, 3H), 1.26 (t, 3H, $^3J_{HH}$=7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.2, 148.5, 118.8–129.5 (C-arom), 60.3, 20.8, 16.6, 14.6, 14.3; IR (neat) 2980, 1720, 1640, 1180 cm^{-1}; MS (70 eV) 245 (M^+, 27). Anal calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.65; H, 7.83; N, 5.65.

3.4.2. Ethyl 4-(*p*-methylphenyl)imino-3-(2-propenyl)-2-pentenoate (5b). Prepared from **4d** following method B; 88 mg (65%) of **5b** as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.47–6.95 (m, 5H), 5.73 (m, 1H), 4.95 (m, 2H), 4.19 (q, 2H, $^3J_{HH}$=7.2 Hz), 3.48 (d, 2H, $^3J_{HH}$=7.2 Hz), 2.32 (s, 3H), 2.18 (s, 3H), 1.26 (t, 3H, $^3J_{HH}$=7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.7, 151.7, 126.5–135.6 (C-arom), 116.5, 112.6, 60.9, 30.5, 26.5, 20.4, 14.2; IR (neat) 2932, 1732, 1520, 1281 cm^{-1}; MS (70 eV) 271 (M^+, 20). Anal calcd for $C_{17}H_{21}NO_2$: C, 75.25; H, 7.80; N, 5.16. Found: C, 75.45; H, 7.85; N, 5.25.

3.4.3. Ethyl 3-benzyl-4-(*p*-methylphenyl)imino-2-pentenoate (5c). Prepared from **3a** following method A; 96 mg (60%) of **5c** as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.51–7.36 (m, 10H), 4.10 (q, 2H, $^3J_{HH}$=7.2 Hz), 3.60 (s, 2H), 2.26 (s, 3H), 2.05 (s, 3H), 1.17 (t, 3H, $^3J_{HH}$=7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3, 165.7, 112.9–148.7 (C-arom), 60.5, 34.2, 20.4, 16.0, 14.3; IR (neat) 2926, 1706, 1513, 1182 cm^{-1}; MS (70 eV) 321 (M^+, 10). Anal calcd for $C_{21}H_{23}NO_2$: C, 78.47; H, 7.21; N, 4.36. Found: C, 78.65; H, 7.25; N, 4.41.

3.4.4. Ethyl 3-methyl-4-(4-methoxyphenyl)imino-2-pentenoate (5d). Prepared from **4c** following method B;

78 mg (60%) of **5d** as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.67–6.84 (m, 4H), 6.31 (s, 1H), 4.19 (q, 2H, $^3J_{HH}$=7.2 Hz), 3.70 (s, 3H), 2.15 (s, 3H), 1.96 (s, 3H), 1.26 (t, 3H, $^3J_{HH}$=7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.2, 151.9, 114.1–121.9 (C-arom), 60.7, 55.5, 16.5, 14.2, 13.0; IR (neat) 2930, 1710, 1520, 1170 cm^{-1}; MS (70 eV) 261 (M^+, 18). Anal calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 69.15; H, 7.37; N, 5.35.

3.4.5. Ethyl 4-(diphenylmethyl)imino-3-methyl-2-pentenoate (5e). Prepared from **4a** following method B; 1.1 g (70%) of **5e** as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10–7.35 (m, 10H), 6.17 and 6.50 (s, 1H), 5.70 (s, 1H); 4.15 and 4.17 (q, 2H, $^3J_{HH}$=7.4 Hz), 2.32 and 2.41 (s, 3H), 2.01 and 2.15 (s, 3H), 1.24 and 1.26 (t, 3H, $^3J_{HH}$=7.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.8, 165.9, 155.8, 155.4, 120.4–145.7 (C-arom), 68.7, 60.7, 60.1, 26.1, 15.1, 15.0, 14.2, 14.1, 13.0; IR (neat) 2979, 1719, 1255, 1189 cm^{-1}; MS (70 eV) 321 (M^+, 20). Anal calcd for $C_{21}H_{23}NO_2$: C, 78.47; H, 7.21; N, 4.36. Found: C, 78.68; H, 7.27; N, 4.38.

3.4.6. Ethyl 3-methyl-4-[1-(±)-(*R*) and (*S*)-phenylethyl] imino-2-pentenoate (5f). Prepared from **4b** following method B; 1.1 g (70%) of **5f** as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18–7.40 (m, 5H), 6.17 (s, 1H), 4.72 (q, 1H, $^3J_{HH}$=6.6 Hz), 4.18 (q, 2H, $^3J_{HH}$=7.2 Hz), 2.39 (s, 3H), 2.01 (s, 3H), 1.44 (d, 3H, $^3J_{HH}$=6.6 Hz), 1.28 (t, 3H, $^3J_{HH}$=7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.6, 156.2, 119.8–145.7 (C-arom), 60.1, 60.0, 25.0, 15.1, 14.6, 14.3; IR (neat) 2979, 1719, 1633, 1188 cm^{-1}; MS (70 eV) 259 (M^+, 9). Anal calcd for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16; N, 5.40. Found: C, 74.27; H, 8.16; N, 5.38.

3.4.7. (*S*)-(−)-Ethyl 3-methyl-4-[1-phenylethyl]imino-2-pentenoate (5g). Prepared from **3e** following method A; 1.0 g (70%) of **5g** as a yellow oil. $[\alpha]_D^{25}$=+33 (CH_2Cl_2, *c* 0.8). Spectral data are the same as described for **5f**.

3.4.8. (*R*)-(+)-Ethyl 3-methyl-4-[1-phenylethyl]imino-2-pentenoate (5h). Prepared from **3f** following method A; 1.1 g (71%) of **5h** as a yellow oil. $[\alpha]_D^{25}$=−31 (CH_2Cl_2, *c* 0.95). Spectral data are the same as described for **5f**.

3.5. General procedures for the synthesis of γ-amino esters (6)

Method A. To a solution of the azadiene (**2** or **5**) (5 mmol) in THF (1 mL) were added EtOH (1 mL) and $NaBH_4$ (22 mg, 15 mmol). The resulting mixture was heated at 70°C and stirred for 1 day. The mixture was then washed with H_2O (2×1 mL), extracted with CH_2Cl_2 (2×5 mL), dried over $MgSO_4$, and chromatographed (SiO_2, hexane/Et_2O) yielding the expected γ-amino esters **6** as sticky oils.

Method B. A suspension of the allylamine **7d** (1 mmol) and Pd/C (10%, 11 mg, 0.1 mmol) in EtOH (1 mL) was shaken in H_2 atmosphere (90 psi) for 2 h. The resulting suspension was then filtered through a short column of SiO_2, the residue washed with EtOAc and the solvents evaporated affording quantitatively the aminoester **6a** as yellowish oil.

3.5.1. Synthesis of (*R*)-(+)-ethyl 4-[phenylethyl]aminopentanoate 6a. Prepared from either **2e** following method A (de: 81%, yield: 61%, of **6a**) or **7d** following method B (de: 72%, yield: 92% of **6a**); (for the mixture obtained with method B): $[\alpha]_D^{25}$=+86 (CH_2Cl_2, *c* 0.85); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.4–7.8 (m, 2H), 7.2–7.4 (m, 3H), 4.27 (q, 1H, $^3J_{HH}$=6.7 Hz), 4.00 (q, 2H, $^3J_{HH}$=7.2 Hz), 2.90 (s, 1H), 1.8–2.5 (m, 5H), 1.78 (d, 3H, $^3J_{HH}$=6.7 Hz), 1.35 (d, 3H, $^3J_{HH}$=6.5 Hz), 1.14 (t, 3H, $^3J_{HH}$=7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 135.7, 129.0, 128.8, 127.7, 60.4, 56.3, 51.0, 29.8, 26.2, 21.1, 17.2, 13.9; IR (neat) 3456, 2893, 1732, 1600, 1374, 1189 cm^{-1}; MS (70 eV) 249 (M^+, 10). Anal calcd for $C_{15}H_{23}NO_2$: C, 72.25; H, 9.30; N, 5.62. Found: C, 72.48; H, 9.44; N, 5.42.

3.5.2. Ethyl 4-(*p*-methylphenylamino)pentenoate (6b). 0.83 (71%) of **6b** as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.44–6.96 (m, 4H), 4.12 (q, 2H, $^3J_{HH}$=7.2 Hz), 3.49 (m, 1H), 2.41 (m, 2H), 2.23 (s, 3H), 1.70 (m, 2H), 1.2–1.3 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.8, 145.6–108.7 (C-arom), 60.4, 48.5, 32.0, 31.2, 20.8, 20.3, 14.2; IR (neat) 3410, 2983, 1715, 1026 cm^{-1}; MS (70 eV) 235 (M^+, 20). Anal calcd for $C_{14}H_{21}NO_2$: C, 71.46; H, 8.99; N, 5.95. Found: C, 71.56; H, 8.82; N, 5.85.

3.6. General procedure for the synthesis of (*E*)-γ-amino-α,β-unsaturated esters 7

Method A. To a −78°C solution of the azadiene **2** and **5** (5 mmol) in ethanol (3 mL) was added $NaBH_4$ (0.3 g, 10 mmol) under nitrogen atmosphere and the resulting suspension was stirred at the same temperature for 2 h. Excess of $NaBH_4$ was then hydrolyzed with H_2O (1 mL) at −78°C, the cold bath was removed. The mixture at room temperature was extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were dried over $MgSO_4$ filtered and concentrated. The resulting residue was purified by flash chromatography (SiO_2, Hexane/EtOAc: 10:1) yielding the expected allylamines **7** as yellowish oils.

Method B. To a −78°C suspension of the β-enamino phosphonium salt **1** (5 mmol) in THF (2 mL) was added MeLi (1.6 M, 5 mmol) under nitrogen atmosphere and the resulting mixture was stirred at the same temperature for h. Then, a solution of freshly distilled ethyl glyoxylate (5 mmol) in THF (mL) was added and the solution was allowed to reach room temperature and stirred for additional 2 h. Afterwards, the obtained mixture was added under nitrogen to a solution of $NaBH(OAc)_3$ (previously prepared from 15 mmol of $NaBH_4$ and mL of acetic acid in CH_3CN) at 0°C and stirred for h. Finally, the resulting mixture was diluted with H_2O (mL), extracted with CH_2Cl_2 (3×5 mL), dried over Na_2SO_4, the solvent evaporated and the resulting residue chromatographed (SiO_2, hexane/EtOAc: 10:1). This method was also applied to the C-α-alkylated phosphine oxides (**4**) generated in situ from **3** or **3′** (Table 3, entry 9).

3.6.1. Ethyl 4-(*p*-methoxyphenyl)amino-2-pentenoate (7a). Prepared from the β-enamino phosphonium salt **1c** following method A; 77 mg (75%) of **7a** as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.81 (dd, 1H, $^3J_{HH}$=15.0, 5.4 Hz), 6.68 and 6.45 (AB system, $^3J_{HH}$=9.0 Hz), 5.91 (d, 1H, $^3J_{HH}$=15.0 Hz), 4.10 (q, 2H, $^3J_{HH}$=7.2 Hz), 3.98 (m, 1H), 3.67 (s, 3H), 3.15 (s, 1H), 1.28 (d, 3H, $^3J_{HH}$=6.9 Hz), 1.20 (t, 3H, $^3J_{HH}$=7.2 Hz); ^{13}C NMR

(75 MHz, $CDCl_3$) δ 166.5, 152.3, 150.9, 140.9, 120.6, 114.4–114.9 (C-arom), 60.3, 55.8, 50.8, 21.1, 14.2; IR (neat) 3400, 2925, 1706, 1513, 1241 cm^{-1}; MS (70 eV) 249 (M^+, 81). Anal calcd for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.68; N, 5.62. Found: C, 67.67; H, 7.68; N, 5.60.

3.6.2. Ethyl 4-(diphenylmethyl)amino-2-pentenoate (7b). Prepared from the azadiene **2a** following method A; 23 mg (68%) of **7c** as a colorless liquid. ^1H NMR (300 MHz, $CDCl_3$) δ 7.1–7.3 (m, 10H), 6.7 (dd, 1H, $^3J_{HH}$=7.7 and 15.6 Hz), 5.81 (d, 1H, $^3J_{HH}$=15.6 Hz), 4.80 (s, 1H), 4.13 (q, 2H, $^3J_{HH}$=7.1 Hz), 3.20 (q, 1H, $^3J_{HH}$=6.5 Hz), 1.47 (m, 1H), 1.23 (t, 3H, $^3J_{HH}$=7.1 Hz), 1.14 (d, 3H, $^3J_{HH}$=6.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5, 151.6, 143.9, 143.5, 128.5, 128.4, 127.4, 127.3, 127.2, 127.0, 126.9, 126.8, 124.7, 120.7, 64.1, 60.2, 51.7, 21.0, 14.2; IR (neat) 3323, 2979, 1699, 1447, 1189, 691 cm^{-1}; MS (70 eV) 309 (M^+, 5). Anal calcd for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49; N, 4.53. Found: C, 77.92; H, 7.29; N, 4.48.

3.6.3. (*R*)-(+)- and (*S*)-(−)-Ethyl 4-[1-phenylethyl] amino-2-pentenoate (7c). Prepared from the β-enamino phosphonium salt **1d** following method B; 77 mg (68%) of **7c** as a yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ major diastereoisomer (*R*,*R*) and (*S*,*S*): 7.14–7.28 (m, 5H), 6.68 (dd, 1H, $^3J_{HH}$=7.6, 15.0 Hz), 5.68 (d, 1H, $^3J_{HH}$=15.0 Hz), 4.14 (q, 2H, $^3J_{HH}$=7.0 Hz), 3.68 (q, 1H, $^3J_{HH}$=6.6 Hz), 3.05 (q, 1H, $^3J_{HH}$=6.8 Hz), 1.25 (d, 3H, $^3J_{HH}$=6.6 Hz overlapped with t at 1.24 ppm), 1.24 (t, 3H, $^3J_{HH}$=7.0 Hz), 1.05 (d, 3H, $^3J_{HH}$=6.8 Hz); minor diastereoisomer (*R*,*R*) and (*S*,*S*):7.14–7.28 (m, 5H), 6.68 (dd, 1H, $^3J_{HH}$=7.6, 15.0 Hz), 5.80 (d, 1H, $^3J_{HH}$=15.0 Hz), 4.14 (q, 2H, $^3J_{HH}$=7.0 Hz), 3.80 (q, 1H, $^3J_{HH}$=6.6 Hz), 3.22 (q, 1H, $^3J_{HH}$=6.8 Hz), 1.24 (d, 3H, $^3J_{HH}$=6.6 Hz), 1.23 (t, 3H, $^3J_{HH}$=7.0 Hz), 1.10 (d, 3H, $^3J_{HH}$=6.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ major diastereoisomer (*R*,*S*) and (*S*,*R*): 166.6, 151.8, 145.3, 126.5–128.5 (C-arom), 120.8, 60.3, 55.3, 51.7, 24.9, 21.7, 14.2; minor diastereoisomer (*R*,*R*) and (*S*,*S*): 166.6, 152.2, 145.3, 126.5–128.5 (C-arom), 120.1, 60.2, 55.1, 51.7, 24.0, 20.4, 14.2; IR (KBr) 3380, 2911, 1198 cm^{-1}; MS (70 eV) 232 (M^+−15, 30). Anal calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.95; H, 8.63; N, 5.70.

3.6.4. (*R*)-(+)-Ethyl 4-[phenylethyl]amino-2-pentenoate (7d). Prepared from either the β-enamino phosphonium salt **1e** following method B; 85 mg (75%), $[\alpha]_D^{20}$=+116.9 (CH_2Cl_2, *c* 1.5, for the obtained mixture) or from the azadiene **2e** (81%), $[\alpha]_D^{20}$=+144.3 (CH_2Cl_2, *c* 0.7, for the obtained mixture). Spectral data of the major and minor diastereoisomers obtained are the same as described for the (*R*,*R*) and (*R*,*S*) diastereoisomers of **7c**. Anal calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.63; H, 8.71; N, 5.82.

3.6.5. (*S*)-(−)-Ethyl 4-[1-phenylethyl]amino-2-pentenoate (7e). Prepared from the β-enamino phosphonium salt **1f** following method B; 91 mg (80%) of **7e** as a yellow oil. $[\alpha]_D^{20}$=−107.8 (CH_2Cl_2, *c* 1.5, for the obtained mixture. Spectral data of the major and minor diastereoisomers obtained are the same as described for the (*S*,*S*) and (*S*,*R*) diastereoisomers of **7c**. Anal calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.55; H, 8.57; N, 5.78.

3.6.6. (*S*)-(−)-Methyl 4-[1-phenylethyl]amino-2-pentenoate (7f). Prepared from the azadiene **2f** following method A; 13 mg (48%) of **7f** as a colorles liquid. $[\alpha]_D^{20}$=−135.2 (CH_2Cl_2, *c* 1.5): ^1H NMR (300 MHz, $CDCl_3$) δ 7.0–7.4 (m, 5H), 6.69 (dd, 1H, $^3J_{HH}$=7.9, 15.7 Hz), 5.81 (d, 1H, $^3J_{HH}$=15.8 Hz, minor diastereoisomer), 5.70 (d, 1H, $^3J_{HH}$=15.7 Hz, major diastereoisomer), 3.67 (s, 3H, overlapping: m, 1H), 3.64 (s, 3H, minor diastereoisomer) 2.9–3.0 (m, 1H), 1.43 (s, 1H), 1.24 (d, 3H, $^3J_{HH}$=6.6 Hz), 1.10 (d, 3H, $^3J_{HH}$=6.6 Hz, minor diasteroisomer), 1.04 (d, 3H, $^3J_{HH}$=6.7 Hz, major diasteroisomer); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.9, 152.1, 145.2, 128.4, 128.3, 126.8, 126.5, 126.4, 120.3, 119.5 (minor diastereoisomer), 55.2, 55.0 (minor), 51.6, 51.3, 24.8, 23.9 (minor), 21.6, 20.3 (minor); IR (neat) 3340, 1740, 1519, 1240 cm^{-1}; MS (70 eV) 233 (M^+, 30). Anal calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 71.89; H, 8.14; N, 5.89.

3.6.7. (*R*)-(+)- and (*S*)-(−)-Ethyl 3-methyl-4-[1-phenylethyl]amino-2-pentenoate (7g). Prepared from the β-enamino phosphine oxide **3d** following method B; 98 mg (75%) of **7g** as a yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ major diastereoisomer: 7.14–7.28 (m, 5H), 5.67 (s, 1H), 4.19 (q, $^3J_{HH}$=7.1 Hz, 2H), 3.60 (q, 1H, $^3J_{HH}$=7.0 Hz), 2.94 (q, 1H, $^3J_{HH}$=6.7 Hz), 2.07 (s, 3H), 1.26 (t, 3H, $^3J_{HH}$=7.1 Hz), 1.25 (d, 3H, $^3J_{HH}$=7.0 Hz), 1.06 (d, 3H, $^3J_{HH}$=6.7 Hz); minor diastereoisomer: 7.14–7.28 (m, 5H), 5.84 (s, 1H), 4.19 (q, 2H, $^3J_{HH}$=7.1 Hz,), 3.70 (q, 1H, $^3J_{HH}$=6.9 Hz), 3.25 (q, 1H, $^3J_{HH}$=6.8 Hz), 2.02 (s, 3H), 1.24 (d, 3H, $^3J_{HH}$=6.9 Hz), 1.26 (t, 3H, $^3J_{HH}$=7.1 Hz), 1.15 (d, 3H, $^3J_{HH}$=6.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ major diastereoisomer: 166.9, 161.6, 145.4, 126.5–128.5 (C-arom), 115.8, 59.6, 58.4, 55.1, 25.0, 21.0, 14.3, 14.0; minor diastereoisomer: 166.9, 161.8, 145.4, 126.5–128.5 (C-arom), 115.7, 59.6, 58.1, 55.1, 23.0, 20.1, 14.3, 14.0; IR (KBr) 3310, 2850, 1220 cm^{-1}; MS (70 eV) 246 (M^+−15, 15). Anal calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.67; H, 8.93; N, 5.29.

3.6.8. (*S*)-(−)-Ethyl 3-methyl-4-[1-phenylethyl]amino-2-pentenoate (7h). Prepared from the azadiene **5g** following method A; 19 mg (69%) of **7h** as a yellow oil $[\alpha]_D^{20}$=−143.1 (CH_2Cl_2, *c* 0.9). Spectral data for both the major and the minor diastereoisomer of **7h** are the same as described for the major and minor diastereoisomers of **7g**. Anal calcd for $C_{16}H_{23}NO_2$: C, 73.49; H, 8.89; N, 5.61. Found: C, 73.38; H, 8.95; N, 5.68.

3.6.9. (*R*)-(+)-Ethyl 3-methyl-4-[1-phenylethyl]amino-2-pentenoate (7i). Prepared from the azadiene **5h** following method A; 11 mg (58%) of **7i** as a yellow oil. $[\alpha]_D^{20}$=+128.1 (CH_2Cl_2, *c* 0.9). Spectroscopical data for both the major and the minor diastereoisomer of **7i** are the same as described for the major and minor diastereoisomers of **7g**. Anal calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.29; H, 8.82; N, 5.31.

3.6.10. Synthesis of ethyl 4-amino-3-methylpentenoate 8. A suspension of the allylamine **7h** (1 mmol) and Pd/C (10%, 11 mg, 0.1 mmol) in EtOH (1 mL) was shaken in H_2 atmosphere (90 psi) for h. The resulting suspension was then filtered through a short column of SiO_2, the residue washed

with EtOAc/MeOH and the solvents evaporated affording quantitatively the aminoester **8** as yellowish oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.0 (q, 2H, $^3J_{HH}$=7.2 Hz), 3.4 (m, 1H), 2.2–2.8 (m, 3H), 0.90–1.40 (m, 8H), 1.15 (t, 3H, $^3J_{HH}$=7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3, 171.8, 60.7, 51.9, 51.5, 37.5, 37.6, 33.8, 33.6, 29.7, 15.8, 15.1, 14.2, 14.1; IR (neat) 3383, 2932, 2965, 2839, 2806, 1726, 1673, 1367 cm^{-1}; Anal calcd for $C_8H_{17}NO_2$: C, 60.35; H, 10.76; N, 8.80. Found: C, 60.68; H, 10.59; N, 8.72.

3.6.11. Synthesis of 4-aminopentanoic acid (9).[11,17] Over a solution of either the allylamine **7d** or **e** (1.0 g, 4.5 mmol) in MeOH (1 mL), was added ammonium formiate (3.1 g, 50 mmol) and Pd/C (10%, 1. g, 1.5 mmol). The resulting suspension was refluxed for h and then filtered through Celite and concentrated under reduced pressure affording quantitatively the 4-aminopentanoic acids **9a** (from **7d**) and **9b** (from **7e**), respectively. Data for **9a** (for the mixture): $[\alpha]_D^{25}$=+14 (CH_2Cl_2, *c* 0.85). Data for **9b** (for the mixture): $[\alpha]_D^{25}$=−6 (CH_2Cl_2, *c* 0.9).

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