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Regio- and stereoselective double alkylation of β-enamino esters with organolithium reagents followed by *one-pot* reduction: convenient method for the synthesis of tertiary γ-amino alcohols

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Abstract—An easy, high yielding and stereoselective procedure for the preparation of tertiary γ-amino alcohols starting from β-enamino esters is presented. In this procedure, the double alkylation of β-enamino esters with organolithium reagents is followed by *one-pot* reduction with sodium borohydride in methanol/acetic acid. A hypothesis of mechanism is given, explaining the observed diastereoselectivity through molecular modeling. The configuration of the products was determined by ^{1}H NMR spectroscopy coupled with conformational analysis.

1. Introduction

A field of great interest in modern organic chemistry is the development of efficient enantioselective catalysts applicable to a wide range of reactions.[1–3] In previous studies[4,5] we have found that a substoichiometric amount of enantiopure aminoalkyl phenols and aminoalkyl naphthols accelerates the alkylation of aldehydes with alkylzincs, affording the corresponding alcohols in good enantiomeric purity. These chiral ligands are stable and highly accessible compounds, obtained by stereoselective reduction[6] or alkylation[7,8] of the corresponding 2-imidoyl phenols, or by aminoalkylation of naphthols.[9,10] Similarly to amino phenols, γ-amino alcohols are efficient chelating agents applicable in asymmetric synthesis promoted by chiral metallic catalyst. In addition γ-amino alcohols are useful building blocks in the synthesis of many natural products, pharmaceuticals, and compounds of biological interest.[11–17] Known procedures for the synthesis of γ-amino alcohols include reduction of isoxazoles and isoxazolines,[18] β-amino carbonyl compounds[19,20] or enaminones,[21,22] reductive amination of β-hydroxy ketones via Schiff bases,[23] or by in situ reduction of the lithiated β-hydroxy imine obtained by directed aldol condensation developed by Wittig.[24–28] All these reductive methods produce only secondary or primary γ-amino alcohols.

The preparation of tertiary γ-amino alcohols is known within the literature but the number of reports are limited.[29–35] We have proposed a general procedure for the preparation of tertiary γ-amino alcohols starting from β-enamino ketones,[36] and to the best of our knowledge other procedures starting from β-enamino esters are not known. In this paper, the scope and limitations of alkylation of β-enamino esters with organolithium compounds are presented as a method for the efficient and diastereoselective preparation of tertiary γ-amino alcohols.

2. Results and discussion

A mild and general method for the regio- and stereoselective synthesis of functionalized tertiary γ-amino alcohols (**2**) proceeds through the double alkylation of β-enamino esters (**1**) with alkyllithium reagents, followed by one-pot reduction of the intermediate dilithium β-hydroxy imines. This double alkylation works well with organolithium reagents in toluene at 0 °C or at room temperature, without the assistance of a Lewis acid. Grignard reagents under these conditions were unreactive. A number of examples were carried out using various organolithium reagents with differently functionalized β-enamino esters and the results are summarized in Table 1. The addition of organolithium reagents to enamino esters under these conditions is regioselective: the double alkylation occurs exclusively to the carbonyl group and not to the imine function.[37,38]

As shown in Table 1, the reduction occurs generally with good yields and *syn* diastereoselectivity in the case of compounds **2k–p**. The overall yields are very good when the R^3 substituent is a phenyl group (Table 1, entries 1–4) while

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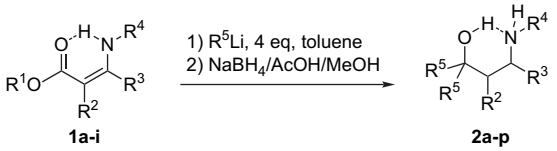
Table 1



1a-i **2a-p**

Entry	1	R^1O	R^2	R^3	R^4	2	R^5	T (°C)	Time (h)	Yield (%)[a]	d.r. (*syn*/*anti*)
1	**1a**	EtO	H	Ph	Ph	**2a**	Me	20	2	90	—
2	**1a**	EtO	H	Ph	Ph	**2b**	Bu	0	1	88	—
3	**1a**	EtO	H	Ph	Ph	**2c**	*i*-Pr	0	1	88 (42)[b]	—
4	**1a**	EtO	H	Ph	Ph	**2d**	Ph	20	1	91	—
5	**1b**	BnO	H	Me	Ph	**2e**	Bu	0	1	49	—
6	**1b**	BnO	H	Me	Ph	**2f**	*i*-Pr	0	1	59	—
7	**1c**	EtO	H	Pr	Ph	**2g**	Bu	0	1	57	—
8	**1d**	EtO	H	Ph	Bn	**2h**	Bu	0	1	65	—
9	**1e**	EtO	H	Ph	R*[c]	**2i**	Bu	20	1	47	73/27[d]
10	**1f**	EtO	Me	Me	Ph	**2j**	Bu	0	1	55	32/68
11	**1g**	EtO	$(CH_2)_3$		Ph	**2k**	Me	50	5	62	64/36
12	**1g**	EtO	$(CH_2)_3$		Ph	**2l**	Bu	0	1	72 (55)[b]	64/36 (76/24)[b]
13	**1h**	EtO	$(CH_2)_3$		Bn	**2m**	Bu	0	1	52	87/13
14	**1i**	EtO	$(CH_2)_4$		Ph	**2n**	Me	20	3	68	69/31
15	**1i**	EtO	$(CH_2)_4$		Ph	**2o**	Bu	0	1	89	65/35
16	**1i**	EtO	$(CH_2)_4$		Ph	**2p**	*i*-Pr	0	1	85	51/49

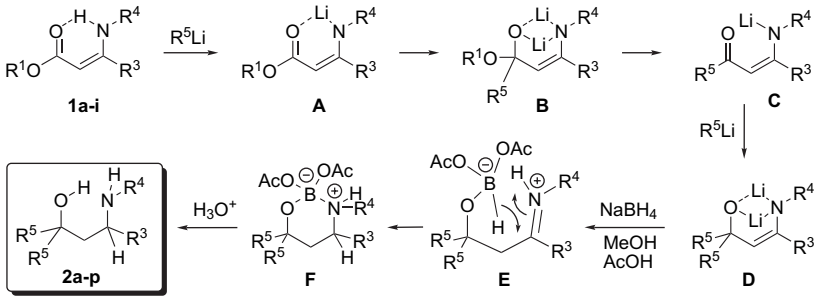
[a] Combined yields of the two isolated diastereomers.
[b] Reduction performed in absence of acetic acid.
[c] R*-NH_2=(*R*)-1-phenylethylamine.
[d] (2*S*,1′*R*)/(*R*,*R*) d.r.

they decreases in the presence of aliphatic groups (entries 5–7). β-Enamino esters derived from aniline (R^4=Ph) present a more electrophile ester function toward the organolithium reagents. Starting from β-enamino ester **1e**, that contains the chiral auxiliary (*R*)-(+)-phenylethylamino group, the reaction affords the amino alcohol (2*S*,1′*R*)-**2i** with reasonable diastereoisomeric excess, and the pure diastereomer can be obtained by flash chromatography. β-Enamino esters **1g–i** afford the amino alcohols *syn*-**2k–p** as major diastereomers (see Table 1).

In the hypothesized mechanism, depicted in Scheme 1, the first metalation of β-enamino esters **1a–i** affords the intermediate **A**, in which the chelated lithium atom enhances the electrophilicity of the ester function, making the addition of a second alkyllithium molecule easier. The dilithiated intermediate **B** eliminates lithium alkoxide with formation of the lithiated enamino ketone **C**. β-Enamino ketones **3** (see Scheme 3) can be isolated in some cases, when only 2.5 equiv of alkyllithium are used.[36] Generally, the lithiated β-enamino ketone **C** is more reactive with respect to the intermediate **A** and adds an organolithium molecule again, forming the intermediate **D**.[17] The *one-pot* reduction of **D** to the γ-amino alcohol **2a–p** occurs intramolecularly through the intermediate **E**.

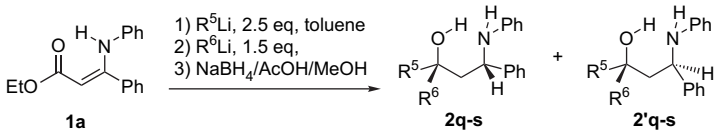
The presence of acetic acid in the reaction mixture in the reduction stage is important, because it allows a faster reduction and better yields in the final γ-amino alcohol **2** than the reduction conducted only in methanol. Anyway in this second case a higher diastereomeric excess is observed (see Table 1, entries 3 and 13 and Table 2, entry 3). After quenching the intermediate lithium alkoxide (**D**) with acid (saturated aqueous NH_4Cl), the free hydroxy imine (**4**) can be isolated (see Scheme 3), but its reduction with sodium borohydride in methanol resulted in lower yields of the γ-amino alcohol (**2**) because the free β-hydroxy imine (**4**) is unstable and dissociates spontaneously into the ketone **10** and imine **11** through a retroaldolic type process, as described in Scheme 2.[39]

On the other hand, the *one-pot* reduction of the reaction mixture with sodium borohydride, after methanol quenching only, does not take place. On the basis of these observations,



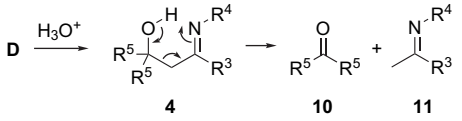
Scheme 1.

Table 2



Entry	1	Step 1			Step 2			2	Yield (%)[a]	d.r. (**2**/**2′**)
		R^5	T (°C)	Time (min)	R^6	T (°C)	Time (min)			
1	**1a**	Ph	0	30	Bu	0	60	**2q**	49	73/27
2	**1a**	Ph	0	30	*i*-Pr	0	60	**2r**	64	86/14
3	**1a**	*t*-Bu	0	60	Bu	20	60	**2s**	77 (41)[b]	84/16 (93/7)[b]

[a] Combined yields of the two diastereomers isolated.
[b] Reduction performed in absence of acetic acid.

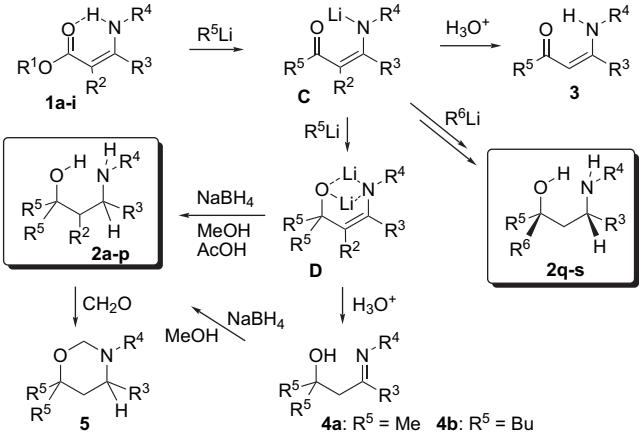


Scheme 2.

the more convenient *one-pot* reduction with sodium borohydride in methanol and acetic acid was chosen.

The *syn* stereochemistry of the hydride transfer can be explained by considering that the aminoborane complex *syn*-**F** is more stable than the corresponding *anti*-**F** (see the PM3 semiempirical level optimized geometries and the relative formation enthalpies in Figure 1).[40] The proposed mechanism is consistent with literature reports[41,42] and the *anti* stereochemistry of the products obtained reflects the intramolecular nature of the reaction. *syn* Products are generally obtained by intermolecular processes.[43]

Generally, the addition of the organometallic reagents to the intermediate lithium enamino ketones (**C**) is faster than the first addition. The intermediate enamino ketones are not isolable even with the use of a stoichiometric amount (2.5 equiv) of the organolithium reagent. Only when phenyllithium or *tert*-butyllithium is used, the preparation of the intermediate β-enamino ketones is possible with good yields[44] (see Scheme 3). This chemoselectivity was utilized for the stereoselective formation of a new stereogenic center at the quaternary carbinolic atom by the addition of a second different organolithium reagent on the intermediate enamino ketone (see Table 2). From the reduction step γ-amino alcohols **2q–s** as major diastereomers were obtained, resulting from the attack of the hydride from the same side of the less bulky group, that is, the R^6 substituent.



Scheme 3.

In the early phase of this research, the possibility of the synthesis of the γ-amino alcohol **2** by inverting the alkylation–reduction sequence was evaluated. As shown in Scheme 4, the β-amino esters **6a**,**b**, obtained by the reduction of the β-enamino esters **1a**,**d**,[45] were treated with *n*-butyllithium. From this sequence, the γ-amino alcohols **2b**,**h** are obtained

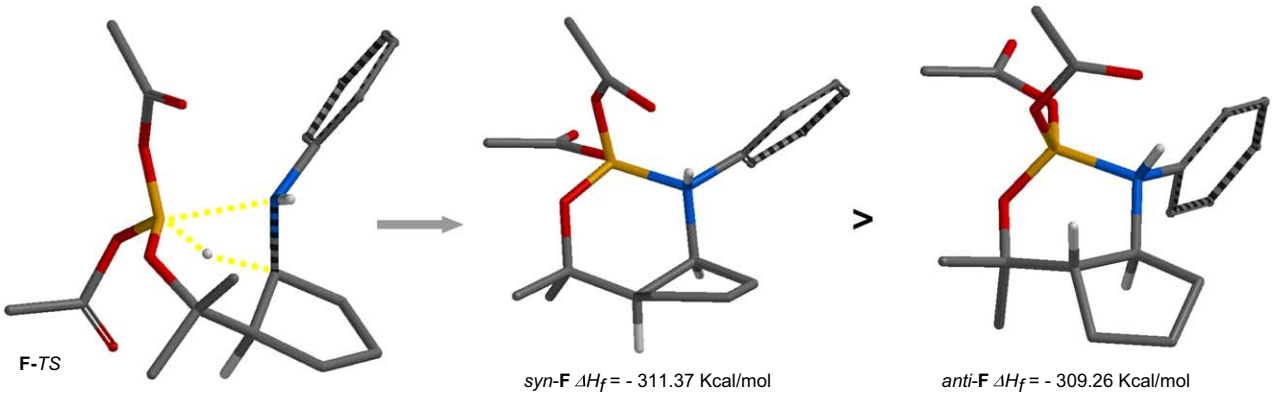
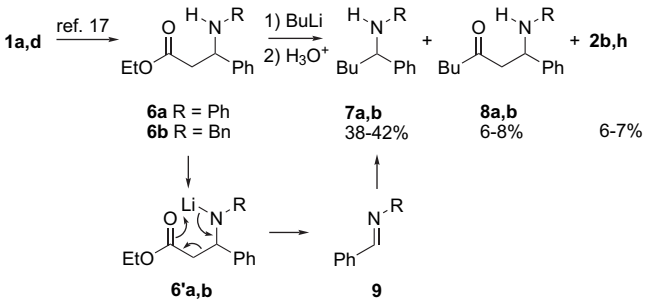


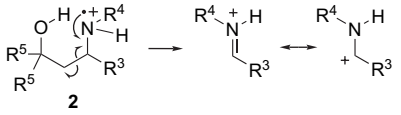
Figure 1. Transition structure for the intramolecular reduction of the β-hydroxy imine through the intermediate **E** with the formation of the thermodynamically more stable aminoborane complex *syn*-**F**.

in very low yields (6–7%). The amines **7a**,**b**, obtained as the main product, are formed by alkylation of the imine **9a**,**b**, derived by the decomposition of the lithiated β-amino ester **6′a**,**b** through a retroaldol pathway, as depicted in Scheme 4.



Scheme 4.

The molecular ion peak in the EI Mass Spectrometry of the β-amino alcohols (**2**) is usually quite weak. The base peak frequently results from C–C cleavage of α–β bond next to the nitrogen atom (see Scheme 5 and Section 5). This preferential fragmentation pathway is useful and routinely used to distinguish the possible regioisomers.



Scheme 5.

3. Stereochemistry

The diastereoisomeric ratio was calculated by integration of the ^{1}H and ^{13}C NMR data from the crude reaction mixture. Separation of pure diastereoisomers was carried out by fractional crystallization or by flash column chromatography.

The configuration of the stereogenic centers of the γ-amino alcohols **2** was assigned by interpreting the chemical shifts' general trend observed in ^{1}H NMR spectra of the isolated isomers on the basis of the more stable conformations calculated by molecular modeling.[40]

In the γ-amino alcohols **2**, an intramolecular hydrogen bond between the proton of the hydroxy group and the nitrogen atom was observed, which makes the cyclic chair conformation rigid and stabilizes the molecule in a conformation similar to that of the corresponding 1,3-tetrahydro oxazine (**5**), as reported also in literature.[22,46]

The attribution of the relative *syn*/*anti* configuration for products **2k**–**p** was made on the basis of N-C*H* signals in ^{1}H NMR for both diastereomers. In the major diastereomers *syn*-**2k**–**p** this proton results in a broad singlet with $W_{1/2}$=8.5–5.3 Hz. In the minor *anti*-**2k**–**m**, the same proton results upshifted by about 0.05–0.19 ppm with a $^{3}J_{ax-ax}$ of 7.2–8.0 Hz. Analogously in the minus diastereomers, *anti*-**2n**–**p**, the N-C*H* proton is upshifted by about 0.47–0.71 ppm with a $^{3}J_{ax-ax}$ of 10.3–10.7 Hz.

In the case of the products (*R**,*R**)-**2q** and (*R**,*S**)-**2q**, the relative configuration of the chiral centers was assigned on the basis of NOE experiments on the corresponding 1,3-tetrahydro oxazine derivative **5q**. The (*R**,*S**) relative configuration was attributed to the diastereomer that showed a strong NOE effect exerted by H-4 (geminal to the phenyl group) on the three nearer methylene protons H-2 and H-5 of the oxazine ring and H-1′ in the lateral butyl chain. Molecular modeling confirmed that in the more stable conformation all these protons are very close to each other, as shown in Figure 2. The (*R**,*R**) relative configuration was attributed to the other diastereomer that presented, instead of the NOE effect, a strong upshift of 0.55 ppm for the H-4 signal with respect to the corresponding proton of the (*R**,*S**) diastereomer. In the more stable conformation the phenyl ring in 6 assumes a position such as to exert a shielding effect on H-4, as shown in Figure 2.

In addition, the absolute configurations of both diastereomers of γ-amino alcohols **2i** were attributed through 1,3-tetrahydro oxazine derivatives **5i**, whose more stable conformations are depicted in Figure 3 and are in agreement with the ^{1}H NMR spectra. In these spectra the H-4 presents ^{3}J values of 11.0 and 11.5 Hz, typical of a *trans*-diaxial coupling, and an axial–equatorial ^{3}J values of 4.0 and 4.2 Hz, respectively. The (*R*,*R*) absolute configuration was attributed to the diastereomer that showed H-2 and H-4 upshifted

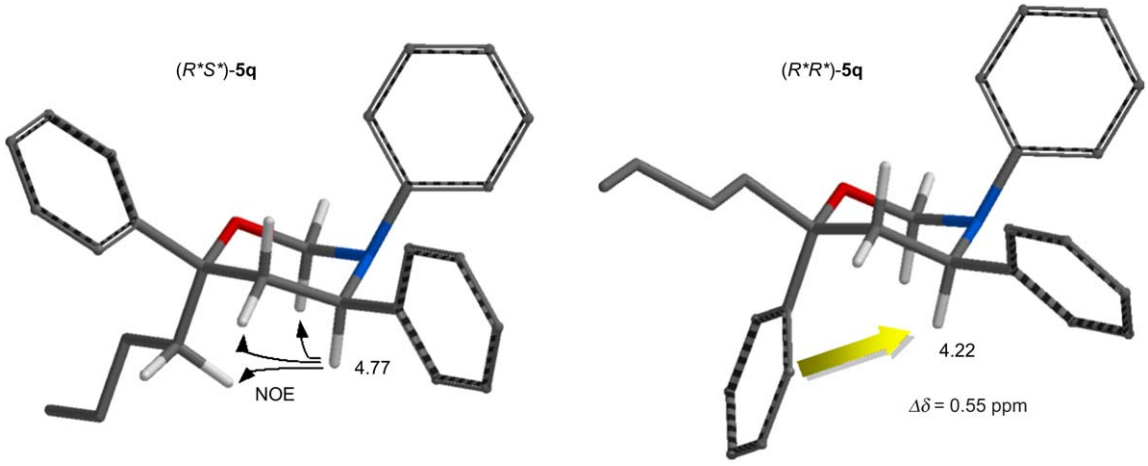


Figure 2. Models for the more stable conformation of **5q** diastereomers.

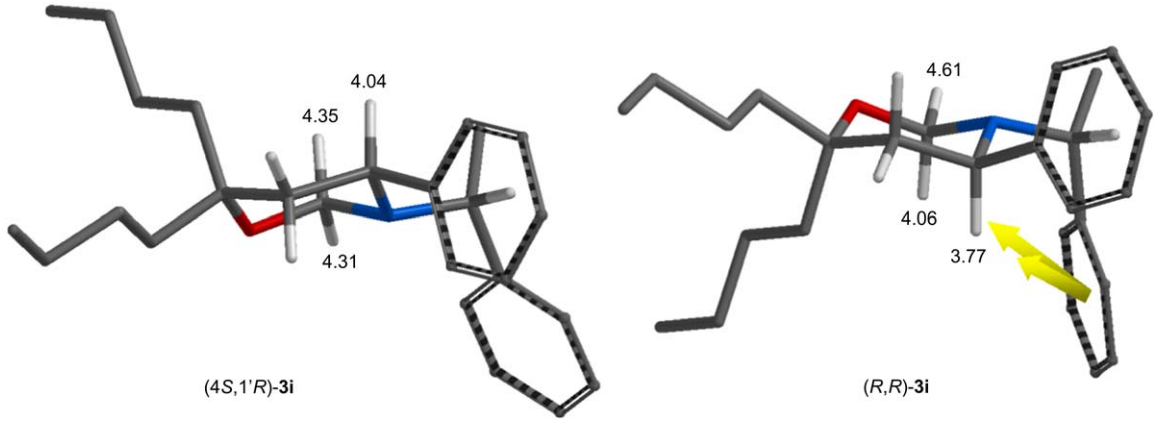


Figure 3. Models for the more stable conformation of **3i** diastereomers.

signals, of 0.25 and 0.27 ppm, respectively, due to the 1′-phenyl group arranged in the position depicted in Figure 3.

The relative trans configuration of (*R**,*R**)-**5j** is attributed on the basis of N-C*H* proton at 3.34 ppm with a $^{3}J_{ax-ax}$ value of 10.2 Hz, that is upshifted by 0.35 ppm with respect to the corresponding proton of *cis*-(*R**,*S**)-**5j**, at 3.69 ppm, with a ^{3}J value of 5.7 Hz.

4. Conclusion

In summary, an easy, general and stereoselective method for the direct preparation of tertiary γ-amino alcohols from β-enamino esters in good yields and satisfactory diastereomeric excess has been developed. The methodology consists of the double alkylation of β-enamino esters **1** with organolithium reagents followed by the *one-pot* reduction of the reaction mixture with sodium borohydride in methanol/acetic acid. The opportune choice of the reaction conditions and reagents enables the generation of a quaternary chiral center on the carbon atom bonded to the hydroxy function. Easily available starting materials and practical experimental conditions allow the facile preparation of these chiral pre-catalysts.

5. Experimental

5.1. General

^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, with $CDCl_3$ as solvent at ambient temperature and were calibrated using residual unadulterated solvents as the internal reference. Coupling constants are given in hertz. IR spectra were recorded using FTIR apparatus.

5.2. Materials and solvents

All reagents were commercially available, were purchased at the highest quality, and were purified by distillation when necessary. Hexane and toluene were distilled and stored on sodium wires before use. The following organolithium reagents were used: MeLi (1.6 M solution in diethylether), BuLi (2.5 M solution in hexane), PhLi (1.8 M solution in cyclohexane/diethylether 70:30), *i*-PrLi (1.7 M solution in pentane).

5.3. Synthesis of β-enamino esters 1a–i

β-Enamino esters **1** were prepared by condensation of β-ketoesters with amines according to standard literature methods.[47] β-Enamino esters **1b**,**c**,**g–i** were prepared in solventless way by mixing the β-ketoester and the amine in equimolecular amounts and stirring the mixture for 2–18 h at room temperature until TLC or GC analysis of the mixture revealed the complete consumption of the starting materials. After this time the reaction mixture was dissolved in *n*-hexane, dried with Na_2SO_4, and filtered. The solvent was removed under reduced pressure and the resulting crude β-enamino ester was purified by crystallization or filtration on SiO_2 with a 97:3 cyclohexane/ethyl acetate mixture as eluent.

5.4. General procedure for the alkylation and *one-pot* reduction of β-enamino esters 1: synthesis of γ-amino alcohols 2a–p

The β-enamino esters **1a–i** (1 mmol) were dissolved in toluene (3 mL), under nitrogen atmosphere, then was added the organolithium reagent (4.0 mmol); according to the reaction conditions and reagents reported in Table 1. Then the reaction mixture was quenched with methanol (1 mL) and concentrated under reduced pressure. The crude mixture was dissolved again in methanol (4 mL) at 0 °C and acetic acid (3 mL) and then $NaBH_4$ (4 mmol) were added in portions. After 1 h the mixture was treated with Na_2CO_3, until basic pH was reached, and extracted with dichloromethane (2×20 mL). The organic layer was dried with anhydrous Na_2SO_4, then filtered and the solvent was removed under reduced pressure. Chromatographic separation of the crude oil on silica gel with AcOEt/cyclohexane (3:97–20:80 v/v) afforded the pure γ-amino alcohols. Spectral data of products **2a–p** are as follow.

5.4.1. 4-Anilino-2-methyl-4-phenylbutan-2-ol [2a]. Colorless oil; IR (Neat) ν 3368, 1602, 1500, 1314, 1269, 751, 699 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.31 (s, 3H, *Me*), 1.42 (s, 3H, *Me*), 1.84 (dd, 1H, J=14.8, 3.3 Hz, H'_b), 2.01 (dd, 1H, J=14.8, 10.9 Hz, H_b), 2.85 (br s, 1H, N*H*), 4.30 (br s, 1H), 4.62 (dd, 1H, J=10.9, 3.3 Hz, H_c), 6.50–6.70 (m, 3H),

7.05–7.40 (m, 7H, Ar-*H*); ^{13}C NMR ($CDCl_3$) δ 28.2, 32.3, 50.9, 56.7, 71.6, 114.8, 118.3, 126.2, 127.2, 129.0, 129.3, 144.8, 147.4; MS (EI, 70 eV): *m/z* 255 (M^+, 14), 182 (100), 104 (14), 93 (22), 77 (22). Anal. Calcd for $C_{17}H_{21}NO$ (255.4): C 79.96; H 8.29; N 5.49. Found: C 79.74; H 8.13; N 5.56.

5.4.2. 1-Anilino-3-butyl-1-phenylheptan-3-ol [2b]. Colorless oil; IR (Neat) ν 3370, 1602, 1500, 1317, 1268, 750, 699 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.91 (t, 3 H, J=6.8 Hz, *Me*), 0.96 (t, 3H, J=6.6 Hz, *Me*), 1.20–1.53 (m, 10H), 1.58–1.75 (m, 2H), 1.81 (dd, 1H, J=15.0, 3.7 Hz, H'_b), 1.93 (dd, 1H, J=15.0, 10.1 Hz, H_b), 2.60 (br s, 1H, N*H*), 4.55 (dd, 1H, J=10.1, 3.7 Hz, H_c), 4.95 (br s, 1H, O*H*), 6.50–6.70 (m, 3H, Ar-*H*), 7.00–7.40 (m, 7H, Ar-*H*); ^{13}C NMR ($CDCl_3$) δ 14.3, 14.4, 23.5, 23.6, 25.6, 26.9, 38.0, 40.9, 47.5, 56.1, 75.4, 114.7, 118.1, 126.2, 127.1, 128.9, 129.2, 145.1, 147.5; MS (EI, 70 eV): *m/z* (%) 339 (M^+, 9), 282 (2), 182 (100), 104 (8), 93 (12), 77 (10). Anal. Calcd for $C_{23}H_{33}NO$ (339.5): C 81.37; H 9.80; N 4.13. Found: C 81.21; H 9.89; N 4.01.

5.4.3. 1-Anilino-3-isopropyl-4-methyl-1-phenylpentan-3-ol [2c]. Colorless oil; IR (Neat) ν 3366, 1602, 1499, 1308, 1265, 752, 692 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.93 (d, 3H, J=7.0 Hz, *Me*), 1.01 (d, 3H, J=7.0 Hz, *Me*), 1.10 (d, 3H, J=7.0 Hz, *Me*), 1.15 (d, 3H, J=7.0 Hz, *Me*), 1.80–2.16 (m, 4H), 3.41 (br s, 1H, N*H*), 4.66 (br s, 1H, O*H*), 4.71 (dd, 1H, J=9.5, 4.4 Hz, H_c), 6.60–6.80 (m, 3H, Ar-*H*), 7.05–7.40 (m, 7H, Ar-*H*); ^{13}C NMR ($CDCl_3$) δ 17.5, 17.7, 18.0, 18.6, 35.2, 36.2, 40.8, 56.6, 77.7, 115.6, 119.0, 126.1, 127.3, 129.0, 129.3, 114.8, 147.0; MS (EI, 70 eV): *m/z* (%) 311 (M^+, 4), 268 (2), 182 (100), 114 (6), 104 (8), 93 (20), 77 (22), 43 (15). Anal. Calcd for $C_{21}H_{29}NO$ (311.5): C 80.98; H 9.38; N 4.50. Found: C 81.13; H 9.49; N 4.31.

5.4.4. 3-Anilino-1,1,3-triphenylpropan-1-ol [2d]. White crystals; mp 128–130 °C (*n*-hexane/CH_2Cl_2); IR (Nujol) ν 3325, 1601, 1496, 1308, 1260, 753, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.66 (dd, 1H, J=14.8, 11.0 Hz, H_b), 2.86 (dd, 1H, J=14.8, 2.0 Hz, H'_b), 4.46 (dd, 1H, J=11.0, 2.0 Hz, H_c), 4.50 (br s, 1H, N*H*), 5.35 (br s, 1H, O*H*), 6.40–6.80 (m, 3H, Ar-*H*), 7.00–7.60 (m, 17H, Ar-*H*); ^{13}C NMR ($CDCl_3$) δ 49.1, 57.2, 78.9, 116.4, 119.9, 125.9, 126.1, 126.5, 127.1, 127.2, 127.5, 128.5, 128.6, 129.0, 129.3, 143.6, 146.3, 146.6, 147.8; MS (EI, 70 eV): *m/z* (%) 379 (M^+, 3), 269 (6), 180 (100), 165 (35), 77 (44). Anal. Calcd for $C_{27}H_{25}NO$ (379.5): C 85.45; H 6.64; N 3.69. Found: C 85.43; H 6.73; N 3.64.

5.4.5. 5-(2-Anilinopropyl)nonan-5-ol [2e]. Colorless oil; IR (Neat) ν 3368, 1602, 1498, 1320, 1252, 1151, 750, 692 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.93 (t, 3H, J=6.6 Hz, *Me*), 0.96 (t, 3H, J=6.6 Hz, *Me*), 2.29 (d, 3H, J=6.2 Hz, *Me*), 1.15–1.50 (m, 10H), 1.55–1.75 (m, 4H), 3.67 (br s, 2H), 3.70–3.90 (m, 1H), 6.70–6.90 (m, 3H, Ar-*H*), 7.15–7.25 (m, 2H, Ar-*H*); ^{13}C NMR ($CDCl_3$) δ 14.3, 14.4, 22.3, 23.5, 23.6, 25.6, 26.8, 38.9, 40.3, 45.3, 47.2, 74.5, 115.7, 119.4, 129.5, 147.0; MS (EI, 70 eV): *m/z* (%) 277 (M^+, 4), 220 (2), 202 (4), 120 (100), 93 (6), 77 (6). Anal. Calcd for $C_{18}H_{31}NO$ (277.4): C 77.92; H 11.26; N 5.05. Found: C 78.12; H 11.44; N 5.11.

5.4.6. 5-Anilino-3-isopropyl-2-methylhexan-3-ol [2f]. Colorless oil; IR (Neat) ν 3350, 1601, 1498, 1381, 1255, 1137, 753, 692 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.90 (d, 3H, J=6.6 Hz, *Me*), 0.95 (d, 3H, J=7.0 Hz, *Me*), 1.01 (d, 3H, J=7.0 Hz, *Me*), 1.02 (d, 3H, J=7.0 Hz, *Me*), 1.13 (d, 3H, J=6.2 Hz, *Me*), 1.51 (dd, 1H, J=15.0, 10.6 Hz, H_b), 1.67 (dd, 1H, J=15.0, 5.9 Hz, H'_b), 1.85 (hept, 1 H, J=6.8 Hz, Me_2CH), 1.94 (hept, 1H, J=7.0 Hz, Me_2CH), 3.10 (br s, 1H, N*H*), 3.75–3.95 (m, 1H, H_c), 4.40 (br s, 1H, O*H*), 6.70–6.90 (m, 3H, Ar-*H*), 7.15–7.25 (m, 2H, Ar-*H*); ^{13}C NMR ($CDCl_3$) δ 17.3, 17.4, 17.8, 18.1, 21.8, 34.8, 36.5, 38.2, 48.6, 76.7, 116.4, 119.9, 129.5, 146.8; MS (EI, 70 eV): *m/z* (%) 249 (M^+, 4), 206 (2), 120 (100), 93 (5), 77 (5). Anal. Calcd for $C_{16}H_{27}NO$ (249.4): C 77.06; H 10.91; N 5.62. Found: C 77.31; H 10.76; N 5.86.

5.4.7. 7-Anilino-5-butyldecan-5-ol [2g]. Colorless oil; IR (Neat) ν 3364, 1602, 1498, 1319, 1253, 1146, 750, 692 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.87 (t, 3H, J=7.3 Hz, *Me*), 0.91 (t, 3H, J=6.6 Hz, *Me*), 0.92 (t, 3H, J=6.6 Hz, *Me*), 1.10–1.65 (m, 17H), 1.72 (dd, 1H, J=15.0, 2.2 Hz, H'_b), 3.55 (br s, 1H, N*H*), 3.55–3.75 (m, 1H, H_c), 3.95 (br s, 1H, O*H*), 6.65 (m, 3H, Ar-*H*), 7.10–7.25 (m, 2H, Ar-*H*); ^{13}C NMR ($CDCl_3$) δ 14.2, 14.3, 14.4, 19.2, 23.5, 23.6, 25.6, 26.7, 38.4, 38.8, 40.4, 42.3, 51.0, 74.4, 115.5, 119.1, 129.5, 147.0; MS (EI, 70 eV): *m/z* (%) 305 (M^+, 4), 262 (1), 230 (5), 148 (100), 120 (53), 106 (22), 77 (9). Anal. Calcd for $C_{20}H_{35}NO$ (305.5): C 78.63; H 11.55; N 4.58. Found: C 78.79; H 11.41; N 4.75.

5.4.8. 5-(2-Benzylamino-2-phenylethyl)nonan-5-ol [2h]. Colorless oil; IR (Neat) ν 3291, 1602, 1205, 1027, 744, 699 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 6H, J=7.0 Hz, 2*Me*), 1.05–1.18 (m, 1H), 1.20–1.45 (m, 10H), 1.50–1.57 (m, 1H), 1.62 (dd, 1H, J=14.6, 2.4 Hz, H'_b), 1.78 (dd, 1H, J=14.6, 11.9 Hz, H_b), 3.48 (d, 1H, J=12.8 Hz, *Bn*), 3.66 (d, 1H, J=12.8 Hz, *Bn*), 3.20 (br s, 2H, N*H*, O*H*), 3.86 (dd, 1H, J=11.9, 2.4 Hz, H_c), 7.20–7.50 (m, 10H, Ar-*H*); ^{13}C NMR ($CDCl_3$) δ 14.3, 14.4, 23.5, 23.6, 25.6, 26.9, 38.5, 40.6, 45.5, 51.1, 58.9, 74.3, 126.6, 127.5, 127.6, 128.7, 128.9, 129.1, 139.2, 143.7; MS (EI, 70 eV): *m/z* (%) 296 (M^+−57, 4), 278 (3), 196 (70), 106 (16), 91 (100). Anal. Calcd for $C_{24}H_{35}NO$ (353.4): C 81.53; H 9.98; N 3.96. Found: C 81.38; H 10.13; N 3.75.

5.4.9. 5-{(2*S*)-2-[(1′*R*)-1′-Phenylethyl]amino-2-phenylethyl}nonan-5-ol [(2*S*,1′*R*)-2i]. Colorless oil $[\alpha]_D^{20}$ −10.8 (*c* 1.9, $CHCl_3$); IR (Neat) ν 3293, 1601, 1375, 1141, 1028, 759, 699 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.89 (t, 3H, J=6.8 Hz, *Me*), 1.01 (t, 3H, J=7.0 Hz, *Me*), 1.18–1.55 (m, 10H), 1.40 (d, 3H, J=6.2 Hz, *Me*-CH), 1.62–1.85 (m, 4H), 3.20 (br s, 1H, N*H*), 3.55 (q, 1H, J=6.3 Hz, Me-C*H*), 4.17 (t, 1H, J=7.0 Hz, H_c), 4.40 (br s, 1H, O*H*), 7.10–7.40 (m, 10H, Ar-*H*); ^{13}C NMR ($CDCl_3$) δ 14.3, 14.4, 21.3, 23.6, 23.7, 25.5, 27.2, 38.6, 40.6, 45.9, 54.6, 57.0, 74.3, 126.3, 126.7, 127.5, 127.6, 128.8, 129.1, 143.5, 145.4; MS (EI, 70 eV): *m/z* (%) 352 (M^+−15, 3), 310 (7), 210 (78), 106 (96), 105 (100). Anal. Calcd for $C_{25}H_{37}NO$ (367.6): C 81.70; H 10.15; N 3.81. Found: C 81.86; H 10.28; N 3.67.

5.4.10. 5-{(2*R*)-2-[(1′*R*)-1′-Phenylethyl]amino-2-phenylethyl}nonan-5-ol [(*R*,*R*)-2i]. Colorless oil; IR (Neat) ν 3297, 1599, 1378, 1140, 1034, 759, 700 cm^{-1}; ^{1}H NMR

($CDCl_3$) δ 0.76 (t, 3H, J=7.0 Hz, *Me*), 0.88 (t, 3H, J=6.2 Hz, *Me*), 0.90–1.40 (m, 12H), 1.28 (d, 3H, J=6.6 Hz, *Me*-CH), 1.50 (dd, 1H, J=14.6, 2.6 Hz, H'_b), 1.75 (dd, 1H, J=14.6, 11.7 Hz, H_b), 3.20 (br s, 1H, N*H*), 3.47 (q, 1H, J=6.6 Hz, Me-C*H*), 3.57 (dd, 1H, J=11.7, 2.6 Hz, H_c), 4.00 (br s, 1H, O*H*), 7.10–7.45 (m, 10H, Ar-*H*); MS (EI, 70 eV): *m*/*z* (%) 352 (M^+-15, 1), 310 (5), 210 (85), 106 (87), 105 (100). Anal. Calcd for $C_{25}H_{37}NO$ (367.6): C 81.7; H 10.15; N 3.81. Found: C 81.61; H 10.29; N 3.62.

5.4.11. 5-[(*R,*R**)-2-Anilino-1-methylpropyl]nonan-5-ol [*trans*-2j].** Oil; ^1H NMR ($CDCl_3$) δ 0.85–1.00 (m, 6H), 1.05–1.18 (m, 6H), 1.20–1.70 (m, 12H), 1.80 (dq, 1H, J=8.8, 7.0 Hz, H_b), 3.65 (br s, 2H, N*H*, O*H*), 3.70 (dq, 1H, J=8.8, 6.3 Hz, H_c), 6.70–7.30 (m, 5H, Ar-*H*); ^{13}C NMR ($CDCl_3$) δ 13.2, 14.4, 14.5, 19.8, 23.7, 23.9, 25.3, 25.7, 36.9, 37.6, 44.4, 52.3, 77.1, 116.0, 119.6, 129.6, 146.8; MS (EI, 70 eV): *m*/*z* (%) 291 (M^+, 2), 120 (100), 93 (9), 77 (6). Anal. Calcd for $C_{19}H_{33}NO$ (291.5): C 78.29; H 11.41; N 4.81. Found: C 78.48; H 11.32; N 4.63.

5.4.12. 5-[(1*R,2*S**)-2-Anilino-1-methylpropyl]nonan-5-ol [*cis*-2j].** Oil; ^1H NMR ($CDCl_3$) δ 0.85–1.00 (m, 6H), 1.05–1.18 (m, 6H), 1.20–1.75 (m, 13H), 3.65 (br s, 2H, N*H*, O*H*), 4.08 (qd, 1H, J=6.3, 2.3 Hz, H_c), 6.70–7.30 (m, 5H, Ar-*H*); ^{13}C NMR ($CDCl_3$) δ 6.6, 14.3, 14.4, 19.3, 23.6, 23.8, 25.9, 26.4, 36.0, 37.9, 41.9, 49.1, 77.7, 115.9, 119.6, 129.6, 146.8; MS (EI, 70 eV): *m*/*z* (%) 291 (M^+, 2), 120 (100), 93 (8), 77 (8). Anal. Calcd for $C_{19}H_{33}NO$ (291.5): C 78.29; H 11.41; N 4.81. Found: C 78.52; H 11.57; N 4.59.

5.4.13. 2-[(1*R,2*S**)-2-Anilinocyclopentyl]propan-2-ol [*cis*-2k].** Colorless oil; IR (Neat) ν 3371, 1601, 1505, 1322, 1190, 748, 693 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27 (s, 3H, *Me*), 1.34 (s, 3H, *Me*), 1.60–2.00 (m, 7H, N*H*), 3.00 (br s, 1H), 3.65 (br s, 1H), 3.90–3.98 (m, 1H, H_c), 6.60–6.80 (m, 3H, Ar-*H*), 7.10–7.30 (m, 2H, Ar-*H*); ^{13}C NMR ($CDCl_3$) δ 21.5, 23.4, 29.9, 30.8, 32.5, 52.7, 57.3, 72.1, 114.4, 117.8, 129.4, 147.9; MS (EI, 70 eV): *m*/*z* (%) 219 (M^+, 34), 204 (6), 186 (6), 132 (84), 119 (100), 106 (14), 93 (39). Anal. Calcd for $C_{14}H_{21}NO$ (219.3): C 76.67; H 9.65; N 6.39. Found: C 76.49; H 9.84; N 6.24.

5.4.14. 2-[(*R,*R**)-2-Anilinocyclopentyl]propan-2-ol [*trans*-2k].** Colorless oil; IR (Neat) ν 3400, 1602, 1503, 1320, 1180, 749, 692 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (s, 6H, 2*Me*), 1.30–1.54 (m, 2H), 1.60–1.88 (m, 4H), 2.02–2.22 (m, 1H), 3.00 (br s, 1H, N*H*), 3.60 (br s, 1H, O*H*) 3.75 (q, 1H, J=7.2 Hz, H_c), 6.60–6.90 (m, 3H, Ar-*H*), 7.10–7.30 (m, 2H, Ar-*H*); ^{13}C NMR ($CDCl_3$) δ 22.9, 25.6, 27.3, 29.8, 33.5, 56.6, 57.4, 72.8, 114.6, 118.3, 129.4, 147.8; MS (EI, 70 eV): *m*/*z* (%) 219 (M^+, 40), 204 (7), 186 (6), 132 (81), 119 (100), 106 (13), 93 (29). Anal. Calcd for $C_{14}H_{21}NO$ (219.3): C 76.67; H 9.65; N 6.29. Found: C 76.72; H 9.58; N 6.46.

5.4.15. 5-[(1*R,2*S**)-2-Anilinocyclopentyl]nonan-5-ol [*cis*-2l].** Colorless oil; IR (Neat) ν 3378, 1601, 1508, 1321, 1269, 747, 692 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86–0.98 (m, 6H, 2*Me*), 1.10–2.00 (m, 21H), 3.85–3.95 (m, 1H, H_c), 6.80–6.90 (m, 3H, Ar-*H*), 7.10–7.30 (m, 2H, Ar-*H*); ^{13}C NMR ($CDCl_3$) δ 14.3, 14.4, 21.1, 22.7, 23.5, 25.9, 26.3, 32.3, 37.8, 38.4, 39.2, 49.7, 56.7, 76.0, 114.4, 117.6, 129.4, 147.9; MS (EI, 70 eV): *m*/*z* (%) 303 (M^+, 11), 285 (3), 246 (14), 228 (16), 132 (74), 119 (100), 106 (13), 93 (32). Anal. Calcd for $C_{20}H_{33}NO$ (303.5): C 79.15; H 10.96; N 4.62. Found: C 79.32; H 10.79; N 4.39.

5.4.16. 5-[(*R,*R**)-2-Anilinocyclopentyl]nonan-5-ol [*trans*-2l].** ^1H NMR ($CDCl_3$) δ 0.85–1.00 (m, 6H, 2*Me*), 1.20–2.05 (m, 20H), 3.60 (br s, 1H, N*H*), 3.85 (td, 1H, J=7.3, 2.2 Hz, H_c), 6.60–7.30 (m, 5H, Ar-*H*).

5.4.17. 5-[(1*R,2*S**)-2-(Benzylamino)cyclopentyl]nonan-5-ol [*cis*-2m].** Colorless oil; IR (Neat) ν 3271, 1605, 1260, 1169, 745, 699 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, 3H, J=7.0 Hz, *Me*), 0.90 (t, 3H, J=7.0 Hz, *Me*), 1.05–1.55 (m, 13H), 1.60–1.82 (m, 8H), 3.18–3.26 (m, 1H, H_c), 3.84 (d, 1H, J=12.4 Hz, *Bn*), 3.66 (d, 1H, J=12.4 Hz, *Bn*), 7.20–7.35 (m, 5H, Ar-*H*); ^{13}C NMR ($CDCl_3$) δ 14.3, 14.4, 20.8, 22.1, 23.6, 23.7, 25.7, 26.3, 31.0, 37.3, 39.4, 49.4, 52.4, 60.3, 74.9, 127.5, 128.6, 128.8, 139.6; MS (EI, 70 eV): *m*/*z* (%) 298 (M^+-19, 2), 277 (4), 260 (44), 146 (43), 106 (26), 91 (100). Anal. Calcd for $C_{21}H_{35}NO$ (317.5): C 79.44; H 11.11; N 4.41. Found: C 79.27; H 11.18; N 4.24.

5.4.18. 5-[(*R,*R**)-2-(Benzylamino)cyclopentyl]nonan-5-ol [*trans*-2m].** ^1H NMR ($CDCl_3$) δ 0.89 (t, 3H, J=7.0 Hz, *Me*), 0.91 (t, 3H, J=6.6 Hz, *Me*), 1.10–1.90 (m, 20H), 2.05–2.25 (m, 1H), 3.00–3.15 (m, 1H, H_c), 3.72 (d, 1H, J=12.8 Hz, *Bn*), 3.91 (d, 1H, J=12.8 Hz, *Bn*), 7.20–7.40 (m, 5H, Ar-*H*).

5.4.19. 2-[(1*R,2*S**)-2-Anilinocyclohexyl]propan-2-ol [*cis*-2n].** White crystals; mp 64–66 °C (*n*-hexane/CH_2Cl_2); IR (Nujol) ν 3367, 1601, 1504, 1243, 1169, 749, 692 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20–1.70 (m, 6H, 2*Me*), 1.22 (s, 3H), 1.34 (s, 3H), 1.80–2.00 (m, 3H), 3.45 (br s, 1H, N*H*), 3.95 (br s, 1H, O*H*), 4.03–4.12 (m, 1H, H_c), 6.70–6.90 (m, 3H, Ar-*H*), 7.15–7.30 (m, 2H, Ar-*H*); ^{13}C NMR ($CDCl_3$) δ 20.1, 21.2, 26.1, 28.6, 29.3, 29.5, 48.6, 50.1, 72.8, 115.7, 119.2, 129.6, 147.0; MS (EI, 70 eV): *m*/*z* (%) 233 (M^+, 31), 218 (9), 200 (6), 132 (100), 119 (26), 106 (20), 93 (42). Anal. Calcd for $C_{15}H_{23}NO$ (233.3): C 77.21; H 9.93; N 6.00. Found: C 77.36; H 10.19; N 5.81.

5.4.20. 2-[(*R,*R**)-2-Anilinocyclohexyl]propan-2-ol [*trans*-2n].** White crystals; mp 122–124 °C (*n*-hexane/CH_2Cl_2); IR (Nujol) ν 3363, 1598, 1505, 1239, 1167, 745, 687 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90–1.16 (m, 2H), 1.18–1.40 (m, 2H), 1.21 (s, 3H, *Me*), 1.26 (s, 3H, *Me*), 1.52 (td, 1H, J=11.2, 3.3 Hz), 1.64–1.84 (m, 2H), 1.85–2.00 (m, 1H), 2.06–2.20 (m, 1H), 3.36 (td, 1H, J=10.7, 3.9 Hz, H_c), 4.15 (br s, 2H, N*H*, O*H*), 6.70–6.90 (m, 3H, Ar-*H*), 7.15–7.30 (m, 2H, Ar-*H*); ^{13}C NMR ($CDCl_3$) δ 24.8, 25.8, 26.3, 29.0, 29.5, 34.6, 52.8, 57.0, 74.2, 116.4, 120.2, 129.5, 146.5; MS (EI, 70 eV): *m*/*z* (%) 233 (M^+, 29), 218 (6), 200 (6), 132 (100), 119 (28), 106 (22), 93 (54). Anal. Calcd for $C_{15}H_{23}NO$ (233.3): C 77.21; H 9.93; N 6.00. Found: C 77.37; H 9.82; N 6.18.

5.4.21. 5-[(1*R,2*S**)-2-Anilinocyclohexyl]nonan-5-ol [*cis*-2o].** Colorless oil; IR (Neat) ν 3366, 1601, 1504, 1242, 1153, 749, 692 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.92 (t, 6H, 2*Me*), 1.10–

1.75 (m, 17H), 1.80–2.00 (m, 4H), 3.80 (br s, 2H, N*H*, O*H*), 3.95–4.05 (m, 1H, H_c), 6.70–6.90 (m, 3H, Ar-*H*), 7.15–7.30 (m, 2H, Ar-*H*); ^{13}C NMR ($CDCl_3$) δ 14.3, 14.4, 20.2, 20.6, 23.6, 23.7, 25.9, 26.2, 26.4, 29.3, 35.4, 37.3, 44.8, 49.8, 77.7, 115.8, 119.3, 129.6, 146.9; MS (EI, 70 eV): *m*/*z* (%) 317 (M^+, 13), 299 (3), 260 (24), 242 (21), 132 (100), 119 (36), 106 (42), 93 (85). Anal. Calcd for $C_{21}H_{35}NO$ (317.5): C 79.44; H 11.11; N 4.41. Found: C 79.53; H 11.02; N 4.60.

5.4.22. 5-[(*R,*R**)-2-Anilinocyclohexyl]nonan-5-ol [*trans*-2o].** Colorless oil; IR (Neat) ν 3359, 1603, 1500, 1245, 1151, 748, 694 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.85–1.00 (m, 6H, 2*Me*), 1.15–1.85 (m, 20H), 2.05–2.20 (m, 1H), 3.46 (td, 1H, *J*=10.3, 3.8 Hz, H_c), 4.00 (br s, 2H, N*H*, O*H*), 6.70–6.90 (m, 3H, Ar-*H*), 7.15–7.25 (m, 2H, Ar-*H*); ^{13}C NMR ($CDCl_3$) δ 14.4, 14.5, 23.8, 24.1, 25.0, 25.6, 26.0, 26.6, 28.6, 35.1, 36.9, 37.3, 49.2, 56.4, 77.0, 116.5, 120.2, 129.6, 146.7; MS (EI, 70 eV): *m*/*z* (%) 317 (M^+, 20), 299 (4), 260 (49), 242 (18), 132 (100), 119 (32), 106 (36), 93 (78). Anal. Calcd for $C_{21}H_{35}NO$ (317.5): C 79.44; H 11.11; N 4.41. Found: C 79.40; H 11.16; N 4.54.

5.4.23. 3-[(1*R,2*S**)-2-Anilinocyclohexyl]-2,4-dimethylpentan-3-ol [*cis*-2p].** Colorless oil; IR (Neat) ν 3369, 1602, 1498, 1242, 1057, 751, 692 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.02 (d, 12H, *J*=7.0 Hz, 4*Me*), 1.25–2.25 (m, 11H), 3.89 (br s, 2H, N*H*, O*H*), 4.04 (s, 1H, H_c), 6.70–6.90 (m, 3H, Ar-*H*), 7.15–7.30 (m, 2H, Ar-*H*); ^{13}C NMR ($CDCl_3$) δ 18.4, 19.1, 19.3, 19.4, 20.2, 22.5, 26.3, 30.0, 32.2, 35.2, 42.4, 50.2, 78.8, 115.9, 119.4, 129.6, 146.6; MS (EI, 70 eV): *m*/*z* (%) 289 (M^+, 30), 271 (8), 246 (100), 228 (14), 132 (99), 106 (48), 93 (97). Anal. Calcd for $C_{19}H_{31}NO$ (289.5): C 78.84; H 10.79; N 4.84. Found: C 78.97; H 10.55; N 4.97.

5.4.24. 3-[(*R,*R**)-2-Anilinocyclohexyl]-2,4-dimethylpentan-3-ol [*trans*-2p].** Colorless oil; IR (Neat) ν 3279, 1602, 1498, 1242, 1060, 994, 754, 692 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.94 (d, 3H, *J*=7.0 Hz, *Me*), 0.99 (d, 3H, *J*=7.0 Hz, *Me*), 1.05 (d, 3H, *J*=7.0 Hz, *Me*), 1.12 (d, 3H, *J*=7.0 Hz, *Me*), 1.12–1.42 (m, 4H), 1.63–1.95 (m, 4H), 1.96–2.30 (m, 3H), 3.57 (td, 1 H, *J*=10.3, 3.9 Hz, H_c), 4.50 (br s, 2H, N*H*, O*H*), 6.70–6.90 (m, 3H, Ar-*H*), 7.15–7.30 (m, 2H, Ar-*H*); ^{13}C NMR ($CDCl_3$) δ 18.0, 18.1, 19.4, 20.2, 25.8, 27.0, 29.2, 33.0, 33.8, 36.0, 48.2, 58.1, 79.4, 116.9, 120.4, 129.5, 146.4; MS (EI, 70 eV): *m*/*z* (%) 289 (M^+, 19), 271 (17), 246 (97), 228 (17), 132 (93), 106 (43), 93 (100). Anal. Calcd for $C_{19}H_{31}NO$ (289.5): C 78.84; H 10.79; N 4.84. Found: C 78.71; H 10.96; N 4.63.

5.5. General procedure for the alkylation and *one-pot* reduction for the synthesis of γ-amino alcohols 2q–s

The β-enamino ester **1a** (1 mmol) was dissolved in toluene (3 mL), under nitrogen atmosphere at 0 °C, then was added the first organolithium reagent (2.5 mmol), according to the reaction conditions and reagents reported in Table 2. After the reaction time (see Table 2) the second organolithium reagent was added (1.5 mmol). After 1 h the reduction procedure was performed (see above). Spectral data of products **2q–s** are as follow.

5.5.1. (1*R,3*S**)-1-Anilino-1,3-diphenylheptan-3-ol [(1*R**,3*S**)-2q].** Colorless oil; IR (Neat) ν 3419, 1601, 1504, 1314, 1266, 751, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.84 (t, 3H, *J*=6.6 Hz, *Me*), 0.90–1.10 (m, 1H), 1.15–1.45 (m, 3H), 1.98 (t, 2H, *J*=7.7 Hz), 2.15–2.40 (m, 2H, H_b, H'_b), 2.95 (br s, 1H, N*H*), 4.30 (br s, 1H, O*H*), 4.68 (t, 1H, *J*=7.0 Hz, H_c), 6.30–6.75 (m, 3H, Ar-*H*), 7.00–7.50 (m, 12H, Ar-*H*); ^{13}C NMR ($CDCl_3$) δ 14.2, 23.2, 25.8, 42.1, 51.6, 55.9, 76.8, 114.6, 118.3, 125.2, 126.4, 126.8, 127.3, 128.2, 128.6, 129.0, 129.2, 144.5, 147.1; MS (EI, 70 eV): *m*/*z* (%) 359 (M^+, 3), 284 (1), 182 (100), 118 (56), 104 (18), 77 (49). Anal. Calcd for $C_{25}H_{29}NO$ (359.5): C 83.52; H 8.13; N 3.90. Found: C 83.47; H 7.92; N 3.68.

5.5.2. (1*R,3*R**)-1-Anilino-1,3-diphenylheptan-3-ol [(1*R**,3*R**)-2q].** Colorless oil; IR (Neat) ν 3425, 1600, 1505, 1312, 1261, 750, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.85 (t, 3H, *J*=7.1 Hz, *Me*), 1.00–1.50 (m, 4H), 1.75–1.90 (m, 2H), 2.20–2.40 (m, 2H, H_b, H'_b), 4.18 (t, 1H, *J*=6.8 Hz, H_c), 4.55 (br s, 2H, N*H*, O*H*), 6.40–6.70 (m, 3H, Ar-*H*), 7.00–7.60 (m, 12H, Ar-*H*); ^{13}C NMR ($CDCl_3$) δ 14.2, 23.2, 25.5, 44.5, 50.0, 56.8, 78.0, 116.2, 119.7, 125.1, 125.7, 125.9, 126.7, 127.2, 128.5, 128.9, 129.2, 143.7, 146.5; MS (EI, 70 eV): *m*/*z* (%) 359 (M^+, 5), 284 (2), 182 (100), 118 (51), 105 (15), 77 (43). Anal. Calcd for $C_{25}H_{29}NO$ (359.5): C 83.52; H 8.13; N 3.90. Found: C 83.73; H 8.01; N 3.73.

5.5.3. (1*R,3*R**)-1-Anilino-4-methyl-1,3-diphenylpentan-3-ol [(1*R**,3*R**)-2r].** Colorless oil; IR (Neat) ν 3418, 1601, 1505, 1316, 1266, 1026, 752, 701 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.77 (d, 3H, *J*=7.0 Hz, *Me*), 0.91 (d, 3H, *J*=6.6 Hz, *Me*), 2.11 (sept, 1H, *J*=6.7 Hz, Me_2CH), 2.31 (dd, 1H, *J*=14.8, 8.8 Hz, H_b), 2.50 (dd, 1H, *J*=14.8, 4.8 Hz, H'_b), 2.77 (br s, 1H, N*H*), 4.02 (br s, 1H, O*H*), 4.55 (dd, 1H, *J*=8.8, 4.8 Hz, H_c), 6.20–6.30 (m, 2H, Ar-*H*), 6.54–6.66 (m, 1H, Ar-*H*), 6.94–7.08 (m, 2H, Ar-*H*), 7.20–7.40 (m, 10H, Ar-*H*); ^{13}C NMR ($CDCl_3$) δ 16.9, 17.7, 38.4, 47.9, 55.5, 78.2, 114.1, 117.9, 125.9, 126.5, 126.7, 127.3, 128.2, 128.9, 129.0, 144.4, 145.5, 146.8; MS (EI, 70 eV): *m*/*z* (%) 345 (M^+, 7), 182 (100), 105 (20), 77 (29). Anal. Calcd for $C_{24}H_{27}NO$ (345.8): C 83.44; H 7.88; N 4.05. Found: C 83.28; H 8.08; N 4.22.

5.5.4. (1*R,3*S**)-1-Anilino-4-methyl-1,3-diphenylpentan-3-ol [(1*R**,3*S**)-2r].** Colorless oil; IR (Neat) ν 3379, 1601, 1500, 1314, 1265, 752, 699 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.73 (d, 3H, *J*=6.6 Hz, *Me*), 1.06 (d, 3H, *J*=6.6 Hz, *Me*), 2.02 (sept, 1H, *J*=6.8 Hz, Me_2CH), 2.26 (dd, 1H, *J*=14.7, 3.3 Hz, H'_b), 2.37 (dd, 1H, *J*=14.7, 10.1 Hz, H_b), 3.88 (br s, 2H, N*H*, O*H*), 4.14 (dd, 1H, *J*=10.1, 3.3 Hz, H_c), 6.15–6.20 (m, 2H, Ar-*H*), 6.60–6.80 (m, 1H, Ar-*H*), 7.00–7.50 (m, 12H, Ar-*H*); ^{13}C NMR ($CDCl_3$) δ 16.9, 17.5, 39.2, 47.4, 57.2, 80.0, 116.2, 119.7, 126.2, 126.7, 127.3, 127.7, 128.4, 128.9, 129.2, 143.9, 146.3, 146.5; MS (EI, 70 eV): *m*/*z* (%) 345 (M^+, 7), 182 (100), 105 (20), 77 (33). Anal. Calcd for $C_{24}H_{27}NO$ (345.8): C 83.44; H, 7.88; N 4.05. Found: C 83.66; H, 7.63; N 4.31.

5.5.5. (1*S,3*R**)-1-Anilino-3-(*tert*-butyl)-1-phenylheptan-3-ol [(1*S**,3*R**)-2s].** White crystals; mp 81–83 °C (*n*-hexane/CH_2Cl_2); IR (Nujol) ν 3369, 1602, 1503, 1312,

1266, 751, 692 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.99 (t, 3H, J=6.8 Hz), 1.06 (s, 9H, *t-Bu*), 1.30–1.75 (m, 6H), 1.86 (dd, 1H, J=15.4, 10.6 Hz, H_b), 2.08 (dd, 1H, J=15.4, 2.6 Hz, H'_b), 3.47 (br s, 1H, N*H*), 4.40 (br s, 1H, O*H*), 4.75 (dd, 1H, J=10.6, 2.6 Hz, H_c), 6.60–6.80 (m, 3H, Ar-*H*), 7.05–7.40 (m, 7H, Ar-*H*); ^{13}C NMR ($CDCl_3$) δ 14.5, 23.8, 26.0, 26.7, 37.8, 39.0, 42.7, 57.0, 77.2, 115.6, 119.1, 126.2, 127.2, 129.0, 129.3, 144.6, 146.8; MS (EI, 70 eV): *m/z* (%) 339 (M^+, 5), 282 (2), 182 (100), 104 (14), 93 (16), 77 (14), 57 (11). Anal. Calcd for $C_{23}H_{33}NO$ (339.5): C 81.37; H 9.80; N 4.13. Found: C 81.46; H 9.64; N 4.26.

5.5.6. (1*R,3*R**)-1-Anilino-3-(*tert*-butyl)-1-phenylheptan-3-ol [(1*R**,3*R**)-2s].** MS (EI, 70 eV): *m/z* (%) 339 (M^+, 6), 278 (11), 182 (100), 104 (15), 93 (17), 77 (22), 57 (17).

5.6. General procedure for the synthesis of β-hydroxy imines 4

The β-enamino ester **1a** (1 mmol) was dissolved in toluene (3 mL), at 0 °C and was added alkyllithium reagent (methyllithium or butyllithium, 4 mmol) according to the reaction conditions and reagents reported in Table 1, entries 1 and 2. The reaction mixture was then quenched with aqueous saturated NH_4Cl (5 mL) and extracted with dichloromethane (2×10 mL). The organic layer was dried with anhydrous Na_2SO_4, then filtered, and the solvent was removed under reduced pressure. Spectral characterization of the β-hydroxy imines **4** was done by analysis of the crude reaction mixture. Spectral data of β-hydroxy imines **4a** and **4b** are as follows.

5.6.1. 2-Methyl-4-phenyl-4-(phenylimino)butan-2-ol [4a]. Yield 58%; Oil; IR (liquid film) ν_{max} 3392, 1630, 1594, 1212, 761, 696 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.43 (s, 6H, 2*Me*), 2.92 (s, 2H, CH_2), 5.93 (s, 1H, O*H*), 6.60–7.30 (m, 10H, Ar-*H*); ^{13}C NMR ($CDCl_3$): δ 29.8, 50.5, 70.6, 121.4, 123.9, 127.7, 128.4, 128.8, 129.1, 138.2, 149.3, 172.6. Anal. Calcd for $C_{17}H_{19}NO$ (253.3): C 80.60; H 7.56; N 5.53%. Found: C 81.74; H 7.79; N 5.29%.

5.6.2. 3-Butyl-1-phenyl-1-(phenylimino)heptan-3-ol [4b]. Yield 63%; Oil; ^1H NMR ($CDCl_3$) δ 0.91 (t, 6H J=6.8 Hz, 2*Me*), 1.25–1.50 (m, 8H), 1.61–1.73 (m, 4H), 2.89 (s, 2H, CH_2), 5.79 (s, 1H, O*H*), 6.65–7.35 (m, 10H, Ar-*H*); ^{13}C NMR ($CDCl_3$) δ 14.4, 23.6, 26.4, 39.5, 47.2, 74.8, 121.4, 123.8, 127.7, 128.4, 128.8, 129.0, 138.4, 149.4, 172.8. Anal. Calcd for $C_{23}H_{31}NO$ (337.5): C 81.85; H 9.26; N 4.15%. Found: C 81.07; H 9.38; N 3.91%.

5.7. General procedure for the synthesis of 1,3-tetrahydro oxazines 5

The γ-amino alcohols **2i**,**j**,**q** (0.5 mmol) were dissolved in THF (1 mL), and was added aqueous formaldehyde 35% (0.085 mL, 1 mmol). After 6 h the solvent was removed under reduced pressure and the crude tetrahydro oxazines purified by short filtration on a thin pad of silica gel with cyclohexane/AcOEt (97:3 v/v) or CH_2Cl_2/*n*-hexane (50:50 v/v) as eluent. Spectral data of tetrahydro oxazines **5** are as follow.

5.7.1. (*R,*R**)-6,6-Dibutyl-4,5-dimethyl-3-phenyl-1,3-oxazinane [(*R**,*R**)-5j].** White crystals; mp 50–52 °C (*n*-esano); IR (Nujol) ν_{max} 1600, 1503, 1379, 1247, 1020, 749, 693 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.74 (t, 3H, J=7.0 Hz, *Me*), 0.90 (d, 3H, J=7.0 Hz, *Me*), 0.94 (t, 3H, J=6.6 Hz, *Me*), 1.00–1.70 (m, 12H), 1.28 (d, 3H, J=6.2 Hz, *Me*), 2.08 (dq, 1H, J=7.0, 10.2 Hz, H_b), 3.34 (dq, 1H, J=6.2, 10.2 Hz, H_c), 4.83 (d, 1H, J=11.0 Hz, O-CH_2-N), 4.89 (d, 1H, J=11.0 Hz, O-CH_2-N), 6.80–7.30 (m, 5H, Ar-*H*); ^{13}C NMR ($CDCl_3$) δ 14.0, 14.2, 14.5, 19.3, 23.5, 23.6, 24.4, 25.4, 33.0, 37.2, 39.7, 56.7, 72.4, 78.4, 117.3, 120.1, 129.2, 149.2. Anal. Calcd for $C_{20}H_{33}NO$ (303.5): C 79.15; H 10.96; N 4.62. Found: C 79.23; H 10.79; N 4.81.

5.7.2. (4*S,5*R**)-6,6-Dibutyl-4,5-dimethyl-3-phenyl-1,3-oxazinane [(4*S**,5*R**)-5j].** Colorless oil; IR (Neat) ν_{max} 1598, 1379, 1252, 1188, 1018, 756, 696 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.84 (d, 3H, J=7.3 Hz, *Me*), 0.88 (t, 3H, J=7.0 Hz, *Me*), 0.96 (t, 3H, J=6.4 Hz), 1.08–1.42 (m, 9H), 1.40 (d, 3H, J=7.3 Hz, *Me*), 1.47–1.63 (m, 2H), 1.92–2.10 (m, 1H), 2.19 (dq, 1H, J=7.3, 5.7 Hz, H_b), 3.69 (dq, 1H, J=7.3, 5.7 Hz, H_c), 4.83 (s, 2H, O-CH_2-N), 6.85–7.35 (m, 5H, Ar-*H*); ^{13}C NMR ($CDCl_3$) δ 13.0, 14.3, 14.4, 15.9, 23.6, 23.8, 25.2, 25.4, 32.7, 35.3, 36.8, 57.9, 70.3, 78.7, 119.4, 120.6, 129.1, 150.6. Anal. Calcd for $C_{20}H_{33}NO$ (303.5): C 79.15; H 10.96; N 4.62. Found: C 79.34; H 10.84; N 4.48.

5.7.3. (4*S*)-6,6-Dibutyl-4-phenyl-3-[(1′*R*)-1′-phenylethyl]-1,3-oxazinane [(4*S*,1′*R*)-5i]. Oil; $[\alpha]_D^{20}$ +1.4 (*c* 1.6, $CHCl_3$); IR (liquid film) ν_{max} 1595, 1498, 1374, 1013, 753, 687 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (t, 3H, J=6.9 Hz, *Me*), 0.98 (t, 3H, J=7.0 Hz, *Me*), 1.12–1.44 (m, 9H), 1.38 (d, 3H, J=7.0 Hz, *Me*-CH), 1.47–1.60 (m, 2H), 1.75 (dd, 1H, J=13.7, 3.9 Hz, H'_b), 1.82–1.94 (m, 1H), 1.85 (dd, 1H, J=13.7, 11.0 Hz, H_b), 3.94 (q, 1H, J=7.0 Hz, Me-C*H*), 4.04 (dd, 1H, J=11.0, 3.9 Hz, H_c), 4.31 (d, 1H, J=10.0 Hz, O-CH_2-N), 4.35 (d, 1H, J=10.0 Hz, O-CH_2-N), 7.15–7.50 (m, 10H, Ar-*H*); ^{13}C NMR ($CDCl_3$) δ 12.6, 14.2, 14.4, 23.4, 23.6, 25.3, 25.6, 33.1, 38.5, 42.5, 55.4, 58.0, 72.1, 75.8, 126.7, 127.2, 127.6, 127.7, 128.2, 128.7, 143.9, 144.4. Anal. Calcd for $C_{26}H_{37}NO$ (379.6): C 82.27; H 9.83; N 3.69. Found: C 82.45; H 9.61; N 3.52.

5.7.4. (*R*)-6,6-Dibutyl-4-phenyl-3-[(*R*)-1′-phenylethyl]-1,3-oxazinane [(*R*,*R*)-5i]. Oil; $[\alpha]_D^{20}$ +96.6 (*c* 1.1, $CHCl_3$); IR (liquid film) ν_{max} 1596, 1501, 1374, 1245, 1016, 748, 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.84 (t, 3H, J=6.8 Hz, *Me*), 0.86 (t, 3H, J=6.6 Hz, *Me*), 1.05–1.35 (m, 9H), 1.35 (d, 3H, J=7.0 Hz, *Me*-CH), 1.40–1.65 (m, 3H), 1.61 (dd, 1H, J=13.9, 4.0 Hz, H'_b), 1.77 (dd, 1H, J=13.9, 11.5 Hz, H_b), 3.77 (dd, 1H, J=11.5, 4.2 Hz, H_c), 3.95 (q, 1H, J=7.0 Hz, Me-C*H*), 4.06 (d, 1H, J=9.9 Hz, O-CH_2-N), 4.61 (d, 1H, J=9.9 Hz, O-CH_2-N), 7.10–7.50 (m, 10H, Ar-*H*); ^{13}C NMR ($CDCl_3$) δ 14.2, 14.3, 20.4, 23.4, 23.5, 25.2, 25.5, 32.4, 39.2, 43.6, 57.6, 58.6, 73.2, 75.8, 127.0, 127.1, 127.5, 128.2, 128.3, 128.8, 141.4, 145.4. Anal. Calcd for $C_{26}H_{37}NO$ (379.6): C 82.27; H 9.83; N 3.69. Found: C 82.43; H 9.60; N 3.88.

5.7.5. (4*S,6*R**)-6-Butyl-3,4,6-triphenyl-1,3-oxazinane [(4*S**,6*R**)-5q].** Colorless oil; IR (Neat) ν_{max} 1600, 1505, 1249, 1026, 753, 696 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.79 (t, 3H, J=7.0 Hz, *Me*), 0.86–1.04 (m, 1H), 1.10–1.42 (m, 3H), 1.78 (ddd, 1H, J=11.6, 4.5, 1.6 Hz), 2.14 (ddd, 1H, J=11.8, 4.1, 1.5 Hz), 2.34 (dd, 1H, J=14.5, 11.8 Hz, H_b),

2.49 (dd, 1H, J=14.5, 5.5 Hz, H'_b), 4.77 (dd, 1H, J=11.8, 5.5 Hz, H_c), 5.14 (d, 1H, J=10.6 Hz, O-CH_2-N), 5.33 (d, 1H, J=10.6 Hz, O-CH_2-N), 6.80–6.95 (m, 3H, Ar-*H*), 7.15–7.45 (m, 12H, Ar-*H*); ^{13}C NMR ($CDCl_3$) δ 14.2, 23.2, 25.8, 40.3, 44.3, 58.2, 75.2, 78.3, 117.2, 120.1, 125.3, 126.4, 126.8, 127.2, 128.3, 128.9, 129.1, 144.1, 146.7, 149.7. Anal. Calcd for $C_{26}H_{29}NO$ (371.5): C 84.06; H 7.87; N 3.77. Found: C 83.87; H 7.73; N 3.59.

5.7.6. (4*R,6*R**)-6-Butyl-3,4,6-triphenyl-1,3-oxazinane [(4*R**,6*R**)-5q].** Colorless oil; IR (neat) ν_{max} 1597, 1505, 1023, 755, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.82 (t, 3H, J=7.0 Hz, *Me*), 1.10–1.35 (m, 4H), 1.80 (t, 2H, J=7.7 Hz), 2.38 (dd, 1H, J=14.3, 11.7 Hz, H_b), 2.57 (dd, 1H, J=14.3, 4.4 Hz, H'_b), 4.22 (dd, 1H, J=11.7, 4.4 Hz, H_c), 5.02 (d, 1H, J=10.3 Hz, O-CH_2-N), 5.12 (d, 1H, J=10.3 Hz, O-CH_2-N), 6.70–6.85 (m, 3H, Ar-*H*), 7.00–7.50 (m, 12H, Ar-*H*); ^{13}C NMR ($CDCl_3$) δ 14.2, 23.2, 25.5, 42.8, 44.5, 58.5, 76.9, 79.3, 119.3, 120.9, 126.5, 126.6, 126.9, 127.2, 128.5, 128.8, 128.9, 143.7, 143.8, 148.2. Anal. Calcd for $C_{26}H_{29}NO$ (371.5): C 84.06; H 7.87; N 3.77. Found: C 84.27; H 7.99; N 3.58.

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Supplementary data

The computational results (Cartesian coordinates of the optimized geometries and semiempirical PM3 level enthalpies of formation) for *cis*-**2k–F**, *trans*-**2k–F**, (*R**,*S**)-**5q**, (*R**,*R**)-**5q**, (4*S*,1′*R*)-**3i**, (*R*,*R*)-**3i** are given. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.07.044.

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