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Photoreduction of imines. An environmentally friendly approach to obtain amines

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Abstract—The photoreduction of different imines to amines in alcoholic solvents is reported. The reduction involves a versatile and chemoselective methodology that is environmentally friendly in that it avoids the use of metal hydrides and other dangerous reducing agents.
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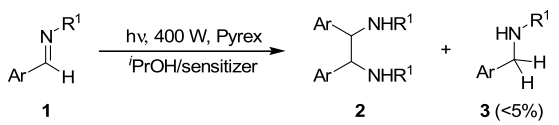
1. Introduction

One of the current challenges that faces organic synthesis, and chemistry in general, is the development of new and cleaner processes that minimise or eliminate the use of hazardous substances.[1] However, a wide variety of reactions that are not environmentally friendly are currently used in the chemical industry. One of these reactions is the reduction of imines—a useful method for the synthesis of secondary amines[2]—which are important precursors of key compounds in the pharmaceutical and agricultural industries.[3] Furthermore, amines play a significant role as pharmacophoric groups in biologically active substances. In this sense, catalytic hydrogenation,[4] metal hydrides[5] and dissolving metals[6] are usually employed for this transformation.

The photochemical behavior of compounds containing a carbon–nitrogen double bond has been the focus of our attention for almost a decade[7] and, more specifically, we have been concerned with the photoreduction of imines-a topic that has not been extensively studied.[8]

In this context, we have previously reported the sensitized photoreductive coupling of aldimines **1**[9] (Scheme 1), which leads to symmetrical vicinal diamines **2** in good-to-excellent yields. The reaction involves the formation of triplet species' that progress to give radical species' through hydrogen abstraction of the isopropyl alcohol.[9a] Interestingly, we detected the presence of secondary amines **3** as minor products ($\leq 5\%$) in this process, particularly in cases where the formation of the imine radical was less effective. This finding prompted us to modify the experimental conditions with the goal of obtaining monoamines as the major products of the photoreaction.



Scheme 1. Sensitized photocoupling of aldimines.

In this report, we present the photoreduction of a wide variety of aldimines and ketimines to amines with the aim of developing a new methodology that is compatible with the principles of green chemistry.[1] In this process the combination of light and an alcoholic solvent is used as the reducing system.

2. Results and discussion

2.1. Photoreduction of aldimines to amines

We initially studied the conditions under which the secondary amines could be obtained as the major products in the photoreaction of aldimines. Our experience in this type of process led us to believe that the control of radical formation is essential to achieve the objective. In this sense, we initially tested the effect of different features such as aldimine concentration, ^{i}PrOH/acetone ratio and filter glass on the reaction of aldimine **1a**.

When a solution of **1a** in a mixture of ^{i}PrOH and acetone was irradiated through Pyrex glass (i.e., sensitized conditions) at different imine concentrations or with different ^{i}PrOH/acetone ratios, amine **3a** was detected by NMR

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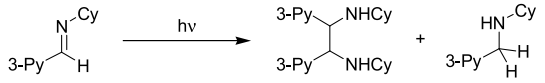
Table 1. Modulation of the photoreduction of aldimine **1a**



1a **2a** **3a**

Entry	Conditions	Concentration **1a**[a]	Ratio **2a/3a**[b]
1	^{i}PrOH/acetone (7/3), Pyrex	3	≥95/5
2	^{i}PrOH/acetone (7/3), Pyrex	1.5	94/6
3	^{i}PrOH/acetone (9/1), Pyrex	1.5	93/7
4	^{i}PrOH, Pyrex	1.5	No reaction
5	^{i}PrOH, Vycor	1.5	55/45
6	^{i}PrOH, Vycor	0.7	≤5/95

[a] 10^{-2} molar concentration.
[b] Determined by ^{1}H NMR analysis of the crude reaction mixture.

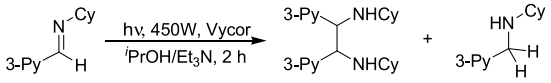
spectroscopy but diamines **2a** were the major products of the reaction (see Table 1, entries 1–3). In any case, amine **3a** could not be isolated from the reaction mixture. Furthermore, the photoreaction through Pyrex glass did not proceed in the absence of acetone and only the starting imine was recovered (Table 1, entry 4).

We therefore, decided to analyse the effect of using a different filter. When a Vycor glass filter was employed, the presence of acetone as a sensitizer was not necessary since **1a** absorbs above 260 nm and, as a result, the irradiation was carried out successfully using only isopropyl alcohol. The reaction was monitored under these conditions and a substantial decrease in the **2a/3a** ratio was observed (see Table 1, entries 5 and 6), particularly when the imine concentration was quite low. This observation demonstrates that the reaction is concentration-dependent. In fact, as shown in entry 6, the irradiation of a 7.5×10^{-3} M solution of imine **1a** in isopropyl alcohol for 2 h through Vycor glass gave amine **3a** almost exclusively (**2a/3a** ratio ≤5/95). The yield of this reaction was 32% after purification by column chromatography. However, prolonged reaction times through Vycor gave large amounts of polymeric material, which indicates that the amine formed may not be photostable under the reaction conditions described above. This photodegradation was also detected in the irradiation of other aldimines tested in this study. This situation clearly limits the utility of the photoreduction, because the yields obtained using this approach were in the range 20–35% in all cases.

It is well known that amines are involved in photoreduction processes of different unsaturated compounds, such as ketones, due to their lower ionization potential.[10] In the context of our photoreduction process, the degradation of the desired monoamines **3** can be explained in terms of a similar process, in which the amine reacts with aldimine **1** but mainly gives polymeric material and, consequently, decreases the yield of the reaction. It would be expected that the presence of a more reactive amine in the irradiation, such as triethylamine (Et_3N), would avoid the photodecomposition of the resulting secondary monoamines **3**.

In fact, the use of an excess of Et_3N in the irradiations led to a considerable improvement in the yield of the desired monoamine **3a**. As can be seen in Table 2, the yield of monoamine **3a** became higher as the amount of Et_3N in the

Table 2. Photoreduction of aldimine **1a** in the presence of Et_3N



1a **2a** **3a**

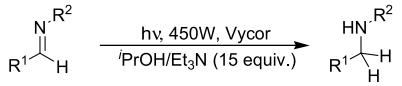
Entry	Et_3N (equiv)[a]	Ratio **2a/3a**[b]	Yield **3a** (%)[c]
1	0	≥5/95	32
2	7	16/84	41
3	10	10/90	48
4	15	15/85	62
5	25	15/85	55

[a] Refer to initial imine **1a**.
[b] Determined by ^{1}H NMR analysis of the crude reaction mixture.
[c] Isolated yield after purification by column chromatography.

photoreaction was increased. The best result was obtained on using 15 equiv of Et_3N with respect to the initial imine **1a** (see entry 4 in Table 2). Fortunately, under these modified reaction conditions, the ratio **2a/3a** was not significantly modified. In these reactions it is Et_3N, which is a tertiary amine in excess, that mainly undergoes the photodegradation and this sacrificial effect leads to an increase in the yield of the secondary amines **3**.

Bearing in mind the effect of Et_3N, we aimed at exploring the scope and synthetic possibilities of monoamine formation. Thus, we tested the reaction with a representative set of aldimines with different R^1 and R^2 groups, imines **1b–1g**, and we carried out the photoreduction of these compounds using the conditions optimized for aldimine **1a** (see Table 3).

Table 3. Photoreduction of different aldimines in the presence of Et_3N



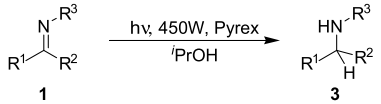
1 **3**

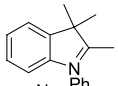
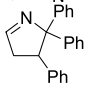
Imine	R^1	R^2	Time (h)	Yield **3** (%)[a]
1a	3-Py	Cy	2	62
1b	3-Py	^{t}Bu	2	65
1c	2-Py	Cy	2	46
1d	4-Py	Cy	2	55
1e	Ph	Cy	2	47[b]
1f	2-Naphthyl	Cy	4	50
1g	2-Quinolyl	Cy	9	30[c]

[a] Isolated yield after purification by column chromatography.
[b] The aminoalcohol resulting from addition of the isopropyl radical was isolated (23%).
[c] The irradiation was carried out through Pyrex glass.

In general, the photoreduction gave the corresponding amines **3** in moderate-to-good yields. As mentioned above, the use of Et_3N has a marked effect on the yield of the photoreaction but hardly alters the diamine/monoamine ratio. However, some points concerning these reactions should be noted. On the one hand, the irradiation of benzaldimine **1e** yielded both the desired monoamine and the aminoalcohol resulting from addition of the isopropyl radical, which is generated by hydrogen abstraction of the alcoholic solvent. On the other hand, the irradiation of aldimine **1g** warrants particular attention since it was possible in this case to carry out the irradiation through Pyrex glass. This finding shows that the UV–vis absorption

Table 4. Photoreduction of ketimines



Imine	R^1	R^2	R^3	Time (h)	Yield **3** (%)[a]
1h	Ph	CH_3	Cy	3	23[b]
1i	2-Naphthyl	CH_3	Cy	7	52[b]
1j	2-Py	CH_3	Cy	11	58
1k	Ph	Ph	H	9	80
1l	Ph	Ph	Cy	12	62
1m	Ph	Ph	*c*-Pr	10	75
1n	Ph	Ph	CH_2CN	6	70
1o	Ph	Ph	CH_2CO_2Et	13	61
1p	Ph	CO_2Et	Cy	5	60[c]
1q	Ph	CO_2Et	(*R*)-$CH(CH_3)_3Ph$	5.5	48[c]
1r				2	15[b]
1s				14	51

[a] Isolated yield after purification by column chromatography.
[b] The irradiation was carried out through Vycor glass in the presence of Et_3N.
[c] The irradiation was carried out through Vycor glass and ethanol was used as the alcoholic solvent.

characteristics of the materials depend on the nature of the substituents on the imine. It is well known that the active band in the photoreduction is an $n\rightarrow\pi^*$ electronic transition ($\lambda\approx$250–285 nm),[8b] which can experience a bathochromic shift-particularly when R^1 (aryl group) includes a heteroatom or is a group that provides conjugation to the system.

2.2. Photoreduction of ketimines and cyclic imines to amines

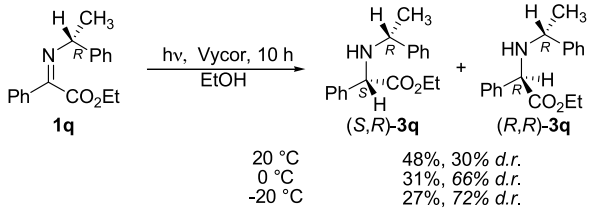
The next step in our study involved exploring the generality and versatility of the photoreduction. In order to achieve this goal we extended this investigation to other imines. As detailed in Table 4, a number of representative ketimines and cyclic imines were irradiated through Pyrex or Vycor glass, depending on the absorption spectrum of the compound in question. The desired monoamines **3** were obtained in moderate-to-good yields.

It is worth noting that the larger substituents in the imine group made the coupling reaction more difficult. As a result, formation of the monoamine is favourable and the photoreduction does not depend on imine concentration-as it did in the case of aldimines. Moreover, ultraviolet irradiation through Pyrex glass (which filters out radiation below 290 nm) of ketimines **1j**–**1o** and **1s** also gave the monoamines in good yields and without decomposition. As example, irradiation of imine **1k** through Vycor glass mainly gave polymeric material; the corresponding amine **3k** was detected but could not be isolated. However, irradiation through Pyrex led to monoamine **3k** in excellent yield. In this case, lower energy radiation is involved and clearly the reaction times required are longer. In contrast, ketimines **1h** and **1i** did not react when Pyrex-filtered light was used and these irradiations were carried out as described previously for aldimines, using Vycor glass and in the presence of Et_3N.

Interestingly, it was observed that the photochemical reduction of different cyclic imines proceeded successfully. Some of the most significant results are gathered in Table 4. As can be seen in this table, the irradiation of imines **1r** and **1s** under general conditions[11] gave the expected amines in moderate yields. Cyclic derivatives of indolenine (such as **1r**) have previously been reported as being unreactive toward hydrogen atom abstraction.[12]

As far as the chemoselectivity of the photoreaction is concerned, it should be noted that photoreduction of bifuncional imines, such as ketimine **1n** and imino esters **1o**–**1q**, was carried out in a chemoselective way and gave only the desired amines. Moreover, in the case of imino esters **1p**–**1q**, we employed Vycor-filtered light since these compounds did not absorb above 290 nm. In addition, it was observed that the resulting amino esters are more stable to the photodegradation than monoamines and, as a consequence, it was not necessary to use Et_3N. Other byproducts, such as diamines or aminoalcohols, could not be detected. Moreover, the reaction rate increased markedly when ethanol was used as the solvent.

Finally, it is worth noting that the photoreduction of chiral imino ester **1q** (Scheme 2) was carried out with moderate/high diastereoselectivity [(*R*,*S*)/(*S*,*S*) ratio = 4:1]. The two diastereomers **3q** could be easily separated by simple column chromatography. As shown in Scheme 2, the



Scheme 2. Stereoselectivity in the photoreduction of ketimines.

diastereoselectivity of the reaction depends on the irradiation temperature and the best diastereomeric excess (72%) was obtained at −20 °C.

The absolute configuration of the amino ester (*R*,*R*)-**3q** was determined by reduction with $LiAlH_4$ and comparison of the resulting aminoalcohol with data reported in the literature.[13] Interestingly, the amino esters **3q** can be transformed into the corresponding α-amino acids,[14] providing an alternative method to that described in the literature[15] to obtain this type of molecule.

3. Conclusions

From the results described above, we conclude that the photoreduction of different imines bearing a hydrogen atom, alkyl or aryl groups leads to the corresponding amines through a new and versatile approach that is compatible with the environment. Moreover, we have modulated, for the first time, the photoreduction of aldimines to obtain secondary amines as reaction products instead of vicinal diamines. The use of Et_3N delays the decomposition of monoamines and improves the synthetic utility of this process.

We have also demonstrated that cyclic imines are reactive toward hydrogen atom abstraction. Moreover, the irradiation of a variety of bifunctional imines has demonstrated that photoreduction of the carbon–nitrogen double bond is chemoselective in the presence of other functional groups such as ester and cyano groups. Finally, the reduction of chiral imino esters led to enantiopure amino esters that can be easily converted into the corresponding α-amino acids, thus providing a new method for the synthesis of this kind of compound. Finally, studies to elucidate the mechanism and to extend the scope of this reaction are in progress.

4. Experimental

4.1. General aspects

^1H and ^{13}C NMR spectra were recorded on a Bruker ARX-300 spectrometer in $CDCl_3$ with TMS as internal standard. Electrospray mass spectra were obtained on an HP 5989 B apparatus with an HP 59987A interface, in positive-ion mode with methanol–water–acetic acid (60/35/5) as the mobile phase. GC–MS spectra were recorded on an HP G1800A apparatus. Elemental analyses were obtained using a CE Instrument Model 1110. Optical rotations were measured on a Perkin-Elmer 341 polarimeter in 1.0 dm cells of 1.0 and 0.35 mL capacity. All solvents were purified by standard procedures and freshly distilled prior to use. Reagents were of commercial grade (Aldrich).

4.2. General procedure for synthesis of imines 1a–s

Imines **1a–j** were prepared by condensation of different carboxaldehydes with the corresponding primary amine in chloroform or toluene under reflux according to literature procedures.[16] Imines **1l** and **1m** were prepared by condensation of benzophenone imine with the corresponding primary amine in dry toluene at 80 °C. Imino esters **1p** and **1q** were prepared by condensation of ethyl benzoylformate with the corresponding amine (1.1 equiv) in toluene at 100 °C catalyzed by $AlCl_3$. Cyclic imine **1s** was obtained by an *N*-cyclopropylimine-1-pyrroline rearrangement.[7] Imines **1k**, **1n**, **1o** and **1r** are commercially available

4.3. General procedure for irradiation of imines 1a–s

Argon was bubbled through a solution of the corresponding imine **1** (0.75 mmol for **1a–g** and **1s**, and 1.5 mmol for **1h–r**) in an alcoholic solvent (100 mL) and the solution was irradiated through Vycor or Pyrex glass (depending on the absorption spectra, see Tables 3 and 4) at room temperature using a medium-pressure mercury lamp (450 W) until complete consumption of starting material was observed (monitored by ^1H NMR spectroscopy and GC–MS chromatography). The alcoholic solvent was distilled off and the residue was purified by ion exchange column chromatography (Amberlite CG-50 I, NH_3/MeOH 0.28 M)-except amino esters **3p–q**, which were purified by silica column chromatography (hexane/AcOEt 9:1).

4.4. Irradiation of imines in presence of triethylamine

Et_3N (1.5 mL, 10 mmol) was added to a solution of the corresponding imine **1** (0.75 mmol) in isopropyl alcohol (20 mL). Isopropyl alcohol was added to give a total volume of 100 mL and argon was bubbled through the solution. The reaction mixture was irradiated through Vycor at room temperature using a medium-pressure mercury lamp (450 W) until 90% conversion of starting material was observed (monitored by ^1H NMR spectroscopy and GC–MS chromatography). The isopropyl alcohol was distilled off and the residue was purified by ion exchange column chromatography (Amberlite CG-50 I, NH_3/MeOH 0.28 M).

4.5. Characterization data of isolated monoamines 3

4.5.1. *N*-[(3-pyridinyl)methyl]cyclohexanamine (3a). ^1H NMR ($CDCl_3$): δ 1.10–1.93 (m, 11H), 2.48 (m, 1H), 3.83 (s, 2H), 7.23–7.27 (m, 1H), 7.67–7.69 (m, 1H), 8.49–8.50 (m, 1H), 8.56 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 25.1, 26.2, 33.8, 48.4, 56.4, 123.4, 135.8, 136.4, 148.4, 149.8. GC–MS: 190, 147, 92. MS-ES(+): 191.2 (M+1). Anal. Calcd for $C_{12}H_{18}N_2$: C, 75.74; H, 9.53; N, 14.72. Found: C, 75.1; H, 9.85; N, 15.05.

4.5.2. *N*-[(3-pyridinyl)methyl]*tert*-butanamine (3b). ^1H NMR ($CDCl_3$): δ 1.19 (s, 9H), 1.53 (br s, 1H), 3.75 (s, 2H), 7.22–7.28 (m, 1H), 7.70–7.73 (m, 1H), 8.48 (m, 1H), 8.5 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 29.2, 44.7, 51.1, 123.5, 136.1, 148.4, 149.9. GC–MS: 163, 149, 92. MS-ES(+): 164.2 (M+1). Anal. Calcd for $C_{10}H_{16}N_2$: C, 73.13; H, 9.82; N, 17.06. Found: C, 73.55; H, 9.75; N, 16.70.

4.5.3. *N*-[(2-pyridinyl)methyl]cyclohexanamine (3c). ^1H NMR ($CDCl_3$): δ 1.10–1.97 (m, 11H), 2.50 (m, 1H), 3.94 (s, 2H), 7.15 (m, 1H), 7.30 (m, 1H), 7.64 (m, 1H), 8.56 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 25.2, 26.3, 33.6, 52.5, 56.8, 122.0, 122.5, 136.6, 149.3, 160.2. GC–MS: 190, 147, 92. MS-

ES(+): 191.2 (M+1). Anal. Calcd for $C_{12}H_{18}N_2$: C, 75.74; H, 9.53; N, 14.72. Found: C, 75.61; H, 9.50; N, 14.73.

4.5.4. *N*-[(2-pyridinyl)methyl]cyclohexanamine (3d). ^{1}H NMR ($CDCl_3$): δ 1.02–1.93 (m, 11H), 2.46 (m, 1H), 3.84 (s, 2H), 7.27 (m, 2H), 8.54 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 25.1, 26.3, 33.7, 49.9, 56.4, 123.1, 150.0. GC–MS: 190, 147, 92. MS-ES(+): 191.2 (M+1). Anal. Calcd for $C_{12}H_{18}N_2$: C, 75.74; H, 9.53; N, 14.72. Found: C, 75.64; H, 9.52; N, 14.70.

4.5.5. *N*-benzylcyclohexanamine (3e). ^{1}H NMR ($CDCl_3$): δ 1.15–1.96 (m, 11H), 2.48–2.60 (m, 1H), 3.84 (s, 2H), 7.25–7.37 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 25.0, 26.0, 33.0, 50.6, 56.1, 127.1, 128.6, 139.6. GC-MS: 189, 146, 91. MS-ES(+): 190.4 (M+1). Anal. Calcd for $C_{13}H_{19}N$: C, 82.48; H, 10.12; N, 7.40. Found: C, 82.02; H, 10.09; N, 7.36.

4.5.6. *N*-[(2-naphthyl)methyl]cyclohexanamine (3f). ^{1}H NMR ($CDCl_3$): δ 0.91–1.98 (m, 11H), 2.49–2.55 (m, 1H), 3.98 (s, 2H), 7.41–7.53 (m, 3H), 7.70–7.82 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 25.2, 26.3, 33.8, 51.3, 56.3, 125.6, 126.1, 126.4, 126.7, 127.7, 127.8, 128.1, 132.7, 133.6, 138.7. GC–MS: 239, 196, 141, 115, 98. MS-ES(+): 240.3 (M+1). Anal. Calcd for $C_{17}H_{21}N$: C, 85.30; H, 8.84; N, 5.85. Found: C, 84.98; H, 8.81; N, 5.83.

4.5.7. *N*-[(2-quinolinyl)methyl]cyclohexanamine (3g). ^{1}H NMR ($CDCl_3$): δ 1.24–2.02 (m, 11H), 2.61 (m, 1H), 4.17 (s, 2H), 7.44–8.18 (m, 6H). ^{13}C NMR ($CDCl_3$): δ 25.1, 26.2, 33.4, 52.8, 57.1, 120.7, 126.2, 127.5, 127.7, 129.1, 129.6, 136.6, 147.8, 160.2. GC–MS: 238, 195, 182, 157, 129, 77, 55. MS-ES(+): 241.3 (M+1). Anal. Calcd for $C_{16}H_{20}N_2$: C, 79.96; H, 8.39; N, 11.66. Found: C, 80.15; H, 8.39; N, 11.46.

4.5.8. *N*-(1-phenylethyl)cyclohexanamine (3h). ^{1}H NMR ($CDCl_3$): δ 1.33 (d, J=7.0 Hz, 3H), 1.01–1.72 (m, 11H), 2.26 (m, 1H), 3.96 (q, J=7.0 Hz, 1H), 7.16–7.34 (m, 5H).

^{13}C NMR ($CDCl_3$): δ 14.2, 25.1, 25.4, 26.3, 33.3, 34.6, 53.8, 54.6, 126.5, 128.5, 146.4. GC–MS: 203, 188, 160, 105, 77, 56. MS-ES(+): 204.3 (M+1). Anal. Calcd for $C_{14}H_{21}N$: C, 82.70; H, 10.41; N, 6.89. Found: C, 82.34; H, 10.43; N, 6.87.

4.5.9. *N*-[1-(2′-naphthyl)ethyl]cyclohexanamine (3i). ^{1}H NMR ($CDCl_3$): δ 1.01–1.12 (m, 5H), 1.40 (d, J=6.6 Hz, 3H), 1.53–1.72 (m, 5H), 2.03 (m, 1H), 2.30 (m, 1H), 4.13 (q, J=6.6 Hz, 1H), 7.41–7.47 (m, 3H), 7.71 (s, 1H), 7.74–7.83 (m, 3H). ^{13}C NMR ($CDCl_3$): δ 25.2, 26.3, 33.4, 34.8, 53.9, 54.8, 125.0, 125.2, 125.5, 126.0, 127.8, 127.9, 128.3, 132.9, 133.6, 144.0. GC–MS: 254, 238, 155, 98, 56, 41. MS-ES(+): 254.4 (M+1). Anal. Calcd for $C_{18}H_{23}N$: C, 85.32; H, 9.15; N, 5.53. Found: C, 84.92; H, 9.11; N, 5.50.

4.5.10. *N*-[1-(2′-pyridinyl)ethyl]cyclohexanamine (3j). ^{1}H NMR ($CDCl_3$): δ 1.02–1.98 (m, 11H), 1.36 (d, J=6.6 Hz, 3H), 2.23 (m, 1H), 4.03 (q, J=6.6 Hz, 1H), 7.12–7.16 (m, 1H), 7.27–7.31 (m, 1H), 7.61–7.66 (m, 1H), 8.54–8.57 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 23.6, 25.1, 25.3, 26.3, 33.4, 34.5, 54.3, 55.9, 121.3, 121.9, 136.5, 149.4, 165.5. GC–MS: 203, 189, 161, 107, 97. MS-ES(+): 205.3 (M+1). Anal. Calcd for $C_{13}H_{20}N_2$: C, 76.42; H, 9.87; N, 13.71. Found: C, 76.81; H, 9.68; N, 13.51.

4.5.11. *N*-benzhydrylcyclohexanamine (3l). ^{1}H NMR ($CDCl_3$): δ 1.06–1.94 (m, 11H), 2.36–2.42 (m, 1H), 5.03 (s, 1H), 7.16–7.39 (m, 10H). ^{13}C NMR ($CDCl_3$): δ 25.2, 26.4, 34.1, 54.1, 63.8, 126.9, 127.5, 128.5, 144.9. GC–MS: 265, 188, 167. MS-ES(+): 266.2 (M+1). Anal. Calcd for $C_{19}H_{23}N$: C, 85.99; H, 8.74; N, 5.28. Found: C, 84.20; H, 8.70; N, 5.31.

4.5.12. *N*-benzhydrylcyclopropanamine (3m). ^{1}H NMR ($CDCl_3$): δ 0.38 (d, J=5.1 Hz, 4H), 1.98 (br s, 1H), 2.07 (m, 1H), 4.91 (s, 1H), 7.12–7.36 (m, 10 H). ^{13}C NMR ($CDCl_3$): δ 6.8, 29.7, 67.3, 127.0, 127.5, 128.5, 144.3. GC–MS: 223, 222, 167, 152. MS-ES(+): 224.3 (M+1). Anal. Calcd for $C_{16}H_{17}N$: C, 86.05; H, 7.67; N, 6.27. Found: C, 85.88; H, 7.72; N, 6.40.

4.5.13. 2-(Benzhydrylamino)acetonitrile (3n). ^{1}H NMR ($CDCl_3$): δ 1.95 (br s, 1H), 3.50 (s, 2H), 5.06 (s, 1H), 7.21–7.44 (m, 10H). ^{13}C NMR ($CDCl_3$): δ 35.4, 65.8, 117.7, 127.4, 127.8, 128.9, 141.9. GC–MS: 222, 167, 145, 104, 67. MS-ES(+): 223.4 (M+1). Anal. Calcd for $C_{15}H_{14}N_2$: C, 81.05; H, 6.35; N, 12.60. Found: C, 81.36; H, 6.52; N, 12.12.

4.5.14. 2-(Benzhydrylamino)acetic acid ethyl ester (3o). ^{1}H NMR ($CDCl_3$): δ 1.24 (t, J=7.2 Hz, 3H), 2.22 (m, 1H), 3.37 (s, 2H), 4.17 (q, J=7.2 Hz, 2H), 4.88 (s, 1H), 7.18–7.47 (m, 10H). ^{13}C NMR ($CDCl_3$): δ 14.3, 49.2, 60.8, 66.7, 127.3, 127.5, 128.6, 143.4, 172.6. GC–MS: 182, 167, 118, 91. MS-ES(+): 270.2 (M+1). Anal. Calcd for $C_{17}H_{19}NO_2$: C, 75.81; H. 7.11; N, 5.20; O, 11.88. Found: C, 75.51; H, 7.33; N, 5.02.

4.5.15. 2-Cyclohexylamino-2-phenyl acetic acid ethyl ester (3p). ^{1}H NMR ($CDCl_3$): δ 1.08–1.84 (m, 13H), 2.03–2.04 (br s, 1H), 2.33–2.37 (m, 1H), 4.08–4.22 (m, 2H), 4.51 (s, 1H), 7.26–7.39 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 14.2, 25.0, 26.2, 33.4, 33.6, 54.6, 61.2, 62.5, 127.4, 128.0, 128.8, 138.9, 173.8. GC–MS: 260, 188, 106, 79. MS-ES(+): 262.1 (M+1). Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36; O, 12.24. Found: C, 73.23; H, 8.69; N, 5.47.

4.5.16. 2-Phenyl-(1′-phenylethylamino)acetic acid ethyl ester [(*S*,*R*)-3q and (*R*,*R*)-3q]. The two diastereomers **3q** were separated by simple column chromatography (silica gel, hexane/AcOEt 9:1). *Major product*: (*S*,*R*)-**3q**. ^{1}H NMR ($CDCl_3$): δ 1.13 (t, J=7.2 Hz, 3H), 1.34 (d, J=6.6 Hz, 3H), 2.30–2.50 (br s, 1H), 3.56 (q, J=6.6 Hz, 1H), 4.00–4.13 (m, 2H), 4.17 (s, 1H), 7.22–7.38 (m, 10H). ^{13}C NMR ($CDCl_3$): δ 14.1, 24.5, 54.8, 61.2, 62.8, 127.1, 127.3, 127.8, 128.1, 128.6, 128.7, 138.6, 144.8, 173.0. $[\alpha]_D^{25}$ (c 0.50, MeOH) +130.6. GC–MS: 283, 210, 105, 79. MS-ES(+): 284.3 (M+1). Anal. Calcd for $C_{19}H_{23}NO_2$: C, 76.73; H, 7.80; N, 4.71; O, 10.76. Found: C, 76.13; H, 7.96; N, 4.60. *Minor product*: (*R*,*R*)-**3q**. ^{1}H NMR ($CDCl_3$): δ 1.22 (t, J=7.2 Hz, 3H), 1.39 (d, J=6.6 Hz, 3H), 2.25–2.40 (br s, 1H), 3.56 (q, J=6.6 Hz, 1H), 4.11–4.26 (m, 3H), 7.23–7.35 (m, 10H). ^{13}C NMR ($CDCl_3$): δ 14.3, 24.9, 56.7, 61.2, 63.1, 127.1, 127.2, 127.3, 128.0, 128.6, 128.7, 128.8, 138.7, 145.0, 173.9. $[\alpha]_D^{25}$ (c 0.49, MeOH) = −19.5. GC–MS: 283, 210, 105, 79. MS-ES(+): 284.3 (M+1). Anal. Calcd for $C_{19}H_{23}NO_2$: C, 76.73; H, 7.80; N, 4.71; O, 10.76. Found: C, 76.24; H, 8.06; N, 4.52.

4.5.17. 2,3,3-Trimethyl-2,3-dihydro-1*H*-indole (3r). ^{1}H NMR ($CDCl_3$): δ 1.04 (s, 3H), 1.18 (d, $J=6.6$ Hz, 3H), 1.28 (s, 3H), 3.52 (q, $J=6.6$ Hz, 1H), 3.76–3.79 (br s, 1H), 6.61–6.64 (m, 1H), 6.72–6.77 (m, 1H), 6.99–7.04 (m, 1H), 7.26 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 15.3, 22.5, 26.3, 43.5, 65.3, 109.5, 119.0, 122.4, 127.3, 139.3, 149.4. GC–MS: 161, 146, 131, 77. MS-ES(+): 162.3 (M+1). Anal. Calcd for $C_{11}H_{15}N$: C, 81.94; H, 9.38; N, 8.69. Found: C, 82.32; H, 9.19; N, 8.49.

4.5.18. 2,2,3-Triphenylpyrrolidine (3s). ^{1}H NMR ($CDCl_3$): δ 2.18–2.34 (m, 2H), 3.08–3.12 (m, 1H), 3.36–3.41 (m, 1H), 3.25 (br s, 1H), 4.12–4.17 (m, 1H), 6.90–7.08 (m, 10H), 7.22–7.35 (m, 3H), 7.54–7.57 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 33.2, 44.0, 52.9, 75.3, 126.0, 126.8, 127.2, 127.9, 128.2, 128.4, 129.4, 142.6, 144.5, 147.6. GC–MS: 299, 194, 135, 116, 91, 77. MS-ES(+): 300.4 (M+1). Anal. Calcd for $C_{22}H_{21}N$: C, 88.25; H, 7.07; N, 4.68. Found: C, 88.61; H, 6.89; N, 4.50.

4.6. Reduction of amino esters 3q

A solution of pure amino ester (*S*,*R*)-**3q** or (*R*,*R*)-**3q** (50 mg, 0.18 mmol) in dry THF (5 mL) was added to a solution of $LiAlH_4$ (40 mg, 1.05 mmoles) in dry THF (10 mL) at 0 °C under argon. The mixture was stirred at room temperature until complete formation of the corresponding aminoalcohol was observed by TLC. The reaction mixture was decomposed by the careful dropwise addition of water (2 mL) and the product extracted with ethyl acetate (3×15 mL). The combined organic layers were dried (Na_2SO_4), concentrated and purified by column chromatography (hexane/AcOEt 1:1) to give the corresponding aminoalcohol in 84% yield (38 mg, 0.15 mmol).

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