Pergamon

Tetrahedron 56 (2000) 8179–8187

TETRAHEDRON

Stereoselective Syntheses of Allylic Amines Through Reduction of 1-Azadiene Intermediates

Enrique Aguilar,* Jesús Joglar,† Isabel Merino, Bernardo Olano, Francisco Palacios‡ and Santos Fustero§

Departamento de Química Orgánica e Inorgánica, Facultad de Química, Avda. Julián Clavería s/n, Universidad de Oviedo, 33006 Oviedo, Spain

Dedicated to Professor José Barluenga on the occasion of his 60th birthday

Received 26 May 2000; revised 2 August 2000; accepted 17 August 2000

Abstract—The stereoselective synthesis of primary and secondary *E*-allylic amines by reduction of 1-azadiene intermediates is described. β-Enamino phosphonium salts are suitable starting materials to prepare secondary allylic amines. Two methods are reported for the obtention of primary allylic amines from 4-amino-1-aza-1,3-dienes. *Method A* leads to the desired compounds by straight reduction with AlH_3 or DIBALH; *method B* is a stepwise procedure that allows for better yields when sterically hindered 4-amino-1-aza-1,3-dienes are employed.

Introduction

Allylic amines have become interesting targets for synthetic organic chemistry, due to the presence of this functionality in several naturally occurring compounds, such as gabaculine or oximicine[1] as well as in vinylogous polypeptides or peptide isosteres[2] and to their huge potential as synthetic intermediates for the preparation of biologically active products, such as the *Streptogramin* antibiotics,[3] alkaloids[4] and antifungal chemotherapeutic agents.[5] Other facts that have contributed to the spurring of research in this field include the ability of allylic amines to inhibit several enzymatic complexes[6] and the wide range of physiological properties they show[7] as well as their applications as insecticides, bactericides or herbicides.[8] The usefulness of allylic amines in organic synthesis is well documented[9] and, for example, they have been widely employed as precursors for β-nitrogen functionalized organometallic intermediates.[10]

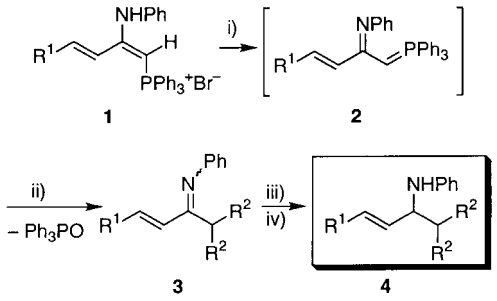
In spite of all these facts, and in contrast to allylic alcohols, their oxygenated analogs, for whose preparation numerous methods have been developed, the number of procedures to synthesize allylic amines is more scarce. Thus, they can be accessed from allylic compounds,[11] olefins,[12] azidirines,[13] epoxides,[14] phosphorylated compounds,[15] alkynes[16] and by Diels–Alder cyclization of aminodienes.[17] A direct route to these structural units is the functionalization of the parent allylamine or the homologation of other allylic amines.[18]

Reduction processes have also been employed to prepare allylic amines. Thus α,β-unsaturated oximes lead to primary allylic amines by treatment with Zn in acetic or formic acid[19] or complex metal hydrides,[20] but in some cases azidirines are obtained as reaction products. More recently, Kocovsky has showed that the protection of the oxime hydroxyl moiety facilitates the reduction with complex metal hydrides, with the mesyl being the activating group that allows for better yields.[21] *N*-Allyl hydroxylamines are suitable precursors of allylic amines by reduction with either complex metal hydrides, microorganisms or Zn/HCl.[22] Other substrates that yield allylic amines by reduction are allylic azides (which can be obtained by Pd-catalyzed amination of allyl esters),[23] propargyl amines,[24] or *N*-allylalkylidene ammonium salts.[25]

In this context, and having in mind that *a good synthesis of allylic amines should be able to control both the position and the geometry of the double bond*, α,β-unsaturated imines have become appropriate substrates to synthesize allylic amines by treatment with sodium borohydride or lithium diethylaminoborohydride.[26] In this paper we would like to report our results in the stereoselective

Keywords: allylic amines; azadienes; phosphonium salts; reduction.
* Corresponding author. Fax: +34-98-510-3446;
e-mail: eah@sauron.quimica.uniovi.es
† Current address: Departamento de Química Orgánica Biológica, Instituto de Investigaciones Químicas y Ambientales de Barcelona (C.S.I.C.), 08034 Barcelona, Spain.
‡ Current address: Departamento de Química Orgánica, Facultad de Farmacia, Universidad del País Vasco/E.H.U., Apartado 450, 01080 Vitoria, Spain.
§ Current address: Departamento de Química Orgánica, Facultad de Farmacia, Avda. Vicente Andrés Estellés s/n, Universidad de Valencia, 46100 Burjassot, Valencia, Spain.

0040–4020/00/$ - see front matter
PII: S0040-4020(00)00736-5



Scheme 1. *Reagents and conditions*: (i) *n*-BuLi, THF, −78°C, 2 h; (ii) H_2O (R^2=H) [or D_2O (R^2=D)]; (iii) $NaBH_4$/MeOH; (iv) H_2O.

preparation of *E*-allylic amines by 1,2-reduction of 1-azadiene intermediates.[27]

Results and Discussion

Synthesis of secondary allylic amines from β-enamino phosphonium salts

β-Enamino phosphonium salts **1** are simply, smoothly and readily accessible compounds that have found application in organic synthesis as intermediates for the preparation of tetrahydropyridines and penta-1,4-dien-3-ones.[28] Those reactions proceeded through the formation of *N*-substituted ylide intermediate **2** (Scheme 1) and we have envisioned that a sequential hydrolysis of **2** followed by a chemoselective reduction of the resulting 1-azadiene **3** could result in an expedient procedure for the formation of secondary allylic amines.

Thus, deprotonation of β-enamino phosphonium salts **1** by treatment with *n*-BuLi at −78°C for 2 h and subsequent hydrolysis yielded 2-alkyl-1-azadienes **3** in good yields (Scheme 1, Table 1). Compounds **3** and triphenylphosphine oxide (Ph_3PO) generated in the reaction were separated by column chromatography and 1-azadienes **3a–c** were further purified by recrystallization in hexane. When the hydrolysis was performed with D_2O instead of H_2O, the deuterated azadiene **3b** was isolated. 1-Azadienes **3d** (R^1=H) and **3e** (R^1=Et) were unstable to chromatography and were used in the following step without further purification. The subsequent treatment of *N*-substituted 2-alkyl-1-azadienes **3** with an excess of $NaBH_4$ in EtOH at 0°C for several hours led, after hydrolysis, to secondary allylic amines **4** (Scheme 1, Table 1).

Table 1. 2-Alkyl-1-aza-1,3-butadienes **3** and secondary allylic amines **4** prepared from β-enamino phosphonium salts **1**

Entry	R^1	R^2	**3**	Yield (%)[a]	**4**	Yield (%)[b]
1	Ph	H	**a**	85	**a**	95
2	Ph	D	**b**	82	**b**	90
3	2-Furyl	H	**c**	80	**c**	93
4	H	H	**d**	–[c]	**d**	75[a]
5	Et	H	**e**	–[c]	**e**	78[a]

[a] Isolated yield from **1**.
[b] Isolated yield from **3**.
[c] These compounds were used without purification in the subsequent reduction step.

Both iminic compounds **3** and allylic amines **4** were fully characterized by their spectroscopical data (IR, MS, ^{1}H and ^{13}C NMR), which indicated that ketimines **3** coexist in solution as a mixture of *E*/*Z* isomers of the carbon–nitrogen double bond.[29] Thus for example, the ^{1}H NMR spectrum for compound **3a** showed two signals at δ 2.48 and 2.05 ppm corresponding to the methyl group for both isomers in a 1:2 ratio. This fact was corroborated by the ^{13}C NMR spectrum which presented two signals at δ 165.1 and 163.6 ppm for the imino group and δ 22.5 and 14.9 ppm for the methyl group of the two isomers. Also, the value of the coupling constants for the vinylic protons (J=16.5 Hz) indicated an *E* configuration for the double bond.

For allylic amines **4** the configuration of the double bond was established to be *E* on the basis of the coupling constant values that were found to be between 15.7 and 17.2 Hz. This fact also indicates that the smooth conditions employed to reduce the C=N bond did not affect the stereochemistry of the double bond in 1-azadienes **3**.

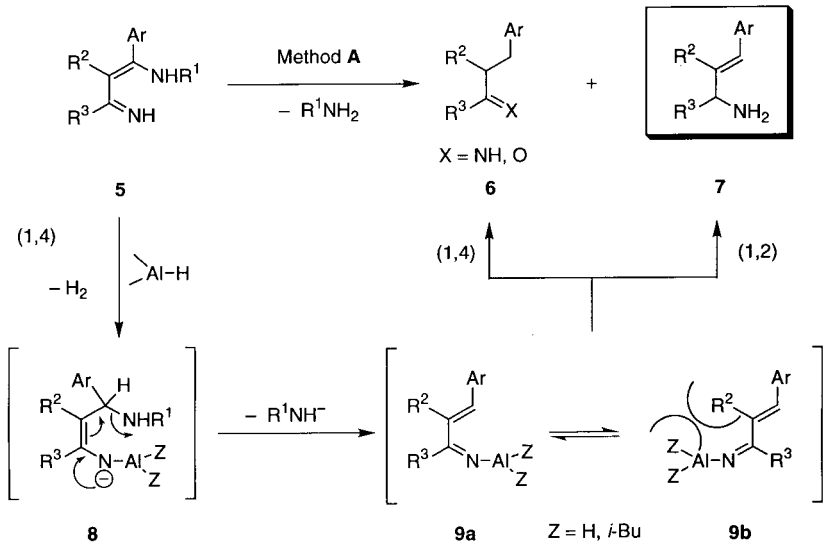
Synthesis of primary allylic amines from 4-amino-1-aza-1,3-dienes 5

The chemistry of 4-amino-1-aza-1,3-dienes **5**[30] has been extensively developed in our group as they have proved to be versatile intermediates for the synthesis of functionalized acyclic and heterocyclic compounds.[31] We thought that they could be suitable starting materials for the preparation of primary allylic amines if we were able to control the reduction conditions. In this regard we now present two different methods (*A* and *B*) that allowed us to achieve our goal.

Method A. Treatment of azadienes **5** with an excess of in situ generated alane ($3LiAlH_4+AlCl_3$)[32] (AlH_3/**5**≥5/1) in diethyl ether at room temperature for several hours yielded primary allylic amines **7**, after hydrolysis. Carbonyl (or iminic) compounds **6**[33] were obtained as by-products in variable amounts depending on the nature of the starting azadiene **5** (Scheme 2, Table 2). Slightly worse selectivity was achieved when the reaction was performed using excess DIBALH (DIBALH/**5**≥3/1) as reducing agent instead of alane (entries 2, 14, *method A*, Table 2).

The reaction chemical yield was, in general, very high, specially when R^2=Me (entries 1–7, Table 2). Work-up and further purification of the products could be easily achieved by an acid–base extraction to separate carbonyl (or iminic) compounds **6** from the mixture of primary allylic amines **7** and saturated amines (R^1NH_2), the latter ones being removed by high vacuum distillation or by flash chromatography.

The preparation of primary allylic amines **7** can be explained by a three-step mechanism. In an initial stage an N–Al bond is formed, with concomitant evolution of H_2, followed by 1,4-addition of hydride to give intermediate **8**. The evolution of **8** by elimination of primary amine



Scheme 2. *Reagents and conditions. Method A*: AlH_3/Et_2O/rt or DIBALH/Toluene/rt.

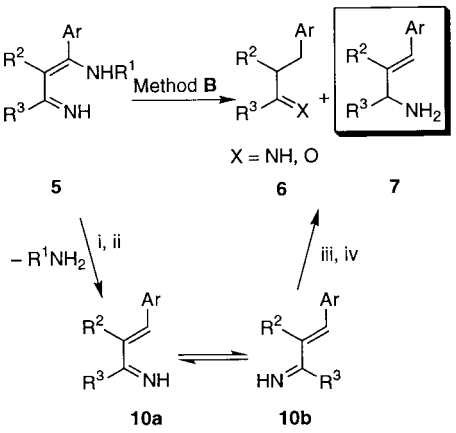
(R^1NH_2) leads to *N*-metallated 1-azadiene intermediate **9**, which should exist as an equilibrium mixture of two conformers *s-cis* **9a** and *s-trans* **9b**. These species may suffer another 1,4- or 1,2-reduction to give respectively carbonyl (or iminic) compounds **6** and primary allylic amines **7** (Scheme 2).

One of the major drawbacks of *method A* is that, in some cases, it leads to mixtures of compounds **6** and primary allylic amines **7**, although they can be easily separated. In fact, when the size of R^2 in starting azadienes **5** (where Ar=R^3=Ph) increases, a remarkable decrease in the ratio of allylic amines **7** to carbonyl compounds **6** is observed (entries 1, 2, 9, 12 and 14, *method A*, Table 2). These results seem to indicate that, for azadienes bearing bulky substituents, the equilibrium between *s-cis* **9a** and *s-trans* **9b** species should be displaced towards **9a**, due to steric hindrance between R^2 and $N–AlZ_2$ (Z=H, *i*-Bu), so 1,4-reduction should be favored leading to carbonyl compounds **6**. On the other hand, for those azadienes having

Table 2. Primary allylic amines **7** prepared from 4-amino-1-aza-1,3-dienes **5**

					Method A				Method B		
					Ratio **7/6**[b]		Yield (%)[c]				
Entry	**7**[a]	R^2	R^3	R^1	AlH_3	DIBALH	AlH_3	DIBALH	**7/6**[b]	**5**/$NaBH_4$	Yield (%)[c]
1	**a**	Me	Ph	*p*Tol	>99/–		96 (82)				
2	**a**	Me	Ph	Ph	>99/–	94/6	97 (80)	96	>99/–	1/2	97
3	**b**	Me	*p*-Tol	*p*-Tol	>99/–		98 (88)				
4	**b**	Me	*p*-Tol	Cy[d]		>99/–		98			
5	**c**	Me	Ph	Ph	>99/–		98 (85)				
6	**d**	Me	*p*-Cl–C_6H_4	*p*-Tol	>99/–		97 (82)				
7	**e**	Me	Cy	Ph	>99/–		93 (77)				
8	**f**	Et	Cy	*p*-Tol	68/32		95 (52)				
9	**g**	Et	Ph	Ph	58/42		94 (50)		70/26[e]	1/2	89 (50)
10	**g**	Et	Ph	Ph					64/15[e]	1/5	98
11	**g**	Et	Ph	*p*-Tol		26/74		93			
12	**h**	Allyl	Ph	Ph	15/85		90		66/31[e]	1/2	92 (50)
13	**h**	Allyl	Ph	Ph					60/15[e]	1/10	95
14	**i**	Bn	Ph	Ph	–/>99	0/57[e]	99	93	74/26	1/5	94 (61)
15	**i**	Bn	Ph	Ph					39/61	1/1	85
16	**j**	H	Ph	Ph	41/30[e]						
17	**j**	H	Ph	*p*-Tol		59/16[e]		91 (50)			
18	**k**	H	Et	Ph		88/5[e]		95 (68)			
19	**l**	Propargyl	Ph	*p*-Tol	[f]	[f]			88/8[e]	1/2	99 (70)
20	**m**[g]	Me	Ph	Ph	>99/1			99 (88)			

[a] Ar=Ph, in all cases except for **7c** (Ar=*p*-Cl–C_6H_4–).
[b] Ratio **7/6** determined from the crude reaction mixture by GC/MS and/or ^1H NMR (300 MHz).
[c] Combined yield of crude product (**6**+**7**) determined by GC/MS or ^1H NMR; in brackets yield of isolated product **7**.
[d] Cy=*c*-C_6H_{11}.
[e] Variable amounts (3–43%) of other compounds, mainly saturated amines, were detected by GC/MS.
[f] A mixture of several products was obtained, among which the compounds resulting from partial (**7h**) and complete reduction of the triple bond.
[g] 1,3-Dideuterated allylic amine that was obtained when performing the reaction with AlD_3.



Scheme 3. *Reagents and conditions. Method B*: (i) DIBALH (2 equiv.)/ Toluene/rt; (ii) MeOH; (iii) $NaBH_4$/MeOH/rt; (iv) Hydrolysis.

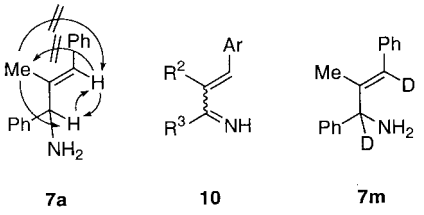


Figure 1.

a small steric effect, the final step should proceed mainly by 1,2-hydride addition[34] thus generating allylic amines **7** (Scheme 2).

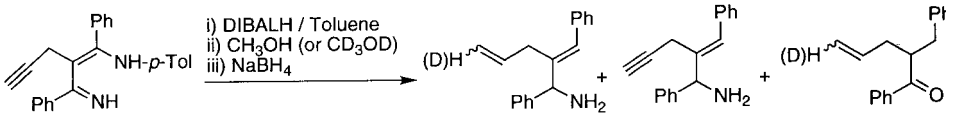
Method B. An alternative procedure was developed in order to avoid the difficulty of preparing primary allylic amines **7** bearing a bulky R^2 substituent. In this new procedure two equivalents of reducing agent (ratio DIBALH/**5**:2/1) in toluene at room temperature were employed. Solvolysis with anhydrous methanol after several hours led to the formation of intermediate **10** (Scheme 3). 1-Azadiene **10** presents a N–H bond instead of the N–Al bond that bore intermediate **9** (Method A, Scheme 2). The repulsive interaction between R^2 and N–Y (Y=AlZ_2 vs H) should therefore be greatly diminished, so possible that, even when the size of R^2 was higher than a methyl group, the major conformer in solution should be *s-trans* **10b** and 1,2-reduction processes could take place leading to the isolation of primary allylic amines **7** as major products.

Thus, in situ treatment of 1-azadiene intermediate **10** with excess $NaBH_4$ in MeOH at room temperature for several hours led, after hydrolysis, to primary allylic amines **7** in the yields and ratios reported in Table 2 (Scheme 3). The best results were achieved when a ratio $NaBH_4$/**5**:2/1 was employed (see Table 2, *method B*, entries 9, 12 vs 10, 13) and it should be noted that a great increase in the regioselectivity and chemoselectivity was afforded when using *method B* instead of *method A* (see Table 2, *method B* vs *method A*, entries 9, 12, 14, 19). Also, by using *method B* it is possible to prepare allylic amines **7i** and **7l** that could not be accessed by *method A* (Table 2, entries 14 and 19).

The reaction was highly stereoselective as only one diastereomer was detected in the crude reaction mixture. Thus, for allylic amines **7j** and **7k** the *E* stereochemistry was easily assigned by straightforward analysis of the coupling constants of the protons in the double bond (15.8 and 15.9 Hz for **7j** and **7k**, respectively, which are in the typical range for *trans* coupling constants). For other allylic amines, the product conformation was determined by NOE experiments, and were also found to be the *E* diastereomers. Thus, for example, for compound **7a** a positive NOE was observed between the olefin hydrogen and the methine group allowing to establish the proposed *E* stereochemistry; moreover, the absence of NOE between the methyl group and the olefin hydrogen corroborates a *trans* disposition for both of these substituents (Fig. 1).

Some additional experimental results that support the proposed mechanism are described below. One comes from the fact that 1-azadiene **10** could be identified by GC/MS and ^1H NMR, in the crude reaction mixture, when the reaction was performed using a DIBALH/**5**:2/1 ratio (*method B*) (Fig. 1). A second one is the formation of dideuterated allylic amine **7m** (entry 20, Table 2, Fig. 1) when the reaction was performed using deuterated alane (AlD_3, prepared in situ from powdered $LiAlD_4$ and $AlCl_3$)[32] as reducing agent. This result is not only evidence for the proposed mechanism, but it also represents a procedure for the synthesis of deuterated allylic amines.

Primary allylic amines **7h** and **7l** bear several functionalities that make them interesting compounds and useful synthetic intermediates. For this reason we decided to look for the best conditions for their preparation; we were also interested in determining whether it was possible to achieve the synthesis of allylic amine **7h** in good yields from propargyl substituted azadienes **5** (R^2=propargyl) instead of allyl



Ratio DIBALH / **5**	**7h**	**7l**	
4.5 / 1	40	12	20
3 / 1	18	29	17
2 / 1	–	88	8

Scheme 4.

substituted azadienes **5** (R^2=allyl). Several essays were performed varying the DIBALH/**5** ratio; thus when an excess of DIBALH (4.5 equiv.) was employed a mixture of several compounds was detected, with allylic amine **7h** (40%) the major component and only a 12% of **7l** observed; considerable amounts of carbonyl compounds **6** and saturated amines were also detected (Scheme 4).

When the excess of DIBALH was reduced to three equivalents, and CD_3OD was used in the solvolysis step, the GC/MS analysis of the crude reaction residue, after reduction with $NaBH_4$, showed an increase in the amount of **7l** as well as a decrease in deuterated-**7h**. Also, the reaction of DIBALH with the triple bond takes place by regioselective addition of aluminum to the terminal carbon, as no addition to the internal carbon was observed. Finally, the best conditions found to prepare **7l** (88%) were the employment of just 2 equiv. of DIBALH; in this case **7h** was not detected (Scheme 4).

In conclusion, 1-aza-dienes are valuable synthetic intermediates for the preparation of both primary and secondary allylic amines. In the case of secondary allylic amines, the required *N*-substitued 1-aza-dienes are easily obtained from β-enamino phosphonium salts **1**, and can be regio- and chemoselectively reduced by treatment with $NaBH_4$. On the other hand, 4-amino-1-aza-1,3-dienes **5** are suitable starting materials to prepare *N*-unsubstituted 1-azadienes that will lead to the synthetically important primary allylic amines. Two efficient, simple, complementary and stereoselective one-pot methods have been developed to that end: in *method A* only one reducing agent is used, either alane or DIBALH, and due to its simplicity, it should be the method of choice for the reduction of 4-amino-1-aza-1,3-dienes **5** bearing a small R^2 substituent (R^2=H, Me), while *method B* requires the sequential employment of two reducing agents (DIBALH, only two equivalents, to avoid further reduction at the *N*-unsubstituted 1-azadiene stage, and $NaBH_4$) and should be the method of choice for the reduction of compounds **5** bearing a bulky R^2 substituent. Moreover, this methodology allows the preparation of primary allylic amines, such as **7h** and **7l**, difficult to obtain by other procedures, that can be highly versatile synthons in organic synthesis.

Experimental

General

THF and diethyl ether were distilled under argon from sodium/benzophenone ketyl as drying agent. Diisopropylamine, used to generate LDA, was refluxed over KOH, distilled, and stored under argon in the presence of 4 Å molecular sieves at 4°C. Solvents used in extractions, recrystallizations and in chromatographic columns were distilled prior to use. β-Enamino phosphonium salts **1** were prepared following previously described procedures.[28] $AlCl_3$ was purchased from Merck, sublimed prior to use, stored under argon and manipulated using inert atmosphere techniques. All other reagents were commercially available and were used without further purification. All reactions which required an inert atmosphere, were conducted under dry argon, and the glassware was oven dried (120°C), evacuated, and purged with argon. Temperatures are reported as bath temperatures. Analytical thin layer chromatograms (TLC) were carried out with Kiesel gel 60 F_{254} on aluminum support; compounds were visualized by UV light (254 nm) and/or iodine. Flash chromatography was performed with silica gel. Melting points are reported uncorrected and were measured on a Buchi–Tottoli apparatus using open capillary tubes. Mass spectral data were measured by electron impact at 70 eV in a Hewlett–Packard 5987A spectrometer. Infrared spectra (cm^{-1}) were obtained in a Perkin–Elmer 298 or Philips PU 9716 FT-IR spectrometers. Oils were analyzed as pure samples while solids were recorded as Nujol mulls or KBr pellets. Elemental analyses were carried out with a Perkin–Elmer 240 B microanalyzer. NMR spectra were recorded with a Bruker AC-200 or a Bruker AC-300 instruments, with tetramethylsilane as the internal standard for ^1H NMR measurements, deuterated chloroform for ^{13}C NMR measurements and H_3PO_4 85% for ^{31}P NMR measurements. ^1H NMR: splitting pattern abbreviations are: s, singlet; bs, broad singlet; d, doublet; t, triplet; q, quartet; m, multiplet. ^{13}C NMR: multiplicities were determined by DEPT experiments, that were performed employing standard pulse sequences. In the cases where a mixture of diastereomers was observed, the abbreviation 'min' refers to the signals assigned to the minor diastereomer and the abbreviation 'maj' to the signals belonging to the major one; in the cases where nothing is specified, either it has not been possible to assign the signal to any of the diastereomers or it belongs to both of them.

General procedure for the synthesis of 2-alkyl-1-aza-1,3-dienes 3a–c

n-BuLi (2.5 mmol, 1 mL, 2.5 M in hexanes) was slowly added to a solution of β-enamino phosphonium salt **1** (2.5 mmol) in dry THF (50 mL) at −78°C under inert atmosphere. After 2 h, the reaction was hydrolyzed at low temperature (−50°C), the stirring was maintained for 12 h at room temperature and the organic layer was extracted with diethyl ether (3×50 mL), dried over Na_2SO_4, and filtered. Solvents were evaporated under vacuum and the oily residue was purified by column chromatography on silica gel using hexane/AcOEt (20/1 to 1/1) as sequential eluents to give 1-azadienes **3** in the yields reported in Table 1. The solid compounds thus obtained could be recrystallized in hexane. ^1H and ^{13}C NMR spectra of compounds **3** show several sets of paired signals due to the presence of *syn*/*anti* isomers. Compounds **3d** and **3e** were unstable to chromatographic purification and therefore, they were reduced to amines **4** without isolation.

1-Aza-2-methyl-1,4-diphenyl-1,3-butadiene 3a. Yellow solid; mp 95–97°C; IR (ν_{max}, cm^{-1}) 1620, 1600, 1590; ^1H NMR ($CDCl_3$, TMS) δ 7.58–6.78 (m, 11H), 6.75 (d, 1H, J=16.5 Hz), 2.48 (s, 3H, min), 2.05 (s, 3H, maj); ^{13}C NMR ($CDCl_3$) δ 165.1 (C=N, maj), 163.6 (C=N, min), 150.1, 149.4, 137.6, 136.3, 130.6, 128.0, 127.8, 127.7, 126.3, 122.5, 119.4, 118.6, 22.5 (CH_3, min), 14.9 (CH_3, maj); MS (EI) (*m*/*z*,%): 221 (M^+), 220 (78), 182 (13), 77 (100); Anal. calcd for $C_{16}H_{15}N$: C 86.84, H 6.83, N 6.33; found: C 87.01, H 6.73, N 6.24.

1-Aza-2-dideuteromethyl-1,4-diphenyl-1,3-butadiene 3b. Yellow solid; mp 97–98°C; ^{1}H NMR ($CDCl_3$, TMS) δ 7.60–6.78 (m, 11H), 6.75 (d, 1H, J=16.5 Hz), 2.36 (m, 1H, CHD_2, min), 1.95 (m, 1H, CHD_2, maj); ^{13}C NMR ($CDCl_3$) δ 166.0 (C=N, maj), 164.5 (C=N, min), 150.9, 150.3, 138.4, 137.1, 135.6, 135.5, 131.8, 131.4, 130.3, 129.1, 129.0, 128.9, 128.6, 128.5, 127.3, 127.1, 120.2, 119.5, 22.0 (m, CHD_2, min), 15.2 (CHD_2, maj); MS (EI) (*m/z*,%): 223 (M^+, 20), 222 (20), 146 (M^+-Ph, 13), 77 (100); Anal. calcd for $C_{16}H_{13}D_2N$: C 86.07, H/D 7.66, N 6.27; found: C 86.21, H/D 7.53, N 6.15.

1-Aza-4-(2-furyl)-2-methyl-1-phenyl-1,3-butadiene 3c. Yellow solid; mp 84–85°C; ^{1}H NMR ($CDCl_3$, TMS) δ 7.46–6.39 (m, 10H), 2.39 (s, 3H, min), 2.00 (s, 3H, maj); ^{13}C NMR ($CDCl_3$) δ 165.6 (C=N, maj), 164.3 (C=N, min), 151.9, 151.6, 143.9, 143.6, 128.7, 125.5, 124.3, 123.4, 123.3, 119.5, 119.1, 111.9, 111.5, 23.0 (CH_3, min), 15.8 (CH_3, maj); MS (EI) (*m/z*,%): 211 (M^+, 5), 196 (M^+-Me, 4), 136 (58), 146 (M^+-NPh, 100), 92 (51); Anal. calcd for $C_{14}H_{13}NO$: C 79.59, H 6.20, N 6.63; found: C 79.77, H 6.11, N 6.71.

General procedure for the synthesis of secondary allylic amines 4a–c

Excess $NaBH_4$ (25 mmol) was added in portions to a solution of the corresponding α,β-unsaturated imine **3** (2.5 mmol) in EtOH (20 mL). After 15 h the reaction was quenched with ice/water, concentrated in vacuum to remove EtOH and extracted with diethyl ether (3×50 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. The crude oily residue was purified by column chromatography (hexane/AcOEt 7/3 as eluent) to give the corresponding secondary allylic amine in the yields reported in Table 1.

(*E*)-*N*,4-Diphenyl-3-buten-2-amine 4a. Yellow oil; R_f= 0.40 (hexane/AcOEt 8/1); IR (ν_{max}, cm^{-1}) 3400, 2950, 1590; ^{1}H NMR ($CDCl_3$, TMS) δ 7.32–6.51 (m, 10H), 6.50 (d, 1H, J=16.0 Hz), 6.30 (dd, 1H, J=5.9, 16.0 Hz), 4.22 (m, 1H), 3.65 (bs, 1H, NH), 1.38 (d, 3H, J=7.0 Hz); ^{13}C NMR ($CDCl_3$) δ147.2, 136.8, 133.0, 129.0, 128.3, 127.1, 126.1, 117.1, 113.2, 50.6 (CH–N), 21.8 (CH_3); MS (EI) (*m/z*,%): 223 (M^+, 32), 131 (M^+-NHPh, 100), 91 (37); Anal. calcd for $C_{16}H_{17}N$: C 86.06, H 7.67, N 6.27; found: C 86.30, H 7.54, N 6.15.

(*E*)-1,1-Dideutero-*N*,4-diphenyl-3-buten-2-amine 4b. Yellow oil; R_f=0.40 (hexane/AcOEt 8/1); IR (ν_{max}, cm^{-1}) 3410, 2970, 1595; ^{1}H NMR ($CDCl_3$, TMS) δ 7.46–6.65 (m, 10H), 6.58 (d, 1H, J=16.0 Hz), 6.22 (dd, 1H, J=5.8, 16.0 Hz), 4.18 (m, 1H), 3.60 (bs, 1H, NH), 1.29 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 147.2, 136.8, 133.0, 129.0, 128.3, 127.1, 126.1, 117.1, 113.2, 50.5 (CH–N), 21.5 (m, CHD_2); Anal. calcd for $C_{16}H_{15}D_2N$: C 85.30, H/D 8.48, N 6.22; found: C 85.18, H/D 8.54, N 6.37.

(*E*)-4-(2-Furyl)-*N*-phenyl-3-buten-2-amine 4c. Yellow oil; R_f=0.38 (hexane/AcOEt 8/1); IR (ν_{max}, cm^{-1}) 3395, 3050, 1595; ^{1}H NMR ($CDCl_3$, TMS) δ 7.35–6.18 (m, 10H), 4.11 (m, 1H), 3.51 (bs, 1H, NH), 1.38 (d, 3H, J= 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 152.5, 147.1, 141.5, 131.5, 129.0, 117.6, 117.2, 113.2, 111.1, 107.3, 50.3 (CH–N), 21.8 (CH_3); MS (EI) (*m/z*,%): 213 (M^+, 34), 131 (M^+-NHPh, 100), 77 (46); Anal. calcd for $C_{14}H_{16}NO$: C 78.84, H 7.56, N 6.57; found: C 78.70, H 7.69, N 6.69.

General procedure for the synthesis of secondary allylic amines 4d–e

LDA (2.5 mmol, prepared in situ from diisopropylamine and *n*-BuLi) was slowly added to a solution of β-enamino phosphonium salt **1d** or **1e** (2.5 mmol) in dry THF (40 mL) under inert atmosphere at −78°C. After stirring for 2 h the reaction was hydrolyzed at low temperature (−50°C), extracted with diethyl ether (3×50 mL) and the combined organic layer was dried over Na_2SO_4. Solvents were evaporated under reduced pressure to give an oil that was dissolved in EtOH (25 mL), treated with an excess of $NaBH_4$ (25 mmol) at 0°C and stirred for 15 h. The reaction mixture was hydrolyzed with ice-water, concentrated in vacuum and extracted with CH_2Cl_2 (3×50 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. The crude oily residue was purified by column chromatography (hexane/AcOEt 7/3 as eluent) to give the corresponding secondary allylic amines in the yields reported in Table 1.

***N*-Phenyl-3-buten-2-amine 4d.** Yellow oil; R_f=0.71 (hexane/AcOEt 7/3); ^{1}H NMR ($CDCl_3$, TMS) δ 7.60–6.52 (m, 5H), 5.81 (ddd, 1H, J=5.6, 10.3, 17.2 Hz), 5.20 (dt, 1H, J=1.3, 17.2 Hz), 5.06 (dt, 1H, J=1.3, 10.3 Hz), 3.97 (m, 1H), 3.40 (bs, 1H, NH), 1.15 (d, 3H, J=6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 147.4, 133.1, 129.1, 129.0, 116.8, 113.1, 48.5 (CH–N), 21.5 (CH_3); Anal. calcd for $C_{10}H_{13}N$: C 81.59, H 8.90, N 9.51; found: C 81.43, H 9.00, N 9.65.

(*E*)-*N*-Phenyl-3-hexen-2-amine 4e. Yellow oil; R_f=0.60 (hexane/AcOEt 7/3); IR (ν_{max}, cm^{-1}) 3380, 2900, 1650; ^{1}H NMR ($CDCl_3$, TMS) δ 7.60–6.58 (m, 5H), 5.62 (dt, 1H, J=5.9, 15.6 Hz), 5.40 (dd, 1H, J=6.1, 15.6 Hz), 3.92 (m, 1H), 3.62 (bs, 1H, NH), 2.00 (m, 2H), 1.26 (d, 3H, J=6.9 Hz), 0.95 (t, 3H, J=7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 147.4, 131.8, 129.1, 128.8, 116.8, 113.2, 50.2 (CH–N), 25.0 (CH_2), 21.8 (CH_3), 13.4 (CH_3); Anal. calcd for $C_{12}H_{17}N$: C 82.23, H 9.78, N 7.99; found: C 82.41, H 9.65, N 7.92.

Synthesis of primary allylic amines 7

***Method A*. Synthesis by direct reduction of 4-amino-1-aza-1,3-butadienes 5 with excess of alane (AlH_3)—General procedure.** A solution of the corresponding 4-amino-1-aza-1,3-diene **5** (10 mmol) in anhydrous diethyl ether (20 mL) was slowly added to a suspension of AlH_3 (50 mmol, prepared in situ by reaction of $3LiAlH_4$+ $AlCl_3$)[32] in ether (20 mL) with stirring at 0°C. Once the addition was complete, the reaction mixture was stirred for several hours (10–14 h.) at room temperature. The resulting white suspension was dropwise solvolyzed with anhydrous methanol (15 mL) at 0°C; water (20 mL) was added and the reaction was extracted with diethyl ether (3×25 mL). The combined organic layer was dried over

Na_2SO_4, filtered and solvents were evaporated under vacuum. The resulting crude residue was analyzed by GC/MS or ^1H NMR (300 MHz) to determine its composition.

When ketones (or imines) **6** were detected, they were separated from the mixture of amines by acid–base extraction and identified. Primary allylic amines **7** were further purified by high vacuum distillation of by flash chromatography (*n*-hexane/ether 7/3). When GC/MS or ^1H NMR analysis indicated the absence of compounds **6**, the crude residue was directly purified by high-vacuum distillation or by flash chromatography.

General procedure for the synthesis by direct reduction of 4-amino-1-aza-1,3-butadienes 5 with excess of DIBALH

DIBALH (50 mmol, 1 M in toluene) was slowly added to a solution of the corresponding 4-amino-1-aza-1,3-diene **5** (10 mmol) at 0°C in an inert atmosphere. Once the addition was complete, the yellow solution was stirred for 10–14 h at room temperature and solvolyzed with anhydrous methanol (15 mL). The reaction mixture was worked up and purified as described above for the reduction with alane.

(*E*)-2-Methyl-1,3-diphenyl-2-propen-1-amine 7a. Yellow oil; purified by high vacuum distillation; bp 91–94°C (10^{-3} mmHg); ^1H NMR ($CDCl_3$, TMS) δ 7.38–7.02 (m, 10H), 6.71 (s, 1H), 4.56 (s, 1H), 1.66 (s, 3H), 1.65 (bs, 2H, NH_2); ^{13}C NMR ($CDCl_3$) δ 145.2 (C), 142.8 (C), 139.2 (CH), 130.2 (CH), 129.4 (CH), 129.2 (CH), 128.1 (CH), 127.3 (CH), 126.0 (CH), 64.3 (CH), 15.9 (CH_3); MS (EI) (*m*/*z*,%): 223 (M^+, 48), 208 (M^+-Me, 100), 106 (83), 91 (16), 77 (18); Anal. calcd for $C_{16}H_{17}N$: C 86.06, H 7.67, N 6.27; found: C 86.31, H 7.51, N 6.22.

(*E*)-2-Methyl-3-phenyl-1-*p*-tolyl-2-propen-1-amine 7b. Yellow oil; purified by high vacuum distillation; bp 102–105°C (10^{-3} mmHg); ^1H NMR ($CDCl_3$, TMS) δ 7.45–7.10 (m, 9H), 6.73 (s, 1H), 4.56 (s, 1H), 2.32 (s+bs, 3H+2H, NH_2), 1.70 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 142.5 (C), 141.7 (C), 138.6 (C), 136.2 (C), 129.5 (CH), 128.5 (CH), 127.2 (CH), 126.2 (CH), 124.9 (CH), 62.9 (CH), 21.0 (CH_3), 14.8 (CH_3); MS (EI) (*m*/*z*,%): 237 (M^+, 31), 222 (M^+-Me), 120, 91, 77; Anal. calcd for $C_{17}H_{19}N$: C 86.03, H 8.07, N 5.90; found: C 85.89, H 8.00, N 6.01.

(*E*)-1-*p*-Chlorophenyl-2-methyl-3-phenyl-2-propen-1-amine 7c. Yellow oil; purified by flash chromatography; ^1H NMR ($CDCl_3$, TMS) δ 7.52–6.71 (m, 9H), 6.56 (s, 1H), 4.45 (s, 1H), 1.66 (bs, 2H, NH_2), 1.50 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 144.5 (C), 143.2 (C), 137.2 (C), 132.4 (C), 131.8 (CH), 129.6 (CH), 128.9 (CH), 126.9 (CH), 124.2 (CH), 63.7 (CH), 15.6 (CH_3); Anal. calcd for $C_{16}H_{16}ClN$: C 74.56, H 6.26, N 5.43; found: C 74.72, H 6.23, N 5.40.

(*E*)-3-*p*-Chlorophenyl-2-methyl-1-phenyl-2-propen-1-amine 7d. Yellow oil; purified by flash chromatography; ^1H NMR ($CDCl_3$, TMS) δ 7.76–6.98 (m, 9H), 6.69 (s, 1H), 4.56 (s, 1H), 1.71 (bs, 2H, NH_2), 1.65 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 143.3 (C), 141.0 (C), 138.6 (C), 133.9 (C), 129.8 (CH), 129.0 (CH), 128.9 (CH), 127.2 (CH), 127.1 (CH), 126.0 (CH), 63.2 (CH), 15.2 (CH_3); Anal. calcd for $C_{16}H_{16}ClN$: C 74.56, H 6.26, N 5.43; found: C 74.64, H 6.18, N 5.36.

(*E*)-1-Cyclohexyl-2-methyl-3-phenyl-2-propen-1-amine 7e. Yellow oil; purified by high vacuum distillation; bp 88–91°C (10^{-3} mmHg); ^1H NMR ($CDCl_3$, TMS) δ 7.41–6.57 (m, 5H), 6.31 (s, 1H), 3.05 (d, 1H, J=8.0 Hz), 1.73 (s, 3H), 2.17–0.67 (m, 11H+2H); ^{13}C NMR ($CDCl_3$) δ 140.6 (C), 137.5 (C), 128.4 (CH), 127.4 (CH), 125.6 (CH), 125.5 (CH), 65.0 (CH), 40.7 (CH), 30.1 (CH_2), 28.9 (CH_2), 26.0 (CH_2), 25.8 (CH_2), 25.7 (CH_2), 12.7 (CH_3); MS (EI) (*m*/*z*,%): 229 (M^+, <5), 146 (M^+-83); Anal. calcd for $C_{16}H_{23}N$: C 83.78, H 10.11, N 6.11; found: C 83.91, H 10.07, N 6.05.

(*E*)-1-Cyclohexyl-2-ethyl-3-phenyl-2-propen-1-amine 7f. Yellow oil; purified by flash chromatography; ^1H NMR ($CDCl_3$, TMS) δ 7.38–7.06 (m, 5H), 6.29 (s, 1H), 3.06 (d, 1H, J=7.3 Hz), 2.17–0.67 (m, 13H+2H), 1.00 (t, 1H, J=6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 147.3 (C), 138.0 (C), 128.4 (CH), 128.0 (CH), 126.0 (CH), 125.2 (CH), 62.9 (CH), 42.0 (CH), 30.9 (CH_2), 28.5 (CH_2), 26.4 (CH_2), 26.2 (CH_2), 22.2 (CH_2), 13.8 (CH_3); MS (EI) (*m*/*z*,%): 243 (M^+, <5), 214 (M^+-Et, <5), 160 (M^+-c-C_6H_{11}, 100), 129 (23); Anal. calcd for $C_{17}H_{25}N$: C 83.89, H 10.36, N 5.75; found: C 83.94, H 10.33, N 5.62.

(*E*)-1,3-Diphenyl-2-propen-1-amine 7j. Yellow oil; purified by flash chromatography; ^1H NMR ($CDCl_3$, TMS) δ 7.38–7.09 (m, 10H), 6.48 (d, 1H, J=15.8 Hz), 6.25 (dd, 1H, J=6.5, 15.8 Hz), 4.57 (d, 1H, J=6.5 Hz), 1.75 (bs, 2H, NH_2); ^{13}C NMR ($CDCl_3$) δ 143.6 (C), 136.0 (C), 133.0 (CH), 127.8 (CH), 127.5 (CH), 126.4 (CH), 126.1 (CH), 125.7 (CH), 125.4 (CH), 56.8 (CH); MS (EI) (*m*/*z*,%): 209 (M^+, 52), 208 (M^+-1, 100), 106 (M^+-103, 28); Anal. calcd for $C_{15}H_{55}N$: C 86.08, H 7.22, N 6.69; found: C 86.10, H 7.17, N 6.61.

(*E*)-1-Phenyl-1-penten-3-amine 7k. Yellow oil; purified by high vacuum distillation; bp 50–53°C (10^{-3} mmHg); ^1H NMR ($CDCl_3$, TMS) δ 7.36–7.15 (m, 5H), 6.43 (d, 1H, J=15.9 Hz), 6.10 (dd, 1H, J=7.2, 15.9 Hz), 3.32 (m, 1H), 1.59 (bs, 2H, NH_2), 1.52 (m, 2H), 0.91 (t, 3H, J=7.4 Hz); ^{13}C NMR ($CDCl_3$) δ 136.8 (C), 134.4 (CH), 128.7 (CH), 128.2 (CH), 126.9 (CH), 125.9 (CH), 55.2 (CH), 30.3 (CH_2), 10.2 (CH_3); MS (EI) (*m*/*z*,%): 161 (M^+, 13), 132 (M^+-Et, 100), 115 (M^+-46, 32), 91 (7), 77 (7); Anal. calcd for $C_{11}H_{15}N$: C 81.94, H 9.38, N 8.68; found: C 81.82, H 9.35, N 8.66.

Reduction with excess AlD_3

Formation of (*E*)-1,3-dideutero-2-methyl-1,3-diphenyl-2-propen-1-amine 7m. A solution of 1-aza-3-methyl-2,4-diphenyl-4-phenylamino-but-1,3-diene (**5**, Ar=R^1=R^3=Ph, R^2=Me) (10 mmol) in anhydrous diethyl ether (20 mL) was slowly added to a suspension of AlD_3 (50 mmol, prepared in situ by reaction of $3LiAlD_4+AlCl_3$)[32] in ether (20 mL) with stirring at 0°C. The following operations were identical to those described above for the reduction with alane. Primary allylic amine **7m** was thus obtained and it was characterized by NMR and MS. Yellow oil; purified by flash chromatography; ^1H NMR ($CDCl_3$, TMS) δ 7.38–7.12 (m, 10H),

1.66 (s, 3H), 1.65 (bs, 2H, NH_2); ^{13}C NMR ($CDCl_3$) δ 143.5, 140.9, 137.7, 130.8, 128.8, 128.2, 127.9, 126.8, 126.7, 126.1, 124.4 (t, $J_{C\text{-}D}$=23.1 Hz), 62.4 (t, $J_{C\text{-}D}$=23.1 Hz), 14.8 (CH_3); MS (EI) (*m/z*,%): 225 (M^+, 30), 210 (M^+−Me, 79), 107 (100), 91 (8), 77 (23); Anal. calcd for $C_{16}H_{15}D_2N$: C 85.30, H/D 8.48, N 6.22; found: C 85.15, H/D 8.58, N 6.36.

***Method B*. Synthesis by sequential reduction of 4-amino-1-aza-1,3-butadienes 5 with DIBALH and $NaBH_4$/MeOH—General procedure.** DIBALH (21 mmol, 1 M in toluene) was dropwise added to a solution of the corresponding 4-amino-1-aza-1,3-diene **5** (10 mmol) in anhydrous toluene (20 mL) at 0°C. After the addition was concluded, the resulting yellow solution was stirred at room temperature for 10–14 h, then solvolyzed with anhydrous methanol (25 mL) and stirred at room temperature for a further 4 h. The resulting solution, almost colorless, was hydrolyzed with water (25 mL), evaporated under vacuum to remove MeOH and extracted with diethyl ether (3×25 mL). The following operations were identical to those described for the reduction with alane (vide supra).

(*E*)-2-Ethyl-1,3-diphenyl-2-propen-1-amine 7g. Pale yellow oil; purified by flash chromatography; ^1H NMR ($CDCl_3$, TMS) δ 7.44–6.87 (m, 10H), 6.73 (s, 1H), 4.62 (s, 1H), 2.41–1.93 (m, 3H, 1H+NH_2), 1.80 (m, 1H), 0.80 (t, 3H, *J*=7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 146.7 (C), 143.9 (C), 137.9 (CH), 128.5 (CH), 128.2 (CH), 128.1 (CH), 127.91 (CH), 127.87 (CH), 127.84 (CH), 127.81 (CH), 127.1 (CH), 126.8 (CH), 126.0 (CH), 124.8 (CH), 60.5 (CH), 22.0 (CH_2), 13.7 (CH_3); MS (EI) (*m/z*,%): 237 (M^+, 14), 208 (M^+−Et, 100), 106 (94); Anal. calcd for $C_{17}H_{19}N$: C 86.03, H 8.07, N 5.90; found: C 86.25, H 8.00, N 5.95.

(*E*)-2-Allyl-1,3-diphenyl-2-propen-1-amine 7h. Pale yellow oil; purified by flash chromatography; ^1H NMR ($CDCl_3$, TMS) δ 7.30–6.92 (m, 10H), 6.84 (s, 1H), 5.72 (m, 1H), 4.96 (m, 2H), 4.60 (s, 1H), 3.00 (dd, 1H, *J*=7.2, 17.9 Hz), 2.52 (dd, 1H, *J*=9.0, 17.9 Hz), 1.56 (bs, 2H, NH_2); ^{13}C NMR ($CDCl_3$) δ 144.1 (C), 142.9 (C), 137.7 (C), 136.4 (CH), 128.7 (CH), 128.5 (CH), 128.3 (CH), 128.2 (CH), 127.4 (CH), 127.2 (CH), 126.6 (CH), 126.1 (CH), 116.1 (CH_2), 60.4 (CH), 33.8 (CH_2); MS (EI) (*m/z*,%): 249 (M^+, 5), 208 (M^+−Allyl, 97), 106 (100); Anal. calcd for $C_{18}H_{19}N$: C 86.70, H 7.68, N 5.62; found: C 86.67, H 7.65, N 5.69.

(*E*)-2-Benzyl-1,3-diphenyl-2-propen-1-amine 7i. Pale yellow oil; purified by flash chromatography; ^1H NMR ($CDCl_3$, TMS) δ 7.35–7.10 (m, 16H), 4.49 (s, 1H), 3.86 (d, 1H, *J*=15.5 Hz), 3.14 (d, 1H, *J*=15.5 Hz), 2.22 (bs, 2H, NH_2); ^{13}C NMR ($CDCl_3$) δ 143.7 (C), 142.5 (C), 139.1 (C), 137.1 (C), 128.0 (CH), 127.9 (CH), 127.8 (CH), 126.8 (CH), 126.6 (CH), 126.0 (CH), 125.7 (CH), 125.5 (CH), 59.0 (CH), 34.7 (CH_2); MS (EI) (*m/z*,%): 299 (M^+, 4), 282 (M^+−NH_3, 10), 208 (M^+−Bn, 100), 106 (90); Anal. calcd for $C_{22}H_{21}N$: C 88.25, H 7.07, N 4.68; found: C 88.18, H 7.00, N 4.61.

(*E*)-1,3-Diphenyl-2-propargyl-2-propen-1-amine 7l. Yellow oil; purified by flash chromatography; ^1H NMR ($CDCl_3$, TMS) δ 7.41–7.15 (m, 10H), 6.83 (s, 1H), 4.87 (s, 1H), 3.22 (bs, 2H, NH_2), 3.15 (m, 1H), 2.72 (m, 1H), 2.02 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 143.4 (C), 138.2 (C), 135.6 (C), 128.7 (CH), 128.6 (CH), 128.5 (CH), 125.9 (CH), 125.6 (CH), 124.9 (CH), 123.5 (CH), 81.5 (C) 68.0 (CH), 59.6 (CH), 18.5 (CH_2); MS (EI) (*m/z*,%): 247 (M^+, 15), 208 (M^+−Propargyl, 70), 170 (M^+−Ph, 35), 106 (100); Anal. calcd for $C_{18}H_{17}N$: C 87.41, H 6.93, N 5.66; found: C 87.32, H 6.84, N 5.69.

Acknowledgements

We are grateful to the DGICYT and to the Ministerio de Educación y Ciencia (Spain) for predoctoral fellowships to I. M. and E. A., respectively. We also thank Dr Pablo Bernard for GC/MS measurements and helpful discussions.

References

1. For an excellent review on the synthesis of allylic amines see: Cheikh, R. B.; Chaabouni, R.; Laurent, A.; Mison, P.; Nafti, A. *Synthesis* **1983**, 685–700.
2. (a) Hagihara, M.; Anthony, N. J.; Stout, T. J.; Clardy, J.; Schreiber, S. L. *J. Am. Chem. Soc.* **1992**, *114*, 6568–6570. (b) Devadder, S.; Verheyden, P.; Jaspers, H. C. M.; Van Binst, G.; Tourué, D. *Tetrahedron Lett.* **1996**, *37*, 703–706.
3. (a) Schlessinger, R. H.; Li, Y.-J. *J. Am. Chem. Soc.* **1996**, *118*, 3301–3302. (b) Tavares, F.; Lawson, J. P.; Meyers, A. I. *J. Am. Chem. Soc.* **1996**, *118*, 3303–3304. (c) Entwistle, D. A.; Jordan, S. I.; Montgomery, J.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1315–1317.
4. (a) Overman, L. E.; Petty, C. B.; Doedens, R. J. *J. Org. Chem.* **1979**, *44*, 4183–4185. (b) Bäckvall, J.-E.; Nordberg, R. E.; Nyström, J.-E.; Högberg, T.; Ulff, B. *J. Org. Chem.* **1981**, *46*, 3479–3483 (and references cited therein).
5. Stütz, A. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 320–328.
6. (a) Petranyi, G.; Ryder, N. S.; Stütz, A. *Science* **1984**, *224*, 1239–1241. (b) McDonald, I. A.; Lacoste, J. M.; Bey, P.; Palfreyman, M. G.; Zreika, M. *J. Med. Chem.* **1985**, *28*, 186–193. (c) Padgette, S. R.; Wimalasena, K.; Herman, H. H.; Sirimanne, S. R.; May, S. W. *Biochemistry* **1985**, *24*, 5826–5839. (d) Ohba, T.; Ikeda, E.; Wakayama, J.; Takei, H. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 219–224.
7. (a) Bartmann, W.; Kaiser, J. Ger. Offen. 2,103,119, 1972; *Chem. Abstr.* **1972**, *77*, 140141m. (b) Kato, H. Ger. Offen. 2,350,125, 1974; *Chem. Abstr.* **1974**, *81*, 37401e.
8. (a) Kawazoe, A. Japan Kokai, 73 58,146, 1973; *Chem. Abstr.* **1974**, *80*, 815w. (b) Morris, L. R. US Patent, US 3,539,632, 1970; *Chem. Abstr.* **1971**, *74*, 42123a.
9. For selected references see: (a) Sibi, M. P.; Li, B. *Tetrahedron Lett.* **1992**, *33*, 4115–4118. (b) Huwe, C. M.; Blechert, S. *Tetrahedron Lett.* **1994**, *35*, 9537–9540. (c) Lemaire-Audoire, S.; Savignac, M.; Genêt, J. P. *Synlett* **1996**, 75–78. (d) Weisenburger, G. A.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 12218–12219. (e) Kitagawa, O.; Suzuki, T.; Taguchi, T. *Tetrahedron Lett.* **1997**, *38*, 8371–8374. (f) Paquette, L.; Leit, S. M. *J. Am. Chem. Soc.* **1999**, *121*, 8126–8127 (and references cited therein).
10. (a) Barluenga, J.; Canteli, R. M.; Flórez, J. *J. Org. Chem.* **1996**, *61*, 3753–3757. (b) Barluenga, J.; Sanz, R.; Fañanás, F. J. *Chem. Eur. J.* **1997**, *3*, 1342–1326. (c) Barluenga, J.; Sanz, R.; Granados, A.; Fañanás, F. J. *J. Am. Chem. Soc.* **1998**, *120*, 4865–

4866. (d) Pares, J.; Moretó, J. M.; Ricart, S.; Barluenga, J.; Fañanás, F. J. *J. Organomet. Chem.* **1999**, *586*, 247–253.
11. (a) Overman, L. E. *Acc. Chem. Res.* **1980**, *13*, 218–224 (and references cited therein). (b) Shea, R. G.; Fitzner, J. N.; Fankhauser, J. E.; Spaltenstein, A.; Carpino, P. A.; Peevey, R. M.; Pratt, D. V.; Tenge, B. J.; Hopkins, P. B. *J. Org. Chem.* **1986**, *51*, 5243–5252. (c) Connel, R. D.; Rein, T.; Åkermark, B.; Helquist, P. *J. Org. Chem.* **1988**, *53*, 3845–3849. (d) Murai, T.; Yamamoto, M.; Kondo, S.; Kato, S. *J. Org. Chem.* **1993**, *58*, 7440–7445. (e) Mukhopadhyay, M.; Reddy, M. M.; Maikap, G. C.; Isqbal, J. *J. Org. Chem.* **1995**, *60*, 2670–2676. (f) Overman, L. E.; Zipp, G. G. *J. Org. Chem.* **1997**, *62*, 2288–2291.
12. (a) Kresze, G.; Münsterer, H. *J. Org. Chem.* **1983**, *48*, 3561–3564 (and references cited therein). (b) Whitesell, J. K.; Yaser, H. K. *J. Am. Chem. Soc.* **1991**, *113*, 3526–3529. (c) Katz, T. J.; Shi, S. *J. Org. Chem.* **1994**, *59*, 8297–8298.
13. (a) Laurent, A.; Mison, P.; Nafti, A.; Cheikh, R. B.; Chaabouni, R. *J. Chem. Res., Miniprint* **1984**, 3164–3195; *J. Chem. Res., Synopsis* **1984**, 354–355. (b) De Kimpe, N.; De Smaele, D.; Bogaert, P. *Synlett* **1994**, 287–288. (c) Pepito, A. S.; Dittmer, D. C. *J. Org. Chem.* **1997**, *62*, 7920–7925. (d) Aoyama, H.; Mimura, N.; Ohno, H.; Ishii, K.; Toda, A.; Tamamura, H.; Otaka, A.; Fujii, N.; Ibuka, T. *Tetrahedron Lett.* **1997**, *38*, 7383–7386.
14. Trost, B. M.; Sudhakar, A. R. *J. Am. Chem. Soc.* **1987**, *109*, 3792–3794.
15. (a) Schweizer, E.; Smucker, L. D.; Votral, R. J. *J. Org. Chem.* **1966**, *31*, 467–471. (b) Linderman, R. J.; Meyers, A. I. *Tetrahedron Lett.* **1983**, *24*, 3043–3046. (c) Burgess, K.; Liu, T.; Pal, B. *J. Org. Chem.* **1993**, *58*, 4758–4763. (d) Koskinen, A. M. P.; Pihko, P. M. *Tetrahedron Lett.* **1994**, *35*, 7417–7420. (e) Shin, W. S.; Lee, K.; Oh, D. Y. *Tetrahedron Lett.* **1995**, *36*, 281–282.
16. (a) Buchwald, S. L.; Watson, B. T.; Wannamaker, M. W.; Dewan, J. C. *J. Am. Chem. Soc.* **1989**, *111*, 4486–4494. (b) Grossman, R. B.; Davis, W. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1991**, *113*, 2321–2322. (c) Petasis, N. A.; Akritopoulou, I. *Tetrahedron Lett.* **1993**, *34*, 583–586. (d) Takai, K.; Odaka, H.; Kataoka, Y.; Utimoto, K. *Tetrahedron Lett.* **1994**, *35*, 1893–1896.
17. Overman, L. E.; Jessup, P. J. *J. Am. Chem. Soc.* **1978**, *100*, 5179–5185 (and references cited therein).
18. (a) Barluenga, J.; Foubelo, F.; Fañanás, F. J.; Yus, M. *J. Chem. Soc., Perkin Trans. 1* **1989**, 553–557. (b) Resek, J. E.; Beak, P. *Tetrahedron Lett.* **1993**, *34*, 3043–3046. (c) Barluenga, J.; Canteli, R. M.; Flórez, J. *J. Org. Chem.* **1994**, *59*, 1586–1588, (and references cited therein).
19. Bicknell, A. J.; Burton, G.; Elder, J. S. *Tetrahedron Lett.* **1988**, *29*, 3361–3364.
20. Seyden-Penne, J. *Reductions par les Aluminio- et Borohydrures en Synthèse Organique*, Technique et Documentation, Lavoisier: París, 1988 (103pp).
21. Kocovsky, P. *Synlett* **1990**, 677–679.
22. (a) Braun, H.; Felber, H.; Krebe, G.; Ritter, A.; Schmidtchen, F. P.; Schneider, A. *Tetrahedron* **1991**, *47*, 3313–3328. (b) Braun, H.; Schmidtchen, F. P.; Schneider, A.; Simon, H. *Tetrahedron* **1991**, *48*, 3329–3334. (c) Murahashi, S.-I.; Imada, Y.; Taniguchi, Y.; Kodera, Y. *Tetrahedron Lett.* **1988**, *29*, 2973–2976.
23. (a) Murahashi, S.-I.; Tanigawa, Y.; Imada, Y.; Taniguchi, Y. *Tetrahedron Lett.* **1986**, *27*, 227–230. (b) Murahashi, S.-I.; Taniguchi, Y.; Imada, Y.; Tanigawa, Y. *J. Org. Chem.* **1989**, *54*, 3292–3303. (c) Sudo, A.; Saigo, K. *J. Org. Chem.* **1997**, *62*, 5508–5513. (d) Tye, H.; Smyth, D.; Eldred, C.; Wills, M. *Chem. Commun.* **1997**, 1053–1054.
24. (a) Roush, W. R.; Straub, J. A.; Brown, R. J. *J. Org. Chem.* **1987**, *52*, 5127–5136. (b) Granitzer, W.; Stütz, A. *Tetrahedron Lett.* **1979**, *34*, 3145–3148. (c) Corriu, R. J. P.; Bolin, G.; Moreau, J. J. E. *Tetrahedron Lett.* **1991**, *32*, 4121–4124. (d) Hanske, J. R.; Dorff, P.; Juliu, S.; Martinelli, G.; Bussolari, J. *Tetrahedron Lett.* **1992**, *33*, 3715–3716.
25. Ofial, A. R.; Mayr, H. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 143–145.
26. (a) De Kimpe, N.; Stanoeva, E.; Verhé, R.; Schamp, N. *Synthesis* **1988**, 587–592. (b) Palacios, F.; Aparicio, D.; García, J. *Synlett* **1994**, 260–262. (c) Palacios, F.; Aparicio, D.; García, J. *Tetrahedron* **1996**, *52*, 9609–9628. (d) Palacios, F.; Aparicio, D.; García, J.; Rodríguez, E. *Eur. J. Org. Chem.* **1998**, 1413–1423. (e) See also Ref. 15e.
27. Barluenga, J.; Aguilar, E.; Joglar, J.; Olano, B.; Fustero, S. *J. Chem. Soc., Chem. Commun.* **1989**, 1132–1134 (preliminary communication).
28. (a) Barluenga, J.; Merino, I.; Palacios, F. *Tetrahedron Lett.* **1990**, *30*, 5493–5496. (b) Barluenga, J.; Merino, I.; Palacios, F. *J. Chem. Soc., Perkin Trans. 1* **1991**, 341–345.
29. Knorr, R.; Hintemeyer-Hilpert, M.; Böhrer, P. *Chem. Ber.* **1990**, *123*, 1137–1141.
30. (a) Hoberg, H.; Barluenga, J. *Synthesis* **1970**, 142–144. (b) Barluenga, J.; Jardón, J.; Gotor, V. *J. Org. Chem.* **1985**, *50*, 802–804. (c) Barluenga, J., del Pozo Losada, C.; Olano, B. *Tetrahedron Lett.* **1993**, *34*, 5497–5498.
31. (a) Barluenga, J. *Bull. Soc. Chim. Belg.* **1988**, *97*, 545–571. (b) Barluenga, J.; Aznar, F.; Fustero, S.; Tomás, M. *Pure Appl. Chem.* **1990**, *62*, 1957–1966. (c) Barluenga, J.; Tomás, M. *Adv. Heterocycl. Chem.* **1993**, *57*, 1–80. (d) Barluenga, J.; Fernández-Marí, F.; Viado, A. L.; Aguilar, E.; Olano, B. *J. Org. Chem.* **1996**, *61*, 5659–5662.
32. House, H. O. *Modern Synthetic Reactions*, 2nd ed.; W.A. Benjamin Inc.: Menlo Park, CA, 1972 (p 48).
33. Barluenga, J.; Aguilar, E.; Olano, B.; Fustero, S. *J. Org. Chem.* **1988**, *53*, 1741–1744.
34. The competition 1,2 versus 1,4 is well documented in the literature for the reduction of α,β-unsaturated carbonyl compounds. See, for example: (a) Brown, H. C.; Hess, H. M. *J. Org. Chem.* **1969**, *34*, 2206–2209. (b) Corey, E. J.; Becker, K. B.; Varma, R. K. *J. Am. Chem. Soc.* **1972**, *94*, 8616–8619. (c) Hutchins, R. O.; Kandasamy, D. *J. Org. Chem.* **1975**, *40*, 2530–2533. (d) Greeves, N. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds., Pergamon: New York, 1991; Vol. 8, 15–16 (and references cited therein).