

Recent developments in cyclization reactions of α -aminoalkyl radicals

José M. Aurrecoechea* and Rubén Suero

Departamento de Química Orgánica II, Facultad de Ciencia y Tecnología, Universidad del País Vasco, Apartado 644, 48080 Bilbao, Spain
E-mail: gopaufem@lg.ehu.es

(received 2 Apr 04; accepted 21 Jun 04; published on the web 28 Jun 04)

Abstract

The intramolecular additions of C-centered neutral α -aminoalkyl radicals onto suitably positioned C-C double bonds provide a ready access into functionalized carbocycles and heterocycles. This strategy offers considerable versatility in the selection of starting materials since a number of methods using different functional groups and reagents are available for α -aminoalkyl radical generation. This review covers the recent progress in this field.

Keywords: α -Aminoalkyl radical, intramolecular radical additions, pyrrolidines, homolytic cleavage, translocation, PET, SmI₂-promoted reductions

Contents

1. Introduction
2. Methods for α -amino radical generation and applications
 - 2.1 Metal hydride-mediated homolysis of C-S or C-Se bonds
 - 2.2 Radical translocation
 - 2.3 Photoinduced single electron transfer (PET) from α -amino silane precursors
 - 2.4 SmI₂-promoted reduction of imines and iminium cations
 - 2.5 Radical cyclization onto enamides and imines
3. Conclusions

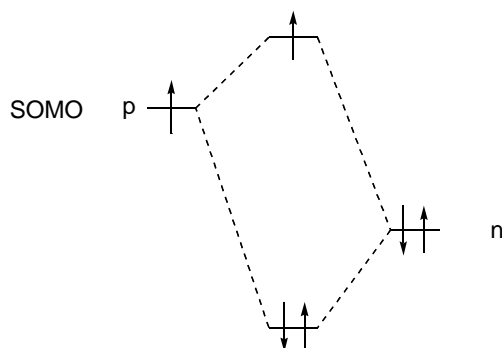
1. Introduction

The chemistry of C-centered α -amino radicals has attracted traditionally the attention of the scientific community mainly due to their involvement in processes of biological or industrial

relevance. Thus, glycine-type α -amino radicals **1** are involved in a number of biochemical processes¹ and, as a consequence, have been the subject of intense scrutiny both at the experimental² and theoretical levels.^{1d,1e,2j,3} Additionally, glycine-type radicals could also be involved as intermediates in the formation of aminoacid derivatives in the interstellar clouds,⁴ as well as in the mechanisms of action of the enediyne family of antitumor antibiotics^{5a} and of some coenzyme B₆-dependent enzymes.^{5b} Simple α -amino radicals are intermediates in the oxidation of amines by monoamine oxidase⁶ while amines themselves are widely used as promoters in polymerization reactions because of their ability to undergo photoinduced conversion into α -amino radicals that then add to monomers to initiate the polymer chain.⁷ Recently, simple α -amino radicals **2** have found application as key intermediates in a new strategy developed by the photographic industry to increase film speed.⁸



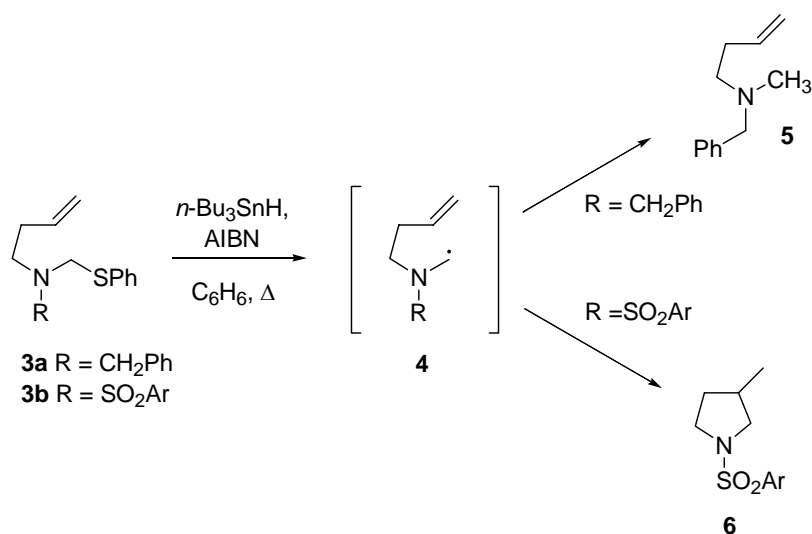
These radicals present some special electronic and structural characteristics. The α -aminomethyl radical ($\bullet\text{CH}_2\text{NH}_2$) has been studied in some detail⁹ and is found to have a C-N bond with some π -character due to the ability of the amino group to delocalize the single electron into the nitrogen lone pair (Scheme 1).^{9a} As also shown in Scheme 1, the interaction between the single electron and the lone pair results in significant net stabilization,¹⁰ thus, the relative ease of α -amino radical generation. Another consequence of delocalization is a rise in SOMO energy that makes this a very *nucleophilic* radical with a strong reducing character.^{9b} Therefore, radical **2**, for example, is a good one-electron donor which is easily converted into the corresponding iminium cation, and this is the basis for its application as a photofilm additive.⁸



Scheme 1

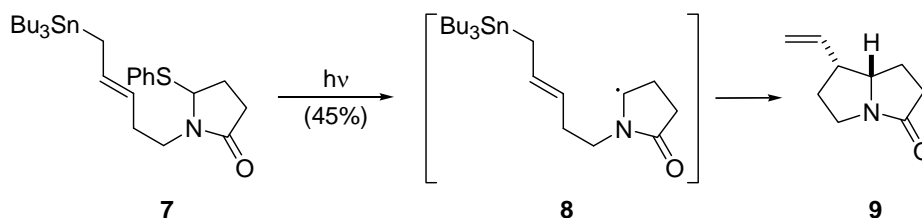
Somewhat surprisingly, the same properties responsible for the relevance of α -amino radicals have limited their application in synthesis, despite their potential for the preparation of nitrogen-

containing heterocycles. For example, attempts by Padwa to effect the *5-exo-trig* cyclization of α -aminomethyl radical **4a** ($R = \text{CH}_2\text{Ph}$) onto a simple unactivated alkene were reported to have met with failure (Scheme 2).¹¹ In this particular case, an aminosulfide precursor **3** was used to generate the α -amino radical under typical tin hydride conditions, and this resulted in no formation of a cyclic product. Instead, the α -aminomethyl radical **4a** abstracted one H-atom from the tin hydride reagent to give **5**, the product of a simple reduction of **3a**. The reasons for this failure probably reside in the very nature of the α -amino radical. Thus, ground state stabilization could account in part for a presumably large activation energy upon addition to the alkene in **4a**. Furthermore, because of its *nucleophilic* character, radical **4a** has little tendency to react with an *electron-rich* alkene. In other words, besides the stability of the radical there is a polarity mismatch¹² that also contributes to increase the activation energy for alkene addition.



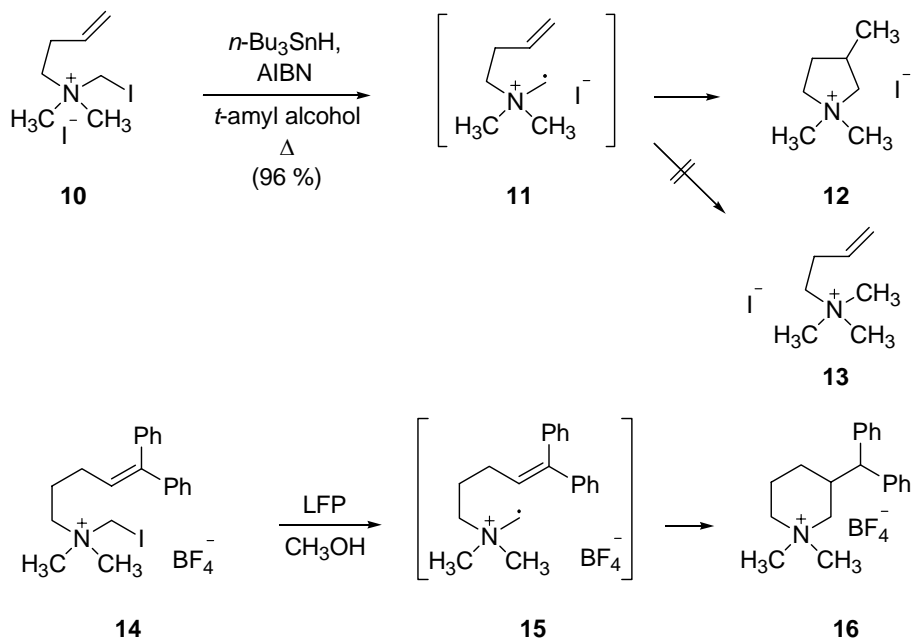
Scheme 2

The above-mentioned problems probably explain why most of the early synthetic applications reported in the literature involved amino groups with electron-withdrawing substituents, that is α -acylamino-type radicals, as exemplified by **8** in Scheme 3.¹³ In this case, the negative effect of the amino nitrogen lone pair upon radical addition is overcome in part by the presence of the electron withdrawing substituent on nitrogen. In this manner the reduced interaction between the lone pair and the singly-occupied orbital results in a more reactive radical and a better polarity match of the reaction partners, leading to the efficient formation of bicyclic product **9**. Likewise, in the work of Padwa of Scheme 2,¹¹ the use of a sulfonyl group as nitrogen substituent in **3b** resulted in formation of cyclic product **6** under conditions that had led to no cyclization with the analogous benzylic amine **3a**.



Scheme 3

A more pronounced effect on radical character and stability is caused by quaternization of nitrogen. Thus, protonation removes the stabilizing effect of the lone pair leading to a very reactive electrophilic α -ammonio radical $\bullet\text{CH}_2\text{-NH}_3^+$ with a negative radical stabilization energy.¹⁰ In line with these ideas 5-*exo* cyclization of **11** (Scheme 4) afforded a very high yield of cyclized product **12** without any of the reduced ammonium salt **13**.^{14a} In fact, this cyclization was too fast to allow measurement of the rate constant by the competition method,^{15a} and attempts at doing so by nanosecond LFP on appropriate substrates were also unsuccessful. However, the corresponding 6-*exo*- rate constants were conveniently measured¹⁵ on **15** and a net 12-fold rate enhancement due to the ammonio group was found when compared with the corresponding all-carbon system.^{15a} For synthetic applications, however, the obvious drawback with this strategy would be the need to dealkylate the cyclized product at some point in the synthetic scheme.¹⁴



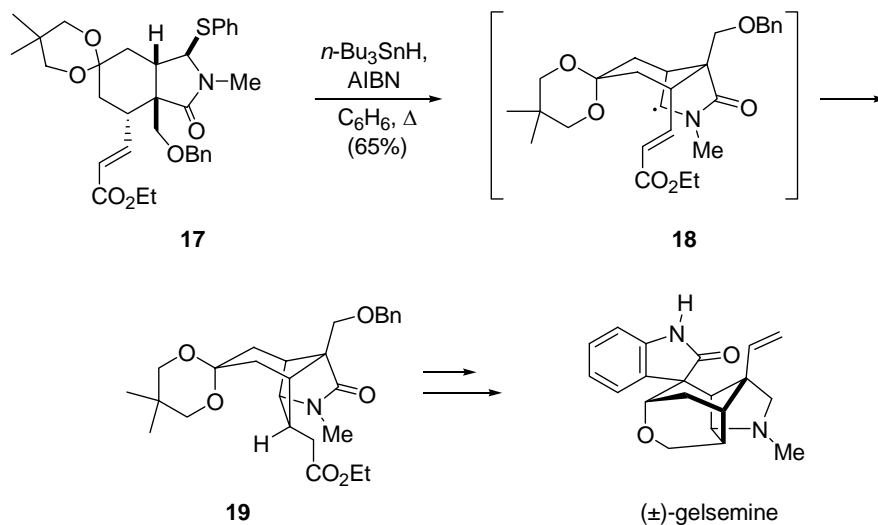
Scheme 4

Despite some of these shortcomings, a number of synthetic applications of neutral α -amino radicals have appeared over the years,¹⁶ with the field of natural product synthesis being particularly well represented.¹⁷ The excellent review by Renaud¹⁶ covers the synthetic applications of α -acyl- and α -alkylamino radicals through 1995. Picking up from that point, the present compilation focuses on recent applications of α -amino radicals in intramolecular processes mainly leading to nitrogen heterocycles.¹⁸ As expected based on their stability, one of the attractive features of the use of these radicals is their ease of generation, and several methods have been developed that perform this task efficiently. In the sections that follow applications are organized according to the method followed for radical generation, with special attention given to reactions of the less often utilized α -(dialkylamino)alkyl radicals.

2. Methods for α -amino radical generation and applications

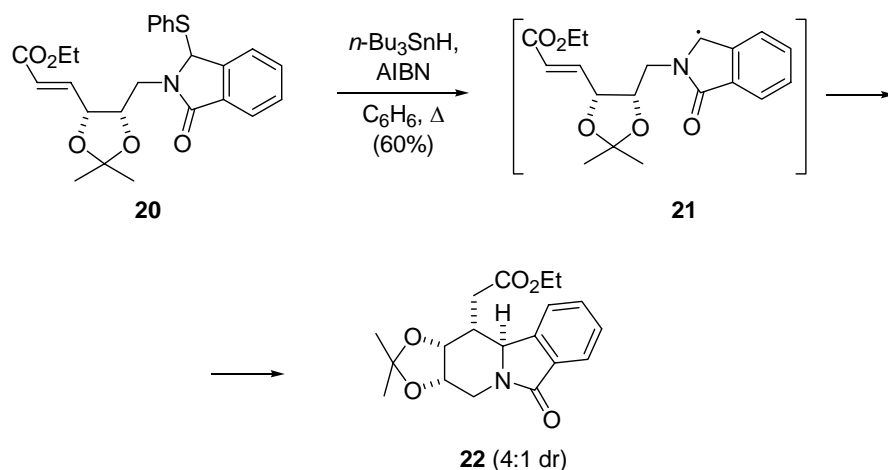
2.1 Metal hydride-mediated homolysis of C-S or C-Se bonds

Pioneered by Hart,¹⁷ this has been traditionally the method of choice for generation of α -acylamino radicals. Amides and carbamates containing an α -sulfanyl or -selenyl group are all adequate precursors, and they have been used in combination with either *n*-tributyltin hydride or tris(trimethylsilyl)silane (TTMSS) in typical radical chain reactions. A recent example that highlights the power of this methodology is the 5-*exo-trig* cyclization of **18** which has been used by Hart in a recent synthesis of gelsemine (Scheme 5).¹⁹ It is interesting that a radical related to **18**, lacking the electron-withdrawing alkene substituent, failed to give a cyclization product,¹⁹ showing that the use of an electron-deficient alkene effectively increases the rate of cyclization, as expected based on polarity grounds.¹²

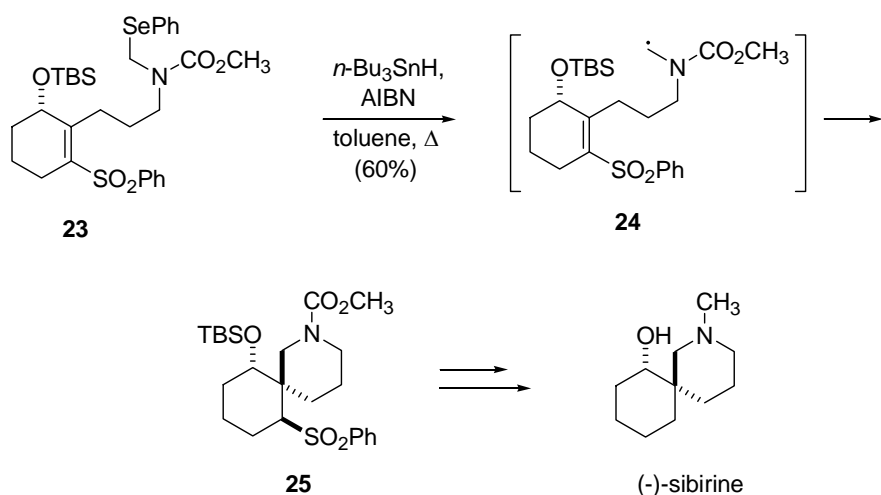


Scheme 5

The same strategy has been used in the formation of simpler aza⁻²⁰ and oxacycles²¹ in 5-*exo-trig* cyclizations, and similar additions have been performed on acylsilanes as well.²² The corresponding 6-*exo-trig* cyclizations appear to be equally effective, as exemplified by the conversion of sulfide **20** and selenide **23** into tricycle **22** (Scheme 6)²³ and spirobicycle **25** (Scheme 7),²⁴ respectively. The latter was then converted into the alkaloid (-)-sibirine. The cyclization **24** → **25** was again found to be facilitated by the presence of the electron-withdrawing substituent on the alkene moiety. In its absence, competition between the desired 6-*exo*- and the alternative 7-*endo* cyclization modes greatly diminished the efficiency of the reaction.



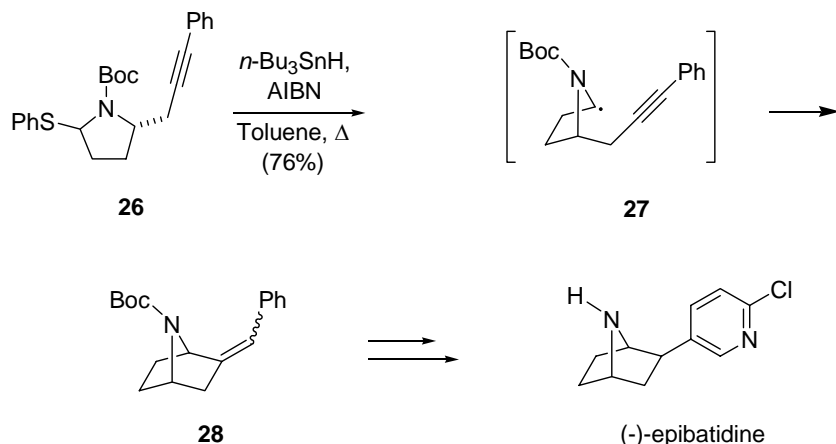
Scheme 6



Scheme 7

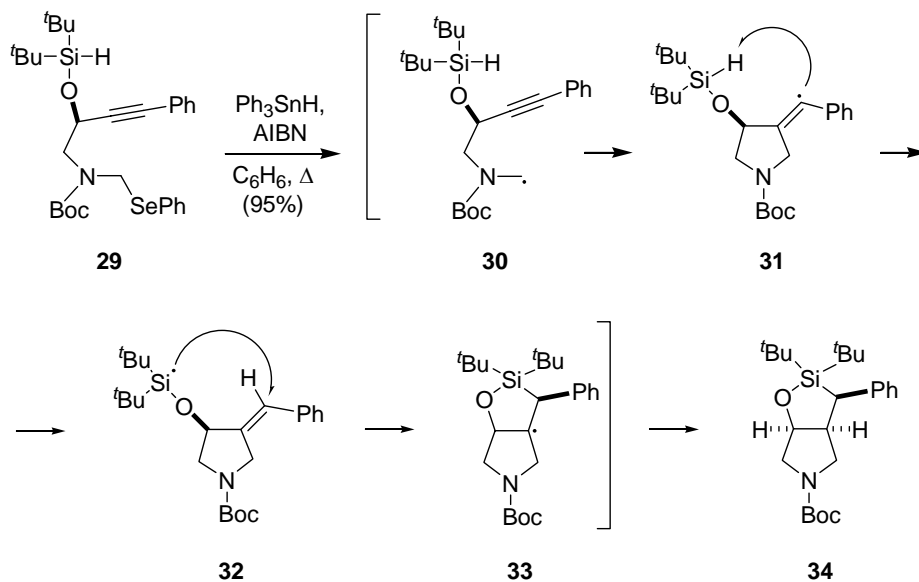
The introduction of alkynes as radical traps opened new avenues for α -acylamino radical cyclizations starting from conventional precursors,²⁵ and efficient syntheses of (-)-swainsonine²⁶

and (+)-biotin²⁷ quickly evolved. More recently, the synthesis of (-)-epibatidine²⁸ has also been described (Scheme 8), where the key step features a 5-*exo-dig* cyclization of α -acylamino radical 27.



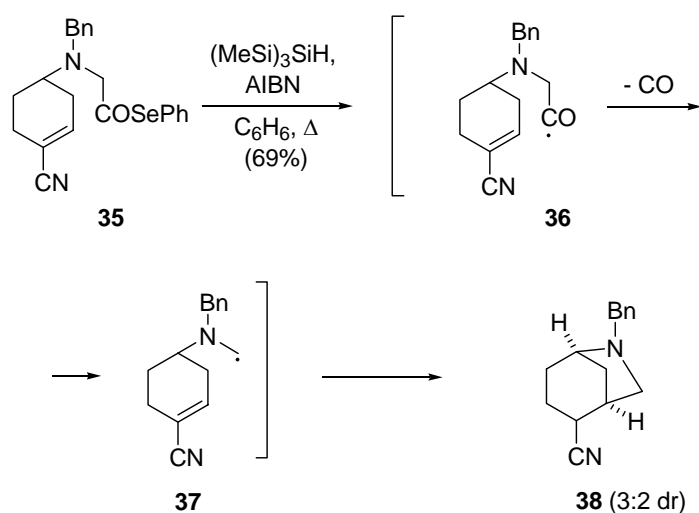
Scheme 8

As becomes obvious from the epibatidine synthesis, one additional attractive feature of alkynes is the unsaturation that is retained in the cyclization product, which offers the possibility of incorporation of the radical cyclization step into useful reaction cascades.²⁹ For example, in the reaction of carbamate 29, the vinyl radical 31 resulting from 5-*exo-dig* cyclization of α -acylamino radical 30 is trapped intramolecularly by 1,5-H transfer from silicon to carbon, and the resulting silicon-centered radical 32 undergoes 5-*endo-trig* ring-closure to give the bicyclic product 34 stereoselectively (Scheme 9).³⁰



Scheme 9

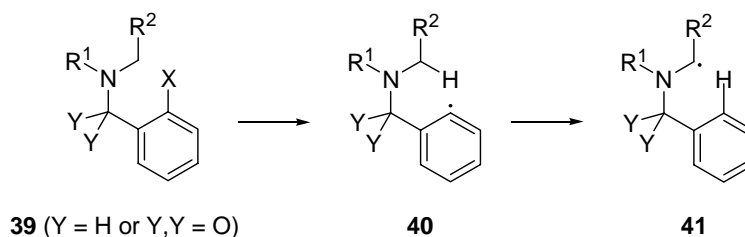
In contrast to the number of applications found in the literature involving α -acylamino-type radicals generated using these methods, reports on the similar use of α -(dialkylamino)alkyl radicals do not abound. This is not surprising given the problems reported with radical **4a** in Scheme 2 and the low stability of the starting α -amino sulfides or selenides.^{31,32} Nonetheless, the successful cyclization of α -amino radical **37**, containing an electron-deficient alkene, has been recently reported and this has provided a ready access to 6-azabicyclo[3.2.1]octane derivatives related to **38** (Scheme 10).^{33a,b} The novelty of this method resides in the use of α -amino selenoester **35** as radical precursor which afforded the α -(dialkylamino)alkyl radical **37** after decarbonylation^{33c} of an initially formed acyl radical **36**. Cyclization failed, however, with a substrate analogous to **35** lacking an electron-withdrawing substituent on the alkene moiety, and this result stresses again the importance of using electron-deficient alkenes in these cyclizations.



Scheme 10

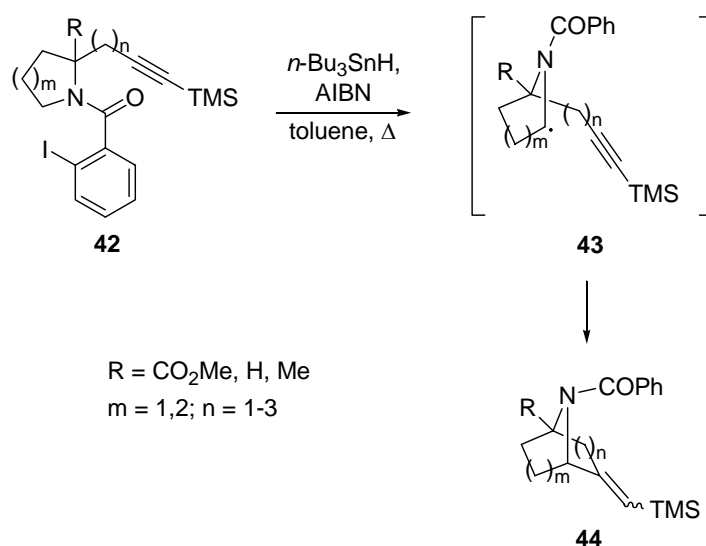
2.2 Radical translocation

Because of the special activation provided by the amino group to adjacent C-H bonds, radical translocation³⁴ has been an effective tool for regioselective generation of α -amino radicals starting typically from *o*-halo benzyl- or benzoyl amines (Scheme 11). In most cases, radical translocation has involved a 1,5-hydrogen shift (as illustrated by **40** \rightarrow **41**) but an unusual 1,4-shift involving a secondary benzylic hydrogen has also been reported.³⁵ Radicals **41** generated in this manner can then enter intramolecular C-C bond-forming pathways leading to cyclic products.



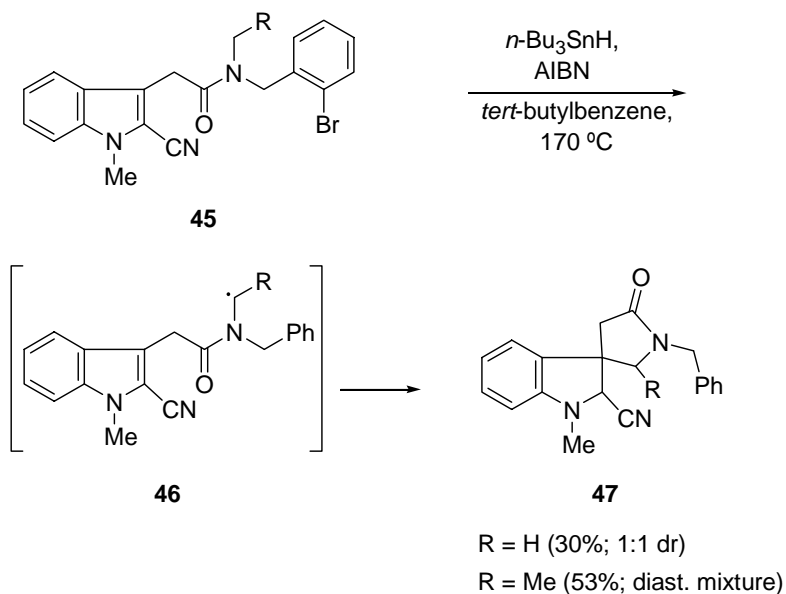
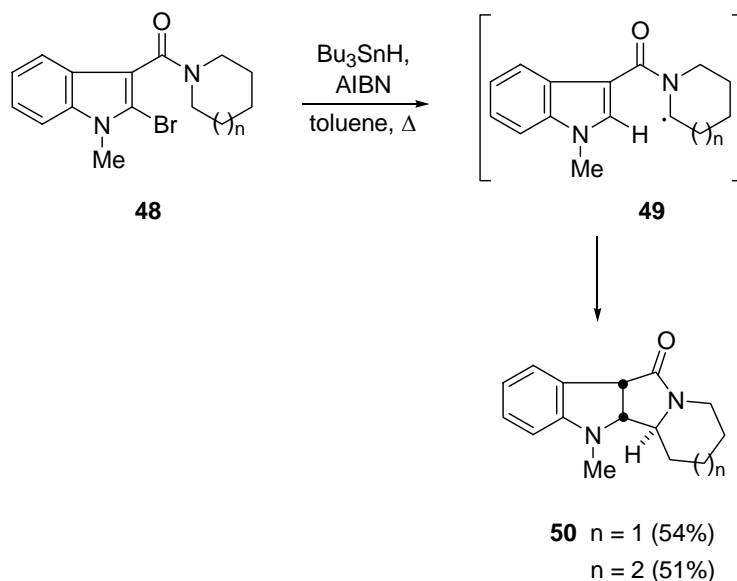
Scheme 11

Following the early reports of Snieckus³⁶ and Curran,³⁷ this strategy has been applied recently to the regioselective generation of α -acylamino radicals of type **43** that, upon subsequent cyclization, lead to the formation of a variety of bridged azabicyclic systems **44** of various ring sizes (Scheme 12).^{34b} Electron-rich alkenes and silyl-substituted alkynes are all useful radical traps, but in the alkene case a terminal substituent is required for good regiocontrol in the cyclization step.³⁸

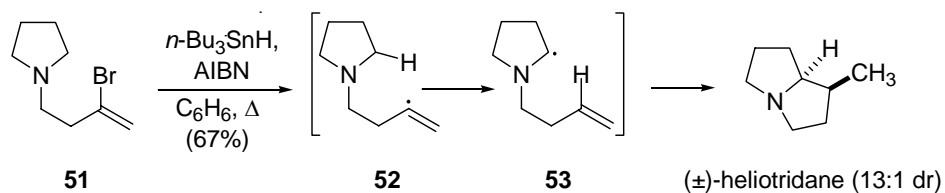


Scheme 12

Similarly, the combined use of the indole nucleus as radical trap and a radical translocation step has led to the preparation of spiroindolenines **47** (Scheme 13)³⁹ and hexahydropyrroloindoles **50** (Scheme 14)⁴⁰ through α -acylamino radicals **46** and **49**, respectively. The incorporation of the strategy depicted in Scheme 13 into a radical cascade has resulted in the preparation of the ABCE ring system of the *Aspidosperma* and *Strychnos* alkaloids.⁴¹

**Scheme 13****Scheme 14**

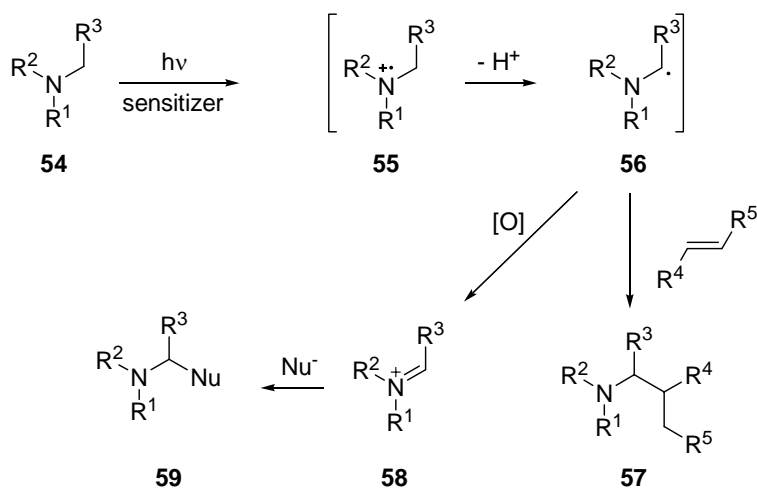
Remarkably, even the more nucleophilic α -(dialkylamino)alkyl radicals are successfully incorporated into the translocation/cyclization protocol with no need for alkene activation.^{42,43} The application of this strategy to the synthesis of a pyrrolizidine natural product⁴² is shown in Scheme 15, and this example also introduces the use of a translocating vinyl radical **52**, rather than the more common aryl radical used in the rest of applications discussed above.



Scheme 15

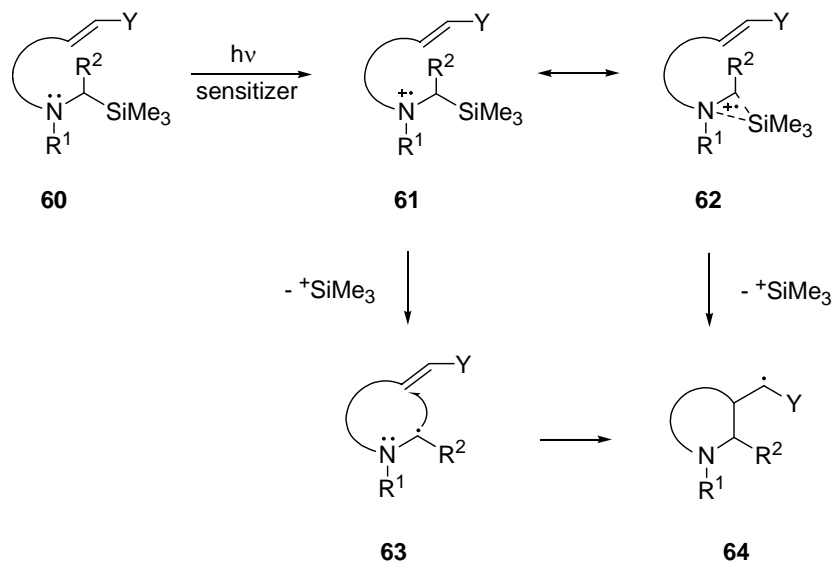
2.3 Photoinduced single electron transfer (PET) from α -amino silane precursors

In the presence of appropriate sensitizers, amines **54** are known to generate α -aminoalkyl radicals **56** that, depending on reaction conditions, can undergo olefin addition or oxidation to an iminium ion **58** (Scheme 16), and these properties have led to applications in the synthetic organic⁴⁴ and polymer fields.⁷



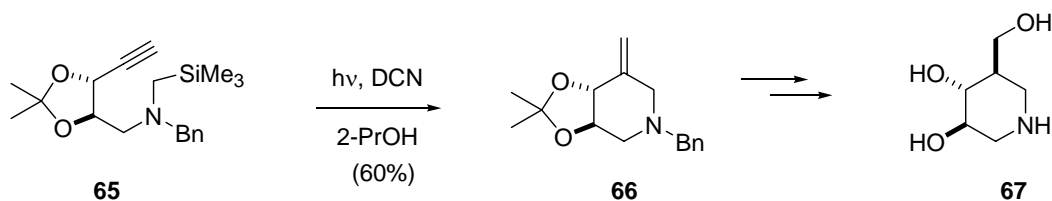
Scheme 16

For regioselective α -amino radical generation, however, the use of α -aminosilanes **60** is more convenient (Scheme 17).⁴⁵ After the initial SET a radical cation **61** \leftrightarrow **62** is formed which, depending on reaction conditions, can either add directly to a tethered olefin with concomitant desilylation, or first undergo desilylation leading to a neutral α -amino radical **63**, which then adds to the olefin. The nature of the tethered olefin may also play a role in directing the cyclization through one of these reaction pathways. Thus, for olefins activated with an electron-withdrawing group, the reaction appears to proceed directly to the neutral radical **63**, that then adds to the electron-deficient olefin.^{45a} On the other hand, in the absence of the electron-withdrawing group, the actual cyclizing species may be the radical cation **61** \leftrightarrow **62** where the diminished assistance of the nitrogen lone pair facilitates its interaction with an electron-rich alkene.^{45b}



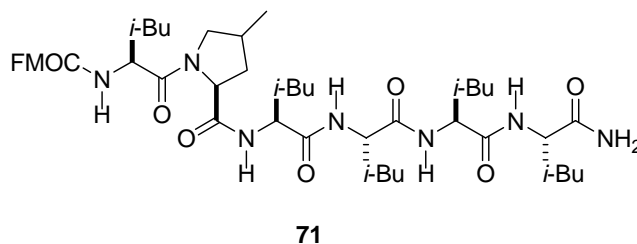
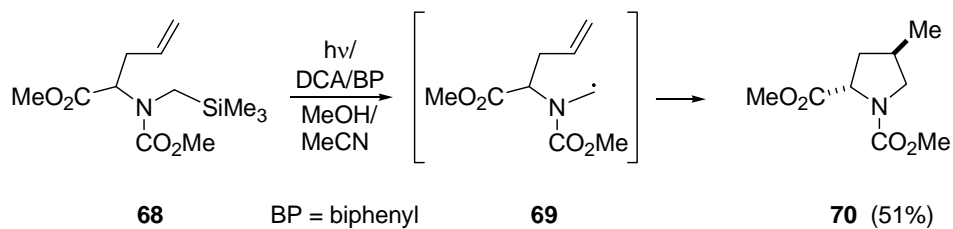
Scheme 17

In any case, these reactions have been extensively applied to the synthesis of pyrrolidines, piperidines and related systems using 5- and 6-*exo*- or *endo*-cyclizations involving both alkenes and alkynes of various electronic characters.⁴⁵⁻⁴⁸ The applications that have continued to evolve in recent years demonstrate the power of this methodology. For example, the synthesis of both enantiomers of isofagomine (**67**) and related 1-*N*-iminosugars has been reported using the PET cyclization of radicals derived from α -trimethylsilylmethylamine **65**, a reaction that features the use of an alkyne as radical trap (Scheme 18).⁴⁷



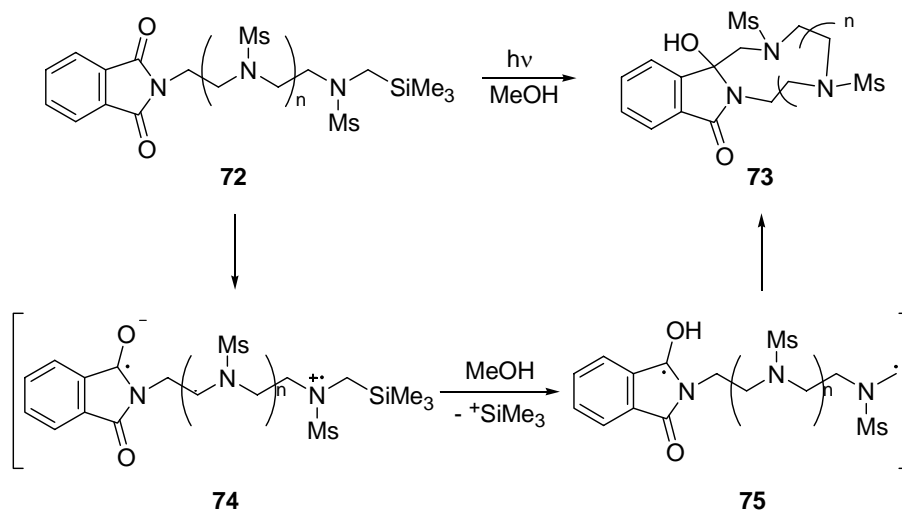
Scheme 18

A new and interesting development in this field has been its application to cyclizations employing unsaturated aminoacid derivatives, such as **68**, to provide proline-type products exemplified by **70** (Scheme 19).⁴⁹ The extension of this reaction to peptide substrates provides a method to introduce changes in the peptide secondary structure, as demonstrated with **71**.



Scheme 19

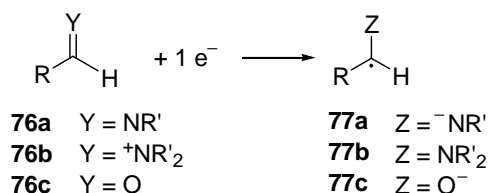
When the foregoing photoinduced generation of α -amino radicals is performed in combination with phthalimide photochemistry⁵⁰ the procedure is useful for the preparation of macrocyclic structures such as **73**. In this case a biradical intermediate of type **75** is generated by photoinduced SET, and intramolecular radical-radical coupling results in formation of the observed product (Scheme 20).^{51a,b} In an extension of this chemistry, the phthalimido group has been incorporated into peptides containing a suitably positioned α -amidosilane group, and this has resulted in the preparation of cyclic peptide mimetics.^{51c}



Scheme 20

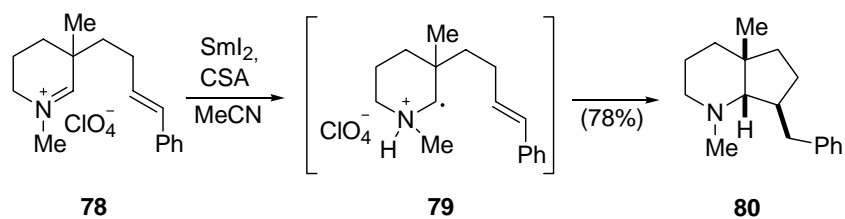
2.4 SmI₂-promoted reduction of imines and iminium cations

Imines and iminium cations, readily available from carbonyl compounds and amines, appear as an attractive source of α -amino radicals by one-electron transfer from a suitable donor (Scheme 21). In fact, radical anion **77a** is the aza-analogue of the ketyl radical anion **77c** for which a very rich and fruitful synthetic chemistry has evolved, particularly in connection with the reducing agent SmI₂.⁵² However, imines **76a** are much less reactive towards SmI₂ than the corresponding aldehydes because of the lower electron deficiency of the former. Thus, SmI₂-promoted pinacol formation from aliphatic aldehydes is an easy process taking place already at 25 °C,⁵³ whereas the corresponding reductive dimerization of aliphatic aldimines requires elevated temperatures.^{54,55}



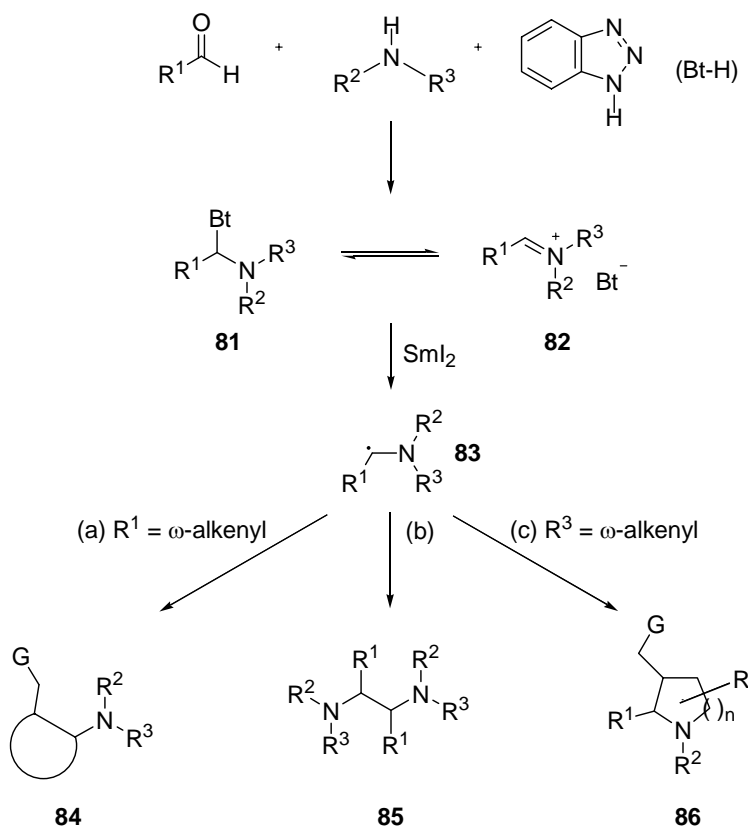
Scheme 21

On the other hand, the cation **76b** is expected to be much more reactive than the neutral compound towards reduction and, furthermore, after a one-electron donation the intermediate formed is a relatively stable α -amino radical **77b**. The first application of the use of SmI₂ to generate neutral α -amino radicals from iminium ions was reported by Martin *at all.*⁵⁶ who found that treatment of iminium salt **78** with SmI₂ and CSA led to the formation of bicyclic product **80** in high yield (Scheme 22). The initial electron transfer from SmI₂ to the iminium cation produces an α -amino radical which is then protonated to give the actual cyclizing species, α -ammonio radical **79**. As discussed above, this is a highly reactive radical that cyclizes rapidly to give the product. In fact, the success of this reaction depends entirely on the presence of CSA in the reaction medium. If this is omitted, the only reactive species is the neutral α -amino radical, which has a low tendency to add to the alkene, as also discussed above. In this scenario, under the reaction conditions, dimerization of the radical prevails over cyclization and vicinal diamines are obtained instead.



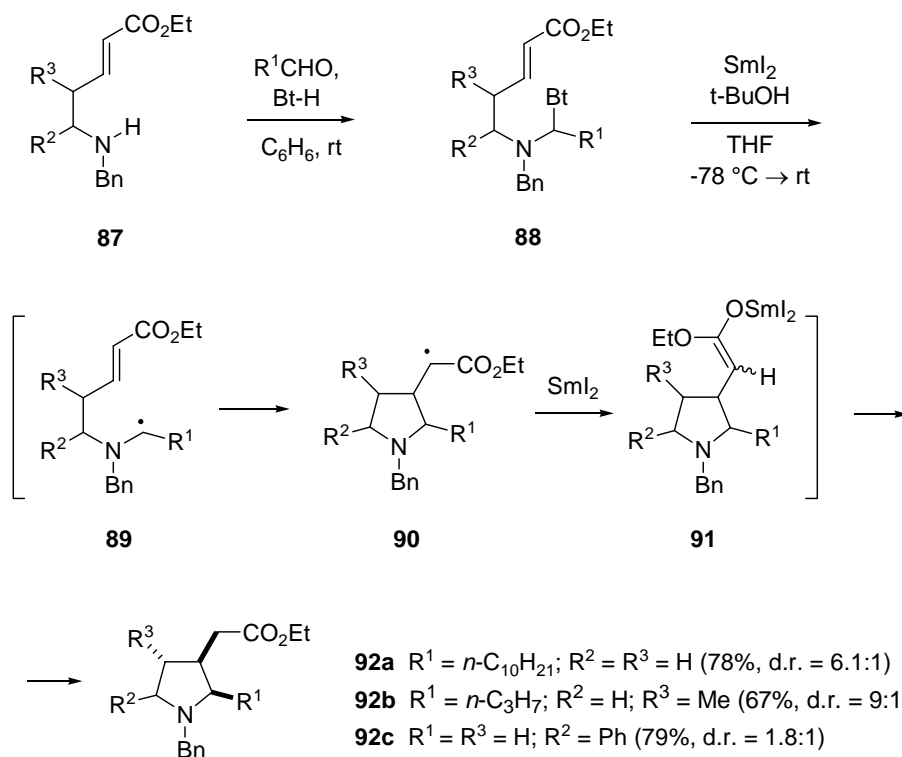
Scheme 22

Vicinal diamines **85** are also the products obtained when benzotriazole adducts **81**, easily formed from aliphatic secondary amines and an aldehyde (aliphatic, aromatic or simply formaldehyde),⁵⁷ are treated with SmI_2 (Scheme 23).⁵⁸ Adducts **81** are known to undergo easy dissociation in solution to give a benzotriazolyl anion and an iminium cation **82**.⁵⁹ Therefore, the formation of **85** is readily interpreted as the result of a one-electron donation from SmI_2 to the iminium ion **82** to generate an α -amino radical **83**, followed by radical-radical coupling.⁶⁰



Scheme 23

As also indicated in Scheme 23, starting from suitable aldehyde and amine fragments, this procedure opens up a way to perform radical cyclizations to afford different types of products depending on the position of the reactive double bond. For example, using amines **87**, featuring an *electron-deficient* double bond, the sequence depicted in Scheme 24 leads to substituted pyrrolidines **92** in good yields through the intermediacy of α -(dialkylamino)alkyl radicals **89**.^{61,62}

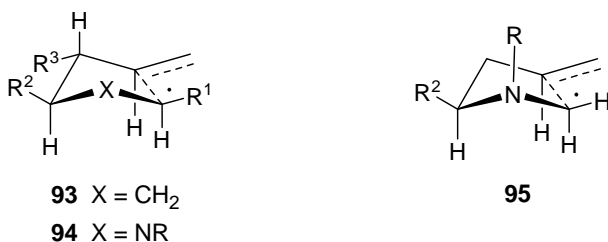


Scheme 24

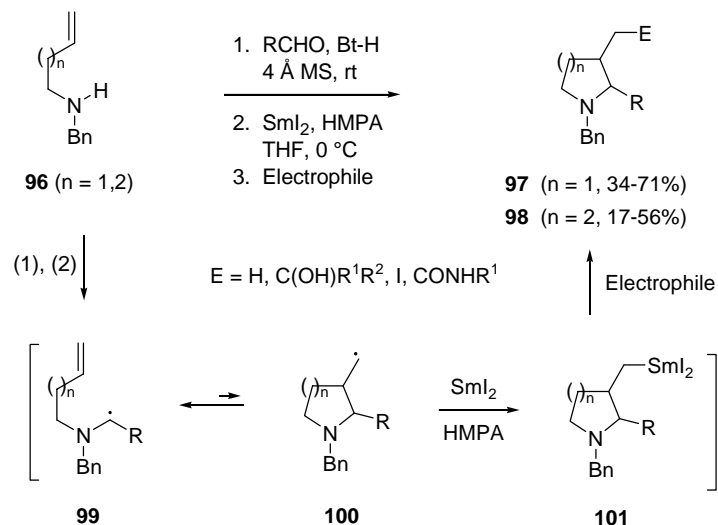
Some representative examples are shown in Scheme 24. For 2,3-dialkyl- ($\text{R}^2 = \text{R}^3 = \text{H}$; e.g. **92a**)^{61a} or 2,3,4-trialkylsubstituted pyrrolidines ($\text{R}^2 = \text{H}$; e.g. **92b**),^{61b} a moderate-to-high 1,5-*cis* preference (hex-5-enyl numbering) is observed, with the substituent at C-4 adopting a *trans* orientation with respect to the other two. In contrast, substitution at C-3 (hex-5-enyl numbering) leads to a significant erosion in stereoselectivity as exemplified with **92c**.^{61b,63} Adducts derived from aromatic aldehydes ($\text{R}^1 = \text{Ar}$) lead to variable stereochemical results ranging from moderate 2,3-*cis*- to moderate 2,3-*trans* selectivities, and this could be due to the reversible nature of the cyclization step when a relatively stable, delocalized, benzylic-type α -amino radical **89** ($\text{R}^1 = \text{Ar}$) is involved.^{61a}

With the above-mentioned possible exception of benzylic radicals ($\text{R}^1 = \text{Ar}$), the stereochemistry of these cyclizations is understood in terms of the Beckwith-Houk model,⁶⁴ that for substituted hex-5-enyl radicals predicts preferred chair-like transition state conformations of type **93** where substituents occupy pseudoequatorial positions. For cyclizations of 2-aza radicals **94** this should result in predominant 1,5-*cis*-, 3,5-*cis*- and 4,5-*trans* relationships (hex-5-enyl numbering). Therefore, the observed preference of 1- and 4-alkyl substituents in α -amino radicals **89** to give 1,5-*cis*- or 4,5-*trans* products, respectively, is in good agreement with the model. The lack of 3,5-selectivity observed in the formation of **92c** and related products, while in line with related literature precedents,^{45b,63} may appear surprising in view of the significantly higher ratio observed in the cyclization of the simple 3-methylhex-5-enyl radical.^{64d} A possible

rationalization is provided by the corresponding chair-like transition structure **95**. Thus, in this conformation the *N*-substituent is forced into a pseudoaxial position by conjugation of the unpaired electron with the *N* lone pair,^{61b} resulting in an unfavorable gauche-type interaction between R and a C-3 substituent R² when the latter adopts the normally preferred pseudoequatorial disposition.

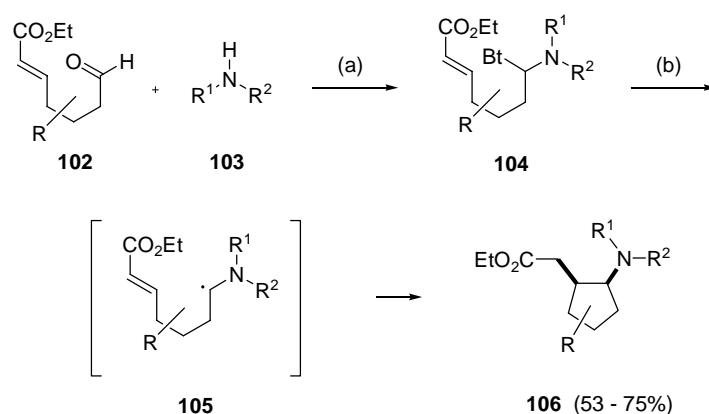


Not surprisingly, the use of electron-deficient alkenes proved to be important in these cyclizations. Thus, if the electron-withdrawing substituent is removed from the double bond as in amines **96**, the corresponding α -(dialkylamino)alkyl radicals **99** simply dimerize leading to the exclusive formation of vicinal diamines (see **85** in Scheme 23).^{61a} According to the mechanisms depicted in Schemes 24 and 25, the probable effect of the electron-withdrawing group is three-fold: (i) increase the stability of the cyclized radical **90**, (ii) provide a better match to the polarity of the α -amino radical, and (iii) facilitate a fast reduction of the cyclized radical **90**, the driving force being the formation of a relatively stable samarium enolate **91** rather than an unstable carbanion **101**. Interestingly, the cyclizations of radicals **99** are possible provided that HMPA is used as additive. Thus, treatment with SmI₂/HMPA of benzotriazole adducts derived from amines **96**, followed by addition of a suitable electrophilic trap (water, aldehydes, ketones, I₂, isocyanides) gives rise to a radical cyclization/nucleophilic addition cascade leading to functionalized pyrrolidines **97**^{65a} or piperidines **98**^{65b} (Scheme 25). These overall observations can be understood if radicals **99** and **100** are involved in an equilibrium which is shifted towards the more stable open species **99**.^{9c,10,66} Electron-donor ligands such as HMPA are known to increase the reducing power of SmI₂,⁶⁷ and the cyclized primary alkyl radical **100** is expected to undergo reduction much more rapidly than the more nucleophilic α -amino radical **99**. The role of HMPA then is to provide the cyclized radical **100** with a fast irreversible step, thus giving a forward thrust to the reaction.



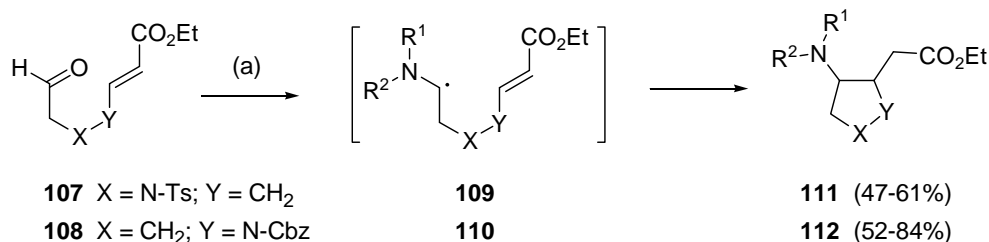
Scheme 25

A different possibility for α -amino radical cyclizations involves an exocyclic amino group, as sketched in path a of Scheme 23. In this other situation a suitable double bond would have to be incorporated into the aldehyde moiety of the starting benzotriazole adduct ($\text{R}^1 = \omega$ -alkenyl). The early application of these ideas resulted in a two-step synthesis of cyclopentylamines **106** via 5-*exo* cyclization of α -(dialkylamino)alkyl radicals **105** derived from aldehydes **102** and amines **103** (Scheme 26).⁶⁸ An interesting feature of this reaction is the very high stereoselectivity observed in the formation of 1,2-disubstituted cyclopentylamines **106** ($\text{R} = \text{H}$) where the *cis* diastereoisomer was often obtained exclusively. Again this sense of stereoselection is in agreement with the Beckwith-Houk model (see **93**),⁶⁴ and additional substituents along the cyclizing chain nicely follow the expected trends.⁶⁸



Scheme 26. (a) Bt-H, 4 Å MS, C₆H₆, rt. (b) SmI₂, THF, -50 °C → rt.

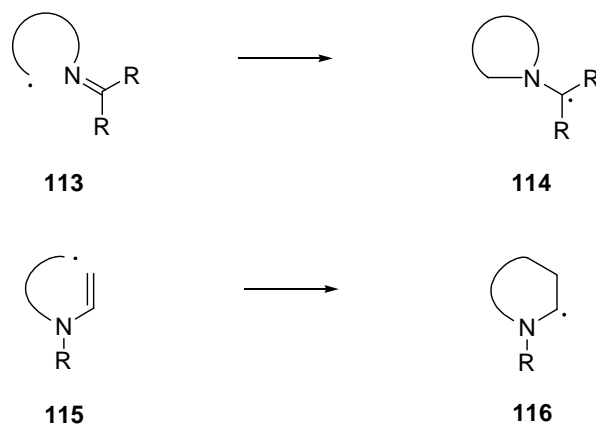
A readily envisaged variant of this methodology leads to 3-aminopyrrolidines. Thus, 5-*exo-trig* cyclizations of α -amino radicals **109** and **110**, derived from secondary amines **103** and aminoaldehydes **107** or **108**, led, respectively, to the corresponding 3-aminopyrrolidines **111** and **112** (Scheme 27). Yields of 3-aminopyrrolidines range from moderate to high but unexpectedly these cyclizations proceed with very low diastereoselectivity.⁶⁹



Scheme 27. (a) (i) **103**, Bt-H, 4 Å MS, THF, rt. (ii) SmI₂, *t*-BuOH, THF, -78 °C → rt.

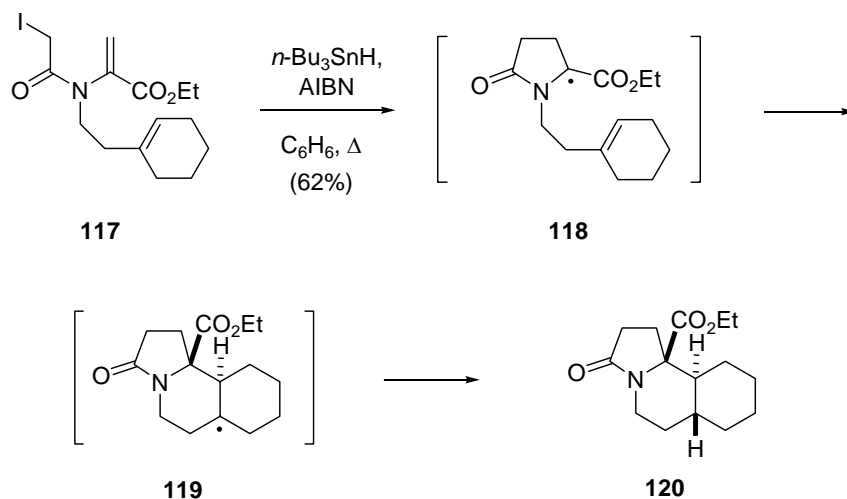
2.5 Radical cyclizations onto enamides

The relative stability of α -amino radicals can be used advantageously to generate C-C bonds by intramolecular radical addition to imine-⁷⁰ or enamine-^{71,72} type double bonds, where an α -amino radical is the initial *addition product* (Scheme 28).



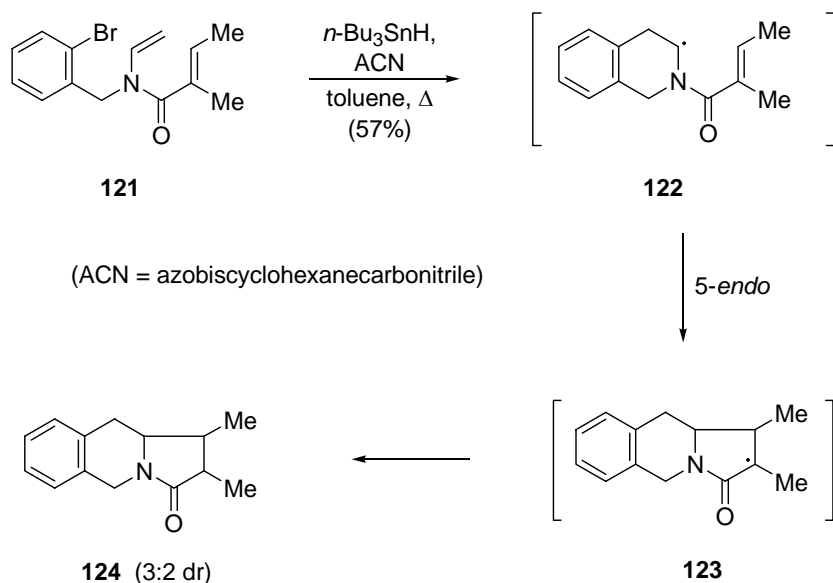
Scheme 28

While no further cyclization has been reported for radicals of type **114**, α -amino radicals **116** generated from *N*-vinyl carbamoylmethyl radicals react *via* the usually "disfavored" 5-*endo-trig* cyclization mode with the enamide double bond leading to substituted pyrrolidinones.^{71,72a,72c-g} With appropriate substitution, the α -amino radicals generated in this manner have been incorporated into reaction cascades where they participate in subsequent cyclizations.^{72e,72k,73,74} In the example shown in Scheme 29, the initial carbamoylmethyl radical cyclization product, α -aminoester **118**, is poised to undergo further cyclization onto a suitably positioned tethered alkene to afford a tricyclic product **120** by overall tandem 5-*endo*/6-*endo* cyclizations.⁷³



Scheme 29

Besides the carbamoylmethyl-type, aryl radicals also participate efficiently in *endo-trig* cyclizations onto enamides^{72i-k} and related derivatives,^{72h} with initial formation of the corresponding α -amino radicals. Thus, after a 6-*endo*-aryl radical cyclization, the newly generated α -acylamino radical **122** undergoes 5-*endo* cyclization to afford tricyclic derivative **124** in a single operation (Scheme 30).^{72k}



Scheme 30

3. Conclusions

α -Amino radicals are useful intermediates in the synthesis of heterocycles. These radicals display a characteristic behavior, which is related to their stability, nucleophilicity and reducing character. While these properties have limited in the past the synthetic use of α -amino radicals, nowadays industrial and synthetic chemists alike take advantage of those same properties in useful new applications that will surely continue to emerge.

Acknowledgements

Our own work in this field has been possible thanks to the generous financial support provided over the years by *Universidad del País Vasco* (current 9/UPV00041.310-14471/2002), *Ministerio de Ciencia y Tecnología*, *Gobierno Vasco* and Janssen-Cilag.

References and Notes

1. See, for example: (a) Massey, V. *Biochem. Soc. Trans.* **2000**, *28*, 283. (b) Marsh, E. N. G. *Bioorg. Chem.* **2000**, *28*, 176. (c) Weber, S.; Mobius, K.; Richter, G.; Kay, C. W. M. *J. Am. Chem. Soc.* **2001**, *123*, 3790. (d) Wetmore, S. D.; Smith, D. M.; Golding, B. T.; Radom, L. *J. Am. Chem. Soc.* **2001**, *123*, 7963. (e) Rauk, A.; Armstrong, D. A.; Berges, J. *Can. J. Chem.* **2001**, *79*, 405, and references cited therein.
2. (a) Easton, C. J. *Chem. Rev.* **1997**, *97*, 53. (b) Easton, C. J. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M., Eds.; Wiley-VCH: Weinheim, 2001; Vol. 2, pp 505. (c) Blakskjaer, P.; Pedersen, L.; Skrydstrup, T. *J. Chem. Soc., Perkin Trans. 1* **2001**, 910. (d) Lu, J. M.; Wu, L. M.; Geimer, J.; Beckert, D. *Phys. Chem. Chem. Phys.* **2001**, *3*, 2053. (e) Knowles, H. S.; Hunt, K.; Parsons, A. F. *Tetrahedron* **2001**, *57*, 8115. (f) Croft, A. K.; Easton, C. J.; Radom, L. *J. Am. Chem. Soc.* **2003**, *125*, 4119.
3. (a) Rega, N.; Cossi, M.; Barone, V. *J. Am. Chem. Soc.* **1997**, *119*, 12962. (b) Galano, A.; Alvarez-Idaboy, J. R.; Montero, L. A.; Vivier-Bunge, A. *J. Comput. Chem.* **2001**, *22*, 1138. (c) Croft, A. K.; Easton, C. J.; Kociuba, K.; Radom, L. *Tetrahedron: Asymmetry* **2003**, *14*, 2919.
4. Basiuk, V. A. *J. Phys. Chem. A* **2001**, *105*, 4252.
5. (a) Jones, G. B.; Plourde, G. W.; Wright, J. M. *Org. Lett.* **2000**, *2*, 811. (b) Agnihotri, G.; Liu, H. W. *Bioorg. Chem.* **2001**, *29*, 234.
6. Silverman, R. B. *Acc. Chem. Res.* **1995**, *28*, 335.
7. See, for example: (a) Jockusch, S.; Turro, N. J. *J. Am. Chem. Soc.* **1999**, *121*, 3921. (b) Encinas, M. V.; Rufs, A. M.; Bertolotti, S.; Previtali, C. M. *Macromolecules* **2001**, *34*, 2845, and references cited therein.

8. (a) Gould, I. R.; Lenhard, J. R.; Muentzer, A. A.; Godleski, S. A.; Farid, S. *J. Am. Chem. Soc.* **2000**, *122*, 11934. (b) Gould, I. R.; Lenhard, J. R.; Muentzer, A. A.; Godleski, S. A.; Farid, S. *Pure Appl. Chem.* **2001**, *73*, 455.
9. (a) Schubert, S.; Renaud, P.; Carrupt, P. A.; Schenk, K. *Helv. Chim. Acta* **1993**, *76*, 2473. (b) Armstrong, D. A.; Rauk, A.; Yu, D. K. *J. Am. Chem. Soc.* **1993**, *115*, 666. (c) Wayner, D. D. M.; Clark, K. B.; Rauk, A.; Yu, D.; Armstrong, D. A. *J. Am. Chem. Soc.* **1997**, *119*, 8925. (d) Jansen, T. L.; Trabjerg, I.; Rettrup, S.; Pagsberg, P.; Sillesen, A. *Acta Chem. Scand.* **1999**, *53*, 1054.
10. Mayer, P. M.; Glukhovtsev, M. N.; Gault, J. W.; Radom, L. *J. Am. Chem. Soc.* **1997**, *119*, 12889.
11. (a) Padwa, A.; Nimmesgern, H.; Wong, G. S. K. *J. Org. Chem.* **1985**, *50*, 5620. (b) Padwa, A.; Dent, W.; Nimmesgern, H.; Venkatramanan, M. K.; Wong, G. S. K. *Chem. Ber.* **1986**, *119*, 813.
12. For examples that illustrate the importance of polarity in radical reactions, see: (a) Johnson, C.C.; Horner, J. H.; Tronche, C.; Newcomb, M. *J. Am. Chem. Soc.* **1995**, *117*, 1684. (b) Newcomb, M.; Horner, J. H.; Filipkowski, M. A.; Ha, C.; Park, S.-U. *J. Am. Chem. Soc.* **1995**, *117*, 3674. (c) Musa, O. M.; Choi, S. Y.; Horner, J. H.; Newcomb, M. *J. Org. Chem.* **1998**, *63*, 786. (d) Simakov, P. A.; Martinez, F. N.; Horner, J. H.; Newcomb, M. *J. Org. Chem.* **1998**, *63*, 1226. (e) Brocks, J. J.; Beckhaus, H. D.; Beckwith, A. L. J.; Ruchardt, C. *J. Org. Chem.* **1998**, *63*, 1935.
13. Keck, G. E.; Enholm, E. J. *Tetrahedron Lett.* **1985**, *26*, 3311.
14. For applications to the generation of bridgehead nitrogen heterocycles, see: (a) Della, E. W.; Knill, A. M.; Smith, P. A. *Chem. Commun.* **1996**, 1637. (b) Della, E. W.; Smith, P. A. *J. Org. Chem.* **1999**, *64*, 1798.
15. (a) Rios, L. A.; Dolbier, W. R.; Paredes, R.; Lusztyk, J.; Ingold, K. U.; Jonsson, M. *J. Am. Chem. Soc.* **1996**, *118*, 11313. (b) Rios, L. A.; Bartberger, M. D.; Dolbier, W. R.; Paredes, R. *Tetrahedron Lett.* **1997**, *38*, 7041.
16. Renaud, P.; Giraud, L. *Synthesis* **1996**, 913.
17. Hart, D. J. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M., Eds.; Wiley-VCH: Weinheim, 2001; Vol. 2, pp 279.
18. General reviews on the synthesis of heterocycles by radical cyclization: (a) Bowman, W. R.; Bridge, C. F.; Brookes, P. *J. Chem. Soc., Perkin Trans 1* **2000**, *1*. (b) Bowman, W. R.; Cloonan, M. O.; Krintel, S. L. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2885. (c) Bowman, W. R.; Fletcher, A. J.; Potts, G. B. S. *J. Chem. Soc., Perkin Trans 1* **2002**, 2747. (d) Majumdar, K. C.; Basu, P. K. *Heterocycles* **2002**, *57*, 2413.
19. Atarashi, S.; Choi, J. K.; Ha, D. C.; Hart, D. J.; Kuzmich, D.; Lee, C. S.; Ramesh, S.; Wu, S. *C. J. Am. Chem. Soc.* **1997**, *119*, 6226.
20. Yuasa, Y.; Ando, J.; Shibuya, S. *J. Chem. Soc., Perkin Trans. 1* **1996**, 465.
21. Lesage, M.; Arya, P. *Synlett* **1996**, 237.
22. Tsai, Y.-M.; Nieh, H.-C.; Pan, J.-S.; Hsiao, D.-D. *Chem. Commun.* **1996**, 2469.

23. Clauss, R.; Hunter, R. *J. Chem. Soc., Perkin Trans. 1* **1997**, 71.
24. Koreeda, M.; Wang, Y. M.; Zhang, L. M. *Org. Lett.* **2002**, 4, 3329.
25. (a) Choi, J. K.; Hart, D. J. *Tetrahedron* **1985**, 41, 3959. (b) Kano, S.; Yuasa, Y.; Asami, K.; Shibuya, S. *Chem. Lett.* **1986**, 735.
26. Dener, J. M.; Hart, D. J.; Ramesh, S. *J. Org. Chem.* **1988**, 53, 6022.
27. Corey, E. J.; Mehrotra, M. M. *Tetrahedron Lett.* **1988**, 29, 57.
28. Clive, D. L. J.; Yeh, V. S. C. *Tetrahedron Lett.* **1998**, 39, 4789.
29. Recent reviews on radical cascade reactions: (a) McCarroll, A. J.; Walton, J. C. *Angew. Chem., Int. Ed.* **2001**, 40, 2225. (b) McCarroll, A. J.; Walton, J. C. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3215. (c) Dhimane, A. L.; Fensterbank, L.; Malacria, M. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M., Eds.; Wiley-VCH: Weinheim, 2001; Vol. 2, p 350.
30. Clive, D. L. J.; Yang, W. *Chem. Commun.* **1996**, 1605.
31. Katritzky, A. R.; Fan, W. Q.; Long, Q. H. *Synthesis* **1993**, 229.
32. Bao, W. L.; Zhang, Y.; Zhou, J. Q.; Zheng, Y. F. *Synth. Commun.* **1996**, 26, 3277.
33. (a) Quirante, J.; Escolano, C.; Bonjoch, J. *Synlett* **1997**, 179. (b) Quirante, J.; Vila, X.; Escolano, C.; Bonjoch, J. *J. Org. Chem.* **2002**, 67, 2323. (c) For an intermolecular application, see: Stojanovic, A.; Renaud, P. *Synlett* **1997**, 181.
34. Recent reviews: (a) Robertson, J.; Pillai, J.; Lush, R. K. *Chem. Soc. Rev.* **2001**, 30, 94. (b) Sato, T.; Ikeda, M. *Heterocycles* **2003**, 59, 429.
35. Quirante, J.; Diaba, F.; Vila, X.; Bonjoch, J.; Lago, E.; Molins, E. *C. R. Acad. Sci. II* **2001**, 4, 513.
36. Snieckus, V.; Cuevas, J.-C.; Sloan, C. P.; Liu, H.; Curran, D. P. *J. Am. Chem. Soc.* **1990**, 112, 896.
37. Curran, D. P.; Liu, H. T. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1377.
38. (a) Sato, T.; Kugo, Y.; Nakaumi, E.; Ishibashi, H.; Ikeda, M. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1801. (b) Ikeda, M.; Kugo, Y.; Sato, T. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1819.
39. Hilton, S. T.; Ho, T. C. T.; Pljevaljcic, G.; Jones, K. *Org. Lett.* **2000**, 2, 2639.
40. Gribble, G. W.; Fraser, H. L.; Badenock, J. C. *Chem. Commun.* **2001**, 805.
41. Hilton, S. T.; Ho, T. C. T.; Pljevaljcic, G.; Schulte, M.; Jones, K. *Chem. Commun.* **2001**, 209.
42. Robertson, J.; Peplow, M. A.; Pillai, J. *Tetrahedron Lett.* **1996**, 37, 5825.
43. Ishizaki, M.; Takano, H.; Hoshino, O. *Heterocycles* **1998**, 49, 305.
44. (a) Santamaria, J. *Pure Appl. Chem.* **1995**, 67, 141. (b) Bertrand, S.; Hoffmann, N.; Pete, J. P. *Eur. J. Org. Chem.* **2000**, 2227. (c) Bertrand, S.; Hoffmann, N.; Humbel, S.; Pete, J. P. *J. Org. Chem.* **2000**, 65, 8690. (d) Marinkovic, S.; Hoffmann, N. *Chem. Commun.* **2001**, 1576. (e) Cossy, J. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M., Eds.; Wiley-VCH: Weinheim, 2001; Vol. 1, pp 229. (f) Brule, U.; Hoffmann, N. *Tetrahedron Lett.* **2002**, 43, 69.
45. For reviews see: (a) Yoon, U. C.; Mariano, P. S. *Acc. Chem. Res.* **1992**, 25, 233. (b) Pandey, G. *Synlett* **1992**, 546. (c) Ref. 16.
46. Pandey, G.; Reddy, G. D.; Chakrabarti, D. *J. Chem. Soc., Perkin Trans. 1* **1996**, 219.

47. (a) Pandey, G.; Kapur, M. *Synthesis* **2001**, 1263. (b) Pandey, G.; Kapur, M. *Org. Lett.* **2002**, 4, 3883. (c) Pandey, G.; Kapur, M.; Khan, M. I.; Gaikwad, S. M. *Org. Biomol. Chem.* **2003**, 1, 3321.
48. Khim, S. K.; Cederstrom, E.; Ferri, D. C.; Mariano, P. S. *Tetrahedron* **1996**, 52, 3195.
49. Jonas, M.; Blechert, S.; Steckhan, E. *J. Org. Chem.* **2001**, 66, 6896.
50. Yoon, U. C.; Mariano, P. S. *Acc. Chem. Res.* **2001**, 34, 523.
51. (a) Yoon, U. C.; Oh, S. W.; Lee, J. H.; Park, J. H.; Kang, K. T.; Mariano, P. S. *J. Org. Chem.* **2001**, 66, 939. (b) Yoon, U. C.; Kwon, H. C.; Hyung, T. G.; Choi, K. H.; Oh, S. W.; Yang, S.; Zhao, Z.; Mariano, P. S. *J. Am. Chem. Soc.* **2004**, 126, 1110. (c) Yoon, U. C.; Jin, Y. X.; Oh, S. W.; Park, C. H.; Park, J. H.; Campana, C. F.; Cai, X.; Duesler, E. N.; Mariano, P. S. *J. Am. Chem. Soc.* **2003**, 125, 10664.
52. Reviews on SmI₂-mediated synthetic applications: (a) Molander, G. A. *Chem. Rev.* **1992**, 92, 29. (b) Molander, G. A. In *Organic Reactions*; Paquette, L. A., Ed.; John Wiley & Sons, New York: 1994; Vol. 46; pp 211-367. (c) Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996**, 96, 307. (d) Molander, G. A.; Harris, C. R. *Tetrahedron* **1998**, 54, 3321. (e) Krief, A.; Laval, A. M. *Chem. Rev.* **1999**, 99, 745. (f) Steel, P. G. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2727. (g) Kagan, H. B. *Tetrahedron* **2003**, 59, 10351.
53. Girard, P.; Namy, J. L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, 102, 2693.
54. Enholm, E. J.; Forbes, D. C.; Holub, D. P. *Synth. Commun.* **1990**, 20, 981.
55. For other reductive processes of imines with SmI₂ and other Sm reagents and/or additives, see: Kim, M.; Knettle, B. W.; Dahlen, A.; Hilmersson, G.; Flowers, R. A. *Tetrahedron* **2003**, 59, 10397, and references cited therein.
56. Martin, S. F.; Yang, C. P.; Laswell, W. L.; Rüeger, H. *Tetrahedron Lett.* **1988**, 29, 6685.
57. For reviews see: (a) Katritzky, A. R.; Rachwal, S.; Hitchings, G. J. *Tetrahedron* **1991**, 47, 2683. (b) Katritzky, A. R.; Lan, X. F.; Yang, J. Z.; Denisko, O. V. *Chem. Rev.* **1998**, 98, 409. (c) Katritzky, A. R. *J. Heterocycl. Chem.* **1999**, 36, 1501. (d) Katritzky, A. R.; Denisko, O. V. *Pure Appl. Chem.* **2000**, 72, 1597. (e) Katritzky, A. R.; Rogovoy, B. V. *Chem. Eur. J.* **2003**, 9, 4586.
58. Aurrecoechea, J. M.; Fernández-Acebes, A. *Tetrahedron Lett.* **1992**, 33, 4763.
59. Katritzky, A. R.; Yannakapoulou, K.; Kuzmierkiewicz, W.; Aurrecoechea, J. M.; Palenik, G. J.; Koziol, A. E.; Szczesniak, M.; Skarjune, R. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2673.
60. The treatment of benzotriazole adducts prepared from primary aromatic amides or sulfonamides and aromatic aldehydes has been recently shown to afford diamine products: Wang, X. X.; Liu, Y. J.; Zhang, Y. M. *Tetrahedron* **2003**, 59, 8257.
61. (a) Aurrecoechea, J. M.; Fernandez, A.; Gorgojo, J. M.; Saornil, C. *Tetrahedron* **1999**, 55, 7345. (b) Bustos, F.; Gorgojo, J. M.; Suero, R.; Aurrecoechea, J. M. *Tetrahedron* **2002**, 58, 6837.
62. Amides derived from aromatic amines related to **87**, when treated with triflic anhydride and SmI₂, also afford 1,2-disubstituted pyrrolidines of type **92** albeit with low

- diastereoselectivity: McDonald, C. E.; Galka, A. M.; Green, A. I.; Keane, J. M.; Kowalchick, J. E.; Micklitsch, C. M.; Wisnoski, D. D. *Tetrahedron Lett.* **2001**, *42*, 163.
63. Pandey, G.; Reddy, G. D.; Kumaraswamy, G. *Tetrahedron* **1994**, *50*, 8185.
64. (a) Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron* **1985**, *41*, 3925. (b) Spellmeyer, D. C.; Houk, K. M. *J. Org. Chem.* **1987**, *52*, 959. (c) Beckwith, A. L. J. *Chem. Soc. Rev.* **1993**, *22*, 143. (d) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions*; VCH: Weinheim, 1996; pp 23-115.
65. (a) Katritzky, A. R.; Feng, D. M.; Qi, M.; Aurrecochea, J. M.; Suero, R.; Aurrekoetxea, N. *J. Org. Chem.* **1999**, *64*, 3335. (b) Katritzky, A. R.; Luo, Z.; Fang, Y.; Feng, D.; Ghiviriga, I. *J. Chem. Soc., Perkin Trans. 2* **2000**, 1375.
66. Jursic, B. S.; Timberlake, J. W.; Engel, P. S. *Tetrahedron Lett.* **1996**, *37*, 6473.
67. (a) Hasegawa, E.; Curran, D. P. *Tetrahedron Lett.* **1993**, *34*, 1717. (b) Imamoto, T.; Yamanoi, Y.; Tsuruta, H.; Yamaguchi, K.; Yamazaki, M.; Inanaga, J. *Chem. Lett.* **1995**, 949. (c) Hou, Z. M.; Zhang, Y. G.; Wakatsuki, Y. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 149. (d) Shabangi, M.; Flowers, R. A. *Tetrahedron Lett.* **1997**, *38*, 1137. (e) Shabangi, M.; Sealy, J. M.; Fuchs, J. R.; Flowers, R. A. *Tetrahedron Lett.* **1998**, *39*, 4429. (f) Shabangi, M.; Kuhlman, M. L.; Flowers, R. A. *Org. Lett.* **1999**, *1*, 2133. (g) Shotwell, J. B.; Sealy, J. M.; Flowers, R. A. *J. Org. Chem.* **1999**, *64*, 5251. (h) Enemaerke, R. J.; Hertz, T.; Skrydstrup, T.; Daasbjerg, K. *Chem. Eur. J.* **2000**, *6*, 3747. (i) Prasad, E.; Flowers, R. A. *J. Am. Chem. Soc.* **2002**, *124*, 6895.
68. Aurrecochea, J. M.; López, B.; Fernández, A.; Arrieta, A.; Cossío, F. P. *J. Org. Chem.* **1997**, *62*, 1125.
69. Suero, R.; Gorgojo, J. M.; Aurrecochea, J. M. *Tetrahedron* **2002**, *58*, 6211.
70. (a) Viswanathan, R.; Prabhakaran, E. N.; Plotkin, M. A.; Johnston, J. N. *J. Am. Chem. Soc.* **2003**, *125*, 163. (b) Nugent, B. M.; Williams, A. L.; Prabhakaran, E. N.; Johnston, J. N. *Tetrahedron* **2003**, *59*, 8877.
71. Reviews: (a) Parsons, A. F. *C.R. Acad. Sci. II* **2001**, *4*, 391. (b) Clark, A. J. *Chem. Soc. Rev.* **2002**, *31*, 1-12. (c) Ishibashi, H.; Sato, T.; Ikeda, M. *Synthesis* **2002**, 695.
72. Recent references: (a) Ishibashi, H.; Kodama, K.; Higuchi, M.; Muraoka, O.; Tanabe, G.; Takeda, Y. *Tetrahedron* **2001**, *57*, 7629. (b) Todd, M. H.; Ndubaku, C.; Bartlett, P. A. *J. Org. Chem.* **2002**, *67*, 3985. (c) Tamura, O.; Matsukida, H.; Toyao, A.; Takeda, Y.; Ishibashi, H. *J. Org. Chem.* **2002**, *67*, 5537. (d) Miranda, L. D.; Zard, S. Z. *Org. Lett.* **2002**, *4*, 1135. (e) Chikaoka, S.; Toyao, A.; Ogasawara, M.; Tamura, O.; Ishibashi, H. *J. Org. Chem.* **2003**, *68*, 312. (f) Clark, A. J.; Dell, C. P.; McDonagh, J. M.; Geden, J.; Mawdsley, P. *Org. Lett.* **2003**, *5*, 2063. (g) Bryans, J. S.; Chessum, N. E. A.; Huther, N.; Parsons, A. F.; Ghelfi, F. *Tetrahedron* **2003**, *59*, 6221. (h) Wu, X. D.; Khim, S. K.; Zhang, X. M.; Cederstrom, E. M.; Mariano, P. S. *J. Org. Chem.* **1998**, *63*, 841. (i) Jabin, I.; Netchitaïlo, P. *Tetrahedron Lett.* **2001**, *42*, 7823. (j) Padwa, A.; Brodney, M. A.; Lynch, S. M. *J. Org. Chem.* **2001**, *66*, 1716. (k) Ishibashi, H.; Ishita, A.; Tamura, O. *Tetrahedron Lett.* **2002**, *43*, 473.

73. Baker, S. R.; Burton, K. I.; Parsons, A. F.; Pons, J. F.; Wilson, M. J. *Chem. Soc., Perkin Trans. 1* **1999**, 427.
74. Parsons, A. F.; Williams, D. A. J. *Tetrahedron* **2000**, 56, 7217.



José M. Aurrecoechea was born in Bilbao, Spain, in 1958. He received his Ph.D. degree in 1985 from the University of Florida working under the guidance of Prof. Alan R. Katritzky. After doing postdoctoral work at the Universities of Florida and California, Riverside (with Prof. William H. Okamura), in 1988 he took up his present academic position at the Universidad del País Vasco. His research interests involve the development of new synthetic methodology using radical and organometallic chemistry.



Rubén Suero has studied chemistry at the Universidad del País Vasco where he has received B.Sc. (1998) and M.Sc. (2001) degrees. He is currently pursuing a Ph.D. at the same University under the supervision of Prof. José M. Aurrecoechea. His research interests are concerned with the use of radical reactions in the synthesis of compounds with potential pharmacological activity.