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: qopaufem@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, SmI$_2$-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 SmI$_2$-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 antibiotics5a 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 (•CH2NH2) 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 = CH₂Ph) 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.

\[
\begin{align*}
N\text{R} & \quad \text{n-Bu₃SnH, AIBN} \\
\text{SPh} & \quad \text{C₆H₆, Δ} \\
3a \text{ R = CH₂Ph} & \quad 3b \text{ R = SO₂Ar} \\
\end{align*}
\]

\[
\begin{align*}
\text{4} & \quad \text{NCH₃} \\
\text{Ph} & \quad R = CH₂Ph \\
\text{R = SO₂Ar} & \quad 6 \\
\end{align*}
\]

**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 •CH$_2$-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 measured$^{15}$ 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 $\alpha$-amino radicals have appeared over the years,\textsuperscript{16} with the field of natural product synthesis being particularly well represented.\textsuperscript{17} The excellent review by Renaud\textsuperscript{16} covers the synthetic applications of $\alpha$-acyl- and $\alpha$-alkylamino radicals through 1995. Picking up from that point, the present compilation focuses on recent applications of $\alpha$-amino radicals in intramolecular processes mainly leading to nitrogen heterocycles.\textsuperscript{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 $\alpha$-(dialkylamino)alkyl radicals.

2. Methods for $\alpha$-amino radical generation and applications

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

Pioneered by Hart,\textsuperscript{17} this has been traditionally the method of choice for generation of $\alpha$-acylamino radicals. Amides and carbamates containing an $\alpha$-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-\textit{exo-trig} cyclization of 18 which has been used by Hart in a recent synthesis of gelsemine (Scheme 5).\textsuperscript{19} It is interesting that a radical related to 18, lacking the electron-withdrawing alkene substituent, failed to give a cyclization product,\textsuperscript{19} showing that the use of an electron-deficient alkene effectively increases the rate of cyclization, as expected based on polarity grounds.\textsuperscript{12}

Scheme 5
The same strategy has been used in the formation of simpler aza-\(^{20}\) and oxacycles\(^{21}\) in 5-\textit{exo-trig} cyclizations, and similar additions have been performed on acylsilanes as well.\(^{22}\) The corresponding 6-\textit{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 \(\rightarrow\) 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-\textit{exo-} and the alternative 7-\textit{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 \(\alpha\)-acylamino radical cyclizations starting from conventional precursors,\(^{25}\) and efficient syntheses of (-)-swainsonine\(^{26}\)
and (+)-biotin\textsuperscript{27} quickly evolved. More recently, the synthesis of (-)-epibatidine\textsuperscript{28} has also been described (Scheme 8), where the key step features a 5-\textit{exo-dig} cyclization of \( \alpha \)-acylamino radical \textsuperscript{27}.

\textbf{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.\textsuperscript{29} For example, in the reaction of carbamate \textsuperscript{29}, the vinyl radical \textsuperscript{31} resulting from 5-\textit{exo-dig} cyclization of \( \alpha \)-acylamino radical \textsuperscript{30} is trapped intramolecularly by 1,5-H transfer from silicon to carbon, and the resulting silicon-centered radical \textsuperscript{32} undergoes 5-\textit{endo-trig} ring-closure to give the bicyclic product \textsuperscript{34} stereoselectively (Scheme 9).\textsuperscript{30}

\textbf{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. 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). 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 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.

![Diagram](attachment:compound_diagram.png)

**Scheme 10**

2.2 Radical translocation

Because of the special activation provided by the amino group to adjacent C-H bonds, radical translocation 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 → 41) but an unusual 1,4-shift involving a secondary benzylic hydrogen has also been reported. Radicals 41 generated in this manner can then enter intramolecular C-C bond-forming pathways leading to cyclic products.
Following the early reports of Snieckus and Curran, 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). 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.

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) and hexahydropyrroloindoles 50 (Scheme 14) 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.
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. The application of this strategy to the synthesis of a pyrrolizidine natural product is shown in Scheme 15, and this example also introduces the use of a translocating vinyl radical, 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 organic and polymer fields.

![Scheme 16](image_url)

For regioselective α-amino radical generation, however, the use of α-aminosilanes 60 is more convenient (Scheme 17). After the initial SET a radical cation 61 ↔ 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. On the other hand, in the absence of the electron-withdrawing group, the actual cyclizing species may be the radical cation 61 ↔ 62 where the diminished assistance of the nitrogen lone pair facilitates its interaction with an electron-rich alkene.
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.\textsuperscript{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 $\alpha$-trimethylsilylmethylamine (65), a reaction that features the use of an alkyne as radical trap (Scheme 18).\textsuperscript{47}

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).\textsuperscript{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 photochemistry\(^5\) 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 SmI\(_2\)-promoted reduction of imines and iminium cations

Imines and iminium cations, readily available from carbonyl compounds and amines, appear as an attractive source of \(\alpha\)-amino radicals by one-electron transfer from a suitable donor (Scheme 21). In fact, radical anion \(\text{77a}\) is the aza-analogue of the ketyl radical anion \(\text{77c}\) for which a very rich and fruitful synthetic chemistry has evolved, particularly in connection with the reducing agent SmI\(_2\).\(^{52}\) However, imines \(\text{76a}\) are much less reactive towards SmI\(_2\) than the corresponding aldehydes because of the lower electron deficiency of the former. Thus, SmI\(_2\)-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](image)

On the other hand, the cation \(\text{76b}\) 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 \(\alpha\)-amino radical \(\text{77b}\). The first application of the use of SmI\(_2\) to generate neutral \(\alpha\)-amino radicals from iminium ions was reported by Martin \textit{at al}.\(^{56}\) who found that treatment of iminium salt \(\text{78}\) with SmI\(_2\) and CSA led to the formation of bicyclic product \(\text{80}\) in high yield (Scheme 22). The initial electron transfer from SmI\(_2\) to the iminium cation produces an \(\alpha\)-amino radical which is then protonated to give the actual cyclizing species, \(\alpha\)-ammonio radical \(\text{79}\). 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 \(\alpha\)-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](image)
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 SmI2 (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 SmI2 to the iminium ion 82 to generate an α-amino radical 83, followed by radical-radical coupling.60

\[
\begin{align*}
R^1 & \quad H \quad R^2 \\
R^3 & \quad N \\
\text{Bt-H} & \quad \text{(Bt-H)} \\
\end{align*}
\]

\[
\begin{align*}
R^1 & \quad N \quad R^3 \\
\text{Bt} \\
\end{align*}
\]

\[
\begin{align*}
R^1 & \quad N \quad R^3 \\
\text{Sml}_2 \\
\end{align*}
\]

\[
\begin{align*}
R^1 & \quad N \quad R^3 \\
\end{align*}
\]

(a) \( R^1 = \omega\text{-alkenyl} \)

(b) \( R^3 = \omega\text{-alkenyl} \)

\[
\begin{align*}
G & \quad N \quad R^2 \\
R^3 & \\
\end{align*}
\]

\[
\begin{align*}
R^2 & \quad N \quad R^3 \\
\end{align*}
\]

\[
\begin{align*}
R^1 & \quad N \quad R^3 \\
\end{align*}
\]

\[
\begin{align*}
R^1 & \quad N \quad R^3 \\
G & \\
\end{align*}
\]

\[
\begin{align*}
R^2 & \quad N \quad R^3 \\
\end{align*}
\]

\[
\begin{align*}
R^1 & \quad N \quad R^3 \\
\end{align*}
\]

\[
\begin{align*}
R^1 & \quad N \quad R^3 \\
\end{align*}
\]

\[
\begin{align*}
R^2 & \quad N \quad R^3 \\
\end{align*}
\]

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
Some representative examples are shown in Scheme 24. For 2,3-dialkyl- (R² = R³ = H; e.g. 92a)⁶¹a or 2,3,4-trialkylsubstituted pyrrolidines (R² = 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 (R¹ = 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 (R¹ = Ar) is involved.⁶¹a

With the above-mentioned possible exception of benzylic radicals (R¹ = 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, resulting in an unfavorable gauche-type interaction between R and a C-3 substituent R’ 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). 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 or piperidines 98 (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. Electron-donor ligands such as HMPA are known to increase the reducing power of SmI2, 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 (R1 = ω-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). An interesting feature of this reaction is the very high stereoselectivity observed in the formation of 1,2-disubstituted cyclopentylamines 106 (R = H) where the cis diastereoisomer was often obtained exclusively. Again this sense of stereoselection is in agreement with the Beckwith-Houk model (see 93), and additional substituents along the cyclizing chain nicely follow the expected trends.

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
Besides the carbamoylmethyl-type, aryl radicals also participate efficiently in endo-trig cyclizations onto enamides\textsuperscript{72i-k} and related derivatives,\textsuperscript{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).\textsuperscript{72k}
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


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.


60. The treatment of benzotriazole adducts prepared from primary aromatic amides and 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.


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


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.