Organic LETTERS

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Aminoketyl Radicals in Organic Synthesis: Stereoselective Cyclization of Five- and Six-Membered Cyclic Imides to 2-Azabicycles Using SmI_2-H_2O

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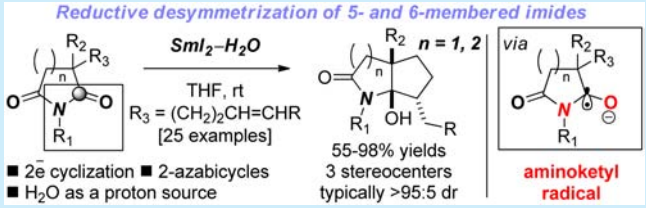
Supporting Information

ABSTRACT: Synthetic application of aminoketyl radicals [R−C•(O⁻)NR′R″] formed by a direct electron capture into the amide bond is limited. Herein, we demonstrate addition of aminoketyl radicals to unactivated alkenes using SmI_2-H_2O as a crucial promoter based on the generic five- and six-membered imide template. Notably, this method enables direct access to aminoketyl radicals with wide-ranging applications in synthesis for the formation of C−C bonds adjacent to nitrogen via polarity reversal.



Aminoketyl radicals are versatile intermediates that have been invoked in degradation of nucleobases[1] and play a central role in electron capture dissociation (ECD) of peptides and proteins.[2] However, the use of aminoketyl radicals in organic synthesis is limited due to the difficulty of a direct electron transfer into the antibonding π^* orbital of the amide function due to $n_N \rightarrow \pi^*_{C=O}$ conjugation.[3] Moreover, the utility of carbon-centered aminoketyl radicals has been hampered by the undesirable fragmentation of the N−C_α bond, generating a new C-centered radical and an enolimine intermediate with a formal negative charge at the nitrogen atom.[4] The facility of this fragmentation has been correlated with the charge density at carbon of the aminoketyl group,[5] restricting the range of acceptors that are amenable to cross-coupling protocols. Aminoketyl radicals can be regarded as a formal merger of the highly nucleophilic and predominantly planar ketyl radicals[6] with the highly stabilized and partially pyramidalized α-aminyl radicals.[7] However, in contrast to widespread applications of ketyl and α-aminyl radicals to forge new C−C bonds for the functionalization of α-C−O[8] and α-C−N bonds,[9] respectively, often proceeding with exquisite control of selectivity,[8,9] the development of practical and general coupling protocols for the addition of aminoketyl radicals to unactivated π-acceptors in a stereoselective manner remains a formidable challenge (Figure 1A,B).[10]

The 2-azabicyclic motif appears in a large number of bioactive natural products and top-selling pharmaceuticals and has been shown to impart novel properties in ligands and small-molecule catalysts (Figure 1C).[11] Moreover, 2-azabicycles serve as key precursors for the synthesis of biologically active heterocycles, such as indoles, pyrroles, and quinolines.[12] New selective methods for the preparation of 2-azabicycles are an important focus of research.[13] In particular, modular entries to 2-azabicycles featuring angular substituents adjacent to the nitrogen atom are highly desirable because this ring system can be found in a variety of biologically active molecules;[11] however, few methods for the stereoselective construction have been reported.[14]

Herein, we report a general strategy to develop synthetically useful, stereoselective, and modular cyclizations of aminoketyl radicals with unactivated π-acceptors using SmI_2-H_2O[15] as a crucial promoter based on the generic five- and six-membered imide template. The reaction provides direct access to 2-azabicyclic motifs featuring three contiguous stereocenters (two quaternary) in excellent selectivity (>95:5 in all cases examined). A direct electron transfer from the activated lanthanide(II) reagent into the antibonding π^* orbital of the amide group to generate an aminoketyl radical anion is the key step.[15] Notably, this process constitutes the first general method for the synthesis of aminoketyl radicals under mild electron transfer conditions.[1−10,16] Considering the versatile role of aminoketyl radicals and the prominence of 2-azabicyclic motifs in organic synthesis, we expect that this strategy will find widespread use for the synthesis of N-containing molecules via open-shell reaction pathways.

Our strategy to achieve a modular, broadly useful generation of aminoketyl radicals[16] to access 2-azabicyclic motifs is based on the following design features: (i) directing-group-controlled activation of the functional group toward electron transfer,[17a] and stabilization of the resulting aminoketyl intermediate by chelation;[17b,c] (ii) pseudoanomeric stabilization of the aminoketyl radical anion intermediate;[17d,e] (iii) lower energy antibonding π^*orbital in the imide template;[17f] (iv) $n_N \rightarrow \pi^*_{CO}$ delocalization into the remaining carbonyl in a conformationally locked system to prevent N−C_α fragmentation;[17g] (v) coordination of the oxophilic Ln(II) reagent to the carbonyl group to lower the redox potential of the precursor.[17h] Suitable

Received: September 22, 2015
Published: October 6, 2015

DOI: 10.1021/acs.orglett.5b02732
Org. Lett. 2015, 17, 5144−5147

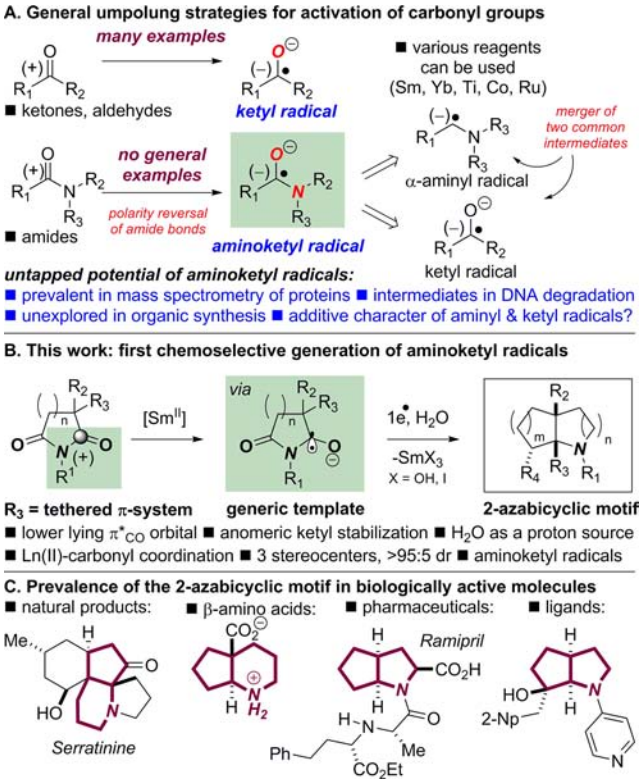
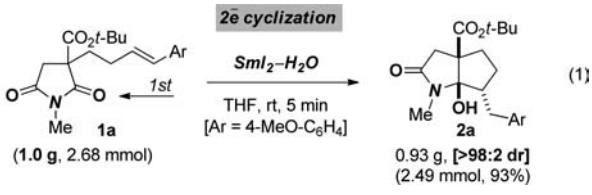


Figure 1. (a) General strategies for polarity reversal of carbonyl groups. (b) This work: the first general chemoselective generation of aminoketyl radicals. (c) 2-Azabicylic motif.

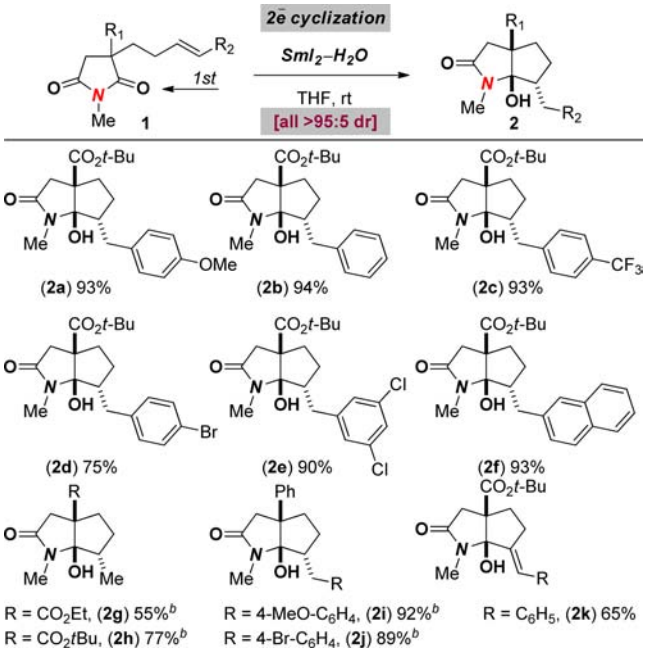
ligands activate the lanthanide(II) reagent and favor electron transfer under thermodynamic control of the reaction pathway.[18] Importantly, the generic imide scaffold can be used as a platform to access a wide range of functionalized 2-azabicycles via postcyclization functionalizations.[11−13]

The following gram scale procedure is representative: a mixture of **1a** (1.0 g, 2.68 mmol), H_2O (19.3 mL, 1.1 mol), and SmI_2 (5.36 mmol, 2.0 equiv) was stirred in THF at 23 °C for 5 min to afford 0.93 g of 2-azabicycle **2a** (93% yield, >98:2 dr) after direct recrystallization from the reaction mixture (eq 1).



We started our investigation by evaluating the addition of a challenging five-membered imide[19] bearing an unactivated alkene tether and an ester directing group[17a] using SmI_2 as a promoter in the presence of various alcohols as ligands (see Table 1-SI, Supporting Information (SI)).[18] The proposed R−C•(O⁻)NR′R″/C−C cross-coupling was indeed feasible in the presence of ligands that have been shown to coordinate to the inner coordination sphere of Sm(II) [MeOH, H_2O, HO-$(CH_2)_2$OH].[20] Employing H_2O as a ligand provided the desired pyrrolidine adduct in the highest yield and selectivity.[18b,c] Notably, in all productive cases examined, the cross-coupling product was obtained with excellent stereoselectivity (>95:5 dr), highlighting the stability of aminoketyl radicals by the $n_N \rightarrow$ SOMO conjugation[21] (vide infra).

Scheme 1. Cyclization of Five-Membered Cyclic Imides via Aminoketyl Radicals Using SmI_2−H_2O[a]



[a]Conditions: SmI_2 (3 equiv), THF, H_2O, 23 °C. [b]SmI_2 (8 equiv), THF, H_2O, 23 °C. See SI for full experimental details.

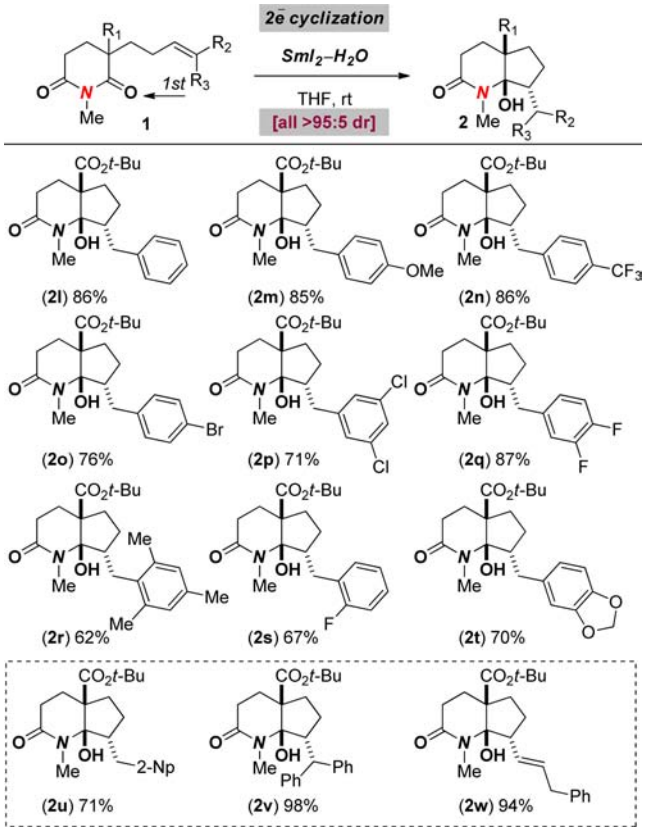
Importantly, reduction of the aminoketyl radical[16a] or over-reduction of the amide group[18a] was not observed under these conditions.

Having identified optimal conditions for the coupling of aminoketyl radicals, we next investigated the scope of the transformation. As revealed in Scheme 1, the reaction accommodates an array of functional groups. Electronically diverse functional groups (**2a**−**2c**) as well as functions sensitive to other electron transfer conditions,[8,15b] such as bromides (**2d**), esters, and amides, are readily tolerated, providing handles for further synthetic manipulations. Importantly, the mild SmI_2−H_2O system tolerates functional groups that are incompatible with Sm(II)-Lewis bases,[18a] such as electron-deficient arenes (**2e**) and polyarenes (**2f**). Moreover, the less activated terminal alkenes undergo the desired cross-coupling with good efficiency (**2g**−**2h**).[22] Furthermore, we were pleased to find that the directing group is not required for efficient coupling (**2i**−**2j**).[17a] The resulting 2-azabicyclic adducts bearing quaternary aryl moieties are versatile precursors to a wide range of biologically active natural products and pharmaceuticals.[11f] In all cases the reaction was fully stereoselective with respect to all three stereocenters.[22c] Moreover, the protocol can be applied to alkynes as radical acceptors (**2k**). Interestingly, anti addition of the aminoketyl radical gives the vinyl radical intermediate, which isomerizes under SmI_2−H_2O conditions.[23] We note that this process sets the stage for cascade reductive transformations on the imide template.[15f]

Next, we focused our attention on the coupling of six-membered precursors (Scheme 2). These substrates are particularly challenging because of the facile reduction of the aminoketyl radical to the anion.[19] Moreover, literature data indicate that ketyl-type radicals in six-membered rings are more than two orders of magnitude more reactive than in five-membered rings,[17a] increasing the potential for side reactions. We were pleased to find that a variety of six-membered

DOI: 10.1021/acs.orglett.5b02732
Org. Lett. 2015, 17, 5144−5147

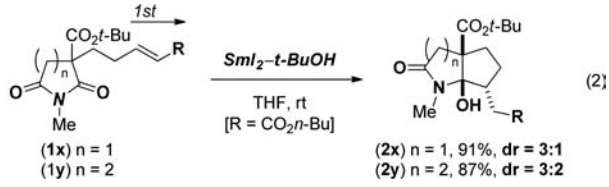
Scheme 2. Cyclization of Six-Membered Cyclic Imides via Aminoketyl Radicals Using SmI_2–H_2O[a]



[a]See Scheme 1. See SI for full experimental details.

precursors participate in the coupling. The reaction tolerates a broad range of functional groups, including bromides (**2o**), chlorides (**2p**), fluorides (**2q**), ethers (**2m**), trifluoromethyl groups (**2n**), heterocycles (**2t**), and electron-deficient arenes (**2p**).[15b] Steric hindrance is not a significant factor in these reactions (**2r**).[16b] Ortho-coordinating groups on the arene (**2s**) have no effect on the product selectivity.[24] Cleavage of the methylene bridge in 1,3-benzodioxole (**2t**) was not observed, attesting to the mild conditions of the coupling.[18] Sterically demanding disubstituted olefin acceptors can be employed without loss in overall yield and stereoselectivity (**2v**).[17e] Moreover, dienyl precursors can be readily employed to give vinyl-substituted 2-azabicycles after radical isomerization (**2w**).

To expand the scope of the synthesis of 2-azabicycles, substrates containing activated π-acceptors have been examined, resulting in efficient coupling (eq 2). Interestingly, the



products were formed as mixtures of diastereoisomers as a result of the "olefin-first" coupling mechanism (cf. "carbonyl-first").[25] The latter mechanism gives the stabilized aminoketyl radical, which permits the acceptor tether to adopt the lowest energy conformation.[21] Undoubtedly, the high stereoselectivity of the reactions involving aminoketyl radicals is a valuable advantage of this coupling manifold.

We conducted several experiments to gain insight into the reaction mechanism (see SI). (1) The reductive cyclization of imides **1a**, **1m**, and **1h** with SmI_2/D_2O (**1a**: >98% D^1; k_H/k_D = 1.49 ± 0.1; **1m**: >98% D^1; k_H/k_D = 1.54 ± 0.1; **1h**: >98% D^1; k_H/k_D = 1.10 ± 0.1) suggests that proton transfer is not involved in the rate-determining step of the reaction, irrespective of the ring size, directing group, and the π-system. (2) The reaction of **1a** with D_2O (1:1 dr at the benzylic position) demonstrates that the alkylsamarium(III) intermediate is not coordinated to the ring oxygen.[17e] (3) Intermolecular competition experiments reveal that six-membered precursors are inherently more reactive, consistent with the anomeric stabilization of the aminoketyl radical intermediate.[17d] (4) Fully chemoselective cyclization of substrates bearing a directing group is observed, consistent with coordination of Sm(II).[17a] (5) Hammett study with 4-substituted arylalkene radical acceptors showed a large positive ρ-value of 0.89, R^2 = 0.99, consistent with the addition of a nucleophilic aminoketyl radical onto the alkene. (6) The rate of cyclization of **1g** with a fixed amount of water[26] is consistent with a stabilizing effect of water on the cyclization.[27] Notably, full chemoselectivity over the reduction of a model lactone, 5-decanolide,[17a,27] is observed, suggesting that myriad reductive transformations of aminoketyl radicals should be readily accomplished.[15] Importantly, the SmI_2–H_2O system can be used at varying concentrations of water to fine-tune the lanthanide(II) reductant, which is not possible with ester-derived radicals, which require a large concentration of water to promote the reduction.

In conclusion, we have developed a general and versatile method for the stereoselective synthesis of complex 2-azabicycles, which relies on the efficient utilization of aminoketyl radicals generated via a direct electron transfer to five- and six-membered cyclic imides using SmI_2–H_2O. Mechanistic data are consistent with the addition of an aminoketyl radical to alkenes as the rate-determining step. Most importantly, these studies advance the electron transfer platform of ketyl radicals to aminoketyl radicals to afford versatile motifs functionalized at the C atom adjacent to nitrogen via an umpolung R–C$^{\bullet}$(O$^-$)NR′R′ synthon. Further investigations into related processes of aminoketyl radicals are underway in our laboratory, and these results will be reported shortly.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02732.

Experimental procedures and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

DOI: 10.1021/acs.orglett.5b02732
Org. Lett. 2015, 17, 5144–5147

■ ACKNOWLEDGMENTS

Financial support was provided by Rutgers University. The Bruker 500 MHz spectrometer used in this study was supported by the NSF-MRI grant (CHE-1229030).

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DOI: 10.1021/acs.orglett.5b02732
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