Synthesis S. Shi et al. Special Topic

Cyclization of Imides to 2-Azabicycles via Aminoketyl Radicals by Using Samarium(II) Iodide–Water: Reaction Development, Synthetic Scope, and Mechanistic Studies

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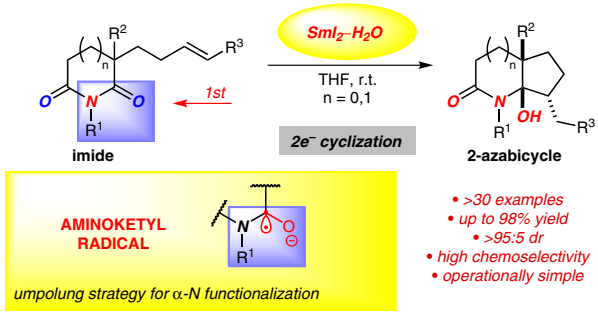
Dedicated to Professor Henri Kagan



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Abstract The first highly selective method for direct addition of aminoketyl radicals [R–C•(O⁻)NR¹R²], generated from five- or six-membered cyclic imides, to nonactivated π-systems by using the SmI_2–H_2O reagent is reported. The transformation is operationally simple, scalable, and provides access to valuable angular 2-azabicycles containing three contiguous stereocenters with excellent diastereoselectivity (>95:5 dr). The protocol accommodates a wide range of π-acceptors that can be modulated by the alcohol additive used. Notably, the transformation provides the first general method for generation of aminoketyl radicals by a direct electron capture to amide bonds, thus opening new vistas for applications of these underutilized intermediates in a diverse array of open-shell reaction pathways. Systematic studies on the effects of additives, the scope and limitations of the reaction, and the reaction mechanism are reported.

Key words azabicycles, samarium diiodide, reductive coupling, aminoketyl radicals, stereoselectivity, cyclizations, umpolung

1 Introduction

Since the introduction of samarium(II) iodide (samarium diiodide, SmI_2) into organic synthesis in 1980 by Kagan,[1] this reagent has become a central electron-transfer reagent for promoting challenging radical transformations.[2,3] The broad range of applications of SmI_2 within the field of organic synthesis results from its exquisite chemoselectivity,[4] which permits access to high-energy open-shell intermediates in the presence of easily reducible functional groups.[5] This is achieved through (i) the use of suitable metal, protic, or Lewis basic additives,[6] (ii) the well-established reversibility of electron-transfer events in reactions mediated by SmI_2,[7] and (iii) the high Lewis acidity of samarium salts in the 2 or 3 oxidation states.[8] Altogether, these effects permit challenging electron transfer events by inner-sphere pathways, and often lead to highly preorganized transition states,[9] affording addition products with exclusive selectivity that cannot be achieved with other reagents.[1–5] Over the last decade, significant advances have been made in the development and application of new SmI_2 reagent systems.[10–12] Extensive mechanistic studies have been reported that permit to rationalize the outcomes of SmI_2-cyclization events and allow the rational design of new donor and acceptor components for SmI_2-mediated reaction pathways.[13] However, whereas SmI_2 reagents are routinely applied for manipulation of oxygen-containing carbonyl electrophiles (Figure 1A), including challenging cyclic esters, as elegantly demonstrated by Procter and co-workers,[14] nitrogen-containing acceptors have received much less attention.[2,3]

This is likely due to two factors: (i) the high activation energy required for a direct electron transfer to nitrogen-containing carbonyl groups,[15] and (ii) the high Lewis basicity of these functional groups, which results in preferential coordination to Sm(II) and displacement of the ligands required for efficient electron-transfer and/or cyclization steps.[16]

To address the challenge of using nitrogen-containing acceptors in SmI_2-mediated cyclization pathways, in 2015 we introduced a new concept for the generation of aminoketyl radicals by a direct electron capture to the amide bond (Figures 1B–1D).[17] This concept is founded on our (M.S.) long-standing interest in the chemicophysical properties of amides,[18] the activation of amide bonds toward unconventional reactivity by low-valent metals,[19] and radical reactions.[20]

We are convinced that reductive cyclizations of aminoketyl radicals by SmI_2 will become a major field of research because: (i) the transformation provides the first general method to directly access underutilized aminoketyl radicals with wide-ranging applications in organic synthesis by ex-

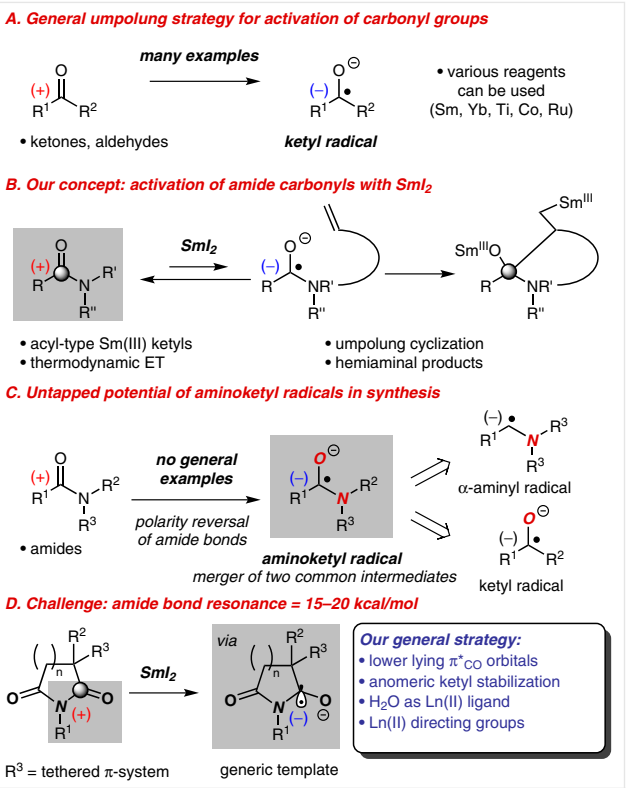


Figure 1 General strategies for polarity reversal of carbonyl groups

ploiting open-shell pathways from simple, stable, and abundant precursors;[21] (ii) the target cyclization products are abundant in a wide range of alkaloids, medicines, ligands, and functional materials (Figure 2);[22] (iii) this reactivity platform significantly expands the scope and utility of the venerable Kagan's reagent to the synthesis of nitrogen-containing motifs.[1–3]

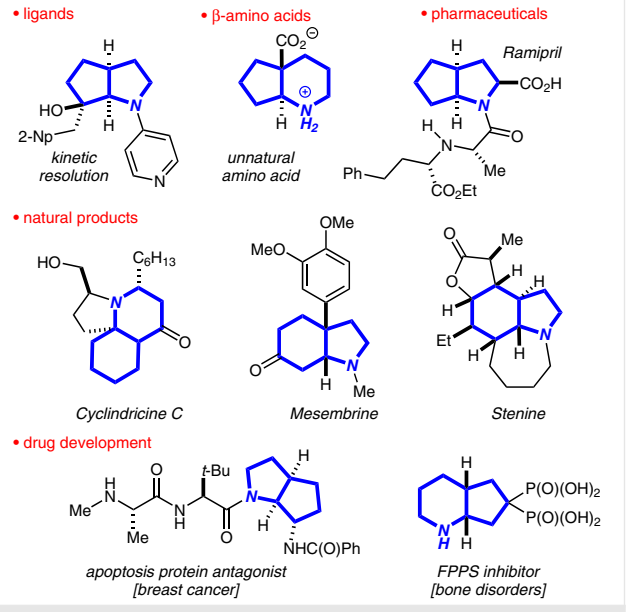


Figure 2 The prevalence of 2-azabicyclic motifs in biologically active molecules

Here, we provide a full account of SmI_2–H_2O-enabled stereoselective cyclizations of five- and six-membered imides to form angularly substituted 2-azabicycles via aminoketyl radicals. Detailed studies on the discovery, optimization, synthetic scope, and limitations of the reaction as well as systematic mechanistic studies pertaining to the electronic character of aminoketyl radicals are presented, together with a detailed description of the structural characterization of the unusual hemiaminal products resulting from both classes of cyclization. Most importantly, a generic strategy is presented for the generation of aminoketyl radicals, and the potential benefits of this amide-bond-activation platform via radical manifolds are outlined.

2 Reaction Development

Following our long-standing research interests (M.S.) in amide bonds and radical reactions,[18–20] in September 2014, we launched a research program based on the activation of amides via radical manifolds. On the basis of preliminary theoretical studies, we hypothesized that bench-stable amides might be employed as precursors for the generation of aminoketyl radicals by a direct electron capture to the amide bond.[23] Initially, we focused on Sm(II)-based reagents because of their high reducing potential[24] and the major benefits of SmI_2 in mediating stereoselective cyclizations with downstream utility in syntheses of pharmaceuticals[25] and complex natural products.[26]

Importantly, we recognized that, if successful, this strategy would provide the first general access to aminoketyl radicals: radical intermediates that have been severely underutilized in organic synthesis due to the lack of methods for their generation.[27] Aminoketyl radicals have been invoked in the degradation of nucleobases and they have been proposed as critical species in electron-capture dissociation of peptides.[21] However, to the best of our knowledge, the use of aminoketyl radicals in organic synthesis is virtually unknown due to the difficulty of direct electron transfer to the antibonding amide π* orbital (Figure 1B).[23] The use of carbon-centered aminoketyl radicals presents a significant challenge due to the ease of fragmentation of the N–C_α bond to form a new carbon-centered radical and an enolimine intermediate, which is facilitated by the high charge density at the carbon atom.[28] Aminoketyl radicals constitute a formal merger of highly nucleophilic and predominantly planar ketyl radicals[29] with highly stabilized and partially pyramidalized α-amino radicals.[30] This offers a unique reactivity platform, permitting the application of these unconventional intermediates in the field of radical chemistry (Figure 1C). However, in contrast to the broad utility of ketyl[1–5] and α-aminyl[31] radicals in the functional-

ization of α-C–O and α-C–N bonds, respectively, the development of practical and general methods for the addition of aminoketyl radicals to nonactivated π-acceptors in a stereoselective manner had received much less attention.[32]

Recently, the use of lanthanide(II) reagents, such as SmI_2,[10,14] $SmBr_2$,[5c] TmI_2,[20d] $SmI_2/Et_3N/H_2O$,[11] and SmI_2/HMPA[12] has promoted useful synthetic transformations under electron-transfer conditions, resulting in a wide range of reductive protocols.[10–14] Despite these significant advances, however, prior to our work the use of nonstabilized electrophilic precursors in addition reactions to nonactivated π-acceptors via aminoketyl radicals using lanthanides(II) remained unknown.[2,3]

Given the exceptional inertness of nonactivated amide bonds toward direct electron transfer (the amide bond resonance energy of 15–20 kcal/mol),[23] we considered that the use of amide precursors with lower-lying π^*_{CO} orbitals[18a] might offer a new retrosynthetic approach to the synthesis of C–C bonds adjacent to nitrogen atoms in a distinct reactivity platform with aminoketyl radicals as the key feature. However, this proposed pathway presents three challenges: (i) the generation of the aminoketyl radical must be accommodated under mild reductive conditions that preserve a long half-life for the aminoketyl radical anion, despite the high redox potential of nonactivated amide precursors and the proclivity of amides to undergo an irreversible second electron transfer;[33] (ii) the fragmentation of the N–C_α bond must be minimized;[28h] (iii) self-condensation of the aminoketyl radical must be prevented.[32a] Therefore, although at the outset it was not clear whether such a reaction would be feasible, we hypothesized that finding an appropriate ligand for Sm(II)[6a–c] and appropriate amide precursors[18a,d] would be nontrivial. Since in our initial screening experiments of approximately 15 amide derivatives, cyclic imides emerged as the most promising precursors, affording aminoketyl radicals with sufficiently long half-lives to permit their reductive cyclizations, consequently, we focused our attention on these precursors.

Our strategy for achieving a modular, broadly useful, generation of aminoketyl radicals to access generic azabicyclic motifs hinged on four major features (Figure 1D): (i) the presence of a low-energy antibonding π*orbital in the imide template,[34a] with $n_N \rightarrow \pi^*_{CO}$ delocalization into the remaining carbonyl in a conformationally locked system to prevent N–C_α fragmentation;[34b] (ii) pseudoanomeric stabilization of the aminoketyl radical anion intermediate to facilitate the initial electron-transfer step;[14a,35] (iii) directing group-controlled activation of the functional group towards electron transfer[36] and stabilization of the resulting aminoketyl intermediate by chelation to prevent irreversible reduction by coordination of the oxophilic lanthanide(II) reagent[8] to the carbonyl group, thereby lowering the redox potential of the precursor; and (iv) the use of protic ligands[6a] to activate the lanthanide(II) reagent and favor electron transfer under thermodynamic conditions.[7]

Importantly, we recognized that if this strategy is successful, the generic imide scaffold could be used as a platform to access a wide range of 2-azabicycles through post-cyclization functionalizations (Figure 2).[37] The 2-azabicyclic motif appears in many bioactive natural products and pharmaceuticals, and it has been shown to impart novel properties in ligands and small-molecule catalysts. 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, and few methods for its stereoselective construction have been reported.[22]

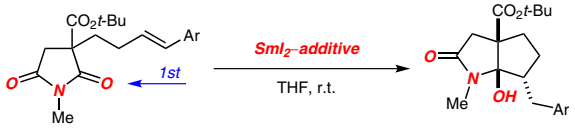
We started our investigation by evaluating electron transfer to a challenging five-membered imide bearing an nonactivated alkene tether and an ester directing group with SmI_2 as a promoter in the presence of various alcohols as ligands (Table 1).[38] The five-membered imide scaffold was selected for the initial studies because aminoketyl radicals generated from six-membered precursors are more easily reduced to anions, as determined in scouting experiments. According to reported precedents, five-membered cyclic substrates are less reactive towards Sm(II) due to less-efficient pseudoanomeric stabilization of the radical anion.[14a,38]

Whereas treatment of solutions of the five-membered imide in THF with SmI_2 alone was not sufficient to promote the generation of the aminoketyl radical required for the addition (Table 1, entry 1), we were delighted to find that 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, or $HO(CH_2)_2OH$; entries 2–5).[6a,b] The use of H_2O as a ligand provided the desired pyrrolidine adduct in the highest yield and selectivity (entry 5).[39] Interestingly, noncoordinating alcohols, such as *t*-BuOH (entry 6), also furnished the 2-azabicyclic product, albeit in lower yields and with lower selectivity. Evaluation of other Sm(II) systems revealed that thermodynamically more powerful reductants based on H_2O/Et_3N (entries 7 and 8), LiCl (entry 9), or HMPA (entries 10 and 11)[2,3,6] as ligands provided inferior results due to the decreased stability of the aminoketyl radical under these conditions. Note that in all the productive cases examined, the cross-coupling product was obtained with excellent stereoselectivity (>95:5 dr), highlighting the nucleophilicity of the aminoketyl radicals by the $n_N \rightarrow$ SOMO conjugation (see below).[27]

Importantly, the developed process operates at room temperature under user-friendly conditions, and with reaction times that are much shorter than that of the natural decay of Sm(II)–H_2O.[39g]

It is particularly noteworthy that direct reduction of the aminoketyl radical (to the anion) or overreduction of the adjacent amide group (to the amine or amino alcohol) was not observed under the optimized conditions.[40] The optimization results demonstrated, for the first time, that gen-

Table 1 Development of the Reductive Cyclization of Imides with SmI_2[a]



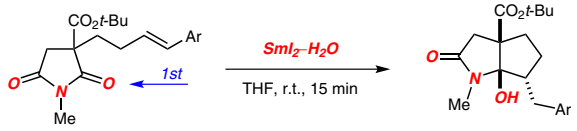
Entry	SmI_2 (Equiv)	Additive	Additive (Equiv)	Time[b]	Yield[c] (%)	Selectivity[c,d]
1	3	–	–	2 h	<5	–
2	3	MeOH	4/1 (v/v)	2 h	87	>95:5
3	3	EG[e]	18	2 h	88	93:7
4	3	H_2O	25	2 h	68	70:30
5	3	H_2O	600	15 min	94	>95:5
6	3	*t*-BuOH	24	2 h	78	>95:5
7	3	Et_3N/H_2O	12/18	5 min	40	74:26
8	3	Et_3N/MeOH	12/18	1 h	59	87:13
9	3	LiCl	36	2 h	78	88:12
10	3	HMPA	12	2 h	<5	–
11	3	HMPA/*t*-BuOH	12/24	2 h	<5	–

[a] All reactions were carried out by using standard Schlenk techniques. SmI_2 was freshly prepared from Sm metal and $I(CH_2)_2I$. Ar = 4-$MeOC_6H_4$.
[b] Quenched with air after the indicated time.
[c] Determined by ^1H NMR.
[d] Cyclization/reduction selectivity.
[e] Ethylene glycol.

eration of aminoketyl radicals from cyclic nonactivated imides was feasible with Sm(II) reagents, and that the cross-coupling with nonactivated π-acceptors could be readily accomplished; this is in contrast to electrophilic olefins (Michael acceptors), which react by a 'olefin-first' mechanism (see below).[41] Importantly, the results demonstrated that five-membered cyclic imide precursors (compared with six-membered precursors) are viable substrates for generation of radicals by using SmI_2–H_2O, which opens new prospects for the development of radical cyclizations with the SmI_2–H_2O reagent system.[2,3,14] Note that prior to our report, only a single example (66% conversion) of a cyclization of a five-membered ester precursor using SmI_2–H_2O had been reported.[36a]

To gain further insight into the role of the water additive on the reactivity of the SmI_2–H_2O complex, we carried out several control experiments (Tables 2–5). In agreement with previous studies,[6a,7,39] the concentration of H_2O is critical for stability of the aminoketyl radical (Table 2), which is consistent with findings regarding an outer-sphere (as opposed to inner-sphere) electron-transfer mechanism of these Sm(II) systems. Whereas water as an additive is clearly required for the cyclization and insufficient conversions are observed at low concentrations of water (Table 1, entry 4; H_2O/SmI_2 = 3:25 (equiv)), the results shown in Table 2 demonstrate that the concentration of water with respect to SmI_2 is critical to prevent reduction of the aminoketyl radical to the anion (Table 2; entry 1, H_2O/SmI_2 = 200:6 (equiv); entry 2, H_2O/SmI_2 = 1200:6 (equiv)). It is well-known that at higher concentrations of water, Sm(II) reagents undergo spontaneous oxidation.[39h] Consequently, the use of lanthanide(II) reagents with low concentrations of protic additives is strongly preferred from the synthetic point of view.[7] Remarkably, it appears that in aminoketyl radical cyclizations, concentrations of H_2O of about 10 M are sufficient; this is an acceptable concentration of water to ensure high reactivity of the reagent system.

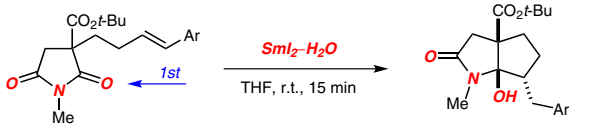
Table 2 Effect of H_2O Stoichiometry on the Reductive Cyclization of Five-Membered Imides by Using SmI_2[a]



Entry	SmI_2 (equiv)	H_2O (equiv)	Yield[b] (%)	Selectivity[b,c]
1	6	200	79	83:17
2	6	1200	90	>95:5
3	6	2400	89	>95:5

[a] All reactions were carried out by standard Schlenk techniques with SmI_2 freshly prepared from Sm metal and $I(CH_2)_2I$. Ar = 4-$MeOC_6H_4$.
[b] Determined by ^1H NMR.
[c] Cyclization/reduction selectivity.

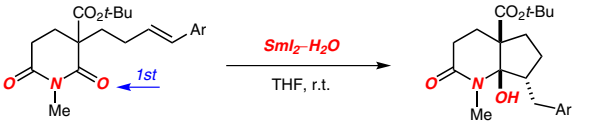
Table 3 Effect of SmI_2 Stoichiometry on the Reductive Cyclization of Five-Membered Imides using SmI_2[a]



Entry	SmI_2 (equiv)	H_2O (equiv)	Yield[b] (%)	Selectivity[b,c]
1	1	200	53	>95:5
2	2	400	83	>95:5
3	3	600	94	>95:5
4	4	800	88	>95:5

[a] All reactions were carried out by standard Schlenk techniques with SmI_2 freshly prepared from Sm metal and $I(CH_2)_2I$. Ar = 4-$MeOC_6H_4$.
[b] Determined by ^1H NMR.
[c] Cyclization/reduction selectivity.

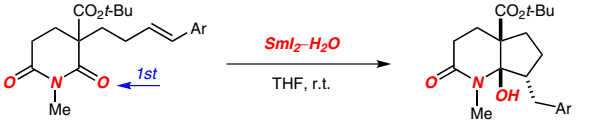
Table 4 Effect of Reaction Conditions on the Reductive Cyclization of Six-Membered Imides by Samarium(II) Iodide[a]



Entry	SmI_2 (equiv)	H_2O (equiv)	Time[b] (min)	Yield[c] (%)	Selectivity[c,d]
1	6	200	5	83	>95:5
2	3	600	1	82	>95:5
3	4	800	1	70	>95:5
4	6	1200	1	70	>95:5
5	6	4800	1	82	>95:5

[a] All reactions were carried out by standard Schlenk techniques with SmI_2 freshly prepared from Sm metal and $I(CH_2)_2I$. Ar = 4-$MeOC_6H_4$.
[b] Quenched with air after the indicated time.
[c] Determined by ^1H NMR.
[d] Cyclization/reduction selectivity.

Table 5 Effect of the Reaction Time on the Reductive Cyclization of Six-Membered Imides by Samarium(II) Iodide[a]



Entry	Time[b]	Yield[c] (%)	Selectivity[c,d]
1	30 s	67	>95:5
2	1 min	70	>95:5
3	5 min	45	>95:5

[a] Reaction conditions: SmI_2 (6 equiv), H_2O (1200 equiv). All reactions were carried out by using standard Schlenk techniques with SmI_2 freshly prepared from Sm metal and $I(CH_2)_I$. Ar = 4-$MeOC_6H_4$.
[b] Quenched with air after the indicated time.
[c] Determined by ^1H NMR.
[d] Cyclization/reduction selectivity.

Furthermore, optimization of the reagent stoichiometry indicated that 2.0 equivalents of the reagent are sufficient for efficient cross-coupling (Table 3, entries 1–4). This compares favorably with previously reported cross-couplings mediated by SmI_2–H_2O with cyclic esters as substrates,[14,36a] and is likely a result of the high nucleophilicity of aminoketyl radicals compared with that of radicals derived from esters (see Section 4).[27] The approximately 50% conversion observed with 1.0 equivalent of the reagent is consistent with a two-electron reductive cyclization process (entry 1). At higher concentrations of the reagent, efficiency of the reaction drops as a result of sensitivity of hemiaminal products and/or aminoketyl radicals to the strong reductant (entry 4).

The results of selected optimization studies on the reductive cyclization of a model six-membered imide are given in Tables 4 and 5. Importantly, the effect of the concentration of H_2O (SmI_2/H_2O) on the stability of aminoketyl radicals derived from six-membered precursors was found to be consistent with the relative reactivity of six-membered rings compared with five-membered rings as determined by previous studies (Table 4).[36a] No reaction was observed in the absence of the water as an additive, which is consistent with the critical role of water in activating Sm(II) toward electron transfer.[6a]

In the six-membered system, the reduction of aminoketyl radicals to anions in a cyclic transition state is particularly facile, as elegantly demonstrated by Procter.[14a] The optimum results for cyclization of six-membered imides were obtained by using 200 equivalents of H_2O with respect to SmI_2 with short reaction times to maintain product integrity under the reductive conditions (Table 5). It is possible that the Lewis acidic nature of Sm(II) and Sm(III) salts[8] also plays an important role in the stability of the resulting aminoketyl radicals (see below).

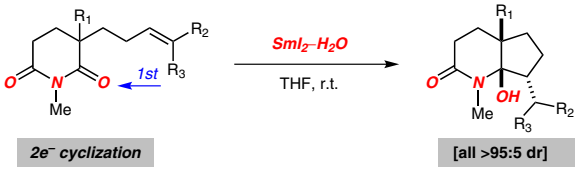
Overall, the results presented in Tables 1–5 demonstrate, for the first time, that cyclizations of nonactivated cyclic imides via aminoketyl radicals proceed under mild and operationally simple conditions to establish three contiguous stereocenters with exquisite stereoselectivity in a 2-azabicyclic ring system. Importantly, both classes of imides, namely those with five- and six-membered rings, can be used as radical cyclization precursors. The use of SmI_2–H_2O reagent is critical for the observed reactivity.

3 Reductive Cyclizations

Having identified the optimal conditions for cross-coupling of cyclic imides with nonactivated π-acceptors via aminoketyl radicals, we next examined the scope of this new cyclization strategy. We also examined the effect of a reverse-addition mode (i.e., olefin first)[41] for comparison purposes, as we had expected that additional substitution of the 2-azabicyclic products would be feasible through nu-

cleophilic addition. The scope of the reaction is discussed in three sections below: Section 3.1: Cyclizations of Five-Membered Imides; Section 3.2: Cyclizations of Six-Membered Imides; and Section 3.2: Cyclizations through Nucleophilic Additions.

Table 6 Stereoselective Cyclizations of Five-Membered Imides to 2-Azabicycles via Aminoketyl Radicals by Using SmI_2–H_2O[a]



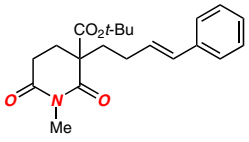
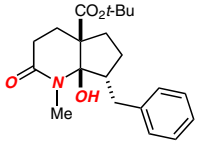
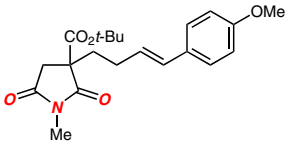
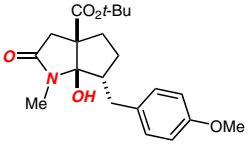
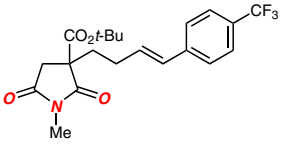
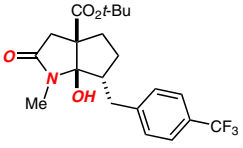
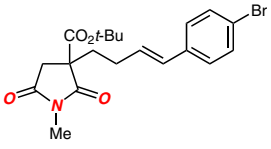
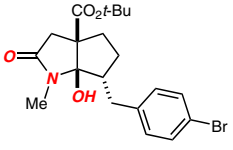
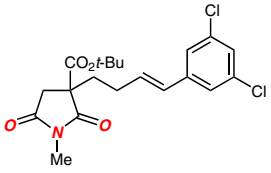
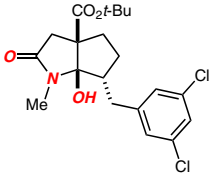
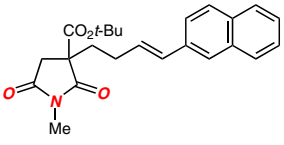
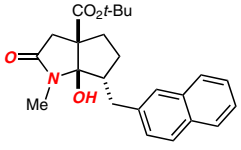
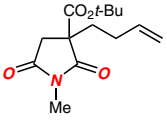
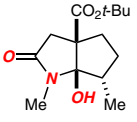
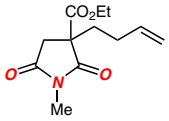
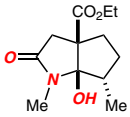
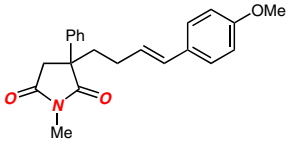
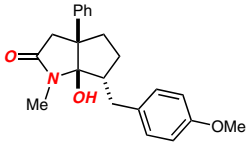
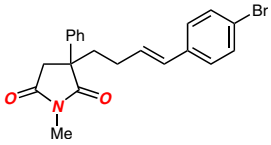
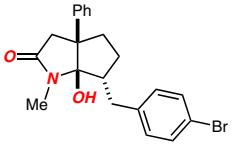
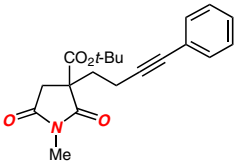
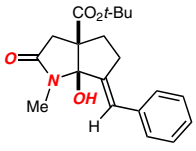
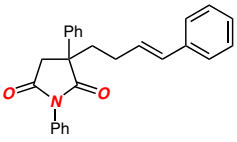
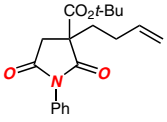
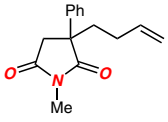
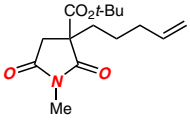
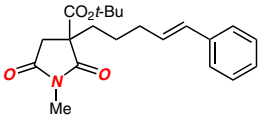
Entry	Imide		Product		Yield (%)	Selectivity[b]
1		**1**		**2**	94	>95:5
2		**3**		**4**	93	>95:5
3		**5**		**6**	93	>95:5
4		**7**		**8**	75	>95:5
5		**9**		**10**	90	>95:5
6		**11**		**12**	93	>95:5
7[c]		**13**		**14**	77	>95:5

Table 6 (continued)

Entry	Imide		Product		Yield (%)	Selectivity[b]
8[c]		**15**		**16**	55	92:8
9[c]		**17**		**18**	92	91:9
10[c]		**19**		**20**	89	>95:5
11		**21**		**22**	65	75:25
12		**23**	–	**24**	<5	–
13		**25**	–	**26**	<5	–
14		**27**	–	**28**	<5	–
15		**29**	–	**30**	<5	–
16		**31**	–	**32**	<5	–

[a] Reaction conditions: SmI_2 (3 equiv), THF, H_2O (600 equiv), 23 °C. All reactions were carried out by using standard Schlenk techniques with SmI_2 freshly prepared from Sm metal and $I(CH_2)_2I$

[b] Cyclization/reduction selectivity.

[c] SmI_2 (8 equiv), H_2O (1200 equiv).

3.1 Cyclizations of Five-Membered Imides

As shown in Table 6, the cyclization of five-membered imides accommodates a broad range of π-acceptors (olefins, alkynes, terminal olefins) and tolerates numerous sensitive functional groups (halides, heterocycles, electron-deficient arenes). Specifically, electronically-diverse functional groups (Table 6, entries 1–3) as well as functions sensitive to electron-transfer conditions, such as bromides or polyhalides (entries 4 and 5) are readily tolerated, providing handles for further synthetic manipulation. Importantly, the mild SmI_2–H_2O system tolerates functional groups that are incompatible with Sm(II)–Lewis base reagents,[10–14] including benzylic ethers (entry 2), benzylic trifluoromethyl groups (entry 3), electron-deficient arenes (entry 5), and naphthalenes (entry 6). Moreover, terminal alkenes undergo the desired cross-coupling with good efficiency (entry 7). Other directing groups can be used in the reaction (entry 8). Furthermore, the directing group is not required for cross-coupling (entries 9 and 10).[36a] The resulting 2-azabicyclic adducts with quaternary aryl motifs are versatile precursors to a wide range of biologically active natural products and pharmaceuticals.[37f] Moreover, the protocol permits the use of alkynes as a radical acceptor, which results in efficient radical cyclization to give an allylic alcohol (entry 11). Interestingly, *anti*-addition of the aminoketyl radical gives the vinyl radical intermediate, which isomerizes under SmI_2–H_2O conditions.[42] Note that this process sets the stage for cascade reductive transformations on the imide template.[3f]

Note that no reduction of the ester or cyclic amide moiety was observed under the developed reaction conditions.[10–14] Moreover, the SmI_2–H_2O reagent system can differentiate between two imide carbonyl groups,[3b] resulting in chemoselective desymmetrization; this illustrates the high chemoselectivity of cyclizations mediated by lanthanide(II) reagents. The ester and amide functional groups provide valuable functional handles for product manipulation.

Particularly noteworthy is the high stereoselectivity of our protocol.[27c] In all cases, the reaction was fully stereoselective with respect to the three newly formed stereocenters (>95:5 dr) as determined by analysis of the crude reaction mixtures. Moreover, with the exception of three examples discussed below (entries 7, 8, and 11), no reduction of the aminoketyl radical to an anion was observed, attesting to its long half-life under the reaction conditions.[43] It is a well-known fact in Sm(II) chemistry that terminal alkenes are less reactive.[14b] Based on the reduction selectivity, the rate of reaction in the cyclization of aminoketyl radicals on the five-membered imide template is in the following order: substituted alkenes > terminal alkenes > alkynes. Moreover, the presence of a directing group results in faster cyclization,[36a] consistent with stabilization of the aminoketyl radical by chelation and the original hypothesis (see above).

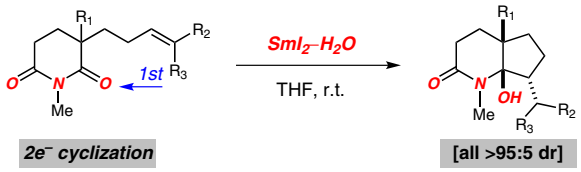
Limitations. Several limitations in the reductive cyclizations of five-membered cyclic imides can be noted at present (Table 6, entries 12–16). First, the reaction is not compatible with electron-withdrawing substituents at nitrogen (entries 12 and 13). The reduction of aminoketyl radical appears to predominate in these cases, consistent with the requirement to fine-tune the redox properties of the reagent system to electronics of the acceptor.[33] Secondly, a directing group is required for the efficient cyclization of terminal alkenes (entry 14), consistent with the design hypothesis and previous studies.[36a] Thirdly and unsurprisingly, 6-exo cyclizations are not feasible at this stage of the reaction development (entries 15 and 16). Currently, there are no examples of 6-exo cyclizations mediated by protic Sm(II) systems, due to the slow rate of such cyclizations.[44] However, new lanthanide(II) reagents, such as Tm(II),[20d] have already shown significant promise in mediating cyclizations of challenging substrates due to a smaller radial size in the 2 oxidation state.[5c]

3.2 Cyclizations of Six-Membered Imides

Next, we evaluated the substrate scope for the cross-coupling of six-membered imides with nonactivated π-systems (Table 7). The cyclization of six-membered ring substrates is particularly challenging because of the ease with which the aminoketyl radical is reduced to an anion in the six-membered transition state.[14a,36a] A report in the literature indicates that ketyl-type radicals in six-membered rings are more than two orders of magnitude more reactive than those in five-membered rings.[36a] Moreover, the well-defined conformation of six-membered rings increases the potential for Lewis acid-promoted side reactions of hemiaminal products.[38] Nevertheless, we were pleased to find that a variety of six-membered precursors participate in the cross-coupling; these precursors include compounds with a range of sensitive functional groups poised for further functionalization. Investigation of the electronic effect revealed that electron-neutral, electron-donating, and electron-withdrawing groups on the radical acceptor afford the corresponding cross-coupling product in uniformly high yields (Table 7, entries 1–3). The reaction tolerates a broad range of functional groups that are incompatible with other Sm(II) systems,[10–14] including bromides (entry 4), polychlorides (entry 5), and polyfluorides (entry 6). As revealed by the cross-coupling of the mesityl acceptor, steric hindrance is well-tolerated in these reactions (entry 7). Note, however, that the cyclization is much slower in this case, as expected. *ortho*-Coordinating groups, such as fluoride, on the arene had no effect of the reaction selectivity (entry 8).[45] Cleavage of the methylene bridge in the medicinally relevant 1,3-benzodioxole was not observed (entry 9). Notably, a substrate bearing the sensitive naphthyl substituent was toler-

ated under our reaction conditions (entry 10). Sterically demanding disubstituted olefin acceptors can be employed without loss in overall yield or stereoselectivity (entry 11). Moreover, a dienyl precursor can be readily employed to give a vinyl-substituted 2-azabicycle after radical isomerization (entry 12).[46]

Table 7 Stereoselective Cyclizations of Six-Membered Imides to 2-Azabicycles via Aminoketyl Radicals by using SmI_2–H_2O[a]



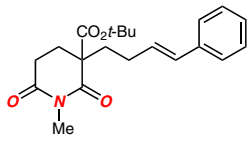
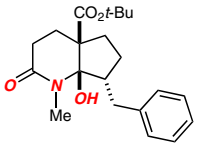
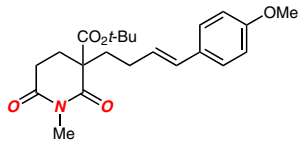
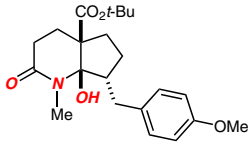
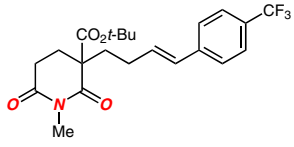
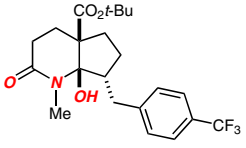
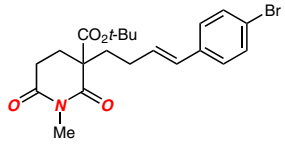
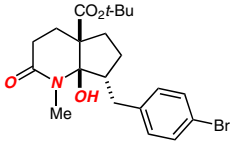
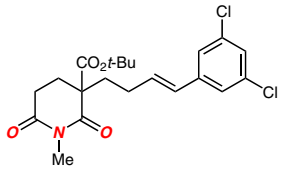
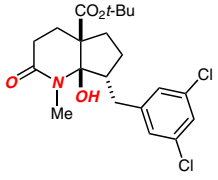
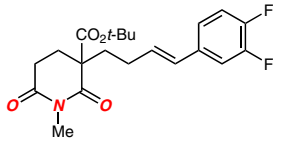
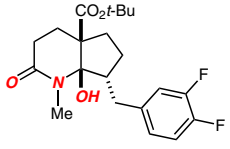
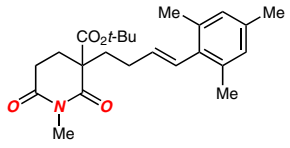
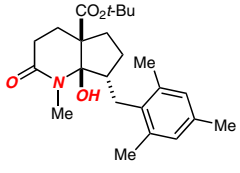
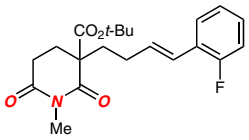
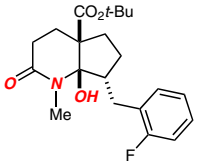
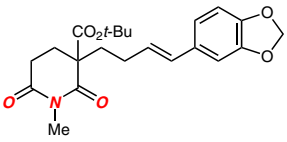
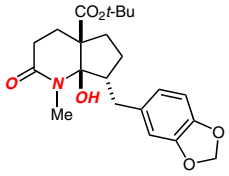
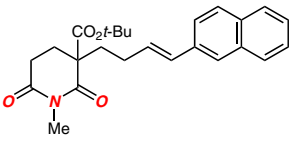
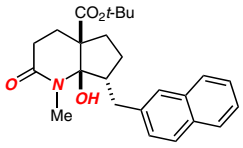
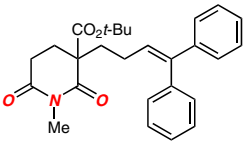
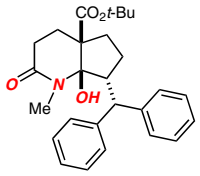
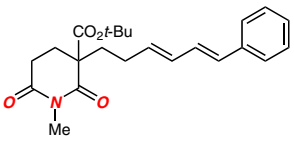
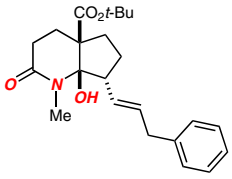
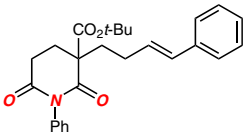
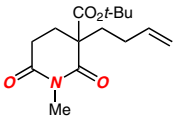
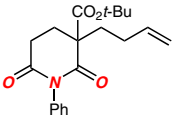
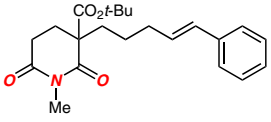
Entry	Imide		Product		Yield (%)	Selectivity[b]
1		**33**		**34**	86	>95:5
2		**35**		**36**	85	>95:5
3		**37**		**38**	86	>95:5
4		**39**		**40**	76	>95:5
5		**41**		**42**	71	>95:5
6		**43**		**44**	87	>95:5
7		**45**		**46**	62	78:22

Table 7 (continued)

Entry	Imide		Product		Yield (%)	Selectivity[b]
8		**47**		**48**	67	>95:5
9		**49**		**50**	70	>95:5
10		**51**		**52**	71	>95:5
11		**53**		**54**	98	>95:5
12		**55**		**56**	94	>95:5
13		**57**	–	**58**	<5	–
14		**59**	–	**60**	<5	–
15		**61**	–	**62**	<5	–
16		**63**	–	**64**	<5	–

[a] Reaction conditions: SmI_2 (3 equiv), THF, H_2O (600 equiv), 23 °C. All reactions were carried out by using standard Schlenk techniques with SmI_2 freshly prepared from Sm metal and $I(CH_2)_2I$.
[b] Cyclization/reduction selectivity.

Importantly, in the cyclization of six-membered imides, exquisite cyclization stereoselectivity was observed in all cases (>95:5 dr). With the exception of one sterically hindered example discussed above (entry 8), reduction products were not observed under the developed reaction conditions. Tolerance toward numerous functional groups sensitive to other Sm(II) reagents attests to the mild conditions of this radical addition[2,3] and bodes well for application of the 2-azabicyclic products in natural-product synthesis.[37]

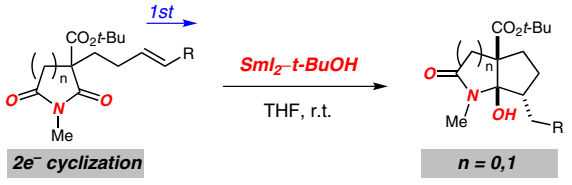
Limitations. Several limitations of our protocol in the reductive cyclizations of six-membered cyclic imides can be noted at present (Table 7, entries 13–16). First, as already observed for the five-membered imide template, the reaction is not compatible with electron-withdrawing substituents at nitrogen due to facile aminoketyl reduction (entry 13).[36] Secondly, terminal alkenes are not compatible due to their slow cyclization rate (entries 14 and 15).[3a] Thirdly and unsurprisingly, tethers poised for 6-exo cyclization are unproductive, in agreement with literature precedents on the use of SmI_2–ROH for higher-order reductive cyclizations. In general, 6-exo ketyl/alkene cyclizations with SmI_2 are extremely challenging. Seminal work by Molander has highlighted the ease of reduction of ketyl radicals to anions in 6-*exo* ketyl cyclizations using SmI_2/HMPA.[44] A recent solution to this problem reported by Procter[14i] utilizes the thermodynamic ketone/ketal equilibrium to minimize the reactive concentration of the carbonyl group. Note that minor products in cyclizations of ketyl-type radicals arise from direct carbonyl reduction.[3b]

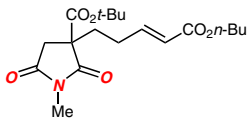
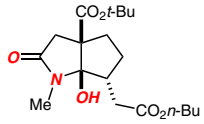
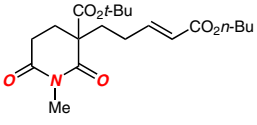
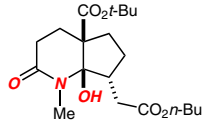
3.3 Cyclizations through Nucleophilic Additions

To further expand the scope of the synthesis of 2-azabicycles from nonactivated cyclic imides via radical intermediates, we considered the use of cyclic precursors containing electrophilic olefin tethers (Table 8).[47] Although it is likely that their reaction does not involve aminoketyl radicals, these substrates might provide 2-azabicycles featuring complementary substitution patterns poised for the synthesis of natural products, which is our target application for this strategy. Accordingly, we prepared substrates containing ester acceptors and we subjected these to the reaction conditions, affording 2-azabicycles in high yields. Interestingly, the products were formed as mixtures of diastereoisomers, suggesting a change in the reaction pathway (i.e., an olefin-first coupling mechanism as opposed to carbonyl-first).[41] We propose that the latter mechanism gives a stabilized aminoketyl radical, which permits the acceptor tether to adopt the lowest energy conformation before the cyclization can occur.[43] Beyond any doubt, the high stereoselectivity of the cross-coupling involving aminoketyl radicals is a valuable advantage of this coupling manifold.

Note that high levels of stereoselectivity have also been observed in ester/olefin cyclizations mediated by SmI_2–H_2O.[14b–d] Taken together, these results underscore the potential of SmI_2–H_2O for mediating highly stereoselective cyclizations unattainable by other methods.[2,3] Minor products in the cyclization of activated acceptors are known to arise from direct olefin reduction.[39c]

Table 8 Stereoselective Cyclizations of Five- and Six-Membered Imides to Give 2-Azabicycles through Nucleophilic Addition using SmI_2–*t*-BuOH[a]



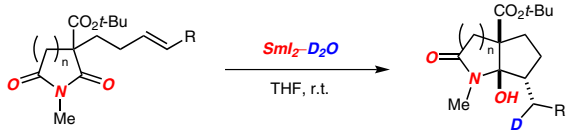
Entry	Imide		Product		Yield (%)	dr[b]
1		**65**		**66**	91	3:1
2		**67**		**68**	87	3:2

[a] Reaction Conditions: SmI_2 (3 equiv), THF, *t*-BuOH (600 equiv), 23 °C. All reactions were carried out using standard Schlenk techniques with SmI_2 freshly prepared from Sm metal and $I(CH_2)I$.
[b] Diastereoselectivity refers to the tertiary carbon stereocenter (two diastereoisomers).

4 Mechanistic Studies

Intrigued by the efficiency of the cyclization of aminoketyl radicals, we conducted several experiments to gain preliminary insight into the reaction mechanism. Specifically, studies were performed to gather evidence about the electronic properties of Sm(III) aminoketyl radicals and to elucidate the effect of water on the properties of the reagent system, which might set the stage for future applications of SmI_2–H_2O as a SET regent capable of generating aminoketyl radicals in organic synthesis.

The reductive cyclization of the five-membered imides **3** and **13** and of the six-membered imide **35** with SmI_2/D_2O under our standard conditions gave the reductive cyclization products with >98% incorporation of deuterium ([D_1]) (Scheme 1). These results are consistent with anions being generated and protonated by H_2O in a series of electron-transfer steps,[7] and with the formation of a well-defined Sm(II) complex.[39e]

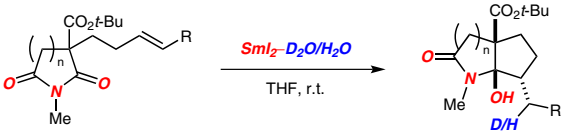


13, n = 1, R = H
3, n = 1, R = 4-MeOC$_6$H$_4$
35, n = 2, R = 4-MeOC$_6$H$_4$

14, 76%, >98% D_1
4, 84%, >98% D_1
36, 81%, >98% D_1

Scheme 1 Deuterium incorporation in the cyclization of imides to 2-azabicycles using SmI_2–D_2O

The kinetic isotope effect in the cyclization of imides **3**, **13**, and **35** (**3**: k_H/k_D = 1.49 ± 0.1; **13**: k_H/k_D = 1.10 ± 0.1; **35**: k_H/k_D = 1.54 ± 0.1) (Scheme 2) suggests that proton transfer is not involved in the rate-determining step of the reaction, irrespective of the ring size of the aminoketyl radical precursor, the directing group, or the electronic nature of the π-system.[48] The small observed kinetic isotope effect is likely a result of differential coordination of D_2O to Sm(II).[7,14b]



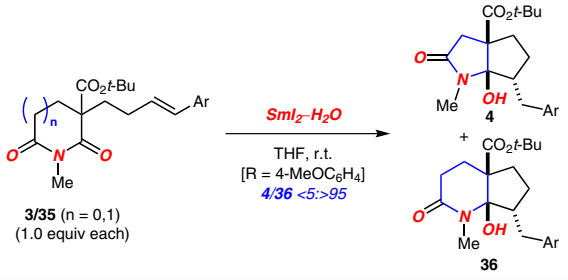
13, n = 1, R = H
3, n = 1, R = 4-MeOC$_6$H$_4$
35, n = 2, R = 4-MeOC$_6$H$_4$

14, 76%, k_H/k_D = 1.10 ± 0.1
4, 83%, k_H/k_D = 1.49 ± 0.1
36, 85%, k_H/k_D = 1.54 ± 0.1

Scheme 2 Kinetic isotope effect in the cyclization of imides to 2-azabicycles using SmI_2–D_2O

The reactions with SmI_2–D_2O of the five-membered imide **3** (1:1 dr at the benzylic position) and the six-membered imide **35** (1:1 dr) suggest that the benzylsamarium(III) intermediate resulting from the reductive cyclization is not coordinated to the ring heteroatoms in either the five- or the six-membered imide ring system.[14b]

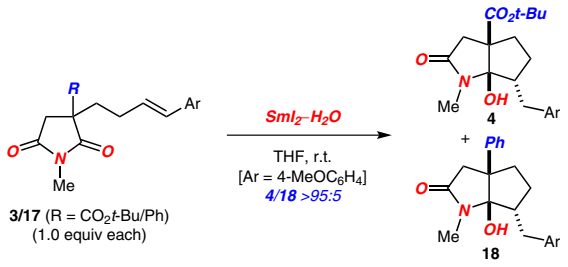
Selectivity studies on the reductive cyclization of five- and six-membered imides with SmI_2–H_2O showed that complete selectivity is obtained in the cyclization of six-membered cyclic precursors (Scheme 3).[49] This is consistent with anomeric stabilization of the radical anion in a six-membered transition state,[14] and further indicates that chemoselectivity levels that are unattainable through ionic mechanisms are possible with Sm(II)/H_2O reagents.[3b]



3/35 (n = 0,1)
(1.0 equiv each)

Scheme 3 Selectivity studies on the cyclization of imides to 2-azabicycles using SmI_2–H_2O

Selectivity studies on the cyclization of various α-substituted imides illustrate that substrates bearing α-directing group undergo fully chemoselective cyclization in the presence of substrates that cannot stabilize the aminoketyl radical intermediate by chelation (Scheme 4), which is consistent with the importance of coordination of Sm(III) in the transition state of the reaction.[36a] This selectivity trend is also supported by the facile reduction of the aminoketyl radical to an anion in the latter substrates. Note that by applying these principles, high levels of chemoselectivity can be achieved through careful fine-tuning of the reagent system (stoichiometry of the reagent/additive) and/or by altering the steric or electronic nature of substituents on the substrate.

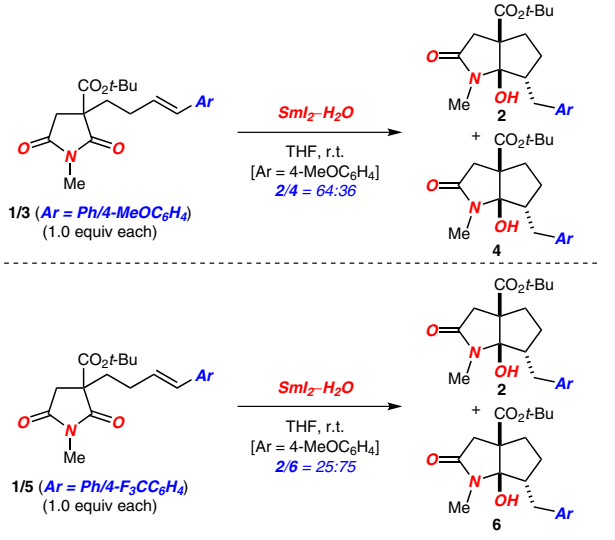


3/17 (R = CO$_2$*t*-Bu/Ph)
(1.0 equiv each)

Scheme 4 Selectivity studies in the cyclization of imides to 2-azabicycles with SmI_2–H_2O

Selectivity studies by using various substituted 4-arylalkene radical acceptors indicated a strong preference for the cyclization of electron-deficient π-acceptors (Scheme 5).[50] A large positive Hammett ρ-value of 0.89 (y = 0.895x –

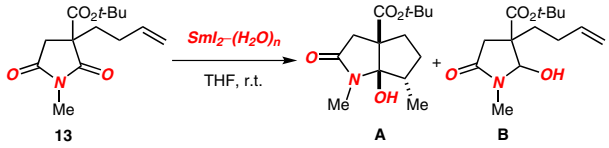
0.005; $R^2 = 0.999$) for the olefin acceptor upon radical cyclization was obtained, compared with a ρ-value of 4.0 for the reduction of benzylic alcohols by SmI_2–amine–H_2O (direct reduction of the aromatic acceptor with Sm(II); cf. cyclization);[11e] this is consistent with a partial buildup of negative charge in the transition state, as expected for the cyclization of a nucleophilic electron-rich aminoketyl radical onto the alkene.[29–31] Moreover, the reaction shows a high selectivity for the cyclization of the aryl moiety over the terminal alkene (**4**/**14** = 86:14, not shown). These selectivity studies are consistent with the cyclization rate being governed by the steric and electronic properties of the π-acceptor.



Scheme 5 Selectivity studies in the cyclization of imides to 2-azabicycles with SmI_2–H_2O

The cyclization of five-membered imide **13** with a fixed amount of water in the presence of a decreasing concentration of SmI_2 did not result in a significant increase in the cyclization/reduction ratio (Table 9), which is consistent with a bimolecular reaction and the stabilizing effect of water on the cyclization (see additional discussion below). The reductive cyclization of **13** was selected as a mechanistic probe to study the effect of the concentrations of SmI_2 and H_2O on the stability of aminoketyl radicals in the present system. The cyclization of **13**, which bears a nonactivated terminal olefin, resulted in a 91:9 cyclization/reduction ratio (**A**/**B**) under the optimized conditions. Cyclizations of other substrates reported in this manuscript are too selective to permit accurate measurement of changes in **A**/**B** on varying the concentration of SmI_2 and/or H_2O. The approximate reduction rates of aminoketyl radicals were calculated by using the rate constant for cyclization of the 5-hexenyl radical.[51] It has been amply demonstrated that the rate of radical anion radical clocks is similar to that of the corresponding neutral radicals.[52] The ratio of products (**A**/**B**) is governed by the bimolecular rate constant for reaction of the aminoketyl radical with SmI_2 (**B**) and by the rate constant for the reductive cyclization of the aminoketyl radical (unimolecular) or the reduction of the radical to the anion by SmI_2 after cyclization (bimolecular) (**A**). Preliminary insights into the reaction mechanism were obtained by studying electronic effects of π-acceptors on the rate of cyclization (Scheme 5); these results were consistent with the cyclization or reduction (post-cyclization) as potentially kinetically relevant steps. To gain insight into the role of the concentrations of SmI_2 and H_2O on the stability of aminoketyl radicals, we studied the cyclization of **13** with a fixed amount of H_2O in the presence of decreasing concentrations of SmI_2 (Table 9).

Table 9 Effects of the Concentration of SmI_2 on the Reduction Rate of the Aminoketyl Radical Derived from the Five-Membered Imide **13** with SmI_2–H_2O[a]



Entry	Conversion[b] (%)	**A**/**B**[b]	$[SmI_2]$	$[H_2O]$	Rate[c] ($10^7 \times M^{-1}\cdot s^{-1}$)
1	>98	75:25	0.072	5.38	0.1065
2	>98	76:24	0.066	4.93	0.1101
3	>98	75:25	0.056	4.24	0.1369
4	>98	64:36	0.040	2.98	0.3234

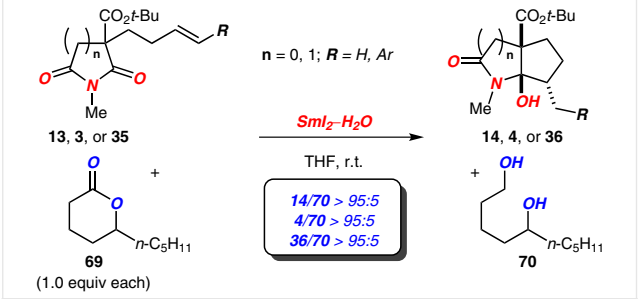
[a] All reactions were carried out by using standard Schlenk techniques with 1200 equiv of H_2O and SmI_2 freshly prepared from Sm metal and $I(CH_2)_2I$. Reactions were quenched with air after 2 h.
[b] Determined by ^1H NMR.
[c] Approximation: calculated by using the rate constant for cyclization of the 5-hexenyl radical: $k_{SmI2} = (red/cycl) \times k_{5\text{-}exo} \times [SmI_2]^{-1}$; ($k_{5\text{-}exo} \approx 2.3 \times 10^5\ s^{-1}$ at 25 °C).

Interestingly, decreasing the concentration of SmI_2 did not result in a significant increase in the cyclization/reduction ratio, which might be consistent with a bimolecular reaction. However, a plot of the rate versus $[SmI_2]$ gave an excellent correlation over the studied range of concentrations ($y = 294.55x^2 - 39.64x + 1.437$; $R^2 = 0.998$). Similarly, a plot of rate versus $[H_2O]$ gave an excellent correlation over the studied range of concentrations ($0.0493x^2 - 0.502x + 1.380$; $R^2 = 0.999$). Taken together, these data are consistent with the C–C bond-forming step being the rate-determining step of the reaction and they suggest that stabilization of the aminoketyl radical by the Sm(II)–H_2O reagent plays an important role in this reaction for the studied range of concentrations of water.[7] The observed approximate rate constant for the reduction of the aminoketyl radical can be compared with the observed approximate rate constant obtained from the reduction/cyclization of a model six-membered lactone bearing an ester directing group, namely eth-

yl 3-(but-3-en-1-yl)-2-oxotetrahydro-2*H*-pyran-3-carboxylate.[7] By using similar SmI_2–H_2O reaction conditions for the cyclization (lactone: 6–800; H_2O/SmI_2 = 133; **13**: 8–1200; H_2O/SmI_2 = 150), the reduction of **13** (to the anion) is more than one order of magnitude slower than that of the lactone, which is consistent with the nucleophilic character of the aminoketyl radicals (N- versus O-stabilization).[29–31] These findings support chemoselectivity studies on the reduction of 5-decanolide (see Scheme 6 below) and strongly suggest that a variety of reductive cyclizations of aminoketyl radicals might be readily accomplished.[2,3]

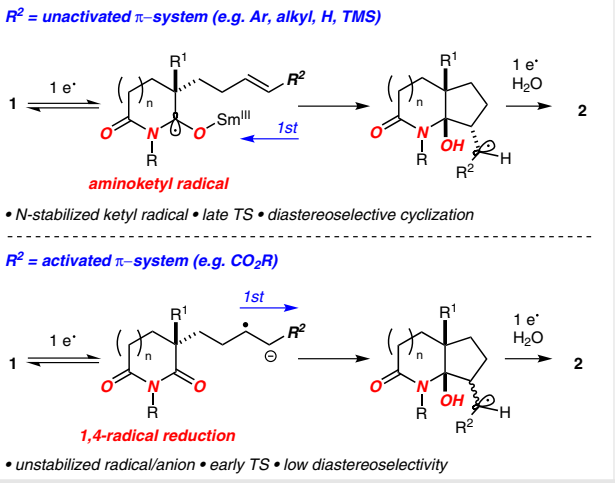
The use of water is critical for the observed reactivity; no reaction is observed in the absence of water, and low selectivity is observed at low concentrations of water. Interestingly, other protic additives (*t*-BuOH, MeOH, or glycol) also promote the reaction,[6a,39] which might be consistent with the role of water as a proton donor[39b] rather than with coordination of water to Sm(II) to enhance the redox potential of the reagent;[39g] however, this point requires further study. It is well established that polar substrates coordinate to Sm(II) centers and displace ligands from the inner coordination sphere,[39h] which might influence the redox properties of the reagent system.

Additional selectivity studies showed that the reaction affords full chemoselectivity across various ring sizes and properties of π-acceptors compared with reduction of a model lactone substrate, 5-decanolide,[7,14a] favoring the cyclization of aminoketyl radicals (Scheme 6). This highlights the nucleophilic character of aminoketyl radicals.[27a] Note that the SmI_2–H_2O system is fully chemoselective with respect to acyclic carboxylic acid derivatives (esters, carboxylic acids, amides), in that no reduction of these functional groups is observed, even when excess of the reagent is used.[3b,11] Importantly, the SmI_2–H_2O system can be used at varying concentrations of water to fine-tune the chemoselectivity of the lanthanide(II) reductant, which is not possible with ester-derived radicals,[14] which require large concentrations of water to promote the reduction.



Scheme 6 Selectivity studies in the reductive cyclization/reduction of cyclic imides and cyclic esters using SmI_2–H_2O

A possible mechanism for the reaction is presented in Scheme 7. The mechanistic observations are consistent with a mechanism involving activation of the imide carbonyl by initial coordination of Sm(II). Electron transfer generates an aminoketyl radical anion that is stabilized by $n_N \rightarrow SOMO$ conjugation. Cyclization through a well-defined late transition state with the π-acceptor in a pseudoequatorial orientation[35] delivers the 2-azabicyclic radical through anti-radical cyclization.[43] We postulate that C–C bond formation is a kinetically relevant step in this cross-coupling.[27c] The high stereoselectivity of the cyclization results from stabilization of the aminoketyl radical by the nitrogen atom, which allows the radical to adopt the most energetically favorable conformation.[27a] In contrast, the olefin-first mechanism proceeds through direct nucleophilic addition of a nonstabilized radical/anion, resulting in lower diastereoselectivity. The observed moderate stereocontrol is in agreement with other studies on SmI_2-mediated cyclizations of radical anions onto carbonyls through an olefin-first mechanism.[3a] Furthermore, the collapse of the aminoketyl radical by fragmentation is disfavored by the conjugation of the N_{lp} into the adjacent carbonyl group.[34a] Notably, over-reduction of the amide carbonyl group is not observed under the cyclization conditions, which attests to the high chemoselectivity of the SmI_2–H_2O reagent compared with the more thermodynamically powerful SmI_2-based reductants SmI_2/LiCl and SmI_2/HMPA.[3b] Kinetic studies to clarify this mechanism are ongoing.



Scheme 7 Proposed mechanism

5 Structural Characterization of the Hemiaminal Products

The 2-azabicycle products of the radical cyclization bearing a hydroxyl group at the angular position constitute a new class of tetrahedral intermediates of amide bond addition reactions.[53] Tetrahedral intermediates formed in the nucleophilic addition to amides are of significant interest as models for acyl-transfer reactions in both biological and synthetic contexts.[54] Moreover, the isolation of tetrahedral

intermediates can provide insights into the trajectory of nucleophilic addition to the carbonyl group for synthetic studies.[55] Furthermore, the structural arrangement around the carbon atom in tetrahedral intermediates permits the prediction of the propensity towards collapse and/or dehydration,[56] which is the critical for isolation and synthetic modifications. To date, only a few examples of tetrahedral intermediates of amide-bond addition have been successfully isolated, due to their transient nature.[53]

We succeeded in full structural characterization of hemiaminal products resulting from the cyclization of five- and six-membered imides via aminoketyl radicals with SmI_2–H_2O (Figures 3 and 4 below).[57] Hemiaminal products from the cyclization of barbituric acids have previously been reported;[20e] however, it should be noted that these intermediates are stabilized by the presence of a conjugated *N*-acylcarbamide moiety, which results in ring planarity, disfavoring the collapse of the α-alkoxy group.

The X-ray crystal structure of **8** (Figure 3) reveals that the α-amino alcohol moiety in **8** is stabilized by a nonplanar arrangement of atoms, which is similar to that in hemiaminals derived from the reductive cyclization of barbituric acids; however, several major differences can be readily noted. The C_1–O_4 bond (1.393 Å) in **8** is shorter than the average C_{sp3}–O bond (1.432 Å)[53a] and is also shorter than the corresponding C–O bond in the barbituric acid hemiaminal (1.407 Å).[20e] The length of N_1–C_1 bond in **8** is 1.471 Å, which corresponds to a typical C_{sp3}–N bond (1.469 Å)[53a] and is similar to that in the barbituric acid hemiaminal (1.466 Å).[20e] The C_1–C_2 bond in **8** (1.582 Å) is significantly longer than the average C_{sp3}–C_{sp3} bond (1.530 Å;[53a] 1.552 Å for barbituric acid hemiaminal).[20e] The torsion angle between N_{lp} and C_1–O_4 of 39.6° in **8** indicates the absence of $N_{lp}\rightarrow\sigma^*_{C\text{–}O}$ interactions (57.3° for barbituric acid hemiaminal).[20e] Moreover, there is a poor overlap between the O_{1lp1} and the N_1–C_1 bond (~142°) and between the O_{1lp2} and the C_1–C_2 bond (~92°) in **8**, compared with ~172° and ~191° torsions for the barbituric acid hemiaminal.[20e] The significantly shortened C_1–O_4 bond and the elongated C_1–C_2 bond in **8** indicate the presence of an anomeric effect resulting from $O_{lp1}\rightarrow\sigma^*_{C1\text{–}N1}$ and $O_{lp2}\rightarrow\sigma^*_{C1\text{–}C2}$ interactions. Thus, the geometry of the N_1 atom indicates the beginning of decomposition of the tetrahedral intermediate by elimination of the N–C(O) group.[53] Interestingly, this effect is more pronounced than that in the barbituric acid hemiaminal, likely due to less-efficient stabilization of the α-amino alcohol function by the interaction of N_{lp} with a single carbonyl group, compared with the conjugated *N*-acylcarbamide moiety in barbituric acid. Thus, hemiaminals derived from the reductive cyclization of five-membered imides not only provide a generic 2-azabicycle scaffold that is abundant in natural products and pharmaceuticals,[37] but also are expected to be much more reactive than barbituric acid hemiaminals; this might have important implications for synthetic functionalization of these unique products.[56]

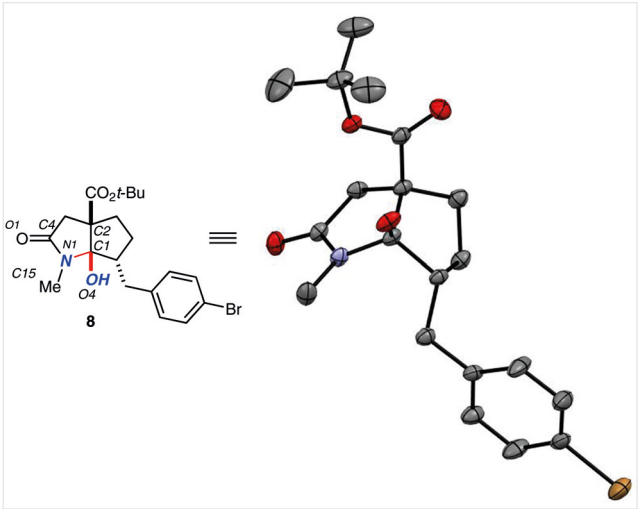


Figure 3 X-ray crystal structure of **8**. Selected bond lengths [Å] and angles [°]: N_1–C_1 1.471, C_1–O_4 1.393, C_1–C_2 1.582, O_4–H_4 0.82, N_1–C_4 1.341, C_4–O_1 1.231, C_3–C_4 1.494, C_4–N_1–C_1–O_4 –123.8, C_{15}–N_1–C_1–O_4 44.7, N_1–C_1–O_4–H_4 –97.7, C_2–C_1–O_4–H_4 148.5, C_1–N_1–C_4–C_3 –1.1, C_4–N_1–C_1–C_2 –4.4, N_1–C_4–C_3–C_2 6.4.

The X-ray crystal structure of hemiaminal **54**, obtained by reductive cyclization of a six-membered cyclic imide, is shown in Figure 4 together with structural parameters relevant to geometry at the anomeric center. The X-ray crystal structure reveals that the C_1–O_4 bond (1.404 Å) is also shorter than the average C_{sp3}–O bond (1.432 Å),[53a] whereas the length of the N_1–C_1 bond is 1.478 Å, close to that of a typical C_{sp3}–N bond (1.469 Å).[53a] The C_1–C_2 bond is slightly longer (1.554 Å) than the average C_{sp3}–C_{sp3} bond (1.530 Å).[53a] The torsion angle between N_{lp} and C_1–O_1 of 51.6° indicates a poor $N_{lp}\rightarrow\sigma^*_{C\text{–}O}$ interaction. In addition, there is a lack of good overlap between the O_{1lp1} and the N_1–C_1 bond (~139°) and between the O_{1lp2} and the C_1–C_2 bond (~102°). Overall, these structural features of **54** indicate the presence of a similar anomeric effect, resulting from $O_{lp1}\rightarrow\sigma^*_{C1\text{–}N1}$ and $O_{lp2}\rightarrow\sigma^*_{C1\text{–}C2}$ interactions, to that in the hemiaminal **8**; however, the bond lengths and angles suggest that this effect is less evident than in **8**. Furthermore, it appears that the stability of hemiaminals in these systems is thermodynamic in origin, with a dynamic equilibrium between cyclic and acyclic forms as well as between the hemiaminal and the corresponding iminium.[53] As such, these structural studies indicate that hemiaminals resulting from reductive imide cyclizations are well-poised for further synthetic manipulations.[56]

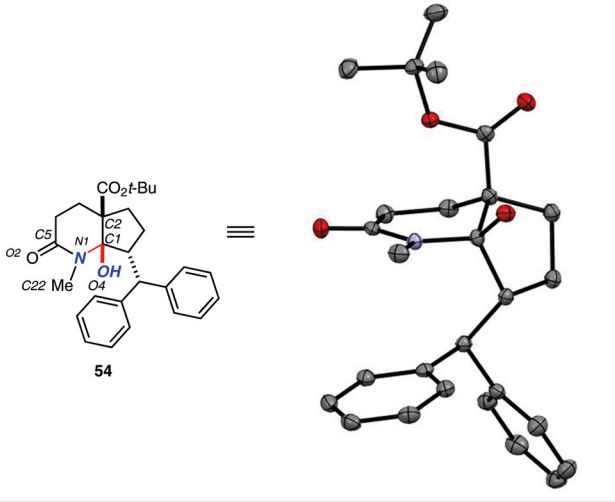


Figure 4 X-ray crystal structure of **54**. Selected bond lengths [Å] and angles [°]: N_1–C_1 1.478, C_1–O_4 1.404, C_1–C_2 1.554, O_4–H_4 0.84, N_1–C_5 1.339, C_5–O_2 1.244, C_4–C_5 1.504, C_5–N_1–C_1–O_4 –137.8, C_{22}–N_1–C_1–O_4 34.7, N_1–C_1–O_4–H_4 –101.3, C_2–C_1–O_4–H_4 138.3, C_1–N_1–C_5–C_4 –5.8, C_5–N_1–C_1–C_2 –22.2, N_1–C_5–C_4–C_3 6.6.

6 Utility in Organic Synthesis

The reaction should be evaluated against: (i) SmI_2-mediated cyclizations of carboxylic acid substrates;[2,3] (ii) generation of aminoketyl radicals in organic synthesis;[27,28] and (iii) stereoselective methods for the synthesis of angularly substituted 2-azabicycles.[22,37]

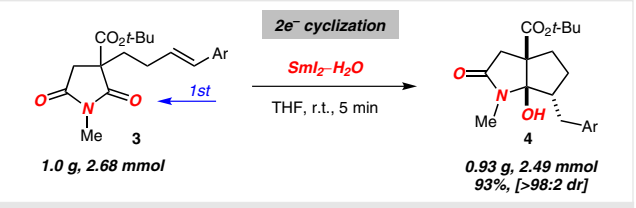
The SmI_2–H_2O mediated cyclization of barbituric acids has been reported.[20e] The SmI_2–*t*-BuOH-mediated cyclization of phthalimides with activated acceptors has been reported.[32a] Elegant work by Procter demonstrated the ease of cyclization of cyclic ester substrates by using SmI_2–H_2O.[14] New selective methods for the preparation of 2-azabicycles are an important focus of research.[22]

Several important advantages pertaining to the synthesis of 2-azabicycles by using the current protocol should be noted.

(1) The present reaction constitutes the first general method for the elaboration of imide frameworks to broadly useful scaffolds by using SmI_2.[32] Cyclizations of barbituric acids[20e] are inherently limited to the hexahydropyrimidine framework, which is much less common in natural products and pharmaceuticals than are 2-azabicyclic motifs based on pyrrolidine and piperidine scaffolds.[37] Cyclizations of phthalimides[32a] are limited to aromatic substrates and activated acceptors, which is not the case with our protocol.

(2) Compared with other cyclizations mediated by SmI_2–H_2O,[10–14] the present method has advantages in terms of its substrate scope, functional-group tolerance and variety of π-acceptors that are amenable to cyclization, including cyclic esters,[14] which are notoriously difficult to cyclize and require long reaction times that compete with decay of the SmI_2–H_2O reagent.[39g] Notably, our study provides the first general method for cyclization of five-membered cyclic precursors in high yields and excellent stereoselectivity by using SmI_2–H_2O.

(3) The present method is scalable. The cyclization can be executed on a gram-scale without a noticeable decrease in yield (Scheme 8), demonstrating the robustness of the method. Importantly, the 2-azabicyclic product can be obtained by direct recrystallization from the reaction mixture, which significantly facilitates purification.

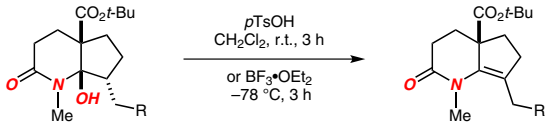


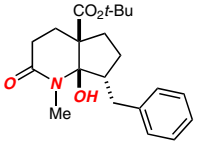
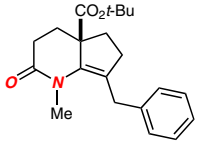
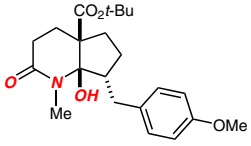
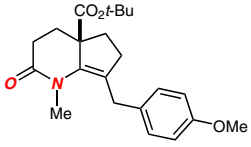
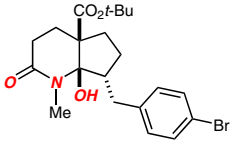
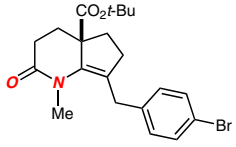
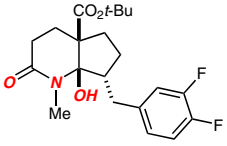
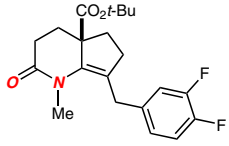
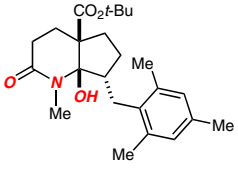
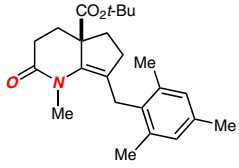
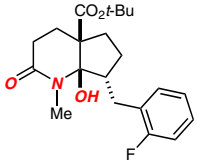
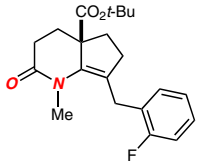
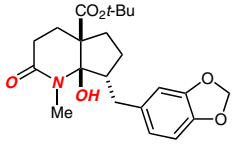
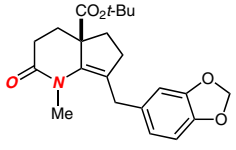
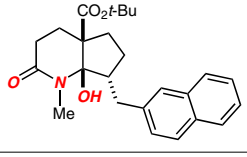
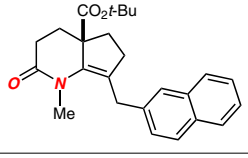
Scheme 8 Gram-scale cyclization of imides to 2-azabicycles via aminoketyl radicals by using SmI_2–H_2O (Ar = 4-$MeOC_6H_4$)

(4) Most importantly, this is the first broadly applicable method for the generation of aminoketyl radicals (R–C(O⁻)NR′R″) in organic synthesis.[27,28] These intermediates have been severely underutilized due to the lack of methods for their generation; however, aminoketyl radicals have been commonly invoked in degradation of nucleobases and mass spectrometry of peptides.[21] As such, our method demonstrates for the first time that the synthetically useful generation of aminoketyl radicals is possible under mild conditions, and that these intermediates can be used in valuable C–C bond-forming events, thereby expanding the reactivity platform of SmI_2 ketyl formation to include nitrogen-containing scaffolds.[1–3] Beyond doubt, this is a valuable advantage as nitrogen-containing heterocycles are more prevalent than are their oxygen-containing counterparts in natural products and pharmaceuticals;[58] furthermore, few reagents other than SmI_2 can be envisioned to engage in direct electron transfer to electron-rich nitrogen-containing functional groups due to the prohibitive redox properties of such groups.[24]

(5) Finally, our preliminary results on the reactivity of 2-azabicyclic products suggest that these intermediates enjoy a reactivity typical of N,O-anomeric substitution.[56] For example, exposure of these hemiaminals to mildly acidic conditions (TsOH or BF_3·Et_2O) results in the formation of enamides containing an endocyclic olefin group for further functionalization (Table 10). The nucleophilic C2-reactivity of these enamides is well established.[20c] Their ease of dehydration bodes well for the use of these hemiaminals to elaborate the 2-azabicyclic scaffold to a wide range of derivatives.

Table 10 Dehydration of Bicyclo-[4.3.0]-2-azanon-3-ones to Form Enamides[a]



Entry	Hemiaminal	Product	Yield (%)
1			94
2[b]			65
3			97
4			74
5			74
6			71
7			64
8			79
9			94

[a] Reaction conditions: TsOH (1 equiv), CH_2Cl_2, r.t., 3 h.
[b] Reaction conditions: $BF_3{\cdot}Et_2O$ (3 equiv), CH_2Cl_2, –78 C, 3 h.

7 Conclusions

In conclusion, we have developed the first broadly applicable method for the generation of aminoketyl radicals. We have also demonstrated, for the first time, that aminoketyl radicals generated by a direct electron transfer to five- or six-membered cyclic imides with SmI_2–H_2O engage in stereoselective addition reactions to generate complex 2-azabicycles featuring three contiguous stereocenters. The scope and limitations of the method have been demonstrated by the synthesis of more than 30 azabicycles. A wide range of sensitive functional groups and diverse π-acceptors are tolerated in this new process. A gram-scale coupling has been demonstrated. The transformation is characterized by complete stereoselectivity at the three contiguous stereocenters. This is unusual in SmI_2/H_2O-mediated reactions and likely originates from the electronic properties of nucleophilic aminoketyl radicals. The reaction therefore clearly has a strategic advantage over cyclizations employing cyclic esters, which currently represent the state-of-the-art in processes mediated by the venerable Kagan's reagent.

Mechanistic data are consistent with the addition of aminoketyl radical to alkenes as the rate-determining step in the reaction. The use of water as an additive to SmI_2 is critical to obtain high yields and preserve the high chemo- and diastereoselectivity of the process. 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. Given the prevalence of nitrogen-containing heterocycles in biologically active natural products and pharmaceuticals, we fully expect that the concept of utilization of aminoketyl radicals for α-N functionalization will find broad applications in organic synthesis.

Further investigations into related processes involving radical umpolung are ongoing in our laboratories and these results will be reported shortly.

All starting materials reported in the manuscript have been previously described in the literature or were prepared by a previously reported method. SmI_2 was prepared by standard methods and titrated before use.[59] All experiments involving SmI_2 were performed by standard techniques under an atmosphere of argon or N_2, unless stated otherwise. All solvents were purchased at the highest commercial grade and used as received or after purification by passing through activated alumina columns or by distillation from Na/benzophenone under N_2. All solvents were deoxygenated before use. All other chemicals were purchased at the highest commercial grade and used as received. Before use, reaction glassware was oven dried at 140 °C for at least 24 h or flame dried, then allowed to cool under vacuum and purged with argon (three cycles).

^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ on Bruker or Varian spectrometers at 500 and 600 MHz (^{1}H NMR), and 125 and 150 MHz (^{13}C NMR). All shifts are referenced to peaks for residual $CHCl_3$ (7.27 and 77.2 ppm, ^{1}H NMR and ^{13}C NMR, respectively). GC/MS chromatography was performed by using an Agilent HP6890 GC System and Agilent 5973A inert XL EI/CI MSD, with helium as the carrier gas (flow rate 1 mL/min) and an initial oven temperature of 50 °C. High-resolution mass spectra were recorded on a 7T Bruker Daltonics FT-MS instrument. All flash chromatography was performed by using 60 Å, 300 mesh, silica gel. TLC analyses were carried out on glass plates coated with silica gel 60 F254 (0.2 mm thickness). The plates were visualized by using a 254 nm UV lamp or aq $KMnO_4$ solutions.

Reductive Cyclizations using SmI_2–H_2O; General Procedure

An oven-dried vial containing a stirrer bar was charged with the appropriate cyclic imide substrate (neat, 1 equiv) then placed under a positive pressure of argon and subjected to three evacuation/backfilling cycles under high vacuum. THF (typically 2.0 mL) and H_2O (typically 600 equiv) were added, followed by a rapid injection of a THF soln of SmI_2 (typically 3 equiv) with vigorous stirring. This resulted in the formation of the characteristic burgundy-red color of the $SmI_2(H_2O)_n$ complex (n > 5 with respect to SmI_2). The mixture was stirred for the indicated time (typically 15 min) and then excess Sm(II) was oxidized by bubbling air through the mixture. The mixture was diluted with Et_2O (30 mL) and 0.1 N aq HCl (20 mL), and the aqueous layer was extracted with Et_2O (3 × 20 mL). The organic layers were combined, dried (Na_2SO_4), filtered, and concentrated. The crude product was analyzed by ^{1}H NMR ($CDCl_3$, C_6D_6 or acetone-d_6) and/or by GC-MS (neat) to determine the product distribution and diastereoselectivity, then purified by chromatography (silica gel) or crystallization, concentrated under reduced pressure, and stored neat or as a solution in acetone.

***tert*-Butyl (3a*R**,6*R**,6a*R**)-6a-Hydroxy-6-(4-methoxybenzyl)-1-methyl-2-oxohexahydrocyclopenta[*b*]pyrrole-3a(1*H*)-carboxylate (4): Representative Procedure for Large-Scale Coupling**

An oven-dried, 250-mL, round-bottomed flask equipped with a stirrer bar was placed under a positive pressure of argon and subjected to three evacuation/backfilling cycles under high vacuum. The flask was charged with imide **3** (neat, 1.00 g, 2.68 mmol, 1.0 equiv), THF (25 mL), and H_2O (19.3 mL, 400 equiv). A 0.10 M soln of SmI_2 in THF (53.6 mL, 2.0 equiv) was added with vigorous stirring, which resulted in the formation of the characteristic burgundy-red color of the $SmI_2(H_2O)_n$ complex (n > 5 with respect to SmI_2). The mixture was stirred at r.t. for 5 min and then excess SmI_2 was oxidized by bubbling air through the mixture. The mixture was then diluted with Et_2O (100 mL) and 0.1 N aq HCl (50 mL). The aqueous layer was extracted with Et_2O (2 × 100 mL) and the organic layers were combined, dried (Na_2SO_4), filtered, and concentrated. Analysis of the crude reaction mixture indicated >98% conversion, >98:2 cyclization/reduction selectivity, and >98:2 diastereoselectivity. Purification by recrystallization gave a white solid; yield: 0.935 g (2.49 mmol, 93%); mp 149–151 °C.

^{1}H NMR (500 MHz, acetone-d_6): δ = 7.15 (d, J = 8.5 Hz, 2 H), 6.85 (d, J = 8.6 Hz, 2 H), 5.05 (s, 1 H), 3.76 (s, 3 H), 3.13–3.05 (m, 2 H), 2.85 (s, 3 H), 2.47 (tdd, J = 11.8, 5.7, 2.9 Hz, 1 H), 2.43–2.32 (m, 2 H), 2.18 (d, J = 17.4 Hz, 1 H), 1.60 (dtt, J = 12.8, 6.9, 3.8 Hz, 2 H), 1.45 (s, 9 H), 1.32 (qd, J = 11.6, 7.3 Hz, 1 H).

^{13}C NMR (125 MHz, acetone-d_6): δ = 172.96, 171.83, 158.02, 133.05, 129.42, 113.56, 100.70, 80.58, 57.48, 54.41, 53.33, 40.62, 34.49, 34.06, 27.62, 27.13, 26.81.

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{21}H_{29}NNaO_5$: 398.1938; found: 398.1950.

Alkylation; General Procedure

A 25 mL round-bottomed flask was charged with 60% NaH (1.1 equiv; typically 1.1 mmol, 0.044 g), THF (typically 2.0 mL), HMPA (2.0 equiv, typically 1.1 mmol, 0.2 mL), and the mixture was stirred at r.t. for 10 min. The mixture was then cooled to 0 °C, a solution of the imide substrate (1.0 equiv) in THF (2.0 mL) was added, and the mixture was stirred at r.t. for 1 h. The mixture was then cooled to 0 °C, a solution of the appropriate alkyl halide (2.0 equiv) in THF (3.0 mL) was added, and the mixture was stirred at 50 °C for 18 h. The mixture was cooled once more to r.t., diluted with H_2O (2 mL), and extracted with Et_2O (30 mL). The organic layers were combined, washed sequentially with water (10 mL), aq $Na_2S_2O_3$ (10 mL), and brine (10 mL), dried, and concentrated. The residue was purified by chromatography [silica gel, EtOAc–hexane (6:1 to 3:1)]. All products were obtained as single olefin isomers.

***tert*-Butyl *(E)*-1-Methyl-2,5-dioxo-3-(4-phenylbut-3-en-1-yl) pyrrolidine-3-carboxylate (1)**

White solid; yield: 0.22 g (64%); mp 82–83 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.32–7.27 (m, 4 H), 7.21 (t, *J* = 7.0 Hz, 1 H), 6.37 (d, *J* = 15.7 Hz, 1 H), 6.12 (dt, *J* = 15.6, 5.9 Hz, 1 H), 3.13 (d, *J* = 18.1 Hz, 1 H), 2.95 (s, 3 H), 2.68 (d, *J* = 18.2 Hz, 1 H), 2.38–2.25 (m, 1 H), 2.16 (dddd, *J* = 19.2, 13.7, 9.3, 4.4 Hz, 3 H), 1.45 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 176.12, 175.43, 168.45, 137.24, 131.27, 128.69, 128.42, 127.42, 126.18, 83.47, 55.64, 37.77, 32.99, 28.28, 27.92, 25.42.

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{20}H_{25}NNaO_4$: 366.1676; found: 366.1687.

***tert*-Butyl 3-[(3*E*)-4-(4-Methoxyphenyl)but-3-en-1-yl]-1-methyl-2,5-dioxopyrrolidine-3-carboxylate (3)**

White solid; yield: 1.25 g (76%); mp 93–94 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.24 (d, *J* = 8.2 Hz, 2 H), 6.83 (d, *J* = 8.1 Hz, 2 H), 6.31 (d, *J* = 15.8 Hz, 1 H), 5.97 (dt, *J* = 13.4, 6.1 Hz, 1 H), 3.80 (s, 3 H), 3.12 (d, *J* = 18.2 Hz, 1 H), 2.93 (s, 3 H), 2.68 (d, *J* = 18.2 Hz, 1 H), 2.32–2.09 (m, 4 H), 1.45 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 176.18, 175.48, 168.50, 159.11, 130.65, 130.08, 127.30, 126.21, 114.11, 83.43, 55.66, 55.43, 37.71, 33.09, 28.28, 27.92, 25.42.

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{21}H_{27}NNaO_5$: 396.1781; found: 396.1794.

***tert*-Butyl 1-Methyl-2,5-dioxo-3-{(3*E*)-4-[4-(trifluoromethyl)phenyl]but-3-en-1-yl}pyrrolidine-3-carboxylate (5)**

White solid; yield: 0.095 g (45%); mp 88–89 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.54 (d, *J* = 8.1 Hz, 2 H), 7.40 (d, *J* = 8.1 Hz, 2 H), 6.41 (d, *J* = 15.8 Hz, 1 H), 6.24 (dt, *J* = 15.8, 6.2 Hz, 1 H), 3.13 (d, *J* = 18.2 Hz, 1 H), 2.96 (s, 3 H), 2.67 (d, *J* = 18.1 Hz, 1 H), 2.36–2.30 (m, 1 H), 2.22–2.12 (m, 3 H), 1.45 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 176.02, 175.28, 168.35, 140.73, 131.35, 130.04, 129.28 (q, J^F = 32.2 Hz), 126.32, 125.67 (q, J^F = 3.8 Hz), 124.34 (q, J^F = 270.1 Hz), 83.60, 55.57, 37.89, 32.82, 28.26, 27.92, 25.43.

^{19}F NMR (470 MHz, $CDCl_3$): δ = –62.47.

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{21}H_{24}F_3NNaO_4$: 434.1550; found: 434.1564.

***tert*-Butyl 3-[(3*E*)-4-(4-Bromophenyl)but-3-en-1-yl]-1-methyl-2,5-dioxopyrrolidine-3-carboxylate (7)**

White solid; yield: 0.16 g (76%); mp 87–88 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.43 (d, *J* = 8.3 Hz, 2 H), 7.19 (d, *J* = 8.4 Hz, 2 H), 6.33 (d, *J* = 15.8 Hz, 1 H), 6.19–6.10 (m, 1 H), 3.14 (d, *J* = 18.2 Hz, 1 H), 2.97 (s, 3 H), 2.69 (d, *J* = 18.2 Hz, 1 H), 2.36–2.27 (m, 1 H), 2.22–2.11 (m, 3 H), 1.47 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 176.06, 175.34, 168.38, 136.18, 131.78, 130.11, 129.35, 127.71, 121.13, 83.53, 55.56, 37.79, 32.83, 28.24, 27.91, 25.43.

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{20}H_{24}BrNNaO_4$: 444.0781; found: 444.0793.

***tert*-Butyl 3-[(3*E*)-4-(3,5-Dichlorophenyl)but-3-en-1-yl]-1-methyl-2,5-dioxopyrrolidine-3-carboxylate (9)**

White solid; yield: 0.092 g (46%); mp 101–103 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.24–7.07 (m, 3 H), 6.27 (d, *J* = 15.8 Hz, 1 H), 6.17 (dt, *J* = 15.8, 5.9 Hz, 1 H), 3.13 (d, *J* = 18.2 Hz, 1 H), 2.98 (s, 3 H), 2.64 (d, *J* = 18.1 Hz, 1 H), 2.35–2.27 (m, 1 H), 2.19–2.09 (m, 3 H), 1.45 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.94, 175.25, 168.29, 140.28, 135.24, 131.72, 128.87, 127.20, 124.56, 83.63, 55.53, 37.93, 32.82, 28.16, 27.92, 25.47.

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{20}H_{23}Cl_2NNaO_4$: 434.0896; found: 434.0910.

***tert*-Butyl 1-Methyl-3-[(3*E*)-4-(2-naphthyl)but-3-en-1-yl]-2,5-dioxopyrrolidine-3-carboxylate (11)**

White solid; yield: 0.18 g (61%); mp 117–118 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.82–7.73 (m, 3 H), 7.65 (s, 1 H), 7.53 (d, *J* = 8.5 Hz, 1 H), 7.43 (p, *J* = 6.7 Hz, 2 H), 6.54 (d, *J* = 15.7 Hz, 1 H), 6.25 (dt, *J* = 15.7, 6.3 Hz, 1 H), 3.14 (d, *J* = 18.1 Hz, 1 H), 2.94 (s, 3 H), 2.71 (d, *J* = 18.1 Hz, 1 H), 2.41–2.31 (m, 1 H), 2.27–2.14 (m, 3 H), 1.46 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 176.12, 175.41, 168.45, 134.69, 133.72, 132.95, 131.35, 128.86, 128.31, 128.03, 127.76, 126.35, 125.86, 125.84, 123.51, 83.46, 55.63, 37.74, 32.98, 28.40, 27.91, 25.42.

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{24}H_{27}NNaO_4$: 416.1832; found: 416.1846.

***tert*-Butyl 3-But-3-en-1-yl-1-methyl-2,5-dioxopyrrolidine-3-carboxylate (13)**

Colorless oil; yield: 0.21 g (45%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.75 (ddt, *J* = 16.5, 10.3, 6.1 Hz, 1 H), 5.02 (d, *J* = 17.1 Hz, 1 H), 4.98 (d, *J* = 10.1 Hz, 1 H), 3.11 (d, *J* = 18.2 Hz, 1 H), 2.99 (s, 3 H), 2.62 (d, *J* = 18.2 Hz, 1 H), 2.14–2.07 (m, 2 H), 2.04–1.93 (m, 2 H), 1.44 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 176.06, 175.46, 168.41, 136.80, 115.92, 83.41, 55.67, 37.90, 32.80, 28.88, 27.89, 25.36.

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{14}H_{21}NNaO_4$: 290.1363; found: 290.1371.

Ethyl 3-But-3-en-1-yl-1-methyl-2,5-dioxopyrrolidine-3-carboxylate (15)

Colorless oil; yield: 0.10 g (59%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.75 (ddt, *J* = 16.7, 10.3, 6.3 Hz, 1 H), 5.03 (d, *J* = 17.0 Hz, 1 H), 4.99 (d, *J* = 10.3 Hz, 1 H), 4.22 (q, *J* = 7.2 Hz, 2 H), 3.20 (d, *J* = 18.2 Hz, 1 H), 3.01 (s, 3 H), 2.65 (d, *J* = 18.2 Hz, 1 H), 2.21–1.96 (m, 4 H), 1.27 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.67, 175.18, 169.40, 136.56, 116.09, 62.66, 54.97, 37.81, 33.11, 28.85, 25.48, 14.15.

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{12}H_{17}NNaO_4$: 262.1050; found: 262.1057.

3-[(3*E*)-4-(4-Methoxyphenyl)but-3-en-1-yl]-1-methyl-3-phenylpyrrolidine-2,5-dione (17)

White solid; yield: 0.21 g (60%); mp 81–82 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.46 (d, *J* = 7.8 Hz, 2 H), 7.37 (t, *J* = 7.6 Hz, 2 H), 7.29 (t, *J* = 7.4 Hz, 1 H), 7.22 (d, *J* = 8.2 Hz, 2 H), 6.82 (d, *J* = 8.7 Hz, 2 H), 6.29 (d, *J* = 15.7 Hz, 1 H), 5.96 (dt, *J* = 15.9, 6.0 Hz, 1 H), 3.79 (s, 3 H), 3.16 (d, *J* = 18.2 Hz, 1 H), 3.00 (s, 3 H), 2.92 (d, *J* = 18.2 Hz, 1 H), 2.27–2.04 (m, 4 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 180.18, 175.60, 159.00, 140.61, 130.37, 130.12, 129.01, 127.66, 127.19, 126.37, 126.20, 114.04, 55.36, 51.74, 41.49, 39.30, 28.49, 25.13.

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{22}H_{23}NNaO_3$: 372.1570; found: 372.1580.

3-[(3*E*)-4-(4-Bromophenyl)but-3-en-1-yl]-1-methyl-3-phenylpyrrolidine-2,5-dione (19)

Colorless oil; yield: 0.050 g (40%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.45 (d, *J* = 7.8 Hz, 2 H), 7.39 (d, *J* = 8.4 Hz, 2 H), 7.38 (t, *J* = 8.0 Hz, 2 H), 7.30 (t, *J* = 7.3 Hz, 1 H), 7.14 (d, *J* = 8.4 Hz, 2 H), 6.27 (d, *J* = 15.7 Hz, 1 H), 6.09 (ddd, *J* = 15.9, 8.0, 4.6 Hz, 1 H), 3.17 (d, *J* = 18.2 Hz, 1 H), 3.00 (s, 3 H), 2.98 (d, *J* = 18.3 Hz, 1 H), 2.28–2.15 (m, 3 H), 2.08 (tdd, *J* = 13.3, 12.0, 5.8, 3.6 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 180.14, 175.55, 140.45, 136.27, 131.75, 129.91, 129.55, 129.11, 127.80, 127.66, 126.23, 121.04, 51.74, 41.63, 39.13, 28.53, 25.21.

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{21}H_{20}BrNNaO_2$: 420.0570; found: 420.0582.

***tert*-Butyl 1-Methyl-2,5-dioxo-3-(4-phenylbut-3-yn-1-yl)pyrrolidine-3-carboxylate (21)**

Colorless oil; yield: 0.045 g (34%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.39–7.33 (m, 2 H), 7.28 (m, 3 H), 3.14 (d, *J* = 18.2 Hz, 1 H), 2.98 (s, 3 H), 2.93 (d, *J* = 18.2 Hz, 1 H), 2.62–2.45 (m, 2 H), 2.32 (dtd, *J* = 21.9, 14.1, 6.9 Hz, 2 H), 1.45 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.79, 175.40, 168.20, 131.66, 128.40, 128.11, 123.30, 87.75, 83.68, 82.29, 55.60, 37.99, 31.79, 27.90, 25.49, 15.34.

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{20}H_{23}NNaO_4$: 364.1519; found: 364.1530.

***tert*-Butyl 1-Methyl-2,6-dioxo-3-[(3*E*)-4-phenylbut-3-en-1-yl]piperidine-3-carboxylate (33)**

Colorless oil; yield: 0.195 g (55%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.33 (d, *J* = 7.2 Hz, 2 H), 7.29 (t, *J* = 7.6 Hz, 2 H), 7.20 (t, *J* = 7.1 Hz, 1 H), 6.42 (d, *J* = 15.8 Hz, 1 H), 6.19 (dt, *J* = 15.8, 6.7 Hz, 1 H), 3.17 (s, 3 H), 2.76 (ddd, *J* = 18.1, 5.0, 3.3 Hz, 1 H), 2.64 (ddd, *J* = 18.1, 12.7, 5.5 Hz, 1 H), 2.47–2.38 (m, 1 H), 2.27–2.11 (m, 3 H), 2.10–1.96 (m, 2 H), 1.45 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.92, 171.66, 169.99, 137.55, 130.80, 129.42, 128.65, 127.23, 126.12, 83.50, 55.17, 34.81, 30.11, 28.35, 27.99, 27.19, 25.89.

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{21}H_{27}NNaO_4$: 380.1832; found: 380.1842.

***tert*-Butyl 3-[(3*E*)-4-(4-Methoxyphenyl)but-3-en-1-yl]-1-methyl-2,6-dioxopiperidine-3-carboxylate (35)**

Colorless oil; yield: 0.51 g (88%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.25 (d, *J* = 5.4 Hz, 2 H), 6.83 (d, *J* = 8.3 Hz, 2 H), 6.35 (d, *J* = 15.9 Hz, 1 H), 6.04 (d, *J* = 15.8 Hz, 1 H), 3.80 (s, 3 H), 3.16 (s, 3 H), 2.75 (dt, *J* = 18.4, 3.9 Hz, 1 H), 2.69–2.59 (m, 1 H), 2.27–2.21 (m, 1 H), 2.20–2.10 (m, 2 H), 2.09–1.94 (m, 3 H), 1.45 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.96, 171.69, 170.02, 158.98, 130.40, 130.16, 127.23, 127.23, 114.08, 83.47, 55.43, 55.20, 34.96, 30.12, 28.33, 28.01, 27.20, 25.86.

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{22}H_{29}NNaO_5$: 410.1938; found: 410.1950.

***tert*-Butyl 1-Methyl-2,6-dioxo-3-{(3*E*)-4-[4-(trifluoromethyl)phenyl]but-3-en-1-yl}piperidine-3-carboxylate (37)**

Colorless oil; yield: 0.18 g (42%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.53 (d, *J* = 8.1 Hz, 2 H), 7.41 (d, *J* = 8.1 Hz, 2 H), 6.45 (d, *J* = 15.9 Hz, 1 H), 6.30 (dt, *J* = 15.7, 6.7 Hz, 1 H), 3.17 (s, 3 H), 2.80–2.72 (m, 1 H), 2.68–2.59 (m, 1 H), 2.52–2.42 (m, 1 H), 2.27–2.12 (m, 3 H), 2.10–1.96 (m, 2 H), 1.45 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.83, 171.64, 169.92, 141.00, 132.28, 129.46, 128.90 (q, J^F = 32.1 Hz), 126.18, 125.49 (q, J^F = 3.6 Hz), 124.31 (q, J^F = 270.0 Hz), 83.64, 55.11, 34.61, 30.09, 28.38, 27.99, 27.20, 26.02.

^{19}F NMR (470 MHz, $CDCl_3$): δ = –62.44.

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{22}H_{26}F_3NNaO_4$: 448.1706; found: 448.1718.

***tert*-Butyl 3-[(3*E*)-4-(4-Bromophenyl)but-3-en-1-yl]-1-methyl-2,6-dioxopiperidine-3-carboxylate (39)**

Colorless oil; yield: 0.090 g (45%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.40 (d, *J* = 8.5 Hz, 2 H), 7.19 (d, *J* = 8.5 Hz, 2 H), 6.35 (d, *J* = 15.8 Hz, 1 H), 6.18 (dt, *J* = 15.8, 6.7 Hz, 1 H), 3.16 (s, 3 H), 2.75 (ddd, *J* = 18.1, 4.9, 3.2 Hz, 1 H), 2.64 (ddd, *J* = 18.1, 12.7, 5.5 Hz, 1 H), 2.42 (tt, *J* = 12.9, 6.1 Hz, 1 H), 2.24 (ddd, *J* = 13.7, 5.4, 3.2 Hz, 1 H), 2.21–2.09 (m, 2 H), 2.08–1.95 (m, 2 H), 1.45 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.87, 171.65, 169.95, 136.50, 131.73, 130.32, 129.67, 127.67, 120.90, 83.58, 55.13, 34.69, 30.10, 28.34, 28.00, 27.20, 25.96.

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{21}H_{26}BrNNaO_4$: 458.0937; found: 458.0951.

***tert*-Butyl 3-[(3*E*)-4-(3,5-Dichlorophenyl)but-3-en-1-yl]-1-methyl-2,6-dioxopiperidine-3-carboxylate (41)**

Colorless oil; yield: 0.036 g (20%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.18–7.17 (m, 3 H), 6.30 (d, *J* = 16.0 Hz, 1 H), 6.26–6.19 (m, 1 H), 3.17 (s, 3 H), 2.80–2.71 (m, 1 H), 2.71–2.57 (m, 1 H), 2.44 (dd, *J* = 13.1, 6.8 Hz, 1 H), 2.27–2.09 (m, 3 H), 2.08–1.93 (m, 2 H), 1.45 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.79, 171.59, 169.87, 140.61, 135.18, 132.71, 128.44, 126.99, 124.53, 83.66, 55.09, 34.59, 30.09, 28.29, 28.00, 27.21, 26.07.

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{21}H_{25}Cl_2NNaO_4$: 448.1053; found: 448.1066.

tert-Butyl 3-[(3*E*)-4-(3,4-Difluorophenyl)but-3-en-1-yl]-1-methyl-2,6-dioxopiperidine-3-carboxylate (43)

Colorless oil; yield: 0.057 g (29%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.13 (ddd, *J* = 11.6, 7.6, 2.1 Hz, 1 H), 7.10–7.03 (m, 1 H), 7.03–6.95 (m, 1 H), 6.32 (d, *J* = 15.7 Hz, 1 H), 6.12 (td, *J* = 15.6, 13.2, 5.6 Hz, 1 H), 3.17 (s, 3 H), 2.76 (ddd, *J* = 18.2, 5.2, 3.1 Hz, 1 H), 2.63 (ddd, *J* = 18.2, 12.7, 5.5 Hz, 1 H), 2.42 (ddt, *J* = 16.9, 12.7, 5.9 Hz, 1 H), 2.26–2.20 (m, 1 H), 2.20–2.09 (m, 2 H), 2.07–1.95 (m, 2 H), 1.45 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.84, 171.64, 169.92, 151.05 (d, J^F = 121.0 Hz), 150.81 (dd, J^F = 120.4, 12.6 Hz), 134.84, 130.63 (d, J^F = 1.9 Hz), 128.85, 122.22 (q, J^F = 3.5 Hz), 117.33 (d, J^F = 17.3 Hz), 114.42 (d, J^F = 17.5.0 Hz), 83.62, 55.11, 34.70, 30.09, 28.21, 28.06, 27.20, 26.00.

^{19}F NMR (470 MHz, $CDCl_3$): δ = –138.16 (d, *J* = 20.9 Hz), –139.97 (d, *J* = 20.9 Hz).

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{21}H_{25}F_2NNaO_4$: 416.1644; found: 416.1655.

tert-Butyl 3-[(3*E*)-4-Mesitylbut-3-en-1-yl]-1-methyl-2,6-dioxopiperidine-3-carboxylate (45)

Colorless oil; yield: 0.102 g (51%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.85 (s, 2 H), 6.34 (d, *J* = 16.0 Hz, 1 H), 5.63 (dt, *J* = 16.0, 6.8 Hz, 1 H), 3.19 (s, 3 H), 2.76 (ddd, *J* = 18.1, 5.2, 3.3 Hz, 1 H), 2.70–2.61 (m, 1 H), 2.46–2.39 (m, 1 H), 2.26 (s, 3 H), 2.24 (s, 6 H), 2.22–2.20 (m, 1 H), 2.15–1.99 (m, 4 H), 1.46 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.96, 171.73, 170.03, 135.97, 135.93, 134.31, 133.97, 128.58, 128.36, 83.51, 55.22, 35.12, 30.11, 28.85, 28.01, 27.20, 25.98, 21.02, 20.04.

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{24}H_{33}NNaO_4$: 422.2302; found: 422.2346.

tert-Butyl 3-[(3*E*)-4-(2-Fluorophenyl)but-3-en-1-yl]-1-methyl-2,6-dioxopiperidine-3-carboxylate (47)

Colorless oil; yield: 0.055 g (29%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.43–7.38 (m, 1 H), 7.20–7.13 (m, 1 H), 7.07 (t, *J* = 7.5 Hz, 1 H), 7.04–6.97 (m, 1 H), 6.56 (d, *J* = 15.9 Hz, 1 H), 6.31–6.23 (m, 1 H), 3.17 (s, 3 H), 2.76 (ddd, *J* = 18.1, 5.2, 3.2 Hz, 1 H), 2.64 (ddd, *J* = 18.1, 12.6, 5.5 Hz, 1 H), 2.51–2.40 (m, 1 H), 2.29–2.12 (m, 3 H), 2.11–1.97 (m, 2 H), 1.45 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.90, 171.65, 169.96, 160.10 (d, J^F = 248.7 Hz), 132.16 (d, J^F = 4.4 Hz), 128.44 (d, J^F = 8.3 Hz), 127.23 (d, J^F = 4.0 Hz), 125.28 (d, J^F = 12.5 Hz), 124.16 (d, J^F = 3.5 Hz), 123.25 (d, J^F = 3.9 Hz), 115.78 (d, J^F = 22.3 Hz), 83.55, 55.17, 34.69, 30.11, 28.77, 28.00, 27.19, 25.93.

^{19}F NMR (470 MHz, $CDCl_3$): δ = –118.74.

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{21}H_{26}FNNaO_4$: 398.1738; found: 398.1751.

tert-Butyl 3-[(3*E*)-4-(1,3-Benzodioxol-5-yl)but-3-en-1-yl]-1-methyl-2,6-dioxopiperidine-3-carboxylate (49)

Colorless oil; yield: 0.285 g (71%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.87 (s, 1 H), 6.82–6.64 (m, 2 H), 6.32 (d, *J* = 15.7, 1 H), 6.01 (dt, *J* = 13.8, 6.8 Hz, 1 H), 5.93 (s, 2 H), 3.16 (s, 3 H), 2.75 (ddd, *J* = 18.1, 5.2, 3.1 Hz, 1 H), 2.69–2.59 (m, 1 H), 2.45–2.31 (m, 1 H), 2.27–2.21 (m, 1 H), 2.19–2.09 (m, 2 H), 2.09–1.95 (m, 2 H), 1.44 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.91, 171.65, 169.97, 148.08, 146.92, 132.08, 130.34, 127.65, 120.52, 108.36, 105.54, 101.09, 83.48, 55.16, 34.89, 30.10, 28.22, 27.99, 27.18, 25.87.

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{22}H_{27}NNaO_6$: 424.1730; found: 424.1744.

tert-Butyl 1-Methyl-3-[(3*E*)-4-(2-naphthyl)but-3-en-1-yl]-2,6-dioxopiperidine-3-carboxylate (51)

Colorless oil; yield: 0.089 g (44%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.77 (t, *J* = 9.0 Hz, 3 H), 7.67 (s, 1 H), 7.56 (d, *J* = 8.6 Hz, 1 H), 7.48–7.38 (m, 2 H), 6.58 (d, *J* = 15.8 Hz, 1 H), 6.33 (dt, *J* = 15.7, 6.8 Hz, 1 H), 3.18 (s, 3 H), 2.77 (ddd, *J* = 18.0, 4.9, 3.3 Hz, 1 H), 2.65 (ddd, *J* = 18.1, 12.7, 5.5 Hz, 1 H), 2.48 (tt, *J* = 13.6, 6.6 Hz, 1 H), 2.32–2.16 (m, 3 H), 2.10 (ddd, *J* = 13.7, 11.3, 4.6 Hz, 1 H), 2.02 (td, *J* = 13.2, 5.2 Hz, 1 H), 1.46 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.92, 171.68, 171.68, 135.02, 133.78, 132.90, 130.91, 129.90, 128.26, 128.00, 127.76, 126.31, 125.74, 125.72, 123.59, 83.53, 55.19, 34.84, 30.12, 28.47, 28.00, 27.20, 25.92.

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{25}H_{29}NNaO_4$: 430.1988; found: 430.2000.

tert-Butyl 3-(4,4-Diphenylbut-3-en-1-yl)-1-methyl-2,6-dioxopiperidine-3-carboxylate (53)

Colorless oil; yield: 0.282 g (65%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.36 (t, *J* = 7.3 Hz, 2 H), 7.30 (d, *J* = 7.3 Hz, 1 H), 7.25 (d, *J* = 9.5 Hz, 2 H), 7.21 (td, *J* = 6.5, 3.3 Hz, 3 H), 7.18–7.09 (m, 2 H), 6.06 (td, *J* = 7.2, 2.2 Hz, 1 H), 3.12 (s, 3 H), 2.68–2.52 (m, 2 H), 2.35–2.24 (m, 1 H), 2.16–2.03 (m, 4 H), 1.78 (td, *J* = 13.6, 13.0, 6.3 Hz, 1 H), 1.36 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.92, 171.60, 169.88, 142.55, 142.47, 139.94, 129.90, 128.41, 128.26, 128.25, 127.33, 127.24, 127.18, 83.39, 55.11, 35.00, 29.99, 27.90, 27.18, 25.45, 25.21.

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{27}H_{31}NNaO_4$: 456.0145; found: 456.0148.

tert-Butyl 1-Methyl-2,6-dioxo-3-[(3*E*,5*E*)-6-phenylhexa-3,5-dien-1-yl]piperidine-3-carboxylate (55)

Colorless oil; yield: 0.254 g (61%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.37 (d, *J* = 7.7 Hz, 2 H), 7.30 (t, *J* = 7.7 Hz, 2 H), 7.20 (t, *J* = 7.5 Hz, 1 H), 6.73 (dd, *J* = 15.7, 10.4 Hz, 1 H), 6.46 (d, *J* = 15.7 Hz, 1 H), 6.24 (dd, *J* = 15.1, 10.5 Hz, 1 H), 5.79 (dt, *J* = 14.6, 6.9 Hz, 1 H), 3.17 (s, 3 H), 2.76–2.71 (m, 1 H), 2.69–2.63 (m, 1 H), 2.37–2.33 (m, 1 H), 2.25–2.21 (m, 1 H), 2.16–2.09 (m, 2 H), 2.05–1.97 (m, 2 H), 1.45 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.92, 171.64, 169.96, 137.58, 133.86, 131.49, 130.98, 129.05, 128.70, 127.41, 126.34, 83.51, 55.16, 50.15, 34.77, 30.10, 28.00, 27.21, 25.93.

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{23}H_{29}NNaO_4$: 406.1989; found: 406.1999.

***tert*-Butyl 3-[(3*E*)-5-Butoxy-5-oxopent-3-en-1-yl]-1-methyl-2,5-dioxopyrrolidine-3-carboxylate (65)**

Colorless oil; yield: 0.025 g (76%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.88 (dt, *J* = 15.6, 6.3 Hz, 1 H), 5.82 (d, *J* = 15.6 Hz, 1 H), 4.11 (t, *J* = 6.7 Hz, 2 H), 3.10 (d, *J* = 18.1 Hz, 1 H), 2.99 (s, 3 H), 2.57 (d, *J* = 18.1 Hz, 1 H), 2.32–2.24 (m, 1 H), 2.18–2.10 (m, 2 H), 2.06–2.00 (m, 1 H), 1.63–1.57 (m, 2 H), 1.43 (s, 9 H), 1.38 (dd, *J* = 15.0, 7.4 Hz, 2 H), 0.92 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.64, 175.02, 168.07, 166.38, 146.40, 122.57, 83.72, 64.39, 55.40, 38.14, 32.03, 30.81, 27.87, 27.28, 25.42, 19.27, 13.82.

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{19}H_{29}NNaO_6$: 390.1887; found: 390.1897.

***tert*-Butyl 3-[(3*E*)-5-Butoxy-5-oxopent-3-en-1-yl]-1-methyl-2,6-dioxopiperidine-3-carboxylate (67)**

Colorless oil; yield: 0.065 g (68%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.92 (dt, *J* = 15.3, 6.7 Hz, 1 H), 5.84 (d, *J* = 15.7 Hz, 1 H), 4.11 (t, *J* = 6.7 Hz, 2 H), 3.15 (s, 3 H), 2.73 (ddd, *J* = 18.3, 5.3, 3.1 Hz, 1 H), 2.60 (ddd, *J* = 18.2, 12.8, 5.5 Hz, 1 H), 2.50–2.39 (m, 1 H), 2.18 (tdd, *J* = 18.1, 8.5, 4.6 Hz, 2 H), 2.04 (dqd, *J* = 25.5, 13.7, 4.8 Hz, 2 H), 1.93 (td, *J* = 13.2, 5.2 Hz, 1 H), 1.62 (p, *J* = 6.9 Hz, 2 H), 1.42 (s, 9 H), 1.41–1.34 (m, 2 H), 0.92 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.66, 171.42, 169.66, 166.60, 147.43, 122.09, 83.73, 64.30, 54.90, 33.52, 30.81, 29.98, 27.93, 27.47, 27.15, 26.17, 19.26, 13.82.

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{20}H_{31}NNaO_6$: 404.2044; found: 404.2052.

***tert*-Butyl (3a*R**,6*R**,6a*R**)-6-Benzyl-6a-hydroxy-1-methyl-2-oxohexahydrocyclopenta[*b*]pyrrole-3a(1*H*)-carboxylate (2)**

Prepared according to the general procedure from **1** (0.10 mmol), SmI_2 (0.30 mmol, 3.0 equiv, 3.0 mL, 0.10 M), and H_2O (1.08 mL, 600 equiv) in THF (2.0 mL) for 15 min, with workup by Et_2O/1.0 N aq HCl as a white solid; yield: 32.4 mg (94%). Recrystallized from CH_2Cl_2–hexanes; mp 134–135 °C (dr >95:5; cyclization/reduction selectivity >95:5). The stereochemistry was determined by 2D NMR experiments and confirmed by X-ray analysis of a derivative.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.29 (t, *J* = 7.4 Hz, 2 H), 7.20 (t, *J* = 7.4 Hz, 1 H), 7.16 (d, *J* = 7.1 Hz, 2 H), 4.07 (s, 1 H), 3.15 (dd, *J* = 12.1, 2.6 Hz, 1 H), 2.95 (d, *J* = 17.3 Hz, 4 H), 2.42–2.26 (m, 3 H), 2.18 (td, *J* = 12.7, 6.5 Hz, 1 H), 1.74–1.67 (m, 1 H), 1.65–1.60 (m, 1 H), 1.48 (s, 9 H), 1.26 (tq, *J* = 12.1, 6.2 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.13, 173.17, 140.42, 128.84, 128.63, 126.36, 100.25, 83.19, 56.79, 54.03, 42.47, 36.20, 34.15, 28.14, 27.89, 27.55.

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{20}H_{27}NNaO_4$: 368.1832; found: 368.1842.

***tert*-Butyl (3a*R**,6*R**,6a*R**)-6a-Hydroxy-6-(4-methoxybenzyl)-1-methyl-2-oxohexahydrocyclopenta[*b*]pyrrole-3a(1*H*)-carboxylate (4)**

Prepared according to the general procedure from **3** (0.10 mmol), SmI_2 (0.30 mmol, 3.0 equiv, 3.0 mL, 0.10 M), and H_2O (1.08 mL, 600 equiv) in THF (2.0 mL) for 15 min with workup by Et_2O/1.0 N aq HCl to give a white solid; yield: 35.0 mg (93%). Recrystallized from CH_2Cl_2–hexanes; mp 149–151 °C; dr >95:5; cyclization/reduction selectivity >95:5. The stereochemistry was determined by 2D NMR experiments and confirmed by X-ray analysis of a derivative.

^{1}H NMR (500 MHz, acetone-d_6): δ = 7.15 (d, *J* = 8.5 Hz, 2 H), 6.85 (d, *J* = 8.6 Hz, 2 H), 5.05 (s, 1 H), 3.76 (s, 3 H), 3.13–3.05 (m, 2 H), 2.85 (s, 3 H), 2.47 (tdd, *J* = 11.8, 5.7, 2.9 Hz, 1 H), 2.43–2.32 (m, 2 H), 2.18 (d, *J* = 17.4 Hz, 1 H), 1.60 (dtt, *J* = 12.8, 6.9, 3.8 Hz, 2 H), 1.45 (s, 9 H), 1.32 (qd, *J* = 11.6, 7.3 Hz, 1 H).

^{13}C NMR (125 MHz, acetone-d_6): δ = 172.96, 171.83, 158.02, 133.05, 129.42, 113.56, 100.70, 80.58, 57.48, 54.41, 53.33, 40.62, 34.49, 34.06, 27.62, 27.13, 26.81.

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{21}H_{29}NNaO_5$: 398.1938; found: 398.1950.

***tert*-Butyl (3a*R**,6*R**,6a*R**)-6a-Hydroxy-1-methyl-2-oxo-6-[4-(trifluoromethyl)benzyl]hexahydrocyclopenta[*b*]pyrrole-3a(1*H*)-carboxylate (6)**

Prepared according to the general procedure from **5** (0.05 mmol), SmI_2 (0.15 mmol, 3.0 equiv, 1.5 mL, 0.10 M), and H_2O (0.54 mL, 600 equiv) in THF (1.0 mL) for 15 min with workup by Et_2O/1.0 N aq HCl to give a white solid ; yield: 19.2 mg (93%). Recrystallized from CH_2Cl_2–hexanes; mp 160–162 °C; dr >95:5; cyclization/reduction selectivity >95:5. The stereochemistry was determined by 2D NMR experiments and confirmed by an X-ray analysis of a derivative.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.54 (d, *J* = 7.9 Hz, 2 H), 7.28 (d, *J* = 8.0 Hz, 2 H), 4.22 (s, 1 H), 3.21 (d, *J* = 9.1 Hz, 1 H), 3.02–2.88 (m, 4 H), 2.45–2.30 (m, 3 H), 2.19 (td, *J* = 12.7, 6.5 Hz, 1 H), 1.71 (dd, *J* = 13.2, 5.8 Hz, 1 H), 1.60–1.54 (m, 1 H), 1.48 (s, 9 H), 1.26 (dq, *J* = 11.5, 5.8 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.99, 173.23, 144.57, 129.13, 128.80 (q, J^F = 32.2 Hz), 125.57 (q, J^F = 3.6 Hz), 124.36 (q, J^F = 271.6 Hz), 100.11, 83.28, 56.66, 53.67, 42.35, 36.04, 34.10, 28.11, 27.89, 27.40.

^{19}F NMR (470 MHz, $CDCl_3$): δ = –62.38.

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{21}H_{26}F_3NNaO_4$: 436.1706; found: 436.1715.

***tert*-Butyl (3a*R**,6*R**,6a*R**)-6-(4-Bromobenzyl)-6a-hydroxy-1-methyl-2-oxohexahydrocyclopenta[*b*]pyrrole-3a(1*H*)-carboxylate (8)**

Prepared according to the general procedure from **7** (0.05 mmol), SmI_2 (0.15 mmol, 3.0 equiv, 1.5 mL, 0.10 M), and H_2O (0.54 mL, 600 equiv) in THF (1.0 mL) for 15 min with workup by Et_2O/1.0 N aq HCl to give a white solid; yield: 16.0 mg (75%). Recrystallized from CH_2Cl_2–hexanes; mp 179–180 °C; dr >95:5; cyclization/reduction selectivity >95:5. The stereochemistry was determined by 2D NMR experiments and confirmed by X-ray analysis.

^{1}H NMR (500 MHz, acetone-d_6): δ = 7.47 (d, *J* = 8.1 Hz, 2 H), 7.22 (d, *J* = 8.0 Hz, 2 H), 5.11 (s, 1 H), 3.14 (d, *J* = 11.1 Hz, 1 H), 3.08 (d, *J* = 17.4 Hz, 1 H), 2.85 (s, 3 H), 2.53–2.36 (m, 3 H), 2.19 (d, *J* = 17.4 Hz, 1 H), 1.63–1.56 (m, 2 H), 1.45 (s, 9 H), 1.39–1.31 (m, 1 H).

^{13}C NMR (125 MHz, acetone-d_6): δ = 174.00, 172.74, 141.72, 132.17, 131.70, 120.11, 101.64, 81.63, 58.39, 53.85, 41.53, 35.74, 35.04, 28.44, 28.13, 27.79.

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{20}H_{26}BrNNaO_4$: 446.0937; found: 446.0938.

***tert*-Butyl (3a*R**,6*R**,6a*R**)-6-(3,5-Dichlorobenzyl)-6a-hydroxy-1-methyl-2-oxohexahydrocyclopenta[*b*]pyrrole-3a(1*H*)-carboxylate (10)**

Prepared according to the general procedure from **9** (0.05 mmol), SmI_2 (0.15 mmol, 3.0 equiv, 1.5 mL, 0.10 M), and H_2O (0.54 mL, 600 equiv) in THF (1.0 mL) for 15 min with workup by Et_2O/1.0 N aq HCl to

give a white solid; yield: 18.7 mg (90%). Recrystallized from CH_2Cl_2–hexanes; mp 189–190 °C; dr >95:5; cyclization/reduction selectivity >95:5. The stereochemistry was determined by 2D NMR experiments and confirmed by an X-ray analysis of a derivative.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.21 (s, 1 H), 7.06 (s, 2 H), 4.19 (s, 1 H), 3.11 (d, *J* = 10.7 Hz, 1 H), 2.94 (d, *J* = 17.5 Hz, 1 H), 2.93 (s, 3 H), 2.37 (d, *J* = 17.9 Hz, 1 H), 2.33–2.12 (m, 3 H), 1.73 (dd, *J* = 13.4, 6.1 Hz, 1 H), 1.62 (dt, *J* = 11.6, 5.6 Hz, 1 H), 1.48 (s, 9 H), 1.23 (dq, *J* = 12.1, 5.8 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.89, 173.06, 143.69, 134.95, 127.20, 126.60, 99.87, 83.25, 56.46, 53.43, 42.23, 35.58, 33.97, 28.00, 27.73, 27.25.

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{20}H_{25}Cl_2NNaO_4$: 436.1053; found: 436.1068.

tert-Butyl (3a*R**,6*R**,6a*R**)-6a-Hydroxy-1-methyl-6-(2-naphthylmethyl)-2-oxohexahydrocyclopenta[*b*]pyrrole-3a(1*H*)-carboxylate (12)

Prepared according to the general procedure from **11** (0.05 mmol), SmI_2 (0.15 mmol, 3.0 equiv, 1.5 mL, 0.10 M), and H_2O (0.54 mL, 600 equiv) in THF (1.0 mL) for 15 min with workup by Et_2O/1.0 N aq HCl to give a white solid; yield: 18.3 mg (93%). Recrystallized from CH_2Cl_2–hexanes; mp 193–195 °C; dr >95:5; cyclization/reduction selectivity >95:5. The stereochemistry was determined by 2D NMR experiments and confirmed by an X-ray analysis of a derivative.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.84–7.74 (m, 3 H), 7.61 (s, 1 H), 7.45 (p, *J* = 7.0 Hz, 2 H), 7.30 (d, *J* = 8.4 Hz, 1 H), 4.14 (s, 1 H), 3.32 (d, *J* = 8.4 Hz, 1 H), 3.01 (s, 3 H), 2.70 (d, *J* = 18.0 Hz, 1 H), 2.56–2.43 (m, 2 H), 2.41 (d, *J* = 18.0 Hz, 1 H), 2.18 (td, *J* = 12.7, 6.6 Hz, 1 H), 1.71 (dd, *J* = 13.4, 6.1 Hz, 1 H), 1.64–1.58 (m, 1 H), 1.49 (s, 9 H), 1.36–1.25 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.99, 173.14, 137.77, 133.54, 132.12, 128.14, 127.63, 127.45, 127.17, 127.00, 126.10, 125.43, 100.19, 83.08, 56.68, 53.83, 42.32, 36.21, 34.01, 28.00, 27.83, 27.48.

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{24}H_{29}NNaO_4$: 418.1989; found: 418.2002.

tert-Butyl (3a*R**,6*S**,6a*R**)-6a-Hydroxy-1,6-dimethyl-2-oxohexahydrocyclopenta[*b*]pyrrole-3a(1*H*)-carboxylate (14)

Prepared according to the general procedure from **13** (0.1 mmol), SmI_2 (0.80 mmol, 8.0 equiv, 8.0 mL, 0.10 M), and H_2O (2.16 mL, 1200 equiv) in THF (1.0 mL) for 1 h with workup by Et_2O/1.0 N aq HCl to give a white solid; yield: 20.7 mg (77%). Recrystallized from CH_2Cl_2–hexanes; dr >95:5; cyclization/reduction selectivity = 91:9. The stereochemistry was determined by 2D NMR experiments and confirmed by an X-ray analysis of a derivative.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.88 (s, 1 H), 2.95 (d, *J* = 17.8 Hz, 1 H), 2.91 (s, 3 H), 2.39–2.33 (m, 2 H), 2.23 (dt, *J* = 11.7, 6.6 Hz, 1 H), 1.86 (dtd, *J* = 12.3, 6.2, 2.4 Hz, 1 H), 1.75 (ddd, *J* = 13.0, 5.9, 2.3 Hz, 1 H), 1.50 (s, 9 H), 1.46 (d, *J* = 4.7 Hz, 1 H), 1.07 (d, *J* = 7.1 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.06, 173.01, 100.89, 83.03, 56.87, 46.31, 42.59, 34.25, 30.65, 28.14, 27.62, 14.73.

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{14}H_{23}NNaO_4$: 292.1519; found: 292.1527.

Ethyl (3a*R**,6*S**,6a*R**)-6a-Hydroxy-1,6-dimethyl-2-oxohexahydrocyclopenta[*b*]pyrrole-3a(1*H*)-carboxylate (16)

Prepared according to the general procedure from **15** (0.1 mmol), SmI_2 (0.80 mmol, 8.0 equiv, 8.0 mL, 0.10 M), and H_2O (2.16 mL, 1200 equiv) in THF (1.0 mL) for 1 h with workup by Et_2O/1.0 N aq HCl to give a white solid; yield: 13.3 mg (55%). Recrystallized from CH_2Cl_2–hexanes; dr >95:5; cyclization/reduction selectivity = 92:8. The stereochemistry was determined by 2D NMR experiments and confirmed by an X-ray analysis of a derivative.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.23 (q, *J* = 7.1 Hz, 2 H), 3.56 (s, 1 H), 3.00 (d, *J* = 17.8 Hz, 1 H), 2.89 (s, 3 H), 2.41 (dt, *J* = 12.7, 6.1 Hz, 1 H), 2.35 (d, *J* = 17.7 Hz, 1 H), 2.21 (tt, *J* = 12.8, 6.6 Hz, 1 H), 1.86 (dtd, *J* = 12.6, 6.4, 2.5 Hz, 1 H), 1.75 (ddd, *J* = 12.7, 5.7, 2.0 Hz, 1 H), 1.37–1.31 (m, 1 H), 1.30 (t, *J* = 7.0 Hz, 3 H), 1.06 (d, *J* = 7.0 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.67, 172.93, 101.03, 62.02, 56.58, 46.21, 42.42, 34.23, 30.75, 27.74, 14.66, 14.28.

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{12}H_{19}NNaO_4$: 264.1206; found: 264.1227.

(3a*S**,6*R**,6a*R**)-6a-Hydroxy-6-(4-methoxybenzyl)-1-methyl-3a-phenylhexahydrocyclopenta[*b*]pyrrol-2(1*H*)-one (18)

Prepared according to the general procedure from **17** (0.1 mmol), SmI_2 (0.80 mmol, 8.0 equiv, 8.0 mL, 0.10 M), and H_2O (2.16 mL, 1200 equiv) in THF (1.0 mL) for 1 h with workup by Et_2O/1.0 N aq HCl to give a white solid; yield: 32.5 mg (92%). Recrystallized from CH_2Cl_2–hexanes; mp 142–144 °C; dr >95:5; cyclization/reduction selectivity >95:5. The stereochemistry was determined by 2D NMR experiments and confirmed by an X-ray analysis of a derivative.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.41 (t, *J* = 7.6 Hz, 2 H), 7.32 (t, *J* = 7.5 Hz, 1 H), 7.27 (d, *J* = 7.8 Hz, 2 H), 7.09 (d, *J* = 8.2 Hz, 2 H), 6.83 (d, *J* = 8.2 Hz, 2 H), 3.79 (s, 3 H), 3.09–3.03 (m, 1 H), 2.96 (s, 3 H), 2.90 (d, *J* = 18.0 Hz, 1 H), 2.71 (d, *J* = 18.0 Hz, 1 H), 2.47–2.34 (m, 2 H), 2.33–2.25 (m, 1 H), 1.94–1.73 (m, 3 H), 1.48 (dp, *J* = 17.3, 6.2, 5.7 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.95, 158.15, 142.20, 132.38, 129.73, 129.46, 127.82, 126.53, 113.99, 100.85, 56.26, 55.38, 54.31, 46.00, 35.73, 34.10, 28.56, 27.71.

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{22}H_{25}NNaO_3$: 374.1727; found: 374.1738.

(3a*S**,6*R**,6a*R**)-6-(4-Bromobenzyl)-6a-hydroxy-1-methyl-3a-phenylhexahydrocyclopenta[*b*]pyrrol-2(1*H*)-one (20)

Prepared according to the general procedure from **19** (0.1 mmol), SmI_2 (0.80 mmol, 8.0 equiv, 8.0 mL, 0.10 M), and H_2O (2.16 mL, 1200 equiv) in THF (1.0 mL) for 1 h with workup by Et_2O/1.0 N aq HCl to give a white solid; yield: 35.5 mg (89%). Recrystallized from CH_2Cl_2–hexanes; mp 137–139 °C; dr >95:5; cyclization/reduction selectivity >95:5. The stereochemistry was determined by 2D NMR experiments and confirmed by an X-ray analysis of a derivative.

^{1}H NMR (500 MHz, acetone-d_6): δ = 7.47 (d, *J* = 8.3 Hz, 2 H), 7.39–7.27 (m, 4 H), 7.24 (d, *J* = 8.5 Hz, 2 H), 7.22 (t, *J* = 6.5 Hz, 1 H), 4.22 (s, 1 H), 3.16 (dd, *J* = 12.4, 2.8 Hz, 1 H), 2.91 (s, 3 H), 2.75 (d, *J* = 17.6 Hz, 1 H), 2.60 (d, *J* = 17.5 Hz, 1 H), 2.49 (t, *J* = 12.2 Hz, 1 H), 2.43–2.33 (m, 2 H), 1.88 (ddd, *J* = 13.0, 6.6, 1.9 Hz, 1 H), 1.68 (dtd, *J* = 12.9, 6.5, 2.0 Hz, 1 H), 1.54 (ddt, *J* = 18.4, 11.6, 6.7 Hz, 1 H).

^{13}C NMR (126 MHz, acetone-d_6): δ = 173.87, 144.61, 141.67, 132.14, 131.80, 128.87, 128.12, 127.20, 120.07, 101.31, 55.89, 54.92, 46.13, 36.42, 36.32, 28.25, 27.75.

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{21}H_{22}BrNNaO_2$: 422.0726; found: 422.0732.

***tert*-Butyl (3a*R**,6*E*,6a*R**)-6-Benzylidene-6a-hydroxy-1-methyl-2-oxohexahydrocyclopenta[*b*]pyrrole-3a(1*H*)-carboxylate (22)**

Prepared according to the general procedure from **21** (0.05 mmol), SmI_2 (0.15 mmol, 3.0 equiv, 1.5 mL, 0.10 M), and H_2O (0.54 mL, 600 equiv) in THF (1.0 mL) for 15 min with workup by Et_2O/1.0 N aq HCl to give a colorless oil; yield: 11.2 mg (65%); dr >95:5; cyclization/reduction selectivity = 75:25, *E*/*Z* >95:5. The stereochemistry was determined by 2D NMR experiments and confirmed by an X-ray analysis of a derivative.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.44–7.37 (m, 4 H), 7.28 (m, 1 H), 6.78 (s, 1 H), 3.70 (s, 1 H), 3.08 (d, *J* = 17.3 Hz, 1 H), 2.94–2.87 (m, 1 H), 2.80 (s, 3 H), 2.66–2.58 (m, 1 H), 2.44 (d, *J* = 17.3 Hz, 1 H), 2.37 (ddd, *J* = 14.4, 9.0, 5.9 Hz, 1 H), 1.86–1.78 (m, 1 H), 1.45 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.95, 172.53, 140.62, 136.50, 129.05, 128.59, 127.58, 125.89, 98.76, 82.87, 55.25, 39.59, 34.39, 28.10, 27.63, 24.49.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{25}NNaO_4$: 366.1676; found: 366.1684.

***tert*-Butyl (4a*R**,7*R**,7a*R**)-7-Benzyl-7a-hydroxy-1-methyl-2-oxooctahydro-4a*H*-cyclopenta[*b*]pyridine-4a-carboxylate (34)**

Prepared according to the general procedure from **33** (0.05 mmol), SmI_2 (0.15 mmol, 3.0 equiv, 1.5 mL, 0.10 M), and H_2O (0.54 mL, 600 equiv) in THF (1.0 mL) for 1 min with workup by Et_2O/1.0 N aq HCl to give a white solid; yield: 15.5 mg (86%); dr >95:5; cyclization/reduction selectivity >95:5. The stereochemistry was determined by 2D NMR experiments and confirmed by an X-ray analysis of a derivative.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.36 (t, *J* = 7.3 Hz, 1 H), 7.20 (t, *J* = 7.4 Hz, 2 H), 7.16 (d, *J* = 7.1 Hz, 2 H) 5.57 (s, 1 H), 3.04 (s, 3 H), 2.78 (d, *J* = 6.4 Hz, 1 H), 2.47 (dd, *J* = 7.3, 4.3 Hz, 1 H), 2.40–2.35 (m, 2 H), 2.29–2.23 (m, 2 H), 2.08–2.05 (m, 2 H), 1.94–1.82 (m, 3 H), 1.47 (s, 9 H).

The title compound was fully characterized after dehydration with TsOH (1.0 equiv) in CH2Cl2 (1.0 mL) at r.t. for 3 h to give ***tert*-butyl 7-benzyl-1-methyl-2-oxo-1,2,3,4,5,6-hexahydro-4a*H*-cyclopenta[*b*]pyridine-4a-carboxylate (34″)** as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.30 (t, *J* = 7.4 Hz, 2 H), 7.26–7.17 (m, 3 H), 3.74 (d, *J* = 16.0 Hz, 1 H), 3.52 (d, *J* = 16.0 Hz, 1 H), 3.28 (s, 3 H), 2.53 (ddt, *J* = 17.7, 14.8, 9.3 Hz, 3 H), 2.39 (ddd, *J* = 12.9, 6.5, 4.3 Hz, 1 H), 2.28 (dd, *J* = 12.9, 8.4 Hz, 1 H), 2.14 (dd, *J* = 15.5, 9.1 Hz, 1 H), 1.80–1.69 (m, 2 H), 1.46 (s, 9 H).

^{13}C NMR (125 MHz, 500 MHz, $CDCl_3$): δ = 173.95, 170.43, 138.92, 137.58, 128.58, 128.26, 126.31, 121.76, 81.27, 57.19, 34.75, 34.21, 34.12, 34.12, 31.40, 30.44, 28.08.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{27}NNaO_3$: 364.1883; found: 364.1894.

***tert*-Butyl (4a*R**,7*R**,7a*R**)-7a-Hydroxy-7-(4-methoxybenzyl)-1-methyl-2-oxooctahydro-4a*H*-cyclopenta[*b*]pyridine-4a-carboxylate (36)**

Prepared according to the general procedure from **35** (0.05 mmol), SmI_2 (0.15 mmol, 3.0 equiv, 1.5 mL, 0.10 M), and H_2O (0.54 mL, 600 equiv) in THF (1.0 mL) for 1 min with workup by Et_2O/1.0 N aq HCl to give a white solid; yield: 16.5 mg (85%); dr >95:5; cyclization/reduction selectivity >95:5. The stereochemistry was determined by 2D NMR experiments and confirmed by an X-ray analysis of a derivative.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.04 (d, *J* = 7.9 Hz, 2 H), 6.81 (d, *J* = 8.2 Hz, 2 H), 5.54 (s, 1 H), 3.77 (s, 3 H), 3.02 (s, 3 H), 2.75 (d, *J* = 12.8 Hz, 1 H), 2.56–2.47 (m, 2 H), 2.32 (dd, *J* = 18.6, 9.2 Hz, 1 H), 2.23–2.14 (m, 2 H), 2.05 (d, *J* = 7.4 Hz, 2 H), 1.92–1.81 (m, 3 H), 1.46 (s, 9 H).

The title compound was fully characterized by dehydration with TsOH (1.0 equiv) in CH2Cl2 (1.0 mL) at r.t. for 3 h to give ***tert*-butyl 7-(4-methoxybenzyl)-1-methyl-2-oxo-1,2,3,4,5,6-hexahydro-4a*H*-cyclopenta[*b*]pyridine-4a-carboxylate (36″)** as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.10 (d, *J* = 8.2 Hz, 2 H), 6.83 (d, *J* = 8.2 Hz, 2 H), 3.79 (s, 3 H), 3.66 (d, *J* = 15.9 Hz, 1 H), 3.45 (d, *J* = 15.8 Hz, 1 H), 3.27 (s, 3 H), 2.54 (dd, *J* = 16.4, 8.0 Hz, 3 H), 2.42–2.33 (m, 1 H), 2.30–2.22 (m, 1 H), 2.13 (dd, *J* = 15.1, 9.3 Hz, 1 H), 1.73 (tt, *J* = 18.9, 9.4 Hz, 2 H), 1.45 (s, 9 H).

^{13}C NMR (125 MHz, 500 MHz, $CDCl_3$): δ = 174.06, 170.53, 158.23, 137.36, 130.93, 129.27, 122.37, 114.09, 81.34, 57.29, 55.42, 34.32, 34.21, 34.15, 33.96, 31.51, 30.55, 28.17.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{22}H_{29}NNaO_4$: 394.1989; found: 394.1998.

***tert*-Butyl (4a*R**,7*R**,7a*R**)-7a-Hydroxy-1-methyl-2-oxo-7-[4-(trifluoromethyl)benzyl]octahydro-4a*H*-cyclopenta[*b*]pyridine-4a-carboxylate (38)**

Prepared according to the general procedure from **37** (0.05 mmol), SmI_2 (0.15 mmol, 3.0 equiv, 1.5 mL, 0.10 M), and H_2O (0.54 mL, 600 equiv) in THF (1.0 mL) for 1 min with workup by Et_2O/1.0 N aq HCl to give a white solid; yield: 18.5 mg (86%). Recrystallized from CH_2Cl_2–hexanes; mp 185–187 °C; dr >95:5; cyclization/reduction selectivity >95:5. The stereochemistry was determined by 2D NMR experiments and confirmed by an X-ray analysis of a derivative.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.54 (d, *J* = 7.9 Hz, 2 H), 7.25 (d, *J* = 7.6 Hz, 2 H), 5.60 (s, 1 H), 3.04 (s, 3 H), 2.87 (dd, *J* = 13.8, 3.5 Hz, 1 H), 2.63–2.51 (m, 2 H), 2.36–2.22 (m, 3 H), 2.20–1.99 (m, 3 H), 1.90 (tdd, *J* = 21.1, 9.1, 4.4 Hz, 2 H), 1.48 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.46, 169.46, 144.17, 129.15 (q, J^F = 32.7 Hz), 129.09, 125.60 (q, J^F = 3.7 Hz), 124.35 (q, J^F = 272.2 Hz), 96.20, 83.30, 54.91, 50.12, 40.03, 33.30, 29.11, 28.08, 28.04, 26.91, 26.83.

^{19}F NMR (470 MHz, $CDCl_3$): δ = –62.40.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{22}H_{28}F_3NNaO_4$: 450.1863; found: 450.1872.

***tert*-Butyl (4a*R**,7*R**,7a*R**)-7-(4-Bromobenzyl)-7a-hydroxy-1-methyl-2-oxooctahydro-4a*H*-cyclopenta[*b*]pyridine-4a-carboxylate (40)**

Prepared according to the general procedure from **39** (0.05 mmol), SmI_2 (0.15 mmol, 3.0 equiv, 1.5 mL, 0.10 M), and H_2O (0.54 mL, 600 equiv) in THF (1.0 mL) for 1 min with workup by Et_2O/1.0 N aq HCl to give a white solid; yield: 16.7 mg (76%); dr >95:5; cyclization/reduction selectivity >95:5. The stereochemistry was determined by 2D NMR experiments and confirmed by an X-ray analysis of a derivative.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.39 (d, *J* = 8.0 Hz, 2 H), 7.01 (d, *J* = 7.5 Hz, 2 H), 5.57 (s, 1 H), 3.02 (s, 3 H), 2.76 (d, *J* = 11.6 Hz, 1 H), 2.59–2.52 (m, 2 H), 2.36–2.27 (m, 3 H), 2.07–2.00 (m, 2 H), 1.95–1.85 (m, 3 H), 1.47 (s, 9 H).

The title compound was fully characterized by dehydration with TsOH (1.0 equiv) in CH_2Cl_2 (1.0 mL) at r.t. for 3 h to give ***tert*-butyl 7-(4-bromobenzyl)-1-methyl-2-oxo-1,2,3,4,5,6-hexahydro-4a*H*-cyclopenta[*b*]pyridine-4a-carboxylate** (**40″**) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.41 (d, *J* = 8.0 Hz, 2 H), 7.08 (d, *J* = 8.0 Hz, 2 H), 3.68 (d, *J* = 16.2 Hz, 1 H), 3.46 (d, *J* = 16.2 Hz, 1 H), 3.25 (s, 3 H), 2.52 (dt, *J* = 17.2, 9.8 Hz, 3 H), 2.43–2.34 (m, 1 H), 2.27 (dd, *J* = 12.4, 8.8 Hz, 1 H), 2.11 (dd, *J* = 15.2, 9.2 Hz, 1 H), 1.73 (dt, *J* = 21.9, 9.6 Hz, 2 H), 1.45 (s, 9 H).

^{13}C NMR (125 MHz, 500 MHz, $CDCl_3$): δ = 173.86, 170.44, 138.07, 138.04, 131.76, 130.09, 120.86, 120.23, 81.49, 57.30, 34.32, 34.23, 34.17, 34.14, 31.41, 30.49, 28.18.

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{21}H_{26}BrNNaO_3$: 442.0988; found: 442.0999.

tert-Butyl (4a*R**,7*R**,7a*R**)-7-(3,5-Dichlorobenzyl)-7a-hydroxy-1-methyl-2-oxooctahydro-4a*H*-cyclopenta[*b*]pyridine-4a-carboxylate (42)

Prepared according to the general procedure from **41** (0.05 mmol), SmI_2 (0.15 mmol, 3.0 equiv, 1.5 mL, 0.10 M), and H_2O (0.54 mL, 600 equiv) in THF (1.0 mL) for 1 min with workup by Et_2O/1.0 N aq HCl to give a white solid; yield: 15.2 mg (71%); dr >95:5; cyclization/reduction selectivity >95:5. The stereochemistry was determined by 2D NMR experiments and confirmed by an X-ray analysis of a derivative.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.20 (s, 1 H), 7.03 (s, 2 H), 5.58 (s, 1 H), 3.03 (s, 3 H), 2.77 (d, *J* = 13.7 Hz, 1 H), 2.52 (dd, *J* = 17.6, 5.2 Hz, 2 H), 2.35–2.16 (m, 3 H), 2.27 (d, *J* = 17.6 Hz, 1 H) 2.10–2.04 (m, 1 H), 2.03–1.90 (m, 2 H), 1.88–1.82 (m, 1 H), 1.47 (s, 9 H).

The title compound was fully characterized by dehydration with TsOH (1.0 equiv) in CH_2Cl_2 (1.0 mL) at r.t. for 3 h to give ***tert*-butyl 7-(3,5-dichlorobenzyl)-1-methyl-2-oxo-1,2,3,4,5,6-hexahydro-4a*H*-cyclopenta[*b*]pyridine-4a-carboxylate** (**42″**) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.23 (s, 1 H), 7.08 (s, 2 H), 3.73 (d, *J* = 16.3 Hz, 1 H), 3.46 (d, *J* = 16.3 Hz, 1 H), 3.25 (s, 3 H), 2.59–2.48 (m, 3 H), 2.39 (ddd, *J* = 13.3, 6.6, 4.1 Hz, 1 H), 2.31 (dd, *J* = 13.1, 8.3 Hz, 1 H), 2.12 (dd, *J* = 15.5, 9.1 Hz, 1 H), 1.80–1.71 (m, 2 H), 1.47 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.77, 170.40, 142.57, 138.98, 135.33, 126.87, 126.81, 119.40, 81.72, 57.32, 34.45, 34.34, 34.18, 34.14, 31.42, 30.46, 28.21.

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{21}H_{25}Cl_2NNaO_3$: 432.1104; found: 432.1115.

tert-Butyl (4a*R**,7*R**,7a*R**)-7-(3,4-Difluorobenzyl)-7a-hydroxy-1-methyl-2-oxooctahydro-4a*H*-cyclopenta[*b*]pyridine-4a-carboxylate (44)

Prepared according to the general procedure from **43** (0.05 mmol), SmI_2 (0.15 mmol, 3.0 equiv, 1.5 mL, 0.10 M), and H_2O (0.54 mL, 600 equiv) in THF (1.0 mL) for 1 min with workup by Et_2O/1.0 N aq HCl to give a white solid; yield: 17.2 mg (87%); dr >95:5; cyclization/reduction selectivity >95:5. The stereochemistry was determined by 2D NMR experiments and confirmed by an X-ray analysis of a derivative.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.05 (dtd, *J* = 10.6, 8.2, 2.5 Hz, 1 H), 6.99–6.91 (m, 1 H), 6.89–6.79 (m, 1 H), 5.57 (d, *J* = 2.4 Hz, 1 H), 3.02 (s, 3 H), 2.77 (d, *J* = 13.9 Hz, 1 H), 2.57–2.46 (m, 2 H), 2.37–2.16 (m, 4 H), 2.10–1.98 (m, 2 H), 1.94–1.81 (m, 2 H), 1.47 (s, 9 H).

The title compound was fully characterized by dehydration with TsOH (1.0 equiv) in CH_2Cl_2 (1.0 mL) at r.t. for 3 h to give ***tert*-butyl 7-(3,4-difluorobenzyl)-1-methyl-2-oxo-1,2,3,4,5,6-hexahydro-4a*H*-cyclopenta[*b*]pyridine-4a-carboxylate** (**44″**) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.08 (q, *J* = 8.5 Hz, 1 H), 7.04–6.98 (m, 1 H), 6.92 (s, 1 H), 3.71 (d, *J* = 16.2 Hz, 1 H), 3.46 (d, *J* = 16.3 Hz, 1 H), 3.25 (s, 3 H), 2.52 (tt, *J* = 9.9, 5.4 Hz, 3 H), 2.40 (ddd, *J* = 13.4, 6.8, 3.9 Hz, 1 H), 2.28 (dd, *J* = 13.2, 8.5 Hz, 1 H), 2.12 (dd, *J* = 15.4, 9.2 Hz, 1 H), 1.75 (dddd, *J* = 15.8, 13.0, 8.1, 5.0 Hz, 2 H), 1.46 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.81, 171.43, 151.10 (d, J^F = 192.0 Hz), 148.80 (dd, J^F = 178.2, 12.6 Hz), 138.40, 136.02 (d, J^F = 4.3 Hz), 124.13 (q, J^F = 3.8 Hz), 120.33, 117.42 (d, J^F = 17.1 Hz), 117.16 (d, J^F = 17.3 Hz), 81.64, 57.33, 34.18, 34.17, 34.16, 34.06, 31.39, 30.46, 28.17.

^{19}F NMR (470 MHz, $CDCl_3$): δ = –137.63 (d, *J* = 21.0 Hz), –141.32 (d, *J* = 21.4 Hz).

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{21}H_{25}F_2NNaO_3$: 400.1695; found: 400.1704.

tert-Butyl (4a*R**,7*R**,7a*R**)-7a-Hydroxy-7-(mesitylmethyl)-1-methyl-2-oxooctahydro-4a*H*-cyclopenta[*b*]pyridine-4a-carboxylate (46)

Prepared according to the general procedure from **45** (0.05 mmol), SmI_2 (0.15 mmol, 3.0 equiv, 1.5 mL, 0.10 M), and H_2O (0.54 mL, 600 equiv) in THF (1.0 mL) for 1 min with workup by Et_2O/1.0 N aq HCl to give a white solid; yield: 12.4 mg (62%); dr >95:5; cyclization/reduction selectivity = 78:22. The stereochemistry was determined by 2D NMR experiments and confirmed by an X-ray analysis of a derivative.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.82 (s, 2 H), 5.52 (s, 1 H), 3.09 (s, 3 H), 2.66–2.59 (m, 2 H), 2.56–2.51 (m, 2 H), 2.38–2.34 (m, 1 H), 2.25 (s, 3 H), 2.23 (s, 6 H), 2.15–2.10 (m, 2 H), 1.86 (ddt, *J* = 10.7, 6.8, 3.3 Hz, 2 H), 1.72 (dt, *J* = 9.6, 4.4 Hz, 2 H), 1.47 (s, 9 H).

The title compound was fully characterized by dehydration with TsOH (1.0 equiv) in CH_2Cl_2 (1.0 mL) at r.t. for 3 h to give ***tert*-butyl 7-(mesitylmethyl)-1-methyl-2-oxo-1,2,3,4,5,6-hexahydro-4a*H*-cyclopenta[*b*]pyridine-4a-carboxylate** (**46″**) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.82 (s, 2 H), 3.64 (d, *J* = 15.7 Hz, 1 H), 3.52 (d, *J* = 15.7 Hz, 1 H), 3.38 (s, 3 H), 2.54–2.40 (m, 2 H), 2.34–2.26 (m, 3 H), 2.25 (s, 3 H), 2.21 (s, 6 H), 1.83 (dd, *J* = 14.0, 8.8 Hz, 1 H), 1.70 (dt, *J* = 13.4, 8.1 Hz, 1 H), 1.53 (dd, *J* = 9.0, 3.8 Hz, 1 H), 1.43 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.12, 171.03, 136.62, 136.46, 135.80, 132.60, 129.08, 124.13, 81.25, 57.22, 35.27, 34.06, 31.89, 31.64, 30.76, 28.69, 28.15, 20.97, 20.26.

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{24}H_{33}NNaO_3$: 406.2353; found: 406.2363.

tert-Butyl (4a*R**,7*R**,7a*R**)-7-(2-Fluorobenzyl)-7a-hydroxy-1-methyl-2-oxooctahydro-4a*H*-cyclopenta[*b*]pyridine-4a-carboxylate (48)

Prepared according to the general procedure from **47** (0.05 mmol), SmI_2 (0.15 mmol, 3.0 equiv, 1.5 mL, 0.10 M), and H_2O (0.54 mL, 600 equiv) in THF (1.0 mL) for 1 min with workup by Et_2O/1.0 N aq HCl to give a white solid; yield: 12.7 mg (67%); dr >95:5; cyclization/reduction selectivity >95:5. The stereochemistry was determined by 2D NMR experiments and confirmed by an X-ray analysis of a derivative.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.21–7.16 (m, 1 H), 7.14 (t, *J* = 6.9 Hz, 1 H), 7.06 (d, *J* = 7.3 Hz, 1 H), 7.04–6.96 (m, 1 H), 5.55 (s, 1 H), 3.05 (s, 3 H), 2.76 (d, *J* = 13.5 Hz, 1 H), 2.61–2.48 (m, 2 H), 2.41–2.21 (m, 4 H), 2.08 (d, *J* = 10.2 Hz, 2 H), 1.91–1.82 (m, 2 H), 1.47 (s, 9 H).

The title compound was fully characterized by dehydration with TsOH (1.0 equiv) in CH_2Cl_2 (1.0 mL) at r.t. for 3 h to give ***tert*-butyl 7-(2-fluorobenzyl)-1-methyl-2-oxo-1,2,3,4,5,6-hexahydro-4a*H*-cyclopenta[*b*]pyridine-4a-carboxylate** (**48″**) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.24–7.17 (m, 2 H), 7.07 (t, *J* = 7.5 Hz, 1 H), 7.03 (t, *J* = 9.1 Hz, 1 H), 3.69 (d, *J* = 16.4 Hz, 1 H), 3.56 (d, *J* = 16.4 Hz, 1 H), 3.27 (s, 3 H), 2.58–2.47 (m, 3 H), 2.38 (ddd, *J* = 13.3, 6.7, 4.2 Hz, 1 H), 2.28 (ddd, *J* = 13.1, 8.2, 1.7 Hz, 1 H), 2.14 (dd, *J* = 15.6, 9.1 Hz, 1 H), 1.80–1.69 (m, 2 H), 1.45 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.96, 170.53, 162.20 (d, J^F = 246.0 Hz), 138.06, 130.03 (d, J^F = 4.5 Hz), 128.20 (d, J^F = 7.9 Hz), 125.95 (d, J^F = 16.0 Hz), 124.23 (d, J^F = 3.6 Hz), 120.51, 115.38 (d, J^F = 21.4 Hz), 81.43, 57.35, 34.15, 34.10, 31.44, 30.52, 28.17, 28.02, 27.99.

^{19}F NMR (470 MHz, $CDCl_3$): δ = –117.42.

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{21}H_{26}FNNaO_3$: 382.1789; found: 382.1798.

tert-Butyl (4a*R**,7*R**,7a*R**)-7-(1,3-Benzodioxol-5-ylmethyl)-7a-hydroxy-1-methyl-2-oxooctahydro-4a*H*-cyclopenta[*b*]pyridine-4a-carboxylate (50)

Prepared according to the general procedure from **49** (0.05 mmol), SmI_2 (0.15 mmol, 3.0 equiv, 1.5 mL, 0.10 M), and H_2O (0.54 mL, 600 equiv) in THF (1.0 mL) for 1 min with workup by Et_2O/1.0 N aq HCl to give a white solid; yield: 14.1 mg (70%); dr >95:5; cyclization/reduction selectivity >95:5. The stereochemistry was determined by 2D NMR experiments and confirmed by an X-ray analysis of a derivative.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.71 (d, *J* = 7.9 Hz, 1 H), 6.62 (s, 1 H), 6.57 (d, *J* = 8.0 Hz, 1 H), 5.91 (s, 2 H), 5.54 (s, 1 H), 3.02 (s, 3 H), 2.73 (dd, *J* = 13.7, 3.7 Hz, 1 H), 2.51 (d, *J* = 17.0 Hz, 2 H), 2.35–2.20 (m, 3 H), 2.15 (t, *J* = 13.0 Hz, 1 H), 2.08–2.00 (m, 2 H), 1.92–1.80 (m, 2 H), 1.47 (s, 9 H).

The title compound was fully characterized by dehydration with TsOH (1.0 equiv) in CH_2Cl_2 (1.0 mL) at r.t. for 3 h to give ***tert*-butyl 7-(1,3-benzodioxol-5-ylmethyl)-1-methyl-2-oxo-1,2,3,4,5,6-hexahydro-4a*H*-cyclopenta[*b*]pyridine-4a-carboxylate** (**50″**) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.74 (d, *J* = 7.9 Hz, 1 H), 6.68 (s, 1 H), 6.65 (d, *J* = 7.9 Hz, 1 H), 5.93 (s, 2 H), 3.65 (d, *J* = 15.9 Hz, 1 H), 3.43 (d, *J* = 16.0 Hz, 1 H), 3.27 (s, 3 H), 2.60–2.47 (m, 3 H), 2.38 (ddd, *J* = 13.2, 6.7, 4.2 Hz, 1 H), 2.31–2.25 (m, 1 H), 2.14 (dd, *J* = 15.6, 9.0 Hz, 1 H), 1.78–1.69 (m, 2 H), 1.46 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.03, 170.53, 148.05, 146.17, 137.63, 132.77, 121.94, 121.14, 108.78, 108.41, 101.08, 81.48, 57.32, 34.50, 34.27, 34.23, 34.16, 31.50, 30.54, 28.20.

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{22}H_{27}NNaO_5$: 408.1781; found: 408.1791.

tert-Butyl (4a*R**,7*R**,7a*R**)-7a-Hydroxy-1-methyl-7-(2-naphthylmethyl)-2-oxooctahydro-4a*H*-cyclopenta[*b*]pyridine-4a-carboxylate (52)

Prepared according to the general procedure from **51** (0.05 mmol), SmI_2 (0.15 mmol, 3.0 equiv, 1.5 mL, 0.10 M), and H_2O (0.54 mL, 600 equiv) in THF (1.0 mL) for 1 min with workup by Et_2O/1.0 N aq HCl to give a white solid; yield: 14.6 mg (71%); dr >95:5; cyclization/reduction selectivity >95:5. The stereochemistry was determined by 2D NMR experiments and confirmed by an X-ray analysis of a derivative.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.78 (dd, *J* = 14.4, 8.0 Hz, 3 H), 7.57 (s, 1 H), 7.44 (dq, *J* = 14.7, 6.8 Hz, 2 H), 7.28 (d, *J* = 8.4 Hz, 1 H), 5.60 (s, 1 H), 3.10 (s, 3 H), 2.99 (d, *J* = 11.8 Hz, 1 H), 2.75–2.66 (m, 1 H), 2.59–2.53 (m, 1 H), 2.41 (t, *J* = 12.8 Hz, 1 H), 2.35 (td, *J* = 12.5, 6.1 Hz, 1 H), 2.31–2.22 (m, 2 H), 2.11 (tt, *J* = 9.5, 5.9 Hz, 2 H), 1.90–1.83 (m, 2 H), 1.48 (s, 9 H).

The title compound was fully characterized by dehydration with TsOH (1.0 equiv) in CH_2Cl_2 (1.0 mL) at r.t. for 3 h to give ***tert*-butyl 1-methyl-7-(2-naphthylmethyl)-2-oxo-1,2,3,4,5,6-hexahydro-4a*H*-cyclopenta[*b*]pyridine-4a-carboxylate** (**52″**) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.86–7.74 (m, 3 H), 7.63 (s, 1 H), 7.46 (t, *J* = 7.3 Hz, 2 H), 7.33 (d, *J* = 8.2 Hz, 1 H), 3.88 (d, *J* = 16.0 Hz, 1 H), 3.70 (d, *J* = 15.9 Hz, 1 H), 3.33 (s, 3 H), 2.63–2.50 (m, 3 H), 2.44–2.36 (m, 1 H), 2.35–2.27 (m, 1 H), 2.18 (dd, *J* = 15.2, 9.1 Hz, 1 H), 1.84–1.70 (m, 2 H), 1.49 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.92, 170.46, 137.72, 136.49, 133.62, 132.19, 128.24, 127.68, 127.45, 126.88, 126.44, 126.19, 125.52, 121.81, 81.27, 57.23, 35.02, 34.36, 34.12, 34.06, 31.45, 30.49, 28.11.

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{25}H_{29}NNaO_3$: 414.2040; found: 414.2044.

tert-Butyl (4a*R**,7*R**,7a*R**)-7-(Diphenylmethyl)-7a-hydroxy-1-methyl-2-oxooctahydro-4a*H*-cyclopenta[*b*]pyridine-4a-carboxylate (54)

Prepared according to the general procedure from **53** (0.05 mmol), SmI_2 (0.15 mmol, 3.0 equiv, 1.5 mL, 0.10 M), and H_2O (0.54 mL, 600 equiv) in THF (1.0 mL) for 1 min with workup by Et_2O/1.0 N aq HCl to give a colorless solid; yield: 21.3 mg (98%). Recrystallized from CH_2Cl_2–hexanes; mp 195–196 °C; dr >95:5; cyclization/reduction selectivity >95:5. The stereochemistry of the major diastereoisomer was determined by 2D NMR experiments and confirmed by X-ray analysis.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.29 (d, *J* = 7.2 Hz, 3 H), 7.25–7.19 (m, 5 H), 7.12 (q, *J* = 7.2 Hz, 2 H), 5.52 (s, 1 H), 3.75 (d, *J* = 10.8 Hz, 1 H), 3.36 (q, *J* = 9.9 Hz, 1 H), 2.60 (d, *J* = 17.3 Hz, 1 H), 2.37 (dt, *J* = 18.9, 10.6 Hz, 1 H), 2.18 (q, *J* = 10.9 Hz, 1 H), 2.08–1.98 (m, 3 H), 2.03 (s, 3 H), 1.70–1.64 (m, 1 H), 1.54–1.48 (m, 1 H), 1.44 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.42, 168.88, 144.73, 144.36, 128.94, 128.76, 128.35, 127.95, 126.54, 126.47, 96.16, 83.12, 56.94, 55.18, 52.68, 32.45, 29.11, 28.90, 28.07, 27.42, 24.71.

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{27}H_{33}NNaO_4$: 458.2302; found: 458.2312.

tert-Butyl (4a*R**,7*R**,7a*R**)-7a-Hydroxy-1-methyl-2-oxo-7-[(1*E*)-3-phenylprop-1-en-1-yl]octahydro-4a*H*-cyclopenta[*b*]pyridine-4a-carboxylate (56)

Prepared according to the general procedure from **55** (0.05 mmol), SmI_2 (0.15 mmol, 3.0 equiv, 1.5 mL, 0.10 M), and H_2O (0.54 mL, 600 equiv) in THF (1.0 mL) for 1 min with workup by Et_2O/1.0 N aq HCl to give a white solid; yield: 18.1 mg (94%); dr >95:5; cyclization/reduction selectivity >95:5. The stereochemistry was determined by 2D NMR experiments and confirmed by an X-ray analysis of a derivative.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.29–7.26 (m, 2 H), 7.18 (t, *J* = 7.3 Hz, 1 H), 7.11 (d, *J* = 7.2 Hz, 2 H), 5.61 (dt, *J* = 14.3, 6.7 Hz, 1 H), 5.48 (s, 1 H), 5.29 (dd, *J* = 15.1, 8.7 Hz, 1 H), 3.30 (d, *J* = 6.8 Hz, 2 H), 2.87 (s, 3 H), 2.44 (d, *J* = 17.9 Hz, 1 H), 2.32–2.23 (m, 2 H), 2.23–2.19 (m, 1 H), 2.16 (d, *J* = 5.4 Hz, 1 H), 1.98–1.93 (m, 2 H), 1.85–1.78 (m, 1 H), 1.71–1.64 (m, 1 H), 1.46 (s, 9 H).

The title compound was fully characterized by dehydration with TsOH (1.0 equiv) in CH_2Cl_2 (1.0 mL) at r.t. for 3 h to give ***tert*-butyl 1-methyl-2-oxo-7-[(1*E*)-3-phenylprop-1-en-1-yl]-1,2,3,4,5,6-hexahydro-4a*H*-cyclopenta[*b*]pyridine-4a-carboxylate** (**56″**) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.30 (t, *J* = 7.4 Hz, 2 H), 7.22 (d, *J* = 7.1 Hz, 1 H), 7.19 (d, *J* = 7.5 Hz, 2 H), 6.45 (d, *J* = 15.4 Hz, 1 H), 5.74 (dt, *J* = 14.3, 6.8 Hz, 1 H), 3.48 (d, *J* = 6.9 Hz, 2 H), 3.28 (s, 3 H), 2.65–2.57 (m, 1 H), 2.53–2.43 (m, 3 H), 2.39–2.29 (m, 2 H), 1.76–1.67 (m, 2 H), 1.41 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.72, 170.45, 140.09, 137.38, 131.41, 128.78, 128.66, 126.40, 125.02, 121.34, 81.45, 57.17, 39.78, 35.86, 33.85, 31.55, 30.99, 30.39, 28.10.

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{23}H_{29}NNaO_3$: 390.2040; found: 390.2050.

tert-Butyl (3a*R**,6a*R**)-6-(2-Butoxy-2-oxoethyl)-6a-hydroxy-1-methyl-2-oxohexahydrocyclopenta[*b*]pyrrole-3a(1*H*)-carboxylate (66)

Prepared according to the general procedure from **65** (0.05 mmol), SmI_2 (0.15 mmol, 3.0 equiv, 1.5 mL, 0.10 M) and *t*-BuOH (24 equiv) in THF (1.0 mL) for 2 h with workup by Et_2O/1.0 N aq HCl to give a colorless oil; yield: 16.8 mg (91%); dr = 75:25 (2 diastereoisomers); cyclization/reduction selectivity >95:5. The stereochemistry of the major diastereoisomer was determined by 2D NMR experiments and confirmed by an X-ray analysis of a derivative. The stereochemistry of the minor diastereoisomer not assigned.

^{1}H NMR (500 MHz, $CDCl_3$): δ (major diastereoisomer) = 4.82 (s, 1 H), 4.11 (t, *J* = 5.5 Hz, 2 H), 3.10 (d, *J* = 17.5 Hz, 1 H), 2.82 (s, 3 H), 2.65–2.59 (m, 2 H), 2.52–2.39 (m, 2 H), 2.27 (d, *J* = 17.0 Hz, 1 H), 1.96–1.85 (m, 3 H), 1.62 (t, *J* = 7.5 Hz, 2 H), 1.47 (s, 9 H), 1.37 (q, *J* = 7.5 Hz, 2 H), 0.93 (t, *J* = 7.5 Hz, 3 H); δ (minor diastereoisomer) = 4.48 (s, 1 H), 4.12 (m, 2 H), 2.86 (s, 3 H), 2.76–2.71 (m, 2 H), 2.52–2.39 (m, 2 H), 2.34–2.31 (m, 2 H), 2.17–2.08 (m, 2 H), 1.97–1.93 (m, 1 H), 1.62 (t, *J* = 7.5 Hz, 2 H), 1.46 (s, 9 H), 1.37 (q, *J* = 7.5 Hz, 2 H), 0.93 (t, *J* = 7.5 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ (major diastereoisomer) = 174.18, 173.76, 172.76, 100.48, 82.60, 65.28, 57.13, 47.49, 41.73, 34.69, 34.56, 30.68, 28.77, 28.12, 27.45, 19.22, 13.77; δ (minor diastereoisomer) = 174.39, 171.12, 169.53, 89.05, 81.87, 65.35, 56.31, 49.72, 40.09, 36.03, 29.83, 28.11, 27.99, 27.88, 26.00, 19.21, 13.79.

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{19}H_{31}NNaO_6$: 392.2044; found: 392.2054.

tert-Butyl (4a*R**,7a*R**)-7-(2-Butoxy-2-oxoethyl)-7a-hydroxy-1-methyl-2-oxooctahydro-4a*H*-cyclopenta[*b*]pyridine-4a-carboxylate (68).

Prepared according to the general procedure from **67** (0.05 mmol), SmI_2 (0.15 mmol, 3.0 equiv, 1.5 mL, 0.10 M) and *t*-BuOH (24 equiv) in THF (1.0 mL) for 2 h with workup by Et_2O/1.0 N aq HCl to give a colorless oil; yield: 16.7 mg (87%); dr = 60:40 (2 diastereoisomers); cyclization/reduction selectivity >95:5. The stereochemistry of the major diastereoisomer was determined by 2D NMR experiments and confirmed by an X-ray analysis of a derivative. The stereochemistry of the minor diastereoisomer not assigned.

The title compound was fully characterized by dehydration with TsOH (1.0 equiv) in CH_2Cl_2 (1.0 mL) at r.t. for 3 h to give ***tert*-butyl 7-(2-butoxy-2-oxoethyl)-1-methyl-2-oxo-1,2,3,4,5,6-hexahydro-4a*H*-cyclopenta[*b*]pyridine-4a-carboxylate** (**68″**) as a colorless oil; yield: 15.1 mg (95%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.10 (t, *J* = 6.6 Hz, 2 H), 3.35 (s, 1 H), 3.31 (s, 3 H), 3.18 (d, *J* = 15.7 Hz, 1 H), 2.65 (dt, *J* = 16.8, 8.6 Hz, 1 H), 2.50 (dp, *J* = 18.0, 6.5 Hz, 2 H), 2.39–2.26 (m, 2 H), 1.78–1.69 (m, 2 H), 1.64–1.58 (m, 3 H), 1.42 (s, 9 H), 1.40–1.34 (m, 2 H), 0.93 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.61, 170.59, 170.42, 138.97, 116.01, 81.40, 64.99, 57.10, 35.22, 34.65, 34.35, 34.15, 31.31, 30.78, 30.41, 28.08, 19.26, 13.82.

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{20}H_{31}NNaO_5$: 388.2094; found: 388.2103.

Selectivity Studies; General Procedure

An oven-dried vial containing a stirrer bar was placed under a positive pressure of argon and subjected to three evacuation/backfilling cycles under high vacuum. A solution of the two substrates (each 0.10 mmol, 1.0 equiv) in THF (2.0 mL) was added followed by H_2O (0.18 mL, 200 equiv) and a 0.10 M soln of SmI_2 in THF (0.10 mmol, 1.0 equiv) with vigorous stirring, which resulted in the formation of the characteristic burgundy-red color of the $SmI_2(H_2O)_n$ complex (*n* > 5 with respect to SmI_2). The mixture was stirred until it decolorized and it was then diluted with Et_2O (30 mL) and 1 N aq HCl (30 mL). The aqueous layer was extracted with Et_2O (3 × 30 mL), and the organic layers were combined, dried (Na_2SO_4), filtered, and concentrated. The sample was analyzed by ^{1}H NMR ($CDCl_3$, 500 MHz) and GC-MS to determine the conversion and yield by using an internal standard and by comparison with authentic samples.

Determination of the Effect of Concentration of SmI_2 on the Rate of Reduction; General Procedure

The cyclic imide (0.05 mmol) was treated with SmI_2 (8 equiv), and H_2O (1200 equiv) in THF for 2 h at r.t. according to the general procedure. After the standard workup, the mixture was diluted with Et_2O (30 mL) and 1 N aq HCl (30 mL). The aqueous layer was extracted with Et_2O (3 × 30 mL), and the organic layers were combined, dried (Na_2SO_4), filtered, and concentrated. The sample was analyzed by ^{1}H NMR ($CDCl_3$, 500 MHz) and GC-MS to determine the conversion and yield by using an internal standard and by comparison with authentic samples.

Determination of Deuterium Incorporation; General Procedure

The cyclic imide (0.05 mmol) was treated with SmI_2 (3–8 equiv) and D_2O (600–1200 equiv) in THF (2.0 mL) for the indicated time at r.t. according to the general procedure. After standard workup as described above, the mixture was diluted with Et_2O (30 mL) and 1 N aq HCl (30 mL). The aqueous layer was extracted with Et_2O (3 × 30 mL), and the organic layers were combined, dried (Na_2SO_4), filtered, and concentrated. The sample was analyzed by ^{1}H NMR ($CDCl_3$, 500 MHz) and ESI-MS to determine the deuterium incorporation.

Determination of Kinetic Isotope Effect; General Procedure

The cyclic imide (0.05 mmol) was treated with SmI_2 (3–8 equiv) and 1:1 H_2O–D_2O (600–1200 equiv) in THF (2.0 mL) for the indicated time at r.t. according to the general procedure. After the standard workup as described above, the mixture was diluted with Et_2O (30 mL) and 1 N aq HCl (30 mL). The aqueous layer was extracted with Et_2O (3 × 30 mL), and the organic layers were combined, dried (Na_2SO_4), filtered, and concentrated. The sample was analyzed by ^{1}H NMR ($CDCl_3$, 500 MHz) and ESI-MS to determine the deuterium incorporation.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1560437.

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(57) Crystallographic data for compounds **8** and **54** have been deposited with the accession numbers CCDC 1449857 and 1449896, respectively, and can be obtained free of charge from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: +44(1223)336033; E-mail: deposit@ccdc.cam.ac.uk; Web site: www.ccdc.cam.ac.uk/conts/retrieving.html.
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