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Dearomatizing Radical Cyclizations and Cyclization Cascades Triggered by Electron-Transfer Reduction of Amide-Type Carbonyls

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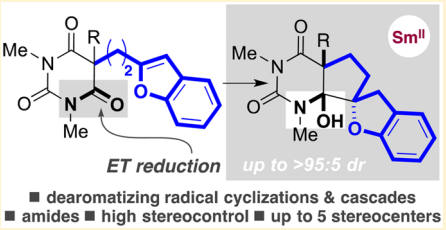
Supporting Information

ABSTRACT: Highly selective dearomatizing radical cyclizations and cyclization cascades, triggered by single electron transfer to amide-type carbonyls by SmI_2–H_2O–LiBr, provide efficient access to unprecedented spirocyclic scaffolds containing up to five stereocenters with high diastereocontrol. The first dearomatizing radical cyclizations involving radicals derived from amide carbonyls by single electron transfer take place under mild conditions and engage a range of aromatic and heteroaromatic systems present in the barbiturate substrates. The radical cyclizations deliver new polycyclic hemiaminals or enamines selectively, depending on the conditions employed, that are based on a medicinally proven scaffold and can be readily manipulated.



1. INTRODUCTION

Dearomatization is a powerful strategy for the construction of diverse three-dimensional structures, including complex, polycyclic scaffolds and natural products, from simple aromatic starting materials.[1] Successful approaches to dearomatization involve, for example, oxidation, cycloaddition, alkylation, arylation, and C–H activation.[2] Radical cyclizations can also be used to achieve dearomatization,[3] and although major advances have been made in this field, the development of new strategies for dearomatization by radical addition, particular those that deliver novel heterocyclic architectures, is an important goal.[1−3] SmI_2 is a highly versatile, commercially available or readily prepared electron transfer (ET) reductant.[4] SmI_2-mediated dearomatizing cyclizations and cyclization cascades have recently been developed, with seminal contributions coming from the teams of Schmalz,[5] Reissig,[6] Fang,[7] Tanaka,[8] Yamashita,[9] Wang and Li.[10] Of particular note, Reissig has exploited an impressive SmI_2-induced dearomatizing cyclization cascade in a concise total synthesis of Strychnine.[6p,s,v] Despite the progress made, until now, SmI_2-mediated dearomatizing reactions were limited to radicals derived from ketone or aldehyde substrates (Scheme 1A). Furthermore, few examples of radical cascade cyclizations involving dearomatization have been reported.[6d,f,p,q,s,v,9] The amide functional group is widely found in biological molecules, pharmaceuticals, natural products, and functional materials.[11] However, because of their resistance to reduction, developing cyclizations and cascades involving ET reduction of amide carbonyls is challenging.[12] Herein, we demonstrate the feasibility of SmI_2-mediated dearomatizing cyclizations and cyclization cascades involving radicals **1** formed by ET reduction of amide-type carbonyls (Scheme 1B).

The processes involve two ET events, thus requiring approximately 2 equiv of the commercial reagent, and construct complex medicinally relevant, polycyclic barbiturates containing up to five stereocenters with high diastereoselectivity.[13] The spirocyclic scaffolds accessible are related to those found in biologically active products, drug targets, and natural products (Scheme 1C).[14]

2. RESULTS AND DISCUSSION

Optimization of the First Dearomatizing Radical Cyclizations of Amides: The Key Role of LiBr. Barbiturate **2a** is available in three steps from commercially available 1,3-dimethylbarbituric acid and was selected as a model substrate for optimization studies. Treatment of **2a** with SmI_2 in THF returned only starting material (Table 1, entry 1). Upon activation of SmI_2 by H_2O,[15] the desired product of dearomatizing cyclization **3a** was obtained in 20% yield, with 32% of **2a** recovered (entry 2). The addition of LiBr to SmI_2[16] gave **3a** in 40% NMR yield (entry 3). However, when LiBr was added to SmI_2 *and* H_2O, the reaction delivered cyclized product **3a** in 78% isolated yield with excellent diastereocontrol (>95:5 dr) (entry 4). Increasing the amount of H_2O did not have a beneficial effect on the reaction (entry 5).

Flowers has proposed that the combination of SmI_2 and LiBr generates a soluble form of $SmBr_2$ *in situ*.[17] Thus, the addition of LiBr may generate $SmBr_2$–H_2O or the ate complex $SmBr_3^-Li^+$–H_2O.[18,19] $SmBr_2$ (approximately −1.55 V vs SCE) has a higher reduction potential than SmI_2 (−0.9 V vs SCE).[17,18] It is therefore surprising that the radical intermediates in dearomatizing cyclizations (cf. **1** in Scheme 1) and cyclization cascades (cf. **13** in Scheme 7) appear less susceptible to reduction to the anion under the SmI_2–H_2O/LiBr conditions and radical cyclization is more efficient. A hindered approach of Sm(II), in the modified reagent system, to the radicals may result in a slower outer-sphere ET process.

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Scheme 1. (A) Known Dearomatizating Radical Cyclizations of Aldehydes and Ketones with Unknown Dearomatizating Radical Cyclizations of Amides; (B) Dearomatizing Radical Cyclizations and Cyclization Cascades of Barbiturates; (C) Importance of Spiro-heterocyclic Scaffolds

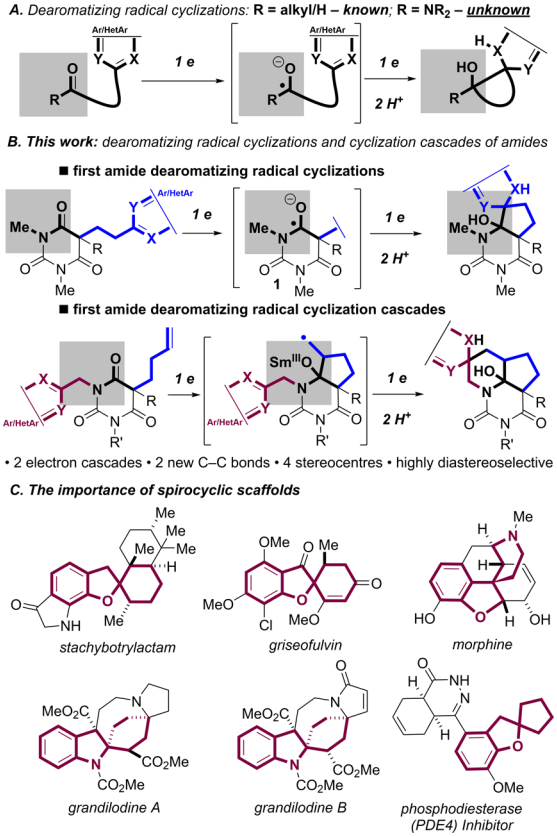
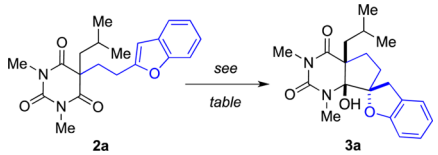


Table 1. Optimization of the Dearomatizing Radical Cyclization of Amide 2a[a,b]

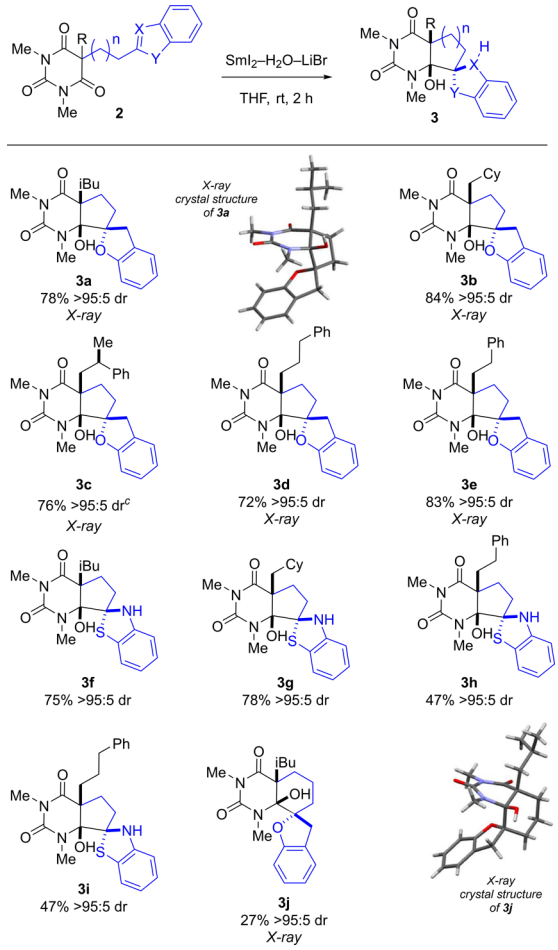


entry	SmI_2 (equiv)	H_2O (equiv)	yield/%[b] 2a	yield/%[b] 3a
1	3	–	100	0
2	3	100	32	20
3[c]	3	–	–	40
4[c]	**3**	**100**	–	**80** (78)[d]
5[c]	3	200	–	73

[a]Reaction conditions: To **2a** (0.1 mmol, in 2 mL THF) at room temperature under N_2 was added H_2O, followed by SmI_2, and the reaction was quenched after 2 h. [b]Yield was determined by ^1H NMR spectroscopy using 2,3,5,6-tetrachloronitrobenzene as an internal standard. [c]LiBr (20 equiv wrt SmI_2) was used. [d]Isolated yield; >95:5 dr, determined by ^1H NMR on the crude product mixture.

Scope of the Dearomatizing Radical Cyclizations of Amides. We next examined the scope of the dearomatizing radical cyclization of amides **2** (Scheme 2). Benzofuran substrates bearing hindered alkyl groups, such as isobutyl (**3a**) and methylcyclohexyl (**3b**), and aryl-containing substituents (**3c–e**) on the barbituric acid ring, exhibited excellent reactivity, and dearomatized spirocyclic products were isolated in good yield and essentially as single diastereoisomers. The relative stereochemistry in **3a–e** was confirmed by X-ray crystallographic analysis.[20]

Scheme 2. Scope of the Dearomatizing Radical Cyclization of Amides[a,b]



[a]Reaction conditions: To a solution of **2a** (0.1 mmol), in THF (2 mL) at room temperature under N_2, was added H_2O, followed by a mixture of SmI_2 and LiBr. The reaction was quenched after 2 h. [b]Isolated yields; >95:5 dr, determined by ^1H NMR on the crude product mixtures. [c]Major product **3c** is a 75:25 mixture of diastereoisomers at the remote stereocenter.

Benzothiazole-containing substrates also underwent smooth dearomatizing radical spirocyclization to give **3f–i** in moderate to high yield and high diastereocontrol. The relative stereochemistry in **3f** was assigned by NOE studies and inferred for analogous products.[21] Finally, barbiturate **3j**, the product of a 6-*exo*-trig amide dearomatizing radical cyclization, was isolated in moderate yield and as a single diastereoisomer. The structure of **3j** was confirmed by X-ray crystallographic analysis (Scheme 2).[20]

Proposed Mechanism for the Dearomatizing Radical Cyclizations of Amides. A mechanism for the dearomatizing radical cyclization of amides is shown in Scheme 3. Radical **4** is formed by ET to the amide-type carbonyl from Sm(II). Subsequent 5-*exo*-trig dearomatizing radical cyclization, via transition structure **5**, and a second ET gives dianion **6**, which, after protonation, gives **3** (Scheme 3). For benzofuran

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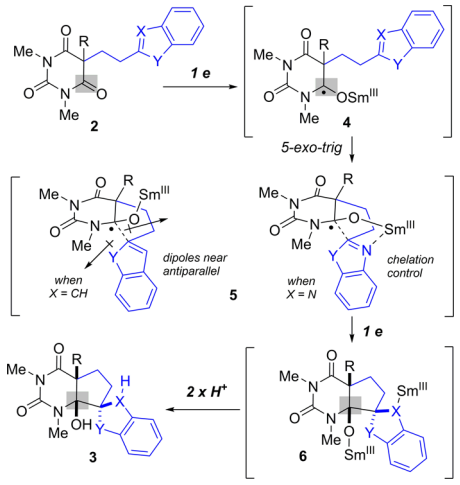
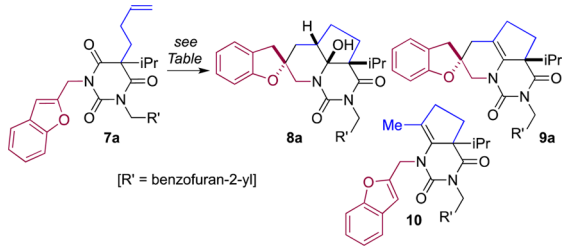
Scheme 3. Proposed Mechanism for the Dearomatizing Radical Cyclizations of Amides



substrates (Y = O, X = CH) the preference for transition structure **5** may arise from the minimization of dipole−dipole interactions. For benzothiazole substrates (Y = S, X = N) coordination of Sm(III) to nitrogen may lead to a preference for transition structure **5**. To date our studies have focused specifically on the chemistry of activated amide-type carbonyls in medicinally relevant barbituric acid substrates although we expect the process to extend to other cyclic imides.[12c,d] Analogous chemistry of simple amides and lactams will likely require the future development of more-reducing Sm(II) reagent systems.[12f]

Optimization of the Dearomatizing Radical Cascade Cyclizations of Amides. Having established the feasibility of dearomatizing radical cyclizations involving radical anions derived from amides by ET, we sought to develop related radical−radical cyclization cascades involving dearomatization of aryl and heteroaryl substituents. Model substrate **7a**, readily synthesized from diethyl-2-isopropylmalonate in three steps, was used to explore novel dearomatizing radical cascades capable of delivering more complex scaffolds in a single operation (Table 2).[22] Treatment of **7a** with SmI_2 returned only starting material (entry 1), thus confirming the importance of H_2O and LiBr for activation of the reductant. Addition of H_2O (100 equiv) to SmI_2 and **7a** led to formation of the desired cascade product **9a** (60% NMR yield), after acid-mediated dehydration of hemiaminal product **8a**, but little diastereocontrol was observed (45:55 dr) (entry 2). Addition of LiBr to SmI_2 gave **9a** in 40% NMR yield (entry 3). However, when LiBr was added to SmI_2 *and* H_2O at room temperature, both the yield and diastereoselectivity of the reaction were increased (71%, 63:27 dr) (entry 4). We next investigated the effect of temperature on the radical cascade. The use of SmI_2−H_2O−LiBr at 0 °C delivered optimal results, and the cascade product **9a** was obtained in good yield and with high diastereocontrol (80% isolated yield, 92:8 dr) and only 10% of monocyclization byproduct **10** was formed (entry 5). Lower reaction temperatures gave lower yields of **9a** and a greater proportion of **10** (entry 6). Without acidic workup, the corresponding hemiaminal product **8a** was isolated in 76% yield and 93:7 dr (entry 7). X-ray crystallographic analysis confirmed the structure of major diastereoisomer **9a** and the corresponding minor diastereoisomer **9a′** (not shown).[20]

Table 2. Optimization of the Dearomatizing Radical Cyclization Cascade of Amide 7a[a]



		yield/% (dr)[b]			
entry	T/°C	7a	8a	9a	10
1[c]	rt	100	–	–	–
2[d]	rt	24	–	60 (45:55)	20
3[e]	rt	–	–	40 (48:52)	15
4	rt	–	–	71 (63:27)	7
5	0	–	–	85 (80)[f] (92:8)	10
6	−15	–	–	57 (95:5)	34
7[g]	0	–	80 (76)[f] (93:7)	7 (93:7)	8

[a]Reaction conditions: To **7a** (0.1 mmol), in THF (2 mL) under N_2 was added H_2O (100 equiv), followed by a mixture of SmI_2 (3 equiv) and LiBr (20 equiv wrt SmI_2). After 2 h, HCl (2 M, 1 mL) was added, and the reaction was stirred for 20 min. [b]Yield determined by ^1H NMR spectroscopy using 2,3,5,6-tetrachloronitrobenzene as an internal standard. Dr was determined by ^1H NMR on the crude product mixtures. [c]Without H_2O and LiBr. [d]Without LiBr. [e]Without H_2O. [f]Isolated yield. [g]Without HCl. *T* = temperature.

Scope of the Dearomatizing Radical Cyclization Cascade of Amides. With optimal conditions established, the generality of the dearomatizing radical cascade cyclization for the construction of tetracyclic hemiaminals **8** or enamines **9** was investigated (Scheme 4). Focusing initially on the dearomatization of benzofurans, various alkyl groups on the barbituric acid ring were tolerated, including bulky isopropyl and isobutyl substituents, and the corresponding cascade products (**8a−c** and **9a−c**) were obtained in good yield. Substrates bearing the hindered isopropyl substituent gave the highest yields and diastereoselectivities. Next we investigated the scope with regards to the benzofuran motif undergoing dearomatization. Benzofurans bearing bromo (**8d**, **8i** and **9d**, **9i**), fluoro (**8e** and **9e**), methyl (**8f** and **9f**), and methoxy (**8g**, **8h** and **9g**, **9h**) groups, as well as naphthyl-fused furans (**8j** and **9j**), were compatible with the cascade process and gave polycyclic products in good to excellent isolated yield (59−85%) and with excellent diastereocontrol (91:9 to 95:5 dr). The relative stereochemistry of the major products **8j** and **9a,c−e,h−j** was confirmed by X-ray crystallographic analysis.[20]

We further investigated the scope of the radical cyclization cascade by varying the aromatic moiety undergoing dearomatization (Scheme 5). Pleasingly, benzothiophene (**8k** and **9k**), naphthalene (**8l** and **9l**), benzoxazole (**8m−p**), and benzothiazole (**8q**) were compatible with the process and provided diverse barbiturates bearing spiro-heterocyclic motifs with essentially complete diastereocontrol (>95:5 dr). Attempts to engage simple benzene substituents in the dearomatizing process have so far proved unsuccessful. Again, fluoro (**8n**), chloro (**8o**), and bromo (**8p**) substituents on the heterocyclic ring were tolerated in the process. The relative stereochemistry in **8o** was assigned by NOE studies and inferred for analogous products.[21]

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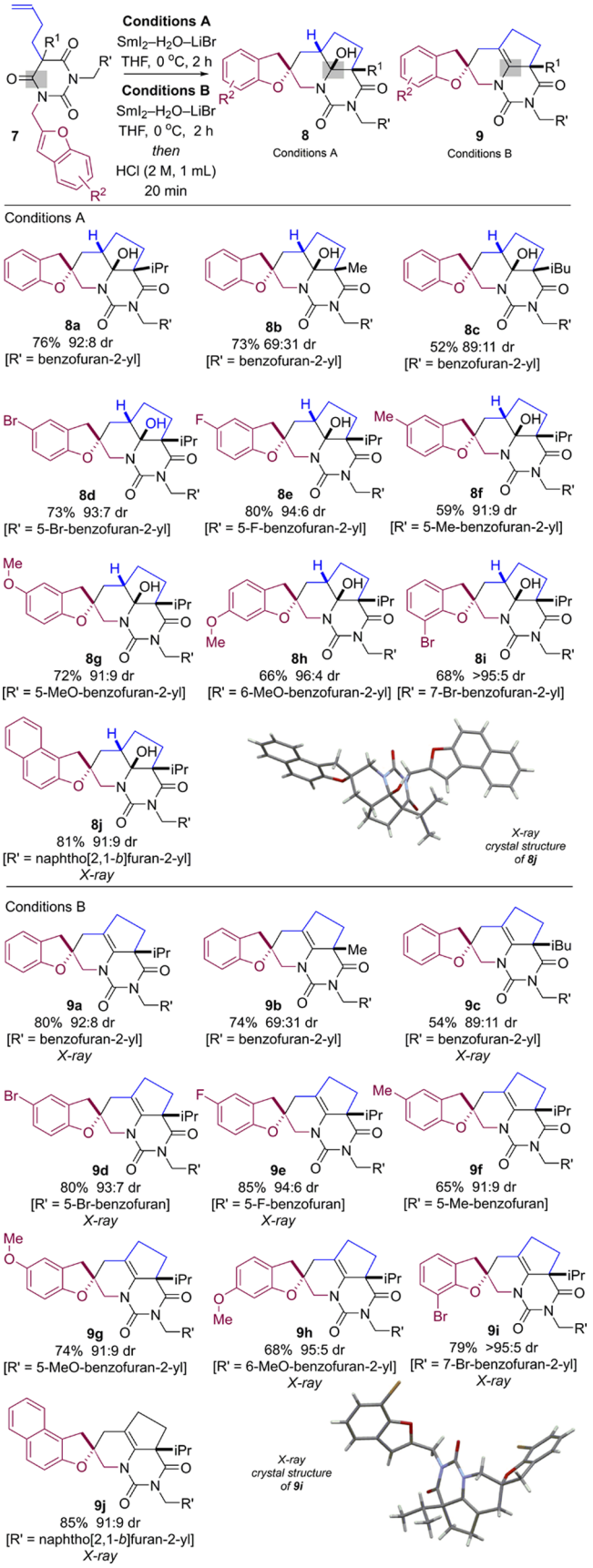
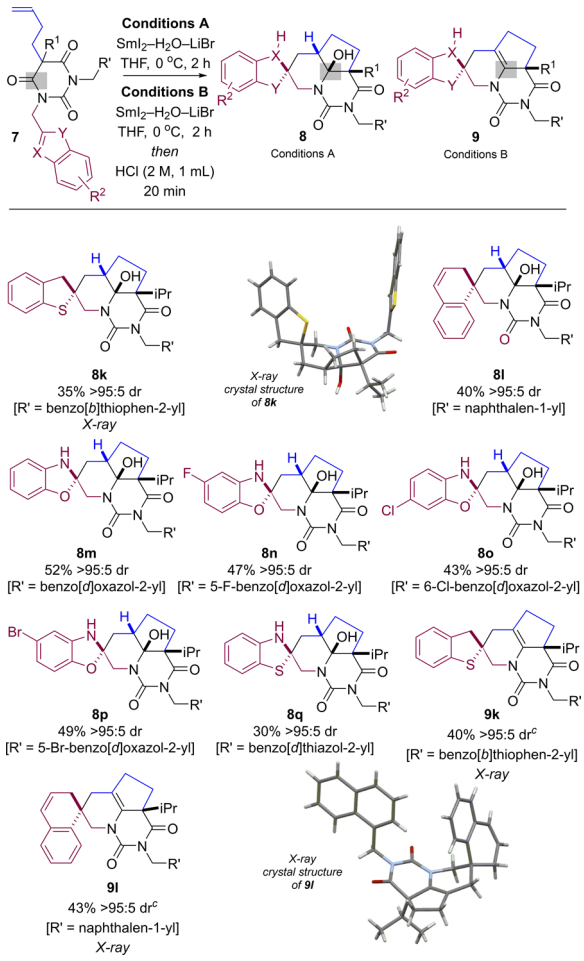
Scheme 4. Scope of the Dearomatizing Radical Cyclization Cascade[a,b]



Scheme 4. continued

[a]Reaction conditions A: To a solution of 7 (0.1 mmol), in THF (2 mL) under N_2, was added H_2O, followed by a mixture of SmI_2 and LiBr; the reaction was quenched after 2 h. Reaction conditions B: To a solution of 7 (0.1 mmol), in THF (2 mL) under N_2, was added H_2O, followed by a mixture of SmI_2 and LiBr; after 2 h, HCl (2 M, 1 mL) was added followed by stirring for 20 min. [b]Isolated yields. Dr determined from ^{1}H NMR of crude product mixtures.

Scheme 5. Radical Cyclization Cascades Involving Dearomatization of Various Heteroaromatic and Aromatic Rings[a,b]



[a]Reaction conditions A: To a solution of 7 (0.1 mmol), in THF (2 mL) under N_2, was added H_2O, followed by a mixture of SmI_2 and LiBr; the reaction was quenched after 2 h. Reaction conditions B: To a solution of 7 (0.1 mmol), in THF (2 mL) under N_2, was added H_2O, followed by a mixture of SmI_2 and LiBr; after 2 h, HCl (2 M, 1 mL) was added followed by stirring for 20 min. [b]Isolated yield. Dr determined by ^{1}H NMR of crude product mixtures. [c]Prepared using Conditions B.

Attempted cascade reactions involving two dearomatization events were unsuccessful. We believe that the high stability and ease of reduction of the benzylic radicals formed during the first dearomatization event (factors that are also key to driving the dearomatization event) rule out trapping of the radical by a second radical acceptor, whether it be another aromatic unit or a simple alkene or alkyne.

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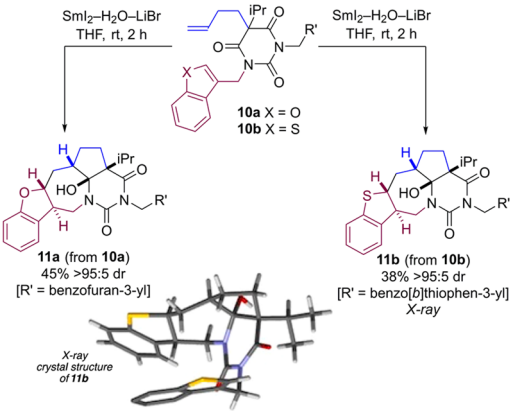
Dearomatizing Cyclization Cascades of Amides Involving 7-*endo*-trig Processes. When a benzofuran and benzothiophene moiety were attached to nitrogen of the barbituric acid unit through the 3-position of the heterocycle, dearomatizing radical−radical cyclization cascades involving 5-*exo*-trig and 7-*endo*-trig processes were observed and azepine-containing products **11a** and **11b** were obtained in moderate yield with excellent diastereocontrol (Scheme 6).

Scheme 6. Dearomatizing Radical Cyclization Cascades Involving 7-*endo*-trig Processes[a,b]



[a]Reaction conditions: To a solution of **10** (0.1 mmol), in THF (2 mL) under N_2, was added H_2O, followed by a mixture of SmI_2 and LiBr. The reaction was quenched after 2 h. [b]Isolated yield. Dr was determined by ^1H NMR of the crude product mixture.

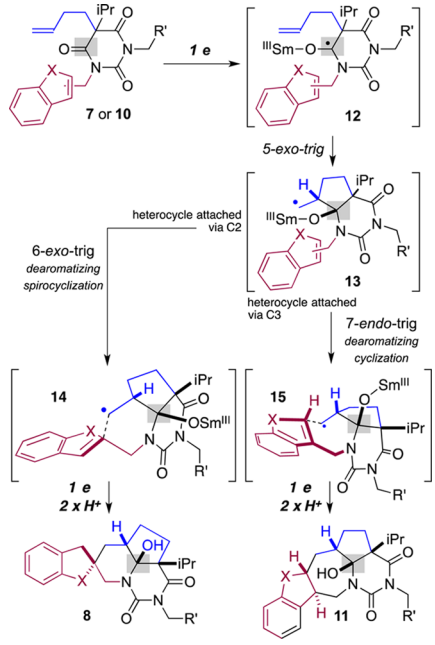
In dearomatizing radical cyclization cascades, ET from Sm(II) to the amide-type carbonyl forms radicals **12**. 5-*Exo*-trig cyclization then forms radical intermediates **13** which undergo either 6-*exo*-trig or 7-*endo*-trig dearomatizing cyclization, depending on the site of attachment of the heteroaryl unit to the barbituric acid scaffold. When the heteroaromatic group is attached via C2, spirocyclization takes place via chair transition structure **14** in which dipole−dipole interactions are minimized. Further ET reduction and protonation then deliver **8**. In contrast, when the heteroaryl unit is attached via C3, 7-*endo*-trig radical cyclization via transition structure **15** leads to **11** (Scheme 7).

Manipulation of the Products of Dearomatizing Amide Radical Cyclizations and Cyclization Cascades. The dearomatizing radical cyclizations and cyclization cascades can be carried out on a larger scale to deliver products such as **3b** and **9a** with excellent diastereocontrol in good isolated yield (Scheme 8).

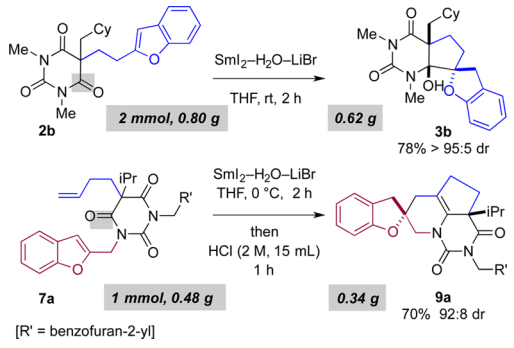
The unusual hemiaminal products arising from dearomatizing amide radical cyclization can be readily manipulated. For example, iminium ion generation, upon exposure of **3b** to $BF_3{\cdot}OEt_2$, and addition of various carbon nucleophiles, delivers complex tertiary amine products **16a−c** with high stereocontrol (Scheme 9).[23]

Similarly, the products of dearomatizing amide radical cyclization cascades can be further elaborated. For example, selective allylic oxidation of tetracyclic enamine **9a** gave ketone **17** in moderate yield (Scheme 10).[24] The cyclic urea moiety in the cascade products can be reduced. For example, reduction of **9a** with DIBALH gave new hemiaminal **18** which can be reduced further by excess reagent to give polycyclic aminal **19**.

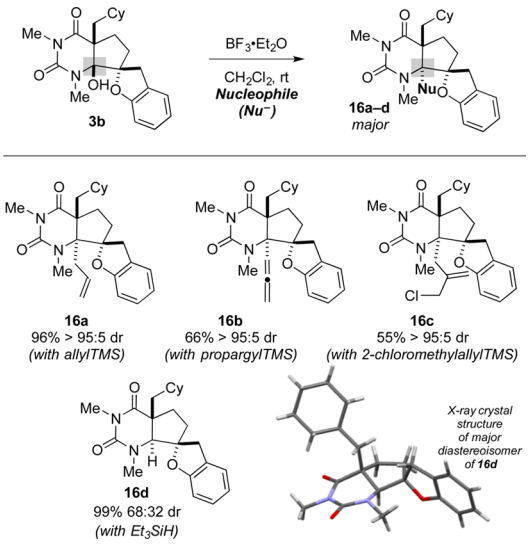
Scheme 7. Proposed Mechanisms for the Dearomatizing Radical Cyclization Cascades



Scheme 8. Larger Scale Dearomatizing Radical Cyclizations and Cyclization Cascades of Amides



Scheme 9. Manipulation of the Hemiaminal Products of the Dearomatizing Radical Cyclization of Amides



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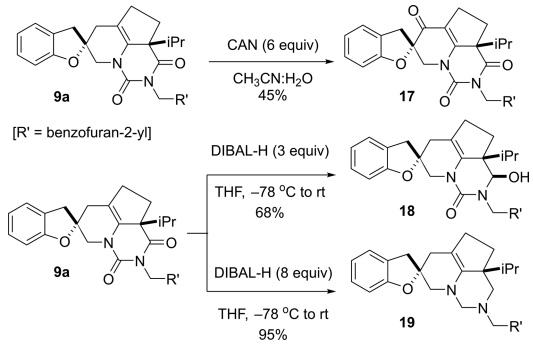
Scheme 10. Manipulation of the Novel Polycyclic Spirobarbiturates



3. CONCLUSION

The first dearomatizing radical cyclizations and cyclization cascades triggered by ET reduction of amide-type carbonyls provide access to unprecedented polycyclic molecular architectures containing up to five stereocenters with high diastereocontrol. The mild process exploits activation of SmI_2 with H_2O and LiBr, exhibits a wide scope with regard to the aromatic system undergoing dearomatization, and delivers novel scaffolds based on a medicinally proven structural platform. While the current method is limited to amide-type carbonyls in cyclic imides, future studies will focus on extending the method to simple lactam substrates.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b12077.

Experimental details, characterization data and spectra, X-ray structures, and NOE studies (PDF)

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Notes

The authors declare no competing financial interest.

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