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SmI₂-catalyzed cyclization cascades by radical relay

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Abstract

Radical cyclization cascades are powerful tools used to construct the complex three-dimensional structures of some of society's most prized molecules. Since its first use forty years ago, SmI₂ has been used extensively for reductive radical cyclizations. Unfortunately, SmI₂ must almost always be used in significant excess thus raising issues of cost and waste. Here we have developed radical cyclization cascades that are catalyzed by SmI₂ and that exploit a radical relay/electron-catalysis strategy. The approach negates the need for a super-stoichiometric co-reductant and requires no additives. Complex cyclic products, including products of dearomatization, containing up to four contiguous stereocenters are obtained in excellent yield. Mechanistic studies support a single-electron transfer radical mechanism. Our strategy provides a long-awaited solution to the problem of how to avoid the need for stoichiometric amounts of SmI₂ and establishes a conceptual platform upon which other catalytic radical processes using the ubiquitous reducing agent can be built.

Introduction

Biologically-active molecules often possess intricate three-dimensional, ring-containing structures. Classical approaches to these complex polycyclic targets, involving the use of many reagents and operations over many reaction steps, are being superseded by strategies employing one-pot sequences, or cascades, of ring-forming reactions that deliver the target in expedient fashion.¹⁻⁴ The unique combination of high reactivity and high selectivity associated with open-shell intermediates makes radical processes^{5,6} ideal for cascade reactions in which simple substrates undergo a series of changes involving bond formation (and bond cleavage) to give complex, high value products and single electron transfer (SET) is commonly used to generate the radical character that drives such processes.⁷⁻⁹ The well-known reductant samarium(II) diiodide (SmI_2 , Kagan's reagent)¹⁰ is arguably one the most important and widely used SET reagents^{11,12} and it has proved adept at unlocking the total synthesis of numerous high profile and complex natural products (Fig. 1A).¹³⁻¹⁸ Many of the most important radical reactions of SmI_2 involve SET to ketones and aldehydes and the generation of ketyl radicals.¹¹ Despite almost 40 years of widespread use, the reductant is almost invariably used in super-stoichiometric amounts, thus raising issues of cost and waste. The development of new and sustainable processes catalytic in SmI_2 would be a major advance. Of the few reports of the use of catalytic SmI_2 , all require the use of super-stoichiometric amounts of a metal co-reductant to regenerate Sm(II) .¹⁹⁻²² For example, Corey described one of the very few SmI_2 -catalyzed radical cyclizations:¹⁹ Unfortunately, the catalytic system requires 15 equivalents of Zn/Hg amalgam (Fig. 1B). Over twenty years later, this system remains the state-of-the-art in the field.

The development of efficient catalytic variants of important reactions requiring stoichiometric reagents is key to the future of synthesis.²³ In the field of radical

chemistry involving SET, radical relay/electron-catalysis strategies are highly attractive and atom economical as radical character is recycled and stoichiometric oxidants and reductants are not required.^{24,25} For example, Yoon,^{26–28} Song,^{29,30} and Meggers³¹ have described elegant examples of this approach in cyclizations and cyclization cascades involving ketyl radicals. However, even in these systems, co-reductants and additives are required. For example, in the only reported radical relay cyclization cascade, stoichiometric La(OTf)₃, TMEDA, and MgSO₄ are employed.²⁶ The work we report here was prompted by the desire to address the longstanding inability to use catalytic amounts of SmI₂ and to advance the application of radical relays in synthesis.

Here we describe radical cyclization cascades mediated solely by a SmI₂ catalyst. Our approach represents the use of the classical SET reagent in a radical relay, converts simple cyclopropyl ketones **1** to complex cyclic ketones **2** (Fig. 1C), avoids the use of co-reductants and additives, involves short reaction times (< 20 min), is operationally straightforward, and exhibits broad scope. Key to the catalytic radical process is the spring-loaded nature of ketyl radical **I** which is formed by reversible SET from SmI₂ to substrate **1a**. Ketyl radical **I** fragments^{32,33} to give distal radical **II**. Cyclization then generates radical **III** which rebounds by addition to the Sm(III)-enolate moiety, regenerating new ketyl radical **IV**. Back electron transfer to Sm(III) regenerates the SmI₂ catalyst and liberates product **2a** (Fig. 1D). The use of substrates bearing alkenes and alkynes as radical acceptors delivers complex products containing two new rings and up to four new stereocenters. Furthermore, dearomatizing radical cyclizations using catalytic SmI₂ are also possible using heteroarene substrates (Fig. 1C).

Fig. 1 | Importance of stoichiometric SmI_2 -mediated cyclizations and the challenge of catalysis using SmI_2 . (A) Selected complex bioactive natural products synthesized using stoichiometric amounts of SmI_2 . (B) A rare example of a SmI_2 -catalyzed radical cyclization requires a large excess of stoichiometric co-reductant and additives. (C) SmI_2 -catalyzed cyclization cascades. (D) Proposed catalytic cycle.

Results

Optimization studies. To assess the feasibility of the proposed catalytic radical process, **1a** (Ar = Ph, R¹ = Me, X = C(CO₂Et)₂) was treated with 30 mol% SmI₂ (Fig. 2). The corresponding bicyclic product **2a** was obtained in 68% isolated yield (see Supplementary Table 1). When the catalyst loading of SmI₂ was decreased to 10 mol%, the yield of **2a** dropped to 56% with **1a** recovered in 31% yield. Pleasingly, the efficiency of the cyclization cascades increased upon heating; using 5 mol% SmI₂ at 65 °C, **2a** was obtained in 87% isolated yield and 71:29 dr, with the reaction complete in <20 min. Formation of **2a** was not observed in the absence of the SmI₂ catalyst and only starting material **1a** was recovered.

Catalytic radical cyclizations of alkynes. The scope of the SmI₂-catalyzed cyclization cascade was initially assessed using a range of alkyne substrates **1a-1v** (Fig. 2). In almost all cases, products were obtained in good yield and with moderate diastereocontrol after short reaction times. Furthermore, gram-scale reaction of **1a** gave cascade product **2a** in an improved 99% yield (1.10 g) in less than 20 minutes. The process tolerated various groups on the alkyne unit including alkyl (**2a**, **2d**), hydrogen (**2b**), silyl (**2c**) and aryl (**2e-h**, **2m**, **2n**). Furthermore, important functional groups including various ester (*e.g.* **2a**, **2i**, **2j**), bromo (**2f**, **2q**), fluoro (**2s**), protected amino (**2k**), methoxy (**2h**, **2r**), naphthyl (**2t**), cyclopropyl (**2v**), and 2-thienyl (**2u**) were compatible with the catalytic radical process. In addition to a wide range of carbocyclic products, including less-substituted carbocycle **2n**, variation of the tether allowed valuable heterocyclic products to be obtained (**2k-m**). SmI₂-catalyzed cyclization of **1v** bearing a medically-relevant cyclopropyl substituent gave cascade product **2v** in excellent yield and with the strained ring intact. This result suggests that 5-*exo-trig* cyclization of the alkenyl radical intermediate (*cf.* **III** in Fig. 1D) is faster than radical fragmentation.³⁴ X-ray crystallographic analysis of **2k**, **2m** and **2o**

confirmed the relative stereochemistry of the major diastereoisomeric cascade products.

Fig. 2 | Substrate scope for alkynes. Reaction conditions: To a solution of **1** (0.1 mmol) in THF (4 mL, 0.025 M) at 65 °C under N₂ was added SmI₂ (5 mol%). The reaction was quenched after 20 minutes by opening to the air. Isolated yields are given. Dr determined by ¹H NMR spectroscopy of crude product mixtures. ^a 10 mol% SmI₂ required. ^b 20 mol% SmI₂ required. ^c 40 mol% SmI₂ required.

Catalytic radical cyclizations of alkenes. We next investigated the capacity of alkenes to participate in the SmI₂-catalyzed cyclization cascade (Fig. 3). In almost all cases, products were obtained in good yield and with good diastereocontrol during the formation of four stereocenters. Alkene **3a** (R¹ = Ph, X = C(CO₂Et)₂) underwent radical cascade cyclization on gram scale upon treatment with only 5 mol% SmI₂ to give product **4a** (0.91g, 83%). The presence of a variety of functional groups was tolerated, including chloro (**4b**), fluoro (**4c**), bromo (**4d-e**), trifluoromethyl (**4f**), methoxy (**4g**), acetoxy (**4h**), chloromethyl (**4i**), naphthyl (**4j**), benzothienyl (**4k** and **4m**) and benzofuranyl (**4l**). Again, variation of the tether allowed access to less-substituted carbocyclic (**4n**) and heterocyclic products (**4o** and **4p**). The relative stereochemistry of the cascade products **4n** and **4o** was confirmed by X-ray crystallography.

Fig. 3 | Substrate scope for alkenes. Reaction conditions: To a solution of **3** (0.1 mmol) in THF (4 mL, 0.025 M) at 65 °C under N₂ was added SmI₂ (5 mol%). The reaction was quenched after 20 minutes by opening to the air. Isolated yields are given. Dr determined by ¹H NMR spectroscopy of crude product mixtures. ^a10 mol% SmI₂ required. ^b15 mol% SmI₂ required.

Catalytic dearomatizing radical cyclizations of heteroarenes. Catalytic dearomatization is a particularly powerful strategy for the construction of complex three-dimensional architectures from simple, two-dimensional starting materials.^{35–37} However, dearomatizing cascades involving radical intermediates are rare and no SmI₂-catalyzed dearomatizing reactions have been reported.³⁸ We have found that heteroaromatic radical acceptors can also be employed and the SmI₂-catalyzed cyclization cascades generate complex products of dearomatization (Fig. 4). Upon treatment with 5 mol% SmI₂, benzofuran-containing substrate **5a** (R¹ = H, R² = H, X = C(CO₂Et)₂) gave complex, tetracyclic product **6a** in 99% yield with 93:7 dr. A gram-scale reaction gave 1.31 g of **6a** in 97% yield. SmI₂-catalyzed dearomatizing radical cyclization cascades typically proceeded in excellent yield and with high diastereocontrol (Fig. 4). The presence of a variety of functional groups was tolerated, including methoxy (**6c**, **6i**, **6o**, **6q**), bromo (**6d**, **6j**), fluoro (**6e**, **6m**, **6p**), trifluoromethyl (**6n**) and naphthyl (**6h**, **6r**). Again, variation of the tether allowed access to less-substituted carbocyclic (**6l**) and heterocyclic products (**6k**). The relative stereochemistry of **6k** and **6l** was confirmed by X-ray crystallographic analysis. Notably, the cyclization cascade of **5s**, bearing a 3-methylbenzofuran-2-yl moiety, delivered **6s** bearing two adjacent quaternary stereocenters in 70% isolated yield and with virtually complete diastereocontrol. Finally, benzothiophene-derivative **5t** gave **6t** in 90% isolated yield and 81:19 dr.

Fig. 4 | Sml₂-catalyzed dearomatizing cyclization cascades. Reaction conditions: To a solution of **5** (0.1 mmol), in THF (4 mL, 0.025 M) at 0 °C under N₂, was added Sml₂ (5 mol%). The reaction was quenched after 20 minutes by opening to the air. All yields are isolated yields, dr determined from ¹H NMR spectroscopy of crude product mixtures. ^a 10 mol% Sml₂. ^b Room temperature. ^c 20 mol% Sml₂. ^d 15 mol% Sml₂. ^e 65 °C.

Discussion

Mechanistic studies. Preliminary studies on the mechanism of the Sml₂-catalyzed cyclization cascade support a radical relay/electron catalysis process (Fig. 5). First, an

alternative mechanism involving Lewis acid-activation of the substrates was investigated; only starting material was recovered when **1a** was exposed to a variety of Lewis acids, including Sm(III)I₃ (Fig. 5A).³⁹ Furthermore, when radical inhibitor TEMPO was present <10% yield of **2a** was obtained. Radical clock experiments were also performed using a cyclopropane-containing substrate and the corresponding ring opening product was detected and confirmed by high resolution accurate mass spectrometry (see Supplementary Figures 1 and 2). To probe the importance of radical addition to the Sm(III)-enolate moiety in **III**, we treated **1a** with 10 mol% SmI₂ in the presence of 200% TMSCl under our otherwise optimized conditions. It is known that TMSCl promotes cleavage of the Sm^{III}-O bond to give silyl ethers.²⁰ In the presence of TMSCl, only 10% yield of **2a** was formed suggesting that the Sm(III)-enolate is trapped by TMSCl thus preventing closure of the catalytic cycle (Fig. 5A). We next sought to rule out a chain-type process initiated by reductive SET^{6,40} in which the ketyl radical intermediate **IV** reduces starting material **1a** by an outer sphere process, to form product **2a** and radical intermediate **I**, rather than regeneration of Sm(II) by back electron transfer to the metal. Chain-type processes involving SET are often characterized by promiscuity with regard to the electron-transfer reagents able to initiate the chain process.^{6,40} The attempted use of the SET reductant Cp*TiCl₃, in place of SmI₂, consistently gave only a low yield of **2a** thus suggesting that Sm(II) and its regeneration plays a key role in the radical cyclization cascade and suggests that a chain-type process is not in operation (Fig. 5A). It is important to note that the reaction mixture typically retains the characteristic blue colour of SmI₂ long after the starting material has been converted to product thus clearly indicating that Sm(II) is regenerated (see Supplementary Figure 3). Finally, an EPR study was performed using **1a** and the spin trap 5,5-dimethyl-1-pyrroline *N*-oxide (DMPO). Pleasingly,

trapped species **7** was observed by EPR and also by high resolution mass spectrometry (Fig. 5B). Similar trapped species were also observed using substrates **3a** and **5a** (see Supplementary Figures 9-18). Thus, our preliminary mechanistic studies on the cyclization cascades support a radical relay/electron catalysis process involving the regeneration of Sm(II).

Fig. 5 | Preliminary mechanistic studies. (A) Probing the importance of Sm(II) and its regeneration. **(B)** An EPR study using the spin trap DMPO.

Fig. 6 | Computational studies. Computed DFT free energy profile for the SmI₂-catalyzed cyclization cascades (PBE/Def2-SVP level).

To further support the proposed catalytic radical relay/electron-catalysis mechanism, detailed DFT calculations were performed. Structures corresponding to the key intermediates in the catalytic cycle and the barriers for their formation are shown in the free energy profile in Figure 6. Coordination of the samarium catalyst to the carbonyl group of **1a** provides complex **1a•SmI₂(THF)₄**. SET from Sm(II) then gives ketyl radical intermediate **I** ($\Delta G = +107.7$ kJ mol⁻¹). After ring opening ($\Delta G = +60.2$ kJ mol⁻¹), radical **II** is formed and undergoes 5-*exo-dig* cyclization ($\Delta G = +28.2$ kJ mol⁻¹). Vinyl radical **III** then undergoes a highly-favourable intramolecular addition

to the Sm(III)-enolate moiety ($\Delta G = +6.9 \text{ kJ mol}^{-1}$) to give new Sm(III)-ketyl radical **IV**. Finally, product complex **2a•SmI₂(THF)₄** is generated after back electron-transfer to Sm(III) to regenerate the Sm(II) catalyst. Calculated transition structures for the key events in the catalytic cycle – cyclopropane fragmentation (**I to II**†), 5-*exo*-dig cyclization (**II to III**†), and 5-*exo*-trig cyclization (**III to IV**†) – are also shown (Fig. 6, inset). Alternative *Z*-enolate intermediates were found to give rise to higher energy intermediates and transition states than those of the corresponding *E*-enolates. Cyclization of **III** and formation of the major diastereoisomer observed in the cyclization cascade was calculated to proceed through a significantly lower energy transition state than that for the formation of the minor diastereoisomer (see Supplementary Figure 23)

Conclusion

Using a radical relay/electron-catalysis approach we have developed SmI₂-catalyzed radical cyclization cascades that operate without a stoichiometric co-reductant or additives. SmI₂ loadings as low as 5 mol% deliver complex three-dimensional polycyclic products containing up to four stereocenters, typically in high yields and with good diastereocontrol. Furthermore, dearomatizing radical cyclizations using catalytic SmI₂ were also successful using the approach. Our strategy provides a long-awaited solution to the problem of how to avoid the use of SmI₂ in stoichiometric amounts and establishes a conceptual platform upon which other catalytic radical processes using the ubiquitous reducing agent can be built.

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Methods

General procedure for the SmI₂-catalyzed cyclization cascades of alkynes and alkenes. An oven-dried vial containing a stirrer bar was charged with the substrate **1** or **3** (0.1 mmol, 1 equiv.) and placed under a positive pressure of nitrogen. THF (0.025 M, 4.0 mL) was added and the reaction heated to 65 °C. SmI₂ (typically 5 mol%, 0.1 M solution in THF, 0.05 mL) was then added. After the specified time (typically 20 min), the reaction was filtered through a pad of silica gel and washed with CH₂Cl₂ (3 × 5 mL). The organic layers were combined and concentrated *in vacuo* to give product (**4** or **6**) typically without the need for further purification. In some case, the product required purification by column chromatography on silica gel.

General procedure for the SmI₂-catalyzed dearomative cascades. An oven-dried vial containing a stirrer bar was charged with substrate **5** (0.1 mmol, 1 equiv.) and placed under a positive pressure of nitrogen. THF (0.025 M, 4.0 mL) was added and,

at the correct temperature (typically, 0 °C), SmI₂ (typically 5 mol%, 0.1 M solution in THF, 0.05 mL) was added. After the specified time (typically 20 min), the reaction was filtered through a pad of silica gel and washed with CH₂Cl₂ (3 × 5 mL). The organic layers were then combined and concentrated *in vacuo* to give the product **6**. In some cases, the product was purified by column chromatography on silica gel.

Data availability

Materials and methods, optimization studies, experimental procedures, mechanistic studies, EPR spectra, NMR spectra and mass spectrometry data are available in the Supplementary Information. Crystallographic data for compounds **2k**, **2m**, **2o**, **4n**, **4o**, **6k** and **6l** are available free of charge from the Cambridge Crystallographic Data Centre under references numbers CCDC 1866917-1866923. All other data is available from the authors upon reasonable request.

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Author contributions

H.-M.H. and D.J.P. conceived and directed the project; H.-M.H. and D.J.P. designed the experiments; H.-M.H. performed and analyzed all the reactions; J.J.W.M. performed all computational studies; H.-M.H. and D.J.P. and wrote the manuscript.

Competing interests The authors declare no conflicts of interest.

Additional information

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