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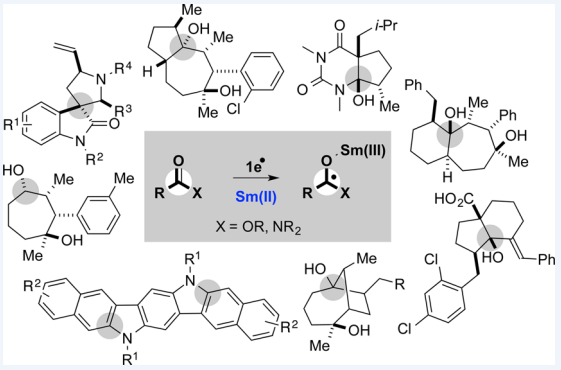
Sm(II)-Mediated Electron Transfer to Carboxylic Acid Derivatives: Development of Complexity-Generating Cascades

Xavier Just-Baringo and David J. Procter*

School of Chemistry, University of Manchester, Manchester M13 9PL, U.K.

CONSPECTUS: Reductive electron transfer (ET) to organic compounds is a powerful method for the activation of substrates via the formation of radicals, radical anions, anions, and dianions that can be exploited in bond-cleaving and bond-forming processes. Since its introduction to the synthetic community in 1977 by Kagan, SmI_2 has become one of the most important reducing agents available in the laboratory. Despite its widespread application in aldehyde and ketone reduction, it was widely accepted that carboxylic acid derivatives could not be reduced by SmI_2; only recently has our work led to this dogma being overturned, and the reduction of carboxylic acid derivatives using SmI_2 can now take its place alongside aldehyde/ketone reduction as a powerful activation mode for synthesis. In this Account, we set out our studies of the reduction of carboxylic acid derivatives using SmI_2, SmI_2–H_2O, and SmI_2–H_2O–NR_3 and the exploitation of the unusual radical anions that are now accessible in unprecedented carbon–carbon bond-forming processes. The Account begins with our serendipitous discovery that SmI_2 mixed with H_2O is able to reduce six-membered lactones to diols, a transformation previously thought to be impossible. After the successful development of selective monoreductions of Meldrum's acid and barbituric acid heterocyclic feedstocks, we then identified the SmI_2–H_2O–NR_3 reagent system for the efficient reduction of a range of acyclic carboxylic acid derivatives that typically present a significant challenge for ET reductants. Mechanistic studies have led us to propose a common mechanism for the reduction of carboxylic acid derivatives using Sm(II), with only subtle changes observed as the carboxylic acid derivative and Sm(II) reagent system are varied. At the center of our postulated mechanism is the proposed reversibility of the first ET to the carbonyl of carboxylic acid derivatives, and this led us to devise several strategies that allow the radical anion intermediates to be exploited productively in efficient new processes. First, we have used internal directing groups in substrates to "switch on" productive ET to esters and amides and have exploited such an approach in tag-removal cyclization processes that deliver molecular scaffolds of significance in biology and materials science. Second, we have exploited external ligands to facilitate ET to carboxylic acid derivatives and have applied the strategy in telescoped reaction sequences. Finally, we have employed follow-up cyclizations with alkenes, alkynes, and allenes to intercept radical anion intermediates formed along the reaction path and have employed this strategy in complexity-generating cascade approaches to biologically significant molecular architectures. From our studies, it is now clear that Sm(II)-mediated ET to carboxylic acid derivatives constitutes a general strategy for inverting the polarity of the carbonyl, allowing nucleophilic carbon-centered radicals to be formed and exploited in novel chemical processes.



1. INTRODUCTION

1.1. Samarium(II) Iodide as a Privileged Reagent for Synthesis

Electron-transfer (ET) is a fundamental process in nature, and the harnessing of ET processes by synthetic chemists has led to some of the most important transformations for molecular construction.[1] In particular, reductive ET to organic compounds is a powerful method for the activation of substrates via the formation of radicals, radical anions, anions, and dianions that can be exploited in bond-cleaving and bond-forming reactions.[1−3] While alkali metals were used in early synthetic ET procedures, the latter half of the 20th century saw the emergence of a new generation of reductive ET reagents. At the vanguard of this new order was samarium diiodide (SmI_2), and the incredible synthetic potential of this reagent was quickly recognized and mapped by the leading synthetic teams of the day.[2−7] Indeed, since its introduction to the synthetic community in 1977 by Kagan,[8,9] SmI_2 has become one of the most important reducing agents available in the laboratory.[2−7,10−14] In his seminal paper, Kagan observed that "carboxylic acid and ester were not reduced by SmI_2", and this view became widely accepted in the field.[9] It has taken over 35 years to overturn this dogma and for the reduction of carboxylic acid derivatives using SmI_2 to take its place alongside aldehyde/ketone reduction as a powerful activation mode for synthesis.

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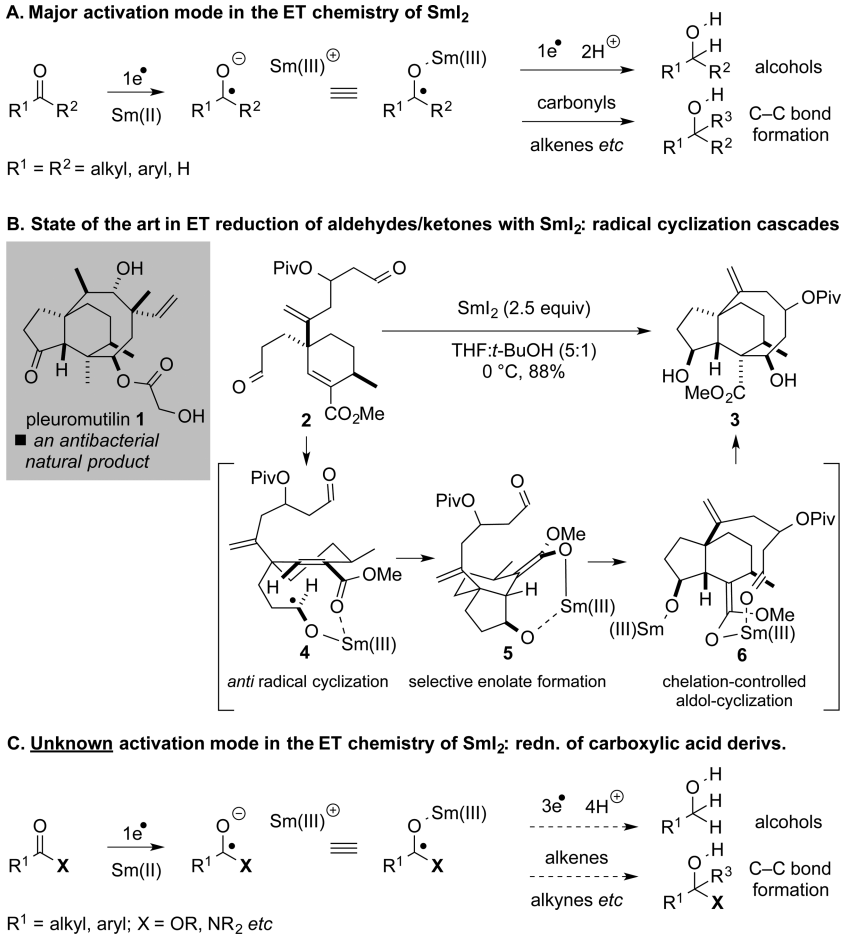
Scheme 1. Carbonyl Activation Modes with SmI_2



1.2. Ketyl Radical Anions from Aldehydes and Ketones

The reduction of aldehydes and ketones to radical anions is one of the most widely used activation modes in the synthetic chemistry of SmI_2 (Scheme 1A).[12] Ketyl radical anion generation from aldehydes/ketones can be used in ET reductions to give important primary and secondary alcohol products, a process that can show advantages over hydride-based reductions (e.g., improved/complementary chemoselectivity/stereoselectivity).[13,14] More importantly, the radical anions generated from aldehydes/ketones by SmI_2 can be used in carbon−carbon bond-forming reactions[3] (e.g., pinacol couplings, carbonyl−alkene cross-coupling), with the state of the art in the field being elaborate reaction cascades that allow complex molecular architectures to be assembled in a single synthetic operation. For example, we have used a dialdehyde cyclization cascade to assemble the core of the antibacterial pleuromutilin (**1**)[15] and thus complete the first enantiospecific total synthesis of the natural product (Scheme 1B).[16] Byproducts arising from "out of sequence" reduction were not observed, and high diastereocontrol was achieved in the construction of four contiguous stereocenters. In recent times, our work with SmI_2 has concentrated on the generation of analogous radical anions from carboxylic acid-derived functional groups, motifs previously thought to be inert to reduction by the reagent (Scheme 1C).

2. ET REDUCTION OF CARBOXYLIC ACID DERIVATIVES

Despite the widely accepted belief that carboxylic acid derivatives lay outside the reducing range of SmI_2, several groups made observations that would prove important for future breakthroughs. Notably, the beneficial effects of H_2O as an additive in SmI_2-mediated reactions was noted by Kagan in his seminal 1980 publication[9] and discussed in detail in 1993 by Curran.[17] Crucially, in 1993 Kamochi and Kudo found that SmI_2−H_2O was able to reduce *aryl* carboxylic acids, esters, amides, and nitriles.[18] More recently, Flowers' studies in 2004 on the mechanism of aldehyde/ketone reduction with SmI_2 in the presence of H_2O[19] showed that H_2O has a high affinity for SmI_2 and displaces solvent from the inner coordination sphere, increasing the reduction potential.[20] It is with this backdrop that we initiated studies on the reduction of aliphatic carboxylic acid derivatives using SmI_2−H_2O-based systems in 2006.

2.1. Reduction of Cyclic Carboxylic Acid Derivatives

2.1.1. Lactone Reduction. In 2003, while investigating a stereoselective conjugate reduction, spirocyclization of unsaturated keto lactones **7** mediated by SmI_2,[21,22] we found that the use of H_2O as an additive in the reaction gave triol **9** in addition to the expected spirolactone **8** (Scheme 2); a striking observation given the accepted dogma that carboxylic acid derivatives could not be reduced by SmI_2.

It was several years later, in 2006, that we began to investigate the potential of the lactone reduction.[22,23]

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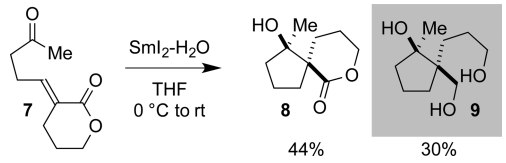
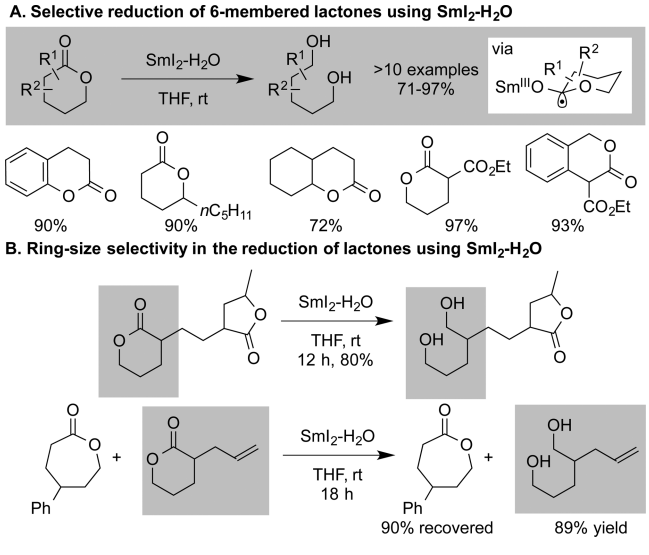
Scheme 2. Discovery of Lactone Reduction Using SmI_2–H_2O



Importantly, the reduction was found to be general: six-membered lactones underwent reduction to give the corresponding diols in good yield. The reduction of lactones bearing acyclic ester substituents was also investigated, and the corresponding diols were obtained in excellent yields with no reduction of the acyclic ester (Scheme 3A).[22,23]

Scheme 3. Selective Reduction of Six-Membered Lactones

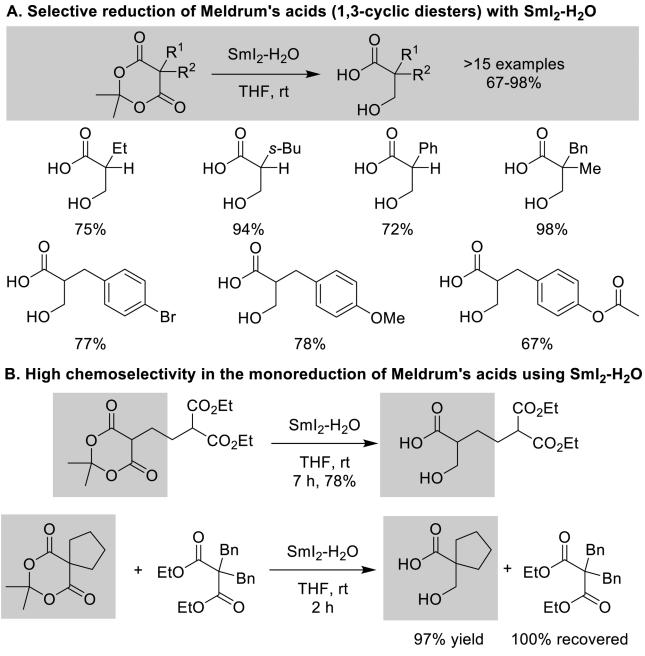


The ring-size-selective nature of the SmI_2–H_2O-mediated lactone reduction was emphasized using competition experiments in which mixtures of six-membered lactones and esters, or other lactones, were treated with SmI_2–H_2O. In all cases, selective reduction of the six-membered lactone occurred smoothly, and no products arising from reduction of other lactones and acyclic esters were observed (Scheme 3B).[22,23] The radicals and anions arising from ET to the carbonyls of six-membered lactones benefit from stabilization by hyperconjugation (an "anomeric effect"), and it is this stabilization that likely promotes conversion to the diol products.

2.1.2. Meldrum's Acid Reduction. In 2009 we reported the first reduction of Meldrum's acid derivatives (malonic acid-derived heterocyclic feedstocks) to the corresponding 3-hydroxypropanoic acids using SmI_2–H_2O and found that significant chemoselectivity is possible (Scheme 4).[24−26] Prior to our report, this transformation required a multistep sequence. Again, an anomeric effect is thought to promote conversion to the hydroxy acid products: computational studies showed that ET to the ester carbonyl of cyclic-1,3-diesters is more favorable than that to acyclic 1,3-diesters.[24]

2.1.3. Barbituric Acid Reduction. SmI_2–H_2O can also selectively reduce barbituric acids to the corresponding hemiaminals.[27] Barbituric acids have played a significant role in medicine and are valuable building blocks for organic synthesis. Prior to our studies, the general monoreduction of

Scheme 4. Selective Monoreduction of Meldrum's Acids



barbituric acids was unknown. The monoreduction of barbituric acids with SmI_2–H_2O delivers unusual stable hemiaminal products (Scheme 5A) that are useful activated intermediates ripe for manipulation (Scheme 5B).[27,28] Furthermore, the hemiaminals formed in the reduction can be directed down different reaction pathways by the careful choice of cosolvent used in conjunction with SmI_2 (Scheme 5C).[29]

2.2. Reduction of Acyclic Carboxylic Acid Derivatives

In 2011 we found that the SmI_2–H_2O–NR_3 reagent system is able to reduce *acyclic* aliphatic esters to alcohols, the first time such a transformation had been achieved with Sm(II) (Scheme 6A).[30] The SmI_2–H_2O–NR_3 reagent system was first reported by Cabri[31] but has recently been popularized in a series of groundbreaking studies on the reduction of other functional groups by Hilmersson.[13,32] We have subsequently extended the use of SmI_2–H_2O–NR_3 to the productive reductive manipulation of all lactones (Scheme 6B),[22,23,33] acids (Scheme 6C),[34] nitriles (Scheme 7A),[35] and amides (Scheme 7B).[36] The reduction of feedstock carboxylic acids with SmI_2–D_2O–NEt_3 permits the mild chemoselective synthesis of α,α-dideuterio alcohols.[37]

We have since applied the Sm(II)-mediated ester reduction in its most challenging setting to date. During our total synthesis of (+)-pleuromutilin (**1**), we found that the reduction of the methyl ester in **10** could not be satisfactorily achieved using hydride reagents. By redirection of the transformation through a radical pathway, the conversion to primary alcohol **11** was achieved in 95% yield upon treatment of **10** with an excess of SmI_2–H_2O–pyrrolidine (Scheme 8).[16] The use of alternative ET reagents (e.g., Na/SiO_2) returned only starting material.[16]

2.3. Mechanistic Considerations

Studies of the reduction of lactones,[23,38] Meldrum's acids,[39] esters,[40,41] acids,[34,41] and amides[36,41] have led us to propose a common mechanism with only subtle changes observed as the carboxylic acid derivative and Sm(II) reagent are varied. In our studies, we have measured rate orders for each component,

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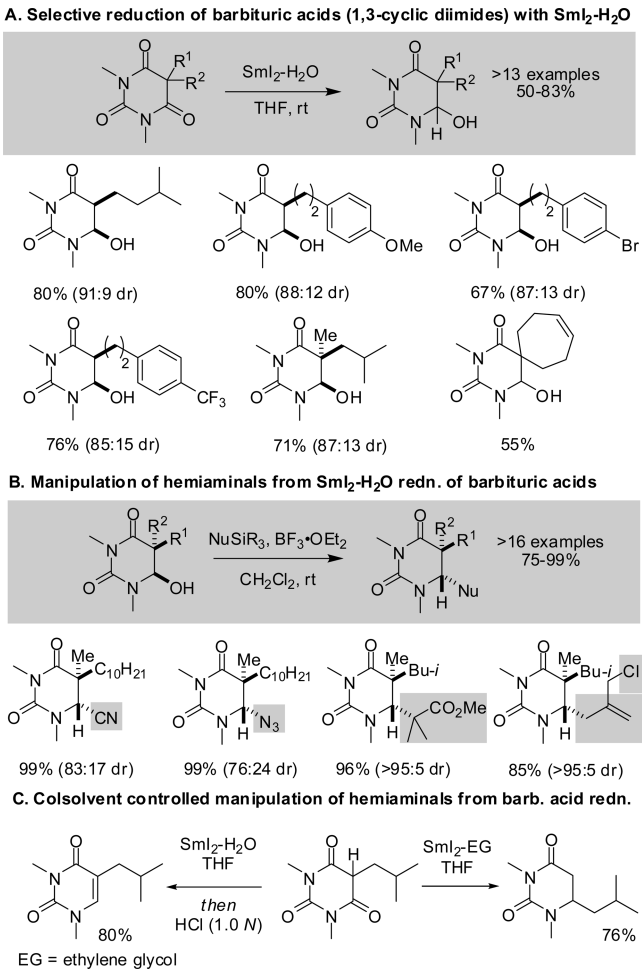
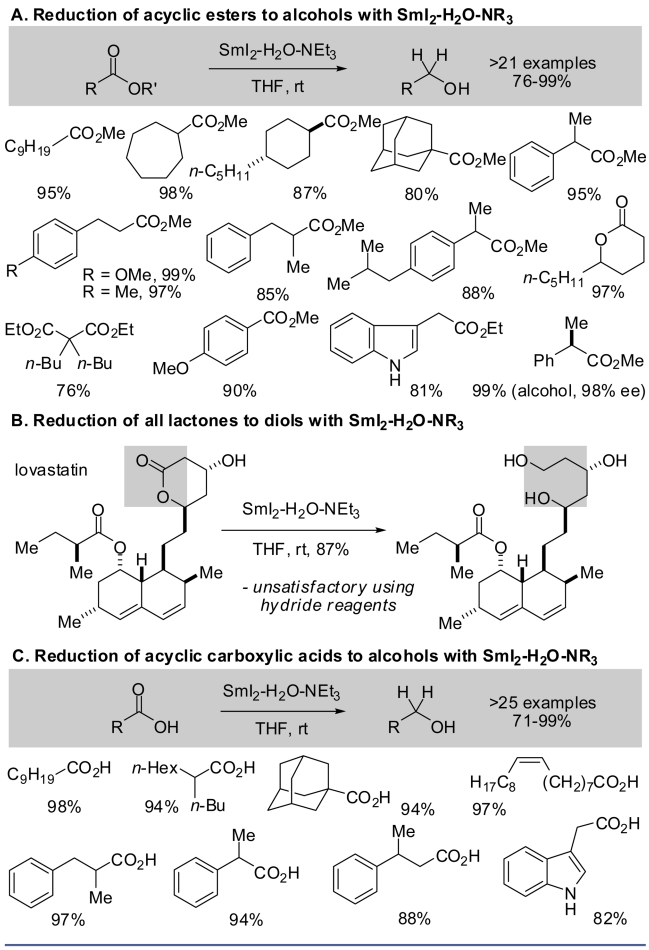
Scheme 5. Selective Reduction of Barbituric Acids and Further Manipulation



Scheme 6. Sm(II)-Mediated Reductions of Acyclic Esters, Lactones, and Carboxylic Acids



carried out Hammett and Taft correlations, utilized radical probes, measured kinetic isotope effects, and conducted isotopic labeling experiments.

The reduction of carboxylic acid derivatives proceeds by a series of electron transfer and protonation events (four electrons and four protons are required). At the center of our postulated mechanism is the proposed reversibility of the first ET to the carbonyl of carboxylic acid derivatives. We have used validated and novel radical probes to investigate the first ET step in several carboxylic acid derivatives.[41] For example, in the study of lactone reduction using SmI_2–H_2O, we used two classes of mechanistic probe to investigate the ET (Scheme 9A).[38] Both probe types utilize fast radical fragmentations to report on the transient formation of radical anions by ET to the carbonyl. In typical experiments involving limiting SmI_2–H_2O and probe type I, products of fragmentation are rapidly formed but no diols are observed. This strongly suggests that the first ET is facile but reversible: the lactone products of fragmentation are reduced further to the corresponding radical anions, but no diol products are formed because the ET is reversible. Crucially, although five-membered lactones do not undergo reduction to diols using SmI_2–H_2O, it is clear that they are reduced, as fragmentation is observed (Scheme 9B). Similarly, with probe type II, five-, six-, and seven-membered substrates undergo fragmentation despite the observation that five- and seven-membered lactones do not undergo conversion to diols using SmI_2–H_2O (Scheme 3). This again suggests that the first ET to all lactones from SmI_2–H_2O is reversible.[38]

The reversibility of ET to carboxylic acid derivatives fits well with the accepted reversibility of the first ET from SmI_2 to ketones and aldehydes.[19] Furthermore, the electrochemical reduction of esters has been shown to be reversible.[42] If one accepts that the first ET to carboxylic acid derivatives is reversible and that favorable follow-up processes are required before reduction manifests itself through product formation, then anomalous observations from the past 35 years of literature can be explained, e.g., the recent fragmentation of cyclopropyl esters[43] and toluates.[44]

The H_2O additive likely plays a number of roles in the reduction of carboxylic acid derivatives. First, seminal work by Flowers has shown that the addition of H_2O increases the reduction potential of SmI_2[20] and displaces iodide but does not inhibit substrate binding to Sm(II).[45] The addition of amine further increases the reduction potential of SmI_2–H_2O.[46] Second, H_2O coordinated to Sm acts as a proton source. For example, in 2009 Hoz showed that bound H_2O accelerates the reduction of α-cyanostilbenes by efficiently protonating, and thus trapping, a short-lived radical anion.[47] Third, our studies suggest that H_2O coordinates to and stabilizes the radical anions formed by ET, thus allowing them to be exploited in synthesis.[38]

In the SmI_2–H_2O–NR_3 reagent system, our kinetic studies have shown that all components are involved in the rate-determining step of the reductions of carboxylic acid

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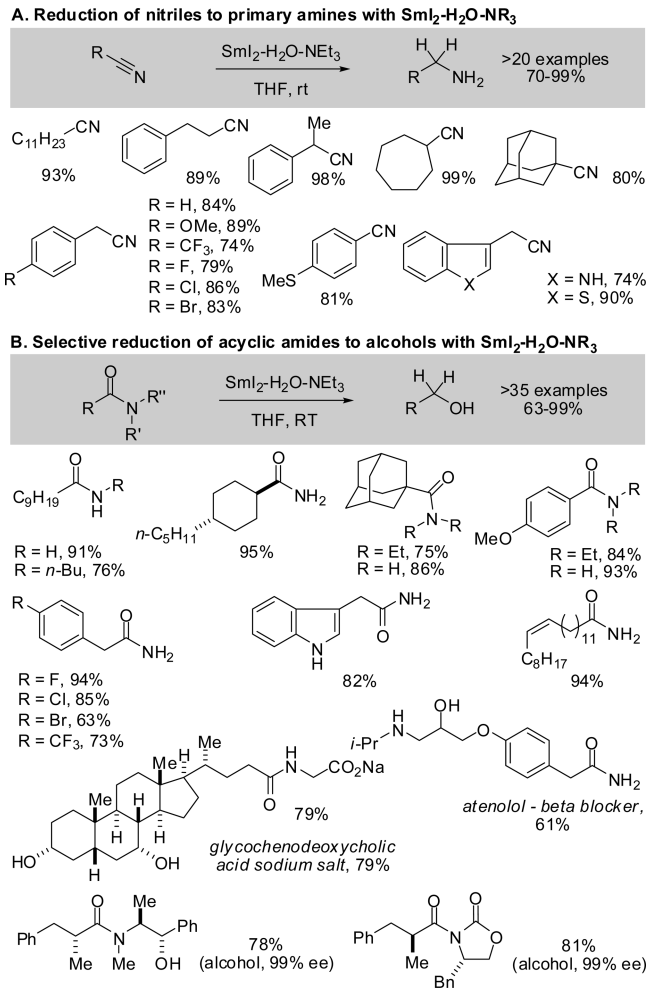
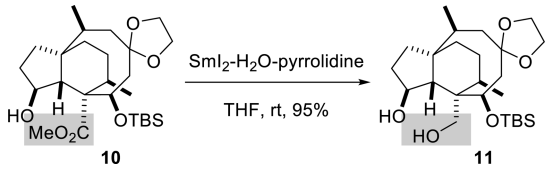
Scheme 7. General ET Reduction of Nitriles and Acyclic Amides



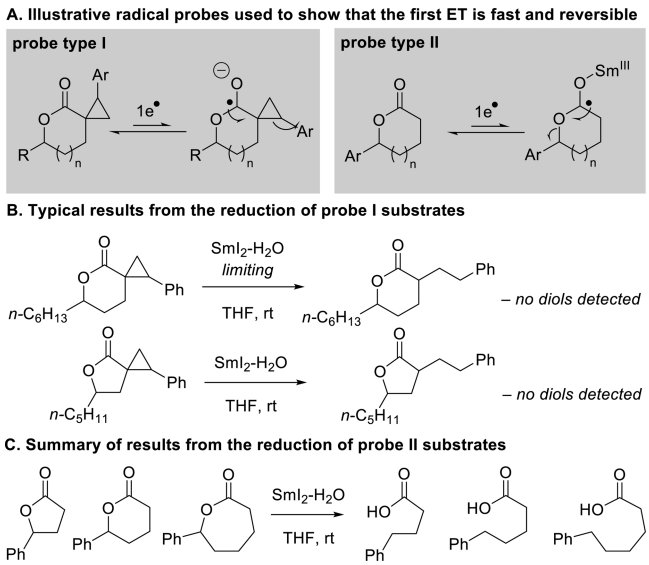
Scheme 8. Sm(II)-Mediated Ester Reduction Unlocks Our Total Synthesis of (+)-Pleuromutilin



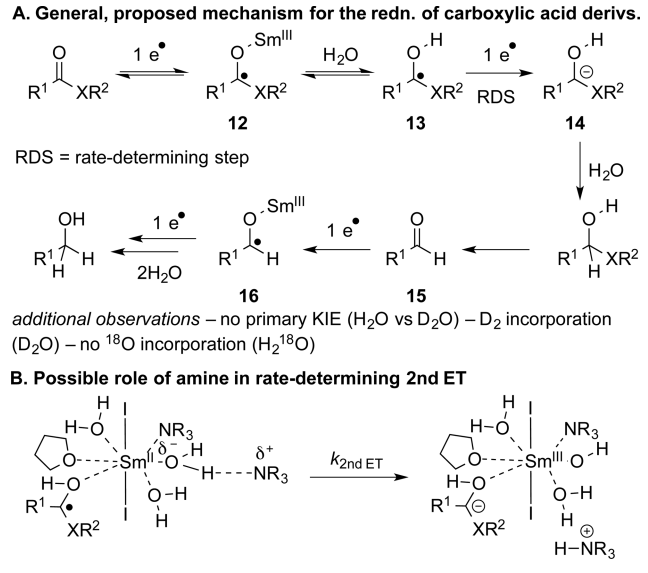
derivatives,[41] and we propose that the role of the amine is to deprotonate a H_2O molecule bound to Sm(II). Thus, the amine additive can be varied to fine-tune the rate of reduction (Schemes 8 and 10B).

A proposed general mechanism for the reduction of carboxylic acid derivatives by SmI_2–H_2O and SmI_2–H_2O–NR_3 is shown in Scheme 10A. The reversible first ET generates radical anion **12**, which is reversibly protonated by H_2O. We believe the rate-determining step is the second ET reduction to form anion **14** (or the corresponding dianion). The transformations then proceed through an aldehyde intermediate **15** that is then reduced to a second radical anion **16**. Subsequent reduction and protonation steps give the alcohol products of reduction (Scheme 10A).

Scheme 9. Studies of Lactone Reduction Using Radical Probes



Scheme 10. Mechanism of the Reduction of Carboxylic Acid Derivatives and Role of Amine



3. EXPLOITING RADICAL ANIONS DERIVED FROM CARBOXYLIC ACIDS IN CASCADE REACTIONS

We utilized three strategies in attempts to harness the unusual radical anions (cf. **12**) in synthesis for the first time (Scheme 11B–D). Notably, our original lactone reduction relied on the extraordinary stability of the six-membered radical and anion intermediates. The first *general* strategy for exploiting the unusual radical anions formed by ET to carboxylic acid derivatives involves the use of an internal ligand in the substrate that coordinates to Sm(III) and promotes radical and anion formation by ET (Scheme 11B). A second strategy involves the use of an external ligand to exert the same effect—one role played by H_2O and amine additives (Scheme 11C). Finally, a third strategy involves the use of a favorable follow-up cyclization to intercept the transient radical anion (Scheme 11D).

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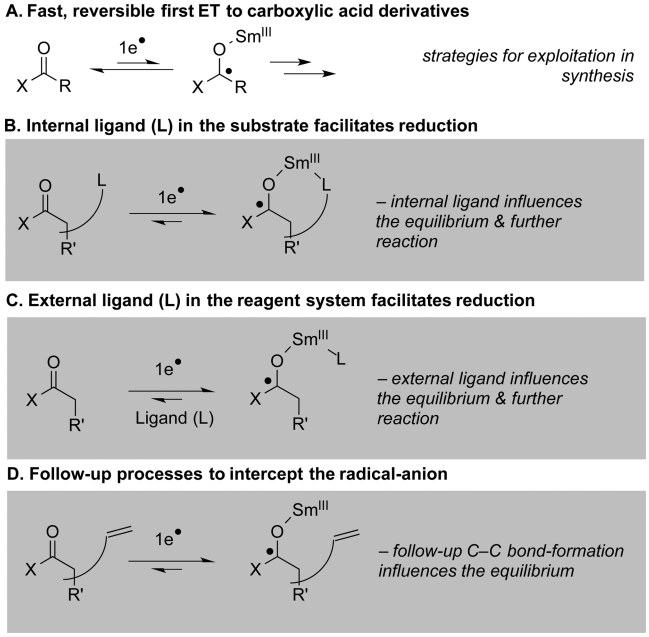
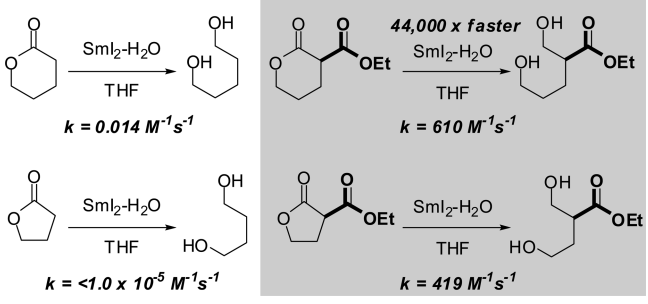
Scheme 11. Exploiting Radical Anions Generated after ET to Carboxylic Acid Derivatives



3.1. Cascade Processes Utilizing an Internal Directing Group

In collaborative studies with Flowers, we presented a rare example of the use of directing groups to "switch on" ET to an otherwise inert substrate and to orchestrate subsequent radical processes.[48] Using kinetic experiments, we quantified the effect of directing groups on the rate of ET to lactones using SmI_2–H_2O (Scheme 12). For example, the use of an ethoxycarbonyl

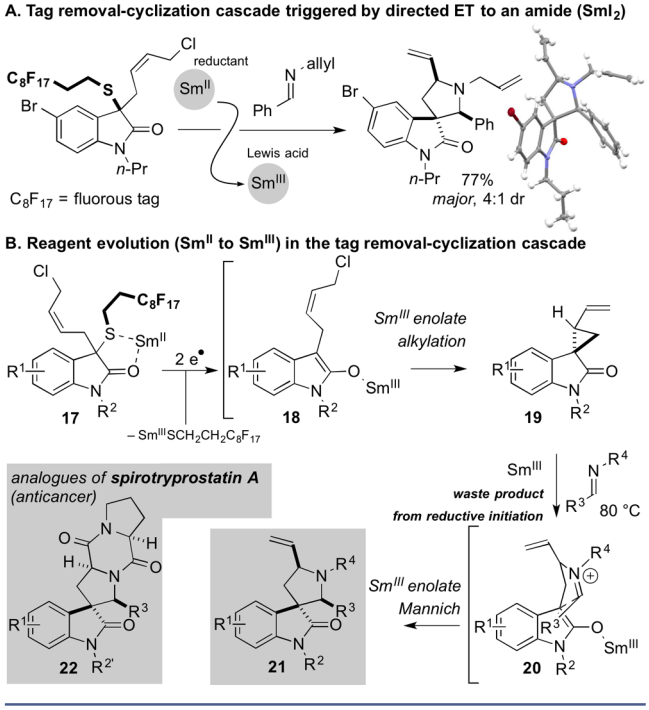
Scheme 12. Use of a Directing Group to "Switch on" ET to Unreactive Substrates



substituent greatly accelerates ET to a six-membered lactone. Crucially, previously inert substrates including five-membered lactones are rendered reactive by the presence of the directing group.

We used a directing group to switch on ET to amide-type carbonyls in our studies on phase tag-removal cyclization cascades. We previously developed a connective Pummerer-type process[49−54] that allows a fluorous tag to be introduced, an N-heterocycle to be constructed, and a sulfur linker system to be established in a one-pot reaction. We next sought to develop a process in which tag removal would trigger a cyclization cascade and an increase in molecular complexity. The tag removal−cyclization sequence is initiated by amide reduction using SmI_2, with the sulfur link to the phase tag acting as a directing group to facilitate ET (Scheme 13A). We first explored such a cascade in an approach to the indoloquinoline

Scheme 13. Directed ET in a Cascade Approach to Biologically Significant Spirooxindoles



natural product neocryptolepine.[54] A more sophisticated variant delivered collections of biologically significant pyrrolidinyl spirooxindoles **21** and analogues of the anticancer natural product spirotryprostatin (**22**) (Scheme 13B).[51] Directed ET to the amide carbonyl in **17** results in expulsion of the tag, formation of Sm(III) enolate **18**,[55] and intramolecular alkylation to give vinyl cyclopropane **19**. Upon heating in the presence of an imine, the Sm(III) waste product from the initiating ET step acts as a Lewis acid in the cyclopropane opening and Mannich cyclization to give spirocycles **21** (Scheme 13B).

Directed ET to amides has also been employed in our approaches to novel organic materials.[52,53] We began by preparing new benzo[*b*]carbazole end-capped oligothiophenes **28** (Scheme 14).[52] Sulfone-directed ET to the amide carbonyl from SmI_2 triggered removal of the fluorous tag, and Sm(III) enolate **24** was then protonated by the alcohol additive. Barbier-type cyclization was then initiated by bromide reduction to give organosamarium **25**, and subsequent dehydration gave **26** (Scheme 14A). After oxidation, **27** underwent cross-coupling with different bis(stannyl)-oligothiophene units (Scheme 14B).

Directed ET to amides has also been used in a two-directional cascade to deliver dibenzo[3,2-*b*]carbazole materials, thus allowing their properties to be evaluated (Scheme 15).[53]

3.2. Cascade Processes Utilizing an External Directing Group

We have exploited ligand-controlled ET to the lactone carbonyl in cascades and telescoped reaction sequences. For example, enantiomerically pure unsaturated lactone **31** undergoes cascade conversion to triol **34** upon treatment with SmI_2–H_2O (Scheme 16A).[56] The process involves reductive

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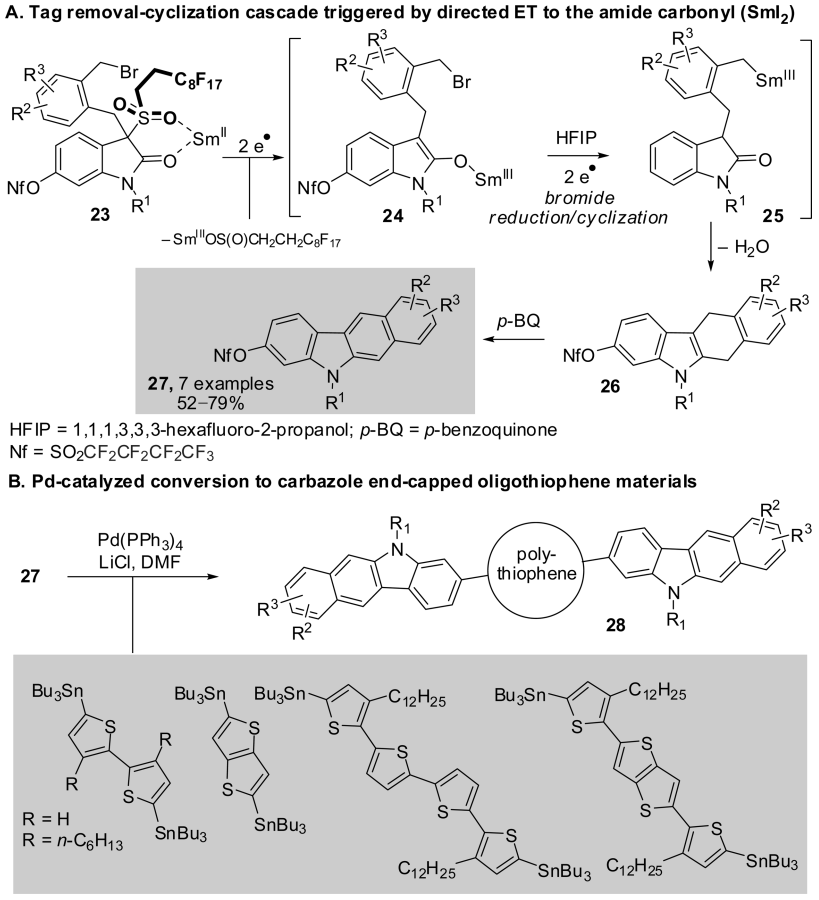
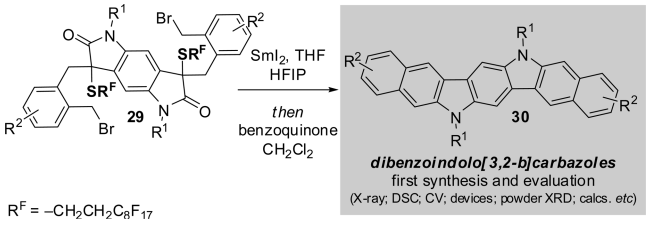
Scheme 14. Cascades Triggered by Directed ET in an Approach to Materials



Scheme 15. Directed ET to Amides in a Two-Directional Cascade



formation of Sm(III) enolate **32**, diastereoselective aldol spirocyclization, and ET reduction of the six-membered lactone. The cascade establishes the two vicinal quaternary stereocenters in the cyclopentyl fragment of stolonidiol.

H_2O and NEt_3 have been used to direct ET to a five-membered lactone in a related process in which a silicon stereocontrol element exerts complete diastereocontrol over the cyclization step and is removed during the final stage of the telescoped sequence (Scheme 16B).[57]

Finally, we have used H_2O-directed ET reduction of a lactone to terminate a dialdehyde cyclization cascade.[58] Exposure of dialdehyde **40** to SmI_2 delivers spirolactone **41**, and addition of H_2O then switches on the ET to the six-membered lactone to give triol **42** (Scheme 17).

3.3. Cascade Processes Utilizing Follow-Up Cyclizations

Radical anions **43** generated from cyclic carboxylic acid derivatives using SmI_2–H_2O undergo cyclization provided that the positioning of a radical acceptor causes cyclization to be faster than further ET to the radical anion. Cyclizations initially give ketone products **44**, but these are often reduced further to give radical anions **45** en route to secondary alcohols **46**. Alternatively, if a second radical acceptor is present, then radical anions **45** can also be used in carbon–carbon bond formation (Scheme 18). These unprecedented cyclization cascades generate complexity, proceed with diastereocontrol, and deliver structures that are either difficult to make using alternative methods or whose preparation is unprecedented.

3.3.1. Monocyclizations of Carboxylic Acid Derivatives. *3.3.1.1. Cyclization of Meldrum's Acids and Barbituric Acids.* Attaching an unsaturated tether to Meldrum's acids allows radical anion intermediates to be trapped, giving rise to cyclopentanol products in excellent yields and diastereoselectivities (Scheme 19).[24,25] Acetophenone cyclic ketals at higher temperatures gave the best diastereoselectivies (≤8:1 dr). The cyclopentanol products were converted to the corresponding cyclopentanones by an esterification/oxidation protocol to clarify the stereoselectivity of the carbon–carbon bond-forming event (≤33:1 dr).[25]

Treatment of barbituric acids bearing a suitably positioned alkene/alkyne with SmI_2–H_2O gives bicyclic products in excellent yields with complete diastereocontrol (Scheme 20).[27]

3.3.1.2. Cyclization of Lactone Derivatives. Radical anions generated by ET to the carbonyl group of six-membered lactones are also amenable to trapping by radical acceptors. Cyclization of lactone substrates bearing an ester directing group with an alkene tethered α to the carbonyl group using SmI_2–H_2O gave cyclopentanones in good to excellent yields with high diastereocontrol (Scheme 21A).[23] In this case, ketone

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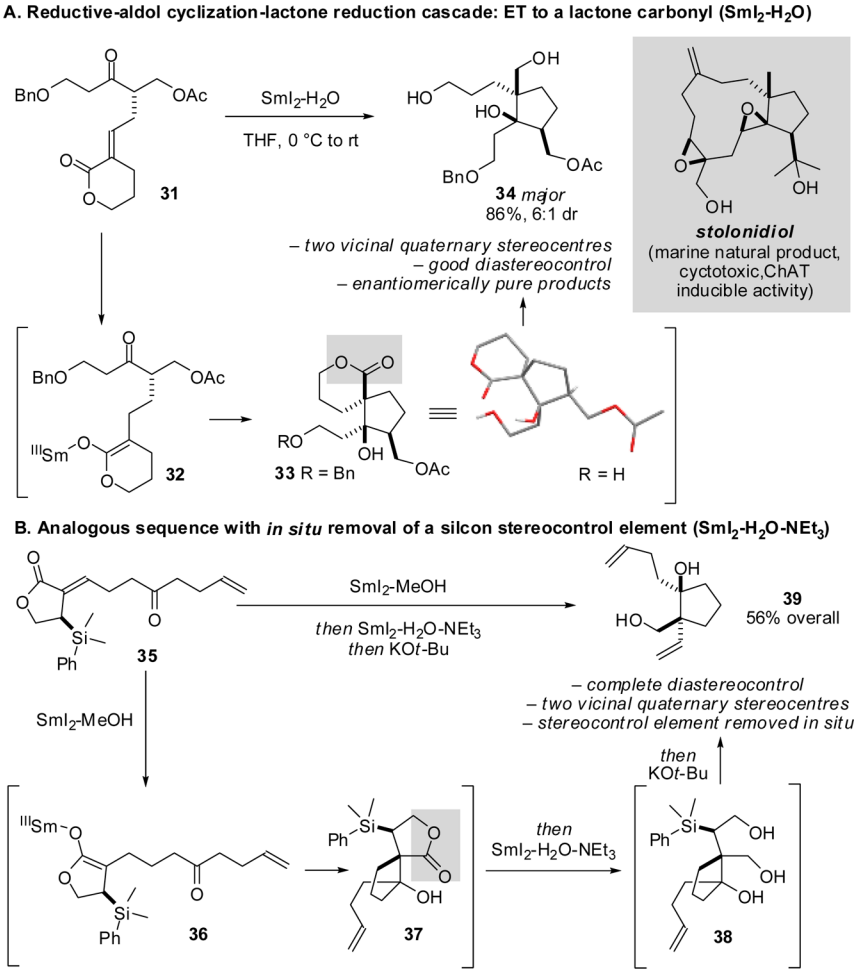
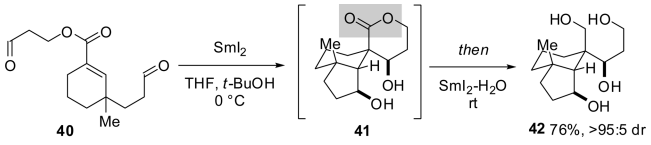
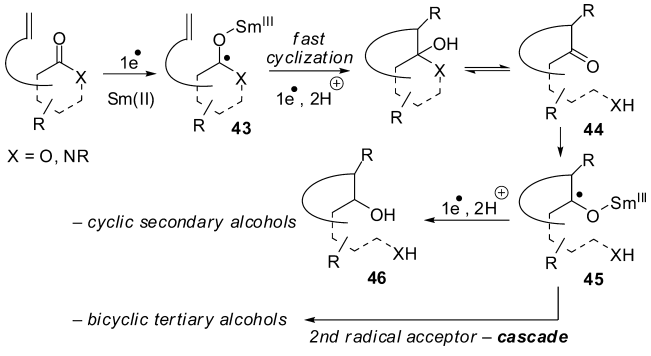
Scheme 16. Stereoselective Conjugate Reduction–Aldol Cyclization–Lactone Reduction



Scheme 17. Cyclization Cascade Terminated by Lactone Reduction

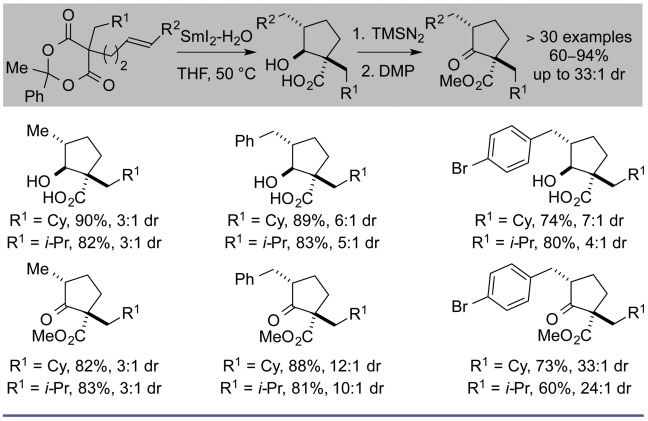


Scheme 18. Cyclization of Radical Anions Derived from Cyclic Carboxylic Acid Derivatives



products were isolated, and further reduction to the corresponding cyclic secondary alcohols was not observed. This is thought to be due to stabilization of the hemiketal

Scheme 19. Stereoselective Cyclizations of Meldrum's Acids



cyclization products by the ethoxycarbonyl substituent. Cyclopentanone products likely arise from cyclization of pseudoaxial radical anion **47** through an endo-type transition state (Scheme 21B).

The cyclization of lactones bearing alkenes, alkynes, and allenes tethered at the δ position was investigated next (Scheme 22). Upon treatment with SmI_2–H_2O, cyclization forms seven-membered carbocycles with up to four contiguous stereocenters in good yields and diastereoselectivities.[59,60] Hemiketal products **48** are further reduced to the diols in most cases

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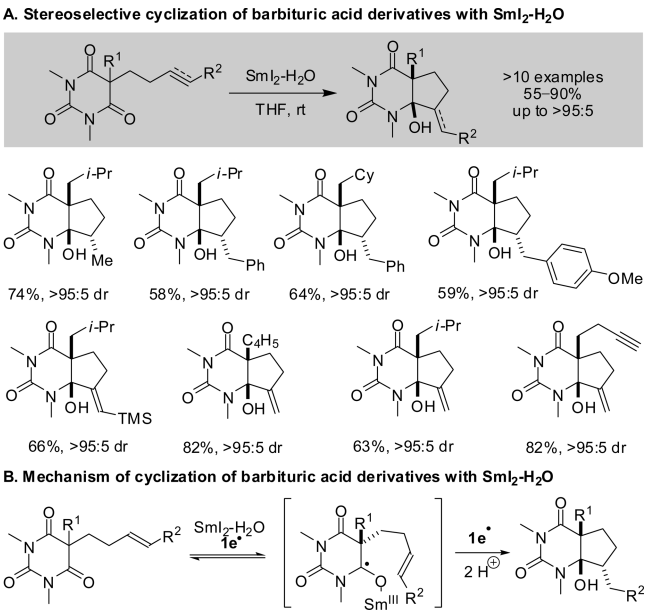
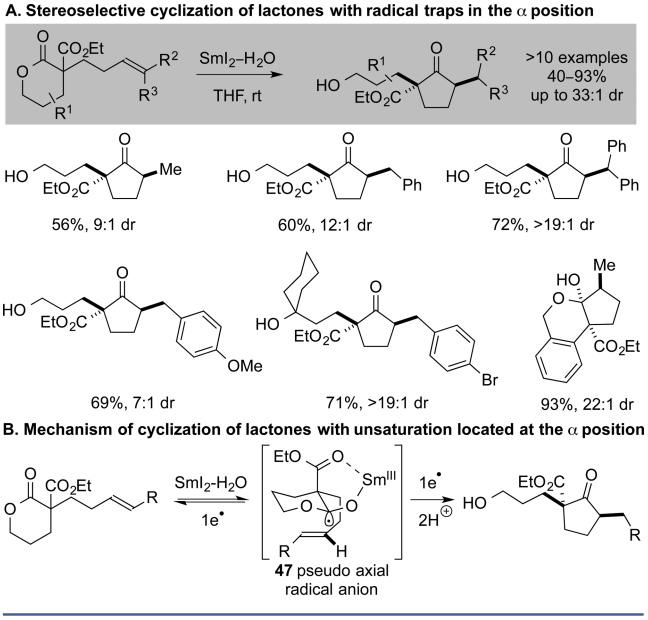
Scheme 20. Stereoselective Cyclization of Barbituric Acid Derivatives



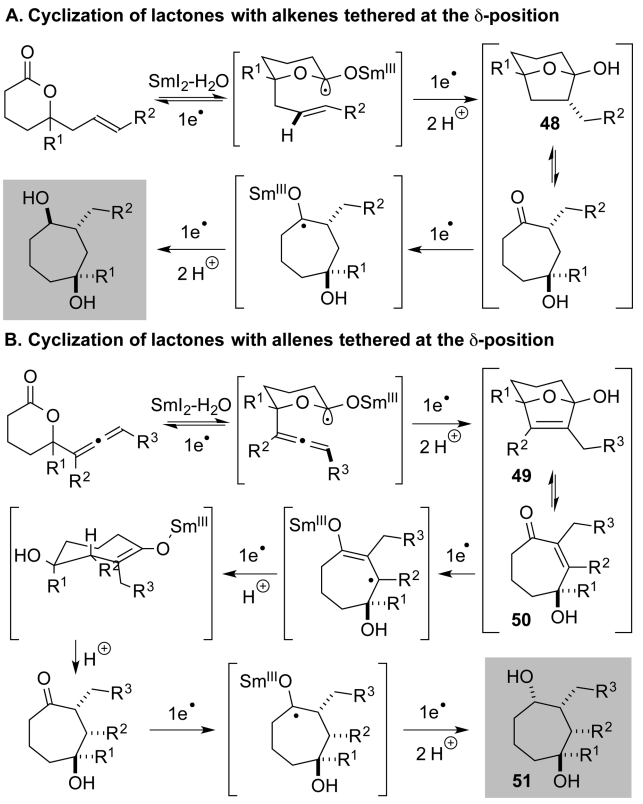
Scheme 21. Stereoselective Cyclizations of Lactones with Alkenes Tethered at the *α* Position



(Scheme 22A). In contrast, allenyllactones undergo cyclization to give unsaturated hemiketals **49**, which collapse to give cycloheptenones **50**. Subsequent conjugate reduction and diastereoselective 1,2-reduction of **50** delivered diol products **51**, the stereochemistry of which is established postcyclization in a relay from position to position around the ring (Scheme 22B).

The scope of the ET-triggered cyclization of lactones bearing alkene and allene groups tethered at the δ position of the ring has been evaluated (Scheme 23). Cyclization of alkenyllactones gives products in good yields even when terminal alkenes are employed as the trap (Scheme 23A). Oxidation of the 1,4-cycloheptanediol products revealed the stereoselectivity observed in carbon–carbon bond-formation.[59] Exposure of

Scheme 22. Stereoselective Cyclizations of Lactones with Alkenes Tethered at the *δ* Position



allenyllactones to SmI_2-H_2O triggered cyclization and highly diastereoselective formation of more decorated 1,4-cycloheptanediols (Scheme 23B).[60]

3.3.2. Cascade Cyclizations of Carboxylic Acid Derivatives. *3.3.2.1. Cascade Cyclizations of Meldrum's Acids.* The ET reduction of carboxylic acid derivatives passes through two radical anion intermediates. Having shown that the first radical anion can be efficiently trapped by an acceptor, we explored the possibility of also intercepting the second radical anion using an additional internal radical trap.

In Meldrum's acid derivatives **52** bearing two radical acceptors, trapping of the first radical anion **53** generates cyclopentanone intermediates **54**. Further reduction generates a second radical anion that is trapped by the remaining unsaturation to give complex bicyclic tertiary alcohols **55** (Scheme 24A).[25,61] Importantly, all substrates **52** possess a plane of symmetry that is broken by ET, and thus, complex chiral products bearing multiple stereocenters can be obtained from simple achiral compounds in a single operation.

A range of Meldrum's acids underwent cascade cyclization upon treatment with SmI_2-H_2O in good yields and often with complete diastereocontrol (Scheme 24B).[25,61] Alkene and alkyne tethers were used as radical acceptors. In the latter case, good selectivity was observed for the formation of the *E* alkene isomer.[61] The cascades can be reprogrammed to deliver alternative products: elongation of a tether results in the assembly of 5,6-fused bicyclic scaffolds (Scheme 24B).[61]

3.3.2.2. Cascade Cyclizations of Lactone Derivatives. We next investigated cascade cyclizations of lactone substrates bearing unsaturated tethers at the α and δ positions. For example, we proposed that treatment of *cis*-lactones **56** with SmI_2-H_2O would give 5,7-fused bicyclic tertiary alcohols **60**

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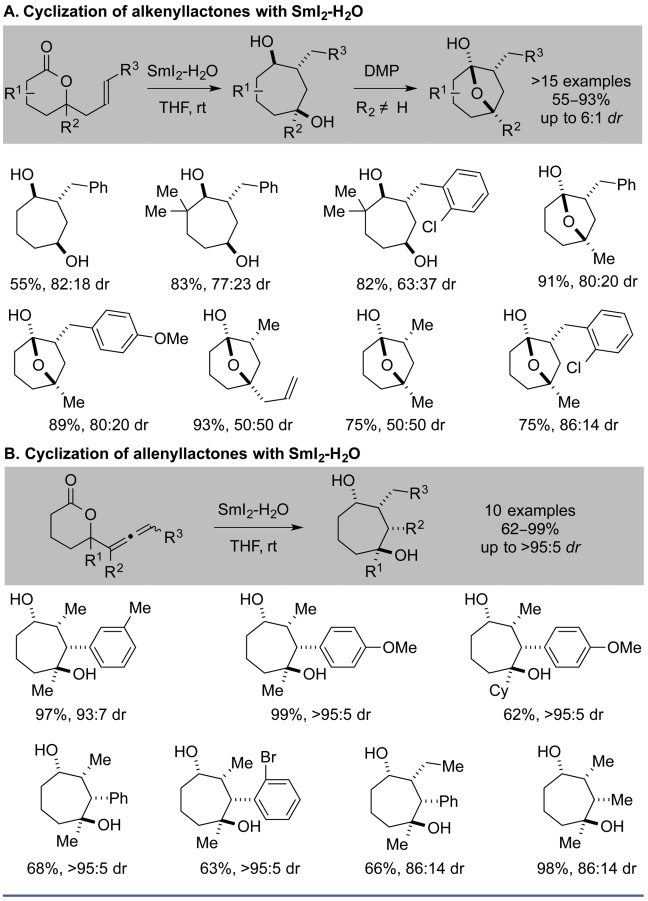
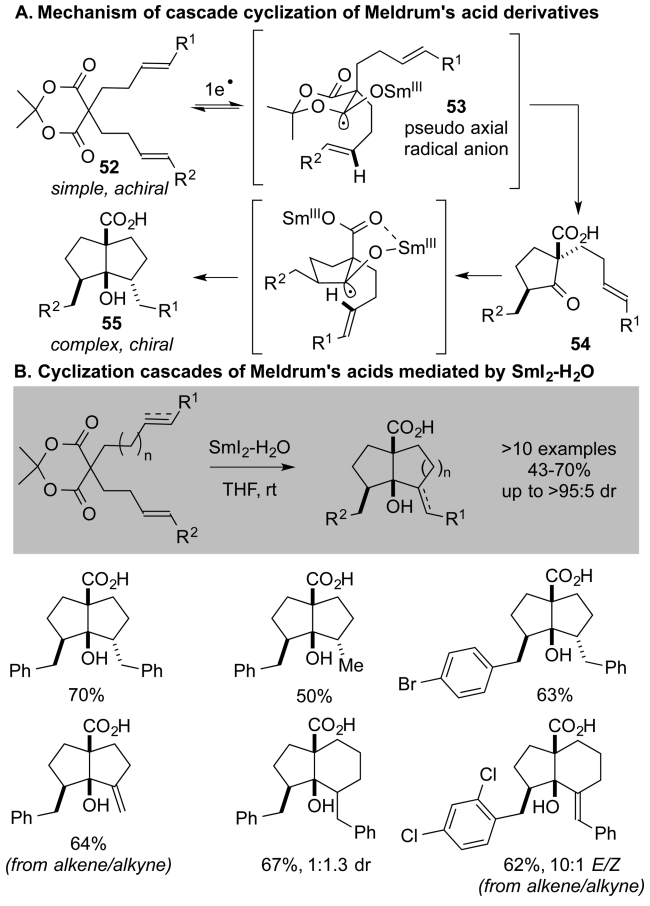
Scheme 23. Stereoselective Cyclization of Alkenyllactones and Allenyllactones



Scheme 24. Stereoselective Cascade Cyclizations of Meldrum's Acid Derivatives

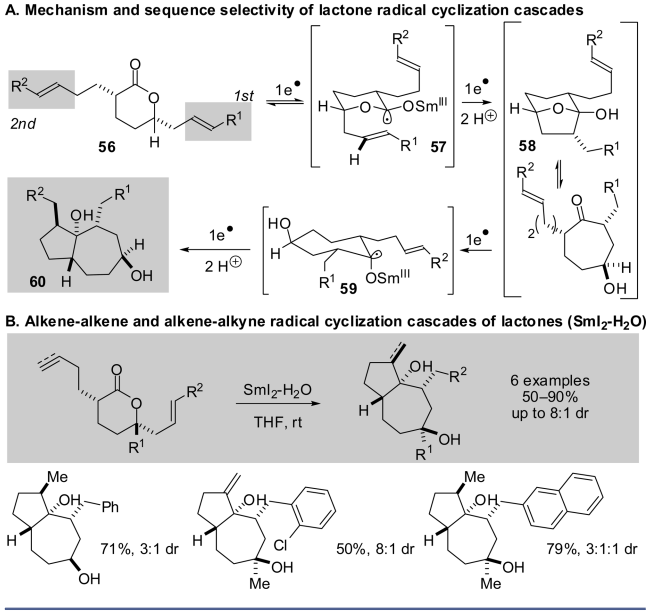


resulting from a well-defined "right then left" sequence (Scheme 25A).[59,60] Theoretical calculations suggested that high sequence integrity would arise from the low activation energy for the cyclization of the axial radical anion **57** onto the unsaturated tether at the δ position. The hemiketal **58** obtained from the first cyclization would be reduced in situ to form a second radical anion **59** that could be intercepted by the second trap (Scheme 25A). Pleasingly, a range of lactone substrates bearing alkene and alkyne radical traps underwent efficient cascade cyclization with high sequence selectivity to give complex bicyclic alcohol products in moderate to good yields with significant diastereocontrol (Scheme 25B).[59,60]

As illustrated in the monocyclization of allenyllactones, we proposed that cascades involving allenyl substrates **61** would deliver products possessing an additional substituent and stereocenter and that these more decorated products might be delivered with higher diastereocontrol.[60] Attractively, cascade cyclization of *cis*-allenyllactones **61** delivered products **62** with a trans ring junction, while treatment of *trans*-allenyllactones **61** with SmI_2–H_2O gave **62** possessing a cis-fused ring junction. Cascade products were obtained with four new stereocenters, often with complete diastereocontrol and in high yield (Scheme 26).[60]

Preliminary studies showed the feasibility of re-engineering the cascade cyclizations to deliver a range of molecular architectures. For example, homologation of the tether at the α position grants access to [5.4.0]bicyclic tertiary alcohol products **63**, albeit in lower yield because of the challenging nature of the 6-exo-trig cyclization that terminates the cascade

Scheme 25. Sequence-Selective Lactone Cyclization Cascades



sequence (Scheme 27A).[62] Furthermore, allenyllactones **64** undergo "right then right" cascade cyclizations upon treatment with SmI_2–H_2O to deliver bridged bicyclic tertiary alcohol products **65** in moderate yields (Scheme 27B).[60]

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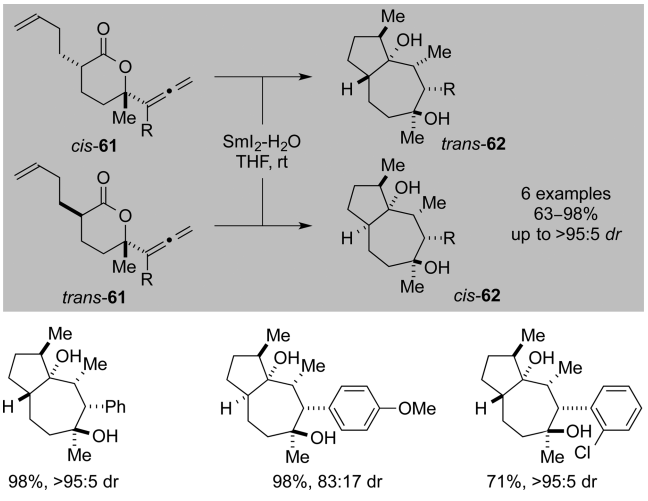
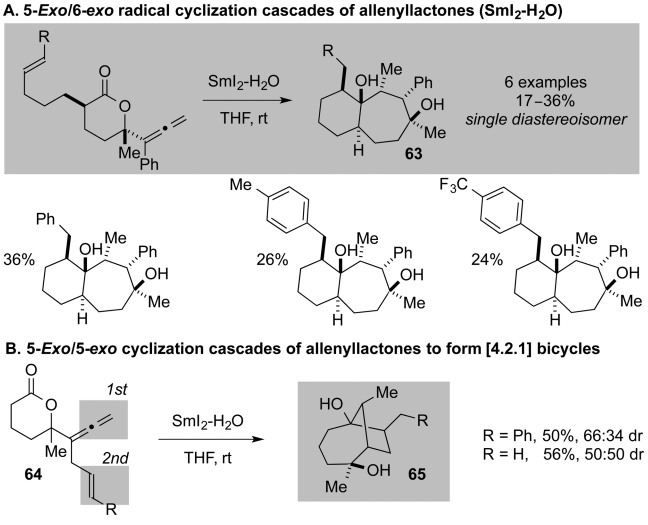
Scheme 26. Allene−Alkene Radical Cyclization Cascades of Lactones



Scheme 27. Reprogramming the Cyclization Cascades of Allenyllactones



4. SUMMARY AND OUTLOOK

We have developed a new activation mode for carbonyl compounds that employs reductive electron transfer from Sm(II). Conversion of carboxylic acid derivatives to the corresponding radical anions upon exposure to Sm(II) has led to the development of a wide range of selective functional group interconversions, including the first monoreduction of Meldrum's acids and barbituric acids and the first general reduction of acyclic amides to alcohols. Radical anions derived from carboxylic acid derivatives have also been used in unprecedented intramolecular carbon−carbon bond-forming reactions. In particular, a range of diverse molecular architectures of significance in biology and materials science can be accessed from simple carboxylic acid-derived feedstocks by complexity-generating cascade sequences mediated by Sm(II). The demand for designer Sm(II) reagents with programmable reactivity and selectivity and the promise of asymmetric catalytic processes suggests a bright future for this nascent field.

AUTHOR INFORMATION

Corresponding Author

*E-mail: david.j.procter@manchester.ac.uk.

Notes

The authors declare no competing financial interest.

Biographies

Xavier Just-Baringo was born in Barcelona, Spain, and received his B.Sc. in chemistry from the University of Barcelona in 2008. After an industrial placement at GlaxoSmithKline (Stevenage, UK) he joined the group of Fernando Albericio and Mercedes Álvarez at the Institute for Research in Biomedicine (Barcelona), where he earned his Master's and Ph.D. degrees in 2010 and 2013, respectively, working on the total synthesis of thiopeptide antibiotics and their structure−activity relationships. He is currently a Postdoctoral Fellow in the group of Prof. David J. Procter, studying radical cyclization cascades promoted by SmI_2 and their application in the synthesis of biologically relevant scaffolds. He is a member of the Reaxys Ph.D. Club.

David John Procter was born in Leyland in Lancashire, England. He obtained his B.Sc. in chemistry from the University of Leeds in 1992 and his Ph.D. in 1995, studying the chemistry of selenoxides with Professor Christopher Rayner. He then spent two years as a Postdoctoral Fellow with Professor Robert Holton at Florida State University in Tallahassee, FL, USA, working on the synthesis of the anticancer agent Taxol. In late 1997 he took up a Lectureship at the University of Glasgow in Scotland and was promoted to Senior Lecturer in February 2004. In September 2004, he moved to a Readership at the University of Manchester and was promoted to Professor in October 2008. He is an EPSRC Established Career Fellow and has been awarded the 2014 Bader Prize (Royal Society of Chemistry), the 2014 Liebig Lectureship (German Chemical Society), and a Leverhulme Trust Research Fellowship (2013). His research interests lie in the development of new synthetic methods, catalysis, and the synthesis of natural and unnatural targets.

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