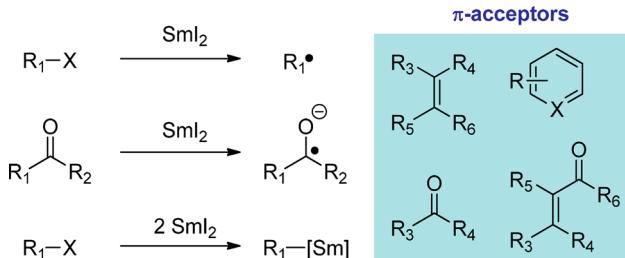


CHEMICAL REVIEWS

Cross-Coupling Reactions Using Samarium(II) Iodide

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CONTENTS

| | |
|---|------|
| 1. Introduction | 5959 |
| 2. Reactivity of Functional Groups toward Samarium Diodide | 5960 |
| 3. Cross-Coupling via Radical Intermediates | 5961 |
| 3.1. Ketyl Radical-Alkene/Alkyne/Arene Cross-Coupling | 5961 |
| 3.1.1. Intramolecular Cross-Coupling of Ketyl Radicals with Alkenes | 5961 |
| 3.1.2. Intermolecular Cross-Coupling of Ketyl Radicals with Alkenes | 5977 |
| 3.1.3. Cross-Coupling of Ketyl Radicals with Alkynes | 5983 |
| 3.1.4. Cross-Coupling of Ketyl Radicals with Allenes | 5984 |
| 3.1.5. Cross-Coupling of Ketyl Radicals with Arenes | 5985 |
| 3.2. Pinacol-Type Couplings | 5989 |
| 3.2.1. Aldehyde–Aldehyde Cross-Coupling | 5990 |
| 3.2.2. Aldehyde–Ketone Cross-Coupling | 5990 |
| 3.2.3. Ketone–Ketone Cross-Coupling | 5992 |
| 3.3. Cross-Coupling of Imines and Equivalents | 5993 |
| 3.3.1. Cross-Coupling with C=C Bonds | 5994 |
| 3.3.2. Cross-Coupling with C=O and C≡N Bonds | 5997 |
| 3.4. Non-Ketyl Radical-Alkene/Alkyne Cross-Coupling | 6002 |
| 3.4.1. Cross-Coupling of Unstabilized Aryl or Alkyl Radicals | 6002 |
| 3.4.2. Reductive Dimerization of Radicals Generated from α,β-Unsaturated Carbonyls | 6004 |
| 3.4.3. Cross-Coupling of Radicals Generated from α,β-Unsaturated Carbonyls with Various Acceptors | 6005 |
| 4. Cross-Coupling via Ionic Intermediates | 6006 |
| 4.1. Grignard and Barbier Reactions | 6007 |
| 4.1.1. Intramolecular Barbier Reactions | 6007 |
| 4.1.2. Intermolecular Grignard and Barbier Reactions | 6010 |
| 4.2. Reformatsky Reactions | 6014 |
| 4.2.1. Intramolecular Reformatsky Reactions | 6015 |
| 4.2.2. Intermolecular Reformatsky Reactions | 6017 |
| 4.3. Aldol Reactions | 6023 |
| 5. Cross-Coupling As Part of Sequential and Cascade Reactions | 6023 |
| 5.1. Cascades Initiated by Radical Intermediates | 6024 |
| 5.2. Cascades Initiated by Anionic Intermediates | 6028 |
| 6. Conclusions | 6030 |
| Author Information | 6030 |
| Corresponding Authors | 6030 |
| Notes | 6030 |
| Biographies | 6030 |
| Acknowledgments | 6031 |
| References | 6031 |
| Note Added in Proof | 6038 |

1. INTRODUCTION

Since its introduction to organic synthesis in 1977 by Kagan,^{1,2} samarium(II) iodide (SmI_2 , Kagan's reagent) has gained the status of one of the most versatile single-electron transfer reagents available in the laboratory.^{3–46} SmI_2 occupies a unique place among other reductants^{47–57} in that it is an extremely powerful^{58–64} yet chemoselective reagent, whose selectivity toward functional groups is fine-tuned by the use of appropriate ligands and additives.^{26–30} Transformations mediated by SmI_2 are performed under user-friendly and operationally simple reaction conditions,¹⁶ resulting in one of the most straightforward ways to achieve single-electron reductions, a fact that has been successfully exploited in both academic and industrial settings.²⁰ Of particular note is the ability of samarium diiodide to operate through either one- or two-electron reductive pathways, often proceeding with exquisite control of structure and stereochemistry, and providing reaction outcomes complementary to other reductants in the processes mediated by this reagent.

In principle, there are two major classes of reactions mediated by samarium(II) iodide: (i) reductive manipulations of functional groups; and (ii) reductive couplings to make C–C bonds. Over the last 35 years, SmI_2 -mediated couplings to make carbon–carbon bonds have become increasingly useful in organic synthesis. In particular, these reactions have found numerous applications for the synthesis of diverse molecular scaffolds, have been utilized in complex cascade sequences that rapidly build-up molecular architectures, and have provided access to challenging carbon–carbon bond disconnections, which are impossible to achieve with other reagents. Despite the fact that SmI_2 -mediated cross-coupling has become an indispensable tool in organic synthesis and significant advances have been reported, a comprehensive review on this topic^{3–14} has not been published in the last 10 years.

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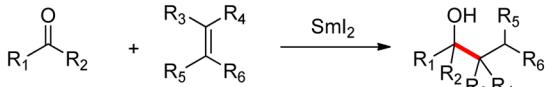
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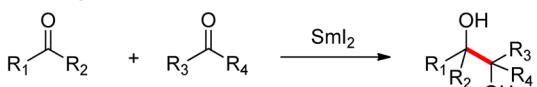
In this Review, we provide a comprehensive survey of cross-coupling reactions mediated by samarium diiodide since 2001 (the year of the last comprehensive review on SmI_2)¹⁴ through 2013, with the focus on advances that have taken place in the field and presenting both the reactions mediated by single-electron and two-electron processes (Figure 1). We believe that by

a) single-electron processes

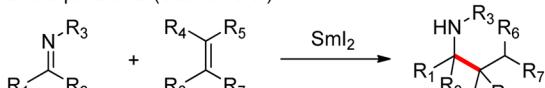
■ ketyl radicals (Section 3.1.)



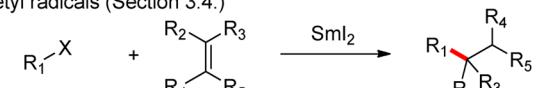
■ pinacol couplings (Section 3.2.)



■ imines and equivalents (Section 3.3.)

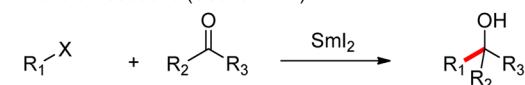


■ non-ketyl radicals (Section 3.4.)

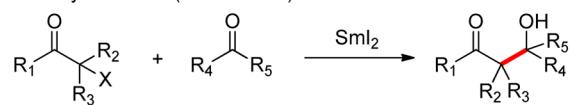


b) two-electron processes

■ Grignard/Barbier reactions (Section 4.1.)



■ Reformatsky reactions (Section 4.2.)



■ aldol reactions (Section 4.3.)

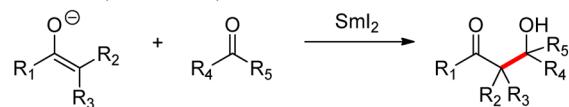


Figure 1. Scope of this Review: (a) reactions proceeding via single-electron mechanisms; and (b) reactions proceeding via two-electron mechanisms.

discussing samarium diiodide-mediated coupling reactions in terms of modern organic synthesis, the reader will be provided with an overview of the area and its complementary, but crucial, role as compared to other methods of cross-coupling to make carbon–carbon bonds,^{65–70} which, arguably, is the most important bond-forming process in organic chemistry.^{71–73}

Samarium(II) iodide has been the subject of previous reviews. These publications have addressed general aspects of application of the reagent,^{3–16} the use of SmI_2 in the synthesis of natural products,^{17–19} chemoselective reductions,²⁰ functional group manipulations,^{21–23} applications in asymmetric synthesis,²⁴ mechanistic aspects,²⁵ influence of the additives,^{26–30} sequential reactions,¹⁰ and specific transformations,^{31–44} among others.^{45,46}

This Review is arranged by the class of the SmI_2 -mediated transformation into radical (section 3) and ionic reactions (section 4), and further by the type of precursors undergoing the cross-coupling event. Additionally, a brief introduction to functional group transformations mediated by SmI_2 has been

included at the beginning of this Review (section 2) to emphasize the recent advances that have taken place in the generation of reactive intermediates for cross-coupling reactions and the mechanistic understanding of these processes. Examples in which both radical and ionic mechanisms for a given process are possible have been highlighted and additionally discussed. Moreover, specific applications of SmI_2 -mediated cross-coupling reactions in complex cascade sequences (section 5) are highlighted in the final section of this Review and serve as a testament to the extraordinary power of the reagent for allowing challenging carbon–carbon bond disconnections. We hope that this Review will serve as a useful reference for chemists involved in using SmI_2 for the reductive formation of carbon–carbon bonds and provide fresh stimulus for further advances in this exciting field.

2. REACTIVITY OF FUNCTIONAL GROUPS TOWARD SAMARIUM DIODIDE

The broad functional group tolerance of SmI_2 has been pivotal to many successful applications of this reagent in the last 35 years.^{3–46} Table 1 lists a selection of major functional groups that can be reduced with SmI_2 . In principle, radical or organo-samarium intermediates generated in these reactions can be utilized for cross-couplings, while their quenching with proton

Table 1. Reactivity of Common Functional Groups toward SmI_2 : Generation of Precursors for Cross-Coupling Reactions^a

| entry | functional group | product | conditions (SmI_2 + additive) |
|-------|---|---|--|
| 1 | R-X | R-H | HMPA, ROH, hν, temp. (X = I, Br, Cl); $\text{Sm}(\text{HMDS})_2$ (X = F) |
| 2 | | $\text{R}_1\text{C}(=\text{O})\text{OH}$ | ROH, EG, HMPA, amine-H ₂ O |
| 3 | $\text{O}=\text{C}(\text{R})\text{O}$ | $\text{O}=\text{C}(\text{R})\text{OH}$ | H_2O |
| 4 | $\text{R}_1\text{C}(=\text{O})\text{XR}_2$ | $\text{R}_1\text{C}(=\text{O})\text{OH}$ | H_2O , amine-H ₂ O |
| 5 | $\text{R}'\text{CN}$ | $\text{R}'\text{NH}_2$ | ROH-hν, amine-H ₂ O |
| 6 | $\text{R}_1\text{C}(=\text{O})\text{R}_2\text{X}$ | $\text{R}_1\text{C}(=\text{O})\text{R}_2\text{H}$ | MeOH, EG, HMPA |
| 7 | $\text{R}_1\text{C}(=\text{O})\text{R}_2\text{R}_3\text{R}_4$ | $\text{R}_1\text{C}(=\text{O})\text{R}_2\text{R}_3\text{H}$ | H_2O , amine-H ₂ O ROH if R_4 = EWG |
| 8 | $\text{R}_1\text{C}(=\text{O})\text{R}_2\text{R}_3\text{R}_4$ | $\text{R}_1\text{C}(=\text{O})\text{R}_2\text{R}_3\text{H}$ | SmI_2 -THF |
| 9 | $\text{R}_1\text{N}-\text{X}$ | $\text{R}_1\text{N}-\text{H}$ | SmI_2 -THF, MeOH, amine-H ₂ O, HMPA |
| 10 | $\text{R}_1\text{S}-\text{R}_2$ | $\text{R}_1\text{S}-\text{R}_2$ | SmI_2 -THF, HMPA |

^aEG = ethylene glycol; EWG = electron-withdrawing group.

sources, *in situ* or upon workup, provides useful protocols for the reduction of common functional groups under mild and orthogonal conditions to other single- and two-electron transfer reductants.²⁰

The selectivity of electron transfer from SmI₂ depends on ligands and additives, solvent, and method of preparation of the reagent.^{26–30} Several major developments in the reduction of common functional groups with Sm(II) have been reported in the past decade and include: (i) chemoselective reduction of cyclic esters with SmI₂–H₂O;⁷⁴ (ii) enhanced reduction of common functional groups with SmI₂–amine–H₂O;^{75–77} (iii) the first general reductions of acyclic esters, carboxylic acids, and amides using SmI₂;^{78–80} (iv) reduction of nitriles using SmI₂–hν;⁸¹ and SmI₂–amine–H₂O systems;⁸² (v) reduction of alkyl fluorides using Sm(HMDS)₂ in hexanes;⁸³ (vi) conjugate reductions and eliminations of α,β- and α,β/γ,δ-unsaturated carboxylic acid derivatives;^{84–88} (vii) reduction of aromatic rings;⁸⁹ and (viii) reduction/elimination of benzylic heteroatoms.^{90,91} Some of these processes have already been successfully applied to the reductive formation of carbon–carbon bonds as summarized in the following sections of this Review. Importantly, in many cases fully chemoselective electron transfer to a selected functional group is possible in the presence of other easily reducible functional groups as a result of thermodynamic control.

In the past decade, new methods of preparation of SmI₂,^{92–101} including synthesis in new solvents^{98,99} and a comprehensive study on practical aspects of the synthesis of SmI₂,^{100,101} have been reported. A number of important ligands and additives have been developed,^{102–108} including the discovery that tripyrroldinophosphoric acid triamide (TPPA) serves as a nontoxic alternative to HMPA^{106–108} and that the use of LiCl and LiBr in conjunction with SmI₂ results in anion metathesis to give thermodynamically more powerful reductants.¹⁰² A separate development includes the discovery that extremely reducing nonclassical lanthanide(II) iodides such as TmI₂, DyI₂, and NdI₂ are sufficiently stable under standard reaction conditions and can perform single-electron transfer reductions with much higher efficiency than SmI₂.^{109–120} Finally, detailed investigations on the role of additives and mechanism of the SmI₂-mediated reactions,^{121–158} including cross-couplings,^{122–124} have been published. These studies give insight into the processes governing electron transfer events and allow users to rationally expand the scope of application of the reagent.

3. CROSS-COUPLING VIA RADICAL INTERMEDIATES

Although SmI₂ can promote cross-coupling reactions via either one- or two-electron mechanisms, currently, cross-couplings via radical intermediates represent the major class of carbon–carbon bond-forming reactions mediated by this reagent. In this section of the Review, we will discuss advances that have taken place in the generation and cross-coupling of ketyl (section 3.1), ketyl-type (section 3.2), imine-derived (section 3.3), and carbon-centered (section 3.4) radicals using SmI₂.

It should be noted that, although the typically proposed mechanism for SmI₂-mediated cross-couplings of carbonyl derivatives with olefins involves the generation of ketyl-type radical intermediates (“carbonyl-first”),¹⁵⁹ recent mechanistic studies suggest that in some cases these reactions may also proceed via an alternative reaction pathway involving reduction of the olefin (“olefin-first”).¹⁶⁰ In addition, specific examples may involve an anionic C–C bond-forming process; however, the current mechanistic evidence does not allow the two pathways to

be distinguished. In the section below, the reactions of carbonyl compounds for which distinct mechanisms have been proposed are highlighted and additionally discussed to alert the reader to the fact that when designing Sm(II)-mediated cross-coupling reactions, changes in the electronic properties of coupling partners can be exploited to increase the efficiency of a given synthetic process.

3.1. Ketyl Radical-Alkene/Alkyne/Arene Cross-Coupling

The first general SmI₂-mediated intermolecular cross-coupling of carbonyl compounds with activated olefins was reported independently by Fukuzawa^{161,162} and Inanaga¹⁶³ in 1986. The intermolecular cross-coupling of ketals (samarium ketals, ketyl radicals) with unactivated π-systems was introduced by Inanaga in 1989 using HMPA and *t*-BuOH as crucial additives.¹⁶⁴ The first intramolecular examples were reported by Molander in 1987 using SmI₂–*t*-BuOH.¹⁶⁵ Since these seminal discoveries, SmI₂-mediated cross-couplings of ketyl-radicals with a wide range of π-acceptors have been applied in the synthesis of numerous targets. Currently, this class of cross-coupling reactions represents one of the most convenient methods for the synthesis of γ-hydroxy carbonyl derivatives by reductive coupling. High levels of stereocontrol can often be achieved by careful choice of additives, fine-tuning of the reaction conditions, and changes in the substrate geometry.

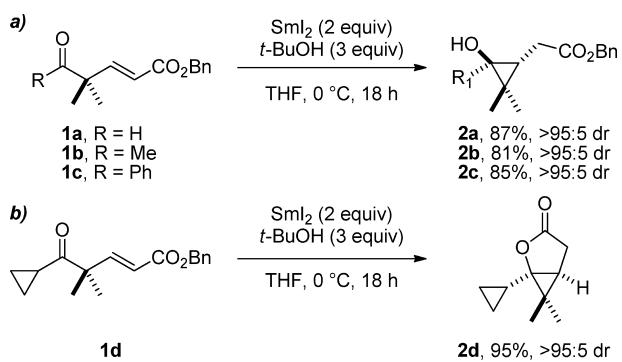
For the purpose of this Review, cross-couplings of ketyl radicals with π-systems have been categorized into the following classes: (i) intramolecular cross-couplings with alkenes; (ii) intermolecular cross-couplings with alkenes; (iii) cross-couplings with alkynes; (iv) cross-couplings with allenes; and (v) cross-couplings with arenes. This classification is justified by the fact that in the past decade the vast majority of cross-couplings of ketyl radicals with π-acceptors mediated by SmI₂ involved olefins, while the use of other π-acceptors in these reactions remains less explored.

3.1.1. Intramolecular Cross-Coupling of Ketyl Radicals with Alkenes. Intramolecular cross-couplings of ketyl radicals with alkenes have been classified based on the type of olefin acceptors and are discussed in the following sections: (i) α,β-unsaturated esters; (ii) α,β-unsaturated amides; (iii) enones; (iv) α,β-unsaturated sulfones/sulfoxides; (v) unactivated alkenes; and (vi) cross-coupling terminating by elimination.

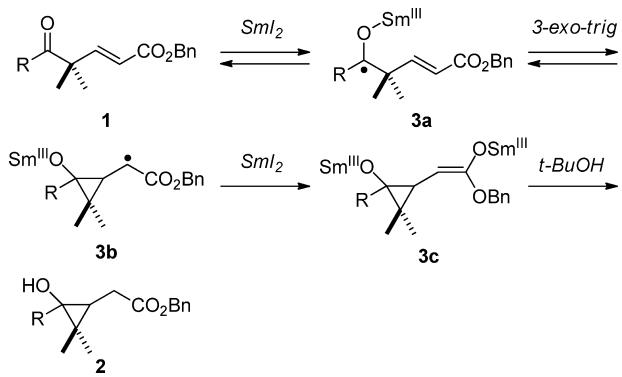
3.1.1.1. Cross-Coupling with α,β-Unsaturated Esters. In the past decade, intramolecular cross-couplings of ketyl radicals with α,β-unsaturated esters promoted by SmI₂ have been utilized to prepare three-, four-, five-, six-, and seven-membered ring systems. In particular, this method has emerged as an attractive procedure for the synthesis of functionalized cyclopropanes and cyclobutanes with high levels of stereocontrol. The examples have been arranged by the size of the ring formed in the SmI₂-mediated cyclization.

In 2002, Guibé reported the stereoselective preparation of *trans*-cyclopropanols via 3-*exo*-trig cyclization of ketones and aldehydes bearing α,β-unsaturated benzyl esters using SmI₂–*t*-BuOH at 0 °C (Scheme 1a).¹⁶⁶ *cis*-Cyclopropanol was formed when the corresponding cyclopropyl ketone was subjected to these reaction conditions (Scheme 1b).¹⁶⁷ The mechanism was proposed to involve the following steps: (i) reduction of the carbonyl group with SmI₂ to give the ketyl radical-anion intermediate, (ii) reversible 3-*exo*-trig cyclization, (iii) single-electron reduction to give the enolate, and (iv) rapid protonation by the *t*-BuOH cosolvent (Scheme 2). Additional mechanistic studies revealed that cyclopropyl ketones, such as **1d** (Scheme

Scheme 1. Synthesis of Functionalized Cyclopropanols by Guibé: (a) Trans-Selectivity; (b) Cis-Selectivity



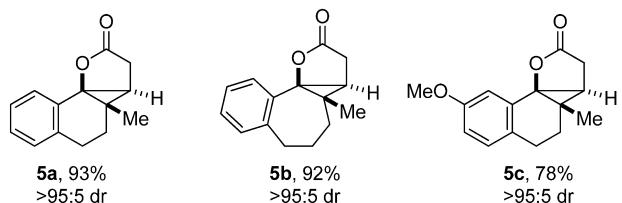
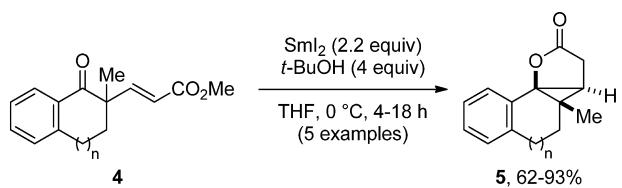
Scheme 2. Proposed Mechanism for the 3-exo-Trig Cyclizations by Guibé



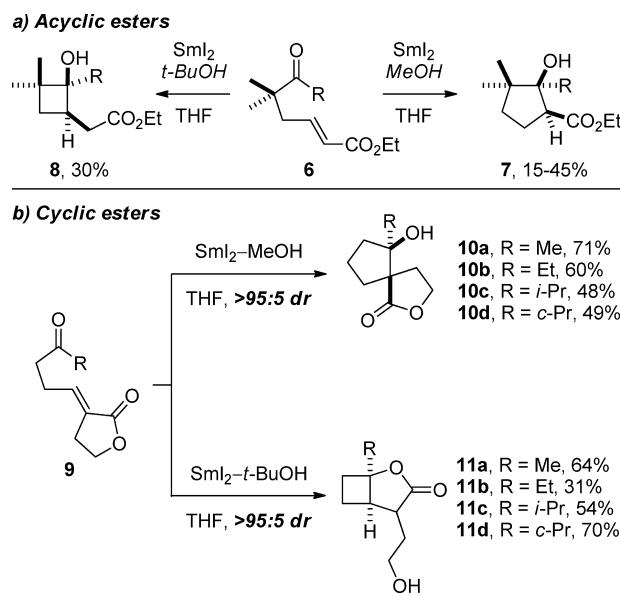
1b), undergo efficient cyclization and lactonization without formation of the cyclopropyl ring opened products. It was proposed that in this case the reaction follows the alternative anionic mechanism (“olefin-first”). The Guibé group extended this methodology to the cross-coupling reactions of benzo-fused ketones bearing an α,β -unsaturated ester in the 2-position (Scheme 3).¹⁶⁸ The couplings produced *cis*-cyclopropanols, which underwent efficient lactonization under the reaction conditions.

In 2002, Procter and co-workers reported an unusual example of a change in reaction pathway for intramolecular carbonyl/olefin cyclizations controlled by the protic additive (Scheme 4a).¹⁶⁹ Treatment of ketone substrates with SmI_2 in the presence of MeOH resulted in stereoselective cyclization to give *cis*-

Scheme 3. Synthesis of Fused Cyclopropanols by Guibé



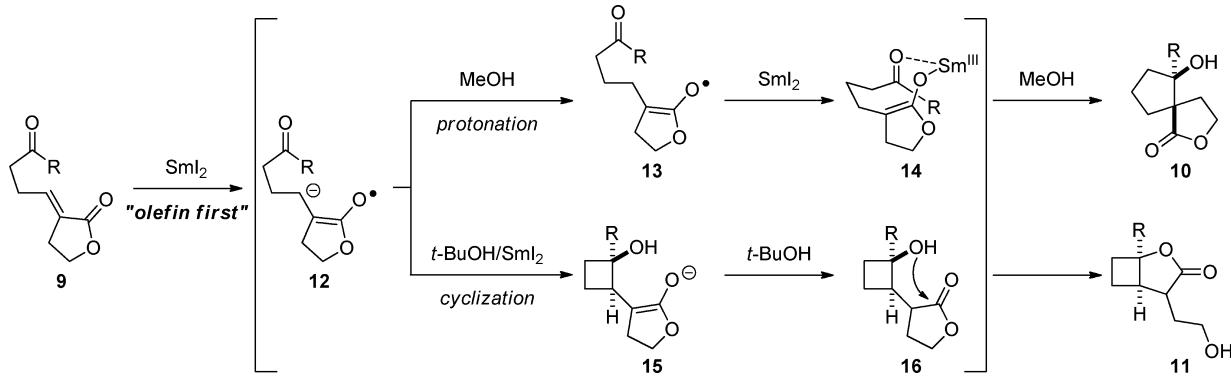
Scheme 4. 4-exo-Trig versus Aldol Cyclization by a Change of SmI_2 -Additive by Procter



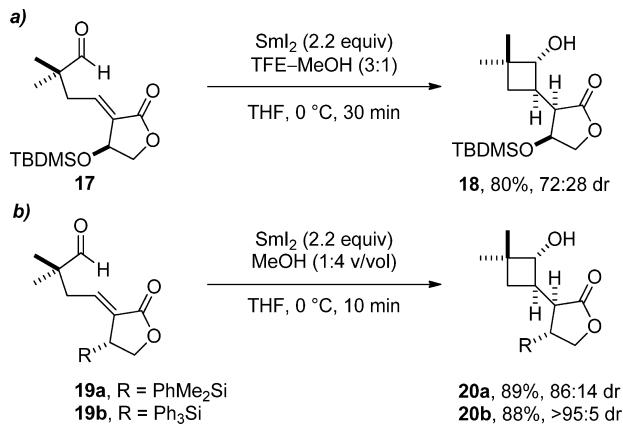
cyclopentanols, while *t*-BuOH as an additive promoted the formation of cyclobutanol products via 4-exo-trig cyclization. The yield of four- and five-membered products using acyclic α,β -unsaturated esters was modest due to competing reduction of the conjugated olefin. Subsequently, the Procter group significantly extended the scope of this cross-coupling by using the more reactive α,β -unsaturated cyclic esters (Scheme 4b).¹⁷⁰ The mechanism was proposed to involve different rates of protonation of the radical anion intermediate resulting in either 4-exo-trig cyclization or aldol spirocyclization (Scheme 5). One-electron reduction of the exomethylene lactone generates radical-anion intermediate, which undergoes rapid protonation (MeOH cosolvent) to give the enolate. In cases when protonation is slow (*t*-BuOH cosolvent), the 4-exo-trig cyclization predominates to give the cyclobutanol products. In the MeOH pathway, aldol cyclization of 14 leads to the cyclopentanol product 10 following protonation. In the *t*-BuOH pathway, protonation of the enolate is followed by lactonization to yield 11. This mechanism is in good agreement with findings by Hoz on the role of protic additives in reductions of activated olefins and ketones mediated by SmI_2 .^{139,141}

Subsequently, Procter reported the stereocontrolled synthesis of functionalized cyclobutanols via the cross-coupling of aldehydes bearing α,β -unsaturated lactones using silyl ethers as stereocontrol elements (Scheme 6).^{171,172} Initially, bulky O-silyl protecting groups were used to control the facial selectivity of the 4-exo-trig cyclizations (Scheme 6a); however, the stereo-selectivity was modest due to chelation between the Sm(III) ketyl and O-silyl group.¹⁷¹ Importantly, it was found that the TFE cosolvent prevents elimination of the O-silyl group to give butenolides. In 2010, Procter reported an improved procedure for the synthesis of functionalized cyclobutanols using C-silyl groups as stereocontrol elements (Scheme 6b, MeOH/THF = 1:4, v/vol).¹⁷² 4-exo-Trig cyclizations of aldehydes with α,β -unsaturated lactones bearing SiPh_3 and SiMe_2Ph groups at the β -position of the ring proceeded in high yields and excellent stereoselectivity. The elimination by-products were not observed. An asymmetric synthesis of the cyclization precursors was also developed to access enantiopure products.¹⁷³

Scheme 5. Proposed Mechanism for the Formation of Cyclobutanes/Spirocycles by Procter

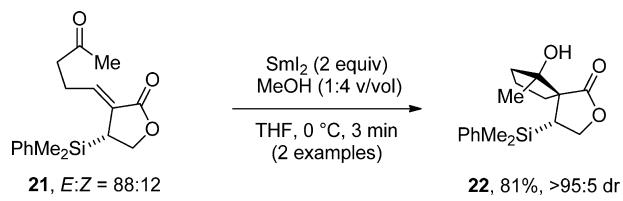


Scheme 6. Silicon Stereocontrol Groups for the Synthesis of Cyclobutanols by Procter



Interestingly, cyclization of the corresponding methyl ketones gave cyclopentanol products in excellent yields and stereoselectivity (Scheme 7). On the basis of this methodology, a

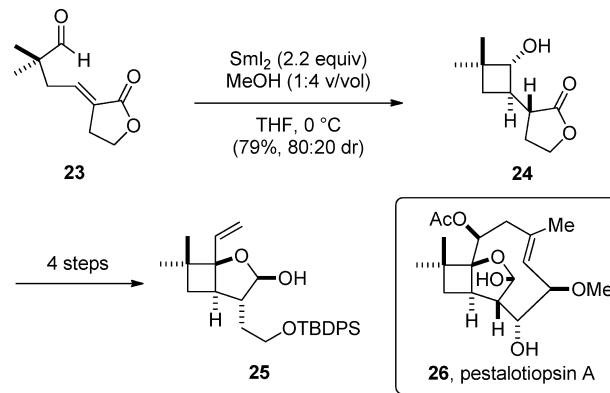
Scheme 7. Silicon Stereocontrol Groups for the Synthesis of Cyclopentanols by Procter



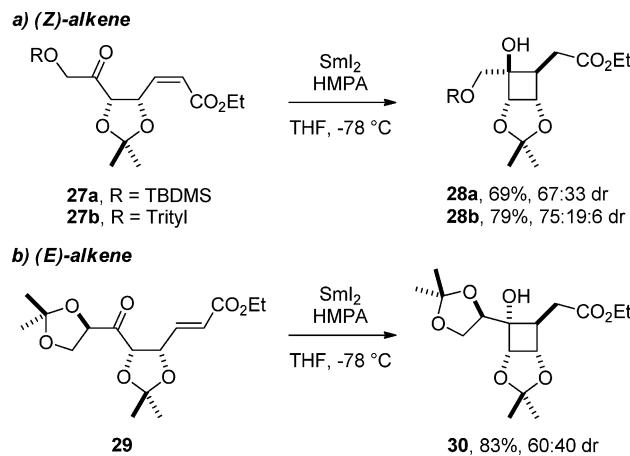
telescoped spirocyclization/lactone reduction/Peterson elimination sequence was developed to furnish cyclopentanols bearing two adjacent quaternary centers with complete diastereoselectivity.¹⁷⁴ This type of 4-exo-trig cyclization was also used by Procter to construct the four-membered core of pestalotiopsis A (Scheme 8).^{175–179} Treatment of 23 with SmI₂-MeOH at 0 °C led to efficient cyclization to yield cyclobutanol 24. This could be elaborated in four steps to a bicyclic tetrahydrofuran-2-ol, which represents the core of pestalotiopsis A. This study culminated in the synthesis of the full skeleton of pestalotiopsis A, and its biomimetic rearrangement to taedolidol sesquiterpenes.¹⁷⁹

The Williams group has also reported the cross-coupling of ketones with α,β -unsaturated esters mediated by SmI₂ to produce cyclobutanols (Scheme 9).^{180,181} Carbohydrate-derived

Scheme 8. Synthesis of Pestalotiopsis A Using 4-exo-Trig Cyclization by Procter



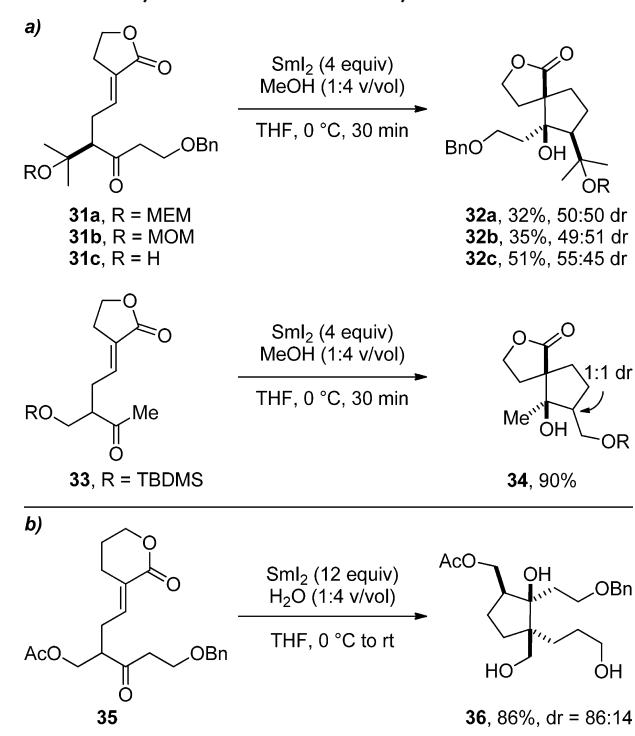
Scheme 9. 4-exo-Trig Cyclization of Carbohydrate-Derived Ketones by Williams



unsaturated ketones underwent efficient 4-exo-trig cyclization using the SmI₂-HMPA system.¹⁸⁰ (Z)- and (E)-olefin isomers provided access to complementary diastereoisomers of the cyclobutanol products. In some cases, the order of addition (substrate to SmI₂-HMPA) was found to be critical to avoid formation of cyclopentane dimers, arising from anionic cyclization/radical dimerization in cases when SmI₂ was added to a solution of substrate in THF/HMPA.¹⁸¹

In 2007, Procter and co-workers reported the use of ketone/ α,β -unsaturated ester spirocyclization to construct the core of stolonidiol, a marine natural product (Scheme 10a).¹⁸² Treat-

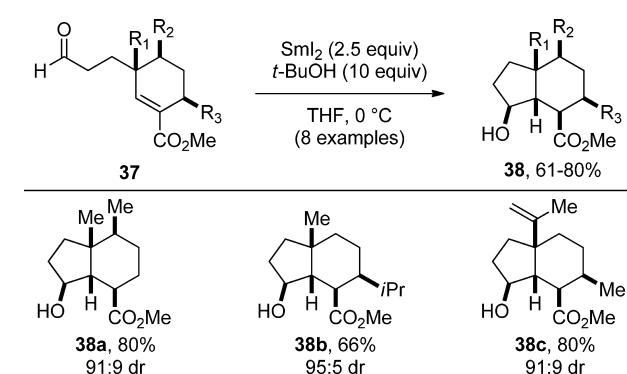
Scheme 10. Spirocyclization of α,β -Unsaturated Lactones toward the Synthesis of Stolonidiol by Procter



ment of unsaturated ketones **31** with $\text{SmI}_2\text{-MeOH}$ resulted in the spirocyclization to yield cyclopentanol products in modest yields due to the steric hindrance at the α -position of the ketone moiety; however, a substrate containing a protected hydroxyl methyl group allowed access to the desired product in high yield. This approach was subsequently utilized to synthesize a functionalized core of stolonidiol using a $\text{SmI}_2\text{-H}_2\text{O}$ -mediated cascade cyclization (Scheme 10b).¹⁸³

In 2008, Procter reported the stereoselective synthesis of the *cis*-hydrindane skeleton, a common motif in several natural products with potent biological activity, such as faurinone, bakkenolide III, and pleuromutilin, via *5-exo*-trig cyclization of aldehydes onto α,β -unsaturated esters embedded in a cyclohexene scaffold (Scheme 11).¹⁸⁴ Treatment of unsaturated aldehydes **37** with $\text{SmI}_2\text{-}t\text{-BuOH}$ resulted in an efficient cyclization generating three new stereocenters with excellent diastereoselectivity. The proposed mechanism involves the following steps: (i) reduction of the aldehyde to give ketyl

Scheme 11. Synthesis of *cis*-Hydrindanes via *5-exo*-Trig Cyclization by Procter



radical-anion, (ii) *5-exo*-trig cyclization, (iii) reduction to the enolate, and (iv) protonation of the Sm(III) enolate from the most sterically accessible face (Scheme 12). This methodology was applied in the synthetic studies toward faurinone and pleuromutilin natural products.¹⁸⁵

In 2011, Yang and co-workers reported the total synthesis of pseudolaric acid A using a *5-exo*-trig cyclization of an aliphatic ketone onto a trisubstituted α,β -unsaturated ester (Scheme 13).¹⁸⁶ Impressively, the cross-coupling proceeded on a gram scale, in an excellent yield, generating three new stereocenters with 91:9 diastereoselectivity. The tertiary alcohol product was isolated as a TMS-ether following treatment with TMSOTf . The high stereocontrol observed in this cross-coupling reaction was proposed to arise from dipole repulsion between the Sm(III) -ketyl radical anion and ester group in the transition state. The total synthesis of pseudolaric acid A was completed in a further 11 steps.

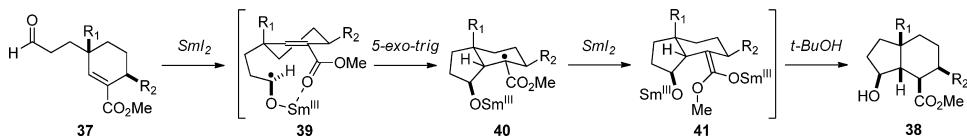
In 2002, Shirahama and co-workers reported the reductive cross-coupling between ketones and α,β -unsaturated esters to form pyrrolidines (Scheme 14).¹⁸⁷ MeOH as a protic additive had significant influence on the stereochemical outcome of the reaction. The use of $\text{SmI}_2\text{-HMPA}$ resulted in the formation of trans-substituted pyrrolidines, while in the presence of $\text{SmI}_2\text{-HMPA-MeOH}$ *cis*-pyrrolidines were formed. It was proposed that protonation of the samarium alkoxide gives the kinetic product by minimizing the steric bias between free hydroxyl and methoxycarbonylmethyl groups in the *cis* orientation. The formal synthesis of FPA, a kainoid amino acid, was demonstrated using this methodology.

Nagaoka and co-workers reported a cascade reaction, involving the cross-coupling of ketones and α,β -unsaturated esters followed by Dieckmann condensation to form decalin and perhydroindane ring systems (Scheme 15).¹⁸⁸ Treatment of ketones **48** with SmI_2 in THF at room temperature triggered *5-exo*-trig or *6-exo*-trig cyclizations. In some cases, depending on the ring size and olefin geometry of the starting material, lactonization of the products was also observed. *Z* and *E* alkenes showed similar levels of reactivity in this cyclization.

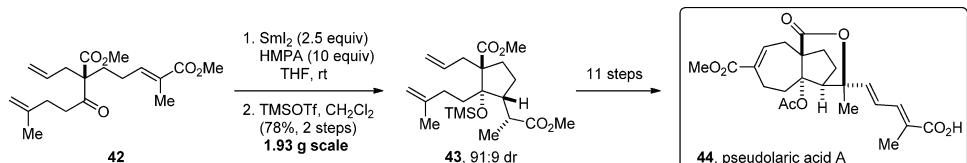
In 2007, Suzuki reported the SmI_2 -mediated *6-exo*-trig cyclization of biaryl ene-aldehydes to give dihydronaphthalenes in good yields (Scheme 16).¹⁸⁹ Treatment of either the *Z* or the *E* olefin isomer with $\text{SmI}_2\text{-MeOH}$ afforded the same trans-substituted product. The reduced selectivity in the cyclization of the *Z* olefin was proposed to arise from inefficient chelation to Sm(III) in the transition state.

The Nakata group has developed several methodologies for the SmI_2 -mediated cross-coupling of aldehydes/ketones with α,β -unsaturated esters for the synthesis of complex tetrahydropyrans and oxepanes.^{43,44} In 2002, Nakata reported the total synthesis of mucocin using a chemoselective *6-exo*-trig cyclization of a dialdehyde/olefin substrate using $\text{SmI}_2\text{-MeOH}$ (Scheme 17).¹⁹⁰ Interestingly, the second aldehyde was retained after the reaction, although the authors noted that prolonged reaction times afforded reduction and pinacol products. Following this seminal study, other examples of selective monocyclizations of dialdehyde substrates using SmI_2 have been reported (see section 5.1). The total synthesis was completed by the Nakata group in 13 steps. The groups of Sabitha¹⁹¹ and Takahashi¹⁹² independently employed a similar cross-coupling strategy for the synthesis of the tetrahydropyran core of aspergillide A (Scheme 18). Treatment of the respective aldehydes with $\text{SmI}_2\text{-MeOH}$ formed the tetrahydropyran ring systems in excellent yields and diastereoselectivity. The formal

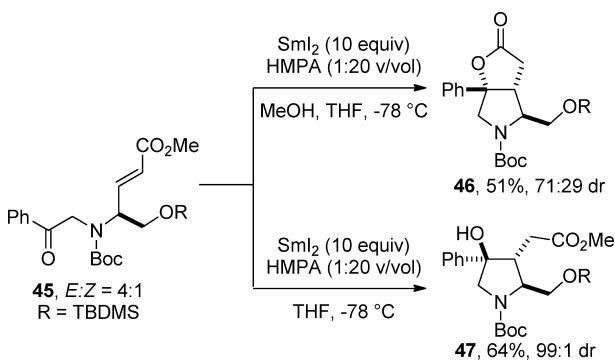
Scheme 12. Proposed Mechanism for the 5-exo-Trig Cyclization by Procter



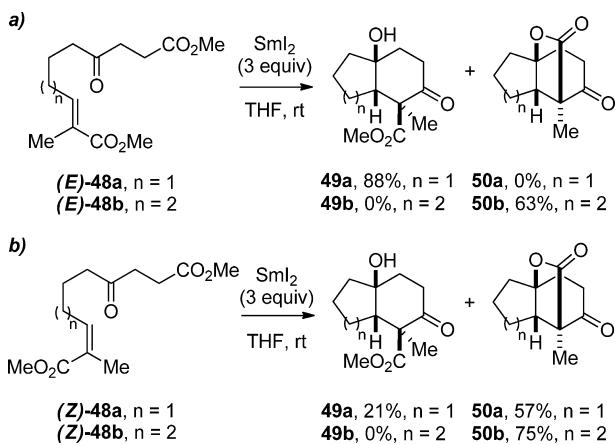
Scheme 13. Synthesis of Pseudolaric Acid A via 5-exo-Trig Cyclization by Yang



Scheme 14. 5-exo-Trig Reductive Cross-Coupling To Form Pyrrolidines by Shirahama



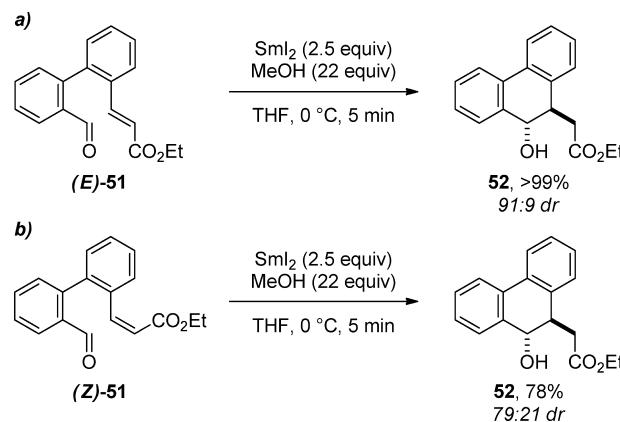
Scheme 15. Synthesis of Decalins and Perhydroindanes via 5-exo-Trig and 6-exo-Trig Cyclizations by Nagaoka



total synthesis of aspergillide A was completed by Takahashi in four steps.

In a particularly elegant example of SmI_2 -mediated cross-coupling reactions, the Nakata group demonstrated iterative 7-exo-trig/6-exo-trig cyclizations in the synthesis of complex polyethers (Scheme 19).^{193–197} In the synthetic studies toward a ladder polyether, maitotoxin, treatment of an advanced ketone intermediate bearing an α,β -unsaturated ester with SmI_2 –MeOH promoted the 7-exo-trig cyclization to form an oxepane ring, which was isolated after ester reduction with LiAlH_4 in excellent yield with >95:5 diastereoselectivity. After oxepane elaboration, treatment of the second cyclization precursor with SmI_2 –MeOH, followed by protection with TMSOTf, afforded a

Scheme 16. Synthesis of Dihydrophenanthrenes via 6-exo-Trig Cyclization by Suzuki

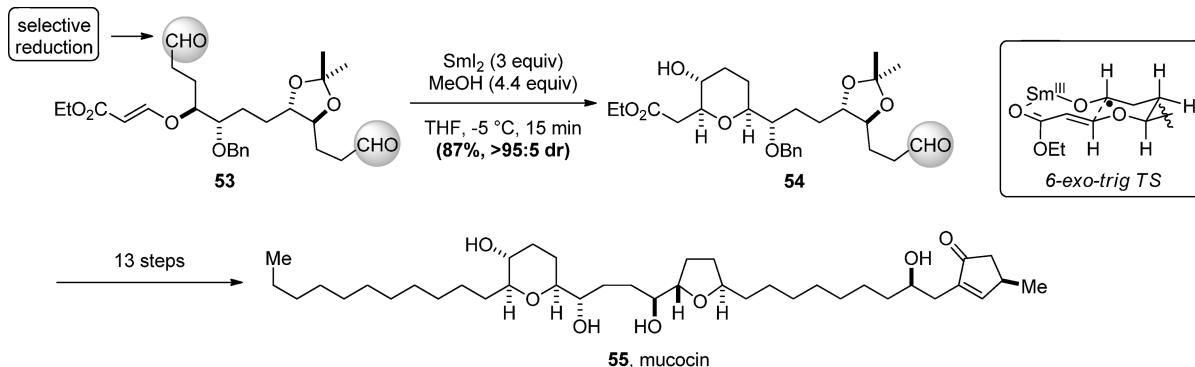


fully functionalized YZA' fragment of maitotoxin in 72% yield as a single diastereoisomer. Nakata extended this SmI_2 -mediated cross-coupling methodology to two-directional cyclization using a dialdehyde substrate (Scheme 20).^{198a} Treatment of the dialdehyde precursor with an excess of SmI_2 –MeOH initiated two-directional 6-exo-trig/7-exo-trig aldehyde/olefin cyclization to give the BCDE fragment of maitotoxin in 60% yield with complete control of stereoselectivity. In addition, 29% yield of the corresponding diester was isolated in this reaction. Nakata proposed that the mechanism of this cyclization involves reduction of the carbonyl by SmI_2 to generate a radical-anion, which undergoes a chelation-controlled cross-coupling step, reduction to the enolate, and protonation to yield the final product (Scheme 21). Nakata also reported a related 6-exo-trig/7-exo-trig ketone/olefin cyclization to construct the CDE fragment of brevetoxin B (not shown).^{198b}

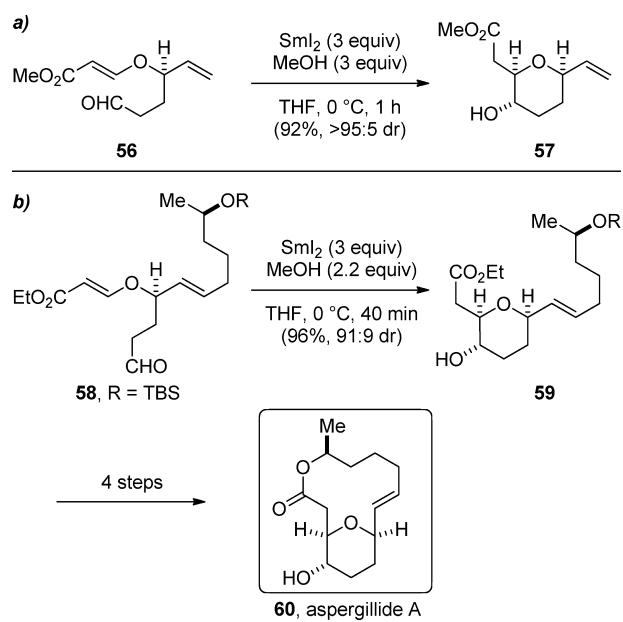
In 2011, Honda utilized the SmI_2 -mediated cross-coupling of an aldehyde and α,β -unsaturated ester to prepare a seven-membered ring during the total synthesis of stemon alkaloid, (–)-stemoamide.¹⁹⁹ The use of SmI_2 –MeOH promoted 7-exo-trig cyclization to yield the tricyclic precursor after in situ lactonization in good yield, however, as a mixture of alcohol diastereoisomers (Scheme 22). The synthesis of stemoamide was completed in four steps.

3.1.1.2. Cross-Coupling with α,β -Unsaturated Amides. The SmI_2 -mediated cross-coupling between carbonyl compounds and α,β -unsaturated amides has received much less attention than that of the corresponding esters despite the fact that the

Scheme 17. Total Synthesis of Mucocin via 6-exo Cyclization by Takahashi and Nakata: A Case of Selective Aldehyde Reduction



Scheme 18. 6-exo-Trig Aldehyde/Ester Coupling in the Synthesis of Aspergillide A: (a) Sabitha; (b) Takahashi



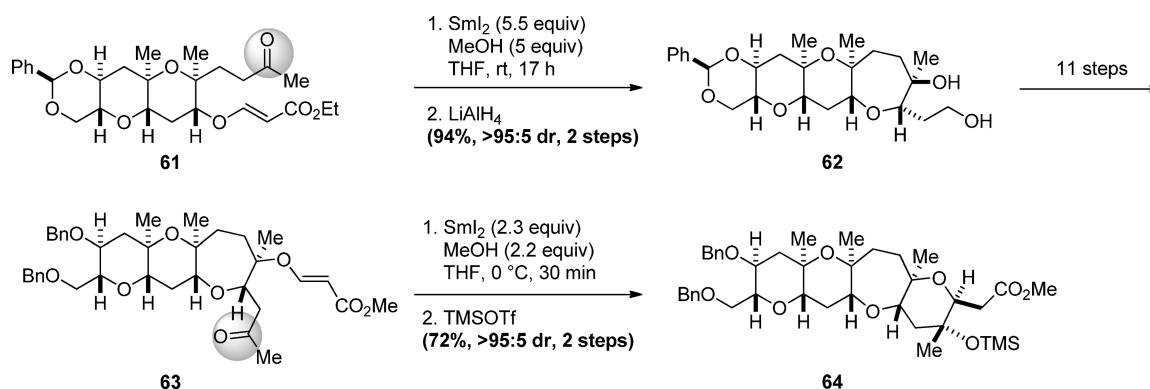
products can be elaborated to nitrogen-containing heterocycles that are prevalent in pharmaceuticals and natural products.

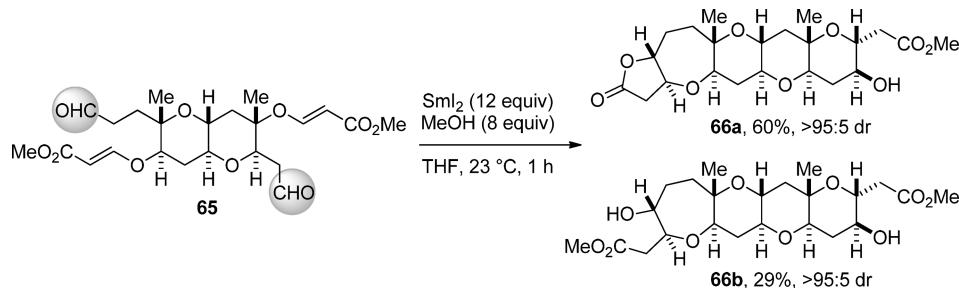
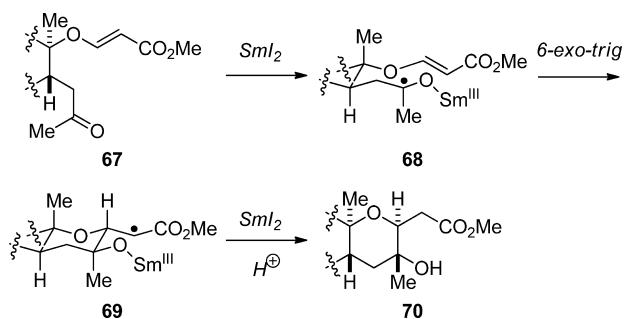
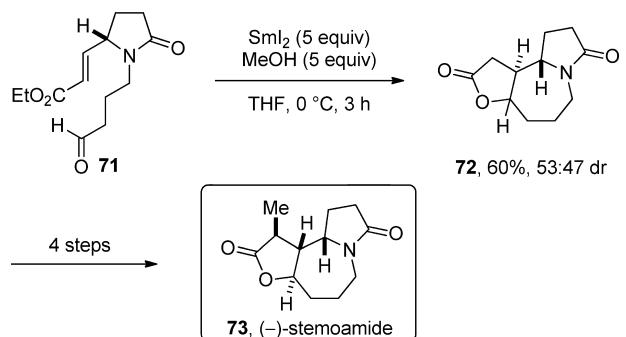
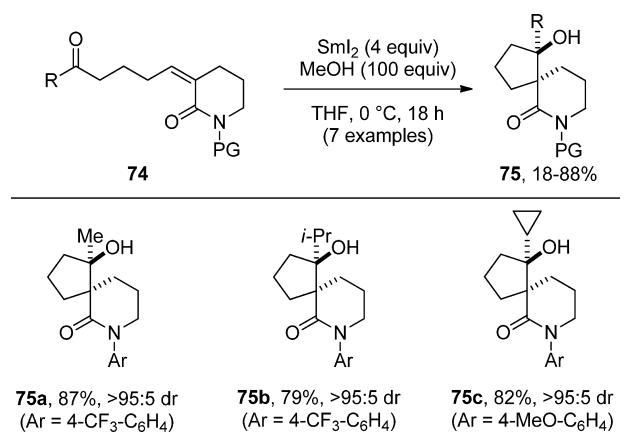
In 2008, Procter reported the first cross-coupling of ketones with α,β -unsaturated lactams (Scheme 23).²⁰⁰ Treatment of keto-amide precursors with SmI_2 –MeOH resulted in reductive cyclization in typically good yields and high stereoselectivity. The cyclization of five-membered lactams was observed to be less

efficient than that of the corresponding six-membered lactams. To investigate the mechanism of the reaction, α,β -unsaturated five- and six-membered lactams **76** and **77** were subjected to the reaction conditions using a limiting amount of SmI_2 –MeOH (Scheme 24). Interestingly, the conjugate reduction of a six-membered lactam occurred with complete chemoselectivity, suggesting that the slower rate of reduction of five-membered lactams contributes to the less efficient cyclization of these substrates. The mechanism of the cyclization was proposed to involve the following steps: (a) reduction of the unsaturated lactam by SmI_2 , (ii) protonation of the radical-anion, (iii) second reduction; (iv) aldol cyclization directed by samarium(III), and (v) protonation of the spirocyclic product (Scheme 25).

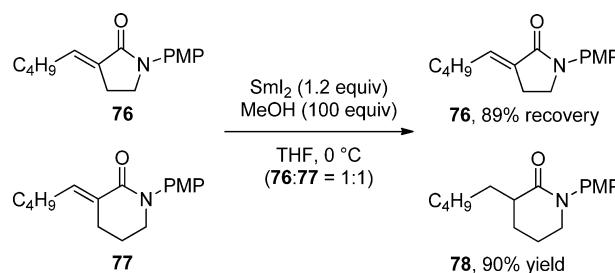
3.1.1.3. Cross-Coupling with Enones. Currently, the SmI_2 -mediated cross-coupling reactions of ketones and aldehydes with enones represent a major area of research. In general, this type of cross-coupling has been used in the synthesis of natural products and natural product-like motifs to construct complex carbocyclic ring systems. The most common class of SmI_2 -mediated cross-couplings is comprised of 5-exo-trig and 6-exo-trig cyclizations; however, this type of reaction has also been applied to other modes of closure (e.g., 6-endo-trig, 7-endo-trig). In general, the synthesis of four- to eight-membered rings can be achieved by this method. In the last 12 years, endocyclic enones have been used almost exclusively as acceptors (cf., exo- or acyclic enones). In this section of the Review, we first present the cross-coupling of simple enones, and then focus on the reductive cross-couplings in the synthesis of natural products. These examples have been arranged by the mode of cyclization and the type of enone acceptor. In addition, examples of cross-couplings with butenolides are included in this section.

Scheme 19. Synthesis of Complex Polyethers via Iterative 7-exo-Trig and 6-exo-Trig Cyclizations by Nakata



Scheme 20. Tandem 7-*exo*-Trig and 6-*exo*-Trig Cyclizations in the Synthesis of Complex Polyethers by Nakata**Scheme 21.** Proposed Mechanism for 6-*exo*-Trig Cyclizations by Nakata**Scheme 22.** Synthesis of (−)-Stemoamide via 7-*exo*-Trig Cyclization by Honda**Scheme 23.** Cross-Coupling between Ketones and α,β -Unsaturated Lactams by Procter

In 2003, Tori and co-workers reported the reductive cyclization between ketones/aldehydes and cyclic enones to form perhydronaphthalenones (Scheme 26).²⁰¹ Three equiv-

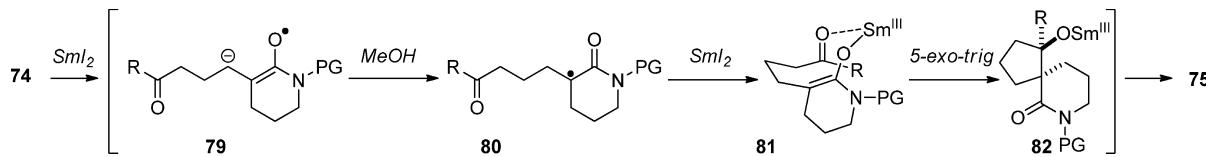
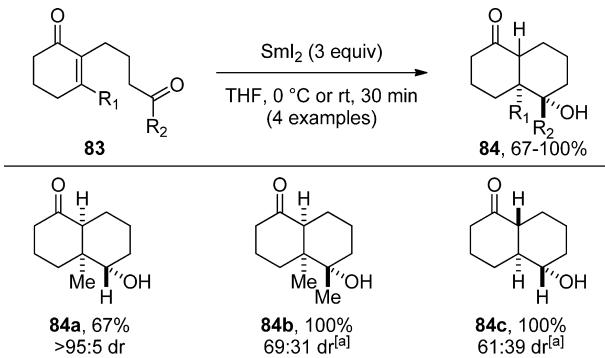
Scheme 24. Competition Experiments in the Reduction of Lactams by Procter

alents of SmI_2 in THF resulted in the efficient cyclization to give decalins bearing three new stereocenters; however, the control of stereoselectivity was rather modest in these reactions. Tori extended this methodology to the synthesis of seven- and eight-membered rings (Scheme 27).²⁰² Treatment of a six-membered cyclic enone bearing a tethered aldehyde at the α position resulted in efficient formation of the seven-membered ring via 7-*endo*-trig cyclization. The cyclization to the corresponding eight-membered ring system proceeded in much lower yield. It was also noted that different additives (e.g., MeOH , HMPA, NiI_2) could influence the diastereoselectivity of the cyclization, presumably due to different rates of protonation of the intermediate enolate. The mechanism was proposed to start by a single-electron reduction of the aldehyde by SmI_2 to generate a radical-anion, which undergoes cyclization onto the enone (Scheme 28). Reduction to the enolate by SmI_2 and protonation (*in situ* or upon workup) yields the final product.

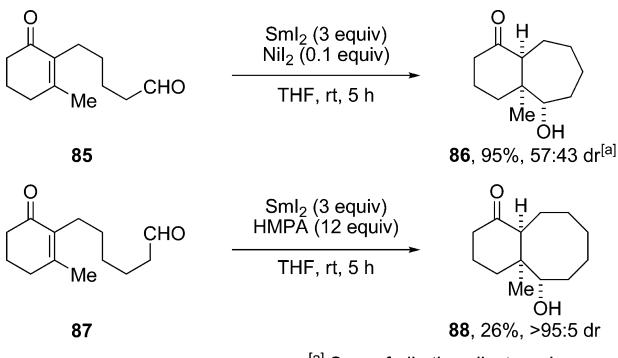
Recently, Tori reported the synthesis of hydrindanones bearing vicinal quaternary carbons via 5-*exo*-trig cyclizations of ketones/aldehydes tethered at the γ -position onto cyclic enones mediated by SmI_2 (not shown).²⁰³ Good yields and diastereoselectivity (quant., up to 87:13 dr) were obtained using SmI_2 /THF and $\text{SmI}_2/\text{NiI}_2$ reagent systems; however, the cyclization of only two substrates was investigated.

Hsu reported a related SmI_2 -mediated cross-coupling of β -tethered aldehydes onto cyclic enones to yield spirocyclic alcohols in good yields and modest stereoselectivity (Scheme 29).²⁰⁴ The best results in terms of yield and diastereoselectivity were obtained using the $\text{SmI}_2\text{-MeOH}$ system at 0 °C. Interestingly, under these conditions, the reduction of the ketone moiety was not observed.¹³⁹

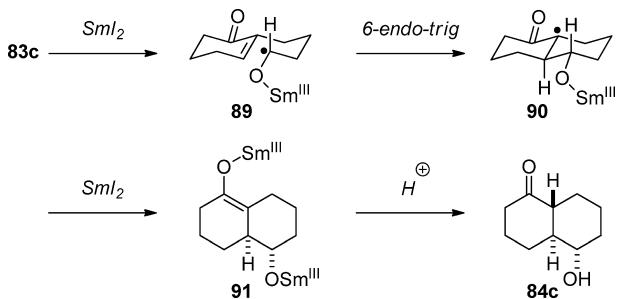
In 2002, Hagiwara utilized aldehyde/enone cyclization in the synthesis of cyclomyltaylane-5 α -ol.²⁰⁵ Treatment of the precursor aldehyde with $\text{SmI}_2\text{-HMPA}$ in the presence of $t\text{-BuOH}$ resulted in the reductive cyclization to yield the tricyclic product in good yield and modest diastereoselectivity (Scheme 30). To overcome problems associated with the recovery of polar keto-alcohol product, the authors applied a simplified workup

Scheme 25. Proposed Mechanism for Cross-Coupling of α,β -Unsaturated Lactams by Procter**Scheme 26. Synthesis of Perhydronaphthalenones via 6-*endo*-Trig Cyclizations by Tori**

^[a] Sum of all other diastereoisomers

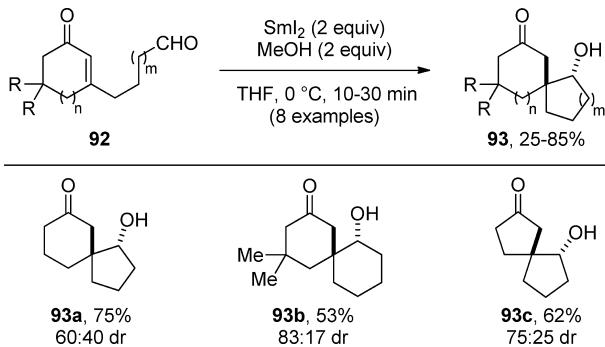
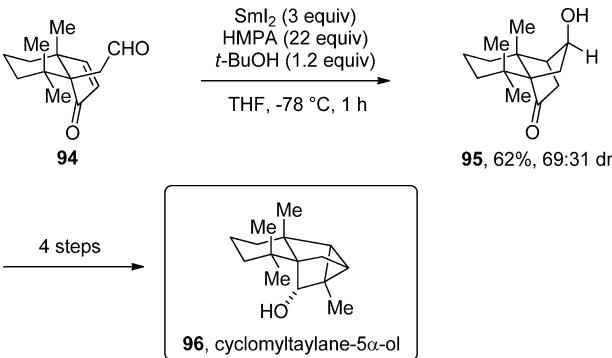
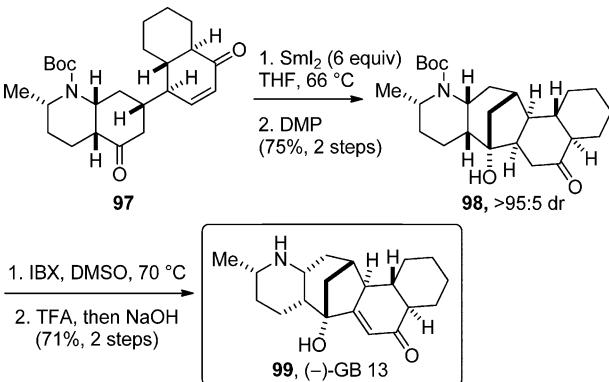
Scheme 27. 7-*endo*-Trig and 8-*endo*-Trig Cyclizations onto Enones by Tori

^[a] Sum of all other diastereoisomers

Scheme 28. Proposed Mechanism for 6-*endo*-Trig Cyclizations by Tori

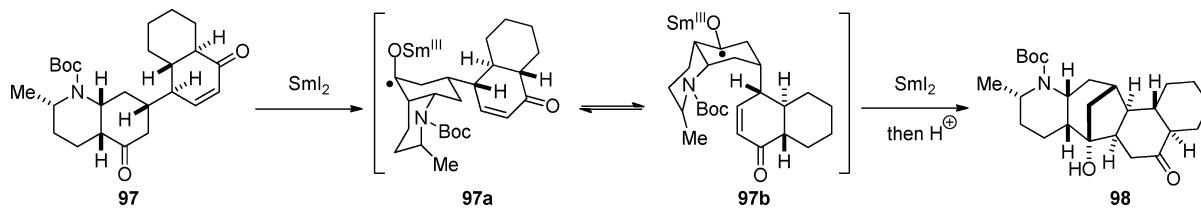
procedure, quenching the reaction with silica gel and directly isolating the desired product. The synthesis of cyclomyltaylane-5 α -ol was completed following a further four steps.

In 2010, Ma and co-workers reported the total synthesis of galbulimima alkaloid ($-$)-GB 13 and (+)-GB 16 utilizing an impressive 5-*exo*-trig reductive ketone/enone cross-coupling in the final stages of the synthesis (Scheme 31).²⁰⁶ Careful optimization of the reaction conditions revealed that a slow addition of the enone substrate to a refluxing solution of SmI₂ in

Scheme 29. Synthesis of Spirocycles via 5-*exo*-Trig and 6-*exo*-Trig Cyclizations onto Enones by Hsu**Scheme 30. 5-*endo*-Trig Cyclization onto Enone in the Synthesis of Cyclomyltaylane-5 α -ol by Hagiwara****Scheme 31. 5-*exo*-Trig Cyclization onto Enone in the Total Synthesis of ($-$)-GB 13 by Ma**

THF in the absence of additives produced the desired pentacycle in good yield as a single diastereoisomer (isolated after oxidation with DMP). The proposed mechanism is depicted in Scheme 32. The reaction is initiated by a single-electron reduction of the ketone to generate the radical-anion intermediate, which adopts the unfavorable axial–axial conformation to afford the desired [3.2.1] bicyclic upon cyclization. The authors proposed that the

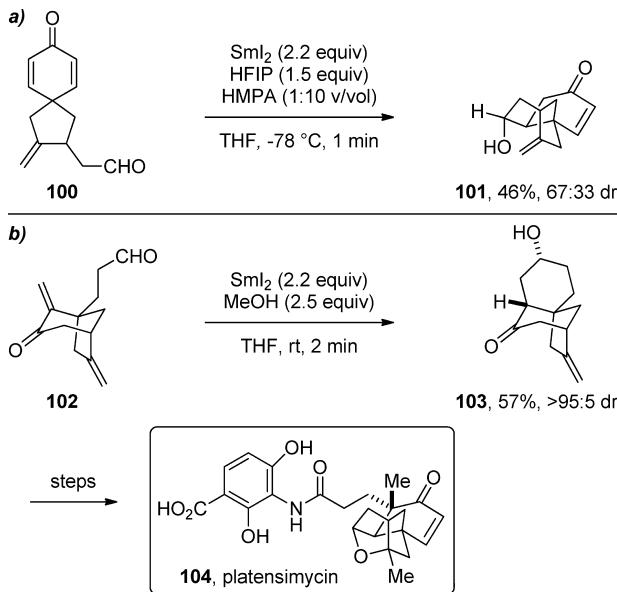
Scheme 32. Proposed Mechanism for 5-exo-Trig Cyclization by Ma



reaction required elevated temperatures to access the less thermodynamically stable diaxial conformer. Cyclization onto the enone, reduction to the enolate, and protonation yield the final product. The total synthesis of (*-*)-GB 13 was completed following a further two steps.

Nicolaou reported the first total synthesis of (\pm)-platensimycin using an elegant 6-exo-trig reductive cross-coupling between aldehyde and enone as the key step (Scheme 33a).^{207,208} The

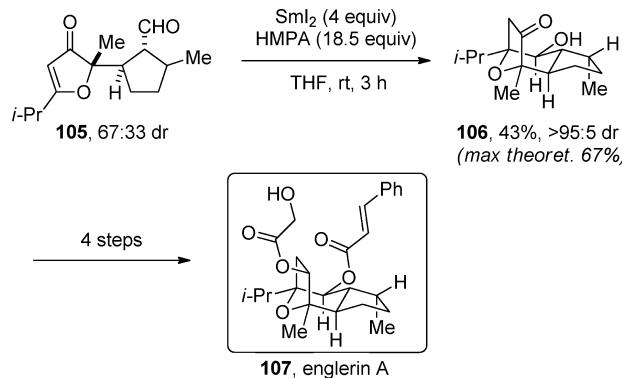
Scheme 33. 6-exo-Trig and 6-endo-Trig Cyclizations in the Synthesis of Platensimycin: (a) Nicolaou; (b) Nicolaou and Chen



carefully optimized protocol involved rapid injection of a solution of SmI_2 in THF to the preformed mixture of substrate, HMPA, and HFIP to yield the desired tricyclic product in modest yield and selectivity. Interestingly, the use of other reagents to promote the radical closure (Ti^{III} , $n\text{-Bu}_3\text{SnH}/\text{AIBN}$, $\text{Et}_3\text{B}/\text{O}_2/n\text{-Bu}_3\text{SnH}$) did not afford the desired product. Recently, Canesi completed a formal asymmetric synthesis of (*-*)-platensimycin utilizing SmI_2 -mediated cross-coupling of a related enone under the same conditions in 36% yield (not shown).²⁰⁹ In 2008, Chen and Nicolaou applied an alternative SmI_2 -mediated 6-*endo*-trig cyclization between an aldehyde and exocyclic six-membered enone in the total synthesis of (*-*)-platensimycin (Scheme 33b).²¹⁰ Treatment of the aldehyde precursor with SmI_2 -MeOH led to significant improvements in both yield and diastereoselectivity, which was explained on the basis of a nine-membered chelated transition state involving Sm(III) ketyl radical anion and the ketone.

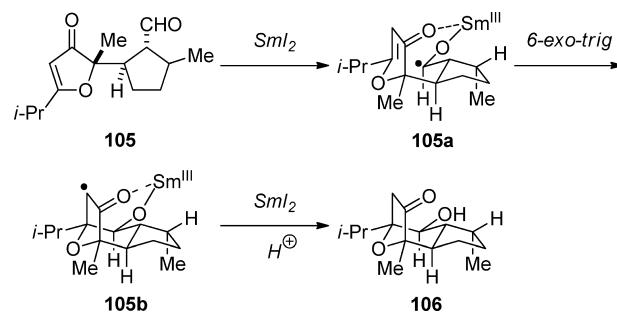
In 2011, Chain and co-workers reported the total synthesis of (*-*)-englerin A²¹¹ utilizing a SmI_2 -promoted 6-exo-trig ketone/

enone cross-coupling to access the tricyclic core of the natural product (Scheme 34).²¹² The use of SmI_2 -HMPA in THF led to

Scheme 34. 6-exo-Trig Cyclization onto Enone in the Total Synthesis of (*-*)-Englerin A by Chain

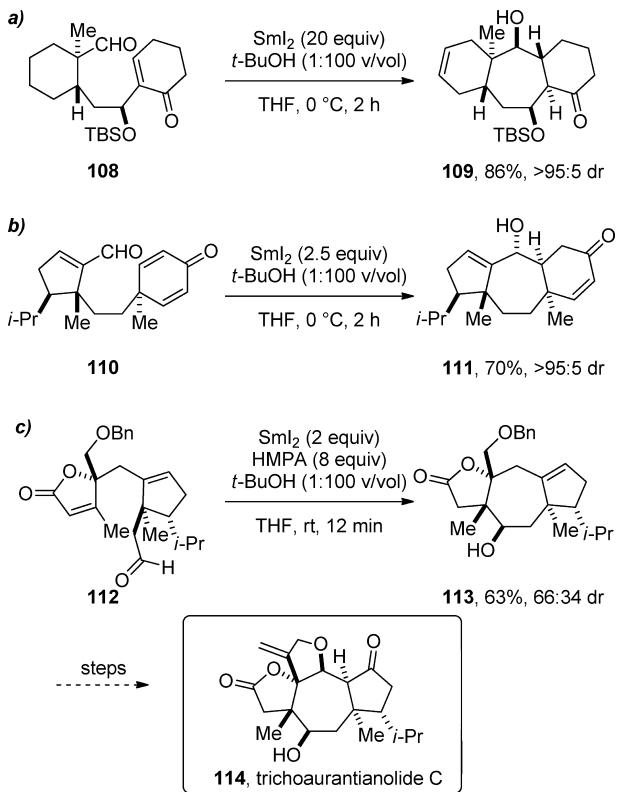
efficient cyclization to give the tricyclic product in good yield (note that the cross-coupling precursor was used as a 2:1 mixture of diastereoisomers) and as a single diastereoisomer. Other SmI_2 -additives, such as LiCl or MeOH , resulted in the undesired pinacol-type couplings and aldehyde reduction, respectively. This report emphasizes the need to carefully tailor the Sm(II) reaction conditions to achieve the desired carbon–carbon bond-forming event when substrates having multiple functionalities are used. The mechanism of the cyclization is presented in Scheme 35. From this advanced intermediate, the total synthesis of (*-*)-englerin A was completed in just four steps.

Scheme 35. Proposed Mechanism for the 6-exo-Trig Cyclization by Chain



SmI_2 -mediated cross-coupling of enones with aldehydes can also be used for the synthesis of seven-membered ring systems with high levels of stereocontrol (Scheme 36).^{213–215} Arimoto and co-workers reported 7-*endo*-trig aldehyde/enone cyclization in synthetic studies on erinacines to form the 6–7–6 core of these natural products in an impressive 86% yield as a single diastereoisomer (Scheme 36a).²¹³ Interestingly, the cyclization precursor diastereoisomeric at the C-OTBS center failed to

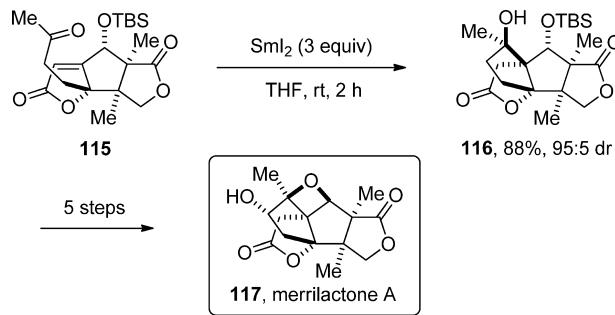
Scheme 36. 7-*endo*-Trig and 7-*exo*-Trig Cyclizations onto Enones: (a) Arimoto; (b) Lee; (c) 7-*exo*-Trig Cross-Coupling in the Synthesis of Trichoaurantianolides by Williams



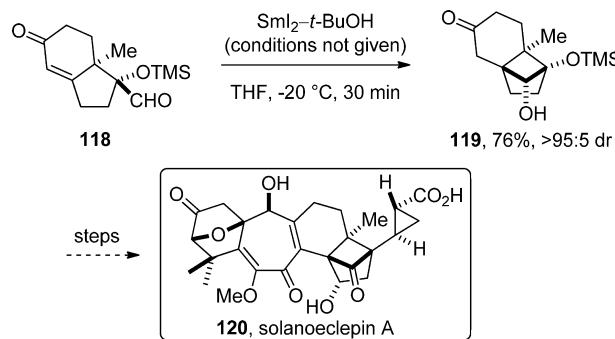
undergo the cyclization, and only alcohols resulting from aldehyde reduction or pinacol coupling were isolated in this reaction. In a related approach, Lee applied a 7-*exo*-trig cyclization onto an enone to prepare the 5-7-6 core of the guanacastepenes (Scheme 36b).²¹⁴ The use of an α,β -unsaturated enone resulted in sluggish cyclization; however, the cross-coupling of a doubly activated cyclohexa-2,5-dienone proceeded in excellent yield. Remarkably, the reaction differentiated between diastereotopic double bonds, delivering the thermodynamically favored cis-fused ring. Recently, Williams applied a similar 7-*exo*-trig cyclization onto a butenolide in an approach toward the total synthesis of the trichoaurantianolides (Scheme 36c).²¹⁵ In contrast to studies by Arimoto and Lee, the reaction required HMPA to minimize the formation of by-products and proceeded with a markedly lower diastereoselectivity. A mechanism involving reduction of the butenolide moiety, followed by anionic cyclization, was proposed (“olefin first”); however, it is possible that a mechanistic pathway initiated by the reduction of the carbonyl group (“carbonyl first”) also plays a role in this reaction. In the context of William’s work, it is important to mention the 2012 total synthesis of merrilactone A by Zhai, utilizing a SmI_2 -mediated ketone/butenolide cross-coupling (Scheme 37).²¹⁶ In this case, 5-*exo*-trig cyclization of a ketone precursor proceeded in an excellent 88% yield, delivering the desired tetracycle in 95:5 dr by treatment with SmI_2 –THF at room temperature.

Recently, Adachi and Nishikawa have demonstrated the first example of SmI_2 -mediated ketone/enone cyclization to afford a highly strained cyclobutane ring in studies toward solanoeclepin A (Scheme 38).²¹⁷ The use of SmI_2 –*t*-BuOH promoted an efficient cyclization to form the desired tricycle as a single

Scheme 37. 5-*exo*-Trig Cyclization in the Total Synthesis of Merrilactone A by Zhai



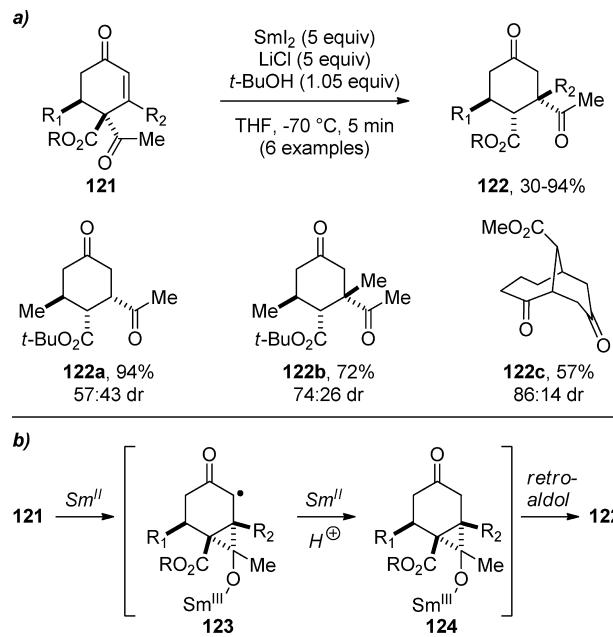
Scheme 38. 4-*exo*-Trig Cyclization by Adachi and Nishikawa toward the Synthesis of Solanoeclepin A

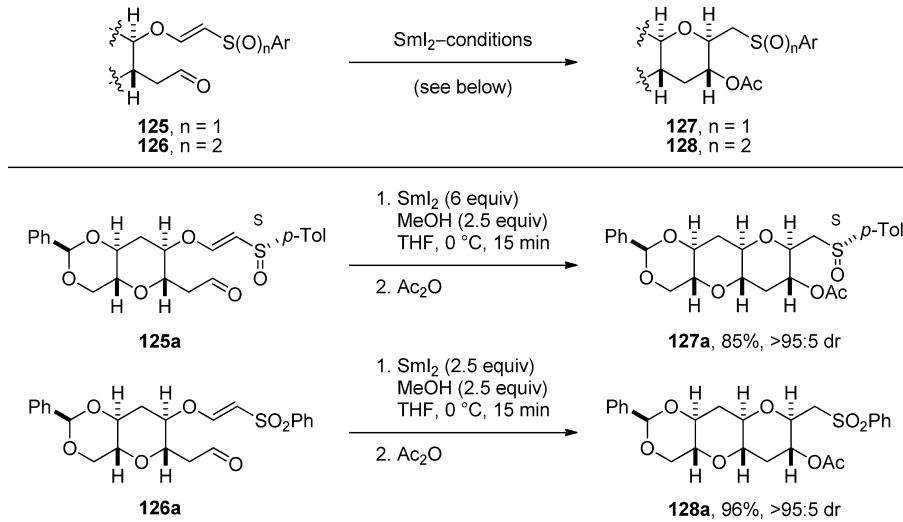
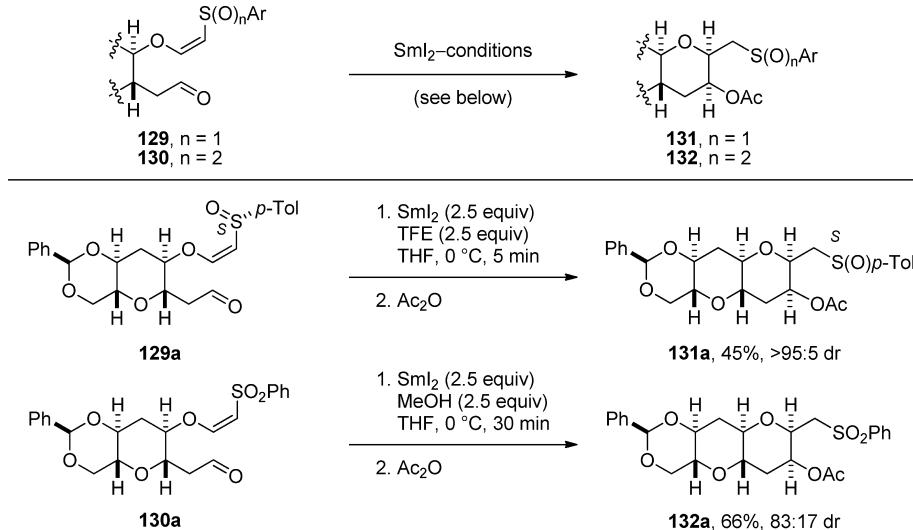


diasteroisomer. Interestingly, the attempted alkyne/enone cross-coupling in the same ring system mediated by AIBN/*n*-Bu₃SnH did not afford the desired product. The authors proposed that the use of SmI_2 results in a better orbital overlap between the sp^3 hybridized ketyl-radical and the enone π system (cf., sp^2/π system overlap as in the case of vinyl radical).

Inokuchi reported a 1,2-acyl transfer reaction, proceeding via a related 3-*exo*-trig cyclization onto an enone (Scheme 39).²¹⁸

Scheme 39. (a) Reductive Acyl Group Transfer by Inokuchi; (b) Proposed Mechanism



Scheme 40. Synthesis of Ladder Polyethers via 6-exo-Trig Cyclizations of (*E*)-Vinylsulfoxides/Sulfones by NakataScheme 41. Synthesis of Ladder Polyethers via 6-exo-Trig Cyclizations of (*Z*)-Vinylsulfoxides/Sulfones by Nakata

Thus, the treatment of 4-acetylcylohexanone with $\text{SmI}_2\text{-LiCl}$ in the presence of *t*-BuOH promoted the 3-*exo*-trig cyclization to form the intermediate cyclopropanol, which underwent retro-aldol reaction to yield the formal 1,2-acyl transfer product. The 1,2-acyl transfer is stereospecific, and the reaction permits the synthesis of quaternary centers. The author suggested that the mechanism involves an anionic pathway initiated by the reduction of the enone moiety; however, a radical pathway (cf., the work by Guibé, Schemes 1–3) cannot be ruled out.

3.1.1.4. Cross-Coupling with α,β -Unsaturated Sulfoxides and Sulfones. Several examples of SmI_2 -mediated cross-couplings between carbonyl compounds and vinyl sulfoxides/sulfones have been reported; however, this type of cross-coupling is vastly underutilized given the ease of preparation of the precursors, their high reactivity in challenging ketyl-radical cyclizations, and the potential for further product manipulation.²¹⁹

In 2007, Nakata reported the first SmI_2 -promoted reductive cyclizations of (*E*)-vinylsulfoxides^{220,221} and sulfones^{222,223} with aldehydes to form tetrahydropyran rings in the synthesis of complex polyethers.³² The 6-*exo*-trig cyclization was found to be efficient for both types of olefin acceptors. Thus, treatment of

vinylsulfoxide substrate with $\text{SmI}_2\text{-MeOH}$, followed by acetylation, yielded the desired product in excellent yield and as a single diastereoisomer (Scheme 40). Impressively, the corresponding vinylsulfone also underwent cross-coupling in 96% yield and full control of diastereoselectivity.

Similarly, Nakata reported the reductive 6-*exo*-trig cyclizations of (*Z*)-vinylsulfoxides^{220,221} and sulfones^{222,223} with aldehydes using the same polycyclic ether substrates (Scheme 41).³² Although the reaction of (*Z*)-isomers was found to be slightly less efficient than that of the corresponding (*E*)-olefins, it provided cis-fused polyethers with high levels of diastereocontrol. The authors proposed that the observed decrease in efficiency resulted from reduced chelation to the Sm(III) ketyl in the transition state (cf., Schemes 17–21).

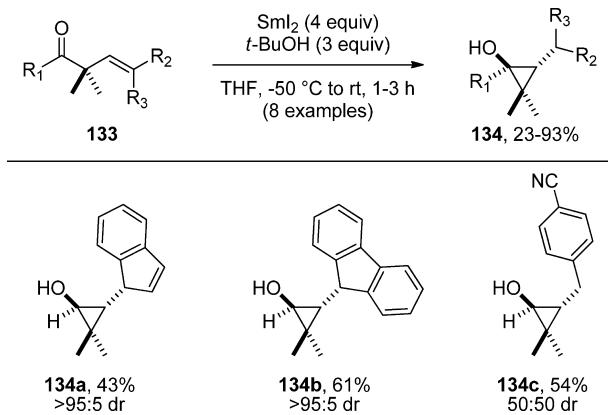
3.1.1.5. Cross-Coupling with Unactivated Alkenes. The first examples of SmI_2 -mediated intramolecular cross-couplings of ketyl-radicals with unactivated alkenes were reported by Molander in 1987 using unsaturated β -ketoesters and β -ketoamides as ketyl-radical precursors.¹⁶⁵ Since this seminal report, SmI_2 -promoted cross-couplings of a wide variety of ketones and aldehydes with simple olefins have been employed for the synthesis of complex carbocyclic frameworks. Generally,

the SmI_2 -promoted 5-*exo*-trig ketyl radical cyclizations have been established as an efficient method for the construction of five-membered ring systems, often with high levels of stereocontrol. However, the major limitation is that these reactions are much less effective for the synthesis of other ring systems.

Examples in this section have been arranged by the type of cyclization and the class of radical precursors. The major advances in this area in the past decade include: (i) expansion of the scope of ketyl-radical precursors to cyclic esters and cyclic 1,3-diesters using $\text{SmI}_2\text{-H}_2\text{O}$ systems; (ii) development of transannular ketyl/olefin cyclizations; and (iii) successful synthesis of large ring systems via 8-*endo*-trig, 9-*endo*-trig, 10-*endo*-trig, and 11-*endo*-trig cyclizations.

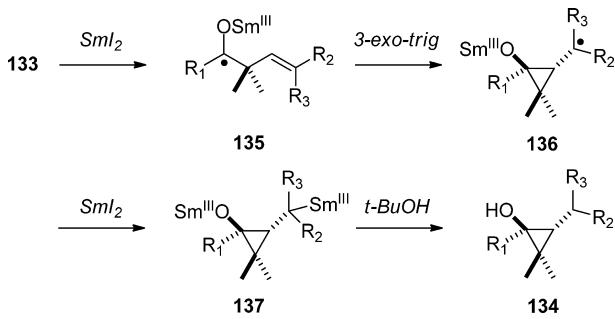
In 2010, Ortiz and Armesto reported the rare example of SmI_2 -mediated 3-*exo*-trig cyclizations of β,γ -unsaturated ketones and aldehydes (Scheme 42).²²⁴ Treatment of the precursors with

Scheme 42. Synthesis of Cyclopropanols via 3-*exo*-Trig Cyclization by Ortiz and Armesto



$\text{SmI}_2\text{-}t\text{-BuOH}$ afforded functionalized cyclopropanols in moderate yields. The authors proposed a mechanism involving the generation of ketyl-type radicals (Scheme 43); however, only

Scheme 43. Proposed Mechanism for 3-*exo*-Trig Cyclization by Ortiz and Armesto

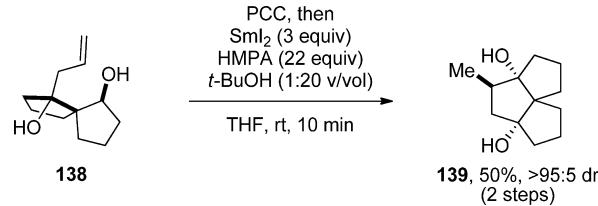


terminal alkenes substituted with activated aromatic groups, such as fluorene, indene, and 4-cyanophenyl, were successful substrates for the reaction (e.g., only alcohol and elimination products were observed using unsubstituted styrene), suggesting that the alternative mechanism involving reduction of the aromatic ring might be operative in this reaction.

Tu and co-workers reported the 5-*exo*-trig cyclization of a ketyl radical derived from a spirocyclic ketone to form a congested [6.3.0.0] tricyclic diol as a common precursor for several terpene natural products as a part of their studies on selective

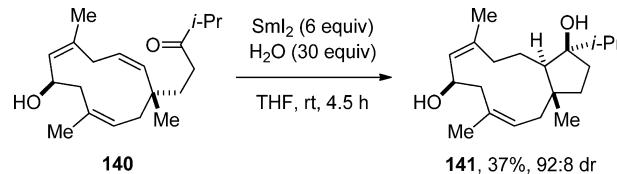
manipulation of 1,3-diols (Scheme 44).²²⁵ Oxidation of the diol precursor with PCC followed by treatment with $\text{SmI}_2\text{-HMPA}$ in the presence of *t*-BuOH afforded the desired tricycle in 50% yield as a single diastereoisomer.

Scheme 44. Synthesis of [6.3.0.0] Tricyclic Diol via 5-*exo*-Trig Cyclization by Tu



In 2009, Tori and Sono reported a biomimetic SmI_2 -mediated 5-*exo*-trig cyclization of denudatenone A, a vibsane-type diterpenoid, to give dolabellane-type terpenoids with high diastereoselectivity (Scheme 45).²²⁶ The cyclization was not

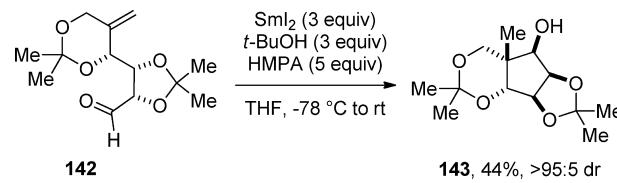
Scheme 45. 5-*exo*-Trig Cyclization in the Synthesis of Dolabellane Diterpenoids by Tori and Sono



observed in the absence of additives. A screen of reaction conditions revealed that water at low concentration (5 equiv with respect to SmI_2) gave higher yields than Lewis basic additives such as HMPA, NMP, and DBU, which could be due to the more efficient generation of the ketyl radical under these conditions.

In 2011, Gómez and López reported a 5-*exo*-trig aldehyde/alkene cyclization of functionalized sugar derivatives (Scheme 46).²²⁷ Under the $\text{SmI}_2\text{-HMPA}\text{-}t\text{-BuOH}$ reaction conditions, a

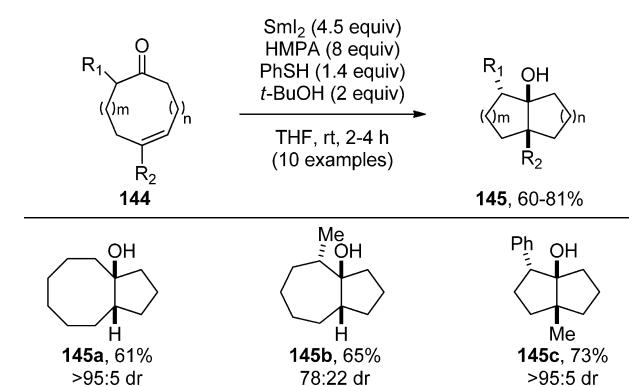
Scheme 46. 5-*exo*-Trig Cyclization in the Synthesis of Carbahexopyranoses by Gómez and López



72:28 ratio of products arising from the 5-*exo*-trig cyclization and competing intermolecular pinacol dimerization was observed. In this study, the use of SmI_2 provided complementary access to the cyclopentanol product versus the cyclopentane obtained via 5-*exo*-trig cyclization of the corresponding alkyl radical (phenyl thionocarbonate/*n*-Bu₃SnH/AIBN method).

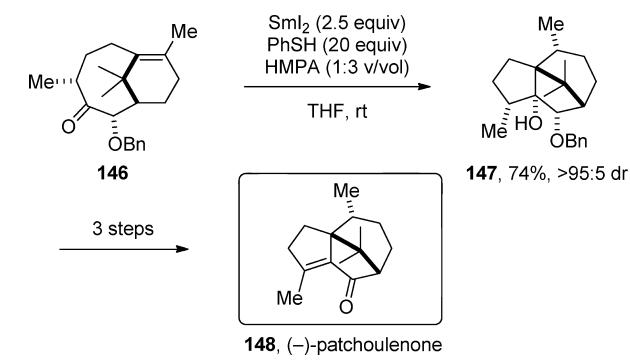
In 2007, Molander reported the synthesis of bicyclic carbocycles via SmI_2 -promoted 5-*exo*-trig transannular ketone–olefin cyclizations (Scheme 47).²²⁸ The use of $\text{SmI}_2\text{-HMPA}$ system in the presence of *t*-BuOH and PhSH as a radical scavenger furnished [3.3.0], [5.3.0], and [6.3.0] ring systems from both exo- and endocyclic olefins in good yields and exclusive *cis*-diastereoselectivity. The cyclization of ketones featuring an additional α -methyl or phenyl stereocenter resulted

Scheme 47. Transannular 5-*exo*-Trig Cyclizations by Molander



in products containing three adjacent stereocenters with high diastereoselectivity (78:22 to >95:5). Thiophenol was found to be the most effective radical scavenger out of the additives screened. The homocoupling of alkyl radicals (postcyclization) was observed in the absence of thiophenol. Banwell and co-workers reported a related SmI_2 -promoted transannular ketone-olefin cyclization as one of the key steps in the total synthesis of (–)-patchoulenone (Scheme 48).²²⁹ The use of PhSH was

Scheme 48. Total Synthesis of (–)-Patchoulenone via 5-*exo*-Trig Cyclization by Banwell



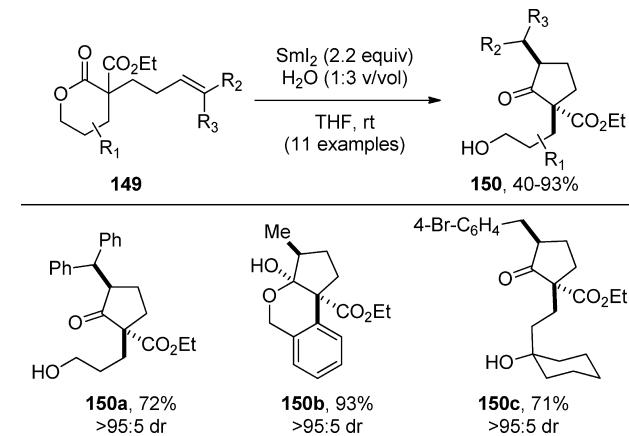
required to prevent disproportionation of the carbon-centered tertiary radical. Interestingly, when identical SmI_2 –HMPA–PhSH conditions were applied to an acyclic model system, only ketone reduction product was observed, a clear demonstration that the rate of SmI_2 -mediated ketyl/olefin cross-couplings can be significantly enhanced by placing the olefin acceptor in close proximity to the Sm(III) ketyls. The total synthesis of (–)-pathoulenone was completed in a further three steps.

Although ketyl/olefin cyclizations mediated by SmI_2 have historically been limited to aldehyde and ketone carbonyl group precursors as a result of the relatively low redox potential of the reductant, recently Procter and co-workers demonstrated in several publications^{230–237} that the use of SmI_2 – H_2O allows for the generation of ketyl-type radicals (i.e., acyl-type radicals) from six-membered cyclic esters and cyclic 1,3-diesters, thus significantly expanding the scope of application of Kagan's reagent.

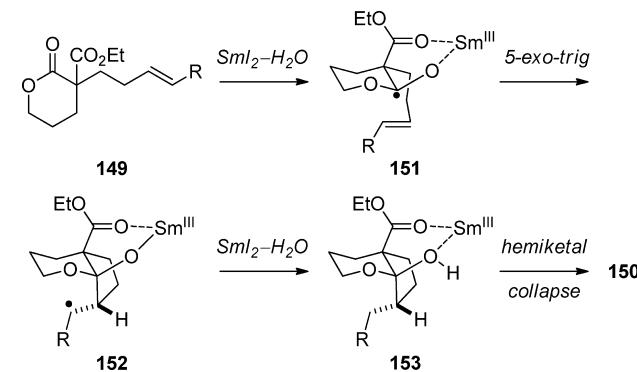
In 2008, Procter reported the first reductions of unactivated six-membered lactones using SmI_2 – H_2O .⁷⁴ In an impressive example of reagent control over a desired transformation, these reductions were fully chemoselective for δ -lactones over other ring sizes and acyclic esters. In 2009, Procter reported the first 5-

exo-trig cyclizations of ketyl-type radical intermediates formed during the SmI_2 -mediated reduction of six-membered lactones to give cyclopentanones in good yields and high diastereoselectivity (Scheme 49).²³⁰ The mechanism was proposed to involve the

Scheme 49. 5-*exo*-Trig Cyclizations of Alkenyl-Six-Membered Lactones by Procter



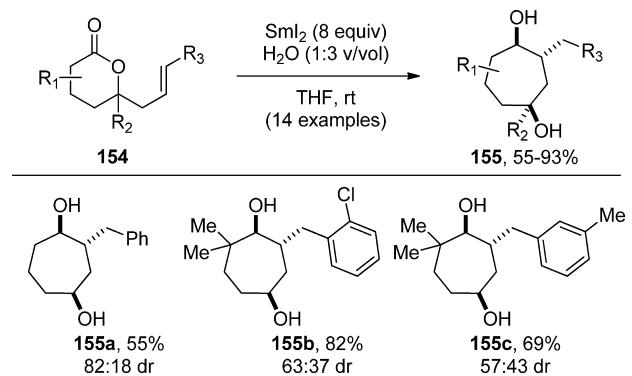
Scheme 50. Proposed Mechanism for 5-*exo*-Trig Cyclizations by Procter



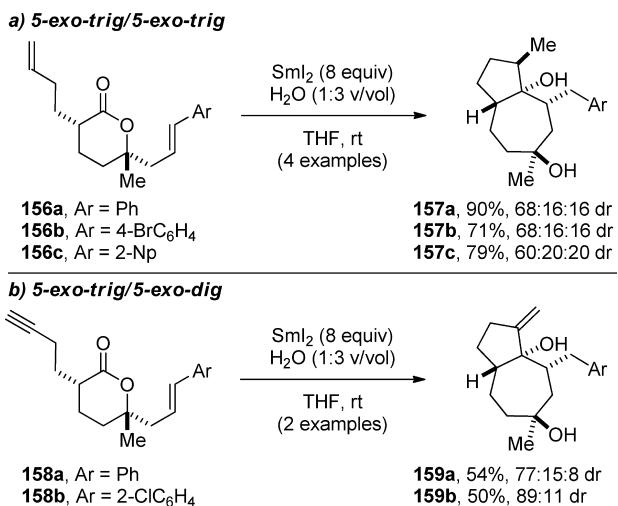
following steps (Scheme 50): (i) one-electron reduction of the lactone carbonyl by water-activated SmI_2 ; (ii) 5-*exo*-trig cyclization of the radical anion; (iii) second reduction by SmI_2 ; (iv) protonation; and (v) hemiketal collapse. The carboethoxy group serves to coordinate Sm(III) and stabilize the hemiketal intermediate to prevent over-reduction to the cyclopentanol. Impressively, the SmI_2 – H_2O reaction conditions tolerate several functional groups that are readily reduced with other Sm(II) systems.

In 2011, Procter reported the stereoselective synthesis of seven-membered-ring diols using SmI_2 – H_2O -promoted 5-*exo*-trig cyclizations of six-membered lactones in which the alkene tether was placed at the 5-position (Scheme 51).²³¹ Treatment of the lactone substrates with SmI_2 – H_2O at room temperature led to the efficient cyclization to give cycloheptan-1,4-diols in good yields but lower diastereoselectivity. The use of a second tether on the six-membered lactone scaffold allowed the interception of cycloheptanone-derived ketyl radicals in a second cyclization leading to radical cascades to give complex azulene motifs via 5-*exo*-trig/5-*exo*-trig and 5-*exo*-trig/5-*exo*-dig cyclizations (Scheme 52). It was determined that cis-arrangement of the side chains

Scheme 51. Synthesis of Seven-Membered Ring Diols via 5-exo-Trig Cyclization of Alkenyl-Lactones by Procter



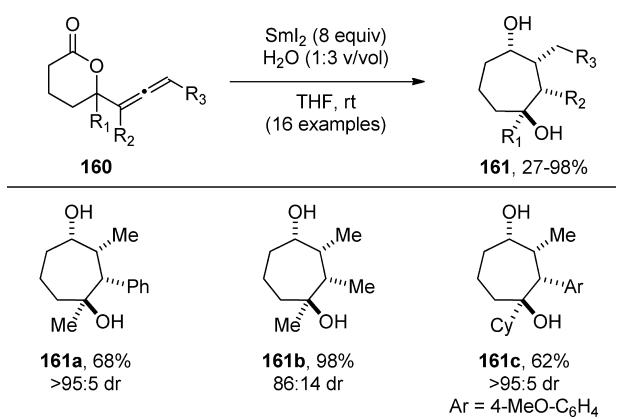
Scheme 52. 5-exo-Trig Cyclization Cascades of Six-Membered Lactones by Procter



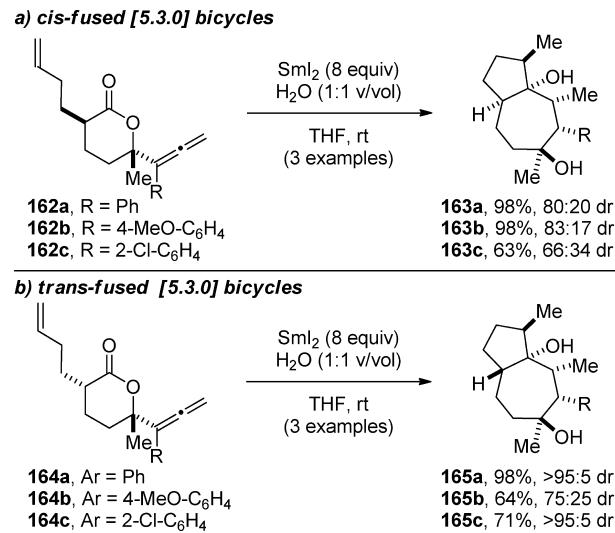
was required for the efficient cascades. Computational studies provided support for the high selectivity in cases when the alkene tethers were *cis* in a chair conformation.

The synthesis of seven-membered rings (Scheme 53), including reductive cyclization cascades (Scheme 54), has recently been extended to allene radical acceptors.²³² This reaction furnishes complex diols featuring from four (single cyclizations) to six contiguous stereocenters (cascade cycliza-

Scheme 53. Cross-Coupling of Six-Membered Lactones with Allenes by Procter



Scheme 54. 5-exo-Trig Cyclization Cascades of Allenyllactones by Procter

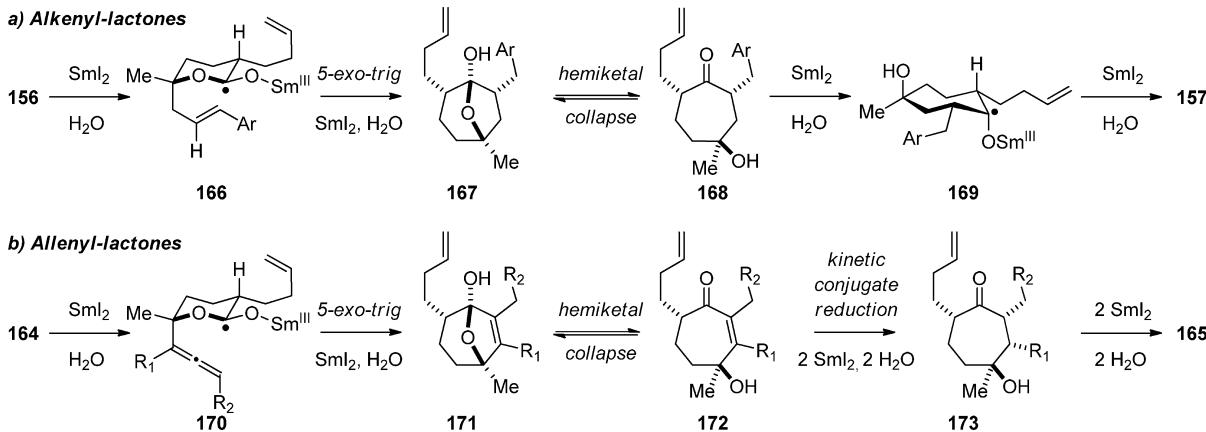


tions) in excellent yields and diastereoselectivity. The proposed mechanism for radical cyclization cascades of six-membered alkenyl- and allenyl-lactones mediated by $\text{SmI}_2-\text{H}_2\text{O}$ is shown in Scheme 55. The high stereoselectivity in the cyclizations involving allene precursors results from the stereoselective conjugate reduction of the enone moiety under kinetic control. The preferential cyclization of the ketyl radical generated during the first SmI_2 reduction onto the alkene tether at the five-position contributes to the high efficiency of the cascade sequence.

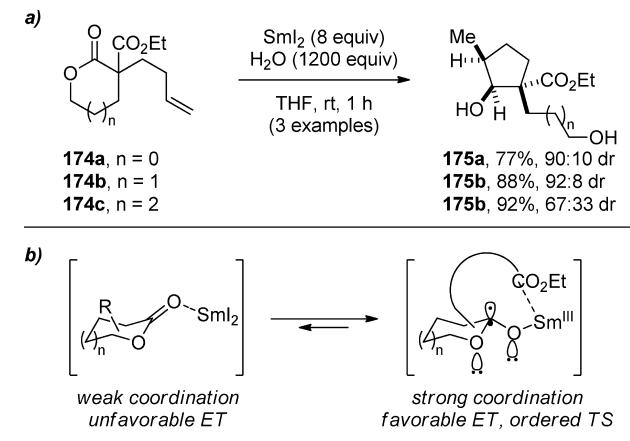
Recently, Szostak and Procter reported the first SmI_2 -mediated reductive 5-exo-trig cross-couplings of lactones having ring sizes other than six with unactivated olefins using a directing group effect (Scheme 56).²³³ With an ester directing group, five- to seven-membered lactones underwent efficient radical cyclization to give cyclopentanols containing three contiguous stereocenters. In the same study, a remarkable thermodynamic rate acceleration (up to 6 orders of magnitude) in the $\text{SmI}_2-\text{H}_2\text{O}$ -mediated reduction of cyclic esters of various ring sizes enabled by transient chelation between a directing group and the $\text{Sm}(\text{II})$ reagent was demonstrated.

In addition to lactones, in the last five years, cyclic 1,3-diesters have been demonstrated to serve as a new class of precursors for ketyl-radical cyclizations mediated by $\text{SmI}_2-\text{H}_2\text{O}$. In 2009, Procter reported the first reductions of cyclic 1,3-diesters (Meldrum's acids) using the $\text{SmI}_2-\text{H}_2\text{O}$ reagent.²³⁴ These reductions were selective for cyclic 1,3-diesters over other acyclic esters, including malonate derivatives. The intermediate ketyl-type radicals formed in the SmI_2 -mediated reduction of Meldrum's acids have been utilized in 5-exo-trig cross-couplings with unactivated olefins to furnish 2-hydroxycyclopentanecarboxylic acids containing three stereocenters in high yields and diastereoselectivity (Scheme 57a).^{234,235} Performing the reaction at higher temperatures improved the diastereoselectivity of the reaction, which was proposed to be due to a more favorable conformation for the cyclization. A transannular 5-exo-trig cyclization involving a ketyl-type radical generated directly from a cyclic 1,3-diester gave a [3.2.1] bridged alcohol as a single diastereoisomer (Scheme 57b). The mechanism of these reactions is proposed to proceed by a single-electron reduction of one of the carbonyls in the Meldrum's acid by $\text{SmI}_2-\text{H}_2\text{O}$ to generate a radical anion, which undergoes 5-exo-trig cyclization.

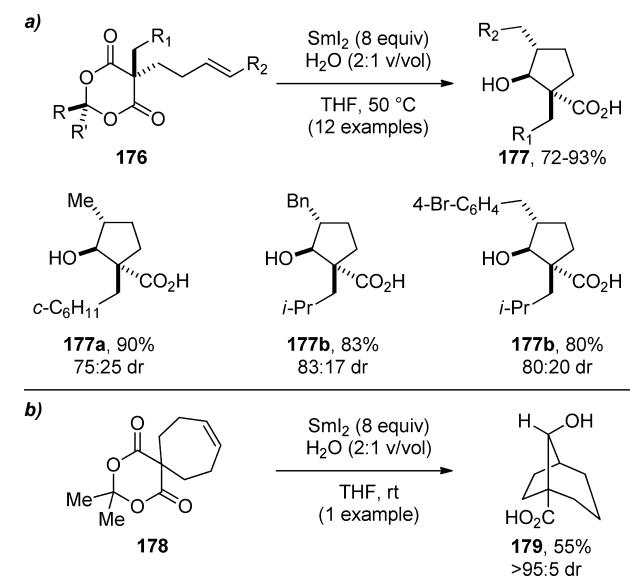
Scheme 55. Proposed Mechanism for Cyclization Cascades of Lactones by Procter



Scheme 56. Reductive Cyclizations of Lactones Enabled by a Directing Group Effect by Szostak and Procter

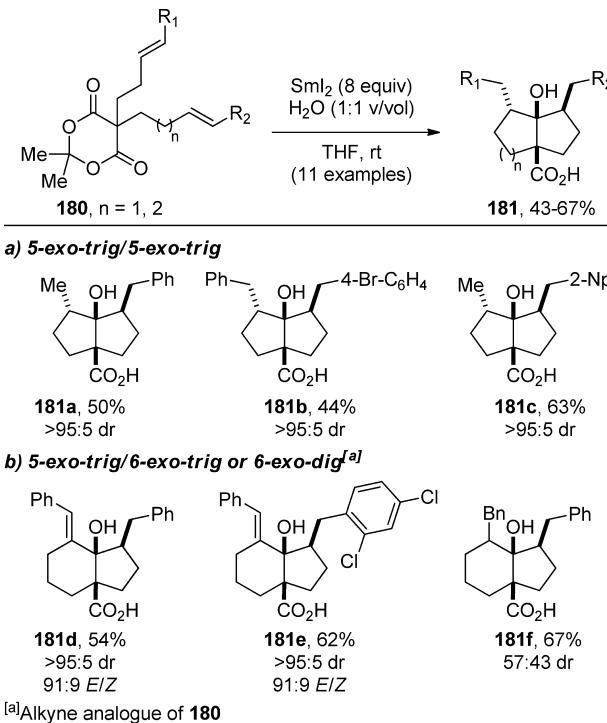


Scheme 57. (a) 5-exo-Trig Cyclization of Meldrum's Acids; (b) Synthesis of a [3.2.1] Bicyclic Alcohol via 5-exo-Trig Transannular Cyclization by Procter



up to four adjacent stereocenters (Scheme 58).²³⁶ It was shown that differential activation of the olefin acceptors allows for high

Scheme 58. 5-exo-Trig Cyclization Cascades of Meldrum's Acids by Procter

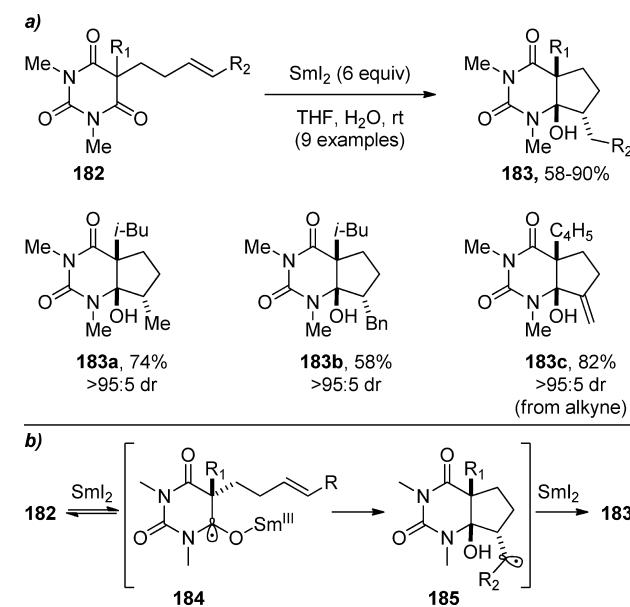


chemoselectivity in the cascade sequences. In one extreme case, the olefin acceptors bearing 4-Br-C₆H₄ and C₆H₅ substituents participated in a fully chemo- and diastereoselective cyclization, which was initiated by a selective cross-coupling of the ketyl radical with the 4-Br-C₆H₄-substituted olefin (cf., C₆H₅). The cyclization selectivity is consistent with the relative stabilization of the product carbon-centered radicals by these substituents.

In 2013, Szostak and Procter reported the first chemoselective reductive cross-couplings of ketyl-type radicals generated from cyclic 1,3-diimides (barbituric acids) using SmI₂-H₂O (Scheme 59).²³⁷ A range of cyclic 1,3-diimides underwent efficient cyclizations with unactivated olefins in good to excellent yields. For the first time in any radical cyclizations mediated by SmI₂-H₂O, the products were formed with perfect control of

Using the Meldrum's acid template, in 2012 Procter reported SmI₂-mediated 5-exo-trig/5-exo-trig and 5-exo-trig/6-exo-trig cyclization cascades leading to complex bicyclic alcohols bearing

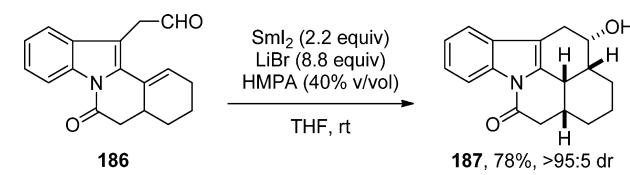
Scheme 59. 5-exo-Trig Cross-Coupling of Cyclic 1,3-Diimides by Szostak and Procter



stereoselectivity around the five-membered ring, which was proposed to result from an increased half-life of the acyl-type radical stabilized by the $n_N \rightarrow$ SOMO conjugation. These cyclizations were extended to 5-exo-dig cross-couplings of barbituric acids with unactivated alkynes, providing general access to a novel class of bicyclic hemiaminals analogous to the elusive tetrahedral intermediates of amide bond addition reactions.

SmI_2 -mediated cross-couplings of carbonyl compounds with unactivated olefins have also been used for the synthesis of larger rings. In 2009, Pagenkopf reported a SmI_2 -mediated 6-endo-trig ketyl/alkene cross-coupling as a concise method for the synthesis of tetrahydroisoquinocarbazoles (Scheme 60).²³⁸ Careful

Scheme 60. Synthesis of Isoquinocarbazoles via 6-endo-Trig Cyclization by Pagenkopf

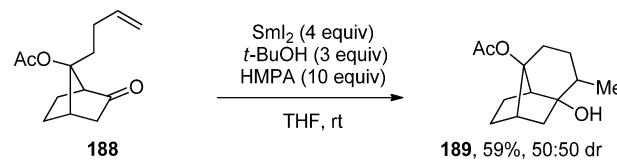


optimization of the reaction conditions revealed that a reagent system based on SmI_2 , HMPA, and LiBr provided the best results in terms of yield and diastereoselectivity of the reaction. SmI_2 -THF also provided a comparable yield of the desired product, however, as a mixture of diastereoisomers. This reaction is particularly noteworthy as it is one of the few examples of radical 6-endo-trig cyclization onto trisubstituted olefins.

Wood reported the SmI_2 -mediated 6-exo-trig ketone/terminal olefin cross-coupling to access a norbornane core during their studies toward phomoidride B (Scheme 61).²³⁹ The use of SmI_2 -HMPA-*t*-BuOH furnished the desired product in good yield, however, as a mixture of diastereoisomers. Alternative protocols employing *n*-Bu₃SnH/AIBN did not afford the cyclization product.

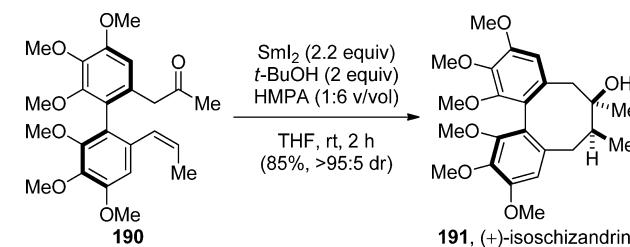
Molander reported an 8-endo-trig ketyl-alkene cyclization promoted by SmI_2 -HMPA-*t*-BuOH in the final step of the

Scheme 61. Synthesis of Norbornanes via 6-exo-Trig Cyclization by Wood



asymmetric total synthesis of (+)-isoschizandrin (Scheme 62).²⁴⁰ The authors proposed that the excellent yield of the

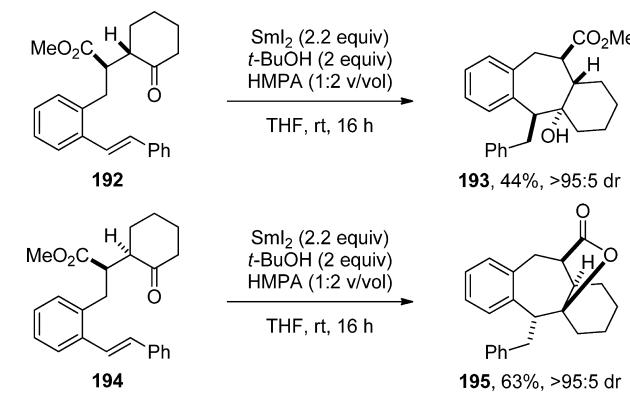
Scheme 62. 8-endo-Trig Cyclization in the Total Synthesis of (+)-Isoschizandrin by Molander



reaction resulted from preorganization of the transition state by the rigid biaryl motif and the presence of an activating substituent on the olefin, which contributed to enhanced SOMO/LUMO interactions. The product was formed as a single diastereoisomer, and this was ascribed to three factors: (i) (Z)-olefin geometry of the starting material; (ii) pseudoequatorial orientation of the alkoxy samarium, additionally enhanced by the HMPA ligands; and (iii) the biaryl stereochemistry.

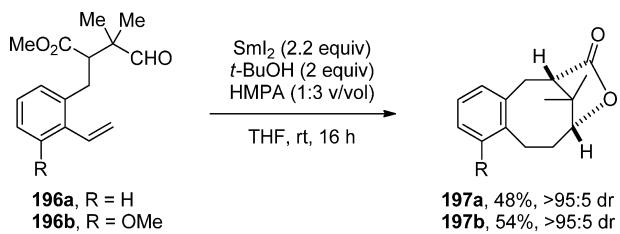
In 2009, Reissig reported a rare example of SmI_2 -mediated 7-exo-trig cyclization in studies on forming benzannulated carbocycles (Scheme 63).²⁴¹ Although the authors initially set

Scheme 63. 7-exo-Trig Ketyl/Olefin Cyclizations by Reissig



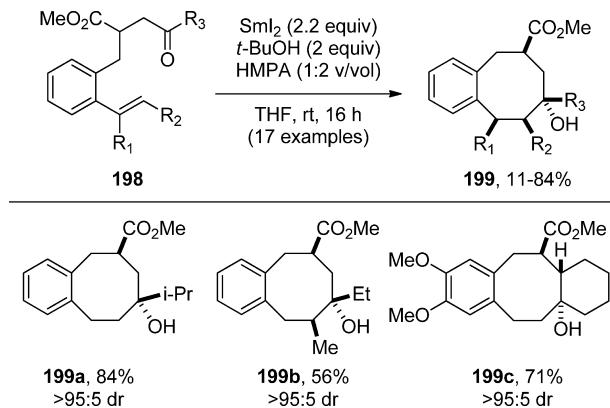
out to explore the scope of SmI_2 -HMPA-*t*-BuOH-promoted 8-endo-trig cyclizations between ketones and terminal unactivated olefins (cf., 8-endo-trig cyclization reported by Molander, Scheme 62),^{242,243} they found that substituting the olefin with another phenyl group led to 7-exo-trig cyclizations. The benzannulated products were formed in good yields and as single diastereoisomers. In contrast, the cross-coupling of aldehydes and ketones with terminal olefins resulted in efficient 8-endo-trig cyclizations to furnish tricyclic lactones and benzannulated cyclooctanols (Schemes 64 and 65).^{242,243} The mechanism was proposed to involve an equilibrium between the

Scheme 64. Synthesis of Bicyclic Lactones via 8-*endo*-Trig Cyclizations by Reissig

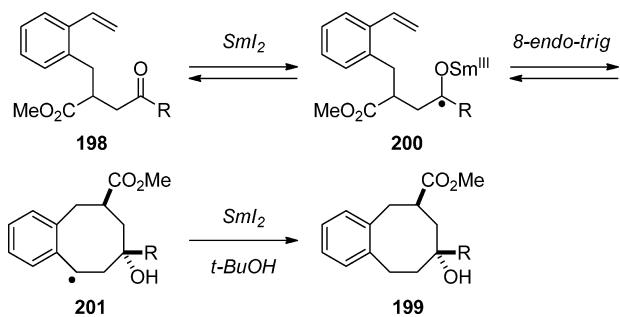


ketyl radical anion and eight-membered benzylic radical, with an irreversible second reduction step (Scheme 66).

Scheme 65. Synthesis of Eight-Membered Carbocycles via 8-*endo*-Trig Cyclizations by Reissig



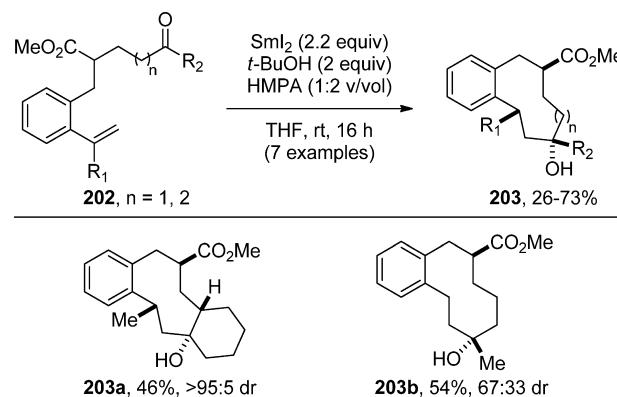
Scheme 66. Proposed Mechanism for 8-*endo*-Trig Cyclizations by Reissig



In 2009, Reissig reported the synthesis of benzannulated medium-sized rings via SmI_2 -mediated 9-*endo*-trig, 10-*endo*-trig, and 11-*endo*-trig cyclizations (Scheme 67).²⁴⁴ The products were obtained in good yields and diastereoselectivity. Importantly, the use of high dilution conditions was not required.

3.1.1.6. Cross-Coupling Terminating by Elimination. Nicolaou reported the SmI_2 -promoted 6-*exo*-trig carbonyl-olefin coupling terminating by β -elimination in the total synthesis of vannusal B (Scheme 68).^{245–249} A carbonate group was selected for the elimination, which was proposed to proceed via an anionic mechanism. After extensive optimization, it was found that a chelating SEM group at the β -position of the aldehyde was required to prevent undesired C–C bond cleavage via Grob-type fragmentation of the ketyl radical. Treatment of the advanced precursor 204 with SmI_2 –HMPA at -10°C triggered the radical cyclization to form the final ring in excellent yield as a 65:35

Scheme 67. 9-*endo*-Trig and 10-*endo*-Trig Ketyl/Olefin Cross-Couplings by Reissig



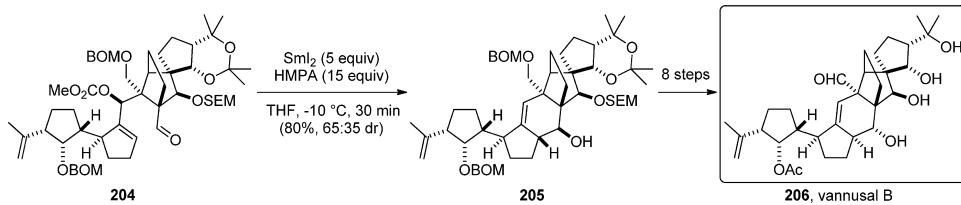
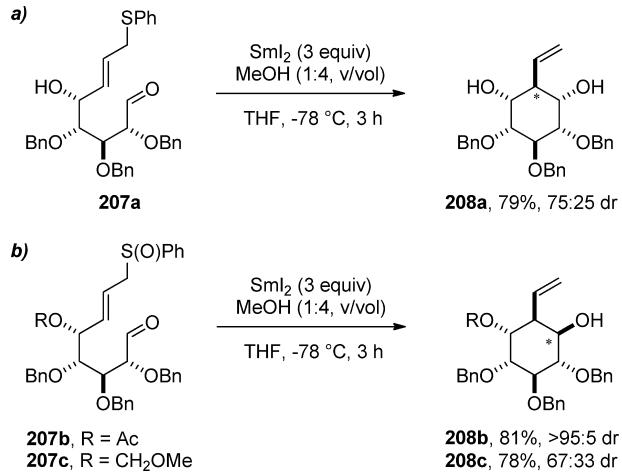
mixture of diastereoisomers. The total synthesis of vannusal B was completed following a further eight steps.

Matsuda reported 6-*exo*-trig ketyl radical/olefin cyclizations terminating by β -elimination on carbohydrate templates using chelating groups to direct the stereochemical outcome of the cyclization (Scheme 69).²⁵⁰ The elimination of sulfide and sulfoxide groups was proposed to proceed via a radical mechanism. The hydroxyl-directed cross-coupling of the δ -hydroxy aldehyde under SmI_2 –MeOH conditions furnished *cis*-1,3-cyclohexanediols (Scheme 69a). In contrast, the acetoxy-directed cross-coupling of the δ -acetoxy aldehyde afforded *trans*-1,3-cyclohexanediols (Scheme 69b). The use of a MOM directing group resulted in a mixture of *cis* and *trans* diastereoisomers. The proposed mechanism is shown in Scheme 70 and involves coordination of the Sm(III) ketyl and hydroxyl or acetyl group to provide complementary stereochemical outcomes in the cyclization.

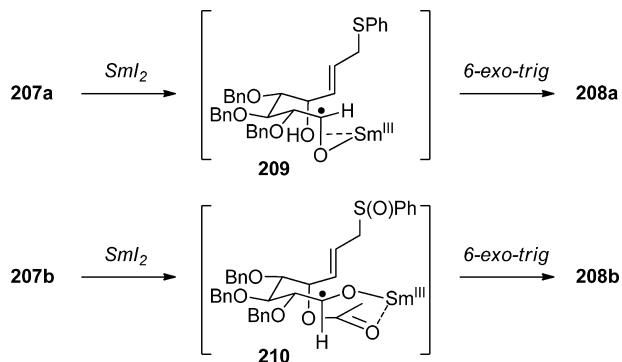
Recently, Fan reported the SmI_2 -mediated 6-*exo*-trig ketyl radical/olefin cross-coupling terminating in radical elimination of phenyl sulfide as a key step in the formal synthesis of morphine (Scheme 71).²⁵¹ The reaction sets two adjacent stereocenters in high yield and with excellent stereocontrol. The authors proposed that unfavorable steric interactions between the Sm(III)-ketyl and allylic thioether contributed to the high stereoselectivity of the reaction. Interestingly, both diastereoisomers of the phenyl sulfide provided the desired product in similar yield and diastereoselectivity.

3.1.2. Intermolecular Cross-Coupling of Ketyl Radicals with Alkenes. In comparison to SmI_2 -mediated intramolecular ketyl/olefin couplings, intermolecular reactions with alkenes are less precedented. In the past decade, this method has been used primarily for the synthesis of γ -lactones by cross-coupling with acrylates, followed by in situ lactonization of the intermediate samarium alkoxide. Furthermore, significant developments have been reported by Skrydstrup and co-workers in the use of thioesters and *N*-acyl oxazolidinones as acyl radical equivalents in cross-couplings with activated olefins. These methodologies allow for the synthesis of 1,4-dicarbonyl compounds under very mild conditions and have already found numerous applications in the synthesis of biologically active compounds. Examples in this section have been organized into the following classes: (i) synthesis of γ -lactones; (ii) cross-couplings with thioesters and *N*-acyl oxazolidinones; and (iii) miscellaneous examples.

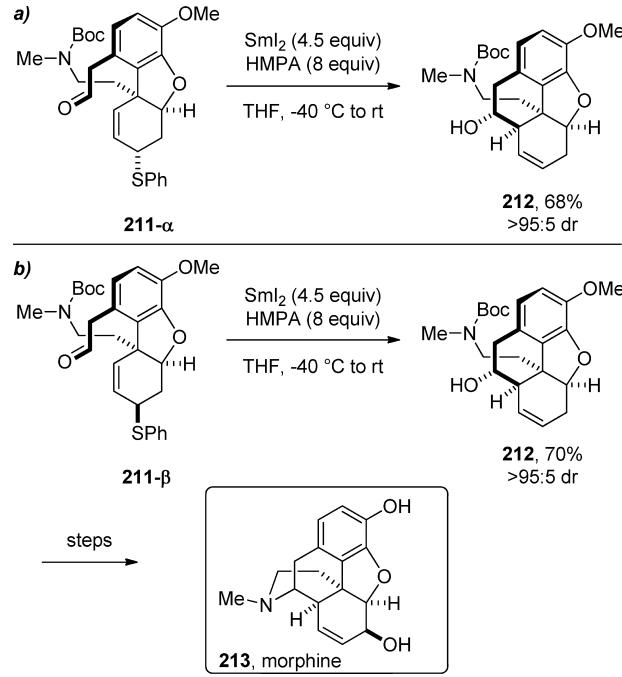
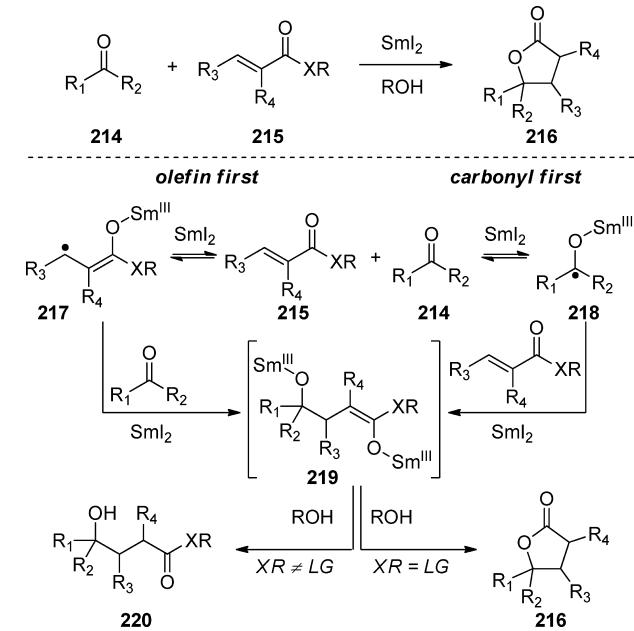
3.1.2.1. Synthesis of γ -Lactones. The first intermolecular SmI_2 -mediated cross-coupling of aldehydes and ketones with acrylates to give γ -lactones was described independently by

Scheme 68. 6-*exo*-Trig Cyclization/Elimination in the Total Synthesis of Vannusal B by NicolaouScheme 69. Chelation-Controlled 6-*exo*-Trig Cyclization/Elimination by Matsuda

Scheme 70. Proposed Mechanism for Chelation-Controlled Cyclization by Matsuda



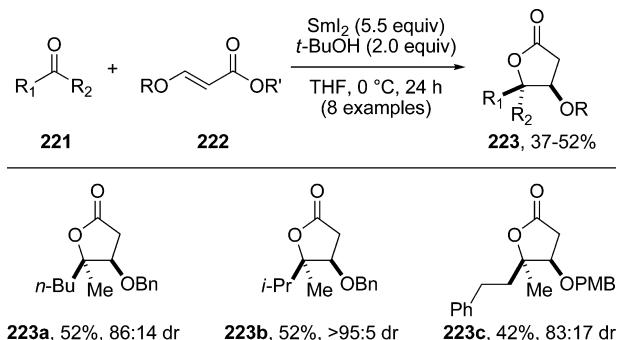
Fukuzawa^{161,162} and Inanaga¹⁶³ in 1986. Since then, many examples have been reported, including in the synthesis of natural products; however, the mechanism of these reactions has still not been elucidated. Two mechanistic pathways can be considered (Scheme 72): (i) reduction of the carbonyl compound to the ketyl radical (“carbonyl-first”), and (ii) conjugate reduction of the olefin to the radical anion (“olefin first”). Both of these radical intermediates could then participate in the cross-coupling to give the samarium enolate **219**, which either will be quenched by a proton source to give γ -hydroxy carboxylic acid derivatives, or more frequently this intermediate would undergo intramolecular cyclization to γ -butyrolactones. While recent work by Tori suggests that the reduction of α,β -unsaturated carbonyls in these reactions might be easier than that of isolated ketones,¹⁶⁰ the precise mechanism will always depend on the specific combination of the substrates. To date, the traditional “carbonyl-first” mechanism appears to be operative in the majority of cases.

Scheme 71. 6-*exo*-Trig Cross-Coupling/Elimination in the Formal Total Synthesis of Morphine by FanScheme 72. General Mechanism for Intermolecular Cross-Couplings of Carbonyl Groups with Alkenes Using SmI_2 

α,β -Unsaturated olefins with heteroatoms at the β -position have not been commonly utilized in SmI_2 -mediated intermo-

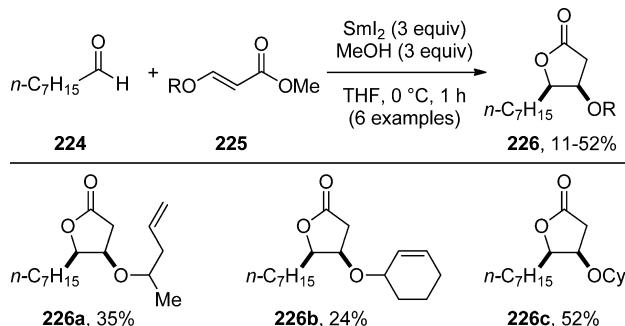
lecular carbonyl-alkene couplings due to their propensity to undergo elimination of the heteroatom substituent and the change in electronics of the π -system. In 2004, Procter reported the cross-coupling of β -alkoxy acrylates with ketones for the synthesis of β -alkoxy- γ -butyrolactones using $\text{SmI}_2-t\text{-BuOH}$ in modest yields but very high diastereoisomeric ratio (Scheme 73).²⁵² The use of β -benzoyl acrylates resulted in the elimination

Scheme 73. Synthesis of β -Alkoxy- γ -butyrolactones by Procter



of the β -heteroatom substituent prior to the cross-coupling. This methodology was applied to the asymmetric synthesis of an antifungal *Mutisia friesiana* γ -butyrolactone by employing a chiral ephedrine derived auxiliary. In 2007, Padrón extended this methodology to the coupling of β -alkoxy acrylates with aliphatic aldehydes using the SmI_2-MeOH reagent system (Scheme 74).²⁵³ The synthesis of a range of β -alkoxy- γ -butyrolactones

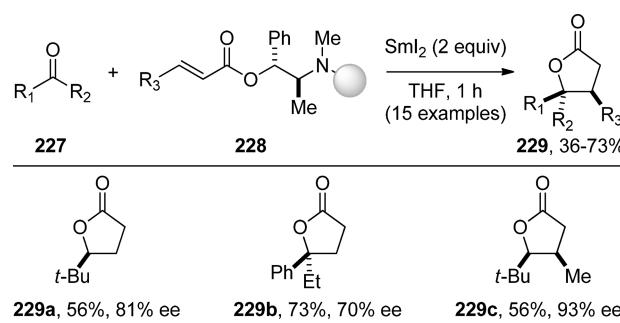
Scheme 74. Synthesis of β -Alkoxy- γ -butyrolactones by Padrón



with exclusive *cis*-diastereoselectivity was reported. A chelation model was proposed, in which the aldehyde ketyl avoids steric interactions with the β -alkoxy substituent.

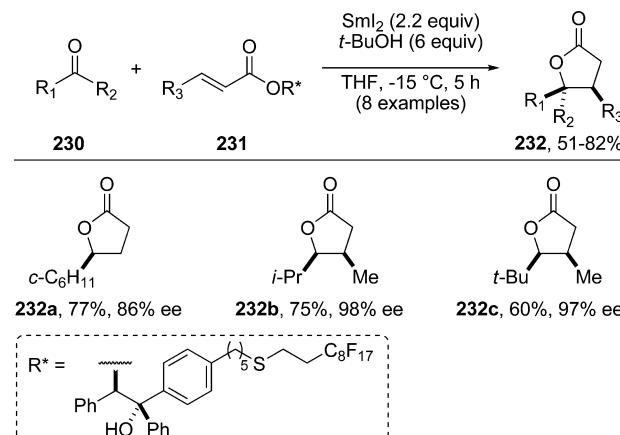
Asymmetric SmI_2 -mediated intermolecular cross-couplings of carbonyl compounds with acrylates have been achieved in the past decade. The first report of the asymmetric synthesis of chiral γ -butyrolactones with SmI_2 was reported by Fukuzawa in 1997 using an ephedrine-type auxiliary on the acrylate.²⁵⁴ In 2003, Procter extended this methodology to the SmI_2 -mediated asymmetric synthesis of γ -butyrolactones on a solid support (Scheme 75).^{255,256} γ -Butyrolactones were synthesized in moderate yields and high enantioselectivities. The resin-bound ephedrine-derived auxiliary on the acrylate could be reused with no decrease in enantioselectivity; however, the obtained yields were substantially lower after two cycles. Crotonate resin was also developed for the synthesis of *cis*- β,γ -disubstituted butyrolactones in high selectivities. This methodology has been applied to a short synthesis of a DNA-binding *Streptomyces* metabolite.

Scheme 75. Asymmetric Synthesis of β,γ -Substituted γ -Butyrolactones by Procter Using a Solid Supported Auxiliary



Subsequently, Procter reported the use of a mandelic acid-derived fluorous auxiliary on the ester for the SmI_2 -mediated coupling of aldehydes with acrylates and crotonates (Scheme 76).²⁵⁷ Interestingly, the cyclopropane carboxaldehyde under-

Scheme 76. Asymmetric Synthesis of β,γ -Substituted γ -Butyrolactones Using Fluorous-Tagged Auxiliary by Procter



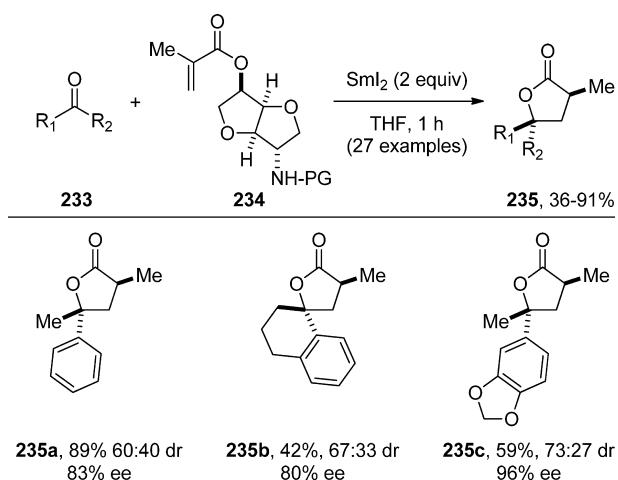
went successful coupling with preservation of the cyclopropane ring, which could suggest that this reaction proceeds through the “olefin-first” mechanism. This methodology could also be applied to the cross-coupling with ketones and nitrones, however, with lower enantioselectivity. The authors proposed that a change to the ‘carbonyl-first’ mechanism could contribute to the lower selectivity in these cases.

Lin and Xu reported a carbohydrate-derived auxiliary on a methacrylate ester for the synthesis of α,γ -substituted γ -butyrolactones with high enantioselectivity (Scheme 77).^{258,259} Interestingly, in cases when a secondary amide group is present on the auxiliary, the reaction proceeds in the absence of an external proton source.²⁵⁹ A number of protecting groups on nitrogen was investigated with Cbz giving the best results.

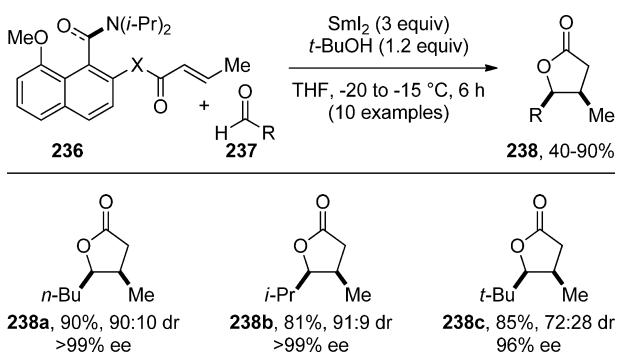
In 2006, Dai reported the use of atropisomeric 1-naphthamides for the asymmetric reductive coupling of aldehydes with crotonates to form γ -butyrolactones mediated by $\text{SmI}_2-t\text{-BuOH}$ in high selectivity (Scheme 78).²⁶⁰ This approach has also been extended to the synthesis on solid support using Rink amide resin attached to the naphthalene ring. Chelation of the samarium ketyl to amide and ester carbonyl oxygens was proposed to explain the observed enantio- and diastereoselectivity.

Dai reported the use of Fukuzawa’s auxiliary to achieve highly diastereoselective coupling with a chiral aldehyde in the synthesis

Scheme 77. Asymmetric Synthesis of α,γ -Substituted γ -Butyrolactones Using a Carbohydrate Auxiliary by Xu

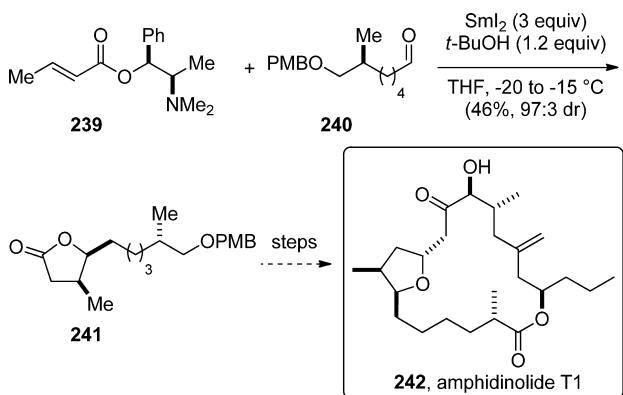


Scheme 78. Asymmetric Synthesis of β,γ -Substituted γ -Butyrolactones Using Atropisomeric Amides by Dai



of a γ -butyrolactone fragment of the marine natural product amphidinolide T1 (Scheme 79).²⁶¹ The modest yield resulted

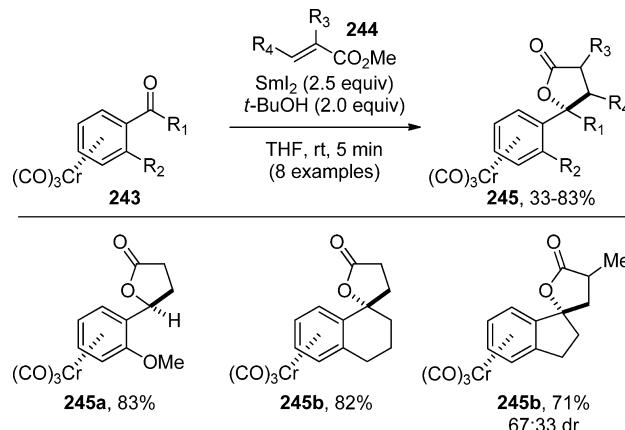
Scheme 79. Synthesis of β,γ -Substituted γ -Butyrolactone toward Amphidinolide T1 by Dai



from the formation of by-products from the aldehyde, which is in line with generally lower yields in the SmI_2 -mediated synthesis of γ -butyrolactones employing straight-chain aldehydes.²⁵⁴ Kang reported the synthesis of a PPAR agonist featuring an α,γ,γ -trisubstituted- γ -butyrolactone unit via a SmI_2 -mediated cross-coupling between ketone precursor and methacrylates bearing pseudoephedrine auxiliaries with moderate enantioselectivity (not shown).²⁶²

Merlic reported an alternative strategy for the asymmetric synthesis of γ -butyrolactones via SmI_2 -mediated reductive coupling using planar chiral tricarbonyl chromium complexes of aromatic ketones and aldehydes (Scheme 80).²⁶³ The

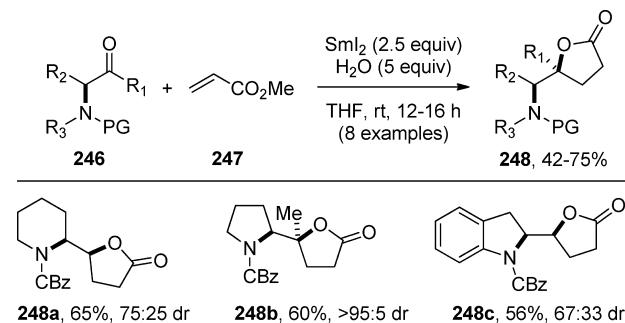
Scheme 80. Synthesis of α,β,γ -Substituted γ -Butyrolactones Using Arene Tricarbonylchromium Complexes by Merlic



reductive coupling of a range of ketones and aldehydes with methyl acrylate afforded products as single diastereoisomers in high yield. Decomplexation with I_2 gave γ -butyrolactones as single enantiomers. Treatment of the enantiomerically pure chromium tricarbonyl complexes of lactone products with $\text{BF}_3 \bullet \text{Et}_2\text{O}$ resulted in a cationic rearrangement with inversion of the stereochemistry at the benzylic carbon.

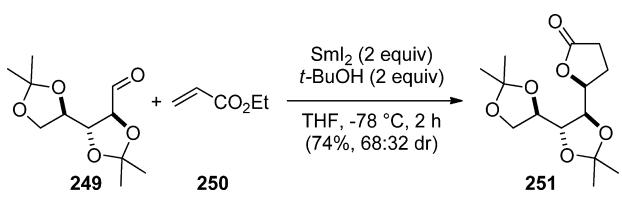
Recently, Burtoloso reported the SmI_2 -mediated coupling of α -amino aldehydes and ketones with methyl acrylate to form γ -aminomethyl- γ -butyrolactones in high yields and diastereoselectivity (Scheme 81).²⁶⁴ Extensive optimization revealed that

Scheme 81. Synthesis of γ -Aminomethyl- γ -Butyrolactones from α -Amino Aldehydes by Burtoloso



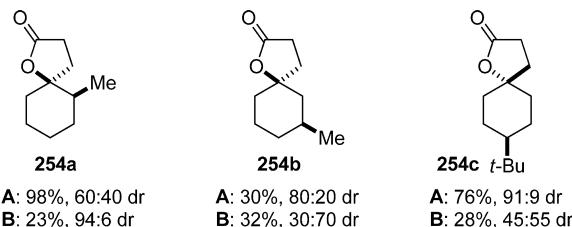
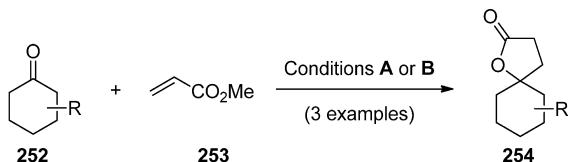
H_2O serves as the optimum additive for this reaction, while MeOH and *t*-BuOH afforded lower yields. Interestingly, reductive cleavage of the C–N bond was not observed under these conditions. The methodology provides a concise access to indolizidine and quinolizidine alkaloids from α -amino acids. Linker reported a related reductive coupling of a chiral α -heteroatom-substituted carbohydrate-derived aldehyde with ethyl acrylate in moderate diastereoselectivity (Scheme 82).²⁶⁵ Coordination of the samarium ketyl to the α -oxygen was proposed to control the stereochemistry; however, due to conformational flexibility of the carbohydrate template, only moderate selectivities were achieved under a variety of conditions.

Scheme 82. Synthesis of Protected 3-Deoxy-D-gluco-oct-2-ulosonic Acid by Linker



Sono reported a detailed study on the reductive cross-coupling of cyclic ketones with methyl acrylate under SmI₂-t-BuOH and electrochemical conditions (Scheme 83).²⁶⁶ In most cases

Scheme 83. Synthesis of γ -Substituted γ -Butyrolactones by Sono Using SmI₂ or Electrolytic Conditions

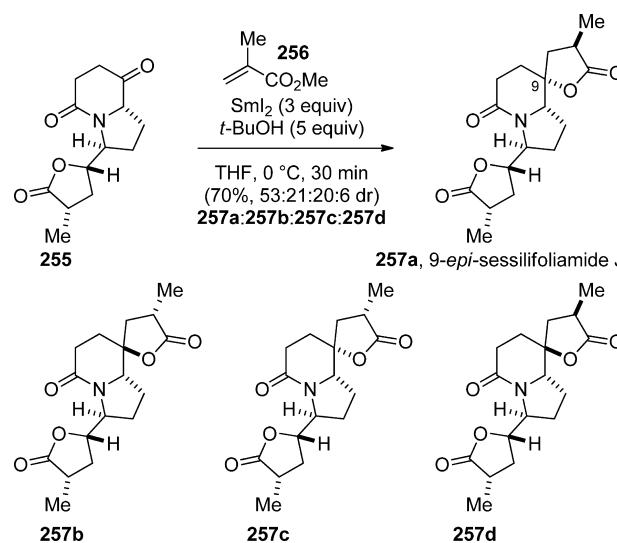


investigated, higher diastereoselectivity and yield were observed using SmI₂. The traditional “carbonyl-first” mechanism involving cross-coupling of an axial ketyl radical with the acrylate was proposed for the SmI₂-mediated process. In contrast, the equatorial addition of acrylate radical or anion occurs in the electrochemical reaction.²⁶⁷

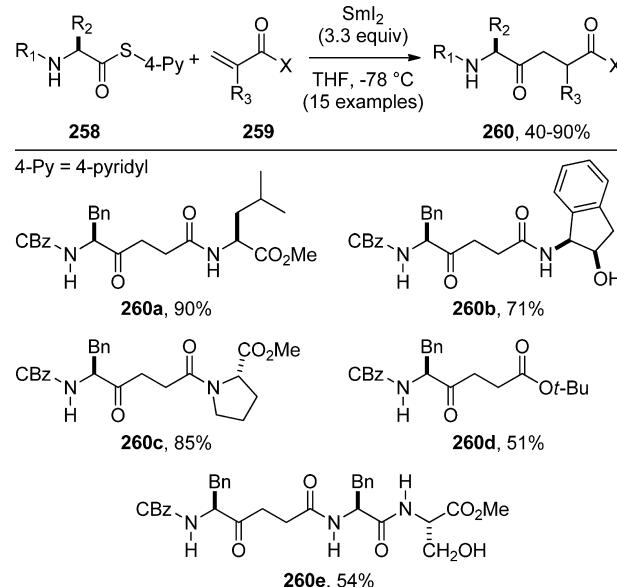
Finally, Huang reported the total synthesis of 9-*epi*-sessilifoliamide J using the SmI₂-mediated reductive coupling with methyl methacrylate as the final step (Scheme 84).²⁶⁷ In an alternative protocol, the cross-coupling with β -bromo-methacrylate, followed by hydrogenation and lactonization under acidic conditions gave improved stereocontrol in this transformation.²⁶⁸

3.1.2.2. Cross-Coupling with Thioesters and N-Acyloxazolidinones as Acyl Radical Equivalents. In 2000, Skrydstrup reported a versatile method for the selective introduction of hydroxylalkyl chains into small peptides using SmI₂-mediated cross-coupling between substrates having 4-pyridyl sulfide groups placed on the amino acid backbone and carbonyl compounds.²⁶⁹ In 2002, they reported a seminal study on the SmI₂-promoted cross-coupling of 4-pyridyl thioesters derived from amino acids with α,β -unsaturated esters and amides for the synthesis of γ -ketoamides and γ -ketoesters (Scheme 85).^{270,271} Optimization of the thioester group revealed that 4-pyridyl thioesters are optimal for the synthesis of 1,4-dicarbonyls, with the 2-pyridyl precursors giving lower yields and over-reduction to the 1,4-amido alcohol products. Remarkably, under these conditions decarbonylation is not observed, indicating that thioesters serve as α -amino acid acyl radical equivalents. Because dipeptides containing α -stereocenters are coupled without

Scheme 84. Late-Stage Synthesis of a γ -Butyrolactone in the Total Synthesis of 9-*epi*-Sessilifoliamide J by Huang

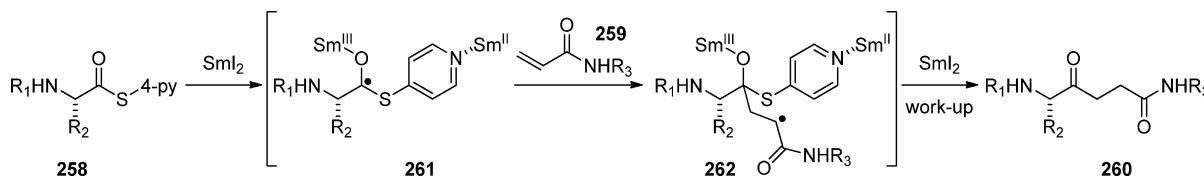
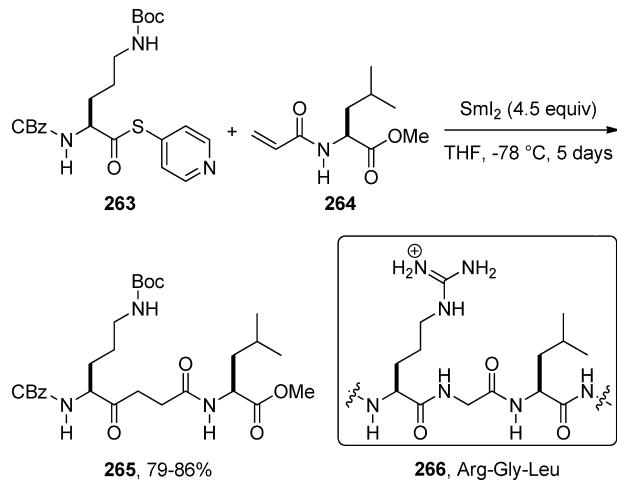


Scheme 85. Synthesis of γ -Dicarbonyls Using Thioesters as Acyl Radical Equivalents by Skrydstrup



racemization, this method constitutes an attractive entry into 1,4-dicarbonyls derived from amino acids for the synthesis of protease inhibitors and ketomethylene isosteres of amide bonds.

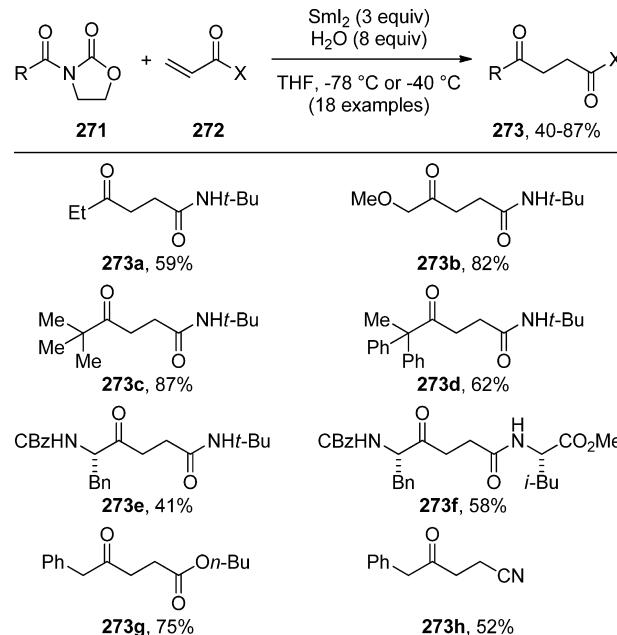
The mechanism was proposed to involve single-electron transfer to the thioester carbonyl group to generate a ketyl radical anion, which then undergoes cross-coupling with the α,β -unsaturated amide or ester acceptor (Scheme 86). The low-temperature stability of the *S,O*-hemiketal generated after the second electron transfer from SmI₂ allows isolation of ketone products upon workup without competing reduction. The application of this methodology has been demonstrated in the synthesis of peptide isosteres (Scheme 87)²⁷² and formal total synthesis of aliskiren, a potent renin inhibitor (Scheme 88).²⁷³ Multiple stereocenters and functional groups are tolerated in these couplings. It was also shown that the intermediate samarium(III) enolates could be intercepted with ketones to

Scheme 86. Proposed Mechanism of SmI_2 -Mediated Coupling of Thioesters with Activated Olefins by Skrydstrup**Scheme 87. Synthesis of Arg-Gly-Leu Hydroxyethylene Isostere by Skrydstrup**

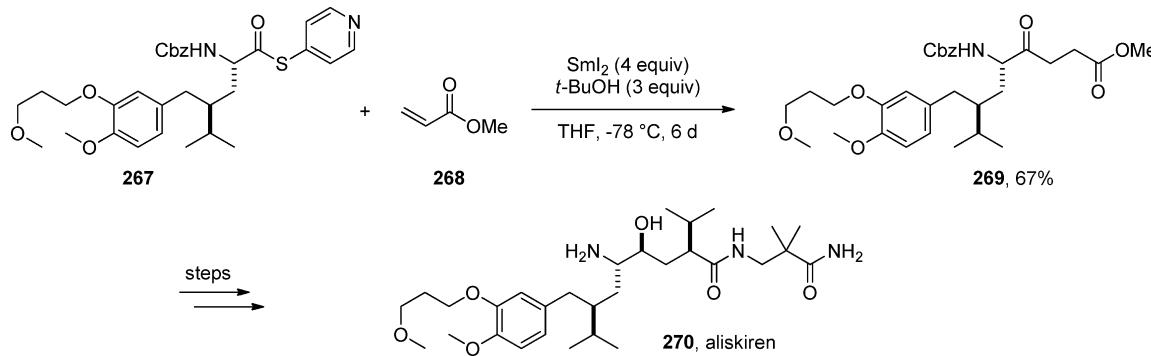
install an additional α -substituent. However, these methods typically require long reaction times to achieve high yields.

In 2005, Skrydstrup reported a significant extension to the scope of the SmI_2 -mediated synthesis of γ -ketoamides and γ -ketoesters by introducing *N*-acyl oxazolidinones as acyl radical equivalents (Scheme 89).²⁷⁴ Using $\text{SmI}_2-\text{H}_2\text{O}$ system, a broad range of substrates, including precursors with secondary, tertiary, and heteroatom substituents in the α -position of *N*-acyl oxazolidinones, were successfully coupled. With respect to the α,β -unsaturated component, the method tolerates substituted α,β -unsaturated esters, amides, and nitriles, giving the 1,4-dicarbonyl products in good to excellent yields. The method employing *N*-acyl oxazolidinones is advantageous over that using thioesters in that the substitution of both reaction components has been found to result in decreased efficiency in the latter protocol.

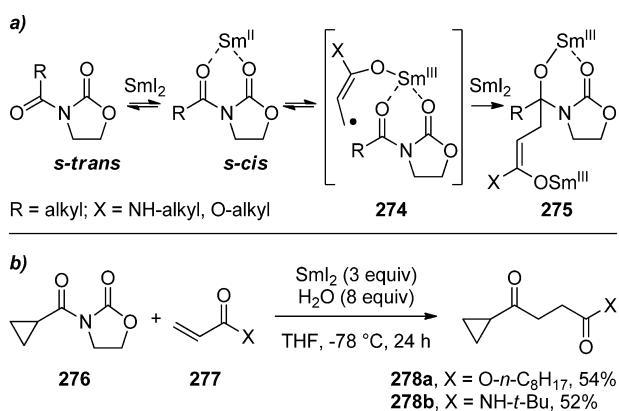
Detailed mechanistic investigations suggested that the SmI_2 -mediated cross-couplings of *N*-acyl oxazolidinones proceed through the reduction of the olefin, followed by chelation-

Scheme 89. Synthesis of γ -Dicarbonyls Using *N*-Acyl Oxazolidinones as Acyl Radical Equivalents by Skrydstrup

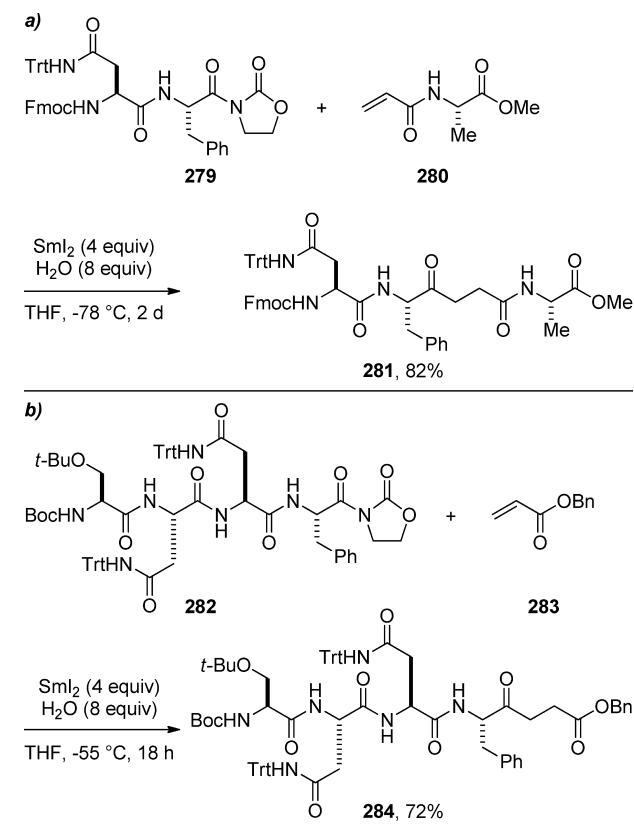
controlled addition of the radical anion to the *N*-acyl carbonyl group (Scheme 90).^{275,276} After the second electron transfer, the hemiaminal product is stable at low temperatures and gives the 1,4-dicarbonyl products upon workup. The hypothesis was supported by kinetic studies and cyclopropyl clock experiments, which suggested that *N*-acyl oxazolidinones are not reduced under the reaction conditions.²⁷⁵ The rate-determining step in these reactions was proposed to involve rotation from the *s-trans* to *s-cis* conformation of the *N*-acyl oxazolidinone.²⁷⁶ Skrydstrup has highlighted this methodology in the synthesis of complex peptides (Scheme 91)^{277,278} and coupling of trisubstituted olefins (Scheme 92).²⁷⁹ Typically, these reactions proceed in excellent yield with complete stereointegrity, affording 1,4-dicarbonyl peptide mimics. Examples range from dipeptides to

Scheme 88. Formal Synthesis of Aliskiren Using SmI_2 -Mediated Coupling of Thioesters with Activated Olefins by Skrydstrup

Scheme 90. (a) Proposed Mechanism of Cross-Coupling of N-Acyl Oxazolidinones by Skrydstrup; (b) Control Experiments with Radical Clocks



Scheme 91. Cross-Coupling of Complex N-Peptidyl Oxazolidinones with Activated Olefins by Skrydstrup: (a) Acrylamides; (b) Acrylates

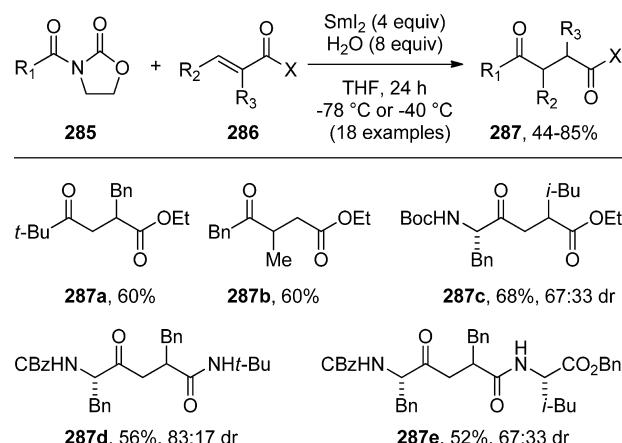


tetrapeptides with no decrease in yield. Skrydstrup has also shown that chiral Evans oxazolidinones provide enantiomerically pure γ -ketoamides in good yields with no racemization observed at the α -center.²⁸⁰

The advances in the coupling of acyl radical equivalents with activated olefins for the mild and selective synthesis of 1,4-dicarbonyls using SmI₂ are a major development in this field in the past decade. A personal account describing the discovery of thioester and *N*-acyl oxazolidinone methodologies has been published.⁴¹

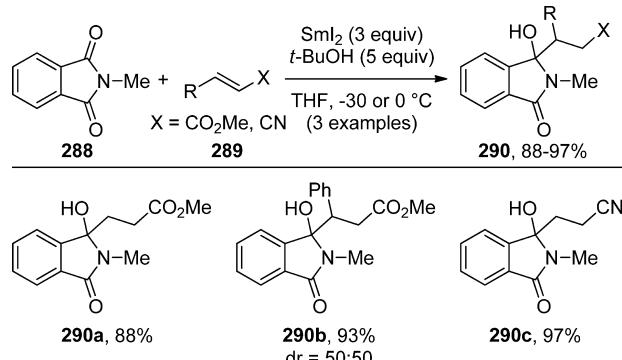
3.1.2.3. Miscellaneous Examples. In 2007, Chiara reported the SmI₂-mediated reductive cross-coupling between phthalimides and

Scheme 92. Cross-Coupling of *N*-Acyl Oxazolidinones with Trisubstituted Olefins by Skrydstrup



mides and activated olefins in high yields (Scheme 93). On the basis of DFT calculations, it was proposed that the reaction

Scheme 93. Cross-Coupling between Phthalimides and Olefins by Chiara



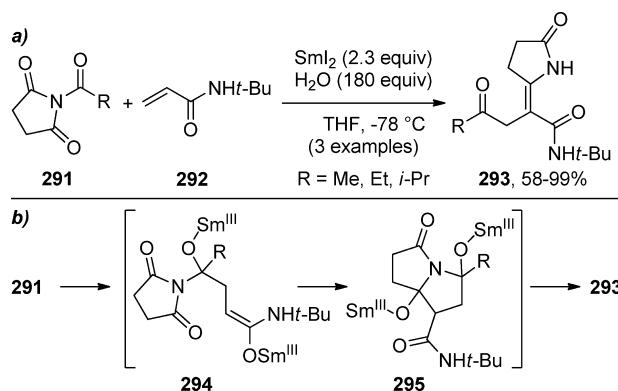
involves a single-electron reduction of the phthalimide, followed by coupling of the resultant ketyl-type radical anion with olefins.²⁸¹ A large excess of olefin is required, and reactions must be carried out at low temperatures. The 1,2-disubstituted olefin underwent cross-coupling with no diastereoselectivity. The method has also been used for intramolecular dimerizations and cross-couplings with activated olefins, nitrones, and oxime ethers, to give α -hydroxy lactams in high yields.

In 2009, Skrydstrup reported the reductive cross-couplings of *N*-acyl succinimides with acrylamides to give (*Z*)- γ -ketoenamides in good yields and high (*Z*)-selectivity (Scheme 94).²⁸² The mechanism involves cross-coupling between the *N*-acyl group and α,β -unsaturated olefin, followed by intramolecular aldol reaction of the intermediate enolate onto the succinimide carbonyl group (Scheme 94b). These reactions proceed in high yields and *Z/E* selectivity; however, they are limited in scope.

3.1.3. Cross-Coupling of Ketyl Radicals with Alkynes.

While SmI₂-mediated ketyl–olefin coupling is one of the most widely studied radical reactions promoted by SmI₂, the use of ketyl–alkyne coupling is considerably less precedented, despite the fact that the rate of radical cyclization onto alkynes is comparable to that onto the corresponding alkenes. The first SmI₂-mediated intramolecular ketyl–alkyne coupling was reported by Molander in 1989.²⁸³ The first intermolecular SmI₂-promoted ketyl–alkyne coupling was reported by Inanaga

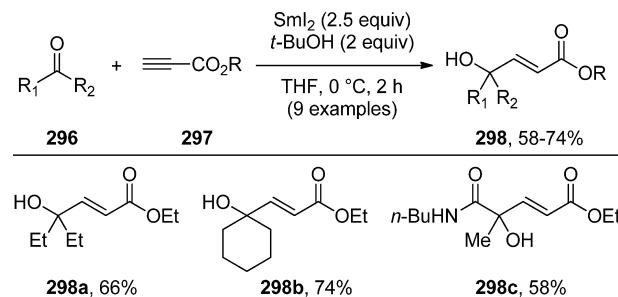
Scheme 94. (a) Cross-Coupling of *N*-Acyl Succinimides and Olefins by Skrydstrup; (b) Proposed Mechanism



in 1991.²⁸⁴ Examples of this type of coupling are scarce; however, this methodology has found utility in the preparation of synthetic intermediates and target synthesis.

In 2001, Kim reported the intermolecular coupling of ketones with propiolates using SmI_2 –*t*-BuOH system at 0 °C for the synthesis of 4-hydroxy-(*E*)-alkenoates with high selectivity in moderate to good yields (Scheme 95).²⁸⁵ α -Ketoamides are also

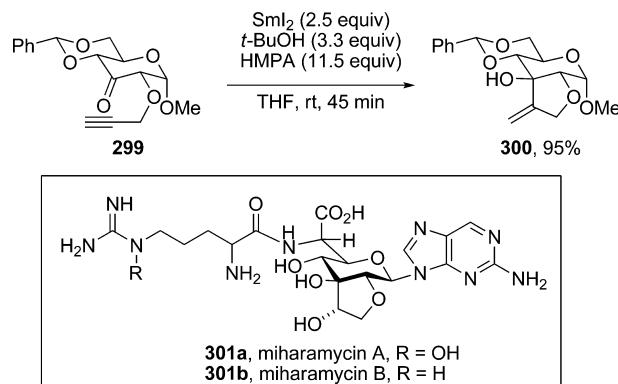
Scheme 95. Synthesis of 4-Hydroxy-(*E*)-2-alkenoic Esters via Intermolecular Ketyl/Alkyne Cross-Coupling by Kim



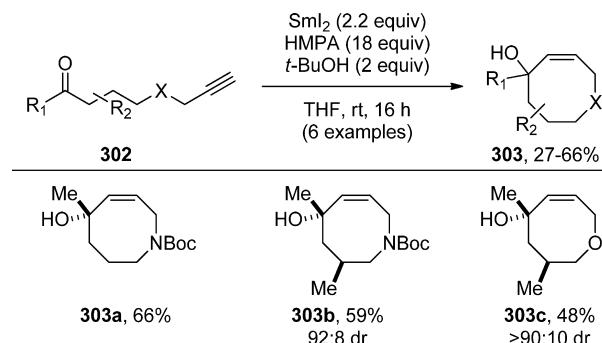
viable substrates for this reaction. Recently, Tori investigated alternative conditions for the coupling of propiolates with cyclic ketones, finding that with the SmI_2 –THF system complementary products resulting from addition at the α - or β -position of the propiolate are formed.^{286a} Reissig reported 8-*endo*-dig and 9-*endo*-dig cyclizations of alkynes.^{244,286b} In 2008, Rauter, Sinaÿ, and Blériot reported the SmI_2 -mediated 5-*exo*-dig cyclization of a propargyl ether in the first synthesis of the core ring system of miharamycin antibiotics (Scheme 96).²⁸⁷ The use of SmI_2 –HMPA–*t*-BuOH afforded the desired product in excellent yield. In 2004, Reissig reported 8-*endo*-dig ketyl/alkyne cyclizations mediated by SmI_2 –HMPA–*t*-BuOH for the synthesis of challenging medium-sized rings (Scheme 97).²⁸⁸ The presence of a fused aromatic ring or a heteroatom substituent on the tether was found to have a beneficial effect on the cyclization. A range of carbocycles and N- and O-containing heterocycles was prepared via this method. Other examples of ketyl-type/alkyne cyclizations have also been reported (see Schemes 52, 58, 59) and demonstrate the potential of this mode of coupling in target-oriented synthesis.

3.1.4. Cross-Coupling of Ketyl Radicals with Allenes. The first SmI_2 -mediated cross-coupling of ketyl radicals with allenes was reported by Gillmann in 1993 utilizing ketyl radicals

Scheme 96. 5-*exo*-Dig Cyclization in the Synthesis of Miharamycin Antibiotics by Rauter, Sinaÿ, and Blériot



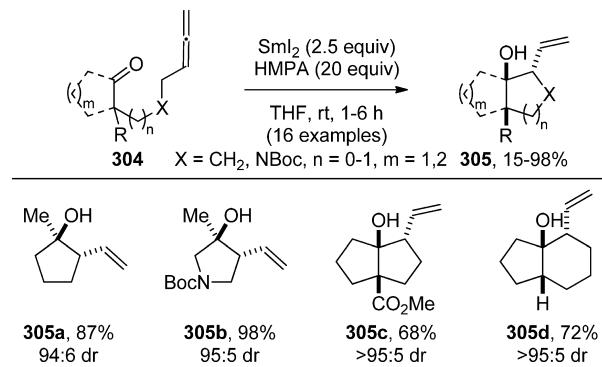
Scheme 97. 8-*endo*-Dig Cyclization in the Synthesis of Heterocyclic Rings by Reissig



generated from aldehydes.²⁸⁹ Since that time, very few examples of this reaction have appeared in the literature.

In 2005, Molander reported the first SmI_2 -promoted intramolecular cross-coupling of ketones with allenes (Scheme 98).²⁹⁰ The reaction furnishes heterocyclic and carbocyclic

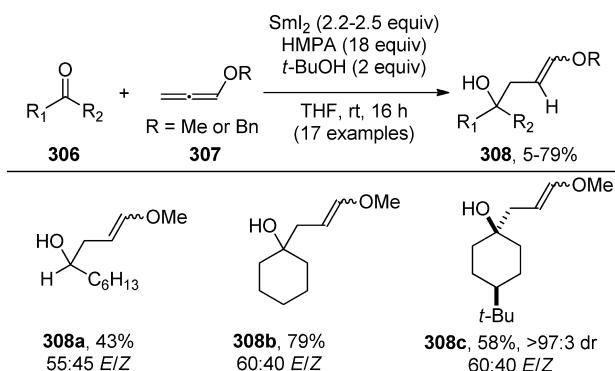
Scheme 98. Intramolecular 5-*exo*-Trig and 6-*exo*-Trig Ketyl/Allene Cross-Couplings by Molander



five- and six-membered rings using cyclic and acyclic ketone precursors in high yields and with excellent diastereoselectivity. The cyclization is fully chemoselective in that addition takes place to the proximal carbon of the allene tether. The formation of five-membered rings proceeds in higher yields than six-membered; shorter tethers afforded complex mixtures of products. While HMPA gave the optimal results, DMPU can also be used as an alternative additive; however, extended reaction times are required.

In 2003, Reissig reported the first intermolecular SmI_2 -mediated ketyl–allene cross-couplings using methoxyallene as an acrolein equivalent (Scheme 99).²⁹¹ Subsequently, this method

Scheme 99. Synthesis of 4-Hydroxy-1-enol Ethers via Intermolecular Allene/Ketyl Cross-Couplings by Reissig



was extended to benzylxoyallene. The products are analogous to the γ -hydroxy aldehydes that would be obtained in the coupling of ketyl radicals with α,β -unsaturated aldehydes.²⁹² The reaction tolerates cyclic and acyclic ketones and aldehydes, giving the products in moderate to good yields. The couplings with 1,3-diphenylallene were also reported, and proceed via the exclusive attack of the ketyl radical at the central carbon of the allene, presumably due to thermodynamic stabilization of the intermediate allyl radical.

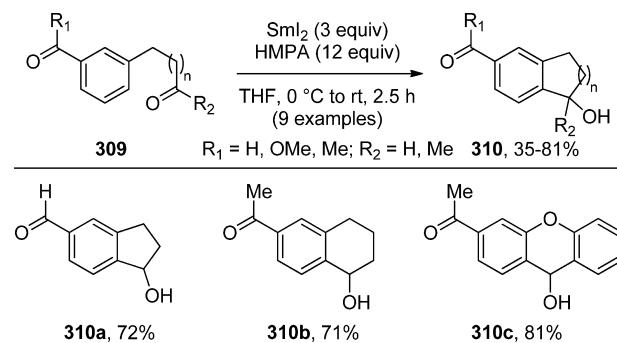
Recently, cross-couplings of allenes with ketyl-type radicals generated by the single-electron reduction of the lactone carbonyl group with $\text{SmI}_2-\text{H}_2\text{O}$ have been reported.²³² These reactions are summarized in the section on cross-couplings of six-membered lactones (see Schemes 53 and 54). In addition, Tori reported one example of the SmI_2 -THF-mediated cross-coupling of the activated ethyl buta-2,3-dienoate with cyclohexanone in high yield.²⁸⁶

3.1.5. Cross-Coupling of Ketyl Radicals with Arenes. In the past decade, arenes have emerged as a particularly useful class of radical acceptors for the SmI_2 -mediated cross-couplings with carbonyl compounds. The first SmI_2 -promoted intramolecular cross-coupling of ketyl-radicals with activated arene-tricarbonyl chromium complexes was reported by Schmalz in 1995.^{293,294} The first examples of the intramolecular cross-coupling of ketyl radicals with unactivated arenes were reported by Reissig in 1999.²⁹⁵ Since these seminal discoveries, there have been many reports of stereoselective intra- and intermolecular coupling of ketyl-radicals with both activated and unactivated aromatic systems. At present, due to the considerable potential to achieve dearomatization of feedstock aromatics under mild conditions, SmI_2 -mediated ketyl–arene coupling is an arena of rapid growth with many applications reported for the synthesis of highly functionalized carbocycles and the preparation of fused and spirocyclic scaffolds. Examples in this section have been arranged according to the type of aromatic ring system that undergoes cross-coupling: (i) cross-coupling with benzenes; (ii) cross-coupling/elimination; (iii) cross-coupling with anilines and thiophenols; (iv) cross-coupling with naphthalenes and quinolines; (v) cross-coupling with indoles and pyrroles; and (vi) miscellaneous examples.

3.1.5.1. Cross-Coupling with Benzenes. In 2001, Fang reported the SmI_2 -mediated cross-coupling of tethered β - and γ -aryl aldehydes and ketones having an additional carbonyl group

(aldehyde, ester, or ketone) placed at the meta position of the aromatic ring using SmI_2-HMPA (Scheme 100).²⁹⁶ These

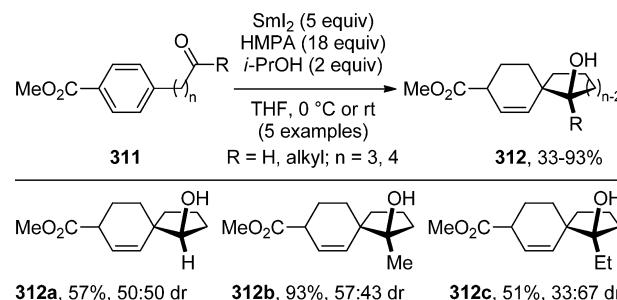
Scheme 100. Intramolecular 5-exo-Trig and 6-exo-Trig Ketyl/Aryl Cross-Couplings by Fang



substrates can be considered as vinyllogous conjugated carbonyls in which the aromatic ring is activated toward the addition by coordination of the Lewis acidic $\text{Sm}(\text{II})$ to the carbonyl acceptor on the aromatic ring. The proposed mechanism involves nucleophilic addition of the cyclohexadienyl organosamarium intermediate to the carbonyl group, followed by oxidative rearomatization by exposure to air on the workup; however, an alternative radical mechanism cannot be excluded.

In 2002, Tanaka reported the first SmI_2 -mediated dearomatizing spirocyclizations of tethered γ - and δ -aryl ketones having an ester group at the para position of the aromatic ring (Scheme 101).²⁹⁷ The use of $\text{SmI}_2-\text{HMPA}-i\text{-PrOH}$ was crucial to obtain

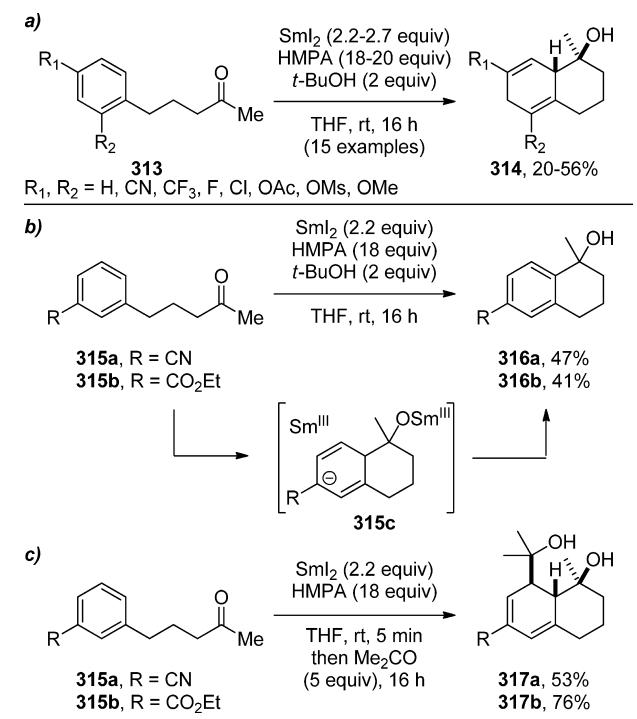
Scheme 101. 5-exo-Trig and 6-exo-Trig Ketyl/Arene Spirocyclization by Tanaka



high yields. The authors proposed a mechanism involving direct ketyl radical cyclization onto the aromatic ring followed by conjugate reduction. Spirocyclization onto an *ortho*-benzoate ester was also demonstrated; in contrast, the corresponding *meta*-substituted precursor afforded fused products.

Following the seminal report,²⁹⁵ Reissig has extensively investigated the SmI_2 -mediated cyclization of γ -aryl ketones (Scheme 102).^{298,299} A range of *ortho* and *para* substituents was tolerated in the cyclization, including electron-donating methoxy groups (Scheme 102a). In line with the studies by Fang, electron-withdrawing groups in the *meta* position (e.g., CN, CO₂Et) afforded the rearomatized bicyclic products (Scheme 102b). The authors proposed that the formation of these rearomatized bicycles was due to the relatively high stability of the cyclohexadienyl anion formed after the second electron transfer. This intermediate would not be protonated by *tert*-butanol and would undergo oxidation on exposure to air during the workup. The unusual stability of the cyclohexadienyl anion was exploited

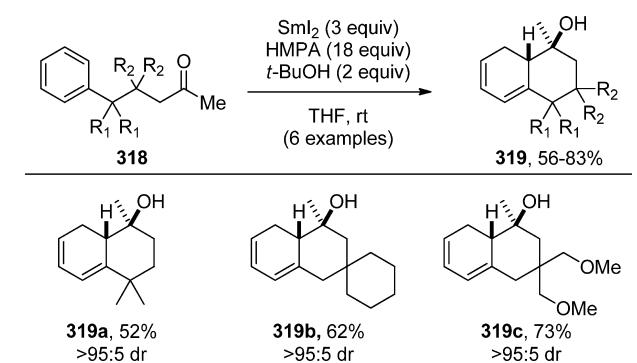
Scheme 102. Intramolecular 6-*exo*-Trig Ketone/Arene Cross-Coupling by Reissig: (a) Ortho-/Para-Substitution; (b) Meta-Substitution; (c) Electrophilic Trapping



by trapping with suitable electrophiles in high stereoselectivity (Scheme 102c).²⁹⁹

In 2011, Reissig reported a significant effect of geminal disubstitution on the alkyl chain on the efficiency of the SmI_2 -promoted ketyl/arene cyclizations of γ -aryl ketones (Scheme 103).³⁰⁰ Interestingly the α,α -gem-dimethyl substrate offered

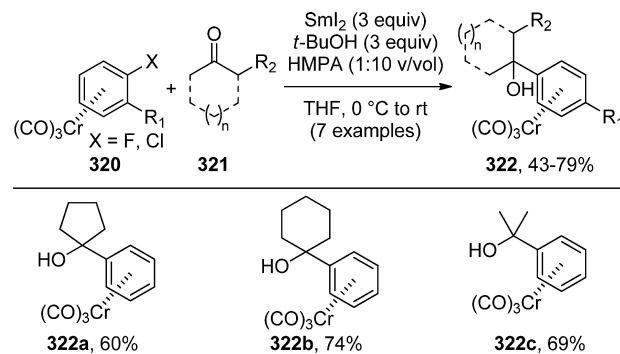
Scheme 103. *gem*-Dimethyl Effect in 6-*exo*-Trig Ketyl/Arene Cross-Couplings by Reissig



lower yields, presumably due to the increased steric hindrance close to the reacting Sm(III) -ketyl. The best results were obtained with the β,β -*gem*-dimethoxymethylene substituent. This approach resulted in significant improvements in yields of the dearomatized products.

3.1.5.2. Cross-Coupling/Elimination. In 2002, Schmalz reported both intramolecular and intermolecular cross-coupling of ketyl radicals with halogenated arene chromium tricarbonyl complexes (Scheme 104).³⁰¹ Addition occurs predominantly meta to the halogen; rearomatization is achieved by elimination of HX . Fluoro- and chloro-substituted arene tricarbonylchromium complexes give good yields of the cross-coupled products;

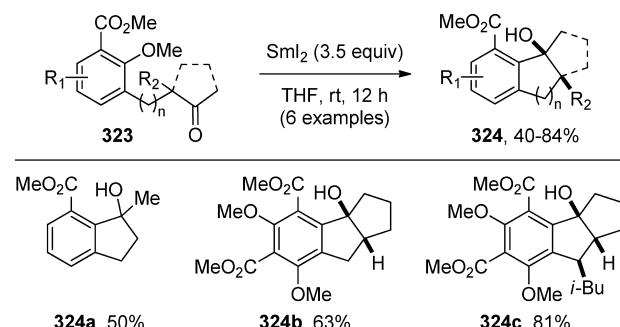
Scheme 104. Cross-Couplings of Ketones with Halogenated Arene–Chromium Tricarbonyl Complexes by Schmalz



in one case, elimination of the methoxy group was also demonstrated. It should be noted that addition of ketyl radicals to the arene tricarbonyl chromium complexes is considerably faster than that to the noncomplexed arenes and that additions are facially selective.³⁰²

In 2003, Tanaka reported the SmI_2 -mediated intramolecular ketyl/arene cross-coupling with the ipso substitution of aromatic methoxy group (Scheme 105).³⁰³ Substrates cyclize under very

Scheme 105. 5-*exo*-Trig and 6-*exo*-Trig Ketyl/Arene Cross-Couplings by Tanaka

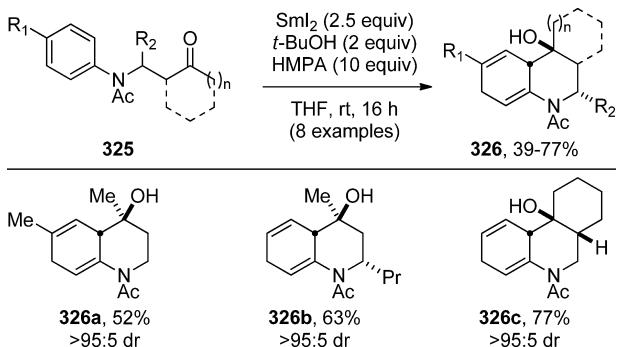


mild conditions using the SmI_2 –THF complex. A switch of the regioselectivity was observed with SmI_2 –HMPA–*i*-PrOH. In these cases, the ketyl radical adds para to the ester group to give bicyclic cyclohexadienes featuring five-, six-, and seven-membered carbocyclic and oxygen-containing rings. The yields are generally high in these reactions; however, in all cases activated substrates are used.

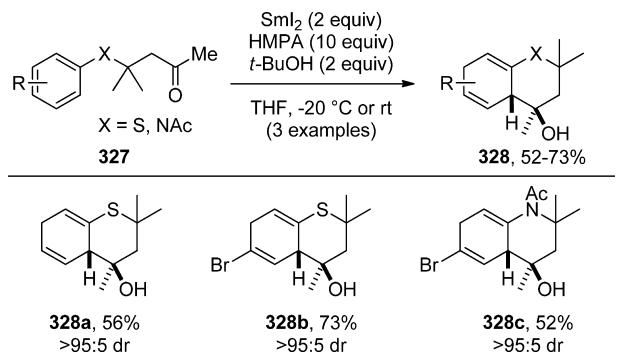
3.1.5.3. Cross-Coupling with Anilines and Thiophenols. The synthesis of hexahydroquinoline derivatives was achieved by Reissig using SmI_2 -mediated cyclizations of aniline derivatives in high yield and diastereoisomeric ratios (Scheme 106).³⁰⁴ When the *t*-BuOH proton source is replaced by phenol in substrates having para-electron-withdrawing groups, spirocyclization is observed, followed by rearomatization via N–C bond cleavage. Reissig demonstrated the synthesis of enantioenriched tricyclic piperidines containing five contiguous stereocenters using cross-coupling of chiral anilines prepared via proline-catalyzed Mannich reactions of a series of cyclic ketones.³⁰⁵ Preliminary results suggested that replacement of the toxic HMPA additive with LiBr and DMI may be possible in these reactions giving similar yields and excellent diastereoselectivity.

Recently, Reissig reported the beneficial effect of geminal disubstitution to promote cyclization of γ -aryl ketones bearing aniline or thiophenol tethers (Scheme 107).³⁰⁶ Remarkably,

Scheme 106. 6-*exo*-Trig Ketone/Aniline Cross-Coupling by Reissig



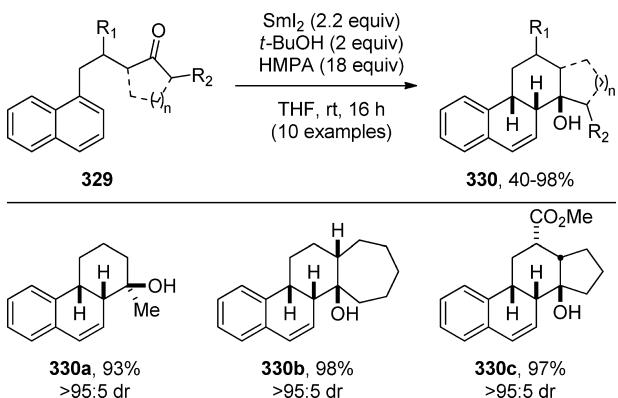
Scheme 107. *gem*-Dimethyl Effect in 6-*exo*-Trig Ketyl/Arene Cross-Couplings with Heteroatom-Containing Tethers by Reissig



cyclizations have been shown to proceed with retention of the *para*-bromo substituent to give products in good yields. Further functionalization via Sonogashira, Heck, and Suzuki reactions afforded a range of dihydrothiochroman derivatives.

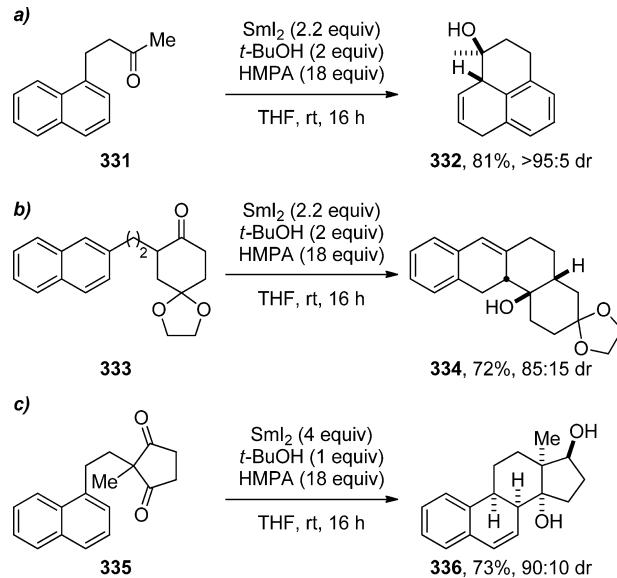
3.1.5.4. Cross-Coupling with Naphthalenes and Quinolines. In 2004, Reissig extended the SmI_2 -mediated intramolecular coupling of ketones and arenes to naphthalene derivatives (Scheme 108).^{307–310} Tetracyclic steroid-like products are accessed from cyclic ketone substrates with excellent diastereoselectivity. Efficient cyclization is observed with five-, six-, and seven-membered ring precursors, while cyclobutane and cyclooctane derivatives cyclize in reduced yield. These reactions have been shown to proceed in slightly higher yield using TPPA

Scheme 108. Intramolecular Ketone/Naphthalene Cross-Coupling by Reissig



(tritypyrrolidinophosphoric acid triamide) as the preferred additive to HMPA.¹⁰⁸ The ketyl/naphthalene cyclization of other substrates was also investigated (Scheme 109). Cross-

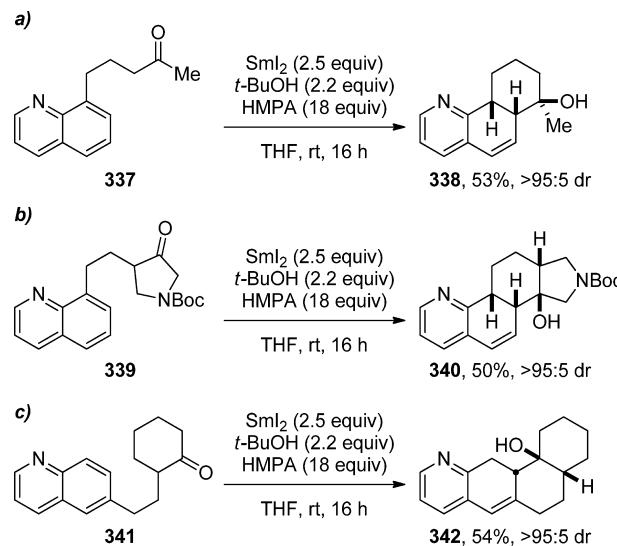
Scheme 109. Intramolecular Ketone/Naphthalene Cross-Coupling by Reissig: (a) Coupling at the 8-Position; (b) 2-Naphthyl Tether; (c) Desymmetrization



coupling of a ketone bearing a 2-carbon tether led to the formation of a fused tricycle in high yield and diastereoselectivity (Scheme 109a).³⁰⁸ Ketones bearing β -naphthyl tethers are also viable substrates for the reaction (Scheme 109b).³⁰⁸ Tethered 1,3-diketones undergo desymmetrization using this approach (Scheme 109c).^{309,310}

In 2008, Reissig reported the SmI_2 -mediated ketyl/arene cyclizations onto quinolines (Scheme 110).³¹¹ γ -Quinolyl ketones substituted at the 8- and 6-positions of the aromatic ring undergo SmI_2 -mediated cyclization in moderate yields and excellent diastereoselectivity, while the β -quinolyl and δ -quinolyl

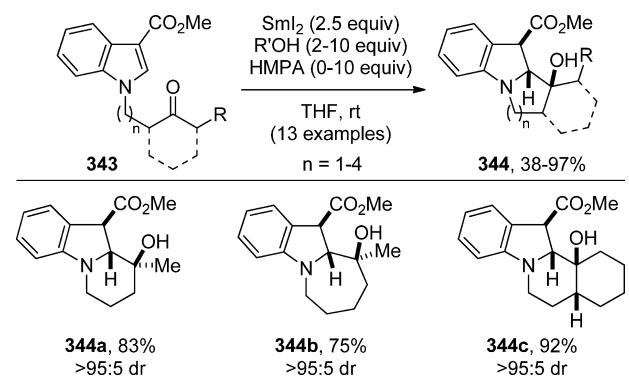
Scheme 110. Intramolecular Ketone/Quinoline Cross-Coupling by Reissig: (a) 8-Quinolinyl Tether; (b) Coupling of Cyclic Ketones; (c) 6-Quinolinyl Tether



ketones cross-couple less efficiently. The reaction provides a convenient route to azasteroids from simple starting materials. In contrast, a γ -keto-2-carbazole did not undergo SmI_2 -mediated ketyl/arene cross-coupling, which was ascribed to the high electron density of the aromatic ring.

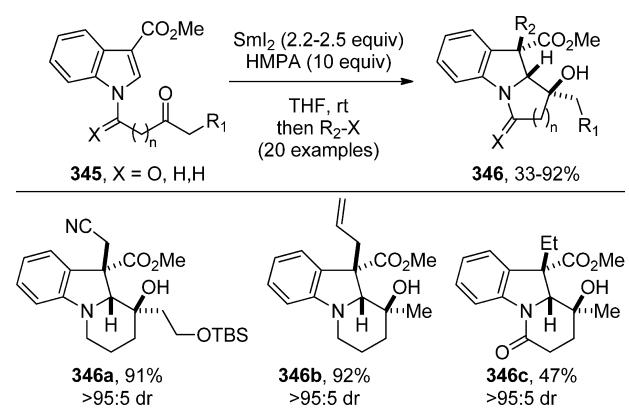
3.1.5.5. Cross-Coupling with Indoles and Pyrroles. As a significant expansion of the scope of the SmI_2 -mediated intramolecular coupling of heteroarenes with ketones, in 2003, Reissig reported the ketyl/arene cyclizations of indoles tethered at the nitrogen to give five-, six-, seven-, and eight-membered tricyclic benzannulated pyrrolidines in high yields (Scheme 111).^{312–316} This reaction proceeds smoothly with high

Scheme 111. Intramolecular Ketone/Indole Cross-Coupling by Reissig



diastereoselectivity in cases where an electron-withdrawing group (e.g., ester, nitrile) is present at the 3-position of the aromatic ring. In the absence of a proton source, the intermediate samarium(III) enolates can be trapped with a range of electrophiles (e.g., alkyl, benzyl, or allyl halides and intramolecular examples) to furnish highly functionalized fused indolines (Scheme 112).^{312,313} Easily accessible *N*-acyl tethers

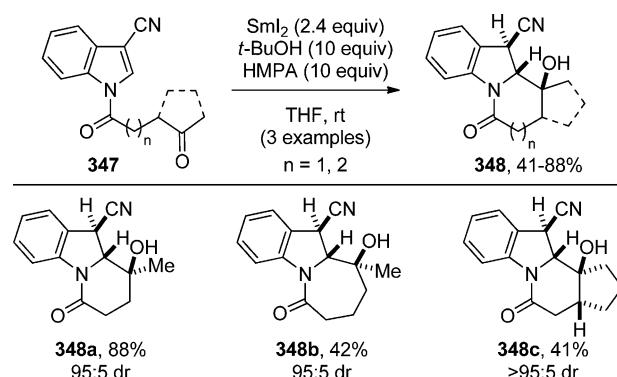
Scheme 112. Intramolecular Ketone/Indole Cross-Coupling/Alkylation Cascade by Reissig



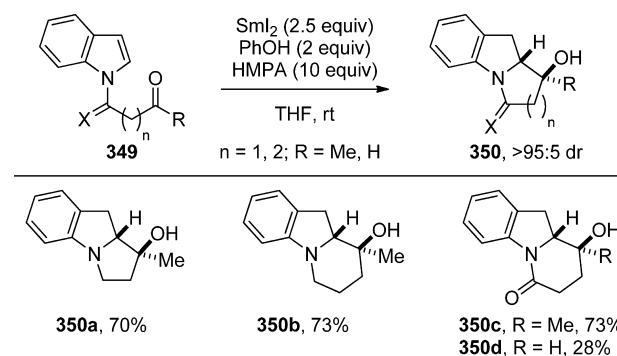
can also be employed (Scheme 113).³¹⁴ Unactivated indoles have been shown to cyclize (Scheme 114);³¹⁵ however, these examples are currently limited to the formation of five- and six-membered rings. In these cases, phenol is the preferred proton source. Ketones attached to the indole ring via *N*-acyl and *N*-alkyl tethers are suitable substrates; however, aldehydes give the cross-coupled products in much lower yields.

Intermolecular SmI_2 -mediated ketyl/indole cross-couplings of ketones and aldehydes have been reported by Reissig in 2006

Scheme 113. Intramolecular Cross-Coupling of Ketones and Activated *N*-Acyl Indoles by Reissig

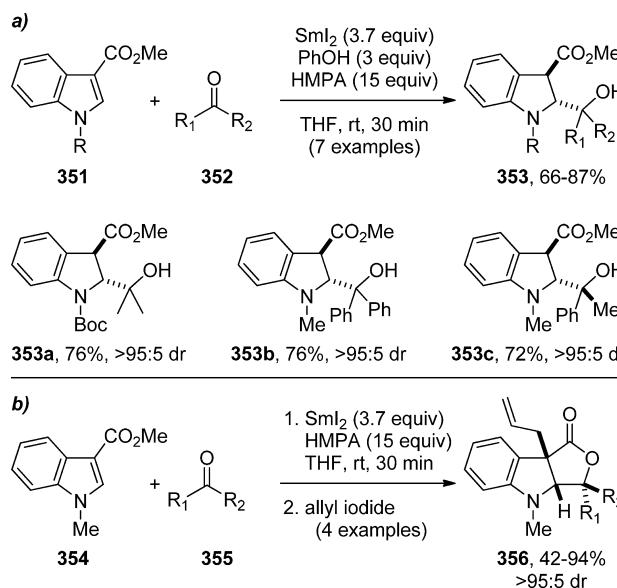


Scheme 114. Intramolecular Cross-Coupling of Ketones and Unactivated Indoles by Reissig



(Scheme 115).³¹⁷ The methodology is currently limited to indoles bearing an electron-withdrawing group at the 3-position; however, the products are formed in high yields and excellent diastereoselectivity. In the absence of a proton source, the intermediate samarium(III) enolates can be trapped with allyl iodide (Scheme 115b). Interestingly, the protonation proceeds under thermodynamic control (PhOH as the proton source),

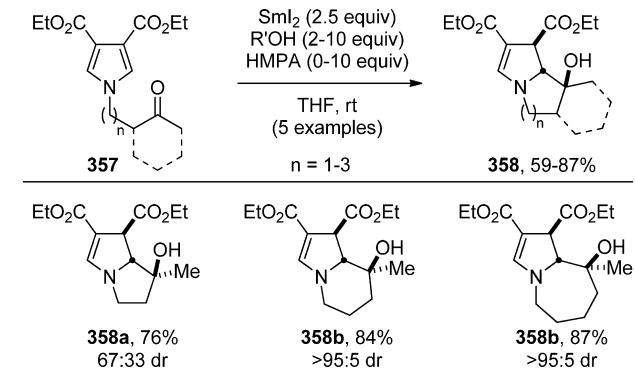
Scheme 115. Intermolecular Ketyl/Indole Cross-Coupling by Reissig



whereas trapping with allyl iodide gives the kinetic product as a single diastereoisomer.

Intramolecular cross-coupling of ketones with pyrroles was reported by Reissig in 2003 (Scheme 116).^{312,315} An electron-

Scheme 116. Intramolecular Ketyl/Pyrrole Cross-Coupling by Reissig

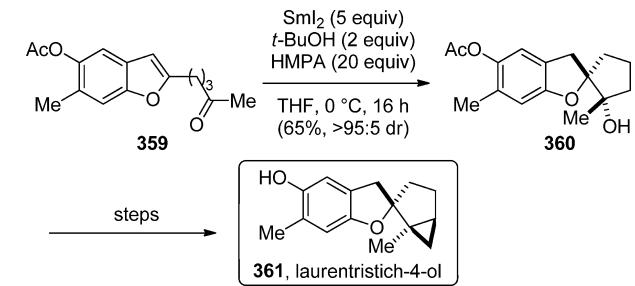


withdrawing group is required at the 3-position of the pyrrole. Five-, six-, and seven-membered rings can be formed in high yields and diastereoselectivity. In some cases, the $\text{SmI}_2\text{-PhOH-HMPA}$ system can be replaced with $\text{SmI}_2\text{-}t\text{-BuOH}$ with no decrease in efficiency.

The SmI_2 -mediated ketyl/indole cross-coupling was used as a key step in the formal total synthesis of strychnine by Reissig (see section 5.1).³¹⁸ Personal accounts of the cross-coupling of ketyl radicals with arenes have been published.^{34–36}

3.1.5.6. Miscellaneous Examples. In 2008, Wang and Li reported the SmI_2 -mediated ketyl/benzofuran cross-coupling as a key step in the total synthesis of laurentristich-4-ol (Scheme 117).³¹⁹ The cyclization was mediated by $\text{SmI}_2\text{-HMPA-t}$ -

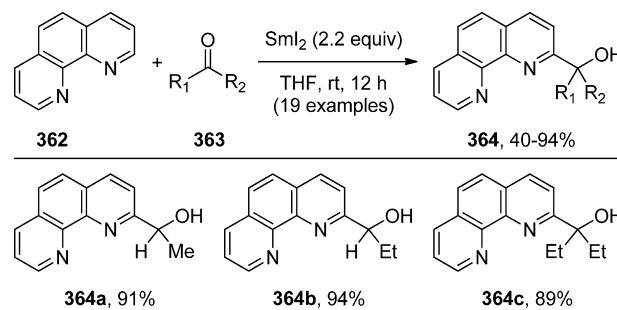
Scheme 117. Intramolecular Ketone/Benzofuran Cross-Coupling in the Synthesis of Laurentristich-4-ol by Wang and Li



BuOH complex at 0 °C, giving the spirocyclic ether in high yield as a single diastereoisomer. The 6-*exo* spirocyclization was also achieved in high yield; however, the product was formed as a mixture of diastereoisomers. Intermolecular cross-couplings proceeded in low yield.

In 2004, Helquist reported the intermolecular coupling of ketones and aldehydes with 1,10-phenanthrolines in high yields (Scheme 118).³²⁰ After deoxygenation, a second ketone or aldehyde can be coupled to the 1,10-phenanthroline to give unsymmetrical 2,9-phenanthroline derivatives. A wide range of carbonyl substrates was successfully coupled in high yields. The use of chiral ketones, such as (-)-thujone and DL-menthone, gave products as single diastereoisomers. The SmI₂-mediated

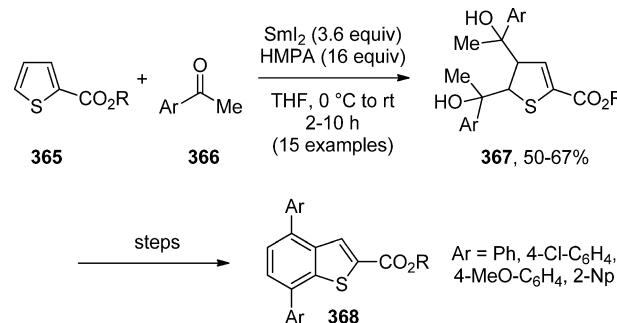
Scheme 118. Intermolecular Ketyl/1,10-Phenanthroline Cross-Couplings by Helquist



cross-coupling of 1,10-phenanthroline with (*R*)-1,2-epoxybutane was also reported by Helquist.³²¹

In 2002, Fang reported the intermolecular double cross-coupling of thiophene-2-carboxylate with aryl ketones mediated by $\text{SmI}_2\text{-HMPA}$ (Scheme 119).³²² The mechanism was

Scheme 119. Intermolecular Ketyl/Thiophene Cross-Couplings by Fang



proposed to involve the following steps: (i) ketyl radical/arene cross-coupling at the C-5 position; (ii) reduction to the samarium(III) enolate; and (iii) vinylgous aldol reaction. The products have been converted to polysubstituted benzothiophenes with photochromic applications in three steps.

3.2. Pinacol-Type Couplings

The first SmI_2 -mediated pinacol coupling of ketones and aldehydes was reported by Kagan in 1983.³²³ This early procedure resulted in a statistical mixture of diastereoisomers; however, high yields for coupling of aromatic and aliphatic ketones and aldehydes forecast the potential of SmI_2 for the synthesis of vicinal diols. Since then, both inter- and intra-molecular SmI_2 -mediated pinacol-type couplings have been well reported in the literature. Currently, this method serves as a valuable alternative to the synthesis of 1,2-diols by dihydroxylation of alkenes and has been widely utilized in target-oriented synthesis.

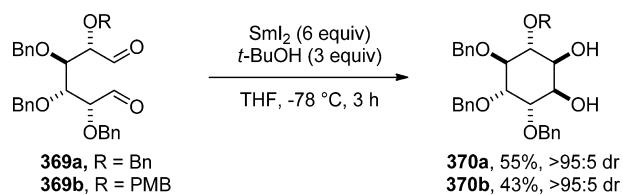
Several exciting developments have been reported in this area in the past decade, including: aldehyde–aldehyde pinacol couplings of chiral biaryls with axial to central chirality transfer and their application in the synthesis of complex natural products, aldehyde–ketone cross-couplings in the synthesis of lycopodium alkaloids with complementary chelation-controlled diastereoselectivity, and highly diastereoselective ketone–ketone couplings for the synthesis of hindered vicinal diols. For the purpose of this Review, pinacol-type cross-couplings mediated by SmI_2 have been classified according to the type of carbonyl group that undergoes the coupling: (i) aldehyde–aldehyde

pinacol-type couplings; (ii) aldehyde–ketone pinacol-type couplings; and (iii) ketone–ketone pinacol-type couplings. Further, examples have been ordered according to the ring size formed in the SmI_2 -mediated reaction.

3.2.1. Aldehyde–Aldehyde Cross-Coupling. SmI_2 -mediated aldehyde–aldehyde couplings provide convenient access to either syn or anti 1,2-diols with the diastereoselectivity being substrate and chelation controlled.

In 2006, d'Alarcao reported highly *cis*-diastereoselective intramolecular aldehyde–aldehyde pinacol coupling for the synthesis of galactosaminyl D-chiro inositols using SmI_2 –*t*-BuOH at -78°C (Scheme 120).³²⁴ The structure of products

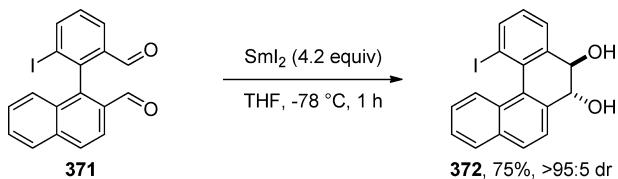
Scheme 120. Aldehyde/Aldehyde Intramolecular Pinacol Coupling in the Total Synthesis of Galactosaminyl D-Chiroinositols by d'Alarcao



was confirmed by an independent synthesis. The *cis*-diastereoselectivity is explained by a nine-membered chelated transition state.³²⁵ The steric and electronic effect of the neighboring α -alkoxy groups has been proposed to explain increased diastereoselectivity in these cases.^{325,326} Sinaÿ reported a related SmI_2 –*t*-BuOH-mediated aldehyde–ketone cross-coupling in the total synthesis of calditol (not shown).³²⁷

In 2003, Cozzi and Siegel reported the SmI_2 -mediated aldehyde–aldehyde coupling in the presence of an aryl iodide as a part of their program on the synthesis of conformationally restricted polycyclic compounds (Scheme 121).³²⁸ The

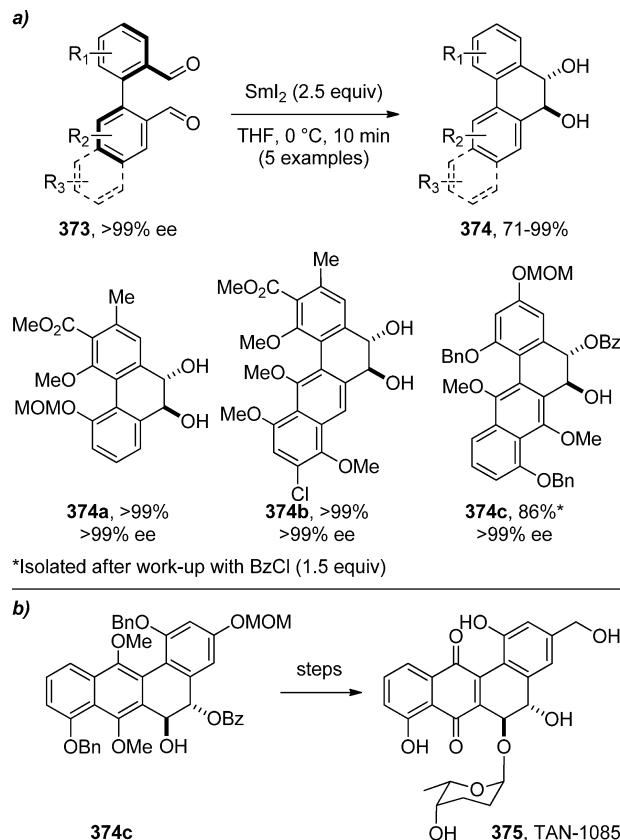
Scheme 121. Aldehyde/Aldehyde Pinacol Coupling in the Presence of an Aryl Iodide by Cozzi and Siegel



attempted McMurry coupling proceeded with concomitant deiodination, and other methods of synthesis of the desired diol failed. In contrast, SmI_2 (-78°C , 1 h, 2 equiv) furnished the product in 75% yield with retention of the iodide, highlighting the mild and selective nature of this reagent. Complete diastereocontrol for the diequatorial diol was observed.

Suzuki reported several remarkable examples of the SmI_2 -mediated pinacol-type cross-couplings of atropisomeric biaryl dialdehydes in the synthesis of Streptomyces antibiotics, observing complete axial to central chirality transfer (Scheme 122).^{329–331} Single atropisomeric dialdehydes undergo cyclization in high yield to give *trans*-diols with no erosion of stereochemistry. The *trans* stereochemistry is explained by the formation of diequatorial alcohols.³³² The direct quenching with benzoyl chloride afforded the selectively protected vicinal diol. The protection is fully selective for the α -alcohol; the formation of the bis-benzoate is not observed. The authors proposed that

Scheme 122. (a) Axial to Central Chirality Transfer via Aldehyde/Aldehyde Pinacol Coupling by Suzuki; (b) Total Synthesis of TAN-1085



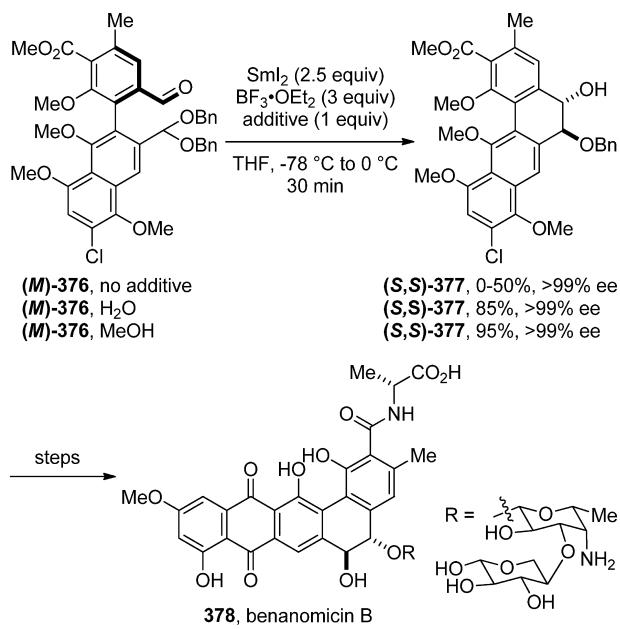
samarium coordination to the adjacent methoxy group prevents formation of the undesired benzoate. This procedure facilitated an efficient synthesis of TAN-1085 (Scheme 122b). Suzuki also reported the SmI_2 -mediated semipinacol cyclization of dibenzyl acetals with aldehydes in the synthesis of benanomicin B (Scheme 123).^{333,334} After extensive optimization, it was determined that SmI_2 – BF_3 • Et_2O promotes the desired cyclization in high yield. This methodology offers a complementary access to differentially protected vicinal diols and proceeds with full chirality transfer.

Paquette reported the SmI_2 -mediated aldehyde–aldehyde pinacol cyclization for the synthesis of the eight-membered ring in studies toward lancifolidilactone G (Scheme 124).³³⁵ The product was formed as an inseparable mixture of diastereoisomers and was isolated after oxidation. The use of high dilution technique (0.003 M) eliminated the formation of intermolecular pinacol-type products. Protection of the tertiary alcohol was necessary to prevent reduction of the dialdehyde to diol.

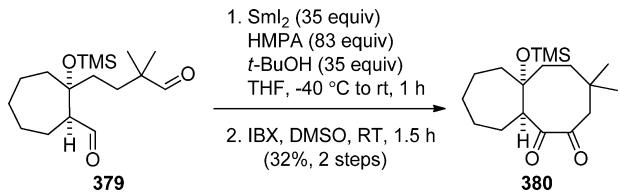
The first SmI_2 -mediated intermolecular catalytic pinacol couplings were reported by Endo in 1996.³³⁶ In 2005, Kanomata reported the substoichiometric SmI_2 -mediated intramolecular pinacol couplings to form medium and large rings in good yields (Scheme 125).³³⁷ The reactions proceed in most cases with 30 mol % of SmI_2 , and magnesium is used as a stoichiometric reductant, in the presence of TMSCl . In contrast to the Endo protocol, HMPA is required to achieve good yields. The products were applied for the synthesis of planar-chiral cyclophanes.

3.2.2. Aldehyde–Ketone Cross-Coupling. As with the SmI_2 -mediated aldehyde–aldehyde pinacol coupling, aldehyde–

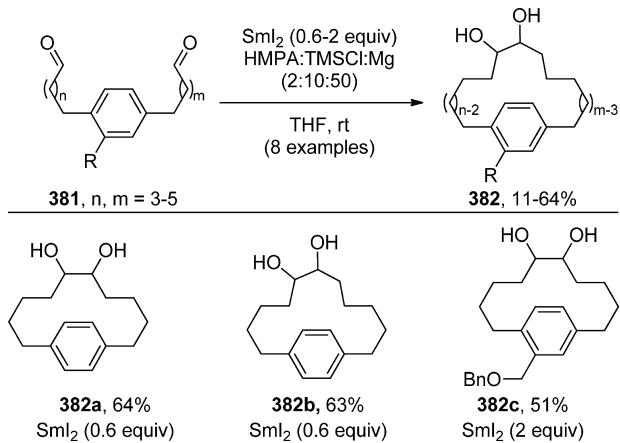
Scheme 123. Axial to Central Chirality Transfer via Semi-pinacol Cross-Coupling in the Synthesis of Benanomicin B by Suzuki



Scheme 124. Aldehyde/Aldehyde Coupling toward Lancifolidactone G by Paquette



Scheme 125. Catalytic Aldehyde/Aldehyde Pinacol Coupling by Kanomata

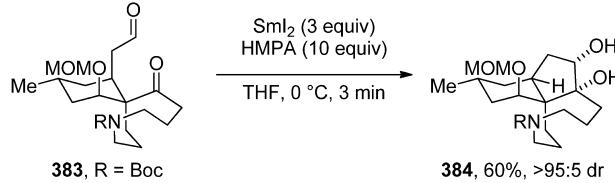


ketone couplings have been well-established in the literature. In the past decade, this method has found numerous applications in the synthesis of natural products.

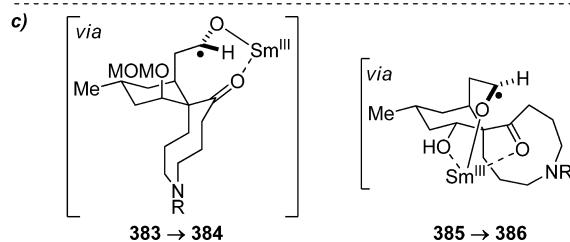
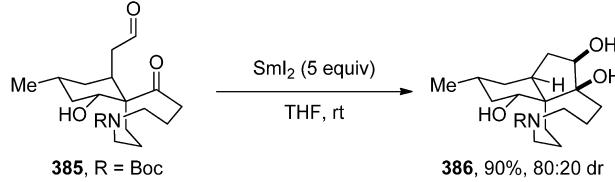
Recently, Tu (Scheme 126a)^{338,339} and Lei (Scheme 126b)^{340,341} independently reported SmI₂-mediated aldehyde–ketone pinacol cyclizations in the synthesis of lycopodium alkaloids to form the same five-membered ring with the opposite relative *cis*-diastereoselectivity of the resulting 1,2-diol. In the total synthesis of alopecuridine, Tu employed a chelation-

Scheme 126. Aldehyde/Ketone Pinacol Coupling in the Total Synthesis of Lycopodium Alkaloids: (a) Tu; (b) Lei; (c) Proposed Mechanism

a) Tu and coworkers



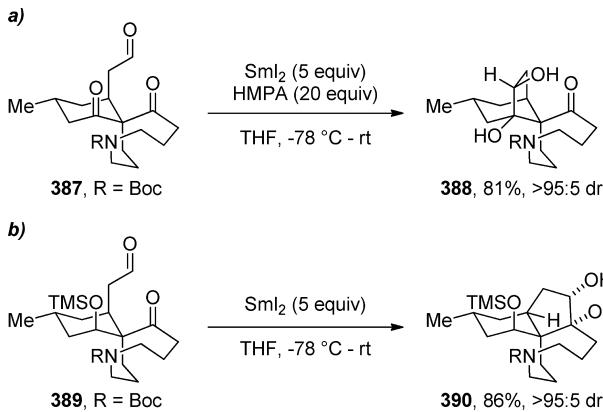
b) Lei and coworkers



controlled pinacol cyclization to afford α -diol in moderate yield and with complete diastereorecontrol (Scheme 126a).^{338,339} It was proposed that coordination of the samarium ketyl to the ketone group controls the selectivity of this reaction. The structure of the diol was confirmed by X-ray crystallographic analysis. In contrast, Lei described a hydroxyl-directed pinacol coupling of the identical (except for the C-13 alcohol) starting material leading to an 80:20 diastereoisomeric ratio in favor of the β -diol in high yield (Scheme 126b).³⁴⁰ The authors proposed that in this case the diastereoselectivity is controlled by the hydroxyl group. Interestingly, the minor *trans*-diol can be synthesized in 67% yield with complete diastereoselectivity using SmI₂–HMPA. Coordination of the sterically demanding HMPA ligand to SmI₂ prevents the directing effect of the hydroxyl group, leading to the reversed selectivity. In an extended study, Lei reported the selective pinacol cyclization of the corresponding diketo aldehyde (Scheme 127a).³⁴¹ Although the SmI₂-mediated cyclization proceeded in excellent yield, chemo-, and diastereoselectivity, it gave the undesired outcome in the context of the synthesis of lycopodium alkaloids.³⁴² Lei determined that the five-membered ring required for the synthesis of lycopodium alkaloids can be accessed by ketone–aldehyde pinacol cyclization of a TMS-protected axial C-13 alcohol in line with findings by Tu (Scheme 127b).

In 2002, Snyder reported the use of a SmI₂-mediated aldehyde–ketone pinacol coupling for the formation of a six-membered ring in the synthesis of 24-nortriterpene analogues (Scheme 128).³⁴³ The reaction requires only *t*-BuOH as the additive and proceeds in high yield and *cis*-diastereoselectivity. The authors proposed that the α -diol selectivity results from steric interactions between the chelated samarium ketyl and the angular methyl group. In 2003, Marcos reported SmI₂-promoted aldehyde–ketone couplings for the synthesis of a six-membered ring in high yield and diastereoselectivity in the total synthesis of (+)-totarol and other diterpenes (Scheme 129).^{344,345} The

Scheme 127. (a) Selective Aldehyde/Bis-ketone Pinacol Coupling; (b) Cis-Selective Aldehyde/Ketone Pinacol Coupling by Lei



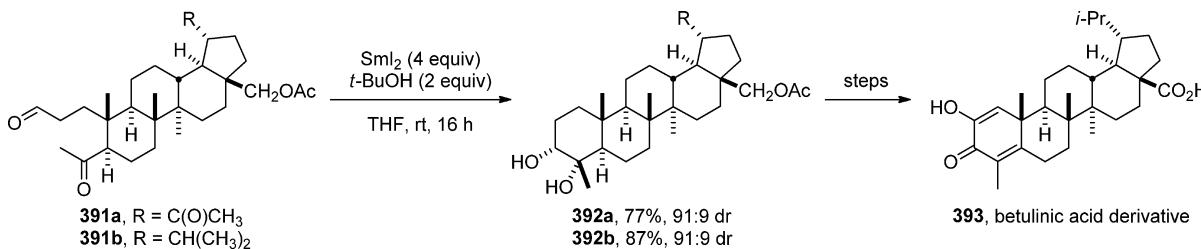
reaction is mediated by the SmI_2 –MeOH system and proceeds with high *cis*-diol selectivity, which is a result of chelation.

Larger rings are also accessible through this type of SmI_2 -mediated pinacol coupling (Schemes 130 and 131).^{346,347} In 2010, Chen and Nicolaou reported the total synthesis of echinopines A and B, using SmI_2 –HMPA to form the key seven-membered ring of these natural products in moderate yield and perfect diastereoisomeric control (Scheme 130).³⁴⁶ The authors proposed that in the absence of other coordinating groups, chelation between the ketyl radicals results in high diastereoselectivity. In 2005, Corey reported the synthesis of a 12-membered ring by SmI_2 -mediated aldehyde–ketone pinacol coupling as a key step in the total synthesis of β -areneosene (Scheme 131).³⁴⁷ Low valent titanium reagents failed to afford the desired product and led to the reduction to the diol. In contrast, SmI_2 –THF (slow addition protocol) provided the macrocycle in excellent yield and diastereoselectivity without the need for HMPA or other additives.

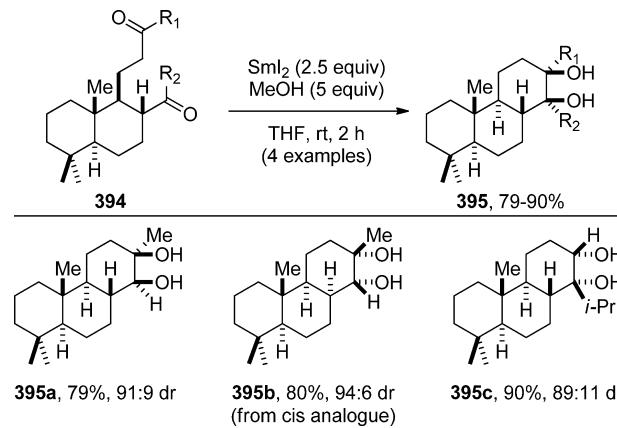
3.2.3. Ketone–Ketone Cross-Coupling. SmI_2 -mediated ketone–ketone pinacol cross-couplings are well documented in the literature; however, these processes are not as common as either the aldehyde–aldehyde or the aldehyde–ketone couplings. These reactions are particularly valuable for the synthesis of highly substituted vicinal diols in five-membered rings.

The mechanism of SmI_2 -promoted ketone–ketone pinacol couplings was investigated by Handa using cyclopropyl radical clocks in 5-*exo*-trig cyclizations (Scheme 132).³⁴⁸ On the basis of the observation that the cyclopropane ring-opening did not occur, the authors proposed that couplings of these ketyl radicals proceed at a faster rate than the cyclopropane ring-opening; however, these results do not rule out an ionic pathway for the cyclization.

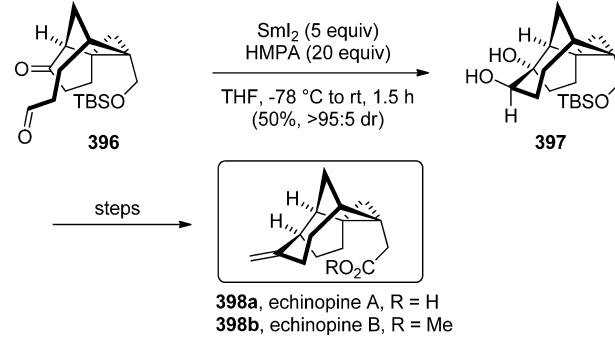
Scheme 128. Aldehyde/Ketone Coupling in the Synthesis of 24-Nortriterpene Analogues by Snyder



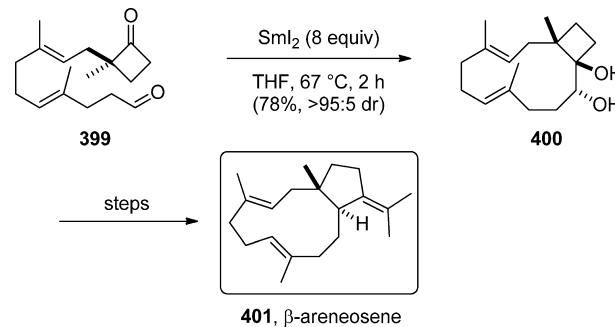
Scheme 129. Aldehyde/Ketone Pinacol Coupling in the Synthesis of Tri- and Tetracyclic Diterpenes by Marcos



Scheme 130. Aldehyde/Ketone Pinacol Coupling in the Total Synthesis of Echinopines A and B by Nicolaou and Chen

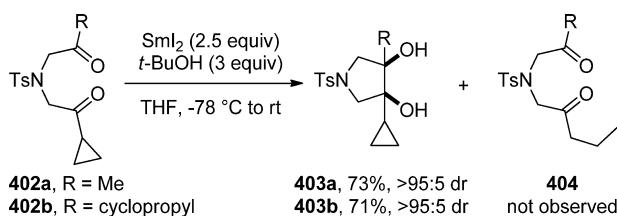


Scheme 131. Aldehyde/Ketone Pinacol Coupling in the Total Synthesis of β -Areneosene by Corey



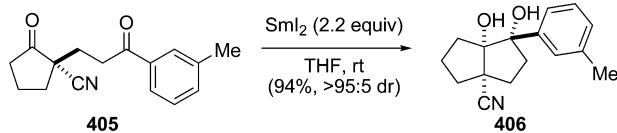
In 2010, Kumagai and Shibasaki reported a highly diastereoselective SmI_2 -mediated pinacol cross-coupling for the synthesis of a chiral [3.3.0] bicycle containing three contiguous

Scheme 132. Ketone/Ketone Pinacol Coupling of Cyclopropyl Ketones by Handa



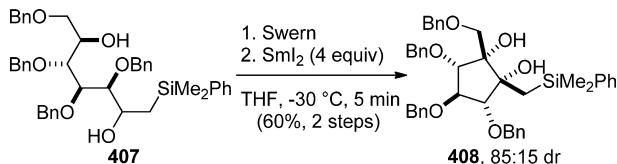
quaternary stereocenters (Scheme 133).³⁴⁹ The precursor was prepared via asymmetric addition of α -cyanoketones to α,β -

Scheme 133. Synthesis of [3.3.0] Bicycles via Ketone/Ketone Pinacol Coupling by Kumagai and Shibasaki



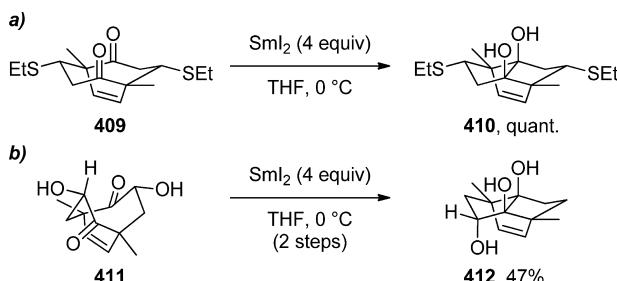
unsaturated ketones. The reductive elimination of the cyano group was not observed under these conditions. In 2006, Chiara reported a one-pot Swern/SmI₂-mediated pinacol cross-coupling for the synthesis of highly functionalized cyclopentandiol (Scheme 134).³⁵⁰ The coupling was remarkably fast with the

Scheme 134. Ketone/Ketone Pinacol Coupling of Unactivated Ketones by Chiara



SmI₂-THF system at $-30\text{ }^{\circ}\text{C}$. The authors proposed that this could be due to facile reduction of the α -silyl carbonyl group as a result of the hyperconjugative stabilization of the α -silyl radical by the proximal C-Si bond. In 2009, Inoue reported a transannular SmI₂-mediated ketone-ketone pinacol coupling of a cyclooctadione in the synthesis of the skeleton of ryanodine (Scheme 135a).³⁵¹ The reaction furnished the desired *cis*-diol bearing vicinal quaternary stereocenters in quantitative yield and was likely facilitated by transannular chelation of the samarium ketyl. Recently, Inoue reported a tandem deoxygenation/

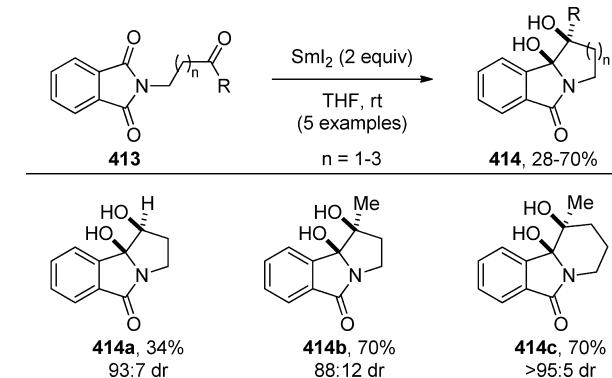
Scheme 135. Synthesis of the Core of Ryanodine by Inoue: (a) Transannular Pinacol Coupling; (b) Tandem Deoxygenation/Pinacol Coupling



pinacol coupling of a similar intermediate in the synthesis of 9-demethyl-10,15-dideoxyryanodol (Scheme 135b).³⁵²

Finally, in a related example, Kise³⁵³ investigated the mechanism of SmI₂-mediated pinacol-type cyclization of *N*-(γ -carbonyl)phthalimides reported earlier by Yoda³⁵⁴ (Scheme 136). It was found that (γ -keto)phthalimides undergo efficient

Scheme 136. Ketone/Phthalimide Coupling by Kise



cyclization to form *cis*-1,2-diols, while the corresponding aldehydes gave much lower yields. This methodology is complementary to the reductive coupling of these substrates under electrochemical conditions, which affords *trans*-1,2-diol products. On the basis of the observation that the reduction of the phthalimide carbonyl group is considerably easier than the ketone, a mechanism involving reduction of the phthalimide followed by cyclization onto the carbonyl group was proposed.

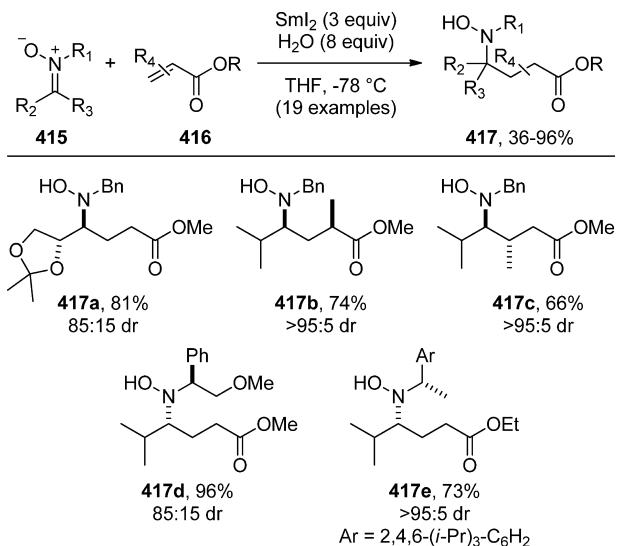
3.3. Cross-Coupling of Imines and Equivalents

In comparison to the SmI₂-mediated cross-coupling of carbonyl groups, the inter- and intramolecular cross-coupling of imines and equivalents (oximes, oxime ethers, hydrazones, nitrones) is much less common because of their lower reactivity. Moreover, few studies have been reported on the mechanisms and the role of additives in these reactions, especially as compared to the relatively well-established cross-couplings of carbonyl derivatives. Nevertheless, in the past decade, the SmI₂-mediated coupling of imines and equivalents has emerged as a valuable synthetic protocol, and several impressive transformations have been published. In this section of the Review, examples have been ordered according to the type of π -acceptor: (i) cross-couplings with C=C bonds; and (ii) cross-couplings with C=O and C=N bonds. Furthermore, these examples have been classified on the basis of the class of imine-type precursor (nitron, imine, oxime ether, etc.).

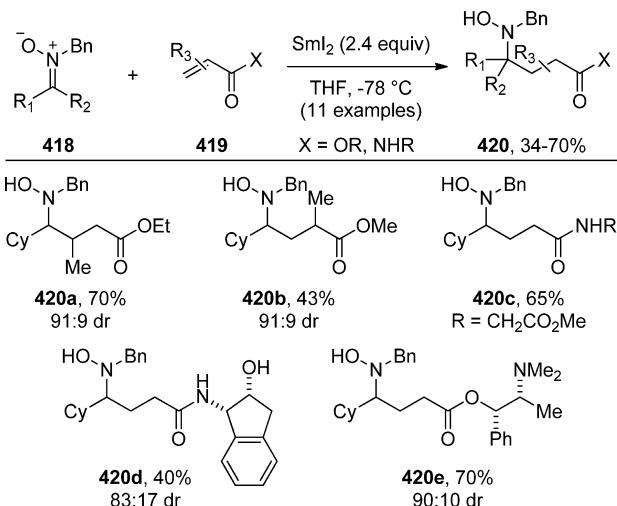
The major advance in this area is the seminal 2002 discovery by Py and Vallée that nitrones serve as excellent radical acceptors for SmI₂-mediated cross-coupling reactions with carbonyl compounds.³⁵⁵ Since then, numerous applications of nitrones and other imine equivalents in reactions with activated olefins, carbonyl compounds, and imine-type acceptors have been reported. In general, these reactions are often characterized by high stereoselectivity. Several auxiliary-based asymmetric approaches have been developed, allowing for the synthesis of biologically important chiral amines via polarity reversal of the C=N bond under mild conditions.³⁵⁶ Finally, this class of cross-couplings has already been adopted in the synthesis of target molecules. For comparison with the section on the couplings of carbonyl derivatives, this part of the Review starts with the examination of cross-couplings involving olefins as π -acceptors.

3.3.1. Cross-Coupling with C=C Bonds. In 2003, the groups of Py and Vallée,^{357,358} and Skrydstrup³⁵⁹ independently reported the first SmI₂-mediated intermolecular cross-coupling of nitrones with activated olefins (Schemes 137 and 138). Py and

Scheme 137. Intermolecular Cross-Coupling of Nitrones and α,β -Unsaturated Esters by Py and Vallée



Scheme 138. Intermolecular Cross-Coupling of Nitrones and α,β -Unsaturated Esters/Amides by Skrydstrup^a



^aRelative stereochemistry not determined.

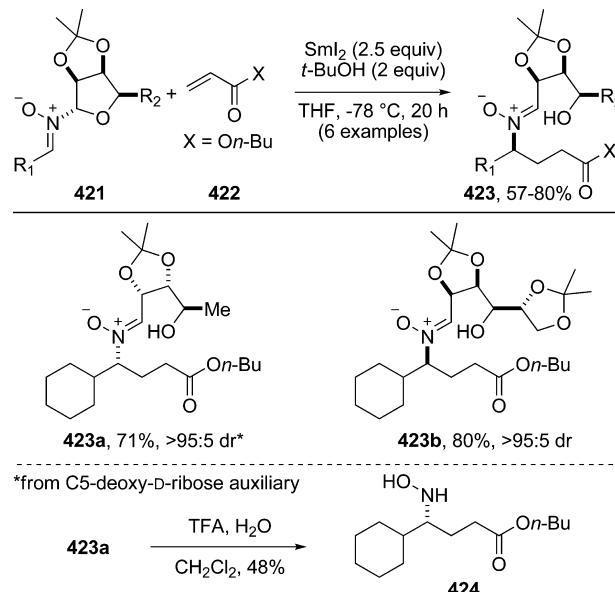
Vallée described the synthesis of γ -amino acid derivatives by the coupling of nitrones with α,β -unsaturated esters in good yields and high diastereoselectivity in the case of disubstituted olefins (Scheme 137).³⁵⁷ Moreover, the use of nitrones with a chiral auxiliary on nitrogen resulted in highly diastereoselective coupling, leading to a concise enantioselective synthesis of γ -amino acids. The developed reaction conditions could be directly applied for the cross-coupling of nitrones with alkynoates in high yields. The authors noted that the water additive had a beneficial effect in some cases, which could be due to the increased redox potential of the reagent. On the basis of the previous studies on the pinacol-type coupling of nitrones with carbonyl compounds (see section 3.3.2), a mechanism involving nitrone reduction to furnish the α -aza-radical, which then couples with the olefin, was

proposed.³⁵⁵ Using D-mannitol-derived nitrones, a highly efficient formal total synthesis of (S)-vigabatrin was also demonstrated.³⁵⁸

By contrast, Skrydstrup described the cross-coupling of nitrones with α,β -unsaturated esters and amides (Scheme 138).³⁵⁹ Under his conditions, the products were formed in generally moderate yields and diastereoselectivity. Notably, the asymmetric synthesis of γ -amino acids by incorporating a chiral auxiliary on the ester or amide group (cf., nitrone, Scheme 137) was reported.

Asymmetric synthesis of γ -amino acid derivatives using the SmI₂-mediated cross-coupling of chiral nitrones with activated olefins was reported by several research groups (Schemes 139–141).^{360–365} In 2004, Skrydstrup reported the use of

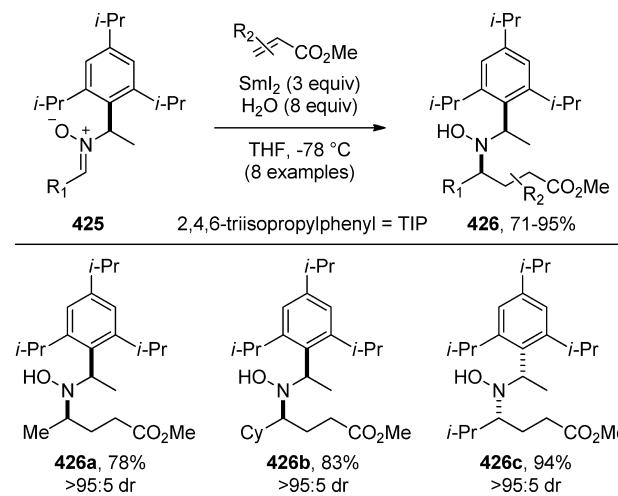
Scheme 139. Cross-Coupling between Nitrones and Acrylates Using Carbohydrate-Derived Auxiliaries by Skrydstrup



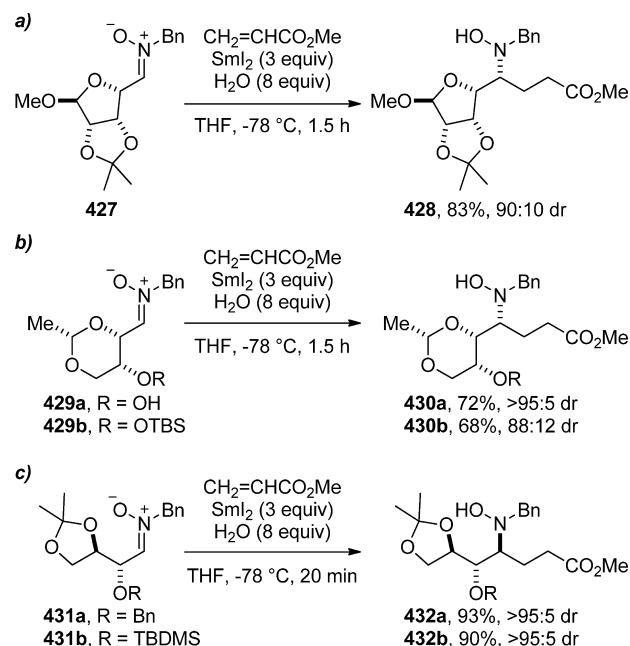
carbohydrate-based chiral auxiliaries on the nitrone in cross-couplings with n-butyl acrylate (Scheme 139).³⁶⁰ High yields and excellent stereoselectivity were observed using a D-mannose-based auxiliary. A D-ribose-based auxiliary offered access to the opposite enantiomer of the product. Cleavage of the auxiliary under mild conditions was demonstrated. In 2007, Py and Greene reported a full study on the use of 1-(2,4,6-trisopropylphenyl)ethylamine as an efficient chiral auxiliary for nitrones in SmI₂-mediated cross-couplings with ethyl acrylate (Scheme 140).³⁶¹ The cross-coupled products were formed in high yields and excellent diastereocontrol. Moreover, this methodology was expanded to include crotonate, methacrylate, and propiolate esters. Fišera reported the coupling of carbohydrate derived chiral nitrones with methyl acrylate (Scheme 141).^{362–365} These reactions afforded highly functionalized γ -amino acid derivatives bearing three to four additional stereocenters in high yields.

The SmI₂-mediated cross-coupling of nitrones with olefins is an attractive methodology for the synthesis of pyrrolizidine alkaloids (Scheme 142, see also Scheme 144).^{366,367} In 2005, Py reported the total synthesis of (+)-hyacinthacine A₂ using the SmI₂-mediated coupling of a chiral L-xylose-derived cyclic nitrone with ethyl acrylate as the key step (Scheme 142a).³⁶⁶ The cross-coupling afforded the N-hydroxypyrrrolidine product

Scheme 140. Cross-Coupling between Nitrones and Acrylates Using 1-(2,4,6-Triisopropylphenyl) Ethylamine Auxiliary by Py and Greene



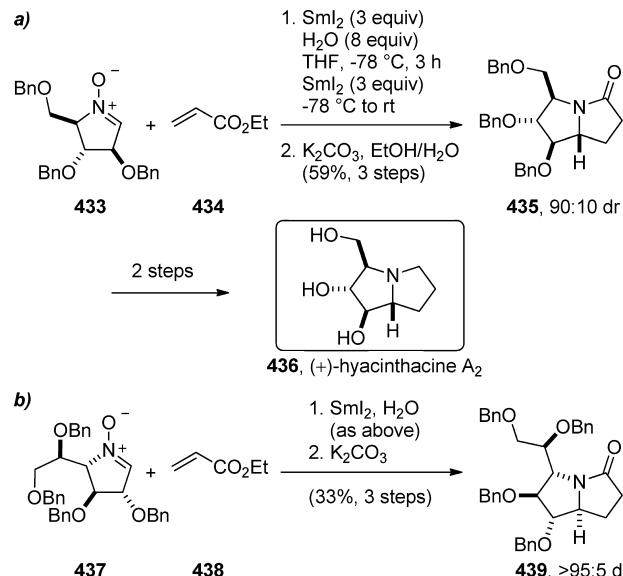
Scheme 141. Cross-Coupling of Carbohydrate-Derived Chiral Nitrones with Acrylates by Fišera



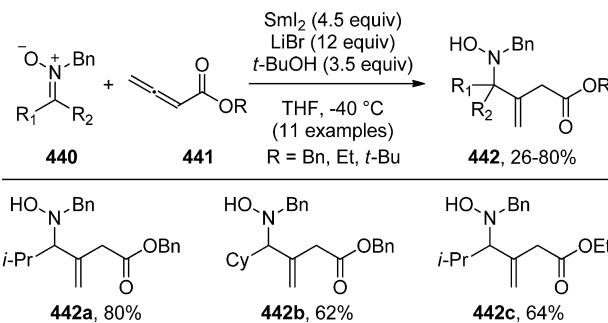
in 64% yield and high diastereoselectivity. Subsequently, it was found that a domino sequence involving cross-coupling, SmI₂-mediated deoxygenation, and base-promoted lactamization directly provided the bicyclic lactam in 59% overall yield. The natural product was obtained after two functional group manipulations. A similar approach was utilized by Desvergne and Py in the synthesis of chiral 1,4-dideoxy-1,4-imino-D-galactitol derivatives as inhibitors of UDP-galactopyranose mutase (Scheme 142b).³⁶⁷

Recently, the scope of SmI₂-mediated cross-couplings of nitrones with olefins has been significantly expanded to include allenotes and β -silyl acrylates as olefin acceptors (Schemes 143 and 144).^{368,369} Huang and Py have developed the coupling of acyclic nitrones with allenotes to form β -methylene- γ -amino acid derivatives (Scheme 143).³⁶⁸ It was shown that a portion-wise addition of the ester gave the highest yields; however, in

Scheme 142. Cross-Coupling of Chiral Cyclic Nitrones with Ethyl Acrylate: (a) Synthesis of (+)-Hyacinthacine A₂ by Py; (b) Synthesis of UDP-Galactopyranose Mutase Inhibitors by Desvergne and Py



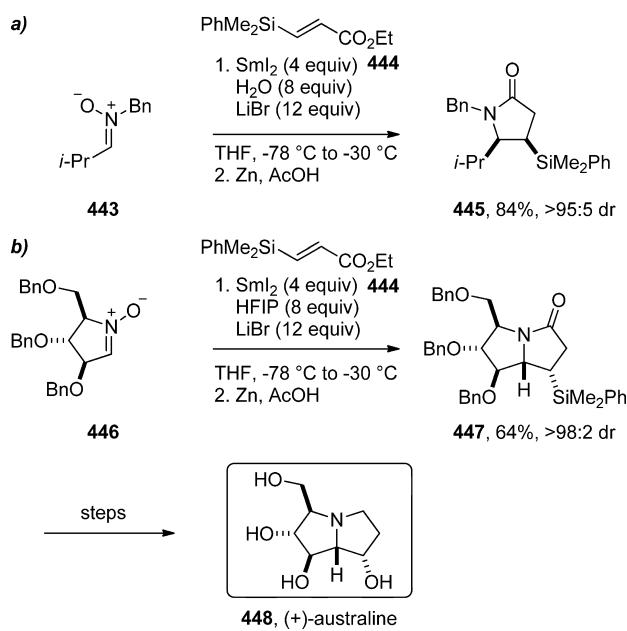
Scheme 143. Cross-Coupling of Nitrones with Allenotes by Huang and Py



some cases, large quantities of the unreacted nitrone were observed in crude reaction mixtures. Substitution of allenotes at α or γ positions led to a significant reduction in yield. The products were converted into β -methylene- γ -lactams on treatment with Zn/acetic acid.

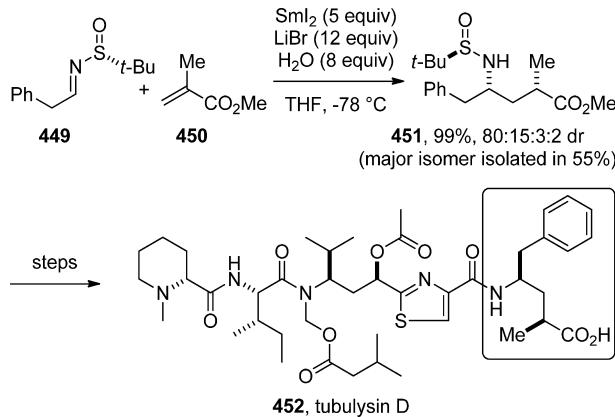
To overcome the difficulties associated with cross-coupling of β -alkoxy acrylates, Py developed the SmI₂-mediated cross-coupling of nitrones with β -silyl acrylates as silicon equivalents of the β -alkoxy group (Scheme 144).³⁶⁹ The reaction was initially optimized using an acyclic nitrone (Scheme 144a). It was found that the addition of both water and LiBr had a significant influence on the yield and stereoselectivity of the coupling, respectively. The authors suggested that the increase of redox potential of the reagent and coordination of the lithium cation to basic oxygens may contribute to the effect of these additives. The utility of this methodology was highlighted by its application as a key step in the total synthesis of (+)-australine (Scheme 144b). Cross-coupling of a cyclic nitrone with ethyl (E)-3-(dimethylphenylsilyl)propenoate, followed by deoxygenation/cyclization with Zn/acetic acid, furnished the bicyclic core of the pyrrolizidine alkaloid in 64% overall yield and as a single diastereoisomer. The β -silicon substituent was converted into a β -hydroxyl group through Fleming-Tamao oxidation.

Scheme 144. (a) Cross-Coupling of Nitrones with β -Silyl Acrylates by Py; (b) Synthesis of (+)-Australine

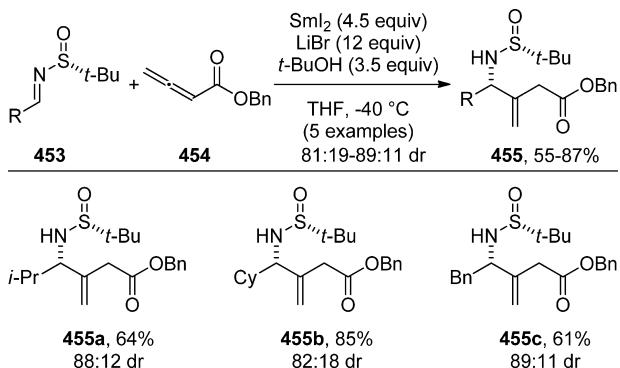


In addition to nitrones, *tert*-butanesulfinyl imines (Schemes 145 and 146) and cyclic *N,O*-acetals (Schemes 147–149) have

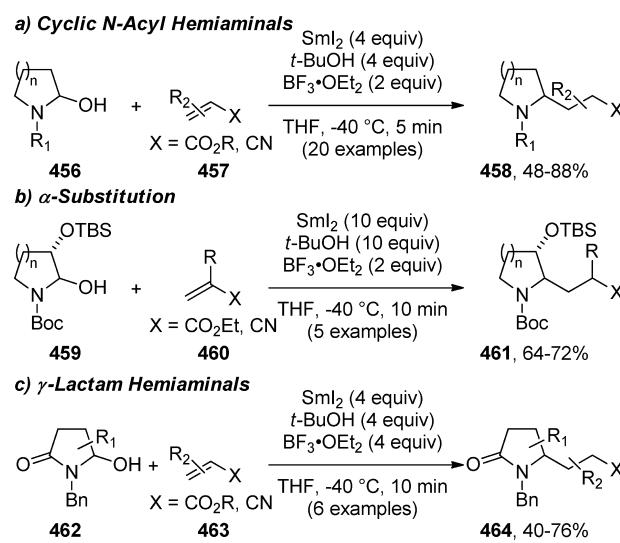
Scheme 145. Cross-Coupling of *N*-*tert*-Butanesulfinyl Imine with Methyl Methacrylate in the Total Synthesis of Tubulysin D by Ellman



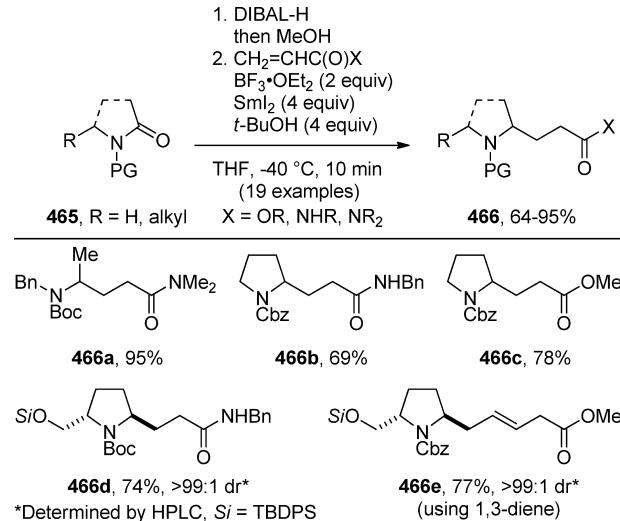
Scheme 146. Cross-Coupling of *N*-*tert*-Butanesulfinyl Imines with Allenoates by Huang and Py



Scheme 147. Intermolecular Cross-Coupling of *N,O*-Acetals and Activated Olefins by Huang

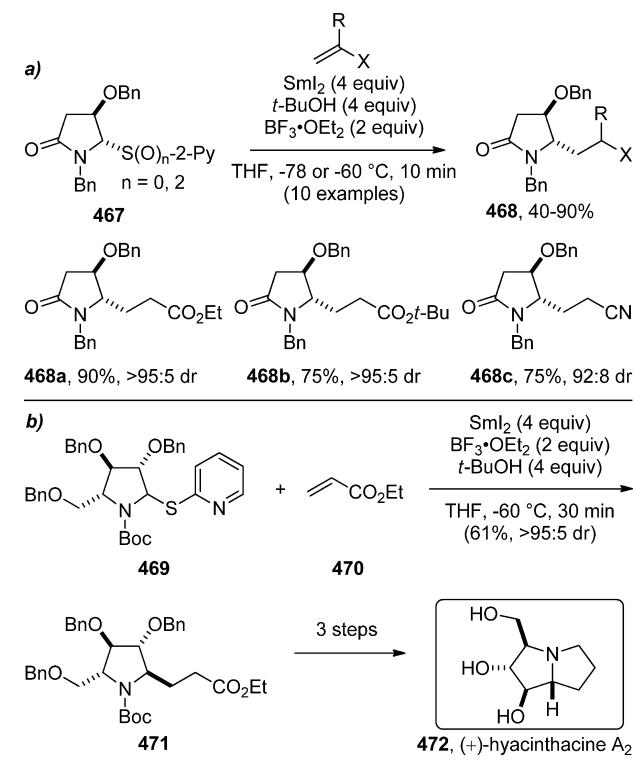


Scheme 148. One-Pot Cross-Coupling of *N*-Acylcarbamates with Activated Olefins by Huang



emerged as new radical precursors for SmI_2 -mediated cross-couplings with activated olefins. In 2006, as part of the total synthesis of tubulysin D, Ellman reported the first coupling of a *N*-*tert*-butanesulfinyl imine with methyl methacrylate to form an α -substituted γ -amino acid derivative (Scheme 145).³⁷⁰ The reaction was highly diastereoselective, and the desired product could be isolated in 55% yield as a single diastereoisomer after separation by HPLC. Cleavage of the *tert*-butanesulfinyl group afforded the enantiopure amine. More recently, Huang and Py reported the SmI_2 -mediated cross-coupling of a range of *N*-*tert*-butanesulfinyl imines with benzyl allenoate (Scheme 146).³⁶⁸ The products were used for the synthesis of enantiopure tetramic acids. It is worth noting that Concellón reported a complementary application of *N*-*tert*-butanesulfinyl imines as electrophilic components in the SmI_2 -mediated diastereoselective coupling of samarium enolates, formed in Reformatsky reactions of α -chloro esters (not shown).³⁷¹ This methodology affords β -amino esters in moderate to high yields and excellent diastereoselectivity.

Scheme 149. (a) Cross-Coupling of *N,S*-Acetals with Olefins by Huang; (b) Application in the Synthesis of (+)-Hyacinthacine A₂ by Zheng and Huang



Huang has pioneered the SmI₂-mediated cross-coupling of olefins with *N*-acyl *N,O*-acetals as precursors to *N*-acyl α -aminyl radicals (Schemes 147–149).^{372–375} On treatment with the BF₃•Et₂O–SmI₂–*t*-BuOH reagent system, cyclic and acyclic *N*-acyl *N,O*-acetals were shown to undergo efficient cross-coupling with α,β -unsaturated esters and nitriles (Scheme 147).³⁷² Huang has since extended this work to one-pot reduction/reductive cross-coupling of amides with activated olefins (Scheme 148).³⁷³ In this protocol, the amide is first reduced to the α -amino alkoxide using DIBAL-H, followed by *N,O*-acetal release with MeOH and standard cross-coupling with olefins under the BF₃•Et₂O–SmI₂–*t*-BuOH conditions to give the coupling products directly from amides in high yields and good diastereoselectivity.

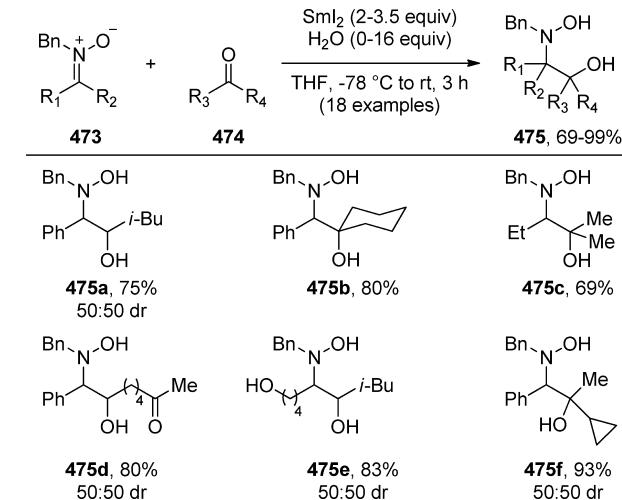
Huang has recently extended this methodology to γ -lactam-*N,S*-acetals and highlighted its application in the synthesis of alkaloids and bioactive molecules (Scheme 149).³⁷⁴ Utilizing the reductive coupling of a chiral *N,S*-acetal with ethyl acrylate mediated by the BF₃•Et₂O–SmI₂–*t*-BuOH reagent, a stereoselective total synthesis of (+)-hyacinthacine A₂ was achieved in good overall yield (Scheme 149b). This *N,S*-acetal coupling chemistry has also been used by Huang in the synthesis of azaprostaglandin E₂ analogues.³⁷⁵

3.3.2. Cross-Coupling with C=O and C=N Bonds. In the past decade, significant advancements in the SmI₂-mediated pinacol-type couplings of imines and equivalents with aldehydes, ketones, and imine derivatives have been reported. In particular, two new classes of radical precursors for the SmI₂-mediated pinacol-type couplings of C=N bonds have been reported: (i) nitrones, and (ii) *N*-*tert*-butanesulfinyl imines. This class of SmI₂-mediated cross-couplings has been frequently employed for the synthesis of symmetrical and unsymmetrical β -diamines and β -amino alcohols. In general, these reactions give high yields and

diastereoselectivity. The SmI₂-mediated cross-couplings of imines with C=O/C=N bonds have proven compatible with the use of chiral auxiliaries, including *N*-*tert*-butanesulfinyl imines. These reactions have already been applied in target synthesis. This section of the Review has been arranged according to the type of precursor for the SmI₂-mediated cross-coupling.

The seminal SmI₂-mediated cross-coupling of nitrones with ketones and aldehydes was reported by Py and Vallée in 2002 (Scheme 150).³⁵⁵ The method utilizes SmI₂–THF complex

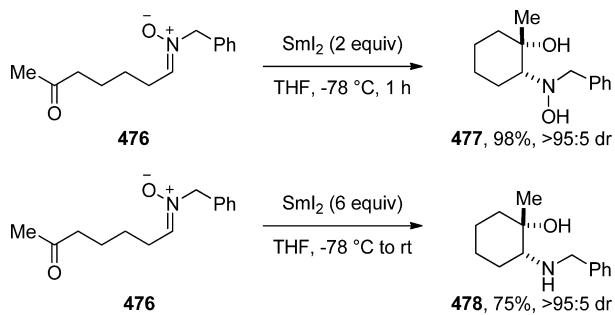
Scheme 150. Intermolecular Cross-Coupling of Nitrones with Ketones/Aldehydes by Py and Vallée



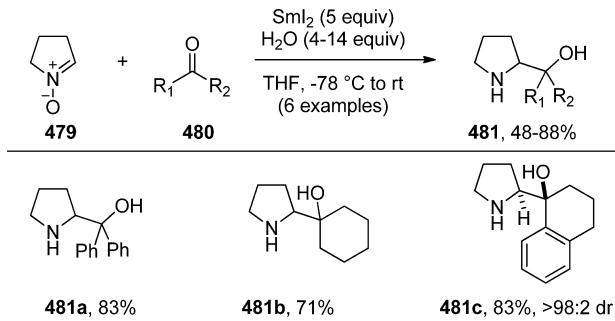
under very mild conditions, alcohol or Lewis basic cosolvents are not required, and the coupling products are formed in high yields. The substrate scope includes aromatic and aliphatic nitrones, ketones, and aldehydes. Moreover, complete chemoselectivity is possible with bifunctional substrates, such as keto-aldehydes. The authors proposed that the mechanism involves the nitrone reduction to afford an α -aza-nucleophilic radical, which then couples to the carbonyl. Several mechanistic experiments supported this hypothesis: (i) 73% of the homocoupled nitrone product was formed in the absence of a carbonyl acceptor; (ii) intramolecular pinacol coupling of a 1,6-keto-aldehyde substrate was not observed; and (iii) reactions involving an α -cyclopropyl ketone yielded the expected cross-coupling product without the cyclopropyl ring-opening. However, the use of α -cyclopropyl nitrones also afforded the cross-coupled products with no observed ring-opening, which was proposed to be due to the fast cross-coupling rate being competitive with the cyclopropane ring-opening.³⁷⁶ Py and Vallée also described the first intramolecular nitrone/ketone cross-coupling to form cyclic β -amino-alcohol as a single *cis*-diastereoisomer (Scheme 151).³⁵⁵

Subsequently, Py and Chavant reported the intermolecular coupling of cyclic nitrones with ketones to form α,α -disubstituted prolinol derivatives using SmI₂–THF (aromatic ketones) or SmI₂–H₂O (aliphatic ketones) (Scheme 152).³⁷⁷ A sequential cross-coupling/hydroxylamine deoxygenation was achieved by further addition of SmI₂ to cleave the N–O bond of the intermediate hydroxylamine. Resolution of the intermediate *N*-hydroxy prolinols provided enantiomerically pure products.

Scheme 151. Seminal Intramolecular Cross-Coupling of Nitrones with Ketones by Py and Vallée

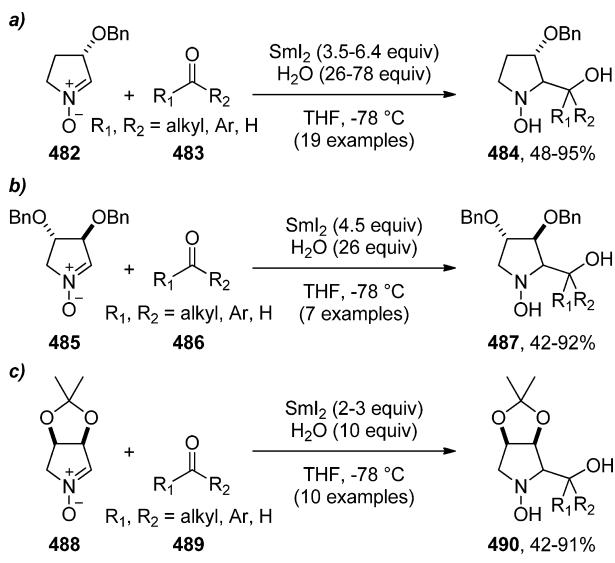


Scheme 152. Intermolecular Cross-Couplings of Cyclic Nitrones and Ketones by Chavant and Py



Huang and Zhang reported intermolecular cross-coupling of chiral cyclic nitrones with aldehydes, ketones, and acid chlorides using $\text{SmI}_2-\text{H}_2\text{O}$ reagent system (Scheme 153).^{378–380} The

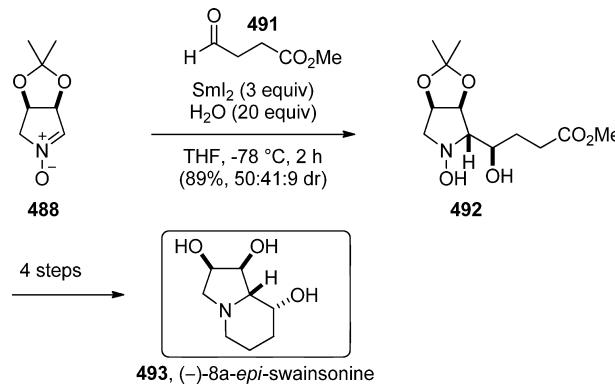
Scheme 153. Intermolecular Cross-Coupling of Chiral Nitrones with Ketones and Aldehydes by Zheng and Huang



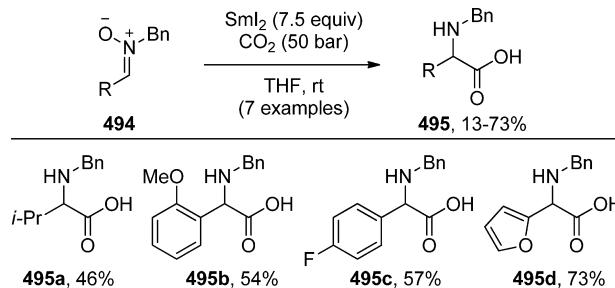
reductive coupling was achieved in generally high yields and good diastereoselectivity. The coupling of acyl chlorides is particularly noteworthy as it leads to the corresponding ketones. Zhang and Huang have highlighted the use of this methodology as the key step in the synthesis of $(-)$ -8*a*-*epi*-swainsonine (Scheme 154).³⁸⁰

Recently, Prikhod'ko, Walter, and Py reported the SmI_2 -mediated cross-coupling of nitrones with CO_2 (Scheme 155).³⁸¹

Scheme 154. Application of the Intermolecular Cross-Coupling of Chiral Nitrones in the Synthesis of 8*a*-*epi*-Swainsonine by Zhang and Huang



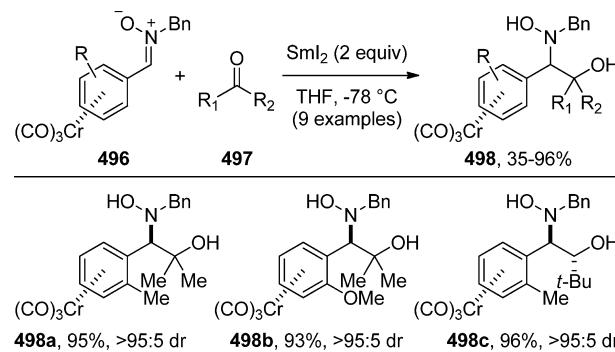
Scheme 155. Cross-Coupling of Nitrones with CO_2 by Prikhod'ko, Walter, and Py



This reaction affords natural and unnatural α -amino acids in moderate to good yields (50 bar CO_2). Preliminary optimization studies revealed that the coupling of the organosamarium radical with CO_2 also proceeded at ambient pressure, but the yield was lower due to competing reductive dimerization of the nitrone.

Chavarot-Kerlidou and Rose-Munch have investigated the SmI_2 -mediated cross-coupling of planar chiral $\text{Cr}(\text{CO})_3$ -complexed aromatic nitrones with ketones and aldehydes (Scheme 156).^{382,383} This reaction was shown to be very sensitive to electronic substitution around the ring with electron-donating ortho groups such as methyl and methoxy giving the highest yields, and electron-donating meta groups shutting down reactivity. High yields of the nitrone dimerization product were observed in the absence of carbonyl group acceptor ($R = \text{H}$, 90%); however, the competing homocoupling was not detected

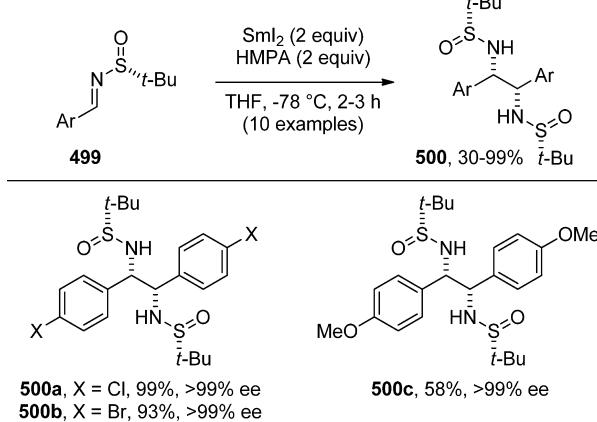
Scheme 156. Cross-Coupling of $\text{Cr}(\text{CO})_3$ -Complexed Aromatic Nitrones with Ketones/Aldehydes by Chavarot-Kerlidou and Rose-Munch



under the reaction conditions. The synthesis of an enantiopure β -amino alcohol complex was achieved in 95% yield with >95:5 dr.

N-tert-Butanesulfinyl imines have been utilized to achieve the SmI₂-promoted diastereoselective pinacol type couplings with imines, nitrones, ketones, and aldehydes. The first SmI₂-mediated dimerization of *N-tert*-butanesulfinyl imines was reported by Xu in 2004 (Scheme 157).³⁸⁴ The method utilizes

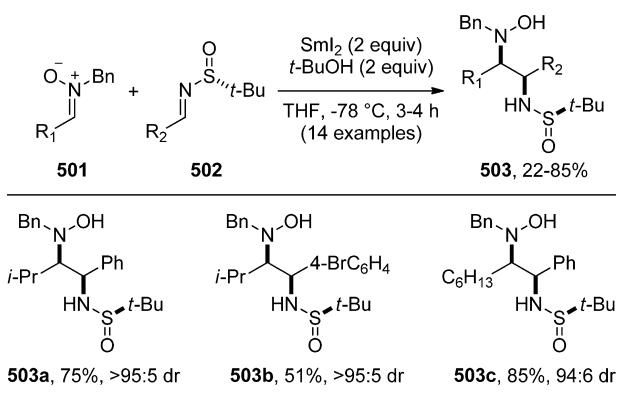
Scheme 157. Highly Diastereoselective Coupling of *N-tert*-Butanesulfinyl Imines by Xu



SmI₂-HMPA complex and leads to the synthesis of chiral *syn*- β -diamines with high diastereoselectivity. The reaction is limited to aromatic *N-tert*-butanesulfinyl imines. The use of other SmI₂ systems, such as SmI₂-THF, SmI₂-*t*-BuOH, and SmI₂-NiI₂, afforded the homocoupled products in good yields, but with low diastereoselectivity.

In 2004, Xu also reported the SmI₂-mediated cross-coupling of *N-tert*-butanesulfinyl imines with nitrones (Scheme 158).³⁸⁵ The

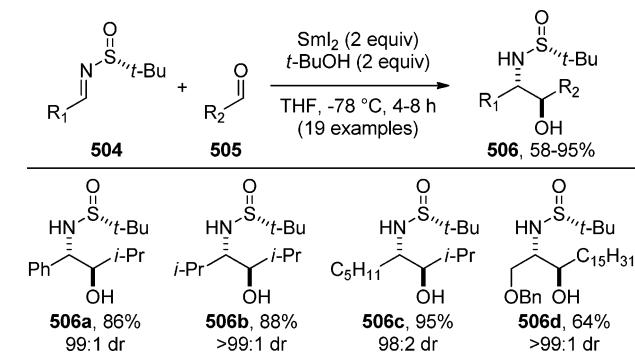
Scheme 158. Highly Diastereoselective *N-tert*-Butanesulfinyl Imine/Nitron Cross-Coupling by Xu



authors proposed a mechanism involving initial nitrone reduction to the α -aza-nucleophilic radical intermediate; however, the exact mechanism of this reaction has yet to be elucidated. The methodology furnishes unsymmetrical *syn*-diamines in moderate to good yields and excellent diastereoselectivity. The use of *t*-BuOH is essential to achieve good yields, and only a slight excess of either of the coupling partners is required for the efficient reaction.

In 2005, Xu and Lin reported the SmI₂-mediated cross-coupling of *N-tert*-butanesulfinyl imines with aldehydes using *t*-BuOH as a proton source (Scheme 159).³⁸⁶ A variety of aromatic

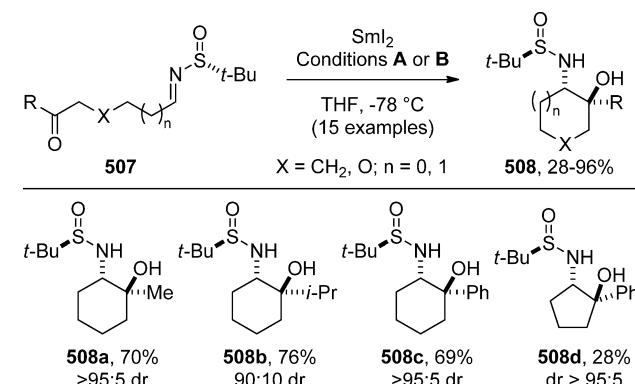
Scheme 159. Highly Diastereoselective *N-tert*-Butanesulfinyl Imine/Aldehyde Cross-Coupling by Xu and Lin



and aliphatic imine substrates and aliphatic aldehydes underwent SmI₂-promoted cross-coupling in excellent yields and diastereoselectivity. Cleavage of the sulfinyl group under acidic conditions afforded chiral β -amino alcohols in >95% ee in all cases reported. The synthesis of two natural products, *D*-*erythro*-spinganine and (3*R*,4*S*)-statine, was accomplished in high yields. This methodology represents an important advance in the direct asymmetric synthesis of β -amino alcohols via pinacol-type coupling reactions.

In 2009, Wang reported the SmI₂-mediated intramolecular cross-coupling of *N-tert*-butanesulfinyl imines with ketones (Scheme 160).³⁸⁷ The reaction furnishes *trans*- β -amino alcohols

Scheme 160. Intramolecular *N-tert*-Butanesulfinyl Imine/Ketone Cross-Coupling by Wang



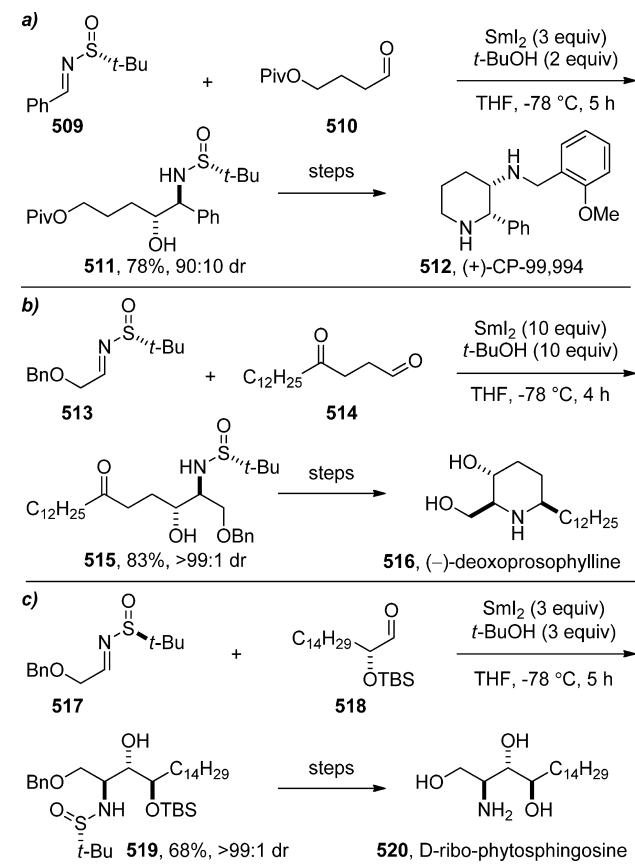
Conditions A: SmI₂ (3 equiv), *t*-BuOH (3 equiv)

Conditions B: SmI₂ (4 equiv), *t*-BuOH (4 equiv), HMPA (16 equiv)

in good yields and excellent diastereoselectivity. Both aryl and alkyl ketones undergo efficient coupling, and the reaction can be used for the synthesis of five- and six-membered rings. *t*-Butanol is required to achieve high conversions. Aliphatic ketones undergo coupling with the SmI₂-HMPA system; however, HMPA is not required for the coupling of aryl ketones. Under these reaction conditions, the intermolecular coupling of *N-tert*-butanesulfinyl imines with ketones was not successful.

The pinacol-type coupling of *N-tert*-butanesulfinyl imines with carbonyl compounds provides rapid access to chiral β -amino alcohols. This methodology has already been applied in the total synthesis of pharmaceuticals and natural products by several research groups (Scheme 161).³⁸⁸⁻³⁹³ Xu and Lin reported the total synthesis of a quinazolinone alkaloid, (+)-febrifugine (not shown).³⁸⁸ Bentley reported the total synthesis of a cytokine modulator, (-)-cytoxazole (not shown).³⁸⁹ Wang, Xu, and Lin

Scheme 161. Application of the Cross-Coupling of *N*-*tert*-Butanesulfenyl Imines in Total Synthesis: (a) CP-99,994 by Wang, Xu, and Lin; (b) Deoxoprosophylline by Wei and Lin; (c) Phytosphingosine by Wei



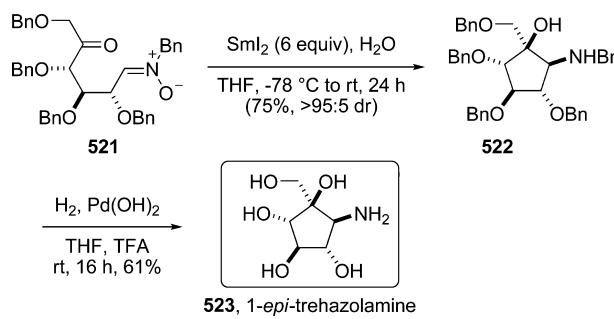
reported the synthesis of NK-1 SP receptor antagonists, (+)-CP-99,994 and (+)-L-733,060 (Scheme 161a).³⁹⁰ Wei and Lin reported the synthesis of a piperidine alkaloid, (−)-deoxoprosophylline (Scheme 161b).³⁹¹ Wei reported the SmI₂-mediated coupling of *N*-*tert*-butanesulfenyl imine with a chiral α -hydroxy aldehyde to set three contiguous stereocenters in the synthesis of phytosphingosine (Scheme 161c).³⁹² Wang reported the synthesis of analogues of 3-hydroxypipericolic acid.³⁹³

Intramolecular SmI₂-mediated cross-coupling of nitrones has also been applied for the synthesis of natural products.^{394,395} Py reported the synthesis of an aminocyclitol, 1-*epi*-trehzolamine, employing the intramolecular ketone–nitrone coupling for the synthesis of a five-membered ring with excellent *cis*-diastereoselectivity (Scheme 162).³⁹⁴ The proposed mechanism involves a chelated transition state. Upon exposure of the precursor δ -keto-nitronate (isolated as a hydrated hemiketal, >95:5 dr) to SmI₂, a smooth cyclization via the keto-nitronate form was observed. The excess of SmI₂ was used to promote reduction of the intermediate hydroxylamine to the amino alcohol.

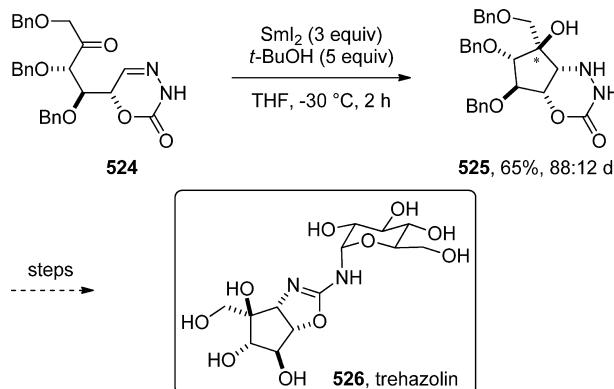
Independently, Chiara reported the SmI₂-mediated cross-coupling of ketones with tethered hydrazones as an approach to aminocyclitol trehzolin (Scheme 163).³⁹⁵ The reaction proceeded with high *trans*-diastereoselectivity as a result of electrostatic repulsion in the transition state.

Skrydstrup reported a related intramolecular coupling of dinitrones to form cyclic *cis*-diamines with high diastereoselectivity (Scheme 164).³⁹⁶ Optimization of the reaction conditions revealed that proton donors dramatically increase the yield and

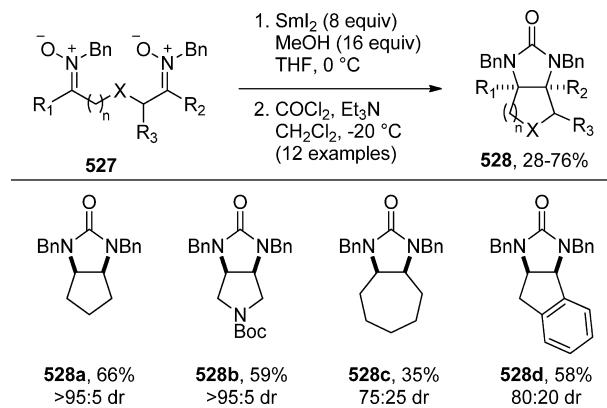
Scheme 162. Nitrone/Ketone Coupling in the Total Synthesis of 1-*epi*-Trehazolamine by Py



Scheme 163. Intramolecular Ketone/Hydrazone Cross-Coupling by Chiara



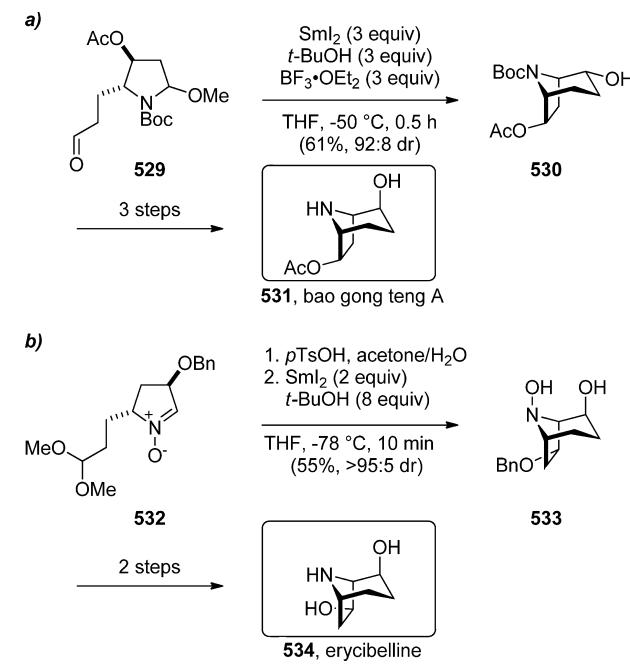
Scheme 164. Intramolecular Nitrone/Nitronate Coupling by Skrydstrup



diastereoselectivity of the coupling, with MeOH providing the optimum results. A two-step procedure, involving the N–O bond cleavage and cyclization to bicyclic ureas, was developed to facilitate the product isolation. The *cis*-relationship was determined by X-ray crystallographic analysis of a crystalline urea.

Huang³⁹⁷ and Yu,³⁹⁸ independently, reported the synthesis of structurally related tropane alkaloids using SmI₂-mediated intramolecular cross-coupling between an aldehyde and imine equivalent to construct the core [3.2.1] ring system (Scheme 165). In the approach by Huang, the total synthesis of (−)-bao gong teng A was achieved by the SmI₂-mediated intramolecular *N*,*O*-acetal/aldehyde coupling (Scheme 165a).³⁹⁷ The reaction favors the formation of an equatorial alcohol (92:8 dr) due to

Scheme 165. (a) *N,O*-Acetal/Aldehyde Coupling in the Total Synthesis of (−)-Bao Gong Teng A by Huang; (b) Nitrone/Aldehyde Coupling in the Total Synthesis of (−)-Erycibelline by Yu



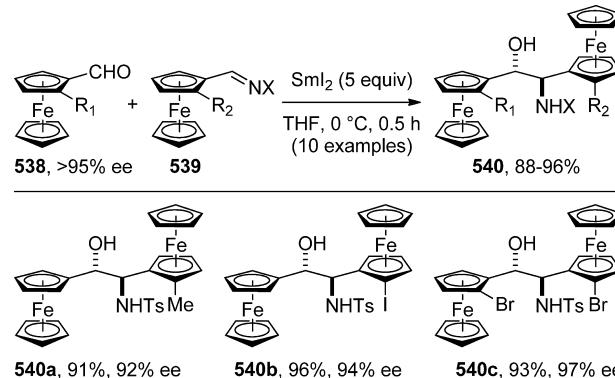
electronic repulsion in the transition state. By contrast, Yu employed intramolecular nitrone/aldehyde coupling in the synthesis of (−)-erycibelline (Scheme 165b).³⁹⁸ In this case, the axial alcohol is formed with >95:5 diastereoselectivity. In line with the previous finding by Py (see Scheme 162), the authors proposed a chelation model involving coordination of the samarium ketyl to the nitrone oxygen to control the diastereoselectivity of the cyclization.

In his classic synthesis of diazonamide A, Nicolaou utilized the SmI_2 -mediated oxime ether/aldehyde cross-coupling to close the 13-membered macrocycle using excess SmI_2 –HMPA (Scheme

166).^{399,400} A mechanism involving coupling of the diradical generated by the reduction of both the aldehyde and the oxime was proposed. A cascade sequence was developed to promote the N–O bond cleavage to afford the β -amino alcohol, which was directly subjected to peptide coupling after aqueous extraction to give the desired product in a respectable yield (63% per operation in a cascade sequence) and as a mixture of diastereoisomers.

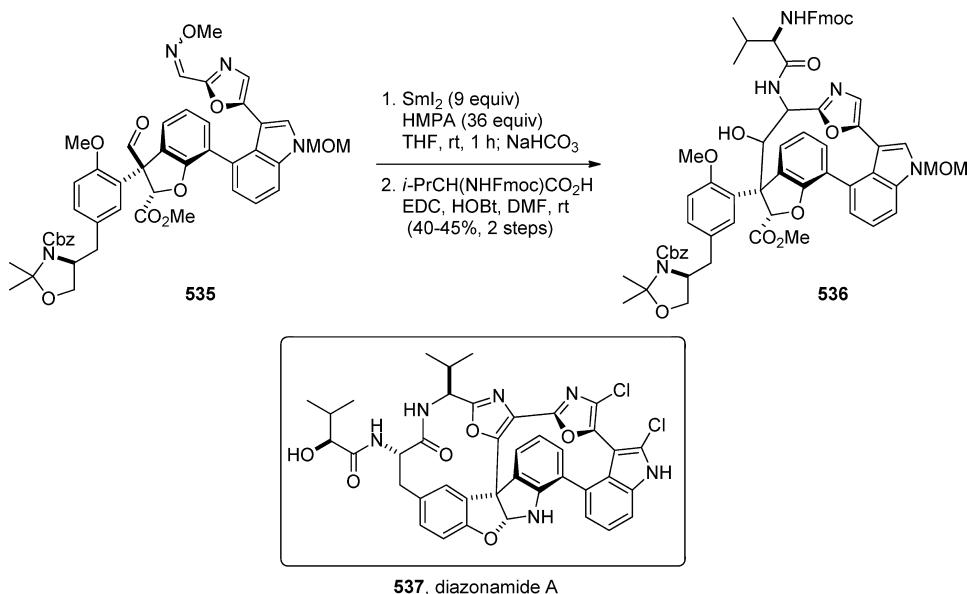
Other examples of SmI_2 -mediated pinacol-type couplings of imines and equivalents have also been reported. Uemura reported the cross-coupling of planar chiral ferrocenecarboxyaldehydes with imines to form *anti*- β -amino alcohols in high enantiomeric excess (Scheme 167).⁴⁰¹ Remarkably, the reaction

Scheme 167. Cross-Coupling of Planar Chiral Arylaldehydes with Imines by Uemura

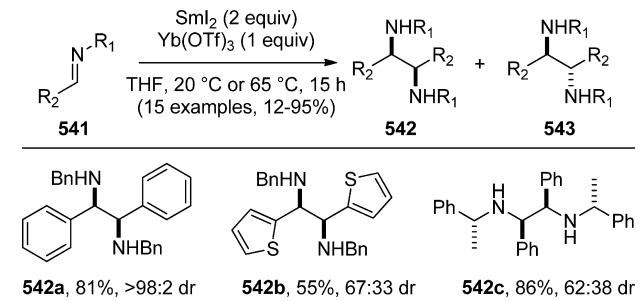


conditions tolerated iodo and bromo substituents on the ferrocene ring. Benaglia and Raimondi reported the use of $\text{SmI}_2/\text{Yb}(\text{OTf})_3$ for dimerization of aromatic aldimines to afford *syn*-diamines in moderate to high stereoselectivity (Scheme 168).⁴⁰² Hilmersson and Flowers reported the reductive dimerization of aromatic aldimines and ketimines using the $\text{SmI}_2\text{-Et}_3\text{N-H}_2\text{O}$ reagent system; however, these reactions afford mixtures of diastereoisomers (Scheme 169).⁴⁰³ The use of the sterically encumbered Sm(II) reductant, $\text{Sm}(\text{HMDS})_2$,

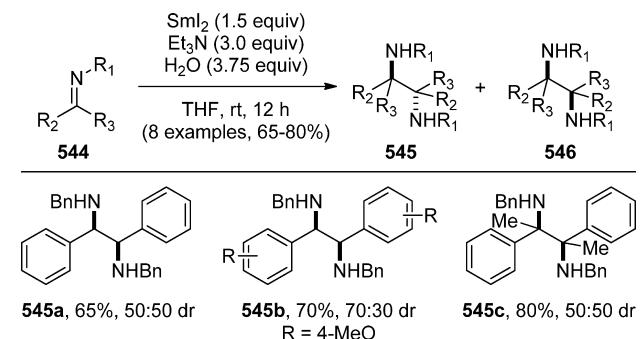
Scheme 166. Intramolecular Oxime Ether/Aldehyde Coupling in the Synthesis of Diazonamide A by Nicolaou



Scheme 168. Intermolecular Pinacol Couplings of Imines Using SmI₂/Yb(OTf)₃ by Benaglia and Raimondi

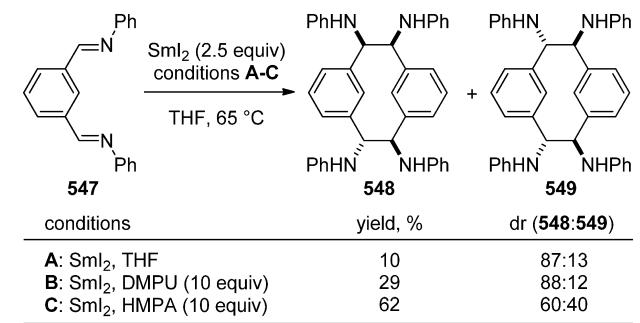


Scheme 169. Intermolecular Pinacol Couplings of Imines Using SmI₂/Et₃N/H₂O by Hilmersson and Flowers



resulted in higher diastereoselectivity (up to 85:15 dr), however, in much lower yields. Kawaji reported the dimerization of diimine 547 to afford metacyclophanes in moderate yields and/or diastereoselectivity (Scheme 170).⁴⁰⁴ In general, the SmI₂-

Scheme 170. 1,2,9,10-Tetrakis(N-phenylamino)[2.2]metacyclophane via Diimine Coupling by Kawaji

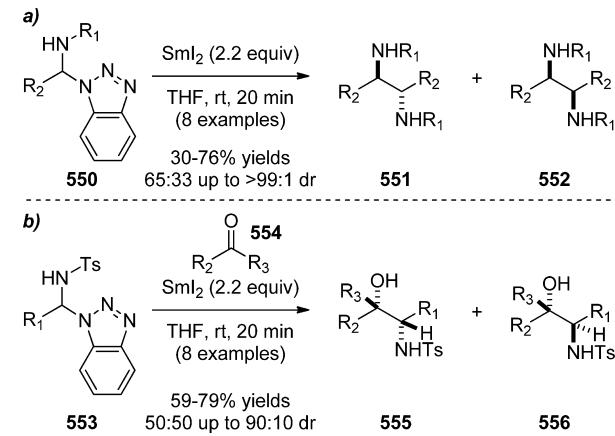


mediated coupling of imines has been less explored due to the lower reactivity of these precursors. Finally, Zhang demonstrated the use of an α -amino benzotriazole group as a reactive imine surrogate under SmI₂ reaction conditions (Scheme 171).⁴⁰⁵ The dimerization and cross-coupling of *N*-(α -benzotriazol-1-ylalkyl)-amides with ketones and aldehydes was demonstrated. A mechanism involving generation of the α -amino radical upon treatment with SmI₂ was proposed for these reactions.

3.4. Non-Ketyl Radical-Alkene/Alkyne Cross-Coupling

In comparison to the cross-coupling of ketyl-type radicals, SmI₂-mediated couplings of alkyl- or aryl-type radicals with π -systems are much less common because of the difficulties in fine-tuning the stability of non-ketyl radicals by the use of Sm(II)-additives, problems associated with homocoupling, and the fact that other

Scheme 171. α -Amino-benzotriazoles as Imine Equivalents: (a) Homocouplings; (b) Cross-Couplings with Ketones and Aldehydes by Zhang



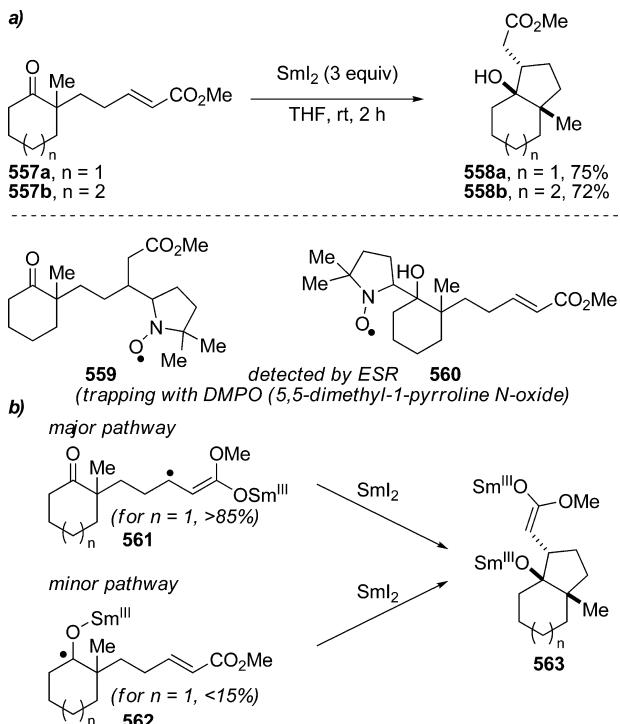
reagents often provide beneficial diastereo- and chemoselective outcomes as compared to SmI₂. Nonetheless, examples reported during the past decade demonstrate that the reductive coupling of non-ketyl-type radicals mediated by SmI₂ remains a valuable synthetic method. In general, three types of cross-coupling of non-ketyl-type radicals with π -systems mediated by SmI₂ have been reported: (i) cross-coupling of unstabilized aryl or alkyl radicals; (ii) reductive dimerization of radicals generated from α,β -unsaturated carbonyls; and (iii) cross-coupling of radicals generated from α,β -unsaturated carbonyl compounds with various acceptors.

It should be noted that a recent investigation on the mechanism of reductive ketone/ α,β -unsaturated ester 5-exo-trig cross-couplings by Tori and co-workers using ESR spectroscopy suggested that these reactions might proceed via the less established pathway involving addition of β -radical anion intermediates to ketones rather than via the coupling of ketyl radical anions to the α,β -unsaturated acceptor, at least in the investigated case of 5-exo-trig ketone/olefin cyclizations (Scheme 172).¹⁶⁰ Further studies are clearly required to confirm the generality of this finding. For the sake of clarity, the vast majority of Sm(II)-mediated reactions employing ketyl-type radical precursors are discussed in the first part of this Review; however, some of these processes may follow the less common “olefin-first” mechanistic manifold as suggested by Tori.¹⁶⁰

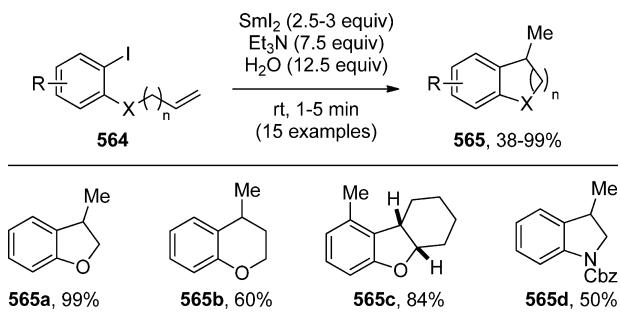
3.4.1. Cross-Coupling of Unstabilized Aryl or Alkyl Radicals. In 2003, Hilmersson reported the SmI₂-amine-H₂O-mediated intramolecular radical cross-couplings between aryl iodides and olefins (Scheme 173).⁴⁰⁶ The reaction was successful for 5-exo and 6-exo cyclizations of terminal, mono-, and disubstituted olefins. Sensitive functional groups, such as pyridine rings, carbamates, benzylic 1,3-dithianes, allyl, and benzyl ethers, were tolerated. The cyclization of a model substrate, 1-(allyloxy)-2-iodobenzene, proceeded instantaneously, demonstrating the much higher reactivity of the SmI₂-amine-H₂O system over other Sm(II)-based reagents previously used for this transformation (e.g., SmI₂-THF, 5 h, rt, 20% yield; SmI₂-H₂O, 5 h, rt, 64% yield).⁴⁰⁷

In 2004, Curran reported 6-exo-trig radical cyclizations of aryl iodides onto cyclobutenes mediated by SmI₂-HMPA, including trapping of the samarium(III) cyclobutyl species with acetone in a radical/polar crossover tandem reaction sequence (Scheme 174).^{408,409} In some cases, minor quantities of the dehalogenated

Scheme 172. Study of the Mechanism of the 5-*exo*-Trig Ketone/Olefin Cross-Coupling via ESR Spectroscopy by Sono, Murai and Tori



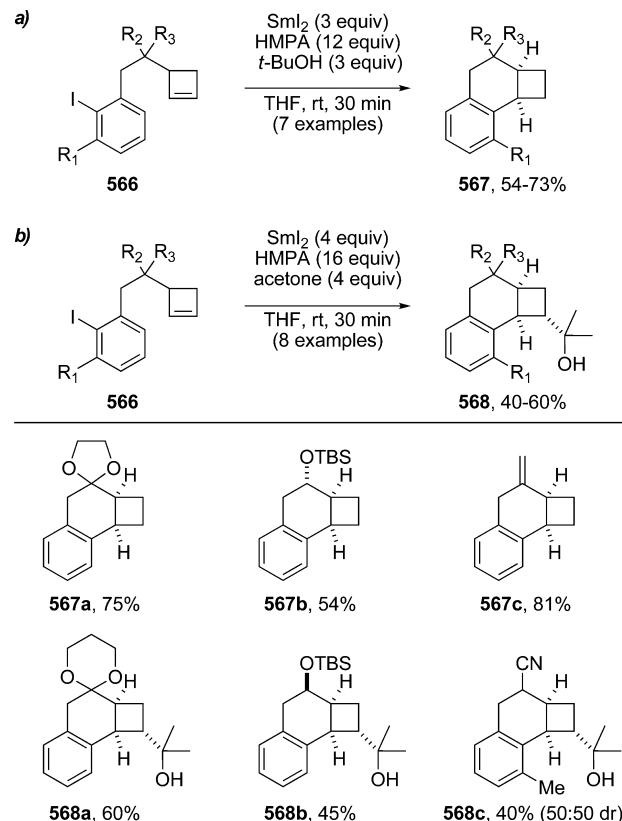
Scheme 173. Diastereoselective Cross-Coupling of Aryl Iodides Using SmI₂/Amine/H₂O by Hilmersson



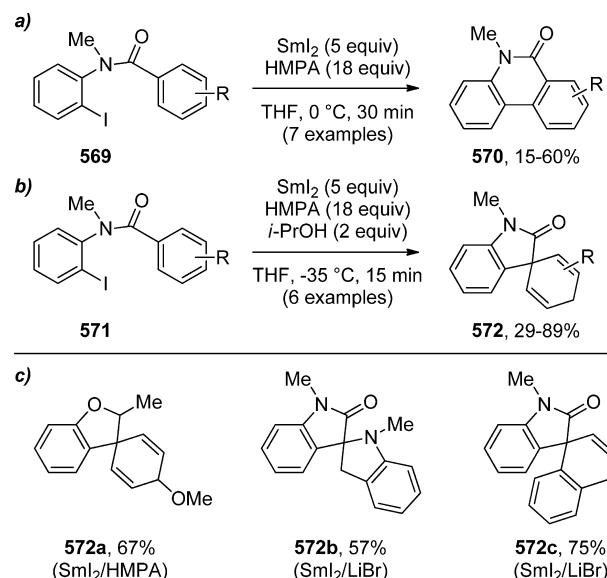
reduction product were formed. It was postulated that the reduced products result from hydrogen abstraction by the aryl radical. The 6-*exo*-trig cyclization showed yields and selectivity similar to those of the process mediated by Bu₃SnH. The radical/polar crossover reactions proceeded with high diastereoselectivity; the use of diastereoisomeric TBS protected alcohols gave the corresponding cyclobutanes containing four contiguous stereocenters. However, the yields were compromised by the formation of the reduced products and minor amounts of products from unsuccessful polar addition. Elaboration of the products provided the fully functionalized BCD ring system of penitrem D, thus demonstrating the use of this methodology in the synthesis of natural products containing fused cyclobutane rings.⁴⁰⁹

In 2008, Tanaka reported the SmI₂-HMPA-mediated cross-coupling between aryl iodides and aromatic rings (Scheme 175).^{410,411} In an initial study, the use of aprotic conditions afforded fused phenanthridinone derivatives (Scheme 175a), while the addition of i-PrOH allowed access to spirocyclic indolin-2-ones (Scheme 175b) from the same precursors.⁴¹⁰

Scheme 174. Cross-Coupling of Aryl Iodides and Cyclobutenes Using SmI₂/HMPA by Curran



Scheme 175. Radical Addition of Aryl Iodides to Aromatic Rings by Sono, Murai, and Tori: (a) Formal Cine Addition; (b) Spirocyclization; (c) Additional Examples

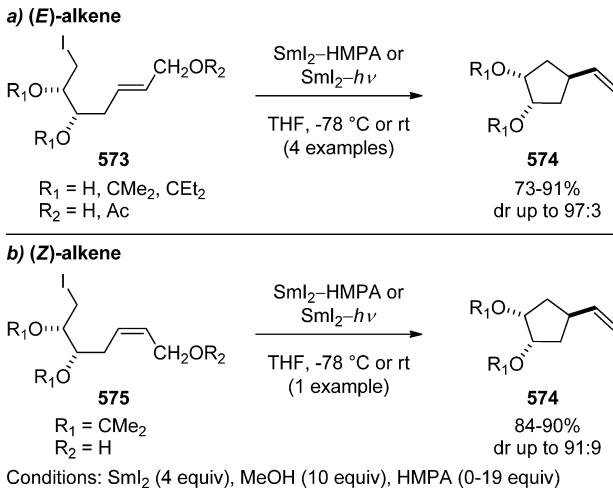


Extensive optimization of the reaction scope demonstrated that the selectivity is also substrate-dependent.⁴¹¹ Mechanistically, it was proposed that the reaction involves 5-*exo*-trig cyclization of the aryl radical, followed by the second reduction and protonation to indolin-2-ones. Alternatively, the rearrangement of the unstable spirocyclic radical could afford phenanthridi-

nones. The reaction was extended to benzofuran, naphthalene, and indole derivatives in good yields (Scheme 175c).

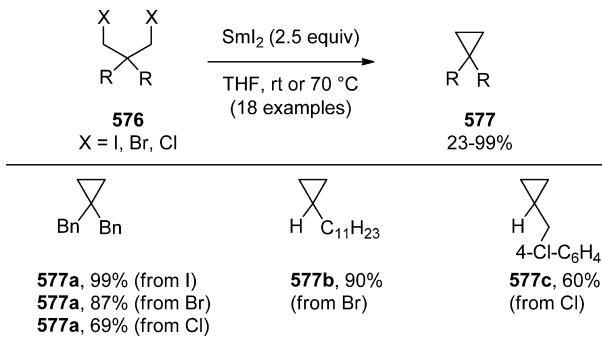
Although alkyl radicals are typically more stable than aryl and vinyl radicals,^{55–57} few examples of the SmI₂-mediated cross-coupling of alkyl radicals have been reported in the past decade. Bennett utilized primary ω -iodoallylic alcohols on a carbohydrate scaffold in reductive cross-couplings using SmI₂-HMPA or SmI₂- $h\nu$ to give vinylcyclopentanediol derivatives in good yields and diastereoselectivity (Scheme 176).⁴¹² Togo reported the

Scheme 176. Stereoconvergent Cross-Coupling/Elimination of Alkyl Iodides and Unactivated Olefins by Bennett



radical 3-*exo*-tet cyclization of 1,3-dihalopropanes to afford cyclopropanes (Scheme 177).⁴¹³ Under the optimized con-

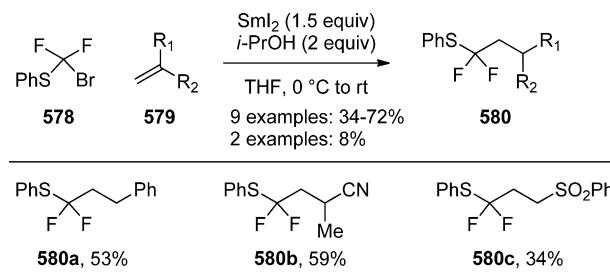
Scheme 177. Radical Coupling of 1,3-Dihalopropanes by Togo



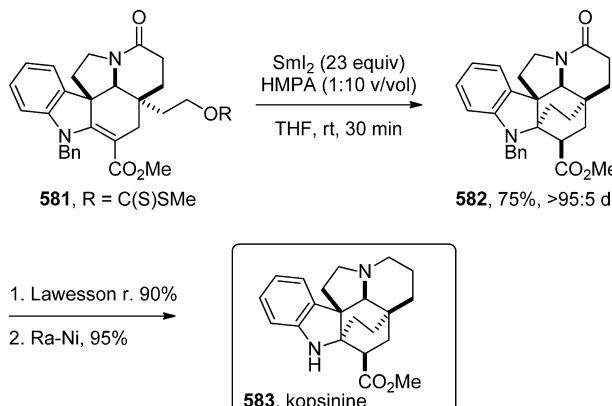
ditions, dichloro, dibromo, and diiodo 1,3-propanes all underwent efficient cross-coupling in high yields. Reutrakul and Pohmakotr⁴¹⁴ applied SmI₂ in cross-couplings of difluorophenylsulfanylmethyl radical with olefins to generate compounds containing the pharmaceutically relevant difluoromethylene motif⁴¹⁵ (Scheme 178). Activated π -acceptors, including styrenes, afforded the desired products in high yields, whereas unactivated olefins were less efficient in this process.

Recently, Boger employed a SmI₂-mediated 6-*endo*-trig radical cyclization of a methyldithiocarbonate precursor onto an activated olefin in the final steps of the total synthesis of kopsinine (Scheme 179).⁴¹⁶ The use of SmI₂-HMPA promoted the desired cyclization in 75% yield, furnishing the desired product as a single diastereoisomer. The authors proposed that the mechanism involves kinetic protonation of the Sm(III)

Scheme 178. Cross-Coupling of 1-Difluorophenylsulfanylmethyl Radical by Reutrakul and Pohmakotr



Scheme 179. Alkyl Dithiocarbonate/ α,β -Unsaturated Ester Cross-Coupling in the Total Synthesis of Kopsinine by Boger



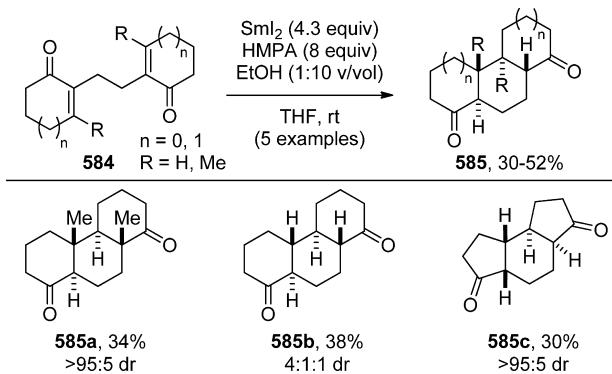
enolate from the more accessible convex face of the molecule. Other radical promoters, such as (TMS)₃SiH, provided the desired product in a comparable yield but with much lower diastereoselectivity.

3.4.2. Reductive Dimerization of Radicals Generated from α,β -Unsaturated Carbonyls. Reductive dimerization of α,β -unsaturated carbonyl derivatives mediated by SmI₂ has emerged as an attractive method to functionalize carbonyl compounds at the β -position and rapidly build up molecular complexity from relatively simple starting materials. The use of SmI₂ is advantageous over other methods in terms of mild, nontoxic (cf., Bu₃SnH/benzene), and user-friendly (cf., electrochemical processes) reaction conditions.

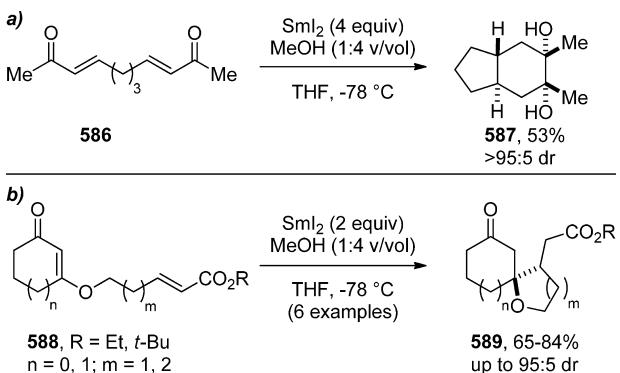
In 2007, Handy reported a comprehensive study on the intramolecular reductive cyclization of cyclic enones using SmI₂-HMPA system with EtOH as a proton source (Scheme 180).⁴¹⁷ Other reaction conditions (proton sources, temperature, mode of addition) proved less effective. Despite modest yields, the tricyclic products were formed with high stereoselectivity, generating up to four adjacent stereocenters in a single transformation. Nagaoka reported a related intramolecular cyclization of bis- α,β -unsaturated esters with the SmI₂-Sm-MeOH system with good selectivity (not shown).⁴¹⁸

In 2009, Kilburn reported intramolecular dimerization of α,β -unsaturated enones and enoates using SmI₂-MeOH system (Scheme 181a).⁴¹⁹ In general, the dimerization was found to proceed with high diastereoselectivity; however, mixtures of products were formed depending on the type of α,β -unsaturated acceptor. Kilburn and Dixon extended this study to the preparation of spirocyclic ethers (Scheme 181b).⁴²⁰ The mechanism has been proposed to involve selective reduction of the cyclic β -alkoxyketone, followed by 5/6-*exo*-trig cyclization;

Scheme 180. Intramolecular Reductive Dimerization of Cyclic Enones by Handy



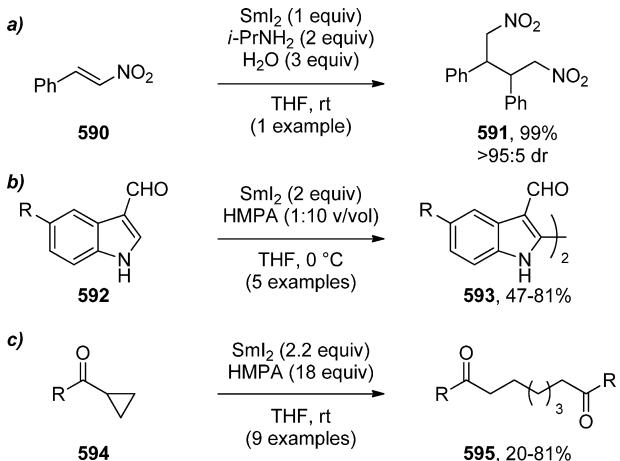
Scheme 181. Intramolecular Reductive Dimerization of Activated Olefins: (a) Kilburn; (b) Kilburn and Dixon



however, it is possible that reduction of the acyclic ester occurs first, especially given that the reduction of β -heteroatom-substituted Michael acceptors using SmI_2 is known to be problematic (see section 3.1.2). This reaction provides an alternative method for the preparation of spirocyclic ethers with high diastereoselectivity.

Several examples of intermolecular dimerization of α,β -unsaturated acceptors have been reported (Scheme 182).^{421–423} During studies on the optimization of nitro group

Scheme 182. Intermolecular Reductive Dimerizations: (a) α,β -Unsaturated Nitroalkanes by Hilmersson; (b) Indole-3-carbaldehydes by Banerji; (c) Cyclopropyl Ketones by Reissig

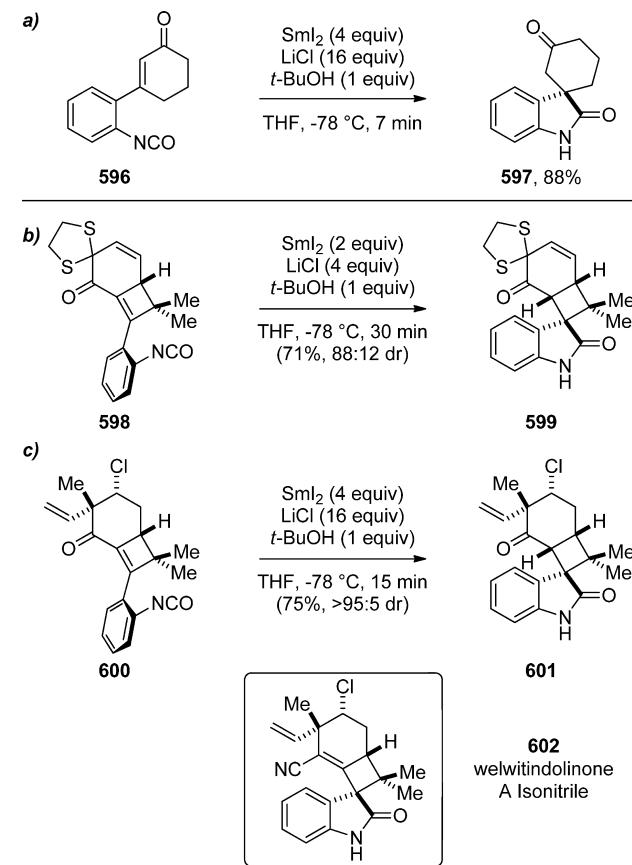


reduction with SmI_2 –amine– H_2O , Hilmersson found that the use of a limiting amount of the reagent affords β -coupled dimers in high yield and excellent diastereoselectivity (Scheme 182a).⁴²¹ Banerji reported the cross-coupling of indole-3-carbaldehydes under SmI_2 –HMPA reaction conditions (Scheme 182b).⁴²² In a related process, Reissig reported a comprehensive study of the radical dimerization of cyclopropyl ketones (Scheme 182c).⁴²³ This methodology furnishes 1,8-diketones in good yields and demonstrates that under the cited reaction conditions (SmI_2 –HMPA, room temperature), the rate of the cyclopropylcarbinyl radical anion opening ($k > 10^7 \text{ s}^{-1}$ at 25 °C)⁴²⁴ is faster than the direct pinacol coupling.

3.4.3. Cross-Coupling of Radicals Generated from α,β -Unsaturated Carbonyls with Various Acceptors. The SmI_2 -mediated cross-coupling of radicals generated from α,β -unsaturated carbonyl compounds occurring at the β -position is an attractive polarity-reversal alternative to nucleophilic additions of organometallic reagents to Michael acceptors.

In 2004, Wood reported SmI_2 –LiCl–*t*-BuOH-mediated cross-coupling of enones with isocyanates to afford spiro-oxindoles under very mild reaction conditions as part of synthetic studies toward welwitindolinone A isonitrile (Scheme 183).^{425–427} The isocyanate is generated *in situ* from the corresponding aniline. Interestingly, no reaction was observed with SmI_2 –THF. Careful optimization of the reaction conditions revealed that LiCl as an additive gave the highest yield, most likely due to increased redox potential of the Sm(II) reagent.⁴²⁵ On the basis of independent control reactions employing enone

Scheme 183. (a) Cross-Coupling between α,β -Unsaturated Ketones and Isocyanates by Wood; (b,c) Application in the Total Synthesis of Welwitindolinone A Isonitrile

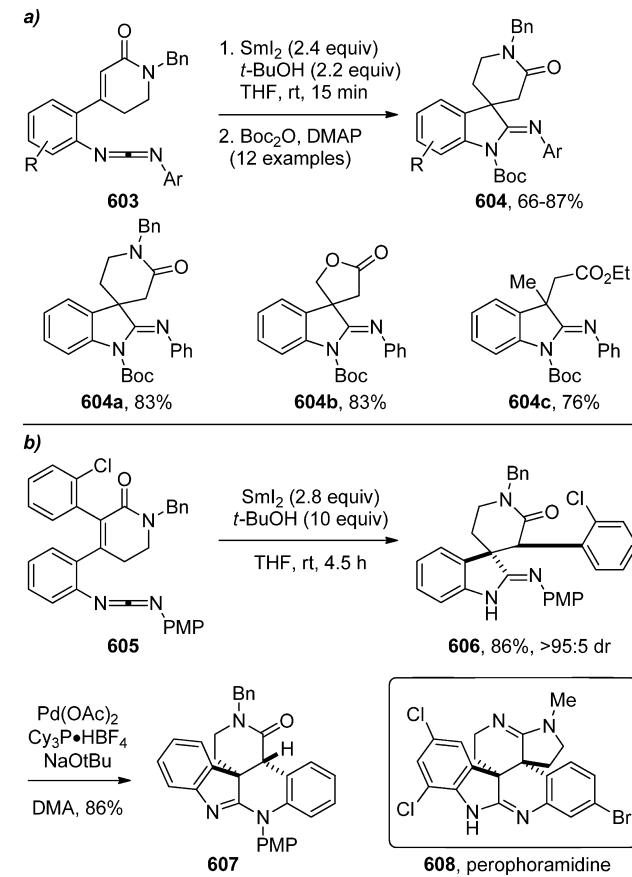


acceptor and phenyl isocyanate, the mechanism was proposed to involve reduction of the olefin and cross-coupling with the isocyanate. The reaction was applied in the synthesis of welwitindolinone A isonitrile (Scheme 183b,c),^{426,427} providing the desired products in excellent yields and diastereoselectivity. Particularly noteworthy is the fact that the reaction tolerates sensitive functionalities such as alkyl chloride and heteroatoms in the α -position to a ketone. This selectivity is in line with mechanistic studies on the SmI_2 –LiCl system by Flowers, showing that this reductant operates via inner-sphere electron transfer.¹⁰²

In a related reaction, Kim reported intramolecular cross-coupling of ketones with isothiocyanates using SmI_2 (not shown).⁴²⁸ This reaction provides a stereocontrolled access to α -hydroxythiolactams, and has been shown to proceed via cross-coupling of ketyl-type radicals and the isothiocyanate moiety, in line with studies by Wood on the cross-coupling of isocyanates.^{425–427}

Recently, Takemoto reported the first example of intramolecular cross-coupling of α,β -unsaturated amides with carbodiimides (Scheme 184a).⁴²⁹ It was shown that a variety

Scheme 184. (a) Cross-Coupling between α,β -Unsaturated Lactams and Carbodiimides by Takemoto; (b) Application in the Synthesis of Perphoramidine

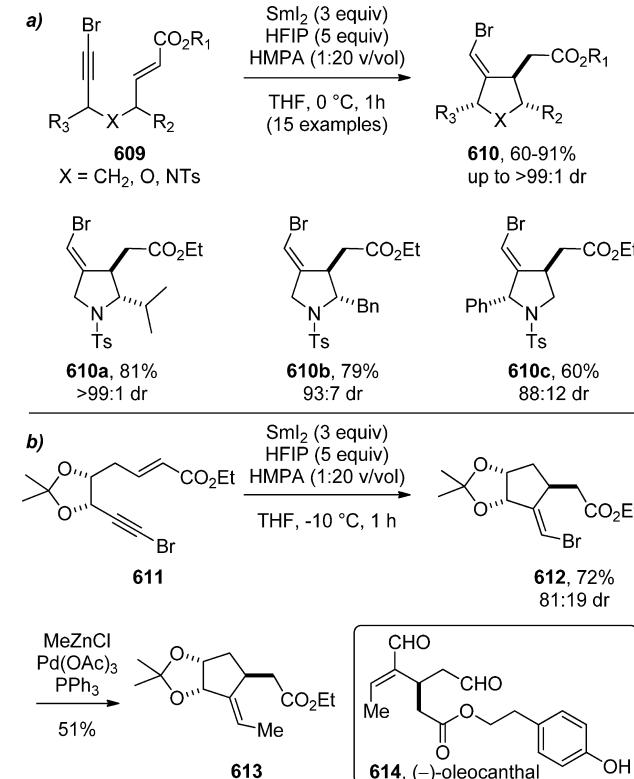


of additives to SmI_2 facilitated the reaction; however, the use of HMPA, *t*-BuOH, or *t*-BuOH/NiCl₂ provided the highest yields. Moreover, α,β -unsaturated lactone and acyclic ester substrates underwent cross-couplings in high yield. The reaction was subsequently applied in the synthesis of a core system of perphoramidine (Scheme 184b).⁴³⁰ The reductive cyclization

afforded a highly functionalized spiro-2-iminoindoline in excellent 86% yield as a single diastereoisomer. Notably, aryl chloride and lactam *N*-benzyl protecting group were tolerated by the reaction conditions. Isomerization of the α -stereocenter and Pd-catalyzed amidination completed the pentacyclic core of perphoramidine.

In 2010, Honda reported intramolecular cross-coupling of α,β -unsaturated esters with bromoalkynes mediated by SmI_2 –HMPA and HFIP as a proton source (Scheme 185). Di-

Scheme 185. (a) Cross-Coupling between α,β -Unsaturated Esters and Bromoalkynes by Honda; (b) Application in the Formal Total Synthesis of (–)-Oleocanthal



and trisubstituted five-membered cyclic products were obtained in high yields and excellent diastereoselectivity. The mechanism was proposed to proceed via a highly ordered transition state involving chelation between the alkynyl bromide, Sm(III), and the ester moiety. Impressively, reductive bromide removal was not observed, highlighting the mild reaction conditions afforded by the SmI_2 system. This methodology was recently applied in the formal total synthesis of (–)-oleocanthal by Honda.⁴³²

4. CROSS-COUPLING VIA IONIC INTERMEDIATES

Although SmI_2 is a single-electron reductant, the reduction of intermediate alkyl radicals via a consecutive electron transfer from SmI_2 generates organosamarium reagents, which are extremely valuable organometallics characterized by much higher chemoselectivity than zinc, magnesium, or lithium-based organometallics. In the last years, SmI_2 -mediated reactions that proceed via ionic mechanisms have been frequently employed for the synthesis of complex molecules, due to the orthogonal chemoselectivity of organosamarium reagents. Nevertheless, as compared to the SmI_2 -mediated cross-coupling reactions that proceed via radical pathways, these processes are under-

developed. In general, ionic reactions mediated by SmI_2 can be categorized into three classes: (i) Grignard and Barbier reactions; (ii) Reformatsky reactions; and (iii) aldol reactions.

4.1. Grignard and Barbier Reactions

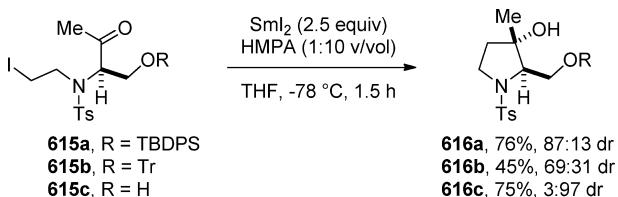
Depending on the type of procedure, organosamarium species can be prepared under Barbier (organosamarium generated in the presence of an electrophile) or Grignard conditions (preformation of the organometallic species followed by the addition of an electrophile), which can change the chemoselectivity of the desired process. The major advantages of using samarium organometallics involve mild and homogeneous reaction conditions, the use of functionalized precursors that are not compatible with other metals, and the ability to merge ionic reactions with radical mechanistic pathways in cascade sequences (see section 5). SmI_2 -mediated Barbier reactions have been reviewed in 1997 by Krief and Laval.¹³ The first intermolecular SmI_2 -mediated Barbier reaction was reported by Kagan in 1977.¹² The first intramolecular version of the SmI_2 -mediated Barbier reaction was reported by Molander in 1984.⁴³³ The SmI_2 -promoted Barbier reactions are typically carried out in the presence of additives such as HMPA, NiI_2 , or Fe(III) .³⁰ Irradiation with light has also been shown to increase the rate of generation of the organosamarium species.¹⁵⁸ Recently, Flowers reported an important study on the mechanism of SmI_2 -promoted, NiI_2 -catalyzed Barbier reactions.¹²² It was conclusively demonstrated that these reactions operate via a $\text{Ni}(0)/(II)$ catalytic cycle, with $\text{Sm}(II)/(III)$ acting as a terminal reductant. This discovery opens the door to the rational design of new ionic processes mediated by the $\text{SmI}_2/\text{NiI}_2$ couple.

For the purpose of this Review, SmI_2 -Barbier and SmI_2 -Grignard reactions are reviewed together in the section below. These reactions have been categorized into two classes: (i) intramolecular Barbier reactions; and (ii) intermolecular Grignard/Barbier reactions. Furthermore, the examples have been organized according to the ring size formed in the reaction (intramolecular variants) and the class of electrophile acceptor utilized in the addition of organosamarium species.

4.1.1. Intramolecular Barbier Reactions. In general, intramolecular SmI_2 -mediated Barbier reactions are very efficient for the synthesis of five- and six-membered rings using alkyl iodides or activated halides (e.g., benzylic, allylic) for the addition to ketone and aldehyde electrophiles. Moreover, several challenging examples for the synthesis of medium-sized rings and macrocycles have been reported in the past decade.

4.1.1.1. Intramolecular Cross-Coupling with Ketones and Aldehydes. Hamada reported a SmI_2 -mediated diastereoselective Barbier cyclization of an alkyl iodide onto a ketone to synthesize a functionalized pyrrolidine ring in the synthesis of polyoxypeptin antibiotics (Scheme 186).⁴³⁴ Reductive cyclization of the β -iodoamine precursor was effected by SmI_2 -HMPA at $-78\text{ }^\circ\text{C}$ giving product in good yield as a 97:3 mixture of

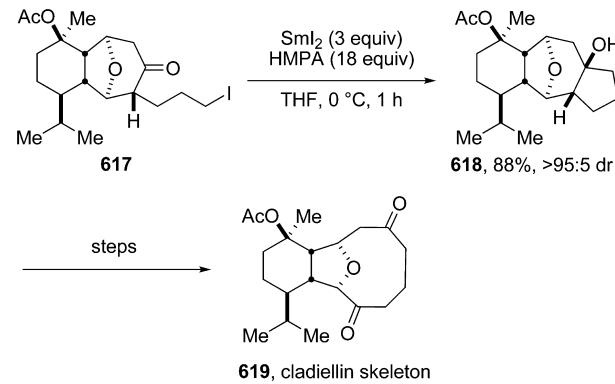
Scheme 186. Stereoselective Barbier/Ketone Cyclization in the Synthesis of Pyrrolidines by Hamada



diastereoisomers. The selectivity was proposed to result from coordination of the organosamarium intermediate to the hydroxyl group in a chair transition state. In agreement with this hypothesis, protected alcohols led to a reversal of selectivity.

In 2006, Molander employed a Barbier iodide/ketone cyclization to form a five-membered ring during the synthetic studies toward polyanthellin A, a cladiellin diterpene (Scheme 187).⁴³⁵ The use of the SmI_2 -HMPA system furnished the

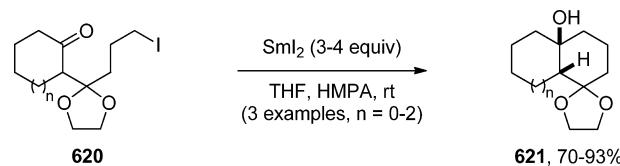
Scheme 187. Barbier/Ketone Cyclization in the Synthesis of Cladiellin Diterpenes by Molander



polycyclic skeleton in 88% yield as a single diastereoisomer. The originally planned SmI_2 -Barbier cyclization of an analogous alkyl iodide onto a less-reactive lactone to form a six-membered ring proved unsuccessful.

In 2005, Markó reported SmI_2 -Barbier cyclizations of iodoketones to generate bicyclic cyclohexanols (Scheme 188).^{436,437} Thus, treatment of iodide precursors with an excess of SmI_2 -HMPA led to smooth coupling to give cyclohexanols in good yields as single *cis*-diastereoisomers.

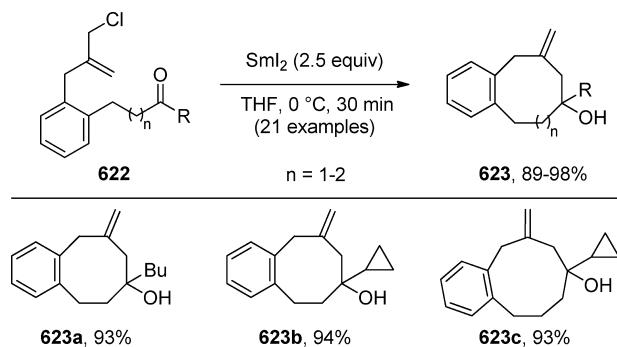
Scheme 188. Barbier/Ketone Cyclization for the Synthesis of Cyclohexanols by Markó



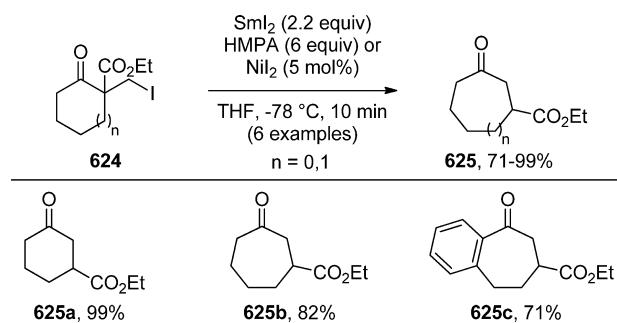
In 2004, Matsuda reported an efficient method for generating medium-sized rings utilizing the SmI_2 -mediated Barbier coupling of allyl chlorides and ketones (Scheme 189).⁴³⁸ Cyclizations were carried out under very mild conditions with the SmI_2 -THF system at $0\text{ }^\circ\text{C}$ to give cyclic alcohols. Various eight- and nine-membered carbocycles could be synthesized in excellent yields. The advantage of the protocol is that it does not require high-dilution conditions. The authors proposed a mechanism involving reduction of the allyl chloride moiety to a π -allyl radical, which undergoes rapid reduction to the π -allylsamarium, followed by 1,2-addition to the carbonyl. In agreement with this hypothesis, fragmentation of a cyclopropyl ring attached to the ketone was not observed.

SmI_2 -mediated Barbier coupling between halides and ketones has been used as part of two-step procedures to achieve one-carbon ring expansion of cyclic ketones via the intermediate cyclopropanols followed by fragmentation (Schemes 190 and 191).⁴³⁹⁻⁴⁴¹ Kim reported a SmI_2 -mediated Barbier coupling of

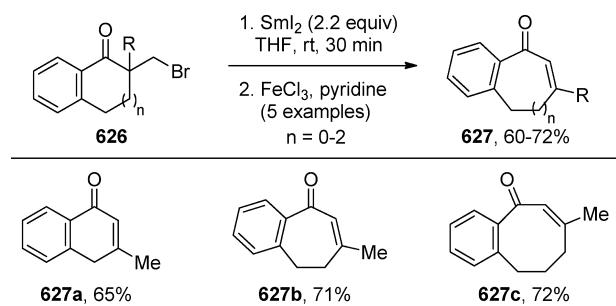
Scheme 189. Barbier/Ketone Cyclization for the Synthesis of Medium-Sized Rings by Matsuda



Scheme 190. Ring Expansion of Cyclic Keto-Esters via Barbier Cyclization/Fragmentation by Kim



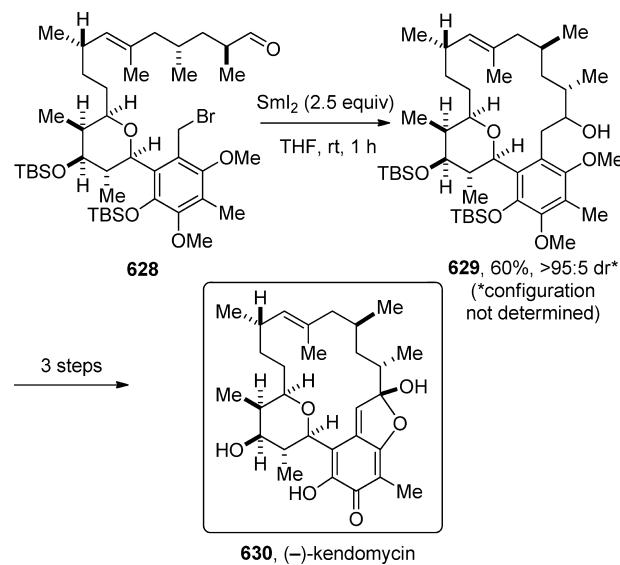
Scheme 191. Ring Expansion of Cyclic Ketones via Barbier Cyclization/Fragmentation by Hasegawa



α -iodomethyl β -ketoesters in the presence of SmI_2 –HMPA or SmI_2 – NiI_2 (Scheme 190).⁴³⁹ The ring expansion occurred in situ via an anionic mechanism. Six- and seven-membered ketones were efficiently prepared using this protocol.⁶ Hasegawa studied a one-carbon ring expansion using the SmI_2 –THF-mediated intramolecular Barbier coupling of unactivated α -bromomethylketones (Scheme 191).^{440,441} It was shown that the intermediate cyclopropanols could be isolated (as cyclopropyl silyl ethers) after the Barbier cyclization, followed by treatment with trimethylsilyl chloride. Ring expansion was achieved in a separate step via oxidative electron transfer using Fe(III) , Ce(IV) , or Mn(III) to furnish ring-expanded keto-enones in moderate to good yields. This second step could be incorporated into a one-pot procedure with FeCl_3 as a stoichiometric oxidant.

In two particularly impressive examples, the Panek group applied SmI_2 -mediated Barbier macrocyclizations to prepare 16- and 23-membered macrocycles during the final stages of total syntheses of (–)-kendomycin⁴⁴² and (–)-virginiamycin^{443,444} (Schemes 192 and 193). In 2008, they reported the total synthesis of (–)-kendomycin in which Barbier cyclization of a

Scheme 192. Barbier/Aldehyde Macrocyclization in a Total Synthesis of (–)-Kendomycin by Panek



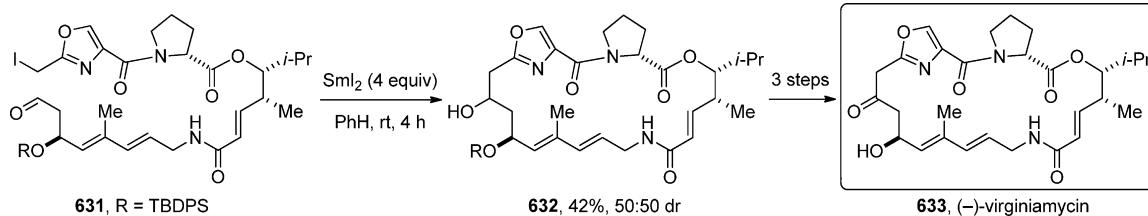
benzyl bromide was employed to build a 16-membered macrocycle (Scheme 192).⁴⁴² Treatment of an advanced intermediate bearing protected alcohol groups with SmI_2 in THF at room temperature led to a smooth macrocyclization and delivered the desired product in 60% yield. The configuration of the alcohol was inconsequential and not determined, but a single diastereoisomer was formed in this reaction. This intermediate was elaborated to (–)-kendomycin in three further steps.

In 2010, Panek reported the total synthesis of (–)-virginiamycin using a SmI_2 -mediated Barbier cyclization of a benzylic iodide to form a 23-membered macrocycle (Scheme 193).^{443,444} Treatment of the iodo-aldehyde precursor with SmI_2 in benzene gave the desired alcohol in 42% yield as a 50:50 mixture of diastereoisomers. The use of benzene over the more commonly employed THF was critical to obtain synthetically useful yields. For example, in THF (dilute solution, 0.002 M), only trace quantities of the product were formed with the dehalogenated methyloxazole and reduced aldehyde contributing to the majority of the mass balance. The authors proposed that in THF the intermediate benzylic radical was quenched by hydrogen-atom abstraction from the solvent, in agreement with the generation of the organosamarium intermediate as being the rate-determining step of the reaction. After the successful coupling, the synthesis of (–)-virginiamycin was completed following three further steps.

4.1.1.2. Intramolecular Cross-Coupling with Esters/Amides. SmI_2 -promoted intramolecular Barbier addition into an ester group constitutes a convenient method for the synthesis of cyclic ketones. The first general procedure for this type of nucleophilic acyl substitution was reported by Molander in 1993.⁴⁴⁵ As expected, addition to esters is much more challenging than the addition of organosamarium to ketones or aldehydes due to the lower electrophilicity of carboxylic acid precursors.

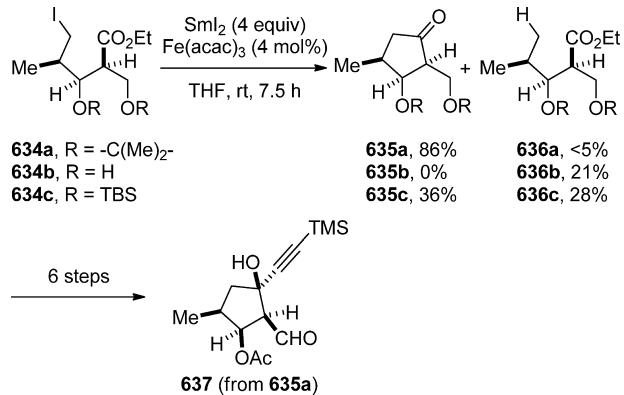
In 2007, Uemura reported a SmI_2 -mediated Barbier cyclization of alkyl iodide onto ester to synthesize the cyclopentane fragment of kansuinine A, a jatrophane diterpene.⁴⁴⁶ Reductive cyclization of the acetonide-protected δ -iodo ester precursor was promoted by SmI_2 – $\text{Fe}(\text{acac})_3$ (4 mol %) at room temperature to give the cyclopentanone in good yield (Scheme 194). The use of

Scheme 193. Barbier/Aldehyde Macrocyclization in a Total Synthesis of (-)-Virginiamycin by Panek



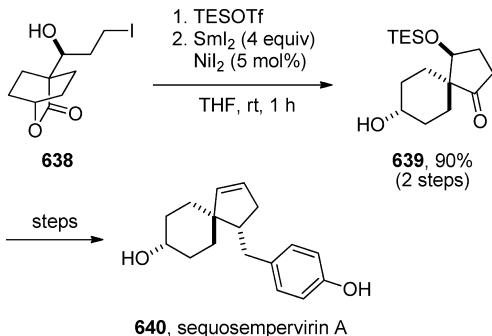
a rigid acetonide protecting group was crucial to prevent reductive dehalogenation.

Scheme 194. Barbier/Ester Cyclization in the Synthesis of Kansuine A by Uemura



In 2011, Honda reported the intramolecular SmI₂-mediated Barbier reaction of a bicyclic lactone containing an alkyl iodide tether at the bridgehead position in the construction of the spiro[4.5]decane ring system, which was a key intermediate in the total synthesis of sequosempervirin A, a taxodiaceae norlignan (Scheme 195).⁴⁴⁷ δ-Iodolactone reacted smoothly

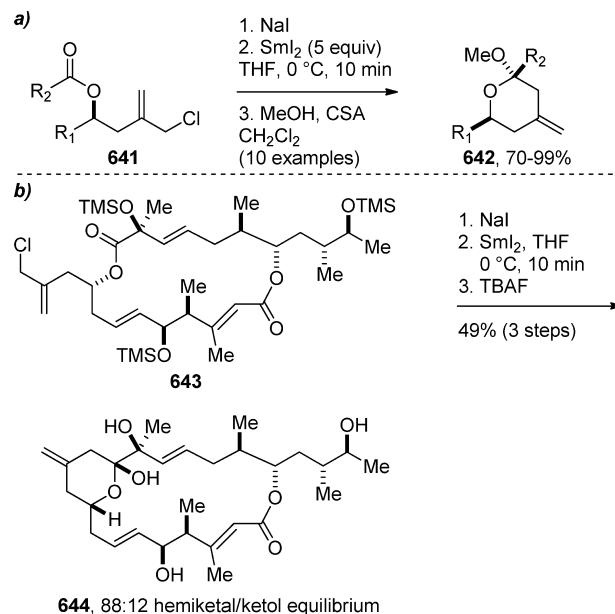
Scheme 195. Barbier/Lactone Cyclization in the Synthesis of Sequosempervirin A by Honda



with SmI₂ in the presence of NiI₂ (5 mol %) at room temperature to deliver the spirocyclic ketone in 86% yield. The authors noted that protection of the secondary alcohol was essential to prevent quenching of the organosamarium species (cf., 636b in Scheme 194). The spirocyclic ketone was elaborated to complete the total synthesis of sequosempervirin A in seven steps.

Keck reported a convergent synthesis of chiral 2,6-disubstituted-2-methoxy-4-methylenepyrans that relied on a SmI₂-mediated Barbier cyclization of allylic iodides onto esters (Scheme 196a).⁴⁴⁸ Extensive optimization revealed that SmI₂-THF at 0

Scheme 196. (a) Synthesis of 2-Alkoxyxypyrans via Barbier/Ester Cyclization by Keck; (b) Application in Studies toward Structure Elucidation of Iriomoteolide by Yang

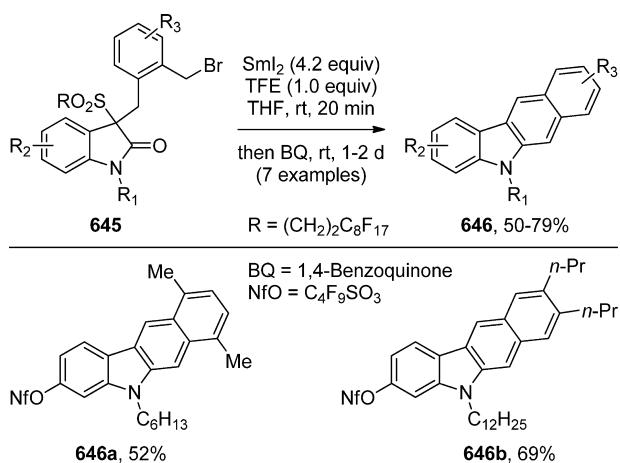


°C was the best system for the cyclization, while the use of SmI₂–NiI₂, SmI₂–HMPA, Mg, In, or *t*-BuLi resulted in much lower yields. A variety of allylic iodides underwent the SmI₂-promoted coupling to afford chiral pyrans in excellent yields. The Barbier cyclization was applied to the synthesis of a simplified bryostatin AB ring system and a macrocyclic 2-methoxyxypiran as single diastereoisomers. Recently, Yang reported application of this methodology to the synthesis of a cyclic hemiketal in their studies toward structural elucidation of iriomoteolide, an amphotidinium macrolide with potent cytotoxic activity (Scheme 196b).⁴⁴⁹

In 2012, Turner and Procter reported a rare example of the SmI₂-mediated Barbier cyclization onto an amide in the synthesis of benzo[*b*]carbazole capped oligothiophene semiconductors (Scheme 197).⁴⁵⁰ The cyclization was carried out as a part of a domino sequence involving SmI₂-mediated removal of the fluorous tag, followed by a Barbier cross-coupling between benzylic bromide and indolin-2-one to give the corresponding hemiaminal. Dehydration under the reaction conditions, followed by oxidation in the presence of benzoquinone, afforded the desired product in good overall yields.

4.1.1.3. Intramolecular Cross-Coupling with α,β-Unsaturated Systems. SmI₂-promoted Barbier-type reactions have also been applied in a variety of intramolecular conjugate addition reactions. In general, these reactions proceed via a stepwise halide or pseudohalide reduction to give the organosamarium species, followed by the conjugate addition, in which 1,4/1,2-selectivity is controlled by the steric and electronic properties of

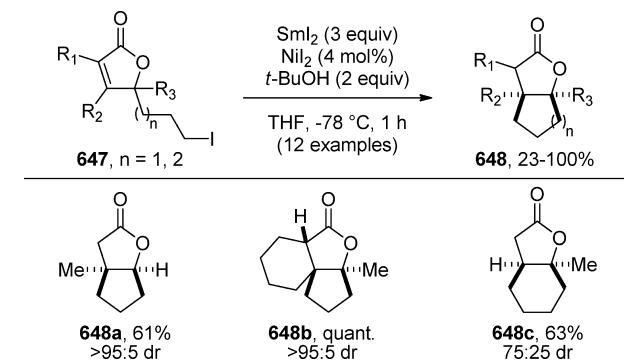
Scheme 197. Barbier/Amide Cyclization in the Synthesis of Benzo[*b*]carbazoles by Turner and Procter



the substrate. In some cases, a radical mechanism cannot be excluded; however, this pathway is unlikely based on the effect of Sm(II) additives observed in these reactions.

In 1997, Molander reported that SmI_2 in conjunction with a catalytic amount of NiI_2 promotes conjugate additions of alkyl iodides onto a variety of acyclic Michael acceptors, including esters, amides, and nitriles.⁴⁵¹ In 2002, Molander demonstrated that this reagent could also be applied to the conjugate addition of alkyl halides onto α,β -unsaturated lactones (Scheme 198).⁴⁵²

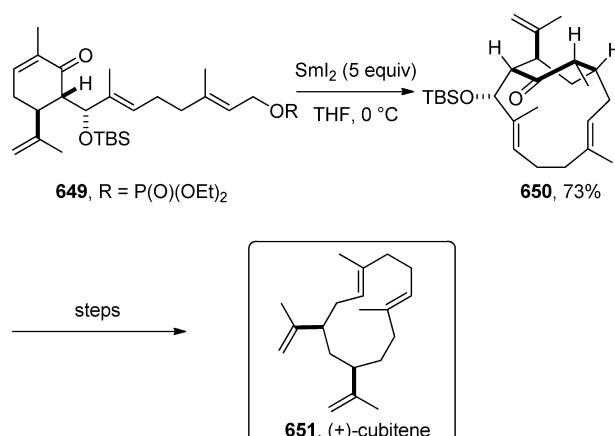
Scheme 198. Barbier Coupling with α,β -Unsaturated Lactones by Molander



Treatment of the five-membered lactones containing an iodoalkyl tether at the γ -position with SmI_2 in the presence of NiI_2 and, in some cases, $t\text{-BuOH}$ gave fused bicyclic lactones in good yields. The reaction was used for the construction of five- and six-membered rings; when longer tethers were applied, only reduction of the iodide was observed. One example of the conjugate addition to a six-membered lactone was also reported.

Lindel demonstrated that allylic phosphates serve as efficient precursors to organosamarium nucleophiles for 1,4-addition to enones using SmI_2 –THF.^{453–455} Reductive Barbier cyclization of (*S*)-carvone-derived diterpenoid allyl phosphate proceeded in modest yield and high regio- and diastereoselectivity. This reaction has been used as a key step in the enantioselective total synthesis of (+)-cubitene (Scheme 199).⁴⁵⁵ Interestingly, only reductive cleavage of the phosphate group was observed in the corresponding fully saturated substrates.⁴⁵³ Retro-aldol fragmentation occurred in allylic phosphates in which the organo-

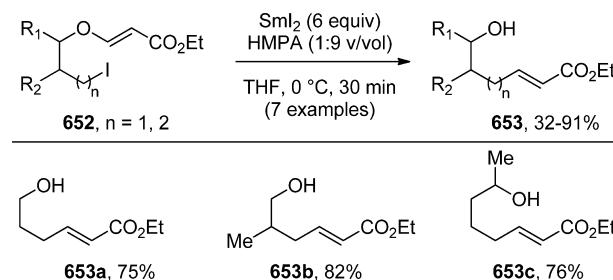
Scheme 199. Barbier Conjugate Addition of Allylic Phosphate in the Total Synthesis of Cubitene by Lindel



samarium was positioned in the vinylogous position to the aldo carbon–carbon bond.⁴⁵⁴

Kang and Choi reported a tandem intramolecular SmI₂-Barbier conjugate addition/elimination reaction of iodo- β -alkoxyacrylates (Scheme 200).⁴⁵⁶ The system based on SmI₂

Scheme 200. Barbier Conjugate Addition into α,β -Unsaturated Esters/Fragmentation by Kang and Choi



HMPA led to a smooth Barbier cyclization at 0 °C, while the concomitant alkoxide elimination afforded the transposition products after protonation. Three- and four-carbon tether lengths were tolerated in the reaction; however, when longer tethers were used, only reduction of the iodide was observed. The reaction provides a useful method for the synthesis of 6- and 7-hydroxy- α,β -unsaturated esters.

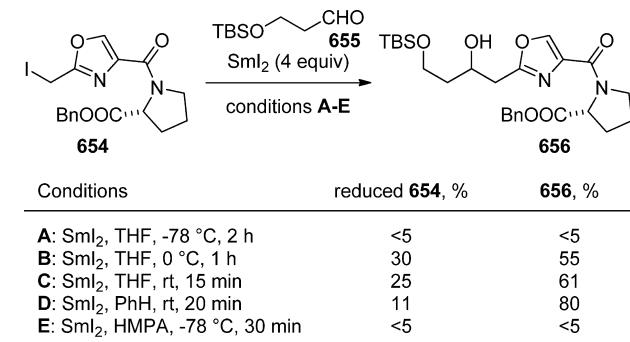
4.1.2. Intermolecular Grignard and Barbier Reactions

The use of intermolecular SmI_2 -mediated Grignard/Barbier reactions is more limited due to multiple side reactions that can occur during the process. In the past decade, this class of reactions has been used primarily in cases when lithium or magnesium organometallics did not afford the required efficiency and/or selectivity. However, several new types of organo-samarium precursors have been developed, which significantly expand the scope of SmI_2 -intermolecular Barbier/Grignard reactions, and include: (i) α -halomethyl heterocycles that contain a heterotom at the position allowing precomplexation of SmI_2 ; (ii) allylic phosphates; (iii) allylic toluates; and (iv) N,S -acetals. Moreover, applications in complex target synthesis have been reported, and the potential of these reactions to rapidly build up molecular complexity in multicomponent reactions has also been documented.

4.1.2.1. Intermolecular Cross-Coupling with Ketones and Aldehydes. In 2011, Panek reported a SmI_2 -mediated inter-

molecular Barbier reaction in their model studies toward the total synthesis of (*-*)-virginiamycin (Scheme 201).⁴⁴⁴ Careful

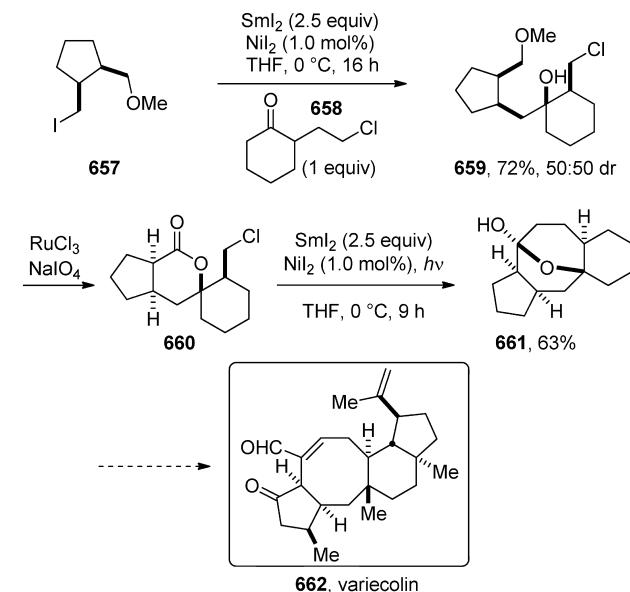
Scheme 201. Intermolecular Barbier/Aldehyde Cross-Couplings by Panek



optimization of the reaction conditions in the cross-coupling of an α -iodomethyloxazole with a TBS-protected aldehyde revealed that SmI_2 in benzene was the preferred reagent system for this transformation, providing the final product in 80% yield as a mixture of diastereoisomers. It is worth noting that, although SmI_2 -THF afforded the desired product in only slightly diminished yield, no reaction was observed at -78 °C, while the use of the more reducing SmI_2 -HMPA resulted in complete decomposition of the substrate. In addition, the SmI_2 procedure provides higher yields than other metal promoters tested, such as $\text{Et}_2\text{Zn}/\text{RhCl}(\text{PPh}_3)_3$, *n*-BuLi, *t*-BuLi, *i*-PrMgCl, and activated zinc.

One of the most elegant examples of the use of a SmI_2 -promoted intermolecular Barbier reaction was reported by Molander in the total synthesis of a variecolin model system, exploiting the different reactivity of SmI_2 toward alkyl iodides and chlorides (Scheme 202).⁴⁵⁷ Intermolecular Barbier addition of a primary alkyl iodide to 2-(2-chloroethyl)cyclohexanone occurred under SmI_2 - NiI_2 conditions at 0 °C to give the product in 72% yield as a 50:50 mixture of diastereoisomers. After

Scheme 202. Sequential Barbier/Ketone-Barbier/Lactone Coupling in Studies toward Variecolin by Molander



oxidative cyclization using $\text{RuCl}_3/\text{NaIO}_4$, the intramolecular Barbier cyclization of an alkyl chloride onto an ester was performed using SmI_2 in the presence of NiI_2 under photochemical conditions affording the polycyclic lactol product in 63% yield.

Nicolaou reported an impressive application of the SmI_2 -mediated intermolecular Barbier reaction in the total synthesis of the polyketide macrocycle monorhizopodin to couple two advanced fragments: an α -iodomethyloxazole and a hindered α,α -dimethyl-substituted aldehyde (Scheme 203).⁴⁵⁸ The authors selected SmI_2 to perform the coupling due to its mild nature that prevented elimination of the alcohol product to form 2-vinyloxazole. Thus, treatment of the two fragments with SmI_2 -THF at room temperature for 5 min resulted in an efficient reaction to give the desired product in 56% as a 50:50 mixture of diastereoisomers. The synthesis of monorhizopodin was completed in a further 11 steps.

Recently, Zhang and Yang reported the intermolecular SmI_2 -mediated Barbier reaction to couple two advanced intermediates during the synthesis of (*-*)-alotaketal A (Scheme 204).⁴⁵⁹ Using an excess of SmI_2 , 1,2-addition of an allyl iodide into an α,β -unsaturated bicyclic lactone was achieved with the SmI_2 -THF system at 0 °C. The unstable lactol product was directly subjected to OTBS deprotection and spirocyclization to give the final product in 40% yield.

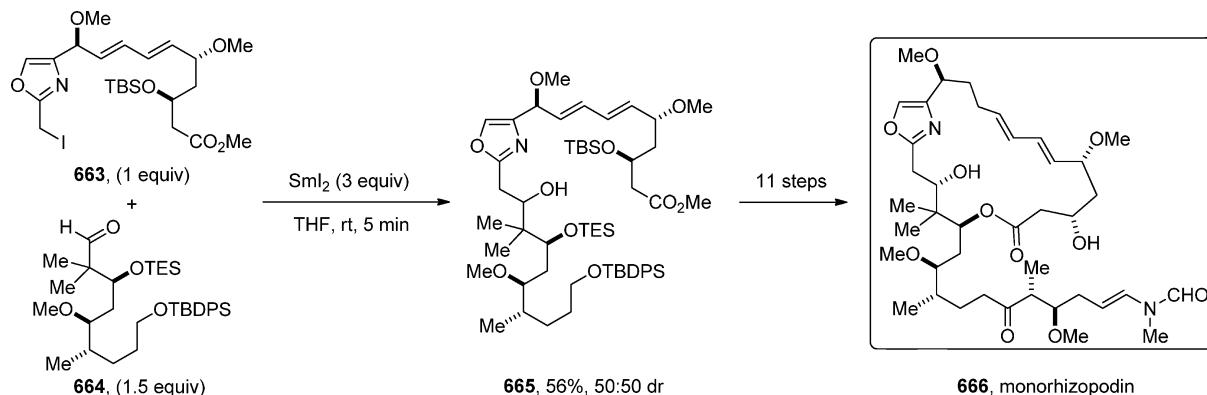
SmI_2 -mediated intermolecular Barbier reactions have been reported as a convenient method to functionalize steroids under mild conditions (Schemes 205 and 206).^{460,461} In 2006, Li described the synthesis of 7-substituted-5-androstene derivatives using SmI_2 -HMPA (Scheme 205).⁴⁶⁰ The addition of functionalized halides having additional chloride or an α -benzyl group was achieved in good yield (not shown). In 2011, Poirier reported intermolecular Barbier additions during the synthesis of estradiol derivatives using SmI_2 to form hindered tertiary alcohols (Scheme 206).⁴⁶¹ A variant utilizing Sm/HgCl_2 (2 equiv/20 mol %) was developed for the addition of several benzylic halides that did not give coupling products under SmI_2 or SmI_2 -HMPA conditions (not shown).⁴⁶¹

Fang reported the intermolecular SmI_2 -Barbier reaction of ferrocenyl carbonyls followed by in situ dehydration for the preparation of ferrocenyl alkenes with applications in material science (Scheme 207).⁴⁶² The reaction is promoted by SmI_2 in THF at 0 °C and provides high yields of dehydrated products. The coupling was also achieved using catalytic SmI_2 and magnesium as a stoichiometric reductant.

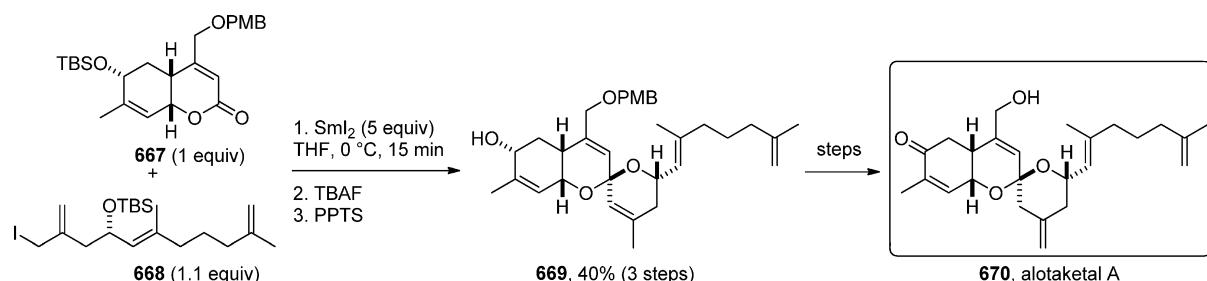
α -Halomethyl-substituted heterocycles, such as oxazoles, oxathiazoles, oxadiazoles, and pyridines, have emerged as a new class of substrates for SmI_2 -Barbier reactions (Schemes 208–211).^{463–467} In 2003, Zhang reported the coupling of 2-chloromethylbenzoxazoles and benzothiazoles with ketones and aldehydes (Scheme 208).⁴⁶³ Treatment of a mixture of the two coupling partners with SmI_2 at room temperature for 5 min resulted in smooth Barbier addition to give homobenzylic alcohol products. In 2005, Zhang extended this methodology to include oxadiazoles (Scheme 209).⁴⁶⁴ Although a variety of aliphatic carbonyls furnished cross-coupling products in good yields, aromatic ketones and aldehydes were not tolerated due to competing pinacol coupling.

Independently, Williams reported the reductive coupling of α -iodomethyloxazoles and thiazoles with aliphatic aldehydes under the SmI_2 -THF reaction conditions (Scheme 210).⁴⁶⁵ The reaction is compatible with a range of functional groups, including aromatic esters and allyl ethers; however, aromatic

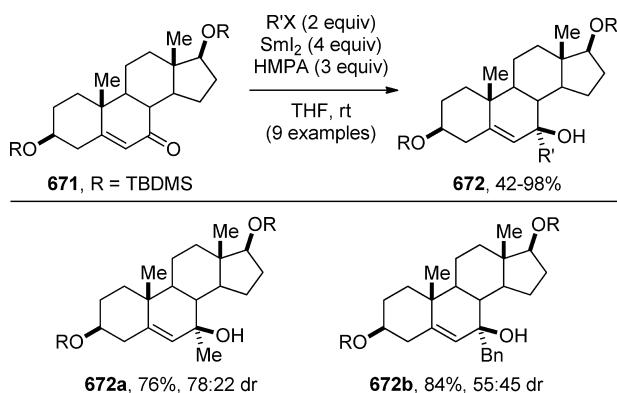
Scheme 203. Barbier/Aldehyde Coupling in the Total Synthesis of Monorhizopodin by Nicolaou



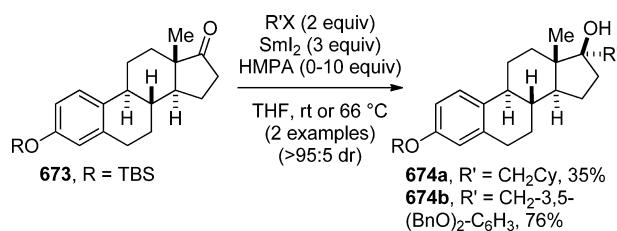
Scheme 204. Intermolecular Barbier/Lactone Coupling in the Synthesis of Alotaketal A by Zhang and Yang



Scheme 205. Intermolecular Barbier/Ketone Couplings with Polycyclic Enones by Li



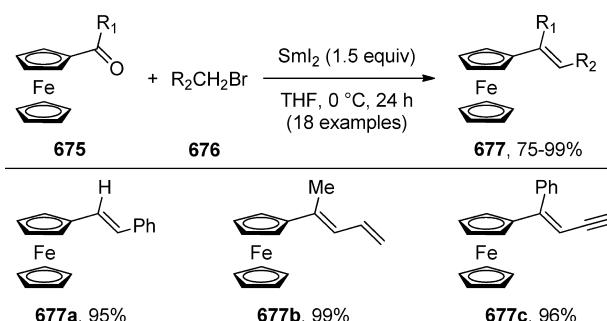
Scheme 206. Intermolecular Barbier/Ketone Couplings of Estradiol Derivatives by Poirier



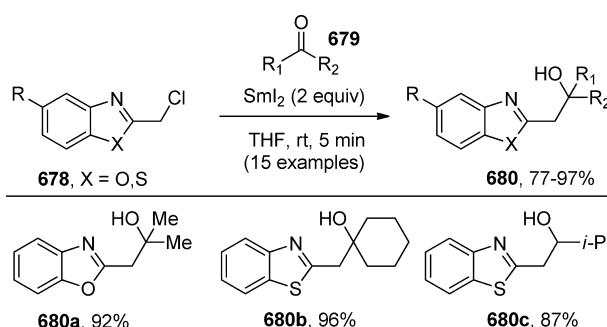
aldehydes gave no coupling products due to dimerization. High yields were obtained for C-2 and C-4 α -halomethyl-substituted oxazoles. This methodology was utilized in the total synthesis of phorbazole A to incorporate an oxazole ring in excellent yield.⁴⁶⁶

In 2005, Helquist reported a related SmI_2 -mediated Barbier reaction for coupling of 2-acetoxymethylpyridines with ketones

Scheme 207. Barbier Couplings with Ferrocenyl-Derived Aldehydes and Ketones by Fang

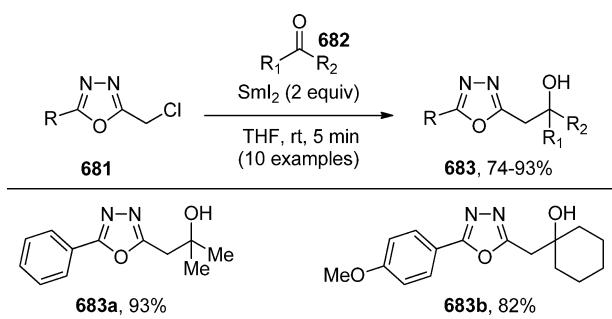


Scheme 208. Intermolecular Barbier/Couplings of 2-Chloromethylbenzoxazoles/Benzothiazoles by Zhang

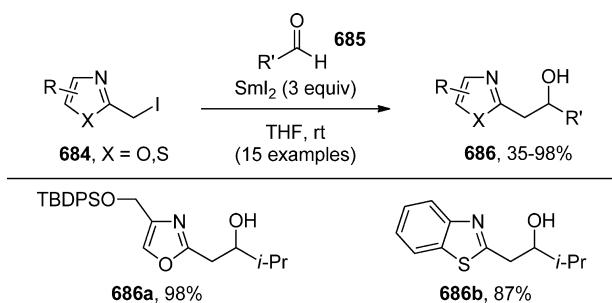


and aldehydes (Scheme 211).⁴⁶⁷ A variety of other 2-acetoxymethyl-substituted electron-deficient heterocycles, including quinolines, isoquinolines, and 1,10-phenanthrolines, are also successful substrates for the reaction. This method tolerates aromatic ketones and aldehydes; however, lower yields are obtained due to competing pinacol coupling. The mechanism

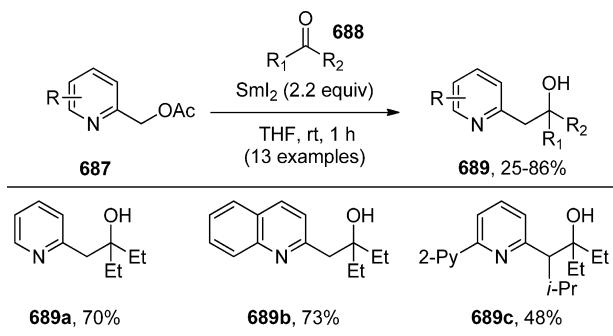
Scheme 209. Intermolecular Barbier Couplings of 2-Chloromethyloxadiazoles by Zhang



Scheme 210. Intermolecular Barbier Couplings of 2-Chloromethyloxazoles with Aldehydes by Williams



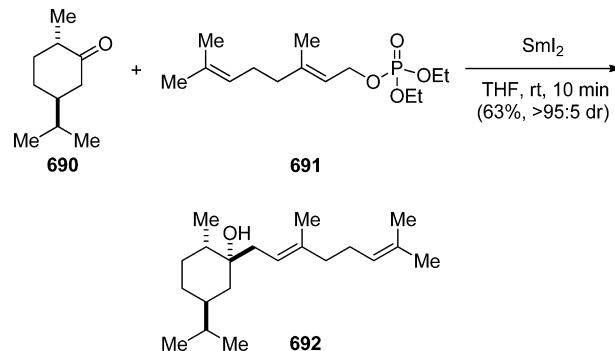
Scheme 211. Intermolecular Barbier Couplings of 2-Acetoxyethylpyridines and Related Heterocycles by Helquist



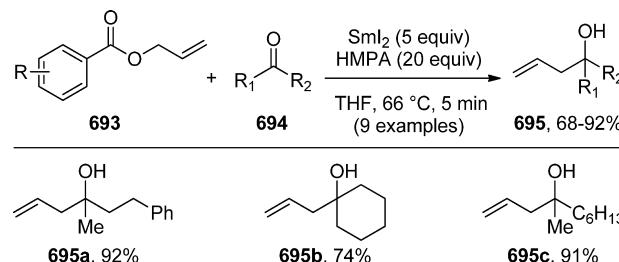
was proposed to involve chelation between samarium, the ring nitrogen, and benzylic acetate. In line with this hypothesis, 4-substituted pyridines gave no coupling products.

In the past decade, allylic phosphates and toluates have been successfully utilized for SmI_2 -mediated intermolecular Barbier reactions (Schemes 212 and 213).^{468,469} In 2005, Lindel reported cross-coupling of an allylic phosphate derived from geraniol with tetrahydrocarvone to give the Barbier product in 63% yield as a single diastereoisomer during the synthetic studies toward cladiellane terpenoids (Scheme 212).⁴⁶⁸ Extended reaction times resulted in lower yields of the coupling product. In 2009, Markó reported Barbier coupling of allyl toluates with ketones promoted by the SmI_2 –HMPA system (Scheme 213).⁴⁶⁹ The reaction requires elevated temperatures to initiate the coupling and generally proceeds in good yield. A variety of aliphatic ketones coupled under the reaction conditions; however, the coupling of aromatic ketones and aldehydes has not been reported. The coupling using activated *p*-trifluoromethylbenzoate precursors does not require the HMPA additive. A practical

Scheme 212. Barbier Coupling of Allylic Phosphates by Lindel



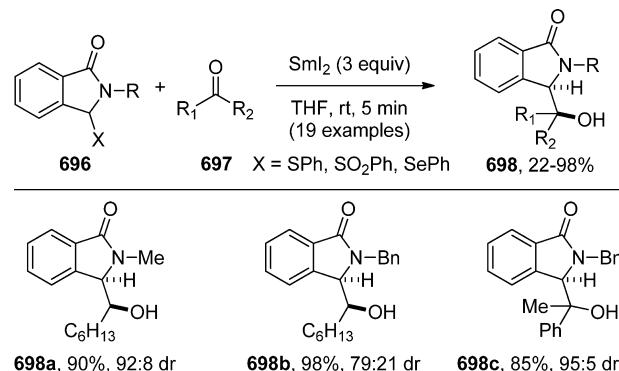
Scheme 213. Barbier Coupling of Toluate Esters by Markó



advantage of using the phosphate and toluate precursors for SmI_2 -mediated Barbier reactions lies in their superior stability as compared to the commonly employed allyl iodides.

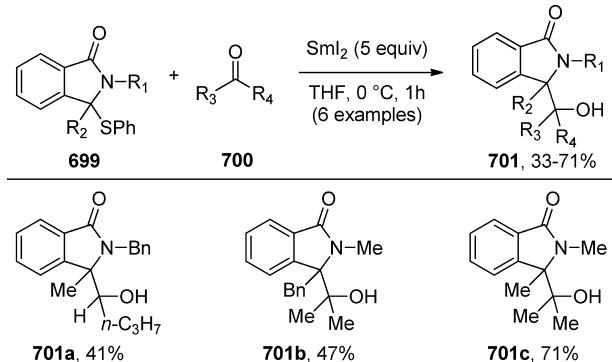
4.1.2.2. Miscellaneous Examples. In 2001, Yoda reported the first SmI_2 -mediated Barbier-type coupling of *N,S*-acetals with ketones and aldehydes to give hydroxyalkylated lactams in generally good yields and modest stereoselectivity (Scheme 214).⁴⁷⁰ In 2003, the reaction was extended to the cross-coupling

Scheme 214. Cross-Coupling of *N,S*-Acetals with Ketones and Aldehydes by Yoda

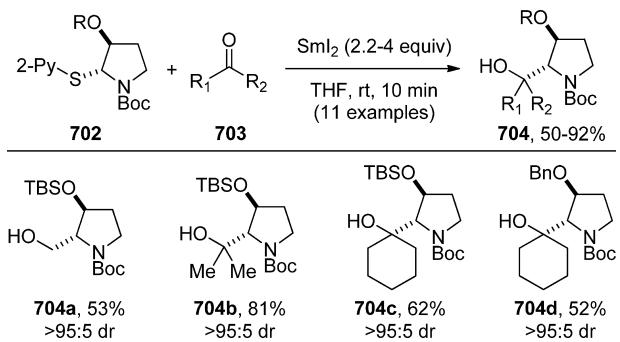


of quaternary *N,S*-acetals leading to the construction of α -hydroxyalkylated lactams bearing vicinal quaternary centers; however, the cross-coupled products were formed with low selectivity with respect to protonation of the organosamarium intermediate (Scheme 215).⁴⁷¹ In 2005, Huang significantly extended the utility of SmI_2 -mediated intermolecular Barbier couplings of *N,S*-acetals with ketones and aldehydes by introducing 2-pyridyl-*N,S*-acetals derived from Boc-pyrrolidine as synthetic imine equivalents (Scheme 216).⁴⁷² The reaction was shown to proceed via the organosamarium intermediate, which is stabilized toward β -elimination by a five-membered chelate with the Boc group. Cross-coupling of chiral 3-

Scheme 215. Cross-Coupling of Substituted *N,S*-Acetals with Ketones and Aldehydes by Yoda



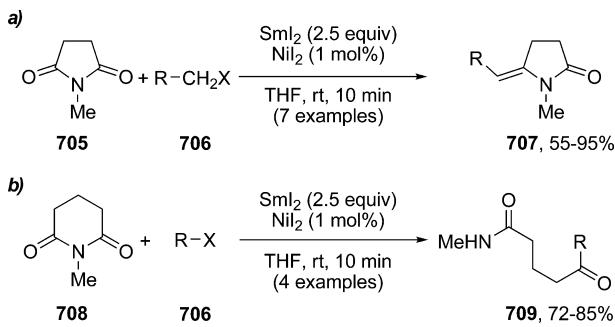
Scheme 216. Cross-Coupling of *N,S*-Acetals with Ketones and Aldehydes by Huang



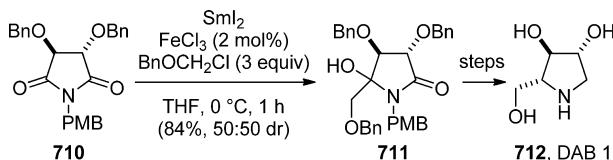
hydroxypyrrolidinyl precursors was achieved in high yields and with excellent *trans*-diastereoselectivity (cf., Schemes 147–149, section 3.3.1).

Imides have been successfully utilized as carbonyl group electrophiles in the SmI_2 -mediated intermolecular Barbier-type couplings (Schemes 217 and 218).^{473,474} Namy reported the

Scheme 217. Barbier Addition to Imides by Namy: (a) Pyrrolidine-2,5-dione; (b) Piperidine-2,6-dione



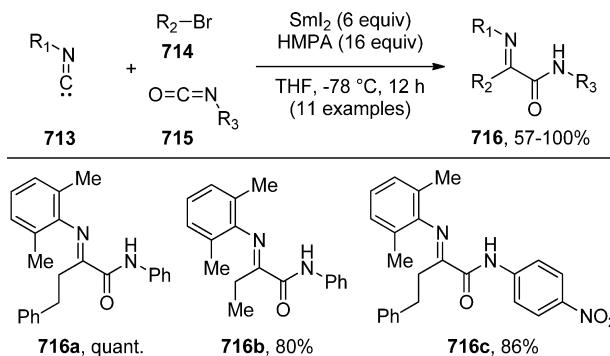
Scheme 218. Intermolecular Imide/Barbier Coupling in the Synthesis of DAB 1 by Huang



addition of alkyl halides to *N*-methylsuccinimide and *N*-methylphthalimide using SmI_2 and a catalytic amount of NiI_2 (Scheme 217).⁴⁷³ The products of the addition to the five-membered lactams were stable to the reaction conditions and underwent dehydration during the workup to give exocyclic enamides. In contrast, the corresponding hemiaminals in the six-membered ring system were shown to collapse to afford 1,5-ketoamides in good yields. In 2007, Huang reported the cross-coupling of benzyloxymethyl chloride with a chiral *N*-PMB protected imide during a total synthesis of DAB 1, a naturally occurring aza-sugar (Scheme 218). Treatment of the imide with SmI_2 – FeCl_3 in the presence of the alkyl chloride delivered the desired product in 84% yield. From this intermediate, DAB 1 was obtained in four further steps.

Recently, Takahashi reported an inventive one-pot, three-component SmI_2 -mediated sequential coupling between alkyl bromides, isocyanides, and isocyanates to furnish iminocarboxamides in high yields (Scheme 219).⁴⁷⁵ The mechanism involves

Scheme 219. Three-Component Barbier Coupling with Isocyanides and Isocyanates by Takahashi

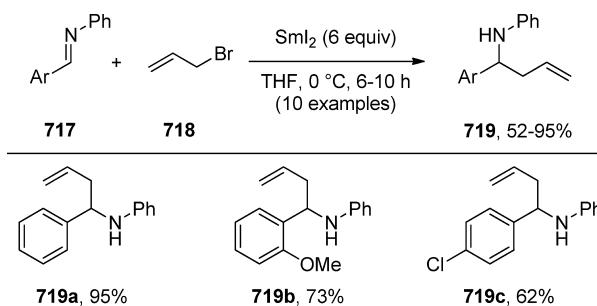


Barbier-type addition of the organosamarium nucleophile to the isocyanide to give imidoysamarium(III), which is trapped by the isocyanate. Optimization of the reaction conditions revealed that HMPA is crucial to obtain high yields of the imidoysamarium. The substrate scope is broad and includes sterically hindered 2,6-disubstituted phenyl isocyanides and isocyanates. Kim reported a SmI_2 -mediated Barbier-type addition of allyl bromide to aldimines to generate aromatic homoallyl amines in good yields (Scheme 220).⁴⁷⁶ The addition of HMPA is not required; however, allyl chlorides undergo coupling in low yield.

4.2. Reformatsky Reactions

The SmI_2 -mediated Reformatsky reaction has been well-established as a mild method for the generation of Sm(III)

Scheme 220. Barbier Coupling of Allylbromide with Aldimines by Kim



enolates from the corresponding α -halocarbonyl compounds. The vast majority of SmI_2 –Reformatsky reactions involve α -halo esters as precursors; however, the use of other α -halo carbonyls has also been reported. The first SmI_2 -mediated Reformatsky reaction was reported by Kagan in 1977.^{1,2} The first asymmetric version of the SmI_2 -mediated Reformatsky reaction was reported by Fukuzawa in 2000.⁴⁷⁷ A review on the generation and reactivity of Sm(III) enolates, including Reformatsky reactions, has been published.³¹

In this section, examples have been categorized into intramolecular and intermolecular Reformatsky reactions, and further arranged by the type of α -halo precursor for the generation of Sm(III) enolate. This classification is justified by the different reactivity of ester, amide, and ketone enolates, which have been the most common classes of precursors for the SmI_2 -mediated Reformatsky reactions reported in the past decade. It is worth noting that Reformatsky reactions constitute a major subclass of Sm(III) -mediated aldol-type reactions. Other examples of Sm(III) -mediated aldol reactions are reviewed separately in the following section.

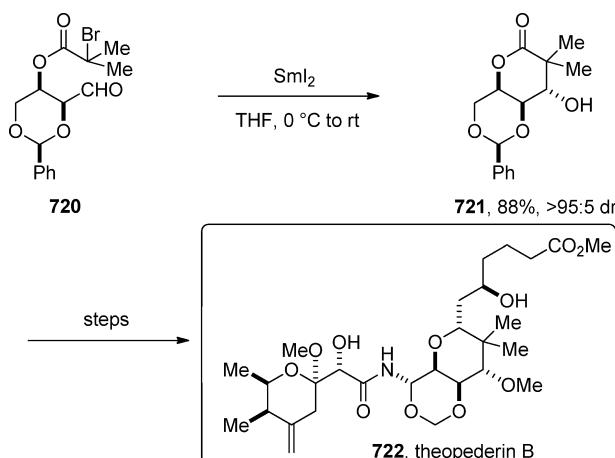
The advantages of using SmI_2 -mediated Reformatsky reactions include exceptionally mild reaction conditions and orthogonal chemoselectivity to other methods of enolate generation. In general, these reactions do not require additives and proceed under cryogenic conditions, tolerating a wide range of functional groups that can be reduced with other SmI_2 systems.

4.2.1. Intramolecular Reformatsky Reactions. Four classes of substrates have been used for the intramolecular SmI_2 -mediated Reformatsky-type reactions in the past decade: (i) α -halo esters; (ii) α -halo amides; (iii) α -halo ketones; and (iv) α -halo nitriles.

4.2.1.1. Cross-Coupling of α -Halo Esters. Several research groups have utilized the intramolecular SmI_2 -mediated Reformatsky reaction of α -halo esters to prepare six-membered lactones. In general, these reactions are highly diastereoselective as a result of a Sm(III) -chelated chairlike transition state.⁴⁷⁸

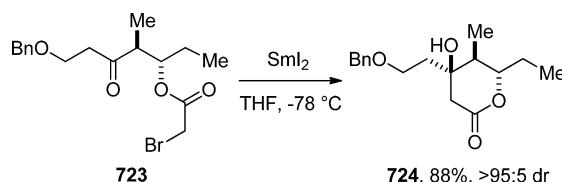
In 2009, Nakata reported the use of the SmI_2 -mediated Reformatsky reaction to synthesize a six-membered lactone intermediate in the total synthesis of theopederin B (Scheme 221).⁴⁷⁹ Treatment of the trisubstituted α -bromo ester with SmI_2 in THF afforded the desired lactone in 88% as a single α -axial diastereoisomer. In 2011, Maier reported the preparation of a six-

Scheme 221. Ester Reformatsky Reaction in the Synthesis of Theopederin B by Nakata



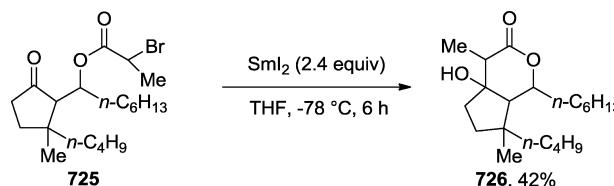
membered lactone in the synthetic studies toward leiodermatolide (Scheme 222).⁴⁸⁰ A smooth intramolecular Reformatsky

Scheme 222. Ester Reformatsky Reaction in Studies toward Leiodermatolide by Maier



cyclization onto a ketone took place at -78°C to give the axial alcohol in 88% yield as a single diastereoisomer. Wu reported the intramolecular SmI_2 -mediated Reformatsky reaction of a cyclic ketone to form a bicyclic lactone in studies toward the total synthesis of clavulactone (Scheme 223).⁴⁸¹ Treatment of the

Scheme 223. Ester Reformatsky Reaction in Studies toward Clavulactone by Wu^a

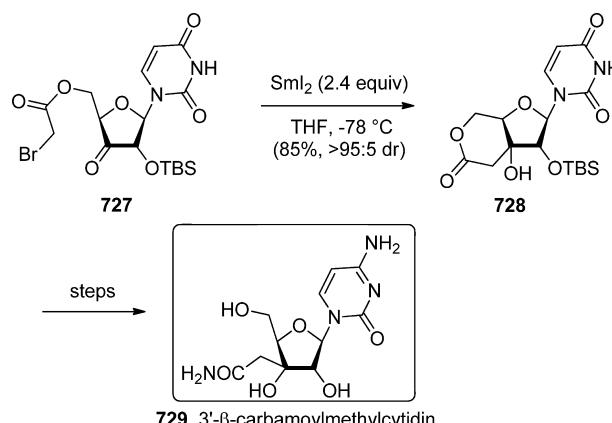


^aStereochemistry not given.

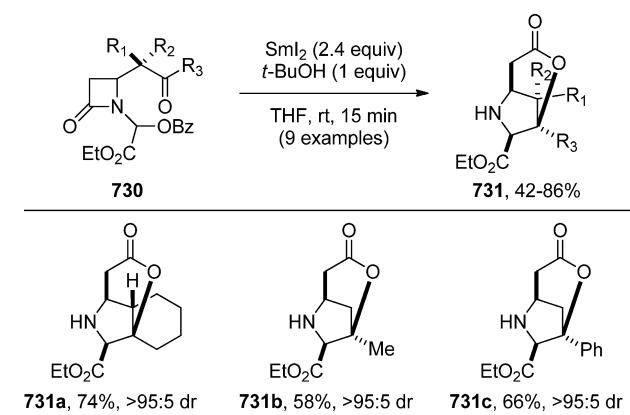
ketone precursor with SmI_2 –THF at -78°C gave bicyclic lactone in modest yield. In 2013, Schultz reported the use of an intramolecular SmI_2 -mediated Reformatsky reaction to prepare δ -trichloromethyl- δ -valerolactones in modest yields and good diastereoselectivity (not shown).⁴⁸²

The SmI_2 -promoted intramolecular Reformatsky reaction has been used for the synthesis of nucleosides and amino acid derivatives (Schemes 224 and 225).^{483,484} In 2006, Ichikawa and Matsuda reported the intramolecular Reformatsky reaction as the key step to introduce a carbon substituent at the 3-position in the synthesis of 3'- β -carbamoylmethylcytidine, a branched-chain nucleoside with potent antitumor activity (Scheme 224).⁴⁸³ Treatment of the α -bromo ester precursor with SmI_2 –THF at -78°C led to smooth cyclization to give the product in 85%

Scheme 224. Ester Reformatsky Reaction in the Synthesis of 3'- β -Carbamoylmethylcytidine by Ichikawa and Matsuda



Scheme 225. Ester Reformatsky/Acyl Transfer Reaction for the Synthesis of Prolines by Skrydstrup

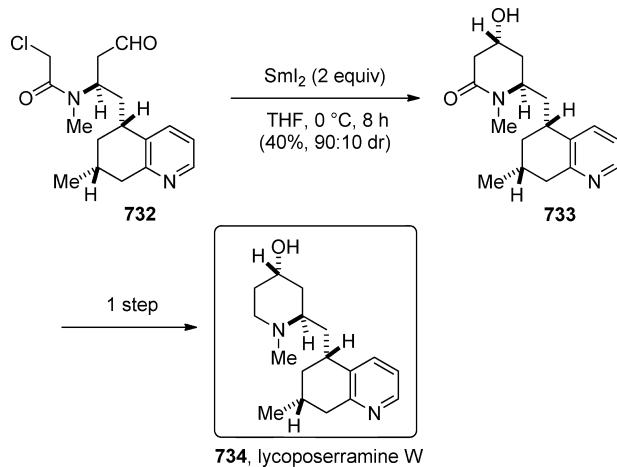


yield as a single α -diastereoisomer. Zinc-promoted reaction failed to provide the desired product. In 2002, Skrydstrup reported highly diastereoselective SmI_2 -mediated intramolecular Reformatsky reactions of 1-(benzoyloxymethyl)azetidin-2-ones 730 containing a carbonyl tether followed by N \rightarrow O acyl transfer to give functionalized proline derivatives (Scheme 225).⁴⁸⁴ The reaction proceeded in good yields and excellent diastereoselectivities with the SmI_2 - t -BuOH system. The role of t -BuOH was proposed to involve protonation of the basic amide intermediate formed after the acyl transfer step. A mechanism involving coordination of the samarium enolate to the β -lactam carbonyl was suggested to explain the stereochemical outcome different from that of the reaction involving lithium enolates.

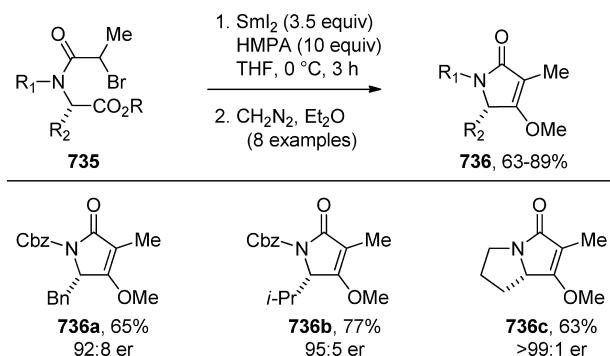
4.2.1.2. Cross-Coupling of α -Halo Amides. In 2007, Takayama reported the SmI_2 -mediated Reformatsky reaction of an α -chloro amide to construct the piperidine ring in the total synthesis of lycoposerramine W (Scheme 226).⁴⁸⁵ The reaction proceeded in modest yield and high diastereoselectivity. The authors noted that SmI_2 freshly prepared from Sm metal and CH_2I_2 gave the best results.

In 2012, Pettus reported a general approach to 3-methyl tetramic acids using SmI_2 -mediated Reformatsky cyclizations of α -bromo amides onto esters as the key step (Scheme 227).⁴⁸⁶ Careful optimization of the reaction conditions demonstrated that carbamate protecting group at the nitrogen, HMPA additive,

Scheme 226. Ester Reformatsky Reaction in the Total Synthesis of Lycoposerramine W by Takayama



Scheme 227. Amide Reformatsky Reaction for the Synthesis of 3-Methyl Tetramic Acids by Pettus



and the reaction temperature of 0 °C are critical to obtain high yields. The reaction was applied to a variety of chiral α -bromo amides prepared from amino acids to give the desired products in good yields and high enantiomeric ratios. Importantly, racemization of the products was not observed under the SmI_2 -reaction conditions to a significant extent. In contrast, exposure of the tetramic acids to KOt-Bu (2 equiv) resulted in complete racemization in less than 60 s.

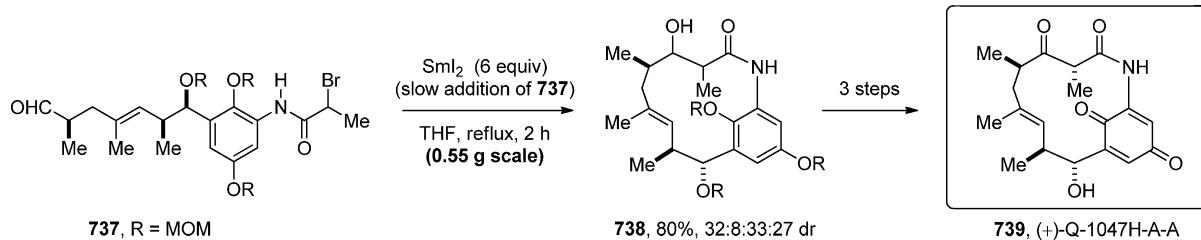
In 2013, Chen and Yang reported an impressive intramolecular SmI_2 -Reformatsky reaction of an α -bromo acetamide as a key step to close the 13-membered macrocycle in the asymmetric total synthesis of ansamacrolactams (+)-Q-1047H-A-A and (+)-Q-1047H-R-A (Scheme 228).⁴⁸⁷ Extensive screening of the reaction conditions revealed that reduction of the aldehyde to alcohol and dehalogenation of the α -bromoester were the only products formed under standard conditions for SmI_2 -mediated reactions. The authors found that slow addition of the amide precursor to the refluxing solution of SmI_2 afforded the desired product in 80% yield as a mixture of diastereoisomers.

In 2008, Procter reported a SmI_2 -mediated Reformatsky-type reaction of an amide bearing an α -sulfanyl fluorous tag in the synthesis of spirocyclic oxindoles (Scheme 229).⁴⁸⁸

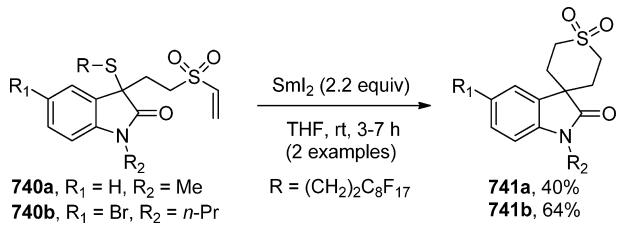
4.2.1.3. Cross-Coupling of α -Halo Ketones. In 2002, Deslongchamps demonstrated an elegant example of the SmI_2 -mediated intramolecular Reformatsky reaction to synthesize a tetracyclic intermediate in studies toward the cardenolide ring system (Scheme 230).⁴⁸⁹ Treatment of an α -bromo ketone precursor with SmI_2 -THF at -78 °C led to the desired product in 84% yield as a single diastereoisomer. The cyclization of an analogous substrate bearing a 3-furyl substituent at the β -position of the ketone acceptor was carried out under both kinetic and thermodynamic control with high selectivity (not shown).

4.2.1.4. Cross-Coupling of α -Halo Nitriles. In 2004, Omura and co-workers utilized a SmI_2 -mediated Reformatsky-type macrocyclization of an α -bromo $\alpha,\beta,\gamma,\delta$ -unsaturated nitrile as a key step in the total synthesis of borrelidin (Scheme 231).^{490,491} The reaction was performed using SmI_2 -HMPA at high dilution at -78 °C. Under these conditions, only traces of the dehalogenated product were formed; however, isomerization of the α,β -double bond occurred to a significant extent. Optimization in a model system revealed that SmI_2 -HMPA gives much higher yields than other metal promoters, including CrCl_2 , Zn/Cu , and $\text{Et}_2\text{Zn/RhCl(PPh}_3)_3$. Moreover, high concentration of HMPA ($\text{HMPA/SmI}_2 = 4:1$) was shown to promote substrate degradation, likely due to the high redox potential of the SmI_2 -HMPA reagent. From the cross-coupling

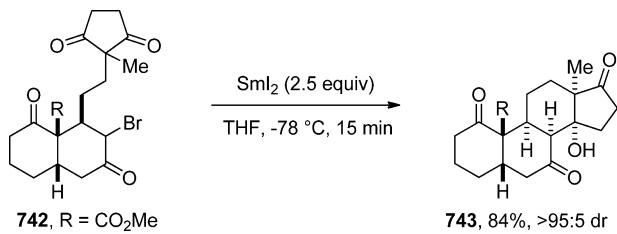
Scheme 228. Amide Reformatsky Reaction in the Total Synthesis of Ansamacrolactams by Chen and Yang



Scheme 229. Amide Reformatsky-Type Reaction for the Synthesis of Spirocyclic Oxindoles by Procter



Scheme 230. Ketone Reformatsky Reaction for the Synthesis of Cardenolides by Deslongchamps



product, the synthesis of borrelidin was completed in five further steps.

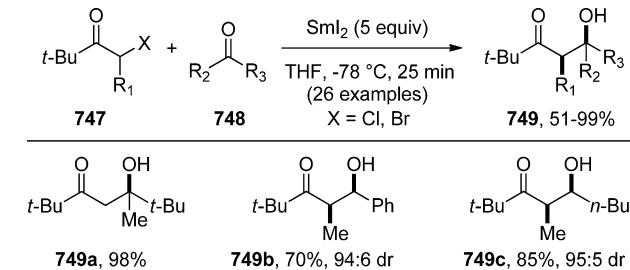
4.2.2. Intermolecular Reformatsky Reactions. In general, intermolecular SmI₂-mediated Reformatsky reactions are more challenging than the intramolecular versions due to competing side reactions, such as carbonyl reduction, pinacol coupling, self-condensation of α -halo carbonyls, and Evans–Tishchenko-type reactions.⁴⁹² In the past decade, intermolecular SmI₂-mediated Reformatsky reactions of several classes of precursors have been reported: (i) α -halo ketones; (ii) α -halo esters; (iii) α -halo amides; and (iv) miscellaneous examples.

The major advancements in this area include: (i) successful Reformatsky reactions of sterically hindered α -halo precursors; (ii) the use of Reformatsky reactions for C-glycosidations of complex carbohydrates; (iii) the use of chiral auxiliaries to control diastereoselectivity; and (iv) development of a series of

Reformatsky reactions of small molecule precursors for the synthesis of advanced intermediates.

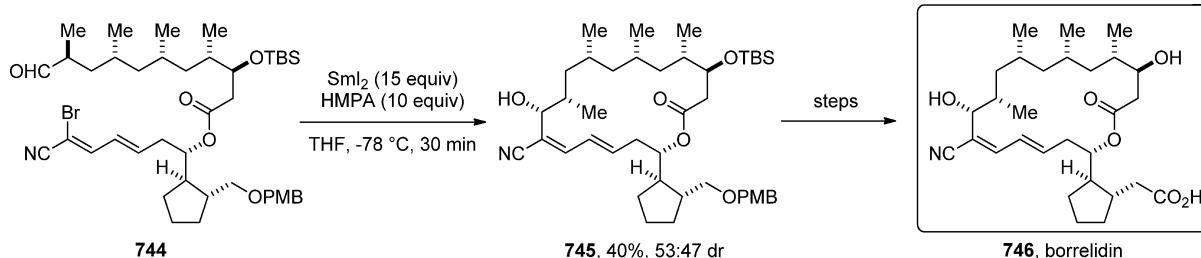
4.2.2.1. Cross-Coupling of α -Halo Ketones. Jamison significantly extended the scope of SmI₂-mediated intermolecular Reformatsky reactions of α -halo ketones by demonstrating that these reactions can be used to couple two extremely hindered ketones (Scheme 232).⁴⁹³ The reactions require excess

Scheme 232. Intermolecular Reformatsky Reaction of Hindered Ketones by Jamison

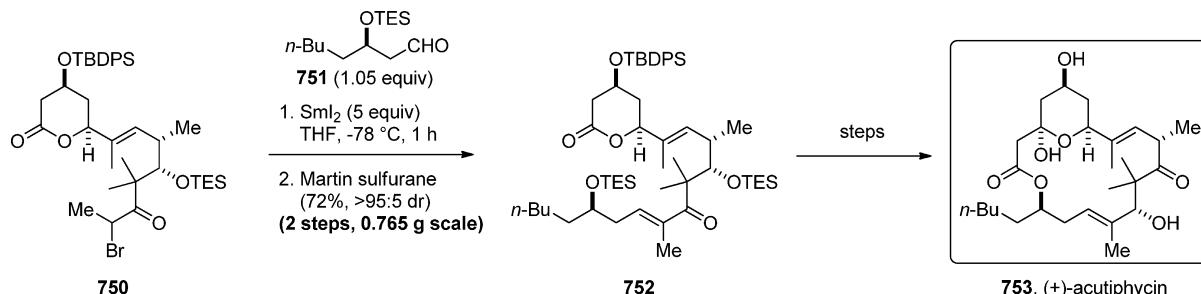
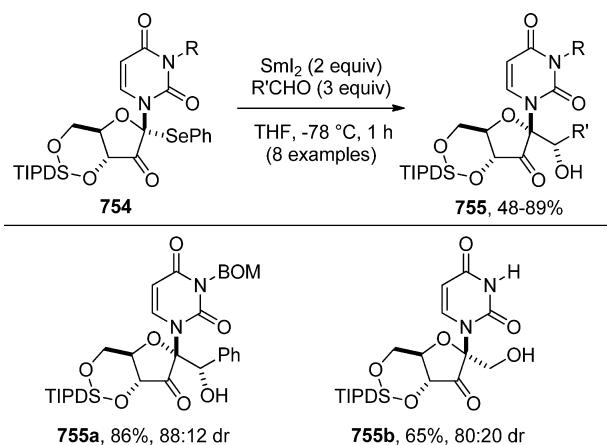
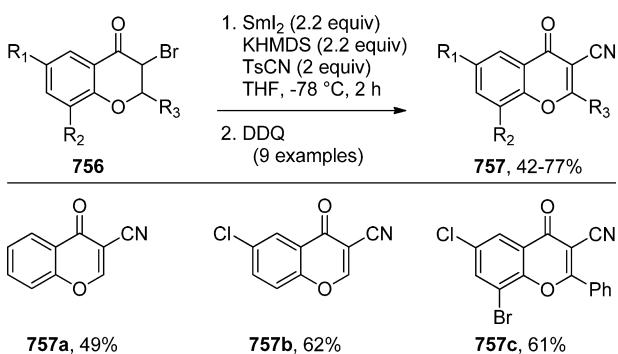


of SmI₂ (5 equiv) and proceed smoothly at -78°C . The presence of a quaternary carbon in the α -halo ketone component prevents possible side reactions. The products are formed in high yields and excellent *syn*-diastereoselectivity. Both α -bromo and α -chloroketones can be used as Sm(III)-enolate precursors. Dehydration using Martin sulfurane affords access to a variety of hindered enones with excellent (*E*)-selectivity. Jamison showcased this methodology in the total synthesis of (+)-acutiphycin (Scheme 233).^{494,495} Treatment of a hindered α -bromo- α' , α' -dimethylketone with SmI₂–THF at -78°C in the presence of an aldehyde, followed by dehydration, gave the advanced intermediate in excellent yield, as a single diastereoisomer. The synthesis of the natural product was completed following a further nine steps.

The intermolecular SmI₂-mediated Reformatsky reactions of α -halo ketones have been applied in the synthesis of biologically active compounds (Schemes 234 and 235).^{496,497} In 2002, Shuto and Matsuda reported a highly diastereoselective SmI₂-promoted Reformatsky reaction of 1-phenylseleno-2-keto-nucleosides for

Scheme 231. $\alpha,\beta/\gamma,\delta$ -Unsaturated Nitrile Reformatsky Reaction in the Synthesis of Borrelidin by Omura

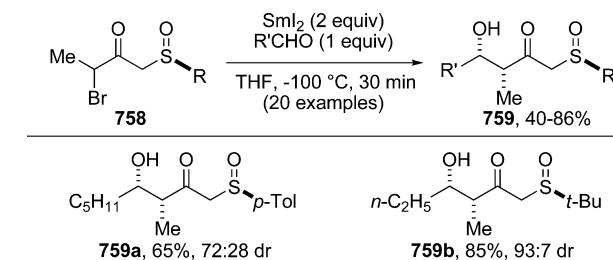
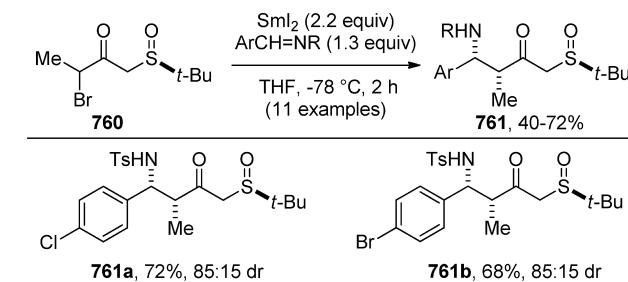
Scheme 233. Intermolecular Ketone Reformatsky Reaction in the Synthesis of (+)-Acutiphycin by Jamison

Scheme 234. Intermolecular Reformatsky Reaction of α -Selenoketones by Shuto and MatsudaScheme 235. Intermolecular Ketone Reformatsky-Type Reaction Promoted by $\text{SmI}_2/\text{KHMDS}$ by Hilmersson

the synthesis of branched uridine derivatives (Scheme 234).⁴⁹⁶ The samarium(III) enolate was generated by the reductive cleavage of the phenylseleno group using SmI_2 -THF at -78°C . Enolate trapping was achieved with aliphatic and aromatic aldehydes in good yields and excellent stereoselectivity. The authors proposed that the high diastereoselectivity of these reactions is a result of a chelation-controlled transition state. In 2010, Hilmersson reported the intermolecular Reformatsky-type reactions of α -bromo ketones with tosyl cyanide for the synthesis of chromanones with potential biological activity using a $\text{SmI}_2/\text{KHMDS}$ reagent (1:1 in THF) (Scheme 235).⁴⁹⁷ The reaction proceeded in high yields with a variety of alkyl and aryl chromanones. A one-pot protocol involving oxidation of the coupling products with DDQ was employed to give the more stable chromones. The authors proposed that the active $\text{Sm}(\text{II})$ reagent utilized in this procedure is the heteroleptic $\text{Sm}(\text{HMDS})_2$.

I complex; other SmI_2 -based systems were tested and proved less effective.

Colobert has pioneered the SmI_2 -mediated intermolecular Reformatsky reactions of chiral α -halo- α' -sulfinyl ketones (Schemes 236 and 237).⁴⁹⁸⁻⁵⁰⁰ In 2003, this group reported

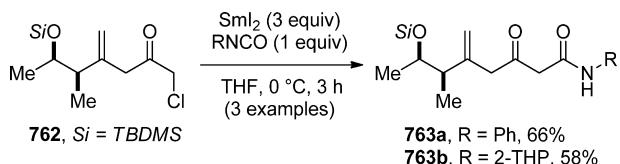
Scheme 236. Intermolecular Reformatsky Reaction of α -Sulfinylketones with Aldehydes by ColobertScheme 237. Intermolecular Reformatsky Reaction of α -Sulfinylketones with Imines by Colobert

highly diastereoselective Reformatsky reactions of α -bromo- α' -sulfinyl ketones with aldehydes (Scheme 236).^{498,499} The products were formed in good yields and high *syn*-selectivity. Other reagents, including CrCl_2 , CrCl_2/LiI , $\text{ZnEt}_2/\text{RhCl}(\text{PPh}_3)_3$, were less selective. The products were elaborated to 2-substituted 1,3-*syn* or 1,3-*anti* diols using protocols for the diastereoselective reduction of β -ketosulfoxides. In 2009, Colobert extended the scope of diastereoselective SmI_2 -mediated Reformatsky reactions of α -bromo- α' -sulfinyl ketones to include imines as electrophiles (Scheme 237).⁵⁰⁰ An account on the diastereoselective Reformatsky-type reactions has been published.⁵⁰¹

In 2004, Hoffman reported a SmI_2 -mediated intermolecular Reformatsky reaction of α -halo ketones using isocyanates as electrophiles in studies directed toward the synthesis of pederic acid (Scheme 238).⁵⁰² This method has been used to prepare ketoamides in moderate yields.

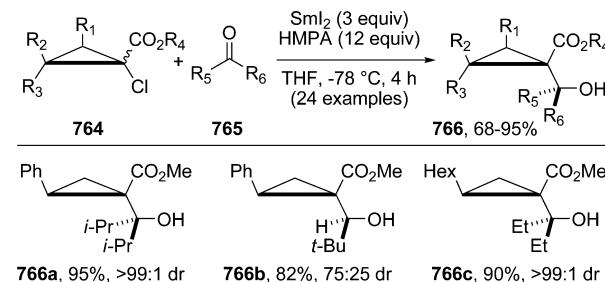
4.2.2.2. Cross-Coupling of α -Halo Esters. In the past decade, the intermolecular SmI_2 -mediated Reformatsky reaction of α -

Scheme 238. Intermolecular Ketone Reformatsky Reaction with Isocyanates by Hoffmann

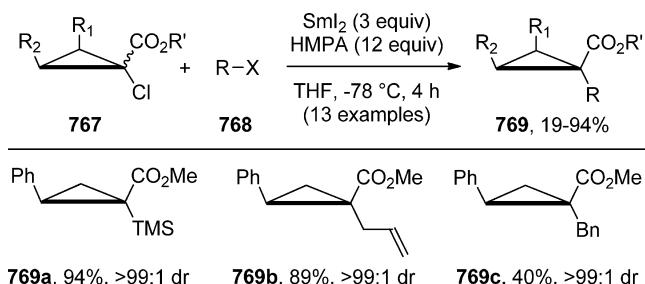


halo esters has been used primarily for functionalization of cyclopropanes (Schemes 239 and 240) and C-glycosidation of complex carbohydrates (Schemes 241 and 242), among other applications (Schemes 243 and 244).

Scheme 239. Intermolecular Reformatsky Reaction of Cyclopropane Esters by Nishii

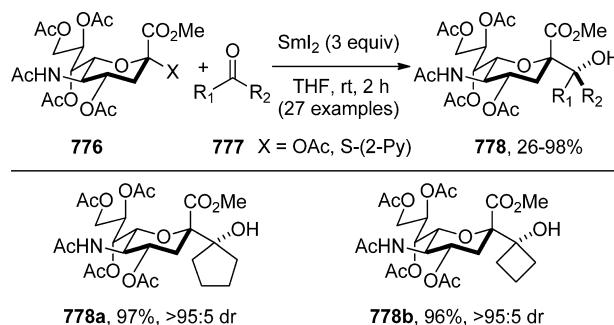


Scheme 240. Intermolecular Reformatsky-Type Reaction of Cyclopropane Esters by Nishii

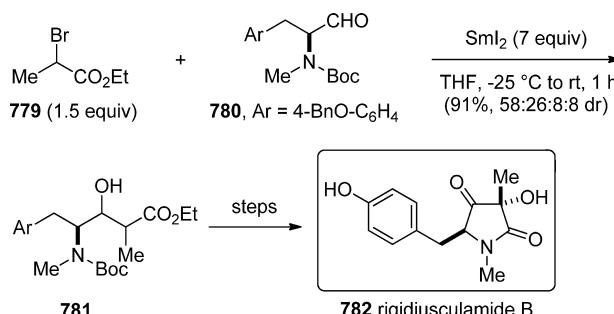


Nishii reported highly stereoselective alkylation of 1-chlorocyclopropanecarboxylates with ketones and aldehydes using SmI_2 -HMPA (Scheme 239).⁵⁰³ The reaction proceeds

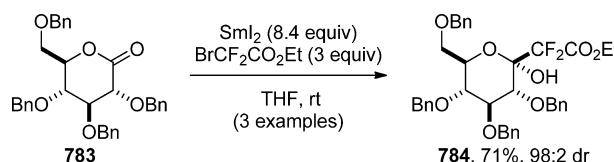
Scheme 242. Ester Reformatsky Reaction of Acetates and a 2-Pyridylsulfide of N-Acetylneurameric Acid by Beau



Scheme 243. Intermolecular Ester Reformatsky Reaction in the Synthesis of Rigidiusculamide B by Huang

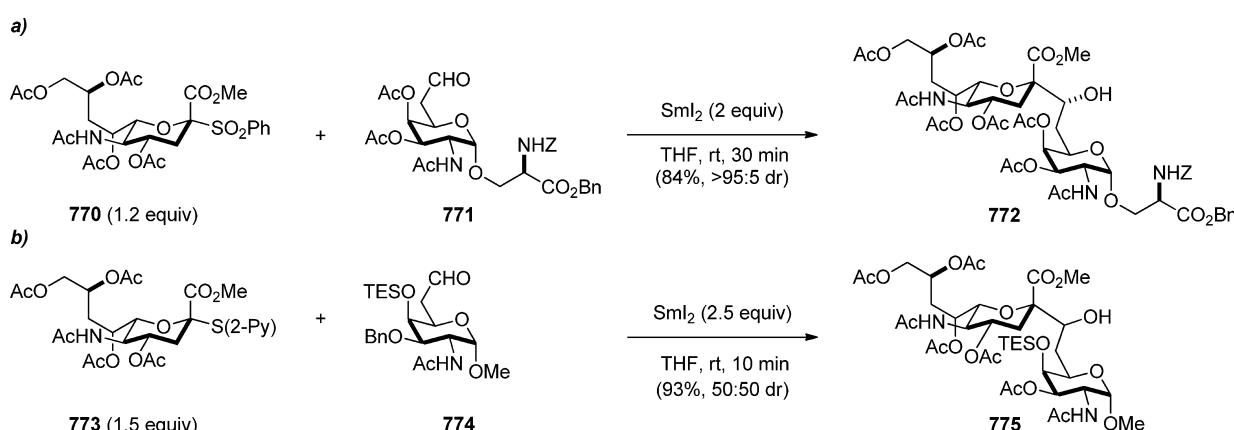


Scheme 244. Reformatsky Reaction of Ethyl Bromodifluoroacetate with Lactones by Pannecoucke and Quirion



with excellent *trans*-selectivity at the α -position (*trans/cis* >99:1), which was explained by the enolate trapping at the more accessible face of the molecule. The use of more traditional approaches, such as alkylation of the corresponding cyclopropanecarboxylates with LDA or $\text{TiCl}_4/\text{Et}_3\text{N}$, resulted in low

Scheme 241. Reformatsky Reaction for the Synthesis of C-Glycosides: (a) α -Sulfonylesters by Linhardt; (b) α -Pyridylsulfanylestes by Beau



yields of the β -hydroxy esters due to retro-aldol and self-condensation reactions. A variant employing acyl chlorides as electrophiles was also developed. Subsequently, Nishii reported C-silylation and C-alkylation of 1-chlorocyclopropanecarboxylates using SmI_2 –HMPA in good yields and excellent *trans*-diastereoselectivity (*trans/cis* >99:1) (Scheme 240).⁵⁰⁴

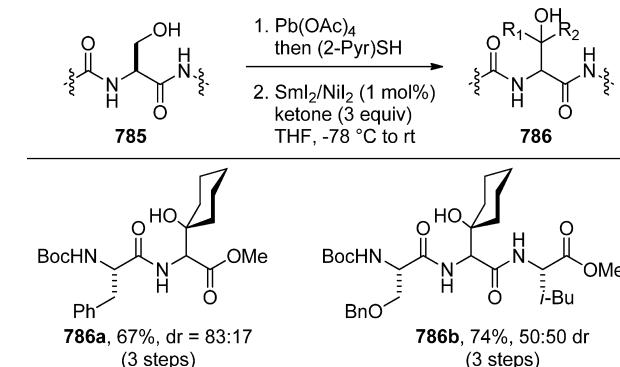
In 2003, Linhardt reported the intermolecular SmI_2 -mediated Reformatsky C-glycosylation reaction of a neuraminic acid sulfone donor with an aldehyde electrophile in the synthesis of C-glycoside analogues of sTn antigen (Scheme 241a).⁵⁰⁵ The reaction took place with SmI_2 -THF at room temperature to give the fully protected sTn α -C-glycoside in 84% yield and as a single diastereoisomer. This method was also applied for the stereoselective synthesis of neuraminic acid-based glycoside polymers⁵⁰⁶ and analogues of polysialic acids.⁵⁰⁷ In 2003, Beau independently reported the intermolecular SmI_2 -mediated Reformatsky reaction between a 2-pyridyl sulfide donor and an aldehyde acceptor in the synthesis of a carbon-linked mimic of the sTn antigen (Scheme 241b).⁵⁰⁸ The reaction proceeded efficiently with the SmI_2 -THF systems; however, the product was formed as a mixture of diastereoisomers. In 2006, Beau extended the scope of the C-glycosidation reaction to anomeric acetates of *N*-acetylneuraminic acid (Scheme 242).⁵⁰⁹ This methodology simplifies the synthetic sequence as acetates are typically employed as precursors for the synthesis of anomeric sulfones and sulfides. The authors proposed a mechanism involving electron transfer to anomeric acetate carbonyl group, followed by fragmentation and reduction to the organosamarium intermediate; however, an alternative mechanism involving electron transfer to the ester carbonyl group cannot be excluded. This method has been applied for the synthesis of α -C-glycosyl derivatives of *N*-acetylneuraminic acid.⁵¹⁰ Skrydstrup⁵¹¹ and Ye⁵¹² reported related SmI_2 -promoted Barbier-type procedures for C-glycosylation of 2-pyridyl sulfones (not shown).

Other applications of this class of SmI_2 -promoted cross-couplings have also been reported. In 2012, Huang reported the intermolecular SmI_2 -mediated Reformatsky reaction between ethyl 2-bromopropanoate and a chiral 2-amino aldehyde in the enantioselective synthesis of rigidiusculamide B (Scheme 243).⁵¹³ The reaction proceeded in good yield to give a mixture of diastereoisomers, which were separated after cyclization to the γ -butyrolactam. In 2005, Quirion reported the intermolecular SmI_2 -mediated Reformatsky addition of ethyl bromodifluoroacetate to various sugar lactones in good yields and high diastereoselectivity in an approach to fluorinated CF_2 -glycosides (Scheme 244).⁵¹⁴ The reaction proved efficient with the SmI_2 -THF system at room temperature; however, a large excess of the reagent was used. Finally, Skrydstrup reported an improved three-step procedure for the C-alkylation of peptides utilizing an intermolecular SmI_2 -mediated Reformatsky reaction (Scheme 245).⁵¹⁵ It was found that the oxidative degradation of serine residues with $\text{Pb}(\text{OAc})_4$, followed by acetate conversion to 2-pyridyl sulfides, provides an attractive alternative to the originally reported method employing selective bromination of glycine residues.²⁶⁹ This new method has been extended to SmI_2 -mediated C-alkylation of cyclic peptides.

4.2.2.3. Cross-Coupling of α -Halo Amides. The major developments in the cross-coupling of α -halo amides include the use of cyclic α -pseudohalo imides and α -halo *N*-acyloxazolidinones as new substrates for intermolecular SmI_2 -mediated Reformatsky reactions.

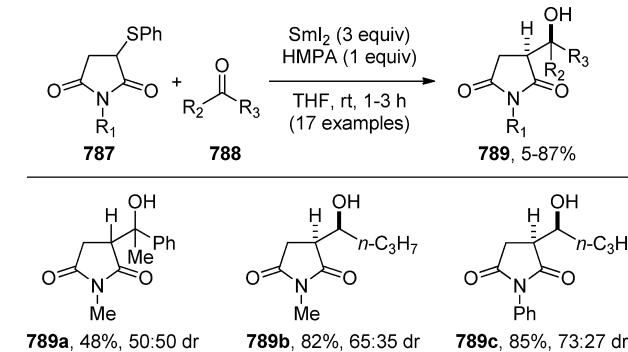
In 2006, Yoda reported the first example of the use of 3-phenylsulfanyl succinimides as pro-nucleophiles for intermolec-

Scheme 245. Improved Protocol for C-Alkylation of Peptides via Reformatsky Reaction by Skrydstrup



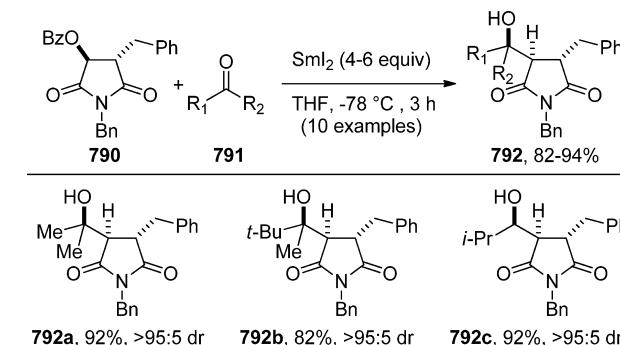
ular SMI₂-mediated Reformatsky reactions with ketones and aldehydes (Scheme 246).⁵¹⁶ The reaction provides useful yields.

Scheme 246. Reformatsky Reaction of Imides by Yoda



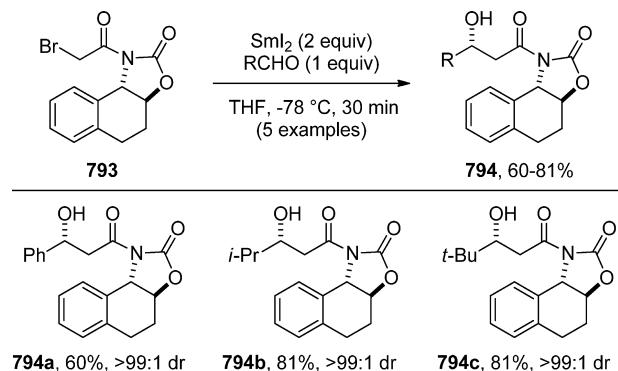
of hydroxyalkylated imides in the absence of additives; however, the SmI_2 -HMPA system gave the best results. A variety of protecting groups at nitrogen were tolerated with bulky protecting groups providing the highest diastereoselectivity. The methodology was exemplified in the total synthesis of a pyrrolizidine alkaloid, isoretronecanol. In 2008, Huang reported the SmI_2 -mediated synthesis of *trans*-3,4-disubstituted succinimides using the α -benzoyloxy group as a pseudohalide and performing the reduction with the SmI_2 -THF system at -78°C (Scheme 247).⁵¹⁷ The additional stereocenter at the β -position effectively controlled the diastereoselectivity of the reaction; in most cases, a single *trans-threo* isomer was formed as a result of a chelated transition state.

Scheme 247. Reformatsky Reaction of β -Substituted Imides by Huang

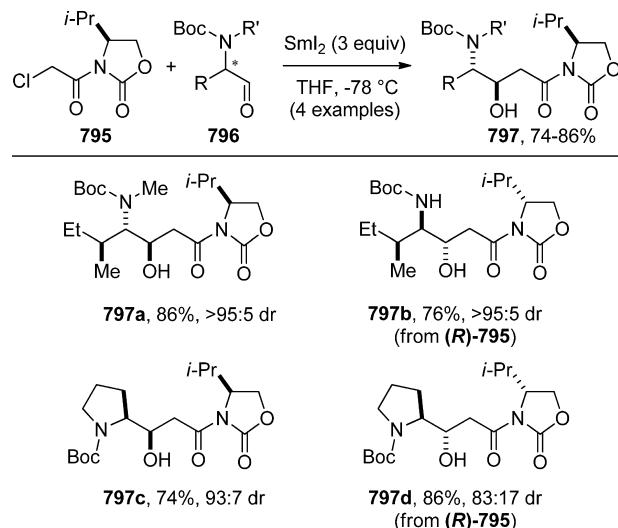


Chiral α -halo N -acyl oxazolidinones have been shown to participate in highly diastereoselective SmI_2 -mediated Reformatsky reactions (Schemes 248 and 249). In 2005, Orsini

Scheme 248. Reformatsky Reactions Using $(1S,2S)$ -1-Amino-2-hydroxy-1,2,3,4-tetrahydronaphthalene Auxiliary by Orsini



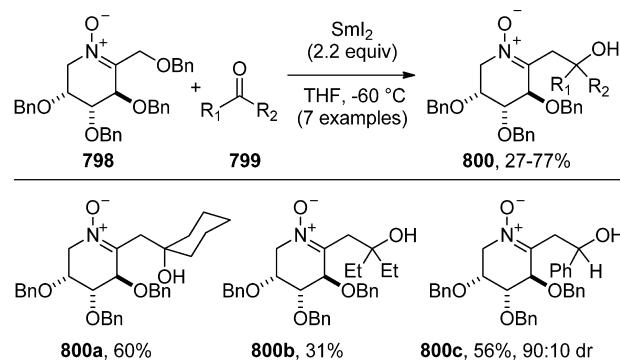
Scheme 249. Reformatsky Reactions of α -Chloroacetylloxazolidinone with Aminoaldehydes by Burke



reported Reformatsky reactions of aldehydes with a chiral α -bromo- N -acyl oxazolidinone based on $(1S, 2S)$ -1-amino-2-hydroxy-1,2,3,4-tetrahydronaphthalene scaffold (Scheme 248).⁵¹⁸ High yields and excellent diastereoselectivities (>99:1) were observed with the SmI_2 -THF system at -78 °C, while both diastereoisomers were obtained at room temperature. In 2012, Burke⁵¹⁹ demonstrated an elegant use of the α -chloroacetyl derivative of Evans' auxiliary to perform SmI_2 -mediated Reformatsky reactions^{520,521} with chiral α -amino aldehydes to give β -hydroxy- γ -amino acids in good yields and excellent stereoselectivity (Scheme 249). The authors demonstrated that the stereochemical outcome of the reaction is controlled by the auxiliary on the Sm(III) enolate. This reaction is one of the few examples of diastereoselective Reformatsky reactions giving β -hydroxy γ -amino acids without the double-diastereo-differentiating effect of α -substituents. Using this methodology, the synthesis of *N*-Boc-isostatine and *N*-Boc-dolaisoleucine was demonstrated.

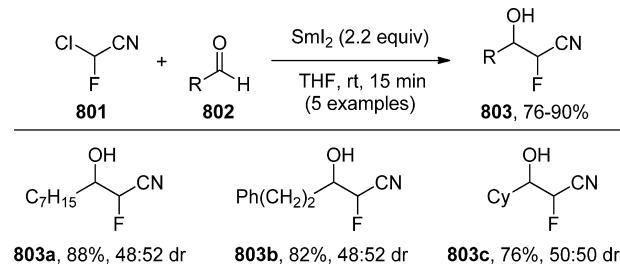
4.2.2.4. Miscellaneous Examples. In 2009, Py reported a SmI_2 -mediated Reformatsky-type reaction of cyclic α -benzyloxynitrone (Scheme 250).⁵²² The authors found that upon

Scheme 250. Reformatsky-Type Reaction of α -Benzylxoy Nitro by Py



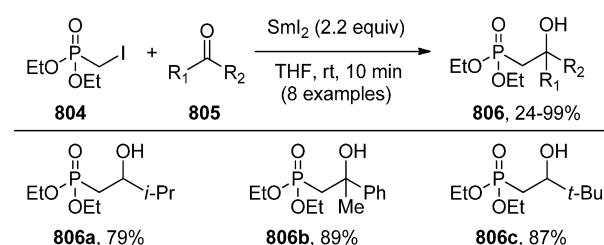
exposure to SmI_2 -THF with careful exclusion of water these substrates undergo β -elimination of the benzyloxy group to give the oxy-enamine intermediate. In the presence of carbonyl compounds, coupling to give hydroxyalkylated products takes place in good yield. Optimization studies revealed that HMPA, DMPU, or NiI_2 additives did not improve the reaction. With prochiral electrophiles, synthetically useful diastereoselectivity was observed. In 2007, Yokoyama reported the intermolecular Reformatsky-type reaction of 2-chloro-2-fluoroacetonitrile with aldehydes using SmI_2 -THF or SmI_2 -LiBr-HMPA (Scheme 251).⁵²³ A variety of aromatic and aliphatic aldehydes were

Scheme 251. Reformatsky Reactions of Chlorofluoroacetonitrile by Yokoyama

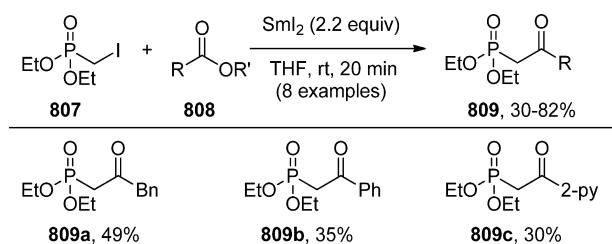


compatible with the reaction conditions; all substrates were transformed to the corresponding 2-fluoroethanols without loss of fluorine. In 2002, Orsini reported the intermolecular Reformatsky-type reaction of α -halophosphonates with ketones, aldehydes, and esters using the SmI_2 -THF system (Schemes 252 and 253).^{524,525} These reactions provide an alternative route to β -ketophosphonates for the synthesis of α,β -unsaturated compounds. Concellón and co-workers reported an impressive collection of SmI_2 -mediated Reformatsky-type reactions for the synthesis of advanced intermediates from commercially or easily

Scheme 252. Reformatsky Reactions of Diethyl Iodomethylphosphonate with Ketones/Aldehydes by Orsini

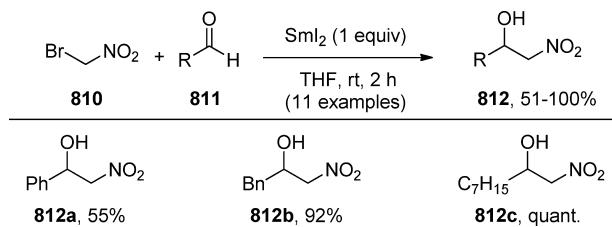


Scheme 253. Reformatsky Reactions of Diethyl Iodomethylphosphonate with Esters by Orsini

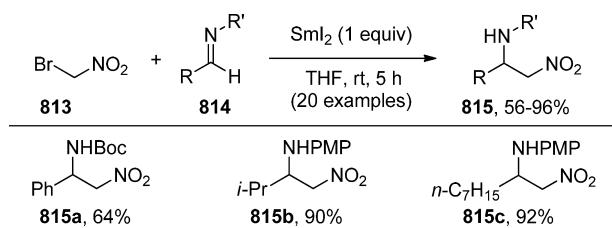


available precursors (Schemes 254–263). These reactions include nitro-aldo reactions using bromo(nitro)methane to

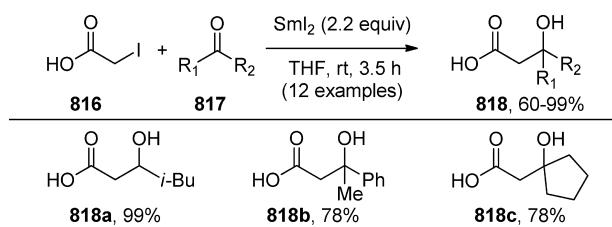
Scheme 254. Reformatsky Reactions of Bromonitromethane with Aldehydes by Concellón



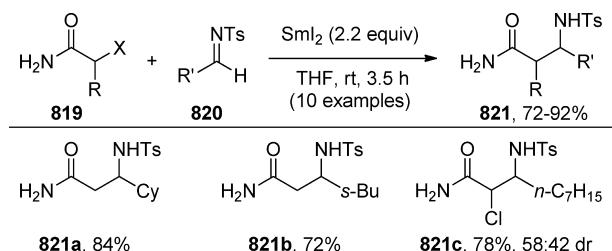
Scheme 255. Reformatsky Reaction of Bromonitromethane with Imines by Rodríguez-Solla



Scheme 256. Reformatsky Reactions of 2-Iodoacetic Acid by Concellón

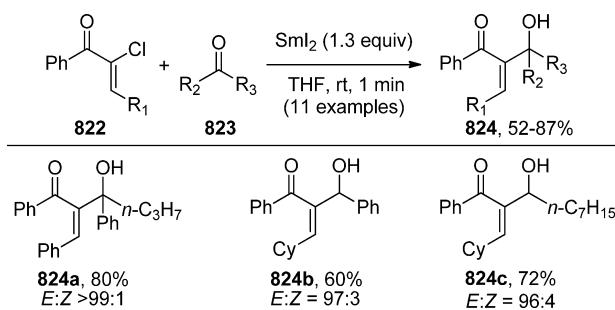


Scheme 257. Reformatsky Reactions of α -Haloamides with Imines by Concellón

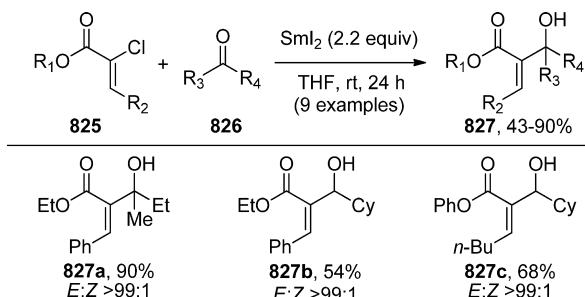


afford Henry-type products (Scheme 254),⁵²⁶ aza-Henry reactions (Scheme 255),⁵²⁷ the synthesis of 3-hydroxyacids from iodoacetic acid (Scheme 256),⁵²⁸ the synthesis of 3-

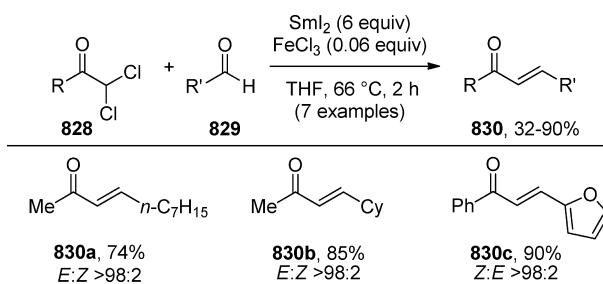
Scheme 258. Reformatsky Reactions of α -Chloroenones by Concellón



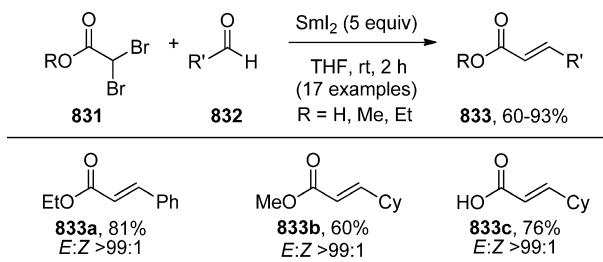
Scheme 259. Reformatsky Reaction of α -Chloro- α,β -Unsaturated Esters by Concellón



Scheme 260. Sequential Reformatsky Reaction/Elimination of Dichloroketones by Concellón

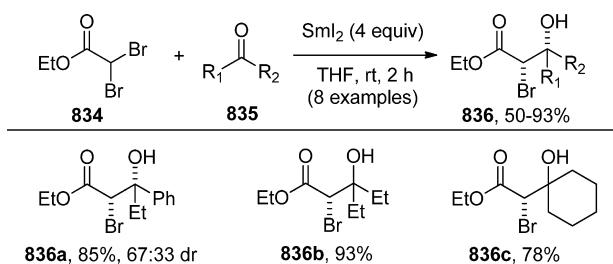


Scheme 261. Sequential Reformatsky Reaction/Elimination of Dibromoesters and Carboxylic Acids by Concellón

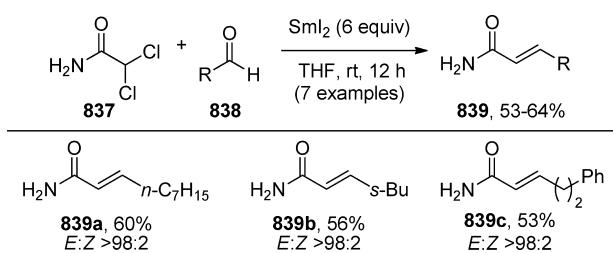


aminoamides using haloamides (Scheme 257),⁵²⁹ Reformatsky-type reactions of α -halo enones (Scheme 258),⁵³⁰ and α -halo enoates (Scheme 259),⁵³¹ sequential Reformatsky/elimination protocols with α,α -dihalo carbonyl derivatives, such as dichloroketones (Scheme 260),⁵³² dibromoesters (Scheme 261),⁵³³ dibromoacetic acid (Scheme 261),⁵³⁴ Reformatsky reactions of ethyl dibromoacetate with ketones (Scheme 262),⁵³⁵ and Reformatsky reaction/elimination of dichloroacetamide (Scheme 263).⁵³⁶

Scheme 262. Reformatsky Reaction of Ethyl Dibromoacetate with Ketones by Concellón



Scheme 263. Sequential Reformatsky Reaction/Elimination Using Dichloroacetamide by Concellón and Rodríguez-Solla

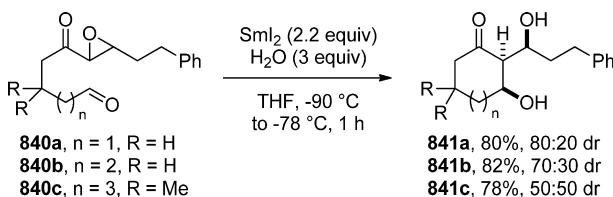


4.3. Aldol Reactions

In this section of the Review, we summarize recent developments in the SmI_2 -mediated aldol reactions that do not involve generation of Sm(III) enolates from α -halo or α -functionalized carbonyl compounds. In comparison to SmI_2 -Reformatsky-type reactions, other methods for reductive aldol processes using SmI_2 are much less developed.

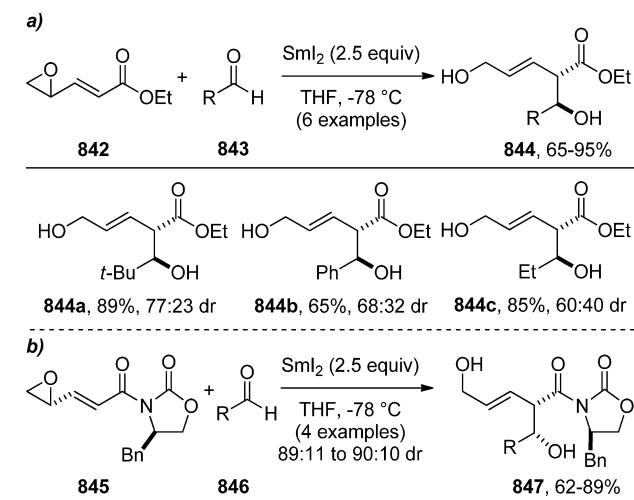
The most widely studied area is the SmI_2 -mediated aldol reactions of acylepoxydes and 2-acylaziridines (Schemes 264–266).^{537–544} After the seminal report on the SmI_2 -mediated

Scheme 264. Intramolecular Reductive Aldol of Sm(III)-Enolates Generated by Epoxide Opening by Mukaiyama

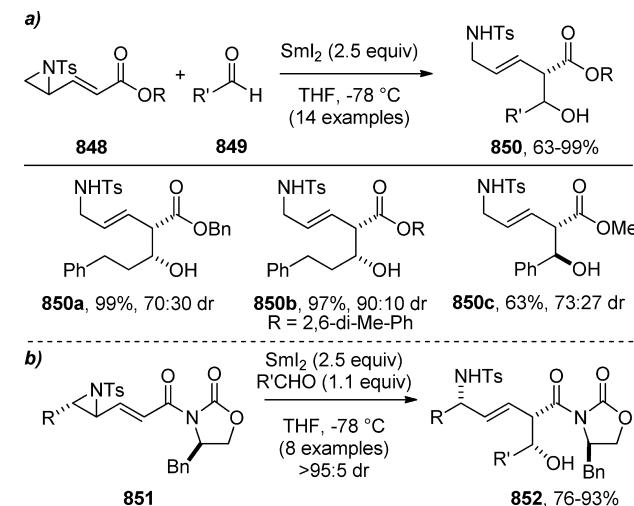


aldol reactions of oxiranyl ketones with aldehydes for the synthesis of unsymmetrical bis-aldols by Mukaiyama,⁵³⁷ a full account of this reaction was reported in 2003.⁵³⁸ The substrate scope was extended, and intramolecular aldols of oxiranyl keto-aldehydes were also reported (Scheme 264).⁵³⁹ In 2005, the SmI_2 -mediated aldol reactions of γ,δ -oxiranyl- α,β -unsaturated esters were reported (Scheme 265).⁵⁴⁰ In general, good yields were obtained with aliphatic and aromatic aldehydes; however, the reaction was not diastereoselective. The asymmetric variant using Evans' auxiliary gave the aldol product with high *syn*-selectivity (Scheme 265b). This method was applied to the enantioselective synthesis of C11–C17 fragment of mycinolide IV. In 2004, Mukaiyama reported the SmI_2 -mediated intermolecular aldol reactions of aziridinyl ketones with aldehydes to give β -hydroxy- β' -aminoketones in good yields but modest selectivities.⁵⁴¹ The reaction was next examined with γ,δ -aziridinyl- α,β -unsaturated esters (Scheme 266).^{542,543} The

Scheme 265. (a) Aldol Reaction of Sm(III)-Enolates Generated by Epoxide Opening by Mukaiyama; **(b)** Asymmetric Variant



Scheme 266. (a) Aldol Reaction of Sm(III)-Enolates Generated by Aziridine Opening by Mukaiyama; **(b)** Asymmetric Variant



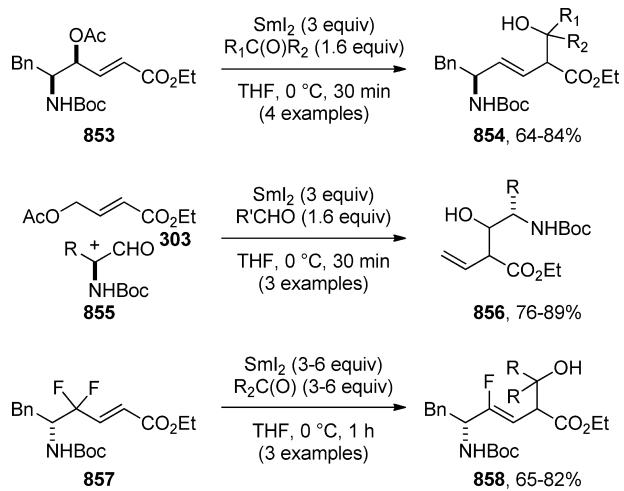
asymmetric version afforded the aldol products in high yields and excellent (>95:5) *syn*-selectivity (Scheme 266b). A chelation model involving coordination of the samarium enolate to the oxazolidinone was proposed to explain the stereoselectivity of the reaction. Independently, in 2001, Tori reported intramolecular aldol reactions of α,β -epoxycyclopentanone.⁵⁴⁴

Several alternative approaches to SmI_2 -mediated aldol reactions have been reported, including aldol-type processes; however, these reactions are typically limited to specific substrates and/or the products are obtained in modest yields (Schemes 267–269).^{545–549} SmI_2 -mediated aldol reactions have also been applied as a part of several SmI_2 -promoted cascade sequences (see section 5).

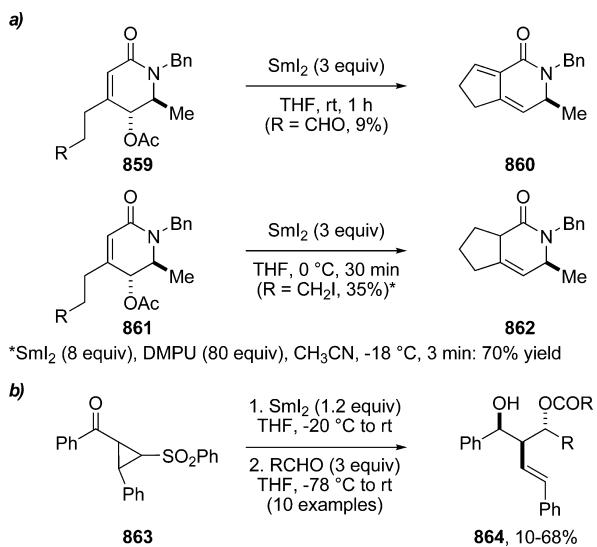
5. CROSS-COUPLING AS PART OF SEQUENTIAL AND CASCADE REACTIONS

In the final section of this Review, we highlight representative examples of SmI_2 -mediated processes as part of sequential and cascade reactions. As a result of the double-mechanistic manifold comprising single- and two-electron pathways, SmI_2 is unique in

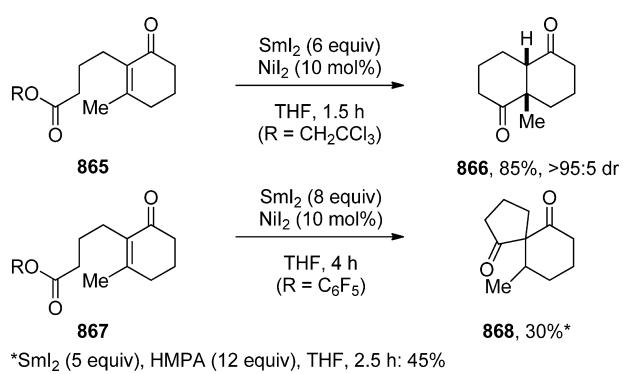
Scheme 267. Samarium Dienolate Aldol by Otaka: (a) Alkene Dipeptide Isosteres; (b) γ -Amino Acid Derivatives; (c) Fluoroalkene Peptide Isosteres



Scheme 268. (a) Reductive Aldol and Enolate Alkylation by Otaka; (b) Dienolate Aldol/Tishchenko Reaction by Reutrakul and Pohmakotr



Scheme 269. Reductive Aldol and Spirocyclization by Sono and Tori



*SmI₂ (5 equiv), HMPA (12 equiv), THF, 2.5 h: 45%

its ability to merge radical and ionic transformations to form challenging carbon–carbon bonds. Exceptional functional group tolerance, mild reaction conditions, operational ease, high Lewis

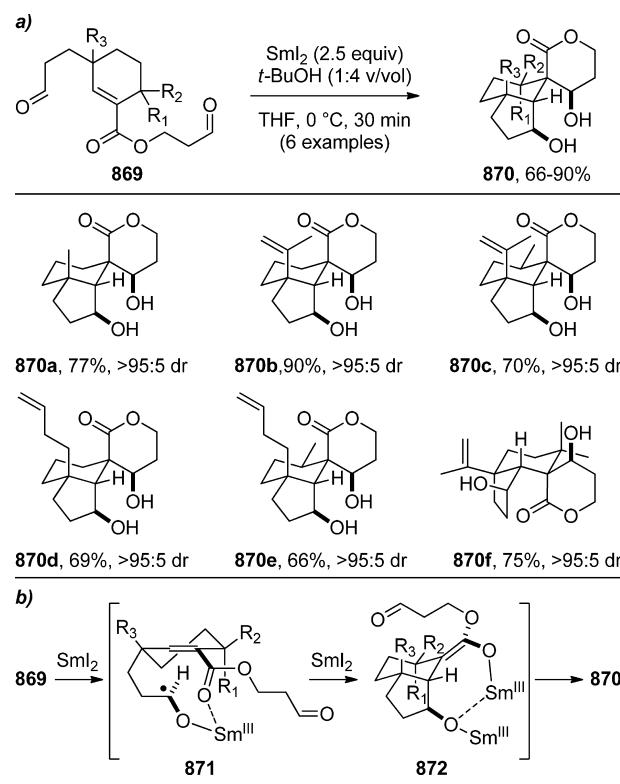
acidity, and the thermodynamic control of single-electron events have made this reagent an indispensable tool to achieve a rapid increase of complexity from simple synthetic precursors, while setting multiple stereocenters in the process.

In the past decade, a large number of SmI₂-mediated cascades have been reported, including numerous applications in the synthesis of complex natural products. In addition to the reactions presented below, several other examples of cascades mediated by SmI₂ have been included in previous sections of this Review (Schemes 52 and 54). Taken together, these transformations illustrate the power of SmI₂ to mediate challenging transformations via radical and ionic mechanisms.

5.1. Cascades Initiated by Radical Intermediates

In 2008, Procter reported the synthesis of *cis*-hydrindanes via 5-*exo*-trig ketyl radical olefin coupling with excellent diastereoccontrol at the three stereocenters generated during the reaction (Scheme 11).^{184,185} In 2009, Procter reported the 5-*exo*-trig ketyl-olefin cyclization/intramolecular aldol cascade for the synthesis of complex spirocyclic lactones, forming two new rings and affording four contiguous stereocenters in a single step in excellent yields and complete diastereoccontrol (Scheme 270).^{550,551} The proposed mechanism involves the following

Scheme 270. (a) 5-*exo*-Trig/Aldol Dialdehyde Spirocyclization Cascade by Procter; (b) Proposed Mechanism

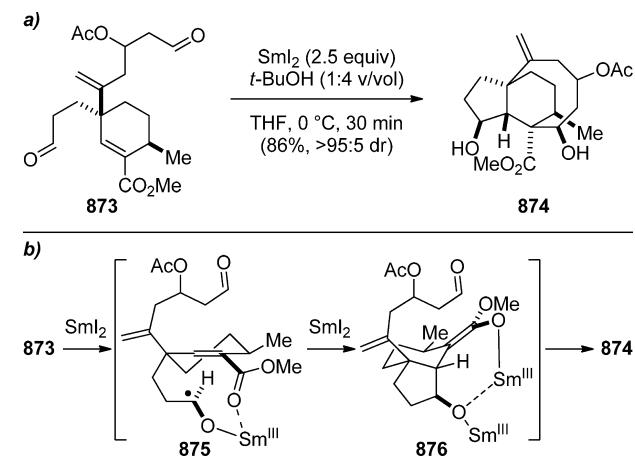


steps: (i) *anti*-selective ketyl olefin cyclization; (ii) reduction to the Sm(III) enolate; and (iii) chelation controlled aldol cyclization through a six-membered transition state. Interestingly, the cyclization cascade of a substrate containing an α -gem-dimethyl group gave the product with the opposite configuration (>95:5 dr) at the quaternary stereocenter formed during the aldol cyclization. The authors proposed that this selectivity arises from a different conformation of the enolate intermediate. This

report demonstrated the feasibility of a SmI_2 -promoted dialdehyde “radical then aldol” cascade sequence for the first time.

In a separate investigation, in 2009, Procter reported the synthesis of a 5,6,8-tricyclic core of pleuromutilin, a bacterial peptidyl transferase inhibitor, using a SmI_2 -mediated 5-*exo*-trig/aldol dialdehyde cascade to form the eight-membered ring during the aldol addition (Scheme 271).⁵⁵² The dialdehyde

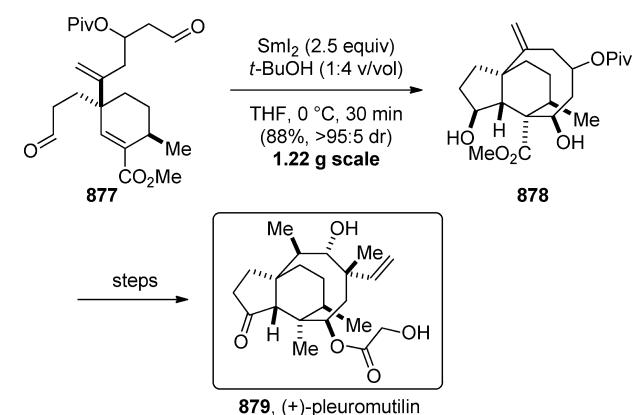
Scheme 271. (a) 5-*exo*-Trig/Aldol Dialdehyde Cascade for the Synthesis of the Pleuromutilin Ring System by Procter; (b) Proposed Mechanism



underwent cyclization upon treatment with $\text{SmI}_2-t\text{-BuOH}$ to form the 5,6,8-tricyclic intermediate with complete diastereoccontrol at the four contiguous stereocenters in 86% overall yield. The reaction starts with the selective electron transfer to the more sterically accessible aldehyde to give the corresponding radical anion, which undergoes chelation-controlled anti-5-*exo*-trig cyclization. After a second electron transfer, the cascade is completed by the diastereoselective aldol cyclization of the (*Z*)- $\text{Sm}(\text{III})$ enolate via a cyclic transition state. Byproducts arising from reduction of the second aldehyde were not detected in this reaction.

Recently, Procter achieved the first total synthesis of (+)-pleuromutilin utilizing the SmI_2 -mediated dialdehyde cascade as a key step (Scheme 272).⁵⁵³ The pivaloyl protecting group on the dialdehyde was critical to increase the stability of

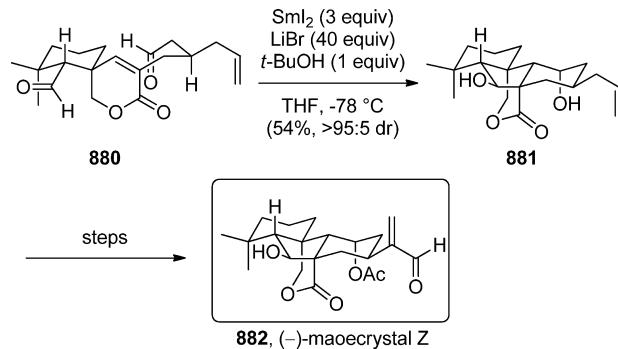
Scheme 272. Application in the Total Synthesis of (+)-Pleuromutilin by Procter



the precursor; after this improvement, the SmI_2 -cascade was demonstrated on a gram scale with no decrease in efficiency.

In 2011, Reisman and co-workers reported an impressive SmI_2 -mediated 6-*endo*-trig ketyl-olefin/aldol cyclization cascade in the total synthesis of (−)-maoecrystal Z (Scheme 273).⁵⁵⁴ The

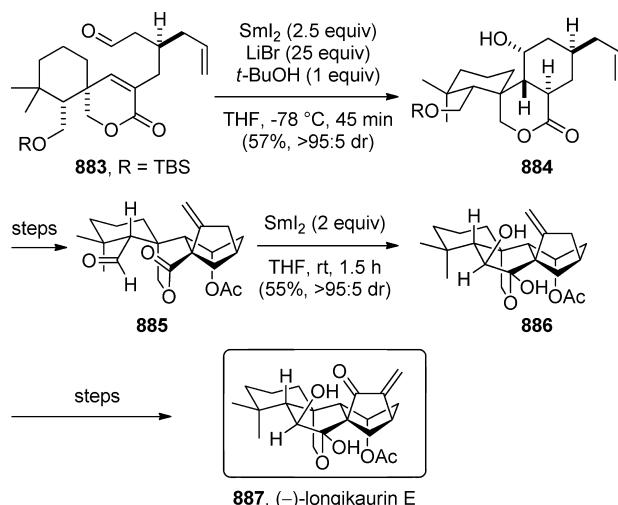
Scheme 273. 6-*endo*-Trig/Aldol Dialdehyde Cyclization Cascade in the Total Synthesis of (−)-Maoecrystal Z by Reisman



cascade allowed for construction of two rings and four contiguous stereogenic centers of this complex natural product in a single step. The product was formed with full diastereoccontrol in 54% yield. Interestingly, the combination of $\text{SmI}_2-\text{LiBr}-t\text{-BuOH}$ proved to be the reagent of choice for this transformation, while the $\text{SmI}_2-\text{LiCl}-t\text{-BuOH}$ system employed in a model study was ineffective.

In 2013, Reisman reported the total synthesis of (−)-longikaurin E employing a related sequential 6-*endo*-trig ketyl-olefin cyclization/aldaldehyde-ester pinacol-type cyclization mediated by SmI_2 (Scheme 274).⁵⁵⁵ As in the studies on (−)-maoecrystal Z,

Scheme 274. Sequential 6-*endo*-Trig/Pinacol-Type Cyclization in the Total Synthesis of (−)-Longikaurin E by Reisman

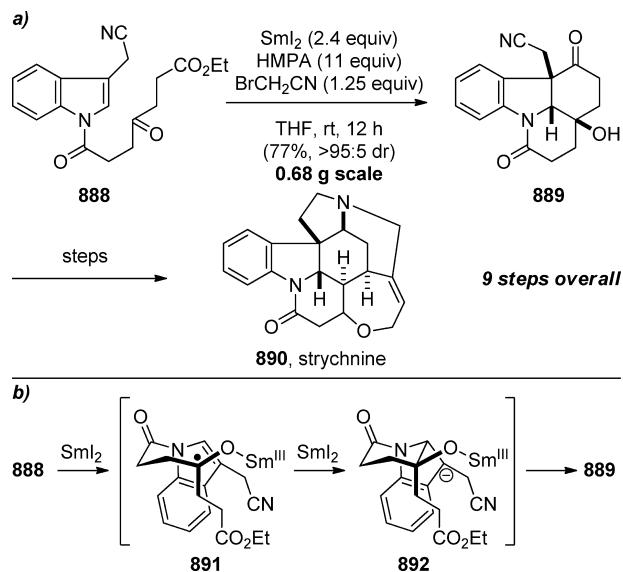


the $\text{SmI}_2-\text{LiBr}-t\text{-BuOH}$ complex was used to trigger the 6-*endo*-trig ketyl-olefin cyclization. In contrast, the SmI_2-THF system provided the best results for the aldehyde-lactone pinacol-type coupling at a later stage of the synthesis, which presumably proceeds through an anionic mechanism.

In 2010, Reissig reported a remarkable nine-step formal total synthesis of strychnine using a SmI_2 -mediated 6-*exo*-trig ketyl-

indole/intramolecular acylation cascade cyclization as the key step (Scheme 275).³¹⁸ The product was formed in excellent yield

Scheme 275. (a) 6-exo-Trig/Intramolecular Acylation Cascade in the Formal Total Synthesis of Strychnine by Reissig; (b) Proposed Mechanism



as a single diastereoisomer. The SmI_2 -cascade formed two rings and set three stereocenters starting from a readily available precursor (one step from commercial material). It should be noted that in this example the organosamarium intermediate is not stabilized by electron-withdrawing groups at the 3-position as in other examples of ketyl/indole couplings reported by the same authors (see section 3.1.5). A small portion (ca. 5%) of the cascade product was found to undergo fragmentation under the reaction conditions losing acetonitrile; however, the authors determined that quenching the reaction with bromoacetonitrile improved the overall yield to 75–80%. The cascade product was converted into a common intermediate in Rawal's synthesis of strychnine,⁵⁵⁶ resulting in one of the most efficient routes to this classic alkaloid reported to date.⁵⁵⁷

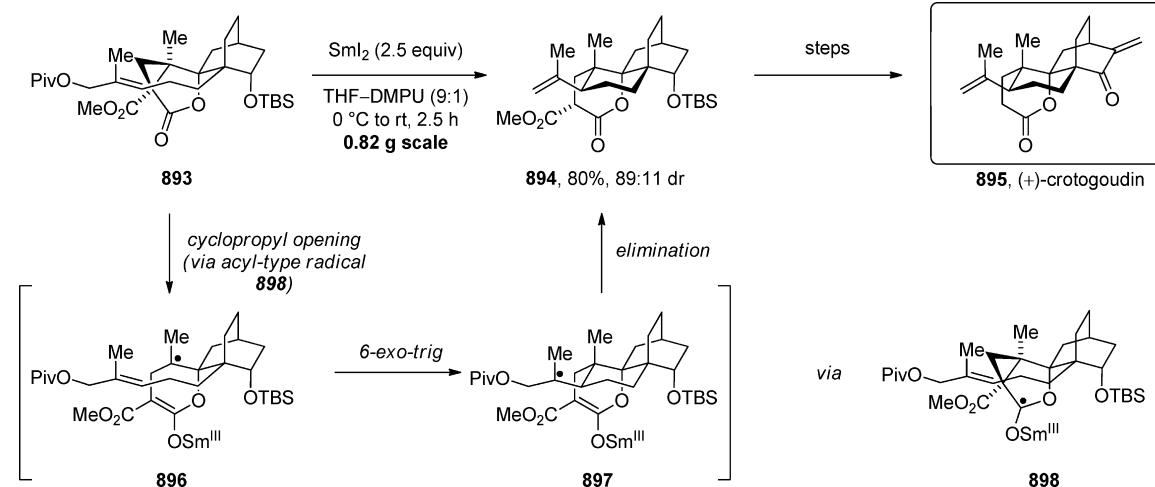
In another beautiful example of the reagent's control over a desired transformation, Carreira reported a SmI_2 -mediated

cyclopropyl opening/6-exo-trig/elimination cascade to form the congested core structure in the total synthesis of (+)-crotogoudin (Scheme 276).⁵⁵⁸ The mechanism of this transformation was proposed to involve the following steps: (i) electron transfer to one of the ester carbonyls, presumably the five-membered lactone; (ii) cyclopropane ring-opening; (iii) 6-exo-trig radical cyclization; (iv) reduction; and (v) anionic elimination of the pivalate. The authors determined that the use of a suitable leaving group was critical to obtain high yields in the cascade. Although the desired product could be formed from the terminal allylic alcohol, the corresponding acetates and carbonates dramatically improved the yield. This is in line with an anionic mechanism for the β -elimination step; however, the alternative radical mechanistic pathway can be achieved with other leaving groups (see section 3.1.5). From this advanced intermediate, only seven steps were required to complete the synthesis of (+)-crotogoudin.

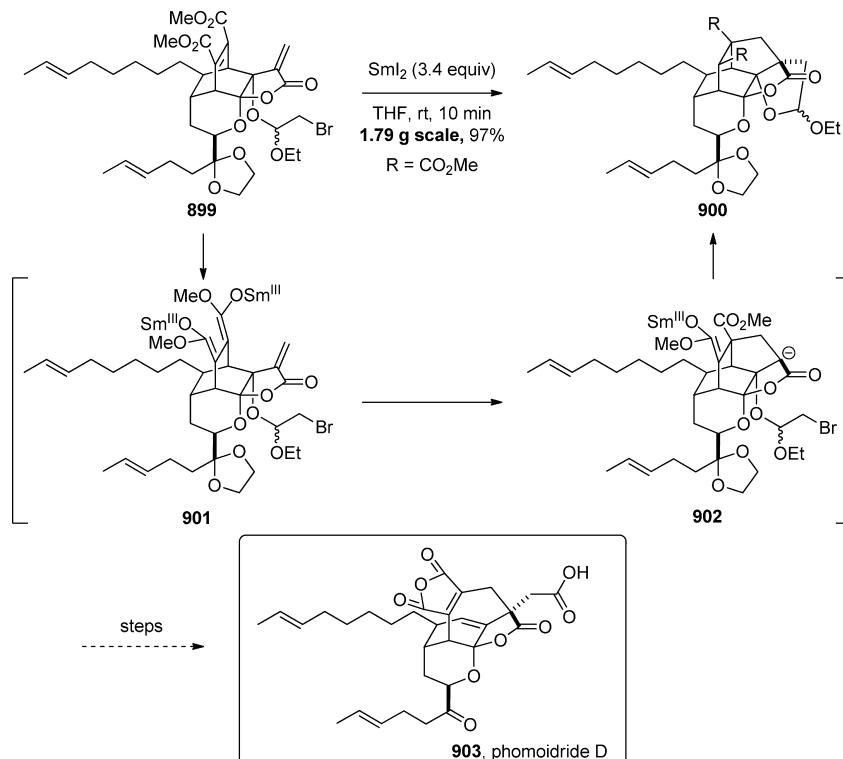
Recently, Wood reported an elegant example of a SmI_2 -mediated cascade initiated by a single-electron reduction of an α,β -unsaturated ester under very mild reaction conditions in the studies directed toward a total synthesis of phomoidride D (Scheme 277).⁵⁵⁹ Initially, other reagents were tested for the transformation with the aim of initiating the cascade by bromide reduction (e.g., Bu_3SnH); however, the yields were compromised by the undesired 6-endo cyclization into the methylenebutyrolactone. In contrast, SmI_2 furnished the desired product in 97% yield. The cascade involves the following steps: (i) conjugate reduction of the maleate; (ii) 5-endo-trig addition to the pendant methylenebutyrolactone; and (iii) 5-exo-tet bromide displacement by the resulting enolate. It was shown that the interrupted cyclization product could be isolated by performing the reaction at lower temperature, thus providing strong support for the proposed mechanism. Impressively, the reaction could be performed on a 1.79 g scale, giving efficient access to a complex phomoidride D intermediate.

Kobayashi reported the stereoselective synthesis of spiro[4.5]-decanes via a ketyl radical-initiated cascade cyclization using SmI_2 –HMPA and SmI_2 –Sm (Scheme 278).⁵⁶⁰ Interestingly, the stereoselectivity of the ketyl radical cyclization onto a pendant activated olefin was found to depend on the additive used for SmI_2 . With SmI_2 –Sm syn cyclization was favored due to chelation control, whereas SmI_2 –HMPA resulted in anti cyclization due to electrostatic repulsion.

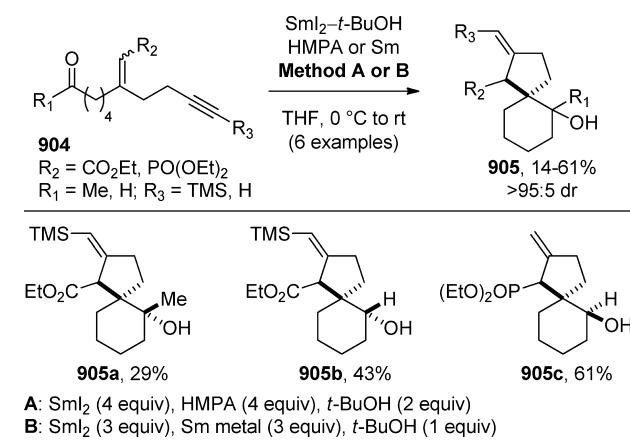
Scheme 276. Cyclopropyl Opening/6-exo-Trig/Elimination Cascade by Carreira



Scheme 277. Conjugate Reduction/ β -Addition/Intramolecular Enolate Alkylation Cascade by Wood



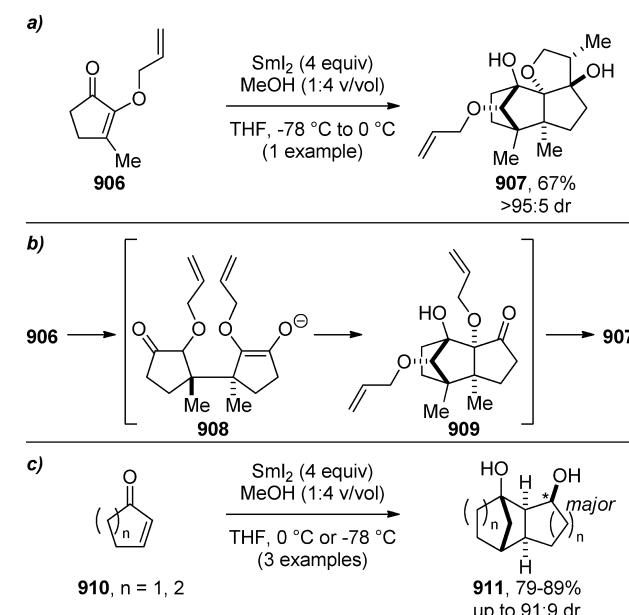
Scheme 278. Ketyl Radical 6-exo-Trig/5-exo-Dig Cyclization Cascade by Kobayashi



In 2004, Kilburn reported one of the most impressive examples of SmI_2 -mediated cascades discovered to date (Scheme 279).⁵⁶¹ Exposure of an α -allyloxy enone to 4 equiv of SmI_2 in THF/MeOH (4:1 v/v) resulted in the formation of a complex tetracycle bearing seven adjacent stereocenters in 67% yield and as a single diastereoisomer. The reaction was proposed to involve the following steps: (i) enone dimerization; (ii) intramolecular aldol cyclization; and (iii) ketyl-radical 5-*exo*-trig cyclization. The capacity of the reagent system to promote the dimerization/aldol condensation of enones to furnish tricyclic diols in good yield and diastereoselectivity was also demonstrated (Scheme 279c).

In 2004, Kilburn reported the SmI_2 -HMPA-promoted 6-exo-trig cyclizations of ketyl radicals onto methylenecyclopropanes⁵⁶² in an extension of their previous studies^{563,564} on 5-exo-trig cyclizations (Scheme 280). Fragmentation of the cyclopropylmethyl radical furnishes 3-methylenecycloheptanyl

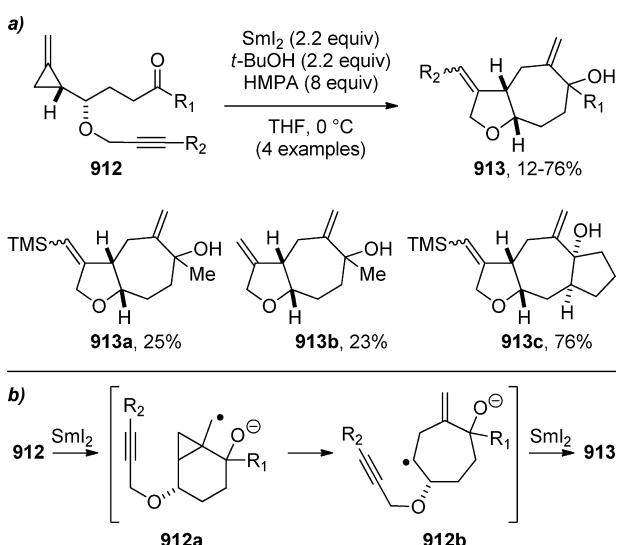
Scheme 279. (a) Enone Dimerization/Aldol/Ketyl Radical/5-exo-Trig Cyclization Cascade by Kilburn; (b) Proposed Mechanism; (c) Reductive Dimerization/Aldol



radical, which undergoes *5-exo*-dig cyclization, providing facile access to the fused [5.3.0] bicyclic ring systems found in several natural products. Although the yields are typically modest due to competing *7-endo*-trig and *8-endo*-dig monocyclizations, the cyclization of a cyclopentane-derived ketyl radical proceeded in a respectable 76% yield.

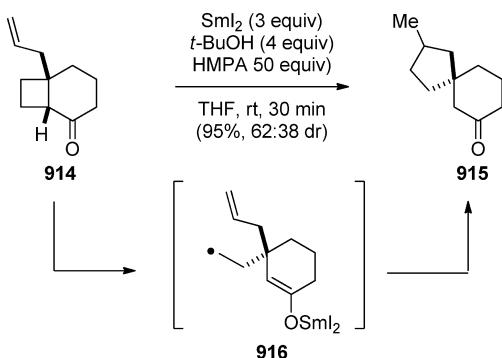
In a related fragmentation/cyclization cascade, Kakiuchi reported radical ring-opening of bicyclo[4.2.0]octan-2-ones/5-exo-trig cyclization promoted by SmI₂-HMPA in the presence of

Scheme 280. (a) 6-exo-Trig/Fragmentation/5-exo-Dig Cyclization Cascade by Kilburn; (b) Proposed Mechanism



t-BuOH (Scheme 281).⁵⁶⁵ This reaction constitutes one of the few examples of a Sm(II) radical sequence initiated by the opening of an unactivated cyclobutane ring.^{566,567}

Scheme 281. Cyclobutane Fragmentation/5-exo-Trig Cyclization Cascade by Kakiuchi

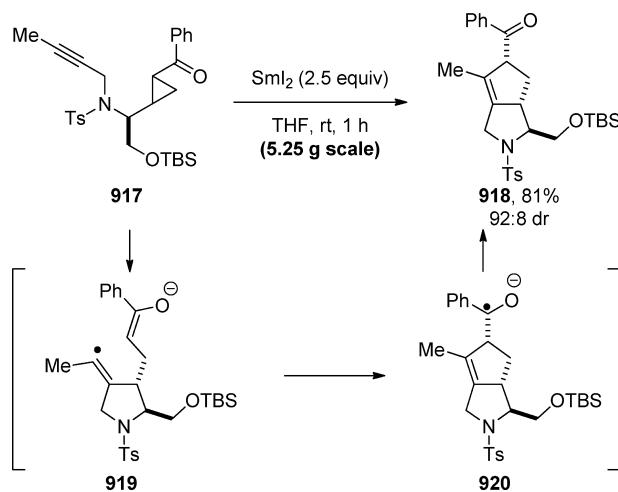


In 2012, Zhou and Li reported the total synthesis of (−)-(α)-kainic acid using a SmI₂-promoted intramolecular formal [3 + 2] cycloaddition cascade as a key step (Scheme 282).⁵⁶⁸ The reaction was proposed to involve the following steps: (i) ketyl radical formation; (ii) cyclopropane ring-opening; (iii) 5-exo-dig cyclization to give the vinyl radical; (iv) 5-exo-trig cyclization; and (v) ketone regeneration. Remarkably, the reaction could be carried out on a 5.25 g scale (2.5 equiv of SmI₂). From the [3 + 2] cycloaddition product, the synthesis of (−)-(α)-kainic acid was completed in eight more steps.

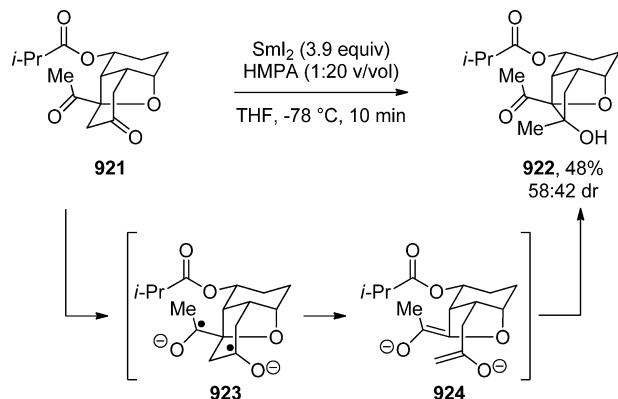
During studies on the synthesis of nodusmicin, Schwartz discovered a reductive fragmentation/aldol cyclization cascade using SmI₂–HMPA (Scheme 283).⁵⁶⁹ Interestingly, no reaction was observed in the absence of HMPA. This reaction is one of the very few examples of radical/ionic cascades involving fragmentation of 1,4-diketones.⁵⁷⁰

In 2010, Hu reported the intramolecular cascade cyclization of cyanamide radicals under the SmI₂–HMPA reaction conditions to afford amidine-containing heterocycles in good yields (Scheme 284).⁵⁷¹ 6-exo-Dig cyclization of aryl radicals into

Scheme 282. Cyclopropane Fragmentation/5-exo-Dig/5-exo-Trig Cyclization Cascade in the Total Synthesis of (−)-(α)-Kainic Acid by Zhou and Li



Scheme 283. 1,4-Dicarbonyl Fragmentation/Aldol Cyclization Cascade by Schwartz

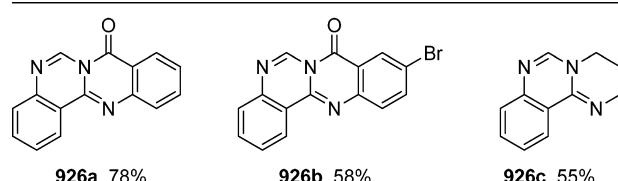
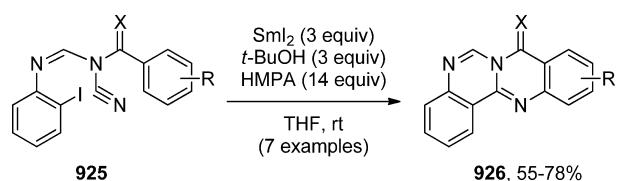


cyanamides resulted in the formation of cyanamide radicals,⁵⁷² which underwent efficient addition to aromatic rings and olefins.

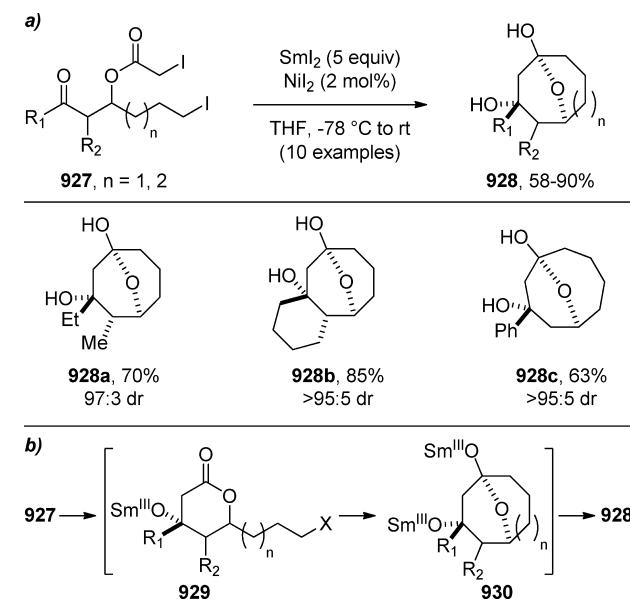
5.2. Cascades Initiated by Anionic Intermediates

Molander reported the synthesis of highly functionalized medium-sized ring carbocycles using a SmI₂-promoted sequential Reformatsky/nucleophilic acyl substitution reaction (Scheme 285).⁵⁷³ The reaction was successful for the preparation

Scheme 284. 6-exo-Dig/6-endo-Trig Cyclization Cascade of Cyanamides by Hu



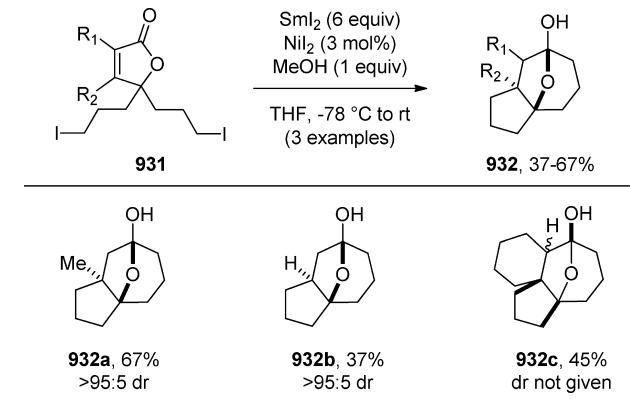
Scheme 285. (a) Intramolecular Reformatsky/Nucleophilic Acyl Substitution Cascade by Molander; (b) Proposed Mechanism



of eight- and nine-membered ring systems. All products were formed as single diastereoisomers (up to four stereocenters). The use of anti- and syn-substituted precursors resulted in a highly stereospecific Reformatsky reaction. Interestingly, NiI_2 was found to be the additive of choice, with other $\text{Sm}(\text{II})$ systems (e.g., $\text{Fe}(\text{DBM})_3, \text{LiCl}$) leading to lower yields.

St. Jean reported the synthesis of tricyclic hemiketals in good yields and excellent diastereoselectivity via a sequential SmI_2 -mediated intramolecular conjugate addition/nucleophilic acyl substitution reaction (Scheme 286).⁵⁷⁴ The use of NiI_2 (3 mol

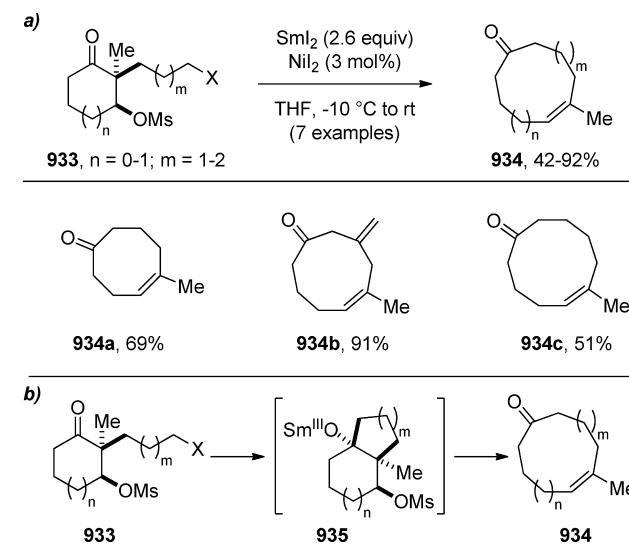
Scheme 286. Sequential Intramolecular Conjugate Addition/Nucleophilic Acyl Substitution by St. Jean



) and MeOH (1 equiv) as a proton source was critical to achieve good yields of the hemiketal products. In the presence of excess MeOH (3 equiv), only trace quantities of the desired product were formed. The tricyclic hemiketals obtained in this process are a common structural feature of the carotene sesquiterpenes.

Molander reported a SmI_2 -promoted sequential intramolecular Barbier/Grob fragmentation reaction for the synthesis of highly functionalized medium-sized ring carbocycles (Scheme 287).⁵⁷⁵ The reaction was found to be effective for cyclopentanes

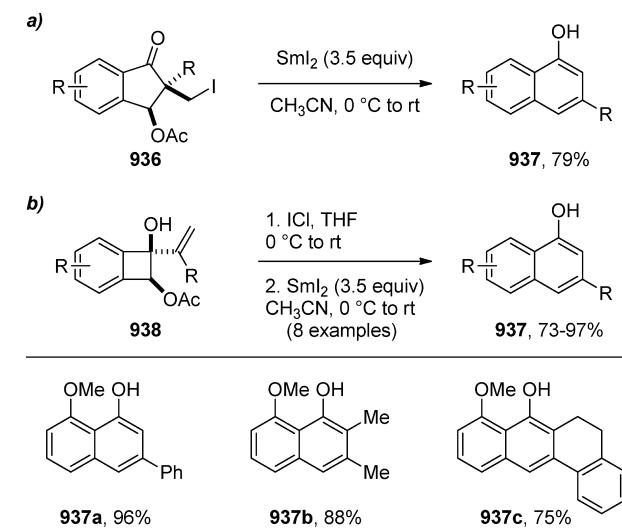
Scheme 287. (a) Intramolecular Ketone Barbier/Grob Fragmentation Cascade by Molander; (b) Proposed Mechanism



and cyclohexanes bearing three- and four-carbon long tethers at the α position, giving eight-, nine-, and ten-membered unsaturated ketones in good yields. Interestingly, methylene isomerization to the more thermodynamically stable endo isomer was not observed.

In 2006, Suzuki reported a tandem intramolecular Barbier reaction/Grob fragmentation of 2-iodomethylene indanones for the synthesis of polyfunctionalized α -naphthols (Scheme 288).⁵⁷⁶ The reaction was sensitive to the conditions used; for

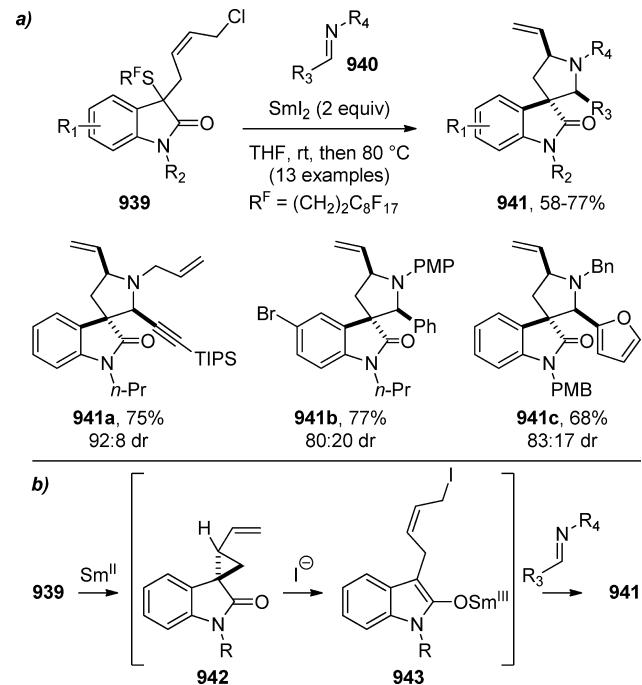
Scheme 288. (a) Intramolecular Ketone Barbier/Grob Fragmentation Cascade of 2-Halomethyl Indanones by Suzuki; (b) Tandem Ring Expansion/ SmI_2 Cascade



example, SmI_2 and SmI_2 -HMPA system did not result in full conversion of the intermediate cyclopropanol; however, the use of SmI_2 in CH_3CN or $\text{SmI}_2\bullet\text{BF}_3\bullet\text{Et}_2\text{O}$ in THF promoted the Grob fragmentation. After the initial optimization, it was found that the alkyl iodide could be generated *in situ* from the corresponding alkenylbenzocyclobutene using ICl . The reaction was extended to generate polycyclic compounds.

In 2011, Procter reported a SmI_2 cyclization cascade for the synthesis of spirooxindoles utilizing a cooperative role for $\text{Sm}(\text{II})/\text{Sm}(\text{III})$ (Scheme 289).⁵⁷⁷ The reaction was initiated by

Scheme 289. (a) Reductive Cleavage/Enolate Alkylation/Vinyl Cyclopropyl Opening Cascade by Procter; (b) Proposed Mechanism



a fluorous tag removal (SmI_2 , THF, room temperature) to afford the $\text{Sm}(\text{III})$ -enolate, which participated in a $\text{S}_{\text{N}}2'$ displacement to form the vinylcyclopropane as a single diastereoisomer. Increasing the temperature to 80 °C in the presence of an imide effected intermolecular vinylcyclopropane opening by the iodide, likely facilitated by coordination of the Lewis acidic $\text{Sm}(\text{III})$ to the lactam carbonyl group. The resulting [3 + 2] cycloaddition afforded highly functionalized spirooxindole motifs. The methodology was applied to the synthesis of spirotryprostatin A analogues with anticancer activity.

6. CONCLUSIONS

As demonstrated in this Review, huge advancements have been made in the field of SmI_2 -mediated cross-couplings in the past decade. The major advantage of using SmI_2 lies in the versatility and exceptional functional group tolerance of the reagent. This is highlighted by the discovery of a wide range of novel diverse coupling partners, the use of SmI_2 -mediated cross-couplings in the synthesis of complex natural products, the development of impressive cascade sequences for the rapid buildup of molecular complexity, and the synthesis of functionalized building blocks from commercial or easily accessible materials. Among the major developments in the field are (i) the discovery of ester-derived ketyl-type radicals in the $\text{SmI}_2-\text{H}_2\text{O}$ -mediated cross-couplings, (ii) the use of *N*-acyl oxazolidinones as efficient coupling partners for the synthesis of peptides, (iii) the use of unactivated arenes as π -acceptors in SmI_2 -mediated reactions, (iv) the application of nitrones as radical precursors for SmI_2 -mediated intermolecular cross-coupling reactions, (v) diastereoselective couplings of *N*-*tert*-butanesulfinyl imines for the asymmetric synthesis of vicinal diamines and aminoalcohols, (vi) diaster-

eoselective pinacol couplings of complex substrates, and (vii) the application of SmI_2 -Reformatsky reactions for the synthesis of C-glycosides. These processes significantly expand the scope of the application of the reagent for the synthesis of valuable organic molecules.

Although the progress in the field has been considerable, many challenges still need to be addressed. The development of robust catalytic protocols, asymmetric SmI_2 -mediated cross-coupling reactions, the development of new intermolecular diastereoselective cross-couplings, the expansion and generalization of the scope of existing reactions, the design of new ligands, and increased mechanistic understanding of the underlying electron transfer processes are among the key areas that need to be resolved. In particular, we believe that future development of new reactions in this field will result from mechanistic studies and detailed understanding of the role of additives to fine-tune the reactivity of Kagan's reagent. Without doubt, the field will continue to inspire the imaginations of chemists in the years to come.

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Notes

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NOTE ADDED IN PROOF

After the submission of this Review, several additional examples of SmI₂-mediated cross-coupling reactions have been published. Ma reported the intramolecular Reformatsky reaction of an α -bromo amide onto an aldehyde to form a seven-membered ring in 78% yield in the first total synthesis of methyl *N*-decarbomethoxychanofruticosinate.⁵⁷⁸ Pattenden reported an impressive example of a SmI₂-mediated cascade reaction involving intramolecular 5-exo-trig ketyl radical/alkene cyclization/ β -hydroxyl elimination/transannular 6-exo-trig ketyl/olefin cyclization during investigation of the biosynthesis of sinulanocembranolide A.⁵⁷⁹ Piva reported the SmI₂-mediated synthesis of chiral cyclopentanols bearing three contiguous stereocenters in good yields and excellent diastereoccontrol utilizing 5-exo-trig ketyl/olefin coupling of substrates prepared via organocatalytic aldol condensation.⁵⁸⁰ Beaudry reported cross-coupling of aminal radicals generated from amidines and amidinium ions with activated olefins using SmI₂ in the presence

of NH₄Cl.⁵⁸¹ Doisneau and Beau reported the synthesis of spirolactonic C-sialosides via intramolecular Reformatsky reaction of glycosyl 2-pyridylsulfides and acetates using SmI₂–THF at room temperature.⁵⁸² Hudlicky investigated the use of SmI₂–HMPA to promote 6-exo-trig ketyl-olefin cyclization in the formal total synthesis of morphine alkaloids.⁵⁸³ Hoz reported the synthesis and application of hydroxylated HMPA derivatives as Lewis basic additives for SmI₂ to facilitate proton transfer to the radical anion within the same ion pair.⁵⁸⁴ Prasad investigated the mechanism of photoinduced electron transfer from EuI₂ complexes to halides and carbonyl compounds.⁵⁸⁵