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COMMUNICATION

# Cyclopentane formation from flexible precursors using samarium(II) reagents

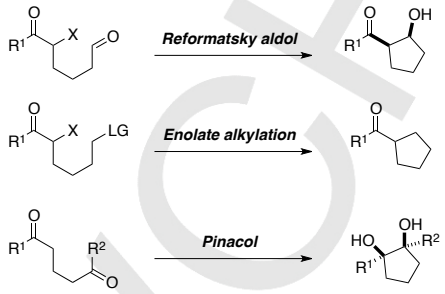
Christopher D. Aretz,[b] Humberto Escobedo, and Bryan J. Cowen*[a]

**Abstract:** Three efficient methods for five-membered ring carbocycle synthesis have been developed from simple starting materials using samarium(II) reagents. A Reformatsky aldol reaction proceeded efficiently with samarium(II) iodide using lithium bromide as an additive. A new intramolecular alkylation of a samarium enolate was realized with a pendant sulfonate ester leaving group. Pinacol cyclization of a simple diketone was also demonstrated giving a diol product in high stereoselectivity. A promising lead result has been established demonstrating enantioselectivity in a chiral ligand controlled Reformatsky aldol reaction.

## Introduction

Since its discovery in 1977 by Kagan, samarium(II) iodide ($SmI_2$) has been employed in several types of organic transformations as a single electron reducing agent.[1] Powerful carbon–carbon bond forming processes like carbonyl–alkene, radical–alkene, pinacol, Reformatsky aldol, Barbier, and Grignard reactions proceed smoothly with $SmI_2$ that would be difficult to accomplish with other methods.[2] Furthermore, tandem processes are often facilitated with this reagent through careful substrate design and judicious choice of reaction conditions.[3] Recent work has confirmed the sensitivity of $SmI_2$ to exogenous ligands and has served to develop additives that increase the reduction potential of $SmI_2$ leading to a more facile electron transfer to the organic substrate acceptor.[4] These studies have greatly expanded the reaction scope and applications of newly discovered ligand–$SmI_2$ systems. Also, the use of the carcinogenic Lewis base additive hexamethylphorsphoramide (HMPA) has become less common with the identification of more benign additives for Sm(II)-promoted reactions. Furthermore, Sm(II) reagents other than $SmI_2$ have proven to be successful reducing agents for a range of organic transformations.[4c,d]

The formation of 5-membered ring carbocycles remains an avenue for further discovery in synthetic organic chemistry. While recent examples of Pauson-Khand[5] reactions and Lewis base promoted [3+2]-cycloadditions[6] provide efficient methods to access these ring systems, more numerous and robust methods exist for the synthesis of 6-membered ring carbocycles, by comparison. Recently, our lab became interested in synthesizing 5-membered rings through application of $SmI_2$-promoted intramolecular Reformatsky aldol, enolate alkylation, and pinacol reactions (Scheme 1). Cyclization precursors were designed to be accessed quickly from common simple starting materials. We selected flexible, unsubstituted carbon chains containing pendant reactive groups as desirable substrates for the synthesis of cyclopentanes through Sm(II)-mediated cyclization reactions.




**Scheme 1.** This work: Sm(II)-promoted cyclizations providing pentacyclic products.

## Results and Discussion

We began our studies with the synthesis of various aryl ketone precursors for reductive cyclization reactions with Sm(II) reagents. Starting from ε-caprolactone (**1**), Grignard addition to the *in situ* generated Weinreb amide gave alcohol product **2** in good yield (Scheme 2).[7] After some experimentation, we found phenyltrimethylammonium tribromide (PTT) as a convenient reagent for the synthesis of α-bromoketone **3** without the requirement for first protecting the primary alcohol.[8] Subsequent oxidation of this alcohol with Dess–Martin periodinane (DMP) provided aldehyde product **4a** in good yield.[9] This three-step sequence proved general for a set of aryl ketones providing substrates to be studied in Sm(II)-promoted intramolecular Reformatsky aldol reactions. Furthermore, simple substitution of DMP for methanesulfonyl chloride (MsCl) in the sequence then provided a method for the synthesis of primary mesylated compounds such as phenyl ketone **5a** in short order. These substrates would be investigated in Sm(II)-promoted intramolecular alkylation reactions. Finally, Grignard addition of 5-bromopentene (**6**) to benzaldehyde (**7**) provided benzylic alcohol **8** which was oxidized with DMP to give aryl ketone **9**. Wacker oxidation of the pendant alkene gave diketone product **10a** which was a desired precursor for studying Sm(II)-promoted intramolecular pinacol cyclization reactions to deliver substituted cyclopentane products.

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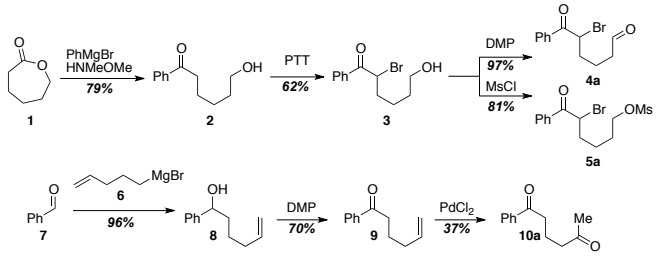
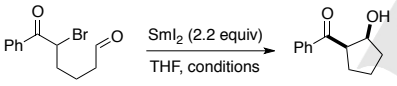



**Scheme 2.** Synthesis of cyclization substrates from ε-caprolactone. PTT = phenyltrimethylammonium tribromide, DMP = Dess–Martin periodinane.

Investigations into the Reformatsky aldol reaction commenced with evaluation of α-bromoketone **4a**. Although there are numerous reports of successful intramolecular Reformatsky aldol reactions using $SmI_2$, most cases invoke α-halo ester substrates to provide six-membered ring products. Surprisingly, there are no reported Sm(II)-promoted cyclization reactions of simple α-halo ketones such as **4a**. We wished to study this reaction for the facile synthesis of disubstituted cyclopentane products. Encouragingly, subjection of **4a** to $SmI_2$ (2.2 equiv) in THF at −15 °C gave β-hydroxyketone product **11a** with high diastereoselectivity (>20:1) albeit in a modest 14% yield (Table 1, entry 1). Raising the temperature to 0 °C increased isolated yield to 53% but lowered the observed diastereomer ratio (dr) to 8:1 (entry 2). Inclusion of HMPA as an additive was detrimental to the reaction leading to no observable product formation (entry 3). However, when lithium bromide was included in the reaction at −15 °C in THF, product **11a** was isolated in 66% yield as a single diastereomer (dr >20:1; entry 4). Presumably, the strong reducing agent, samarium(II)bromide ($SmBr_2$), is generated with this additive allowing for smooth Reformatsky aldol cyclization.[10]

***Table 1.*** Optimization of an intramolecular Reformatsky aldol cyclization

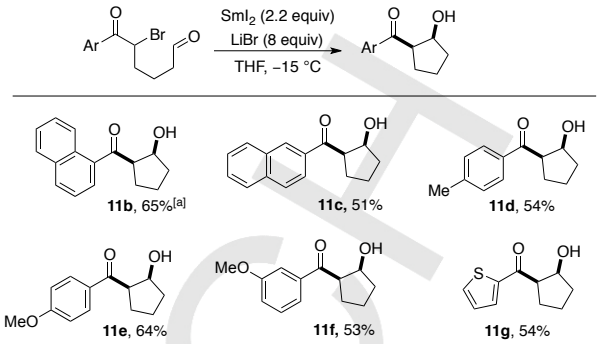



**4a** **11a**

| Entry | Temperature (°C) | Additive | Yield (%)[a] | dr[b] |
|---|---|---|---|---|
| 1 | −15 | None | 14 | >20:1 |
| 2 | 0 | None | 53 | 8:1 |
| 3 | 0 | HMPA[c] | 0 | – |
| 4 | −15 | LiBr[d] | 66 | >20:1 |

[a] Isolated yield after silica gel chromatography. [b] Determined by $^1H$ NMR spectroscopy of the crude reaction mixture. [c] 10 equiv. [d] 8 equiv.

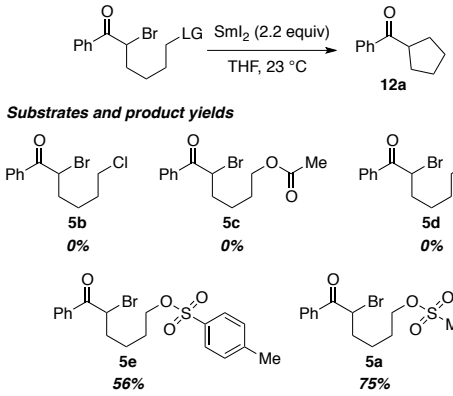
Various aromatic α-bromoketones gave similarly good results. The 1-naphthyl derivative cyclized under the optimized conditions to give β-hydroxyketone product **11b** in 65% yield (Figure 1). The 2-naphthyl substrate underwent reductive Reformatsky aldol cyclization to provide product **11c** in 51% yield. A *p*-tolyl substituted ketone cyclized to give cyclopentane product **11d** in 54% yield. Electron-rich substrates were competent in the cyclization with the *p*-methoxy derivative providing product **11e** in 64% yield and *m*-methoxy ketone giving β-hydroxyketone **11f** in 53% yield.[11] A heteroaromatic derivative was also shown to undergo the Sm(II)-promoted intramolecular Reformatsky aldol reaction with a thiophene derivative cyclizing to provide product **11g** in 54% yield (entry 6). While side products resulting from over reduction of the carbonyl moieties provided the mass balance of these reactions, it is notable that all cyclcopentanes were isolated as the single *syn* diastereomer.




[a] Isolated yield after silica gel chromatography. All products isoldated as a single diastereomer (>20:1 dr as determined by $^1H$ NMR spectroscopy of the crude reaction mixture).

**Figure 1.** Substrate scope for intramolecular Reformatsky aldol cyclization

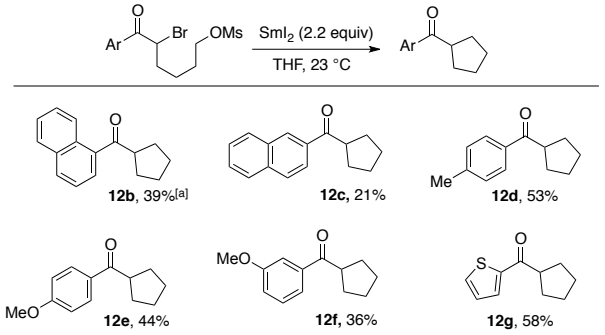
We next investigated the intramolecular alkylative cyclization of mesylated substrate **5a**. Unlike the Sm(II)-promoted Reformatsky reaction, enolate alkylation reactions mediated by $SmI_2$ are rare.[12],[13] Thus we wished to establish an additional method for cyclopentane synthesis while also expanding the scope of Sm(II)-promoted reactions. A survey of a set of substrates bearing different leaving groups at the ε-position to the carbonyl group were synthesized and studied in a $SmI_2$-promoted cyclization reaction (Scheme 3). When alkyl halide derivative **5b** was treated with a THF solution of $SmI_2$ (2.2 equiv) at 23 °C no cyclization to the desired product was observed.[14] Ester substrates **5c** and **5d** also led only to recovery of starting material. However, sulfonate ester **5e** smoothly cyclized to cyclopentane **12** which was isolated in 56% yield. Better results were obtained using the mesylate derivative **5a** giving product **12a** in 75% yield. Notably, additives like LiBr did not improve the reaction efficiency as seen previously for the Reformatsky aldol reaction.




**Scheme 3.** Alkylative cyclization reactions promoted by $SmI_2$.

Investigation of the substrate scope paralleled the types of starting materials evaluated for the Reformatsky aldol cyclization. For example, cyclization of the 1-naphthyl derivative gave product **12b** in a moderate 39% yield (Figure 2). The 2-naphthyl derivative was less efficient delivering product **12c** in 21% yield. Treatment of the *p*-tolyl substrate with $SmI_2$ in THF resulted in cyclization to cyclopentane **12d** in 53% yield. An electron-rich *p*-methoxy α-bromoketone cyclized providing product **12e** in 44% isolated yield. The *m*-methoxy derivative also cyclized to give product **12f** in 36% yield. We also evaluated our method using a heterocyclic

substrate as thiophene-substituted α-bromoketone smoothly underwent the intramolecular cyclization to give product **12g** in 58% yield.

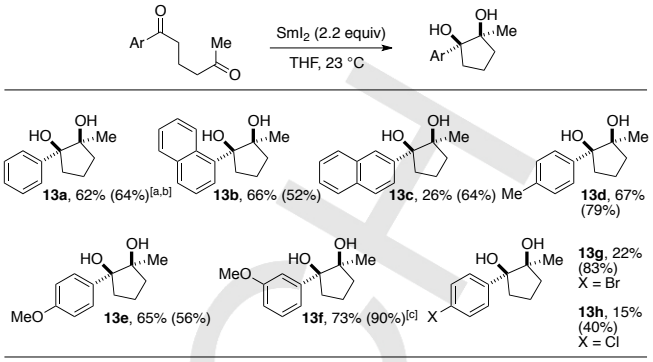



[a] Isolated yield after silica gel chromatography.

**Figure 2.** Substrate scope for intramolecular alkylative cyclization.

The next reaction we sought to exploit for the synthesis of functionalized 5-membered carbocycles was the intramolecular pinacol cyclization. Sm(II)-promoted pinacol cyclizations are well established in the literature, although the reaction's utilization for the synthesis of cyclopentanes is limited. Implementing the three-step route to access diketone substrates (see Scheme 2), we wondered how efficient intramolecular pinacol cyclization of such flexible precursors to *β*-hydroxy ketone products would be and if the resulting diastereomer ratio could be controlled. Notably, these types of substrates have been cyclized under electroreductive conditions and using *in situ* generated Ti(III) do give *anti* and *syn* diastereomers of product respectively.[15] Since the more convenient $SmI_2$ reagent has not been reported to act on these substrates, we investigated the pinacol cyclization of aryl ketone substrates similar to those evaluated in the Reformatsky aldol and alkylative cyclization reactions. This reaction would lead to cyclopentane diols with synthetic utility.

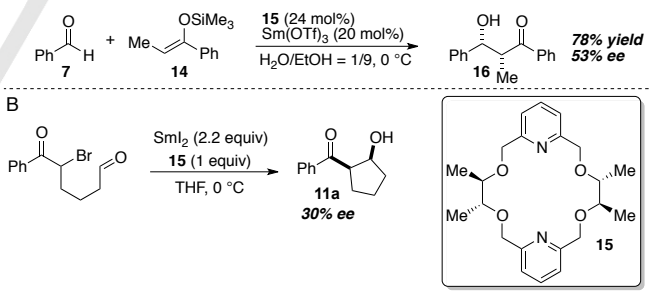
Pleasingly, we quickly identified suitable conditions for the intramolecular pinacol cyclization reaction of diketone **10a**. Treatment with $SmI_2$ (2.2 equiv) in THF at 23 °C led to diol product **13a** in 62% isolated yield as a single diastereomer (Figure 3). Inclusion of LiBr in the reaction led to significant improvement in isolated yields in several cases.[16] While the 1-naphthyl substituted diketone cyclized efficiently to give diol product **13b** in 66% yield, the corresponding 2-naphthyl derivative led to only a modest 26% yield of diol **13c**. However, this yield increased to 64% of **13c** with LiBr as an additive. The *p*-tolyl-substituted ketone underwent a smooth pinacol cyclization to give product **13d** in 67% yield. The electron rich *p*-methoxy diketone underwent the pinacol cyclization to give diol **13e** in 65% yield. The *m*-methoxy analog was even more efficient in the $SmI_2$-promoted cyclization providing product **13f** in 73% isolated yield. Aryl ketones bearing *p*-substituted halogens were less efficient in the process with the bromo derivative giving diol product **13g** in 22% yield and the chloro derivative providing product **13h** in 15% yield. Pleasingly, these yields increased to 83% (**13g**) and 40% (**13h**) with inclusion of LiBr.




[a] Isolated yield after silica gel chromatography. All products isolated as a single diastereomer (>20:1 dr as determined by $^1H$ NMR spectroscopy of the crude reaction mixture). [b] Yields in parentheses for reactions run with LiBr (8 equiv). [c] Based on recovered starting material.

**Figure 3.** Substrate scope for intramolecular pinacol cyclization.

Our lab is also interested in the identification of suitable chiral ligands for samarium that would result in the enantioselective formation of cyclopentane products. Sm(II)-promoted reactions in total synthesis often result in highly diastereoselective reactions but ligand systems for general enantioselective Sm(II)-promoted reactions have been elusive.[17] Considering that a Sm(III)-enolate intermediate species is likely operative in the Reformatsky aldol cyclization reaction, we sought ligands that were able to bind the radius of this oxidized lanthanide intermediate. Kobayashi investigated the intermolecular Mukaiyama aldol reaction of benzaldehyde (**7**) with silyl enol ether **14** using crown ether type ligand **15** and various lanthanide (III) triflates (Scheme 4A).[18] $Sm(OTf)_3$ catalyzed the reaction to give *syn*-product **16** in 78% yield with 53% ee. Preliminary results using this ligand in the intramolecular Reformatsky aldol reaction gave product **11a** with a promising 30% ee (Scheme 4B). Further investigation of these types of crown ligands for enantioselective transformations of Sm(II)-reagents are underway in our lab.




**Scheme 4.** Enantioselective aldol reactions with chiral crown ether **15**.

## Conclusions

In summary, we have identified conditions for three Sm(II)-promoted intramolecular cyclization reactions *en route* to cyclopentane products. Two such reactions, an intramolecular Reformatsky aldol and a pinacol cyclization, are highly diastereoselective. In regard to the former, we found LiBr as an effective additive in terms of isolated product yields presumably through formation of $SmBr_2$ from $SmI_2$. We have also established that primary mesylates are efficient electrophilic handles for intramolecular alkylation reactions of samarium enolates. Alkylation of such enolates is only sporadically reported in the literature and use of primary mesylates could allow for further

applications of this functional group in Sm(II)-mediated processes. Finally, we have demonstrated modest enantiocontrol in an intramolecular Reformatsky cyclization reaction using a crown ether type ligand. Further investigation into asymmetric reactions using Sm(II)-species is ongoing in our laboratory.

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**Keywords:** samarium(II) iodide • cyclopentane • alkylation • pinacol • reductive cyclization

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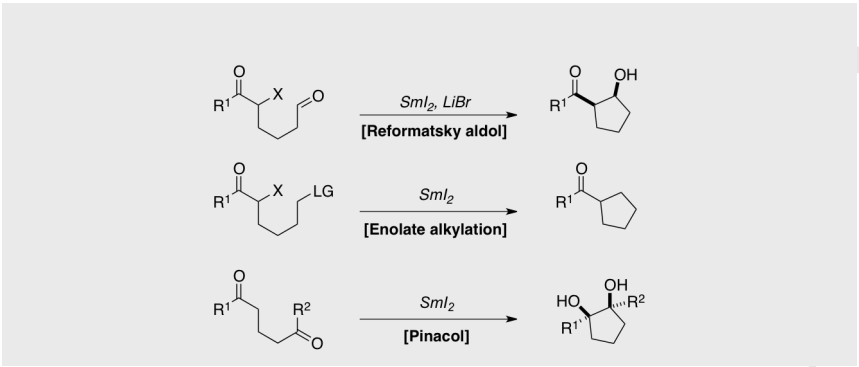


**Sm(II)-Mediated Cyclizations**

*Christopher D. Aretz, Humberto Escobedo, and Bryan J. Cowen**

**Cyclopentane formation from flexible precursors using samarium(II) reagents**

This study presents three efficient methods for five-membered ring carbocycle synthesis using samarium(II) reagents. Simple organic starting materials engage in intramolecular Reformatsky aldol, enolate alkylation, and pinacol cyclizations. A promising lead result has also been established demonstrating enantioselectivity in a chiral ligand controlled Reformatsky aldol reaction.