DOI: 10.1002/anie.201201065

Reductive Coupling

Beyond Samarium Diiodide: Vistas in Reductive Chemistry Mediated by Lanthanides(II)

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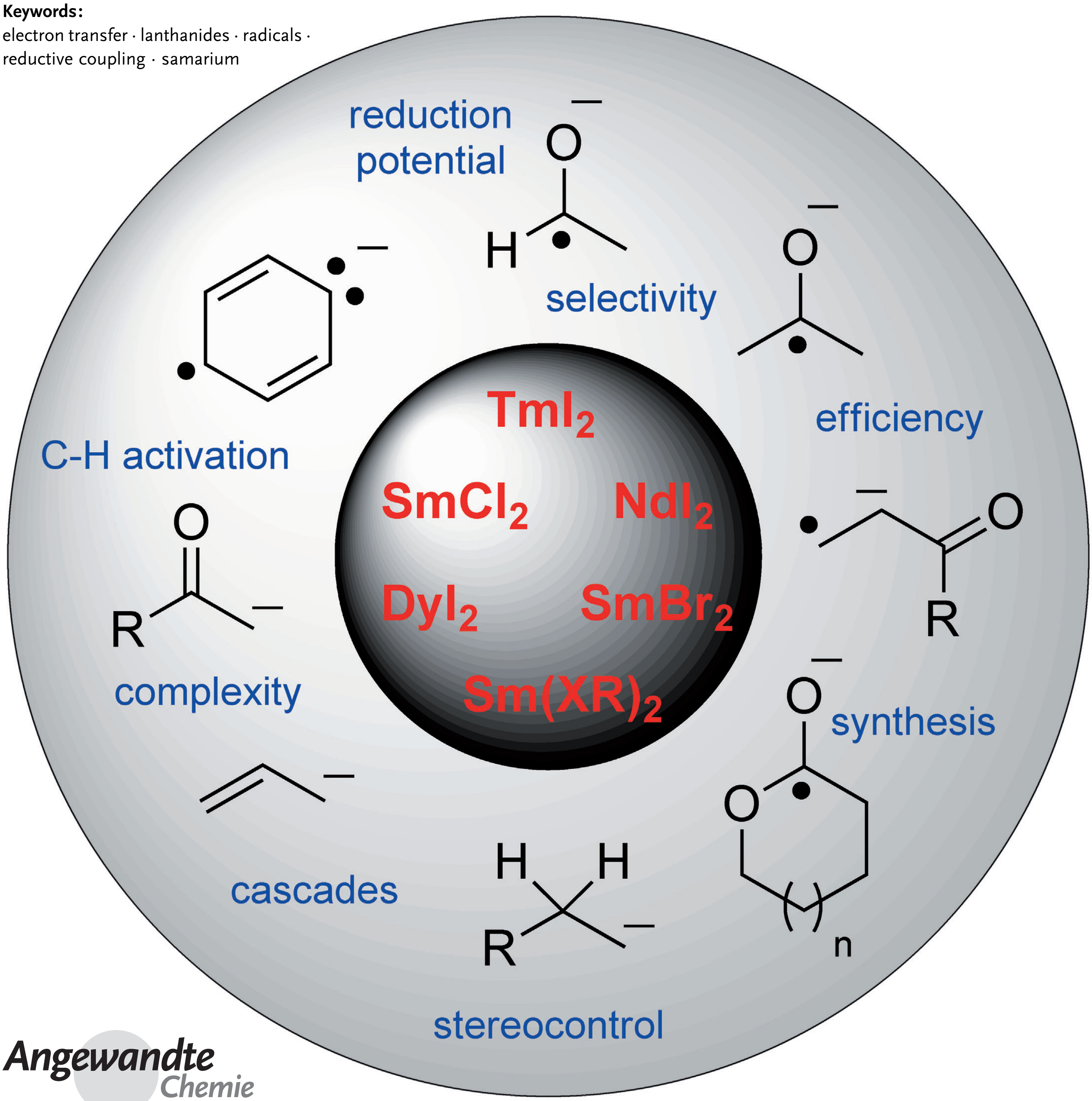
Keywords:
electron transfer · lanthanides · radicals · reductive coupling · samarium



Angewandte Chemie

Reactions proceeding through open-shell, single-electron pathways offer attractive alternative outcomes to those proceeding through closed-shell, two-electron mechanisms. In this context, samarium diiodide (SmI_2) has emerged as one of the most important and convenient-to-use electron-transfer reagents available in the laboratory. Recently, significant progress has been made in the reductive chemistry of other divalent lanthanides which for many years had been considered too reactive to be of value to synthetic chemists. Herein, we illustrate how new samarium(II) complexes and nonclassical lanthanide(II) reagents are changing the landscape of modern reductive chemistry.

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1. Introduction

Lanthanides (Figure 1) are employed in a wide range of industries and have found general application in such diverse products as car engines, television screens, lasers, fuel cells and magnetic resonance imaging (MRI) contrast agents.[1] For example, neodymium (Nd) and dysprosium (Dy) have become essential elements for high-performance Nd-Fe-B magnets used in car motors for hybrid and electric vehicles.[1d] In contrast, the red-emitting phosphors in plasma display panels rely on sharp 4f–4f transitions of the Eu^{3+} ion.[1e] According to current estimates, the use of lanthanides will increase in the industrialized world.[1f–h]

Figure 1. Lanthanide series. La = Lanthanum. Ce = Cerium. Pr = Praseodymium. Nd = Neodymium. Pm = Promethium. Sm = Samarium. Eu = Europium. Gd = Gadolinium. Tb = Terbium. Dy = Dysprosium. Ho = Holmium. Er = Erbium. Tm = Thulium. Yb = Ytterbium. Lu = Lutetium.

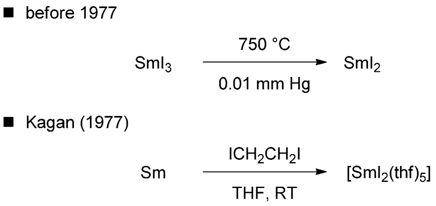
In organic chemistry, lanthanides have provided many exciting opportunities in catalysis and reductive chemistry that are not available when using other reagents.[2] Since the 4f orbitals of lanthanides are shielded by $5s^2$ and $5p^6$ orbitals, they do not participate in bonding and, in general, similar chemical properties can be expected across the series of lanthanides.[1a–c,3] Furthermore, the lanthanide contraction results in a gradual decrease in ionic radius with increasing atomic number (Table 1).[3a] Lanthanides are highly electropositive (1.1 on the Pauling scale), which contributes to the ionic character of lanthanide complexes.[3b] Relatively high Lewis acidity[3d–e] and strong oxophilicity (expressed in terms of the dissociation energy of the corresponding oxides)[3e] also play important roles in defining the outcome of transformations mediated by lanthanides. Finally, although the most stable oxidation state of lanthanides is trivalent, some lanthanides exist in their divalent oxidation state, which leads to their application as strong reductants in synthetic chemistry.[3f]

Table 1: Properties of selected lanthanides.

Entry	Ln	Electron configuration of Ln	Ionic radius Ln^{II} [Å][a]	Ionic radius Ln^{III} [Å][b]	Oxophilicity D_0(Ln-O) [kcal mol^{-1}][c]	$E°$ Ln^{III}/L^{II} [V][d]
1	Nd	$[Xe]4f^46s^2$	1.29	1.16	179	−2.62
2	Sm	$[Xe]4f^66s^2$	1.27	1.13	138	−1.55
3	Eu	$[Xe]4f^76s^2$	1.25	1.12	93	−0.35
4	Dy	$[Xe]4f^{10}6s^2$	1.19	1.08	145	−2.56
5	Tm	$[Xe]4f^{13}6s^2$	1.09	1.05	116	−2.22
6	Yb	$[Xe]4f^{14}6s^2$	1.14	1.04	88	−1.15

[a] Eight-coordinate Ln^{II}; Ref. [3a]. [b] Nine-coordinate Ln^{III}; Ref. [3a]. [c] Ref. [3e]. [d] vs NHE in H_2O; Ref. [3f].

Of the lanthanide(II) reagents, samarium diiodide (SmI_2, Kagan's reagent) has attracted most interest.[4] Although, this reagent has been known in the solid state since 1906 and frequently utilized in inorganic chemistry,[5] the solution synthesis of SmI_2 by Kagan and co-workers in 1977 marked the beginning of an era in which SmI_2 has found widespread use in organic chemistry (Scheme 1).[6] There is little doubt that SmI_2 is one of the most important electron-transfer



Scheme 1. Synthesis of samarium diiodide (SmI_2, Kagan's reagent). thf = tetrahydrofruran.

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reagents available in the laboratory.[7] With its ability to initiate challenging chemical processes through either one-electron, open-shell or two-electron, closed-shell pathways (often proceeding with precise control of structure and stereochemistry) merged with its suitability for the orchestration of powerful cascade processes (often utilized in complex natural product synthesis), SmI_2 has changed the way we consider difficult bond disconnections in organic chemistry.[8]

In recent years there have been many exciting advances in the reductive chemistry of divalent lanthanides other than SmI_2, including the synthesis of new Sm^{II} reagents and the preparation of nonclassical lanthanide(II) reagents in solution (Figure 2).[9]

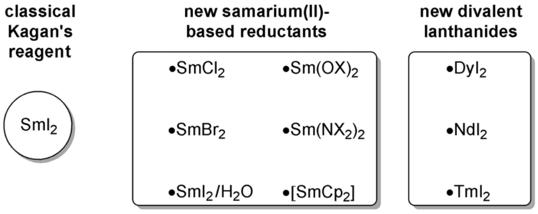
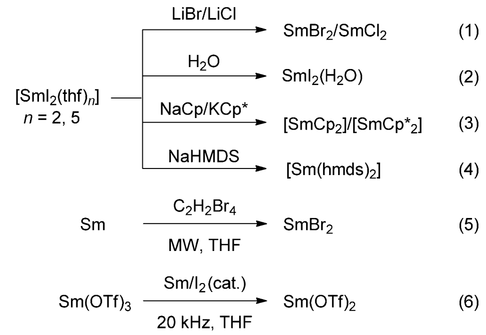


Figure 2. New vistas in reductive chemistry mediated by lanthanides. $Cp = C_5H_5$.

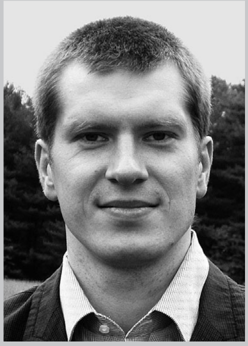
The new complexes of Sm^{II} and the first low-valent complexes of nonclassical lanthanides, such as dysprosium (Dy), neodymium (Nd), and thulium (Tm) are much more powerful reductants than SmI_2. As a result, new Sm^{II} complexes have dramatically expanded the chemistry mediated by SmI_2 and are potential replacements for SmI_2/HMPA (HMPA = hexamethylphosphormaide), a complex in which the ligands are toxic. The recently discovered reductive power of the nonclassical divalent lanthanides brings benchmark reactions in reductive organic chemistry, for example the Birch reduction, within reach, while preserving the selectivity exhibited by SmI_2. Thus, entirely new vehicles are now available for the delivery of electrons and the subsequent exploitation of open-shell reaction pathways. In a broader sense, the solution availability of new lanthanides(II) characterized by remarkably different reducing properties (reduction potentials ranging from -0.35 to -2.62 V, see Table 1) and gradually changing metal ion size, but otherwise similar chemical properties, offers unprecedented opportunities for the fine-tuning and optimization of selective electron-transfer reactions. In this Review we will give a taste of recent innovations in the area of reductive lanthanide chemistry and illustrate how the new lanthanide(II) complexes have already had a major impact on the field of organic synthesis.

2. New Samarium(II) Reagents: Beyond Samarium Diiodide

In addition to SmI_2, six major samarium(II)-based reagent systems have been used to mediate organic transformations: 1) samarium(II) bromide ($SmBr_2$), 2) samarium(II) chloride ($SmCl_2$), 3) samarium(II) iodide/water complex (SmI_2/H_2O), 4) samarium(II) amides, 5) samarium(II) alkoxides, and 6) samarium(II) cyclopentadienyl complexes. In general, these single-electron reductants are characterized by higher reduction potentials than SmI_2, thus permitting activation of recalcitrant substrates by electron transfer. Moreover, the new samarium(II)-based reagents provide a high degree of chemo-, regio-, and diastereoselectivity, and show good functional-group tolerance. Accordingly, the use of new samarium(II)-based reductants has been demonstrated to be beneficial in many examples from the literature. In analogy to SmI_2, the increasing importance of new samarium(II)-based reagents is due to their ready availability under standard laboratory conditions (Scheme 2).



Scheme 2. Synthesis of samarium(II)-based reductants. $Cp^* = C_5Me_5$, $HMDS = N(SiMe_3)_2$, MW = microwaves, Tf = trifluoromethanesulfonyl.



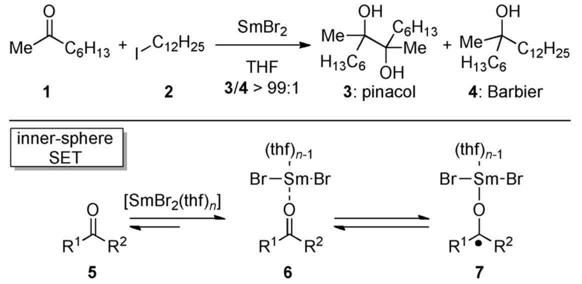
Michal Szostak received his MSc from Wroclaw Medical University, Poland, in 2005 under the supervision of Prof. Stanislaw Ryng. He received his PhD from the University of Kansas in 2009, working with Professor Jeffrey Aubé. After postdoctoral research at Princeton University with Professor David MacMillan, he joined the group of Professor David Procter at the University of Manchester, where he works on samarium(II) iodide chemistry.

David Procter received his PhD from the University of Leeds, working with Prof. Christopher Rayner. After postdoctoral work with Prof. Robert Holton at Florida State University, he took up a Lectureship at the University of Glasgow. After moving to the University of Manchester, he was promoted to Professor in 2008. His research interests lie in the development of organic reactions and their application in biology, medicine and materials science. He is joint author of the research text "Organic synthesis using samarium diiodide".

2.1. Samarium(II) Bromide

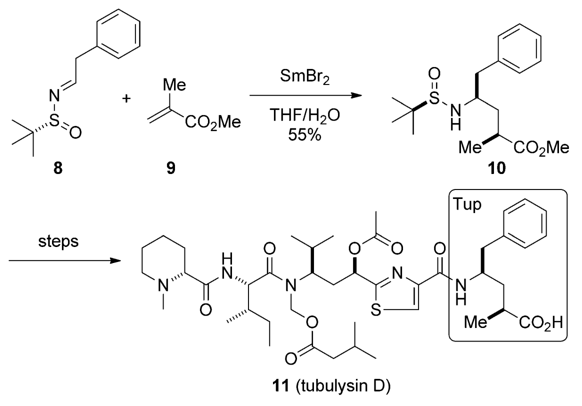
Although $SmBr_2$ is a powerful reductant ($SmBr_2$: −1.55 V vs SCE in THF; SmI_2: −0.98 V vs SCE in THF),[10] remarkable levels of selectivity are possible with this reagent. It was shown by Kagan and co-workers that $SmBr_2$ can be conveniently prepared by the reduction of $SmBr_3$ with metallic lithium,[11] while Namy and co-workers reported another straightforward synthesis of $SmBr_2$ from samarium metal and tetrabromoethane.[12] The latter procedure was recently refined by Dahlén and Hilmersson [Scheme 2, Eq. (5)].[13] However, perhaps the most convenient method of synthesis of $SmBr_2$ was reported by Flowers and co-workers who utilized readily available SmI_2 and LiBr [Scheme 2, Eq. (1)].[14]

Flowers and co-workers have investigated the use of $SmBr_2$ in C−C bond-forming reactions of alkyl halides and carbonyl compounds, and observed complete selectivity for pinacol coupling in the presence of reactive alkyl iodides (Scheme 3).[10] With $SmBr_2$ as a reductant, complete selectivity for pinacol coupling in the presence of reactive alkyl iodides was observed. Interestingly, mixtures of products were detected in reactions mediated by SmI_2 or $SmCl_2$ (see Section 2.2 for a discussion of the characteristics of $SmCl_2$), while SmI_2/HMPA[15] (SmI_2/HMPA: −1.75 V vs SCE in THF) exclusively afforded the Barbier products **4**. Mechanistic studies indicated that the reduction of ketones with $SmBr_2$ proceeds through an inner-sphere mechanism, whereas the reduction of alkyl iodides with SmI_2/HMPA is an outer-sphere process.[15] This study by Flowers is a beautiful example of the ability to fine-tune the selectivity and reactivity of Sm^{II} reagents based on a detailed understanding of the underlying mechanism.



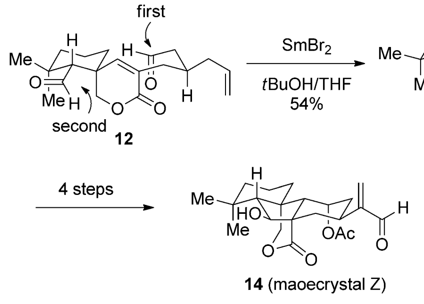
Scheme 3. Chemoselective $SmBr_2$-mediated reductive coupling of alkyl ketones by Flowers and co-workers.[10] SET = single-electron transfer.

Ellman and co-workers have utilized $SmBr_2$ in a pivotal asymmetric cross-coupling reaction between a chiral sulfinyl imine and an α-substituted α,β-unsaturated ester in an elegant synthesis of tubulysin D, a potent anticancer agent (Scheme 4).[16a] This reaction was the first example of an asymmetric synthesis of an α-substituted γ-amino-acid derivative by direct coupling of an imine and provided the coupling product in 99% yield with 80:15:3:2 diastereoselectivity. Chromatographic purification gave the pure product **10** in 55% yield. Interestingly, in addition to $SmBr_2$, the water cosolvent proved essential in this reaction, thus suggesting that $SmBr_2$/H_2O might have considerable potential as a reagent for synthesis (see, Section 2.3 for the properties of SmI_2/H_2O). Moreover, the Ellman group employed $SmBr_2$ generated in situ from SmI_2 and LiBr.[14] Therefore, it is quite likely that the lithium cation present in solution played a significant role in providing a highly ordered transition state in the reported coupling. This hypothesis is supported by the recent report by Gilles and Py, who determined that the lithium cation is required to obtain high levels of diastereoselectivity in a $SmBr_2$-mediated cross-coupling of nitrones with β-silyl-α,β-unsaturated esters.[16b]



Scheme 4. Asymmetric $SmBr_2$-mediated reductive coupling between a sulfinyl imine and methyl methacrylate in a total synthesis of tubulysin B by Ellman and co-workers.[16a] Tup = tubuphenylalanine.

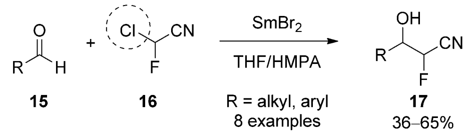
One of the most dramatic examples of the effect of a Sm^{II} reagent was recently reported by Reisman and co-workers in the first total synthesis of the complex cytotoxic diterpene maoecrystal Z (Scheme 5).[17] The reductive coupling of a ketyl radical (generated selectively at the less hindered side chain) with the double bond of the α,β-unsaturated lactone, followed by a second electron-transfer reaction and aldol condensation, forged two rings and four stereocenters, thereby providing impressive access to a late-stage intermediate in the synthesis. Interestingly, $SmBr_2$ proved to be the reagent of choice for the cascade cyclization of dialdehyde **12**, whereas both SmI_2 (used in the first examples of this family of cascade processes by our group)[18] and $SmCl_2$ (employed



Scheme 5. Diastereoselective $SmBr_2$-mediated dialdehyde cyclization cascade in a total synthesis of maoecrystal Z by Reisman and co-workers.[17]

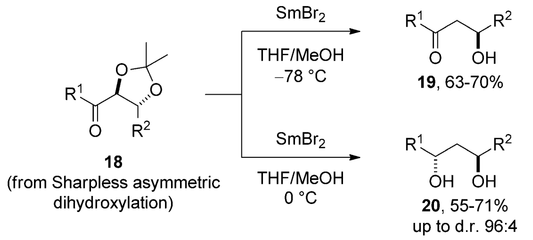
successfully in a model system) were ineffective. Reisman's work clearly demonstrates that a judicious choice of lanthanide(II) reagent can have a major influence on the outcome of a desired transformation.

Fluorine-containing compounds are valuable in the pharmaceutical and agrochemical industries. Yokoyama and co-workers reported the synthesis of 2-fluoroethanols by the selective Reformatsky-type cyanofluorination of aldehydes through exploiting $SmBr_2$ as an electron-transfer reagent (Scheme 6).[19] Notably, $SmBr_2$ promoted the couplings of aromatic and aliphatic aldehydes at low temperatures to give the desired products in good yields. Flowers and co-workers have studied the properties of a related $SmBr_2$/HMPA complex, and found that the addition of HMPA to $SmBr_2$ results in a significant increase of the redox potential of the reagent ($SmBr_2$: −2.07 V; $SmBr_2$/HMPA: −2.63 V, both vs $Ag/AgNO_3$ in THF).[20]



Scheme 6. Chemoselective $SmBr_2$-mediated cyanofluorination of aldehydes by Yokoyama and co-workers.[19]

Enantiomerically pure 1,3-diols are useful building blocks for the synthesis of natural products. Zörb and Brückner reported that $SmBr_2$ mediates a novel reduction of acetonides (generated by Sharpless asymmetric dihydroxylation) to give enantiomerically pure 3-hydroxy ketones (Scheme 7).[21] Furthermore, by applying the established protocol for the diastereoselective reduction of hydroxy ketones,[22] the reaction was extended to the synthesis of 1,3-*anti* diols with good selectivity.

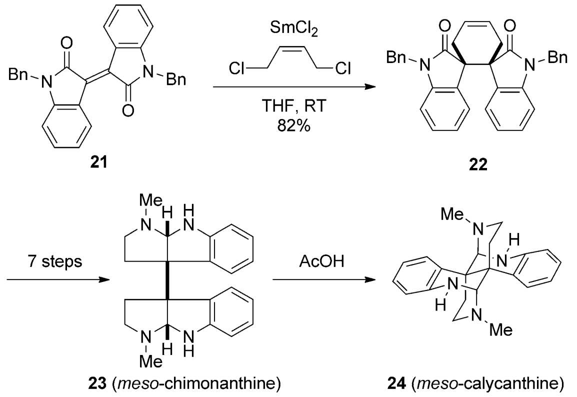


Scheme 7. $SmBr_2$-mediated synthesis of enantiomerically pure β-hydroxyketones and 1,3-diols by Zörb and Brückner.[21]

2.2. Samarium(II) Chloride

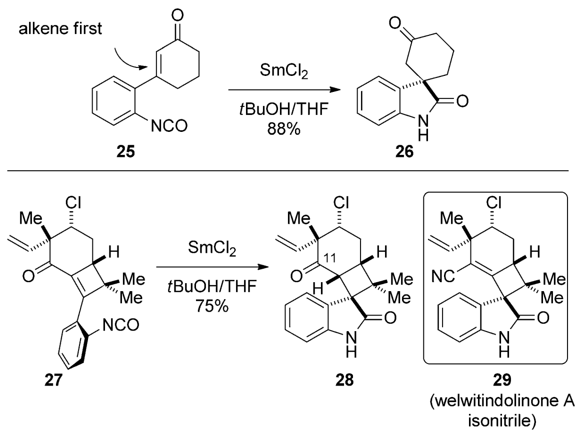
The redox potential of samarium(II) chloride ($SmCl_2$: −1.78 V vs SCE in THF) is higher than that of SmI_2 (SmI_2: −0.98 V vs SCE in THF).[10] The method of choice for the formation of $SmCl_2$ involves the in situ reaction between SmI_2 and LiCl reported by Flowers and co-workers [Scheme 2, Eq. (1)].[14] A recent study by Matsukawa et al. suggests, rather surprisingly, that this reagent can also be prepared from $SmCl_3$ and Sm metal in water.[23] $SmCl_2$ is an excellent promoter of challenging electron-transfer reactions.

Link and Overman showcased the use of $SmCl_2$ in the reductive dialkylation of isoindigo **21** with *cis*-1,4-dichloro-2-butene under mild reaction conditions (Scheme 8).[24] The reaction mediated by $SmCl_2$ was sufficiently powerful, establishing two all-carbon quaternary centers with excellent control over stereoselectivity, that it forged the key step in the first total synthesis of polyindoline alkaloids *meso*-chimonanthine and *meso*-calycanthine. The impressive levels of stereocontrol (> 20:1) were rationalized by chelation of both carbonyl groups to Sm^{III}, thereby leading to a highly organized transition state with subsequent diastereoselective alkylation of the samarium enolate.[25] Interestingly, other reagent systems including alternative Sm^{II} systems (SmI_2, SmI_2/HMPA) and more traditional approaches based on deprotonation of the corresponding saturated substrates, afforded mixtures of products, thus demonstrating the remarkable potential of $SmCl_2$ in the synthesis of complex natural products.



Scheme 8. Diastereoselective $SmCl_2$-mediated reductive dialkylation in a total synthesis of *meso*-chimonanthine and *meso*-calycanthine by Link and Overman.[24] Bn = benzyl.

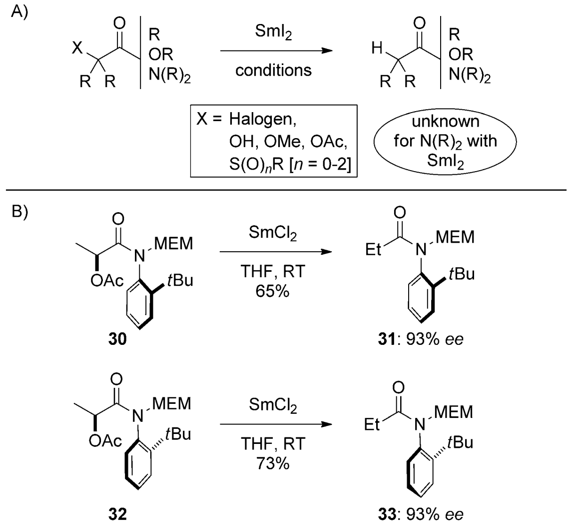
Wood and co-workers have reported the highly stereoselective synthesis of quaternary centers using intramolecular couplings of isocyanates mediated by $SmCl_2$ in an approach to welwitindolinone A isonitrile, a highly functionalized oxindole alkaloid (Scheme 9).[26] The reaction was first explored in the model system **25**. These studies demonstrated that $SmCl_2$ was the reagent of choice for the desired transformation, and that the reaction proceeds by a pathway in which the alkene is coupled to the isocyanate ("alkene first") rather than the more traditional "carbonyl first" mechanism.[8] With the optimized reaction conditions in hand, the pivotal coupling of the isocyanate **27** generated the complex oxindole **28** in excellent yield with complete diastereocontrol. In agreement with studies by Flowers and co-workers (see, also Scheme 3),[10] reduction of the sensitive alkyl chloride moiety was not observed, thus illustrating the selectivity and



Scheme 9. $SmCl_2$-mediated synthesis of oxindoles by the reductive coupling of isocyanates in an approach to welwitindolinone A isonitrile by Wood and co-workers.[26]

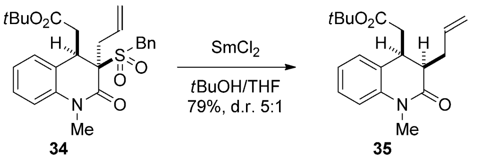
functional-group tolerance possible with this samarium(II) reagent.

The reduction of α-heteroatom-substituted carbonyl compounds to the parent carbonyl derivatives is one of the most common uses of SmI_2 (Scheme 10 A).[7,8] In the context of the enantioselective synthesis of atropoisomeric anilides, Simpkins and co-workers reported the $SmCl_2$-mediated α-deoxygenation of amides under mild reaction conditions (Scheme 10 B).[27] In extending the scope of the reductions, Simpkins showed that $SmCl_2$ is also the reagent of choice for the deoxygenation of other amide substrates, a reaction that has not been achieved with SmI_2. The ease of the deoxygenation of amides with the strong reductant $SmCl_2$ suggests that the mechanism involves a chelation-assisted electron transfer to the carbonyl group, which is initiated by coordination of the samarium to both the α-heteroatom substituent and the carbonyl group.[8]



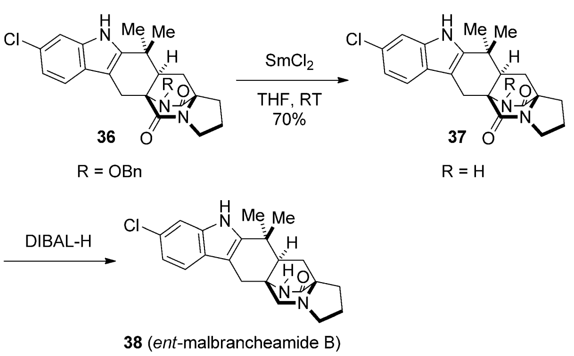
Scheme 10. A) Reduction of α-heteroatom-substituted carbonyl groups using SmI_2. B) $SmCl_2$-mediated reduction of atropoisomeric α-acyloxy amides by Simpkins and co-workers.[27] MEM = 2-methoxyethoxymethyl.

Our group has reported the reductive α-desulfonylation of tetrahydroquinolones mediated by $SmCl_2$ as part of a program directed towards a new linker strategy for the solid-phase synthesis of nitrogen heterocycles (Scheme 11).[28] In the solution-phase model system **34**, the combined use of $SmCl_2$ and *t*BuOH as a proton source afforded the *syn*-product **35** in good yield and diastereoselectivity. Subsequently, these conditions were successfully applied to a solid-phase synthesis of a library of diverse tetrahydroquinolones.



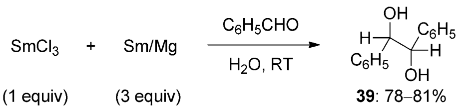
Scheme 11. $SmCl_2$-mediated cleavage of an α-heteroatom substitutent in the synthesis of tetrahydroquinolones by Procter and co-workers.[28]

The selectivity of $SmCl_2$ has also been exploited in the reductive cleavage of an N–O bond in the penultimate step of the total synthesis of *ent*-malbrancheamide B (**38**) reported by Simpkins and co-workers (Scheme 12).[29] Subsequent regioselective amide reduction afforded the complex natural product. $SmCl_2$ has been used in a similar context in the final steps of the synthesis of structurally related *ent*-breviamide B.[30] Notably, the congested bicyclo[2.2.2]diazaoctane framework did not interfere with the strong reductant, thus further demonstrating the strategic advantage of using $SmCl_2$ in complex settings.



Scheme 12. $SmCl_2$-promoted reductive N–OBn cleavage in a total synthesis of *ent*-malbrancheamide B by Simpkins and co-workers.[29] DIBAL-H = diisobutylaluminum hydride.

Matsukawa et al. reported that $SmCl_2$ generated in situ can be used for the pinacol coupling reactions of ketones and aldehydes in water (Scheme 13).[23] Mechanistically, it was shown that both Sm and Mg metals can serve as co-reductants with $SmCl_3$. The formation of $SmCl_2$ in the aqueous environment was confirmed by UV/Vis experiments. Although pinacol couplings can be conveniently achieved with other



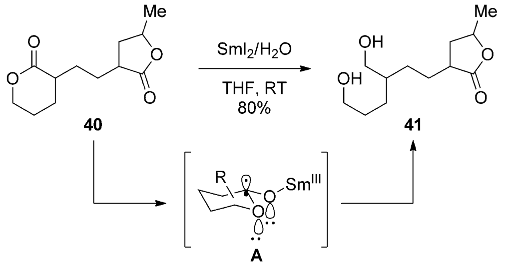
Scheme 13. SmCl$_2$-mediated pinacol coupling of aldehydes in water by Matsukawa et al.[23]

reagents,[7,8] an important ramification of this study is that it suggests that samarium(II) reductants other than SmI$_2$ can act as powerful single-electron donors in water (see Section 2.3). Accordingly, a range of new SmX$_2$/H$_2$O species can be readily envisioned for applications in electron-transfer chemistry.

2.3. Samarium(II) Iodide/Water Complex

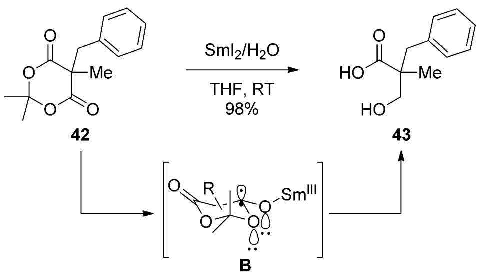
Complexes of SmI$_2$ and water provide a family of powerful reductants that enable new transformations proceeding via radical intermediates to be developed.[31] Detailed mechanistic studies have demonstrated that complexation of water to SmI$_2$ generates a strong reductant (SmI$_2$/H$_2$O: up to -1.9 V vs Ag/AgNO$_3$ in THF; SmI$_2$: -1.33 V vs Ag/AgNO$_3$ in THF).[32] Furthermore, in SmI$_2$/H$_2$O complexes, water resides in close proximity to coordination sites on the substrate, thus imparting selectivity by facile protonation of the formed radical anions.[33] Although the exact nature of the SmI$_2$/H$_2$O reagent has yet to be determined, Prasad and Flowers demonstrated that depending upon the concentration of water (50 or >100 equiv with respect to SmI$_2$ in THF) two distinct SmI$_2$/H$_2$O complexes can be prepared.[32] The benign nature of the water additive and the operationally simple reaction protocols contribute to the increased attention that these complexes have received during the last decade.

In 2008, we reported the first reductions of unactivated cyclic esters using SmI$_2$/H$_2$O (Scheme 14).[34] Importantly, prior to this study it was thought that ester carbonyl groups could not be reduced by SmI$_2$.[7] Intriguingly, the SmI$_2$/H$_2$O complex enabled complete selectivity for the reduction of lactones over esters and showed remarkable ring-size selectivity in that only six-membered lactones were converted into the corresponding diols. For example, the bis(lactone) **40** was selectively reduced to **41**. We rationalized that the unusual selectivity originated from the first electron transfer to the lactone carbonyl to give the ketyl radical anion **A**, stabilized by an anomeric effect, which would be particularly pronounced in six-membered ring systems.[35]



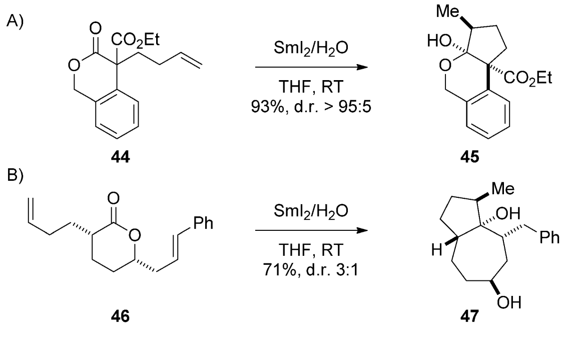
Scheme 14. Ring-size-selective reduction of six-membered lactones using SmI$_2$/H$_2$O by Procter and co-workers.[34]

We have also developed a selective reduction of Meldrum's acids using SmI$_2$/H$_2$O (Scheme 15).[36] A range of diverse derivatives of Meldrum's acids underwent monoreduction to provide the corresponding 3-hydroxy acids in excellent yields. Sensitive functional groups, such as aryl bromides and esters were tolerated, thus underlining the mild reaction conditions possible with the SmI$_2$/H$_2$O system. In analogy to the reduction of six-membered lactones, anomeric stabilization of the radical anion **B** was proposed to be crucial for the reactivity. This transformation provided the first direct entry to important 3-hydroxy acid building blocks from readily available cyclic 1,3-diesters.



Scheme 15. Selective monoreduction of Meldrum's acids using SmI$_2$/H$_2$O by Procter and co-workers.[36]

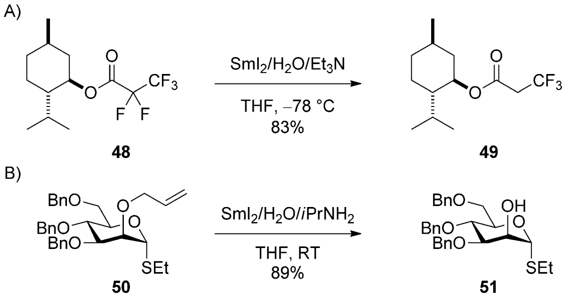
Subsequently, we have exploited the radical-anion intermediates formed in the reduction of six-membered lactones with SmI$_2$/H$_2$O in unprecedented intramolecular couplings with alkenes (Scheme 16 A).[37] These studies have culminated in cascade cyclization processes which allow molecular complexity to be increased rapidly in a single operation (Scheme 16 B).[38] The reactions allowed access to five- and seven-membered oxygenated scaffolds and azulene motifs in excellent yields and good diastereoselectivities. Interestingly, the water cosolvent was crucial for the observed reactivity and cyclizations were not observed in the presence of other additives. Recently, we have extended these studies to cyclization cascades of Meldrum's acids mediated by SmI$_2$/



Scheme 16. Reductive cyclization of six-membered lactones using SmI$_2$/H$_2$O by Procter and co-workers:[37,38] A) monocyclizations; B) cyclization cascades.

H_2O to generate a family of congested carbobicyclic 3-hydroxy acid scaffolds featuring two adjacent quaternary stereocenters.[39]

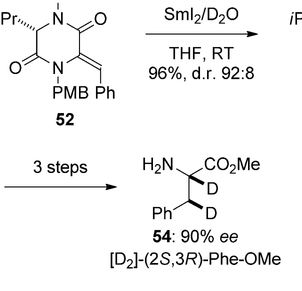
Hilmersson and co-workers have pioneered the use of SmI_2/H_2O/amine complexes (Scheme 17).[40] The addition of Lewis bases was found to enhance the reactivity of SmI_2 by coordination to the metal center, thus increasing the redox potential of the reagent. Hilmersson demonstrated that this highly reducing system (−2.8 V vs SCE in DMF)[41] can serve as a practical alternative to hydride and dissolving metal reductions, while preserving the selectivity associated with SmI_2. For example, the selective α-defluorination of easily accessible perfluoroalkyl esters and amides (Scheme 17 A),[42] and the selective cleavage of allyl ethers in complex carbohydrates promoted by SmI_2/H_2O/amine complexes (Scheme 17 B) have been reported.[43] Of note is the high functional-group tolerance despite the strong reducing properties of the reagent system.



Scheme 17. Selected uses of SmI_2/H_2O/amine complexes by Hilmersson and co-workers:[40] A) α,α-didefluorination of esters; B) cleavage of allyl ethers in complex carbohydrates. Bn = benzyl.

We have recently utilized SmI_2/H_2O/amine complexes in the first reductions of aliphatic esters,[44a] aliphatic carboxylic acids,[44b], and all ring sizes of lactones[44c] using samarium(II)-based reagents.

Concellón et al. have developed the SmI_2/D_2O system for deuteration of activated double bonds.[45] An intriguing application of this reagent system was reported by Davies and co-workers in a synthesis of deuterated amino acids (Scheme 18).[46] Conjugate reduction of the diketopiperazine **52** afforded the dideuterated product **53** in high yield and diastereoselectivity. Removal of the PMB group and cleavage of the diketopiperazine template under acidic conditions gave the phenylalanine methyl ester **54** in 90 % *ee* and with greater than 99 % deuterium incorporation. This approach demonstrates the utility of SmI_2/D_2O for the stereoselective introduction of deuterium during the synthesis of biologically relevant molecules.



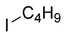
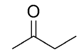
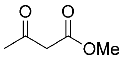
Scheme 18. Synthesis of dideuterated amino acids using the SmI_2/D_2O complex by Davies and co-workers.[46] PMB = 4-methoxybenzyl. Phe = phenylalanine.

2.4. Samarium(II) Amides

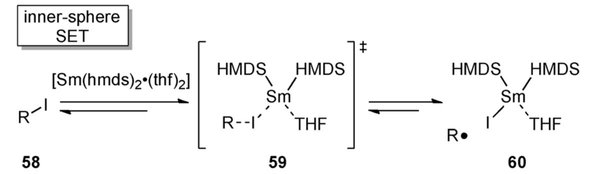
Amides are well known for their role as ligands in a wide range of lanthanide complexes.[47] Samarium(II) amides are prepared in a single step by reaction of SmI_2 with the corresponding anions [Scheme 2, Eq. (4)].[48] These ligands allow fine-tuning of the properties of the samarium(II) complex by modulating the redox potential of the system and providing more sterically encumbered reductants. In addition, samarium(II) amides are useful because of their favorable solubility in comparison to SmI_2. In the last decade, the (trimethylsilyl)amide ligand (HMDS) has emerged as an important precursor to Sm^{II} complexes applied in organic and inorganic transformations.

Flowers and co-workers have studied the properties of the $[Sm(hmds)_2]$ complex by examining the reduction of alkyl halides and ketones (Table 2).[49] It was shown that the thermodynamic redox potential of $[Sm(hmds)_2]$ is intermediate between that of SmI_2 and $[SmI_2(hmpa)]$ ($[Sm(hmds)_2]$: −2.1 V; SmI_2: −1.58 V; $[SmI_2(hmpa)]$: −2.35 V, all vs Ag/$AgNO_3$ in THF). Strikingly, despite moderate reducing potential, $[Sm(hmds)_2]$ promoted the reduction of alkyl iodides and alkyl ketones at much higher rates than the more reducing $[SmI_2(hmpa)]$ system. This surprising difference was explained by the fact that solvated $[(hmds)_2Sm(thf)_2]$ contained bent amide ligands[48] and upon THF dissociation the metal center might be more available for interaction with substrates. Detailed examination of activation parameters suggested that the reduction of alkyl iodides and ketones with $[Sm(hmds)_2]$ proceeds through an inner-sphere mechanism (Scheme 19), thus validating the mechanistic proposal. Another key observation from this work was that the $[Sm(hmds)_2]$ complex can serve as a useful replacement for the popular but carcinogenic $[SmI_2(hmpa)]$ system.

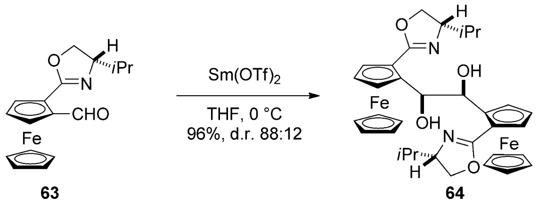
Table 2: Rate of reduction of different functional groups with $[Sm(hmds)_2]$ by Flowers and co-workers.[49]

Entry	SmX_2	k [$M^{-1}\,s^{-1}$]		
		 **55**	 **56**	 **57**
1	$[Sm(hmds)_2]$	19	1.7×10^{2}	2×10^{3}
2	$[SmI_2(hmpa)]$	2.6	8×10^{-3}	9
3	SmI_2	8×10^{-4}	7×10^{-4}	2×10^{-1}

Hilmersson and co-workers reported the heteroleptic [Sm(hmds)I] complex as the reagent of choice for the

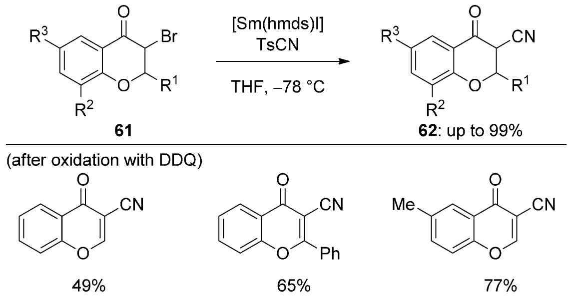


Scheme 19. Proposed mechanism for the reduction of alkyl iodides with [Sm(hmds)$_2$] by Flowers and co-workers.[49] HMDS = N(SiMe$_3$)$_2$.



Scheme 21. Sm(OTf)$_2$-mediated diastereoselective coupling of planar chiral oxazoline formylferrocenes by Fukuzawa et al.[53]

α functionalization of biologically significant chromanones under mild reaction conditions (Scheme 20).[50] A variety of alkyl and aryl chromanones underwent α cyanation in excellent yields. However, the sensitive nature of these products prevented their efficient isolation. To address this problem, the authors employed a one-pot protocol involving the oxidation of substrates **62** with DDQ to give the more stable chromones. Alternative methods, including direct cyanation of 4-chromanones, did not provide the desired products, thus emphasizing the remarkable efficiency of the samarium(II) reagent in this transformation.



Scheme 20. [Sm(hmds)I]-promoted α cyanation of alkyl and arylchroman-4-ones by Hilmersson and co-workers.[50] DDQ = 2,3-dichloro-5,6-dicano-1,4-benzoquinone.

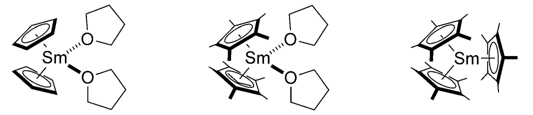
2.5. Samarium(II) Alkoxides

Samarium(II) triflate [Sm(OTf)$_2$] is another valuable samarium(II) system for organic synthesis.[51] This reagent are prepared in situ by reduction of Sm(OTf)$_3$ with Grignard or organolithium reagents. The properties of Sm(OTf)$_2$ formed by this method can be influenced by Mg or Li salts present in the solution. Recently, Flowers and co-workers have reported a practical method for the synthesis of Sm(OTf)$_2$ involving the reaction between Sm(OTf)$_3$ and Sm metal [Scheme 2, Eq. (6)].[52] Although the redox potential of Sm(OTf)$_2$ has not been determined, the reagent is capable of mediating transformations analogous to those promoted by SmI$_2$. In some cases, the use of Sm(OTf)$_2$ gives enhanced diastereoselectivities and higher yields for reductive processes.

Fukuzawa et al. applied Sm(OTf)$_2$ in the pinacol coupling of planar chiral ferrocenes, thus achieving high levels of stereoselectivity (Scheme 21).[53] Examination of different reaction conditions revealed that Sm(OTf)$_2$ obtained from the reduction of Sm(OTf)$_3$ with *s*-BuLi provided optimal results for the coupling of the chiral *ortho*-oxazoline-substituted formylferrocene **63**. In contrast, SmI$_2$ afforded a mixture of all possible diastereoisomers, thus demonstrating the advantage of using Sm(OTf)$_2$ as the electron-transfer reagent in this case. The high selectivity in the reaction mediated by Sm(OTf)$_2$ was ascribed to the steric influence of the large triflate anion in the transition state.

2.6. Samarium(II) Cyclopentadienyl Complexes

Samarium(II) cyclopentadienyl complexes are the most powerful samarium(II)-based reductants as a result of their unique structures and high redox potentials (Figure 3).[4c]



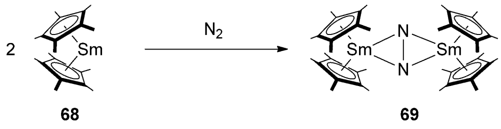
65 [Cp$_2$Sm(thf)$_2$] **66** [Cp*$_2$Sm(thf)$_2$] **67** [Cp*$_3$Sm]

Figure 3. Structures of cyclopentadienyl-based samarium complexes. Cp* = C$_5$Me$_5$.

The dicyclopentadienylsamarium **65**, conveniently prepared from SmI$_2$ by ligand metathesis using NaCp [Scheme 2, Eq. (3)],[54] is characterized by a very high redox potential ([Cp$_2$Sm]: −2.66 V vs [Cp$_2$Fe]$^+$/[Cp$_2$Fe] in THF).[55] However, as a result of its limited solubility in common organic solvents, this reagent has remained largely unexplored in organic synthesis. Nevertheless, it has been reported that the use of [Cp$_2$Sm] can be advantageous over SmI$_2$.[56] For example, cross-couplings between aldehydes or ketones and alkyl halides proceed in higher yields and under milder reaction conditions with [Cp$_2$Sm] than with SmI$_2$.[56a]

The solution synthesis of the solvated decamethylsamarocene **66**, from readily available SmI$_2$ and KCp* by Evans et al. [Scheme 2, Eq. (3)],[57] is an important landmark in the field of organolanthanide chemistry. In contrast to its Cp analogue **65**, [Cp*$_2$Sm] is soluble in a range of organic solvents, thus allowing it to be employed as a convenient starting point for the assembly of other samarium(II) complexes. The estimated redox potential of [Cp*$_2$Sm] ([Cp*$_2$Sm]: −2.44 V vs SCE in DMF)[58] makes **66** one of the strongest samarium(II) reductants known to date.

Evans et al. have reported that upon heating under vacuum, the decamethylsamarocene **66** gave the desolvated complex **68** which possesses a bent structure (see Scheme 22 for structure of **68**. Note that in the iron analogue, ferrocene, the Cp rings are parallel; Scheme 22).[59] The highly reactive, coordinatively unsaturated complex **68** has opened up new avenues in reductive lanthanide chemistry.[60] For example, Evans reported that **68** was the first lanthanide complex capable of dinitrogen activation (Scheme 22).[61] More recently, nitrogen activation has also been achieved by complexes of nonclassical divalent lanthanides.[62] Furthermore, various organic and inorganic molecules react with **68** and **66**.[63]



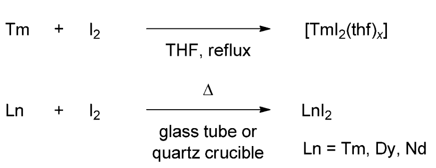
Scheme 22. Synthesis of the first dinitrogen complex of lanthanides using decamethylsamarocene by Evans et al.[61]

In another striking breakthrough, Evans et al. found that the extremely sterically crowded complex **67** (Figure 3), containing three Cp* rings around the Sm metal, can be structurally characterized and that it acts as a powerful single-electron reductant despite the three-valent oxidation state of Sm.[64] The authors demonstrated that in the sterically crowded environment a Cp* ligand oxidizes to give a Cp* radical and a Sm^{II} species in a process which proved to be general for other lanthanide complexes.[65]

Harder and co-workers have made substantial progress in the field of samarium metallocenes.[9e,66] Using super-bulky $Cp^{BIG}H$ [$Cp^{BIG}H = (4\text{-}n\text{BuC}_6\text{H}_4)_5\text{C}_5\text{H}$)] ligands, these researchers accomplished the synthesis of [$(Cp^{BIG})_2Sm$] by reduction of the [(2-Me_2N-benzyl)$_3$Sm] precursor. The reaction involves a spontaneous reduction of [$(Cp^{BIG})_2$(2-Me_2N-benzyl)Sm] to give the desired metallocene and a 2-Me_2N-benzyl radical, which dimerizes under the reaction conditions. Besides structural characterization of [$(Cp^{BIG})_2Sm$], the successful application of the sterically induced reduction concept is noteworthy. More recently, the Mitzel group reported a spontaneous reduction of $Sm(AlMe_4)_3$, induced by the bulky 1,3,5-tricyclohexyl-1,3,5-triazacyclohexane (TCyTAC), to afford [$(TCyTAC)_2Sm(AlMe_4)_2$].[9f,67] This process also bears many similarities to the spontaneous reduction in the [Cp^*_3Sm] system developed by Evans.

3. Reductive Chemistry Mediated by New Divalent Lanthanides

A large number of divalent lanthanides have been known in the solid state for the better part of the last century.[68] However, for years it had been thought that their reductive chemistry in solution was limited to three "classical" elements: Sm^{II}, Yb^{II}, and Eu^{II},[69] with the latter exhibiting significantly lower redox potential than Sm^{II}.[3f] In the last decade, the groups of Evans[9a] and Bochkarev[9b] discovered that three "nonclassical" divalent lanthanides, Tm^{II}, Dy^{II} and Nd^{II}, can be synthesized using more practical procedures than those typically required for the solid-state synthesis (Scheme 23),[70] and that TmI_2, DyI_2 and NdI_2 are powerful SET reagents capable of mediating challenging coupling reactions under mild reaction conditions in ethereal solvents.[9] Thus, the number of available divalent lanthanides for reductive chemistry has increased twofold, providing unprecedented opportunities for advances in the reductive chemistry of lanthanides and electron-transfer reactions. Although it has been shown that all three new LnI_2 compounds are stable and soluble in the usual solvents such as THF and DME,[71] perhaps the most attractive is NdI_2 because of its very high redox potential,[3f] low cost,[72] and the general availability[73] of neodymium(II) precursors.

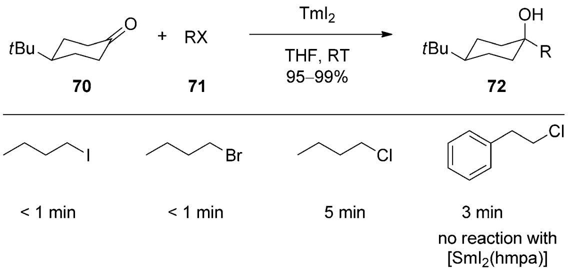


Scheme 23. Practical synthesis of nonclassical lanthanide(II) halides by the groups of Evans and Bochkarev.[70, 76]

3.1. Thulium(II) Iodide

With a redox potential of −2.3 V (Tm^{III}/Tm^{II}, vs NHE), thulium(II) is significantly more reducing than samarium(II) (Sm^{III}/Sm^{II}: −1.55 V vs NHE).[3f,74] For decades it had been assumed that thulium(II) would be too reactive to be stable in solution. Indeed, attempts to prepare this ion were unsuccessful and colored solutions typical for divalent lanthanides were seen only transiently.[68d] In 1997, a joint effort by the groups of Evans and Bochkarev resulted in the structural characterization of the first thulium(II) complex, [$TmI_2(dme)_3$].[75] The pentagonal bypiramidal geometry of this complex showed many parallels to the samarium analogue, [$SmI_2(thf)_5$].

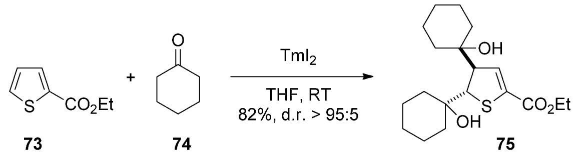
Subsequently, Evans and Allen have pioneered the use of TmI_2 in organic synthesis (Scheme 24).[76] TmI_2 proved



Scheme 24. Reductive coupling of unactivated alkyl halides using TmI_2 by Evans and Allen.[76] TmI_2 = thulium diiodide.

significantly more efficient than SmI$_2$ in promoting cross-couplings of alkyl halides and ketones. Notably, even cross-couplings of alkyl chlorides, which are notoriously difficult substrates, occurred almost instantaneously at room temperature. In contrast, [SmI$_2$(hmpa)], a lanthanide(II) reagent of choice for this type of cross-coupling,[8] proved to be ineffective under the conditions examined. Evans also reported that complexes of thulium(II) reduce dinitrogen,[77] which might explain why preparation of this reagent failed during previous attempts.

Evans and co-workers additionally investigated the utility of TmI$_2$ as a SET reagent in the cross-coupling reactions of thiophene-2-carboxylate with carbonyl compounds (Scheme 25).[78] Interestingly, the coupling of the thiophene 73 and cyclohexanone 74 resulted in reductive dearomatization to give the difunctionalized dihydrothiophene 75 (by 1,6-addition and electrophilic trapping by a thulium enolate). It is worth noting that under analogous reaction conditions SmI$_2$ was ineffective, thus demonstrating the utility of TmI$_2$ for the synthesis of heterocyclic scaffolds.

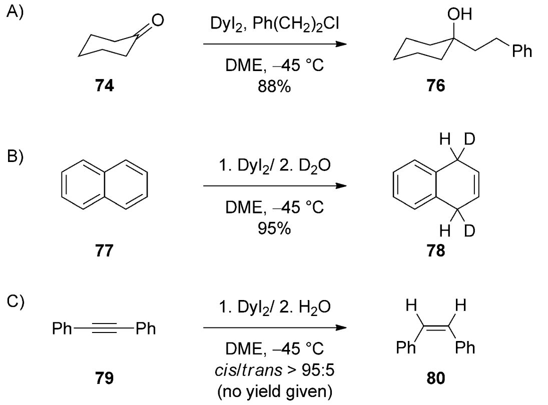


Scheme 25. TmI$_2$-mediated reductive cross-coupling between thiophene and cyclohexanone by Evans, Fang, and co-workers.[78]

3.2. Dysprosium(II) Iodide

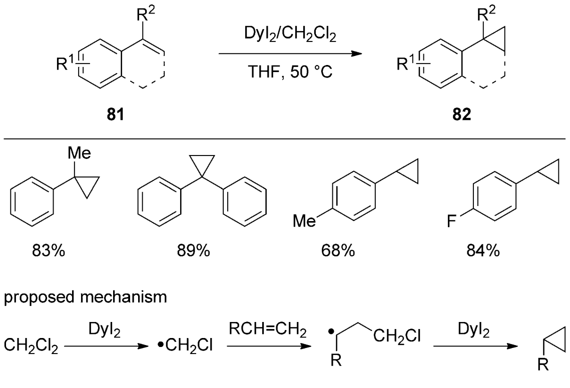
The first structurally validated complex of dysprosium(II) was reported by Evans et al. in 2000.[79] [DyI$_2$(dme)$_3$] was found to be isomorphous with [SmI$_2$(dme)$_2$]. Moreover, with a redox potential of -2.5 V (Dy^{III}/Dy^{II}, vs NHE),[3f] dysprosium(II) is approaching the reductive power of classical reagents used for electron-transfer processes (Mg: -2.4 V; Na: -2.7 V; K: -2.9 V vs NHE). Importantly, its structural similarity to SmI$_2$ provides an attractive platform for the development of selective functional group transformations.

Evans et al. investigated the use of DyI$_2$ in organic synthesis (Scheme 26).[79] When compared to TmI$_2$, DyI$_2$ is a more powerful reductant in cross-coupling reactions between alkyl chlorides and alkyl ketones (Scheme 26A). Remarkably, the high redox potential of DyI$_2$ means that it is the first lanthanide(II) reagent capable of promoting Birch reductions of aromatic systems (Scheme 26B). The mild reaction conditions for reduction of naphthalene with DyI$_2$ compare favorably with the traditionally employed alkali metals in liquid ammonia.[80] Furthermore, DyI$_2$ can reduce alkynes with synthetically useful selectivity (Scheme 26C). Dysprosium(II) has also been shown to have a rich dinitrogen chemistry.[81]



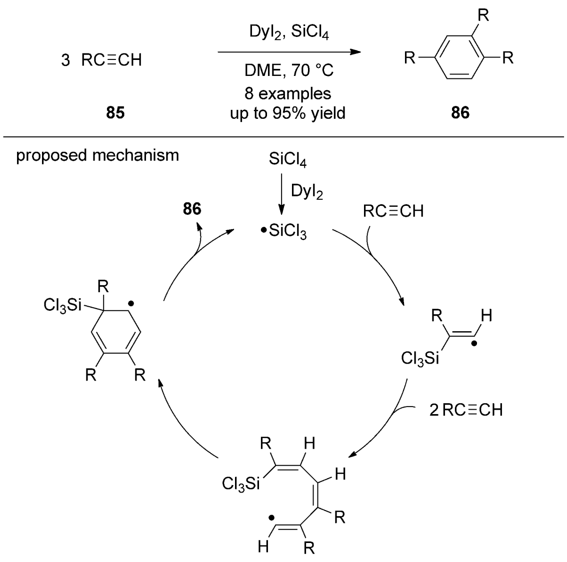
Scheme 26. Reductive transformations using DyI$_2$ by Evans et al.:[79] A) Cross-coupling; B) Birch reduction; C) alkyne reduction. DyI$_2$ = dysprosium diiodide.

Another recent advance in the reductive chemistry of dysprosium(II) is the activation of simple commodity chemicals, such as dichloromethane or acetylenes, to form synthetically useful products. Zhou and co-workers exploited the high redox potential of DyI$_2$ in the cyclopropanation of alkenes using dichloromethane as a methylene transfer reagent (Scheme 27).[82] The desired cyclopropanes were isolated in excellent yields when a sixfold excess of dichloromethane was employed. Other electron-transfer reagents, including SmI$_2$ and Na, did not promote the reaction. The stability of dichloromethane means that it is rarely used as a reagent in organic synthesis.[83]



Scheme 27. DyI$_2$-mediated cyclopropanation of styrenes using CH$_2$Cl$_2$ as the methylene transfer reagent by Zhou and co-workers.[82]

A regioselective cyclotrimerization of terminal alkynes promoted by DyI$_2$ has been developed by Zhou and co-workers (Scheme 28).[84] Other reductants, including SmI$_2$, did not promote the reaction, and other sources of silyl radical proved less efficient. The high regioselectivity was ascribed to the cooperative role of Dy^{II} and Dy^{III} in the catalytic cycle. The authors have also found that DyI$_2$/SiCl$_4$ promotes the polymerization of methyl methacrylate. This study demonstrated for the first time that a nonclassical divalent lanthanide reagent can be employed as a catalyst for a valuable synthetic transformation (see, Section 5 for other systems catalytic in Ln^{II}).

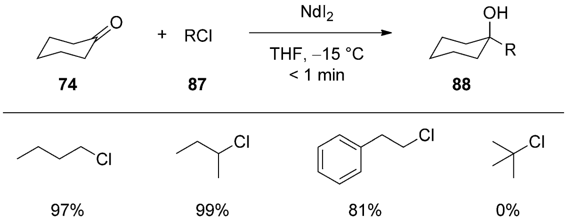


Scheme 28. DyI_2-promoted regioselective cyclotrimerization of terminal alkynes by Zhou and co-workers.[84]

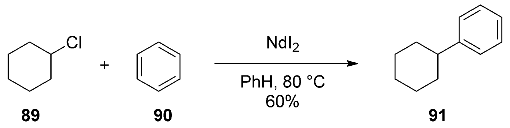
3.3. Neodymium(II) Iodide

The first fully characterized, divalent complex of neodymium, $[NdI_2(thf)_5]$, was reported by Bocharkev and Schumann in 2001.[85] Examination of its structural properties revealed that $[NdI_2(thf)_5]$ is isotypic to $[SmI_2(thf)_5]$. Neodymium(II) iodide (Nd^{III}/Nd^{II} reduction potential of −2.6 V vs NHE),[3f] is the most powerful lanthanide reductant analogous to SmI_2 isolated to date.

Evans et al. explored the utility of NdI_2 as a reductant in organic synthesis (Scheme 29).[86] As expected from the reduction potential, NdI_2 proved to be more reactive in the cross-couplings of alkyl chlorides and ketones than other lanthanide(II) iodides. Remarkably, the reaction of secondary alkyl chlorides was successful at cryogenic temperatures. However, no reaction occurred with a tertiary chloride. In addition, NdI_2 was found to promote the Birch reduction of naphthalene and cross-couplings between alkyl chlorides and aldehydes.



Scheme 29. Reductive coupling of alkyl chlorides at cryogenic temperatures using NdI_2 by Evans et al.[86] NdI_2 = neodymium diiodide.



Scheme 30. Cross-coupling of alkyl chlorides and benzene using NdI_2 by Evans, Bochkarev, and co-workers.[87]

Evans, Bochkarev, and co-workers have extended the scope of the reactions of NdI_2 with organohalides (Scheme 30).[87] In THF, NdI_2 promoted the reduction of aryl halides to the corresponding hydrocarbons with minor quantities of products arising from the Wurtz coupling. However, in benzene, a cross-coupling between alkyl chlorides and solvent was observed.[88] The authors proposed a mechanism involving the reduction of **89** to give $[NdI_2Cl]$ and subsequent Friedel–Crafts alkylation. As the cooperative role of Sm^{II}/Sm^{III} is well-precedented in organic synthesis,[89] this report sets the stage for the future development of Ln^{II}/Ln^{III} cooperative processes using nonclassical lanthanides.

Overall, the isolation of the first divalent complexes of Tm, Dy, and Nd and initial forays into their application in organic synthesis provide a convincing argument for the use of TmI_2, DyI_2, and NdI_2 in reaction discovery and the optimization of electron-transfer processes which are currently executed using alkali metals or samarium(II)-based reagents. As summarized in Table 3, the nonclassical lanthanide(II) reductants are much more powerful than the popular $[SmI_2(hmpa)]$ complex and, as such, should prove valuable in organic chemistry.[90]

Table 3: Comparison of reductive properties of divalent lanthanides.

Entry	Reagent	$E°$ (Ln^{III}/L^{II})[a]	Unactivated R-Cl[b]	Birch reduction
1	$[SmI_2(hmpa)]$	−2.05 V	−	−
2	TmI_2	−2.22 V	+	−
3	DyI_2	−2.56 V	+	+
4	NdI_2	−2.62 V	+	+

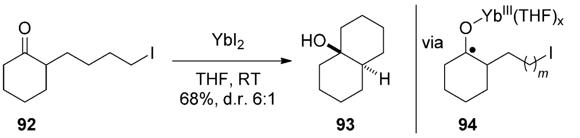
[a] For entry 1 values are vs $Ag/AgNO_3$ in THF;[20b] for entries 2–4 values are vs NHE.[87] [b] For entry 1: 25 °C, 18 h; for entry 2: 0 °C, 1 h; for entries 3 and 4: <0 °C, <5 s.

4. Other Lanthanide(II) Reagents

Additional lanthanide(II) reagents include lanthanide(II) halides derived from lanthanides with lower and higher redox potentials than samarium(II), namely ytterbium(II), europium(II), and cerium(II) (Ln^{III}/Ln^{II}: Yb: −1.15 V; Eu: −0.35 V; Ce: −3.2 V; Sm: −1.55 V, all vs NHE),[3f] organometallic lanthanide(II) complexes, and divalent lanthanides prepared transiently from their three-valent precursors and characterized by much higher redox potential than neodymium(II) (Ln^{III}/Ln^{II}: Nd: −2.6 V; Ho: −2.9 V; Er: −3.1 V; La: −3.1 V; Tb: −3.7 V; Gd: −3.9 V; Lu, Y: not available, all vs NHE).[3f]

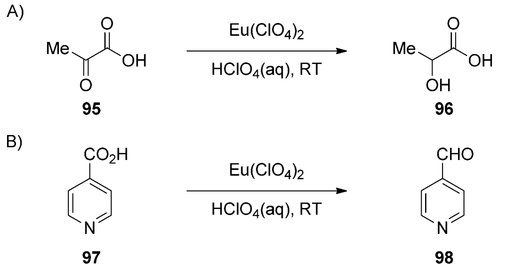
Although YbI_2, EuI_2, and CeI_2 are not as popular as their Sm^{II} counterpart, benefits arising from the use of these or related reductants have been reported. In analogy to SmI_2, the solution synthesis of YbI_2 and EuI_2 from 1,2-diiodoethane and the corresponding metal provides straightforward access to these reagents (see Scheme 1).[6,91]

With the redox potential of −1.02 V (vs Ag/AgNO$_3$), YbI$_2$ is a powerful SET reagent capable of mediating the vast majority of transformations typical to SmI$_2$ (SmI$_2$: −1.55 V vs Ag/AgNO$_3$).[92] The differences in redox potential between the two reagents can be further modified by the use of appropriate additives.[41] A practical advantage of using YbI$_2$ is that enhanced levels of stereoselectivity can be obtained, especially for chelating substrates. For example, Molander and Etter reported that YbI$_2$ provides high diastereocontrol in the annulation of 2-(iodoalkyl)ketones to five- and six-membered carbocycles (Scheme 31).[93] It was proposed that the short ytterbium–oxygen bond and the large solvated radius of Yb^{III} ion in the proposed ketyl radical **94** contribute to the observed stereoselectivity. It is important to note that an alternative mechanism involving an organoytterbium intermediate cannot be discounted.[7c] Similar findings have been reported during studies on the electrochemical generation of ytterbium(II).[94] However, the full synthetic potential of size optimization of this lanthanide(II) reagent has yet to be explored. Among other ytterbium(II) species,[95] YbBr$_2$ has attracted the most attention.[96] Fujiwara and co-workers reported a straightforward synthesis of YbBr$_2$ from Yb metal and TMSBr, and its subsequent use in the coupling of imines,[96a] ketones,[96b] and α,β-unsaturated compounds.[96c]



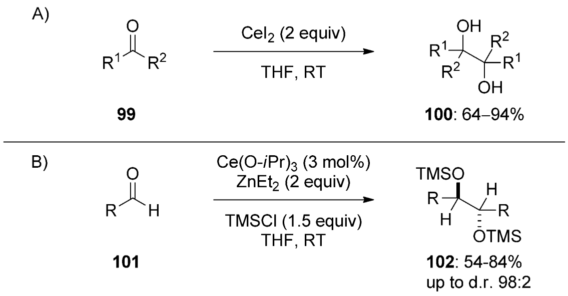
Scheme 31. YbI$_2$-mediated diastereoselective ring annulation by Molander and Etter.[93]

The use of europium(II) reagents as reductants in organic chemistry is rare due to their low reactivity.[7a] Katakis and co-workers were able to accomplish the reduction of pyruvic and isonicotinic acids by utilizing europium(II) perchlorate in aqueous acidic solutions (Scheme 32).[97] On the basis of kinetic studies, the mechanism involving two SETs from europium(II) has been proposed. Perhaps the most intriguing aspect of this work is that nicotinic and picolinic acids[97b] as well as dialkylketones[13] were shown to be unreactive towards europium(II), thus showing the potential for chemoselective reductions. Furthermore, it is worth noting that both YbI$_2$ and EuI$_2$ provide important entry points to organometallic complexes of ytterbium and europium with downstream applications in inorganic chemistry, catalysis and polymerization.[1a–c]



Scheme 32. Europium(II)-mediated reductions by Katakis and co-workers:[97] A) reduction of pyruvic acid; B) reduction of isonicotinic acid.

Cerium(II) iodide is another lanthanide(II) reagent that has been used in organic synthesis (Scheme 33).[98] Imamoto et al. reported a chemoselective pinacol coupling of ketones and aldehydes mediated by CeI$_2$, which was prepared in situ from Ce metal and iodine (Scheme 33 A).[99] Although pinacol couplings can be accomplished using other reagents,[100] interesting features of this reaction include mild reaction conditions and good functional group compatibility. Recently, Groth and Jeske reported an attractive advancement in cerium-mediated pinacol couplings (Scheme 33 B).[101] It was found that the pinacol coupling of aldehydes mediated by catalytic Ce(O-*i*Pr)$_3$ and diethylzinc as the co-reductant afforded the corresponding 1,2-diols with high *anti* selectivity. The reaction could be scaled up to more than 5 g with a 1 mol % catalyst loading. The proposed mechanism involves a SET from cerium(II) to the carbonyl group, however, an electron transfer from diethylzinc to the carbonyl group may lead to an alternative pathway.[102]



Scheme 33. Ce^{II}-mediated transformations: A) stoichiometric pinacol couplings by Imamoto et al;[99] B) catalytic variant by Groth and Jeske.[101] TMS = trimethylsilyl.

Although a comprehensive survey of organometallic lanthanide(II) reagents is beyond the scope of this Review, it is worthwhile to mention several recent advances in this area (see, Figure 4 for some representative examples).[1a–c,103] In 2002, Evans et al. reported the synthesis and structural characterization of the first organometallic complex of thulium(II), [Cp″$_2$Tm(thf)] (see, Figure 4 for the structure), through the metathesis reaction of TmI$_2$ with KCp″ in THF.[81] This reaction capitalizes on the solution availability of the thulium(II) iodide precursor described earlier. Nief and co-workers achieved the first synthesis of organodysprosium[104] and organoneodymium[105] complexes by applying a reductive pathway from lanthanide(III) precursors. In this case, the limited stability of DyI$_2$ and NdI$_2$ in polar solvents prevented the successful use of metathesis reactions from the respective iodides.

Another breakthrough in this area is the synthesis of isolable lanthanide(II) complexes by Lappert and co-workers (Scheme 34).[106] These researchers also accomplished the first synthesis of a cerium(II) complex (as a mixed valence Ce^{II}/Ce^{III} complex).[106] Recently, Evans investigated the reactivity of the lanthanide(II) complex **104** with nitrogen.[107] Thus,

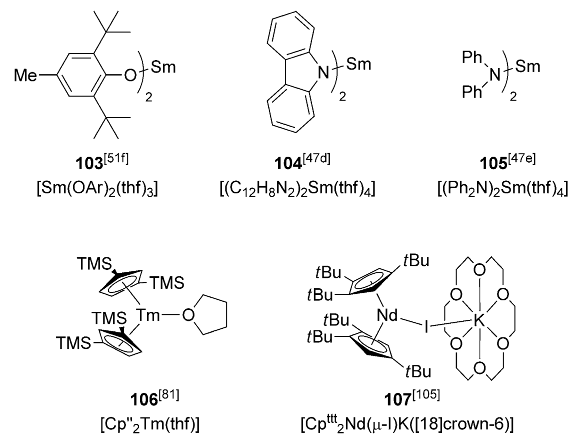
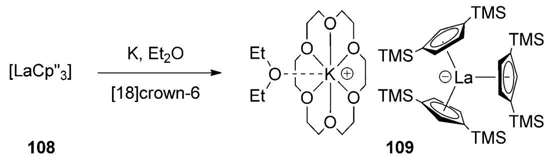


Figure 4. Structures of selected complexes of divalent lanthanides. In structures **103**–**105** THF ligands are omitted for clarity. Cp'' = 1,3-$C_5H_3(SiMe_3)_2$. Cp^{ttt} = 1,2,4-$C_5H_2(tBu)_3$.



Scheme 34. Synthesis of a molecular complex of lanthanide(II) by Lappert and co-workers.[106] Cp'' = 1,3-$C_5H_3(SiMe_3)_2$.

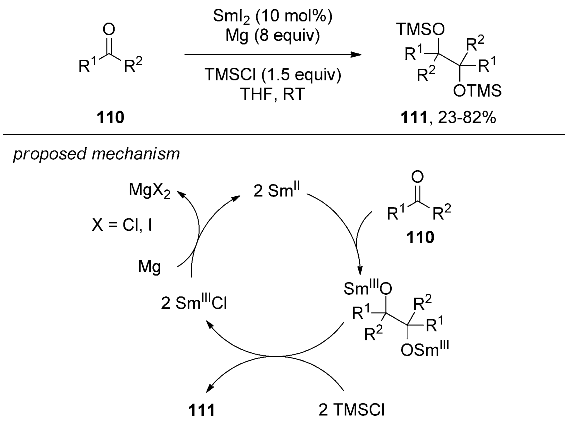
molecular compounds of eight different lanthanides have already been isolated and characterized in the divalent oxidation state.[108]

Finally, while investigating dinitrogen activation using nonclassical lanthanides (Tm, Dy and Nd), Evans et al. reported an intriguing approach to other divalent lanthanides by the in situ reduction of their three-valent precursors.[109] In particular, dinitrogen activation occurred when lanthanide(III) amides, [Ln(hmds)$_3$], were reacted with alkali metals, thus indicating the transient presence of divalent lanthanide intermediates. Remarkably, this reaction sequence proved successful with Tm, Nd, Dy, Ho, Er, Tb, Gd, Y, and Lu. Importantly, Ho^{II} chemistry had not been previously reported. This discovery demonstrated that lanthanides with extremely high redox potentials are accessible for reductive lanthanide(II) chemistry by their in situ preparation. Although this method has not yet been used in organic synthesis, the potential of this approach has been illustrated by the successful synthetic application of Sm(OTf)$_2$[51–53] and NdI$_2$,[86b] prepared in situ from their three-valent precursors.

5. Reductive Chemistry Catalytic in Divalent Lanthanides

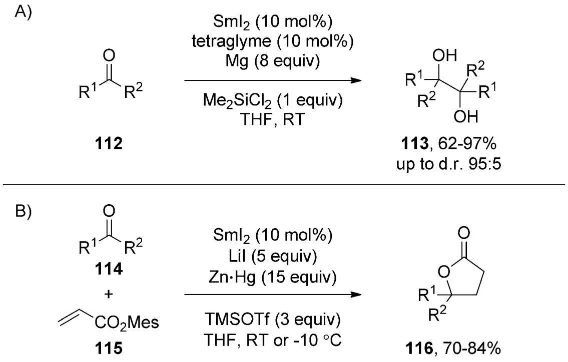
The major drawback of using divalent lanthanides as reductants in organic synthesis is the requirement for stoichiometric quantities of lanthanide(II) species. Despite the central role that lanthanides occupy in electron-transfer processes,[7] reactions catalytic in lanthanide(II) have been slow to emerge.[110]

The pioneering studies by Endo and co-workers demonstrated the possibility of using SmI$_2$ as a catalyst in pinacol coupling reactions (Scheme 35).[111] In this system, Mg acts as a stoichiometric co-reductant, whereas TMSCl serves to regenerate SmI$_2$Cl from the initially formed samarium(III) pinacolate. However, the modest yields and low diastereoselectivities obtained with this system, especially when compared to pinacol couplings mediated by stoichiometric samarium(II) reagents,[7] have limited its utility in synthesis.



Scheme 35. Seminal SmI$_2$-catalyzed pinacol coupling of ketones and aldehydes by Endo and co-workers.[111]

Subsequently, other systems catalytic in SmI$_2$ have been described (Scheme 36). An approach by Greeves and co-workers relies on a stoichiometric use of tetraglyme (with respect to SmI$_2$) to improve the diastereoselectivity of the SmI$_2$-catalyzed pinacol coupling reaction originally developed by Endo (Scheme 36 A).[112] Notably, substantial levels of selectivity could be achieved with the sterically encumbered Sm^{II}/tetraglyme reductant. Moreover, intramolecular pinacol couplings catalytic in SmI$_2$ proceeded in high yields. Corey and Zheng reported a SmI$_2$ catalytic system for the annulation of ketones to γ lactones (Scheme 36 B).[113] The



Scheme 36. Other SmI$_2$-catalyzed reductive transformations: A) diastereoselective pinacol coupling by Greeves and co-workers;[112] B) annulation of ketones to γ-lactones by Corey and Zheng.[113] Mes = mesityl.

key feature of this approach was the use of zinc amalgam and TMSOTf as more efficient co-reductant and capping reagents, respectively. In addition, LiI was employed to facilitate the conversion of SmI$_2$OTf into SmI$_3$. In other systems, the metathesis with chloride or alkoxide ligands complicates the catalyst turnover because of the slow reduction rate and problems with the low solubility of the SmX$_3$ species.

Systems catalytic in other lanthanide(II) reductants have also been reported with SmBr$_2$/mischmetall in pinacol coupling reactions,[12] SmI$_2$/mischmetall in Barbier-type reactions,[114] SmI$_2$/Mg in Reformatsky reactions[115] and SmI$_2$ in atom-transfer radical addition reactions.[116] Furthermore, the use of nonclassical lanthanides(II), DyI$_2$[84] and TmI$_2$,[9c] in catalytic quantities has already been documented. Overall, these studies provide a solid foundation for the future development of practical systems catalytic in lanthanide(II) reductants.[117]

6. Conclusion

The design of new reagents and strategies for selective transformations is of central importance to advances in organic synthesis. The unique properties of SmI$_2$ have been exploited by organic chemists for the last 35 years. In the last decade, important developments have been made in the synthesis, mechanistic understanding, and application of divalent complexes of lanthanides other than SmI$_2$. These novel electron-transfer reductants are more powerful than SmI$_2$, yet the remarkable functional-group tolerance and selectivity possible with Kagan's reagent is often retained, and these reagents have already proven to be indispensable tools for organic synthesis. In particular, the different structural and redox characteristics of the new lanthanide complexes allow them to be fine-tuned to promote transformations impossible to achieve with other reagents, often in complex molecular settings.

It is worth noting that the lanthanide reagents described in this Review constitute only a small subset of the large family of recently designed and structurally characterized lanthanide complexes and further advances in their development and application can be expected. The future advances in this field may cover redox-active ligands,[118] photoinduced reductions,[119] enantioselective variants,[120] and theoretical studies using computational models.[121] Collectively, the exciting innovations in the reductive chemistry of lanthanides provide a fresh impetus in the quest to develop electron-transfer processes that proceed with useful efficiency and selectivity, mediated by new, tailor-made lanthanide reductants.

We gratefully acknowledge the EPSRC for financial support.

Received: February 8, 2012
Revised: April 3, 2012
Published online: August 15, 2012

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