Samarium(II)-mediated Reactions in Organic Synthesis - Method Development and Mechanistic Investigation

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Abstract

This thesis describes the development of methods using divalent samarium reagents in organic synthesis. The main focus is placed on functional group reductions, but reductive formation of carbon-carbon bonds has also been investigated.

The reduction of aliphatic nitro compounds was successfully performed using SmI_2, amine and water giving the resulting amine in high yield (90%). The reaction was found to tolerate a wide range of other functional groups.

The reductive cleavage of benzyl heteroatom bonds using SmI_2, amine and water was mechanistically studied and it was found that the reaction order was unity in all components. Furthermore, water displayed a complex relationship and was found to inhibit the reaction at high concentration. The results obtained were used to develop a novel method for the defunctionalization of benzylic alcohols, amines and thiols.

A protocol for efficient removal of the toluenesulfonyl protecting group has been developed. The method was tolerant to highly sensitive functional groups and structures. The deprotection was very fast and high yielding (generally over 90%) at rt for all the evaluated substrates.

An important addition to a new carbon-carbon bond forming reaction was found during the efforts to synthesize 3-cyanochromones. The combination of two counter ions, iodide and HMDS, results in a Sm(II)-reagent that displays a unique reactivity in a Reformatsky inspired method.

The SmI_2/amine/H_2O system could also be used for the reductive defluorination of polyfluorinated esters and amides. Pentafluoropropionyl esters and amides were efficiently modified to yield the β, β, β-trifluoropropionyl derivative in high yield. It was interesting to find that the incorporation of a chiral auxiliary induced some selectivity (2:1) in this reduction.

List of publications

This thesis is based on the following papers, which are referred to in the text by their Roman numerals. Reprints were made with permission from the publishers.

I.   **Instantaneous SmI$_2$/H$_2$O/amine mediated reduction of nitroalkenes and α,β-unsaturated nitroalkenes** Tobias Ankner and Göran Hilmersson. *Tetrahedron Lett.* **2007**, 48, 5707-5710.

II.   **SmI$_2$/H$_2$O/amine promoted reductive cleavage of benzyl-heteroatom bonds: optimization and mechanism** Tobias Ankner and Göran Hilmersson. *Tetrahedron* **2009**, 65, 10856-10862.

III. **Instantaneous Deprotection of Tosylamides and Esters with SmI$_2$/Amine/Water** Tobias Ankner and Göran Hilmersson. *Organic Lett.*, **2009**, 11, 503-506.

IV.   **KHMDS Enhanced SmI$_2$-Mediated Reformatsky Type α-Cyanation** Tobias Ankner, Maria Fridén-Saxin, Nils Pemberton, Tina Seifert, Morten Grøtli, Kristina Luthman, Göran Hilmersson. *Submitted for publication to Organic Letters.*

V.   **Selective α-Defluorination of Polyfluorinated Esters and Amides Using SmI$_2$/Et$_3$N/H$_2$O** *Manuscript.*

Abbreviations

Ac$_2$O	Acetic acid anhydride
Bn	Benzyl
Boc	*tert*-butylcarbamate
Cbz	Benzylcarbamate
CSA	Camphorsulfonic acid
CTFB	*p*-Trifluoromethylbenzylcarbamate
d.e.	Diastereoisomeric exess
DCE	Dichloroethane
DDQ	2,3-Dichloro-5,6-dicyano-*p*-benzoquinone
DIPA	Diisopropylamine
DMAP	4-Dimethylaminopyridine
DMPU	*N,N'*-dimethylpropyleneurea
Fc	Ferrocene/ferrocenium
GC/MS	Gas chromatography/Mass spectrometry
HFIP	Hexafluoroisopropanol
HMDS	Hexamethyldisilazane
HMPA	Hexamethylphosportriamide
HPLC	High Pressure Liquid Chromatography
KHMDS	Potassium bis(trimethylsilyl)amide
KIE	Kinetic isotope effect
MW	Microwave heating
NMP	*N*-methylpyrrolidone
Py-Br	Pyridinium bromide
Ra-Ni	Raney Nickel
SET	Single electron transfer

THF	Tetrahydrofuran
THP	Tetrahydropyran
TMG	Tetramethylguanidine
TMPA	Trimorpholinophosphortriamide
TMS-Cl	Trimethylsilyl chloride
TMU	Tetramethylurea
TPPA	Tripyrrolidinophosphortriamide
TsCN	*p*-Toluenesulfonyl cyanide
TsOH	*p*-Toluenesulfonic acid

Contents

1. Introduction

Manipulation of functional groups by reductive processes constitutes one of the fundamental reaction classes in organic synthesis. Development of methods for transformations of this kind has received, and still is receiving considerable attention. In a broad sense, reactions of this type can be divided into reductive carbon-carbon bond forming reactions and reduction of functional groups.

Bond forming reactions utilizing a nucleophilic carbon species was pioneered by P. Barbier.[1] He found that a ketone and an alkyl iodide gave an alcohol when reacted with magnesium in diethyl ether (Figure 1).
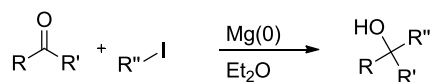

Figure 1. Schematic presentation of the Barbier reaction.

This reaction is thought to begin with the single electron transfer (SET) reduction of the alkyl halide, forming an R-MgI compound. This, being a powerful nucleophile, adds to the ketone forming a new carbon-carbon bond.[2] In addition, there are similar reactions such as the Reformatsky reaction,[3] where an α-halocarbonyl forms a metal enolate that acts as a nucleophile (Figure 2).

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[1] Barbier, P. *C. R. Acad. Sci.* **1899**, 110.
[2] For a detailed study on this see: Moyano, A.; Perica´s, M. A.; Riera, A.; Luche, J.-L., *Tetrahedron Lett.* **1990**, 31, 7619.
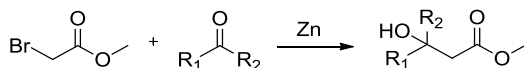[3] Reformatsky, S. *Ber.* **1887**, 20, 1210.

Figure 2. Schematic presentation of a Reformatsky reaction.

The pinacol reaction[4] is also mediated by a SET pathway. In this reaction, two ketones or aldehydes are joined to form a diol, *via* the formation of a ketyl radical anion (Figure 3).
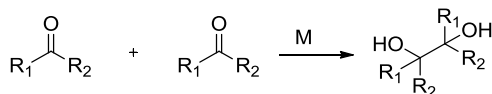

Figure 3. Schematic presentation of the pinacol coupling using a metal (M).

Advances in bond forming reactions have since introduced a large variety of alternative metals such as indium[5] and samarium.[6] Furthermore, low valent metal salts such as Sm(II),[7] Cr(II)[8] and Ti(III)[9] has been successfully employed instead of elemental metals. These reactions all have in common that the sequence starts with the single electron transfer from the metal to an electrophilic site (*i.e.* an alkyl halide or a carbonyl), inverting the polarity and forming a nucleophile.

The reduction of functional groups was first accomplished with dissolving metals such as Li, Na, Zn, Sn, and Fe in various media such as water, alcohols, mineral acids and liquid ammonia (Figure 4).[10] The reduction in these cases proceeds with stepwise transfer of electrons and protons.

[4] See Adams, R and Adams E. W., *Org Synth. Coll* 1, **1941**, 448.
[5] Pitts, M. R.; Harrison, J. R.; Moody, C. J., *J. Chem. Soc.-Perin. Trans. 1* **2001**, 955.
[6] Banik, B. K., *Eur. J. Org. Chem.* **2002**, 2431.
[7] See for example Krief, A.; Laval, A.-M., *Chem. Rev* **1999**, 99, 745.
[8] Wessjohann, L. A.; Scheid, G. n., *Synthesis* **1999,** 1999, 1.
[9] Ladipo, F. T., *Curr. Org. Chem.* **2006,** 10, 965.
[10] See Brown, H. C.; Krishnamurthy, S., *Tetrahedron* **1979**, 35, 567 and references therein
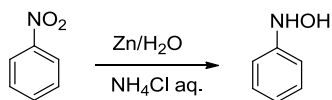
Figure 4. Reduction of nitrobenzene to N-phenyl hydroxylamine.[11]

Transition metal catalyzed hydrogenation is another reduction method, utilizing for instance palladium and platinum. This has broadened the scope of reducible functions as well as providing methods that are more reliable and suitable for large scale synthesis.[12] A major breakthrough came with the introduction of the complex metal hydrides in the 1940s.[13] These reagents are amendable to a high degree of fine-tuning to allow for example reductive amination without preformation of the imine (Figure 5).[14]
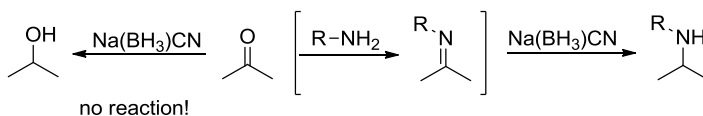

Figure 5. Schematic presentation of the selectivity between a ketone and an imine using sodium cyanoborohydride.

In light of the above discussion, the central character in this thesis – SmI$_2$, is best described as a homogenous electron transfer reagent and is in many ways similar to the metals already mentioned. Since its introduction by Kagan,[15] the use of SmI$_2$ in this context has been applied to all of the above bond-forming reactions and covered the reduction of almost all common functional groups, including carbonyls, acids, amides, nitriles, halogens, and sulfonates.[16] However, there is a continuing need to develop reactions that can enable selective transformations of the sensitive intermediates often encountered in modern organic synthesis.

[11] O. Kamm, *Org Synth. Coll* 1, 435 (1941).

[12] (a) M. Hudlicky, *Reduction in Organic Chemistry*, American Chemical Society, Washington, DC, 2nd ed, 1996.(b) B. M. Trost; I. Fleming, *Comp. Org. Syn.*, Pergamon Press, Oxford, 1991, vol. 8.

[13] Finholt, A. E.; Bond, A. C.; Schlesinger, H. I., *J. Am. Chem. Soc.* **1947,** 69, 1199.

[14] Borch, R. F.; Bernstein, M. D.; Durst, H. D., *J. Am. Chem. Soc.* **1971,** 93, 2897.

[15] Girard, P.; Namy, J. L.; Kagan, H. B., *J. Am. Chem. Soc.* **1980,** 102, 2693.

[16] For an excellent book see: Procter, D.J.; Flowers, R.A.; Skrydstrup, T. *Organic Synthesis using Samarium Diiodide*. RCS Publishing, Cambridge 2010

1.1 Samarium

Samarium is element number 62 in the periodic chart and belongs to the f-block or lanthanide series (Figure 6).[17] The name stems from the mineral samarskit, which in turn comes from the Russian mine official, Colonel V. E. Samarsky. The main source of samarium today is from the lanthanide ores Bastnäsite ($LnFCO_3$), Monazite ((Ln, Th)PO_4) and Xenotime ((Y, Ln)PO_4).

Figure 6. Highlighting of samarium in the periodic table.

[17] Cotton, S.A. *Lanthanide and actinide chemistry*. 2nd Ed., John Wiley & Sons, West Sussex, England, 2006

Samarium is a metal that reacts slowly with water and oxidizes in air. In contrary to the general belief it is a rather abundant element in the earth's crust and constitutes 7 grams per ton. This can be compared to for example tin (6 g/ton), silver (0.1 g/ton), copper (70 g/ton) and iron (50 kg/ton). However, the process for obtaining pure samarium is costly as it needs to be separated from the other lanthanide metals present in the mineral. Currently it is mainly used as an alloy together with cobalt in super strong permanent magnets.[18]

Samarium has two stable oxidation states, +2 and +3, where the latter is the most stable. This property makes samarium in its divalent state a one-electron donor and hence a reducing agent. The oxidation potential, defined as the propensity to donate one electron, is determined to -1.41 V *vs* ferrocene (Fc) in tetrahydrofuran (THF).[19]

The coordination chemistry of samarium (and other lanthanides as well) is not as predictable as for the d-block elements. Ligands tend to add until the coordination sphere is saturated, rather than adopting a specific geometry. Thus sterical factors govern the number of ligands that can bind.[20]

Samarium is considered a hard Lewis acid and is electropositive. As a consequence it tends to form stable bonds with hard π-donor ligands such as OR, NR_2 and F.[20]

[18] Beaudry, B. J.; Gschneidner, J. K. A.; Karl A. Gschneidner, Jr.; LeRoy, E., Chapter 2 Preparation and basic properties of the rare earth metals. In *Handbook on the Physics and Chemistry of Rare Earths*, Elsevier: 1978; Vol 1, pp 173.

[19] Enemaerke, R. J.; Daasbjerg, K.; Skrydstrup, T., *Chem. Commun.* **1999**, 343.

[20] Crabtree, R. H., *The organometallic chemistry of the transition metals.* 4th Ed. Wiley, New York, 2005.

1.2 Background to samarium(II)-mediated organic synthesis

In organic chemistry, electron donors come in many shapes and forms. The earliest discovered being metals such as zinc[21] as well as direct electrolysis.[22] Later, the chemistry of tributyltin hydride was introduced as a radical reagent.[23] All of these mediate organic redox processes such as functional group reductions and radical ion formation that can be exploited for C-C bond forming reactions.[24]

Sm(II)-salts has become a very popular one electron transfer reagent. This stems from the fact that the most common Sm(II)-halide, samarium(II)iodide is easy to prepare and store as a THF solution (ca 0.1 M). Furthermore, its reactivity can be fine-tuned over a wide range using different additives and solvents. SmI_2 has now become a standard reagent in many laboratories and it is frequently used in the synthesis of complex organic compounds. An example is a key step in the synthesis of the antibiotic natural product platensimycin (Figure 7).[25]
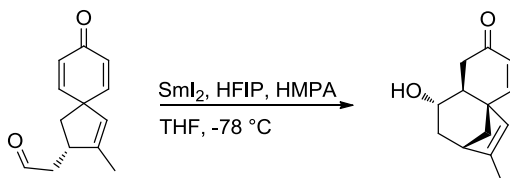
Figure 7. A ketyl-olefin cyclization promoted by SmI_2 using hexafluoroisopropanol (HFIP) as proton source and hexamethylphosphortriamide (HMPA) as additive.

[21]See McBride, J. M., *Tetrahedron* **1974**, 30, 2009 and references therein.

[22] Kolbe, H., *Annalen der Chemie und Pharmacie* **1849**, 69, 257.

[23] Menapace, L. W.; Kuivila, H. G., *J. Am. Chem. Soc.* **1964**, 86, 3047.

[24] Zard, S. Z. Radical Reaction in Organic Synthesis; Oxford University Press: Oxford, 2003.

[25] Nicolaou, K. C.; Li, A.; Edmonds, D. J.; Tria, G. S.; Ellery, S. P., *J. Am. Chem. Soc.* **2009**, 131, 16905.

1.2.1 Fine-tuning the reactivity of Sm(II)

As mentioned above, the reactivity of Sm(II) reagents can be altered by addition or variation of one or more of the following; solvent, proton donors, co-solvent, catalytic amounts of metal salts or, as recently revealed, presence or absence of light.[26]

Solvents: The most commonly used solvent for SmI_2 is THF, but there have been reports on the use of tetrahydropyran,[27] benzene,[28] acetonitrile,[29] alcohols[30] and even water.[31] This field is not very well explored since SmI_2 is nearly always prepared in THF. However, recently SmI_2 (along with other divalent lanthanide iodides) were made commercially available as solvent-free salts thus enabling the use of any suitable solvent.

Proton donors: In most of the reductive processes there is a need to protonate anions resulting from the transfer of two electrons. If no proton source is present the protons are usually furnished from the solvent or the subsequent aqueous work-up. Aliphatic alcohols, water or glycols is frequently added as proton donors. The effects of proton donors on the chemistry of Sm(II) has been extensively studied by the groups of Hoz[32] and Flowers,[33,31] and it has become clear that the role of the proton donors is not only to supply protons but that they also function as reactivity enhancing additives. Addition of large amounts of water (500 equiv.) increases the reduction potential by -0.6 V, thus acting as a co-solvent as well.[33d]

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[26] Mazal, A.-L.; Shmaryahu, H., *Chem. Eur. J.* **2010**, 16, 805.

[27] Murakami, M.; Hayashi, M.; Ito, Y., *J. Org. Chem.* **1992**, 57, 793.

[28] Kunishima, M.; Tanaka, S.; Kono, K.; Hioki, K.; Tani, S., *Tetrahedron Lett.* **1995**, 36, 3707.

[29] Ruder, S. M., *Tetrahedron Lett.* **1992**, 33, 2621.

[30] Joseph, A. T., Jr.; Antharjanam, P. K. S.; Edamana, P.; Esther, N. P.; Robert, A. F., II, *Eur. J. Inorg. Chem.* **2008**, 2008, 5015.

[31] Flowers, R. A., *Synlett* **2008**, 1427.

[32] (a) Yacovan, A.; Hoz, S.; Bilkis, I., *J. Am. Chem. Soc.* **1996**, 118, 261. (b) Tarnopolsky, A.; Hoz, S., *Organic & Biomolecular Chemistry* **2007**, 5, 3801. (c) Tarnopolsky, A.; Hoz, S., *J. Am. Chem. Soc.* **2007**, 129, 3402. (d) Farran, H.; Hoz, S., *Org. Lett.* **2008**, 10, 865.

[33] (a) Chopade, P. R.; Davis, T. A.; Prasad, E.; Flowers, R. A., *Org. Lett.* **2004**, 6, 2685. (b) Chopade, P. R.; Prasad, E.; Flowers, R. A., *J. Am. Chem. Soc.* **2004**, 126, 44. (c) Prasad, E.; Knettle, B. W.; Flowers, R. A., *J. Am. Chem. Soc.* **2004**, 126, 6891. (d) Prasad, E.; Flowers, R. A., *J. Am. Chem. Soc.* **2005**, 127, 18093. (e) Teprovich, J. A.; Balili, M. N.; Pintauer, T.; Flowers, R. A., *Angew. Chem.,Int. Ed. Engl.* **2007**, 46, 8160.

Co-solvents: Inanaga's discovery that addition of HMPA markedly increased the reactivity of SmI_2 can be considered a milestone in this field.[34] For many reactions involving SmI_2 the addition of HMPA is absolutely crucial. Over the years, several research groups have studied the effect of added HMPA and it has been found that the reduction potential increases with increasing concentration of HMPA. The maximum is reached with 4 equivalents as judged from the oxidation potential going from -1.41 V to -2.31.[35] Following this discovery many new additives have been explored including *N,N'*-dimethylpropyleneurea (DMPU), tetramethylurea (TMU) and *N*-methylpyrrolidone (NMP),[16,31,36] none are however as efficient as HMPA. Thus there is still a need to find alternatives to HMPA as it is a known carcinogen.

Metal salts: Kagan *et al.* demonstrated that the addition of Fe(III) to a Sm(II) reducing medium alters the reactivity.[37] This is inspired from the early days of Birch reductions when it was found that iron salts (probably from the accidental contamination of rusty cylinders of ammonia) promoted reduction reactions. This was studied further and it was found that NiI_2 was the most effective metal salt.[38] Lithium halides are also known to increase the reactivity, and it has been shown that the oxidation potential is increased by -0.78 V with the addition of 12 equiv. LiCl.[39]

Recently it has been found that light play an important role in enhancing the reducing power of $SmI_2.$ Hoz *et al.* demonstrated that many reactions involving SmI_2 are inhibited when put under a UV-lamp at 254 nm. SmI_2 absorbs light in the 600 nm range, and excitation at this wavelength allows the electrons to become excited and more easily transferred to a substrate.[26] Once the electron is transferred from Sm(II) in an excited state, back transfer is very unfavorable.

[34] Otsubo, K.; Inanaga, J.; Yamaguchi, M., *Tetrahedron Lett.* **1986**, 27, 5763.
[35] Enemaerke, R. J.; Hertz, T.; Skrydstrup, T.; Daasbjerg, K., *Chem.- Eur. J.* **2000**, 6, 3747.
[36] (a) Shabangi, M.; Sealy, J. M.; Fuchs, J. R.; Flowers, R. A., *Tetrahedron Lett.* **1998**, 39, 4429. (b) Kagan, H. B.; Namy, J.-L., *Top. Organomet. Chem.* **1999**, 2, 155. (c) Dahlen, A.; Hilmersson, G., *European Journal of Inorganic Chemistry* **2004**, 3393.
[37] Girard, P.; Namy, J. L.; Kagan, H. B., *J. Am. Chem. Soc.* **1980**, 102, 2693.
[38] Machrouhi, F.; Hamann, B.; Namy, J. L.; Kagan, H. B., *Synlett* **1996**, 633.
[39] Fuchs, J. R.; Mitchell, M. L.; Shabangi, M.; Flowers, R. A., *Tetrahedron Lett.* **1997**, 38, 8157

Other Sm(II) based reagents have been studied, but not as well as SmI_2. There are a few reports on $SmCl_2$[39] and $SmBr_2$,[39,40] both are more reactive than SmI_2, but they are rarely employed in organic synthesis because of their very low solubility. Samarium(II)-bis(trimethylsilyl)amide ($Sm(HMDS)_2$) is easy to prepare and have been used in a few reactions where it displays slightly different reactivity compared to SmI_2. In addition it has the benefit of being soluble in non-polar solvents such as hexane.[41]

Our group has been interested in SmI_2 mediated reduction reactions for almost a decade and focus has been on the exploration of the combination of two additives; an aliphatic amine and water. It was found that these additives accelerated the reduction of ketones to remarkable rates. In the work by Dahlén *et al.* the basic facts about this reagent was studied in detail.[42] Since then, it has been evaluated as a powerful reductant capable of promoting a broad range of reactions.[40f, 43] Within the scope of this thesis the reagent has been evaluated further to include more elaborate reactions, and foremost the limitations of this reagent have been sought.

1.2.2 Sm(II)-mediated organic reactions

In the area of functional group reductions, SmI_2 was first considered unsuitable as a reductant as the reaction rates were very low. A ketone for instance was reduced slowly over the course of several days.[37] As detailed above, the addition of proton donors and co-solvents increases the rates tremendously, and the use of SmI_2 as a reductant is thus feasible (Figure 8).

[40] (a) Lebrun, A.; Namy, J. L.; Kagan, H. B., *Tetrahedron Lett.* **1993**, 34, 2311. (b) Lebrun, A.; Rantze, E.; Namy, J. L.; Kagan, H. B., *New J. Chem.* **1995**, 19, 699. (c) Helion, F.; Lannou, M.-I.; Namy, J.-L., *Tetrahedron Lett.* **2003**, 44, 5507. (d) Fuchs, J. R.; Mitchell, M. L.; Shabangi, M.; Flowers, R. A., *Tetrahedron Lett.* **1997**, 38, 8157. (e) Miller, R. S.; Sealy, J. M.; Shabangi, M.; Kuhlman, M. L.; Fuchs, J. R.; Flowers, R. A., *J. Am. Chem. Soc.* **2000**, 122, 7718. (f) Kim, M.; Knettle, B. W.; Dahlen, A.; Hilmersson, G.; Flowers, R. A., *Tetrahedron* **2003**, 59, 10397

[41] (a) Hou, Z.; Fujita, A.; Zhang, Y.; Miyano, T.; Yamazaki, H.; Wakatsuki, Y., *J. Am. Chem. Soc.* **1998**, 120, 754. (b) Brady, E. D.; Clark, D. L.; Keogh, D. W.; Scott, B. L.; Watkin, J. G., *J. Am. Chem. Soc.* **2002**, 124, 7007.

[42] (a) Dahlen, A.; Hilmersson, G., *Tetrahedron Lett.* **2002**, 43, 7197. (b) Dahlen, A.; Hilmersson, G., *Chem.-Eur. J.* **2003**, 9, 1123. (c) Dahlen, A.; Hilmersson, G.; Knettle, B. W.; Flowers, R. A., *J. Org. Chem.* **2003**, 68, 4870. (d) Dahlen, A.; Hilmersson, G., *J. Am. Chem. Soc.* **2005**, 127, 8340.

[43] (a) Dahlen, A.; Hilmersson, G., *Tetrahedron Lett.* **2003**, 44, 2661. (b) Dahlen, A.; Petersson, A.; Hilmersson, G., *Org. Biomol. Chem.* **2003**, 1, 2423. (c) Dahlen, A.; Sundgren, A.; Lahmann, M.; Oscarson, S.; Hilmersson, G., *Org. Lett.* **2003**, 5, 4085.
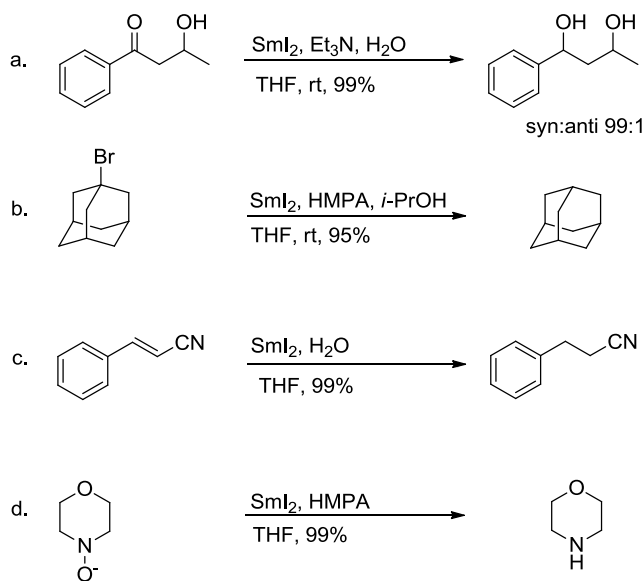
Figure 8. Reduction of a) ketone,[44] b) tertiary bromide,[45] c) activated double bond,[46] d) N-oxide.[47]

It has also been found in numerous cases over the years that Sm(II) reductions frequently give rise to unique selectivity as in Procter's lactone reduction.[48] In this case there is selectivity towards reduction of a 6-membered lactone in preference of a 5-membered one (Figure 9).
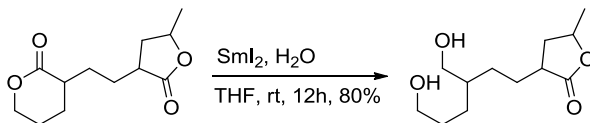

Figure 9. Selective reduction of a six-membered lactone in preference of a five-membered.

[44] Davis, T. A.; Chopade, P. R.; Hilmersson, G.; Flowers, R. A., *Org. Lett.* **2005**, 7, 119.
[45] Inanaga, J.; Ishikawa, M.; Yamaguchi, M., *Chem. Lett.* **1987**, 1485.
[46] Kamochi, Y.; Kudo, T., *Chem. Lett.* **1993**, 1495.
[47] Handa, Y.; Inanaga, J.; Yamaguchi, M., *J. Chem. Soc., Chem. Commun.* **1989**, 298.
[48] Parmar, D.; Duffy, L. A.; Sadasivam, D. V.; Matsubara, H.; Bradley, P. A.; Flowers, R. A.; Procter, D. J., *J. Am. Chem. Soc.* **2009**, 131, 15467.

Recently a very important addition to the arsenal of Sm(II) mediated reductions was reported by Markos *et al*. They have developed a deoxygenation protocol utilizing toluate esters as SET susceptible functional groups (Figure 10).[49]
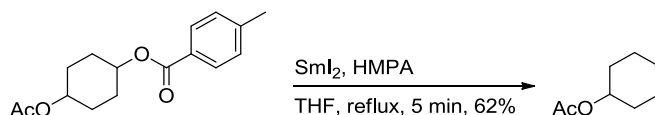

Figure 10. Deoxygenation in presence of an ester using SmI$_2$ and HMPA.

The area that SmI$_2$ has made the largest impact on, apart from functional group transformations, is the carbon-carbon bond forming reactions. There appears to be no reagent more efficient than SmI$_2$ in promoting the intramolecular reactions used in for instance total synthesis. There are to date thousands of examples where Sm(II) reagents has been used in highly elaborate syntheses. Its versatility in this type of reactions is outstanding and it has been successfully used in reactions such as Barbier-,[50] and Reformatsky[51] reactions as well as ketyl-olefin,[52] and pinacol couplings (Figure 11).[53]
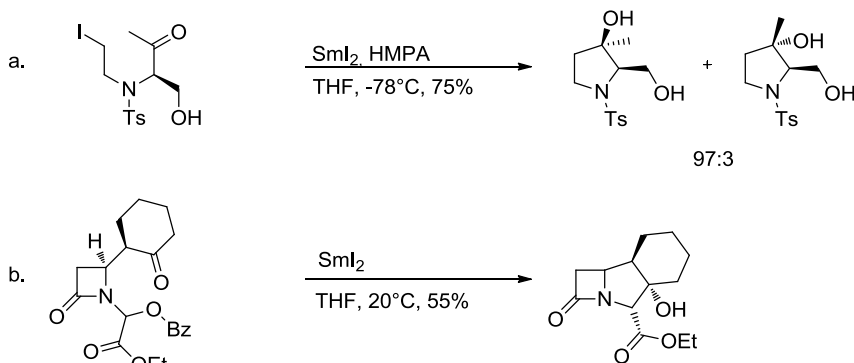
[49] Lam, K.; Markó, I. E., *Tetrahedron* **2009**, 65, 10930.
[50] Makino, K.; Kondoh, A.; Hamada, Y., *Tetrahedron Lett.* **2002**, 43, 4695.
[51] Jacobsen, M. F.; Turks, M.; Hazell, R.; Skrydstrup, T., *J. Org. Chem.* **2002**, 67, 2411.
[52] Molander, G. A.; McKie, J. A., *J. Org. Chem.* **1994**, 59, 3186.
[53] Zhong, Y.-W.; Dong, Y.-Z.; Fang, K.; Izumi, K.; Xu, M.-H.; Lin, G.-Q., *J. Am. Chem. Soc.* **2005**, 127, 11956.
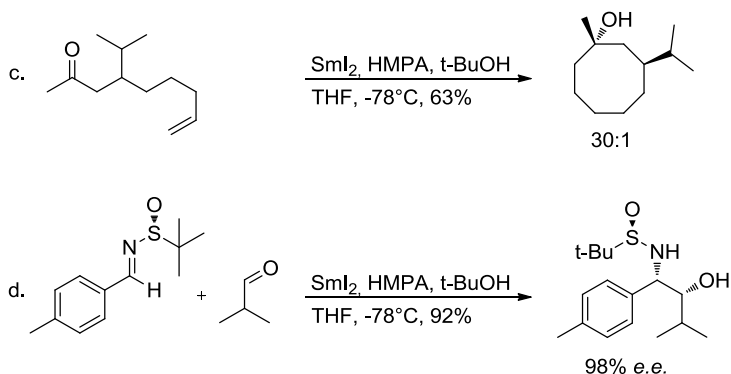
Figure 11. Examples of a) Barbier reaction[50] b) Reformatsky reaction[51] c) Ketyl-olefin cyclization[52] and d) Imino pinacol coupling.[53]

To conclude, SmI_2 and other Sm(II)-reagents are becoming more widely used and they appear in about 100 publications annually.[54] As a reducing agent, it has to compete with cheap bulk reagents such as hydrides and hydrogen. It can however carve a niche as a reagent capable of more selective reduction reactions. In the example below, the authors successfully employed a SmI_2 reduction after attempting catalytic hydrogenation without success (Figure 12).[55]
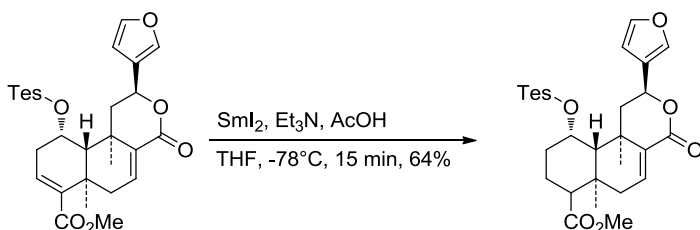

Figure 12. The selective reduction of a conjugated double bond using SmI_2.

Comparing the reductive processes that are promoted by SmI_2 to other methods, a few aspects become clear. The relatively high cost of samarium, the low solubility (0.13 M in THF) of SmI_2 and the requirement of large amounts of hazardous and toxic co-

[54] www.scifinder.org

[55] Hagiwara, H.; Suka, Y.; Nojima, T.; Hoshi, T.; Suzuki, T., *Tetrahedron* **2009**, 65, 4820.

solvents such as HMPA is likely to prevent large scale synthesis. Another aspect is the enormous amount of literature covering the subject, with endless combinations of additives and different reaction conditions. Hopefully more general and robust methods can be developed using non-toxic additives for SmI_2 so more chemists can experience the exciting chemistry of this reagent!

2. Functional group reductions

A large part of the work presented herein concerns reductive processes of functional groups in organic compounds. The aim has been to develop selective reactions that are suitable in multifunctional substrates. To achieve this, mechanistic studies have been undertaken to understand what factors govern the reactivity. In the cases where this has not been possible due to very high reaction rates, efforts to establish the scope and limitation of the reaction have been made. Throughout this chapter comparisons are made between Sm(II)-based reductions and other methods, and the differences in selectivity are also discussed.

2.1 Reduction of the nitro group

The nitro group is one of the most valuable functional groups as it is easily converted into a wide range of other groups, such as carbonyls, nitriles and amines.[56] The reduction of the nitro group to amine is one of the most common transformations in the pharmaceutical industry and is considered a key reaction in the preparation of intermediates and active drugs.[57] A distinction is usually made between aromatic and aliphatic nitro compounds as they differ in reactivity, where the latter is easier to reduce.[58] Although there is a large number of alternatives for this type of reduction, all known methods have their drawbacks. For instance, reactions involving transition metal catalysis can have selectivity issues if double bonds are present in the molecule and the use of LiAlH$_4$ is seldom used on multifunctional substrates due to its very high

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[56] Ono, N. *The Nitro Group in Organic Synthesis*. Wiley-VCH Weinheim, 2001.
[57] (a) Dugger, R. W.; Ragan, J. A.; Ripin, D. H. B., *Organic Process Research & Development* **2005**, 9, 253. (b)Carey, J. S.; Laffan, D.; Thomson, C.; Williams, M. T., *Organic & Biomolecular Chemistry* **2006**, 4, 2337.
[58] Hudlicky, M. *Reductions in Organic Chemistry*. 2nd Ed. ACS, Washington, DC. 1996.

reactivity. Although considered old fashioned, the use of dissolving metals (especially Zn) for reduction of nitro groups still finds its place in modern organic synthesis due to its ease of handling and low cost.[59] The drawback with dissolving metal reductions is the fact that the reaction takes place on the surface of the metal (the same holds for heterogeneous catalytic reductions with hydrogen), making it almost impossible to take advantage of reactivity differences of various functional groups in the molecule. In the light of this, SmI_2 constitute an excellent complement to these methods as it combines high reactivity with a high chemoselectivity.

2.1.1 Reduction of aliphatic nitro compounds (Paper I)

The reduction of aliphatic nitro compounds to amines is accomplished with only a few methods compared to the reduction of nitroaryls to anilines. The SET reduction of the nitro group has been proposed to occur in several stages and is generally accepted to operate in the Sm(II)-mediated reduction (Figure 13).[60]
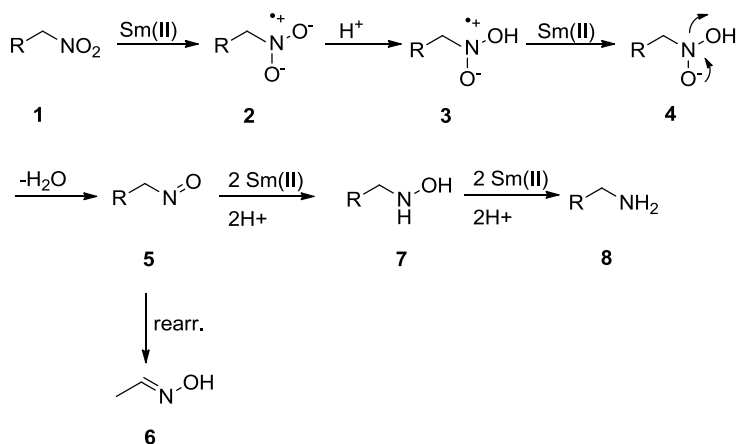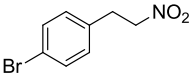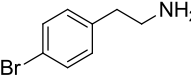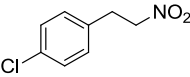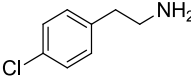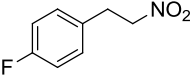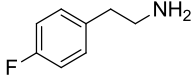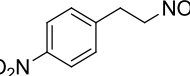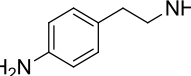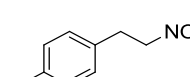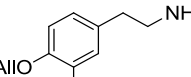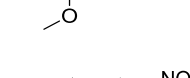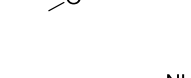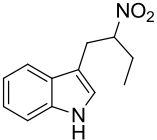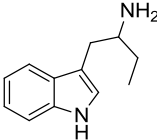

Figure 13. Mechanism of the single electron reduction of nitro compounds.

[59] See for example a) Anderson, J. C.; Blake, A. J.; Mills, M.; Ratcliffe, P. D., *Org. Lett.* **2008**, 10, 4141. b) Castanedo, G.; Clark, K.; Wang, S. M.; Tsui, V.; Wong, M. L.; Nicholas, J.; Wickramasinghe, D.; Marsters, J. C.; Sutherlin, D., *Bioorg.Med. Chem. Lett.* **2006**, 16, 1716.
[60] House H., *Modern Synthetic Reactions*, W A Benjamin, Menlo Park 1972.

The combination of SmI$_2$, isopropylamine and water was applied to a range of different aliphatic nitro compounds (Table 1, entries 1-8). The reaction was fast, high yielding and the work-up could be initiated after mixing of the reagents.

Table 1. Reduction of aliphatic nitro compounds.

Entry	Starting material	Product	Isolated yield (%)[a]
1			95[b]
2			60
3			95
4			87
5			86
6			85
7			94
8			99

[a] Reaction conditions: To a stirred solution of SmI$_2$ (6 equiv., 0.1 M in THF), water (60 equiv.) and isopropylamine (12 equiv.) was added dropwise a solution of the nitro compound in THF at rt.
[b] Chemical yield determined by GC comparing with an internal standard.

During the screening of reaction conditions, it was found that a higher yield was obtained when an increased amount of water was present prior to the addition of the nitro compound. The reason for this is probably that the anionic radical intermediates (Figure 13, 2 and 3) are intercepted by protons before they have a chance to dimerize or polymerize. Existing methods that employs SmI_2 as a reductant can be used to synthesize hydroxylamines (Figure 13, 7).[61] Unfortunately, using fewer equivalents with this method did not stop the reaction at these intermediate stages. This only resulted in lower conversion.

Substrates containing halogens were chosen as interesting models once the optimal reaction conditions had been established using the simple aliphatic compound (Table 1, entry 1). It was discovered that aromatic bromides were reasonably compatible with this system, but unfortunately total selectivity between reductive dehalogenation and nitro reduction could not be achieved, yielding approximately 60% of the desired product (entry 2). On the other hand substrates containing aromatic chlorides (entry 3) and fluorides (entry 4) were cleanly reduced to the desired amine, without fission of the carbon-halogen bond. This is comparable with results obtained with $LiAlH_4$-reductions of similar substrates found in the literature.[62]

As expected the nitro substituted substrate (entry 5) yielded *p*-aminophenyl-2-ethylamine, while functional groups such as allyl (entry 6) and benzyl ethers (entry 7) were left unchanged. In control experiments, the use of $NiB_2/NaBH_4$ or Pd/C in the reduction of these substrates gave deallylated and debenzylated amines, albeit with high conversion (Figure 14).
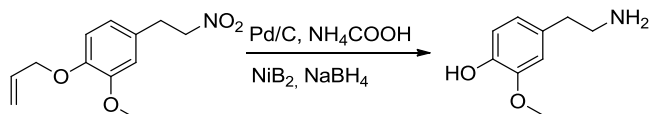

Figure 14. Reduction of the nitro group using palladium or nickel catalysts lead to deallyllation.

[61] Kende, A. S.; Mendoza, J. S., *Tetrahedron Lett.* **1991**, 32, 1699.
[62] a.) Torres, M. A.; Cassels, B.; Rezende, M. C., *Synth. Commun.* **1995**, 25, 1239. b.) Bourguignon, J.; Lenard, G.; Queguiner, G., *Can. J. Chem.* **1985**, 63, 2354.

Although both deallylation[43c] and debenzylation [63] reactions are promoted by SmI$_2$/amine/H$_2$O, the rate of the nitro reduction is obviously higher resulting in the observed selectivity.

SET reduction reactions are known to affect aromatic compounds (Birch reaction), but no reduction of the indole nucleus was observed, and the tryptamine derivative (entry 8) could be isolated in quantitative yield.

In conclusion, this method offers a quick and clean method for the reduction of aliphatic nitro compounds and the yields are consistently high. In addition, it is tolerant to functions that are not compatible with existing methods and can serve as a complementary method to hydrogenations or metal hydride reduction.

2.1.2 Reduction of nitroalkenes (Paper I)

α,β-Unsaturated nitroalkenes are very useful synthons that usually are readily synthesized from the condensation of the appropriate nitroalkane with a carbonyl compound in presence of a base.[64] Nitroalkenes have been reduced to the corresponding saturated amine with varying yields using reducing agents such as dissolving metals,[65] LiAlH$_4$,[66] electrolysis,[67] hydrogenation[68] and BH$_3$/NaBH$_4$.[69] The reason for the variation in yields is probably due to the propensity for polymerization, especially for the conjugated derivatives. In addition to the saturated amine it can give rise to enamides,[70] carbonyls,[71] oximes[72] and nitroalkanes (Figure 15).[73]

[63] Ankner, T.; Hilmersson, G., *Tetrahedron* **2009**, 65, 10856
[64] Kabalka, G. W.; Varma, R. S., *Org. Prep. Proced. Int.* **1987**, 19, 283
[65] see for example Pachaly, P.; Schafer, M., *Arch. Pharm. (Weinhem, Ger.)* **1989**, 322, 477
[66] Gilsdorf, R. T.; Nord, F. F., *J. Am. Chem. Soc.* **1952**, 74, 1837.
[67] Alles, G. A. *J. Am. Chem. Soc.* **1931**, 54, 271.
[68] Kohno, M.; Sasao, S.; Murahashi, S., *Bull. Chem. Soc. Jpn.* **1990**, 63, 1252.
[69] Kabalka, G. W.; Guindi, L. H. M.; Varma, R. S., *Tetrahedron* **1990**, 46, 7443.
[70] Laso, N. M.; QuicletSire, B.; Zard, S. Z., *Tetrahedron Lett.* **1996**, 37, 1605.
[71] Monti, D.; Gramatica, P.; Speranza, G.; Manitto, P., *Tetrahedron Lett.* **1983**, 24, 417.
[72] Koos, M., *Tetrahedron Lett.* **1996**, 37, 415.
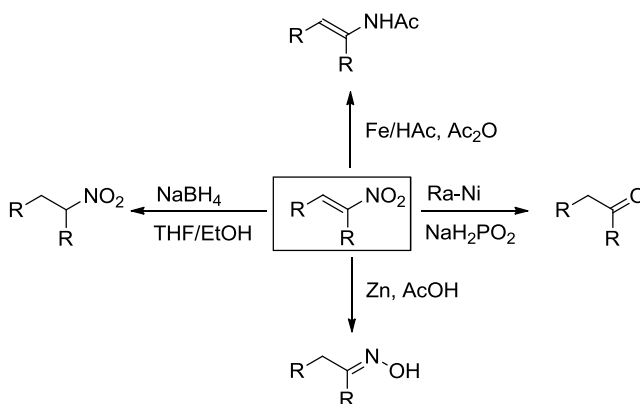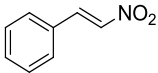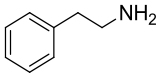[73] Varma, R. S.; Kabalka, G. W., *Synth. Commun.* **1984**, 14, 1093.

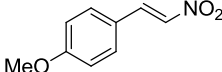R—CH=C(R)—NHAc

Fe/HAc, Ac$_2$O

R—CH(R)—CH—NO$_2$ NaBH$_4$ / THF/EtOH   ←   R—CH=C(R)—NO$_2$ Ra-Ni / NaH$_2$PO$_2$ →   R—CH$_2$—C(R)=O

Zn, AcOH

R—CH$_2$—C(R)=N—OH
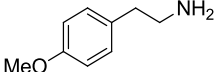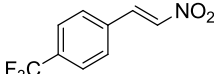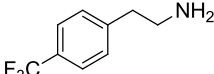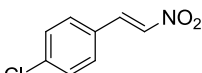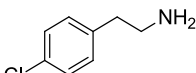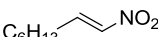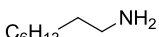
Figure 15. Nitroalkenes give rise to a wide array of products depending on the choice of reagent.

Initial experiments aiming to reduce nitroalkenes to the saturated amine with SmI$_2$/amine/H$_2$O revealed that the order of addition was crucial for a successful reaction. If no water was present when the isopropylamine and nitroalkene was added very small amounts of product could be recovered. It was found that a set of nitrostyrenes gave modest to good yields of the product (Table 2).

In an effort to examine the underlying details of this reaction, a range of substrates with varying electronic properties was exposed to the reagent. The nitrostyrenes (Table 2, entries 1-4) gave similar results and no trend could be discerned. The aliphatic substrate (entry 5) and the aromatic substrate (entry 6) were reduced with a more promising yield.

Table 2. Reduction of nitroalkenes using SmI$_2$.

Entry	Starting material	Product	Isolated yield(%)[a]
1			60
2			36
3			45
4			47
5			70
6			90

[a] Reaction conditions: To a stirred solution of SmI$_2$ (10 equiv., 0.1 M in THF), water (100 equiv.) and isopropylamine (20 equiv.) was added dropwise a solution of the nitroalkenes in THF at rt.

The yields for the reduction of unsaturated nitro compounds are not as impressive as for the aliphatic nitro compounds but it compares favorably with existing methods. However the reaction is extremely fast and safe which lies in its favor. The method is probably more effective for more substituted nitroalkenes as these are less prone to dimerize as can be seen for the α-methyl substituted nitroalkene (Figure 16).
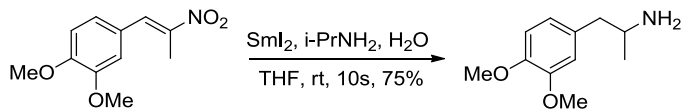
Figure 16. Reduction of a α-substituted nitroalkene.

2.1.3 Sm(II)-mediated synthesis of pyrroles

In the absence of a proton source the yield of amine was diminished for all examined nitro compounds. The nitro alkenes however, gave almost no wanted product at all without the addition of water. Instead, the reaction resulted in a coupled product that

was at least as interesting. The addition of one equiv. SmI$_2$ to a solution of nitrostyrene gave the dimer in high yields and with a diastereoselectivity above 95% (Figure 17).
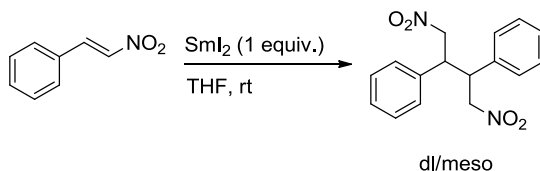
Figure 17. Instantaneous dimerization of nitrostyrene with SmI$_2$.

With the addition of more SmI$_2$ (in total 6 equiv.) a new product was formed that proved to be 2,3-diphenylpyrrole. To explore this intriguing reaction a screening campaign was initiated with a number of combinations of additives and reagents. Unfortunately, the yield of this product was consistently low and no set of conditions could be found that gave the pyrroles in high yield (Table 3). According to GC analysis the starting material was consumed indicating that the low yield was due to extensive polymerization.
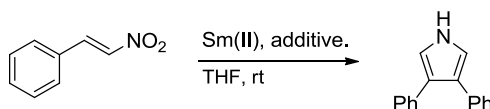
Table 3. Optimization of additives and counter-ions.

Entry	Sm(II)-source	Additive (equiv)	Yield (%)[a]
1	SmI$_2$	None	<5
2	SmBr$_2$	None	<5
3	Sm(HMDS)$_2$	None	<5
4	SmI$_2$	TPPA (5)	<5
5	SmBr$_2$	TPPA (5)	15
6	SmBr$_2$	t-BuOH (3)	11
7	SmBr$_2$	DMPU (5)	<5
8	SmBr$_2$	TMG (10)	19

[a] Reaction conditions: The nitroalkene was added as a dilute THF solution to the Sm(II) mixture (6 equiv., 0.1 M in THF) at rt. Yields determined using GC/MS comparing to an internal standard after work-up with K$_2$CO$_3$-Na/K-tartrate solution and extraction with Et$_2$O.

The optimal conditions using tetramethylguanidine (TMG) and SmBr$_2$ (entry 8) were employed when screening a series of substituted nitrostyrenes and it was found that the electronic character greatly influenced the yield (Table 4).
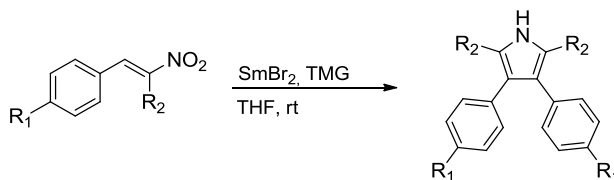
Table 4. Substrate variation using the optimal conditions.

Entry	R$_1$	R$_2$	Yield (%)[a]
1	-CF$_3$	H	44
2	-OCH$_3$	H	22
3	-CF$_3$	-CH$_3$	44
4	-F	-CH$_3$	16
5	-Cl	-H	35

[a] Reaction conditions: The nitroalkenes were added as a THF solution to SmBr$_2$ (6 equiv.) and TMG (10 equiv.) in THF at rt. Yields determined using GC/MS comparing to an internal standard after work-up with K$_2$CO$_3$- Na/K-tartrate solution and extraction with Et$_2$O.

The results in Table 4 indicate that electron deficient nitrostyrenes are best suited for this reaction. This effect is due to the ability of these ring substituents to stabilize the radical intermediate, thus allowing it to dimerize in greater extent.

The reaction sequence starts with the dimerization of the nitroalkene. This is reduced further and finally cyclization and elimination yields the final pyrrole. The formation of pyrroles from nitrostyrenes has been observed before using a buffered aqueous Ti(III)Cl$_3$ solution.[74] The yields were comparable to the Sm(II)-mediated reaction, yielding 32% of the pyrrole.

2.1.4 Reduction of related unsaturated substrates

In addition to the reduction of the unsaturated nitro compounds above, other α,β-unsaturated compounds were exposed to SmI$_2$/Et$_3$N/H$_2$O. Previously it has been

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[74] Sera, A.; Fukumoto, S.; Yoneda, T.; Yamada, H., *Heterocycles* **1986**, 24, 697.

demonstrated that the double bond in cinnamic acid was selectively reduced using either SmI_2/H_2O or $SmI2/Et_3N/H_2O$.[75] As illustrated in Figure 18, vinylic bromides react in a similar fashion as previously reported.[45]
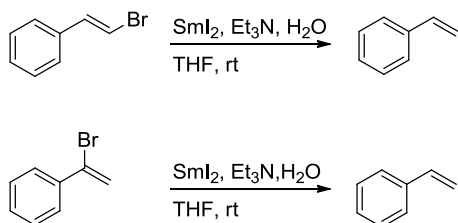
Figure 18. Reduction of 1 equiv. bromostyrene using 2 equiv. SmI_2, 4 equiv. Et_3N and 6 equiv. H_2O.

Examination of α,β-unsaturated ketones revealed that these reacted with moderate selectivity yielding a mixture of reduced product and a dimer (Figure 19).

17%   78%
70% d.e.
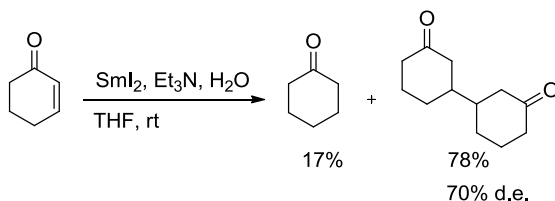
Figure 19. Cyclohexenone is dimerized in favor of conjugate reduction. Reaction conditions: The substrate was added to a SmI_2 solution in THF (2 equiv.) followed by water (6 equiv.) and triethylamine (4 equiv.) at rt.

This is similar to the Birch reduction of α,β-unsaturated ketones were the dimerization product is common, especially in the absence of proton donors.[76]

[75] a.) Cabrera, A.; Alper, H., *Tetrahedron Lett.* **1992**, 33, 5007, b.) Dahlen, A.; Hilmersson, G., *Chem.- Eur. J.* **2003**, 9, 1123.
[76] Caine, D., *Org. React.* **1976**, 23, 19.

2.2 Reductive removal of benzylic heteroatoms (Paper II)

The fission of the benzyl carbon-heteroatom bond is a very important reaction as it includes the deprotection of benzyl protected amines, alcohols and thiols. This reaction is mainly performed using transition metal catalyzed hydrogenation[77] or under Birch conditions.[78]

The combination of amine and water together with SmI_2 has an oxidation potential estimated to be higher than that determined for SmI_2/HMPA (approx -2.3 V *vs* Fc).[79] This is in proximity with the alkali metals (-2.64 V for Li/NH_3 and -2.25 V for Na/NH_3 *vs* Fc).[80] This fact was closely examined (Paper II) and it was found that it indeed does share some similarities with the dissolving alkali metal reductions. It was known prior to this study that the reagent could remove benzylic oxygen, and in contrast to most reductions promoted by SmI_2/amine/H_2O it appeared to have a rate suitable for mechanistic studies. As a result of this we set out to elucidate the mechanism and to establish the scope of this reaction.

2.2.1 Kinetic study

As a first step the stoichiometry of the reaction was determined and it was discovered that at least 2 equiv. of SmI_2 was needed, and that 4 equiv. amine and 6 equiv. of water was crucial for full conversion of benzyl alcohol to toluene (Figure 20). Lower amounts gave incomplete conversion of starting material. This is in agreement with a previous mechanistic study of the reduction of 1-chlorodecane to decane using SmI_2/amine/H_2O.[42d]

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[77] Elamin, B.; Anantharamaiah, G. M.; Royer, G. P.; Means, G. E., *J. Org. Chem.* **1979**, 44, 3442.
[78] Reist, E. J.; Bartuska, V. J.; Goodman, L., *J. Org. Chem.* **1964**, 29, 3725.
[79] Dahlen, A.; Nilsson, A.; Hilmersson, G., *J. Org. Chem.* **2006**, 71, 1576.
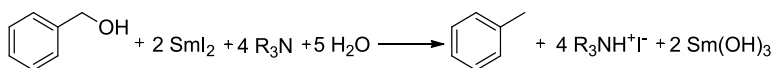[80] Connelly, N. G.; Geiger, W. E., *Chem. Rev.* **1996**, 96, 877.

Figure 20. Suggested balanced reaction for the deoxygenation of benzyl alcohol.

The rate orders were determined using the initial rate method in the reduction of benzyl alcohol.[81] The rate orders for SmI_2 and amine respectively was determined and both were found to be unity in the concentration range studied. (Figure 21 and 22).

Figure 21. Initial log (rate) *vs* log (concentration) of SmI_2 (12-955 mM). Reaction conditions; 200 mM Et_3N, 300 mM H_2O, 14 mM benzyl alcohol.

In contrast to the 1-chloroalkane reduction previously mentioned, where the rate order for SmI_2 was found to be two,[42d] the benzyl alcohol reacts with different kinetics indicating that a different mechanism is operating.

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[81] a) Cox, Brian G. *Modern liquid phase kinetics.* Oxford University Press, Oxford. b) Casado, J.; Lopezquintela, M. A.; Lorenzobarral, F. M., *J. Chem. Ed.* **1986**, 63, 450. c) Hall, K. J.; Quickenden, T. I.; Watts, D. W., *J. Chem. Ed.* **1976**, 53, 493.
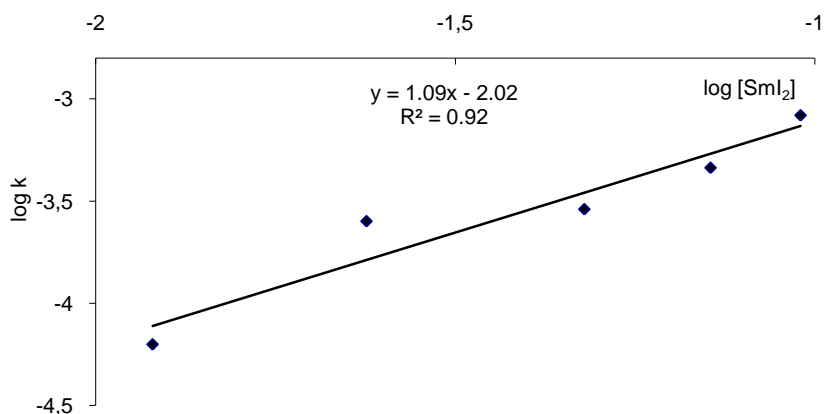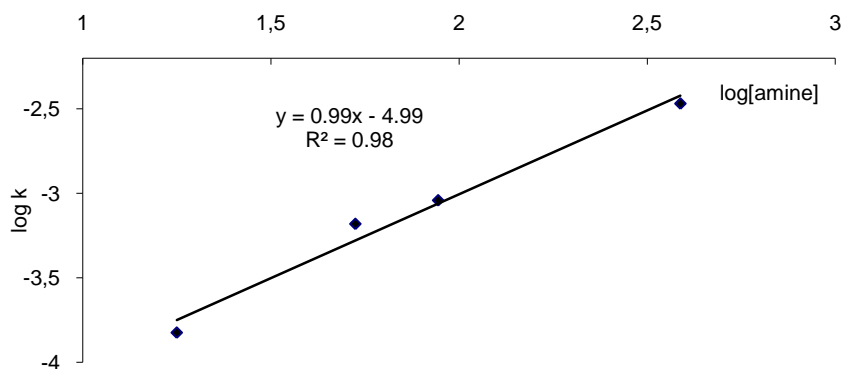
Figure 22. Initial log (rate) *vs* log (concentration) of amine (18-388 mM). Reaction conditions; 100 mM SmI$_2$, 300 mM H$_2$O, 14 mM benzyl alcohol.

The determination of the rate order for the remaining two components proved to be more intriguing. The benzyl alcohol displayed a non-linear behavior; specifically there were two different reaction orders depending on the concentration of the alcohol (Figure 23). In the low concentration range (below 20 mM) the rate order was found to be one. When the higher concentrations were reached the rate order was gradually approaching 0.5. This behavior was interpreted as a result of benzyl alcohol existing as a dimer at high concentrations or that the concentration is high enough to displace ligands around the metal center, which changes the mechanism.
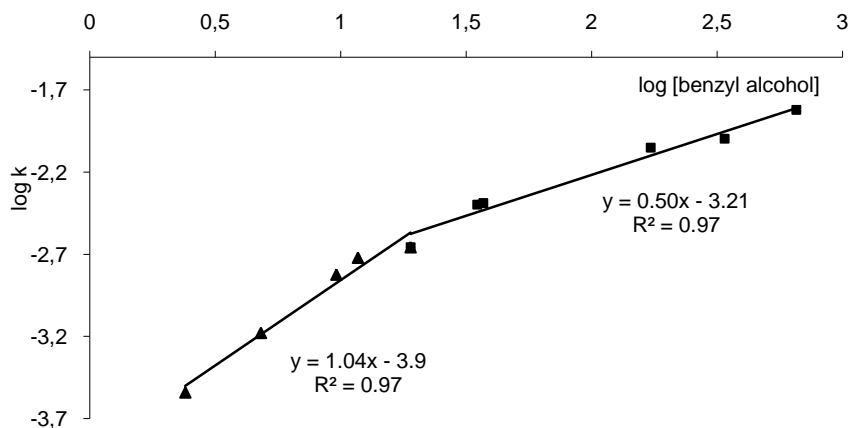
Figure 23. Initial log (rate) *vs* log (concentration) of benzyl alcohol (2.4-654 mM). Reaction conditions; 100 mM SmI$_2$, 200 mM Et$_3$N and 300 mM H$_2$O.

Subsequent UV studies also confirmed that benzyl alcohol indeed is capable of displacing THF (Figure 24). A small hypochromic shift is noted with increasing amounts of benzyl alcohol added to a dilute solution of SmI$_2$.
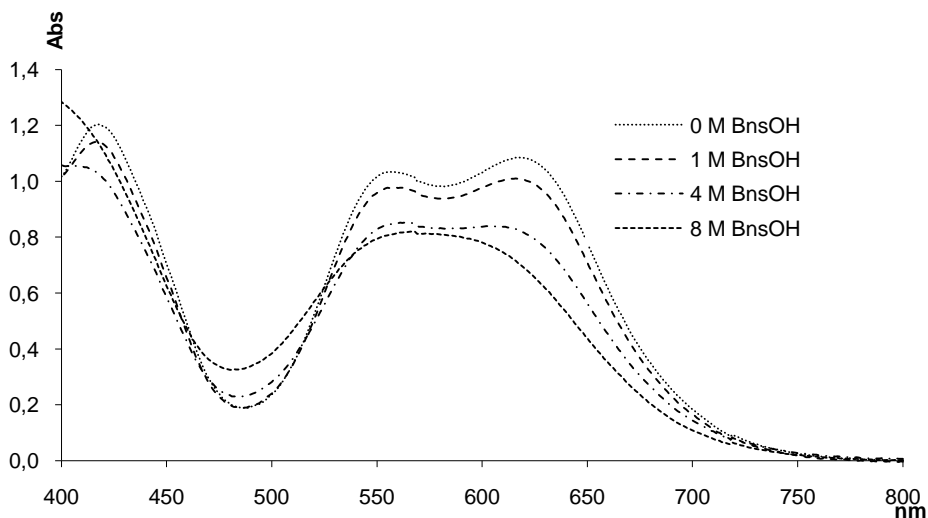
Figure 24. Absorption spectra of SmI$_2$ (2 mM) in the presence of increasing amounts of benzyl alcohol. Several lines are omitted for clarity.

28

In addition to this an identical rate study was performed on *N*-methyl benzyl amine, and it was found that this substrate gave identical results with those of benzyl alcohol, *i.e.* the rate order was found to be unity.

The determination of the rate order for water revealed an even more complex behavior (Figure 25). The rate order was determined to be approximately unity at low concentrations of water (<0.3 M). Then, in a rather narrow concentration interval, the reduction was shut down and the rate dropped quickly. This manifests itself as a curve that comes to a maximum and then quickly levels off. The maximum in rate is reached when approximately three equivalents of water to every Sm(II) is present in the reaction mixture. Hoz *et al* have reported a similar relationship using methanol as proton source in the reduction of naphtalene.[26]
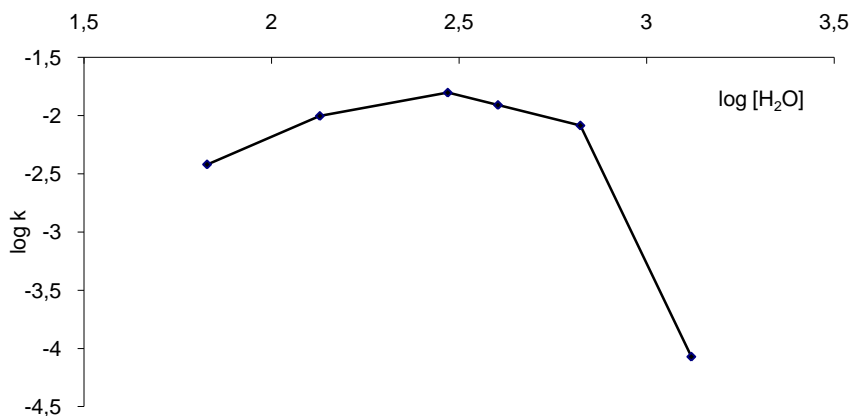
**Figure 25.** Initial log (rate) *vs* log (concentration) of water (67-1316 mM). Reaction conditions; 100 mM SmI$_2$, 200 mM Et$_3$N and 14 mM benzyl alcohol.

In the high concentration area (approx. 1 M H$_2$O) the reduction of benzyl alcohol was very slow. However, it was evident that the mixture still contained Sm(II) as judged by the color; although it had shifted from dark blue to dark purple. To verify this assumption, a ketone was added, and it was found that the mixture was able to reduce this ketone instantaneously to the alcohol. This indicates that the strong coordination of water to the metal effectively shields the weaker coordinating benzyl alcohol from the

inner sphere and inhibits electron transfer. The ketone, being a potent Lewis base, is effective in replacing the water and an electron can be transferred in an inner sphere mechanism. A similar line of reasoning was proposed by Flowers and co-workers regarding the use of HMPA, where a large excess inhibits the reduction of ketones.[33c] Thus, the results presented above further illustrate the complexity surrounding the addition of proton sources where the outcome of the reaction can be fundamentally different depending on substrate and the structure of the proton source.[32,33]

In addition, the kinetic isotope effect (KIE) was measured exchanging H_2O with D_2O. As the rate dependence of water was non-linear the KIE was determined at two concentrations (before and after the maxima), but found to be the same ($k^{H_2O}/k^{D_2O} = 1.9$). This effect is expected as the transfer of protons is rate determining.

2.2.2 Activation Parameters

The reaction orders in the reduction of benzyl alcohol with a mixture of SmI_2, H_2O and an aliphatic amine (Et_3N, or pyrrolidine) were thus found to be first order in benzyl alcohol, amine, water and SmI_2 respectively, yielding the following rate expression.

$$v = k \left[SmI_2 \right] \left[BnOH \right] \left[Et_3N \right] \left[H_2O \right]$$

(Note that this is only valid in certain concentration ranges, but applies under the normal reaction conditions.)

The activation parameters for the $SmI_2/Et_3N/H_2O$ mediated reduction were calculated from the temperature dependence using the Eyring equation assuming a rate order of one in each component (Figure 26). The initial rates were studied over the temperature interval 0-50 °C, with 10 °C increments.
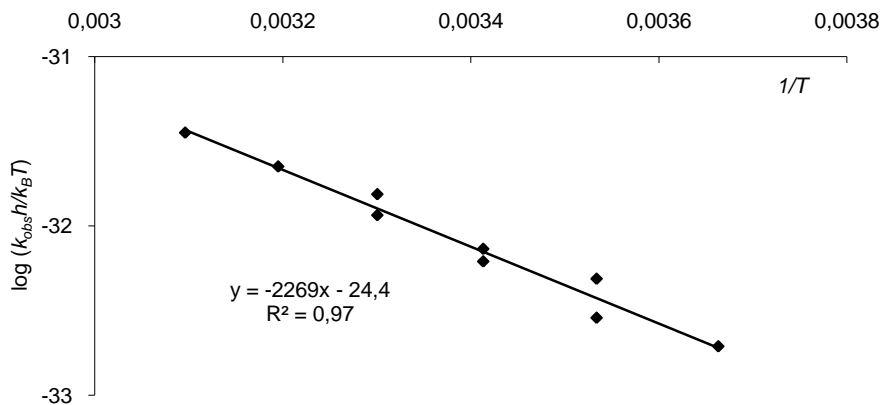
Figure 26. The Eyring plot for the reduction of benzyl alcohol. Reaction conditions; 100 mM SmI$_2$, 200 mM Et$_3$N and 300 mM water and 14 mM benzyl alcohol.

The linear combination of k_{obs} values using the Eyring equation $[\ln(k_{obs}h/k_BT) = -\Delta H^{\ddagger}/RT + \Delta S^{\ddagger}/R]$ gave the following activation parameters:

$\Delta H^{\ddagger} = 18.9 \pm 1.0$ kJ mol^{-1}

$\Delta S^{\ddagger} = -260 \pm 30$ J K^{-1} mol^{-1}

$\Delta G^{\ddagger}_{298K} = 97 \pm 10$ kJ mol^{-1}

As expected there is a large drop in entropy for this reaction it being fourth order overall, thus requiring the assembly of four components in the rate determining step.

2.2.3 Amine basicity

The influence of the amine was examined, and as previously observed,[42d] the pK$_{BH+}$ influences the rate in that higher values (*i.e.* more basic amines) give an increased rate. The reason for this is unclear, but it has been proposed that the function of the amine is to deprotonate water bound to samarium.

2.2.4 Relative cleavage rates of benzyl heteroatom bonds

Table 5. Relative rates determined from comparison of initial rates.

entry	relative-rate	α substituted benzyl alcohols	ring substituted benzyl alcohols	benzylamines and thiols
1	>500			
2	93			
3	1,5			
4	1			
5	0,5			
6	0,25			
7	0,18			
8	0,125			
9	0,05			
10	0,025			
11	0,012			

The relative rates of different substrates containing benzylic heteroatoms were examined (Table 5). Inspection of the results in Table 5 reveals that steric properties play a large role in determining the outcome of the reaction. This is probably due to the fact that coordination to the metal is a prerequisite for transfer of electrons from the Sm(II) species to the substrate. Substitution of α- or hydroxylic hydrogens with a methyl or bigger alkyl group thus effectively slows down the reduction due to decreased ability to coordinate to the metal.

Electronic effects also influence the reactivity to a significant degree. A very slow reaction was noted for 4-fluoro and 4-methoxy substituted benzyl alcohols. On the other hand a tremendous rate enhancement was achieved with the introduction of one or more electron withdrawing substituents. The bis-trifluoromethyl substituted benzyl alcohol (Table 5, entry 1) thus reacts more than 40.000 times faster than 4-methoxybenzyl alcohol (entry 11)!

2.2.5 Mechanism Proposal

With the above data in hand it is possible to make a proposal for the mechanism operating (Figure 27). We can conclude that the reaction takes place in an inner sphere fashion and that the there must be an equilibrium between SmI_2, water and benzyl alcohol. This is supported by the fact that high concentrations of water inhibits the reaction and that substrates with substituents α to the alcohol significantly lowers the rate. The relative rates also reveal that the electronic properties strongly influence the rate implying that the electron is transferred to the aromatic nuclei. This intermediate is greatly stabilized by electron withdrawing substituents and *vice versa* with electron donating ones such as 4-methoxy. It is then assumed that the formed radical anion rearranges to a benzylic radical that is rapidly reduced and protonated to yield the product.
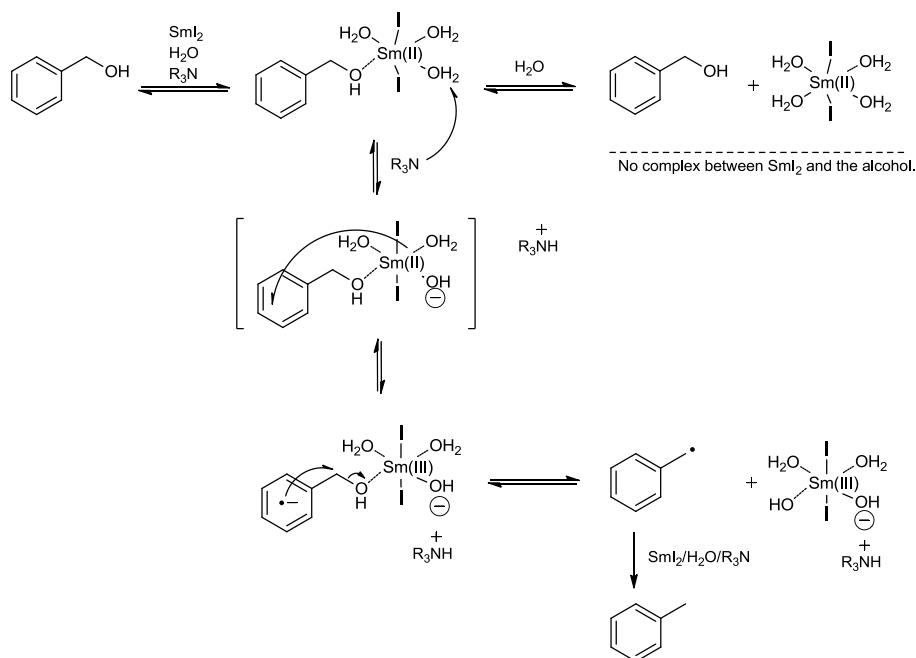
Figure 27. Mechanism proposal based on the rate study.

2.2.6 A practical method for cleavage of the benzyl-heteroatom bond

A set of substrates containing benzylic heteroatoms were exposed to the reagent (Table 6). The optimal reaction conditions were found to be at –20 °C during approximately 20 h using pyrrolidine as base. The choice of base comes from the fact that the combination of SmI$_2$, amine and water decomposes over time, and the more basic the amine the faster the breakdown (Figure 28). However, cooling of the reaction seemed to mitigate this effect while the reactivity towards the substrates in consideration was maintained.
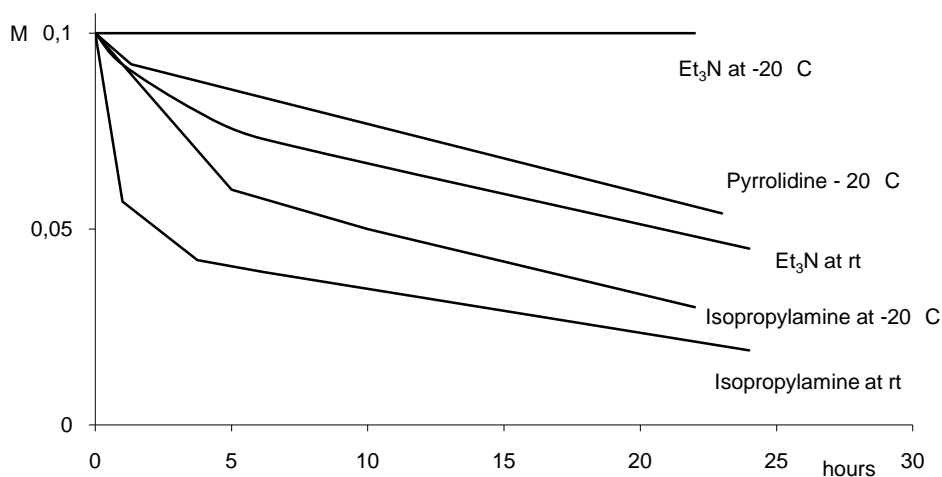
Figure 28. Breakdown of mixtures of SmI_2 and water with amine bases.

Interestingly, the breakdown of Et_3N/H_2O was found to be inhibited at -20 °C, however at this temperature the reduction was very slow and hence impractical to use. Isopropylamine was found to decompose fast both at rt and -20 °C, while pyrrolidine was found to be suitable as it maintained the reactivity while the decomposition was reasonably slow.

Table 6. Reductive cleavage of the benzyl-heteroatom bond.

Entry	Substrate	Product	Yield[a]
1			95
2			62
3			85[b]

Table 6 continued.

Entry	Substrate	Product	Yield[a]
4	OH (indanol)	(indane)	80
5	(naphthalene-CH2OH)		24
6	OH / NH2	NH2	88[c]
7	MeO–C6H4–CH2OH		38
8	F–C6H4–CH2OH	F	5
9	F3C–C6H4–CH2OH	F3C	99
10	F3C, CF3 substituted CH2OH	F3C, CF3	99
11	benzyl-N(H)Me		95
12	benzyl-N(H)cyclohexyl		76
13	benzyl-SH		95

[a] Reaction conditions: To a cooled solution of SmI_2 (5 equiv. 0.1 M in THF), amine (10 equiv.) and water (15 equiv.) was added the benzyl-compound and the temperature was kept at -20 °C for approximately 20 hours. Yields determined with GC/MS comparing to an internal standard after work-up unless stated otherwise.
[b] Isolated yield. [c] Yield determined using HPLC.

The simple benzylic alcohols (entries 1-4, Table 6) display a reactivity that is mostly dependent on steric hindrance, where the 1-phenyletanol is reacting slowly. The 2-napthalene methanol (entry 5) was found to yield varying degree of ring reduction products. It has previously been demonstrated that conjugated aromatic systems are

easily reduced using this reagent.[79] The result from reduction of substrates substituted at the aromatic ring was in accordance with the rate studies, *i.e.* the 4-methoxy and 4-fluoro derivatives, afforded the desired product in low yields (entries 7-8). The trifluoromethylated derivatives (entries 9-10) on the other hand gave instant reduction at room temperature.

On closer inspection the result from the reduction of 4-methoxybenzyl alcohol revealed some interesting details. The conversion into 4-methoxy toluene was low, however it was found that the reaction yielded small amounts of ring reduced products, much like in a Birch reduction. This was not detected in any of the other substrates used, thus it can be concluded that the methoxy substituent is crucial for this transformation.

Within this study the deprotection reaction of amines was examined to some degree, but unfortunately the high yield obtained with the unsubstituted substrates was diminished somewhat (Table 6, entry 12). In an effort to increase the reactivity the benzyl group was substituted with 3,5-bis-trifluoromethyl (Figure 29), but surprisingly the bond between the benzyl moiety was left largely unchanged, instead efficiently cleaving the carbon-fluorine bonds.
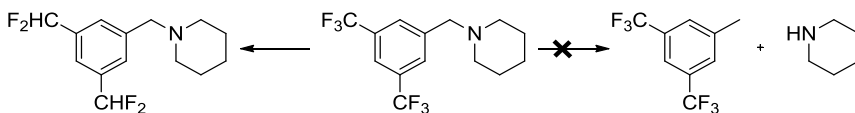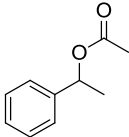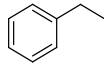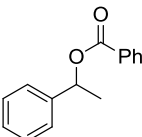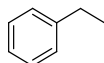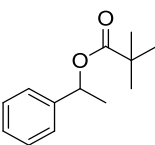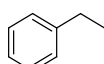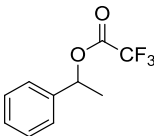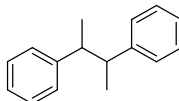

Figure 29. Reduction of 1-(3,5-bistrifluoromethylbenzyl)piperidine with $SmI_2/Et_3N/H_2O$ at -20 °C.

To further explore this, 4-trifluorotoluene was exposed to the same reaction conditions. Examination of the reaction mixture showed almost no sign of defluorination, and again the importance of coordination sites on the substrate is apparent. Defluorination reactions have been studied in more detail and will be discussed in section 2.3.

In an effort to enhance the deoxygenation efficiency, the hydroxyl group was substituted with acyl groups (Table 7).

Table 7. Deoxygenation of benzylic esters using SmI_2/pyrrolidine/ H_2O.

Entry	Substrate	Product	Yield (%)[a]
1			73
2			91
3			84
4			60

[a] Reaction conditions: To a solution of SmI_2 (5 equiv. 0.1 M in THF), pyrrolidine (10 equiv.) and water (15 equiv.) was added the ester at rt. After mixing of the reagents the reaction was worked up and the yield was determined using GC/MS by comparing to an internal standard.

This methodology has been explored previously in many deoxygenation protocols,[82] including SmI_2 mediated ones for mandelate derivatives.[83] This was effective for this reaction as well, providing the deoxygenated product in high yield at rt instantly after mixing of the reactants. The benzoate (entry 2) and pivalate (entry 3) was found to be the most effective in the series, while the trifluoromethylacetate (entry 4) did not undergo the same reaction. Instead SmI_2/pyrrolidine/H_2O mediated a coupling reaction in good yields. As a consequence of this, analogs of the benzoate ester were subjected to

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[82] See Sakai, N.; Moriya, T.; Fujii, K.; Konakahara, T., *Synthesis* **2008**, 3533 for a recent example.
[83] Kusuda, K.; Inanaga, J.; Yamaguchi, M., *Tetrahedron Lett.* **1989**, 30, 2945.

1 and 2 equiv. SmI_2 with pyrrolidine and water added (Table 8 and 9). It was found that this low amount was sufficient for good conversion.
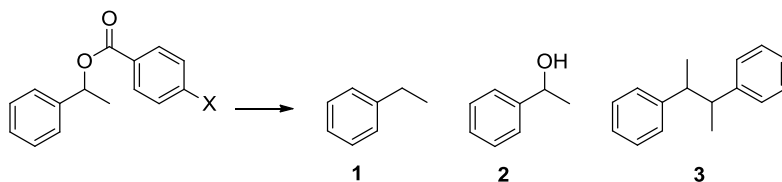

Table 8. Reduction of 1-phenylethylbenzoic acid ester using 1 equiv. of SmI_2.

X	Product distribution			Conversion[a]
	1	**2**	**3**	
-H	47%	4%	49%	63%
-CF$_3$	38%	14%	38%	34%
-OMe	40%	8%	52%	73%

[a] Reaction conditions: To a solution of SmI_2 (1 equiv.), water (2 equiv.) and pyrrolidine (3 equiv.) was added the phenylethylbenzoic acid ester at rt. Yields were determined comparing the disappearance of starting material comparing to an internal standard.

Table 9. Reduction of 1-phenylethylbenzioc acid ester using 2 equiv. of SmI_2.

X	Product distribution			Conversion[a]
	1	**2**	**3**	
-H	57%	12%	30%	94%
-CF$_3$	50%	15%	35%	86%
-OMe	47%	11%	42%	94%

[a] Reaction conditions: To a solution of SmI_2 (2 equiv.), water (4 equiv.) and pyrrolidine (6 equiv.) was added the phenylethylbenzoic acid ester at rt. Yields were determined comparing the disappearance of starting material comparing to an internal standard.

In an attempt to apply this reaction on a more demanding molecule, the benzoic esters of quinine was synthesized and subjected to similar reaction conditions (Figure 30). However, the best yield achieved was a mere 21%.
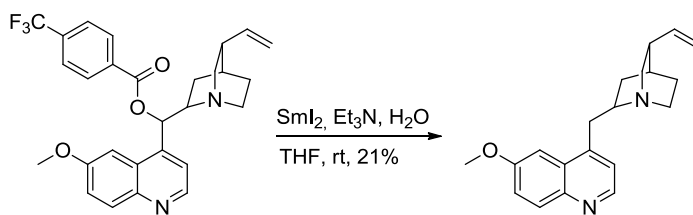
Figure 30. Deoxygenation of quinineesters with 2.5 equiv. SmI$_2$, 5 equiv. Et$_3$N and 7.5 equiv. H$_2$O.

The reason for this disappointing result lies mainly in the competing reduction of the isoquinoline ring, and in addition the purification of the product was very difficult.

2.3 Reductive defluorination (Paper V)

The carbon-fluorine bond is scarcely found in nature, however there is an enormous amount of man-made fluorine containing chemicals. The introduction of fluorine in organic molecules give rise to unique properties and this is of great interest in many areas of chemistry, especially in the production of new pharmaceutical [84] and agrochemical agents.[85] For example, 1 out of 5 new drug candidates[86] under recent years have a fluorine atom incorporated in its structure, verifying the importance of organofluorine chemistry. The reason for the interest in this element in biologically active compounds is due to the fact that it can act as a bioisostere in various structural moieties as well as influencing their binding properties and pharmacokinetics.[87]

As the title suggests this chapter is dealing with the removal of fluorine. The ability to selectively introduce such atoms is limited as the carbon-fluorine bond is very stable, often leading to multi-fluorinated compounds.[88] Thus, the reductive removal of fluorine from such compounds is a very effective route to partially fluorinated substances.

The reductive removal of fluorine has previously been achieved on many organofluorine compounds using electron transfer reagents. The carbon-fluorine in aliphatic compounds is very difficult to break, however Li/4,4´-di-*tert*-butylbiphenyl/1,2-bis(trimethylsilyl)benzene successfully cleaves this bond.[89] Carbon-fluorine bonds next to a π-system are easier to reduce and have been accomplished using magnesium metal and trimethylsilyl chloride (TMS-Cl) [90] as well as zinc

[84] (a) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V., *Chem. Soc. Rev.* **2008**, 37, 320. (b) Hagmann, W. K., *J. Med. Chem.* **2008**, 51, 4359.
[85] Peter, J., *ChemBioChem* **2004**, 5, 570
[86] Ojima, I. *Fluorine in medicinal chemistry and chemical biology.* Wiley-Blackwell, Oxford, UK, 2010.
[87] Muller, K.; Faeh, C.; Diederich, F., *Science* **2007**, 317, 1881.
[88] Kirsch, P. *Modern fluoroorganic chemistry: Synthesis, reactivity, applications*; Wiley-VCH: Weinheim, 2004.
[89] Guijarro, D.; Martinez, P.; Yus, M., *Tetrahedron* **2003**, 59, 1237.
[90] Amii, H.; Kobayashi, T.; Hatamoto, Y.; Uneyama, K., *Chem. Commun.* **1999**, 1323.

amalgam,[91] and there is one report of a successful reaction involving samarium(II) iodide.[92]

After our finding that the carbon fluorine bond was cleaved in some of the substrates described in the preceding chapters, we were intrigued to explore this further. A set of fluorinated substances was subjected to reduction where the aim was to selectively remove one or more fluorine atoms from a (poly-) fluorinated compound.

It was known from before (see 2.2.6) that ethers and amines with aromatic trifluoromethyl groups were reduced to mono-, di- and tri- defluorinated analogs. It was also known that trifluoromethylbenzene was considerably more resistant towards reduction. Therefore simple fluorinated compounds were subjected to the SmI_2/amine/H_2O combination. Benzyl fluoride was instantaneously reduced to toluene with very high conversion, while 1-fluorodecane was resistant to all attempts of reduction (Figure 31).
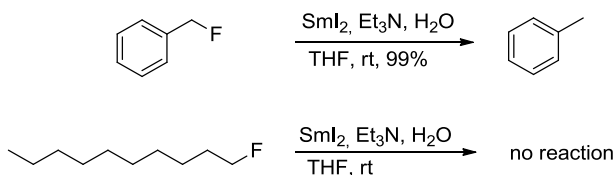

Figure 31. Use of SmI_2/Et_3N/H_2O in defluorination reactions.

Next, trifluoromethylacetophenone was subjected to the reaction conditions, but gave a mixture of products; pinacol coupling, reduction of the carbonyl along with defluorination (Figure 32).

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[91] (a) Eliseenkov, E. V.; Koginov, A. S.; Dneprovskii, A. S., *Zh. Org. Khim.* **1978**, 14, 781. (b) Moskalev, N. V.; Zhuravkov, S. P.; Ogorodnikov, V. D., *Russ. Chem. Bull.* **1996**, 45, 2461.
[92] Otaka, A.; Watanabe, J.; Yukimasa, A.; Sasaki, Y.; Watanabe, H.; Kinoshita, T.; Oishi, S.; Tamamura, H.; Fujii, N., *J. Org. Chem.* **2004**, 69, 1634.
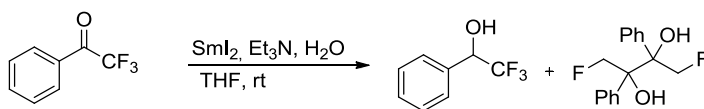
Figure 32. Attempt to defluorinate a trifluoromethyl ketone. The figure shows the major products as determined by GC/MS analysis.

Surprisingly, it was found that that simple esters and amides of trifluoroacetic acid and pentafluoropropionic acid underwent very rapid defluorinations at rt in lieu of the expected ester cleavage (Figure 33). This transformation has previously been reported using the Mg/TMS-Cl system.[93] The fact that the most abundant product was the completely defluorinated derivative inspired us to find reaction conditions that could enable us to remove one or two fluorine atoms.
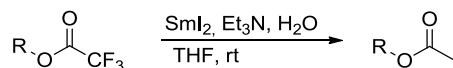
Figure 33. Exhaustive defluorination of trifluoroacetylester.

While defluorination of the trifluoroacetylesters certainly was interesting, it appeared at least to us, that the synthetic utility was limited. Of more interest was the selective removal of one or two fluorine atoms from such compounds. Therefore as set of esters (Table 10) and amides (Table 11) were prepared and were subjected to various reaction conditions. There was a big difference in reactivity between the esters and amides, and as suspected the primary ester was the most reactive (Table 10, entry 1). In order to mono-defluorinate these, temperature was held at -78 °C and the amine base was omitted (Table 10, entries 2- 4). The removal of two fluorines from the α-position could efficiently be performed in presence of Et$_3$N at -78 °C (entry 5).

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[93] (a) Amii, H.; Kobayashi, T.; Uneyama, K., *Synthesis* **2000**, 2001. (b) Nakamura, Y.; Ozeki, Y.; Uneyama, K., *J. Fluorine Chem.* **2008**, 129, 274.

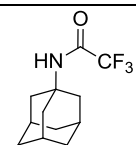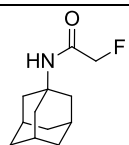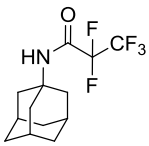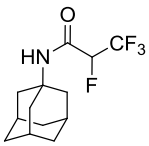**Table 10.** Defluorination of tri- and pentafluoro esters.
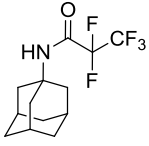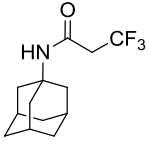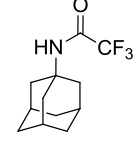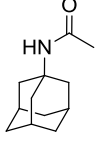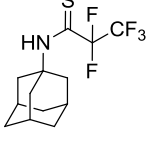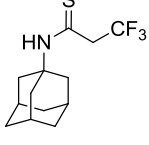
Entry	Starting material	Product	Amine	Yield[a]
1	n-C$_{10}$H$_{21}$ O—C(O)—CF$_3$	n-C$_{10}$H$_{21}$ O—C(O)—CH$_3$	Et$_3$N	73
2	n-C$_{10}$H$_{21}$ O—C(O)—CF$_3$	n-C$_{10}$H$_{21}$ O—C(O)—CHF$_2$	None	30
3	n-C$_{10}$H$_{21}$ O—C(O)—CF$_3$	n-C$_{10}$H$_{21}$ O—C(O)—CH$_2$F	None	30
4	menthyl O—C(O)—CF$_2$CF$_3$	menthyl O—C(O)—CHFCF$_3$	None	82 (1:2)
5	menthyl O—C(O)—CF$_2$CF$_3$	menthyl O—C(O)—CH$_2$CF$_3$	Et$_3$N	83

[a] Reaction conditions: SmI$_2$ was cooled to −78 °C and a solution (cooled to −78 °C) of the ester (0.1 M in THF) was added with stirring.

One highly interesting fact was noted when the monodefluorinated product obtained from pentafluoropropionyl menthol was analyzed using ^{1}H-NMR. It was found that the chiral menthol was able to induce selectivity as the pair of diastereoisomers was present in unequal amounts (entry 4). The reason for this observation might lie in the fact that fluorine can coordinate well to Sm(III) and form a stable intermediate that can be protonated preferentially from one side within the ion-pair. This is a significant result as this may allow the formation of fluorine containing stereo centers.

Aliphatic amides were similarly reduced to give the defluorinated products in good yields (Table 11). In comparison, these starting materials were found to be more resistant to competing amide cleavage, and triethylamine was crucial. The optimal conditions for selective removal of one fluorine (entries 1-2) required that the reduction was run at −78 °C, while it was found that exhaustive α-defluorination was feasible at rt (entries 3-4).

Table 11. Defluorination reactions of fluorinated amides and thioamides.

Entry	Starting material	Product	T °C	Yield (%)
1	HN–C(=O)–CF₃ (adamantyl)	HN–C(=O)–CH₂F (adamantyl)	-78	28
2	HN–C(=O)–CF₂–CF₃ (adamantyl)	HN–C(=O)–CHF–CF₃ (adamantyl)	-78	75
3	HN–C(=O)–CF₂–CF₃ (adamantyl)	HN–C(=O)–CH₂–CF₃ (adamantyl)	rt	69
4	HN–C(=O)–CF₃ (adamantyl)	HN–C(=O)–CH₃ (adamantyl)	-78	88
5	HN–C(=S)–CF₂–CF₃ (adamantyl)	HN–C(=S)–CH₂–CF₃ (adamantyl)	rt	30

Reaction conditions: SmI_2 was cooled to −78 °C and a solution (cooled to −78 °C) of the ester (0.1 M in THF) was added with stirring.

Thioamide (entry 5) was also defluorinated although in lower yield. This particular product proved very difficult to purify, hence the low yield.

It is clear that it is difficult to control the degree of defluorination. Electrochemical studies on reductive cleavage of trifluoromethylarenes have shown that the standard potentials at which mono-, di-, and trifluoromethylarenes forms anion radicals are very

close and that the main product is completely defluorinated.[94] Furthermore, the standard potential increases going from mono- to trifluoro derivatives.

In order to increase the yields both $SmBr_2$ and $Sm(HMDS)_2$ were examined as potential reductants. While $SmBr_2$/MeOH offered no advantage over SmI_2, $Sm(HMDS)_2$/MeOH was found to have an extraordinary reactivity towards these substrates. In an attempt to achieve α-defluorination of a pentafluoropropionylester, the main product was found to be the completely defluorinated propionylester. This implies that this reagent is capable of breaking the C-F bond even though it is not situated next to a π-system. Reinvestigation of the 1-fluorodecane reduction to decane using $Sm(HMDS)_2$ did indeed turn out to be successful. Reduction using only $Sm(HMDS)_2$ was slow and yielded 15% decane after 3 days at rt.
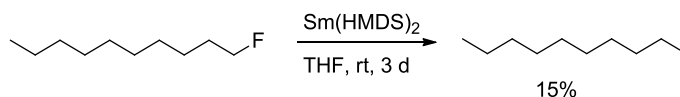

Figure 34. Defluorination using $Sm(HMDS)_2$.

Addition of MeOH as a proton source did not accelerate the reaction at this point. The reason for the observed reactivity may lie in the fact that the trimethylsilyl groups of HMDS are able to activate the fluorine-carbon bond.[89,95]

In the light of these results, using Sm(II) as a tool for the removal of fluorine atoms appears to hold great promise for more elaborate transformations.

[94] Andrieux, C. P.; Combellas, C.; Kanoufi, F.; Saveant, J. M.; Thiebault, A., *J. Am. Chem. Soc.* **1997,** 119, 9527.
[95] Shibato, A.; Itagaki, Y.; Tayama, E.; Hokke, Y.; Asao, N.; Maruoka, K., *Tetrahedron* **2000**, 56, 5373

2.4 Concluding remarks on the use of SmI$_2$/amine/ H$_2$O as a reducing agent for functional groups

The combination of SmI$_2$, amine and water appears to be a good general reductant for the functional groups discussed in this chapter. One distinguishing feature of the reactions is that it proceeds very smooth at room temperature with no evolution of heat or flammable gases. This is in sharp contrast to for instance LiAlH$_4$ that is highly energetic and requires special precautions and prolonged reaction times for full conversion of similar substrates. This reagent combination usually promotes extremely rapid reactions, yielding the product after a minimal and safe work up procedure.

In general, the use of SmI$_2$ with amine and H$_2$O is not only an efficient reducing agent for ketones, imines and alkyl halides. It is also efficient and chemoselective in the reduction of nitro compounds, cleavage of benzyl-heteroatom bonds and for facile reduction of the fluorine-carbon bond.

The reduction of nitro compounds appears to be a good alternative to existing methods with the benefit of being extremely rapid and high yielding. It is easy to take advantage of the reactivity difference between functional groups to selectively reduce the nitro group.

The cleavage reaction of the benzylic substrates does not possess the benefit of the extremely short reaction times that have been observed previously. The comparably low reaction rate is a drawback since other functional groups also may react, thus lowering the chemoselectivity. However, esterification of the alcohol significantly increases the reactivity and furnishes the product more or less instantaneously.

3. Deprotection reactions promoted by SmI$_2$

Closely related to functional group reductions is the removal of protective groups, a field in organic synthesis that is constantly developing with the introduction of new protecting groups as well as new protocols for their removal. In fact there is quite a few protecting groups that are removed reductively (for instance benzyl, benzylcarbamate (CBz), p-toluenesulfonyl (tosyl or -Ts), allyl and propargyl) using either catalytic hydrogenation or various SET reagents.[96]

Samarium(II)-reagents, being excellent electron donors, are becoming increasingly useful for efficient and selective removal of SET labile protecting groups. SmI$_2$ is capable of removing benzyl,[63] allyl,[97] propargyl[98] and tosylamides[99] depending on the choice of additives. A specially designed pyridine-2-sulfonamide protecting group has been developed that is cleanly removed with SmI$_2$.[100] Herein lies the real benefit of using SmI$_2$ as the reactivity can be fine-tuned for selective removal of the protecting group of choice. In addition, the protecting group can be customized in such a way that it become susceptible to single electron transfer. This was partly explored in chapter 2 where it was found that substitution of the benzyl ring with a trifluoromethyl group increased the reactivity by three orders of magnitude compared with the 4-methoxy substituted benzyl. Unfortunately, the 4-trifluoromethylbenzyl derivatives of various amines and alcohols proved very difficult to cleave selectively using SmI$_2$/amine/H$_2$O because defluorination was faster and thus consuming the reagent. However, this

[96] Greene, T. W.; Wuts, P. G. M. Protective groups in organic synthesis, 4th ed; John Wiley & Sons: New York: New Jersey, 2007.

[97] Dahlen, A.; Sundgren, A.; Lahmann, M.; Oscarson, S.; Hilmersson, G., *Org. Lett.* **2003**, 5, 4085.

[98] Manabe, S.; Ueki, A.; Ito, Y., *Tetrahedron Lett.* **2008**, 49, 5159.

[99] (a) Vedejs, E.; Lin, S. Z., *J. Org. Chem.* **1994**, 59, 1602. (b) Alonso, D. A.; Andersson, P. G., *J. Org. Chem.* **1998**, 63, 9455. (c) Grach, G.; Santos, J. S. D.; Lohier, J. F.; Mojovic, L.; Ple, N.; Turck, A.; Reboul, V.; Metzner, P., *J. Org. Chem.* **2006**, 71, 9572. (d) Duan, H. F.; Jia, Y. X.; Wang, L. X.; Zhou, Q. L., *Org. Lett.* **2006**, 8, 2567.

[100] Goulaouicdubois, C.; Guggisberg, A.; Hesse, M., *J. Org. Chem.* **1995**, 60, 5969.

concept was developed further to include trifluoromethylated benzylidenes and benzyl carbamates. These derivatives displayed a considerably higher reactivity towards Sm(II) reagents and were also efficiently removed.

3.1 Deprotection of arenesulfonamides and esters (Paper III)

Benzenesulfonyl and tosyl groups are among the best suited protecting groups for amines.[96] They are easy to prepare under relatively mild conditions, the resulting amide is often crystalline, neatly fitted with a chromophore[101] and stable to both strong bases and acids. However, their high stability unfortunately renders them very difficult to remove. In principle there are two alternatives; hydrolysis using strong mineral acids[102] or reduction using various SET reagents such as alkali metals,[103] Mg/MeOH[104] or electrolysis.[105] All of these methods have their drawbacks as they are either excessively harsh thus limiting the presence of other functional groups, or requires the handling of highly dangerous and reactive chemicals.

Previously, SmI_2 have been used as a deprotection reagent for tosyl protected amines, but was only effective in the deprotection of N-tosyl amides (Figure 35).[106]
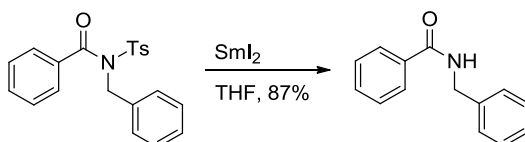
Figure 35. Desulfonylation of an amide.

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[101] In addition to becoming visible in UV light the 4-methyl group is a convenient NMR-tag.
[102] See Jordis, U.; Sauter, F.; Siddiqi, S. M.; Kuenburg, B.; Bhattacharya, K., *Synthesis* **1990**, 925. for an illustrative example.
[103] See Alonso, E.; Ramon, D. J.; Yus, M., *Tetrahedron* **1997**, 53, 14355. for an illustrative example.
[104] Nyasse, B.; Grehn, L.; Ragnarsson, U., *Chem. Commun.* **1997**, 1017.
[105] (a) Oda, K.; Ohnuma, T.; Ban, Y., *J. Org. Chem.* **1984**, 49, 953. (b) Senboku, H.; Nakahara, K.; Fukuhara, T.; Hara, S., *Tetrahedron Lett.* **2010**, 51, 435.
[106] Knowles, H.; Parsons, A. F.; Pettifer, R. M., *Synlett* **1997**, 271.

Addition of HMPA or DMPU has enabled the cleavage of tosylamides,[99] but the yields are usually unsatisfactory and require refluxing conditions. However, we found that the addition of an aliphatic amine and water to SmI_2 selectively and rapidly cleaved the N-S bond in the tosyl derivatives, leaving the deprotected amine in nearly quantitative yield. During the evaluation of this reaction three different tosylamides were chosen (Figure 36, 1-3). Thus, the following compounds were subjected to the reaction conditions.
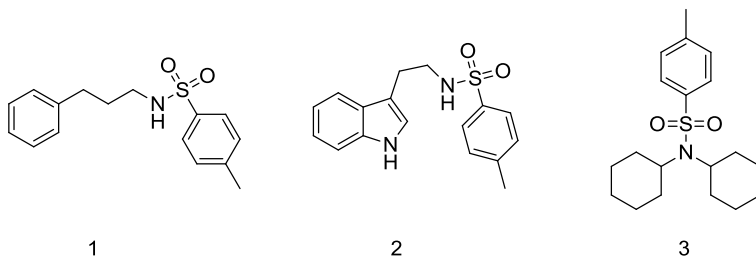
Figure 36. Model substrates selected for the deprotection reaction.

Cleavage of the N-S bond requires 2 equiv. of Sm(II) provided that bond is cleaved first, but only modest yields were obtained using this amount of SmI_2. Consumption of all starting material required a total of 6 equiv. of SmI_2. No difference was seen between the sterically demanding dicyclohexylamide (3) and the primary amines (1 and 2), and no over-reduction of the indole core (2) was detected. Furthermore, the reaction was very fast and was completetd after mixing the reagents.

In addition to the above substrates, the study was extended to tosylamides containing additional functional groups (Table 12). The benzyl tosyl amide (entry 1) gave clean deprotection of the tosyl group and no cleavage of the carbon-nitrogen bond could be detected. Furthermore, tosyl amides with aromatic chlorine (entry 2), N-Boc (entry 3), cyclic ketal (entry 4) and highly sensitive aziridines (entries 5 and 6) were not affected under the reaction conditions.

Table 12. Deprotection of tosyl protected amines and anilines.

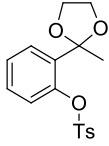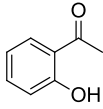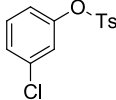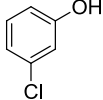| Entry	Starting material	Product	Yield (%)[a]
1			98
2			96
3			94
4			95
5			93
6			94
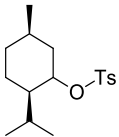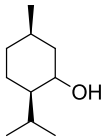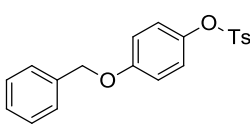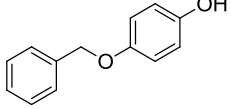
[a] Reaction conditions: Tosylamide (1 equiv.) was added to a SmI$_2$ solution (0.13 M in THF, 6 equiv.) followed by water (18 equiv.) and amine (12 equiv.) at rt.

The choice of amine base in these experiments was found to be of minor importance, but judging from color changes during the addition of the reagents it appears that triethylamine gave a slightly slower reaction than pyrrolidine and isopropylamine. However, certain sensitive substrates such as the aziridines (entries 5-6) can react with nucleophilic bases such as pyrrolidine and in these cases it is advisable to use triethylamine.

Although considered easier to cleave, a similar set of substances were prepared with tosylesters derived from aliphatic alcohols and phenols (Table 13). Again it was clear

that these reaction conditions were highly efficient in removing the tosyl group without any serious side reactions. The bis-protected phenol (entry 2) could be selectively detosylated in 85% yield, and satisfyingly no reduction of the aromatic chlorine or the phenols were observed (entry 3 and 4).

Table 13. Deprotection of tosyl protected alcohols and phenols.

Entry	Starting material	Product	Yield (%)[a]
1			94
2			85
3			96
4			93

[a] Reaction conditions: Tosylamide (1 equiv.) was added to a SmI$_2$ solution (0.13 M in THF, 6 equiv.) followed by water (18 equiv.) and amine (12 equiv.) at rt.

In addition to tosyl, a set of other amides derived from sulfonic acids was also evaluated. Aliphatic sulfonic amides (mesyl and triflate, Table 14, entries 1-2) were resistant to the reagent, thus making them orthogonal to the arenesulfonyl groups. The bulky arenesulfonamides (entries 3-5) were also cleaved, although with slightly lower yield. No significant effect of electronic or steric properties was thus observed.

Table 14. Cleavage of alkyl and arylsulfonamides.

Entry	Starting material	Product	Yield (%)[a]
1	Ph—(chain)—N(H)—SO$_2$—CH$_3$	n/a	n/r
2	Ph—(chain)—N(H)—SO$_2$—CF$_3$	n/a	n/r
3	Ph—(chain)—N(H)—SO$_2$—(2,4,6-trimethylphenyl)	Ph—(chain)—NH$_2$	95
4	Ph—(chain)—N(H)—SO$_2$—(2,4,6-triisopropylphenyl)	"	85
5	Ph—(chain)—N(H)—SO$_2$—(4-OMe-phenyl)	"	85

[a] Reaction conditions: Tosylamide (1 equiv.) was added to a SmI$_2$ solution (0.13 M in THF, 6 equiv.) followed by water (18 equiv.) and amine (12 equiv.) at rt.

Closer inspection of the reaction mixture also revealed that cleavage not only did occur between the N-S bond, but to some extent also between the S-C bond leaving the desulfurized aryl (Figure 37).
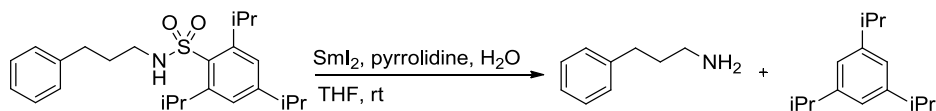
Figure 37. SmI2/pyrrolidine/H$_2$O mediates the desulfurization of the aryl moiety.

This side reaction was not pursued further at this point, but it has been noted before that SmI$_2$ is capable of cleaving sulfones.[107] It is possible that the right reaction conditions could be found that would allow facile fission of this bond as well.

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[107] Girard, P.; Namy, J. L.; Kagan, H. B., *J. Am. Chem. Soc.* **1980**, 102, 2693.

In conclusion, this protocol offers a chemoselective and rapid method for the removal of arenesulfonamides and esters in very high yield. The method requires no hazardous chemicals and the work-up procedure is quick and safe.

3.2 Exploring electron deficient benzyl derivatives as protecting groups in organic synthesis

Inspired by the tremendous rate enhancements observed for the trifluoromethylated benzyl alcohols, an investigation for removal of *p*-trifluoromethylbenzyl containing protecting groups was initiated. The aim was to develop an amine (and alcohol) protecting group that was labile towards electron transfer and orthogonal to other protecting groups.

The first set of reactions focused on *p*-trifluoromethylbenzyl substituted amines (Figure 38, 1), alcohols and phenols using the SmI_2/amine/ H_2O system. As have been detailed above, the desired transformation is always competing with the reductive defluorination of these substrates. Furthermore, when the benzylic heteroatom is substituted it becomes considerably more resistant towards fission. This led us to explore the *p*-trifluoromethyl benzylidene (2) and *p*-trifluoromethyl carbamate (3) as SET labile protecting groups.
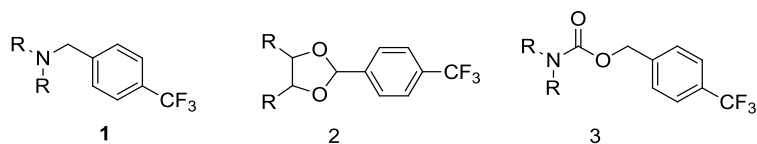
Figure 38. Electron deficient protecting groups investigated using Sm(II)-reduction.

3.2.1 *p*-Trifluoromethyl benzylidene

Electron deficient benzylidene substrates have not been explored as protecting group to any great extent even though they have properties that are desirable, for instance increased resistance towards acid hydrolysis. Most likely, they are also more resistant towards hydrogenation in analogy with the electron deficient benzyl protecting groups.[108]

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[108] Kanai, M.; Yasumoto, M.; Kuriyama, Y.; Inomiya, K.; Katsuhara, Y.; Higashiyama, K.; Ishii, A., *Chem. Lett.* **2004**, 33, 1424.

Initial studies concentrated on very simple model substrates and revealed that the conversion of starting material was excellent using both SmI_2/amine/H_2O and $Sm(HMDS)_2$ with pyrrolidine as proton source (Figure 39).[109]
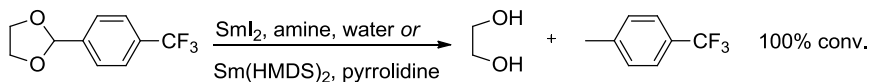
Figure 39. Cleavage of the p-trifluoromethylbenzylidene. In both cases the reaction was very fast.

A simple competitive experiment between benzylidenes with varying electronic character indicated significant reactivity difference between *p*-trifluoromethylbenzylidene and *p*-methoxybenzylidene proving a possible selective removal of this group in the presence of the *p*-methoxy benzylidene. As can be seen in the graph the *p*-methoxy substituted benzylidene was largely unaffected by the reaction conditions, while the *p*-trifluoromethyl benzylidene was cleaved instantly (Figure 40).
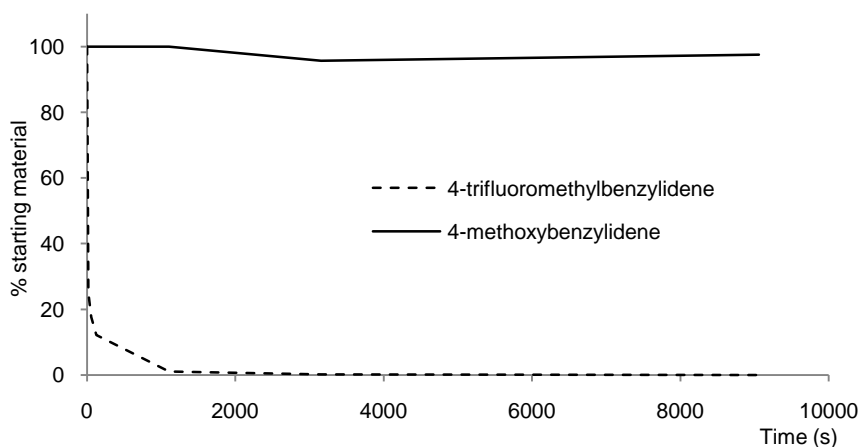
Figure 40. $Sm(HMDS)_2$ (0.1M in THF) and pyrrolidine added to a solution of p-trifluoromethyl- and p-methoxybenzylidenes.

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[109] It was found that addition of alcohols and water as proton sources was ineffective as rapid decomposition of the $Sm(HMDS)_2$ was noted, thus preventing high conversion.

Deprotection of the *p*-trifluoromethylbenzylidene derivative of trans-1,2-cyclohexanediol on a preparative scale proved to be a little more demanding (Figure 41). Attempts using the amine/H$_2$O additive system were unsuccessful due to a slow reaction combined with inability to find a work-up procedure that could release the diol from the samarium salts. Sm(HMDS)$_2$/pyrrolidine on the other hand rapidly released the diol.
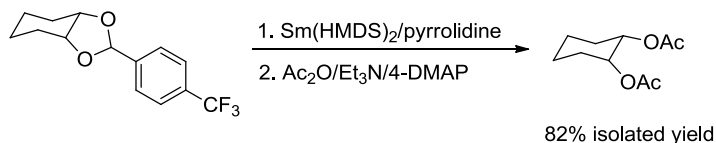
Figure 41. Cleavage of a trifluoromethylbenzylidene protected 1,2-diol.

The isolation of this diol demanded some kind of derivatization due to its high solubility in water, and was therefore acetylated. Interestingly the formation of the di-acetyl was inhibited in favor of the mono-acetyl using acetic anhydride and pyridine as acetylating agent. This behavior has previously been utilized in protocols for the lanthanide catalyzed mono acetylation of symmetrical diols.[110] The use of Et$_3$N, acetic anhydride and a catalytic amount of 4-dimethylaminopyridine (DMAP) was found to give the bi-acetyl preferentially.

3.2.2 *p*-Trifluoromethylbenzyl carbamate

The use of the *p*-trifluoromethylbenzyl carbamate protecting group (dubbed CTFB) has been described in an article by Papageorgiou *et. al.* where it was explored as an orthogonal protecting group to 2-napthylcarbamate using hydrogenation as reductive cleavage method.[111] Furthermore it was possible to remove benzyl esters and ethers in its presence. The authors also observed that the cleavage of the *p*-trifluoromethylbenzyl carbamate by hydrogenation was slow. In contrast, evaluation of a

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[110] Clarke, P. A.; Kayaleh, N. E.; Smith, M. A.; Baker, J. R.; Bird, S. J.; Chan, C., *J. Org. Chem.* **2002**, 67, 5226.
[111] Papageorgiou, E. A.; Gaunt, M. J.; Yu, J.-q.; Spencer, J. B., *Org. Lett.* **2000**, 2, 1049.

Sm(HMDS)$_2$/pyrrolidine mediated deprotection using a simple protected amine (adamantyl amine) proved successful (Figure 42).
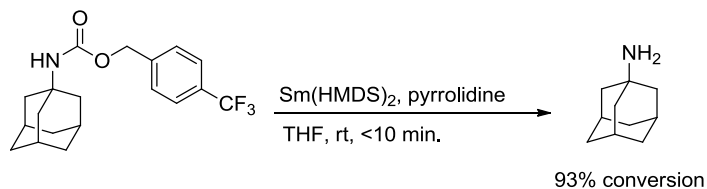
Figure 42. Deprotection of a CTFB protected aliphatic amine.

A competitive experiment where the regular CBz protected adamantylamine were treated by Sm(HMDS)$_2$ and pyrrolidine in the presence of CTFB protected amine revealed a similar correlation as described above (Figure 43). However the difference in reactivity was smaller than that observed in Figure 40.
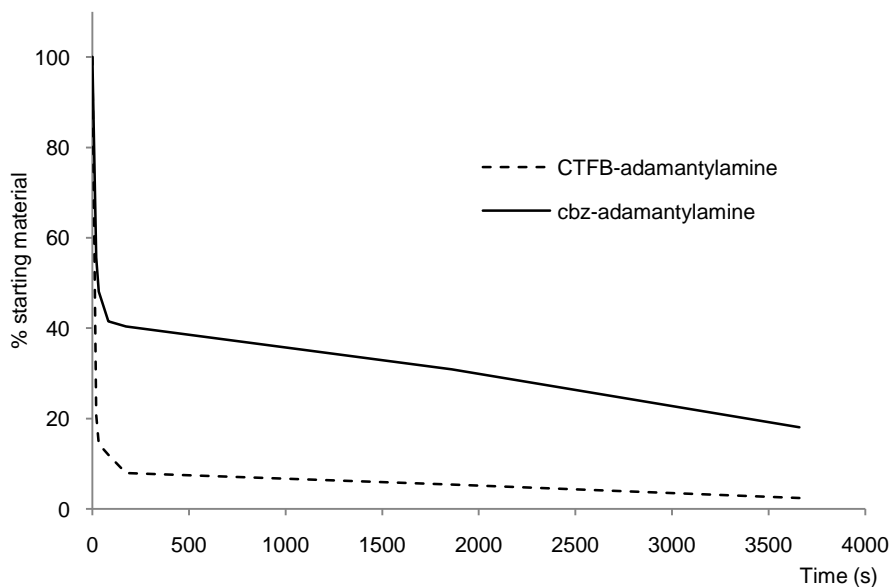

Figure 43. Sm(HMDS)$_2$ (0.1 M in THF) and pyrrolidine was added to a solution of the carbamates in THF at rt.

To conclude, the *p*-trifluoromethylbenzylidene and *p*-trifluorobenzylcarbamate groups appear to have great potential as electron transfer labile protecting groups. The rate differences between the conventional protecting groups indicate that selective removal can be accomplished. In addition, they have features that are highly desirable; increased stability towards acid hydrolysis and they are easy to incorporate.

4. Reductive carbon-carbon bond forming reactions promoted by SmI$_2$

Since its introduction, the use of SmI$_2$ in carbon-carbon bond forming reaction has increased steadily and holds a firm position as a very powerful reagent for a number of selective transformations.[112]

The use of samarium enolates derived from Reformatsky type substrates (α-halo carbonyls) is frequently encountered in inter- and intramolecular processes.[113] The reactivity of the formed enolate is considered to be very different from that of other metal enolates, but very little is known about the details of the Sm-enolates. This chapter deals with the investigation of the effect of additives and counter-ions in the Reformatsky reaction.

4.1 A Reformatsky inspired Sm(II)-mediated α-cyanation protocol (Paper IV)

After a number of unsuccessful efforts to synthesize 3-cyano chromone derivatives the question arose if SmI$_2$ could serve as a suitable reagent to introduce a cyano group in the 3-position of the chromone scaffold. We envisioned a modified Reformatsky-type reaction inspired by Collums α-cyanation reaction using tosyl cyanide as a source of electrophilic cyanide.[114] Reactions of this type are rare and few examples exist in the primary literature.

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[112] Nicolaou, K. C.; Shelby , P. E.; Jason , S. C., *Angew. Chem. Int. Ed.* **2009**, 48, 7140.
[113] Rudkin, I. M.; Miller, L. C.; Procter, D. J., *Organomet. Chem.* **2008**, 34, 19.
[114] Kahne, D.; Collum, D. B., *Tetrahedron Lett.* **1981**, 22, 5011.

4.1.1 Finding the right reaction conditions

Attempts to perform the reaction at rt failed and only dehalogenated product could be recovered, probably due to instability of the intermediate enolate. It was however noted that additives such as TMG, tripyrrolidinophosphortriamide (TPPA) and trimorpholinophosphortriamide (TMPA) afforded traces of product. Fortunately, when the reaction was performed at -78°C with SmI_2 the wanted product was obtained in a moderate yield. The additives were reevaluated at low temperature and some interesting facts were revealed. The TPPA and TMG additives were found to be effective in promoting the reaction and gave the α-cyano ketone as major product. These additives may thus be used as less toxic alternatives to HMPA. Interestingly, substoichiometric amounts of TMG (0.4 equiv.) was even more effective in promoting the α-cyanation.

Other counter-ions were also examined, but it was found that both $SmBr_2$ and $Sm(HMDS)_2$ were unsuitable. Inspired by the fact that substoichiometric amounts of additive was effective, we tried a 1:1 combination of the two counter-ions HMDS and iodide. This gave a very selective reagent that was capable of introducing the cyano group in the 3-position of 3-bromochromanone without dehalogenation. Strikingly, a totally different result was obtained using either SmI_2 or $Sm(HMDS)_2$, indicating that the presence of *one* HMDS anion in the reaction solution is crucial for the success of this reaction (Figure 44).
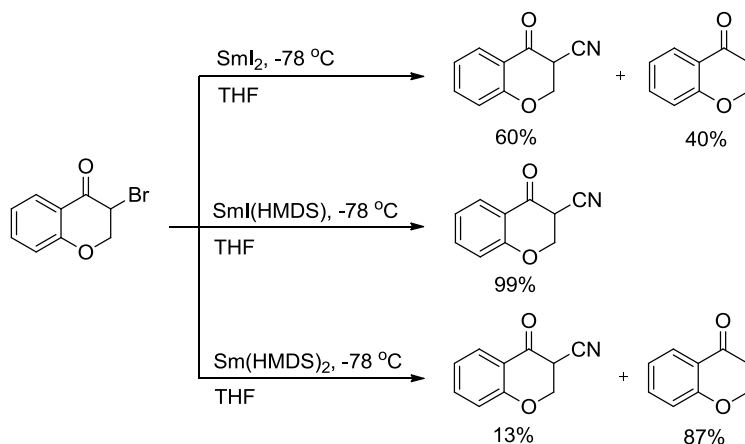
Figure 44. The dramatic effect of using different counter-ions in the α-cyanation.

Heteroleptic Sm(II)-complexes with one HMDS anion {[(Me$_3$Si)NSm(µ-I)(DME)(THF)$_2$} have been isolated and reported by Evans,[115] but there is no evidence of the existence of such complexes in solution.[39] SmI$_2$ precipitates upon cooling a solution of SmI(HMDS), leaving Sm(HMDS)$_2$ in solution indicating that there is a fast anion exchange equilibrium.
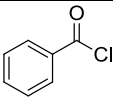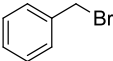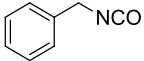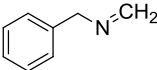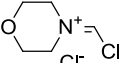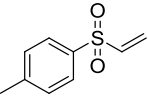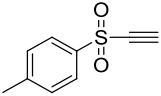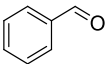
One explanation for this observation is that the tightly coordinating HMDS anions are large enough to hinder the formation of the enolate in preference of a reductive dehalogenation using Sm(HMDS)$_2$. However, the presence of one HMDS anion might be enough to promote the formation of the enolate (in the same way HMPA does) and still allow access to the metal core.

4.1.2 Efforts to expand the choice of electrophile

The high selectivity that was achieved using SmI(HMDS) in the α-cyanation inspired us to examine more electrophiles using the same reaction conditions (Table 15). The scope was chosen so that different reactivities were included in the set. Of these, some gave a positive reaction (the acid chlorides, entries 1-2), while most of them gave no product or

[115] Evans, W. J.; Drummond, D. K.; Zhang, H.; Atwood, J. L., *Inorg. Chem.* **1988**, 27, 575.

Table 15. The selection of electrophiles evaluated as potential coupling partners.

Entry	Electrophile	Comment
1	(benzoyl chloride)	10-20% yield
2	(acetyl chloride)	10-20% yield
3	(benzyl bromide)	No reaction
4	(butyl chloride)	"
5	(benzyl isocyanate, NCO)	"
6	(N-benzyl methanimine, =CH₂)	"
7	(N,N-dimethylacetamide)	"
8	(Boc–N=N–Boc)	"
9	(morpholinium chloromethylene, Cl⁻)	"
10	(p-tolyl vinyl sulfone)	"
11	(p-tolyl ethynyl sulfone)	"
12	BrCN	48% dehalogenation, 52% 3-Br-chromanone
13	(2-nitropropene, NO₂)	60% conversion
14	(benzaldehyde)	50% conversion

only traces of product. The idea behind evaluating the sulfones (entries 10-11) was to explore reagents similar to tosyl cyanide, but disappointingly they gave no product at all. Surprisingly, cyanogen bromide (entry 12) did not undergo the same reaction as tosyl cyanide. However, it was found that it did not only yield dehalogenated product, but also starting material. It is possible that the enolate was formed, but that the reaction took place with bromine as electrophile, thus returning the starting material. Nitropropene (entry 13) was slightly more promising and gave reasonable yields of the 2-nitropropyl derivative (Figure 45). This was hydrolyzed under the acidic work-up condition and furnished the ketone (*i.e.* the Nef reaction). Benzaldehyde (entry 14) was also modestly successful giving a mixture of diastereoisomers and various dehydrated products (Figure 45). The yield of both of these reactions can probably be optimized once the correct reaction and work-up conditions are found.
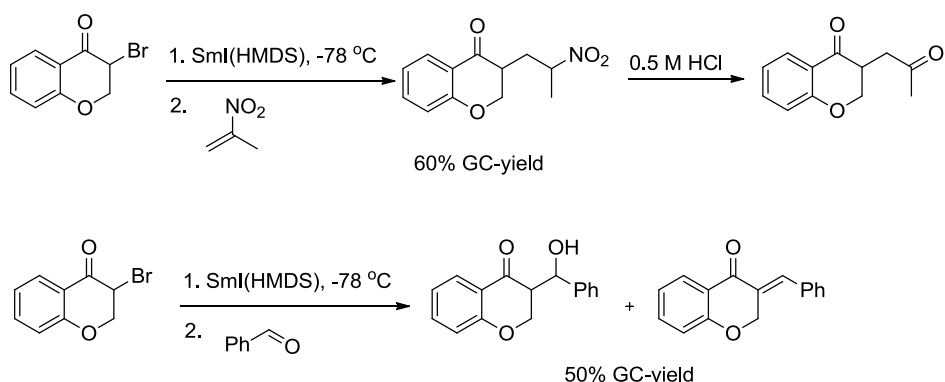
Figure 45. The use of nitropropene and benzaldehyde as electrophiles.

4.1.3 Evaluation of α-bromocarbonyl compounds

Once the optimal conditions were found we evaluated this on a small selection of 3-bromo-chroman-4-ones (Table 16). The non commercial ones were synthesized according to a previous published method (Figure 46).[116]

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[116] Friden-Saxin, M.; Pemberton, N.; Andersson, K. d. S.; Dyrager, C.; Friberg, A.; Grotli, M.; Luthman, K., *J. Org. Chem.* **2009**, 74, 2755.
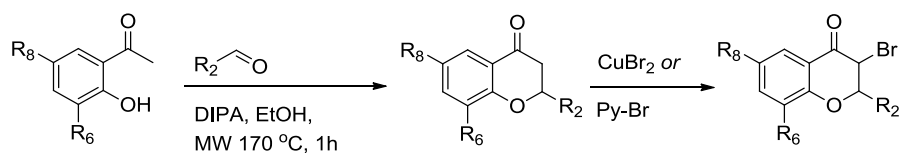
65

Figure 46. Synthesis of the starting α-bromo ketone.

During the efforts to scale-up this procedure it was soon realized that the unsubstituted (R_{2-8} = H) 3-cyanochroman-4-one (Figure 47, 2) was very sensitive to all forms of manipulation. This led us to directly without purification oxidize it to the chromone (3). The use of DDQ in dioxane installed the double bond, but unfortunately the yields of the final 3-cyano chromone (3) did not reflect the results that we saw in the screening study.
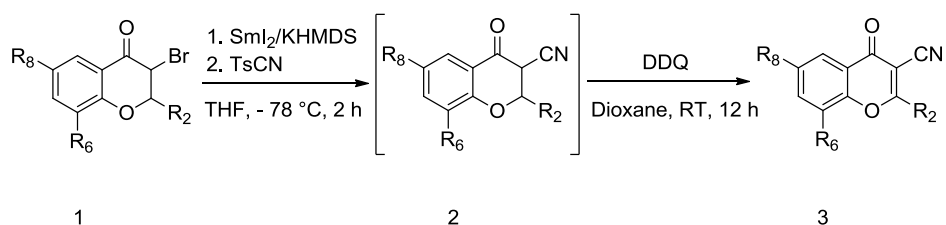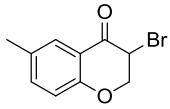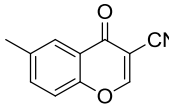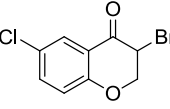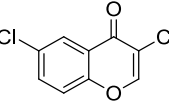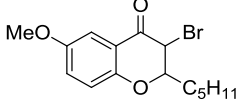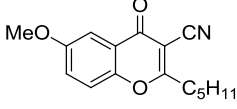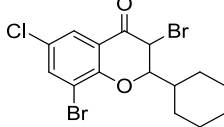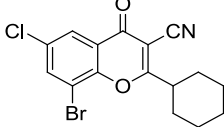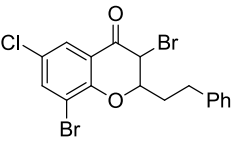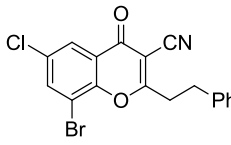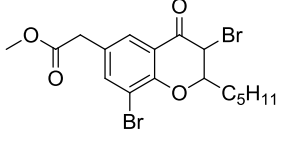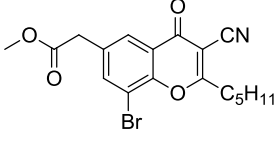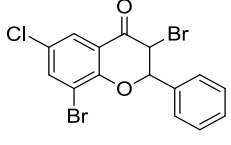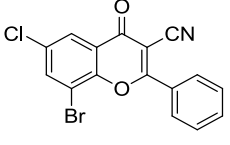
Figure 47. Two step synthesis of 3-cyanochromones from 3-bromochroman-2-ones.

This was investigated by mixing the starting 3-bromochromanone with an internal standard (dodecane) that was allowed to follow through the reaction sequence. Measurements of the concentr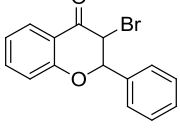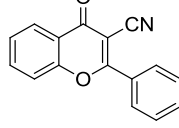ation before and after the addition of the oxidant revealed that the oxidation step led to degradation of the intermediate chroman-4-one.

Table 16. Cyanation and oxidation to 3-cyano-chromones.

Entry	Starting material	Product	Yield (%)[a]
1			49

Table 16 continued.

66

Entry			Yield
2	(6-methyl-3-bromo-chroman-4-one)	(6-methyl-3-cyano-chromone)	77
3	(6-Cl-3-bromo-chroman-4-one)	(6-Cl-3-cyano-chromone)	62
4	(6-MeO-2-C_5H_{11}-3-bromo-chroman-4-one)	(6-MeO-2-C_5H_{11}-3-cyano-chromone)	42
5	(6-Cl-8-Br-2-cyclohexyl-3-bromo-chroman-4-one)	(6-Cl-8-Br-2-cyclohexyl-3-cyano-chromone)	76
6	(6-Cl-8-Br-2-(2-phenylethyl)-3-bromo-chroman-4-one)	(6-Cl-8-Br-2-(2-phenylethyl)-3-cyano-chromone)	59
7	(methyl ester, 8-Br-2-C_5H_{11}-3-bromo-chroman-4-one)	(methyl ester, 8-Br-2-C_5H_{11}-3-cyano-chromone)	61
8	(2-phenyl-3-bromo-chroman-4-one)	(2-phenyl-3-cyano-chromone)	65
9	(6-Cl-8-Br-2-phenyl-3-bromo-chroman-4-one)	(6-Cl-8-Br-2-phenyl-3-cyano-chromone)	61

[a]Reaction conditions: SmI$_2$ (2.2 equiv.) and KHMDS (2.2 equiv) was cooled to -78 °C. A solution of the 3-bromo-chromane-2-one in THF was added. After 2 h a solution of tosylcyanide was added and the reaction was stirred for 1 h. DDQ oxidation was done on the crude 3-cyano-chroman-2-one.
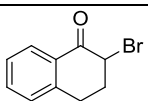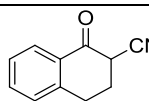
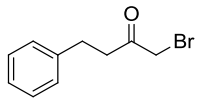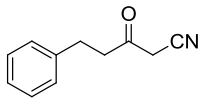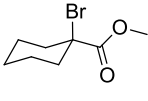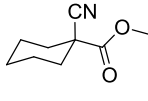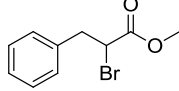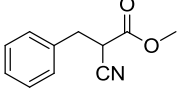In general, all substrates gave the product in moderate to good yields (Table 16). It was found that substituents in the R$_2$ position were important for the stability of the intermediate chroman-4-one. Pleasingly the aromatic halogens (entries 3,5,6,7 and 9)

and the methyl ester (entry 7) were compatible with the reaction conditions as these are important handles for further elaboration of these substances.

The R_2 substituted 3-bromo-chroman-4-ones were generally obtained in high cis/trans ratios, however this ratio was diminished, likely due to the formation of a planar samarium enolate. The reaction between the enolate and the electrophile was however somewhat selective as verified by NMR spectroscopy on the intermediate 3-cyano-chroman-4-ones. Possibly, the nucleophilic site on the cyclic enolate preferentially approaches the electrophile from the least hindered face

We also evaluated other carbonyl compounds for the α-cyanation reaction. For this purpose we selected a series of simple α-bromo ketones and esters and subjected them to the same reaction conditions (Table 17).

Table 17. Examination of α-bromo ketones and esters.

Entry	Starting material	Product	Yield (%)
1			84
2			-
3			90
4			-

ᵃReaction conditions: SmI$_2$ (2.2 equiv.) and KHMDS (2.2 equiv) was cooled to -78 °C. A solution of the α-bromocarbonyl compound in THF was added. After 2 h a solution of tosylcyanide was added and the reaction was stirred at this temperature for 1 h.

For 2-bromotetralone (entry 1) the reaction was successful and gave almost quantitative yield of the cyano ketone. The methyl ketone (entry 2) did not undergo addition of the nitrile and gave only traces of product as determined by GC/MS analysis. This result is

similar to that of Collum *et al.* who observed that this ketone did not undergo α-cyanation using the LDA promoted reaction with tosyl cyanide.[114] These types of compounds are very prone to polymerize,[117] and probably this is the reason for the low yields noted. No other product could be detected using GC/MS. The α-bromo esters were also successful and the tertiary ester (entry 3) gave a very high yield of the α-cyano ester. A straight chain α-bromo ester was however not as successful (entry 4).

The fact that this protocol is useful for both esters and ketones is very promising, and hopefully the electrophile scope can be expanded to include more useful functional groups in the future.

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[117] Vinick, F. J.; Pan, Y.; Gschwend, H. W., *Tetrahedron Lett.* **1978**, 19, 4221

5. Concluding remarks and future outlook

It appears that the possible transformations with Sm(II) are never ending and that new types of reactions constantly are being developed. This is due to the very broad reactivity window of this reagent, thus allowing for a diverse range of reactions. In comparison with other single electron transfer reagents it is easy to handle and non-toxic which should be in favor for a continued use.

Future areas using this type of reagent are not easy to predict, but there is still much to evaluate and develop in the field of selective carbon-carbon bond forming reactions. Much of the effort that have been invested into this project so far have been dealing with the development of new Sm(II)-based reagents, and the preliminary results indicate that there is a lot of exciting chemistry still to be discovered in this field.

It appears that one of these reagent classes, the samarium(II)-amides, are powerful reagents for cyclizations and other bond forming reactions. The ability to elaborate the amide offers endless variations in reactivity and not least stereoselectivity with the introduction of a chiral amide. The difficulties encountered in this field are numerous, and this is reflected in the small number of published Sm(II)-amides.[118] Primarily, these amides are very prone to β-elimination, so the suitable amines are limited to tertiary amines which restrict the readily available candidates severely. We have evaluated both achiral and chiral amides in a handful test reactions (Figure 48)

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[118] Evans, W. J.; Rabe, G. W.; Ziller, J. W., *Organometallics* **1994**, 13, 1641. Rabe, G. W.; Yap, G. P. A.; Rheingold, A. L., *Inorg. Chem.* **1995**, 34, 4521. Minhas, R. K.; Ma, Y. L.; Song, J. I; Gambarotta, S., *Inorg. Chem.* **1996**, 35, 1866. Deacon, G. B.; Delbridge, E. E.; Skelton, B. W.; White, A. H., *Eur. J. Inorg. Chem.* **1999**, 751. Evans, W. J.; Johnston, M. A.; Clark, R. D.; Anwander, R.; Ziller, J. W., *Polyhedron* **2001**, 20, 2483. Evans, W. J.; Brady, J. C.; Ziller, J. W., *Inorg. Chem.* **2002**, 41, 3340.
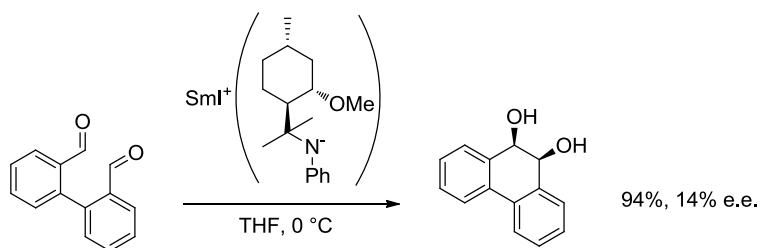
Figure 48. Intramolecular pinacol coupling promoted by a samarium(II) amide.

Another field that has been partly explored is the modification of HMPA. In Paper IV, we evaluated alternative additives to promote the α-cyanation reaction and the HMPA analogue TPPA was found to be effective. It lies close at hand to synthesize other HMPA analogues, preferably chiral, and evaluate them in reactions of this type. Bidentate analogues would be particularly interesting, and recently an additive of this type for use in SmI$_2$ chemistry was reported (Figure 49).[119]
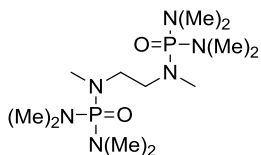

Figure 49. diHMPA additive.

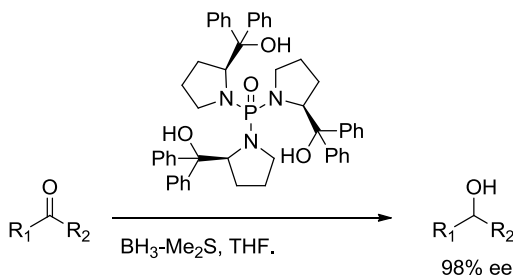"Chiral"-HMPA have been evaluated in a few reactions with encouraging results (Figure 50).[120]

Figure 50. Borane reduction of a ketone using 5 mol% catalyst.

[119] McDonald, C. E.; Ramsey, J. D.; Grant, J. A.; Howerter, K. A., *Tetrahedron Lett.* **2009**, 50, 5308.
[120] Du, D. M.; Fang, T.; Xu, J. X.; Zhang, S. W., *Organic Letters* **2006**, 8, 1327.

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Paper I

Paper II

Paper III

3

Paper IV

Paper V