The Characterization of the Reactivity of the Complexes Formed between Samarium(II) Iodide and Dipyrrolidinomethylaminophosphoric Acid Triamide

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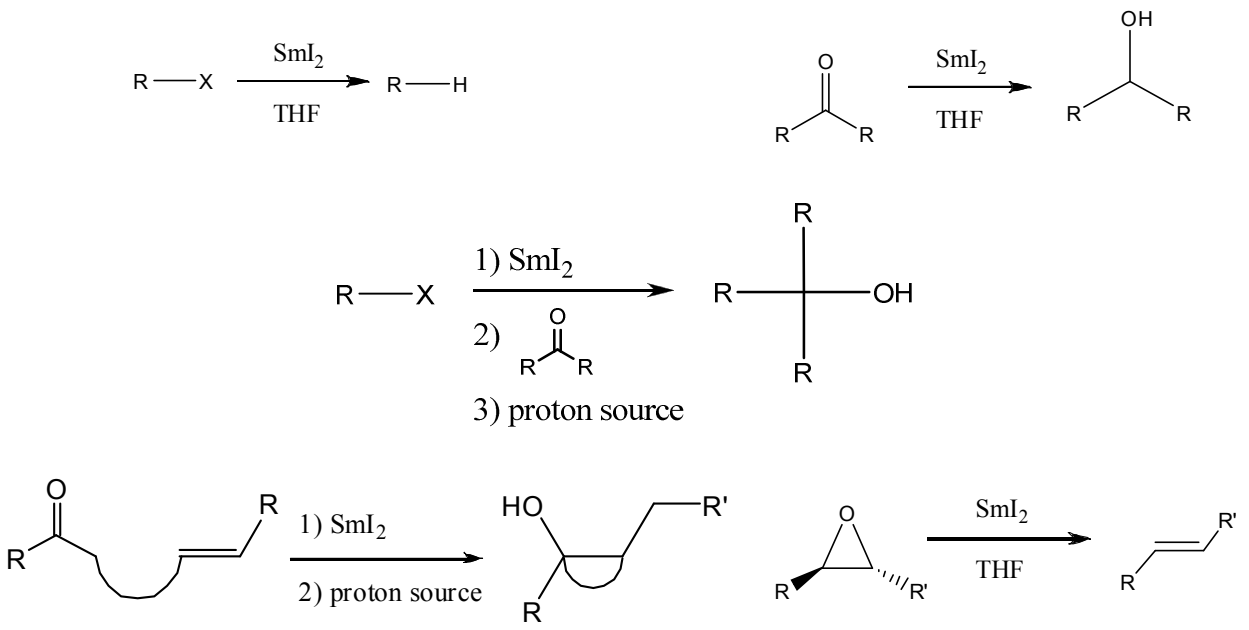
Abstract

Samarium diiodide can be used to perform single-electron reductions on organic functionalities. Hexamethylphosphoramide (HMPA) is the best known ligand for the activation of samarium diiodide reductions, but due to its mutagenicity, an HMPA-substitute is highly desirable. Therefore, dipyrrolidinomethylaminophosphoric acid triamide (DPMPA) and its conjugate base ($DPMPA^-$) were characterized as activators for samarium diiodide. The deprotonated phosphoramide showed promise as a ligand with extremely high electron-donating capabilities, and therefore was evaluated and shown to activate samarium diiodide reductions to a previously unrealized extent.

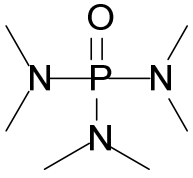
Introduction

Samarium diiodide is widely used in organic synthesis as a versatile single electron reductant.[1,2] Halogens on organic molecules are replaced by hydrogen using samarium diiodide, while aldehydes and ketones are reduced to alcohols. A halide can first be reduced to an organosamarium species which can then react as an anionequivalent with the carbonyl carbon of the aldehyde or ketone to form a carbon-carbon bond, substantiallyadding to the synthetic utility of samarium diiodide. Samarium diiodide has several other synthetically useful capabilities as well, including the reduction of epoxides to alkenes and the single-electron reduction of ketones to ketyl radial anions bound to a samarium(III) atomwhich can then react with carbon-carbon double bonds (**Scheme 1**).[3,4]

Scheme 1. Reductions of Several Functional Groups using Samarium Diiodide



Hexamethylphosphoramide (HMPA, **1**) is one of the most polar aprotic cosolvents known. It has one of the highest Lewis basicities of any known polar aprotic solvent.[5] In 1987, Inanaga reported the increased reactivity of samarium diiodide complexed by HMPA towards organic halides relative to uncomplexed SmI_2. Using a 5% HMPA solution in THF, near quantitative yields of dehalogenated products were observed from the reduction of alkyl and aryl halides in as little as ten minutes (**eq 1**). When samarium diiodide is used without HMPA, the same reaction can take hours or even days to reach completion (**eq 2**).[7] When the SmI_2•$(HMPA)_4$ complex was compared to SmI_2, the standard potential decreases from -1.33 V to -2.05 V, as measured by cyclic voltammetry a difference of -0.72 V.[8]



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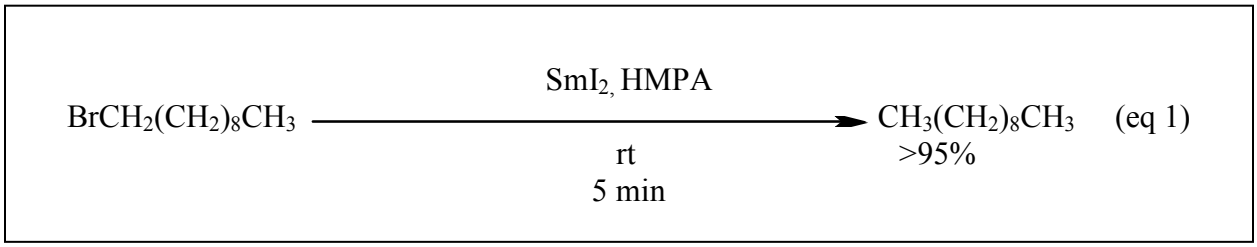
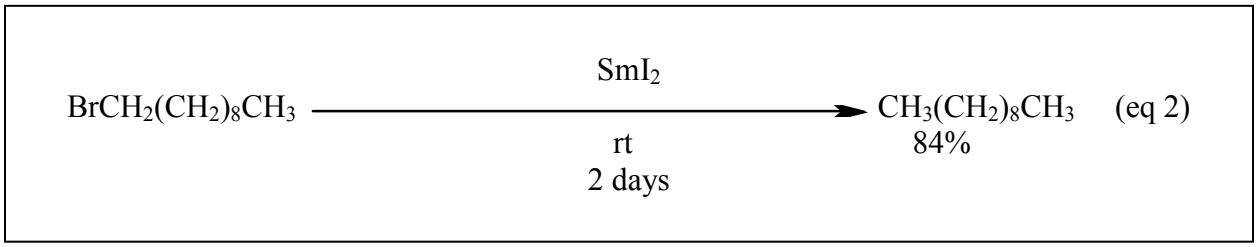
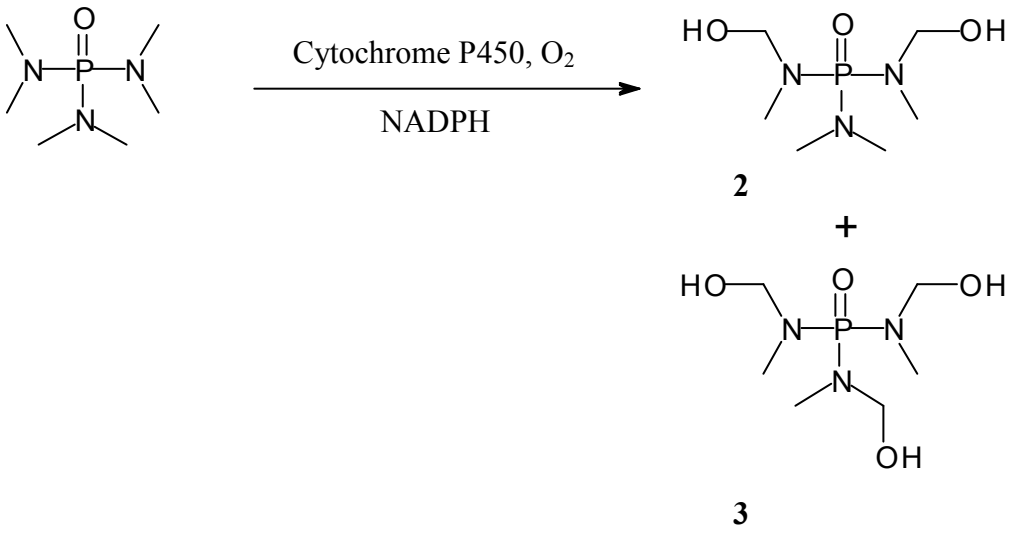




The UV-vis spectrum of SmI_2 dissolved in THF has two maxima, one at 558 nm and another at 616 nm (λ_{max}). As equivalents of HMPA were added to solution, the peak at 616 nm becomes less intense until it almost gone. At the same time, the peak at 558 nm broadens and shifts to a lower wavelength with each equivalent of HMPA until settling at 540 nm with addition of four or more equivalents of HMPA per equivalent of SmI_2.[6] This corresponds to a change from a dark blue to a deep purple solution.

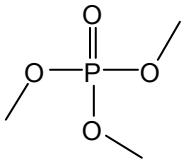
HMPA, though, has been found to have several negative health effects. HMPA has been reported to cause nasal tumors in rats,[9] as well as sterility.[10] The basis of the carcinogenic properties of HMPA appears to be the reaction of HMPA within the cells of the nasal passages to form the dihydroxylated (**2**) and trihydroxylated HMPA (**3**) metabolites (**eq 3**) which then react with DNA to cause tumor formation. Analogous hydroxylated molecules do not seem to formif there are not at least two separate *N*-methyl groups.[11] This carcinogenic activity has led to several countriesbanning the use of HMPA.[12]

Eq 3. The metabolism of HMPA to form polyhydroxylated mutagens



Due to the hazards of working with HMPA, several substitutes have been proposed as activators for samarium diiodide.Trimethylphosphate (**4**), pentamethylphosphoramidate (**5**), and, most commonly, dimethylpropylene urea (**6**) (**Scheme 2**) are some of the substitutes used in place of HMPA to increase the reductive abilities of samarium diiodide. Though these cosolvents do increase the reactivity of samarium diiodide, none of these are able to compare to HMPA.[13] Recently, two cosolvents that were previously evaluated in Professor McDonald's lab have shown promise as replacements for HMPA.Both ligands have an expected toxicity that is far less than that of HMPA. The examined ligands were diHMPA (**7**), the dehydrodimer of HMPA, and tripyrrolidinophosphoric acid triamide (TPPA) (**8**).[14-17]

Scheme 2. Previously Reported HMPA-Substitutes Used as Activators for Samarium(II) Iodide Reductions



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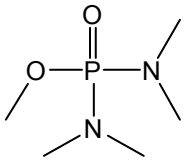

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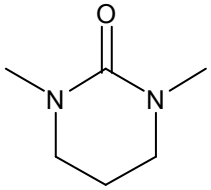

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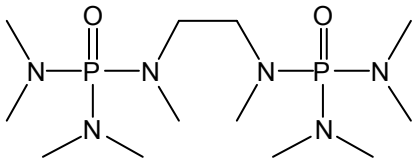

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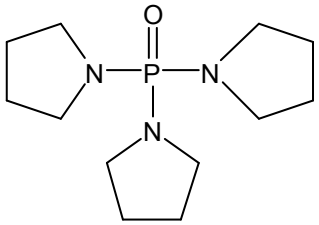

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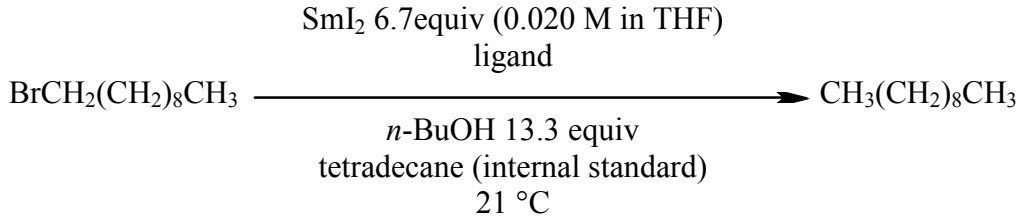
SmI_2/diHMPA was developed first as a replacement for SmI_2/HMPA. Due to the larger size of diHMPA, its vapor pressure would be drastically decreased, making it less dangerous, since the inhalation of HMPA is its greatest hazard. Since diHMPA has two HMPA-like moieties, it acts as a bidentate ligand. When diHMPA was combined with SmI_2 in THF, the effects to the UV-vis spectrum of the SmI_2 solution were essentially identical to those of addition of HMPA to SmI_2, again turning the solution from blue to purple. When electrochemical studies were performed on the SmI_2/diHMPA complex, they yielded, again, similar results to SmI_2•$(HMPA)_4$ with a standard potential of -2.03V.[15]

Despite these similarities, SmI_2/diHMPA was not as strong of a reducant as the analogous HMPA complex, but still proved better than other HMPA-substitutes. Using pseudo-first-order kinetic techniques, the complexes between SmI_2 and HMPA, diHMPA and DMPU were evaluated by reducing 1-bromodecane to decane (**Scheme 3**). HMPA produced a relatively high rate constant, approximately five-fold that of DMPU. One equivalent of diHMPA produced

kinetics approximately equal to those of DMPU, and the complex formed between SmI_2 and two equivalents of diHMPA was much faster than DMPU, producing a rate constant between those of DMPU and HMPA. [15]

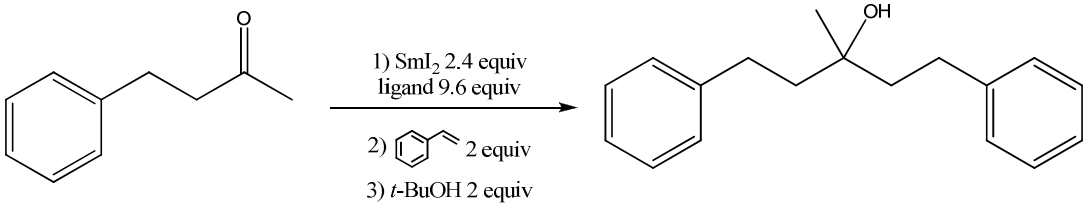
Scheme 3. Kinetic study of the reduction of 1-bromodecane by samarium diiodide using HMPA, DMPU and diHMPA



Ligand	Equiv Ligand/ equiv SmI_2	Rate constant (s^{-1})
HMPA	4	0.0094
DMPU	8	0.0020
diHMPA[a]	1	0.0022
diHMPA[b]	2	0.0069

As a synthetic complex, SmI_2/diHMPA was often able to produce similar yields to the corresponding HMPA complex.[15] Using the complexes formed between SmI_2 and HMPA, diHMPA and DMPU, 4-phenylbutanone was reduced to a ketyl radical anion bound to samarium(III). This is then reacted with styrene, reduced again, presumably to an organosamarium species, and then quenched with a proton source (*t*-BuOH) (**eq 5**). Using HMPA, this reaction produced an almost stoichiometric yield[3]; with diHMPA, slightly less; and with DMPU, far less.[15]

Scheme 4. SmI_2-mediated addition of 4-phenylbutanone to styrene using HMPA, diHMPA and DMPU



Ligand	Yield (%)
HMPA	97[a]
diHMPA	82[b]
DMPU	52[b]

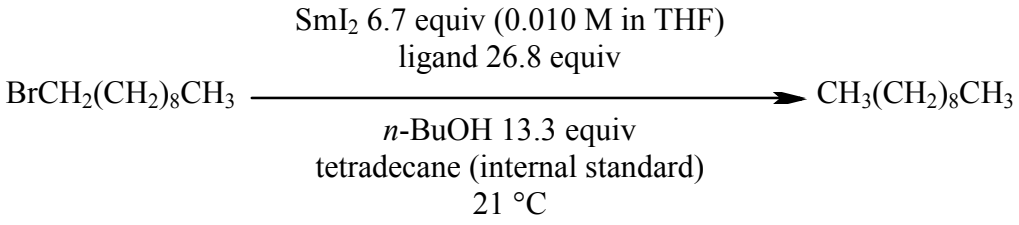
a. ref. 3
b. ref. 15

The complex between tripyrrolidinophosphoric acid triamide (TPPA) and samarium diiodide was also evaluated as a substitute for HMPA in SmI_2 reactions.[17] When a solution of SmI_2 in THF is treated with 4 equivalents of TPPA, its UV-vis spectrum goes through an almost identical transformation as when HMPA is added to a solution of SmI_2, turning the solution from dark blue to dark purple, shifting λ_{max} to 540 nm, just as HMPA does. The standard potential of the complex between samarium diiodide and 4 equivalents of TPPA is quite similar to those between samarium diiodide and 4 equivalents of HMPA, as well, with a potential of -1.94 V.[17]

Kinetically, SmI_2/TPPA was shown to be far superior to SmI_2/HMPA. Again using pseudo-first-order kinetic techniques, the rate constants of the reduction between each of the two complexes and 1-bromodecane (**Scheme 5**) were determined and compared. Using more dilute conditions than the diHMPA kinetic experiments to avoid excessive substrate depletion, the rate

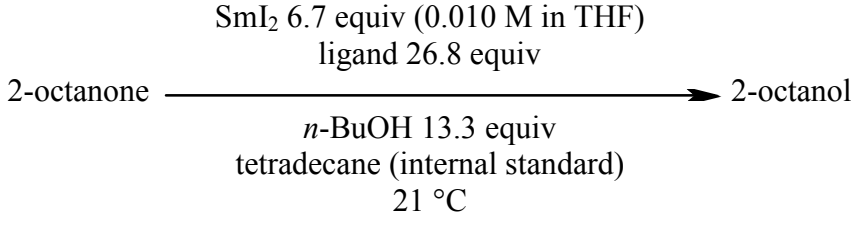
constant for the reduction of 1-bromodecane using SmI_2/HMPA and SmI_2/TPPAwere determined. A kinetic study of the reduction of 2-octanone (**Scheme 6**) by the two complexes was also performed. In both cases, SmI_2/TPPA was found to reduce the substrate with a rate constants several fold beyond that of SmI_2/HMPA.

Scheme 5. Kinetic studies of the reduction of 1-bromodecane using HMPA and TPPA



Ligand	Rate constant (s^{-1})
HMPA	0.0094
TPPA	0.0020

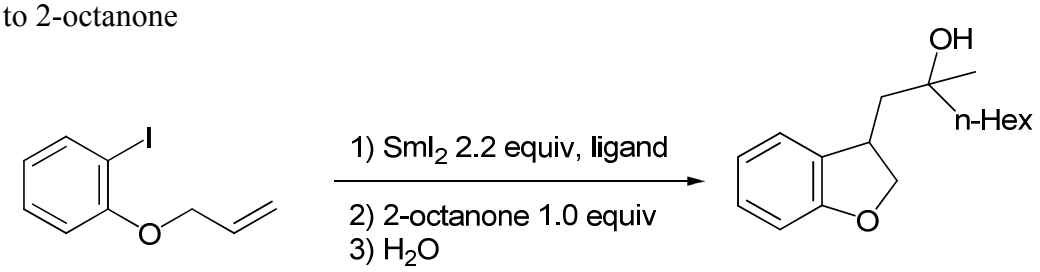
Scheme 6. Kinetic studies of the reduction of 2-octanone using HMPA and TPPA



Ligand	Rate constant (s^{-1})
HMPA	0.00037
TPPA	0.0054

Synthetically, TPPA again gave similar results to HMPA as an activator for samarium diiodide. Using a samarium complex, *O*-allyl-2-iodophenol was reduced in a single-electron fashion, allowed it to cyclize, reduced again it to an organosamarium species which was then be used as an anion equivalent to react with 2-octanone and quenched by a proton to form the dihydrobenzofuran shown (**Scheme 7**). SmI_2/HMPA and SmI_2/TPPA gave almost identical results for this reaction. SmI_2/DMPU, however, yielded a very modest conversion of halide to cyclized product, and SmI_2/diHMPA was unable to perform this reaction. For the reaction between 4-phenylbutanone and styrene, SmI_2/TPPA facilitated the reaction to a yield of slightly below that of the SmI_2/HMPA complex (**Scheme 8**).[17]

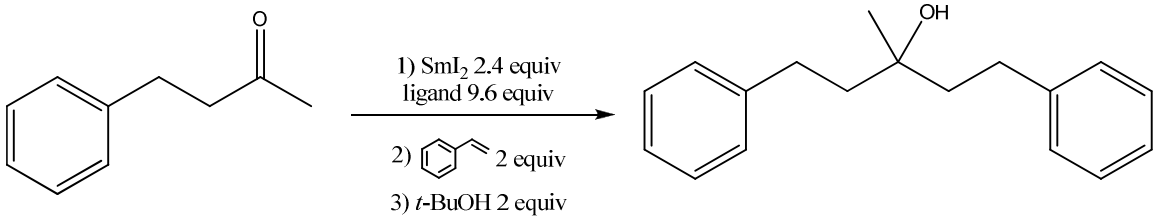
Scheme 7. SmI_2-mediated addition of trapped reductively cyclized *O*-allyl-2-iodophenol to 2-octanone



Ligand	Yield (%)
HMPA	80[a]
TPPA	76[b]
DMPU	30[b]

a. ref. 18
b. ref. 17

Scheme 8. SmI_2-mediated addition of 4-phenylbutanone to styrene using HMPA, TPPA and DMPU

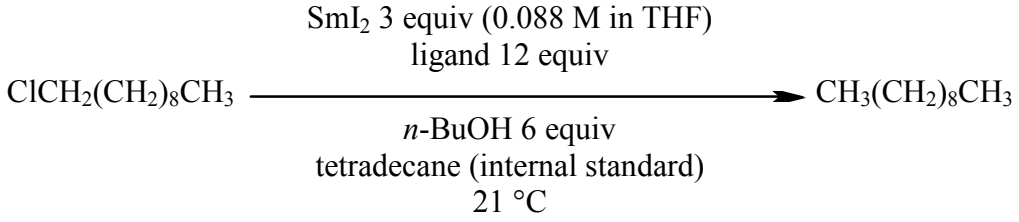


Ligand	Yield (%)
HMPA	97[a]
TPPA	89[b]
DMPU	52[c]

a. ref. 3
b. ref. 17
c. ref. 15

Because SmI_2/TPPA reacted more quickly than SmI_2/HMPA, it was likely substrates that are sluggish to react using HMPA would be more practical to reduce with TPPA. To evaluate this hypothesis, a reluctant substrate, 1-chlorodecane, was chosen to be reduced by each complex. Alkyl chlorides are much harder for samarium diiodide complexes to reduce than alkyl bromides and alkyl iodides and, therefore, are a reasonable test for a highly reactive samarium complex.[7]Each complex was allowed to react with 1-chlorodecane (**Scheme 9**) for a set period of time, and the data was compared. After 10 minutes, SmI_2/HMPA had converted only a quarter as much decane as SmI_2/TPPA had. SmI_2/DMPU, however, did not produce any decane.[17]

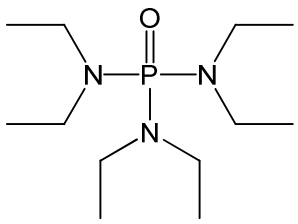
Scheme 9. Reduction of 1-chlorodecane using HMPA, TPPA and DMPU



Ligand	Yield decane after 10 min (%)[a]
HMPA	4
TPPA	16
DMPU	0

a. ref. 12

Hexaethylphosphoramide (HEPA) (**9**) was also evaluated as a possible replacement for HMPA in SmI_2 reductions.[17] Presumably because of its lack of *N*-methyl groups, HEPA showed no mutagenic effects on Drosophila melanogaster and caused no sterility during testing.[10,11] During initial trials, HEPA appeared to be a worthy activator for SmI_2 reactions, quantitatively reducing 1-bromodecane. When concentrations were lowered for kinetic studies, though, HEPA proved to be far inferior to HMPA. Based on voltammetric studies and reactivities of HEPA complexes, data suggests that HEPA is too bulky to bind four times around a samarium atom.[17]Therefore, low-bulk ligands are preferred as alternatives for SmI_2-reductions.



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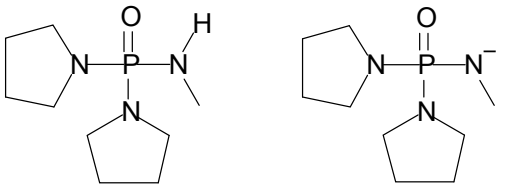
Phosphoramides that include only one methylamino or one dimethylamino group appear to be much safer than HMPA.[11] This suggests that there needs to be two separate nitrogens attached to a phosphorous, each also including a methyl substituent directly bound to the nitrogen, for the hydroxylation of the metabolite to form a mutagenic agent. Therefore, phosphoramides with two pyrrolidino rings and one methylamino group should have little, if any, mutagenic potential.

In addition to phosphoramides that only have a single *N*-methyl moiety, TPPA is expected to be far less toxic than HMPA, as well, because HEPA was shown to be less mutagenic than HMPA.[11] Since TPPA excludes *N*-methyl groups by replacing them with *N*-methylene groups, it follows that it shouldn't have the mutagenic properties associated with HMPA. This is because the moieties of HMPA that cause its mutagenicity seem to be the methyl groups attached to the phosphoramide nitrogens.

As shown by Ozari and Jagur-Grodzinski, adding pyrrolidino groups to the phosphoramide moiety raises its electron-donating abilities. As dimethylamino groups on HMPA were sequentially replaced by pyrrolidino groups, the polarity and Lewis basicity of the resultant compoundsincreased.[5]The largest difference was between the electron-donation of the monopyrrolidinophosphoramide and the dipyrrolidinophosphoramide. Therefore, due to the high Lewis basicity of phophoramides including two pyrrolidino groups and the low mutagenicity of molecules including only a single *N*-methyl group, dipyrrolidinomethylaminophosphoramide (DPMPA, **7**) and deprotonated DPMPA ($DPMPA^-$, **8**) were synthesized and studied as low-toxicity, low-bulk activators for samarium diiodide reductions.

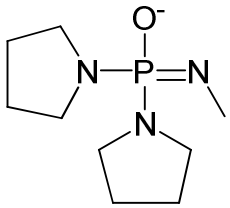


7 **8**

Though TPPA has been developed as a nonmutagenic SmI_2 activator with synthetic properties similar to those of HMPA,[15] little else has been found to surpass the capabilities of HMPA. The SmI_2/amine/H_2O complex is one of the few known species that extend the synthetic abilities of SmI_2 beyond those of SmI_2/HMPA.[19-22] To date, no organic ligand has been discovered to activate SmI_2 to a further extent than HMPA or TPPA.[7,17] DPMPA is expected to activate SmI_2 to approximately the same extent as or slightly more that the previously reported phosphoramides. $DMPMA^-$, however, could possibly form a complex with SmI_2 that is able to reduce substrates to a previously unseen extent.

DPMPA is very similar to HMPA and TPPA in several ways. The major difference is the inclusion of a proton directly attached to one of the nitrogens. HMPA and TPPA both have two alkyl substituents on each nitrogen. The ability to remove this proton is what makes the ligand DPMPA worth investigating. Once deprotonated, forming $DPMPA^-$, the nitrogen previously bound to the proton will have two lone pairs of electrons and a full negative charge, which makes it much more capable of resonance. Because oxygen is more electronegative, the predominant resonance structure (**9**) observed will most likely be that where there are three lone pairs of electrons and a negative charge on the oxygen, with a double bond forming between the phosphorous and the nitrogen. Since samarium is oxophilic, and since the oxygen of $DPMPA^-$ would be more likely to bind than if it were neutral and had two bonds, the samarium is expected to bind tightly to the oxygen. Once it binds, the $DPMPA^-$ should be much more stable than when

it is not bound to the samarium because all the atoms of the $DPMPA^-$ molecule will have neutral charges.



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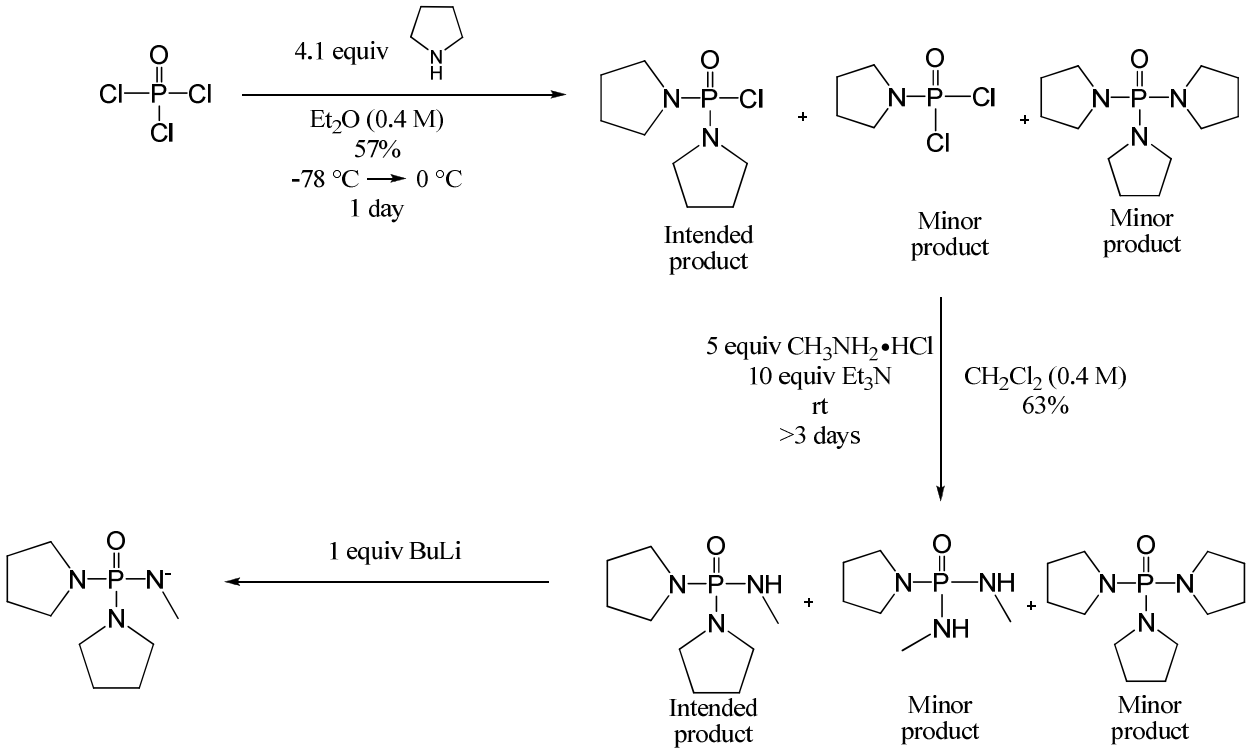
In the SmI_2/HMPA complex, the oxygen of HMPA will donate fewer electrons to the samarium than in those of $DPMPA^-$ do in the $SmI_2/DPMPA^-$ complex. This is because the oxygen and each of the nitrogens in HMPA share a partial positive charge when bound to the samarium. $DPMPA^-$, on the other hand,will become neutral overall once the negatively charged oxygen binds to the samarium atom. This makes the oxygen have more of a partial bond to the samarium, therefore donating less electron density. Because of these things, it is expected that $DPMPA^-$ will be able to be utilized to carry out reductions with samarium diiodide that no other SmI_2 complex has been able to do at a practical rate.

Results and Discussion

DPMPAwas synthesized in a simple fashion by diamination of phosphorous oxychloride using 4.1 equivalents of pyrrolidine in ether followed by a third amination using excess methylamine hydrochloride and triethylamine in dichloromethane for an overall yield of 36% (**Scheme 10**). The first step of this reaction, the replacement of two chlorides with two pyrrolidino groups, was originally performed in dichloromethane using triethylamine as a base. This yielded less of the intended intermediate, dipyrrolidinophorphorousoxychloride, and more of the two byproducts, *N',N''*-dimethylaminopyrrolidinophosporamide and TPPA. Therefore, the reaction is run in ether using pyrrolidine as both a nucleophile and a base.

Scheme 10. Synthesis of DPMPA and DPMPA$^-$



Pyrrolidine is used as a base in the first step because it is a stronger base than triethylamine. When triethylamine was used as a base in the first step, some of the pyrrolidine used was being protonated, making it unable to react with the phosphorous oxychloride. Therefore, more equivalents of pyrrolidine had to be added in order to form a large percentage of the desired dipyrrolidinated product. This, though, seemed to lead to rather impure formation of the intended product.

Ether was used in place of dichloromethane because it is less polar. A large portion of the pyrrolidinium hydrochloride formed would stay in solution in dichloromethane. When the triethlamine was added for the methylamination of the dipyrrolidinated species, some of theleftover pyrrolidine would add to the phosphorous instead of the methylamine, forming TPPA. Using ether, a less polar solvent, most of the pyrrolidinium hydrochloride precipitated out of solution and was filtered away from the dipyrrolidinophosphorous oxychloride. If large

amounts of TPPA were formed, they were able to be washed away after formation of DPMPA using ice-cold hexane.

The resultant product was then distilled under vacuum. The distillate, high-purity (~98%) DPMPA, was a colorless, hygroscopic, low-melting solid. The anion $DPMPA^-$ was formed *in situ* by the addition of butyllithium to a solution of DPMPA in THF. This solution was light blue upon addition of the first portion of butyllithium but became a pale yellow solution upon full addition.

For these complexes, the more negative the standard potential of the complex, the more active of a reduction the complex is. Cyclic voltammetry (CV) was performed on SmI_2complexed by DPMPA to determine its standard potential (**Table 1**), both in its neutral and anionic forms. SmI_2•$(DPMPA)_4$ yielded a modest standard potential, butthe SmI_2•$(DPMPA^-)_1$ complex and SmI_2•$(DPMPA^-)_2$ gave rather impressive results for the number of equivalents of ligand used. CV has not yet been performed on SmI_2complexed by three or four equivalents of $DPMPA^-$, but based on the results of the complexes using anionic ligand, it appears that the complexes using three and four equivalents will give substantially more negative standard potentials than SmI_2complexed by four neutral phosphoramides.

Table 1. Standard potential of several SmI_2/phosphoramide complexes

Complex	Equivalents of Ligand/ Equivalent of Samarium	Standard Potential (V)	ΔE relative to SmI_2 (V)
SmI_2	---	-1.33[a]	---
SmI_2/HMPA	2	-1.46[a]	-0.13
SmI_2/HMPA	4	-2.05[a]	-0.72
SmI_2/diHMPA	1	-1.43[b]	-0.10
SmI_2/diHMPA	2	-2.03[b]	-0.70
SmI_2/TPPA	2	-1.41[c]	-0.08
SmI_2/TPPA	4	-1.94[c]	-0.61
SmI_2/DPMPA	4	-1.79[d]	-0.46
SmI_2/$DPMPA^-$	1	-1.51[d]	-0.18
SmI_2/$DPMPA^-$	2	-1.93[d]	-0.60

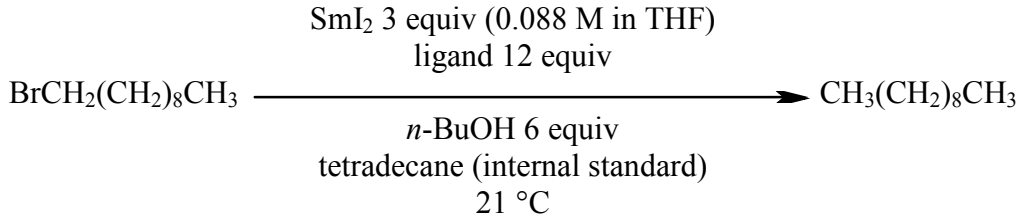
a. ref. 8
b. ref. 15
c. ref. 17
d. Unpublished data from Professor McDonald's lab

When comparing the results for SmI_2•$(DPMPA^-)_2$ with those of SmI_2•$(HMPA)_2$, SmI_2•$(diHMPA)_1$, and SmI_2•$(TPPA)_2$, it is apparent that $DPMPA^-$ is a much stronger activator for SmI_2 than are these neutral phosphoramides. Where two equivalents of HMPA have a -0.13V effect, two equivalents of $DPMPA^-$ have an effect almost five times greater. This suggests that SmI_2•$(DPMPA^-)_4$ will likely have abilities previously unobserved for SmI_2 complexes.

As an initial probe of the reactivity of the complex formed between SmI_2 and DPMPA, a solution of SmI_2 was added to four equivalents of DPMPA, which turned the solution from blue to purple as is typical of SmI_2/phosphoramide solutions. To this solution, 1-butanol (proton

source) and tetradecane (internal standard) were added. Lastly, 1-bromodecane was then added to the solution (**Scheme 11**). Ten minutes after the addition of 1-bromodecane, an aliquot was removed and quenched with I_2. To the resultant solution was added aqueous HCl and ether. The organic layer was then analyzed using gas chromatography, and after 10 minutes, the SmI_2/DPMPA complex had reduced 88% of the 1-bromodecane to decane. Both the SmI_2/HMPA complex and the SmI_2/TPPA complex had reduced over 95% of the 1-bromodecane using the same conditions.[4,12] In the case of the two near-quantitative reactions, the peak for 1-bromodecane was not observed when analyzed by gas chromatography, but with the SmI_2/DPMPA complex, a small peak was still observed for 1-bromodecane. The complex between SmI_2 and $DPMPA^-$ was not tested in the reduction of 1-bromodecane.

Scheme 11. Reduction of 1-bromodecane using HMPA, TPPA and DPMPA



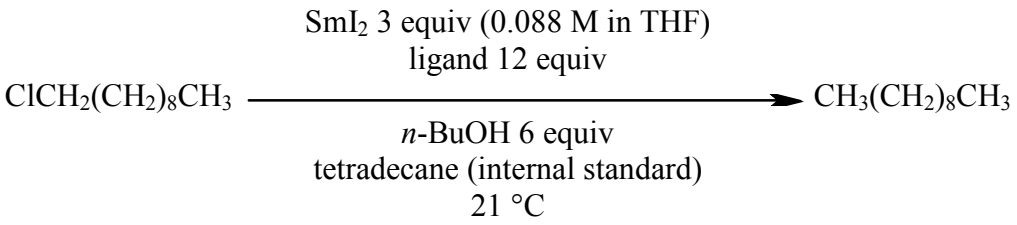
Ligand	Yield after 10 min (%)
HMPA	>95[a]
TPPA	95[a]
DPMPA	88

d. ref. 12

As previously mentioned, alkyl chlorides are reluctant substrates for SmI_2 reductions. Therefore, both the SmI_2/DPMPA and the SmI_2/$DPMPA^-$ were characterized by the reduction of 1-chlorodecane to decane (**Scheme 12**). For initial 1-chlorodecane reductions, the reactions were

set up and analyzed as they were for 1-bromodecane reductions. Each reaction was run with the indicated proportions of each reactant, but the complex of SmI_2/DPMPA$^-$ experiment was performed at a concentration of 0.062 M SmI_2, where the experiments examining SmI_2/HMPA, SmI_2/TPPA and SmI_2/DPMPA were all performed at 0.088 M SmI_2.[13] The reason for the concentration difference is that THF was used to first solvate the DPMPA, and the butyllithium was used as a 2.5 M solution in hexanes. The yield of decane using DPMPA suggested that it was less activating than HMPA and TPPA, but the yield from the reaction using DPMPA$^-$ showed that it was far more activating than either HMPA or TPPA. The yield when half of the DPMPA was deprotonated prior to addition of SmI_2 persisted with very little further reduction 1.5 h after addition of the 1-chlorodecane. Therefore, it is likely that the initial SmI_2 added bound to four equivalents of the more reactive, anionic DPMPA$^-$, while the latter SmI_2 bound to four equivalents of the neutral DPMPA, which should not bind as quickly or as strongly. This would likely lead to a very fast reduction using the SmI_2/DPMPA$^-$ complex at first and sluggish reduction with the leftover SmI_2/DPMPA complex once all of the SmI_2/DPMPA$^-$ complex had reacted.

Scheme 12. SmI_2-mediated reduction of 1-chlorodecane using neutral and anion ligands

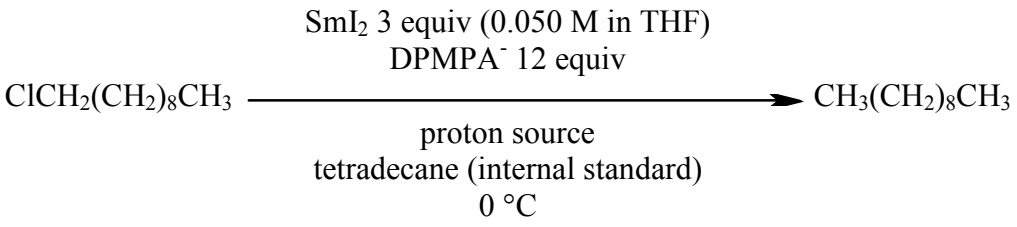


Ligand	Yield after 10 min (%)
HMPA	4[a]
TPPA	16[a]
DPMPA	1.8
½ DPMPA / ½ $DPMPA^-$	29[b]
$DPMPA^-$	74[b]

a. ref. 12
b. $[SmI_2]$ = 0.062 M

Since $DPMPA^-$ is basic, different proton sources were evaluated to determine if better yields were produced with a less acidic alcohol. Reactions were run using six equivalents of *n*-butanol and others were run using two equivalents of *t*-butanol (**Scheme 13**). The results showed that two equivalents of *t*-butanol gave better yields; therefore, two equivalents of *t*-butanol were used for all subsequent reductions where a proton source was used with $DPMPA^-$.

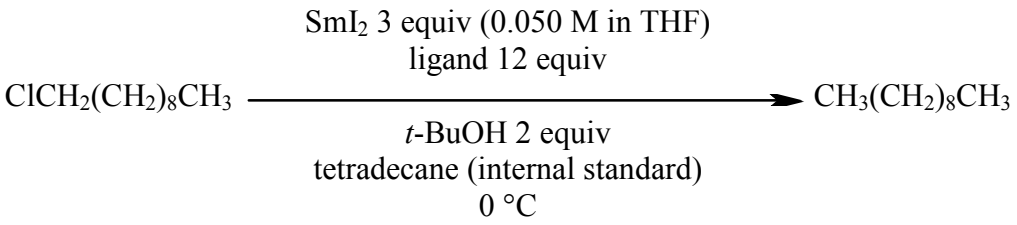
Scheme 13. Effect of different proton sources on the SmI_2/DPMPA$^-$-mediated reduction of 1-chlorodecane



Proton Source	Equivalents proton source	Yield (%)
n-BuOH	6	91
t-BuOH	2	100

Since reactions performed with two equivalents of *t*-butanol proved superior for SmI_2/DPMPA$^-$ reductions, all 1-chlorodecane reductions were repeated with two equivalents of *t*-butanol (**Scheme 14**). In an attempt to better compare the relative reactivity of the complexes, the temperature was lowered from 21 °C to 0 °C. Also, the concentration of SmI_2 was lowered to 0.050 M. The results show that DPMPA$^-$ is even more activating toward SmI_2then previously realized compared to neutral phosphoramides. SmI_2/DPMPA$^-$ even appears to be more active than the SmI_2/amine/H_2O complex, as it took SmI_2/Et_3N/H_2O 14 h to reach a yield of 95% using 0.10 M SmI_2 and 7 equivalents of SmI_2 per equivalent of 1-chlorodecane.[21]

Scheme 14. Effect of an anionic ligand on the ability of SmI_2 to reduce 1-chlorodecane

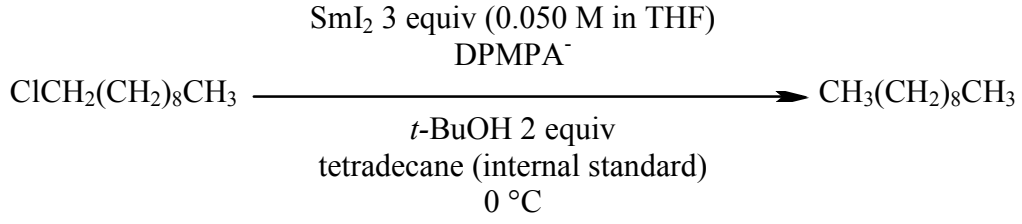


Ligand	Yield @ 1 min (%)	Yield @ 2 min (%)	Yield @ 5 min (%)	Yield @ 10 min (%)
HMPA	<1	<1	<1	<1
TPPA	<1	<1	<1	<1
DiHMPA[a]	0%	0%	0%	0%
DPMPA	<1	<1	<1	<1
$DPMPA^-$	90	92	96	96

a. 6 equiv diHMPA

Using less DPMPA for each reduction is attractive for two reasons. DPMPA takes several days to produce, so the less of it used, the less often it has to be synthesized. Also, there are times where a substrate will include more than one functional group that can be reduced by SmI_2. In the case where only one of these functional groups is intended to be reduced, it is convenient to have a reductant that is less reactive. Therefore, "low-ratio" $SmI_2/DPMPA^-$complexes (those using less than four equivalents of $DPMPA^-$) were used to reduce 1-chlorodecane (**Scheme 15**).

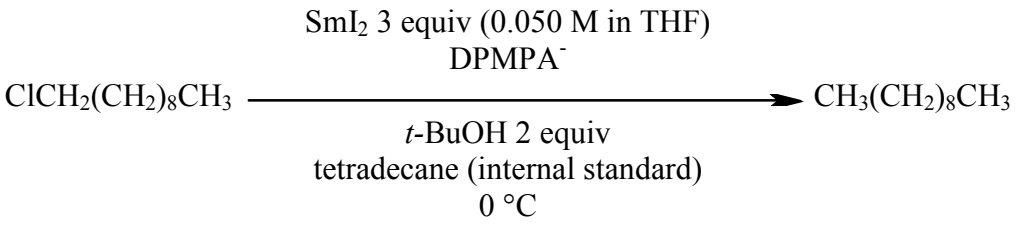
Scheme 15. Ability of low-ratio SmI_2/$DPMPA^-$ complexes to reduce 1-chlorodecane



Equivalents $DPMPA^-$/ Equivalent SmI_2	Yield after 1 min (%)
1	20
2	65
3	79
4	90

Due to the strong bond predicted to form between $DPMPA^-$ and the samarium atom of SmI_2, it seems likely that adding a solution of SmI_2 to $DPMPA^-$ will form a variety of SmI_2/$DPMPA^-$ complexes rather than the single complex desired. In an attempt to more cleanly form discrete low-ratio complexes of SmI_2/$DPMPA^-$, a solution of $DPMPA^-$ was slowly added to a cold solution of SmI_2 to determine if this is a possibility (**Scheme 16**). When compared to the results of the normal addition method, the results of the inverse addition ($DPMPA^-$ added to SmI_2) shows that there are different complexes formed if inverse addition is performed. It is more likely that with inverse addition, a single desired complex is formed.

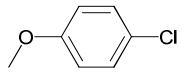
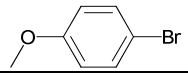
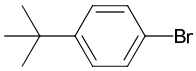
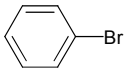
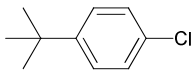
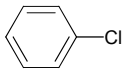
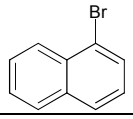
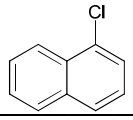
Scheme 16. Reduction of 1-chlorodecane using low-ratio SmI_2/$DPMPA^-$ complexes



Equivalents $DPMPA^-$/ Equivalent SmI_2	Yield Decane after 1 min (%)	Yield after 1 h (%)
1	0	2.8
2	47	66
3	72	93

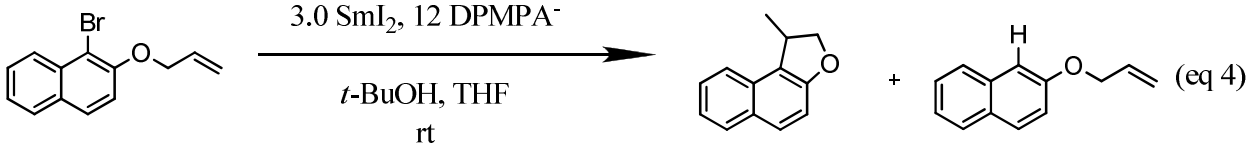
Reductions using SmI_2/$DPMPA^-$ were performed on several haloarenes (**Table 2**). These reactions were compared to reductions performed on similar substrates using either SmI_2/HMPA or $SmI_2/H_2O/Et_3N$ complexes. In each case, SmI_2/$DPMPA^-$ performed at least as well as the other two complexes. Particularly intriguing is the reduction of *p*-chloroanisole. Since SmI_2/HMPA took eight hours to completely reduce *p*-bromoanisole, the reduction of the more reluctant chlorinated analog is especially impressive.

Table 2. Reduction of several haloarenes using SmI_2/HMPA, $SmI_2/H_2O/Et_3N$and SmI_2/DPMPA$^-$.

Haloarene	Yield and reaction time using SmI_2/HMPA	Yield and reaction time using $SmI_2/H_2O/Et_3N$	Yield and reaction time using SmI_2/DPMPA$^-$ [a]
	---	---	96%, 30 min
	82%, 8 h[b]	---	100%, 15 min
	---	---	100%, 15 min
	---	95%, 40 min[c]	---
	---	---	88%, 50 min
	---	95%, 5 h[c]	---
	98%, 5 min[b]	---	91%, 10 min
	95%, 15 min[b]	---	94%, 10 min

a. Unpublished results from Professor McDonald's lab, 0.062 M SmI_2, 0 °C
b. ref. 7
c. ref. 21

To evaluate the synthetic capabilities of the SmI_2/DPMPA$^-$ complex, an intramolecular carbon-carbon bond formation was attempted. *O*-Allyl-1-bromo-2-naphthol was reacted with SmI_2/DPMPA$^-$in order to form the intended cyclic ether **10** (**eq 4**). During the initial experiment, several products were observed. The intended product was approximately 80% of the observed product, while the dehalogenated, uncyclized product (**11**) made up approximately 20% of the observed product. Trace amounts of starting material were also present.

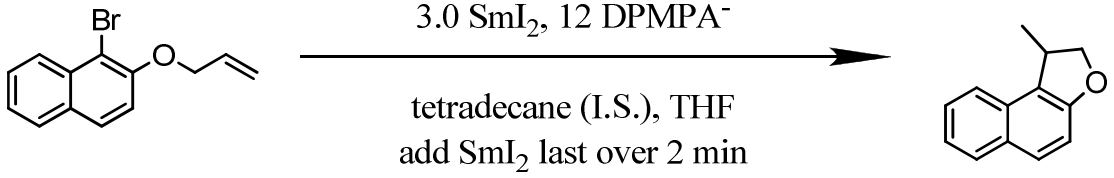


10 **11**

In order to reduce the amount of uncyclized product, in subsequent reactions, samarium was added last, rather than the substrate. This was done in order to keep the concentration of reductant down while the initial radical was forming, in case the radical was immediately being reduced to an anion and, thus, unable to cyclize. Also, the reaction was cooled to 0 °C in order to slow anion formation. The only observed product, in this case, was naphthalene.

t-Butanol was removed from the reaction mixture and the amount of desired product compared to other products increased. Also, reducing the amount of time that the substrate was exposed to $DPMPA^-$ prior to SmI_2 addition appeared to raise the amount of desired product formed (**Scheme 17**). As temperature was lowered, yields of desired product went up, while yields of undesired product went down. ^{1}H-NMR also showed a much cleaner crude product for lower temperature reactions.

Scheme 17. Cyclization of *O*-allyl-1-bromo-2-naphthol using $SmI_2/DPMPA^-$



Experiment	Temperature (°C)	Yield (%)[a]
1	0	68
2	-40	81
3	-50	90 (88)[b]

a. Yield obtained by gas chromatography
b. Isolated yield

Similar reactions were performed on *O*-allyl-1-chloro-2-naphthol. At 0 °C, the chlorinated substrate gave a 52% yield of desired product. At -50 °C, the same reaction produced

a yield of 62%. Further reductions have not been performed on this substrate, but as temperature is reduced, it possible that yields for this reaction will continue to rise.

Based on the results observed and the data accumulated, DPMPA appears to be a moderate activator for samarium diiodide reductions. Also, based on Zijlstra's results, DPMPA is expected to have little if any mutagenicity.[9] However, it is apparent that it is less effective as an activator than TPPA and even appears less so than HMPA, and it requires a more involved synthesis than does TPPA, so it doesn't seem like an attractive substitute. The deprotonated phosphoramide, $DPMPA^-$, though, was shown to be highly effective as an activator when used in combination with samarium diiodide, but the optimization of cyclization of *O*-allyl-1-chloro-2-naphthol has yet to be accomplished.

Experimental

General Methods. Reactions were run under an inert atmosphere of nitrogen or argon. All glassware was oven-dried. 1-Bromodecane, 1-chlorodecane and 1-butanol were distilled onto molecular sieves prior to use. Pyrrolidine, triethylamine and dichloromethane were distilled from calcium hydride prior to use. Tetrahydrofuran and diethylether were distilled from sodium/benzophenone prior to use. *N,N*-Dimethylformamide was dried over sieves prior to use. 2-Chlorophenol and allyl bromide were used as received from Sigma-Aldrich Company. Potassium carbonate was used as received from Fisher Scientific. SmI_2 in THF was used as received from Strem Chemicals Inc.

Synthesis of dipyrrolidinophosphorousoxychloride. Pyrrolidine (2.23 mL, 26.8 mmol) in diethyl ether (6.3 mL) was added to a solution of phosphorous oxychloride (0.600 mL, 6.53 mmol) in diethyl ether (10 mL) at -78 °C. The solution was allowed to warm to 0 °C, and was stirred in a cold room at 0 °C for 24 h. The solution was filtered to remove pyrrolidine

hydrochloride, the solvent was washed with 1:1ether:hexane and the solvent was removed from the filtrate *in vacuo*, yielding a white, solid crude product (1.0211g, 4.5892 mmol, 70.3% from phosphorous oxychloride).

Synthesis of methylaminodipyrrolidinophosphorictriamide (7). Methylamine hydrochloride (1.76 g, 26.1 mmol) was added to a solution of dipyrrolidinophosphorousoxychloride (1.9337 g, 8.6908 mmol) and triethylamine (7.32 mL, 52.2 mmol) in dichloromethane (22 mL) at room temperature. The solution was stirred for 48 h. Water (25 mL) and aqueous saturated sodium chloride (5 mL) were added to solution, and the organic layer was separated. Dichloromethane (3 X 10 mL) was then used to extract the aqueous layer. The combined organic layers were washed with 10% (w/v) aqueous NaOH solution (2 X 10 mL) and then water (1 X 10 mL). The organic layer was dried ($MgSO_4$) and filtered. The solvent was removed *in vacuo*. The crude product was then distilled using a Kugelrohr distillation apparatus at 185 °C and 2.0 mmHg. If contaminated with TPPA, the distillate was washed with ice cold hexane (5 X 15 mL) to yield a white solid (0.9496g, 4.376 mmol, 50% from dipyrrolidinophosphorusoxychloride). IR (ATR): cm^{-1} 3200, 2966, 1429, 1346, 1207, 1183, 1073, 1010. ^1H NMR (300 MHz, $CDCl_3$): δ 1.82 (8H, quint, J = 3.0 Hz), 2.26 (1H, s), 2.62 (3H,dd, J = 12.0 Hz, 6.0 Hz), 3.18 (8H, quint, J = 3.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.4, 26.5, 27.3, 46.4, 46.5. MS: *m/z* 218 (100), 187 (67), 147 (37), 72 (21), 70 (51).

Procedure for the reduction of 1-bromodecane. DPMPA (0.4062 g, 1.872 mmol) was added and allowed to dry under vacuum for at least 120 min. A 0.093 M solution of SmI_2 (5.0 mL, 0.47mmol) was added followed by addition of THF (0.286 mL). To this mixture, 1-butanol (85.6 µL, 0.936 mmol) and tetradecane (10.0 µL, 0.0387 mmol) were added and the solution was stirred for 5 min. 1-Bromodecane (32.6 µL, 0.156 mmol), was then added to the solution after

the reaction was adjusted to 21 °C. After 10.0 min, an aliquot was removed. The aliquot was then quenched with I_2 immediately after removal. To the resultant mixture, 0.1 mL of 0.1 M HCl and 1.0 mL of ether were added. Gas chromatography was used to analyze the organic layer.

Procedure for the reduction of 1-chlorodecane with SmI_2/DPMPA. DPMPA (0.3539 g, 1.631 mmol) was added and allowed to dry under vacuum for at least 120 min. A 0.094 M solution of SmI_2 (4.6 mL, 0.41mmol) was added followed by addition of THF (0.3 mL). To this mixture, 1-butanol (74.6 μL, 0.816 mmol) and tetradecane (10.0 μL, 0.0387 mmol) were added and the solution was stirred for 5 min. 1-chlorodecane (27.5 μL, 0.136 mmol), was then added after the reaction was adjusted to 21 °C. After 10.0 min, an aliquot was removed. The aliquot was then quenched with I_2 immediately after removal. To the resultant mixture, 0.1 mL of 0.1 M HCl and 1.0 mL of ether were added. Gas chromatography was used to analyze the organic layer.

Procedure for the reduction of 1-chlorodecane with SmI_2/DPMPA/DPMPA$^-$. DPMPA (0.1821 g, 0.8392 mmol) was added and allowed to dry under vacuum for at least 120 min. At this point, 2.5 M butyllithium (0.169 mL, 0.420mmol) was added to the solid phosphoramide. A 0.094 M solution of SmI_2 (2.2 mL, 0.21 mmol) was then added. To this solution, 1-butanol (38.4 μL, 1.69 mmol) and tetradecane (10.0 μL, 0.0387 mmol) were added and the solution was stirred for 5 min. 1-chlorodecane (14.2 μL, 0.0699 mmol), was then added. After 10.0 min, an aliquot was removed. The aliquot was then quenched with I_2 immediately after removal. To the resultant mixture, 0.1 mL of 0.1 M HCl and 1.0 mL of ether were added. Gas chromatography was used to analyze the organic layer.

Procedure for the reduction of 1-chlorodecane with SmI_2/DPMPA$^-$using six equivalents *n*-butanol. DPMPA (0.2269 g, 1.046 mmol) was added and allowed to dry under vacuum for at least 120 min. THF (1.0 mL) was added to solvate the solid phosphoramde. At this point, 2.5 M

butyllithium (0.42 mL, 1.1mmol) was added to solution. A 0.094 M solution of SmI_2 (2.78 mL, 0.261 mmol) was added. To this mixture, 1-butanol (47.8 μL, 0.523 mmol) and tetradecane (10.0 μL, 0.0387 mmol) were added and the solution was stirred for 5 min. 1-chlorodecane (17.7 μL, 0.0871 mmol), was then added. After 10.0 min, an aliquot was removed. The aliquot was then quenched with I_2 immediately after removal. To the resultant mixture, 0.1 mL of 0.1 M HCl and 1.0 mL of ether were added. Gas chromatography was used to analyze the organic layer.

Procedure for the reduction of 1-chlorodecane with SmI_2/DPMPA$^-$ comparing six equivalents of *n*-butanol and two equivalents of *t*-butanol. DPMPA (12 equiv) was added and allowed to dry under vacuum for at least 120 min. THF was added to solvate the solid phosphoramde. At this point, 2.5 M butyllithium (12 equiv) was added to solution. A 0.088 M solution of SmI_2 (3 equiv) was added. To this mixture, 1-butanol (6 equiv) or *tert*-butanol (2 equiv) was added. Next, tetradecane (10.0 μL, 0.0387 mmol) was added and the solution was stirred for 5 min. 1-chlorodecane (1 equiv), was then added. After 10.0 min, an aliquot was removed. The aliquot was then quenched with I_2 immediately after removal. To the resultant mixture, 0.1 mL of 0.1 M HCl and 1.0 mL of ether were added. Gas chromatography was used to analyze the organic layer.

Procedure for the reduction of 1-chlorodecane with SmI_2 using neutral phosphramides at 0 °C. HMPA, TPPA, DPMPA (12 equiv) or diHMPA (6 equiv) was added and allowed to dry under vacuum for at least 120 min. A 0.088 M solution of SmI_2 (3 equiv) was added followed by addition of THF. To this mixture, *tert*-butanol (2 equiv) and tetradecane (10.0 μL, 0.0387 mmol) were added and the solution was stirred for 5 min. 1-chlorodecane (1 equiv), was then added after the reaction was adjusted to 0 °C. At 1 min, 2 min, 5 min and 10 min, an aliquot was removed. The aliquot was then quenched with I_2 immediately after removal. To the resultant

mixture, 0.1 mL of 0.1 M HCl and 1.0 mL of ether were added. Gas chromatography was used to analyze the organic layer.

Procedure for the reduction of 1-chlorodecane with SmI_2/DPMPA$^-$ for comparison with neutral phosphoramide complexes at 0 °C. DPMPA (12 equiv) was added and allowed to dry under vacuum for at least 120 min. THF was added to solvate the solid phosphoramde. At this point, 2.5 M butyllithium (12 equiv) was added to solution. A 0.088 M solution of SmI_2 (3 equiv) was added. To this mixture, *tert*-butanol (2 equiv) was added. Next, tetradecane (10.0 μL, 0.0387 mmol) was added and the solution was stirred for 5 min. 1-chlorodecane (1 equiv), was then added after the solution was allowed to cool to 0 °C. At 1 min, 2 min, 5 min and 10 min, an aliquot was removed. The aliquot was then quenched with I_2 immediately after removal. To the resultant mixture, 0.1 mL of 0.1 M HCl and 1.0 mL of ether were added. Gas chromatography was used to analyze the organic layer.

Procedure for normal addition low ratio SmI_2/DPMPA$^-$ reductions of 1-chlorodecane. DPMPA (3, 6, 9 or 12 equiv) was added and allowed to dry under vacuum for at least 120 min. THF was added to solvate the solid phosphoramde. At this point, 2.5 M butyllithium (3, 6, 9 or 12 equiv) was added to solution. A 0.088 M solution of SmI_2 (3 equiv) was added. To this mixture, *tert*-butanol (2 equiv) was added. Next, tetradecane (10.0 μL, 0.0387 mmol) was added and the solution was stirred for 5 min. 1-chlorodecane (1 equiv), was then added after the solution was allowed to cool to 0 °C. At 1 min, an aliquot was removed. The aliquot was then quenched with I_2 immediately after removal. To the resultant mixture, 0.1 mL of 0.1 M HCl and 1.0 mL of ether were added. Gas chromatography was used to analyze the organic layer.

Procedure for inverse addition low ratio SmI_2/DPMPA$^-$ reductions of 1-chlorodecane. DPMPA (3, 6 or 9 equiv) was added to a pear-shaped flask and allowed to dry under vacuum for

at least 120 min. THF was added to solvate the solid phosphoramde. At this point, 2.5 M butyllithium (3, 6, 9 or 12 equiv) was added to solution. A 0.088 M solution of SmI_2 (3 equiv) was added to a Schlenck flask and cooled to 0 °C. To the SmI_2 solution, the solution of deprotonated ligand was added slowly. *tert*-Butanol (2 equiv) was added to this solution. Next, tetradecane (10.0 μL, 0.0387 mmol) was added and the solution was stirred for 5 min. 1-chlorodecane (1 equiv), was then added after the solution. At 1 min and 1 h, an aliquot was removed. The aliquot was then quenched with I_2 immediately after removal. To the resultant mixture, 0.1 mL of 0.1 M HCl and 1.0 mL of ether were added. Gas chromatography was used to analyze the organic layer.

Procedure for initial cyclization of *O*-allyl-1-bromo-2-naphthol. DPMPA (0.3785 g, 1.774 mmol) was added to a round-bottom Schlenck flask and allowed to dry under vacuum for at least 120 min. THF (1.0 mL) was added to solvate the solid phosphoramide. The solution was cooled to 0 °C, and a 2.5 M solution of butyllithium (0.698 mL, 1.7 mmol) was added. A 0.093 M solution of SmI_2 (4.69 mL, 0.44 mmol) was added to this mixture, along with *tert*-butanol (27.8μL, 0.291 mmol). The reaction was stirred and while coming to room temperature. A solution of *O*-allyl-1-bromo-2-naphthol (38.2 mg, 1.45 mmol) was added to the SmI_2/DPMPA$^-$ solution. After 30 min, the reaction was quenched with 0.1 M HCl (8 mL). 1:1 Ether:hexane was used to extract the product (3 X 5 mL). Gas chromatography and ^{1}H-NMR were then used to analyze the crude product.

Procedure for initial cyclization of *O*-allyl-1-bromo-2-naphthol adding SmI_2 last. DPMPA (0.5798 g, 2.672 mmol) was added to a round-bottom Schlenck flask and allowed to dry under vacuum for at least 120 min. THF (2.0 mL) was added to solvate the solid phosphoramide. The solution was cooled to 0 °C, and a 2.5 M solution of butyllithium (1.07 mL, 2.7mmol) was

added. t*ert*-Butanol (42.6 μL, 0.445mmol) was added to the solution. The reaction was stirred and while coming to room temperature. A solution of *O*-allyl-1-bromo-2-naphthol (38.2 mg, 1.45 mmol) was added to the SmI_2/DPMPA$^-$ solution. After 30 min, the reaction was quenched with 0.1 M HCl (8 mL). 1:1 Ether:hexane(3 X 5 mL) was used to extract the product. The organic layers were combined and the solvent was removed *in vacuo*. Gas chromatography and ^{1}H-NMR were then used to analyze the crude product.

Procedure for cyclization of *O*-allyl-1-bromo-2-naphthol without *t*-butanol. DPMPA (12 equiv) was added to a round-bottom Schlenck flask and allowed to dry under vacuum for at least 120 minutes. THF was added to solvate the solid phosphoramide. The solution was cooled to 0 °C, and a 2.5 M solution of butyllithium (12 equiv) was added. The solution was then cooled to the desired temperature and *O*-allyl-1-bromo-2-naphthol (1 equiv) was added to the solution. As soon after the addition of the substrate as possible, a solution of SmI_2 was added (3 equiv) over 2 min. After at least 30 min, tetradecane (10 μL, 0.0387 mmol) was added to the reaction was quenched with 0.1 M HCl (8 mL). 1:1 Ether:hexane (3 X 5 mL) was used to extract the product. The organic layers were combined and the solvent was removed *in vacuo*. The crude product was analyzed by gas chromatography and ^{1}H-NMR. The product was purified by column chromatography, and the purified product was characterized by ^{1}H-NMR.

Procedure for cyclization of *O*-allyl-1-chloro-2-naphthol. DPMPA (12 equiv) was added to a round-bottom Schlenck flask and allowed to dry under vacuum for at least 120 minutes. THF was added to solvate the solid phosphoramide. The solution was cooled to 0 °C, and a 2.5 M solution of butyllithium (12 equiv) was added. The solution was then cooled to the desired temperature and *O*-allyl-1-chloro-2-naphthol (1 equiv) was added to the solution. As soon after the addition of the substrate as possible, a solution of SmI_2 was added (3 equiv) over 2 min. After

at least 30 min, tetradecane (10 μL, 0.0387 mmol) was added to the reaction was quenched with 0.1 M HCl (8 mL). 1:1 Ether:hexane (3 X 5 mL) was used to extract the product. The organic layers were combined and the solvent was removed *in vacuo*. The crude product was analyzed by gas chromatography and ^{1}H-NMR.

1,2-Dihydro-1-methylnaphtho[2,1-*b*]furan. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.45 (3H, d, J = 6.9 Hz), 3.89 (1H, mult), 4.37 (1H, dd, J = 8.7 Hz, 3.8 Hz), 4.80 (1H, t, J = 8.7 Hz), 7.10 (1H, d, J = 8.8 Hz), 7.30 (1H, mult), 7.45 (1H, t), 7.70 (2H, mult), 7.82 (1H, d). MS: *m/z*184 (54), 169 (100), 141 (100) 115 (31).

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