A New Ligand for SmI_2

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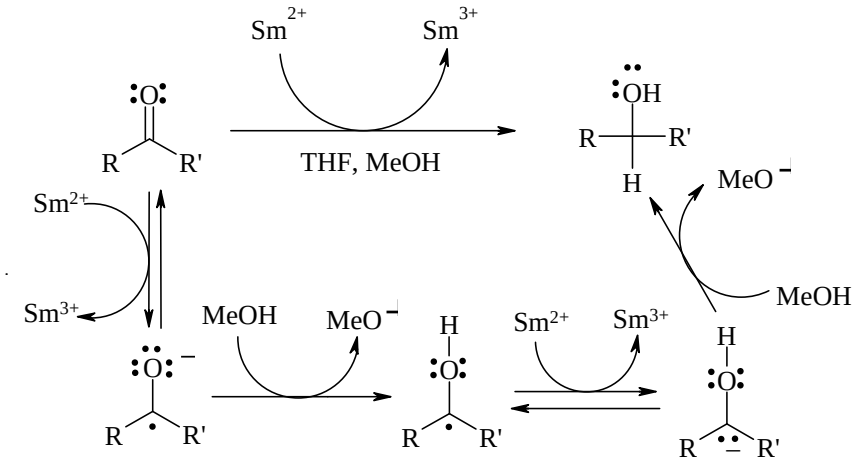
Abstract

This paper reports the synthesis of a 3-hydroxypropyl analog of HMPA. This ligand will be coordinated to SmI_2, and kinetic studies are performed. This is worthy of study because the protonation step of the reduction mechanism, which typically occurs intermolecularly in SmI_2-mediated reductions of carbonyls, will occur intramolecularly; thus, the potential exists for rate enhancement. The complex between SmI_2 and the synthesized ligand, N, N, N', N', N''-pentamethylphosphorotriamidic-N''-propan-1-ol, was able to successfully reduce 1-bromodecane and 3-octanone. However, kinetic studies performed on 3-octanone revealed a rate constant that was smaller than the rate observed for the corresponding HMPA complex.

Introduction

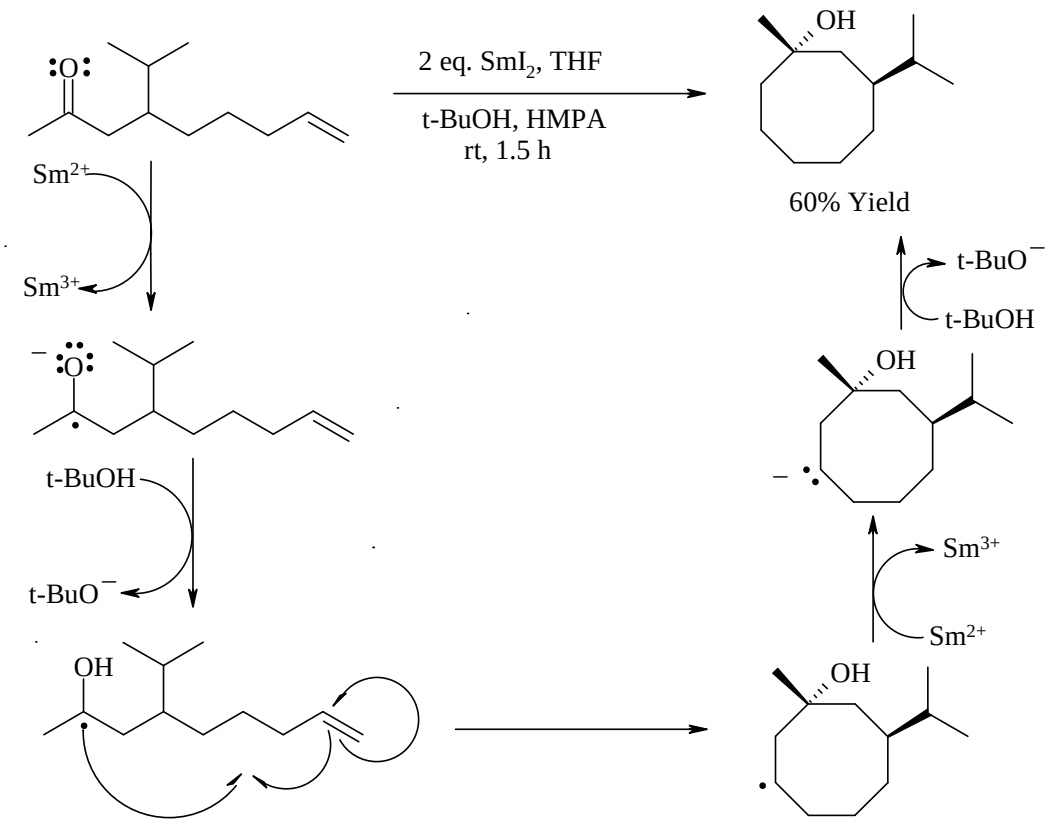
Since Kagan's discovery in 1980[1], samarium diiodide (SmI_2) has been used as a reductant in a variety of organic reactions. His experiments proved that SmI_2 can reduce organic functional groups such as halides, aldehydes, ketones, and carboxylic acids. He also concluded that under the right conditions, SmI_2 can be used to form carbon-carbon bonds.[1] In 2003, Kagan wrote an overview of the developments made since his discovery summarizing the state of the art in SmI_2-mediated reductions, citing successful organic reductions.[2] SmI_2 functions as a reductant in organic reactions by donating single electrons to the substrate. An indication of reduction can be seen because Sm^{2+} in tetrahydrofuran (THF) is dark blue, and the resultant Sm^{3+} is yellow in color.[2] An example of a carbonyl reduction can be seen in Scheme 1. In the reaction, samarium donates an electron to the original carbonyl π bond. This breaks up the carbonyl bond, which allows the proton from the methanol to create an alcohol group from the carbonyl. Samarium donates another electron to the radical formed from the first electron donation, forming an anion. Another proton donation from the methanol completes the reduction, forming an alcohol.

Scheme 1



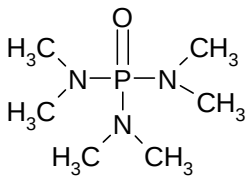
Scheme 2 shows that the intermediate carbon radical can be intercepted by a tethered alkene to ultimately construct a cyclooctanone.[2] Forming rings of this size by traditional cyclization is difficult to achieve (for entropic reasons), but is accomplished with SmI_2 in good yield. Here, reduction of the ketone is followed by addition of the radical to the alkene. This forms the ring and the resultant radical is reduced to the anion. Subsequent protonation by t-butanol yields the product.

Scheme 2



Inanaga and coworkers reported that at room temperature, the rate of reaction of ketones and esters with SmI_2 in THF was slow. However, the addition of hexamethylphosphoric triamide (HMPA, **1**) dramatically increased the rate. Without HMPA, an organic halide reduction at room temperature will take up to 6 h to fully reduce with a 95% yield.[2] Inanaga's reduction of 1-bromodecane at room temperature with HMPA proceeded to completion in 10 minutes with a yield >95%.[3] The use of HMPA with SmI_2 has since found wide acceptance in the synthetic organic community. This comes at a cost because HMPA is carcinogenic.[4] DMPU (N,N'-dimethylpropyleneurea, **2**) has been cited as a non-toxic alternative. In comparison to HMPA, there needs to be 7.5 times more DMPU to obtain the same rate using cyclic

voltammetry and there are many SmI_2-mediated reductions where DMPU is not a suitable alternative to HMPA.[5]



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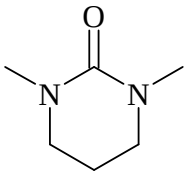
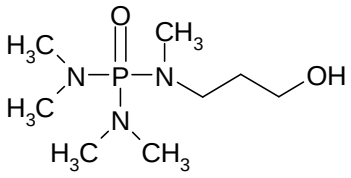


2

The goal of my research is to explore alternatives to HMPA in facilitating reduction reactions with SmI_2. An analog of **1** is synthesized, replacing one of the methyl groups with a 3-hydroxypropyl group. This compound (**3**) will be exposed to SmI_2 and the resultant complex is characterized via kinetic studies in reduction reactions. Analogous to HMPA, the ligand is expected to increase the rate of SmI_2 mediated-reductions because of the electron-rich phosphoric triamide bond (P=O), which donates electron density to Sm^{+2} when the complex is formed, thus making it easier to donate an electron. In addition, the complex may accelerate the reduction since the protonation that occurs in the second step of the reaction could be intramolecular (see Scheme 1). This second step protonation is typically the rate determining step in Sm^{2+} reductions of carbonyls and is analyzed using kinetic studies.[6]



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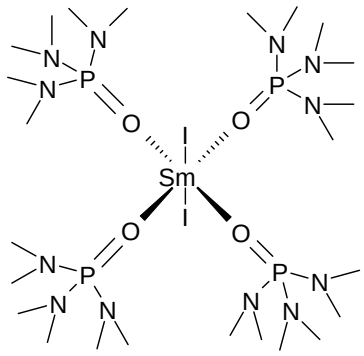
Background

Dahlén and Hilmersson have performed kinetic trials of various combinations of amines for SmI_2 ligands, with alcohols or water as the proton donor. Their highest rates and yields in a reduction of 3-heptanone have come from a combination of water and an

amine (triethyl amine, TMEDA, and PMDTA).[6] Most of the calculated values were based on estimates because the yields were 100% in only 10 s. Without a proton donor, reactions with amines were slow, taking over 3 hours to come within 0.01% yield. Water alone had a similar result, with minimal yields, but with a better rate than the amine.[6]

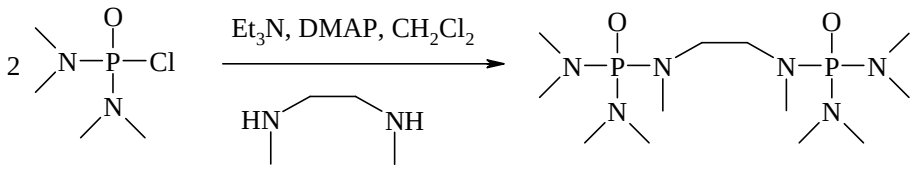
Kagan also reported the effect of HMPA on the rate of SmI_2 reductions, including the mode of coordination and the effect of other additives. The maximum rate of reaction is observed when four equivalents of HMPA are used, which is consistent with Inanaga's findings.[1] Hou has characterized the structure of the HMPA-SmI_2 complex using crystallography to be $SmI_2(HMPA)_4$**, 4**.[7] Kagan suggests that THF also coordinates to SmI_2 to produce an "ionic cluster", $[Sm(HMPA)_4(THF)_2]^{2+}\ 2\ I^-$.[1]



4

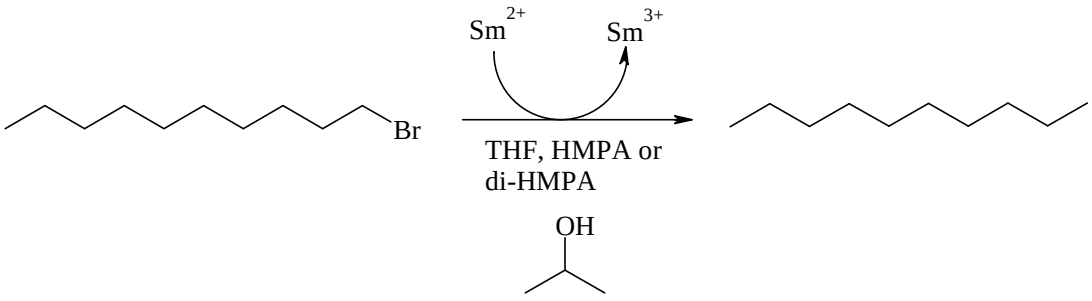
McDonald and Grant have prepared a new ligand for SmI_2 reductions: a dimeric form of HMPA simply termed "di-HMPA."[8] Di-HMPA was prepared by treating N, N, N', N'-tetramethylphophorodiamidic chloride with an amine tether, triethylamine, and DMAP in dichloromethane (Scheme 3).

Scheme 3

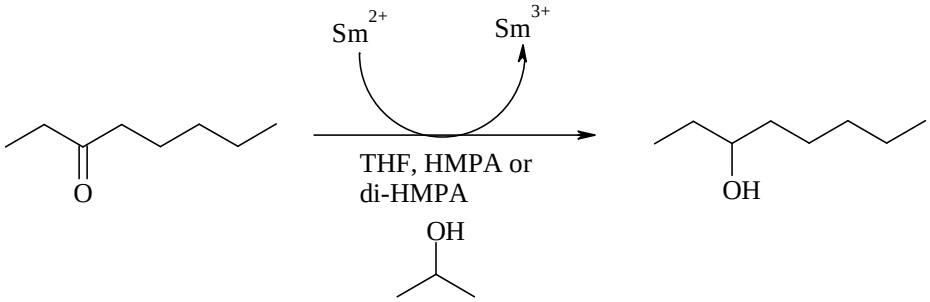


To analyze the reactivity of the HMPA and di-HMPA complexes, kinetic trials were preformed on reductions of 1-bromodecane and 3-octanone (Schemes 4 and 5, respectively). The reactions with di-HMPA were observed to be approximately 3 times slower than reactions with HMPA. However, in comparison to DMPU, the best alternative to HMPA, di-HMPA had a substantially faster rate. Moreover, if a toxicity test proves di-HMPA to be non-toxic, it would make it even more valuable as a ligand for SmI_2. It is reasonable to assume that di-HMPA will be less carcinogenic than HMPA because of di-HMPA's lower volatility. Exposure of rats by continuous inhalation to 50 ppb HMPA resulted in formulation of nasal tumors after 12 months. Feeding rats HMPA (625 mg/kg per day) for two years led to no carcinogenic effects.[9]

Scheme 4



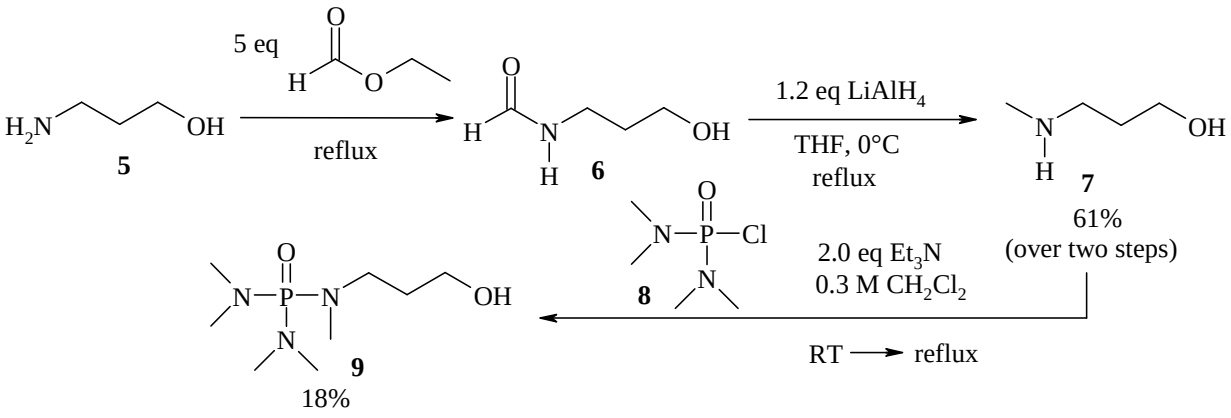
Scheme 5



Results and Discussion

Synthesis of the Ligand. The synthesis of **7** (*N*-methyl-3-hydroxypropylamine) was adapted from a literature procedure.[10] Commercially available 3-amino-1-propanol, **5**, was treated with ethyl formate to afford the corresponding formamide. Reduction of **6** with $LiAlH_4$ in THF produced **7** in 61% yield.

Scheme 6

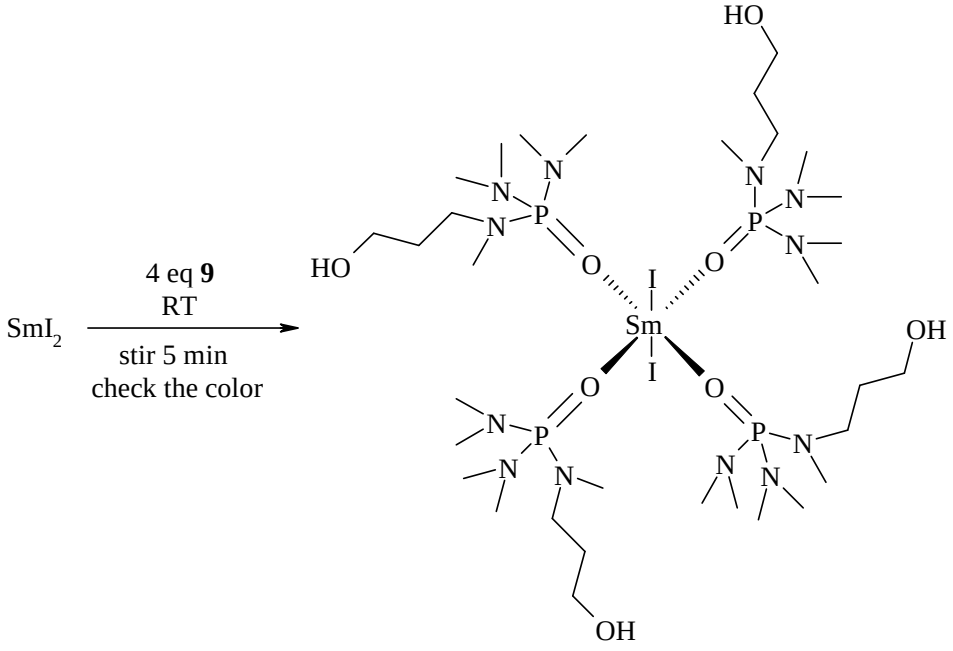


N-Methyl-3-hydroxypropylamine, **7**, was then reacted with N, N, N', N'-tetramethylphophorodiamidic chloride, **8**. The crude mixture was purified using column chromatography. Originally, the mobile phase regimen used earlier in the purification of di-HMPA performed by James Grant was utilized for this purification.[11] However problems did arise and alterations of the purification technique were made to produce a

pure ligand. Instead of purifying via column chromatography, Kugelrohr distillation was performed under 240 mTorr at 120°C. If the distillation was conducted at a higher pressure, some decomposition of the product is observed. The low yield is a result of multiple attempts at purification.

Coordinating the Ligand to SmI_2. The next task was to determine if **9** would coordinate to SmI_2 in a manner analogous to HMPA. Evidence for coordination would be a color change from blue (the color of SmI_2 in THF) to purple. Electron-rich ligands such as HMPA, di-HMPA, and DMPU form a purple complex with SmI_2.[2] SmI_2 was added to a Schlenk flask containing 4 equivalents of compound **9** under an argon atmosphere (Equation 1). A purple color indicated that the ligand had been successfully coordinated. This purple color is visually consistent with the color that results when HMPA or di-HMPA is coordinated to SmI_2.

Equation 1



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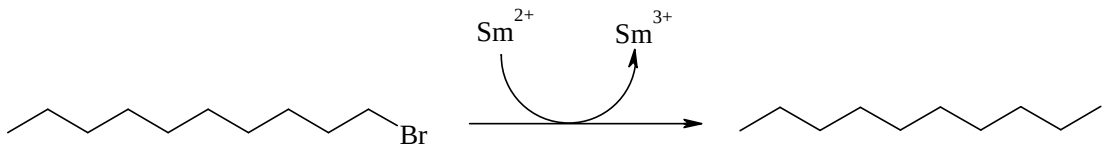
A problem was observed with initial attempts at forming the complex of SmI_2 and compound **9**. Upon addition of SmI_2 to the ligand, the initial purple color would dissapate over a 5 min period. This was attributed to trace impurities in the ligand. Evidence of these trace impurities could be found by TLC after purification by column chromatography. The TLC plate of the impure ligand had shown multiple markings around the area where the ligand was believed to exist on the plate. When properly purified ligand **9** (by Kugelrohr distillation) was complexed with SmI_2, the purple color would persist for hours.

Characterization of the SmI_2 Complex. To prove that the complex was capable of reacting, a sample reduction was performed. Since ligand **9** is an analog of HMPA, the complex was expected to reduce alkyl halides and carbonyl compounds, such as 1-bromodecane or 3-octanone. 1-Bromodecane was added to a reaction vessel of the complex along with tetradecane as an internal standard. Within fifteen minutes of addition, the purple color changed to a pale yellow color, indicating complete consumption of the Sm^{2+}. Gas chromatography analysis revealed a 49% yield of product. This provided evidence that this complex can reduce alkyl bromides in a manner that is similar to that of the HMPA-SmI_2 complex.



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In addition to the 1-bromodecane reduction, a kinetic study on the reduction of 3-octanone was performed. Once the 3-octanone was added to the complex, aliquots were removed and quenched (with I_2). The quenched solutions were analyzed by GC with

dodecyl alcohol as the internal standard (Figure 1).

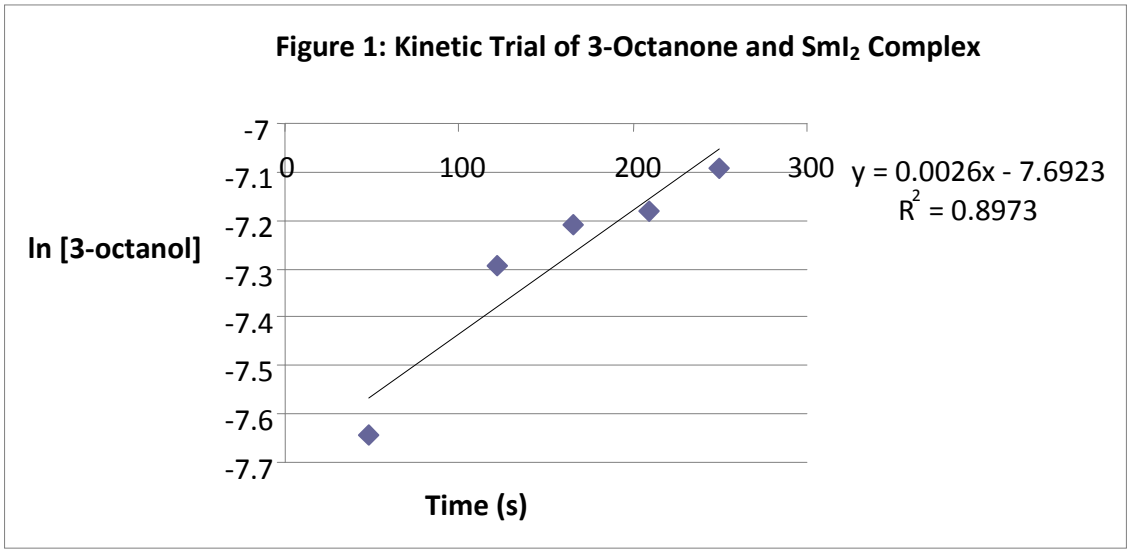


Table 1: Kinetic Trial of 3-Octanone and SmI_2 Complex

Time (s)	[3-octanol]	ln[3-octanol]
48	0.00048	-7.641724454
122	0.00068	-7.29341776
166	0.00074	-7.208860372
209	0.00076	-7.182192125
250	0.00083	-7.094084857

Table 2: Reaction Rates of Ligands

Ligand	Rate Constant (s^{-1})
Di-HMPA	0.0054
HMPA	0.0045
9	0.0026
DMPU	0.0

Figure 1 relates the concentration of the reduced product, 3-octanol, to the

duration of the reaction. The slope of the curve is the rate constant (s^{-1}) which is compared to the rate constants determined in this laboratory in Table 2. Even though the R^2 shows that the calculated slope has error, it does provide enough evidence to draw a conclusion.

Although there was starting material present from the GC analysis (showing that the reaction did not proceed to completion), results from the test reduction of 1-bromodecane provide evidence that the complex is capable of reducing alkyl bromides in a similar manner for reactions typical to SmI_2.[3]

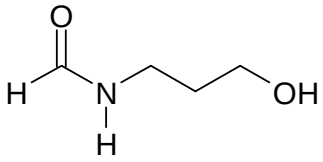
Kinetic studies of 3-octanone confirmed that the complex can reduce a ketone as well and at a moderate rate, albeit at a slower rate than that observed for di-HMPA and HMPA complexes.[11]

Future work will entail varying the length of the tether between phosphoamide and alcohol, which may affect the rate of reduction. It would also be valuable to analyze the complex via UV-vis spectrometry to observe if the alcohol on the ligand has complexed to SmI_2 as well.

Experimental

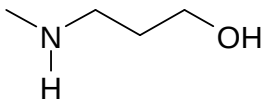
General Methods. All reactions were performed under a nitrogen or argon atmosphere unless otherwise noted. Glassware and syringes were oven-dried and subsequently cooled under nitrogen atmosphere. All distillations were performed under nitrogen or argon. Solvents and reagents were distilled with the following drying agents: THF was distilled with sodium/benzophenone, CH_2Cl_2 was distilled from CaH_2, and Et_3N was distilled from CaH_2. Column chromatography was performed using silica gel with varying proportions of hexane and ethyl acetate. The product from column chromatography was identified through thin-layer chromatography, using plastic-backed

alumna plates with 100% ethyl acetate as mobile phase. TLC plates were visualized by placing the plates into I_2 chambers for durations of 10-15 minutes. SmI_2 used in the reductions was provided in a 0.1M solution in THF. Nuclear Magnetic Resonance spectra were recorded on a Bruker 300 Avance NMR Spectrometer. ^1H spectra were recorded at 300 MHz, using $CDCl_3$ as the solvent and TMS as the reference peak ($\delta = 0$).



6

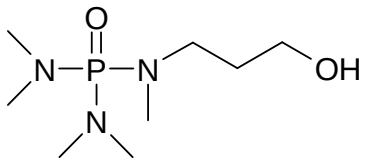
***N*-Formyl-3-amino-1-propanol (6).** Ethyl formate (107 mL, 1.33 mol) and 3-amino-1-propanol (20.0 g, 0.266 mol) were added to a 250-mL round bottom flask with a stir bar. A condenser was attached and the solution was refluxed for 2.25 h. The solvent was removed under reduced pressure. The product was used without purification. ^1H NMR (300 MHz, $CDCl_3$, δ), 1.69 (p, 2H, $CH_2C\mathbf{H_2}CH_2$), 3.37 (m, 2H, $CH_2C\mathbf{H_2}OH$), 3.63 (t, 2H, $NHC\mathbf{H_2}CH_2$), 4.07 (b, 1H, OH), 6.99 (b, 1H, NH), 8.11 (s, 1H, HCO).



7

***N*-Methyl-3-hydroxypropylamine (7).**[10] N-Formyl-3-amino-1-propanol, (10.0 g, 0.0970mol), was added to dry THF (8 mL) in an addition funnel. The mixture was added to a vigorously stirred 0°C suspension of $LiAlH_4$ (4.42 g, 0.116 mmol) in THF (33 mL) in a 500-mL three-neck round bottom flask with a stir bar, and a condenser attached to the opposite neck along with a septum on the middle neck at 0 °C. The reaction was

heated to reflux for 3 h, and then cooled back to 0 °C, where water (4.42 mL) was added slowly followed 10% NaOH (13.3 mL) and water (4.42 mL) again to hydrolyze the mixture. The resultant suspension was filtered, then the solid was transferred back to the funnel where ethyl acetate was added and refluxed for 5 min and filtered again. This process was repeated two more times. The solvent was then removed under reduced pressure. The filtrate was then dried with sodium sulfate, filtered and distilled (BP = 50°C, 500 milliTorr) with a 61% yield (5.2 g).[10] ^{1}H NMR (300 MHz, $CDCl_3$, δ), 1.54 (p, 2H, $CH_2C\mathbf{H_2}CH_2$), 2.25 (s, 3H, NHC$\mathbf{H_3}$), 2.59 (t, 2H, CH_2N), 3.28 (b, 2H, NH and OH), 3.54 (t, 2H, CH_2O).



9

***N, N, N', N', N''*-Pentamethylphosphorotriamidic-*N''*-propanol (9).** In a 30-mL syringe, *N*-methyl-3-hydroxypropylamine **7** (5.206 g, 0.05839 mol) was added to Et_3N (16.2 mL) and CH_2Cl_2 (130 mL) in a 250-mL round bottom flask with a stir bar. N, N, N', N'-Tetramethylphosphorodiamidic chloride (8.65 mL, 0.0584 mol) was added via 10-mL syringe to CH_2Cl_2 (65 mL) in an addition funnel. The resultant solution was slowly added to the round bottom containing the amine. The reaction stirred overnight and was extracted the next day with $NaCl_{(aq)}$ (1x 50 mL) and CH_2Cl_2 (1x 50 mL) into a 500-mL Erlenmeyer flask. The product was dried with sodium sulfate and a small amount of sodium carbonate. After removing the drying agents by filtration, the solvent was removed under reduced pressure. Originally the product was purified via column chromatography, using 200 mL of 25% hexane/ 75% ethyl acetate and 1.5 L of 100%

ethyl acetate. Pure ligand was obtained via Kugelrohr distillation at ~120 °C and 240 mTorr with an 18% yield. ^{1}H NMR (300 MHz, $CDCl_3$, δ), 1.97 (p, 2H, $CH_2C\mathbf{H_2}CH_2$), 2.62 (m, 15H, $(CH_3N)_5$), 3.04 (q, 2H, CH_2N), 3.53 (t, 2H, CH_2OH).

Reduction of 1-bromodecane with SmI_2 and Ligand 9. A 15 mL Schlenk flask was cooled to room temperature, tared, evacuated and filled with argon. Ligand **9** (0.295 g, 1.32 mmol) was added to the flask with 2 mL of toluene, which was then evacuated to dry the ligand azeotropically. After backfilling with argon, SmI_2 in THF (3.30 mL, 0.330mmol) was introduced to the flask and the resulting purple solution was observed. Then 1-bromodecane (17.1 µL, 0.0825 mmol) and tetradecane (21.4 µL, 0.0825 mmol), the internal standard, were added to the reaction vessel. When the reduction was complete, a 200 µL aliquot was removed and treated with 100 µL of 0.1 M HCl and 1mL of ether. The organic layer was then removed and placed into a vial for GC analysis.

Rate constant determination for the reduction of 3-octanone with SmI_2 and Ligand 9. A 15 mL Schlenk flask was cooled to room temperature, tared, evacuated, and filled with argon. After backfilling, ligand **9** (0.390 g, 1.75 mmol) was added with Toluene to the flask under reduced pressure for 3h to dry the ligand azeotropically. Once the flask was filled with argon, SmI_2 in THF(4.4 mL, 0.44 mmol) was added to the vessel and cooled to 0°C. Then 3-octanone (9.3 µL, 0.060 mmol) and dodecyl alcohol (11 µL, 0.0490 mmol), the internal standard, were added to the flask. Every minute, a 200 µL aliquot was removed from the vessel and quenched in a vial with 100 µL 0.1 M solution of I_2/ether for a total of 6 min. After quenching, 100 µL of 0.12 M HCl and 1 mL of ether were added to the vials and the organic layer was extracted for GC analysis.

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