# The Use of Amides as Substrates in Radical Cyclization Reactions

Presented to the Faculty of Lycoming College
For Departmental Honors in Chemistry

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*Abstract:*

Samarium diiodide has been shown to be a versatile one-electron reductant for halides and carbonyl compounds and has shown great synthetic utility in generating carbon-based radicals from a variety of organic functional groups. Previously, research was performed to examine the use of various carbonyl and masked carbonyl derivatives as radical precursors with the ultimate goal of adding the incipient radical to alkenes in an intramolecular fashion. Previously, work has involved treating amides with triflic anhydride as the electrophile, then adding samarium diiodide and HMPA, and eventually water. Yields were meager and significant amounts of starting amide were recovered. Recently, nickel iodide was used as an electron transfer catalyst, along with t-butanol, which increased yields significantly. Overall, the parent reaction of this series was optimized. Now attempts are being made to examine the effect of substitution on the various atoms of the incipient ring, whether 6-membered rings can be formed, and whether an intermolecular version of the reaction is viable.

*Introduction:*

One of the greatest feats in synthetic organic chemistry is the formation and manipulation of carbon-carbon bonds. The past twenty years has been a remarkable time for the development of various methodologies in radical synthetic chemistry. Samarium diiodide has been shown to be a versatile one-electron reductant for halides and carbonyl compounds. But little work has been done using amides as radical precursors in similar reactions due to their low reactivity as electron acceptors. However, amides are active nucleophiles. If amides are treated with an appropriate electrophile, they become a species that is more receptive to reduction. The resultant radical can serve as the

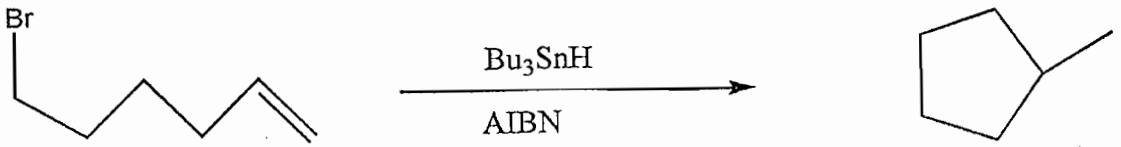
"initiator" for the new carbon-carbon bond formation given that a carbon radical acceptor functionality is present within the molecule. The radical acceptor functionality can possibly be an alkene with an appropriate conjugated electron withdrawing group.

***Background:***

The main goal of this project was to find new methods for generating radicals for the synthesis of intramolecular carbon-carbon bonds. There are many well-established radical reactions that have been previously exploited to produce a 5-exo-trig cyclization. Overall, the preference for ring formation begins with 5-membered rings then 6 and eventually 7-membered rings.[1] The cause for this preference has been traced to stereoelectronic effects. In order for bonding interaction to occur, the radical center must interact with the $\pi^*$ orbital of the alkene. According to molecular orbital calculations, a preferred direction of attack is from an angle of about $70^0$ with respect to the plane of the double bond. Most ring closures also prefer exo cyclizations because they are easier and faster to form. They are also favored because steric and angle strain imposed on the transition state is lessened.[2]

For example, Scheme 1 involves a common way to induce a 5-exo-trig cyclization using tributyltin hydride on olefinic halides. In this case, the alkyl bromide (1) is the radical precursor, and the radical is generated by abstracting the bromine. Overall, the substrate was treated with $Bu_3SnH$ and AIBN to produce the methyl cyclopentane (2) and cyclohexane (not pictured) in a 49:1 ratio.[3]

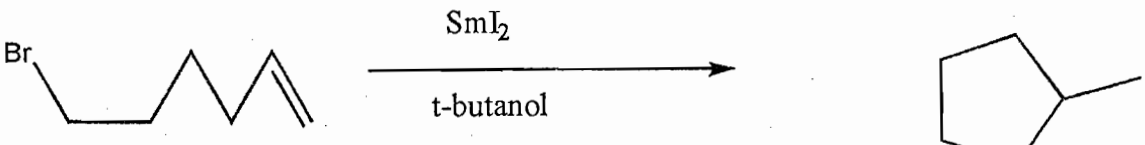
**Scheme 1**




1 2

In Scheme 2, Molander and co-workers now use samarium diiodide and t-butanol on the olefinic halide to produce the five-membered ring (4).[4]

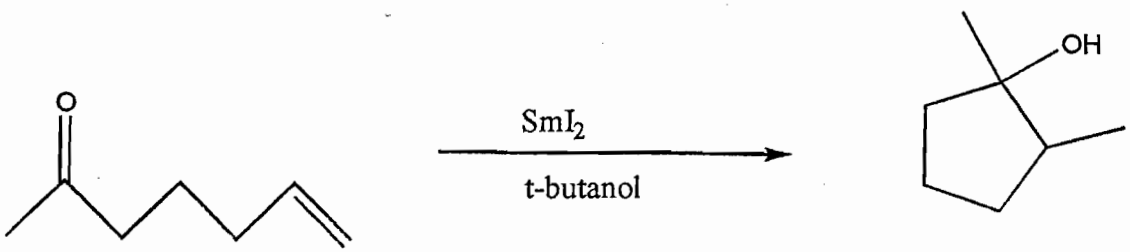
**Scheme 2**




3 4

And in Scheme 3 , Molander demonstrates how olefins with ketone or aldehydic functional groups attached can also be reduced by $SmI_2$ to produce the five-membered ring (6).[4]

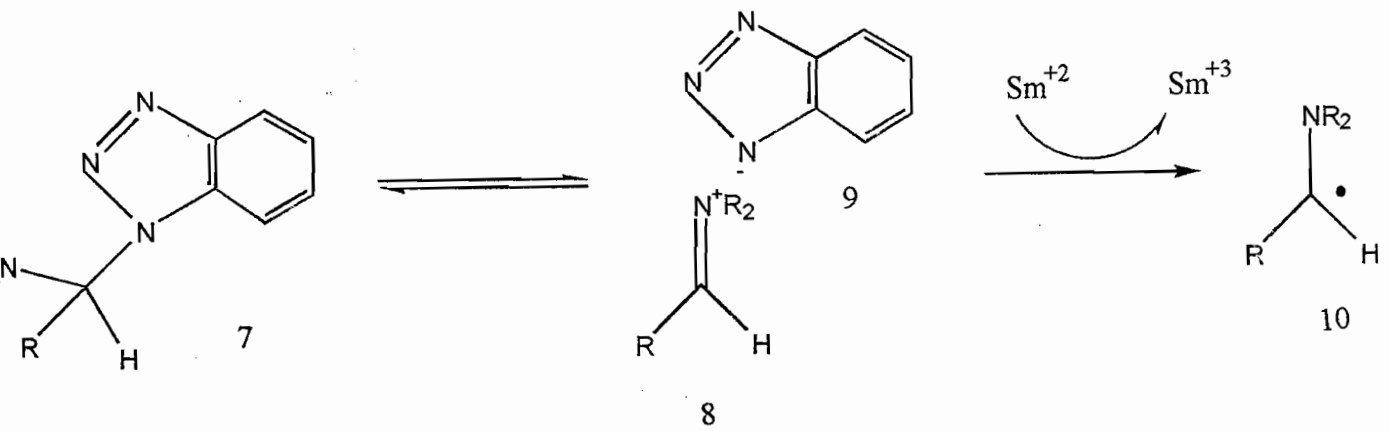
**Scheme 3**




5 6

Work by Aurrecoechea, shown in Scheme 4 is actually where the idea of this project originated. In this reaction, a N,N acetal (7) is used as a radical precursor. Loss of benzentriazole produces an iminium cation (8). The cation (8) is then reduced by $SmI_2$ to form a nitrogen stabilized radical which is capable of reacting with appropriately situated olefins.[5] The efforts of this project will focus on mechanistically similar radical generation methods using various amide substrates. Aurrecoechea's N-N acetals are not robust molecules, whereas the amides that will be used in this project are very stable carbonyl derivatives that can be purified by chromatography..

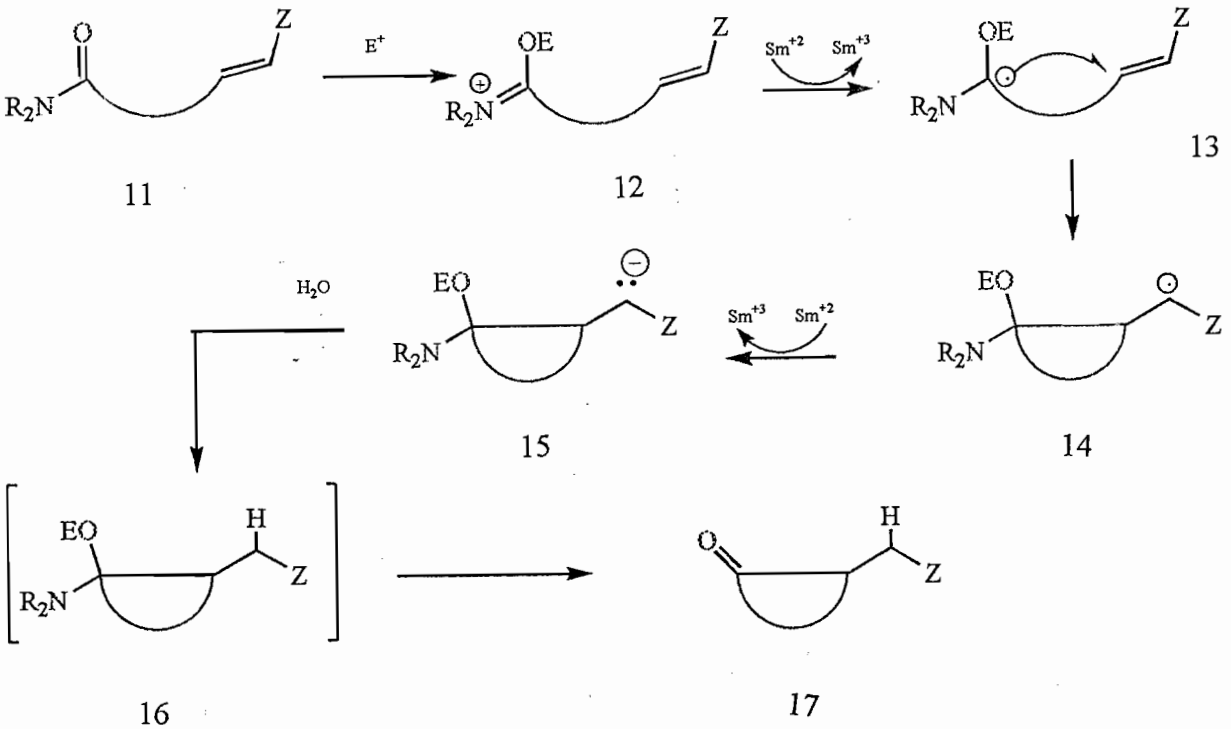
**Scheme 4**




The focus of this project has originally been to optimize the parent reaction. In Scheme 5, the amide (11) is treated with an appropriate electrophile. The electrophile will react at the oxygen to produce an oxygen-substituted iminium ion (12). One electron reduction by samarium diiodide should then provide the requisite radical which in turn could react with an activated olefin to produce a product radical (14). Treatment with $SmI_2$ again produces the enolate (15), which is then protonated by water. Finally, a

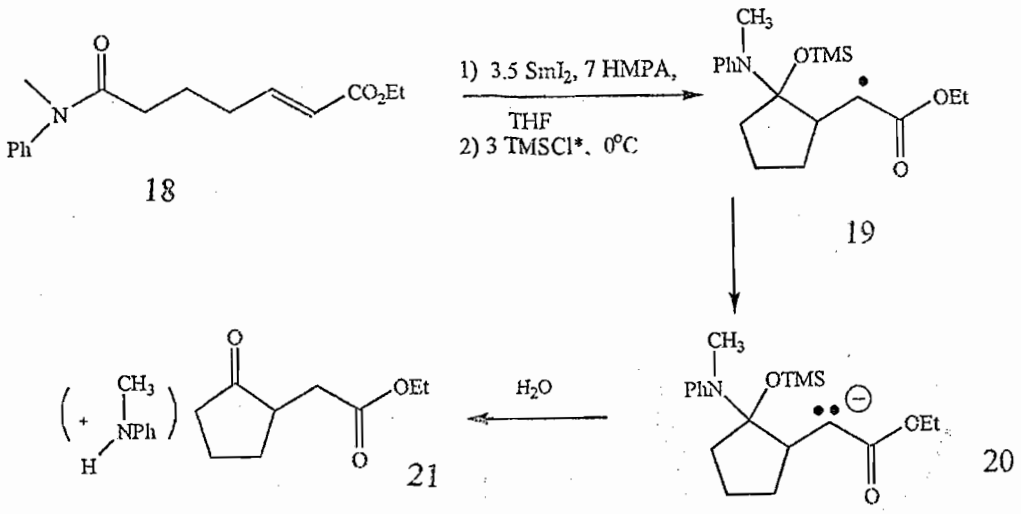
hydrolysis reaction takes place with the water to form the carbonyl attached to the five-membered ring (17) and liberate N-methyl aniline.

**Scheme 5**




An initial test reaction was performed in 1998 in Dr. McDonald's laboratory (see Scheme 6 ). The initial reaction used chlorotrimethylsilane as the electrophile which produced a 22% yield of cyclized product (21).

**Scheme 6**




Since then many variables have been examined, which include varying the proportions of chemicals, identifying the appropriate electrophile, the use of HMPA to increase the reactivity of the $Sm^{+2}$ reagent, temperature, order/timing of addition, the nature of the amide N-moieties, the identity of the solvent, and potential catalytic variants of the reaction.

First, various electrophiles were tested to determine which was best suited for the reaction. Problems were encountered while testing the various electrophiles (see Scheme 7). The electrophile would react with the THF (22) in the $SmI_2$/THF solution to produce various ring opened (23) by products. In this competing side reaction, it was believed that the nucleophilic oxygen of the THF would attack the electrophile. The molecule would then undergo a nucleophilic substitution with iodide as the nucleophile. Triflic

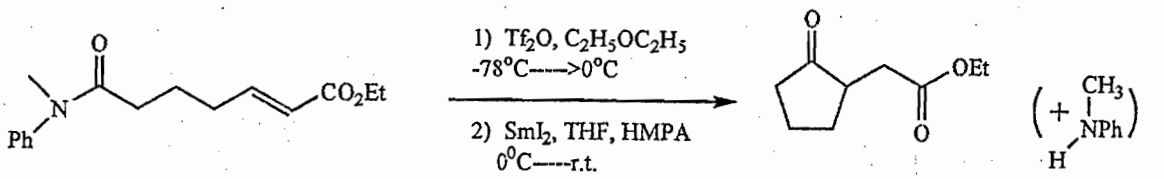
anhydride and chlorotrimethylsilane, if used in correct amounts and at sufficiently low temperatures minimized this competing side reaction.[6]

**Scheme 7**


22 23

Overall, triflic anhydride proved to be the best electrophile (see Scheme 8). The amide (18) was treated with 1.05 eq. triflic anhydride in ether at –78°C and then $SmI_2$ in THF along with HMPA was added to produce the cyclized product (24) in a 39% yield.

**Scheme 8**

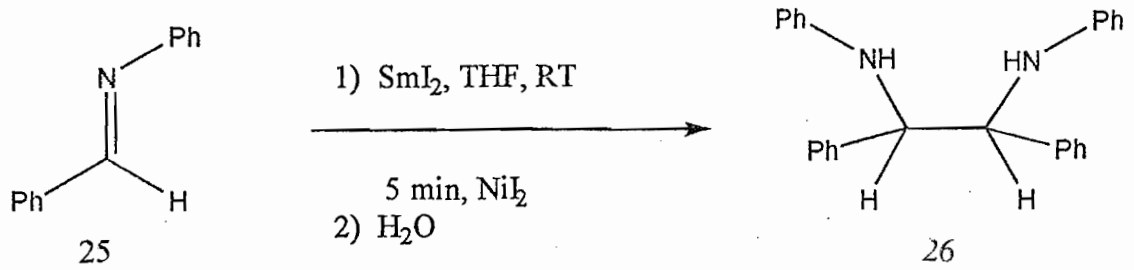



18 24

After a year of little improvement in yields, a literature search revealed the use of nickel iodide as an electron transfer catalyst with $SmI_2$ (see Scheme 9). If the $NiI_2$ was used with the $SmI_2$ the reaction occurred in 5 minutes. Without $NiI_2$ present, the reaction

took six to twelve hours at 65°C..[7] Therefore $NiI_2$ seemed to greatly facilitate electron transfer in $SmI_2$ reactions and would replace HMPA in future reactions.

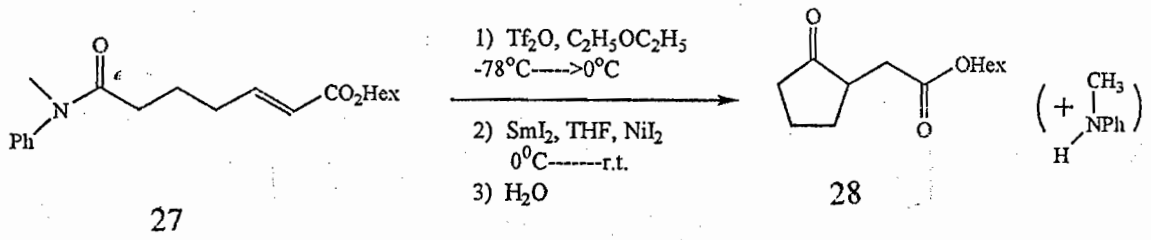
**Scheme 9**




25 26

A reaction was then performed with $Tf_2O$, $SmI_2$, and $NiI_2$, to produce a yield of 64% (see Scheme 10).

**Scheme 10**



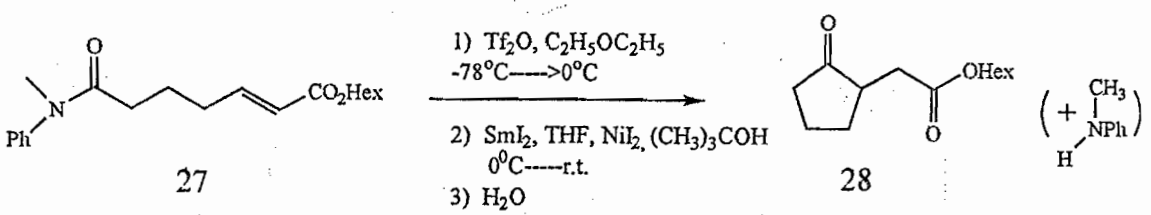

27 28

During this time, various attempts were made by Dr. McDonald and co-workers to identify the best combination of R-groups on the nitrogen. A combination had to be chosen that would provide the best environment for radical formation. If the amide carbonyl π-system was too electron rich, the radical formed may prove too stable to react. Whereas, if the amide carbonyl π-system was too electron poor, the initial

nucleophilic/electrophilic reaction to produce the oxygen substituted iminium ion may not occur. Therefore, various R-groups were chosen that would modify the electron donating capabilities of the nitrogen's lone pair. Some R-groups were chosen that would slightly tie up the lone pair on the nitrogen via resonance. Overall, it was determined that the best combination included the methyl and phenyl substituents.

Overall, the optimized reaction has been achieved, by treating the amide (27) with triflic anhydride in ether at –78 $^0$C then adding the samarium diiodide in THF along with nickel iodide used as an electron transfer catalyst and t-butanol to protonate the resulting enolate at 0$^0$C (see Scheme 11). This produces the desired five-membered ring (28) in an 87% yield. Now attempts are being made to vary the chain length, to see if an intermolecular version of the reaction is possible, and to uncover the best functional group to activate the alkene as a better radical acceptor.

**Scheme 11**



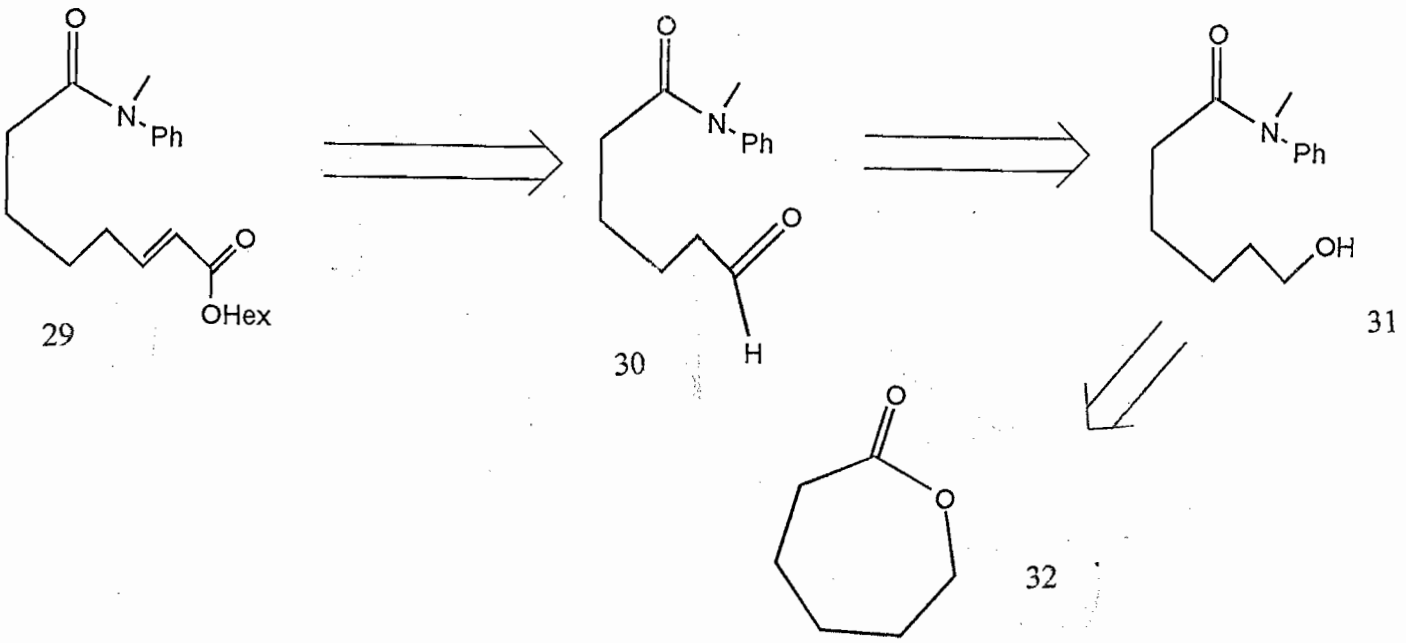

27 28

***Results and Discussion***

The compound *trans*-N-hexyl-8-(N-methyl-N-phenyloxamido)-2-octenoate (29) needed to be synthesized in order to attempt a samarium reaction that would result in a six-membered cyclized product. Retrosynthetically in Scheme 12, the substrate (29) can

be envisioned to be constructed from aldehyde (30). In turn, the aldehyde is generated by a single oxidation of the primary alcohol (31) . The starting material for this synthesis is 6-hexanolactone (32), which will provide a difunctionalized terminally differentiated reagent after ring-opening.

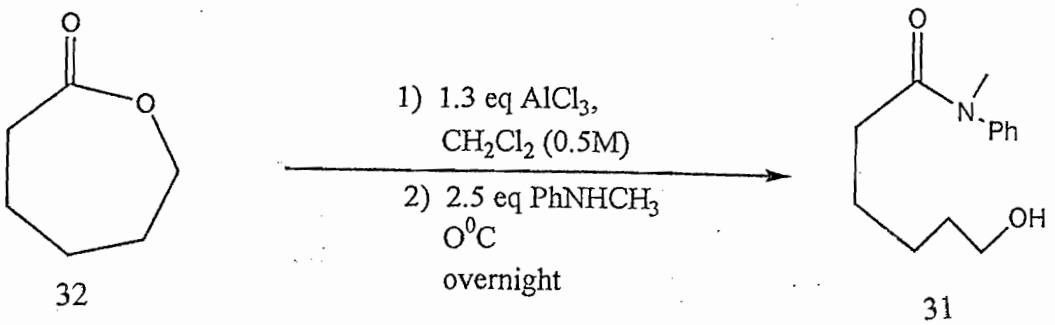
**Scheme 12**




The first step in the synthesis that converted the lactone (32) to the ring-opened hydroxyamide (31) was a successful reaction that produced a 63% yield after column chromatography (see Scheme 13). Upon completion, the product was characterized through $^{1}H$ NMR and IR. In this synthesis the lactone was treated with aluminium chloride and N-methylaniline in a Lewis acid catalyzed nucleophilic acyl substitution

reaction to produce the ring opened hydroxyamide. This reaction was performed according to a procedure developed by Lesimple and Bigg. The researchers stated that medium-ring lactones react cleanly with primary and secondary aliphatic or aromatic amines in the presence of aluminum chloride at room temperature to afford ω-Hydroxyalkylamides.[8]

**Scheme 13**

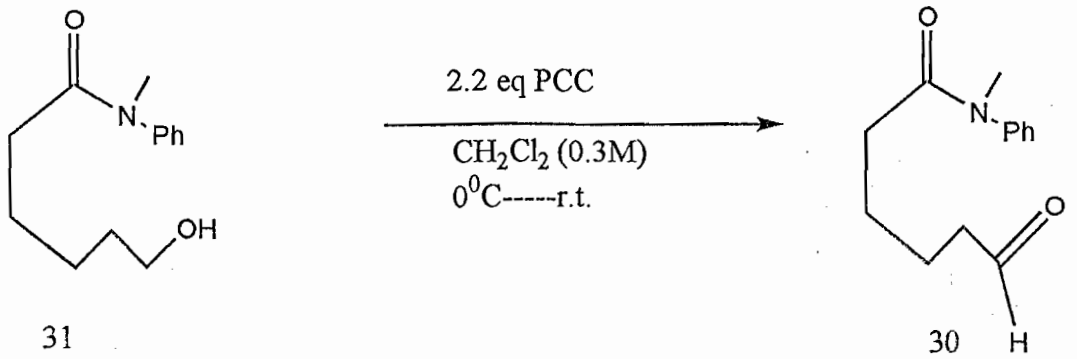



32 31

The next step of the synthesis was the pyridinium chlorochromate reaction (see Scheme 14). The aldehyde (30) was formed from the alcohol (31) by treating the alcohol with PCC. Corey and Suggs found that PCC is a good reagent for limited oxidation of primary alcohols to aldehydes. It provides high efficiency and can be particularly useful for moderate to large scale oxidations.[9] Therefore it was used immediately in the Wittig reaction. But the PCC reaction was TLC'd against the starting material after two hours of stirring to see if aldehyde was present. The TLC indicated some starting material present, so more PCC was added and it stirred for another twenty minutes before quenching the reaction and using it in the last Wittig reaction sequence. The aldehyde synthesized was never characterized according to $^1H$ NMR and a yield was

never calculated because aldehydes are only moderately stable. In the future, we plan to use a Swern oxidation because we are unsatisfied with PCC.

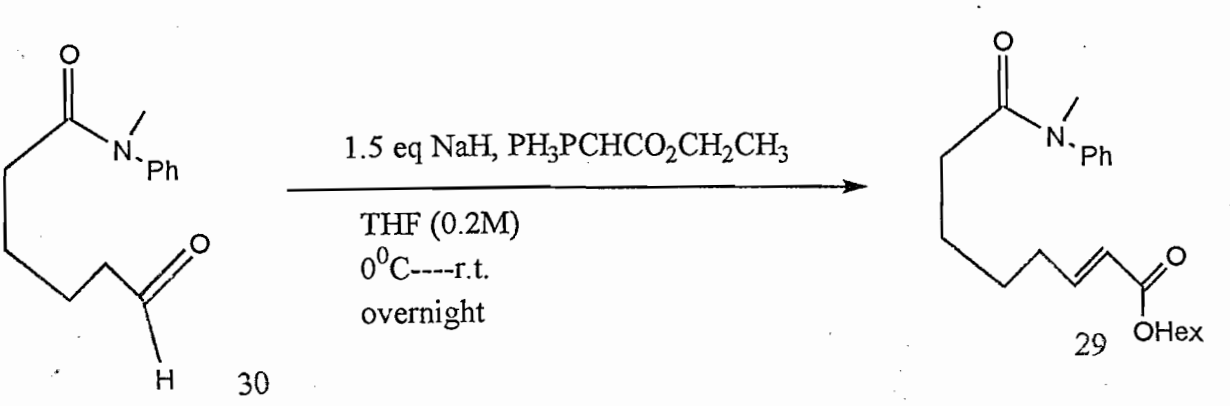
**Scheme 14**




31 30

In Scheme 15, the substrate (30) underwent a Wittig reaction to insert the alkene into the four carbon chain. This is a well-established reaction that was discovered in 1954 by Georg Wittig.[10] Although the Wittig reaction produced the appropriate product, it is believed that this reaction occurred under non-optimized conditions because the yield of 33% was rather meager. The Wittig reagent, carbhexoxymethylene triphenylphosphorane, is synthesized in this lab and was about nine months old. Therefore it is believed that the reaction would have produced a better yield if the Wittig reagent was newly synthesized. After column chromatography the product was confirmed through $^1$H NMR, which indicated the presence of the trans alkene hydrogens ($^3$J=15.6 Hz) and absence of the aldehydic hydrogen. The product was also confirmed through IR and $^{13}$C NMR.

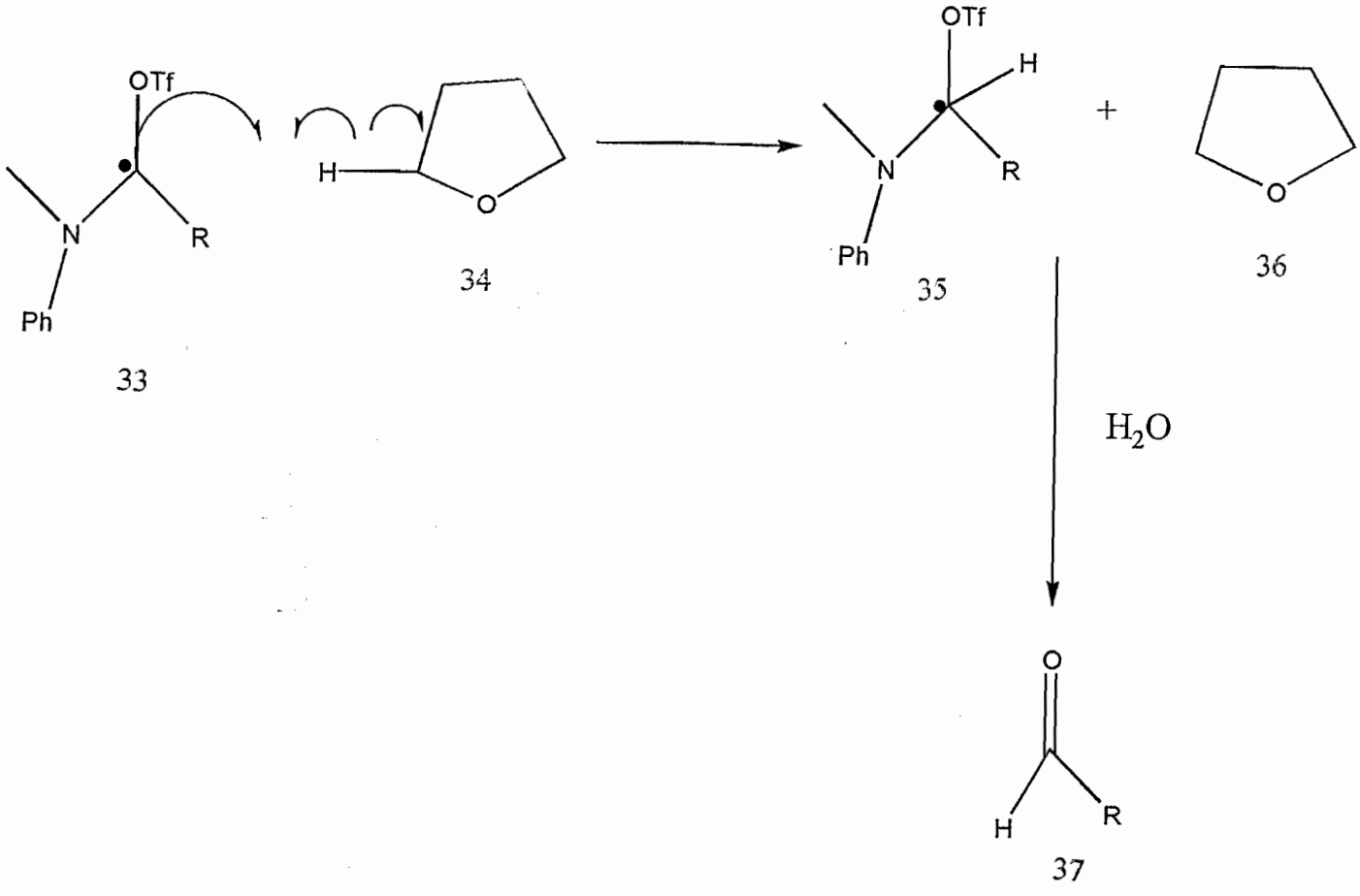
**Scheme 15**




30 29

Once the appropriate substrate was synthesized, several $SmI_2$ reactions were performed. In the first reaction performed, 0.10 eq. $NiI_2$ was added to the amide. Then 1.2 eq $Tf_2O$ and dry ether were added to the reaction flask at $-78^0C$. The reaction was allowed to warm to $-20^0C$ and 4 eq. $SmI_2$ along with 2 eq. t-butanol were syringed into the flask simultaneously. The reaction was allowed to warm to room temperature and stir for 2 hours. After column chromatography, the product was isolated with THF ring opening product as a contaminant. Along with THF ring opening, aldehyde was also isolated (see Scheme 16). This became a problem in this reaction. It is assumed that the radical that forms on the carbon abstracts a hydrogen from the THF (33) solution, which eventually forms the aldehyde (37) when water is added. Logically, the longer the carbon chain, the longer the time it would take this molecule to cyclize and therefore would give this side reaction more time to occur.

**Scheme 16**

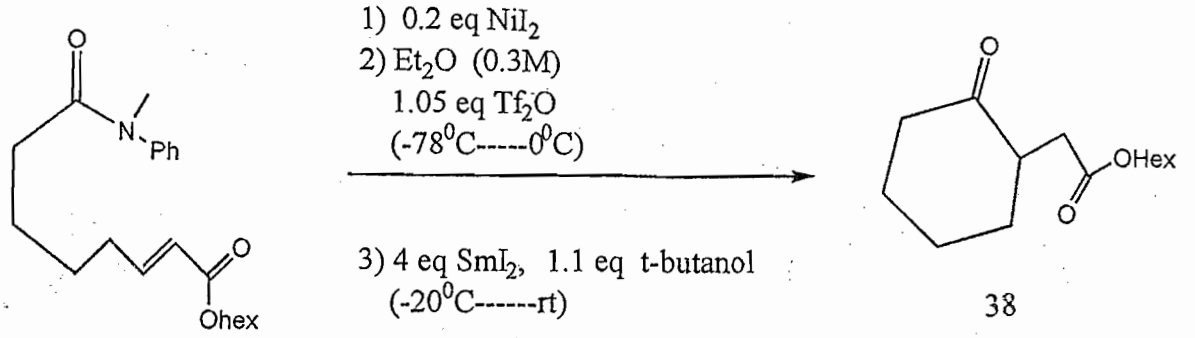



In the next $SmI_2$ reaction, the $NiI_2$ was increased to 0.20 eq , and it appeared that after column chromatography the same results were obtained. There was still a significant amount of a mixture of THF ring opened by product and desired product. Aldehyde along with starting material were also recovered.

Therefore in the next $SmI_2$ reaction, the $Tf_2O$ was decreased to 1.05 eq (see Scheme 17). After column chromatography, pure cyclized product (38) was obtained in a 17% yield. This was confirmed both through $^1H$ NMR, $^{13}C$ NMR, and IR. But 18% aldehyde

was recovered along with 51% starting material. Overall, it appeared that the decrease in $Tf_2O$ helped to eliminate THF ring opening.

**Scheme 17**

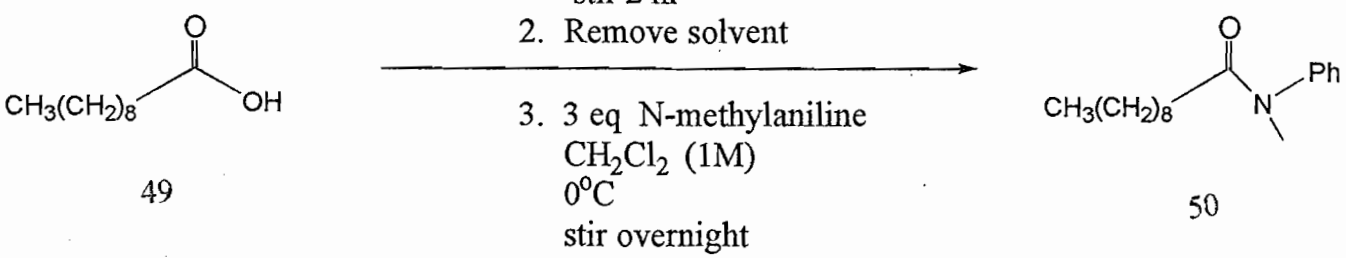



29 38

The reaction was attempted one more time. This time the amide was treated with 1.1 eq. $Tf_2O$ but the $SmI_2$ was increased to 5 eq. After column chromatography, the pure cyclized product was obtained in a 14% yield and was confirmed through $^1H$ NMR. Aldehyde was recovered in a 7.8% yield along with starting material in a 49% yield, and it appeared that THF ring opening was eliminated.

An attempt was also made to see if an intermolecular version of this reaction is viable. First, the test substrate was synthesized from decanoic acid (39), treating it with oxayl chloride, and then N-methyl aniline in a nucleophilic acyl substitution reaction to afford the appropriate substrate (see Scheme 18). The amide product was characterized by $^1H$ NMR.

**Scheme 18**

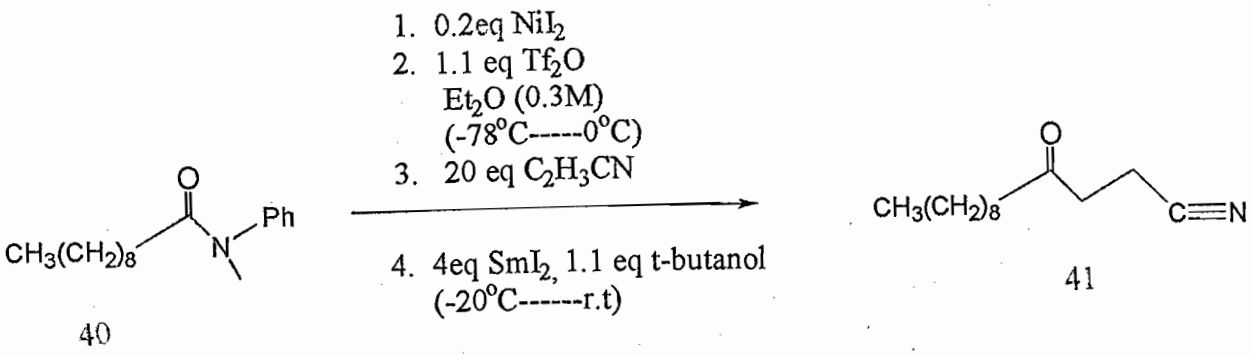



49 50

Several $SmI_2$ reactions were then performed with this substrate. In the first reaction, 119 mg of amide (40) was treated with 0.20 eq. $NiI_2$, 1.1 eq $Tf_2O$, 5 eq. acrylonitrile, 5 eq. $SmI_2$, and 2 eq. t-butanol. After column chromatography, there was no product found, but THF ring opening was evident. Starting material was also recovered.

When the reaction was performed again, all conditions remained the same, but the acrylonitrile was increased to 20 eq. (see Scheme 19). After column chromatography, a mass spectrum was taken of two separate column chromatographic groupings, which indicated the presence of both a mixture of product, starting material, and other unidentified impurities. These groups were combined and chromatographed again. Unfortunately, a combination of starting material and product was recovered once again. From the $^1H$ NMR taken a yield of product was calculated to be 9% with a mixture of approximately 17% starting material.

**Scheme 19**




40 41

The reaction was performed one more time. All conditions remained the same, except the $SmI_2$ was increased to 5.5 eq. and 200 mg of the starting amide (40) was used. The results were similar to the previous attempted reaction. After column chromatography, the product was again not obtained in pure form. It was a combination of both product and starting material. From the $^1H$ NMR, a 5% yield of product was determined.

***Conclusion:***

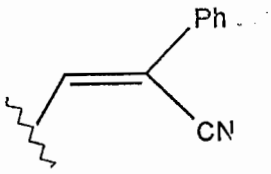
Overall the synthesis of the six-membered ring substrate was successful. It appears that a six-membered ring is possible but is much more difficult to form. The conditions were altered several times and although THF ring opening product was eliminated, a considerable amount of starting material and aldehyde still resulted.

Likewise, the synthesis of the intermolecular substrate was successful. It also appears that an intermolecular version of this reaction is possible but is much more difficult to perform. The conditions were altered several times, like in the 6-exo-trig cyclization, and although THF ring opening product was eliminated, the final product

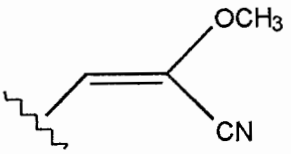
was never recovered in pure form. The material recovered was a combination of both product and starting material. It appears the oxygen and nitrogen substituted radical is not sufficiently reactive to be useful in intermolecular carbon-carbon bond forming reactions, even with the excellent radical acceptor, acrylonitrile.

***Future Exploration:***

Although the reactions performed did indeed work, they provided low yields. Future work can be to done to optimize these reactions. Six-exo-trig cyclizations and intermolecular carbon-carbon bond formations may be possible if a more highly activated radical acceptor (42, 43) is used.




42




43

Other variables that can be tested include varying the amounts of $NiI_2$ used, adding the $SmI_2$ at even lower temperatures, and testing bulkier proton sources.

***Experimental:***

*General Notes:*

All oven-dried flasks were used in the reactions. They were sealed with septa and cooled under nitrogen. All liquids were transferred with oven-dried syringes that were cooled in a nitrogen filled, septa sealed flask and most reactions were under a nitrogen

atmosphere except reactions using samarium diiodide which were under an argon atmosphere, with oven-dried syringes cooled under argon.

Purification was done using column chromatography, using silica gel supplied by Aldrich. All TLC was done using Analtech glass coated plates, various mixtures of ethyl acetate in hexane, and visualized in both UV and iodine.

All IR spectra were obtained with a Mattson Polaris spectrometer, mass spectral information was obtained using a Varian 3500 Capillary Gas Chromatograph coupled to a Finnigan MAT 700 Ion Trap Detector, and NMR spectra was obtained using a Bruker DPX-300 NMR spectrometer.

***AMG-55: Preparation of alcohol (31)***

Dichloromethane was distilled from calcium hydride. Then 6.07 g of aluminum chloride (1.3 eq., 0.0455 mol) was placed in a 250-mL oven-dried round bottom flask and via syringe, 70.08 mL of the distilled dichloromethane (0.5M) was added and cooled to $0^0$C. While cooling, 9.48 mL of N-methylaniline (2.5 eq., 0.0875 mol) was distilled onto molecular sieves and placed via syringe into the reaction vessel. Upon addition, the mixture turned from clear to brown. The 6-hexanolactone monomer (4.0 g, 0.035 mol) was added at room temperature. Once the lactone was added, the $AlCl_3$ went into solution and the rbf was warm to touch. The reaction was then stirred overnight and upon return a grayish-white precipitate had formed. After stirring 100 mL of saturated sodium bicarbonate solution was added very slowly. The reaction was transferred to a 500-mL beaker and sodium bicarbonate was also added. The solution was then vacuum filtered and water (25 mL) was added and then extracted with ether (3 x 75 mL). A TLC of the crude product was taken in both 15% ethyl acetate in hexane and 100% ethyl

acetate. The crude product was then rotovapped and vacuum pumped producing a yellow viscous product.

***Isolation/Purification:***

The crude product was then chromatographed using a 24/40 column, full of silica gel using the following mobile phase series: 300 mL 15% ethyl acetate in hexane; 1000 mL 100% ethyl acetate until finish. TLC in 100% EtOAc/hexane indicated product in fractions 4-12. Fractions 4-12 were then rotovapped and vacuum pumped to yield 4.9 g of a yellow viscous liquid with a yield of 63%.

***Characterization:***

Infrared spectra (neat, $cm^{-1}$): 3501, 3155, 2937, 2937, 1839, 1497, 1252, 908.; $^1H$ NMR (300MHz, $CDCl_3$): 1.27 (m, 2H), 1.49 (m,2H) ,1.60 (m, 2H), 2.09 (t, J=7.4 Hz, 2H), 3.25 (s, 3H), 3.60 (t, J=6.5 Hz, 2H), 7.16 (d, J=5.0 Hz, 2H), 7.35 (2H, t, J=7.5 Hz, 1H), 7.40 (m, 2H)

***AMG-56: Preparation of aldehyde (30)***

Dichloromethane was distilled from calcium hydride. The alcohol (0.3202 g, 0.001450 mol) was placed in a 25-mL round bottom flask and via syringe the dichloromethane (0.3M) was added to the reaction vessel and cooled to $0^0$C. Then 0.664 g of pyridinium chlorochromate (2.2 eq., 0.00308 mol) was then added and the ice bath was removed and allowed to warm to room temperature. Upon addition of the PCC the reaction turned brown. The reaction stirred for 2 hours and a TLC was taken in both 20% EtOAc/hexane and 50% EtOAc/hexane. Another 0.170 g of PCC was added and allowed to stir for 20 more minutes. After the 20 minutes, dry ether (2.4 mL, ½ as much

dichloromethane) was added. The reaction was then vacuum filtered and washed with dry ether and placed into a 50-mL pbf. The mixture was then rotovapped and vacuum pumped and the resulting brown oil was used immediately in the next reaction.

***AMG-57: Preparation of alkene (29)***

Tetrahydrofuran was distilled from sodium benzophenone and the phosphorus ylide was then prepared by mixing 1.021 g of the Wittig reagent (1.8 eq., 0.002520 mol) and 5 mL of the distilled THF (0.2M) in a 25-mL round bottom flask. The rbf was then cooled to $0^0$C and 0.087 g of sodium hydride (1.5 eq., 0.0021 mol) was added and allowed to stir for 15 minutes (little fizzing occurred). The remaining 2.24 mL of THF was used to transfer the 320 mg aldehyde into the reaction flask. A condenser was then added and the mixture was heated in a hot oil bath to maintain $40^0$C overnight. The reaction was TLC'd the next day in 50% EtOAc/hexane and indicated consumption of aldehyde. Water (5 mL) was then added and extracted with ether (3 x 10 mL), vacuum filtered, rotovapped, vacuum pumped and a crude $^1$H NMR was taken of the dark brown oil.

***Isolation/Purification:***

The resulting crude product was chromatographed using a 19/22 column, 2/3 full of silica gel using the following mobile phase series: 200 mL 5% ethyl acetate in hexane; 100 mL 15% ethyl acetate in hexane; 250 mL 20% ethyl acetate in hexane; 100 mL 30 % ethyl acetate in hexane; 75 mL 100% ethyl acetate until finish. TLC in 50% EtOAc/hexane indicated product in fractions 13-19. Fractions 13-19 were then rotovapped and vacuum pumped to produce 0.1606 g of a yellow oil in a 33.3% yield.

***Characterization:***

Infrared spectra (neat, $cm^{-1}$): 3155, 2931, 1641, 1468, 1097, 909; $^{1}H$ NMR (300MHz, $CDCl_3$): 0.90 (t, J=6.8 Hz, 3H), 1.35 (m, 8H), 1.62 (m, 4H), 2.10 (m, 4H), 3.25 (s, 3H), 4.10 (t, J=6.7 Hz, 2H), 5.75 (d, J=15.6 Hz, 1H), 6.87 (dt, J= 6.9, J=15.6 Hz, 1H), 7.19 (d, J=6.9, 2H), 7.35 (m, 3H ), 7.40 (m, 2H); $^{13}C$ NMR (300 MHz, $CDCl_3$): 14.0, 22.5, 25.0, 25.6, 27.6, 28.6, 31.5, 31.9, 33.8, 37.3, 64.4, 76.6, 77.0, 77.2, 77.4, 121.5, 127.3, 129.8, 148.7, 166.8, 172.8

***AMG 58: Preparation of aldehyde (30)***

Dichloromethane was distilled from calcium hydride. The alcohol (0.9127 g, 0.004130 mol) was placed in a 25-mL round bottom flask and via syringe, 13.77 mL of the dichloromethane (0.3M) was added to the reaction vessel and cooled to $0^0C$. Then 2.493 g of pyridinium chlorochromate (2.8 eq., 0.003080 mol) was then added and the ice bath was removed and allowed to warm to room temperature. Upon addition of the PCC the reaction turned brown. The reaction stirred for 2 hours and a TLC was taken in 50% EtOAc/hexane which indicated the presence of starting material. Another 0.2493 g of PCC was added and allowed to stir for 20 more minutes. After the 20 minutes, dry ether (6.89 mL, ½ as much dichloromethane) was added. The reaction was then vacuum filtered and washed with dry ether and placed into a 50-mL pbf. The mixture was then rotovapped and vacuum pumped and the resulting brown oil was used immediately in the next reaction.

***AMG-59: Preparation of alkene (29)***

Tetrahydrofuran was distilled from sodium and the phosphorus ylide was then prepared by mixing 2.68 g of the Wittig reagent (1.6 eq., 0.00661 mol) and 4 mL of the

distilled THF (0.6M) was syringed into a 50-mL round bottom flask. The rbf was then cooled to $0^0$C and 0.1817 g of sodium hydride (1.1 eq., 0.004540 mol) was added and allowed to stir for 15 minutes (fizzing occurred). The remaining 2.88 mL of THF was used to transfer the aldehyde into the reaction flask. The reaction was allowed to stir at room temperature for two days. The reaction was TLC'd two days later in 50% EtOAc/hexane. A mini extraction (0.5 mL) was done using water and ether. A crude $^1$H NMR was taken to ensure the consumption of aldehyde. After taking the crude NMR which indicated no starting material present, water (15 mL) was then added and the reaction was extracted with ether (3 x 30 mL), vacuum filtered, rotovapped, and vacuum pumped. The resulting crude product was a yellowish-brown oil.

***Isolation/Purification:***

The resulting crude product was chromatographed using a 24/40 column, 2/3 full of silica gel using the following mobile phase series: 500 mL 5% ethyl acetate in hexane; 250 mL 15% ethyl acetate in hexane; 600 mL 20% ethyl acetate in hexane; 500 mL 30 % ethyl acetate in hexane; 200 mL 100% ethyl acetate until finish. TLC in 50% EtOAc/hexane indicated product in fractions 10-15. Fractions 10-15 were then rotovapped and vacuum pumped to produce 0.35 g of a yellow oil in a 25% yield.

***AMG-60: $SmI_2$ Ring Cyclization (38)***

The amide (0.0990g, $2.87 \times 10^{-4}$ mol) was transferred into a tared Schlenk flask with a new septum. The amide was vacuum pumped for 50 minutes then filled with nitrogen. Then 0.00898g of nickel (II) iodide (0.10 eq., $2.87 \times 10^{-5}$ mol), vacuum pumped for another 90 minutes and filled with argon. The 1.0 mL of dry ether (0.3M) was then added via syringe and the reaction vessel was cooled in a chloroform/liquid nitrogen bath.

Then 0.058 mL of triflic anhydride (1.2 eq., 3.4 x $10^{-4}$) was added. It was noted that the amide did not precipitate out. The reaction flask was allowed to warm to $-10^0$C and was then switched to an ice-salt bath. Two argon-cooled syringes were used to co-syringe the 11.5 mL of samarium diiodide (4 eq., 0.00115 mol) and 0.054 mL of tert-butanol (2eq., 5.7 x $10^{-4}$) (needed to be warmed with a heat gun) over a one minute period with rapid stirring. The reaction turned a dark-brownish color and stirred for two hours.

Aqueous sodium bicarbonate (5 mL) was added (drop by drop for first mL). The resultant mixture was extracted with ether (10 mL first, then 3 x 5 mL). The organic layers were combined in a small separatory funnel and washed with 1 M hydrochloric acid (2 x 2 mL), then sodium bicarbonate (2 mL). The reaction was then TLC'd in both 5% and 25% ethyl acetate in hexane, rotovapped, vacuum pumped, and a crude $^1$H NMR was taken of the brown oil.

***Isolation/Purification:***

The resulting crude product was chromatographed using a 14/20 column, full of silica gel using the following mobile phase series: 100 mL 1% ethyl acetate in hexane; 100 mL 2% EtOAc/hexane; 100 mL 3% EtOAc/hexane; 100 mL 5% EtOAc/hexane; 100 mL 7% EtOAC/hexane; 100 mL 30% EtOAc/hexane. TLC in 5% EtOAc/hexane indicated product and THF ring opening contamination in fractions 21-24.

***AMG-61: $SmI_2$ Ring Cyclization (38)***

The amide (0.1014, 2.939 x $10^{-4}$ mol) was transferred into a tared Schlenk flask with a new septum. The amide was vacuum pumped for 50 minutes then filled with nitrogen. Then 0.1840g of nickel (II) iodide (0.20 eq., 5.878 x $10^{-5}$ mol), vacuum pumped for

another 90 minutes and filled with argon. The 1.0 mL of dry ether (0.3M) was then added via syringe and the reaction vessel was cooled in a chloroform/liquid nitrogen bath. Then 0.059 mL of triflic anhydride (1.2 eq., $3.5 \times 10^{-4}$) was added. It was noted, the amide did not precipitate out. While warming the reaction vessel to $-20^0$C, 0.056 mL of tert-butanol (2eq., $5.9 \times 10^{-4}$) (needed to be warmed with heat gun) was placed in a 5 mL pear bottom flask along with 1 mL of distilled ether to help with transfer. After warming the reaction flask to $-20^0$C, two argon-cooled syringes were used to co-syringe the 11.5 mL of samarium diiodide that was placed in the freezer half an hour previously (4 eq., 0.00115 mol) and tert-butanol/dry ether mixture over a one minute period with rapid stirring. The reaction turned a dark-brownish color and stirred for two hours and placed in the freezer.

Aqueous sodium bicarbonate (5 mL) was added (drop by drop for first mL). The resultant mixture extracted with ether (10 mL first, then 3 x 5 mL). The organic layers were combined in a small separatory funnel and washed with 1 M hydrochloric acid (2 x 2 mL), then sodium bicarbonate (2 mL). The reaction was then TLC'd in 5% ethyl acetate in hexane, rotovapped, and vacuum pumped. After vacuum pumping the crude product a large amount of a white precipitate formed and a crude $^1$H NMR was taken.

***Isolation/Purification***

Due to the white precipitate, the crude sample was first chromatographed on a 19/22 column, 2/3 full of silica gel and using 500 mL EtOAc/hexane. TLC in 5% EtOAc/hexane indicated product in fractions 2-3 and a crude 1HNMR was taken. The resulting product was chromatographed again using a 14/20 column, full of silica gel using the following mobile phase series: 100 mL 1% ethyl acetate in hexane; 100 mL 2%

EtOAc/hexane; 100 mL 3% EtOAc/hexane; 100 mL 5% EtOAc/hexane; 100 mL 7% EtOAC/hexane; 100 mL 30% EtOAc/hexane. TLC in 5% EtOAc/hexane indicated product and THF ring opening contamination in fractions 19-22.

*AMG-62: $SmI_2$ Ring Cyclization (38)*

Amide (0.1161, $3.365 \times 10^{-4}$ mol) was transferred into a tared Schlenk flask with a new septum. The amide was vacuum pumped for 50 minutes then filled with nitrogen. Then 0.02107g of nickel (II) iodide (0.20 eq., $6.730 \times 10^{-5}$ mol), vacuum pumped for another 90 minutes and filled with argon. The 1.1 mL of dry ether (0.3 M) was then added via syringe and the reaction vessel was cooled in a chloroform/liquid nitrogen bath. Then 0.059 mL of triflic anhydride (1.05 eq., $3.5 \times 10^{-4}$) was added. At this point, the amide did not precipitate out. While warming the reaction vessel to $-20^0$C, 0.063 mL of tert-butanol (2eq., $6.7 \times 10^{-4}$) (needed to be warmed with heat gun) was placed in a 5 mL pear bottom flask along with 1 mL of distilled ether to help with transfer. After warming the reaction flask to $-20^0$C, two argon-cooled syringes were used to co-syringe the 11.5 mL of samarium diiodide that was placed in the freezer half an hour previously (4 eq., 0.00135 mol) and the tert-butanol/dry ether mixture over a one minute period with rapid stirring. The reaction turned a dark-brownish color after half an hour.

So aqueous sodium bicarbonate (5 mL) was added (drop by drop for first mL). The resultant mixture extracted with ether (10 mL first, then 3 x 5 mL). The organic layers were combined in a small separatory funnel and washed with 1 M hydrochloric acid (2 x 2 mL), then sodium bicarbonate (2 mL). The reaction was then TLC'd in 5% ethyl

acetate in hexane, rotovapped, vacuum pumped, and a crude $^1$H NMR was taken of the brown oil.

***Isolation/Purification:***

The resulting crude product was chromatographed using a 14/20 column, full of silica gel using the following mobile phase series: 100 mL 1% ethyl acetate in hexane; 100 mL 2% EtOAc/hexane; 100 mL 3% EtOAc/hexane; 100 mL 5% EtOAc/hexane; 100 mL 7% EtOAC/hexane; 100 mL 30% EtOAc/hexane. TLC in 5% EtOAc/hexane indicated product in fractions 19-22. Fractions 19-22 were then rotovapped and vacuum pumped to yield 0.0136 g of a yellow oil with a 16.8% yield.

***Characterization:***

Chemical ionization mass spectrum, m/e, (relative intensity): 241 (20), 139 (97), 85 (25); Infrared spectrum (neat, $cm^{-1}$): 2959, 2932, 2862, 1711, 1276, 1172, 908; $^1$H NMR (300 MHz, $CDCl_3$) δ (ppm): 0.90 (m, 3H),1.30 (m, 8H), 1.63 (m, 4H), 2.20 (m, 2H), 2.35 (m, 1H), 2.93 (m, 2H), 4.10 (m, 2H); $^{13}$C NMR ($CDCl_3$, 300 MHz): 211.028, 172.703, 64.678, 44.7155, 41.847, 35.930, 34.467, 33.904, 31.453, 28.558, 25.626, 25.573, 25.222,14.006

***AMG-63: $SmI_2$ Ring Cyclization (38)***

The amide (0.1511, $4.3797 \times 10^{-4}$ mol) was transferred into a tared Schlenk flask with a new septum. The amide was vacuum pumped for 50 minutes then filled with nitrogen. Then 0.02742 g of nickel (II) iodide (0.20 eq., $8.759 \times 10^{-5}$ mol), vacuum pumped for another 90 minutes and filled with argon. The 1.5 mL of dry ether (0.3 M) was then added via syringe and the reaction vessel was cooled in a chloroform/liquid nitrogen bath. Then 0.081 mL of triflic anhydride (1.1 eq., $4.818 \times 10^{-4}$) was added. It was noted the

amide did not precipitate out. While warming the reaction vessel to $-20^0$C, 0.083 mL of tert-butanol (2eq., $8.759 \times 10^{-4}$) (needed to be warmed with heat gun) was placed in a 5 mL pear bottom flask along with 1 mL of distilled ether to help with transfer. After warming the reaction flask to $-20^0$C, two argon-cooled syringes were used to co-syringe the 21.9 mL of samarium diiodide that was placed in the freezer half an hour previously (5 eq., 0.02190 mol) and the tert-butanol/dry ether mixture over a one minute period while rapidly stirring. The reaction was stirred for 2 hours.

Then aqueous sodium bicarbonate (5 mL) was added (drop by drop for first mL). The resultant mixture was extracted with ether (10 mL first, then 3 x 5 mL). The organic layers were combined in a small separatory funnel and washed with 1 M hydrochloric acid (2 x 2 mL), then sodium bicarbonate (2 mL). The reaction was then TLC'd in 5% ethyl acetate in hexane, rotovapped, vacuum pumped, and a brown oil resulted.

***Isolation/Purification:***

The resulting crude product was chromatographed using a 14/20 column, full of silica gel using the following mobile phase series: 100 mL 1% ethyl acetate in hexane; 100 mL 2% EtOAc/hexane; 100 mL 3% EtOAc/hexane; 100 mL 5% EtOAc/hexane; 100 mL 7% EtOAC/hexane; 100 mL 30% EtOAc/hexane. TLC in 5% EtOAc/hexane indicated product in fractions 19-22. Fractions 19-22 were then rotovapped and vacuum pumped to yield 0.0151 g of a yellow oil with a 14.4% yield.

***AMG-64: Preparation of Amide (40)***

Decanoic acid (1.0 g, 0.0058 mol) was placed in a 50-mL rbf with a stir bar. Then 11.61 mL of the distilled benzene was placed in the reaction vessel. The 0.91 mL of oxalic acid (0.5 M) was placed in the rbf and fizzing took place. The reaction was

allowed to stir for 2 hours until the fizzing ceased. The reaction was then placed on an aspirator pump and then the vacuum pump. Then  of distilled dichloromethane was placed in the reaction vessel. The reaction vessel was then cooled to $0^0$C the n-methyl amine was added. The rbf was allowed to warm to room temperature and stir overnight. Upon return the reaction was a yellow solution.

Then aqueous sodium bicarbonate (5 mL) was added and extracted with ether (4 x 5 mL). A TLC was taken in 20% ethyl acetate in hexane, rotovapped, vacuum pumped, and a brown solution resulted.

***Isolation/Purification:***

The resulting crude product was chromatographed using a 24/40 column, ¾ full of silica gel using the following mobile phase series: 500 mL 4% EtOAc/hexane; 500 mL 8% EtOAc/hexane; 500 mL 13% EtOAc/hexane. TLC in 20% EtOAc/hexane indicated product in fractions 7-11. These fractions were then rotovapped and vacuum pumped to yield a clear oil.

***Characterization:***

$^1$H NMR (300 MHz, $CDCl_3$) δ (ppm): 0.91 (t, J=2.5 Hz, 3H), 1.20 (m, 12H), 1.57 (m, 2H), 2.10 (t, 7.6 Hz, 2H), 3.29 (s, 3H), 7.20 (d, J=7.3 Hz, 2H), 7.35 (m, 2H), 7.41 (m, 1H).

***AMG-65: $SmI_2$ (41)***

The amide (0.1185, $4.523 \times 10^{-4}$ mol) was transferred into a tared Schlenk flask with a new septum. The amide was vacuum pumped for 50 minutes then filled with nitrogen. Then 0.0283g of nickel (II) iodide (0.2 eq., $9.05 \times 10^{-5}$ mol), vacuum pumped for another 90 minutes and filled with argon. The 1.5 mL of distilled ether (0.3 M) was then added

via syringe and the reaction vessel was cooled in a chloroform/liquid nitrogen bath. Then 0.084 mL of triflic anhydride (1.1 eq., $5.0 \times 10^{-4}$) was added. It was noted that the amide did not precipitate out. While warming the reaction vessel to $-20^0$C, 0.086 mL of tert-butanol (2eq., $9.1 \times 10^{-4}$) (needed to be warmed with heat gun) was placed in a 5 mL pear bottom flask along with 1 mL of distilled ether to help with transfer. After warming the reaction flask to $-20^0$C, the 0.15 mL of acrylonitrile (5 eq., 0.0023 mol) was placed into the reaction vessel. Then two argon-cooled syringes were used to co-syringe the 22.6 mL of samarium diiodide (5 eq., 0.00230 mol) (that was placed in the freezer half an hour previously) and the tert-butanol/dry ether mixture over a one minute period while rapidly stirring. The reaction turned a dark-bluish color.

So aqueous sodium bicarbonate (5 mL) was added (drop by drop for first mL). The resultant mixture was extracted with ether (10 mL first, then 3 x 5 mL). The organic layers were combined in a small separatory funnel and washed with 1 M hydrochloric acid (2 x 2 mL), then sodium bicarbonate (2 mL). The reaction was then TLC'd in 5% ethyl acetate in hexane, rotovapped, vacuum pumped, and a crude $^1$H NMR was taken of the brown oil.

***Isolation/Purification:***

The resulting crude product was chromatographed using a 14/20 column, full of silica gel using the following mobile phase series: 100 mL 1% ethyl acetate in hexane; 100 mL 2% EtOAc/hexane; 100 mL 3% EtOAc/hexane; 100 mL 5% EtOAc/hexane; 100 mL 6% EtOAC/hexane; 100 mL 8% EtOAc/hexane; 100 mL 30% EtOAc/hexane. TLC in 5% EtOAc/hexane showed no products in the reaction observed.

***AMG-66: $SmI_2$***

The amide (0.1158, 4.420 x $10^{-4}$ mol) was transferred into a tared Schlenk flask with a new septum. The amide was vacuum pumped for 50 minutes then filled with nitrogen. Then 0.0277 g of nickel (II) iodide (0.2 eq., 8.84 x $10^{-5}$ mol), vacuum pumped for another 90 minutes and filled with argon. The 1.5 mL of distilled ether (0.3 M) was then added via syringe and the reaction vessel was cooled in a chloroform/liquid nitrogen bath. Then 0.082 mL of triflic anhydride (1.1 eq., 4.9 x $10^{-4}$) was added. It was noted, the amide did not precipitate out. While warming the reaction vessel to $-20^0$C, 0.084 mL of tert-butanol (2eq., 8.8 x $10^{-4}$) (needed to be warmed with heat gun) was placed in a 5 mL pear bottom flask along with 1 mL of distilled ether to help with transfer. After warming the reaction flask to $-20^0$C, the 0.58 mL of acrylonitrile (20 eq., 0.0088 mol) was placed into the reaction vessel. Then two argon-cooled syringes were used to co-syringe the 22.1 mL of samarium diiodide (5 eq., 0.00220 mol) (that was placed in the freezer half an hour previously) and the tert-butanol/dry ether mixture over a one-minute period while rapidly stirring. The reaction turned a dark-bluish color.

So aqueous sodium bicarbonate (5 mL) was added (drop by drop for first mL). The resultant mixture was extracted with ether (10 mL first, then 3 x 5 mL). The organic layers were combined in a small separatory funnel and washed with 1 M hydrochloric acid (2 x 2 mL), then sodium bicarbonate (2 mL). The reaction was then TLC'd in 5% ethyl acetate in hexane, rotovapped, vacuum pumped, and a crude $^1$H NMR was taken of the brown oil.

***Isolation/Purification:***

The resulting crude product was chromatographed using a 14/20 column, full of silica gel using the following mobile phase series: 100 mL 1% ethyl acetate in hexane; 100 mL

2% EtOAc/hexane; 100 mL 3% EtOAc/hexane; 100 mL 5% EtOAc/hexane; 100 mL 6% EtOAC/hexane; 100 mL 8% EtOAc/hexane; 100 mL 30% EtOAc/hexane. TLC in 5% EtOAc/hexane showed both product and starting material in fractions 28-33. Therefore fractions 28-33 were chromatographed again using a 14/20column, ¾ full of silica gel taking 20 mL fractions and using the following mobile phase series: 100 mL 5% EtOAc/hexane; 100 mL 7% EtOAc/hexane; 100 mL 9% EtOAc/hexane; 100 mL 11% EtOAc/hexane; 100 mL 13% EtOAc/hexane; 100 mL 15% EtOAc/hexane. TLC in 15% EtOAc/hexane still showed product and starting material in fractions 14-18 but a yield of product was determined to be 0.00818 g, 8.86%.

***Characterization:***

Chemical ionization mass spectrum, m/e (relative intensity): 210 (40), 193 (30), 175 (70), 121 (30), 98 (32), 79 (39), 69 (100); $^1$H NMR (300 MHz, $CDCl_3$) δ (ppm): 0.90 (m, 3H), 1.18 (m, 16H), 2.30 (t, J=7.6 Hz, 2H), 2.40 (t, J=7.6 Hz, 2H), 2.60 (t, J=7.3, 2H)

***AMG 67: $SmI_2$ (41)***

The amide (0.1907, $7.279 \times 10^{-4}$ mol) was transferred into a tared Schlenk flask with a new septum. The amide was vacuum pumped for 50 minutes then filled with nitrogen. Then 0.0456 g of nickel (II) iodide (0.2 eq., $1.46 \times 10^{-4}$ mol), vacuum pumped for another 90 minutes and filled with argon. The 2.4 mL of distilled ether (0.3 M) was then added via syringe and the reaction vessel was cooled in a chloroform/liquid nitrogen bath. Then 0.13 mL of triflic anhydride (1.1 eq., $8.0 \times 10^{-4}$) was added. It was noted, the amide did not precipitate out. While warming the reaction vessel to $-20^0$C, 0.14 mL of tert-butanol (2eq., 0.0015 mol) (needed to be warmed with heat gun) was placed in a 5 mL pear bottom flask along with 1 mL of distilled ether to help with transfer. After warming the

reaction flask to $-20^0$C, the 0.96 mL of acrylonitrile (20 eq., 0.015 mol) was placed into the reaction vessel. Then two argon-cooled syringes were used to co-syringe the 40.0 mL of samarium diiodide (5.5 eq., 0.00400 mol) (that was placed in the freezer half an hour previously) and the tert-butanol/dry ether mixture over a one-minute period while rapidly stirring. The reaction turned a dark-bluish color.

So aqueous sodium bicarbonate (10 mL) was added (drop by drop for first mL). The resultant mixture was extracted with ether (20 mL first, then 3 x 10 mL). The organic layers were combined in a small separatory funnel and washed with 1 M hydrochloric acid (2 x 4 mL), then sodium bicarbonate (4 mL). The reaction was then TLC'd in 5% ethyl acetate in hexane, rotovapped, vacuum pumped, and a crude $^1$H NMR was taken of the brown oil.

***Isolation/Purification:***

The resulting crude product was chromatographed using a 19/22 column, ¾ full of silica gel using the following mobile phase series: 300 mL 2% ethyl acetate in hexane; 150 mL 5% EtOAc/hexane; 150 mL 7% EtOAc/hexane; 150 mL 9% EtOAc/hexane; 150 mL 11% EtOAC/hexane; 150 mL 13% EtOAc/hexane; 150 mL 15% EtOAc/hexane. TLC in 15% EtOAc/hexane showed both product and starting material in fractions 25-29. The yield of product was calculated to be 5%.

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