Using Magnesium and TPPA to Create Carbon-Carbon Bonds

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ABSTRACT:

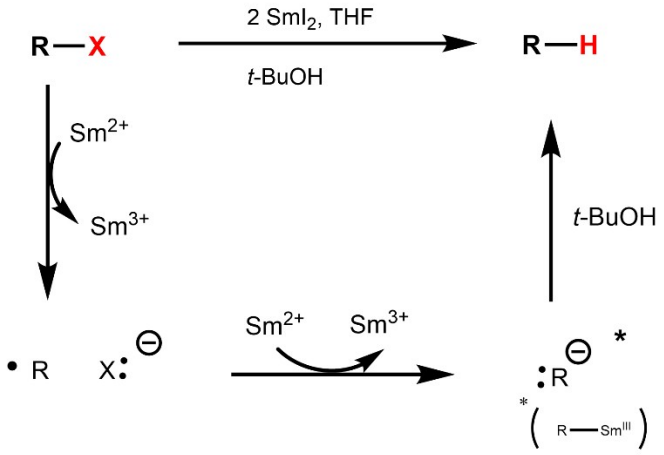
Attempts were made to create a catalytic SmI_2 system employing TPPA as a ligand. This system proceeded to reduce and dimerize molecules with or without the presence of SmI_2. Results show that a system consisting of magnesium, TPPA, and TMSCl results in the reductive dimerization of alkyl halides. The dimerization process is aided by the inclusion of TFE in the system. This system is also able to cyclize haloalkenes to create six-membered heterocycles, meaning this novel Mg/TPPA system has a great deal of synthetic potential.

INTRODUCTION:

Samarium diiodide (SmI_2) has proven to be a useful reagent for synthetic organic chemists for nearly forty years. It has been shown to be a very capable one-electron reductant with very broad applicability.[1] It is able to reduce carbonyls and alkyl halides as well as initiate radical cyclizations.[1-3] Methods of carbon-carbon bond formation are essential to synthetic organic chemistry as developing the carbon skeleton is often the most difficult part of developing a synthesis route for a target molecule.

Scheme 1 demonstrates the mechanism for reducing alkyl halides. First, a one electron oxidation from Sm^{2+} to Sm^{3+}, along with concomitant reduction of the alkyl halide, results in a carbon radical and halide anion.[4] A second one electron reduction of the incipient radical results in a carbanion, which is protonated to get the corresponding alkane product.[4]

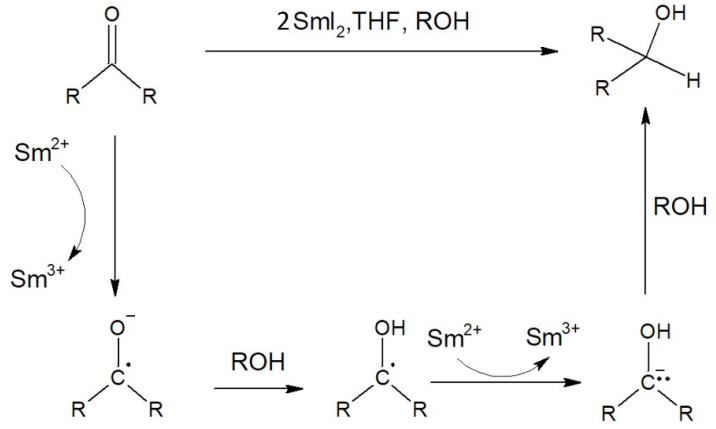
Scheme 1: Reduction of Alkyl Halides using Samarium Diiodide



Scheme 2 depicts the reduction of carbonyls. This mechanism is similar to that of the reduction of alkyl halides, where a one electron reduction of the carbonyl occurs, creating a ketyl

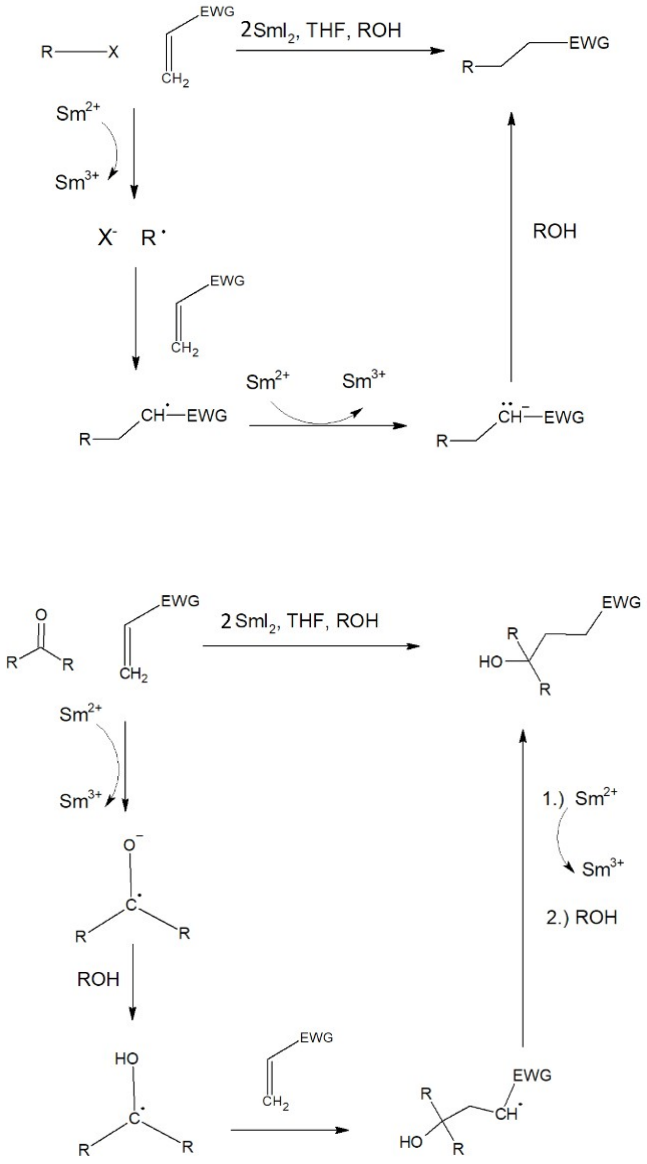
radical anion.[4] A protonation occurs at the oxygen, and a second one electron reduction takes place creating a carbanion which is then protonated to acquire the final product.[4]

Scheme 2: Reduction of Ketones using Samarium Diiodide



Inter- and intramolecular carbon-carbon bond formation can occur via a mechanism described by Scheme 3. An appropriate radical precursor such as an alkyl halide or carbonyl undergoes the same initial one electron reduction, and the carbon radical then adds to an alkene attached to an electron withdrawing group, creating a carbon-carbon bond.[4] The radical then undergoes another one electron reduction and protonation analogous to the previous reductions.[4]

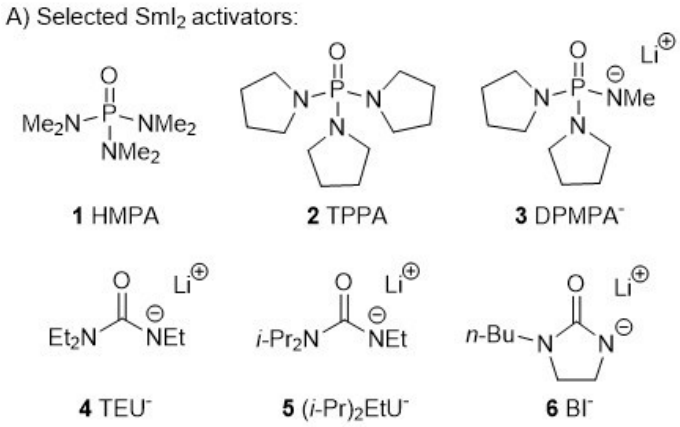
Scheme 3: Carbon-Carbon Bond Formation using Samarium Diiodide



The Sm^{2+} metal center contained in SmI_2 exists as an octahedral complex in solution, usually with tetrahydrofuran (THF) as the solvent.[5] THF coordinates to the Sm^{2+} at two sites, while a ligand (Scheme 4) coordinates to the metal at another four.[5] These ligands donate electron density to the Sm^{2+}, making it more likely to undergo a reduction.

Traditionally in stoichiometric SmI_2 reactions, HMPA (**1**) is a popular ligand choice, however it is antispermatogenic, mutagenic, and can cause nasal tumors (Scheme 4).[6] HMPA's ethyl analogue, hexaethylphosphoric acid triamide (HEPA) is 300 times less mutagenic than HMPA but very sterically bulky, and the tricyclic analogue of HEPA, tripyrrolidinophosphoric acid (TPPA, **2**) has not been observed to be toxic or mutagenic.[6] TPPA has similar electrochemical properties to HMPA, and activates the samarium metal center at approximately one order of magnitude greater than HMPA,[6] making it a suitable substitute ligand for HMPA to use in any potential catalytic SmI_2 systems.

Scheme 4: Various Ligands used in SmI_2 Reactions

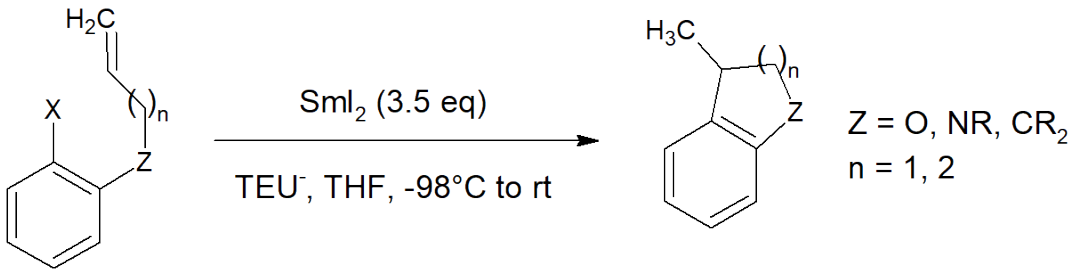


Another safer ligand choice for SmI_2 reactions is $DPMPA^-$ (3), an anionic phosphoramide ligand that activates the samarium metal center at least two orders greater than HMPA. Other anionic ligands developed by the McDonald lab include the ureates TEU^- (4)[7], PPU^- (5), and BI^- (6). These anionic ligands have similar activation rates to $DPMPA^-$ due to their anionic nature which donates extra electron density, making the metal center more likely to donate electrons. The downside to these strongly basic anionic ligands like phosphoramidates and ureates is that they may be incompatible with electrophilic components in potential catalytic systems, so when

developing a catalytic system intended to have broad applicability, a neutral ligand is ideal even though the cost is roughly an order of magnitude of reactivity.[7]

It should be noted that a SmI_2/TEU^- stoichiometric system can cyclize haloalkenes with much more success than the SmI_2/phosphoramide ligand stoichiometric systems, while the SmI_2/ phosphoramide ligand systems cyclize carbonyl-alkene systems with more ease (Scheme 5).[7]

Scheme 5: Cyclization of Halo-alkenes Using Samarium Diiodide with Triethylurea Ligand

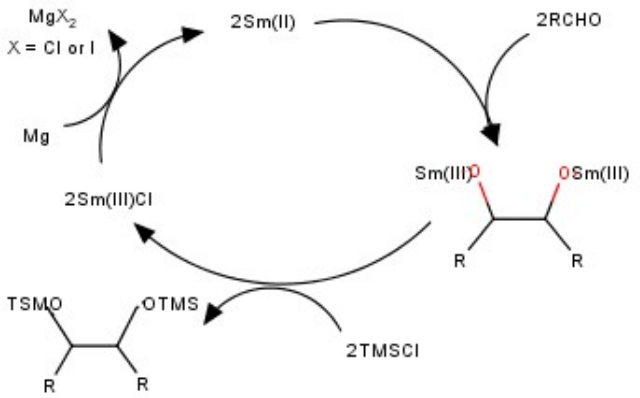


Despite the broad applicability of SmI_2 chemistry, it has some drawbacks. Due to being diluted, typically in 0.1 M THF, and requiring lots of activator—100 mg of substrate may require one gram of activator, 0.86 moles of SmI_2 and 30 mL of solvent—doing SmI_2 reactions stoichiometrically is far from favorable.[8,9] To remedy this issue, various catalytic systems have been developed for SmI_2 reactions using various ligands, usually tetraglyme.[1,8,9]

In 1996, Endo proposed an early SmI_2 catalytic system. Endo's system (Scheme 6) employs magnesium as a terminal reductant to reduce Sm^{3+} to Sm^{2+} observed through a color change from yellow to dark blue, which is a trend seen in other successful catalytic systems.[8] Endo applied his catalytic system to pinacol couplings, which required keeping the concentration of Sm^{2+} higher than the concentration of carbonyl species to avoid competing reactions involving

Sm^{3+} including benzoin condensation and the Tishchenko reaction.[8] He achieved this by ensuring the regeneration rate for Sm^{2+} was rather quick and by using chlorotrimethylsilane (TMSCl) to transform the Sm(III) pinacolate into its silyl ether and form the corresponding Sm(III) chloride salt.[5] When exploring the system, he found that reducible functional groups like ester and cyano tended to decrease yield, but the system was tailored such that methoxy and dimethylamino groups remained intact.[8]

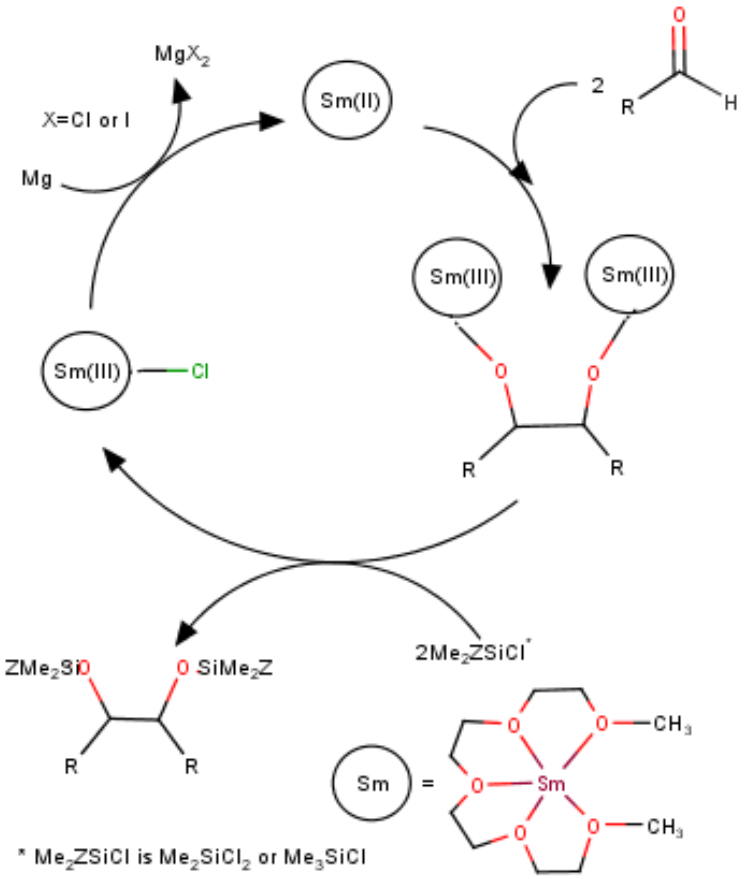
Scheme 6: Endo Catalytic System



An SmI_2 catalytic system proposed by Greeves (Scheme 7) involves pinacol coupling, using magnesium as a terminal reductant in excess (sixteen equivalents), tetraglyme as a ligand, and SmI_2 in catalytic amounts.[9] This system takes inspiration from the previously described system created by Endo.[9] The use of magnesium in this system differs from previously developed catalytic SmI_2 systems which used electrochemical reduction, zinc, or mischmetall as the terminal reductant.[9] Compared to the aforementioned system proposed by Endo also involving pinacol coupling, Greeves's system allows for chemoselectivity by taking advantage of the differences in the LUMO energy of aromatic and aliphatic carbonyls.[9] Using magnesium as a

terminal reductant is a common theme seen throughout SmI_2 catalytic systems.[1,8,9] The main difference between the Greeves system and Endo system is the use of other silyl based protecting groups other than TMSCl, but mechanistically both are similar.[8,9]

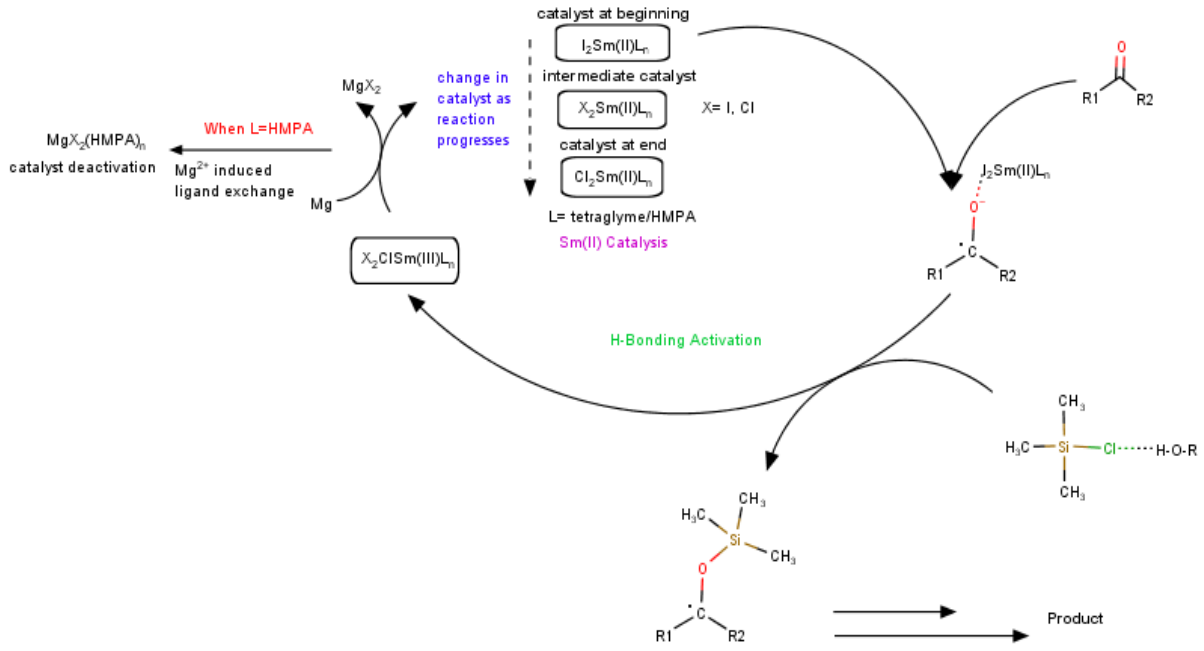
Scheme 7: Greeves Catalytic System



Flowers' proposed system (Scheme 8) again employs magnesium as a terminal reductant, and the system is activated by TMSCl along with a H-bond donor (TFE).[1] Using TFE as a H-bond donor increases the Lewis acidity of the TMSCl, and facilitates the efficiency and selectivity of the cleavage of the (Sm III—O) bond.[1] This system, though innovative due to its

ability to employ HMPA as a ligand, has its issues. Silanes that are critical to the reaction decrease the efficiency of the system, the $MgCl_2$ byproduct deactivates the catalyst by displacing HMPA ligand from the samarium, and using magnesium as a terminal reductant increases reaction times despite being both accessible and inexpensive.[1] With this system, Flowers was able to reduce carbonyls to alcohols with great success using both tetraglyme and HMPA as ligands.[1] This result suggests that TPPA would be a suitable substitute for HMPA due to TPPA's greater Sm^{2+} activation ability.

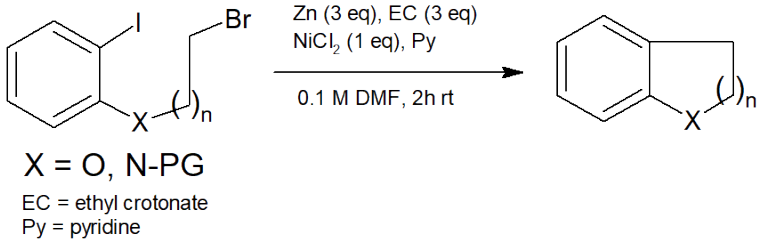
Scheme 8: SmI_2 Catalytic System Proposed by Flowers



During work completed in the fall of 2019, attempts were made to create a catalytic SmI_2 system using TPPA as an HMPA substitute by building on the work from the Flowers group (Scheme 8) as a starting point. It was found that magnesium and TPPA are able to reduce carbonyls without the use of SmI_2. We will also be interested in organohalide reductions including halide cross coupling reactions.

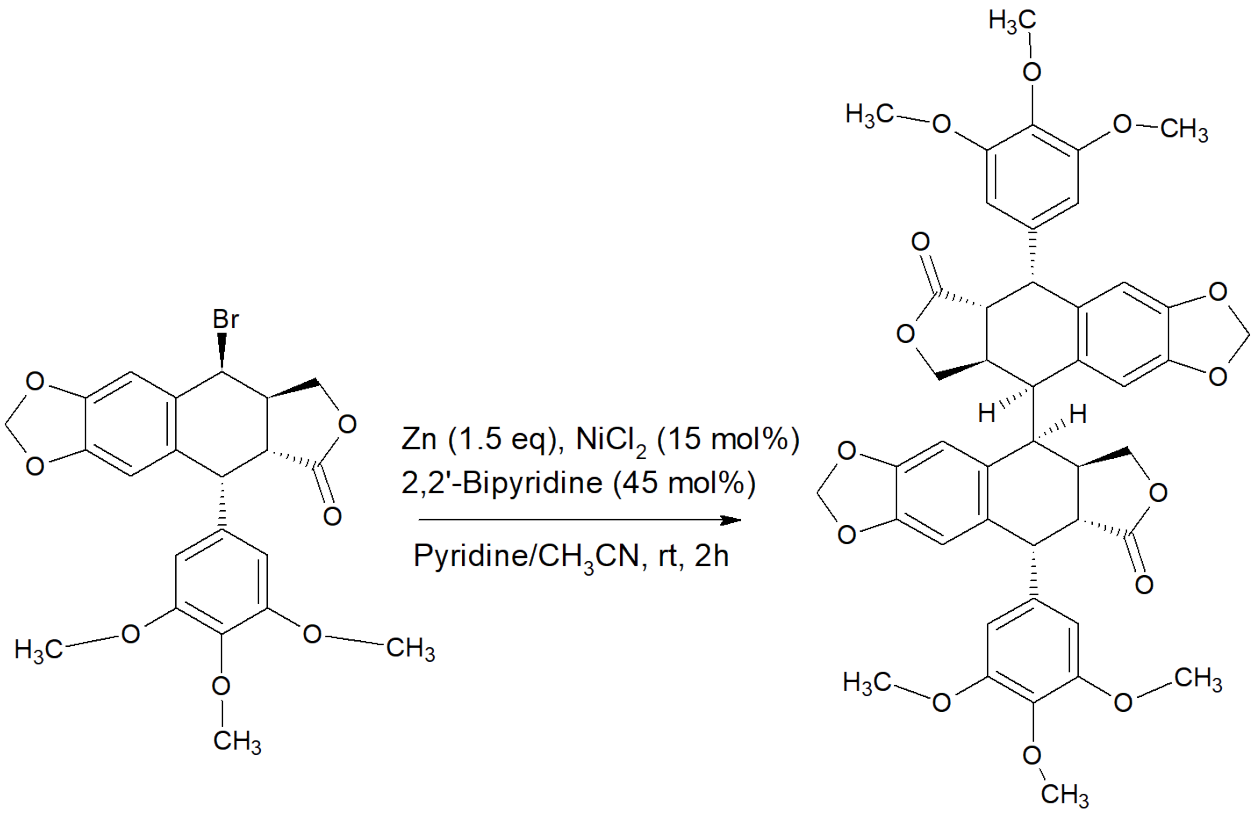
Similar reductive cross-coupling reactions involving alkyl bromides have been performed by utilizing a system involving a nickel catalyst and zinc, rather than magnesium, as a stoichiometric reductant.[10] The Peng group was able to use nickel(II) chloride in order to join two ends of halides together and create a heterocycle (Scheme 9).[10] Substrates of note chosen for this cyclization feature *O*-iodoanilines or *O*-iodophenols coupled to a bromoalkyl moiety.[10] The resultant heterocycle provides precedent for a sp^2 center and sp^3 center to be coupled by reductive cross-coupling.[10]

Scheme 9: Nickel-mediated Reductive Cross-Coupling



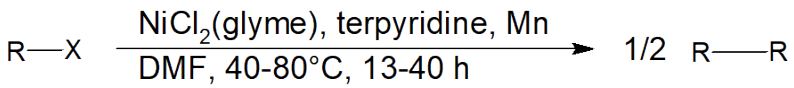
The Peng research group also investigated the use of the same reagent system to create dimers of many different types of compounds with great success (Scheme 10).[11] Upon varying solvents, it was found that acetonitrile was most optimal and provided the highest yields (96%).[11] Even some extremely sterically hindered homocoupling were accomplished with this system, with podophyllotoxin, a monomer used in anticancer drugs being dimerized with specificity.[11] This suggests that not only does this nickel catalyzed system have broad applicability with being able to both cross-couple and homo-couple, but also additional synthetic use due to its diastereoselectivity.[1]

Scheme 10: Nickel-Catalyzed Reductive Dimerization of Podophyllotoxin



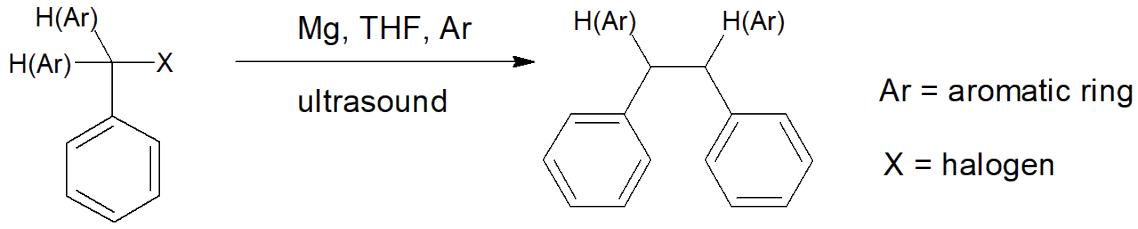
This same type of nickel mediated cross coupling was achieved by the Weix group.[12] They employed a similar system of using a nickel(II) chloride catalyst in order to achieve reductive dimerization of alkyl halides, but expanded the reach of their system and applied it to alkyl mesylates, alkyl trifluoroacetates, and allylic acetates (Scheme 11).[12] These results show a broader applicability of these metal catalyzed reductive dimerization reactions and a decently sized functional group tolerance.[12] A key difference between the Weix and Peng systems is that the Weix system involves heating the reaction mixture for thirteen to forty hours, rather than stirring at room temperature for two hours.[10,12] The Weix group also opts to use an equivalent of manganese rather than zinc in their system.

Scheme 11: Weix Nickel Mediated Cross Coupling



Carbon-carbon bond formation through the use of Grignard reagents also has literature precedence. The Gozhina group was able to accomplish dimerization of benzylic halides by the use of Grignard reagents formed through ultrasound (Scheme 12).[13] The scope of this system was extremely limited, and only proceeded with primary and secondary benzylic bromides, and was unable to dimerize alkyl halides or aromatic halides.[13] This is likely due to the higher reactivity of benzylic bromides compared to alkyl or aromatic halides.[13]

Scheme 12: Coupling of Benzylic Halides through Ultrasound



RESULTS AND DISCUSSION:

The first substrate chosen to test the catalytic system was 4-phenyl-2-butanone due to it being a ketone, and thus similar to substrates used in the Flowers system.[1] Our early attempts to reduce 4-phenyl-2-butanone to 4-phenyl-2-butanol (Scheme 13) resulted in extremely low yields of product. Reactions were performed by first adding magnesium powder, then degassed solvent, TPPA, TFE, and substrate. Upon adding TMSCl to the reaction vessel, bubbling was also observed, indicating that a reaction was taking place. Addition of small quantities of SmI_2 to the bubbling mixture resulted in immediate decoloration of the reagent. Even with adjustments to attempt to improve the system such as decreasing solvent amount, the reaction did

not go to completion, and trimethylsilyl groups formed on the resultant alcohol, necessitating an acidic workup to hydrolyze the silyl ether, but this did little to improve product yield.

Our initial attempts to reduce this ketone did not employ activation of the magnesium (entry 1) while all further attempts (entries 2-5) involved activation with heat and iodine crystals, similar to the activation for a Grignard reagent.[14] Attempts were made to increase product yield by decreasing solvent amounts (entries 2-4), however; there did not seem to be a discernable effect on product yield.

Scheme 13: Reduction of 4-Phenyl-2-butanone with SmI_2/TPPA Catalytic System

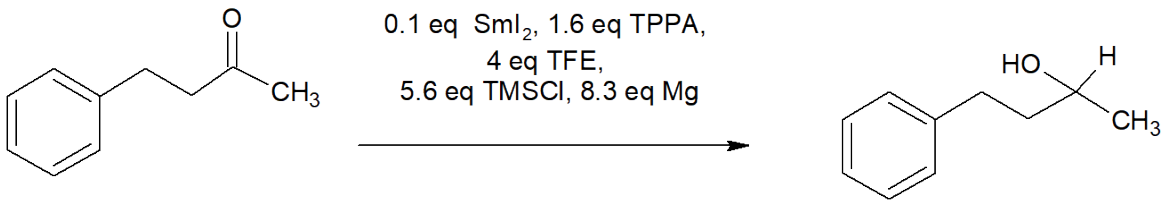


Table 1: Results of Using SmI_2/TPPA Catalytic System to Reduce 4-phenyl-2-butanone

Entry	% Starting Material	% Product	Reaction Conditions
1	33	N/A*	Mg not activated

2	70	10	Mg activated, decreased solvent
3**	52	38	Mg activated, decreased solvent
4	82	N/A*	Mg activated, decreased solvent
5	64	22	Mg activated, acidic workup

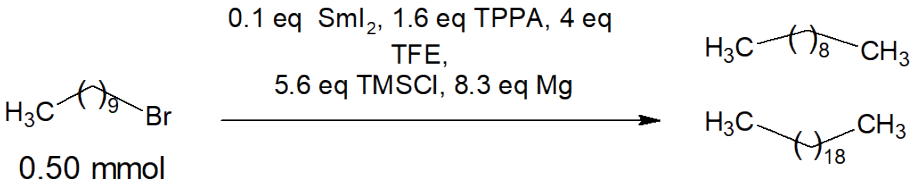
* indicates only product with trimethylsilyl group formed, could not be analyzed with relative detector response (by extension all product yields are reported lower than they are in reality with the exception of entry 5)
** indicates HMPA was used in place of TPPA as a ligand

To determine this system's usefulness in reducing alkyl halides, 1-bromodecane was chosen as a substrate (Scheme 14). As opposed to the reactions run using 4-phenyl-2-butanone as a substrate, a dark inky green color persisted in the reaction vessel upon addition of SmI_2 and the reaction went to completion with no starting material present when analyzed via gas chromatography. An additional product was formed under these reaction conditions, which was identified through gas chromatography and ^{1}H NMR to be eicosane, the dimer of decane, indicating this system can induce coupling. This suggests that magnesium is acting as a reducing agent and is capable of coupling two sp^3 hybridized centers together, which is extremely significant as carbon-carbon bond formation is taking place.

The mechanism of this reaction is still uncertain, but one possibility includes the very polar TPPA weakening the carbon-bromine bond. HMPA has shown to coordinate to carbon-halogen bonds and activate their reduction, so it is very possible TPPA is acting in a similar manner.[15] Another speculation on the mechanism is that the increased polarity of the system leads to conditions that are more favorable for S_N2 reactions. HMPA has also been shown to complex with magnesium, so TPPA once again may be behaving in a similar manner.[1,16] To

investigate this further, reaction conditions were adjusted to determine the necessity of various reagents in the system.

Scheme 14: Reduction and Dimerization of 1-bromodecane



Through altering reaction conditions, it was found that SmI_2 was in fact not needed at all in order for the reduction to proceed cleanly, and both decane and eicosane still formed. (Table 2). This indicates that a novel reaction is occurring where magnesium is acting as the reducing agent in conjunction with TPPA and TMSCl. This new reaction is capable of creating carbon-carbon bonds at sp^3 hybridized centers.

Table 2: Effects of the Adjustment of Reagents in the Reduction of 1-bromodecane

Entry	Reaction Conditions	% Decane	% Eicosane
1	WITH SmI_2	36	25
2	NO SmI_2	28	22
3	NO TMSCl	No Reaction	
4	NO TFE	52	19
5	NO TPPA	No Reaction	
6	THF Halved	31	23

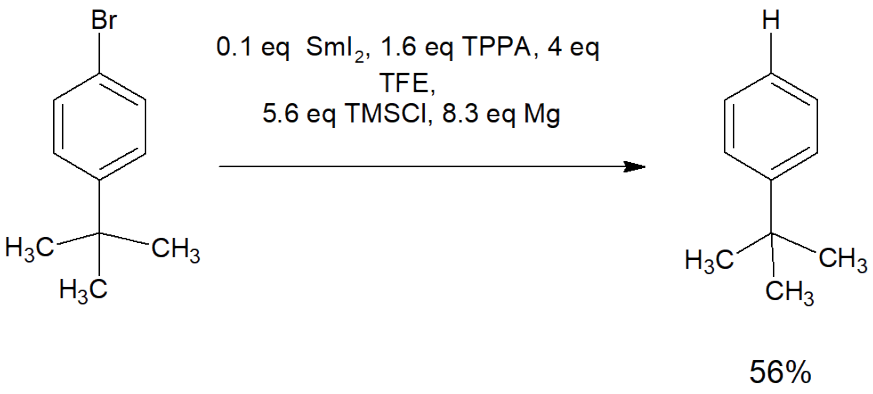
Omitting SmI_2 from the reagent system (entry 2) resulted in similar yields of dimerized product forming as compared to when samarium was included (entry 1). The reaction vessel remained colorless when omitting SmI_2, with copious amounts of bubbling upon the addition of TMSCl to the reaction mixture. When TMSCl was left out of the reagent system (entry 3), no

reaction took place. No bubbling was visible in the reaction vessel and only 1-bromodecane and TPPA had peaks when the reaction was analyzed via GC. Leaving out TFE (entry 4) resulted in more reduced product and less dimer formed. Significantly less bubbling was observed upon addition of TMSCl to the reaction vessel. The omission of TPPA (entry 5) lead to no reaction occurring, with similar results to when TMSCl was left out. Halving the amount of solvent used (entry 6) or omitting TFE had minimal effect on the course of the reaction (entry 4).

These results indicate that both TPPA and TMSCl are necessary for the reaction to take place. The addition of TFE as a H-bond donor seems to increase the formation of dimerized product. Addition of TMSCl into the reaction vessel always caused bubbling, possibly hydrogen gas, which was considerably less vigorous when TFE was omitted from the system, indicating that TFE is assisting TMSCl as an H-bond donor, similar to what was observed by Flowers.[1]

In order to determine the scope of this system's ability to reductively dimerize alkyl halides, another substrate, 1-bromo-4-*tert*-butylbenzene was subjected to similar reaction conditions in an attempt to form a carbon-carbon bond by coupling two sp^2 hybridized centers together (Scheme 15).

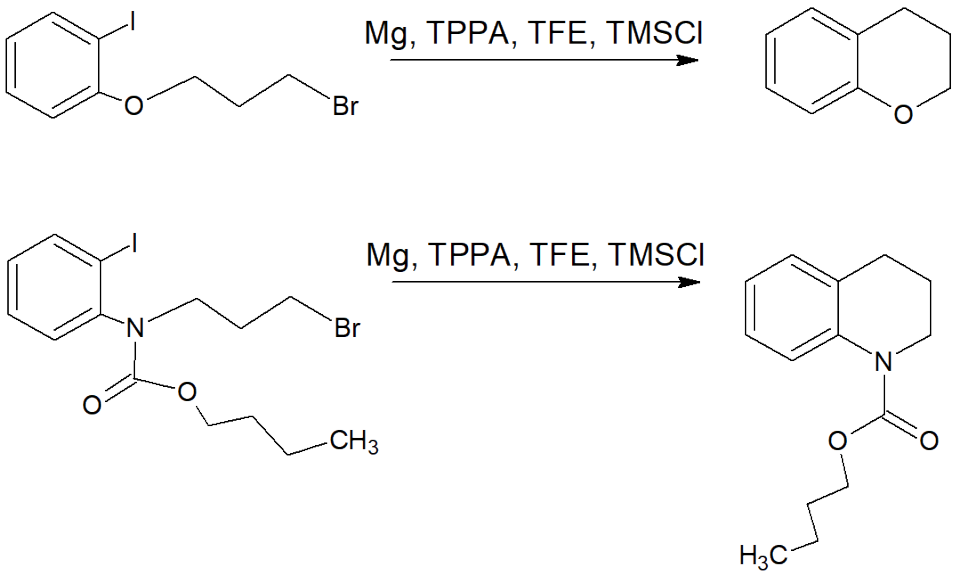
Scheme 15: Reduction of 1-Bromo-4-*tert*-butylbenzene



This reaction did not go to completion, and no dimerized product was formed, showing that while this system can couple two sp^3 centers together, it cannot do the same for two sp^2 hybridized centers. This suggests dimerization is occurring via a S_N2-like process.

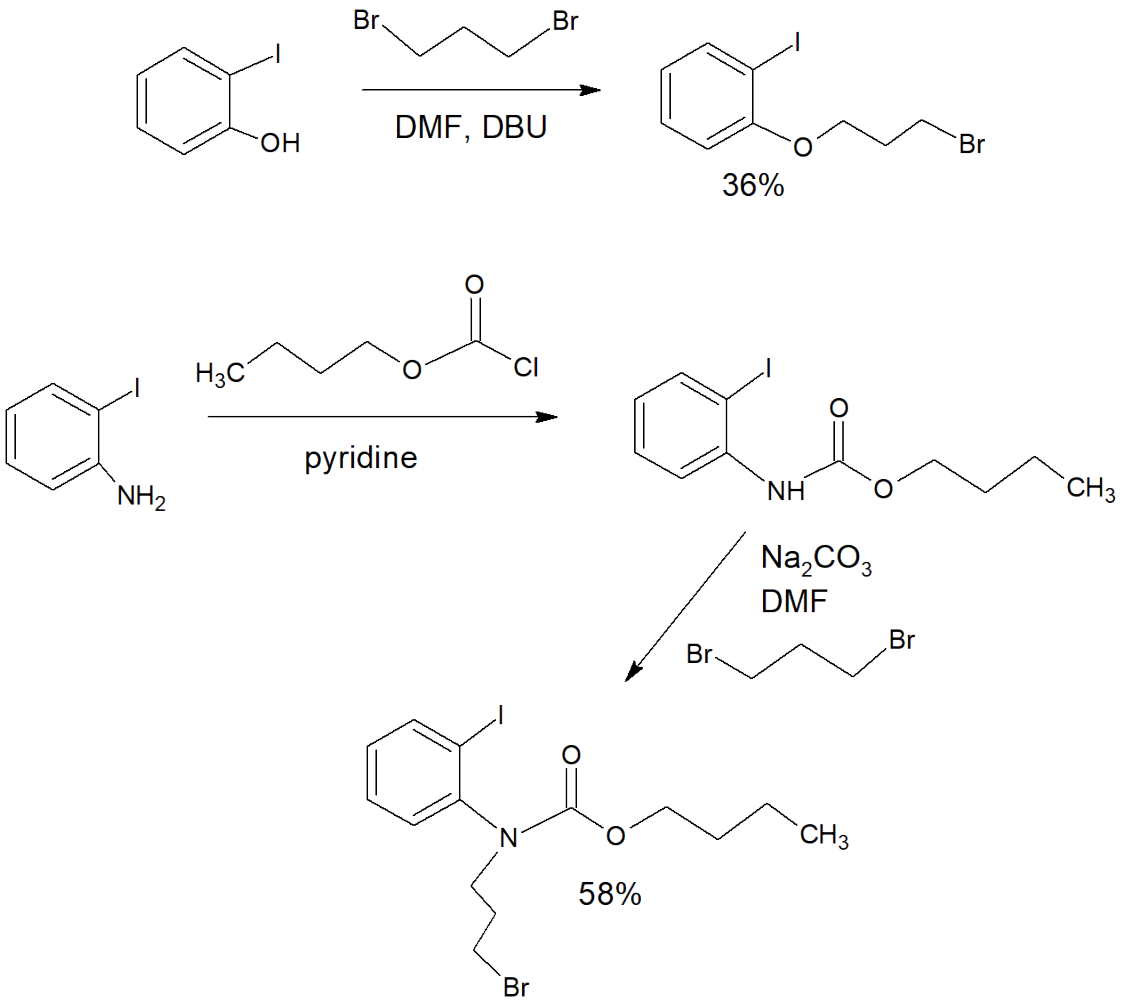
In order to explore this new reaction and expand the scope of this work, this project attempted to utilize this novel reaction to attempt more entropically favorable cyclizations. Scheme 16 shows planned synthetic pathways to create substrates for the aforementioned cyclizations.

Scheme 16: Planned Mg/TPPA Cyclizations



Substrates were chosen (Scheme 16) that were analogous to those the Peng group[10] chose —a benzene ring with an iodine ortho to a heteroatom followed by an alkyl bromide chain. One substrate has a more electronegative oxygen as the heteroatom, while another has a carbamate functional group. The oxygen containing substrate was synthesized through an S_N2 addition of 1,3-dibromo propane to 2-iodophenol, using DMF as a polar aprotic solvent. (Scheme 17). The nitrogen containing substrate was synthesized through a two-step synthesis from 2-iodoaniline. The first step is a nucleophilic acyl substitution with an acid chloride, and the second step is a S_N2 reaction with 1,3-dibromopropane, once again using DMF as a solvent.

Scheme 17: Syntheses of Planned Substrates

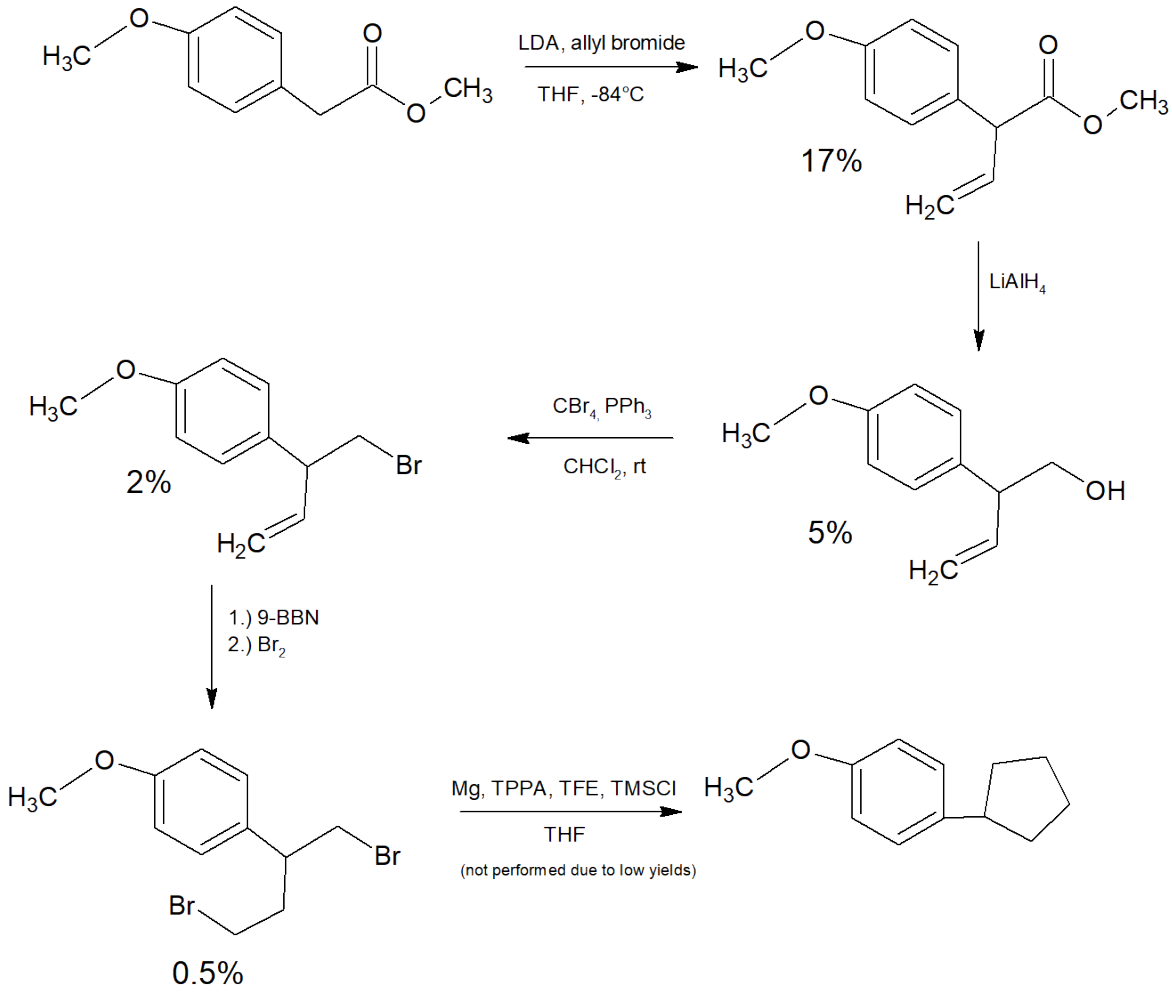


These substrates were chosen as targets for cyclization since if successful, it shows our Mg/TPPA system is capable of coupling a sp^2 hybridized center with an sp^3 hybridized center. We envision an initial reduction of the more labile sp^2 C-I bond to generate a nucleophile which undergoes an S_N2-like process with the pendant alkyl bromide.

A third substrate was chosen (Scheme 18) that would have hypothetically coupled two sp^3 hybridized centers together in order to form a ring. This substrate was made through a multi-step synthesis—the initial ester underwent a deprotonation with LDA, followed by alkylation with an allyl bromide, followed by a reduction with lithium aluminum hydride, followed by bromination with carbon tetrabromide through the Appel reaction, followed by a one-pot

hydroboration bromination sequence utilizing 9-BBN for anti-Markovnikov addition[17] to get the final substrate, which would hypothetically have been subjected to the reaction conditions of the Mg/TPPA system in order to form a five-membered ring. The multi-step synthesis was run twice, but a sufficient amount of substrate to run the Mg/TPPA reaction was not able to be recovered and isolated.

Scheme 18: Synthesis of Third Planned Substrate

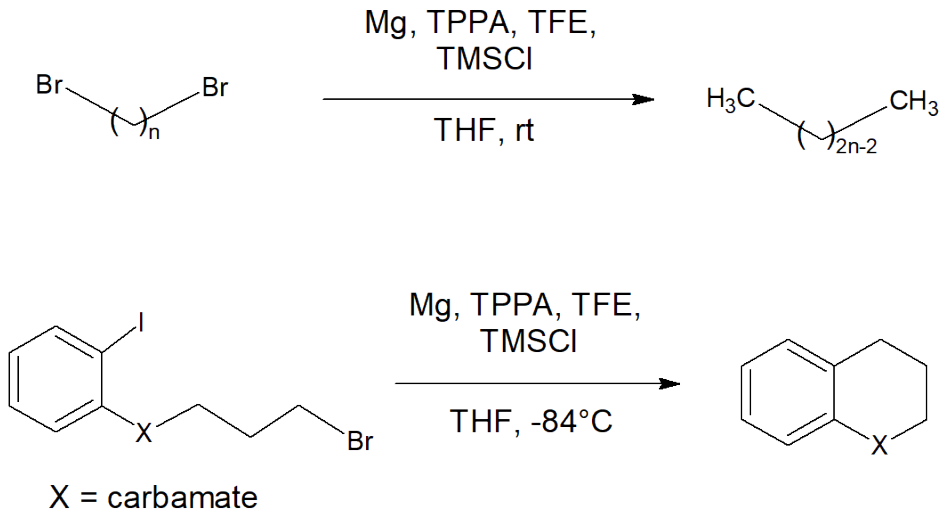


When cyclization was attempted with the oxygen-containing substrate, there was a mixture of products that could not be adequately separated through column chromatography. As

a result, the confirmation of a cyclized product could not be determined through NMR, and the results of this experiment are inconclusive.

The carbamate containing substrate was successfully able to be cyclized to form a nitrogen containing heterocycle attached to an aromatic ring with a yield of 30%. This result, supported by incredibly clean ^{1}H and ^{13}C NMR spectra, as well as IR and ESI HRMS data confirms that this Mg/TPPA system can join an sp^2 center with an sp^3 center, and that ring formation is possible, meaning the coupling of the Mg/TPPA system works intramolecularly.

Scheme 19: Summary of Mg/TPPA Reaction Capabilities



CONCLUSION:

Replacing HMPA with TPPA in order to create a catalytic system similar to that proposed by Flowers[1] resulted in simply the reduction of the ketone to its corresponding alcohol. On the other hand, reducing alkyl halides with this similar TPPA system results in a coupled product with or without the presence of SmI_2, suggesting that magnesium is the real reductant at play. TPPA and TMSCl are also necessary for both the reductive dimerization of alkyl halides to

proceed, and TFE aids the reaction as an H-bond donor. This magnesium-based reagent system cannot couple two sp^2 hybridized centers together, but can couple two sp^3 hybridized centers together, as well as an aromatic sp^2 hybridized center with a sp^3 hybridized center to create six-membered heterocycles connected to an aromatic ring.

This suggests that while Suzuki-like sp^2-sp^2 couplings are not possible with this reagent system, this novel system of carbon-carbon bond formation has significant potential for broad utility as it has been proven to be able to reduce alkyl halides, dimerize alkyl halides, and form six-membered heterocycles attached to aromatic rings intramolecularly, making it of particular synthetic interest.

EXPERIMENTAL:

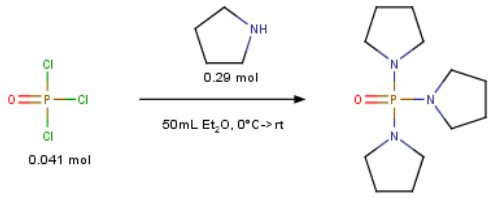
General:

Samarium diiodide was purchased from Sigma Aldrich, as a 0.1 M solution in THF. THF was purified through distillation from sodium, and sparged with Ar for 8-10 minutes before use. All reactions were done under either nitrogen or argon atmosphere with oven dried glassware. All SmI_2 and magnesium reactions were run in oven dried Schlenkware under an argon atmosphere. Glassware was evacuated with a vacuum pump then backfilled with Ar prior to addition of reagents. Reagent transfer was accomplished using gas-tight syringes. Teflon stir bars were used in all SmI_2 and Mg reactions, while a mechanical stirrer was used in the synthesis of TPPA.

NMR spectra were recorded at room temperature (300 MHz for ^{1}H and 75 MHz for ^{13}C) in $CDCl_3$. Chemical shifts are reported in δ parts per million referenced to residual solvent proton resonance of $CDCl_3$ (7.28 ppm) or the solvent carbon resonance of $CDCl_3$ (77.0 ppm).

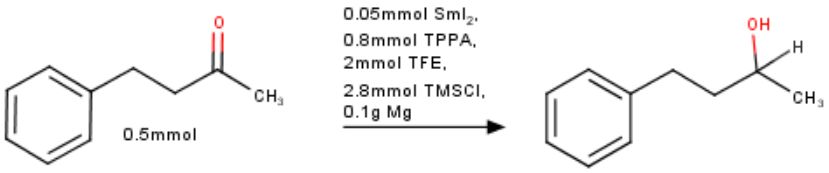
GC analyses were performed using a GC system equipped with a column of fused silica (length 30 m, internal diameter 0.25 mm, film 0.25 μm of diphenyl dimethyl polysiloxane) and an FID detector. He was used as the carrier gas. The injector temperature was 250 °C. The initial oven temperature was 50 °C with an initial hold time of 2 min, with a 10 °C/min ramp to a final temperature of 250 °C and then held at that temperature for 10 min. A split ratio of 16.8 was employed. Yields were determined through the use of alpha values using tetradecane (10 μL) as a standard. It was added to reaction mixtures after 24 hours and stirred for 5 minutes. After extraction, aliquots were taken from the ether extract and analyzed on the GC.

Synthesis of TPPA:



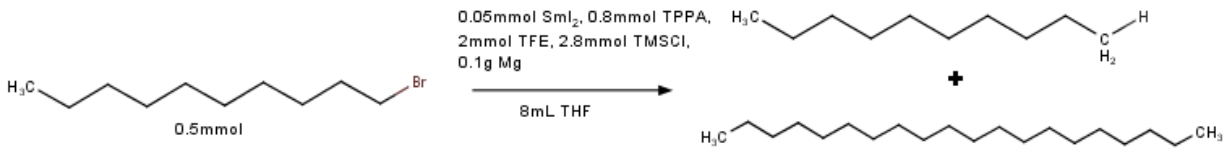
Phosphorous oxychloride (6.25 mL, 0.041 mol) was added to diethyl ether (84 mL) at 0°C. To this mixture, pyrrolidine (40 mL, 1.68 mol) and diethyl ether (42 mL) were added dropwise with an addition funnel and mechanically stirred overnight. Purification was achieved by vacuum filtration, followed by drying with sodium sulfate, vacuum filtration, and removing solvent *in vacuo*. Purification yielded 8.00 g (76%) of product as a yellow viscous liquid. ^{1}H NMR (300 MHz; $CDCl_3$ δ, ppm) 3.08 (m, 12H), 2.08 (m, 12H). ^{13}C NMR (75 MHz; $CDCl_3$ δ, ppm) 26.2, 46.0.

Synthesis of 4-phenyl-2-butanol:



Distilled and degassed THF (8 mL) was added to 0.10 g (4.17 mmol) magnesium powder in a 15 mL Schlenk flask equipped with a magnetic stir bar under argon atmosphere. TPPA (0.184 mL, 0.8 mmol) was added, followed by TFE (0.146 mL, 2.0 mmol), 4-phenyl-2-butanone, (0.073 mL, 0.5 mmol), TMSCl (0.355 mL, 2.8 mmol), and SmI_2 (0.556 mL, 0.056 mmol). The reaction mixture was stirred overnight at room temperature, 5 mL water and 10 mL of 1M HCl were added and the reaction mixture was stirred for one hour. It was then extracted with ether (3 x 5 mL), then solvent was evaporated *in vacuo*. The product was isolated and identified through gas chromatography using a tetradecane standard. Average yields were found to be around 16% 4-phenyl-2-butanol by analysis with GC and GC-MS

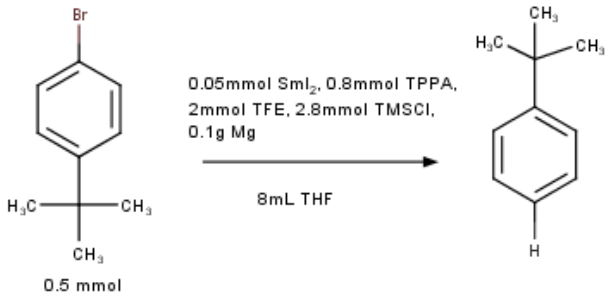
Reduction and Dimerization of Bromodecane:



Distilled and degassed THF (8 mL) was added to 0.10 g (4.17 mmol) magnesium powder in a 15 mL Schlenk flask equipped with a magnetic stir bar under argon atmosphere. TPPA (0.184 mL, 0.8 mmol) was added, followed by TFE (0.146 mL, 2.0 mmol), decane (0.104 mL, 0.5 mmol), and TMSCl (0.355 mL, 2.8 mmol). SmI_2 (0.556 mL, 0.056 mmol) was added if applicable. The reaction mixture was stirred overnight at room temperature, 5 mL water were added, and the reaction mixture was then extracted with ether (3 x 5 mL), then solvent was evaporated *in vacuo*. The product was isolated and identified through gas chromatography using

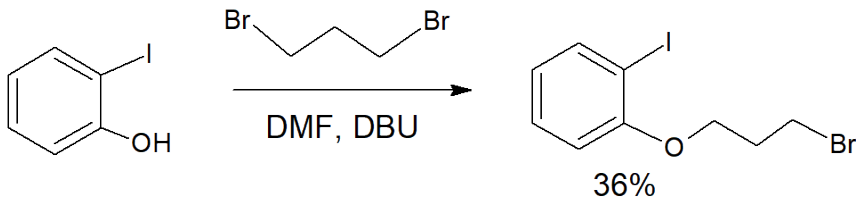
a tetradecane standard. Average yields were found to be around 22% eicosane and 37% decane by analysis with GC and GC-MS.

Synthesis of Tert-butyl benzene:



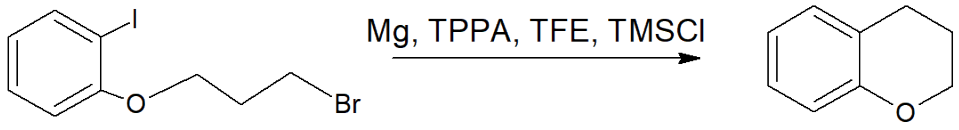
Distilled and degassed THF (8 mL) was added to 0.10 g (4.17 mmol) magnesium powder in a 15 mL Schlenk flask equipped with a magnetic stir bar under argon atmosphere. TPPA (0.184 mL, 0.8 mmol) was added, followed by TFE (0.146 mL, 2.0 mmol), 4-bromo-1-tert-butyl benzene, (0.085 mL, 0.5 mmol), and TMSCl (0.355 mL, 2.8 mmol). SmI_2 (0.556 mL, 0.056 mmol) was added if applicable. The reaction mixture was stirred overnight at room temperature, 5 mL water were added, and the reaction mixture was then extracted with ether (3 x 5 mL), then solvent was evaporated *in vacuo*. The product was isolated and identified through gas chromatography using a tetradecane standard. Product yield was determined to be 56% tert-butyl benzene by analysis with GC and GC-MS.

Synthesis of 1-iodo-2-(3-bromo)propoxy benzene



2-iodophenol (600 mg, 0.00273 mol) was added to a 10 mL round bottom flask with 2.05 mL DMF, 0.733 mL (4.9 mmol) DBU, and 0.52 mL (4.9 mmol) 1,3-dibromopropane. Reaction mixture was stirred for 24 hours at room temperature, and another 24 hours at 45°C. 10 mL of water were added and reaction mixture was extracted with 2:1 hexane:ether. The product was purified through silica gel column chromatography (hexanes). Purification yielded 0.3169 g (36%) of 1-iodo-2-(3-bromo)propoxybenzene as a clear oil. ^{1}H NMR (400 MHz; $CDCl_3$ δ, ppm) 7.77 (m, 1H), 7.30 (m, 1H), 6.87 (m, 1H), 6.70 (m, 1H), 4.14 (t, J = 5.5 Hz, 2H), 3.71 (t, J = 6.4 Hz, 2H), 1.71 (quint, J = 6.0 Hz, 2H). ^{13}C NMR (100 MHz; $CDCl_3$ δ, ppm) 156.99, 139.36, 139.29, 129.47, 122.73, 112.19, 112.09, 86.62, 66.27, 32.20, 30.32.

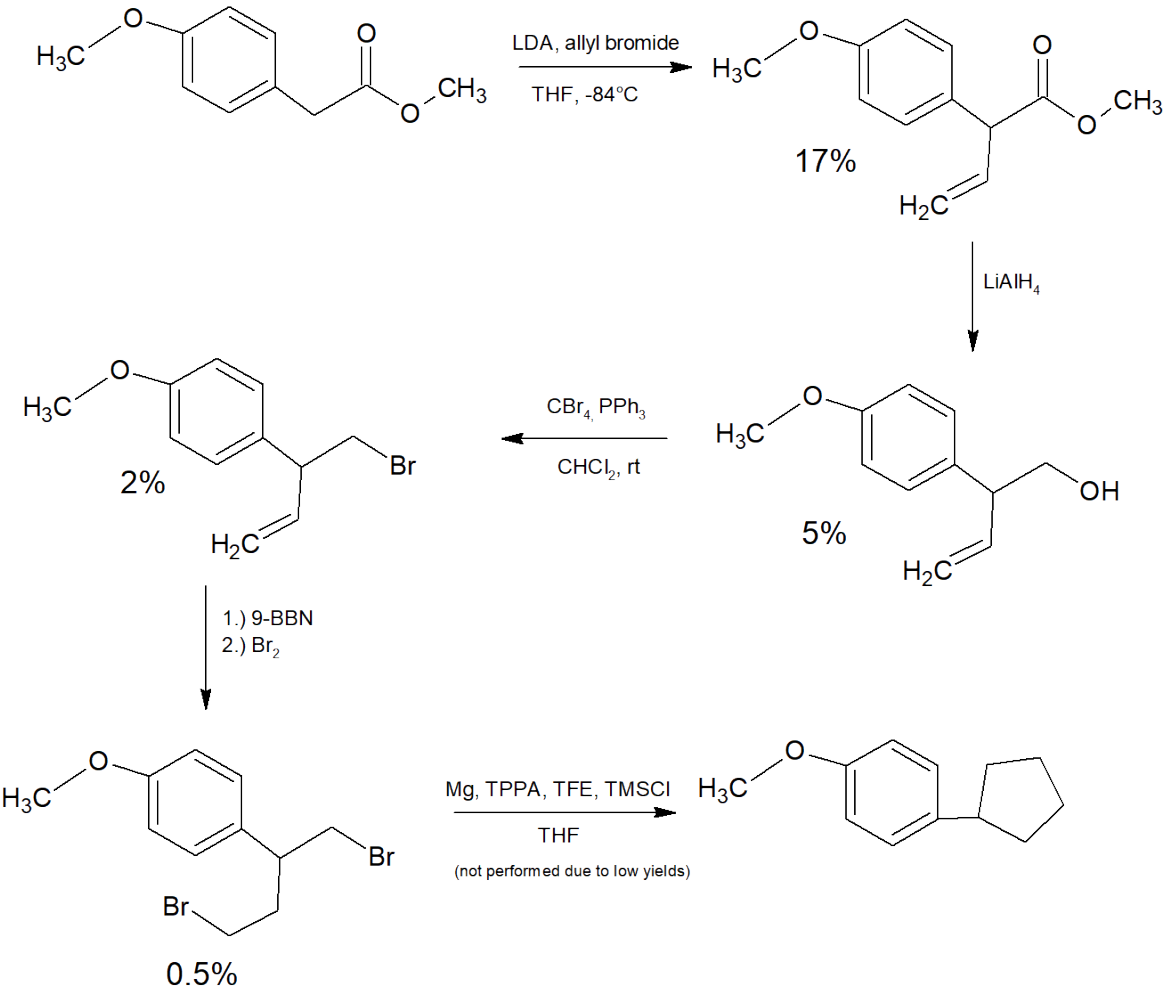
Synthesis of Dihydrobenzopyran



Distilled and degassed THF (8 mL) was added to 0.10 g (4.17 mmol) magnesium powder in a 15 mL Schlenk flask equipped with a magnetic stir bar under argon atmosphere. TPPA (0.184 mL, 0.8 mmol) was added, followed by TFE (0.146 mL, 2.0 mmol), and 1-iodo-2-propoxybenzene (0.1705g, 0.5 mmol). The reaction mixture was cooled to -43°C and TMSCl (0.355 mL, 2.8 mmol) was added. The reaction mixture was stirred overnight at room temperature, 5 mL water was added, and then extracted with 2:1 hexane:diethyl ether (3 x 5 mL),

then solvent was evaporated *in vacuo*. Silica gel chromatography was used to purify the concentrated reaction mixture (hexane-1% ethyl acetate in hexane). This yielded two products that were not able to be separated.

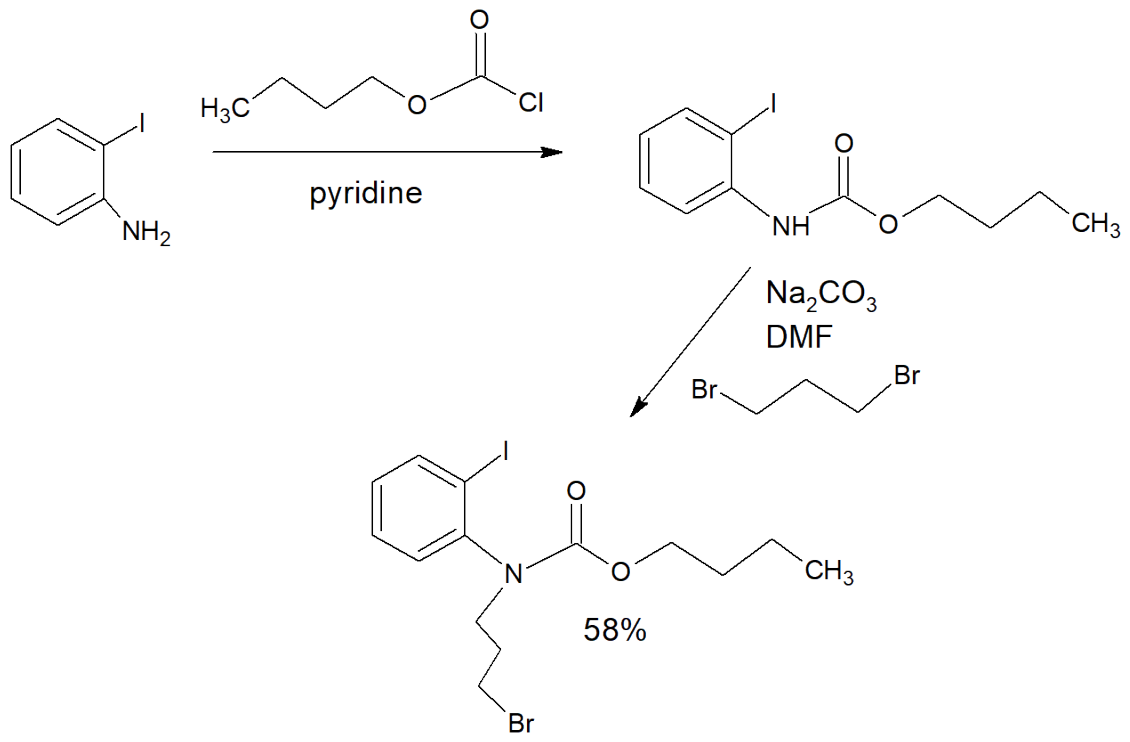
Synthesis of 1-((1-bromomethyl)bromopropyl)-4-methoxy benzene



LDA was made by cooling 3.38 mL (24.2 mmol) of distilled iPr_2NH in 88 mL THF to 0°C. BuLi (2.28 mL, 24.2 mmol) was added dropwise, and the reaction mixture was stirred for 10 minutes before cooling to -84°C. 2-(4-methoxyphenyl)acetate (4.0 g, 22 mmol) in 3 mL THF was added dropwise, and the reaction mixture was stirred for 30 minutes. Distilled alkyl

bromide (2.28 mL, 26.4 mmol) in 3 mL THF was added dropwise, followed by 2.30 mL (13.8 mmol) of HMPA. The reaction mixture was left to warm to room temperature and stir overnight, and was then extracted with 1:1 ether:hexane and washed with ammonium chloride and salt brine (3 x 20 mL), dried on sodium sulfate, filtered, and concentrated in vacuo. Product of this step was isolated through silica gel column chromatography (1-6% ethyl acetate in hexane). This ester product was then treated with lithium aluminum hydride (0.292 g, 7.68 mmol) in 7.6 mL THF at 0°C. The reaction mixture was left to warm to room temperature and stirred overnight, then cooled to 0°C once more for a nn3n workup and concentrated in vacuo. The alcohol product from this step was then stirred with 0.326 g (1.24 mmol) triphenylphosphine, and 0.4174 g (1.26 mmol) carbon tetrabromide in 1.9 mL dichloromethane at room temperature overnight. It was then extracted with ether (3 x 10 mL) and concentrated in vacuo. This step's product was isolated through silica gel column chromatography (hexane-3% ethyl acetate in hexane). It was then added to a three necked 25 mL flask with 0.177 mL THF and was cooled to 0°C. 9BBN (1.14 mL, 0.57 mmol) was added and the reaction mixture was allowed to warm to room temperature and was stirred for one hour. Methanol (0.0035 mL) was added, and 0.0283 mL of bromine and 0.0315 g of sodium methoxide (0.583 mmol) were added simultaneously to the reaction mixture which was stirred for 30 minutes at room temperature. The reaction mixture was extracted with 10% sodium carbonate and hexane (3 x 5 mL). The final product was purified through silica gel column chromatography (hexane-2% ethyl acetate in hexane). Purification yielded 0.0296 g (0.5% from 2-(4-methoxyphenyl)acetate) of 1-((1-bromomethyl)bromopropyl)-4-methoxy benzene.

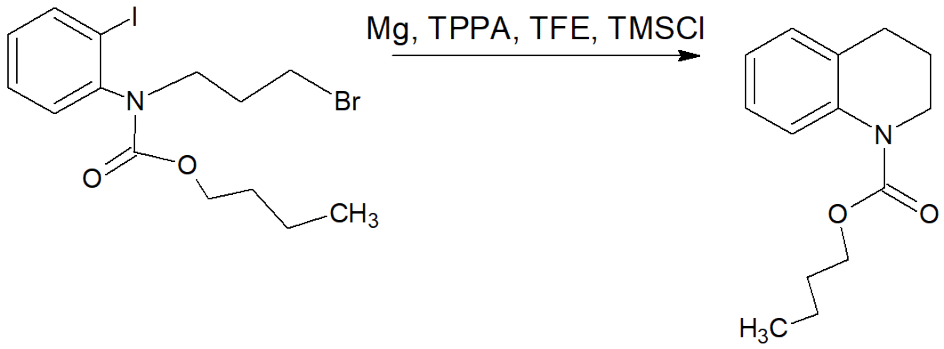
Synthesis of N-3-Bromopropyl-N-2-iodophenyl-O-butylcarbamate:



Pyridine (14 mL) and *N*,*N*-dimethylaminopyridine (20 mg) was added to 2-iodoaniline (3.00 g, 12.7 mmol) and the mixture was cooled to 0 ˚C with stirring. Butylchloroformate (2.61 mL, 20.4 mmol) was added over 5 min. The resultant mixture was allowed to warm to rt overnight. Water (20 mL) was added and the mixture was extracted with ether (3 X 15 mL). The combined organic extracts were dried with Na_2SO_4, filtered, and the solvent was removed under reduced pressure to provide the crude iodophenyl carbamate as a viscous dark-brown oil. DMF (14 mL) was added to the crude carbamate along with 5.81 g of Cs_2CO_3 (5.81 g, 17.8 mmol) and the mixture was cooled to 0 ˚C. 1,3-Dibromopropane (1.82 mL, 17.8 mmol) was added and the resultant mixture was allowed to warm to rt overnight. Water (20 mL) was added and the mixture was extracted with 1:1 mixture of hexane and ether (3 X 15 mL). The solvent was removed under reduced pressure to provide the crude carbamate as a viscous dark-brown oil. The resultant mixture was allowed to warm to rt overnight. Water (20 mL) was added and the mixture was extracted with ether (3 X 15 mL). The combined organic extracts were dried with

Na_2SO_4, filtered, and the solvent was removed under reduced pressure to provide the crude carbamate as a viscous dark-brown oil. The crude product was purified by column chromatography (SiO_2, 1-3% EtOAc in hexanes) to provide 3.53 g of *N*-3-Bromopropyl-*N*-2-iodophenyl-*O*-butylcarbamate as a colorless viscous oil (58% from 2-iodoaniline). IR (ATR) cm^{-1} 2957, 1697, 1603, 1492. ^1H NMR (400 MHz; $CDCl_3$ δ, ppm) 9.91 (d, *J* = 7.8 Hz, 1H), 7.42-7.36 (m, 1H), 7.26-7.16 (m, 1H), 7.07-7.00 (m, 1H), 4.31-3.88 (m, 2H), 3.55-3.41 (m, 4H), 2.25-2.13 (m, 2H), 1.78-1.42 (m, 2H), 1.26-1.14 (m, 2H), 1.02-0.77 (m 3H) ^{13}C NMR (100 MHz; $CDCl_3$ δ, ppm) 155.2, 143.9, 139.7, 129.4, 129.2, 129.1, 100.3, 65.8, 49.0, 31.5, 30.8, 30.6, 19.0, 13.6.

Synthesis of Butyl 3,4-dihydro-1(2H)-quinolinecarboxylate



Distilled and degassed THF (8 mL) was added to 0.10 g (4.17 mmol) magnesium powder in a 15 mL Schlenk flask equipped with a magnetic stir bar under argon atmosphere. TPPA (0.184 mL, 0.8 mmol) was added, followed by TFE (0.15 mL, 2.0 mmol), and *N*-3-bromopropyl-*N*-2-iodophenyl-*O*-butylcarbamate (0.220 g, 0.5 mmol). The reaction mixture was cooled to -84°C and TMSCl (0.355 mL, 2.8 mmol) was added. The reaction mixture was stirred overnight at room temperature, 5 mL water was added, and then extracted with 1:1 hexane:diethyl ether (3 x 5 mL) then solvent was evaporated *in vacuo*. Silica gel chromatography was used to purify the

concentrated reaction mixture (1-3% ethyl acetate in hexane). Purification yielded 0.036 g (30%) of product as a yellow oil. HRMS (ESI) *m/z*: $[M]^+$ calc'd for $C_{14}H_{19}O_2N$ 233.3333, found [M+H] 234.1484. ^1H NMR (300 mHz; $CDCl_3$ δ, ppm) 7.61-7.68 (d, *J* = 7.8 Hz, 1H), 7.121-7.161 (t, *J* = 8.0 Hz, 1H), 7.06-7.08 (d, *J* = 7.3 Hz, 1H), 6.97-7.01 (t, *J* = 7.3 Hz, 1H), 4.16-4.20 (t, *J* = 6.4 Hz, 2 H), 3.74-3.77 (t, *J* = 6.4 Hz, 2H), 2.75-2.78 (t, *J* = 6.4 Hz, 2 H), 1.90-1.96 (m, 2H), 1.63-1.70 (m, 2H), 1.37-1.46 (s, *J* = 7.8 Hz, 2H), 0.93-0.96 (t, *J* = 7.3 Hz, 3H), 0.86-0.89. ^{13}C NMR (75 mHz; $CDCl_3$ δ, ppm) 155.1, 138.4, 130.0, 128.7, 126.0, 124.0, 123.6, 65.8, 65.5, 44.8, 31.1, 27.5, 23.6, 19.4, 13.9.

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