Palladium-Catalyzed Decarboxylative alpha-Arylation

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Honors Distinction Project

Abstract

The original goal of this project was to further investigate the utility of palladium-catalyzed decarboxylative α-arylation reactions with new starting materials, mainly phosphonates, sulfones, and sulfoxides. Additionally, we intended to further perfect the existing reaction with esters and conduct kinetic trials of the esters' decarboxylation. Work was done using standard undergraduate-level synthetic organic lab techniques. Data was primarily analyzed by using NMR spectroscopy and Gas Chromatography. Phosphonates and Sulfoxides did not react in significant yields. Sulfones underwent decarboxylation but did not couple to palladium in significant yields. Data was collected on ester decarboxylation kinetics in relation to the addition of zinc catalyst and the data was inconsistent. Future work will likely be in an entirely different direction than decarboxylative reactions.

Introduction

In organic chemistry, the controlled formation of carbon-carbon bonds is very important because it allows us to make complex structures that are biologically or pharmacologically significant. While there are many ways to make carbon-carbon bonds, they all have their limitations and drawbacks. For example one way of making carbon-carbon bonds relies on nucleophilic attacks on a highly electrophilic carbonyl. However, simple nucleophiles and electrophiles are not the only way of making carbon-carbon bonds and are in fact limited in what they can accomplish.

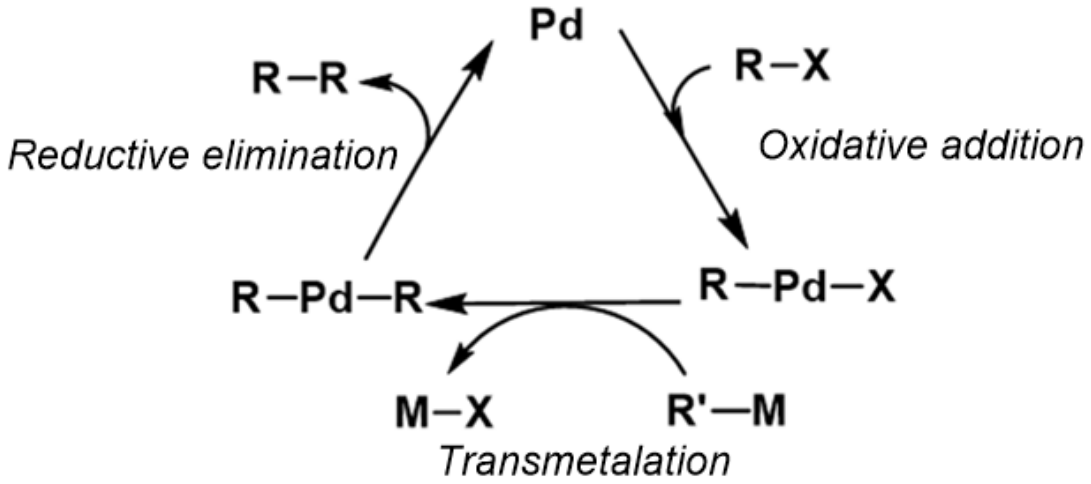
One of the most powerful ways of making carbon-carbon bonds is by using organometallic reagents. Ninety one elements on the periodic table are metals, and the transition metals have proven to be particularly useful in organic synthesis. Some of the earliest metals used in organic synthesis, magnesium and lithium, were used to make carbon nucleophiles for attacking carbonyls. Organomagnesium compounds are called Grignard reagents and are formed

by inserting into a carbon-halogen bond this carbon anion which can then attack an electrophile like a carbonyl or open an epoxide. However, for more complex target molecules, a more nuanced and versatile reaction may be required. One of the main drawbacks of using Grignard reagents is that any acidic protons or water will react with an destroy the Grignard. To solve this problem organic chemists have made useful catalysts out of the transition metals and the unstable magnesium reagents are less often used because of their limited adaptability.(1) One of the most versatile, useful, and adaptable metals in the synthetic toolbox is palladium. Dozens of different methods have been devised using palladium as a catalyst for organic synthesis and thousands of important synthesis have been accomplished due in large part to the utility of palladium as a way of making carbon-carbon bonds.

Making carbon-carbon bonds with an aromatic ring is different than making bonds with a non-aromatic system and requires more extreme reagents than most organic reactions with aliphatic compounds. Two common ways of making carbon-carbon bonds between aromatic and non aromatic organic molecules are Friedel-Crafts and Grignard reactions. Friedel-Crafts reactions involve the use (7) F-C reactions work by using aluminium metal and a halogen to create a positive charge on a carbon atom, the cation can then add to the aromatic ring to form a sigma complex and eliminate a proton. Both Grignards and Friedel-Crafts require some kind of metal to form carbon-carbon bonds Grignards use magnesium and F-C use aluminum.(7) Sometimes however, a milder approach is required. There are, however, limitations on these reactions chemo and stereoselectivity, importantly for us none of these methods can put a ring in the alpha position to a carbonyl. Aromaticity means that they have a stable ring of p orbitals and breaking the p orbitals is highly unfavored. It should be noted that Sn1 and Sn2 reactions, some of the most basic reaction is organic chemistry, do not work on aromatic rings because the atoms

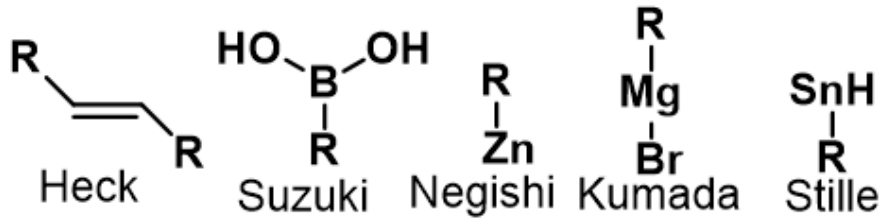
in the ring are sp^2 hybridized. Because aromaticity is so stable such strong reagents are needed to make these bonds. Palladium coupling can also be used to make carbon-carbon bonds with aromatic rings. The first Suzuki couplings were done with aromatic rings and actually bonded two aromatic rings together.

Palladium coupling works through a fairly straightforward mechanism. There are three basic steps: oxidative addition, transmetallation, and reductive elimination. (scheme 01) Oxidative addition is when palladium adds to a carbon-halogen bond, in a similar fashion to how Grignards are made, and is oxidized from Pd^0 to Pd^{2+}, because of palladium's d orbitals it can and do this relatively easily. Transmetallation is the step in which a carbon-metal species complexes with the carbon-palladium-halogen and the non-palladium metal swaps places with the halogen and is then removed as a salt leaving a carbon-palladium-carbon complex. The final step, reductive elimination, is when the palladium leaves the carbon-palladium-carbon complex and is reduced from Pd^{2+} back to Pd^0 and can catalyze further couplings leaving a carbon-carbon bond, the desired product. Most changes in palladium coupling reactions come from changes to the transmetalation step. (2)



(Scheme 01)

Palladium reactions in organic synthesis are so important that the 2010 Nobel prize in chemistry was given for work with palladium coupling. The recipients Akira Suzuki, Ei-ichi Negishi, and Richard F Heck all developed ways of palladium coupling by altering the basic mechanism. Suzuki coupling uses organoboranes to transmetalate in the presence of base, similar to hydroboration, with vinyl and aryl halides and later alkyl groups. Negishi coupling uses zinc in place of the less adaptable magnesium and lithium reagents for transmetalation. The Heck coupling uses olefins, double bonds, and can alkylate or arylate them. Heck was also the first to demonstrate that palladium could be used catalytically for coupling purposes. (1)

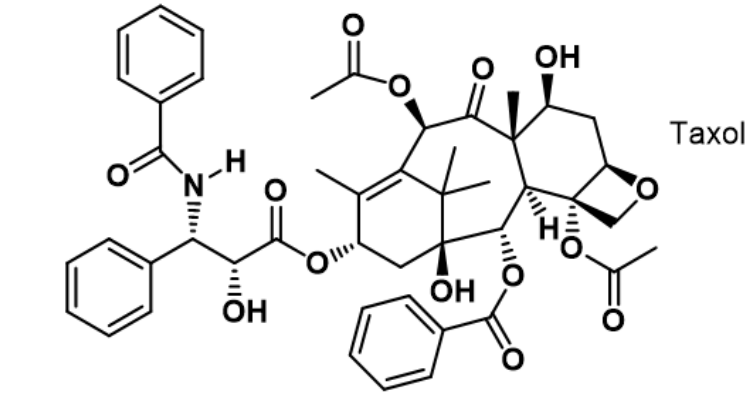


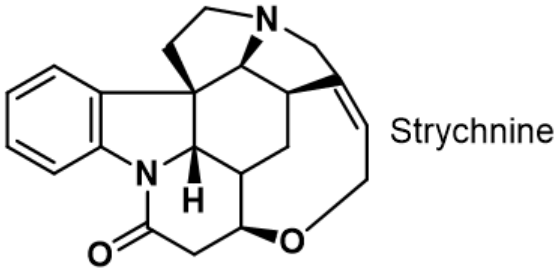
(Figure 01) Pd coupling methods

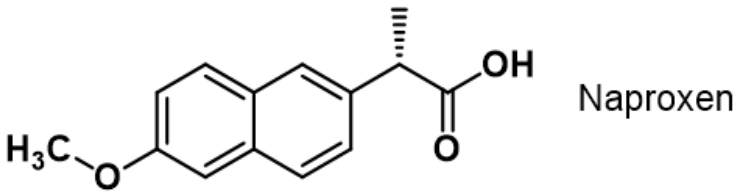
Heck coupling involves the oxidative addition to an R group which can be aryl, alkyl, or vinyl and the palladium-carbon bond complexing to an olefin. The R group of the palladium will then rearrange to the olefin and go through a process called beta-hydride elimination to make a carbon-carbon bond and go back to an olefin double bond. The Heck reaction does not go through a transmetalation step. Other variations on palladium coupling are Stille coupling and Kumada coupling. Stille coupling uses organotin reagents that are highly toxic. Kumada coupling uses grignard reagents.

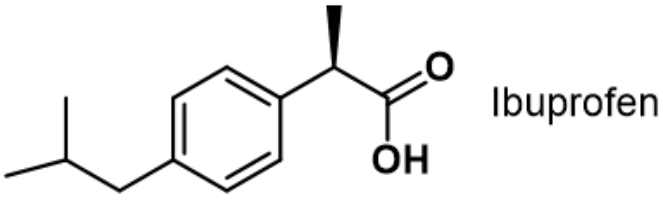
Palladium coupling had been used in many important synthesis since its inception in the 1960s. One of the most important synthesis that used palladium coupling was the synthesis of

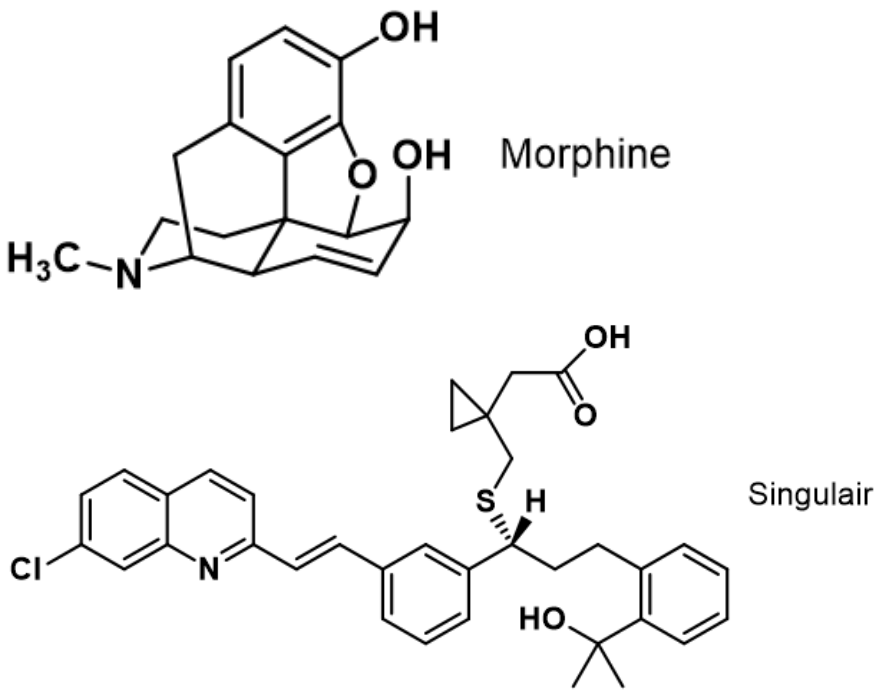
taxol, and important chemotherapy drug, as well as a possible way of making morphine. Heck coupling has also been employed in making various steroids, the lethal cytotoxin strychnine, and other chemotherapy drugs. Naproxen, an NSAID drug and Singulair an anti asthma medication are more examples of the utility and historical importance of Heck palladium coupling reactions. (1)





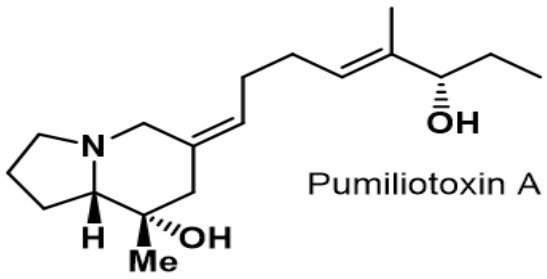


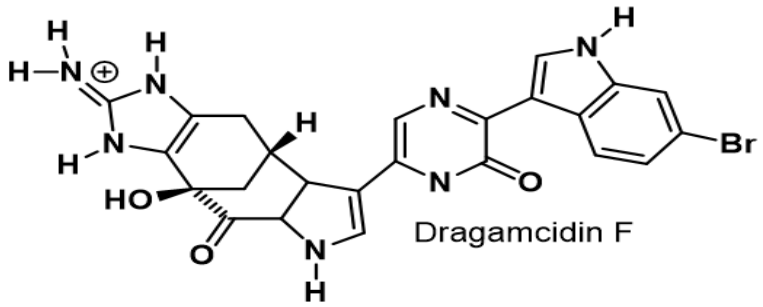




(Figure 02-07) Example molecules

Suzuki and Negishi coupling reactions have been used to make countless biologically interesting molecules. Negishi coupling was employed in the making of Pumiliotoxin A, found in the skin of some frogs. Suzuki couplings were used in the synthesis of the alkaloid dragamacidin F. Countless other synthesis of important pharmaceuticals and biologically active compounds have been achieved with the countless variations of palladium coupling. Palladium coupling has dramatically changed the science of organic synthesis and its usefulness and utility is still being explored and exploited in many fields of organic chemistry. (1)





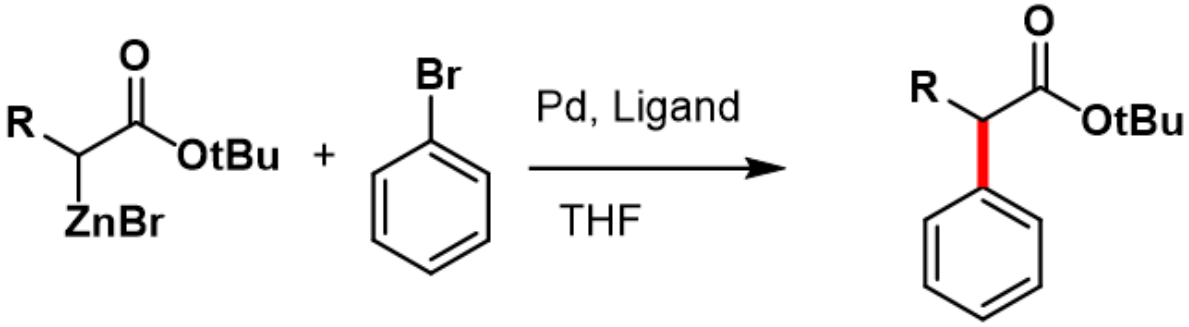
(Figure 08, 09) Example molecules

Aromatic rings in the alpha position to a carbonyl is an important structure in many medications and biologically important compounds. For example the NSAID drugs naproxen and ibuprofen both have aromatic functional groups in the alpha position to a carboxylic acid. The antihistamine drug Allegra (fexofenadine hydrochloride) and countless other molecules share this structure.(3) However, creating this structure in the lab has proved somewhat challenging. While there are other established synthesis for ibuprofen the drug naproxen has been made using palladium coupling. Other biologically or pharmacologically important molecules that have the alpha to carbonyl structure could potentially be made using palladium couplings. There are numerous variations to the alpha to carbonyl structure such as ketones, aldehydes, amides, and for our studies, esters. A better understand of how these structures can be made synthetically without the use of extreme reagents would be very valuable to synthetic chemists.

Alpha-arylation with palladium coupling is potentially a far better way of making alpha-aryl structures under milder conditions. The Hartwig group developed several ways of doing this with zinc enolates. Building on Negishi coupling that uses zinc to transmetalate with palladium the Hartwig group used zinc for this step. However, their synthesis of the zinc enolates and the substrate scope of the methods involved is very interesting from a synthetic standpoint. The existing method utilizes alkali metal enolates which are extremely basic, which limits substrate scope and prevents asymmtertic arylations. Their two different methods of making the zinc

enolates were by isolating the zinc enolates and then using them as a separate reactant and by making them in the reaction as it happened. The Hartwig group started by using alpha-halo carbonyl compounds (Reformatsky reagents) and reacting them with zinc to isolate the resulting enolate. The problem with the use of Reformatsky reagents with zinc enolates is that there is a limit to the amount of isolatable Reformatsky reagents that are available.(3) Before Hartwig, there was relatively little success with the alpha-arylation with palladium, requiring stoichiometric quantities and getting relatively low yields. Hartwig goes on to report the successful alpha-arylation of Reformatsky reagents with a number of electronically varied aryl bromides and different noncyclic esters and lactones. Hartwig uses several different ligands combinations and reports the effectiveness of them. (3)

The second method the Hartwig group used to make zinc enolates for alpha-arylation was by generating them *in situ* (in the reaction) by using Reinke activated zinc.(3) Reinke activated zinc is prepared by reduction of zinc powder with lithium metal. The Reinke zinc enolates are generated in situ during the reaction and have a broader substrate scope than the isolated Reformatsky reagents did.(3) This is probably due to the in situ zinc enolates can be made from a wider array of starting esters and tolerate more functional groups.(3)

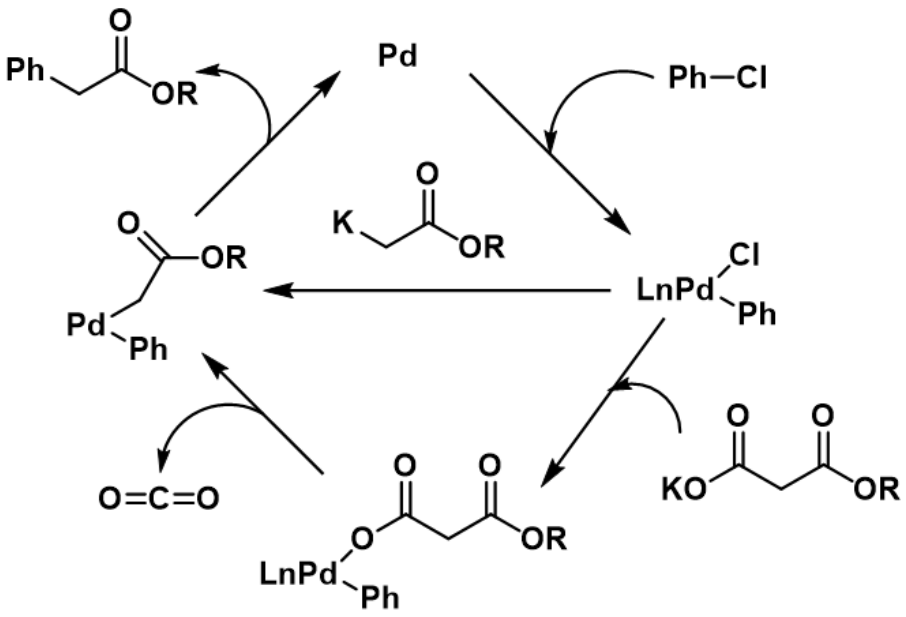


(scheme 02) Hartwig's reaction

The Hartwig group's results largely form the basis for our project. We seek an alternative method of generating enolates that can undergo transmetalation and reductive elimination with

palladium. Our project centers on the decarboxylative method of generating enolates and alpha-arylating them, based on the work of (4,5,6). Also, we look to examine the effectiveness of zinc in aiding decarboxylation of alkali metal carboxylate salts isolated separately. (7) We also look to expand on the work of (7) in terms of kinetic data for the decarboxylation of malonic acid derivatives.

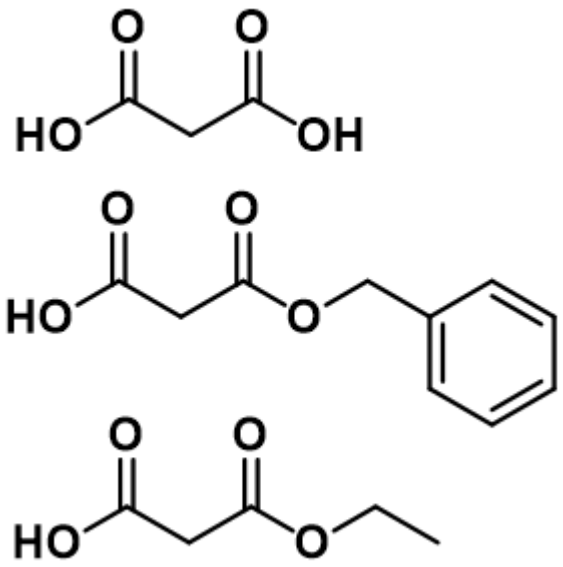
The decarboxylative method of producing enolates be they zinc or alkali metal enolates has several potential advantages over either Reformatsky reagents or in situ Reinke zinc enolates. Both of Hartwig's methods require a base to generate the enolate and while Hartwig's reaction shows surprising functional group tolerance reducing the basicity needed for the reaction could prove to be an attractive synthetic alternative.



(Scheme 03) Reaction cycle

Various malonic acid derivatives have been prepared using methods outlined in (4,5,6). The palladium reaction involves the Pd^0 to Pd^{2+} coupling cycle as outlined above and that has been used synthetically for decades. Various phosphine ligands, solvents, and palladium sources

have been tested with some success consistent with (4,5,6). The overall purpose of the project is to investigate the utility of the decarboxylative process in palladium coupling of malonic acid derivatives and aryl-halides. Expanding on the results of (4,5,6) as well as adding to Hartwig's work we look to test further functional group tolerance, the importance of the halide in the aryl halide, and testing additives such as various zinc complexes and 18 crown 6 to further asses the utility of the decarboxylative process. While the decarboxylative pathway eliminates the need for basic reaction conditions the decarboxylation requires a considerable amount of heat. The amount of heat the decarboxylation requires is interesting because a similar reaction, the Tsuji-Trost reaction, also involves palladium coupling and decarboxylation. However, Tsuji-Trost takes place at room temperature and below. Part of our project is to try and understand why the decarboxylation requires such intense heat and why Tsuji Trost does not.



(Figure 10-12) Malonic acid and example malonic acid derivatives

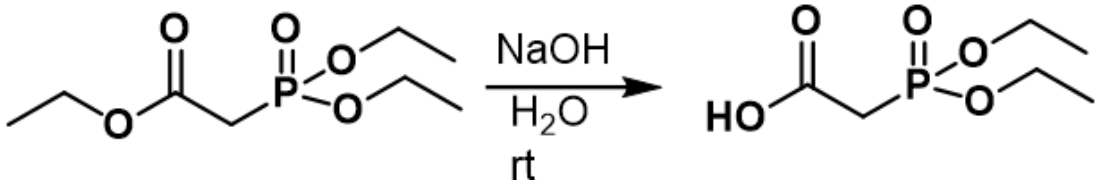
The main focus of our project is to try and develop a decarboxylative method for generating alpha aryl compounds, with either alkali metals or zinc, and to lower the amount of heat needed for the decarboxylative method to work. in addition to our work with malonic acid

derivatives we seek to broaden the substrate scope of the decarboxylative method. We are looking to investigate the palladium reaction with phosphonate and sulfone electron withdrawing groups.

Results and Discussion

The original intention of the project was to expand on the work of Hartwig, involving palladium-catalyzed decarboxylative alpha-arylation. The main focus of the expansion was to test if phosphonates, sulfones, and sulfoxides would undergo the same decarboxylative coupling as the nitriles and esters in an effort to further moderate the reaction conditions of the Hartwig reaction.

We successfully synthesized and characterized the phosphonate and ran the palladium reaction with it. The reaction is a simple hydrolysis reaction where the ethyl group is replaced with a hydroxy group. This happens because nucleophilic hydroxide attacks the electrophilic carbonyl, the ethoxy group is protonated from water and leaves. A 30% yield was achieved.



Scheme (04)

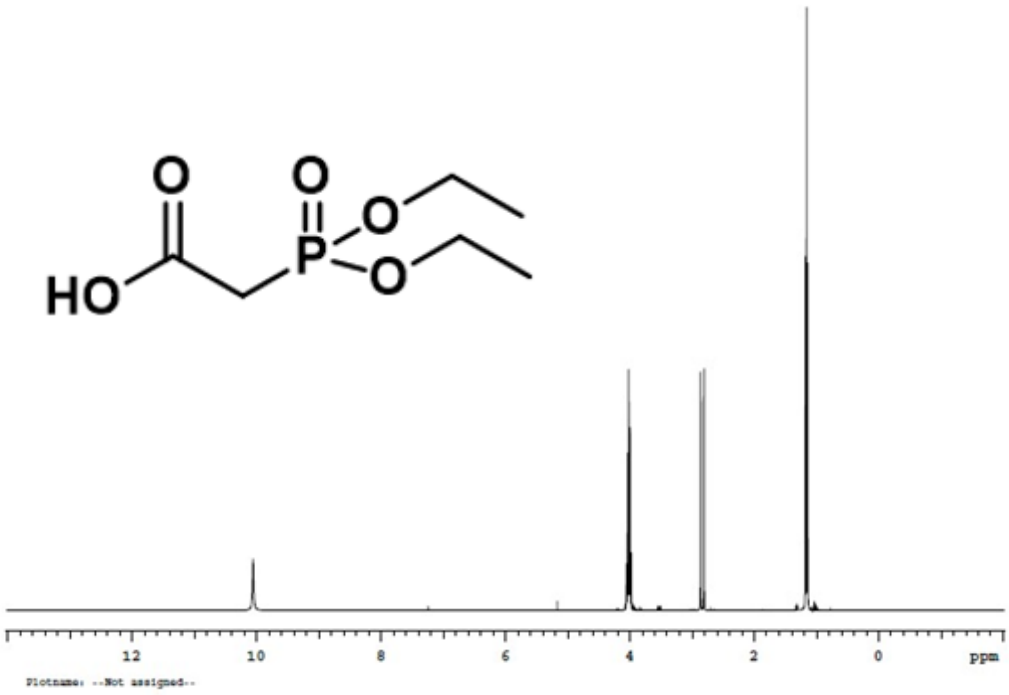


Figure (13) Proton spectrum of phosphonate acid

The sharp singlet at 10 shows that this is the desired acid, although it is unusual for an acid peak to be so sharp. The doublet at 3 is due to the phosphorous being NMR sensitive and splitting those nearby protons. From this we know we have the right starting material to make the potassium salt that goes into the palladium reaction.

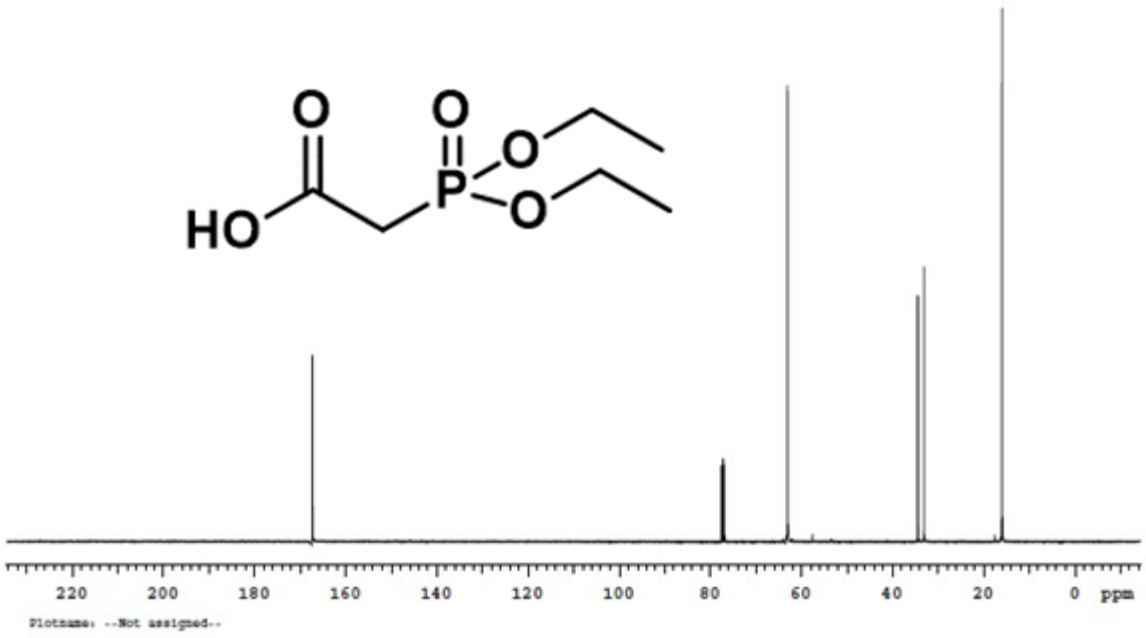


Figure (14) carbon spectrum of phosphonate acid

This is the carbon spectrum from the phosphate acid. The peak at 170 is the carbonyl peak. The doublet at 35 is the carbon between the carbonyl and the phosphorus, it is split because of its proximity to the phosphorus. This is further confirmation that we have the right material to make the salt for the palladium reaction.

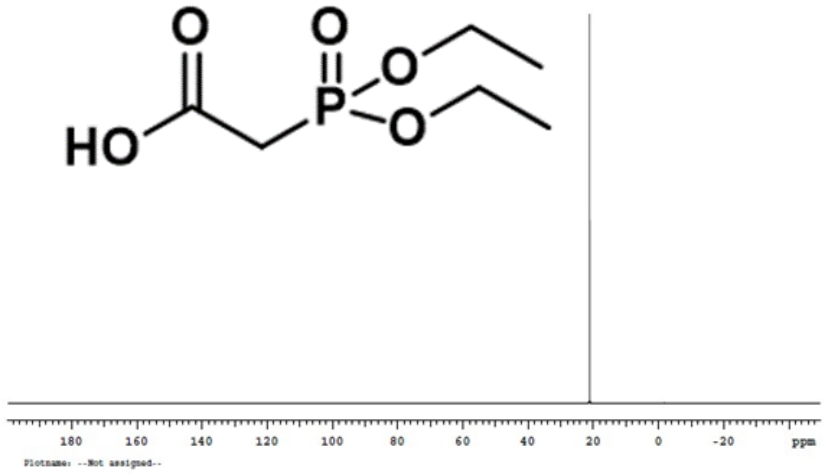


Figure (15) phosphorous spectrum of phosphonate acid

This further confirms that we have the right material and that there is in fact phosphorus in the sample.

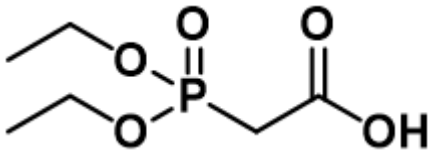


Figure (16)

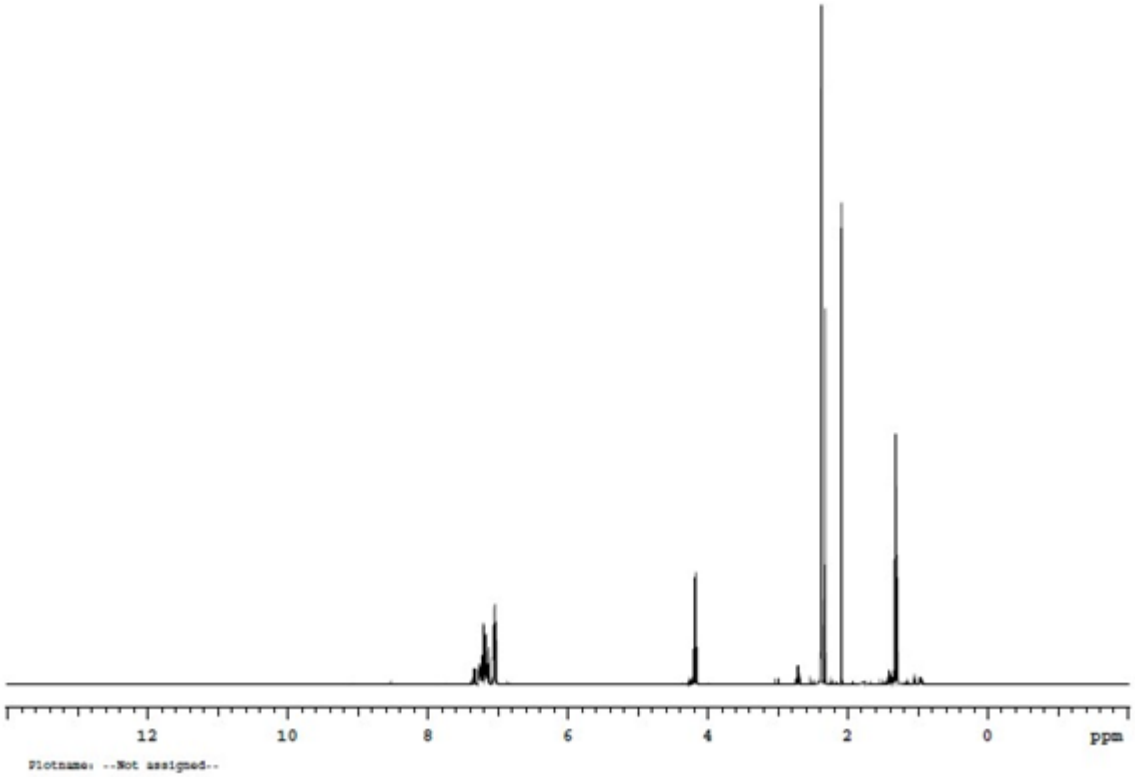


Figure (17) Pd rxn with phosphonate salt

We found no evidence of alpha-arylation as shown by this spectrum. We would expect a doublet at around 1.4-1.5 ppm but we see no evidence of this. What we see is mostly ethyl acetate. From this we can conclude that the reaction didn't work. More specifically we can conclude that no decarboxylation happened. If this was the case we would see evidence of the methyl protons that would be left from the decarboxylation. Without the decarboxylation there is no enolate to couple to the palladium for the coupling reaction.

Sulfone and sulfoxide

After testing the phosphonate and not seeing any evidence of coupling or decarboxylation we moved on to sulfoxides and sulfones. Sulfoxides and sulfones are the more oxidized versions of thiol compounds.

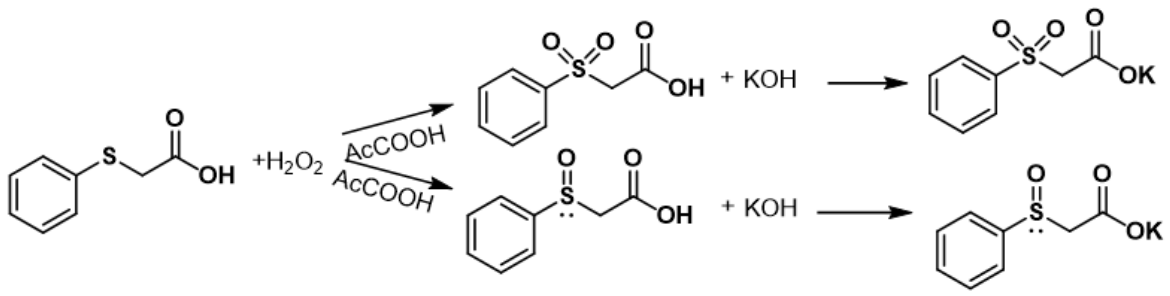


Figure (18)

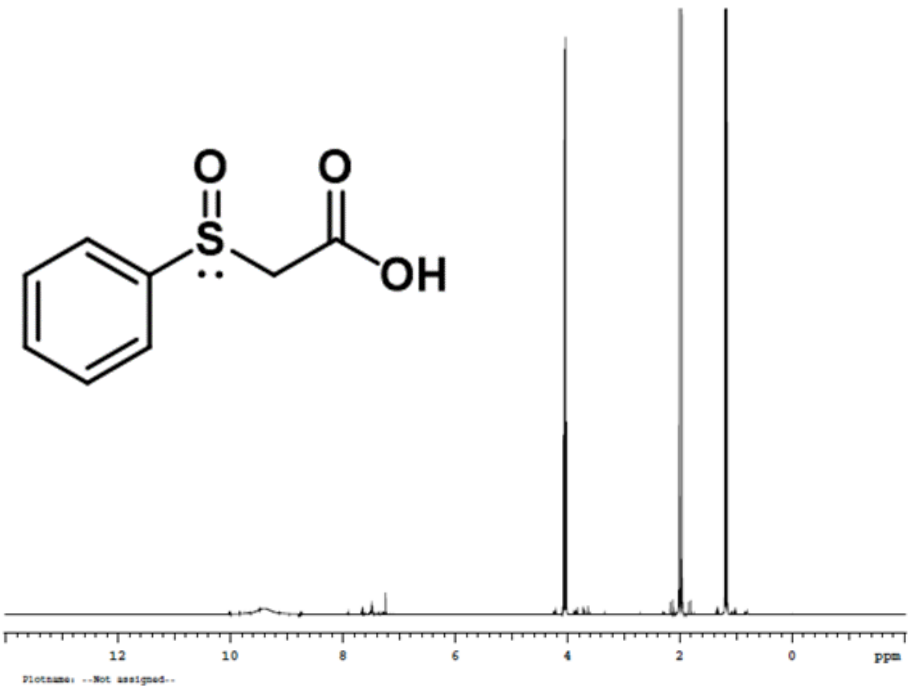


Figure (19) Sulfoxide proton NMR

Our original procedure for the sulfone synthesis gave us the sulfoxide. This may have been due to using hydrogen peroxide, the oxidizing agent, that was slightly diluted. We know

that this is the sulfoxide and not the sulfone because at 2 ppm there is a doublet, though the resolution is not great, this is due to the sulfur atom being a chiral center and splitting the adjacent hydrogen into a doublet.

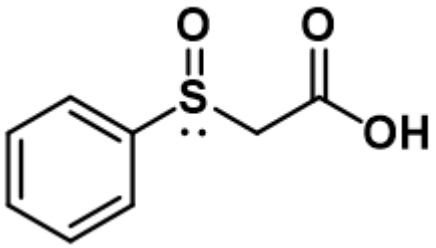


Figure (20) The Sulfoxide

NMR

The sulfone is the full oxidation product of the reaction. Instead of adding one oxygen double bonded to the sulfur two oxygens are double bonded to the sulphur.

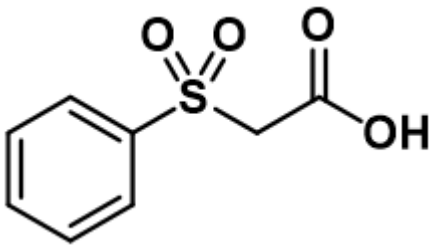


Figure (21) The sulfone

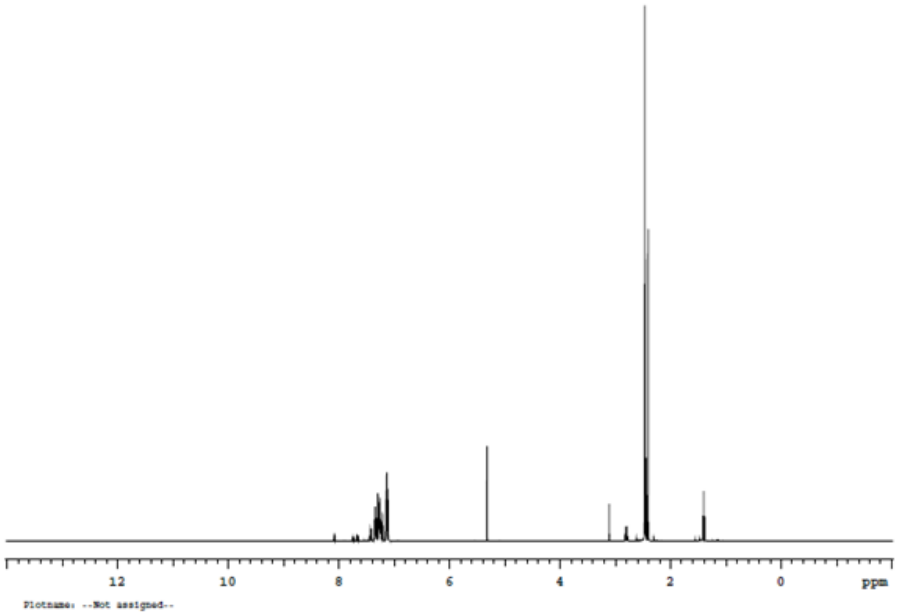


Figure (22) Pd rxn with sulfone

This is a spectrum from the sulfone reaction. The sulfone showed slightly more promise than the sulfone did because we saw evidence of decarboxylation. The small singlet peak at 3.1 ppm is from the methyl hydrogen left over after decarboxylation. Though we did see evidence of decarboxylation we saw no evidence that we could get the molecule to couple to palladium. We tried X and S phos ligands as well as several different reaction temperatures, between 80-140^0 c and still saw no coupling with palladium.

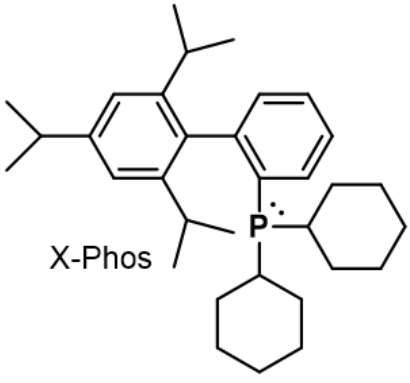


Figure (23) X-phos ligand

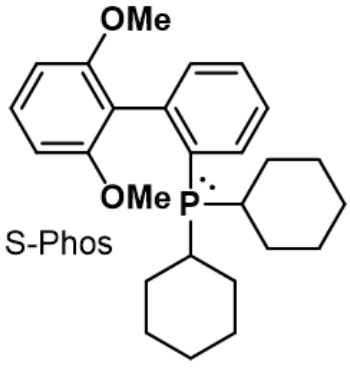


Figure (24) S-phos ligand

Esters and nitriles

Seeing as no palladium-catalyzed decarboxylative alpha-arylations were working we decided to check against some of our old results with ester and nitrile salts. While these reactions worked a couple months ago they did not work when we investigated them a second time.

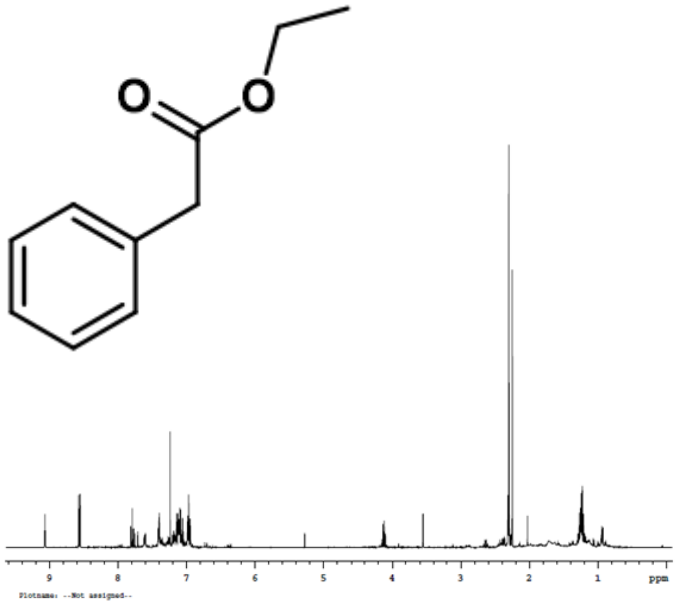


Figure (25) Ester reaction NMR that worked

The singlet peak at 3.6 is the benzyl proton from when the reaction works this NMR was taken several months ago.

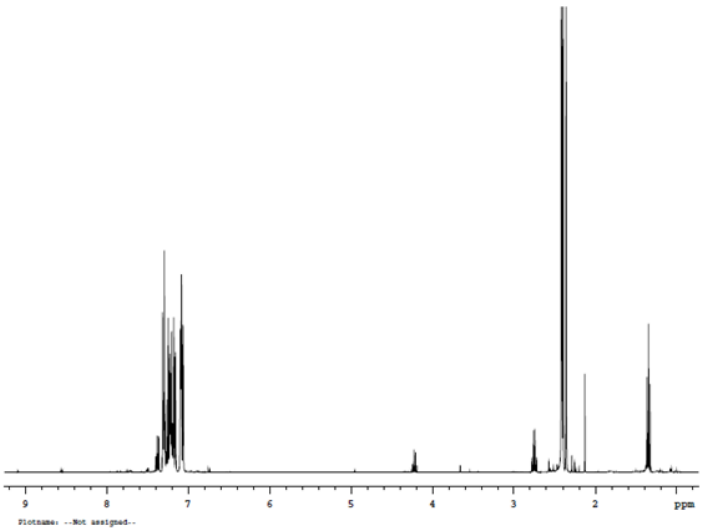


Figure (26) Ester reaction NMR that didn't work

This NMR was taken recently. There is hardly any peak at 3.6 and further analysis shows us that percent yield in intolerably small whereas before it was small but tolerable.

The same thing happened with the nitriles. The nitriles have been investigated extensively by other groups so we would have expected there to be at least some evidence of coupled product.

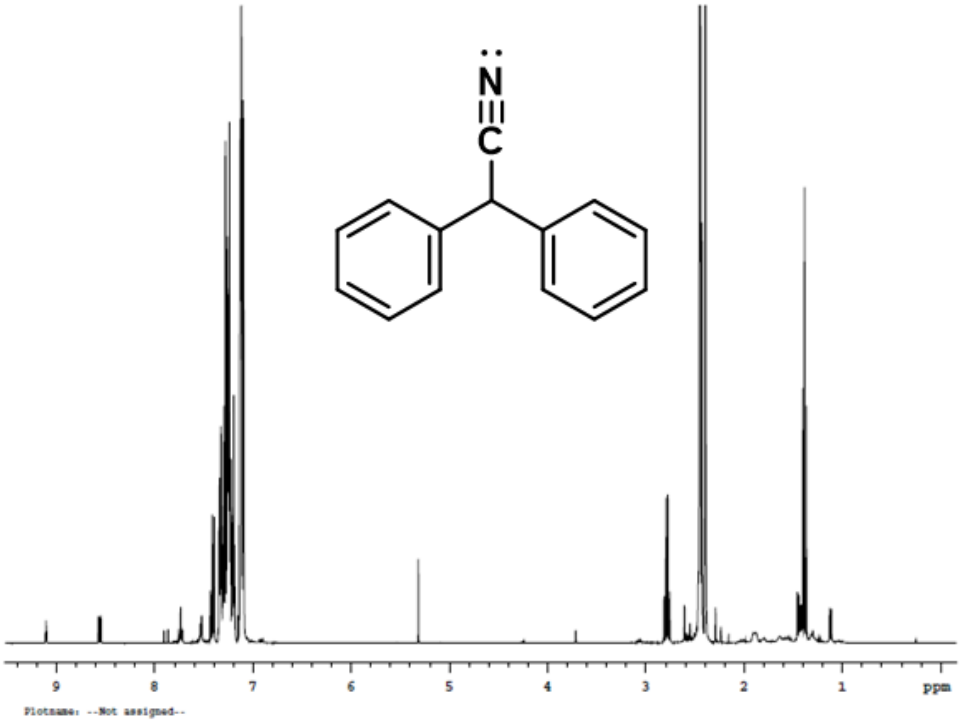


Figure (27) Nitrile reaction NMR that worked

The singlet peak at 5.2 is the singlet from a nitrile reaction when it works. It is upshifted because the nitrile salts arylate twice. This spectrum was taken several months ago.

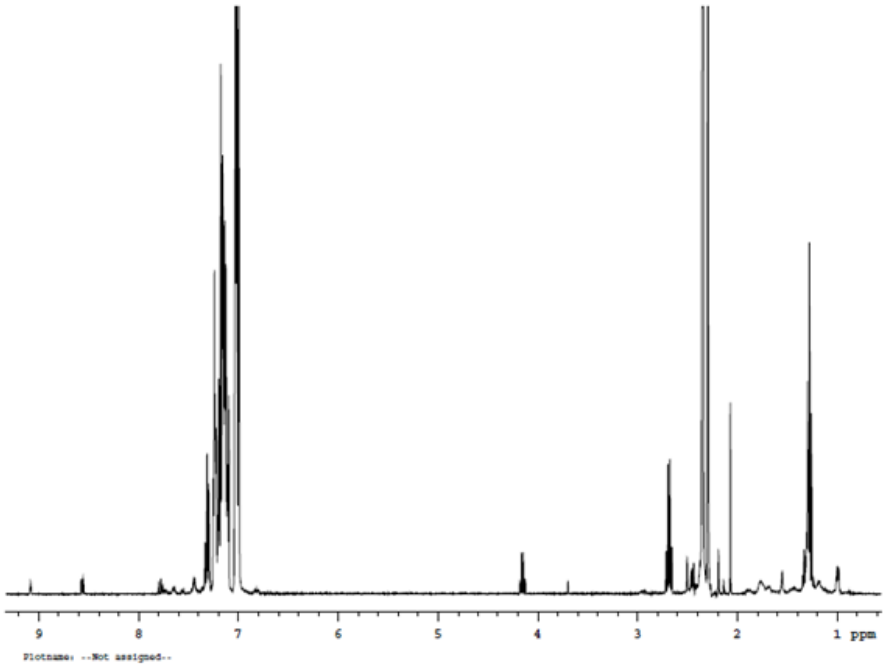


Figure (28) Nitrile reaction NMR that didn't work

This spectrum was taken recently and shows no evidence of any coupling reaction. We are unsure at this time what is making the reactions fail. While yields were never great there was usually enough to calculate a percent yield. We know that there is not a problem with the palladium source because other reactions with the same palladium sources worked normally. Other reasons the reaction may fail are exposure to water or oxygen gas. While care is taken to ensure that neither water or air is in the reaction container it is possible that it gets in. The materials are dried on vacuum for 1-2 hours before being reacted and the xylene solvent is freeze pump thawed every few months. Freeze pump thaw works by freezing the xylene solvent, this process will trap air bubbles in the ice. As the solvent thaws the bubble are released into the headspace of the flask and then vacuum pumped off.

Water interferes with the decarboxylation and the decarboxylation is necessary to make palladium carbon bonds. Oxygen will oxidize palladium itself removing it from the catalytic cycle and shutting down the reaction.

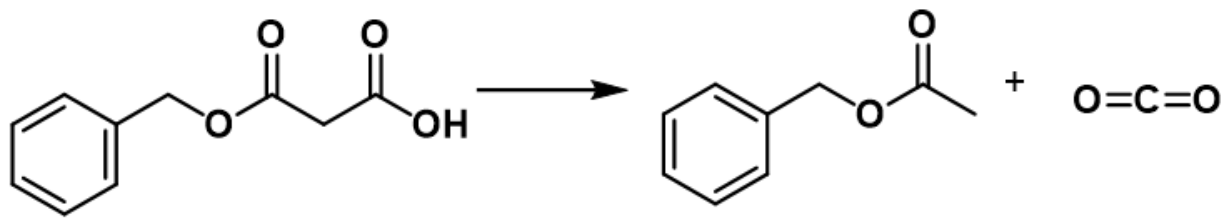
Kinetics

Kinetics runs were carried out at different temperatures and in different solvents. In the end we settled on xylene as the solvent for the reactions. We considered methyl THF, ethylene glycol and isopropanol. Ethylene glycol was abandoned because our internal standard, Dichlorobenzene, does not dissolve in it. The other solvents gave inconsistent data, and in the end xylene was settled on. Xylene is a good solvent for the reaction because it's boiling point is high enough that the reaction can take place and in and it will not boil off. The reaction is typically done at 120^0 C and the bp of xylene is 140. After settling on xylene we tried different concentrations and different temperatures to better understand the reaction. We tried bringing down the temperature and changing the concentration as well as adding zinc.

Kinetics with Zinc

There are several references that support the idea that zinc can accelerate the rate of decarboxylation in malonic acid derivatives. To test this we synthesized a zinc phenanthroline complex and compared the rate of benzyl acetate formation in reactions with and without the zinc complex. It was found that different things happened at different temperatures. Zinc can help accelerate the reaction by complexing to the middle sp^3 carbon and the carbon-oxygen

bonds. This cleaves the carboxylate off into carbon dioxide and leaves a carbanion that is then protonated.



Scheme (05)

At 105 degrees the rate of benzyl acetate formation is excessively slow with or without zinc.

No zinc kvalue	No Zinc half life	Zinc k value	Zinc half life
2.90000E-05	24000 minutes	2.50000E-05	28000 minutes

Figure (29)

No Zinc			Zinc		
Entry	k (min^{-1})	$t_{1/2}$ minutes	Entry	k (min^{-1})	$t_{1/2}$ minutes
1	$3.8x10^{-4}$	1900	1	$8.6x10^{-4}$	800
2	$2.9x10^{-4}$	2400	2	$7.2x10^{-4}$	1000
3	$4.2x10^{-4}$	1700	x		
Avg	**$3.6x10^{-4}$**	**2000**	**Avg**	**$7.9x10^{-4}$**	**900**

Figure (30)

This shows that at 140 degrees the rate of benzyl acetate formation is increased by the presence of the zinc complex. The implications for this in the palladium reaction are yet to be investigated.

Conclusion

The data we gathered over the course of this project is inconsistent. Early success was called into question by later failure. We can found that phosphonates and sulfoxide salts do not undergo palladium-catalyzed decarboxylative coupling. Sulfones undergo decarboxylation but but do not couple. It is possible that with the right ligand and at the right temperature sulfones could also undergo coupling. Further work is necessary. Early success with esters could not be replicated during the course of the summer. It can be concluded that palladium-catalyzed decarboxylative alpha-arylation is not an effective alpha-arylation technique compared to existing methods that require base catalysts.

Kinetics data was more consistent. Zinc catalysis of decarboxylation were observed to have different effects at different temperatures. At 140^{o} c zinc accelerated the rate of decarboxylation but not by a significant margin. For decarboxylative coupling to be useful a different catalyst must be used.

Future work will be continued to “greenify” the Hartwig alpha-arylation. However, decarboxylation clearly is an inefficient method for that purpose. One possible vein of research that is interesting to pursue would be to perform the original Hartwig reactions in water instead

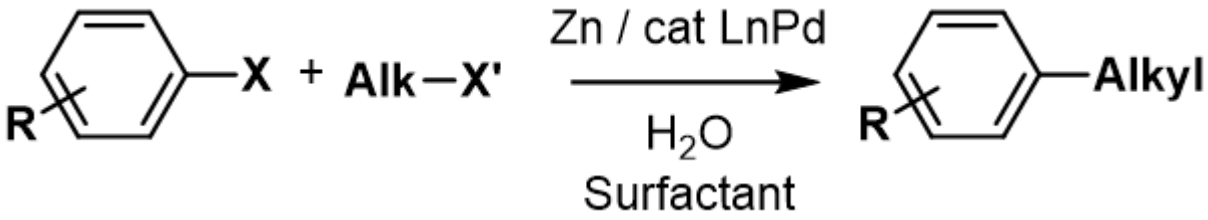
of organic solvent. There are existing methods for zinc reactions in various surfactants and this will most likely be our avenue of future research.

Introduction to Reformatsky Work

The overwhelming majority of synthetic chemistry is done in liquid solutions of two major types: aqueous ones with water that are polar and organic ones that are nonpolar solutions. Most organic reactions are run in nonpolar solvents such as toluene or dichloromethane, due to the nonpolar nature of most organic molecules. However, this can present a problem for a few reasons. Many organic solvents are harsh and bad for the environment, particularly concerning are solvents like benzene, acetone and dichloromethane that are thought to be carcinogenic. Many organic solvents are flammable, making reactions with extreme or reactive reagents such as flammable alkyllithiums that readily combust in air and are dangerous.(12) Water is obviously far cheaper than most organic solvents and is not flammable. In addition, water has a higher boiling point than most organic solvents and thus can be heated higher without reflux

While the use of water-based solutions could have many benefits to synthetic chemists the organic molecules are not soluble in water. This problem can be solved by the use of surfactants. A surfactant is an amphipathic molecule that has both a polar and a nonpolar end, allowing it to form micelles, or small bubbles that has a polar outside that favorably interacts with the water and a nonpolar inside that favorably interacts with itself and other nonpolar things. It has been demonstrated that micelles can be used to conduct organic reactions in aqueous solvents (8,9,10,11). [BW1] Micelles allow reactions of nonpolar molecules to occur in polar solvents by giving a nonpolar molecules a place for the reaction to actually occur within.

This nonpolar bubble acts as a pocket that molecules can move in and out of so that reactant molecules can move into the nonpolar part, react and then move out.



Scheme (06) (Lipshutz reaction in water)

The use of micelles to conduct organic reactions of nonpolar materials in aqueous solvents is relatively new and the work was mostly pioneered by Lipschutz and coworkers (11) and mostly focusing on coupling reactions with palladium and sp^2-sp^3 carbon-carbon bond formation. In addition to work with palladium couplings Lipschutz has also reported the copper catalyzed conjugate additions of alkyl groups to alpha-beta unsaturated ketones, an important synthetic reaction that has broad applicability. This work is important to the idea of "greenifying" synthetic reactions or otherwise making them more efficient, more environmentally friendly, and cheaper. Broadening the scope of micellar reactions could prove highly useful to organic synthesis. In the case of Lipschutzs' work the yields are often in the high 80-90% range which is synthetically useful. There is reason to believe that micellar reactions have made steps toward "greenifying" synthetic chemistry.

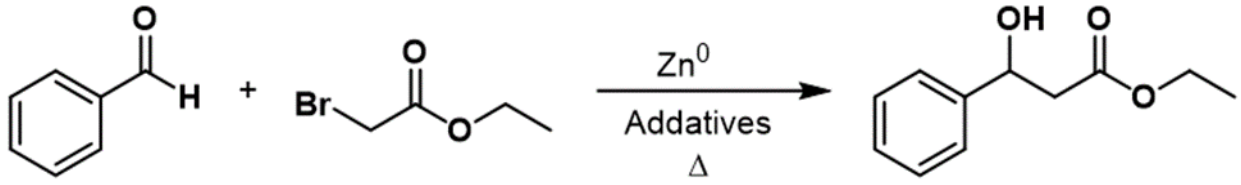
Micellar catalysts in water solvents are an attractive synthetic alternative to organic solvents because they can eliminate the need for harsh organic solvents that can adversely affect the reaction or disturb the functional groups present. Work has already been done using cross-coupling reactions with palladium and forming a sp^2-sp^3 bond, but nucleophilic additions to

carbonyls are not as prevalent in the literature. Nucleophilic additions to carbonyls with organometallic enolates are some of the most fundamental reactions in organic chemistry and are ubiquitous throughout synthetic work. Enolate chemistry is very important because it provides us with reliable and predictable nucleophiles. Optimizing reactions of organometallic nucleophiles with carbonyls in water solvent with micellar catalysts would be beneficial to organic synthesis and green chemistry. Our work focused primarily on the Reformatsky reaction (2) which utilizes a zinc enolate, to act as a nucleophile for nucleophilic addition to carbonyls.

The zinc enolates are a promising class of reactants molecules for surfactant-water reactions because they are less reactive than some other organometallic nucleophiles, and should exist long enough to move into the micelle bubble and react with some electrophile. Their ability to do this has already been demonstrated for palladium coupling reactions and copper conjugate addition reactions (8,9,10,11). Another reason why the Reformatsky reaction is of interest is because it is relatively versatile with a wide-functional group tolerance compared to other more reactive species. The ability to do these reactions in water and use a mild but effective nucleophile such as a zinc enolate would be an attractive set of tools to synthetic chemists looking for milder reaction conditions. Another advantage of using zinc enolates for reactions in water is the fact that they can be formed *in situ* without pretreatment. The ability of organozinc reagents to be made *in situ* under aqueous conditions has been established by Lipschutz(8,9,10) Typical organometallic reagents need to be made immediately before the reaction because they have a short shelf life and often require technical glassware setups. This is a benefit because it makes the reactions less time consuming and less technically demanding. Our *in situ* formation of zinc enolates leads to a simple “dump and run” one pot reaction that can left alone at room temperature, making it an even more attractive alternative to previous reactions.

The focus of our work was to investigate the reactivity of Reformatsky reactions in water solvents with surfactants in the context of nucleophilic reactions with carbonyls for the purpose of establishing optimal conditions for a micellar catalyzed Reformatsky reaction that would be high yield, easy to perform, greener than established methods, and most importantly synthetically useful. This was explored by reacting zinc enolates of different halogen group and ester type figure (32) with benzaldehyde, a standard electrophile, that is used because the lack of alpha-protons eliminates the possibility of deleterious side reactions. The reactions are done in different water/surfactant combinations and with or without various additives. We report the efficiency and percent yield of these reactions in aqueous and organic solvent conditions and explore some of the reasons why they work and don't work.

The main purpose of this work was to investigate the reactivity of zinc enolates in the Reformatsky reaction in water solvents with surfactants. Reactions were performed as small scale 2:3:3 mmol ratios of benzaldehyde to ester to zinc as prescribed by the literature regarding Reformatsky reactions. The reactants were added to a 20 mL scintillation vials and let react for several hours or overnight. Proton NMR was taken to confirm whether the reaction worked using 1,3-dimethoxybenzene as an internal standard and to calculate percent yields.



Scheme (07) general reaction performed

Figure 32 shows an example proton NMR that was taken after a later change in the ratio of reactants. The doublet of doublets at 2.7 ppm is product, we know this because the carbon-

carbon bond formation leads to diastereotopic carbon center between the alpha position of the Reformatsky reagent and the carbonyl of the benzaldehyde giving us the doublet of doublets. The large peak at 3.8 ppm is the methoxy peak of the 1,3-dimethoxybenzene, using simple calculations percent yield was calculated.

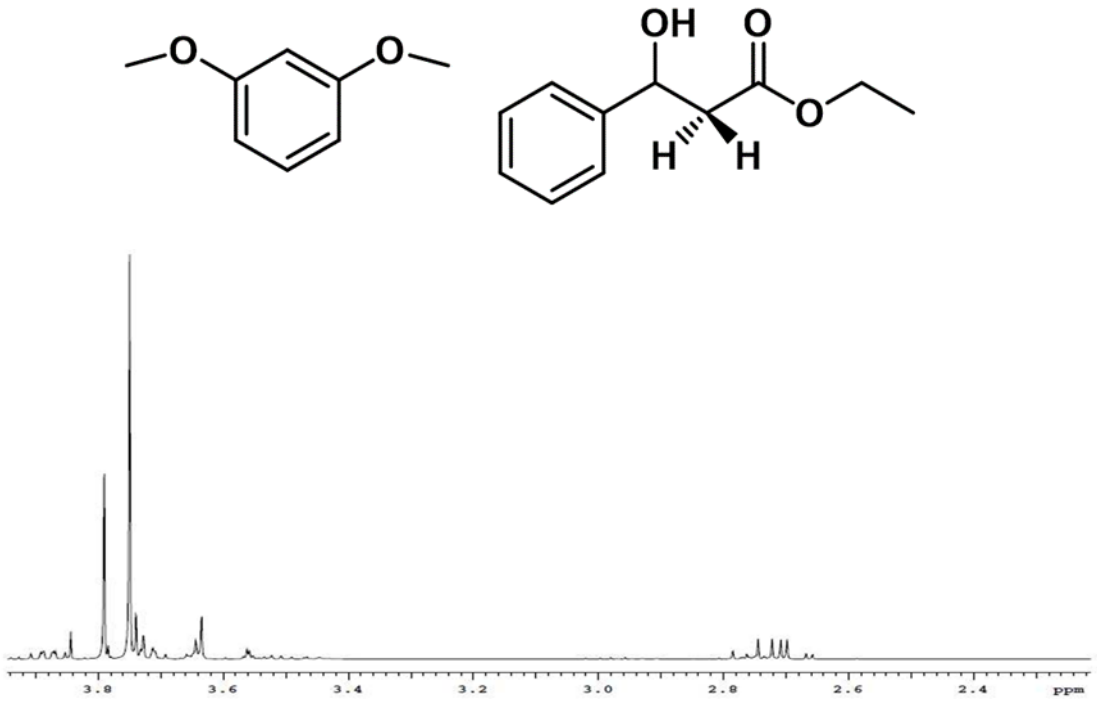


Figure (32) (NMR from Reformatsky reaction with inverted stoichiometry)

Reactions were done in a combination of water with either an octanoic acid/octanol mixture or tocopherol, a vitamin E derivative as the surfactant. The idea to use tocopherol as a surfactant came from (9,10) in which Lipshutz and coworkers use another vitamin E derivative as a surfactant in palladium couplings. Vitamin E derivatives make sense as a source of surfactants because vitamin E is a fat soluble vitamin that acts a radical scavenger, and is amphipathic. The idea for the octanoic acid came from (11) in which Buchwald and coworkers use octanoic acid as a surfactant for Negishi style cross couplings in water. Again octanoic acid

makes sense because it is amphipathic and naturally occurring. Control trials were done in methyl THF a relatively clean organic solvent derived from corn. All solvents and surfactants were purchased.

It was found that none of the surfactants worked except for a few good trials of the octanoic acid/octanol combination which had a 53% yield. Subsequent trials were conducted in other surfactants and methyl THF and none had percent yields above 10%.

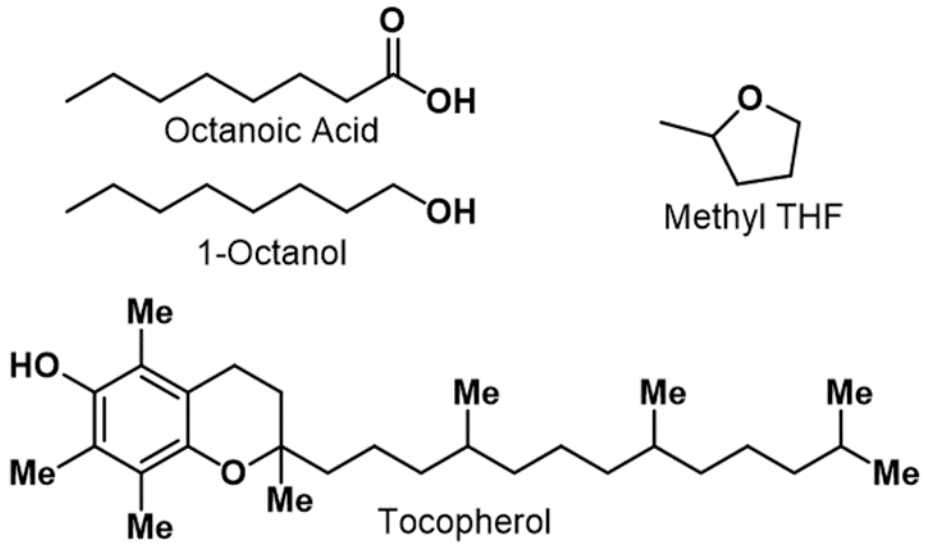


Figure (31) (surfactants and solvents used)

In addition to changes to solvent/surfactant we made changes to the halogen in the alpha position, between chlorine and bromine, and changes to the ester group between ethyl and tert-butyl were also conducted. All reactants were purchased. The tert-butyl ester should theoretically be more soluble inside the micelle than the water. However, it was found that besides a few good initial results no changes to halogen type or ester group lead to an increase in percent yield.

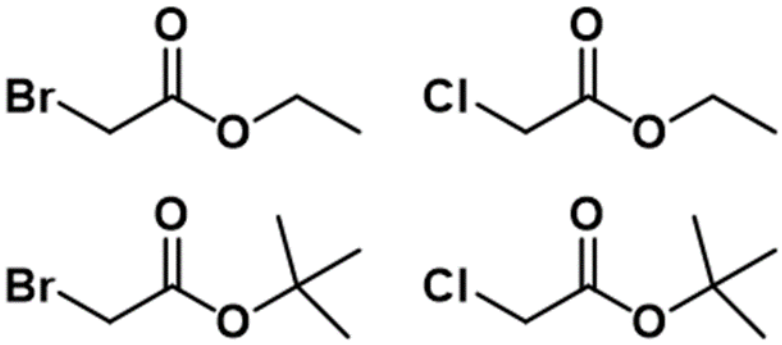


Figure (32) (esters used)

Reactions were also done with or without a variety of additives including: N,N,N,N-tetramethylethylenediamine, Trimethylsilyl chloride, and ammonium chloride. The TMSCl acts as a Lewis acid and should help the formation of the cyclic intermediate that undergoes the actual reaction. However, it was found that when TMSCl was added there was no conclusive increase or decrease in the percent yield. It should be noted that TMSCl was only ever added to the reactions when they were conducted in methyl THF, it is possible that the right Lewis acid could make the reaction work as there is sound bases as to why a Lewis acid would catalyze the reaction.

TMEDA and ammonium chloride should work as chelating ligands to the zinc to help its oxidative addition to the carbon-halogen bond. TMEDA was used for a similar purpose by Lipshutz in (8,9) and was shown to improve yields in both cases. In our work TMEDA had no effect when used in a water/surfactant mixture and saw a slight decrees in percent yield when used in methyl THF. All percent yields where below 10%. NH_4Cl was used in some aqueous trials in place of TMEDA, this was done theorizing that the NH_4Cl would complex to the zinc just the same as TMEDA does. A slight improvement was seen when NH_4Cl was used but all trials were below 10% yield.

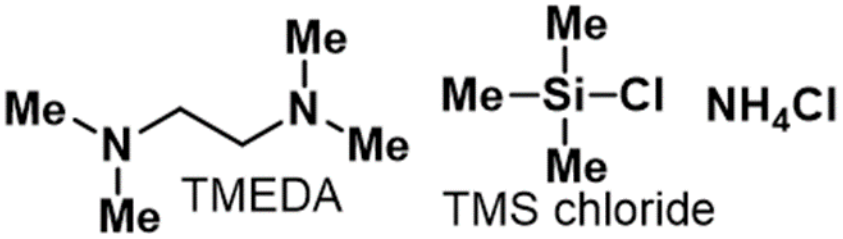


Figure (33)

Results were gathered by proton NMR and percent yields calculated results are summarized in the table below, it should be noted that there were significant problems with reproducibility after the initial good trial of the bromo, ethyl Reformatky in the octanol/octanoic acid combination. It was found that none of the additives had a significant effect on percent yield, although ammonium chloride did increase it by a few points, percent yields were consistently below 10%. It was found that changing the halogen from bromine to chlorine caused a small drop in % yield but consistently below 10%. Changing the ester group did also did nothing to change percent yield and all percent yields from the tert-butyl esters were below 10%. Despite initial results all trials done in octanoic acid/octanol and tocopherol saw percent yields below 10%. Even control trials conducted in methyl THF saw yields below 10% regardless of halogen type, ester group, or additives.

Solvent	Enolate	Ester	Ratio	Yield
Octanoic Acid/octanol	Br	ethyl	2:3:3	53%
Octanoic Acid/octanol	Cl	ethyl	2:3:3	10%
Methyl THF	Br	ethyl	2:3:3	10%
Methyl THF	Cl	ethyl	2:3:3	10%
Methyl THF	Br	t-Butyl	2:3:3	10%
Methyl THF	Cl	t-Butyl	2:3:3	10%
Methyl THF	Br	ethyl	3:2:2	30%

Figure (34) (table)

The one change made that did have a positive effect on the percent yield was the ratio of reactants. Most literature sources have the reactants in a 2:3:3 ratio, of benzaldehyde, zinc, and ester. However, when the reaction was performed in a 3:2:2 ratio of benzaldehyde in excess relative to the ester and the zinc it was found that it had a significantly higher yield, increasing from below to 30%. Further trials have to be conducted as to why this may be the case and what additives and reaction conditions can be optimized to raise the yield further.

Conclusions

Data gathered was inconsistent and despite numerous trials we were unable to get the same initial results. Most reactions performed has yields that were below 10% and despite trying

several things nothing really changed the yield except the ratio change at the end. Reformatsky reagents in water solvents are not an efficient way of making carbon-carbon bonds and more work will be needed to establish a method for using zinc enolates in water solvents if it is possible at all.

Future work will focus on the use of photoredox catalysts to affect carbon-carbon bond formation, based on the work of MacMillan, as an efficient way of making the alpha-aryl structure that had eluded us in past work. Work has already begun on this avenue of research but there is nothing of significance to report yet.

Acknowledgements

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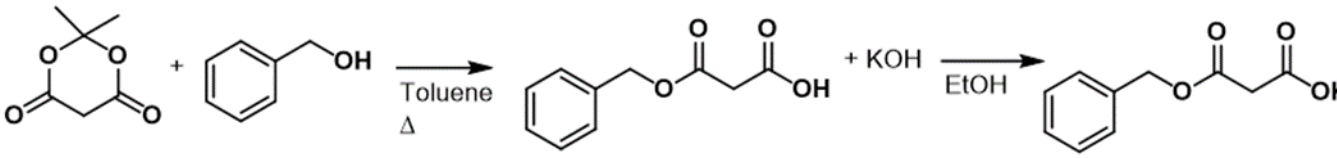
Methods and Materials

Synthesis of Potassium salts for the palladium reaction

Ethyl ester salt - A molar equivalent of KOH in ethanol was mixed with a solution of diethyl malonate 6 ml .04 mol. in ethanol and was let stir for several minutes. The mixture was then chilled on ice for 15 minutes and filtered using a buchner funnel. The remaining white lumpy powder was than washed with diethyl ether and then dried using a vacuum pump for several hours.

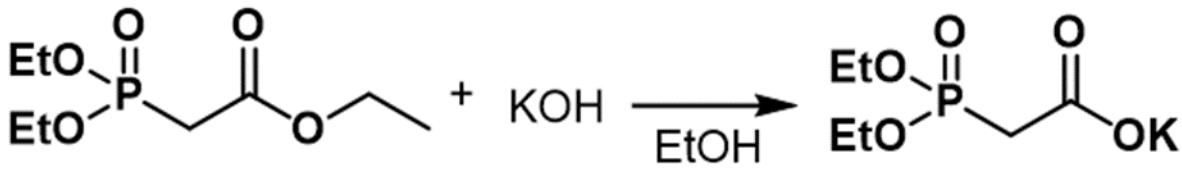
Scheme (06) Ester salt synthesis

Benzyl ester salt - It should be noted that this procedure was not always effective when scaled up and the ester would hydrolyze back into starting materials. A 1:2 mixture of meldrum's acid and benzyl alcohol was mixed in 20ml of toluene and stirred with heat overnight. 20 ml of ethyl acetate are added and then extracted using sodium carbonate. The organic layer was then acidified with concentrated HCl until red on litmus paper. This was then dissolved in ethyl acetate and sodium carbonate was used to extract. It is then washed with ethyl acetate and rotovapped. Ttered the material was then dissolved in ethanol and mixed with KOH in ethanol and filtered and dried.



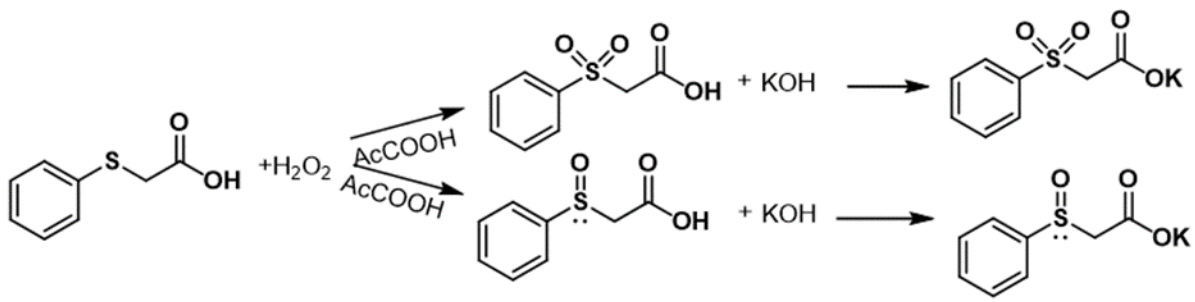
Scheme (07) Benzyl ester salt synthesis

Phosphonate salt - The phosphonate starting material triethyl phosphonoacetate was mixed with 101 molar percent NaOH and dissolved in water and let stir at room temperature overnight. It was then acidified with 1M HCl and extracted with CH2Cl2 and rotovaped. A colorless oil is formed which is consistent with the literature. The potassium salt was then arrived at using the same procedure as the other salts.



Scheme (08) Phosphonate synthesis

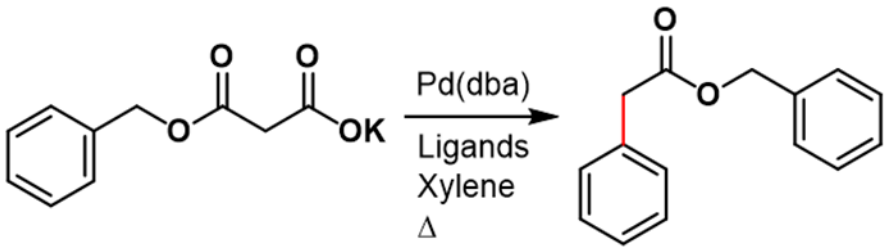
Sulfone/Sulfoxide salt - 5 grams of the starting material 2-phenylthio acetic acid are dissolved in 8 ml of glacial acetic acid and 7ml of hydrogen peroxide. And let stir at room temperature for 2 hours. 1 gram of this was then dissolved in ethanol and a molar equivalent of KOH is dissolved in ethanol then mixed. This is then cooled over ice and filtered, washed with diethyl ether, and dried under vacuum for several hours. Note that the first time this was done slightly used hydrogen peroxide was used and initial this yielded the sulfoxide which is the incomplete oxidation product.



Scheme (09) Sulfone/sulfoxide synthesis

Palladium reactions - palladium reaction are done under reflux and under a nitrogen environment. Approximately 1 gram of starting material is used followed by 1.5 mol% of palladium and 6 mol% of the ligand being used, as well as 10-20 mol% of the internal standard, meta dinitrobenzene. These solid/powders are then put under vacuum for 1-2 hours. The container was then backfilled with nitrogen gas and 1 mol equiv of 4 chlorotoluene and 2 ml of xylene solvent are inserted through a septum cap. The mixture was then put on a heating block

that is already set to the desired temperature and let stir overnight, being checked periodically to ensure that the temperature is right.



Scheme (10) Pd reaction

Kinetics - Kinetic trials were done using the acid form of the benzyl ester salt and using para dichlorobenzene as the internal standard rather than meta dinitrobenzene. Approximately .1 grams of starting material and approximately .075 grams of internal standard were used. The solvent was para xylene unless otherwise specified. The reaction was conducted in a round bottom flask and under reflux for trials conducted at 140 degrees celsius. Aliquots were taken at the beginning and every half hour for the first 2 or 3 time points and then taken every hour. Aliquots of approximately .1 ml were taken and worked up in 1 ml of hexanes and 1 ml of sodium carbonate with the water layer being removed quickly after. Measurements were taken using gas chromatography.

Safety Assignment

This project is an investigation of palladium coupling reactions with halo-benzenes and carboxylates, as well as palladium catalyzed decarboxylations of carboxylate salts with varying

electron withdrawing groups. The project may change focus to carboxylic acid decarboxylation rather than carboxylate decarboxylation. The purpose being to determine the effectiveness of the process on varying electron withdrawing groups and to better understand the kinetics of the palladium catalyzed decarboxylation product.

Chemicals:

Pd2(dba)3 - The main source of palladium in the reactions being conducted is Pd2(dba)3. The Pd acts as a catalyst for the reaction and the (dba)is a neutral ligand that keeps the Pd as Pd0 to ensure its usefulness in the reaction.

MW - 915.72, Black powder.

Should be stored in proper container, will degrade on contact with the air.

Sigma Aldrich recommends gloves be worn.

Triethyl phosphonoacetate - A starting material in making the phosphonate salts and their carboxylic acid derivatives.

MW - C8H17O5P, Clear liquid at RT,

Should be stored in proper bottle, is flammable.

Chemical should only be disposed of in proper waste container.

HCl - Hydrochloric acid is a strong mineral acid used to hydrolyze during separation and purification while synthesizing substrates for the main palladium reaction

MW - 36.46, clear liquid at RT,

Concentrated HCl should only be stored in the acid cabinets in the stockroom and should always be transported in an acid bucket. It should only be worked with in the flame hood and should be returned to the acid cabinet when finished.

HCl is a strong acid and an extreme health hazard causing skin, eye, and respiratory irritation. Gloves and lab coat should be worn at all times.

Ethyl acetate - USed as a solvent

MW - 88.11, Chemical Formula - C4H8O2 Clear liquid at RT

5 liter bottle should be kept in flame cabinet. Squirt bottle can be kept out.

Ethyl acetate is flammable and can cause skin, eye, and respiratory irritation.

Hexanes - Used as solvent

MW - 86.18, Chemical Formula - C6H14, Clear liquid at RT

Should be stored in flame cabinet when not in use. Gloves and lab coat should be worn.

Extremely flammable liquid and vapor, can cause skin, eye, and respiratory irritation.

Acetone - Used to clean glassware

MW - 58.08, Chemical Formula - (CH3)2CO, clear liquid at RT

5 liter bottle should be stored in flame cabinet, squirt bottles for cleaning can be left out.

Highly flammable. Recommended that gloves be worn when handling but health effects take years to accumulate for skin exposure.

Toluene - Used as a solvent

MW - 92.14, Chemical formula -C6H5CH3, Clear liquid at RT

5 liter bottle should be stored in flame cabinet.

Highly flammable. Highly toxic. Can cause skin, eye, respiratory irritation.

Dichloromethane - Used as a solvent

MW - 84.93, Chemical formula - CH2Cl2 Clear liquid at RT

Should be stored in flame cabinet and used in fume hood.

Flammable and toxic. Can cause skin, eye, and respiratory irritation. Cancer suspect agent.

Chloroform - Used as solvent/ NMR solvent.

MW - 119.38, Chemical formula - CHCl3 , Clear liquid at RT

Large bottle should be stored in flame cabinet. Small bottle for NMR can be kep out.

Flammable, Can cause skin, eye, and respiratory irritation. Cancer suspect agent.

NaOH - Used as a base

MW - 40, Chemical Formula - NaOH, White solid at RT. Often dissolved in water.

Should be stored in container and kept in stockroom. Gloves should be worn.

Strong base, can cause skin, eye, and respiratory iirritation. Combusts with certain organic materials.

Na2CO3 - Used as a base for extracting.

MW - 105.98, White powder at RT, often dissolved in water.

Should be kept in proper container and solutions can be kept in plastic bottles.

Strong base. Can cause skin irritation.

Ethanol - Used as a solvent

MW 46.07, Chemical formula - C2H5OH, CLear liquid at RT

Should be kept in flame cabinet when not in use.

Highly flammable. Toxic if ingested. Can cause skin and eye irritation.

DMSO - used as an NMR solvent

MW - 84.17, Chemical formula -(CH3)2SO, Clear liquid

Should be kept in flame cabinet, though small bottle can be kept out when in use.

Flammable and toxic. Can cause skin, eye, and respiratory irritation.

Xylene - Used as a solvent. There are ortho, para, and meta variations though p is primarily used.

MW - 106.17, Chemical formula - C8H10 , Clear liquid at RT

Should be kept in bottle, stored in flame cabinet. Gloves should be worn.

Flammable and Toxic. Can cause skin, eye, respiratory irritation.

K2CO3 - Used as base when extracting

MW - 132.1, white powder at RT, often in solution

Should be kept in bottle, in solution can be kept in plastic bottle. Stored in gen chem stock room.

Toxic. Gloves should be worn. Can cause skin, eye, respiratory irritation.

Hydrogen peroxide

MW - 34.01, Molecular formula - H_2O_2, Clear liquid at RT. Usually in 30% solution with water

Keep in proper bottle and cold when not in use.

Toxic. Potentially explosive at high concentrations. Use gloves and keep in fume hood. Not flammable at usual concentrations.

Dibenzylmalonate

MW - 284.31, Molecular formula - $C_{17}H_{16}O_4$, slightly yellow liquid at RT

Keep in proper bottle in flame cabinet

Flamablable. Cane cause skin, eye, respiratory irritation.

Phenylthioacetic acid

MW - 168.21, Molecular formula - $C_6H_5SCH_2COOH$, white/yellowish powder at RT

Keep in proper container.

Can cause skin, eye, respiratory irritation.

P-chlorotoluene

MW - 126.58. Molecular formula - C_7H_7Cl, Clear liquid at RT

Keep in container in flame cabinet

Flammable. Wear gloves. Can cause skin, eye, respiratory irritation.

Procedures and Techniques:

Schlenck line - The schlenck line involves vacuum and there is a danger of the glass imploding. A mask must be worn at all times to keep from getting glass in eye in the event of an implosion. The schlenck line is used to extract water and oxygen from reaction containers and to help pull solvent out of a reaction workup.

Extraction - Extraction is used to isolate and purify the products of my reactions. This often done using bases such as sodium carbonate and organic solvents such as ethyl acetate and dichloromethane.

Acidification - Part of the reaction I am doing requires the use of HCl to acidify a carboxylate into a carboxylic acid. This is done using a pasteur pipette to drip concentrated HCl into the reaction.

Filtration - After the main Pd reaction I have to use a buchner funnel to filter off the Pd salt and to isolate the products of the reaction. Buchner funnel is mostly used because the vacuum helps pull the products down and isolates the solid Pd salt.

Rotovap - The rotovap is used to concentrate down a solution by pulling solvent out with while under vacuum and rotating in a heated water bath. This is used to concentrate down solutions before taking NMR.

Instruments and Equipment:

NMR - The NMR will be used to confirm that the right substance has been formed or isolated. I will primarily be using Proton NMR though carbon 13 and phosphorus nmr will also be used. The main safety concern with NMR is simply knowing what to do. If there is any kind of problem with the instrument I am to contact Dr. Brenzovich or Dr. Miller as soon as possible.

GC - The GC will be used during kinetic the studies to measure the rates of reactions. The main safety concern with the instrument is to not touch the gold injector or the FID flame because they are very hot and can cause burns. The instrument also uses H2 gas for the flame and H2 gas is very explosive.

Wastes:

Most wastes generated can go into the main organic waste container in the lab. Acid wastes from acidification and extraction can be neutralized with sodium bicarbonate and then put down the drain with excess water. The NMR and GC generate no waste of their own. The Pd salt generated in the main reaction can go into the garbage along with other normal garbage.