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Greener and renewable methods for Pd-catalyzed cross-coupling and alkoxycarbonylation reactions

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by

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DEDICATION

To Betty Jean,

The memories with you I will cherish,

Since it was last year that you did perish,

And ever since my world has been a little more nightmarish

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LIST OF ABBREVIATIONS

CO	carbon monoxide
CMC	critical micelle concentration
CTAB	Cetyl trimethylammonium bromide
dba	dibenzylideneacetone
DEAD	diethyl azodicarboxylate
DiPEA	N,N-diisopropylethylamine
DIAD	diisopropyl azodicarboxylate
DMA	dimethylacetamide
DMSO	dimethylsulfoxide
d'bpmb	Ditertbutyl phosphine methyl benzene
dppp	1,3-diphenylphosphino propane
d'bpp	1,3-ditertbutylphosphino propane
dppm	1,3-diphenylphosphinomethane
ESI	electrospray ionization
Et	ethyl
EtOAc	Ethyl Acetate
EtOH	ethanol
eqn	equation
g	gram
mg	milligram

GC	gas chromatography
GC-MS	gas chromatography coupled with mass spectrometry
h	hour
L	liter
LMS	lutidinium mesylate
MsOH	methane sulfonic acid
MSA	methane sulfonic acid
Me	methyl
MeOH	methanol
Mes	mesitylene
MHz	megahertz
mL	milliliter
nBu	n-butyl
OAc	acetate
OTf	triflate
OTs	tosylate
[ox]	oxidation
2-PisMS	2-picolinium mesylate
4-PisMS	4-picolinium mesylate
psi	pounds per square inch
PMS	pyridinium mesylate
ppm	parts per million

NaC	Sodium Cholate
µL	microliter
mL	milliliter
min	minute
mo.	month
mol	mole
mmol	millimole
µmol	micromole
NEt_3	triethylamine
NHC	N-heterocyclic carbene
NMR	nuclear magnetic resonance
Ph	phenyl
Ph_3P	triphenyl phosphine
rt	room temperature
rxn	reaction
SDS	Sodium dodecyl sulfate
TEA	triethylamine
THF	tetrahydrofuran
TsOH	p-toluenesulfonic acid
PTSA	p-toluenesulfonic acid
wt%	weight percent

ABSTRACT

In response to current environmental issues and concerns, an abundance of chemical literature focuses upon green, benign methodologies. Considering these issues, work presented within this thesis focuses upon development of greener synthetic techniques that are robust and versatile in both and Pd-catalyzed cross-coupling reactions and alkoxycarbonylation.

Sonogashira coupling between terminal alkynes and aryl bromides or iodides was high yielding with $Pd(PPh_3)_2Cl_2$ in water at 40 °C using commercially available surfactants such as SDS and CTAB. An iodide and Cu(I) inhibition was observed under these micellar conditions with aryl bromide substrates, leading to development of Cu(I)-free conditions. Studies under Cu(I)-free conditions suggest two competing mechanistic cycles. Both cycles (deprotonation and carbopalladation) lead to traditional Sonogashira products, but the carbopalladation cycle also produces an enyne product. The surfactant solution (either 2 wt% SDS or CTAB) can be recycled up to 3 times without reduction in yield when coupling 1-iodoanpthalene with 1-octyne in the presence of excess piperidine, 5 mol% CuI, and 2 mol% $Pd(PPh_3)_2Cl_2$.

The effect of the phosphine ligand structure was evaluated in aqueous phase Heck cross-coupling reactions. A methyl cholate derivative was modified with a tri-aryl phosphine moiety, creating a novel ligand that effectively coordinated to $Pd(OAc)_2$ when dissolved in methanol. The cholate-Pd complex proved to be an

efficient catalyst for Heck cross-coupling between various olefins and aryl iodide substrates under basic aqueous conditions with mild heating. The cholate ligand appears to enhance reaction yields by creating a localized hydrophobic environment around the Pd center, which attracts and increases the local concentration of nonpolar coupling reagents near the active catalytic site. Homogeneity studies show that the catalytically active Pd species remains heterogeneous throughout the reaction duration.

Finally, palladium catalysts can also be effective in the conversion of olefinic molecules to aliphatic esters. Palladium complexes, generated from $Pd(OAc)_2$ and benzimidazolium salts were developed as effective catalysts for the alkoxycarbonylation of olefins in high yields (>88%). Alkoxycarbonylation of 1-hexene in dimethylacetamide was achieved within 24 h at 110 °C using 1 mol % catalyst, 1000 psi CO, and ethanol. Reactions can be prepared in air, without auxiliary acid additives, to produce ethyl 2-methylhexanoate and ethyl heptanoate in approximately a 2:1 ratio. This method was also applied to unsaturated fatty acid esters to form α,ω-bifunctional molecules such as ethyl adipate, demonstrating potential as a novel methodology for making bioderrived monomers for polymer synthesis.

CHAPTER I: IMPORTANCE OF GREEN CHEMISTRY

As the consequences of fossil fuel usage increase and the demand for environmentally benign technologies rise, there is an ever increasing prevalence of terms such as biorenewable, biodegradable, sustainable, energy efficient and green to describe various aspects of environmentally minded research.[1–15] While the definition of these terms can seem nebulous due to their ubiquitous use in chemical literature, a precedent for environmentally benign research was set by Anastasis et al. in 1998 by defining the '12 Principals of Green Chemistry' (Appendix A).[8,16–18] These principals pay particular attention to atom economy, waste reduction, toxicity/hazard reduction, feedstock renewability, and catalysis, thereby giving a practical guideline to development and improvement of technologies in the chemical field.

Traditional petrochemical technology dominates the production of our day-to-day products, including adhesives, plastics, and pharmaceuticals. Even if the production pathway is relatively short from raw materials to product inherent features remain that are unsuitable for green technologies, such as feedstocks from nonrenewable resources or excessive organic waste material from reaction solvent, auxiliary reagents, and product purification. In addressing these problematic areas using green principles, researchers focus upon three main objectives: 1) improvement of catalytic systems and atom economy, 2) utilization of raw

materials from renewable resources and 3) elimination of hazardous organic solvents.

Consequently, the research presented in this thesis was undertaken with these three goals in mind. In particular, we address improving Pd-catalytic performance in aqueous media as well as the catalytic transformation of renewable feedstocks to produce industrially viable materials. Herein follows a brief introduction on the importance of Pd-catalysis and the impact of water as reaction solvent on synthesis, especially in the presence of surfactants.

Transition Metal Catalyzed Carbon-Carbon Bond Formation via Coupling Reactions

Development of transition metal-catalyzed cross-coupling reactions is one of the most important discoveries in chemistry to happen within the past 100 years. The catalytic conditions developed provide the most versatile and useful reactions for forming new carbon-carbon bonds, allowing synthesis of various natural products, pharmaceuticals and industrially valuable materials.[19–24] This field began in the late 1800's with the use of stoichiometric organometallic compounds of copper and alkali/alkaline earth metals for the homocoupling of terminal alkynes, and aryl or alkyl halides.[25] For the first few decades, progress in this area moved rather slowly, making modest advances in development of catalytic organometallic conditions and milder reagents. However, it wasn't until the mid 1960's that this field saw an explosion of progress with the introduction of the palladium-catalyzed

Heck reaction. From this point forward, the field of coupling-chemistry has been dominated by the benefits of palladium complex reactivity and versatility, ultimately culminating in a Nobel Prize to the founding fathers of this field, Richard Heck, Akira Suzuki, and Ei-ichi Negishi.[25]

Palladium Catalyzed Cross-Coupling reactions

An ideal catalyst is not only active enough to offer high turnover numbers in a short time period for a variety of substrates, but is also robust enough to tolerate a wide range of functionalities, pH variations and atmospheric levels of oxygen and water. While no catalyst completely meets all of these criteria, the performance of many Pd-complexes by far comes closest to the mark, especially under cross-

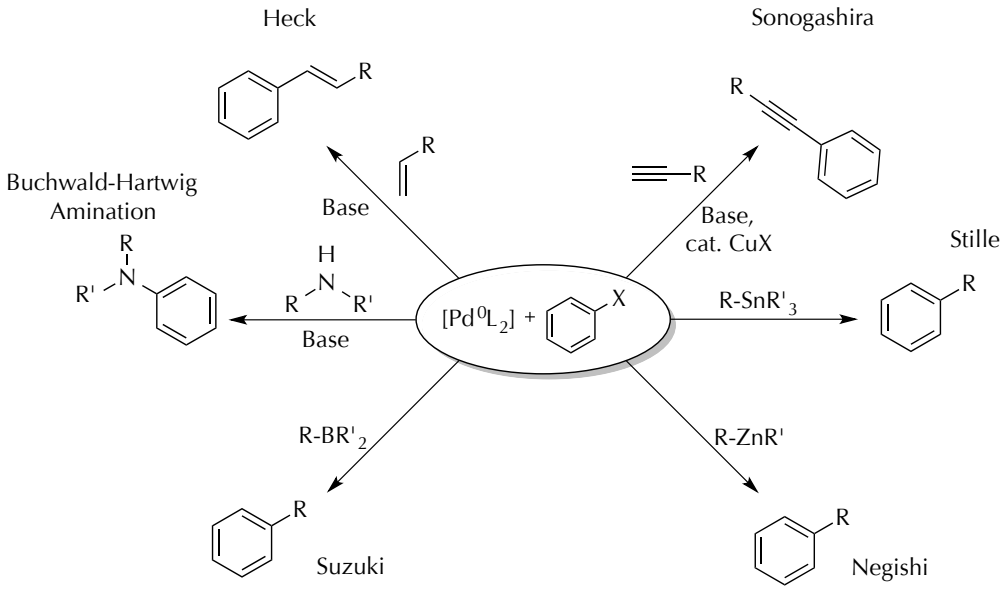


Figure 1. Summary of Common Pd-Catalyzed Cross-Coupling Reactions.

coupling conditions. Today, there are six common branches of Pd-catalyzed cross-couplings, all of which couple an organic electrophile or organohalide with a nucleophile, which is often an organometallic species (Figure 1).[21,22,25,26] These couplings, with the exception of the Heck reaction, adhere to a general catalytic cycle (Figure 2).[21,22,27,28] Initially, oxidative addition of an organohalide forms a Pd^{II} species. The nucleophile then adds to the metal center in one of two ways. If the nucleophile is an organometallic species (e.g. organozinc or organoboron), the R-group of the nucleophile is transferred to the Pd center via transmetallation. However, if the nucleophile is an amine (or a terminal alkyne under copper-free Sonogashira conditions), it coordinates to the Pd-center and subsequently

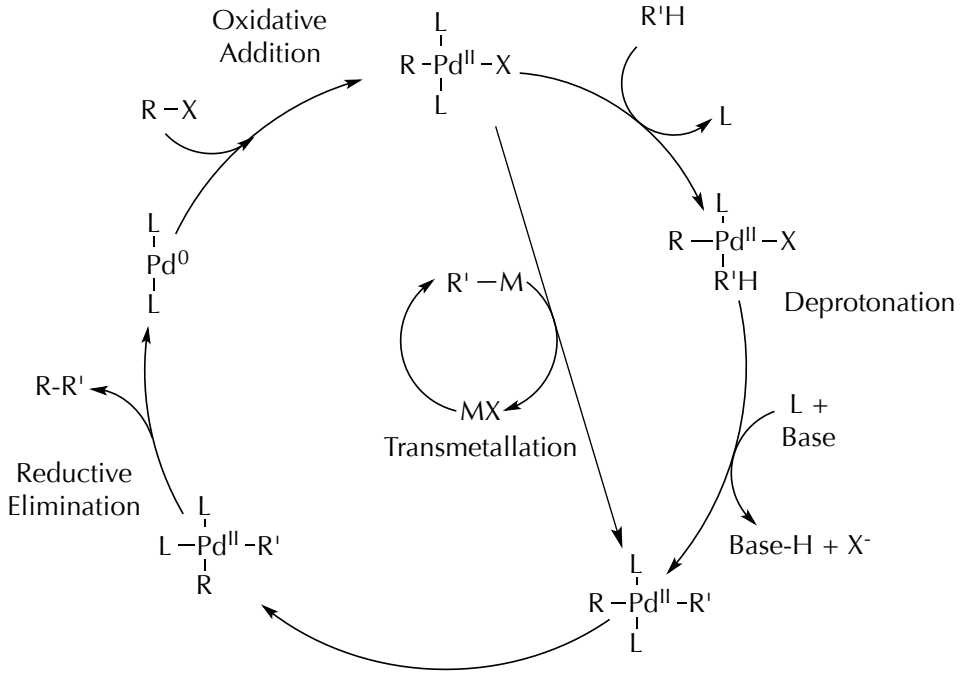


Figure 2. Catalytic Cycle for Cross-Coupling Reactions; R'H = amine or 1-alkyne.

undergoes a base assisted deprotonation. The final step is reductive elimination of product to reform the initial Pd^0 catalyst.

The key differences in the Heck catalytic cycle lie in the addition of the nucleophilic olefin to the Pd-center and elimination of product (Figure 3).[29,30] The olefin undergoes insertion after oxidative addition of the organohalide, and the substituted product is formed by β-hydride elimination from the Pd-center. The final step is base assisted reduction of Pd^{II} back to Pd^0.

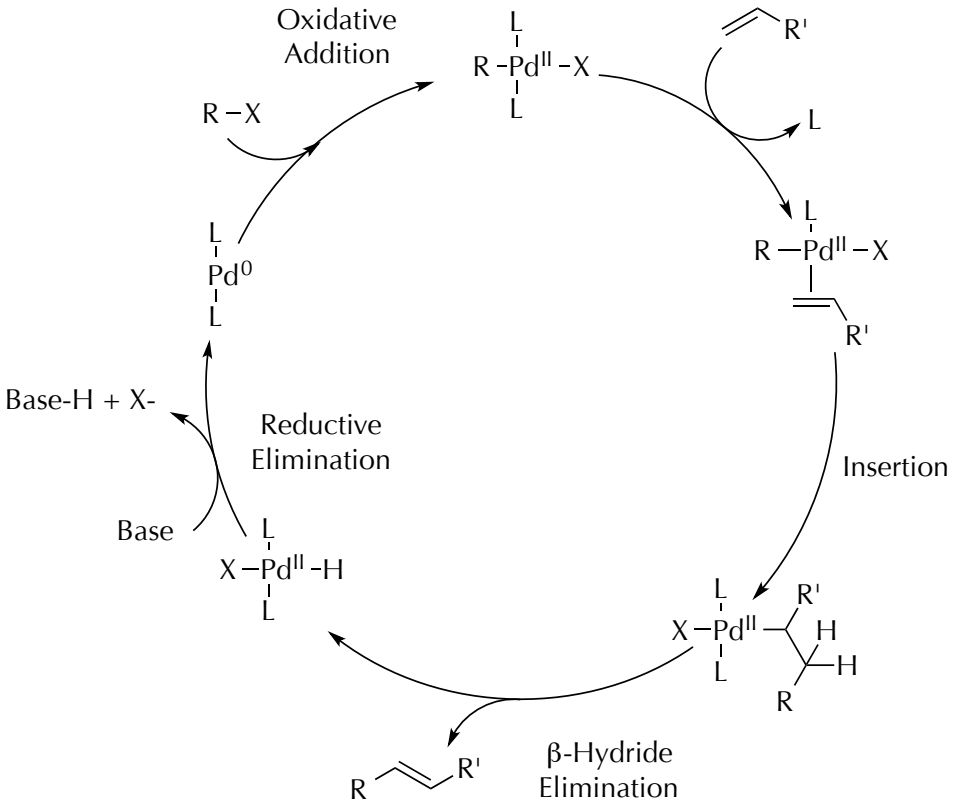


Figure 3. Catalytic Cycle for Heck Coupling.

Although the catalytic cycles involve an L_2Pd^0 complex, many simple and cheap Pd^{II} and Pd^0 complexes can be used as catalyst precursors. Among these complexes are the commercially available $Pd(OAc)_2$, $Pd(PPh_3)_4$, $PdCl_2(PPh_3)_2$, and $Pd_2(dba)_3$. While moderate success can be achieved in coupling activated, electronically poor aryl iodide substrates with these commercial Pd complexes, they are not particularly useful for a wide range of substrates or less active organohalides.[21,22] Therefore, a variety of auxiliary ligands and Pd complexes have been used to improve conditions, substrate scope and catalytic activity (Figure 4).[19–21,30,31] Classically, addition of trisubstituted phosphine ligands has

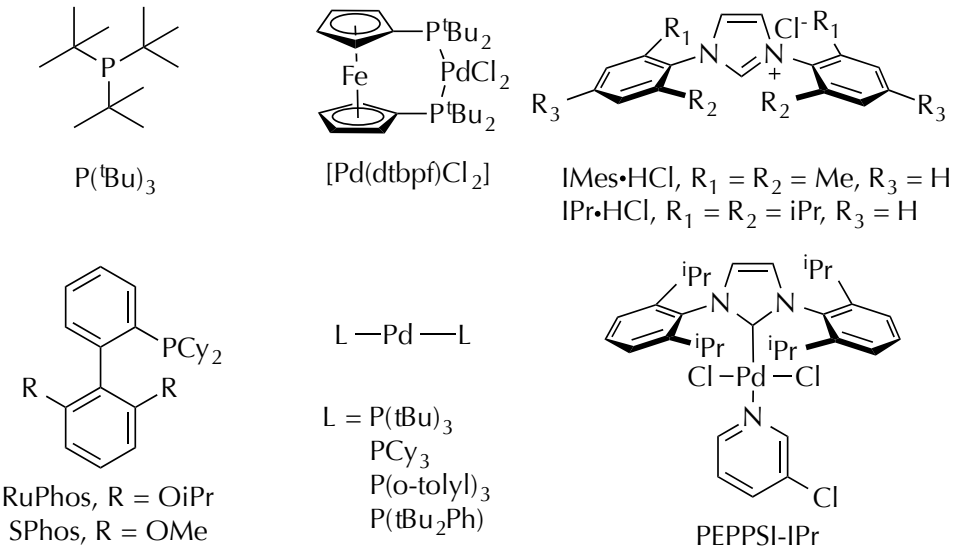


Figure 4. Common Ligands and Pd-Complexes Used for Cross-Coupling.

given favorable improvements in all three areas, with PPh_3 being the most commonly employed.[21,22] Moreover, as the electron density of the phosphine

ligand increases, the oxidative addition of the organohalide becomes more facile, which was first demonstrated with use of $P(tBu)_3$ in Pd-catalyzed amination reactions.[21] This ligand not only improved oxidative addition enough to use aryl chlorides as reagents, but its steric bulk also enhanced product elimination from the Pd center.[32,33] Although many examples of coupling reaction enhancement via bulky, electron-rich phosphines have been published, catalytic coupling with deactivated aryl chlorides and alkyl-halides remains a challenge.

More recently, Pd-complexes using N-heterocyclic carbene (NHC) ligands have been developed and have shown to be more robust and have superior catalytic performance, even when replacing the most active phosphine ligands.[34,35] Since the seminal use of N-heterocyclic carbenes as ligands in Pd catalysis, there have been a myriad of examples of both monodentate and chelating NHC ligands used to make Pd-complexes. However, preformation of a Pd-NHC complex is often unnecessary since addition of the imidazolium salts such as IMes•HCl to reactions with $Pd(OAc)_2$, and $Pd_2(dba)_3$ have also been very successful at forming coupling product (Figure 4). Of the successes with Pd-NHC complexes, the most notable progress has been in coupling of deactivated aryl chloride compounds.[36]

For the coupling reactions discussed above, the electrophilic organohalides (R-X) in the oxidative addition step were initially limited to aryl- or alkenyl-halides, due to competitive β-hydride elimination. Today, the catalysts available are amenable to practically any substrate desired, including vinyl-, allyl-, alkyl-, and acyl halides.[26] Outside of the typical halosubstituents (i.e. iodide and bromide) for

the electrophilic coupling compounds, other common substituents are tosylates, triflates and cheap, yet low activity chlorides. The relative rate of oxidative addition for each of these groups is represented below.[21]

$$I^- > {}^-OTf / {}^-OTs > Br^- >> Cl^-$$

An additional factor in the rate of oxidative addition is the electron density of the substrate. In general, electronically poor compounds will oxidatively add faster than those with greater electron density.

Differentiation between the various classes of coupling relies on the type of nucleophilic or organometallic reagent used. The Heck reaction uses substituted olefins such as acrylates and has become the model coupling reaction for developing better, more efficient palladium catalysts and reaction conditions.[29] This reaction is so flexible and expandable that it has been used in conjunction with other systems such as cyclization, polymerization, and carbonylation. In fact, other coupling reactions such as Stille and Suzuki could be considered modifications of the Heck coupling in which a hydrogen of the nucleophilic olefin is replaced with either tin or boron bearing substituents.[26] More recently, the development of Cu-free Sonogashira reactions indicate that the conditions and catalytic cycle may closely resemble that of the Heck reaction, eliciting a renaming of these new reaction conditions to Heck alkynylations.

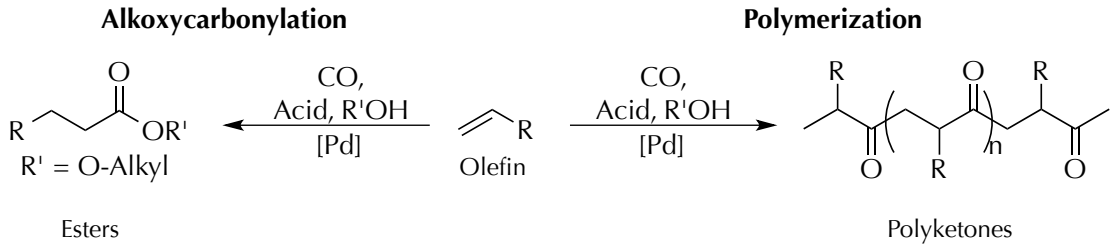
The progress in all of these coupling reactions has broadened the scope of C-C bonds that can be formed, and depending on the target molecule, these coupling reactions can be interchangeable, giving similar results and product yield. However, the choice of one type of coupling reaction may be beneficial over another. For example, the Sonogashira reaction is widely used in pharmaceutical productions for forming extended conjugated systems of alkynes and arenes commonly found in natural products.[20,21,25] Very active organozinc nucleophiles have relatively low toxicity, which makes the Negishi reaction a greener coupling with less active organohalides.[26] In addition, the Suzuki reaction is extensively used for making conjugated polyene products as well as $C(sp^2)$–$C(sp^3)$ and some $C(sp^3)$–$C(sp^3)$ bonds.[26] Ultimately, the field of cross-coupling chemistry has been so broadly explored that a large variety of C-C bonds can be made with the right organohalide, nucleophile and Pd complex.

Transition Metal Catalyzed Carbon-Carbon Bond Formation via Carbonylation

The insertion of a CO unit into various organic substrates (e.g. olefins, and alcohols) is important in many industrial processes, producing a range of products from short chain compounds to polymeric materials.[37–39] The most well known applications of these processes are hydroformylation to form aldehydes, carbonylation of methanol to form acetic acid, and Pd-catalyzed carbonylation of olefins. The first two processes have been used industrially for decades. Aldehyde

formation is commonly accomplished with Rh catalysts (e.g. $[HRh(CO)(PPh_3)_3]$) via formal addition of formaldehyde to a double bond and is an important first step in the formation of aliphatic alcohols for detergents and plasticizers.[40] Acetic acid, which is traditionally formed via Rh catalysis in the Monsanto Process, is most recently made by the relatively efficient and green Cativa™ process, using $[Ir(CO)_3I_2]^-$.[41]

Palladium catalyzed carbonylation of olefins can undergo two different cycles, co-polymerization to form polyketones or alkoxycarbonylation to form ester products (Scheme 1). These carbonylation reactions have been known since the 1960's but it wasn't until the development in the 1980's of active cationic Pd^{II}-phosphine complexes by Shell Research that the field really started to advance.[42,43]



Scheme 1. Pd-Catalyzed Carbonylation of Olefins.

Palladium Catalyzed Alkoxycarbonylation

Both polyketone and single insertion ester products are formed via similar catalytic cycles, where chemoselectivity is controlled by the nature of the

phosphine ligand. Figure 5 shows some of the most common phosphine ligands used for either co-polymerization or alkoxycarbonylation.[38,44] For the most active phosphine ligands, only a slight excess of ligand is needed with respect to Pd.

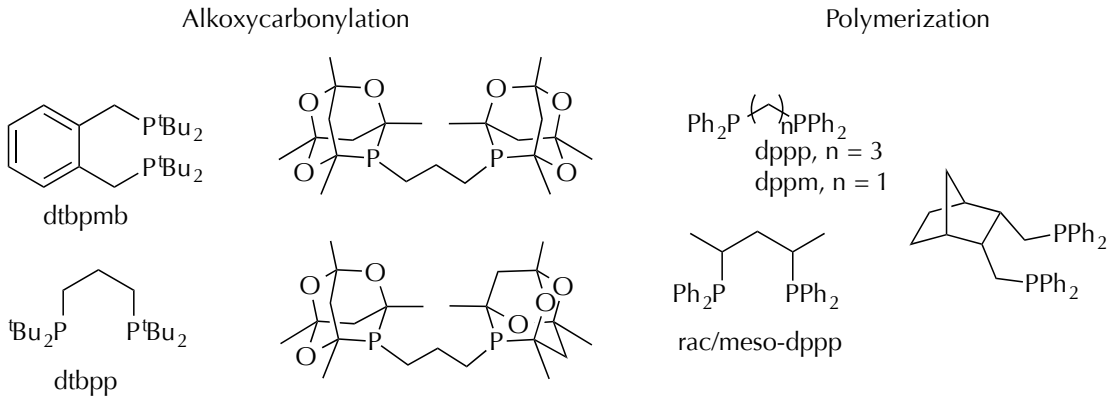


Figure 5. Ligands Used in Pd-Catalyzed Carbonylation of Olefins.

While preformed Pd-phosphine complexes are successfully used in these reactions, the active catalytic species is most often formed *in situ* with a bidentate phosphine ligand, a Brønsted acid, and either $Pd(OAc)_2$, $PdCl_2$, or $Pd_2(dba)_3$. The best Brønsted acids have a conjugate base that is weakly coordinating to the Pd catalyst, with sulfonic acids being the most common choice (e.g. *p*-toluenesulfonic acid, TsOH; and methane sulfonic acid, MsOH). The relative rate of alkoxycarbonylation with $Pd(PPh_3)_2X_2$ complexes is shown below.[38,42,43]

$$X = Cl^-, BF_4^- < CF_3SO_3^- < TsO^-$$

There are two proposed catalytic cycles for this system, a 'hydride' cycle and a 'carboalkoxy' cycle (Figure 6).[37,45–49] After coordination of the phosphine, the Pd^0-complex undergoes protonation via the Brønsted acid to form a cationic [Pd^{II}]-hydride complex. The [Pd^{II}]-hydride can enter the hydride cycle or interact with the alcohol solvent to form a [Pd^{II}]-alkoxy complex that initiates the carboalkoxy cycle.[38] In the hydride mechanism, olefin coordination is followed by insertion into the [Pd^{II}]-H bond. Subsequent coordination and insertion of CO affords a [Pd^{II}]-acyl complex that can either coordinate additional olefin leading to polymerization or undergo alcohol assisted ester product elimination (alcoholysis) to regenerate the [Pd^{II}]-hydride.

In the alkoxide cycle, the [Pd^{II}]-alkoxide complex can undergo coordination and insertion of CO into the [Pd^{II}]-OR bond. The resulting carboalkoxy complex, [Pd^{II}]-COOR, can coordinate and insert olefin. Continuous coordination and insertion of CO and olefin would produce polyketone, whereas the single insertion ester product can be eliminated via alcoholysis to reform the [Pd^{II}]-alkoxide.

The crucial role of the phosphine ligand in product selectivity was discovered when trying to selectively form methyl propionate with ethylene, CO and methanol as solvent.[42,43] Reactions with $Pd(OAc)_2$ and excess PPh_3 were chemoselective for propionate formation, but when the ligand was switched to a chelating phosphine (e.g. dppp), chemoselectivity favored the polyketone product. The selectivity was rationalized by the geometric preferences of monodentate

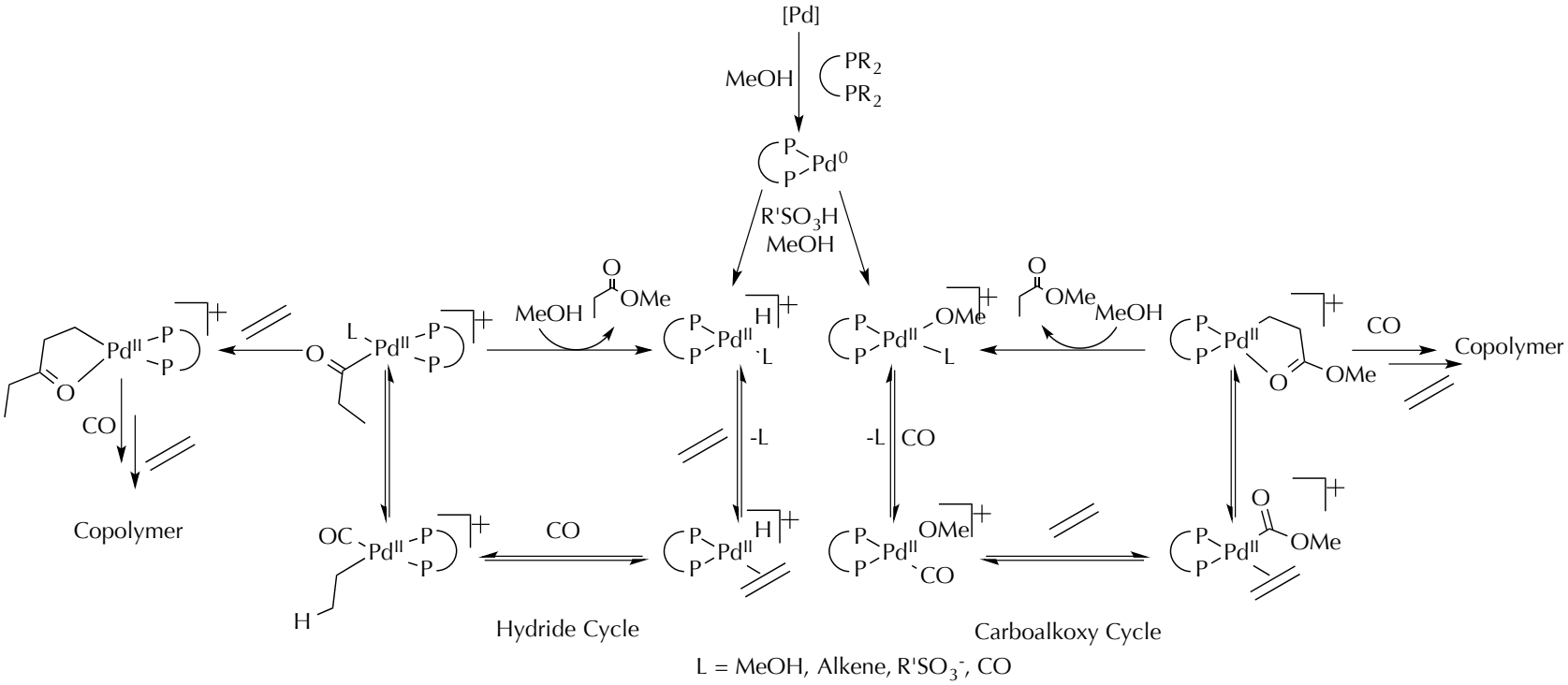


Figure 6. Hydride and Carboalkoxy Cycles for the Formation of Esters and Polymers.

versus chelating phosphine ligands. For insertion of either CO or olefin to occur, the unsaturated substrate needs to coordinate *cis* to the growing polymer chain. Monodentate phosphines fluctuate between *cis* and *trans* coordination about palladium, decreasing the amount of time the growing polymer chain is *cis* to either CO or olefin. This lowers the rate of insertion that lengthens the polymer chain and favors product elimination. However, chelating phosphines with short alkyl linkers are forced to remain *cis*, ensuring that an open coordination site is always adjacent to the growing polymer chain, facilitating insertion and chain extension.

The best ligands for polymerization tend to have an alkyl linker of three methylene units, as in dppp (Figure 5). In surveying a variety of chelating ligands, it was found that the longer the alkyl linker between the two phosphine moieties, the more likely single insertion ester product will be formed, presumably due to the linker length allowing a trans configuration of the phosphines. When the linker is shortened to one methylene unit (dppm), catalytic activity overall was greatly reduced for forming either polymer or ester product.[38]

The second key factor in determining selectivity was the steric bulk of the phosphine ligand. While carbonylation in the presence of PPh_3 favors ester product formation, using substrates with carbon chains longer than ethylene results in both branched and linear ester products. Additionally, as the steric bulk of a chelating phosphine ligand increased (e.g. changing dppp to d^{t}bpp) the selectivity started to favor the single insertion product.[38,50] This finding led to the development

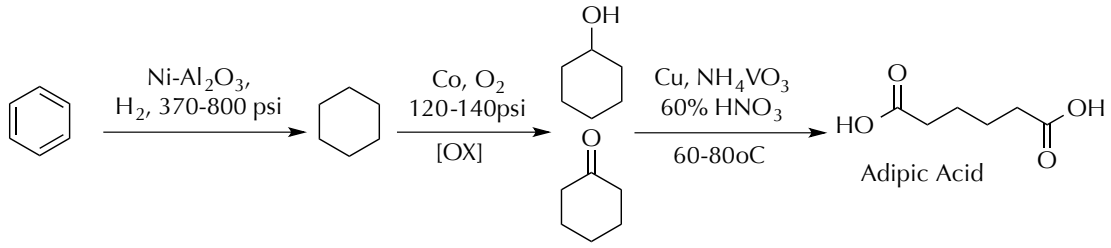
of dtbpmb, which is selective in the formation of linear ester products from a variety of internal and terminal olefinic substrates.[38] Additionally, this ligand was beneficial in determining the active catalytic cycle for alkoxycarbonylation.

Polymer chain end group analysis demonstrated that both hydride and carboalkoxy cycles are active for polymerization.[38] However, only the hydride is active in alkoxycarbonylation.[38,46,47,51] While Pd-alkoxide species have been previously reported, attempts to form [Pd^{II}]-alkoxide with bulky chelates, such as dtbpmb, failed.[38] The Pd-hydride selectively inserts alkene over CO and the resulting Pd-alkyl inserts CO quickly to form a Pd-acyl.[38] Isolated Pd-acyl complexes not only quantitatively react with alcohol to form the expected ester product, but also are catalytically active for alkoxycarbonylation.[38]

Pd-Catalyzed Alkoxycarbonylation for Biorenewable Production of Adipate

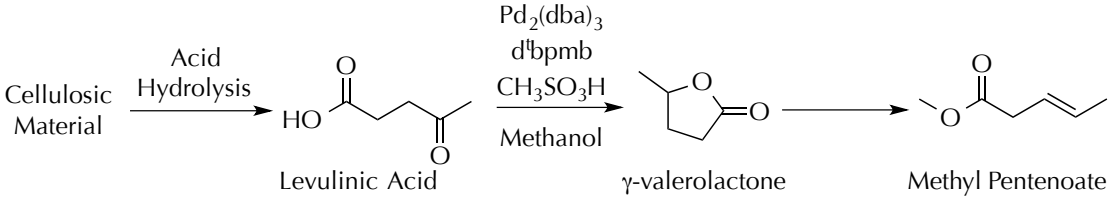
In the polymer industry, access to cheap and abundant feedstocks is highly desirable to keep the cost of polymer related products reasonable. One of the most important types of monomer used in polymer synthesis is α,ω-bifunctionalized molecules. These molecules are an aliphatic chain, terminated with various functional groups, e.g. carboxylic acids, esters, and amides. Amongst the most used bifunctionalized molecule is adipic acid, which is synthesized in the billions of kilograms per annum for its used in the production of nylon.[52] Currently, the synthesis is dependent upon petroleum resources, and begins with the reduction of

benzene to make cyclohexane, followed by subsequent oxidation and ring opening to form adipic acid. (Scheme 1).[40]



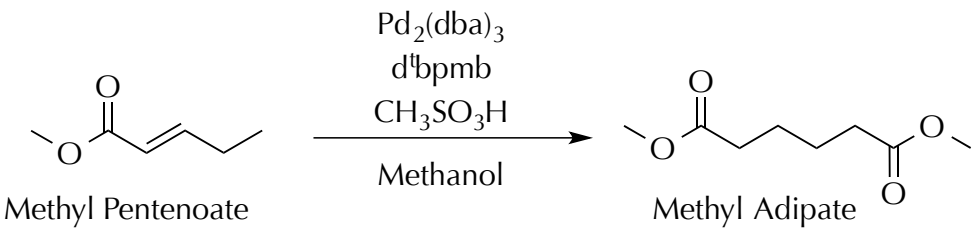
Scheme 1. Petroleum Based Synthesis of Adipic Acid.

Alternatively, unsaturated fatty acid esters may be a viable replacement for petroleum in the production of adipic acid and adipate. These unsaturated esters can be produced from various biosources including enzymatic catalysis and processing of cellulosic materials, and often result in hydrocarbon chains of varying lengths with internal double bond(s). In applying Pd-catalyzed alkoxycarbonylation to these unsaturated esters, the catalyst would not only need to isomerize the internal double bond but also selectively alkoxycarbonylate at the terminal position. For production of adipic acid or adipate, this would require the



Scheme 2. Synthesis of Methyl Pentenoate From Cellulosic Material.

unsaturated 5-carbon ester pentenoate, which can be derived from cellulose. Conversion of cellulosic biomass to methyl pentenoate via levulinic acid is shown in Scheme 2.[53] Subsequent synthesis of α,ω-bifunctionalized monomers from unsaturated fatty acid esters was demonstrated with $Pd_2(dba)_3$, and dtbpmb (scheme 3).[54,55]



Scheme 3. Pd-Catalyzed Synthesis of Methyl Adipate.

Alternatives to Organic Solvents

Use of organic solvents is prevalent in all areas of manufacturing, and product synthesis. In the pharmaceutical industry alone, it has been estimated that 22 kg of solvent are needed to make 1 kg of an active pharmaceutical ingredient.[56] Such large excess is due to using solvent as a reaction medium as well as for product purification. Moreover, common industrial solvents such as dichloroethane and cyclohexane are not only formed from petroleum resources, but are toxic to the environment.[57] Continued use of these solvents not only perpetuates environmental damage, but also contributes a negative economic impact due governmental sanctions and regulations for disposal. To address these

issues, many tactical approaches have been considered. On a very basic level, improving current manufacturing and processing efficiency can ameliorate environmental impact by minimizing extraneous solvent usage. However, more aggressive efforts include replacing toxic, nonsustainable solvents with greener alternatives.

Solvents considerations for reactions include two major alternatives. One involves replacing the current solvent with biosourced analogues (often short chain alcohols or acetates) that have similar physical and chemical properties to the toxic organic solvent analogue.[56–59] The other option is replacing the current solvent with non-traditional media (e.g. supercritical fluids, ionic liquids, fluorous solvents, etc.).[60–67] Although various successes have been achieved with all of these alternatives, the biggest contender for a greener reaction solvent is water. Water is very abundant, very inexpensive and essentially nontoxic.[68,69]

Researchers typically overlook or reject water as an adequate solvent often due to reagent sensitivity and/or solubility, but some very interesting results can arise from organic reactions in water. One of the cornerstone examples is the Diels-Alder reaction. Due to hydrophobic effects, cyclopentadiene reacts with butenone 700 times faster in water than organic solvent.[70,71] In general pericyclic reactions are accelerated due to the decrease in volume of activation in the transition state, which alleviates some of the aqueous solvent pressure.

Unfortunately, not all reactions experience this kind of reactivity enhancement in water, requiring additional methods to allow water to be used as

solvent. One of the most promising adaptations is the addition of surfactants or detergents.[72–78] These molecules tend to form micelles in water and have a superior ability to dissolve organic reagents within aqueous media. Many terms can be used to describe micelle forming materials – detergent, soap, amphiphile, and surfactant, to list a few. These terms are often used interchangeably even though they describe slightly different groups of molecules, but to avoid confusion, surfactant will be exclusively used here.

Molecular Structure Of Normal and Cholate Surfactants

Surfactants, or surface active agents, are amphiphilic molecules consisting of a polar (hydrophilic) and a nonpolar (hydrophobic) moieties. Most surfactants fall under the 'normal' classification, represented with a polar head group and a nonpolar tail (Figure 7).[79,75,72,80] Differentiation between groups of surfactants is dependent upon the nature of the head group. The four surfactant classes are anionic, cationic, neutral and zwitterionic.

A surfactant that lies outside of the 'normal' classification is sodium cholate. Sodium cholate is the salt of cholic acid, a bile acid synthesized from cholesterol in the liver of mammals. The amphiphilicity of sodium cholate is arranged facially rather than head to tail (Figure 8). The convex face (β-face) is hydrophilic and the concave (α-face) is hydrophilic.

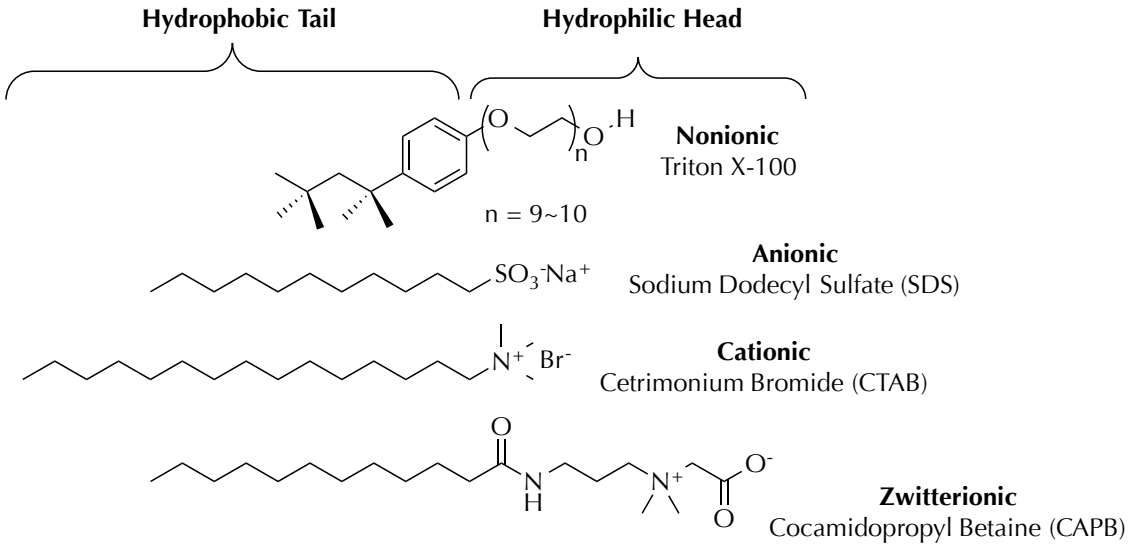
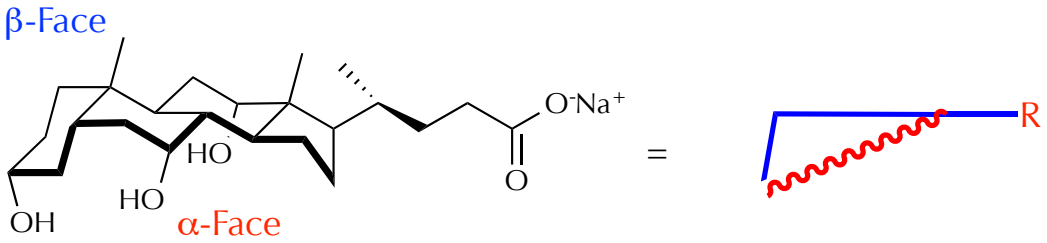


Figure 7. Examples of the Four Surfactant Classes



Sodium Cholate

Figure 8. Structure of Sodium Cholate.

Aggregation Of Normal and Cholate Surfactants in Water

At a very fundamental level, normal surfactants form spherical micelles under aqueous conditions.[72,75,79] In this arrangement of surfactant molecules the polar head groups are oriented towards bulk water and the nonpolar tails are sequestered into an organic 'pocket' (Figure 9). Aggregation of surfactants occur when the hydrophobic portion becomes large enough that the energy released due to solvation is too low to overcome the energy required for ordered arrangement of water around a single surfactant molecule.[72] However, aggregation does not fully result in micelle formation until the critical micelle concentration (CMC) is reached. The CMC is dependent upon temperature, pH, additives, ionic strength, and surfactant structure.[81–85] The effect of variations in each of these conditions is largely dependent upon the charge of the polar group. For example, addition of a hydrophilic ion can interact with a charged head group, decreasing the electrostatic interactions between adjacent head groups and thus decreasing the CMC.[78] The same effect would not occur with uncharged surfactants.

Micelles are often depicted as ordered arrangements of surfactant molecules in a perfect sphere, but this is an oversimplification of the actual structure. Most likely, head and tail overlap of adjacent molecules occurs in forming a more disordered aggregation (Figure 9b). The arrangement of surfactant molecules is not only dynamic but it is also highly dependent upon surfactant structure and aqueous conditions. It is generally agreed that around the CMC, the micelle structure is

near spherical, and as surfactant concentration increases, overall size of the micelle increases and shape changes occur. These larger micelles have been described as thread-like, disc-like and rod-like.[78]

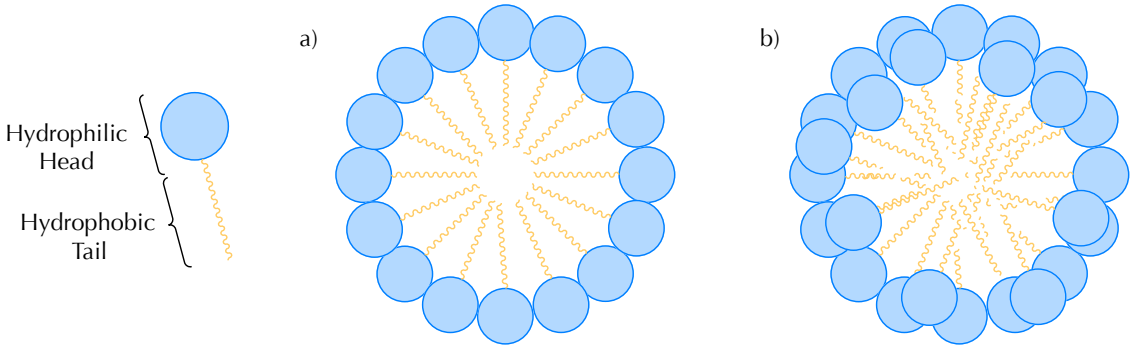


Figure 9. Orientation of Normal Surfactants In Water.

The aggregation behavior of sodium cholate and its derivatives is very different from that of normal surfactants, and does not result in spherical micelles. Primary cholate micelles or aggregates are generally small, with less than ten cholate molecules. At low concentrations of cholate, the aggregates can be dimers, tetramers, octamers, etc. (Figure 10a-c). These small aggregates are formed via hydrophobic interactions of the face. The size of the micelle in solution is typically polydisperse and very dependent on cholate concentration. This makes determination of the CMC for cholates difficult. Rather than a single concentration value, the CMC for cholate is typically reported as a range. Cholate micelle formation tends to be stepwise. Initially, dimers are formed and as concentration

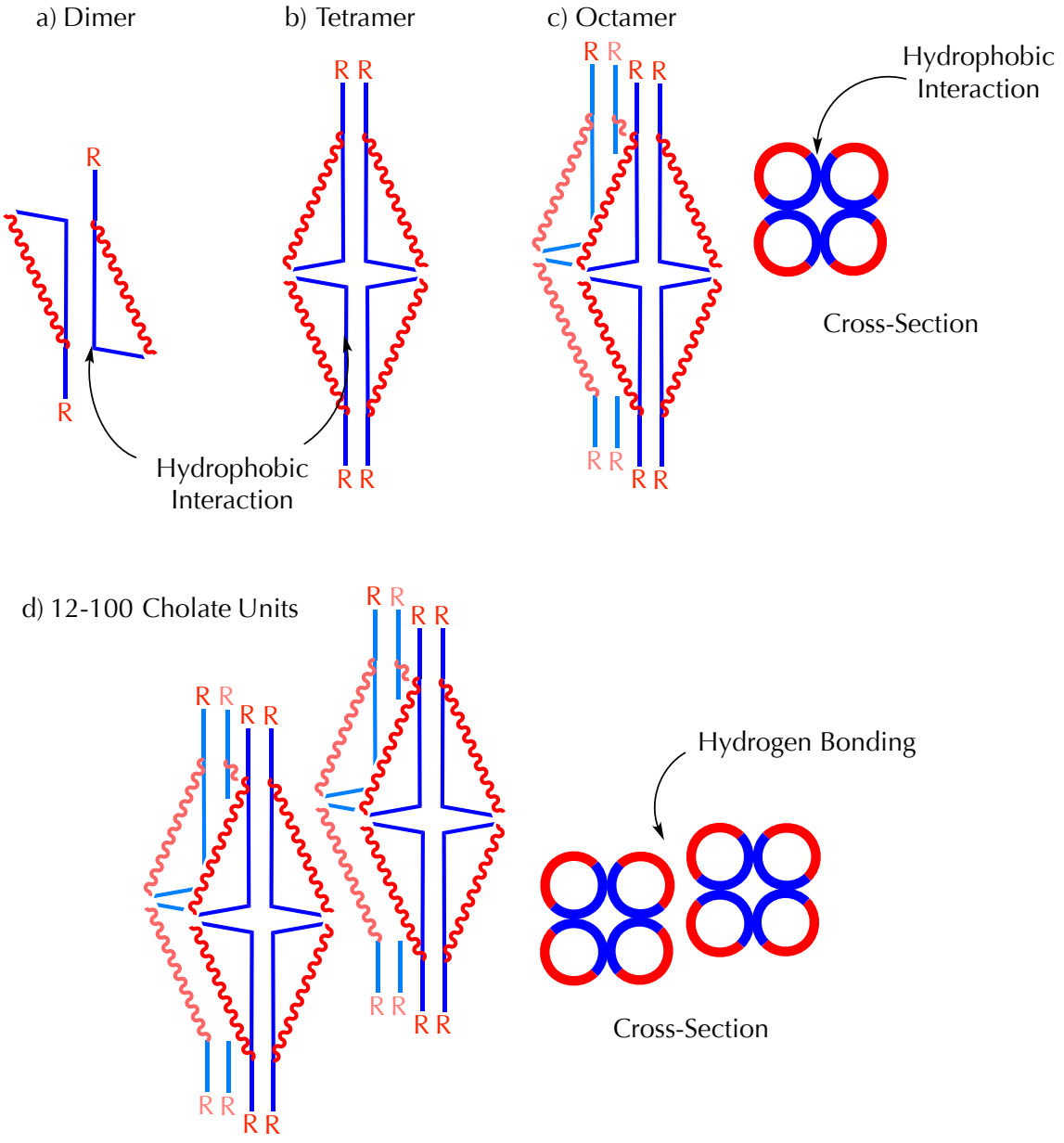


Figure 10. Micelle Formation of Cholate Surfactants and Cholate Derivatives in Water.

increases the dimers aggregate into larger micelles. For the cholate molecule, a trihydroxy salt, aggregation stops at primary micelles or dimers. However, if a hydroxyl group is removed from the concave face of cholate (a dihydroxy salt) primary aggregates will associate into larger units. These larger micelles are primarily octamers, formed from aggregation that is partially due to H-bonding between α-faces. As with normal micelles, micelle formation is ultimately subject to the aqueous conditions.

Influence of Micelles on Organic Reactions

Addition of surfactants to aqueous organic reactions are often cited to benefit reaction rate, with the rate increases being referred to as micellar catalysis. This delineation is arguably a misnomer, since the surfactant is a spectator and not actually involved in the reaction like a traditional catalyst. However, if a catalyst is defined as a reaction additive that accelerates rate without being changed or consumed, and is capable of being reused, then micelles could rightfully be considered catalytic. Reaction rate enhancement (or in some cases inhibition) can be attributed to two general areas, localized solvent effects and/or concentration effects.

Solvent effects are considered the sole reason for micelle assisted rate acceleration in unimolecular reactions and can be influential in affecting the stability of reagents or transition states. As a molecule is incorporated into the

micelle, it is solvated in an organic, hydrophobic environment. If the molecule happens to be charged or rather polar, interaction with this environment destabilizes the molecule, increasing its likelihood to react and form product. However, micelles have the added benefit of the internal nonpolar environment being in proximity of polar, possibly charged head regions. An organic reagent may be well solubilized in the hydrophobic environment, but if it undergoes a reaction that has a charged transition state, electrostatic interaction with nearby polar head groups can stabilize that transition state, thereby increasing rate.

While bimolecular reactions also benefit from solvent effects, the majority of rate enhancement is due to concentration effects.[72,75,78] Attraction or binding of substrates and catalysts to a micelle is driven by either hydrophobic or electrostatic interactions. Since both interactions are possible, both nonpolar and polar substrates can be incorporated to varying extent within a micelle or at the surface. This causes the reactants and catalyst to be much more concentrated within and around the micelle increasing instances of product forming interactions. For example, the rate of hydrolysis of an organic molecule under basic conditions is likely to be enhanced in water by the presence of a cationic surfactant. The organic reagent would be solubilized within the micelle, and the cationic surface would attract hydroxyls to the micelle surface bringing them in proximity of the reagent.

While there are extensive studies on the influence on micelles on organic transformations the exact influence is not easy to predict. Overall, acceleration of

reaction rate is highly condition dependent, i.e. ionic strength, surfactant type, and reagents.

Summary and Outlook

Given the green focus of current research, and the importance of Pd-catalyzed transformations, we sought to explore the activity of commercially available and synthesized Pd complexes in new catalytic environments. Cross-coupling reactions were assessed in water either assisted by commercially available surfactants or a novel phosphine containing cholate surfactant. Furthermore, acid-free and robust methods were developed for alkoxycarbonylation of olefins using N-heterocyclic complexes of palladium.

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CHAPTER 2: SONOGASHIRA COUPLING OF ARYL HALIDES WITH 1-ALKYNES UNDER MILD AQUEOUS CONDITIONS: SURVEY OF SURFACTANT ROLE IN CROSS-COUPLING REACTIONS

Modified from a paper to be submitted to *Green Chemistry*

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Abstract

The Sonogashira coupling between lipophilic terminal alkynes and aryl bromides or iodides was moderate to high yielding with $Pd(PPh_3)_2Cl_2$ in water at 40 °C using readily available and inexpensive surfactants (2.0 wt% in water) such as SDS and CTAB. An iodide and Cu(I) inhibition was observed in these micellar conditions with aryl bromide substrates. Studies under Cu(I)-free conditions reveal two competing cycles. A deprotonation cycle gives rise to the traditional Sonogashira product (**3**), while a carbopalladation cycle produces enyne, **5**. The surfactant solution (SDS or CTAB) can be recycled up to three times for coupling between 1-octyne and 1-iodonapthalene in the presence of CuI before coupling yields start to decrease.

Key words: micelle, aqueous, Sonogashira coupling, room temperature, surfactant, SDS, CTAB

Introduction

Solvent is a key component in metal-catalyzed cross-coupling reactions, serving to suspend or solubilize reactants and catalysts, as well as influence product selectivity, rate of reaction, and chemical equilibria. However, traditional organic solvents typically have biological and environmental hazards that entail costly processing and disposal. These issues have stimulated demands for more environmentally benign reaction media.[1–5] As a result, substantial effort has been directed towards developing new catalysis technology in non-traditional media such as ionic liquids,[6–17] supercritical fluids,[11,18–28] fluorous solvents,[11,29–31] and water.[32–47] Industrial criteria for these technologies to be adapted and considered a reliable green alternative to current practices include adherence to the 'twelve principles of Green Chemistry', a low value for the 'E-factor', and economically competitive production costs.[48–53] When considering the benefits of non-traditional media under these constraints, water stands out as a particularly attractive alternative, due to its abundance, low expense, and nontoxic properties.

As exemplified by abundant precedence, cross-coupling reactions are quite versatile and useful in synthetic chemistry.[54–57] Traditional coupling conditions employ a variety of organic solvents, which offer a range of physical characteristics to match the needs of the desired reaction. Limiting the reaction medium to water introduces solubility complications for catalysts and organic reagents. For some transformations, such as the Diels-Alder reaction, aqueous solubility is a minimal concern because rates and yields are enhanced by hydrophobic effects

encountered by the nonpolar reagents in neat water.[43,47] However, most metal mediated cross-coupling reactions require additional methods of enhancing solubility of reagents and thus improving reactivity in water. Amongst popular ways to enhance aqueous solubility and reactivity are the use of biphasic water-organic solvent systems; water miscible, organic co-solvents; phase transfer catalysts; and substrates or ligands with polar moieties (e.g. sulfonates, quaternary amines, hydroxyls and sugars). While successful, these methods maintain a dependence on organic solvents and can reduce substrate scope. Alternatively, one of the simplest ways to enhance solubility in water is by the addition of surfactants, creating micelles with an organic interior or pocket that can entrain organic substrates. Even though the interior pocket is largely hydrophobic in nature, micelles have regions of varying polarity, allowing incorporation of reagents that are both polar and nonpolar.[58–60]

Despite the number of examples of aqueous metal-mediated reactions, studies on the scope of surfactant influence on these reactions have been limited, largely due to the fact that surfactants are commonly considered similar in properties and relatively interchangeable.[41,59,61–86] This view has previously suppressed systematic development of surfactant reaction conditions and new surfactant molecules for the purpose of synthesis. Within the last decade, pioneering work in this area has come from Bruce Lipshutz and his advancement of versatile, three-component designer surfactants derived from vitamin E (Figure 1).[69,79,87–101] These surfactants are not only developed from a green perspective, but

have also proven to be very useful for Pd-catalyzed cross couplings and Ru-catalyzed metathesis, providing a marked decrease in reaction temperature and time.

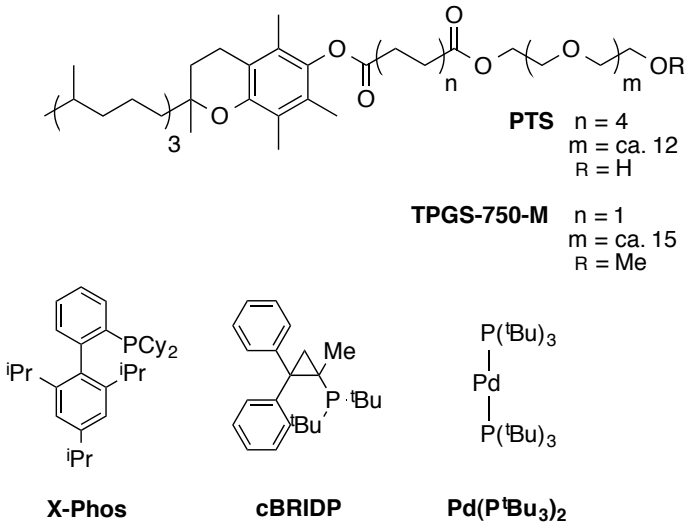


Figure 1. Representative surfactants, ligands and palladium catalyst employed in Lipshutz's work.[96,99]

To expand upon the influence surfactants have on Pd-catalyzed cross couplings, we turned our attention to a systematic study of the Sonogashira reaction using commercially available surfactants. The Sonogashira coupling is one of the most practical C-C bond forming reactions in the synthesis toolbox, allowing formation of many alkynyl substrates.[102–105] However, only a few examples of aqueous Sonogashira reactions are reported, with even fewer that incorporate surfactants.[62,66,72,74,83,96] The limited substrate, catalyst, and/or surfactant scope, affords an ideal opportunity for further study. Herein, we explore the

influence of inexpensive, commercially available surfactants on the Sonogashira cross-coupling reaction and provide additional insight on the catalytic cycle, influence of Cu(I) salts, and the recyclability of the surfactant solution.

Results and Discussion

In this study, we employed four common and inexpensive surfactants (Figure 2), sodium cholate (critical micelle concentration, CMC, 0.388 - 0.603% w/v%), cetyl trimethylammonium bromide (CTAB; CMC 0.32 w/v%), sodium dodecylsulfate (SDS; CMC 0.173 - 0.230 w/v%), and Triton X-100 (CMC 0.0155 w/v%).[58,106] For convenience and economics of the reaction, air-stable $Pd(PPh_3)_2Cl_2$ was selected as the catalyst for this modification of the Sonogashira coupling. This catalyst also provided an additional benchmark due to its ubiquitous use in Cu(I)

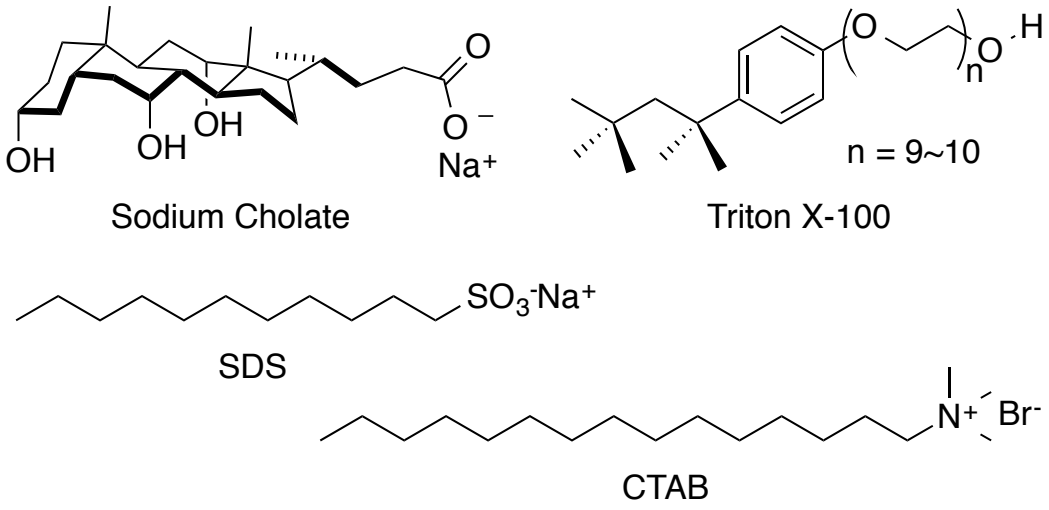


Figure 2. Surfactants used in this work.

co-catalyzed couplings. Furthermore, complexes such as $PdCl_2$, Na_2PdCl_4, and $Pd(OAc)_2$ in the absence of phosphine ligands were not effective catalysts for coupling.

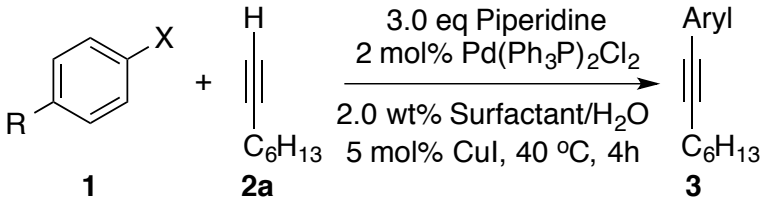
Surfactant Screening

Initial screening of surfactants for the coupling of 1-octyne with an electron deficient aryl halide, 4-iodobenzonitrile, indicated that each surfactant was able to facilitate quantitative coupling as long as CuI was present (Table 1). When the aryl halide was switched to the more electron rich 4-iodoanisole, differences between the efficacy of the surfactants emerged. Lower coupling yields in the presence of sodium cholate and Triton X-100 led us to focus on the more effective surfactants, SDS and CTAB, in subsequentstudies. Within this initial screening, it was also found that copper iodide strongly hindered the coupling of 4-bromobenzonitrile and octyne with all four surfactants. Moreover, reactions with the electron-rich 4-bromoanisole provided no coupling product within 4 h.

Effect of Base on Sonogashira Coupling

In addition to surfactants, a variety of bases were also screened using SDS and CTAB in the presence and absence of CuI (Table 2). Addition of base is critical to the Sonogashira reaction because it aids in the abstraction of the acetylenic proton during alkynylation of the metal center (either Cu or Pd) and facilitates the

Table 1. Surfactant Screening for the Sonogashira Coupling of Aryl Halides with 1-Octyne.

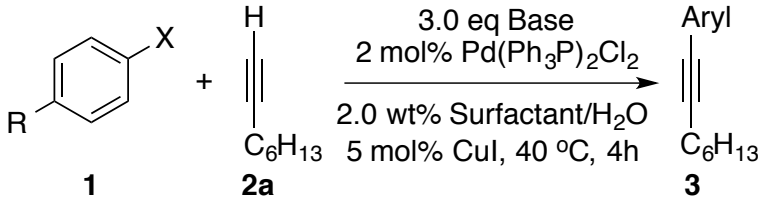


1 1.0 eq **2a** 1.3 eq **3**

				% Yield **3**[a]	
Entry	R	X	Surfactant	(CuI)[b]	(No CuI)
1	CN	I	Sodium cholate	Quant.	48
2	CN	I	CTAB	97	57
3	CN	I	SDS	Quant.	61
4	CN	I	Triton X-100	Quant.	58
5	OMe	I	Sodium cholate	74	30
6	OMe	I	CTAB	92	38
7	OMe	I	SDS	85	30
8	OMe	I	Triton X-100	68	29
9	CN	Br	Sodium cholate	24	42
10	CN	Br	CTAB	20	57
11	CN	Br	SDS	16	55
12	CN	Br	Triton X-100	32	44

Reaction conditions: 0.08 mmol aryl halide, 0.1 mmol 1-octyne, 0.24 mmol piperidine, 2.0 mol% $Pd(PPh_3)_2Cl_2$, 0.8 mL surfactant (2.0 wt% in H_2O), 40 ºC, 4 h; [a]Average ^1H NMR yields for duplicate runs (±3). [b] 5 mol% CuI.

Table 2. Base Screening for the Sonogashira Coupling of Aryl Halides with 1-Octyne.



1 1.0 eq **2a** 1.3 eq **3**

					% Yield **3**[b]	
Entry[a]	R	X	Surfactant	Base	(CuI)[c]	(No CuI)
1	OMe	I	SDS	Piperidine	85	30
2	OMe	I	CTAB	Piperidine	92	38
3	OMe	I	SDS	Pyrrolidine	81	32
4	OMe	I	CTAB	Pyrrolidine	75	33
5	OMe	I	SDS	NEt_3	87	22
6	OMe	I	CTAB	NEt_3	90	17
7	OMe	I	SDS	Cs_2CO_3	21	15
8	OMe	I	CTAB	Cs_2CO_3	10	12
9	CN	Br	SDS	Piperidine	18	40
10	CN	Br	CTAB	Piperidine	31	59
11	CN	Br	SDS	Pyrrolidine	20	26
12	CN	Br	CTAB	Pyrrolidine	18	55
13	CN	Br	SDS	NEt_3	23	57
14	CN	Br	CTAB	NEt_3	20	60
15	CN	Br	SDS	Cs_2CO_3	9	10
16	CN	Br	CTAB	Cs_2CO_3	24	17

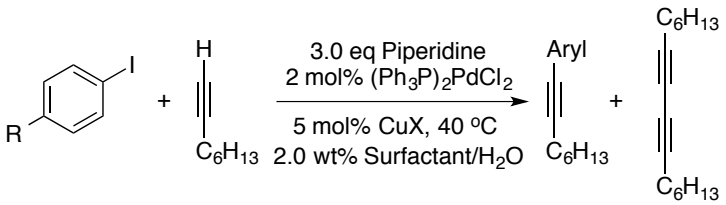
Reaction conditions: 0.08 mmol aryl halide, 0.1 mmol 1-octyne, 0.24 mmol base, 2.0 mol% $Pd(PPh_3)_2Cl_2$, 0.8 mL surfactant (2.0 wt% in H_2O), 40 ºC; [a] Rxn 1-8 ran 4 h, Rxn 9-16 ran 12 h; [b] Average ^1H NMR yields for duplicate runs (±3). [c] 5 mol% CuI.

elimination of product from the Pd center.[103,105,107] Overall, water-soluble inorganic bases such as K_2CO_3, NaOAc, and Cs_2CO_3 resulted in low to no coupling product. However, water-soluble amines such as NEt_3, piperidine and pyrrolidine enabled coupling in high yields. Due to its improvement of yields and ease of handling, piperidine was selected as the base of choice for this study. Since the properties of the hydrophilic moiety (carboxylate, sulfate, amine, etc.) can affect the pH of water, possibly altering the efficacy of the base, the pH of the Sonogashira reaction conditions was monitored (Table S.1). A 2.0 wt% solution of each surfactant had different pH values before addition of the Sonogashira reagents. However, once the reagents are added to the solution, especially piperidine, the pH changed to ~11.0 at 40 °C and remained at this level through out the reaction, regardless of the surfactant.

Functional Group Scope of Sonogashira Coupling in Aqueous Surfactant Solutions

As shown in Table 3, the optimized aerobic reaction conditions for the Sonogashira coupling of aryl iodides with 1-octyne was quite general and tolerant of a range of functionalities on the aryl substrate. Both electron deficient and electron rich *p*-substituents afforded high yields of coupled product. When using aryl bromide substrates, moderate yields were also obtained for most substrates (Table 4, entries 1-8), except electron rich aryl bromides (entries 9-12). While

Table 3. Sonogashira Coupling of Various Aryl-I in the Presence of SDS and CTAB.



1 1.0 eq | **2a** 1.3 eq | **3** | **4a**

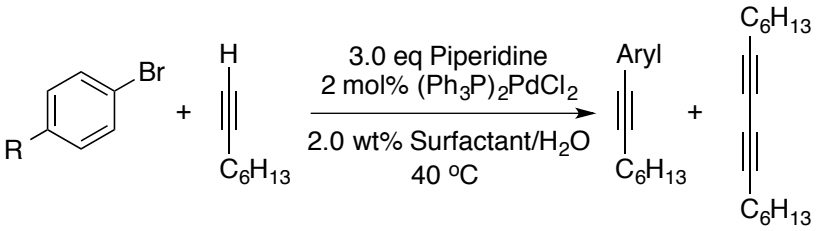
Entry[a]	R	CuX	Surfactant	% Yield **3**[b,c]	Yield **4a** (μmol)
1	CN	CuI	CTAB	97 (57)	12
2	CN	CuBr	CTAB	Quant. (57)	12
3	CN	CuI	SDS	Quant. (61)	11
4	CN	CuBr	SDS	Quant. (61)	10
5	CF_3	CuI	CTAB	Quant. (68)	9
6	CF_3	CuBr	CTAB	97 (68)	10
7	CF_3	CuI	SDS	Quant. (60)	10
8	CF_3	CuBr	SDS	90 (60)	9
9	NO_2	CuI	CTAB	91 (75)	14
10	NO_2	CuI	SDS	92 (74)	18
11	Ac	CuI	CTAB	96 (61)	17
12	Ac	CuI	SDS	Quant. (60)	13
13	CO_2Me	CuI	CTAB	89 (50)	18
14	CO_2Me	CuI	SDS	87 (57)	17
15	OMe	CuI	CTAB	97 (50)	16
16	OMe	CuBr	CTAB	93 (50)	17
17	OMe	CuI	SDS	90 (34)	18
18	OMe	CuBr	SDS	94 (34)	18
19	Me	CuI	CTAB	92 (50)	13

20	Me	CuBr	CTAB	88 (50)	13
21	Me	CuI	SDS	81 (39)	16
22	Me	CuBr	SDS	80 (39)	12
23[d]	Naphthyl	CuI	CTAB	97 (63)	10
24[d]	Naphthyl	CuI	SDS	Quant. (41)	9

Reaction conditions: 0.08 mmol aryl halide, 0.10 mmol 1-octyne, 0.24 mmol piperidine, 2.0 mol% $Pd(PPh_3)_2Cl_2$, 40 ºC, 0.80 mL surfactant (2.0 wt% in H_2O); [a] Rxns 1-14 ran 4 h, Rxns 15-24 ran 5 h. [b]Average ^{1}H NMR yields for duplicate runs (±3); [c] Parenthetical value is Cu(I)-free yield; [d] Aryl-I is 1-iodonapthalene.

coupling was achieved with either aryl-iodides or bromides, the reaction conditions were distinctly different for these two types of halide reagents. Both CuI and CuBr increased product yield in the coupling of aryl-iodide compounds with 1-octyne, but strongly inhibited coupling of aryl-bromides, despite the choice of surfactant or base (Tables 1-3). This inhibitory effect of Cu(I) with less active aryl-halides was noted earlier, resulting in development of alternative copper-free Sonogashira conditions.[66,96,108–121] Inhibition has been reported to be a result of Cu(I)-catalyzed homocoupling (Glaser coupling) of terminal alkynes, which requires oxygen to proceed.[122–130] In all of our reactions, under aerobic conditions, a secondary diyne product was present, resulting from the homocoupling of the alkyne (*vide infra*).

Table 4. Sonogashira Coupling of Various Aryl-Br in the Presence of SDS and CTAB.



1 1.0 eq **2a** 1.3 eq **3** **4a**

Entry	R	Surfactant	% Yield **3**[a] (No CuBr)	% Yield **3**[a] (CuBr)	Yield **4a**[b] (μmol)
1	CN	SDS	67	29	14
2	CN	CTAB	63	41	20
3	NO_2	SDS	64	8	9
4	NO_2	CTAB	74	20	17
5	CHO	SDS	67	8	12
6	CHO	CTAB	63	9	8
7[c]	Napthyl	SDS	68	4	10
8[c]	Napthyl	CTAB	67	10	15
9	Me	SDS	23	8	9
10	Me	CTAB	45	10	13
11	OMe	SDS	22	7	6
12	OMe	CTAB	35	9	8

Reaction conditions: 0.08 mmol aryl halide, 0.10 mmol 1-octyne, 0.24 mmol piperidine, 2.0 mol% $Pd(PPh_3)_2Cl_2$, 0.80 mL surfactant (2.0 wt% in H_2O), 40 ºC, 20 h; [a] Average ^1H NMR yields for duplicate runs (±3); [b] Yield of **4a** in reaction with CuBr; [b] Aryl-Br is 1-bromonapthalene.

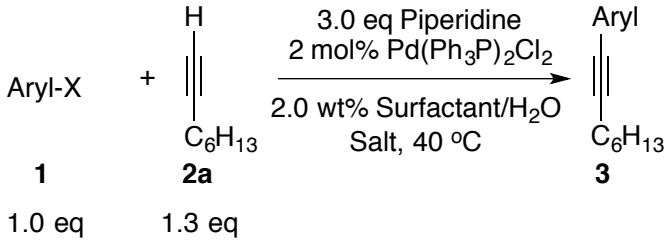
Cu(I) Salt and Iodide Inhibition on Sonogashira Coupling of Aryl Bromide Reagents

Further exploration showed that CuI was more inhibitory than CuBr in aryl bromide reactions (Table 5). Moreover, the coupling of 1-iodonapthalene and 4-bromobenzonitrile was assessed in the presence of various potassium halide salts. These studies demonstrate that the 4-bromobenzonitrile reactions were strongly inhibited by the presence of iodide. Even at a concentration of 0.05 M, KI lowered coupling product yield by 23% and 34% in both SDS and CTAB respectively (Figure 3). The reduction in Sonogashira coupling is most likely due to competitive iodide binding to Pd, possibly hindering the oxidative addition of the aryl bromide, and thus decreasing catalytic activity.

Formation of an Enyne Product

Coupling of phenylacetylene with aryl iodide was explored to determine if Cu(I) could be eliminated by using a more reactive alkyne substrate. When coupling excess phenylacetylene to 4-iodoanisole, product yields were high to quantitative using either SDS or CTAB as the surfactant, both with and without CuI (Table 6). However, in the absence of CuI a significant amount of an enyne side product (**5a**) was observed (Table 6). This side product was previously observed by Djakovitch et al. and proposed to originate from the insertion of phenylacetylene **2** into the initial Sonogashira product **3** under thermal or palladium-catalyzed

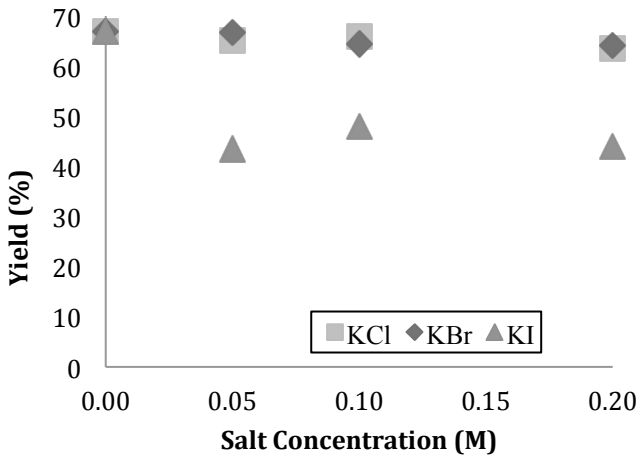
Table 5. Effect of salt on Sonogashira coupling of aryl halides with 1-octyne.



Entry[a]	Aryl-X	Salt (0.2 M)	% Yield **3**[b]	
			SDS	CTAB
1	1-iodonapthalene	none	19	45
2	1-iodonapthalene	CuI[c]	86	86
3	1-iodonapthalene	CuBr[c]	88	86
4	1-iodonapthalene	KCl	26	45
5	1-iodonapthalene	KBr	24	43
6	1-iodonapthalene	KI	22	39
7	4-bromobenzonitrile	none	67	63
8	4-bromobenzonitrile	CuI[c]	0	10
9	4-bromobenzonitrile	CuBr[c]	29	41
10	4-bromobenzonitrile	KCl	64	62
11	4-bromobenzonitrile	KBr	62	61
12	4-bromobenzonitrile	KI	47	24

Reaction conditions: 0.08 mmol aryl halide, 0.1 mmol 1-octyne, 0.24 mmol piperidine, 2.0 mol% $Pd(PPh_3)_2Cl_2$, 40 ºC, 0.80 mL surfactant (2.0 wt% in H_2O; 0.2 M in Salt); [a] Rxn 1-6 ran 4 h, Rxn 7-12 ran 20 h. [b] Average ^1H NMR yields for duplicate runs (±3). [c] 5 mol% CuX was used, SDS and CTAB solutions contained no salt.

a)



b)

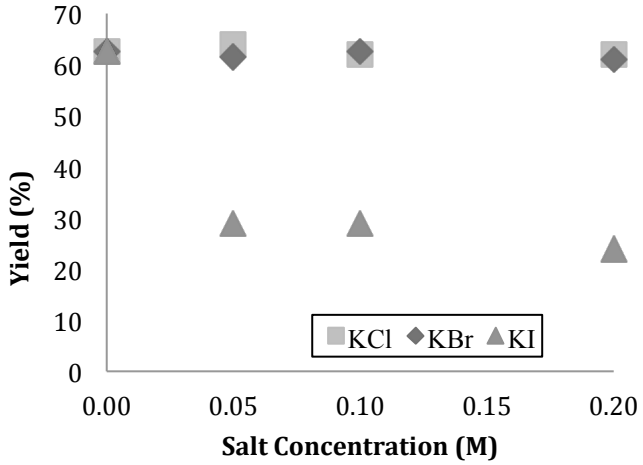
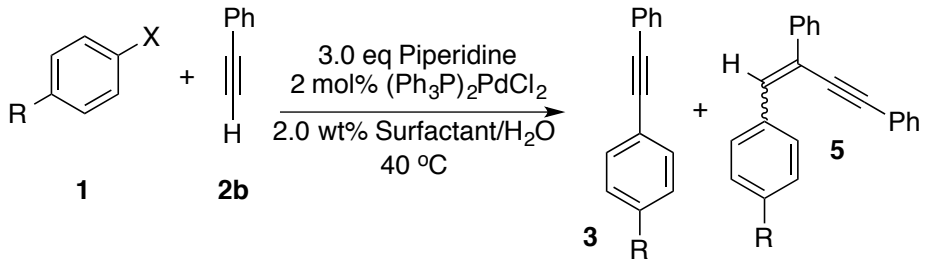


Figure 3. Effect of potassium halide salts on coupling of 4-bromobenzonitrile with 1-octyne. Reaction conditions: 0.08 mmol aryl halide, 0.1 mmol 1-octyne, 0.24 mmol piperidine, 2 mol% $Pd(PPh_3)_2Cl_2$, 0.80 mL, surfactant solution (2.0 wt% in water), 40 ºC, 20 h; Average ^1H NMR yields for duplicate runs (±3); a) SDS; b) CTAB.

Table 6. Cu(I)-free Sonogashira Coupling of Aryl-Halides and Phenylacetylene in the Presence of SDS and CTAB.



1 2b 3 5

Entry[a]	R	X	Surfactant	Ratio **1**:**2b**	% Yield **3**[b,c]	% Yield **5**[b,c]
1	OMe	I	SDS	1:5	58 (Quant.)	39 (0)
2	OMe	I	SDS	1:2	75 (92)	19 (0)
3	OMe	I	SDS	1:1	72 (82)	8 (0)
4	OMe	I	SDS	2:1	50 (71)	8 (0)
5	OMe	I	CTAB	1:5	61 (Quant.)	39 (0)
6	OMe	I	CTAB	1:2	75 (Quant.)	21 (0)
7	OMe	I	CTAB	1:1	65 (84)	10 (0)
8	OMe	I	CTAB	2:1	68 (83)	6 (0)
9	CN	Br	SDS	1:5	62	13
10	CN	Br	SDS	1:2	40	8
11	CN	Br	SDS	1:1	25	3
12	CN	Br	SDS	2:1	27	3
13	CN	Br	CTAB	1:5	69	12
14	CN	Br	CTAB	1:2	45	10
15	CN	Br	CTAB	1:1	27	8
16	CN	Br	CTAB	2:1	28	9

Reaction conditions: 0.24 mmol piperidine, 2.0 mol% $Pd(PPh_3)_2Cl_2$, 40 ºC, 0.80 mL surfactant (2.0 wt% in H_2O); [a] Rxns 1-8 ran 4 h, Rxns 9-16 run for 20 h. [b]Average ^{1}H NMR yields for duplicate runs (±3); [c] Parenthetical value is yield in presence of 5 mol% CuI, homocoupling product yield not determined.

conditions (*vide infra*).[110] In contrast, the analogous enyne product, that could result from using 1-octyne as the alkyne, was never detected under any reaction conditions. When CuI was present, **5** was not detected. Instead, quantitative Sonogashira product was produced and all excess phenylacetylene was converted to diyne (**4b**), according to GC analysis. In the Cu(I)- free coupling of 4-bromobenzonitrile and phenylacetylene, both the desired product and **5b** were formed albeit with overall lower yields (Table 6, entries 9-16).

Recycling of Aqueous Surfactant Solution.

The recyclability of the surfactant solution for Sonogashira coupling was assessed for 1-iodonapthalene and 1-octyne (Figure 4). A typical 1.0-mL scale coupling reaction between 1-iodonapthalene and 1-octyne was conducted in a 1.7-mL microcentrifuge tube. After 4 h, 200 µL of EtOAc was added to the tube. The mixture was thoroughly agitated and centrifuged at 10,000 RPM for 2 min to separate the organic reagents from the surfactant solution. This EtOAc wash, centrifugation, and separation was done a total of three times. The aqueous surfactant layer was removed and reused in another coupling reaction between 1-iodonapthalene and 1-octyne. Figure 4 illustrates that over 3 reaction cycles, yields of coupling product remained relatively constant, but decreased with subsequent cycles. Reuse of the CTAB solution caused the surfactant to precipitate over time, contributing to the lower yields.

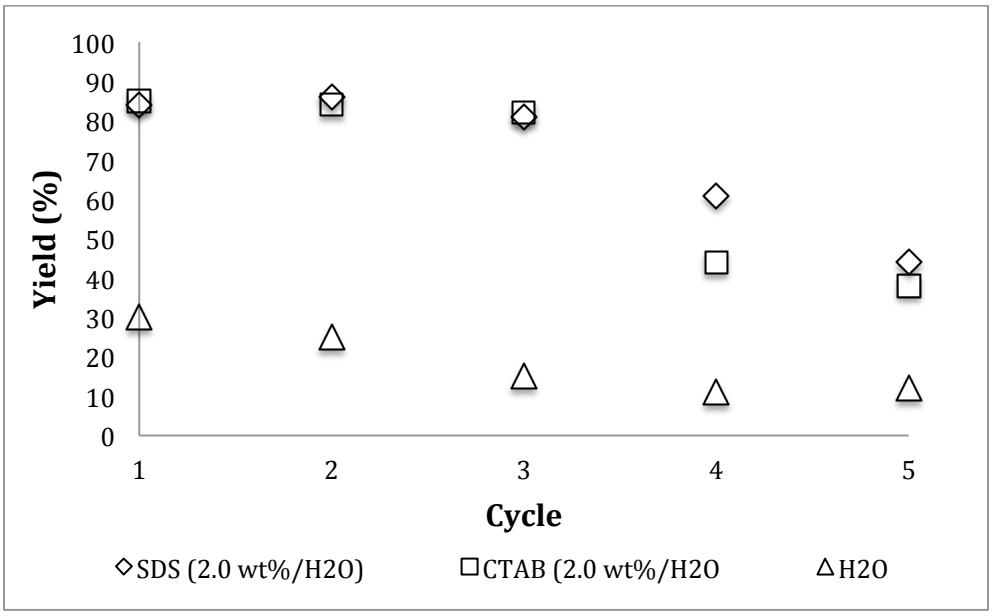


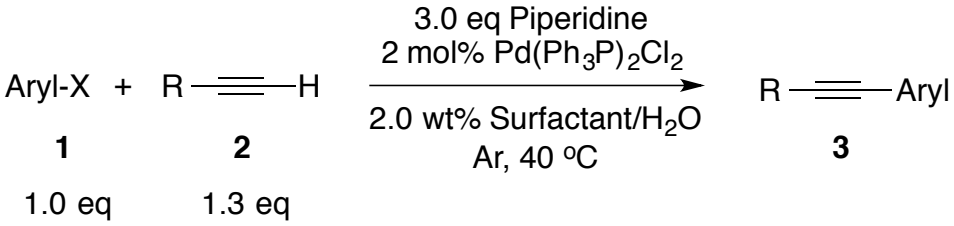
Figure 4. Recycling of surfactant solution for the Sonogashira coupling between 1-iodonapthalene and 1-octyne. Each cycle run for 4 h at 40 ºC.

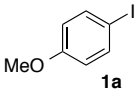
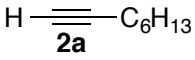
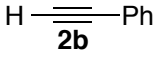
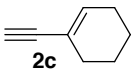
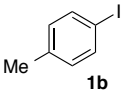
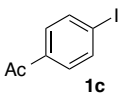
Product Purification

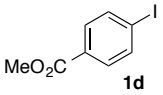
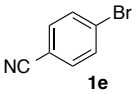
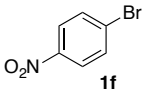
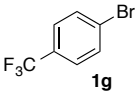
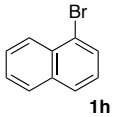
To determine the ease of product purification from surfactant, both the aryl iodide and bromide reactions were scaled up ten-fold (Table 7). In addition to employing the optimized conditions developed above, all reagents were added under argon and the aqueous surfactant solution was sparged with argon for 30 min before addition to the reaction vessel. Reducing the atmospheric oxygen lowered or eliminated the formation of the homocoupling product, **4**, in Cu(I) co-catalyzed reactions and gave an increase in isolated yield for aryl-bromide reactions. The alkyne product was easily extracted from the aqueous surfactant solution using hexanes or ethyl acetate. Passing the extracted solution through a plug of silica gel eliminated trace surfactant contamination and residual catalyst.

Purification difficulties arose when the homocoupling product was also present. The diyne products (**4a** and **4b**) co-eluted with the Sonogashira product during flash column chromatography, even when using neat hexane as the eluent.

Table 7. Isolated Sonogashira Coupling Yields for Aryl-I and Aryl-Br Substrates.



Entry	Aryl halide	Alkyne	Surfactant	CuI (5 mol%)	Product (% Yield)
1	 **1a**	 **2a**	CTAB	-	45 (**3a**)
2	**1a**	**2a**	CTAB	CuI	92 (**3a**)
3	**1a**	 **2b**	CTAB	-	54 (**3b**)
4	**1a**	**2b**	CTAB	CuI	96 (**3b**)
5	**1a**	 **2c**	CTAB	CuI	93 (**3c**)
6	 **1b**	**2a**	SDS	CuI	91 (**3d**)
7	**1b**	**2b**	SDS	CuI	96 (**3e**)
8	**1b**	**2c**	SDS	CuI	94 (**3f**)
9	 **1c**	**2a**	SDS	-	61 (**3g**)
10	**1c**	**2a**	SDS	CuI	96 (**3g**)
11	**1c**	**2b**	SDS	-	72 (**3h**)
12	**1c**	**2b**	SDS	CuI	97 (**3h**)

13	**1c**	**2c**	SDS	CuI	95 (**3i**)
14	 **1d**	**2a**	CTAB	CuI	91 (**3j**)
15	**1d**	**2b**	CTAB	CuI	93 (**3k**)
16	**1d**	**2c**	CTAB	CuI	98 (**3l**)
17	 **1e**	**2a**	CTAB	-	77 (**3m**)
18	**1e**	**2b**	CTAB	-	78 (**3n**)
19	**1e**	**2c**	CTAB	-	81 (**3o**)
20	 **1f**	**2a**	SDS	-	79 (**3p**)
21	**1f**	**2b**	SDS	-	87 (**3q**)
22	**1f**	**2c**	SDS	-	80 (**3r**)
23	 **1g**	**2a**	SDS	-	74 (**3s**)
24	**1g**	**2b**	SDS	-	79 (**3t**)
25	**1g**	**2c**	SDS	-	76 (**3u**)
26	 **1h**	**2a**	CTAB	-	63 (**3v**)
27	**1h**	**2b**	CTAB	-	72 (**3w**)
28	**1h**	**2c**	CTAB	-	66 (**3x**)

Condition: 0.8 mmol aryl halide, 1.0 mmol alkyne, 3.0 mmol piperidine, 2 mol% $Pd(PPh_3)_2Cl_2$, 5 mol% CuI if indicated, 8.0 mL surfactant (2.0 wt% in water), 40 °C, under Ar, 5 h for aryl-I and 20 h for aryl-Br reactions.

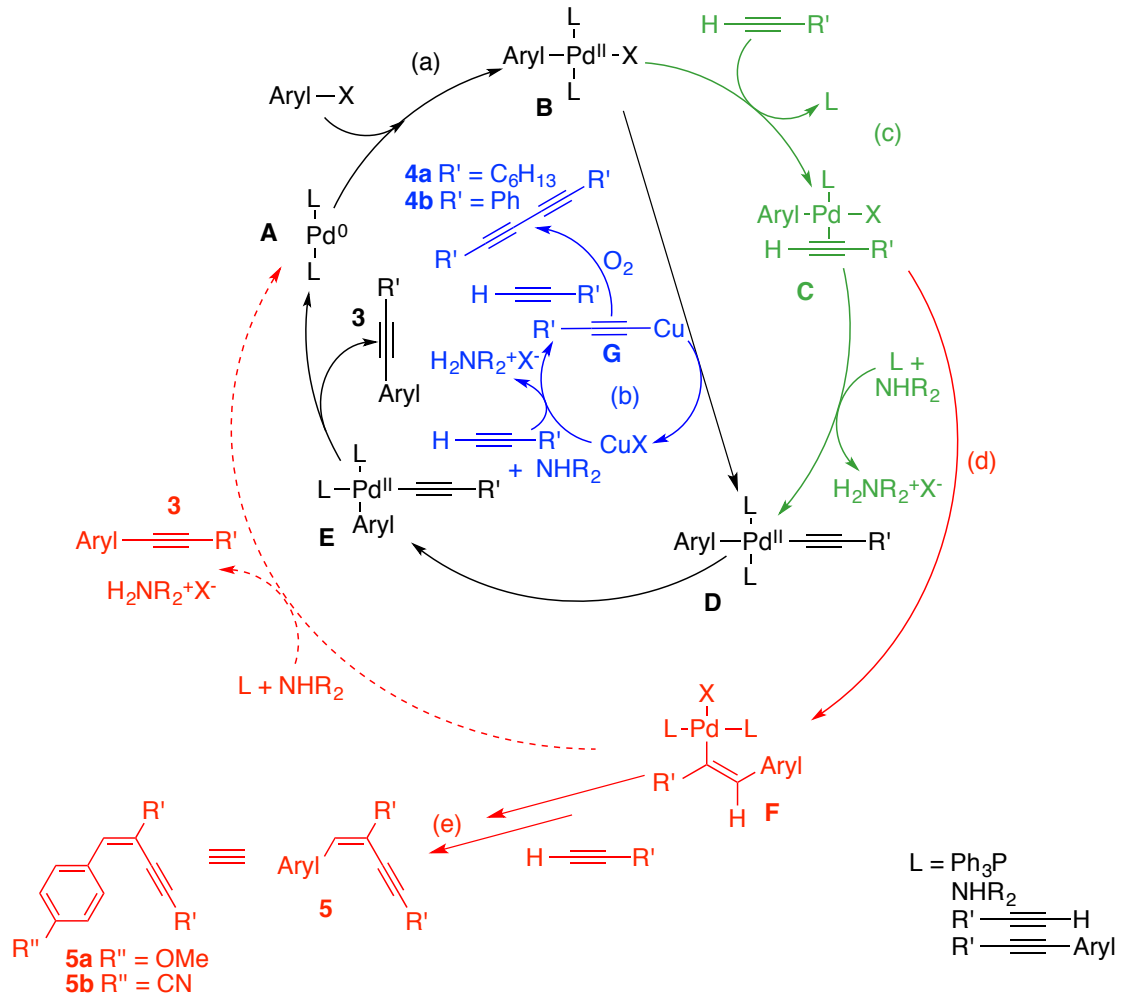


Figure 5. Proposed mechanism of the Sonogashira coupling in the presence of piperidine, with and without a Cu(I) co-catalyst; (a) Traditional Cu(I) co-catalyzed Sonogashira; (b) Catalytic cycle for Cu(I) including formation of diyne, **4**; (c) Cu(I)-free coupling via deprotonation mechanism; (d) Cu(I)-free carbopalladiation cycle forming product **5**.

Mechanistic Considerations

Copper(I) co-catalyzed Sonogashira reactions are commonly agreed to have three fundamental steps, 1) oxidative addition of the aryl halide to Pd(0), 2) transmetallation of the acetylide moiety from Cu(I) to the Pd center, and 3) subsequent reductive elimination of alkyne product (Figure 5a).[105] The key benefit of Cu is facilitating the formation of the Pd-acetylide, which occurs through the formation of a Cu-acetylide intermediate (**G**). However, the Cu-acetylide is also active for homocoupling under aerobic conditions that leads to a diyne product, **4**, a cycle that would divert the alkyne substrate from forming the desired Sonogashira product. In our aryl iodide system, this homocoupling cycle was not detrimental to the formation of desired product, **3**. Moreover, homocoupling is also unlikely to be the cause of reduced yields in the aryl bromide reactions. In these cases, the formation of diyne, **4a**, was low (< 20 μmol) in all reactions involving aryl bromides. It is also unlikely that low yield in aryl bromide reactions is caused by Cu–catalyzed oligomerization of the 1-octyne. No oligomers were detected in these reactions and a substantial amount of 1-octyne remained at the end of the reaction.

In seeking to improve the yields of the aryl bromide reactions, we examined the role of the alkyne substrate by varying its amount and rate of addition (Table 8). When 1-octyne was the limiting reagent in reactions with 1-bromonaphthalene, the yield of product **3v** was quantitative, based upon the loading of the alkyne. As the amount of 1-octyne was increased, the yield of **3v** decreased. However, if the

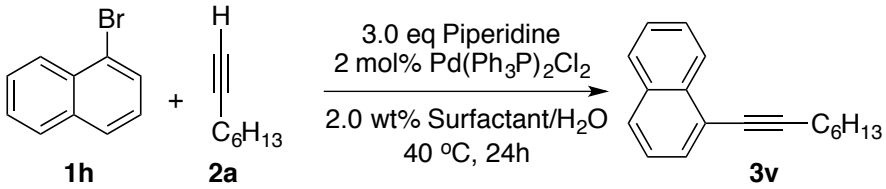
alkyne was added in smaller aliquots throughout the duration of the reaction, the yield of **3v** was significantly improved (78%, Table 8, entry 4) as compared to a reaction with the same loading of 1-octyne added entirely at the beginning of the reaction (51%, Table 8, entry 3). This alkyne inhibition with aryl bromides is consistent with a catalytic cycle in which the oxidative addition step becomes rate determining (Figure 5, step a) relative to transmetallation to form **D**.[105,131] Moreover, coordination of an alkyne to Pd^0L_2 (**A**) can form an $(\eta^2\text{-RC}\equiv\text{CR}')Pd^0L_2$ complex, which is less electron rich, further inhibiting the oxidative addition of the aryl halide.[132]

While the formation of product **3v** was inhibited by excess terminal alkyne, this did not explain why yields in the aryl bromide reactions were even lower in the presence of Cu(I). Since it appears that the reduced yields are not solely due to Cu-catalyzed side reactions, the yield may also be reduced by preferential binding of the diyne product to Pd^0L_2 (**A**), further inhibiting oxidative addition of the aryl-bromide. To assess this, 1,4-diphenylbuta-1,3-diyne, **4b**, was added to the coupling of 1-bromonapthalene and 1-octyne (Table 8). For the reactions with 20 μmol (25 mol%) diyne, the yield of product **3v** was reduced to 51and 53% for CTAB and SDS respectively.

Two mechanisms have been proposed for the copper-free Sonogashira coupling: a 'deprotonation mechanism' and a 'carbopalladation mechanism'

(Figure 5c and 5d respectively). Recently, a number of experimental and computational studies indicate that the latter is more feasible than the former. Mårtensson et al. argued against the carbopalladation mechanism because isolated intermediates such as **F** do not β-hydride eliminate to produce product **3** and intermediate **A** in the presence or absence of NEt_3.[108] Additionally, a computational study for the ambient-temperature coupling of iodobenzene and phenylacetylene catalyzed by $Pd(PPh_3)_2$ produced a calculated energy barrier of 40.4 kcal·mol^{-1} for the pyrrolidine-assisted β-H elimination from intermediate **F** to form product **3**.[133] However, the deprotonation mechanism does not explain the formation of the side product, **5**. We confirmed that under our conditions diphenylacetylene does not form an enyne product with phenylacetylene, indicating that product **5** is not due to alkyne addition to product **3** (Scheme 1). More likely, **5** is formed due to trapping of intermediate **F** via excess alkyne.[108] Therefore, under Cu(I)-free conditions both mechanisms are expected to be competing. When alkyne coordinates and intermediate **C** is formed, it can either undergo base assisted deprotonation to form Pd-acetylide, **D**, or undergo *syn* addition form intermediate **F**. When the concentration of phenylacetylene is high enough, **F** is trapped to form product **5**. When Cu(I) is present, the transmetallation step is so fast that intermediate **C** may not form in high enough concentration, disfavoring the cycle to **5**.

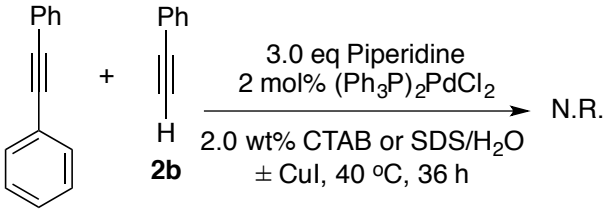
Table 8. Influence of Alkyne and Diyne (**4b**) on Coupling in Cu-Free Aryl-Bromide Reactions.



1h **2a** **3v**

Entry	**1h**:**2a**	**4b** (mol%)	Surfactant	% Yield **3v**[a]
1	1:0.7	-	CTAB	Quant. (67)[b,c]
2	1:1	-	CTAB	56
3	1:1.7	-	CTAB	51
4	1:1.7[d]	-	CTAB	78
5	1:1.3	-	CTAB	67
6	1:1.3	25	CTAB	51
7	1:1.3	-	SDS	68
8	1:1.3	25	SDS	53

Reaction conditions: 0.08 mmol aryl halide, 0.24 mmol piperidine, 2.0 mol% $Pd(PPh_3)_2Cl_2$, 40 ºC, 0.80 mL surfactant (2.0 wt% in water); [a] Average ^1H NMR yields for duplicate runs (±3); [b] % Yield based upon the loading of 1-octyne, 0.05 mmol; [c] Parenthetical value is conversion of 1-bromonapthalene; [d] 0.07 mmol 1-octyne added at t = 0 h and 8 h.



Scheme 1. Attempt to Form Enyne Product From Diphenylacetylene and Phenylacetylene.

Summary and Outlook

Our work has shown that inexpensive, commercially available surfactants such as SDS and CTAB are effective in the aqueous-phase formation of Sonogashira coupling products for various aryl iodide and bromide substrates, providing a substantial improvement upon coupling yields achieved in neat water at the same temperature. Under the surfactant conditions described above, both the deprotonation and carbopalladation mechanisms appear to be active. The deprotonation mechanism forms the desired Sonogashira product, but in the presence of excess phenylacetylene, the enyne product (**5**) derived from a carbopalladation cycle, is formed. Copper(I) salts and excess alkyne are inhibitory to aryl bromide reactions. Consequently, aryl bromide reactions benefit from slow addition of the alkyne reagent under Cu-free conditions.

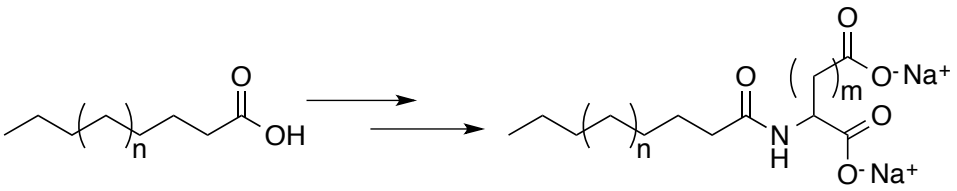
Overall, use of a surfactant enhances reactivity in water and thus minimizes environmental impact by eliminating the need for organic solvents. However, contaminated water is still considered waste if it cannot be recycled or reused after

retrieving the desired product, detracting from its green benefits. Both SDS and CTAB solutions proved recyclable, maintaining moderate to high yields for both 1-bromo- and 1-iodonapthalene.

The efficacy and recyclability of these surfactant solutions as reaction media demonstrates that these conditions are a good foundation for further modifications, including utilizing a more reactive Pd-complex, adapting the surfactant structure, and expanding the scope to other catalytic reactions. A more efficient catalyst would not only allow better access to less reactive aryl halides, but also allow exclusion of Cu(I) salts. In addition, modification of the surfactant structure may help improve coupling yields as well as reduce the reaction temperature.

Micelle enhancement of organic reactions in aqueous solution is attributed to factors such as 1) high localized concentration of reagents at or within the micelle; 2) favorable interactions between charged transitions states and the polar surfactant head groups; and/or 3) solvent effects due to interaction within the micelle core.[59] For example, if a charged or polar organic molecule enters the hydrophobic portion of the micelle (e.g. sodium benzoate) unfavorable interactions will destabilize the reagent and make it more reactive, enhancing rate. It has also been shown that the overall diameter of the micelle, and thus the organic 'solvent' pocket plays a critical role in reaction yields, presumably due to better incorporation of substrate and catalyst.[134] Therefore, SDS and CTAB provide a potential starting point as promising design templates for the development of improved surfactants.

New surfactant syntheses based on CTAB and SDS features could readily involve green principles by modifying long chain, aliphatic alcohols derived from plant materials such as coconut oil, or long chain fatty acids biologically synthesized from bacteria such as E. coli.[135,136] In addition to modifying the hydrophobic chain length, various diacid linkers (e.g. succinic acid) could be inserted between the head and tail moieties. This would serve as an additional way to modify the size of the micelle and thus possibly better incorporate reagents and catalysts for improved reaction yields and rate. The charged head group could also be easily altered to incorporate versatile head groups from biobased molecules, such as aspartates and glutamates (Scheme 2).[137] The modifications suggested here have the possibility to not only enhance Sonogashira coupling under milder reaction conditions, but also to incorporate green concepts, while expanding the scope of available surfactants for organic synthesis.



Scheme 2. Proposed Surfactant Modification

Experimental Section

General Considerations. All surfactants, aryl-halides, alkynes, bases and copper salts were purchased commercially (≥97% purity) and used without further purification. Bis(triphenylphosphine)dichloropalladium(II) was prepared and characterized according to the literature.[138] All surfactant solutions were prepared using deionized water. All NMR-scale reactions were performed in 1.7 mL microcentrifuge tubes from Corning Incorporated and were shaken with an Eppendorf Thermomixer R for the time and temperature indicated. Preparative scale reactions were performed in 20-mL scintillation vials, sealed with cap containing a Poly-Seal cone liner. ^{1}H, and ^{13}C NMR spectra were obtained using a Varian MR400 MHz NMR. Mass spectra were collected on a Waters GCT GC-MS.

NMR Scale Procedure for the Sonogashira Reaction. A suspension of 47 mg (67 μmol) $Pd(PPh_3)_2Cl_2$ was made with 1.0 mL of piperidine in a 20-mL glass vial. If indicated, 168 μmol of CuX (X = I or Br) was also included in this suspension. The suspension was sonicated until homogeneous and clear (30 min), resulting in a bright yellow Pd solution in the absence of Cu(I) and a dark green Pd solution with Cu. A 1.7-mL microcentrifuge tube was charged with 0.08 mmol aryl halide and 0.1 mmol alkyne, and 0.8 mL of aqueous surfactant solution (2.0 wt%). Finally, 24 μL of the sonicated base/catalyst solution was added. This resulted in 0.24 mmol of piperidine, 1.6 μmol (2 mol%) of $Pd(PPh_3)_2Cl_2$ and 4.0 μmol (5 mol%) CuX per

reaction. The tube was sealed, thoroughly mixed and shaken at 1100 rpm and 40 °C for the time indicated. After reaction completion, the mixture was cooled to ambient temperature, and 50 µL of a standard solution (400 mg mesitylene diluted to 10 mL with $CDCl_3$) was added. The samples were extracted with neat $CDCl_3$ (2 x 0.4 mL). To assist separation of the organic and water layers, the tubes were centrifuged at 1200 rpm for 2 min after each extraction. The extracts were combined and passed through a plug of Al_2O_3 and $MgSO_4$, into a NMR tube. Yields were determined by ^1H NMR. Each reaction was performed in duplicate.

Preparative Scale Procedure for the Sonogashira Reaction. The indicated aqueous surfactant solution (2.0 wt%) was sparged with Ar for 30 min. During this time, a suspension of 47 mg (67 µmol) $Pd(PPh_3)_2Cl_2$ was made in 1.0 mL of piperidine in a 20-mL glass vial. If indicated, 168 µmol of CuX (X = I; 32 mg or Br; 24 mg) was also included in this suspension. The suspension was sonicated until the mixture became homogeneous and clear (30 min), resulting in a bright yellow solution in the absence of Cu(I) and a dark green solution with Cu. Under Ar, a 20-mL glass vial was charged with a stir bar, 0.8 mmol aryl halide, 1.0 mmol alkyne, and 8.0 mL of the sparged aqueous surfactant solution, and 0.24 mL of the sonicated catalyst solution. The vial was briefly purged with Ar (5 min), sealed with a cap and stirred while gently heating at 40 °C for the time indicated. After reaction completion, all volatiles were removed under reduced pressure, and the aqueous solution was extracted with EtOAc (3x5 mL). The combined EtOAc extracts were

washed with saturated NaCl (3x5 mL), dried with $MgSO_4$, filtered, and all solvent was removed under reduced pressure. The crude product was purified via flash column chromatography using hexane or hexane/EtOAc as the eluent. Product yields were determined via ^{1}H NMR and GC-MS analysis. Characterization data for all coupling products matched literature values.

1-methoxy-4-(oct-1-yn-1-yl)benzene (**3a**)[139] Clear oil, 161 mg, 92%; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.31 (d, *J* = 8.8 Hz, 2H), 6.80 (d, *J* = 8.8 Hz, 2H), 3.79 (s, 3H), 2.38 (t, *J* = 6.6 Hz, 2H), 1.59-1.52 (m, 2H), 1.42-1.36 (m, 2H), 1.32-1.26 (m, 4H), 0.89 (t, *J* = 6.0 Hz, 2H); EI-MS: m/z (rel. intensity %) 216.2 (M^+, 52), 187.2 (19), 173.1 (48), 159.1 (34), 145.1 (100), 130.1 (18), 121.1 (25), 115.1 (22), 102.1 (24), 97.1 (17).

1-methoxy-4-(phenylethynyl)benzene (**3b**)[139] White solid, 162 mg, 96%; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.54-7.51 (m, 2H), 7.48 (d, *J* = 9.0 Hz, 2H), 7.37-7.30 (m, 3H), 6.99 (d, *J* = 9.0 Hz, 2H), 3.84 (s, 3H); EI-MS: m/z (rel. intensity %) 208.1 (M^+, 100), 193.1 (63), 165.1 (32), 139.1 (6), 115.1 (3), 104.1 (5).

1-(cyclohex-1-en-1-ylethynyl)-4-methoxybenzene (**3c**)[140] Clear oil, 155 mg, 94%; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.35 (d, *J* = 8.8 Hz, 2H), 6.83 (d, *J* = 8.8 Hz, 2H), 6.18-6.16 (m, 1H), 3.80 (m, 3H), 2.24-2.20 (m, 2H), 2.15-2.11 (m, 2H), 1.70-

1.56 (m, 4H); EI-MS: m/z (rel. intensity %) 212.2 (M^+, 100), 197.2 (11), 184.2 (27), 169.2 (15), 153.1 (8), 141.1 (12), 132.1 (8), 121.1 (4), 115.1 (11).

1-methyl-4-(oct-1-yn-1-yl)benzene (**3d**)[139] Clear oil, 151 mg, 91%; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.30 (d, *J* = 8.0 Hz, 2H), 7.08 (d, *J* = 8.0 Hz, 2H), 2.39 (t, *J* = 7.0 Hz, 2H), 2.33 (s, 3H), 1.60-1.57 (m, 2H), 1.34-1.30 (m, 6H), 0.91 (t, *J* = 5.6 Hz, 3H); EI-MS: m/z (rel. intensity %) 200.2 (M^+, 38), 185.2 (4), 171.2 (12), 157.1 (45), 142.1 (33), 129.1 (100), 115.1 (22), 105.1 (18), 91.1 (9).

1-methyl-4-(phenylethynyl)benzene (**3e**)[139] White solid, 149 mg, 96%; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.55-7.52 (m, 2H), 7.44 (d, *J* = 8.0 Hz, 2H), 7.38-7.32 (m, 3H), 7.16 (d, *J* = 8.0 Hz, 2H), 2.38 (s, 3H); EI-MS: m/z (rel. intensity %) 192.1 (M^+, 100), 176.1 (2), 165.1 (11), 152.1 (3), 139.1 (4), 115.1 (4), 96.1 (2).

1-(cyclohex-1-en-1-ylethynyl)-4-methylbenzene (**3f**)[141] Clear oil, 153 mg, 94%; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.32 (d, *J* = 8.0 Hz, 2H), 7.01 (d, *J* = 8.0 Hz, 2H), 6.20-6.18 (m, 1H), 2.34 (s, 3H), 2.34-2.20 (m, 2H), 2.16-2.12 (m, 2H), 1.69-1.56(m, 4H); EI-MS: m/z (rel. intensity %) 196.2 (M^+, 100), 181.2 (84), 165.1 (63), 153.1 (40), 139.1 (16), 128.1 (12), 115.1 (17), 105.1 (7), 89.1 (4).

1-(4-(oct-1-yn-1-yl)phenyl)ethan-1-one (**3g**)[139] Yellow oil, 178 mg, 96%; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.85 (d, *J* = 8.4 Hz, 2H), 7.44 (d, *J* = 8.4 Hz, 2H), 2.58

(s, 3H), 2.41 (t, *J* = 7.2 Hz, 2H), 1.63-1.59 (m, 4H), 1.35-1.31 (m, 4H) 0.90 (t, *J* = 6.8 Hz, 3H); EI-MS: m/z (rel. intensity %) 228.2 (M^+, 60), 213.1 (100), 185.1 (47), 143.1 (43), 129.1 (82),114.1 (42), 43.0 (53).

1-(4-(phenylethynyl)phenyl)ethan-1-one (**3h**)[139] White solid, 174 mg, 97%; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.95 (d, *J* = 8.4 Hz, 2H), 7.62 (d, *J* = 8.4 Hz, 2H), 7.59-7.54 (m, 2H), 7.40-7.36 (m, 3H), 2.63 (s, 3H); EI-MS: m/z (rel. intensity %) 220.2 (M^+, 99), 205.1 (100), 176.1 (94), 151.1 (52), 126.1 (11), 102.6 (12), 88.1 (14).

1-(4-(cyclohex-1-en-1-ylethynyl)phenyl)ethan-1-one (**3i**)[142] Clear oil, 175 mg, 95%; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.86 (d, *J* = 8.4 Hz, 2 H), 7.46 (d, *J* = 8.4 Hz, 2 H), 6.27-6.21 (m, 1 H), 2.56 (s, 3 H), 2.40-2.09 (m, 4 H), 1.71-1.55 (m, 4 H).

methyl 4-(oct-1-yn-1-yl)benzoate (**3j**)[139] White solid, 178 mg, 91%; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.96 (d, *J* = 8.8 Hz, 2H), 7.45 (d, *J* = 8.8 Hz, 2H), 3.92 (s, 3H), 2.43 (t, *J* = 7.0 Hz, 2H), 1.62 (m, 2H), 1.46 (m, 2H), 1.33 (m, 4H), 0.92 (t, *J* = 6.8 Hz, 3H).

methyl 4-(phenylethynyl)benzoate (**3k**)[139] White solid, 177 mg, 98%; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.03 (d, *J* = 8.3 Hz, 2H), 7.60 (d, *J* = 8.3 Hz, 2H), 7.57-7.55 (m, 2H), 7.39-7.37 (m 3H), 3.94 (s, 3H).

methyl 4-(cyclohex-1-en-1-ylethynyl)benzoate (**3l**)[143] Clear oil, 179 mg, 93%; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.00-7.95 (m, 2H), 7.56-7.45 (m, 2H), 6.25 (s, 1H), 3.91 (s, 3H), 2.23-2.14 (m, 4H), 1.69-1.60 (m, 4H);

4-(oct-1-yn-1-yl)benzonitrile (**3m**)[139] Pale yellow oil, 136 mg, 77%; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.56 (d, *J* = 8.0 Hz, 2H), 7.45 (d, *J* = 8.0 Hz, 2H), 2.42 (t, *J* = 7.2 Hz, 2H), 1.62-1.59 (m, 2H), 1.45-1.43 (m, 2H), 1.33-1.29 (m, 4H), 0.90 (t, *J* = 6.6 Hz, 3H); EI-MS: m/z (rel. intensity %) 211.2 (M^+, 38), 182.1 (60), 168.1 (100), 154.1 (71), 140.1 (79), 127.1 (37), 116.1 (37), 95.1 (11).

4-(phenylethynyl)benzonitrile (**3n**)[139] White solid, 135 mg, 81%; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.57-7.30 (m, 10H).

4-(cyclohex-1-en-1-ylethynyl)benzonitrile (**3o**)[116] Light yellow solid, 133 mg, 78%; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.54 (d, J = 8.0 Hz, 2H), 7.44 (d, J = 8.0 Hz, 2H), 6.25 (m, 1H), 2.13–2.21 (m, 4H), 1.59–1.68 (m, 4H).

1-nitro-4-(oct-1-yn-1-yl)benzene (**3p**)[139] Yellow oil, 143 mg, 79%; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.15 (d, *J* = 8.0 Hz, 2H), 7.51 (d, *J* = 8.0 Hz, 2H), 2.44 (t, *J* = 7.2 Hz, 2H), 1.64-1.60 (m, 2H), 1.46-1.43 (m, 2H), 1.33-1.30 (m, 4H), 0.90 (t, *J* = 6.6 Hz, 3H).

1-nitro-4-(phenylethynyl)benzene (**3q**)[139] Yellow solid, 152 mg, 87%; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.11 (d,2H), 7.56 (d, 2H), 7.46 (m, 2H), 7.29 (m, 3H).

1-(cyclohex-1-en-1-ylethynyl)-4-nitrobenzene (**3r**)[144] Yellow Solid, 142 mg, 80%; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.15 (d, *J* = 8.8 Hz, 2H), 7.52 (d, *J* = 8.8 Hz, 2H), 6.32-6.29 (m, 1H), 2.23-2.16 (m, 4H), 1.73-1.61 (m, 4H).

1-(oct-1-yn-1-yl)-4-(trifluoromethyl)benzene (**3s**)[145] Pale yellow oil, 146 mg, 74%; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.53 (d, *J* = 8.0 Hz, 2H), 7.48 (d, *J* = 8.0 Hz, 2H), 2.42 (t, *J* = 7.0 Hz, 2H), 1.63-1.59 (m, 2H), 1.45-1.43 (m, 2H), 1.33-1.29 (m, 4H), 0.90 (t, *J* = 6.6 Hz, 3H); EI-MS: m/z (rel. intensity %) 254.2 (M^+, 48), 235.2 (25), 225.2 (79), 211.2 (100), 197.2 (46), 183.1 (84), 170.1 (35), 159.1 (48), 129.1 (51), 115.1 (27), 95.1 (18).

1-(phenylethynyl)-4-(trifluoromethyl)benzene (**3t**)[140] Light yellow solid, 151 mg, 79%; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.66-7.60 (m, 4H), 7.57-7.54 (m, 2H), 7.40-7.36 (m, 3H); EI-MS: m/z (rel. intensity %) 246.1 (M^+, 100), 227.1 (12), 196.1 (8), 176.1 (10), 151.1 (4),123.1 (6), 98.1 (9).

1-(cyclohex-1-en-1-ylethynyl)-4-(trifluoromethyl)benzene (**3u**) Light yellow oil, 148 mg, 76%; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.66-7.60 (m, 4H), 6.25 (m, 1H), 2.13–2.21 (m, 4H), 1.59–1.68 (m, 4H).

1-(oct-1-yn-1-yl)naphthalene (**3v**)[146] Clear oil, 115 mg, 63%; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.36 (d, *J* = 8.4 Hz, 1H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.63 (d, *J* = 7.2 Hz, 1H), 7.58-7.49 (m, 2H), 7.42-7.38 (m, 1H), 2.58 (t, *J* = 7.0 Hz, 2H), 1.74-1.70 (m, 2H), 1.56-1.53 (m, 2H), 1.39-1.36 (m, 4H), 0.92 (t, *J* = 6.6 Hz, 3H);[i] EI-MS: m/z (rel. intensity %) 236.2 (M^+, 51), 221.2 (4), 207.2 (11), 193.1 (21), 178.1 (20), 165.1 (100), 152.1 (17), 141.1 (8).

1-(phenylethynyl)naphthalene (**3w**)[146] White Solid, 133 mg, 76%; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.47 (d, *J* = 8.0 Hz, 1H), 7.88 (t, *J* = 8.0 Hz, 2H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.69-7.38 (m, 8H).

1-(cyclohex-1-en-1-ylethynyl)naphthalene (**3x**) Clear oil, 119 mg, 66%; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.36 (d, *J* = 8.4 Hz, 1H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.63 (d, *J* = 7.2 Hz, 1H), 7.58-7.49 (m, 2H), 7.42-7.38 (m, 1H), 6.25 (m, 1H), 2.13–2.21 (m, 4H), 1.59–1.68 (m, 4H).

4-(oct-1-yn-1-yl)benzaldehyde (**3y**)[147] Clear oil, 11 mg, 67%; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.98 (s, 1H), 7.80 (d, *J* = 8.3 Hz, 2H), 7.53 (d, *J* = 8.3 Hz, 2H), 2.45 (t, *J* = 6.8 Hz, 2H), 1.28–1.64 (m, 8H), 0.90 (t, *J* = 7.3 Hz, 3H).

Procedure for Recyclability Study. A suspension of 47 mg (67 μmol) of $Pd(PPh_3)_2Cl_2$ and 32 mg CuI was made with 1.0 mL of piperidine in a 20-mL glass vial. The suspension was sonicated until the mixture became homogeneous, green, and translucent (30 min). A 1.7-mL microcentrifuge tube was charged with 0.08 mmol 1-iodonapthalene and 0.1 mmol 1-octyne, and 0.8 mL of aqueous surfactant solution (2.0 wt%). Finally, 24 μL of the sonicated base/catalyst solution was added. This resulted in 0.24 mmol of piperidine, 1.6 μmol (2 mol%) of $Pd(PPh_3)_2Cl_2$ and 4.0 μmol (5 mol%) CuI per reaction. The tube was sealed, thoroughly mixed and shaken at 1100 rpm and 40 °C for 4 h. At reaction completion, the mixture was cooled to ambient temperature and extracted with EtOAc (3x200 μL). To assist separation of the organic and water layers, the tubes were centrifuged at 1200 rpm for 2 min after each extraction. The extracts were combined, and all volatiles removed under reduced pressure. The crude product was purified via a short column of silica gel. The extracted surfactant solution was added to another aliquot of reagents and catalyst/piperidine solution and treated for the same temperature and time. This procedure was repeated 5 times.

Preparative Scale Procedure for the Synthesis of Diyne (**4**). A suspension of 47 mg (67 μmol) of $Pd(PPh_3)_2Cl_2$ and 32 mg CuI was made with 1.0 mL of piperidine in a 20-mL glass vial. The suspension was sonicated until homogeneous, translucent, and green in color (30 min). A 25-mL round bottom flask was charged with 0.80 mmol of aryl halide, 1.0 mmol of alkyne, and 8.0 mL of aqueous CTAB (2.0 wt%).

Subsequently, 240 µL of the sonicated catalyst solution was added. The reaction was stirred at 40 °C for 12 h without exclusion of oxygen. After reaction completion, all volatiles were removed under reduced pressure, and the aqueous solution was extracted with EtOAc (3x5 mL). The combined EtOAc extracts were washed with saturated NaCl (3x5 mL) and all solvent was removed under reduced pressure. The crude product was redissolved in hexane and residual catalyst was removed by passing through a plug of neutral Al_2O_3 and silica gel. Removal of hexane under vacuum afforded pure diyne product, which was confirmed via ^{1}H NMR and GC-MS analysis. Characterization data for the diyne products matched literature values.

hexadeca-7,9-diyne (**4a**)[148] Clear oil: 77 mg, 69%; 1H NMR (400 MHz, CDCl3): d 2.24 (t, J = 7.0 Hz, 4H), 1.56 - 1.47 (m, 4H), 1.42 - 1.34 (m, 4H), 1.29 (ddd, J = 10.2, 8.7, 2.5 Hz, 8H), 0.89 (t, J = 6.9 Hz, 6H).

1,4-diphenylbuta-1,3-diyne (**4b**)[149] 106 mg, 98%; 1H NMR (400 MHz, CDCl3): 7.56-7.53 (m, 4H), 7.41-7.33 (m, 6H).

Preparative Scale Procedure for the Synthesis of Enyne Addition Product (5). An aqueous CTAB solution (2.0 wt%) was sparged with Ar for 30 m. While sparging, a suspension of 47 mg $Pd(PPh_3)_2Cl_2$ was made with 1.0 mL of piperidine in a 20-mL glass vial. The suspension was sonicated until homogeneous and clear (30 m),

resulting in a bright yellow Pd solution. Under Ar, a 20 mL-glass vial was charged with a stir bar, 0.8 mmol aryl halide, 500 μL (4.5 mmol) phenylacetylene, 8.0 mL of the sparged aqueous surfactant solution, and 0.24 mL of the sonicated catalyst solution. The vial was briefly purged with Ar (5 min), sealed with a cap and stirred while heated at 40 °C for 24 h. At reaction completion, all volatiles were removed under reduced pressure, and the aqueous solution was extracted with EtOAc (3x5 mL). The combined EtOAc extracts were washed with saturated NaCl (3x5 mL) and all solvent was removed under reduced pressure. The crude product was purified via flash column chromatography using hexane. Product yields were determined via NMR and GC-MS analysis.

(*Z*)-(4-(4-methoxyphenyl)but-3-en-1-yne-1,3-diyl)dibenzene (**5a**)[118] Yellow solid, 75 mg, 30%; ^{1}H NMR (400 MHz, $CDCl_3$) NMR (400 MH*J* = 8 Hz, 2H), 7.80-7.78 (m, 2H), 7.58-7.55 (m, 2H), 7.41-7.32 (m, 6H), 7.18 (s, 1H), 6.97-6.94 (m, 2H), 3.86 (s, 3H); EI-MS: m/z (rel. intensity %) 310.2 (M^+, 100), 295.2 (31), 279.2 (19), 265.1 (23), 252.1 (18), 239.1 (9), 202.1 (8), 189.1 (14), 165.1 (10).

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Supporting Information

Table S.1. The pH Effect of SDS, CTAB, Sodium Cholate and Triton X-100 on the pH of Sonogashira Conditions at 40 °C.

Surfactant	Temp (°C)	Piperidine (mmol)	pH
Sodium Cholate	RT	-	7.8
Sodium Cholate	40	-	8.3
Sodium Cholate	RT	2.4	11.6
Sodium Cholate	40	2.4	11.1
CTAB	RT	-	6.5
CTAB	40	-	6.2
CTAB	RT	2.4	11.5
CTAB	40	2.4	11.1
SDS	RT	-	8.4
SDS	40	-	8.5
SDS	RT	2.4	11.7
SDS	40	2.4	10.7
Triton X-100	RT	-	6.0
Triton X-100	40	-	7.2
Triton X-100	RT	2.4	11.6
Triton X-100	40	2.4	11.0

Conditions: 2.0 wt% solution of surfactant in water with and without piperidine. The pH remained constant over 5 h at RT and 40 °C for each entry.

CHAPTER 3: PHOSPHINE-MODIFIED CHOLATE LIGANDS FOR PALLADIUM CATALYZED CROSS-COUPLING REACTIONS UNDER AQUEOUS CONDITIONS

Modified from a paper to be submitted to *Journal of Organic Chemistry*

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Abstract

Modification of methyl cholate with a triaryl phosphine moiety afforded a new ligand, **1**, which was effective for use with palladium in generating an efficient catalyst for Heck cross-coupling reactions between various olefins and aryl iodide substrates, under mild, aqueous reaction conditions. High yields, up to 99%, were achieved for the coupling of aryl iodides with alkyl acrylates in water at 40 °C. In competition studies, the least water soluble substrate (*n*-Bu acrylate) was preferred over the most water soluble substrate (methyl acrylate). Moreover, homogeneity tests demonstrate that the catalytically active Pd species remains heterogeneous throughout the reaction duration.

Introduction

Transition metal-catalyzed reactions in water have attracted significant research attention in recent decades.[1,2] An important motivation comes from the low cost, abundance, nonflammability, and nontoxicity of water as a green solvent. If the reactants are organic and phase-separates from water while the catalysts stay in the aqueous phase, the products can be easily separated and the water-soluble catalysts can be reused. Traditionally, transition metal catalysts are made water-soluble by installing water-solubilizing groups such as sulfonate on the metal-coordinating ligands.[2-4] However, this method is limited to substrates with substantial solubility in water and highly nonpolar substrates tend to have difficulty accessing catalysts located in the aqueous phase.

Because surfactant micelles can solubilize a wide variety of nonpolar compounds, chemists have also performed transition metal-catalyzed reactions in the micellar phase.[5-7] The benefit of micelles is that they provide a local hydrophobic microenvironment to the transition metal catalysts and may help enhance the local concentration of the substrate near the catalysts if both are solubilized in the same micelle. On the other hand, the surface activity of the surfactants may contaminate the products and could also hamper the product isolation by emulsion formation.

Cholic acid and its associated bile salts (cholates) are formed in the liver and used as a surfactant for emulsifying lipids and cholesterol.[8] Its rigid ring structure provides unusual facial amphiphilicity leading to the hydrophilic and hydrophobic

moieties residing on opposite faces rather than in the conventional head-to-tail arrangement of traditional amphiphiles such as sodium dodecyl sulfate (SDS). Its unique structure makes it very useful in supramolecular chemistry.[9-12] According to Small's primary/secondary aggregation model, cholates form primary micelles at low concentrations in water, with 2-10 monomers in the structure stabilized mainly by hydrophobic interactions. As the cholate concentration increases, these primary micelles can aggregate to larger secondary structures through hydrogen bonding, leading to increased polydispersity in solution.[6,21–23]

In this work, we report the synthesis of cholate-functionalized phosphine ligands and their applications in palladium-catalyzed Heck cross-coupling reactions. The cholate group was found to highly influence the activity and selectivity of the reactions, owing to the strong facial amphiphilicity of the ligands.

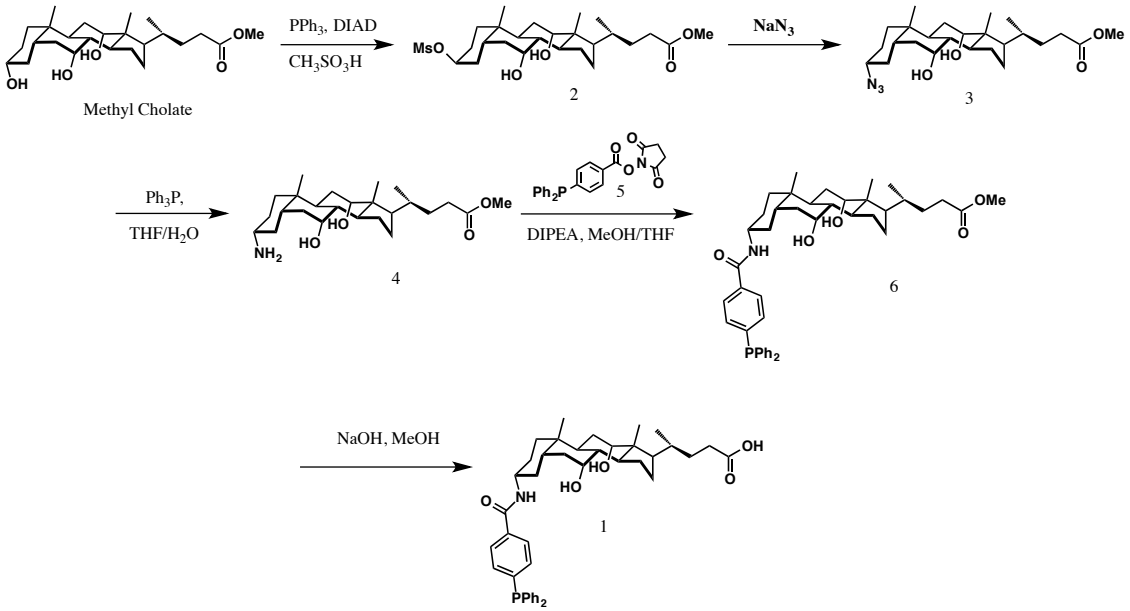
Results and Discussion

Ligand Synthesis

Phosphine ligand **1** was readily derived from methyl cholate as shown in Scheme 1. Of the three hydroxyl groups, the most reactive hydroxyl resides at the C-3 position.[24–26] Thus, the 3α-hydroxyl was selectively transformed into an azide by initially forming the β-mesylate (**2**) under Mitsunobu conditions with methansulfonic acid, and subsequently treating the mesylate with sodium azide.[27] The overall stereochemistry of the 3α-hydroxyl was retained in azide compound **3**.

Azide reduction to amine **4** was achieved with PPh_3 in aqueous THF, and the phosphine moiety was added via formation of an amide linkage between **4** and activated ester **5**. The methyl ester functionality of **6** was hydrolyzed with 1.0 M NaOH in MeOH. Isolation of the carboxylic acid, **1** was achieved by purification on a silica gel column. Similar to cholic acid,[6] **1** was essentially insoluble in water and sparingly to moderately soluble in ethanol, methanol, chloroform and dichloromethane. The ^{31}P NMR spectrum of **1** exhibited a single phosphine signal at -5.0 ppm with triphenyl phosphate (-17.0 ppm) as an external standard ($CDCl_3/CD_3OD$, 1:1).[28]

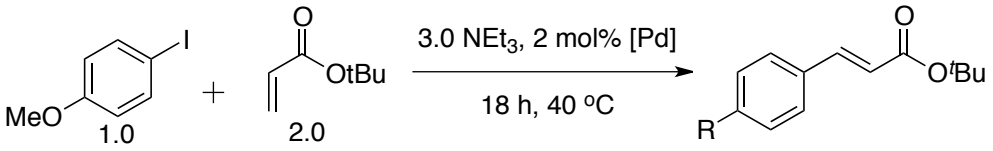
Scheme 1



Initial attempts at forming a catalytically active palladium complex with ligand **1** *in situ* were unsuccessful and likely due to the limited solubility of both $Pd(OAc)_2$ and **1** in water. To help solubilize **1**, sodium cholate (NaChol) was added due to its efficacy at solubilizing cholesterol derivatives in biological systems.[9] A 28:1 ratio of NaChol:**1** was needed to fully solubilize **1** in water. When this solution was added directly to $Pd(OAc)_2$, *tert*-butyl acrylate, 4-iodoanisole, and triethylamine (TEA), the mixture only provided a trace amount of Heck product after stirring at 40 °C for 18 h (Table 1). In neat water, similar conditions produced a 17% yield of product after 18 h. This yield was only slightly higher than that produced from catalysis via $Pd(OAc)_2$ in the absence of ligand **1**. If the palladium source was switched to the slightly more aqueous soluble $PdCl_2(CH_3CN)_2$ complex, the cinnamate product was produced in 18% yield with NaChol (Table 1, entry 5). Notably, in the absence of NaChol the yield improved to 30%. Regardless of the palladium source, formation of palladium black was evident within a few hours of heating in the above reactions.

The poor *in situ* formation of an effective palladium catalyst complex, led to development of a precatalyst complexation methodology. Sonication of the $Pd(OAc)_2$ and three equiv. of **1** in methanol produced a light yellow, hazy suspension within 30 min at ambient temperature. Removing methanol under vacuo provided a solid yellow residue that was insoluble in water, methanol and other common organic solvents; proving only to be sparingly soluble in 1:1 $CHCl_3$:MeOH. Complete dissolution in water was not possible but addition of TEA

Table 1. Heck Coupling Using $Pd(OAc)_2$ and **1** in aqueous media: Attempts at *in situ* Pd-complex formation.



Rxn	[Pd]	mol % **1**	Solvent Composition	% Yield[b]
1	$Pd(OAc)_2$	-	H_2O	12
2	$Pd(OAc)_2$	6	H_2O	17
3	$Pd(OAc)_2$	6	8.7 wt% NaChol in H_2O	Trace
4	$PdCl_2(CH_3CN)_2$	6	H_2O	30
5	$PdCl_2(CH_3CN)_2$	6	8.7 wt% NaChol in H_2O	18

[a]Conditions: 5.0 x 10^{-3} mmol [Pd], 15.0 x 10^{-3} mmol **1**, 0.24 mmol 4-iodoanisole, 0.48 mmol *tert*-butyl acrylate, 0.72 mmol TEA, and 2.0 mL H_2O. Stirred at 40 °C for 18 h. [b]Yields determined by NMR using mesitylene as an internal standard.

caused the mixture to form an evenly dispersed suspension. This increased dispersion was likely due to deprotonation of the carboxylic acid moiety of **1**, producing a charged Pd-L complex. In line with this behavior are the facts that cholic acid has a pK_a of 5.5 and that cholate aggregation will only occur at pH values above its pK_a.[29]

Studies by Jutand and coworkers established that a Pd^0 complex was formed between $Pd(OAc)_2$ and PPh_3, and the dominate species was directly dependent on the amount of phosphine added to the system.[30–33] Three equiv. of phosphine, in

the presence of wet DMF, led to the overall formation of an anionic palladium(0) species (**7**) and phosphine oxide, identified by ^{31}P NMR.

$$3\,PPh_3 + Pd(OAc)_2 + H_2O \longrightarrow O{=}PPh_3 + \underset{\mathbf{7}}{[Pd(PPh_3)_2OAc^-]} + AcOH + H^+ \quad (1)$$

Under a similar study with ligand **1**, analogous ^{31}P NMR peaks were obtained. A solvent mixture of 1:1 $CDCl_3$:CD_3OD was required to adequately solubilize the Pd complex. When ^{31}P NMR analysis was performed within 2 h of dissolution, three ^{31}P signals were observed (-5.0, 16.9, and 32.6 ppm). The signals at -5.0 and 32.6 ppm corresponded to free and oxidized ligand **1**, respectively. The peak at 16.9 ppm was assigned to a Pd^0 complex, **8**, coordinated with two equiv. of **1**. After ~4 h complex **8** partially decomposed to palladium black, resulting in an increase in the phosphine oxide signal and other unidentified phosphine products with broad peaks around 30 ppm. ^{1}H NMR analysis also revealed that both aryl and cholate backbone proton signals were broader than those of free ligand **1**. If only two equiv. of **1** were used, the isolated complex decomposed too rapidly for NMR analysis. Increasing the amount of phosphine to 4 equiv. of **1**, provided similar results as those with 3 equiv., with the appearance of a transient broad peak around 5-7 ppm, which may correspond to higher coordinate palladium complexes, $Pd(L)_n$ (n = 3-4).[31,34]

MS analysis of complex **8** produced from the 1:3 Pd:**1** mixture supported the formation of a single bis-ligated palladium species with a mass cluster centered at 1498 m/z, and an isotopic mass pattern consistent with a PdL_2 complex. However,

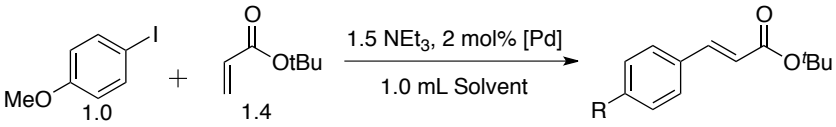
the existence of any bound acetate ligands were not observed via MS. In addition, the mass spectrum exhibited a peak at 710 m/z indicating the presence of the phosphine oxide form of ligand **1.**

The yellow palladium complex, **8**, could be directly used for Heck coupling with TEA as the base (Table 2). Neat water proved to be the best reaction solvent. Under aqueous conditions, the complex was active at both ambient temperature and 40 °C. The highest activity was achieved at 40 °C, with yields up to 99%. Temperatures above 40 °C led to increased catalyst decomposition but not increased yields. In using 1.4 and 1.5 equiv. of *tert*-butyl acrylate and TEA relative to iodoanisole, the reaction needed 24 h to reach completion. However, when *tert*-butyl acrylate and TEA were increased to 2-fold and 3-fold excesses respectively, the reaction reached completion within 4-5 h at 40 °C. Other solvents were less effective. For example in methanol, iodoanisole and *tert*-butyl acrylate were coupled in a 14% yield in 2 h at 40 °C. Mild heating at 40 °C was necessary for coupling in MeOH, but also caused complete catalyst decomposition within the 2 h. In 1:1, MeOH:H_2O, the palladium residue became catalytically active at ambient temperature, resulting in 24% cinnamate product in 4 h. Longer reaction times and heating did not provide a significant increase in yields.

Although many phosphine complexes tend to be air sensitive, the activity of our catalyst was not significantly affected by the presence of oxygen. As a dry solid, the catalyst residue could be stored under light and air for more than 6

months with no substantial loss in activity (Table 2). In water, the catalyst complex could be heated at 40 °C under atmospheric conditions for more than 3 days without any significant decomposition. In the presence of TEA, heat and water, the catalyst visibly formed palladium black within 24 h and fully decomposed within 48 h.

Table 2. Optimization of Heck Coupling Reaction Conditions Using Complex **8** in Aqueous Media[a]



Rxn	Solvent	Time (h)	T (°C)	Yield(%)[b]
1[c]	MeOH	5	RT	-
2[c]	MeOH	2	40	14
3[c]	MeOH	2	60	14
4	MeOH/ H_2O	4	RT	24
5	MeOH/ H_2O	4	60	29
6	CH_3CN	2	40	48
7[d]	CH_3CN	2	40	56
8[e]	H_2O	18	40	16
9[d]	H_2O	4	40	69
10	H_2O	4	RT	41
11	H_2O	4	40	78
12	H_2O	4	60	73
13	H_2O	12	40	81

14	H_2O	24	40	99
15[f]	H_2O	4	40	98
16[g]	H_2O	4	40	95
17[g,h]	H_2O	4	40	76

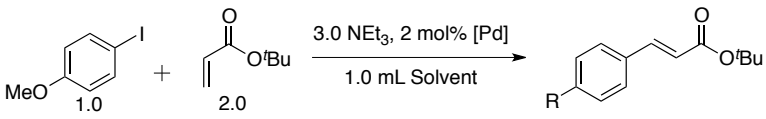
[a]Conditions: See experimental for precatalyst coordination methodology. 2.4 x 10^{-3} mmol $Pd(OAc)_2$, 7.5 x 10^{-3} mmol **1**, 0.12 mmol iodoanisole, 0.17 mmol *tert*-butyl acrylate, 0.18 mmol TEA, and 1 mL H_2O. Stirred at 40 °C for 18 h. [b]Yields determined by NMR using mesitylene as an internal standard. [c]Catalyst/MeOH solution used directly as reaction medium. [d]$PdCl_2(CH_3CN)_2$ was used as the palladium source instead of $Pd(OAc)_2$. [e]$Pd(OAc)_2$ and **1** were preactivated for 30 m in water at 60 °C before adding to reagents. [f] Used 0.24 mmol tert-butyl acrylate and 0.36 mmol TEA. [g] Catalyst was formed, dried and stored for 6 mo before use in Heck coupling. [h] Ethyl acrylate was used as the olefin source.

Since $PdCl_2(CH_3CN)_2$ provided higher product yields for the *in situ* couplings, its activity with ligand **1** was also evaluated for use as a catalyst precursor. Complexation in CH_3CN with three equiv. of ligand **1** and either $PdCl_2(CH_3CN)_2$ or $Pd(OAc)_2$ provided a yellow suspension as observed with methanol. If the CH_3CN solutions were used directly for coupling, formation of the cinnamate product occurred in 48% or 56% yield in 2 h at 40 °C with $Pd(OAc)_2$ or $PdCl_2(CH_3CN)_2$ respectively. After 2 h, both mixtures had completely decomposed to palladium black. If the "PdL_2" complex was isolated from the CH_3CN suspension by removal of volatiles under vacuo, and reconstituted in H_2O, the coupling yield increased to 69% in 4 h at 40 °C. However, high yields with

precatalysts derived from $PdCl_2(CH_3CN)_2$ were never achieved as compared to those preformed from $Pd(OAc)_2$ in methanol, despite extended reaction times.

Several reports indicated that Heck couplings were increased with the use of inorganic bases when water was the reaction medium. However in our cholate phosphine-Pd system, a substantial decrease in yield was seen when TEA was replaced with either NaOAc or K_2CO_3 (Table 3). Catalyst decomposition was extensive within 4 h with either of these inorganic bases. Conversely, if the alkyl groups of the amine were lengthened from ethyl to *n*-octyl, activity was strongly inhibited, but catalyst robustness was enhanced. For example, with $N(octyl)_3$, only a trace amount of product was detected for the coupling between 4-iosoanisole and *tert*-butyl acrylate, and no catalyst decomposition was visible after 24 h at 40 °C.

Table 3. Effect of Base on Heck Coupling with Complex **8** in Aqueous Media [a]



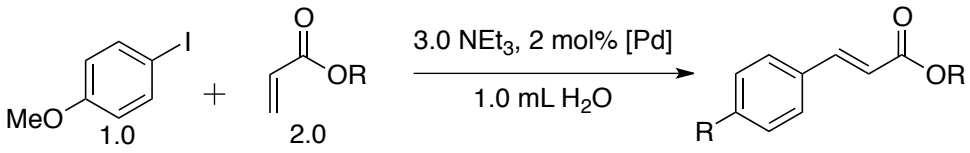
Rxn	R	Base	t (h)	Yield(%)[b]
1	tBu	NaOAc	4	4
2	tBu	K_2CO_3	4	21
3	tBu	$N(C_8H_{17})_3$	24	Trace

[a] Conditions: See experimental for precatalyst complexation method. 2.4 x 10^{-3} mmol $Pd(OAc)_2$, 7.5 x 10^{-3} mmol **1**, 0.12 mmol iodoanisole, 0.24 mmol *tert*-butyl acrylate, 0.36 mmol TEA, and 1 mL H_2O. Stirred at 40 °C.

[b] Yields determined by NMR using mesitylene as an internal standard.

To assess the hydrophobic interactions between the substrates and the catalyst complex, the yields of various cinnamate products were determined as a function of the water solubility of the substituted acrylates (Table 4). A series of acrylates were chosen that maintained similar steric bulk, so that product selectivity was not unduly influenced by steric demands. As the alkyl substituent of an acrylate ester lengthens from methyl to hexyl, its solubility in water essentially decreases to zero. Accompanying this decrease in solubility was an increase in yield for coupling between the acrylate and iodoanisole (Table 4). For example, 2-ethylhexyl and *n*-butyl acrylates produced yields of 90 and 92%, respectively.

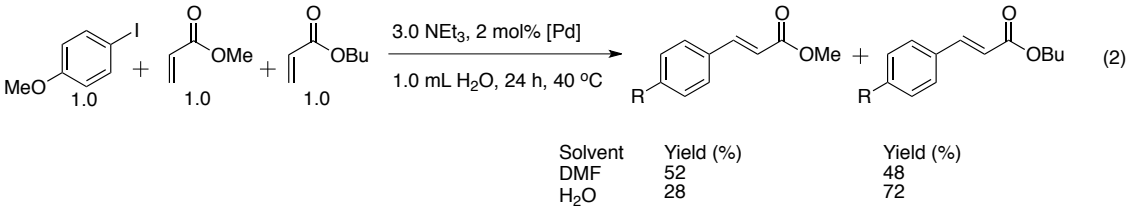
Table 4. Effect of Acrylate Solubility on Heck Coupling with Complex **8** in Aqueous Media[a]



Rxn	R	Acrylate[b] (g/L)	t(h)	Yield 1(%)[c]
1	Me	60	4	12
2	Et	15	4	77
3	*n*-Bu	1.4	4	92
4	2-ethylhexyl	-	4	90

[a] Conditions: 2.4 x 10^{-3} mmol $Pd(OAc)_2$, 7.5 x 10^{-3} mmol **1**, 0.12 mmol iodoanisole, 0.24 mmol acrylate, 0.36 mmol TEA, and 1 mL H_2O. Stirred at 40 °C. [b] Solubility of acrylate in water. [c] Yields determined by NMR using mesitylene as an internal standard.

Conversely, in more polar media (such as DMF) no acrylate selectivity was observed. The catalytic complex was slightly more soluble in DMF than water, but was still predominantly a suspension, implying that the hydrophobic interactions within the catalyst may be reduced but not diminished. In a competition study using both methyl acrylate and *n*-butyl acrylate for coupling to 4-iodoanisole, a product ratio of 1:1 was achieved when DMF was the solvent (eqn 2). In an analogous study, using water as the solvent the product ratio favored the *n*-butyl cinnamate product over the methyl analog (2.6:1).



Although the catalytic system appeared heterogeneous, it was possible that the active palladium species during the reaction was water-soluble. To determine the phase of the active species, a heterogeneity test was performed with a reaction that was centrifuged after 2 h at 40 °C. The solid and supernatant fractions were separated, and a second aliquot of reagents was added to each. Water was also added to the solid fraction. After an additional 2 h at 40 °C, only the solid fraction proved to remain catalytically active, resulting in a total yield of 94%. No trace of product was detected by NMR analysis of the supernatant fraction, even after heating at 40 °C for an additional 6 h.

Lack of reactivity with the supernatant fraction indicated that no active palladium species were dissolved in the aqueous layer. However, we were also interested in the distribution of **1** between the solid and supernatant fractions. In an additional separation study, a catalytic reaction was removed from heat after 2 h and the solid and solution phases were separated by centrifugation. Both fractions were thoroughly dried in vacuo. Upon dissolving each of the residues in 1:1 $CDCl_3$:CD_3OD, ^{31}P NMR analysis indicated that all the phosphorous containing material remained in the original solid fraction. No detectable amount of cholate species was present in the solution fraction.

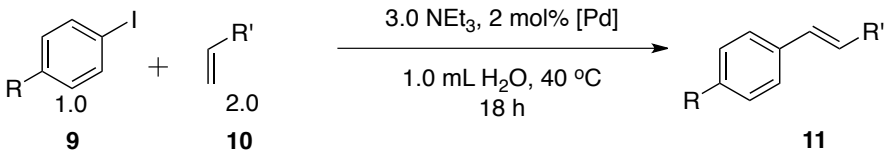
The scope of the catalyst's reactivity is exhibited in Table 5. In general, no (Z)-isomers were formed under these reaction conditions. The catalyst was also not active for aryl bromides or aryl chlorides. Both electron donating and electron withdrawing substituents produced good to excellent yields with extended reaction times at 40 °C.

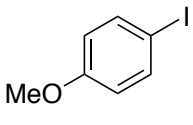
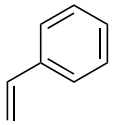
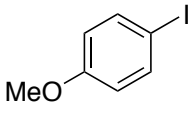
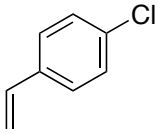
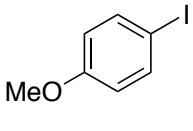
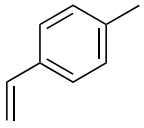
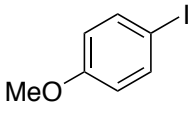
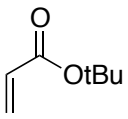
Summary and Outlook

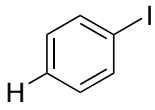
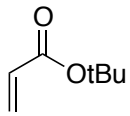
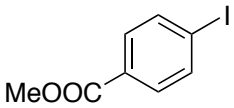
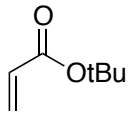
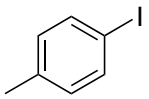
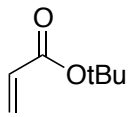
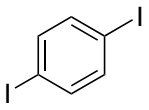
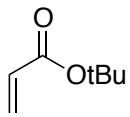
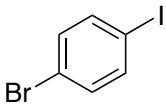
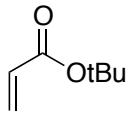
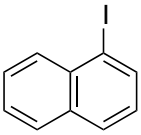
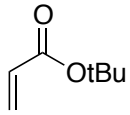
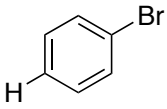
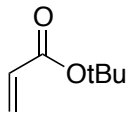
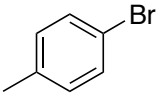
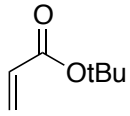
Cholate-phosphine complex **8** is a novel heterogeneous Heck catalyst for efficient coupling of nonpolar substrates in water. Heterogeneity is attributed to the increased hydrophobic character and aqueous insolubility of cholate-based ligand **1** due to the presence of the phosphine moiety. As discussed above, cholate aggregation is driven by both hydrophobic forces (primary) and hydrogen bonding (secondary, detected when cholate concentrations are above 50 mM).[23,36] While

reduced aqueous solubility prevented 'traditional' cholate-like aggregates to form with complex **8**, its analogous structure to cholate suggests that significant hydrophobic interactions could be responsible for the observed trends, including catalyst durability and product selectivity (Tables 2 and 4). Complex **8** presumably aggregates through intermolecular hydrophobic interactions. These interactions

Table 5.[a] Heck Cross-Coupling Reactions Catalyzed by **8** in Aqueous Media[a]



Rxn	**9**	**10**	Yield **11** (%)[b]
1			62
2			70
3			61
4			100

5			94
6			92
7			98
8			16 (67)[c]
9			94[d]
10			89
11			-
12			-

[a] Conditions: 2.4 x 10^{-3} mmol $Pd(OAc)_2$, 7.5 x 10^{-3} mmol **1**, 0.12 mmol arylhalide, 0.24 mmol olefin, 0.36 mmol TEA, and 1 mL H_2O. Stirred at 40 °C. [b] Yields determined by NMR using mesitylene as an internal standard. [c] Yield in parenthesis is of the double insertion product. [d] No double insertion product detected.

would help protect the catalyst from decomposition by creating an organic 'pocket' around the active Pd center. This pocket could attract nonpolar organic reagents, creating a high, localized concentration of nonpolar reagents.

Addition of ethanol (mole fraction ≥ 0.3) to an aqueous surfactant solution has been reported to effectively disrupt hydrophobic interactions, inhibiting primary aggregation in cholate solutions.[37,38] A similar phenomena appeared to occurr when **8** was used in the presence of methanol. Neat methanol or methanol:H_2O, 1:1 as the reaction medium significantly reduced both yield and catalyst longevity (Table 2). For complex **8**, disruption of hydrophobic interactions would reduce or eliminate the organic pocket formation, exposing the active center towards decomposition via air or water, as well as diminishing the ability to produce a locally high concentration of reagents near the active site.

However, not all hydrophobic interactions were eliminated in the presence of methanol. Both NMR and MS analysis detected only one dominant Pd species, which was coordinated to two molecules of **1**. In the ^{1}H NMR for complex **8**, the methyl peaks of the cholate backbone shift and the peaks are broadened, indicative of hydrophobic interactions between backbone portions of adjacent ligands.[39,40] If the presence of CD_3OD is assumed to reduce intermolecular hydrophobic interactions, the broadening would then be likely due to adjacent ligands on the same Pd atom. Several studies have shown that even primary cholate aggregates have the ability to incorporate small molecules into the apolar space between cholate backbones.[41–45]

The ability of complex **8** to form a local nonpolar active site environment and attract nonpolar organic reagents is supported by the acrylate studies (Table 4 and eqn 2). Enhanced product yield with decreased aqueous solubility indicated that **8** preferentially favored nonpolar reagents within its local organic environment, enhancing likelihood of substrate interaction and coupling. This behavior is supported by competition reactions between butyl and methyl acrylates. Nonpolar interactions were expected to enhance the butyl acrylate concentration around the catalyst relative to that of methyl acrylate. As a result, catalytic production of butyl cinnamate was favored. While complex **8** remains heterogeneous in either water or DMA, both acrylate species are soluble in DMA. Therefore, no preferential nonpolar interactions were expected with either methyl or butyl acrylate species and complex **8** in DMA**.** The related DMA competition study supports this conclusion with a 1:1 selectivity of cinnamate products.

Overall, attachment of cholate to a phosphine moiety proved to form an effective ligand for Pd-catalyzed Heck cross-coupling. This modification reduced aqueous solubility, allowing complex **8** to undergo aggregation due to hydrophobic interactions in aqueous coupling conditions. Further modification of the cholate structure, with various phosphine or solubilizing moieties may be a means to enhance reactivity of the palladium catalyst and also tune product selectivity in an aqueous environment.

Experimental Section

Materials and Common Methods

All reagents and solvents were of ACS-certified grade or higher, and were used as received from commercial suppliers, unless otherwise indicated. The aqueous reactions used deionized water without further purification or degassing. Routine ^{1}H, ^{31}P and ^{13}C NMR spectra were recorded on a Varian VXR-400 spectrometer. Mass spectrometry was performed on a Waters GCT GC-MS. Centrifugation was performed with a Fisher Scientific Micro 17R Microcentrifuge. Syntheses of complexes **2**-**4** were accomplished as previously reported.[46]

Synthesis of compound 5: 4-(diphenylphosphino)benzoic acid (153 mg, 0.5 mmol), N-hydroxysuccinimide (87 mg**,** 0.75 mmol) and 1,3-dicyclohexylcarbodiimide (DCC, 155 mg, 0.75 mmol) were mutually dissolved in the mixture of 4 mL of anhydrous CH_3CN and THF (3:1). The mixture was stirred at room temperature for ~12 h. The urea was separated by filtration and the filtrate evaporated to dryness leaving the active ester as a light yellow powder (203.3 mg, 100%), which was used in the next step without further purification.

Synthesis of compound 6: Compound **5** (202 mg, 0.5 mmol), diisopropylethylamine (DIPEA, 350 µL, 2.0 mmol) and **4** (253 mg, 0.6 mmol) were dissolved in the mixture of MeOH (2 mL) and THF (2 mL). The mixture was stirred

at room temperature for 48 h. The solvent was removed under reduced pressure, and the product was purified by column chromatography (CH_2Cl_2:CH_3OH from 60:1 to 30:1) to give a white powder (203.5 mg, 57%). ^{1}H NMR (400 MHz, $CDCl_3$:CD_3OD, 1:1) δ 7.74 (d, J = 8.0 Hz, 2H), 7.40-7.24 (m, 12H), 5.40 (bs, 1H, NH), 3.96 (s, 1H), 3.81 (s, 1H), 3.75 (t, J = 12 Hz, 1H), 3.65 (s, 3H, OCH3), 2.45-1.0 (m, 26H), 0.98 (d, J = 8.0 Hz, 3H), 0.94 (s, 3H) 0.70 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$:CD_3OD, 1:1) δ 174.95, 167.12, 141.32, 141.19, 135.86, 135.76, 134.30, 133.32, 133.12, 132.79, 132.60, 128.51, 128.08, 128.01, 126.55, 126.48, 72.31, 67.46, 50.78, 49.87, 46.36, 45.80, 41.63, 41.23, 38.92, 35.57, 35.45, 34.96, 34.24, 34.02, 33.13, 30.46, 27.69, 27.02, 26.58, 26.04, 25.06, 24.38, 22.59, 21.91, 16.30, 11.70; ^{31}P NMR (400 MHz, $CDCl_3$:CD_3OD, 1:1) δ -6.2; High resolution ACPI-MS (*m/z*): $[M+H]^+$ calcd for $C_{44}H_{57}NO_5P$, 710.3969; found, 710.3979.

Synthesis of Ligand 1: Compound **6** (200 mg, 0.282 mmol) was dissolved in MeOH (10 mL) followed by addition of NaOH (1.0 M, 2.82 mL). The reaction mixture was stirred at room temperature for 12 h and monitored via TLC. With completion of the reaction, the solvent was removed by rotary evaporation. The yellow solid collected was purified by column chromatography (CH_2Cl_2: CH_3OH = 20:1) to give a white powder (183 mg, 93%). ^{1}H NMR (400 MHz, $CDCl_3$:CD_3OD, 1:1) δ 8.04 (d, J = 12.0 Hz, 1H, COOH), 7.74 (d, J = 8.0 Hz, 2H), 7.40-7.12 (m, 12H), 3.96 (s, 1H), 3.81 (s, 1H), 3.76 (bs, 1H), 3.35 (bs, 1H, NH), 2.40-1.04 (m, 26H), 1.0 (d, J =

6.0 Hz, 3H), .93 (s, 3H) 0.7 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$:CD_3OD, 1:1) δ 176.44, 166.87, 141.20, 141.07, 135.75, 135.64, 134.06, 133.12, 132.92, 132.58, 132.39, 128.32, 127.91, 127.84, 126.43, 126.36, 72.08, 67.22, 49.78, 46.15, 45.61, 41.50, 41.05, 38.83, 35.32, 34.80, 34.04, 33.88, 32.93, 30.39, 27.58, 26.87, 26.43, 25.90, 24.90, 24.21, 22.44, 21.79, 16.16, 11.58; ^{31}P NMR (400 MHz, $CDCl_3$:CD_3OD, 1:1) δ -5.0; High resolution ESI-MS (*m/z*): $[M-H]^-$ calcd for $C_{43}H_{53}NO_5P$, 694.3656; found, 694.3649.

General procedure for *in situ* Heck reaction: To a 20 mL vial, both 5 x 10^{-3} mmol [Pd], and 15 x 10^{-3} mmol of **1** were added followed by 0.24 mmol 4-iodoanisole, 0.48 mmol tBu-acrylate, 0.72 mmol NEt_3, and 2 mL H_2O. The reaction was mixed by sonication for 10 min and then stirred at 40 °C for 18 h. At the completion of the reaction, all volatiles were removed under vacuum for ~30 min, and 2 μL of mesitylene was added to the vial. The reaction was then extracted with $CDCl_3$ (3x 200 μL). All organic extracts were combined and passed through a plug of celite and $MgSO_4$ into an NMR tube. Yield was determined by NMR.

Precoordination of $Pd(OAc)_2$ with ligand 1: Both $Pd(OAc)_2$ (5.4 mg, 2.4 x 10^{-2} mmol) and **1** (50 mg, 7.2 x 10^{-2} mmol) were combined in MeOH (10 mL) and sonicated at 25 °C for 30 min, resulting in a hazy, yellow solution. Into 20 mL glass vials, 1.0 mL of this solution was aliquoted and all volatiles were removed under vacuum, ~1 h, leaving a yellow residue to be directly used for catalysis.

General procedure for preactivated Heck reaction: To the activated catalyst residue, after removal of all MeOH, the aryl iodide (0.12 mmol), acrylate (0.24 mmol), 1 mL H_2O, and TEA (51 µL, 0.36 mmol) were added to the vial in that order. The reaction was thoroughly mixed via sonication for 10 m and subsequently stirred for the indicated time and temperature. At the completion of the reaction, all volatiles were removed under vacuum for ~30 min, and 2 µL of mesitylene was added to the vial. The reaction was then extracted with $CDCl_3$ (3x 200 µL). All organic extracts were combined and passed through a plug of celite and $MgSO_4$ into an NMR tube. Yield was determined by NMR.

General procedure for centrifugation reactions: To the activated catalyst residue, after removal of all MeOH, iodoanisole (0.12 mmol), tBu-acrylate (0.24 mmol), 1 mL H_2O, and TEA (51 µL, 0.36 mmol) were added to the vial in that order. The reaction was thoroughly mixed via sonication for 10 min and subsequently stirred at 40 °C for 2h. At 2 h, the reaction was centrifuged at 18 °C and 16,200 g for 30 min. The two fractions were separated and to the solid fraction more iodoanisole (0.12 mmol), tBu-acrylate (0.24 mmol), H_2O (1 mL), and TEA (51 µL, 0.36 mmol) were added. The solid fraction was stirred under these conditions at 40 °C for an additional 2 h. To the supernatant fraction, more iodoanisole (0.12 mmol), tBu-acrylate (0.24 mmol), and TEA (51 µL, 0.36 mmol) were added. The supernatant fraction was stirred at 40 °C for an additional 6 h. After the second reaction period for both fractions, all volatiles were removed under vacuum for ~30 min, and 2 µL

of mesitylene was added to the vial. The fraction was then extracted with $CDCl_3$ (3x 200 µL). The organic extracts from that fraction were combined and passed through a plug of celite and $MgSO_4$ into an NMR tube. The yield for each fraction was determined by NMR. This procedure was performed in triplicate. The overall average yield of cinnamate product from the solid fractions was 96%, whereas the supernatant fractions never provided more than a trace amount of product via NMR.

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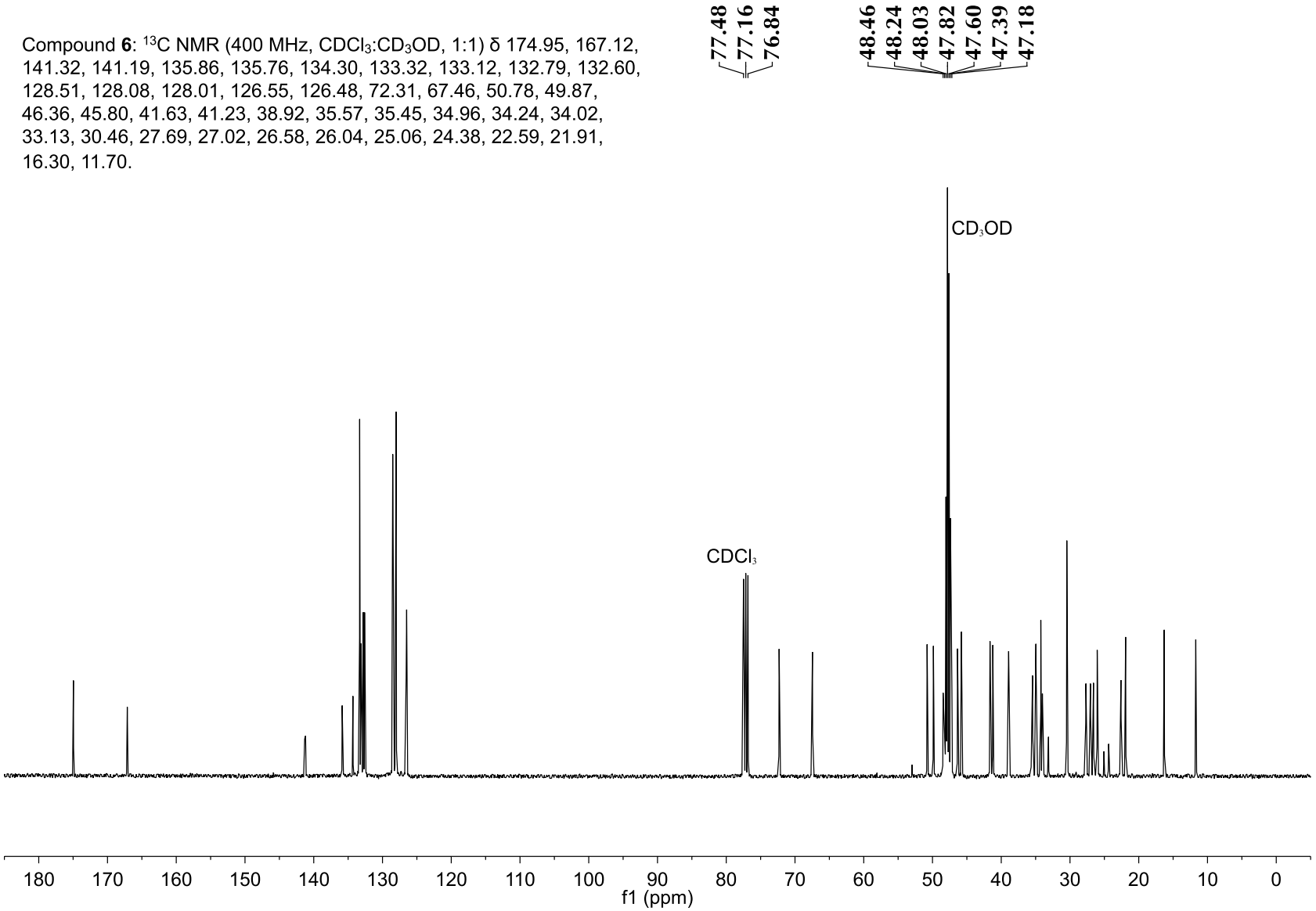
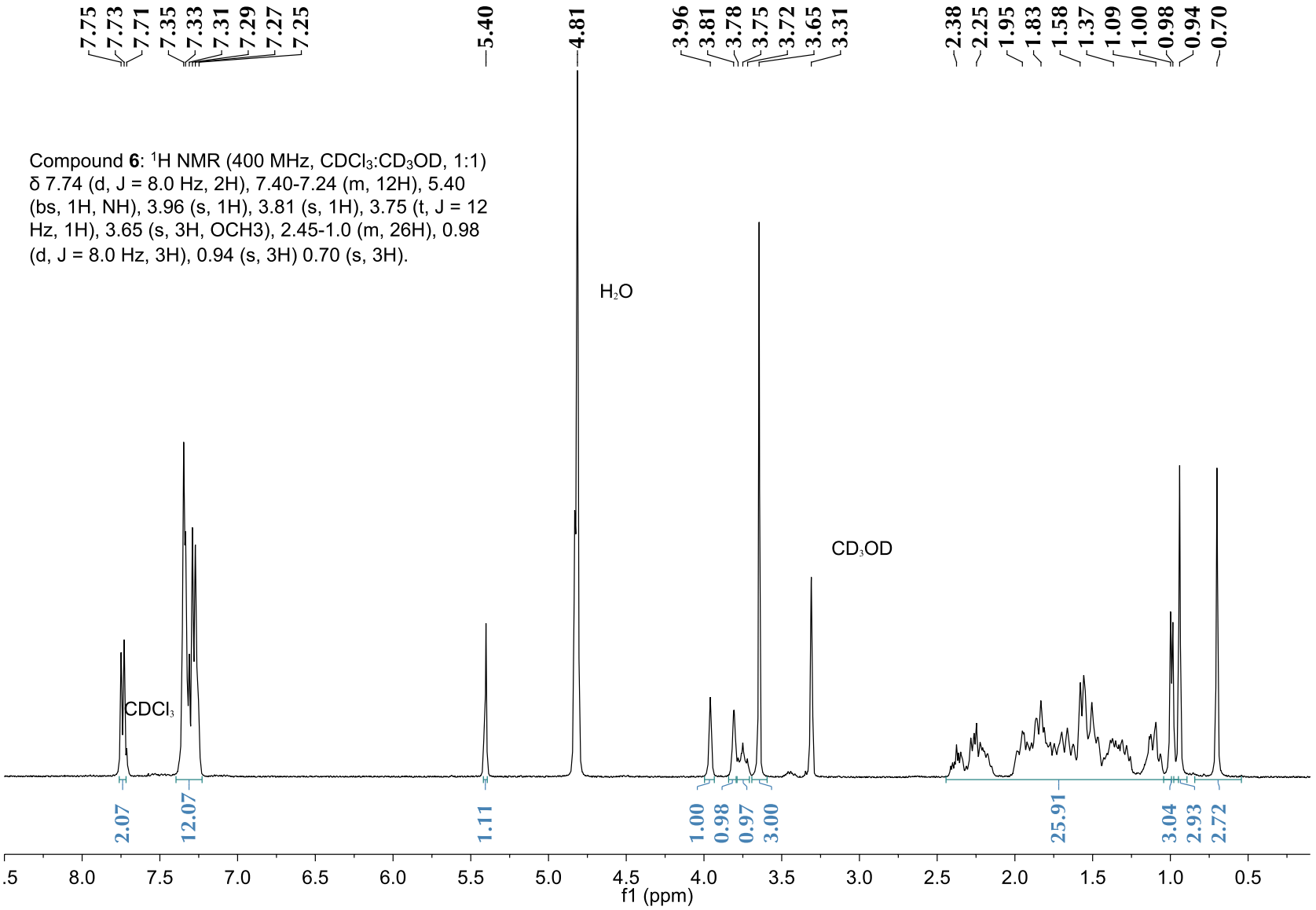
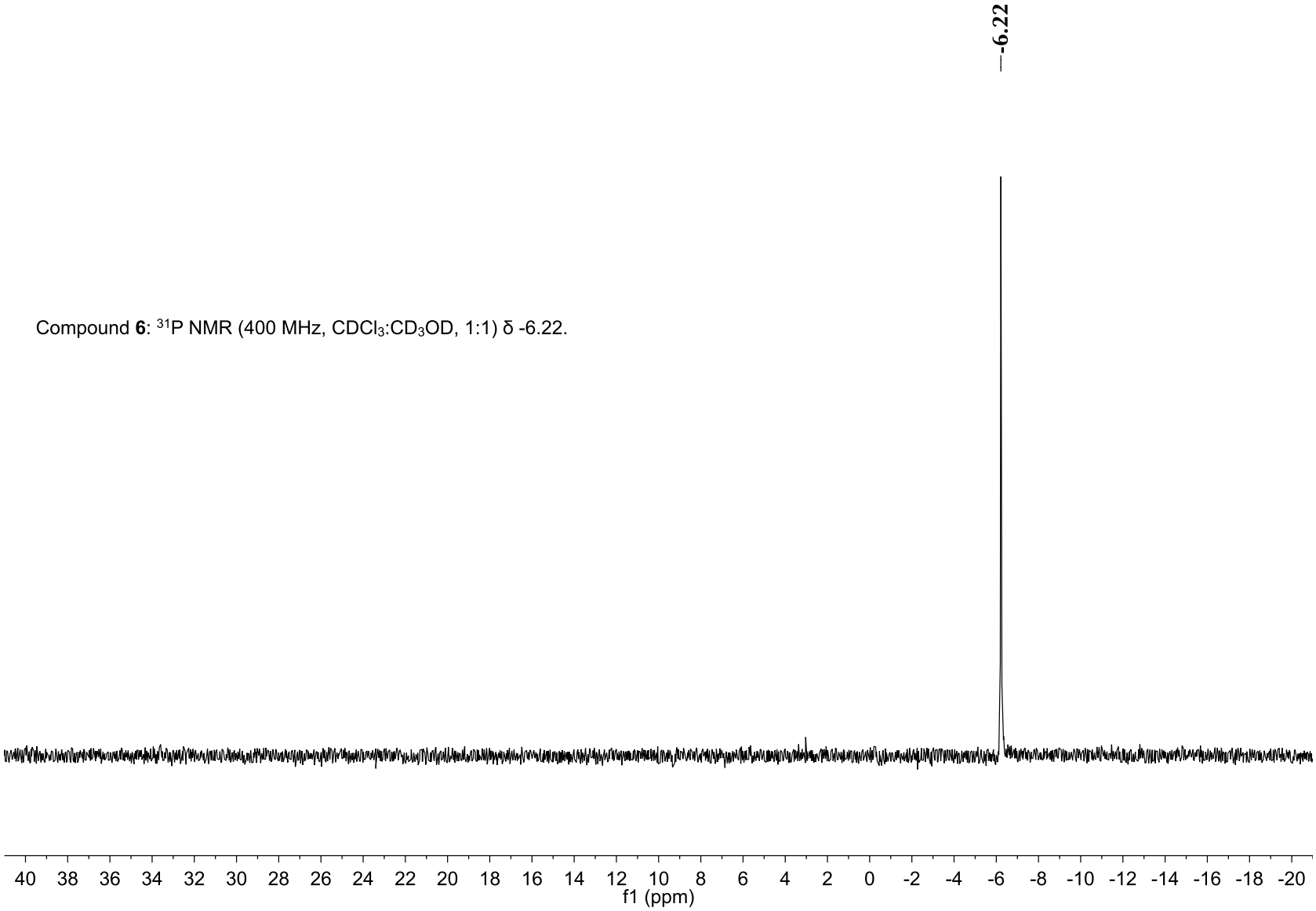
Supporting Information

Compound **6**: ^{13}C NMR (400 MHz, $CDCl_3$:CD_3OD, 1:1) δ 174.95, 167.12, 141.32, 141.19, 135.86, 135.76, 134.30, 133.32, 133.12, 132.79, 132.60, 128.51, 128.08, 128.01, 126.55, 126.48, 72.31, 67.46, 50.78, 49.87, 46.36, 45.80, 41.63, 41.23, 38.92, 35.57, 35.45, 34.96, 34.24, 34.02, 33.13, 30.46, 27.69, 27.02, 26.58, 26.04, 25.06, 24.38, 22.59, 21.91, 16.30, 11.70.

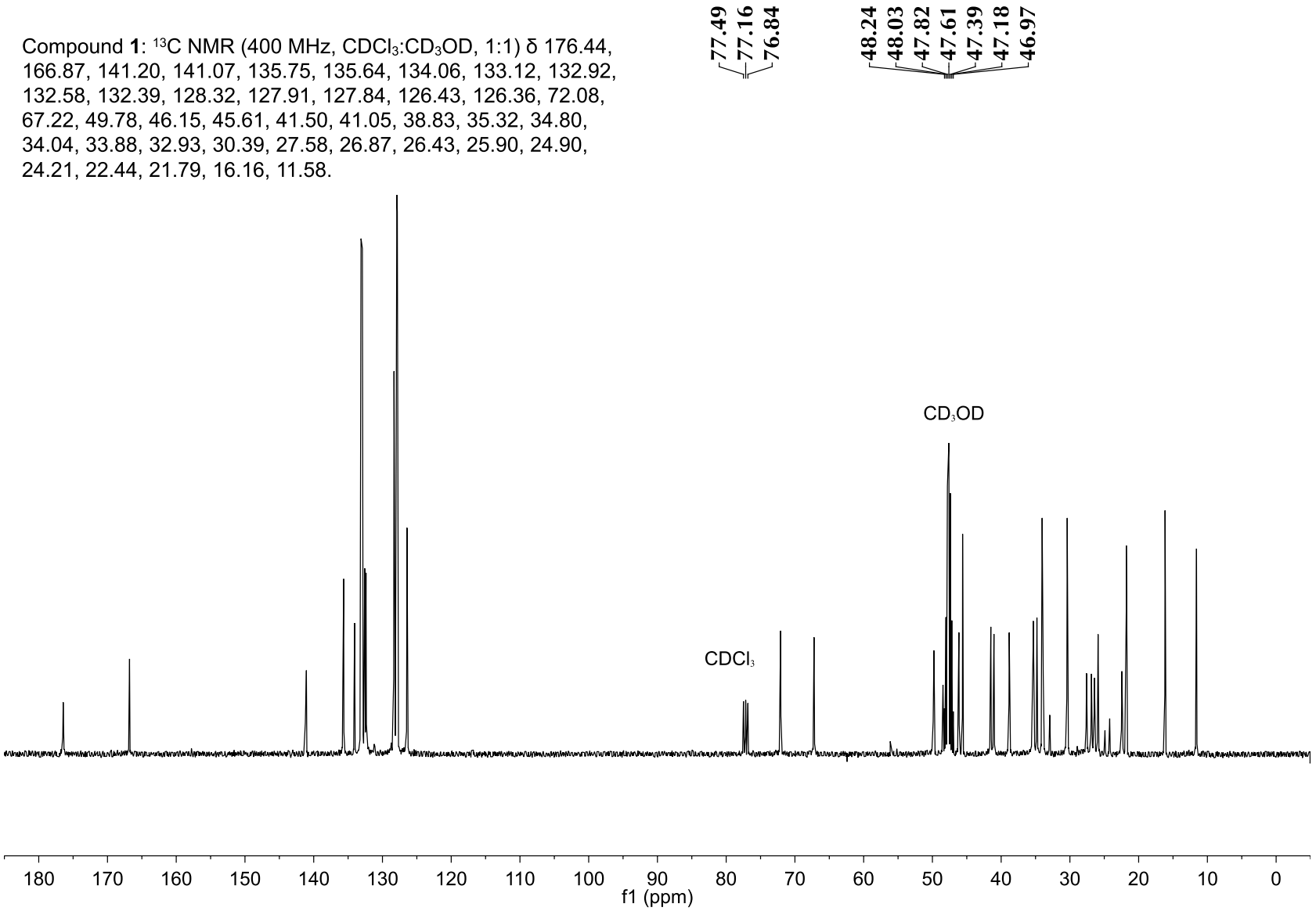


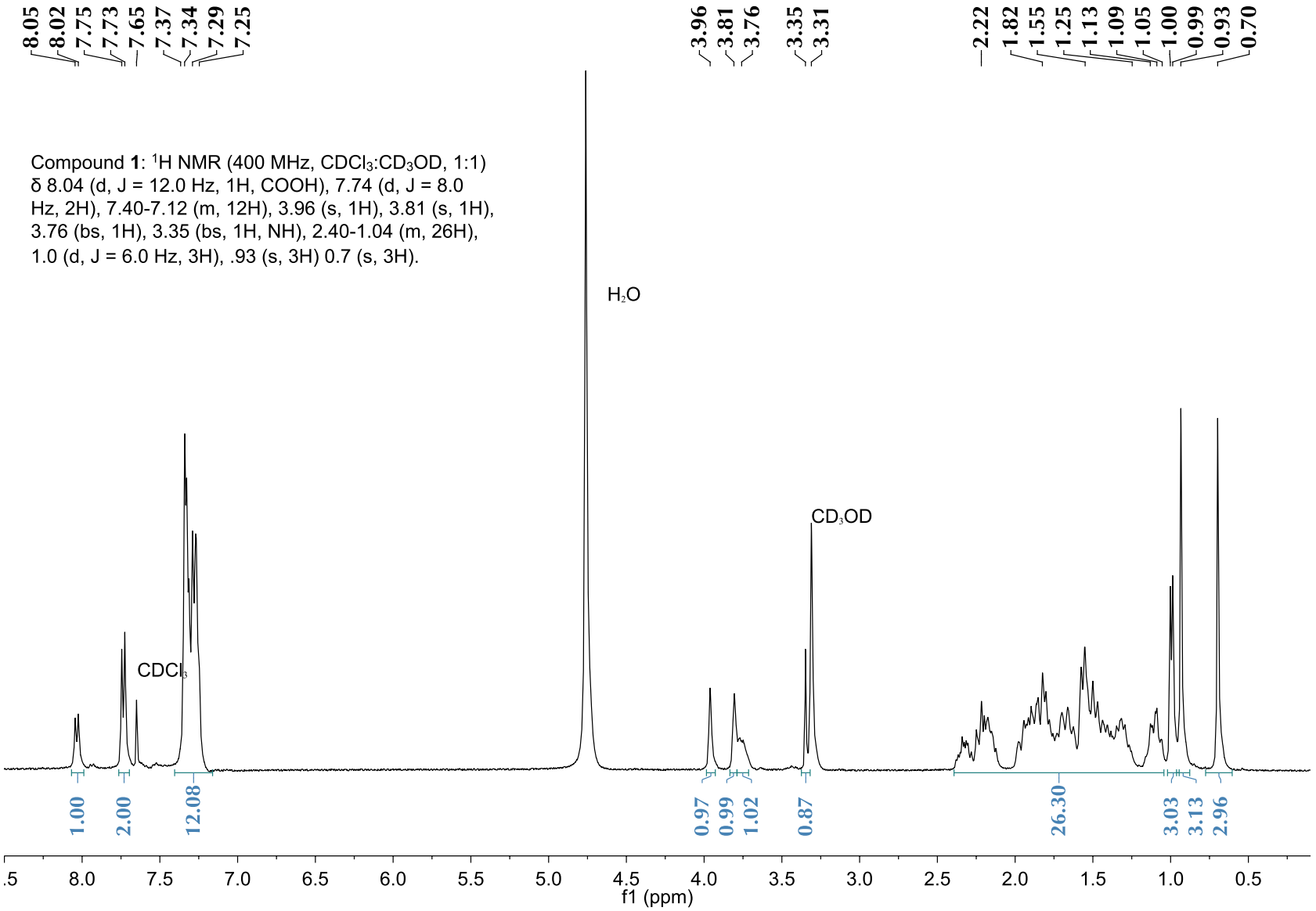


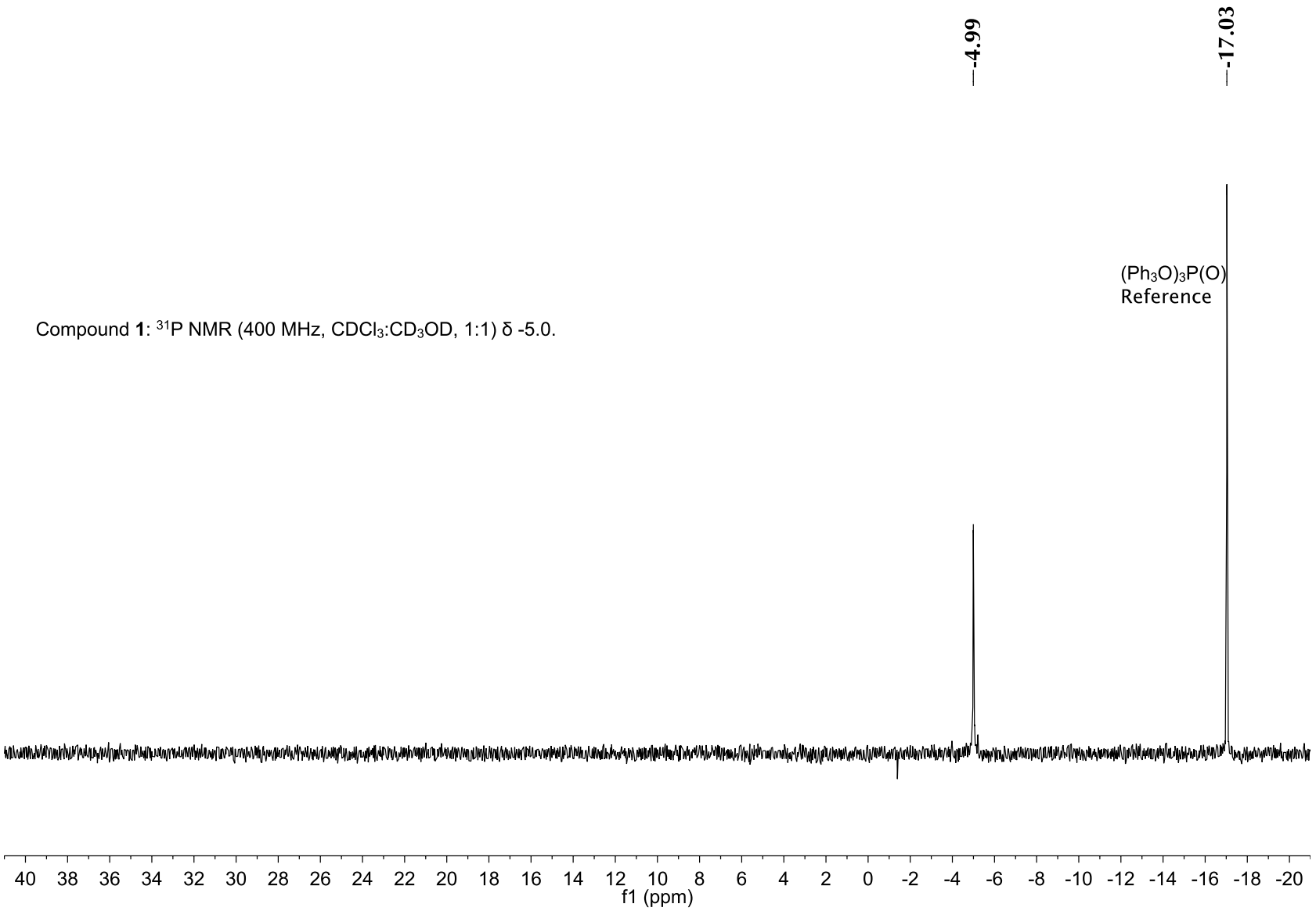
Compound **6**: ^{31}P NMR (400 MHz, $CDCl_3$:CD_3OD, 1:1) δ -6.22.



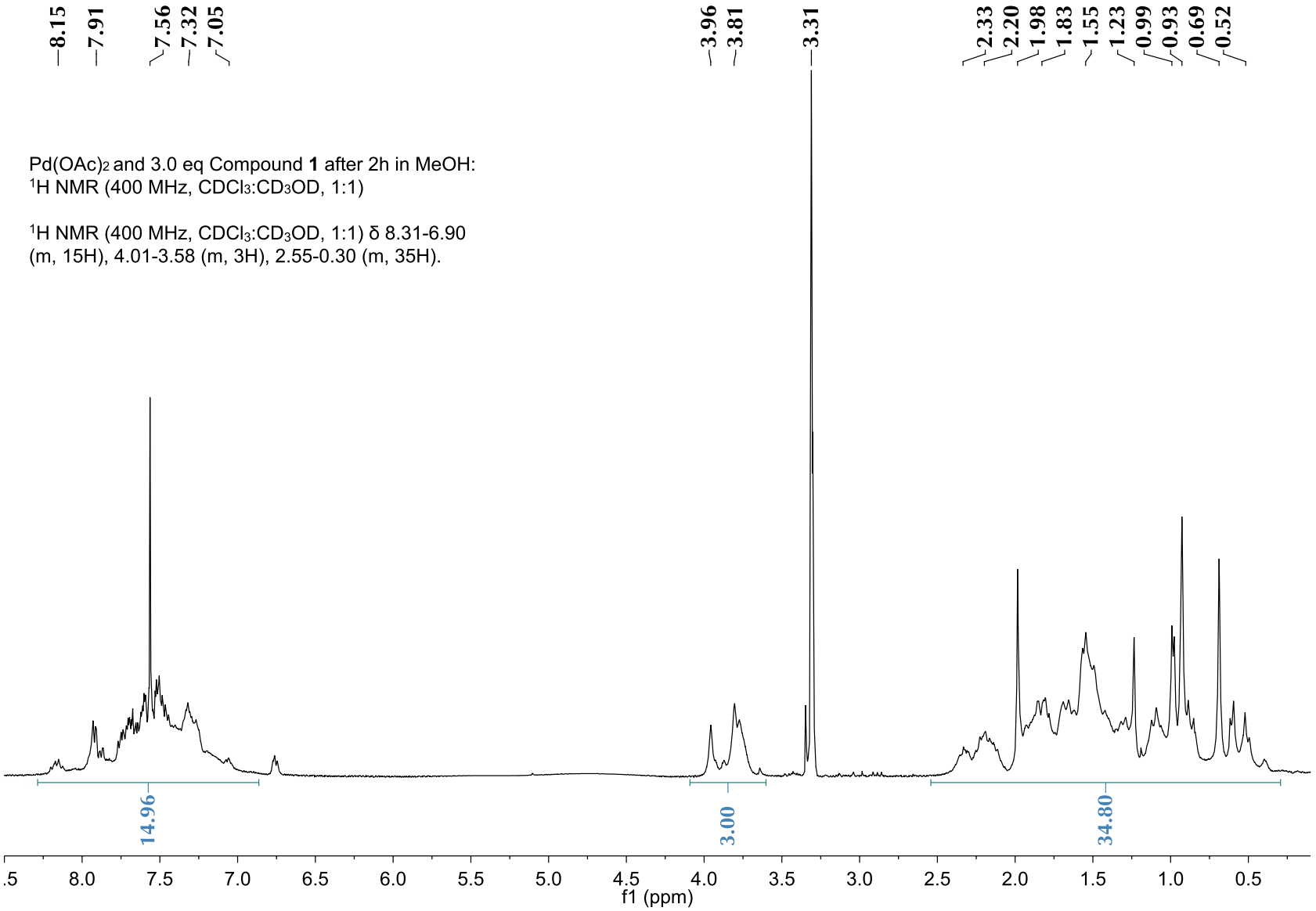
Compound **1**: ^{13}C NMR (400 MHz, $CDCl_3$:CD_3OD, 1:1) δ 176.44, 166.87, 141.20, 141.07, 135.75, 135.64, 134.06, 133.12, 132.92, 132.58, 132.39, 128.32, 127.91, 127.84, 126.43, 126.36, 72.08, 67.22, 49.78, 46.15, 45.61, 41.50, 41.05, 38.83, 35.32, 34.80, 34.04, 33.88, 32.93, 30.39, 27.58, 26.87, 26.43, 25.90, 24.90, 24.21, 22.44, 21.79, 16.16, 11.58.

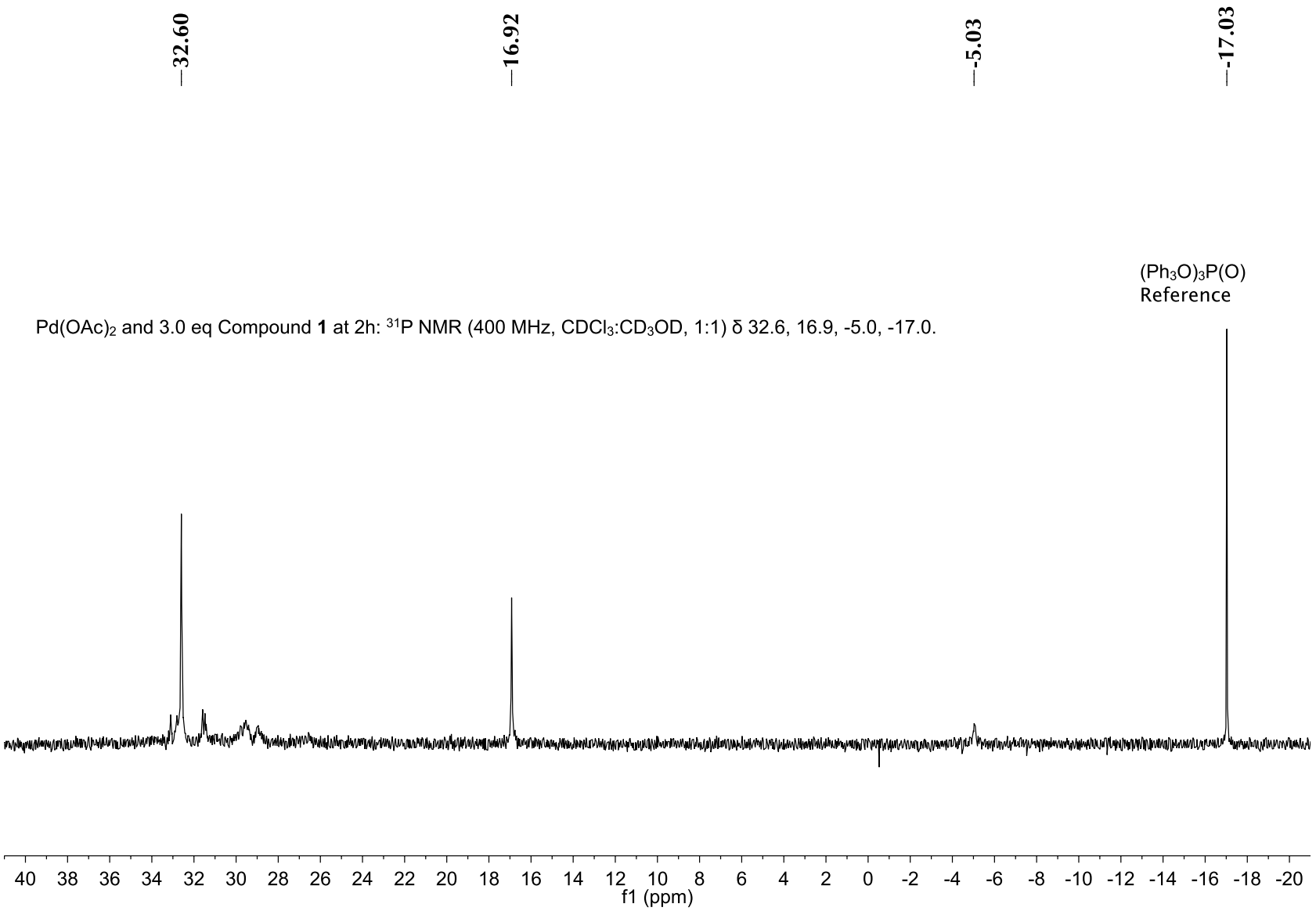






Compound **1**: ^{31}P NMR (400 MHz, $CDCl_3$:CD_3OD, 1:1) δ -5.0.





CHAPTER 4: PALLADIUM COMPLEXES WITH N-HETEROCYCLIC CARBENE LIGANDS AS CATALYSTS FOR THE ALKOXYCARBONYLATION OF OLEFINS

Modified from a paper published in *Organometallics*

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Abstract

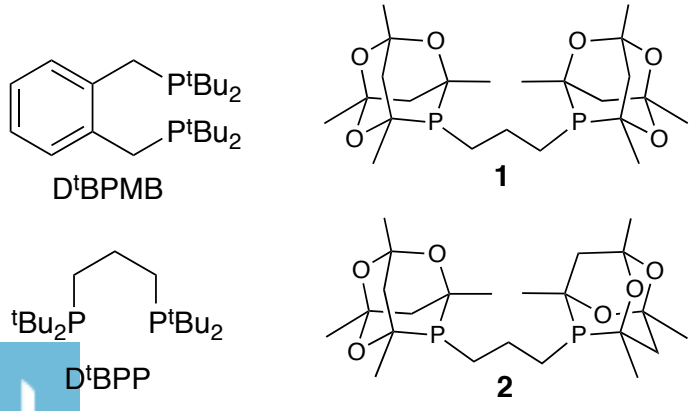
Palladium catalysts, generated from $Pd(OAc)_2$ and two equiv. of N,N-dialkylbenzimidazolium iodide, are effective for the alkoxycarbonylation of olefins in high yields (>88%). Alkoxycarbonylation of 1-hexene in dimethylacetamide is achieved within 24 h at 110 °C using 1 mol % catalyst, 1000 psi CO, and ethanol. Reactions can be prepared in air, without the need of an acid additive to produce ethyl 2-methylhexanoate and ethyl heptanoate in approximately a 2:1 ratio.

[1] ERC CBiRC REU student

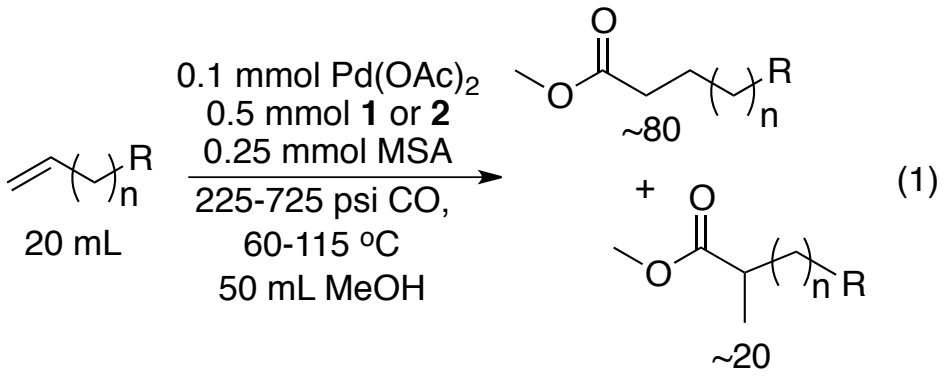
Introduction

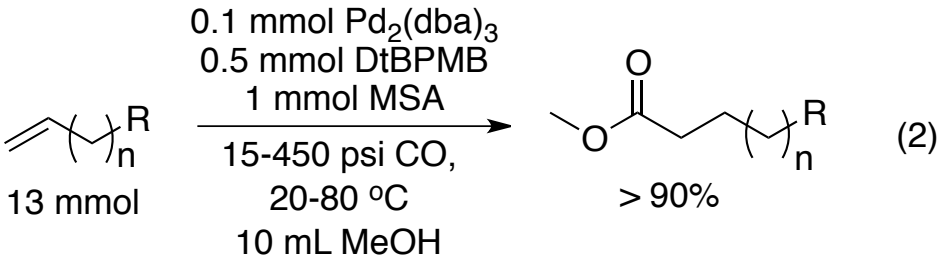
Carbonylation reactions have been used to synthesize a wide variety of valuable polymer and oxygenate material.[1] Interest in Pd-phosphine catalysts for polymerization and alkoxycarbonylation of olefinic materials was piqued in the early 1980's with the discovery that cationic palladium-phosphine complexes could effectively copolymerize α-olefins with CO in the presence of methanol.[2–6] Subsequent studies of ligand influence indicated that bidentate tertiary phosphines favored polymerization (i.e. generation of polyketones), whereas monodentate tertiary phosphines favored single insertion alkoxycarbonylation products.[3,7–10] While monodentate phosphines, such as triphenylphosphine, provided good yields of methyl propanoate from ethylene, longer chain olefins resulted in poor regioselectivity with mixtures of branched and linear esters.[7,11] Improvements by the research groups of Drent[12], Pringle[12,13], Tooze[14,15], and Cole-Hamilton[16] have led to new Pd ligands (Chart 1) that greatly enhanced the linear selectivity for alkoxycarbonylation. Although these ligands were chelating, the enhanced steric

Chart 1. Chelating Phosphine Ligands for Alkoxycarbonylation of Olefins.



bulk of these phosphines effectively resulted in conversion of terminal and internal C5-C14 olefins to the corresponding linear ester products (eqns. 1-2).



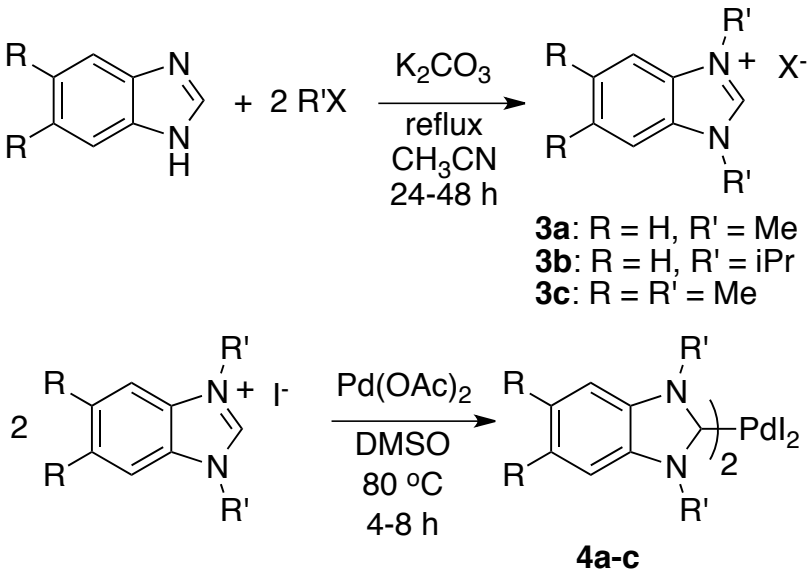


In seeking to develop more robust carbonylation catalysts, we evaluated palladium N-heterocyclic carbene complexes. Use of NHC ligands avoids the oxygen sensitivity and multistep ligand syntheses that are often associated with the use of phosphines.[13,17] To date, very few Pd-NHC catalyzed carbonylation reactions have been reported. Examples are limited to carbonylation of aryl halides, oxidative carbonylation of phenolic and amino compounds, and copolymerization of ethylene with CO.[18–22] Herein, we report our preliminary results for the first known alkoxycarbonylation of olefins using bis(benzimidazolylidene)palladium complexes (**4a-c**). These studies illustrate the

systematic differences between NHC and phosphine ligands in alkoxycarbonylation.

Results and Discussion

Scheme 1. Synthesis of Benzimidazolium Salts **3a-c** and Pd-NHC Complexes **4a-c**.

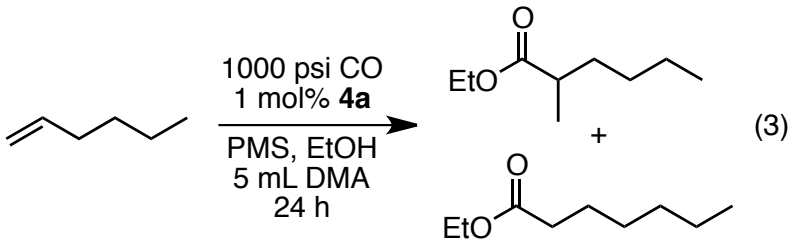


Simple N-alkyl substituted benzimidazolium salts and the corresponding palladium catalysts were readily prepared as summarized in Scheme 1. Symmetrically substituted salts **3a-c** were synthesized from benzimidazole and 1° or 2° alkyl halides by heating in CH_3CN with base.[23] Formation of the corresponding benzimidazolylidene complexes was accomplished via adapted procedures by heating $Pd(OAc)_2$ and the salt in a minimal amount of DMSO in air.[24,25]

The general reaction conditions for Pd-phosphine carbonylation of olefins commonly involve 1) the use of alcohol as solvent; 2) the addition of strong Brønsted acids as activating additives; and 3) the use of phosphine steric bulk to control product selectivity. Specifically, alkoxycarbonylation with ligands from Chart 1 was optimized with methanol as the solvent and methane sulfonic acid (MSA), which presumably generates an active hydridoPd(II)-phosphine complex.[4,7,15,16,26] However, attempts to carbonylate 1-hexene with **4a** under similar conditions only resulted in catalyst decomposition, via elimination of the NHC ligands from Pd. These results led us to examine systematically the Pd-NHC reaction conditions.

Initially it was assumed that the failure of **4a** to carbonylate hexene under conditions similar to those used for eqns. 1-2 was due to the strength of MSA and the poor solubility of the catalyst in alcohol. Therefore we employed a milder acid (pyridinium mesylate, PMS) and DMA as a co-solvent (Table 1). Under conditions of excess EtOH to 1-hexene (4:1), a 1 mol% loading of **4a** was moderately active for carbonylation in the presence of 15 mol% PMS and DMA. Moreover, maintaining reagent ratios and increasing the catalyst loading to 5 mol% did not significantly increase the yield of ester product, even with prolonged reaction times. Notable yield increase was seen when the EtOH to hexene ratio was reversed. It was found that **4a** (1 mol%) and PMS (15 mol%) could achieve overall ester product yields of 88% within 24 h at 110 °C and 1000 psi CO with a four-fold excess of 1-hexene to EtOH (Table 1, entry 6). These reactions could be prepared

in air using reagents as received from the supplier without reduction in yield. The transformation of 1-hexene under these conditions resulted in two major products, ethyl 2-methylhexanoate (branched) and ethyl heptanoate (linear) in a 2:1 (b:l) ratio.



(3)

Table 1. Optimization of Alkoxycarbonylation Conditions for catalyst **4a**.

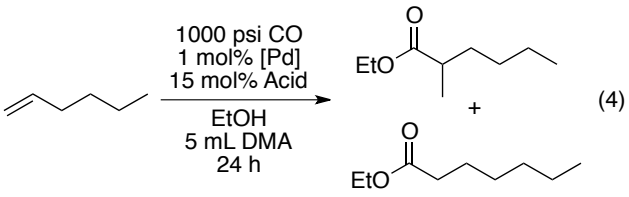
Entry	PMS (mol%)	EtOH/1-hexene	T (°C)	yield % (b:l)
1	5	1:4	100	32 (2.3)
2	10	1:4	100	44 (2.4)
3	15	1:4	100	58 (2.4)
4	10	1:4	110	80 (1.8)
5	15	1:4	110	88 (2.0)
6	15	1:1	110	22 (2.1)
7	15	4:1	110	6 (2.1)[a]

Conditions: 14 mmol EtOH, 56 mmol 1-hexene, 1 mol% **4a** and 5 mL DMA, 1000 psi CO, 24 h. [a] 14 mmol 1-hexene and 56 mmol EtOH used.

Although high yields of ester product were obtained, modification of the NHC structure as well as the pyridinium acids was explored for possible improvement of regioselectivity. Increasing the steric bulk of the N-bound substituents of the NHC ligand (**4b)** or increasing the electron donation of the NHC backbone (**4c)** indicated that ligand structure did not have a substantial influence on yield or selectivity. Both **4b** and **4c** maintained similar conversions and selectivity as those observed for **4a**. These results brought into question the nature of the active species and the lability of the NHC ligands during catalysis. Analogous concerns with the lability of the NHC ligand(s) arose for Rh-NHC catalyzed hydroformylations and Pd-NHC catalyzed aryl halide carbonylations.[19] In examining this issue with our system, it was found that alkoxycarbonylation did not occur in the absence of NHC ligands. For example, alkoxycarbonylation was ineffective with PMS and Pd sources such as $Pd_2(dba)_3$ or $Pd(OAc)_2$, under similar conditions that gave high conversion with **4a**. However, $Pd(OAc)_2$ became active for carbonylation (32% yield of products) in the presence of **3a** (15 mol%), producing a nearly 1:1 ratio of branched to linear products. Catalyst **4a** also remained active when PMS was replaced with a similar loading of dimethylbenzimidazolium iodide (**3a**), resulting in a 95% yield of products and an improved linear selectivity (b:l = 1:1). The presence of Pd was necessary as salt **3a** alone was inactive for carbonylation in the absence of a palladium source.

Improvement to the linear selectivity by replacing the acid additive PMS with **3a** suggested that altering the acid source might be key to catalytic

performance (Table 2). Initially, the influence of the pyridinium acid structure was explored. Neither the presence of a single methyl group on the pyridinium ring (2-picolinium, 2-PicMS; 4-picolinium, 4-PicMS) nor the inclusion of 2,6-methyl groups (lutidinium, LMS) resulted in a significant change in product selectivity. It was also noted that similar yield and selectivity was maintained if the mesylate anion was switched to triflate. Therefore, the range of acids was expanded to include Lewis acids ($ZnCl_2$, Ph_3B), nonanoic acid, and sulfonic acids (MSA; p-toluene sulfonic acid, PTSA), none of which provided an improvement to selectivity or yield. Surprisingly, reevaluation of the catalytic system revealed that quantitative alkoxycarbonylation could be obtained without any acid additive.



(4)

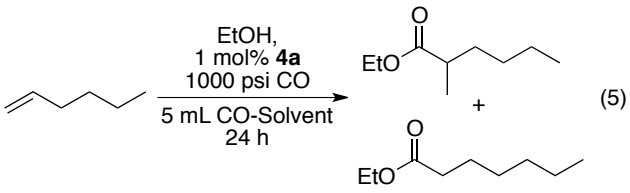
Table 2. Effect of Acid and NHC Ligand Structure on Alkoxycarbonylation.

entry	[Pd]	acid	yield % (b:l)
1	**4a**	PMS	88 (2.0)
2	**4a**	2-PicMS	94 (1.6)
3	**4a**	4-PicMS	90 (1.8)
4	**4a**	LMS	90 (1.6)

5	**4a**	PTF	83 (1.8)
6	**4b**	PMS	87 (2.0)
7	**4b**	LMS	94 (1.6)
8	**4c**	PMS	84 (1.9)
9	**4a**	MSA	76 (1.8)
10	**4a**	PTSA	85 (1.7)
11	**4a**	Ph_3B	81 (1.7)
12	**4a**	Nonanoic acid	91 (1.7)
13	**4a**	$ZnCl_2$	trace
14	**4a**	**3a**	95 (1.0)
15	$Pd(OAc)_2$	**3a**	21 (1.1)
16	$Pd(OAc)_2$	**-**	trace
17	**4a**	**-**	100 (1.6)

Conditions: 14 mmol EtOH, 56 mmol 1-hexene, 1 mol% **4a**, 15 mol% acid, 5 mL DMA, 1000 psi CO, 24 h.

Since the optimized system was not dependent upon acid for catalysis, further evaluation of the importance of the co-solvent was undertaken. Addition of DMA was key to achieving high carbonylation yields. Yields of 8% or less occurred at 110 °C after 3 d in the absence of DMA. However, use of DMA also



(5)

Table 3. Effect of Co-Solvent on Alkoxycarbonylation with catalyst **4a**.

entry	acid	EtOH/1-hexene	solvent	yield % (b:l)
1	PMS	1:4	DMF	trace
2	PMS	1:4	CH_3CN	78 (1.4)
3	-	1:4	CH_3CN	59 (1.4)
4	PMS	1:4	THF	27 (1.0)
5	-	1:4	THF	30 (1.1)
6	PMS	1:4	-	3 (1.0)[a]
7	-	1:4	-	8 (1.1)[a]
8	PMS	1:4	DMA	89 (1.8)
9	-	1:4	DMA	100 (1.6)
10	PMS	4:1	DMA	6 (2.1)[b]
11	MSA	4:1	DMA	7 (1.8)[b]
12	-	4:1	DMA	10 (1.8)[b]

Conditions: 14 mmol EtOH, 56 mmol 1-hexene, 1 mol% **4a**, 15 mol% acid, 5 mL DMA, 1000 psi CO, 24 h. [a] Reaction ran in the absence of DMA for 72 h. [b] 14 mmol 1-hexene and 56 mmol EtOH used.

produced small amounts (< 3%) of side products, N-N-dimethylheptanamide and N,N-dimethyl-2-methylhexanamide, which resulted from addition of DMA to hexene. To eliminate side product formation, other solvents were evaluated. Use of THF or CH_3CN as co-solvent resulted in a lower overall yield, but an improvement in linear selectivity and reduction in side products (Table 3).

Pd-NHC-catalyzed alkoxycarbonylation of additional olefins generally resulted in quantitative conversion of terminal olefins to ester product (Table 4). It is also important to note that alkoxycarbonylation of internal olefins was dramatically improved over systems that included an acid additive such as PMS. When using compounds containing vinylic functionality (e.g. styrene and ethyl acrylate), a large amount of polymeric material was formed.

Summary

We have shown that Pd benzimidazolylidene complexes are robust and high-yielding alkoxycarbonylation catalysts in the absence of acid additives. While many reports indicate analogies between phosphines and NHC ligands, it is evident from our preliminary work that Pd-NHC alkoxycarbonylation systems are quite disparate from those of Pd-phosphines. The nature of the active Pd intermediates remains unclear, but there is strong evidence that the NHC is vital to reactivity. Future studies will focus on identifying catalytic intermediates in hopes of better understanding the systematic and mechanistic differences between Pd-NHC and

Pd-phosphine complexes as well as developing the scope and applicability of these catalysts in a variety of carbonylation reactions.

Table 4. Alkoxycarbonylation of Various Olefins With Catalyst **4a**.

entry	substrate	acid	yield % (b:l)
1	1-pentene	PMS	85 (1.8)
2	1-pentene	-	99 (1.6)
3	1-octene	-	100 (1.6)
4	cyclohexene	PMS	16
5	cyclohexene	-	83
6	ethyl 4-pentenoate	-	100 (2.1)
7	styrene	PMS	27 (2.2)[a]
8	ethyl acrylate	PMS	31[a]

Conditions: 14 mmol EtOH, 56 mmol olefin, 1 mol% **4a**, 15 mol% PMS, 5 mL DMA, 1000 psi CO, 24 h. [a] Large amount of polymer product was detected.

Experimental Section

General Considerations. All reagents and solvents were of reagent grade or higher and were used as received. 4,5-Dimethylbenzimidazole[27] and 1,3-diisopropylbenzimidazolium bromide[23] were synthesized following previously reported procedures. Benzimidazolium salts (**3a-c**) and the corresponding catalysts (**4a-c**) were synthesized without rigorous exclusion of air and water. The carbonylation reactions were prepared in open air prior to sealing and pressurizing the reactor. Routine NMR spectra were recorded on a Varian VXR-400 spectrometer. Gas chromatography was performed on an HP-6890 instrument fitted with a HP-5 capillary column (30 m length, 0.25 mm internal diameter, 0.25 μm film thickness).

Synthesis and Characterization of Benzimidazolium salts 3a and 3c. As adapted from published reports,[23] a flask was charged with CH_3CN (10 mL), benzimidazole (8.5 mmol), and K_2CO_3 (1.18g, 8.5 mmol). MeI (4.0 eq, 2.1 mL, 33.7 mmol) was added and the reaction was heated at reflux for 18 h. After reaction completion, all volatiles were removed under vacuo. The residue was washed with CH_2Cl_2 and the filtrates were collected. CH_2Cl_2 was removed under vacuo, resulting in a sticky residue. Removal of the remaining benzimidazole and isolation of a solid product was achieved by sonicating the residue with EtOAc (3 x 5 mL), decanting after each sonication step. The solid was then filtered, and washed with EtOAc. The white

powder was dried under vacuum for at least 24 h before use. Yield 85-91%. NMR analysis for **3a** matched published values.[28] 1,3,4,5-tetramethylbenzimidazolium iodide (**3c**) ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.92 (s, 1H, NC*H*N), 7.43 (s, 2H, Aryl-H), 4.20 (s, 6H, NCH_3), 4.29 (s, 6H, Aryl-CH_3).

Synthesis and Characterization of Benzimidazolium salt 3b. After dissolving 1,3-diisopropylbenzimidazolium bromide (1.0 g, 3.5 mmol) in acetone (5 mL), NaI (0.6 g, 4.0 mmol) was added. A white precipitate immediately formed, and the solution was filtered through celite, washing with small portions of acetone. The filtrate was collected and dried under vacuo. The resulting residue was washed with dichloromethane, filtering again through celite and the filtrate was dried under vacuo. Removal of the remaining benzimidazole and isolation of a solid product was achieved by sonicating the residue with EtOAc (3 x 5 mL), decanting after each sonication step. The solid was then filtered, and washed with EtOAc. The white powder was dried under vacuum for at least 24 h before use. Yield 89%. NMR analysis for **3b** matched published values.[25]

Adapted general synthesis of catalysts 4a and 4c.[24] In a 20-mL flask, both $Pd(OAc)_2$ (0.5 g, 2.2 mmol) and the appropriate benzimidazolium salt (2.1 eq, 4.7 mmol) were dissolved in a minimal amount of DMSO (5 mL). The reaction was stirred with gentle heating (30-60 ^{o}C) for 6 h. During this time the dark red-brown solution lightened to orange. The DMSO solution was filtered and washed with

small amounts of DMSO, to separate any Pd black from the solution. To the DMSO filtrate, 50 mL of H_2O was added to precipitate the product. The solid was collected via filtration, washed with water (3 x 50 mL) and dried under suction for 5 m. The resulting orange solid was subsequently washed with several small portions of ether and hexanes, until the filtrates were clear. The solid was dried under vacuo for at least 24 h before use. Products **4a** and **4c** were mixtures of *cis*- and *trans*-isomers, with the trans isomer prevalent. The isomer mixtures were used as the carbonylation catalysts.

Cis- and *Trans*-**4c** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.15 (s, 2H, Ar-H), 7.09 (s, 2H, Ar-H), 4.19 (s, 6H, NCH_3), 4.17 (2, 6H, NCH_3), 2.40 (s, 6H, Ar-CH_3), 2.35 (s, 6H, Ar-CH_3).

Adapted synthesis of catalyst 4b.[25] In a 20-mL flask, both $Pd(OAc)_2$ (0.5 g, 2.2 mmol) and **3b** (1.3 g, 4.6 mmol) were dissolved in a minimal amount of DMSO (5 mL). The reaction was stirred at 80 °C for 12 h, then at 100 °C until the reaction lightened to yellow-orange. To the DMSO filtrate, 50 mL of H_2O was added to precipitate the product. The solid was collected via filtration, washed with water (3 x 50 mL) and dried under suction for 5 m. The resulting orange solid was subsequently washed with several small portions of ether and hexanes, until the filtrates were clear. The solid was then washed with CH_2Cl_2, collecting the filtrate. All volatiles were removed under vacuo, and the solid was dried under vacuo for at

least 24 h before use. A minor amount of cis-**4b** was present (<5%) and excess **3b** prevented Pd-dimer formation.

General High Pressure Reactions. To a high-pressure bomb, catalyst (0.14 mmol), acid (2.13 mmol), co-solvent (5.0 mL), olefin (55.8 mmol), and EtOH (0.83 mL, 14.2 mmol) were added in that order. The reactor was sealed and pressurized with CO to 1000 psi. The reaction was heated with stirring at the indicated temperature and pressure for the noted duration. After reaction completion, the reactor was cooled to 25 °C and depressurized. To the reaction solution, 30 mL of hexane and 100 μL of decane were added, which was subsequently washed with saturated $NaHCO_3$ (3 x 5 mL) and saturated NaCl (3 x 5 mL). The resulting organic layer was evaluated via GC to determine product yields.

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Supporting Information

General Methods

All reagents and solvents were of reagent grade or higher. 4,5-Dimethylbenzimidazole[1] and 1,3-diisopropylbenzimidazolium bromide[2] were synthesized following previously reported procedures. All solvents for carbonylation reactions were dried, degassed and stored under N_2 between uses. The carbonylation reactions were prepared in an inert atmosphere using a glove box. Benzimidazolium salts (**3a-c**) and the corresponding catalysts (**4a-c**) were synthesized in open atmosphere without exclusion of water. Routine NMR spectra were recorded on a Varian VXR-400 spectrometer. Gas chromatography was performed on an HP-6890 instrument fitted with a HP-5 capillary column (30 m length, 0.25 mm internal diameter, 0.25 μm film thickness).

Synthesis of benzimidazolium salts **3a** and **3c**

Procedure was adapted from published reports.[2] A flask was charged with CH_3CN (10 mL), benzimidazole (8.5 mmol), and K_2CO_3 (1.18g, 8.5 mmol). 4.0 eq of MeI (2.1 mL, 33.7 mmol) was added and the reaction was refluxed for 18 h. At reaction completion, all volatiles are removed under vacuo. The residue was washed with CH_2Cl_2 and the filtrates were collected. All CH_2Cl_2 was removed under vacuo, resulting in a sticky residue. To remove remaining benzimidazole and powder the product, the residue was sonicated with EtOAc (3 x 5 mL) and then filtered,

washing with EtOAc. The white powder was dried under vacuum for at least 24 h before use. Yield 85-91%. NMR analysis for **3a** matched published values.[3]

1,3,4,5-tetramethylbenzimidazolium iodide (**3c**) ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.92 (s, 1H, NC*H*N), 7.43 (s, 2H, Ar-H), 4.20 (s, 6H, NCH_3), 4.29 (s, 6H, Ar-CH_3).

Synthesis of benzimidazolium salt **3b**

1,3-Diisopropylbenzimidazolium bromide (1.0 g, 3.5 mmol) was dissolved in acetone (5 mL). To the solution, NaI (0.6 g, 4.0 mmol) was added. A white precipitate immediately formed, and the solution was filtered through celite, washing with small portions of acetone. The filtrate was collected and dried under vacuo. The resulting residue was washed with dichloromethane, filtering again through celite and the CH_2Cl_2 filtrate was dried under vacuo. The product residue was sonicated with EtOAc (3 x 5 mL) and then filtered, washing with EtOAc. The white powder was dried under vacuum for at least 24 h before use. Yield 89%. NMR analysis for **3b** matched published values.[4]

General synthesis of catalysts **4a** and **4c**

Adapted from a published procedure.[5] In 20 mL flask, both $Pd(OAc)_2$ (0.5 g, 2.2 mmol) and the according benzimidazolium salt (2.1 eq, 4.7 mmol) were dissolved in a minimal amount of DMSO (5 mL). The reaction was stirred with gentle heating (30-60 °C) for 6 h. During this time the dark red-brown solution lightens to orange. The DMSO solution was filtered through a plug of celite washing with

small amounts of DMSO, to separate any Pd black from the solution. To the DMSO filtrate, 50 mL of H_2O was added causing the product to precipitate. The solid was collected via filtration, washed with water (3 x 50 mL) and dried under suction for 5 m. The resulting orange solid was subsequently washed with several small portions of ether and hexanes, until the filtrates were clear. The filtrates were discarded. The solid was dried under vacuo for at least 24 h before use and stored under N_2. Product **4a** and **4c** were mixutres of *cis*- and *trans*-isomers. The isomer mixtures were used as the carbonylation catalysts.

Cis- and *Trans*-**4c** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.15 (s, 2H, Ar-H), 7.09 (s, 2H, Ar-H), 4.19 (s, 6H, NCH_3), 4.17 (2, 6H, NCH_3), 2.40 (s, 6H, Ar-CH_3), 2.35 (s, 6H, Ar-CH_3).

Synthesis of catalyst **4b**

Adapted from reported procedure.[4] In 20 mL flask, both $Pd(OAc)_2$ (0.5 g, 2.2 mmol) and **3b** (1.3 g, 4.6 mmol) were dissolved in a minimal amount of DMSO (5 mL). The reaction was stirred at 80 °C for 12 h and 100 °C until the reaction lightened to yellow-orange. To the DMSO filtrate, 50 mL of H_2O was added causing the product to precipitate. The solid was collected via filtration, washed with water (3 x 50 mL) and dried under suction for 5 m. The resulting orange solid was subsequently washed with several small portions of ether and hexanes, until the filtrates were clear. The filtrates were discarded. The solid was then washed with CH_2Cl_2, collecting the filtrate. All volatiles were removed under vacuo, and

the solid was dried under vacuo for at least 24 h before use and stored under N_2. A minor amount of cis-**4b** was present (<5%) and excess **3b** prevented Pd-dimer formation.

General High Pressure Reaction

To a high-pressure bomb, under an inert atmosphere, catalyst (0.14 mmol), pyridinium salt (2.13 mmol), co-solvent (5.0 mL), 1-hexene (7.2 mL, 55.8 mmol), and EtOH (0.83 mL, 14.2 mmol) were added in that order. The reactor was sealed under an inert atmosphere and pressurized with CO to 1000 psi. The reaction was stirred for the time and pressure indicated. After reaction completion, the reactor was cooled to 25 °C and depressurized. To the reaction solution, 30 mL of hexane and 150 mL of decane were added, which was subsequently washed with saturated $NaHCO_3$ (3 x 5 mL) and saturated NaCl (3 x 5 mL). The resulting organic layer was evaluated via GC to determine product yield.

Supporting Information References

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CHAPTER 5: CONCLUSION

Adapting synthesis and manufacturing technology is crucial for keeping up with the needs and demands occurring in society. Since the exigency for environmentally benign technologies is ever growing, the focus should be directed on finding more efficient, nontoxic routes to the consumable products that we need in our day-to-day lives. Palladium complexes have proven to be excellent catalysts for C-C bond formation under a variety of conditions, making it only reasonable that the area of Pd-catalyzed organic reactions is exploited to find these routes.

We have presented the idea that commercially available surfactant molecules are efficient additives to enhance Pd-catalyzed Sonogashira coupling reactions under mild aqueous conditions. Surfactants such as SDS and CTAB give high to quantitative coupling yields for aryl iodide and activated aryl bromide substrates with aromatic or aliphatic terminal alkynes. Since aryl bromide reactions proceed better without addition of the auxiliary reagent CuI, it would be beneficial to adapt and modify the representative surfactant conditions to enhance coupling yield. Substantial enhancement to reaction conditions is expected to originate from use of a more reactive Pd-catalyst as well as modification of the surfactant molecule. Both the structures of SDS and CTAB can be easily modified from biosourced reagents (i.e. aliphatic alcohols and bioengineered molecules from *E. coli*) to assess what structural changes to the existing surfactant molecule improves reaction yields and conditions.

Additionally, nontraditional surfactants, such as sodium cholate, can also have an influence on coupling reactions. Modification of methyl cholate with a phosphine moiety proved to be an effective ligand in Pd-catalyzed reactions in water. The cholate-phosphine ligand produced a heterogeneous Pd complex that was an efficient catalyst for Heck coupling of nonpolar substrates in water. Addition of the phosphine moiety increased the hydrophobic nature of cholate enough that the resultant Pd-complex was not soluble in water. However, the complex provided enhanced reactivity due to a hydrophobic effect, creating a localized high concentration of organic reagents around the metal center. Modification to the cholate molecule (e.g. multiple carboxylic acid groups) may be a way to enhance solubility in water or complex aggregation into cholate-like micelles of the resultant Pd-complex, allowing improvement in coupling yields, and possible access to less activated aryl halides.

Lastly, palladium complexes with NHC ligands proved to be active alkoxycarbonylation catalysts for a variety of terminal olefins. These complexes were active for high to quantitative conversion of substrate without exclusion of air or water, while not needing additional auxiliary reagents such as acids. Moreover, they have significant advantages over the analogous Pd-phosphine system which is limited by the phosphine ligand sensitivity to oxygen and poor catalytic activity without strongly acidic activating additives. The initial results suggest that modification to the NHC ligands by increasing steric bulk might enhance product selectivity. Also, reaction analyses indicate that one NHC is lost *in situ* to generate

the active catalytic species; therefore improved catalytic activity may also be achieved via dimeric Pd-NHC complexes that provide a 1:1 Pd-NHC composition.

Together, these research projects highlight three important areas of green chemistry – improving catalysis conditions, using greener solvents and expanding transformations of bioderrived feedstocks. Each area provides a foundation for further development of simple, often inexpensive, Pd-catalysts and C-C bond forming conditions.

APPENDIX A

12 Principles of Green Chemistry

Developed by Paul Anastas and John Warner

1. Prevention - It is better to prevent waste than to treat or clean up waste after it has been created.
2. Atom Economy - Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product.
3. Less Hazardous Chemical Syntheses – Wherever practicable, synthetic methods should be designed to use and generate substances that possess little or no toxicity to human health and the environment.
4. Designing Safer Chemicals – Chemical products should be designed to affect their desired function while minimizing their toxicity.
5. Safer Solvents and Auxiliaries – The use of auxiliary substances (e.g., solvents, separation agents, etc.) should be made unnecessary wherever possible and innocuous when used.
6. Design for Energy Efficiency – Energy requirements of chemical processes should be recognized for their environmental and economic impacts and should be minimized. If possible, synthetic methods should be conducted at ambient temperature and pressure.

7. Use of Renewable Feedstocks – A raw material or feedstock should be renewable rather than depleting whenever technically and economically practicable.
8. Reduce Derivatives – Unnecessary derivatization (use of blocking groups, protection/ deprotection, temporary modification of physical/chemical processes) should be minimized or avoided if possible, because such steps require additional reagents and can generate waste.
9. Catalysis – Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.
10. Design for Degradation – Chemical products should be designed so that at the end of their function they break down into innocuous degradation products and do not persist in the environment.
11. Real-time analysis for Pollution Prevention – Analytical methodologies need to be further developed to allow for real-time, in-process monitoring and control prior to the formation of hazardous substances.
12. Inherently Safer Chemistry for Accident Prevention – Substances and the form of a substance used in a chemical process should be chosen to minimize the potential for chemical accidents, including releases, explosions, and fires.