Carbonylative Cross-Coupling of *ortho*, *ortho*-Disubstituted Arenes

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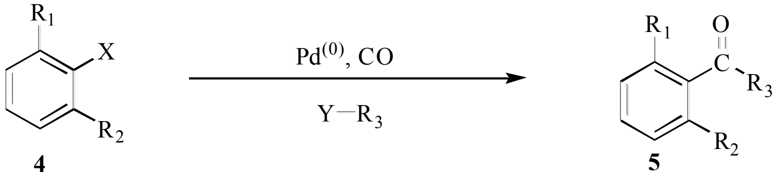
Beckman Scholarship Final Report

Over the past several decades, palladium-catalyzed cross-coupling has developed into extremely useful transformations in organic synthesis.[1] These cross-coupling reactions have been extended to a wide variety of organometallic nucleophiles, including organolithiums,[2] organozincs,[3] organostannanes,[4] and organosilicons,[5] following a common methodology (eq 1).

$$\underset{\mathbf{1}}{R_1{-}X} + \underset{\mathbf{2}}{R_2{-}M} \xrightarrow{\text{Pd catalyst}} \underset{\mathbf{3}}{R_1{-}R_2} \qquad (1)$$

One transformation of particular interest is the palladium-catalyzed carbonylative coupling of aryl halides with various organometallic reagents, allowing preparation of a wide number of unsymmetrically substituted aryl ketones. Although this methodology has been extended to a wide variety of substrates, there has been little success in the carbonylative coupling of very sterically hindered aryl halides. There are many examples of coupling with *ortho*-substituted aryl halides, but only one example of a carbonylative coupling with an *ortho*, *ortho*-disubstitued aryl halide is present in the literature.[6] Therefore, the focus of this project was to expand the carbonylative coupling methodology to such sterically hindered substrates (eq 2).

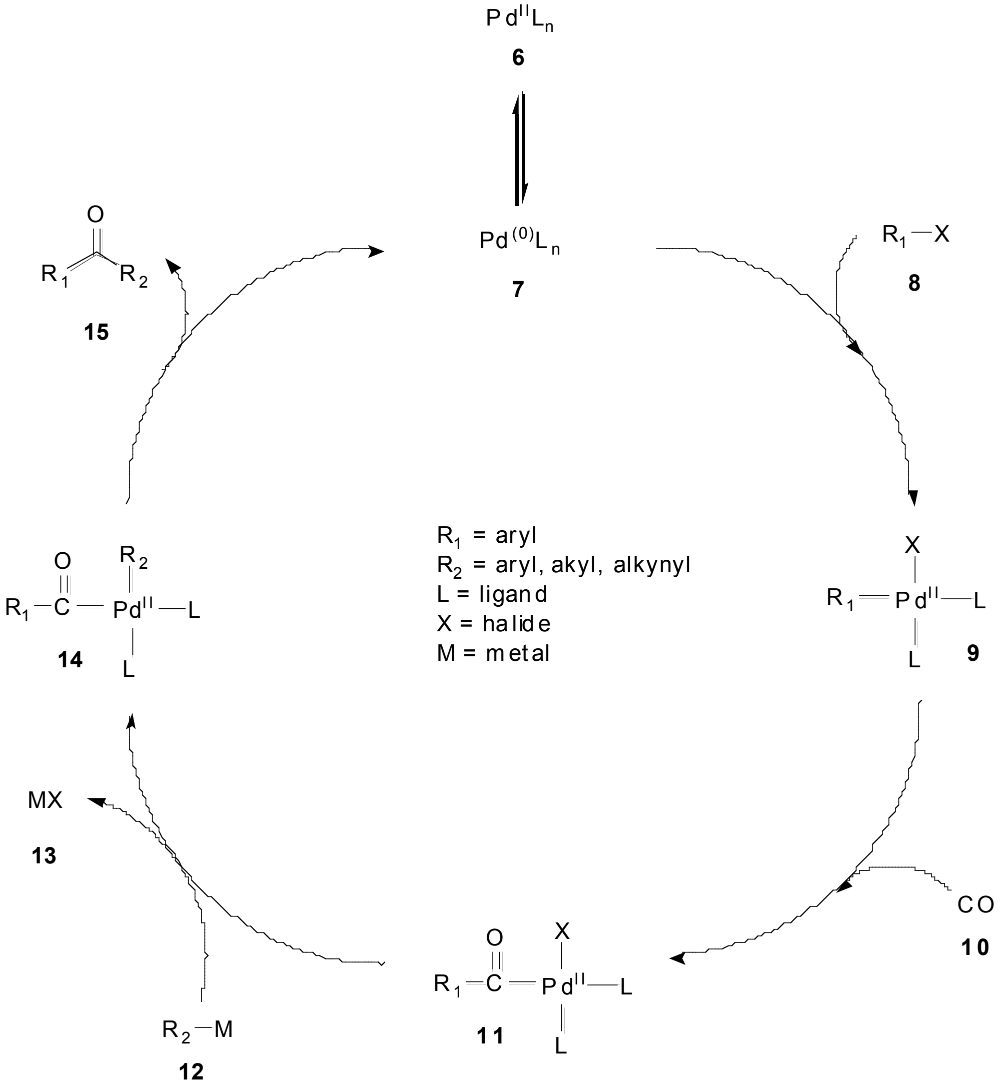


4 **5** (2)

R_1/R_2 = alkyl, aryl, heteroatom
R_3 - alkyl, alkenyl, aryl
X = halogen, metal
Y = halogen, metal

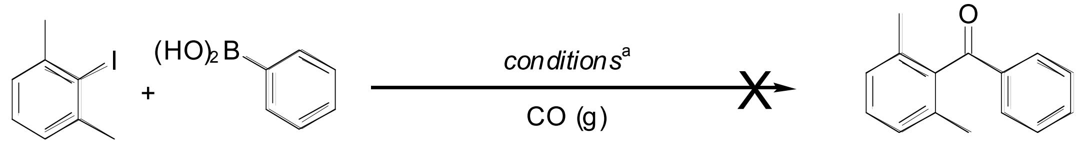
The catalytic cycle of this carbonylative coupling involves a reactive $Pd^{(0)}$ complex on which the halide oxidatively inserts. Migratory insertion of carbon monoxide into the palladium-aryl bond, transmetallation with the nucleophile, and then reductive elimination generates the aryl ketone and regenerates the catalyst (Figure 1).

Figure 1. The catalytic cycle for carbonylative cross-coupling



There are a number of factors that play an influential role on the success of this catalytic cycle. First the type of halide: the rate of oxidative addition of the aryl halide occurs in the order of I > OTf > Br >> Cl, and often is the rate-determining step in the catalytic cycle.[7] Also, the rate of carbonyl insertion into the aryl-palladium bond is very important, as the catalytic cycle can proceed to transmetallation without CO incorporation, leading to a non-carbonylative coupling product. Choosing a suitable nucleophile for transmetallation is essential, as well as the correct solvents and/or bases to alter its nucleophilicity. Finally, of ultimate importance is the choice of the catalyst system, particularly the ligands on the palladium species. As the mechanism of the catalytic cycle involves dissociation and reassociation of these ligands, the selected ligands will largely determine the success of the reaction.

Initial efforts utilized palladium catalysts with phosphorus based ligands, but under a variety of conditions these catalysts failed to give the desired ketone (eq 3).



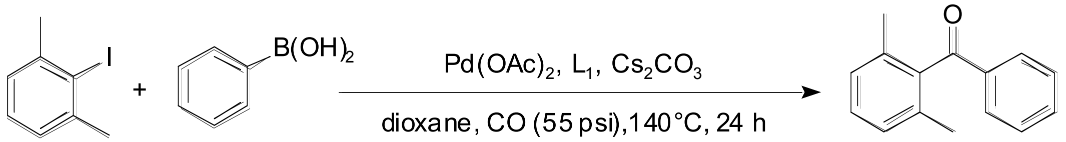
(3)

16 **17** **18**

[a] Pd catalysts: $PdCl_2(PPh_3)_2$, $Pd(PPh_3)_4$, $Pd(OAc)_2$/dppf, $PdCl_2/PPh_3$, $Pd(OAc)_2$/2-(di-*t*-butylphosphino)biphenyl; Bases: K_2CO_3, $Ba(OH)_2$, $KHCO_3$, NEt_3, Bu_2NH, K_3PO_4, KF, ${}^{i}Pr_2NH$, solvents: dioxane, toluene, glyme, anisole, DMF, water, THF, benzene; pressures: ballon-pressure, 55 psi; temperatures: RT, solvent reflux, 140°C; time: 6 h, 12 h, 18 h, 24 h.

Generally, unreacted starting material was observed, and it was thought that perhaps the oxidative addition step of the catalytic cycle was the problem. As the aryl halide is the electrophile in this reaction, increasing the electronic density on the palladium center would be advantageous for the oxidative addition step. Switching to ligands that were good σ-donors should increase the electron density on the palladium metal.

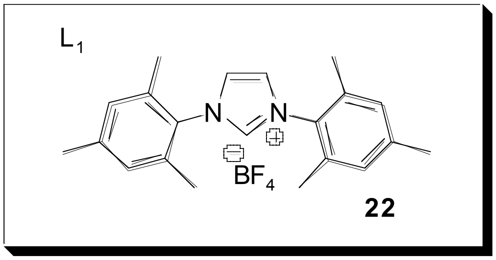
N-heterocyclic carbene ligands, first isolated in stable form in 1991 by Arduengo,[8] are a class of strong donor ligands with minimal π-back bonding from the metal center.[9] In addition, they are easily tunable by varying the side chains of the carbene and many are commercially available. It was recently shown by Zheng et al. that 2-methyliodobenzene efficiently couples with phenylboronic acid with an NHC/Pd catalyst under carbonylative conditions to give the benzophenone.[10] Modifiying Zheng's conditions, the following reaction was examined (eq 4).



(4)

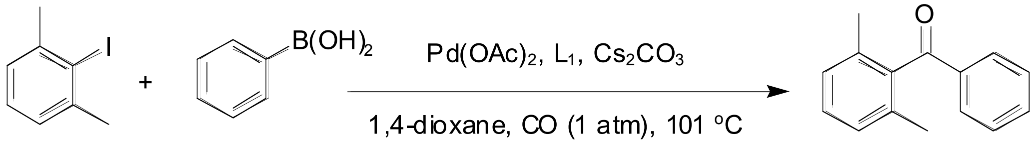
19 **20** **21**

45%



22

This reaction represented the first real success of the project. All of the starting material was consumed and the non-carbonylative coupling was observed as the majority of the remaining mass balance. Unfortunately, this reaction employed harsh conditions: 140 °C is well above the reflux temperature of dioxane, and a CO pressure of 55 psi is operationally more demanding. It was hoped that under less harsh conditions, 101 °C and balloon-pressure of CO, that similar results would be achieved (eq. 5).



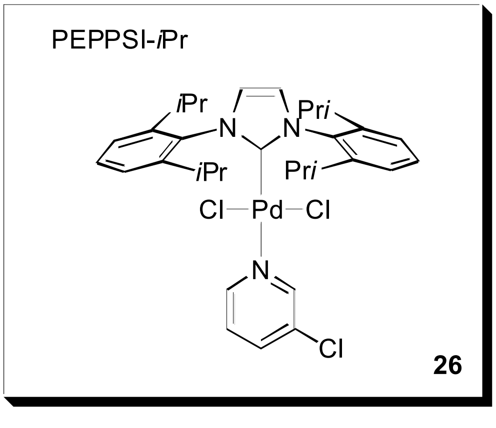
23 **24** **25**

11% (5)

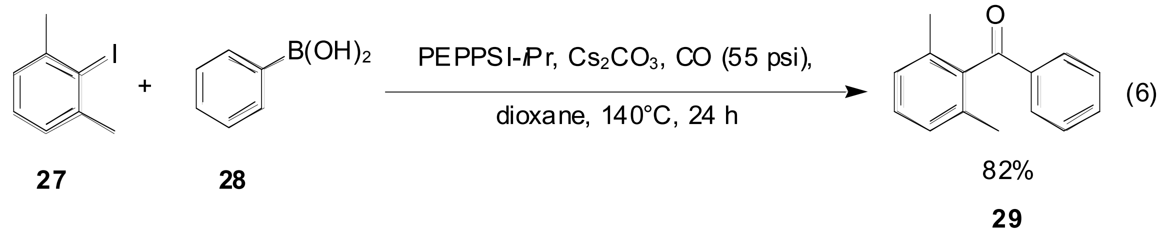
Disappointingly, the yield decreased to 11% isolated yield. However the starting material was still completely consumed, forming the non-carbonylative product as the major product, suggesting that the problem now lay with promoting migratory insertion of carbon monoxide into the palladium/aryl bond. It was thought that with sufficient screening of NHC ligands, bases, and solvents, the selectivity might be altered.

So far the NHC/Pd complexes had been generated in situ, from a Pd^{II} source and the NHC salt. However over the course of researching NHC ligands, a specific Pd/ligand system was discovered, the so-called PEPPSI-*i*Pr catalyst (Pyridine, Enhanced, Precatalyst, Preparation, Stabilization and Initiation) (see Figure 2).

Figure 2. The PEPPSI-*i*Pr catalyst.

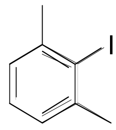
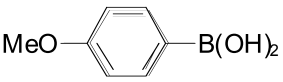
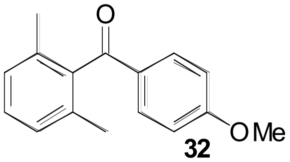
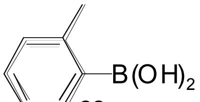
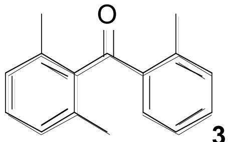
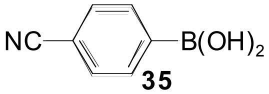
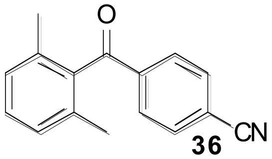
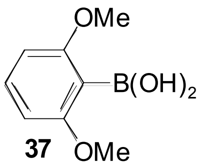
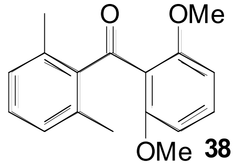
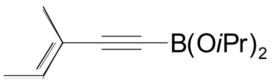
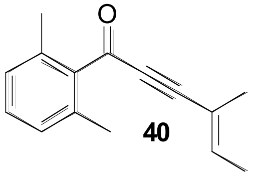
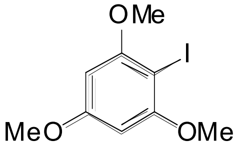
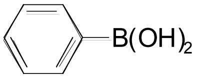
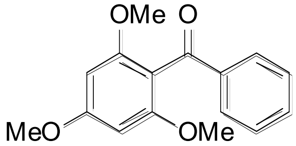
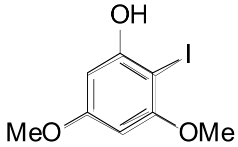
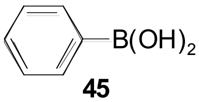
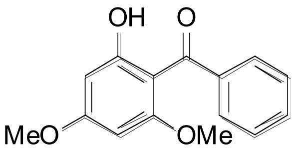


The PEPPSI catalyst has been shown to be very effective in catalyzing the coupling of sterically hindered chloroarenes, particularly with Grignards by Kumada-Tamao-Corriu coupling[11] and organotins by Stille coupling,[12] and boronic acids by Suzuki coupling,[13] all testaments to the catalyst's ability to facilitate difficult oxidative additions. It was thought that the key to its excellent reactivity was due to the high electron density on the palladium center which aids in oxidative addition, and the steric bulk of the NHC side chains which facilitate reductive elimination leading to an efficient catalytic cycle.[9] In addition, the incorporation of the 3-chloropyridine as a "throw-away ligand" on the precatalyst ensures the availability of an empty coordination site on palladium, which is necessary for several of the catalytic cycle processes.[12] Conveniently, the PEPPSI catalyst is air-stable and commercially available. Utilization of the PEPPSI catalyst in the coupling of 2-iodo-*m*-xylene and phenylboronic acid proceeded in good yield (eq 6).



It was hoped that the reaction would proceed at lower temperature and pressure conditions, but it was found with this base and solvent combination that the high temperature was necessary for full consumption of starting material within 24 hours, and the high pressure of carbon monoxide was needed to favor the ketone over the non-carbonylative product. To demonstrate the versatility of this coupling, Michael O'Keefe extended these conditions to a range of boronic acids (Figure 3). Yields went down significantly for iodobenzenes **41** and **44**, as to be expected for an electron-rich electrophile, and yields were improved using a more electron rich nucleophile such as boronic acid **31**. Conversely the yield went down upon using the electron deficient nucleophile **35**. These results correspond to previous trends observed for Suzuki coupling reactions.[6] Interesting, the poor yield of entry 4 showed that steric hindrance on the nucleophile had a significant effect on reaction yield, despite the electron-donating methoxy groups on the nucleophile. Entry 5 showed a method of generating ynones other than by Sonogashira coupling.

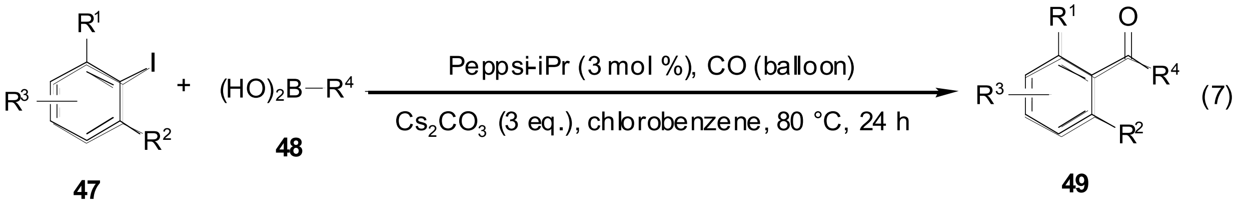
Figure 3. Examining the Scope of the Suzuki Coupling

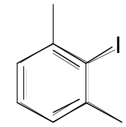
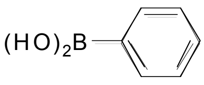
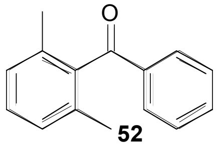
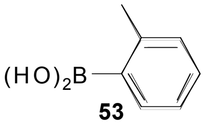
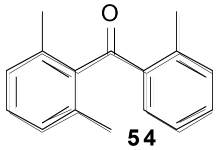
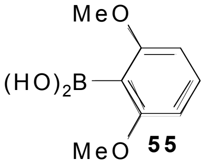
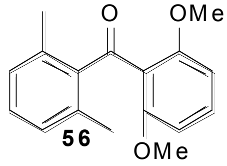
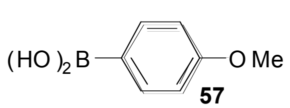
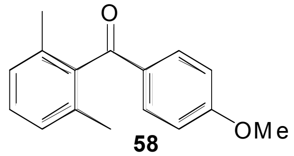
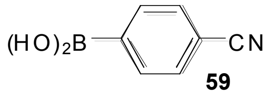
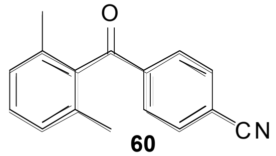
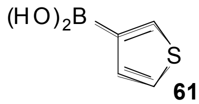
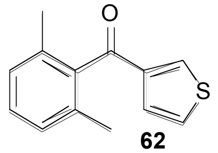
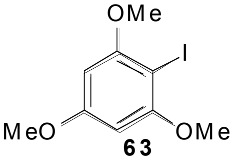
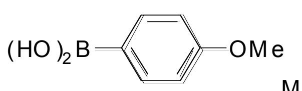
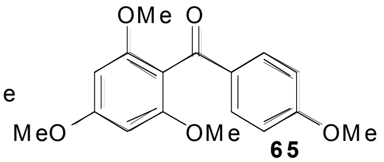
Entry	Iodide	Boronic Acid/Ester	Product	Isolated Yield
1	 **30**	 **31**	 **32**	92%
2		 **33**	 **34**	92%
3		 **35**	 **36**	42%
4		 **37**	 **38**	57%
5		 **39**	 **40**	50%[b]
6	 **41**	 **42**	 **43**	29%
7	 **44**	 **45**	 **46**	22%[b]

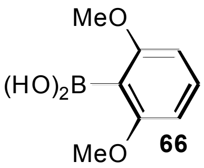
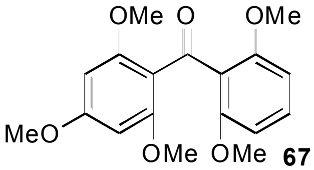
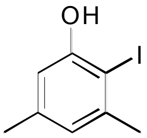
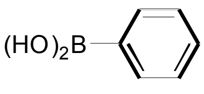
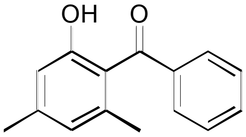
[a] Isolated Yields were average of two runs
[b] Yield from only one run

Unsatisfied with these harsh conditions, we continued to screen for reaction parameters at lower temperatures and carbon monoxide pressures. It was previously shown by Miyaura that anisole was an excellent solvent for carbonylative cross coupling.[6] Investigations into other polar aromatic solvents revealed chlorobenzene to be an excellent solvent for carbonylative cross-couplings with the Peppsi-*i*Pr catalyst. Optimization of parameters led us to reaction conditions that facilitated carbonylative coupling at moderate temperature and balloon-pressure carbon monoxide to generate the desired substituted benzophenones in good to excellent yields (Figure 4).

Figure 4. Suzuki coupling under milder conditions.[a]

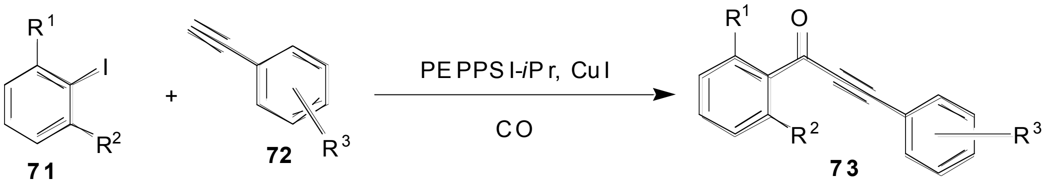


Entry	Iodide	Boronic Acid/Ester	Product	Isolated Yield
1	 **50**	 **51**	 **52**	95%
2		 **53**	 **54**	98%
3		 **55**	 **56**	95%
4		 **57**	 **58**	72%(92%)[c]
5		 **59**	 **60**	12(42%)[c]
6		 **61**	 **62**	64%
7	 **63**	 **64**	 **65**	52%

8		 **66**	 **67**	33%
9	 **68**	 **69**	 **70**	51%[d]

[a] Reaction conditions: 3 mol % PEPPSI-*i*Pr, 1.0 mmol aryl iodide, 2.0 mmol boronic acid, and 3.0 mmol Cs_2CO_3 in 5 mL chlorobenzene at 80 °C for 24 h. [b] Average isolated yield from two runs. [c] Dioxane was used as the solvent; CO pressure increased to 60 psi; temperature increased to 140 °C. [d] K_2CO_3 used as base.

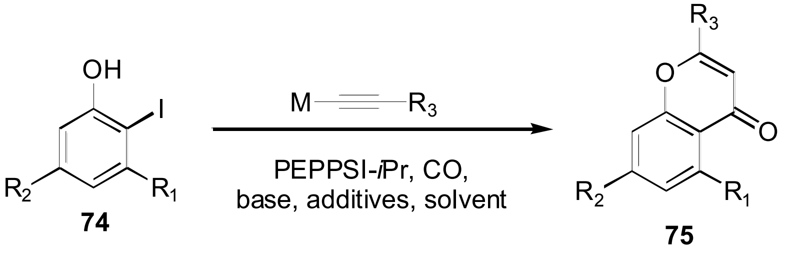
In addition to boronic acids, it was hoped to extend this methodology to the coupling of sterically hindered aryl iodides with acetylenic nucleophiles in a Sonogashira type reaction to generate ynones (eq. 8).



(8)

R^1 = alkyl, aryl, heteroatom R^3 = H, alkyl, aryl
R^2 = alkyl, aryl, heteroatom

Of particular interest is to use these formed ynones, in the presence of an amine, to form a flavone core by an intramolecular cyclization from a suitably substituted ynone (eq. 9).



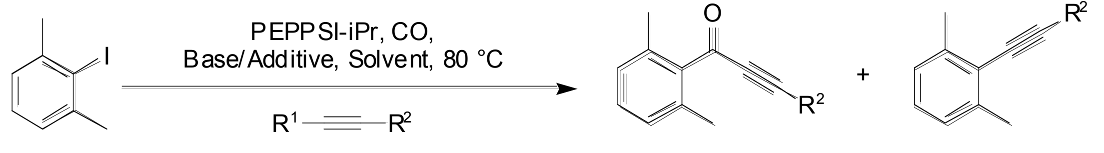
(9)

R_1 = aryl, alkyl
R_2 = aryl, alkyl, heteroatom
R_3 = aryl, alkyl
M = metal, H

It is hoped that formation of the ynone and ensuing cyclization could be done in one pot, by utilizing amine as the base, to generate a one-step procedure for substituted flavones from the corresponding *ortho*-hydroxy ynone. This type of cyclization procedure has been used before in synthesis of natural products with a flavone core[14]; in particular one of the initial motivations for beginning this project was to perform this reaction in the synthesis of Kidamycin currently being developed by Michael O'Keefe. Ynones used in these cyclization reactions are typically generated from either the acid chloride or from the ester *via* photo-Fries, both multistep procedures.

Initially we investigated Sonogashira type conditions; however extensive screening of bases and solvents failed to yield both satisfactory starting material consumption or carbonylative product selectivity. We therefore widened our screen to a variety of alkynyl metal nucleophiles (Figure 5).

Figure 5. Carbonylative cross-coupling of 2,6-dimethyliodobenzene with alkynyl nucleophiles.[a]



(10)

76 77 78

Entry	R^1	R^2	Additive/Base	Solvent	CO (psi)	**76**:**77**:**78** [b]
1	H	Ph	NEt_3/CuI	PhCl	balloon	5:2:1
2	KF_3B	Ph	Cs_2CO_3/TBAI[c]	MeCN	balloon	1:1:1
3	Bu_3Sn	Ph	none	PhCl	60	2:4:1
4	TMS	Ph	TBAF	PhCl	balloon	1:2:19
5	ZnBr	Ph	NaI	THF	60	39%[e]
6	ZnBr	Ph	LiBr	THF/NMP[f]	60	79%[e]

[a] Reaction conditions: 3 mol% Peppsi-iPr catalyst, 1 mmol aryl iodide, 2.0 mmol nucleophile, 5 mL solvent, 24 h reaction time. [b] Ratios determined by 1H NMR. [c] tetrabutylammonium iodide. [d] tetrabutylammonium fluoride. [e] Isolated yield of **77**. [f] N-methyl-2-pyrrolidone.

We were pleased to discover that zinc alkynyl nucleophiles gave moderate yield of the ynone in THF (entry 5) and upon addition of the cosolvent NMP and changing the additive to LiBr, the yield was improved to 79% (entry 6). Currently efforts are underway to extend this carbonylative coupling with zinc alkynyl nucleophiles to *ortho*-disubstituted aryl iodides that possess at least one *ortho*-oxygen group. This would access the substrates needed for the transformation envisioned in eq. 9. Efforts are also underway to apply this carbonylative alkynyl coupling to natural product synthesis. At present we are writing up our results with the Suzuki and Negishi carbonylative couplings and after some further investigation into the Negishi coupling on *ortho*-oxygen group disubstituted aryl iodides, we plan to submit for publication.

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