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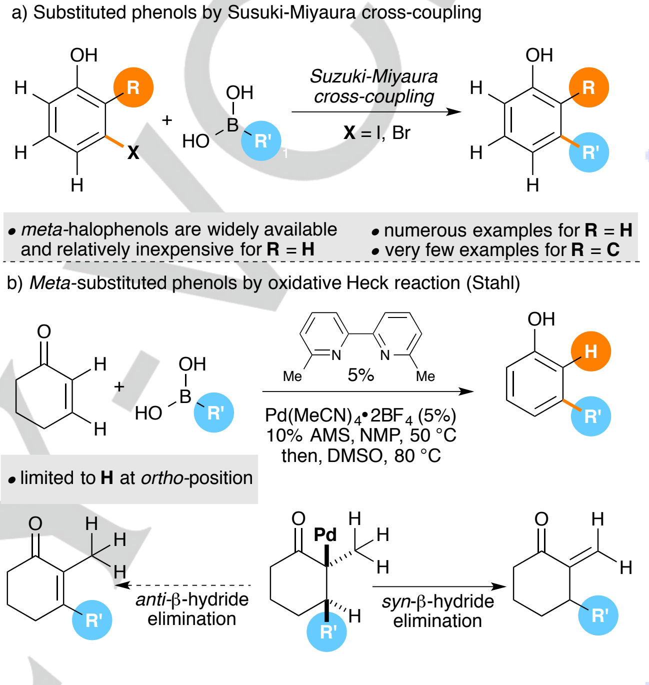
Convenient Access to *meta*-Substituted Phenols by Palladium-Catalyzed Suzuki-Miyaura Cross-Coupling and Oxidation

Zi Wang and Arturo Orellana*[a]

Abstract: We report a new approach to the synthesis of *meta*-substituted phenols in which a single palladium catalyst accomplishes a Suzuki-Miyaura cross-coupling between a β-chlorocyclohexenone and an arylboronic acid, and oxidation of the resulting cyclohexenone to the corresponding phenol upon introduction of a terminal oxidant and electron transfer mediator. Notably, this method also allows ready access to *ortho, meta*-disubstituted phenols, sterically congested biaryl phenols, and more highly substituted phenols.

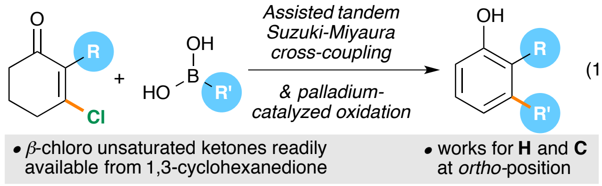
Introduction

Polysubstituted phenols are an important class of aromatic compounds found in pharmaceuticals and natural products, or as intermediates in the synthesis of complex molecules.[1] Their preparation can be challenging or lengthy, particularly when the final product includes a *meta*-substituent relative to the phenol hydroxyl group. This is not surprising since the inherent reactivity of phenols in electrophilic aromatic substitution reactions provides *ortho*- and *para*-substituted products readily, but does not allow access to *meta*-substituted products. Similarly, directed *ortho*-metallation strategies have limited use in the generation of *meta*-substituted phenols.[2] Palladium-catalyzed cross-coupling reactions of *meta*-halophenols with organometallic reagents provide a viable route to *meta*-substituted phenols, however this approach is limited by the availability of these electrophilic partners. Indeed, while a large number of Suzuki-Miyaura cross-coupling reactions using *meta*-halophenols have been reported,[3] very few examples have a carbon substituent at the *ortho*-position between the hydroxyl group and the *meta*-substituent, and of these only four bear an alkyl group at that position (Scheme 1a).[4] Furthermore, the classic conversion of nitrobenzene to *meta*-halophenol is not suitable when an alkyl substituent is desired at the *ortho*-position relative to the nitro group.[5] Clearly, the challenging preparation of these electrophilic partners severely limits the use of cross-coupling strategies to access meta-substituted phenols. Recently, the palladium-catalyzed oxidation of cyclohexanone derivatives to phenols has received considerable attention as a method to access substituted phenols.[6,7] Stahl and co-workers have demonstrated that the palladium-catalyzed oxidative Heck reaction between boronic acids and cyclohexenone, and the subsequent palladium-catalyzed oxidation of the coupled product in the same pot provides access to *meta*-substituted phenols (Scheme 1b).[7e] This route, however, does not allow access to phenols substituted at both the *ortho*- and *meta*-positions. Presumably this limitation arises because exocyclic *syn*-β-hydride elimination would outcompete the difficult endocyclic *anti*-β-hydride elimination[8] or palladium enolate isomerization (not shown) required for subsequent endocyclic *syn*-β-hydride elimination.



Scheme 1. Selected methods for the synthesis of *meta*-substituted phenols..

We have devised a new approach to the synthesis of poly-substituted phenols that is complementary to the above methods and exhibits broader scope with respect to the electrophilic partner. We envisioned an assisted tandem catalysis[9] approach to phenols that integrates the Suzuki-Miyaura[10] cross-coupling of β-chlorocyclohexenones[11] with boronic acids, and the palladium-catalyzed oxidation of the coupled products upon introduction of an oxidative switch[12-13] (Equation 1). β-chlorocyclohexenones are easily and quantitatively prepared from the corresponding 1,3-cyclohexanediones by treatment with oxalyl chloride (not shown).[14] Furthermore, 1,3-cyclohexanediones are readily alkylated at the 2-position (not shown), providing convenient access to *ortho,meta*-disubstituted phenols.[15] Thus, our method complements the gold-catalyzed synthesis of annelated *ortho, meta*-disubstituted phenols from alkynes and furans.[16]



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Results and Discussion

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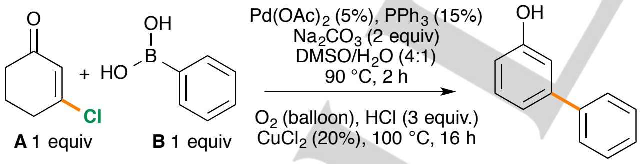
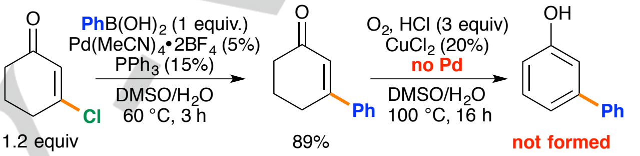
We chose to use β-chlorocyclohexenone and phenylboronic acid as substrates for initial reaction development and to optimize both steps of the tandem reaction at once. Because the oxidative addition partner is a vinylogous acid chloride and should therefore undergo facile oxidative addition, we constrained ourselves to the use of a simple catalyst system consisting of triphenylphosphine and palladium(II) salts. We also chose solvent systems that are well-suited for oxidative palladium chemistry,[17] and limited ourselves to oxygen or hydrogen peroxide as terminal oxidants with the goal of maintaining high atom economy. Table 1 shows selected results from our optimization study. We quickly established that a solvent mixture consisting of DMSO, which has long been used in oxidative palladium chemistry,[18] and water was suitable for cross-coupling using $Pd(OAc)_2$ as the palladium source, and that simply using a balloon of oxygen was insufficient for oxidation (entry 1). We reasoned that liberating palladium from its phosphine ligands after completion of the cross-coupling may facilitate the oxidation and therefore added excess hydrogen peroxide to oxidize triphenylphosphine to the phosphine oxide, and to act as a terminal oxidant, however this was ineffective (entry 2). Pyridines have proven to be effective ligands in oxidative palladium reactions,[19] however the use of 2-methoxypyridine in our reaction was not fruitful (entry 3). In contrast, the use of excess HCl and 20% $CuCl_2$ as an electron transfer mediator[20] led to a significant improvement in yield, and we chose this system for future oxidations (entry 4). The beneficial effect of HCl may be due to acid-catalyzed formation of the enol, which can in principle lead to a palladium enolate and subsequent oxidation by β-hydride elimination. Other solvent systems commonly used for Suzuki-Miyaura coupling did not improve the reaction (entries 5-7). Changing the base to more soluble Cs_2CO_3 provided a further improvement (entry 9). We noted that the vinylogous acid chloride underwent some decomposition upon storage. Reasoning that this may be a problem during the reaction, we used a slight excess and observed a corresponding improvement in yield (entry 9). Using $PdCl_2$ instead of $Pd(OAc)_2$ led to a reduction in yield, however using $Pd(MeCN)_4{\bullet}2BF_4$ provided the phenol in 88% isolated yield.

Table 1. Optimization of *meta*-phenol synthesis by tandem Suzuki-Miyaura cross-coupling and oxidation.



entry	change from above	yield
1	no HCl, no $CuCl_2$	0%
2	no HCl, no $CuCl_2$, 5 equiv. H_2O_2 added	<10%
3	no HCl, no $CuCl_2$, 20% 2-methoxypyridine	0%
4	none	53%
5	$PhMe/EtOH/H_2O$ instead of $DMSO/H_2O$	0%
6	$PhMe/DMSO/H_2O$ instead of $DMSO/H_2O$	20%
7	DMAc/DMSO/H2O instead of $DMSO/H_2O$	26%
8	Cs_2CO_3 instead of Na_2CO_3	64%
9	10% excess **A**	83%
10	10% excess **A**, $PdCl_2$ instead of $Pd(OAc)_2$	73%
11	10% excess **A**, $Pd(MeCN)_4(BF_4)_2$ instead of $Pd(OAc)_2$	88%

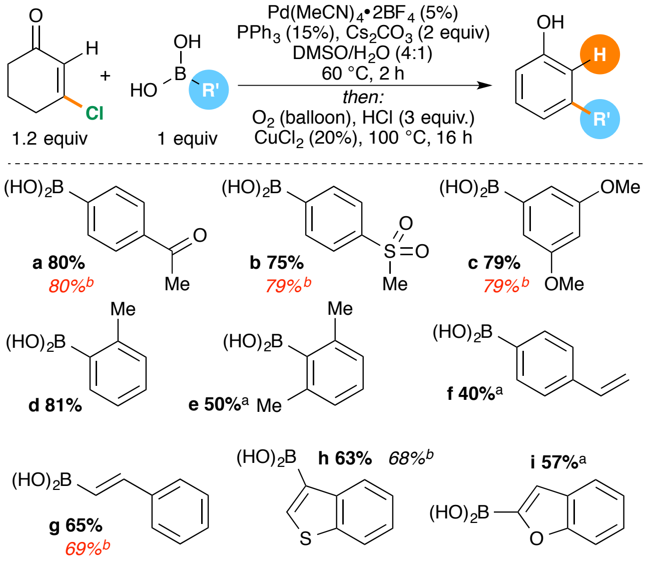
Concerned that the vinyloguos acid chloride may be decomposing at 90 °C, we optimized the temperature of the cross-coupling step and determined that when conducted at 60 °C, the first step yields 89% isolated yield of the coupled product in the simplest case possible (Scheme 2). We therefore implemented this slight change in substrate scope studies (see below). In a separate control experiment we also verified that the oxidation step is indeed catalyzed by palladium (Scheme 2). This experiment also confirms that $CuCl_2$ acts as an electron transfer mediator and is not directly responsible for the oxidation[21] of the cyclohexenone to the phenol.



Scheme 2. Optimized temperature for cross-coupling and control experiment verifying palladium-catalyzed oxidation to phenol.

We next explored the scope of the tandem reaction by using the β-chlorocyclohexenone and a variety of boronic acids (Table 2). The phenol synthesis (yields in bold) works equally well when electron-deficient (entries **a** and **b**) or electron-rich arylboronic acids are used (entry **c**). Similarly, *ortho*-tolylboronic acid gives the coupled product in good yield (entry **d**), however, the use of more sterically demanding 2,6-xylylboronic acid gave the coupled product in significantly lower yield (entry **e**). 4-Vinylphenyl boronic acid gave a relatively low yield (entry **f**), which may be the result of side reactions with the vinyl group. *trans*-2-Phenyl vinylboronic acid (entry **g**) and electron-rich heterocyclic boronic acids (entries **h** and **i**) all provided the coupled products in moderate yields. In some cases (entries **a**, **b**, **c**, **g** and **h**) we conducted parallel reactions that were stopped after the coupling step and compared the isolated yields of the coupled product (in italics) with the yields of the corresponding phenol. The close agreement between these two values suggests that the overall yield is largely determined by the success of the coupling step.

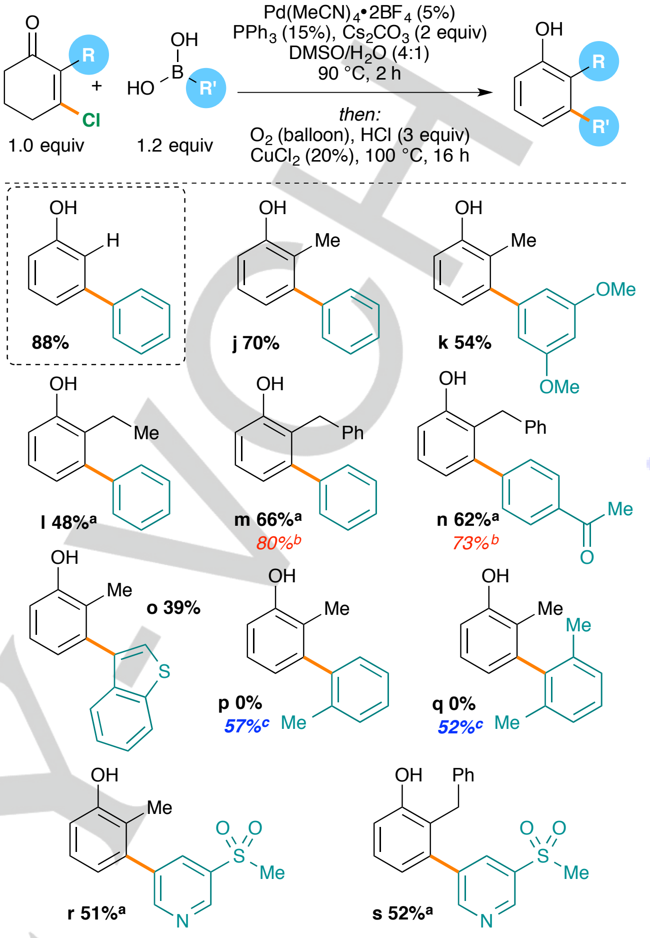
Table 2. Synthesis of *meta*-substituted phenols by Suzuki-Miyaura cross-coupling and oxidation.



a) Using $Pd(OAc)_2$ instead of $Pd(MeCN)_4•2BF_4$. b) Isolated yield of cross-coupled product in a parallel reaction.

We then progressed to the more challenging synthesis of *ortho,meta*-disubstituted phenols. The required β-chlorocyclohexenones were readily prepared by alkylation of the 1,3-diketone and chlorination with oxalyl chloride. These substrates proved more robust than the parent chloride and were therefore used as the limiting reagent in all future experiments. Table 3 shows that substitution at the α-position of the cyclohexenone renders the coupling step more challenging and the overall process lower yielding (entries **j**-**n**). In two instances (entries **l** and **n**) parallel reactions were stopped after the cross-coupling step, and comparison of the yield of isolated coupled product (in red italics) with the isolated yield of phenol revealed a significant difference, suggesting that the oxidation step may be more challenging for these substrates. A significant drop in yield was also observed when benzo[*b*]thien-3-ylboronic is used (entry **o**), which may reflect the increased steric environment or the electron-rich nature of this system. The cross-coupling reaction fails completely under standard conditions when it involves two sterically demanding partners (entries **p** and **q**). Fortunately, this limitation can be addressed by using more sophisticated catalysts (yields in blue italics, see discussion below). Finally, entries **r** and **s** demonstrate that this simple catalytic system enables the synthesis of biaryl systems bearing medicinally-relevant functional group content.

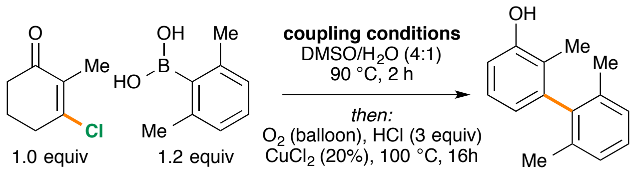
Table 3. Synthesis of *ortho,meta*-disubstituted phenols by Suzuki-Miyaura cross-coupling and oxidation.



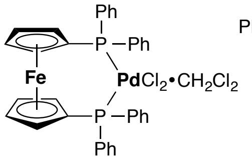
a) Using $Pd(OAc)_2$ instead of $Pd(MeCN)_4•2BF_4$. b) Isolated yield of cross-coupled product in a parallel reaction. c) Using re-optimized conditions reported in table 4.

Given the simple catalyst system used in our initial work, it is not surprising that the isolated yields of *ortho,meta*-disubstituted phenol are, in general, lower than those of *meta*-phenols, and we attribute these lower yields to the more challenging cross-coupling step. A wealth of more sophisticated phosphine ligands have been developed to address challenging cross-coupling reactions leading to congested biaryls. We therefore reasoned that one of these reactions should provide the desired congested phenol after some optimization, and re-investigated the cross-coupling step in the tandem reaction using the most challenging example (Table 3, entry **q**) using dppe, DPEPhos and SPhos as ligands on palladium since they are known to provide highly hindered biaryls by Suzuki-Miyaura cross-coupling (Table 4).[22] Changing the base from Cs_2CO_3 to KOH had a significant improvement in yield (entry 1). Using DPEPhos did not provide the desired product (entry 2), and changing the ligand to SPhos gave marginally better results (entry 3). In contrast, using $Pd(dppf)Cl_2•CH_2Cl_2$ as the catalyst provided the disubstituted phenol in 52% yield, which is significant given the congested nature of this product and the fact that palladium catalyzes both steps. The same conditions also provided product **p** (Table 3) in 57% yield.

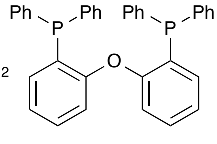
Table 4. Re-optimization of catalyst system for the synthesis of sterically congested *meta*-phenols.



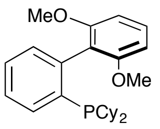
entry	coupling conditions	yield
1	5% Pd(OAc)$_2$, 15% PPh$_3$, 200% KOH	21%
2	5% Pd(OAc)$_2$, 15% DPEPhos, 200% KOH	0%
3	5% Pd(OAc)$_2$, 15% SPhos, 200% KOH	<10%
4	5% Pd(dppf)Cl$_2$•CH$_2$Cl$_2$, 200% KOH	52%



Pd(dppf)Cl$_2$•CH$_2$Cl$_2$

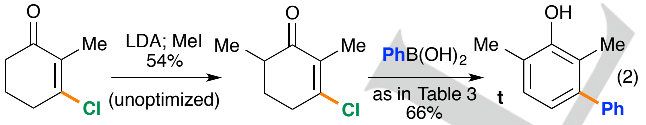


DPEPhos



SPhos

Equation 2 demonstrates that this tandem reaction constitutes a convenient approach to polysubstituted phenols. Alkylation of the α-position of the vinylogous chloride proceeds as expected by simple enolate formation with LDA and introduction of an alkyl electrophile. This is preferable to alkylation of the 2-methyl-1,3-cyclohexanedione followed by treatment with oxalyl chloride since this latter approach leads to mixtures of vinylogous chlorides (not shown). Tandem cross-coupling and oxidation using standard conditions leads to the trisubstituted phenol in 66% yield.



Conclusions

We have demonstrated a new method for the synthesis of *meta*-substituted phenols in which palladium catalyzes both a Suzuki-Miyaura cross-coupling and the oxidation of the coupled product to the corresponding phenol. This tandem reaction can also be used to prepare *ortho,meta*-disubstituted sterically congested phenols, as well as trisubstituted phenols, and avoids many limitations inherent in more traditional approaches to these valuable intermediates. Lastly, the modular nature of this approach to the synthesis of polysubstituted phenols makes it well-suited for the synthesis of small molecule libraries.

Acknowledgements

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Keywords: Phenols • Palladium • Cross-coupling • Oxidation • Tandem Catalysis

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Catalytic two-step: The tandem palladium-catalyzed cross-coupling of b-chlorocyclohexenones and subsequent palladium-catalyzed oxidation provide access to *meta*-substituted and *ortho,meta*-disubstituted phenols.

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