

Regiospecific Synthesis of Unsymmetrical 2,3-Diarylquinones via Stepwise Pd(0)-Catalyzed Couplings of Arylstannanes to Doubly Activated Quinone Equivalents

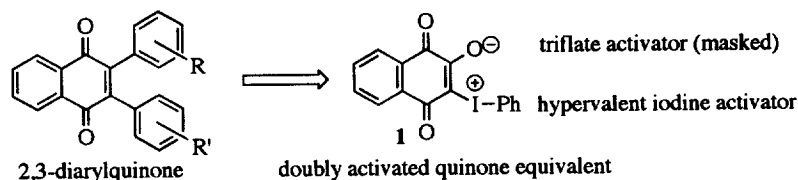
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Abstract: Coupling of arylstannanes to 2-phenyliodonio-1,4-naphthoquinone-3-oxide in the presence of a tetrakis(triphenylphosphine)palladium(0)-cuprous iodide catalyst yields 3-aryl-2-hydroxy-1,4-naphthoquinones which are converted to the corresponding 3-aryl-2-trifluoromethanesulfonyloxy-1,4-naphthoquinone and coupled to a different arylstannane to yield unsymmetrical 2,3-diaryl-1,4-naphthoquinones in good yields.
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In recent years, the palladium-catalyzed cross-coupling reaction has evolved as a powerful synthetic tool for the construction of complex quinones. The reaction usually involves an arylmetal species (ArM) acting upon a quinone electrophile (QX) in the presence of a Pd(0) catalyst.¹ Two versions of this reaction featuring aryltins (ArSnR₃)² and aryl boronic acids (ArB(OH)₂)³ as the arylmetal species are known. However, for all practical purposes, the quinone electrophile has been limited to the use of bromoquinones.⁴

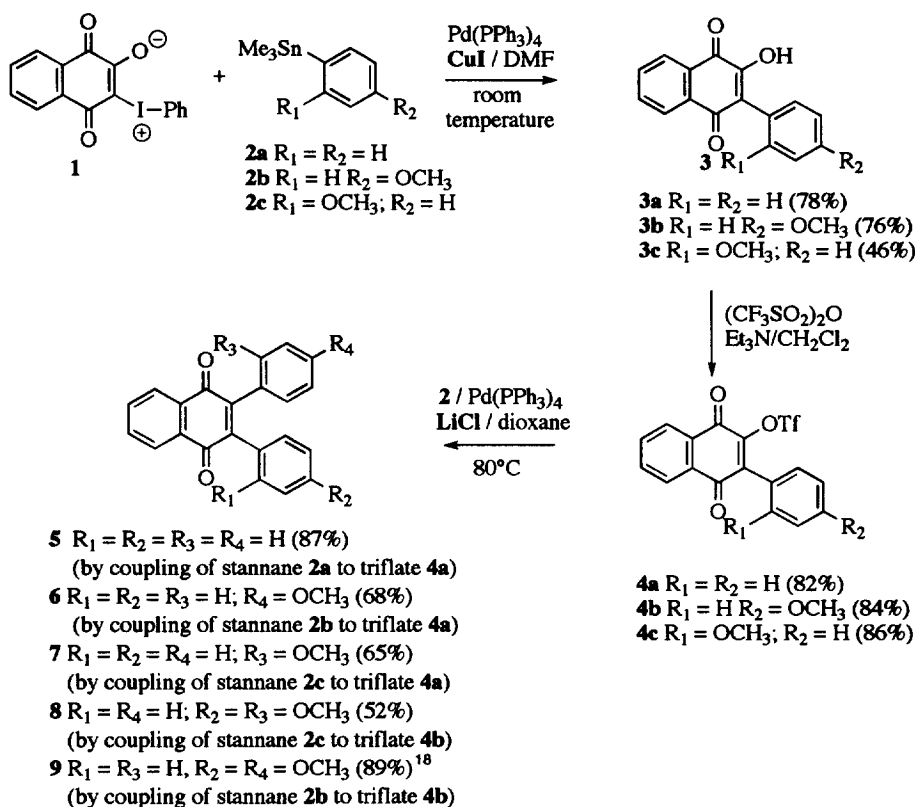
In this communication, we report that triflates and hypervalent iodines are also useful quinone electrophile components in these coupling reactions. Furthermore, when both of these groups are attached to the quinone core, regiospecific coupling of two different aryl groups is possible.



We reasoned that phenyliodonium 1,4-dipoles **1**⁵ could serve as doubly activated quinone equivalents in stepwise Pd(0)-catalyzed couplings⁶ since they were armed with both a hypervalent iodine and a triflate (in masked form). The first coupling would take place at the carbon bearing the hypervalent iodine yielding an aryl hydroxyquinone which could be subsequently activated as the triflate for a second coupling reaction. A recent report describing the use of 1,4-dipole **1** in Pd(II)-catalyzed couplings with stannylated acetylenes,⁷ prompted us to disclose our results on their use in Pd(0)-catalyzed cross-coupling reactions with arylstannanes.

Initial screening of the reaction conditions with 1,4-dipole **1** and phenylstannane **2a**⁸ revealed that the usual Stille coupling conditions, Pd(PPh₃)₄/CuI/DMF,⁹ yielded 3-phenylhydroxyquinone **3a**¹⁰ at *room temperature* as opposed to the high temperatures required for bromoquinone couplings,² **Scheme 1**. As anticipated, the coupling reaction proceeded exclusively at the carbon bearing the hypervalent iodine. After a series of experiments, it was determined that both the Pd(PPh₃)₄ catalyst and CuI cocatalyst¹¹ were required for the coupling reaction to proceed.

Scheme 1



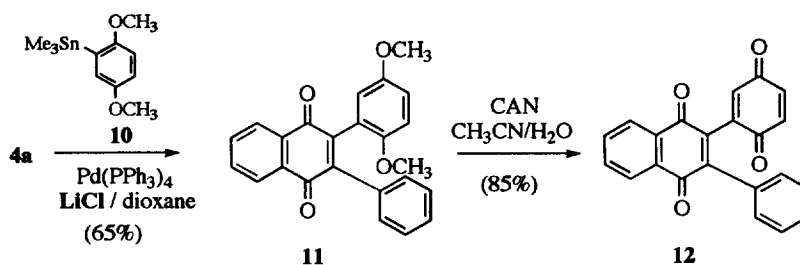
The synthetic efficacy of the reaction was studied with two other aryl stannanes, **2b** and **2c**, which yielded aryl hydroxyquinones **3b** and **3c**¹² in moderate yields. In the case of **3c**, the formation of 3-methyl-2-hydroxy-1,4-naphthoquinone (15%), by methyl transfer from the arylstannane, contributed to the lower yield.

Since the present cross coupling reaction successfully led to arylhydroxyquinones **3**, this opened a new synthetic option for the further functionalization of the quinone core. Reaction of the free hydroxyl in **3a** with triflic anhydride provided the isomerically pure *para*-quinonylphenyl triflate **4a**.¹³ However, triflation of quinones **3b** and **3c**, which possess electron rich aryls, afforded **4b** and **4c** as major products along with the *ortho*-quinonylphenyl triflate isomers in 13% and 10% yields, respectively.¹⁴

In sharp contrast to Pd(0)-catalyzed coupling of phenylstannane **2a** to 1,4-dipole **1**, Pd(0)-catalyzed coupling of phenylstannane **2a** to the phenyl triflate **4a** required increased reaction temperatures and the use of a LiCl cocatalyst¹⁵ to produce the known 2,3-diphenyl-1,4-naphthoquinone **5**.¹⁶ Under similar reaction conditions,¹⁷ different arylstannane and arylquinonyl triflate combinations (noted in parentheses) were coupled to form brilliantly colored 2,3-diarylquinones **5-9**¹⁸ in respectable yields.

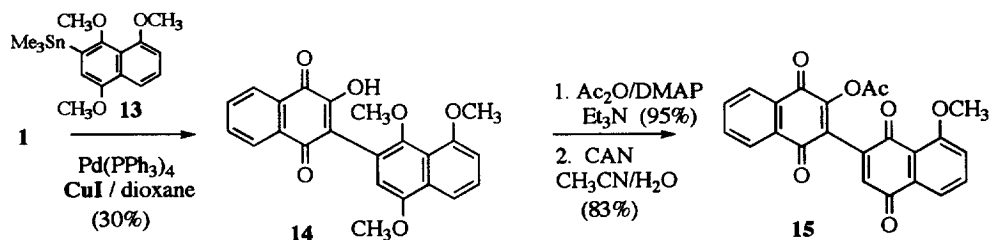
With the eventual goal of extending the method to the regiocontrolled synthesis of dimeric and trimeric quinones,¹⁹ we also explored couplings using *para*-dimethoxyarylstannanes as masked quinone equivalents. Palladium(0)-catalyzed coupling of 2,5-dimethoxyphenylstannane **10** with the phenyl triflate **4a** provided good quantities of the 2,3-diarylquinone **11**. Subsequent ceric ammonium nitrate (CAN) oxidation²⁰ yielded the *unsymmetrical* quinone dimer **12**, **Scheme 2**.

Scheme 2



Direct coupling of stannylated juglone **13**²¹ to the 1,4-dipole **1** afforded the naphthylhydroxyquinone **14**. Protection of the free hydroxyl as the acetate²² followed by CAN oxidation²⁰ yielded the lawsone/juglone dimer **15** in 24% yield from **1**, **Scheme 3**.

Scheme 3



In summary, we have demonstrated that both hypervalent iodines and triflates are useful quinone electrophile components in Stille coupling reactions. The described three step protocol enables two carbon-carbon bonds to be formed on the quinone core in a stepwise and regioselective manner. Applications of this technology to the synthesis of biologically active trimeric naphthoquinones¹⁹ and other naturally occurring quinones is currently in progress.

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- A typical procedure for the preparation of arylquinonyl triflates **4**: To a solution of the hydroxyquinone **3** (1 mmol) in dry methylene chloride (8 mL) at 0°C was added triethylamine (1.2 mmol) followed by neat (CF₃SO₂)₂O (1.5 mmol). The reaction mixture was stirred for an additional 20 min at 0°C and then concentrated at reduced pressure. Purification by flash chromatography over silica eluting with ether/hexane provided bright orange needles of the triflate **4**. 300 MHz ¹H-NMR **4b** (CDCl₃): 3.89 (s, 3H); 7.02 (d, J = 8.8 Hz, 2H); 7.39 (d, J = 8.8 Hz, 2H); 7.83-7.86 (m, 2H); 8.18-8.26 (m, 2H); **4b** mp=160-162.
- The assignment of the major products as 1,4-naphthoquinone triflates was confirmed by the preparation of known, symmetrical 2,3-diaryl-1,4-naphthoquinones **5** and **9** from **4a** and **4b**, respectively.
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