Cross-Coupling

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Construction of Substituted Benzene Rings by Palladium-Catalyzed Direct Cross-Coupling of Olefins: A Rapid Synthetic Route to 1,4-Naphthoquinone and Its Derivatives**

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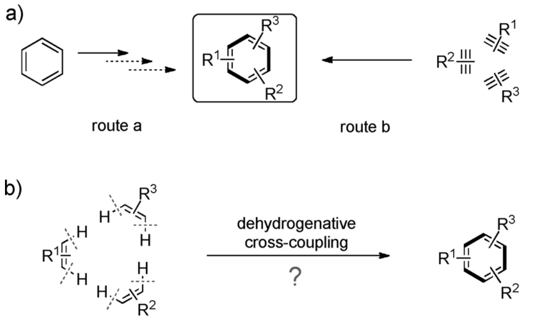
Dedicated to Professor Christian Bruneau on the occasion of his 60th birthday

Benzene rings can be found in about 30% of all industrial chemicals and in over half of the top 50 drugs.[1] This fact clearly illustrates the immense scientific and commercial value of aromatic compounds in modern society. These compounds usually bear more than one substituent on the benzene ring, and are traditionally constructed by the stepwise introduction of substituents through electrophilic aromatic substitution (Scheme 1 a). Because the substituents on benzene rings strongly influence both the reactivity of the rings toward further substitution and the orientation of that substitution, careful choice of the reagents and the synthetic route is crucial to achieve high regioselectivities in the syntheses of polysubstituted benzene rings. Furthermore, in cases in which the substitution pattern of an aromatic compound would direct new substituents into the wrong positions, tedious synthetic routes that involve conversion and/or protection–deprotection of functional groups are often required to access the desired products. An alternative approach to polysubstituted benzene rings is the transition-metal-catalyzed [2+2+2] cyclotrimerization of alkynes.[2] This route has the advantage of the rapid construction of highly functionalized molecular frameworks in one step compared with electrophilic aromatic substitution reactions (Scheme 1 a). By using this strategy, intermolecular reactions provide a versatile tool for the ring synthesis of complex molecular products.[2a] However, intermolecular three-component cross-coupling reactions of alkynes are strictly restricted to specific substrates, and in most cases suffer from a lack of control of chemo- and regioselectivity.[2b]



Scheme 1. a) Existing synthetic routes to substituted benzene rings. Route a: stepwise introduction of substituents to benzene through electrophilic aromatic substitution or C–H functionalization; route b: [2+2+2] cycloaddition of alkynes. b) Construction of substituted benzene rings by cross-coupling of olefins: direct conversion of olefinic C–H bonds to C–C bonds.

The metal-catalyzed direct functionalization of aromatic carbon–hydrogen (C–H) bonds is emerging as an effective means for the elaboration of arenes.[3–6] Despite significant advances in this field, the vast majority of metal-catalyzed aromatic C–H functionalization reactions have focused on C–H arylation[3a–f] and C–H olefination,[3h,6a] and intermolecular reactions for the transformation of C–H bonds into carbon–heteroatom bonds such as C–O and C–N bonds are mainly limited to benzene derivatives that bear pyridyl groups,[6b,c] and heterocycles (such as azoles) that bear acidic C–H bonds.[6d]

Both electrophilic aromatic substitution reactions and metal-catalyzed aromatic C–H functionalization reactions produce benzene derivatives by modifying parent aromatic rings, and thus depend on the nature of the existing substituents. Our interest in the rapid synthesis of substituted benzene rings with diverse substituents and substitution patterns led us to question whether a direct cross-coupling of olefins to generate polysubstituted benzene rings through the conversion of olefinic C–H bonds to C–C bonds might be possible (Scheme 1 b). This cross-coupling reaction of three olefin components would result in substituted products through the actual formation of benzene rings, therefore presenting a fundamentally new approach for the construction of these compounds. However, achievement of this target reaction with high selectivity remains a great challenge because the successive cross-coupling of olefins would be required in this process. Even the metal-catalyzed direct

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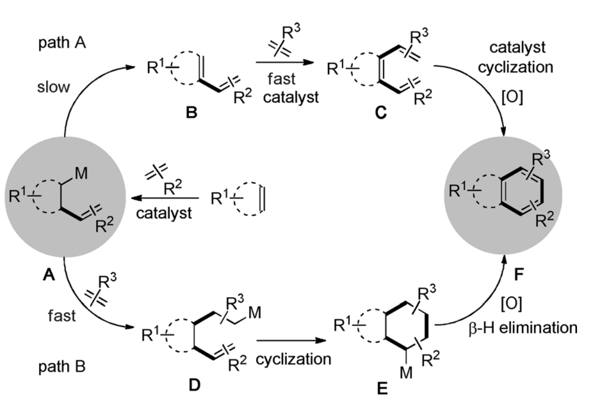
coupling between two different olefin components has hardly been developed, though this reaction provides a highly efficient approach to a diene moiety that is commonly found in naturally occurring compounds. Only four examples of metal-catalyzed cross-coupling of olefins to dienes have been reported since Ishii and co-workers presented the first example in 2004.[7] The paucity of methods for the catalytic cross-coupling of olefins indicates the difficulty for olefins to undergo this type of transformation. In addition to the reactivity issue, another challenge in achieving the cross-coupling of three olefin components is the control of selectivity. All the reported metal-catalyzed cross-coupling reactions of olefins produce the dimerization products without further incorporation of the third olefin component into the molecular framework. For example, ruthenium- or rhodium-catalyzed couplings of two different olefins results in the alkylation of one coupling partner by addition of a C−H bond across a C=C double bond,[8] and palladium-catalyzed reactions generate diene compounds.[7] Therefore, the key to constructing substituted benzene rings by cross-coupling of olefins is to identify an active catalyst system that is capable of catalyzing the cross-coupling of olefins in a domino manner. There are two possible ways to achieve this goal: 1) the catalyst system preferentially promotes the reaction of diene **B** with an olefin rather than the initial formation of diene **B** (path A, Scheme 2); 2) the catalyst system enables the olefin to intercept intermediate **A** prior to its β-hydrogen elimination (path B, Scheme 2). For path B, a strategy to intercept intermediate **A** is the use of a cyclic olefin as one of the coupling partners. The metal/cycloalkyl-complex intermediate derived from the cyclic olefin through the carbometalation of the double bond is reluctant to form a *syn*-coplanar conformation for β-hydrogen elimination and consequently reacts with an additional olefin molecule.

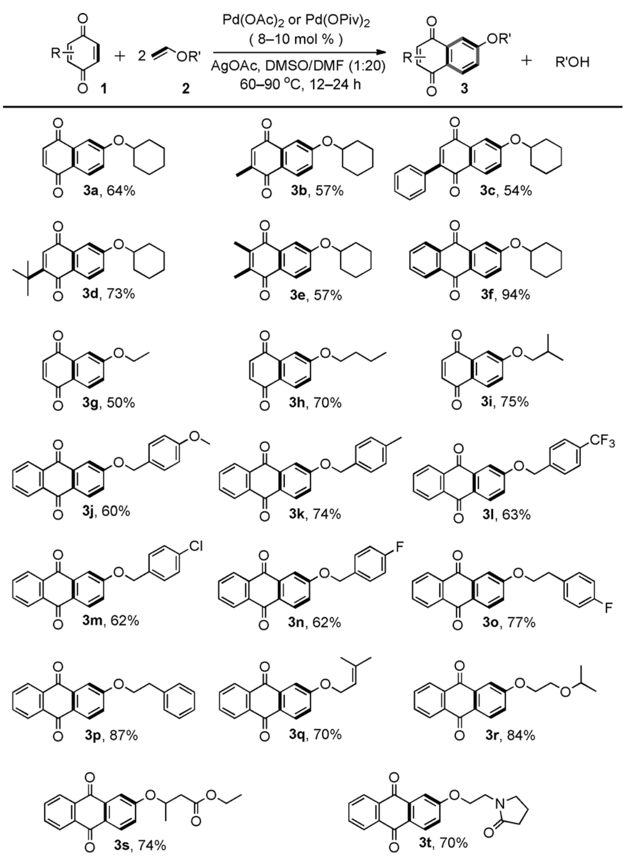


Scheme 2. Construction of substituted benzene rings by cross-coupling of olefins.

Herein, we verify the feasibility of the catalytic cross-coupling of olefins to furnish substituted benzene rings with high selectivity. A versatile catalyst system has been developed for the direct coupling of electron-deficient cyclic olefins (1,4-benzoquinone or its derivatives) with electron-rich olefins (alkyl vinyl ethers) to produce alkoxy-substituted 1,4-naphthoquinones or 9,10-anthraquinones through the construction of benzene rings. This method allows the reaction to occur under mild conditions, and is compatible with a broad range of functional groups. Notably, no product from olefin dimerization was detected in the crude reaction mixture, thus illustrating that this cross-coupling reaction of olefins to produce benzene rings proceeds in a domino manner.

Initially, the reaction of 1,4-benzoquinone (**1a**) with cyclohexyl vinyl ether (**2a**) was chosen as a model reaction for optimization of the reaction conditions. The product of this model reaction, 6-cyclohexyloxy-1,4-naphthoquinone (**3a**), was characterized by NMR spectroscopy and X-ray single-crystal diffraction analysis;[9] the results confirmed that the cross-coupling of olefins to substituted benzene ring was accompanied by loss of an alkoxyl group. A variety of reaction parameters were observed to have an impact on the efficiency of this reaction. Among the palladium sources that were examined, $Pd(OAc)_2$ afforded the best catalytic reactivity. Control experiments showed that palladium sources were indispensable for this reaction to occur. In contrast, other additives, such as silver salts, were not crucial to achieve catalytic turnover. For example, the reaction of two equivalents of **1a** with **2a**, in which **1a** acted as both the reagent and the oxidant, provided **3a** in 44% yield in the absence of AgOAc. However, addition of AgOAc or a combination of Ag_2CO_3 with carboxylic acids considerably enhanced the turnover when **1a** was the limiting reagent. Other oxidants that were commonly used for reoxidation of Pd^0 to Pd^{II}, for example, various Cu^{II} salts, also worked for this reaction but were inferior to AgOAc.[9] A survey of solvents showed that coordinating DMSO was required for this reaction to occur. However, the introduction of DMF or 1,2-dimethoxyethane (DME) as a cosolvent with DMSO significantly improved this reaction compared with the use of DMSO alone, and the variation of concentration of DMSO in a mixed solvent influenced the reaction outcomes. The optimum reaction medium was found to be 5% (v/v) DMSO in DMF. These observations suggested that a palladium complex with DMSO as the ligand may be involved in the catalytic process. This hypothesis was supported by the fact that replacement of DMSO with its analogue tetramethylene sulfoxide gave a comparable result. The combination of these efforts established that the best yield of **3a** (64%) could be achieved by the reaction of **1a** with four equivalents of **2a** conducted in a mixed solvent of DMSO in DMF (5% v/v) at 60 °C for 12 h with 8 mol% $Pd(OAc)_2$ as a catalyst and six equivalents of AgOAc as an oxidant (Scheme 3).[10]

With the optimized reaction conditions established, we next examined the generality of this transformation. As shown in Scheme 3, both mono- and disubstituted 1,4-benzoquinones underwent smooth coupling with **2a** to form the desired products in good yields (**3b**–**3e**). Reactions of monosubstituted 1,4-benzoquinones resulted in a regioisomeric mixture of 6- and 7-substituted 1,4-naphthoquinones with 6-substituted isomers as main products. Interestingly, the regioselectivity toward 6-substituted products could be improved by increasing the steric bulk of the substituents in monosubstituted 1,4-benzoquinones, as illustrated by a comparison between the yields of 2-*tert*-butyl-1,4-benzoquinone

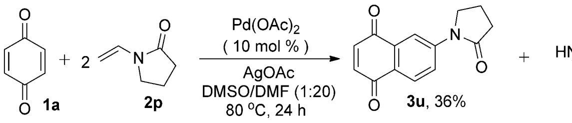


Scheme 3. Substrate scope of Pd-catalyzed direct cross-coupling of olefins for the synthesis of substituted benzene rings. Yields of isolated products are given. The 6-substituted products **3b**, **3c**, and **3d** were formed together with their corresponding 7-substituted isomers **3b′**, **3c′**, and **3d′** (**3b**/**3b′** = 2:1, **3c**/**3c′** = 5:1, **3d**/**3d′** = 6:1). DMF = *N*,*N*-dimethylformamide, DMSO = dimethyl sulfoxide, Piv = pivaloyl.

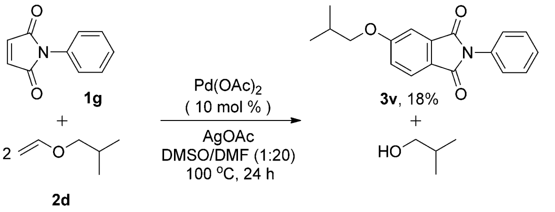
(**3d**) and 2-methyl-1,4-benzoquinone (**3b**). As a coupling partner, 1,4-naphthoquinone exhibited an excellent reactivity in the direct cross-coupling of olefins to substituted benzene rings (**3f**). This reaction tolerated a broad range of substrates with regard to alkyl vinyl ethers (**3g**–**3t**), and was compatible with a variety of functional groups on the alkyl portion of alkyl vinyl ethers; these groups include trifluoromethyl, chlorine, fluorine, alkene, ether, ester, and amide. Although good yields were generally obtained with the examined alkyl vinyl ethers, the observed effects that functional groups had on the reactivity of alkyl vinyl ethers were presumably a result of the electronic factors. For instance, alkyl vinyl ethers with aryl groups at the β position of the ether linkage afforded higher yields than ethers with aryl groups at the α position of the ether linkage (**3n** versus **3o**).

The obtained products, both alkoxy-substituted 1,4-naphthoquinones and 9,10-anthraquinones, are prevalent as building blocks in natural products.[11] Additionally, nickel- or palladium-catalyzed cross-coupling through C−O bond cleavage allows these products to be further elaborated.[12] Compared with the Dötz benzannulation reaction,[13] which produces a substituted hydroquinone by using stoichiometric amounts of toxic chromium carbenes, our protocol is operationally simple. As a result, the reaction reported here will find applications in organic synthesis.

Inspired by the fact that the cross-coupling of olefins to substituted benzene rings occurred between two electronically different olefins, we further expanded the substrate scope of this reaction. As an electron-rich olefin, *N*-vinyl-2-pyrrolidone (**2p**) reacted with **1a** to produce the corresponding product **3u** in 36% yield [Eq. (1)]. *N*-phenylmaleimide (**1g**) could serve as an electron-deficient olefin in the cross-coupling reaction with **2d**, although **3v** was produced in much lower yield [Eq. (2)]. Our attempts to improve the yields of these reactions failed at this stage.



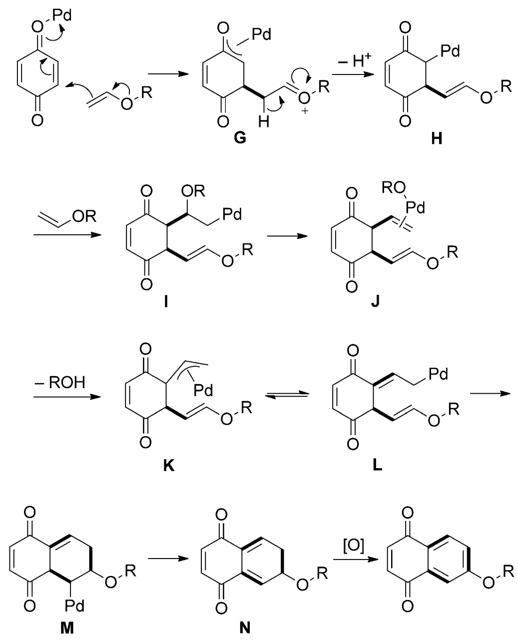
(1)



(2)

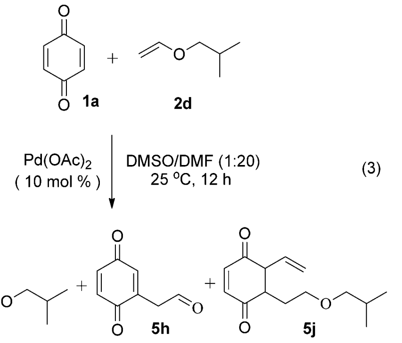
Because the cross-coupling of olefins to substituted benzene rings is similar to the Nenitzecu indole synthesis with respect to the selectivity and the nature of the reactants,[14] it is reasonable to assume that these two reactions share common elementary steps in the initial stages of their catalytic cycles. As in the Nenitzecu indole synthesis, the cross-coupling reaction could be initiated by a palladium-promoted conjugate addition of an electron-rich vinyl ether to 1,4-benzoquinone to generate intermediate **H** (Scheme 4); the Pd salt would act as a Lewis acid catalyst in this reaction.[15] Olefin insertion into the Pd−C bond in intermediate **H** followed by Pd–OR elimination and deprotonation would lead to the formation of π-allyl–palladium complex **K**, which could undergo intramolecular olefin insertion via its tautomer **L** and subsequent β-hydrogen elimination to form intermediate **N**. Finally, oxidative dehydrogenation of intermediate **N** would take place to form the product. Intermediate **N** may form 1,4-naphthoquinone by elimination of ROH, thus explaining the observation that 1,4-naphthoquinone or 9,10-anthraquinone are generated as side products in these transformations (less than 2% yield in all cases).

To support the mechanistic hypothesis, we carried out the reaction of 1,4-benzoquinone with isobutyl vinyl ether at varied temperatures. We anticipated that the reactions at low temperatures may be slow and thus allow us to capture reaction intermediates. GC–MS analysis[9] showed that the reaction that was run for 12 h at room temperature produced



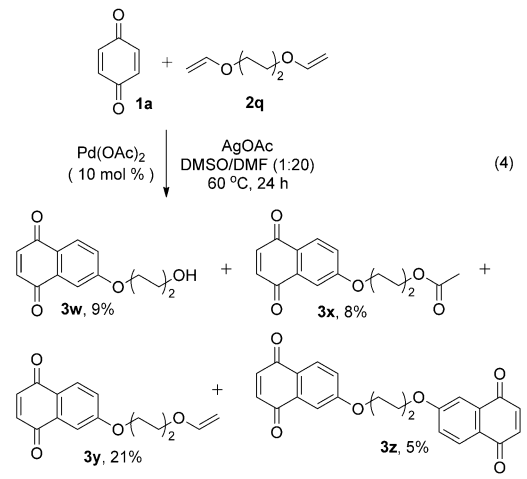
Scheme 4. Proposed mechanism for Pd-catalyzed cross-coupling of olefins to substituted benzene rings.

not only the target compound **3i** but also the two by-products **5h** and **5j** [Eq. (3)]. Compound **5h** may derive from the intermediate **H** by Pd–H elimination and subsequent hydrolysis. Compound **5j** may derive from the intermediate **J** by demetalation and hydrogenation. These two by-products, which were closely related to the above-mentioned reaction intermediates, provided circumstantial evidence for the proposed mechanism. Compound **5h** was also observed in the reaction of **1a** with **2d** at room temperature when 10 mol% of other Lewis acids such as $ZnCl_2$ and AgOTf were used in place of $Pd(OAc)_2$ and AgOAc.[9] In addition, the reaction of **1a** with 1,4-butanediol divinyl ether (**2q**) afforded four products [Eq. (4)], and the formation of **3w** and **3x** clearly illustrated the fate of one of the alkoxy groups of alkoxy vinyl ethers; the group was liberated as ROH during the reaction, a result that was consistent with the mechanistic hypothesis.



(3)

In summary, we have established the palladium-catalyzed direct cross-coupling of electron-deficient 1,4-benzoquinone and its derivatives with a variety of electron-rich vinyl ethers. These reactions occur under mild conditions and furnish substituted benzene rings with high selectivity and in good yields. This work provides the first example of the direct cross-coupling of olefins to substituted benzene rings, and may open up new routes for the synthesis of the latter compounds. Ongoing work is focused on expanding the scope of this transformation with respect to both electron-rich and electron-deficient olefins.



(4)

Experimental Section

In a glove box, a 25 mL tube equipped with a stirrer bar was charged with $Pd(OAc)_2$ (0.02 mmol), 1,4-benzoquinone (0.2 mmol), AgOAc (1.2 mmol or 1.4 mmol), vinyl ethers (0.8 mmol or 1.2 mmol), DMSO (0.1 mL), and DMF (2 mL). The tube was fitted with a Teflon screw cap and removed from the glove box. The reaction mixture was stirred at 60–90°C for 12–24 h. After cooling, the reaction mixture was diluted with diethyl ether (10 mL) and filtered through a pad of silica gel, which was then washed with the same solvent (20–50 mL). The filtrate was washed with saturated aqueous solution of NaCl (30 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was then purified by column chromatography on silica gel with 3–30% diethyl ether in hexane as eluent to provide the corresponding product.

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[10] An excess of the vinyl ether was required to afford a good yield, presumably because the vinyl ether decomposed under the reaction conditions. The best results were obtained when four equivalents of the vinyl ether were used. Optimization studies showed that six equivalents of AgOAc were required to obtain the best yield, and that the use of less than six equivalents of AgOAc decreased the yields significantly, presumably because several Pd^0–Pd^{II} oxidation cycles were involved in this reaction. See the Supporting Information for details.

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