Synthesis of Aryl- and Alkylquinones through Rhodium-Catalyzed C–C Coupling under Mild Conditions

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Abstract: A direct arylation, alkylation of quinones with aryl and alkyl boronic acids through rhodium-catalyzed C–C coupling has been developed under mild conditions. $[Cp^*RhCl_2]_2$ was shown to be the most effective catalyst for the transformation. More importantly, good to excellent yields were obtained under room temperature and base-free conditions. This reaction provides a practical, efficient method for the synthesis of aryl- and alkylquinones.

Keywords: arylation, alkylation, quinones, rhodium, coupling

Aryl- and alkyl-substituted quinones are important natural products for medicinal chemistry, particularly for pharmaceuticals.[1] Many researchers have already found that aryl- and alkyl-substituted quinones have many biological activities.[2] To date, quinones have revealed inhibitory, antibiotic, antiviral, antitumor, antimalarial, and antidiabetic activities, etc.[3] As important inhibitors of β-secretase (BACE1),[4] aryl- and alkyl-substituted quinones could halt the production of β-amyloid peptide by the inhibition of BACE1. Therefore, it has been considered an attractive therapeutic modality for the treatment of Alzheimer's disease.[5] Recently, Bermejo-Bescós et al. conducted tests of several arylquinones as inhibitors (Figure 1).[6] Kingston et al. isolated 2-methoxy-6-pentyl-1,4-benzoquinone (**D**) from the leaves of *Miconia lepidota* present in the forests of Surinam. Alkyl-substituted quinones **D** exhibited antitumor activity toward mutant yeast strains based on *Saccharomyces cerevisiae*.[7,8] Although aryl and alkyl quinones are very useful compounds in medicinal chemistry, only limited methods were found for the preparation arylquinones.[9]

Recently, Molina and Csákÿ developed the first coupling of quinones with arylboronic acids by using palladium as a catalyst.[10a] In 2011, Baran reported the practical C–H functionalization of quinones with boronic acids through silver-catalyzed cross-coupling.[10b] Yu and Zhang described the coupling reaction of quinones with arylboronic acids by an aryl radical transfer pathway.[10c] Bermejo-Bescós and Csákÿ reported the palladium-catalyzed arylation of quinones with arylboronic acids with moderate to good yields.[6] Maiti showed the iron-catalyzed C–H arylation of heterocycles and quinones with arylboronic acids.[10d] Singh and Vishwakarma developed an iron-catalyzed cross-coupling reaction of electron-deficient heterocycles and quinone with organoboron species.[10e] Demchuk reported the arylation of quinones and naphthoquinones by potassium trifluorarylboronates under convenient aerobic reaction conditions.[10f] Komeyama proved that $FeSO_4 \cdot 7H_2O$ was an effective promoter for the direct arylation of benzoquinones with aryl boronic acids.[10g] Herein, we report the rhodium-catalyzed direct C–C coupling of quinones with aryl and alkyl boronic acids with excellent yields (Scheme 1).

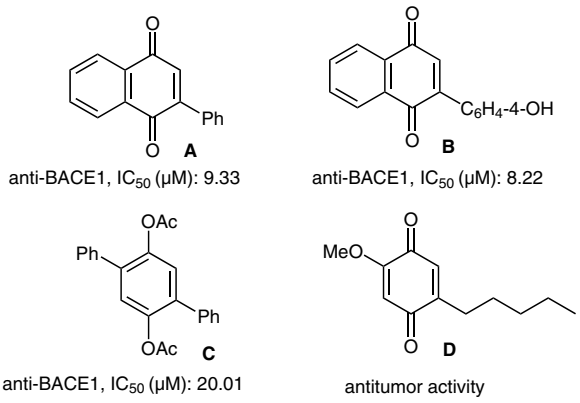
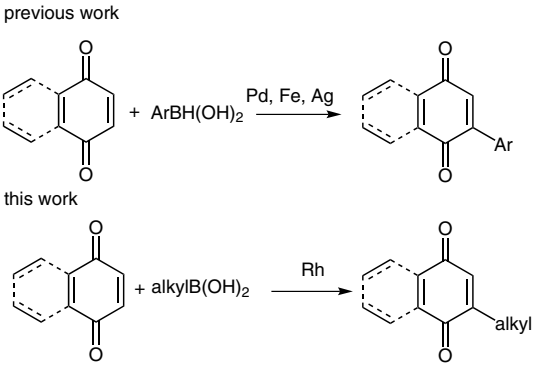


Figure 1 Several selected BACE1 inhibitors



Scheme 1 Synthesis of aryl- and alkyl-substituted quinones

First, we investigated the effect of metal complexes in the direct arylation of benzoquinone with phenylboronic acid. These results are summarized in Table 1. When $[Cp^*RhCl_2]_2$ (5 mol%) was added to a mixture of benzoquinone and phenylboronic acid (1.5 equiv), the desired 2-phenyl-1,4-benzoquinone was obtained at 88% yield (Table 1, entry

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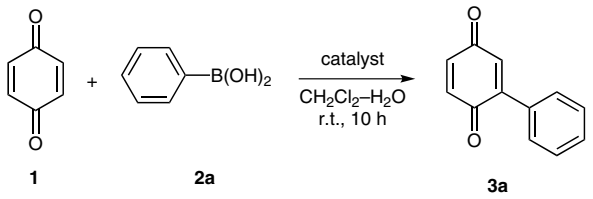
2). Next, we discussed the influence of solvent on the reaction, and the results revealed that a dichloromethane to water ratio of 2:1 was the best ratio for this reaction.

Table 1 Screening of Reaction Conditions[a]



1 2a 3a

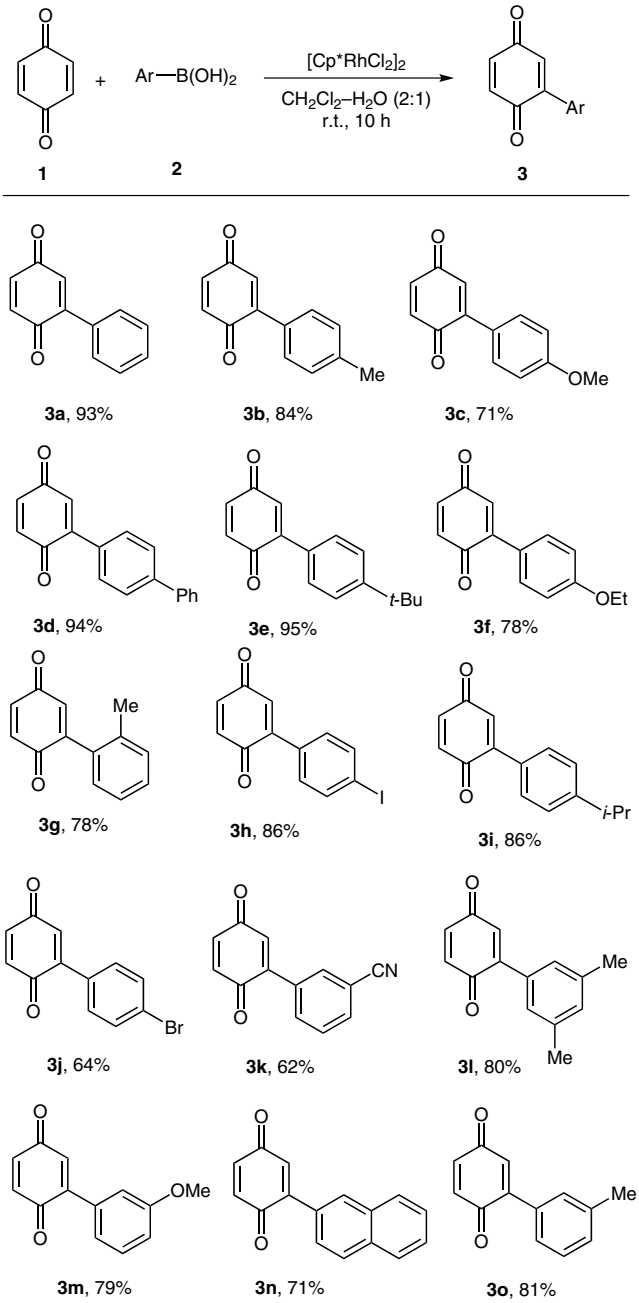
Entry	Catalyst	CH_2Cl_2/H_2O	Yield (%)[b]
1	$RhCl_3$	1:1	23
2	$[Cp^*RhCl_2]_2$	1:1	88
3	$[(COD)RhCl]_2$	1:1	47
4	none	1:1	<5
5	$[Cp^*RhCl_2]_2$	1:2	83
6	$[Cp^*RhCl_2]_2$	1:3	79
7	$[Cp^*RhCl_2]_2$	2:1	93
8	$[Cp^*RhCl_2]_2$	3:1	86

[a] Conditions: benzoquinone (0.5 mmol, 1.0 equiv) phenylboronic acid (1.5 equiv), [Rh] (5 mol%), solvent (3 mL), 10 h, r.t.
[b] Isolated yields based on benzoquinone.

Subsequently, with the optimal reaction conditions in hand, we explored the scope for the cross-coupling reaction of benzoquinone with arylboronic acids. As shown in Scheme 2, various arylboronic acids were smoothly transformed into the corresponding products with moderate to good yields. The scope of the substituents was found to be very broad electron donating, and electron-withdrawing groups were well tolerated. Arylboronic acids with alkyl substitution at any position in the ring reacted well under the standard conditions (**3b**,**e**,**g**,**l**,**o**).

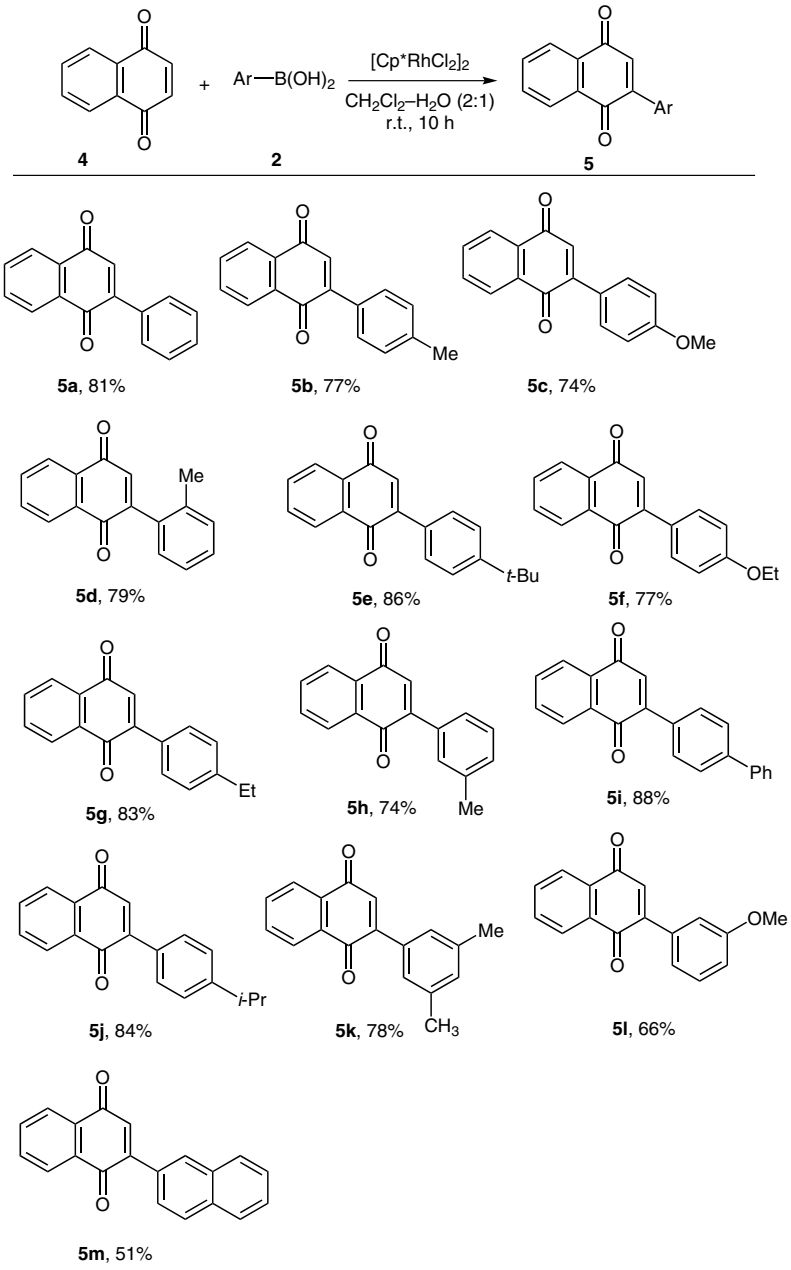
Next, we attempted to apply the upper methodology to the cross-coupling of naphthoquinone with arylboronic acids. Relative to the productive rate of benzoquinone with arylboronic acids, the yield of naphthoquinone with arylboronic acids seemed slightly lower. Generally, however, the reaction could still proceed well with moderate to good yields. As illustrated in Scheme 3, good yields were achieved with nearly all the substituents.

After we finished the direct arylation of quinones with arylboronic acids, we challenged the direct alkylation of quinones with alkylboronic acid. Fortunately, the present method under optimized conditions, when performed with quinones and alkylboronic acid, also resulted in a monoarylated product. As shown in Scheme 4, alkylboronic acids provided coupling products with moderate yields for both linear (**6a**,**b**,**d**,**e**) and cyclic (**6c**,**f**) systems.[11]



Scheme 2 Substrate expansion of quinones. *Reagents and conditions*: benzoquinone (0.5 mmol, 1.0 equiv), arylboronic acid (1.5 equiv), $[Cp^*RhCl_2]_2$ (5 mol%), CH_2Cl_2–H_2O (2:1, 3 mL), 10 h, r.t. Isolated yields, based on benzoquinone, are reported.

Additionally, the rhodium-catalyzed C–C coupling of quinones with boronic acids provides an easy way to prepare inhibitors of β-secretase (BACE1). We could easily obtain 2-phenylnaphthalene-1,4-dione (**A**) with good yield by using this method (Scheme 3, **5a**). For another inhibitor of β-secretase, 2-(4-hydroxyphenyl)naphthalene-1,4-dione (**B**), the coupling product **5c** was converted in one more step by treatment with boron tribromide to remove protecting group (Scheme 5).



Scheme 3 Substrate expansion of naphthoquinones. *Reagents and conditions*: naphthoquinone (0.5 mmol, 1.0 equiv), arylboronic acid (1.5 equiv), $[Cp^*RhCl_2]_2$ (5 mol%), CH_2Cl_2–H_2O (2:1, 3 mL), 10 h, r.t. Isolated yields, based on naphthoquinone, are reported.

In summary, a concise, efficient method with which to obtain aryl and alkyl quinones through rhodium-catalyzed C–C coupling of quinones with aryl and alkyl boronic acids has been developed under room temperature without any base. Moreover, this methodology proves to be a versatile synthetic tool for the preparation of aryl and alkyl quinones, producing good to excellent yields.

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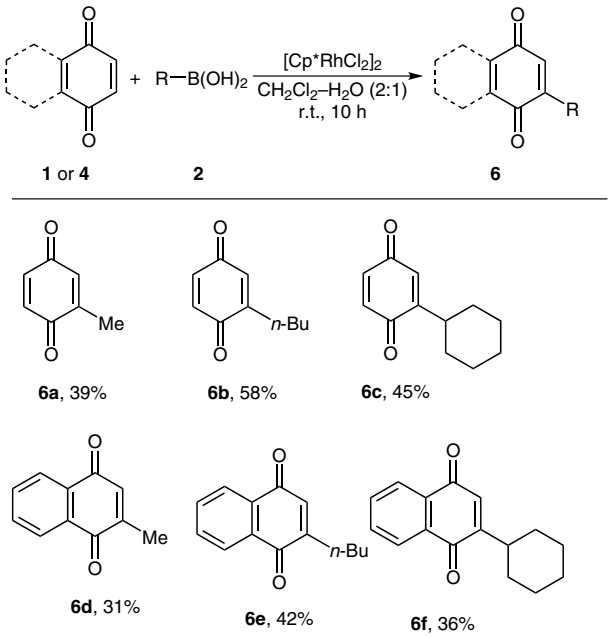
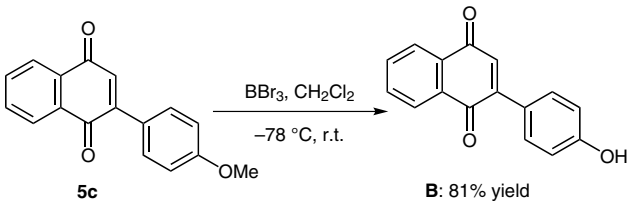


Scheme 4 Substrate expansion of alkyl boronic acids. *Reagents and conditions*: benzoquinone or naphthoquinone (0.5 mmol, 1.0 equiv), alkylboronic acid (1.5 equiv), $[Cp^*RhCl_2]_2$ (5 mol%), CH_2Cl_2–H_2O (2:1, 3 mL), 10 h, r.t. Isolated yields are reported.



Scheme 5 Preparation of BACE1 inhibitor **B**

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(11) **General Procedure for the Reaction of Benzoquinone with Boronic Acid**

To a solution of benzoquinone (0.5 mmol, 1.0 equiv) and $[Cp^*RhCl_2]_2$ (0.025 mmol, 5 mol%) in CH_2Cl_2 (2 mL) was added the boronic acid (0.75 mmol, 1.5 equiv), H_2O (1 mL). Then the solution was stirred vigorously at r.t. for 10 h. Upon completion, the reaction was diluted with CH_2Cl_2 (3 mL) and washed with 5% $NaHCO_3$. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 4 mL), dried over Na_2SO_4, and was evaporated to give the residue. The residue was then purified by column chromatography on silica gel (EtOAc–PE, 1:10) to provide the corresponding product 2-*p*-tolyl[1,4]benzoquinone (**3b**). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39 (d, *J* = 8.2 Hz, 2 H), 7.26 (d, *J* = 8.0 Hz, 2 H), 6.88–6.77 (m, 3 H), 2.40 (s, 3 H).

