Synthesis of 3,4-Disubstituted Quinolin-2(1*H*)-ones via Palladium-catalyzed Regioselective Cross-coupling Reactions of 3-Bromo-4-trifloxyquinolin-2(1*H*)-one with Arylboronic Acids

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Palladium-catalyzed regioselective cross-coupling reactions of 3-bromo-4-trifloxyquinolin-2(1*H*)-one with arylboronic acids provide an efficient and practical route for the synthesis of 3,4-disubstituted quinolin-2(1*H*)-ones.

A goal of chemical genetics is to find small molecules that modulate the individual functions of gene products with high potency and high specificity.[1,2] Natural products and natural product–derived compounds provide many of the most striking examples, particularly in terms of their specificity. It seems unlikely that natural products alone will provide the hypothetical "complete" set of small molecules that would allow the functions of all proteins, as well as their individual domains, to be determined. For chemistry to have its maximal effect on biology, efficient methods for discovering this set of small molecules are in great demand.

The quinolin-2(1*H*)-one core is widely found in various alkaloids, many of which possess interesting biological activity. There has been considerable interest in developing quinolin-2(1*H*)-ones as anticancer,[3] antiviral,[4] and antihypertensive agents.[4] Quinolin-2(1*H*)-ones are also valuable intermediates in organic synthesis, since they are easily converted into 2-chloro- and then 2-aminoquinoline derivatives.[5]

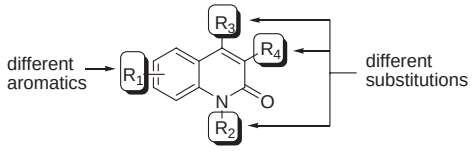
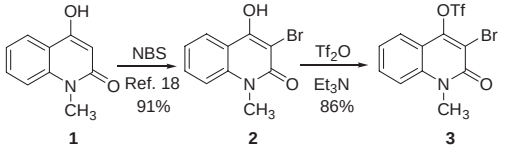


Figure 1. Diversity based on quinolin-2(1*H*)-one scaffold.

Our continued interest to build up a quinolin-2(1*H*)-one based combinatorial library led us to devote our efforts to develop efficient methods for the synthesis of diversified quinolin-2(1*H*)-one molecules. Our library model is shown in Figure 1, which includes four centers for introduction of diversity into quinolin-2(1*H*)-one molecule. We, therefore, initiated a program to develop the corresponding methods for generating a quinolin-2(1*H*)-one library, which includes developing a novel synthetic method to construct 1-substituted-4-hydroxyquinolin-2(1*H*)-one scaffold, and attaching diversified R_3 and R_4 groups to the quinolin-2(1*H*)-one scaffold. Herein, we described our recent efforts for the synthesis of 3,4-disubstituted quinolin-2(1*H*)-ones via palladium-catalyzed regioselective cross-coupling reactions[6] of 3-bromo-4-trifloxyquinolin-2(1*H*)-one (derived from 4-hydroxyquinolin-2(1*H*)-one) with arylboronic acids.

Although there are classic methods for the synthesis of a wide variety of 3- or 4-substituted quinolin-2(1*H*)-ones,[7–9] the utility of these reactions for the synthesis of 3,4-disubstituted quinolin-2(1*H*)-ones is quite limited.[10] On the other hand, several other methods including palladium-catalyzed reactions for the synthesis of 3,4-disubstituted quinolin-2(1*H*)-ones usually suffer from low yields, harsh conditions, and limitation of substrates scope.[11–17] It is of great interest to develop general protocols for the synthesis of 3,4-disubstituted quinolin-2(1*H*)-ones under mild reaction conditions.

Recently, Yang[18] reported Lewis acid $Mg(ClO_4)_2$, combined with NBS, in CH_3CN or EtOAc provided mild and fast bromination of 1,3-dicarbonyl compounds. In particular, this protocol could be applied to the α-monobromination of α-unsubstituted β-keto esters. Inspired by this result, we therefore selected 4-hydroxy-1-methylquinolin-2(1*H*)-one as a model and treated with NBS[18] and Tf_2O subsequently to afford the corresponding 3-bromo-4-trifloxyquinolin-2(1*H*)-one **3** in good yield (Scheme 1).

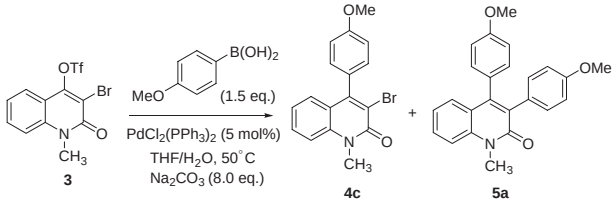


Scheme 1.

We reasoned that the 4-trifloxy group attached to the electron-withdrawing α,β-unsaturated double bond in compound **3** may increase its capability to oxidative addition to the transition metals. Therefore, the regioselective cross-couplings of **3** for the synthesis of 3,4-disubstituted-quinolin-2(1*H*)-ones are possible. Due to their easy handling and long shelf life, arylboronic acid derivatives would be the starting materials of choice. Thus, we started to explore the possibility of using **3** as an electrophile for the Suzuki–Miyaura reaction.[19]

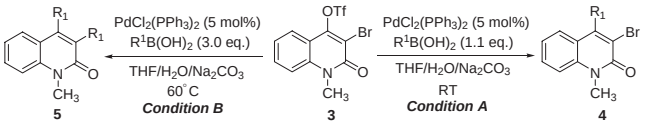
Initial studies were performed by using $PdCl_2(PPh_3)_2$ (5 mol %) as catalyst in the reaction of compound **3** with 4-methoxyphenylboronic acid (1.5 equiv.) at 50 °C (Scheme 2).

To our delight, we observed the formation of the corresponding product **4c** (20% yield) combined with disubstituted product **5a** (60% yield). Fortunately, changing temperature im-



Scheme 2.

Table 1. Palladium-catalyzed cross-coupling reactions of 3-bromo-4-trifloxyquinolin-2(1*H*)-one **3** with arylboronic acids



Entry	R^1	Condition	Product	Yield/%[a]
1	Ph	**A**	**4a**	80
2	2-$MeOC_6H_4$	**A**	**4b**	85
3	4-$MeOC_6H_4$	**A**	**4c**	81
4	3,4-Methylene-dioxyphenyl	**A**	**4d**	71
5	3-NCC_6H_4	**A**	**4e**	72
6	3-$CF_3C_6H_4$	**A**	**4f**	78
7	4-FC_6H_4	**A**	**4g**	69
8	4-$MeOC_6H_4$	**B**	**5a**	87
9	3-NCC_6H_4	**B**	**5b**	73
10	3-$CF_3C_6H_4$	**B**	**5c**	71

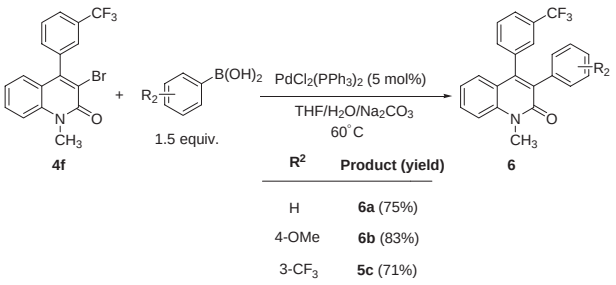
[a]Isolated yield based on 3-bromo-4-trifloxyquinolin-2(1*H*)-one **3**.

proved the reaction selectivity and yield. When the reaction was carried out at room temperature, **4c** was obtained as the major product (78% yield) and only a trace amount of di-substituted product **5a** was detected. When the usage of 4-methoxyboronic acid was reduced to 1.1 equiv., **4c** was the only product (81% yield). Furthermore, when the reaction temperature was elevated to 60 °C, in the presence of 2.5–3.0 equiv. of 4-methoxyboronic acid, only **5a** was generated (87% yield) as expected. Thus, regiocontrolled cross-coupling of 3-bromo-4-trifloxyquinolin-2(1*H*)-one **3** could be fulfilled by tuning the reaction temperature and amount of arylboronic acids.

To demonstrate the generality of this method, the scope of this reaction was investigated and the results are summarized in Table 1. These conditions (condition **A** and condition **B**) have proved to be useful for coupling a range of arylboronic acids. Both electron-rich and electron-poor arylboronic acids which are suitable partners in this process give similar yields. The reactions were very clean and the desired products were afforded in good yields. For example, when 3-trifluoromethylphenylboronic acid was employed in the reaction, 78% yield of the corresponding product **4f** was obtained under condition **A** (Entry 6) and 71% yield of desired product **5c** was generated under condition **B** (Entry 10).

Compound **4** could be further elaborated under the conditions below (Scheme 3). For example, when compound **4f** was employed as substrate in the Suzuki–Miyaura reaction, good yields of the corresponding products were obtained. We were also pleased to find that electron-withdrawing as well as electron-donating substituents attached on arylboronic acid are tolerated under these conditions, although boronic acids with electron-donating group gave better result.

In summary, the palladium-catalyzed regioselective cross-coupling reactions of 3-bromo-4-trifloxyquinolin-2(1*H*)-one with arylboronic acids disclosed herein represent a simple, efficient, and practical synthesis of 3,4-disubstituted quinolin-2(1*H*)-ones. The advantages of this method include good substrate generality, mild reaction conditions, and experimental



Scheme 3.

ease. We believe that this method provides an excellent complement to the palladium-catalyzed 3,4-disubstituted quinolin-2(1*H*)-ones synthesis. Combinatorial synthesis of these natural product-like compounds on solid support is under investigation in our research group.

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