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Ferrocene as a leaving group; Unexpected rearrangement reactions for the synthesis of 2,3-diarylnapthoquinones

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ABSTRACT

In general, Suzuki-Miyaura coupling reaction between aryl bromide and arylboronic acids form the new C-C bond in the presence of Pd-catalyst. In the present study, 2-bromo-3-ferrocenyl-1,4-naphthoquinone 2 intermediate is synthesized by starting from 2,3-dibromo-1,4-naphthoquinone via Suzuki-Miyaura Coupling reaction. Then, it is investigated that the reaction between 2 and arylboronic acids give a new rearrangement reaction involving free radicals. Ferrocene structure displays critical roles for the formation of 2,3-diaryl-1,4-naphthoquinones. This reaction could be first example for the radical C-C bond cleavage reactions including ferrocene.

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1. Introduction

Design and synthesis of new biologically important organic compounds have been gained crucial importance over the last decades. In fact, 1,4-naphthaquinone and their derivatives have been well known organic structures in medicinal and material chemistry.[1] They have two carbonyl groups increasing the activities of naphthaquinones.[2] Moreover, naphthoquinone based structures show different kinds of biological properties. They have been used as antiviral,[3] cardiovascular,[4] antibacterial,[5] antiparasitic,[6] anticancer,[6] and radical scavenging[7] agents. Some of napthaquinones have critical roles for the treatments of some diseases like anticancer[4]. For example, Daunorubicin,[8] Doxorubicin,[9] Mitomycin[10], and Mitoxantron[11] are commercially available naphthaquinone based drugs in the markets. Many naphthaquinone derivatives are isolated from nature.[12] Napthaquinones have been also used as oxidizing agents in organic reactions for the formation of more complex structures.[13]

Ferrocene structure, consisting of two cyclopentadien and an iron, has been used for the preparation of novel organic compounds since 1951.[14] Ferrocene have many vital properties in organic reactions such as; neutral, highly stable and non-toxic compound. Therefore, not only biologically active ferrocene based organic molecules[15] but also high conductive ferrocene based organic materials[16] have been designed and synthesized in last decades. It was reported that ferrocene moities increases biological activities[17] or creates different biological properties. Ferrocenyl aspirin, ferroquine, and ferrocifen are commercial drugs consisting of ferrocene on the structures (Scheme 1).[18]

There are different kinds of ferrocene based organic molecules in literature. If organic molecules are modified with ferrocene moieties, they can be change properties and create new activities [14, 19, 20]. Ferrocene have higher redox properties, with lower oxidation potential, so it may be oxidized easily to form the Fe (+3) isomers. Recently, we synthesized new ferrocene based molecules for optoelectronic and sensor applications (Figure 1).[16, 21] Structure **1** may be new generation small organic structures for organic solar cells, and compound 2 displayed higher sensor activities for the detection of peroxides (Fig. 1).[16] Moreover, Compound 2 has high stability and reproducibility than Pd-based electrochemical sensors.[22]

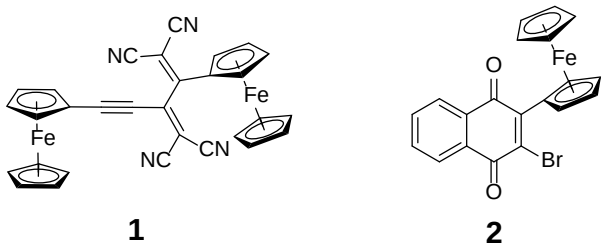

Figure 1. *Previously synthesized ferrocene based molecules.*

In the lights of previous studies, we thought that new ferrocenyl naphthoquinones may be synthesized by using Pd-catalyzed cross coupling reactions. Hence, Pd-catalyst cross coupling reaction was applied for elaboration reactions. Suzuki-Miyaura reactions are most known coupling reactions to form the new carbon-carbon bond between aryl/alkylboronic acids and halogenated aromatics. Suzuki-Miyaura coupling reactions need to aryl halide, aryl/alkyl boronic acids, weak bases and Pd-catalyst. On the other hand, there are a variety of modified reaction procedure in literature. Generally, carbon-carbon bonds between ferrocene moieties and aromatic compounds are very strong, so it is not possible to broken these carbon-carbon bonds. Moreover, there is not any study about ferrocene which was used as a leaving group in literature. In the present study, we investigated a new rearrangement reaction involving free radicals between 2-bromo-3-ferrocene-1,4-naphthoquinone 2 and arylboronic acids. Ferrocene structures played very unique roles for the formation of 2,3-diaryl-1,4-napthquinones (Fig. 2).

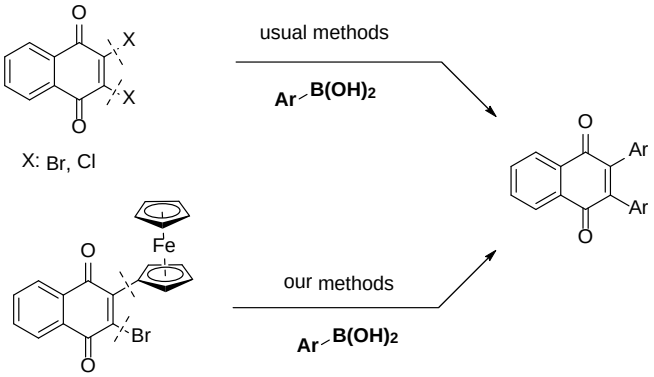

Figure 2. *Synthesis of 2,3-diaryl-1,4-naphthoquinone.*

2. Results and discussion

Naphthoquinone derivatives have been well known organic structures for a variety of applications. They have critical roles not only biological applications, but also material sciences. Recently, we synthesized novel ferrocene based naphthoquinone derivatives, and found its electrochemical properties, there are a few studies about the synthesis of ferrocene based naphthoquinones.[20] In the present study, ferrocenyl-naphthoquinone was prepared by using Suzuki-Miyaura cross-coupling reaction [24] under the mild reaction conditions. There are different kinds of modified Suzuki-Miyaura coupling procedure between boronic acids and halo-substituted aromatics in literature.[25] Our previous study, 2,3-dibromo-1,4-naphthoquinone was reacted with ferroceneboronic acid, under reflux for overnights to gave the 2-bromo-3-ferrocenyl-1,4-naphthoquinone 2 (38% yield) and 2,3-diferrocenyl-1,4-naphthoquinone 5 (17% yield) [16] (Fig. 3**)**.

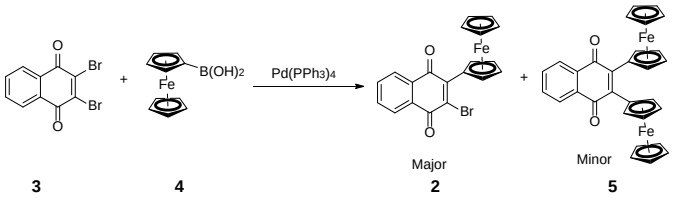

Figure 3. *Synthesis of 2-bromo-3-ferrocenyl-1,4-naphthoquinone **2**.*

After isolation of structure 2, we tried to synthesized 2-aryl-3-ferrocenyl- naphthoquinone (7 and 10) derivatives via Suzuki-Miyaura reactions. When 2-bromo-3-ferrocene-1,4-naphthoquinone 2 was underwent to react with phenylboronic acid 6 with Pd-catalyst under reflux for 24 hours, desired compound 7 was not formed. Unexpectedly, we isolated only 2,3-diphenyl-1,4-naphthoquinone 8 in 49% yield (Fig. 4). The same reaction condition was repeated for the synthesis of compound 10 by the reaction between 2-bromo-3-ferrocene-1,4-naphthoquinone 2 and p-tolylboronic acid 9, 80% yields of compound 11 was isolated after purification (Fig. 4). Unexpectedly, we did not obtain our desired products (7 and 10).

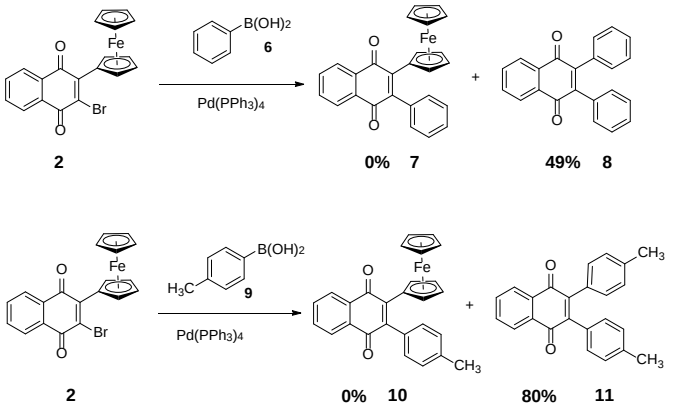

Figure 4. *The reaction between compound **2** and arylboronic acids.*

There are different reaction methodologies for the formation of 2,3-diaryl-1,4-naphthoquinone derivatives in literature. In general, 2,3-diaryl-1,4-naphthoquinones are obtained via Suzuki-Miyaura or Stille cross coupling reactions between 2,3-dibromo/chloro-1,4-naphthoquinones and $ArB(OH)_3$/$ArSnBu_3$. [26] [27] [23] They are also prepared

from the Fischer carbene complex with alkynes.[28] [29] Moreover, Patil et *al*. was reported that oxidative arylation of naphthoquinones using *o*-iodoxybenzoic acid and phenylhydrazines formed the 2,3-diaryl-1,4-naphthoquinones.[30] A new method for the direct arylation of quinones was demonstrated by Baran et *al*. by using arylation agents as $AgNO_3/K_2S_2O_8$ and arylboronic acids for the preparation of arylated quinones.[31] Then, it was found that $FeS/K_2S_2O_8$ catalyst was to be formed the mono-susbtituted quinones under mild reaction conditions.[32] Different kind of boronic acids were undergone to coupling reactions with 1,4-benzoquinone. In 2013, Komeyama et *al.* investigated the direct arylation reactions of benzoquinones with arylboronic acids in the presence of $FeSO_4/ K_2S_2O_8$ catalyst system.[33] Related with these studies, $Fe(acac)_2$, $Fe(NO_3)_3$ and $Mn(OAc)_3$ were also used as a catalyst for the preparation of 2-aryl-1,4-naphthoquinone by the reaction between 1,4-naphthoquinone and arylboronic acids.[34] The direct arylation of quinones with arylboronic acids without any metal catalyst was tested in the presence of $K_2S_2O_8$ by Ilangovan et *al*.[35] They improved that arylboronic acids turned to corresponding aryl radicals before addition of quinones. Therefore, this formation could be important for the proposing reaction mechanism for the formation of 2,3-diaryl-1,4-naphthoquinone derivatives.

The possible reaction mechanism was proposed for the formation of 2,3-diaryl-1,4-naphthoquinones (Fig. 5). Firstly, Suzuki-Miyaura cross coupling reaction between compound 2 and arylboronic acids in the presence of Pd-catalyst was carried out. Oxidative addition, transmetallation and reductive elimination reactions gave the coupled intermediate 15. After formation of intermediate 15, ferrocene moieties may be activated radical reactions, because it was improved that Fe-catalyst help to generation of radical intermediates for the direct arylation of naphthaquinones. As shown in Figure 5, ferrocene may be oxidized to +3, this electron combine with arylboronic acids to form hypothetical intermediates 17. Then, cleavage of the aryl-boron bond produces the nucleophilic aryl radical 18. Subsequent, this radical attack to intermediate 16 for the formation of intermediate 19. Then the final product 20 was obtained by the rearrangement reaction and cleavage C-C bonds between ferrocene and naphthaquinone (Fig. 5).

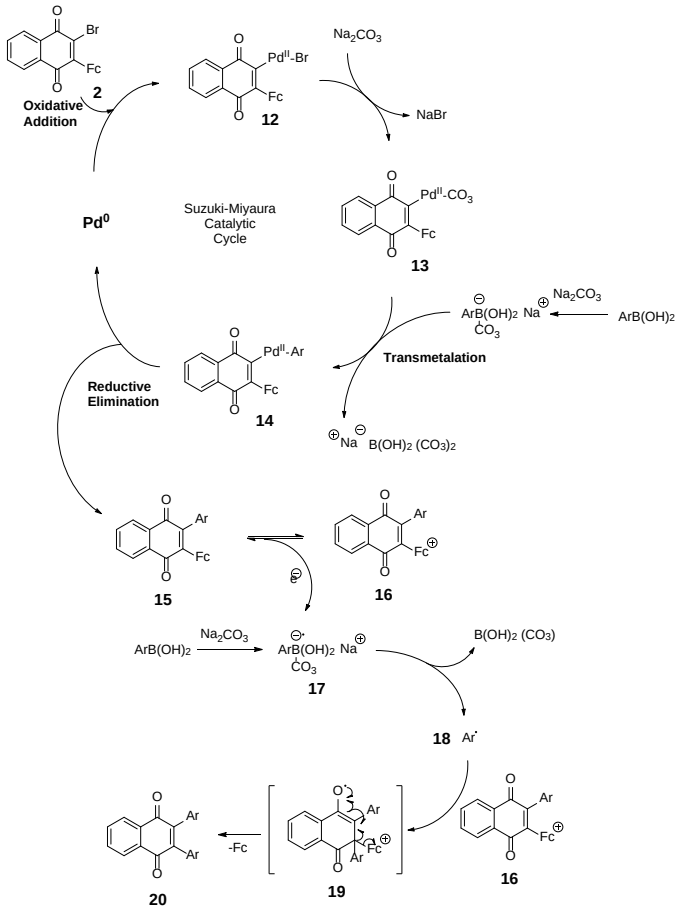

Figure 5. *The plausible reaction mechanism.*

The effects of two ferrocene moieties was also tested for the formation 2,3-diaryl-1,4-naphthaquinones. When diferrocenyl-1,4-naphthaquinone was allowed to react with arylboronic acids by using same reaction conditions (Fig. 6), only starting compound was recovered.

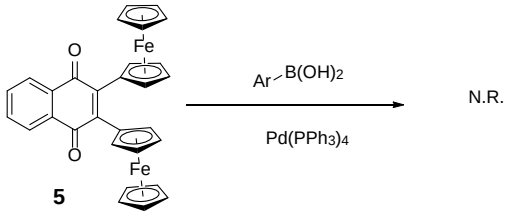

Figure 6. The reaction between 2,3-diferrocenyl-1,4-naphhaquinones.

3. Conclusions

Herein, new rearrangement reactions between 2-bromo-3-ferrocenyl-1,4-naphthoquinone 2 and arylboronic acids was investigated. In the first part, we prepared 2-bromo-3-ferrocenyl-1,4-naphthoquinone 2 by using Suzuki-Miyaura coupling reactions between 2,3-dibromo-1,4-naphthoquinone

and ferrocene boronic acid. Then, new rearrangement reactions involving radical intermediates for the formation of 2,3-diaryl-1,4,-naphthaquinone derivatives was investigated. It could be first example for the C-C bond cleavage of ferrocene structure and naphthoquinones in literature. According to proposed mechanism, ferrocene played very unique roles for the formation of arylation of napthaquinones as a leaving group. As a result, this study could also be useful for the design of novel rearrangement reactions for future chemical synthesis applications.

4. Experimental

2. 1. Synthesis of 2-bromo-3-ferrocenyl-1,4-naphthoquinone

2,3-Dibromo-1,4-naphthoquinone (200 mg, 0.63 mmol) and ferroceneboronic acid (303.4 mg, 1.32 mmol) were stirred in dioxane at room temperature. Then, $Pd(PPh_3)_4$ (34.6 mg, 0.03 mmole), potassium carbonate (552 mg, 3.98 mmole) and water (2 mL) were added under argon atmospheres. The mixture was stirred under reflux at 90 ^oC for 24 hours. The reaction mixture extracted with EtOAc (3x25 mL). The combined organic layers were dried over anhyd. $MgSO_4$ and organic solvent was removed under reduced pressure. Compounds was purified by flash chromatography on silica gel using EtOAc/Hexane (1:19) as the eluent to afford 2,3-diferrocenyl-1,4-naphthoquinone (17%) and 2-bromo-3-ferrocenyl-1,4-naphthoquinone (38%). The spectral data were in agreement with those reported previously for this compound. [16]

2.2. The reaction between 2-bromo-3-ferrocenyl-1,4-naphthoquinone 2 and boronic acids

2.2.1. Synthesis of 2,3-diphenylnaphthalene-1,4-dione 8

2-Bromo-3-ferrocenyl-1,4-naphthoquinone (52 mg, 0.12 mmol), phenylboronic acid (32 mg, 0,25 mmol), $Pd(PPh_3)_4$ (7 mg, 5%) and potassium carbonate (105 mg, 0,75 mmol) were stirred in dioxane/water (16/2 mL) under argon atmospheres. The resulting mixture was undergone to MW irradation at 120 ^oC for 45 minutes. After reaction was over, reaction mixture extracted with EtOAc (3x25 mL). The combined organic layers were dried over anhyd. $MgSO_4$ and organic solvent was removed under reduced pressure. Product was purified by flash chromatography on silica gel using EtOAc/Hexane (1:19) as the eluent to afford 2,3-diphenylnaphthalene-1,4-dione **8** (49% yield). 1H NMR (400 MHz, $CDCl_3$) δ 8.2 (m, 2H), 7.79 (m, 2H), 7.23 (m, 6H), 7.07 (m. 4H); 13C NMR (100 MHz, $CDCl_3$) δ 184.8, 145.8, 133.8, 133.2, 132.1, 130.5, 128.2, 127.6, 126.6. The spectral data were in agreement with those reported previously for this compound.[23]

2.2.2. Synthesis of 2,3-di-p-tolylnaphthalene-1,4-dione 11.

2-Bromo-3-ferrocenyl-1,4-naphthoquinone (52 mg, 0.12 mmol) and p-tolylboronic acid (34 mg, 0,25 mmol) $Pd(PPh_3)_4$ (7 mg, 5%) and potassium carbonate (105 mg, 0,75 mmol) were stirred in dioxane/water (16/2 mL) under argon atmospheres. The resulting mixture was undergone to MW irradation at 120 ^oC for 45 minutes. After reaction was over, reaction mixture extracted with EtOAc (3x25 mL). The combined organic layers were dried over anhyd. $MgSO_4$ and organic solvent was removed under reduced pressure. Product was purified by flash chromatography on silica gel using EtOAc/Hexane (1:19) as the eluent to afford 2,3-di-p-tolylnaphthalene-1,4-dione **11** (80% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 8.2 (m, 2H), 7.77 (m, 2H), 7.05 (d, J = 8 Hz, 4H), 6.99 (d, J = 8.1 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.9, 145.4, 138.0, 133.7, 132.2, 130.5, 130.4, 128.4, 126.5, 21.3. The spectral data were in agreement with those reported previously for this compound.[23]

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