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HIGHLY REGIOSELECTIVE INTRAMOLECULAR BIARYL COUPLING REACTION OF A PHENYL BENZOATE DERIVATIVE FOR THE SYNTHESIS OF GRAPHISLACTONE G

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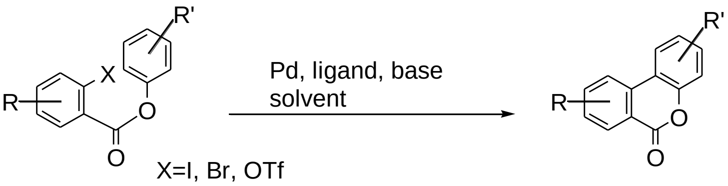
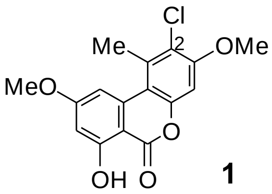
Abstract – The 6*H*-dibenzo[*b*,*d*]pyran-6-one type natural product graphislactone G was synthesized using a palladium-mediated aryl-aryl coupling reaction of the phenyl benzoate derivative. The regioselectivity in the coupling step was also investigated.

A palladium-catalyzed intramolecular aryl-aryl coupling reaction is a useful technique for preparing heterocyclic compounds.[1] For example, phenyl benzoates are good precursors for constructing a 6*H*-dibenzo[*b*,*d*]pyran-6-one ring system (Scheme 1).[2] Using this strategy, we synthesized several natural products possessing a 6*H*-dibenzo[*b*,*d*]pyran-6-one skeleton,[3] such as graphislactones A-D[4] and H,[5] and alternariol.[6,7]



Scheme 1. Intramolecular biaryl coupling reaction of phenyl benzoate

Recently, the total synthesis of graphislactone G (**1**), which is a phenolic constituent isolated from *Cepharosporium acremonium* IFB-E007 in 2005,[8] was reported by Cudaj and Podlech.[9] Structually, compound **1** possesses a highly functionalized 6*H*-dibenzo[*b*,*d*]pyran-6-one ring system and has a chlorine atom at the 2-position. Biologically, **1** is cytotoxic to the SW1116 cell line.[8] In



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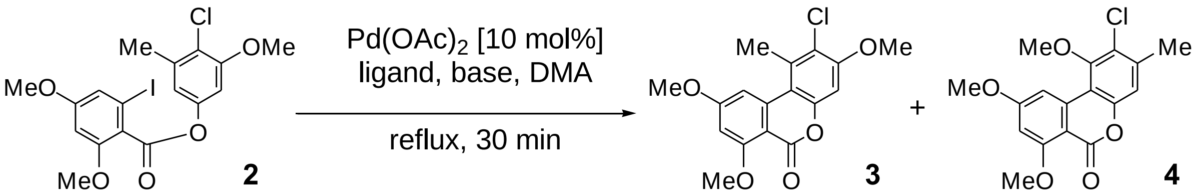
the Podlech's synthesis, they employed the Suzuki-Miyaura coupling reaction as the key step.[9]

In this study, we planned the synthesis of **1**, using the intramolecular aryl-aryl coupling reaction of a phenyl benzoate derivative. Initially, we prepared the ester (**2**) by simple condensation between the corresponding phenol and benzoic acid derivative as a precursor for the intramolecular biaryl coupling reaction. Several reaction conditions were examined for the palladium-mediated biaryl coupling of **2** in order to construct the 6*H*-dibenzo[*b*,*d*]pyran-6-one skeleton (Table 1).

Table 1. Reactivity and regioselectivity in the palladium-mediated biaryl coupling



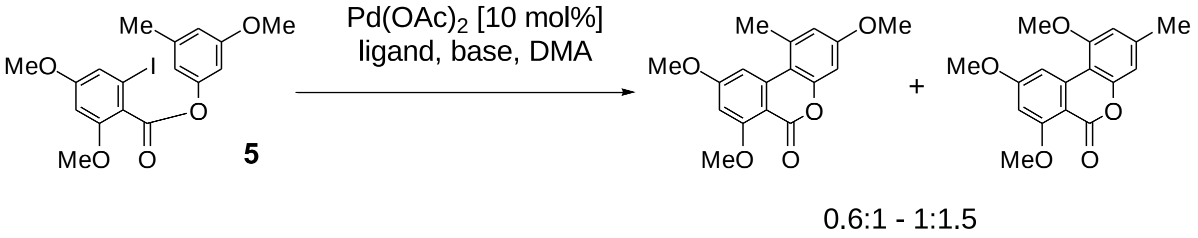
Run	Ligand [mol%]	Base	Yield (%) **3** + **4**	Ratio a) **3** : **4**
1	P(*o*-tolyl)$_3$ [20]	K_2CO_3	63	>20 : 1
2	PPh_3 [20]	K_2CO_3	68	11 : 1
3	^{n}Bu$_3$P [20]	K_2CO_3	57	7.7 : 1
4	DPPP [10], ^{n}Bu$_3$P [10]	Ag_2CO_3	80	1.4 : 1

a) Determined by NMR analysis

In each case, the coupling reaction proceeded smoothly, producing the lactone compounds **3** and **4** in moderate to good yield. The product ratio of **3** and **4** changed dramatically with the reaction conditions. When P(*o*-tolyl)$_3$ was used as the ligand, extremely high regioselectivity was observed (run 1), generating the product **3**, which was reacted at the position *ortho* to the methyl group. By contrast, the DPPP-^{n}Bu$_3$P combination system[10] was not effective for regioselectivity (run 4).

These results are very different from our previous report on the synthesis of alternariol, in which the similar coupling reaction of **5** proceeded with the regioselectivity of 0.6:1 to 1.5:1 ratio (Scheme 2).[6] This difference of selectivity indicates that the chlorine atom on the phenoxy group exhibits a powerful directing property in the coupling reaction. The mechanistic aspect of this selectivity is being studied intensively in our laboratory.

Using the major cyclized product **3**, selective demethylation was achieved with Node's protocol ($AlCl_3$-NaI/MeCN-CH_2Cl_2, 0 °C to rt, 84%),[11] to complete the synthesis of graphislactone G (**1**). The ^{1}H- and ^{13}C-NMR data of the product were identical to those reported by Podlech *et al*.[9]



Scheme 2. Intramolecular biaryl coupling reaction of **5**

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