

Pd-catalyzed Cyclization of Terminal Alkynes using Diazonaphthoquinones: Synthesis of Naphtho[1,2-*b*]furans

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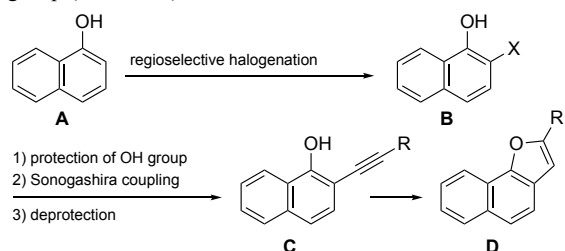
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Naphtho[1,2-*b*]furans were synthesized via a Pd-catalyzed reaction of diazonaphthoquinones and terminal alkynes in the presence of CuI and diisopropylamine. This method was then successfully applied to the synthesis of natural product, furomollugin.

Keywords: Diazo compound, Palladium, Naphthofuran

The main text of the article should appear here with headings as appropriate. Naphthofuran and its derivatives, which are often found in nature, have significant biological and pharmacological properties.¹ Naphthofurans can be synthesized in a method similar to the preparation of benzofuran, which involves the cyclization of 2-alkynyl-1-phenol derivatives.^{2,3} However, several synthetic challenges have remained with respect to the preparation of the precursor for this cyclization. For example, in the preparation of 2-alkynyl naphthol **C**, which is the precursor for naphtho[1,2-*b*]furan **D**, it is required to perform a regioselective halogenation of naphthol **A** and a series of protection and deprotection reactions of the hydroxyl group (Scheme 1).⁴



Scheme 1. Synthesis of naphtho[1,2-*b*]furan.

2-Diazonaphthalen-1-(2*H*)-ones

(diazonaphthoquinones, DNQs)⁵ are unique α -diazocarbonyl compounds that have an aryl diazonium resonance form (Figure 1) and are commonly used as photoresists.⁶ DNQs are regarded as protected naphthol derivatives and are potentially good aromatic building blocks, especially for naphthol derivatives. Previously, we have developed an efficient regioselective method for the synthesis of DNQs from the corresponding naphthols via a diazo-transfer with 2-azido-1,3-dimethylimidazolium chloride (ADMC).⁷ This approach allowed the regioselective synthesis of 2-diazonaphthalen-1-(2*H*)-ones from 1-naphthols through a reaction with ADMP. Additionally, we have also investigated the metal-catalyzed synthesis of substituted-naphthol derivatives using DNQs.^{8,9}

Recent studies have extensively investigated the Pd-catalyzed cross coupling using α -diazocarbonyl compounds via a migratory insertion of a ligand on palladium carbene.^{10,11} In fact, we have already successfully synthesized 2-arylnaphthol through a Pd(OAc)₂-catalyzed cross coupling between DNQ and aryl boronic acid.^{9a} In a continuation study on the Pd-catalyzed cross-coupling

reaction of DNQ, we focused on the reaction with alkyne derivatives.

Although the metal-catalyzed reaction between DNQ and alkyne has not yet been reported, reactions between α -diazocarbonyl compounds and alkynes have been previously attempted and several efficient methodologies such as furan synthesis,¹² alkynylation,¹³ and allenylation¹⁴ have been developed. In the furan synthesis approach, the Rh-catalyzed reaction via cyclopropanation and the successive ring opening reaction were initially developed,^{12a} with several metals being tested for the reactions.¹² Recently, Wang et al. reported the Cu-catalyzed synthesis of furan derivatives through a cascade coupling/cyclization of terminal alkynes using α -diazocarbonyl compounds via Cu-carbene.^{12k,1}

In this work, we examined the Pd-catalyzed reaction of DNQ with alkyne, and developed a new method for the synthesis of naphtho[1,2-*b*]furan.

Our study was initiated with the reaction of alkynyl stannane and DNQ in the presence of Pd(0), with the aim to form 2-alkynynaphthalene. The cross-coupling between (tert-butyl)dimethylsilyl)ethynyl stannane and DNQ **1a** proceeded with the addition of catalytic amounts of Pd(OAc)₂ and 1,1'-bis(diphenylphosphino)ferrocene (DPPF) in the presence of LiCl in DMF to afford 2-alkynyl naphthalene **2** (Table 1, run 1). In the reaction with alkyl- and phenyl-substituted alkynyl stannanes, the formation of 2-alkynyl naphthalenes **2** was initially observed by thin layer chromatography (TLC), but these were later consumed to afford naphtho[1,2-*b*]furan **3** (runs 2 and 3). By adding CuI to the reaction mixture, the formation of 2-alkynyl naphthalene **2** was not detected, and naphthofuran **3c** was obtained as a sole product (run 4). In addition, when the reaction was carried out using 1-hexyne as a coupling partner via copper acetylide in the presence of K₂CO₃, naphthofuran was formed (run 5). Therefore, naphtho[1,2-*b*]furan derivatives could be successfully synthesized by the Pd-catalyzed reaction of DNQ without using toxic alkynyl stannanes.¹⁵ In order to develop an efficient synthetic method of naphtho[1,2-*b*]furan in particular, we then focused on the Pd-catalyzed reaction of DNQ and terminal alkynes in the presence of Cu salt.

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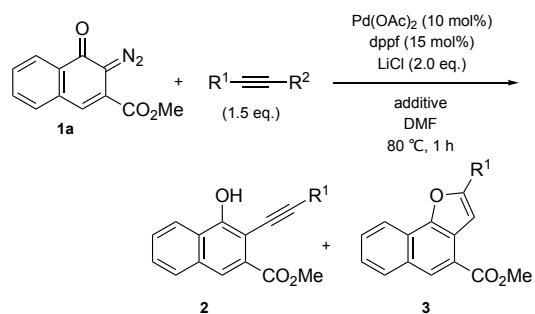
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Table 1. Pd-catalyzed coupling of DNQ **1a** and alkynyl stannanes.



Run	R ¹	R ²	Additive (equiv.)	Product (Yield/%)
1 ^a	TBS	<i>n</i> -Bu ₃ Sn	-	2a (46) 3a (0)
2 ^a	Ph	<i>n</i> -Bu ₃ Sn	-	3b (40)
3 ^a	<i>n</i> -Bu	<i>n</i> -Bu ₃ Sn	-	3c (24)
4 ^a	<i>n</i> -Bu	<i>n</i> -Bu ₃ Sn	CuI (2)	3c (68)
5 ^b	<i>n</i> -Bu	H	CuI (2) K ₂ CO ₃ (2)	3c (70)

^aThe reaction was performed at 80 °C as a bath temperature. ^bThe reaction was performed in the presence of 1-hexyne (3.0 equiv.) and K₂CO₃ (2.0 equiv.) at 40 °C for 30 min and then 60 °C for 40 min.

Initially, the reaction conditions were optimized from the reaction between DNQ **1a** and 1-hexyne (Table 2). When the reaction was carried out at 50 °C with 10 mol% Pd(PPh₃)₄, 30 mol% CuI, and 2 equiv. K₂CO₃ in DMF for 3 h, the simple coupling product **2** was not obtained and instead, naphthofuran **3c** was obtained in 18% yield (run 1). Then, we examined several combinations of palladium, phosphine, and copper reagents (runs 2-4). As a result, the use of Pd(OAc)₂ with DPPF in combination with CuI improved the reaction significantly, giving **3c** in 69% yield (run 4). In addition, *i*-Pr₂NH was found to be the best base among the ones tested (runs 4-7), with naphthofuran **3c** being formed in 87% when 1.2 equiv. of *i*-Pr₂NH was used (run 8).

Further optimization studies on the reaction conditions, including solvents (runs 9-12) and catalyst loading (runs 8 and 13), revealed that 1.5 mol% Pd(OAc)₂ with 2.2 mol% DPPF and 4.5 mol% CuI in DMF in the presence of 1.2 equiv. *i*-Pr₂NH at 50 °C efficiently afforded **3a** in 87% yield (Run 13). Although **3a** was still obtained in a reasonable yield (72%) when catalytic amounts (10 mol%) of *i*-Pr₂NH were used instead (run 14), no cyclized product **3a** was formed in the absence of base (run 15). As shown from the results of runs 16-18, the addition of a Pd catalyst, Cu salt, and DPPF is indispensable for this cyclization reaction.

Notably, when Pd(0) complex such as Pd₂(dba)₃ [tris(dibenzylideneacetone)dipalladium] was used instead of Pd(OAc)₂, **3a** was obtained in 89% (run 19). In the reaction with Pd₂(dba)₃, the presence of DPPF was also important for the efficient cyclization (runs 19 and 20).

These results suggested that the Pd(OAc)₂-catalyzed reaction proceeded via a Pd(0)-cycle, and that DPPF was used not only as a reductant of the Pd(II) complex but also as a suitable ligand for the Pd(0) complex in the cyclization.

Table 2. Optimization studies on the synthesis of naphthofuran **3c**^a

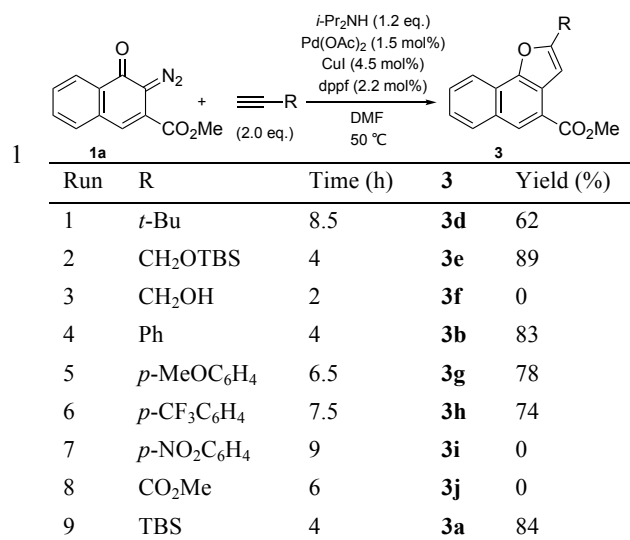
Run	Pd(OAc) ₂ (mol%)	DPPF (mol%)	CuI (mol%)	Base (equiv.)	T ^b (h)	Yd ^b (%)
1	- ^c	-	30	K ₂ CO ₃ ^d	3	18
2	10	- ^e	30	K ₂ CO ₃ ^d	2	22
3	10	- ^f	30	K ₂ CO ₃ ^d	2	3
4 ^g	10	15	30	K ₂ CO ₃ ^d	1	69
5	10	15	30	Et ₃ N ^d	4.5	62
6	10	15	30	Et ₂ NH ^d	5	60
7	10	15	30	<i>i</i> -Pr ₂ NH ^d	5	77
8	10	15	30	<i>i</i> -Pr ₂ NH ^h	4.5	83
9 ⁱ	10	15	30	<i>i</i> -Pr ₂ NH ^h	7	45
10 ^j	10	15	30	<i>i</i> -Pr ₂ NH ^h	8	9
11 ^k	10	15	30	<i>i</i> -Pr ₂ NH ^h	6	42
12 ^l	10	15	30	<i>i</i> -Pr ₂ NH ^h	4.5	26
13	1.5	2.2	4.5	<i>i</i> -Pr ₂ NH ^h	4.5	87
14	1.5	2.2	4.5	<i>i</i> -Pr ₂ NH ^m	9	72
15	1.5	2.2	4.5	-	5	0
16	-	2.2	4.5	<i>i</i> -Pr ₂ NH ^h	5	0
17	1.5	2.2	-	<i>i</i> -Pr ₂ NH ^h	4	0
18	1.5	-	4.5	<i>i</i> -Pr ₂ NH ^h	5	trace
19	- ⁿ	2.2	4.5	<i>i</i> -Pr ₂ NH ^h	3	89
20	- ⁿ	-	4.5	<i>i</i> -Pr ₂ NH ^h	5	2

^aReaction conditions: **1a** (0.5 mmol), 1-hexyne (2.0 equiv.), cat. Pd(OAc)₂, CuI, DPPF, base in DMF (5 mL) at 50 °C. ^bT: Temperature. Yd: Yield. ^c10 mol% Pd(PPh₃)₄ was used instead of Pd(OAc)₂. ^d2 equiv. of base were used. ^e30 mol% PPh₃ was used instead of DPPF. ^f30 mol% *t*-Bu₃P-HBF₄ was used instead of DPPF. ^gWhen Cu(MeCN)₄PF₆, Cu(OTf)₂, Cu(OAc)₂, and Cu powder was used instead of CuI, **3c** was obtained in 59, 60, 49, and 12%, respectively. ^h1.2 equiv. of base was used. ⁱIn THF. ^jIn MeCN. ^kIn toluene. ^lIn (ClCH₂)₂. ^m0.1 equiv. of base was used. ⁿ0.75 mol% Pd₂(dba)₃ was used instead of Pd(OAc)₂.

Then, having established the optimized reaction conditions, the scope of the cyclization reaction of terminal alkynes and DNQ was explored.

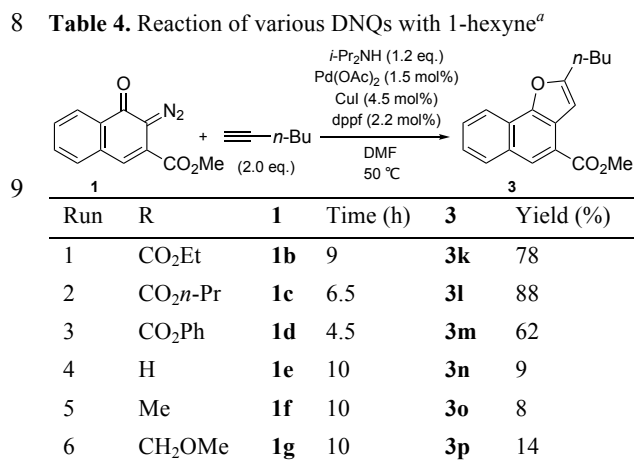
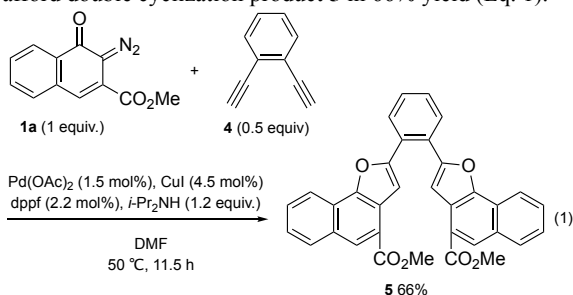
First, the substituent effect of terminal alkynes was examined (Table 3). Various terminal alkynes with alkyl, aryl, and silyl groups, including bulky *tert*-butyl and *tert*-butyldimethylsilyl (TBS) groups, reacted with DNQ **1a** to afford the corresponding naphthofurans. However, no cyclized product was obtained from the reaction with propargyl alcohol or alkynes substituted with strong electron withdrawing groups (runs 3, 7, 8).

Table 3. Reaction of DNQ with various terminal alkynes^a



2 ^aReaction conditions: **1a** (0.5 mmol), alkyne (2.0 equiv.), Pd(OAc)₂
 3 (1.5 mol%), CuI (4.5 mol%), dppf (2.2 mol%), *i*-Pr₂NH (1.2 equiv.) in
 4 DMF (5 mL) at 50 °C.

5 The reaction of **1a** with diyne **4** also proceeded to
 6 afford double cyclization product **5** in 66% yield (Eq. 1).



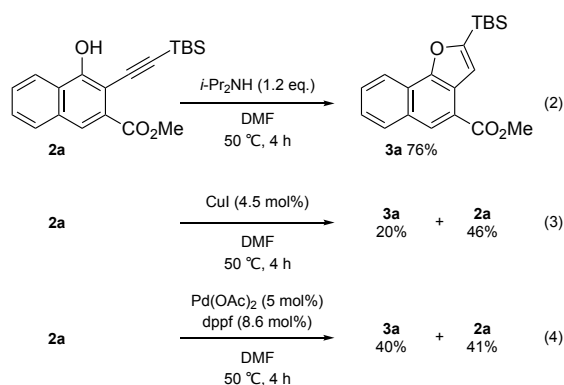
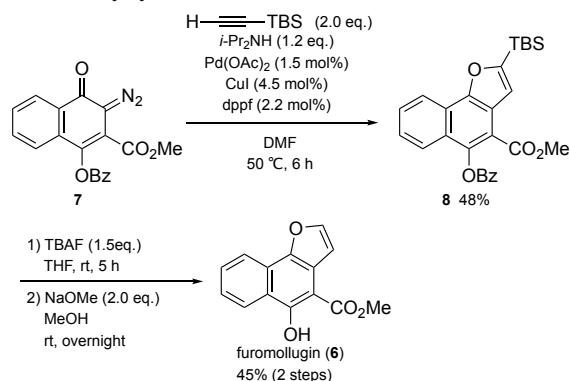
10 ^aReaction conditions: **1** (0.5 mmol), 1-hexyne (2.0 equiv.), Pd(OAc)₂
 11 (1.5 mol%), CuI (4.5 mol%), dppf (2.2 mol%), *i*-Pr₂NH (1.2 equiv.) in
 12 DMF (5 mL) at 50 °C.

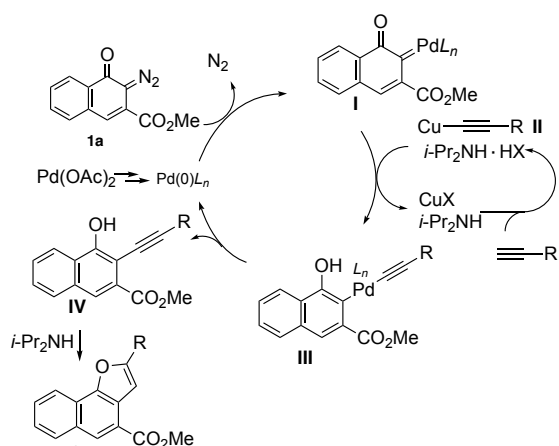
13 Next, various 3-substituted DNQs **1** were examined
 14 for the naphthofuran formation. As a result, we found that the
 15 cyclization was strongly affected by the substituents (Table 4).
 16 When substituent R at C-3 position of DNQ was an ester group,
 17 the cyclization proceeded efficiently (runs 1-3). However,

18 unsubstituted or alkyl-group substituted DNQ **1e-g** gave
 19 naphthofuran **3n-p** in lower yield (runs 4-6).

20 To demonstrate the efficiency of our newly developed
 21 method for naphthofuran formation, we addressed the synthesis
 22 of the natural product furomollugin (**6**) (Scheme 2).¹⁶

23 The Pd-catalyzed cyclization of 3-methoxycarbonyl-
 24 4-benzoyloxy diazonaphthoquinone **7** with (*tert*-
 25 butyldimethylsilyl)acetylene in the presence of CuI proceeded
 26 expectedly to afford naphthofuran **8** in 48% yield. After the
 27 removal of the TBS group using tetrabutylammonium fluoride
 28 (TBAF) and the subsequent removal of the benzoyl group via
 29 treatment with sodium methoxide, furomollugin (**6**) was
 30 successfully synthesized.





Scheme 3. Possible reaction mechanisms

In conclusion, we found that the Pd-catalyzed cross-coupling between (*tert*-butyldimethylsilyl)ethynyl stannane and DNQ could successfully proceed to afford alkynyl naphthol. In this work, we developed a method for the synthesis of naphtho[1,2-*b*]furans via a Pd-catalyzed reaction of DNQ and terminal alkynes in the presence of CuI and *i*-Pr₂NH. This approach was then successfully applied to the synthesis of fumomollugin. Currently, we are continuously working on the development of a new method to the preparation of aromatic compounds with the use of diazonaphthoquinone.

Supporting Information

Electronic Supplementary Information (ESI) available: experimental procedures and characterization data, including ¹H and ¹³C NMR spectra for new compounds (file type, i.e., PDF). Supporting Information is available on http://dx.doi.org/10.1246/cl.*****.

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