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# Synthesis of indolequinones via a Sonogashira coupling/cyclization cascade reaction

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**abstract**— A mild strategy for constructing indolequinone motifs is described on the basis of the Sonogashira reactionand a copper-catalyzed intramolecular cyclization cascade reaction. The first step involves the palladium-and copper-catalyzed reaction between halogenated naphthoquinone and terminal acetylene to generate a coupling product, which then reacts in a copper-catalyzed intramolecular cyclization withthe nitrogen functional group adjacent to the carbon–carbon triple bond.

**Keywords:** Indolequinones Sonogashira coupling Cascade reaction Copper Palladium

Heterocycles, particularly indoles, are interesting and valuable because they are widely found in various biologically active natural and artificial compounds.[1] Therefore, development of efficient methods to synthesize these compounds continues to be an active research area. In particular, the intramolecular cyclization of o-alkynylanilines, which is typically prepared from o-haloanilines via the Sonogashira reaction, has been widely reported. [2,3] Despite the early successes using this method, there are limited applications for synthesizing indolequinones. These motifs are often found in antitumor agents such as mitomycin C[4] and EO9.[5] Recently, Shvartsberg group reported the stepwise synthesis of indolequinones from 3-acetylamino-2-bromo-1,4-naphthoquinone and terminal acetylenes by the Sonogashira reaction followed by the intramolecular cyclization of the isolated coupling products with $K_2CO_3$ in MeCN at 80 ℃.[6] Some significant drawbacks of this method are the limitation of substituents on naphthoquinone substrates and the undesired elimination reactions during the cyclization step. In addition, we found that the dehalogenated compound of starting naphthoquinone **1a** was gradually formed during the reaction with increasing temperature. Thus, development of one-pot synthesis of indolequinones under mild conditions is still challenging in organic synthesis (Scheme 1). Herein, we describe the development of a cascade reaction for constructing indolequinone motifs involving the Sonogashira reaction and intramolecular cyclization.

To screen the optimal reaction conditions, 2-bromo-3-(methylamino)naphthalene-1,4-dione (**1a**) having an electron-donating substituent on amino group was selected, because no coupling reaction was observed under the reported conditions.[6] The results are shown in Table 1. According to the procedure in the Castro–Stephens reaction,[7] the reaction of **1a** with **4a** (10 equiv with respect to **1a**) in the presence of $Cu_2O$ (1 equiv with respect to **1a**) and pyridine (50 equiv with respect to **1a**, pyridine:copper = 25:1) in DMF at room temperature was examined. However, no conversion was observed. Alternatively, adding of 3 mol % Pd $(OAc)_2$ to the reaction mixture showed a mild conversion to the coupling product **2aa** and the cyclized product **3aa** in 3% and 6% yields, respectively (Table 1, entry 2). The use of 20 equiv of pyridine (pyridine:copper = 10:1) did not give the desired product, while 100 equiv of pyridine (pyridine:copper = 50:1) gave the desired product in moderate yield (41%) (Table 1, entry 3). Moreover, the use of 200 equiv of pyridine (pyridine:copper = 100:1) was not effective in increasing the yield further, which suggests that the optimum amount of pyridine is 100 equiv (pyridine:copper = 50:1). In addition, using 200 equiv of pyridine decreased the yield because of a slower cyclization process (Table 1, entry 4). The best result was obtained using 2.0 equiv of acetylene **4a** with respect to **1a** with a reaction time of 24 h (Table 1, entry 5). Regardless of the amount of acetylene, coupling reactions were completed within about 4 h (TLC monitoring). We

speculate that the cyclization process starts from the ligation of the acetylene moiety of the coupling product **2aa** to the copper atom. Therefore, decreasing the amount of acetylene **4a** probably made the cyclization reaction faster. Decreasing the amount of $Cu_2O$ caused no cyclized products to form after 48 h (Table 1, entry 6).[8] Meanwhile, increasing the amount of $Cu_2O$ or $Pd(OAc)_2$ did not improve the yield either (Table 1, entries 7 and 8). The reaction with other copper(I) salts (CuBr, CuI)[9] yielded trace amounts of the cyclized product (Table 1, entries 9 and 10). Using DMF as a solvent is not essential, although the yield of **3aa** slightly decreased in the absence of DMF (Table 1, entry 11). [10] Iodide **1b** was also tested as a substrate in this reaction, and a slightly better yield was obtained compared to that obtained when using bromide **1a** as the substrate (Table 1, entry 12). Some palladium catalysts, such as $Pd(PPh_3)_2Cl_2$ and $Pd(PPh_3)_4$ were also used, but they gave a lower yield of **3aa** and formed byproducts such as the dehalogenated compound of **1a**.[11]

Further investigations were performed by varying the substituents on pyridine. The results are summarized in Table 2. Reaction of **1a** with 2,4-dimethylpyridine and 4-methylpyridine gave products **3aa** in 33% and 55% yields, respectively (Table 2, entries 2 and 3), while reaction with 2,6-dimethylpyridine, having a sterically hindered nitrogen atom, gave no cyclized product owing to the formation of unknown byproducts (Table 2, entry 1). Triethylamine was ineffective in promoting the coupling reaction of halogenated naphthoquinone **1a** with acetylene **4a**, although it is generally used as a base in the Sonogashira reaction (Table 2, entry 4). These results suggest that pyridine acts both as a base to deprotonate acetylene as well as a ligand for promoting the reaction. Similar results were reported as amine effects.[12] Coordination of pyridine to a dimeric or polymeric copper catalyst possibly produced an active monomeric catalyst (Scheme 2). Usually, bidentate or polydentate ligands are known to promote copper-mediated coupling reactions;[2a] our results showed that monodentate pyridine also promoted the coupling reaction.[13]

**Scheme 1.** Construction of indolequinone motifs.

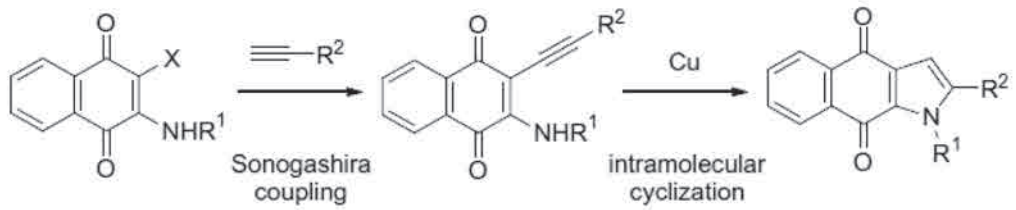
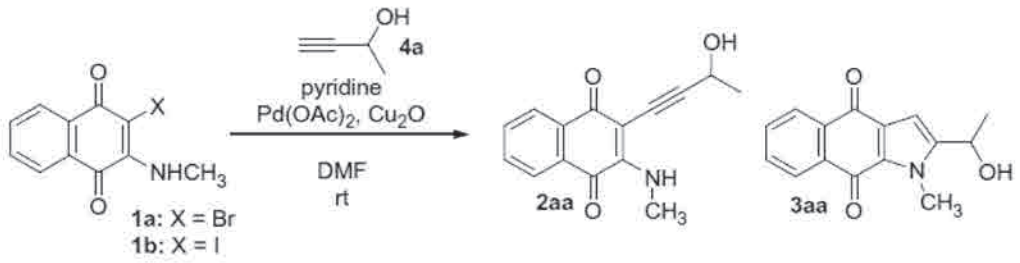



**Table 1**

Reaction of 2-bromo-3-(methylamino)naphthalene-1,4-dione with but-3-yn-2-ol[a]



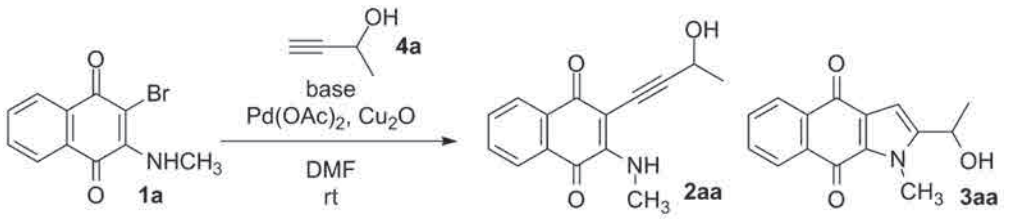

| Entry | Time (h) | Alkyne **4a** (equiv) | Ratio of pyridine to Cu | **2aa** Yield[b](%) | **3aa** Yield[b](%) |
|---|---|---|---|---|---|
| 1 | 48 | 10 | 10:1 | trace | 0 |
| 2 | 48 | 10 | 25:1 | 3 | 6 |
| 3 | 48 | 10 | 50:1 | 2 | 41 |
| 4 | 48 | 10 | 100:1 | 15 | 28 |
| 5 | 24 | 2 | 50:1 | 0 | 56 |
| 6[c] | 48 | 2 | 500:1 | 10 | 0 |
| 7[d] | 12 | 2 | 25:1 | 0 | 52 |
| 8[e] | 12 | 2 | 50:1 | 0 | 51 |
| 9[f] | 24 | 2 | 50:1 | 0 | trace |
| 10[g] | 24 | 2 | 50:1 | <13 | trace |
| 11[h] | 24 | 2 | 50:1 | 0 | 47 |
| 12[i] | 24 | 2 | 50:1 | 0 | 62 |

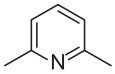
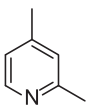
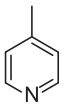
[a] Substrate **1** (0.5 mmol), $Pd(OAc)_2$ (3 mol%), $Cu_2O$ (0.5 mmol), acetylene, and pyridine were stirred in DMF at rt. [b] Isolated yield. [c] $Cu_2O$ (0.05 mmol) was used. [d] $Cu_2O$ (1.0 mmol) was used. [e] $Pd(OAc)_2$ (10 mol%) was used. [f] CuBr was used instead of $Cu_2O$. [g] CuI was used instead of $Cu_2O$. [h] DMF was omitted. [i] **1b** was used as the substrate.

In order to determine which species play an important role in the final cyclization step, we isolated the coupling product **2aa** and tested it under various reaction conditions.[14] Following the optimized reaction conditions shown in Table 1, we obtained less than 5% of the cyclized product **3aa** (Table 3, entry 1). Meanwhile, almost no reaction occurred in the absence of $Cu_2O$ even if **1a** was added to its reaction mixture (Table 3, entries 3 and 4). These results suggest that the cyclization is not induced by Palladium salts or Ar-Pd-Br species[15] which are formed during the Sonogashira coupling. It is noteworthy that the reaction of **2aa** in the presence of 5 mol % or 20 mol % CuBr gave better results, and formed the cyclized product **3aa** in 9% and 45% yields, respectively (Table 3, entries 5 and 6). Furthermore, no conversion to **3aa** was observed and only the starting material **2aa** was recovered when the reaction of **2aa** without acetylene under the conditions used in entry 6 was tested (Table 3, entry 7). Shvartsberg also reported that intramolecular cyclization of vic-amino (alkynyl)quinones proceeded in the presence of cuprous acetylide. Meanwhile, cuprous halides were not effective.[16] Differently from pyridine, triethylamine was ineffective in promoting the cyclization reaction of **2aa** (Table 3, entry 8). Thus, we suppose that CuBr promotes the formation of cuprous acetylide and its pyridine complex plays a crucial role in the intramolecular cyclization step.

Next, using the optimized reaction conditions found in Table 1 entry 5, a series of halogenated naphthoquinones **1** and terminal acetylenes **4** were chosen to test the cascade reaction. The results are summarized in Table 4. No coupling reaction occurred when naphthoquinone was used with an unprotected $NH_2$ group even on increasing the reaction temperature to 70 ℃ (Table 4, entry 1).[17] Shvartsberg reported that the coupling of halogenated naphthoquinone **1d** with various acetylenes gave only the coupling product.[6] However, the coupling product, which initially forms during the reaction between **1d** and **4a**, was converted into the cyclized product **3da**, along with the migration of the acetyl group on the nitrogen atom to the adjacent hydroxyl group (Table 4, entry 2). Acetylene **4b** containing the tertiary alcohol moiety was also tested. The reaction of **1a** with **4b** gave the cyclized product **3ab** in 63% yield after 24 h (Table 4, entry 4). Differently from this result, the acetyl group of the cyclized product **3db** was simultaneously eliminated to give alkene **5db** in 61% yield when the reaction of **1d** with **4b** was carried out at rt. On the other hand, the coupling reaction was not observed at 0℃. To obtain the desired product **3db**, reaction temperatures were carefully controlled.

**Table 2**
Effect of pyridine on the formation of coupling product **2aa** and cyclized product **3aa**[a]




| Entry | Time (h) | Base | **2aa** Yield[b](%) | **3aa** Yield[b](%) | Recovered **1a** Yield[b](%) |
|---|---|---|---|---|---|
| 1 | 96 |  | 0 | 0 | 17 |
| 2 | 48 |  | 0 | 33 | 43 |
| 3 | 24 |  | 0 | 55 | 5 |
| 4 | 48 | $Et_3N$ | Trace | 0 | 66 |

a Substrate **1a** (0.5 mmol), $Pd(OAc)_2$ (3 mol %), $Cu_2O$ (0.5 mmol), acetylene (1.0 mmol), and base (50 mmol) were stirred in DMF at rt.
b Isolated yield.

**Scheme 2** Proposed mechanism of copper- and/or palladium-catalyzed coupling and cyclization

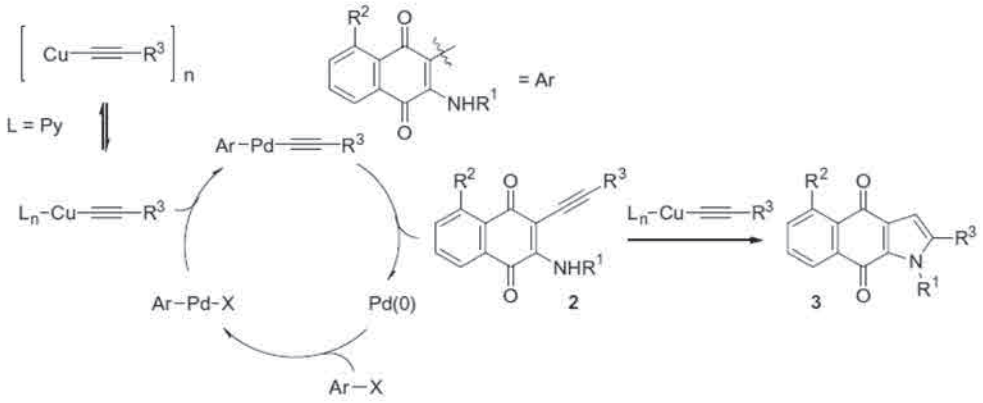
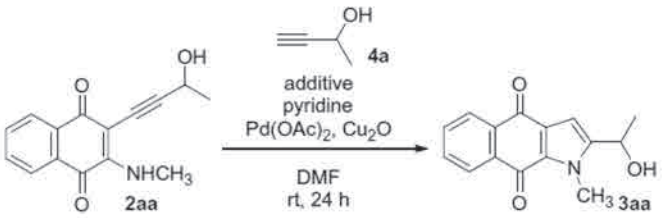



**Table 3**

Effect of additives on the conversion of coupling product **2aa** to cyclized product **3aa**[a]




| Entry | Additive | 3aa Yield[b] (%) |
|---|---|---|
| 1 | - | <5 |
| 2[c] | - | <5 |
| 3[d] | - | Trace |
| 4[d] | **1a** (20 mol %) | Trace |
| 5 | CuBr (5 mol %) | 9 |
| 6 | CuBr (20 mol %) | 45 |
| 7[c,d,e] | CuBr (20 mol %) | 0 |
| 8[f] | CuBr (20 mol %) | Trace |

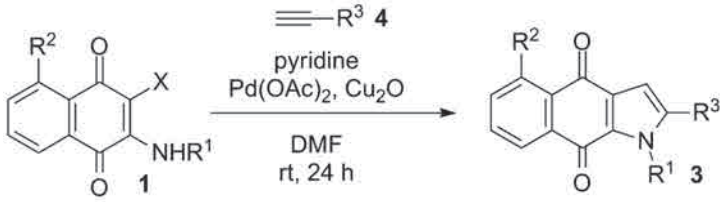
a Substrate **2aa** (0.08 mmol), $Pd(OAc)_2$ (3 mol %), $Cu_2O$ (0.08 mmol), acetylene **4a** (0.08 mmol), and pyridine (8.0 mmol) were stirred in DMF at rt for 24 h.
b Isolated yield.
c Without $Pd(OAc)_2$.
d Without $Cu_2O$.
e Without acetylene **4a**.
f $Et_3N$ was used instead of pyridine.

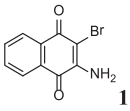
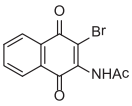
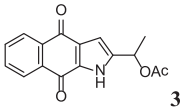
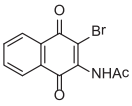
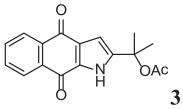
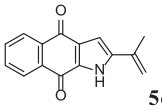
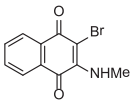
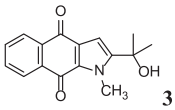
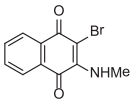
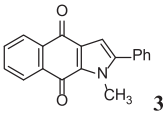
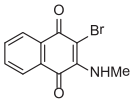
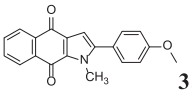
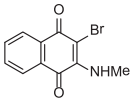
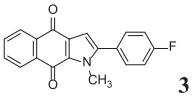
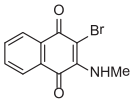
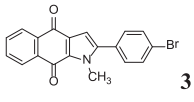
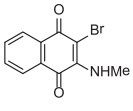
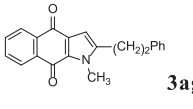
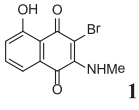
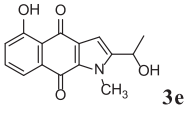
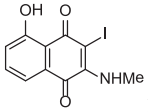
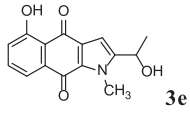
After stirring for 2 h at rt, the reaction mixture was cooled to 0 ℃ and stirred for an additional 10 h. Finally, **3db** was obtained in 28% yield (Table 4, entry 3). These motifs could not be obtained by the reported method.[6] Reactions of **4c**, **4d**, **4e**, and **4f**, which bear an aryl group on the alkynyl moiety, gave the corresponding 2-arylindolequinones **3ac**, **3ad**, **3ae**, and **3af**, respectively, in moderate yields (Table 4, entries 5–8). It is noteworthy that the reaction with 1-bromo-4-ethynylbenzene (**4f**) afforded the desired product **3af** without loss of the halogen substituent, although the palladium catalyst was present. Alkynes bearing an alkyl substituent reacted smoothly with halogenated naphthoquinone **1a** to give the desired product **3ag** in moderate yields (Table 4, entry 9). Finally, halogenated naphthoquinone having a hydroxyl group on the aromatic ring was tested because such a phenolic hydroxy group is commonly seen in naturally occurring naphthoquinones.[18] A higher reaction temperature (80 ℃) was required to obtain **3ea**, demonstrating that the reactivity of bromide **1e** is rather lower than that of bromide **1a** (Table 4, entry 10).[19] A satisfactory result was obtained when using iodide **1f** as the substrate (Table 4, entry 11).

In conclusion, we have developed a cascade reaction based on the Sonogashira reaction and the subsequent cyclization. We have demonstrated a mild and general one-pot method for constructing substituted indolequinones. We have also shown that $Cu_2O$ is the best copper catalyst. In addition, we have found that pyridine, which acts both as a base and a ligand in this cascade reaction, is required in large equivalent excess to copper metal. The detailed mechanistic studies, catalytic version, and future applications of this strategy are under investigation and will be reported in duecourse.

**Table 4**

Effect of varying substituents on the conversion of naphthoquinones **1** to cyclized product **3aa**[a]




| Entry | Substrate | $R^3$ | Product | Yield[b](%) |
|---|---|---|---|---|
| 1[c] |  **1c** | $CH(OH)CH_3$ (**4a**) | | 0 |
| 2[d] |  **1d** | $CH(OH)CH_3$ (**4a**) |  **3da** | 48 |
| 3[e] |  **1d** | $C(OH)(CH_3)_2$ (**4b**) |  **3db** | 28 |
| | | |  **5db** | 17 |
| 4 |  **1a** | $C(OH)(CH_3)_2$ (**4b**) |  **3ab** | 63 |
| 5 |  **1a** | Ph (**4c**) |  **3ac** | 44 |
| 6 |  **1a** | *p*-$MeOC_6H_4$ (**4d**) |  **3ad** | 52 |
| 7 |  **1a** | *p*-$FC_6H_4$ (**4e**) |  **3ae** | 43 |
| 8 |  **1a** | *p*-$BrC_6H_4$ (**4f**) |  **3af** | 39 |
| 9 |  **1a** | $CH_2CH_2Ph$ (**4g**) |  **3ag** | 56 |
| 10[f,g] |  **1e** | $CH(OH)CH_3$ (**4a**) |  **3ea** | 58 |
| 11[f,g,h] |  **1f** | $CH(OH)CH_3$ (**4a**) |  **3ea** | 82 |

a Substrate **1a** (0.5 mmol), $Pd(OAc)_2$ (3 mol %), $Cu_2O$ (0.5 mmol), acetylene **4** (1.0 mmol), and pyridine (50 mmol) were stirred in DMF at rt. b Isolated yield. c At 70 ℃.
d Reaction time was 4 h. e At rt for 2h, then at 0 ℃ for 10 h. f At 80 ℃.
g Reaction time was 1 h. h 200 equivalents of pyridine were used.

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.07.008.

## References and notes

1. (a) Ishikura, M.; Yamada, K. *Nat. Prod. Rep*. **2009,** 26, 803; (b) Sundberg, R. J. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Ress, C. W., Scriven, E. F. V., Bird, C. W., Eds.; Pergamon Press: Oxford, 1996; vol. 2, p 119; (c) Gribble,G. W. In Comprehensive Heterocyclic Chemistry II; Katritzky, A. R., Ress, C. W.,Scriven, E. F. V., Bird, C. W., Eds.; Pergamon Press: Oxford, 1996; vol. 2, p 207; (d) Sundberg, R. J. Indoles; Academic Press: London, 1996.
2. For recent reviews, see: (a) Monnier, F.; Taillefer, M. *Angew. Chem., Int. Ed.* **2009**,48, 6954; (b) Krüger, K.; Tillack, A.; Beller, M. *Adv. Synth. Catal.* **2008**, 350, 2153;(c) Patil, N. T.; Yamamoto, Y. *Chem. Rev*. **2008**, 108, 3395; (d) Humphrey, G. R.; Kuethe, J. T. *Chem. Rev*. **2006**, 106, 2875; (e) Cacchi, S.; Fabrizi, G. *Chem. Rev*.**2005**, 105, 2873.
3. Selected examples on palladium- and/or copper-catalyzed synthesis of indoles from o-haloaniline or o-alkynylaniline derivatives, see: (a) Han, X.; Lu, X. *Org.Lett*. **2010**, 12, 3336; (b) Shen, Z.; Lu, X. *Adv. Synth. Catal*. **2009**, 351, 3107; (c) Ye,S.; Ding, Q.; Wang, Z.; Zhou, H.; Wu, J. *Org. Biomol. Chem.* **2008**, 6, 4406; (d)Ohno, H.; Ohta, Y.; Oishi, S.; Fujii, N. *Angew. Chem., Int. Ed*. **2007**, 46, 2295; (e)Liu, F.; Ma, D. J. *Org. Chem*. **2007**, 72, 4844; (f) Ambrogio, I.; Cacchi, S.; Fabrizi, G.*Org. Lett.* **2006**, 8, 2083; (g) Lu, B. Z.; Zhao, W.; Wei, H.-X.; Dufour, M.; Farina, V.; Senanayake, C. H. *Org. Lett.* **2006**, 8, 3271; (h)Arcadi, A.; Cacchi, S.; Fabrizi, G.; Marinelli, F.; Parisi, L. M. J. *Org.Chem*. **2005**, 70, 6213; (i) Saejueng, P.; Bates, C.G.; Venkataraman, D. *Synthesis* **2005**, 1706; (j) Hiroya, K.; Itoh, S.; Sakamoto, T.J. *Org. Chem.* **2004**, 69, 1126; (k) Cacchi, S.; Fabrizi, G.; Parisi, L. M. *Org.Lett*.**2003**, 5, 3843; (l) Rodriguez, A. L.; Koradin, C.; Dohle, W.; Knochel, P. *Angew.Chem., Int. Ed.* **2000**, 39, 2488.
4. (a) Carter, S. K.; Crooke, S. T. *Mitomycin C*: *Current Status and New Developments*;Academic Press: New York, 1979; (b) Remers, W. A.; Dorr, R. T. In Alkaloids In Pelletier, S. W., Ed.; Wiley: New York, 1988; p 1; (c) Franck, R. W.; Tomasz,M. In *Chemistry of Antitumor Agents*; Wilman, D. E. V., Ed.; Blackie & Son Ltd.:Glasgow, 1990; pp 379–393.
5. (a) Oostveen, E. A.; Speckamp, W. N. *Tetrahedron* **1987**, 43, 255; (b) Jain, A.;Phillips, R. M.; Scally, A. J.; Lenaz, G.; Beer, M.; Puri, R. *Urology* **2009**, 73, 1083.
6. Shvartsberg, M. S.; Kolodina, E. A.; Lebedeva, N. I.; Fedenok, L. G. *TetrahedronLett*. **2009**, 50, 6769.
7. (a) Doad, G. J. S.; Barltrop, J. A.; Petty, C. M.; Owen, T. C. *Tetrahedron Lett*. **1989**,30, 1597; (b) Kobayashi, K.; Uneda, T.; Kawakita, M.; Morioka, O.; Konishi, H.*Tetrahedron Lett.* **1977**, 38, 837.
8. Starting product **1a** was recovered in 62% yield. Although the reaction temperature was raised to 70 ℃, only trace amount of cyclized product **3aa** was observed. Dehalogenated compound of starting naphthoquinone **1a** was gradually formed during the reaction at high temperature. Moreover, additionof bidentate ligands such as bipyridine, phenanthroline, and L-proline were not effective.
9. Reaction with copper(II) salt (CuO, $CuBr_2$, and $CuCl_2$) was also tested; no cyclized product was obtained using each of the three metal salts even on increasing the temperature to 70 ℃.
10. DMF was used to easily dissolve substrate 3. See Supplementary data fordetailed reaction procedure.
11. The following conversion of **1a** to **3aa** was observed in DMF at room temperature using $Cu_2O$ (100 mol %), acetylene (2 equiv), and pyridine(pyridine:copper = 50:1), 3 mol % of palladium salt: using $Pd(PPh_3)2Cl_2$, 20% yield of **3aa** was obtained; using $Pd(PPh_3)_4$, only trace amount of **3aa** was obtained. Reaction with $PdCl_2$ gave a comparable result to that when using$Pd(OAc)_2$; however, a longer reaction time was required (48 h, 52% yield).
12. (a) Gonda, Z.; Tolnai, G. L.; Novák, Z. *Chem. Eur. J*. **2010**, 16, 11822; (b) Heinre, J.E.; Fokin, V. V. *Chem. Soc. Rev*. **2010**, 39, 1302; (c) Zuidema, E.; Bolm, C. *Chem.Eur. J*. **2010**, 16, 4181.
13. Copper-catalyzed reaction promoted by monodentate pyridine, see: Hayashi, H.; Kawasaki, K.; Fujii, M.; Kainoh, A.; Okazaki, T. *J. Catal.* **1976**, 41, 367.
14. The coupling product was obtained by quenching the reaction after 4 h. Coupling product **2aa** and cyclized product **3aa** were obtained in 37% and 31% yields, respectively.
15. Nakamura, I.; Yamamoto, Y. *Chem. Rev*. **2004**, 104, 2127.
16. Shvartberg, M. S.; Barabanov, I. I.; Fedenok, L. G. *Russ. Chem. Rev*. **2004**, 73, 161.
17. Starting material **1a** was recovered in 62% yield and dehalogenated compoundof **1a** was obtained in 9% yield.
18. Yamashita, M.; Kaneko, M.; Tokuda, H.; Nishimura, K.; Kumeda, Y.; Iida, A.*Bioorg. Med. Chem*. **2009**, 17, 6286.
19. No coupling reaction was observed at room temperature.

# テトラヘドロン・レターズ

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## 菌頭反応／環化カスケード反応を経由するインドールキノンの合成


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**【要旨】**菌頭反応と銅により触媒される分子内環化カスケード反応に基づきインドールキノン骨格を構築するための穏和な合成戦略が述べられている。第一段階ではハロゲン化ナフトキノンと末端アセチレンとの間のパラジウムおよび銅により触媒される反応を伴い、その結果、カップリング生成物を生じる。そしてその生成物は銅により触媒される分子内環化において炭素ー炭素三重結合に隣接した窒素官能基と反応する。



**【キーワード】**インドールキノン、 菌頭カップリング、 カスケード反応、 銅、 パラジウム


ヘテロ環、特にインドールは様々な生物活性天然物や合成品に幅広く見られることから興味と価値あるものである。それゆえに、これら化合物の効果的な合成法の開発は、いまだ常に活発な研究領域である。特に、一般的に菌頭反応によりo - ハロゲン化アニリンから合成されるo - アルキニルアニリンの分子内環化は、広く報告されている。

この手法を用いた初期の成功例にも関わらず、インドールキノン類合成への応用は限られている。これらの骨格は、マイトマイシンCやE09といった抗腫瘍剤にしばしば見うけられる。最近、Shvartsbergらは3ーアセチルアミノー2ーブロモー1,4ーナフトキノンと末端アセチレンの菌頭反応とそれに続く、アセトニトリル溶液中、反応温度80℃での単離されたカップリング生成物と炭酸カリウムの分子内環化反応よるインドールキノンの段階的合成を報告した。

この手法のいくつかの大きな欠点は、ナフトキノン基質上の置換基の制限と環化の際の望ましくない脱離反応である。さらに、我々は出発物質**1a**の脱ハロゲン化化合物が、反応中、温度の上昇とともに徐々に形成されたことを見出した。したがって、穏和な条件下でのインドールキノンのワンポット合成法の開発は、有機合成においていまだ意欲をかき立てるものである（Scheme 1）。ここに我々は、菌頭反応と分子内環化を含むインドールキノン骨格形成のためのカスケード反応について説明する。

最適な反応条件を明らかにするため、アミノ基に電子供与基を有する2ーブロモー3ー（メチルアミノ）ナフタレンー1,4ージオン （**1a**） を基質に選んだ。これは、報告されている条件下では、この基質のカップリング反応が進行しないためである。その結果をTable 1に示す。

カストローステファンズ反応の手順に従って、DMF溶液中、酸化銅（**1a**に対して1当量）およびピリジン（**1a**に対して50当量、ピリジン：銅＝25：1）存在下、室温にて**1a**と**4a**（**1a**に対して10当量）の反応を行った。しかしながら、変換は見られなかった。一方、その反応液に3mol%の酢酸パラジウム（II）を加えたところ、わずかに変換が見られ、カップリング生成物および環化生成物がそれぞれ3%、6%で得られた。20当量のピリジン（ピリジン：銅＝10：1）を使用した際には、目的生成物は得られなかった。しかし、ピリジンを100当量使用すると中程度の収率（41%）で目的生成物を得ることができた（Table 1, entry 3）。さらに、ピリジンを200当量（ピリジン：銅＝100：1）使用したが、さらなる収率の向上に効果はなかった。このことは、ピリジンの最適な量が100当量（ピリジン：銅＝50：1）であることを示唆している。

加えて、200当量のピリジンを使用した際には、環化の過程が遅くなり収率が低下した（Table 1, entry 4）。最も良い結果は反応時間24時間で**1a**に対して2当量のアセチレン**4a**を使用した際に得られた（Table 1, entry 5）。アセチレンの量に関わらず、カップリング反応は約4時間以内で完結した（TLCで確認）。我々は、カップリング生成物**2aa**のアセチレン部位が銅原子へ結合することで環化のプロセスが始まると推測している。それゆえに、アセチレン**4a**の使用量を減らすことで環化反応がより速くなったと考えられる。酸化銅（I）の使用量を減らすと48時間後でも環化生成物を形成しなかった（Table 1, entry 6）。一方、酸化銅（I）あるいは酢酸パラジウム（II）の使用量を増やした場合では、それぞれ収率は向上しなかった（Table 1, entry 7,8）。

他の銅（I）塩（臭化銅、ヨウ化銅）を用いた反応では、環化生成物がわずかに得られた（Table 1, entry 9,10）。反応溶媒であるDMFを使用することは、必須ではないが、DMF非存在下では**3aa**の収率わずかに減少した（Table 1, entry 11）。ヨウ素体**1b**についてもこの反応の基質として用いたところ、基質にブロモ体**1a**を使用した際に得られた収率に比べわずかに良い収率が得られた（Table 1, entry 12）。ビス（トリフェニルホスフィン）パラジウム（II）ジクロリドやテトラキス（トリフェニルホスフィン）パラジウム（0）のようないくつかのパラジウムも用いたが、**3aa**を低い収率でしか得られず、**1a**の脱ハロゲン化化合物といった副生成物の形成が見られた。

**Scheme 1.** Construction of indolequinone motifs.

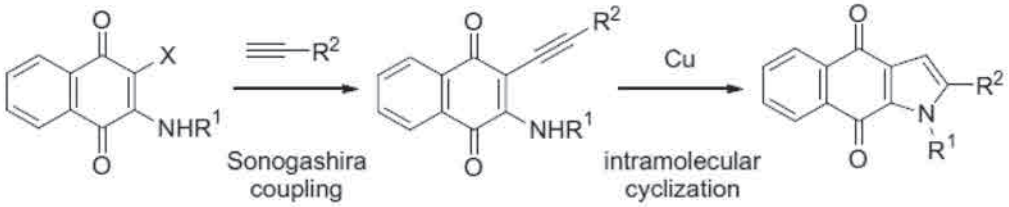



**Table 1**
Reaction of 2-bromo-3-(methylamino)naphthalene-1,4-dione with but-3-yn-2-ol[a]

| Entry | Time (h) | Alkyne **4a** (eq) | Ratio of pyridine to Cu | **2aa** Yield[b](%) | **3aa** Yield[b](%) |
|---|---|---|---|---|---|
| 1 | 48 | 10 | 10:1 | trace | 0 |
| 2 | 48 | 10 | 25:1 | 3 | 6 |
| 3 | 48 | 10 | 50:1 | 2 | 41 |
| 4 | 48 | 10 | 100:1 | 15 | 28 |
| 5 | 24 | 2 | 50:1 | 0 | 56 |
| 6[c] | 48 | 2 | 500:1 | 10 | 0 |
| 7[d] | 12 | 2 | 25:1 | 0 | 52 |
| 8[e] | 12 | 2 | 50:1 | 0 | 51 |
| 9[f] | 24 | 2 | 50:1 | 0 | trace |
| 10[g] | 24 | 2 | 50:1 | <13 | trace |
| 11[h] | 24 | 2 | 50:1 | 0 | 47 |
| 12[i] | 24 | 2 | 50:1 | 0 | 62 |

[a] Substrate **1** (0.5 mmol), $Pd(OAc)_2$ (3 mol%), $Cu_2O$ (0.5 mmol), acetylene, and pyridine were stirred in DMF at rt.
[b] Isolated yield. [c] $Cu_2O$ (0.05 mmol) was used. [d] $Cu_2O$ (1.0 mmol) was used. [e] $Pd(OAc)_2$ (10 mol%) was used.
[f] CuBr was used instead of $Cu_2O$. [g] CuI was used instead of $Cu_2O$. [h] DMF was omitted. [i] **1b** was used as the substrate.

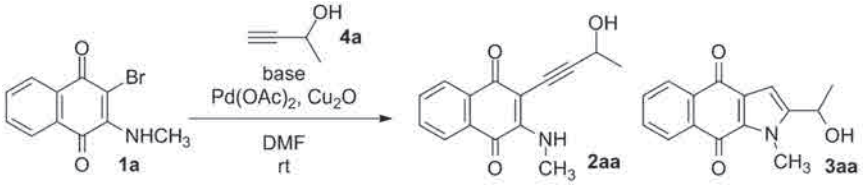
ピリジン誘導体を用いて，さらに研究を行った。その結果がTable 2にまとめられている。2,4－ジメチルピリジンあるいは4－ジメチルピリジンを用いた**1a**の反応では、生成物**3aa**をそれぞれ33%、55%で得た（Table 2, entry 2,3）。一方、立体的に障害となる窒素原子を含む2,6－ジメチルピリジンを用いた反応では、未知の副生成物が形成されたため環化生成物が全く得られなかった（Table 2, entry 1）。トリエチルアミンはハロゲン化ナフトキノン**1a**とアセチレン**4a**のカップリング反応の促進には効果がなかった。しかし、トリエチルアミンは薗頭反応の塩基として一般的に用いられている（Table 2, entry 4）。これらの結果は、ピリジンがアセチレンを脱プロトン化する塩基と反応を促進するリガンドの両方の役割を果たしていることを示している。おそらく二量体あるいは多量体の銅触媒へピリジンが配位することで、活性な単量体の触媒が生成される（Scheme 2）。

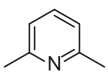
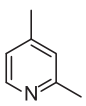
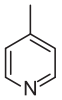
通常、二座配位子または多座配位子は銅により活性化されるカップリング反応を促進することが知られており、我々の結果は、単座配位子もカップリング反応を促進したことを示した。最後の環化ステップで重要な役割を果たしている種を決定するため、カップリング生成物**2aa**を単離し、様々な反応条件で検討を行った。Table1で示した最適条件下、我々は5%以下の環化生成物を得た（Table 3, entry 1）。一方、酸化銅（I）非存在下では、たとえ**1a**を反応溶液に加えても反応はほとんど進行しなかった（Table 3, entry 3,4）。これらの結果は、環化反応が薗頭反応中に形成されたパラジウム塩あるいはAr - Pd - Br種により誘導されていないことを示している。注目すべきは、5mol%または20mol%の臭化銅（I）を加えた**2aa**の反応が良い結果をもたらし、それぞれ9%、45%収率で環化生成物**3aa**を形成したことである（Table 3, entry 5,6）。さらに、entry6の反応条件下、アセチレンを加えない場合、**3aa**への変換が見られず、出発物質**2aa**のみが回収された（Table 3, entry 7）。Shvartsbergも*vis*－アミノ（アルキニル）キノンの分子内環化が銅アセチリド存在下で進行したと報告している。一方、ハロゲン化銅は効果的ではなかった。ピリジンではなく、トリエチルアミンでは**2aa**の環化反応の促進に効果はなかった（Table 3, entry 8）。

したがって、我々は臭化銅（I）が銅アセチリドの形成を促進し、それのピリジン錯体が分子内環化において重要な役割を果たしていることを明らかにした。

次に、Table 1, entry 5で見出した最適条件を用い、カスケード反応の検討のために一連のハロゲン化ナフトキノン**1**と末端アセチレン**4**を選んだ。その結果は、Table 4にまとめられている。無保護のアミノ基が結合したナフトキノンを用いた際、反応温度70℃でさえカップリング反応は進行しなかった（Table 4, entry 1）。Shvartsbergはハロゲン化ナフトキノン**1d**と種々のアセチレンとのカップリング反応ではカップリング生成物のみが得られたと報告している。しかしながら、**1d**と**4a**の反応中、最初に形成するカップリング生成物は、窒素原子上のアセチル基が隣接した水酸基へ転位することで環化生成物**3da**に変換された（Table 4, entry 2）。*tert*–アルコール部位を含むアセチレン**4b**も用いた。**1a**と**4b**の反応では、反応時間24時間で環化生成物**3ab**が63%収率で得られた。この結果とは異なり、**1d**と**4b**の反応を室温で行った場合、環化生成物**3db**のアセチル基が環化と同時に脱離し、61%収率でアルケン**5db**が得られた。一方、反応温度0℃ではカップリング反応は進行しなかった。目的生成物**3db**を得るため、反応温度は注意深く制御された。

**Table 2** Effect of pyridine on the formation of coupling product **2aa** and cyclized product **3aa**[a]




| Entry | Time (h) | Base | 2aa Yield[b](%) | 3aa Yield[b](%) | Recovered 1a Yield[b](%) |
|---|---|---|---|---|---|
| 1 | 96 |  | 0 | 0 | 17 |
| 2 | 48 |  | 0 | 33 | 43 |
| 3 | 24 |  | 0 | 55 | 5 |
| 4 | 48 | $Et_3N$ | trace | 0 | 66 |

a Substrate **1a** (0.5 mmol), $Pd(OAc)_2$ (3 mol %), $Cu_2O$ (0.5 mmol), acetylene (1.0 mmol), and base (50 mmol) were stirred in DMF at rt. b Isolated yield.

**Scheme 2** Proposed mechanism of copper- and/or palladium-catalyzed coupling and cyclization

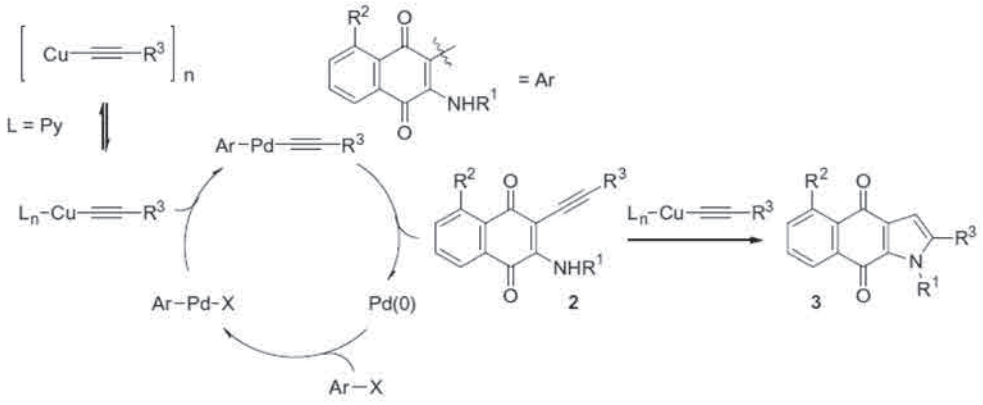
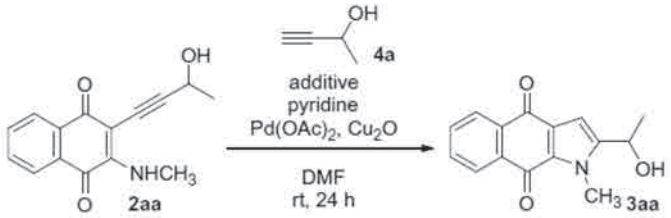



**Table 3** Effect of additives on the conversion of coupling product **2aa** to cyclized product **3aa**[a]




| Entry | Additive | 3aa Yield[b] (%) |
|---|---|---|
| 1 | - | <5 |
| 2[c] | - | <5 |
| 3[d] | - | Trace |
| 4[d] | **1a** (20 mol %) | Trace |
| 5 | CuBr (5 mol %) | 9 |
| 6 | CuBr (20 mol %) | 45 |
| 7[c,d,e] | CuBr (20 mol %) | 0 |
| 8[f] | CuBr (20 mol %) | Trace |

a Substrate **2aa** (0.08 mmol), $Pd(OAc)_2$ (3 mol %), $Cu_2O$ (0.08 mmol), acetylene **4a** (0.08 mmol), and pyridine (8.0 mmol) were stirred in DMF at rt for 24 h.
b Isolated yield.
c Without $Pd(OAc)_2$.
d Without $Cu_2O$.
e Without acetylene **4a**.
f $Et_3N$ was used instead of pyridine.

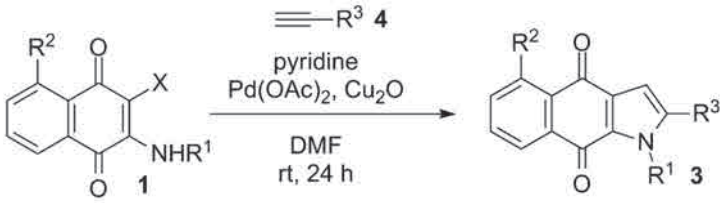
室温で2時間撹拌した後、反応液を0℃に冷却し、さらに10時間撹拌した。最終的に、**3db**は28%収率で得られた（Table 4, entry 3）。これらの化合物は、報告されている手法では得られていない。アルキニル部位に芳香環を有する**4c**、**4d**、**4e**、**4f**の反応は、それぞれ中程度の収率で対応するインドールキノン**3ac**、**3ad**、**3ae**、**3af**を与えた。注目すべきは、1−ブロモ−4−エチニルベンゼン（**4f**）との反応が、パラジウム触媒存在下にもかかわらずハロゲン置換基の欠損もなく目的生成物**3af**を得られたことである。アルキル置換基を含むアルキンは、ハロゲン化ナフトキノン**1a**とゆっくり反応し、中程度の収率で目的生成物**3ag**を与えた（Table 4, entry 9）。

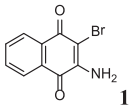
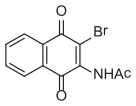
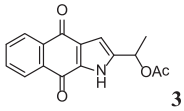
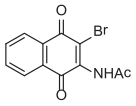
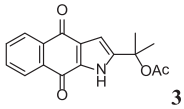
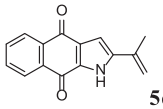
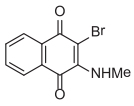
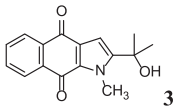
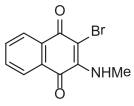
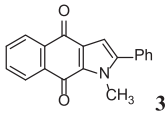
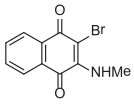
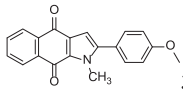
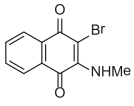
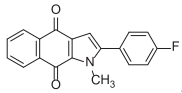
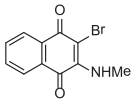
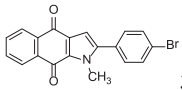
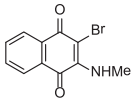
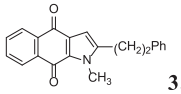
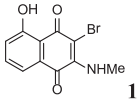
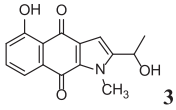
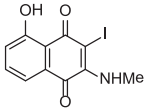
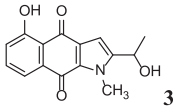
最後に、フェノール性水酸基が天然に存在するナフトキノンによく見られることから、芳香環に水酸基を有するハロゲン化ナフトキノンを用い反応を行った。**3ea**を得るために高い反応温度（80℃）が必要となり、これはブロモ体**1e**の反応性がブロモ体**1a**に比べかなり低いことを示している（Table 4, entry 10）。基質にヨウ素体**1f**を用いた際には、満足いく結果が得られた（Table 4, entry 11）。

結論として、我々は薗頭反応とそれに続く環化反応を基盤としたカスケード反応を開発した。我々は置換基を含むインドールキノンを構築するための緩和で一般性のあるワンポッド合成法を示した。我々は酸化銅が最も適した銅触媒であることも示した。加えて、我々はこのカスケード反応において塩基とリガンドの両方の役割を果たすピリジンは、銅金属に対して大過剰必要とされることを見出した。詳細なメカニズム、触媒化、この戦略のさらなる応用は研究中であり、近々報告する予定である。

**Table 4**

Effect of varying substituents on the conversion of naphthoquinones **1** to cyclized product **3aa**[a]




| Entry | Substrate | $R^3$ | Product | Yield[b](%) |
|---|---|---|---|---|
| 1[c] |  **1c** | $CH(OH)CH_3$ (**4a**) | | 0 |
| 2[d] |  **1d** | $CH(OH)CH_3$ (**4a**) |  **3da** | 48 |
| 3[e] |  **1d** | $C(OH)(CH_3)_2$ (**4b**) |  **3db** | 28 |
| | | |  **5db** | 17 |
| 4 |  **1a** | $C(OH)(CH_3)_2$ (**4b**) |  **3ab** | 63 |
| 5 |  **1a** | Ph (**4c**) |  **3ac** | 44 |
| 6 |  **1a** | *p*-$MeOC_6H_4$ (**4d**) |  **3ad** | 52 |
| 7 |  **1a** | *p*-$FC_6H_4$ (**4e**) |  **3ae** | 43 |
| 8 |  **1a** | *p*-$BrC_6H_4$ (**4f**) |  **3af** | 39 |
| 9 |  **1a** | $CH_2CH_2Ph$ (**4g**) |  **3ag** | 56 |
| 10[f,g] |  **1e** | $CH(OH)CH_3$ (**4a**) |  **3ea** | 58 |
| 11[f,g,h] |  **1f** | $CH(OH)CH_3$ (**4a**) |  **3ea** | 82 |

a Substrate **1a** (0.5 mmol), $Pd(OAc)_2$ (3 mol %), $Cu_2O$ (0.5 mmol), acetylene **4** (1.0 mmol), and pyridine (50 mmol) were stirred in DMF at rt. b Isolated yield. c At 70 ℃.
d Reaction time was 4 h. e At rt for 2h, then at 0 ℃ for 10 h. f At 80 ℃.
g Reaction time was 1 h. h 200 equivalents of pyridine were used.

## Acknowledgment

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.07.008.

## References and notes

1. (a) Ishikura, M.; Yamada, K. *Nat. Prod. Rep.* **2009,** 26, 803; (b) Sundberg, R. J. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Ress, C. W., Scriven, E. F. V., Bird, C. W., Eds.; Pergamon Press: Oxford, 1996; vol. 2, p 119; (c) Gribble,G. W. In Comprehensive Heterocyclic Chemistry II; Katritzky, A. R., Ress, C. W.,Scriven, E. F. V., Bird, C. W., Eds.; Pergamon Press: Oxford, 1996; vol. 2, p 207; (d) Sundberg, R. J. Indoles; Academic Press: London, 1996.
2. For recent reviews, see: (a) Monnier, F.; Taillefer, M. *Angew. Chem., Int. Ed.* **2009**,48, 6954; (b) Krüger, K.; Tillack, A.; Beller, M. *Adv. Synth. Catal.* **2008**, 350, 2153;(c) Patil, N. T.; Yamamoto, Y. *Chem. Rev*. **2008**, 108, 3395; (d) Humphrey, G. R.; Kuethe, J. T. *Chem. Rev*. **2006**, 106, 2875; (e) Cacchi, S.; Fabrizi, G. *Chem. Rev*.**2005**, 105, 2873.
3. Selected examples on palladium- and/or copper-catalyzed synthesis of indoles from o-haloaniline or o-alkynylaniline derivatives, see: (a) Han, X.; Lu, X. *Org.Lett*. **2010**, 12, 3336; (b) Shen, Z.; Lu, X. *Adv. Synth. Catal*. **2009**, 351, 3107; (c) Ye,S.; Ding, Q.; Wang, Z.; Zhou, H.; Wu, J. *Org. Biomol. Chem.* **2008**, 6, 4406; (d)Ohno, H.; Ohta, Y.; Oishi, S.; Fujii, N. *Angew. Chem., Int. Ed*. **2007**, 46, 2295; (e)Liu, F.; Ma, D. J. *Org. Chem*. **2007**, 72, 4844; (f) Ambrogio, I.; Cacchi, S.; Fabrizi, G.*Org. Lett.* **2006**, 8, 2083; (g) Lu, B. Z.; Zhao, W.; Wei, H.-X.; Dufour, M.; Farina, V.; Senanayake, C. H. *Org. Lett.* **2006**, 8, 3271; (h)Arcadi, A.; Cacchi, S.; Fabrizi, G.; Marinelli, F.; Parisi, L. M. J. *Org.Chem*. **2005**, 70, 6213; (i) Saejueng, P.; Bates, C.G.; Venkataraman, D. *Synthesis* **2005**, 1706; (j) Hiroya, K.; Itoh, S.; Sakamoto, T.J. *Org. Chem.* **2004**, 69, 1126; (k) Cacchi, S.; Fabrizi, G.; Parisi, L. M. *Org.Lett*.**2003**, 5, 3843; (l) Rodriguez, A. L.; Koradin, C.; Dohle, W.; Knochel, P. *Angew.Chem., Int. Ed.* **2000**, 39, 2488.
4. (a) Carter, S. K.; Crooke, S. T. *Mitomycin C*: *Current Status and New Developments*;Academic Press: New York, 1979; (b) Remers, W. A.; Dorr, R. T. In Alkaloids In Pelletier, S. W., Ed.; Wiley: New York, 1988; p 1; (c) Franck, R. W.; Tomasz,M. In *Chemistry of Antitumor Agents*; Wilman, D. E. V., Ed.; Blackie & Son Ltd.:Glasgow, 1990; pp 379–393.
5. (a) Oostveen, E. A.; Speckamp, W. N. *Tetrahedron* **1987**, 43, 255; (b) Jain, A.;Phillips, R. M.; Scally, A. J.; Lenaz, G.; Beer, M.; Puri, R. *Urology* **2009**, 73, 1083.
6. Shvartsberg, M. S.; Kolodina, E. A.; Lebedeva, N. I.; Fedenok, L. G. *TetrahedronLett*. **2009**, 50, 6769.
7. (a) Doad, G. J. S.; Barltrop, J. A.; Petty, C. M.; Owen, T. C. *Tetrahedron Lett*. **1989**,30, 1597; (b) Kobayashi, K.; Uneda, T.; Kawakita, M.; Morioka, O.; Konishi, H.*Tetrahedron Lett.* **1977**, 38, 837.
8. Starting product **1a** was recovered in 62% yield. Although the reaction temperature was raised to 70 ℃, only trace amount of cyclized product **3aa** was observed. Dehalogenated compound of starting naphthoquinone **1a** was gradually formed during the reaction at high temperature. Moreover, additionof bidentate ligands such as bipyridine, phenanthroline, and L-proline were not effective.
9. Reaction with copper(II) salt (CuO, $CuBr_2$, and $CuCl_2$) was also tested; no cyclized product was obtained using each of the three metal salts even on increasing the temperature to 70 ℃.
10. DMF was used to easily dissolve substrate 3. See Supplementary data fordetailed reaction procedure.
11. The following conversion of **1a** to **3aa** was observed in DMF at room temperature using $Cu_2O$ (100 mol %), acetylene (2 equiv), and pyridine(pyridine:copper = 50:1), 3 mol % of palladium salt: using $Pd(PPh_3)2Cl_2$, 20% yield of **3aa** was obtained; using $Pd(PPh_3)_4$, only trace amount of **3aa** was obtained. Reaction with $PdCl_2$ gave a comparable result to that when using$Pd(OAc)_2$; however, a longer reaction time was required (48 h, 52% yield).
12. (a) Gonda, Z.; Tolnai, G. L.; Novák, Z. *Chem. Eur. J*. **2010**, 16, 11822; (b) Heinre, J.E.; Fokin, V. V. *Chem. Soc. Rev*. **2010**, 39, 1302; (c) Zuidema, E.; Bolm, C. *Chem.Eur. J*. **2010**, 16, 4181.
13. Copper-catalyzed reaction promoted by monodentate pyridine, see: Hayashi, H.; Kawasaki, K.; Fujii, M.; Kainoh, A.; Okazaki, T. *J. Catal.* **1976**, 41, 367.
14. The coupling product was obtained by quenching the reaction after 4 h. Coupling product **2aa** and cyclized product **3aa** were obtained in 37% and 31% yields, respectively.
15. Nakamura, I.; Yamamoto, Y. *Chem. Rev*. **2004**, 104, 2127.
16. Shvartberg, M. S.; Barabanov, I. I.; Fedenok, L. G. *Russ. Chem. Rev*. **2004**, 73, 161.
17. Starting material **1a** was recovered in 62% yield and dehalogenated compoundof **1a** was obtained in 9% yield.
18. Yamashita, M.; Kaneko, M.; Tokuda, H.; Nishimura, K.; Kumeda, Y.; Iida, A.*Bioorg. Med. Chem*. **2009**, 17, 6286.
19. No coupling reaction was observed at room temperature.