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# Transition-Metal-Free One-Pot Synthesis of Naphthoquinonefuran Derivatives Through Sequential Nucleophilic Substitution–Nucleophilic Addition Reaction

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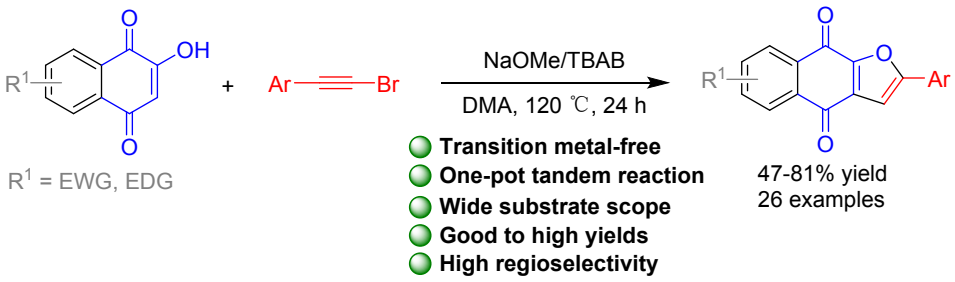
[#] Xiang Li and Peng Sun contributed equally to this work.

## Abstract




A transition-metal-free route for tandem one-pot synthesis of naphthoquinonefuran derivatives from 2-hydroxynaphthoquinones has been developed. The sequentially accomplished process comprises an intermolecular alkynylation of $sp^2$-carbon at the 3 position of 2-hydroxynaphthoquinones with arylethynyl bromides, followed by a base-promoted intramolecular nucleophilic annulation reaction. A broad range of functional groups are compatible with this reaction, and diverse naphtho[2,3-*b*]furan-4,9-diones can be obtained with good yields and excellent regioselectivity.

As an important privileged scaffold, the naphthofuroquinone is a well-known pharmacophoric unit present in natural products, drugs and drug candidates.[1] A great number of naphthofuroquinones have exhibited diverse biological activities such as antitumor,[2] anti-inflammatory,[2a] anti-leukemic activity,[3] trypanocidal,[4] cytotoxic activity toward KB[5] and Vero cells,[6] inhibitor of HaCaT cell growth,[7] and inhibitor of human keratinocyte hyperproliferation.[8] The wide spectrum of biological activities has attracted widespread interest in the field of medicinal chemistry, therefore, much effort has been focused on the synthetic methods of naphthofuroquinone derivatives. Over the past decades, base-catalyzed,[9] bromine-mediated,[10] different annulation[11-15] (such as thermal cyclization,[11] photoaddition,[12] oxidative cycloaddition,[13] Diels-Alder cycloaddition/aromatization,[14] oxidative cyclization/isomerization,[15]) one-pot cascade,[16] and transition-metal-catalyzed[17] syntheses of the naphthofuroquinone skeleton have been reported.

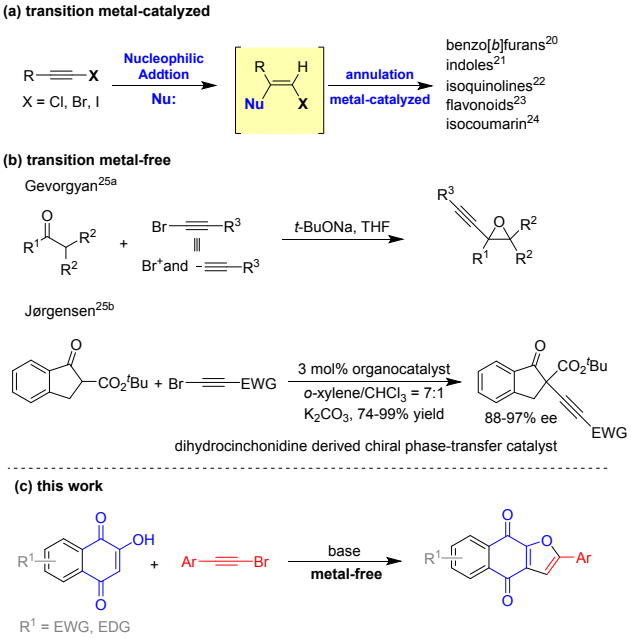
Tandem reactions, through the integration of two or more distinct transformations into one-pot processes, play an important role in the rapid buildup of molecular complexity and diversity.[18] As a dual functionalized compounds, haloalkynes have emerged as versatile building blocks for the construction of heterocycle through a sequential one-pot procedure in recent years.[19] Impressive effort has also been devoted to the development of transition metal-catalyzed methodologies for the syntheses of diverse heterocyclic architectures (Scheme 1a). For instance, benzo[*b*]furans,[20] indoles and 1,2-

benzothiazine 1,1-dioxides backbones,[21] imidazole-fused or quinolinone-fused isoquinolines,[22] flavonoids,[23] and isocoumarin[24] have been constructed through the nucleophilic addition/Pd-catalyzed C-H bond cyclization by Wang,[20] Urabe,[21] Wu and Jiang,[24] and our group,[22,23] respectively. Compared with the well-developed transition metal-catalyzed methods using haloalkynes as the building blocks, metal-free examples for heterocycle preparation are much less documented. Gevorgyan[25a] pioneered the study of haloalkynes serving as a source of both $X^+$ and acetylide ions, and demonstrated a metal-free one-step synthesis of alkynylepoxides from easily available enolizable ketones (Scheme 1b). In addition, Jørgensen[25b] described an organocatalytic enantioselective direct α-alkynylation of β-ketoesters and 3-acyl oxindoles in the presence of $K_2CO_3$ (Scheme 1b). Inspired by Gevorgyan and Jørgensen's works[25] and our ongoing studies on the chemistry of haloalkynes,[22,23] herein, we design a simple one-pot and transition metal-free protocol to obtain naphthofuroquinone derivatives by the alkynylation of 2-hydroxynaphthoquinones with alkynyl bromides and subsequent intramolecular nucleophilic addition (Scheme 1c).

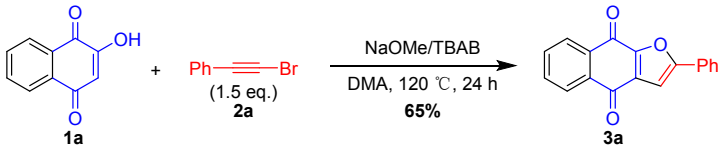
Wang's previous work revealed that alkynyl bromides can undergo nucleophilic addition by phenols to generate (*Z*)-2-bromovinyl phenyl ethers regio- and stereoselectively with high yields in the presence of $Cs_2CO_3$ using DMF as the solvent at 110 °C.[20] On the other hand, Gevorgyan demonstrated that alkynyl bromides can also be used as equivalents of the corresponding $Br^+$ ion and nucleophilic acetylide ions in the presence of stronger base (KHMDS) to afford a

mixture of brominated and alkynated products.[25] Due to the dual nature of haloalkynes, we first needed to address chemical selectivity issue (nucleophilic addition[20] vs bromination[25,26] or alkynation[25]) when using 2-hydroxy-1,4-naphthoquinones as the substrates (Scheme 1c).

**Scheme 1. The construction of heterocyclic architectures using haloalkynes**




**Scheme 2.** Fundamental Data for Reaction Condition Optimization[a]




*modified parameters based on standard conditions*

| base/yield[b] | solvent/yield[b] | additive[c]/yield[b] |
|---|---|---|
| CsF, 46% | DMF, 53% | ——, 0% |
| PivONa, 41% | DMSO, 40% | TBAC, 26% |
| $Cs_2CO_3$, 15% | NMP, 32% | TBAI, 36% |
| KOAc, 13% | MeCN, 12% | BTEAC, 48% |
| $Et_3N$, 11% | 1,4-dioxane, 30% | 18-crown-6, 56% |
| KOH, 9% | Toluene, 36% | TBAB, 41%[d]; 56%[e] |
| *trace*: $K_2CO_3$, $Li_2CO_3$, $KHCO_3$ | *trace*: THF, DCE | temperature/yield[b] |
| HCOONa, NaOAc, KF, $K_3PO_4$ | time/yield[b] | 80 ℃, trace |
| *t*-BuOK, *t*-BuONa, *t*-BuOLi | 12 h, 33% | 100 ℃,42% |
| NaOH, Pyridine, DBU | 48 h, 67% (63%)[f] | 140 ℃, 62% |

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), base (3 equiv), additive (3 equiv) and solvent (1.0 mL), 24 h, air. [b] Isolated yields after chromatography. [c] Abbreviations: TBAB = tetrabutylammonium bromide, TBAC = tetrabutylammonium chloride, TBAI = tetrabutylammonium iodide, BTEAC= benzyltriethylammonium chloride. [d] TBAB (1 equiv) was used. [e] TBAB (2 equiv) was used. [f] One millimole scale.

2-Hydroxy-1,4-naphthoquinone (**1a**) and bromoethynylbenzene (**2a**) as model substrates were selected for sequential alkynylation and intramolecular annulation reaction to construct the naphthofuroquinone **3a** (Scheme 2). Based on the results by Gevorgyan,[25] Wang,[20] and others,[21-24] some new investigations are carried out using the bromoethynylbenzene (**2a**) as the reagent. First, the nature and careful selection of base was very important to the reaction outcome, shown in the left column of Scheme 2. Various bases such as weak bases ($Cs_2CO_3$, $K_2CO_3$, $Li_2CO_3$, $KHCO_3$, KF, $K_3PO_4$, KOAc, and NaOAc), strong bases ($NaO^tBu$, $KO^tBu$, $LiO^tBu$, KOH, and NaOH), organic bases ($Et_3N$, pyridine and DBU) gave the desired product **3a** from a trace quantity to 15% yield; the product **3a** can be obtained in 46 and 41% yields when CsF and PivONa were respectively used; and NaOMe gave a better result and provided **3a** in 65% yield. Second, with NaOMe as the base, polar solvents (DMA, DMF, DMSO, and NMP) generally provided better results than those obtained in less-polar solvents such as 1,4-dioxane, acetonitrile, THF, and DCE; non-polar toluene can give a comparable yield of 36% with DMSO (the second column, Scheme 2). Third, the additive was found to be essential for the efficient formation of furonaphthoquinone **3a**. In the absence of the additive, no expected naphthofuroquinone product **3a** was obtained in all the cases (right column, Scheme 2). The above result indicated that the use of TBAB can increase the dissociation of $C_{sp}$-Br bond probably through the formation of stable tetrabutylammonium acetylide. Thus, TBAB, TBAC, TBAI, BTEAC, and 18-crown-6 were explored as the additive. It was found that a higher ratio of TBAB relative to

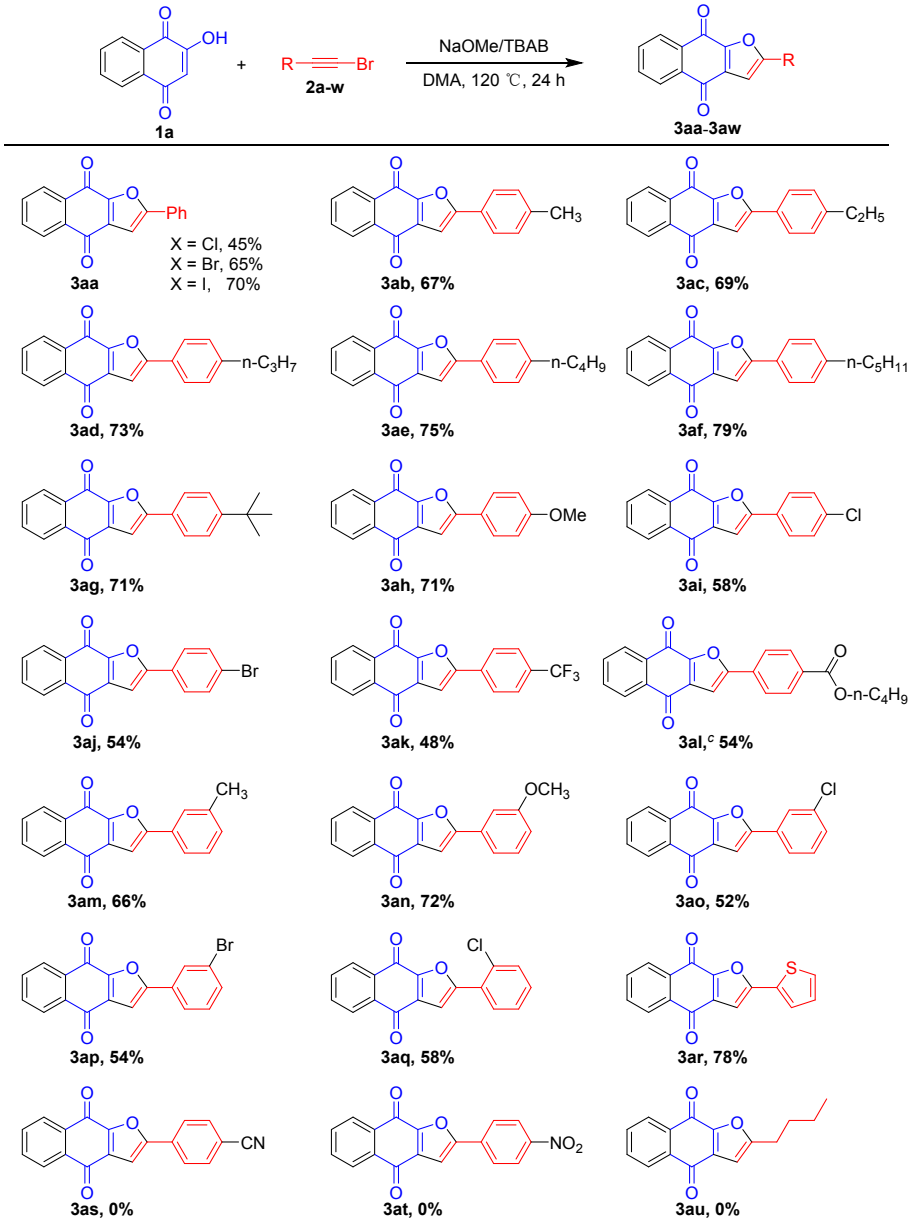
**1a** is preferable to afford a better result [41% (1:1), 56% (2:1), and 65% (3:1)], however, the use of chloride or iodide analogues (TBAC, TBAI, and BTEAC) to effect the transformation afforded inferior results than TBAB. Finally, a set of experiments were carried out to reveal the role of the reaction temperature and time (right and second column, Scheme 2), 120 °C for 24 h was found to be suitable for this tandem reaction. In addition, the reaction can be carried out on a 1.0 mmol scale without compromising the yield (63% vs 65%, Scheme 2). In general, in the presence of combinations of TBAB and NaOMe, the synthesis of naphthofuroquinones **3** was conducted in a one-pot fashion using DMA as the solvent at 120 °C for 24 h.

With the optimized reaction conditions in hand, the scope of this tandem annulation reaction was then examined. A variety of diversely substituted furonaphthoquinone **3** was obtained in moderate to good yields (Tables 1 and 2). Firstly, the scope and generality of haloalkyne substrates were explored in this process (Table 1). The nature of halogen at the alkynyl halide was examined. It was found that alkynyl iodide is superior over the chloride and bromide analogues in that reaction. The yield for the alkynyl halide substrates follows the order alkynyl iodide > alkynyl bromide > alkynyl chloride. As shown in Table 1, a great variety of substituted aryl and heteroaryl bromoacetylenes **2a**-**2r** can be converted into the naphthofuroquinones **3** in moderate to good yields (48-79%). The standard reaction conditions were compatible with various groups including diverse alkyl substituents (methyl, ethyl, *n*-propyl, *n*-butyl, *n*-pentyl, and *tert*-

butyl), methoxy, bromine, chlorine, trifluoromethyl and ester functionality. In general, the *para*-, *metal*-, and *ortho*-substituted aryl bromoacetylenes **2b**-**2q** can smoothly undergo sequential alkynylation/annulation reaction to afford the desired products in good yields. The electronic nature of the aromatic motifs heavily affected the reaction outcome, the introduction of electron-donating substituents (alkyl and methoxy) can afford higher yields than electron-withdrawing substituents (Cl, Br, $CF_3$, and ester). The presence of stronger electron-withdrawing substituents (such as CN and $NO_2$, **2s** and **2t**) at the aromatic ring led to failed reactions under standard reaction conditions. For the *para*-alkyl substituted aryl bromoacetylenes **2b**-**2f**, with the length of carbon chain (from C1 to C5) increasing, the yield increased from 67% to 79%. When extending the substrate scope to alkyl bromoacetylene **2u**, unfortunately, the reaction cannot proceed to give the corresponding product **3au.** It is worth noting that the reaction of methyl ester substrate **2l** and 2-hydroxy-1,4-naphthoquinone **1a** generated the *n*-butyl ester product **3al** in 54% through tandem annulation reaction and subsequent a sodium methoxide-promoted transesterification of methyl ester with TBAB. Secondly, we then explored the scope of 2-hydroxy-1,4-naphthoquinone substrates using bromoethynylbenzene **2a** as the coupling partner (Table 2). A variety of substituents on the aryl moiety were applicable, affording the corresponding cyclized products **3ba**-**3ga** in good yields (65-76%, Table 2). Both electron- donating (−Me, −OMe) and -withdrawing groups (−F, −Cl, and −Br) were tolerant under the reaction conditions. The electronic nature of the

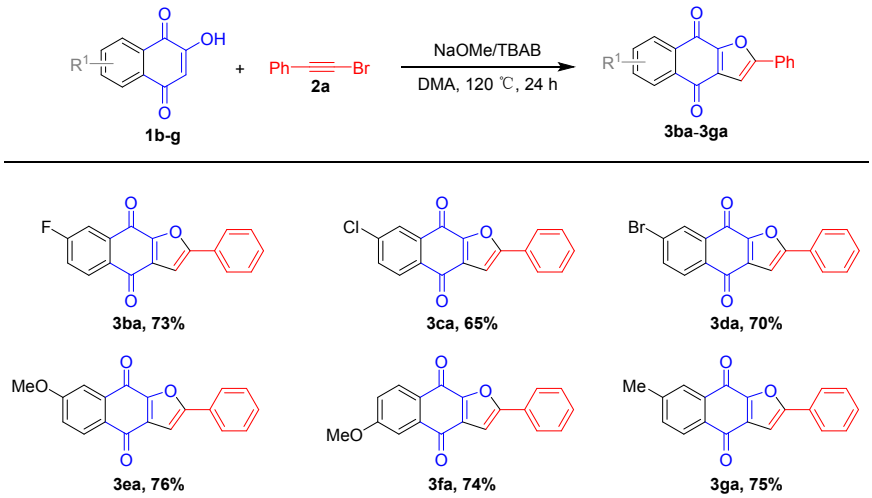
aromatic motifs of 2-hydroxy-1,4-naphthoquinone skeleton did not seem to affect the efficiency: these substituents can be incorporated at the C6 and C7 positions and gave the corresponding products with similar yields.

**Table 1. Variation of the Alkynyl Bromide Substrates**[a,b]



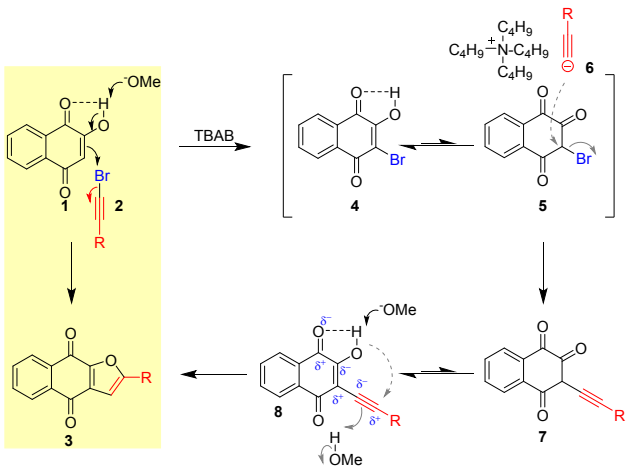

[a] Standard conditions unless otherwise stated: **1a** (0.2 mmol), **2** (0.3 mmol), MeONa (3 equiv), TBAB (2 equiv) and DMA (1.0 mL), 120 ℃, 24 h, air. [b] Yield of isolated product. [c] Methyl 4-(bromoethynyl)benzoate **2l** was used.

**Table 2. Scope of 2-Hydroxynaphthoquinones**[a,b]




[a] Standard conditions unless otherwise stated: **1** (0.2 mmol), **2a** (0.3 mmol), MeONa (3 equiv), TBAB (2 equiv) and DMA (1.0 mL), 120 ℃, 24 h, air. [b] Yield of isolated product.

On the basis of the above results, a plausible reaction pathway for the one-pot tandem synthesis of naphthofuroquinone derivatives was outlined in Scheme 3. A sodium methoxide-promoted deprotonation of 2-hydroxynaphthoquinones **1** produced sodium enolate, which was then brominated at the 3-position of **1** to form the intermediate **4** using the alkynylbromide **2** as the source of $Br^+$.[26] The tautomeric isomer **5** in the keto-form from **4** undergwent a nucleophilic attack by the produced arylacetylide **6** to give the alkynated intermediate **7**, which was transformed into 3-alkynated hydroxynaphthoquinone **8** through a keto–enol tautomeric process. A sodium methoxide-promoted deprotonation and subsequent intramolecular nucleophilic addition of enolate anion to conjugated ynone furnished the cyclized product **3**. To prove the mechanism, the intermediate 4[27] was used to react with ethynylbenzene in the presence of sodium methoxide in DMA at 120 ℃ for 24 h, 3aa can be obtained in 72% yield.




**Scheme 3.** Proposed Mechanism for the tandem synthesis of Naphthofuroquinones **3**.

In conclusion, we have developed a transition metal-free tandem formal [3+2] approach for rapid syntheses of diverse naphtho[2,3-*b*]furan-4,9-dione derivatives through a base-promoted alkynylation and subsequent intramolecular addition reaction of 2-hydroxynaphthalene-1,4-diones with aryl bromoacetylenes. The success of this one-pot domino reaction heavily relies on the careful selection of proper base and additive. The combination of sodium methoxide and TBAB was found to be essential for the efficient formation of furonaphthoquinones. This method allows the synthesis of a variety of multi-substituted furonaphthoquinone derivatives with good functional group tolerance and yields. Considering considerable valance of the products for medicinal science, this tandem reaction could be of synthetic utility for the discovery of drugs.

## Experimental Section

**General Information.** Chemicals were all purchased from commercial suppliers and used without further purification unless otherwise stated. Solvents were

dried and purified according to the standard procedures before use. Reactions were monitored by analytical thin-layer chromatography (TLC). All reactions were conducted in dried glassware. Purification of reaction products was done by flash chromatography with 230–400 mesh silica gel. Hydroxynaphthoquinones **1a**–**1g**[28] and alkynyl halides **2**[22b] were prepared according to the literature methods. Melting points were determined on a melting point apparatus in open capillaries and are uncorrected. Infrared spectra of samples were recorded from 4,000 to 500 $cm^{-1}$ in ATR (attenuated total reflectance) mode using an FT-IR instrument. $^{1}H$ NMR spectra were recorded on a 500 MHz spectrometer, and $^{13}C$ NMR spectra were recorded at 126 MHz. Unless otherwise stated, deuterochloroform ($CDCl_3$) was used as a solvent. Chemical shifts (δ) are given in parts per million downfield relative to tetramethylsilane (TMS). Chemical shifts for carbon resonances are reported in parts per million and are referenced to the carbon resonance of the solvent $CHCl_3$ (δ = 77.16 ppm). The splitting patterns are reported as s (singlet), d (doublet), dd (double doublet), td (triplet of doublet), t (triplet), q (quartet), br (broad), and m (multiplet). Coupling constants are given in hertz. High-resolution mass spectra were recorded on a BIO TOF Q mass spectrometer equipped with an electrospray ion source (ESI), operated in the positive mode.

**General procedures for the synthesis of 2-arylnaphtho[2,3-*b*]furan-4,9-diones 3**. A 10 mL vial equipped with a magnetic stirring bar was charged with 2-hydroxynaphthalene-1,4-diones **1** (0.2 mmol, 1.0 equiv), alkynyl bromides **2**

(0.3mmol, 1.5 equiv), and then sodium methoxide (0.6 mmol, 32.4 mg) and tetrabutylammonium bromide (TBAB, 0.4 mmol, 129.8 mg) were added. Finally, DMA (1.0 mL) was added to the mixture via syringe at room temperature under air. The tube was sealed and put into a preheated oil bath at 120 ℃ for 24 h. The mixture was cooled to room temperature, quenched with water (5 mL), and diluted with ethyl acetate (5 mL). The layers were separated, and the aqueous layer was extracted with 2 × 5 mL of ethyl acetate. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The crude product was then purified by flash chromatography on silica gel (H), eluting with the mixture of ethyl acetate and petroleum ether (1:5).

*2-Phenylnaphtho[2,3-b]furan-4,9-dione (**3aa**).* The reaction was carried out on a 1.0 mmol scale. Red solid, mp 248-252 ℃ (lit.[15b] mp 249-251 ℃); yield, 63% (172.5 mg, Eluent: EtOAc/petroleum ether = 1/5); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.26 – 8.23 (m, 1H), 8.20 – 8.18 (m, 1H), 7.89 (d, $J$ = 7.2 Hz, 2H), 7.78 – 7.73 (m, 2H), 7.51 – 7.44 (m, 3H), 7.19 (s, 1H). $^{13}$C{$^1$H} NMR (126 MHz, $CDCl_3$) $\delta$ 180.8, 173.1, 160.3, 151.6, 134.0, 133.7, 133.1, 132.8, 132.4, 130.3, 129.1, 128.3, 127.0, 126.9, 125.6, 103.0.

*2-(p-Tolyl)naphtho[2,3-b]furan-4,9-dione (**3ab**).* Yield, 67% (38.6 mg, Eluent: EtOAc/petroleum ether = 1/5); yellow solid, mp 264–267 ℃ (lit.[15b] mp 266-267 ℃); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.25 – 8.21 (m, 1H), 8.18 (dd, $J$ = 7.2, 1.4 Hz, 1H), 7.79 – 7.72 (m, 4H), 7.29 – 7.26 (m, 2H), 7.12 (s, 1H), 2.40 (s, 3H). $^{13}$C{$^1$H} NMR (126 MHz, $CDCl_3$) $\delta$ 180.9, 172.9, 160.7, 151.3, 140.7, 134.0, 133.5, 133.1, 132.9,

132.5, 129.8, 126.9, 126.8, 125.6, 125.5, 102.3, 21.5.

*2-(4-Ethylphenyl)naphtho[2,3-b]furan-4,9-dione (**3ac**).* Yield, 69% (41.7 mg, Eluent: EtOAc/petroleum ether = 1/5); yellow solid, mp 186–188 °C (lit.[29] mp 186-189 °C); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.19 – 8.16 (m, 1H), 8.12 (dd, $J$ = 7.1, 1.4 Hz, 1H), 7.74 (d, $J$ = 8.1 Hz, 2H), 7.71 – 7.65 (m, 2H), 7.25 (d, $J$ = 8.1 Hz, 2H), 7.07 (s, 1H), 2.64 (q, $J$ = 7.6 Hz, 2H), 1.21 (t, $J$ = 7.6 Hz, 3H). $^{13}$C{$^1$H} NMR (126 MHz, $CDCl_3$) $\delta$ 181.0, 173.0, 160.7, 151.3, 147.0, 134.0, 133.6, 133.1, 132.9, 132.6, 128.7, 126.9, 126.8, 125.8, 125.6, 102.3, 28.9, 15.3.

*2-(4-Propylphenyl)naphtho[2,3-b]furan-4,9-dione (**3ad**).* Yield, 73% (46.1 mg, Eluent: EtOAc/petroleum ether = 1/5); yellow solid, mp 166–169 °C (lit.[29] mp 167-169 °C); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.19 – 8.16 (m, 1H), 8.14 – 8.10 (m, 1H), 7.74 (d, $J$ = 8.2 Hz, 2H), 7.71 – 7.65 (m, 2H), 7.22 (d, $J$ = 8.2 Hz, 2H), 7.07 (s, 1H), 2.57 (t, $J$ = 7.5 Hz, 2H), 1.65 – 1.57 (m, 2H), 0.90 (t, $J$ = 7.3 Hz, 3H). $^{13}$C{$^1$H} NMR (126 MHz, $CDCl_3$) $\delta$ 181.0, 173.0, 160.8, 151.3, 145.5, 134.0, 133.6, 133.1, 132.9, 132.6, 129.2, 126.9, 126.8, 125.8, 125.6, 102.3, 38.0, 24.3, 13.8.

*2-(4-Butylphenyl)naphtho[2,3-b]furan-4,9-dione (**3ae**).* Yield, 75% (49.6 mg, Eluent: EtOAc/petroleum ether = 1/5); yellow solid, mp 174–175 °C; IR (KBr, cm$^{-1}$): 2958, 2776, 1663, 1614, 1594, 1487, 1457, 1439, 1364, 1259; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.19 – 8.15 (m, 1H), 8.14 – 8.08 (m, 1H), 7.73 (d, $J$ = 8.2 Hz, 2H), 7.71 – 7.65 (m, 2H), 7.23 (d, $J$ = 8.2 Hz, 2H), 7.07 (s, 1H), 2.60 (t, $J$ = 7.5 Hz, 2H), 1.59 – 1.53 (m, 2H), 1.35 – 1.27 (m, 2H), 0.87 (t, J = 7.4 Hz, 3H). $^{13}$C{$^1$H} NMR (126 MHz, $CDCl_3$) $\delta$ 179.9, 171.9, 159.7, 150.3, 144.7, 132.9, 132.5, 132.1, 131.9, 131.5, 128.2,

125.9, 125.8, 124.7, 124.5, 101.3, 34.6, 32.3, 21.3, 12.9. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{22}H_{19}O_3^+$ 331.1329; Found 331.1327.

*2-(4-Pentylphenyl)naphtho[2,3-b]furan-4,9-dione (**3af**).* Yield, 79% (54.4 mg, Eluent: EtOAc/petroleum ether = 1/5); yellow solid, mp 163–164 °C; IR (KBr, $cm^{-1}$): 3119, 2924, 1662, 1615, 1595, 1487, 1456, 1439, 1370, 1353, 958; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 8.19 – 8.16 (m, 1H), 8.12 (dd, $J$ = 7.2, 1.7 Hz, 1H), 7.74 (d, $J$ = 8.2 Hz, 2H), 7.71 – 7.65 (m, 2H), 7.23 (d, $J$ = 8.2 Hz, 2H), 7.07 (s, 1H), 2.59 (t, $J$ = 8.0 Hz, 2H), 1.61 – 1.55 (m, 2H), 1.30 – 1.24 (m, 4H), 0.83 (t, $J$ = 6.9 Hz, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) $\delta$ 179.9, 171.9, 159.8, 150.3, 144.8, 132.9, 132.5, 132.1, 131.9, 131.5, 128.2, 125.9, 125.8, 124.8, 124.6, 101.3, 34.9, 30.4, 29.9, 21.5, 13.0. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{23}H_{21}O_3^+$ 345.1485; Found 345.1484.

*2-(4-(tert-Butyl)phenyl)naphtho[2,3-b]furan-4,9-dione (**3ag**).* Yield, 71% (46.9 mg, Eluent: EtOAc/petroleum ether = 1/5); orange solid, mp 170–172 °C (lit.[29] mp 169-172 °C); $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 8.19 – 8.16 (m, 1H), 8.12 (dd, $J$ = 7.3, 1.4 Hz, 1H), 7.76 (d, $J$ = 8.4 Hz, 2H), 7.70 – 7.65 (m, 2H), 7.44 (d, $J$ = 8.4 Hz, 2H), 7.08 (s, 1H), 1.29 (s, 9H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) $\delta$ 179.9, 171.9, 159.6, 152.9, 150.3, 132.9, 132.5, 132.1, 131.9, 131.5, 125.9, 125.8, 125.1, 124.5, 124.4, 101.4, 34.0, 30.1.

*2-(4-Methoxyphenyl)naphtho[2,3-b]furan-4,9-dione (**3ah**).* Yield, 71% (46.9 mg, Eluent: EtOAc/petroleum ether = 1/5); red solid, mp 213–215 °C (lit.[15b] mp 215-216 °C); $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 8.25 – 8.22 (m, 1H), 8.20 – 8.16 (m, 1H), 7.83 (d, $J$ = 8.8 Hz, 2H), 7.77 – 7.71 (m, 2H), 7.05 (s, 1H), 7.00 (d, $J$ = 8.8 Hz, 2H), 3.88 (s,

3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) $\delta$ 181.0, 172.8, 161.3, 160.6, 151.1, 134.0, 133.5, 133.1, 133.0, 132.7, 127.3, 126.9, 126.8, 121.1, 114.6, 101.4, 55.5.

*2-(4-Chlorophenyl)naphtho[2,3-b]furan-4,9-dione (**3ai**).* Yield, 58% (35.8 mg, Eluent: EtOAc/petroleum ether = 1/5); red solid, mp 276–278 °C (lit.[10] mp 276-277.5 °C); $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 8.17 (d, $J$ = 6.2 Hz, 1H), 8.13 (d, $J$ = 6.4 Hz, 1H), 7.76 (d, $J$ = 8.2 Hz, 2H), 7.72 – 7.67 (m, 2H), 7.40 (d, $J$ = 8.2 Hz, 2H), 7.11 (s, 1H). $^{13}C\{^1H\}$NMR (126 MHz, $CDCl_3$) $\delta$ 179.6, 172.0, 158.1, 150.7, 135.3, 133.1, 132.7, 132.0, 131.8, 131.3, 128.4, 126.0, 125.9, 125.8, 125.7, 102.3.

*2-(4-Bromophenyl)naphtho[2,3-b]furan-4,9-dione (**3aj**).* Yield, 54% (38.4 mg, Eluent: EtOAc/petroleum ether = 1/5); brown solid, mp 267–269 °C (lit.[10] mp 267-268 °C); $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 8.18 – 8.16 (m, 1H), 8.12 (dd, $J$ = 7.1, 1.7 Hz, 1H), 7.71 – 7.66 (m, 4H), 7.56 – 7.52 (m, 2H), 7.12 (s, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) $\delta$ 179.6, 172.0, 158.1, 150.7, 133.1, 132.7, 132.0, 131.8, 131.4, 131.3, 126.2, 126.0, 125.9, 125.9, 123.7, 102.3.

*2-(4-(Trifluoromethyl)phenyl)naphtho[2,3-b]furan-4,9-dione (**3ak**).* Yield, 48% (32.8 mg, Eluent: EtOAc/petroleum ether = 1/5); light yellow solid, mp 205–209 °C; IR (KBr, $cm^{-1}$): 2784, 1662, 1598, 1445, 1385, 1366, 1113; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 8.19 (d, $J$ = 6.3 Hz, 1H), 8.15 (d, $J$ = 5.8 Hz, 1H), 7.95 (d, $J$ = 7.5 Hz, 2H), 7.77 – 7.64 (m, 4H), 7.24 (s, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) $\delta$ 179.6, 172.1, 157.5, 150.8, 133.1, 132.8, 132.1, 132.0, 131.7, 131.2, 129.6, 129.2, 127.4, 126.0, 125.9, 123.0, 122.3, 102.9. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{19}H_{10}F_3O_3^+$ 343.0577; Found 343.0585.

*Butyl 4-(4,9-dioxo-4,9-dihydronaphtho[2,3-b]furan-2-yl)benzoate (**3al**).* Yield, 54% (40.3 mg, Eluent: EtOAc/petroleum ether = 1/5); light yellow solid, mp 203–205 °C; IR (KBr, $cm^{-1}$): 2775, 1714, 1664, 1596, 1537, 1440, 1365, 1287, 1222, 1109, 957; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 8.21 – 8.17 (m, 1H), 8.15 – 8.12 (m, 1H), 8.08 (d, $J$ = 8.4 Hz, 2H), 7.88 (d, $J$ = 8.4 Hz, 2H), 7.73 – 7.67 (m, 2H), 7.23 (s, 1H), 4.29 (t, $J$ = 6.6 Hz, 2H), 1.74 – 1.69 (m, 2H), 1.47 – 1.39 (m, 2H), 0.93 (t, $J$ = 7.4 Hz, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) $\delta$ 179.5, 172.1, 164.8, 157.9, 151.0, 133.1, 132.8, 132.0, 131.7, 131.2, 131.0, 130.7, 129.3, 126.0, 125.9, 124.3, 103.6, 64.2, 29.7, 18.3, 12.8. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{23}H_{19}O_5^+$ 375.1227; Found 375.1220.

*2-(m-Tolyl)naphtho[2,3-b]furan-4,9-dione (**3am**).* Yield, 66% (38.4 mg, Eluent: EtOAc/petroleum ether = 1/5); yellow solid, mp 241–243 °C; IR (KBr, $cm^{-1}$): 2777, 1668, 1615, 1594, 1540, 1486, 1457, 1366, 956; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 8.18 (dd, $J$ = 7.2, 1.5 Hz, 1H), 8.12 (dd, $J$ = 7.2, 1.5 Hz, 1H), 7.72 – 7.64 (m, 3H), 7.61 (d, $J$ = 7.8 Hz, 1H), 7.30 (t, $J$ = 7.7 Hz, 1H), 7.19 (s, 1H), 7.10 (s, 1H), 2.37 (s, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) $\delta$ 179.8, 172.0, 159.6, 150.4, 137.9, 133.0, 132.6, 132.1, 131.9, 131.4, 130.1, 128.0, 127.2, 125.9, 125.8, 125.1, 121.8, 101.8, 20.4. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{19}H_{13}O_3^+$ 289.0859; found 289.0857.

*2-(3-Methoxyphenyl)naphtho[2,3-b]furan-4,9-dione (**3an**).* Yield, 72% (47.1 mg, Eluent: EtOAc/petroleum ether = 1/5); yellow solid, mp 206–211 °C; IR (KBr, $cm^{-1}$): 2779, 1669, 1614, 1595, 1532, 1473, 1366, 1218; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 8.18 – 8.15 (m, 1H), 8.12 – 8.10 (m, 1H), 7.71 – 7.65 (m, 2H), 7.39 (d, $J$ = 7.7 Hz,

1H), 7.32 – 7.29 (m, 2H), 7.10 (s, 1H), 6.90 (dd, *J* = 8.1, 2.1 Hz, 1H), 3.82 (s, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) $\delta$ 179.8, 172.0, 159.2, 159.1, 150.5, 133.0, 132.6, 132.0, 131.8, 131.4, 129.2, 128.5, 125.9, 125.8, 117.1, 115.4, 109.4, 102.2, 54.5. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{19}H_{13}O_4^+$ 305.0808; Found 305.0807.

*2-(3-Chlorophenyl)naphtho[2,3-b]furan-4,9-dione (**3ao**).* Yield, 52% (33.7 mg, Eluent: EtOAc/petroleum ether = 1/5); brown solid, mp 299–302 ℃ (lit.[10] mp 300-301 ℃); $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 8.27 – 8.25 (m, 1H), 8.22 – 8.20 (m, 1H), 7.90 (s, 1H), 7.81 – 7.75 (m, 3H), 7.48 – 7.41 (m, 2H), 7.23 (s, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) $\delta$ 181.4, 173.9, 157.0, 151.9, 134.7, 134.5, 133.9, 133.5, 132.7, 132.6, 131.8, 131.5, 130.0, 128.0, 127.8, 127.7, 127.6, 109.2.

*2-(3-Bromophenyl)naphtho[2,3-b]furan-4,9-dione (**3ap**).* Yield, 54% (38.1 mg, Eluent: EtOAc/petroleum ether = 1/5); yellow solid, mp 288–290 ℃; IR (KBr, $cm^{-1}$): 2831, 2779, 1666, 1615, 1595, 1441, 1271, 1073; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 8.27 – 8.25 (m, 1H), 8.22 – 8.19 (m, 1H), 8.06 (s, 1H), 7.82 – 7.75 (m, 3H), 7.57 (d, *J* = 7.9 Hz, 1H), 7.37 (t, *J* = 7.9 Hz, 1H), 7.22 (s, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) $\delta$ 180.6, 173.2, 158.5, 151.9, 134.1, 133.8, 133.1, 133.0, 132.8, 132.2, 130.7, 130.2, 128.4, 127.1, 127.0, 124.1, 123.3, 103.9. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{18}H_{10}O_3Br^+$ 352.9808; Found 352.9804 (100%), 354.9787 (84%).

*2-(2-Chlorophenyl)naphtho[2,3-b]furan-4,9-dione (**3aq**).* Yield, 58% (35.9 mg, Eluent: EtOAc/petroleum ether = 1/5); orange solid, mp 185–187 ℃ (lit.[10] mp 185-186 ℃); $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 8.20 – 8.17 (m, 1H), 8.16 – 8.14 (m, 1H), 8.04 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.73 – 7.69 (m, 2H), 7.62 (s, 1H), 7.46 (dd, *J* = 7.8, 1.3

Hz, 1H), 7.37 – 7.29 (m, 2H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) $\delta$ 179.6, 172.2, 155.3, 150.2, 133.0, 132.8, 132.1, 131.7, 130.9, 130.8, 130.1, 129.7, 128.3, 126.3, 126.0, 126.0, 125.9, 107.5.

*2-(Thiophen-2-yl)naphtho[2,3-b]furan-4,9-dione (**3ar**).* Yield, 78% (43.7 mg, Eluent: EtOAc/petroleum ether = 1/5); red solid, mp 218–222 °C; IR (KBr, $cm^{-1}$): 3113, 2026, 1661, 1615, 1492, 1371, 1355, 1233; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 8.24 – 8.22 (m, 1H), 8.18 (dd, $J$ = 7.3, 1.6 Hz, 1H), 7.78 – 7.72 (m, 2H), 7.62 (dd, $J$ = 3.7, 1.0 Hz, 1H), 7.47 (dd, $J$ = 5.0, 1.0 Hz, 1H), 7.15 – 7.13 (m, 1H), 7.01 (s, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) $\delta$ 179.6, 171.7, 154.7, 149.9, 133.0, 132.6, 132.0, 131.8, 131.5, 129.8, 127.4, 127.3, 126.1, 125.9, 125.8, 101.6. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{16}H_9O_3S^+$ 281.0267; Found 281.0260.

*7-Fluoro-2-phenylnaphtho[2,3-b]furan-4,9-dione (**3ba**).* Yield, 73% (43.7 mg, Eluent: EtOAc/petroleum ether = 1/5); red solid, mp 205–206 °C; IR (KBr, $cm^{-1}$): 2779, 1667, 1616, 1532, 1456, 1370, 1353, 1264; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 8.17 (dd, $J$ = 8.5, 5.3 Hz, 1H), 7.83 (d, $J$ = 8.1 Hz, 2H), 7.45 – 7.39 (m, 3H), 7.35 – 7.31 (m, 1H), 7.14 (s, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) $\delta$ 178.5, 170.6, 165.3 (166.3, 164.3, d, $^1J_{C\text{-}F}$ = 257 Hz), 159.8, 150.3, 134.7 (134.8, 134.7, d, $^3J_{C\text{-}F}$ = 8 Hz), 131.7, 129.5, 129.0 (129.0, 128.9, d, $^3J_{C\text{-}F}$ = 9 Hz), 128.5 (128.6, 128.5, d, $^4J_{C\text{-}F}$ = 5 Hz), 128.1, 127.1, 124.6, 119.4 (119.5, 119.3, d, $^2J_{C\text{-}F}$ = 23 Hz), 113.0 (113.1, 112.9, d, $^2J_{C\text{-}F}$ = 24 Hz), 102.1. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{18}H_{10}FO_3^+$ 293.0609; Found 293.0608.

*7-Chloro-2-phenylnaphtho[2,3-b]furan-4,9-dione (**3ca**).* Yield, 65% (40.1 mg,

Eluent: EtOAc/petroleum ether = 1/5); pink solid, mp 201–203 °C; IR (KBr, $cm^{-1}$): 2831, 2779, 1667, 1615, 1479, 1367, 1256, 1099; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 8.14 (s, 1H), 8.07 (d, $J$ = 8.2 Hz, 1H), 7.83 (d, $J$ = 7.3 Hz, 2H), 7.63 (d, $J$ = 8.2 Hz, 1H), 7.45 – 7.39 (m, 3H), 7.13 (s, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) $\delta$ 178.8, 170.7, 159.8, 150.2, 140.0, 133.1, 132.5, 131.7, 130.3, 129.5, 128.1, 127.5, 127.1, 126.0, 124.6, 102.0. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{18}H_{10}ClO_3^+$ 309.0313; Found 309.0312.

*7-Bromo-2-phenylnaphtho[2,3-b]furan-4,9-dione (**3da**).* Yield, 70% (49.8 mg, Eluent: EtOAc/petroleum ether = 1/5); yellow solid, mp 214–217 °C; IR (KBr, $cm^{-1}$): 2836, 2780, 1662, 1618, 1594, 1441, 1273, 1070; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 8.30 (s, 1H), 7.99 (d, $J$ = 8.1 Hz, 1H), 7.84 – 7.80 (m, 3H), 7.45 – 7.38 (m, 3H), 7.13 (s, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) $\delta$ 178.9, 170.7, 159.7, 150.0, 135.5, 133.0, 131.6, 130.6, 129.5, 129.0, 128.5, 128.1, 127.5, 127.1, 124.6, 102.0. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{18}H_9O_3Br^+$ 374.9627; Found 374.9627 (100%), 376.9606 (98%).

*7-Methoxy-2-phenylnaphtho[2,3-b]furan-4,9-dione (**3ea**).* Yield, 76% (49.2 mg, Eluent: EtOAc/petroleum ether = 1/5); orange soild, mp 218–221 °C; IR (KBr, $cm^{-1}$): 2815, 2776, 1669, 1613, 1489, 1369, 1261, 1181; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 8.18 (d, $J$ = 8.6 Hz, 1H), 7.90 - 7.87 (m, 2H), 7.66 (d, $J$ = 2.7 Hz, 1H), 7.51 - 7.42 (m, 3H), 7.21 (dd, $J$ = 8.6, 2.7 Hz, 1H), 7.17 (s, 1H), 3.98 (s, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) $\delta$ 181.8, 174.1, 161.2, 161.1, 152.6, 135.1, 134.7, 134.1, 133.9, 133.5, 131.3, 130.6, 128.0, 119.2, 117.5, 111.5, 104.3, 56.6. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{19}H_{13}O_4^+$ 305.0808; Found 305.0806.

*6-Methoxy-2-phenylnaphtho[2,3-b]furan-4,9-dione (**3fa**).* Yield, 74% (48.9 mg, Eluent: EtOAc/petroleum ether = 1/5); orange solid, mp 225–229 °C; IR (KBr, $cm^{-1}$): 2819, 1662, 1614, 1583, 1533, 1477, 1454, 1363, 1219, 1188; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 8.11 (d, $J$ = 8.6 Hz, 1H), 7.83 – 7.80 (m, 2H), 7.59 (d, $J$ = 2.7 Hz, 1H), 7.44 – 7.37 (m, 3H), 7.14 (dd, $J$ = 8.6, 2.7 Hz, 1H), 7.11 (s, 1H), 3.91 (s, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) $\delta$ 179.7, 171.6, 163.1, 158.8, 150.9, 134.3, 131.0, 129.1, 128.3, 128.1, 127.4, 125.1, 124.4, 118.5, 110.3, 101.8, 55.0. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{19}H_{13}O_4^+$ 305.0808; found 305.0807.

*7-Methyl-2-phenylnaphtho[2,3-b]furan-4,9-dione (**3ga**).* Yield, 75% (43.2 mg, Eluent: EtOAc/petroleum ether = 1/5); red soild, mp 204–206 °C; IR (KBr, $cm^{-1}$): 2779, 1664, 1611, 1595, 1547, 1484, 1456, 1363, 941; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 8.02 (d, $J$ = 7.8 Hz, 1H), 7.98 (s, 1H), 7.84 – 7.82 (m, 2H), 7.46 (d, $J$ = 7.8 Hz, 1H), 7.44 – 7.36 (m, 3H), 7.12 (s, 1H), 2.45 (s, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) $\delta$ 179.8, 172.4, 159.2, 150.6, 144.2, 133.2, 131.8, 131.5, 129.8, 129.2, 128.1, 127.4, 126.4, 126.2, 124.5, 102.0, 20.8. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{19}H_{13}O_3^+$ 289.0859; Found 289.0859.

## ASSOCIATED CONTENT

### Supporting Information

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$^1H$ and $^{13}C$ NMR spectra of the products and High-resolution mass spectra of new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

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