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Copper-Catalyzed One-Pot Cross-Dehydrogenative Thienannulation: Chemoselective Access to Naphtho[2,1-*b*]thiophene-4,5-diones and Subsequent Transformation to Benzo[*a*]thieno[3,2-*c*]phenazines

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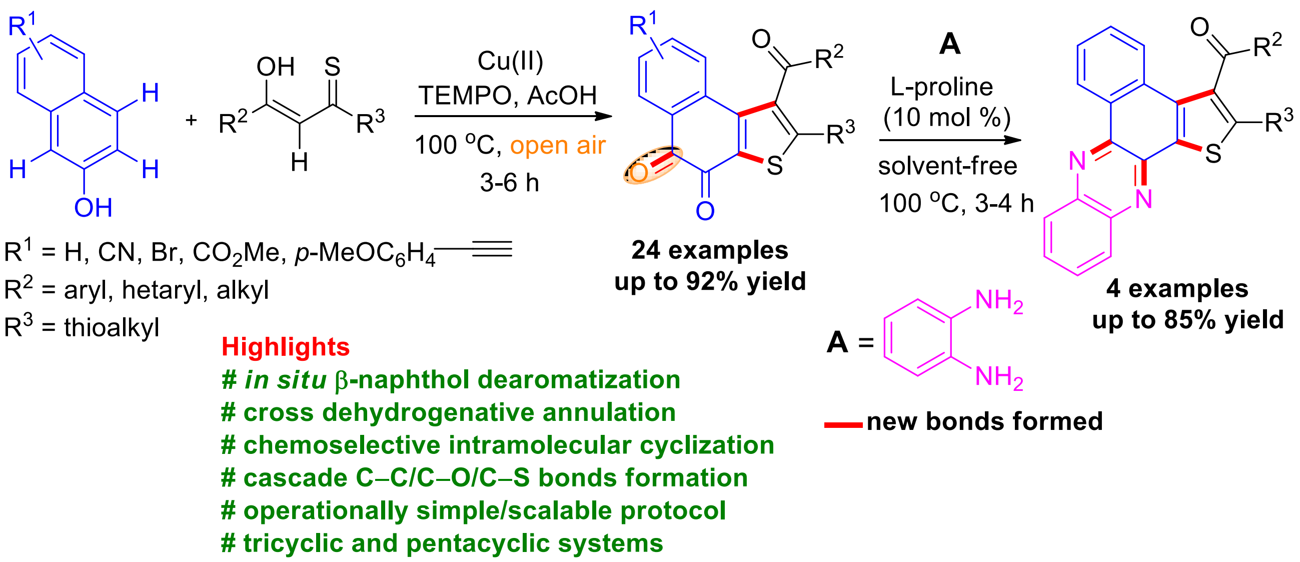


ABSTRACT: A facile, cost-effective and highly efficient copper-catalyzed, TEMPO-mediated straightforward synthesis of 2,3-disubstituted naphtho[2,1-*b*]thiophene-4,5-diones has been achieved via Cross-Dehydrogenative Thienannulation (CDT). The reaction proceeded via in situ generated naphthalene-1,2-diones by dearomatization of β-naphthols, followed by oxidative heteroannulation with α-enolic dithioesters chemoselectively in an open-flask. Further, the naphtho[2,1-*b*]thiophene-4,5-diones undergo L-Proline-catalyzed cross-dehydrative coupling with *ortho*-phenylenediamine enabling pentacyclic benzo[*a*]thieno[3,2-*c*]phenazines in good yields under solvent-free conditions. A mechanistic rationale for this cascade reaction sequence is well supported by the control experiments.

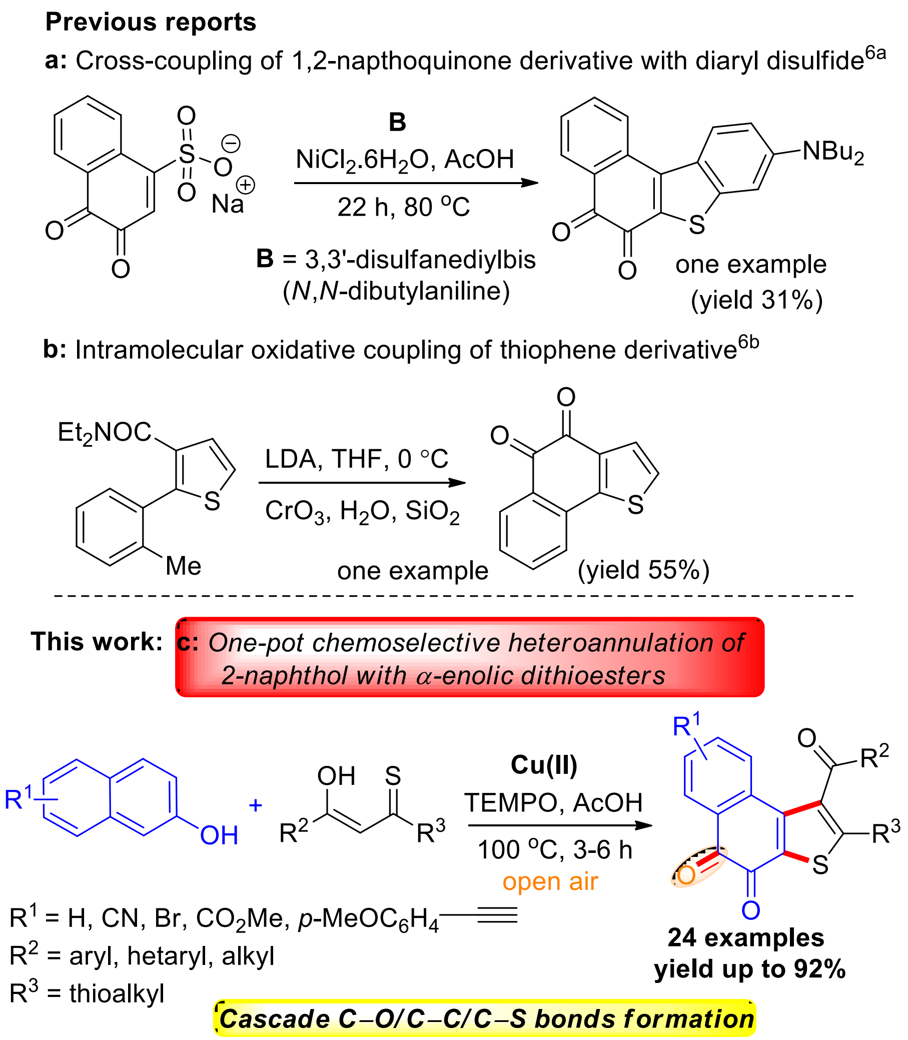
INTRODUCTION

Polycyclic molecules are important skeletal units that are widely distributed in a number of natural products and biologically active compounds.[1] Sulfur and its compounds have been used extensively for centuries and are important to our daily lives. In particular, fused sulfur heterocycles are key structural motifs of many active pharmaceutical ingredients and material science.[2] Among them, naphtho fused thiophenes such as naphtho[2,1-*b*]thiophene-4,5-diones, naphtho[1,2-*b*]thiophene-4,5-diones and naphtho[2,3-*b*]thiophene-4,9-diones are notable due to their massive applications in various fields. Some of their derivatives show antitumor, antibacterial or antimicrobial activities, and high efficacy toward the cell lines that were highly resistant to treatment with doxorubicin such as MDA-MB435 (melanoma), IGROV (ovarian) and SF-295 (glioblastoma) human cell lines.[3] Moreover, naphthothiophene derivatives possess unique semi-conducting properties that not only could be used in solar cells, but also exploited in the preparation of organic nanotubes. Some of them have been utilized for the preparation of dyes, which are further employed in dye-sensitized solar cells.[4] Hence, significant interest has been directed toward the development of efficient and concise methods for the synthesis of naphtho-fused thiophene derivatives.

Literature reports[5] for the construction of naphtho[1,2-*b*]thiophene-4,5-diones and naphtho[2,3-*b*]thiophene-4,9-diones involve C–H activation of thiophene derivatives employing different metallic reagents followed by oxidation of corresponding naphthothiophenes. Yoshida and co-workers[6a] reported the synthesis of 1,2-naphthoquinone fused thiophene derivatives via oxidative cyclization of Folin's reagent or sodium 1,2-naphthoquinone-4-sulfonate with diaryl disulfide in the presence of nickel salt at 80 ^{o}C. Snieckus and coworkers[6b] disclosed the synthesis of 1,2-naphthoquinone fused thiophene by intramolecular oxidative coupling of suitably substituted thiophene derivative (Scheme 1a and 1b). However, the reported strategies suffer from significant limitations such as poor yields, lack of generality and pre-functionalization of starting materials. The direct methods for the synthesis of naphtho[2,1-*b*]thiophene-4,5-diones are rather limited. Therefore, it is still challenging and highly desirable to explore operationally simple, efficient and widely applicable general approach for the construction of structurally diverse naphtho-fused thiophene derivatives.

To the best of our knowledge, no report is known to date on the synthesis of naphtho[2,1-*b*]thiophene-4,5-diones utilizing α-enolic dithioesters (EDTEs). With this in mind, we envisioned the viability of annulation between readily available and inexpensive β-naphthols and α-enolic dithioesters for the direct construction of naphtho[2,1-*b*]thiophene-4,5-dione scaffolds. With the aim of triggering annulation, we performed different experiments employing β-naphthols and α-enolic dithioesters modifying the variables, which enabled the optimized reaction conditions for the formation of naphtho[2,1-*b*]thiophene-4,5-diones in high yield (Scheme 1c).

Scheme 1. Strategies for Naphtho[2,1-*b*]thiophene-4,5-diones



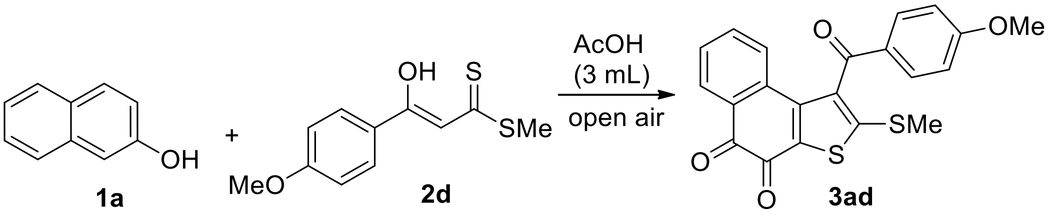
RESULTS AND DISCUSSION

The development of metal-catalyzed cross-coupling reactions over the past 30 years has revolutionized the way, carbon–carbon bonds are formed. The development of this chemistry is highly important because it offers a great opportunity to diminish the dependence of synthetic chemistry on traditional cross-coupling reactions, which heavily rely on prefunctionalization of the coupling partners and precious metals. These methods have profoundly changed the protocols for the construction of simple/complex molecules for organic materials, polymers, and lead compounds in medicinal chemistry from simpler entities.[7a-e] In view of green and economical synthesis, coupling between two partners under oxidative conditions has been developed recently for the formation of chemical bonds and revolutionized the classical coupling technology. Oxidative cross-coupling[7f-i] (OCC) is a hot research topic that covers aspects of classical coupling, C-H functionalization, oxidation reactions, and radical chemistry for chemical, materials, and biological synthesis. Cascade processes have received tremendous development over the past decades, and remain one of the most powerful tools to create carbon–carbon or carbon–heteroatom bonds in one-pot due to their ecologic and economic competence.[8] These strategies are not only limited to the synthesis of simple molecules (carbocycles/heterocycles), but also have been utilized for biomimetic synthesis of several natural products,[9] thus revolutionized the field dramatically. Utilizing these tools, chemists improved their skills in communicating chemistry to non-experts, thereby also reflecting their perceptions on research. Therefore, one of the important frontiers of modern synthesis is the development of cascade processes incorporating the chemoselective intramolecular reaction.

The demand for better synthetic methods towards bioactive heterocyclic scaffolds and their derivatives is high and continuous. β-Oxodithioesters exert diverse and amazing reactivity as novel multi-role-synthons, and have been widely utilized as a practical key intermediate for the construction of diverse important heterocyclic frameworks.[10] As part of an on-going study into the design and development of operationally simple and efficient methodologies for the construction of valuable heterocycles utilizing β-oxo/α-enolic dithioesters,[11] we envisioned to employ inexpensive and easily viable β-naphthols as one of the reaction partner for annulation with α-enolic dithioesters with the aim to trigger new naphtho fused sulfur heterocycles. During the recent past, β-naphthol has been employed as a reaction partner in various organic transformations.[12] Herein, we report the first concise example of a copper-catalyzed, TEMPO-mediated cross-dehydrogenative annulation of β-naphthols with α-enolic dithioesters in open air, which enabled 2,3-disubstituted naphtho[2,1-*b*]thiophene-4,5-diones in good yields (Scheme 1c). Of particular interest is the chemoselectivity of the reactions, consistent with a cascade process.

Initially, we performed the reaction of β-naphthol **1a** (1 mmol) with α-enolic dithioesters **2d** (1 mmol) in AcOH (3 mL) in the absence of catalyst, and with 10 mol% of CuCl separately at room temperature. Under both conditions, we did not observe the trace of the desired product **3ad**, even after 12 h of stirring, and the starting materials remained completely unreacted (Table 1, entries 1 and 2). In an effort to trigger the reaction, we carried out the model reaction in the presence of 2 equiv of TEMPO at room temperature. TEMPO triggered the reaction producing the desired product **3ad**, albeit in only 10% isolated yield (Table 1, entry 3). The above observation was encouraging enough to optimize the reaction conditions. To improve the efficiency of the reaction, the test reaction was carried out at higher temperatures (Table 1, entries 4 and 5). It has been found that maximum conversion occurred at 100 °C, providing the desired product **3ad** in 40% yield after 10 h (Table 1, entry 5). The improvement in the result of the protocol prompted us to investigate some other copper salts such as $CuBr_2$, $Cu(OAc)_2$ and $Cu(OTf)_2$ (Table 1, entries 6-8). To our satisfaction, 10 mol% of $Cu(OTf)_2$ provided the best result affording the desired product **3ad** in 75% yield (Table 1, entry 8).

Table 1. **Optimization of Reaction Conditions**[a]



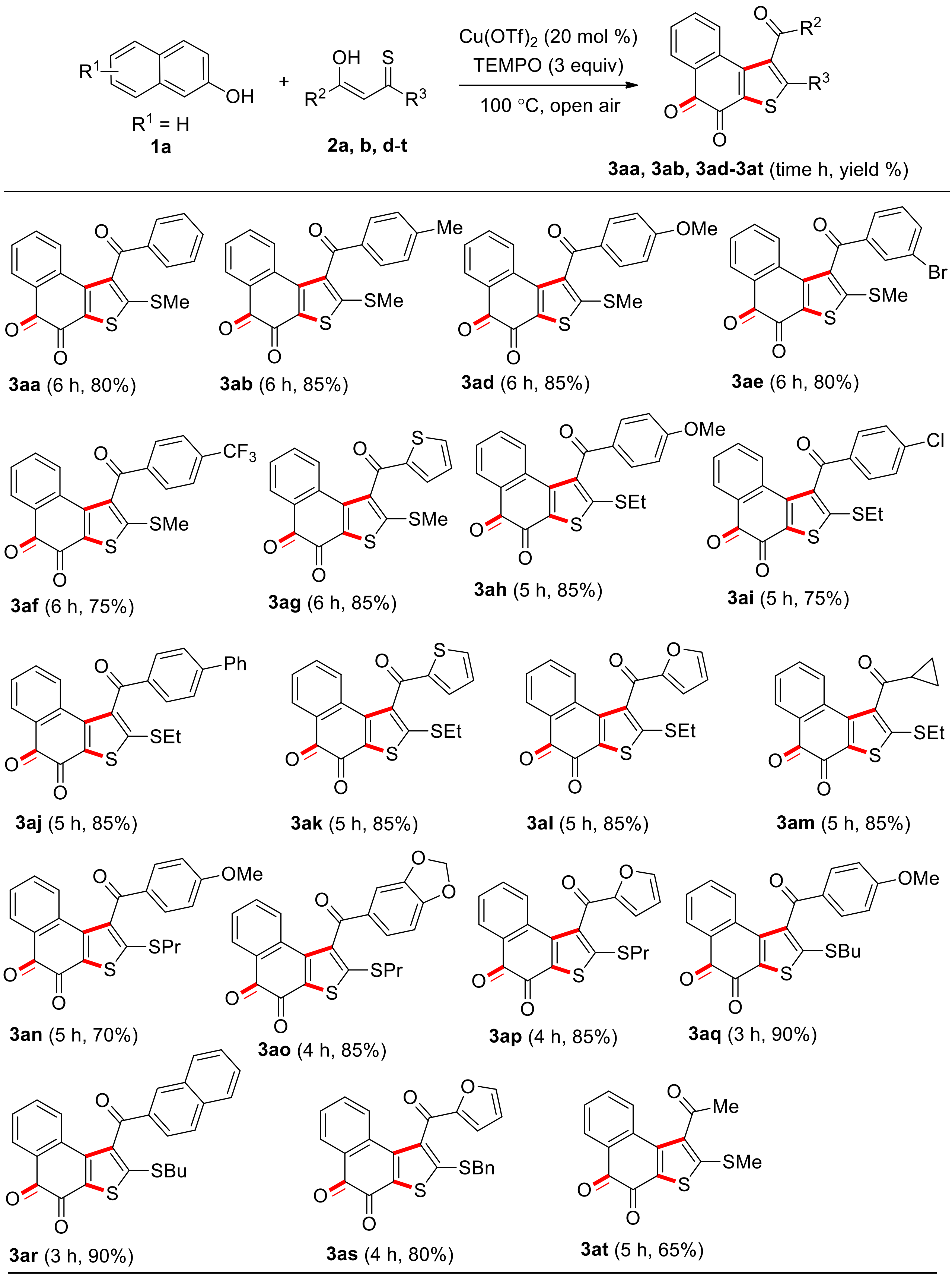
entry	catalyst (mol%)	oxidant (equiv)	temp (°C)	time (h)	yield (%)[b]
1	none	none	rt	12	ND
2	CuCl (10)	none	rt	12	ND
3	CuCl (10)	TEMPO (2)	rt	12	10
4	CuCl (10)	TEMPO (2)	80	12	20
5	CuCl (10)	TEMPO (2)	100	10	40
6	$CuBr_2$ (10)	TEMPO (2)	100	10	60
7	$Cu(OAc)_2$ (10)	TEMPO (2)	100	8	65
8	$Cu(OTf)_2$ (10)	TEMPO (2)	100	8	75
9	$Cu(OTf)_2$ (20)	TEMPO (2)	100	7	80
10	$Cu(OTf)_2$ (30)	TEMPO (2)	100	7	80
11	$Cu(OTf)_2$ (20)	TEMPO (3)	100	6	85
12	$Cu(OTf)_2$ (20)	TEMPO (4)	100	6	85
13	$Cu(OTf)_2$ (20)	TEMPO (3)	120	6	65
14	$Cu(OTf)_2$ (20)	TBHP (4)	100	12	30

[a]Reaction conditions: All the reactions were performed with **1a** (1 mmol), **2d** (1 mmol), $Cu(OTf)_2$ (20 mol%), TEMPO (3 equiv) in 3 mL of AcOH at 100 °C in open air. [b]Isolated yield. ND = Not Detected.

Encouraged by the efficacy of $Cu(OTf)_2$, next we optimized its loading. It was found that 20 mol% of $Cu(OTf)_2$ furnished the desired product **3ad** in 80% isolated yield within 7 h (Table 1, entry 9). Further increasing the amount of $Cu(OTf)_2$ could not improve the result (Table 1, entry 10). Finally, we screened the loading of TEMPO, and it was observed that 3 equiv of TEMPO afforded maximum conversion in minimum time providing the desired product **3ad** in 85% yield (Table 1, entries 11 and 12). Further elevating the reaction temperature (120 ^{o}C) was found to be detrimental to the reaction (Table 1, entry 13) that could be due to decomposition of dithioester at higher temperature. Use of other oxidant TBHP did mediate the reaction, but could not provide the better result (Table 1, entry 14). Thus, the optimum condition for the synthesis of **3ad** was achieved by employing **1a** (1 mmol), **2d** (1 mmol), 20 mol% of $Cu(OTf)_2$, TEMPO (3 equiv) in 3 mL of AcOH at 100 °C in open flask (Table 1, entry 11).

With the established optimal conditions in hand, we then set out to explore the generality and the scope of the protocol by using a variety of structurally diverse α-enolic dithioesters **2**, and the results are summarized in Scheme 2. α-Enolic dithioesters (EDTEs) bearing an electron-donating or electron-withdrawing group on the phenyl ring (R^2 moiety) could tolerate well the reaction conditions forming the target product **3** in good yield, revealing no obvious electronic impact from the substituents. The variants of the substituents like Me, OMe, OCH_2O, Cl, Br, and strong electron-withdrawing CF_3 group on the phenyl ring (R^2 moiety) were found to be compatible well and did not hamper the reaction process. Importantly, EDTEs bearing heteroaromatic groups such as 2-thienyl and 2-furyl at R^2 moiety were also well tolerated furnishing the corresponding products **3** up to 85% yields (Scheme 2, **3ag**, **3ak**, **3al**, **3ap**, and **3as**). It is noteworthy that α-enolic dithioesters bearing not only aromatic and heteroaromatic groups at R^2 moiety, but extended aromatics such as biphenyl and 2-naphthyl groups also found to be compatible well under the optimized conditions (Scheme 2, **3aj** and **3ar**). Halo-substituted derivatives could be potential precursors for further synthetic manipulations to access useful compounds.

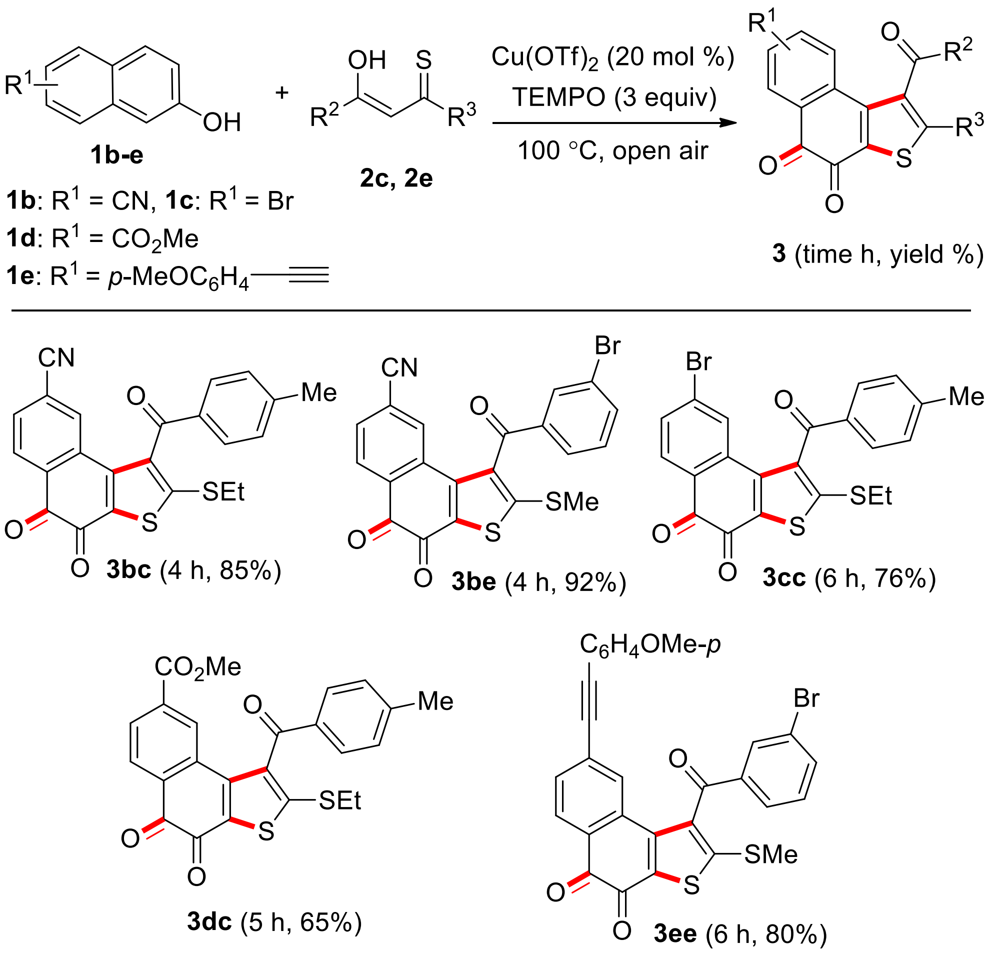
Scheme 2. Substrate Scope with different EDTEs to Access Products 3



Notably, aliphatic based cyclopropyl and methyl substituted dithioesters **2m** and **2t** also underwent the reaction smoothly to give the products **3am** and **3at** in 85% and 65% yield, respectively. Next, in order to probe the effect of R^3 substituent of dithioester, we evaluated the substrate **2** bearing different substituents at R^3. Replacing the R^3 thiomethyl with groups such as thioethyl, thiopropyl, thiobutyl and thiobenzyl were successfully amenable to this protocol affording the corresponding naphtho[2,1-*b*]thiophene-4,5-diones **3** in high yields (Scheme 2, **3ah**-**3at**), revealing the broad adaptability of this method. The consecutive formation of C−C and C−S bonds enabled a thiophene ring over naphthoquinone moiety, and made this strategy an excellent tool toward molecular diversity. It is worthy to note that the excellent regio-selectivity profile was observed for this cascade heterocyclization. The chemoselective strategy reported herein allows a novel entry to naphtho[2,1-*b*]thiophene-4,5-diones with full control over substitution at the various ring positions, which would otherwise be more difficult to prepare by alternative routes.

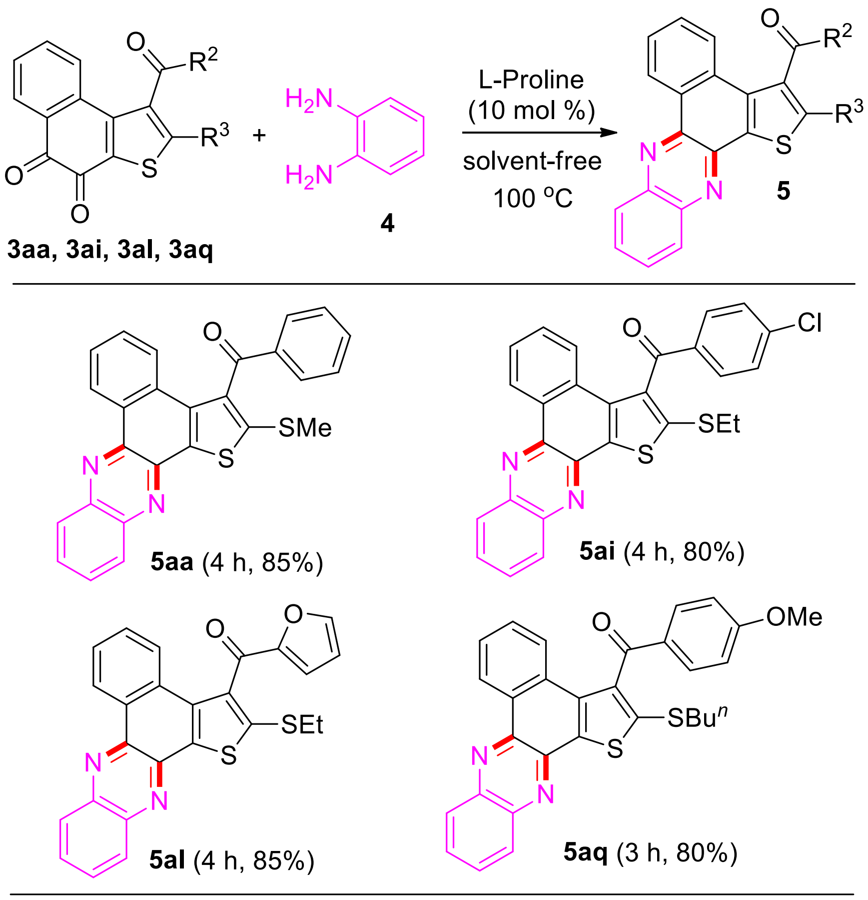
To further extend the utility of this reaction, we also investigated four β-naphthol derivatives having different substituents (**1b**-**1e**) with a view to add further diversity to naphtho[2,1-*b*]thiophene-4,5-dione frameworks. Subsequently, 6-cyano-2-naphthol **1b**, 6-bromo-2-naphthol **1c**, 6-carbomethoxy-2-naphthol **1d** and 6-(*p*-methoxyphenylethynyl)-2-naphthol **1e** upon treatment with dithioesters (**2c**, **2e)** separately under the previously described one-pot standard conditions afforded 8-substituted naphtho[2,1-*b*]thiophene-4,5-diones in 76-92% yields (Scheme 3, **3bc**, **3be**, **3cc**, **3dc**, **3ee**).

Scheme 3. **Use of Various β-Naphthol Derivatives toward the Synthesis of Naphtho[2,1-*b*]thiophene-4,5-diones**



Since the naphtho[2,1-*b*]thiophene-4,5-diones **3** bear adjacent keto groups, we considered evaluating their scope with 1,2-diaminobenzene[13] with the vision to get phenazine derivatives, which have immense applications in various fields such as dyes, pharmaceuticals and antibiotics.[14] Subsequently, we treated compound **3** with 1,2-diaminobenzene **4** in the presence of 10 mol% of L-proline at 100 ^{o}C under solvent-free conditions (for detail optimization refer to Supporting Information, Table S1). The reaction proceeded well affording the corresponding pentacyclic phenazine derivatives **5** in good yields (Scheme 4). Differently decorated naphtho[2,1-*b*]thiophene-4,5-diones could be successfully employed.

Scheme 4. Construction of Pentacyclic Phenazine Derivatives 5



The structures of all the newly synthesized naphtho[2,1-*b*]thiophene-4,5-diones **3** and their corresponding phenazine derivatives **5aa**, **5ai**, **5al** and **5aq** were fully characterized by their satisfactory spectral (^{1}H, ^{13}C, and HRMS) studies. Further, the structure of one of the representative naphtho[2,1-*b*]thiophene-4,5-dione **3ap** was unambiguously established by the single crystal X-ray diffraction analysis (see Supporting Information for X-ray structure and other details).[15]

To gain some insights into the mechanism of the reaction, we conducted a series of control experiments. The standard reaction without TEMPO was unsuccessful even after 24 h (Scheme 5, Eq. 1). Similarly, another standard experiment without Cu(II) provided **3aa** in only 30% isolated yield along with the formation of several undesired overlapping spots on TLC plate, which could not be isolated, indicating crucial role of Cu(II) for successful clean transformation (Scheme 5, Eq. 2). To prove the intermediacy of naphthalene-1,2-dione **6**, we conducted two different sets of reaction.

First the oxidation of β-naphthol under our optimized reaction conditions and next the reaction of isolated naphthalene-1,2-dione intermediate with α-enolic dithioester. When β-naphthol **1a** was treated with 20 mol% of Cu(II) and 1 equiv of TEMPO in AcOH at 100 ^{o}C in open flask, to our great pleasure, the corresponding intermediate **6** was obtained in 80% yield within 0.5 h (Scheme 5, Eq. 3). Further treatment of **6** with **2a** under the standard reaction conditions without TEMPO and with 2 equiv of TEMPO furnished the desired product **3aa** in 40% and 75% yield, respectively (compare with Scheme 2, entry **3aa**) validating the intermediacy of compound **6** and the key role of TEMPO in oxidative cyclization (Scheme 5, Eqs. 4 and 5). To ascertain the role of the atmospheric oxygen during the transformation, we performed the standard reaction of **1a** with **2a** under the argon atmosphere. The desired product **3aa** was obtained only in 15% yield even after 24 h of heating at 100 ^{o}C. The above observation indicates that molecular oxygen is necessary for the oxidation of **1** to intermediate **6** (Scheme 5, Eq. 6).

Scheme 5. Control Experiments

$$\mathbf{1} + \mathbf{2a} \xrightarrow[\text{without TEMPO, 24 h}]{\text{optimized conditions}} \mathbf{3aa}\ (0\%) \qquad \textbf{Eq. 1}$$

$$\mathbf{1} + \mathbf{2a} \xrightarrow[\text{without Cu(II)}]{\text{optimized conditions}} \mathbf{3aa}\ (30\%) + \text{complex TLC pattern} \qquad \textbf{Eq. 2}$$

$$\mathbf{1} \xrightarrow[\text{AcOH, 100 }^{o}\text{C, 0.5 h, open atm.}]{\text{Cu (II), TEMPO}} \mathbf{6}\ (80\%) \qquad \textbf{Eq. 3}$$

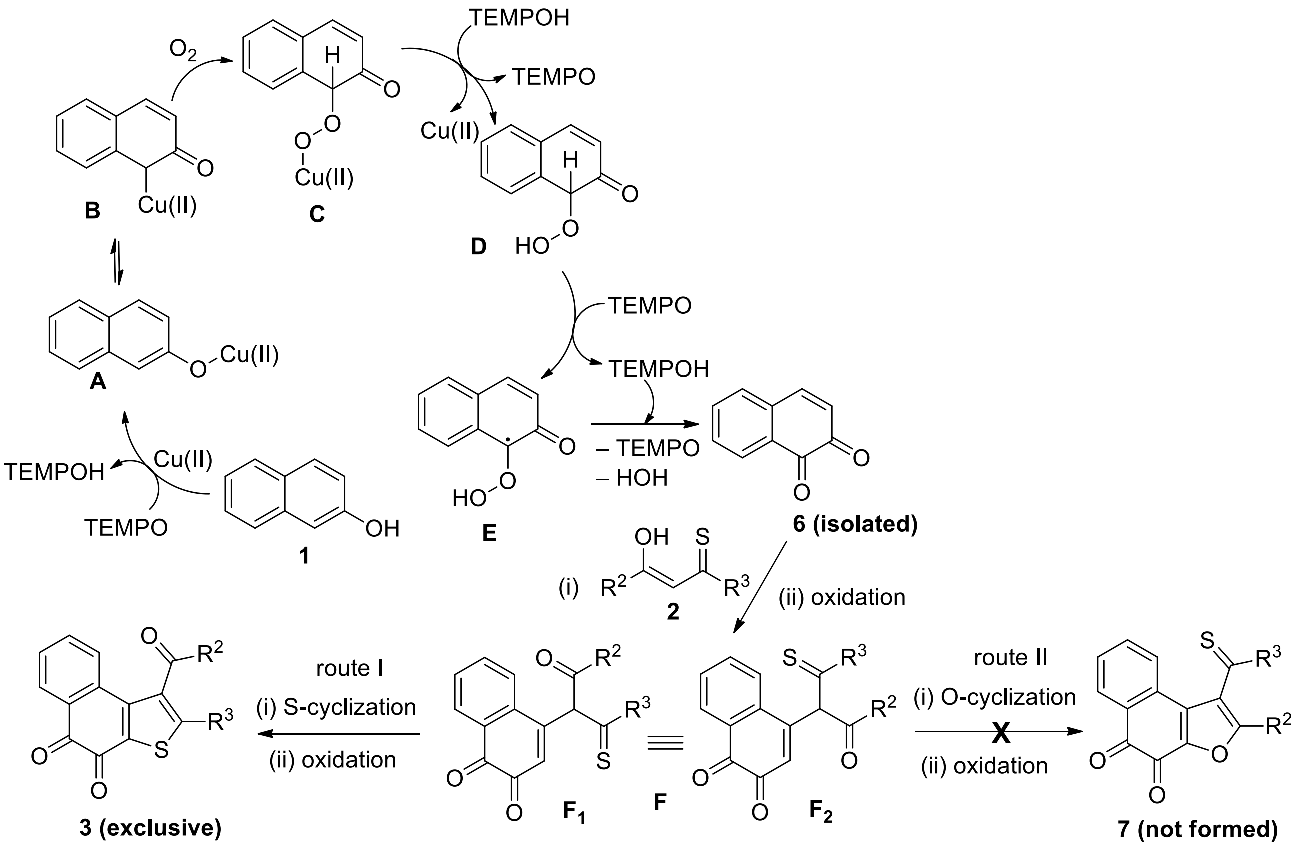
$$\mathbf{6} + \mathbf{2a} \xrightarrow[\text{without TEMPO, 12 h}]{\text{optimized conditions}} \mathbf{3aa}\ (40\%) \qquad \textbf{Eq. 4}$$

$$\mathbf{6} + \mathbf{2a} \xrightarrow[\text{TEMPO (2 equiv), 6 h}]{\text{optimized conditions}} \mathbf{3aa}\ (75\%) \qquad \textbf{Eq. 5}$$

$$\mathbf{1} + \mathbf{2a} \xrightarrow[\text{under argon atm., 24 h}]{\text{optimized conditions}} \mathbf{3aa}\ (15\%) \qquad \textbf{Eq. 6}$$

On the basis of our experimental observations and control experiment studies, a plausible mechanistic proposal is depicted in Scheme 6. The first step is believed to be the copper-catalyzed, TEMPO mediated oxidation of β-naphthol to naphthalene-1,2-dione intermediate **6** that has been isolated and fully characterized. Oxidative addition of β-naphthol **1** to Cu(II) catalyst would lead to species **A**, which undergoes tautomerization to more favoured form **B**. Species **B** on reaction with atmospheric oxygen could produce a copper stabilized peroxide intermediate **C**, which reacts with TEMPOH to generate another peroxide intermediate **D**. Intermediate **D** upon reaction with TEMPO generates a radical intermediate **E**, which upon oxidation produces naphthalene-1,2-dione intermediate **6** that acts as Michael acceptor. Subsequent a Michael-type attack of α-enolic dithioester **2** via its α-C atom to intermediate **6** provided open chain intermediate **F**. Intermediate **F** may undergo intramolecular cyclization via its two possible rotamers $\mathbf{F_1}$ and $\mathbf{F_2}$ through pathways I and II to furnish tricyclic naphtho[2,1-*b*]thiophene-4,5-dione **3** and naphtho[2,1-*b*]furan-4,5-dione **7**, respectively. Rotamer $\mathbf{F_1}$ undergoes chemoselective S-cyclization via route I followed by oxidation to give the desired compound **3**. The alternative O-cyclization of rotamer $\mathbf{F_2}$ could lead to naphtho fused furan derivative **7** via route II. During the course of our present investigation, we did not observe a trace of compound **7**, and compound **3** was obtained exclusively. It should be emphasized that under the present conditions only S-cyclization took place making the protocol highly chemoselective (Scheme 6). It could be due to the thioalkyl group attached to the thiocarbonyl carbon, which increases the nucleophilicity of thiocarbonyl sulfur making it more efficient toward nucleophilic attack than carbonyl oxygen. Moreover, the aromatic ring attached to the carbonyl carbon further decreases the nucleophilicity of carbonyl oxygen making it almost inefficient toward nucleophilic attack.

Scheme 6. **Proposed Mechanism for the Formation of Naphtho[2,1-*b*]thiophene-4,5-dione 3**



CONCLUSION

In summary, we have developed a new cascade C-O/C-C/C-S bonds formation via synergistic Cu-catalyzed TEMPO-mediated cross-dehydrogenative annulation (CDA) of β-naphthols with α-enolic dithioesters that enabled efficient construction of tricyclic 2,3-disubstituted naphtho[2,1-*b*]thiophene-4,5-diones **3**. The reaction involved *in situ* formation of naphthalene-1,2-diones **6** from dearomatization of β-naphthols **1** followed by thienannulation with α-enolic dithioesters via Michael-type addition/oxidation/cyclization/oxidation cascade sequence. Non-toxic conditions, flexible structural modification, broad substrate scope, excellent chemoselectivity, and good functional group tolerance are the practical advantages of this new domino protocol. Further transformation of compound **3** to pentacyclic fused phenazine derivatives **5** makes this strategy highly viable for future applications. It is worth to note that the described cascade chemistry is general, eco-compatible and low cost, making this protocol a good alternative to existing ones.

EXPERIMENTAL SECTION

General: Chemicals were purchased from commercial suppliers and used without further purification. α-Enolic dithioesters could be easily prepared by reported procedure.[16] All the ^{1}H and ^{13}C NMR spectra if not mentioned otherwise, have been recorded at room temperature on JEOL AL 500 FT-NMR spectrometer. Chemical shifts are given as δ value (in parts per million, ppm) with reference to tetramethylsilane (TMS) as the internal standard, and the coupling constants (J) were given in Hz. Proton-decoupled ^{13}C{^{1}H} NMR spectra were recorded at 125 MHz. Mass spectra were recorded on Agilent 6530 Accurate-Mass Q-TOF and Thermo Exactive orbitrap instruments. Melting points were determined with Büchi B-540 melting point apparatus and are uncorrected. All the reactions were monitored by TLC using pre-coated sheets of silica gel G/UV-254 plates of 0.25 mm thickness (Merck 60F_{254}) using different organic solvent mixtures.

General Experimental Procedures for the Synthesis of Compounds 3 and 5

*Typical procedure for the synthesis of compound **3*** (Schemes 2 and 3). A dry 25 mL round-bottomed flask equipped with a magnetic stir bar was charged with a solution of β-naphthol **1** (1.0 mmol) and TEMPO (3.0 equiv) in 3 mL acetic acid followed by addition of 20 mol% of $Cu(OTf)_2$. The reaction mixture was stirred at 100 ^{o}C for 10 min, then α-enolic dithioester **2** (1.0 mmol) was added to this. The resulting mixture was then allowed to stir at 100 ^{o}C for the stipulated period of time (Scheme 2). After completion of the reaction (monitored by TLC), the reaction mixture was diluted with 30 mL of ethyl acetate followed by washing with aqueous $NaHCO_3$ (2 x 10 mL) to neutralize excess of acetic acid. The organic layer was dried over anhydrous Na_2SO_4, and solvent was evaporated under reduced pressure. The crude residue thus obtained was purified by column chromatography over silica gel

(100-200 mesh) using increasing percentage of ethyl acetate in hexane as eluent to afford the pure products **3**.

Typical procedure for the synthesis of ***5*** (Scheme 4). A mixture of compound **3** (0.5 mmol), *ortho*-phenylenediamine **4** (0.5 mmol), and L-Proline (10 mol%) was taken in 10 mL oven dried round bottom flask and stirred at 100 ^{o}C for the stipulated period of time (Scheme 3). After completion of the reaction (monitored by TLC), the mixture was diluted with 20 mL of $CHCl_3$ followed by washing with aqueous NH_4Cl (2 x 10 mL). The organic layer was dried over anhydrous Na_2SO_4, and solvent was evaporated under reduced pressure. The crude residue thus obtained was purified by column chromatography over silica gel (100-200 mesh) using increasing percentage of ethyl acetate in hexane as eluent to afford the pure phenazine derivative **5**.

1-Benzoyl-2-(methylthio)naphtho[2,1-b]thiophene-4,5-dione (**3aa**): (yield 80%, 291 mg); Red solid; m. p. = 148-150 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, J = 9.00 Hz, 1H), 7.93 (d, J = 7.00 Hz, 2H), 7.64 (t, J = 8.00 Hz, 1H), 7.49 (t, J = 8.00 Hz, 2H), 7.33-7.27 (m, 2H), 7.17 (d, J = 7.50 Hz, 1H), 2.61 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.4, 180.6, 171.1, 157.7, 144.9, 136.1, 135.9, 135.5, 135.1, 134.7, 132.0, 131.2, 130.9, 130.1, 130.0, 129.5, 128.9, 126.9, 124.2, 19.3; HRMS [ESI, $(M+Na)^+$]: $C_{20}H_{12}NaO_3S_2$, Calcd.: 387.0126, Found: 387.0137.

1-(4-Methylbenzoyl)-2-(methylthio)naphtho[2,1-b]thiophene-4,5-dione (**3ab**): (yield 85%, 321 mg); Red solid; m. p. = 155-157 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (d, J = 6.50 Hz, 1H), 7.86 (d, J = 8.00 Hz, 2H), 7.34-7.22 (m, 5H), 2.62 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.8, 180.6, 170.9, 157.0, 146.4, 144.7, 136.1, 135.9, 135.4, 134.6, 133.6, 132.7, 132.2, 131.9, 131.1, 130.8, 130.1, 129.8, 126.7, 21.6, 19.0; HRMS [ESI, $(M+Na)^+$]: $C_{21}H_{14}NaO_3S_2$, Calcd.: 401.0282, Found: 401.0291.

1-(4-Methoxybenzoyl)-2-(methylthio)naphtho[2,1-b]thiophene-4,5-dione (**3ad**): (yield 85%, 335 mg); Red solid; m. p. = 197-199 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02-8.01 (m, 1H), 7.85 (d, J = 8.50 Hz, 2H), 7.26-7.25 (m, 2H), 7.19-7.17 (m, 1H), 6.89 (d, *J* = 9.00 Hz, 2H), 3.80 (s, 3H), 2.54 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.6, 180.6, 170.9, 165.1, 156.9, 144.6, 136.2, 135.5, 134.6, 132.5, 131.9, 131.0, 130.8, 129.8, 129.0, 126.6, 114.7, 113.9, 55.5, 19.1; HRMS [ESI, $(M+Na)^+$]: $C_{21}H_{14}NaO_4S_2$, Calcd.: 417.0231, Found: 417.0240.

1-(3-Bromobenzoyl)-2-(methylthio)naphtho[2,1-b]thiophene-4,5-dione (**3ae**): (yield 80%, 354 mg); Gummy red; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, *J* = 7.25 Hz, 1H), 7.71-7.69 (m, 1H), 7.61-7.59 (m, 1H), 7.41-7.34 (m, 5H), 2.63 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.2, 180.5, 171.1, 161.0, 145.8, 138.0, 134.9, 133.9, 132.3, 131.7, 130.9, 130.7, 129.8, 127.8, 127.4, 122.3, 19.0; HRMS [ESI, $(M+Na)^+$]: $C_{20}H_{11}BrNaO_3S_2$, Calcd.: 466.9210, Found: 466.9218.

2-(Methylthio)-1-(4-(trifluoromethyl)benzoyl)naphtho[2,1-b]thiophene-4,5-dione (**3af**): (yield 75%, 324 mg); Red solid; m. p. = 186-188 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (d, *J* = 7.30 Hz, 1H), 8.06 (d, *J* = 8.05 Hz, 2H), 7.77 (d, *J* = 8.15 Hz, 2H), 7.38-7.31 (m, 2H), 7.10 (d, *J* = 7.60 Hz, 1H), 2.64 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.1, 180.2, 170.8, 157.9, 144.6, 138.5, 135.7, 135.3, 134.7, 134.5, 131.5, 131.2, 130.7, 130.1, 130.0, 126.5, 126.3, 126.3, 19.1; HRMS [ESI, $(M+Na)^+$]: $C_{21}H_{11}F_3NaO_3S_2$, Calcd.: 454.9999, Found: 454.9998.

2-(Methylthio)-1-(thiophene-2-carbonyl)naphtho[2,1-b]thiophene-4,5-dione (**3ag**): (yield 85%, 314 mg); Gummy red; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13-8.11 (m, 1H), 7.83 (d, *J* = 4.95 Hz, 1H), 7.59 (d, *J* = 3.40 Hz, 1H), 7.38-7.36 (m, 3H), 7.13 (d, *J* = 4.25 Hz, 1H), 2.65 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.9, 180.5, 170.9, 157.8, 144.3, 143.3, 137.2, 136.2, 135.5, 134.6, 131.8, 131.1, 130.8, 129.9, 129.0, 126.6, 19.2; HRMS [ESI, $(M+Na)^+$]: $C_{18}H_{10}NaO_3S_3$, Calcd.: 392.9690, Found: 392.9699.

2-(Ethylthio)-1-(4-methoxybenzoyl)naphtho[2,1-b]thiophene-4,5-dione (**3ah**): (yield 85%, 347 mg); Gummy red; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11-8.10 (m, 1H), 7.92 (d, *J* = 8.00 Hz, 2H), 7.34-7.33 (m, 2H), 7.27-7.26 (m, 1H), 6.97 (d, *J* = 9.00 Hz, 2H), 3.88 (s, 3H), 3.06 (q, *J* = 7.50 Hz, 2H), 1.37 (t, *J* = 7.50 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.5, 180.5, 170.8, 165.1, 156.8, 144.5, 136.2, 135.4, 132.5, 131.9, 131.0, 130.7, 129.7, 129.0, 126.6, 114.6, 55.6, 29.7, 19.0; HRMS [ESI, $(M+Na)^+$]: $C_{22}H_{16}NaO_4S_2$, Calcd.: 431.0388, Found: 431.0410.

1-(4-Chlorobenzoyl)-2-(ethylthio)naphtho[2,1-b]thiophene-4,5-dione (**3ai**): (yield 75%, 309 mg); Red solid; m. p. = 147-149 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (d, *J* = 8.35 Hz, 1H), 7.89 (d, *J* = 8.20 Hz, 2H), 7.48 (d, *J* = 8.40 Hz, 2H), 7.36-7.34 (m, 2H), 7.15 (d, *J* = 8.00 Hz, 11H), 3.07 (q, *J* = 7.33 Hz, 2H), 1.37 (t, *J* = 7.27 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.2, 180.3, 171.1, 155.0, 144.3, 141.7, 136.7, 135.5, 135.4, 134.4, 131.7, 131.2, 130.7, 129.9, 129.8, 126.4, 31.3, 14.0; HRMS [ESI, $(M+Na)^+$]: $C_{21}H_{13}ClNaO_3S_2$, Calcd.: 434.9892, Found: 434.9897.

1-([1,1'-Biphenyl]-4-carbonyl)-2-(ethylthio)naphtho[2,1-b]thiophene-4,5-dione (**3aj**): (yield 85%, 386 mg); Red solid; m. p. = 146-148 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13-8.11 (m, 1H), 8.02 (d, *J* = 8.00 Hz, 2H), 7.73 (d, *J* = 8.00 Hz, 2H), 7.63 (d, *J* = 7.50 Hz, 2H), 7.49-7.40 (m, 3H), 7.35-7.34 (m, 2H), 7.27-7.25 (m, 1H), 3.08 (q, *J* = 7.50 Hz, 2H), 1.38 (t, *J* = 7.50 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.0, 180.5, 171.1, 154.7, 147.6, 144.4, 139.3, 137.5, 135.6, 134.8, 131.9, 131.2, 130.6, 129.9, 129.1, 128.8, 127.9, 127.4, 126.6, 31.4, 14.1; HRMS [ESI, $(M+Na)^+$]: $C_{27}H_{18}NaO_3S_2$, Calcd.: 477.0595, Found: 477.0599.

2-(Ethylthio)-1-(thiophene-2-carbonyl)naphtho[2,1-b]thiophene-4,5-dione (**3ak**): (yield 85%, 326 mg); Gummy red; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (d, *J* = 6.50 Hz, 1H), 7.84 (d, *J* = 5.00 Hz, 1H), 7.59 (d, *J* = 3.50 Hz, 1H), 7.40-7.36 (m, 3H), 7.14 (t, *J* = 4.50 Hz, 1H), 3.09 (q, *J* = 7.20 Hz, 2H), 1.40 (t, *J* = 7.70 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.1, 180.4, 171.1, 155.3, 144.0, 143.5, 137.2, 137.1, 136.2, 135.6, 135.3, 131.8, 131.1, 130.7, 129.9, 129.1, 126.5, 31.4, 14.0; HRMS [ESI, $(M+Na)^+$]: $C_{19}H_{12}NaO_3S_3$, Calcd.: 406.9846, Found: 406.9838.

2-(Ethylthio)-1-(furan-2-carbonyl)naphtho[2,1-b]thiophene-4,5-dione (**3al**): (yield 85%, 313 mg); Red solid; m. p. = 111-113 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (d, *J* = 6.65 Hz, 1H), 7.67 (s, 1H), 7.41-7.36 (m, 2H), 7.29 (d, *J* = 7.30 Hz, 1H), 6.59 (s, 1H), 3.10 (q, *J* = 7.26 Hz, 2H), 1.40 (t, *J* = 7.32 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.5, 179.6, 171.1, 156.4, 152.2, 148.8, 144.4, 135.5, 132.0, 131.1, 130.7, 129.8, 126.4, 113.3, 31.3, 14.0; HRMS [ESI, $(M+Na)^+$]: $C_{19}H_{12}NaO_4S_2$, Calcd.: 391.0075, Found: 391.0083.

1-(Cyclopropanecarbonyl)-2-(ethylthio)naphtho[2,1-b]thiophene-4,5-dione (**3am**): (yield 85%, 291 mg); Red solid; m. p. = 120-122 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (d, *J* = 7.50 Hz, 1H), 7.56-7.55 (m, 2H), 7.44-7.41 (m, 1H), 3.10 (q, *J* = 7.50 Hz, 2H, $-SCH_2$), 2.29-2.24 (m, 1H), 1.47-1.42 (m, 5H, 1 X $–CH_3$, 1 X $-CH_2-$), 1.18-1.14 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.9, 180.6, 171.0, 156.4, 144.0, 138.3, 135.2, 134.6, 132.0, 131.2, 131.1, 130.8, 127.1, 30.8, 29.7, 24.1, 14.5, 13.8; HRMS [ESI, $(M+Na)^+$]: $C_{18}H_{14}NaO_3S_2$, Calcd.: 365.0282, Found: 365.0289.

1-(4-Methoxybenzoyl)-2-(propylthio)naphtho[2,1-b]thiophene-4,5-dione (**3an**): (yield 70%, 295 mg); Gummy red; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12-8.10 (m, 1H), 7.92 (d, *J* = 7.25 Hz, 2H), 7.35-7.33 (m, 3H), 6.97 (d, *J* = 8.50 Hz, 2H), 3.88 (s, 3H), 3.01 (t, *J* = 7.27 Hz, 2H), 1.78-1.70 (m, 2H), 0.99 (t, *J* = 7.27 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.7, 180.5, 171.0, 165.0, 154.8, 144.2, 137.6, 135.4, 132.4, 131.9, 131.0, 130.7, 129.7, 129.1, 126.5, 114.5, 55.6, 38.9, 22.2, 13.2; HRMS [ESI, $(M+Na)^+$]: $C_{23}H_{18}NaO_4S_2$, Calcd.: 445.0544, Found: 445.0546.

1-(Benzo[d][1,3]dioxole-5-carbonyl)-2-(propylthio)naphtho[2,1-b]thiophene-4,5-dione (**3ao**): (yield 85%, 371 mg); Red solid; m. p. = 110-112 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12-8.10 (m, 1H), 7.51 (br s, 1H), 7.43 (br s, 1H), 7.37-7.35 (m, 2H), 7.26-7.23 (m, 1H), 6.84(d, *J* = 8.00 Hz, 1H), 6.10 (s, 2H), 3.01 (t, *J* = 7.00 Hz, 2H), 1.77-1.72 (m, 2H), 1.00 (t, *J* = 7.50 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.3, 180.4, 171.0, 154.7, 153.5, 148.9, 144.2, 137.4, 135.4, 135.1, 131.8, 131.0, 130.6, 129.7, 127.7, 126.3, 108.5, 102.3, 39.0, 22.2, 13.2; HRMS [ESI, $(M+Na)^+$]: $C_{23}H_{16}NaO_5S_2$, Calcd.: 459.0337, Found: 459.0325.

1-(Furan-2-carbonyl)-2-(propylthio)naphtho[2,1-b]thiophene-4,5-dione (**3ap**): (yield 85%, 325 mg); Red solid; m. p. = 144-146 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (d, *J* = 6.50 Hz, 1H), 7.67 (s, 1H), 7.41-7.37 (m, 2H), 7.35-7.28 (m, 2H), 6.59 (d, J = 3.75 Hz, 1H), 3.05 (t, J = 7.35 Hz, 2H), 1.79-1.75 (m, 2H), 1.02 (t, J = 7.42 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.4, 179.6, 171.0, 156.9, 152.1, 148.7, 144.4, 135.7, 135.4, 134.9, 131.9, 131.0, 130.6, 129.7, 126.3, 113.2, 39.0, 22.2, 13.2; HRMS [ESI, $(M+Na)^+$]: $C_{20}H_{14}NaO_4S_2$, Calcd.: 405.0231, Found: 405.0252.

2-(Butylthio)-1-(4-methoxybenzoyl)naphtho[2,1-b]thiophene-4,5-dione (**3aq**): (yield 90%, 392 mg); Red solid; m. p. = 130-132 ^oC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10-8.08 (m, 1H), 7.91 (d, J = 8.00 Hz, 2H), 7.33-7.31 (m, 2H), 7.26-7.25 (m, 1H), 6.95 (d, J = 9.00 Hz, 2H), 3.87 (s, 3H), 3.02 (t, J = 7.70 Hz, 2H), 1.70-1.64 (m, 2H), 1.40-1.36 (m, 2H), 0.89 (t, J = 7.50 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.8, 180.6, 171.1, 165.1, 155.0, 144.3, 137.6, 135.5, 135.1, 132.5, 132.0, 131.1, 130.7, 129.7, 129.2, 126.5, 114.6, 55.7, 36.8, 30.8, 21.8, 13.5; HRMS [ESI, $(M+Na)^+$]: $C_{24}H_{20}NaO_4S_2$, Calcd.: 459.0701, Found: 459.0691.

1-(2-Naphthoyl)-2-(butylthio)naphtho[2,1-b]thiophene-4,5-dione (**3ar**): (yield 90%, 392 mg); Red solid; m. p. = 140-142 ^oC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34 (br s, 1H), 8.11 (t, J = 8.50 Hz, 1H), 7.98 (t, J = 8.50 Hz, 1H), 7.92-7.90 (m, 2H), 7.66-7.63 (m, 1H), 7.55 (t, J = 8.00 Hz, 1H), 7.30-7.26 (m, 3H + 1H in $CDCl_3$), 3.03 (t, J = 7.50 Hz, 2H), 1.68-1.62 (m, 2H), 1.38-1.35 (m, 2H), 0.86 (t, J = 7.50 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.5, 180.5, 171.1, 155.4, 144.5, 137.4, 136.5, 135.5, 135.3, 133.6, 133.1, 132.6, 131.9, 131.2, 130.7, 130.1, 129.8, 129.6, 129.5, 128.0, 127.3, 126.5, 124.1, 36.9, 30.8, 21.8, 13.4; HRMS [ESI, $(M+Na)^+$]: $C_{27}H_{20}NaO_3S_2$, Calcd.: 479.0752, Found: 479.0740.

2-(Benzylthio)-1-(furan-2-carbonyl)naphtho[2,1-b]thiophene-4,5-dione (**3as**): (yield 80%, 344 mg); Red solid; m. p. = 152-154 ^oC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (dd, J = 7.70 and 2.0 Hz, 1H), 7.64 (br s, 1H), 7.38-7.33 (m, 2H), 7.29-7.24 (m, 7H), 6.52 (dd, J = 4.00 and 2.0 Hz, 1H), 4.21 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.3, 179.6, 171.3, 153.9, 152.2, 148.9, 144.0, 137.5, 136.0, 135.6, 134.7, 132.0, 131.1, 130.6, 129.8, 129.1, 128.9, 128.3, 126.3, 122.2, 113.3, 41.7; HRMS [ESI, $(M+Na)^+$]: $C_{24}H_{14}NaO_4S_2$, Calcd.: 453.0231, Found: 453.0229.

1-Acetyl-2-(methylthio)naphtho[2,1-b]thiophene-4,5-dione (**3at**): (yield 65%, 98 mg); Red solid; m. p. = 80-82 ^{o}C; ^{1}H NMR (500 MHz) δ 8.16 (d, J = 7.55 Hz, 1H), 7.61-7.58 (m, 1H), 7.49-7.46 (m, 1H), 7.33 (d, J = 7.80 Hz, 1H), 2.68 (s, 3H), 2.60 (s, 3H); ^{13}C NMR (125 MHz) δ 199.7, 180.5, 170.9, 157.2, 146.9, 143.9, 135.4, 132.0, 131.3, 130.9, 130.1, 126.5, 32.0, 19.1; HRMS [ESI, (M+Na)+]: $C_{15}H_{10}NaO_3S_2$, Calcd.: 324.9964, Found: 324.9964.

2-(Ethylthio)-1-(4-methylbenzoyl)-4,5-dioxo-4,5-dihydronaphtho[2,1-b]thiophene-8-carbonitrile (**3bc**): (yield 85%, 177 mg); Brown solid; m. p. = 188-190 ^{o}C; ^{1}H NMR (500 MHz) δ 8.15 (d, J = 7.80 Hz, 1H), 7.85 (d, J = 7.85 Hz, 2H), 7.76 (d, J = 7.60 Hz, 1H), 7.57 (s, 1H), 7.30 (d, J = 8.15 Hz, 2H), 3.09 (q, J = 7.46 Hz, 2H), 2.42 (s, 3H), 1.39 (t, J = 7.47 Hz, 3H); ^{13}C NMR (125 MHz) δ 192.7, 179.9, 170.5, 167.0, 146.7, 143.3, 139.2, 137.1, 135.5, 133.6, 132.6, 132.0, 131.3, 130.3, 130.0, 129.1, 128.7, 127.8, 125.4, 31.3, 22.0, 13.9; HRMS [ESI, (M+Na)+]: $C_{23}H_{15}NNaO_3S_2$, Calcd.: 440.0386, Found: 440.0386.

1-(3-Bromobenzoyl)-2-(methylthio)-4,5-dioxo-4,5-dihydronaphtho[2,1-b]thiophene-8-carbonitrile (**3be**): (yield 92%, 215 mg); Red solid; m. p. = 201-203 ^{o}C; ^{1}H NMR (500 MHz) δ 8.19 (d, J = 7.95 Hz, 1H), 8.09 (s, 1H), 7.84 (d, J = 7.60 Hz, 1H), 7.78-7.74 (m, 2H), 7.56 (s, 1H), 7.40-7.36 (m, 1H), 2.68 (s, 3H); ^{13}C NMR (125 MHz) δ 191.6, 179.8, 170.3, 166.8, 159.5, 143.7, 139.2, 137.9, 132.7, 132.4, 131.8, 131.4, 131.0, 128.5, 125.9, 123.8, 19.2; HRMS [ESI, (M+Na)+]: $C_{21}H_{10}BrNNaO_3S_2$, Calcd.: 489.9178, Found: 489.9178.

8-Bromo-2-(ethylthio)-1-(4-methylbenzoyl)naphtho[2,1-b]thiophene-4,5-dione (**3cc**): (yield 76%, 179 mg); Red solid; m. p. = 232-234 ^{o}C; ^{1}H NMR (500 MHz) δ 7.87 (d, J = 8.45 Hz, 1H), 7.75 (d, J = 7.75 Hz, 2H), 7.40 (dd, J_1 = 1.72 Hz, J_2 = 8.52 Hz, 1H), 7.29 (s, 1H), 7.24 (d, J = 8.15 Hz, 2H), 3.01 (q, J = 7.10 Hz, 2H), 2.37 (s, 3H), 1.32 (t, J = 7.35 Hz, 3H); ^{13}C NMR (125 MHz) δ 192.5, 179.7, 170.6, 155.3, 146.5, 142.6, 137.4, 135.9, 133.7, 133.1, 132.8, 132.2, 131.1, 130.2, 130.0, 129.8, 129.3, 31.3, 22.0, 14.0; HRMS [ESI, (M+Na)+]: $C_{22}H_{15}BrNaO_3S_2$, Calcd.: 492.9538, Found: 492.9538.

1-(3-Bromobenzoyl)-8-((4-methoxyphenyl)ethynyl)-2-(methylthio)naphtho[2,1-b]thiophene-4,5-dione (**3ee**): (yield 80%, 229 mg); Red solid; m. p. = 195-197 ^oC; ^1H NMR (500 MHz) δ 8.18 (s, 1H), 8.07 (d, J = 7.80 Hz, 1H), 7.78-7.75 (m, 2H), 7.41 (m, 3H), 7.37-7.34 (m, 1H), 7.17 (s, 1H), 7.39 (d, J = 8.70 Hz, 2H), 3.84 (s, 3H), 2.66 (s, 3H); ^{13}C NMR (125 MHz) δ 191.5, 179.6, 170.9, 160.6, 158.5, 143.9, 138.1, 137.7, 135.1, 134.6, 133.6, 132.2, 132.0, 131.5, 131.2, 131.1, 130.8, 129.7, 129.1, 128.6, 123.8, 114.2, 96.2, 87.0, 55.4, 19.2; HRMS [ESI, (M+Na)+]: $C_{29}H_{17}BrNaO_4S_2$, Calcd.: 594.9644, Found: 594.9644.

Methyl 2-(ethylthio)-1-(4-methylbenzoyl)-4,5-dioxo-4,5-dihydronaphtho[2,1-b]thiophene-8-carboxylate (**3dc**): (yield 65%, 146 mg); Red solid; m. p. = 202-204 ^oC; ^1H NMR (500 MHz) δ 8.16 (d, J = 8.00 Hz, 1H), 7.96-7.95 (m, 1H), 7.90-7.86 (m, 2H), 7.30 (d, J = 5.40 Hz, 2H), 7.27 (s, 1H), 3.80 (s, 3H), 3.11 (q, J = 7.11 Hz, 2H), 2.43 (s, 3H), 1.40 (t, J = 7.40 Hz, 3H); ^{13}C NMR (125 MHz) δ 192.5, 180.2, 170.5, 164.9, 155.5, 146.3, 143.5, 137.6, 135.7, 135.5, 133.7, 133.2, 131.9, 130.9, 130.4, 130.0, 130.0, 127.8, 52.6, 31.3, 22.0, 14.0; HRMS [ESI, (M+Na)+]: $C_{24}H_{18}NaO_5S_2$, Calcd.: 473.0488, Found: 473.0488.

(2-(Methylthio)benzo[a]thieno[3,2-c]phenazin-3-yl)(phenyl)methanone (**5aa**): (yield 85%, 185 mg); Orange solid; m. p. = 200-202 ^oC; ^1H NMR (500 MHz, $CDCl_3$) δ 9.43 (d, J = 8.00 Hz, 1H), 8.35 (d, J = 7.00 Hz, 1H), 8.30 (d, J = 7.30 Hz, 1H), 8.01 (d, J = 7.65 Hz, 2H), 7.88-7.87 (m, 2H), 7.77 (d, J = 8.05 Hz, 1H), 7.66-7.60 (m, 2H), 7.50-7.46 (m, 3H), 2.62 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.1, 143.4, 142.3, 142.2, 141.4, 139.6, 138.8, 137.2, 137.0, 136.9, 134.3, 130.4, 130.1, 130.0, 129.8, 129.7, 129.0, 128.8, 127.2, 126.5, 125.1, 20.8; HRMS [ESI, $(M+H)^+$]: $C_{26}H_{17}N_2OS_2$, Calcd.: 437.0782, Found: 437.0779.

(4-Chlorophenyl)(2-(ethylthio)benzo[a]thieno[3,2-c]phenazin-3-yl)methanone (**5ai**): (yield 80%, 194 mg); Orange solid; m. p. = 206-208 ^oC; ^1H NMR (500 MHz, $CDCl_3$) δ 9.44 (d, J = 8.00 Hz, 1H), 8.36 (d, J = 7.05 Hz, 1H), 8.30 (d, J = 9.10 Hz, 1H), 7.94 (d, J = 8.10 Hz, 2H), 7.89-7.88 (m, 2H), 7.73 (d, J

= 8.10 Hz, 1H), 7.68-7.65 (m, 1H), 7.53-7.50 (m, 1H), 7.44 (d, J = 8.30 Hz, 2H), 3.02 (q, J = 7.30 Hz, 2H), 1.34 (t, J = 7.37 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.1, 142.3, 141.4, 140.9, 140.1, 139.5, 138.1, 136.5, 135.5, 131.3, 130.5, 130.2, 129.8, 129.8, 129.4, 129.1, 128.8, 127.3, 126.6, 124.8, 32.5, 14.7; HRMS [ESI, $(M+H)^+$]: $C_{27}H_{18}ClN_2OS_2$, Calcd.: 485.0549, Found: 485.0552.

(2-(Ethylthio)benzo[a]thieno[3,2-c]phenazin-3-yl)(furan-2-yl)methanone (**5al**): (yield 85%, 176 mg); Yellow solid; m. p. = 183-185 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.43 (d, J = 8.65 Hz, 1H), 8.35-8.33 (m, 1H), 8.30-8.28 (m, 1H), 7.89-7.86 (m, 3H), 7.70-7.66 (m, 2H), 7.59-7.55 (m, 1H), 7.13 (s, 1H), 3.07 (q, J = 7.15 Hz, 2H), 1.37 (t, J = 7.27 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 181.8, 153.0, 148.4, 142.3, 142.2, 141.4, 139.5, 136.5, 130.4, 130.3, 130.2, 129.7, 129.3, 128.8, 127.2, 126.5, 124.8, 112.9, 32.6, 14.7; HRMS [ESI, $(M+H)^+$]: $C_{25}H_{17}N_2O_2S_2$, Calcd.: 441.0731, Found: 441.0735.

(2-(Butylthio)benzo[a]thieno[3,2-c]phenazin-3-yl)(4-methoxyphenyl)methanone (**5aq**): (yield 80%, 203 mg); Yellow solid; m. p. = 138-140 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.29 (d, J = 9.50 Hz, 1H), 8.22-8.15 (m, 2H), 7.91 (d, J = 9.00 Hz, 2H), 7.77-7.73 (m, 3H), 7.53 (t, J = 7.50 Hz, 1H), 7.43-7.39 (m, 1H), 6.86 (d, J = 9.50 Hz, 2H), 3.76 (s, 3H), 2.91 (t, J = 7.20 Hz, 2H), 1.58-1.17 (m, 4H), 0.79 (t, J = 7.50 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.8, 164.4, 142.1, 142.0, 141.3, 140.8, 140.5, 139.5, 137.7, 136.6, 132.4, 130.3, 130.2, 130.1, 129.6, 129.5, 129.3, 128.7, 127.0, 126.4, 124.8, 114.2, 55.5, 38.0, 31.4, 21.6, 13.5; HRMS [ESI, $(M+H)^+$]: $C_{30}H_{25}N_2O_2S_2$, Calcd.: 509.1357, Found: 509.1367.

ASSOCIATED CONTENT

Supporting Information

Optimization of reaction condition for compound **5**, copies of ^{1}H and ^{13}C NMR spectra of all compounds and X-ray crystallography data for compound **3ap**. The Supporting Information is available free of charge on the ACS Publications website.

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Notes

The authors declare no competing financial interest.

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(15) Monocrystal of **3ap** was obtained after recrystallization in methanol (see the SI for details Figure S1). The crystallographic coordinates have been deposited with the Cambridge Crystallographic Data Centre; Deposition no. CCDC 1535633 (**3ap**). These data can be obtained free

of charge from the Cambridge Crystallographic Data Centre, 12 Union Rd., Cambridge CB2 1EZ, UK.

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