Synthesis B. K. Dinda et al. Paper

A Five-Step Cascade for the Modular and Regiodefined Synthesis of Naphth[2,1-*d*]oxazoles

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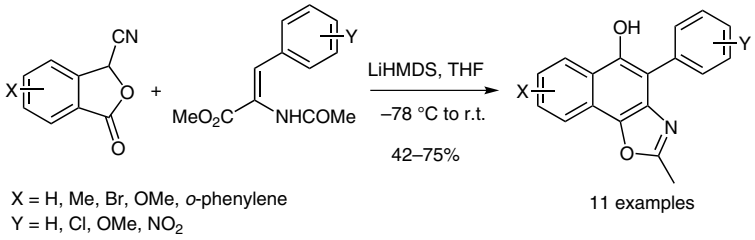

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Abstract The reaction of 3-nucleofugal phthalides with 2-amidoacrylates is shown to provide a synthesis of densely substituted naphth[2,1-*d*]oxazoles in good yields. It is proposed to proceed via a five-step cascade which includes phthalide annulation, demethoxycarbonylation, and heterocyclization. The methodology is free from regiochemical ambiguity of the products. In certain cases, the corresponding 2-amidonaphthoquinones are directly formed.

Key words demethoxycarbonylative annulation, naphth[2,1-*d*]oxazoles, phthalides, cascade, heterocycles

The naphthoxazole framework consists of a naphthalene ring fused to an oxazole ring.[1] Compounds with a naphthoxazole moiety exhibit various biological activities such as immune complex inhibition,[2] anticancer (prostate cancer),[3] antioxidant (e.g. **1**–**5**, Figure 1),[4] and bacteriostatic[5] activities, cysteine protease inhibition (cathepsin inhibitors),[6] trypanocidal (Chagas disease) activity,[7] topoisomerase II inhibition,[8] PTP-1B (protein tyrosine phosphatase-1B) inhibition,[9] lysophosphatidic acid acyltransferase-β inhibition,[10] inhibition of *Mycobacterium tuberculosis* H37Rv,[11] and cytotoxicity.[4,12] The traditional Chinese medicine 'Danshen' (TCM) containing salviamine A–F (see **6**–**9**, Figure 1) has been used worldwide in folk medicine since ancient times.[13a] It is used for the treatment of menstrual disorders, menostasis, menorrhalgia, insomnia, arthritis, and coronary heart diseases, particularly angina pectoris and myocardial infarction.[13] Naphthoxazoles, regarded as masked 2-aminonaphthoquinones, are important synthetic precursors of biologically and pharmacologically active 2-aminonaphthoquinones. 2-Aminonaphthoquinone frameworks are widespread among the members of the ansamycin family. Some of them are also marketed as important drugs, e.g. rifabutin and rifapentine.[14,15] Some other important ansamycins, e.g. hygrocin B (**10**),[16,17] divergolide C (**11**),[17] and divergolide D[17] show antibacterial and anticancer activities (Figure 1). Jadomycin B (**12**)[18] is an important natural product of the angucycline family consisting of the unusual 8*H*-benz[*b*]oxazolo[3,3-*f*]phenanthridine ring system. It dis-

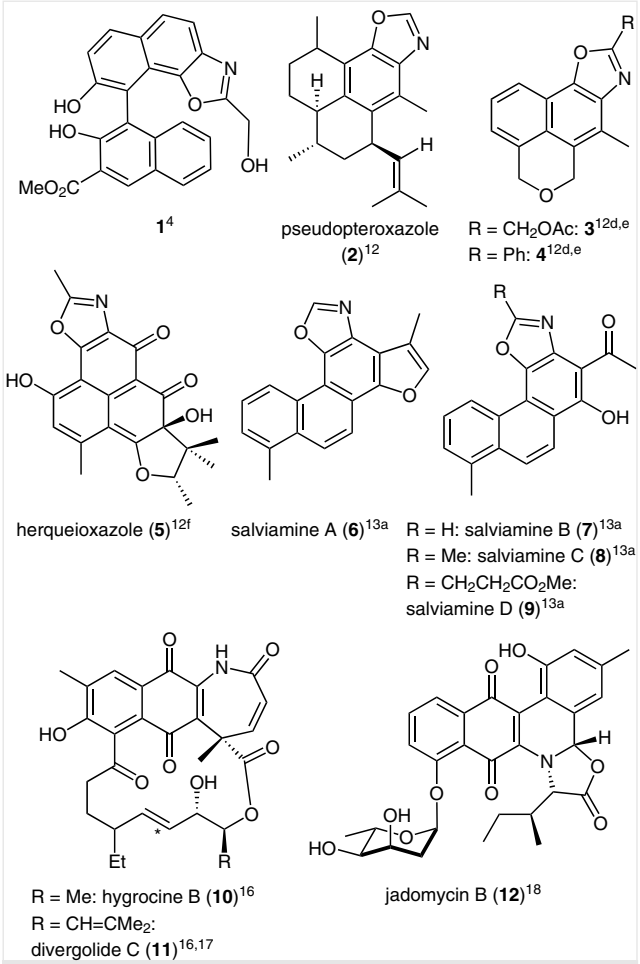
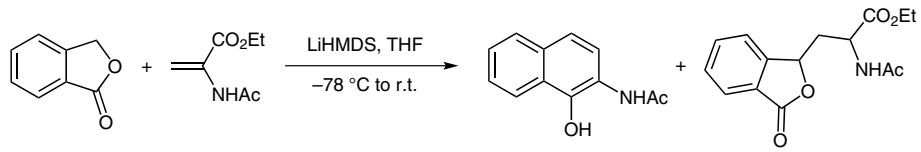


Figure 1 Representative naphthoxazole and aminonaphthoquinone natural products

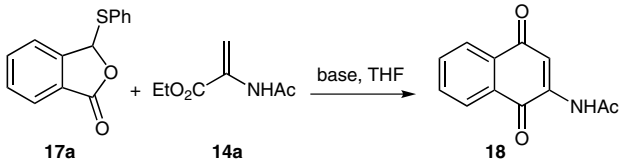


Scheme 1 Reaction between phthalide (**13**) and ethyl 2-acetamidoacrylate (**14a**)

plays antitumor, antimicrobial, and antiviral activities. Therefore, the development of practical and flexible synthetic methods for 2-aminonaphthoquinones[19] and naphthoxazoles[9,20] is always in demand.

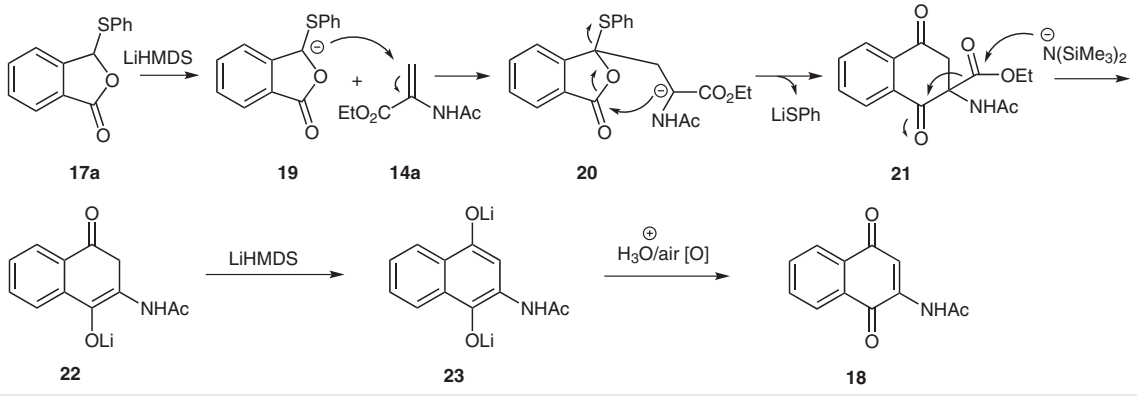
The literature syntheses of 2-amino-1,4-naphthoquinones encompass three types of reactions, namely (a) Diels–Alder reactions,[19a–c] (b) direct 1,4-type addition of amines to naphthoquinones,[19d–f] and (c) nucleophilic displacement of the halogens with amines.[19g] Considering the regiochemical issues, we explored the use of [4+2] benzannulation of phthalides with 2-azidoacrylates.[21] Quite interestingly, the reactions produced benzazepinones instead of the desired 2-azido-1-naphthols.[22] Alternatively, demethoxycarbonylative annulation with α-acylaminoacrylates for the synthesis of 2-amino-1-naphthols was envisaged, which forms the subject of the present report. Although the reactivities of amidoacrylates are well established, their annulation behavior is less explored.[23] To test the reactivity of amidoacrylates in anionic annulation, the reaction of phthalide (**13**) with ethyl 2-acetamidoacrylate (**14a**)[24] was attempted first in the presence of LiHMDS as the base in THF at –78 °C (Scheme 1). The reaction produced the desired product, 2-acetamido-1-naphthol (**15**)[25] in 20% yield along with the Michael addition adduct **16** (50%) as a 1:1 diastereomeric mixture. Use of LDA as the base in the reaction furnished similar results and did not improve the outcome of the annulation. However, the partial success of the annulation encouraged us to scrutinize the reactions of **14a** with 3-nucleofugal phthalides (e.g., **17**) for the synthesis of the title compounds.

Table 1 Screening of Bases for the Annulation of 3-(Phenylsulfanyl)phthalide with Ethyl 2-Acetamidoacrylate (**14a**)



Entry	Base	Temp	Yield (%)
1	*t*-BuOLi	–60 °C to r.t.	0
2	LiHMDS	–78 °C to r.t.	10
3	LDA	–78 °C to r.t.	trace

We first attempted the reactions of 3-(phenylsulfanyl)phthalide (**17a**)[26a] and 3-(phenylsulfonyl)phthalide (**17b**)[26b] with ethyl 2-acetamidoacrylate (**14a**),[24] owing to their ready accessibility. The reaction of **17a** with **14a** was examined in the presence of *t*-BuOLi, LiHMDS, and LDA in THF at low temperature. As shown in Table 1, the reaction in the presence of *t*-BuOLi in THF at –60 °C produced an intractable mixture of products (entry 1). Interestingly, the same reaction in the presence of LiHMDS in THF at –78 °C furnished naphthoquinone **18** in 10% yield (entry 2).[27] Use of LDA as the base in the reaction provided a trace amount of the product **18** (entry 3).



Scheme 2 Probable mechanism for the formation of 2-acetamidonaphthoquinone (**18**)

Formation of 2-acetamidonaphthoquinone (**18**) can be explained by the speculative mechanism shown in Scheme 2. At low temperature, the incipient phthalide anion **19** adds to the amidoacrylate **14a** in Michael addition mode to form new anion **20**. This anion further attacks at the carbonyl group of the phthalide, resulting in the removal of lithium phenylthiolate to produce dihydronaphthoquinone **21**. Attack of LiHMDS at the ester carbonyl produces **22** via deethoxycarbonylation. Intermediate **22** then undergoes enolization to produce **23**. Acidic workup followed by aerial oxidation of **23** produces **18**.

Initially, we reasoned that the deprotonation of the NH hydrogen was responsible for the low yields. Later, we thought of experimenting with different nucleofuges in **17**, because such a tactic is reported in the literature.[21] Accordingly, we investigated the reaction of 3-(phenylsulfonyl)phthalide (**17b**, Table 2, entry 2). Its reaction with **14a** in the presence of LiHMDS in THF at –78 °C was quite interesting. A mixture of 2-(ethoxycarboxamido)naphthoquinone (**24**) (20%) and phenylsulfonyl-substituted naphthoxazole **25** (20%) was produced. Mechanistic interpretation of the formation of **24** and **25** is presented in the Supporting Information (SI).

Table 2 [4+2] Benzannulation of 2-Amidoacrylates with 3-Cyanophthalides[a]

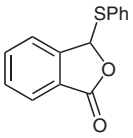
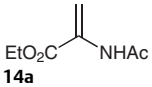
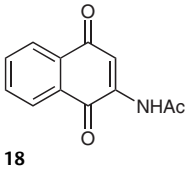
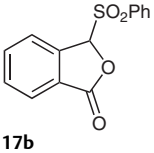
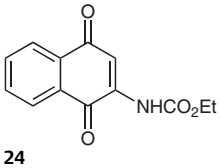
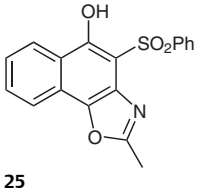
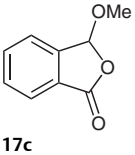
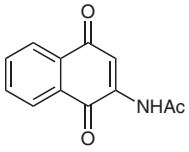
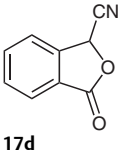
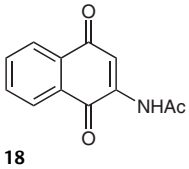
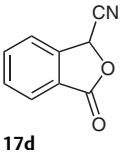
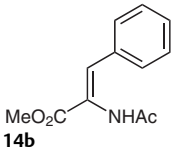
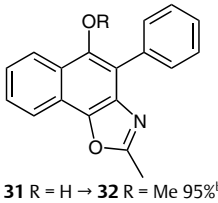
Entry	Phthalide **17**	Amidoacrylate **14**	Products		Yield (%)
1	 **17a**	 **14a**	 **18**		10
2	 **17b**	**14a**	 **24**	 **25**	20 (**24**) 20 (**25**)
3	 **17c**	**14a**	 **18**		30
4	 **17d**	**14a**	 **18**		75
5	 **17d**	 **14b**	 **31** R = H → **32** R = Me 95%[b]		70 (**31**)

Table 2 (continued)

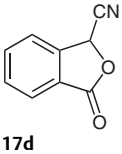
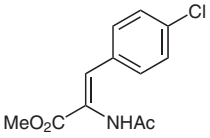
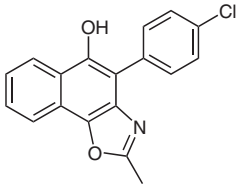
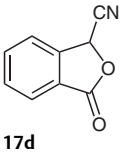
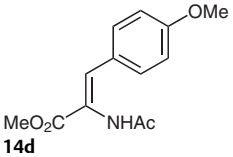
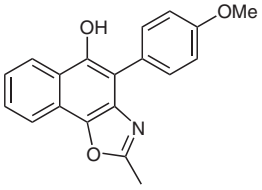
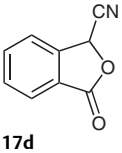
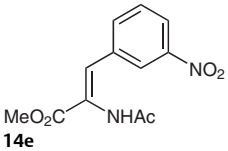
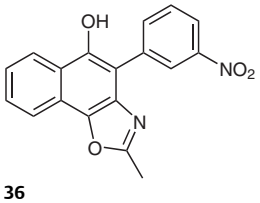
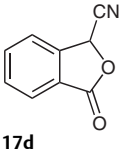
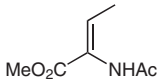
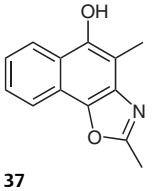
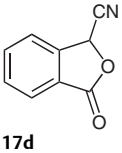
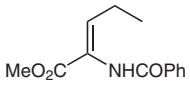
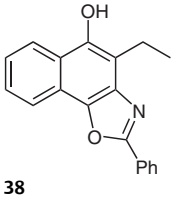
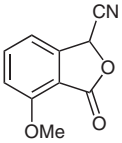
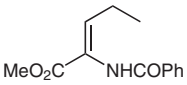
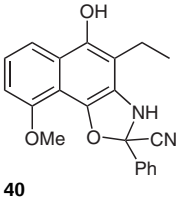
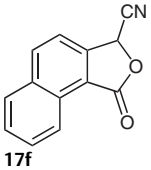
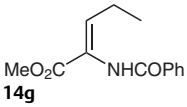
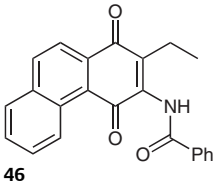
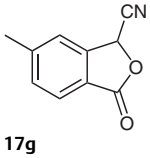
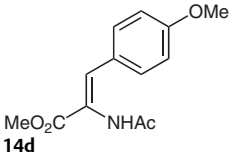
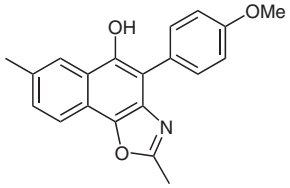
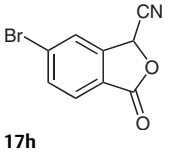
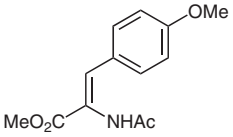
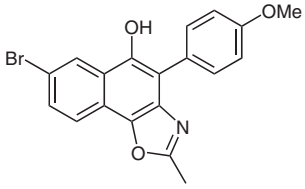
Entry	Phthalide **17**	Amidoacrylate **14**	Products	Yield (%)
6	 **17d**	 **14c**	 **33**	72
7	 **17d**	 **14d**	 **34**	50[d]
8	 **17d**	 **14e**	 **36**	50
9	 **17d**	 **14f**	 **37**	68
10	 **17d**	 **14g**	 **38**	55[d]
11	 **17e**	 **14g**	 **40**	50[c]
12	 **17f**	 **14g**	 **46**	57

Table 2 (continued)

Entry	Phthalide **17**	Amidoacrylate **14**	Products	Yield (%)
13	 **17g**	 **14d**	 **47**	52[d]
14	 **17h**	 **14d**	 **49**	42

[a] Reaction conditions: phthalide **17** (1.0 mmol), amidoacrylate **14** (1.0 mmol), LiHMDS (3.5 mmol), THF (15 mL), –78 °C to r.t.
[b] Reaction conditions: K_2CO_3, MeI, acetone, r.t. Yield of **32** for the one step from **31**.
[c] Yields of dihydronaphthoxazoles.
[d] Side products of the annulation are reported in the SI.

The outcome of the annulations of **17a** and **17b** with **14a** (Table 2, entries 1 and 2) prompted us to explore the reactivities of a few other 3-nucleofugal phthalides (e.g., **17c** and **17d**). With 3-methoxyphthalide (**17c**),[28] the Michael addition of the resulting methoxide ion was anticipated to be less likely than that of lithium benzenesulfinate (**18**→**29**; see Scheme 3 in the SI). When donor **17c** was treated with **14a** in the presence of LiHMDS in THF at –78 °C, the reaction produced **18** exclusively in an improved yield (30%) (Table 2, entry 3). In seeking further improvement in the yield, we utilized 3-cyanophthalide (**17d**)[29] in the annulation reaction. That the cyanide group is a better electron-withdrawing group as well as a better leaving group compared to the methoxy group is well known in the literature.[30] The annulation of **17d** with **14a** in the presence of LiHMDS in THF at –78 °C produced **18** in 75% yield (entry 4). This result was exciting with respect to both yield and selectivity. Enthused by the success (entry 4), we carried out the annulations of 3-cyanophthalide (**17d**) with different 3-aryl-2-acetamidoacrylates **14b**–**e** (entries 5–8).[31]

When the reaction of **17d** was carried out with **14b** in the presence of LiHMDS in THF at –78 °C (Table 2, entry 5), it produced 2-methyl-4-phenylnaphth[2,1-*d*]oxazol-5-ol (**31**) in 70% yield. It was characterized by its NMR data. The characteristic peak for the C2 methyl protons appeared at δ = 2.71 ppm as a sharp singlet. For further confirmation of the structure, the hydroxy group of **31** was *O*-methylated by the treatment of **31** with K_2CO_3 and MeI in acetone to produce methoxy derivative **32** (entry 5). NMR data of the compound conformed to the structure of **32**. Protons of the methyl group appeared at δ = 2.73 ppm and those of the methoxy group at δ = 3.60 ppm. Finally, the structure of **32** was confirmed by analysis of its X-ray crystal data (see SI). From the ORTEP diagram of **32**, it is obvious that the phenyl ring and the naphthalene ring are not coplanar. This orientation conforms to the low chemical shift value of the aromatic methoxy group (δ = 3.60 ppm) that arises from the anisotropic effect of phenyl ring.

Next, we submitted 2-acetamido-3-(4-chlorophenyl)acrylate **14c**[31] to the reaction with **17d** in the presence of LiHMDS in THF at –78 °C (Table 2, entry 6). This reaction produced naphthoxazole **33** in 72% yield. Similarly, the reaction of **17d** with 2-acetamido-3-(4-methoxyphenyl)acrylate **14d** under the same reaction conditions furnished (4-methoxyphenyl)-substituted naphthoxazole **34** in 50% yield (entry 7). In addition to **34**, a side product was also isolated from the reaction mixture. On analysis of its spectral data (NMR, IR, and HRMS), it was assigned as the 2-cyano-2-methyl derivative of **34**, structure **35** (see SI). The formation of **35** can be explained by addition of cyanide to the imine bond of naphthoxazole **34**.

To increase the scope of the annulation, the reaction of **17d** with nitro group containing acceptor **14e** was attempted (Table 2, entry 8). The reaction produced naphthoxazole **36** in 50% yield. The reaction was not accompanied by any dihydronaphthoxazole derivative of **36**. Relatively low solubility of **14e** in THF was presumed to be responsible for the lower yield. The results of entries 5–8 showed that the annulation of **17d** was compatible with a variety of 3-aryl-2-acetamidoacrylates to produce arylnaphthoxazoles. To check the reaction compatibility of 3-alkyl-substituted 2-acetamidoacrylate, we examined the reactivity of com-

pound **14f** (entry 9).[32] The reaction of **14f** with **17d** in the presence of LiHMDS in THF at –78 °C exclusively produced naphthoxazole **37** in 68% yield (entry 9). It shows that 3-alkyl substitution of the amidoacrylate **14f** has little adverse effect on the outcome of the annulation. Our next target was to investigate the reaction of **17d** with benzamido acrylate **14g**[33] to ascertain if the benzoyl group is tolerated in the annulation (entry 10). The reaction in the presence of LiHMDS in THF at –78 °C produced naphthoxazole **38** in 55% yield (entry 10) with a minor amount of dihydronaphthoxazole **39** (15%) (see SI). Hence, entries 5–10 show that various amidoacrylates are compatible in the annulation with **17d** to produce naphthoxazoles. Our next objective was to check the reactivity of a substituted 3-cyanophthalide. For this, we chose cyano(methoxy)phthalide **17e**[29] to react with **14g** in the presence of LiHMDS in THF at –78 °C (entry 11). The reaction produced cyanonaphthoxazole **40** in 50% yield. No other side product was found in the reaction mixture. Hence, the methodology is also compatible with methoxy-substituted cyanophthalide.

As a model study on the synthesis of salviamines (e.g., Figure 1, 6–9), annulation of an angular phthalide was planned. To this end, we chose cyanonaphthofuranone **17f** to employ in the annulation (Table 2, entry 12). The reaction of **17f** with **14g** was carried out under the established conditions, in the presence of LiHMDS in THF at –78 °C. The reaction produced phenanthrenedione **46** in 57% yield (entry 12) via an aerial oxidation of the initial annulated hydroxy precursor. The quinone **46** was characterized by its spectral data. Thus, the reaction is also compatible with an angular cyanophthalide. The failure to obtain the corresponding oxazole may be attributed to the peri effect. To further generalize the reaction, substituted cyanophthalides **17g**[35] and **17h**[35] were submitted to the annulation with the acceptor **14d** (entries 13 and 14). Expectedly, the naphthoxazoles **47** and **49** were obtained in 52% and 42% yields, respectively.

In summary, we have shown that the reaction between 3-cyanophthalides and acetamidoacrylates provides a direct and general regiodefined synthesis of 5-hydroxynaphth[2,1-*d*]oxazoles via tandem demethoxycarbonylative benzannulation and heterocyclization. It is direct and regiospecific by virtue of the initial Michael addition and subsequent domino steps. The methodology is compatible with a variety of substrates. Two important trends emerged from this study. The heterocyclization, i.e. the formation of the oxazole ring, is driven by a β-substituent in the acrylate acceptors and inhibited by a peri effect. Studies on the potential of the method in the total synthesis of natural products such as jadomycines and salviamines are underway.

All reactions involving moisture sensitive reagents were performed under inert atmosphere. Solvents were dried prior to use, according to the standard protocols. General chemicals were used after purification. Reactions were monitored by TLC carried out on 0.25 mm silica gel plates (60-F254). All solvents for chromatography were distilled prior to use. The products were purified by column chromatography on silica gel. Columns were prepared with silica gel (60–120 or 230–400 mesh). ^{1}H and ^{13}C NMR spectra for all compounds were recorded at 200/400/600 and 50/100/150 MHz (Bruker Avance 200, Bruker Avance II 400, Bruker Ascend 600), respectively, and are referenced to the signal of $CHCl_3$ at 7.26 ppm (^{1}H) and 77.23 ppm (^{13}C) for $CDCl_3$. Sometimes DMSO-d_6 (2.50 ppm for ^{1}H, 39.51 ppm for ^{13}C) was used as solvent for recording NMR data. IR spectra were recorded with a Perkin–Elmer FTIR instrument by using KBr pellets. Melting points are uncorrected. High-resolution mass spectra were recorded with a mass spectrometer in positive ion mode. The phrase 'usual workup' or 'worked up in the usual manner' refers to washing of the organic phase with H_2O (2 × 1/3 of the volume of the organic phase) and brine (1 × 1/4 of the volume of the organic phase), drying (Na_2SO_4), filtration, and concentration under reduced pressure. Solvents used for column chromatography were EtOAc and *n*-hexane. All the known compounds were characterized by comparison with the ^{1}H NMR data reported in the literature. Substrates **14a**,[24] **14b–e**,[31] **14g**,[33] **7a**,[26a] **17b**,[26b] **17c**,[28] **17d**,[29] **17e**,[29] and **42**[34] were prepared according to literature procedures.

Annulation Reaction in Presence of LiHMDS; General Procedure

A solution of 3-functionalized phthalide **17** (1.0 mmol) in THF (5 mL) was added to a stirred solution of LiHMDS (3.5 mmol) in THF (15 mL) at –78 °C under an inert gas. The resulting red/yellow solution was stirred at –78 °C for 30 min and then a solution of 2-amidoacrylate **14** (1.0 mmol) in THF (5 mL) was slowly added. The cooling bath was removed after approximately 30 min, and the reaction mixture was allowed to reach r.t. over a period of 1–2 h, and then stirred at r.t. for 6–7 h. Upon completion of the reaction (monitored by TLC), 3 N HCl (15 mL) was added, and the resulting solution was concentrated under reduced pressure. The residue was extracted with EtOAc (3 × 50 mL), and the organic layer was washed with H_2O (3 × 20 mL). The resulting organic layer was washed with brine (2 × 20 mL), and the combined organic part was dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography on silica gel.

(*Z*)-Methyl 2-Acetamidobut-2-enoate (14f)[32]

To a stirred solution of thionyl chloride (0.584 mL, 8.05 mmol) in anhydrous MeOH (10 mL) was added L-threonine (960 mg, 8.05 mmol) at 0 °C. After stirring at the same temperature for 30 min, the reaction mixture was allowed to reach r.t. and stirred for 24 h. Then the reaction mixture was evaporated under reduced pressure and the residue was triturated with petroleum ether (3 × 20 mL) to provide the intermediate ester compound. The ester without further purification was dissolved in triethylamine (8.65 mL, 62 mmol) and the reaction mixture was stirred at 0 °C for 30 min. Then acetic anhydride (1.91 mL, 20.2 mmol) was added and the reaction mixture was allowed to stir at r.t. for 24 h. Then anhydrous MeOH (50 mL) was added and the mixture was heated at 60 °C for 24 h. Solvent was evaporated and the crude residue was dissolved in EtOAc (120 mL) and then washed with 10% aq $NaHCO_3$ solution (3 × 30 mL). Usual workup of the EtOAc part followed by chromatographic purification produced amidoacrylate **14f** as a semisolid (55% overall yield). The compound was characterized by comparing its ^{1}H NMR data with the reported values.[32b]

N-(1-Hydroxynaphthalen-2-yl)acetamide (15)[25]

It was obtained as a side product with compound **16**. Yellow solid. Yield: 30 mg (20%).

IR (KBr): 3303, 1651, 1525, 1387, 1295, 771 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.58 (br s, 1 H), 8.39 (d, *J* = 8.8 Hz, 1 H), 7.75 (d, *J* = 7.2 Hz, 1 H), 7.54–7.45 (m, 3 H), 7.35 (d, *J* = 8.8 Hz, 1 H), 6.96 (d, *J* = 8.8 Hz, 1 H), 2.34 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.7 (CO), 144.6, 133.0, 127.7, 127.3 (CH), 126.5 (CH), 126.0 (CH), 123.4 (CH), 121.2 (CH), 120.5 (CH), 119.2, 24.0 (CH_3).

Ethyl 2-Acetamido-3-(3-oxo-1,3-dihydroisobenzofuran-1-yl)propanoate (16)

It was obtained as a diasteromeric mixture by the reaction of phthalide (**13**; 134 mg, 1 mmol) and compound **14a** (157 mg, 1 mmol) in the presence of LiHMDS (3.2 equiv) following the general procedure for annulation. Yellowish semisolid (dr = 1:1). Yield: 109 mg (50%).

IR (KBr): 3457, 1751, 1654, 1636, 1544, 1375, 742 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.93–7.87 (m, 2 H), 7.74–7.66 (m, 2 H), 7.58–7.44 (m, 4 H), 6.54 (unresolved d, 1 H), 6.26 (unresolved d, 1 H), 5.53 (unresolved dt, 2 H), 4.83–4.74 (m, 2 H), 4.27 (unresolved q, 4 H), 2.73–2.58 (m, 2 H), 2.30–2.16 (m, 2 H), 2.10 (s, 3 H), 1.96 (s, 3 H), 1.28 (unresolved t, 6 H)

^{13}C NMR (50 MHz, $CDCl_3$): δ = 171.5 (CO), 170.7 (CO), 170.5 (CO), 170.1 (CO), 149.3 (CO), 149.1 (CO), 134.4 (2 CH), 129.6 (CH), 129.5 (CH), 125.9 (CH), 125.8 (CH), 125.7, 125.6, 122.2 (CH), 122.0 (CH), 78.4 (CH), 77.8 (CH), 62.2 (CH_2), 62.0 (CH_2), 50.2 (CH), 50.0 (CH), 37.0 (CH_2), 36.5 (CH_2), 23.1 (CH_3), 23.0 (CH_3), 14.2 (CH_3), 14.1 (CH_3).

HRMS (ESI): *m*/*z* calcd for $C_{15}H_{18}NO_5$ [M + H]$^+$: 292.1185; found: 292.1225.

1-Oxo-1,3-dihydronaphtho[1,2-*c*]furan-3-carbonitrile (17f)

To a stirred suspension of 3-hydroxy-3*H*-naphtho[1,2-*c*]furan-1-one (100 mg, 0.50 mmol) in H_2O (6 mL) was added KCN (91 mg, 1.40 mmol) in portions, and the mixture was allowed to stir at r.t. for 10 min. The reaction mixture was then cooled to 0 °C and treated with concd HCl (1.5 mL) and again stirred at r.t. for another 5 h. Then the reaction mixture was kept in a deep freeze overnight without stirring. The mixture was then extracted with EtOAc (3 × 20 mL), and the combined extracts were subjected to usual workup to get a semisolid compound (cyanohydrin **45**). A solution of this cyanohydrin **45** in MeCN (4 mL), without further purification, was added to a solution of Vilsmeier reagent, prepared from anhydrous DMF (0.30 mL, 4.13 mmol) and oxalyl chloride (0.30 mL, 3.31 mmol) in MeCN (2 mL) at –20 °C (CCl_4/liq N_2). After 15 min, pyridine (0.60 mL, 7.8 mmol) was added and the mixture was stirred for an additional 30 min at the same temperature. The reaction was quenched with 3 N HCl (4 mL) and the mixture was extracted with EtOAc (3 × 20 mL). After usual workup and column chromatographic purification, compound **17f** was isolated as a white solid.

Yield: 68 mg, 0.33 mmol (66%); R_f = 0.4 (EtOAc–*n*-hexane, 1:2); mp 202–204 °C.

IR (KBr): 1775, 1176, 1097, 773 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.94 (d, *J* = 8.4 Hz, 1 H), 8.30 (d, *J* = 8.4 Hz, 1 H), 8.04 (d, *J* = 8.4 Hz, 1 H), 7.81 (t, *J* = 7.4 Hz, 1 H), 7.74 (t, *J* = 7.6 Hz, 1 H), 7.69 (d, *J* = 8.4 Hz, 1 H), 6.16 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.0 (CO), 143.4, 137.5 (CH), 134.5, 130.3 (CH), 129.1, 129.0 (CH), 128.9 (CH), 123.7 (CH), 119.6, 118.3 (CH), 114.0, 65.6 (CH).

HRMS (ESI): *m*/*z* calcd for $C_{13}H_8NO_2$ [M + H]$^+$: 210.0555; found: 210.0563.

3-Chloronaphtho[1,2-*c*]furan-1(3*H*)-one (17f')

It was obtained as a side product with compound **17f**. White solid. Yield: 11 mg, 0.05 mmol (10%); R_f = 0.6 (EtOAc–*n*-hexane, 1:7.5); mp 139–140 °C.

IR (KBr): 1778, 1319, 1175, 1096, 1003, 772 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.88 (d, *J* = 8.0 Hz, 1 H), 8.21 (d, *J* = 8.4 Hz, 1 H), 7.99 (d, *J* = 8.0 Hz, 1 H), 7.76 (t, *J* = 7.6 Hz, 1 H), 7.68 (t, *J* = 7.6 Hz, 1 H), 7.62 (d, *J* = 8.4 Hz, 1 H), 7.14 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.8 (CO), 149.0, 137.0 (CH), 134.4, 129.9 (CH), 128.9 (CH), 128.8, 128.6 (CH), 123.9 (CH), 119.6, 119.3 (CH), 85.3 (CH).

***N*-(1,4-Dioxo-1,4-dihydronaphthalen-2-yl)acetamide (18)**[27]

According to the general procedure for annulation, the condensation of **17d** (95 mg, 0.60 mmol) with **14a** (94 mg, 0.60 mmol) in the presence of LiHMDS (2.10 mL, 2.10 mmol) produced 2-acetamidonaphthoquinone **18** as a yellow solid.

Yield: 97 mg, 0.45 mmol (75%); R_f = 0.3 (EtOAc–*n*-hexane, 1:3).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.36 (br s, 1 H), 8.09 (dd, *J* = 7.6, 0.8 Hz, 2 H), 7.84 (s, 1 H), 7.77 (t, *J* = 7.4 Hz, 1 H), 7.71 (t, *J* = 7.6 Hz, 1 H), 2.28 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 185.4 (CO), 181.2 (CO), 169.6 (CO), 140.1, 135.2 (CH), 133.5 (CH), 132.4, 130.1, 126.9 (CH), 126.6 (CH), 117.4 (CH), 25.2 (CH_3).

Ethyl 1,4-Dioxo-1,4-dihydronaphthalen-2-ylcarbamate (24)

According to the general procedure for annulation, the condensation of **17b** (274 mg, 1.0 mmol) with **14a** (157 mg, 1.0 mmol) in the presence of LiHMDS (3.5 mL, 3.5 mmol) produced 2-amidonaphthoquinone **24** as a white solid.

Yield: 49 mg, 0.20 mmol (20%); R_f = 0.3 (EtOAc–*n*-hexane, 1:3); mp 145 °C.

IR (KBr): 1719, 1642, 1613, 1444, 1317, 1268, 1130, 895 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09 (dd, *J* = 7.6, 1.2 Hz, 2 H), 7.85 (br s, 1 H), 7.77 (td, *J* = 7.5, 1.5 Hz, 1 H), 7.70 (td, *J* = 7.5, 1.3 Hz, 1 H), 7.50 (s, 1 H), 4.28 (q, *J* = 7.2 Hz, 2 H), 1.34 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 184.9 (CO), 180.8 (CO), 152.5 (CO), 141.0, 135.1 (CH), 133.4 (CH), 132.4, 130.3, 126.9 (CH), 126.6 (CH), 115.5 (CH), 62.7 (CH_2), 14.6 (CH_3).

HRMS (ESI): *m*/*z* calcd for $C_{13}H_{12}NO_4$ [M + H]$^+$: 246.0766; found: 246.0804.

2-Methyl-4-(phenylsulfonyl)naphth[2,1-*d*]oxazol-5-ol (25)

It was obtained as a side product with 2-amidonaphthoquinone **24** as a light yellow solid.

Yield: 65 mg, 0.20 mmol (20%); R_f = 0.2 (EtOAc–*n*-hexane, 1:3); mp decomposed over 150 °C.

IR (KBr): 1740, 1628, 1559, 1457, 1384, 1271, 1062 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.97 (s, 1 H), 8.50 (d, *J* = 8.4 Hz, 1 H), 8.27 (d, *J* = 7.6 Hz, 2 H), 8.03 (d, *J* = 8.0 Hz, 1 H), 7.75–7.71 (m, 1 H), 7.59–7.49 (m, 4 H), 2.67 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.0, 153.2, 141.8, 141.0, 134.0 (CH), 133.4, 130.9 (CH), 129.2 (CH), 128.1 (CH), 126.1 (CH), 125.6 (CH), 123.5, 123.3, 120.0 (CH), 107.6, 15.1 (CH_3).

HRMS (ESI): *m*/*z* calcd for $C_{18}H_{14}NO_4S$ [M + H]$^+$: 340.0644; found: 340.0659.

2-Methyl-4-phenylnaphth[2,1-*d*]oxazol-5-ol (31)

According to the general procedure for annulation, the condensation of **17d** (159 mg, 1.0 mmol) with **14b** (219 mg, 1.0 mmol) in the presence of LiHMDS (3.5 mL, 3.5 mmol) produced naphthoxazole **31** as a yellow solid.

Yield: 193 mg, 0.70 mmol (70%); R_f = 0.15 (EtOAc–*n*-hexane, 1:3); mp 168–170 °C.

IR (KBr): 1735, 1671, 1653, 1522, 1459, 1058, 726 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.38 (d, *J* = 8.4 Hz, 1 H), 8.15 (d, *J* = 8.4 Hz, 1 H), 7.66–7.52 (m, 6 H), 7.47 (t, *J* = 7.0 Hz, 1 H), 2.71 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.4, 145.5, 141.3, 136.8, 132.9, 130.6 (CH), 130.0 (CH), 128.8 (CH), 127.5 (CH), 125.2 (CH), 124.0 (CH), 122.7, 120.1, 119.9 (CH), 113.7, 15.1 (CH_3).

HRMS (ESI): *m*/*z* calcd for $C_{18}H_{14}NO_2$ $[M + H]^+$: 276.1025; found: 276.1044.

5-Methoxy-2-methyl-4-phenylnaphth[2,1-*d*]oxazole (32)

To a stirred solution of **31** (138 mg, 0.50 mmol) in anhydrous acetone (15 mL) was added K_2CO_3 (207 mg, 1.50 mmol) and MeI (0.16 mL, 2.50 mmol) at r.t. and the mixture was allowed to stir at the same temperature for 6 h. The solvent was evaporated and the crude residue was diluted with H_2O (20 mL) and extracted with EtOAc (3 × 40 mL). After usual workup, the solid crude was purified by column chromatography to produce naphthoxazole **32** as a white solid.

Yield: 137 mg, 0.48 mmol (95%); R_f = 0.4 (EtOAc–*n*-hexane, 1:3); mp 132–134 °C.

IR (KBr): 1701, 1653, 1560, 1542, 1458, 1260, 1108 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.30 (d, *J* = 8.0 Hz, 1 H), 8.19 (d, *J* = 8.4 Hz, 1 H), 7.82 (d, *J* = 8.0 Hz, 2 H), 7.65–7.61 (m, 1 H), 7.60–7.51 (m, 3 H), 7.45–7.27 (m, 1 H), 3.60 (s, 3 H), 2.73 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.4, 150.5, 143.4, 137.3, 134.0, 130.8 (CH), 128.5 (CH), 127.9 (CH), 127.2 (CH), 126.5, 125.8 (CH), 123.9 (CH), 123.3, 120.3 (CH), 120.1, 61.8 (OCH_3), 15.0 (CH_3).

HRMS (ESI): *m*/*z* calcd for $C_{19}H_{16}NO_2$ $[M + H]^+$: 290.1181; found: 290.1208.

4-(4-Chlorophenyl)-2-methylnaphth[2,1-*d*]oxazol-5-ol (33)

According to the general procedure for annulation, the condensation of **17d** (159 mg, 1.0 mmol) with **14c** (254 mg, 1.0 mmol) in the presence of LiHMDS (3.5 mL, 3.5 mmol) produced naphthoxazole **33** as a light yellow solid.

Yield: 223 mg, 0.72 mmol (72%); R_f = 0.4 (EtOAc–*n*-hexane, 1:5); mp 221–222 °C.

IR (KBr): 1709, 1650, 1556, 1542, 1265, 1100 cm^{-1}.

^1H NMR (600 MHz, DMSO-d_6): δ = 9.29 (s, 1 H), 8.38 (d, *J* = 9 Hz, 1 H), 8.12 (d, *J* = 7.8 Hz, 1 H), 7.75 (d, *J* = 7.8 Hz, 2 H), 7.73–7.68 (m, 1 H), 7.60–7.57 (m, 1 H), 7.56 (d, *J* = 7.8 Hz, 2 H), 2.66 (s, 3 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 163.4, 146.6, 140.7, 137.2, 133.6, 133.2, 132.2, 128.3, 128.0, 125.4, 124.6, 124.5, 119.9, 119.6, 115.3, 14.7.

HRMS (ESI): *m*/*z* calcd for $C_{18}H_{13}NO_2Cl$ $[M + H]^+$: 310.0635; found: 310.0637.

4-(4-Methoxyphenyl)-2-methylnaphth[2,1-*d*]oxazol-5-ol (34)

According to the general procedure for annulation, the condensation of **17d** (159 mg, 1.0 mmol) with **14d** (249 mg, 1.0 mmol) in the presence of LiHMDS (3.5 mL, 3.5 mmol) produced naphthoxazole **34** as a brown solid.

Yield: 153 mg, 0.50 mmol (50%); R_f = 0.3 (EtOAc–*n*-hexane, 1:2); mp 166–168 °C.

IR (KBr): 1561, 1510, 1291, 1248, 1034, 820 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.37 (d, *J* = 8.4 Hz, 1 H), 8.14 (d, *J* = 8.0 Hz, 1 H), 7.65–7.52 (m, 4 H), 7.11 (d, *J* = 8.0 Hz, 2 H), 5.86 (s, 1 H), 3.87 (s, 3 H), 2.70 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.3, 159.9, 145.4, 141.2, 137.2, 131.7 (CH), 131.5, 127.3 (CH), 125.1 (CH), 124.8, 123.9 (CH), 122.6, 119.9 (CH), 115.4 (CH), 113.5, 55.6 (OCH_3), 14.9 (CH_3).

HRMS (ESI): *m*/*z* calcd for $C_{19}H_{16}NO_3$ $[M + H]^+$: 306.1130; found: 306.1140.

5-Hydroxy-4-(4-methoxyphenyl)-2-methyl-2,3-dihydronaphth[2,1-*d*]oxazole-2-carbonitrile (35)

It was obtained as a side product with naphthoxazole **34** as a white solid.

Yield: 100 mg, 0.30 mmol (30%); R_f = 0.1 (EtOAc–*n*-hexane, 1:2); mp 208–210 °C.

IR (KBr): 2224, 1656, 1574, 1514, 1289, 1251, 1172, 1032, 773 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 10.68 (br s, 1 H), 9.11 (s, 1 H), 8.31 (d, *J* = 8.4 Hz, 1 H), 8.03 (d, *J* = 8.4 Hz, 1 H), 7.77 (t, *J* = 7.4 Hz, 1 H), 7.64 (t, *J* = 7.6 Hz, 1 H), 7.30 (d, *J* = 8.4 Hz, 2 H), 7.03 (d, *J* = 8.0 Hz, 2 H), 3.81 (s, 3 H), 1.77 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 170.8, 159.8, 154.9, 147.4, 132.8, 131.0 (CH), 129.9 (CH), 128.7, 126.9 (CH), 124.7 (CH), 124.4, 123.8 (CH), 118.3, 118.1, 113.9 (CH), 99.6, 55.6 (OCH_3), 23.3 (CH_3).

HRMS (ESI): *m*/*z* calcd for $C_{20}H_{17}N_2O_3$ $[M + H]^+$: 333.1239; found: 333.1265.

2-Methyl-4-(3-nitrophenyl)naphth[2,1-*d*]oxazol-5-ol (36)

According to the general procedure for annulation, the condensation of **17d** (159 mg, 1.0 mmol) with **14e** (264 mg, 1.0 mmol) in the presence of LiHMDS (3.5 mL, 3.5 mmol) produced naphthoxazole **36** as a light yellow solid.

Yield: 160 mg, 0.50 mmol (50%); R_f = 0.2 (EtOAc–*n*-hexane, 1:2); mp decomposed over 160 °C.

IR (KBr): 1711, 1650, 1560, 1545, 1463, 1257, 1110 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 9.58 (s, 1 H), 8.58 (m, 1 H), 8.39 (d, *J* = 8.4 Hz, 1 H), 8.25–8.22 (m, 1 H), 8.20–8.18 (m, 1 H), 8.12 (d, *J* = 8.4 Hz, 1 H), 7.81–7.77 (m, 1 H), 7.72–7.68 (m, 1 H), 7.61–7.57 (m, 1 H), 2.66 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 163.8, 148.1, 147.2, 140.8, 138.3 (CH), 136.9, 136.5, 129.9 (CH), 128.4 (CH), 126.0 (CH), 125.7 (CH), 124.6 (CH), 124.5, 122.4 (CH), 120.1 (CH), 120.0, 114.1, 14.8 (CH_3).

HRMS (ESI): *m*/*z* calcd for $C_{18}H_{13}N_2O_4$ $[M + H]^+$: 321.0875; found: 321.0878.

2,4-Dimethylnaphth[2,1-*d*]oxazol-5-ol (37)

According to the general procedure for annulation, the condensation of **17d** (159 mg, 1.0 mmol) with **14f** (157 mg, 1.0 mmol) in the presence of LiHMDS (3.5 mL, 3.5 mmol) produced naphthoxazole **37** as a white solid.

Yield: 145 mg, 0.68 mmol (68%); R_f = 0.3 (EtOAc–*n*-hexane, 1:3); mp 110 °C.

IR (KBr): 1654, 1560, 1401, 1242, 1073, 774 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.24 (d, *J* = 8.8 Hz, 1 H), 8.09 (d, *J* = 8.4 Hz, 1 H), 7.57 (t, *J* = 7.6 Hz, 1 H), 7.50 (t, *J* = 7.2 Hz, 1 H), 2.74 (CH_3), 2.61 (CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.1, 146.0, 141.1, 138.1, 126.5 (CH), 125.0 (CH), 123.0, 122.7 (CH), 120.0 (CH), 119.0, 109.5, 14.9 (CH_3), 10.4 (CH_3).

HRMS (ESI): *m*/*z* calcd for $C_{13}H_{12}NO_2$ $[M + H]^+$: 214.0868; found: 214.0893.

4-Ethyl-2-phenylnaphth[2,1-*d*]oxazol-5-ol (38)

According to the general procedure for annulation, the condensation of **17d** (159 mg, 1.0 mmol) with **14g** (233 mg, 1.0 mmol) in the presence of LiHMDS (3.5 mL, 3.5 mmol) produced naphthoxazole **38** as a white solid.

Yield: 145 mg, 0.55 mmol (55%); R_f = 0.5 (EtOAc–*n*-hexane, 1:2); mp 154 °C.

IR (KBr): 1645, 1500, 1476, 1285, 1256, 723 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.46 (br s, 1 H), 8.15 (dd, *J* = 7.4, 1.4 Hz, 1 H), 8.08 (dd, *J* = 7.4, 1.4 Hz, 1 H), 7.97–7.95 (m, 2 H), 7.76 (td, *J* = 7.5, 1.5 Hz, 1 H), 7.71 (td, *J* = 7.5, 1.5 Hz, 1 H), 7.62–7.60 (m, 1 H), 7.55–7.51 (m, 2 H), 2.75 (q, *J* = 7.5 Hz, 2 H), 1.20 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 184.7, 182.6, 165.5, 140.9, 137.6, 134.7 (CH), 133.8, 133.6 (CH), 133.0 (CH), 130.8, 129.2 (CH), 128.1 (CH), 127.0 (CH), 126.5 (CH), 21.9 (CH_2), 12.4 (CH_3) (one quaternary C peak overlaps with another peak).

HRMS (ESI): *m*/*z* calcd for $C_{19}H_{16}NO_2$ $[M + H]^+$: 290.1181; found: 290.1173.

4-Ethyl-5-hydroxy-2-phenyl-2,3-dihydronaphth[2,1-*d*]oxazole-2-carbonitrile (39)

It was obtained as the side product with naphthoxazole **38** as a brown solid.

Yield: 47 mg, 0.15 mmol (15%); R_f = 0.2 (EtOAc–*n*-hexane, 1:2); mp 246–248 °C.

IR (KBr): 3446, 2343, 1636, 1507, 1235, 1026, 772 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 10.84 (br s, 1 H), 9.88 (s, 1 H), 8.28 (d, *J* = 8.0 Hz, 1 H), 8.05–7.98 (m, 3 H), 7.74 (t, *J* = 7.2 Hz, 1 H), 7.61–7.53 (m, 4 H), 2.85 (m, 2 H), 1.16 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 167.3, 155.3, 150.2, 134.7, 133.0, 132.1 (CH), 129.8 (CH), 128.7 (CH), 128.4 (CH), 126.4 (CH), 124.3 (CH), 124.2, 123.9 (CH), 118.7, 117.8, 98.3, 25.6 (CH_2), 14.8 (CH_3).

HRMS (ESI): *m*/*z* calcd for $C_{20}H_{17}N_2O_2$ $[M + H]^+$: 317.1290; found: 317.1325.

4-Ethyl-5-hydroxy-9-methoxy-2-phenyl-2,3-dihydronaphth[2,1-*d*]oxazole-2-carbonitrile (40)

According to the general procedure for annulation, the condensation of **17e** (189 mg, 1.0 mmol) with **14g** (233 mg, 1.0 mmol) in the presence of LiHMDS (3.5 mL, 3.5 mmol) produced naphthoxazole **40** as a greenish semisolid.

Yield: 173 mg, 0.50 mmol (50%); R_f = 0.4 (EtOAc–*n*-hexane, 1:1).

IR (KBr): 3310, 2924, 2211, 1781, 1648, 1484, 1399, 1301, 1078, 769 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 10.23 (s, 1 H, D_2O exchangeable), 7.98 (d, *J* = 7.2 Hz, 2 H), 7.81 (d, *J* = 8.4 Hz, 1 H), 7.59–7.50 (m, 5 H, one proton is D_2O exchangeable), 6.88 (d, *J* = 7.6 Hz, 1 H), 4.08 (s, 3 H), 3.07 (q, *J* = 7.6 Hz, 2 H), 1.31 (t, *J* = 7.6 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.7, 156.5, 154.6, 150.4, 135.6, 134.3, 132.2 (CH), 129.1 (CH), 129.0 (CH), 127.7 (CH), 119.2 (CH), 118.4, 117.7, 113.7, 105.4 (CH), 100.3, 56.8 (OCH_3), 25.7 (CH_2), 14.8 (CH_3).

HRMS (ESI): *m*/*z* calcd for $C_{21}H_{19}N_2O_3$ $[M + H]^+$: 347.1396; found: 347.1391.

***N*-(2-Ethyl-1,4-dioxo-1,4-dihydrophenanthren-3-yl)benzamide (46)**

According to the general procedure for annulation, the condensation of **17f** (105 mg, 0.50 mmol) with **14g** (117 mg, 0.50 mmol) in the presence of LiHMDS (1.75 mL, 1.75 mmol) produced compound **46** as a yellow solid.

Yield: 101 mg, 0.285 mmol (57%); R_f = 0.5 (EtOAc–*n*-hexane, 1:3); mp decomposed at high temperature.

IR (KBr): 2923, 1701, 1458, 1277, 1120, 772 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.46 (d, *J* = 8.8 Hz, 1 H), 8.66 (br s, 1 H), 8.23 (dd, *J* = 23.4, 8.6 Hz, 2 H), 8.01 (d, *J* = 7.2 Hz, 2 H), 7.91 (d, *J* = 7.6 Hz, 1 H), 7.72 (t, *J* = 7.2 Hz, 1 H), 7.66–7.62 (m, 2 H), 7.56 (t, *J* = 7.8 Hz, 2 H), 2.76 (q, *J* = 7.2 Hz, 2 H), 1.23 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 185.6 (CO), 185.3 (CO), 165.6 (CO), 138.4, 137.7, 136.4, 136.0 (CH), 133.9, 133.6, 133.0 (CH), 130.5 (CH), 130.0, 129.2 (CH), 129.1 (CH), 128.7 (CH), 128.0 (CH), 127.8 (CH), 125.9, 122.6 (CH), 21.5 (CH_2), 12.4 (CH_3).

HRMS (ESI): *m*/*z* calcd for $C_{23}H_{18}NO_3$ $[M + H]^+$: 356.1287; found: 356.1292.

4-(4-Methoxyphenyl)-2,7-dimethylnaphtho[2,1-*d*]oxazol-5-ol (47)

According to the general procedure for annulation, the condensation of **17g** (87 mg, 0.50 mmol) with **14d** (125 mg, 0.50 mmol) in the presence of LiHMDS (1.75 mL, 1.75 mmol) produced compound **47** as a white solid.

Yield: 83 mg, 0.26 mmol (52%); R_f = 0.5 (EtOAc–*n*-hexane, 1:3); mp 242 °C.

IR (KBr): 3241, 2928, 1560, 1509, 1423, 1402, 1290, 1244, 1172, 1033 cm^{-1}.

^1H NMR (600 MHz, DMSO-d_6): δ = 8.90 (s, 1 H), 8.14 (s, 1 H), 8.00 (d, *J* = 8.4 Hz, 1 H), 7.65 (d, *J* = 8.4 Hz, 2 H), 7.49 (d, *J* = 8.4 Hz, 1 H), 7.07 (d, *J* = 8.4 Hz, 2 H), 3.84 (s, 3 H), 2.64 (s, 3 H), 2.54 (s, 3 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 162.7, 158.8, 145.7, 140.8, 136.8, 134.5, 132.6, 129.4, 126.9, 124.9, 123.4, 119.9, 117.4, 116.5, 113.8, 55.6, 22.1, 14.7.

HRMS (ESI): *m*/*z* calcd for $C_{20}H_{17}NO_3$ $[M + H]^+$: 320.1287; found: 320.1293.

5-Hydroxy-4-(4-methoxyphenyl)-2,7-dimethyl-2,3-dihydronaphtho[2,1-*d*]oxazole-2-carbonitrile (48)

Obtained as a side product with naphthoxazole **47** as a yellow solid.

Yield: 48 mg, 0.14 mmol (28%); R_f = 0.1 (EtOAc–*n*-hexane, 1:3); mp 254 °C.

^1H NMR (600 MHz, DMSO-d_6): δ = 10.60 (s, 1 H), 9.08 (s, 1 H), 8.23 (d, *J* = 9 Hz, 1 H), 7.82 (s, 1 H), 7.50 (d, *J* = 9 Hz, 1 H), 7.31 (d, *J* = 8.4 Hz, 2 H), 7.04 (d, *J* = 9 Hz, 2 H), 3.83 (s, 3 H), 2.56 (s, 3 H), 1.79 (s, 3 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 170.8, 159.8, 155.0, 147.4, 139.8, 133.1, 131.0, 128.9, 128.8, 123.8, 123.6, 122.6, 118.2, 117.7, 113.8, 98.9, 55.6, 23.3, 22.0.

HRMS (ESI): *m*/*z* calcd for $C_{21}H_{18}N_2O_3$ [M + H]$^+$: 347.1396; found: 347.1412.

7-Bromo-4-(4-methoxyphenyl)-2-methylnaphtho[2,1-*d*]oxazol-5-ol (49)

According to the general procedure for annulation, the condensation of **17h** (119 mg, 0.50 mmol) with **14d** (125 mg, 0.50 mmol) in the presence of LiHMDS (1.75 mL, 1.75 mmol) produced compound **49** as a white solid.

Yield: 81 mg, 0.21 mmol (42%); R_f = 0.4 (EtOAc–*n*-hexane, 1:3); mp >280 °C.

IR (KBr): 3395, 3330, 3240, 1752, 1651, 1556, 1506, 1420, 1395, 1246 cm^{-1}.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 9.22 (s, 1 H), 8.52 (s, 1 H), 8.07 (d, *J* = 9 Hz, 1 H), 7.78 (d, *J* = 9 Hz, 1 H), 7.65 (d, *J* = 8.4 Hz, 2 H), 7.08 (d, *J* = 9 Hz, 2 H), 3.84 (s, 3 H), 2.66 (s, 3 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 163.8, 159.0, 145.4, 140.5, 138.2, 132.6, 130.3, 126.5, 126.3, 125.9, 122.3, 118.5, 118.0, 117.6, 113.9, 55.6, 14.7.

HRMS (ESI): *m*/*z* calcd for $C_{19}H_{14}BrNO_3$ [M + H]$^+$: 384.0235; found: 384.1261.

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Supporting Information

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