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Substituent-Enabled Oxidative Dehydrogenative Cross-Coupling of 1,4-Naphthoquinones with Alkenes

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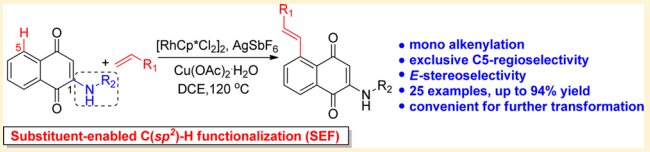
Supporting Information

ABSTRACT: A Rh-catalyzed oxidative dehydrogenative cross-coupling of 1,4-naphthquinones with alkenes was achieved by using a substituent-enabled C(sp^2)−H functionalization (SEF) strategy. The method shows high functional group tolerance, broad substrate scope, and great potential for further functional transformations.



INTRODUCTION

1,4-Naphthoquinones (1,4-NQs) are a class of aromatic motifs that are widely present among natural products and synthetic analogues.[1] Even simple 1,4-NQs bearing limited substituents generally possess a wide spectrum of biological activities. For example, alkylamino-substituted 1,4-NQ (**I**) (Figure 1) showed

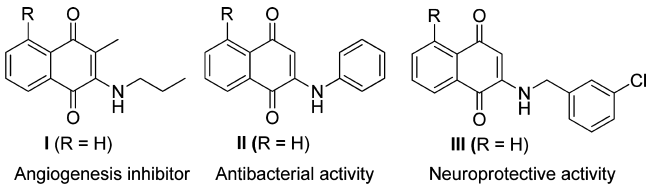


Figure 1. Representative bioactive 1,4-naphthoquinolines.

dose-dependent antiangiogenic activity in rat aortic ring assay.[2a] Phenylamino substituted 1,4-NQ (**II**) belongs to a class of antimycrobacterial agents.[2b] 1,4-NQ (**III**) bearing a benzylamino substituent is an analogue of vitamin K possessing neuroprotective effects against neuronal oxidative stress.[2c] Therefore, 1,4-NQs are ideal medicinal hits or leads for the development of novel derivatives with higher potency through further structural modification.

Because of their electron-deficient character, 1,4-NQs are generally used as substrates for transition-metal-catalyzed addition,[3a] nucleophilic addition,[3b] or cycloaddition[3c] reactions (eq a, Figure 2) to provide new 1,4-NQs with substituents exclusively on the quinone ring as that in **I**−**III**. Direct and regioselective C−H functionalization on the phenyl part of 1,4-NQs, however, is rare. In 2012, Kakiuchi and co-workers reported a ruthenium-catalyzed C−H alkylation of anthraquinone with alkenes leading to new anthracenes bearing four alkyl groups on the two phenyl rings (eq b, Figure 1).[4]

During our studies on the development of 1,4-NQ derivatives, there is a need to introduce an alkenyl functionality at the C5 position. In view of the rapid advances in the

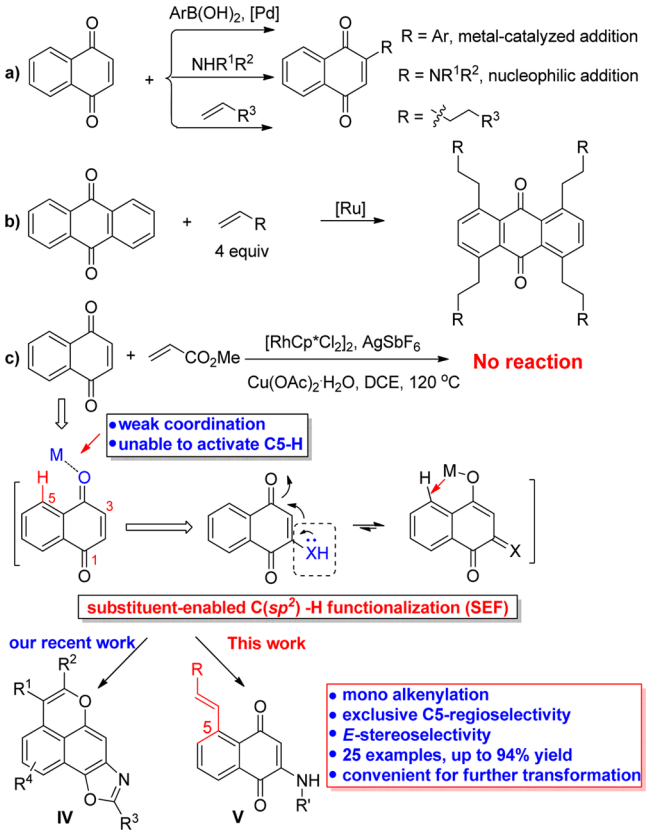


Figure 2. Reported reactions of 1,4-NQs and our proposal.

transition-metal-catalyzed oxidative dehydrogenative cross-coupling of arenes with alkenes,[5] we initially conducted a rhodium-catalyzed oxidative Heck-type alkenylation[6,7] by

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treating 1,4-NQ with methyl acrylate (eq c, Figure 2). Unfortunately, no reaction occurred. We envisioned that the failure of this reaction was due to the electron-deficiency of the 1,4-NQ substrate leading to formation of a weak coordination between the metal catalyst and substrate, which was insufficient to activate the C5−H and then to trigger subsequent dehydrogenative cross-coupling.

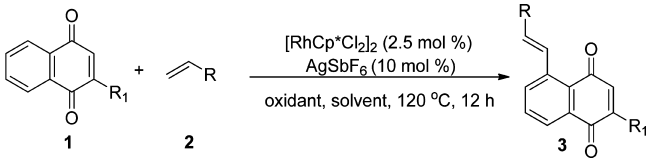
Very recently, we found that the electron deficiency and poor metal coordination of 1,4-NQs could be compensated by introducing an alkylamino group to the 1,4-NQ substrates; therefore, a one-pot cascade process including C−H activation, oxidative addition, and cyclization was readily achieved leading to formation of tetracyclic naphthoxazole derivatives (**IV**).[8] Inspired by this result, we decided to reconduct the Rh-catalyzed oxidative dehydrogenative cross-coupling of 1,4-NQs with alkenes using the same substituent-enabled C_{sp2}−H functionalization (SEF) strategy (Figure 2) to yield the expected alkenylated products **V**.

RESULTS AND DISCUSSION

To find the optimal substituent to maximally compensate the electron deficiency of 1,4-NQs and to enhance the catalyst-substrate coordination, a series of substituents were screened by using $[RhCp^*Cl_2]_2$ (2.5 mol %) and $AgSbF_6$ (10 mol %) as the catalytic system, $Cu(OAc)_2{\cdot}H_2O$ (2 equiv) as the oxidant, and methyl (**2a**) or benzyl (**2c**) acrylate as the alkenylation agent in DCE at 120 °C for 12 h. It was found that 1-hydroxyl-substituted 1,4-NQ was unstable under the reaction conditions, and 1-methoxy NQ did not promote the reaction at all (entries 2 and 3, Table 1). 1.4-NQ with a free amino substituent ignited the coupling reaction slowly and provided the corresponding product in 12% yield (entry 4). The yield was increased dramatically when the *n*-propylamino moiety was introduced as the C2-substituent (57%, entry 5). Meanwhile, other reaction parameters were also optimized. DCE was found to be more effective than *t*-AmOH, dioxane, and THF (entries 5−8). Oxidants other than $Cu(OAc)_2{\cdot}H_2O$ decreased the yield (entries 9−11). Interestingly, when the loading of $Cu(OAc)_2{\cdot}H_2O$ was decreased from 2 to 0.2 equiv, the desired product **3ca** was produced in 80% isolated yield (entries 5 and 12−15). Control experiments showed that without $[RhCp^*Cl_2]_2$, $AgSbF_6$, $Cu(OAc)_2{\cdot}H_2O$, or O_2, the reaction either did not occur or offered product in much lower yields (entries 16−19).

With the optimized conditions in hand, the scope of the alkenylation reaction was extended to various alkenes (Scheme 1). It was found that methyl acrylate (**2a**), ethyl acrylate (**2b**), benzyl acrylate (**2c**), and *n*-butyl acrylate (**2d**) all reacted with 2-(propylamino)-1,4-NQ (**1a**) smoothly and provided the corresponding alkenylation products in excellent yields (80−94%). Meanwhile, electron-neutral styrenes, although slightly less active, also took part in the coupling and offered 5-alkenylated 1,4-NQs **3e** and **3f** in moderate yields (51% and 40%, respectively). The olefinic substrate was further extended to other various α,β-unsaturated systems such as sulfone **2g**, phosphate **2h**, and nitrile **2i** and all reacted with 1,4-NQ (**1**) very well, generating the expected products in good yields (61−68%). It was found that an additional phenyl substituent at the C2 of 1,4-NQs was well tolerated, and the corresponding products were formed in good yields (**3bb**−**hb**). Form the variously substituted alkenes tested above, it was apparent that electron-deficient alkenes reacted well, whereas low yields were obtained for the electron-rich alkenes (styrenes).

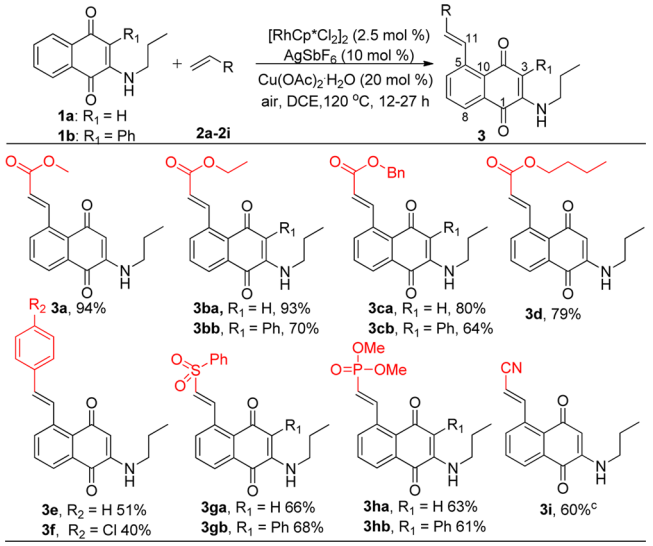
Table 1. Optimization of Substrates and Reaction Conditions[a]



entry	R_1	oxidant (equiv)	solvent	yield[b] (%)
1	H	$Cu(OAc)_2{\cdot}H_2O$ (2)	DCE	0[c]
2	OH	$Cu(OAc)_2{\cdot}H_2O$ (2)	DCE	0[c]
3	OMe	$Cu(OAc)_2{\cdot}H_2O$ (2)	DCE	0[c]
4	NH_2	$Cu(OAc)_2{\cdot}H_2O$ (2)	DCE	12[c]
5	NHPr-*n*	$Cu(OAc)_2{\cdot}H_2O$ (2)	DCE	57[d]
6	NHPr-*n*	$Cu(OAc)_2{\cdot}H_2O$ (2)	dioxane	50[d]
7	NHPr-*n*	$Cu(OAc)_2{\cdot}H_2O$ (2)	THF	55[d]
8	NHPr-*n*	$Cu(OAc)_2{\cdot}H_2O$ (2)	*t*-AmOH	48[d]
9	NHPr-*n*	Ag_2CO_3 (2)	DCE	27[d]
10	NHPr-*n*	NaOAc (2)	DCE	46[d]
11	NHPr-*n*	CsOAc (2)	DCE	11[d]
12	NHPr-*n*	$Cu(OAc)_2{\cdot}H_2O$ (1)	DCE	68[d]
13	NHPr-*n*	$Cu(OAc)_2{\cdot}H_2O$ (0.5)	DCE	78[d]
14	**NHPr-*n***	**$Cu(OAc)_2{\cdot}H_2O$ (0.2)**	**DCE**	**86 (80)**[d]
15	NHPr-*n*	$Cu(OAc)_2{\cdot}H_2O$ (0.1)	DCE	33[d]
16	NHPr-*n*	$Cu(OAc)_2{\cdot}H_2O$ (0.2)	DCE	16[d,e]
17	NHPr-*n*	$Cu(OAc)_2{\cdot}H_2O$ (0.2)	DCE	0[d,f]
18	NHPr-*n*	none	DCE	5[d]
19	NHPr-*n*	$Cu(OAc)_2{\cdot}H_2O$ (0.2)	DCE	7[d,g]

[a]The reactions were performed with 1,4-NQ (**1**) (0.1 mmol), alkene **2** (0.2 mmol), $[RhCp^*Cl_2]_2$ (2.5 mol %), $AgSbF_6$ (10 mol %), and oxidant in solvent (0.5 mL) in a sealed tube under air at 120 °C for 12 h. [b]Yields determined by ^1H NMR analysis using 1,2-dibromomethane as internal standard (isolated yield in parentheses). [c]Methyl acrylate (**2a**) was used. [d]Benzyl acrylate (**2c**) was used. [e]Without $AgSbF_6$. [f]Without $[RhCp^*Cl_2]_2$. [g]Under N_2.

Scheme 1. Substrate Scope with Various Olefins[a,b]



[a]The reactions were performed with 1,4-NQ (**1**) (0.1 mmol), alkene **2** (0.2 mmol), $[RhCp^*Cl_2]_2$ (2.5 mol %), $AgSbF_6$ (10 mol %), and $Cu(OAc)_2{\cdot}H_2O$ (20 mol %) in DCE (0.5 mL) in a sealed tube under air at 120 °C. [b]Isolated yields are listed. [c]*Z*/*E* (1:3).

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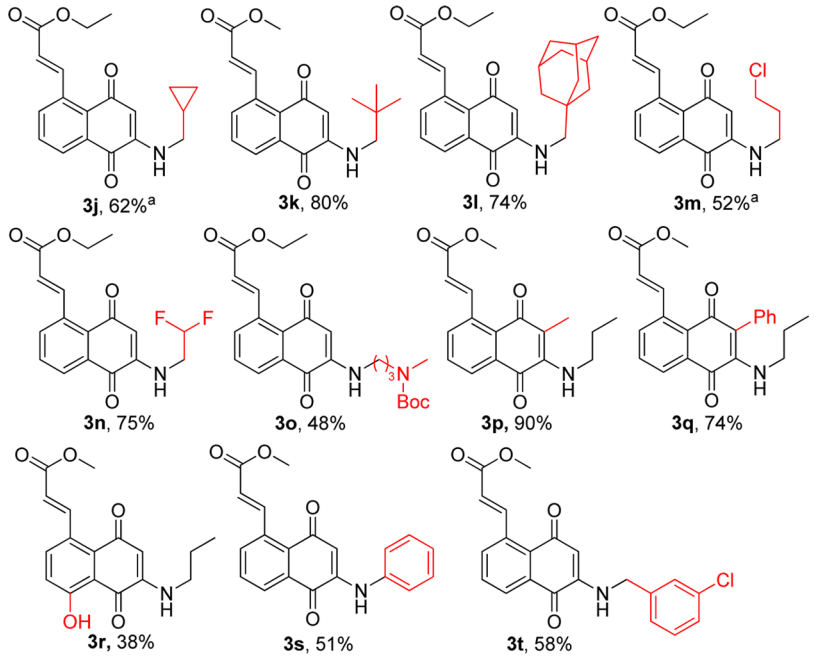
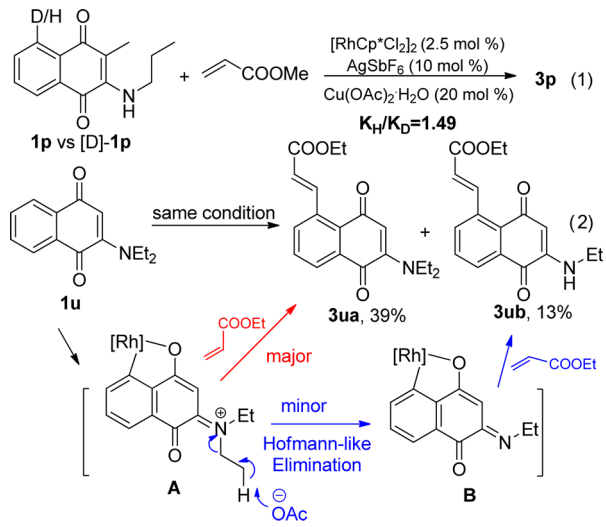


Figure 3. Substrate scope with diversified 1,4-NQs. Key: (a) 50 mol % $Cu(OAc)_2 \cdot H_2O$ was used.

To further explore the scope and limitation of the reaction, 1,4-NQs bearing diversified substituents were evaluated. As shown in Figure 3, 1,4-NQs containing a bulky alkylamino group were well tolerated, and products **3j**–**l** were obtained in 62–80% yields. Additional halogen- or amino-substituted substrates were also tolerant, leading to the corresponding products **3m**–**o** in slightly lower yields (48–75%). Meanwhile, a C3-methyl or phenyl substituent in 1,4-NQs (**1**) had no impact om the reaction, and products **3p** and **3q** were obtained in 90% and 74% yields, respectively. Although the existence of C8-hydroxy might cause additional coordination with the catalyst, the expected product **3r** was still obtained in moderate yield. 1-(Phenylamino)- and 1-(benzylamino)-substituted 1,4-NQs also took part in the reaction, smoothly yielding products **3s** and **3t** in 51% and 58% yields, respectively. However, the reaction with (*p*-methoxyphenyl)amino-substituted substrate occurred very sluggishly, likely due to the electron-donating property of the methoxy group interfering with the tautomerization of the substrate during the catalysis. All of the reactions showed high C5-regioselectivity, which was confirmed by the HMBC spectrum. For example, in the HMBC spectra of compound **3ba**, typical correlations between the quaternary carbon C-10 (δ_C = 130.1 ppm) and vinyl H-11 (δ_H = 8.73 ppm), as well as correlations between C-10 and H-3 (δ_H = 5.68 ppm), were observed, suggesting the alkene group sits at C-5 rather than C-8 (Supporting Information). The newly formed C5 alkenyl moiety was exclusively *E*-configurated except **3i** (*Z*/*E* = 1:3) as determined by the NMR spectra.

Although the exact mechanism of the reaction was unclear, a possible pathway similar to our recent report[8] could be proposed. As shown in Scheme 2, rhodacycle **A** would be formed as the key intermediate through tautomerization of the 1,4-NQ substrates followed by C5–H activation. This hypothesis was supported by the kinetic isotope effect (KIE) of 1.49 (K_H/K_D) observed from reactions of substrates **1p** and [D-5]-**1p** with methyl acrylate, implying that cleavage of the C5–H bond was involved in the rate-determining step. Meanwhile, we also conducted reaction of diethylamino-

Scheme 2. Mechanism Study and Supporting Reactions



substituted substrate **1u** with ethyl acrylate and found that compound **3ua** was obtained in low yield, together with the de-ethyl side product **3ub** in 13% yield. Compound **3ub** likely formed through intermediate **B** that was generated from proposed intermediate **A** via Hofmann-like elimination. This result suggested that the NH substituent in 1,4-NQs was crucial for the tautomerization.

It must be mentioned that compounds **3p**, **3s** ,and **3t** (Figure 3) are the corresponding C5-alkenylated products of the bioactive 1,4-NQs **I**–**III** (Figure 1); therefore, these compounds can be used directly for biological assays.

On the basis of the above data and precedent literature,[8] a plausible mechanism is proposed in Scheme 3. The reaction cycle is likely initiated by tautomerization of **1a** to phenol **1a′**, which then undergoes a well-known Rh(III)-catalyzed C–H activation with the assistance of $AgSbF_6$[9] to form a five-membered rhodacycle **C**. Insertion of alkene **2a** to the Rh–C_{phenyl} bond would generate a seven-membered species **D**.

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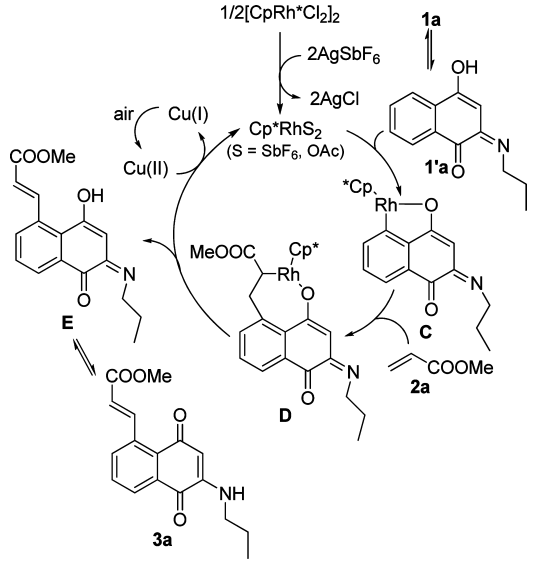
Scheme 3. Proposed Mechanism



Subsequent β-H elimination of the intermediate **D** leads to formation of intermediate **E**, which then undergoes isomerization to afford final product **3a**. Rh(III) would be regenerated under the oxidation of $Cu(OAc)_2{\cdot}H_2O$. Meanwhile, reduced copper is then oxidized by air.

In summary, we have developed a Rh-catalyzed oxidative dehydrogenative cross-coupling of 1,4-naphthquinones with alkenes by using a substituent-enabled C_{sp2}–H functionalization (SEF) strategy. This is the earliest example of rhodium-catalyzed oxidative Heck-type alkenylations on the electron-deficient naphthoquiones. Excellent C5-regioselectivity and vinyl *E*-stereoselectivity were achieved in the product. The method shows high functional group tolerance, broad substrate scope, and great potential for further functional transformations.

EXPERIMENTAL SECTION

General Information. All reactions were performed in glassware containing a Teflon-coated stir bar. All solvents and chemical reagents were obtained from commercial sources and used without further purification. ^{1}H and ^{13}C NMR spectra were recorded with tetramethylsilane as an internal reference. High-resolution mass spectrometry (HRMS) analysis was recorded by electron ionization (EI-TOF). Flash column chromatography on silica gel (200–300 mesh) was used for the routine purification of reaction products. The column output was monitored by TLC on silica gel (100–200 mesh) precoated on plates (15 × 50 mm) and spots were visualized by UV light at 254 or 365 nm. Alkenes **2** were purchased directly from commercial sources. Substrates **1** were either commercially available or prepared by following literature procedures that include the characterization data for the known 2-amino-1,4-naphthoquinones.[8,10]

General Procedure for Synthesis of 5-Alkenylated 1,4-Naphthoquinones. A solution of C2-amino-1,4-naphthoquinones **1** (0.1 mmol), alkene **2** (0.2 mmol), $[RhCp^*Cl_2]_2$ (2.5 mol %), $AgSbF_6$ (10 mol %), and $Cu(OAc)_2{\cdot}H_2O$ (20 mol %) in DCE (0.5 mL) was stirred in a sealed tube at 120 °C for 12–24 h. The reaction was then cooled to room temperature, concentrated in vacuum, and purified by column chromatography using petroleum ether/ethyl acetate to afford the corresponding olefinated products **3**.

*(E)-Methyl 3-(5,8-dioxo-6-(propylamino)-5,8-dihydronaphthalen-1-yl)acrylate (**3a**):* red solid, 28 mg (94%); mp = 126–128 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.73 (d, J = 16.0 Hz, 1H), 8.10 (d, J = 7.5 Hz, 1H), 7.68 (d, J = 7.4 Hz, 1H), 7.57 (t, J = 7.7 Hz, 1H), 6.16 (d, J = 16.0 Hz, 1H), 5.78 (s, 1H), 5.68 (s, 1H), 3.80 (s, 3H), 3.12 (m, 2H), 1.79–1.63 (m, 2H), 0.99 (t, J = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 184.5, 181.8, 167.0, 147.0, 146.0, 136.8, 135.2, 131.8, 131.7, 130.6, 128.0, 120.7, 102.3, 51.8, 44.2, 21.6, 11.5; EI-MS (m/z) 299 (M^+); HRMS (EI) calcd for $C_{17}H_{17}NO_4$ (M^+) 299.1158, found 299.1163.

*(E)-Ethyl 3-(5,8-dioxo-6-(propylamino)-5,8-dihydronaphthalen-1-yl)acrylate (**3ba**):* red solid, 29 mg (93%); mp = 108–109 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.73 (d, J = 15.9 Hz, 1H), 8.09 (d, J = 7.5 Hz, 1H), 7.68 (d, J = 7.6 Hz, 1H), 7.57 (t, J = 7.7 Hz, 1H), 6.15 (d, J = 15.9 Hz, 1H), 5.78 (s, 1H), 5.68 (s, 1H), 4.26 (q, J = 7.1 Hz, 2H), 3.11 (m, 2H), 1.75–1.61 (m, 2H), 1.32 (t, J = 7.1 Hz, 3H), 0.99 (t, J = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 184.0, 181.3, 166.1, 146.4, 145.2, 136.4, 134.8, 131.3, 131.2, 130.1, 127.5, 120.8, 101.8, 60.1, 43.7, 21.1, 13.9, 11.1; EI-MS (m/z) 313 (M^+); HRMS (EI) calcd for $C_{18}H_{19}NO_4$ (M^+) 313.1314, found 313.1315.

*(E)-Ethyl 3-(5,8-dioxo-7-phenyl-6-(propylamino)-5,8-dihydronaphthalen-1-yl)acrylate (**3bb**):* red solid, 27 mg (70%); mp = 97–99 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.62 (d, J = 15.9 Hz, 1H), 8.17 (d, J = 7.4 Hz, 1H), 7.63 (m, 2H), 7.42–7.32 (m, 3H), 7.27 (m, 2H), 6.11 (d, J = 15.9 Hz, 1H), 5.83 (s, 1H), 4.20 (q, J = 7.1 Hz, 2H), 2.51 (m, 2H), 1.32 (m, 5H), 0.68 (t, J = 7.4 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 183.8, 182.9, 166.5, 146.2, 143.6, 137.4, 135.7, 134.3, 131.7, 131.5, 131.3(2), 130.6, 127.8(3), 127.7, 121.2, 116.2, 60.5, 46.3, 23.2, 14.4, 11.0; EI-MS (m/z) 389 (M^+); HRMS (EI) calcd for $C_{24}H_{23}NO_4$ (M^+) 389.1627, found 389.1633.

*(E)-Benzyl 3-(5,8-dioxo-6-(propylamino)-5,8-dihydronaphthalen-1-yl)acrylate (**3ca**):* red solid, 30 mg (80%); mp = 75–76 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.79 (d, J = 15.9 Hz, 1H), 8.09 (d, J = 7.6 Hz, 1H), 7.67 (d, J = 7.6 Hz, 1H), 7.56 (t, J = 7.7 Hz, 1H), 7.46–7.28 (m, 5H), 6.20 (d, J = 15.9 Hz, 1H), 5.79 (s, 1H), 5.69 (s, 1H), 5.26 (s, 2H), 3.11 (m, 2H), 1.76–1.61 (m, 2H), 0.99 (t, J = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 184.0, 181.3, 165.8, 146.4, 145.9, 136.3, 135.7, 134.8, 131.3, 131.2, 130.2, 128.1(2), 127.8(2), 127.7, 127.6, 120.3, 101.8, 65.9, 43.8, 21.1, 11.1; EI-MS (m/z) 375 (M^+); HRMS (EI) calcd for $C_{23}H_{21}NO_4$ (M^+) 375.1471, found 375.1466.

*(E)-Benzyl 3-(5,8-dioxo-7-phenyl-6-(propylamino)-5,8-dihydronaphthalen-1-yl)acrylate (**3cb**):* orange solid, 29 mg (64%); mp = 106–107 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.68 (d, J = 15.8 Hz, 1H), 8.17 (d, J = 7.3 Hz, 1H), 7.62 (m, 7.5, 2H), 7.41–7.26 (m, 10H), 6.15 (d, J = 15.9 Hz, 1H), 5.84 (s, 1H), 5.20 (s, 2H), 2.52 (m, 2H), 1.43–1.26 (m, 2H), 0.68 (t, J = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 183.7, 182.9, 166.2, 146.9, 143.6, 137.2, 136.2, 135.6, 134.3, 131.7, 131.5, 131.3(2), 130.7, 128.5(2), 128.3(2), 128.1, 127.8, 127.7(3), 120.7, 116.2, 66.2, 46.3, 23.2, 11.0; EI-MS (m/z) 451 (M^+); HRMS (EI) calcd for $C_{29}H_{25}NO_4$ (M^+) 451.1784, found 451.1782.

*(E)-Butyl 3-(5,8-dioxo-6-(propylamino)-5,8-dihydronaphthalen-1-yl)acrylate (**3d**):* red solid, 27 mg (79%); mp = 85–87 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.73 (d, J = 15.9, 1H), 8.11 (d, J = 7.6 Hz, 1H), 7.69 (d, J = 7.6 Hz, 1H), 7.58 (t, J = 7.6 Hz, 1H), 6.16 (d, J = 15.8 Hz, 1H), 5.78 (s, 1H), 5.69 (s, 1H), 4.21 (t, J = 6.5 Hz, 2H), 3.12 (m, 2H), 1.68 (m, 4H), 1.43 (m, 2H), 1.06–0.87 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 184.0, 181.3, 166.2, 146.4, 145.2, 136.4, 134.8, 131.3, 131.2, 130.1, 127.5, 120.8, 101.9, 64.0, 43.8, 30.3, 21.1, 18.8, 13.3, 11.1. EI-MS (m/z) 341 (M^+); HRMS (EI) calcd for $C_{20}H_{23}NO_4$ (M^+) 341.1627, found 341.1618.

*(E)-2-(Propylamino)-5-styrylnaphthalene-1,4-dione (**3e**):* red solid, 16 mg (51%); mp = 167–169 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.45 (d, J = 16.2 Hz, 1H), 8.03 (d, J = 7.2 Hz, 1H), 7.89 (d, J = 7.6 Hz, 1H), 7.56 (m, 3H), 7.33 (m, 3H), 6.93 (d, J = 16.2 Hz, 1H), 5.71 (s, 1H), 5.67 (s, 1H), 3.10 (m, 2H), 1.69 (m, 2H), 0.99 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 185.2, 181.8, 146.2, 139.2, 137.1, 134.3, 131.5, 131.3, 130.9, 128.7(2), 128.2(2), 127.4, 126.6(2), 126.0, 102.5, 43.7, 21.2, 11.1; EI-MS (m/z) 317 (M^+); HRMS (EI) calcd for $C_{21}H_{19}NO_2$ (M^+) 317.1416, found 317.1400.

*(E)-5-(4-Chlorostyryl)-2-(propylamino)naphthalene-1,4-dione (**3f**):* red solid, 14 mg (40%); mp = 152–153 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.40 (d, J = 16.3 Hz, 1H), 8.02 (d, J = 7.5 Hz, 1H), 7.84 (d, J = 7.8 Hz, 1H), 7.51 (m, 3H), 7.30 (m, 2H), 6.84 (d, J = 16.2 Hz, 1H), 5.72 (s, 1H), 5.66 (s, 1H), 3.10 (m, 2H), 1.75–1.61 (m, 2H),

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0.99 (t, J = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 185.1, 181.7, 146.2, 138.8, 135.6, 134.2, 133.0, 131.5, 131.0, 129.8, 129.3, 128.8, 128.4(2), 127.7(2), 126.2, 102.4, 43.7, 21.2, 11.1; EI-MS (m/z) 351 (M^+); HRMS (EI) calcd for $C_{21}H_{18}ClNO_2$ (M^+) 351.1026, found 351.1005.

*(E)-5-(2-(Phenylsulfonyl)vinyl)-2-(propylamino)naphthalene-1,4-dione (**3ga**):* orange solid, 25 mg (66%); mp = 160−162 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.71 (d, J = 15.3 Hz, 1H), 8.08 (d, J = 6.2 Hz, 3H), 7.62−7.52 (m, 5H), 6.56 (d, J = 15.3 Hz, 1H), 5.83 (s, 1H), 5.69 (s, 1H), 3.12 (m, 2H), 1.77−1.60 (m, 2H), 0.99 (t, J = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 183.9, 181.4, 147.0, 145.18, 140.6, 135.2, 134.6, 133.3, 131.8, 131.6, 131.0, 129.2(3), 128.5, 127.9(2), 101.8, 44.2, 21.5, 11.5; ESI-MS (m/z) 382 ([M + H]$^+$); HRMS (ESI): calcd for $C_{21}H_{20}NO_4S$ ([M + H]$^+$) 382.1113, found 382.1104.

*(E)-3-Phenyl-5-(2-(phenylsulfonyl)vinyl)-2-(propylamino)-naphthalene-1,4-dione (**3gb**):* red solid, 31 mg (68%); mp = 68−70 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.71 (d, J = 15.3 Hz, 1H), 8.16 (m, 1H), 8.01 (d, J = 7.3 Hz, 2H), 7.66−7.31 (m, 8H), 7.31−7.21 (m, 2H), 6.56 (d, J = 15.3 Hz, 1H), 5.84 (s, 1H), 2.51 (m, 2H), 1.40−1.28 (m, 2H), 0.67 (t, J = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 182.7, 182.2, 144.6, 143.4, 140.2, 134.9, 134.2, 133.7, 132.7, 131.3, 131.0, 130.9(2), 130.7, 128.7(3), 128.0, 127.5(2), 127.3(3), 115.6, 45.9, 22.7, 10.5; EI-MS (m/z) 457 (M^+); HRMS (EI) calcd for $C_{27}H_{23}NO_4S$ (M^+) 457.1348, found 457.1344.

*(E)-Dimethyl 2-(5,8-dioxo-6-(propylamino)-5,8-dihydronaphthalen-1-yl)vinyl-phosphonate (**3ha**):* orange solid, 22 mg (63%); mp = 107−108 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.44 (dd, J_{H-P} = 22.1, 17.6 Hz, 1H), 8.11 (d, J = 7.5 Hz, 1H), 7.62 (m, 2H), 5.95 (dd, J_{H-P} = 19.7, 17.6 Hz, 1H), 5.81 (s, 1H), 5.66 (s, 1H), 3.87 (s, 3H), 3.83 (s, 3H), 3.11 (m, 2H), 1.68 (m, 2H), 0.99 (t, J = 7.4 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 184.4, 181.7, 150.3, 147.0, 135.1, 131.8, 131.6, 130.3, 128.0, 116.1, 114.8, 102.1, 52.9, 52.8, 44.2, 21.6, 11.5; EI-MS (m/z) 349 (M^+); HRMS (EI) calcd for $C_{17}H_{20}NO_5P$ (M^+) 349.1079, found 349.1085.

*(E)-Dimethyl 2-(5,8-dioxo-7-phenyl-6-(propylamino)-5,8-dihydronaphthalen-1-yl)vinyl phosphonate (**3hb**):* red solid, 26 mg (61%); mp = 101−102 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.39 (dd, J_{H-P} = 21.9, 17.6 Hz, 1H), 8.14 (d, J = 7.5 Hz, 1H), 7.72−7.52 (m, 2H), 7.40−7.29 (m, 3H), 7.25 (m, 2H), 5.94 (dd, J_{H-P} = 19.5, 17.5 Hz, 1H), 5.80 (s, 1H), 3.77 (s, 3H), 3.73 (s, 3H), 2.48 (m, 2H), 1.30 (m, 2H), 0.66 (t, J = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 183.5, 182.8, 150.4(2), 143.7, 135.3, 134.3, 131.8, 131.4, 131.3(2), 130.4, 127.9, 127.7(3), 116.2, 114.7, 52.7(2), 46.3, 23.1, 11.0; EI-MS (m/z) 425 (M^+); HRMS (EI) calcd for $C_{23}H_{24}NO_5P$ (M^+) 425.1392, found 425.1389.

*3-(5,8-Dioxo-6-(propylamino)-5,8-dihydronaphthalen-1-yl)-acrylonitrile (**3i**).* The title compound was obtained as an inseparable mixture of E,Z isomers: orange solid, 16 mg (60%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (d, J = 16.5 Hz, 1H), 8.19 (m, 1H), 7.96−7.67 (m, 1H), 7.66 (d, J = 3.7 Hz, 1H), 5.86 (s, 1H), 5.73 (d, J = 11.2 Hz, 1H), 5.66 (m, 1H), 3.17 (m, 2H), 1.83−1.67 (m, 2H), 1.05 (t, J = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 184.1, 181.4, 152.0, 147.1, 147.0, 136.1, 135.4, 134.7, 134.5, 131.9(2), 131.8, 131.6, 130.9, 130.4, 128.7, 128.4, 117.8, 116.8, 102.1, 101.7, 98.9, 97.2, 44.2, 21.6, 11.5; EI-MS (m/z) 266 (M^+); HRMS (EI) calcd for $C_{16}H_{14}N_2O_2$ (M^+) 266.1055, found 266.1050.

*(E)-Ethyl 3-(6-(cyclopropylmethylamino)-5,8-dioxo-5,8-dihydronaphthalen-1-yl)acrylate (**3j**):* red solid, 20 mg (62%); mp = 107−109 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.71 (d, J = 15.9 Hz, 1H), 8.09 (d, J = 7.3 Hz, 1H), 7.67 (d, J = 7.6 Hz, 1H), 7.56 (t, J = 7.5 Hz, 1H), 6.14 (d, J = 15.9 Hz, 1H), 5.87 (s, 1H), 5.64 (s, 1H), 4.25 (dd, J = 13.9, 6.9 Hz, 2H), 2.97 (m, 2H), 1.31 (t, J = 6.9 Hz, 3H), 1.09 (s, 1H), 0.60 (d, J = 7.2 Hz, 2H), 0.27 (d, J = 3.9 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 184.5, 181.7, 166.5, 146.8, 145.7, 136.8, 135.3, 131.7(2), 130.5, 128.0, 121.2, 102.4, 60.6, 47.5, 14.3, 9.7, 3.8(2); EI-MS (m/z) 325 (M^+); HRMS (EI) calcd for $C_{19}H_{19}NO_4$ (M^+) 325.1314, found 325.1312.

*(E)-Methyl 3-(6-(neopentylamino)-5,8-dioxo-5,8-dihydronaphthalen-1-yl)acrylate (**3k**):* orange solid, 26 mg (80%); mp = 146−147 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.73 (d, J = 15.9 Hz, 1H), 8.11 (d, J = 7.5 Hz, 1H), 7.68 (d, J = 7.5 Hz, 1H), 7.58 (t, J = 7.7 Hz, 1H), 6.15 (d, J = 15.9 Hz, 1H), 5.86 (s, 1H), 5.71 (s, 1H), 3.80 (s, 3H), 2.93 (d, J = 6.2 Hz, 2H), 0.99 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 184.5, 181.8, 166.9, 147.3, 145.9, 136.7, 135.2, 131.7, 131.6, 130.6, 128.0, 120.7, 102.2, 53.9, 51.8, 32.4, 27.5(3); EI-MS (m/z) 327 (M^+); HRMS (EI) calcd for $C_{19}H_{21}NO_4$ (M^+) 327.1471, found 327.1476.

*(E)-Ethyl 3-(6-((adamantan-1-ylmethyl)amino)-5,8-dioxo-5,8-dihydronaphthalen-1-yl)acrylate (**3l**):* red solid, 31 mg (74%); mp = 190−192 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.75 (d, J = 15.9 Hz, 1H), 8.13 (d, J = 7.5 Hz, 1H), 7.69 (d, J = 7.6 Hz, 1H), 7.58 (t, J = 7.7 Hz, 1H), 6.16 (d, J = 15.9 Hz, 1H), 5.89 (s, 1H), 5.73 (s, 1H), 4.27 (q, J = 7.1 Hz, 2H), 2.83 (d, J = 6.3 Hz, 2H), 2.00 (s, 3H), 1.78−1.53 (m, 12H), 1.34 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 184.6, 181.9, 166.6, 147.5, 145.7, 136.9, 135.3, 131.8, 131.6, 130.6, 128.0, 121.2, 102.2, 60.6, 54.4, 40.5(3), 36.8(3), 34.5, 28.1(3), 14.4; EI-MS (m/z) 419 (M^+); HRMS (EI) calcd for $C_{26}H_{29}NO_4$ (M^+) 419.2097, found 419.2091.

*(E)-Ethyl 3-(6-(3-chloropropylamino)-5,8-dioxo-5,8-dihydronaphthalen-1-yl)acrylate (**3m**):* orange solid, 18 mg (52%); mp =98−100 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.71 (d, J = 15.9 Hz, 1H), 8.10 (d, J = 7.3 Hz, 1H), 7.69 (d, J = 7.4 Hz, 1H), 7.58 (t, J = 7.6 Hz, 1H), 6.16 (d, J = 15.9 Hz, 1H), 5.86 (s, 1H), 5.74 (s, 1H), 4.26 (q, J = 6.9 Hz, 2H), 3.62 (m, 2H), 3.45−3.33 (m, 2H), 2.18−2.05 (m, 2H), 1.33 (t, J = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 184.5, 181.6, 166.5, 146.7, 145.5, 136.9, 135.3, 131.8, 131.7, 130.4, 128.0, 121.4, 102.7, 60.6, 42.0, 40.0, 30.6, 14.4; EI-MS (m/z) 347 (M^+); HRMS (EI) calcd for $C_{18}H_{18}ClNO_4$ (M^+) 347.0924, found 347.0925.

*(E)-Ethyl 3-(6-(2,2-difluoroethylamino)-5,8-dioxo-5,8-dihydronaphthalen-1-yl)acrylate (**3n**):* yellow solid, 25 mg (75%); mp = 160−162 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.68 (d, J = 16.0 Hz, 1H), 8.12 (d, J = 7.3 Hz, 1H), 7.71 (d, J = 7.4 Hz, 1H), 7.61 (t, J = 7.6 Hz, 1H), 6.18 (d, J = 15.8 Hz, 1H), 5.87 (m, 3H), 4.27 (q, J = 6.9 Hz, 2H), 3.60 (t, J = 13.4 Hz, 2H), 1.33 (t, J = 7.0 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 184.8, 181.2, 166.5, 146.6, 145.2, 137.0, 135.4, 132.1, 131.6, 130.0, 128.1, 121.7, 113.1 (t, J = 243.1 Hz), 103.9, 60.7, 44.6 (t, J = 25.7 Hz), 14.3; EI-MS (m/z) 335 (M^+); HRMS (EI) calcd for $C_{17}H_{15}F_2NO_4$ (M^+) 335.0969, found 335.0969.

*(E)-Ethyl 3-(6-(3-(tert-butoxycarbonyl(methyl)amino)-propylamino)-5,8-dioxo-5,8-dihydronaphthalen-1-yl)acrylate (**3o**):* red solid, 21 mg (48%); mp = 89−91 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.73 (d, J = 16.0 Hz, 1H), 8.12 (d, J = 7.6 Hz, 1H), 7.69 (d, J = 7.5 Hz, 1H), 7.58 (t, J = 7.7 Hz, 1H), 6.16 (d, J = 15.9 Hz, 1H), 5.69 (s, 1H), 4.27 (q, J = 7.1 Hz, 2H), 3.32 (t, J = 6.4 Hz, 2H), 3.24−3.12 (m, 2H), 2.84 (s, 3H), 1.82 (s, 2H), 1.45 (s, 9H), 1.33 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 184.5, 181.7, 166.6, 156.3, 155.6, 147.0, 145.8, 136.9, 135.2, 131.7, 130.6, 128.0, 121.2, 102.0, 79.9, 60.6, 45.5, 39.3, 34.3, 28.5(3), 25.8, 14.4; EI-MS (m/z) 442 (M^+); HRMS (EI) calcd for $C_{24}H_{30}N_2O_6$ (M^+) 442.2104, found 442.2088.

*(E)-Methyl 3-(7-methyl-5,8-dioxo-6-(propylamino)-5,8-dihydronaphthalen-1-yl)acrylate (**3p**):* red solid, 28 mg (90%); mp = 93−94 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.64 (d, J = 15.9 Hz, 1H), 8.04 (d, J = 7.3 Hz, 1H), 7.56 (m, 2H), 6.12 (d, J = 15.9 Hz, 1H), 5.61 (s, 1H), 3.79 (s, 3H), 3.46 (m, 2H), 2.17 (s, 3H), 1.71−1.54 (m, 2H), 0.96 (t, J = 7.3 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 184.9, 182.2, 167.0, 146.4, 145.4, 136.6, 134.9, 131.6, 131.4, 130.6, 127.7, 120.4, 113.3, 51.8, 47.2, 24.1, 11.4, 11.2; EI-MS (m/z) 313 (M^+); HRMS (EI) calcd for $C_{18}H_{19}NO_4$ (M^+) 313.1314, found 313.1312.

*(E)-Methyl 3-(5,8-dioxo-7-phenyl-6-(propylamino)-5,8-dihydronaphthalen-1-yl)acrylate (**3q**):* red solid, 28 mg (74%); mp = 89−91 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.64 (d, J = 15.9 Hz, 1H), 8.16 (d, J = 7.2 Hz, 1H), 7.72−7.54 (m, 2H), 7.42−7.31 (m, 3H), 7.27 (m, 2H), 6.11 (d, J = 15.9 Hz, 1H), 5.84 (s, 1H), 3.73 (s, 3H), 2.51 (m, 2H), 1.41−1.27 (m, 2H), 0.68 (t, J = 7.4 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 183.8, 182.8, 166.9, 146.4, 143.6, 137.2, 135.6, 134.3, 131.8, 131.5, 131.3(2), 130.6, 127.9, 127.8(2), 127.7, 120.7, 116.2, 51.7, 46.3, 23.2, 11.0; EI-MS (m/z) 375 (M^+); HRMS (EI) calcd for $C_{23}H_{21}NO_4$ (M^+) 375.1471, found 375.1462.

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*(E)-Methyl 3-(4-hydroxy-5,8-dioxo-6-(propylamino)-5,8-dihydronaphthalen-1-yl)acrylate (**3r**):* red solid, 12 mg (38%); mp = 145−146 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.20 (s, 1H), 8.64 (d, J = 16.0 Hz, 1H), 7.63 (d, J = 8.8 Hz, 1H), 7.12 (d, J = 8.9 Hz, 1H), 6.14 (d, J = 16.0 Hz, 1H), 5.78 (s, 1H), 5.67 (s, 1H), 3.79 (s, 3H), 3.12 (m, 2H), 1.70 (m, 2H), 1.01 (t, J = 7.3 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 186.5, 183.7, 167.1, 163.2, 146.6, 145.3, 138.5, 130.0, 128.9, 122.6, 120.2, 114.3, 102.7, 51.7, 44.3, 21.6, 11.5; EI-MS (m/z) 315 (M^+); HRMS (EI) calcd for $C_{17}H_{17}NO_5$ (M^+) 315.1107, found 315.1109.

*(E)-Methyl 3-(5,8-dioxo-6-(phenylamino)-5,8-dihydronaphthalen-1-yl)acrylate (**3s**):* red solid, 17 mg (51%); mp = 187−189 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.71 (d, J = 15.9 Hz, 1H), 8.20 (d, J = 7.4 Hz, 1H), 7.74 (d, J = 7.6 Hz, 1H), 7.64 (t, J = 7.7 Hz, 1H), 7.42 (m, 3H), 7.21 (m, 2H), 6.39 (s, 1H), 6.20 (d, J = 15.9 Hz, 1H), 3.81 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 185.3, 181.9, 166.8, 145.4, 143.6, 137.4, 136.8, 135.3, 132.0, 131.6, 130.2, 129.7(2), 128.2, 125.5, 122.4(2), 121.2, 105.0, 51.8. EI-MS (m/z) 333 (M^+); HRMS (EI) calcd for $C_{20}H_{15}NO_4$ (M^+) 333.1001, found 333.1005.

*(E)-Methyl 3-(6-(3-chlorobenzylamino)-5,8-dioxo-5,8-dihydronaphthalen-1-yl)acrylate (**3t**):* Red solid, 22 mg (58%); mp = 137−138 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.68 (d, J = 15.9 Hz, 1H), 8.09 (d, J = 7.4 Hz, 1H), 7.67 (d, J = 7.4 Hz, 1H), 7.58 (t, J = 7.6 Hz, 1H), 7.25 (d, J = 4.0 Hz, 3H), 7.16 (s, 1H), 6.15 (d, J = 16.0 Hz, 2H), 5.68 (s, 1H), 4.34 (d, J = 5.5 Hz, 2H), 3.78 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 184.6, 181.6, 166.9, 146.6, 145.8, 138.1, 136.8, 135.3, 134.9, 131.9, 131.7, 130.3(2), 128.3, 128.1, 127.5, 125.6, 120.9, 103.6, 51.8, 46.1; ESI-MS (m/z): 404 ([M + Na]$^+$); HRMS (ESI) calcd for $C_{21}H_{16}ClNO_4Na$ ([M + Na]$^+$) 404.0666, found 404.0655.

*(E)-Ethyl 3-(6-(diethylamino)-5,8-dioxo-5,8-dihydronaphthalen-1-yl)acrylate (**3ua**):* red solid, 13 mg (39%); mp = 94−96 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.82 (d, J = 15.9 Hz, 1H), 8.02 (d, J = 7.4 Hz, 1H), 7.69 (d, J = 7.6 Hz, 1H), 7.58 (t, J = 7.7 Hz, 1H), 6.21 (d, J = 15.9 Hz, 1H), 5.84 (s, 1H), 4.29 (q, J = 6.9 Hz, 2H), 3.57−3.45 (m, 4H), 1.36 (t, J = 7.2 Hz, 3H), 1.28 (t, J = 6.8 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 184.2, 183.5, 166.6, 150.1, 145.3, 135.8, 134.2, 133.9, 131.5, 129.9, 128.1, 121.2, 106.8, 60.6, 46.5(2), 14.3, 12.6(2); EI-MS (m/z) 327 (M^+); HRMS (EI) calcd for $C_{19}H_{21}NO_4$ (M^+) 327.1471, found 327.1462.

*(E)-Ethyl 3-(6-(ethylamino)-5,8-dioxo-5,8-dihydronaphthalen-1-yl)acrylate (**3ub**):* red solid, 4 mg (13%); mp = 87−89 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.74 (d, J = 16.1 Hz, 1H), 8.12 (d, J = 7.4 Hz, 1H), 7.70 (d, J = 7.2 Hz, 1H), 7.58 (t, J = 7.5 Hz, 1H), 6.16 (d, J = 15.9 Hz, 1H), 5.69 (s, 2H), 4.27 (q, J = 6.7 Hz, 2H), 3.28−3.11 (m, 2H), 1.33 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 184.6, 181.8, 166.6, 146.8, 145.7, 136.9, 135.3, 131.8, 131.7, 130.6, 128.0, 121.3, 102.4, 60.6, 37.3, 14.4, 13.6; EI-MS (m/z) 299 (M^+); HRMS (EI) calcd for $C_{17}H_{17}NO_4$ (M^+) 299.1158, found 299.1154.

Kinetic Isotope Effect Experiments. A solution of substrate **1p** or [D_5]-**1p** (0.2 mmol), alkene **2a** (0.4 mmol), $[RhCp^*Cl_2]_2$ (2.5 mol %), $AgSbF_6$ (10 mol %), and $Cu(OAc)_2{\cdot}H_2O$ (20 mol %) in DCE (1 mL) was stirred in a sealed tube at 120 °C. A portion of the crude solution (0.1 mL) was taken out every 15 min, concentrated in vacuum, and then subjected to ^{1}H NMR measurement with 1,2-dibromomethane as the internal standard (experimental data in the Supporting Information).

■ ASSOCIATED CONTENT

Supporting Information

Copies of NMR spectra of all new compounds and kinetic isotope effect experimental data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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