Dehydrative C–H/N–OH Functionalizations in H₂O by Ruthenium(II) Catalysis: Subtle Effect of Carboxylate Ligands and Mechanistic Insight

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Supporting Information



ABSTRACT: A ruthenium(II) complex derived from the electron-deficient aromatic carboxylic acid $3-(F_3C)C_6H_4CO_2H$ proved to be a highly efficient catalyst for dehydrative alkyne annulation by NH-free hydroxamic acids in water. The C-H/N-OH functionalization occurred with excellent positional selectivity as well as ample substrate scope, setting the stage for effective intermolecular alkenylations of hydroxamic acids. Detailed mechanistic studies were suggestive of a kinetically relevant C-H metalation by carboxylate assistance along with subsequent migratory alkyne insertion, reductive elimination, and intramolecular oxidative addition.

INTRODUCTION

Methods for the activation and functionalization of otherwise unreactive C–H bonds represent powerful tools for the development of step-economical syntheses of bioactive heterocycles.^{1,2} Particularly, the oxidative annulation of alkynes by C– H/N–H cleavages has recently emerged as a useful strategy for the sustainable preparation of N-heterocycles.^{3–5} These approaches largely required the use of stoichiometric or catalytic amounts of terminal oxidants.^{3–6} However, catalyzed C–H/N–O functionalizations with N-substituted benzamides featuring internal oxidants provided the means to avoid the use of external oxidants with notable advances through independent studies.^{7,8}

In recent years, ruthenium(II)-catalyzed C–H functionalizations have been recognized as increasingly viable methods for oxidative heterocycle synthesis.^{9,10} In 2011 we devised reaction conditions for ruthenium(II)-catalyzed alkyne annulations by C–H/N–O cleavages¹¹ for a green isoquinolone synthesis in H_2O^{12-14} (Scheme 1),¹⁵ while Li and Wang independently disclosed effective annulations in methanol.^{16,17}

Our previous optimization of alkyne annulation by *N*-methoxybenzamides highlighted $MesCO_2K$ as the cocatalytic additive of choice.¹⁵ While the byproduct of these C–H functionalizations was MeOH, a more atom-economical and sustainable approach to isoquinolones was established with the use of NH-free hydroxamic acids, thereby generating H₂O as the sole byproduct.¹⁵ Given the environmentally benign nature

of this strategy, we performed detailed studies of dehydrative alkyne annulations with free hydroxamic acids, which led to a significantly more powerful catalyst derived from electron-deficient *m*-(trifluoromethyl)benzoic acid. Herein we present a full account of the development of our second-generation catalyst for C–H/N–OH functionalizations with alkynes or alkenes as well as detailed mechanistic insight into these dehydrative transformations.

RESULTS AND DISCUSSION

Optimization Studies. At the outset of our studies, we tested various solvents for the C–H/N–O functionalization with free hydroxamic acid **1a** (Table 1). Among a set of representative reaction media, H₂O proved to be optimal for the dehydrative transformation (entries 1–5). While [RuCl₂(*p*-cymene)]₂ was found to be the ruthenium precatalyst of choice (entries 6 and 7), cocatalytic additives furnished improved yields of the desired product **3a** (entries 8–27), with the optimal results being accomplished with the potassium salt of the electron-deficient carboxylic acid $3-(F_3C)C_6H_4CO_2H$ (entry 22).

Substrate Scope. With an optimized ruthenium(II) catalyst in hand, we next explored its substrate scope in the

Special Issue: Mechanisms in Metal-Based Organic Chemistry

Received: August 15, 2014

Scheme 1. Evolution of Dehydrative C–H/N–OH Alkyne Annulation in H_2O



Table 1. Optimization of Oxidative Alkyne Annulation by C-H/N-O Cleavage^a

	$H = \frac{1}{1a} + \frac{Ph}{Ph} + \frac$	[RuCl ₂ (<i>p</i> -cymene)] ₂ (5.0 mol %) additive (30.0 mol %) solvent, 100 °C, 18 h	NH Ph 3aa
entry	additive	solvent	vield (%)
1	MesCO ₂ K	H ₂ O	62
2	MesCO ₂ K	1.4-dioxane	7
3	MesCO ₂ K	t-AmOH	11
4	MesCO ₂ K	DMF	12
5	MesCO ₂ K	PhMe	6
6	MesCO ₂ K	H ₂ O	trace ^b
7	MesCO ₂ K	H ₂ O	trace ^c
8	_	H ₂ O	25
9	K ₂ CO ₃	H ₂ O	13
10	KPF ₆	H ₂ O	23
11	AgSbF ₆	H ₂ O	38
12	TBAB	H ₂ O	27
13	KOAc	H ₂ O	55
14	PhCO ₂ K	H ₂ O	66
15	$2-(MeO)C_6H_4CO_2K$	H ₂ O	59
16	$4-(MeO)C_6H_4CO_2K$	H ₂ O	61
17	$4-FC_6H_4CO_2K$	H_2O	68
18	$4-(O_2N)C_6H_4CO_2K$	H ₂ O	71
19	$2,6-(F_3C)_2C_6H_4CO_2K$	H_2O	66
20	$3,5-(F_3C)_2C_6H_4CO_2K$	H ₂ O	70
21	3,4,5-F ₃ C ₆ H ₄ CO ₂ K	H ₂ O	66
22	$3-(F_3C)C_6H_4CO_2K$	H_2O	76
23	$3-(F_3C)C_6H_4CO_2Na$	H ₂ O	74
24	$3-(F_3C)C_6H_4CO_2Cs$	H ₂ O	74
25	$3-(F_3C)C_6H_4CO_2K$	H ₂ O	60^a
26	$3-(F_3C)C_6H_4CO_2K$	H ₂ O	34 ^e
27	$3-(F_3C)C_6H_4CO_2K$	H ₂ O	69^t

^{*a*}Reaction conditions: **1a** (0.5 mmol), **2a** (0.75 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), additive (30.0 mol %), solvent (2.0 mL), 100 °C, 18 h. Average isolated yields of two independent catalytic reactions are shown. ^{*b*} $[RuCl_2(cod)]_n$ (5.0 mol %). ^{*c*} $RuCl_2(PPh_3)_3$ (5.0 mol %). ^{*d*}Additive (20.0 mol %). ^{*e*} $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol %). ^{*f*}Reaction at 80 °C.

dehydrative alkyne annulation by C-H/N-OH cleavages (Scheme 2). The annulation of aryl-substituted alkynes

proceeded efficiently, thereby delivering NH-isoquinolones 3 in high yields. The robust ruthenium(II) catalyst displayed

Article

Scheme 2. Substrate Scope with Aromatic Alkynes 2



Scheme 3. Annulations of Aliphatic Alkynes 4



remarkable chemoselectivity in that valuable functional groups such as fluoro, chloro, bromo, iodo, and nitro substituents were well-tolerated. Different aryl-substituted alkynes **2** were efficiently converted by the ruthenium(II) catalyst as well. Intramolecular competition experiments with *meta*-substituted arenes indicated the excellent positional selectivity of the C–H/N-OH functionalization. While the site selectivity was largely controlled by steric interactions (3ia–3ka), the

Scheme 4. Regioselectivity with Unsymmetrically Substituted Alkynes 6



Scheme 5. Dehydrative Alkenylation



inductive effect of a fluoro substituent led to exclusive C-C bond formation at C2 of hydroxamic acid 11.

The ruthenium(II) catalyst was not restricted to aromatic alkynes **2**. Indeed, alkyl-substituted analogues **4** were also converted with high catalytic efficacy (Scheme 3). Again, the considerable tolerance of electrophilic functional groups became apparent by the preparation of isoquinolones **5** bearing useful functionalities.

The regioselectivity of the C–H/N–OH functionalization with unsymmetrically substituted alkynes was found to be synthetically useful, generally placing the aliphatic substituent distal to nitrogen (Scheme 4).^{10k} Notably, the robust ruthenium(II) catalyst proved to be tolerant of an unprotected hydroxyl group and a thiophene moiety, among others.

It is noteworthy that the dehydrative C-H/N-OH functionalization strategy was not restricted to transformations of alkynes. Hence, this strategy also enabled the efficient intermolecular alkenylation with hydroxamic acids 1 to furnish

the corresponding styrene derivatives 9 in a step-economical manner (Scheme 5).

Mechanistic Studies. Given the unique chemoselectivity of the robust ruthenium(II) catalyst, we became interested in unraveling its mode of action. To this end, we performed intermolecular competition experiments between differently substituted alkynes 2, which illustrated the improved reactivity of electron-deficient alkyne 2c (Scheme 6).

The intermolecular competition between electronically different hydroxamic acids 1 revealed the inherently higher reactivity of more weakly coordinating, electron-deficient arenes (Scheme 7). This observation is not in agreement with an electrophilic activation mode but can be rationalized in terms of a carboxylate-assisted^{18,19} deprotonative C–H ruthenation.²⁰

As to the elementary step of N–O cleavage, a set of competition experiments highlighted that hydroxamic acids 1 were more reactive than the *N*-methoxybenzamides 10

Article

Scheme 6. Intermolecular Competition Experiments between Alkynes 2



(Scheme 8). These findings indicated the cleavage of the N– OH bond to be more facile than that of the N–OMe bond. Moreover, our studies unraveled remarkably different reactivities of methyl- versus ethyl-substituted arenes.

Subsequently, we conducted experiments with isotopically labeled solvents and substrates (Scheme 9). These studies uncovered a minor H/D exchange in the absence of an alkyne (Scheme 9a) as well as a minor D/H scrambling in the product $[D_n]$ -**3aa** (Scheme 9b).

In accordance with these observations, a kinetic isotope effect (KIE) of $k_{\rm H}/k_{\rm D} \approx 2.6$ was suggestive of a kinetically relevant C–H ruthenation step (Scheme 10).

A crossover experiment demonstrated that the N–O bond cleavage likely occurred in an intramolecular fashion (Scheme 11).

On the basis of our mechanistic studies, we propose that the ruthenium(II)-catalyzed C-H/N-OH functionalization is initiated by a kinetically relevant C-H ruthenation step with the in situ-generated complex **11** by carboxylate assistance (Scheme 12). Subsequent migratory insertion of alkyne **2** with cyclometalated complex **13** delivers benzannulated azaruthena-

(II)cycloheptene 14, which upon reductive elimination furnishes ruthenium(0) intermediate 15. Thereafter, we propose that oxidative addition of the N–OH bond onto the ruthenium(0) species takes place, likely in an intramolecular fashion, to yield ruthenium(II) amide 16. Finally, protodeamidation releases the desired product 3 while at the same time regenerating the catalytically active ruthenium(II) biscarboxylate catalyst 11.

CONCLUSIONS

In summary, we have reported on a novel ruthenium(II) biscarboxylate catalyst for dehydrative alkyne annulations by C-H/N-OH functionalizations in water. Thus, an in situgenerated ruthenium(II) catalyst derived from the electrondeficient carboxylic acid 3-(F₃C)C₆H₄CO₂H enabled efficient annulations of various alkynes by NH-free hydroxamic acids. The catalyst displayed a remarkable broad substrate scope and set the stage for highly regio- and site-selective C-H functionalizations. The ruthenium(II) biscarboxylate complex was not limited to functionalizations with alkynes, but likewise allowed for effective intermolecular alkenylations of hydroxamic acids with water as the reaction medium. Detailed mechanistic studies provided strong support for an initial kinetically relevant C-H ruthenation along with a subsequent migratory alkyne insertion. The proposed catalytic cycle furthermore features a reductive elimination and an intramolecular N-OH oxidative addition.

EXPERIMENTAL SECTION

General Remarks. Catalytic reactions were carried out under an atmosphere of N₂ in predried Schlenk tubes. H₂O was degassed. The following starting materials were synthesized according to previously described methods: N-Hydroxybenzamides 1,²¹ N-Methoxybenzamides 10,^{8k} and alkynes 2b,²² 2c,²² and 4a–c.²³ Other chemicals were obtained from commercial sources and were used without further purification. Yields refer to isolated compounds, estimated to be >95% pure as determined by ¹H NMR spectroscopy. NMR spectra were recorded in the indicated solvents; chemical shifts (δ) are given in parts per million. High-resolution mass spectrometry (HRMS) was performed by FTICR.

Representative Procedure for Ruthenium-Catalyzed C–H/ N–OH Alkyne Annulations: Synthesis of 3,4-Diphenylisoquinolin-1(2H)-one (3aa). A mixture of N-hydroxybenzamide (1a) (69 mg, 0.50 mmol), diphenylacetylene (2a) (134 mg, 0.75 mmol), [RuCl₂(p-cymene)]₂ (15.3 mg, 5.0 mol %), and potassium 3-





Scheme 8. Relative Reactivities of N-Methoxybenzamides 10 and Hydroxamic Acids 1







(trifluoromethyl)benzoate (34 mg, 30.0 mol %) in H₂O (2 mL) was stirred at 100 °C under an atmosphere of N₂ for 16 h. At ambient temperature, the reaction mixture was diluted with H₂O (25 mL) and extracted with EtOAc (3×25 mL). The combined organic phase was washed with brine (50 mL) and dried over sodium sulfate. After filtration and evaporation of the solvent in vacuo, the crude product was purified by column chromatography on silica gel (*n*-pentane/ EtOAc 2/1) to yield **3aa** (113 mg, 76%) as a colorless solid (mp =

253–255 °C). ¹H NMR (300 MHz, DMSO-*d*₆): δ = 11.48 (s, 1H), 8.33 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.63 (ddd, *J* = 8.4, 7.1, 1.6 Hz, 1H), 7.51 (ddd, *J* = 8.1, 7.2, 1.3 Hz, 1H), 7.36–7.11 (m, 11H). ¹³C NMR (75 MHz, DMSO-*d*₆): δ = 161.6 (C_q), 138.5 (C_q), 138.0 (C_q), 135.8 (C_q), 134.5 (C_q), 132.3 (CH), 131.6 (CH), 129.7 (CH), 128.1 (CH), 128.0 (CH), 127.5 (CH), 126.9 (CH), 126.7 (CH), 126.1 (CH), 124.9 (C_q), 124.8 (CH), 115.3 (C_q). IR (neat): 3161, 3017, 2885, 1641, 1606, 1446, 1343, 693 cm⁻¹. MS (EI) *m/z* (relative intensity): 297 ([M⁺],

Scheme 10. Kinetic Isotope Effect of the C-H/N-OH Functionalizations







100), 296 (55), 278 (21), 190 (5), 165 (15), 139 (7), 77 (8). HRMS (EI) m/z: calcd for $C_{21}H_{15}NO^+$ [M⁺] 297.1154, found 297.1156. The analytical data are in accordance with those reported in the literature.^{8k}

6-Methyl-3,4-diphenylisoquinolin-1(2H)-one (**3ba**). The representative procedure was followed using N-hydroxy-4-methylbenzamide (**1b**) (76 mg, 0.50 mmol). Purification by column chromatography (*n*-pentane/EtOAc 2/1) yielded **3ba** (103 mg, 66%) as a colorless solid (mp = 277–279 °C). ¹H NMR (300 MHz, CDCl₃): δ = 9.17 (s, 1H), 8.37 (d, *J* = 8.2 Hz, 1H), 7.35–7.12 (m, 12H), 2.38 (s, 3H). ¹³C NMR (75 MHz, CDCl₃): δ = 162.6 (C_q), 143.3 (C_q), 138.7 (C_q), 137.1 (C_q), 135.8 (C_q), 135.2 (C_q), 131.8 (CH), 129.2 (CH), 128.5 (CH), 128.3 (CH), 128.3 (CH), 128.2 (CH), 127.5 (CH), 127.2 (CH), 125.3 (CH), 122.9 (C_q), 117.0 (C_q), 22.1 (CH₃). IR (neat): 3171, 3021, 2898, 1648, 1614, 1488, 1161, 698 cm⁻¹. MS (EI) *m/z* (relative intensity): 311 ([M⁺], 100), 310 (54), 292 (12), 178 (11), 104 (7), 77 (16). HRMS (EI) *m/z*: calcd for C₂₂H₁₇NO⁺ [M⁺] 311.1310, found 311.1297. The analytical data are in accordance with those reported in the literature.¹⁶

6-Methoxy-3,4-diphenylisoquinolin-1(2H)-one (**3ca**). The representative procedure was followed using *N*-hydroxy-4-methoxybenza-mide (**1c**) (84 mg, 0.50 mmol). Purification by column chromatography (*n*-pentane/EtOAc 2/1 → 1/1 → 1/2) yielded **3ca** (96 mg, 59%) as an off-white solid (mp = 292–294 °C). ¹H NMR (300 MHz, DMSO-*d*₆): δ = 11.38 (s, 1H), 8.23 (d, *J* = 8.8 Hz, 1H), 7.37–7.05 (m, 11H), 6.49 (d, *J* = 2.5 Hz, 1H), 3.65 (s, 3H). ¹³C NMR (75 MHz, DMSO-*d*₆): δ = 162.2 (C_q), 161.2 (C_q), 140.0 (C_q), 139.1 (C_q), 135.8 (C_q), 134.6 (C_q), 131.6 (CH), 129.7 (CH), 129.0 (CH), 128.1 (CH), 128.0 (CH), 127.5 (CH), 126.9 (CH), 118.8 (C_q), 115.0 (C_q), 114.4 (CH), 107.1 (CH), 55.1 (CH₃). IR (neat): 3020, 2979, 2884, 1639, 1608, 1275, 1027, 694 cm⁻¹. MS (EI) *m*/*z* (relative intensity): 327 ([M⁺], 100), 326 (50), 283 (7), 254 (7), 152 (12), 104 (6), 77 (8). HRMS (EI) *m*/*z*: calcd for C₂₂H₁₇NO₂⁺ [M⁺] 327.1259, found 327.1266. The analytical data are in accordance with those reported in the literature.^{8k}

6-Fluoro-3,4-diphenylisoquinolin-1(2H)-one (3da). The representative procedure was followed using 4-fluoro-N-hydroxybenzamide (1d) (78 mg, 0.50 mmol). Purification by column chromatography (npentane/EtOAc 2/1) yielded 3da (128 mg, 81%) as a colorless solid (mp = 251–253 °C). ¹H NMR (300 MHz, DMSO- d_6): δ = 11.58 (s, 1H), 8.37 (dd, J = 8.9, 6.1 Hz, 1H), 7.38-7.13 (m, 11H), 6.73 (dd, J = 10.9, 2.5 Hz, 1H). ¹³C NMR (125 MHz, DMSO- d_6): δ = 164.3 (d, $J_{C-F} = 249.2$ Hz, C_q), 160.7 (C_q), 140.5 (d, $J_{C-F} = 9.7$ Hz, C_q), 140.0 (C_q), 135.1 (C_q), 134.0 (C_q), 131.3 (CH), 130.3 (CH), 130.2 (CH), 129.5 (CH), 128.2 (CH), 127.5 (CH), 127.1 (CH), 121.7 (d, J_{C-F} = 1.6 Hz, C_q), 114.7 (d, J_{C-F} = 3.4 Hz, C_q), 114.5 (d, J_{C-F} = 23.6 Hz, CH), 109.4 (d, J_{C-F} = 23.2 Hz, CH). ¹⁹F NMR (283 MHz, DMSO d_6): $\delta = -106.4$ (ddd, J = 10.9, 8.4, 6.3 Hz). IR (neat): 3116, 3030, 2917, 1644, 1610, 1450, 1178, 695 cm⁻¹. MS (EI) m/z (relative intensity): 315 ([M⁺], 60), 314 (36), 296 (12), 183 (9), 98 (22), 57 (32), 43 (100). HRMS (EI) m/z: calcd for $C_{21}H_{14}FNO^+$ [M⁺] 315.1059, found 315.1064. The analytical data are in accordance with those reported in the literature.¹⁵

6-Chloro-3,4-diphenylisoquinolin-1(2H)-one (**3ea**). The representative procedure was followed using 4-chloro-N-hydroxybenzamide (**1e**) (86 mg, 0.50 mmol). Purification by column chromatography (*n*-pentane/EtOAc 2/1) yielded **3ea** (103 mg, 62%) as a colorless solid (mp = 270–272 °C). ¹H NMR (300 MHz, DMSO-*d*₆): δ = 11.65 (s, 1H), 8.31 (d, *J* = 8.5 Hz, 1H), 7.54 (dd, *J* = 8.6, 2.0 Hz, 1H), 7.36–7.13 (m, 10H), 7.05 (d, *J* = 2.0 Hz, 1H). ¹³C NMR (125 MHz, DMSO-*d*₆): δ = 160.8 (C_q), 140.1 (C_q), 139.5 (C_q), 137.4 (C_q), 134.9 (C_q), 131.4 (CH), 129.5 (CH), 129.1 (CH), 128.2 (CH), 128.2 (CH), 127.5 (CH), 127.1 (CH), 126.1 (CH), 123.6 (CH), 123.4 (C_q), 114.3 (C_q). IR (neat): 3155, 3022, 2882, 1644, 1594, 1442, 1080, 696 cm⁻¹. MS (EI) *m/z* (relative intensity): 331 ([M⁺], 100), 330 (50), 295 (15), 267 (12), 163 (15), 77 (15). HRMS (EI) *m/z*: calcd for C₂₁H₁₄CINO⁺ [M⁺] 331.0764, found 331.0762. The analytical data are in accordance with those reported in the literature.¹⁵

6-Bromo-3,4-diphenylisoquinolin-1(2H)-one (3fa). The representative procedure was followed using 4-bromo-N-hydroxybenzamide

Article





(1f) (108 mg, 0.50 mmol). Purification by column chromatography (*n*-pentane/EtOAc 2/1) yielded 3fa (138 mg, 73%) as a colorless solid (mp = 285–286 °C). ¹H NMR (300 MHz, DMSO-*d*₆): δ = 11.69 (s, 1H), 8.21 (d, *J* = 8.6 Hz, 1H), 7.66 (dd, *J* = 8.6, 1.9 Hz, 1H), 7.39–7.09 (m, 11H). ¹³C NMR (75 MHz, DMSO-*d*₆): δ = 161.1 (C_q), 140.2 (C_q), 139.8 (C_q), 135.1 (C_q), 134.1 (C_q), 131.5 (CH), 129.6 (CH), 129.2 (CH), 129.0 (CH), 128.3 (CH), 127.6 (CH), 127.3 (CH), 126.8 (CH), 126.7 (C_q), 123.8 (C_q), 114.3 (C_q). IR (neat): 3164, 3020, 2902, 1645, 1588, 1438, 1066, 696 cm⁻¹. MS (EI) *m/z* (relative intensity): 376 ([M⁺], 95), 375 (100), 295 (28), 267 (16), 239 (13), 163 (25), 77 (20). HRMS (EI) *m/z*: calcd for C₂₁H₁₄⁻⁷⁹BrNO⁺ [M⁺] 375.0259, found 375.0272. The analytical data are in accordance with those reported in the literature.^{8k}

6-lodo-3,4-diphenylisoquinolin-1(2H)-one (**3ga**). The representative procedure was followed using N-hydroxy-4-iodobenzamide (**1g**) (132 mg, 0.50 mmol). Purification by column chromatography (*n*-pentane/CH₂Cl₂/EtOAc 2/1/1) yielded **3ga** (81 mg, 38%) as a colorless solid (mp = 311–312 °C). ¹H NMR (300 MHz, DMSO-*d*₆): δ = 11.67 (s, 1H), 8.03 (d, *J* = 8.4 Hz, 1H), 7.83 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.43 (d, *J* = 1.6 Hz, 1H), 7.36–7.09 (m, 10H). ¹³C NMR (125 MHz, DMSO-*d*₆): δ = 161.3 (C_q), 139.9 (C_q), 139.7 (C_q), 135.1 (C_q), 134.7 (CH), 134.2 (C_q), 133.1 (CH), 131.6 (CH), 129.7 (CH), 128.7 (CH), 128.3 (CH), 128.3 (CH), 127.6 (CH), 127.2 (CH), 124.1 (C_q), 114.1 (C_q), 101.1 (C_q). IR (neat): 3160, 3020, 2934, 1648, 1597, 1437, 1154, 697 cm⁻¹. MS (EI) *m/z* (relative intensity): 423 ([M⁺], 100), 422 (28), 295 (14), 267 (11), 239 (9), 163 (15), 77 (10).

HRMS (EI) m/z: calcd for $C_{21}H_{14}INO^+$ [M⁺] 423.0120, found 423.0123. The analytical data are in accordance with those reported in the literature.¹⁶

6-Nitro-3,4-diphenylisoquinolin-1(2H)-one (**3ha**). The representative procedure was followed using N-hydroxy-4-nitrobenzamide (**1h**) (91 mg, 0.50 mmol). Purification by column chromatography (*n*-pentane/EtOAc 2/1) yielded **3ha** (114 mg, 67%) as a yellow solid (mp = 260–262 °C). ¹H NMR (300 MHz, CDCl₃): δ = 10.12 (s, 1H), 8.65–8.50 (m, 1H), 8.31–8.15 (m, 2H), 7.42–7.23 (m, 8H), 7.22–7.14 (m, 2H). ¹³C NMR (75 MHz, CDCl₃): δ = 161.7 (C_q), 150.6 (C_q), 139.7 (C_q), 139.5 (C_q), 134.3 (C_q), 134.1 (C_q), 131.6 (CH), 129.6 (CH), 129.2 (CH), 129.2 (CH), 128.9 (CH), 128.6 (C_q), 128.5 (CH), 128.1 (CH), 121.2 (CH), 120.1 (CH), 117.1 (C_q). IR (neat): 3332, 3022, 1664, 1611, 1525, 1340, 701 cm⁻¹. MS (EI) *m*/*z* (relative intensity): 342 ([M⁺], 100), 341 (18), 295 (16), 268 (14), 190 (12), 165 (12), 121 (15). HRMS (EI) *m*/*z*: calcd for C₂₁H₁₄N₂O₃⁺ [M⁺] 342.1004, found 342.1001. The analytical data are in accordance with those reported in the literature.

7-Methyl-3,4-diphenylisoquinolin-1(2H)-one (3ia). The representative procedure was followed using *N*-hydroxy-3-methylbenzamide (1i) (76 mg, 0.50 mmol) at 120 °C. Purification by column chromatography (CH₂Cl₂/Et₂O 5/1) yielded 3ia (94 mg, 60%) as a colorless solid (mp = 292–293 °C). ¹H NMR (300 MHz, DMSO-*d*₆): δ = 11.38 (s, 1H), 8.12 (dd, *J* = 1.9, 0.9 Hz, 1H), 7.47 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.33–7.19 (m, 8H), 7.17–7.10 (m, 2H), 7.06 (d, *J* = 8.3 Hz, 1H), 2.45 (s, 3H). ¹³C NMR (75 MHz, DMSO-*d*₆): δ = 161.0 (C₀),

138.0 (C_q), 136.5 (C_q), 136.3 (C_q), 136.3 (C_q), 135.1 (C_q), 134.2 (CH), 132.1 (CH), 130.3 (CH), 128.6 (CH), 128.5 (CH), 128.1 (CH), 127.4 (CH), 126.8 (CH), 125.5 (C_q), 125.4 (CH), 115.8 (C_q), 21.3 (CH₃). IR (neat): 3138, 3026, 2911, 1642, 1616, 1444, 1342, 696 cm⁻¹. MS (EI) *m*/*z* (relative intensity): 311 ([M⁺], 100), 310 (48), 292 (9), 178 (7), 104 (5), 77 (12). HRMS (EI) *m*/*z*: calcd for $C_{22}H_{17}NO^+$ [M⁺] 311.1310, found 311.1313. The analytical data are in accordance with those reported in the literature.^{8j}

7-(*Trifluoromethyl*)-3,4-diphenylisoquinolin-1(2H)-one (**3***ja*). The representative procedure was followed using N-hydroxy-3-(trifluoromethyl)benzamide (**1***j*) (103 mg, 0.50 mmol). Purification by column chromatography (CH₂Cl₂/Et₂O 10/1) yielded **3***j*a (76 mg, 42%) as a colorless solid (mp = 234–235 °C). ¹H NMR (300 MHz, CDCl₃): δ = 9.90 (s, 1H), 8.77–8.67 (m, 1H), 7.76 (dd, *J* = 8.6, 2.0 Hz, 1H), 7.47 (d, *J* = 8.6 Hz, 1H), 7.38–7.23 (m, 8H), 7.21–7.14 (m, 2H). ¹³C NMR (125 MHz, CDCl₃): δ = 162.1 (C_q), 141.0 (C_q), 139.5 (C_q), 134.9 (C_q), 134.3 (C_q), 131.6 (CH), 129.1 (CH), 129.0 (CH), 128.6 (CH), 128.5 (CH), 128.4 (CH), 128.3 (d, *J*_{C-F} = 33.3 Hz, C_q), 127.6 (CH), 126.5 (CH), 125.1 (dd, *J*_{C-F} = 8.2, 4.0 Hz, CH), 124.8 (C_q), 123.8 (d, *J*_{C-F} = 271.7 Hz, C_q), 116.7 (C_q). ¹⁹F NMR (283 MHz, CDCl₃): δ = -62.4 (s). IR (neat): 3153, 3034, 2929, 1653, 1618, 1320, 1121, 697 cm⁻¹. MS (EI) *m/z* (relative intensity): 365 ([M⁺], 100), 364 (55), 346 (19), 267 (8), 239 (5), 163 (5), 77 (13). HRMS (EI) *m/z*: calcd for C₂₂H₁₄F₃NO⁺ [M⁺] 365.1027, found 365.1024. The analytical data are in accordance with those reported in the literature.^{8k}

3,4-Diphenylbenzo[g]isoquinolin-1(2H)-one (**3ka**). The representative procedure was followed using *N*-hydroxy-2-naphthamide (**1k**) (94 mg, 0.50 mmol). Purification by column chromatography (*n*-pentane/EtOAc 2/1) yielded **3ka** (126 mg, 73%) as a pale-green solid (mp = 287–289 °C). ¹H NMR (300 MHz, DMSO-*d*₆): δ = 11.29 (s, 1H), 9.02 (s, 1H), 8.28–8.13 (m, 1H), 7.88–7.80 (m, 1H), 7.63 (s, 1H), 7.61–7.50 (m, 2H), 7.41–7.16 (m, 10H). ¹³C NMR (75 MHz, DMSO-*d*₆): δ = 162.1 (C_q), 137.3 (C_q), 136.0 (C_q), 134.8 (C_q), 134.7 (C_q), 134.6 (C_q), 131.7 (CH), 130.7 (C_q), 129.7 (CH), 129.0 (CH), 128.2 (CH), 128.1 (CH), 128.0 (CH), 128.0 (CH), 127.7 (CH), 127.6 (CH), 127.0 (CH), 126.0 (CH), 123.8 (C_q), 123.3 (CH), 115.2 (C_q). IR (neat): 3051, 3024, 2884, 1649, 1616, 1596, 1357, 697 cm⁻¹. MS (EI) *m*/*z* (relative intensity): 347 ([M⁺], 100), 346 (22), 328 (12), 251 (12), 158 (6), 77 (5). HRMS (EI) *m*/*z*: calcd for C₂₅H₁₇NO⁺ [M⁺] 347.1310, found 347.1301. The analytical data are in accordance with those reported in the literature.¹⁶

5-Fluoro-3,4-diphenylisoquinolin-1(2H)-one (3la). The representative procedure was followed using 3-fluoro-N-hydroxybenzamide (11) (78 mg, 0.50 mmol). Purification by column chromatography (CH₂Cl₂/Et₂O 5/1) yielded 3la (91 mg, 58%) as a colorless solid (mp = 250–252 °C). ¹H NMR (300 MHz, CDCl₃): δ = 9.50 (s, 1H), 8.29 (dd, J = 7.9, 1.3 Hz, 1H), 7.44 (td, J = 8.0, 4.5 Hz, 1H), 7.34-7.12 (m, 11H). ¹³C NMR (125 MHz, CDCl₃): δ = 161.6 (d, J_{C-F} = 3.1 Hz, C_q), 158.6 (d, J_{C-F} = 255.5 Hz, C_q), 138.5 (C_q), 137.4 (d, J_{C-F} = 3.9 Hz, C_q), 134.8 (C_q), 131.0 (d, $J_{C-F} = 3.7$ Hz, CH), 129.3 (CH), 128.7 (${
m CH}$), 128.2 (${
m CH}$), 127.5 (CH), 127.4 (d, J_{C-F} = 2.5 Hz, C_q), 127.3 (d, $J_{C-F} = 8.4$ Hz, CH), 127.3 (d, $J_{C-F} = 8.8$ Hz, C_q), 126.9 (CH), 123.7 (d, J_{C-F} = 4.0 Hz, CH), 119.8 (d, J_{C-F} = 22.6 Hz, CH), 113.3 (d, $J_{C-F} = 2.1 \text{ Hz}, C_q$). ¹⁹F NMR (283 MHz, CDCl₃): $\delta = -107.3 \text{ (dd, } J = -107.3$ 12.4, 4.5 Hz). IR (neat): 3165, 3016, 2888, 1652, 1613, 1444, 1253, 697 cm⁻¹. MS (EI) m/z (relative intensity): 315 ([M⁺], 100), 314 (20), 296 (7), 183 (12), 104 (4), 77 (8). HRMS (EI) m/z: calcd for $C_{21}H_{14}FNO^{+}$ [M⁺] 315.1059, found 315.1071. The analytical data are in accordance with those reported in the literature.¹⁵

3,4-Bis(4-methoxyphenyl)isoquinolin-1(2H)-one (**3ab**). The representative procedure was followed using 1,2-bis(4-methoxyphenyl)-ethyne (**2b**) (179 mg, 0.75 mmol). Purification by column chromatography (*n*-pentane/EtOAc 2/1 → 1/1 → 1/3) yielded **3ab** (103 mg, 58%) as an off-white solid (mp = 265–267 °C). ¹H NMR (300 MHz, DMSO-*d*₆): δ = 11.42 (s, 1H), 8.27 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.65–7.56 (m, 1H), 7.46–7.51 (m, 1H), 7.15–7.12 (m, 3H), 7.04 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 6.77 (d, *J* = 8.6 Hz, 2H), 3.72 (s, 3H), 3.69 (s, 3H). ¹³C NMR (75 MHz, DMSO-*d*₆): δ = 161.7 (C_q), 158.8 (C_q), 157.9 (C_q), 138.5 (C_q), 138.3 (C_q), 132.7 (CH), 132.2 (CH), 131.0 (CH), 127.9 (C_q), 126.9 (C_q), 126.6 (CH),

125.8 (CH), 124.8 (CH), 124.8 (C_q), 114.7 (C_q), 113.7 (CH), 113.0 (CH), 55.0 (CH₃), 54.9 (CH₃). IR (neat): 3156, 3003, 2834, 1645, 1603, 1509, 1243, 1031 cm⁻¹. MS (EI) m/z (relative intensity): 357 ([M⁺], 100), 356 (14), 342 (11), 282 (7), 152 (7), 77 (3). HRMS (EI) m/z: calcd for C₂₃H₁₉NO₃⁺ [M⁺] 357.1365, found 357.1366. The analytical data are in accordance with those reported in the literature.¹⁶

3,4-Bis(4-fluorophenyl)isoquinolin-1(2H)-one (3ac). The representative procedure was followed using 1,2-bis(4-fluorophenyl)ethyne (2c) (161 mg, 0.75 mmol). Purification by column chromatography (n-pentane/EtOAc 2/1) yielded 3ac (105 mg, 63%) as a colorless solid (mp = 296–298 °C). ¹H NMR (300 MHz, DMSO- d_6): δ = 11.58 (s, 1H), 8.30 (dd, J = 8.0, 1.5 Hz, 1H), 7.64 (ddd, J = 8.4, 7.2, 1.6 Hz, 1H), 7.51 (ddd, J = 8.1, 7.0, 1.2 Hz, 1H), 7.31–7.03 (m, 9H). ¹³C NMR (125 MHz, DMSO- d_6): δ = 161.5 (d, J_{C-F} = 245.4 Hz, C_q), 161.4 (C_q), 160.9 (d, J_{C-F} = 243.8 Hz, C_q), 137.8 (C_q), 137.7 (C_q), 133.4 (d, J_{C-F} = 8.1 Hz, CH), 132.4 (CH), 131.9 (d, J_{C-F} = 8.5 Hz, CH), 131.8 (d, $J_{C-F} = 3.3$ Hz, C_q), 130.7 (d, $J_{C-F} = 3.3$ Hz, C_q), 126.6 (CH), 126.1 (CH), 124.9 (C_q), 124.6 (CH), 114.8 (d, $J_{C-F} = 21.3$ Hz, CH), 114.5 (d, J_{C-F} = 21.7 Hz, CH), 114.4 (C_q). ¹⁹F NMR (283 MHz, DMSO- d_6): $\delta = -113.1$ (tt, J = 9.0, 5.5 Hz), -115.1 (tt, J = 8.9, 5.7Hz). IR (neat): 3160, 3066, 2916, 1648, 1613, 1506, 1223, 773 cm⁻¹. MS (EI) m/z (relative intensity): 333 ([M⁺], 100), 332 (52), 314 (22), 183 (16), 122 (7), 95 (7). HRMS (EI) m/z: calcd for $C_{21}H_{13}F_2NO^+$ [M⁺] 333.0965, found 333.0961. The analytical data are in accordance with those reported in the literature.¹⁵

3,4-Di-n-propylisoquinolin-1(2H)-one (5aa). The representative procedure was followed using oct-4-yne (4a) (83 mg, 0.75 mmol). Purification by column chromatography (*n*-pentane/EtOAc 2/1) yielded 5aa (86 mg, 75%) as a colorless solid (mp = 188–190 °C). ¹H NMR (300 MHz, CDCl₃): δ = 10.99 (s, 1H), 8.44 (dt, *J* = 8.0, 1.1 Hz, 1H), 7.68–7.63 (m, 2H), 7.42 (dt, *J* = 8.1, 4.1 Hz, 1H), 2.73–2.61 (m, 4H), 1.81–1.66 (m, 2H), 1.66–1.51 (m, 2H), 1.04 (t, *J* = 7.3 Hz, 3H), 1.03 (t, *J* = 7.3 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃): δ = 163.8 (C_q), 138.6 (C_q), 138.2 (C_q), 132.4 (CH), 127.8 (CH), 125.4 (CH), 125.3 (C_q), 123.2 (CH), 113.1 (C_q), 33.1 (CH₂), 28.8 (CH₂), 23.7 (CH₂), 22.9 (CH₂), 14.5 (CH₃), 14.1 (CH₃). IR (neat): 3164, 3025, 2869, 1653, 1628, 1470, 1167, 774 cm⁻¹. MS (EI) *m*/*z* (relative intensity): 229 ([M⁺], 30), 201 (20), 200 (100), 172 (12), 115 (10), 77 (6). HRMS (EI) *m*/*z*: calcd for C₁₅H₁₉NO⁺ [M⁺] 229.1467, found 229.1462. The analytical data are in accordance with those reported in the literature.^{8j}

6-Methoxy-3,4-di-n-propylisoquinolin-1(2H)-one (5ca). The representative procedure was followed using N-hydroxy-4-methoxybenza-mide (1c) (84 mg, 0.50 mmol) and oct-4-yne (4a) (83 mg, 0.75 mmol). Purification by column chromatography (*n*-pentane/EtOAc 1/1) yielded 5ca (91 mg, 70%) as an off-white solid (mp = 158–160 °C). ¹H NMR (300 MHz, CDCl₃): δ = 10.97 (s, 1H), 8.38 (d, *J* = 9.6 Hz, 1H), 7.07–6.96 (m, 2H), 3.93 (s, 3H), 2.68–2.57 (m, 4H), 1.80–1.54 (m, 4H), 1.05 (t, *J* = 7.3 Hz, 3H), 1.04 (t, *J* = 7.3 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃): δ = 163.3 (C_q), 163.0 (C_q), 140.7 (C_q), 139.0 (C_q), 129.9 (CH), 119.2 (C_q), 114.0 (CH), 112.6 (C_q), 105.4 (CH), 55.5 (CH₃), 33.2 (CH₂), 28.9 (CH₂), 23.4 (CH₂), 22.9 (CH₂), 14.5 (CH₃), 14.1 (CH₃). IR (neat): 3156, 2966, 2864, 1632, 1601, 1467, 1232, 833 cm⁻¹. MS (EI) *m*/z (relative intensity): 259 ([M⁺], 40), 231 (32), 230 (100), 202 (14), 189 (8), 115 (6), 77 (3). HRMS (EI) *m*/z: calcd for C₁₆H₂₁NO₂⁺ [M⁺] 259.1572, found 259.1574.

6-*Fluoro-3,4-di-n-propylisoquinolin-1(2H)-one* (**5***da*). The representative procedure was followed using 4-fluoro-*N*-hydroxybenzamide (**1d**) (78 mg, 0.50 mmol) and oct-4-yne (**4a**) (83 mg, 0.75 mmol). Purification by column chromatography (*n*-pentane/EtOAc 2/1) yielded **5da** (94 mg, 76%) as a colorless solid (mp = 170–172 °C). ¹H NMR (300 MHz CDCl₃): δ = 11.24 (s, 1H), 8.45 (ddd, *J* = 8.9, 6.2, 2.9 Hz, 1H), 7.27 (dd, *J* = 10.9, 2.7 Hz, 1H), 7.13 (td, *J* = 8.5, 2.5 Hz, 1H), 2.72–2.58 (m, 4H), 1.82–1.68 (m, 2H), 1.66–1.51 (m, 2H), 1.06 (t, *J* = 7.3 Hz, 3H), 1.04 (t, *J* = 7.3 Hz, 3H). ¹³C NMR (125 MHz, CDCl₃): δ = 165.6 (d, *J*_{C-F} = 251.3 Hz, C_q), 163.1 (C_q), 141.1 (d, *J*_{C-F} = 9.7 Hz, C_q), 139.8 (C_q), 130.8 (d, *J*_{C-F} = 10.2 Hz, CH), 121.8 (d, *J*_{C-F} = 1.5 Hz, C_q), 114.0 (d, *J*_{C-F} = 23.6 Hz, CH), 112.7 (d, *J*_{C-F} = 3.5 Hz, C_q), 108.4 (d, *J*_{C-F} = 22.6 Hz, CH), 33.2 (CH₂), 28.9 (CH₂), 23.6 (CH₂), 23.0 (CH₂), 14.5 (CH₃), 14.2 (CH₃).

CDCl₃): $\delta = -106.2$ (ddd, J = 11.1, 8.1, 6.2 Hz). IR (neat): 3027, 2954, 2871, 1666, 1614, 1461, 1188, 863 cm⁻¹. MS (EI) m/z (relative intensity): 247 ([M⁺], 21), 219 (15), 218 (100), 202 (7), 190 (12), 133 (7), 43 (13). HRMS (EI) m/z: calcd for C₁₅H₁₈FNO⁺ [M⁺] 247.1372, found 247.1364. The analytical data are in accordance with those reported in the literature.¹⁵

6-lodo-3,4-di-n-propylisoquinolin-1(2H)-one (**5ga**). The representative procedure was followed using N-hydroxy-4-iodobenzamide (**1g**) (132 mg, 0.50 mmol) and oct-4-yne (**4a**) (83 mg, 0.75 mmol). Purification by column chromatography (*n*-pentane/EtOAc 2/1) yielded **5ga** (122 mg, 69%) as an off-white solid (mp = 184–186 °C). ¹H NMR (300 MHz, DMSO-d₆): δ = 11.19 (s, 1H), 7.98 (s, 1H), 7.89 (d, *J* = 8.3 Hz, 1H), 7.71 (d, *J* = 8.3 Hz, 1H), 2.61–2.42 (m, 4H), 1.64–1.34 (m, 4H), 1.00–0.83 (m, 6H). ¹³C NMR (125 MHz, DMSO-d₆): δ = 161.3 (C_q), 140.3 (C_q), 139.4 (C_q), 133.7 (CH), 131.4 (CH), 128.8 (CH), 124.1 (C_q), 109.7 (C_q), 101.0 (C_q), 31.7 (CH₂), 27.4 (CH₂), 23.0 (CH₂), 22.4 (CH₂), 13.9 (CH₃), 13.5 (CH₃). IR (neat): 3169, 2953, 2867, 1666, 1625, 1589, 1455, 775 cm⁻¹. MS (EI) *m*/*z* (relative intensity): 355 ([M⁺], 40), 327 (15), 326 (100), 298 (7), 199 (20), 184 (6), 102 (5). HRMS (EI) *m*/*z*: calcd for C₁₅H₁₈INO⁺ [M⁺] 355.0433, found 355.0433.

7-Methyl-3,4-di-n-propylisoquinolin-1(2H)-one (*5ia*). The representative procedure was followed using N-hydroxy-3-methylbenzamide (1i) (76 mg, 0.50 mmol) and oct-4-yne (4a) (83 mg, 0.75 mmol). Purification by column chromatography (*n*-pentane/EtOAc 2/1) yielded **5ia** (85 mg, 70%) as a colorless solid (mp = 176–178 °C). ¹H NMR (300 MHz, CDCl₃): δ = 10.44 (*s*, 1H), 8.24 (*s*, 1H), 7.58 (dd, *J* = 8.4, 1.7 Hz, 1H), 7.49 (dt, *J* = 8.4, 1.9 Hz, 1H), 2.72–2.60 (m, 4H), 2.48 (*s*, 3H), 1.82–1.51 (m, 4H), 1.08–1.00 (m, 6H). ¹³C NMR (125 MHz, CDCl₃): δ = 163.2 (C_q), 136.6 (C_q), 136.0 (C_q), 135.1 (C_q), 133.7 (CH), 127.1 (CH), 125.0 (C_q), 123.0 (CH), 112.9 (C_q), 32.9 (CH₂), 28.7 (CH₂), 23.7 (CH₂), 22.7 (CH₂), 21.2 (CH₃), 14.4 (CH₃), 14.0 (CH₃). IR (neat): 2956, 2930, 2870, 1659, 1629, 1352, 900, 815 cm⁻¹. MS (EI) *m/z* (relative intensity): 243 ([M⁺], 32), 215 (15), 214 (100), 186 (13), 115 (12), 77 (3). HRMS (EI) *m/z*: calcd for C₁₆H₂₁NO⁺ [M⁺] 243.1623, found 243.1629.

3,4-Diethylisoquinolin-1(2H)-one (*5ab*). The representative procedure was followed using hex-3-yne (4b) (62 mg, 0.75 mmol) at 80 °C. Purification by column chromatography (*n*-pentane/EtOAc 2/1) yielded **5ab** (87 mg, 86%) as a colorless solid (mp = 178–180 °C). ¹H NMR (300 MHz, CDCl₃): δ = 11.31 (s, 1H), 8.48 (dt, *J* = 7.8, 1.1 Hz, 1H), 7.77–7.62 (m, 2H), 7.44 (ddd, *J* = 8.1, 5.8, 2.3 Hz, 1H), 2.68–2.81 (m, 4H), 1.34 (t, *J* = 7.6 Hz, 3H), 1.22 (t, *J* = 7.5 Hz, 3H). ¹³C NMR (125 MHz, CDCl₃): δ = 164.0 (C_q), 139.3 (C_q), 138.3 (C_q), 132.4 (CH), 127.8 (CH), 125.3 (CH), 125.2 (C_q), 122.9 (CH), 114.0 (C_q), 24.5 (CH₂), 19.7 (CH₂), 15.2 (CH₃), 14.3 (CH₃). IR (neat): 3163, 2966, 2872, 1648, 1631, 1474, 1163, 769 cm⁻¹. MS (EI) *m/z* (relative intensity): 201 ([M⁺], 43), 187 (15), 186 (100), 168 (10), 128 (10), 115 (20), 77 (6). HRMS (EI) *m/z*: calcd for C₁₃H₁₅NO⁺ [M⁺] 201.1154, found 201.1152. The analytical data are in accordance with those reported in the literature.¹⁶

3,4-Di-n-butylisoquinolin-1(2H)-one (**5ac**). The representative procedure was followed using dec-5-yne (**4c**) (104 mg, 0.75 mmol). Purification by column chromatography (CH₂Cl₂/Et₂O 4/1) yielded **5ac** (101 mg, 78%) as a colorless solid (mp = 85–87 °C). ¹H NMR (300 MHz, CDCl₃): δ = 11.24 (s, 1H), 8.43 (d, *J* = 8.0 Hz, 1H), 7.66 (m, 2H), 7.41 (dt, *J* = 8.1, 4.0 Hz, 1H), 2.76–2.61 (m, 4H), 1.68 (tt, *J* = 7.9, 6.3 Hz, 2H), 1.60–1.38 (m, 6H), 0.96 (t, *J* = 7.2 Hz, 6H). ¹³C NMR (75 MHz, CDCl₃): δ = 163.7 (C_q), 138.5 (C_q), 138.3 (C_q), 132.2 (CH), 127.6 (CH), 125.2 (CH), 125.1 (C_q), 122.9 (CH), 112.9 (C_q), 32.6 (CH₂), 31.6 (CH₂), 30.8 (CH₂), 26.2 (CH₂), 23.0 (CH₂), 22.7 (CH₂), 14.0 (CH₃), 13.8 (CH₃). IR (neat): 3164, 2961, 2926, 2861, 1649, 1627, 1471, 769 cm⁻¹. MS (EI) *m*/*z* (relative intensity): 257 ([M⁺], 58), 215 (23), 214 (100), 173 (22), 172 (83), 144 (10), 115 (12), 77 (5). HRMS (EI) *m*/*z*: calcd for C₁₇H₂₃NO⁺ [M⁺] 257.1780, found 257.1788.

4-n-Butyl-3-phenylisoquinolin-1(2H)-one (7aa). The representative procedure was followed using hex-1-yn-1-ylbenzene (6a) (119 mg, 0.75 mmol). Purification by column chromatography (*n*-pentane/ EtOAc 2/1) yielded 7aa (110 mg, 79%) as a colorless solid (mp = 154–155 °C). ¹H NMR (300 MHz, CDCl₃): δ = 8.86 (s, 1H), 8.43 (dt, *J* = 8.0, 1.1 Hz, 1H), 7.77–7.66 (m, 2H), 7.53–7.37 (m, 6H), 2.68–2.56 (m, 2H), 1.61–1.47 (m, 2H), 1.27 (tt, *J* = 7.3, 7.3 Hz, 2H), 0.81 (t, *J* = 7.3 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃): δ = 162.3 (C_q), 138.1 (C_q), 136.9 (C_q), 135.7 (C_q), 132.8 (CH), 129.3 (CH), 129.1 (CH), 128.9 (CH), 128.1 (CH), 126.4 (CH), 126.0 (C_q), 123.9 (CH), 114.5 (C_q), 32.9 (CH₂), 27.1 (CH₂), 22.9 (CH₂), 13.9 (CH₃). IR (neat): 3160, 2950, 2869, 1646, 1615, 1469, 1157, 761 cm⁻¹. MS (EI) *m/z* (relative intensity): 277 ([M⁺], 35), 235 (15), 234 (100), 216 (19), 178 (6), 77 (11), 43 (24). HRMS (EI) *m/z*: calcd for C₁₉H₁₉NO⁺ [M⁺] 277.1467, found 277.1461.

4-n-Butyl-3-(4-methoxyphenyl)isoquinolin-1(2H)-one (7ab). The representative procedure was followed using 1-(hex-1-yn-1-yl)-4methoxybenzene (6b) (141 mg, 0.75 mmol). Purification by column chromatography (*n*-pentane/EtOAc $2/1 \rightarrow 1/1$) yielded 7ab (100 mg, 65%) as an off-white solid (mp = 167-169 °C). ¹H NMR (300 MHz, DMSO- d_6): $\delta = 11.09$ (s, 1H), 8.28 (dd, J = 7.9, 1.0 Hz, 1H), 7.83– 7.71 (m, 2H), 7.50 (dt, J = 8.1, 4.1 Hz, 1H), 7.39–7.32 (m, 2H), 7.08-7.01 (m, 2H), 3.83 (s, 3H), 2.56-2.49 (m, 2H), 1.53-1.39 (m, 2H), 1.23 (tt, J = 7.3, 7.3 Hz, 2H), 0.77 (t, J = 7.3 Hz, 3H). ¹³C NMR (125 MHz, DMSO- d_6): δ = 161.0 (C_q), 159.1 (C_q), 137.8 (C_q), 137.2 (C_q), 132.2 (CH), 130.4 (CH), 127.1 (C_q), 126.9 (CH), 125.5 (CH), 125.5 (C_q), 123.4 (CH), 113.4 (CH), 112.0 (C_q), 55.1 (CH₃), 32.2 (CH₂), 26.2 (CH₂), 22.0 (CH₂), 13.5 (CH₃). IR (neat): 2955, 2932, 2869, 1634, 1604, 1245, 1023, 532 cm⁻¹. MS (EI) m/z (relative intensity): 307 ([M⁺], 50), 265 (20), 264 (100), 249 (12), 233 (18), 165 (6), 102 (6), 43 (15). HRMS (EI) m/z: calcd for $C_{20}H_{21}NO_2^+$ [M⁺] 307.1572, found 307.1580. The analytical data are in accordance with those reported in the literature.¹

4-n-Butyl-3-(4-fluorophenyl)isoquinolin-1(2H)-one (7ac). The representative procedure was followed using 1-fluoro-4-(hex-1-yn-1yl)benzene (6c) (132 mg, 0.75 mmol). Purification by column chromatography (n-pentane/EtOAc 3/1) yielded 7ac (102 mg, 69%) as a colorless solid (mp = 182-184 °C). ¹H NMR (300 MHz, $CDCl_3$: $\delta = 9.44$ (s, 1H), 8.39 (dt, J = 7.8, 1.0 Hz, 1H), 7.77–7.66 (m, 2H), 7.54–7.37 (m, 3H), 7.22–7.13 (m, 2H), 2.65–2.54 (m, 2H), 1.52 (tt, J = 8.0, 6.3 Hz, 2H), 1.28 (tt, J = 7.3, 7.3 Hz, 2H), 0.82 (t, J = 7.3 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃): δ = 163.2 (d, J_{C-F} = 249.2 Hz, C_q), 162.5 (C_q), 138.0 (C_q), 136.1 (C_q), 132.8 (CH), 131.6 (d, $J_{C-F} = 3.5 \text{ Hz}, C_q$), 131.2 (d, $J_{C-F} = 8.4 \text{ Hz}, C\text{H}$), 128.1 (CH), 126.5 (CH), 126.0 (C_q), 123.9 (CH), 116.0 (d, $J_{C-F} = 21.6 \text{ Hz}, C\text{H}$), 114.8 (C_{a}) , 32.9 (CH_{2}) , 27.1 (CH_{2}) , 22.9 (CH_{2}) , 13.9 (CH_{3}) . ¹⁹F NMR $(2\dot{83} \text{ MHz}, \text{CDCl}_3): \delta = -111.6 \text{ (tt, } J = 8.6, 5.3 \text{ Hz}\text{)}. \text{ IR (neat): 3163,}$ 2929, 2860, 1644, 1602, 1221, 840 cm⁻¹. MS (EI) m/z (relative intensity): 295 ([M⁺], 18), 253 (20), 252 (100), 234 (29), 196 (6), 77 (5). HRMS (EI) *m/z*: calcd for C₁₉H₁₈FNO⁺ [M⁺] 295.1372, found 295.1368.

4-(*Methoxymethyl*)-3-phenylisoquinolin-1(2H)-one (**7ad**). The representative procedure was followed using (3-methoxyprop-1-yn-1-yl)benzene (**6d**) (110 mg, 0.75 mmol). Purification by column chromatography (*n*-pentane/EtOAc 1/1 → 1/2) yielded **7ad** (97 mg, 73%) as an off-white solid (mp = 236–238 °C). ¹H NMR (300 MHz, CDCl₃): δ = 9.33 (s, 1H), 8.40 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.91–7.82 (m, 1H), 7.75 (ddd, *J* = 8.3, 7.0, 1.4 Hz, 1H), 7.61–7.45 (m, 6H), 4.42 (s, 2H), 3.40 (d, *J* = 1.1 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃): δ = 162.9 (Cq), 140.6 (Cq), 138.2 (Cq), 134.5 (Cq), 133.2 (CH), 129.9 (CH), 129.1 (CH), 129.0 (CH), 127.8 (CH), 126.8 (CH), 125.6 (Cq), 124.2 (CH), 110.4 (Cq), 68.4 (CH₂), 58.1 (CH₃). IR (neat): 3171, 2971, 2886, 2807, 1653, 1608, 1090, 697 cm⁻¹. MS (EI) *m/z* (relative intensity): 265 ([M⁺], 40), 235 (18), 234 (100), 216 (30), 178 (8), 102 (15), 77 (22). HRMS (EI) *m/z*: calcd for C₁₇H₁₅NO₂⁺ [M⁺] 265.1103, found 265.1102.

4-(4-Hydroxybutyl)-3-phenylisoquinolin-1(2H)-one (**7ae**). The representative procedure was followed using 6-phenylhex-5-yn-1-ol (**6e**) (131 mg, 0.75 mmol). Purification by column chromatography (*n*-pentane/EtOAc 1/3) yielded **7ae** (103 mg, 70%) as a colorless solid (mp = 113–115 °C). ¹H NMR (300 MHz, CDCl₃): δ = 8.95 (s, 1H), 8.41 (d, J = 7.7 Hz, 1H), 7.77–7.65 (m, 2H), 7.52–7.34 (m, 6H), 3.51 (t, J = 6.4 Hz, 2H), 2.70–2.57 (m, 2H), 1.77 (s, 1H), 1.70–1.41 (m, 4H). ¹³C NMR (125 MHz, CDCl₃): δ = 162.2 (C_q), 137.9

(C_q), 137.0 (C_q), 135.5 (C_q), 132.8 (CH), 129.3 (CH), 129.0 (CH), 128.9 (CH), 128.1 (CH), 126.4 (CH), 125.9 (C_q), 123.8 (CH), 114.1 (C_q), 62.5 (CH₂), 32.6 (CH₂), 27.1 (CH₂), 26.9 (CH₂). IR (neat): 3167, 2931, 2860, 1647, 1606, 1359, 1053, 764 cm⁻¹. MS (EI) *m/z* (relative intensity): 293 ([M⁺], 35), 235 (17), 234 (100), 216 (25), 204 (10), 178 (8), 77 (10). HRMS (EI) *m/z*: calcd for C₁₉H₁₉NO₂⁺ [M⁺] 293.1416, found 293.1423.

4-n-Butyl-3-(thiophen-2-yl)isoquinolin-1(2H)-one (7af). The representative procedure was followed using 2-(hex-1-yn-1-yl)thiophene (6f) (123 mg, 0.75 mmol). Purification by column chromatography (n-pentane/EtOAc 2/1) yielded 7af (63 mg, 44%) as an off-white solid (mp = 164–166 °C). ¹H NMR (300 MHz, DMSO- d_6): δ = 11.18 (s, 1H), 8.28 (dd, J = 7.8, 1.1 Hz, 1H), 7.83-7.77 (m, 2H), 7.75 (dd, J = 5.1, 1.2 Hz, 1H), 7.54 (ddd, J = 8.1, 5.1, 3.1 Hz, 1H), 7.31 (dd, J = 3.6, 1.2 Hz, 1H), 7.19 (dd, J = 5.1, 3.6 Hz, 1H), 2.72–2.60 (m, 2H), 1.52 (tt, J = 7.9, 6.2 Hz, 2H), 1.32 (tt, J = 7.3, 7.3 Hz, 2H), 0.84 (t, J = 7.3 Hz, 3H). ¹³C NMR (125 MHz, DMSO- d_6): $\delta = 160.9$ (C_a), 136.7 (C_q), 134.6 (C_q), 132.4 (CH), 130.6 (C_q), 129.0 (CH), 127.6 (CH), 126.9 (CH), 126.9 (CH), 126.2 (CH), 125.8 (C_q), 123.7 (CH), 114.4 (C_a), 32.5 (CH₂), 26.7 (CH₂), 22.1 (CH₂), 13.5 (CH₃). IR (neat): 3067, 2952, 2849, 1641, 1600, 1156, 764 cm⁻¹. MS (EI) m/z(relative intensity): 283 ([M⁺], 35), 241 (18), 240 (100), 222 (13), 184 (6), 128 (5), 77 (3). HRMS (EI) m/z: calcd for C₁₇H₁₇NOS⁺ [M⁺] 283.1031, found 283.1027.

4-n-Butyl-3-(cyclohex-1-en-1-yl)isoquinolin-1(2H)-one (7ag). The representative procedure was followed using 1-(hex-1-yn-1-yl)cyclohex-1-ene (6g) (122 mg, 0.75 mmol). Purification by column chromatography (CH₂Cl₂/Et₂O 5/1) yielded 7ag (69 mg, 49%) as a colorless solid (mp = 152-154 °C). ¹H NMR (300 MHz, CDCl₃): δ = 9.05 (s, 1H), 8.43 (d, J = 8.0 Hz, 1H), 7.74-7.62 (m, 2H), 7.45 (dt, J = 8.2, 4.1 Hz, 1H), 5.91 (dd, J = 3.8, 2.1 Hz, 1H), 2.66 (dd, J = 9.9, 6.0 Hz, 2H), 2.31-2.14 (m, 4H), 1.87-1.65 (m, 4H), 1.63-1.35 (m, 4H), 0.96 (t, I = 7.2 Hz, 3H). ¹³C NMR (125 MHz, CDCl₂): $\delta = 162.6$ (C_a), 139.2 (C_a), 138.3 (C_a), 133.3 (C_a), 132.3 (CH), 130.9 (CH), 127.8 (CH), 125.7 (CH), 125.5 (C_q), 123.6 (CH), 112.9 (C_q), 33.0 (CH₂), 28.9 (CH₂), 27.1 (CH₂), 25.2 (CH₂), 23.0 (CH₂), 22.7 (CH₂), 21.8 (CH₂), 13.9 (CH₃). IR (neat): 2958, 2922, 2856, 1650, 1622, 1460, 764 cm⁻¹. MS (EI) m/z (relative intensity): 281 ([M⁺], 40), 239 (20), 238 (100), 196 (23), 178 (11), 115 (9), 77 (6). HRMS (EI) m/ z: calcd for C₁₉H₂₃NO⁺ [M⁺] 281.1780, found 281.1770.

Ethyl (E)-3-(2-Carbamoylphenyl)acrylate (9aa). The representative procedure was followed using ethyl acrylate (8a) (75 mg, 0.75 mmol) at 60 °C. Purification by column chromatography (CH₂Cl₂/EtOAc 2/1) yielded 9aa (90 mg, 82%) as a colorless solid (mp = 161–163 °C). ¹H NMR (300 MHz, CDCl₃): δ = 8.10 (d, *J* = 16.0 Hz, 1H), 7.65–7.56 (m, 2H), 7.50–7.39 (m, 2H), 6.39 (d, *J* = 16.0 Hz, 1H), 6.12 (br s, 1H), 5.91 (br s, 1H), 4.25 (q, *J* = 7.1 Hz, 2H), 1.32 (t, *J* = 7.1 Hz, 3H). ¹³C NMR (125 MHz, CDCl₃): δ = 170.5 (C_q), 166.4 (C_q), 141.8 (CH), 135.8 (C_q), 133.1 (C_q), 130.8 (CH), 129.7 (CH), 127.7 (CH), 127.3 (CH), 121.1 (CH), 60.6 (CH₂), 14.3 (CH₃). IR (neat): 3378, 3180, 2980, 1716, 1637, 1315, 1182, 634 cm⁻¹. MS (EI) *m/z* (relative intensity): 219 ([M⁺], 5), 190 (14), 174 (15), 146 (100), 131 (25), 117 (12), 103 (14), 77 (11). HRMS (EI) *m/z*: calcd for C₁₂H₁₃NO₃⁺ [M⁺] 219.0895, found 219.0894. The analytical data are in accordance with those reported in the literature.¹⁷

Ethyl (*E*)-3-(2-*Carbamoyl-5-methylphenyl)acrylate* (**9ba**). The representative procedure was followed using 4-methyl-N-hydroxybenzamide (**1b**) (76 mg, 0.5 mmol) and ethyl acrylate (**8a**) (75 mg, 0.75 mmol) at 60 °C. Purification by column chromatography (CH₂Cl₂/ EtOAc 2/1) yielded **9ba** (93 mg, 80%) as a colorless solid (mp = 172–174 °C). ¹H NMR (300 MHz, acetone-*d*₆): δ = 8.22 (d, *J* = 16.0 Hz, 1H), 7.67 (s, 1H), 7.50 (d, *J* = 7.8 Hz, 1H), 7.32–7.21 (m, 2H), 6.81 (br s, 1H), 6.46 (d, *J* = 16.0 Hz, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 2.40 (s, 3H), 1.28 (t, *J* = 7.1 Hz, 3H). ¹³C NMR (125 MHz, acetone-*d*₆): δ = 170.8 (C_q), 166.9 (C_q), 143.5 (CH), 141.0 (C_q), 135.6 (C_q), 133.7 (C_q), 131.1 (CH), 128.6 (CH), 128.2 (CH), 120.3 (CH), 60.7 (CH₂), 21.1 (CH₃), 14.6 (CH₃). IR (neat): 3375, 3198, 1690, 1656, 1294, 1040, 643 cm⁻¹. MS (EI) *m*/*z* (relative intensity): 233 ([M⁺], 3), 204 (9), 188 (10), 160 (100), 145 (22), 115 (28), 77 (5). HRMS (EI) *m*/*z*: calcd for C₁₃H₁₅NO₃⁺ [M⁺] 233.1052, found 233.1058.

Ethyl (E)-3-(2-Carbamoyl-5-fluorophenyl)acrylate (9da). The representative procedure was followed using 4-fluoro-N-hydroxybenzamide (1d) (78 mg, 0.5 mmol) and ethyl acrylate (8a) (75 mg, 0.75 mmol) at 60 °C. Purification by column chromatography (CH₂Cl₂/ EtOAc 2/1) yielded 9da (80 mg, 67%) as an off-white solid (mp = 162–164 °C). ¹H NMR (300 MHz, acetone- d_6): $\delta = 8.17$ (dd, J =16.0, 1.7 Hz, 1H), 7.70-7.59 (m, 2H), 7.38 (br s, 1H), 7.23 (td, J = 8.4, 2.6 Hz, 1H), 6.93 (br s, 1H), 6.56 (d, J = 16.0 Hz, 1H), 4.22 (q, J = 7.1 Hz, 2H), 1.29 (t, J = 7.1 Hz, 3H). ¹³C NMR (125 MHz, acetone d_6): δ = 169.9 (C_q), 166.6 (C_q), 164.1 (d, J_{C-F} = 247.4 Hz), 141.9 (d, $J_{C-F} = 2.2 \text{ Hz}$, 136.5 (d, $J_{C-F} = 8.2 \text{ Hz}$), 134.9 (d, $J_{C-F} = 3.3 \text{ Hz}$), 131.0 (d, $J_{C-F} = 8.8 \text{ Hz}$), 122.0 (CH), 117.1 (d, $J_{C-F} = 22.0 \text{ Hz}$), 114.2 (d, $J_{C-F} = 22.9 \text{ Hz}$), 60.9 (CH₂), 14.6 (CH₃). ¹⁹F NMR (283 MHz, acetone- d_6): $\delta = -107.1$ (dddd, J = 9.7, 7.7, 5.7, 1.7 Hz). IR (neat): 3389, 3203, 3004, 1688, 1650, 1388, 1215, 978 cm⁻¹. MS (EI) m/z(relative intensity): 237 ([M⁺], 1), 208 (5), 192 (6), 164 (100), 149 (15), 135 (9), 120 (9). HRMS (EI) m/z: calcd for $C_{12}H_{13}FNO_3^+$ [M + H⁺] 238.0879, found 238.0876.

n-Butyl (E)-3-(2-Carbamoylphenyl)acrylate (9ab). The representative procedure was followed using butyl acrylate (8b) (96 mg, 0.75 mmol) at 60 °C. Purification by column chromatography (CH₂Cl₂/ EtOAc 2/1) yielded 9ab (90 mg, 73%) as a colorless solid (mp = 140–141 °C). ¹H NMR (300 MHz, CDCl₃): δ = 8.10 (d, J = 16.0 Hz, 1H), 7.68-7.54 (m, 2H), 7.52-7.37 (m, 2H), 6.40 (d, J = 16.0 Hz, 1H), 6.03 (br s, 1H), 5.87 (br s, 1H), 4.19 (t, J = 6.7 Hz, 2H), 1.73-1.63 (m, 2H), 1.50–1.35 (m, 2H), 0.95 (t, J = 7.3 Hz, 3H). ¹³C NMR (125 MHz, CDCl₃): δ = 170.4 (C_q), 166.5 (C_q), 141.8 (CH), 135.7 (C_q), 133.1 (C_q), 130.8 (CH), 129.7 (CH), 127.8 (CH), 127.3 (CH), 121.2 (CH), 64.6 (CH₂), 30.7 (CH₂), 19.2 (CH₂), 13.7 (CH₃). IR (neat): 3356, 3167, 2952, 1707, 1626, 1276, 974, 766 cm⁻¹. MS (EI) *m*/*z* (relative intensity): 247 ([M⁺], 6), 190 (15), 174 (12), 146 (100), 131 (25), 117 (11), 77 (8). HRMS (EI) m/z: calcd for C₁₄H₁₈NO₃⁺ [M + H⁺] 248.1287, found 248.1282. The analytical data are in accordance with those reported in the literature.⁸

Benzyl (E)-3-(2-Carbamoylphenyl)acrylate (9ac). The representative procedure was followed using benzyl acrylate (8c) (122 mg, 0.75 mmol) at 60 °C. Purification by column chromatography (CH₂Cl₂/EtOAc 2/1) yielded 9ac (115 mg, 82%) as a colorless solid (mp = 149–151 °C). ¹H NMR (300 MHz, acetone- d_6): δ = 8.26 (d, *J* = 16.1 Hz, 1H), 7.90–7.83 (m, 1H), 7.59 (dd, *J* = 7.1, 1.9 Hz, 1H), 7.55–7.28 (m, 8H), 6.91 (br s, 1H), 6.56 (d, *J* = 16.1 Hz, 1H), 5.25 (s, 2H). ¹³C NMR (125 MHz, acetone- d_6): δ = 170.8 (C_q), 166.8 (C_q), 143.8 (CH), 138.6 (C_q), 137.5 (C_q), 133.5 (C_q), 130.8 (CH), 130.6 (CH), 129.3 (CH), 129.0 (CH), 128.8 (CH), 128.5 (CH), 127.7 (CH), 120.2 (CH), 66.5 (CH₂). IR (neat): 3377, 3181, 1709, 1639, 1276, 1162, 765 cm⁻¹. MS (EI) *m*/*z* (relative intensity): 281 ([M⁺], 7), 237 (3), 190 (19), 146 (100), 131 (30), 91 (72), 77 (17). HRMS (EI) *m*/*z*: calcd for C₁₇H₁₅NO₃⁺ [M⁺] 281.1052, found 281.1051. The analytical data are in accordance with those reported in the literature.¹⁷

(É)-2-(3-Oxobut-1-en-1-yl)benzamide (9ad). The representative procedure was followed using but-3-en-2-one (8d) (105 mg, 1.50 mmol) at 60 °C. Purification by column chromatography (CH₂Cl₂/ acetone 2/1) yielded 9ad (49 mg, 52%) as an off-white solid (mp = 148–150 °C). ¹H NMR (300 MHz, acetone- d_6): δ = 8.10 (d, J = 16.3 Hz, 1H), 7.83 (dd, J = 7.4, 1.7 Hz, 1H), 7.62 (dd, J = 7.3, 1.7 Hz, 1H), 7.54–7.43 (m, 2H), 7.36 (br s, 1H), 6.91 (br s, 1H), 6.70 (d, J = 16.3 Hz, 1H), 2.31 (s, 3H). ¹³C NMR (125 MHz, acetone- d_6): δ = 197.9 (C_q), 170.8 (C_q), 141.7 (CH), 138.5 (C_q), 134.0 (C_q), 130.9 (CH), 130.5 (CH), 129.4 (CH), 128.7 (CH), 127.6 (CH), 27.4 (CH₃). IR (neat): 3354, 3173, 1644, 1616, 1247, 971, 625 cm⁻¹. MS (EI) *m*/*z* (relative intensity): 189 ([M⁺], 5), 174 (3), 146 (100), 132 (24), 118 (12), 103 (16), 77 (15). HRMS (EI) *m*/*z*: calcd for C₁₁H₁₁NO₂⁺ [M⁺] 189.0790, found 189.0796.

Intermolecular Competition Experiments between Alkynes 2 (Scheme 6). The representative procedure was followed using 1,2bis(4-fluorophenyl)ethyne (2c) (214 mg, 1.0 mmol) and 1,2-bis(4methoxyphenyl)ethyne (2b) (238 mg, 1.0 mmol). Purification by column chromatography (*n*-pentane/EtOAc $2/1 \rightarrow 1/1$) yielded 3ac (86 mg, 52%) and 3ab (36 mg, 20%).

The Journal of Organic Chemistry

Relative Reactivities of *N*-Methoxybenzamides 10 and Hydroxamic Acids 1 (Scheme 8a). The representative procedure was followed using 4-methyl-*N*-methoxybenzamide (10b) (165 mg, 1.0 mmol), 4-ethyl-*N*-hydroxybenzamide (1m) (165 mg, 1.0 mmol), and 1,2-diphenylethyne (2a) (89 mg, 0.5 mmol). Purification by column chromatography (CH₂Cl₂/Et₂O 3/1) yielded a mixture of 3ba and 3ma (19 mg) in which the ratio of 3ba to 3ma was determined to be 10/90 by ¹H NMR spectroscopy.

Relative Reactivities of *N*-Methoxybenzamides 10 and Hydroxamic Acids 1 (Scheme 8b). The representative procedure was followed using 4-methyl-*N*-hydroxybenzamide (1b) (151 mg, 1.0 mmol), 4-ethyl-*N*-methoxybenzamide (10m) (179 mg, 1.0 mmol), and 1,2-diphenylethyne (2a) (89 mg, 0.5 mmol). Purification by column chromatography (CH₂Cl₂/Et₂O 3/1) yielded a mixture of 3ba and 3ma (41 mg) in which the ratio of 3ba to 3ma was determined to be 61/39 by ¹H NMR spectroscopy.

6-Ethyl-3,4-diphenylisoquinolin 1(2H)-one (**3ma**). Off-white solid (mp = 256–258 °C). ¹H NMR (300 MHz, CDCl₃): δ = 8.94 (s, 1H), 8.41 (d, J = 8.2 Hz, 1H), 7.48–7.06 (m, 12H), 2.66 (q, J = 7.6 Hz, 2H), 1.19 (t, J = 7.6 Hz, 3H). ¹³C NMR (125 MHz, CDCl₃): δ = 162.4 (C_q), 149.4 (C_q), 138.7 (C_q), 136.9 (C_q), 135.7 (C_q), 135.2 (C_q), 131.7 (CH), 129.0 (CH), 128.5 (CH), 128.3 (CH), 128.2 (CH), 127.5 (CH), 127.1 (CH), 127.0 (CH), 124.2 (CH), 123.1 (C_q), 117.1 (C_q), 29.4 (CH₂), 15.4 (CH₃). IR (neat): 3118, 3022, 2885, 1640, 1611, 1442, 1151, 695 cm⁻¹. MS (EI) *m*/*z* (relative intensity): 325 ([M⁺], 100), 324 (45), 295 (12), 178 (10), 104 (8), 77 (13). HRMS (EI) *m*/*z*: calcd for C₂₃H₁₉NO⁺ [M⁺] 325.1467, found 325.1465.

C–H/N–OH Functionalizations with Isotopically Labeled Solvent (Scheme 9a). A mixture of *N*-hydroxybenzamide (1a) (69 mg, 0.50 mmol), $[RuCl_2(p-cymene)]_2$ (15.3 mg, 5.0 mol %), and potassium 3-(trifluoromethyl)benzoate (34 mg, 30.0 mol %) in D₂O (2 mL) was stirred at 100 °C under an atmosphere of N₂ for 18 h. D₂O was removed in vacuo. Purification by column chromatography on silica gel (CH₂Cl₂/acetone 2/1) recovered [D_n]-1a (62 mg, 87%) with approximately 8% H incorporation at the *ortho* positions as estimated by ¹H NMR spectroscopy.

C–H/N–OH Functionalizations with Isotopically Labeled Substrate $[D_5]$ -1a (Scheme 9b). The representative procedure was followed using $[D_5]$ -1a (71 mg, 0.50 mmol). Purification by column chromatography (*n*-pentane/EtOAc 2/1) yielded $[D_4]$ -3aa (101 mg, 67%) with approximately 15% deuterium incorporation at the *ortho* position as estimated by ¹H NMR spectroscopy.

3,4-Diphenylisoquinolin-1(2H)-one-5,6,7,8-d₄ ([D₄]-**3aa**). Colorless solid (mp = 254–256 °C). ¹H NMR (300 MHz, DMSO-d₆): δ = 11.53 (s, 1H), 7.35–7.07 (m, 10H). ¹³C NMR (125 MHz, DMSO-d₆): δ = 161.4 (C_q), 138.3 (C_q), 137.8 (C_q), 135.6 (C_q), 134.4 (C_q), 131.7 (t, *J* = 22.7 Hz, CD), 131.5 (CH), 129.6 (CH), 128.0 (CH), 127.9 (CH), 127.4 (CH), 126.8 (CH), 126.5 (t, *J* = 22.7 Hz, CD), 124.8 (t, *J* = 22.7 Hz, CD), 124.7 (C_q), 124.3 (t, *J* = 22.7 Hz, CD), 115.2 (C_q). IR (neat): 3149, 3017, 2886, 1642, 1327, 902, 697 cm⁻¹. MS (EI) *m/z* (relative intensity): 301 ([M⁺], 100), 300 (80), 282 (14), 271 (9), 169 (12), 104 (5), 77 (11). HRMS (EI) *m/z*: calcd for C₂₁H₁₁D₄NO⁺ [M⁺] 301.1405, found 301.1408. The analytical data are in accordance with those reported in the literature.¹⁵

Kinetic Isotope Effect of the C–H/N–OH Functionalizations (Scheme 10). The representative procedure was followed using *N*-hydroxybenzamide (1a) (137 mg, 1.0 mmol), *N*-hydroxybenzamide- d_s ([D_s]-1a) (142 mg, 1.0 mmol), and 1,2-diphenylethyne (2a) (89 mg, 0.5 mmol). Purification by column chromatography (*n*-pentane/EtOAc 2/1) yielded a mixture of [D_n]-3aa (15 mg). The kinetic isotope effect of this reaction was determined to be 2.6 as estimated by ¹H NMR spectroscopy.

ASSOCIATED CONTENT

S Supporting Information

Copies of ¹H and ¹³C NMR spectra for all products. 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.

ACKNOWLEDGMENTS

Support by the Chinese Scholarship Council (fellowship to F.Y.), the CaSuS Ph.D. Program, and the European Research Council under the European Community's Seventh Framework Program (FP7 2007–2013)/ERC Grant Agreement 307535 is gratefully acknowledged.

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