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Copper-Catalyzed C-N Bond Formation / Rearrangement Sequence: Synthesis of 4*H*-3,1-Benzoxazin-4-ones

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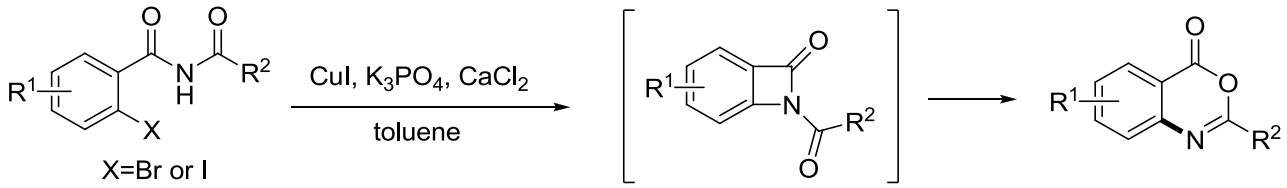


ABSTRACT: A facile and efficient copper-catalyzed method for the synthesis of 4*H*-3,1-benzoxazin-4-one derivatives has been developed. This procedure is based on a tandem intramolecular C-N coupling / rearrangement process. This method would provide a new and useful strategy for construction of N-heterocycles.

INTRODUCTION

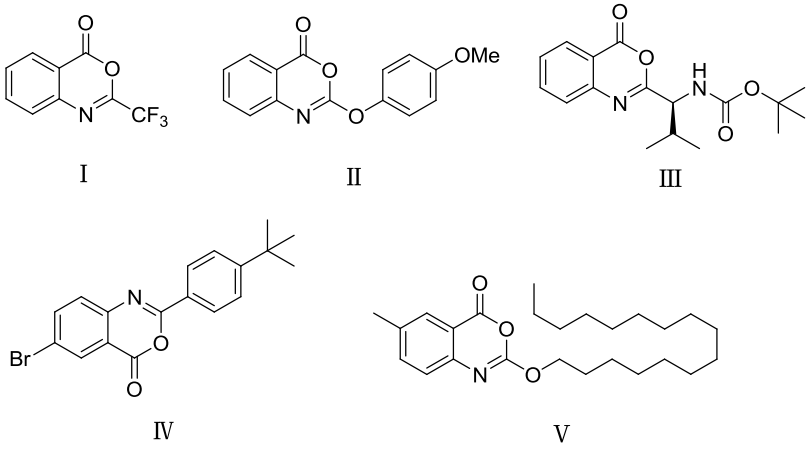
4*H*-3,1-Benzoxazin-4-ones are a class of fused heterocycles that are of interest to organic chemists owing to their biological activities.[1-8] For instance, some of 2-substituted 4*H*-3,1-benzoxazin-4-ones act as chymotrypsin inactivators (Ⅰ),[1] HSV-1 protease inhibitors (Ⅱ),[2] and inhibitors of human leukocyte elastase (Ⅲ),[3] cathepsin G,[4] C1r serine protease[5] and

human chymase.[6] Besides, compound Ⅳ, shown in Figure 1, has the ability to lower the level of plasma cholesterol and triglyceride.[7] Moreover, Cetilistat (Ⅴ), a novel lipase inhibitor, was reported to be used as an anti-obesity remedy.[8] In addition, 2-substituted 4*H*-3,1-benzoxazin-4-ones are useful synthetic intermediates for the synthesis of pharmaceutically active compounds.[9] Therefore, it is not surprising that there is an ever increasing number of synthetic approaches toward the preparation of 4*H*-3,1-benzoxazin-4-one derivatives, especially 4*H*-3,1-benzoxazin-4-ones substituted in the 2-position.[10-17] Among these methodologies, cyclization of anthranilic acid or N-acylanthranilic acid, and ring transformation of isatoic anhydride are most popular.[11] Other notable methods include oxidation of 2-aryl-3*H*-indol-3-ones, 2-phenyl-3-oxo-3*H*-indole 1-oxide, or 2-aryl-4*H*-benzo[*d*][1,3]oxazines,[12] thermolysis of benzo[*d*][1,2,3]triazin-4(3*H*)-ones or isatoic anhydride,[13] electrochemical cyclization of *o*-trichloroacetylanilides,[14] cyclization of 2-ureidobenzoic acids, alkyl 2-ureidobenzoates, or 2-ureidobenzamides,[15] palladium-catalyzed carbonylation with CO,[16] and palladium-catalyzed cyclization of azidoalkynes.[17] Some of these methods still suffer from either harsh reaction conditions or hazardous materials. Consequently, we are making an effort to investigate a further efficient method for the synthesis of this class of N-heterocycles.

Very recently, our group reported a novel copper(I)-catalyzed reaction of 1-(2-halophenyl)-1,3-diones,[18] which involves a rearrangement process as a key step. We hypothesized that the similar strategy might be applicable to prepare benzoxazinones from N-acyl-2-halobenzamides. In a continuation to our interest in copper-catalyzed tandem cyclization reactions, herein, we would like to report a new strategy for the synthesis of

2-substituted benzoxazinones *via* a copper-catalyzed reaction of N-acyl-2-halobenzamides.

Figure 1. Structures of Some Bioactive 2-Substituted 4*H*-3,1-Benzoxazin-4-ones.

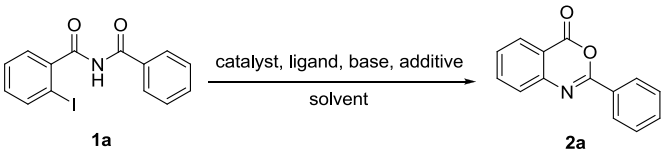


RESULTS AND DISCUSSION

We initially investigated the reaction conditions by employing N-phenyl-2-iodobenzamide (**1a**) as the model substrate (Table 1). Considering that 2-picolinic acid was used as the best ligand of CuI in our previous study,[18] we tested the reaction in the presence of CuI (10 mol %), 2-picolinic acid (20 mol %), and K_2CO_3 (2 equiv) in anhydrous toluene (5 mL) at 120 °C, and a 42% yield of the desired product was obtained after 6 h (Table 1, entry 1). Then, several ligands and a ligand-free condition were tested in this reaction, and a comparable yield was obtained in the absence of ligand (Table 1, entries 2-4). Base screening tests revealed that K_3PO_4, in comparison with other bases, produced **2a** by the yield increased to 60% (Table 1, entries 5-9). Analytical results showed that benzoic acid was a major by-product. Considering that adventitious moisture might result in the generation of benzoic acid in the reaction, we

tested several drying agents, and a 81% yield was obtained in the presence of $CaCl_2$ (Table 1, entries 10-13). Other solvents, such as o-xylene, 1,4-dioxane, and THF, proved to be less effective (Table 1, entries 14-16). A comparison of catalysts showed that CuI was superior to the others (Table 1, entries 17-19). Based on these considerations, our products could be easily obtained from **1a** in the presence of CuI (10 mol %), K_3PO_4 (2 equiv), and $CaCl_2$ (2 equiv) in anhydrous toluene (5 mL) within a sealed tube under nitrogen at 120 °C for 6h.

Table 1: Optimizations of Conditions for Benzoxazinone Synthesis [a]



1a **2a**

entry	catalyst	ligand [b]	base	solvent [c]	additive	yield(%) [d]
1	CuI	L1	K_2CO_3	toluene	-	42
2	CuI	L2	K_2CO_3	toluene	-	36
3	CuI	L3	K_2CO_3	toluene	-	38
4	CuI	-	K_2CO_3	toluene	-	42
5	CuI	-	Cs_2CO_3	toluene	-	35
6	CuI	-	NaO*t*Bu	toluene	-	0
7	CuI	-	NaOAc	toluene	-	0
8	CuI	-	KF	toluene	-	25
9	CuI	-	K_3PO_4	toluene	-	60
10	CuI	-	K_3PO_4	toluene	MS 4 Å	63

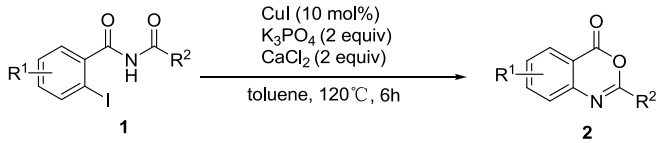
11	CuI	-	K_3PO_4	toluene	$MgSO_4$	69
12	CuI	-	K_3PO_4	toluene	CaO	65
13	CuI	-	K_3PO_4	toluene	$CaCl_2$	81
14	CuI	-	K_3PO_4	o-xylene	$CaCl_2$	75
15	CuI	-	K_3PO_4	1,4-dioxane	$CaCl_2$	65
16	CuI	-	K_3PO_4	THF	$CaCl_2$	58
17	CuBr	-	K_3PO_4	toluene	$CaCl_2$	73
18	CuCl	-	K_3PO_4	toluene	$CaCl_2$	71
19	$Cu(OAc)_2$	-	K_3PO_4	toluene	$CaCl_2$	70

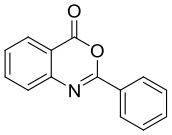
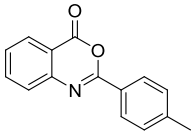
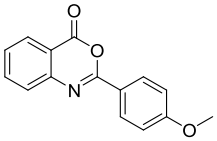
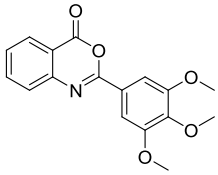
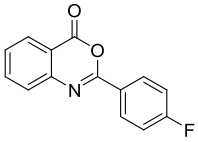
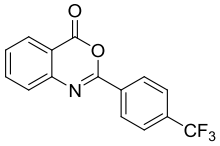
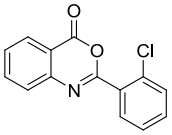
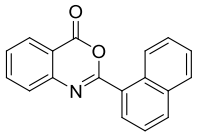
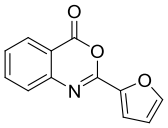
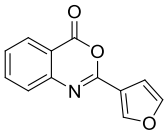
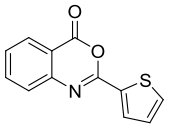
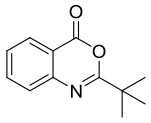
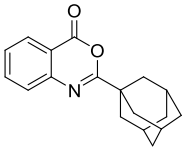
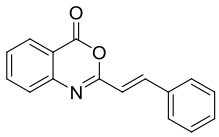
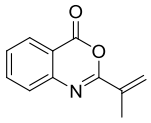
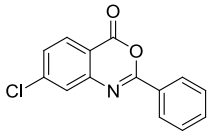
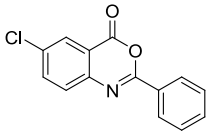
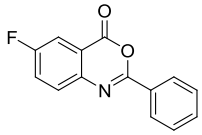
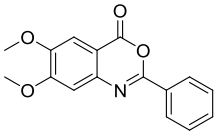
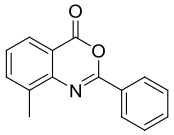
[a]All reactions were run with **1a** (0.5 mmol) , catalyst (0.05 mmol) , ligand (0.1 mmol) , base (1.0 mmol) , additive (1.0 mmol) and solvent (5 mL) under nitrogen in a sealed tube for 6h. [b]L1: 2-picolinic acid, L2: (±)-trans-1,2-diaminocyclohexane, L3: 1,10-phenanthroline. [c]The reaction temperature: 1,4-dioxane and toluene were at 120 °C, o-xylene was at 150 °C, and THF was at 70 °C. [d]Isolated yield.

To evaluate the scope and generality of the methodology, different substrates with varying substituents were synthesized and investigated under the standard reaction conditions, and the results are summarized in Tables 2 and 3. Substrates bearing both electron-rich and electron-poor aromatic groups on R^2 generated the desired products in moderate to good yields (**2b**-**2h**). Similar results were obtained when R^2 was furanyl (**2i** and **2j**), and a lower yield was observed when it was thiophen-2-yl (**2k**). The reaction proceeded smoothly to give the

desired products in moderate yields, as for a variety of substrates with alkyl and alkenyl substituents on R^2 (**2l**-**2o**). It was also of note that electronic properties of R^1 had no significant effect on this reaction, and desired products were obtained in good yields (**2p**-**2t**).

Table 2: copper-catalyzed reaction of substituted N-acyl-2-iodobenzamide [a]

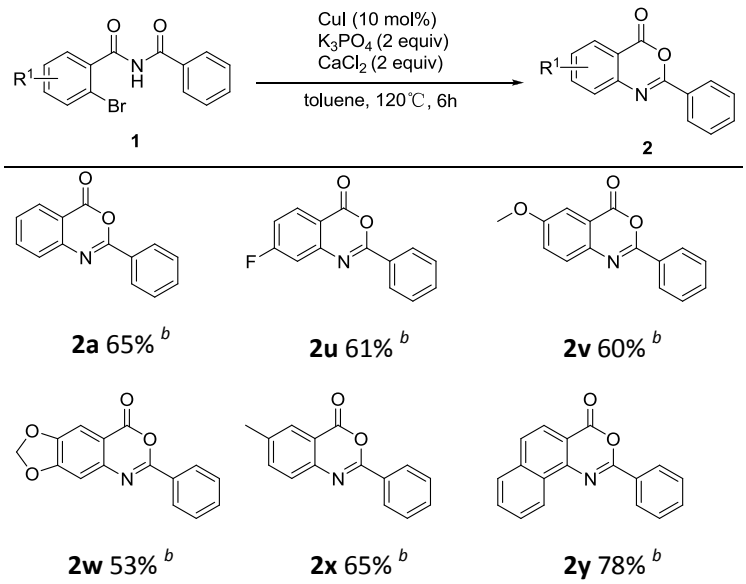


 **2a** 81% [b]	 **2b** 90% [b]	 **2c** 83% [b]	 **2d** 84% [b]
 **2e** 77% [b]	 **2f** 60% [b]	 **2g** 53% [b]	 **2h** 70% [b]
 **2i** 64% [b]	 **2j** 59% [b]	 **2k** 36% [b c]	 **2l** 42% [b]
 **2m** 61% [b]	 **2n** 67% [b]	 **2o** 53% [b]	 **2p** 75% [b]
 **2q** 87% [b]	 **2r** 84% [b]	 **2s** 79% [b d]	 **2t** 85% [b]

[a]The reactions were performed in a sealed tube with **1** (0.5 mmol), CuI (0.05 mmol), K_3PO_4 (1.0 mmol), and $CaCl_2$ (1.0 mmol) in toluene (5 mL) at 120 °C under nitrogen for 6 h. [b]Isolated yield. [c]80% conversion, 140 °C, 48 h. [d]140 °C, 20 h.

As illustrated in Table 3, when the substrate was changed from iodoarene to bromoarene, a slightly lower yield was observed (**2a**). Various substituted N-benzoyl-2-bromobenzamides were also examined, and the target products were produced in moderate yields (**2u**-**2y**). We found that **2y** was generated in a good yield when 1-(1-bromonaphthalen-2-yl) was the substituent on substrate **1y** probably owing to the weak aromaticity of the naphthalene ring.

Table 3: copper-catalyzed reaction of substituted N-benzoyl-2-bromobenzamide [a]

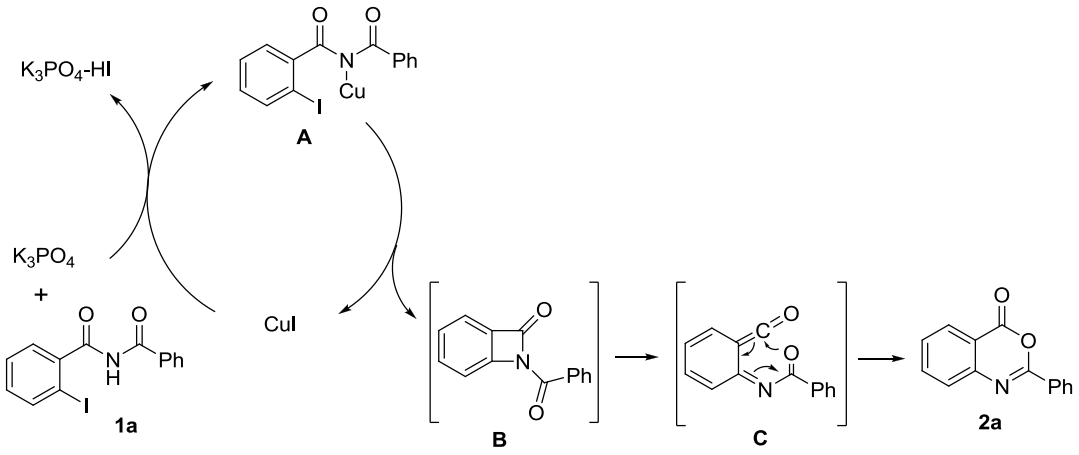


[a]The reactions were performed in a sealed tube with **1** (0.5 mmol), CuI (0.05 mmol), K_3PO_4 (1.0

mmol), and $CaCl_2$ (1.0 mmol) in toluene (5 mL) at 120 °C under nitrogen for 6 h. [b]Isolated yield.

On the basis of the above experimental results and related reports,[13c,17] a plausible mechanism for this reaction was depicted in Scheme 1. Copper iodide would activate N-benzoyl-2-iodobenzamide (**1a**) to generate a copper(I) complex **A**, which would then produce N-benzoyl benzazetone (**B**) *via* the C−N coupling process. Immediately, release of ring strain led to the ketene compound **C** *via* the C−N bond cleavage. Ring closure of **C** would then yield the target product **2a**.

Scheme 1. Postulated Reaction Mechanism.



CONCLUSION

In summary, we have developed an efficient and rapid method for the synthesis of 4*H*-3,1-benzoxazin-4-one derivatives from easily available N-acyl-2-halobenzamides. Key step

of this transformation is the C-N bond formation / rearrangement sequence. Considering mild reaction conditions and a wide functional-group tolerance, this protocol is expected to be beneficial to organic synthesis.

EXPERIMENTAL SECTION

General Remarks. Chemicals and reagents were purchased from commercial suppliers and used without special instructions. All anhydrous solvents used in the reactions were dried and freshly distilled. Thin-layer chromatography (TLC) was performed using silica HSGF254 plates. Melting points were determined without correction on a digital melting-point apparatus. ^{1}H and ^{13}C NMR spectra were obtained from a solution in $CDCl_3$ with tetramethylsilane (TMS) as internal standard using a 400/101 MHz ($^{1}H/^{13}C$) or 300/75 MHz ($^{1}H/^{13}C$) spectrometer, δ in parts per million (ppm), and J in hertz (Hz). Infrared (IR) spectra were recorded in KBr tablets, and wavenumbers in cm^{-1}. HRMS analyses were carried out on an electrospray ionization (ESI) apparatus using time-of-flight (TOF) mass spectrometry.

General procedure for the synthesis of compounds 2a-2y. A sealed tube was charged with a magnetic stir bar, substrate **1** (0.5 mmol),[19] CuI (0.05 mmol, 10 mg), K_3PO_4 (1.0 mmol, 212 mg), $CaCl_2$ (1.0 mmol, 111 mg) and anhydrous toluene (5 mL). The tube was purged with nitrogen gas, and stirred at 120 °C for the indicated time. After completion of reaction, the mixture was filtered through a short plug of celite, and washed with EtOAc (2×3mL). The combined filtrates were concentrated on a rotary evaporator and purified on a silica gel column using petroleum ether/EtOAc as eluent to give the pure target product.

Characterization Data of the Isolated Compounds. *2-Phenyl-4H-3,1-benzoxazin-4-one*

*(**2a**).*[17] From substrate N-benzoyl-2-iodobenzamide, yield 78% (87 mg); from substrate N-benzoyl-2-bromobenzamide, yield 65% (73 mg). White solid, m.p. 108 – 110 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 – 8.28 (m, 2H), 8.22 (d, *J* = 7.7 Hz, 1H), 7.81 (t, *J* = 7.4 Hz, 1H), 7.67 (d, *J* = 7.9 Hz, 1H), 7.58 – 7.55 (m, 1H), 7.52-7.48 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.7, 157.2, 147.1, 136.7, 132.7, 130.3, 128.8, 128.7, 128.4, 128.4, 127.3, 117.1. IR (KBr): v = 1764, 1617, 1472, 1316, 1259, 1062, 1009, 762, 682, 629 cm^{-1}. LRMS (ESI): m/z calcd for $C_{14}H_{10}NO_2$ $[M + H]^+$, 224.1; found, 224.1.

*2-p-Tolyl-4H-3,1-benzoxazin-4-one (**2b**)*.[17] Yield 90% (107 mg). White solid, m.p. 138 – 140 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 – 8.18 (m, 3H), 7.81 (t, *J* = 7.3 Hz, 1H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.49 (t, *J* = 7.4 Hz, 1H), 7.30 (d, *J* = 7.7 Hz, 2H), 2.43(s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.8, 157.4, 147.2, 143.5, 136.6, 129.6, 128.7, 128.4, 128.1, 127.5, 127.2, 117.0, 21.8. LRMS (ESI): m/z calcd for $C_{15}H_{12}NO_2$ $[M + H]^+$, 238.1; found, 238.1.

*2-(4-Methoxyphenyl)-4H-3,1-benzoxazin-4-one (**2c**).*[17] Yield 83% (105 mg). White solid, m.p. 144 – 145 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 (t, *J* = 9.0 Hz, 3H), 7.76 (t, *J* = 7.7 Hz, 1H), 7.60 (d, *J* = 8.0 Hz, 1H), 7.44 (t, *J* = 7.5 Hz, 1H), 6.95 (d, *J* = 8.7 Hz, 2H), 3.86 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.3, 159.8, 157.1, 147.4, 136.5, 130.3, 128.6, 127.7, 127.0, 122.5, 116.7, 114.2, 55.5. LRMS (ESI): m/z calcd for $C_{15}H_{12}NO_3$ $[M + H]^+$, 254.1; found, 245.1.

*2-(3,4,5-Trimethoxyphenyl)-4H-3,1-benzoxazin-4-one (**2d**).*[11d] Yield 84% (132 mg). White solid, m.p. 179 – 181 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, *J* = 7.7 Hz, 1H), 7.80 (t, *J* = 7.4 Hz, 1H), 7.65 (d, *J* = 7.9 Hz, 1H), 7.55 – 7.46 (m, 3H), 3.98 (s, 6H), 3.95 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.6, 156.7, 153.2, 147.0, 142.0, 136.6, 128.6, 128.1, 127.0, 125.2, 116.7, 105.4, 61.0, 56.4. LRMS (ESI): m/z calcd for $C_{17}H_{16}NO_5$ $[M + H]^+$, 314.1; found, 314.1.

*2-(4-Fluorophenyl)-4H-3,1-benzoxazin-4-one (**2e**).*[12d] Yield 77% (93 mg). White solid, m.p. 176 – 177 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (dd, *J* = 8.1, 5.7 Hz, 2H), 8.22 (d, *J* = 7.7 Hz, 1H), 7.82 (t, *J* = 7.5 Hz, 1H), 7.66 (d, *J* = 8.1 Hz, 1H), 7.51 (t, *J* = 7.5 Hz, 1H), 7.18 (t, *J* = 8.5 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.3, 163.9, 159.4, 156.2, 146.9, 136.6, 130.8, 130.7, 128.6, 128.3, 127.2, 126.4, 126.4, 116.8, 116.2, 115.9. LRMS (ESI): m/z calcd for $C_{14}H_9FNO_2$ $[M + H]^+$, 242.1; found, 242.1.

*2-(4-(Trifluoromethyl)phenyl)-4H-3,1-benzoxazin-4-one (**2f**).*[16h] Yield 60% (87 mg). White solid, m.p. 127 – 128 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (s, 1H), 8.48 (d, *J* = 7.7 Hz, 1H), 8.24 (d, *J* =7.7 Hz, 1H), 7.87 – 7.81 (m, 2H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.65 (t, *J* = 7.7 Hz, 1H), 7.55 (t, *J* = 7.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 155.7, 147.4, 146.6, 136.9, 131.7, 131.4, 131.3, 131.2, 129.5, 129.1, 129.1, 128.9, 128.8, 127.5, 125.3, 125.3, 122.0, 120.0, 117.1, 112.8, 112.4. LRMS (ESI): m/z calcd for $C_{15}H_9F_3NO_2$ $[M + H]^+$, 292.1; found, 292.1.

*2-(2-Chlorophenyl)-4H-3,1-benzoxazin-4-one (**2g**).*[11c] Yield 53% (68 mg). White solid, m.p. 135 – 137 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, *J* = 7.7 Hz, 1H), 7.90 (d, *J* = 7.5 Hz, 1H), 7.85 (t, *J* = 7.6 Hz, 1H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.57 (t, *J* = 7.5 Hz, 1H), 7.52(d, *J* = 7.8 Hz, 1H), 7.46 (t, *J* = 7.4 Hz, 1H), 7.40 (t, *J* = 7.3 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.2, 156.5, 146.4, 136.7, 133.4, 132.4, 131.5, 131.1, 130.3, 129.0, 128.6, 127.4, 127.0, 117.0. LRMS (ESI): m/z calcd for $C_{14}H_9ClNO_2$ $[M + H]^+$, 258.0; found, 258.0.

*2-(Naphthalen-1-yl)-4H-3,1-benzoxazin-4-one (**2h**).*[11e] Yield 70% (96 mg). Yellow solid, m.p. 118 – 120 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.14 (d, *J* = 8.6 Hz, 1H), 8.30 – 8.24 (m, 2H), 8.01(d, *J* = 8.1 Hz, 1H), 7.89 (d, *J* = 8.0 Hz, 1H), 7.82 (t, *J* = 7.5 Hz, 1H), 7.75 (d, *J* = 7.9 Hz, 1H), 7.63 (t, *J* = 7.6 Hz, 1H), 7.56 – 7.50 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.7, 157.6,

146.8, 136.6, 134.1, 133.3, 130.8, 130.1, 128.9, 128.6, 128.5, 127.9, 127.4, 126.9, 126.4, 125.8, 124.8, 117.0. LRMS (ESI): m/z calcd for $C_{18}H_{12}NO_2$ $[M + H]^+$, 274.1; found, 274.1.

*2-(Furan-2-yl)-4H-3,1-benzoxazin-4-one (**2i**).*[10a] Yield 64% (68 mg). Yellow solid, m.p. 95 – 96 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, *J* = 7.6 Hz, 1H), 7.80 (t, *J* = 7.4 Hz, 1H), 7.72 – 7.67 (m, 2H), 7.49 (t, *J* = 7.3 Hz, 1H), 7.37 – 7.33 (m, 1H), 6.61 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.6, 149.8, 147.1, 146.7, 144.4, 136.8, 128.8, 128.3, 127.2, 117.2, 116.9, 112.6. LRMS (ESI): m/z calcd for $C_{12}H_8NO_3$ $[M + H]^+$, 214.0; found, 214.0.

*2-(Furan-3-yl)-4H-3,1-benzoxazin-4-one (**2j**).* Yield 59% (63 mg). White solid, m.p. 71 – 73 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 – 8.10 (m, 2H), 7.76 (t, *J* = 7.6 Hz, 1H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.50 (s, 1H), 7.45 (t, *J* = 7.5 Hz, 1H), 6.95 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.1, 153.3, 146.8, 146.4, 144.4, 136.5, 128.5, 128.0, 126.7, 119.7, 116.9, 109.0. IR (KBr): v = 1766, 1635, 1604, 1397, 1163, 1006, 875, 769, 688, 595 cm^{-1}. HRMS (ESI): m/z calcd for $C_{12}H_7NNaO_3$ $[M + Na]^+$, 236.0318; found, 236.0318.

*2-(Thiophen-2-yl)-4H-3,1-benzoxazin-4-one (**2k**).* Yield 36% (41 mg). White solid, m.p. 124 – 126 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, *J* = 7.8 Hz, 1H), 7.98 – 7.96 (m, 1H), 7.81 (t, *J* = 7.6 Hz, 1H), 7.65 – 7.61 (m, 2H), 7.49 (t, *J* = 7.5 Hz, 1H), 7.18 (t, *J* = 3.9 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 153.9, 147.2, 136.8, 134.3, 132.6, 132.0, 128.9, 128.5, 128.1, 127.0, 116.8. HRMS (ESI): m/z calcd for $C_{12}H_8NO_2S$ $[M + H]^+$, 230.0270; found, 230.0276.

*2-tert-Butyl-4H-3,1-benzoxazin-4-one (**2l**).*[17] Yield 42% (43 mg). White solid, m.p. 124 – 125 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, *J* = 7.7 Hz, 1H), 7.79 (t, *J* = 7.6 Hz, 1H), 7.60 (d, *J* = 8.0 Hz, 1H), 7.50 (t, *J* = 7.5 Hz, 1H), 1.41 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 160.4, 146.7, 136.5, 128.4, 128.2, 127.1, 116.9, 38.1, 27.8. LRMS (ESI): m/z calcd for $C_{12}H_{14}NO_2$ [M

+ H]$^+$, 204.1; found, 204.1.

*2-Adamantyl-4H-3,1-benzoxazin-4-one (**2m**).* Yield 61% (86 mg). White solid, m.p. 94 – 96 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 7.7 Hz, 1H), 7.78 (t, *J* = 7.4 Hz, 1H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.48 (t, *J* = 7.5 Hz, 1H), 2.11 (s, 3H), 2.08 (s, 6H), 1.82 – 1.74 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.8, 160.4, 146.8, 136.4, 128.4, 128.1, 127.0, 117.1, 39.8, 39.4, 36.5, 28.0. IR (KBr): v = 2904, 2850, 1756, 1632, 1606, 1451, 1210, 1037, 1003, 765, 685, 620 cm^{-1}. HRMS (ESI): m/z calcd for $C_{18}H_{19}NNaO_2$ [M + Na]$^+$, 304.1308; found, 304.1321.

*(E)-2-Styryl-4H-3,1-benzoxazin-4-one (**2n**).*[16c] Yield 67% (84 mg). White solid, m.p. 144 – 146 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 7.7 Hz, 1H), 7.80 – 7.73 (m, 2H), 7.57 – 7.53 (m, 3H), 7.44 (t, *J* = 7.4 Hz, 1H), 7.40 – 7.33 (m, 3H), 6.73 (d, *J* = 16.1 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.2, 157.2, 147.0, 141.9, 136.5, 134.6, 130.3, 129.0, 128.6, 128.1, 128.0, 126.9, 118.8, 116.9. LRMS (ESI): m/z calcd for $C_{16}H_{12}NO_2$ [M + H]$^+$, 250.1; found, 250.1.

*2-(Prop-1-en-2-yl)-4H-3,1-benzoxazin-4-one (**2o**).* Yield 53% (50 mg). White solid, m.p. 92 – 93 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 – 8.18 (m, 1H), 7.83 – 7.76 (m, 1H), 7.67 – 7.60 (m, 1H), 7.54 – 7.47 (m, 1H), 6.35 (s, 1H), 5.71 (s, 1H), 2.17 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.6, 157.5, 146.8, 136.5, 135.8, 128.6, 128.5, 127.5, 124.3, 117.2, 18.9. HRMS (ESI): m/z calcd for $C_{11}H_{10}NO_2$ [M + H]$^+$, 188.0706; found, 188.0704.

*7-Chloro-2-phenyl-4H-3,1-benzoxazin-4-one (**2p**).*[11g] Yield 75% (97 mg). White solid, m.p. 180 – 182 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 – 8.26 (m, 2H), 8.16 (d, *J* = 8.3 Hz, 1H), 7.69 (s, 1H), 7.63 – 7.56 (m, 1H), 7.56 – 7.40 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.9, 158.4, 148.2, 143.1, 133.2, 130.0, 129.9, 128.9, 128.9, 128.6, 127.1, 115.5. LRMS (ESI): m/z calcd for $C_{14}H_9ClNO_2$ [M + H]$^+$, 258.0; found, 258.0.

*6-Chloro-2-phenyl-4H-3,1-benzoxazin-4-one (**2q**)*.[17] Yield 87% (112 mg). White solid, m.p. 152 – 153 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 – 8.26 (m, 1H), 8.26 – 8.24 (m, 1H), 8.16 (d, *J* = 2.4 Hz, 1H), 7.73 (dd, J = 8.6, 2.4 Hz, 1H), 7.64 – 7.54 (m, 2H), 7.50 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.5, 157.4, 145.6, 136.9, 133.9, 133.0, 129.9, 128.9, 128.9, 128.4, 128.0, 118.2. LRMS (ESI): m/z calcd for $C_{14}H_9ClNO_2$ $[M + H]^+$, 258.0; found, 258.0.

*6-Fluoro-2-phenyl-4H-3,1-benzoxazin-4-one (**2r**).*[17] Yield 84% (101 mg). White solid, m.p. 130 – 131 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, *J* = 7.5 Hz, 2H), 7.87 (dd, *J* = 7.5, 2.2 Hz, 1H), 7.73 – 7.67 (m, 1H), 7.61 – 7.45 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.1, 159.8, 158.9, 158.9, 156.6, 156.6, 143.6, 143.6, 132.8, 130.0, 129.7, 129.6, 128.9, 128.3, 125.0, 124.7, 118.4, 118.3, 114.2, 113.8. LRMS (ESI): m/z calcd for $C_{14}H_9FNO_2$ $[M + H]^+$, 242.1; found, 242.1.

*6,7-Dimethoxy-2-phenyl-4H-3,1-benzoxazin-4-one (**2s**).*[11f] Yield 79% (112 mg). White solid, m.p. 197 – 198 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, *J* = 7.3 Hz, 2H), 7.58 – 7.40 (m, 4H), 7.06 (s, 1H), 4.01 (s, 3H), 3.97 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.4, 156.6, 156.4, 149.6, 143.3, 132.3, 130.4, 128.7, 128.0, 109.6, 108.1, 107.5, 56.6, 56.4. LRMS (ESI): m/z calcd for $C_{16}H_{14}NO_4$ $[M + H]^+$, 284.1; found, 284.1.

*8-Methyl-2-phenyl-4H-3,1-benzoxazin-4-one (**2t**).* Yield 85% (101 mg). White solid, m.p. 121 – 123 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 6.6 Hz, 2H), 8.01 (d, *J* = 7.1 Hz, 1H), 7.59 (d, *J* = 6.4 Hz, 1H), 7.51 (d, *J* = 6.0 Hz, 1H), 7.46 (d, *J* = 6.5 Hz, 2H), 7.35 – 7.29 (m, 1H), 2.59 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.1, 155.8, 145.2, 137.3, 136.2, 132.4, 130.5, 128.7, 128.2, 127.7, 126.1, 116.9, 17.1. HRMS (ESI): m/z calcd for $C_{15}H_{12}NO_2$ $[M + H]^+$, 238.0863; found, 238.0869.

*7-Fluoro-2-phenyl-4H-3,1-benzoxazin-4-one (**2u**).*[11g] Yield 61% (74 mg). White solid, m.p. 150 – 152 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 – 8.21 (m, 3H), 7.62 – 7.56 (m, 1H), 7.55 – 7.48 (m, 2H), 7.34 (d, *J* = 9.1 Hz, 1H), 7.22 (t, *J* = 8.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.6, 166.2, 158.7, 158.4, 149.7, 149.5, 133.1, 131.6, 131.4, 129.9, 128.9, 128.56, 116.9, 116.6, 113.7, 113.6, 113.5, 113.2. LRMS (ESI): m/z calcd for $C_{14}H_9FNO_2$ $[M + H]^+$, 242.1; found, 242.1.

*6-Methoxy-2-phenyl-4H-3,1-benzoxazin-4-one (**2v**).*[17] Yield 60% (76 mg). White solid, m.p. 137 – 139 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, *J* = 7.3 Hz, 2H), 7.62 – 7.56 (m, 2H), 7.55 – 7.44 (m, 3H), 7.36 (d, *J* = 7.3 Hz, 1H), 3.90 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.9, 159.3, 155.3, 141.2, 132.3, 130.4, 128.8, 128.8, 128.0, 126.0, 117.8, 108.7, 56.0. LRMS (ESI): m/z calcd for $C_{15}H_{12}NO_3$ $[M + H]^+$, 254.1; found, 245.1.

*6,7-Methylenedioxy-2-phenyl-4H-3,1-benzoxazin-4-one (**2w**).*[16f] Yield 53% (71 mg). Yellow solid, m.p. 185 – 187 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, *J* = 7.4 Hz, 2H), 7.59 – 7.44 (m, 4H), 7.05 (s, 1H), 6.13 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.3, 156.5, 155.0, 148.2, 145.1, 132.5, 130.3, 128.8, 128.2, 111.3, 106.3, 105.6, 102.8. LRMS (ESI): m/z calcd for $C_{15}H_{10}NO_4$ $[M + H]^+$, 268.1; found, 268.1.

*6-Methyl-2-phenyl-4H-3,1-benzoxazin-4-one (**2x**).*[17] Yield 65% (77 mg). White solid, m.p. 136 – 138 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 – 8.22 (m, 2H), 7.99 (d, *J* = 11.2 Hz, 1H), 7.63 – 7.40 (m, 5H), 2.44 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.8, 156.4, 144.8, 138.7, 137.8, 132.4, 130.4, 128.8, 128.2, 127.0, 116.7, 21.4. LRMS (ESI): m/z calcd for $C_{15}H_{12}NO_2$ $[M + H]^+$, 238.1; found, 238.1.

*2-Phenyl-4H-naphtho[1,2-d][1,3]oxazin-4-one (**2y**).*[17] Yield 78% (107 mg). Yellow solid, m.p.

180 – 182 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.91 (d, *J* = 7.7 Hz, 1H), 8.37 (d, *J* = 7.5 Hz, 2H), 8.03 (d, *J* = 8.6 Hz, 1H), 7.85 – 7.75 (m, 2H), 7.71 – 7.62 (m, 2H), 7.60 – 7.48 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.9, 158.0, 146.0, 137.2, 132.8, 130.4, 130.2, 129.2, 128.8, 128.5, 128.4, 128.0, 127.4, 125.4, 122.4, 112.9. LRMS (ESI): m/z calcd for $C_{18}H_{12}NO_2$ $[M + H]^+$, 274.1; found, 274.1.

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Supporting Information: copies of ^{1}H, ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org/.

REFERENCES

(1) Hedstrom, L.; Moorman, A. R.; Dobbs, J.; Abeles, R. H. *Biochemistry* **1984**, *23*,1753.

(2) Jarvest, R. L.; Parratt, M. J.; Debouck, C. M.; Gorniak, J. G.; John Jennings, L.; Serafinowska, H. T.; Strickler, J. E. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2463.

(3) (a) Stein, R. L.; Strimpler, A. M.; Viscarello, B. R.; Wildonger, R. A.; Mauger, R. C.; Trainor, D. A. *Biochemistry* **1987**, *26*, 4126. (b) Krantz, A.; Spencer, R. W.; Tam, T. F.; Liak, T. J.; Copp, L. J.; Thomas, E. M.; Rafferty, S. P. *J. Med. Chem.* **1990**, *33*, 464.

(4) Gütschow, M.; Neumann, U. *Bioorg. Med. Chem.* **1997**, *5*, 1935.

(5) Hays, S. J.; Caprathe, B. W.; Gilmore, J. L.; Amin, N.; Emmerling, M. R.; Michael, W.; Nadimpali, R.; Nath, R.; Raser, K. J.; Stafford, D.; Watson, D.; Wang, K.; Jaen, J. C. *J. Med. Chem.* **1998**, *41*, 1060.

(6) Neumann, U.; Schechter, N. M.; Gütschow, M. *Bioorg. Med. Chem.* **2001**, *9*, 947.

(7) Fenton, G.; Newto, C. G.; Wyman, B. M.; Bagge, P.; Dron, D. I.; Riddell, D.; Jones, G. D. *J. Med. Chem.* **1989**, *32*, 265.

(8) (a) Halford, J. C. *Curr. Opin. Investig. Drugs* **2006**, *7*, 312. (b) Kopelman, P.; Bryson, A.; Hickling, R.; Rissanen, A.; Rossner, S.; Toubro, S.; Valensi, P. *Int. J. Obes.* **2007**, *31*, 494. (c) Yamada, Y.; Kato, T.; Ogino, H.; Ashina, S.; Kato, K. *Horm. Metab. Res.* **2008**, *40*, 539. (d) Padwal, R. *Curr. Opin. Investig. Drugs* **2008**, *9*, 414.

(9) (a) Errede, L. A.; Oien, H. T.; Yarian, D. R. *J. Org. Chem.* **1977**, *42*, 12. (b) Clémence, F.; LeMartret, O.; Collard, J. *J. Heterocycl. Chem.* **1984**, *21*, 1345. (c) Habib, O. M.; Moawad, E. B.; Girges, M. M.; El-Shafei, A. M. *Boll. Chim. Farm.* **1995**, *134*, 503. (d) Ibrahim, S. S.; Abdel-Halim, A. M.; Gabr, Y.; El-Edfawy, S.; Abdel-Rahman, R. *J. Chem. Res., Synop.* **1997**, 154. (e) Bratt, K.; Sunnerheim, K.; Bryngelsson, S.; Fagerlund, A.; Engman, L.; Andersson, R. E.; Dimberg, L. H. *J. Agric. Food Chem.* **2003**, *51*, 594. (f) Eissa, A. M. F.; El-Sayed, R. *J. Heterocyclic Chem*. **2006**, *43*, 1161. (g) Kostakis, I. K.; Elomri, A.; Seguin, E.; Iannelli, M.; Besson, T. *Tetrahedron Letters* **2007**, *48*, 6609. (h) Kumar, S.; Kaur, H.; Singh, I.; Sharma, M.; Vishwakarma, P.; Saxena, K. K.; Kumar, A. *World J. Chemistry*, **2009**, *4*, 195. (i) Li, X.; Huo, X.;

Li, J.; She, X.; Pan, X. *Chin. J. Chem.* **2009**, *27*, 1379. (j) Gupta, A.; Kashaw, S. K.; Jain, N.; Rajak, H.; Soni, A.; Stables, J. P. *Med. Chem. Res.* **2011**, *20*, 1638.

(10) For reviews on benzoxazinones synthesis, see: (a) Coppola, G. M. *J. Heterocycl. Chem.* **1999**, *36*, 563. (b) Coppola, G. M. *J. Heterocycl. Chem.* **2000**, *37*, 1369.

(11) (a) Beck, J. R.; Yahner, J. A. *J. Org. Chem.* **1973**, *38*, 2450. (b) Zentmyer, D. T.; Wagner, E. C. *J. Org. Chem.* **1949**, *14*, 967. (c) Papadopoulos, E. P.; Torres, C. D. *Heterocycles* **1982**, *19*, 1039. (d) Rose, U. *J. Heterocycl. Chem.* **1991**, *28*, 2005. (e) Clayden, J.; Vallverdú, L.; Helliwell, M. *Org. Biomol. Chem.* **2006**, *4*, 2106. (f) Nayak, M. K.; Kim, B. H.; Kwon, J. E.; Park, S.; Seo, J.; Chung, J. W.; Park, S. Y. *Chem. Eur. J.* **2010**, *16*, 7437. (g) Manivannan, E.; Chaturvedi, S. C. *Bioorg. Med. Chem*. **2011**, *19*, 4520.

(12) (a) Bristow, T. H. C.; Foster, H. E.; Hooper, M. *J. Chem. Soc., Chem. Commun.* **1974**, 677. (b) Richman, R. J.; Hassner, A. *J. Org. Chem.* **1968**, *33*, 2548. (c) Adam, J.; Winkler, T. *Hel. Chim. Acta* **1984**, *67*, 2186. (d) Kumar, R. A.; Maheswari, C. U.; Ghantasala, S.; Jyothi, C.; Reddy, K. R. *Adv. Synth. Catal.* **2011**, *353*, 401.

(13) (a) Crabtree, H. E.; Smalley, R. K.; Suschitzky, H. *J. Chem. Soc. C* **1968**, 2730. (b) Smalley, R. K.; Suschitzky, H. *Tetrahedron Lett.* **1966**, *29*, 3465. (c) Archer, J. G.; Barker, A. J.; Smalley, R. K. *J. Chem. Soc., Perkin Trans. 1* **1973**, 1169.

(14) Molina, P.; Conesa, C.; Velasco, M. D. *Tetrahedron Lett.* **1993**, *34*, 175.

(15) Gütschow, M. *J. Org. Chem.* **1999**, *64*, 5109.

(16) (a) Larock, R. C.; Fellows, C. A. *J. Org. Chem.* **1980**, *45*, 363. (b) Cacchi, S.; Fabrizi, G.; Marinelli, F. *Synlett* **1996**, 997. (c) Larksarp, C.; Alper, H. *Org. Lett.* **1999**, *1*, 1619. (d)

Salvadori, J.; Balducci, E.; Zaza, S.; Petricci, E.; Taddei, M. *J. Org. Chem.* **2010**, *75*, 1841. (e) Houlden, C. E.; Hutchby, M.; Bailey, C. D.; Ford, J. G.; Tyler, S. N. G.; Gagne, M. R.; Loyd-Jones, G. C.; Booker-Milburn, K. I. *Angew. Chem.* **2009**, *121*, 1862. (f) Giri, R.; Lam, J. K.; Yu, J. Q.; *J. Am. Chem. Soc.* **2010**, *132*, 686. (g) Ács, P.; Mueller, E.; Rangits, G.; Lorand, T.; Kollar, L. *Tetrahedron* **2006**, *62*, 12051. (h) Wu, X.-F.; Schranck, J.; Neumann, H.; Beller, M. *Chem. Eur. J.* **2011**, 17, 12246. (i) Wu, X.-F.; Neumann, H.; Beller, M. *Chem. Eur. J.* **2012**, 18, 12599. (j) Xue, L.; Shi, L.; Han, Y.; Xia, C.; Huynh, H. V.; Li, F. *Dalton Trans.* **2011**, *40*, 7632.

(17) Liu, Q.; Chen, P.; Liu, G. *ACS Catal*. **2013**, *3*, 178.

(18) Ge, Z.-Y.; Fei, X.-D.; Tang, T.; Zhu, Y.-M.; Shen, J.-K. *J. Org. Chem.* **2012**, *77*, 5736.

(19) Li, X.; Fang, Y.; Deng, P.; Hu, J.; Li, T.; Feng, W.; Yuan, L. *Org. Lett.* **2011**, *13*, 4628.