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Recyclable Heterogeneous Palladium-Catalyzed Cyclocarbonylation of 2-Iodoanilines with Acyl Chlorides in the Biomass-Derived Solvent 2-Methyltetrahydrofuran

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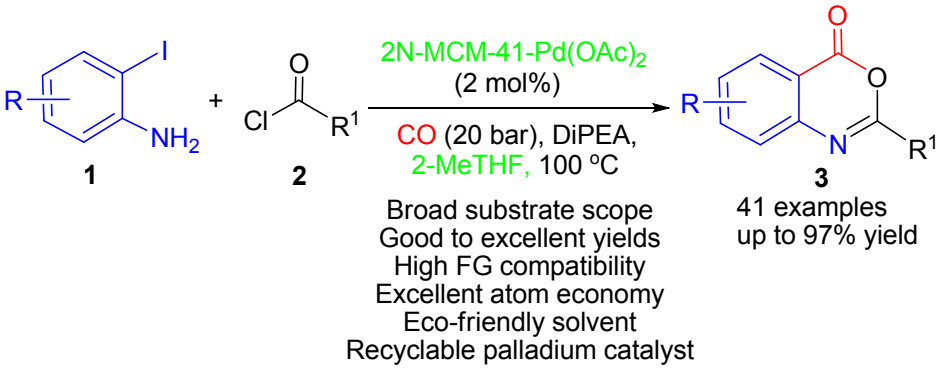


ABSTRACT: A highly efficient, green palladium-catalyzed cyclocarbonylation of 2-iodoanilines with acyl chlorides has been developed that proceeds smoothly in a biomass-derived solvent 2-methyltetrahydrofuran (2-MeTHF) with *N,N*-diisopropylethylamine (DiPEA) as base at 100 ºC under 20 bar of carbon monoxide using an 2-aminoethylamino-modified MCM-41-anchored palladium acetate complex [2N-MCM-41-Pd(OAc)$_2$] as a heterogeneous catalyst, yielding a wide variety of 2-substituted 4*H*-3,1-benzoxazin-4-one derivatives in good to excellent yields. This supported palladium catalyst could be facilely obtained by a two-step procedure from easily available starting materials and readily recovered via a simple filtration process and recycled at least 8 times without any apparent decrease in catalytic efficiency. The developed methodology not only avoids the use of toxic solvents such as THF and DMF, but also solves the basic problem of expensive palladium catalyst recovery and reuse, and prevents effectively palladium contamination of the desired product.

INTRODUCTION

4*H*-3,1-Benzoxazin-4-ones are a class of important *N*-heterocycles of considerable interest and have found a wide range of applications in pharmaceutical research.[1] Particularly, 2-substituted 4*H*-3,1-benzoxazin-4-ones exhibit a variety of biological activities and can act as chymotrypsin inactivators, C1r protease inhibitors, HDL elevators, and pancreatic lipase inhibitors.[2] Moreover, 2-substituted 4*H*-3,1-benzoxazin-4-ones are also versatile and valuable synthetic intermediates for the synthesis of bioactive *N*-substituted quinazolinone derivatives and their derived pharmaceuticals.[3] Therefore, many methods have been developed for the construction of 4*H*-3,1-benzoxazin-4-ones over the past decades.[4] The most popular methods for the construction of 4*H*-3,1-benzoxazin-4-ones are the cyclization of anthranilic acid or its derivatives, *N*-acylanthranilic acids, and isotoic anhydride.[5] In order to improve the yield and reduce the cost of the reaction, other notable synthetic pathways have also been reported for the synthesis of 4*H*-3,1-benzoxazin-4-ones. These methods include copper-catalyzed reactions such as cyclization of *N*-acyl-*o*-iodobenzamides,[6] oxidative cyclization of *N*-TFA-protected 2-alkynylanilines[7] or *o*-iodobenzoic acids with benzyl amines,[8] oxidation of 2-arylindoles,[9] aza-Wittig reaction of 2-azido phenyl anhydrides,[10] palladium-catalyzed carbon-carbon triple bond cleavage of 2-azidoalkynylbenzenes,[11] and $CoCl_2$ or Ag_2O-mediated intramolecular oxidative cyclization.[12] Besides, transition-metal-free syntheses of 4*H*-3,1-benzoxazin-4-ones have also been developed through the oxidation of 2-arylindoles with oxone as the sole oxidant, oxidative cyclization of 2-aminobenzoic acids with arylaldehydes or 2-aminobenzyl alcohols with aldehydes.[13] Despite these significant progress made in

their synthetic methodologies, the availability or scope of substrates and required reaction conditions make these methods of limited synthetic utility.

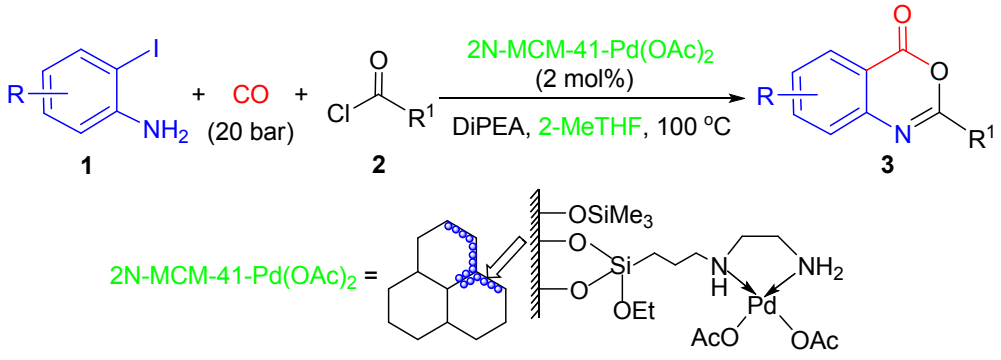
Palladium-catalyzed carbonylative transformations of readily available (hetero)aryl halides with carbon monoxide have proven to be a general and straightforward route for the construction of various benzoic acid derivatives.[14] Combining such carbonylative reactions with subsequent intramolecular cyclization processes would allow for a highly efficient synthesis of diverse heterocycles.[15] Some papers have reported the use of palladium-catalyzed carbonylation strategy for the construction of 2-substituted 4*H*-3,1-benzoxazin-4-ones.[16] Larock and Fellows reported the first carbonylative synthesis of 2-substituted 4*H*-3,1-benzoxazin-4-ones via a stoichiometric thallation and subsequent palladium-catalyzed carbonylation of *N*-acetylaniline.[16a] Cacchi and coworkers described Pd(0)-catalyzed carbonylation of *o*-iodoanilines with unsaturated halides or triflates towards 2-substituted 4*H*-3,1-benzoxazin-4-ones.[16b] Palladium-catalyzed cyclocarbonylation of *o*-iodoanilines with acid chlorides were reported by the Alper group[16c] and the Petricci group.[16d] Recently, Wu and Beller have developed palladium-catalyzed carbonylative coupling of 2-bromoanilines with aryl bromides,[16e] acid anhydrides,[16f] or isocyanates,[16g] respectively. Palladium-catalyzed carbonylative C–H activation of benzanilides or aryl urea derivatives were independently reported by the Yu group and the Lloyd-Jones and Booker-Milburn group for the synthesis of 4*H*-3,1-benzoxazin-4-ones.[17] Besides, carbonylative cyclization of *N*-acyl-2-haloanilines under the catalysis of palladium using paraformaldehyde, phenyl formate, or oxalyl chloride as CO surrogates has also been developed for the synthesis of

2-substituted 4*H*-3,1-benzoxazin-4-ones.[18]

Although the palladium-catalyzed carbonylation methodology is highly efficient for the construction of 2-substituted 4*H*-3,1-benzoxazin-4-ones,[16-18] these carbonylation reactions are usually conducted using homogeneous palladium catalysts in toxic solvents such as toluene, THF and DMF. Homogeneous palladium catalysis suffers from difficult separation and non-recyclability of the expensive catalysts. What's more, homogeneous catalysis might cause unacceptable palladium contamination in the desired isolated products owing to palladium leaching. The complete removal of residual palladium is a great problem for pharmaceutical products where carryover of palladium impurities may result in serious issues in the production of many formulations.[19] Thus, facile separation and recycle of expensive catalysts remain a scientific challenge and represent one of the most important features in green organic synthesis from economic and environmental viewpoints. In order to address these issues, anchoring homogeneous palladium catalysts on various solid supports is a promising option since the supported catalysts can be conveniently recovered via a simple filtration process. Recently, there has been increasing interest in the development of heterogeneous palladium catalytic systems that can be effectively recycled whilst maintaining the inherent catalytic activity.[20] Petricci and coworkers reported Pd/C-catalyzed cyclocarbonylation of *o*-iodoanilines with acid chlorides in DMF under microwave dielectric heating, but the catalytic activity of Pd/C was obviously lower than that of $Pd(OAc)_2$ and the catalyst can be recycled only two times due to palladium leaching.[16d]

Biomass solvents derived from renewable raw materials have recently attracted significant interest because of exceedingly zero or negligible impact on the environment and health as well as the continuous increase in the price of petroleum. 2-Methyltetrahydrofuran (2-MeTHF) is definitely an eco-friendly solvent derived from renewable resources like corn cobs and oat hulls, and has already a wide application in organic synthesis and pharmaceutical industry due to its low toxicity and high biodegradability.[21] In continuation of our efforts to develop green and sustainable catalytic systems for organic transformations,[22] herein we wish to report a highly efficient, green palladium-catalyzed cyclocarbonylation of 2-iodoanilines with acyl chlorides in the bio-based solvent 2-MeTHF by using an 2-aminoethylamino-modified MCM-41-anchored palladium acetate complex [2N-MCM-41-Pd(OAc)$_2$] as a recyclable heterogeneous catalyst, yielding a wide variety of 2-substituted 4*H*-3,1-benzoxazin-4-one derivatives in good to excellent yields from commercially easily available starting materials (Scheme 1).

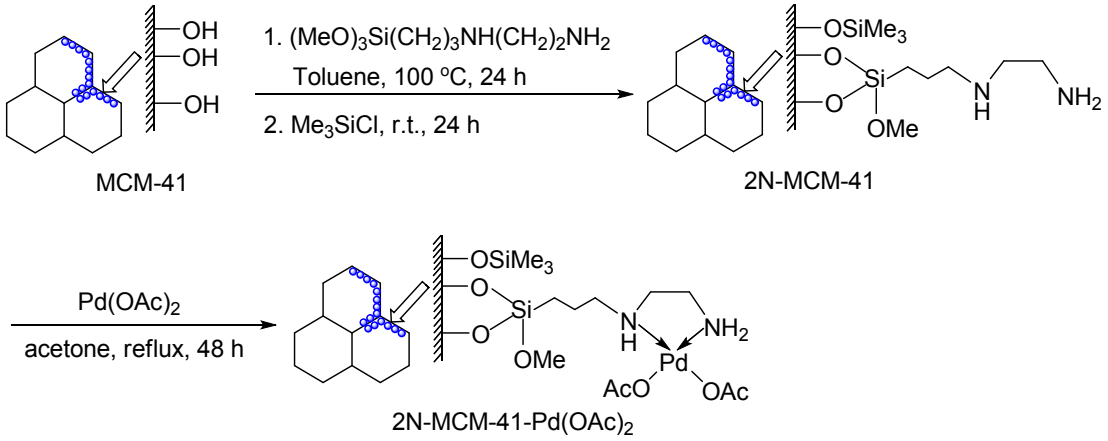
Scheme 1. Heterogeneous Palladium-Catalyzed Cyclocarbonylation of 2-Iodoanilines with Acyl Chlorides in 2-MeTHF.



RESULTS AND DISCUSSION

The 2-aminoethylamino-modified MCM-41-anchored palladium acetate complex [2N-MCM-41-Pd(OAc)$_2$] was facilely prepared according to our previously reported similar procedure, as shown in Scheme 2.[22a] The condensation reaction of mesoporous MCM-41 with commercially available and inexpensive 3-(2-aminoethylamino)-propyltrimethoxysilane at 100 ºC in toluene, followed by treating with Me_3SiCl in toluene at room temperature gave an 2-aminoethylamino-modified MCM-41 material (2N-MCM-41). Subsequent coordination reaction of 2N-MCM-41 with Pd(OAc)$_2$ in acetone at reflux for 48 hours afforded the 2-aminoethylamino-modified MCM-41-anchored palladium acetate complex [2N-MCM-41-Pd(OAc)$_2$] as a light yellow powder with palladium content of 0.39 mmol/g based on ICP-AES analysis.

Scheme 2. Preparation of the 2N-MCM-41-Pd(OAc)$_2$ Complex.

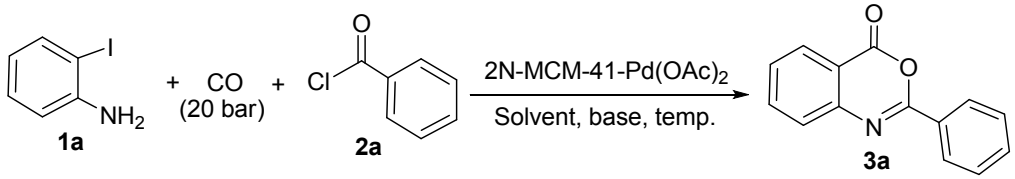


The 2N-MCM-41-Pd(OAc)$_2$ complex was then employed as the catalyst for the cyclocarbonylation reaction of 2-iodoanilines with acyl chlorides. Initial experiments, with 2-iodoaniline **1a** and benzoyl chloride **2a** under 20 bar of carbon monoxide, were conducted to determine the optimal reaction conditions, and the results are given in Table 1. At first, the effect of various common solvents on the model reaction was

evaluated in the presence of 2 mol% of 2N-MCM-41-Pd(OAc)$_2$ with DiPEA as base at 100 ºC, and a remarkable solvent effect was observed (entries 1-7). When DMF and THF were used as solvents, the target product **3a** was isolated in 84-95% yields and THF gave the best result (entry 4), while other solvents such as NMP, DMSO, dioxane, MeCN, and toluene were substantially less effective and afforded relatively lower yields of **3a**. To our delight, replacement of THF with the eco-friendly solvent 2-MeTHF afforded the desired **3a** in a slightly higher yield of 97% (entry 8). So, the use of 2-MeTHF as solvent in this reaction was the best choice. Our next studies focused on the influence of base on the model reaction using 2-MeTHF as solvent (entries 9-13). Performing the reaction using other organic bases such as Et_3N, *n*-Bu_3N, DBU, and TMEDA provided the desired product **3a** in 78-87% yields and K_2CO_3 gave a low yield of **3a**, thus, DiPEA was the most efficient base (entry 8). Lowering reaction temperature to 90 ºC led to a decreased yield (entry 14), whilst raising reaction temperature to 110 or 120 ºC also resulted in a slightly decreased yield of **3a** (entries 15 and 16), thus the reaction run at 100 ºC gave the best result (entry 8). Finally, the palladium catalyst loadings were also screened. Reducing the amount of the catalyst to 1 mol% provided the desired **3a** in only 75% yield even after 36 h (entry 17), while increasing the amount of the catalyst to 4 mol% could shorten the reaction time to 16 h, but did not improve the yield further (entry 18). When a homogeneous Pd(OAc)$_2$ (2 mol%) was used as catalyst, the desired product **3a** was also isolated in 96% yield (entry 19), indicating that the catalytic efficiency of 2N-MCM-41-Pd(OAc)$_2$ was comparable to that of homogeneous Pd(OAc)$_2$ catalyst.

Therefore, the optimized reaction conditions for this cyclocarbonylation are the use of 2N-MCM-41-Pd(OAc)$_2$ (2 mol%), DiPEA (3 equiv.) as base in 2-MeTHF as a green solvent at 100 °C under 20 bar of CO for 24 h (Table 1, entry 8).

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



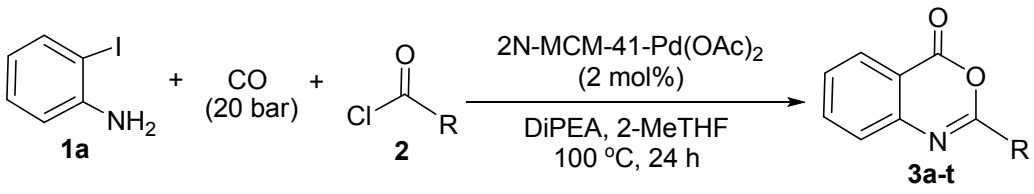
entry	solvent	base	temp. (ºC)	Pd loading (mol%)	yield (%)[b]
1	NMP	DiPEA	100	2	73
2	DMF	DiPEA	100	2	84
3	DMSO	DiPEA	100	2	62
4	THF	DiPEA	100	2	95
5	dioxane	DiPEA	100	2	71
6	MeCN	DiPEA	100	2	56
7	Toluene	DiPEA	100	2	69
8	2-MeTHF	DiPEA	100	2	97
9	2-MeTHF	Et_3N	100	2	78
10	2-MeTHF	*n*-Bu_3N	100	2	84
11	2-MeTHF	DBU	100	2	87
12	2-MeTHF	TMEDA	100	2	81
13	2-MeTHF	K_2CO_3	100	2	43
14	2-MeTHF	DiPEA	90	2	67
15	2-MeTHF	DiPEA	110	2	93
16	2-MeTHF	DiPEA	120	2	89
17[c]	2-MeTHF	DiPEA	100	1	75
18[d]	2-MeTHF	DiPEA	100	4	97
19[e]	2-MeTHF	DiPEA	100	2	96

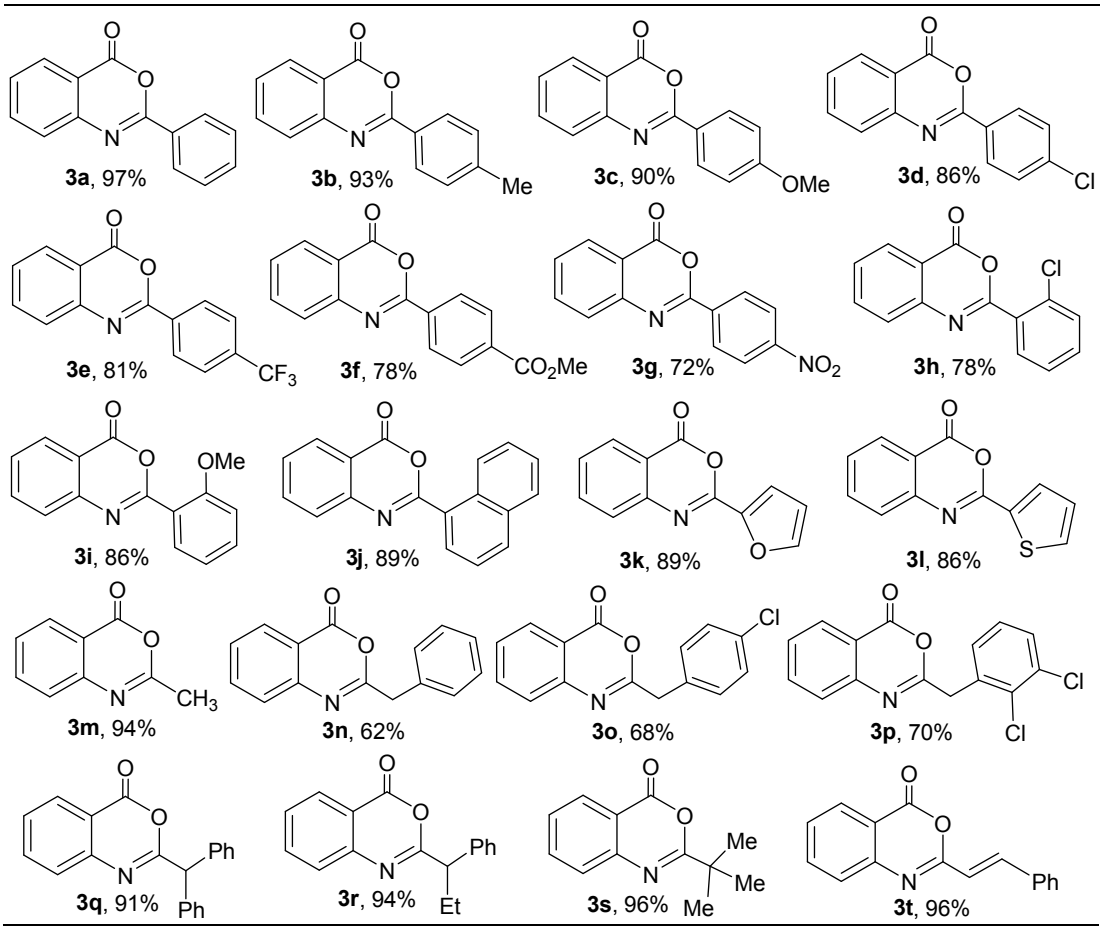
[a] Reaction conditions: **1a** (1.0 mmol), **2a** (1.0 mmol), base (3.0 mmol), solvent (5 mL) under 20 bar of CO for 24 h. [b] Isolated yield. [c] For 36 h. [d] For 16 h. [e] 2 mol% of Pd(OAc)$_2$ was used as the catalyst.

With the optimal reaction conditions in hand, we started to investigate the substrate scope of this heterogeneous palladium-catalyzed cyclocarbonylation reaction by using a wide variety of acyl chlorides and various *o*-iodoanilines as substrates. Firstly, the substrate scope of acyl chlorides was studied by evaluating a variety of aromatic and aliphatic acyl chlorides and the results are summarized in Table 2. *para*-Substituted benzoyl chlorides **2b-g** bearing either electron-donating or electron-withdrawing groups could undergo the cyclocarbonylation with 2-iodoaniline **1a** smoothly to give the corresponding 2-substituted 4*H*-3,1-benzoxazin-4-ones **3b-g** in good to excellent yields. Electron-rich benzoyl chlorides **2b-c** showed a higher reactivity than electron-deficient ones **2d-g**. Sterically hindered *ortho*-substituted benzoyl chlorides **2h-i** were also compatible with the standard conditions and furnished the desired products **3h-i** in good yields. Besides, bulky 1-naphthoyl chloride **2j** proved to be a good substrate and provided the target product **3j** in 89% yield. Notably, heteroaroyl chlorides such as 2-furoyl chloride **2k** and thiophene-2-carbonyl chloride **2l** also reacted well in this transformation and delivered the expected 2-heteroaryl-4*H*-3,1-benzoxazin-4-ones **3k** and **3l** in high yields. Subsequently, the cyclocarbonylation of 2-iodoaniline **1a** with a variety of aliphatic acid chlorides were investigated under the optimized conditions and the results are also given in Table 2. To our delight, aliphatic acid chlorides exhibited a similar reactivity with aromatic acid chlorides and afforded a wide variety of 2-alkyl-substituted 4*H*-3,1-benzoxazin-4-ones in good to excellent yields. For example, cyclocarbonylation of acetyl chloride **2m** with 2-iodoaniline **1a** proceeded smoothly to give the desired product **3m** in 94% yield. α-Monosubstituted acid

chlorides **2n-p** were compatible with the standard conditions and provided the corresponding 2-alkyl-substituted 4*H*-3,1-benzoxazin-4-ones **3n-p** in 62-70% yields. Notably, α-di- or trisubstituted acid chlorides **2q-s** exhibited a higher reactivity than α-monosubstituted analogues and afforded the desired products **3q-s** in excellent yields. Interestingly, when (*E*)-cinnamoyl chloride **2t** was employed for the palladium-catalyzed cyclocarbonylation reaction with 2-iodoaniline **1a**, (*E*)-2-styryl-4*H*-3,1-benzoxazin-4-one **3t** was obtained in 96% yield. A range of electron-donating or electron-withdrawing functional groups such as alkyl, methoxy, chloro, ester, nitro, and trifluoromethyl as well as bulky 1-naphthyl, *t*-butyl and heteroaryl were tolerated well. The above results indicate the superiority of this methodology in comparison with previously reported palladium-catalyzed carbonylative synthesis of 2-substituted 4*H*-3,1-benzoxazin-4-ones. For instance, **3i** was isolated in 86% yield while the yield of **3i** was 29% by Pd(0)-catalyzed carbonylation of 2-methoxyiodobenzene with 2-iodoaniline **1a**.[16b] Also **3t** was obtained by the reaction described herein while the yield of **3t** was 47% by Pd(0)-catalyzed carbonylation of β-bromostyrene with 2-iodoaniline **1a**.[16b] In addition, **3m** was formed in 94% yield while 40 and 60% yields of **3m** were obtained from the thallation/Pd-catalyzed carbonylation of *N*-acetylaniline[16a] and Pd-catalyzed carbonylation of *N*-acetyl-2-iodoaniline,[16b] respectively.

Table 2. Heterogeneous Palladium-Catalyzed Cyclocarbonylation of 2-Iodoaniline 1a with Various Acyl Chlorides.[a,b]



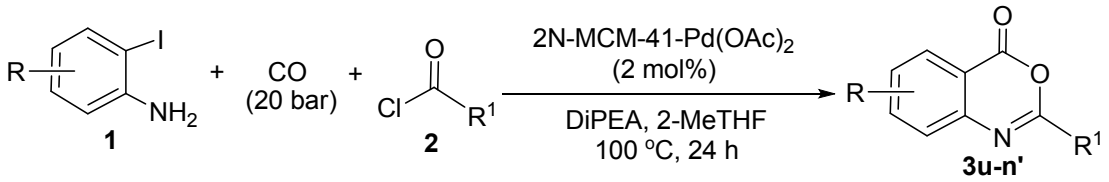


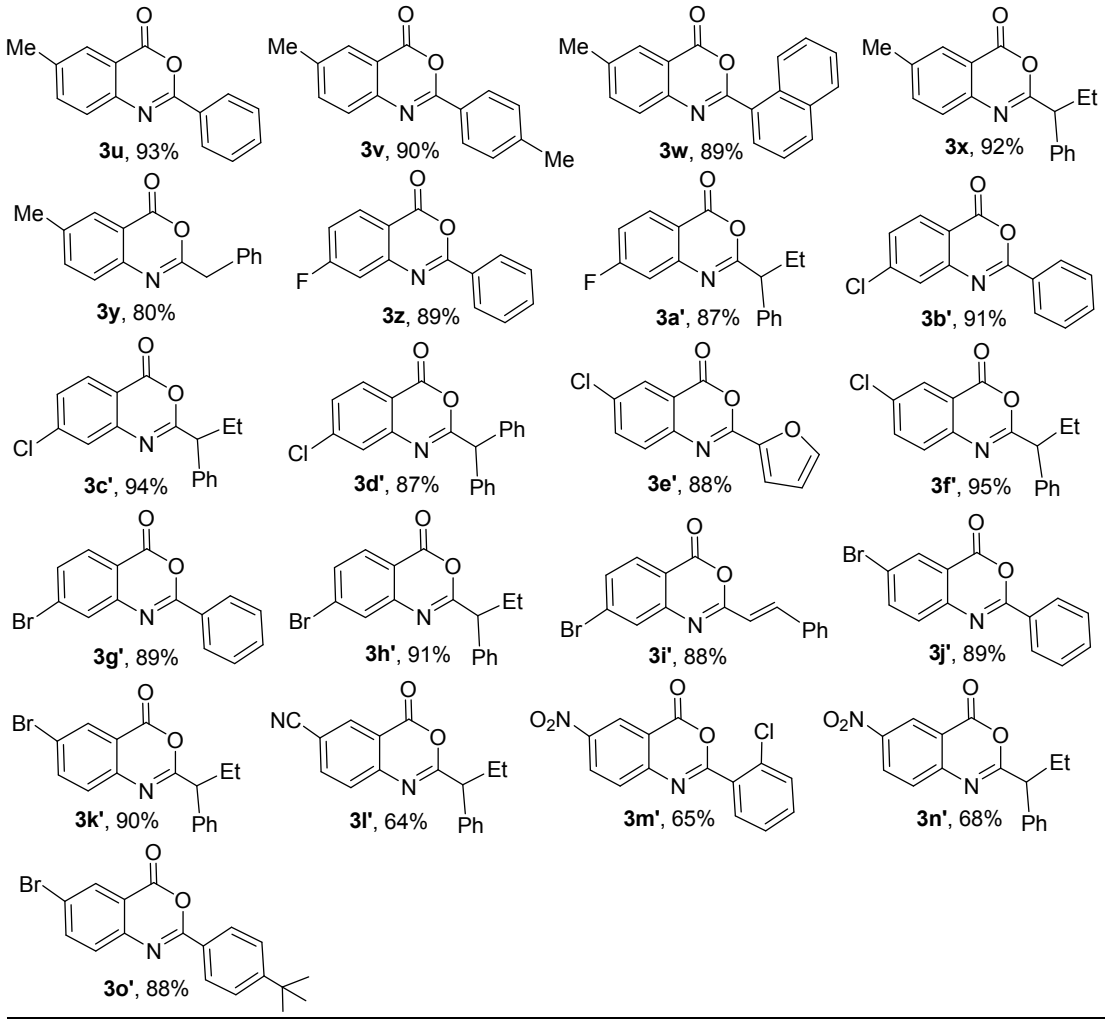
[a] Reaction conditions: **1a** (1.0 mmol), **2** (1.0 mmol), DiPEA (3.0 mmol), 2N-MCM-41-Pd(OAc)$_2$ (2 mol%), 2-MeTHF (5 mL) at 100 ºC under 20 bar of CO for 24 h. [b] Isolated yield.

Encouraged by the above promising results, we next examined the substrate scope of 2-iodoanilines **1** under the optimal reaction conditions and the results are listed in Table 3. To our delight, we found this heterogeneous palladium-catalyzed cyclocarbonylation reaction to be quite general for various substituted 2-iodoanilines. For example, 2-iodo-4-methylaniline **1b** could undergo the cyclocarbonylation reaction smoothly with a variety of aromatic or aliphatic acid chlorides to give the corresponding 2-substituted 4*H*-3,1-benzoxazin-4-ones **3u-y** in 80-93% yields. Furthermore, 5- or 4-(fluoro or chloro)-substituted 2-iodoanilines **1c-e** also showed good reactivity and produced the desired 7- or 6-(fluoro or chloro)-substituted 2-aryl(alkyl)-

4*H*-3,1-benzoxazin-4-ones **3z-f'** in 87-95% yields. It is noteworthy that, 5- or 4-bromo-2-iodoanilines **1f** and **1g** could undergo this transformation chemoselectively with various acid chlorides, affording the corresponding 7- or 6-bromo-substituted 2-aryl(alkyl)-4*H*-3,1-benzoxazin-4-ones **3g'-k'** in 88-91% yields. However, 2-iodo-anilines bearing strong electron-withdrawing groups such as 4-cyano-2-iodoaniline **1h** and 2-iodo-4-nitroaniline **1i** displayed a relatively lower reactivity and led to the expected products **3l'-n'** in only 64-68% yields. Notably, 6-bromo-2-(4-*tert*-butyl-phenyl)-4*H*-benzo[*d*][1,3]oxazin-4-one **3o'**, a high-density lipoprotein (HDL) elevator,[2c] was prepared in 88% yield by the reaction of 4-bromo-2-iodoaniline **1g** with 4-*tert*-butylbenzoyl chloride **2u** under the standard conditions. In addition, we also performed cyclocarbonylation reaction of 2-bromoanilines with acid chlorides, unfortunately, no desired products were detected even at higher reaction temperatures and under higher pressures of carbon monoxide since the oxidative addition reaction of aryl bromides to a heterogeneous palladium(0) complex was too slow, hence, 7- or 6-bromo-substituted 2-aryl(alkyl)-4*H*-3,1-benzoxazin-4-ones **3g'-k'** were selectively formed in high yields. A range of functional groups such as methyl, fluoro, chloro, bromo, cyano, and nitro on the phenyl ring of 2-iodoanilines were tolerated well. The present method is applicable to a wide range of acyl chlorides and various 2-iodoanilines and provides a novel, highly efficient, green and practical procedure for the construction of 2-substituted 4*H*-3,1-benzoxazin-4-ones from readily available starting materials.

Table 3. Heterogeneous Palladium-Catalyzed Cyclocarbonylation of Various Substituted 2-Iodoanilines with Acyl Chlorides.[a,b]





[a] Reaction conditions: **1** (1.0 mmol), **2** (1.0 mmol), DiPEA (3.0 mmol), 2N-MCM-41-Pd(OAc)$_2$ (2 mol%), 2-MeTHF (5 mL) at 100 °C under 20 bar of CO for 24 h. [b] Isolated yield.

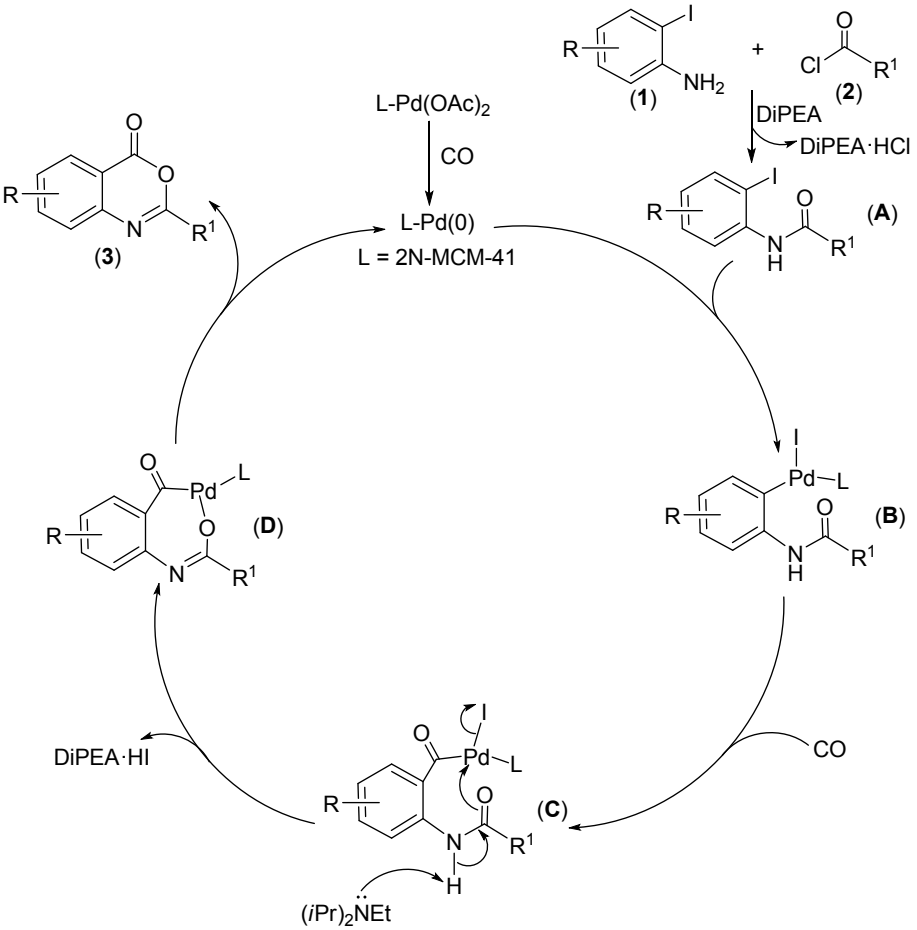
To ensure that the high activity of 2N-MCM-41-Pd(OAc)$_2$ results from the palladium sites on the channel inner walls of the MCM-41 support and not from the leached Pd species from 2N-MCM-41-Pd(OAc)$_2$, the heterogeneity of the 2N-MCM-41-Pd(OAc)$_2$ complex was investigated by hot filtration test.[23] We focused on the

cyclocarbonylation reaction of 2-iodoaniline **1a** (2.0 mmol) and benzoyl chloride **2a** (2.0 mmol) in 2-MeTHF (10 mL) by using 2N-MCM-41-Pd(OAc)$_2$ (103 mg, 0.04 mmol) as the catalyst and DiPEA (6.0 mmol) as the base. After the reaction was conducted for 8 h, the reaction mixture was cooled to 80 ºC and excess CO was released carefully. The palladium catalyst was then removed from the reaction mixture by filtration at 80 ºC via a heat preserving glass funnel and the catalyst-free filtrate was allowed to react further under identical conditions for 24 h. It was found that no increase in conversion of 2-iodoaniline **1a** was observed in the clear solution, demonstrating that the observed high activity should not arise from the soluble Pd species leached from 2N-MCM-41-Pd(OAc)$_2$. In addition, no palladium species could be detected in the filtrate based on ICP-AES analysis. The above results confirm the fact that the 2N-MCM-41-Pd(OAc)$_2$ catalyst is stable during the cyclocarbonylation and supports heterogeneous nature of the cyclocarbonylation reaction.

A possible mechanism for this heterogeneous Pd-catalyzed cyclocarbonylation reaction of 2-iodoanilines with acyl chlorides is illustrated in Scheme 3. Firstly, the 2N-MCM-41-Pd(OAc)$_2$ complex can be reduced to the 2N-MCM-41-Pd(0) in the presence of carbon monoxide. Oxidative addition of amide intermediate (**A**) formed in situ from the reaction of 2-iodoaniline (**1**) with acyl chloride (**2**) to 2N-MCM-41-Pd(0) generates an MCM-41-anchored arylpalladium(II) complex intermediate (**B**), which is followed by migratory insertion of CO furnishing an MCM-41-anchored acylpalladium(II) complex intermediate (**C**). Then intermediate (**C**) undergoes intramolecular cyclization by a deprotonation of the amide proton (or the proton of its enol tautomer)

in the presence of DiPEA to give intermediate (**D**). Finally, reductive elimination of intermediate (**D**) affords the desired 2-substituted 4*H*-3,1-benzoxazin-4-one (**3**) and regenerates 2N-MCM-41-Pd(0) to complete the catalytic cycle.

Scheme 3. Proposed Catalytic Cycle.



For the practical application of a heterogeneous precious metal catalyst, its ease of separation and the ability to recycle the catalyst are key factors that have to be examined. The 2N-MCM-41-Pd(OAc)$_2$ complex can be easily separated from the product and recovered via a simple filtration process. We then investigated the recycle of 2N-MCM-41-Pd(OAc)$_2$ in the cyclocarbonylation reaction of 2-iodoaniline **1a** and

benzoyl chloride **2a**. After the reaction was completed, the reaction mixture was diluted with EtOAc and filtered. The palladium catalyst was washed with distilled water and ethanol, and dried in vacuo at 100 ºC for 3 h. The recovered catalyst was used in the next run with the same substrates under the identical reaction conditions. As illustrated in Figure 1, the recovered 2N-MCM-41-Pd$(OAc)_2$ catalyst can be reused at least seven times without apparent decrease in catalytic activity and the yield of **3a** was above 94%. In addition, the Pd leaching in this supported catalyst was also examined and the Pd content of the recovered 2N-MCM-41-Pd$(OAc)_2$ catalyst after eight consecutive cycles was found to be 0.38 mmol/g based on ICP-AES analysis, showing a negligible Pd leaching.

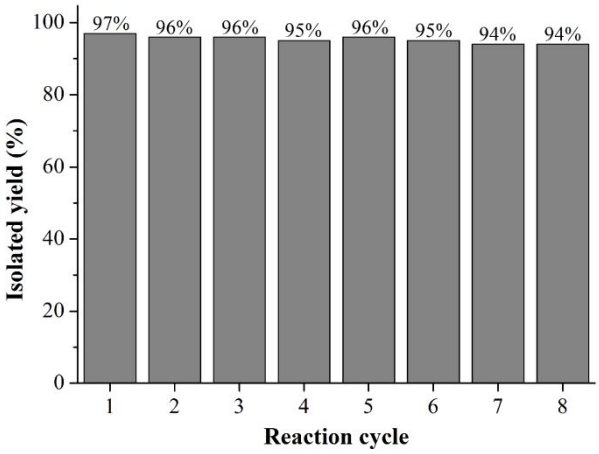


Figure 1. Recycle of the 2N-MCM-41-Pd$(OAc)_2$ Complex.

CONCLUSIONS

In conclusion, we have developed a novel, efficient and green methodology for the synthesis of 2-substituted 4*H*-3,1-benzoxazin-4-one derivatives from readily available

2-iodoanilines and acyl chlorides through a heterogeneous palladium-catalyzed cyclocarbonylation reaction in the eco-friendly solvent 2-MeTHF. In contrast to classical routes for the preparation of 2-substituted 4*H*-3,1-benzoxazin-4-ones, this heterogeneous cyclocarbonylation strategy displays many attractive features, including: (1) the scope of both acyl chloride and 2-iodoaniline substrates are broad, and a variety of aromatic or aliphatic acyl chlorides and various 2-iodoanilines are allowed; (2) the cyclocarbonylation reaction afforded a wide variety of 2-aryl(heteroaryl) or alkyl-substituted 4*H*-3,1-benzoxazin-4-ones in good to excellent yields; (3) the reaction can tolerate a wide range of functional groups; (4) 2-MeTHF derived from renewable resources can be employed as a highly efficient and green solvent; (5) this phosphine-free heterogeneous palladium catalyst can be easily obtained via a simple two-step procedure from commercially readily available materials and recovered by filtration, and recycled up to eight times without apparent decrease in catalytic activity. Our protocol not only avoids the use of toxic solvents such as THF and DMF, but also solves the basic problem of expensive palladium catalyst recovery and reuse.

EXPERIMENTAL SECTION

General Methods. 2-Iodoanilines **1a-i** and acyl chlorides **2a-u** were purchased from different commercial suppliers (TCI and Aldrich) and were used without further purification. THF and 2-MeTHF were distilled from sodium ketyl and stored under argon and other solvents were also purified by drying and distillation. Mesoporous MCM-41 material was prepared according to our previous method.[22a] Products were

isolated by column chromatography on silica gel (100-200 mesh) with a mixture of diethyl ether and light petroleum ether as eluent. The products were confirmed by the comparison of their spectra and physical data with authentic samples. ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra were recorded at 400 or 100 MHz with $CDCl_3$ as the solvent and TMS as an internal standard. Chemical shifts are reported in δ (ppm) relative to TMS. HRMS spectra were recorded on a Q-Tof spectrometer with micromass MS software using electrospray ionization (ESI). Melting points are uncorrected. The content of palladium was measured by ICP-AES analysis.

General Procedure for the Preparation of 2N-MCM-41-Pd(OAc)$_2$ Complex

A mixture of 1.50 g of 3-(2-aminoethylamino)propyltrimethoxysilane and 2.1 g of the MCM-41 in 160 mL of dry toluene was stirred at reflux (in an oil bath) for 24 h under Ar. Then the product was filtered and washed by chloroform (30 mL), and dried in vacuo at 120 °C for 6 h. The dried powdery product was then treated with 3.1 g of Me_3SiCl in 120 mL of dry toluene at room temperature for 24 h and filtered. The product was washed with diethyl ether (3 × 20 mL) and dried in vacuo at 100 °C for 3 h to afford 3.35 g of 2-aminoethylamino-modified MCM-41 material (2N-MCM-41). The nitrogen content was measured to be 1.86 mmol/g by elemental analysis.

A mixture of 2N-MCM-41(2.0 g) and 0.191 g (0.85 mmol) of $Pd(OAc)_2$ in 50 mL of dry acetone was stirred at reflux (in an oil bath) for 48 h under Ar. The solid product was collected by filtration, washed with distilled water and acetone and dried at 80 °C in vacuo under Ar for 6 h to deliver 2.09 g of a light yellow palladium complex [2N-MCM-41-$Pd(OAc)_2$]. The nitrogen and palladium contents were

measured to be 1.71 mmol/g and 0.39 mmol/g, respectively.

General Procedure for the Heterogeneous Palladium-Catalyzed Cyclocarbonylative Synthesis of 2-Substituted 4*H*-3,1-Benzoxazin-4-ones

A mixture of *o*-iodoaniline **1** (1.0 mmol), acyl chloride **2** (1.0 mmol), 2N-MCM-41-$Pd(OAc)_2$ (2 mol%), DiPEA (3.0 mmol), and dry 2-MeTHF (5.0 mL) was reacted in an autoclave at 20 bar of carbon monoxide at 100 ºC (in a heating mantle) for 24 h. Upon completion of the reaction, the reaction mixture was cooled to ambient temperature and excess CO was released carefully. Ethyl acetate (15 mL) was then added and the resulting mixture was filtered. The 2N-MCM-41-$Pd(OAc)_2$ catalyst was washed with distilled water (2 × 5 mL) and ethanol (2 × 5 mL), followed by drying in vacuo at 100 ºC for 3 h and reused in the next run. The filtrate was washed with water (10 mL) and dried over anhydrous Na_2SO_4 and concentrated by rotary evaporation. The residue was purified by silica gel column chromatography (diethyl ether–light petroleum ether = 1:1) to afford the desired products **3**.

2-Phenyl-4H-benzo[d][1,3]oxazin-4-one ***(3a)***.[16c] The product was isolated via column chromatography (eluent diethyl ether/petroleum ether = 1:1 (v/v)) as a white solid (216.5 mg, 97%). m.p. = 123-125 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.27 (d, J = 7.2 Hz, 2H), 8.20 (d, J = 7.6 Hz, 1H), 7.81-7.76 (m, 1H), 7.65 (d, J = 8.0 Hz, 1H), 7.55 (t, J = 7.4 Hz, 1H), 7.51-7.45 (m, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 159.5, 157.1, 147.0, 136.5, 132.6, 130.2, 128.7, 128.6, 128.3, 128.2, 127.2, 117.0.

2-(p-Tolyl)-4H-benzo[d][1,3]oxazin-4-one ***(3b)***.[24] The product was isolated via column chromatography (eluent diethyl ether/petroleum ether = 1:1 (v/v)) as a white

solid (220.7 mg, 93%). m.p. = 137-139 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (d, J = 7.6 Hz, 1H), 8.11 (d, J = 8.0 Hz, 2H), 7.77-7.72 (m, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.43 (t, J = 7.6 Hz, 1H), 7.23 (d, J = 8.0 Hz, 2H), 2.37 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 159.5, 157.2, 147.1, 143.3, 136.4, 129.4, 128.5, 128.3, 127.9, 127.4, 127.1, 116.9, 21.7.

2-(4-Methoxyphenyl)-4H-benzo[d][1,3]oxazin-4-one ***(3c)***.[16e] The product was isolated via column chromatography (eluent diethyl ether/petroleum ether = 1:1 (v/v)) as a white solid (227.9 mg, 90%). m.p. = 151-152 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22 (d, J = 8.8 Hz, 2H), 8.18 (dd, J = 8.0, 1.2 Hz, 1H), 7.80-7.75 (m, 1H), 7.61 (d, J = 8.0 Hz, 1H), 7.45 (t, J = 7.6 Hz, 1H), 6.97 (d, J = 8.8 Hz, 2H), 3.87 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 163.3, 159.7, 157.1, 147.3, 136.4, 130.3, 128.5, 127.7, 126.9, 122.5, 116.7, 114.1, 55.5.

2-(4-Chlorophenyl)-4H-benzo[d][1,3]oxazin-4-one ***(3d)***.[24] The product was isolated via column chromatography (eluent diethyl ether/petroleum ether = 1:1 (v/v)) as a white solid (221.6 mg, 86%). m.p. = 190 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24-8.21 (m, 3H), 7.82 (t, J = 7.6 Hz, 1H), 7.66 (d, J = 8.4 Hz, 1H), 7.51 (t, J = 7.6 Hz, 1H), 7.46 (d, J = 8.4 Hz, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 159.2, 156.2, 146.8, 139.1, 136.6, 129.6, 129.1, 128.7, 128.6, 128.4, 127.2, 117.0.

2-(4-(Trifluoromethyl)phenyl)-4H-benzo[d][1,3]oxazin-4-one ***(3e)***.[16e] The product was isolated via column chromatography (eluent diethyl ether/petroleum ether = 1:1 (v/v)) as a white solid (235.8 mg, 81%). m.p. = 80-82 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.38 (d, J = 8.4 Hz, 2H), 8.21 (d, J = 8.0 Hz, 1H), 7.85-7.80 (m, 1H), 7.73

(d, J = 8.4 Hz, 2H), 7.67 (d, J = 8.0 Hz, 1H), 7.53 (t, J = 7.6 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 158.9, 155.6, 146.4, 136.7, 133.9 (q, J = 32.6 Hz), 133.5, 128.9, 128.7, 128.6, 127.4, 125.7 (q, J = 3.7 Hz), 123.7 (q, J = 271.0 Hz), 117.1.

Methyl 4-(4-oxo-4H-benzo[d][1,3]oxazin-2-yl)benzoate ***(3f)***. The product was isolated via column chromatography (eluent diethyl ether/petroleum ether = 1:1 (v/v)) as a white solid (219.4 mg, 78%). m.p. = 166-167 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 8.38 (d, J = 8.4 Hz, 2H), 8.26 (dd, J = 7.8, 1.0 Hz, 1H), 8.17 (d, J = 8.4 Hz, 2H), 7.87-7.83 (m, 1H), 7.72 (d, J = 8.0 Hz, 1H), 7.59-7.54 (m, 1H), 3.97 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 166.3, 159.2, 156.2, 146.7, 136.7, 134.2, 133.6, 129.9, 128.8, 128.7, 128.3, 127.5, 117.2, 52.4. HRMS (ESI) *m/z*: $[M]^+$ calcd for $C_{16}H_{11}NO_4$, 281.0688; found, 281.0693.

2-(4-Nitrophenyl)-4H-benzo[d][1,3]oxazin-4-one ***(3g)***.[13c] The product was isolated via column chromatography (eluent diethyl ether/petroleum ether = 1:1 (v/v)) as a yellow solid (193.1 mg, 72%). m.p. = 204-205 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 8.51 (d, J = 9.2 Hz, 2H), 8.37 (d, J = 9.2 Hz, 2H), 8.28 (dd, J = 7.8, 1.4 Hz, 1H), 7.92-7.87 (m, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.63-7.58 (m, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 158.5, 155.0, 150.2, 146.3, 136.9, 135.9, 129.3, 129.2, 128.9, 127.7, 123.9, 117.2.

2-(2-Chlorophenyl)-4H-benzo[d][1,3]oxazin-4-one ***(3h)***.[12b] The product was isolated via column chromatography (eluent diethyl ether/petroleum ether = 1:1 (v/v)) as a white solid (201.1 mg, 78%). m.p. = 137-139 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 8.26 (d, J = 7.8 Hz, 1H), 7.90 (dd, J = 7.8, 1.4 Hz, 1H), 7.87-7.82 (m, 1H), 7.71 (d, J

= 8.0 Hz, 1H), 7.57 (t, *J* = 7.6 Hz, 1H), 7.53-7.51 (m, 1H), 7.46 (td, *J* = 7.6, 1.6 Hz, 1H), 7.39 (td, *J* = 7.6, 1.2 Hz, 1H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 159.2, 156.6, 146.4, 136.7, 133.5, 132.4, 131.5, 131.1, 130.3, 129.0, 128.6, 127.4, 126.9, 117.0.

2-(2-Methoxyphenyl)-4H-benzo[d][1,3]oxazin-4-one ***(3i)***.[24] The product was isolated via column chromatography (eluent diethyl ether/petroleum ether = 1:1 (v/v)) as a white solid (217.8 mg, 86%). m.p. = 150-152 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.88-7.80 (m, 2H), 7.70 (d, *J* = 8.0 Hz, 1H), 7.55-7.48 (m, 2H), 7.09-7.02 (m, 2H), 3.93 (s, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 159.9, 158.7, 157.8, 147.1, 136.4, 133.2, 131.3, 128.4, 128.3, 127.3, 120.6, 117.0, 112.2, 56.1.

2-(Naphthalen-1-yl)-4H-benzo[d][1,3]oxazin-4-one ***(3j)***.[25] The product was isolated via column chromatography (eluent diethyl ether/petroleum ether = 1:1 (v/v)) as a white solid (243.2 mg, 89%). m.p. = 138 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.13 (d, *J* = 8.8 Hz, 1H), 8.26 (d, *J* = 7.2 Hz, 1H), 8.21 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.97 (d, *J* = 8.4 Hz, 1H), 7.86 (d, *J* = 8.4 Hz, 1H), 7.79-7.75 (m, 1H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.63-7.59 (m, 1H), 7.54-7.45 (m, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 159.7, 157.5, 146.8, 136.5, 134.1, 133.2, 130.8, 130.1, 128.9, 128.6, 128.5, 127.9, 127.4, 126.9, 126.4, 125.9, 124.8, 117.0.

2-(Furan-2-yl)-4H-benzo[d][1,3]oxazin-4-one ***(3k)***.[26] The product was isolated via column chromatography (eluent diethyl ether/petroleum ether = 1:1 (v/v)) as a yellow solid (189.7 mg, 89%). m.p. = 102 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.83-7.78 (m, 1H), 7.70-7.67 (m, 2H), 7.49 (t, *J* = 7.6 Hz, 1H), 7.35

(d, J = 3.6 Hz, 1H), 6.62 (dd, J = 3.6, 1.6 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 158.5, 149.7, 147.1, 146.6, 144.4, 136.7, 128.7, 128.2, 127.1, 117.2, 116.9, 112.5.

2-(Thiophen-2-yl)-4H-benzo[d][1,3]oxazin-4-one ***(3l)***.[25] The product was isolated via column chromatography (eluent diethyl ether/petroleum ether = 1:1 (v/v)) as a white solid (197.2 mg, 86%). m.p. = 133-135 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 8.22 (dd, J = 7.8, 1.0 Hz, 1H), 7.97 (dd, J = 3.8, 1.0 Hz, 1H), 7.81 (t, J = 7.4 Hz, 1H), 7.65-7.60 (m, 2H), 7.49 (t, J = 7.4 Hz, 1H), 7.18 (dd, J = 5.0, 3.8 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 159.1, 153.8, 147.1, 136.6, 134.3, 132.4, 131.8, 128.8, 128.3, 128.0, 126.9, 116.8.

2-Methyl-4H-benzo[d][1,3]oxazin-4-one ***(3m)***.[16c] The product was isolated via column chromatography (eluent diethyl ether/petroleum ether = 1:1 (v/v)) as a white solid (151.5 mg, 94%). m.p. = 81-82 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 8.12 (dd, J = 8.0, 1.2 Hz, 1H), 7.75-7.70 (m, 1H), 7.48 (d, J = 8.0 Hz, 1H), 7.43 (t, J = 7.6 Hz, 1H), 2.40 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 160.3, 159.7, 146.4, 136.5, 128.4, 128.2, 126.4, 116.7, 21.3.

2-Benzyl-4H-benzo[d][1,3]oxazin-4-one ***(3n)***.[16c] The product was isolated via column chromatography (eluent diethyl ether/petroleum ether = 1:1 (v/v)) as a yellow solid (147.1 mg, 62%). m.p. = 86-88 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 8.16 (dd, J = 7.6, 0.8 Hz, 1H), 7.79 (td, J = 8.2, 1.2 Hz, 1H), 7.58 (d, J = 8.0 Hz, 1H), 7.48 (t, J = 7.4 Hz, 1H), 7.42 (d, J = 7.6 Hz, 2H), 7.35 (t, J = 7.2 Hz, 2H), 7.30-7.25 (m, 1H), 3.98 (s, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 161.2, 159.6, 146.4, 136.5, 134.2, 129.3, 128.8, 128.5, 128.4, 127.5, 126.8, 116.8, 41.6.

2-(4-Chlorobenzyl)-4H-benzo[d][1,3]oxazin-4-one ***(3o)***.[16c] The product was isolated via column chromatography (eluent diethyl ether/petroleum ether = 1:1 (v/v)) as a yellow solid (184.7 mg, 68%). m.p. = 143-145 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (d, J = 8.0 Hz, 1H), 7.79 (td, J = 8.4, 1.2 Hz, 1H), 7.58 (d, J = 8.0 Hz, 1H), 7.50 (t, J = 7.6 Hz, 1H), 7.35 (d, J = 8.4 Hz, 2H), 7.31 (d, J = 8.4 Hz, 2H), 3.95 (s, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 160.7, 159.4, 146.3, 136.6, 133.5, 132.6, 130.7, 129.0, 128.6, 128.5, 126.8, 116.8, 40.9.

2-(2,3-Dichlorobenzyl)-4H-benzo[d][1,3]oxazin-4-one ***(3p)***. The product was isolated via column chromatography (eluent diethyl ether/petroleum ether = 1:1 (v/v)) as a yellow solid (214.3 mg, 70%). m.p. = 125-127 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18 (dd, J = 8.0, 1.2 Hz, 1H), 7.78 (t, J = 7.6 Hz, 1H), 7.54 (d, J = 8.0 Hz, 1H), 7.51 (t, J = 7.6 Hz, 1H), 7.44 (dd, J = 8.0, 1.6 Hz, 1H), 7.33-7.30 (m, 1H), 7.21 (t, J = 7.8 Hz, 1H), 4.19 (s, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 159.5, 159.4, 146.2, 136.6, 134.6, 133.6, 133.1, 129.8, 129.7, 128.6, 128.5, 127.4, 126.9, 116.8, 39.8. HRMS (ESI) *m/z*: $[M]^+$ calcd for $C_{15}H_9Cl_2NO_2$, 305.0010; found, 305.0017.

2-Benzhydryl-4H-benzo[d][1,3]oxazin-4-one ***(3q)***.[16c] The product was isolated via column chromatography (eluent diethyl ether/petroleum ether = 1:1 (v/v)) as a yellow solid (285.1 mg, 91%). m.p. = 120-122 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (dd, J = 7.8, 1.0 Hz, 1H), 7.60 (t, J = 7.2 Hz, 1H), 7.45 (d, J = 8.0 Hz, 1H), 7.35-7.27 (m, 5H), 7.24-7.19 (m, 4H), 7.18-7.13 (m, 2H), 5.27 (s, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 162.3, 159.5, 146.4, 138.6, 136.5, 129.0, 128.8, 128.6, 128.5, 127.6, 127.2, 117.0, 57.1.

2-(1-Phenylpropyl)-4H-benzo[d][1,3]oxazin-4-one ***(3r)***.[16c] The product was isolated via column chromatography (eluent diethyl ether/petroleum ether = 1:1 (v/v)) as a yellow solid (249.4 mg, 94%). m.p. = 135-136 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (dd, J = 8.0, 1.2 Hz, 1H), 7.75 (td, J = 8.4, 1.6Hz, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.47-7.42 (m, 3H), 7.35-7.30 (m, 2H), 7.27-7.23 (m, 1H), 3.78 (t, J = 7.8 Hz, 1H), 2.37-2.30 (m, 1H), 2.06-2.01 (m, 1H), 0.97 (t, J = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 163.6, 159.7, 146.5, 139.2, 136.4, 128.8, 128.4, 128.2, 127.5, 126.9, 117.0, 53.3, 26.5, 12.2.

2-(tert-Butyl)-4H-benzo[d][1,3]oxazin-4-one ***(3s)***.[16c] The product was isolated via column chromatography (eluent diethyl ether/petroleum ether = 1:1 (v/v)) as a green solid (195.1 mg, 96%). m.p. = 117-118 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10-8.07 (m, 1H), 7.71-7.66 (m, 1H), 7.49 (dd, J = 8.0, 1.2 Hz, 1H), 7.42-7.37 (m, 1H), 1.32 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 168.2, 160.1, 146.6, 136.3, 128.3, 128.0, 126.9, 116.8, 37.9, 27.7.

(E)-2-Styryl-4H-benzo[d][1,3]oxazin-4-one ***(3t)***.[16c] The product was isolated via column chromatography (eluent diethyl ether/petroleum ether = 1:1 (v/v)) as a yellow solid (239.3 mg, 96%). m.p. = 144-146 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20 (dd, J = 8.0, 1.2 Hz, 1H), 7.83 (d, J = 16.4 Hz, 1H), 7.79 (t, J = 7.0 Hz, 1H), 7.61-7.55 (m, 3H), 7.51-7.47 (m, 1H), 7.42-7.36 (m, 3H), 6.77 (d, J = 16.0 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 159.3, 157.3, 147.2, 142.0, 136.6, 134.7, 130.3, 129.0, 128.7, 128.2, 128.0, 127.0, 118.9, 117.0.

6-Methyl-2-phenyl-4H-benzo[d][1,3]oxazin-4-one ***(3u)***.[27] The product was isolated

via column chromatography (eluent diethyl ether/petroleum ether = 1:1 (v/v)) as a white solid (220.7 mg, 93%). m.p. = 114-115 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.29 (d, J = 7.6 Hz, 2H), 8.03 (s, 1H), 7.64-7.48 (m, 5H), 2.48 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 159.8, 156.4, 144.9, 138.7, 137.8, 132.4, 130.4, 128.7, 128.2, 127.0, 116.7, 21.3.

6-Methyl-2-(p-tolyl)-4H-benzo[d][1,3]oxazin-4-one ***(3v)***. The product was isolated via column chromatography (eluent diethyl ether/petroleum ether = 1:1 (v/v)) as a white solid (226.2 mg, 90%). m.p. = 165-167 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 (d, J = 7.2 Hz, 2H), 7.99 (s, 1H), 7.59 (d, J = 8.4 Hz, 1H), 7.53 (d, J = 8.4 Hz, 1H), 7.28 (d, J = 8.0 Hz, 2H), 2.46 (s, 3H), 2.41 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 159.8, 156.6, 145.0, 143.1, 138.4, 137.7, 129.5, 128.2, 128.1, 127.6, 126.9, 116.6, 21.7, 21.3. HRMS (ESI) *m/z*: $[M]^+$ calcd for $C_{16}H_{13}NO_2$, 251.0946; found, 251.0938.

6-Methyl-2-(naphthalen-1-yl)-4H-benzo[d][1,3]oxazin-4-one ***(3w)***. The product was isolated via column chromatography (eluent diethyl ether/petroleum ether = 1:1 (v/v)) as a yellow solid (255.7 mg, 89%). m.p. = 112-114 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.05 (d, J = 8.4 Hz, 1H), 8.19 (d, J = 7.2 Hz, 1H), 7.96 (s, 1H), 7.92 (d, J = 8.0 Hz, 1H), 7.81 (d, J = 8.4 Hz, 1H), 7.58-7.51 (m, 3H), 7.49-7.43 (m, 2H), 2.39 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 159.9, 156.9, 144.7, 139.1, 137.8, 134.1, 133.0, 130.8, 129.9, 128.8, 128.1, 127.8, 127.2, 127.1, 126.4, 125.9, 124.8, 116.7, 21.4. HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{19}H_{14}NO_2$, 288.1025; found, 288.1014.

6-Methyl-2-(1-phenylpropyl)-4H-benzo[d][1,3]oxazin-4-one ***(3x)***. The product was isolated via column chromatography (eluent diethyl ether/petroleum ether = 1:1 (v/v))

as a yellow solid (256.9 mg, 92%). m.p. = 98-99 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (s, 1H), 7.54 (dd, J = 8.4, 1.6 Hz, 1H), 7.48 (d, J = 8.0 Hz, 1H), 7.44 (d, J = 7.2 Hz, 2H), 7.32 (t, J = 7.6 Hz, 2H), 7.25 (t, J = 7.2 Hz, 1H), 3.76 (t, J = 7.8 Hz, 1H), 2.42 (s, 3H), 2.35-2.29 (m, 1H), 2.08-2.01 (m, 1H), 0.96 (t, J = 7.4 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 162.8, 160.0, 144.3, 139.3, 138.6, 137.6, 128.7, 128.2, 128.0, 127.5, 126.7, 116.7, 53.2, 26.5, 21.2, 12.2. HRMS (ESI) *m/z*: $[M]^+$ calcd for $C_{18}H_{17}NO_2$, 279.1259; found, 279.1257.

2-Benzyl-6-methyl-4H-benzo[d][1,3]oxazin-4-one ***(3y)***.[16c] The product was isolated via column chromatography (eluent diethyl ether/petroleum ether = 1:1 (v/v)) as a yellow solid (201.1 mg, 80%). m.p. = 187-189 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (s, 1H), 7.59 (dd, J = 8.2, 1.8 Hz, 1H), 7.48 (d, J = 8.4 Hz, 1H), 7.42 (d, J = 7.2 Hz, 2H), 7.36-7.32 (m, 2H), 7.29 (d, J = 7.2 Hz, 1H), 3.97 (s, 2H), 2.45 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 160.4, 159.9, 144.3, 138.8, 137.7, 134.4, 129.3, 128.8, 128.0, 127.4, 126.6, 116.5, 41.6, 21.2.

7-Fluoro-2-phenyl-4H-benzo[d][1,3]oxazin-4-one ***(3z)***. The product was isolated via column chromatography (eluent diethyl ether/petroleum ether = 1:1 (v/v)) as a white solid (214.7 mg, 89%). m.p. = 132-134 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.31-8.26 (m, 2H), 8.24 (dd, J = 8.8, 6.0 Hz, 1H), 7.58 (t, J = 7.4 Hz, 1H), 7.50 (t, J = 7.4 Hz, 2H), 7.33 (dd, J = 9.2, 2.4 Hz, 1H), 7.23-7.18 (m, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 167.8 (d, J = 256.4 Hz), 158.6, 158.4, 149.5 (d, J = 13.3 Hz), 133.0, 131.3 (d, J = 10.8 Hz), 129.9, 128.8, 128.5, 116.6 (d, J = 23.2 Hz), 113.6, 113.3 (d, J = 22.4 Hz). HRMS (ESI) *m/z*: $[M]^+$ calcd for $C_{14}H_8FNO_2$, 241.0539; found, 241.0533.

7-Fluoro-2-(1-phenylpropyl)-4H-benzo[d][1,3]oxazin-4-one ***(3a')***. The product was isolated via column chromatography (eluent diethyl ether/petroleum ether = 1:1 (v/v)) as a yellow solid (246.4 mg, 87%). m.p. = 90-92 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (dd, J = 8.8, 6.0 Hz, 1H), 7.42 (d, J = 7.2 Hz, 2H), 7.33 (t, J = 7.2 Hz, 2H), 7.29-7.26 (m, 2H), 7.20-7.16 (m, 1H), 3.77 (t, J = 7.8 Hz, 1H), 2.35-2.28 (m, 1H), 2.08-2.00 (m, 1H), 0.97 (t, J = 7.4 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 167.7 (d, J = 256.3 Hz), 165.1, 158.8, 149.0 (d, J = 13.3 Hz), 138.9, 131.2 (d, J = 10.8 Hz), 128.8, 128.2, 127.7, 116.7 (d, J = 23.1 Hz), 113.6 (d, J = 2.3 Hz), 113.1 (d, J = 22.5 Hz), 53.3, 26.5, 12.2. HRMS (ESI) *m/z*: $[M]^+$ calcd for $C_{17}H_{14}FNO_2$, 283.1009; found, 283.1014.

7-Chloro-2-phenyl-4H-benzo[d][1,3]oxazin-4-one ***(3b')***. The product was isolated via column chromatography (eluent diethyl ether/petroleum ether = 1:1 (v/v)) as a white solid (234.5 mg, 91%). m.p. = 190-192 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.28 (d, J = 7.6 Hz, 2H), 8.15 (d, J = 8.4 Hz, 1H), 7.68 (d, J = 1.6 Hz, 1H), 7.59 (t, J = 7.4 Hz, 1H), 7.51 (t, J = 7.6 Hz, 2H), 7.46 (dd, J = 8.4, 2.0 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 158.8, 158.3, 148.1, 143.0, 133.0, 129.9, 129.8, 128.8, 128.7, 128.5, 127.0, 115.4. HRMS (ESI) *m/z*: $[M]^+$ calcd for $C_{14}H_8ClNO_2$, 257.0244; found, 257.0251.

7-Chloro-2-(1-phenylpropyl)-4H-benzo[d][1,3]oxazin-4-one ***(3c')***. The product was isolated via column chromatography (eluent diethyl ether/petroleum ether = 1:1 (v/v)) as a yellow solid (281.7 mg, 94%). m.p. = 150-151 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (d, J = 8.4 Hz, 1H), 7.59 (d, J = 1.6 Hz, 1H), 7.43-7.36 (m, 3H), 7.32

(t, J = 7.4 Hz, 2H), 7.25 (t, J = 7.2 Hz, 1H), 3.76 (t, J = 7.8 Hz, 1H), 2.35-2.27 (m, 1H), 2.07-1.99 (m, 1H), 0.96 (t, J = 7.4 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 165.1, 158.9, 147.5, 142.8, 138.9, 129.7, 128.8, 128.7, 128.2, 127.7, 126.8, 115.4, 53.2, 26.5, 12.2. HRMS (ESI) *m/z*: $[M]^+$ calcd for $C_{17}H_{14}ClNO_2$, 299.0713; found, 299.0716.

2-Benzhydryl-7-chloro-4H-benzo[d][1,3]oxazin-4-one ***(3d')***. The product was isolated via column chromatography (eluent diethyl ether/petroleum ether = 1:1 (v/v)) as a white solid (302.6 mg, 87%). m.p. = 167-169 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.98 (d, J = 2.0 Hz, 1H), 7.55 (dd, J = 8.8, 2.4 Hz, 1H), 7.40 (d, J = 8.8 Hz, 1H), 7.29-7.13 (m, 10H), 5.26 (s, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 162.7, 158.5, 144.8, 138.3, 136.8, 134.2, 129.0, 128.8, 127.8, 127.7, 118.1, 57.0. HRMS (ESI) *m/z*: $[M]^+$ calcd for $C_{21}H_{14}ClNO_2$, 347.0713; found, 347.0708.

6-Chloro-2-(furan-2-yl)-4H-benzo[d][1,3]oxazin-4-one ***(3e')***. The product was isolated via column chromatography (eluent diethyl ether/petroleum ether = 1:1 (v/v)) as a white solid (217.9 mg, 88%). m.p. = 161-163 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 8.13 (d, J = 8.4 Hz, 1H), 7.72-7.68 (m, 2H), 7.46 (dd, J = 8.4, 1.2 Hz, 1H), 7.39 (d, J = 3.2 Hz, 1H), 6.64 (dd, J = 2.8, 0.8 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 157.8, 150.8, 147.8, 147.5, 144.2, 143.2, 130.0, 128.8, 126.9, 118.0, 115.3, 112.7. HRMS (ESI) *m/z*: $[M]^+$ calcd for $C_{12}H_6ClNO_3$, 247.0036; found, 247.0043.

6-Chloro-2-(1-phenylpropyl)-4H-benzo[d][1,3]oxazin-4-one ***(3f')***.[16c] The product was isolated via column chromatography (eluent diethyl ether/petroleum ether = 1:1 (v/v)) as a yellow solid (284.8 mg, 95%). m.p. = 119-121 °C. ^1H NMR (400 MHz,

$CDCl_3$): δ 8.06 (d, J = 2.4 Hz, 1H), 7.66 (dd, J = 8.8, 2.4 Hz, 1H), 7.53 (d, J = 8.4 Hz, 1H), 7.42 (d, J = 7.2 Hz, 2H), 7.32 (t, J = 7.4 Hz, 2H), 7.25 (t, J = 7.2 Hz, 1H), 3.76 (t, J = 7.8 Hz, 1H), 2.34-2.27 (m, 1H), 2.07-1.99 (m, 1H), 0.96 (t, J = 7.4 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 163.9, 158.6, 144.9, 138.9, 136.6, 133.8, 128.8, 128.5, 128.2, 127.7, 127.6, 118.1, 53.2, 26.5, 12.2.

7-Bromo-2-phenyl-4H-benzo[d][1,3]oxazin-4-one ***(3g')***.[13c] The product was isolated via column chromatography (eluent diethyl ether/petroleum ether = 1:1 (v/v)) as a yellow solid (268.9 mg, 89%). m.p. = 172-174 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 8.29 (d, J = 7.6 Hz, 2H), 8.07 (d, J = 8.4 Hz, 1H), 7.87 (d, J = 1.2 Hz, 1H), 7.62 (dd, J = 8.4, 1.6 Hz, 1H), 7.58 (t, J = 7.2 Hz, 1H), 7.51 (t, J = 7.6 Hz, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 158.9, 158.3, 148.0, 133.0, 131.6, 131.5, 130.2, 129.9, 129.8, 128.8, 128.5, 115.8.

7-Bromo-2-(1-phenylpropyl)-4H-benzo[d][1,3]oxazin-4-one ***(3h')***. The product was isolated via column chromatography (eluent diethyl ether/petroleum ether = 1:1 (v/v)) as a yellow solid (313.2 mg, 91%). m.p. = 89-91 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.87 (d, J = 8.4 Hz, 1H), 7.69 (d, J = 1.6 Hz, 1H), 7.46 (dd, J = 8.4, 2.0 Hz, 1H), 7.32 (d, J = 7.6 Hz, 2H), 7.23 (t, J = 7.4 Hz, 2H), 7.19-7.13 (m, 1H), 3.66 (t, J = 7.6 Hz, 1H), 2.24-2.18 (m, 1H), 1.97-1.91 (m, 1H), 0.87 (t, J = 7.4 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 165.1, 159.1, 147.5, 138.9, 131.6, 131.4, 129.9, 129.7, 128.8, 128.2, 127.7, 115.8, 53.2, 26.5, 12.2. HRMS (ESI) *m/z*: $[M]^+$ calcd for $C_{17}H_{14}BrNO_2$, 343.0208; found, 343.0206.

(E)-7-Bromo-2-styryl-4H-benzo[d][1,3]oxazin-4-one ***(3i')***. The product was

isolated via column chromatography (eluent diethyl ether/petroleum ether = 1:1 (v/v)) as a yellow solid (288.6 mg, 88%). m.p. = 155-156 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (d, J = 8.4 Hz, 1H), 7.86 (d, J = 16.0 Hz, 1H), 7.77 (d, J = 1.2 Hz, 1H), 7.62-7.56 (m, 3H), 7.45-7.39 (m, 3H), 6.76 (d, J = 16.0 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 158.8, 158.5, 148.2, 143.0, 134.5, 131.6, 131.5, 130.6, 129.9, 129.1, 128.2, 118.6, 115.7. HRMS (ESI) *m/z*: $[M]^+$ calcd for $C_{16}H_{10}BrNO_2$, 326.9895; found, 326.9892.

6-Bromo-2-phenyl-4H-benzo[d][1,3]oxazin-4-one ***(3j')***.[13c] The product was isolated via column chromatography (eluent diethyl ether/petroleum ether = 1:1 (v/v)) as a white solid (268.9 mg, 89%). m.p. = 179-181 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.36 (d, J = 2.0 Hz, 1H), 8.29 (d, J = 7.6 Hz, 2H), 7.91 (dd, J = 8.8, 2.0 Hz, 1H), 7.61-7.55 (m, 2H), 7.52 (t, J = 7.6 Hz, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 158.3, 157.5, 145.9, 139.7, 132.9, 131.1, 129.9, 128.9, 128.8, 128.4, 121.5, 118.4.

6-Bromo-2-(1-phenylpropyl)-4H-benzo[d][1,3]oxazin-4-one ***(3k')***. The product was isolated via column chromatography (eluent diethyl ether/petroleum ether = 1:1 (v/v)) as a yellow solid (309.7 mg, 90%). m.p. = 96-98 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25 (d, J = 2.4 Hz, 1H), 7.85 (dd, J = 8.8, 2.4 Hz, 1H), 7.48 (d, J = 8.4 Hz, 1H), 7.41 (d, J = 7.2 Hz, 2H), 7.33 (t, J = 7.4 Hz, 2H), 7.28-7.24 (m, 1H), 3.76 (t, J = 7.8 Hz, 1H), 2.35-2.26 (m, 1H), 2.08-1.99 (m, 1H), 0.96 (t, J = 7.4 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 164.1, 158.5, 145.3, 139.5, 138.8, 130.9, 128.8, 128.7, 128.2, 127.7, 121.5, 118.4, 53.2, 26.4, 12.2. HRMS (ESI) *m/z*: $[M]^+$ calcd for $C_{17}H_{14}BrNO_2$, 343.0208; found, 343.0211.

4-Oxo-2-(1-phenylpropyl)-4H-benzo[d][1,3]oxazine-6-carbonitrile ***(3l')***.[16c] The product was isolated via column chromatography (eluent diethyl ether/petroleum ether = 1:1 (v/v)) as a yellow solid (185.8 mg, 64%). m.p. = 145-147 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.40 (d, J = 1.6 Hz, 1H), 7.97 (dd, J = 8.4, 2.0 Hz, 1H), 7.71 (d, J = 8.8 Hz, 1H), 7.42 (d, J = 7.2 Hz, 2H), 7.33 (t, J = 7.6 Hz, 2H), 7.26 (t, J = 7.2 Hz, 1H), 3.80 (t, J = 7.8 Hz, 1H), 2.37-2.30 (m, 1H), 2.10-2.01 (m, 1H), 0.97 (t, J = 7.4 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 166.6, 157.7, 149.3, 138.7, 138.4, 133.1, 128.9, 128.3, 128.2, 127.8, 117.8, 117.2, 112.0, 53.3, 26.4, 12.2.

2-(2-Chlorophenyl)-6-nitro-4H-benzo[d][1,3]oxazin-4-one ***(3m')***. The product was isolated via column chromatography (eluent diethyl ether/petroleum ether = 1:1 (v/v)) as a yellow solid (196.5 mg, 65%). m.p. = 130-131 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.11 (s, 1H), 8.66 (dd, J = 9.0, 1.4 Hz, 1H), 8.00 (d, J = 7.6 Hz, 1H), 7.89 (d, J = 8.8 Hz, 1H), 7.60-7.50 (m, 2H), 7.45 (t, J = 7.4 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 159.3, 157.4, 150.7, 147.0, 134.0, 133.3, 131.9, 131.6, 130.8, 129.2, 129.1, 127.1, 124.7, 117.5. HRMS (ESI) *m/z*: $[M]^+$ calcd for $C_{14}H_7ClN_2O_4$, 302.0094; found, 302.0097.

6-Nitro-2-(1-phenylpropyl)-4H-benzo[d][1,3]oxazin-4-one ***(3n')***. The product was isolated via column chromatography (eluent diethyl ether/petroleum ether = 1:1 (v/v)) as a yellow solid (211.2 mg, 68%). m.p. = 146-148 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.99 (d, J = 2.4 Hz, 1H), 8.58 (dd, J = 8.8, 2.8 Hz, 1H), 7.77 (d, J = 8.8 Hz, 1H), 7.43 (d, J = 7.6 Hz, 2H), 7.35 (t, J = 7.4 Hz, 2H), 7.31-7.26 (m, 1H), 3.82 (t, J = 7.8 Hz, 1H), 2.38-2.31 (m, 1H), 2.12-2.04 (m, 1H), 0.98 (t, J = 7.4 Hz, 3H). ^{13}C{^{1}H}

NMR (100 MHz, $CDCl_3$): δ 167.1, 157.9, 150.8, 146.6, 138.3, 130.6, 128.9, 128.6, 128.2, 127.9, 124.6, 117.5, 53.4, 26.4, 12.2. HRMS (ESI) *m/z*: $[M]^+$ calcd for $C_{17}H_{14}N_2O_4$, 310.0954; found, 310.0953.

6-Bromo-2-(4-tert-butylphenyl)-4H-benzo[d][1,3]oxazin-4-one ***(3o')***.[2c] The product was isolated via column chromatography (eluent diethyl ether/petroleum ether = 1:1 (v/v)) as a white solid (315.2 mg, 88%). m.p. = 142-143 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.33 (d, J = 2.0 Hz, 1H), 8.19 (d, J = 8.4 Hz, 2H), 7.87 (dd, J = 8.6, 2.2 Hz, 1H), 7.54 (d, J = 8.4 Hz, 1H), 7.52 (d, J = 8.8 Hz, 2H), 1.37 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 158.4, 157.6, 156.8, 146.1, 139.6, 131.0, 128.8, 128.3, 127.1, 125.8, 121.1, 118.3, 35.2, 31.1.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org.

Copies of ^{1}H and ^{13}C NMR spectra of all compounds (PDF).

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Notes

The authors declare no competing financial interest.

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