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Palladium-Catalyzed One-Step Synthesis of Isoindole-1,3-diones by Carbonylative Cyclization of *o*-Halobenzoates and Primary Amines

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Abstract

The palladium-catalyzed aminocarbonylation of *o*-halobenzoates produces 2-substituted isoindole-1,3-diones in good yields. This methodology provides a good one-step approach to this important class of heterocycles and tolerates a variety of functional groups, including methoxy, alcohol, ketone, and nitro groups.

Introduction

Isoindole-1,3-diones, commonly known as phthalimides, are key structural units of a variety of biologically important compounds, many of which are pharmaceutically significant. The drug thalidomide [2-(2,6-dioxo-3-piperidyl)isoindoline-1,3-dione], was originally developed as a sedative, an alternative to barbiturates, but was withdrawn from the market in the 1960s, because it displayed teratogenic properties.¹ Recently, interest in this compound has increased, because of its interesting antiinflammatory and antiangiogenic² properties and its possible use in the treatment of acquired immunodeficiency syndrome (AIDS) caused by the human immunodeficiency virus (HIV),^{3,4} leprosy,⁵ and other diseases.^{6–8} The isoindole-1,3-dione *N*-phthaloyl-L-glutamic acid is a selective glutamate receptor agonist,⁹ while 1,8-naphthalimide is known for its cytotoxicity against the growth of human cancer cultured cells.¹⁰ Some isoindole-1,3-dione derivatives are active in reducing the growth of colon adenocarcinoma, osteosarcoma, and KB nasopharynx.¹¹ Isoindole-1,3-diones are also known for their antiviral,¹² antiinflammatory,¹³ Chk1 inhibitory,¹⁴ sedative,¹⁵ bactericidal, and fungicidal¹⁶ properties. They also find important applications as synthetic intermediates in the dye,¹⁷ pesticide,¹⁸ and polymer¹⁹ industries.

Due to their biological, pharmaceutical, and industrial importance, the synthesis of isoindole-1,3-diones has received considerable attention in the literature. The most common method reported in the literature for the synthesis of isoindole-1,3-diones involves the reaction of a phthalic acid anhydride and a primary amine.²⁰ Syntheses of isoindole-1,3-

diones have also been reported with other approaches, including the ammoxidation of *o*-xylenes by vanadium/titanium/oxygen catalysis and subsequent oxidation of intermediate *o*-tolunitriles,²¹ microwave irradiation of *N*-hydroxymethylphthalimides with aryl amines or phthalic anhydrides with urea, the microwave-induced cleavage of solid-supported *o*-amidoesters,²² the palladium-catalyzed carbonylation of *o*-haloamides, and a combination of carbonylation and nitrogenation of *o*-halophenyl alkyl ketones.²³

The development of new methods for the simultaneous formation of both carbon–carbon and carbon–heteroatom bonds in a single step is quite advantageous to the organic chemist, since it allows the assembly of complex molecules from simple precursors. Transition metal-catalyzed reactions, especially palladium-catalyzed processes, which involve the insertion of unsaturated molecules, such as carbon monoxide, alkynes, and alkenes, into a carbon–metal bond are an important step toward this goal. In the past couple of years, we have developed in our laboratories the palladium-catalyzed annulation of dienes and internal alkynes by aromatic and vinylic halides bearing a neighboring nucleophilic substituent as an efficient way to synthesize a wide variety of carbocyclic and heterocyclic compounds,²⁴ including indoles, isoquinolines,²⁵ benzofurans, benzopyrans, isocoumarins,²⁶ α -pyrones,²⁶ indenones, naphthalenes, and phenanthrenes. CO insertion into the aryl–palladium bond to form an acylpalladium complex is a ubiquitous process in organic synthesis.²⁷ The resulting acylpalladium complexes react with various nucleophiles to give aryl carbonyl compounds. When nitrogen acts as the nucleophile, the process is aminocarbonylation,²⁸ which is an important method for the synthesis of amides. While many examples of such processes have been reported to form acyclic amides,²⁹ relatively few have been reported for the formation of cyclic amides. Ban et al. have reported the palladium-catalyzed formation of isoindole-1,3-diones from *o*-bromobenzamides and CO,³⁰ while Perry et al. have prepared isoindole-1,3-diones from *o*-dihaloarenes in the presence of CO, a primary amine, a catalytic amount of palladium, and a base in dipolar aprotic solvents.³¹ However, these routes either limit the groups that can be introduced on the nitrogen of the isoindole-1,3-dione, because one first needs to prepare the starting benzamides, or they require high pressures of CO and specialized equipment, like pressure reactors. To the best of our knowledge, the synthesis of *N*-substituted isoindole-1,3-diones by the palladium-catalyzed aminocarbonylation of simple *o*-halobenzoates has not been reported previously. We report herein a number of examples of such a one-step synthesis of this important class of heterocycles in good yields using readily available starting materials.

Results and Discussion

The focus of our early studies was the palladium-catalyzed aminocarbonylation of *o*-halobenzoates to give 2-substituted isoindole-1,3-diones in good yields. Methyl 2-iodobenzoate (**1a**) was used as a model system for optimization of the reaction conditions with benzylamine (**2a**) as the amine. Early in this work, the reaction was run with 0.5 mmol of **1a**, 1.2 equiv of benzylamine, 5 mol % of Pd(OAc)₂, 10 mol % of PPh₃, and 2 equiv of Cs₂CO₃ as a base in 6 mL of toluene at 95 °C under 1 atm of CO to obtain a 75% isolated yield of the desired 2-benzylisoindole-1,3-dione (**3a**) (eq 1).

The yield of the desired product **3a** slightly increased to 76%

when the amount of palladium catalyst and the triphenylphosphine ligand was increased to 10 and 20 mol %, respectively (Table 1, entry 1). No desired product was obtained when the reaction was carried out in the absence of the ligand PPh₃.

Noting the importance of the ligand in the reaction, various ligands were screened with the aim of increasing the yield of the imide. More sterically hindered triarylphosphines gave significantly lower yields (entries 2 and 3). More basic tricyclohexylphosphine gave a high yield (entry 4), but PEt₃ gave a poor yield (entry 5). Heterocyclic tri(2-furyl)phosphine afforded a modest yield of imide (entry 6). Diphenyl-2-pyridylphosphine improved the yield dramatically to 84% (entry 7), but other bulky monodentate ligands gave only modest yields (entries 8–11).

Since the yields of imide are highly dependent on the ligands employed, we decided to screen bidentate ligands under similar reaction conditions. BINAP and dppf gave poor yields, while Tol-BINAP and Xantphos gave 71% and 78% yields, respectively, which were close to those obtained with the parent triphenylphosphine (entries 12–15). The ligands dppm and dppe reduced the yields drastically to 34% and 5%, respectively (entries 16 and 17), while dppp improved the yield to 91% (entry 18). With further elongation of the carbon chain of the bidentate ligand, the yields decreased. Thus, 1,4-bis(diphenylphosphino)butane and 1,5-bis(diphenylphosphino)pentane gave 81% and 64% yields, respectively (entries 19 and 20).

With dppp as the ligand of choice, the reaction was carried out in various solvents. Reactions in the low boiling polar solvents CH₃CN and CH₃OH had to be carried out at lower temperatures and they did not give the desired product (Table 2, entries 1 and 2). The higher boiling polar solvents DMSO and DMF gave extremely poor yields at 95 °C (entries 3 and 4). Nitromethane gave a 10% yield of the desired product at 95 °C (entry 5), while THF gave a 42% yield of the desired product at the lower temperature of 60 °C (entry 6). Reaction in toluene as the solvent at the lower temperature of 80 °C reduced the yield to 79% (entry 7). A reduction in the amount of phosphine ligand to 10 mol % reduced the yield to 76% (entry 8). When the reaction was carried out with 10 mol % of the dppp ligand and 5 mol % of the palladium catalyst, the yield increased to 89% (entry 9), indicating that the ratio 1:2 of palladium catalyst to phosphine ligand works better than a ratio of 1:1. Maintaining the ratio of the palladium catalyst and phosphine at 1:2, but reducing the amount of palladium to 2 mol %, the yield dropped to 78% (entry 10). An excess of the ligand reduced the yield further to 49% (entry 11). Excess ligand with 5 mol % of palladium also gave a poor yield of 53% (entry 12). The base Cs₂CO₃ proved to be very important for the reaction as the yield was reduced to 73% when using only 1.5 equiv of the base (compare entries 9 and 13). Increasing the amount of the base afforded no significant increase in the yield (entry 14). A reduced reaction time gave a lower yield of 78% (entry 15). Thus, our optimized conditions for the carbonylative cyclization are 0.5 mmol of **1a**, 1.2 equiv of **2a**, 5 mol % of Pd(OAc)₂, 10 mol % of dppp, and 2 equiv of Cs₂CO₃ in 6 mL of toluene at 95 °C under 1 atm of CO for 24 h.

After obtaining our best reaction conditions for aminocarbonylation, we examined the scope of this reaction on various substrates. The *o*-halo esters **1a**, **1b**, **1d**, and **1e** were obtained from commercial sources, while **1c** was prepared according to a literature procedure.³² The model system under our optimized conditions with benzylamine gave an 89% isolated yield of the desired product **3a** (Table 3, entry 1). Compound **3a** was obtained in a slightly lower 85% yield, when the reaction was carried out on a larger scale (entry 2). A reaction with methyl 2-bromobenzoate (**1b**) gave a reduced yield of 55% (entry 3). This is probably due to the fact that the oxidative insertion of Pd(0) into a C–Br bond is less facile than that into a C–I bond. For similar reasons, when two electron-donating methoxy groups were placed on

the *o*-iodobenzoate, the yield was reduced to 46% (entry 4). Electron donation by methoxy substituents is known to slow oxidative addition to aromatic halides. The limited electron-withdrawing effect of a bromo-substituent para to the iodo group in the benzoate ester **1d** sharply lowered the yield to 51% when compared with that of the parent system (entry 5). The presence of a strong electron-withdrawing NO₂ group para to the bromo group in the benzoate ester **1e** increased the yield from 55% to 71% (compare entries 3 and 6).

We have also examined the reactivity of an ester bearing a vinylic halide. When methyl 2-bromocyclohept-1-enecarboxylate was subjected to aminocarbonylation under our optimized conditions with use of benzyl amine, the desired product was obtained in only a poor yield (<15%).

We also studied the scope of the reaction using various amines. The reaction of **1a** with phenethylamine (**2b**) gave the desired product **3e** in an 81% yield (entry 7). The more hindered aliphatic amine cyclohexyl amine gave an excellent 92% yield of the desired product **3f** (entry 8). The lower boiling alcohol-containing amine **2d** gave a poor yield of 25% (entry 9), but the yield was increased to 41% when the reaction was carried out with an excess of the amine (entry 10). The reaction with benzyl amine bearing an electron-donating *p*-methoxy group gave a 68% yield of the desired product **3h** (entry 11). Oxygen- and sulfur-containing heterocyclic amines worked well under our optimized conditions (entries 12–14). The nitrogen-containing heterocyclic amines *N*-(3-aminopropyl)morpholine and *N*-(3-aminopropyl)imidazole failed to give the desired products under our reaction conditions for reasons not presently understood.

After screening the above-mentioned aliphatic amines, we decided to study the scope of the reaction with aromatic amines. Amines **2i** and **2j** with electron-donating methyl groups gave 79% and 77% yields of the desired products **3l** and **3m**, respectively (entries 15 and 16). 4-Aminophenol failed to give the desired product apparently due to solubility problems. An electron-withdrawing fluoro group did not have much of an effect on the yield (entry 17). But the presence of a bromo or iodo substituent at the para position of the aniline gave somewhat lower yields of 68% and 57%, respectively (entries 18 and 19). It is possible that the desired products are perhaps undergoing further reaction with palladium. The presence of an electron-withdrawing ketone group on the amine drastically reduced the yield of the desired product **3q** to 25% (entry 20). The presence of strong electron-withdrawing NO₂ and CF₃ groups on the amine failed to give the desired cyclic products. Instead these substrates formed **3r** and **3s** in 62% and 61% yields, respectively (entries 21 and 22). Amine **2q** also failed to form the desired cyclic product (entry 23). To establish if the reason this substrate failed to carbonylate and cyclize was its slightly electron-deficient nature or its steric bulk, we studied the aminocarbonylation of 1-naphthylamine (**2r**). To our surprise, this substrate also failed to carbonylate and cyclize. Instead we obtained ester **3u** in a 55% isolated yield (entry 24). We have also examined the reaction of amine **2s** to confirm that sterically hindered aromatic amines fail to give the desired cyclic isoindole-1,3-diones under our reaction conditions. Again an amino ester was obtained (entry 25). Even the simple mono ortho-substituted amines **2t** and **2u** failed to give the desired cyclic products, but afforded decent yields of the corresponding amino esters (entries 26 and 27).

We believe that the mechanism of these carbonylative cyclizations involves a two-step process: (1) palladium-catalyzed formation of the corresponding *o*-amidocarboxylates, followed by (2) base-catalyzed cyclization of these *o*-amidocarboxylates to the cyclic isoindole-1,3-diones (Scheme 1). Palladium undergoes oxidative insertion into the carbon–halogen bond to give Pd(II) intermediate **I**, which then inserts CO to form the acylpalladium complex **II**. The acylpalladium complex then reacts with the amine to give the *o*-amidocarboxylate **III**. This species then participates in a base-catalyzed cyclization. The

base extracts the amide proton to give anionic nitrogen species **IV**, which attacks the ester carbonyl to afford cyclic intermediate **V**, which results in formation of the final isoindole-1,3-dione **VI** by loss of a methoxy group. The insertion of CO in the Pd(II) intermediate **I** to form the acylpalladium complex **II** is a reversible process. We believe that the desired *o*-amidocarboxylate **III** is obtained in the presence of a more nucleophilic amine by trapping the acylpalladium intermediate **II**. Amines with strong electron-withdrawing groups, due to their poor nucleophilicity, fail to trap the acylpalladium complex **II** to form the corresponding *o*-amidocarboxylate **III**, but apparently they react with the Pd(II) intermediate **I** to form the corresponding amino ester (refer to Table 3, entries 21 and 22). Amino ester products **3t** to **3x** (refer to Table 3, entries 23 to 27) are apparently formed by more rapid reaction of the intermediate arylpalladium intermediate **I** directly with the more hindered amine rather than the acylpalladium intermediate **II**.

An alternative mechanism might involve initial conversion of the ester to an amide and subsequent carbonylation and cyclization as suggested by Wu.²³ However, we have never observed such *o*-halobenzamides as side products in any reactions, even those run only partially to completion, which seems to disfavor such a mechanism.

The isoindole-1,3-diones obtained by this simple palladium-catalyzed aminocarbonylation process appear to be promising intermediates for the preparation of more highly substituted isoindole-1,3-diones. To expand the scope of our chemistry, we subjected isoindole-1,3-dione **3c** to a palladium/copper-catalyzed Sonogashira reaction to obtain an excellent 86% isolated yield of the substituted isoindole-1,3-dione **4** (Scheme 2). The Suzuki coupling of **3c** with *p*-methoxyphenylboronic acid gave a 51% yield of the desired product **5**.

Conclusions

A range of isoindole-1,3-diones have been obtained by the one-step palladium-catalyzed aminocarbonylation of simple *o*-halobenzoate ester starting materials that are readily available or easily synthesized. The reaction conditions are mild and the products are easy to isolate in good yields. A halogen moiety can also be introduced into the products, which provides a useful handle for further functionalization of the resulting heterocycles. The Sonogashira and Suzuki products **4** and **5** have been obtained in good to excellent yields in this manner. Our methodology tolerates a number of functional groups, including alcohol, ketone, methoxy, and nitro groups, and works well for both aliphatic and aromatic primary amines. The methodology provides a very convenient one-step approach to this important class of heterocycles.

Experimental Section

General Procedure for the Palladium-Catalyzed Carbonylative Cyclization of *o*-Halobenzoates and Primary Amines

To a solution of 0.5 mmol of the *o*-halobenzoate in PhCH₃ (6 mL) was added the primary amine (1.2 equiv), Pd(OAc)₂ (5 mol %), dppp (10 mol %), and Cs₂CO₃ (2.0 equiv). The flask was then sealed and flushed with CO. A balloon filled with CO was placed on the top of the flask and the reaction was stirred at 95 °C for 24 h. After the reaction was over, the resulting solution was diluted with EtOAc (10 mL) and filtered through celite. The celite was thoroughly washed with EtOAc (15 mL) to ensure complete extraction of the crude product. The combined EtOAc fractions were dried over anhydrous Na₂SO₄ and concentrated under vacuum to yield the crude product, which was purified by flash chromatography on silica gel with use of ethyl acetate/hexanes as the eluent. Solid products were further recrystallized from ethanol.

2-Benzylisoindoline-1,3-dione (3a)

This compound was obtained as a white solid: mp 119–121 °C (lit.^{22d} mp 118–120 °C); ¹H NMR (400 MHz, CDCl₃) δ 4.84 (s, 2H), 7.25–7.33 (m, 3H), 7.43 (d, *J* = 7.1 Hz, 2H), 7.67–7.70 (m, 2H), 7.82–7.84 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 41.7, 115.4, 123.4, 127.9, 128.7, 132.2, 134.1, 136.5, 168.1; IR (neat, cm⁻¹) 2926, 2253, 1770, 1712, 1394, 909; HRMS *m/z* 237.07927 (calcd C₁₅H₁₁NO₂, 237.07898).

2-Benzyl-5-(phenylethynyl)isoindoline-1,3-dione (4)

This compound was prepared by the following procedure. To a solution of 63 mg of 2-benzyl-5-bromoisindoline-1,3-dione (**3c**) (0.2 mmol) in Et₃N (2 mL) was added PdCl₂(PPh₃)₂ (2 mol %) and CuI (1.5 mol %), and the mixture was stirred for 10 min under Ar. A solution of 0.3 mmol of phenylacetylene dissolved in 0.5 mL of Et₃N was then added dropwise and the reaction mixture was allowed to stir at 60 °C for 24 h. The reaction was monitored by TLC. After the reaction was over, the resulting solution was diluted with H₂O (5 mL) and extracted with ethyl acetate (3 × 10 mL). The combined ethyl acetate fractions were dried over anhydrous Na₂SO₄ and concentrated under vacuum to yield the crude product, which was purified by flash chromatography on silica gel by using hexanes/ethyl acetate as the eluent to obtain the desired compound **4** in an 86% yield as a pale brown solid: mp 166–167 °C; ¹H NMR (400 MHz, CDCl₃) δ 4.84 (s, 2H), 7.25–7.44 (m, 8H), 7.54–7.56 (m, 2H), 7.81 (d, *J* = 0.6 Hz, 2H), 7.95 (s, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 41.9, 87.9, 94.0, 122.2, 123.5, 126.3, 128.0, 128.7, 128.8, 128.9, 129.4, 129.7, 130.9, 132.0, 132.5, 136.3, 137.0, 167.5, 167.6; IR (neat, cm⁻¹) 2924, 1708, 1627, 1436, 1359, 1106, 955; HRMS *m/z* 337.11077 (calcd C₂₃H₁₅NO₂, 337.11028).

2-Benzyl-5-(4-methoxyphenyl)isoindoline-1,3-dione (5)

This compound was prepared by the following procedure. To 63 mg of 2-benzyl-5-bromoisindoline-1,3-dione (**3c**) (0.2 mmol) was added 46 mg (1.5 equiv) of 4-methoxyphenylboronic acid, PdCl₂ (5 mol %), KHCO₃ (1.5 equiv) and 4:1 DMF/H₂O (5 mL). The reaction mixture was stirred at 80 °C for 12 h. The resulting solution was cooled to room temperature, diluted with H₂O (5 mL), and extracted with ethyl acetate (3 × 15 mL). The combined ethyl acetate fractions were washed with brine, dried over anhydrous Na₂SO₄, and concentrated under vacuum to yield the crude product, which was further purified by flash chromatography on silica gel by using hexanes/ethyl acetate as the eluent to obtain the desired compound **5** in a 51% yield as a white solid: mp 167–168 °C; ¹H NMR (400 MHz, CDCl₃) δ 3.86 (s, 3H), 4.86 (s, 2H), 7.01 (d, *J* = 8.8 Hz, 2H), 7.24–7.34 (m, 3H), 7.44 (d, *J* = 7.2 Hz, 2H), 7.57 (d, *J* = 8.6 Hz, 2H), 7.85 (d, *J* = 0.8 Hz, 2H), 8.01 (s, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 41.8, 55.6, 114.8, 121.5, 123.9, 127.9, 128.6, 128.7, 128.8, 129.9, 131.5, 132.0, 133.2, 136.6, 147.2, 160.5, 168.2, 168.3; IR (neat, cm⁻¹) 2916, 1774, 1700, 1596, 1250, 1033; HRMS *m/z* 343.12126 (calcd C₂₂H₁₇NO₃, 343.12084).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Scheme 1.

Scheme 2.

Table 1

Optimization of the Palladium-Catalyzed Carbonylative Cyclization of Methyl 2-Iodobenzoate and Benzylamine, Using Various Phosphine Ligands (eq 1)^a

entry	ligand (20 mol %)	% isolated yield
1	PPh ₃	76
2	P(<i>o</i> -tolyl) ₃	14
3	tri(2-methoxyphenyl)phosphine	38
4	tricyclohexylphosphine	82
5	triethylphosphine	39
6	tri(2-furyl)phosphine	66
7	diphenyl-2-pyridylphosphine	84
8	(2-biphenyl)di- <i>tert</i> -butylphosphine	31
9	tri- <i>tert</i> -butylphosphine	53
10	2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (S-PHOS)	66
11	2-dicyclohexylphosphino-2'-(<i>N,N</i> -dimethylamino)biphenyl (DavePhos)	64
12	(±)-2,2'-bis(diphenylphosphino)-1,1'-binaphthalene (BINAP)	19
13	2,2'-bis(di- <i>p</i> -tolylphosphino)-1,1'-binaphthalene (Tol-BINAP)	71
14	4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos)	78
15	1,1'-bis(diphenylphosphino)ferrocene (dppf)	17
16	1,1-bis(diphenylphosphino)methane (dppm)	34
17	1,2-bis(diphenylphosphino)ethane (dppe)	~5
18	1,3-bis(diphenylphosphino)propane (dppp)	91
19	1,4-bis(diphenylphosphino)butane	81
20	1,5-bis(diphenylphosphino)pentane	64

^a Representative procedure: methyl 2-iodobenzoate (0.5 mmol), benzylamine (1.2 equiv), Pd(OAc)₂ (10 mol %), ligand (20 mol %), Cs₂CO₃ (2 equiv), and toluene (6 mL) were placed in a 4 dram vial. The vial was sealed and flushed with CO. The reaction was then stirred at 95 °C for 24 h with a CO balloon on top of the vial.

Table 2

Optimization of the Palladium-Catalyzed Carbonylative Cyclization of Methyl 2-Iodobenzoate and Benzylamine with dppp as the Ligand (eq 1)^a

entry	Pd(OAc) ₂ (mol %)	dppp (mol %)	Cs ₂ CO ₃ (equiv)	solvent	time (h)	temp (°C)	% yield ^b
1	10	20	2.0	CH ₃ CN	24	75	0
2	10	20	2.0	CH ₃ OH	24	60	0
3	10	20	2.0	DMSO	24	95	~5 ^c
4	10	20	2.0	DMF	24	95	~5 ^c
5	10	20	2.0	CH ₃ NO ₂	24	95	10
6	10	20	2.0	THF	24	60	42
7	10	20	2.0	PhCH ₃	24	80	79
8	10	10	2.0	PhCH ₃	24	95	76
9	5	10	2.0	PhCH ₃	24	95	89
10	2	4	2.0	PhCH ₃	24	95	78
11	2	10	2.0	PhCH ₃	24	95	49
12	5	20	2.0	PhCH ₃	24	95	53
13	5	10	1.5	PhCH ₃	24	95	73
14	5	10	3.0	PhCH ₃	24	95	90
15	5	10	2.0	PhCH ₃	12	95	78

^aRepresentative procedure: methyl 2-iodobenzoate (0.5 mmol), benzylamine (1.2 equiv), Pd(OAc)₂, dppp, Cs₂CO₃, and the solvent (6 mL) were placed in a 4 dram vial. The vial was sealed and flushed with CO. The reaction was then stirred at 95 °C for the indicated time with a CO balloon on top of the vial.

^bIsolated yields.

^cGC yields.

Table 3Synthesis of Isoindole-1,3-diones by the Aminocarbonylative Cyclization of *o*-Halobenzoate Esters^a

entry	<i>o</i> -halo ester	amine	product	% isolated yield
1				89
2	1a	2a	3a	85 ^b
3		2a	3a	55
4		2a		46
5		2a		51
6		2a		71
7	1a			81
8	1a			92
9	1a			25

entry	<i>o</i> -halo ester	amine	product	% isolated yield
10	1a	2d	3g	41 ^c
11	1a	2e	3h	68
12	1a	2f	3i	61
13	1a	2g	3j	77
14	1a	2h	3k	71
15	1a	2i	3l	79
16	1a	2j	3m	77
17	1a	2k	3n	71
18	1a	2l	3o	68
19	1a	2m	3p	57

entry	<i>o</i> -halo ester	amine	product	% isolated yield
20	1a	2n	3q	25
21	1a	2o	3r C ₆ H ₄ NO ₂ - <i>p</i>	62
22	1a	2p	3s C ₆ H ₄ CF ₃ - <i>m</i>	61
23	1a	2q	3t	57
24	1a	2r	3u	55
25	1a	2s	3v	61
26	1a	2t	3w	62

entry	<i>o</i> -halo ester	amine	product	% isolated yield
27	1a	2u	3x	55

^aRepresentative procedure: *o*-halobenzoate ester **1** (0.5 mmol), amine **2** (1.2 equiv), Pd(OAc)₂ (5 mol %), dppp (10 mol %), Cs₂CO₃ (2 equiv), and toluene (6 mL) were placed in a round-bottomed flask. The flask was sealed and flushed with CO. The reaction was stirred at 95 °C for 24 h with a CO balloon on top of the flask.

^bThe reaction was scaled up to 2 mmol of halo ester.

^cThe reaction was carried out with 10 equiv of amine.