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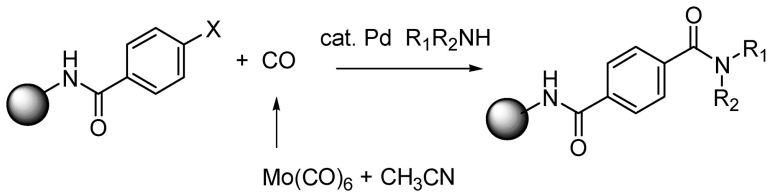


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# Carbonylation Reaction of Aryl Halides on a Polymer Support Using In Situ-Generated Carbon Monoxide without the Assistance of Microwaves

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Palladium-catalyzed carbonylation, which was based on a ligand exchange reaction, efficiently converted immobilized aryl halides to amides under mild reaction conditions using molybdenum hexacarbonyl [$Mo(CO)_6$] as the carbon monoxide source. The method easily operates without irradiating with microwaves and yields a wide range of highly pure amides after cleaving from the resin. The method could also be applied to the carbonylation of immobilized amines with aryl halides and to construct heterocyclic systems via a carbonylative cyclization.

## Introduction

Solid-phase organic synthesis is commonly used to rapidly create diverse libraries and to optimize pharmaceutical leads.[1] Formation of carbon−carbon and carbon−heteroatom bonds is important in solid-phase reactions. In particular, palladium-catalyzed carbon−carbon bond-forming reactions such as Stille, Heck, Suzuki, and Sonogashira coupling in solid phase are robust methods that are well documented.[2]

Palladium-catalyzed carbonylation is an important and convenient method for preparing aromatic and alkenyl carboxylic acid derivatives from the corresponding halides.[3] In 1999, Takahashi first successfully applied palladium-catalyzed carbonylation of immobilized amines with aryl halides on the Multipin system, and a few additional applications have also been reported.[4] However, all of these reactions were conducted using gaseous carbon monoxide from a cylinder. Depending on the equipment, using gaseous carbon monoxide may cause serious problems in a parallel synthesis.

Numerous studies have modified this process in order to avoid the problems of using gaseous carbon monoxide. Direct aminocarbonylations of aryl halides using DMF derivatives as an amide source have been demonstrated.[5] These methods have overcome the trouble of using gaseous carbon monoxide in carbonylation, but further investigations are necessary to apply this method to high-throughput synthesis because of the corresponding *N*,*N*-dimethylamides production. Larhed and co-workers reported a microwave-assisted palladium-catalyzed carbonylation, which was based on the concept of microwave-assisted thermal decomposition, using DMF, formamide, or molybdenum hexacarbonyl [$Mo(CO)_6$] as the CO source.[6] This method appears to overcome the trouble of gaseous carbon monoxide from a cylinder and seems suitable for high-throughput synthesis of diverse amides and esters.[7] Intrigued by these reports, we investigated facile solid-phase carbonylation using $Mo(CO)_6$ as a CO source with the chemical modification of the CO releasing method.

Heating metal carbonyl complexes in $CH_3CN$ produces $(CH_3CN)_3M(CO)_3$ and carbon monoxide by a ligand exchange.[8] We examined the applicability of this process on a polymer support using $Mo(CO)_6$ as a CO source on the basis of the concept of ligand exchange reaction as shown in Figure 1. While the manuscript was being prepared, one closely related methodology using DBU as the displacing ligand toward solid-phase application appeared in the most recent papers.[9] Herein, we report our studies of solid-phase palladium-catalyzed carbonylation of aryl halide using in situ-generated carbon monoxide released from a metal carbonyl complex by the action of $CH_3CN$ under mild reaction conditions.

## Results and Discussion

In an initial study, $Cr(CO)_6$ and $Mo(CO)_6$ were tested for their utility in a carbonylation reaction in $CH_3CN$ at 80 °C. However, these complexes showed a marked tendency to sublime in $CH_3CN$. Then conditions were examined to minimize sublimation, and it was determined that combining $CH_3CN$ and toluene minimized sublimation under the conditions given in Table 1. When 1.5−2.0 equiv of $Mo(CO)_6$ was used, the best result was obtained (entry 4). A slightly lower yield was obtained without a ligand (entry 6). Using 1.5 equiv of $W(CO)_6$ as a CO source gave a similar yield without subliming (entry 7). $Pd^{II}$ salts work better than $Pd^0$ complexes as the palladium source for this process.

On the basis of the above results, the scope of this new protocol was explored. Table 2 summarizes the results. Under these conditions, a relatively hindered benzhydrylamine and low nucleophilic aniline resulted in good to moderate yields (Table 2, entries 1, 2). Cyclic, acyclic secondary amines,

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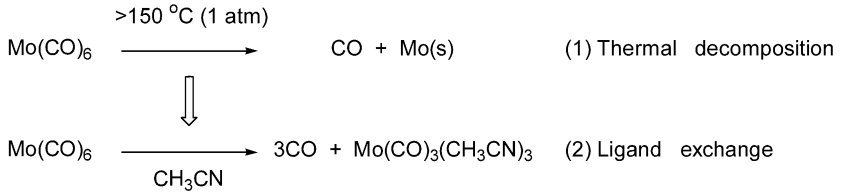
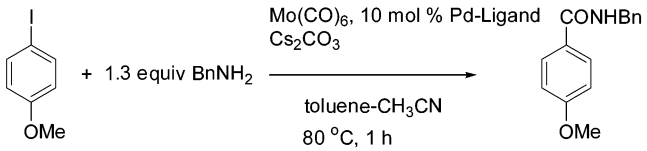



**Figure 1.**

**Table 1.** Palladium-Catalyzed Carbonylation of 4-Iodoanisole with Benzylamine Using In Situ-Generated Carbon Monoxide[a]




| entry | equiv $Mo(CO)_6$ | Pd | ligand | yield (%)[b] |
|---|---|---|---|---|
| 1 | 2.5 | $PdCl_2(CH_3CN)_2$ | BINAP | 42 |
| 2 | 2.5 | $Pd(OAc)_2$ | BINAP | 48 |
| 3 | 2.0 | $Pd(OAc)_2$ | BINAP | 63 |
| 4 | 1.5 | $Pd(OAc)_2$ | BINAP | 63 |
| 5 | 1.0 | $Pd(OAc)_2$ | BINAP | 51 |
| 6 | 1.5 | $Pd(OAc)_2$ | none | 52 |
| 7 | $W(CO)_6$ | $Pd(OAc)_2$ | BINAP | 61 |

[a] Reaction conditions: all reactions were performed using **1** (0.5 mmol) and $Cs_2CO_3$ (0.5 mmol) under argon in a mixture of toluene (1.5 mL) and $CH_3CN$ (1.0 mL). Catalyst loading was not minimized. [b] Isolated yield.

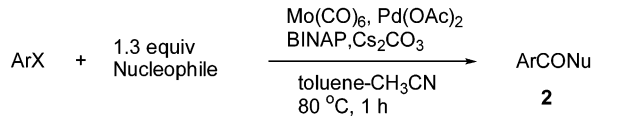
and methanol as the nucleophile also gave good yields (Table 2, entries 3−5). Using electron neutral iodo- or bromobenzene gave moderate yields (Table 2, entries 6−8); however, electron-rich 4-bromoanisole afforded a poor yield and an incomplete conversion under the same conditions (Table 2, entry 9). In contrast, aryl halides with electron-withdrawing groups in the para position easily coupled, but heteroaryl halides gave moderate yields (Table 2, entries 10−15). In the above reactions, the BINAP ligand was more suitable for the aryl bromides than the other ligand we tested.

On the basis of the above studies, the solid-phase application of this protocol was examined. For our solid-phase reactions, aryl halides were immobilized on Wang and Rink amide resin under standard conditions.[10,11] The solid-phase application was performed after adjusting the reaction conditions, and good to excellent yields were obtained after cleaving with trifluoroacetic acid (TFA), as shown in Table 3.

The most common method for attaching carboxylic acid in solid-phase chemistry involves the reaction of immobilized amine with carboxylic acids using coupling reagents. The method gives an excellent result in most cases, but is limited in its utility if the required carboxylic acid is not readily available.

Palladium-catalyzed carbonylation synthesis of primary aromatic amides was difficult, as compared to secondary and tertiary aromatic amides. A modified process has only recently been reported.[12] In these modifications, hexamethyldisilazane[12a] and formamide[12b,6b] were used as an ammonia equivalent. In solid-phase chemistry, the Rink amide resin

**Table 2.** Palladium-Catalyzed Carbonylation of Aryl and Heteroaryl Halides with Nucleophiles[a]



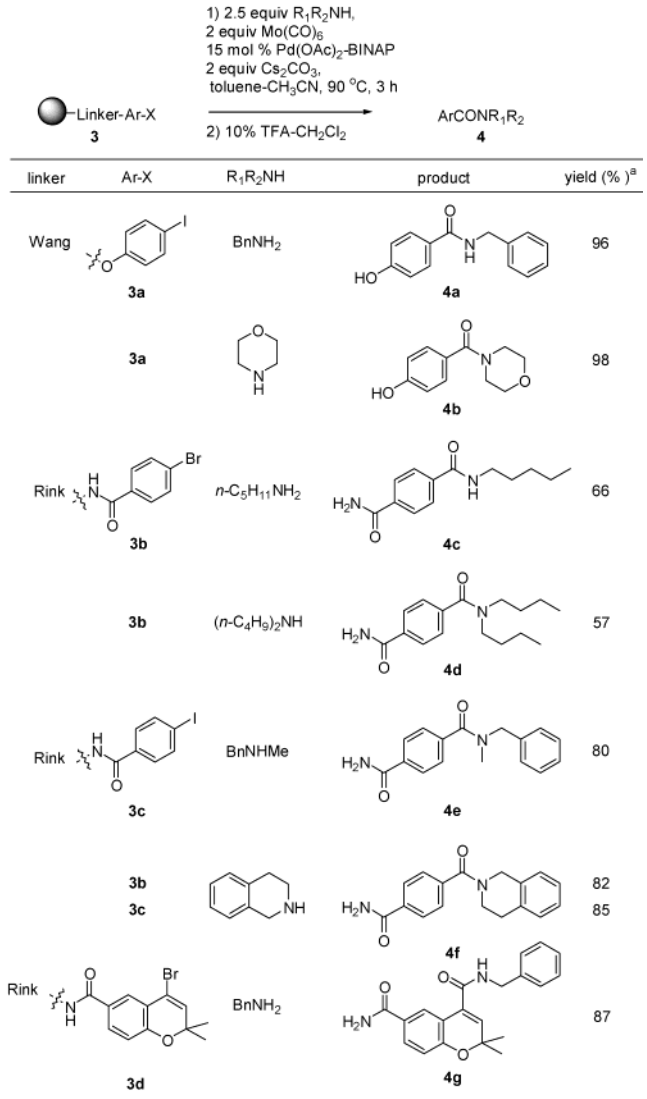

| entry | ArX | nucleophile | product | yield (%) |
|---|---|---|---|---|
| 1 | 4-MeO−PhI | benzhydrylamine | **2b** | 73 |
| 2 | 4-MeO−PhI | aniline[b] | **2c** | 63 |
| 3 | 4-MeO−PhI | morpholine | **2d** | 72 |
| 4 | 4-MeO−PhI | $(n\text{-butyl})_2NH$ | **2e** | 80 |
| 5 | 4-MeO−PhI | MeOH[c] | **2f** | 76 |
| 6 | PhI | $BnNH_2$ | **2g** | 47 |
| 7 | PhBr | $BnNH_2$ | **2g** | 57[d] |
| 8 | 3-MeO−PhBr | $BnNH_2$ | **2h** | 70[d] |
| 9 | 4-MeO−PhBr | $BnNH_2$ | **2a** | 12[d] |
| 10 | 4-$CO_2$Et−PhI | $BnNH_2$ | **2i** | 85 |
| 11 | 4-$CO_2$Et−PhI | morpholine | **2j** | 78 |
| 12 | 4-$CO_2$Et−PhBr | $BnNH_2$ | **2i** | 88 |
| 13 | 2-I-pyridine | $BnNH_2$ | **2k** | 47 |
| 14 | 3-Br-pyridine | MeOH[c] | **2l** | 39 |
| 15 | 2-I-thiophene | $BnNH_2$ | **2m** | 29 |

[a] See Table 1. [b] 2 equiv of aniline was used. [c] 10 equiv of methanol was used. [d] Pd/ligand = 1:2.

was already used in the Ugi reaction and in the palladium-catalyzed amination as an ammonia equivalent.[13] Thus, the Rink amide resin and other immobilized amino resins were used to create diverse aromatic amides libraries, since relatively hindered primary amines, such as benzhydrylamine and secondary amines, were a suitable nucleophile, as described above (Table 2). The reaction conditions for this transformation were optimized, but unexpected results were initially obtained. As shown in Scheme 1, a considerable amount of **5** was formed. We hypothesized that the acetylated product **5** was resulted by the reaction with acetic acid or Mo−$CH_3CN$ complex. Hence, the conditions were adjusted to avoid the side reaction in this transformation. It was determined that $PdCl_2(CH_3CN)_2$ solved the problem. Then the scope of the protocol using an amino resin was explored. Table 4 summarizes the results.

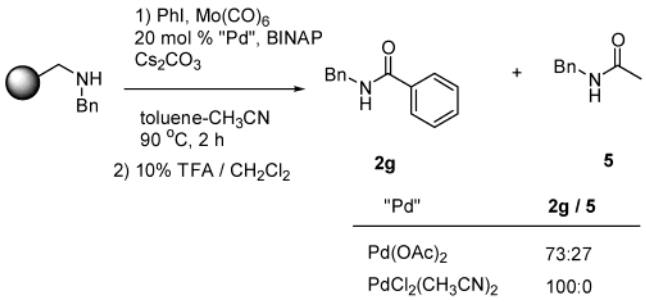
A trend similar to the trend in the solution phase was observed in the solid phase. Typically, highly pure, desired amides were obtained after TFA cleavage because the amine itself does not cleave in TFA.[14] For the Rink amide resin with an electron-rich aryl iodide, complete consumption of free amino groups (Kaiser test) was confirmed after 3 h, and the corresponding primary amides were obtained in good to moderate yields (Table 4, entries 1−3). Although a longer reaction time (6 h) was required for complete consumption of free amino groups, other aryl halides gave moderate yields (Table 4, entries 4−6). In contrast to the Rink amide resin,

**Table 3.** Palladium-Catalyzed Carbonylation of Immobilized Aryl Halides




[a] Isolated yield of **4a**−**g** (>95% pure, as judged by NMR and HPLC analysis) after $SiO_2$ column chromatography was based on the loading of **3a**−**d**.(0.6 mmol/g).

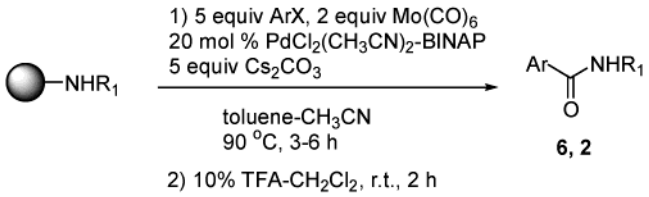
**Scheme 1**




the PAL resin and the Sieber amide resin gave unsatisfactory yields of **6a** (Table 4, entries 7, 8). Immobilized secondary amines[15] derived from 2-(4-formyl-3-methoxyphenoxy)ethyl polystyrene resin (FMPE) or (3-formylindolyl) acetoamidomethyl polystyrene resin also gave moderate yields, but further modifications seem necessary to attach these resins.

Finally, this protocol was investigated for constructing a heterocyclic system via carbonylative cyclization. Palladium-catalyzed cyclization of **7** using a similar protocol gave a good yield of the corresponding isoquinolone **8**. Solid-phase application using immobilized substrate **10**[16] gave isoquinolone **11** with excellent purity.

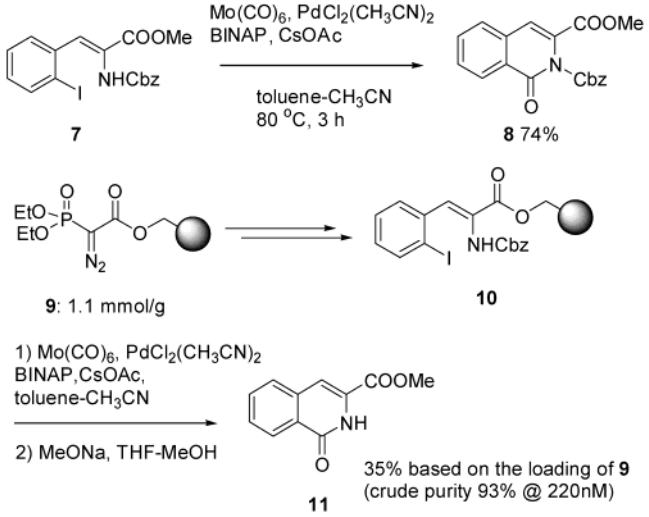
**Table 4.** Palladium-Catalyzed Carbonylation Using Amino Resin as a Nitrogen Source




| entry | $R_1$ | linker | ArX | product | purity (%)[a] | yield (%)[b] |
|---|---|---|---|---|---|---|
| 1 | H | Rink | 4-I-PhOMe | **6a** | 95 | 70 |
| 2 | H | Rink | 2-I-PhOMe | **6b** | 95 | 72 |
| 3 | H | Rink | 2-I-PhMe | **6c** | 93 | 59 |
| 4 | H | Rink | PhI | **6d** | 97 | 57 |
| 5 | H | Rink | 3-Br-PhOMe | **6e** | 98 | 43 |
| 6 | H | Rink | 4-I-PhCOOEt | **6f** | 86 | 46 |
| 7 | H | PAL | 4-I-PhOMe | **6a** | 86 | 45 |
| 8 | H | Sieber | 4-I-PhOMe | **6a** | 42 | 13[c] |
| 9 | Bn | FMPE | 4-I-PhOMe | **2a** | 85 | 40 |
| 10 | $n$-$C_5H_{11}$ | FMPE | 4-I-PhOMe | **2n** | 92 | 37 |
| 11 | 4-MeOPh$CH_2CH_2$ | FMPE | 4-I-PhOMe | **2o** | 98 | 31 |
| 12 | Bn | Indolyl | 4-I-PhCOOEt | **2i** | 83 | 30 |

[a] Purity determined by HPLC at 220 nm of the crude product. [b] Isolated yield (>95% pure, as judged by NMR and HPLC analysis) after $SiO_2$ column chromatography was based on the loading of Rink amide resin (0.51−0.61 mmol/g), PAL resin (0.5 mmol/g), Sieber amide resin (0.51 mmol/g), 2-(4-formyl-3-methoxyphenoxy)ethyl polystyrene (FMPE) resin (0.96 mmol/g), or (3-formylindolyl) acetoamidomethyl polystyrene (indolyl) resin (1.1 mmol/g). [c] Crude yield.

**Scheme 2**




## Conclusions

Palladium-catalyzed carbonylation reactions on a polymer support, which were based on a ligand exchange reaction, have been demonstrated using in situ-generated carbon monoxide. The major advantages of this protocol are that it is easy to use and has relatively mild reaction conditions. We believe this protocol is easily amenable to the parallel synthesis of amides on a polymer support.

## Experimental Section

**General Comments.** All of the dry solvents and reagents were purchased from commercial sources and were used without further purification. All polystyrene resins were purchased from Calbiochem-Novabiochem Corp and Advanced ChemTech. $^1$H NMR (400 MHz) and $^{13}$C NMR (100 MHz) spectra were recorded on a JNM-EX400 using tetramethylsilane as an internal standard. HPLC data was obtained on a Hitachi HPLC L-4200 (detector), L-6000 (pump), L-7300 (column oven) using an L-column ODS (4.6 × 250 mm); mobile phase $CH_3CN$/pH 6.0 McIlvaine's buffer (1/10-fold aqueous solution) = 3:1; flow rate, 1 mL/min; temperature, 40 °C; detection, UV at 220 nm.

**General Procedure for Solution-Phase Carbonylation (Tables 1, 2).** A test tube was charged with palladium acetate (11 mg, 0.05 mmol), BINAP (31 mg, 0.05 mmol), $Mo(CO)_6$ (198 mg, 0.75 mmol), and $Cs_2CO_3$ (164 mg, 0.5 mmol). The test tube was evacuated, backfilled with argon, and then toluene (1.5 mL), the aryl halide (0.5 mmol), the amine (0.65 mmol), and $CH_3CN$ (1 mL) were added. The tube was sealed with a Teflon screwcap and the mixture was stirred at 80 °C for 1 h. The mixture was cooled to room temperature, and then $I_2$ (254 mg, 1 mmol) was added. The mixture was stirred at room temperature for 1 h and filtered through a Celite pad, and the filtrate was diluted with ethyl acetate. The organic solution was washed with saturated aqueous $Na_2SO_3$, water, and brine; dried over $Na_2SO_4$; and evaporated to afford the crude product, which was purified by chromatography on silica gel using hexane−ethyl acetate to afford **2**.

***N*-Benzyl-4-methoxybenzamide 2a.** $^1$H NMR ($CDCl_3$) $\delta$ (ppm): 3.84 (3H, s), 4.64 (2H, d, $J$ = 5.4 Hz), 6.32 (1H, brs), 6.92 (2H, d, $J$ = 8.8 Hz), 7.25−7.40 (5H, m), 7.76 (2H, d, $J$ = 8.8 Hz). $^{13}$C NMR ($CDCl_3$) $\delta$ (ppm): 44.1 ($CH_2$), 55.4 ($CH_3$), 113.8 (2CH), 126.6 (C), 127.5 (CH), 127.9 (2CH), 128.8 (2CH), 128.8 (2CH), 138.4 (C), 162.2 (C), 166.9 (C). MS (EI) *m*/*z*: 241 ($M^+$). HRMS Calcd for $C_{15}H_{15}NO_2$, 241.1102, Found, 241.1104.

**General Procedure for Solid-Phase Carbonylation (Table 3).** A test tube was charged with resin 3 (500 mg, 0.3 mmol), palladium acetate (10 mg, 0.045 mmol), BINAP (28 mg, 0.045 mmol), $Mo(CO)_6$ (161 mg, 0.6 mmol), and $Cs_2CO_3$ (199 mg, 0.6 mmol). The test tube was evacuated, backfilled with argon, and then toluene (3 mL), the amine (0.75 mmol), and $CH_3CN$ (2 mL) were added. The tube was sealed with a Teflon screwcap and the mixture was stirred at 90 °C for 3 h. The resin was separated by filtering and washing with toluene (5 mL × 3), DMF (5 mL × 3), DMF/$H_2O$ = 1:1 (5 mL × 3), DMF (5 mL × 3), THF (5 mL × 3), $CH_2Cl_2$ (5 mL × 3), and MeOH (5 mL × 3). The resin was dried under a reduced pressure at 40 °C. The above resin was treated with 10% TFA−$CH_2Cl_2$ (5 mL) at room temperature for 2 h. The resin was separated by filtering and washing with $CH_2Cl_2$. The filtrate was evaporated to afford the crude product, which was purified by chromatography on silica gel to afford **4**.

***N*-Benzyl-4-hydroxybenzamide 4a.** $^1$H NMR ($CDCl_3$) $\delta$ (ppm): 4.62 (2H, d, $J$ = 5.4 Hz), 6.47 (1H, t, $J$ = 5.4 Hz), 6.85 (2H, d, $J$ = 8.8 Hz), 7.25−7.37 (5H, m), 7.64 (2H, d, $J$ = 8.8 Hz). MS (EI) *m*/*z*: 227 ($M^+$). HRMS Calcd for $C_{14}H_{13}NO_2$, 227.0946. Found, 227.0931.

**General Procedure for Solid-Phase Carbonylation (Table 4).** A test tube was charged with deprotected Rink amide resin (0.3 mmol), dichlorobis(acetonitrile) palladium(II) (16 mg, 0.06 mmol), BINAP (38 mg, 0.06 mmol), $Mo(CO)_6$ (161 mg, 0.6 mmol), and $Cs_2CO_3$ (497 mg, 1.5 mmol). The test tube was evacuated and backfilled with argon, and then toluene (3 mL), the aryl halide (1.5 mmol), and $CH_3CN$ (2 mL) were added. The tube was sealed with a Teflon screwcap, and the mixture was stirred at 90 °C for 3 h. The resin was separated by filtering and washing with toluene (5 mL × 3), DMF (5 mL × 3), DMF/$H_2O$ = 1:1 (5 mL × 3), DMF (5 mL × 3), THF (5 mL × 3), $CH_2Cl_2$ (5 mL × 3), and MeOH (5 mL × 3). The resin was dried under a reduced pressure at 40 °C. The above resin was treated with 10% TFA−$CH_2Cl_2$ (5 mL) at room temperature for 2 h. The resin was separated by filtering and washing with $CH_2Cl_2$. The filtrate was evaporated to dryness. The crude product was dissolved in $CHCl_3$ and washed with saturated $NaHCO_3$. The organic layer was dried over $Na_2SO_4$ and evaporated. (The residue was dissolved in $CH_3CN$ and then analyzed by HPLC.) The crude product was purified by chromatography on silica gel to afford **6**.

**4-Methoxybenzamide 6a.** $^1$H NMR ($CDCl_3$) $\delta$ (ppm): 3.86 (3H, s), 5.50−6.20 (2H, br), 6.94 (2H, d, $J$ = 8.8 Hz), 7.78 (2H, d, $J$ = 8.8 Hz). MS (EI) *m*/*z*: 151 ($M^+$). HRMS Calcd for $C_8H_9NO_2$, 151.0633. Found, 151.0609.

**2-Benzyl-3-methyl-1-oxoisoquinoline-2,3(1*H*)-dicarboxylate 8.** A test tube was charged with **7** (109 mg, 0.25 mmol), dichlorobis(acetonitrile) palladium(II) (6.5 mg, 0.0025 mmol), BINAP (15.6 mg, 0.0025 mmol), $Mo(CO)_6$ (330 mg, 1.25 mmol), and CsOAc (72 mg, 0.375 mmol). The test tube was evacuated and backfilled with argon, and then toluene (1.5 mL) and $CH_3CN$ (1 mL) were added. The tube was sealed with a Teflon screwcap, and the mixture was stirred at 80 °C for 3 h. The mixture was cooled to room temperature and then filtered through a Celite pad, and the filtrate was diluted with ethyl acetate. The organic solution was washed with water and brine, dried over $Na_2SO_4$, and evaporated to afford the crude product, which was purified by chromatography on silica gel using hexanes−ethyl acetate to afford 62 mg (74%) of **8**. $^1$H NMR ($CDCl_3$) $\delta$ (ppm): 3.86 (3H, s), 5.49 (2H, s), 7.30−7.55 (6H, m), 7.60−7.68 (2H, m), 7.72 (1H, t, $J$ = 8.3 Hz), 8.44 (1H, d, $J$ = 8.3 Hz). $^{13}$C NMR ($CDCl_3$) $\delta$ (ppm): 53.1 ($CH_3$), 71.1 ($CH_2$), 113.6 (CH), 127.5 (C), 128.2 (CH), 128.3 (C), 128.6 (CH), 128.8 (2CH), 128.9 (CH), 129.0 (2CH), 130.1 (CH), 133.7 (CH), 134.1 (C), 134.3 (C), 152.4 (C), 160.7 (C), 161.7 (C). MS (EI) *m*/*z*: 337 ($M^+$). HRMS Calcd for $C_{19}H_{15}NO_5$, 337.0950. Found, 337.0969.

**Methyl 3-Isoquinolonecarboxylate 11.** A test tube was charged with resin **10** (400 mg, 0.32 mmol), dichlorobis(acetonitrile) palladium(II) (12.5 mg, 0.048 mmol), BINAP (30 mg, 0.048 mmol), $Mo(CO)_6$ (253 mg, 0.96 mmol), and CsOAc (184 mg, 0.96 mmol). The test tube was evacuated and backfilled with argon, and then toluene (2.5 mL) and $CH_3CN$ (1.3 mL) were added. The tube was sealed with a Teflon screwcap, and the mixture was stirred at 80 °C for 3 h. The resin was separated by filtering and washing with

toluene (5 mL × 3), DMF (5 mL × 3), DMF/$H_2O$ = 1:1 (5 mL × 3), DMF (5 mL × 3), THF (5 mL × 3), $CH_2Cl_2$ (5 mL × 3), and MeOH (5 mL × 3), and the resin was dried under a reduced pressure at 40 °C. The above resin and NaOMe (17 mg, 0.32 mmol) in THF (4 mL) and MeOH (2 mL) was agitated at room temperature for 7 h. The resin was separated by filtering and washing with ethyl acetate. The filtrate was washed with saturated aqueous $NH_4Cl$, water, and brine, dried over $Na_2SO_4$, and evaporated to afford the crude product. (The residue was dissolved in $CH_3CN$ and then analyzed by HPLC.) The crude product was purified by chromatography on silica gel using hexane−ethyl acetate (1:1) to afford 23 mg (35%) of **11** as a colorless solid. $^1H$ NMR ($CDCl_3$) $\delta$ (ppm): 4.00 (3H, s), 7.38 (1H, s), 7.61−7.77 (3H, m), 8.47 (1H, d, $J$ = 8.0 Hz), 9.17 (1H, brs). MS (EI) $m/z$: 203 ($M^+$). HRMS Calcd for $C_{11}H_9NO_3$, 203.0582. Found, 203.0607.

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**Supporting Information Available.** Experimental procedures and characterization data for compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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