JOC The Journal of Organic Chemistry

Article

Synthesis of Amides by Mild Palladium-Catalyzed Aminocarbonylation of Arylsilanes with Amines Enabled by Copper(II) Fluoride

Jin Zhang, Yanyan Hou, Yangmin Ma, and Michal Szostak

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.8b02874 • Publication Date (Web): 06 Dec 2018

Just Accepted

ACS Publications

is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

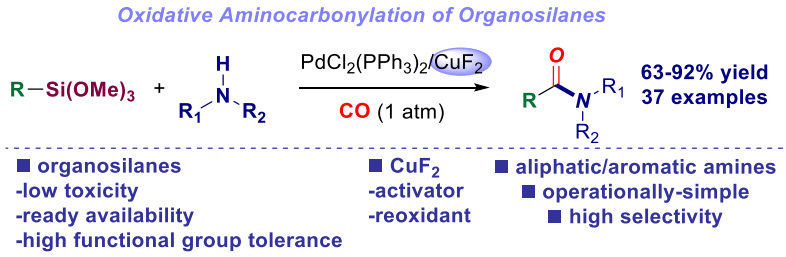
Synthesis of Amides by Mild Palladium-Catalyzed Aminocarbonylation of Arylsilanes with Amines Enabled by Copper(II) Fluoride

Jin Zhang*,†,§ Yanyan Hou,† Yangmin Ma,*,†,§ and Michal Szostak*,‡

†College of Chemistry and Chemical Engineering, Shaanxi University of Science and Technology, Xi'an 710021, China

§Shaanxi Key Laboratory of Chemical Additives for Industry, Shaanxi University of Science and Technology, Xi'an 710021, China

‡Department of Chemistry, Rutgers University, 73 Warren Street, Newark, New Jersey 07102, United States



ABSTRACT: A general Pd-catalyzed synthesis of amides by oxidative aminocarbonylation of arylsilanes under mild conditions has been accomplished for the first time. The reaction is promoted by a commercially available copper(II) fluoride, which acts as a dual silane activator and mild oxidant, enabling highly efficient aminocarbonylation of versatile arylsilanes at atmospheric CO pressure. The reaction is tolerant of a wide range of arylsilanes and various sensitive halide functional groups, as well as a broad scope of amines are compatible with this oxidative process using cheap CO. A significant aspect involves the increased efficiency by the catalyst system. The reaction represents a segue into the powerful Pd-catalyzed oxidative transformations of organosilanes.

INTRODUCTION

The amide bond is an essential structural motif found ubiquitously in best-selling pharmaceuticals, numerous agrochemicals and myriad natural products.[1,2] Recent surveys demonstrate that the amid bond is

present in more than 25% of pharmaceuticals, while amide bond forming reactions represent the most common reaction performed by medicinal chemists.[3] Considering the key importance of the amide bond, it comes as no surprise that various methods have been established for the preparation of amides.[1–3] Traditionally, the synthesis of amides is based on coupling of activated carboxylic acids and derivatives with amines.[3c,d] However, these methods are restricted by harsh reaction conditions and low atom-economy.[4,5] As a consequence, an array of alternative methods for preparation of amides has been established.[2a,b] Pioneered by Heck, aminocarbonylations of aryl halides represent an important class of amide bond forming reactions.[6] Carbonylation reactions are particularly attractive as a method to prepare amides due to low price and availability of carbon monoxide, which represents an important C1 building block in organic synthesis in both academic and industrial settings.[7,8]

The recent years have witnessed the emerging utility of powerful Pd-catalyzed oxidative transformations in organic synthesis.[9] Among the advantages of oxidative manifold are (i) improved functional group tolerance, especially with respect to halides, (ii) orthogonal Pd(II)/(0) mechanistic cycle, (iii) mild reaction conditions, and (iv) broad availability of ancillary ligands and co-catalysts that promote direct oxidation of Pd(0). With respect to amide bond formation, only few examples of aminocarbonylations of carbon nucleophiles have been reported.[10–12] In their seminal study, Wu's group described a Pd-catalyzed electrophilic aminocarbonylation of boronic acids with N-chloroamines under high CO pressure (Figure 1A).[10] Oxidative addition of a N–Cl bond to Pd(0), followed by transmetallation and CO insertion afforded acyl-Pd-amide intermediate. More recently, Jiao and co-workers developed a direct synthesis of tertiary amides by Pd-catalyzed oxidative aminocarbonylation of boronic acids with amines (Figure 1B).[11] The authors demonstrated a beneficial role of copper on the cross-coupling. Recent examples of oxidative coupling include the use of isocyanides as carbon monoxide equivalents. [12d,12e]

Unfortunately, despite these important advances, Pd-catalyzed direct aminocarbonylation of organosilanes remains elusive.[13–15] Organosilicon reagents have a number of unique advantages in organic synthesis, including (i) low toxicity, (ii) high-functional group tolerance, (iii) ready availability, and a wide range of organosilanes have been employed as cross-coupling partners in the Hiyama cross-coupling.[13] While organosilanes provide multiple alternative sources of carbon nucleophiles, the central challenge in developing oxidative Hiyama cross-coupling reactions is low nucleophilicity of organosilicon reagents.

Our interest in amide bond activation[16a,b] and Hiyama cross-coupling[16c,d] led us to interrogate organosilanes as potential carbon nucleophiles for the synthesis of amides. Herein, we report the successful realization of this concept and present the first aminocarbonylation of arylsilanes with amines using cheap carbon monoxide (Figure 1C).

The following features of our study are noteworthy: (1) the method represents the first example of an oxidative carbonylation by Hiyama cross-coupling;[13] (2) the method utilizes benign organosilane reagents, which are less toxic than related organoboranes;[14] (3) the method allows for broad functional group tolerance, including aryl halides, which are not tolerated in related carbonylative cross-couplings of halides;[7] (4) the use of CuF_2 as a dual silane activator and re-oxidant allows to obviate the use of flammable and non-commercial mixtures of gases that are used in related methods.[11] The method is fundamentally different from previous processes involving organoboranes as coupling partners under oxidative conditions.[11,12a]

The reaction exploits readily available copper(II) fluoride, which acts as a dual silane activator and mild oxidant, enabling highly efficient aminocarbonylation of versatile arylsilanes at practical atmospheric CO pressure. The method further enriches the powerful toolbox of oxidative reactions for the synthesis of amides and opens the door to applications of versatile organosilicon reagents in Pd-catalyzed oxidative transformations under mild and operationally-convenient reaction conditions. The method features a broad

substrate scope with respect to the organosilane and amine component, allowing for the rapid synthesis of amides in high to excellent yields.

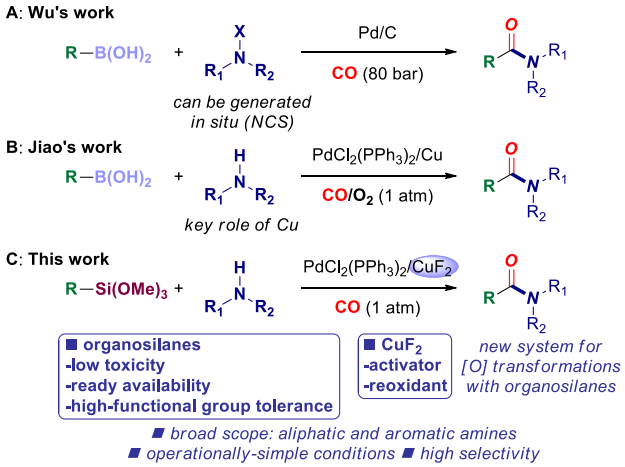


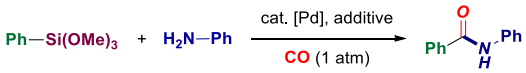
Figure 1. Synthesis of amides by aminocarbonylation of organometallic reagents: (a) Wu's work. (b) Jiao's work. (c) This study: the first aminocarbonylation of organosilanes and identification of CuF_2 as a viable co-mediator.

RESULTS AND DISCUSSION

The reaction of trimethoxyphenylsilane (**1a**) and aniline (**2a**) was selected as our model system. Selected optimization results are summarized in Table 1. To enhance the synthetic utility of the process, from the outset we selected to perform the cross-coupling under operationally-convenient atmospheric pressure conditions. We were delighted to find that the treatment of aniline with $PhSi(OMe)_3$ in the presence of $Pd(OAc)_2$ (10 mol%) and CuF_2 (2.0 equiv) as both fluoride source and oxidant under 1 atm CO pressure in CH_3CN at 80 °C afforded the desired *N*-phenylbenzamide coupling product in 27% yield (entry 1). Screening of other palladium catalysts (entries 1-5) demonstrated that the cheap $Pd(PPh_3)_2Cl_2$ proved to be best with 90% yield for the cross-coupling product (entry 3). Control experiments established that the desired product was not formed in the absence of either $Pd(PPh_3)_2Cl_2$ or CuF_2 (entries 6-7), indicating that both the palladium catalyst and fluoride source are indispensable in this transformation, in agreement with our design. Subsequently,

evaluation of a series of fluoride sources, such as CsF, KF, NaF and TBAF, further demonstrated that CuF_2 is the optimal promoter for the cross-coupling (entries 8-11). A brief optimization of solvents revealed CH_3CN to be the best solvent (12-20), while further optimization indicated that temperature of 80 °C provided the optimum yield of the product (entries 21-22). In agreement with previous studies,[16c] the use of NMP, DMSO, DMF, toluene and 1,4-dioxane is not compatible with the oxidative Hiyama cross-coupling. It should be noted that 2.0 equiv of CuF_2 are required for the efficient coupling, which is analogous to previous studies on the use of CuF_2 as silane activator.[16d] Our ongoing studies are focused on expanding the scope of oxidative cross-couplings of organosilanes. Finally, examination of different carbon monoxide sources demonstrated that replacement of CO with $Co_2(CO)_8$ or $Mo(CO)_6$ provided inferior results (entries 23-24); however, the promising result using the *in situ* CO-releasing $Mo(CO)_6$ should be noted (entry 24).

Table 1. Optimization of Aminocarbonylation Reaction[a]



1a 2a 3a

entry	catalyst	additive	solvent	yield (%)[b]
1	$Pd(OAc)_2$	CuF_2	CH_3CN	27
2	$PdCl_2$	CuF_2	CH_3CN	45
3	$Pd(PPh_3)_2Cl_2$	CuF_2	CH_3CN	90
4	$Pd(dppf)Cl_2$	CuF_2	CH_3CN	65
5	$Pd(TFA)_2$	CuF_2	CH_3CN	45
6	-	CuF_2	CH_3CN	0
7	$Pd(PPh_3)_2Cl_2$	-	CH_3CN	0
8	$Pd(PPh_3)_2Cl_2$	CsF	CH_3CN	27
9	$Pd(PPh_3)_2Cl_2$	KF	CH_3CN	23
10	$Pd(PPh_3)_2Cl_2$	NaF	CH_3CN	10
11	$Pd(PPh_3)_2Cl_2$	TBAF	CH_3CN	0
12	$Pd(PPh_3)_2Cl_2$	CuF_2	anisole	40
13	$Pd(PPh_3)_2Cl_2$	CuF_2	NMP	0
14	$Pd(PPh_3)_2Cl_2$	CuF_2	DMSO	0
15	$Pd(PPh_3)_2Cl_2$	CuF_2	DMF	0
16	$Pd(PPh_3)_2Cl_2$	CuF_2	DCE	13

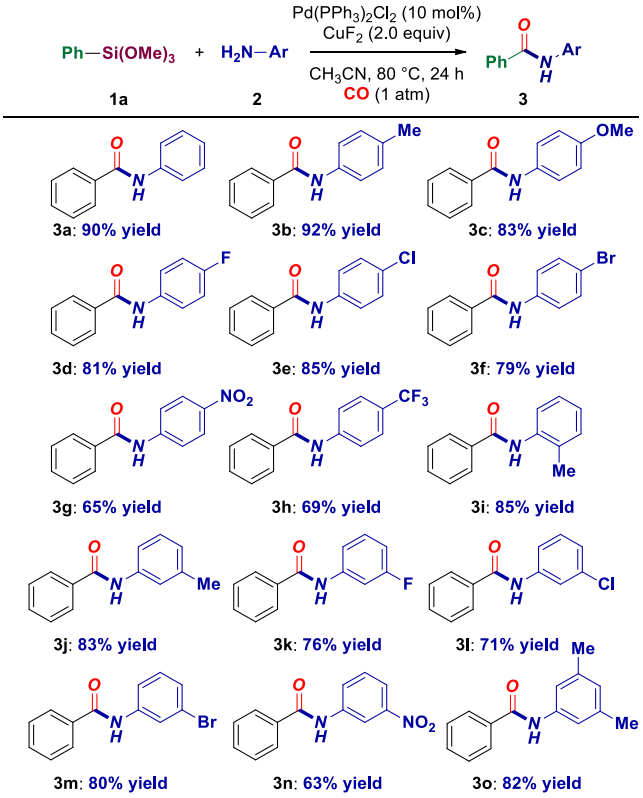
17	$Pd(PPh_3)_2Cl_2$	CuF_2	toluene	8
18	$Pd(PPh_3)_2Cl_2$	CuF_2	CH_3CH_2OH	20
19	$Pd(PPh_3)_2Cl_2$	CuF_2	2-propanol	17
20	$Pd(PPh_3)_2Cl_2$	CuF_2	1,4-dioxane	0
21[c]	$Pd(PPh_3)_2Cl_2$	CuF_2	CH_3CN	55
22[d]	$Pd(PPh_3)_2Cl_2$	CuF_2	CH_3CN	50
23[e]	$Pd(PPh_3)_2Cl_2$	CuF_2	CH_3CN	0
24[f]	$Pd(PPh_3)_2Cl_2$	CuF_2	CH_3CN	42

[a]Conditions: $PhNH_2$ (0.50 mmol), $PhSi(OMe)_3$ (0.75 mmol), [Pd] (10 mol%), additive (2.0 equiv), solvent (3.0 mL), CO (1 atm), 80 °C, 24 h. [b]Yield of isolated product. [c]100 °C. [d]60 °C. [e]$Co_2(CO)_8$ (0.75 mmol) instead of CO. [f] $Mo(CO)_6$ (0.75 mmol) instead of CO.

Experiments to probe the scope of the amine component in our oxidative aminocarbonylation protocol are summarized in Schemes 1 and 2. Most notably, we were pleased to find that a broad range of aromatic amines bearing electron-donating, electron-withdrawing and sterically-hindered substituents at para-, meta- and ortho-positions coupled in high yields. Since anilines are not tolerated the related aminocarbonylations,[10,11] the capacity to form synthetically-useful anilides[16a] provides an important advantage of the present method. Furthermore, a variety of anilines bearing sensitive halide functional handles (**3e**, **3f**, **3l**, **3m**) as well as nitro groups (**3g**, **3n**) and medicinally-relevant fluoro-substituents (**3d**, **3h**, **3k**) poised for further functionalization are suitable substrates for this protocol. Moreover, various aliphatic amines, such as primary and secondary amines can be successfully applied in this protocol (Scheme 2). Notably, these reactions include simple long-chain, benzyl and -branched primary amines, such as *n*-propylamine (**3p**), benzylamine (**3q**), cyclopentylamine (**3r**), and cyclohexylamine (**3s**), as well as various secondary amines, such as acyclic diethylamine (**3t**), sterically-hindered Bn_2NH (**3u**) and BnMeNH (**3v**), and alicyclic pyrrolidine (**3w**), indoline (**3x**) and morpholine (**3y**). It is worthwhile to note that the amide products of these reactions constitute some of the most privileged pharmacophores in medicinal chemistry research.[3a,b] At present stage of the reaction development the synthesis of non-planar amides, including N-carbazoles and

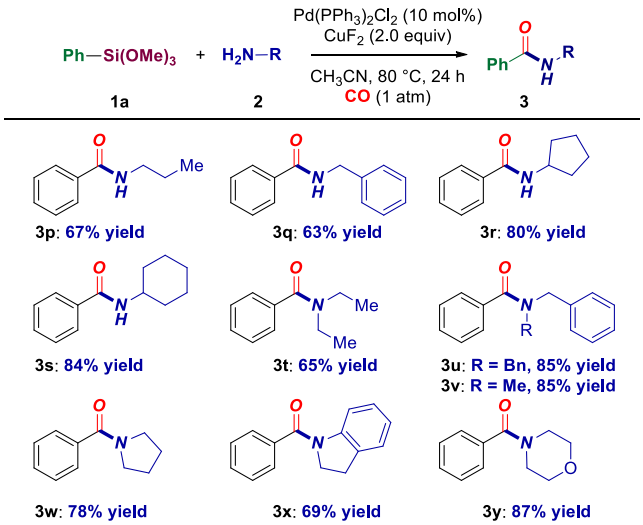
N,N-diphenyl amides has not been tested. The use of $HN(TMS)_2$ is not compatible with the reaction conditions. Future studies will focus on expanding the scope of oxidative Hiyama cross-couplings.

Scheme 1. Aromatic Amine Scope in Pd-Catalyzed Aminocarbonylation of Arylsilanes[a,b]



[a]$ArNH_2$ (0.50 mmol), $PhSi(OMe)_3$ (0.75 mmol), [Pd] (10 mol%), CuF_2 (2.0 equiv), CH_3CN (3.0 mL), CO (1 atm), 80 °C, 24 h. [b]Isolated yields.

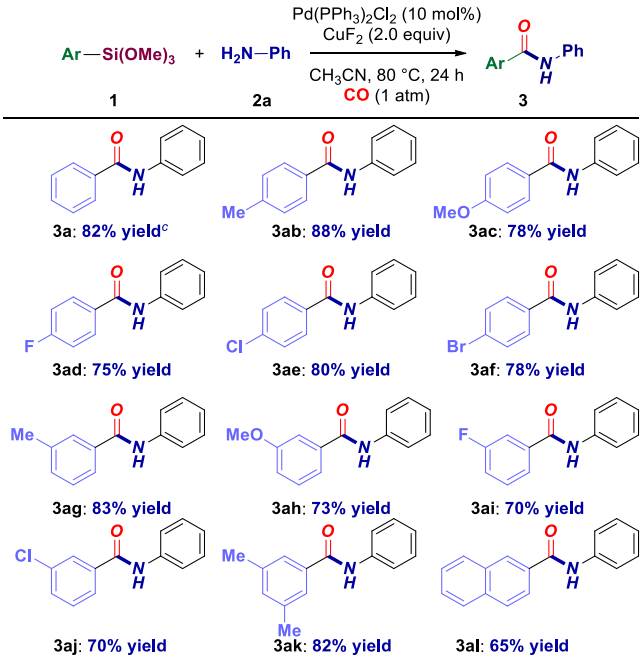
Scheme 2. Aliphatic Amine Scope in Pd-Catalyzed Aminocarbonylation of Arylsilanes[a,b]



[a,b]See Scheme 1.

The scope of aminocarbonylation reactions with representative arylsilanes is shown is Scheme 3. We were pleased to find that the arylsilane scope is also very broad and accommodates organosilanes bearing various electron-donating, electron- withdrawing and sensitive halide functional groups. Triethoxyphenylsilane was similarly effective as trimethoxyphenylsilane without modification of the reaction conditions (**3a**). Arylsilanes bearing various substituents, including electron-rich (**3ab**, **3ac**) and electron-deficient substituents (**3ad**, **3ae**, **3af**) at the conjugating para as well as at the meta position (**3ag-3ak**) performed well in the reaction. Notably, 2-(trimethoxysilyl)naphthalene also worked smoothly to give the corresponding naphthylamide product in good yield (**3al**). It is particularly noteworthy that the reaction tolerates halides suitable for conventional cross-coupling protocols.

Scheme 3. Organosilane Scope in Pd-Catalyzed Aminocarbonylation of Arylsilanes[a,b]



[a,b]See Scheme 1. [c]Using $PhSi(OEt)_3$.

In order to gain insight into the mechanism, preliminary studies were conducted (Figure 2). (1) A control experiment using BHT as a radical scavenger gave the desired product in 85% yield under standard conditions, suggesting that the reaction does not involve a radical process (Figure 2A). (2) Competition experiments demonstrate that electron-deficient organosilanes are inherently more reactive (4-F:4-Me = 85:15) (Figure 2B). (3) Furthermore, electron-deficient amines react preferentially (4-F:4-Me = 87:13) (Figure 2C). Overall, these findings strongly support amine deprotonation and coordination to the silicon atom to facilitate ligand exchange. We propose that electron-deficient amines react preferentially due to coordination to the silicon during the ligand exchange step.[16c] Further studies to elucidate the mechanism are ongoing.

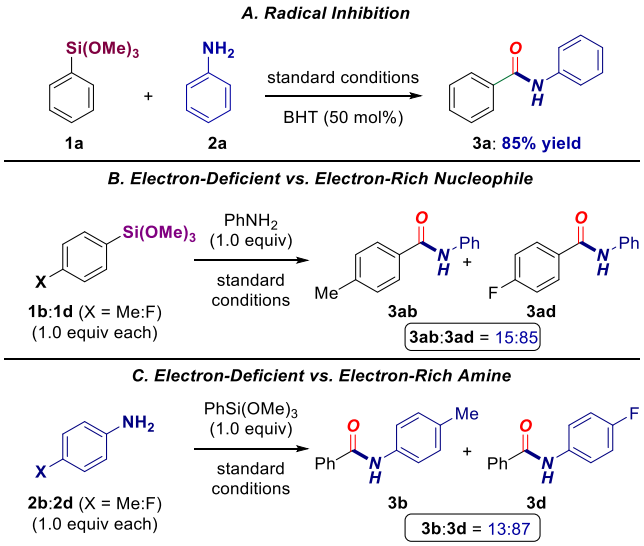


Figure 2. Mechanistic studies

A tentative mechanism for the Pd-catalyzed aminocarbonylation with arylsilanes is proposed.[10,11,17] Transmetalation of Pd(II) with arylsilane assisted by CuF_2 could afford arylpalladium, which undergoes CO insertion, ligand exchange and reductive elimination. However, we detected the formation of 1,3-diphenylurea;[18] thus, the alternative pathway could also involve imidoyl-Pd(II) species followed by CuF_2-assisted transmetallation with arylsilane and reductive elimination. The key point involves the use of CuF_2, which dramatically promotes the efficiency of this transformation due to ease of Pd(0) re-oxidation to Pd(II) to complete the catalytic cycle.

CONCLUSION

In summary, these studies present the first efficient protocol for Pd-catalyzed synthesis of amides by oxidative aminocarbonylation of arylsilanes. A key aspect involves the use of copper(II) fluoride, which acts as a dual silane activator and mild oxidant, and permits highly efficient aminocarbonylation at atmospheric CO pressure. The presented method is versatile, high yielding, and has a broad substrate scope. Remarkably, the aminocarbonylation was successfully demonstrated with both aliphatic and aromatic amines, which is advantageous over related aminocarbonylation protocols. In a general sense, we expect that the catalyst system

reported herein will facilitate the development of powerful Pd-catalyzed oxidative transformations of organosilanes. Further studies on the mechanism and carbonylation reactions of organosilanes are in progress.

EXPERIMENTAL SECTION

General Information. All reaction yields represent isolated yields after flash column chromatography on silica gel 300-400 mesh. ^{1}H and ^{13}C {1H} NMR spectra were recorded on Bruker Avance III 400 MHz (chemical shifts (ppm)) are given relative to solvent residual peaks. Spectral data are reported in ppm relative to tetramethylsilane (TMS) as internal standard in $CDCl_3$ or DMSO-d_6 as solvent. Data are reported as follows: multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and dd = doublet doublet). HRMS analysis was carried out with gradient elution (5% CH_3CN to 100% CH_3CN) on an Agilent 1200 RRLC with a photodiode array UV detector and an Agilent 6224 TOF mass spectrom. All reactions were carried out under an atmosphere of CO (1 atm) in oven-dried Schlenk tubes. All reagents were purchased from Meryer or Energy chemical company and used without further purification. Functionalized silanes were prepared according to the literature.

General Procedure for Synthesis of Amides (3). Trimethoxyphenylsilane (148.55 mg, 0.75 mmol), $Pd(PPh_3)_2Cl_2$ (35.1 mg, 0.05 mmol) and CuF_2 (0.101 g, 2.0 equiv.) were added to a 10 mL schlenk tube. The tube was then equipped with a magnetic stir-bar. After air-evacuation and refilled with CO (1 atm.) mixture for three times, amines (2, 0.5 mmol) and CH_3CN (3.0 mL) was added via syringe. The reaction mixture was stirred at 80 °C for 24 h. The solution was then cooled to room temperature followed by diluting with ethyl acetate (10 mL). After being extracted with saturated NaCl aqueous solution (10 mL), the organic portion was separated. The aqueous portion was combined and extracted with ethyl acetate (5 mL). Then the organic portions were combined, dried over anhydrous $MgSO_4$, filtered, and evaporated under vacuum. The residue was purified through flash column chromatography on silica gel (petroleum ether: ethyl acetate) to afford

amides **3**.

Radical Inhibition Procedure. Trimethoxyphenylsilane (**1a**) (148.55 mg, 0.75 mmol), $Pd(PPh_3)_2Cl_2$ (35.1 mg, 0.05 mmol), CuF_2 (0.101 g, 2.0 equiv.) and BHT (50 mol%, 110.2 mg) were added to a 10 mL schlenk tube. The tube was then equipped with a magnetic stir-bar. After air-evacuation and refilled with CO (1 atm) mixture for three times, aniline (**2a**) (46.56 mg, 0.5 mmol) and CH_3CN (3.0 mL) was added via syringe. The reaction was purified through flash column chromatography on silica gel (petroleum ether: ethyl acetate) to afford **3a** (85 % yield).

Competition Experiments Procedure

Procedure A: Trimethoxy(p-tolyl)silane **1b** (106.04 mg, 0.5 mmol), (4-fluorophenyl)trimethoxysilane **1d** (108.03 mg, 0.5 mmol), $Pd(PPh_3)_2Cl_2$ (35.1 mg, 0.05 mmol), CuF_2 (0.101g, 2.0 equiv.) were added to a 10 mL Schlenk tube. The tube was than equipped with a magnetic stir-bar, after air-evacuation and refilled with CO (1 atm) for three times, aniline **2a** (46.56 mg, 0.5 mmol) and CH_3CN (3.0 mL) was added via syringe. The formed mixture was stirred at 80 °C for 24 h. The mixture was cooled and analyzed by GC-MS, the result showed **3ab**/**3ad** = 15%/85%, which revealed that arylsilanes with electron-withdrawing groups are more efficient substrates.

Procedure B: Trimethoxy(phenyl)silane **1a** (148.55 mg, 0.5 mmol), $Pd(PPh_3)_2Cl_2$ (35.1 mg, 0.05 mmol), CuF_2 (0.101g, 2.0 equiv.) were added to a 10 mL Schlenk tube. The tube was than equipped with a magnetic stir-bar, after air-evacuation and refilled with CO (1 atm) for three times, *p*-toluidine **2b** (53.58 mg, 0.5 mmol), p-fluoroaniline **2d** (55.56 mg, 0.5 mmol) and CH_3CN (3.0 mL) was added via syringe. The formed mixture was stirred at 80 °C for 24 h. The mixture was cooled and analyzed by GC-MS, the result showed that **3b**/**3d** = 13%/87%, which revealed that anilines with electron-withdrawing groups are more efficient substrates.

Physical Properties and Characterization Data of the Synthesized Compounds. Characterization data for arylsilanes and amides products have been previously reported[12a,16e,19,20]. All arylsilanes were comparison with literature data: trimethoxy(*p*-tolyl)silane[19a], trimethoxy(4-methoxyphenyl)silane[19b], (4-fluorophenyl)trimethoxysilane[19c], (4-chlorophenyl)trimethoxysilane[19a], (4-bromophenyl)trimethoxysilane[19d], trimethoxy(*m*-tolyl)silane[19b], trimethoxy(3-methoxyphenyl)silane[19b], (3-fluorophenyl)trimethoxysilane[19e], (3-chlorophenyl)trimethoxysilane[19b], (3,5-dimethylphenyl)trimethoxysilane[19f], trimethoxy(naphthalen-2-yl)silane[19g].

N-phenylbenzamide (**3a**).[12a] White solid, petroleum ether/ethyl acetate = 10/1, yield 90 % (88mg), ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.27 (s, 1H), 7.96 (d, J = 7.1 Hz, 2H), 7.79 (d, J = 7.8 Hz, 2H), 7.66 - 7.48 (m, 3H), 7.36 (t, J = 7.9 Hz, 2H), 7.11 (t, J = 7.4 Hz, 1H). ^{13}C {1H} NMR (101 MHz, DMSO-d_6) δ 165.5, 139.2, 135.0, 131.5, 128.6, 128.4, 127.6, 123.6, 120.3. HR-MS (ESI, positive): m/z calculated for $C_{13}H_{12}NO$ $[M+H]^+$ 198.0913, found: 198.0910.

N-(*p*-Tolyl)benzamide (**3b**).[12a] White solid, petroleum ether/ethyl acetate = 10/1, yield 92 % (97mg), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, J = 7.3 Hz, 2H), 7.51 (tt, J = 14.9, 7.3 Hz, 5H), 7.17 (d, J = 8.2 Hz, 2H), 2.34 (s, 3H). ^{13}C {1H} NMR (101 MHz, $CDCl_3$) δ 165.1, 134.9, 134.6, 133.7, 131.2, 129.1, 128.3, 126.5, 119.8, 20.4. HR-MS (ESI, positive): m/z calculated for $C_{14}H_{14}NO$ $[M+H]^+$ 212.1070, found: 212.1075.

N-(4-Methoxyphenyl)benzamide (**3c**).[20a] White solid, petroleum ether/ethyl acetate = 10/1, yield 83 % (94mg), ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.15 (s, 1H), 7.95 (d, J = 7.1Hz, 2H) 7.69 (d, J = 9.0 Hz, 1H), 7.60 - 7.51 (m, 3H), 6.94 (d, J = 8.9 Hz, 1H), 3.75 (s, 3H). ^{13}C {1H} NMR (101 MHz, DMSO-d_6) δ 165.1, 155.5, 135.0, 132.2, 131.4, 128.3, 127.5, 121.9, 113.7, 55.1. HR-MS (ESI, positive): m/z calculated for $C_{14}H_{14}NO_2$ $[M+H]^+$ 228.1019, found: 228.1027.

N-(4-Fluorophenyl)benzamide (**3d**).[12a] White solid, petroleum ether/ethyl acetate = 10/1, yield 81 %

(87mg), ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.33 (s, 1H), 8.00 - 7.92 (m, 2H), 7.81 (dd, J = 9.1, 5.1 Hz, 2H), 7.57 (dt, J = 14.7, 7.1 Hz, 3H), 7.21 (t, J = 8.9 Hz, 2H). ^{13}C {1H} NMR (101 MHz, DMSO-d_6) δ 165.4, 159.4 (d, J = 241.4 Hz), 135.5 (d, J = 3.0 Hz), 134.8, 131.6, 128.4, 127.6, 122.2 (d, J = 7.1 Hz), 115.3 (d, J = 22.2 Hz). HR-MS (ESI, positive): m/z calculated for $C_{13}H_{11}FNO$ $[M+H]^+$ 216.0819, found: 216.0811.

N-(4-Chlorophenyl)benzamide (**3e**).[12a] White solid, petroleum ether/ethyl acetate = 10/1, yield 85 % (98mg), ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.38 (s, 1H), 7.96 (d, J = 7.3 Hz, 2H), 7.83 (d, J = 8.8 Hz, 2H), 7.57 (dt, J = 26.3, 7.2 Hz, 3H), 7.42 (d, J = 8.8 Hz, 2H). ^{13}C {1H} NMR (101 MHz, DMSO-d_6) δ 165.6, 138.1, 134.7, 131.7, 128.5, 128.4, 127.6, 127.2, 121.8. HR-MS (ESI, positive): m/z calculated for $C_{13}H_{11}ClNO$ $[M+H]^+$ 232.0524, found: 232.0531.

N-(4-Bromophenyl)benzamide (**3f**).[12a] White solid, petroleum ether/ethyl acetate = 10/1, yield 79 % (108mg), ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.39 (s, 1H), 7.95 (d, J = 7.2 Hz, 2H), 7.78 (d, J = 8.8 Hz, 2H), 7.70 - 7.49 (m, 5H). ^{13}C {1H} NMR (101 MHz, DMSO-d_6) δ 165.6, 138.6, 134.7, 131.7, 131.4, 128.4, 127.7, 122.2, 115.3. HR-MS (ESI, positive): m/z calculated for $C_{13}H_{11}BrNO$ $[M+H]^+$ 276.0019, found: 276.0015.

N-(4-Nitrophenyl)benzamide (**3g**).[20c] White solid, petroleum ether/ethyl acetate = 10/1, yield 65 % (78mg), ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.83 (s, 1H), 8.27 (t, J = 6.0 Hz, 2H), 8.08 (d, J = 9.3 Hz, 2H), 8.04 - 7.95 (m, 2H), 7.61 (dt, J = 14.9, 7.2 Hz, 3H). ^{13}C {1H} NMR (101 MHz, DMSO-d_6) δ 166.3, 145.5, 142.4, 134.2, 132.1, 128.5, 127.9, 124.7, 119.8. HR-MS (ESI, positive): m/z calculated for $C_{13}H_{11}N_2O_3$ $[M+H]^+$ 243.0764, found: 243.0751.

N-(4-(Trifluoromethyl)phenyl)benzamide (**3h**).[20a] White solid, petroleum ether/ethyl acetate = 10/1, yield 69 % (91mg), ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.61 (s, 1H), 8.01 (dd, J = 20.4, 7.8 Hz, 4H), 7.73 (d, J = 8.6 Hz, 2H), 7.67 - 7.51 (m, 3H). ^{13}C {1H} NMR (101 MHz, DMSO-d_6) δ 166.0, 142.8, 134.5, 131.9, 128.4, 127.8, 125.9（q, J = 3.8 Hz） 124.4（q, J = 270.1 Hz）, 123.6（q, J = 32.1 Hz）, 120.1. HR-MS (ESI,

positive): m/z calculated for $C_{14}H_{11}F_3NO$ $[M+H]^+$ 266.0787, found: 266.0769.

N-(*o*-Tolyl)benzamide (**3i**).[12a] White solid, petroleum ether/ethyl acetate = 10/1, yield 85 % (89mg), ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 7.99 (d, J = 7.1 Hz, 2H), 7.62-7.51 (m, 3H), 7.39 - 7.12 (m, 4H), 2.24 (s, 3H). ^{13}C {1H} NMR (101 MHz, DMSO-d_6) δ 165.2, 136.4, 134.5, 133.7, 131.5, 130.3, 128.4, 127.6, 126.6, 125.9, 17.9. HR-MS (ESI, positive): m/z calculated for $C_{14}H_{14}NO$ $[M+H]^+$ 212.1070, found: 212.1075.

N-(*m*-Tolyl)benzamide (**3j**).[12a] White solid, petroleum ether/ethyl acetate = 10/1, yield 83 % (87mg), ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.19 (s, 1H), 7.96 - 7.94 (m, 2H), 7.64 - 7.51 (m, 5H), 7.23 (t, J = 7.8 Hz, 1H), 6.93 (d, J = 7.5 Hz, 1H), 2.31 (s, 3H). ^{13}C {1H} NMR (101 MHz, DMSO-d_6) δ 165.4, 139.1, 137.7, 135.0, 131.5, 128.4, 128.3, 127.6, 124.3, 120.9, 117.5, 21.2. HR-MS (ESI, positive): m/z calculated for $C_{14}H_{14}NO$ $[M+H]^+$ 212.1070, found: 212.1081.

N-(3-Fluorophenyl)benzamide (**3k**).[12a] White solid, petroleum ether/ethyl acetate = 10/1, yield 76 % (81mg), ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.46 (s, 1H), 7.96 (d, J = 7.1 Hz, 2H), 7.77 (d, J = 11.8 Hz, 1H), 7.59 (dq, J = 21.2, 7.2 Hz, 4H), 7.40 (q, J = 8.2 Hz, 1H), 6.97-6.92 (m, 1H). ^{13}C {1H} NMR (101 MHz, DMSO-d_6) δ 165.8, 163.2 (d, J = 241.4 Hz), 141.0 (d, J = 11.1 Hz), 134.6, 131.8, 130.3 (d, J = 10.1 Hz), 128.4, 127.7, 115.9 (d, J = 3.0 Hz), 110.2 (d, J = 20.2 Hz), 107.0 (d, J = 27.3 Hz). HR-MS (ESI, positive): m/z calculated for $C_{13}H_{11}FNO$ $[M+H]^+$ 216.0819, found: 216.0824.

N-(3-Chlorophenyl)benzamide (**3l**).[12a] White solid, petroleum ether/ethyl acetate = 10/1, yield 71 % (82mg), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 - 7.84 (m, 2H), 7.78 (t, J = 2.0 Hz, 1H), 7.56 (t, J = 7.4 Hz, 1H), 7.48 (t, J = 7.4 Hz, 3H), 7.29 (d, J = 8.1 Hz, 1H), 7.11 (d, J = 8.0 Hz, 1H). ^{13}C {1H} NMR (101 MHz, $CDCl_3$) δ 165.4, 138.6, 134.2, 134.0, 131.6, 129.5, 128.3, 126.6, 124.1, 119.9, 117.7. HR-MS (ESI, positive): m/z calculated for $C_{13}H_{11}ClNO$ $[M+H]^+$ 232.0524, found: 232.0518.

N-(3-Bromophenyl)benzamide (**3m**).[12a] White solid, petroleum ether/ethyl acetate = 10/1, yield 80 %

(109mg), ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.41 (s, 1H), 8.12 (s, 1H), 7.99 - 7.91 (m, 2H), 7.77 (dt, J = 7.6, 1.7 Hz, 1H), 7.66 - 7.50 (m, 3H), 7.38 - 7.26 (m, 2H). ^{13}C {1H} NMR (101 MHz, DMSO-d_6) δ 165.7, 140.9, 134.5, 131.8, 130.6, 128.4, 127.7, 126.2, 122.5, 121.4, 118.9. HR-MS (ESI, positive): m/z calculated for $C_{13}H_{11}BrNO$ $[M+H]^+$ 276.0019, found: 276.0021.

N-(3-Nitrophenyl)benzamide (**3n**).[12a] Yellow solid, petroleum ether/ethyl acetate = 10/1, yield 63 % (76mg), ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.72 (s, 1H), 8.82 (t, J = 2.1 Hz, 1H), 8.20 (d, J = 7.0 Hz, 1H), 8.07 - 7.94 (m, 3H), 7.62 (ddd, J = 27.4, 15.6, 7.6 Hz, 4H).7.69 - 7.62 (m, 2H), 7.59 - 7.55 (m, 2H). ^{13}C {1H} NMR (101 MHz, DMSO-d_6) δ 166.0, 147.9, 140.3, 134.2, 132.0, 130.0, 128.5, 127.7, 126.1, 118.1, 114.3. HR-MS (ESI, positive): m/z calculated for $C_{13}H_{11}N_2O_3$ $[M+H]^+$ 243.0764, found: 243.0769.

N-(3,5-Dimethylphenyl)benzamide (**3o**).[12a] White solid, petroleum ether/ethyl acetate = 10/1, yield 82 % (92mg), ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.10 (s, 1H), 7.95 (d, J = 7.1 Hz, 2H), 7.64 - 7.48 (m, 3H), 7.43 (s, 2H), 6.80 (s, 1H), 2.27 (s, 6H). ^{13}C {1H} NMR (101 MHz, DMSO-d_6) δ 165.4, 138.9, 137.5, 135.0, 131.4, 128.3, 127.6, 125.2, 118.1, 21.1. HR-MS (ESI, positive): m/z calculated for $C_{15}H_{16}NO$ $[M+H]^+$ 226.1226, found: 226.1221.

N-Propylbenzamide (**3p**).[12a] White solid, petroleum ether/ethyl acetate = 10/2, yield 67 % (54mg), ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.46 (s, 1H), 7.94 - 7.72 (m, 2H), 7.48 (dt, J = 24.6, 7.7 Hz, 3H), 3.21 (dd, J = 13.4, 6.5 Hz, 2H), 1.53 (dd, J = 14.4, 7.3 Hz, 2H), 0.89 (t, J = 7.4 Hz, 3H). ^{13}C {1H} NMR (101 MHz, DMSO-d_6) δ 166.1, 134.7, 130.9, 128.2, 127.1, 40.9, 22.4, 11.4. HR-MS (ESI, positive): m/z calculated for $C_{10}H_{14}NO$ $[M+H]^+$ 164.1070, found: 164.1065.

N-Benzylbenzamide (**3q**).[12a] White solid, petroleum ether/ethyl acetate = 10/1, yield 63 % (66mg), ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.10 (s, 1H), 7.51 (dt, J = 25.7, 7.1 Hz, 3H), 7.37 - 7.29 (m, 4H), 7.25 (dd, J = 8.8, 3.8 Hz, 1H), 4.49 (d, J = 6.0 Hz, 2H). ^{13}C {1H} NMR (101 MHz, DMSO-d_6) δ 166.2, 139.7, 134.3, 131.2,

128.3, 128.2, 127.2, 127.2, 126.7, 42.6. HR-MS (ESI, positive): m/z calculated for $C_{14}H_{14}NO$ $[M+H]^+$ 212.1070, found: 212.1072.

N-Cyclopentylbenzamide (**3r**).[20d] White solid, petroleum ether/ethyl acetate = 10/1, yield 80 % (75mg), ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.28 (d, J = 7.0 Hz, 1H), 7.83 (dd, J = 8.2, 1.2 Hz, 2H), 7.53 - 7.37 (m, 3H), 4.22 (dd, J = 14.0, 7.1 Hz, 1H), 1.95 - 1.80 (m, 2H), 1.70 (d, J = 2.0 Hz, 2H), 1.54 (dt, J = 13.8, 9.2 Hz, 4H). ^{13}C {1H} NMR (101 MHz, DMSO-d_6) δ 165.9, 134.8, 130.9, 128.1, 127.3, 50.9, 32.1, 23.6. HR-MS (ESI, positive): m/z calculated for $C_{12}H_{16}NO$ $[M+H]^+$ 190.1226, found: 190.1225.

N-Cyclohexylbenzamide (**3s**).[20a] White solid, petroleum ether/ethyl acetate = 10/1, yield 84 % (85mg), ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.20 (d, J = 7.8 Hz, 1H), 7.84 - 7.82 (m, 2H), 7.47 (dt, J = 25.8, 7.1 Hz, 3H), 3.76 (d, J = 3.6 Hz, 1H), 1.77 (dd, J = 32.1, 6.2 Hz, 4H), 1.61 (d, J = 12.2 Hz, 1H), 1.41-1.20 (m, 4H), 1.20-0.82 (m, 1H). ^{13}C {1H} NMR (101 MHz, DMSO-d_6) δ 165.3, 134.9, 130.9, 128.1, 127.2, 48.3, 32.4, 25.2, 24.9. HR-MS (ESI, positive): m/z calculated for $C_{13}H_{18}NO$ $[M+H]^+$ 204.1383, found: 204.1385.

N,N-Diethylbenzamide (**3t**).[16e] Colorless oil, petroleum ether/ethyl acetate = 100/15, yield 65 % (38mg), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (s, 5H), 3.48 (s, 2H), 3.18 (s, 2H), 1.18 (s, 3H), 1.03 (s, 3H). ^{13}C {1H} NMR (101 MHz, $CDCl_3$) δ 171.3, 137.3, 129.1, 128.4, 126.3, 43.3, 39.2, 14.2, 12.9. HR-MS (ESI, positive): m/z calculated for $C_{11}H_{16}NO$ $[M+H]^+$ 178.1226, found: 178.1231.

N,N-Dibenzylbenzamide (**3u**).[20a] White solid, petroleum ether/ethyl acetate = 10/2, yield 85 % (127mg), ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.51 - 7.11 (m, 15H), 4.49 (d, J = 78.6 Hz, 4H). ^{13}C {1H} NMR (101 MHz, DMSO-d_6) δ 171.2, 137.0, 136.6, 136.2, 129.5, 128.7, 128.5, 127.6, 127.4, 127.2, 126.8, 126.4, 51.4, 46.8. HR-MS (ESI, positive): m/z calculated for $C_{21}H_{20}NO$ $[M+H]^+$ 302.1539, found: 302.1532.

N-benzyl-*N*-methylbenzamide (**3v**).[16e] Colorless oil, petroleum ether/ethyl acetate = 10/1, yield 85 % (95mg), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, J = 7.2 Hz, 2H), 7.30 (d, J = 18.6 Hz, 6H), 7.22 (d, J = 5.8 Hz,

1H), 7.09 (s, 1H), 4.69 (s, 1H), 4.43 (s, 1H), 2.95 (s, 1.5H), 2.78 (s, 1.5H). ^{13}C {1H} NMR (101 MHz, $CDCl_3$) δ 172.3, 171.6, 137.1, 136.6, 136.3, 136.2, 129.6, 128.8, 128.7, 128.5, 128.4, 128.2, 127.6, 127.6, 127.5, 127.0, 126.8, 126.8, 55.2, 50.8, 37.0, 33.2. HR-MS (ESI, positive): m/z calculated for $C_{15}H_{16}NO$ $[M + H]^+$ 226.1226, found: 226.1229.

Phenyl(pyrrolidin-1-yl)methanone (**3w**).[16e] Colorless oil, petroleum ether/ethyl acetate = 2/1, yield 78 % (68mg), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 - 7.33 (m, 5H), 3.54 (d, *J* = 68.9 Hz, 4H), 1.92 (m, 4H). ^{13}C {1H} NMR (101 MHz, $CDCl_3$) δ 169.7, 137.3, 129.8, 128.2, 127.1, 49.6, 46.2, 26.4, 24.5. HR-MS (ESI, positive): m/z calculated for $C_{11}H_{14}NO$ $[M+H]^+$ 176.1070, found: 176.1073.

Indolin-1-yl(phenyl)methanone (**3x**).[20b] White solid, petroleum ether/ethyl acetate = 10/2, yield 69 % (76mg), ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.29 - 6.77 (m, 9H), 3.99 (t, *J* = 8.2 Hz, 2H), 3.08 (t, *J* = 8.3 Hz, 2H). ^{13}C {1H} NMR (101 MHz, DMSO-d_6) δ 167.9, 142.5, 136.9, 132.6, 129.9, 128.4, 126.9, 126.7, 124.9, 123.6, 116.3, 50.2, 27.6. HR-MS (ESI, positive): m/z calculated for $C_{15}H_{14}NO$ $[M+H]^+$ 224.1070, found: 224.1072.

Morpholino(phenyl)methanone (**3y**).[16e] Colorless oil, petroleum ether/ethyl acetate = 4/1, yield 87 % (83mg), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, J = 6.3 Hz, 5H), 3.98 – 3.35 (m, 8H). ^{13}C {1H} NMR (101 MHz, $CDCl_3$) δ 170.4, 135.3, 129.9, 128.6, 127.1, 66.9. HR-MS (ESI, positive): m/z calculated for $C_{11}H_{14}NO_2$ $[M+H]^+$ 192.1019, found: 192.1013.

4-Methyl-*N*-phenylbenzamide (**3ab**).[12a] White solid, petroleum ether/ethyl acetate = 10/1, yield 88 % (92mg), ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.14 (s, 1H), 7.87 (d, *J* = 8.2 Hz, 2H), 7.77 (d, *J* = 7.6 Hz, 2H), 7.34 (t, *J* = 7.1 Hz, 4H), 7.09 (t, *J* = 7.4 Hz, 1H). ^{13}C {1H} NMR (101 MHz, DMSO-d_6) δ 165.3, 141.5, 139.2, 132.0, 128.9, 128.5, 127.6, 123.5, 120.3, 21.0. HR-MS (ESI, positive): m/z calculated for $C_{14}H_{14}NO$ $[M+H]^+$ 212.1070, found: 212.1079.

4-Methoxy-*N*-phenylbenzamide (**3ac**).[20f] White solid, petroleum ether/ethyl acetate = 10/1, yield 78 % (88mg), ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.08 (s, 1H), 7.97 (d, *J* = 8.8 Hz, 2H), 7.77 (d, *J* = 7.7 Hz, 2H), 7.34 (t, *J* = 7.9 Hz, 2H), 7.08 (dd, *J* = 10.7, 8.1 Hz, 3H), 3.84 (s, 3H). ^{13}C {1H} NMR (101 MHz, DMSO-d_6) δ 164.8, 161.8, 139.3, 129.5, 128.5, 127.0, 123.4, 120.3, 113.6, 55.4. HR-MS (ESI, positive): m/z calculated for $C_{14}H_{14}NO_2$ $[M+H]^+$ 228.1019, found: 228.1025.

4-Fluoro-*N*-phenylbenzamide (**3ad**).[12a] White solid, petroleum ether/ethyl acetate = 10/1, yield 75 % (80mg), ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.26 (s, 1H), 8.04 (dd, *J* = 8.8, 5.5 Hz, 2H), 7.76 (d, *J* = 8.6 Hz, 2H), 7.61 - 7.19 (m, 4H), 7.11 (t, J = 7.3 Hz, 1H). ^{13}C {1H} NMR (101 MHz, DMSO-d_6) δ 165.2, 164.3 (d, *J* = 161.6 Hz), 138.9, 131.3 (d, *J* = 3.0 Hz), 130.3 (d, *J* = 9.1 Hz), 128.5, 123.6, 120.3, 115.3 (d, *J* = 22.2 Hz). HR-MS (ESI, positive): m/z calculated for $C_{13}H_{11}FNO$ $[M+H]^+$ 216.0819, found: 216.0823.

4-Chloro-*N*-phenylbenzamide (**3ae**).[12a] White solid, petroleum ether/ethyl acetate = 10/1, yield 80 % (92mg), ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.32 (s, 1H), 8.20 - 7.88 (m, 2H), 7.77 (d, *J* = 7.6 Hz, 2H), 7.61 (d, *J* = 8.5 Hz, 2H), 7.36 (t, *J* = 7.9 Hz, 2H), 7.12 (t, *J* = 7.4 Hz, 1H). ^{13}C {1H} NMR (101 MHz, DMSO-d_6) δ 164.4, 138.9, 136.3, 133.6, 129.6, 128.6, 128.4, 123.8, 120.4. HR-MS (ESI, positive): m/z calculated for $C_{13}H_{11}ClNO$ $[M+H]^+$ 232.0524, found: 232.0523.

4-Bromo-*N*-phenylbenzamide (**3af**).[12a] White solid, petroleum ether/ethyl acetate = 10/1, yield 78 % (107mg), ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.32 (s, 1H), 7.92 (d, *J* = 8.5 Hz, 2H), 7.76 (t, *J* = 7.1 Hz, 4H), 7.36 (t, *J* = 7.9 Hz, 2H), 7.12 (t, *J* = 7.4 Hz, 1H). ^{13}C {1H} NMR (101 MHz, DMSO-d_6) δ 164.5, 138.9, 133.9, 131.4, 129.8, 128.6, 125.3, 123.8, 120.4. HR-MS (ESI, positive): m/z calculated for $C_{13}H_{11}BrNO$ $[M+H]^+$ 276.0019, found: 276.0023.

3-Methyl-*N*-phenylbenzamide (**3ag**).[12a] White solid, petroleum ether/ethyl acetate = 10/1, yield 83 % (87mg), ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.22 (s, 1H), 7.77 (t, *J* = 10.8 Hz, 4H), 7.56 - 7.29 (m, 4H), 7.10

(t, J = 7.3 Hz, 1H), 2.40 (s, 3H). ^{13}C {1H} NMR (101 MHz, DMSO-d_6) δ 165.6, 139.2, 137.6, 134.9, 132.1, 128.5, 128.2, 128.1, 124.8, 123.5, 120.3, 20.9. HR-MS (ESI, positive): m/z calculated for $C_{14}H_{14}NO$ $[M+H]^+$ 212.1070, found: 212.1085.

3-Methoxy-*N*-phenylbenzamide (**3ah**).[20e] White solid, petroleum ether/ethyl acetate = 10/1, yield 73 % (82mg), ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.22 (s, 1H), 7.78 (d, J = 8.1 Hz, 2H), 7.62 - 7.41 (m, 3H), 7.36 (t, J = 7.8 Hz, 2H), 7.26 - 6.96 (m, 2H), 3.84 (s, 3H). ^{13}C {1H} NMR (101 MHz, DMSO-d_6) δ 165.2, 159.1, 139.1, 136.4, 129.5, 128.5, 123.7, 120.4, 119.8, 117.2, 112.9, 55.3. HR-MS (ESI, positive): m/z calculated for $C_{14}H_{14}NO_2$ $[M+H]^+$ 228.1019, found: 228.1027.

3-Fluoro-*N*-phenylbenzamide (**3ai**).[12a] White solid, petroleum ether/ethyl acetate = 10/1, yield 70 % (75mg), ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.32 (s, 1H), 7.80 (dd, J = 18.2, 7.8 Hz, 4H), 7.63 - 7.56 (m, 1H), 7.45 (td, J = 8.6, 2.6 Hz, 1H), 7.37 (t, J = 7.9 Hz, 2H), 7.12 (t, J = 7.4 Hz, 1H). ^{13}C {1H} NMR (101 MHz, DMSO-d_6) δ 164.1 (d, J = 3.0 Hz), 161.9（d, J = 245.4 Hz）, 160.7, 138.8, 137.2 (d, J = 7.1 Hz), 130.6 (d, J = 8.1 Hz), 128.6, 123.9 (d, J = 2.1 Hz), 123.8, 120.4, 118.5 (d, J = 21.2 Hz), 114.5 (d, J = 22.2 Hz). HR-MS (ESI, positive): m/z calculated for $C_{13}H_{11}FNO$ $[M+H]^+$ 216.0819, found: 216.0824.

3-Chloro-*N*-phenylbenzamide (**3aj**).[12a] White solid, petroleum ether/ethyl acetate = 10/1, yield 70 % (80mg), ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.36 (s, 1H), 8.01 (s, 1H), 7.92 (d, J = 7.7 Hz, 1H), 7.77 (d, J = 7.9 Hz, 2H), 7.67 (d, J = 7.1 Hz, 1H), 7.58 (t, J = 7.8 Hz, 1H), 7.37 (t, J = 7.8 Hz, 2H), 7.12 (t, J = 7.4 Hz, 1H). ^{13}C {1H} NMR (101 MHz, DMSO-d_6) δ 164.0, 138.8, 136.9, 133.2, 131.4, 130.4, 128.6, 127.4, 126.5, 123.9, 120.4. HR-MS (ESI, positive): m/z calculated for $C_{13}H_{11}ClNO$ $[M+H]^+$ 232.0524, found: 232.0522.

3,5-Dimethyl-*N*-phenylbenzamide (**3ak**).[12a] White solid, petroleum ether/ethyl acetate = 10/1, yield 82 % (92mg), ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.16 (s, 1H), 7.77 (d, J = 7.6 Hz, 2H), 7.55 (s, 2H), 7.34 (t, J = 7.9 Hz, 2H), 7.22 (s, 1H), 7.09 (t, J = 7.4 Hz, 1H), 2.36 (s, 6H). ^{13}C {1H} NMR (101 MHz, DMSO-d_6) δ

165.7, 139.2, 137.5, 135.0, 132.7, 128.5, 125.3, 123.5, 120.3, 20.8. HR-MS (ESI, positive): m/z calculated for $C_{15}H_{16}NO$ $[M+H]^+$ 226.1226, found: 226.1229.

N-Phenyl-2-naphthamide (**3al**).[12a] White solid, petroleum ether/ethyl acetate = 10/1, yield 65 % (80mg), ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (s, 1H), 7.91 (q, *J* = 8.2 Hz, 4H), 7.70 (d, *J* = 7.6 Hz, 2H), 7.57 (d, *J* = 6.9, 1.4 Hz, 2H), 7.39 (t, *J* = 8.0 Hz, 2H), 7.17 (t, *J* = 7.4 Hz, 1H). ^{13}C {1H} NMR (101 MHz, $CDCl_3$) δ 165.8, 138.0, 134.9, 132.6, 132.2, 129.1, 128.9, 128.8, 127.9, 127.8, 127.5, 126.9, 124.6, 123.5, 120.3. HR-MS (ESI, positive): m/z calculated for $C_{17}H_{14}NO$ $[M+H]^+$ 248.1070, found: 248.1078.

ASSOCIATED CONTENT

Supporting Information

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

AUTHOR INFORMATION

Corresponding Author

E-mail: zhangjin@sust.edu.cn

mym63@sina.com

michal.szostak@rutgers.edu

ORCID

Jin Zhang: 0000-0002-6616-7087

Yangmin Ma: 0000-0002-6980-9532

Michal Szostak: 0000-0002-9650-9690

ACKNOWLEDGMENT

J.Z. thanks the China Scholarship Council (No. 201808610096). Financial support was provided by

Scientific Research Project of Shaanxi Province Education Department, China (17JK0107) and the Foundation for Young Scholars of Shaanxi University of Science and Technology (No. BJ12-26). M.S. thanks Rutgers University and the NSF (CAREER CHE-1650766) for support.

REFERENCES

(1) Greenberg, A.; Breneman, C. M.; Liebman, J. F., Eds. *The Amide Linkage: Structural Significance in Chemistry, Biochemistry, and Materials Science*; Wiley: New York, **2000**.

(2) For reviews, see: (a) de Figueiredo, R. M.; Suppo, J. S.; Campagne, J. M. Nonclassical Routes for Amide Bond Formation. *Chem. Rev.* **2016**, *116*, 12029-12122. (b) Ojeda-Porras, A.; Gamba-Sanchez, D. Recent Developments in Amide Synthesis Using Nonactivated Starting Materials. *J. Org. Chem.* **2016**, *81*, 11548-11555. (c) Pattabiraman, V. R.; Bode, J. W. Rethinking Amide Bond Synthesis. *Nature*, **2011**, *480*, 471-479. (d) Allen, C. L.; Williams, J. M. Metal-Catalysed Approaches to Amide Bond Formation. *Chem. Soc. Rev.* **2011**, *40*, 3405-3415. (e) Valeur, E.; Bradley, M. Amide Bond Formation: Beyond the Myth of Coupling Reagents. *Chem. Soc. Rev.* **2009**, *38*, 606-631.

(3) (a) Brown, D. G.; Boström, J. Analysis of Past and Present Synthetic Methodologies on Medicinal Chemistry: Where Have All the New Reactions Gone? *J. Med. Chem.* **2016**, *59*, 4443-4458. (b) Roughley, S. D.; Jordan, A. M. The Medicinal Chemist's Toolbox: An Analysis of Reactions Used in the Pursuit of Drug Candidates. *J. Med. Chem.* **2011**, *54*, 3451-3479. (c) Montalbetti, C. A. G. N.; Falque, V. Amide Bond Formation and Peptide Coupling. *Tetrahedron*, **2005**, *61*, 10827-10852. (d) Dunetz, J. R.; Magano, J.; Weisenburger, G. A. Large-Scale Applications of Amide Coupling Reagents for the Synthesis of Pharmaceuticals. *Org. Process Res. Dev.* **2016**, *20*, 140-177. (e) Zhang, J.; Liu, J.; Ma, Y.; Ren, D.; Cheng, P.; Zhao, J.; Zhang, F.; Yao, Y. One-Pot Synthesis and Antifungal Activity against Plant Pathogens of Quinazolinone derivatives Containing an Amide Moiety. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 2273-2277. (f)

Zhang, J.; Zhao, J.-W; Wang, L.-P; Liu, J.; Ren, D.-C; Ma, Y.-M. Design, Synthesis and Docking Studies of some Spiro-Oxindole Dihydroquinazolinones as Antibacterial agents. *Tetrahedron,* **2016**, *72*, 936-943.

(4) For an excellent perspective, see: Constable, D. J. C.; Dunn, P. J.; Hayler, J. D.; Humphrey, G. R.; Leaser, Jr., J. L.; Linderman, R. J.; Lorenz, K.; Manley, J.; Pearlman, B. A.; Wells, A.; Zaks, A.; Zhang, T. Y. Key Green Chemistry Research Areas—A Perspective from Pharmaceutical Manufacturers. *Green Chem.* **2007**, *9*, 411-420.

(5) (a) Shangguan, N.; Katukojvala, S.; Greenberg, R.; Williams, L. J. The Reaction of Thio Acids with Azides: A New Mechanism and New Synthetic Applications *J. Am. Chem. Soc.* **2003**, *125*, 7754-7755. (b) Wu, X.; Hu, L. Efficient Amidation from Carboxylic Acids and Azides via Selenocarboxylates: Application to the Coupling of Amino Acids and Peptides with Azides. *J. Org. Chem.* **2007**, *72*, 765-774.

(6) (a) Schoenberg, A.; Heck, R. F. Palladium-Catalyzed Amidation of Aryl, Heterocyclic, and Vinylic Halides. *J. Org. Chem.* **1974**, *39*, 3327-3331. (b) Roy, S.; Roy, S.; Gribble, G. W. Metal-catalyzed Amidation. *Tetrahedron,* **2012**, *68*, 9867-9923. (c) *Science of Synthesis: Cross-Coupling and Heck-Type Reactions*, Molander, G. A.; Wolfe, J. P.; Larhed, M., Eds.; Thieme: Stuttgart, **2013**.

(7) For leading reviews, see: (a) Beller, M.; Wu, X.-F. *Transition Metal Catalyzed Carbonylation Reactions*; Springer: Berlin, **2013**. (b) Wu, X.-F.; Neumann, H.; Beller, M. Synthesis of Heterocycles via Palladium-Catalyzed Carbonylations. *Chem. Rev.* **2013,** *113*, 1-35. (c) Wu, X.-F.; Neumann, H.; Beller, M. Palladium-Catalyzed Carbonylative Coupling Reactions between Ar-X and Carbon Nucleophiles. *Chem. Soc. Rev.* **2011**, *40*, 4986-5009. (d) Brennfuhrer, A.; Neumann, H.; Beller, M. Palladium-Catalyzed Carbonylation Reactions of Aryl Halides and Related Compounds. *Angew. Chem. Int. Ed.* **2009,** *48*, 4114-4133. (e) Barnard, C. F. J. Palladium-Catalyzed Carbonylation - A Reaction Come of Age. *Organometallics,* **2008**, *27*, 5402-5422. (f) Fang, W.; Zhu, H.; Deng, Q.; Liu, S.; Liu, X.; Shen, Y. Tu, T. Design and Development of Ligands for Palladium-

Catalyzed Carbonylation Reactions. *Synthesis*, **2014,** *46,* 1689-1708. (g) Wu, X.-F.; Fang, X.; Wu, L.; Jackstell, R.; Neumann, H.; Beller, M. Transition-Metal-Catalyzed Carbonylation Reactions of Olefins and Alkynes: A Personal Account. *Acc. Chem. Res.* **2014,** *47,* 1041-1053. (h) Peng, J. B.; Qi, X.; Wu, X.-F. Recent Achievements in Carbonylation Reactions: A Personal Account. *Synlett,* **2017**, *28,* 175-194. (i) Shen, C.; Wu, X.-F. Palladium-Catalyzed Carbonylative Multicomponent Reactions. *Chem. Eur. J.* **2017**, *23,* 2973-2987.

(8) For select recent developments, see: (a) Friis, S. D.; Lindhardt, A. T.; Skrydstrup, T. The Development and Application of Two-Chamber Reactors and Carbon Monoxide Precursors for Safe Carbonylation Reactions. *Acc. Chem. Res.* **2016**, *49,* 594-605. (b) Gautam, P.; Bhanage, B. M. Recent Advances in the Transition Metal Catalyzed Carbonylation of Alkynes, Arenes and Aryl Halides Using CO Surrogates. *Catl. Sci. Technol.* **2015**, *5,* 4663-4702. (c) Wu, L.; Liu, Q.; Jackstell, R.; Beller, M. Carbonylations of Alkenes with CO Surrogates. *Angew. Chem. Int. Ed.* **2014**, *53,* 6310-6320.

(9) Wang, D.; Weinstein, A. B.; White, P. B.; Stahl, S. S. Ligand-Promoted Palladium-Catalyzed Aerobic Oxidation Reactions. *Chem. Rev.* **2018**, *118,* 2636-2679.

(10) (a) Li, W. F.; Wu, X.-F. Palladium-Catalyzed Aminocarbonylation of *N*-chloroamines with Boronic Acids. *Chem. Eur. J.* **2015**, *21,* 7374-7378. See also: (b) Yin, Z. P.; Li, W. F.; Wu, X.-F. Copper-Catalyzed Carbonylative Cross-Coupling of Arylboronic Acids with N-Chloroamines for the Synthesis of Aryl Amides. *Eur. J. Org. Chem.* **2017**, *2017*,1769-1772.

(11) (a) Ren, L.; Li, X.; Jiao, N. Dioxygen-Promoted Pd-Catalyzed Aminocarbonylation of Organoboronic Acids with Amines and CO: A Direct Approach to Tertiary Amides. *Org. Lett.* **2016**, *18,* 5852-5855. See also: (b) Ren, L.; Jiao, N. Pd/Cu-cocatalyzed Aerobic Oxidative Carbonylative Homocoupling of Arylboronic Acids and CO: A Highly Selective Approach to Diaryl Ketones. *Chem. Asian J.* **2014**, *9,* 2411-2414.

(12) For select examples of oxidative cross-couplings, see: (a) Zhang, J.; Ma, Y.-Q; Ma, Y.-M. Synthesis of Secondary Amides through the Palladium(II)-Catalyzed Aminocarbonylation of Arylboronic Acids with Amines or Hydrazines and Carbon Monoxide. *Eur. J. Org. Chem.* **2018,** *2018*, 1720-1725. (b) Zhou, Q.; Wei, S.; Han, W. In Situ Generation of Palladium Nanoparticles: Ligand-free Palladium Catalyzed Pivalic Acid assisted Carbonylative Suzuki Reactions at Ambient Conditions. *J. Org. Chem.* **2014**, *79*, 1454-1460. (c) Xu, T.; Sha, F.; Alper, H. Highly Ligand-Controlled Regioselective Pd-Catalyzed Aminocarbonylation of Styrenes with Aminophenols. *J. Am. Chem. Soc.* **2016**, *138*, 6629-6635. (d) Lu, F.; Chen, Z.; Li, Z.; Wang, X.; Peng, X.; Li, C.; Fang, L.; Liu, D.; Gao, M.; Lei, A. Palladium/Copper-Catalyzed Oxidative Coupling of Arylboronic Acids with Isocyanides: Selective Routes to Amides and Diaryl Ketones. *Org. Lett.* **2017**, *19*, 3954-3957. (e) Zhu, F.; Wu X.-F. Palladium-catalyzed construction of amidines from arylsilanes in the absence of a ligand under oxidative conditions. *New J. Chem.* **2018**, *42*, 10396-10399.

(13) For reviews, see: (a) Denmark, S. E.; Ambrosi, A. Why You Really Should Consider Using Palladium-Catalyzed Cross-Coupling of Silanols and Silanolates. *Org. Process Res. Dev.* **2015**, *19*, 982-994. (b) Denmark, S. E.; Liu, J. H. Silicon-based Cross-Coupling Reactions in the Total Synthesis of Natural Products. *Angew. Chem. Int. Ed.* **2010**, *49*, 2978-2986. (c) Denmark, S. E.; Regens, C. S. Palladium-Catalyzed Cross-Coupling Reactions of Organosilanols and their Salts: Practical Alternatives to Boron- and Tin-based Methods. *Acc. Chem. Res.* **2008**, *41*, 1486-1499. (d) Komiyama, T.; Minami, Y.; Hiyama, T. Recent Advances in Transition-Metal-Catalyzed Synthetic Transformations of Organosilicon Reagents. *ACS Catal.* **2017**, *7*, 631-651. (e) Nakao, Y.; Hiyama, T. Silicon-based Cross-Coupling Reaction: An Environmentally Benign Version. *Chem. Soc. Rev.* **2011**, *40*, 4893-4901.

(14) Reports on mutagenicity of boronic acids: (a) Hansen, M. M.; Jolly, R. A.; Linder, R. J. Boronic Acids and Derivatives - Probing the Structure-Activity Relationships for Mutagenicity. *Org. Process Res. Dev.*

2015, *19*, 1507-1516. (b) O'Donovan, M. R.; Mee, C. D.; Fenner, S.; Teasdale, A.; Phillips, D. H. Boronic Acids-A Novel Class of Bacterial Mutagen. *Mutat. Res. Genet. Toxicol. Environ. Mutagen.* **2011**, *724*, 1-6.

(15) Reviews on cross-couplings with organometallic reagents: (a) Jana, R.; Pathak, T. P.; Sigman, M. S. Advances in Transition Metal (Pd, Ni, Fe)-Catalyzed Cross-Coupling Reactions Using Alkyl-organometallics as Reaction Partners *Chem. Rev.* **2011**, 111, 1417-1492. (b) Giri, R.; Thapa, S.; Kafle, A. Palladium-Catalysed, Directed C-H Coupling with Organometallics. *Adv. Synth. Catal.* **2014**, *356*, 1395-1411.

(16) (a) Shi, S.; Nolan, S. P.; Szostak, M. Well-Defined Palladium(II)-NHC Precatalysts for Cross-Coupling Reactions of Amides and Esters by Selective N-C/O-C Cleavage. *Acc. Chem. Res.* **2018**, 51, 2589-2599. (b) Meng, G.; Szostak, M. General Olefin Synthesis by the Palladium-Catalyzed Heck Reaction of Amides:Sterically Controlled Chemoselective N-C Activation. *Angew. Chem. Int. Ed.* **2015**, *54*, 14518-14522. (c) Nareddy, P.; Jordan, F.; Szostak, M. Highly Chemoselective Ruthenium(ii)-Catalyzed Direct Arylation of Cyclic and *N,N*-dialkyl Benzamides with Aryl Silanes. *Chem. Sci.* **2017**, *8*, 3204-3210. (d) Nareddy, P.; Jordan, F.; Szostak, M. Ruthenium(II)-Catalyzed Direct C-H Arylation of Indoles with Arylsilanes in Water. *Org. Lett.* **2018**, *20*, 341-344.

(17) Zhou, C.; Larock, R. C. Tetrasubstituted Olefin Synthesis via Pd-Catalyzed Addition of Arylboronic Acids to Internal Alkynes Using O_2 as an Oxidant. *J. Org. Chem.* **2006**, *71*, 3184-3191.

(18) Chen, B.; Peng, J.-B.; Ying, J.; Qi, X.-X.; Wu, X.-F. A Palladium-Catalyzed Domino Procedure for the Synthesis of Unsymmetrical Ureas. *Adv. Synth. Catal.* **2018**, *360*, 2820-2824.

(19)(a) Murata, M.; Suzuki, K.; Watanabe, S.; Masuda, Y . Synthesis of Arylsilanes via Palladium(0)-Catalyzed Silylation of Aryl Halides with Hydrosilane. *J. org. Chem.* **1997**, 62, 8569-8571. (b) Manoso, A. S.; Ahn, C.; Soheili, A.; Handy, C. J.; Correia, R.; DeShong, P. Improved Synthesis of Aryltrialkoxysilanes via Treatment of Aryl Grignard or Lithium Reagents with Tetraalkyl Orthosilicates. *J. org. Chem.* **2004**, *69*, 8305-

8314. (c) Yu, J.; Liu, J.; Shi, G,; Shao, C.; Zhang, Y. Ligand-Promoted Oxidative Cross-Coupling of Aryl Boronic Acids and Aryl Silanes by Palladium Catalysis. *Angew. Chem. Int. Ed.* **2015**, *54*, 4079-4082. (d) Taylor, P. G.; Bassindale, A. R.; Pourny, M.; Stevenson, R.; Hursthouseb, M. B.; Coles, S. J. Further studies of fluoride ion entrapment in octasilsesquioxane cages; X-ray crystal structure studies and factors that affect their formation. *Dalton Trans.* **2012**, *41*, 2048-2059. (e) Cheng, K.; Zhao, B.-L.; Hu, S.; Zhang, X.-M.; Qi, C.-Z. Pd-catalyzed cross-coupling reactions of arenediazonium salts with arylsilanes and aryltrifluoroborates in water. *Tetra. Lett.* **2013**, *54*, 6211−6214. (f) Luo, F,; Pan, C.-D.; Qian, P.-C.; Cheng, J. Copper(II)-Catalyzed Esterification of Arenecarboxylic Acids with Aryl- and Vinyl-Substituted Trimethoxysilanes. *Synthesis,* **2010**, *12,* 2005-2010. (g) Diachun,N. A.; Marcus, A. H.; Hussey, D. M.; Fayer, M. D. Dynamics in Polydimethylsiloxane: The Effect of Solute Polarity. *J. Am. Chem. Soc.* **1994**, *116*, 1027-1032.

(20) (a) Gockel, S. N.; Hull, K. L. Chloroform as a Carbon Monoxide Precursor: In or Ex Situ Generation of CO for Pd-Catalyzed Aminocarbonylations. *Org. Lett.* **2015**, *17*, 3236-3239. (b) Li, W.-J.; Zhao, F.-F.; Ding, M.-W. Unexpected Synthesis of *N*-Acyl Indolines via A Consecutive Cyclization of iminophosphorane. *Synlett*, **2011**, 265-267. (c) Otsuka, R.; Maruhashi, K.; Ohwada, T. Latent Brønsted Base Solvent-Assisted Amide Formation from Amines and Acid Chlorides. *Synthesis*, **2018,** *50,* 2041-2057. (d) Zultanski, S. L.; Zhao J.-Y.; Stahl, S. S. Practical Synthesis of Amides via Copper/ABNO-Catalyzed Aerobic Oxidative Coupling of Alcohols and Amines. *J. Am. Chem. Soc.* **2016**, *138*, 6416-6419. (e) Qian, C.-W.; Zhang X.-M.; Zhang Y.; Shen, Q. Heterobimetallic Complexes of Lanthanide and Lithium Metals with Dianionic Guanidinate Ligands: Syntheses, Structures and Catalytic Activity for Amidation of Aldehydes with Amines. *J. Organometallic. Chem.* **2010**, *695* ,747-752. (f) Hu, Q.-H.; Wang, L.-L.; Wang, C.; Wu, Y.-B.; Ding Z.-X.; Yuan. R.-S. Ligand-free Pd(0)/SiO_2-Catalyzed Aminocarbonylation of Aryl Iodides to Amides under Atmospheric CO Pressure. *RSC Adv.*, **2017**, *7*, 37200-37207.