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Palladium Catalyzed C−H Functionalization of *O*-Arylcarbamates: Selective *ortho*-Bromination Using NBS

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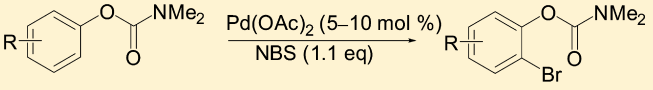
Supporting Information

ABSTRACT: A series of cyclometalated palladium complexes derived from *O*-phenylcarbamates has been synthesized by the reaction of the respective carbamates with $Pd(OAc)_2$ in the presence of acids, CF_3CO_2H, CF_3SO_3H, and *p*-TsOH. The palladacycles were observed to coordinate amines and electron rich anilines but not sulfonamides or carboxamides. Analysis of the ^{t}Bu-NH_2 adduct of the palladacycle **2b** (**2b**·^{t}Bu-NH_2) by NMR spectroscopy (NOE) revealed a *cis*-coordination of the amine. However, the amine adducts failed to undergo *ortho*-amination (C−N bond formation) under varied reaction conditions. Notably, the palladacycle **1d** was found to react efficiently with *N*-iodosuccinimide (NIS) to yield the *ortho*-iodinated carbamate, **1e**. More significantly, this reaction can be extended to a palladium-catalyzed *ortho* C−H bromination of aryl-*O*-carbamates even at 5 mol % loading of $Pd(OAc)_2$ using *N*-bromosuccinimide (NBS).



42–89 % yield

INTRODUCTION

The emergence and development of aromatic C−H functionalization chemistry for the formation of Ar−C and Ar−X (X = halogen, O, S, N) bonds has relied heavily on Pd catalysis.[1] However, it must be pointed out that unlike the more widely encountered C−C or other C−heteroatom bond formation, palladium catalyzed C−N bond-forming reactions have been achieved with limited success.[2] Many of the challenges associated with development of synthetically useful C−H amination reactions are reminiscent of those encountered during the early progress of the Buchwald−Hartwig amination reaction.[3]

Synthetic efforts to-date have focused on both the intramolecular as well as the intermolecular versions of the C−H amination reaction.[4,1d−f] Significantly, intramolecular C−H amination reactions have been demonstrated to efficiently generate several key aromatic *N*-heterocycles.[5] The intermolecular reactions, on the other hand, count on employing suitable chelating groups, like anilides,[6] *N*-heterocycles,[7] amides,[8] ketones,[9] and oximes[7] to direct the C−H functionalization. Interestingly, a plethora of *N*-reagents ranging from simple amides[7,9] to alkyl amines[8] have been shown to participate in the reaction and are used either with an internal or external oxidant. From a mechanistic viewpoint, Pd(II)/Pd(0),[10] Pd(0)/Pd(II),[6a] or Pd(II)/Pd(IV)[11] pathways have been proposed to be operational in the reactions.

Among the *N*-reagents found useful in synthetically relevant C−H amination reactions, the sulfonamides and carboxamides deserve special mention since the resulting aminated products can be readily converted to the respective free amines. In this respect, it is worth pointing out that in a recent report on C−H amidation of ketones, Liu[9] et al. have indicated that an initial coordination of the amide reagent to the Pd center in the C−H activated substrate is crucial for the subsequent oxidative C−N bond formation reaction. An earlier study by the Che[6] group had suggested the incorporation of the amide reagent through the intermediacy of a nitrene species.

In keeping with our longstanding interest in C−H amination reactions[12] we became interested in exploring the Pd-catalyzed C−H amination of the relatively little explored *O*-aryl carbamates using amide *N*-reagents, which could produce synthetically important *o*-aminophenol derivatives. To our knowledge the only C−H functionalizations reported of *O*-aryl carbamate substrates are Pd-[13] and Rh-catalyzed[14] *ortho* arylation/olefination reactions, respectively. The *O*-aryl carbamates represent an interesting class of compounds since they can undergo a variety of Ni-catalyzed transformations involving cleavage of the C−O bond.[15] More importantly, the carbamate functionality also serves as a latent directing group, since it can be removed post *ortho*-functionalization to generate the parent arene.[16]

Herein we report the synthesis of cyclometalated palladium complexes derived from *O*-phenyl carbamates and their amine adducts. Attempts to achieve C−N bond formation from these adducts under oxidative conditions have been unsuccessful. However, the palladacycles were found to efficiently yield *ortho*-halogenated products upon reaction with *N*-halosuccinimide (NXS) reagents, and we were able to render the *ortho*-bromination reaction catalytic under suitable conditions.

RESULTS AND DISCUSSION

Toward Dehydrogenative Amination. A recent report of palladium-catalyzed dehydrogenative arylation of *O*-phenyl-

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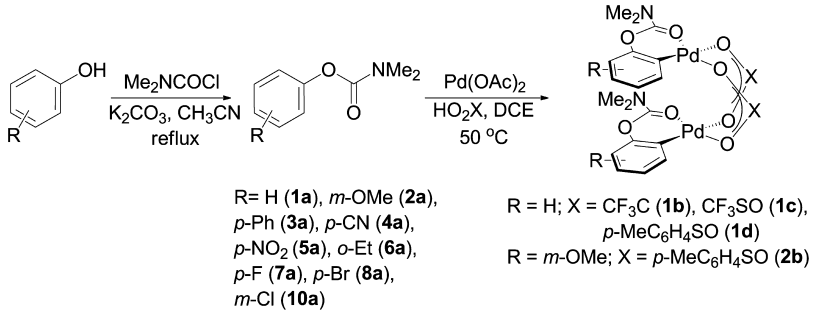
Scheme 1. Synthesis of Carbamates and the Cyclometalated Palladium Complexes



carbamates[13a] by Dong et al. led us to reason that the intermediate palladacycles could potentially react with a suitable *N*-reagent to generate *ortho*-aminated carbamates. However, we were disappointed that no amidation product was observed upon reaction of **1a** (Scheme 1) with either Tos-NH_2 or Nos-NH_2 using a catalytic amount of $Pd(OAc)_2$ (10 mol %) in the presence of TFA (50 mol %) as additive and $K_2S_2O_8$ as a stoichiometric oxidant. Furthermore, NMR analysis of the reaction mixture revealed that the palladacycle (even in stoichiometric amount) resulting from C−H activation of **1a** was not generated during the reaction. At this point, we decided to synthesize the palladacycle and explore its reactivity with various *N*-reagents. The cyclopalladated complex **1b** was prepared by a procedure analogous to that reported by Dong[13a] et al. (Scheme 1) and was characterized by ^1H, $^{13}C\{^1H\}$, and ESI-MS analysis. The ^1H NMR spectrum of **1b** exhibited a characteristic[13a] downfield-shifted proton at 6.68 ppm, relative to that at 7.10 ppm in **1a**, corresponding to the ortho C−H of the cyclometalated palladium complex. With palladacycle **1b** in hand, we set out to explore its reactivity with potential *N*-reagents, including Tos-NH_2, Nos-NH_2, benzamide, and trifluoroacetamide, under various oxidizing conditions ($K_2S_2O_8$, oxone, $PhI(OAc)_2$, O_2, *N*-fluorobenzenesulfonimide (NFSI), Selectfluor, at 80−120 °C). NMR analysis of the reaction mixtures revealed that the palladacycle was either completely unreacted or underwent decomposition to **1a**.

At this juncture, we note that Liu and co-workers[9] recently reported a palladium catalyzed intermolecular amidation of aromatic ketones, in which tuning the electrophilicity of the palladium center was found to be crucial for coupling, presumably to enable coordination of the amide partner to the palladium center. Accordingly, we synthesized the palladium complexes **1c**[17] and **1d** bearing triflate (OTf) and tosylate (OTs) ligands, respectively (Scheme 1). However, no amidation was observed even with these electronically modulated palladacycles under conditions used with **1b**, and NMR analysis also revealed that the amide *N*-reagents do not coordinate to the palladium center. It appears that all of the **1b−d** complexes exist as bimetallic species in noncoordinating solvents, which convert to the monomer in a donor solvent. This is supported by the marked differences observed for the ^1H NMR aromatic resonances in case of the palladacycle **1d** (Figure 1) recorded in CD_3CN vs $CDCl_3$ (see the Supporting Information).

Upon testing the reactivity of the palladacycles **1** with a range of *N*-donors, it was observed that only aliphatic amines, like $^tBu-NH_2$, coordinate to palladium in the cyclometalated complexes. The amine adduct[18] was synthesized by stirring a dichloromethane solution of the palladium complex with the

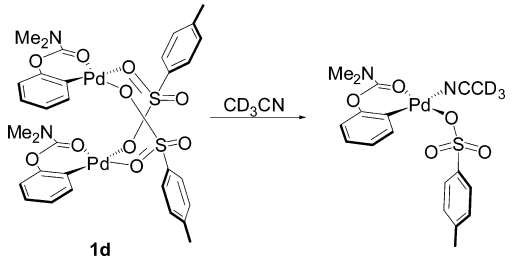


Figure 1. Dimer to monomer transformation in CD_3CN.

amine at room temperature (Figure 2) and was characterized extensively by ^1H, $^{13}C\{^1H\}$, and ESI-MS (high-resolution).

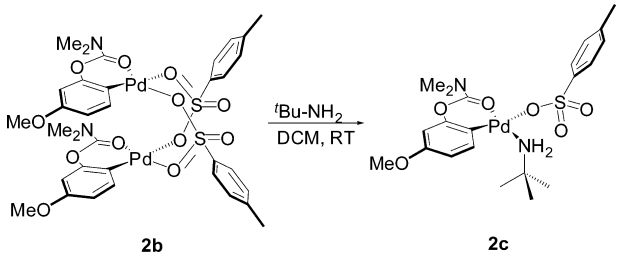


Figure 2. Synthesis of amine adduct (**2c**) of palladacycle **2b**.

The ^1H NMR spectrum of the amine adduct **2c** exhibits a characteristic resonance for the *ortho* C−H proton of the palladacycle, slightly upfield shifted with respect to that in **2b**. The ESI mass spectrum of **2c** has a molecular ion peak at m/z = 373 corresponding to $[M - OTs]^+$. However, upon subjecting the amine adducts of the palladium complexes to oxidative coupling conditions ($K_2S_2O_8$, oxone, $PhI(OAc)_2$, O_2, NFSI, Selectfluor, etc., at 80−120 °C, up to 16 h), rapid decomposition to either the respective carbamate or the palladacycle was observed. To determine if the unreactivity of the amine adducts could be the result of an unfavorable *trans* geometry between the coordinated amine and the *ortho*-carbon, NMR correlation spectroscopy experiments were carried out. In fact, nuclear Overhauser effect (NOE) studies of **2c** confirmed the *cis* disposition of the amine and aryl group, since irradiation of the *t*-butyl resonance at 1.20 ppm resulted in NOE enhancement of the *ortho* C−H proton signal at 6.59 ppm (see the Supporting Information).

Stoichiometric and Catalytic *ortho*-Halogenation. While exploring the reactivity of the palladacycle **1d** toward several potential *N*-reagents, we were delighted to observe a quantitative formation of an *ortho*-iodinated product, **1e**, upon reaction with *N*-iodosuccinimide (NIS).[19] Though the reaction exhibited similar efficiency starting from the *O*-phenyl-

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carbamate using stoichiometric $Pd(OAc)_2$, efforts to render the reaction catalytic (10 mol %) suffered from competing acid (*p*-TsOH) promoted *para*-iodination. However, we soon realized that this competing *p*-halogenation can be almost completely eliminated by employing NBS to yield the corresponding *ortho*-brominated *O*-phenylcarbamate, **1f**. Specifically, when a mixture of phenyl-*O*-carbamate (**1a**), NBS (1.1 equiv), and *p*-TsOH (0.5 equiv) were heated in the presence of 10 mol % $Pd(OAc)_2$ in 1,2-dichloroethane (DCE) at 60 °C, the *ortho*-brominated product, **1f**, was obtained in 95% isolated yield. Furthermore, the reaction proceeded with negligible loss of efficiency even at 5 mol % of Pd loading. We note that Bedford[20] and co-workers recently reported an example of palladium-catalyzed *ortho*-chlorination of a carbamate substrate, which proceeds under solvent-free conditions at an elevated temperature of 120 °C.

Since electron-rich carbamates underwent selective uncatalyzed *para*-bromination to the respective electron-donating groups, we focused on electron-poor carbamates for the palladium-catalyzed reaction. A brief optimization study suggested the need for higher temperature (ca. 90 °C) and catalyst loading (10 mol %) to achieve efficient brominations (Figure 3). With suitable reaction conditions at our disposal, we

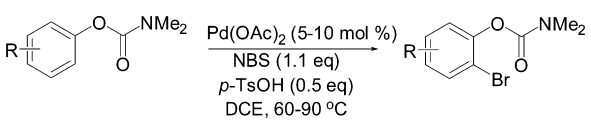
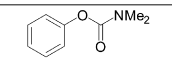
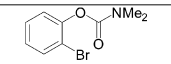
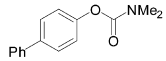
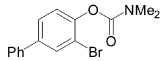
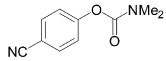
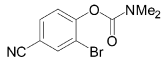
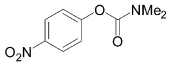
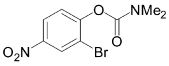
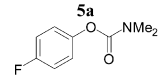
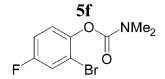
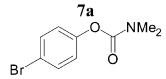
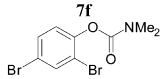
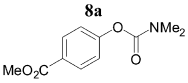
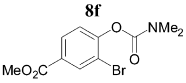
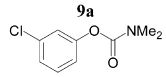
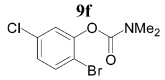


Figure 3. Palladium catalyzed *ortho*-bromination of aryl-*O*-carbamates.

undertook a brief survey of the *ortho*-bromination reaction (see Table 1). Significantly, the *ortho*-brominated carbamates were obtained in moderate to good isolated yields. The low yield observed with the highly electron-poor nitro carbamate **5a** (Table 1, entry 4) is apparently due to its reduced propensity to undergo electrophilic activation. It is worth mentioning that for the electron-rich carbamate, **6a**, competitive formation of the *ortho*-brominated product **6f** was observed under palladium catalysis (Scheme 2). Importantly, the inclusion of potentially reactive groups like halogen (Table 1, entries 5, 6 and 8) and carbomethoxy (Table 1, entry 7) further highlights the functional group compatibility of the method. Interestingly, for a carbamate bearing a *meta* chloro substituent (Table 1, entry 8), a higher reaction temperature (ca. 120 °C) over a longer period of time was needed to achieve good conversion.

We note that this palladium catalyzed *ortho*-bromination is complementary to the widely used directed *ortho*-metalation method, which uses highly reactive organolithium reagents stoichiometrically to produce *ortho*-brominated aryl-*O*-carbamates.[21,15a] A plausible mechanism for the present *ortho*-bromination reaction could involve Pd(II)/Pd(IV) catalysis. Initial C−H activation of the carbamate substrate would generate the palladacycle, which can then oxidatively add the NBS to furnish the corresponding Pd(IV) intermediate. In this respect, it must be mentioned that recent studies do support the ability of NXS reagents to promote oxidation of Pd(II) to Pd(IV) and subsequent reductive elimination from the Pd(IV) manifold to release organic products.[1b] Alternatively, the reaction may also proceed via a bimetallic Pd(III)−Pd(III) pathway for halogenation of aromatics as identified by Ritter and co-workers.[22]

Table 1. Palladium-Catalyzed *ortho*-Bromination of *O*-Aryl Carbamates[a]

entry	substrate	product	catalyst loading (mol %)	time (h)	yield[c] (%)
1	 **1a**	 **1f**	5	8	89
2	 **3a**	 **3f**	10	12	83[b]
3	 **4a**	 **4f**	10	16	81
4	 **5a**	 **5f**	10	16	42
5	 **7a**	 **7f**	10	16	52(58)
6	 **8a**	 **8f**	10	16	46(52)
7	 **9a**	 **9f**	10	16	62(70)
8[d]	 **10a**	 **10f**	10	22	71(83)

[a]*O*-Aryl carbamate (0.614 mmol), NBS (0.679 mmol), *p*-TsOH (0.308 mmol), and $Pd(OAc)_2$ (5 or 10 mol %) in DCE (ca. 2 mL) at 60−90 °C for the indicated period of time. [b]NMR yield, **3a** and **3f** have similar R_f values. [c]Isolated yield, ^{1}H NMR conversion in parentheses. [d]Reaction carried out at 120 °C.

CONCLUSION

In summary, we have synthesized and characterized amine adducts of some cyclometalated palladium complexes derived from the *O*-phenyl carbamate motif. NOE studies suggest a *cis* disposition of the amine relative to the aryl moiety in these amine adducts; however, they failed to undergo any C−N bond formation under oxidative conditions. Significantly the cyclometalated palladacycles undergo reaction with NXS reagents to yield the corresponding *ortho*-halogenated carbamates; a palladium catalyzed *ortho*-bromination reaction of *O*-aryl carbamates has been achieved at 5−10 mol % loading of $Pd(OAc)_2$.

EXPERIMENTAL SECTION

General Procedures. All manipulations were carried out using Schlenk tube techniques under an inert atmosphere. $Pd(OAc)_2$, dichloroethane, phenol(s), and dimethylcarbamoyl chloride were purchased from commercial sources. Dichloroethane was distilled over CaH_2 and subsequently stored over activated 4 Å molecular sieves. ^{1}H and $^{13}C\{^1H\}$ NMR spectra were recorded either on a 300 or 400 MHz NMR spectrometer. ^{1}H NMR peaks are labeled as singlet (s), doublet (d), triplet (t), and multiplet (m). Mass spectra were acquired in the ESI (+) mode.

General Procedure for the Synthesis of Carbamates. A mixture of the phenol (10.0 mmol) and Me_2NCOCl (1.38 mL, 14.9 mmol) and K_2CO_3 (2.07 g, 14.9 mmol) in 25 mL of CH_3CN was refluxed for 5 h. The reaction mixture was cooled to room temperature and concentrated under a vacuum. The residue was dissolved in H_2O (ca. 50 mL) and extracted with Et_2O (ca. 2 × 20 mL). The organic fractions were combined and then washed successively with 1 M KOH (ca. 25 mL) and water. Finally the organic layer was separated, dried over anhydrous $MgSO_4$, and concentrated under a vacuum to yield the corresponding carbamates.

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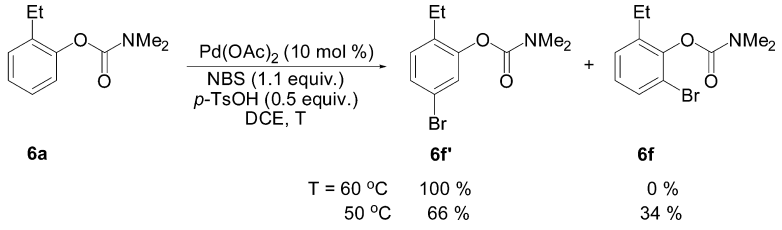
Scheme 2. Temperature Effect on *ortho*/*para*-Halogenation Selectivity



Phenyl Dimethylcarbamate (1a). White crystalline solid (1.20 g, 73%):[23] ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C) δ 7.34 (t, $^3J_{HH}$ = 8.1 Hz, 2H), 7.17 (t, $^3J_{HH}$ = 8.1 Hz, 1H), 7.10 (d, $^3J_{HH}$ = 8.1 Hz, 2H), 3.09 (s, 3H), 3.00 (s, 3H).

3-Methoxyphenyl Dimethylcarbamate (2a). Pale yellow oil (0.989 g, 65%):[14a] ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C) δ 7.24 (t, $^3J_{HH}$ = 9.0 Hz, 1H), 6.76−6.68 (m, 3H), 3.79 (s, 3H), 3.09 (s, 3H), 3.00 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz, 25 °C) δ 160.5, 154.9, 152.6, 129.7, 114.1, 111.4, 107.8, 55.5, 36.8, 36.6.

Biphenyl-4-yl Dimethylcarbamate (3a). Off-white solid (1.59 g, 66%): mp 130−132 °C; ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C) δ 7.59−7.56 (m, 4H), 7.43 (t, J_{HH} = 7.5 Hz, 2H), 7.34 (t, J_{HH} = 7.2 Hz, 1H), 7.18 (d, J_{HH} = 8.1 Hz, 2H), 3.13(s, 3H), 3.04 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz, 25 °C) δ 155.1, 151.1, 140.7, 138.4, 128.9, 128.1, 127.3, 127.3, 122.2, 36.9, 36.6; IR (KBr pellet, cm^{-1}) 1730 (s), 1485 (m), 1393 (m), 1221 (s), 1196 (s), 1171 (s); LRMS (ESI) 242 [(M + H)$^+$]; HRMS (ESI) Calcd for $C_{15}H_{16}NO_2$ (M + H)$^+$ requires m/z = 242.1181, found m/z = 242.1177.

4-Cyanophenyl Dimethylcarbamate (4a). White solid (1.29 g, 68%): mp 61−62 °C; ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C) δ 7.66 (d, J_{HH} = 8.1 Hz, 2H), 7.25 (d, J_{HH} = 8.1 Hz, 2H), 3.11 (s, 3H), 3.02 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz, 25 °C) δ 155.0, 153.7, 133.6, 122.8, 118.6, 108.9, 36.9, 36.7; IR (KBr pellet, cm^{-1}) 2228 (m), 1732 (s), 1389 (m), 1223 (s), 1159 (s); LRMS (ESI) 191 [(M + H)$^+$]; HRMS (ESI) Calcd for $C_{10}H_{11}N_2O_2$ (M + H)$^+$ requires m/z = 191.0821, found m/z = 191.0814.

4-Nitrophenyl Dimethylcarbamate (5a). Pale yellow solid (1.65 g, 78%): mp 104−105 °C; ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C) δ 8.24 (d, J_{HH} = 8.7 Hz, 2H), 7.29 (d, J_{HH} = 8.7 Hz, 2H), 3.12 (s, 3H), 3.03 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz, 25 °C) δ 156.5, 153.5, 144.7, 125.1, 122.3, 36.9, 36.6; IR (KBr pellet, cm^{-1}) 1728 (s), 1520 (s), 1344 (m), 1227 (m); LRMS (ESI) 211 [(M + H)$^+$]; HRMS (ESI) Calcd for $C_9H_{11}N_2O_4$ (M + H)$^+$ requires m/z = 211.0719, found m/z = 211.0712.

2-Ethylphenyl Dimethylcarbamate (6a). Pale yellow oil (1.09 g, 57%):[13a] ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C) δ 7.25−7.11 (m, 3H), 7.08 (dd, J_{HH} = 7.5 and 1.8 Hz, 1H), 3.13 (s, 3H), 3.03 (s, 3H), 2.61 (q, J_{HH} = 7.5 Hz, 2H), 1.22 (t, J_{HH} = 7.8 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz, 25 °C) δ 154.9, 149.6, 136.1, 129.3, 126.8, 125.6, 122.6, 36.8, 36.5, 23.4, 14.4.

4-Fluorophenyl Dimethylcarbamate (7a). Clear liquid (1.09 g, 60%):[13a] ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C) δ 7.06−7.02 (m, 4H), 3.09 (s, 3H), 3.00 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz, 25 °C) δ 161.5, 158.3, 154.9, 147.4, 147.3, 123.2, 123.1, 115.9, 115.6, 36.7, 36.4; ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C) δ −118.2.

4-Bromophenyl Dimethylcarbamate (8a). Clear oil (1.27 g, 53%):[24] ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C) δ 7.45 (d, J_{HH} = 8.7 Hz, 2H), 7.00 (d, J_{HH} = 8.7 Hz, 2H), 3.08 (s, 3H), 3.00 (s, 3H).

Methyl 4-(Dimethylcarbamoyloxy)benzoate (9a). To a stirred suspension of NaH (0.394 g, 9.85 mmol, 60% in oil) in THF (ca. 25 mL) at ice bath temperature was added slowly methyl 4-hydroxybenzoate (1.00 g, 6.57 mmol). The mixture was allowed to stir for 30 min, followed by the addition of Me_2NCOCl (0.66 mL, 7.16 mmol), and continued to stir for 8 h while allowing it to warm up to room temperature. The reaction mixture was washed with cold water, and the organics extracted into diethyl ether (ca. 20 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under a vacuum to yield the product as a white solid (1.93 g, 87%):[15c] ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C) δ 8.04 (d, J_{HH} = 8.7 Hz, 2H), 7.19 (d, J_{HH} = 8.7 Hz, 2H), 3.90 (s, 3H), 3.11 (s, 3H), 3.02 (s, 3H).

3-Chlorophenyl Dimethylcarbamate (10a). Clear liquid (1.31 g, 65%):[13a] ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C) δ 7.28 (t, J_{HH} = 8.4 Hz, 1H), 7.19−7.15 (m, 2H), 7.02 (d, J_{HH} = 8.4 Hz, 1H), 3.08 (s, 3H), 3.01 (s, 3H).

Synthesis of the Cyclopalladated Complexes 1b−d and 2b.

[(Phenyl Dimethylcarbamate)Pd(μ-TFA)]$_2$ (1b). A mixture of phenyl-*O*-carbamate (**1a**) (0.132 g, 0.800 mmol) and $Pd(OAc)_2$ (0.150 g, 0.668 mmol) in DCE (ca. 2 mL) in a 2-dram vial was stirred at room temperature for 5 min. To the stirred solution trifluoroacetic acid (0.076 g, 0.667 mmol) was added dropwise, and the reaction mixture was stirred for another 30 min. At the end of this period, ca. 5 mL of hexanes were added to the stirred mixture, and the palladacycle precipitated from the solution as a light gray solid (0.142 g, 69%): mp (decomp.) 200−202 °C; ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C) δ 7.10 (dt, $^3J_{HH}$ = 6.9 and 1.8 Hz, 1H), 7.04−6.40 (m, 2H), 6.68 (dd, $^3J_{HH}$ = 6.6 and 0.9 Hz, 1H), 2.72 (s, 3H), 2.31 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz, 25 °C) δ 166.2 (q, J = 37.8 Hz), 154.4, 148.5, 133.2, 126.1, 124.1, 115.1 (q, J = 285 Hz), 115.0, 111.7, 36.8, 36.6; LRMS (ESI) 270 [(M − CF_3COO)$^+$]; IR (KBr pellet, cm^{-1}) 1676 (s), 1634 (s), 1450 (m), 1412 (m), 1202 (s); HRMS (ESI) Calcd for $C_9H_{10}NO_2Pd$ (M − CF_3COO)$^+$ requires m/z = 269.9746, found m/z = 269.9753.

[(Phenyl Dimethylcarbamate)Pd(μ-OTf)]$_2$ (1c). A mixture of phenyl-*O*-carbamate (**1a**) (0.110 g, 0.667 mmol) and $Pd(OAc)_2$ (0.100 g, 0.445 mmol) in DCE (ca. 2 mL) in a 2-dram vial was stirred at room temperature for 5 min. To the stirred solution was added triflic acid (0.067 g, 0.446 mmol) dropwise, and the reaction mixture was stirred for another 15 min. At the end of this period, ca. 5 mL of hexanes were added to the stirred reaction mixture, and the palladacycle precipitated as a light gray solid (0.191 g, 67%): mp (decomp.) 140−142 °C. The precipitated product was washed further with hexanes (ca. 5 mL) and then dried under a vacuum: ^{1}H NMR (DMSO-d_6, 300 MHz, 25 °C) δ 7.29 (d, $^3J_{HH}$ = 8.4 Hz, 1H), 7.11 (t, $^3J_{HH}$ = 7.5 Hz, 1H), 6.99 (t, $^3J_{HH}$ = 7.5 Hz, 1H), 6.85 (d, $^3J_{HH}$ = 8.1 Hz, 1H), 3.20 (s, 3H), 2.97 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz, 25 °C) δ 155.6, 152.8, 135.7, 129.9, 127.1, 125.8, 122.0, 37.0; IR (KBr pellet, cm^{-1}) 3287 (br), 1643 (s), 1414 (m), 1259 (br, s), 1176 (s), 1034 (s), 756 (m), 644 (s); HRMS (ESI) Calcd for $C_9H_{10}NO_2Pd$ (M − OTf)$^+$ requires m/z = 269.9746, found m/z = 269.9725.

[(Phenyl Dimethylcarbamate)Pd(μ-OTs)]$_2$ (1d). A mixture of phenyl-*O*-carbamate (**1a**) (0.215 g, 1.30 mmol) and $Pd(OAc)_2$ (0.219 g, 0.975 mmol) in DCE (ca. 3 mL) in a 2-dram vial was stirred at room temperature for 5 min. To the stirred solution was added *p*-TsOH (0.188 g, 1.09 mmol), and the reaction mixture was continued to stir at 80 °C for another 30 min. At the end of this period, the reaction mixture was cooled to room temperature and treated with hexanes (ca. 10 mL) while stirring, causing the palladacycle to precipitate as a light gray solid (0.410 g, 82%): mp (dec.) 148−151 °C; ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C) δ 7.67 (d, $^3J_{HH}$ = 8.1 Hz, 2H), 7.37 (dd, $^3J_{HH}$ = 7.5 and 1.2 Hz, 1H), 7.10 (d, $^3J_{HH}$ = 8.4 Hz, 2H), 7.05 (dd, $^3J_{HH}$ = 8.7 and 1.2 Hz, 1H), 6.97 (dt, $^3J_{HH}$ = 8.1 and 1.2 Hz, 1H), 6.74 (dd, $^3J_{HH}$ = 8.7 and 1.2 Hz, 1H), 3.13 (s, 3H), 2.97 (s, 3H), 2.28 (s, 3H); ^{1}H NMR (acetonitrile-d_3, 300 MHz, 25 °C) δ 7.67 (d, $^3J_{HH}$ = 8.1 Hz, 2H), 7.20 (d, $^3J_{HH}$ = 8.1 Hz, 2H), 7.15 (dt, $^3J_{HH}$ = 7.8 and 1.8 Hz, 1H), 7.07 (dd, $^3J_{HH}$ = 7.5 and 1.8 Hz, 1H), 6.97 (dt, $^3J_{HH}$ = 8.1 and 1.5 Hz, 1H), 6.85 (dd, $^3J_{HH}$ = 8.1 and 1.8 Hz, 1H), 3.19 (s, 3H), 3.02 (s, 3H), 2.35 (s,

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3H); $^{13}C\{^1H\}$ NMR (acetonitrile-d_3, 75 MHz, 25 °C) δ 156.5, 151.1, 146.3, 140.2, 137.3, 134.4, 129.7, 128.0, 127.0, 125.9, 119.7, 37.9, 37.8, 21.6; IR (KBr pellet, cm^{-1}) 1643 (s), 1408 (m), 1261 (s), 1126 (m), 1001 (m); HRMS (ESI) Calcd for $C_9H_{10}NO_2Pd$ $(M - OTs)^+$ requires m/z = 269.9746, found m/z = 269.9755.

[(3-Methoxyphenyl Dimethylcarbamate)Pd(μ-OTs)]$_2$ (2b). A mixture of phenyl-*O*-carbamate (**2a**) (0.200 g, 1.02 mmol) and $Pd(OAc)_2$ (0.148 g, 0.659 mmol) in DCE (ca. 3 mL) in a 2-dram vial was allowed to stir at room temperature for 5 min. To the stirred solution was added *p*-TsOH (0.125 g, 0.727 mmol), and the reaction mixture was continued to stir at room temperature for 10 min followed by at 70 °C for another 30 min. At the end of this period, the reaction mixture was cooled to room temperature, and then ca. 10 mL of hexanes were added while stirring. The palladacycle then precipitated from the solution as a light gray solid (0.271 g, 87%): mp (dec.) 122−124 °C; ^1H NMR (acetonitrile-d_3, 300 MHz, 25 °C) δ 7.66 (d, $^3J_{HH}$ = 8.1 Hz, 2H), 7.19 (d, $^3J_{HH}$ = 8.1 Hz, 2H), 6.92 (d, $^3J_{HH}$ = 9.0 Hz, 1H), 6.62 (dd, $^3J_{HH}$ = 8.7 and 3.0 Hz, 1H), 6.54 (d, $^3J_{HH}$ = 3.0 Hz, 1H), 3.75 (s, 3H), 3.17 (s, 3H), 3.02 (s, 3H), 2.35 (s, 3H); $^{13}C\{^1H\}$ NMR (acetonitrile-d_3, 75 MHz, 25 °C) δ 160.4, 156.2, 150.8, 145.4, 140.6, 137.0, 129.7, 126.9, 112.1, 104.9, 56.4, 37.9, 37.8, 21.5; IR (KBr pellet, cm^{-1}) 3152 (br), 1647 (s), 1472 (m), 1385 (m), 1200 (s), 1169 (s); HRMS (ESI) Calcd for $C_{10}H_{12}NO_3Pd$ $(M - OTs)^+$ requires m/z = 299.9852, found m/z = 299.9851.

Synthesis of the Amine Adduct of the Cyclopalladated Complex (2c). (3-Methoxyphenyl Dimethylcarbamate)Pd(OTs)(^{t}Bu-NH$_2$) (2c). To a stirred suspension of **2b** (0.051 g, 0.108 mmol) in dichloromethane (ca. 2 mL) was added ^{t}Bu-NH_2 (0.020 g, 0.274 mmol), and the reaction mixture was allowed to stir at room temperature for 1 h. The reaction mixture was subsequently filtered and concentrated under a vacuum to yield the product as a dark gray solid (0.043 g, 73%): mp (dec.) 166−168 °C; ^1H NMR ($CDCl_3$, 300 MHz, 25 °C) δ 7.75 (d, $^3J_{HH}$ = 8.1 Hz, 2H), 7.19 (d, $^3J_{HH}$ = 8.1 Hz, 2H), 7.10 (d, $^3J_{HH}$ = 8.4 Hz, 1H), 6.59 (dd, $^3J_{HH}$ = 8.4 and 2.4 Hz, 1H), 6.40 (d, $^3J_{HH}$ = 1.8 Hz, 1H), 3.73 (s, 3H), 3.39 (d, $^3J_{HH}$ = 9.0 Hz, 1H), 3.33 (s, 3H), 3.13 (s, 3H), 2.93 (d, $^3J_{HH}$ = 11.1 Hz, 1H), 2.36 (s, 3H), 1.20 (s, 9H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz, 25 °C) δ 158.4, 157.0, 154.7, 141.7, 140.6, 138.4, 129.0, 126.0, 118.0, 111.5, 107.7, 55.3, 53.1, 37.1, 36.9, 31.6, 21.5; IR (KBr pellet, cm^{-1}) 3277 (br), 3225 (br), 3144 (br), 2968 (m), 1703 (s), 1375 (m), 1180 (br), 1005 (m); LRMS (ESI) 373 [$(M - OTs)^+$]; HRMS (ESI) Calcd for $C_{14}H_{23}N_2O_3Pd$ $(M\text{-}OTs)^+$ requires m/z = 373.0744, found m/z = 373.0747.

2-Iodophenyl Dimethylcarbamate (1e).[22] To a stirred solution of **1d** (0.032 g, 0.072 mmol) in CH_2Cl_2 (ca. 1 mL) was added *N*-iodosuccinimide (0.016 g, 0.071 mmol), and the reaction mixture was allowed to stir at room temperature for 8 h. The reaction mixture was filtered through a silica pad, and the filtrate was concentrated under a vacuum to yield **1e** as an off-white solid (0.020 g, 95%): ^1H NMR ($CDCl_3$, 300 MHz, 25 °C) δ 7.79 (d, $^3J_{HH}$ = 6.9 Hz, 1H), 7.35 (t, $^3J_{HH}$ = 7.5 Hz, 1H), 7.18 (d, $^3J_{HH}$ = 7.8 Hz, 1H), 6.95 (t, $^3J_{HH}$ = 8.1 Hz, 1H), 3.19 (s, 3H), 3.05 (s, 3H).

General Procedure for Palladium Catalyzed *ortho*-Bromination of *O*-Arylcarbamates. To a stirred solution of the substituted carbamate (0.614 mmol) in dichloroethane (ca. 2 mL) was added *N*-bromosuccinimide (0.121 g, 0.679 mmol), *p*-TsOH (0.053 g, 0.308 mmol), and $Pd(OAc)_2$ (5−10 mol %). The reaction mixture was stirred at 60−90 °C for the stipulated period of time. After solvent evaporation, silica gel column chromatography of the reaction residue using ether/hexanes yielded the pure *ortho*-brominated products.

2-Bromophenyl Dimethylcarbamate (1f).[25] Off-white solid (0.133 g, 89%): ^1H NMR ($CDCl_3$, 300 MHz, 25 °C) δ 7.58 (dd, $^3J_{HH}$ = 7.5 and $^4J_{HH}$ = 1.2 Hz, 1H), 7.31 (dt, $^3J_{HH}$ = 6.9 Hz and $^4J_{HH}$ = 1.2 Hz, 1H), 7.21 (dd, $^3J_{HH}$ = 8.4 Hz and $^4J_{HH}$ = 1.8 Hz, 1H), 7.08 (dt, $^3J_{HH}$ = 8.1 Hz and $^4J_{HH}$ = 1.8 Hz, 1H), 3.17 (s, 3H), 3.04 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz, 25 °C) δ 153.7, 148.8, 133.1, 128.3, 126.7, 124.2, 116.4, 36.8, 36.6.

3-Bromobiphenyl-4-yl Dimethylcarbamate (3f). Off-white solid: mp 78−82 °C; ^1H NMR ($CDCl_3$, 300 MHz, 25 °C) δ 7.79 (d, J_{HH} = 2.4 Hz, 1H), 7.54−7.50 (m, 3H), 7.46−7.36 (m, 3H), 7.28 (d, J_{HH} = 9.1 Hz, 1H), 3.19 (s, 3H), 3.05 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz, 25 °C) δ 153.7, 148.4, 138.8, 138.1, 132.0, 131.4, 128.7, 127.8, 126.9, 124.4, 122.2, 36.9, 36.6; IR (KBr pellet, cm^{-1}) 2926 (w), 1720 (s), 1227(m), 1169(m); HRMS (ESI) Calcd for $C_{15}H_{15}BrNO_2$ $(M + H)^+$ requires m/z = 320.0286, found m/z = 320.0289.

2-Bromo-4-cyanophenyl Dimethylcarbamate (4f). White solid (0.133 g, 81%): mp 90−92 °C; ^1H NMR ($CDCl_3$, 300 MHz, 25 °C) δ 7.64 (d, J_{HH} = 9 Hz, 1H), 7.53 (d, J_{HH} = 2.4 Hz, 1H), 7.22 (dd, J_{HH} = 9.0 and 2.4 Hz, 1H), 3.09 (s, 3H), 3.03 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz, 25 °C) δ 155.1, 153.8, 135.0, 133.7, 126.8, 121.5, 117.1, 112.4, 37.0, 36.7; IR (KBr pellet, cm^{-1}) 2228 (m), 1734 (s), 1391 (m), 1225 (m), 1163 (m); HRMS (ESI) Calcd for $C_{10}H_9N_2BrO_2Na$ $(M + Na)^+$ requires m/z = 290.9745, found m/z = 290.9743.

2-Bromo-4-nitrophenyl Dimethylcarbamate (5f). Pale yellow solid (0.074 g, 42%): mp 114−116 °C; ^1H NMR ($CDCl_3$, 300 MHz, 25 °C) δ 8.50 (d, J_{HH} = 3 Hz, 1H), 8.21 (dd, J_{HH} = 8.7 Hz and 2.4 Hz, 1H), 7.46 (d, J_{HH} = 8.7 Hz, 1H), 3.19 (s, 3H), 3.06 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz, 25 °C) δ 154.1, 152.7, 128.8, 124.4, 123.9, 116.9, 115.6, 37.2, 36.9; IR (KBr pellet, cm^{-1}) 1744 (s), 1524 (m), 1348 (m), 1254 (m), 1161 (m), 1113 (m); HRMS (ESI) Calcd for $C_9H_{10}BrN_2O_4$ $(M + H)^+$ requires m/z = 288.9824, found m/z = 288.9818.

2-Bromo-6-ethylphenyl Dimethylcarbamate (6f) and 5-Bromo-2-ethylphenyl Dimethylcarbamate (6f′). Data: ^1H NMR ($CDCl_3$, 300 MHz, 25 °C) δ 7.41 (d, J_{HH} = 7.5 Hz, 0.6H), 7.35 (d, J_{HH} = 2.4 Hz, 1.1H), 7.30 (dd, J_{HH} = 8.1 and 2.1 Hz, 1.5H), 7.18 (d, J_{HH} = 7.8 Hz, 0.5H), 7.03 (t, J_{HH} = 7.8 Hz, 0.6H), 6.95 (d, J_{HH} = 8.7 Hz, 1H), 3.18 (s, 1H), 3.11 (s, 3.9H), 3.04 (s, 1.6H), 3.01 (s, 4.0H), 2.55 (q, J_{HH} = 7.8 Hz, 3.5H), 1.23−1.17 (m, 6.9H); HRMS (ESI) Calcd for $C_{11}H_{15}BrNO_2$ $(M + H)^+$ requires m/z = 272.0286, found m/z = 272.0280.

2-Bromo-4-fluorophenyl Dimethylcarbamate (7f). Off-white liquid (0.084 g, 52%): ^1H NMR ($CDCl_3$, 300 MHz, 25 °C) δ 7.31 (dd, J = 7.5 and 3.0 Hz, 1H), 7.19−7.15 (m, 1H), 7.05−6.99 (m, 1H), 3.15 (s, 3H), 3.02 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz, 25 °C) δ 161.4, 158.1, 153.8, 145.3, 125.0, 124.9, 120.3, 119.9, 116.9, 116.7, 115.4, 115.1, 37.0, 36.7; ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C) δ −115.4; IR (KBr pellet, cm^{-1}) 1736 (s), 1599 (w), 1485 (m), 1387 (m), 1184 (m), 1159 (s); HRMS (ESI) Calcd for $C_9H_{10}BrFNO_2$ $(M + H)^+$ requires m/z = 261.9879, found m/z = 261.9898.

2,4-Dibromophenyl Dimethylcarbamate (8f). Off-white liquid (0.091 g, 46%): ^1H NMR ($CDCl_3$, 300 MHz, 25 °C) δ 7.71 (d, J_{HH} = 2.4 Hz, 1H), 7.42 (dd, J_{HH} = 8.7 and 2.4 Hz, 1H), 7.10 (d, J_{HH} = 8.4 Hz, 1H), 3.14 (s, 3H), 3.02 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz, 25 °C) δ 153.4, 148.1, 135.3, 131.4, 125.4, 118.7, 117.4, 36.9, 36.6; IR (KBr pellet, cm^{-1}) 1734 (s), 1466 (m), 1389 (m), 1225 (m), 1159 (m); HRMS (ESI) Calcd for $C_9H_{10}{}^{81}Br^{79}BrNO_2$ $(M + H)^+$ requires m/z = 323.9058, found m/z = 323.9054.

Methyl 3-Bromo-4-(dimethylcarbamoyloxy)benzoate (9f). Clear liquid (0.115 g, 62%): ^1H NMR ($CDCl_3$, 300 MHz, 25 °C) δ 8.25 (d, J_{HH} = 1.5 Hz, 1H), 7.97 (dd, J_{HH} = 8.4 and 1.5 Hz, 1H), 7.30 (d, J_{HH} = 9.0 Hz, 1H), 3.89 (s, 3H), 3.15 (s, 3H), 3.02 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz, 25 °C) δ 165.3, 153.0, 152.4, 134.5, 129.7, 128.5, 123.9, 116.3, 52.4, 36.9, 36.6; IR (KBr pellet, cm^{-1}) 1732 (s), 1599 (w), 1385 (m), 1283 (s), 1250 (s), 1157 (s), 1111 (m), 762 (m); HRMS (ESI) Calcd for $C_{11}H_{13}BrNO_4$ $(M + H)^+$ requires m/z = 302.0028, found m/z = 302.0022.

2-Bromo-5-chlorophenyl Dimethylcarbamate (10f). Off-white liquid (0.121 g, 71%): ^1H NMR ($CDCl_3$, 300 MHz, 25 °C) δ 7.49 (d, J_{HH} = 8.7 Hz, 1H), 7.26 (d, J_{HH} = 2.4 Hz, 1H), 7.07 (dd, J_{HH} = 8.7 Hz and 2.4 Hz, 1H), 3.15 (s, 3H), 3.03 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz, 25 °C) δ 153.3, 149.4, 133.7, 133.6, 127.1, 124.8, 114.7, 37.0, 36.7; IR (KBr pellet, cm^{-1}) 1738(s), 1466(m), 1377(m), 1157(m); HRMS (ESI) Calcd for $C_9H_{10}BrClNO_2$ $(M + H)^+$ requires m/z = 277.9583, found m/z = 277.9576.

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■ ASSOCIATED CONTENT

Supporting Information

Spectral data for all new compounds reported. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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