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Palladium-Catalyzed Carbamate-Directed Regioselective Halogenation: A Route to Halogenated Anilines

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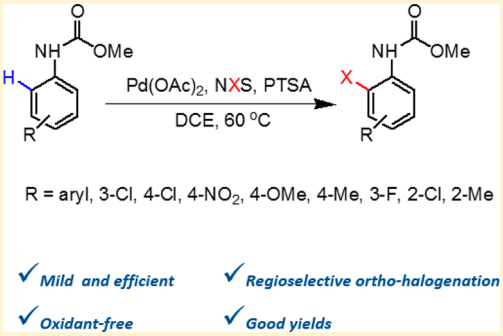
Supporting Information

ABSTRACT: This study describes an efficient method for ortho-selective halogenation of *N*-arylcarbamates under mild conditions for the first time. Although being weakly coordinating, *N*-arylcarbamates act very well as a removable directing group for activation of C−H bonds. The developed procedure results in extremely valuable halogenated *N*-arylcarbmates that can further be hydrolyzed to halogenated anilines. The obtained reaction conditions showed broad scope and wide functional group tolerance. All the products were formed in good yields with extremely high selectivity.



INTRODUCTION

Apart from being abundant in natural products and pharmaceuticals,[1,2] aryl halides have always been extremely important synthetic intermediates for substitution reactions.[3] On the other hand, cross-coupling reactions have become one of the most encountered organic reactions that necessitate the use of prefunctionalized starting materials such as aryl halides and *pseudo*-halides;[4−8] so, introducing halogens specially bromine and iodine, due to their higher reactivity toward oxidative insertion relative to chlorine, on aromatic structures is extremely valuable from the synthetic point of view.[2,4−8] Regarding this fact, finding efficient methods for the synthesis of these structural motifs is of great importance. Traditional methods for synthesis of halogenated aromatic compounds include direct electrophilic halogenations,[9] halogen-metal exchange,[10] and diazotization/halogenations.[11] However, these methods suffer from serious drawbacks such as harsh reaction conditions, poor regioselectivity, necessity for use of hazardous chemicals, long reaction times, being limited to electron rich structures, and in some cases low yields.[12]

One of the newest methodologies for C−halogen bond formation is via transition metal-catalyzed C−H activation. However, regioselective functionalization of a C−H bond is possible only through employment of DGs activating a special C−H bond by forming cyclometallates.[13−18] These DGs generally contain electron donating atoms or π-donating functional groups capable of coordination to the employed transition metal catalyst.[19−31] Transition metal-catalyzed C−halogen bond formation through activating C−H bonds was reported first by Shi et al. that showed the regioselective ortho-halogenations of anilide derivatives (Scheme 1a).[32−35] Then, Sanford introduced *N*-halosuccinimides as halogen source in Pd-catalyzed ortho-halogenation of arenes to improve the former halogenation method (Scheme 1b).[36−39] However, the number of reports in this context is considerably less than that of other C-heteroatom bond formations.[32−35] Previous research studies have investigated the catalytic activity of Cu,[12,36,37,40] Pd,[34,35,41−51] Rh,[52−54] Ru,[55,56] Au[57,58] and Co[59] in such

Scheme 1. Comparison of the Presented Halogenation Conditions

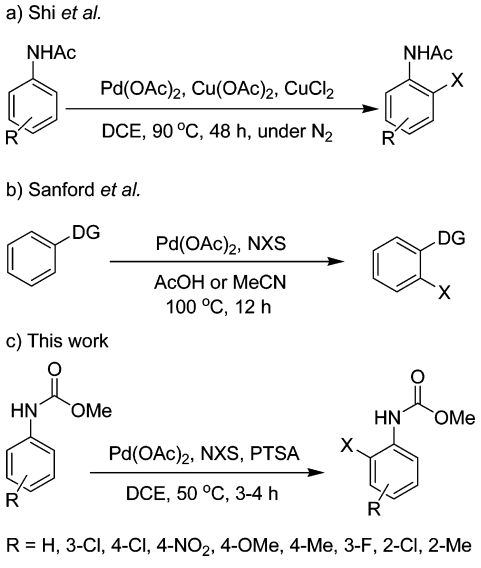


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Table 1. Optimization of Reaction Conditions for C−H Halogenation of Methyl *N*-Arylcarbamates[a]

entry	X source	temp. (°C)	solvent	catalyst (5 mol %)	additive (equiv)	yield (%)
1	NBS	100	MeCN	$Pd(OAc)_2$	-	62
2	NBS	100	MeCN	-	-	15
3	NBS	100	MeCN	$Cu(OAc)_2$	-	33
4	NBS	100	MeCN	$PdCl_2$	-	54
5	NBS	100	DCE	$Pd(OAc)_2$	-	Trace
6	NBS	100	1,4-Dioxane	$Pd(OAc)_2$	-	Trace
7	NBS	100	PhCN	$Pd(OAc)_2$	-	15
8	NBS	100	MeCN	$Pd(OAc)_2$	PTSA (0.5)	78
9	NBS	100	MeCN	$Pd(OAc)_2$	TFA (0.5)	70
10	NBS	100	MeCN	$Pd(OAc)_2$	AcOH (0.5)	40
11	NBS	100	MeCN	$Pd(OAc)_2$	$Zn(OAc)_2$ (0.5)	37
12	NBS	100	DCE	$Pd(OAc)_2$	PTSA (0.5)	93
13	NBS	100	1,4-Dioxane	$Pd(OAc)_2$	PTSA (0.5)	59
14	NBS	100	DCE	$Pd(OAc)_2$	PTSA (0.5)	24
15	NBS	100	DCE	$Pd(OAc)_2$	PTSA (1)	92
16	NBS	100	DCE	$Pd(OAc)_2$	PTSA (0.25)	74
17	NBS	100	DCE	$Pd(OAc)_2$	$Cu(OAc)_2$ (0.5)	35
18	NBS	100	DCE	$Pd(OAc)_2$	AgOAc + PTSA	25
19	NBS	100	DCE	$Pd(OAc)_2$	$K_2S_2O_8$(2)+PTSA	50
20[b]	NBS	100	DCE	$Pd(OAc)_2$	PTSA (0.5)	43
21[c]	NBS	100	DCE	$Pd(OAc)_2$	PTSA (0.5)	92
22[d]	NBS	100	DCE	$Pd(OAc)_2$	PTSA (0.5)	91
23[e]	NBS	100	DCE	$Pd(OAc)_2$	PTSA (0.5)	90
24	NBS	80	DCE	$Pd(OAc)_2$	PTSA (0.5)	93
25	**NBS**	**60**	**DCE**	**$Pd(OAc)_2$**	**PTSA (0.5)**	**91**
26	NBS	r.t.	DCE	$Pd(OAc)_2$	PTSA (0.5)	52

[a]Reaction conditions: methyl *N*-(*p*-tolyl)carbamate (1 mmol), NBS (*X* mmol), Additive (*X* mmol), catalyst (*X* mol %), solvent (2 mL) and temperature. [b]2.5 mol % of catalyst. [c]10 mol % of catalyst. [d]1.5 equiv of NBS was used. [e]3 equiv of NBS was used.

reactions. Different types of halogen sources have been employed in the metal-catalyzed halogenation reactions such as LiX,[36,37] CuX_2,[34] CaX_2,[60] DDQ,[35] and *N*-halosuccinimides.[12,32,33,61] Generally, these kinds of reactions require the use of an oxidant along with the halogen source. The dual role of *N*-halosuccinimides to act as both oxidant and halogen source excludes the need for use of an external oxidant; so, in terms of atom economy, this type of halogen source has a great privilege over the others. However, C−halogen bond formation has remained a challenging task, probably due to the fact that formation of carbon−halogen bond through reductive elimination from the corresponding cyclometallate is disfavored relative to oxidative insertion.[62]

Carbamates are important functional moieties frequently encountered in naturally occurring compounds, herbicides, pesticides, and polyurethanes.[63,64] *O*-Arylcarbamates have shown great capability as removable directing groups (DG).[65] Some of the previously investigated carbamate-directed C−H functionalizations include alkenylation,[66,67] arylation,[68,69,19] halogenations,[52,70,71] and oxygenation[72] reactions. Although they are structurally and electronically similar to *O*-aryl carbamates, after being introduced by Li et al.[65] as an effective and removable DG, *N*-arylcarbamates have not been investigated as C−H activation DG. Contrary to many of the previously used DGs,[28−30] this is also a removable functionality that can be used as a versatile key intermediate in organic synthesis. Furthermore, their ease of preparation, pronounced stability, and low reactivity toward Pd(0) are among other advantages of these functionalities.[73] So, not only are *N*-arylcarbamate-directed C−H activation reactions suitable for preparation of functionilized derivatives of *N*-protected amines, but they can also be used to access 2-substituted anilines. 2-Haloanilines and ortho-halogenated derivatives of *N*-arylcarbamtes are found in various natural products and pharmaceuticals;[74,75] moreover, they are key intermediates in the synthesis of diverse useful heterocyclic compounds such as indoles,[76,77] carbazoles,[78] phenazines,[79] etc. Hence, mild and efficient methods for their preparation are of great desire.

To the best of our knowledge, this is the first report of application of *N*-arylcarbamates as DG in C−halogen bond formation. The importance of regioselective transition metal-catalyzed halogenation reactions in modern synthetic chemistry, along with the salient feature of *N*-arylcarbamate DGs, tempted us to report a very efficient, general, and operationally facile methodology for regioselective formation of C−halogen bonds. This report explains ortho-selective halogenations of different *N*-arylcarbamates bearing various functional groups on the aromatic rings to afford the corresponding products in good yields that can be hydrolyzed to ortho-halogenated anilines.

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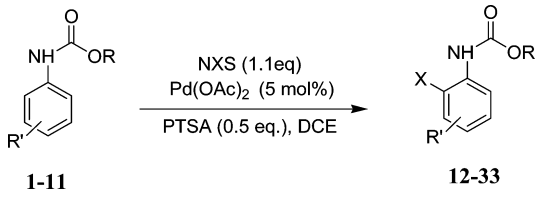
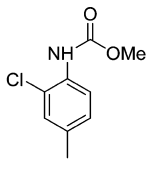
Table 2. Halogenation of Methyl *N*-Arylcarbamate Derivatives[a]

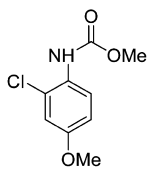


1-11 **12-33**

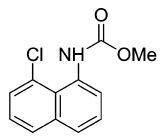
NCS



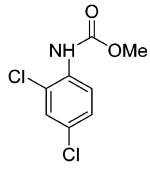
12
4h; 84%[b,c]



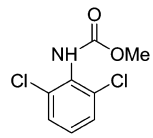
13
3.5h; 80%



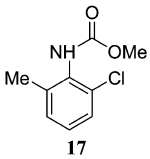
14
5h; 82%



15
3.5h; 87%



16
8h; 0%



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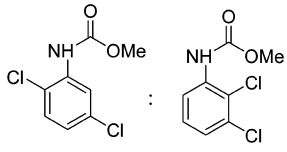
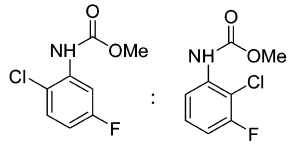
8h; 0%

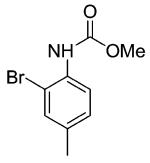


18: 18'; 3.8:1
4h; 84%

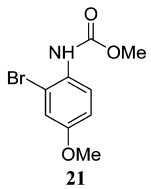


19: 19'; 2.6:1
3.5h; 88%

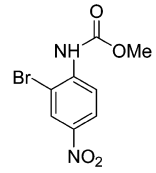
NBS



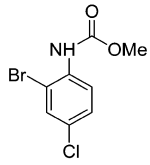
20
3h; 88%



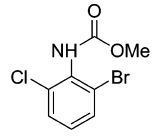
21
2.5 h; 86%



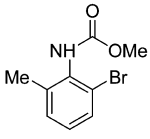
22
4h; 77%



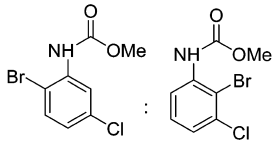
23
2h; 90%



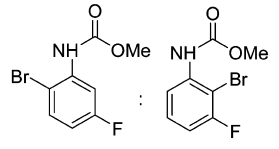
24
8h; 0%



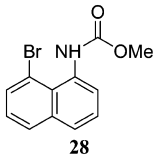
25
8h; 0%



26: 26'; 4.4: 1
2.5h; 90%

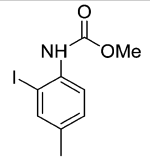


27: 27'; 3.4:1
3h; 84%

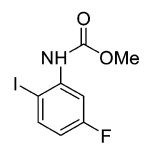


28
4h; 87%

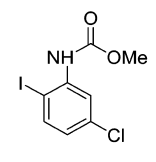
NIS



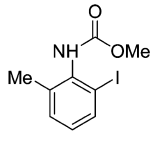
29
3h; 89%



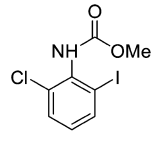
30
3h; 86%



31
3h; 91%



32
8h; 0%



33
8h; 0%

[a]Rection conditions: *N*-arylcarbamate (1 mmol), NXS (1.1 mmol), PTSA (0.5 mmol), $Pd(OAc)_2$ (5 mol %) in DCE (2 cc) at 60 °C. [b,c]Reaction times and yields, respectively.

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RESULTS AND DISCUSSION

Our exploration began by reacting NBS with methyl *N*-(*p*-tolyl)carbamate in the presence of 5 mol % $Pd(OAc)_2$ as catalyst and acetonitrile as solvent; after a heating step at 100 °C for 2 h, the desired product, methyl *N*-(2-bromo-4-methylphenyl) carbamate, was formed in 62% yield (Table 1, entry 1). Being delighted by this result, we conducted various optimization experiments to obtain the optimal reaction conditions using the above-mentioned reaction as the model reaction.

First, dependence of the result on the presence of transition metal catalyst was checked (entries 1−4). It was found that the presence of a palladium source is essential for the progress of the reaction and copper could not act as an efficient catalyst under these conditions. Among the palladium sources examined, palladium acetate proved to be the most effective one (entry 1); so, it was chosen as the optimal catalyst.

Exploring the effect of solvents on halogenation reaction showed that the model reaction did not proceed in DCE and 1,4-dioxane (entries 5 and 6). Surprised by this result, we first assumed that the coordinative nature of acetonitrile might be essential for this reaction; so, benzonitrile was tested as another coordinative solvent; but the reaction also did not afford the desired product in good yield (entry 7).

Inspired by the work of DeVries and van Leeuwen's,[80] the effect of the presence of different additives was later examined, and to this end, *p*-toluenesulfonic acid (PTSA) was tested as an additive. Application of 0.5 equiv of PTSA proved to enhance the yield by a considerable amount; therefore, a wide variety of acidic additives, both Lewis acid and protic acids, were tested in acetonitrile as solvent (entries 8−11). The best results were obtained using PTSA as additive in the model reaction. Thereafter, the combination of PTSA and different solvents was investigated as the reaction medium (entries 12 and 13), and to our pleasure, the reaction proceeded with higher yield in DCE compared to entry 1 while an acidic additive was introduced. Therefore, DCE was chosen as the optimal solvent in the presence of PTSA as optimal additive. An experiment was also conducted in the absence of palladium acetate and using PTSA and DCE as the optimal medium (entry 14); it was demonstrated that the desired product could not produce in good yield without transition metal catalyst.

To optimize the loading of the acidic additive, the model reaction was treated also with 1 and 0.25 equiv of PTSA (entries 15 and 16). No significant change was observed in the presence of 1 equiv of additive; however, reaction afforded a lower yield when the amount of PTSA was reduced to 0.25 equiv.

On the other hand, the effect of addition of different types of co-oxidants was examined, and experiments showed that none of them had any obvious influence on the reaction progress (entries 17−19).

The amount of catalyst required for such transformation was optimized in the next step. It was shown that reducing the amount of catalyst to 2.5 mol % resulted in a decrease in the yield, while increasing that to 10 mol % had no significant influence on the rate and yield of the reaction (entries 20 and 21).

In addition, the reaction yield did not show any improvement upon increasing the amount of NBS to 1.5 equiv. Increasing the amount of NBS further to 3 equiv also did not result in the formation of the dihalogenated product indicating the monoselectivity of the reaction (entries 22 and 23).

Finally, conducting the model reaction at room temperature resulted in the formation of the desired product with moderate yield. Increasing the temperature to 60 °C caused better formation of the halogenated product. However, when the temperature was raised to 80 or 100 °C, the formation of the desired product was not affected seriously; so, 60 °C was selected as the optimal temperature for this reaction (entries 24−26).

Having obtained the optimal reaction conditions, we set out to explore the scope of the reaction of different methyl *N*-arylcarbamates. The results are listed in Table 2. As can be seen, the optimal conditions can also be applied to chlorination and iodination as well as bromination of methyl *N*-arylcarbamates. Furthermore, the halogenated products were accessible regardless of the electronic nature of the methyl *N*-arylcarbamates.

The effect of the presence of both electron-donating and electron-withdrawing groups on the aromatic ring was considered. The results proved that the electronic characteristics of substituents on the aromatic ring have no considerable influence on the reaction yields. Also, different types of ortho-, meta-, and para-substituted methyl *N*-arylcarbamates were investigated under optimized reaction conditions. Results showed that para-substituted carbamates afford the corresponding monohalogenated products with very good regioselectivity (**12**, **20**, **22** and **29**). The reaction was also chemoselective in the case of methyl-substituted arylcarbamates. As it is demonstrated, NXSs are superior reagents for halogenations of benzylic positions; however, in this case, methyl *N*-(2-halo-4-methylphenyl)carbamate was obtained in a chemospecific manner. The halogenation of more electron-rich derivative, i.e., methyl 4-methoxyphenylcarbamate also proceeds regioselectively (**13** and **21**).

In fact, from the two available positions, only the one ortho to the DG is halogenated. With the use of methyl *N*-(2-chlorophenyl)carbamate, application of the optimized reaction conditions failed to produce the desired product even under much longer reaction times (**16**, **24**, and **33**). This result is in accord with the observation that the dihalogenated products were not also produced using other *m*- or *p*-substituted *N*-arylcarbamates. The same results were obtained using methyl *N*-(2-methylphenyl)carbamate (**17**, **25**, and **32**). However, application of 3-substituted carbamates could theoretically result in two different products from substitution on two possible ortho positions. Fortunately, our optimized conditions proceeded with very good regioselectivity for substitution on the ortho position farther from the subtituent on meta position that could be attributed to the steric hindrance (**18**, **19**, **26**, and **27**). However, in both meta-substituted substrates, using NIS as the halogenating source, only one product is produced maybe due to more steric demand of iodine compared to bromine and chlorine (**30** and **31**). With the use of methyl *N*-(1-naphthyl)carbamate as substrate, chlorination and bromination reactions only occurred on the 8-position (**14**, **28**).

To investigate the effect of alkoxyl group in carbamates on the reaction, *iso*-propyl- and *t*-butyl *N*-(4-methylphenyl)-

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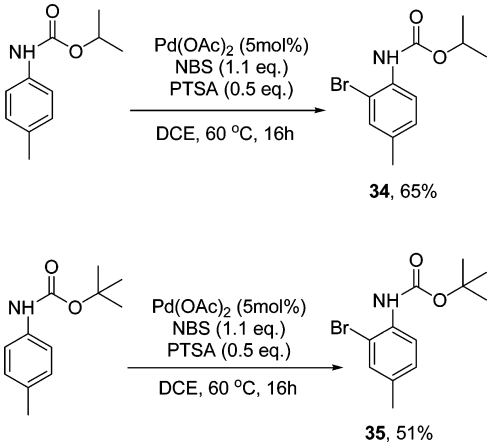
carbamate derivatives were reacted with NBS under optimized conditions (Scheme 2).

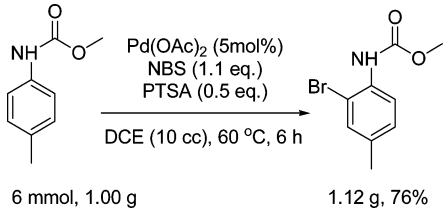
Scheme 2. Effect of Alkoxyl Group on the Halogenation Reaction



Our investigation revealed that both the reactions resulted in the formation of the predicted brominated products; however, increasing the size of alkoxyl group increases the steric hindrance around the ortho positions and, thereby, decreases the yield of reaction even after much longer reaction time.

To indicate the scalability of the procedure, bromination of methyl *N*-(4-methylphenyl)carbamate was explored under optimized reaction conditions in 10 mmol scale (Scheme 3). Results show that the proposed procedure has the potential to be employed for large-scale synthesis of halogenated carbamates.

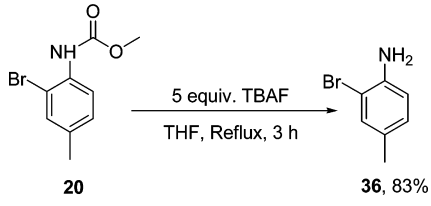
Scheme 3. Examining Scalability of the Reaction



Also, as it is mentioned above, deprotection of these halogenated carbamates can produce the corresponding halogenated anilines. To this end, the procedure reported by Coudert et al.[81] was employed to deprotect compound **20** (Scheme 4) and resulted in the formation of 2-bromo-4-methylaniline (**36**) in 83% yield.

To account for the observations, a possible mechanism is proposed (Scheme 5). A Pd^{II}/Pd^{IV} catalytic system seems to be responsible for this transformation. The reaction starts with chelation-assisted C−H activation step in which the corresponding cyclopalladate **A** is formed. This step is followed by oxidative insertion of *N*-halosuccinimide to cyclopalladate **A** to form intermediate **B**. Subsequently, reductive elimination of intermediate **B** affords the halogenated product and regenerates Pd^{II}. PTSA is assumed to have a dual role in this mechanism. First, it activates *N*-halosuccinimed by protonating one of the two carbonyl groups rendering it a more efficient source of X^+, and second, it forms a more electrophilic palladium catalyst.

Scheme 4. Deprotection of Compound 20, a Route to Halogenated Anilines



According to the proposed mechanism, the unreactivity of the ortho-substituted alkyl *N*-arylcarbamates could be attributed to the steric hindrance around the *ortho*-C−H bond; in fact, the presence of a substituent on one of the two ortho positions of the carbamate directing group causes the formation of the expected palladacycle to be more difficult due to the steric repulsion between alkoxy group of carbamate and the ortho-substituent.

In summary, this report introduces a mild and practical method for preparation of ortho-halogenated *N*-arylcarbamates through Pd-catalyzed C−H bond activation. The optimized reaction conditions can conduct the halogenation reaction with excellent regioselectvity for ortho position of DG. Different *N*-halosuccinimides including NIS, NBS, and NCS serve both as oxidant and halogen source at the same time excluding the need for an external oxidant. This report depicts one of the few reports of application of alkyl *N*-arylcarbamates as removable DGs paving the way for synthesis of both ortho-halogenated derivatives of alkyl *N*-arylcarbamates and anilines. The reaction showed wide functional group tolerances and resulted in the desired products with very good yields.

The proposed mechanism for this reaction encounters a Pd^{II}/Pd^{IV} catalytic cycle in which PTSA is assumed to have a dual role of activating *N*-halosuccinimide through protonation and forming a more electrophilic Pd catalyst.

EXPERIMENTAL SECTION

General Information. Unless otherwise stated, all experiments were conducted in oven-dried glassware under air. All chemicals were purchased from commercial sources and were used without any further purification. Palladium acetate was purchased from Sigma-Aldrich with 98% purity. All ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ as solvent at RT on a 500 MHz NMR spectrometer. All chemical shifts (δ) were reported in ppm relative to TMS. Melting point data are uncorrected. High-resolution mass spectra (HRMS) were recorded by ESI on an iFunnel Q-TOF (time-of-flight) mass spectrometer.

Column chromatographic purification of compounds was performed by using silica gel (mesh 100−200) and a hexane−ethyl acetate mixture as eluent. Thin layer chromatography was done on 20 × 20 cm^2 silica gel plates. All the alkyl *N*-arylcarbamate derivatives and also NIS were prepared according to the procedures reported in the following.

Procedure A for the Synthesis of N-Arylcarbamates ***1−7****.* The *N*-arylcarbamates **1−7** were prepared according to the procedure reported by Keillor et al. with some modifications.[82] To a round-bottomed flask equipped with a magnetic stirring bar and condenser was added the corresponding benzamide (1 mmol) and NBS (1 mmol, 178 mg) followed by the addition of methanol (7 mL). Then, potassium *t*-butoxide (1.5 mmol, 168 mg) was added to the mixture and it stirred at 80 °C for ca. 40 min (in the case of 4-nitrobenzamide, the reaction mixture should be stirred overnight to be completed). The reaction mixture was further concentrated under reduced pressure after completion. The residue was diluted with dichloromethane (20 mL) and washed with HCl (20 mL, 15% aq solution) followed by $NaHCO_3$ (20 mL, saturated aq solution). The organic layer was concentrated under vacuum and purified using gradient elution

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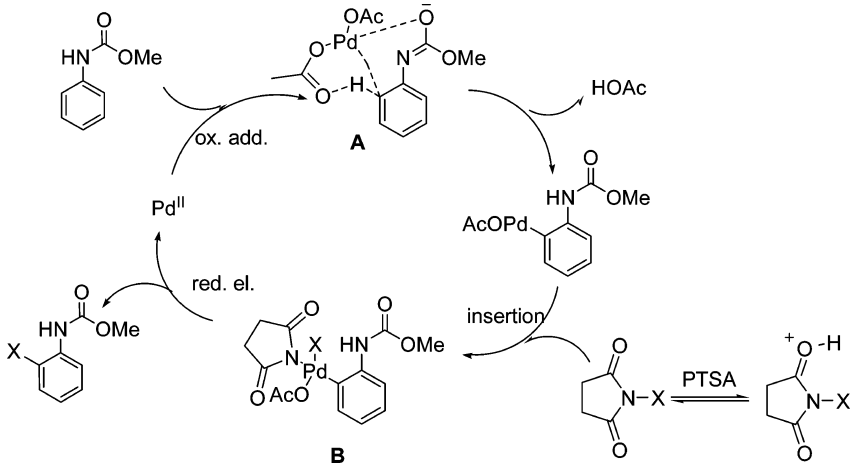
Scheme 5. Plausible Mechanism for Ortho-Halogenation of Alkyl *N*-Arylcarbamates



column chromatography on silica gel (*n*-hexane/ethyl acetate). With the use of this procedure, the desired *N*-arylcarbamates were prepared in 75−85% yields.

*Methyl N-(4-Methylphenyl)carbamate (**1**).* Yield: 151.8 mg (92%).[83]

*Methyl N-(4-Methoxyphenyl)carbamate (**2**).* Yield: 162.9 mg (90%).[85]

*Methyl N-(4-Nitrophenyl)carbamate (**3**).* Yield: 186.2 mg (95%).[83]

*Methyl N-(4-Chlorophenyl)carbamate (**4**).* Yield: 172.5 mg (93%).[83]

*Methyl N-(2-Chlorophenyl)carbamate (**5**).* Yield: 155.8 mg (84%).[86]

*Methyl N-(2-Methylphenyl)carbamate (**6**).* Yield: 141.9 mg (86%).[83]

*Methyl N-(3-Fluorophenyl)carbamate (**7**).* Yield: 148.7 mg (88%).[83]

*Procedure B for the Synthesis of N-Arylcarbamates **8**−**11**.* The *N*-arylcarbamates **8**−**11** were prepared according to the previous reported method.[75]

*Methyl N-(1-Naphthyl)carbamate (**8**).* Yield: 186.9 mg (93%), light pink powder; mp 154−157 °C. ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 7.69−7.65 (m, 2H), 7.45 (d, 1H, J = 7.7), 7.33−7.29 (m, 3H), 7.21 (d, 1H, J = 7.6), 6.84 (brs, 1H), 3.87 (s, 3H). HRMS (ESI-TOF) (m/z): calcd for $C_{12}H_{11}NO_2$ $[M]^+$ 201.0790; found 201.0790.

*Methyl N-(3-Chlorophenyl)carbamate (**9**).* Yield: 170.0 mg (90%).[83]

*Isopropyl N-(4-Methylphenyl)carbamate (**10**).* Yield: 178.5 mg (93%).[83]

*t-Butyl N-(4-Methylphenyl)carbamate (**11**).* Yield: 188.4 mg (91%), cream crystals; mp 59−62 °C. ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 7.36 (d, 2H, J = 8.0), 7.19 (d, 2H, J = 8.0), 6.87 (brs, 1H), 2.35 (s, 3H), 1.46 (s, 9H). HRMS (ESI-TOF) (m/z): calcd for $C_{12}H_{17}NO_2$ $[M + H]^+$ 207.1260; found 207.1260.

Procedure for the Preparation of *N*-Iodosuccinimide. *N*-iodosucinimide was prepared according to the procedure reported by Vankar et al. with some modifications.[84] NaI (10 mmol, 2.25 g) and NCS (10 mmol, 1.34 g) were individually dissolved in acetone (25 mL). The two solutions were mixed in a 100 mL round-bottomed flask equipped with a magnetic stirring bar. After it stirred for 15 min, the NaCl formed during the course of reaction was filtered; the filtrate was concentrated under reduced pressure. To remove iodine from the crude product, the solid was washed several times with 15 mL portions of diethyl ether until a bright yellow-colored powder was obtained. The NIS produced using this procedure was used without further purification. Bright yellow-colored powder; yield, 2.115 g (94%); mp = 196−198 °C [lit.[84] 200−201 °C].

General Procedure for Preparation of O-Halogenated Alkyl *N*-Arylcarabamtes. Methyl *N*-arylcarbamate (1 mmol), NXS (1.1 mmol), PTSA·$2H_2O$ (0.5 mmol, 90 mg) and $Pd(OAc)_2$ (0.05 mmol, 10 mg) were added to a sealed tube equipped with a magnetic stirring bar followed by the addition of DCE (2 mL). The reaction mixture was stirred at 60 °C and the completion of the reaction was monitored using TLC (*n*-hexane/ethyl acetate/methanol; 20:5:2). After the reaction was completed, the mixture was cooled to room temperature and diluted with dichloromethane (2 × 10 mL). The organic layer was further washed with HCl (20 mL, 10% aq solution) followed by $NaHCO_3$ (20 mL, saturated aq solution). Afterward, the organic layer was separated and dried over anhydrous $MgSO_4$ and concentrated under reduced pressure using a rotary evaporator. Purification was accomplished using thin layer chromatography on 20 × 20 cm^2 silica gel plates (*n*-hexane/ethyl acetate/methanol; 25:5:2).

*Methyl N-(2-Chloro-4-methylphenyl)carbamate (**12**).* Yield: 167.5 mg (84%), orange powder; mp 60−62 °C. ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 8.03 (d, 1H, J = 6.8), 7.19 (brs, 1H), 7.10−7.08 (m, 2H), 3.83 (s, 3H), 2.23 (s, 3H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$, ppm): δ 153.9, 139.0, 136.3, 132.6, 128.1, 121.7, 120.1, 53.4, 22.9. HRMS (ESI-TOF) (m/z): calcd for $C_9H_{10}NO_2Cl$ $[M]^+$ 199.0395; found 199.0392.

*Methyl N-(2-Chloro-4-methoxyphenyl)carbamate (**13**).* Yield: 172.5 mg (80%), white crystals; mp 54−58 °C. ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 7.99 (s, 1H), 6.95 (d, 1H, J = 2.6), 6.92 (brs, 1H), 6.86 (dd, 1H, J = 2.5, J = 9.0), 3.82 (s, 3H), 3.81 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$, ppm): δ 158.2, 153.9, 135.5, 134.8, 131.9, 121.5, 116.1, 55.1, 53.1. HRMS (ESI-TOF) (m/z): calcd for $C_9H_{10}NO_3Cl$ $[M]^+$ 215.0349; found 215.0349.

*Methyl N-(8-Chloro-1-naphthyl)carbamate (**14**).* Yield: 207.2 mg (88%), light yellow powder; mp182−184 °C. ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 7.90 (d, 1H, J = 8.6), 7.74−7.64 (m, 2H), 7.46−7.40 (m, 2H), 7.22 (d, 1H, J = 8.8), 6.87 (brs, 1H), 3.86 (s, 3H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$, ppm): δ 153.9, 139.4, 139.0, 135.6, 132.7, 128.8, 126.9, 124.4, 122.1, 121.9, 112.3, 53.2. HRMS (ESI-TOF) (m/z): calcd for $C_{12}H_{10}NO_2Cl$ $[M]^+$ 235.0400; found 235.0394.

*Methyl N-(2,4-Dichlorophenyl)carbamate (**15**).* Yield: 191.5 mg (87%), yellow crystals; mp 52−55 °C. ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 8.16 (d, 1H, J = 8.5), 7.40 (d, 1H, J = 2.5), 7.28 (dd, 1H, J = 8.9, J = 2.2), 7.13 (brs, 1H), 3.80 (s, 3H), ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$, ppm): δ 153.9, 138.1, 135.6, 129.9, 128.6, 123.5, 115.8, 53.2, HRMS (ESI-TOF) (m/z): calcd for $C_8H_7NO_2Cl_2$ $[M + H]^+$ 219.9927; found 219.9928.

*Methyl N-(2,5-Dichlorophenyl)carbamate (**18**).* Yield: 185.1 mg (84%), cream solid; mp 63−68 °C. ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 8.30 (s, 1 H), 7.30 (d, 1H, J = 3.0), 7.19 (brs, 1H), 7.01 (dd, 1H, J = 2.4, J = 6.1), 3.86 (s, 3H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$, ppm): δ 153.7, 136.0, 134.1, 130.1, 124.0, 120.4, 120.1, 53.2. HRMS (ESI-TOF) (m/z): calcd for $C_8H_7NO_2Cl_2$ $[M + H]^+$ 219.9927; found 219.9928.

*Methyl N-(2-Chloro-5-fluorophenyl)carbamate (**19**).* Yield: 168.5 mg, (83%), yellow powder; mp 91−93 °C. ^{1}H NMR (500 MHz,

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$CDCl_3$, ppm): δ 8.06 (d, 1H, J = 9.6), 7.32 (dd, 1H, J = 9.0, J = 6.0), 7.23 (brs, 1H), 6.75 (dd, 1H, J = 8.0, J = 3.0), 3.86 (s, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, ppm): δ 164.8 (d, J = 246), 153.4, 139.9 (d, J = 9.4), 135.4 (d, J = 3.3), 128.7 (d, J = 23.3), 118.7 (d, J = 9), 116.3 (d, J = 23), 53.2. HRMS (ESI-TOF) (m/z): calcd for $C_8H_7NO_2ClF$ $[M]^+$ 203.0149; found 203.0150.

*Methyl N-(2-Bromo-4-methylphenyl)carbamate (**20**).* Yield: 215 mg (88%), yellow solid; mp 121−124 °C. ^1H NMR (500 MHz, $CDCl_3$, ppm): δ 8.01 (d, 1H, J = 7.5), 7.36 (d, 1H, J = 1.2), 7.13 (dd, 1H, J = 8.0, J = 1.2), 7.07 (brs, 1H), 3.84 (s, 3H), 2.32 (s, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, ppm): δ 153.9, 134.6, 132.9, 130.4, 129.0, 122.9, 122.0, 53.3, 21.2. HRMS (ESI-TOF) (m/z): calcd for $C_9H_{10}BrNO_2$ $[M + H]^+$ 243.9968; found 243.9970.

*Methyl N-(2-Bromo-4-methoxyphenyl)carbamate (**21**).* Yield: 224 mg (86%), light orange powder; mp 63−67 °C. ^1H NMR (500 MHz, $CDCl_3$, ppm): δ 7.92 (brs, 1H), 7.07 (d, 1H, J = 2.8), 6.86 (dd, 1H, J = 9.0, J = 2.8), 3.78 (s, 3H), 3.77 (s, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, ppm): δ 154.5, 152.9, 139.6, 138.2, 129.6, 118.0, 114.5, 56.1, 52.9. HRMS (ESI-TOF) (m/z): calcd for $C_9H_{10}NO_3Br$ $[M]^+$ 258.9839; found 258.9834.

*Methyl N-(2-Bromo-4-nitrophenyl)carbamate (**22**).* Yield: 212 mg (77%), yellow crystals; mp193−195 °C. ^1H NMR (500 MHz, $CDCl_3$, ppm): δ 8.49 (d, 1H, J = 2.8), 8.47 (d, 1H, J = 9.4), 8.25 (dd, 1H, J = 9.3, J = 2.5), 7.52 (brs, 1H), 3.91 (s, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, ppm): δ 154.0, 142.8, 140.3, 134.7, 133.3, 130.4, 125.5, 53.3. HRMS (ESI-TOF) (m/z): calcd for $C_8H_7N_2O_4Br$ $[M]^+$ 273.9584; found 273.9584.

*Methyl N-(2-Bromo-4-chlorophenyl)carbamate (**23**).* Yield: 238 mg (90%), cream crystals; mp 86−89 °C. ^1H NMR (500 MHz, $CDCl_3$, ppm): δ 8.10 (d, 1H, J = 9.0), 7.70 (d, 1H, J = 2.0), 7.46 (dd, 1H, J = 9.0, J = 2.0), 7.14 (brs, 1H), 3.85 (s, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, ppm): δ 153.9, 135.1, 132.1, 129.0, 128.9, 121.2, 113.0, 53.1. HRMS (ESI-TOF) (m/z): calcd for $C_8H_7NO_2BrCl$ $[M + H]^+$ 262.9343; found 262.9340.

*Methyl N-(2-Bromo-5-chlorophenyl)carbamate (**26**).* Yield: 238 mg (90%), yellow powder. Mp. 97−99 °C. ^1H NMR (500 MHz, $CDCl_3$, ppm): δ 8.27 (s, 1H), 7.45 (d, 1H, J = 8.5), 7.18 (brs, 1H), 6.95 (dd, 1H, J = 8.5, J = 1.6), 3.86 (s, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, ppm): δ 153.8, 137.2, 134.8, 133.3, 124.6, 120.4, 110.4, 53.2. HRMS (ESI-TOF) (m/z): calcd for $C_8H_7NO_2BrCl$ $[M]^+$ 262.9343; found 262.9343.

*Methyl N-(2-Bromo-5-fluorophenyl)carbamate (**27**).* Yield: 208 mg (84%), cream powder. Mp. 108−111 °C ^1H NMR (500 MHz, $CDCl_3$, ppm): δ 8.04 (dd, 1H, J = 11.0, J = 2.0), 7.49 (dd, 1H, J = 5.8, J = 3.1), 7.23 (brs, 1H), 6.70 (ddt, 1H, J = 9.5, J = 3.0, J = 1.1), 3.85 (s, 3H); $^{13}C\{^1H\}$ NMR (400 MHz, $CDCl_3$, ppm): δ 163.8 (d, J = 245), 153.9, 138.6 (d, J = 8.1), 131.0 (d, J = 20.7), 118.7 (d, J = 2.6), 112.0 (d, J = 20.5), 108.7 (d, J = 8.4), 53.2. HRMS (ESI-TOF) (m/z): calcd for $C_8H_7NO_2BrF$ $[M]^+$ 246.9644; found 246.9645.

*Methyl N-(8-Bromo-1-naphthyl)carbamate (**28**).* Yield: 223 mg (87%), cream powder. Mp. 199−202 °C. ^1H NMR (500 MHz, $CDCl_3$, ppm) δ 7.81 (d, 1H, J = 8.0), 7.60−7.56 (m, 2H), 7.40−7.33 (m, 2H), 7.18 (d, 1H, J = 7.1), 6.88 (brs, 1H), 3.85 (s, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, ppm): δ 153.9, 136.1, 133.5, 128.0, 127.3, 124.6, 121.1, 119.2, 118.9, 117.0, 111.7, 53.3. HRMS (ESI-TOF) (m/z): calcd for $C_{12}H_{10}NO_2Br$ $[M]^+$ 278.9895; found 278.9894.

*Methyl N-(2-Iodo-4-methylphenyl)carbamate (**29**).* Yield: 259 mg, (89%), yellow crystals. Mp. 83−85 °C. ^1H NMR (500 MHz, $CDCl_3$, ppm): δ 7.90 (s, 1H), 7.62 (d, 1H, J = 7.0), 7.16 (d, 1H, J = 8.5), 6.90 (brs, 1H), 3.82 (s, 3H), 2.29 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, ppm): δ 154.4, 139.5, 136.3, 135.6, 130.4, 120.9, 120.8, 52.9, 20.7. HRMS (ESI-TOF) (m/z): calcd for $C_9H_{10}NO_2I$ $[M]^+$ 290.9751; found 290.9756.

*Methyl N-(5-Fluoro-2-iodophenyl)carbamate (**30**).* Yield: 254 mg (86%), orange oil. ^1H NMR (500 MHz, $CDCl_3$, ppm): δ 7.98 (dd, 1H, J = 11, J = 9.0), 7.72 (dd, 1H, J = 9.0, J = 6.0), 7.07 (brs, 1H), 6.62 (ddt, 1H, J = 9.0, J = 3.0, J = 1.0), 3.86 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, ppm): δ 163.9 (d, J = 243), 153.9, 139.7 (d, J = 9.0), 128.9 (d, J = 7.1), 127.5, 112.6 (d, J = 22.4), 107.9 (d, J = 29.0), 53.2; HRMS (ESI-TOF) (m/z): calcd for $C_8H_7NO_2FI$ $[M]^+$ 294.9500; found 294.9494.

*Methyl N-(5-Chloro-2-iodophenyl)carbamate (**31**).* Yield: 283.5 mg (91%), yellow crystals. Mp 109−113 °C. ^1H NMR (500 MHz, $CDCl_3$, ppm): δ 8.20 (s, 1H), 7.69 (d, 1H, J = 8.4), 7.02 (brs, 1H), 6.85 (dd, 1H, J = 2.4, J = 6.0), 3.86 (s, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, ppm): δ 153.9, 139.8, 136.0, 125.5, 115.6, 107.2, 107.0, 53.2. HRMS (ESI-TOF) (m/z): calcd for $C_8H_7NO_2ClI$ $[M]^+$ 310.9204; found 310.9202.

*Iso-propyl N-(2-Bromo-4-methylphenyl)carbamate (**34**).* Yield: 242 mg (89%), cream powder. Mp 129−131 °C. ^1H NMR (500 MHz, $CDCl_3$, ppm): δ 7.73 (d, 1H, J = 8.0), 7.42−7.39 (m, 1H), 7.32 (d, 1H, J = 8.0), 6.89 (brs, 1H), 4.28 (hep, 1H, J = 9.1), 2.33 (s, 3H), 1.44 (d, 6H, J = 9.1). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, ppm): δ 153.9, 139.9, 136.8, 133.3, 128.3, 127.4, 121.0, 62.8, 27.8, 26.2; HRMS (ESI-TOF) (m/z): calcd for $C_{11}H_{14}NO_2Br$ $[M]^+$ 271.0208; found 271.0207.

*t-Butyl N-(2-Bromo-4-methylphenyl)carbamate (**35**).* Yield: 248.5 mg (87%), white powder. Mp 122−125 °C.^1H NMR (500 MHz, $CDCl_3$, ppm): δ 7.68 (s, 1H), 7.42 (d, 1H, J = 8.0), 7.19 (dd, 1H, J = 7.7, J = 2.0), 6.90 (brs, 1H), 2.31 (s, 3H), 1.40 (s, 9H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, ppm): δ 153.7, 138.8, 134.3, 131.5, 128.6, 125.7, 118.5, 61.8, 28.4, 25.8. HRMS (ESI-TOF) (m/z): calcd for $C_{12}H_{16}NO_2Br$ $[M]^+$ 285.0364; found 285.0366.

*2-Bromo-4-methylaniline (**36**).* Yield: 154.4 mg (83%).[87]

Procedure for Gram-Scale Reaction. Methyl *N*-(4-methyl phenyl)carbamate (6 mmol, 1.00 g), NBS (1.1 mmol, 1.17 g), PTSA (0.5 mmol, 0.5 g), and $Pd(OAc)_2$ (0.05 mmol, 60 mg) were added to a sealed tube equipped with a magnetic stirring bar followed by the addition of DCE (10 mL). The reaction mixture was stirred at 60 °C and the completion of the reaction was monitored using TLC (*n*-hexane/ethyl acetate/methanol; 20:5:2). After the reaction was completed, the mixture was cooled to room temperature and the reaction mixture was diluted with dichloromethane (3 × 30 mL). The organic layer was further washed with HCl (100 mL, 10% aq solution) followed by $NaHCO_3$ (100 mL, saturated aq solution). Afterward, the organic layer was separated and dried over anhydrous $MgSO_4$ and concentrated under reduced pressure using a rotary evaporator. Purification was accomplished using column chromatography using silica gel as the stationary phase (*n*-hexane/ethyl acetate; 4:1).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00329.

^1H and ^{13}C NMR spectra of the synthesized starting materials and products (PDF)

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Notes

The authors declare no competing financial interest.

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