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C–H Activation

Room-Temperature *ortho*-Alkoxylation and -Halogenation of *N*-Tosylbenzamides by Using Palladium(II)-Catalyzed C–H Activation

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Abstract: The *N*-tosylcarboxamide group can direct the room-temperature palladium-catalyzed C–H alkoxylation and halogenation of substituted arenes in a simple and mild procedure. The room-temperature stoichiometric cyclopalladation of *N*-tosylbenzamide was first studied, and the ability of the palladacycle to react with oxidants to form C–X and C–O bonds under mild conditions was demonstrated. The reaction conditions were then adapted to promote room-temperature *ortho*-alkoxylations and *ortho*-halogenations of *N*-tosylbenzamides using palladium as catalyst. The scope and limitation of both alkoxylations and halogenations was studied and the subsequent functional transformation of the *N*-tosylcarboxamide group through nucleophilic additions was evaluated. This methodology offers a simple and mild route to diversely functionalized arenes.

Introduction

Over the past four decades, the development of transition-metal-catalyzed transformations has profoundly revolutionized organic chemistry. Among them, Pd-catalyzed cross-coupling reactions are probably the most prominent examples of such a progress, finding applications in all the areas in which organic chemistry is involved.[1] More recently, transition-metal-catalyzed C–H bond functionalization has emerged as a new and promising method for more atom-economical transformations extending the scope of this chemistry.[2] In this field, the aromatic C(sp^2)-H functionalization has been successfully applied to the formation of C–C, C–N, C–O, and C–X bonds using, in most cases, a directing group to enhance regioselectivity in the *ortho* position.[3] However, these reactions generally require the use of harsh reaction conditions: high temperature and/or acidic conditions.[4] More recently, the development of milder reaction conditions has become the subject of deep investigations.[5,6] To date, the most prominent examples of groups able to direct mild C–H activation reactions can be divided in two main categories: amino and carbonyl-based derivatives. Thus, C–C, C–X, and C–O bonds have been formed at the *ortho* position of azo compounds,[7] anilides,[8] ureas,[9] and carbamates.[10] Ketones[11] and imines[12] have been used to perform the mild formation of C–C and C–O bonds, whereas *N*-methoxy-[13] and *N*-pivaloyloxybenzamide[14] groups have been used to create both C–C and C–N bonds leading to heterocycles such as phenanthridin-6(5*H*)-ones and isoquinolinones at room temperature. Most of these transformations are directing-group dependent and groups able to direct multiple C–H transformations at room temperature are still needed. The *N*-tosylcarboxamide group has recently been described in the synthesis of isoindolinone derivatives through C–H activation reactions,[15] and by our group as a transformable group able to direct *ortho* C–H arylation.[16] In these examples, the reactions were all performed between 120 and 130 °C. During the investigations of this directing group in other C–H transformations, we found that *ortho*-alkoxylation could occur at room temperature. Herein, we wish to report our investigations on the use of *N*-tosylbenzamides in room-temperature C–H alkoxylation and halogenation.

Results and Discussion

In aromatic C–H activation reactions using Pd^{II} as a catalyst, the insertion of the metal in the C–H bond leading to a palladacycle is commonly accepted as the determining step.[17] We started by screening various solvents to evaluate the cyclopalladation reaction at room temperature starting from the *N*-tosylbenzamide **1a** and using stoichiometric amounts of [$Pd(OAc)_2$] (Table 1). In all cases the reactions were stopped after 18 h, and the ratio of **1a**/**2a** was determined by ^{1}H NMR spectroscopy (Table 1). In solvents commonly used in C–H activation reactions (Table 1, entries 1–6), a partial conversion of **1a** in a nearly 1:1 ratio was observed. But using MeOH as the solvent, we were pleased to see that the reaction was almost

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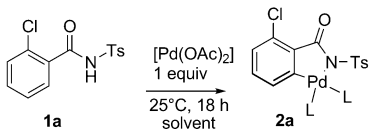
Table 1. Solvent screening for room-temperature formation of palladacycle **2a**.



1a **2a**

Entry	Solvent	1a/2a[a]
1	AcOH	46:54
2	MeCN	44:56
3	1,2-DCE[c]	47:53
4	PhMe	49:51
5	$AcOH/CHCl_3$ (2:1)	40:60
6	1,4-dioxane	39:61
7	MeOH	3:97
8	EtOH	14:86
9	*i*PrOH	59:41
10	CF_3CH_2OH	50:50
11	CD_3OD[b]	15:85

[a] Ratio determined by using ^{1}H NMR spectroscopy. [b] Temperature was set to 22 °C (see the Supporting Information for details). [c] 1,2-Dichloroethane.

complete.[13b,14a,b,18] The use of other alcohols as solvents did not improve the conversion, whereas performing the reaction in CD_3OD allowed us to monitor the formation of palladacycle **2a** by recording NMR spectra at different times (Figure 1).[19]

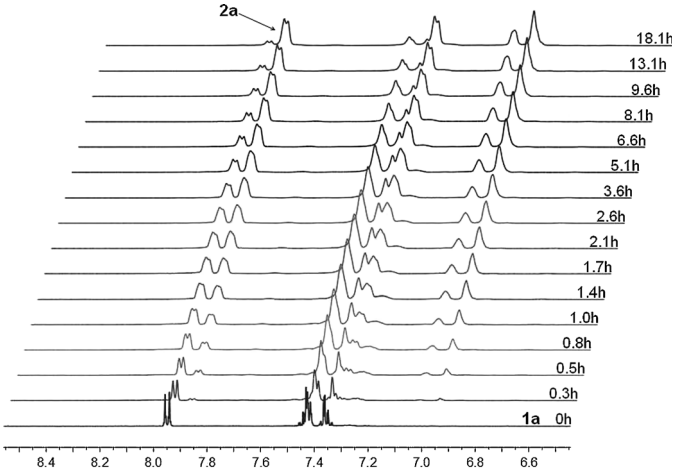
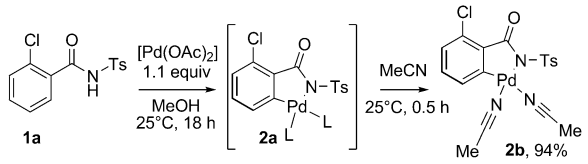


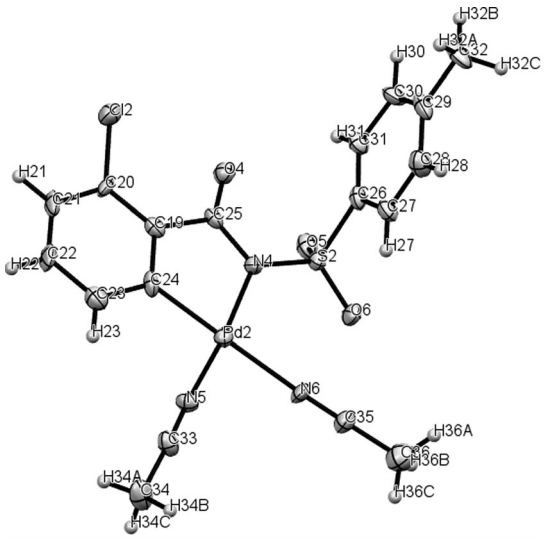
Figure 1. Formation of **2a** in CD_3OD monitored by using ^{1}H NMR spectroscopy.

To confirm the structure of palladacycle **2a**, the reaction was repeated using a slight excess of $[Pd(OAc)_2]$ (1.1 equiv) in MeOH (Scheme 1). Unfortunately, attempts to characterize **2a** in a pure form failed and the exact nature of the ligands L was not established. Nevertheless, the crude palladacycle **2a**, was stirred in MeCN at room temperature for 0.25 h to afford a characterizable palladacycle. Thus, palladacycle **2b** was isolated in 94% yield and suitable single-crystals for X-ray analysis were obtained from slow evaporation in MeCN. The obtained ORTEP plot for **2b** is depicted in Scheme 2.



1a **2a**

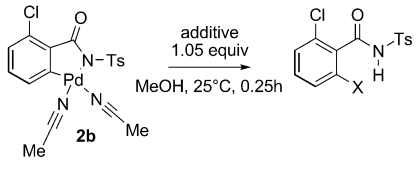
Scheme 1. Synthesis of palladacycle **2b** (yield of isolated **2b**).



Scheme 2. X-ray structure of palladacycle **2b**.

The reactivity of **2b** in MeOH at room temperature toward various additives commonly used in C–H activation reactions was then investigated. Thus, palladacycle **2b** was treated at 25 °C for 0.25 h with $PhI(OAc)_2$, *N*-iodosuccinimide (NIS), or IOAc[20] and ^{1}H NMR spectra of the crudes were recorded (Table 2). By using $PhI(OAc)_2$, a full conversion to the corresponding methoxylated derivative **3a** was observed, and the use of NIS and IOAc led quantitatively to the iodinated compound **4a**. Taken together, these results with stoichiometric amounts of $[Pd(OAc)_2]$ indicates that both the formation of the

Table 2. Methoxylation and iodination of palladacycle **2b**.



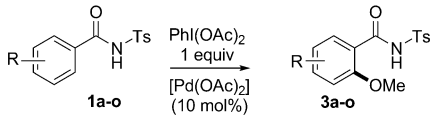
Additive	Observed products (X)	^{1}H NMR ratio[a]
$PhI(OAc)_2$	**3a** (OMe)	100
NIS	**4a** (I)	100
IOAc[b]	**4a** (I)	100

[a] Ratio determined by using ^{1}H NMR spectroscopy and a pure sample of material as a reference. [b] Reaction conditions: IOAc (1.05 equiv; generated from $PhI(OAc)_2$ (0.52 equiv) and I_2 (0.52 equiv)).[20]

palladacycle and the subsequent functionalization can be performed at room temperature in MeOH with $PhI(OAc)_2$, NIS, and IOAc.

The catalytic methoxylation at room temperature was then investigated by using $[Pd(OAc)_2]$ (10 mol%) and $PhI(OAc)_2$ (1 equiv) in MeOH (Table 3). Starting from **1a**, we observed the clean formation of the expected methoxylated compound **3a** isolated in 95% yield. The scope of the reaction was further studied with various substituted *N*-tosylbenzamides **1b**–**o**. The methoxylated compounds were easily obtained by using *ortho*- and *meta*-substituted starting materials and the reactions were generally completed within 24–48 h. In the case of deactivated starting material **1d** and **1i**, total conversion was never observed resulting in lower yields even if an extended reaction time was used for **3d**. Starting from *para*-substituted substrates **1j**–**n**, the decreased yields of the isolated products were due in all cases to the formation of dimethoxylated compounds. Substantial amounts of dimethoxylated derivatives were isolated starting from **1j**,**k**,**n**. The unsubstituted *N*-tosylbenzamide **1o** showed a similar reactivity affording a mixture of di- and monomethoxylated derivatives, thus **3o** was isolated in 76% yield.

Table 3. Catalytic room-temperature methoxylation of *N*-tosylbenzamides.[a]



1a-o → **3a-o**

3a, 24 h, 95% | **3b**, 24 h, 95% | **3c**, 48 h, 93%

3d, 504 h, 65% | **3e**, 8.5 h, 89% | **3f**, 8 h, 90%[b]

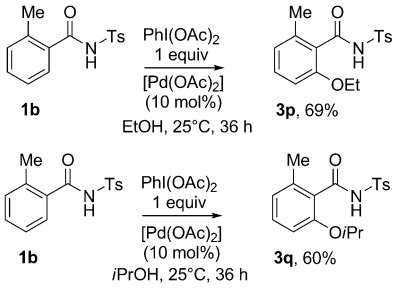
3g, 18 h, 72% | **3h**, 36 h, 78% | **3i**, 48 h, 51%

3j, 48 h, 51%
3jj, 31%[c] | **3k**, 72 h, 47%
3kk, 43%[c] | **3l**, 20 h, 69%

3m, 18 h, 47% | **3n**, 24 h, 65%
3nn, 25%[c] | **3o**, 24 h, 76%

[a] Yields of the isolated products. [b] A scale of 2 g was used. [c] Yields of the isolated dimethoxylated compounds.

Compound **1b** was then evaluated toward alkoxylation using EtOH and *i*PrOH as solvents (Scheme 3). Thus, using the same protocol, the corresponding ethoxy and isopropoxy derivatives **3p**,**q** were isolated in 69 and 60% yields, respectively. In both cases, the total completion was not observed even if the reaction times or the amount of $PhI(OAc)_2$ were increased. The use of *t*BuOH as solvent under the same conditions did not afford the corresponding alkoxylated derivative. As previously reported,[8c,21] only starting material was recovered unchanged even if the temperature of the reaction was increased (result not shown).



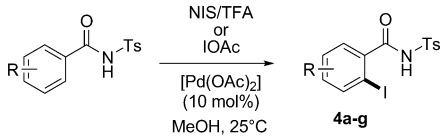
1b

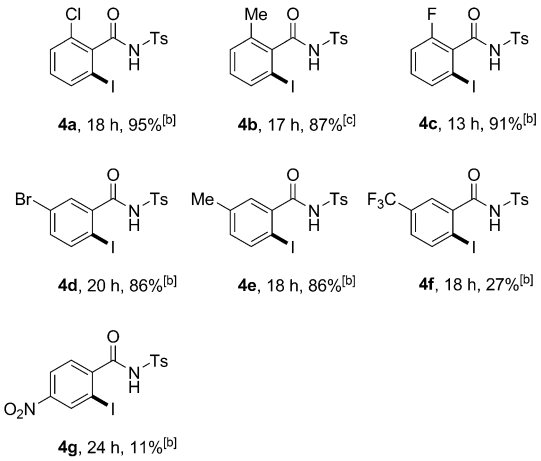
Scheme 3. Catalytic room-temperature alkoxylation of *N*-tosylbenzamide **1b** (yield of isolated **1b**).

We then turned our attention to the room-temperature catalyzed *ortho*-halogenation. Unlike the methoxylation, the conditions of halogenation had to be optimized for the catalytic process to work in MeOH. Therefore, starting from 2-methyl-*N*-tosylbenzamide **1b** and using NIS as the halogenating agent, the reaction had to be performed in the presence of trifluoroacetic acid (TFA)[7,8b,22] to afford the corresponding *ortho*-iodinated product **4b** with a good conversion (Table 4). Regarding the acidic conditions used for iodination with NIS, we found that iodination can be performed using IOAc.[20] Thus, under these neutral conditions, 2-chloro and 2-fluoro-*N*-tosylbenzamides **1a**,**e** were iodinated in high yields. These conditions were successfully applied to 3-bromo- and 3-methyl-*N*-tosylbenzamides **1f**,**g** affording the *ortho*-iodinated derivatives **4d**,**e** in good yields. As for the methoxylation, starting from the deactivated 3-trifluoromethyl-*N*-tosylbenzamide (**1i**) the reaction did not go to completion and a lower yield was isolated. We then studied the catalytic *ortho*-iodination from *para*-substituted substrates. Thus, using **1k**, **1l**, **1n**, or **1m**, the reaction led to inseparable mixtures of starting material, *ortho*-iodinated and *ortho*-diiodinated products (results not shown). For example, the 4-NO_2 derivative **4g** was isolated in only 11% yield.

The room-temperature catalytic bromination was then evaluated by using *ortho*- and *meta*-substituted starting materials (Table 5). Thus, by treating **1a**, **1b**, **1f**, and **1g** with *N*-bromosuccinimide (NBS) and TFA we were pleased to isolate after

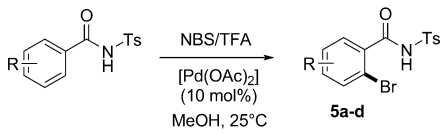
Table 4. Catalytic room-temperature iodination of *N*-tosylbenzamides.[a]

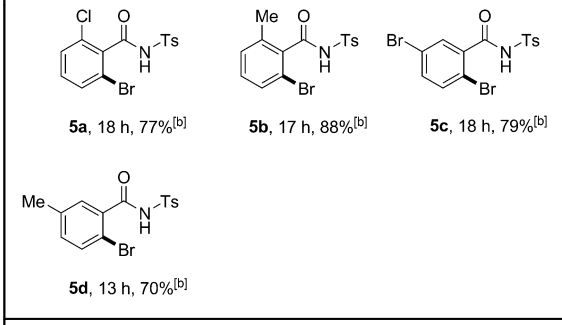




[a] Yields of the isolated products. [b] Reaction conditions: IOAc 1.5 equiv (generated from $PhI(OAc)_2$ 0.75 equiv and I_2 0.75 equiv).[20] [c] Reaction conditions: NIS 1.2 equiv, TFA 10 equiv

Table 5. Catalytic room-temperature bromination of *N*-tosylbenzamides.[a]

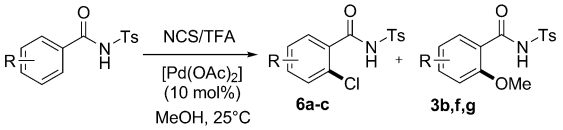


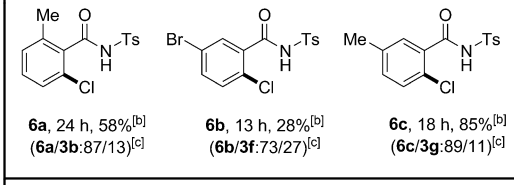


[a] Yields of the isolated products. [b] Reaction conditions: NBS (1.2 equiv), TFA (10 equiv).

complete conversion the expected *ortho*-brominated derivatives **5a**–**d** in good yields. The same reaction conditions were then applied to perform chlorination (Table 6). Therefore, by replacing NBS by *N*-chlorosuccinimide (NCS), compound **1b** was *ortho*-chlorinated to give **6a** along with the *ortho*-methoxylated derivative **3b** in a ratio of 87:13. Similar results were observed by using *meta*-substituted starting materials **1f** and **1g**. It appears that using NCS in MeOH leads to a competition between chlorination and methoxylation. These results taken together with the clean halogenation reactions observed with NBS, NIS, and IOAc indicates that NCS behaves differently. Therefore, we can hypothesize that either NCS is playing the role of $PhI(OAc)_2$ to form a pro-methoxylation active species and/or that a competition between C–O and C–Cl bond formation takes place at the reductive-elimination step.

Table 6. Catalytic room-temperature chlorination of *N*-tosylbenzamides.[a]



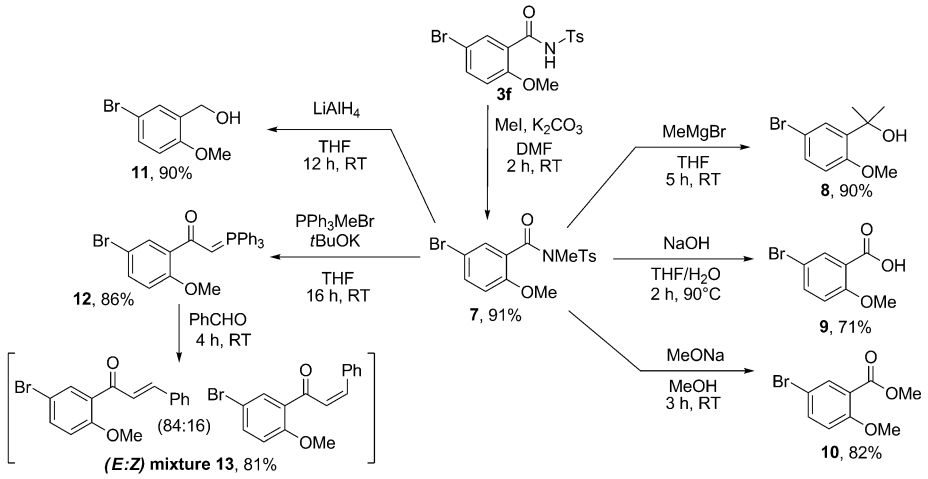


[a] Yields of the isolated products. [b] Reaction conditions: NCS (1.2 equiv), TFA (10 equiv). [c] Ratio in parentheses are of chlorinated/methoxylated products in the crude material as determined by ^1H NMR spectroscopy.

Finally, the ability of the *N*-tosylcarboxamide group to give valuable synthetic intermediates through functional transformations was evaluated (Scheme 4). Starting from **3f**, the *N*-tosylcarboxamide group was first methylated[15,23] to give **7**, which was submitted to various nucleophilic additions. Thus, using MeMgBr (2 equiv), the addition of two methyl groups was observed and compound **8** was isolated in 90% yield. The use of NaOH and MeONa as nucleophiles gave the corresponding carboxylic acid **9** and ester **10** in 71 and 82% yields, respectively. Reduction with $LiAlH_4$ afforded the expected benzylic alcohol **11** in 90% yield. Interestingly, phosphorus ylide **12** was obtained in 86% yield by treating **7** with methyltriphenylphosphonium bromide. Ylide **12** was then further treated with benzaldehyde to afford a mixture of *Z* and *E* alkenes **13** in 81% yield.

Conclusion

We have found that the palladium-catalyzed *ortho*-alkoxylation and *ortho*-halogenations of *N*-tosylbenzamides can be performed in good yields at room temperature using methanol as the solvent. Both alkoxylation using $PhI(OAc)_2$ and iodination with IOAc, generated from the mixture I_2/$PhI(OAc)_2$, occurred in very mild conditions using a simple procedure. However, the alkoxylation reaction scope seems to be limited to the use of non-hindered alcohols. With regard to the halogenation reactions, the use of *para*-substituted starting materials led to complex mixtures, whereas the use of NCS afforded both chlorinated and methoxylated derivatives. Furthermore, the ability of the *N*-tosylcarboxamide group to be transformed in a variety of relevant functional groups has been highlighted. These results could serve in the development of other C–H activation



Scheme 4. *N*-methylation and subsequent functional transformations of **3 f**.

reactions and find applications in the synthesis of functionalized arenes under mild conditions.

Experimental Section

Syntheses

General procedure A for the preparation of substituted *N*-tosylbenzamides 1 a–o: A round-bottom flask under N_2 was filled with *p*-toluene sulfonamide (1 equiv), EtOAc (2 mL mmol^{-1}), NEt_3 (2.5 equiv), and 4-dimethylaminopyridine (DMAP; 0.005 equiv). A solution of acyl chloride (1.1 equiv) in PhMe (0.8 mL mmol^{-1}) was added through a syringe over 15 min. The mixture was stirred for 1 hour at 55 °C under N_2, cooled to room temperature and quenched with an aqueous solution of hydrochloric acid (0.5 M, 3 mL mmol^{-1}). The resulting mixture was then extracted with EtOAc (3 times). The combined organic layers were dried on $MgSO_4$, filtered and evaporated. The crude was purified by passing through a pad of silica gel eluting with CH_2Cl_2.

2-Fluoro-N-(4-methylbenzenesulfonyl)benzenecarboxamide (**1 e**): Starting from 2-fluorobenzoyl chloride (2.43 g, 15.3 mmol), using general procedure A, *N*-tosylbenzamide **1 e** was obtained as a white solid (3.93 g, 92% yield). M.p. 137–138 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.01 (br s, 1H), 8.05 (d, J = 8.4 Hz, 2H), 7.99 (td, J = 12.3, 4.0 Hz, 1H), 7.56 (m, 1H), 7.36 (d, J = 8.4 Hz, 2H), 7.26 (td, J = 7.6, 0.9 Hz, 1H), 7.16 (ddd, J = 12.3, 8.4, 0.9 Hz, 1H), 2.44 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.0 (d, J = 249 Hz), 160.5 (d, J = 3 Hz), 145.5, 135.8 (d, J = 10 Hz), 135.5, 132.6, 129.8 (2C), 129.0 (2C), 125.5 (d, J = 3 Hz), 118.6 (d, J = 10 Hz), 116.6 (d, J = 25 Hz), 21.8 ppm; IR (KBr): $\tilde{\nu}$ = 3325, 3088, 2923, 1705, 1595, 1428, 1350, 1167, 753 cm^{-1}; HRMS/ESI: *m/z* calcd for $C_{14}H_{13}FNO_3S$: 294.0594 $[M+H]^+$; found: 294.0597.

Synthesis of palladacycle **2 b**: $[Pd(OAc)_2]$ (0.229 g, 1.02 mmol) was added to a solution of **1 a** (0.300 g, 0.97 mmol) in MeOH (6 mL). The reaction mixture was stirred at 25 °C for 18 h. The crude mixture was filtered through a pad of Celite. The Celite pad was washed with MeOH (25 mL) and the solution was evaporated to dryness. MeCN (25 mL) was added, the solution was stirred at 25 °C for 0.5 h and evaporated to afford palladacycle **2 b** as a yellow solid (0.452 g, 94%). M.p. > 250 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.95 (d, J = 8.3 Hz, 2H), 7.28 (d, J = 8.3 Hz, 2H), 6.87 (d, J = 7.8 Hz, 1H), 6.42 (t, J = 7.8 Hz, 1H), 6.23 (d, J = 7.8 Hz, 1H), 2.47 (s, 3H), 2.39 (s, 3H), 2.02 ppm (s, 3H); ^{13}C NMR (500 MHz, $CDCl_3$): δ = 175.7, 143.5, 143.2, 138.8, 132.7, 131.5, 131.3, 129.9, 129.3 (2C), 127.7 (2C), 127.5, 21.7, 4.1, 2.1 ppm; IR (KBr): $\tilde{\nu}$ = 3420, 3067, 2928, 2321, 2294, 1659, 1552, 1432, 1281, 1251, 933, 841, 746, 661, 579, 550 cm^{-1}; HRMS/ESI: *m/z* calcd for $C_{16}H_{14}ClN_2O_3PdS$: 454.9448 $[M-CH_3CN+H]^+$; found: 454.9463.

General procedure B for *ortho*-alkoxylation of *N*-tosylbenzamide 1 a–o: In a round bottom flask, *N*-tosylbenzamide **1 a–o** (1 equiv) was added to a solution of $PhI(OAc)_2$ (1 equiv) and $[Pd(OAc)_2]$ (0.1 equiv) in MeOH, EtOH, or *i*PrOH (8.3 mL mmol^{-1} of **1 a–o**). This mixture was stirred at 25 °C (see Table 2 and Scheme 4 for reaction times) and monitored by TLC. Upon completion, the resulting mixture was diluted with EtOAc, filtered through a pad of Celite and the solvent was evaporated. The crude residue was purified by silica gel chromatography using cyclohexane/EtOAc (4:1 to 3:2 gradient) as the eluent to obtain the desired products **3 a–q**.

2-Chloro-6-methoxy-N-(4-methylbenzenesulfonyl)benzenecarboxamide (**3 a**): Starting from *N*-tosylbenzamide **1 a** (0.200 g, 0.65 mmol), using general procedure B, compound **3 a** was obtained as a white solid (0.208 g, 95%). M.p. 140–142 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.97 (d, J = 8.3 Hz, 2H), 7.35 (d, J = 8.3 Hz, 2H), 7.27 (t, J = 8.3 Hz, 1H), 6.94 (d, J = 8.7 Hz, 1H), 6.79 (d, J = 8.4 Hz, 1H), 3.76 (s, 3H), 2.45 ppm (s, 3H); the NH signal is missing; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.4, 157.6, 145.4, 135.5, 132.6, 132.3, 129.7 (2C), 128.8 (2C), 123.1, 122.3, 109.7, 56.3, 21.7 ppm; IR (KBr): $\tilde{\nu}$ = 3198, 3045, 2946, 1691, 1595, 1466, 1272, 1151, 783 cm^{-1}; HRMS/ESI: *m/z* calcd for $C_{15}H_{14}ClNO_4SNa$: 362.0230 $[M+Na]^+$; found: 362.0212.

General procedure C for *ortho*-halogenation of *N*-tosylbenzamide 1 a,b,f,g using NXS: In a round-bottom flask, *N*-tosylbenzamide **1 a**,**b**,**f**,**g** (1 equiv) and trifluoroacetic acid (10 equiv) was added to a solution of NXS (1.2 equiv) and $[Pd(OAc)_2]$ (10 mol%) in MeOH (12.8 mL mmol^{-1} of **1 a**,**b**,**f**,**g**). The reaction was stirred at 25 °C (see Tables 3–5 for reaction times). The resulting mixture was diluted with EtOAc, filtered through a pad of Celite and the solvent was evaporated. The crude was purified by silica gel chromatography using cyclohexane/EtOAc (4:1 to 3:2 gradient) as the eluent to obtain the desired product **4 b** or **5 a–d** or **6 a–c**.

2-Bromo-6-chloro-N-(4-methylbenzenesulfonyl)benzenecarboxamide (**5 a**): Starting from *N*-tosylbenzamide **1 a** (0.100 g, 0.32 mmol), using general procedure C with NBS, compound **5 a** was obtained as a white solid (0.097 g, 77%). M.p. 72–74 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99 (d, J = 8.1 Hz, 2H), 7.42 (d, J = 8.0 Hz, 1H), 7.36 (d, J = 8.2 Hz, 2H), 7.30 (d, J = 8.1 Hz, 1H), 7.19 (t, J = 8.1 Hz, 1H), 2.46 ppm (s, 3H); the NH signal is missing; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.6, 145.8, 135.4, 134.9, 132.3, 132.2, 131.4, 129.8 (2C), 128.9 (2C), 128.8, 120.1, 21.9 ppm; IR (KBr): $\tilde{\nu}$ = 3216, 3045, 2923, 1712, 1448, 1349, 1170, 1090, 776 cm^{-1}; HRMS/ESI: *m/z* calcd for $C_{14}H_{12}BrClNO_3S$: 387.9404 $[M+H]^+$; found: 387.9404.

General procedure D for *ortho*-iodination of *N*-tosylbenzamide 1 a,e,f,g,i,m using IOAc: $PhI(OAc)_2$ (0.75 equiv), I_2 (0.75 equiv) and MeOH (12.8 mL mmol^{-1} of **1 a**,**e**,**f**,**g**,**i**,**m**) were added in a round-bottom flask. The reaction was stirred for 0.25 h at room tempera-

ture. *N*-Tosylbenzamide **1a**,**e**,**f**,**g**,**i**,**m** (1 equiv) and $[Pd(OAc)_2]$ (10 mol%) were added to the solution and the reaction was stirred at 25 °C (see Table 3 for reaction times). The resulting mixture was diluted with EtOAc, filtered through a pad of Celite, and the solvent was evaporated. The crude residue was purified by silica gel chromatography using cyclohexane/EtOAc (4:1 to 3:2 gradient) as the eluent to obtain the desired product **4a**,**c**–**g**.

2-Chloro-6-iodo-N-(4-methylbenzenesulfonyl)benzenecarboxamide (**4a**): Starting from *N*-tosylbenzamide **1a** (0.100 g, 0.32 mmol), using the general procedure D, compound **4a** was obtained as a white solid (0.134 g, 95%). M.p. 85–86 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.41 (br s, 1H), 8.02 (d, J = 8.2 Hz, 2H), 7.67 (dd, J = 8.0, 0.8 Hz, 1H), 7.37 (d, J = 8.2 Hz, 2H), 7.34 (dd, J = 8.0, 0.9 Hz, 1H), 7.03 (t, J = 8.0 Hz, 1H), 2.46 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.1, 145.8, 139.1, 137.9, 134.8, 132.5, 131.3, 129.8 (2C), 129.6, 129.1 (2C), 92.1, 21.9 ppm; IR (KBr): $\tilde{\nu}$ = 3214, 3058, 2959, 1702, 1445, 1349, 1170, 1089, 777 cm^{-1}; HRMS/ESI: *m/z* calcd for $C_{14}H_{12}ClINO_3S$: 435.9265 $[M+H]^+$; found: 435.9266.

5-Bromo-2-methoxy-N-methyl-N-(4-methylbenzenesulfonyl)benzenecarboxamide (**7**): K_2CO_3 (1.21 g, 8.74 mmol) and iodomethane (544 μL, 8.74 mmol) were added to a stirred solution of **3f** (1.68 g, 0.74 mmol) in DMF (30 mL). After stirring at room temperature during 3 h, the solution was evaporated, water (50 mL) was added and the resulting mixture was extracted with ethyl acetate (3× 80 mL). The combined organic layers were dried on $MgSO_4$, filtrated and evaporated. The crude product was purified by silica gel chromatography using cyclohexane/EtOAc (7:3) as the eluent. **7** was obtained as a white solid (1.57 g, 91% yield). M.p. 139–141 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71 (d, J = 8.4 Hz, 2H), 7.46 (dd, J = 8.8, 2.5 Hz, 1H), 7.31 (d, J = 8.4 Hz, 2H), 7.16 (d, J = 2.5 Hz, 1H), 6.75 (d, J = 8.8 Hz, 1H), 3.75 (s, 3H), 3.31 (s, 3H), 2.45 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.4, 155.1, 145.0, 135.7, 134.3, 130.8, 129.6 (2C), 128.2 (2C), 126.9, 112.7, 112.5, 55.9, 33.6, 21.6 ppm; IR (KBr): $\tilde{\nu}$ = 3006, 2954, 2850, 1682, 1595, 1488, 1350, 1164, 1026, 829, 691 cm^{-1}; HRMS/ESI: calcd for $C_{16}H_{16}BrNO_4SNa$: 419.9876 $[M+Na]^+$; found: 419.9877.

2-(5-Bromo-2-methoxyphenyl)propan-2-ol (**8**): Methylmagnesium bromide (3.0 M in diethyl ether, 0.335 mL, 1.0 mmol) was added dropwise to a solution of **7** (0.200 g, 0.50 mmol) in THF (4 mL) under N_2 at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 6 h under N_2. The resulting mixture was quenched with water (10 mL) and extracted with ethyl acetate (3×15 mL). The combined organic layers were washed with a saturated solution of NaCl then dried on $MgSO_4$, filtrated and evaporated. The crude product was purified by silica gel chromatography using cyclohexane/ethyl acetate (9:1) as the eluent. **8** was obtained as a white solid (0.110 g, 90% yield). M.p. 76–78 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44 (d, J = 2.5 Hz, 1H), 7.34 (dd, J = 8.7, 2.5 Hz, 1H), 6.79 (d, J = 8.7 Hz, 1H), 3.89 (s, 3H), 1.58 ppm (s, 6H); OH signal is missing; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.0, 138.1, 130.7, 129.0, 113.6, 113.0, 72.3, 55.5, 29.4 (2C); IR (KBr): $\tilde{\nu}$ = 3292, 3073, 2962, 2934, 2838, 1486, 1390, 1240, 1070, 809, 627 cm^{-1}; HRMS/ESI: *m/z* calcd for $C_{10}H_{13}BrO_2Na$: 266.9991 $[M+Na]^+$; found: 266.9993.

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FULL PAPER

C–H Activation

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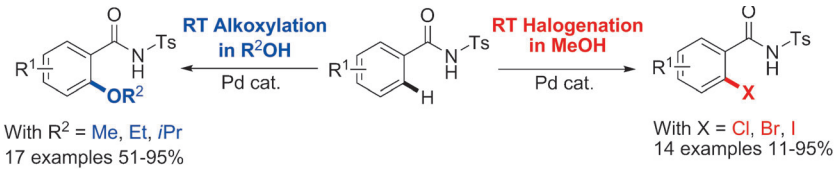
■■ – ■■

Room-Temperature *ortho*-Alkoxylation and -Halogenation of *N*-Tosylbenzamides by Using Palladium(II)-Catalyzed C–H Activation



Mild method for diverse arenes: Room-temperature palladium-catalyzed *ortho*-alkoxylations and *ortho*-halogenations of *N*-tosylbenzamides are described. Along with the ability of the *N*-tosylcarboxamide group to be transformed in useful functional groups, this methodology offers a simple and mild route to diversely functionalized arenes (see scheme).