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Ligand and solvent tuned chemoselective carbonylation of bromoaryl triflates

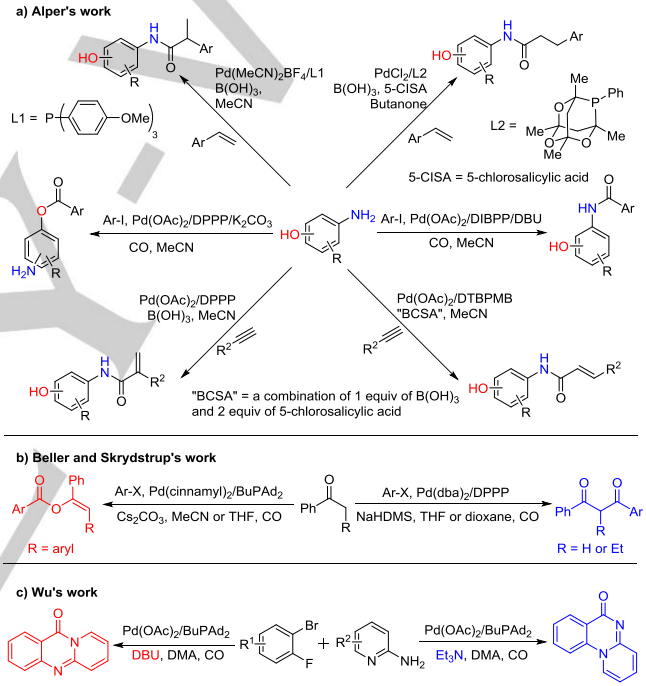
Chaoren Shen,‡ Zhihong Wei,‡ Haijun Jiao* and Xiao-Feng Wu*[a]

Abstract: Palladium-catalyzed chemoselective carbonylation of bromoaryl triflates is reported. The selective C-Br vs. C-OTf functionalization can be remarkably tuned by the combination of ligand (Xantphos vs. DPPF) and solvent (toluene vs. DMSO). The respective ligand and solvent effects are rationalized by DFT calculation. In contrast, monodentate $BuPAd_2$ and $^tBu_3P$ prefer the selective C-Br activation and are solvent insensitive.

Introduction

With the respect of reaction efficiency and environmental sustainability (i.e. generating less waste) as well as creating diverse chemical structures through iterative and programmable synthetic approaches,[1,2] chemoselectivity is one of the primary concerns in catalysis. Palladium-catalyzed cross-coupling has been demonstrated to be a powerful tool in forming carbon-carbon and carbon-heteroatom bonds in academia and industry.[3] As one of the elementary steps, oxidative addition determines the chemoselectivity of palladium-catalyzed cross-coupling of poly(pseudo)halogenated arenes.[4] Although the relative ease degree in the oxidative addition of Pd^0 to C(sp^2)-X bond is frequently referred to as C-I > C-OTf ≈ C-Br > C-Cl,[5] this empirical sequence cannot precisely provide a priori prediction of the favored coupling site. The selective C(sp^2)-X functionalization (X = Cl or Br *vs.* OTf)[6] is always associated with those subtle factors on substrate (electronic/steric),[7] catalyst (ligand/ligation state),[5a,5c,8] solvent (polarity)[9] and additives.[10] Since the early discovery of Hayashi and co-workers,[8a] progress has been made in deep and intuitive understanding into the chemoselectivity of multiple (pseudo)halogenated arenes in Suzuki, Kumada, Negishi cross couplings.[7a,9,11,16] However, the insight on this issue is still confined in rather finite reaction type.

Since the pioneering work of Tsuji and Heck,[12] palladium-catalyzed carbonylation, an efficient pathway in constructing carbonyl containing skeletons, has become a versatile tool in creating chemical diversity.[13] Long-lasting interests have been focused on the chemoselectivity of palladium-catalyzed carbonylation of one nucleophile bearing two nucleophilic sites (Scheme 1),[14] e.g.; chemoselective carbonylation of aminophenols (alkoxycarbonylation *vs.* aminocarbonylation, Scheme 1a),[14a-c] selective carbonylative synthesis of 1,3-diketones and vinylbenzoates from ketones with α-hydrogen (carbonylative *α*-arylation *vs. o*-benzoylation, Scheme 1b)[14d-h] and base-controlled tunable synthesis of linear- and angular-fused quinazolinones with 2-aminopyridine (two different nucleophilic nitrogen centers, Scheme 1c).[14i]



Scheme 1. Palladium-catalyzed chemoselective carbonylation of nucleophiles bearing two nucleophilic sites.

Despite some efforts, the tunable selective activation of one electrophile bearing two or more C(sp^2)-X bonds in palladium-catalyzed carbonylation has not been well-solved and well-balanced; and the reaction either always gave the mixture of products or did not give the fine-tunable selectivity.[15] On the basis of our previous studies on carbonylation and our interest in exploring the selectivity, we herein report a combined experimental and density functional theory investigation into the palladium-catalyzed ligand- and solvent-controlled carbonylation of bromoaryl triflates with fine-tunable activity and chemoselectivity.

Results and Discussion

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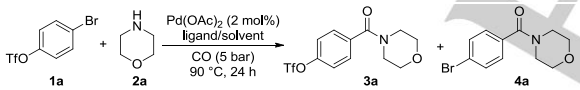
Supporting information for this article is given via a link at the end of the document.

Initially, 4-bromophenyl triflate (**1a**) and morpholine (**2a**) were chosen to optimize the reaction conditions (Table 1). After screening a series of ligands, it was found that Xantphos in toluene gave high conversion and high chemoselectivity of C-Br functionalized **3a** (Table 1, entry 1). When toluene was replaced by aprotic polar DMSO and DMF, not only the conversion went sluggish but also the chemoselectivity dropped (Table 1, entries 2 and 3). The conversion in a mixture of toluene and DMSO was higher than in only DMSO or DMF, but the chemoselectivity was not improved (Table 1, entry 4). Elevating the reaction temperature from 90°C to 110 °C did not diminish the conversion and selectivity (Table 1, entry 5). DPEphos, an analogue of Xantphos with less-rigid skeleton, gave lower conversion and selectivity (Table 1, entry 6). Further optimization revealed that mixtures of DPPF/DMSO and DPPF/DMF were able to switch the selectivity from C-Br activation to C-O activation with high conversion (Table 1, entries 7 and 8). In aprotic polar NMP, the selectivity retained, the conversion dropped (Table 1, entry 9). Nonpolar toluene and 1,4-dioxane suppressed the selectivity and conversion (Table 1, entries 10 and 11). Mixture of toluene and DMSO had no impact on chemoselectivity (Table 1, entry 12). Higher temperature does not affect the conversion and selectivity (Table 1, entry 13). Xantphos in nonpolar toluene gave high conversion and high chemoselectivity of C-Br functionalized **3a**, while DPPF in polar DMSO and DMF gave high conversion and high chemoselectivity of C-O functionalized **4a**. Moreover, $BuPAd_2$ and $^tBu_3P$, bulky and electron-rich monodentate phosphine ligands, gave high conversion and high selectivity of C-Br functionalized **3a** (Table 1, entries 14-17). Different from the scenarios of Xantphos and DPPF, it is noted that the selectivity of $BuPAd_2$ and $^tBu_3P$ was solvent insensitive.

Table 1. Optimization of the reaction condition.[a]

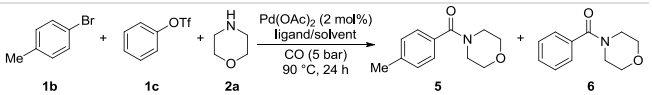


Entry	Ligand/Solvent	Conv. **1a** (%)[b]	**3a**/**4a**[b]
1	Xantphos/toluene	>99	>99/1 (84%)
2	Xantphos/DMSO	32	50/50
3	Xantphos/DMF	39	58/42
4	Xantphos/toluene-DMSO[c]	62	67/33
5	Xantphos/toluene	>99	>99/1 (86%)[d]
6	DPEphos/toluene	75	69/31
7	DPPF/DMSO	>99	<1/99 (81%)
8	DPPF/DMF	>99	<1/99 (77%)
9	DPPF/NMP	32	<1/99
10	DPPF/toluene	41	45/55
11	DPPF/dioxane	12	31/69
12	DPPF/toluene-DMSO[c]	74	<1/99 (68%)
13	DPPF/DMSO	>99	<1/99 (84)[d]
14	$BuPAd_2$/toluene	>99	>99/1 (80%)
15	$BuPAd_2$/DMSO	94	>99/1 (77%)
16	$^tBu_3P$•HBF_4/toluene	>99	>99/1 (89%)
17	$^tBu_3P$•HBF_4/DMSO	42	>99/1 (40%)

(a) Unless otherwise specified: 0.5 mmol of **1a**, 0.5 mmol of **2a**, 2 mol % of $Pd(OAc)_2$, Pd/P = 1/2 (for bidentate phosphine ligand) or 1/3 (for monophosphine ligand), 0.75 mmol of *N*,*N*-diisopropylethylamine (1.5 equiv.), 2 mL solvent, CO (5 bar), 90°C, 24 h. Abbreviations: Xantphos, 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene; DPEphos, bis[(2-diphenylphosphino)phenyl] ether; DPPF, 1,1'-bis(diphenylphosphino)ferrocene; Ad, adamantly; DMSO, dimethyl sulfoxide; DMF, *N*,*N*-dimethylformamide; NMP, *N*-methyl-2-pyrrolidone. (b) Determined by GC-FID with tetradecane as an internal standard. Isolated yield of major product is given in parentheses. (c) Solvent mixture of toluene and DMSO (v/v =1/1). (d) Reaction temperature 110°C.

On the basis of the observed C-Br chemoselectivity by using $BuPAd_2$ and $^tBu_3P$ ligands, cross experiments of 4-bromo-toluene (**1b**), phenyl triflate (**1c**) and morpholine (**2a**) were performed to investigate the electronic effect in selectivity (Table 2). Both $BuPAd_2$/toluene and $tBu_3P{\cdot}HBF_4$/toluene protocols demonstrated high C-Br selectivity with high yields (Table 2, entries 1 and 2). The solvent effect on the C-O selectivity still existed, for example, the DPPF/DMSO protocol preferred the selective C-O activation (Table 2, entry 3), while the DPPF/toluene protocol gave lower selectivity (Table 2 , entry 4); and this is the same as found for substrate **1a** (Table 1, entries 7-11).

Table 2. Chemoselective carbonylation between 4-bromotoluene and phenyl triflate.[a]



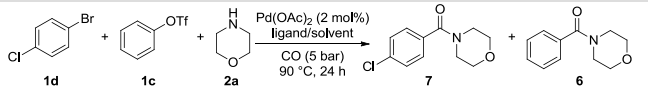
Entry	Ligand/Solvent	Ratio of **5**/**6**[b]
1	$BuPAd_2$/toluene	> 99/1 (82%)
2	$^tBu_3P{\cdot}HBF_4$/toluene	> 99/1 (85%)
3	DPPF/DMSO	<1/99 (90%)
4	DPPF/toluene	32/68[c]

(a) Conditions unless specified otherwise: 0.5 mmol of **1b**, 0.5 mmol of **1c**, 0.5 mmol of **2a**, 2 mol % of $Pd(OAc)_2$, Pd/P = 1/2 (for bidentate phosphine ligand)

or 1/3 (for mono phosphine ligand), 0.75 mmol of *N*,*N*-diisopropylethylamine (1.5 equiv.), 2 mL solvent, CO (5 bar), 90 °C, 24 h. (b) Conversion and ratio of **5/6** were determined by GC-FID with tetradecane as an internal standard. Isolated yield of major product is given in parentheses. (c) The conversion of **1b** and **1c** is 17% and 30%, respectively.

To further investigate the electronic effect in selectivity, 1-bromo-4-chlorobenzene was used (Table 3). Once again, both $BuPAd_2$ and $^tBu_3P{\cdot}HBF_4$ in toluene demonstrated high C-Br selectivity with high conversion and yields (Table 3, entries 1 and 2). With the respect of the selectivity of **1b** and **1c** in DPPF/DMSO (Table 2), the C-Br chemoselectivity of **1d** increased and the C-O chemoselectivity of **1c** decreased significantly (Table 3, entry 3). This might be due to the introduced electron-withdrawing chloro substituent, which activates the C-Br bond for oxidative addition and enhances the C-Br selectivity

Table 3. Chemoselective carbonylation between 1-bromo-4-chlorobenzene and phenyl triflate.[a]



Entry	Ligand/Solvent	Ratio of **7**/**6**[b]
1	$BuPAd_2$/toluene	95/5[c]
2	$^tBu_3P{\cdot}HBF_4$/toluene	> 99/1 (94%)
3	DPPF/DMSO	23/77[d]

(a) Unless specified otherwise: 0.5 mmol of **1d**, 0.5 mmol of **1c**, 0.5 mmol of **2a**, 2 mol % of $Pd(OAc)_2$, Pd/P = 1/2 (for bidentate phosphine ligand) or 1/3 (for mono phosphine ligand), 0.75 mmol of *N*,*N*-diisopropylethylamine (1.5 equiv.), 2 mL solvent, CO (5 bar), 90 °C, 24 h. (b) Conversion and ratio of **7/6** were determined by GC-FID with tetradecane as an internal standard. Isolated yield of major product is given in parentheses. (c) The conversion of **1d** and **1c** is 94% and 16%; respectively. (d) The conversion of **1d** and **1c** is 17% and 84%; respectively.

Our results demonstrate remarkable effects of ligand and solvent on the chemoselective C-Br vs. C-O activation in the carbonylation reaction of 4-bromophenyl triflate. To understand these effects, comparative DFT computation was performed on real-size ligands (Xantphos and DPPF) and substrate (4-bromophenyl triflate) without any structural simplifications and constrains. In our calculations, hybrid B3LYP calculation[9a,16] was carried out in gas phase as well as in nonpolar (toluene) and polar (DMSO) solvents by using the CPCM solvation model.[17] The effective core potential of Hay and Wadt with double-ξ valance basis set (LanL2DZ) was chosen for Pd,[18] and the TZVP basis set[19] was used for all other elements.

Since the elementary step of oxidative addition determines the chemoselectivity of carbonylation reactions, we only calculated the corresponding kinetic parameters of the C-Br and C-O activation. Since there are plentiful theoretical investigations into the mechanisms of C-X bonds oxidative addition in palladium-catalyzed coupling reactions;[20] we did not consider the complexes between catalyst and substrate and focused only on the apparent barriers of this single step. The computed results are shown in Figure 1.

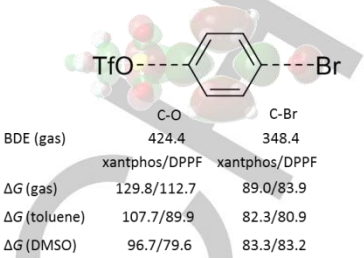


Figure 1. BDEs as well as free-energy barrier for the oxidative addition of $C(sp^2)$-Br and $C(sp^2)$-O bonds.

At first we calculated the gas phase energy of the homolytic dissociation of the C-Br and C-O bonds in 4-bromophenyl triflate It is found that the homolytic dissociation energy of the C-O bond is much larger than that of the C-Br bond (424.4 vs. 348.4 kJ/mol), indicating that the C-O bond is much stronger than the C-Br bond.

In gas phase, the computed Gibbs free energy barrier of C-O oxidative addition using Xantphos and DPPF are higher than that of C-Br (128.9 and 112.7 vs. 89.0 and 83.0 kJ/mol, respectively); indicating that C-Br oxidative addition in gas phase should be much easier and more selective than C-O oxidative addition and these barriers show the same trend of the homolytic bond dissociation energies. In addition, it is noted that the barriers using DPPF are lower than those using Xantphos by 16.2 kJ/mol for the C-O bond activation and by 6.0 kJ/mol for the C-Br bond activation in gas phase, indicating the stronger ligand effect of DPPF over Xantphos in both C-O and C-Br activation, albeit in larger extent of C-O bond over C-Br bond.

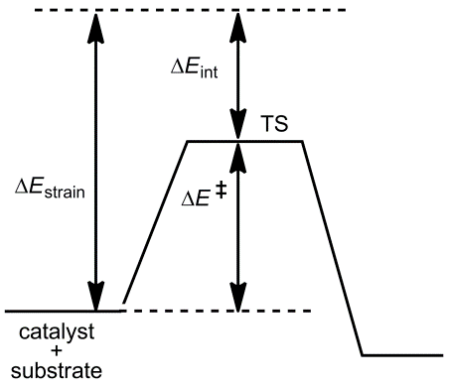


Figure 2. Activation strain model.

From gas phase into toluene, the barrier of C-O oxidative addition using Xantphos and DPPF is reduced significantly by 22.1 and 22.8 kJ/mol, respectively; indicating very strong effect of solvation. In contrast, the barrier of C-Br oxidative addition using Xantphos and DPPF is reduced only slightly by 6.7 and

3.0 kJ/mol, respectively. This might reflect the different polarity of the C-O and C-Br bonds. In toluene using Xantphos, the lower barrier of C-Br oxidative addition than C-O oxidative addition by 25.4 kJ/mol (82.3 vs. 107.7 kJ/mol) reveals the highly favored chemoselective C-Br activation, in full agreement with the experiment (Table 1, entry 1).

In toluene using DPPF, the barrier difference between C-Br and C-O activations becomes much smaller (80.9 vs. 89.9 kJ/mol) than that by using Xantphos, indicating the significantly reduced chemoselectivity using DPPF (Table 1, entry 10). Although the calculated chemoselective C-Br over the C-O activation using DPPF does not fully agree with the observed results (C-Br/C-O = 45/55), the reduction of the barrier difference from Xantphos to DPPF (25.4 vs. 9.0 kJ/mol) reveal the highly enhanced chemoselectivity of Xantphos over DPPF.

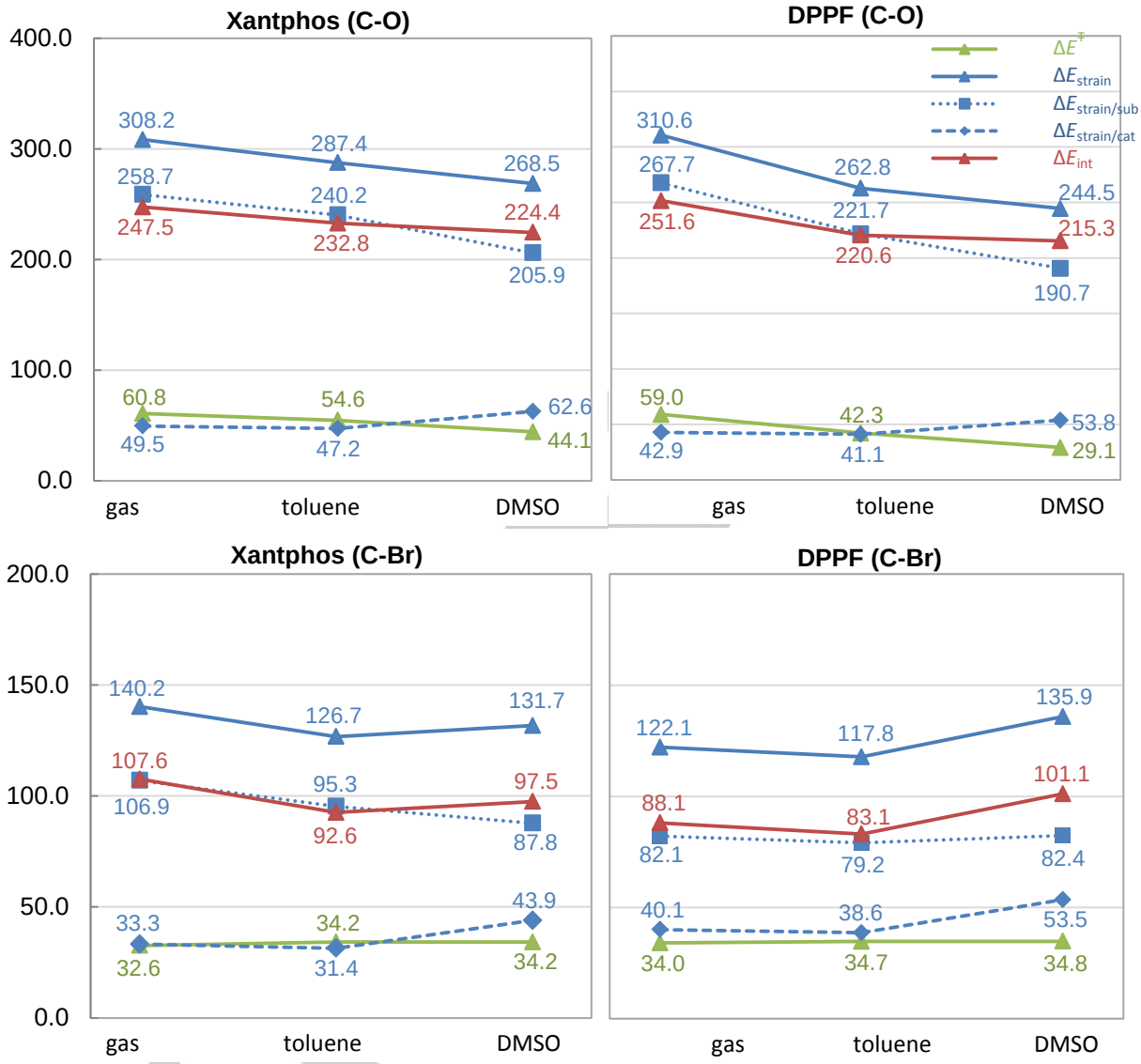


Figure 3. ASM analysis of TS involving Xantphos and DPPF as ligand in gas phase as well as in toluene and DMSO.

From toluene to DMSO, the barrier of C-O activation becomes lower using Xantphos and DPPF by 11.0 and 10.3 kJ/mol (96.7/79.6 vs. 107.7/89.9 kJ/mol), respectively. However, the barrier of C-Br activation does not change significantly using Xantphos (82.3 vs. 83.3 kJ/mol) and DPPF (80.9 vs. 83.2 kJ/mol) from toluene to DMSO. This indicates once again the larger solvation effect of the C-O bond over the C-Br bond in oxidative addition.

Using Xantphos, the C-Br chemoselectivity decreased from toluene to DMSO and this is reflected by the reduction of the barrier difference between C-Br and C-O activations from toluene to DMSO (25.4 vs. 13.4 kJ/mol, respectively). Although the computed C-Br chemoselectivity does not exactly agree with

the experiment, the predicated trend of the significantly reduced chemoselectivity in DMSO than in toluene agrees with the experiment.

Using DPPF, the C-Br chemoselectivity is switched from C-Br in toluene to C-O in DMSO (83.2 vs. 79.7 kJ/mol); and this is reflected by change from the slightly lower C-Br activation barrier over C-O activation barrier (80.9 vs. 89.9 kJ/mol) to the slightly higher C-Br activation barrier over C-O activation barrier (83.2 vs. 79.7 kJ/mol). Although the computed C-Br chemoselectivity does not exactly agree with the experiment in numbers, the computed switch in chemoselectivity from toluene to DMSO agrees with the experiment.

To understand the effect of both ligand and solvent in the chemoselective C-Br vs. C-O activation in 4-bromophenyl triflate, we dissected the electronic activation energy of the transition state (TS, $\Delta E^{\ddagger}$) into the geometrical strain energy (ΔE_{strain}) and interaction energy (ΔE_{int}) by using the proposed activation strain model (ASM, Figure 2),[16a,16c,21] where the electronic activation energy $\Delta E^{\ddagger}$ is defined as the electronic energy difference between the optimized TS and the sum of substrate and catalyst in their optimized structures; and the geometrical strain energy ΔE_{strain} is defined as the electronic energy difference between the sum of the structurally deformed substrate and catalyst individually taken from the optimized TS and the sum of reactant and catalyst in their optimized structures. Accordingly, the difference between ΔE_{strain} and $\Delta E^{\ddagger}$ is the interaction energy between substrate and catalyst in the TS. In addition, ΔE_{strain} can be divided into the strain energy of substrate ($\Delta E_{strain/sub}$) and catalyst ($\Delta E_{strain/cat}$) accordingly and $\Delta E_{strain} = \Delta E_{strain/sub} + \Delta E_{strain/cat}$. All these data are shown in Figure 3.

As shown in Figure 3, solvent influences the ΔE_{strain} of substitute and catalyst as well as the ΔE_{int} between substitute and catalyst. From gas phase into toluene and DMSO, the $\Delta E^{\ddagger}$ and ΔE_{strain} for C-O activation decrease gradually using Xantphos and DPPF. The same decreasing trend is also found for the $\Delta E_{strain/sub}$ using Xantphos and DPPF. However, the $\Delta E_{strain/cat}$ does not follow this trend; and it decreases from gas phase into toluene and then increases into DMSO using Xantphos and DPPF. In addition, the $\Delta E_{strain/sub}$ is much larger than the $\Delta E_{strain/cat}$ and also dominates the ΔE_{strain}; and consequently, the ΔE_{int} also decreases from gas phase into toluene and DMSO using Xantphos and DPPF.

For C-Br activation, the $\Delta E^{\ddagger}$ is more or less solvent insensitive; however, the ΔE_{strain} decreases gradually from gas phase into toluene and then increases in DMSO using Xanthphos and DPPF. For the substrate, the $\Delta E_{strain/sub}$ decreases from gas phase into toluene and DMSO using Xantphos, while decreases from gas phase into toluene and then increases in DMSO using Xantphos. For the catalyst, the $\Delta E_{strain/cat}$ decreases slightly from gas phase into toluene and then increases into DMSO using Xantphos and DPPF. Once again, the $\Delta E_{strain/sub}$ is much larger than the $\Delta E_{strain/cat}$ and also dominates the ΔE_{strain}. Consequently, the ΔE_{int} decreases from gas phase into toluene and increases in DMSO using Xantphos and DPPF.

Indeed, such solvent-mediated change of these energy terms can be explained by the electron transfer von Pd^0 into the C-Br or C-O bond in the transition state of oxidative addition on the basis of the electronegativity differences among C (2.544), O (3.610) and Br (2.685) atoms.[22] In addition, we computed natural charge of C, O, Br and Pd atoms in free substrate and catalyst as well as in the transition states using Xantphos and DPPF on the basis of the natural bond orbital analysis. All these data are summarized in Table 3.

Table 4. Computed C-O and C-Br distances as well as natural charges in substitute, catalyst and transition state

C-Br activation				C-O activation			
Sub/Pd	Sub/Pd	TS(Xantphos)	TS(DPPF)	C–O bond	Sub/Pd	TS(Xantphos)	TS(DPPF)
C–Br (Å)	1.915	2.278	2.192	C–O/Å	1.410	2.048	2.067
$^{\delta}$(Pd/Cat)	-0.209	-0.106	-0.173	$^{\delta}$(Pd/Cat)	-0.209	0.100	0.067
$^{\delta}$(C)	-0.074	0.001	-0.037	$^{\delta}$(C)	0.218	0.144	0.124
$^{\delta}$(Br)	0.063	-0.131	-0.078	$^{\delta}$(O)	-0.655	-0.853	-0.889
$^{\delta}$(Sub)	0.000	-0.256	-0.244	$^{\delta}$(Sub)	0.000	-0.643	-0.677

For the C-Br bond in 4-bromophenyl triflate in gas phase, the C atom is slightly negatively (-0.074) charged and the Br atom is slightly positively 0.063 charged, for the C-O bond, the C atom is positively charged (0.218) and the O atom is negatively (-0.655) charged. This charge differences indicate that the C-Br bond is much less polarized than the C-O bond, and the C-O bond should be more sensitive to polar solvent than the C-Br bond. It is noted that the palladium in catalyst with both Xantphos and DPPF has the same negative charge (-0.209).

In the transition state of C-Br oxidative addition using Xantphos, charge transfer from the Pd to the C and Br atoms take place. The Pd atom is oxidized and becomes less negatively charged (-0.106), while the C atom is oxidized (0.001) and the Br atom is reduced (-0.132). Compared with the free substrate, umpolung takes place between the C and Br atoms. Totally, the substitute fragment in TS becomes negatively charged (-0.256).

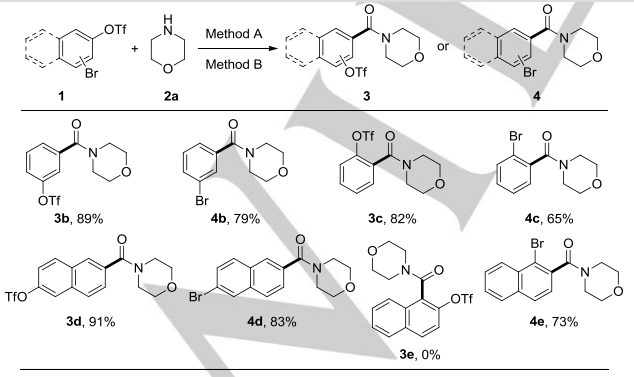
For C-O activation using Xantphos, the Pd atom changes from negatively (-0.209) to positively charged (0.100), while the

C atom becomes less positively charged (0.144) and the O atom becomes more negatively charged (-0.853). Totally, the substitute fragment in TS becomes negatively charged (-0.643). Comparison shows the C-O activation needs stronger charge transfer than C-Br activation; and C-O activation has stronger charge separation than C-Br activation (0.997 vs. 0.132). This indicates that C-Br activation prefers nonpolar solvent; and C-O activation needs polar solvent to stabilize the corresponding transition state. This explains the observed high chemoselectivity of C–Br bond in toluene and the dropped chemoselectivity between C-Br and C-O bonds in DMSO by using Xantphos.

In the transition state of C-Br oxidative addition using DPPF, the Pd atom is oxidized and becomes less negatively charged (-0.173), while the C atom become less negatively charged (-0.037) and the Br atom is reduced (-0.078). Totally, the substitute fragment in TS becomes negatively charged (-0.244). For C-O activation using DPPF, the Pd atom changes from negatively to positively charged (0.067), while the C atom becomes less positively charged (0.124) and the O atom becomes more negatively charged (-0.889). Totally, the substitute fragment in TS becomes negatively charged (-0.677). These show that C-O activation needs stronger charge transfer than C-Br activation; and C-O activation has stronger charge separation than C-Br activation (1.013 vs. 0.041). This indicates that C-Br activation prefers nonpolar solvent; and C-O activation needs polar solvent to stabilize the corresponding transition state.

With the optimized reaction condition in hand, we further explored the substrate scope (Scheme 2). It is found that bromoaryl triflates reacted well to give the corresponding C-Br functionalized (**3b**-**3d**) and C-O functionalized amide products (**4b**-**4d**) in good yields and chemoselectivity. For 1-bromo 2-naphthyl triflate, the C-O selective functionalized product was obtained in good yield (**4e**). However, the protocol of the selective C-Br cleavage was not able to convert 1-bromo 2-naphthyl triflate to the desired product (**3e**). That might be due to that the C-Br site is sterically shielded by *ortho* OTf and phenyl ring.

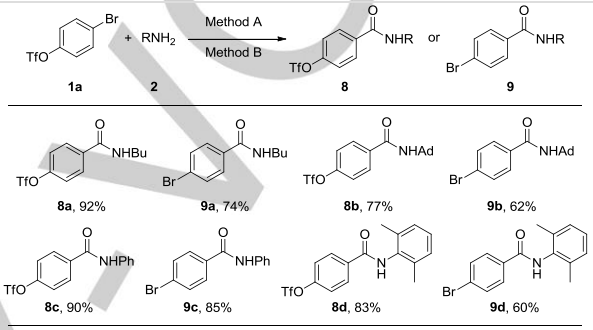
Scheme 2. Chemoselective carbonylation of bromoaryl triflates.



Reaction condition: for the selective carbonylation of aryl bromide (**Method A**); 0.5 mmol of **1**, 0.5 mmol of **2a**, 2 mol % of $Pd(OAc)_2$, 2 mol% Xantphos, 0.75 mmol of *N*,*N*-diisopropylethylamine (1.5 equiv.), 2 mL toluene, CO (5 bar), 90 °C, 24 h; and for the selective carbonylation of aryl triflate (**Method B**); 0.5 mmol of **1**, 0.5 mmol of **2a**, 2 mol % of $Pd(OAc)_2$, 2 mol% DPPF, 0.75 mmol of *N*,*N*-diisopropylethylamine (1.5 equiv.), 2 mL DMSO, CO (5 bar), 90 °C, 24 h.

In addition to 2a, a number of amines were examined with 4-bromophenyl triflate (Scheme 3). Both linear and bulky aliphatic amine gave the corresponding C-Br (8a, 8b) and C-O (9a, 9b) functionalized amides in good to moderate yield. Both protocols also worked well with aniline (8c, 9c) and ortho-disubstituted sterically hindered aniline (8d, 9d).

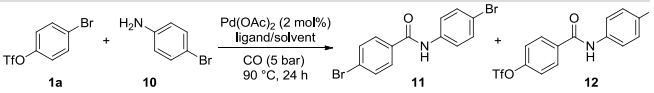
Scheme 3. Chemoselective carbonylation of 4-bromophenyl triflate with amines.



Reaction condition: For carbonylation of aryl bromide (**Method A**); 0.5 mmol of **1a**, 0.5 mmol of **2**, 2 mol % of $Pd(OAc)_2$, 2 mol% Xantphos, 0.75 mmol of *N*,*N*-diisopropylethylamine (1.5 equiv.), 2 mL toluene, CO (5 bar), 90 °C, 24 h; for carbonylation of aryl triflate (**Method B**); 0.5 mmol of **1a**, 0.5 mmol of **2**, 2 mol % of $Pd(OAc)_2$, 2 mol% DPPF, 0.75 mmol of *N*,*N*-diisopropylethylamine (1.5 equiv.), 2 mL DMSO, CO (5 bar), 90 °C, 24 h.

Furthermore, these protocols were examined in the chemoselective carbonylation of 4-bromoaniline (**10**) with **1a** (Table 5). For Xantphos/toluene, $BuPAd_2$/toluene and $^tBu_3P{\cdot}HBF_4$/toluene, **10** was fully converted and but the product from C-O coupling (**11**) was not formed, and **1a** was still observed on GC and the desired product **12** was only isolated in low yield (Table 5, entries 1-3). In contrast, DPPF/DMSO gave the only exclusive C-O coupling product **11** in moderate yield (Table 5, entry 4) and no other products could be detected.

Table 5. Carbonylation of 4-bromophenyl triflate with 4-bromoaniline.



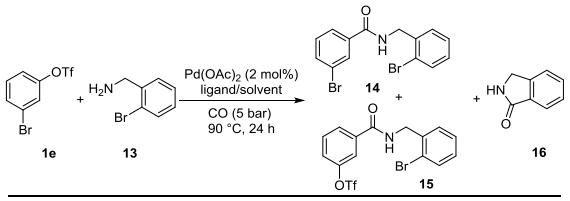
Entry	Ligand/Solvent	Product (Yield)
1	Xantphos/toluene	**12** (47%)
2	$BuPAd_2$/toluene	**12** (44%)
3	$^tBu_3P{\cdot}HBF_4$/toluene	**12** (38%)
4	DPPF/DMSO	**11** (67%)

Reaction conditions: 0.5 mmol of **1a**, 0.5 mmol of **10**, 2 mol % of $Pd(OAc)_2$, Pd/P = 1/2 (for bidentate phosphine ligand) or 1/3 (for mono phosphine

ligand), 0.75 mmol of *N*,*N*-diisopropylethylamine (1.5 equiv.), 2 mL solvent, CO (5 bar), 90 °C, 24 h.

In addition, we tested DPPF with different solvents in the carbonylation of 3-bromophenyl triflate (**1e**) with 2-bromobenzylamine (**13**) (Table 6). Among the aprotic polar solvents, DMSO gave the C-O selective coupling product (**14**) in higher yield than DMF and MeCN (Table 6, entries 1-3), and the selective C-Br coupling products (**15** and **16**) were not formed in all cases. In toluene, however, the products from C-O coupling as well as intermolecular and intramolecular C-Br couplings were formed (Table 6, entry 4).

Table 6. Carbonylation of 3-bromophenyl triflate with 2-bromobenzylamine.[a]

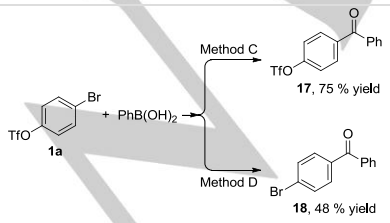


Entry	Ligand/Solvent	Product (Yield)
1	DPPF/DMSO	**14** (60%)
2	DPPF/DMF	**14** (47%)
3	DPPF/MeCN	**14** (49%)
4	DPPF/Toluene	Mixture of **14**, **15** and **16**[b]

(a) Unless specified otherwise: 0.5 mmol of **1a**, 0.5 mmol of **10**, 2 mol % of $Pd(OAc)_2$, 2 mol % of DPPF, 0.75 mmol of *N*,*N*-diisopropylethylamine (1.5 equiv.), 2 mL solvent, CO (5 bar), 90 °C, 24 h. (b) Determined by GC-FID and GC-MS.

Besides aminocarbonylation, we extended these protocols to the carbonylative Suzuki coupling of 4-bromophenyl triflate (**1a**) (Scheme 4). $BuPAd_2$ in toluene in the presence of K_2CO_3 gave the desired C-Br selective carbonylative Suzuki coupling product in 75% yield. DPPF in acetonitrile with additives (CsF and TBAB) also gave the desired C-O selectivity and 4-bromo-biphenyl was not generated, and the conversions of 4-bromophenyl triflate and phenylboronic acid were slow; and, therefore, the yield of the desired product was low.

Scheme 4. Chemoselective carbonylative Suzuki coupling of 4-bromophenyl triflate with phenylboronic acid.[a]



(a) **1a** (0.5 mmol), phenylboronic acid (0.5 mmol); **Method C**: $Pd(OAc)_2$ (2 mol%), $BuPAd_2$ (6 mol%), K_2CO_3 (2 equiv.) in toluene, 90 °C, 24 h; **Method D**: $Pd(OAc)_2$ (2 mol%), DPPF (2 mol%), CsF (2 equiv.), TBAB (10 mol%) in MeCN, 90 °C, 24 h. abbreviations: TBAB, tetra-*n*-butylammonium bromide.

Conclusions

Palladium-catalyzed chemoselective carbonylation of bromoaryl triflates is reported. Using 4-bromophenyl triflate as substrate, the selective carbonylation of the C-Br and C-OTf bonds can be achieved by using Xantphos in toluene and DPPF in DMSO, respectively, however, Xantphos in DMSO or DPPF in toluene is not chemoselective. In addition, monodentate BuPAd2 and tBu_3P prefer only the selective C-Br activation and are solvent insensitive. The observed chemoselectivity was controlled by the experiment by using 4-bromotoluene, 1-bromo-4-chlorobenzene and different bromoaryl triflates with different amines. The respective chemoselective mechanisms were rationalized by comparative DFT calculations; and it is found the chemoselectivity is originated from the different polarities of the C-Br and C-OTf bond in both ground states and transition states; and the transition state of the C-Br oxidative addition has less charge separation and is more preferred in nonpolar toluene, while the transition state of the C-O oxidative addition has stronger charge separation and can be stabilized by polar DMSO to a large extend.

Experimental Section

General procedure for the synthesis of aryl triflates
To a cooled (-70 °C) solution of bromo-substituted phenol or naphthol (9.05 mmol) and Et_3N (2.52 mL, 18.9 mmol) in DCM (20 mL) was added dropwise Tf_2O (1.74 mL, 10.3 mmol). The reaction was allowed to slowly warm to room temperature and stirred for 12 hours. Thereafter, water (or saturated aqueous $NaHCO_3$ in the case of basic products) was added to the mixture, followed by extraction with Et_2O. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated under reduced pressure. The obtained crude material was purified by silica gel column chromatography.

General procedure for the selective C(sp^2)-Br aminocarbonylation
A 4 mL vial was charged with $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 2 mol%), Xantphos (6.0 mg, 0.01 mmol, 2 mol%; when Xantphos is replaced by $BuPAd_2$, 10.8 mg, 0.03 mmol; when Xantphos is replaced by $tBu_3P{\cdot}HBF4$ 8.7 mg, 0.03 mmol), amine (for the case of solid amine, 0.5 mmol) and a magnetic stirring bar. Then under argon, toluene (2 mL), bromo-substituted aryl triflate (0.5 mmol), amine (when amine is liquid, 0.5 mmol) and *N*,*N*-diisopropylethylamine (131 µL, 1.5 mmol, 3.0 equiv.) were injected by syringe. The vial (or several vials) was placed in an alloy plate, which was transferred into a 300 mL autoclave of the 4560 series from Parr Instruments® under Ar atmosphere. After flushing the autoclave three times with CO, a pressure of 5 bar CO was adjusted at ambient temperature. The reaction was performed at 90 °C
The reaction mixture was diluted with acetone (ca. 2 mL) and passed through a pad of Celite® once under reduced pressure. The filter cake was washed with additional acetone (ca. 5 mL). The filtrate was then collected and filtered through a pad of Celite® once more. After evaporation of the solvent the residue was adsorbed on silica gel and the

crude product was purified by column chromatography using n-pentane/AcOEt as eluent.

General procedure for the selective C(sp^2)-OTf aminocarbonylation
A 4 mL vial was charged with $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 2 mol%), DPPF (5.7 mg, 0.01 mmol, 2 mol%), amine (for the case of solid amine, 0.5 mmol) and a magnetic stirring bar. Then under argon, DMSO (2 mL), bromo-substituted aryl triflate (0.5 mmol), amine (when amine is liquid, 0.5 mmol) and *N*,*N*-diisopropylethylamine (131 µL, 1.5 mmol, 3.0 equiv.) were injected by syringe. The vial (or several vials) was placed in an alloy plate, which was transferred into a 300 mL autoclave of the 4560 series from Parr Instruments® under Ar atmosphere. After flushing the autoclave three times with CO, a pressure of 5 bar CO was adjusted at ambient temperature. The reaction was performed at 90 °C
The reaction mixture was diluted with acetone (ca. 2 mL) and passed through a pad of Celite® once under reduced pressure. The filter cake was washed with additional acetone (ca. 5 mL). The filtrate was then collected and filtered through a pad of Celite® once more. After evaporation of the solvent the residue was adsorbed on silica gel and the crude product was purified by column chromatography using n-pentane/AcOEt as eluent.

General procedure for the selective C(sp^2)-Br carbonylative Suzuki coupling
A 4 mL vial was charged with $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 2 mol%), $BuPAd_2$ (10.8 mg, 0.03 mmol, 6 mol%), phenylboronic acid (61 mg, 0.5 mmol), K_2CO_3 (207 mg, 1.5 mmol) and a magnetic stirring bar. Then under argon, toluene (2 mL), 4-bromophenyl triflate (96 µL, 0.5 mmol) were injected by syringe. The vial was placed in an alloy plate, which was transferred into a 300 mL autoclave of the 4560 series from Parr Instruments® under Ar atmosphere. After flushing the autoclave three times with CO, a pressure of 5 bar CO was adjusted at ambient temperature. The reaction was performed at 90 °C
The reaction mixture was diluted with acetone (ca. 2 mL) and passed through a pad of Celite® once under reduced pressure. The filter cake was washed with additional acetone (ca. 5 mL). The filtrate was then collected and filtered through a pad of Celite® once more. After evaporation of the solvent the residue was adsorbed on silica gel and the crude product was purified by column chromatography using n-pentane/AcOEt as eluent.

General procedure for the selective C(sp^2)-OTf carbonylative Suzuki coupling
A 4 mL vial was charged with $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 2 mol%), DPPF (5.7 mg, 0.01 mmol, 2 mol%), phenylboronic acid (61 mg, 0.5 mmol), CsF (228 mg, 1.5 mmol), TBAB (16 mg, 10 mol%) and a magnetic stirring bar. Then under argon, MeCN (2 mL), 4-bromophenyl triflate (96 µL, 0.5 mmol) were injected by syringe. The vial (or several vials) was placed in an alloy plate, which was transferred into a 300 mL autoclave of the 4560 series from Parr Instruments® under Ar atmosphere. After flushing the autoclave three times with CO, a pressure of 5 bar CO was adjusted at ambient temperature. The reaction was performed at 90 °C
The reaction mixture was diluted with acetone (ca. 2 mL) and passed through a pad of Celite® once under reduced pressure. The filter cake was washed with additional acetone (ca. 5 mL). The filtrate was then collected and filtered through a pad of Celite® once more. After evaporation of the solvent the residue was adsorbed on silica gel and the crude product was purified by column chromatography using n-pentane/AcOEt as eluent.

4-(Morpholine-4-carbonyl)phenyl trifluoromethanesulfonate (**3a**)
White solid, ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.54-7.48 (2H, m), 7.36-7.30 (2H, m), 3.88-3.27 (8H, m).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.48, 150.17, 135.65, 129.37, 121.80, 118.72 (q, *J* = 318.8 Hz), 66.81, 48.38, 42.81.
^{19}F NMR (282 MHz, $CDCl_3$): δ = -72.4
GC-MS (EI, 70 eV): m/z (%) = 339 (11), 338 (24), 253 (96), 206 (27), 178 (17), 161 (14), 120 (25), 92 (50), 86 (23), 69 (100), 64 (27), 63 (22), 56 (44).
HRMS (ESI-TOF): calcd. for $C_{12}H_{13}F_3NO_5S$ $[M + H]^+$ 340.0461, found 340.04631; calcd. for $C_{12}H_{12}F_3NO_5SNa$ $[M + H]^+$ 362.02805, found 362.02787.

(4-Bromophenyl)(morpholino)methanone (**4a**)
White solid, 1H NMR (300 MHz, CDCl3): δ = 7.63-7.58 (2H, m), 7.36-7.31 (2H, m), 3.76-3.50 (8H, m),
13C NMR (75 MHz, CDCl3): δ = 169.40, 134.10, 131.85, 128.87, 124.29, 66.85, 48.14, 42.71.
GC-MS (EI, 70 eV): m/z (%) = 271 (12), 270 (30), 269 (13), 268 (30), 185 (97), 183 (100), 157 (44), 155 (48), 104 (13), 86 (24), 76 (49), 75 (41), 74 (22), 56 (54), 50 (26), 42 (24).
HRMS (ESI-TOF): calcd. for $C_{11}H_{13}{}^{79}BrNO_2$ $[M + H]^+$ 270.01242, found 270.01239; calcd. for $C_{11}H_{13}{}^{81}BrNO_2$ $[M + H]^+$ 272.01046, found 272.01027; calcd. for $C_{11}H_{12}{}^{79}BrNO_2Na$ $[M + H]^+$ 291.99436, found 291.99411, calcd. for $C_{11}H_{12}{}^{81}BrNO_2Na$ $[M + H]^+$ 293.9924, found 293.9921.

3-(Morpholine-4-carbonyl)phenyl trifluoromethanesulfonate (**3b**)
Viscous oil, ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.52 (1H, dd, *J* = 7.6, 1.1 Hz) 7.46 (1H, dt, *J* = 7.6, 1.3 Hz), 7.37-7.32 (2H, m), 3.87-3.35 (8H, m).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.92, 149.29, 137.67, 130.80, 127.23, 122.83, 120.84, 120.49, 118.72 (q, *J* = 318.8 Hz), 66.77, 48.16, 42.79.
^{19}F NMR (282 MHz, $CDCl_3$): δ = -72.3
GC-MS (EI, 70 eV): m/z (%) = 339 (8), 324 (15), 253 (56), 206 (37), 178 (20), 178 (20), 120 (43), 92 (49), 86 (28), 69 (100), 64 (32),63 (30), 56 (55).
HRMS (EI): calcd. for $C_{12}H_{12}O_5NF_3S$ $[M]^+$ 339.03828, found 339.03811.

(3-Bromophenyl)(morpholino)methanone (**4b**)[3]
Viscous oil, ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.52-7.49 (1H, m), 7.48 (1H, d, *J* = 1.8 Hz), 7.26-7.24 (1H, m), 7.23-7.19 (1 H, m), 3.77-3.31 (8H, m).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.69, 137.27, 132.98, 130.22, 130.17, 125.62, 122.76, 66.85, 48.38, 42.70.
GC-MS (EI, 70 eV): m/z (%) = 270 (45), 268 (44), 256 (10), 185 (100), 183 (96), 157 (56), 155 (61), 104 (11), 86 (40), 76 (68), 56 (71), 50 (35).
HRMS (EI): calcd. for $C_{11}H_{13}{}^{79}BrNO_2$ $[M + H]^+$ 270.01242, found 270.01264, calcd. for $C_{11}H_{13}{}^{81}BrNO_2$ 272.01046, found 272.01073; calcd. for $C_{11}H_{12}{}^{79}BrNO_2Na$ $[M + Na]^+$ 291.99436, found 291.99475; calcd. for $C_{11}H_{12}{}^{81}BrNO_2$ $[M + Na]^+$ 293.9924, found 293.99274.

2-(Morpholine-4-carbonyl)phenyl trifluoromethanesulfonate (**3c**)
Viscous oil, ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.52 (1H, dd, *J* = 7.6, 1.0 Hz) 7.46 (1H, dt, *J* = 7.7, 1.4 Hz), 7.37-7.32 (2H, m), 3.86-3.34 (8H, m).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.92, 149.29, 137.67, 130.80, 127.23, 122.83, 120.49, 118.72 (q, *J* = 318.8 Hz), 66.77, 48.01, 42.60.
^{19}F NMR (282 MHz, $CDCl_3$): δ = -72.3
GC-MS (EI, 70 eV): m/z (%) = 339 (7), 324 (12), 253 (51), 206 (32), 178 (16), 178 (16), 176 (11), 120 (36), 92 (55), 86 (28), 69 (100), 64 (33), 63 (32), 56 (53).
HRMS (EI): calcd. for $C_{12}H_{12}O_5NF_3S$ $[M]^+$ 339.03828, found 339.03792.

(2-Bromophenyl)(morpholino)methanone[3] (**4c**)
Viscous oil, ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.52-7.47 (2H, m), 7.29-7.19 (2H, m), 3.78-3.26 (8H, m).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.68, 137.27, 132.98, 130.22, 130.16, 125.62, 122.75, 66.84, 48.31, 42.71.

GC-MS (EI, 70 eV): m/z (%) = 270 (47), 268 (44), 256 (13), 254 (12), 185 (100), 183 (97), 157 (63), 155 (64), 104 (17), 86 (47), 76 (73), 75 (59), 56 (90), 50 (42), 42 (30).
HRMS (ESI-TOF): calcd. for $C_{11}H_{13}{}^{79}BrNO_2$ $[M + H]^+$ 270.01242, found 270.01266; calcd. for $C_{11}H_{13}{}^{81}BrNO_2$ $[M + H]^+$ 272.01046, found 272.01078; calcd. for $C_{11}H_{12}{}^{79}BrNO_2Na$ $[M + Na]^+$ 291.99436, found 291.99469; calcd. for $C_{11}H_{12}{}^{81}BrNO_2Na$ $[M + Na]^+$ 293.9924, found 293.99276.

6-(Morpholine-4-carbonyl)naphthalen-2-yl trifluoromethanesulfonate (**3d**)
White solid, ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.03 (1H, d, *J* = 1.8 Hz), 7.90-7.87 (1H, m), 7.77 (2H, ddd, *J* = 16.4, 8.6, 0.7 Hz), 7.61 (1 H, dd, *J* = 8.7, 2.0 Hz), 7.51 (1 H, dd, *J* = 8.4, 1.7 Hz), 3.96- 3.38 (8H, m)
^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.05, 134.73, 133.08, 131.16, 130.33, 130.02, 129.95, 127.57, 127.06, 125.35, 123.20 (q, *J* = 267 Hz), 66.94, 48.23, 42.87.
^{19}F NMR (282 MHz, $CDCl_3$): δ = -72.31
GC-MS (EI, 70 eV): m/z (%) = 389 (42), 388 (30), 361 (5), 303 (100), 256 (9), 211 (8), 170 (59), 142 (73), 114 (64), 86 (21), 69 (67), 56 (27).
HRMS (ESI-TOF): calcd. for $C_{16}H_{15}F_3NO_5S$ $[M + Na]^+$ 390.06175, found 390.06234; calcd. for $C_{16}H_{14}F_3NO_5SNa$ $[M + Na]^+$ 412.0437, found 412.04374.

(6-Bromonaphthalen-2-yl)(morpholino)methanone (**4d**)
White solid, ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.03 (1H, d, *J* = 1.9 Hz), 7.90 – 7.87 (1H, m), 7.80 (1H, d, *J* = 8.4 Hz), 7.74 (1H, d, *J* = 8.7 Hz), 7.61 (1H, dd, *J* = 8.8, 2.0), 7.51 (1H, dd, *J* = 8.4, 1.6 Hz), 3.97-3.38 (8 H, m).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.05, 134.72, 133.08, 131.16, 130.33, 130.02, 129.94, 127.57, 127.06, 125.36, 124.99, 121.42, 66.94, 47.96, 42.35.
GC-MS (EI, 70 eV): m/z (%) = 321 (17), 319 (18), 235 (62), 233 (64), 207 (24), 205(24),154 (8), 126 (100), 56 (24).
HRMS (ESI-TOF): calcd. for $C_{15}H_{15}{}^{79}BrNO_2$ $[M + H]^+$ 320.02807, found 320.02817; calcd. for $C_{15}H_{15}{}^{81}BrNO_2$ $[M + H]^+$ 322.02616, found 322.0264; calcd. for $C_{15}H_{14}{}^{79}BrNO_2Na$ $[M + Na]^+$ 342.01001, found 342.01019; calcd. for $C_{15}H_{14}{}^{81}BrNO_2Na$ $[M + Na]^+$ 344.00811, found 344.00823.

(1-Bromonaphthalen-2-yl)(morpholino)methanone (**4e**)
Viscous slurry, ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.29 (1 H, d, *J* = 8.4 Hz), 7.89- 7.82 (2H, m), 7.61 (2H, dddd, *J* = 21.6, 8.0, 6.9, 1.3 Hz), 7.31 (1H, d, *J* = 8.3 Hz), 3.96-3.52 (6H, m), 3.35-3.15 (2H, m).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.25, 135.37, 134.11, 131.83, 128.82, 128.34, 128.29, 127.53, 127.30, 123.86, 119.53, 66.80, 66.69, 47.12, 42.03, 41.03.
GC-MS (EI, 70 eV): m/z (%) = 321 (13), 319 (16), 235 (70), 233 (73), 207 (21), 205 (20), 155 (5), 126 (100), 86 (14), 56 (29).
HRMS (ESI-TOF): calcd. for $C_{15}H_{15}{}^{79}BrNO_2$ $[M + H]^+$ 320.02807, found 320.0286; calcd. for $C_{15}H_{15}{}^{81}BrNO_2$ $[M + H]^+$ 322.02616, found 322.02645; calcd. for $C_{15}H_{14}{}^{79}BrNO_2Na$ $[M + Na]^+$ 342.01001, found 342.01033; calcd. for $C_{15}H_{14}{}^{81}BrNO_2Na$ $[M + Na]^+$ 344.00811, found 344.00863.

4-(Butylcarbamoyl)phenyl trifluoromethanesulfonate (**8a**)
White solid, ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.88-7.81 (2H, m), 7.37-7.28 (2H, m), 6.25 (1H, brs), 3.45 (2H, td, *J* = 7.2, 5.7 Hz), 1.66-1.53 (2H, m), 1.48-1.32 (2H, m), 0.95 (3H, t, *J* = 7.3 Hz).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.83, 151.27, 135.16, 129.14, 121.58, 118.71 (q, *J* = 318.8 Hz), 40.06, 31.65, 20.16, 13.78.
^{19}F NMR (282 MHz, $CDCl_3$): δ = -72.3
GC-MS (EI, 70 eV): m/z (%) = 325 (4), 310 (3), 296 (2), 283 (19), 282 (25), 253 (100), 192 (8), 161 (9), 120 (25), 92 (39), 69 (68), 41 (17).
HRMS (ESI-TOF): calcd. for $C_{12}H_{15}F_3NO_4S$ $[M + H]^+$ 326.06684, found 326.06725; calcd. for $C_{12}H_{14}F_3NO_4SNa$ $[M + Na]^+$ 348.04878, found 348.04929.

4-Bromo-N-butylbenzamide (**9a**)
White solid, ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.65-7.60 (2H, m), 7.58-7.52 (2H, m), 6.19 (1H, brs), 3.43 (2H, td, *J* = 7.1, 5.6 Hz), 1.65-1.53 (2H, m), 1.47-1.33 (2 H, m), 0.95 (3H, t, *J* = 7.3 Hz).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.56, 133.67, 131.77, 131.75, 128.50, 125.96, 39.94, 31.71, 20.19, 13.81.
GC-MS (EI, 70 eV): m/z (%) = 257 (8), 255 (9), 228 (6), 226 (7), 215 (23), 214 (23), 213 (28), 212 (23), 185 (100), 183 (97), 157 (27), 155 (34), 105 (14), 104 (15), 75 (31), 41 (32).
HRMS (ESI-TOF): calcd. for $C_{11}H_{15}{}^{79}BrNO$ $[M + H]^+$ 256.03315, found 256.0337; calcd. for $C_{11}H_{15}{}^{81}BrNO$ $[M + H]^+$ 258.03118, found 258.03139; calcd. for $C_{11}H_{14}{}^{79}BrNONa$ $[M + Na]^+$ 278.0151, found 278.01536; calcd. for $C_{11}H_{14}{}^{81}BrNONa$ $[M + Na]^+$ 280.01313, found 280.01338.

4-(((3s,5s,7s)-Adamantan-1-yl)carbamoyl)phenyl trifluoromethanesulfonate (**8b**)
White solid, ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.85-7.76 (2H, m), 7.36-7.28 (2H, m), 5.76 (1H, brs), 2.11 (9H, s), 1.72 (6H, s).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.88, 151.10, 136.38, 129.01, 121.49, 118.72 (q, *J* = 318.8 Hz), 52.75, 41.62, 36.32, 29.48
^{19}F NMR (282 MHz, $CDCl_3$): δ = -72.3
GC-MS (EI, 70 eV): m/z (%) = 403 (45), 346 (100), 310 (7), 270 (15), 253 (43), 213 (18), 189 (9), 161 (11), 120 (22), 92 (45), 79 (18), 69 (80)

N-((3s,5s,7s)-Adamantan-1-yl)-4-bromobenzamide (**9b**)
White solid, ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.61-7.50 (4H, m), 5.74 (1H, brs), 2.11 (9H, s), 1.72 (6 H, s).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.59, 134.86, 131.63, 128.36, 125.59, 52.49, 41.63, 36.34, 29.48.
GC-MS (EI, 70 eV): m/z (%) = 335 (39), 334 (24), 333 (40), 332 (16), 278 (71), 276 (69), 185 (100), 183 (99), 157 (42), 155 (44), 91 (26), 76 (23), 41 (26).

4-(Phenylcarbamoyl)phenyl trifluoromethanesulfonate (**8c**)
White solid, ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.98-7.92 (2H, m), 7.87 (1H, brs), 7.62 (2H, dd, *J* = 8.7, 1.2 Hz), 7.42-7.35 (4H, m), 7.22-7.15 (1H, m).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.08, 151.57, 137.43, 135.28, 129.36, 129.24, 125.13, 124.98, 121.88, 120.40, 118.73 (q, *J* = 318.8 Hz).
^{19}F NMR (282 MHz, $CDCl_3$): δ = -72.3
GC-MS (EI, 70 eV): m/z (%) = 345 (42), 253 (100), 184 (9), 161 (14), 120 (20), 92 (59), 69 (67).
HRMS (EI): calcd. for $C_{14}H_{10}O_4NF_3S$ $[M]^+$ 345.02771, found 345.02753.

4-Bromo-*N*-phenylbenzamide[4] (**9c**)
White solid, ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.78-7.72 (3H, m), 7.67-7.60 (4H, m), 7.43-7.34 (2H, m), 7.21-7.14 (1H, m).
^{13}C NMR (75 MHz, d_6-DMSO): δ = 164.48, 138.90, 133.96, 131.35, 129.75, 128.59, 125.27, 123.78, 120.35.
GC-MS (EI, 70 eV): m/z (%) = 277 (28), 275 (26), 185 (99), 183 (100), 157 (43), 155 (49), 104 (9), 92 (40), 76 (42), 65 (65), 50 (25), 39 (24).

4-((2,6-Dimethylphenyl)carbamoyl)phenyl trifluoromethanesulfonate (**8d**)
White solid, ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.02-7.88 (2H, m), 7.68 (1H, brs), 7.39-7.28 (2H, m), 7.21-7.07 (3H, m), 2.23 (6H, s).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.31, 151.58, 135.55, 134.56, 133.51, 129.56, 128.40, 127.78, 121.76, 116.75 (q, *J* = 318.8 Hz), 18.44.
^{19}F NMR (282 MHz, $CDCl_3$): δ = -72.3
GC-MS (EI, 70 eV): m/z (%) = 373 (40), 253 (100), 161 (15), 120 (85), 92 (39), 77 (20), 69 (69), 64 (20).
HRMS (ESI-TOF): calcd. for $C_{16}H_{15}F_3NO_4S$ $[M + H]^+$ 374.06684, found 374.06737; calcd. for $C_{16}H_{14}F_3NO_4SNa$ $[M + Na]^+$ 396.04878, found 396.04919

4-Bromo-*N*-(2,6-dimethylphenyl)benzamide (**9d**)

White solid, ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.79-7.72 (2H, m), 7.63-7.56 (2H, m), 7.51 (1H, brs), 7.19-7.08 (3H, m), 2.24 (6H, s).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.04, 135.54, 133.65, 133.23, 131.99, 128.87, 128.35, 127.61, 126.52, 18.48.
GC-MS (EI, 70 eV): m/z (%) = 305 (25), 303 (25), 185 (92), 183 (100), 157 (52), 155 (45), 120 (73), 104 (17), 91 (39), 76 (33).
HRMS (ESI-TOF): calcd. for $C_{15}H_{15}{}^{79}BrNO$ $[M + H]^+$ 304.03315, found 304.03364; calcd. for $C_{15}H_{15}{}^{81}BrNO$ $[M + H]^+$ 306.03123, found 306.03166; calcd. for $C_{15}H_{14}{}^{81}BrNONa$ $[M + Na]^+$ 326.0151, found 326.01562; calcd. for $C_{15}H_{14}{}^{81}BrNONa$ $[M + Na]^+$ 328.01318, found 328.01378.

4-((4-Bromophenyl)carbamoyl)phenyl trifluoromethanesulfonate (**12**)
White solid, ^{1}H NMR (300 MHz, d_6-DMSO): δ = 10.54 (1H, brs), 8.13-8.07 (2H, m), 7.78-7.66 (4H, m), 7.58-7.52 (2H, m).
^{13}C NMR (75 MHz, d_6-DMSO): δ = 164.18, 150.95, 138.23, 135.32, 131.46, 130.34, 122.16, 121.62, 118.2 (q, *J* = 318.8 Hz), 115.61.
^{19}F NMR (282 MHz, d_6-DMSO): δ = -72.3.
GC-MS (EI, 70 eV): m/z (%) = 425 (21), 423 (19), 253 (100), 211 (5), 161 (14), 120 (17), 92 (40), 69 (66).
HRMS (EI): calcd. for $C_{14}H_9O_4N^{79}BrF_3S$ $[M]^+$ 422.93823, found 422.93867; calcd. for $C_{14}H_9O_4N^{79}BrF_3S$ $[M]^+$ 424.93618, found 424.93691.

4-Bromo-*N*-(4-bromophenyl)benzamide (**11**)
Pale yellow solid, ^{1}H NMR (300 MHz, d_6-DMSO): δ = 10.43 (1H, brs), 7.92 – 7.87 (2H, m), 7.79-7.71 (4H, m), 7.57-7.51 (2H, m).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.59, 138.31, 133.67, 131.42, 131.40, 129.78, 125.48, 122.21, 115.48.
GC-MS (EI, 70 eV): m/z (%) = 357 (11), 355 (24), 353 (12), 185 (94), 183 (100), 172 (15), 170 (14), 157 (49), 155 (52), 145 (11), 143 (11), 104 (11), 91 (29), 76 (40), 63 (22), 50 (24).
HR-MS (ESI-TOF): calcd. for $[M + H]^+$ $C_{13}H_{10}{}^{79}Br_2NO$ 353.91237, found 353.91310; calcd. for $[M + H]^+$ $C_{13}H_{10}{}^{79}Br^{81}BrNO$ 355.91037, found 355.91134; calcd. for $[M + H]^+$ $C_{13}H_{10}{}^{81}Br_2NO$ 357.90847, found 357.90847, found 357.90923; calcd. for $[M + Na]^+$ $C_{13}H_9{}^{79}Br_2NONa$ 375.89431, found 375.89431; calcd. for $[M + Na]^+$ $C_{13}H_9{}^{79}Br^{81}BrNONa$ 377.89231, found377.89273; calcd. for $[M + Na]^+$ $C_{13}H_9{}^{81}Br_2NONa$ 379.89041, found 379.89106.

3-Bromo-*N*-(2-bromobenzyl)benzamide (**14**)
White solid, ^{1}H NMR (300 MHz, d_6-DMSO): δ = 9.18 (1H, t, *J* = 5.7 Hz), 8.11 (1H, t, *J* = 1.8 Hz), 7.92 (1H, dt, *J* = 7.8, 1.3 Hz), 7.77 (1H, ddd, *J* = 8.0, 2.0, 1.0 Hz), 7.63 (1H, dd, *J* = 7.9, 1.1 Hz), 7.47 (1H, t, *J* = 7.9 Hz), 7.41-7.32 (2H, m), 7.26-7.19 (1H, m), 4.50 (2H, d, *J* = 5.7 Hz).
^{13}C NMR (75 MHz, d_6-DMSO): δ = 164.87, 137.48, 136.15, 134.11, 132.34, 130.63, 129.95, 128.91, 128.71, 127.74, 126.47, 122.27, 121.68, 43.19, 40.31, 40.03, 39.75, 39.47, 39.20, 38.92, 38.64.
GC-MS (EI, 70 eV): m/z (%) = 369 (1), 367 (0.5), 291 (15), 290 (100), 289 (20), 288 (98), 209 (5), 185 (53), 184 (28), 183 (49), 157 (57), 155 (58), 107 (81), 89 (28), 76 (71), 50 (42).
HRMS (ESI-TOF): calcd. for $C_{14}H_{12}{}^{79}Br_2NO$ $[M + H]^+$ 367.92802, found 367.92838; calcd. for $C_{14}H_{12}{}^{79}Br\ {}^{81}BrNO$ $[M + H]^+$ 369.92603, found 369.92649; calcd. for $C_{14}H_{12}{}^{79}Br\ {}^{81}BrNO$ $[M + H]^+$ $C_{14}H_{12}{}^{81}Br_2NO$ 971.92414, found 371.92454.

Morpholino(*p*-tolyl)methanone[5] (**5**)
Viscous colorless oil, ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.32-7.27 (2H, m), 7.23-7.17 (2H, m), 3.67 (8H, brs), 2.36 (3H, s).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.63, 140.08, 132.29, 129.14, 127.22, 66.91, 21.38.
GC-MS (EI, 70 eV): m/z (%) = 205 (9), 204 (19), 119 (100), 91 (44), 65 (21), 56 (12).

Morpholino(phenyl)methanone[6] (**6**)
Viscous colorless oil, ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37-7.27 (m, 5H), 3.36-3.86 (m, 8H).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.34, 135.28, 129.83, 128.52, 127.05, 127.00, 77.64, 77.22, 76.79, 66.83, 48.09, 42.48.
GC-MS (EI, 70 eV): m/z (%) = 191 (11), 105 (100), 86 (11), 77 (71), 56 (18), 51 (28).

(4-Chlorophenyl)(morpholino)methanone[3] (**7**)
White solid, ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.42-7.30 (4H, m), 3.68 (8H, s).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.33, 136.00, 133.61, 128.85, 128.66, 66.82, 48.26, 42.60.
GC-MS (EI, 70 eV): m/z (%) = 226 (10), 225 (10), 224 (27), 210 (6), 141 (32), 139 (100), 113 (15), 111 (49), 86 (15), 75 (33), 56 (29).

4-Benzoylphenyl trifluoromethanesulfonate (**17**)
Viscous colorless oil, ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.94-7.88 (2H, m), 7.82-7.76 (2H, m), 7.67-7.60 (1H, m), 7.55-7.48 (2 H, m), 7.44-7.37 (2 H, m).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 194.77, 151.96, 137.62, 136.74, 133.07, 132.18, 130.03, 128.58, 123.0 (q, *J* = 318.8 Hz), 121.42
^{19}F NMR (282 MHz, $CDCl_3$): δ = -72.3
GC-MS (EI, 70 eV): m/z (%) = 330 (44), 253 (37), 197 (6), 169 (29), 141 (42), 115 (36), 105 (89), 92 (17), 77 (67), 69 (100), 63 (24), 51 (22).

(4-Bromophenyl)(phenyl)methanone[7] (**18**)
White solid, ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.80-7.75 (2H, m), 7.71-7.63 (4H, m), 7.62- 7.57 (1 H, m), 7.52-7.46 (2 H, m).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 195.65, 137.16, 136.30, 132.68, 131.62, 131.57, 129.94, 128.41, 127.52, 123.42
GC-MS (EI, 70 eV): m/z (%) = 262 (36), 260 (60), 185 (46), 183 (43), 181 (20), 105 (95), 77 (100), 51 (50).

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[4] In this context, a 'pseudo-halogen' is a functional group capable of undergoing oxidative addition (OA) with Pd^0 (e.g. a triflate). In this article the term 'halide' implicitly encompasses pseudo-halides.

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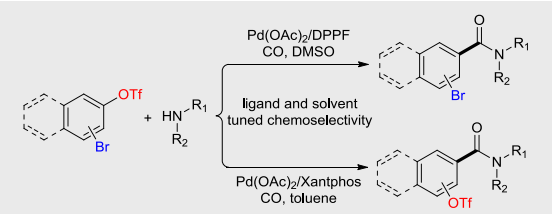

Palladium-catalyzed chemoselective carbonylation of bromoaryl triflates is reported. The selective C-Br vs. C-OTf functionalization can be remarkably tuned by the combination of ligand (Xantphos vs. DPPF) and solvent (toluene vs. DMSO). The respective ligand and solvent effects are rationalized by DFT calculation. In contrast, monodentate $BuPAd_2$ and $^tBu_3P$ prefer the selective C-Br activation and are solvent insensitive.

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Ligand and solvent tuned chemoselective carbonylation of bromoaryl triflates