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Palladium-catalyzed directing group-assisted C8-triflation of naphthalenes†

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The transition-metal-catalyzed direct triflation of naphthyl amides and naphthyl ketones has been accomplished for the first time. Benzophenone (BP) was found to be a suitable ligand for the cross-coupling reactions. Density functional theory (DFT) calculations revealed that excessive amounts of HOTf inhibit the reductive elimination of the C–F bond to realize the unusual reductive elimination of the C–OTf bond.

Reductive elimination is a fundamentally important step in transition-metal-catalyzed cross-coupling reactions for the construction of various chemical bonds.¹ Although a lot of carbon-carbon and carbon-heteroatom bond-forming reactions have been reported,² the formation of some bonds, e.g. C-F^{3,4} and $C-CF_{3}$,⁵ is challenging mainly because of the high kinetic barrier for the reductive elimination of these bonds from transition-metal centers.^{3a} To circumvent this problem, two strategies are usually employed.⁶ The first is to perform reductive elimination on high oxidation state metal species^{3a,b,7} and the other is to develop suitable ligands to facilitate this process.^{3b,8} With the aid of these two strategies, the generation of C-F and C-CF₃ bonds has been realized. For example, Ar-CF₃ was obtained via reductive elimination from the Pd(IV) complex, which was a Pd(IV) intermediate coordinated with CF₃⁻, F⁻ and TfO⁻ and was separated by Sanford's group.⁶ Yu's group used NFTPT (N-fluoro-1,3,5-trimethylpyridinium triflate) as the fluorinating reagent to realize the ortho-fluorination of triflamideprotected benzylamines. It was proposed that the fluorinated product was formed via the C-F bond-forming reductive elimination from the TfO⁻, F⁻ coordinated Pd(w) complex (eqn (1)).^{4,9} Of particular note is that Sanford's group¹⁰ and Dong's group¹¹ recently realized C(sp³)-OTs bond formation via S_N2-type C(sp³)-O coupling from Pd(IV) complexes (eqn (2)). But to our knowledge,

the C–OTf bond-formation *via* reductive elimination from the transition metal center has no precedent in the literature,¹² although the trifluoromethane sulfonyl moiety has received great attention.¹³ Herein we report the Pd-catalyzed naphthyl C–H activation/C–OTf bond-forming reaction with the combination of NFTPT, HOTf and a necessary benzophenone-type ligand (eqn (3)).

previous work:



this work:

$$\begin{array}{c} O \\ Ar \\ R^2 \end{array} \stackrel{R^1}{\underset{R^2}{\overset{NFTPT}{Pd(OAc)_2}}} \begin{array}{c} OTf \\ Ar \\ R^2 \end{array} \stackrel{R^1}{\underset{R^2}{\overset{NFTPT}{R^2}}} (3)$$

Inspired by the work of Sanford's group on competing sp³-C-F and sp³-C-NHT bond-forming reductive elimination from Pd(IV),¹⁴ and our group's previous work on the directed C-H amidation of aromatic ketones,¹⁵ we originally attempted to explore Pd(OAc)₂-catalyzed triflation of aryl C-H bonds of aryl ketones and aryl amides separately. As shown in Scheme 1, the reaction of benzophenone (BP) as a substrate (0.1 mmol) with NFTPT (2) (0.2 mmol) was conducted in the presence of Pd(OAc)₂ (0.01 mmol, 10 mol%) and HOTf (0.05 mmol)^{14,16} in DCE at 80 °C for 8 hours in air. Unfortunately, no triflation product was detected. The triflation of 1a also failed to afford the desired product after extensive screening. To our surprise, 3a was obtained in 6% yield when the mixture of 1a and BP was added into the reaction (Scheme 1). But the compound BP-OTf, which was produced by ortho C-H bond triflation of BP, was not detected at all. These results made us speculate that BP acts as the ligand to promote the formation of 3a.

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Encouraged by this result and our assumption, we turned to explore this C–H bond triflation reaction by using **1a** as the model reactant and BP as the ligand. After screening of catalysts, oxidants and solvents,¹⁷ we found that the reaction of **1a** with 2.0 equiv. of NFTPT (2) in the presence of 10 mol% Pd(OAc)₂, 50 mol% BP, 1.2 equiv. of HOTf¹⁸ and 0.8 equiv. of TMSOTf in 1,2-dichlorobenzene (ODCB) at 110 °C for 2 hours afforded the desired product **3a** in 74% ¹⁹FNMR yield. In addition, NMP,⁴ DMSO,¹⁹ CH₃CN and DMF¹⁶ were also used as ligands to conduct the reaction, but none of them were effective in this reaction. Note that the desired triflation products cannot be found when Pd(OAc)₂ was absent in this reaction.¹⁷

We next examined the substrate scope of this process. **1a** was triflated smoothly to provide product **3a** in 69% isolated yield. A variety of *N*,*N*-disubstituted-1-naphthamides could be undergo C-H triflation reaction smoothly and provide in moderate to good yields (**3b-h**). The configuration of **3g** was confirmed *via* X-ray characterization (Fig. 1). Moreover, the bromo, fluoro, methyl, methoxyl and ester substitutions (**3i-o**) were tolerated (Table 1). *N*,*N*-Dimethy-9-phenanthramide was also successfully functionalized to afford the corresponding derivative **3p** in 58% yield. Importantly, the cross-coupling reactions using naphthalene-1-yl ketones as substrates were also carried out in moderate yields (Table 2, **3q-s**). It is worth addressing the fact that upon increasing the substrates **1a** and **1r** scale to 1 mmol, the exact same yield was isolated with the substrates added on the 0.1 mmol scale.

N,*N*-Dicyclohexyl-3-methoxybenzamide was found to undergo the desired triflation reaction successfully and provide **3t** in 46% yield. This result demonstrated that the present protocol could also be applied to some benzamine derivatives (Scheme 2).



Fig. 1 X-ray crystallographic structure of 3g.

 Table 1
 Pd(OAc)₂-catalyzed direct triflation of naphthylamides^{ab}



^a Reaction conditions: substrate 1 (0.1 mmol), 2 (2.0 equiv.), Pd(OAc)₂ (10 mol%), BP (50 mol%), HOTf (1.2 equiv.), TMSOTf (0.8 equiv.), ODCB (0.4 mL), 110 °C, 2 h. ^b Isolated yield.

Table 2 Pd(OAc)₂-catalyzed direct triflation of naphthylketones^{ab}



^{*a*} Reaction conditions: substrate 1 (0.1 mmol), 2 (2.0 equiv.), $Pd(OAc)_2$ (10 mol%), BP (50 mol%), HOTf (0.5 equiv.), ODCB (0.4 mL), 110 °C, 2 h. ^{*b*} Isolated yield.

Based on literature precedents and our previous work, 9,14,15 we proposed that the reaction proceeds through a Pd($\pi/n\nu$) catalytic cycle. First, Pd(OAc)₂ is coordinated with BP and reacts with HOTf to form the active catalyst Pd(π) species **4**. **4** mediates the C-H activation of **1**, and then it was oxidized by NFTPT (2) to produce the Pd($n\nu$) species **5**. Then **5** could undergo direct C-OTf reductive elimination to obtain the product **3r** (Path A2) or further react with HOTf to generate **6** with the release of HF



(Path B). Thereafter, C–OTf reductive elimination of **8** occurs to deliver the product **3r** and regenerates the active catalyst (Fig. 2).

Preliminary DFT studies were conducted¹⁷ to provide insight into the C-OTf and C-F reductive elimination from intermediates 5 and 6 (Fig. 2). To simplify the description of these mechanisms, 4 was considered as the reference point. 5 could generate the fluorinated product *via* **TS1** (Path A1, $\Delta G^{\neq} = 9.3$ kcal mol⁻¹) or the triflated product *via* **TS2** (Path A2, $\Delta G^{\neq} = 18.8 \text{ kcal mol}^{-1}$). The former path is kinetically favored by 9.5 kcal mol^{-1} . indicating that C-F bond formation is more feasible via the reductive elimination of 5. However, 5 could further form the palladium triflate complex 6 by reacting with the excess HOTf in the solution. This process is exergonic by 7.9 kcal mol^{-1} due to the formation of weak acid HF from HOTf. From 6, only C-OTf reductive elimination is possible. It occurs via TS3 and is more kinetically favored than TS1 by 1.9 kcal mol^{-1} overall. The calculation results indicate that the excessive amounts of HOTf could act as a fluorine scavenger that removes F⁻ from the Pd center and inhibits the competitive C-F reductive elimination process.

We have successfully developed the first Pd-catalyzed C–H activation/C–OTf bond-forming reaction. It provides a stepeconomic way to obtain aryl triflates from naphthyl ketones and naphthyl amides. The originally favored C–F reductive elimination is suppressed by the excessively strong acid HOTf, which removes the fluoride atom from the palladium intermediate to form the key intermediate. We note that there are still some deficiencies in the current catalytic system. Unreacted starting materials exist in our reactions while the secondary amides and the substrate bearing strong electron-withdrawing and electrondonating groups are less active in our reactions. Further studies focusing on resolving these deficiencies, applying this strategy to



Fig. 2 Energy profiles of Path A and Path B to generate the fluorination product or triflation product. The relative free energies are given in kcal mol^{-1} .

benzene derivatives like **3t** and the details of reaction mechanism are ongoing in our laboratory.

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