Palladium-Catalyzed Oxidative Acylation of \(N\)-Benzyltriflamides with Aldehydes via C–H Bond Activation

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Abstract: A palladium-catalyzed ortho-acylation of \(N\)-benzyltriflamides with aldehydes via direct \(sp^2\) C–H bond activation is described. Benzylamines with a triflamide directing group in the presence of palladium acetate, acetic acid, and tert-butyl hydroperoxide as an oxidant can be effectively coupled with aryl and alkyl aldehydes to provide ortho-acyl-N-benzyltriflamides with a high regioselectivity.

Keywords: acylation; \(N\)-benzyltriflamides; catalysis; C–H activation; palladium

The transition metal-catalyzed cross-coupling reaction is a powerful tool available for synthetic chemists to create or reproduce intricate organic scaffolds.[1] In particular, carbon-carbon cross-coupling reactions involving selective activation of carbon-hydrogen bonds, which cannot be easily cleaved under classical reaction conditions, are extremely challenging due to the minimization of stoichiometric metallic waste and the costs associated with the preparation of starting materials.[2] Since the pioneering discovery of C–H bond activation by Murai,[3] recent progress has been focused on dehydrogenative cross-coupling between \(sp^2\) or \(sp^3\) C–H bonds and \(sp^2\) C–H bonds of arenes or alkenes.[4] In this area of research, various directing groups such as ketones,[5] carboxylic acids,[6] amides,[7] pyrrole/pyridine,[8] anilides,[9] carbamate,[10] urea,[11] and azine N-oxide[12] can provide an anchor for catalytic ortho-metalation of aromatic rings. Although the reactions using arenes or alkenes as coupling partners have been well documented, the reactions between the aromatic \(sp^2\) C–H bond and aldehydes remain relatively unexplored. In 2009, Cheng first reported a palladium-catalyzed cross-coupling reaction between arenes containing a pyridine directing group and aryl aldehydes to afford aryl ketones.[13] Later, palladium-catalyzed \(sp^2\) C–H bond acylations of 2-arylpyridines,[14] oxime,[15] acetonilides,[16] and indole[17] with aldehydes or alcohols were described. Decarboxylative C–H bond acylations of arylpyridines,[18] acetonilides,[19] and enamides[20] using \(\alpha\)-oxocarboxylic acids as acyl surrogates were also reported. Furthermore, the Pd-catalyzed acylation of 2-arylpyridines via C–H bond activation and the C–C bond cleavage of \(\alpha\)-diketones were reported.[21] Recently, the rhodium-catalyzed addition of aryl C–H bonds to ethyl glyoxylate[22] or aryl aldehydes[23] to produce the corresponding alcohols was demonstrated.

Inspired by our recent studies on rhodium-catalyzed oxidative acylation of tertiary[24] and secondary[25] benzamides with aldehydes, we herein report the palladium-catalyzed oxidative ortho-acylation of triflamide-protected benzylamines with aryl and alky aldehydes via C–H bond activation (Figure 1). This new method is complementary to Friedel–Crafts acylation[26] and direct lithiation/acylation processes.[27]
Palladium-Catalyzed Oxidative Acylation of N-Benzyltriflamides with Aldehydes

More importantly this method provides aryl ketones, which are important structural units and synthetic intermediates in pharmaceuticals, natural products, and functional materials. Our initial investigation focused on the coupling of benzylamine derivatives with p-anisaldehyde. After extensive screening of benzylamine protecting groups, including trifuoromethanesulfonyl, acetyl, pivaloyl, p-toluenesulfonyl and p-nitrobenzenesulfonyl, benzylamine 1a with triflamide as a directing group was found to couple with aldehyde 2a in the presence of 5 mol% of Pd(OAc)$_2$, and 3 equiv. of tert-butyl hydrogen peroxide (TBHP) in DMF solvent at 100°C for 20 h to give the desired product 3a in 33% yield (Table 1, entry 1). Further investigation of the effect of various transition metal catalysts, including Pd[(OCOCF$_3$)$_2$], Pd(PPh$_3$)$_2$Cl$_2$, Pd(PCy$_3$)$_2$Cl$_2$, Cp*Rh[(CH$_3$CN)$_3$(SbF$_6$)$_2$, [RuCl$_2$(p-cymene)]$_2$, were performed, and Pd(OAc)$_2$ was found to be the most effective in this coupling reaction.

Variation of the oxidant showed that TBHP is superior to other oxidants such as (PhCOO)$_2$, Ag$_2$CO$_3$, Cu(OAc)$_2$, benzoquinone and (NH$_4$)$_2$S$_2$O$_8$ (Table 1, entries 2–6). Since aldehydes are sensitive to some oxidants, choosing a proper oxidant is crucial for this transformation. Solvent screening showed that an improved chemical yield could be obtained by using MeCN as solvent, producing the ortho-acylation product 3a in 42% yield (Table 1, entry 11), whereas other solvents, such as DCE, THF, toluene and $\alpha$-amyl alcohol, were less effective (Table 1, entries 7–10). After further optimization, the use of 50 mol% AcOH as an additive resulted in the acylation of an sp$^2$ C–H bond in triflamide-protected benzylamine 1a to afford the desired product 3a in 55% yield, as shown in entry 12. However, either increasing the amount of AcOH or adding other acid additives (TFA, TfOH) was relatively ineffective (Table 1, entries 13–15). The best results were obtained using a treatment of 7.5 mol% of Pd(OAc)$_2$, 50 mol% of AcOH and 4 equiv. of TBHP in MeCN:DMF (1:1) at 100°C for 40 h to afford 3a in high yield (71%), as shown in entry 17.

With the optimized reaction conditions established, the substrate scope with respect to aldehydes was examined, and the results are summarized in Scheme 1. Benzaldehyde (2b) and aldehydes 2a and 2c–2e with electron-donating groups, regardless of the substituent position on the phenyl ring, displayed high reactivity under the present reaction conditions to afford the corresponding ortho-acylation products 3a–3e. This reaction was also compatible with hydroxy-substituted aldehyde 2f, which provides a versatile synthetic functionality for further manipulation of the product.

In contrast, electron-deficient aldehydes 2g and 2h were relatively less reactive under these reaction conditions. Halogen-substituted aldehydes 2i and 2j were smoothly converted to the corresponding products 3i and 3j, respectively. In particular, the chloro moiety of 3j remained intact during the course of the reaction, allowing further cross-coupling reactions on the product. In addition, 2-fluoroanisaldehyde (2k) and 2-naphthaldehyde (2l) also smoothly underwent this reaction to generate the corresponding products. To our delight, this reaction is not limited to ary aldehydes. Aliphatic aldehydes such as 1-hexanal (2m) and iso-butyaldehyde (2n) also participated in the oxidative coupling to furnish 3m and 3n in 69% and 51% yields, respectively.

To further explore the substrate scope and limitations of this process, the coupling of a variety of N-benzyltriflamides 1b–1k and p-anisaldehyde 2a under identical reaction conditions was screened, as shown in Scheme 2. The substituted N-benzyltriflamides 1b–1j with electron-donating and electron-withdrawing

Table 1. Selected optimization parameters for the reaction conditions.[a]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Oxidant</th>
<th>Additive</th>
<th>Solvent</th>
<th>Yield [%][b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TBHP</td>
<td></td>
<td>DMF</td>
<td>33</td>
</tr>
<tr>
<td>2</td>
<td>(PhCOO)$_2$</td>
<td></td>
<td>DMF</td>
<td>17</td>
</tr>
<tr>
<td>3</td>
<td>Ag$_2$CO$_3$</td>
<td></td>
<td>DMF</td>
<td>N.R.</td>
</tr>
<tr>
<td>4</td>
<td>Cu(OAc)$_2$</td>
<td></td>
<td>DMF</td>
<td>N.R.</td>
</tr>
<tr>
<td>5</td>
<td>benzoquinone</td>
<td></td>
<td>DMF</td>
<td>N.R.</td>
</tr>
<tr>
<td>6</td>
<td>(NH$_4$)$_2$S$_2$O$_8$</td>
<td></td>
<td>DMF</td>
<td>N.R.</td>
</tr>
<tr>
<td>7</td>
<td>TBHP</td>
<td></td>
<td>DCE</td>
<td>23</td>
</tr>
<tr>
<td>8</td>
<td>TBHP</td>
<td></td>
<td>THF</td>
<td>12</td>
</tr>
<tr>
<td>9</td>
<td>TBHP</td>
<td></td>
<td>toluene</td>
<td>7</td>
</tr>
<tr>
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<td>TBHP</td>
<td></td>
<td>$\alpha$-amyl alcohol</td>
<td>trace</td>
</tr>
<tr>
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<td>AcOH</td>
<td>MeCN</td>
<td>42</td>
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<tr>
<td>12</td>
<td>TBHP</td>
<td>AcOH</td>
<td>MeCN</td>
<td>55</td>
</tr>
<tr>
<td>13[c]</td>
<td>TBHP</td>
<td>AcOH</td>
<td>MeCN</td>
<td>50</td>
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<td>14</td>
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<td>TFA</td>
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<td>15</td>
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<td>TiOH</td>
<td>MeCN</td>
<td>12</td>
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<tr>
<td>16[d]</td>
<td>TBHP</td>
<td>AcOH</td>
<td>MeCN</td>
<td>62</td>
</tr>
<tr>
<td>17[d]</td>
<td>TBHP</td>
<td>AcOH</td>
<td>MeCN:DMF (1:1)</td>
<td>71</td>
</tr>
</tbody>
</table>

[a] Reaction conditions: 1a (0.3 mmol), 2a (0.9 mmol), Pd(OAc)$_2$ (5 mol%), oxidant (3 equiv.), additive (50 mol%), solvent (0.6 mL) at 100°C for 20 h under N$_2$ in 13×100 mm$^2$ pressure tubes.
[b] Yield isolated by column chromatography.
[c] AcOH (1 equiv.).
[d] Pd(OAc)$_2$ (7.5 mol%), TBHP (4 equiv.), 40 h.
Scheme 1. Scope of aldehydes. Yields given in parentheses are of isolated products after column chromatography.

Scheme 2. Scope of N-benzyltriflamides. Yields given in parentheses are combined isolated yields of monoacylated and diacylated products.
groups on the benzene rings were found to be favored in the reaction to afford the desired products 4b–4j in good yields. Notably, the reaction of meta-substituted N-benzyltriflamides 1c preferentially occurred at the more sterically accessible position to afford the corresponding product 4c as a single regioisomer owing to the steric effect that caused interference with either the formation of the cyclopalladated intermediate or the approach of the aldehyde into the cyclopalladated intermediate. However, symmetric N-benzyltriflamides 1e–1h gave a separable mixture of monoacylated and diacylated products under these reaction conditions. Finally, α-substituted N-benzyltriflamide 1k displayed a significantly decreased reactivity under the present reaction conditions.

To gain an insight of the reaction pathway, we examined the effect of a radical scavenger, ascorbic acid, under the standard reaction conditions in a dose-dependent manner, resulting in the drastically reduced formation of acylated products. These results indicate that the reaction proceeds through a radical pathway (see the Supporting Information for a plausible reaction mechanism). To further support the radical pathway for this reaction, competition experiments between aryl aldehyde and aliphatic aldehyde were undertaken (Scheme 3). Exposure of N-benzyltriflamide 1a to equimolar quantities of aryl aldehyde 2a and aliphatic aldehyde 2m under the standard conditions provided 3a and 3m in 62% yield in a 3.5:1 ratio. These results indicate that an alkyl acyl radical may be more prone to decarbonylate under high temperature (100 °C) and thus led to lower formation of 3m.

Further investigation on the synthetic utility of the triflamide directing group was conducted. As shown in Scheme 4, acylated compound 5a, obtained from the reaction of N-benzyltriflamide 1g and aldehyde 2b, was easily transformed to 5b, which is a useful synthetic precursor for the preparation of analgesic nefopam.

In conclusion, we have developed an efficient protocol for the Pd-catalyzed oxidative ortho-acylation of N-benzyltriflamides with aldehydes via C–H bond activation. The triflamide directing group can be readily transformed to functional groups with a broad range of synthetic utility. Further applications of this method to the synthesis of biologically active compounds and a more detailed mechanistic investigation are in progress.

**Experimental Section**

**Typical Procedure for the Acylation of Triflamides**

To an oven-dried sealed tube under one atmosphere of nitrogen gas charged with 2-methoxybenzyltriflamide (1a) (80.8 mg, 0.3 mmol, 1 equiv.), Pd(OAc)$_2$ (5.1 mg, 0.0225 mmol, 7.5 mol%), TBHP (0.22 mL, 1.2 mmol, 4 equiv.), and AcOH (9 mL, 0.15 mmol, 50 mol%) in anhydrous DMF:CH$_3$CN (0.6 mL, 1:1) was added 4-methoxybenzaldehyde (2a) (109.5 mL, 0.9 mmol, 3 equiv.). The reaction mixture was allowed to stir at 100 °C for 40 h. After cooling at room temperature, the reaction mixture was evaporated onto silica gel. Purification of the product by column chromatography (SiO$_2$: n-hexanes/EtOAc) provided 3a; yield: 85.9 mg (71%).

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