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Rhodium-Catalyzed Oxidative Coupling of N-Acyl Anilines with Alkynes Using an Acylamino Moiety as the Traceless Directing Group†

Kaijun Geng,‡ Zhioulang Fan‡ and Ao Zhang*‡

A rhodium-catalyzed oxidative annulation of N-acyl anilines with alkynes was developed by using the acylamino group as a traceless directing group for the first time. Various N-acyl anilines and para- or meta-substituted diphenylacetylenes were well tolerated, and a series of 1,2,3,4-tetrasubstituted naphthalenes were readily synthesized in good to excellent yields. Meanwhile, this method also provides a new strategy for the N-dearylation of N-phenylamines.

Polycyclic aromatic compounds are widely used as organic semiconductors and luminescent materials in material sciences due to their unique electron- and photochemical properties.1

Traditional synthetic methods to this class of compounds generally suffer from harsh reaction condition and low yields. In the past decades, significant breakthroughs have been achieved in directing group-assisted transition-metal catalyzed oxidative coupling of aromatic substrates with internal alkynes, providing an alternative option to the synthesis of such π-conjugated molecules.2 Among which, the recently developed traceless directing group (TDG) strategy is particularly appealing, due to the easy pre-attaching and traceless cutting-off.3 For example, carboxylic acid,4 boronic acid,5 sodium sulfonate6 and aldehyde7 have been successfully used as the TDGs in transition metal-catalyzed oxidative couplings for synthesis of fused aromatic or heteroaromatic compounds.

The acylamino group, as a directing group, has been widely used in diversified ortho C-H functionalizations.8 For example, Fangou, Tanaka and Lu’s laboratories have reported that multisubstituted indoles could be synthesized via Rh- or Pd-catalyzed intermolecular C-H activation/annulation of alkynes and acetonilides (Scheme 1a).9 Moreover, the Wu group disclosed an ortho- and meta- position dual C-H activation strategy to synthesize the highly substituted naphthalenes with similar substrates under a Pd(OAc)2/K2S2O4 catalytic system (Scheme 1b).10 In these examples, the acylamino group served as the directing group and retained as a part of the products.

Scheme 1 Metal-catalyzed oxidative coupling of acetonilides with alkynes.

In view of the advantages of the TDGs, we decide to explore the possibility of using an acylamino group as a TDG in the rhodium-catalyzed ortho- and ipso-selective oxidative annulation of N-acyl anilines with alkynes that would lead to readily synthesis of 1,2,3,4-tetrasubstituted naphthalenes (Scheme 1c). This method not only provides a new example of TDGs in the C-H activation toolbox, and also offers a new strategy to remove the N-phenyl protecting group of N-phenylamines.

Our investigation on the rhodium-catalyzed C-H activation/annulation began with the reaction of N-phenylpivalamide (1a) with diphenylacetylene (2a) in the presence of 2.5 mol % [Cp*RhCl2]. Results of screening the
oxidants and solvents were shown in Table 1. Using Cu(OAc)₂·H₂O as the oxidant and methanol as the solvent only gave trace of 1,2,3,4-tetraphenylbutadiene (3a) (entry 1). After several attempts, it was found that 3a was obtained in 83% yield in the presence of hexafluorosopropanol (HFIP) (entry 4), and nearly no reaction took place using other solvents, including DMF, toluene and i-PrOH. Among various oxidants tested, no superior one was found than Cu(OAc)₂·H₂O (entries 6-9). Further optimization on the loading amounts of Cu(OAc)₂·H₂O showed that 1 equivalent of Cu(OAc)₂·H₂O is optimal (entries 10-12). Meanwhile, an excellent isolated yield of 3a (90%, entry 13) was achieved when increasing the rhodium catalyst from 2.5 to 5 mol %. Based on these screening results, the best reaction condition was reached as follows: N-acyl anilines 1 (1 equiv.), internal alkenes 2 (2 equiv.), [Cp*RhCl₂] (5 mol %) and Cu(OAc)₂·H₂O (1 equiv.) in HFIP at 110 °C in a sealed tube.

Table 1 Reaction optimization for the synthesis of 3a.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Oxidant (x equiv)</th>
<th>Solvent</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cu(OAc)₂·H₂O (1.0)</td>
<td>MeOH</td>
<td>trace</td>
</tr>
<tr>
<td>2</td>
<td>Cu(OAc)₂·H₂O (1.0)</td>
<td>DMF</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>Cu(OAc)₂·H₂O (1.0)</td>
<td>toluene</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>Cu(OAc)₂·H₂O (1.0)</td>
<td>HFIP</td>
<td>83</td>
</tr>
<tr>
<td>5</td>
<td>Cu(OAc)₂·H₂O (1.0)</td>
<td>i-PrOH</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>AgOAc (2.0)</td>
<td>HFIP</td>
<td>trace</td>
</tr>
<tr>
<td>7</td>
<td>Ag₂O₂ (1.0)</td>
<td>HFIP</td>
<td>trace</td>
</tr>
<tr>
<td>8</td>
<td>Ph(ΦOAc)₂ (1.0)</td>
<td>HFIP</td>
<td>trace</td>
</tr>
<tr>
<td>9</td>
<td>K₂S₂O₄ (1.0)</td>
<td>HFIP</td>
<td>trace</td>
</tr>
<tr>
<td>10</td>
<td>Cu(OAc)₂·H₂O (1.5)</td>
<td>HFIP</td>
<td>78</td>
</tr>
<tr>
<td>11</td>
<td>Cu(OAc)₂·H₂O (0.5)</td>
<td>HFIP</td>
<td>65</td>
</tr>
<tr>
<td>12</td>
<td>Cu(OAc)₂·H₂O (0.1)</td>
<td>HFIP</td>
<td>52</td>
</tr>
<tr>
<td>13a</td>
<td>Cu(OAc)₂·H₂O (1.0)</td>
<td>HFIP</td>
<td>94(90)</td>
</tr>
</tbody>
</table>

“Reaction conditions: 1a (0.1 mmol), 2a (0.2 mmol), [Cp*RhCl₂] (2.5 mol %), oxidant (x equiv), solvent (1 ml) in a sealed tube at 110 °C for 5 h. aYield was determined by 1H NMR analysis using 1,2-dibromomethane as an internal standard; dash line indicates product was not detected. b5 mol % [Cp*RhCl₂]. cIsolated yield when using 0.5 mmol 1a. HFIP = hexafluorosopropanol.”

With the optimized reaction conditions in hand, we firstly investigated various acylamino groups as the traceless directing groups and the results were summarized in Scheme 2. The cyclic alkyl acylaminoles (1c-1d) gave higher yields than the aliphatic acyl and aromatic acyl substrates (1b, 1e and 1f). We speculated that the steric hinderance on the aliphatic alkyl portion likely makes the TDG more prone to cleave during the C-H activation process. N-Phenyl lactams 1g-1h proceeded smoothly in the reaction but afforded product 3a in much lower yields. For the five-membered (1i) or six-membered (1j) heterocycle-bearing TDGs, such as pyrazolones and pyridazinones, the corresponding product 3a was obtained in 15% and 70% yields, respectively, suggesting the pyridazinonyl-TDG has higher inductive effect. Interestingly, 1-acetyl-2-phenylhydrazine (1k) took part in the reaction as well, though in a lower yield (17%). In addition, N-methylacetanilide 1l was applied in this reaction, but no product was obtained. We propose that the steric congestion of the N-methyl on the TDG might deteriorate the reaction. N-Methylaniline 1m lacking the carbonyl group as the DG also failed in this reaction.

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Scheme 2 Reaction of various N-acyl anilines with diphenylacetylene (2a).

Scheme 3 Reaction of substituted N-phenylpivalamides 1 with diphenylacetylene (2a). Yields were listed in the parentheses when employing meta-substituted N-phenylpivalamides.

Next, various substituted N-phenylpivalamides were used to explore the reaction scope and limitation. As shown in scheme 3, all these substrates reacted with diphenylacetylene (2a) and gave the corresponding highly substituted naphthalenes in good to excellent yields (Scheme 3). N-Phenylpivalamides bearing electron-donating or -withdrawing substituents on the para-position offered the corresponding products 3b-3g in 80-91% yields. Some meta-substituents (Cl-, Me-, OMe- and CF₃-) were also well tolerated and afforded products 3b-3e in 81-
89% yields, which were shown in the parentheses in Scheme 3. Subsequently, ortho-methyl or -chloro substituted N-phenylpivalamides were explored, the products 3h-3j were obtained in 56% and 73% yields, respectively. Moreover, bicyclo-N-phenylpivalamides were found to participate in the reaction as well and afforded the annulated products 3k-3l in 65-77% yields.

In addition, 1a was used to react with meta-substituted diphenylacetylenes occurred smoothly. However, the alkyl-alkyl disubstituted alkynes and terminal alkynes failed in the reaction, and the unsymmetric aryl-aryl disubstituted alkynes gave inseparable complex mixtures.

Scheme 5 N-Dearylation of N-phenylpivalamides.

In addition to the TDG-assisted rhodium-catalyzed oxidative annihilation of N-acyl anilines, the current protocol also provides a new strategy for the N-dearylation of amides. To validate the practicality, N-acyl anilines 1m and 1n were reacted with diphenylacetylene (2a) under the optimized reaction conditions and the corresponding dephenylated products 4 and 5 were obtained in 65% and 62% yields, respectively (Scheme 5). This approach would be valuable in the peptide synthesis.

To gain more insights on the reaction pathway, additional experiments were performed. In order to demonstrate the sequence of C-N cleavage and C-H activation, we re-conducted the reaction with 1m as the substrate but without 2a under the standard condition. The C-N cleavage product 4 was not detected, even when increasing the amount of Rh-catalyst or adding HOAc as the proton source (Scheme 6a). Therefore, it is unlikely that the C-N cleavage occurred prior to the C-H activation in the protocol.

a) Control experiments:

b) Isotopic labeling studies:

To probe the C−H activation process, we conducted C−H cleavage experiments were performed. In order to demonstrate the rate-determining step (Scheme 6c). That the C−H cleavage was probably involved in the rate-determining step (Scheme 6c). That the C−H cleavage was probably involved in the rate-determining step (Scheme 6c).
combination of catalyst precursor [Cp*RhCl]$_2$ and Cu(OAc)$_2$H$_2$O would give the cationic rhodium (III) complex A, which is then converted to a rhodacycle B via a C-H bond cleavage process. Insertion of alkyne 2a to the complex B affords the rhodium complex C. The complex C is then converted to a five-membered rhodacycle D, accompanied by the C-N bond cleavage. The intermediate D then undergoes the second insertion of alkyne 2a to give the 7-membered metallacycle E, which then proceeds via a reductive elimination to form the desired product 3a and rhodium (I) complex F. The active cationic rhodium (III) complex A was regenerated under the oxidation of Cu(OAc)$_2$H$_2$O and air and used for further catalysis.

Scheme 7 Proposed mechanism.

In conclusion, we have reported the first example of using the acylamino group as a traceless directing group to initiate a rhodium-catalyzed oxidative annihilation of N-acyl anilines with internal alkynes. In this approach, various N-acyl anilines and para- or meta-substituted diphenylacetylenes were well tolerated, and a series of 1,2,3,4-tetrasubstituted naphthalenes were readily synthesized in good to excellent yields. Meanwhile, this method also represents a new strategy of removal of the N-phenyl protective group of N-phenylamides.

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Notes and references


