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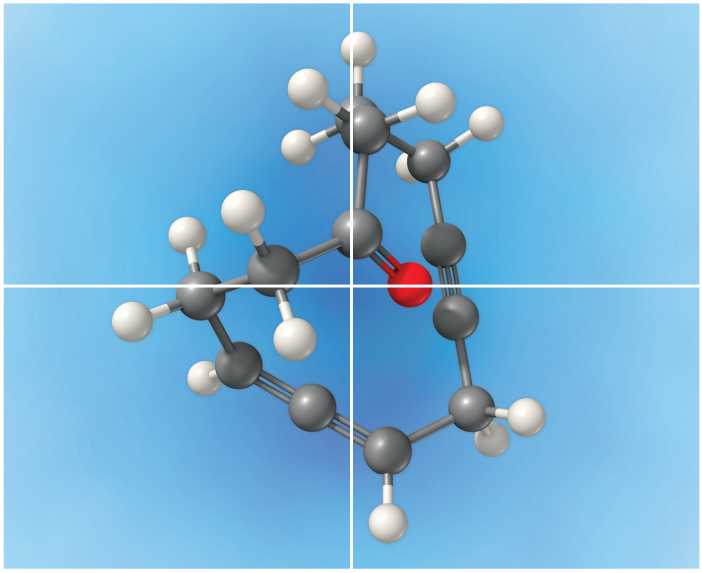

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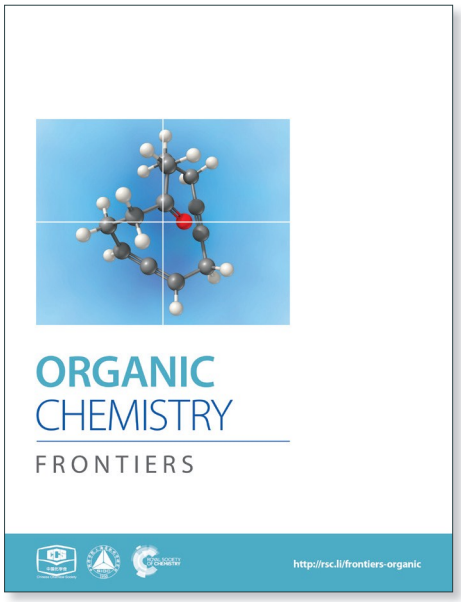


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# Rhodium-Catalyzed Oxidative Coupling of *N*-Acyl Anilines with Alkynes Using an Acylamino Moiety as the Traceless Directing Group†

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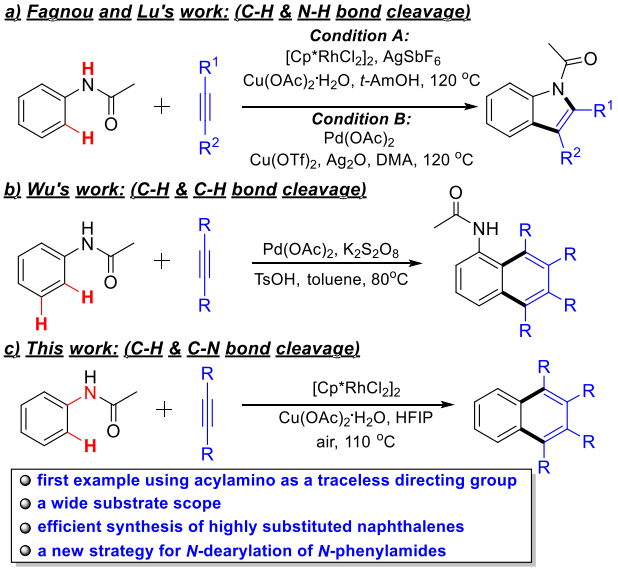
**A rhodium-catalyzed oxidative annulation of *N*-acyl anilines with alkynes was developed by using the acylamino group as a traceless directing group for the first time. Various *N*-acyl anilines and *para*- or *meta*-substituted diphenylacetylenes were well tolerated, and a series of 1,2,3,4-tetrasubstituted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

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 breakthrough has 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 sulfonate[6] and aldehyde[7] 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, Fagnou, 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 acetanilides (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 $Pd(OAc)_2/K_2S_2O_8$ 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 acetanilines 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*-phenylamides.

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 % $[Cp^*RhCl_2]_2$. Results of screening the

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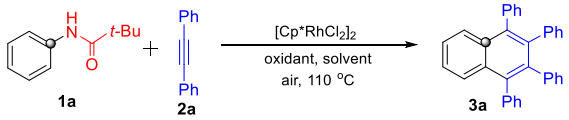
oxidants and solvents were shown in Table 1. Using $Cu(OAc)_2{\cdot}H_2O$ as the oxidant and methanol as the solvent only gave trace of 1,2,3,4-tetraphenylnaphthalene (**3a**) (entry 1). After several attempts, it was found that **3a** was obtained in 83% yield in the presence of hexafluoroisopropanol (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 $Cu(OAc)_2{\cdot}H_2O$ (entries 6-9). Further optimization on the loading amounts of $Cu(OAc)_2{\cdot}H_2O$ showed that 1 equivalent of $Cu(OAc)_2{\cdot}H_2O$ 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 alkynes **2** (2 equiv.), $[Cp^*RhCl_2]_2$ (5 mol %) and $Cu(OAc)_2{\cdot}H_2O$ (1 equiv.) in HFIP at 110 °C in a sealed tube.

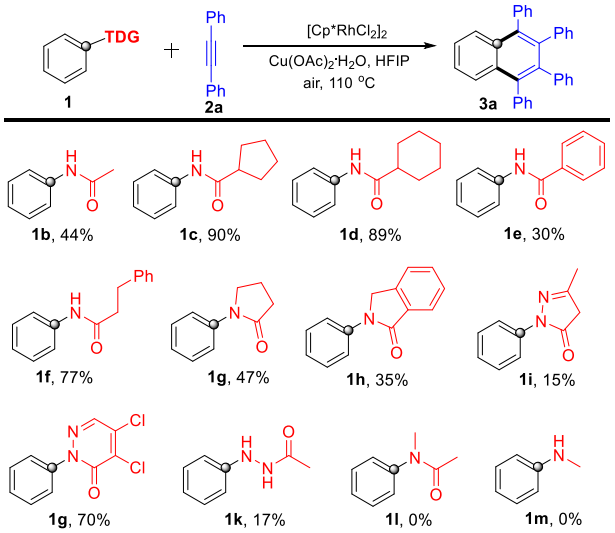
**Table 1** Reaction optimization for the synthesis of **3a.**[a]



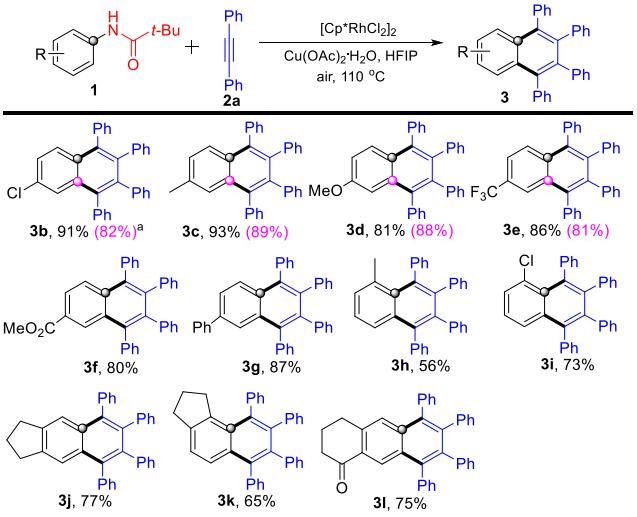

| Entry | Oxidant (x equiv) | Solvent | Yield (%)[b] |
|---|---|---|---|
| 1 | $Cu(OAc)_2{\cdot}H_2O$ (1.0) | MeOH | trace |
| 2 | $Cu(OAc)_2{\cdot}H_2O$ (1.0) | DMF | - |
| 3 | $Cu(OAc)_2{\cdot}H_2O$ (1.0) | toluene | - |
| 4 | $Cu(OAc)_2{\cdot}H_2O$ (1.0) | HFIP | 83 |
| 5 | $Cu(OAc)_2{\cdot}H_2O$ (1.0) | *i*-PrOH | - |
| 6 | AgOAc (2.0) | HFIP | trace |
| 7 | $Ag_2CO_3$ (1.0) | HFIP | trace |
| 8 | $PhI(OAc)_2$ (1.0) | HFIP | trace |
| 9 | $K_2S_2O_8$ (1.0) | HFIP | trace |
| 10 | $Cu(OAc)_2{\cdot}H_2O$ (1.5) | HFIP | 78 |
| 11 | $Cu(OAc)_2{\cdot}H_2O$ (0.5) | HFIP | 65 |
| 12 | $Cu(OAc)_2{\cdot}H_2O$ (0.1) | HFIP | 52 |
| 13[c] | $Cu(OAc)_2{\cdot}H_2O$ (1.0) | HFIP | 94(90)[d] |

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol %), oxidant (x equiv), solvent (1 ml) in a sealed tube at 110 °C for 5 h. [b]Yield was determined by $^1H$ NMR analysis using 1,2-dibromomethane as an internal standard; dash line indicates product was not detected. [c]5 mol % $[Cp^*RhCl_2]_2$. [d]Isolated yield when using 0.5 mmol **1a**. HFIP = hexafluoroisopropanol.

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 acylanilines (**1c-1d**) gave higher yields than the acyclicalkyl 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[11] and pyridazinones,[12] 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*-methyl-acetanilide **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.[13] *N*-Methylaniline **1m** lacking the carbonyl group as the DG also failed in this reaction.



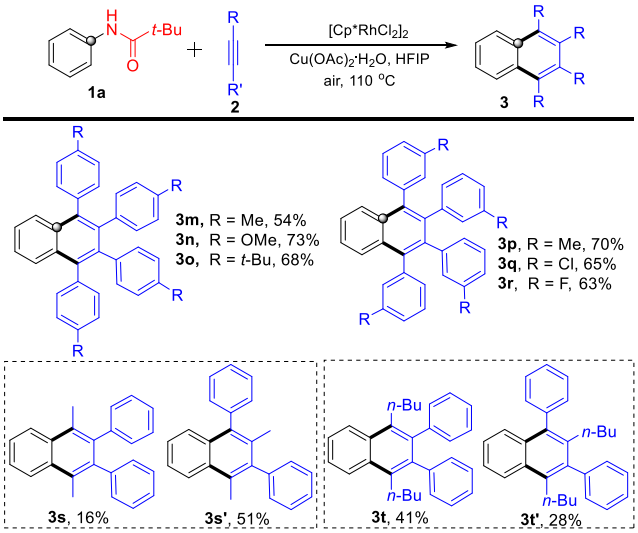

**Scheme 2** Reaction of various *N*-acyl anilines with diphenylacetylene (**2a**).




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

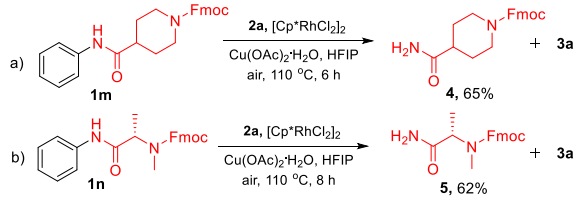
Next, various substituted *N*-phenylpivalamides were used to explore the reaction scope and limitation. As shown in scheme 3, all these substrates reacted with diphenylacetylene (**2a**) and gave the corresponding highly substituted naphthalenes in good to excellent yields (Scheme 3). *N*-Phenylpivalamides 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 $CF_3$-) 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-3i** 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 **3j-l** in 65-77% yields.




**Scheme 4** Reactions of *N*-phenylpivalamide (**1a**) with substituted diphenylacetylenes **2.**

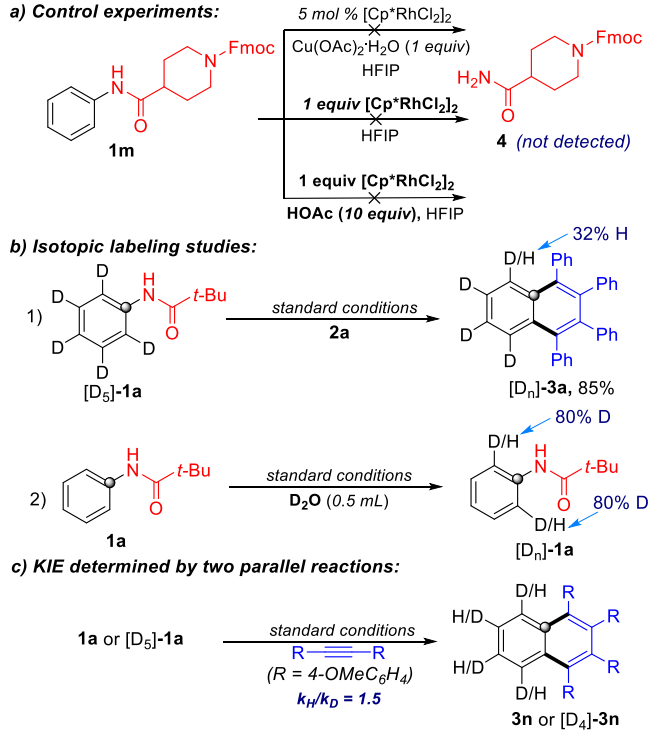
Further, different internal alkynes were used to react with *N*-phenylpivalamide **1a** under the optimized reaction conditions (Scheme 4). The *para*-methyl, -methoxyl, and -*tert*-butyl substituted phenylacetylenes participated in the reaction very well and gave 1,2,3,4-tetrasubstituted naphthalenes **3m-3o** in moderate to good yields. It is worthy of noting that similar to the *para*-substituted congeners, reactions of **1a** with *meta*-substituted diphenylacetylenes occurred smoothly to afford products **3p-3r** in 63-70% yields. In addition, 1-phenyl-1-propyne and 1-phenyl-1-hexyne also reacted with **1a** to give symmetric 1,2,3,4-tetrasubstituted naphthalenes **3s** and **3t**, along with unsymmetric isomers **3s'** and **3t'**. The structures were deduced by NOE experiments (see the Supporting Information). Although the reaction generally occurred smoothly, it still suffered from inevitable substrate limitation. For example, 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*-phenylamides.

In addition to the TDG-assisted rhodium-catalyzed oxidative annulation of *N*-acyl anilines, the current protocol also provides a new strategy for the *N*-dearylation of amides.[14] 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.

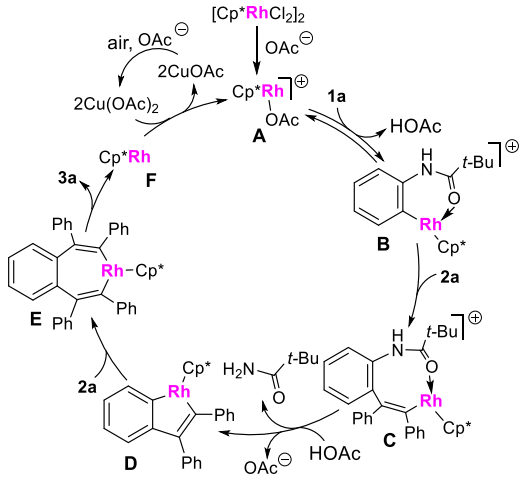



**Scheme 6** Preliminary mechanistic studies.

To probe the C–H activation process, we conducted C-H functionalization with isotopically labeled substrates. First, [$D_5$]-**1a** was used to react with **2a** under the standard condition. The *ortho*-D/H partially exchanged product [$D_n$]-**3a** was obtained in 85% yield. Meanwhile, *ortho*-D/H exchange was observed when treating **1a** with $D_2O$ under the same catalytic condition but without **2a** (Scheme 6b). These results confirmed that the C-H bond metalation/activation in the *ortho*-position of the N-phenylpivalamide was the first step and this process was reversible. Subsequently, the kinetic isotopic effect (KIE) of *ortho*-C-H cleavage was determined to be 1.5 by two independent reactions of substrates **1a** and [$D_5$]-**1a**, indicating that the C–H cleavage was probably involved in the rate-limiting step (Scheme 6c).

A plausible mechanism was then presented in Scheme 7 (based on the model reaction of **1a** and **2a**).[9a,d] Firstly, the

combination of catalyst precursor $[Cp^*RhCl_2]_2$ and $Cu(OAc)\cdot H_2O$ 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 rhodium complex **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 $Cu(OAc)_2\cdot H_2O$ 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 annulation 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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