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Efficient Copper-Catalyzed Multicomponent Synthesis of N-Acyl Amidines via Acyl Nitrenes

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Supporting Information

Abstract: Direct synthetic routes to amidines are desired, as they are widely present in many biologically active compounds and organometallic complexes. N-Acyl amidines in particular can be used as a starting material for the synthesis of heterocycles and have several other applications. Here, we describe a fast and practical copper-catalyzed three-component reaction of aryl acetylenes, amines, and easily accessible 1,4,2-dioxazol-5-ones to N-acyl amidines, generating CO2 as the only byproduct. Transformation of the dioxazolones on the Cu catalyst generates acyl nitrenes that rapidly insert into the copper acetylide Cu=C bond rather than undergoing an undesired Curtius rearrangement. For nonaromatic dioxazolones, [Cu(OAc)(Xantphos)] is a superior catalyst for this transformation, leading to full substrate conversion within 10 min. For the direct synthesis of N-benzoyl amide derivatives from aromatic dioxazolones, [Cu(OAc)(Xantphos)] proved to be inactive, but moderate to good yields were obtained when using simple copper(I) iodide (CuI) as the catalyst. Mechanistic studies revealed the aerobic instability of one of the intermediates at low catalyst loadings, but the reaction could still be performed in air for most substrates when using catalyst loadings of 5 mol %. The herein reported procedure not only provides a new, practical, and direct route to N-acyl amidines but also represents a new type of C–N bond formation.

Introduction

Amidines are useful substrates with a variety of applications. The amidine structure in 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) is used frequently as a non-nucleophilic base in synthetic chemistry, and more complex amidines are even considered to be “superbases”.

Amidines also have been used as ligands for organometallic complexes and as starting material for the synthesis of N-heterocycles. The structure itself is present in various natural products and biologically active compounds such as janoxepin, pentamidine, and sildena...

However, the general (kinetic) stability of most triazoles puts severe limitations on the applicability of other azides, and this method also proved to be unsuitable for the synthesis of N-benzoyl or N-acyl amidines. Nicasio and Pérez showed that a copper-catalyzed reaction of acetylenes with N-aryl or N-acyl azides produces triazoles or oxazoles instead of N-acyl amidines. In fact, development of direct methods for the synthesis of N-acyl amidines remains an unsolved challenge. Current synthetic routes to N-acyl amidines usually rely on reactions of preformed primary amides with amino acetals or acylation of amidines with stoichiometric coupling reagents. A direct, atom-efficient synthetic strategy is thus desired.

N-Acyl amidines are a particularly interesting class of compounds. They are important substrates in a variety of medicines and have been used as precursors for cyclization reactions as ligands for catalysts and other molecular

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of new C-metallocarbenes and metallonitrenes for the catalytic formation of electronic assemblies, or as substrates for reductive alkylation. We therefore focused on developing a new method for the direct synthesis of N-acyl amidines via a one-pot multicomponent reaction.

Since our group is focusing on C−H activation using metallocarbenes and metallonitrenes for the catalytic formation of new C–C and C–N bonds, we considered that a related acyl nitrene transfer strategy could be useful for the synthesis of N-acyl amidines. However, realizing new strategies to convert acyl nitrenes in a selective manner is rather troublesome. While amides are among the most stable nitrogen-containing moieties, acyl nitrenes are intrinsically unstable. Even when bound to a metal, alkyl migration via the Curtius rearrangement generally rapidly leads to an isocyanate (Scheme 1, left). Hence, in the context of seeking protocols to couple acyl nitrenes to C-nucleophiles, such Curtius rearrangements are undesired and thus represent a selectivity problem, in particular for aliphatic acyl nitrenes. The barrier for this rearrangement is lower for aliphatic acyl nitrenes than for aromatic derivatives, and the intrinsic instability of aliphatic acyl azides makes them challenging to isolate and unsuitable for prolonged storage.

In addition to the intrinsic instability of acyl nitrenes, efficient formation of these reactive intermediates constitutes an additional challenge. Conventional precursors used for metallonitrene chemistry are iminiodinanes, haloamines, organic azides, and hydroxylamines, most of which are difficult to prepare and display poor solubility, require elevated temperatures to activate, or are associated with selectivity and sustainability issues. Cyclic nitrene precursors were recently shown to be efficient nitrene precursors, which are more practical. In particular, 1,4,2-dioxazol-5-ones are noteworthy acyl nitrene precursors in this perspective. They are stable until at least 100 °C, have a low activation barrier upon coordination to a metal, and produce only CO2 as a side product. They can be synthesized by two practical steps from acids, esters, or acyl chlorides. Although these properties have been known for over 50 years, this class of substrates only have become popular for applications in catalysis since the work of Bolm in 2014.

Still, the intrinsic instability of N-acyl metallonitrenes generated from these substrates is a major issue. Successful approaches to use N-acyl metallonitrenes in catalysis typically rely on directed C−H activation or generation of the acylnitrene on a metal center already containing a preactivated co-substrate.

Inspired by the work of Wang on copper-catalyzed carbene insertion into C–H bonds, we anticipated that acyl nitrenes could be coupled to terminal alkynes as a new type of C−N bond formation. We envisioned that the activation of 1,4,2-dioxazol-5-ones on copper acetylides could readily form an acyl nitrene on copper that should rapidly insert into the Cu−C bond to furnish a C−N bond, avoiding decomposition by the Curtius rearrangement and thus providing a direct route to acylated amidines (Scheme 1, right).

# RESULTS AND DISCUSSION

In an initial attempt to couple acyl nitrenes to acetylenes, we added dioxazolone 1a to a mixture of copper bromide, chloroform, phenylacetylene (2a), and diisopropylamine (3a). The yellow color, typical for copper acetylide complexes, slowly turned dark green upon addition of the dioxazolone. Analysis of the crude reaction mixture by mass spectrometry suggested that a three-component reaction had taken place.

H NMR analysis indeed confirmed the formation of the three-component reaction product 4aaa in 63% yield (Table 1). The reaction thus readily gives access to this N-acyl amidine. To optimize the reaction conditions, we explored the efficiency of the reaction using different Cu(I) catalysts and different solvents (ligands used in this study are shown in Figure 2). Most copper salts worked equally well (Table 1, entries 1–5). The [Cu(MeCN)4]⁺ salts appeared to work slightly better, which is commonly observed for copper-catalyzed reactions. We also employed some well-defined Cu(I)-ligand complexes, including complexes containing the Xanphos ligand (Xanphos = 4,5-bis(diphenylphosphino)-9,9-dimethyloxanthene) (Table 1, entries 6–11). Surprisingly, while most complexes perform poorly, [Cu(OAc)(Xanphos)] gave a very high selectivity. The reaction works well in a variety of different solvents under aerobic conditions at room temperature (Table 1, entries 12–19). Results obtained in toluene and ethyl acetate show that the reaction is selective in both polar and apolar solvents. In methanol and acetonitrile, the desired product was not observed, which is suggestive of catalyst inhibition by coordination of these solvents to copper. In tetrahydrofuran (THF), however, full conversion toward the product is observed. Excellent yield is obtained with 5 mol %
Yields are determined by 1H NMR spectroscopy in solvent (1 mL), stirred overnight in a closed 4 mL vial at room temperature. Further screening (see the SI) demonstrated that secondary amines are able to activate and decompose 1,4,2-dioxazol-5-ones, resulting in the urea (Scheme 2). This side reaction and the Curtius rearrangement catalyzed by an oxidized copper complex likely explain the decreased yields when using lower catalyst concentrations under aerobic conditions (Table 1, entries 21 and 22).

The copper-catalyzed three-component reaction produces only CO₂ as a byproduct. In view of the atom efficiency of the process, we tested the efficacy of this reaction with a lower ratio of phenylacetylene and diisopropylamine relative to the dioxazolone substrate (see the SI).

The use of fewer equivalents of acetylene has a larger effect on the yield than lowering the amount of diisopropylamine (56% and 84% yield, respectively). When one equivalent of all reactants was used, we still obtained 70% of the N-acyl amide. It should be noted that a lower yield is obtained when using just one equivalent of phenylacetylene in combination with a higher concentration of diisopropylamine. This indicates that fast formation of a copper acetylide species is important and that this process must outcompete the diisopropylamine-assisted decomposition of the dioxazolone to obtain high yields of the desired N-acyl amide.

**Scope of the (Xantphos)Cu-Catalyzed Reaction.** The catalytic reaction is not limited to the use of phenylethyl dioxazolone 1a (Table 2) and actually has a relatively large substrate scope. Longer dioxazolone substrates can be used without a decrease in yield (4baa−4daa), and double bonds are tolerated as well (4eaa). The yield dropped significantly for benzyl dioxazolone 1f and cyclohexyl dioxazolone 1g. Presumably, slower activation of the bulkier substrates on the copper acetylide species leads to faster aerobic decomposition of the catalyst. The fact that under an atmosphere of N₂ products 4faa and 4gaa are obtained in good yields supports this hypothesis. An oxygen atom at the β-position of the dioxazolone is deleterious for the yield, as 62% of urea 5aa was obtained when 1i was used. We suspect that this is the result of chelation of the substrate or product to copper, inhibiting the formation of the acetylide on the metal. A first attempt to apply para-toly acetylene as a terminal alkyne in the copper-catalyzed three-component reaction yielded only 35% of N-acyl amide 4aba. However, again under a protective atmosphere of nitrogen we observed high yields of the desired product (see Table 2). Para-, meta-, and ortho-tolyl acetylene all gave a similar high yield, suggesting a negligible influence of steric at the acetylene (4aba−4ada). The electron-rich 4-ethyl anisole gave slightly lower yields (4eaa), which could be related to the lower acidity of the acetylene C=H bond, thus leading to less efficient formation of the copper acetylide complex. When using an alkyl acetylene (2j), which is even less acidic, product 4aja was not observed. Electron-withdrawal phenyl acetylenes, on the other hand, were converted with high catalytic efficiency (4bna−4gna).

The reaction intermediates could inhibit catalysis. Indeed, performing the reactions under an N₂ atmosphere led to high yields of the product (Table 1, entries 12, 21, and 25). Surprisingly, in the absence of a catalyst but in the presence of amine 3a full conversion of dioxazolone 1a to urea 5aa was observed at room temperature.

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**Table 1. Optimization of Reaction Conditions**

<table>
<thead>
<tr>
<th>no.</th>
<th>catalyst (mol % Cu)</th>
<th>solvent</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CuCl (10)</td>
<td>CHCl₃</td>
<td>55</td>
</tr>
<tr>
<td>2</td>
<td>CuBr (10)</td>
<td>CHCl₃</td>
<td>63</td>
</tr>
<tr>
<td>3</td>
<td>Cu (10)</td>
<td>CHCl₃</td>
<td>62</td>
</tr>
<tr>
<td>4</td>
<td>[Cu(NCMe)₃]BF₄ (10)</td>
<td>CHCl₃</td>
<td>65</td>
</tr>
<tr>
<td>5</td>
<td>[Cu(NCMe)₃]PF₆ (10)</td>
<td>CHCl₃</td>
<td>75</td>
</tr>
<tr>
<td>6</td>
<td>[Cu(TpBr₃)(NCMe)] (10)</td>
<td>CHCl₃</td>
<td>5</td>
</tr>
<tr>
<td>7</td>
<td>[Cu(TpMe₃)(THF)] (10)</td>
<td>CHCl₃</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>[CuCl(lpr)] (10)</td>
<td>CHCl₃</td>
<td>37</td>
</tr>
<tr>
<td>9</td>
<td>[Cu(lpr)(Xantphos)] (10)</td>
<td>CHCl₃</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>[Cu(OAc)(Xantphos)] (10)</td>
<td>CHCl₃</td>
<td>98</td>
</tr>
<tr>
<td>11</td>
<td>[Cu(NCMe)₃(Xantphos)]BF₄ (10)</td>
<td>CHCl₃</td>
<td>72</td>
</tr>
<tr>
<td>12</td>
<td>[Cu(OAc)(Xantphos)] (10)</td>
<td>DCM</td>
<td>58 (97%)</td>
</tr>
<tr>
<td>13</td>
<td>[Cu(OAc)(Xantphos)] (10)</td>
<td>THF</td>
<td>95</td>
</tr>
<tr>
<td>14</td>
<td>[Cu(OAc)(Xantphos)] (10)</td>
<td>EtOAc</td>
<td>92</td>
</tr>
<tr>
<td>15</td>
<td>[Cu(OAc)(Xantphos)] (10)</td>
<td>DCE</td>
<td>74</td>
</tr>
<tr>
<td>16</td>
<td>[Cu(OAc)(Xantphos)] (10)</td>
<td>toluene</td>
<td>93</td>
</tr>
<tr>
<td>17</td>
<td>[Cu(OAc)(Xantphos)] (5)</td>
<td>CHCl₃</td>
<td>97</td>
</tr>
<tr>
<td>18</td>
<td>[Cu(OAc)(Xantphos)] (2)</td>
<td>CHCl₃</td>
<td>43 (94%)</td>
</tr>
<tr>
<td>19</td>
<td>[Cu(OAc)(Xantphos)] (1)</td>
<td>CHCl₃</td>
<td>10 (19%)</td>
</tr>
<tr>
<td>20</td>
<td>[Cu(OAc)(Xantphos)] (0.5)</td>
<td>CHCl₃</td>
<td>0</td>
</tr>
<tr>
<td>21</td>
<td>[Cu(OAc)(Xantphos)] (0.1)</td>
<td>CHCl₃</td>
<td>0</td>
</tr>
<tr>
<td>22</td>
<td>[Cu(OAc)(Xantphos)] (5)</td>
<td>CHCl₃</td>
<td>0 (98%)</td>
</tr>
<tr>
<td>23</td>
<td>[Cu(OAc)] + dppe (5)</td>
<td>CHCl₃</td>
<td>74%</td>
</tr>
<tr>
<td>24</td>
<td>[Cu(OAc)] + 2 PPh₃ (5)</td>
<td>CHCl₃</td>
<td>82%</td>
</tr>
</tbody>
</table>

"Reaction of 1a (0.5 mmol), 2a (2 equiv), 3a (2 equiv), and catalyst in solvent (1 mL), stirred overnight in a closed 4 mL vial at room temperature in air. Yields are determined by 1H NMR spectroscopy with 1,3,5-trimethoxybenzene as external standard. "Reactions performed in a N₂-filled glovebox. "10 mL of chloroform was used.

---

**Scheme 2. Desired Catalyzed Reaction vs the Uncatalyzed Side Reaction (Urea Formation)**

The use of fewer equivalents of acetylene has a larger effect on the yield than lowering the amount of diisopropylamine (56% and 84% yield, respectively). When one equivalent of all reactants was used, we still obtained 70% of the N-acyl amide. It should be noted that a lower yield is obtained when using just one equivalent of phenylacetylene in combination with a higher concentration of diisopropylamine. This indicates that fast formation of a copper acetylide species is important and that this process must outcompete the diisopropylamine-assisted decomposition of the dioxazolone to obtain high yields of the desired N-acyl amide.

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**Figure 2. Ligands used in this work.**

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**Catalyst Loading** (or more), but the yield drops with lower catalyst loadings (Table 1, entries 20−24). Notably, when the reaction is diluted 10 times, formation of the product 4aaaa was not observed (Table 1, entry 25). Instead, 1,1-diisopropyl-3-phenylethurea compound 5aa was formed, indicating a Curtius rearrangement of the acyl nitrene. Replacing the Xanthpos ligand by 1,2-bis(diphenylphosphino)ethane (dppe) or 2 equiv of PPh₃ results in a decreased yield of 4aaaa (Table 1, entries 26 and 27).

We hypothesized that aerobic oxidation of one or more reaction intermediates could inhibit catalysis. Indeed, performing the reactions under an N₂ atmosphere led to high yields of the product (Table 1, entries 12, 21, and 25). Surprisingly, in
operating efficiency (4afa–4aga). Even the use of the heteroaromatic acetylenes 3-ethynylpyridine and 3-ethynylthiophene resulted in efficient formation of the desired products 4aha and 4aja (79% and 98%, respectively).

Next, we explored the scope of using different amines as coupling partners in reactions catalyzed by [Cu(OAc)](Xantphos) (Table 3). We initially were disappointed to see that benzylamine, isopropylamine, and diethylamine did not yield any N-acyl amidine (3b–3d). Dicyclohexylamine (3h), however, did show a very high yield for the formation of the desired product. We hypothesized that the less bulky amines might coordinate too strongly to the copper atom and compete with coordination of the dioxazolone and thereby inhibit the reaction. To verify our assumption, we further explored the effect of changing the steric bulk of the amine. Indeed, the less bulky amines N-ethylisopropylamine (3e) and N-methyl-tert-butylamine (3g) do not result in any desired product formation, while the bulkier amine N-ethyl-tert-butylamine (3f) produced the desired product 4aag in high yield (96%). The change from 3f to 3g might seem abrupt, but note that in amine 3g the ethyl group is pushed away from the tert-butyl group when coordinated to Cu(I), thus making it much bulkier and hence a weaker donor. The combined results suggest that smaller amines poison the catalyst, while the bulkier amines fit poorly in the “Xantphos pocket”, resulting in negligible catalyst inhibition and thus a high product yield (see Figure 3). Upon increasing the steric bulk of the amine further, i.e., employing 2,2,6,6-tetramethylpiperidine (3i) as nucleophile, we observed formation of the desired product as the enamine tautomer (4aai, see the SI).

Mechanistic Investigations. To gain more information about the reaction mechanism, we studied the formation of copper species with 31P NMR spectroscopy, investigated the kinetics of the reaction, and performed supporting density functional theory (DFT) studies.

Table 2. Scope of the [Cu(OAc)(Xantphos)]-Catalyzed Three-Component Reaction

<table>
<thead>
<tr>
<th>Reaction of</th>
<th>Isolated Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1x (0.5 mmol), 2y (2 equiv), 3a (2 equiv), and [Cu(OAc)(Xantphos)] (5 mol %) in CHCl3 (1 mL), stirred for 10 min in a closed 4 mL vial at room temperature</td>
<td>4aaa 97%</td>
</tr>
<tr>
<td>[Cu(OAc)(Xantphos)] (5 mol %) in CHCl3 (1 mL), stirred for 10 min in a closed 4 mL vial at room temperature</td>
<td>4aaa 96%</td>
</tr>
<tr>
<td>[Cu(OAc)(Xantphos)] (5 mol %) in CHCl3 (1 mL), stirred for 10 min in a closed 4 mL vial at room temperature</td>
<td>4aaa 92%</td>
</tr>
<tr>
<td>[Cu(OAc)(Xantphos)] (5 mol %) in CHCl3 (1 mL), stirred for 10 min in a closed 4 mL vial at room temperature</td>
<td>4aaa 88%</td>
</tr>
<tr>
<td>[Cu(OAc)(Xantphos)] (5 mol %) in CHCl3 (1 mL), stirred for 10 min in a closed 4 mL vial at room temperature</td>
<td>4aaa 79%</td>
</tr>
<tr>
<td>1H NMR with 1,3,5-trimethoxybenzene as internal standard</td>
<td>4aaa 92%</td>
</tr>
</tbody>
</table>

aReaction of 1a (0.5 mmol), 2a (2 equiv), 3e (2 equiv), and [Cu(OAc)(Xantphos)] (5 mol %) in CHCl3 (1 mL), stirred for 10 min in a closed 4 mL vial at rt. Isolated yields for 4aae are given. bPerformed under an N2 atmosphere. cQuantitative formation of product according to 1H NMR with 1,3,5-trimethoxybenzene as internal standard. dThe urea was formed as the main product.

Table 3. Scope of Amines Used for the [Cu(OAc)(Xantphos)]-Catalyzed Three-Component Reaction

<table>
<thead>
<tr>
<th>Reaction of</th>
<th>Isolated Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a + 2a + 3z [Cu(OAc)(Xantphos)] (5 mol %) in CHCl3 (1 mL), stirred for 10 min in a closed 4 mL vial at rt.</td>
<td>4aae 79%</td>
</tr>
<tr>
<td>1a + 2a + 3z [Cu(OAc)(Xantphos)] (5 mol %) in CHCl3 (1 mL), stirred for 10 min in a closed 4 mL vial at rt.</td>
<td>4aae 95%</td>
</tr>
<tr>
<td>1a + 2a + 3z [Cu(OAc)(Xantphos)] (5 mol %) in CHCl3 (1 mL), stirred for 10 min in a closed 4 mL vial at rt.</td>
<td>4aae 84%</td>
</tr>
<tr>
<td>1a + 2a + 3z [Cu(OAc)(Xantphos)] (5 mol %) in CHCl3 (1 mL), stirred for 10 min in a closed 4 mL vial at rt.</td>
<td>4aae 90%</td>
</tr>
<tr>
<td>1a + 2a + 3z [Cu(OAc)(Xantphos)] (5 mol %) in CHCl3 (1 mL), stirred for 10 min in a closed 4 mL vial at rt.</td>
<td>4aae 0%</td>
</tr>
<tr>
<td>1a + 2a + 3z [Cu(OAc)(Xantphos)] (5 mol %) in CHCl3 (1 mL), stirred for 10 min in a closed 4 mL vial at rt.</td>
<td>4aae 0%</td>
</tr>
</tbody>
</table>

aReaction of 1a (0.5 mmol), 2a (2 equiv), 3e (2 equiv), and [Cu(OAc)(Xantphos)] (5 mol %) in CHCl3 (1 mL), stirred for 10 min in a closed 4 mL vial at rt. Isolated yields for 4aae are given. bA tautomer (enamine) was isolated.

Figure 3. Proposed catalyst poisoning by small amine substrates.
both reactants were added to the solution of [Cu(OAc)(Xantphos)] in CDCl3 in air, a new signal was observed at δ = +29 ppm, which corresponds to Xantphos-P-dioxide, and a small broad peak at δ = −13 ppm emerged as well (Figure 4D).

Under an N2 atmosphere, we did not observe ligand oxidation and detected a new singlet at δ = −15 ppm, along with a signal at δ = −19 ppm corresponding to free Xantphos (Figure 4E). Coordination of Xantphos to copper acetylide or salt metathesis of [CuCl(Xantphos)] with lithium phenylacetylide (Figure 4F) led to the same 31P NMR signal at δ = −15 ppm, supporting the formation of [Cu(CCPh)(Xantphos)]. Rapid formation of copper acetylide complex [Cu(CCPh)(Xantphos)] upon addition of a base to a reaction mixture containing both [Cu(OAc)(Xantphos)] and phenylacetylene is further associated with a characteristic color change from colorless to bright yellow. The influence of air on the yield of the catalytic reactions in the case of lower catalyst loadings or when sterically more demanding dioxazolones are used implies that [Cu(CCPh)(Xantphos)] reacts with water or dioxygen from air.

Together with the formation of the acetylide complex, we could always observe a broad peak at δ = −13 ppm and free Xantphos, which might result from clustering of copper species. Dimers could be observed in mass spectrometry, and indication for the formation of [Cu(CCCp)(Xantphos)] species was obtained by single-crystal X-ray diffraction (low-quality data set; see the SI for a connectivity plot).

To get more insight into the reaction mechanism, we investigated the kinetics of the reaction, following the pressure buildup caused by CO2 release during the reaction in a dedicated closed system as a measure of the substrate conversion over time. The observed rates are plotted as a function of the concentrations of the catalyst and each of the substrates 1a, 2a, and 3a (Figure 5A–D).

The reaction is clearly first order in both [catalyst] and [dioxazolone] and (nearly) zero order in [iPr2NH]. The rate dependence of [PhCCH] (Figure 5C) is more complex and suggestive of saturation kinetics. This behavior is most likely caused by a (slightly endergonic) pre-equilibrium between [Cu(OAc)(Xantphos)] and [Cu(CCPh)(Xantphos)]. The
existence of such an equilibrium could be confirmed by H/D exchange studies. Burk and co-workers showed with H/D scrambling that copper acetates and copper acetylides are in fast equilibrium.90 In a similar experiment, using [Cu(OAc)-(Xantphos)] as the catalyst, we also observed H/D scrambling of phenylacetylene-D and 4-CF3-phenylacetylene (see the SI for details). Combined with the 31P NMR studies shown in Figure 4 and the small effect of [iPr2NH] on the rate, the data suggest that this pre-equilibrium shifts toward the acetylide complex in the presence of the amine.

From the catalyst screening studies presented in Table 1, it is clear that the “unsaturated” [Cu(NCMe)2(Xantphos)]BF4 complex is less selective than [Cu(OAc)(Xantphos)] for the formation of the N-acyl amidine, indeed confirming that the acetate plays a prominent role in the catalytic cycle. When comparing the conversion over time between the reaction catalyzed by [Cu(OAc)(Xantphos)] and the [Cu-(NCMe)2(Xantphos)]BF4 (Figure 5E), we observed a very large difference in rate, confirming that the acetate is important for rapid formation of the acetylide complex.91 In fact, the X-ray structure of the [Cu(OAc)(Xantphos)]-HCCPh adduct, obtained by crystallization of [Cu(OAc)(Xantphos)] in the presence of an excess of phenylacetylene, reveals a direct hydrogen-bonding (H-bonding) interaction between the copper-bound κ2-acetate fragment and the acidic proton of the acetylene (Figure 5F).

Further mechanistic information was obtained using DFT calculations (Figure 6, see the SI for details). While rapid formation of acetylide complex B was observed experimentally during the NMR studies, DFT calculations show that the acetylene activation pre-equilibrium step is endergonic by about +3 kcal/mol. This small discrepancy is likely a medium effect, a result of the reaction being performed under nonstandard concentration conditions or a combination thereof.92 N-Coordination and subsequent activation of the dioxazolone substrate on the Cu center, leading to CO2 dissociation, over TS1 produces acyl nitrene acetylide intermediate D. Interestingly, two possible transition states need to be considered for the C–N bond formation step, involving acyl nitrene insertion into the Cu–C bond of the acetylide fragment. In TS2-1, the acyl nitrene is κ1-N coordinated and C–N coupling leads to a η1-N coordination of the amide moiety. In TS2-2, the acyl nitrene coordinates in a κ2-N,O fashion and C–N bond formation leads to a chelating coordination of the carbonyl and the triple bond.

The transition state barriers of these processes (from D) are very similar (∼7.5 kcal mol⁻¹). The resulting intermediates, E for TS2-1 and F for TS2-2, are different by only 3.5 kcal/mol and connected by a low energy barrier transition state TS3 and thus can both be present during the reaction. The undesired Curtius rearrangement from intermediate D was calculated to be ∼3 kcal higher in energy than TS2-1 and TS2-2, which is in line with the experimental observations (see the SI for further details). For the protodemetalation of the vinylideneamide by an incoming equivalent of acetylene, acetic acid, or even diisopropylamine, many pathways can be considered from either E or F. The protodemetalation was therefore not included in the DFT studies.

The combined information gathered from the catalytic studies and the mechanistic investigations led us to the proposed catalytic cycle shown in Scheme 3. The reaction sequence involves activation of acetylene 2a by complex A to form acetylide complex B, most likely assisted by the amine.

Scheme 3. Proposed Catalytic Cycle
Electron-rich as well as electron-poor aryl dioxazolones (4jaa, 4kaa). The reaction still seems to be affected by steric, but o-phenyl dioxazolone still produced 4laa in 34% isolated yield.

**CONCLUSION**

In this work we have presented a new, fast, efficient, and practical three-component reaction of an acyl nitrene precursor catalyzed by copper to produce N-acylamidines and benzoyl amidines. To the best of our knowledge, this is the first reported catalytic procedure to synthesize these types of products. This atom-efficient reaction uses dioxazolone substrates that are easily accessible and only generates CO₂ byproduct under mild conditions, making this an attractive methodology for both small- and large-scale organic synthesis.

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(92) When one equivalent of both iPr₂NH and PhCCH were used compared to [(Xantphos)Cu(OAc)], under identical reaction conditions, we did not observe the conversion of this complex (see the SI).