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

Kaj M. van Vliet,[†] Lara H. Polak,[†] Maxime A. Siegler,[‡] Jarl Ivar van der Vlugt,[†] Célia Fonseca Guerra,[§,‖] and Bas de Bruin*,[†]

†Homogeneous, Supramolecular and Bio-inspired Catalysis Group (HomKat), van 't Hoff Institute for Molecular Sciences (HIMS), Universiteit van Amsterdam (UvA), Amsterdam 1012 WX, The Netherlands
‡Department of Chemistry, John Hopkins University, Baltimore, Maryland 21218, United States
§Department of Theoretical Chemistry and Amsterdam Center for Multiscale Modeling, Vrije Universiteit Amsterdam (VU), De Boelelaan 1083, 1081 HV Amsterdam, The Netherlands
‖Leiden Institute of Chemistry, Gorlaeus Laboratories, Úniversiteit Leiden, Einsteinweg 55, 2333 CC Leiden, The Netherlands

Ⓢ *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 CO_2 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 amidine 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.
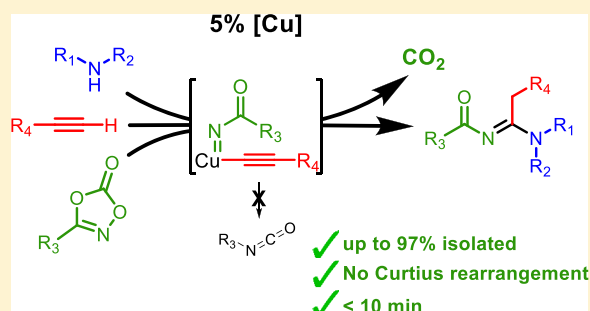
■ INTRODUCTION

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,[1] and more complex amidines are even considered to be "superbases".[2] Amidines also have been used as ligands for organometallic complexes[3] and as starting material for the synthesis of *N*-heterocycles.[4−10] The structure itself is present in various natural products and biologically active compounds such as janoxepin, pentamidine, and sildenafil (see Figure 1).[11,12]

Multiple methods exist for the synthesis of amidines in general, including the Pinner reaction,[13] substitution of phenoxyimidates,[14] Beckman-type rearrangements,[15] and dehydrogenative coupling reactions,[16,17] or by catalysis with palladium[14,18−21] or nickel,[22] as well as some multicomponent reactions.[23−33] Chang developed strategies for the synthesis of sulfonated and phosphorylated amidines via traditional click chemistry with azides, followed by a thermal N₂ exclusion, resulting in a net coupling of a nitrene to an alkyne.[29,34−45]

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.[45,46] Nicasio and Pérez showed that a copper-catalyzed reaction of acetylenes with *N*-aroyl or *N*-acyl azides produces triazoles or oxazoles instead of *N*-acyl amidines.[47,48] 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 premade primary amides with amino acetals[49] or acylation of amidines with stoichiometric coupling reagents.[50−52] A direct, atom-efficient synthetic strategy is thus desired.

N-Acyl amidines are a particularly interesting class of compounds. They are important substructures in a variety of medicines[53,54] and have been used as precursors for cyclization reactions,[50,53] as ligands for catalysts and other molecular
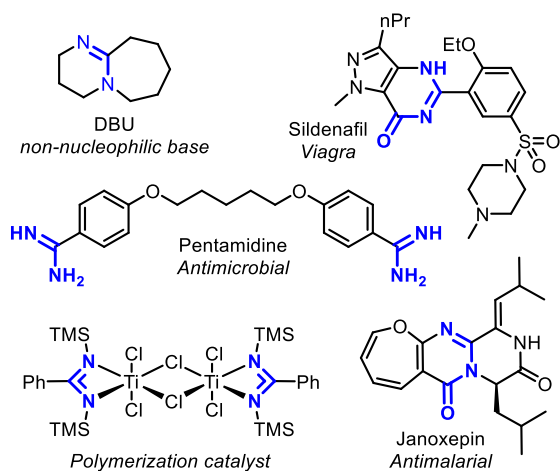
Figure 1. Several amidine compounds and their applications.

assemblies,[54] or as substrates for reductive alkylation.[55] 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,[56−62] 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).[63−65] Hence, in the context of seeking

Scheme 1. Acyl Nitrene Formation from 1,4,2-Dioxazol-5-ones, Followed by an Undesired Metal-Induced Curtius Rearrangement (Left) versus Desired Nitrene Insertion into an M−C$_{acetylide}$ Bond (Right)
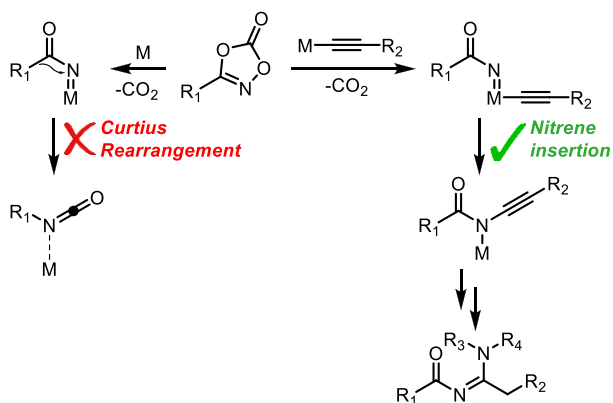
protocols to couple acyl nitrenes to *C*-nucleophiles, such Curtius rearrangements are undesired and thus represent a selectivity problem, in particular for aliphatic acyl nitrenes. The barrier for this rearrangement is lower for aliphatic acyl nitrenes than for aromatic derivatives, and the intrinsic 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 iminoiodinanes, haloamines, organic azides, and hydroxylamines,[66] 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,[67] 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 CO_2 as a side product.[68] They can be synthesized by two practical steps from acids, esters, or acyl chlorides.[69] 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.[70]
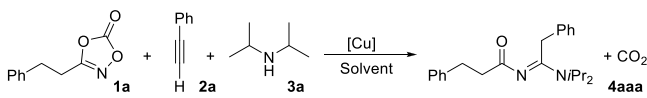
Still, the intrinsic instability of *N*-acyl metallonitrenes generated from these substrates is a major issue. Successful approaches to use *N*-acyl metallonitrenes in catalysis typically rely on directed C−H activation or generation of the acylnitrene on a metal center already containing a preactivated co-substrate.[71−77]

Inspired by the work of Wang on copper-catalyzed *carbene* insertion into C−H bonds,[82] 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.

^{1}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.[83] We also employed some well-defined Cu(I)-ligand complexes, including complexes containing the Xantphos ligand (Xantphos = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene) (Table 1, entries 6−11).[84−86] Surprisingly, while most complexes perform poorly, [Cu(OAc)(Xantphos)] 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 %

Table 1. Optimization of Reaction Conditions[a]

no.	catalyst (mol % Cu)	solvent	yield (%)
1	CuCl (10)	CHCl$_3$	55
2	CuBr (10)	CHCl$_3$	63
3	CuI (10)	CHCl$_3$	62
4	[Cu(NCMe)$_4$]BF$_4$ (10)	CHCl$_3$	65
5	[Cu(NCMe)$_4$]PF$_6$ (10)	CHCl$_3$	75
6	[Cu(TpBr$_3$)(NCMe)] (10)	CHCl$_3$	5
7	[Cu(TpMs)(THF)] (10)	CHCl$_3$	0
8	[CuCl(IPr)] (10)	CHCl$_3$	37
9	[CuI(Xantphos)] (10)	CHCl$_3$	0
10	[Cu(OAc)(Xantphos)] (10)	CHCl$_3$	98
11	[Cu(NCMe)$_2$(Xantphos)]BF$_4$ (10)	CHCl$_3$	72
12	[Cu(OAc)(Xantphos)] (10)	DCM	58 (97%[b])
13	[Cu(OAc)(Xantphos)] (10)	THF	95
15	[Cu(OAc)(Xantphos)] (10)	EtOAC	92
17	[Cu(OAc)(Xantphos)] (10)	DCE	74
19	[Cu(OAc)(Xantphos)] (10)	toluene	93
20	[Cu(OAc)(Xantphos)] (5)	CHCl$_3$	97
21	[Cu(OAc)(Xantphos)] (2)	CHCl$_3$	43 (94%[b])
22	[Cu(OAc)(Xantphos)] (1)	CHCl$_3$	10 (19%[b])
23	[Cu(OAc)(Xantphos)] (0.5)	CHCl$_3$	0
24	[Cu(OAc)(Xantphos)] (0.1)	CHCl$_3$	0
25[c]	[Cu(OAc)(Xantphos)] (5)	CHCl$_3$	0 (98%[b])
26	[Cu(OAc)] + dppe (5)	CHCl$_3$	74%[b]
27	[Cu(OAc)] + 2 PPh$_3$ (5)	CHCl$_3$	82%[b]

[a]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 ^{1}H NMR spectroscopy with 1,3,5-trimethoxybenzene as external standard. [b]Reactions performed in a N$_2$-filled glovebox. [c]10 mL of chloroform was used.
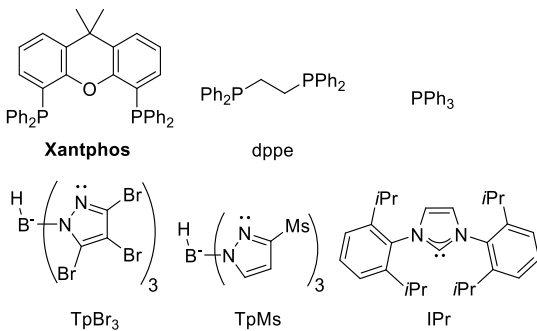

Figure 2. Ligands used in this work.

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 **4aaa** was not observed (Table 1, entry 25). Instead, 1,1-diisopropyl-3-phenethylurea compound **5aa** was formed, indicating a Curtius rearrangement of the acyl nitrene. Replacing the Xantphos ligand by 1,2-bis(diphenylphosphino)ethane (dppe) or 2 equiv of PPh$_3$ results in a decreased yield of **4aaa** (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 N$_2$ 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. 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

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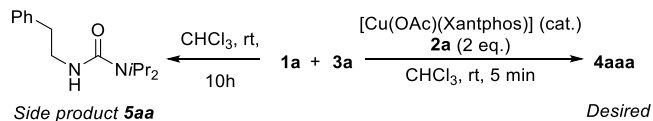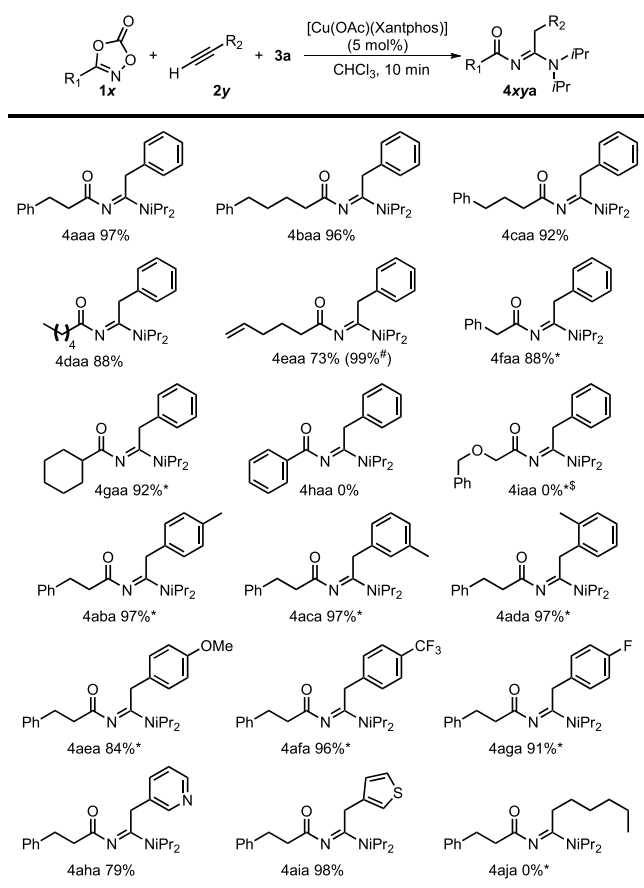

catalyzed by an oxidized copper complex likely explain the decreased yields when using lower catalyst concentrations under aerobic conditions (Table 1, entries 21 and 22).

The copper-catalyzed three-component reaction produces only CO$_2$ 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 amidine. 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 amidine.

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 N$_2$ products **4faa** and **4gaa** are obtained in good yields supports that hypothesis. An oxygen atom at the β-position of the dioxazolone is deleterious for the yield, as 62% of urea **5ia** 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-tolyl acetylene as a terminal alkyne in the copper-catalyzed three-component reaction yielded only 35% of N-acyl amidine **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 sterics at the acetylene (**4aba−4ada**). The electron-rich 4-ethynyl anisole gave slightly lower yields (**4aea**), 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-withdrawing phenyl acetylenes, on the other hand, were converted with high

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

4aaa 97%   4baa 96%   4caa 92%

4daa 88%   4eaa 73% (99%[#])   4faa 88%*

4gaa 92%*   4haa 0%   4iaa 0%*[$]

4aba 97%*   4aca 97%*   4ada 97%*

4aea 84%*   4afa 96%*   4aga 91%*

4aha 79%   4aia 98%   4aja 0%*

[a]Reaction of **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. Isolated yields are given. *Performed under an N₂ atmosphere. [#]Quantitative formation of product according to ¹H NMR with 1,3,5-trimethoxybenzene as internal standard. [$]The urea was formed as the main product.

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 **3f** do not result in any desired product formation, while the bulkier amine N-ethyl-*tert*-butylamine **3g** 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

Table 3. Scope of Amines Used for the [Cu(OAc)(Xantphos)]-Catalyzed Three-Component Reaction[a]
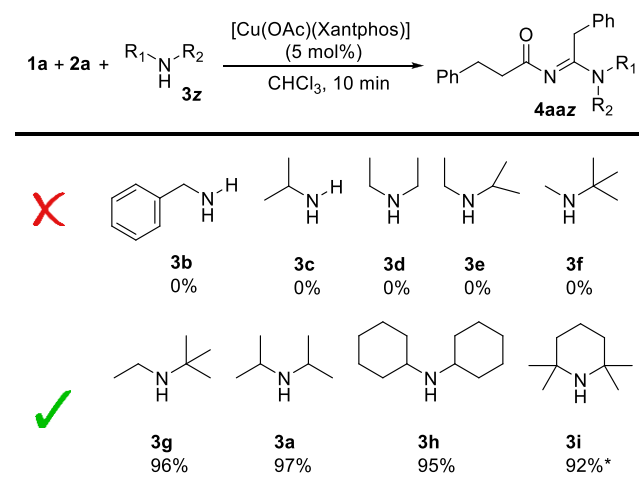
[a]Reaction of **1a** (0.5 mmol), **2a** (2 equiv), **3z** (2 equiv), and [Cu(OAc)(Xantphos)] (5 mol %) in CHCl₃ (1 mL), stirred for 10 min in a closed 4 mL vial at rt. Isolated yields for **4aaz** are given. *A tautomer (enamine) was isolated.

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
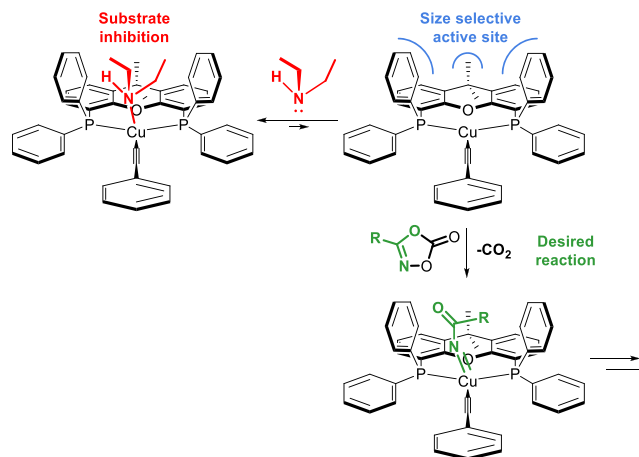
Figure 3. Proposed catalyst poisoning by small amine substrates.

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.

We used ³¹P NMR spectroscopy to study the formation of [Cu(CCPh)(Xantphos)] under optimized reaction conditions, both in air and under a nitrogen atmosphere. [Cu(OAc)-(Xantphos)] in CDCl₃ gave a ³¹P NMR signal at $\delta = -17$ ppm (Figure 4A), which remained unchanged upon addition of phenylacetylene *or* diisopropylamine (Figure 4B/C). When
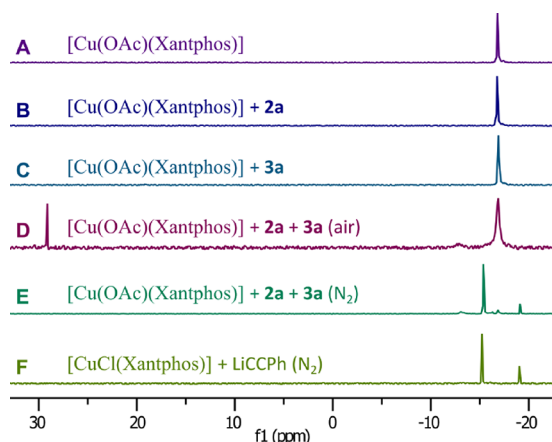
Figure 4. ^{31}P NMR studies on the formation of [Cu(CCPh)(Xantphos)]. ^{31}P NMR spectra measured under an N_2 atmosphere in CDCl$_3$. (A) [Cu(OAc)(Xantphos)]; (B) [Cu(OAc)(Xantphos)] with 40 equiv of phenylacetylene; (C) [Cu(OAc)(Xantphos)] with 40 equiv of iPr$_2$NH; [Cu(OAc)(Xantphos)] with 40 equiv of both phenylacetylene and iPr$_2$NH under (D) air or (E) N$_2$; (F) [Cu(CCPh)(Xantphos)] formed from salt metathesis from [CuCl-(Xantphos)] and lithium phenylacetylide.

both reactants were added to the solution of [Cu(OAc)-(Xantphos)] in CDCl$_3$ 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 N$_2$ 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 ^{31}P 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.[87] 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$_3$(CCPh)$_3$(Xantphos)$_2$] 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 CO$_2$ release during the reaction in a dedicated closed system as a measure of the substrate conversion over time.[88,89] 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 [iPr$_2$NH]. 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
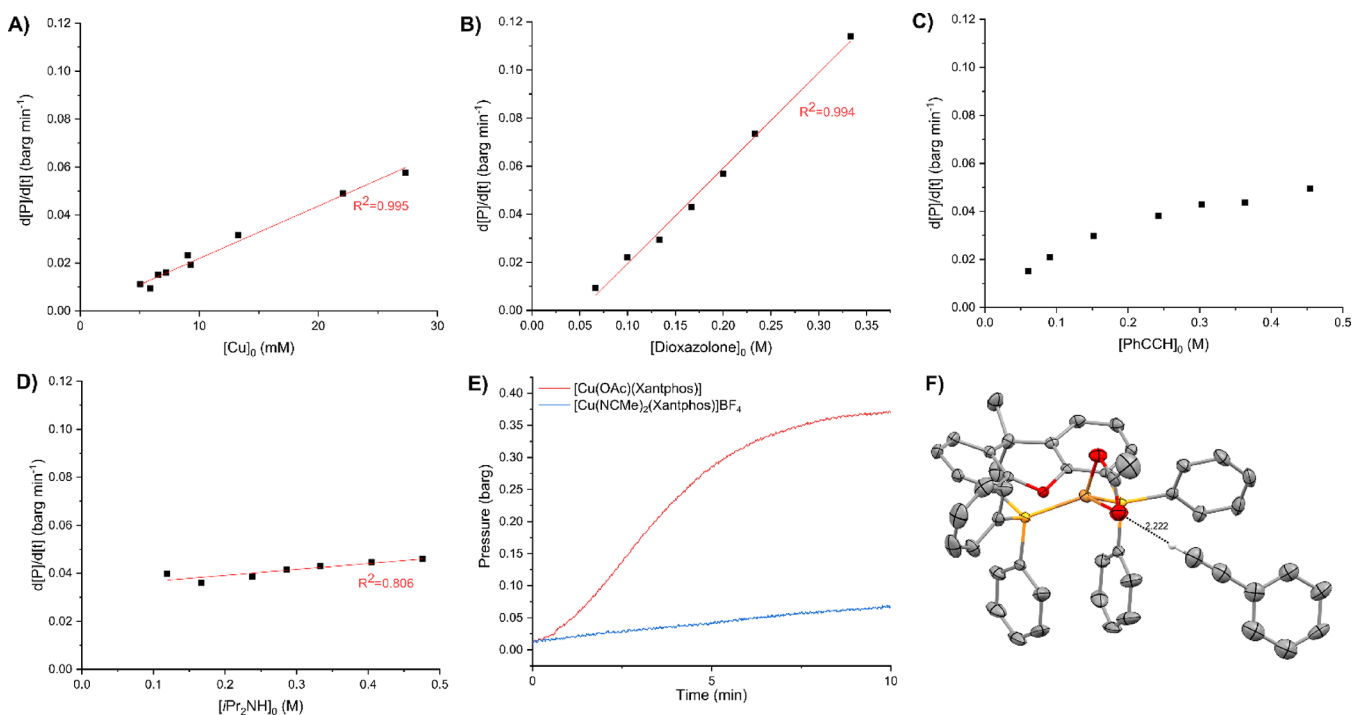

Figure 5. Kinetic experiments and X-ray structure of the catalyst interacting with phenyl acetylene. We varied the concentration of the catalyst and all three substrates and calculated the slope of the steepest part in the graph as the reaction rate. These rates have been plotted over the related concentration to give graphs **A**, **B**, **C**, and **D**. Graph **E** shows the pressure during the reaction toward **4aaa** for [Cu(OAc)(Xantphos)] (red) and [Cu(NCMe)$_2$(Xantphos)]BF$_4$ (blue). **F** shows the crystal structure obtained by crystallization in the presence of acetylene, showing a H-bonding interaction with the acetate.
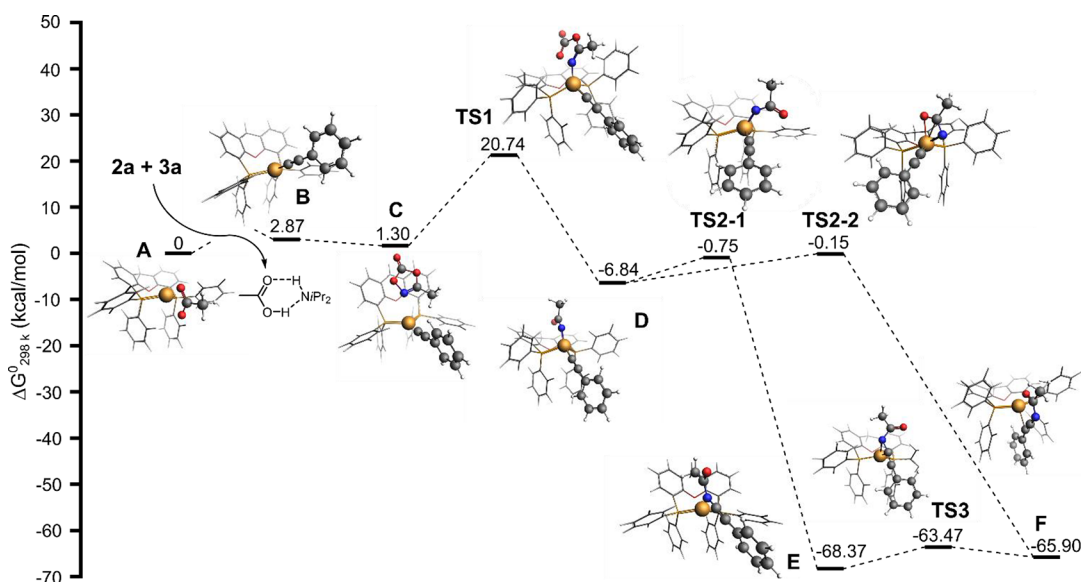
Figure 6. DFT (B3LYP-D3-TZ2P)-computed energies of the acyl nitrene activation and insertion.

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-CF_3-phenylacetylene (see the SI for details). Combined with the ^{31}P NMR studies shown in Figure 4 and the small effect of [iPr$_2$NH] 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)]BF$_4$ 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)]BF$_4$ (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 κ^2-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 CO_2 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 κ^1-N

coordinated and C−N coupling leads to a η^1-N coordination of the amide moiety. In **TS2-2**, the acyl nitrene coordinates in a κ^2-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
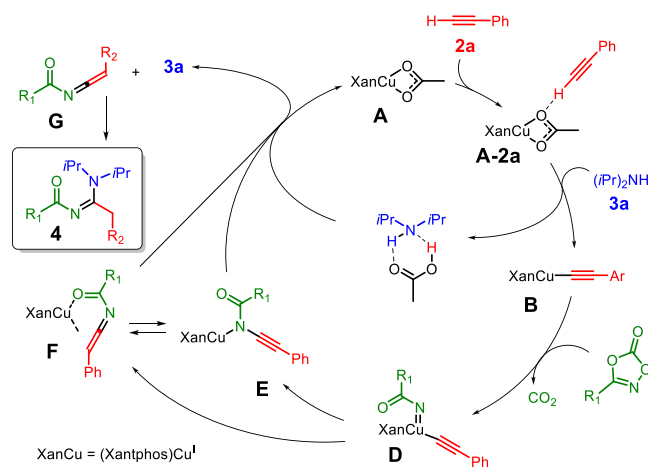
Subsequently, **B** activates the dioxazolone to form acyl nitrene intermediate **D**, which leads to either **E** or **F**, followed by protodemetalation to regenerate **A** and to form vinyl-ideneamide **G**. Finally, reaction of the amine with the electrophilic intermediate **G** produces the *N*-acylamidine product **4**.

Expanding the Scope to Benzoyl Amidines Using CuI.

As shown in Table 2, phenyl dioxazolone **1h** is not converted by [Cu(OAc)(Xantphos)], thus preventing the one-pot three-component synthesis of benzoyl amidines when using this catalyst. However, we argued that it might well be possible to expand the substrate scope of the newly discovered one-pot Cu-catalyzed three-component reaction from alkyl dioxazoles to aryl dioxazolones if we would use a less bulky Cu catalyst. Such reactions are desirable, as (just like for N-acyl amidines) there are currently no practical or high-yielding reactions available for the efficient one-pot (multicomponent) synthesis of benzoyl amidines. Sharpless and Chang published a method to synthesize the corresponding amidine from a benzoyl azide, but the desired compound was obtained in only very low yield (9% based on ^{1}H NMR spectroscopy).[44] Hence, we considered that it remained important to develop new catalytic methods to convert aryl dioxazolones to benzoyl amidines. Therefore, we decided to investigate the reactivity of less bulky, phosphine-free copper salts in reactions using these substrates. Gratifyingly, CuI proved to be a suitable catalyst to extend the protocol to the synthesis of *N*-benzoyl amidine derivatives. Using 10 mol % of CuI as the catalyst and phenyl dioxazolone as the substrate yielded the desired product in 68% isolated yield (see Table 4). This method works for

Table 4. Synthesis of *N*-Benzoyl Amidines from Aryl-1,4,2-dioxazol-5-ones Catalyzed by CuI[a]
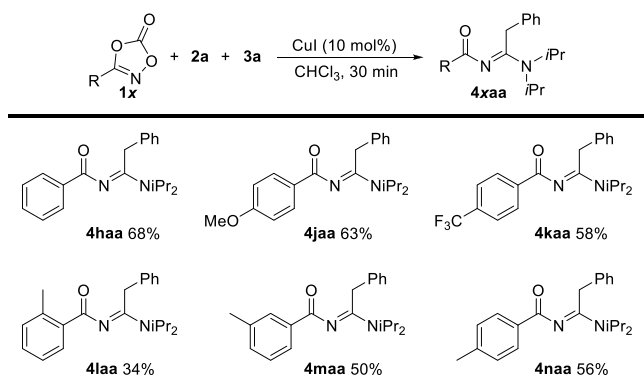
[a]Reaction of **1a** (0.5 mmol), **2a** (2 equiv), **3z** (2 equiv), and CuI (10 mol %) in CHCl₃ (1 mL), stirred for 30 min in a closed 4 mL vial at room temperature. Isolated yields are shown.

electron-rich as well as electron-poor aryl dioxazolones (**4jaa**, **4kaa**). The reaction still seems to be affected by sterics, 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 CO_2 as byproduct under mild conditions, making this an attractive methodology for both small- and large-scale organic synthesis.

■ ASSOCIATED CONTENT

ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.9b07140.

> Experimental procedures, kinetic experiments, NMR spectra, crystallographic data, and coordinates of calculated structures (PDF)
>
> X-ray crystallographic data (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*b.debruin@uva.nl

ORCID ⓘ

Lara H. Polak: 0000-0001-6013-6215

Maxime A. Siegler: 0000-0003-4165-7810

Jarl Ivar van der Vlugt: 0000-0003-0665-9239

Célia Fonseca Guerra: 0000-0002-2973-5321

Bas de Bruin: 0000-0002-3482-7669

Notes

The authors declare no competing financial interest.

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(91) We believe that the induction period visible in the graph is due to a delayed pressure buildup because of solubility of CO_2 in the solvent.

(92) When one equivalent of both iPr$_2$NH 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).