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

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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 3-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 by-product. 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 non-aromatic dioxazolones, [Cu(OAc)(Xantphos)] is a superior catalyst for this transformation, leading to full substrate conversion within 10 minutes. 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 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 does not only provide 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]un-dec-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 Janoxapin, 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] dehydrogenative coupling reactions,[16,17] or by catalysis with palladium[14,18–21] or nickel,[22] as well as some multi-component reactions.[23–33] Chang developed strategies for the synthesis of sulfonated and phosphorylated amidines via traditional click chemistry with azides, followed by a thermal N_2 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 to 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.

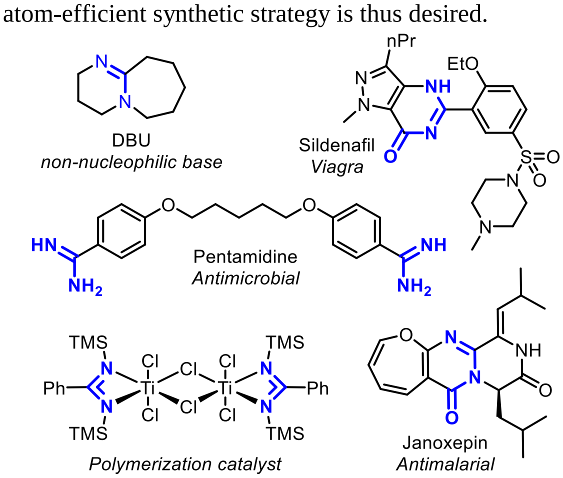
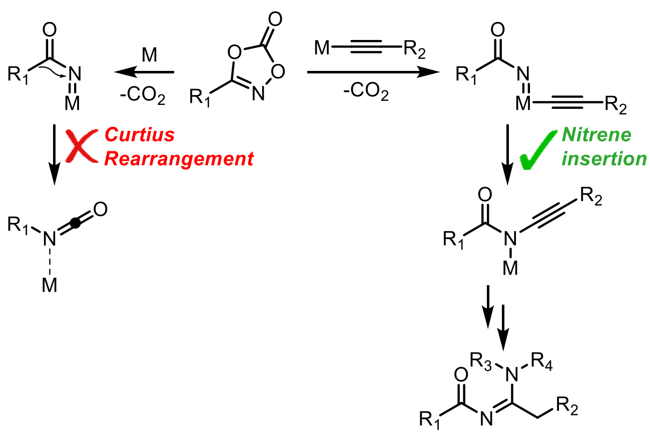


Figure 1. Several amidine compounds and their applications.

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 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 multi-component 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 amongst 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 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.

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 a M-C$_{acetylide}$ bond (right).



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, azides and hydroxylamines,[66] most of which are difficult to prepare, poorly soluble, require elevated temperatures to activate or 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 are known for over 50 years, these 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 pre-activated 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**) as a base. 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 3-component reaction had taken place.

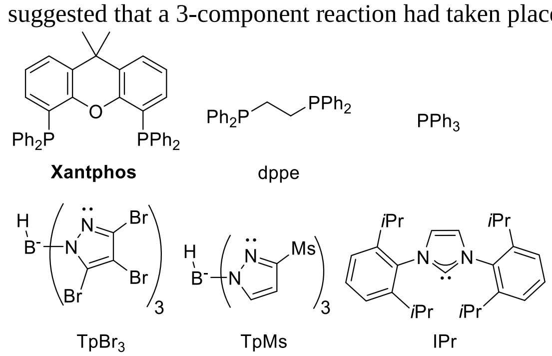
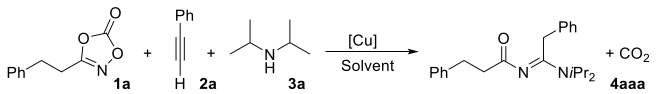


Figure 2. Ligands used in this work.

^{1}H NMR analysis indeed confirmed the formation of the 3-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-dimethylxan-thene) (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 THF, however, full conversion towards the product is observed. Excellent yield is obtained with 5% 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 ethylenebis(diphenylphosphine) (dppe) or 2 equivalents of PPh_3 results in a decreased yield of **4aaa** (Table 1, entries 26-27).

Table 1. Optimization of reaction conditions.



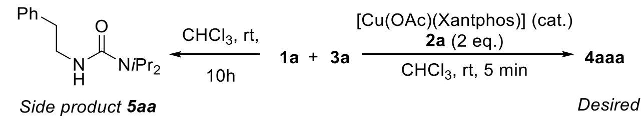
#	Catalyst (mol% Cu)	Solvent	Yield (%)
1	CuCl (10)	$CHCl_3$	55
2	CuBr (10)	$CHCl_3$	63
3	CuI (10)	$CHCl_3$	62
4	$[Cu(NCMe)_4]BF_4$ (10)	$CHCl_3$	65
5	$[Cu(NCMe)_4]PF_6$ (10)	$CHCl_3$	75
6	$[Cu(TpBr_3)(NCMe)]$ (10)	$CHCl_3$	5
7	[Cu(TpMs)(THF)] (10)	$CHCl_3$	0
8	[CuCl(IPr)] (10)	$CHCl_3$	37
9	[CuI(Xantphos)] (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%*)
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%*)
22	[Cu(OAc)(Xantphos)] (1)	$CHCl_3$	10 (19%*)
23	[Cu(OAc)(Xantphos)] (0.5)	$CHCl_3$	0
24	[Cu(OAc)(Xantphos)] (0.1)	$CHCl_3$	0
25[#]	[Cu(OAc)(Xantphos)] (5)	$CHCl_3$	0 (98%*)
26	[Cu(OAc)] + dppe (5)	$CHCl_3$	74%*****
27	[Cu(OAc)] + 2 PPh_3 (5)	$CHCl_3$	82%*****

Reaction of **1a** (0.5 mmol), **2a** (2 eq.), **3a** (2 eq.) 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. * Reactions performed in a N_2 filled glovebox. # 10 mL of chloroform was used. § Full conversion to 1,1-diisopropyl-3-phenethylurea was observed.

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, without a catalyst full conversion of dioxazolone **1a** to urea **5aa** was observed in the presence of amine **3a** at room temperature. Further screening (see ESI) 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 21-22).

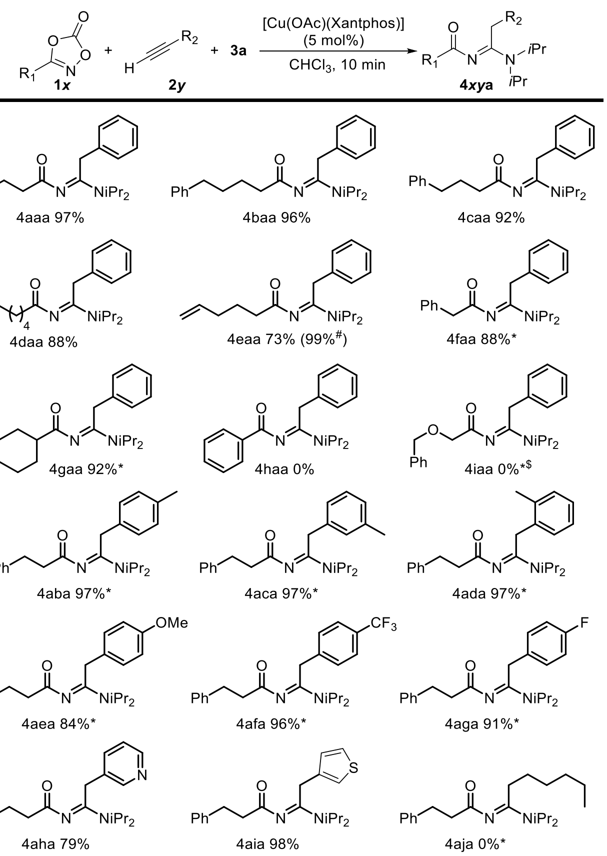
The copper catalyzed 3-component reaction produces only CO_2 as a by-product. In view of the atom efficiency of the process, we tested the efficacy of this reaction with a lower ratio of phenylacetylene and diisopropylamine relative to the dioxazolone substrate (see ESI).

Scheme 2. The desired catalyzed reaction vs. the uncatalyzed side reaction (urea formation).



The use of less 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.

Table 2. Scope of the [Cu(OAc)(Xantphos)] catalyzed 3-component reaction.

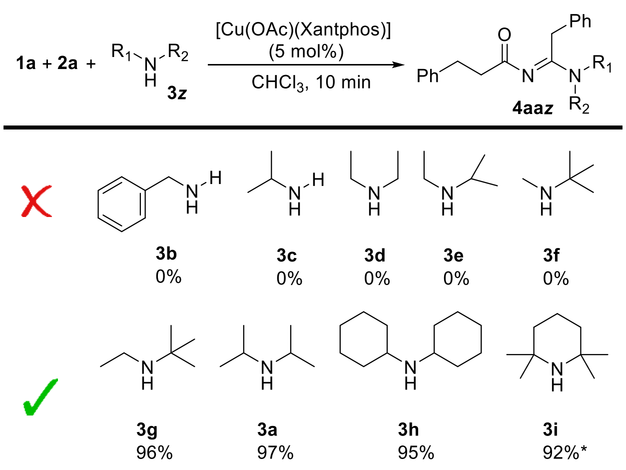


Reaction of **1x** (0.5 mmol), **2y** (2 eq.), **3z** (2 eq.) and [Cu(OAc)(Xantphos)] (5 mol%) in $CHCl_3$ (1 mL), stirred for 10 minutes in a closed 4 mL vial at room temperature. Isolated yields are given. * Performed under an N_2 atmosphere. # quantitative formation of product according to ^{1}H NMR with 1,3,5-trimethoxybenzene as internal standard. $ The urea was formed as the main product.

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 another terminal alkyne, *para*-tolyl acetylene, in the copper catalyzed 3-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 a result of a 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 efficiency (**4afa-4aga**). Even the use of heteroaromatic acetylenes 3-ethynylpyridine and 3-ethynylthiophene resulted in efficient formation of the desired products **4aha** and **4aja** (79% and 98%, respectively).

Table 3. The scope of amines used for the [Cu(OAc)(Xantphos)] catalyzed 3-component reaction



Reaction of **1a** (0.5 mmol), **2a** (2 eq.), **3z** (2 eq.) and [Cu(OAc)(Xantphos)] (5 mol%) in $CHCl_3$ (1 mL), stirred for 10 minutes in a closed 4 mL vial at r.t.. Isolated yields for **4aaz** are given. * A tautomer (enamine) was isolated.

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*-ethyl-*iso*-propylamine **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 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 ESI).

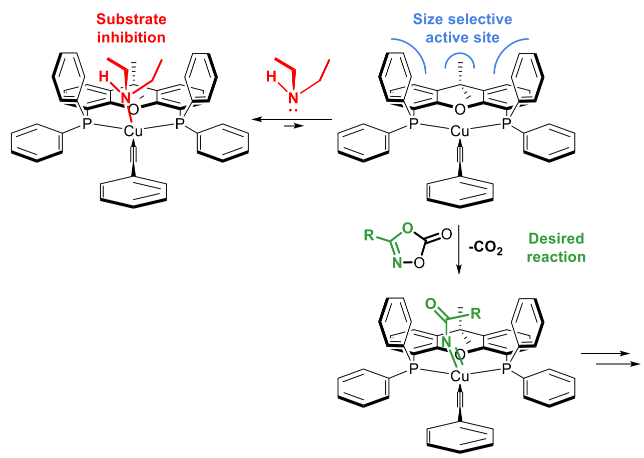


Figure 3. Proposed catalyst poisoning by small amine substrates.

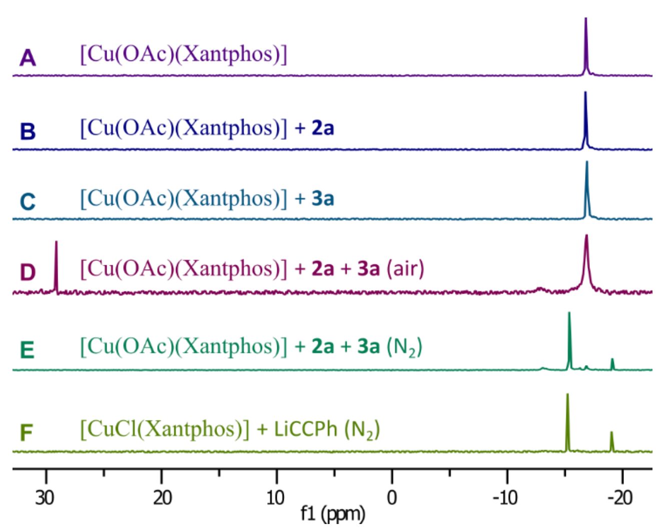


Figure 4. ^{31}P NMR studies on the formation of [Cu(CCPh)(Xantphos)]. ^{31}P NMR spectra measured under an N_2 atmosphere in $CDCl_3$. (A) [Cu(OAc)(Xantphos)]; (B) [Cu(OAc)(Xantphos)] with 40 equivalents phenylacetylene; (C) [Cu(OAc)(Xantphos)] with 40 equivalents *i*Pr_2NH; [Cu(OAc)(Xantphos)] with 40 equivalents or both phenylacetylene and iPr_2NH under (D) air or (E) N_2; (F) [Cu(CCPh)(Xantphos)] formed from salt metathesis from [CuCl(Xantphos)] and lithium phenylacetylide.

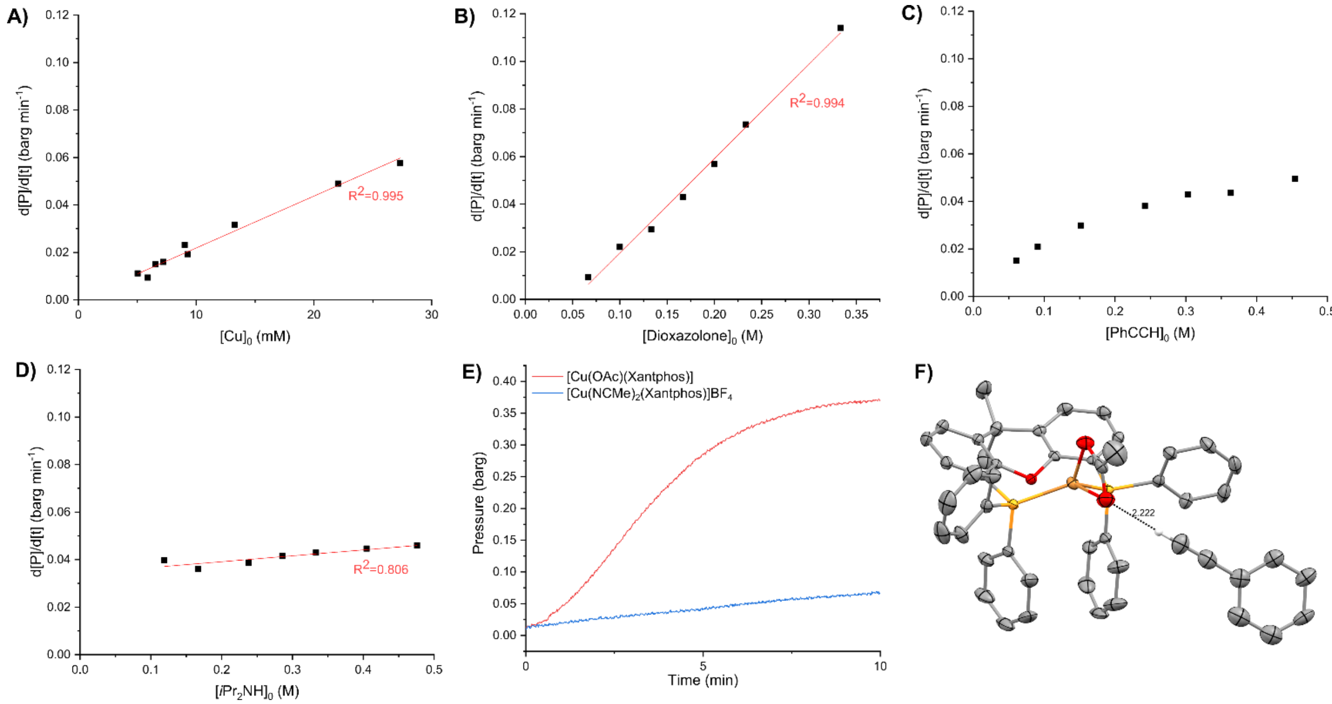


Figure 5. Kinetic experiments and X-ray structure of the catalyst interacting with phenyl acetylene. We varied the concentration of the catalyst and all three substrates, and calculated the slope of the steepest part in the graph as the reaction rate. These rates have been plotted over the related concentration to give graphs **A**, **B**, **C** and **D**. Graph **E** shows the pressure during the reaction towards **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.

Mechanistic investigations

To gain more information about the reaction mechanism, we studied the formation of copper species with ^{31}P NMR spectroscopy, investigated the kinetics of the reaction and performed supporting DFT studies.

We used ^{31}P 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 $CDCl_3$ gave a ^{31}P NMR signal at δ = –17 ppm (Figure 4A), which remained unchanged upon addition of phenylacetylene *or* diisopropylamine (Figure 4B/4C). When *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 –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 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 ESI for a connectivity plot).

To get more insight into the reaction mechanism we investigated the kinetics of the reaction, following the pressure build-up 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 [*i*Pr$_2$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 existence of such an equilibrium could be confirmed by H/D exchange studies. Burk and coworkers 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 ESI for details). Combined with the ^{31}P NMR studies shown in Figure 4 and the small effect of [*i*Pr$_2$NH] on the rate, the data suggest that this pre-equilibrium shifts towards the acetylide complex in the presence of the amine.

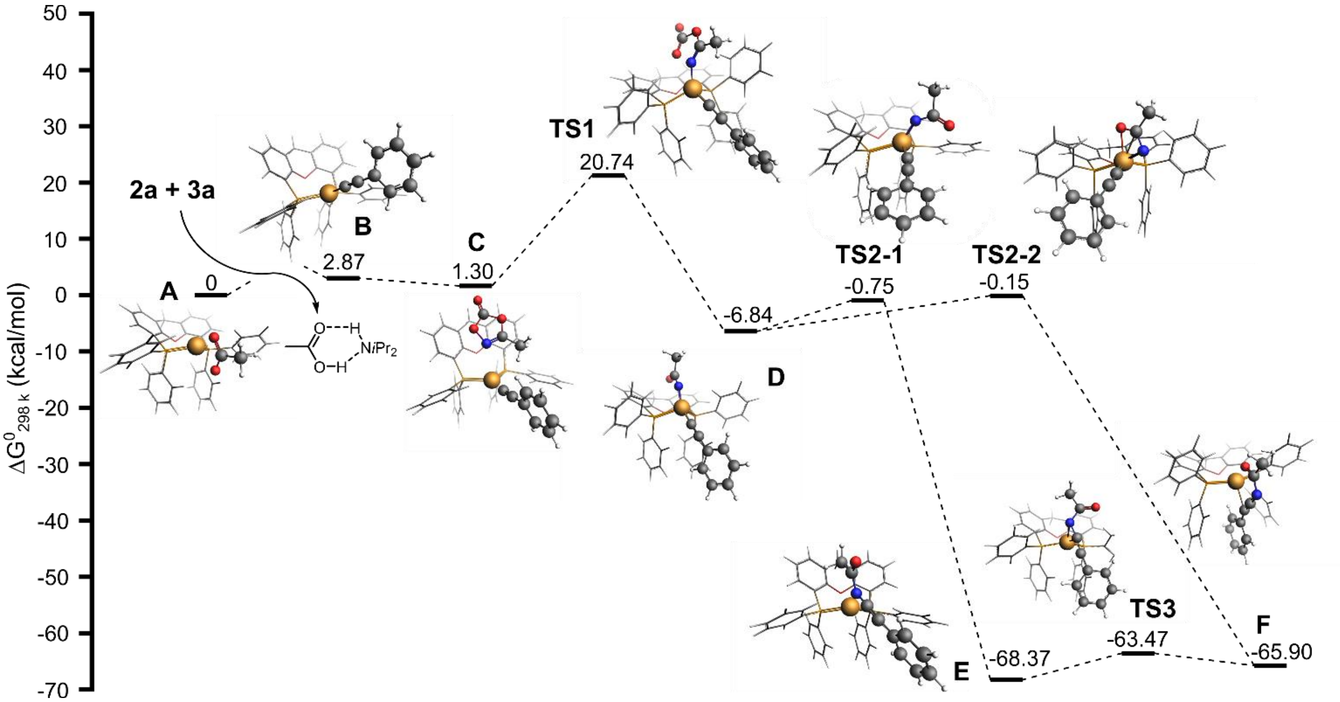


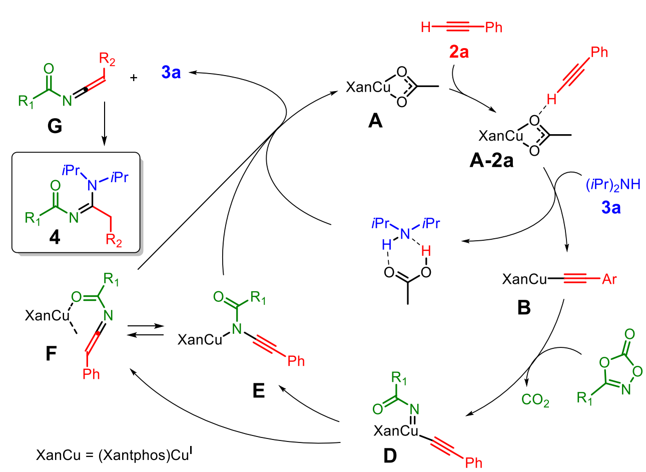
Figure 6. DFT (B3LYP-D3-TZ2P) computed energies of the acyl nitrene activation and insertion.

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 density functional theory (DFT) calculations (Figure 6, see ESI 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 non-standard 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.

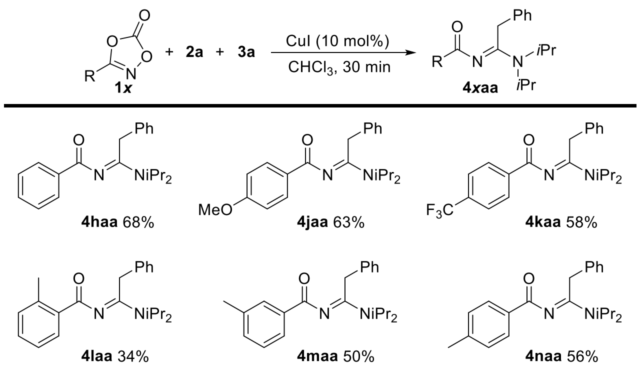
The barriers of these transition states (from **D**) are very similar (~ 7.5 kcal mol^{-1}). The resulting intermediates, **E** for **TS2-1** and **F** for **TS2-2**, are different by only 3.5 kcal/mol and connected by a low energy barrier transition state **TS3** and thus can both be present during 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 ESI 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.

Scheme 3. Proposed catalytic cycle.



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. 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 vinylideneamide **G**. Finally, reaction of the amine with the electrophilic intermediate **G** produces the *N*-acylamidine product **4**.

Table 4. Synthesis of *N*-benzoyl amidines from aryl-1,4,2-dioxazol-5-ones catalyzed by CuI.



Reaction of **1a** (0.5 mmol), **2a** (2 eq.), **3z** (2 eq.) and CuI (10 mol%) in $CHCl_3$ (1 mL), stirred for 30 minutes in a closed 4 mL vial at room temperature. Isolated yields are shown.

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 3-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 3-compentent 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 were up until now 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 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 3-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 type of products. This atom-efficient reaction uses dioxazolones substrates that are easily accessible and only generates CO_2 as by-product under mild conditions, making this an attractive methodology for both small and large scale organic synthesis.

ASSOCIATED CONTENT

Experimental procedures, kinetic experiments, NMR spectra, crystallographic data and coordinates of calculated structures can be found in the Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

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The manuscript was written through contributions of all authors.

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REFERENCES

(1) Nand, B.; Khanna, G.; Chaudhary, A.; Lumb, A.; M. Khurana, J. 1,8-Diazabicyclo[5.4.0]Undec-7-Ene (DBU): A Versatile Reagent in Organic Synthesis. *Curr. Org. Chem.* **2015**, *19*, 790–812.

(2) Ishikawa, T.; Kumamoto, T. Amidines in Organic Synthesis. In *Superbases for Organic Synthesis*; John Wiley & Sons, Ltd: Chichester, UK; pp 49–91.

(3) Collins, S. Polymerization Catalysis with Transition Metal Amidinate and Related Complexes. *Coord. Chem. Rev.* **2011**, *255*, 118–138.

(4) McGowan, M. A.; McAvoy, C. Z.; Buchwald, S. L. Palladium-Catalyzed *N*-Monoarylation of Amidines and a One-Pot Synthesis of Quinazoline Derivatives. *Org. Lett.* **2012**, *14*, 3800–3803.

(5) Wang, Y. F.; Zhu, X.; Chiba, S. Copper-Catalyzed Aerobic [3+2]-Annulation of *N*-Alkenyl Amidines. *J. Am. Chem. Soc.* **2012**, *134*, 3679–3682.

(6) Wang, J.; Wang, J.; Lu, P.; Wang, Y. Copper-Catalyzed Cascade Preparation of Dihydropyrimidin-4-Ones from *N*-(Prop-2-Yn-1-Yl)Amides and Azides. *J. Org. Chem.* **2013**, *78*, 8816–8820.

(7) Li, S.; Li, Z.; Yuan, Y.; Li, Y.; Zhang, L.; Wu, Y. Gold(I)-Catalyzed Aminohalogenation of Fluorinated *N′*-Aryl-*N*-Propargyl Amidines for the Synthesis of Imidazole Derivatives under Mild Conditions. *Chem. Eur. J.* **2013**, *19*, 1496–1501.

(8) Rajagopal, B.; Chen, Y.-Y.; Chen, C.-C.; Liu, X.-Y.; Wang, H.-R.; Lin, P.-C. Cu(I)-Catalyzed Synthesis of Dihydropyrimidin-4-Ones toward the Preparation of β- and β^3-Amino Acid Analogues. *J. Org. Chem.* **2014**, *79*, 1254–1264.

(9) Deibl, N.; Ament, K.; Kempe, R. A Sustainable Multicomponent Pyrimidine Synthesis. *J. Am. Chem. Soc.* **2015**, *137*, 12804–12807.

(10) Li, J.; Tang, M.; Zang, L.; Zhang, X.; Zhang, Z.; Ackermann, L. Amidines for Versatile Cobalt(III)-Catalyzed Synthesis of Isoquinolines through C-H Functionalization with Diazo Compounds. *Org. Lett.* **2016**, *18*, 2742–2745.

(11) Greenhill, J. V.; Lue, P. Amidines and Guanidines in Medicinal Chemistry. *Prog. Med. Chem.* **1993**, *30*, 203–326.

(12) Sprogøe, K.; Manniche, S.; Larsen, T. O.; Christophersen, C. Janoxepin and Brevicompanine B: Antiplasmodial Metabolites from the Fungus Aspergillus Janus. *Tetrahedron* **2005**, *61*, 8718–8721.

(13) Wang, Z. Pinner Reaction. In *Comprehensive Organic Name Reactions and Reagents*; John Wiley & Sons, Inc.: Hoboken, NJ, USA, 2010; pp 2237–2240.

(14) Saluste, C. G.; Whitby, R. J.; Furber, M. Palladium-Catalysed Synthesis of Imidates, Thioimidates and Amidines from Aryl Halides. *Tetrahedron Lett.* **2001**, *42*, 6191–6194.
(15) Fleury, L. M.; Wilson, E. E.; Vogt, M.; Fan, T. J.; Oliver, A. G.; Ashfeld, B. L. Amine-Free Approach toward *N*-Toluenesulfonyl Amidine Construction: A Phosphite-Mediated Beckmann-Like Coupling of Oximes and *p*-Toluenesulfonyl Azide. *Angew. Chem. Int. Ed.* **2013**, *52*, 11589–11593.
(16) Rouzi, A.; Hudabaierdi, R.; Wusiman, A. Synthesis of N - Sulfonylformamidines by *Tert*-Butyl Hydroperoxide–Promoted, Metal-Free, Direct Oxidative Dehydrogenation of Aliphatic Amines. *Tetrahedron* **2018**, *74*, 2475–2481.
(17) Zheng, Y.; Mao, J.; Chen, J.; Rong, G.; Liu, D.; Yan, H.; Chi, Y.; Xu, X. Unexpected C=N Bond Formation via NaI-Catalyzed Oxidative de-Tetra-Hydrogenative Cross-Couplings between *N*,*N*-Dimethyl Aniline and Sulfamides. *RSC Adv.* **2015**, *5*, 50113–50117.
(18) DeKorver, K. A.; Johnson, W. L.; Zhang, Y.; Hsung, R. P.; Dai, H.; Deng, J.; Lohse, A. G.; Zhang, Y.-S. *N*-Allyl-*N*-Sulfonyl Ynamides as Synthetic Precursors to Amidines and Vinylogous Amidines. An Unexpected N-to-C 1,3-Sulfonyl Shift in Nitrile Synthesis. *J. Org. Chem.* **2011**, *76*, 5092–5103.
(19) Saluste, C. G.; Crumpler, S.; Furber, M.; Whitby, R. J. Palladium Catalysed Synthesis of Cyclic Amidines and Imidates. *Tetrahedron Lett.* **2004**, *45*, 6995–6996.
(20) Tetala, K. K. R.; Whitby, R. J.; Light, M. E.; Hurtshouse, M. B. Palladium-Catalysed Three Component Synthesis of α,β-Unsaturated Amidines and Imidates. *Tetrahedron Lett.* **2004**, *45*, 6991–6994.
(21) Saluste, C. G.; Whitby, R. J.; Furber, M. A Palladium-Catalyzed Synthesis of Amidines from Aryl Halides. *Angew. Chem. Int. Ed.* **2000**, *39*, 4156–4158.
(22) Garduño, J. A.; García, J. J. Synthesis of Amidines and Benzoxazoles from Activated Nitriles with Ni(0) Catalysts. *ACS Catal.* **2015**, *5*, 3470–3477.
(23) Zhou, M.; Li, J.; Tian, C.; Sun, X.; Zhu, X.; Cheng, Y.; An, G.; Li, G. A Metal-Free Three-Component Reaction of Trans-β-Nitrostyrene Derivatives, Dibromo Amides, and Amines Leading to Functionalized Amidines. *J. Org. Chem.* **2019**, *84*, 1015–1024.
(24) Zhang, Z.; Huang, B.; Qiao, G.; Zhu, L.; Xiao, F.; Chen, F.; Fu, B.; Zhang, Z. Tandem Coupling of Azide with Isonitrile and Boronic Acid: Facile Access to Functionalized Amidines. *Angew. Chem. Int. Ed.* **2017**, *56*, 4320–4323.
(25) Shojaei, S.; Ghasemi, Z.; Shahrisa, A. Three-Component Synthesis of N -Sulfonylformamidines in the Presence of Magnetic Cellulose Supported *N*-Heterocyclic Carbene-Copper Complex, as an Efficient Heterogeneous Nanocatalyst. *Tetrahedron Lett.* **2017**, *58*, 3957–3965.
(26) Kim, J.; Stahl, S. S. Cu-Catalyzed Aerobic Oxidative Three-Component Coupling Route to *N*-Sulfonyl Amidines via an Ynamine Intermediate. *J. Org. Chem.* **2015**, *80*, 2448–2454.
(27) Dai, Q.; Jiang, Y.; Yu, J. T.; Cheng, J. Palladium-Catalyzed Three-Component Reaction of *N*-Tosyl Hydrazones, Isonitriles and Amines Leading to Amidines. *Chem. Commun.* **2015**, *51*, 16645–16647.
(28) Xu, X.; Gao, J.; Cheng, D.; Li, J.; Qiang, G.; Guo, H. Copper-Catalyzed Highly Efficient Multicomponent Reactions of Terminal Alkynes, Acid Chlorides, and Carbodiimides: Synthesis of Functionalized Propiolamidine Derivatives. *Adv. Synth. Catal.* **2008**, *350*, 61–64.
(29) Seok, H. K.; Doo, Y. J.; Chang, S. Phosphoryl Azides as Versatile New Reaction Partners in the Cu-Catalyzed Three-Component Couplings. *J. Org. Chem.* **2007**, *72*, 9769–9771.
(30) Bae, I.; Han, H.; Chang, S. Highly Efficient One-Pot Synthesis of N-Sulfonylamidines by Cu-Catalyzed Three-Component Coupling of Sulfonyl Azide, Alkyne, and Amine. *J. Am. Chem. Soc.* **2005**, *127*, 2038–2039.
(31) Keung, W.; Bakir, F.; Patron, A. P.; Rogers, D.; Priest, C. D.; Darmohusodo, V. Novel α-Amino Amidine Synthesis via Scandium(III) Triflate Mediated 3CC Ugi Condensation Reaction. *Tetrahedron Lett.* **2004**, *45*, 733–737.
(32) Zhu, S.; Xu, Y.; Jin, G. A Novel Synthesis of N - Fluoroalkanesulfonylamidines Using a Three-Component Reaction. *Can. J. Chem.* **2003**, *81*, 265–268.
(33) McFarland, J. W. Reactions of Cyclohexylisonitrile and Isobutyraldehyde with Various Nucleophiles and Catalysts. *J. Org. Chem.* **1963**, *28*, 2179–2181.
(34) Husmann, R.; Na, Y. S.; Bolm, C.; Chang, S. Copper-Catalyzed One-Pot Synthesis of α-Functionalized Imidates. *Chem. Commun.* **2010**, *46*, 5494–5496.
(35) Yoo, E.; Chang, S. Copper-Catalyzed Multicomponent Reactions: Securing a Catalytic Route to Ketenimine Intermediates and Their Reactivities. *Curr. Org. Chem.* **2009**, *13*, 1766–1776.
(36) Kim, J. Y.; Kim, S. H.; Chang, S. Highly Efficient Synthesis of α-Amino Amidines from Ynamides by the Cu-Catalyzed Three-Component Coupling Reactions. *Tetrahedron Lett.* **2008**, *49*, 1745–1749.
(37) Hwang, S. J.; Cho, S. H.; Chang, S. Evaluation of Catalytic Activity of Copper Salts and Their Removal Processes in the Three-Component Coupling Reactions. *Pure Appl. Chem.* **2008**, *80*, 873–879.
(38) Cho, S. H.; Hwang, S. J.; Chang, S. Copper-Catalyzed Three-Component Reaction of 1-Alkynes, Sulfonyl Azides, and Water: *N*-(4-Acetamidophenylsulfonyl)-2-Phenylacetamide. *Org. Synth.* **2008**, *85*, 131–137.
(39) Yoo, E. J.; Chang, S. A New Route to Indolines by the Cu-Catalyzed Cyclization Reaction of 2-Ethynylanilines with Sulfonyl Azides. *Org. Lett.* **2008**, *10*, 1163–1166.
(40) Kim, J.; Lee, S. Y.; Lee, J.; Do, Y.; Chang, S. Synthetic Utility of Ammonium Salts in a Cu-Catalyzed Three-Component Reaction as a Facile Coupling Partner. *J. Org. Chem.* **2008**, *73*, 9454–9457.
(41) Cho, S. H.; Chang, S. Room Temperature Copper-Catalyzed 2-Functionalization of Pyrrole Rings by a Three-Component Coupling Reaction. *Angew. Chem. Int. Ed.* **2008**, *47*, 2836–2839.
(42) Yoo, E. J.; Bae, I.; Cho, S. H.; Han, H.; Chang, S. A Facile Access to N-Sulfonylimidates and Their Synthetic Utility for the Transformation to Amidines and Amides. *Org. Lett.* **2006**, *8*, 1347–1350.
(43) Cho, S. H.; Yoo, E. J.; Bae, I.; Chang, S. Copper-Catalyzed Hydrative Amide Synthesis with Terminal Alkyne, Sulfonyl Azide, and Water. *J. Am. Chem. Soc.* **2005**, *127*, 16046–16047.
(44) Yoo, E. J.; Ahlquist, M.; Bae, I.; Sharpless, K. B.; Fokin, V. V.; Chang, S. Mechanistic Studies on the Cu-Catalyzed Three-Component Reactions of Sulfonyl Azides, 1-Alkynes and Amines, Alcohols, or Water: Dichotomy via a Common Pathway. *J. Org. Chem.* **2008**, *73*, 5520–5528.
(45) Yoo, E. J.; Ahlquist, M.; Kim, S. H.; Bae, I.; Fokin, V. V.; Sharpless, K. B.; Chang, S. Copper-Catalyzed Synthesis of *N*-Sulfonyl-1,2,3-Triazoles: Controlling Selectivity. *Angew. Chem. Int. Ed.* **2007**, *46*, 1730–1733.
(46) Eun, J. Y.; Ahlquist, M.; Bae, I.; Sharpless, K. B.; Fokin, V. V.; Chang, S. Mechanistic Studies on the Cu-Catalyzed Three-Component Reactions of Sulfonyl Azides, 1-Alkynes and Amines, Alcohols, or Water: Dichotomy via a Common Pathway. *J. Org. Chem.* **2008**, *73*, 5520–5528.
(47) Cano, I.; Álvarez, E.; Nicasio, M. C.; Pérez, P. J. Regioselective Formation of 2,5-Disubstituted Oxazoles via Copper(I)-Catalyzed Cycloaddition of Acyl Azides and 1-Alkynes. *J. Am. Chem. Soc.* **2011**, *133*, 191–193.
(48) Haldón, E.; Álvarez, E.; Carmen Nicasio, M.; Pérez, P. J. 1,2,3-Triazoles from Carbonyl Azides and Alkynes: Filling the Gap. *Chem. Commun.* **2014**, *50*, 8978–8981.
(49) Barber, C. G.; Blakemore, D. C.; Chiva, J. Y.; Eastwood, R. L.; Middleton, D. S.; Paradowski, K. A. 1-Amido-1-Phenyl-3-Piperidinylbutanes - CCR5 Antagonists for the Treatment of HIV: Part 2. *Bioorganic Med. Chem. Lett.* **2009**, *19*, 1499–1503.
(50) Li, E.; Wang, M.; Wang, Z.; Yu, W.; Chang, J. NBS-Mediated Practical Cyclization of *N*-Acyl Amidines to 1,2,4-Oxadiazoles via Oxidative N–O Bond Formation. *Tetrahedron* **2018**, *74*, 4613–4618.
(51) Gupta, P. K.; Hussain, M. K.; Asad, M.; Kant, R.; Mahar, R.; Shukla, S. K.; Hajela, K. A Metal-Free Tandem Approach to Prepare Structurally Diverse N-Heterocycles: Synthesis of 1,2,4-Oxadiazoles and Pyrimidinones. *New J. Chem.* **2014**, *38*, 3062–3070.
(52) Castanedo, G. M.; Seng, P. S.; Blaquiere, N.; Trapp, S.; Staben, S. T. Rapid Synthesis of 1,3,5-Substituted 1,2,4-Triazoles from Carboxylic Acids, Amidines, and Hydrazines. *J. Org. Chem.* **2011**, *76*, 1177–1179.
(53) Asad, M.; Gupta, P. K.; Jaiswal, S. K.; Hajela, K. Iodine–induced Oxidative Cyclisation of *N*-Acyl Amidines: A Rapid Synthesis of 3,5-Disubstituted-1,2,4-Oxadiazoles. *ChemistrySelect* **2016**, *1*, 4753–4757.
(54) Clodt, J. I.; Fröhlich, R.; Eul, M.; Würthwein, E. U. Metallomacrocyclic Complexes by Self-Assembly of Ni II and Cu II Ions and Chelating Bis(*N*-Acylamidines). *Eur. J. Inorg. Chem.* **2012**, 1210–1217.
(55) Ronson, T. O.; Renders, E.; Van Steijvoort, B. F.; Wang, X.; Wybon, C. C. D.; Prokopcová, H.; Meerpoel, L.; Maes, B. U. W. Ruthenium-Catalyzed Reductive Arylation of *N*-(2-Pyridinyl)Amides with Isopropanol and Arylboronate Esters. *Angew. Chem. Int. Ed.* **2019**, *58*, 482–487.
(56) te Grotenhuis, C.; de Bruin, B. Radical-Type Reactions Controlled by Cobalt: From Carbene Radical Reactivity to the Catalytic Intermediacy of

Reactive *o*-Quinodimethanes. *Synlett* **2018**, *29*, 2238–2250.
(57) Chirila, A.; van Vliet, K. M.; Paul, N. D.; de Bruin, B. [Co(MeTAA)] Metalloradical Catalytic Route to Ketenes via Carbonylation of Carbene Radicals. *Eur. J. Inorg. Chem.* **2018**, 2251–2258.
(58) Karns, A. S.; Goswami, M.; de Bruin, B. Catalytic Synthesis of Indolines by Hydrogen Atom Transfer to Cobalt(III)–Carbene Radicals. *Chem. Eur. J.* **2018**, *24*, 5253–5258.
(59) te Grotenhuis, C.; van den Heuvel, N.; van der Vlugt, J. I.; de Bruin, B. Catalytic Dibenzocyclooctene Synthesis via Cobalt(III)–Carbene Radical and Ortho-Quinodimethane Intermediates. *Angew. Chem. Int. Ed.* **2018**, *57*, 140–145.
(60) Kuijpers, P. F.; van der Vlugt, J. I.; Schneider, S.; de Bruin, B. Nitrene Radical Intermediates in Catalytic Synthesis. *Chem. Eur. J.* **2017**, *23*, 13819–13829.
(61) Goswami, M.; de Bruin, B. Porphyrin Co(III)-Nitrene Radical Mediated Pathway for Synthesis of *o*-Aminoazobenzenes. *Molecules* **2018**, *23*, 1052.
(62) Goswami, M.; Geuijen, P.; Reek, J. N. H.; de Bruin, B. Application of [Co(Corrole)] – Complexes in Ring-Closing C–H Amination of Aliphatic Azides via Nitrene Radical Intermediates. *Eur. J. Inorg. Chem.* **2018**, 617–626.
(63) Ghosh, A. K.; Brindisi, M.; Sarkar, A. The Curtius Rearrangement: Applications in Modern Drug Discovery and Medicinal Chemistry. *ChemMedChem* **2018**, *13*, 2351–2373.
(64) Li, D.; Wu, T.; Liang, K.; Xia, C. Curtius-like Rearrangement of an Iron-Nitrenoid Complex and Application in Biomimetic Synthesis of Bisindolylmethanes. *Org. Lett.* **2016**, *18*, 2228–2231.
(65) Lebel, H.; Leogane, O. Boc-Protected Amines via a Mild and Efficient One-Pot Curtius Rearrangement. *Org. Lett.* **2005**, *7*, 4107–4110.
(66) Park, Y.; Kim, Y.; Chang, S. Transition Metal-Catalyzed C–H Amination: Scope, Mechanism, and Applications. *Chem. Rev.* **2017**, *117*, 9247–9301.
(67) Shimbayashi, T.; Sasakura, K.; Eguchi, A.; Okamoto, K.; Ohe, K. Recent Progress on Cyclic Nitrenoid Precursors in Transition-Metal-Catalyzed Nitrene-Transfer Reactions. *Chem. – A Eur. J.* **2018**, *25*, 3156–3180.
(68) Sauer, J.; Mayer, K. K. Thermolyse Und Photolyse von 3-Subtituierten Δ_2-1.4.2-Dioxazolinonen-(5), Δ^2-1.4.2-Dioxazolin-Thionen-(5) Und 4-Substituierten Δ^3-1.2.5.3-Thiadioxazolin-s-Oxiden. *Tetrahedron Lett.* **1968**, *9*, 319–324.
(69) Hong, S. Y.; Park, Y.; Hwang, Y.; Kim, Y. B.; Baik, M.-H.; Chang, S. Selective Formation of *γ*-Lactams via C–H Amidation Enabled by Tailored Iridium Catalysts. *Science* **2018**, *359*, 1016–1021.
(70) Bizet, V.; Buglioni, L.; Bolm, C. Light-Induced Ruthenium-Catalyzed Nitrene Transfer Reactions: A Photochemical Approach towards *N*-Acyl Sulfimides and Sulfoximines. *Angew. Chem. Int. Ed.* **2014**, *53*, 5639–5642.
(71) Yu, Y.; Luo, G.; Yang, J.; Luo, Y. Cobalt-Catalysed Unactivated C(Sp3)–H Amination: Two-State Reactivity and Multi-Reference Electronic Character. *Catal. Sci. Technol.* **2019**, *9*, 1879–1890.
(72) Shi, H.; Dixon, D. J. Dithiane-Directed Rh(III)-Catalyzed Amidation of Unactivated C(Sp3)–H Bonds. *Chem. Sci.* **2019**, *10*, 3733–3737.
(73) Lei, H.; Rovis, T. Ir-Catalyzed Intermolecular Branch-Selective Allylic C-H Amidation of Unactivated Terminal Olefins. *J. Am. Chem. Soc.* **2019**, *141*, 2268–2273.
(74) Fukagawa, S.; Kato, Y.; Tanaka, R.; Kojima, M.; Yoshino, T.; Matsunaga, S. Enantioselective C(Sp3)-H Amidation of Thioamides Catalyzed by a Cobalt III /Chiral Carboxylic Acid Hybrid System. *Angew. Chem. Int. Ed.* **2019**, *58*, 1153–1157.
(75) Huang, D. Y.; Yao, Q. J.; Zhang, S.; Xu, X. T.; Zhang, K.; Shi, B. F. Amide-Directed Cobalt(III)-Catalyzed C-H Amidation of Ferrocenes. *Org. Lett.* **2019**, *21*, 951–954.
(76) Xu, L.; Li, T.; Wang, L.; Cui, X. Rh(III)-Catalyzed One-Pot Synthesis of Benzimidazoquinazolines via C-H Amidation-Cyclization of *N*-LG-2-Phenylbenzoimidazoles. *J. Org. Chem.* **2019**, *84*, 560–567.
(77) In a few recent examples alkyl-1,4,2-dioxazol-5-one were converted without co-substrate pre-activation, enabled by catalyst optimization to inhibit the Curtius rearrangement[78-80] or stabilization of the acyl nitrene by a genetically engineered enzyme.[81]
(78) Park, Y.; Chang, S. Asymmetric Formation of γ-Lactams via C–H Amidation Enabled by Chiral Hydrogen-Bond-Donor Catalysts. *Nat. Catal.* **2019**, *2*.
(79) Hwang, Y.; Park, Y.; Kim, Y. B.; Kim, D.; Chang, S. Revisiting Arene C(sp^2)−H Amidation by Intramolecular Transfer of Iridium Nitrenoids: Evidence for a Spirocyclization Pathway. *Angew. Chem. Int. Ed.* **2018**, *57*, 13565–13569.
(80) Hong, S. Y.; Son, J.; Kim, D.; Chang, S. Ir(III)-Catalyzed Stereoselective Haloamidation of Alkynes Enabled by Ligand Participation. *J. Am. Chem. Soc.* **2018**, *140*, 12359–12363.
(81) Cho, I.; Jia, Z. J.; Arnold, F. H. Site-Selective Enzymatic C-H Amidation for Synthesis of Diverse Lactams. *Science* **2019**, *364*, 575–578.
(82) Xu, S.; Chen, R.; Fu, Z.; Gao, Y.; Wang, J. Cu(I)-Catalyzed Coupling of Bis(Trimethylsilyl)Diazomethane with Terminal Alkynes: A Synthesis of 1,1-Disilyl Allenes. **2018**, *83*, 6186–6192.
(83) Panera, M.; Díez, J.; Merino, I.; Rubio, E.; Gamasa, M. P. Synthesis of Copper(I) Complexes Containing Enantiopure Pybox Ligands. First Assays on Enantioselective Synthesis of Propargylamines Catalyzed by Isolated Copper(I) Complexes. *Inorg. Chem.* **2009**, *48*, 11147–11160.
(84) Gonell, S.; Caumes, X.; Orth, N.; Ivanović-Burmazović, I.; Reek, J. N. H. Self-Assembled $M_{12}L_{24}$ Nanospheres as a Reaction Vessel to Facilitate a Dinuclear Cu(I) Catalyzed Cyclization Reaction. *Chem. Sci.* **2019**, *10*, 1316–1321.
(85) Kamer, P. C. J.; Van Leeuwen, P. W. N. M.; Reek, J. N. H. Wide Bite Angle Diphosphines: Xantphos Ligands in Transition Metal Complexes and Catalysis. *Acc. Chem. Res.* **2001**, *34*, 895–904.
(86) Kranenburg, M.; van der Burgt, Y. E. M.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Goubitz, K.; Fraanje, J. New Diphosphine Ligands Based on Heterocyclic Aromatics Inducing Very High Regioselectivity in Rhodium-Catalyzed Hydroformylation: Effect of the Bite Angle. *Organometallics* **1995**, *14*, 3081–3089.
(87) De Boer, S. Y.; Gloaguen, Y.; Lutz, M.; Van Der Vlugt, J. I. Cu I Click Catalysis with Cooperative Noninnocent Pyridylphosphine Ligands. *Inorganica Chim. Acta* **2012**, *380*, 336–342.
(88) Chirila, A.; Brands, M. B.; de Bruin, B. Mechanistic Investigations into the Cyclopropanation of Electron-Deficient Alkenes with Ethyl Diazoacetate Using [Co(MeTAA)]. *J. Catal.* **2018**, *361*, 347–360.
(89) Luconi, L.; Osipova, E. S.; Giambastiani, G.; Peruzzini, M.; Rossin, A.; Belkova, N. V; Filippov, O. A.; Titova, E. M.; Pavlov, A. A.; Shubina, E. S. Amine Boranes Dehydrogenation Mediated by an Unsymmetrical Iridium Pincer Hydride: (PCN) vs (PCP) Improved Catalytic Performance. *Organometallics* **2018**, *37*, 3142–3153.
(90) Kalvet, I.; Tammiku-Taul, J.; Mäeorg, U.; Tämm, K.; Burk, P.; Sikk, L. NMR and DFT Study of the Copper(I)-Catalyzed Cycloaddition Reaction: H/D Scrambling of Alkynes and Variable Reaction Order of the Catalyst. *ChemCatChem* **2016**, *8*, 1804–1808.
(91) We believe that the induction period visible in the graph is due to a delayed pressure build-up because of solubility of CO_2 in the solvent.
(92) When one equivalent of both iPr_2NH and PhCCH were used compared to [(Xantphos)Cu(OAc)], under identical reaction conditions, we did not observe the conversion of this complex (See ESI).

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