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Copper-Catalyzed Carbamoylation of Terminal Alkynes with Formamides via Cross-Dehydrogenative Coupling

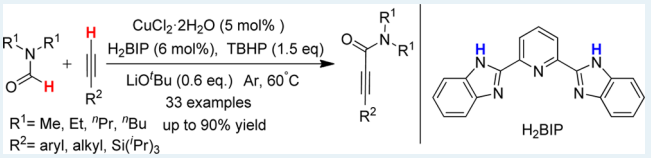
Jin-Ji Wu,[†] Yinwu Li,[†] Hai-Yun Zhou,[‡] A-Hao Wen,[†] Chu-Chu Lun,[†] Su-Yang Yao,[†] Zhuofeng Ke,*[,†] and Bao-Hui Ye*[,†]

[†]MOE Key Laboratory of Bioinorganic and Synthetic Chemistry, School of Chemistry and Chemical Engineering, Sun Yat-Sen University, Xigang Xilu 135, Guangzhou 510275, China

[‡]Instrumental Analysis and Research Center, Sun Yat-Sen University, Xigang Xilu 135, Guangzhou 510275, China

Supporting Information

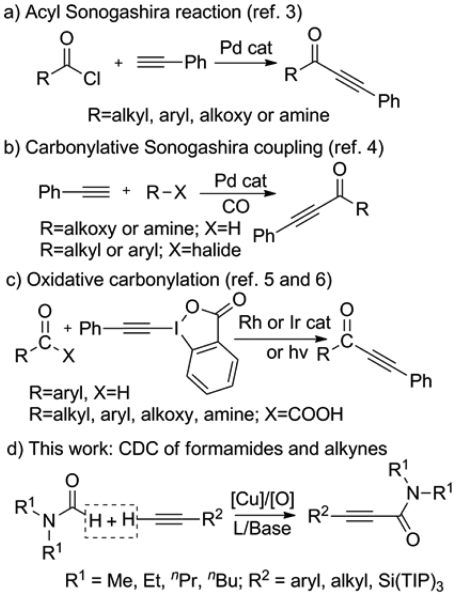
ABSTRACT: An efficient approach for direct carbamoylation of terminal alkynes with formamides affording propiolamides has been developed by copper-catalyzed oxidative cross coupling of C(sp)-H and C(sp^2)-H bonds in the presence of a pincer ligand with two imidazolyl groups. The catalytic reaction is compatible with diverse functional groups but sensitive to the electronic effect of terminal alkyne and the steric effect of formamides. KIE study indicates the cleavage of the carbamoyl C−H bond affording formamide radical is the rate-determining step.



KEYWORDS: *carbonylation, cross-dehydrogenative coupling, copper-catalyzed, propiolamide, aminocarbonylation*

The oxidative carbonylation of terminal alkynes leads to the direct synthesis of ynones, ynoates, and ynamides,[1] which are important intermediates for the synthesis of natural products and heterocyclic compounds.[2] Traditionally, synthetic methods for these carbonylate compounds are Pd-catalyzed acyl Sonogashira reaction,[3] or carbonylative Sonogashira coupling (Scheme 1).[4] However, the acyl chlorides are moisture-sensitive, unstable and commercially limited; CO is a highly toxic gas and hard to handle in the laboratory.

Scheme 1. General Approaches to Carbonylattion of Alkynes



Recently, a new carbonylation of terminal alkynes has been exploited on the basis of the hypervalent iodine(III) reagent (Scheme 1c).[5,6] However, the substrates need to be preactivated and functionalized. Moreover, ynones can also be synthesized by the addition of alkynyl to aldehyde, followed by oxidation of the propargyl alcohols.[7] A more straightforward method for carbonylation of terminal alkynes is cross-dehydrogenative coupling (CDC) of terminal alkynes and carbonyl hydrogens of aldehydes, formates, or formamides.[1] Although oxidative coupling of aromatic C(sp^2)-H and C(sp)-H bonds has been well-documented,[8] directly CDC of formyl C(sp^2)-H and unactived terminal alkyne C(sp)-H bonds has never been reported.[1] This may be attributed to the lower reactivity of the formyl C−H bond than the carbonyl group and decarbonylation in harsh condition. Therefore, metal-catalyzed activation of formyl C−H bond mostly leads to the addition of formyl C−H bonds into alkynes, namely, hydroacylation,[9] hydrocarboxylation,[10] hydroesterification,[11] or hydrocarbamoylation.[12] On the other hand, formamides are multipurpose reagents and widely used in chemistry.[13] Recent studies on the aminocarbonylation with DMF have demonstrated that direct activation of the formamide C−H bond is possible.[14] We are thus interested in carbamoylation of terminal alkynes with readily available formamides using a copper complex as a catalyst to provide an efficient and straightforward synthetic approach to propiolamides (Scheme 1d).

We initially examined the CDC reaction of formamides and alkynes via model compounds of N,N-diethylformamide (DEF,

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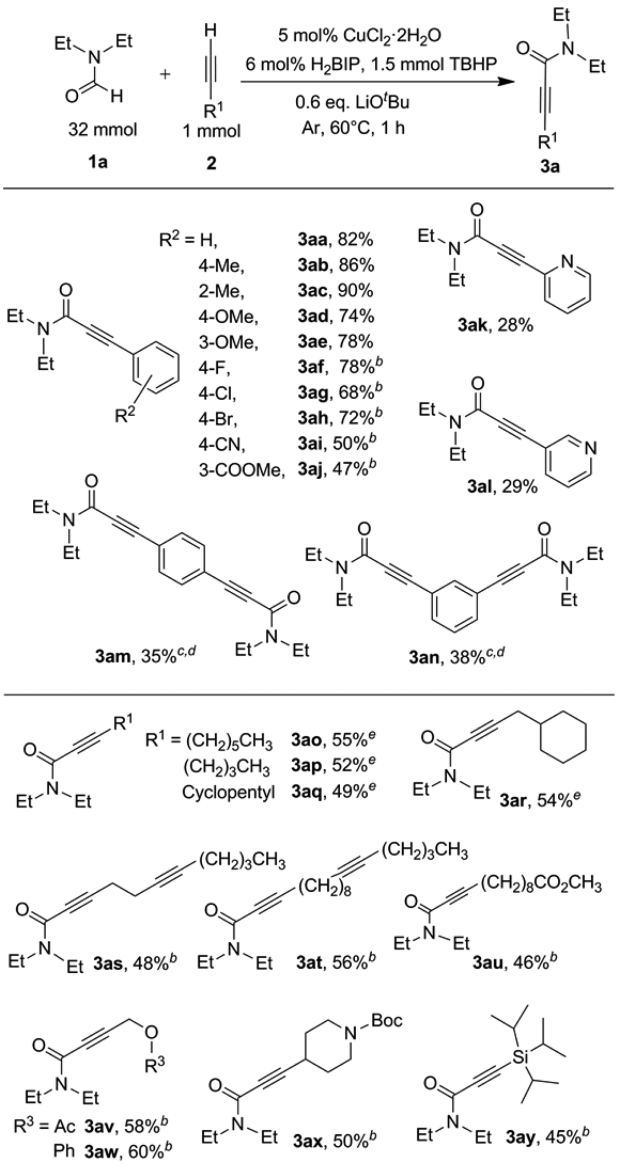
1a) and phenylacetylene (2a) at 60 °C, using 5 mol % of CuBr and TBHP (1.5 equiv) as cocatalyst with and without LiO^{t}Bu (0.6 equiv) as a base (Table S1, entries 1 and 2). However, no desired product but unreacted **2a** was detected. To promote the copper-catalyzed performance, ligands 2,9-dimethyl-1,10-phenanthroline (DMPhen), 2,2′:6′,2″-terpyridine (TPy), 2,2′-biimidazole (H_2BIm), and 2,2′-bibenzimidazole (H_2BBIm) were added, respectively, to form the Cu complex. A negative result was observed, but a small amount of the homocoupling product **4** was detected. To our delight, when ligand 2,6-bis(benzimidazol-2′-yl)pyridine (H_2BIP) or 2,6-bis-(benzimidazol-2′-yl)-4-hydroxypyridine (H_3OBIP) was used, the reaction was triggered, affording 81% or 74% yield (entries 7 and 8). To elucidate the differences between the ligands, 2,6-bis(1′-methylbenzimidazol-2′-yl)pyridine (BMIP) and 2,6-bis-(1′-methylbenzimidazol-2′-yl)-4-hydroxypyridine (HOBMIP) derived from H_2BIP and H_3OBIP by methylation were examined, the negative result (entries 9 and 10) indicated the nature of tridentate-chelate ligand and N−H groups in imidazolyl moieties play key roles in the reaction. This may be attributed to the subtle property of imidazole ligand that would modulate its coordination capability via deprotonation and protonation, further mediating the reactivity of metal center.[15] The control experiments indicated that copper salt, ligand, base, and oxidant are indispensable for the reaction (see Table S1).

We next turned our attention to screen base, copper salt, and oxidant as well as temperature. Screening of bases indicated that the optimal amount of LiO^{t}Bu was 0.6 equiv to **2a** (see Table S1). The strong base LiOH was equally optimal (78%, Table S2), and KO^{t}Bu and NaOH were moderate (64% and 73%). The weak bases K_2CO_3, Na_3PO_4, and DABCO were inferior in the reaction. NaOAc and urotropine led to no conversion. Both Cu(I) and Cu(II) salts were active for the reaction (Table S3). Among them, $CuCl_2$ gave a higher yield of **3aa** (83%). Then, we evaluated the effect of oxidant; H_2O_2 and DTBP gave no desired product, whereas CHP provided a moderate yield of **3aa** (47%, Table S4). The reaction worked well at 40 to 90 °C and gave a higher yield at 60 °C. In addition, the amount of substrates and catalyst as well as reaction time were also optimized (Table S5). The best ratio is **1a**:**2a**:Cu(II):ligand:oxidant = 32:1:0.05:0.06:1.5 with 0.6 equiv of LiO^{t}Bu. Finally, variation of the reaction time indicated that the reaction was completed in 1 h under the optimal conditions.

With the optimal conditions in hand, we investigated the scopes and limitations of the reaction. Under the optimal conditions, a variety of terminal arylalkynes (**2a**−**2n**, Table 1) bearing an electron-rich methyl or methoxyl group afforded **3ab**−**3ae** smoothly in yields of 74−90%. The high yield in *ortho*-methyl substituted alkyne (**3ac**) indicates that steric effect of the alkyne terminus is insensitive to the reaction. Bearing an electron-deficient group such as 4-F, 4-Cl, 4-Br, 4-CN, or 3-COOMe at the aromatic ring also afforded **3af**−**3aj** in moderate yields of 47−78% by extending the reaction time to 2 h. Functional groups such as aryl bromide, aryl nitrile, and ester sensitive to metal-catalysis remained intact in the reaction, which could be readily used as sources for further derivations. However, when pyridinyl alkynes were used, the reaction became sluggish, affording 28% (**3ak**) and 29% (**3al**) yields. Moreover, diethynyl benzenes also afforded ditopic products **3am** and **3an** in moderate yields. Thus, the terminal alkynes with various substituents on aromatic ring are compatible, and

Table 1. CDC Reaction of 1a with Terminal Alkynes[a]



[a]Isolated yields. [b]Reaction in 2 h. [c]Diethynyl benzene is 0.5 mmol. [d]Reaction in 4 h. [e]3 equiv of LiO^{t}Bu and 12 h.

moderate to good isolated yields have been afforded under the optimal conditions. Efficient reactivity was also observed with aliphatic alkynes (**2o**−**2x**). We were pleased to find that alkylalkynes with long aliphatic chains were viable to furnish propiolamides (**3ao**−**3ar**) in moderate yields of 49−55% by prolonging the reaction time. Importantly, alkylalkynes bearing internal alkyne (**2s** and **2t**), ester (**2u**), ether (**2v** and **2w**), and N-Boc-piperidine (**2x**) functional groups were tolerated in the reaction with moderated yields, providing opportunities for further additional modification of the products. Gratifyingly, Si(^{i}Pr)$_3$ protected alkyne (**2y**) was a suitable coupling partner and delivered **3ay** in 45% yield, which has potential applications in further synthesis.

Then, we turned our attention to formamides (Table 2). When DMF was used to react with terminal alkynes, the corresponding products **3ba**, **3bb**, **3bc**, **3bd**, and **3bh** were isolated in moderate yields of 32−52%, which are significantly lower than those of DEF. To disclose the reasons, full analysis of the reaction products of DMF and **2a** was performed. In

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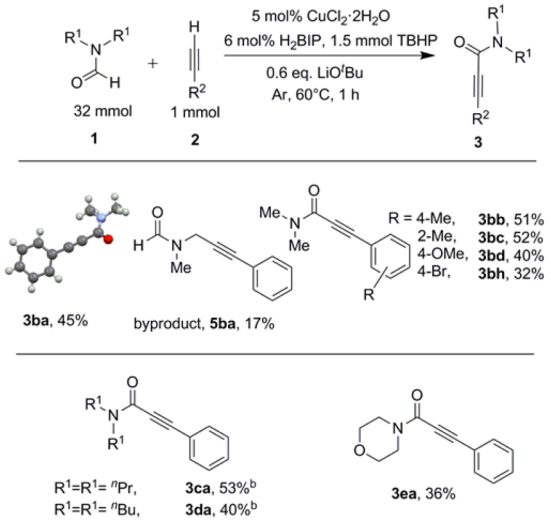
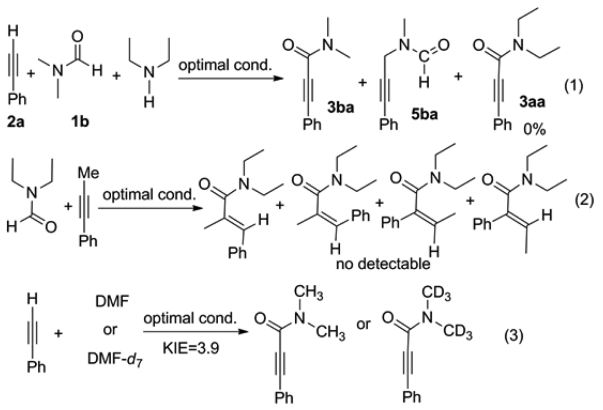
Table 2. CDC Reaction of Phenylacetylene with Various Formamides[a]



[a]Isolated yields. [b]Reaction in 12 h.

addition to **3ba** being afforded in 45% yield, which has been confirmed by single-crystal analysis (see SI), **5ba** was also isolated in 17% yield as a byproduct, demonstrating that a competition reaction involving alkynylation of C(sp^3)-H bond adjacent to the nitrogen atom occurred under the experiment conditions.[16] When *N*,*N*-di-*n*-propylformamide and *N*,*N*-di-*n*-butylformamide were used, the reaction became sluggish, and low yields of **3ca** and **3da** afforded concomitant with the unreacted **2a**. Extending the reaction time to 12 h gave **3ca** and **3da** in yields of 53% and 40%, respectively. The bulky groups at formamides such as *N*,*N*-diisopropylformamide and *N*-methylformanilide failed to couple with **2a** under the optimal conditions, indicating that the reaction is highly sensitive to the steric effect of formamides. In addition, the cyclo-formamide *N*-formylmorpholine was also examined to couple with **2a**, affording the desired product **3ea** in a moderate yield of 36%.

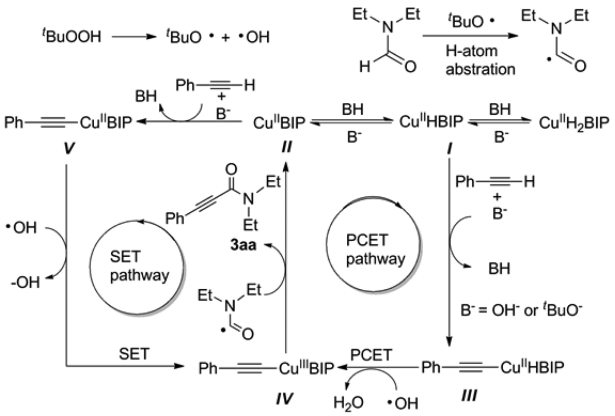
To understand the reaction mechanism, several control experiments were carried out. First, the reaction of **1a** and **2a** was conducted in the presence of the radical scavenger TEMPO. No desired product **3aa** was detected, indicating that a radical mechanism might be involved in the coupling process, which is often observed in Cu-TBHP catalyzed oxidation reactions.[14] Second, the reaction might proceed via aminocarbonylation of alkyne with CO and amine which are generated by decomposition of formamides at high temperature.[17] A competition experiment was conducted. When the reaction of DMF with **2a** was performed in the presence of excess diethylamine (see eqn 1), **3ba**, **5ba**, and **3aa** would be generated. However, no **3aa** was detected, indicating that the mechanism involving the generation of CO and amine in situ could be ruled out. Third, the reaction might involve a two-step procedure, addition of formamide to alkyne, followed by α-H or β-H elimination.[18] In this case, the alkene intermediate would be observed when the hydrogen elimination process failed to deliver. Thus, 1-phenyl-1-propyne was introduced to react with DEF. No reaction was observed (see eq 2). Thus, the mechanism involving electrophilic attack of formamide to alkyne followed by hydrogen elimination can be ruled out. On the other hand, the mechanism of nucleophilic attack of alkynyl



to formamide, formation of a progargylic alcohol intermediate, followed by oxidation to produce propiolamide was also precluded. According to Journet and co-workers' report on the addition of terminal alkyne anion to DMF, the intermediate α−aminoalkoxide may collapse to α,β-acetylenic aldehydes and other byproducts.[19] However, these products were not detected in our experiment. Moreover, 4-fluorobenzaldehydes and 2,3,4-trimethoxybenzaldehyde were used to couple with **2a** under the modified conditions (see SI). The desired ynones had yields of 10% and 34%, respectively, indicating the electron-withdrawing substitution, which may promote the nucleophilic addition of carbonyl group, has a negative influence on the reaction. These results exclude the possibility of the nucleophilic mechanism. Finally, the kinetic isotope effect (KIE, see eqn 3) experiment was conducted giving the KIE = 3.9. The high KIE value (see SI) indicates that the cleavage of formyl C−H bond is the rate-determining step in the reaction.

On the basis of our findings and the literatures, two proposed pathways were depicted in Scheme 2. Under basic condition,

Scheme 2. Proposed Mechanism of the Copper-Catalyzed CDC Reaction



complex CuH_2BIP might be deprotonated and transformed to CuHBIP (***I***), or further deprotonated to CuBIP (***II***). Species ***II*** may promote the reaction via a SET pathway. Species ***II*** coordinates with the terminal alkyne with the aid of base, forming an alkynyl adduct ***V***. In the meantime, TBHP dissociates into a hydroxyl radical and a butoxy radical through a homolytic cleavage. Species ***V*** was then converted to Cu(III) species ***IV*** through a SET process with the aid of the hydroxyl radical.[14b,c] On the other hand, the formamide radical, analogous to the acyl radicals, which has been postulated in

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aminocarbonylation of azoles, alkene or phenol with formamides,[14] was afforded by butoxy radical through H atom abstraction. The formamide radical would react with the intermediate ***IV***,[14e] delivering the product **3aa** and species ***II***. It is inferred that the Cu(III) species ***IV*** is a key intermediate for the C−C bond formation, in which the deprotonated ligand BIP^{2-} play a key role in stabilization of Cu(III) ion. Alternatively, a mechanism triggered from species ***I*** via a PCET pathway could also be possible. Species ***I*** coordinates with the terminal alkyne in the presence of base, forming an alkynyl adduct ***III***. Species ***III*** was then converted to the Cu(III) species ***IV*** intermediate through a concerted PCET process with the aid of the hydroxyl radical,[14e,20] in which the ligand $HBIP^-$ is further deprotonated into BIP^{2-} to stabilize Cu(III) ion. Similarly, the C−C bond formed via the reaction of formamide radical and alkynyl ligand from species ***IV***, delivering product **3aa** and species ***II***. To regenerate the catalytic cycle, species ***II*** will be converted to species ***I*** by protonation.

To further insight into the proposed mechanisms, DFT calculation investigation was carried out with the M06 functional (see SI). Potential energy surfaces for both SET and PCET pathways are depicted in Figure 1 and S73. The

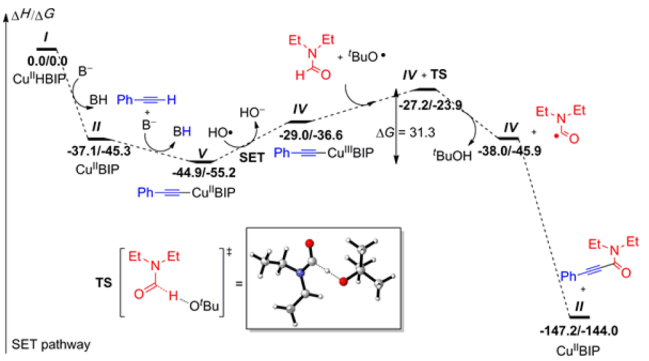

Figure 1. Potential free energy profiles of the copper-catalyzed CDC reaction in the SET pathway (Δ*H*/Δ*G* are given in kcal/mol).

calculation revealed that the SET pathway is relatively more plausible. The further deprotonation of species ***I*** to ***II*** is thermodynamically favored (Δ*G* = −45.3 *k*cal/mol) in basic condition. The terminal alkyne coordinates to species ***II*** after depronation, forming the alkynyl intermediate ***V*** spontaneously (Δ*G* = −9.9 *k*cal/mol). Then, the SET step transfers species ***V*** to ***IV***, which is only uphill by 18.6 *k*cal/mol. In the whole cycle, the H atom abstraction by butoxy radical is the rate-determining step, with an activation free energy of 31.3 *k*cal/mol, relative to species ***V***. This is in agreement with our observation of the KIE experiment. The C−C bond formation between formamide radical and alkynyl species ***IV*** is found to be barrierless with a large driving force due to the high reactivity of the Cu(III) species and formamide radical.[15,21] On the contrary, the PCET pathway encounters a highly endergonic step in regeneration of species ***I*** from ***II*** (Figure S73), which is expected to be less feasible in the basic condition.

In summary, we have developed the first catalytic aminocarbonylation of terminal alkynes with formamides through CDC of C(sp)-H and $C(sp^2)$-H bonds in the presence of CuH_2BIP complex as a catalyst, which provides a direct and efficient approach to synthesize propiolamides with a broad substrate scope and excellent functional group compatibility. Preliminary mechanism studies revealed that the cleavage of carbamoyl C−H bond affording formamide radical is the rate-determining step.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.5b02881.

Experimental procedures, characterization data, the kinetic isotope effect experiment, and DFT calculation (PDF)

Crystallographic data of **3ba** (CIF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail for B.Y.: cesybh@mail.sysu.edu.cn.

*E-mail for Z.K.: kezhf3@mail.sysu.edu.cn.

Notes

The authors declare no competing financial interest.

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