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Cleavage of C–N bonds in guanidine derivatives and its relevance to efficient C–N bonds formation

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ABSTRACT

Efficient nonenzymatic decomposition of guanidine derivatives with high structural and functional diversity into anilide products is achieved in the presence of Pd^{II}/Cu(II) carboxylates/CO, relying on a dual C–N bonds cleavage strategy. In this decomposition process, the cooperative action of Pd^{II} species, Cu(II) carboxylates, and CO provides not only the *N*-acylating agents but also an initiator to trigger this C–N bonds cleavage sequence. The current results indicate that Pd^{II}/Cu(II) carboxylates/CO system provides a convenient and practical method for highly selective cleavage of unreactive C–N single bonds.

1. Introduction

Over the past few decades, successful cleavage and/or formation of the carbon–nitrogen single bonds with the help of the transition metal complexes has remained one of the most important and challenging issues in organometallic chemistry,[1] which has attracted considerable attention of synthetic chemists because of their potential applications in organic synthesis and pharmaceutical research. Despite the significant progress made in this field, there are relatively few available protocols concerning the cleavage of the unactivated carbon–nitrogen single bonds, such as *N*-imino bonds[2] and *N*-cyano bonds,[3] with concomitant formation of new C–N bonds. It is worth noting that in 2013 Wang and Falck have reported a first example of intramolecular cyanation of a styrene by a rhodium-catalyzed N–CN cleavage reaction.[3b]

Among the numerous types of organic compounds possessing the carbon–nitrogen bonds, guanidines were chosen to test the selective cleavage of unreactive C–N bonds because they are C–N rich compounds including different types of C–N bonds. In addition, it is noteworthy that the decomposition of guanidine derivatives with C–N cleaving enzymes in water existed extensively in nature.[4] However, very little information is available for the transition metal promoted decomposition of guanidine derivatives, and as such cleavage of even one C–N bond in guanidine derivatives performed by transition metals had never been observed until recently (Scheme 1).[5] Herein, we describe a new class of valuable cleavage of unreactive C–N single bonds using a Pd^{II}/Cu(II) carboxylates/CO system, whereby nitrogen-rich guanidine derivatives serve as double 'N' atom sources of amides through highly selective cleavage of two carbon–nitrogen single bonds in the presence of carbon–nitrogen multiple bonds. In contrast with enzymatic decomposition of guanidine derivatives,[4] our strategy involving the consecutive cleavage of two C–N single bonds is an appealing alternative to the decomposition of guanidine derivatives to substituted amines. To the best of our knowledge, the present study constitutes the first example of the corresponding amide bond construction from highly selective C–N bonds cleavage of basic guanidine derivatives regardless of the electronic nature and steric hindrance of the substituent on the aromatic ring.

2. Results and discussions

To explore the feasibility of the cleavage of two individual C–N single bonds of guanidine derivatives in a one-pot procedure, we commenced our investigations by examining the decomposition reaction of diphenyl guanidine (**1a**) as a twofold aniline moiety with various acetate salts. Although ammonium carboxylate salts have been widely utilized for amidation by strong heating since 1885,[6] little was known that the acetate salts alone can act as a selective *N*-acetylating agent.[7] After some experimentation, we were intrigued to find that $Cu(OAc)_2$ was more efficient than other

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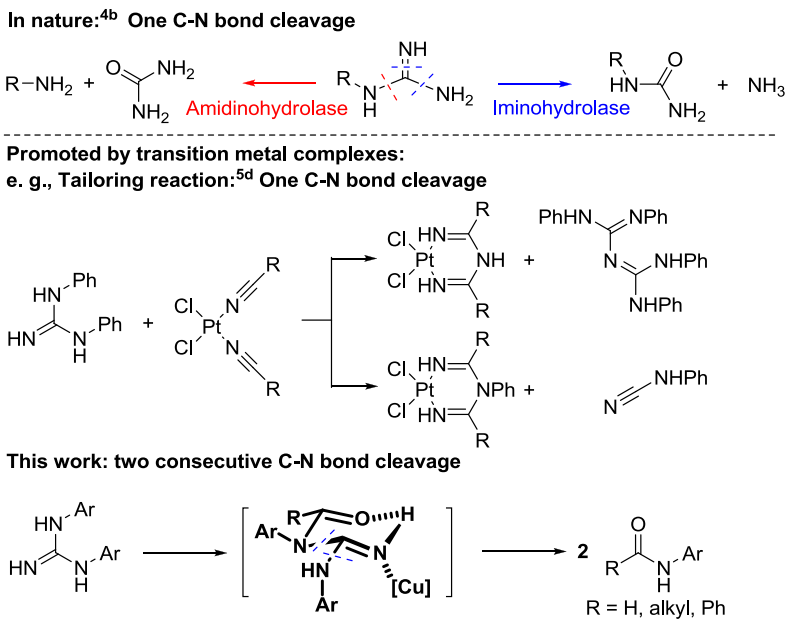
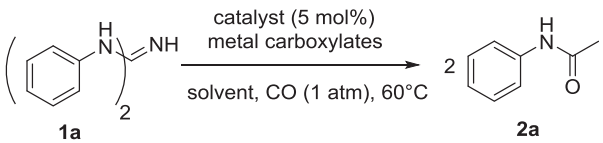


Scheme 1. Unreactive C–N bonds cleavage of guanidine derivatives.

metal salts (Table 1, entries 1–4), and the decomposition reaction of diphenyl guanidine (**1a**) with 2.2 equiv of $Cu(OAc)_2$ in acetonitrile in the presence of CO afforded 16% yield of expected acetanilide (**2a**). It showed that the needed reactivity is dramatically affected by subtle changes of the metal used. It is worth noting that the existence of CO atmosphere is indispensable for desired reactivity, as verified by control experiments (Table 1, entries 5 and 6). Gratifyingly, further investigation revealed that the addition of catalytic Pd^{II} species, such as $PdCl_2$ and $Pd(OAc)_2$, gave dramatically improved yield of the expected products (Table 1, entries 7 and 8). Notably, the key modification to achieve higher yields was the use of benzonitrile as a solvent at 120 °C (Table 1, entry 9), which significantly affects both the rate and outcome of the reaction, and yield up to 70% after column chromatography purification. At higher temperature (150 °C) complex mixtures were observed and anilide product **2a** was obtained in a slightly lower yield of 58% (Table 1, entry 10); lower temperatures below 60 °C slowed down the reaction without leading to better yields even after extended reaction times. Furthermore, the amount of $Cu(OAc)_2$ could be reduced to 1 equiv with only a slight decrease in the product yield, while further decrease caused a significant yield drop to 40% (Table 1, entries 11 and 12). Finally, various additives (KI and NaI), ligands (PPh_3, XPhos, 1,2-bis(diphenylphosphino)ethane (dppe), etc.) and solvents (DMSO and 1,4-dioxane) were also examined; however, no improvement in yield was observed, alas to no avail. Based on the facts mentioned above, the reaction conditions described in entries 7–9 and 11 were selected as the standard conditions for further investigations depending on the specific substrates involved.

Table 1
Optimization of the reaction conditions[a]

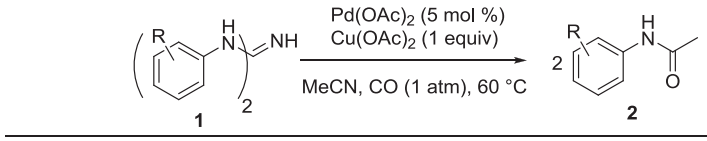


Entry	Solvent	M.C.[f] (equiv)	Catalyst	Yield[g] (%)
1	MeCN	KOAc (2.2)	—	n.d.[h]
2	MeCN	AgOAc (2.2)	—	n.d.[h]
3	MeCN	$Pd(OAc)_2$ (2.2)	—	n.d.[h]
4	MeCN	$Cu(OAc)_2$ (2.2)	—	16
5[b]	MeCN	$Cu(OAc)_2$ (2.2)	—	n.d.[h]
6[c]	MeCN	$Cu(OAc)_2$ (2.2)	—	n.d.[h]
7	MeCN	$Cu(OAc)_2$ (2.2)	$PdCl_2$	61
8	MeCN	$Cu(OAc)_2$ (2.2)	$Pd(OAc)_2$	65
9[d]	PhCN	$Cu(OAc)_2$ (2.2)	$Pd(OAc)_2$	70
10[e]	PhCN	$Cu(OAc)_2$ (2.2)	$Pd(OAc)_2$	58
11	MeCN	$Cu(OAc)_2$ (1.0)	$Pd(OAc)_2$	62
12	MeCN	$Cu(OAc)_2$ (0.5)	$Pd(OAc)_2$	40

[a] Reaction conditions: **1a** (0.2 mmol), metal carboxylates, catalyst (0.01 mol), solvent (2 mL), stirred at 60 °C for 12 h under CO (1 atm).
[b] N_2 (1 atm) instead of CO.
[c] Air (1 atm) instead of CO.
[d] PhCN (2 mL), stirred at 120 °C for 3 h.
[e] PhCN (2 mL), stirred at 150 °C for 3 h.
[f] M.C.=Metal carboxylates.
[g] Yield of the isolated product={n(**2a**)/[2×n (**1a**)]}×100%, n=mole number of the corresponding compounds.
[h] Not detectable.

With the optimized reaction conditions established, a wide variety of symmetrical *N*,*N*′-diaryl guanidines were submitted to the decomposition process to investigate its substrate scope and generality (Table 2). As might be anticipated, the reaction proceeded with moderate to good yields in the presence of both electron-deficient and electron-rich aromatic systems. Thus, substrates bearing substituents *meta*- and *para*-to the guanidines underwent the decomposition to form anilide products in 38–89% yields. In general, guanidines bearing electron-donating groups showed better reactivity than those containing electron-withdrawing groups. For instance, the reactions of substrate **1j** with a methoxyl group at the 4-position of the benzene ring, could be successfully converted into the desired product **2j** in 89% yield. On the other hand, the substrates with *p*-COMe and *p*-CO_2Me groups on the benzene ring afforded the desired products **2g** and **2h** in 51% and 45% yields, respectively. Next to the expected products, 3% of 4-aminoacetophenone and 34% of methyl 4-aminobenzoate as the byproduct were identified. In addition, various kinds of functional groups such as alkyl, alkoxyl, fluoro, chloro, bromo, trifluoromethyl, ester, ketone, and even oxidizable functional groups, such as –SMe, were also tolerated under the established catalytic conditions. Importantly, the successful preparation of **2e**, **2f**, **2k**, and **2r** with an intact chlorine/bromine provide ample opportunities for

Table 2
Scope of symmetrical *N*,*N*′-diarylguanidines[a,d]



2a	R = H	70%[b]	**2n**	51%[c]	
2b	R = 3-Me	58%			
2c	R = 4-Me	59%			
2d	R = 4-F	64%			
2e	R = 4-Cl	67%			
2f	R = 4-Br	54%			
2g	R = 4-Ac	51%			
2h	R = 4-CO_2Me	45%			
2i	R = 4-CF_3	61%			
2j	R = 4-OMe	89%[b]			
2k	R = 3-Cl	46%			
2l	R = 3-OMe	38%			
2m		53%[c]	**2o**	0%	
2p	R = 2-Me	37%	**2s**	0%	
2q	R = 2-F	53%	**2t**	R = 2-OMe 70%[c]	
2r	R = 2-Cl	69%[c]	**2u**	R = 2-SMe 34%[c]	
			2v	0%	

[a] Reaction conditions: **1** (0.2 mmol), $Cu(OAc)_2$ (0.2 mmol), $Pd(OAc)_2$ (0.01 mmol), MeCN (2 mL), stirred at 60 °C under CO (1 atm). [b] Used: **1** (0.2 mmol), $Cu(OAc)_2$ (0.44 mmol, 2.2 equiv), $Pd(OAc)_2$ (0.01 mmol), PhCN (2 mL), stirred at 120 °C under CO (1 atm). [c] Used: **1** (0.2 mmol), $Cu(OAc)_2$ (0.44 mmol, 2.2 equiv), $Pd(OAc)_2$ (0.01 mmol), MeCN (2 mL), stirred at 60 °C under CO (1 atm). [d] Yield of the isolated product = {n (**2a-v**) / [2 × n (**1a-v**)]} × 100%, n = mole number of the corresponding compounds.

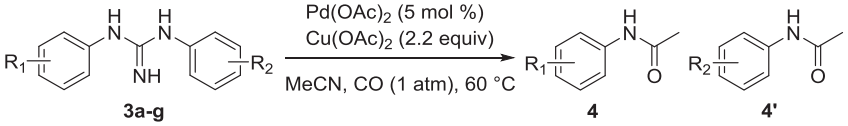
subsequent functionalization via conventional transition metal-catalyzed cross-coupling techniques. Besides the benzene ring, naphthyl-substituted guanidine **1n** was also compatible with this novel decomposition, generating the corresponding anilide **2n** in 51% yield. Surprisingly, substituting the arene ring with pyridine completely impeded the formation of the corresponding anilide **2o**, and we therefore reasoned that the nitrogen center of pyridine with a basic lone pair of electrons can coordinate readily with transition metal ions, which is detrimental for the C–N single bond cleavage process. In contrast to similar *para* substituted guanidine derivatives, the presence of a substituent *ortho* to the guanidines affords the anilides in slightly lower yield owing to the increased effective size of metal coordination sphere. In the meantime, we turned our attention to evaluating two substituents at the aryl groups of guanidines, and we found that the desired 3′,5′-methylacetanilide **2m** could be furnished from **1m** with a satisfactory yield of 53%. However, it is hard to observe the generation of 2′-bromo-4′-methylacetanilide **2s** when we use **1s** as the substrate, and we assumed that the *ortho*-Br is fragile under our transition metal system and incompatible in the reaction. Notably, the protected N–H guanidine **1v** failed to give the desired product **2v** under identical conditions, suggesting that the existence of N–H bonds is essential. Furthermore, we have examined 1,3-dibenzylguanidine (**1w**) and 1,3-dicyclohexylguanidine (**1x**) under our standard conditions, and no expected products were detected.

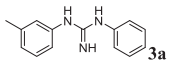
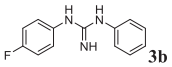
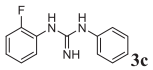
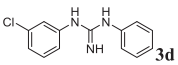
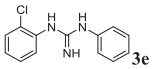
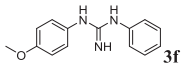
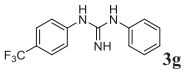
Subsequently, the scope of unsymmetrical *N*,*N*′-diaryl guanidines was assessed under the standard reaction conditions, and the results are summarized in Table 3. As might be expected, the unsymmetrical guanidine derivatives bearing electron-donating or electron-withdrawing substituents on the aniline moieties could be successfully converted to two kinds of expected decomposition products in reasonable yields, which mean that two C–N bonds have been successively cleaved under the current catalytic condition. Actually, the irregular and slight ratio fluctuation of **4**/**4**′ around 1:1 strongly supported that two successive C–N bonds cleavage of symmetrical and unsymmetrical guanidine derivatives were realized in two relatively independent transition pathways, respectively.

To evaluate the potential of our system, we further envisaged the scope and limitations of decomposition process with various Cu(II) carboxylates as illustrated in Table 4, which would enlarge the molecular diversity. To our great delight, the decomposition protocol took place efficiently and was successfully applied to various Cu(II) carboxylates, such as cupric propionate **5a**, cupric formate **5b**, cupric 2-ethylhexanoate **5c**, cupric *n*-octadecanoate **5d**, and cupric benzoate **5e**. Cu(II) trifluoroacetate **5f** and Cu(II) methanesulfonate **5g**, failed to produce the desired anilide products.

Based on the known copper and palladium chemistry and the above experimental results, the catalytic cycle of this process was hypothesized as shown in Scheme 2. Similar to related reactions with stoichiometric quantities of Pt complexes,[5d] it seems likely that the mechanism proceeds via acetonitrile (or benzonitrile) coordinated palladium(II) complexes. Their intermediacy can explain the fact that the nature of the solvent has an important role for the efficiency of the reaction; in acetonitrile or benzonitrile solution, full conversion and high yields can be achieved presumably because acetonitrile or benzonitrile coordinated to the $Pd(OAc)_2$. CO is known to reduce Pd^{II} species to Pd^0,[8a] and Pd^0 was assumed to be

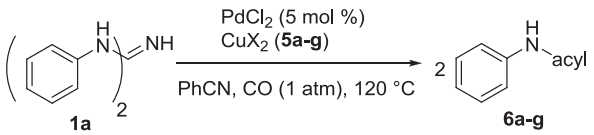
Table 3
Scope of unsymmetrical *N*,*N*′-diarylguanidines[a,d]

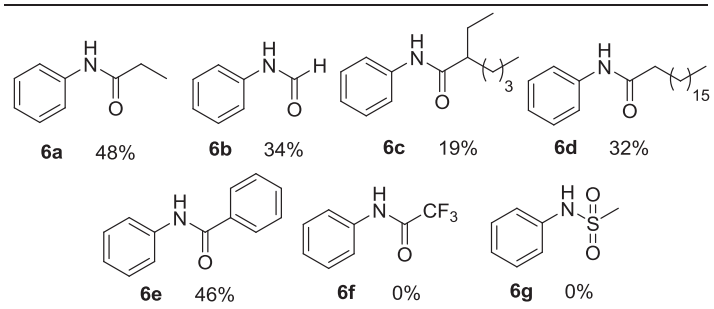


Entry	Substrate	Product	Yield[b] (%)
1		R_1=3-Me R_2=H	50% 50%
2		R_1=4-F R_2=H	57% 57%
3		R_1=2-F R_2=H	69%[c] 50%[c]
4		R_1=3-Cl R_2=H	48% 57%
5		R_1=2-Cl R_2=H	76% 40%
6		R_1=4-OMe R_2=H	51% 65%
7		R_1=4-CF_3 R_2=H	48% 50%

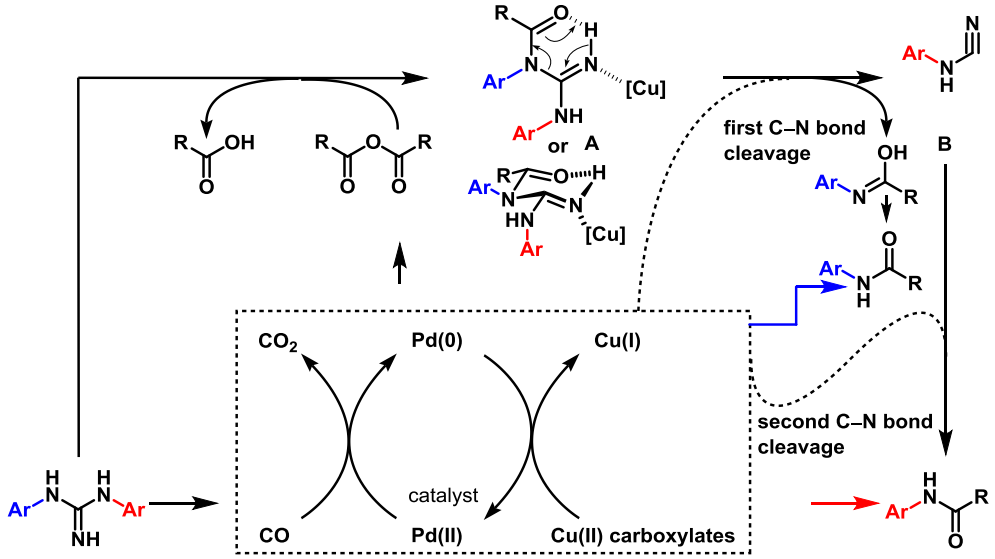
[a] Reaction conditions: **3** (0.2 mmol), $Cu(OAc)_2$ (0.44 mmol), $Pd(OAc)_2$ (0.01 mmol), MeCN (2 mL), stirred at 60 °C under CO (1 atm).
[b] Yield based on NMR.
[c] Isolated yield.
[d] Yield of the product=[*n*(**4** or **4**′)/*n*(**3a**–**g**)]×100%, *n*=mole number of the corresponding compounds.

Table 4
Scope of Cu(II) carboxylates[a,b]





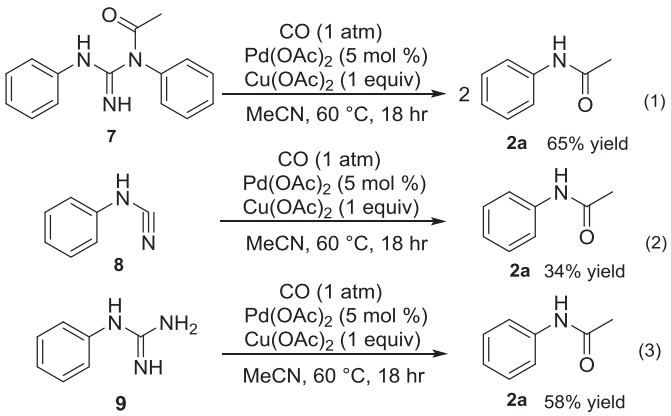
[a] Reaction conditions: **1a** (0.2 mmol), CuX_2 (0.44 mmol, 2.2 equiv), $PdCl_2$ (0.01 mmol), PhCN (2 mL), stirred at 120 °C under CO (1 atm). [b] Yield of the isolated product = {n (**6a-g**) / [2 × n (**1a**)]} × 100%, n = mole number of the corresponding compounds.



Scheme 2. Proposed mechanism.

readily oxidized by $Cu(OAc)_2$ to re-generate the active Pd^{II} catalyst and liberate carboxylic anhydride.[8b] Subsequently, carboxylic anhydride reacts with *N*,*N*′-diaryl guanidine to give intermediate A as proposed in Scheme 2. The acylation intermediate **A** was decomposed into the anilide products and *N*-arylcyanamide **B**, which is the first C–N bond cleavage. Finally, the *N*-arylcyanamide **B** was further decomposed to another anilide product, which would likely have undergone secondary cleavage of the C–N bond.[3a,3b] Although the mechanism details for the decomposition processes are not completely clear yet, we believe that both the stability and the reactivity of this intermediate **A** and **B** are crucial for the fate of this transform. Meanwhile, the existence of Cu(II) carboxylates actually play three roles in this reaction, which not only helped to cleave two individual C–N bonds in the decomposition process but also served as acylating agents and oxidants.

To validate our supposition about the reaction mechanism, several experimental results that support our tentative mechanism were performed under our optimized conditions (Scheme 3). First, the reaction of *N*,*N*′-diphenyl guanidine **1a** with acetic anhydride was carried out in acetonitrile at room temperature, and mono-acetyl guanidine **7** was isolated, which is in line with the previous reports.[9] Second, the reaction of independently synthesized **7** under the optimized conditions (Scheme 3, Eq. 1), which includes 5 mol % $Pd(OAc)_2$, 1.0 equiv of $Cu(OAc)_2$, under CO at 60 °C, could afford the desired product **2a** in 65% yield with almost equal efficiency to *N*,*N*′-diphenyl guanidine **1a** as the substrate. This fact clearly indicated that mono-acyl guanidines **A** might form at the outset of the process. Third, the potential occurrence of *N*-arylcyanamide **B** in our C–N bond cleavage approach was confirmed by examining the reaction of **8** (Scheme 3, Eq. 2), which led to the formation of acetanilide **2a** in 34% yield. Particularly in Kukushkin's report,[5d] phenyl cyanamide **8** survived and failed to undergo further C–N bond cleavage in the presence of stoichiometric quantities of Pt(II)bis-nitrile complexes, which indicated our catalytic system is unique and unusual for two successive C–N single bonds cleavage. Fourth, the use of nitrogen-rich *N*,*N*′-diphenyl urea and *N*,*N*′-diphenyl thiourea as substrates failed to give access to decomposition products, thus implying that the existence of –C(=NH) is necessary for our C–N bond cleavage reaction. To our delight, *N*-phenylguanidine **9** including the –C(=NH) group could be normally decomposed into acetanilide **2a** with a synthetically useful yield (Scheme 3, Eq. 3). Taken together, all of the above mentioned verified our hypothesis to some extent. As far as we know, typical synthetic routes to guanidines could be irreversibly offered by the reaction of amines with different guanylating reagents in the previous literature. However, our work may provide a first beneficial complement and experimental evidence for the reverse transformation from guanidines to protected amines (anilides).



Scheme 3. Mechanistic studies.

3. Conclusion

To conclude, we have unveiled an unprecedented one-step decomposition process of guanidine derivatives with high structural and functional diversity into anilide products in the presence of Pd^{II}/Cu(II) carboxylates/CO, relying on a dual C–N bonds cleavage strategy. Particularly, this study shows clearly, for the first time that the weakly acidic anilides could be obtained from the decomposition of strong basic *N*,*N*′-diaryl guanidines as double aniline backbones through a rather challenging cleavage of inert *N*-imino and *N*-cyano single bonds, thus standing out from known amide syntheses. In this decomposition process, the cooperative action of Pd^{II} species, Cu(II) carboxylates, and CO, which acted not only as the *N*-acylating agents but also an initiator to trigger this C–N bond cleavage sequence, is crucial to promoting this reaction with good yields. In parallel with the enzymatic decomposition pathway, we offered a novel and interesting possibility for guanidine decomposition under transition metal-catalyzed reaction conditions. More importantly, it would provide a revealing insight

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for exploring the ability of our competent Pd^{II}/Cu(II) carboxylates/CO system for the highly selective cleavage and transformation of other compounds including inert C–N bonds. Further mechanistic investigations, extensive explorations and synthetic applications of Pd^{II}/Cu(II) carboxylates/CO system in various C–N bonds cleavage are currently underway in our laboratory.

4. Experimental section

4.1. General comments

Unless otherwise noted, all reagents were purchased from commercial sources and used without further purification. The reaction solvent, MeCN was dried by refluxing over CaH_2, and freshly distilled prior to use. All reactions were monitored by TLC and visualized by UV lamp (254 nm)/or by staining with a solution of 10 g phosphomolybdic acid and 100 mL EtOH followed by heating. Flash column chromatography was performed using 230–400 mesh silica gel. Melting point ranges were determined on a BÜCHI Melting Point B-540 apparatus and are uncorrected. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were obtained on Bruker AV-400 instrument. Chemical shifts for ^{1}H NMR spectra were reported in δ parts per million (ppm) referenced to an internal $SiMe_4$ standard. The abbreviations s, br s, d, t, q, and m stand for the resonance multiplicity singlet, broad singlet, doublet, triplet, quartet, and multiplet, respectively. HR-ESI-MS spectra were recorded on a Bruker Esquire LC mass spectrometer using electrospray ionization.

Caution: CO is particularly dangerous. These procedures should be carried out by knowledgeable laboratory scientists.

1a and **1p** were obtained from commercial suppliers.

4.2. General procedure for synthesis of symmetrical *N,N′*-disubstituted guanidines 1b, 1c, 1e, 1g, 1h, 1i, 1j, and 1o according to Ma's method[10] (method A)

A Schlenk tube was charged with aryl halides (1.0 mmol), guanidine nitrate (1.0 mmol), *N*-methylglycine (8.9 mg, 0.1 mmol (for aryl iodides) or 17.8 mg, 0.2 mmol (for aryl bromides)), recrystallized CuI (9.5 mg, 0.05 mmol (for aryl iodides) or 19.0 mg, 0.1 mmol (for aryl bromides)), and K_3PO_4 (1.27 g, 6 mmol). The tube was evacuated and back-filled with N_2 before MeCN (5 mL) was added. The reaction mixture was stirred at 70 °C until the corresponding aryl halide was completely consumed as monitored by TLC. The reaction mixture was extracted with ethyl acetate. The organic layer was washed with water and brine and dried over Na_2SO_4. Removal of solvent by evaporation in vacuo followed by purification with column chromatography on silica gel (50:1–20:1 methylene chloride/methanol as eluent) provided the desired products.

*4.2.1. 1,3-Di-m-tolylguanidine (**1b**).* White solid. Mp: 110–111 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.16 (t, J=7.6 Hz, 2H; H_{Ar}), 6.84–6.92 (m, 6H; H_{Ar}), 2.28 (s, 6H; CH_3). HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{15}H_{18}N_3$) requires *m*/*z* 240.1501, found *m*/*z* 240.1510.

*4.2.2. 1,3-Di-p-tolylguanidine (**1c**).* White solid. Mp: 168–170 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.11 (d, J=8.2 Hz, 4H; H_{Ar}), 7.00 (d, J=8.2 Hz, 4H; H_{Ar}), 2.31 (s, 6H; CH_3). HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{15}H_{18}N_3$) requires *m*/*z* 240.1501, found *m*/*z* 240.1501.

*4.2.3. 1,3-Bis(4-chlorophenyl)guanidine (**1e**).* White solid. Mp: 145–147 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 (d, J=8.7 Hz, 4H; H_{Ar}), 7.00 (d, J=8.7 Hz, 4H; H_{Ar}). HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{13}H_{12}Cl_2N_3$) requires *m*/*z* 280.0408, found *m*/*z* 280.0417.

*4.2.4. 1,3-Bis(4-acetylphenyl)guanidine (**1g**).* Pale-yellow solid. Mp: 211–212 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (d, J=8.6 Hz, 4H; H_{Ar}), 7.23 (d, J=8.6 Hz, 4H; H_{Ar}), 2.58 (s, 6H; CH_3). HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{17}H_{18}N_3O_2$) requires *m*/*z* 296.1399, found *m*/*z* 296.1408.

*4.2.5. Dimethyl 4,4′-(iminomethylene)bis(azanediyl)dibenzoate (**1h**).* White solid. Mp: 201–202 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (d, J=8.5 Hz, 4H; H_{Ar}), 7.19 (d, J=8.5 Hz, 4H; H_{Ar}), 3.90 (s, 6H; OCH_3). HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{17}H_{18}N_3O_4$) requires *m*/*z* 328.1297, found *m*/*z* 328.1299.

*4.2.6. 1,3-Bis(4-(trifluoromethyl)phenyl)guanidine (**1i**).* White solid. Mp: 165–166 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 (d, J=8.4 Hz, 4H; H_{Ar}), 7.23 (d, J=8.4 Hz, 4H; H_{Ar}). HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{15}H_{12}F_6N_3$) requires *m*/*z* 348.0935, found *m*/*z* 348.0937.

*4.2.7. 1,3-Bis(4-methoxyphenyl)guanidine (**1j**).* White solid. Mp: 154–156 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.04 (d, J=8.5 Hz, 4H; H_{Ar}), 6.85 (d, J=8.5 Hz, 4H; H_{Ar}), 3.78 (s, 6H; OCH_3). HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{15}H_{18}N_3O_2$) requires *m*/*z* 272.1399, found *m*/*z* 272.1398.

*4.2.8. 1,3-Di(pyridin-2-yl)guanidine (**1o**).* White solid. Mp: 175–176 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19–8.20 (m, 2H; H_{Ar}), 7.38–7.51 (m, 2H; H_{Ar}), 6.65–6.84 (m, 4H; H_{Ar}). HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{11}H_{12}N_5$) requires *m*/*z* 214.1093, found *m*/*z* 214.1093.

4.3. General procedure for synthesis of symmetrical *N,N′*-disubstituted guanidines 1d, 1f, 1k, 1l, 1m, 1n, 1q, 1r, 1s, 1t, 1u, and 1v according to Keana's method[11] (method B)

To a stirred solution of the appropriate amine (10 mmol) in EtOH (3–5 mL) at 0 °C was carefully added a solution of BrCN (11 mmol, 1.1 equiv) in EtOH (1–2 mL). After the exotherm subsided, the reaction mixture was allowed to warm to 25 °C and was then heated at 150 °C for 15–30 min, while N_2 was swept through the flask to completely remove the boiling solvent. The fused reaction mixture was allowed to cool to 25 °C, and the resulting glassy solid was taken up in hot EtOH (10–15 mL), treated with decolorizing charcoal (50–60 mg), and filtered through Celite. The filtrate was diluted with aqueous 1 N NaOH (10–20 mL), and the precipitated guanidine free base was filtered off. The analytical sample was obtained by repeated crystallizations from aqueous EtOH.

*4.3.1. 1,3-Bis(4-fluorophenyl)guanidine (**1d**).* White solid. Mp: 136–138 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.17–6.90 (m, 8H; H_{Ar}), 4.96 (br s, 3H; NH). HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{13}H_{12}F_2N_3$) requires *m*/*z* 248.0994, found *m*/*z* 248.1001.

*4.3.2. 1,3-Bis(4-bromophenyl)guanidine (**1f**).* Yellow solid. Mp: 155–157 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (d, J=7.0 Hz, 4H; H_{Ar}), 7.00 (d, J=7.0 Hz, 4H; H_{Ar}), 4.62 (br s, 3H; NH). HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{13}H_{12}Br_2N_3$) requires *m*/*z* 369.9372, found *m*/*z* 369.9373.

*4.3.3. 1,3-Bis(3-chlorophenyl)guanidine (**1k**).* White solid. Mp: 147–148 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21–7.25 (m, 2H; H_{Ar}), 7.18–7.12 (m, 2H; H_{Ar}), 7.06–6.96 (m, 4H; H_{Ar}), 4.82 (br s, 3H; NH).

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HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{13}H_{12}Cl_2N_3$) requires *m/z* 280.0403, found *m/z* 280.0410.

*4.3.4. 1,3-Bis(3-methoxyphenyl)guanidine (**1l**).* White solid. Mp: 133–134 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19–7.23 (m, 2H; H_{Ar}), 6.74–6.66 (m, 4H; H_{Ar}), 6.60–6.63 (m, 2H; H_{Ar}), 3.76 (s, 6H; OCH_3). HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{15}H_{18}N_3O_2$) requires *m/z* 272.1394, found *m/z* 272.1397.

*4.3.5. 1,3-Bis(3,5-dimethylphenyl)guanidine (**1m**).* White solid. Mp: 159–160 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.72 (s, 4H; H_{Ar}), 6.70 (s, 2H; H_{Ar}), 2.27 (s, 12H; CH_3). HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{17}H_{22}N_3$) requires *m/z* 268.1808, found *m/z* 268.1820.

*4.3.6. 1,3-Di(naphthalen-1-yl)guanidine (**1n**).* Gray solid. Mp: 201–202 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.30–7.31 (m, 14H; H_{Ar}). HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{21}H_{18}N_3$) requires *m/z* 312.1495, found *m/z* 312.1508.

*4.3.7. 1,3-Bis(2-fluorophenyl)guanidine (**1q**).* White solid. Mp: 116–117 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45–7.49 (m, 2H; H_{Ar}), 7.07–7.11 (m, 4H; H_{Ar}), 6.98–7.03 (m, 2H; H_{Ar}), 4.73 (br s, 3H; NH). HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{13}H_{12}F_2N_3$) requires *m/z* 248.0994, found *m/z* 248.1009.

*4.3.8. 1,3-Bis(2-chlorophenyl)guanidine (**1r**).* White solid. Mp: 166–167 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53–7.64 (m, 2H; H_{Ar}), 7.36–7.42 (m, 2H; H_{Ar}), 7.20–7.25 (m, 2H; H_{Ar}), 6.95–7.02 (m, 2H; H_{Ar}). HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{13}H_{12}Cl_2N_3$) requires *m/z* 280.0403, found *m/z* 280.0409.

*4.3.9. 1,3-Bis(2-bromo-4-methylphenyl)guanidine (**1s**).* White solid. Mp: 193–194 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31–7.43 (m, 4H; H_{Ar}), 7.05–7.13 (m, 2H; H_{Ar}), 2.29 (s, 6H; CH_3). HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{15}H_{16}Br_2N_3$) requires *m/z* 397.9685, found *m/z* 397.9692.

*4.3.10. 1,3-Bis(2-methoxyphenyl)guanidine (**1t**).* Brown solid. Mp: 99–101 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (d, *J*=6.9 Hz, 2H; H_{Ar}), 7.02–6.88 (m, 6H; H_{Ar}), 3.84 (s, 6H; OCH_3). HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{15}H_{18}N_3O_2$) requires *m/z* 272.1394, found *m/z* 272.1390.

*4.3.11. 1,3-Bis(2-(methylthio)phenyl)guanidine (**1u**).* White solid. Mp: 140–141 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26–7.29 (m, 4H; H_{Ar}), 7.16–7.19 (m, 2H; H_{Ar}), 7.03–7.07 (m, 2H; H_{Ar}), 2.41 (s, 6H; CH_3). HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{15}H_{18}N_3S_2$) requires *m/z* 304.0942, found *m/z* 304.0947.

*4.3.12. 1,3-Diethyl-1,3-diphenylguanidine (**1v**).* Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.14 (t, *J*=7.9 Hz, 4H; H_{Ar}), 6.96 (t, *J*=7.4 Hz, 2H; H_{Ar}), 6.88 (d, *J*=8.6 Hz, 4H; H_{Ar}), 3.63 (q, *J*=7.1 Hz, 4H; CH_2), 1.08 (t, *J*=7.1 Hz, 6H; CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.6 (C=NH), 144.8 ($2C_{Ar}$), 128.6 ($4CH_{Ar}$), 124.3 ($2CH_{Ar}$), 123.6 ($4CH_{Ar}$), 45.8 ($2CH_2$), 13.1 ($2CH_3$). HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{17}H_{22}N_3$) requires *m/z* 268.1808, found *m/z* 268.1810.

*4.3.13. 1,3-Dibenzylguanidine (**1w**).* White solid. Mp: 187–188 °C. ^{1}H NMR (400 MHz, DMSO) δ 8.16 (br s, 3H, NH), 7.52–7.14 (m, 10H), 4.47 (s, 4H, CH_2). ^{13}C NMR (150 MHz, DMSO) δ 156.2 (C=NH), 137.4 ($2C_{Ar}$), 128.5 ($4CH_{Ar}$), 127.4 ($2CH_{Ar}$), 127.2 ($4CH_{Ar}$), 43.9 ($2CH_2$). HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{15}H_{18}N_3$) requires *m/z* 240.1495, found *m/z* 240.1494.

*4.3.14. 1,3-Dicyclohexylguanidine (**1x**).* White solid. Mp: 157–158 °C. ^{1}H NMR (400 MHz, DMSO) δ 7.32 (br d, *J*=59.2 Hz, 3H, NH), 3.46 (s, 2H, 2CH), 1.92–1.42 (m, 10H), 1.40–0.79 (m, 10H). ^{13}C NMR (150 MHz, DMSO) δ 153.8 (C=NH), 49.4 (2C), 32.2 ($4CH_2$), 24.8 ($4CH_2$), 24.1 ($2CH_2$). HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{13}H_{26}N_3$) requires *m/z* 224.2121, found *m/z* 224.2124.

4.4. General procedure for the synthesis of unsymmetrical *N,N′*-disubstituted guanidines 3a, 3b, 3c, 3d, 3e, 3f, and 3g according to Keana's method[11] (method C)

A stirred mixture of the appropriate cyanamide (10 mmol) and amine hydrohalide salt (10 mmol) in chlorobenzene (30 mL) was heated at 90–130 °C under N_2 for 2–10 h. The reaction was monitored by TLC ($CHCl_3$/EtOH/Et_3N, 75:20:5). On cooling to 25 °C, the title compounds precipitated from solution as their hydrohalide salts were filtered off, and washed with dichloromethane (CH_2Cl_2) (3×5 mL) to remove residual chlorobenzene. When the guanidine hydrohalide did not precipitate from the cooled reaction mixture, the solvent was evaporated, and the residue was taken up in aqueous 1 N HCl (15 mL). The solution was basified with 1 N NaOH, and the precipitated guanidine free base was filtered off. The guanidine free base was crystallized by dissolution in EtOH (20–30 mg/mL), followed by slow addition of H_2O. The analytical sample was obtained after two further recrystallizations. Typically, the guanidine hydrohalide salts were crystallized inside a closed Et_2O-containing chamber, by the slow diffusion of Et_2O into a loosely covered flask containing a solution of the guanidine salt in absolute EtOH (20–40 mg/mL). Two such recrystallizations provided the analytical material.

*4.4.1. 1-Phenyl-3-m-tolylguanidine (**3a**).* Pink solid. Mp: 116–118 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28–7.35 (m, 2H; H_{Ar}), 7.24–6.79 (m, 7H; H_{Ar}), 4.95 (br s, 3H; NH), 2.32 (s, 3H; CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.0 (C=NH), 139.4, 129.4, 129.3, 123.6, 122.9, 119.9, 21.4 (CH_3). HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{14}H_{16}N_3$) requires *m/z* 226.1339, found *m/z* 226.1343.

*4.4.2. 1-(4-Fluorophenyl)-3-phenylguanidine (**3b**).* Pink solid. Mp: 114–116 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28–7.35 (m, 2H; H_{Ar}), 7.15–6.96 (m, 7H; H_{Ar}), 4.91 (br s, 3H; NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.4 (C=NH), 129.5, 124.6, 122.9, 116.2, 116.0. HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{13}H_{13}FN_3$) requires *m/z* 230.1088, found *m/z* 230.1098.

*4.4.3. 1-(2-Fluorophenyl)-3-phenylguanidine (**3c**).* White solid. Mp: 121–122 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31–7.35 (m, 3H; H_{Ar}), 7.17–7.22 (m, 2H; H_{Ar}), 7.06–7.12 (m, 3H; H_{Ar}), 6.97–6.99 (m, 1H; H_{Ar}), 4.81 (br s, 3H; NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 129.5, 124.7 (d, *J*=3.7 Hz), 123.0, 116.1, 115.9. HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{13}H_{13}FN_3$) requires *m/z* 230.1088, found *m/z* 230.1098.

*4.4.4. 1-(3-Chlorophenyl)-3-phenylguanidine (**3d**).* Brown solid. Mp: 104–105 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29–7.36 (m, 2H; H_{Ar}), 7.25–7.14 (m, 3H; H_{Ar}), 7.13–7.07 (m, 2H; H_{Ar}), 7.03–6.92 (m, 2H; H_{Ar}), 4.91 (br s, 3H; NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.0 (C=NH), 130.4, 129.5, 122.9, 122.8, 121.0. HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{13}H_{13}ClN_3$) requires *m/z* 246.0793, found *m/z* 246.0801.

*4.4.5. 1-(2-Chlorophenyl)-3-phenylguanidine (**3e**).* White solid. Mp: 124–125 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28–7.43 (m, 4H; H_{Ar}), 7.20–7.22 (m, 3H; H_{Ar}), 7.09–7.11 (m, 1H; H_{Ar}), 6.94–6.99 (m, 1H; H_{Ar}), 4.78 (br s, 3H; NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.8 (C=NH), 123.0, 129.5, 127.7, 124.3, 123.5, 122.8. HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{13}H_{13}ClN_3$) requires *m/z* 246.0793, found *m/z* 246.0793.

*4.4.6. 1-(4-Methoxyphenyl)-3-phenylguanidine (**3f**).* Brown solid. Mp: 129–130 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27–7.38 (m, 2H;

H_{Ar}), 6.96–7.16 (m, 5H; H_{Ar}), 6.81–6.93 (m, 2H; H_{Ar}), 3.79 (s, 3H; OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.8 (C=NH), 129.5, 125.4, 123.0, 114.8, 55.5 (OCH_3). HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{14}H_{16}N_3O$) requires m/z 242.1288, found m/z 242.1299.

*4.4.7. 1-Phenyl-3-(4-(trifluoromethyl)phenyl)guanidine (**3g**).* Brown solid. Mp: 163–164 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.51–7.62 (m, 2H; H_{Ar}), 7.30–7.42 (m, 2H; H_{Ar}), 7.04–7.24 (m, 5H; H_{Ar}), 5.03 (br s, 3H; NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.9 (C=NH), 129.6, 126.6 (q, J=3.8 Hz), 124.4, 123.0, 122.5. HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{14}H_{13}F_3N_3$) requires m/z 280.1056, found m/z 280.1069.

Note: Because of the presence of tautomers, we found that, as previously reported by other,[12] some ^{13}C NMR signals are hardly detectable for most of guanidines; only obvious signals are reported.

4.5. General procedure for the synthesis of acetanilides from guanidines

To a screw-cap reaction tube was added symmetrical *N*,*N*′-disubstituted guanidines **1a** (0.2 mmol), $Pd(OAc)_2$ (5 mol %, 2.2 mg), $Cu(OAc)_2$ (0.2 mmol, 36.3 mg). The reaction tube was evacuated and back-filled with CO (three times, balloon). MeCN (2 mL) was added using a syringe and the mixture was heated to the desired temperature with use of an oil bath. When the reaction was completed (detected by TLC), the mixture was cooled to room temperature and vented to discharge the excess CO. The solvent was concentrated by evaporation in vacuo. The residue was purified by flash column chromatography on silica gel to afford the desired product amides **2a** with petroleum ether/ethyl acetate as the eluent.

*4.5.1. N-Phenylacetamide (**2a**).* White solid, 37.9 mg, 70% isolated yield. Mp: 113–114 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.72 (br s, 1H; NH), 7.43 (d, J=7.9 Hz, 2H; H_{Ar}), 7.19–7.24 (m, 2H; H_{Ar}), 7.02 (t, J=7.4 Hz, 1H; H_{Ar}), 2.07 (s, 3H; CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.8 (C=O), 138.0 (C_{Ar}), 129.0 ($2CH_{Ar}$), 124.3 (CH_{Ar}), 120.1 ($2CH_{Ar}$), 24.5 (CH_3). HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_8H_{10}NO$) requires m/z 136.0757, found m/z 136.0762.

*4.5.2. N-m-Tolylacetamide (**2b**).* Brown solid, 34.6 mg, 58% isolated yield. Mp: 64–65 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.02 (br s, 1H; NH), 7.35 (s, 1H; H_{Ar}), 7.29 (d, J=8.0 Hz, 1H; H_{Ar}), 7.16 (t, J=7.8 Hz, 1H; H_{Ar}), 6.89 (d, J=7.5 Hz, 1H; H_{Ar}), 2.28 (s, 3H; CH_3), 2.12 (s, 3H; CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.0 (C=O), 138.8 (C_{Ar}), 138.0 (C_{Ar}), 128.7 (CH_{Ar}), 125.1 (CH_{Ar}), 120.8 (CH_{Ar}), 117.2 (CH_{Ar}), 24.4 (CH_3), 21.5 (CH_3). HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_9H_{12}NO$) requires m/z 150.0913, found m/z 150.0917.

*4.5.3. N-p-Tolylacetamide (**2c**).* White solid, 35.3 mg, 59% isolated yield. Mp: 148–149 °C; ^1H NMR (400 MHz, acetone): δ 9.09 (br s, 1H; NH), 7.51 (d, J=8.3 Hz, 2H; H_{Ar}), 7.08 (d, J=8.3 Hz, 2H; H_{Ar}), 2.26 (s, 3H; CH_3), 2.05 (s, 3H; CH_3). ^{13}C NMR (100 MHz, acetone): δ 168.7 (C=O), 138.0 (C_{Ar}), 133.2 (C_{Ar}), 129.9 ($2CH_{Ar}$), 120.0 ($2CH_{Ar}$), 24.2 (CH_3), 20.8 (CH_3). HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_9H_{12}NO$) requires m/z 150.0913, found m/z 150.0916.

*4.5.4. N-(4-Fluorophenyl)acetamide (**2d**).* White solid, 39.4 mg, 64% isolated yield. Mp: 152–153 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.53 (br s, 1H; NH), 7.46–7.30 (m, 2H; H_{Ar}), 6.74–7.02 (m, 2H; H_{Ar}), 2.08 (s, 3H; CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.5 (C=O), 158.4 (d, J=243.5 Hz; C_{Ar}-F), 132.9 (d, J=2.6 Hz; C_{Ar}), 120.9 (d, J=7.8 Hz; $2CH_{Ar}$), 114.6 (d, J=22.4 Hz; $2CH_{Ar}$), 23.3 (CH_3). HRMS (ES+) exact mass calculated for $[M+H]^+$ (C_8H_9FNO) requires m/z 154.0663, found m/z 154.0662.

*4.5.5. N-(4-Chlorophenyl)acetamide (**2e**).* White solid, 45.6 mg, 67% isolated yield. Mp: 174–175 °C; ^1H NMR (400 MHz, acetone): δ 9.29 (br s, 1H; NH), 7.52 (d, J=8.9 Hz, 2H; H_{Ar}), 7.15 (d, J=8.9 Hz, 2H; H_{Ar}), 1.94 (s, 3H; CH_3). ^{13}C NMR (100 MHz, acetone): δ 168.4 (C=O), 138.5 (C_{Ar}), 128.5 ($2CH_{Ar}$), 127.4 (C_{Ar}), 120.6 ($2CH_{Ar}$), 23.3 (CH_3). HRMS (ES+) exact mass calculated for $[M+H]^+$ (C_8H_9ClNO) requires m/z 170.0367, found m/z 170.0375.

*4.5.6. N-(4-Bromophenyl)acetamide (**2f**).* White solid, 46.5 mg, 54% isolated yield. Mp: 165–166 °C; ^1H NMR (400 MHz, MeOD): δ 7.48 (d, J=8.9 Hz, 2H; H_{Ar}), 7.42 (d, J=8.9 Hz, 2H; H_{Ar}), 2.11 (s, 3H; CH_3). ^{13}C NMR (100 MHz, MeOD): δ 171.7 (C=O), 139.3 (C_{Ar}), 132.8 ($2CH_{Ar}$), 122.8 ($2CH_{Ar}$), 117.4 (C_{Ar}), 23.8 (CH_3). HRMS (ES+) exact mass calculated for $[M+H]^+$ (C_8H_9BrNO) requires m/z 213.9862, found m/z 213.9865.

*4.5.7. N-(4-Acetylphenyl)acetamide (**2g**).* White solid, 36.3 mg, 51% isolated yield. Mp: 166–167 °C; ^1H NMR (400 MHz, MeOD): δ 7.99–7.92 (m, 2H; H_{Ar}), 7.69 (d, J=8.8 Hz, 2H; H_{Ar}), 2.56 (s, 3H; CH_3), 2.15 (s, 3H; CH_3). ^{13}C NMR (100 MHz, MeOD): δ 199.4 (C=O), 172.0 (C=O), 144.8 (C_{Ar}), 133.6 (C_{Ar}), 130.7 ($2CH_{Ar}$), 120.0 ($2CH_{Ar}$), 26.5 (CH_3), 24.1 (CH_3). HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{10}H_{12}NO_2$) requires m/z 178.0863, found m/z 178.0868.

*4.5.8. Methyl 4-acetamidobenzoate (**2h**).* Yellow solid, 34.8 mg, 45% isolated yield. Mp: 127–128 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.15 (br s, 1H; NH), 7.98 (d, J=8.6 Hz, 2H; H_{Ar}), 7.62 (d, J=8.6 Hz, 2H; H_{Ar}), 3.90 (s, 3H; OCH_3), 2.20 (s, 3H; CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.0 (C=O), 166.8 (C=O), 142.4 (C_{Ar}), 130.8 ($2CH_{Ar}$), 125.5 (C_{Ar}), 118.9 ($2CH_{Ar}$), 52.1 (OCH_3), 24.7 (CH_3). HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{10}H_{12}NO_3$) requires m/z 194.0812, found m/z 194.0812.

4.5.9. Methyl 4-aminobenzoate. Yellow solid, 20.7 mg, 34% isolated yield. Mp: 129–130 °C; ^1H NMR (400 MHz, acetone): δ 7.88 (d, J=8.8 Hz, 2H; H_{Ar}), 7.02 (d, J=8.8 Hz, 2H; H_{Ar}), 3.73 (s, 3H; OCH_3). ^{13}C NMR (100 MHz, acetone): δ 166.6 (C=O), 144.1 (C_{Ar}), 132.2 ($2CH_{Ar}$), 125.7 (C_{Ar}), 115.7 ($2CH_{Ar}$), 52.2 (OCH_3). HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_8H_{10}NO_2$) requires m/z 152.0706, found m/z 152.0713.

*4.5.10. N-(4-(Trifluoromethyl)phenyl)acetamide (**2i**).* White solid, 49.9 mg, 61% isolated yield. Mp: 149–150 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.63 (d, J=8.3 Hz, 2H; H_{Ar}), 7.56 (d, J=8.3 Hz, 2H; H_{Ar}), 2.20 (s, 3H; CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.7 (C=O), 140.9 (C_{Ar}), 126.3 (q, J=4.0 Hz; $2CH_{Ar}$), 126.0 (q, J=33.0 Hz; C_{Ar}), 124.1 (q, J=271.5 Hz; CF_3), 119.4 ($2CH_{Ar}$), 24.7 (CH_3). HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_9H_9F_3NO$) requires m/z 204.0631, found m/z 204.0631.

*4.5.11. N-(4-Methoxyphenyl)acetamide (**2j**).* White solid, 58.8 mg, 89% isolated yield. Mp: 124–125 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.81 (br s, 1H; NH), 7.37 (d, J=9.0 Hz, 2H; H_{Ar}), 6.81 (d, J=9.0 Hz, 2H; H_{Ar}), 3.76 (s, 3H; OCH_3), 2.10 (s, 3H; CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.7 (C=O), 156.4 (C_{Ar}), 131.1 (C_{Ar}), 122.1 ($2CH_{Ar}$), 114.1 ($2CH_{Ar}$), 55.5 (OCH_3), 24.2 (CH_3). HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_9H_{12}NO_2$) requires m/z 166.0863, found m/z 166.0867.

*4.5.12. N-(3-Chlorophenyl)acetamide (**2k**).* Brown solid, 31.5 mg, 46% isolated yield. Mp: 79–81 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.02 (br s, 1H; NH), 7.56 (s, 1H; H_{Ar}), 7.26 (d, J=8.0 Hz, 1H; H_{Ar}), 7.12 (t, J=8.1 Hz, 1H; H_{Ar}), 6.98 (d, J=7.9 Hz, 1H; H_{Ar}), 2.09 (s, 3H; CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.1 (C=O), 139.1 (C_{Ar}), 134.5 (C_{Ar}), 129.9 (CH_{Ar}), 124.3 (CH_{Ar}), 120.1 (CH_{Ar}), 118.0 (CH_{Ar}), 24.5 (CH_3). HRMS (ES+) exact mass calculated for $[M+H]^+$ (C_8H_9ClNO) requires m/z 170.0367, found m/z 170.0371.

*4.5.13. N-(3-Methoxyphenyl)acetamide (**2l**).* White solid, 25.2 mg, 38% isolated yield. Mp: 87–88 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.27

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(s, 1H; H_{Ar}), 7.20 (t, J=8.1 Hz, 1H; H_{Ar}), 6.96 (d, J=7.9 Hz, 1H; H_{Ar}), 6.66 (d, J=8.2 Hz, 1H; H_{Ar}), 3.80 (s, 3H; OCH_3), 2.17 (s, 3H; CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.3 (C=O), 160.2 (C_{Ar}), 139.1 (C_{Ar}), 129.7 (CH_{Ar}), 111.9 (CH_{Ar}), 110.1 (CH_{Ar}), 105.7 (CH_{Ar}), 55.3 (OCH_3), 24.7 (CH_3). HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_9H_{12}NO_2$) requires m/z 166.0863, found m/z 166.0864.

*4.5.14. N-(3,5-Dimethylphenyl)acetamide (**2m**).* Brown solid, 34.8 mg, 53% isolated yield. Mp: 135–137 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (br s, 1H; NH), 7.05 (s, 2H; H_{Ar}), 6.64 (s, 1H; H_{Ar}), 2.17 (s, 6H; CH_3), 2.05 (s, 3H; CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.8 (C=O), 138.6 ($2C_{Ar}$), 137.9 (C_{Ar}), 126.0 (CH_{Ar}), 117.9 ($2CH_{Ar}$), 24.5 (CH_3), 21.3 ($2CH_3$). HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{10}H_{14}NO$) requires m/z 164.1070, found m/z 164.1072.

*4.5.15. N-(Naphthalen-1-yl)acetamide (**2n**).* Gray solid, 38.0 mg, 51% isolated yield. Mp: 160–161 °C; ^{1}H NMR (400 MHz, MeOD): δ 8.07–7.37 (m, 7H; H_{Ar}), 2.27 (s, 3H; CH_3). ^{13}C NMR (100 MHz, MeOD): δ 172.9 (C=O), 135.8 (C_{Ar}), 134.2 (C_{Ar}), 130.2 (C_{Ar}), 129.4 (CH_{Ar}), 127.6 (CH_{Ar}), 127.3 (CH_{Ar}), 127.2 (CH_{Ar}), 126.5 (CH_{Ar}), 124.1 (CH_{Ar}), 123.4 (CH_{Ar}), 23.2 (CH_3). HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{12}H_{12}NO$) requires m/z 186.0913, found m/z 186.0913.

*4.5.16. N-o-Tolylacetamide (**2p**).* Brown solid, 22.1 mg, 37% isolated yield. Mp: 125–126 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (d, J=8.0 Hz, 1H; H_{Ar}), 7.41 (br s, 1H; NH), 7.10–7.20 (m, 2H; H_{Ar}), 7.05 (t, J=7.3 Hz, 1H; H_{Ar}), 2.20 (s, 3H; CH_3), 2.12 (s, 3H; CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.8 (C=O), 135.7 (C_{Ar}), 130.5 (CH_{Ar}), 130.2 (C_{Ar}), 126.6 (CH_{Ar}), 125.5 (CH_{Ar}), 124.1 (CH_{Ar}), 24.0 (CH_3), 17.8 (CH_3). HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_9H_{12}NO$) requires m/z 150.0913, found m/z 150.0914.

*4.5.17. N-(2-Fluorophenyl)acetamide (**2q**).* White solid, 32.7 mg, 53% isolated yield. Mp: 74–76 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25 (t, J=7.9 Hz, 1H; H_{Ar}), 7.61 (br s, 1H; NH), 7.00–7.12 (m, 3H; H_{Ar}), 2.21 (s, 3H; CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.6 (C=O), 152.5 (d, J=243.4 Hz; C_{Ar}-F), 126.3 (d, J=10.0 Hz; C_{Ar}), 124.5 (d, J=3.6 Hz, CH_{Ar}), 124.4 (d, J=7.6 Hz; CH_{Ar}), 122.1 (CH_{Ar}), 114.8 (d, J=19.3 Hz; CH_{Ar}), 24.5 (CH_3). HRMS (ES+) exact mass calculated for $[M+H]^+$ (C_8H_9FNO) requires m/z 154.0663, found m/z 154.0666.

*4.5.18. N-(2-Chlorophenyl)acetamide (**2r**).* Gray solid, 46.8 mg, 69% isolated yield. Mp: 86–88 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.32 (d, J=8.0 Hz, 1H; H_{Ar}), 7.69 (br s, 1H; NH), 7.34 (d, J=8.0 Hz, 1H; H_{Ar}), 7.28–7.19 (m, 1H; H_{Ar}), 7.02 (t, J=7.5 Hz, 1H; H_{Ar}), 2.22 (s, 3H; CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.3 (C=O), 134.6 (C_{Ar}), 129.0 (CH_{Ar}), 127.7 (CH_{Ar}), 124.7 (CH_{Ar}), 122.7 (C_{Ar}), 121.8 (CH_{Ar}), 24.8 (CH_3). HRMS (ES+) exact mass calculated for $[M+H]^+$ (C_8H_9ClNO) requires m/z 170.0367, found m/z 170.0373.

*4.5.19. N-(2-Methoxyphenyl)acetamide (**2t**).* White solid, 48.2 mg, 70% isolated yield. Mp: 79–81 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.35 (d, J=7.1 Hz, 1H; H_{Ar}), 7.77 (br s, 1H; NH), 6.85–7.05 (m, 3H; H_{Ar}), 3.87 (s, 3H; OCH_3), 2.19 (s, 3H; CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.2 (C=O), 147.7 (C_{Ar}), 127.7 (C_{Ar}), 123.6 (CH_{Ar}), 121.1 (CH_{Ar}), 119.8 (CH_{Ar}), 109.9 (CH_{Ar}), 55.6 (OCH_3), 24.8 (CH_3). HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_9H_{12}NO_2$) requires m/z 166.0863, found m/z 166.0866.

*4.5.20. N-(2-(Methylthio)phenyl)acetamide (**2u**).* White solid, 24.9 mg, 34% isolated yield. Mp: 103–104 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.27–8.29 (m, 2H; NH, H_{Ar}), 7.46 (d, J=7.5 Hz, 1H; H_{Ar}), 7.27 (t, J=7.6 Hz, 1H; H_{Ar}), 7.06 (t, J=7.4 Hz, 1H; H_{Ar}), 2.38 (s, 3H), 2.23 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.4 (C=O), 138.3 (C_{Ar}), 132.8 (CH_{Ar}), 128.8 (CH_{Ar}), 125.2 (C_{Ar}), 124.4 (CH_{Ar}), 120.7 (CH_{Ar}), 24.9 (CH_3), 18.9 (CH_3). HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_9H_{12}NOS$) requires m/z 182.0634, found m/z 182.0633.

4.6. General procedure for the synthesis of anilides by other copper(II) carboxylates

To a screw-cap reaction tube was added symmetrical *N*,*N*′-disubstituted guanidines **1a** (0.2 mmol), $PdCl_2$ (5 mol %, 1.8 mg), CuX_2 (0.44 mmol). The reaction tube was evacuated and back-filled with CO (three times, balloon). PhCN (2 mL) was added using a syringe and the mixture was heated to the desired temperature with use of an oil bath. When the reaction was completed (detected by TLC), the mixture was cooled to room temperature and vented to discharge the excess CO. After the reaction was completed, the solvent was concentrated by evaporation in vacuo. The residue was purified by flash column chromatography on silica gel to afford the desired product Amides **6a** with petroleum ether/ethyl acetate as the eluent.

*4.6.1. N-Phenylpropionamide (**6a**).* White solid, 28.8 mg, 48% isolated yield. Mp: 106–108 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47–7.58 (m, 2H; H_{Ar}), 7.26–7.36 (m, 2H; H_{Ar}), 7.05–7.16 (m, 1H; H_{Ar}), 2.51–2.27 (m, 2H; CH_2), 1.21–1.27 (m, 3H; CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.3 (C=O), 138.0 (C_{Ar}), 129.0 ($2CH_{Ar}$), 124.2 (CH_{Ar}), 119.9 ($2CH_{Ar}$), 30.7 (CH_2), 9.7 (CH_3). HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_9H_{12}NO$) requires m/z 150.0913, found m/z 150.0918.

*4.6.2. N-Phenylformamide (**6b**).* Brown solid, 16.6 mg, 34% isolated yield. Mp: 46–48 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.71 (d, J=9.5 Hz, 1H), 8.38 (s, 1H), 8.22 (s, 1H), 7.54 (d, J=7.7 Hz, 2H), 7.32–7.38 (m, 4H), 7.23–7.00 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.6, 159.0, 136.9, 136.7, 129.8, 129.1, 125.3, 124.9, 120.0, 118.9. HRMS (ES+) exact mass calculated for $[M+H]^+$ (C_7H_8NO) requires m/z 122.0600, found m/z 122.0606.

*4.6.3. 2-Ethyl-N-phenylhexanamide (**6c**).* White solid, 17.0 mg, 19% isolated yield. Mp: 86–88 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (d, J=7.9 Hz, 2H; H_{Ar}), 7.31 (t, J=7.8 Hz, 2H; H_{Ar}), 7.10 (t, J=7.4 Hz, 1H; H_{Ar}), 2.05–2.15 (m, 1H; CH), 1.64–1.78 (m, 2H; CH_2), 1.45–1.60 (m, 2H; CH_2), 1.23–1.38 (m, 4H; $2CH_2$), 0.95 (t, J=7.4 Hz, 3H; CH_3), 0.88 (t, J=6.7 Hz, 3H; CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.5 (C=O), 138.0 (C_{Ar}), 129.0 ($2CH_{Ar}$), 124.2 (CH_{Ar}), 120.0 ($2CH_{Ar}$), 50.8 (CH), 32.6 (CH_2), 29.9 (CH_2), 26.2 (CH_2), 22.8 (CH_2), 14.0 (CH_3), 12.1 (CH_3). HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{14}H_{22}NO$) requires m/z 220.1696, found m/z 220.1698.

*4.6.4. N-Phenylstearamide (**6d**).* White solid, 46.3 mg, 32% isolated yield. Mp: 82–83 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (d, J=8.0 Hz, 2H; H_{Ar}), 7.31 (t, J=7.9 Hz, 2H; H_{Ar}), 7.19 (br s, 1H), 7.09 (t, J=7.3 Hz, 1H; H_{Ar}), 2.34 (t, J=7.6 Hz, 2H; CH_2), 1.82–1.62 (m, 2H; CH_2), 1.20–1.40 (m, 28H; CH_2), 0.88 (t, J=6.8 Hz, 3H; CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.4 (C=O), 138.0 (C_{Ar}), 129.0 ($2CH_{Ar}$), 124.2 (CH_{Ar}), 119.8 ($2CH_{Ar}$), 37.9, 31.9, 29.7–29.3, 25.6, 22.7, 14.1. HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{24}H_{42}NO$) requires m/z 360.3261, found m/z 360.3268.

*4.6.5. N-Phenylbenzamide (**6e**).* White solid, 36.4 mg, 46% isolated yield. Mp: 161–163 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (d, J=7.3 Hz, 2H; H_{Ar}), 7.64 (d, J=7.7 Hz, 2H; H_{Ar}), 7.58–7.34 (m, 5H; H_{Ar}), 7.15 (t, J=7.4 Hz, 1H; H_{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.8 (C=O), 134.0 (C_{Ar}), 135.0 (C_{Ar}), 131.8 (CH_{Ar}), 129.1 ($2CH_{Ar}$), 128.8 ($2CH_{Ar}$), 127.0 ($2CH_{Ar}$), 124.6 (CH_{Ar}), 120.2 ($2CH_{Ar}$). HRMS (ES+) exact mass

calculated for $[M+H]^+$ ($C_{13}H_{12}NO$) requires m/z 198.0913, found m/z 198.0918.

4.7. Synthesis of *N*-phenyl-*N*-(*N*-phenylcarbamimidoyl)acetamide (7)

Diphenylguanidine (10 mmol, 2.11 g) was dissolved in 30 mL acetonitrile. Acetic anhydride (5 mmol) dissolved in acetonitrile (20 mL) was slowly added to the mixture and stirred overnight at room temperature. The reaction mixture was extracted with ethyl acetate. The organic layer was washed with water and brine and dried over Na_2SO_4. Removal of solvent by evaporation in vacuo followed by purification with column chromatography on silica gel provided the desired products.

*4.7.1. N-Phenyl-N-(N-phenylcarbamimidoyl)acetamide (**7**).* White solid. Mp: 92–94 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53–7.18 (m, 7H; H_{Ar}), 6.96 (t, J=7.3 Hz, 1H; H_{Ar}), 6.77 (d, J=7.1 Hz, 2H; H_{Ar}), 6.21 (br s, 2H), 1.96 (s, 3H; CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.1 (C=O), 150.6 (C=NH), 148.0 (C_{Ar}), 140.6 (C_{Ar}), 129.5 ($2CH_{Ar}$), 129.4 ($2CH_{Ar}$), 129.0 ($2CH_{Ar}$), 128.4 (CH_{Ar}), 122.8 (CH_{Ar}), 121.9 ($2CH_{Ar}$), 26.4 (CH_3). HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{15}H_{16}N_3O$) requires m/z 254.1288, found m/z 254.1298.

4.8. Synthesis of *N*-phenylcyanamide (8) according to Neuville's method[13]

Cyanogen bromide (20.0 mmol, 2.08 g, 2.0 equiv) was dissolved in 20 mL toluene under argon, aniline (10.0 mmol, 1.0 equiv) and $NaHCO_3$ (35.0 mmol, 2.94 g, 3.5 equiv) were added to the mixture and stirred for 3 h at room temperature. The mixture was quenched with water and extracted with EtOAc (3×40 mL). The organic layers were combined, washed with H_2O and brine, dried by $MgSO_4$, and concentrated under reduced pressure to give a residue, which was purified by flash chromatography (SiO_2, eluent: DCM/heptane=1:1).

*4.8.1. N-Phenylcyanamide (**8**).* Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 (t, J=7.9 Hz, 2H; H_{Ar}), 7.09 (t, J=7.5 Hz, 1H; H_{Ar}), 7.06–6.97 (m, 2H; H_{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.2 (C_{Ar}), 129.8 ($2CH_{Ar}$), 123.7 (CH_{Ar}), 115.4 ($2CH_{Ar}$), 111.3 (CN). HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_7H_7N_2$) requires m/z 119.0604, found m/z 119.0605.

4.9. Synthesis of 1-phenylguanidine (9)

According to Al-Mourabit's method.[14]

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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2015.01.050.

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