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1,2-Dichloroethane, a widely produced chemical raw material, has attracted considerable attention due to its versatility in various applications. Herein, we report an efficient strategy for the synthesis of acrylamides *via* palladium-catalyzed carbonylation, using 1,2-dichloroethane and amines as starting materials. The catalytic system demonstrated remarkable tolerance towards a broad range of amines, producing the corresponding acrylamides in good to excellent yields. Remarkably, a variety of aromatic and alkyl amines were completely converted within 40 minutes, delivering the target products with an impressive 99% yield. Additionally, the strategy's versatility was confirmed by its successful application in the synthesis of functionalized acrylates. Importantly, the reaction was scaled up to 1 mmol scale with consistent yields, underscoring its potential for practical use in organic synthesis.

Introduction

1,2-Dichloroethane, an indispensable chemical raw material, plays a central role in industrial production. Particularly, it has been crucial in the preparation of vinyl chloride,^{1,2} which has directly propelled the development of polyvinyl chloride (PVC) in the field of new materials.^{3–6} Given its significance in the industry, the production processes and output of 1,2-dichloroethane have been continuously optimized and improved. As a valuable raw material in organic synthesis, the accessibility and cost-effectiveness of 1,2-dichloroethane make it an ideal choice for the preparation of high-value-added compounds, a field that merits further exploration and development.

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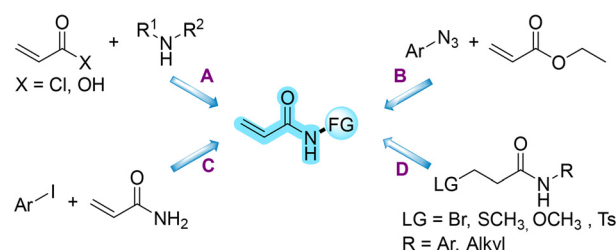
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Acrylamides from 1,2-dichloroethane *via* palladium-catalyzed carbonylation†Ren-Rui Xu,^{ab} Chang-Sheng Kuai^{id bc} and Xiao-Feng Wu^{id *abc}

Acrylamides, which are very important compounds in organic chemistry, have structures that are the main ones of various natural products and bioactive molecules and are widely used in fields such as food,^{7,8} medicine,⁹ and materials.¹⁰ In the past decade, acrylamides have been widely used in the research and development of targeted covalent drugs due to their electrophilicity.^{11–16} These drug molecules achieve precise regulation of specific biological processes through covalently binding to target proteins.¹⁷ Furthermore, acrylamides are pivotal polymer monomers, serving as a key component in numerous significant processes and offering unique benefits in the investigation of enhanced material performance.¹⁸ In recent years, the production of polyacrylamide has reached several hundred tons, representing a significant increase in output compared to previous years.¹⁹ Due to its excellent performance, it is currently employed extensively, particularly in the context of oil extraction.²⁰ Acrylamides were traditionally mainly synthesized by the acylation of acryloyl chlorides and their derivatives with amines as nitrogen sources (Scheme 1A).^{21,22} In addition, under the catalysis of samarium diiodide, a one-step synthesis of acrylamides from azide and ester compounds was achieved (Scheme 1B).²³ The synthesis of *N*-phenylacrylamide *via* the coupling reaction of aryl iodide with acrylamide was achieved using CuTC as a catalyst,

Traditional procedure to acrylamides

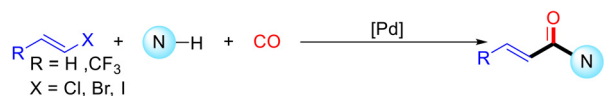


Scheme 1 Traditional procedure to obtain acrylamides.

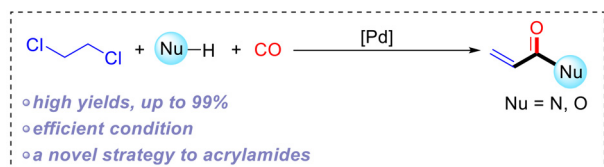
A. Pd-catalyzed hydroaminocarbonylation of acetylene



B. Pd-catalyzed carbonylation of vinyl halides



C. This work



Scheme 2 Previous carbonylation reactions for synthesizing acrylamides and this work.

eliminating the need for additional ligands (Scheme 1C).²⁴ The synthesis of acrylamides through deprotonation of 3-substituted-*N*-phenylpropanamide was also reported, involving leaving groups such as $-\text{Br}$,²⁵ $-\text{SCH}_3$,²⁶ $-\text{OCH}_3$,²⁷ $-\text{Ts}$ (ref. 28) in these works (Scheme 1D). Nevertheless, the study of synthesizing acrylamides remains a subject of ongoing interest.

Carbon monoxide (CO) is a highly significant C1 unit in organic chemistry, exhibiting optimal economic efficiency and extensive applicability. By adjusting the pressure of carbon monoxide, it is possible to achieve reactions that would otherwise be difficult to carry out with some carbon monoxide substitutes.^{29,30} Over the past five decades, remarkable progress has been made in the synthesis of high-

value carbonyl compounds, such as aldehydes,³¹ carboxylic acids,³² carboxylic esters,³³ amides,³⁴ and others,^{35–37} through carbonylation. Given the increasing importance of acrylamides, there have been numerous reports in recent years on their synthesis *via* transition-metal-catalyzed carbonylation reactions. Beller *et al.* reported a modular and diverse synthesis of acrylamides using palladium-catalyzed hydroaminocarbonylation of acetylene (Scheme 2A).³⁸ Notably, bioactive compound derivatives such as ibrutinib and osimertinib can be synthesized through this strategy. Acrylamides have also been synthesized *via* carbonylation reactions using vinyl halides, including vinyl chloride and vinyl iodide, as starting materials (Scheme 2B).^{39,40} In industrial settings, vinyl chloride is primarily produced by the high-temperature cracking of 1,2-dichloroethane, typically at 500–550 °C and 25–35 bar.^{1,2} Research has also explored the electrochemical removal of HCl from 1,2-dichloroethane to generate vinyl chloride.⁴¹ Additionally, the synthesis of vinyl chloride from acetylene has been well-documented over the past decade.^{42–44} We propose the direct synthesis of acrylamides *via* carbonylation using 1,2-dichloroethane as the substrate under palladium-catalyzed conditions (Scheme 2C).

Results and discussion

To investigate an efficient catalytic reaction system, 1,2-dichloroethane (**1a**) and *p*-toluidine (**2a**) were selected as model substrates. The reaction was performed with 1 mL of 1,2-dichloroethane (**1a**), 0.2 mmol of *p*-toluidine (**2a**), $\text{Pd}(\text{acac})_2$ (5 mol%), BuPAD_2 (10 mol%), and 2.5 equivalents of KO^tBu under 10 bar of CO at 100 °C for 20 hours. To our delight, the desired product **3aa** was obtained in a 79% yield (Table 1, entry 1). Next, a series of bidentate and monodentate phosphine ligands were evaluated. The reaction

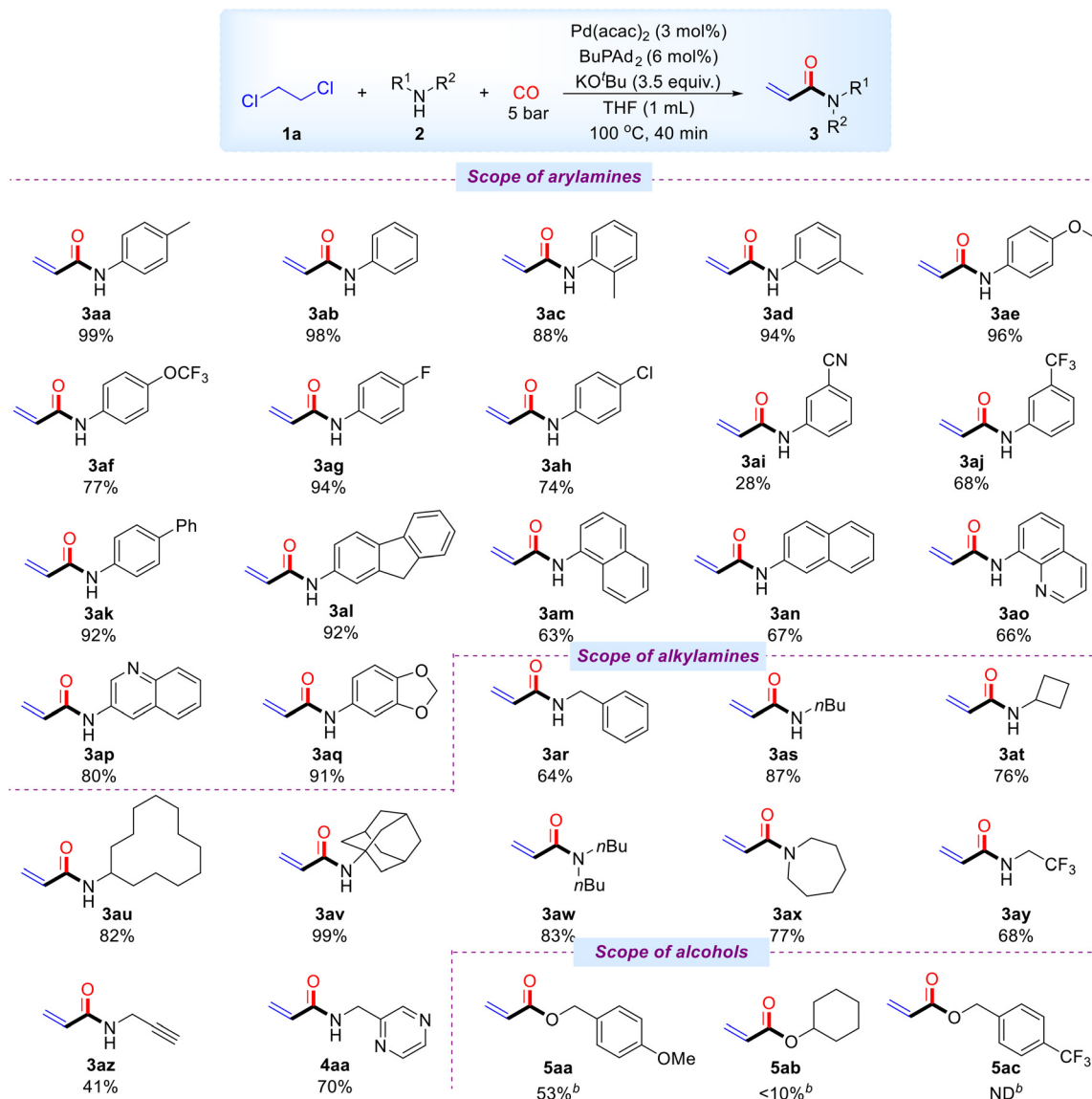
Table 1 Optimization of reaction conditions^a

Entry	Ligand	Solvent	Time	Yield ^b (%)
1	BuPAD_2	w/o	20 h	79
2	PPh_3	w/o	20 h	11
3	PCy_3	w/o	20 h	17
4	TFP	w/o	20 h	14
5	DPPP	w/o	20 h	ND
6	Xantphos	w/o	20 h	ND
7	BINAP	w/o	20 h	ND
8	DPPF	w/o	20 h	ND
9 ^d	BuPAD_2	w/o	20 h	91
10 ^e	BuPAD_2	THF	20 h	91
11 ^{e,f}	BuPAD_2	THF	40 min	99
12 ^{e,f,g}	BuPAD_2	THF	40 min	99 (96 ^c)

^a Reaction conditions: **1a** (1 mL), **2a** (0.2 mmol), CO (10 bar), $\text{Pd}(\text{acac})_2$ (5 mol%), BuPAD_2 (10 mol%), KO^tBu (2.5 equiv.) at 100 °C for 20 hours.

^b Yields were determined by GC-FID analysis using *n*-dodecane as internal standard. ^c Yield of isolated product. ND = not detection. ^d KO^tBu (3.5 equiv.). ^e **1a** (2 mmol, 10 equiv.). ^f CO (5 bar). ^g $\text{Pd}(\text{acac})_2$ (3 mol%), BuPAD_2 (6 mol%).





Scheme 3 Substrate scope^a ^aReaction conditions: **1a** (2 mmol, 10 equiv.), **2** (0.2 mmol), CO (5 bar), Pd(acac)₂ (3 mol%), BuPAD₂ (6 mol%), KO^tBu (3.5 equiv.), THF (1 mL) at 100 °C for 40 minutes, isolated yields. ^b**1a** (1 mL), 4-methoxybenzylalcohol (0.2 mmol), CO (10 bar), Pd₂(dba)₃ (3.6 mg, 2 mol%), BuPAD₂ (2.9 mg, 4 mol%), K₂CO₃ (3.5 equiv., 96.8 mg) at 100 °C for 20 hours, isolated yield.

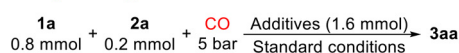
was first tested with monodentate phosphine ligands, including PPh₃, PCy₃, and TFP, but resulted in low yields of **3aa** (Table 1, entries 2–4). However, when using bidentate phosphine ligands such as DPPP, Xantphos, BINAP, and DPPF, the target product **3aa** was successfully detected (Table 1, entries 5–8). Increasing the amount of KO^tBu to 3.5 equivalents led to a significant increase in the yield of **3aa**, reaching 91% (Table 1, entry 9). The reduction of 1,2-dichloroethane was also crucial. When the solvent was switched to THF and the amount of 1,2-dichloroethane was reduced to 10 equivalents, the yield of **3aa** remained at 91% (Table 1, entry 10). Further optimization of reaction time, temperature, and CO pressure was conducted (Table 1, entries 11–12). Under optimized conditions, with 10 equivalents of 1,2-dichloroethane (**1a**), 0.2 mmol of

p-toluidine (**2a**), Pd(acac)₂ (3 mol%), BuPAD₂ (6 mol%), and 3.5 equivalents of KO^tBu under 5 bar of CO at 100 °C for 40 minutes, the desired product **3aa** was obtained in an excellent 99% yield (Table 1, entry 12). However, further decrease the pressure of CO to atmospheric pressure led to low yield of the desired product.

Subsequently, we explored the scope of various amine compounds under optimal reaction conditions (Scheme 3). Aryl substrates bearing electron-donating groups, such as methyl, methoxy, and trifluoromethoxy, were well-tolerated, and the corresponding acrylamides were obtained in good to excellent yields ranging from 77% to 99% (**3ab–3af**). Substrates with halogen substituents, such as fluoro and chloro, also gave the desired products in good yields (**3ag**, **3ah**). However, aryl substrates with electron-withdrawing

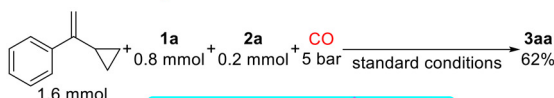


A. Radical quenching

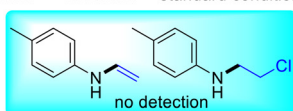
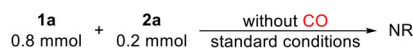


Entry	Additive	Yield (%)
1	w/o	84
2	TEMPO	19
3	BHT	25
4	DPE	71

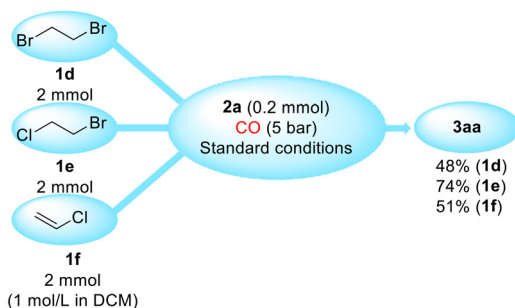
B. Radical clock experiment



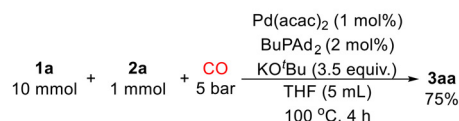
C. Conditions without CO



D. Experiments with other halides



E. Scale up synthesis



Scheme 4 Control experiments and scale-up reaction.

groups performed less satisfactorily, yielding **3ai** and **3aj** in 28% and 68%, respectively. We also investigated the impact of biphenyl and 2-nitro-9H-fluorene moieties, both of which produced the corresponding products in 92% yields (**3ak**, **3al**). 1-Naphthylamine and 2-naphthylamine were suitable for this transformation, yielding **3am** and **3an** in 69% and 67%, respectively. Furthermore, the catalytic system demonstrated good tolerance for heterocyclic amines, including 3,4-methylenedioxyaniline, 8-aminoquinoline, and 3-aminoquinoline, with yields ranging from 66% to 91% (**3ao**–**3aq**). In addition, a variety of alkyl amines reacted smoothly and efficiently with 1,2-dichloroethane. Primary alkyl amines such as benzylamine, *n*-butylamine, cyclobutylamine, cyclododecylamine, and amantadine were highly compatible, yielding products in 64% to 99%

(**3ar**–**3av**). The system also converted secondary amines, such as butylamine and hexamethyleneimine, producing the target compounds in 83% and 77% yields (**3aw**, **3ax**). Notably, alkyl amines containing electron-withdrawing groups or carbon-carbon triple bonds also reacted successfully, yielding products in 68% and 41% (**3ay**, **3az**). Furthermore, a heteroaryl-substituted alkylamine was also compatible with standard conditions, for example, 2-(aminomethyl)pyrazine (**4aa**). 4-Methoxybenzyl alcohol was smoothly converted to the corresponding acrylate **5aa** with a yield of 53% under prolonged reaction conditions. Cyclohexanol was used as a substrate, and a small amount of the target product (**5ab**) was detected by GC-MS. (4-(Trifluoromethyl) phenyl) methanol cannot be converted into the corresponding acrylate in the catalytic system. Unfortunately, phenols and thiophenols were incompatible with this catalytic system and could not be smoothly transformed under standard or prolonged reaction conditions. It is worth to mention that the reactions failed when 1,2-dichloropropane, 1,1,2-trichloroethane, and 1,1,2,2-tetrachloroethane were tested instead of DCE under our standard conditions.

To further explore the reaction mechanism of the catalytic system, several control experiments were conducted. First, the amount of 1,2-dichloroethane was reduced to 0.8 mmol, and radical scavengers TEMPO (1.6 mmol), BHT (1.6 mmol), or DPE (1.6 mmol) were added under standard conditions, resulting in the target product **3aa** with yields of 19%, 25%, and 71%, respectively (Scheme 4A). Next, a radical clock experiment was performed by adding (1-cyclopropylvinyl) benzene (1.6 mmol) under standard conditions, yielding **3aa** in 67% yield, with no radical-captured products detected (Scheme 4B). These results indicate that the reaction does not proceed *via* a radical pathway. In another control experiment without carbon monoxide, neither 4-methyl-*N*-vinylaniline nor *N*-(2-chloroethyl)-4-methylaniline was detected, and *p*-toluidine (**2a**) remained unreacted (Scheme 4C). The catalytic system also exhibited good tolerance for 1,2-dibromoethane and 1-bromo-2-chloroethane, yielding **3aa** in 48% and 51%, respectively, under standard conditions. Additionally, vinyl chloride was converted into **3aa** with a yield of 51% under the same conditions (Scheme 4C). Based on these results and previous reports,^{39,40} it is likely that the catalytic system involves the elimination of 1,2-dichloroethane to form C(sp²)-Cl bonds, followed by oxidative addition with Pd(0) to initiate the reaction. Finally, the reaction was successfully scaled up to 1 mmol using a 1 mol% catalyst and a 4-hour reaction time, delivering the target product **3aa** in 75% yield (Scheme 4D).

Conclusions

In summary, we have developed a novel and efficient method for preparing acrylamides using 1,2-dichloroethane and amines as substrates. This catalytic system demonstrated broad substrate versatility, allowing amines to be smoothly converted into the corresponding acrylamides with good to



excellent yields, reaching up to 99%. The reaction was successfully scaled up to a 1 mmol scale. Furthermore, this strategy is also applicable to the preparation of acrylates.

Data availability

The data supporting this article have been included as part of the ESI.†

Conflicts of interest

There are no conflicts to declare.

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