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Article

Synthesis of α-CF_3 Amides via Palladium-Catalyzed Carbonylation of 2-Bromo-3,3,3-trifluoropropene

Xiao Rui Wen, Wen Qing Zhu,* Cai Lin Zhang, Hong Li, Jin Zhang, Min Ge Yang, Yong Li Kou, Yu Xia Liu, and Yang Li*

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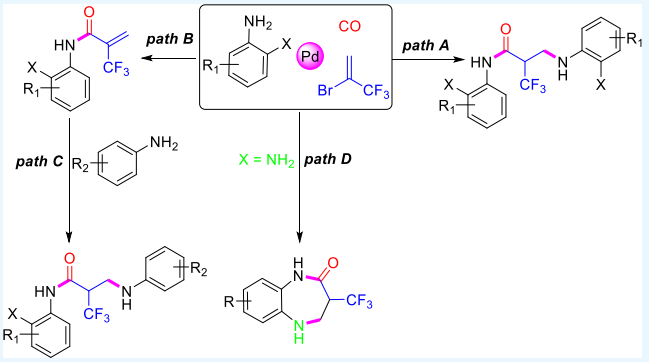
ABSTRACT: Amide compounds are important organic compounds, which play an important role in biomedical chemistry, materials science, life science, and other fields. The synthesis of α-CF_3 amides, especially compounds containing 3-(trifluoromethyl)-1,3,4,5-tetrahydro-2*H*-benzo[*b*][1,4]diazepine-2-one, has long been a challenge due to the tensile properties and instability of the rings. Here, we report an example of palladium-catalyzed carbonylation of CF_3-containing olefin to form α-CF_3 acrylamide. By controlling the ligands, we can get different amide compounds as products. This method has good substrate adaptability and functional group tolerance.



INTRODUCTION

Fluorine-containing compounds are of considerable interest because of their superior physicochemical properties in materials chemistry and their favorable pharmacokinetic properties in medicinal chemistry.[1] Along with fluorine-containing compounds, α-CF_3 amides are an important class of organic compounds that play a key role in biomedical chemistry, materials science, life science, and other areas.[2] In addition, α-CF_3 amides can serve as versatile precursors for the synthesis of α-trifluoromethylated carboxylic acids,[3] α-trifluoromethylated alcohols,[4] and amines.[5] However, due to their high propensity for β-fluoride elimination, which is triggered by strong metal−fluorine interactions,[6] limited examples have been reported thus far regarding the synthesis of their trifluoromethylated derivatives.[7−9] In particular, only one example of the synthesis of seven-membered rings containing α-CF_3 amides has been reported till date.[10]

2-Bromo-3,3,3-trifluoro-1-propene is environmentally friendly (atmospheric greenhouse effect, GWP = 0; atmospheric ozone depletion value, ODP = 0) and used in many organic syntheses, such as the synthesis of α-(trifluoromethyl)-styrenes,[11] trifluoromethylated vinyl boron reagent,[12] ethyl 3,3,3-trifluoropropionate,[13] difluoromethyl-substituted 2,3-dihydrobenzoheteroles,[14] trifluoroacrylic acid,[15] and 3-trifluoromethylpyrazole.[16] Developing methods to efficiently convert the compound into fluorine-containing fine chemicals remains a very meaningful area for future research. To develop a simpler and more efficient method to synthesize α-CF_3 amides and as part of our continued interest in the area of trifluoromethylation[17] and carbonylation,[18] here, we envisaged a one-step sequential synthetic strategy that involved the direct carbonylation of anilines with an inexpensive and available trifluoromethylated olefin that could yield the desired α-CF_3 amides in a controlled manner (Scheme 1).

RESULTS AND DISCUSSION

We chose *p*-methoxyaniline **1a** and **2** as the substrates for the model reaction. $PdCl_2$ (2 mol %) was used as the catalyst, PCy_3 (4 mol %) was used as the ligand, and carbon monoxide (8 atm) was used to react in 1,4-dioxane at 100 °C for 12 h. Disappointingly, we obtained target compound **3a** in a poor yield (6%) (Table 1, entry 1). Therefore, we performed a large number of experiments to optimize the conditions for this reaction. First, we screened palladium sources and examined two different palladium catalysts. As a result, we found that $Pd(PPh_3)_2Cl_2$ was the best palladium source (Table 1, entries 2−3). Phosphine ligands are the focus of our investigation. We examined a total of eight phosphine ligands herein, including monodentate and bidentate ligands. We found that ligand **B** had the best effect on this reaction, resulting in a reaction yield of 72% (Table 1, entries 4−11). Next, we examined the reaction solvents. We investigated solvents with different polarities and found that tetrahydrofuran (THF) was the best

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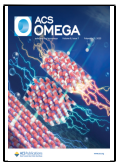


Scheme 1. Palladium-Catalyzed Carbonylation of Anilines

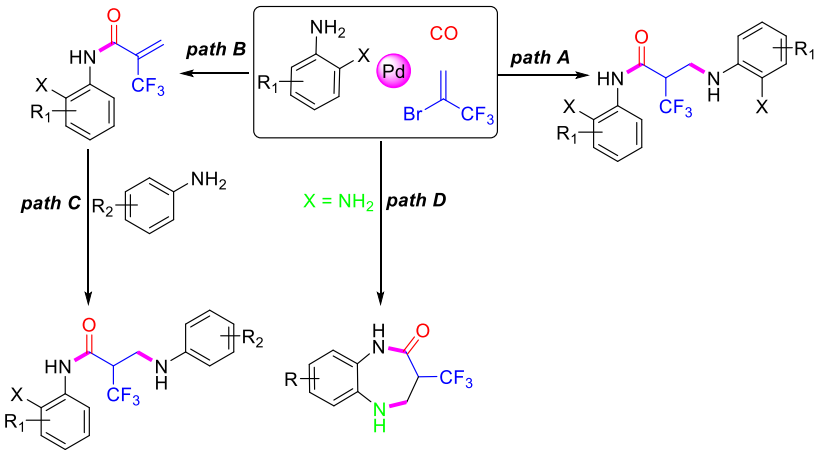
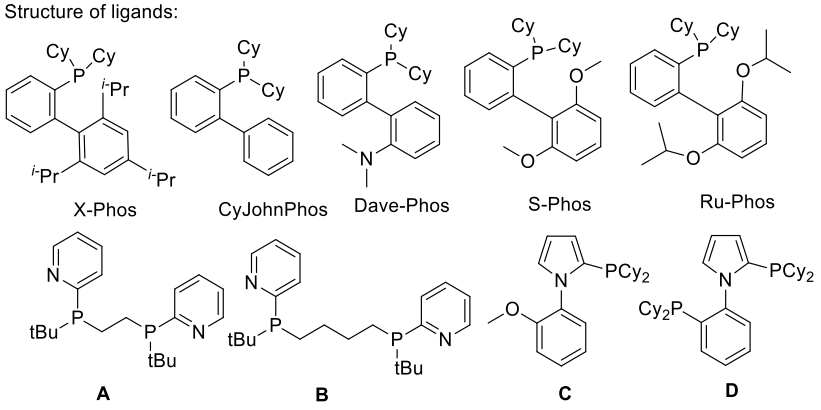


Table 1. Optimization of the Reaction Conditions[a]

entry	catalyst	ligand	base	solvent	yield (%)[b]
1	$PdCl_2$	PCy_3	$NaHCO_3$	1,4-dioxane	6
2	$Pd(OAc)_2$	PCy_3	$NaHCO_3$	1,4-dioxane	29
3	$Pd(PPh_3)_2Cl_2$	PCy_3	$NaHCO_3$	1,4-dioxane	45
4	$Pd(PPh_3)_2Cl_2$	S-Phos	$NaHCO_3$	1,4-dioxane	36
5	$Pd(PPh_3)_2Cl_2$	Ru-Phos	$NaHCO_3$	1,4-dioxane	31
6	$Pd(PPh_3)_2Cl_2$	X-Phos	$NaHCO_3$	1,4-dioxane	26
7	$Pd(PPh_3)_2Cl_2$	Dave-Phos	$NaHCO_3$	1,4-dioxane	19
8	$Pd(PPh_3)_2Cl_2$	CyJohnPhos	$NaHCO_3$	1,4-dioxane	23
9	$Pd(PPh_3)_2Cl_2$	A	$NaHCO_3$	1,4-dioxane	51
10	$Pd(PPh_3)_2Cl_2$	B	$NaHCO_3$	1,4-dioxane	72
11	$Pd(PPh_3)_2Cl_2$	C	$NaHCO_3$	1,4-dioxane	58
12	$Pd(PPh_3)_2Cl_2$	D	$NaHCO_3$	1,4-dioxane	16
13	$Pd(PPh_3)_2Cl_2$	B	$NaHCO_3$	MeCN	22
14	$Pd(PPh_3)_2Cl_2$	B	$NaHCO_3$	THF	84
15	$Pd(PPh_3)_2Cl_2$	B	$NaHCO_3$	MePh	23
16	$Pd(PPh_3)_2Cl_2$	B	$NaHCO_3$	DMF	35
17	$Pd(PPh_3)_2Cl_2$	B	Na_2CO_3	THF	74
18	$Pd(PPh_3)_2Cl_2$	B	$KHCO_3$	THF	81
19	$Pd(PPh_3)_2Cl_2$	B	K_2CO_3	THF	76

[a]Reaction conditions: **1a** (1.0 mmol), **2** (2.0 mmol), catalyst (2 mol %), ligand (4 mol %), base (2.0 mmol), CO (8 atm), solvent (2.0 mL), 100 °C, 12 h. [b]Isolated yield.

Structure of ligands:



solvent for this reaction and that the reaction yield could be increased to as high as 84% (Table 1, entries 12−15). We also examined other types of bases, and we observed that $NaHCO_3$ was the best base for this reaction (Table 1, entries 16−18). Thus, the following conditions were determined to be optimal for the reaction: $Pd(PPh_3)_2Cl_2$ as the catalyst, phosphine ligand **B**, $NaHCO_3$ as the reaction base, and THF as the solvent. The reaction was performed at 100 °C for 12 h.

To investigate the universality of this method, we performed a substrate extension experiment. Most of the aniline derivatives could be well converted into the corresponding acrylamides (Table 2). Especially for aniline with para-

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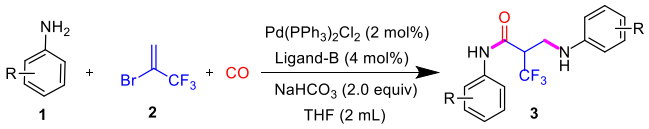
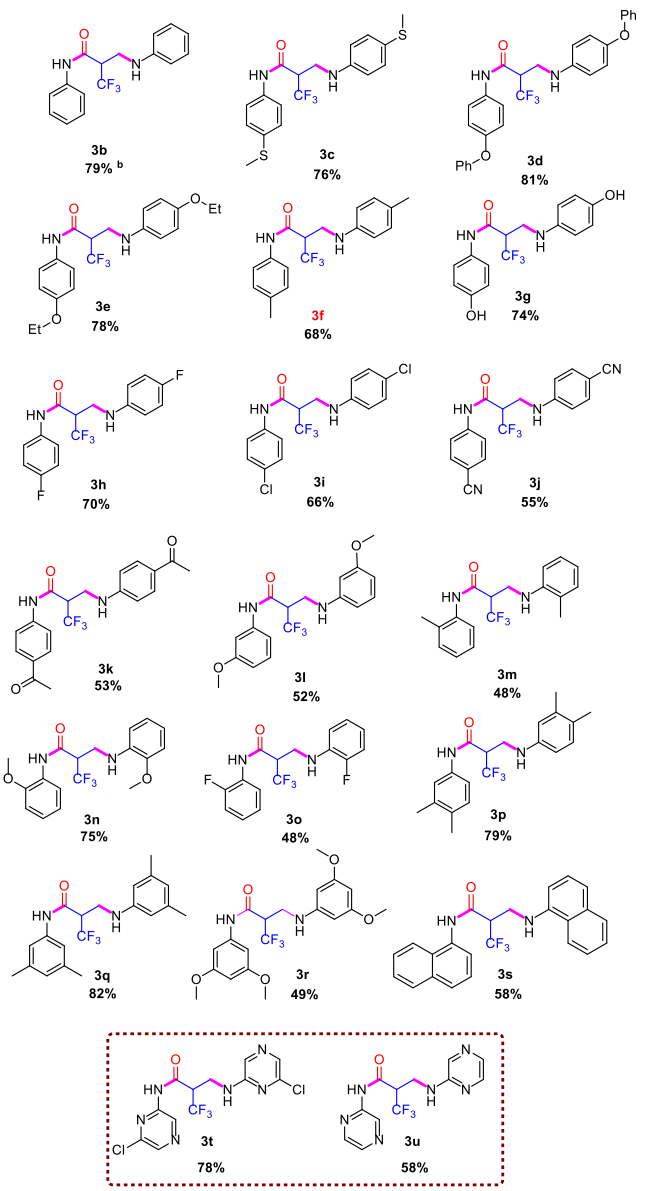
Table 2. Palladium-Catalyzed Carbonylation to α-CF_3 Amides[a]





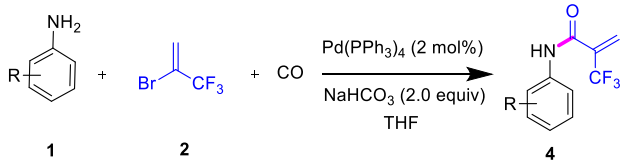
[a]Reaction conditions: aniline (**1**) (1.0 mmol), **2** (2.0 mmol), $Pd(PPh_3)_2Cl_2$ (2 mol %), ligand-B (4 mol %), $NaHCO_3$ (2.0 equiv), CO (8 atm), THF (2.0 mL), 100 °C, 12 h. [b]Isolated yield.

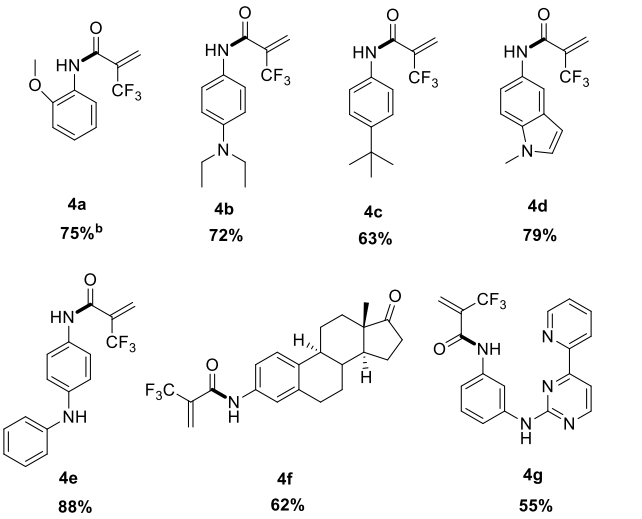
electron-rich substituents, this conversion process proceeded very smoothly, and the target compounds were obtained in good to excellent yields (Table 2, entries 3b−3g). Aniline substrates containing an electron-deficient substituent at the para position could also be ideally converted into the desired target compound under the optimized reaction conditions (Table 2, entries 3h−3k). Next, we investigated aniline-containing meta-substituents. To our satisfaction, anilines containing meta-rich substituents could also generate the corresponding acrylamides in moderate yields (Table 2, entry 3l). Third, we performed experiments on anilines containing substituents at the ortho position. It was also pleasing that these anilines could promote this conversion in good yields, regardless of whether electron-deficient or electron-rich substituents were in the ortho position (Table 2, entries 3m−3o). We also investigated disubstituted anilines. It was found that they were also smoothly converted into the corresponding products, regardless of whether the substituents were present in the 3 and 5, 3 and 4 positions (Table 2, entries 3p−3r). In addition, we explored 1-naphthylamine as a substrate. To our delight, it was also converted into the corresponding amide in a moderate yield (Table 2, entry 3s). Finally, we applied this method to pyrazine substrates. Gratifyingly, these substrates were also converted into the corresponding products in moderate yields (Table 2, entries 3t−3u).

To further explore the substrate universality of this reaction, we explored substrates for the formation of acrylamides by synthetic route **B** (Table 3). First, anilines could be converted into the corresponding acrylamides, regardless of whether they contained electron-rich substituents in the ortho- or para-position (Table 3, entries 4a−4d). Second, we also tried an indole-substituted amine and found that it could also be converted into the corresponding acrylamide product in good yields (Table 3, entry 4e). Finally, we also investigated biologically active substrates. Favorably, they were converted into the desired acrylamides (Table 3, entries 4f−4g).

Next, we conducted a substrate expansion test for reaction path **C**. We found that when *N*-phenyl acrylamide was used as a substrate, it underwent intermolecular Michael addition

Table 3. Palladium-Catalyzed Carbonylation to Acrylamides[a]





[a]Reaction conditions: aniline (1.0 mmol), **2** (2.0 mmol), $Pd(PPh_3)_4$(2 mol %), $NaHCO_3$ (2.0 equiv), THF (4.0 mL), CO (8 atm), 100 °C, 12 h. [b]Isolated yield.

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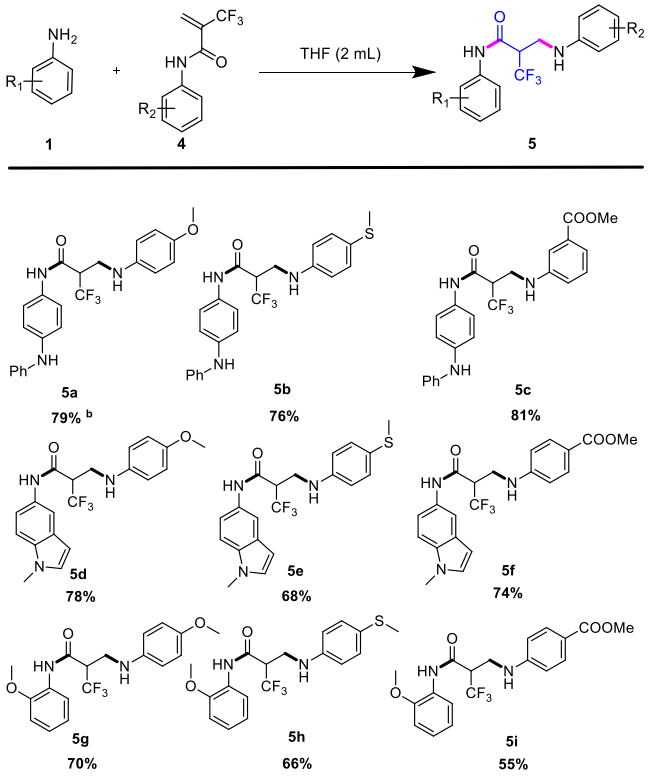
reactions with different types of aromatic amines. The reaction only needed to be carried out in THF at 80 °C for 5 h (Table 4, 5a−5c). We tried the same reaction with indole-acrylamine as the substrate. Gratifyingly, the results obtained were the same as the previous results; namely, three different types of aromatic amines underwent Michael addition reactions well, and the isolated yields were all above moderate (Table 4, 5d−5f). Finally, we used *ortho*-methoxyacrylamide with a sterically hindered group as the substrate. Under the same conditions, the intermolecular Michael addition still proceeded very smoothly, and the isolated yield of the product was above 50% (Table 4, 5g−5i). The realization of this conversion pathway provides a good method for the future synthesis of trifluoromethylated propanamides with different substituents.

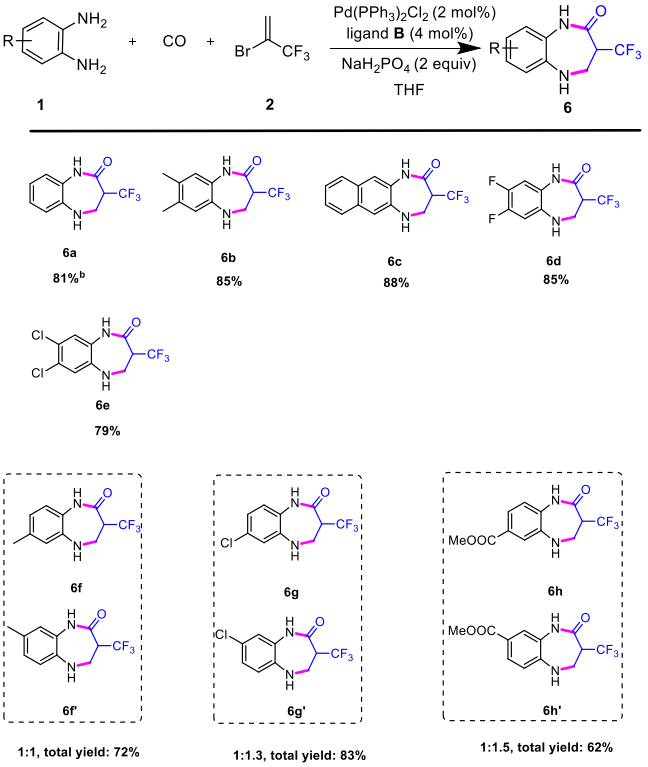
Table 4. Substrate Scope of Anilines for Michael Addition[a]



[a]Reaction conditions: acrylamide (**4**) (1.0 mmol), aniline (**1**) (1.0 mmol), THF (4.0 mL), 80 °C, 5 h. [b]Isolated yield.

Due to structural instability, N-hetero seven-membered cyclic amides are difficult to synthesize. We found that under our reaction conditions **D**, benzene-1,2-diamine can undergo an intramolecular cycloaddition reaction, thereby forming an acrylamide 3-(trifluoromethyl)-1,3,4,5-tetrahydro-2*H*-benzo[*b*][1,4]diazepin-2-one. In the same way, we also optimized the synthesis route considerably and finally obtained an ideal synthesis process. Here, we examined the substrate universality of this synthetic method. Benzene-1,2-diamine containing various substituents could be well converted into 3-(trifluoromethyl)-1,3,4,5-tetrahydro-2*H*-benzo[*b*][1,4]-diazepin-2-one (Table 5). Substituted benzene-1,2-diamine, *o*-resistant diamine, and benzene-1,2-diamine containing a double substituent at the 3 and 4 positions all resulted in a single benzoic seven-membered cyclic acrylamide in good yields (Table 5, 6a−6e). For benzene-1,2-diamine containing a single substituent at the 3 or 4 position, both electron-deficient and electron-rich substituted benzene-1,2-diamine could be converted into the corresponding acrylamides in moderate yields (Table 5, 6f−6h). The disadvantage is that all these products exist as mixtures, and basically all are obtained in a ratio of 1:1 to 1:2. However, this method provided a new technique to synthesize 3-(trifluoromethyl)-1,3,4,5-tetrahydro-2*H*-benzo[*b*][1,4]diazepin-2-one.

Table 5. Synthesis of 3-(Trifluoromethyl)-1,3,4,5-tetrahydro-2*H*-benzo[*b*][1,4]diazepin-2-one[a]



[a]Reaction conditions: benzene-1,2-diamine (1.0 mmol), **2** (2.0 mmol), $Pd(PPh_3)_2Cl_2$ (2 mol %), ligand **B** (4 mol %), NaH_2PO_4 (2.0 equiv), THF (2.0 mL), 100 °C, 12 h. [b]Isolated yield.

To examine the amplification effect of this reaction, we performed a scale-up experiment. The reaction yield decreased only slightly, which shows that this method has good scale-up potential (Scheme 2). The actual picture of the product is also displayed.

A possible mechanism for the palladium-catalyzed carbonylation of aniline is described in Scheme 3. Initially, the reaction starts with the reduction of Pd(II) to Pd(0) by the ligand, and then an oxidative addition occurs between vinyl bromide and Pd(0), yielding intermediate **A**. After coordination to form **B** and insertion with CO, acyl palladium **C** is formed;[19] then, aniline attacks intermediate **C** to form Compound **D**. Finally, intermediate **D** undergoes reductive elimination to afford amide **E** and Pd(0). Intermediate **E** undergoes a Michael addition under different reaction conditions and produces compounds **F** and **G**.

CONCLUSIONS

In summary, we developed a new strategy for the facile synthesis ofα-CF_3 acrylamides via a Pd(0)-catalyzed fluorinated carbonylation reaction. Importantly, this conversion process exhibit excellent regioselectivity and chemoselectivity,

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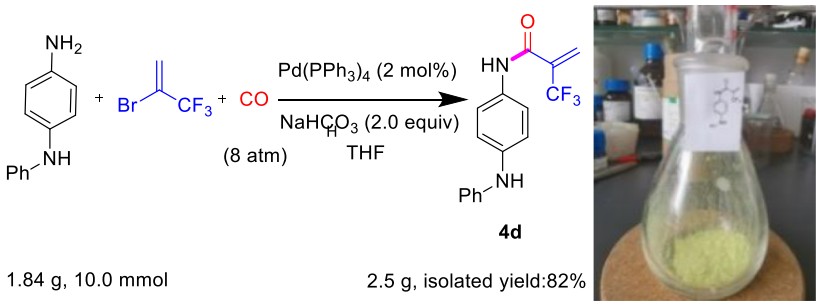
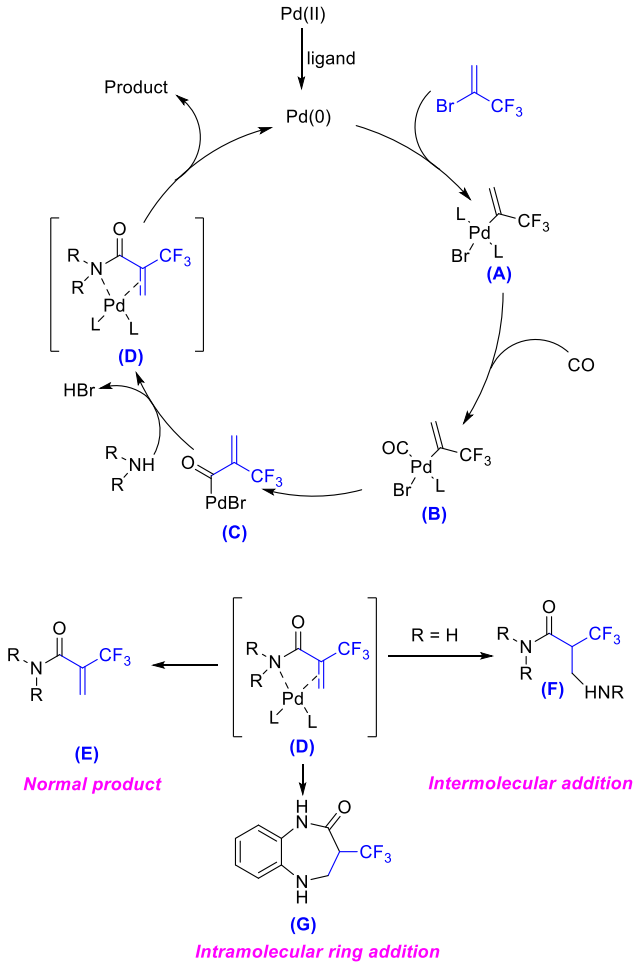
Scheme 2. Gram-Scale Experiment



Scheme 3. Reaction Mechanism



and the reaction has good compatibility with substrate functional groups. Furthermore, this process does not require the addition of any metal additives and appears to be a simple and efficient method. We expect that the discovery of this reaction will play an important role in the synthesis of α-CF_3 amides.

EXPERIMENTAL SECTION

The reaction was carried out in an autoclave containing a 5.0 mL glass reaction tube, and $Pd(PPh_3)_2Cl_2$ (0.02 mmol), ligand **B** (0.04 mmol), aniline (1.0 mmol), $NaHCO_3$ (2.0 mmol), THF (2.0 mL), and 2-bromo-3,3,3-trifluoro-1-propene (2.0 mmol) were added to the tube. The tube was placed in the autoclave. Once sealed, the autoclave was purged three times with CO, then pressurized to 8 atm at room temperature, and heated in an oil bath at 100 °C for 12 h. After the reaction, the autoclave was then cooled to room temperature and vented to discharge CO. The crude product was purified by column chromatography on silica gel using a mixture of ethyl acetate and petroleum ether as the eluent to give the following compounds.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.2c08206.

^{1}H NMR (^{13}C NMR and ^{19}F NMR) spectra for all compounds (PDF)

AUTHOR INFORMATION

Corresponding Authors

Wen Qing Zhu − *School of Environmental and Chemical Engineering, Xi'an Polytechnic University, Xi'an 710048, China*; Email: wqzhu2008@163.com

Yang Li − *School of Environmental and Chemical Engineering, Xi'an Polytechnic University, Xi'an 710048, China*; orcid.org/0000-0001-7009-0871; Email: liyang@xpu.edu.cn

Authors

Xiao Rui Wen − *School of Environmental and Chemical Engineering, Xi'an Polytechnic University, Xi'an 710048, China*

Cai Lin Zhang − *School of Environmental and Chemical Engineering, Xi'an Polytechnic University, Xi'an 710048, China*

Hong Li − *School of Environmental and Chemical Engineering, Xi'an Polytechnic University, Xi'an 710048, China*

Jin Zhang − *School of Environmental and Chemical Engineering, Xi'an Polytechnic University, Xi'an 710048, China*

Min Ge Yang − *School of Environmental and Chemical Engineering, Xi'an Polytechnic University, Xi'an 710048, China*

Yong Li Kou − *Shaanxi Coal Chemical Industry Technology Research Institute Co., Ltd., Xi'an 710065, China*

Yu Xia Liu − *Shaanxi Natural Carbohydrate Resource Engineering Research Center, College of Food Science and Technology, Northwest University, Xi'an 710127, China*

Complete contact information is available at: https://pubs.acs.org/10.1021/acsomega.2c08206

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Notes

The authors declare no competing financial interest.

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