Palladium-Catalyzed Oxidative Aminocarbonylation: A New Entry to Amides via C—H Activation

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ABSTRACT



A novel palladium-catalyzed oxidative aminocarbonylation reaction via $C(sp^3)$ —H activation was established, which provides a convenient and general method for the construction of arylacetamides via the carbonylation reaction of alkyl aromatics and amines. By using this protocol, the marketed drug ibuprofen could be easily obtained.

Transition-metal-catalyzed direct and selective functionalization of C–H bonds has become one of the most promising synthetic strategies in organic synthesis.¹ As an attractive strategy for constructing a diversity of carbonyl compounds without the need for a prefunctionalized site, transition-metal-catalyzed C–H carbonylation reactions have attracted broad interest from both academia and industry.² Since the pioneer studies of Fujiwara in 1980,³ a growing number of C–H carbonylation catalyses that allow for carbonyl group formation have been developed by Chatani, Orito, Yu, and others.^{4,5} However, most of the current C–H carbonylation reactions for forming carbonyl group are typically limited to substrates with directing groups. To the best of our knowledge, only a few examples have been demonstrated on the transition-metalcatalyzed nondirected $C(sp^3)$ -H bonds carbonylation with CO,⁶ which indicated that the direct carbonylation of simple $C(sp^3)$ -H is still a great challenge.

Amides are important chemicals that exist in pharmaceuticals, natural products, and many functional materials.⁷ As a type of important amides, arylacetamides have gained considerable attention because of their pharmacological and biological activities.⁸ Driven by this prevalence, various methods have been developed for the synthesis of these compounds.9 Among methods documented, direct amidation of carboxylic acids¹⁰ or their derivatives¹¹ provides the most straightforward procedure for the synthesis of arylacetamides (Scheme 1, paths A and B). However, these reactions generally require harsh conditions (>150 °C) or multistep operations. Alternatively, transition-metalcatalyzed aminocarbonylation has emerged as an efficient strategy toward such types of compounds. Although some interesting examples of palladium-catalyzed aminocarbonylation of benzyl halides with ammonia and primary amines have recently been described (Scheme 1, path C),¹² the aminocarbonylation of benzyl halides with secondary amines and aliphatic primary amines was

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Scheme 1. Synthetic Methods of Phenylacetamides



expected to be a very challenging endeavor because these amines tend to react with benzyl halides directly to form benzyl amines due to their high nucleophilicity. As a result, further development of new and versatile strategies for establishing an efficient aminocarbonylation reaction toward such arylacetamides is highly desired. One of the goals in our laboratory is the development of some strategies to synthesize the valuable organic compounds

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via $C(sp^3)$ -H bond functionalization reactions.¹³ Recently, we showed that Pd(Xantphos)Cl₂ is capable of catalyzing the carbonylation of alkyl aromatics to afford the arylacetic acid esters via nondirected C-H activation.^{6c} Herein, we wish to report a novel methodology for the synthesis of arylacetamides via a palladium-catalyzed aminocarbonylation of alkyl aromatics with different amines.

On the basis of our experience with palladium-catalyzed carbonylation reactions, toluene (1a) and dibenzylamine (2a) were chosen as model substrates, and the reaction was performed under 10 atm of CO at 120 °C for 16 h. With Pd(Xantphos)Cl₂ as the catalyst precursor and TBP as the oxidant, N,N-dibenzyl-2-phenylacetamide 3aa was obtained in 41% yield, while other oxidants gave lower yields (Table 1, entries 1–5). Furthermore, when the ratio of TBP/2a was increased from 1.2/1 to 1.8/1, the yield of product 3aa dramatically increased to 71% (Table 1, entry 6). With 1.8 equiv of TBP as the oxidant, other reaction

Table 1. Optimization of the Reaction Conditions^a



1^b	PdCl ₂	Xantphos	TBP	41
2^b	$PdCl_2$	Xantphos	TBHP	NR
3^b	$PdCl_2$	Xantphos	DCP	40
4^b	$PdCl_2$	Xantphos	NFSI	NR
5^b	$PdCl_2$	Xantphos	$PhI(OAc)_2$	NR
6	$PdCl_2$	Xantphos	TBP	71
7	$Pd(CF_3COO)_2$	Xantphos	TBP	39
8	$Pd_2(dba)_3$	Xantphos	TBP	53
9	$RhCl_3 \cdot XH_2O$	Xantphos	TBP	38
10	$NiBr_2$	Xantphos	TBP	NR
11	$RuCl_3 \cdot XH_2O$	Xantphos	TBP	NR
12	$PdCl_2$	BINAP	TBP	NR
13	$PdCl_2$	MeO-BIPHIEP	TBP	21
14	$PdCl_2$	DPPE	TBP	NR
15^c	$PdCl_2$	Xantphos	TBP	58
16^d	$PdCl_2$	Xantphos	TBP	61
17^e	$PdCl_2$	Xantphos	TBP	35
18^{f}	$PdCl_2$	Xantphos	TBP	47
19			TBP	0

^{*a*} General conditions: **1a** (20 mmol), **2a** (0.2 mmol), [M] (5 mol %), ligand (5 mol %), oxidant (0.36 mmol), CO (10 atm), at 120 °C for 16 h, isolated yield. ^{*b*} Oxidant (0.24 mmol). ^{*c*} CO (5 atm). ^{*d*} CO (20 atm). ^{*e*} 100 °C instead of 120 °C. ^{*f*} 140 °C instead of 120 °C.

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parameters were investigated. Screening of metal salts revealed that PdCl₂ was the most effective palladium source (Table 1, entries 7-11). To achieve better results, various commercially available phosphine ligands were screened, and the results proved that Xantphos was the best choice (Table 1, entries 12–14). After these optimized conditions were developed, the effects of pressure of CO and temperature were also examined. With either an increase or decrease of the pressure of CO, inferior results were observed. The best yield of 3aa was obtained when the reaction was conducted at 120 °C. Finally, control reactions revealed that the desired product was not detected at all in the absence of palladium catalyst (Table 1, entry 19). Taken together, we can conclude that the carbonylation was carried out by stirring a solution of toluene, dibenzylamine, 5 mol % of Pd(Xantphos)Cl₂, and 1.8 equiv of TBP at 120 °C under 10 atm of CO for 16 h to give the product in the best yield.

With the optimized reaction conditions in hand, we next investigated the substrate scope of amines. First, a series of substituted dibenzylamines were subjected to the present reaction, and the corresponding carbonylation products **3aa–3ae** were obtained in moderate to good yields. Among them, *N*-benzyl-1-(naphthalen-1-yl)methanamine was transformed into the corresponding amide in 82%

Scheme 2. Substrate Scope of Amines^a

CONR¹P² Pd(Xantphos)Cl-TBP, 120 °C ö 3aa 71% . 3ab 64% **3ac** 71% 75% 3ad 82% 3ae 3af 33% ö ő 3ag 61% 3ah 71% 58% 3ai č **3ak** 59% 3aj 42% 3al 68% č 3am 34% 3an 70% 3ao 65%

 a Reaction conditions: **1a** (20 mmol), **2** (0.2 mmol), Pd(Xantphos)Cl₂ (5 mol %), TBP (0.36 mmol), CO (10 atm), at 120 °C for 16 h, isolated yield.

yield. N-Benzyl aromatic amines were also suitable substrates, and moderate yields were obtained. However, an obvious steric hindrance effect was observed when aliphatic benzylamines were used as substrates. For example, N-benzylpropan-1-amine smoothly furnished the desired amide 3ah in 71% yield, but the sterically hindered *N*-benzyl-2-methylpropan-2-amine gave the product **3ai** in 58% yield. Besides benzylamines, the reactions of other secondary amines also proceeded smoothly and gave the amide products in moderate yields (Scheme 2, 3aj, 3ak, and **3al**). Not surprisingly, the aminocarbonylation reaction of the primary amines proceeded smoothly. Although the reaction of aniline yielded the corresponding product in lower yield, the reactions of aliphatic primary amines proceeded smoothly. Both cyclohexanamine and n-propylamine could be utilized as amine sources, and the corresponding products were obtained in 70 and 65% yields, respectively. Notably, when the catalyst loading was decreased from 5 to 0.125 mol %, product **3ad** was obtained in 39% yield with a turnover number (TON) of 312 (see Supporting Information), which could increase the practicality of our reaction process dramatically.



R - U	$H_{+} \bigcirc H_{+} \odot H_{+} \bigcirc H_{+} \odot H_{+} \bigcirc H_{+} \bigcirc H_{+} \odot H_{+} \bigcirc H_{+} \bigcirc H_{+} \bigcirc H_{+} \odot H_{+} \odot H_{+} \odot H_{+} O_{+} O_$	Pd(Xantphos)Cl₂ R ← C	
entry	R	product	yield (%)
1	Н	3ad	82
2	2-Me	3bd	82
3	3-Me	3cd	83
4	4-Me	3dd	85
5	4-MeO	3ed	85
6	4-F	3fd	74
7	2-Cl	3gd	52
8	3-Cl	3hd	52
9	4-Cl	3id	67
10	1-naphthyl	3jd	70
11^b	2-naphthyl	3kd	67

^{*a*} General conditions: **1** (20 mmol), **2d** (0.2 mmol), Pd(Xantphos)Cl₂ (5 mol %), TBP (0.36 mmol), CO (10 atm), at 120 °C for 16 h, isolated yield. ^{*b*} **1k** (10 mmol) in 1 mL of benzene.

To further explore the synthetic potential of this process, a series of alkyl aromatics were subjected to this reaction under the optimized reaction conditions. As summarized in Table 2, various alkyl aromatics were found to be tolerated in this carbonylation process. For example, substrates bearing electron-rich substituents (Table 2, entries 2-5) on the aryl ring underwent this reaction to furnish the corresponding products in high yields (82-85%). However, substrates containing an electron-withdrawing group encountered some difficulties in our procedure, affording the desired amides in relatively lower yields under the same conditions (Table 2, entries 6-9). It is worth noting that the tolerance of halogens on the aromatic ring in this transformation offers an opportunity for subsequent cross-coupling, which facilitates expedient synthesis of complex arylacetamides. An obvious steric hindrance effect on

the reactivity was also observed: 4-chlorotoluene could give the amide product in 67% yield, but 2-chlorotoluene gave the corresponding product in 52% yield (Table 2, entry 7 vs entry 9). Besides, 1-methylnaphthalene also worked well in our reaction system, furnishing the corresponding amide in 70% yield (Table 2, entry 10). With benzene as solvent, the solid substrate 2-methylnaphthalene was smoothly converted to the corresponding product in 67% yield (Table 2, entry 11).

Through further optimization of the reaction conditions (see Supporting Information), we were delighted to find that the challenging ethylbenzene was successfully employed in the aminocarbonylation reaction, and the corresponding amide 3ld was obtained in 75% yield when the pressure of CO was increased to 40 atm and an additional 2.5 mol % of Xantphos was introduced into the catalytic system. The carbonylation reaction with other secondary amines proceeded smoothly and gave rise to the corresponding amides in moderate to good yields (Scheme 3). Furthermore, 1-ethyl-4-isobutylbenzene 1m was successfully converted to the corresponding amide 3md in good yield under the above conditions. Through simple hydrolysis, this amide 3md could be transformed into ibuprofen, which has been widely used for pain relief, fever reduction, and to reduce swelling.

Scheme 3. Aminocarbonylation of Ethylbenzene Derivatives^a



^{*a*} Reaction conditions: **1** (20 mmol), **2** (0.2 mmol), Pd(Xantphos)Cl₂ (5 mol %), Xantphos (2.5 mol %), TBP (1 mmol), CO (40 atm), at 120 °C for 16 h, isolated yield. ^{*b*} **1m** (30 mmol), **2d** (0.3 mmol), TBP (1.5 mmol).

To gain insight into the mechanism, the following experiments were carried out. When radical scavengers, such as TEMPO or 1,1-diphenylethylene, were introduced into the standard reaction, the desired aminocarbonylation was stopped, which suggested that a free radical process was involved with aminocarbonylation (see Supporting Information). Subsequently, when *tert*-butyl-2-phenylacetate served as a substrate to react with dibenzylamine under other identical conditions (Scheme 4, eq 1), no desired product was detected, indicating that the amide product was not formed via the aminolysis of *tert*-butyl-2phenylacetate.^{6c} The tribenzylamine could be generated from the reaction of toluene and dibenzylamine in the presence of TBP (Scheme 4, eq 2), indicating that the aminyl radical might be involved in the present reaction. However, amide **3aa** could not be generated from the carbonylation of tribenzylamine under the standard conditions (Scheme 4, eq 3), which revealed that tribenzylamine was not invovled in the present carbonylation process.

Scheme 4. Controlling Experiments

Pd(Xantphos)Cl ₂ BnCO ₂ t-Bu + CO + Bn ₂ NH <u>(5 mol %)</u> → 3aa C ₆ H ₆ , 120 °C, 16 h Not observed	eq. 1
Toluene + Bn₂NH <u>TBP</u> Bn₃N 120 °C, 16 h Bn₃N 11% yield	eq. 2
$\begin{array}{rcl} & & & \operatorname{Pd}(\operatorname{Xantphos})\operatorname{Cl}_2\\ & & & (5 \ \operatorname{mol}\ \%) \\ & & & & & \\ & & & & & \\ & & & & \\ & & & $	eq. 3

Although the detailed reaction mechanism remains to be elucidated, we believe that the aminocarbonylation reaction proceeds via a benzylpalladium intermediate which could be formed via direct oxidative addition of radicals to Pd(0).^{6c} CO insertion and subsequent reductive elimination would afford the amide product, and the Pd(0) species could be regenerated to complete the catalytic cycle.

In summary, we have successfully developed a novel synthetic method toward arylacetamides through palladiumcatalyzed oxidative C–H aminocarbonylation of simple alkyl aromatics. The catalysis accommodates a diverse set of functional groups including fluoride, chloride, as well as alkoxy groups. Moreover, this reaction can also be employed to synthesize the 2-arylpropanamides via C–H activation, which are precursors for many important marketed drugs. Further investigations to gain a detailed mechanistic understanding of this reaction and developing more synthetically useful and mechanistically novel transformation by exploration of this powerful C–H activation strategy are currently in progress.

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Supporting Information Available. Experimental details and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.