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## Palladium-catalyzed carbonylation of allylamines via C–N bond activation leading to $\beta,\gamma$ -unsaturated amides†

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$\text{Pd}(\text{Xantphos})\text{Cl}_2$  has been identified as an efficient catalyst for the direct carbonylation of allylamines via C–N bond activation. The reaction proceeds smoothly and provides  $\beta,\gamma$ -unsaturated amides in good to excellent yields under relatively mild conditions.

The amide functional group is one of the most important motifs and exists in many natural products, pharmaceutical molecules as well as functional materials. As a result, method development for the efficient synthesis of amides continues to attract much interest from both academia and industry.<sup>1</sup> Many synthetic routes, including many named reactions (Beckmann, Wolff, Schmidt, Ritter, and Ugi reaction, *etc.*),<sup>2</sup> amino-carbonylation,<sup>3</sup> carbonylation of aryl halides with formamides and their derivatives,<sup>4</sup> transamidation reactions,<sup>5</sup> and oxidative coupling reactions with amines,<sup>6</sup> have been developed to access such kinds of molecules.

As an important class of amides,  $\beta,\gamma$ -unsaturated amides have gained considerable attention because of their unique synthetic utility.<sup>7</sup> Among the many types of synthesis methods access to  $\beta,\gamma$ -unsaturated amides documented, transition-metal-catalyzed carbonylation of allyl halides or pseudohalides with amines and CO has provided a rapid and straightforward access to such kind of amide skeletons.<sup>8</sup> However, the use of organic halides or pseudohalides produced large amounts of wasteful by-products which leads to low atom-economy. To circumvent this problem, the direct carbonylation of allylamines via C–N bond cleavage has been firstly developed by Murahashi and co-workers,<sup>9</sup> revealing one of the most atom and step economical process. Despite the significance of the reaction, the harsh reaction conditions were still needed. Therefore, a practical and efficient catalytic protocol for

the direct carbonylation of allylamines with CO under relatively mild condition is still urgent. Inspired by the results and in connection with our interests in the carbonylation and C–N bonds activation.<sup>10</sup> Herein, we present an efficient palladium catalytic system for the carbonylation of allylamines, which provides a highly atom economical protocol for the synthesis of  $\beta,\gamma$ -unsaturated amides under mild condition.

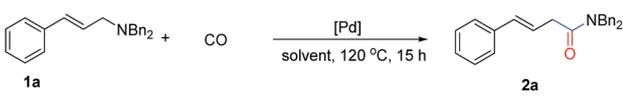
Our initial investigation was conducted in the presence of 10 atm of CO by using *N,N*-dibenzyl-3-phenylprop-2-en-1-amine (**1a**) as model substrate for optimizing the reaction conditions. On the basis of our experience with carbonylation reactions,<sup>10c,10e</sup> a series of Pd complexes were firstly investigated. To our delight, the desired product **2a** was obtained in 43% yield with  $\text{PdCl}_2$  as the catalyst and NMP/THF (1 : 1) as the solvent (Table 1, entry 1). Several other palladium species, such as  $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ ,  $\text{Pd}(\text{DPPP})\text{Cl}_2$ ,  $\text{Pd}(\text{Xantphos})\text{Cl}_2$ ,  $\text{Pd}(\text{BINAP})\text{Cl}_2$  and  $\text{Pd}(\text{DPEPhos})\text{Cl}_2$  were examined, but most of them furnished poor results except  $\text{Pd}(\text{Xantphos})\text{Cl}_2$  (Table 1, entries 2–6). Once a suitable catalyst was identified, optimizations of solvent, CO pressure were conducted. Screening of solvents revealed that the reaction performed in toluene and xylene could afford the desired product with more than 90% yields (Table 1, entries 7–12). The best yield of **2a** was obtained when the reaction conducted under 10 atm of CO whereas no appreciable increase in yield was obtained under decreasing pressure of CO. It was noteworthy that the reaction still worked well even at 6 atm of CO and **2a** was obtained in 90% yield (Table 1, entries 13 and 14). The catalyst loading was lowered from 5 to 0.1 mol%, giving the corresponding product **2a** in 16% yield (TON = 160) (Table 1, entry 15). In the absence of the Pd catalyst, however, no carbonylation reaction occurred under otherwise identical conditions (Table 1, entry 16).

With the optimized conditions in hand, we next investigated the substrate scope of allylamines. As summarized in Table 2, many cinnamyl amines derived from dialkyl amines were well-tolerated in this carbonylation process, furnishing the corresponding products **2a–2f** in good to excellent yields. It appeared that the steric hindrance of the substituents on the amine

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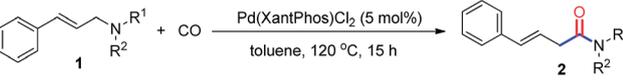
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Table 1 Optimize of the reaction conditions<sup>a</sup>


Entry	[Pd] (5 mol%)	CO (atm)	Solvent	Yield (%)
1	PdCl <sub>2</sub>	10	NMP/THF (1/1)	43
2	Pd(PPh <sub>3</sub> ) <sub>2</sub> Cl <sub>2</sub>	10	NMP/THF (1/1)	38
3	Pd(DPPP)Cl <sub>2</sub>	10	NMP/THF (1/1)	0
4	Pd(Xantphos)Cl <sub>2</sub>	10	NMP/THF (1/1)	82
5	Pd(BINAP)Cl <sub>2</sub>	10	NMP/THF (1/1)	0
6	Pd(DPEPhos)Cl <sub>2</sub>	10	NMP/THF (1/1)	29
7	Pd(Xantphos)Cl <sub>2</sub>	10	NMP	77
8	Pd(Xantphos)Cl <sub>2</sub>	10	THF	87(81) <sup>b</sup>
9	Pd(Xantphos)Cl <sub>2</sub>	10	CH <sub>3</sub> CN	0
10	Pd(Xantphos)Cl <sub>2</sub>	10	Toluene	99(91) <sup>b</sup>
11	Pd(Xantphos)Cl <sub>2</sub>	10	Xylene	99
12	Pd(Xantphos)Cl <sub>2</sub>	10	Mesitylene	22
13	Pd(Xantphos)Cl <sub>2</sub>	6	Toluene	90
14	Pd(Xantphos)Cl <sub>2</sub>	2	Toluene	44
15	Pd(Xantphos)Cl <sub>2</sub>	10	Toluene	16 <sup>b,c</sup>
16	—	10	Toluene	0

<sup>a</sup> Reaction conditions: **1a** (0.5 mmol), CO (10 atm), [Pd] (0.025 mmol) solvent (2.0 mL), 120 °C, 15 h, yields determined by GC using *n*-hexadecane as an internal standard. <sup>b</sup> Isolated yields. <sup>c</sup> Pd(Xantphos)Cl<sub>2</sub> (0.1 mol%), 48 h.

Table 2 Effect of amine moiety of allylamine<sup>a</sup>


Entry	R <sup>1</sup>	R <sup>2</sup>	Yield <sup>b</sup> (%)
1	Bn	Bn	<b>2a</b> , 91 (9 : 1) <sup>c</sup>
2	Et	Et	<b>2b</b> , 93 (9 : 1) <sup>c</sup>
3	<i>n</i> -Pr	<i>n</i> -Pr	<b>2c</b> , 82 (13 : 1) <sup>c</sup>
4	<i>i</i> -Pr	<i>i</i> -Pr	<b>2d</b> , 78 (>20 : 1) <sup>c</sup>
5	<i>n</i> -Bu	<i>n</i> -Bu	<b>2e</b> , 75 (11 : 1) <sup>c</sup>
6	1-Octane	1-Octane	<b>2f</b> , 72 (7 : 1) <sup>c</sup>
7	-(CH <sub>2</sub> ) <sub>4</sub> -		<b>2g</b> , 51 (12 : 1) <sup>c</sup>
8	-(CH <sub>2</sub> ) <sub>5</sub> -		<b>2h</b> , 66 (13 : 1) <sup>c</sup>
9	-(CH <sub>2</sub> CH <sub>2</sub> OCH <sub>2</sub> CH <sub>2</sub> )-		<b>2i</b> , 83 (19 : 1) <sup>c</sup>
10	Bn	<i>n</i> -Pr	<b>2j</b> , 63 (7 : 1) <sup>c</sup>

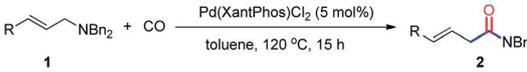
<sup>a</sup> Reaction conditions: allylamine **1** (0.5 mmol), Pd(Xantphos)Cl<sub>2</sub> (0.025 mmol) in toluene (2.0 mL) under CO (10 atm) at 120 °C for 15 h. <sup>b</sup> Isolated yields. <sup>c</sup> Ratios of *Z/E* determined by <sup>1</sup>H NMR are given within parentheses. Major isomers are shown.

moiety of the allylamines has no remarkable influence on the reactivity (Table 2, entries 2–6). Moreover, cinnamyl amines derived from cyclic amines could also be used as carbonylation partners, giving the corresponding β,γ-unsaturated amides **2g–2i** in 51%, 66% and 83% yields, respectively. Besides, *N*-benzyl-3-phenylprop-2-en-1-amine **1j** was transformed into the corresponding amide **2j** in 63% yield.

Allylamines with different substituents attached in aromatic rings were also investigated in this carbonylation

reaction (Table 3). The carbonylation of cinnamyl amines bearing an electron-withdrawing or electron-donating group at the *meta* or *para* position of the phenyl ring proceeded smoothly to provide corresponding adducts **2k–2r** in 73–86% yields. It is noteworthy that the tolerance of halide substituents in this transformation offers an opportunity for subsequent cross-coupling reactions, which facilitates expedient synthesis of functional amides. *N,N*-dibenzyl-3-(naphthalen-2-yl)prop-2-en-1-amine **1s** was a suitable substrate, giving the desired amide **2s** in 84% yield under the optimized conditions. Besides cinnamyl amines, the simple alkyl group substituted allylamine **1t** was subjected to the reaction and transformed into the corresponding product **2t** in 67% yields, but with lower stereoselectivity.

On the basis of our experimental results and previous work, a plausible reaction pathway was outlined in Fig. 1. Initially, Pd(0) species **A** derived from the reduction of Pd(II) serve as an effective catalytic species to react with allylamine **1a** to give rise to the intermediate **B** through oxidative addition. Then, the intermediate **C** would be generated *via* CO insertion. Finally, reductive elimination of **C** afforded the desired product **2a** and

Table 3 Substrate scope of allylamines<sup>a</sup>


Entry	R	Yield <sup>b</sup> (%)
1	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	<b>2k</b> , 75 (7 : 1) <sup>c</sup>
2	3-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	<b>2l</b> , 73 (>20 : 1) <sup>c</sup>
3	4- <i>t</i> -BuC <sub>6</sub> H <sub>4</sub>	<b>2m</b> , 76 (6 : 1) <sup>c</sup>
4	4-MeOC <sub>6</sub> H <sub>4</sub>	<b>2n</b> , 74 (6 : 1) <sup>c</sup>
5	4-EtOC <sub>6</sub> H <sub>4</sub>	<b>2o</b> , 74 (14 : 1) <sup>c</sup>
6	4-FC <sub>6</sub> H <sub>4</sub>	<b>2p</b> , 86 (8 : 1) <sup>c</sup>
7	4-ClC <sub>6</sub> H <sub>4</sub>	<b>2q</b> , 77 (7 : 1) <sup>c</sup>
8	4-AcOC <sub>6</sub> H <sub>4</sub>	<b>2r</b> , 83 (9 : 1) <sup>c</sup>
9	Naphthyl-2-yl	<b>2s</b> , 84 (13 : 1) <sup>c</sup>
10	CH <sub>3</sub>	<b>2t</b> , 67 (3 : 1) <sup>c</sup>

<sup>a</sup> Reaction conditions: allylamine **1** (0.5 mmol), Pd(Xantphos)Cl<sub>2</sub> (0.025 mmol) in toluene (2.0 mL) under CO (10 atm) at 120 °C for 15 h. <sup>b</sup> Isolated yields. <sup>c</sup> Ratios of *Z/E* determined by <sup>1</sup>H NMR are given within parentheses. Major isomers are shown.

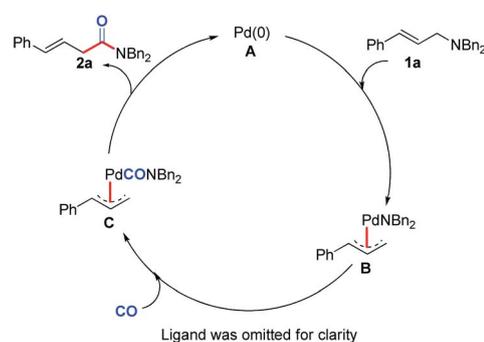


Fig. 1 Proposed mechanism of allylic carbonylation.

along with regeneration of the active catalyst species **A** for the next catalytic cycle.

In summary, we have identified Pd(Xantphos)Cl<sub>2</sub> can act as an efficient catalyst for the direct carbonylation of simple allylamines *via* C–N activation under mild reaction conditions. With 5 mol% of Pd(Xantphos)Cl<sub>2</sub> as the catalyst, the carbonylation reaction can proceed smoothly to afford the desired β,γ-unsaturated amides in good to excellent yields. Further studies on exploring new reactions *via* C–N activation are ongoing in our group.

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