RSC Advances

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/advances

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE

Palladium-catalyzed carbonylation of allylamines via C−N bond activation leading to β,γ-unsaturated amides

Hui Yu,[a] Guoying Zhang,[b] Zong-Jian Liu,*[a] and Hanmin Huang*[a,b]

Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX

DOI: 10.1039/b000000x

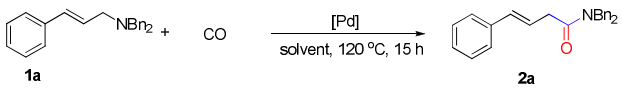
Pd(Xantphos)Cl_2 has been identified as an efficient catalyst for the direct carbonylation of allylamines via C−N bond activation. The reaction proceed smoothly and provide β,γ-unsaturated amides in good to excellent yields under realtively mild conditions.

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, the method development for the efficient synthsis of amides continues to attract much interests from both academia and industry.[1] Many synthetic routs, including many named reactions (Beckmann, Wolff, Schmidt, Ritter, and Ugi reaction, etc.),[2] aminocarbonylation,[3] carbonylation of aryl halides with formamides and their derivatives,[4] transamidation reactions,[5] and oxidative coupling reactions with amines,[6] have been developed to access to such kind of molecules.

As an important class of amides, β,γ-unsaturated amides have gained considerable attention because of their unique synthetic utility.[7] Among the many types of synthesis methods access to β,γ-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.[8] However, the use of organic halides or pseudohalides produced large amounts of wasteful by-products which leads to low atom-economy. To circumvent this probem, the direct carbonylation of allylamines via C-N bond cleavage has been firstly developed by Murahashi and co-workers,[9] 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.[10] Herein, we present an efficient palladium catalytic system for the carbonylation of allylamines, which provides a highly atom economical protocol for the synthesis of β,γ-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,[10c,10e] a series of Pd complexes were firstly investigated. To our delight, the desired product **2a** was obtained in 43% yield with $PdCl_2$ as the catalyst and NMP/THF (1:1) as the solvent (Table 1, entry 1). Several other palladium species, such as Pd(PPh$_3$)$_2$Cl$_2$, Pd(DPPP)Cl$_2$,

Table 1. Optimize of the reaction conditions [a]



1a 2a

Entry	[Pd] (5 mol%)	CO (atm)	Solvent	Yield (%)
1	$PdCl_2$	10	NMP/THF (1/1)	43
2	Pd(PPh$_3$)$_2$Cl$_2$	10	NMP/THF (1/1)	38
3	Pd(DPPP)Cl$_2$	10	NMP/THF (1/1)	0
4	Pd(Xantphos)Cl$_2$	10	NMP/THF (1/1)	82
5	Pd(BINAP)Cl$_2$	10	NMP/THF (1/1)	0
6	Pd(DPEPhos)Cl$_2$	10	NMP/THF (1/1)	29
7	Pd(Xantphos)Cl$_2$	10	NMP	77
8	Pd(Xantphos)Cl$_2$	10	THF	87(81)[b]
9	Pd(Xantphos)Cl$_2$	10	CH_3CN	0
10	Pd(Xantphos)Cl$_2$	10	toluene	99(91)[b]
11	Pd(Xantphos)Cl$_2$	10	xylene	99
12	Pd(Xantphos)Cl$_2$	10	mesitylene	22
13	Pd(Xantphos)Cl$_2$	6	toluene	90
14	Pd(Xantphos)Cl$_2$	2	toluene	44
15	Pd(Xantphos)Cl$_2$	10	toluene	16[b,c]
16	—	10	toluene	0

[a] Reaction conditions: **1a** (0.5mmol), 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. [b] Isolated yields. [c] Pd(Xantphos)Cl$_2$ (0.1 mol%), 48h

Pd(Xantphos)Cl_2, Pd(BINAP)Cl_2 and Pd(DPEPhos)Cl_2 were examined, but most of them furnished poor results except Pd(Xantphos)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

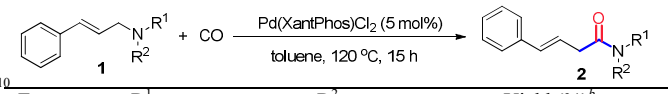
[a]*College of Chemical Engineering, Zhejiang University of Technology, Hangzhou 310024, China; E-mail: zjliu@zjut.edu.cn*

[b]*State Key Laboratory for Oxo Synthesis and Selective Oxidation, Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences, Lanzhou 730000, China; E-mail: hmhuang@licp.cas.cn*

† Electronic supplementary information (ESI) available. DOI: 10.1039/0000000x/

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, entries 15). In the absence of the Pd catalyst, however, no carbonylation reaction occurred under otherwise identical conditions (Table 1, entry 16).

Table 2. Effect of amine moiety of allylamine [a]

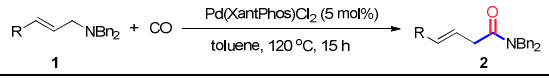


Entry	R^1	R^2	Yield (%)[b]
1	Bn	Bn	**2a**, 91 (9:1)[c]
2	Et	Et	**2b**, 93 (9:1)[c]
3	*n*-Pr	*n*-Pr	**2c**, 82 (13:1)[c]
4	*i*-Pr	*i*-Pr	**2d**, 78 (>20:1)[c]
5	*n*-Bu	*n*-Bu	**2e**, 75 (11:1)[c]
6	1-Octane	1-Octane	**2f**, 72 (7:1)[c]
7	-$(CH_2)_4$-		**2g**, 51 (12:1)[c]
8	-$(CH_2)_5$-		**2h**, 66 (13:1)[c]
9	-$(CH_2CH_2OCH_2CH_2)$-		**2i**, 83 (19:1)[c]
10	Bn	*n*-Pr	**2j**, 63 (7:1)[c]

[a] Reaction conditions: allylamine **1** (0.5 mmol), Pd(Xantphos)Cl_2 (0.025 mmol) in toluene (2.0 mL) under CO (10 atm) at 120 °C for 15 h. [b] Isolated yields. [c] Ratios of *Z*/*E* determined by ^{1}H NMR are given within parentheses. Major isomers are shown.

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

Table 3. Substrate scope of allylamines [a]



Entry	R	Yield (%)[b]
1	4-$CH_3C_6H_4$	**2k**, 75 (7:1)[c]
2	3-$CH_3C_6H_4$	**2l**, 73 (>20:1)[c]
3	4-*t*-BuC_6H_4	**2m**, 76 (6:1)[c]
4	4-$MeOC_6H_4$	**2n**, 74 (6:1)[c]
5	4-$EtOC_6H_4$	**2o**, 74 (14:1)[c]
6	4-FC_6H_4	**2p**, 86 (8:1)[c]
7	4-ClC_6H_4	**2q**, 77 (7:1)[c]
8	4-$AcOC_6H_4$	**2r,** 83 (9:1)[c]
9	Naphthyl-2-yl	**2s**, 84 (13:1)[c]
10	CH_3	**2t**, 67 (3:1)[c]

[a] Reaction conditions: allylamine **1** (0.5 mmol), Pd(Xantphos)Cl_2 (0.025 mmol) in toluene (2.0 mL) under CO (10 atm) at 120 °C for 15 h. [b] Isolated yields. [c] Ratios of *Z*/*E* determined by ^{1}H NMR are given within parentheses. Major isomers are shown.

corresponding products **2a-2f** in good to excellent yields. It appeared that the steric hindrance of the substituents on the amine 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-phenyl-*N*-propylprop-2-en-1-amine **1j** was transformed into the corresponding amide **2j** in 63% yield.

Allylamines with different substitutents 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 Figure 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 along with regeneration of the active catalyst species **A** for the next catalytic cycle.

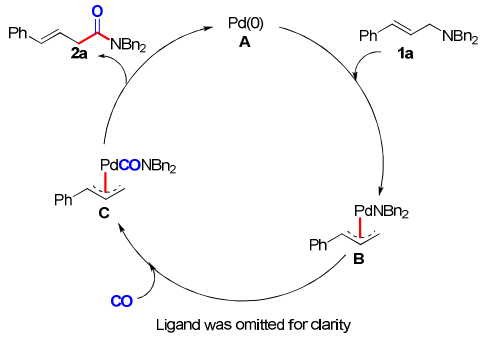


Figure 1: Proposed mechanism of allylic carbonylation

In summary, we have identified Pd(Xantphos)Cl_2 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_2 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.

Acknowledgements

This research was supported by the Chinese Academy of Sciences and the National Natural Science Foundation of China (21222203, 21372231 and 21133011).

Notes and references

1 (a) J. M. Humphrey, A. R. Chamberlin, *Chem. Rev,* 1997, **97,** 2243; (b) M. A. Mintzer, E. E. Simanek, *Chem. Rev.*, 2009, **109,** 259; (c)

V. R. Pattabiraman, J. W. Bode, *Nature*, 2011, **480**, 471; (d) C. L. Allen, J. M. J. Williams, *Chem. Soc. Rev.* 2011, **40**, 3405; (e) D. W. Zhang, X. Zhao, J. L. Hou, Z. T. Li, *Chem. Rev.*, 2012, **112**, 5271.

2 (a) E. Beckmann, *Ber. Dtsch. Chem. Ges.* 1886, **89**, 988; (b) L. Wolff, *Justus Liebigs Ann. Chem.* 1912, **384**, 25; (c) R. F. Schmidt, *Ber. Dtsch. Chem. Ges.* 1924, **57**, 704; (d) J. J. Ritter, P. P. Minieri, *J. Am. Chem. Soc.* 1948, **70**, 4045; (e) I. Ugi, *Angew. Chem. Int. Ed.* 1962, **1**, 8.

3 (a) A. Schoenberg, R. F. Heck, *J. Org. Chem.* 1974, **39**, 3327; (b) M. Beller, B. Cornils, C. D. Frohning, C. W. Kohlpaintner, *J. Mol. Catal. A* 1995, **104**, 17; (c) D. J. Knapton, T. Y. Meyer, *Org. Lett*. 2004, **6**, 687; (d) S. H. Cho, E. J. Yoo, I. Bae, S. Chang, *J. Am. Chem. Soc*. 2005, **127**, 16046; (e) J. R. Martinelli, T. P. Clark, D. A. Watson, R. H. Munday, S. L. Buchwald, *Angew. Chem. Int. Ed.* 2007, **46**, 8460; (f) E. M. Beccalli, G. Broggini, M. Martinelli, S. Sottocornola, *Chem. Rev.* 2007, **107**, 5318; (g) Y. Yasui, Y. Takemoto, *Chem. Rec*. 2008, **8**, 386; (h) J. R. Martinelli, D. A. Watson, D. M. M. Freckmann, T. E. Barder, S. L. Buchwald, *J. Org. Chem.* 2008, **73**, 7102; (i) A. Brennführer, H. Neumann, M. Beller, *Angew. Chem. Int. Ed.* 2009, **48**, 4114; (j) X.-F. Wu, H. Neumann, M. Beller, *Chem. Asian J.* 2010, **5**, 2168; (k) M. V. Khedkar, T. Sasaki, B. M. Bhanage, *ACS Catal.* 2013, **3**, 287.

4 (a) P. J. Tambade, Y. P. Patil, M. J. Bhanushali, B. M. Bhanage, *Tetrahedron Lett.* 2008, **49**, 2221; (b) Y. Jo, J. Ju, J. Choe, K. H. Song, S. Lee, *J. Org. Chem.* 2009, **74**, 6358; (c) D. N. Sawant, Y. W. Wagh, P. J. Tambade, K. D. Bhatte, B. M. Bhanage, *Adv. Synth. Catal.* 2011, **353**, 781; (d) T. He, H. Li, P. Li, L. Wang, *Chem. Commun.* 2011, **47**, 8946; (e) Y.-X. Xie, R.-J. Song, X.-H. Yang, J-N. Xiang, J.-H. Li, *Eur. J. Org. Chem.* 2013, **2013**, 5737.

5 (a) S. E. Eldred, D. A. Stone, S. H. Gellman, S. S. Stahl, *J. Am. Chem. Soc.* 2003, **125**, 3422; (b) A. Klapars, S. Parris, K. W. Anderson, S. L. Buchwald, *J. Am. Chem. Soc.* 2004, **126**, 3529; (c) T. A. Dineen, M. A. Zajac, A. G. Myers, *J. Am. Chem. Soc.* 2006, **128**, 16406; (d) N. A. Stephenson, J. Zhu, S. H. Gellman, S. S. Stahl, *J. Am. Chem. Soc*. 2009, **131**, 10003; (e) T. B. Nguyen, J. Sorres, M. Q. Tran, L. Ermolenko, A. Al-Mourabit, *Org. Lett.*, 2012, **14** ,3202; (f) C. L. Allen, B. N. Atkinson, J. M. Williams, *Angew. Chem. Int. Ed.* 2012, **51**, 1383; (g) M. Zhang, S. Imm, S. Bähn, L. Neubert, H. Neumann, M. Beller, *Angew. Chem. Int. Ed.* 2012, **51**, 3905.

6 (a) Y. Tamaru, Y. Yamada, Z. Yoshida, *Synthesis* **1983**, 474; (b) T. Naota, S. Murahashi, *Synlett* **1991**, 693; (c) A. Tillack, I. Rudloff, M. Beller, Eur. *J. Org. Chem*. **2001**, 523; (d) W.-J. Yoo, C.-J. Li, *J. Am. Chem. Soc.* 2006, **128**, 13064; (e) C. Gunanathan, Y. Ben-David, D. Milstein, *Science* 2007, **317**, 790; (f) J. W. W. Chang, P. W. H. Chan, *Angew. Chem. Int. Ed.* 2008, **47**, 1138; (g) C. Zhang, N. Jiao, *J. Am. Chem. Soc.* 2010, **132**, 28; (h) C. Zhang, Z. Xu, L. Zhang, N. Jiao, *Angew. Chem. Int. Ed.* 2011, **50**, 11088; (i) Y. Wang, D. P. Zhu, L. Tang, S. J. Wang, Z. Y. Wang, *Angew. Chem. Int. Ed.* 2011, **50**, 8917; (j) Z. Liu, J. Zhang, S. Chen, E. Shi, Y. Xu, X. Wan, *Angew. Chem. Int. Ed.* 2012, **51**, 3231.

7 (a) K.-K. Chan, G. Saucy, *J. Org. Chem*. 1977, **42** , 3828; (b) B. J. L. Royles, *Chem. Rev.* 1995, **95**, 1981; (c) F. Yokokawa, T. Shioiri, *J. Org. Chem.* 1998, **63**, 8638; (d) F.-T. Luo, T.-Y. Lub, C. H. Xue, *Tetrahedron*. *Lett*. 2003, **44**, 7249.

8 (a) P. Doz, G. P. Chiusoli, L. Cassar, *Angew. Chem. Int. Ed.* 1967, **6**, 124;. (b) S.-I. Murahashi and Y. Imada, *Chem. Lett*., 1985, 1477; (c) Y. Imada, O. Shibata, S.-I.Murahashi, *J. Organomet.Chem*. 1993, **451**, 183; (d) T.-a. Mitsudo, N. Suzuki, T. Kondo, Y. Watanabe, *J. Org. Chem*. 1994, **59**, 7759; (e) T.-P. Loh, G.-Q. Cao, Z. Yin, *Tetrahedron*. *Lett*., 1999, 40, 2649. (f) R. J. van Haaren, H. Oevering, P. C. J. Kamer, K. Goubitz, J. Fraanje, P. W. N. M. van Leeuwen, G. P. F. van Strijdonck, *J. Organomet.Chem*. 2004, **689**, 3800.

9 (a) S.-I. Murahashi, Y. Imada, K. Nishimura, *J. Chem. Soc. Chem. Commun*. 1988, 1578; (b) S.-I Murahashi, Y. Imada, K. Nishimura, *Tetrahedron*. 1994, **50**, 453.

10 (a) S. Guo, B. Qian, Y. Xie, C. Xia, H. Huang, *Org. Lett.*, 2011, **13** , 522; (b) Y. Xie, J. Hu, Y. Wang, C. Xia, H. Huang, *J. Am. Chem. Soc.*, 2012, **134**, 20613; (c) P. Xie, Y. Xie, B. Qian, H. Zhou, C. Xia, H. Huang, *J. Am. Chem. Soc.*, 2012, **134**, 9902;.(d) Y. Xie, J. Hu, P. Xie, B. Qian, H. Huang, *J. Am. Chem. Soc.*, 2013, **135**, 18327; (e) P. Xie, C. Xia, H. Huang, *Org. Lett.*, 2013, **15**, 3370; (f) J. Hu, Y. Xie, H. Huang, *Angew. Chem. Int. Ed*. 2014, **53**, 7272.