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Pd-Catalyzed C(sp^3)−H Carbonylation of Alkylamines: A Powerful Route to γ-Lactams and γ-Amino Acids

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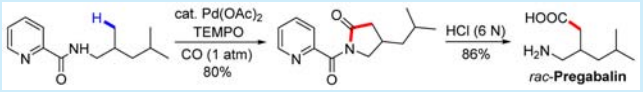
Supporting Information

ABSTRACT: A novel Pd-catalyzed direct C(sp^3)−H carbonylation of alkylamines for the synthesis of γ-lactams and γ-amino acids has been developed, in which TEMPO was used as the crucial sole oxidant. The synthetic prospect was demonstrated by the concise total synthesis of *rac*-Pregbalin.

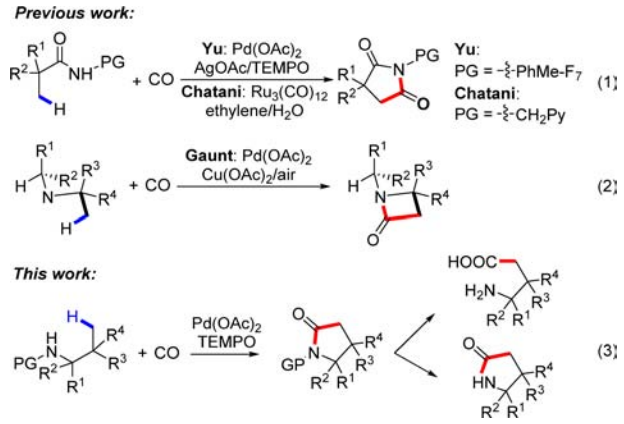


Transition-metal catalyzed carbonylation with carbon monoxide (CO), the most important and readily available C1 feedstock, has attracted extensive attention in academic research and industrial applications.[1] While a variety of transition-metal catalyzed insertions of CO into C(sp^2)−H bonds have been developed in recent decades,[2] the direct carbonylation of C(sp^3)−H bonds has been less studied and remains as a big challenge. Since the pioneering research work of Fujiwara in 1989,[3] palladium-catalyzed carbonylation via nondirected alkyl and benzylic C(sp^3)−H bond activation under 10−50 atm of CO has been accomplished to introduce the easily transformable carbonyl group to simple alkanes[4] and toluenes.[5,6] Unfortunately, these methods are still hampered by some limitations such as the requirement of a large excess of alkanes or toluenes, high pressure of CO, and/or lack of regioselectivity.

To address these issues in nondirected C(sp^3)−H carbonylation, a directing group strategy has been introduced to transition-metal catalyzed C(sp^3)−H bond activation in recent years. The Yu group[7] and the Chatani group[8] described the Pd- and Ru-catalyzed β-carbonylation of aliphatic amides to afford the succinimides independently (eq 1, Scheme 1). Recently, a protocol for the synthesis β-lactams via Pd-catalyzed carbonylation of secondary aliphatic amines was reported by Gaunt and co-workers,[9] in which a four-membered-ring cyclopalladium intermediate was proposed (eq 2, Scheme 1). With the only examples mentioned above developed, the palladium-catalyzed directed C(sp^3)−H carbonylation is still at its first stage and the substrate scope remains limited. Herein, we report a novel Pd-catalyzed C(sp^3)−H carbonylation of alkylamines for the synthesis of γ-lactams and γ-amino acids, with TEMPO used as the crucial sole oxidant, and the synthetic utility was demonstrated by the concise total synthesis of *rac*-Pregabalin.

We commenced our study by examining the C(sp^3)−H activation/CO insertion of *N*-isobutylpicolinamide (**1a**), in which picolinamide developed by Daugulis was used as a bidentate directing group,[10] the pilot substrate under 1 atm of

Scheme 1. Pd-Catalyzed Directed C(sp^3)−H Carbonylation with CO



carbon monoxide (CO) in the presence of a catalytic amount of $Pd(OAc)_2$ (10 mol %) at 130 °C. While most of the commonly used oxidants in both Pd(II)/Pd(0) and Pd(II)/Pd(IV) catalytic cycles, such as Cu(II), Ag(I), $PhI(OAc)_2$, DDQ, NFSI, CAN, $K_2S_2O_8$, etc., showed no reactivity in this transformation, to our excitement, the desired carbonylation product **2a** was obtained when 2 equiv of TEMPO were used as the sole oxidant, albeit in low yield (38%, entry 8, Table 1). Gratifyingly, the yield was improved to 80% when the amount of TEMPO was increased to 4 equiv (entry 9, Table 1), and a slight reduction of the temperature to 120 °C had almost no effect to the transformation. To improve the yield further, a careful survey of solvents was then performed, which revealed both *p*-xylene (85% yield) and anisole (84% yield) were the optimal choice (entries 11−17). Lastly, as a control experiment, we confirmed that the result showed none of the desired

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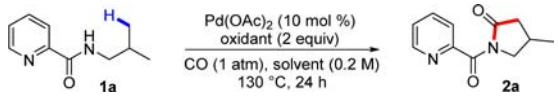
Table 1. Pd-Catalyzed C(sp^3)−H Carbonylation of *N*-Alkylpicolinamides: Optimization of Conditions[a,b]



entry	oxidant	solvent	yield (%)
1	$PhI(OAc)_2$	toluene	0
2	$Cu(OAc)_2$	toluene	0
3	AgOAc	toluene	0
4	DDQ	toluene	0
5	NFSI	toluene	0
6	CAN	toluene	0
7	$K_2S_2O_8$	toluene	0
8	TEMPO	toluene	38
9[c]	TEMPO	toluene	80
10[c,d]	TEMPO	toluene	81
11[c,d]	TEMPO	THF	trace
12[c,d]	TEMPO	DCE	0
13[c,d]	TEMPO	*o*-xylene	74
14[c,d]	TEMPO	*m*-xylene	74
15[c,d]	TEMPO	*p*-xylene	85
16[c,d]	TEMPO	mesitylene	72
17[c,d]	TEMPO	anisole	84
18[c,d,e]	TEMPO	*p*-xylene	0

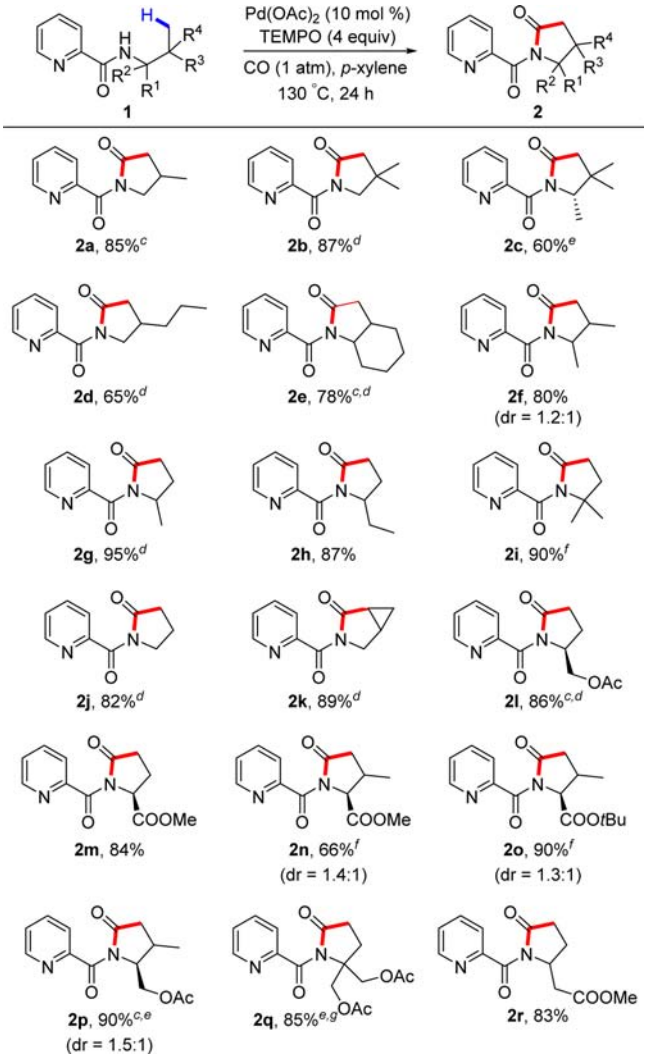
[a]Unless otherwise noted, the reaction conditions were as follows: **1a** (0.2 mmol, 1.0 equiv), $Pd(OAc)_2$ (10 mol %), oxidant (0.4 mmol, 2.0 equiv), CO (1 atm), solvent (1.0 mL), 130 °C, 24 h. [b]Isolated yield. [c]4.0 equiv of TEMPO were used. [d]120 °C. [e]No $Pd(OAc)_2$.

product could be found in the absence of palladium acetate (entry 18).

With the optimized conditions in hand, we next moved on to examine the scope of *N*-alkylpicolinamide **1**. The carbonylation of 2-pyridyl-protected alkylamines with a quaternary *β*-carbon atom proceeded smoothly to afford the corresponding pyrrolidones in good to excellent yields (**2b−c**, Scheme 2). While substrates containing a hydrogen atom at the carbon atom adjacent to the reaction site showed lower reactivity in the reported methods,[7,8] protected alkylamines bearing only one (**2d−f**) or even no *β*-alkyl group (**2g−i**) were well tolerated in our catalytic system without any decline of catalytic activity. Notably, *n*-propylamine derivative **1j** was also well tolerated to give pyrrolidone **2j** in good yield (82%). To our best knowledge, this is the first example of Pd-catalyzed directed C−H carbonylation of nonsubstituted linear functionalized alkanes so far. Additionally, a cyclopropyl C(sp^3)−H bond was also well compatible with this transformation to give an excellent yield (**2k**, 89%).

As the most commercially available chiral sources, the *α*-amino acids and amino alcohols have been widely used in organic synthesis. Establishing streamlined synthetic approaches for the preparation of unnatural chiral derivatives via C−H activation of these readily available chiral compounds is an important research focus and has drawn much interest from different groups recently. A range of commercial *α*-amino acids and amino alcohols were converted to the corresponding picolinamides and subjected to the catalytic system. To our great pleasure, a number of such chiral substrates were compatible with our newly developed protocol, affording the corresponding *γ*-lactams in good yields (**2l−p**). Interestingly, the *β*-amino acid derivative was also the suitable substrate in this transformation (83%, **2r**).

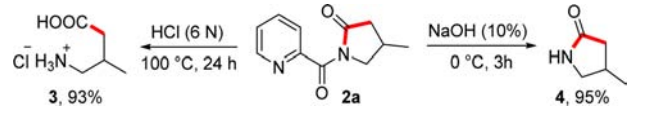
Scheme 2. Scope of *N*-Alkylpicolinamides[a,b,h]



[a]Unless otherwise noted, the reaction conditions were as follows: **1** (0.2 mmol, 1.0 equiv), $Pd(OAc)_2$ (10 mol %), TEMPO (4.0 equiv), *p*-xylene (1 mL), CO (1 atm), 130 °C, 24 h. [b]Isolated yield. [c]120 °C. [d]Anisole was used as solvent. [e]48 h. [f]$Pd(OAc)_2$ (20 mol %). [g]140 °C. [h]The diastereoisomeric ratio was determined by ^1H NMR.

To demonstrate the synthetic utility of this novel method, *N*-pyridyl protected pyrrolidone **2a** was converted to a *γ*-amino acid or *γ*-lactam with high selectivity, by subjection to simple acidic or basic conditions, respectively (Scheme 3). Upon

Scheme 3. Synthetic Derivatization of Picolinoylpyrrolidone



treatment of **2a** with 6 N HCl at 100 °C, both amide bonds were hydrolyzed to give a *γ*-amino acid salt in 93% isolated yield. Meanwhile, treatment of **2a** with NaOH (10%) at 0 °C afforded the 4-methylpyrrolidone **4** in 95% yield by removal of the pyridyl protecting group only. The excellent control of transformation to *γ*-amino acids or *γ*-lactams, both existing expansively in biologically important natural and unnatural

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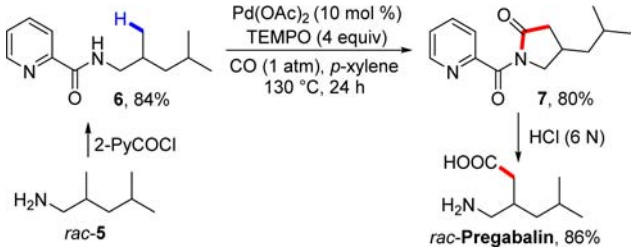
products, clearly indicated the applicational prospect of this method.

To further exhibit the synthetic potential of this transformation, we next attempted to carry out a concise total synthesis of *rac*-Pregabalin, whose (*S*)-isomer was known as an anticonvulsant drug and as an adjunct therapy for partial seizures.[11] Starting from the recemic alkylamine **5**, protection with 2-pyridyl chloride afforded the bidentated amide **6**, which underwent the Pd-catalyzed carbonylation of C(sp^3)−H bond to give the protected γ-lactam **7** in 80% yield. The *rac*-Pregabalin was then obtained in 86% yield followed by deprotection of **7** upon treatment with 6 N HCl and neutralization (Scheme 4).

Scheme 4. Total Synthesis of *rac*-Pregabalin



In conclusion, we have developed a direct carbonylation of alkylamines via Pd-catalyzed C(sp^3)−H bond activation under 1 atm of CO for syntheses of γ -lactams and γ-amino acids, in which TEMPO was found to be the crucial sole oxidant. The synthetic potential was demonstrated by concise total synthesis of *rac*-Pregbalin. Further research to apply this protocol to the total synthesis of complex natural products is currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedure and characterization of all new compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01658.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Brunet, J.-J.; Chauvin, R. *Chem. Soc. Rev.* **1995**, *24*, 89. (b) Eilbracht, P.; Bärfacker, L.; Buss, C.; Hollmann, C.; Kitsos-Rzychon, B. E.; Kranemann, C. L.; Rische, T.; Roggenbuck, R.; Schmidt, A. *Chem. Rev.* **1999**, *99*, 3329. (c) Brummond, K. M.; Kent, J. L. *Tetrahedron* **2000**, *56*, 3263. (d) Sugihara, T.; Yamaguchi, M.; Nishizawa, M. *Chem. - Eur. J.* **2001**, *7*, 1589. (e) Kiss, G. *Chem. Rev.* **2001**, *101*, 3435. (f) Skoda-Földes, R.; Kollár, L. *Curr. Org. Chem.* **2002**, *6*, 1097. (g) Gibson, S. E.; Stevenazzi, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1800. (h) Laschat, S.; Becheanu, A.; Bell, T.; Baro, A. *Synlett* **2005**, 2547. (i) Arndtsen, B. A. *Chem. - Eur. J.* **2009**, *15*, 302. (j) Brennführer, A.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 4114. (k) Lee, H.-W.; Kwong, F.-Y. *Eur. J. Org. Chem.* **2010**, *2010*, 789. (l) Omae, I. *Coord. Chem. Rev.* **2011**, *255*, 139. (m) Wu, X.-F.; Neumann, H.; Beller, M. *Chem. Soc. Rev.* **2011**, *40*, 4986. (n) Liu, Q.; Zhang, H.; Lei, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 10788. (o) Wu, X.-F.; Neumann, H. *ChemCatChem* **2012**, *4*, 447. (p) Gabriele, B.; Mancuso, R.; Salerno, G. *Eur. J. Org. Chem.* **2012**, *2012*, 6825. (q) Wu, X.-F.; Neumann, H.; Beller, M. *Chem. Rev.* **2013**, *113*, 1. (r) Pospech, J.; Fleischer, I.; Franke, R.; Buchholz, S.; Beller, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 2852. (s) Wu, X.-F.; Fang, X.; Wu, L.; Jackstell, R.; Neumann, H.; Beller, M. *Acc. Chem. Res.* **2014**, *47*, 1041. (t) Sumino, S.; Fusano, A.; Fukuyama, T.; Ryu, I. *Acc. Chem. Res.* **2014**, *47*, 1563. (u) Kitagaki, S.; Inagaki, F.; Mukai, C. *Chem. Soc. Rev.* **2014**, *43*, 2956. (v) Fukuyama, T.; Totoki, T.; Ryu, I. *Green Chem.* **2014**, *16*, 2042. (w) Gadge, S. T.; Bhanage, B. M. *RSC Adv.* **2014**, *4*, 10367.

(2) Fujiwara, Y.; Takaki, K.; Taniguchi, Y. *Synlett* **1996**, 591.

(3) Fujiwara, Y.; Takaki, K.; Watanabe, J.; Uchida, Y.; Taniguchi, H. *Chem. Lett.* **1989**, 1687.

(4) (a) Fujiwara, Y.; Jintoku, T.; Uchida, Y. *New J. Chem.* **1989**, *13*, 649. (b) Satoh, K.-I.; Watanabe, J.; Takaki, K.; Fujiwara, Y. *Chem. Lett.* **1991**, 1433. (c) Nakata, K.; Watanabe, J.; Takaki, K.; Fujiwara, Y. *Chem. Lett.* **1991**, 1437. (d) Nishiguchi, T.; Nakata, K.; Takaki, K.; Fujiwara, Y. *Chem. Lett.* **1992**, 1141. (e) Miyata, T.; Nakata, K.; Yamaoka, Y.; Taniguchi, Y.; Takaki, K.; Fujiwara, Y. *Chem. Lett.* **1993**, 1005. (f) Nakata, K.; Yamaoka, Y.; Miyata, T.; Taniguchi, Y.; Takaki, K.; Fujiwara, Y. *J. Organomet. Chem.* **1994**, *473*, 329. (g) Lin, M.; Sen, A. *Nature* **1994**, *368*, 613. (h) Kurioka, M.; Nakata, K.; Jintoku, T.; Taniguchi, Y.; Takaki, K.; Fujiwara, Y. *Chem. Lett.* **1995**, 244.

(5) (a) Xie, P.; Xie, Y.; Qian, B.; Zhou, H.; Xia, C.; Huang, H. *J. Am. Chem. Soc.* **2012**, *134*, 9902. (b) Xie, P.; Xia, C.; Huang, H. *Org. Lett.* **2013**, *15*, 3370.

(6) For nondirected C(sp^3)−H carbonylation with CO catalyzed by transition metals other than palladium, see: (a) Nizova, G. V.; Süss-Fink, G.; Stanislas, S.; Shul'pin, G. B. *Chem. Commun.* **1998**, *17*, 1885. (b) Stahl, S. S.; Labinger, J. A.; Bercaw, J. E. *Angew. Chem., Int. Ed.* **1998**, *37*, 2180. (c) Taniguchi, Y.; Hayashida, T.; Shibasaki, H.; Piao, D.; Kitamura, T.; Yamaji, T.; Fujiwara, Y. *Org. Lett.* **1999**, *1*, 557. (d) Asadullah, M.; Kitamura, T.; Fujiwara, Y. *Chem. Lett.* **1999**, 449. (e) Asadullah, M.; Taniguchi, Y.; Kitamura, T.; Fujiwara, Y. *Tetrahedron Lett.* **1999**, *40*, 8867. (f) Kirillova, M. V.; Kirillov, A. M.; Kuznetsov, M. L.; Silva, J. A. L.; da Silva, J. J. R. F.; Pombeiro, A. J. L. *Chem. Commun.* **2009**, 2353. (g) Kirillova, M. V.; Kirillov, A. M.; Pombeiro, A. J. L. *Chem. - Eur. J.* **2010**, *16*, 9485.

(7) Yoo, E. J.; Wasa, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 17378.

(8) (a) Hasegawa, N.; Charra, V.; Inoue, S.; Fukumoto, Y.; Chatani, N. *J. Am. Chem. Soc.* **2011**, *133*, 8070. (b) Hasegawa, N.; Shibata, K.; Charra, V.; Inoue, S.; Fukumoto, Y.; Chatani, N. *Tetrahedron* **2013**, *69*, 4466.

(9) McNally, A.; Haffemayer, B.; Collins, B. S. L.; Gaunt, M. J. *Nature* **2014**, *510*, 129.

(10) (a) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 13154. (b) He, G.; Chen, G. *Angew. Chem., Int. Ed.* **2011**, *50*, 5192. (c) He, G.; Zhao, Y.; Zhang, S.; Lu, C.; Chen, G. *J. Am. Chem. Soc.* **2012**, *134*, 3. (d) Xie, Y.; Yang, Y.; Huang, L.; Zhang, X.; Zhang, Y. *Org. Lett.* **2012**, *14*, 1238. (e) Zhang, S.-Y.; He, G.; Zhao, Y.; Wright, K.; Nack, W. A.; Chen, G. *J. Am. Chem. Soc.* **2012**, *134*, 7313. (f) Zhang, S.-Y.; He, G.; Nack, W. A.; Zhao, Y.; Li, Q.; Chen, G. *J. Am. Chem. Soc.* **2013**, *135*, 2124. (g) Roman, D. S.; Charette, A. B. *Org. Lett.* **2013**, *15*, 4394. (h) Nadres, E. T.; Santos, G. I. F.; Shabashov, D.; Daugulis, O. *J. Org. Chem.* **2013**, *78*, 9689. (i) Ju, L.; Yao, J.; Wu, Z.; Liu, Z.; Zhang, Y. *J. Org. Chem.* **2013**, *78*, 10821. (j) Cheng, T.; Yin, W.; Zhang, Y.; Zhang, Y.; Huang, Y. *Org. Biomol. Chem.* **2014**, *12*,

DOI: 10.1021/acs.orglett.5b01658
Org. Lett. 2015, 17, 3698−3701

1405. (k) Seki, A.; Takahashi, Y.; Miyake, T. *Tetrahedron Lett.* **2014**, *55*, 2838. (l) Li, Q.; Zhang, S.-Y.; He, G.; Nack, W. A.; Chen, G. *Adv. Synth. Catal.* **2014**, *356*, 1544. (m) Cui, W.; Chen, S.; Wu, J.-Q.; Zhao, X.; Hu, W.; Wang, H. *Org. Lett.* **2014**, *16*, 4288. (n) Zhang, L.-S.; Chen, G.; Wang, X.; Guo, Q.-Y.; Zhang, X.-S.; Pan, F.; Chen, K.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2014**, *53*, 3899.

(11) (a) Wensel, T. M.; Powe, K. W.; Cates, M. E. *Ann. Pharmacother.* **2012**, *46*, 424. (b) Bennett, M. I.; Laird, B.; van Litsenburg, C.; Nimour, M. *Pain Med.* **2013**, *14*, 1681.

(12) When this manuscript was in preparation for submission, an oxalyl amide assisted Pd-catalyzed γ-C(sp^3)−H carbonylation, with AgOAc used as oxidant and *m*-CF_3PhCO_2H as additive, was reported online; see: Wang, C.; Zhang, L.; Chen, C.; Han, J.; Yao, Y.; Zhao, Y. *Chem. Sci.* **2015**, DOI: 10.1039/c5sc00519a. Some comparisons between this reported method and our protocol were listed as follows: (a) While substrates containing a hydrogen atom at the carbon atom adjacent to the reaction site showed lower reactivity in Yao and Zhao's method (23%−56% yields), protected alkylamines bearing only one (**2d**−**f**) or even no β-alkyl group (**2g**−**i**) were well tolerated in our catalytic system without any decline in catalytic activity (65%−90% yields). (b) *n*-Propylamine derivative **1j** was tolerated in our catalytic system to give a good yield (82%), but was not compatible with Yao and Zhao's case (<5%). (c) TEMPO, the lower cost oxidant, was used in our system instead of silver salts. (d) To demonstrate the synthetic perspective, we converted the carbonylation product to the lactam and γ-amino acid, and the novel method was also used for the total synthesis of Pregabalin.

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