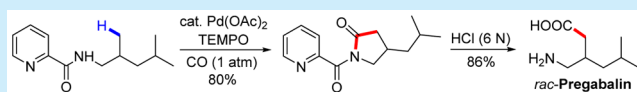


Pd-Catalyzed C(sp³)–H Carbonylation of Alkylamines: A Powerful Route to γ -Lactams and γ -Amino AcidsPei-Long Wang,[†] Yan Li,[†] Yun Wu,[†] Chao Li,[†] Quan Lan,[†] and Xi-Sheng Wang^{*,†,‡}[†]Department of Chemistry, University of Science and Technology of China, Hefei 230026, China[‡]Key Laboratory of Synthetic and Self-Assembly Chemistry for Organic Functional Molecules, Chinese Academy of Sciences, Shanghai Institute of Organic Chemistry, Shanghai, 200032, China

Supporting Information

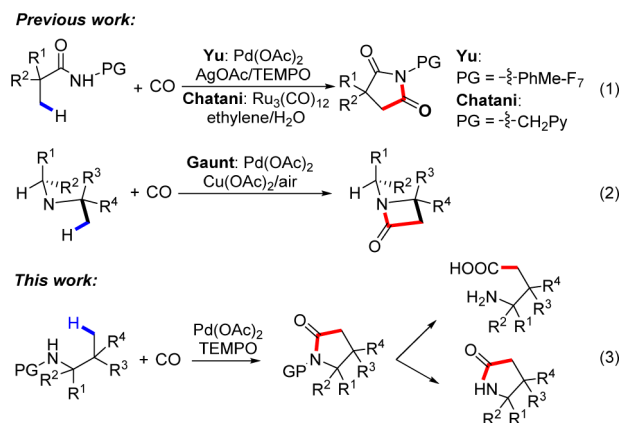
ABSTRACT: A novel Pd-catalyzed direct C(sp³)–H carbonylation of alkylamines for the synthesis of γ -lactams and γ -amino acids has been developed, in which TEMPO was used as the crucial sole oxidant. The synthetic prospect was demonstrated by the concise total synthesis of *rac*-Pregabalin.



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(sp²)–H bonds have been developed in recent decades,² the direct carbonylation of C(sp³)–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(sp³)–H bond activation under 10–50 atm of CO has been accomplished to introduce the easily transformable carbonyl group to simple alkanes⁴ 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.

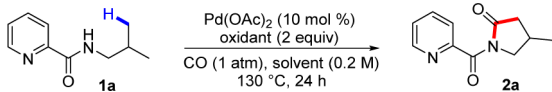
To address these issues in nondirected C(sp³)–H carbonylation, a directing group strategy has been introduced to transition-metal catalyzed C(sp³)–H bond activation in recent years. The Yu group⁷ and the Chatani group⁸ described the Pd- and Ru-catalyzed β -carbonylation of aliphatic amides to afford 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(sp³)–H carbonylation is still at its first stage and the substrate scope remains limited. Herein, we report a novel Pd-catalyzed C(sp³)–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(sp³)–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(sp³)–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, K₂S₂O₈, 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(sp³)-H Carbonylation of *N*-Alkylpicolinamides: Optimization of Conditions^{a,b}


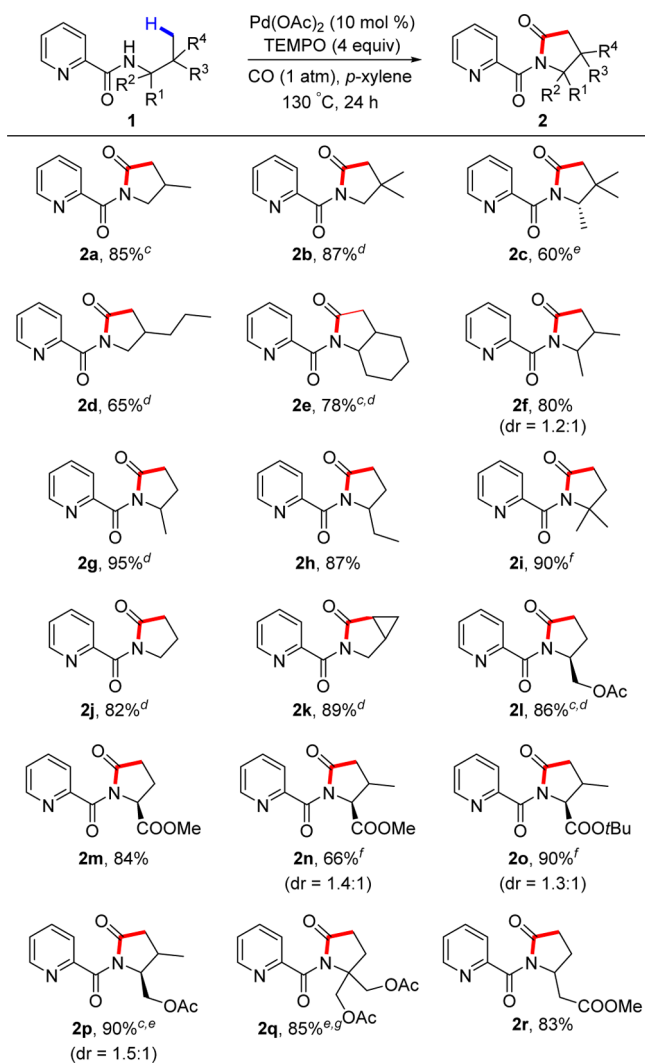
entry	oxidant	solvent	yield (%)
1	PhI(OAc) ₂	toluene	0
2	Cu(OAc) ₂	toluene	0
3	AgOAc	toluene	0
4	DDQ	toluene	0
5	NFSI	toluene	0
6	CAN	toluene	0
7	K ₂ S ₂ O ₈	toluene	0
8	TEMPO	toluene	38
9 ^c	TEMPO	toluene	80
10 ^{c,d}	TEMPO	toluene	81
11 ^{c,d}	TEMPO	THF	trace
12 ^{c,d}	TEMPO	DCE	0
13 ^{c,d}	TEMPO	<i>o</i> -xylene	74
14 ^{c,d}	TEMPO	<i>m</i> -xylene	74
15 ^{c,d}	TEMPO	<i>p</i> -xylene	85
16 ^{c,d}	TEMPO	mesitylene	72
17 ^{c,d}	TEMPO	anisole	84
18 ^{c,d,e}	TEMPO	<i>p</i> -xylene	0

^aUnless 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. ^bIsolated yield. ^c4.0 equiv of TEMPO were used. ^d120 °C. ^eNo Pd(OAc)₂.

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

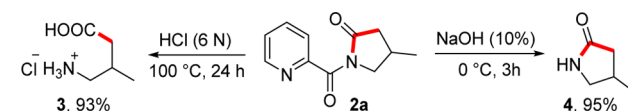
With the optimized conditions in hand, we next moved on to examine the scope of *N*-alkylpicolinamide **1**. The carbonylation of 2-pyridyl-protected alkylamines with a quaternary β-carbon atom proceeded smoothly to afford the corresponding pyrrolidones in good to excellent yields (**2b–c**, Scheme 2). 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(sp³)-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}

^aUnless 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. ^bIsolated yield. ^c120 °C. ^dAnisole was used as solvent. ^e48 h. ^fPd(OAc)₂ (20 mol %). ^g140 °C. ^hThe 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

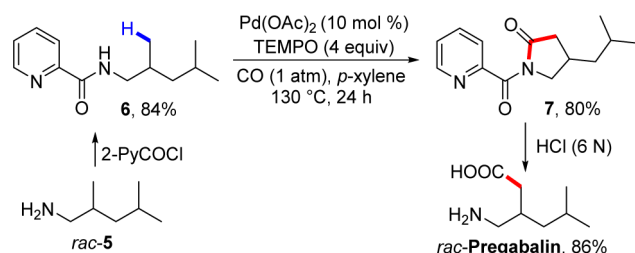
Scheme 3. Synthetic Derivatization of Picolinoylpyrrolidone

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

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(sp³)-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(sp³)-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*-Pregabalin. 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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(12) When this manuscript was in preparation for submission, an oxalyl amide assisted Pd-catalyzed γ -C(sp³)-H carbonylation, with AgOAc used as oxidant and *m*-CF₃PhCO₂H 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.