

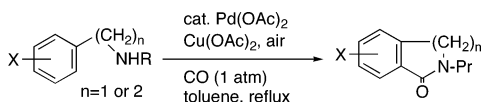
Preparation of Benzolactams by Pd(OAc)₂-Catalyzed Direct Aromatic Carbonylation

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There have been many reported methods for the direct or indirect carbonylation of aromatic compounds using carbon monoxide and transition-metal catalysts.¹ Mori and Ban reported the synthesis of benzolactams and benzolactones by Pd(0)-catalyzed carbonylation in 1978 and 1979.² Since then, such carbonylation via a halogen-metal exchange has been extensively studied to develop methods for the syntheses of a variety of biologically active heterocyclic compounds. In contrast, there has been no method established for the catalytic transformation of ω -arylalkylamines by a direct aromatic metalation to the corresponding benzolactams, although it has been reported that carbonylation of azobenzenes and benzalimines using carbonyl complexes of Co, Mo, or Cr as catalysts or cyclopalladation products of *N,N*-dialkylbenzylamines afforded benzolactams.^{3,4} In this report, we describe a Pd(II)-catalyzed carbonylation using Pd(OAc)₂ and Cu(OAc)₂ in an atmosphere of CO gas containing air. This phosphine-free catalytic system provides five- or six-membered benzolactams from *N*-alkyl- ω -arylalkylamines.



Carbonylation was carried out by stirring a suspension of a secondary amine **1**,⁵ Pd(OAc)₂ (5 mol %), and Cu(OAc)₂ (50 mol %) in a 0.1 M toluene solution in an oil bath at 120 °C in an atmosphere of CO gas containing air (0.5 molar equiv of O₂), delivered from a toy balloon.⁶ The reaction mixture was then filtered to remove insoluble materials, and the filtrate was concentrated to afford a crude product, which was purified by crystallization or preparative TLC.

Carbonylation of phenethylamine **1a** proceeded slowly to give benzolactam **2a** in 64% yield after 24 h. Carbonylation of 3,4-dialkoxyphenethylamine derivative **1b** or **1c** afforded a single benzolactam **2b** (86%, 2 h) or **3c** (24%, 24 h), respectively, with different regioselectivity. Benzylic amines underwent carbonylation at a rate much faster than that of the corresponding phenethylamines. The rate of the five-membered ring formation was 11 times greater than that of the six-membered ring formation (entry 7 in Table 1). The presence of a methylenedioxy group at the 3,4-positions increased the reaction rate by 10-fold in the six-membered ring closure (entry 8) and by 4-fold in the five-membered ring closure (entry 9). 3,4-Methylenedioxydibenzylamine **1e** gave two regioisomers of benzolactams in a 4:1 ratio of **2e** and **3e**, which is similar to the result in entry 9, and 3,4-dimethoxybenzylamine **1f** gave **2f** together with **3f** in a 3:1 ratio. A similar carbonylation of the same amine (**1f**) using Pd(OAc)₂ (1 equiv) without Cu(OAc)₂ produced **2f** and **3f** in a 1:9 ratio, and Pd(OAc)₂·2PPh₃ (1 equiv) afforded a 1:2 mixture, suggesting that Cu(OAc)₂ works as a ligand⁷ as well as an oxidant.

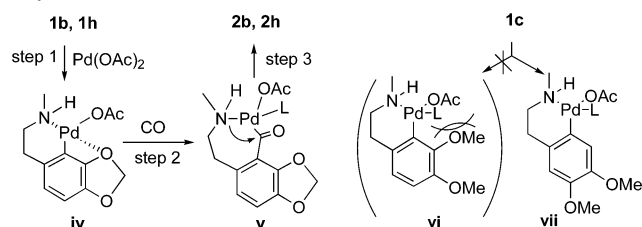
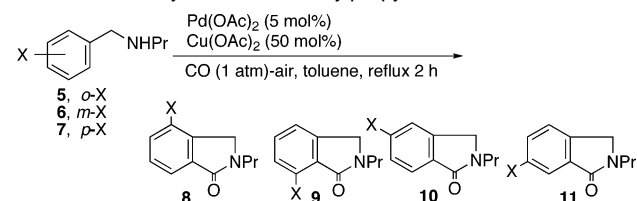
Table 1. Carbonylation of *N*-Alkyl- ω -arylalkylamines **1**^a

Entry	Substrate	Reaction time	Product and Yield
1		24 h	
2		2 h	
3		24 h	
4		2 h	
5		2 h	
6		2 h	
7		24 h	
8		24 h	
9		2 h	
10		2 h	
11		2 h	
12		2 h	

Bn = benzyl, Ar = 3,4-(methylenedioxy)phenyl

^a Under CO gas containing air (0.5 molar equiv of O₂); the substrate, Pd(OAc)₂ (5 mol %), and Cu(OAc)₂ (50 mol %) were suspended in toluene (0.1 M) and heated in an oil bath at 120 °C for 2 or 24 h. ^b Product ratios were determined by ¹H NMR analysis.

The electronic effects of substituents on the phenyl group were examined. A 2,3-methylenedioxy group did not accelerate the

Scheme 1. Direct Aromatic Carbonylation of *N*-Alkylphenethylamines**Table 2.** Carbonylation of *N*-Benzylpropylamines 5–7^a

a, X = OMe	78% (67%)	48% (36%)	49% (38%)	79% (67%)
b, X = Me	92% (76%)	25% (18%)	68% (59%)	85% (72%)
c, X = Cl	81% (73%) ^b	45% (21%)	45% (31%)	82% (71%)
d, X = Br	55% (50%) ^b	28% (22%)	58% (54%)	79% (68%)
e, X = CN	^c	51% (27%)	45% (24%)	93% (74%)
f, X = NO ₂	90% (69%)	0%	81% (68%)	81% (72%)

^a ¹H NMR yields; isolated yields are in parentheses. ^b **2d** was also formed in **5** and 36% yields from **5c** and **5d**, respectively (ref 12). ^c No data are available.

carbonylation (entry 10). No difference between nitro and alkoxy groups was observed in *p*-substitution (entry 11). The *m*-nitro group in **11** caused a slight deactivation in the carbonylation process (entry 12).

It is thought that this carbonylation started from *ortho*-palladation⁸ (step 1, Scheme 1) with Pd(OAc)₂ coordinated with Cu(OAc)₂ and was followed by insertion of a molecular CO into the resultant cyclopalladation product (**iv**), leading to the formation of an acyl-palladium complex (**v**) (step 2). The successive amide bond formation by a nucleophilic attack of an internal amino group on the carbonyl group (step 3) completes the carbonylation to give a benzolactam and Pd(0). Regeneration of Pd(OAc)₂ by oxidation of Pd(0) with Cu(OAc)₂ starts this catalytic cycle, in a manner similar to that of the Wacker process.⁹ A 3',4'-methylenedioxy group provides an efficient chelation¹⁰ with a Pd(II) in the six-membered transition state. A vicinal dimethoxy group inhibits the chelation due to its enhanced steric repulsion,¹¹ as shown in **vi**, and carbonylation via an alternative cyclopalladation product, **vii**, replaces that via **vi**. Cyclopalladation of benzylic amines proceeds too fast, even without substituents, to keep the above excellent regioselectivities.

As shown in Table 2, most of the benzylic amines with an electron-withdrawing group also underwent smooth carbonylation to give the corresponding benzolactams in good yields, similar to those in the case of benzylic amines with an electron-donating group. As observed in the formation of benzolactams **9** and **10**, it was, again, disclosed that the present direct aromatic carbonylation proceeded mainly due to the chelation or steric repulsion between the Pd(II) and *m*-substituent in the cyclopalladation process. Carbonylation of *m*-nitrobenzylamine **6f** produced only 5-nitroben-

zolactam **10f** and not its 7-nitro isomer **9f**, presenting an ultimate steric effect in the present study (see also entry 12 in Table 1).

In summary, we have developed a Pd(II)-catalyzed direct aromatic carbonylation, which proceeds with remarkable site selectivity to afford a variety of five- or six-membered benzolactams from secondary *ω*-phenylalkylamines in a phosphine-free catalytic system using Pd(OAc)₂ and Cu(OAc)₂ in an atmosphere of CO gas containing air.¹³ Studies designed to produce other nitrogen-containing heterocyclic ring systems are currently underway.

Acknowledgment. We thank the Akiyama Foundation for generous financial support, and N.E. CHEMCAT Corporation for the generous donation of palladium catalysts.

Supporting Information Available: Experimental procedures and spectral data for substrates and products **1–11**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (5) Carbonylation of primary amines, including benzylicamines or phenethylamines, under the same conditions, produced no benzolactams but produced ureas in good yields. The details will be reported elsewhere.
- (6) Air (oxygen) is also slowly supplied through the surface of the balloon (Knudsen flow).
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- (8) For *ortho*-palladation products with Pd(OAc)₂ of benzylicamines and phenethylamines with hydrogen on their nitrogen atoms, see: (a) Fuchita, Y.; Tsuchiya, H. *Polyhedron* **1993**, *12*, 2079–2080. (b) *Inorg. Chim. Acta* **1993**, *209*, 229–230. (c) Vicente, J.; Saura-Llamas, I.; Palin, M. J.; Jones, P. G.; Ramírez de Arellano, M. C. *Organometallics* **1997**, *16*, 826–833.
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- (10) This selectivity is similar to those results of the *ortho*-lithiation of benzylic alcohols: Orito, K.; Hatakeyama, T.; Takeo, M.; Uchiito, S.; Tokuda, M.; Sugimoto, H. *Tetrahedron* **1998**, *54*, 8403–8410.
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- (12) Benzolactam **2d** was probably formed via a halogen–metal exchange with a Pd(0) catalyst generated in situ.
- (13) It should be noted that carbonylation of the hydrochloride of phenethylamine **1c** at 20 atm of CO afforded benzolactam **3c** in 79% yield, probably as a result of an electrophilic aromatic carbonylation.

JA045342+