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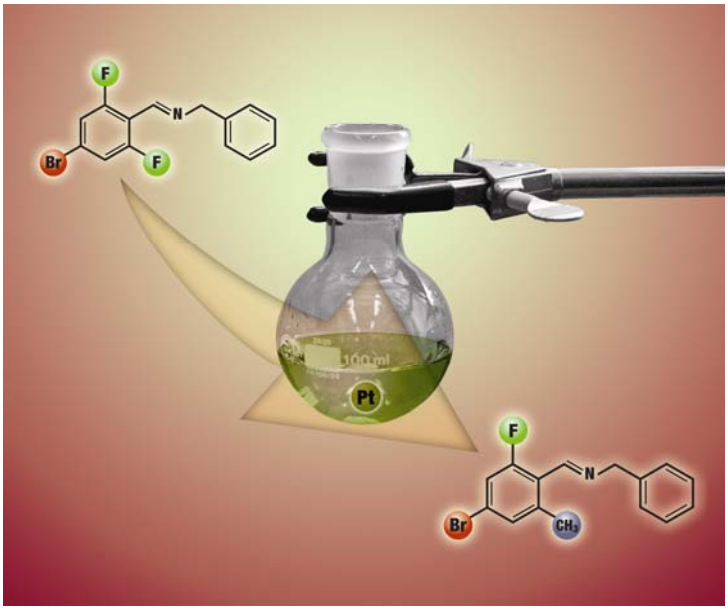


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# LiCl-Promoted Pd(II)-catalyzed *ortho* carbonylation of *N*,*N*-dimethylbenzylamines†‡

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Palladium-catalyzed highly regioselective carbonylation of substituted *N*,*N*-dimethylbenzylamines with the assistance of LiCl was developed. The *ortho*-functionalized *N*,*N*-dimethylbenzylamine was further transformed into *ortho*-methyl benzoate under mild conditions. These two transformations could be combined into one pot to produce the desired product in moderate yield. Applications of this methodology to synthesize the fragments of variolaric acid were also studied.

## Introduction

Carbon monoxide is one of the most important readily available $C_1$ feedstocks. In recent decades, transition metal-catalyzed carbonylation of aryl halides, triflates and tosylates with CO has been well developed and became one of the most straightforward and useful methods to produce carboxylic acids.[1] Among those methods, Pd-catalyzed carbonylations of aromatics with CO are valuable methodologies to synthesize various aryl carboxylic acid derivatives in organic synthesis.[2] Typically, such carbonylation was initiated by the oxidative addition of aryl halides (or their derivatives) to Pd(0) species. Nevertheless, direct carbonylation from easily available arenes would be ideal and environmentally benign.

Very recently, Pd-catalyzed direct transformation of C–H bonds to different functionalities have been well developed.[3] Compared to other transformations, direct carbonylation of C–H bonds with CO still faces many challenges: 1) strong binding ability of CO might inhibit the electrophilic attack of Pd(II) species toward aromatic C–H bonds by occupying the active sites; 2) the unique π-back bonding might also decrease the electron density on Pd-center with CO as an excellent π-acid; 3) the excellent reducing ability of CO might induce the reduction of Pd(II) species to Pd(0) to inhibit the electrophilic attack. Thus, although CO insertion to palladacycles has been thoroughly investigated in carbonylation from aryl halides and their derivatives, the *ortho*-selective C–H bond carbonylation is considerably more difficult because the depalladation process is often complicated by reduction of Pd(II) to Pd(0) nanoparticles under CO atmosphere.[4] In fact, the Pd(II)-catalyzed direct functionalization of C–H bonds into carboxylic acids was first reported by Fujiwara in 1999.[2] However, the investigations in this field are very limited. Recently, directed regioselective *ortho* carbonylation of aryl C–H bonds catalyzed by Pd(II) has started to attract widespread attention.[3] In these reactions, the metallocycles are considered as the key intermediates.

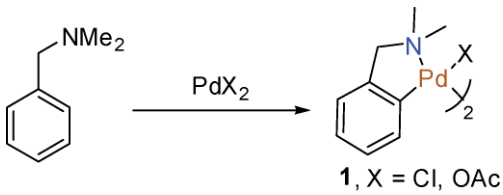
Recently, we reported an efficient Pd(II)-catalyzed *ortho* olefination of *N*,*N*-dimethylbenzylamines and further transformation to afford *ortho*-functionalization of substituted toluene in one pot.[5] In the report, we successfully controlled the reactivity and binding ability of *N*,*N*-dimethylbenzylamine by tuning the acidity of the reaction system. As mentioned, the *N*,*N*-dimethylaminomethyl group could be easily transformed into different functionalities, such as methyl group, aldehyde, and alkene.[6] Thus, we further sought to develop the *ortho*-carbonylation of C–H bonds to form *ortho*-substituted benzoic acid derivatives, which frequently occur in many natural and synthetic biologically active molecules.

## Results and discussion

### Screening of reaction conditions of *ortho* carbonylation of *N*,*N*-dimethylbenzylamines

In 1975, Heck reported the stoichiometric carbonylation reaction of *N*,*N*-dimethylbenzylamine palladacycle with CO.[7] However, a catalytic transformation faced both challenges of the use of *N*,*N*-dimethylamino group as a directing group and Pd(II)-catalyzed direct C–H activation in the presence of CO, which were not easily conquered, as mentioned above.

Considering the palladacycle *via* electrophilic substitution of Pd(II) catalyst to aryl C–H bond of *N*,*N*-dimethylbenzylamine was the key intermediate in our previous work (eqn (1)), we envisioned that Pd(II)-catalyzed *ortho* carbonylation of *N*,*N*-dimethylbenzylamines with CO *via* selective aryl C–H activation might be achieved using this substrate and catalytic system. To our delight, in the previous $PdCl_2/Cu(OAc)_2$ catalyst and TFEol/HOAc solvent system, the use of CO instead of acrylic acid esters gave a small amount of carbonylation product of *N*,*N*-dimethylbenzylamine during the initial exploration (eqn (2)).




**1**, X = Cl, OAc (1)

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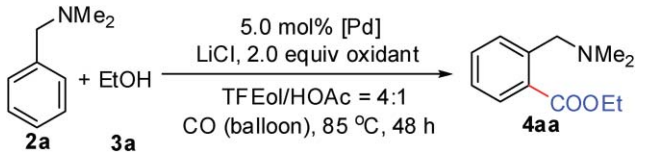
‡ Electronic supplementary information (ESI) available: Additional experimental details, characterization data and NMR spectra. See DOI: 10.1039/c0dt00451k

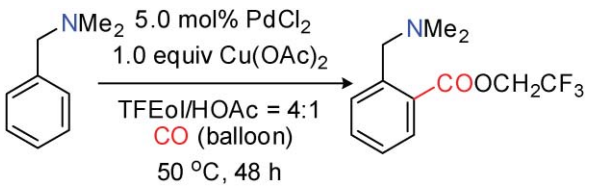
 

**Table 1** Optimization of *ortho* carbonylation of **2a** *via* Pd catalysis.[a]




| Entry | [Pd] | Oxidant | LiCl | GC yield[b] |
|---|---|---|---|---|
| 1 | $PdCl_2$ | $Cu(OAc)_2$ | — | 50 |
| 2 | $PdCl_2$ | $Cu(OAc)_2$ | 10 mol% | 58 |
| 3 | $PdCl_2$ | $Cu(OAc)_2$ | *50 mol%* | 70(64) |
| 4 | $PdCl_2$ | $Cu(OAc)_2$ | 1.0 equiv. | 60 |
| 5 | $PdCl_2$ | $Cu(OAc)_2$ | 1.5 equiv. | 56 |
| 6 | $PdCl_2$ | $Cu(OAc)_2$ | 2.0 equiv. | 52 |
| 7 | $PdCl_2$ | $Cu(OAc)_2$ | 4.0 equiv. | 21 |
| 8 | $PdCl_2(PPh_3)_2$ | $Cu(OAc)_2$ | 50 mol% | 50 |
| 9 | $Pd(OAc)_2$ | $Cu(OAc)_2$ | 50 mol% | 63 |
| 10 | $Pd(OCH_2CF_3)_2$ | $Cu(OAc)_2$ | 50 mol% | 59 |
| 11 | $PdCl_2$ | Oxone | 50 mol% | <5 |
| 12 | $PdCl_2$ | $PhI(OAc)_2$ | 50 mol% | <5 |
| 13 | — | $Cu(OAc)_2$ | 50 mol% | <5 |
| 14 | $PdCl_2$ | — | 50 mol% | <5 |

[a] The reactions were carried out in 0.50 mmol of **2a** in the presence of the proper catalyst, additive, and oxidant in 1.0 mL EtOH, 0.50 mL HOAc, and 2.0 mL TFEol as solvent under CO atmosphere in a balloon. [b] Determined by GC using dodecane as an internal standard. Isolated yield is given in parenthesis.



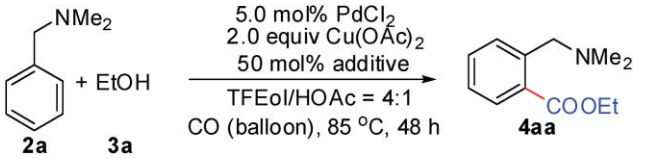
(2)

Such a result encouraged us to further optimize this carbonylation. When EtOH was used as the nucleophile, the desired ester was produced in 50% GC yield at 85 °C (Table 1, entry 1). After the literature search, we found that lithium chloride was generally considered as Lewis acid to promote the insertion of CO into C–Pd bond.[8] In fact, we observed the enhancement of yield with the increase of LiCl from 0 to 50 mol% (Table 1, entries 1–3). However, the yield of desired product dropped with more than 50 mol% of LiCl (Table 1, entries 4–7).

Further studies indicated that the counter anions of palladium catalysts effected the efficacy of carbonylation and $PdCl_2$ showed the best efficiency (Table 1, entries 8–10). The oxidants were further screened. Common oxidants in Pd-catalyzed direct C–H transformations, such as $PhI(OAc)_2$ and oxone, were not efficient for this transformation (Table 1, entries 11 and 12). Undoubtedly, both catalyst and oxidant were essential for this reaction since no desired product was obtained in the absence of either one (Table 1, entries 13 and 14).

Previously, Lu and others reported the effect of halides on the carbonylation reactions and other transformations of C–Pd species.[9] In our case, the obvious effect of various anion additives was also observed (Table 2, entries 1–7). Interestingly, the counter alkali ions also showed different reactivity, which may arise from the solubility and binding ability of different salts (Table 2, entries 8 and 9). Other Lewis acids were further tested but showed a slightly lower efficacy (Table 2, entries 10–12). Among the additives, LiCl

**Table 2** Pd(II)-catalyzed *ortho* carbonylation of **2a** with different additives.[a]




| Entry | Additive | GC yield[b] |
|---|---|---|
| 1 | LiF | 37 |
| 2 | LiBr | 63 |
| 3 | LiI | <5 |
| 4 | LiOAc | 70 |
| 5 | LiOTf | 65 |
| 6[c] | LiOAc | 57 |
| 7[d] | LiOTf | <5 |
| 8 | NaCl | 54 |
| 9 | KCl | 60 |
| 10 | $InCl_3$ | 50 |
| 11 | $ZnCl_2$ | 42 |
| 12 | $Me_4NCl$ | 67 |

[a] The reactions were carried out in 0.50 mmol of **2a** in the presence of the proper catalyst, additive, and oxidant in 1.0 mL EtOH, 0.50 mL HOAc, and 2.0 mL TFEol as solvent under CO atomsphere in a balloon. [b] Determined by GC using dodecane as an internal standard. [c] $Pd(OAc)_2$ was used as catalyst. [d] $Pd(TFA)_2$ was used as catalyst, and 0.50 mL trifluoromethanesulfonic acid was added rather than acetic acid.

was found to be most effective for the carbonylation reaction, which was consistent with the previous report.[9a–9c]

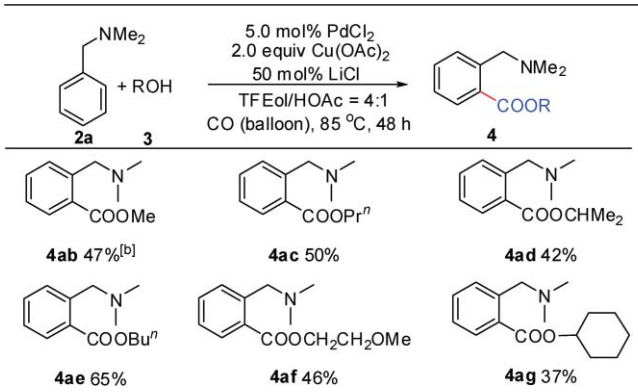
### Carbonylation with different alcohol nucleophiles

Under these optimized conditions, different alcohols were further surveyed as nucleophiles for this carbonylation. To our interest, we found that ethanol was the best one. When methanol was substituted, only 47% yield was obtained (Table 3, **4ab**). Longer chain aliphatic alcohols were also suitable for this transformation (Table 3, **4ac** and **4ae**). However, steric hindered alcohols exhibited lower efficiency (Table 3, **4ad** and **4ag**). 2-Methoxyethanol was also tested and the desired product was isolated in 46% yield (Table 3, **4af**). Other nucleophiles, such as phenol and amines, completely failed for this carbonylation.

### Evaluation of various *N*,*N*-dimethylbenzylamines

Furthermore, the substrate scope of different substituents on the phenyl ring of *N*,*N*-dimethylbenzylamine was expanded. We found that both electron-donating groups and electron-withdrawing groups were tolerated under the developed carbonylation. Generally, electron-rich substituents were helpful for this *ortho* carbonylation due to the enhancement of electron density of phenyl rings (Table 4, **4ba-4ka**). Only mono carbonylation took place when both *ortho*-positions were available. Notably, the *meta*-substituents obviously affected the reactivity and the carbonylation took place at the less hindered *ortho* positions of the dimethylaminomethyl groups (Table 4, **4ba**, **4ea**, and **4ia**). Obviously, electron-deficient groups decreased the reactivity, and poor to moderate yields were achieved with even higher catalyst loading, with the recovery of substrates (Table 4, **4la–4oa**). These results were also consistent with the proposed electrophilic substitution pathway. It was important to note that the relatively

**Table 3** *ortho* Carbonylation of **2a** with different alcohols as nucleophiles.[a]

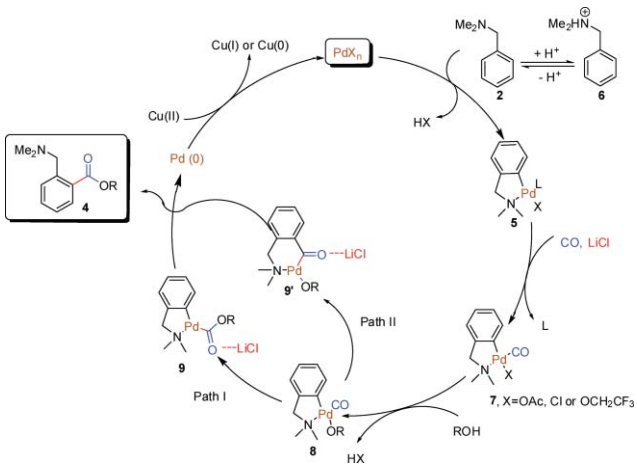



[a] Conditions: **2a** (0.50 mmol), **3** (1.0 mL), $PdCl_2$ (0.025 mmol), LiCl (0.25 mol), $Cu(OAc)_2$ (1.0 mmol), TFEol (2.0 mL), HOAc (0.50 mL), under CO atomsphere in a balloon, 85 °C, 8 h; isolated yields. [b] 2.0 mL methanol was used.

stable C–Cl bond survived well under this transformation, which could be further transformed into different functionalities (Table 4, **4na**).

## Proposed mechanism

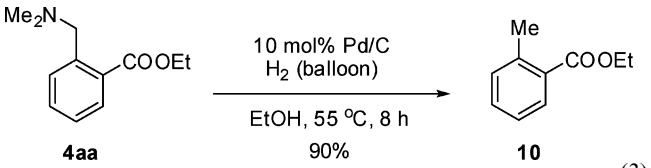
On the basis of the above results and previous studies, the mechanism of the carbonylation reaction was proposed as shown in Scheme 1. As we have reported before, the proper acidic conditions are critical for tuning the concentration of free tertiary amine. Chelation-assisted *ortho* palladation of free tertiary amine **2** by Pd(II) cation formed the key five-membered palladacycle **5**. After ligand exchange, intermediate **8** was produced followed by path I (nucleophilic attack on coordinated ligand) or path II (migration insertion of CO into the C–Pd bond) with the assistance of LiCl to form intermediate **9** or **9′**. Finally, reductive elimination of **9** or **9′** gave the desired product **4** and Pd(0), which was oxidized to Pd(II) by Cu(II) to regenerate the catalyst and finish the catalytic cycle.



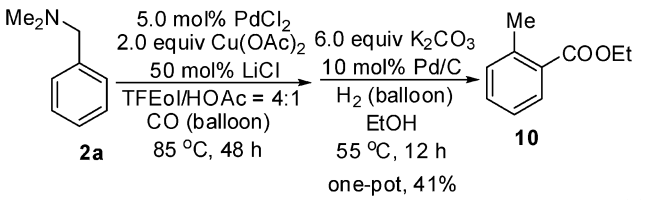

**Scheme 1** Proposed mechanism of *ortho* carbonylation of *N*,*N*-dimethylbenzylamine.

## Applications of *ortho* carbonylation of *N*,*N*-dimethylbenzylamines

With the development of *ortho* carbonylation of *N*,*N*-dimethylbenzylamines in hand, further transformation through catalytic hydrogenation to substituted toluene was explored. Under reductive hydrogen atmosphere with Pd/C as catalyst, the *N*,*N*-dimethylaminomethyl group could be converted into a methyl group in excellent yield (eqn (3)). Thus, the methodology offered a useful method to produce *ortho*-functionalized toluene in an indirect way. Further studies to combine *ortho* carbonylation and hydrogenation into one pot were conducted. After completion of the carbonylation step, the Pd/C catalyst and 6.0 equiv of $K_2CO_3$ were directly added into the reaction system followed by changing atmosphere from air to hydrogen gas. The desired product **10** was obtained in moderate yield, which offered a process to perform this two-step transformation in one pot (eqn (4)).

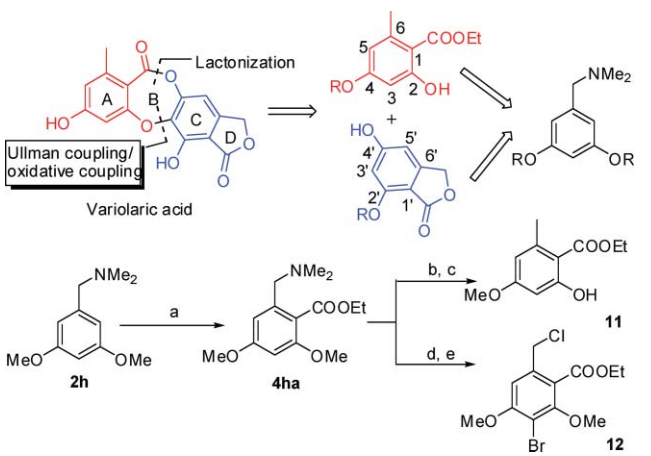



(3)




(4)

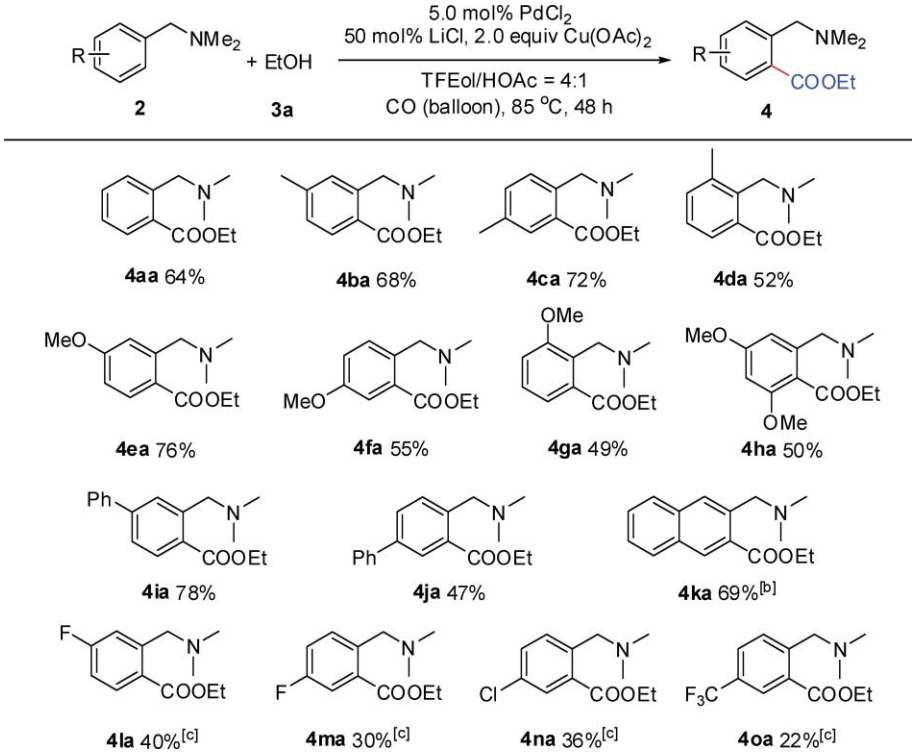
Furthermore, *ortho*-methylbenzoic acids, which can be easily constructed from the functionalized *N*,*N*-dimethylbenzylamine derivatives, were important and common building blocks in natural products.[10] Based on the retrosynthetic analysis of natural variolaric acid, two key segments were proposed as key




**Scheme 2** Retrosynthetic analysis of variolaric acid and the syntheses of its two fragments. Reaction conditions: a. $PdCl_2$ (5.0 mol%), LiCl (50 mol%), $Cu(OAc)_2$ (2.0 equiv.), EtOH/TFEol/HOAc, CO (balloon pressure), 85 °C, 48 h, 50% yield; b. Pd/C (20 mol%), $H_2$ (40 atm), EtOH/HCl (1000 : 1), 70 °C, 60 h, 70% yield; c. $AlCl_3$ (3.0 equiv.), $CH_2Cl_2$, rt, 10 h, 77% yield; d. $ClCO_2Et$ (1.8 equiv.), $CHCl_3$, rt, 3 h, 63% yield; e. NBS (1.5 equiv.), BPO (10 mol%), $CCl_4$, reflux, 5 h, 79% yield.

**Table 4** *ortho* Carbonylation of differently substituted benzylamines with ethanol.[a]




[a] Conditions: **2** (0.50 mmol), **3a** (1.0 mL), $PdCl_2$ (0.025 mmol), LiCl (0.25 mmol), $Cu(OAc)_2$ (1.0 mmol), TFEol (2.0 mL), HOAc (0.50 mL), under CO atomsphere in a balloon, 85 °C, 48 h; isolated yields. [b] 1.0 equiv. LiCl (0.50 mmol) was added. [c] The reactions were catalyzed by 10 mol% of $PdCl_2$ (0.050 mmol).

intermediates for its total synthesis. In fact, such two molecular segments have similar framework, which can be synthesized by directed *ortho* carbonylation through two different pathways from the same substrate (Scheme 2). This convergent synthetic scheme is considered to have higher efficiency with fewer steps.

Based on our previous studies, the *ortho* carbonylation was performed and the designed ester **4ha** was produced in good yield. After further hydrogenation and deprotection, the first segment **11** was produced with good efficiency. Meanwhile, starting from the same intermediate **4ha**, the chlorination and bromination occurred to produce the segment **12**, which might be transformed to the designed lactone fragment (Scheme 2). Thus, this developed method showed a potential application in organic synthesis.

## Conclusions

In summary, we developed a Pd(II)-catalyzed directed *ortho* carbonylation of *N*,*N*-dimethylbenzylamines *via* selective aryl C–H activation with the assistance of LiCl. Further hydrogenation of desired product could synthesize the *ortho*-functionalized toluene. These two transformations could be combined in one pot to offer a more concise and environmentally friendly process. This methodology was further used to construct important structural units of natural products and biologically active compounds. Further studies to increase the efficiency and apply such methods into organic synthesis are in progress.

## Experimental section

### Typical procedure for Pd(II)-catalyzed *ortho* carbonylation of *N*,*N*-dimethylbenzylamines

In a typical experiment, $PdCl_2$ (4.4 mg, 0.025 mmol), LiCl (11 mg, 0.25 mmol), $Cu(OAc)_2$ (0.18 g, 1.0 mmol), and TFEol (2.0 mL) were added into a Schlenk tube. To a solution *N*,*N*-dimethylbenzylamine **2** (0.50 mmol) was added, followed by HOAc (0.50 mL, 8.0 mmol) and alcohol **3** (1.0 mL). The tube was stoppered and heated at 85 °C in an oil bath under a balloon CO atmosphere for 48 h. The mixture was neutralized to pH = 7~8 with a saturated $Na_2CO_3$ aqueous solution (3.0 mL), and a light blue precipitate appeared. The suspension was filtered through a Celite pad and extracted with $CH_2Cl_2$ three times. The combined organic layers were dried over anhydrous $Na_2SO_4$ and evaporated in vacuo. The desired products **4** were obtained in the corresponding yields as a colorless to light yellow oil after purification by flash chromatography on silica gel with petroleum ether/EtOAc (10 : 1, 5% v./v. triethylamine contained).

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## References


1 For transition metal-catalyzed carbonylation of aryl halides and related compounds, see: (*a*) A. Brennführer, H. Neumann and M. Beller, *Angew. Chem., Int. Ed.*, 2009, **48**, 4114; (*b*) Y. Zhao, L. Jin, P. Li and A. Lei, *J. Am. Chem. Soc.*, 2008, **130**, 9429; (*c*) R. H. Munday, J. R. Martinelli and S. L. Buchwald, *J. Am. Chem. Soc.*, 2008, **130**, 2754; (*d*) W. Mägerlein, A. F. Indolese and M. Beller, *Angew. Chem., Int. Ed.*, 2001, **40**, 2856; (*e*) A. Schoenberg, I. Bartoletti and R. F. Heck, *J. Org. Chem.*, 1974, **39**, 3318.

2 W. Lu, Y. Yamaoka, Y. Taniguchi, T. Kitamura, K. Takaki and Y. Fujiwara, *J. Organomet. Chem.*, 1999, **580**, 290.

3 For Pd(II)-catalyzed directed *ortho* carbonylation of aryl C–H bonds, see: (*a*) S. Ohashi, S. Sakaguchi and Y. Ishii, *Chem. Commun.*, 2005, 486; (*b*) C. E. Houlden, M. Hutchby, C. D. Bailey, J. G. Ford, S. N. G. Tyler, M. R. Gagne, G. C. Lloyd-Jones and K. I. Booker-Milburn, *Angew. Chem., Int. Ed.*, 2009, **48**, 1830; (*c*) R. Giri and J.-Q. Yu, *J. Am. Chem. Soc.*, 2008, **130**, 14082; (*d*) K. Orito, A. Horibata, T. Nakamura, H. Ushito, H. Nagasaki, M. Yuguchi, S. Yamashita and M. Tokuda, *J. Am. Chem. Soc.*, 2004, **126**, 14342.

4 (*a*) Z.-H. Guan, Z.-H. Ren, S. M. Spinella, S. Yu, Y.-M. Liang and X. Zhang, *J. Am. Chem. Soc.*, 2009, **131**, 729; (*b*) W.-Y. Yu, W. N. Sit, K.-M. Lai, Z. Zhou and A. S. C. Chan, *J. Am. Chem. Soc.*, 2008, **130**, 3304.

5 G. Cai, Y. Fu, Y. Li, X. Wan and Z. Shi, *J. Am. Chem. Soc.*, 2007, **129**, 7666.

6 For the derivation of *N*,*N*-dimethylaminomethyl group, see: (*a*) B. Balagam and D. E. Richardson, *Inorg. Chem.*, 2008, **47**, 1173; (*b*) E. Tayama and H. Kimura, *Angew. Chem., Int. Ed.*, 2007, **46**, 8869; (*c*) S. Iida and H. Togo, *Tetrahedron*, 2007, **63**, 8274; (*d*) E. L. Eliel and R. P. Anderson, *J. Am. Chem. Soc.*, 1952, **74**, 547; (*e*) S. W. Kantor and C. R. Hauser, *J. Am. Chem. Soc.*, 1951, **73**, 4122.

7 J. M. Thompson and R. F. Heck, *J. Org. Chem.*, 1975, **40**, 2667.

8 R. C. Larock and C. A. Fellows, *J. Am. Chem. Soc.*, 1982, **104**, 1900.

9 Z. Wang, Z. Zhang and X. Lu, *Organometallics*, 2000, **19**, 775.

10 F. M. Dean, *Naturally Occurring Oxygen Ring Compounds*, Butterworth, Inc., Washington D. C., 1963.




 