Letter

# Palladium-Catalyzed Carbonylative Direct Transformation of Benzyl Amines under Additive-Free Conditions

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# Palladium-Catalyzed Carbonylative Direct Transformation of Benzyl Amines under Additive-Free Conditions

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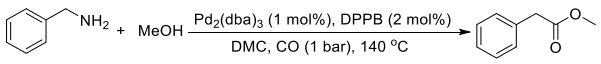
**ABSTRACT:** In this communication, we developed a new procedure for the direct carbonylative transformation of benzyl amines. Using dimethyl carbonate as the solvent, methyl 2-arylacetates can be produced in good to excellent yields from the corresponding primary, secondary and tertiary benzyl amines with palladium as the catalyst. Notably, no base or any other additive is required here. Additionally, our procedure can also be applied in the preparation of methylphenidate, which is a marketing drug and used in the treatment of attention deficit hyperactivity disorder (ADHD) and narcolepsy.

KEYWORDS: benzyl amines; carbonylation; palladium catalyst; green solvent; ester

The preciseness transformation of readily available feedstocks to more functionalized products is one of the ideas in organic chemistry. Carbonylative transformations, which using carbon monoxide as one of the most important C1 building blocks, represent prime examples for such transformations.[1] The importance of transition-metal-catalysed carbonylations have also been verified by the broad interests from both scientific research and industrial productions. Among the various carbonylation procedures, carbonylative transformation of benzylic substrates is attractive. On one hand, the obtained products are important moiety presents in many medical molecules and acting as key intermediates in synthetic organic chemistry as well; on the other hand, the $Csp^3$-X character of the reaction site makes their activation become more challenge than the most frequently studied $Csp^2$-X bonds.[2] The existed achievements in this area are mainly focused on using benzyl chlorides/bromides, benzyl carbonates/acetates, and benzyl phosphates as the substrates.[3] Obviously, additional efforts costed for the preparation of those pre-activated substrates and also generates significant amount of wastes in the usage of these activating groups.

Additionally, C-N bond is a popular chemical bond that present widely in nature.[4,5] Due to the high activating energy of the C-N bonds and good nucleophilicity of the amine group, amines are more commonly applied as nucleophiles in organic chemistry. For the usage as electrophiles, amines were usually transformed into the corresponding diazonium salts or quaternary ammonium salts.[6] Such type of strategies usually producing large amount of wastes and cannot match with the requests of 'sustainable development'. Moreover, organic carbonates are considered as green reaction media in nowadays.[7] Advantages including low toxicity and biodegradability are attracting more and more attention to explore their applications. In this communication, we developed a new procedure for the direct carbonylative transformation of benzyl amines. Using dimethyl carbonate as the green solvent, methyl 2-arylacetates can be produced in good to excellent yields from the corresponding various benzyl amines. Notably, no base or any other additive is required here.

**Table 1.** Reaction conditions studies.[a]



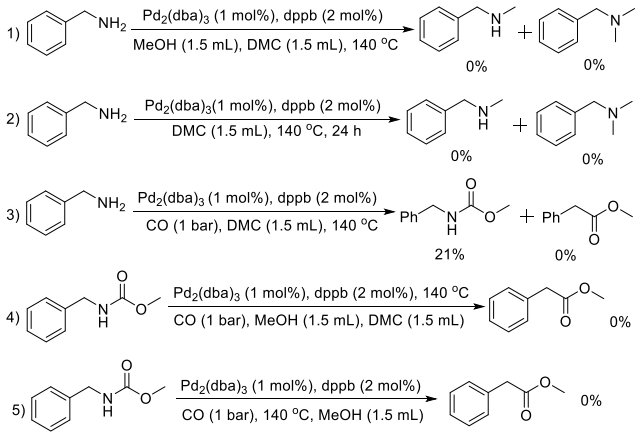

| Entry | Variations from the standard conditions | Yield[b] |
|---|---|---|
| **1** | standard conditions | 96% |
| **2** | Without CO | - |
| **3** | Without catalyst/ligand | - |
| **4** | $Pd(OAc)_2$ instead of $Pd_2(dba)_3$ | 86% |
| **5** | DPPP instead of DPPB | 61% |
| **6** | DPPPe instead of DPPB | 53% |
| **7** | Xantphos instead of DPPB | 67% |
| **8** | THF or 1,4-Dioxane instead of DMC | - |
| **9** | 20 bar CO instead of 1 bar CO | 82% |
| **10** | MeOH (0.2 mL) | 73% |

[a] Benzyl amine (0.25 mmol), $Pd_2(dba)_3$ (1 mol%), DPPB (2 mol%), CO (1 bar), $N_2$ (19 bar), MeOH (1.5 mL), DMC (1.5 mL), 24 h. [b] GC yields. DPPB: 1,4-bis(diphenylphosphino)butane. DPPP: 1,3-bis(diphenylphosphino)-propane. DPPPe: 1,5-bis(diphenylphosphino)pentane. DMC: dimethyl carbonate.

Initially, we choose benzyl amine as the model substrate to establish the reaction conditions. After intensive and systematic studies, we found that 96% of methyl 2-phenylacetate can be produced with $Pd_2(dba)_3$ and DPPB as the catalytic system (Table 1, entry 1). The reaction was carried out in DMC, under 1 bar of carbon monoxide. Methanol has been used as the reaction partner and also as co-solvent, no additional base or additive is necessary. As we expected, no desired ester could be detected in the absence of CO or catalytic system (Table 1, entries 2 and 3). Good yield of the target product can still be

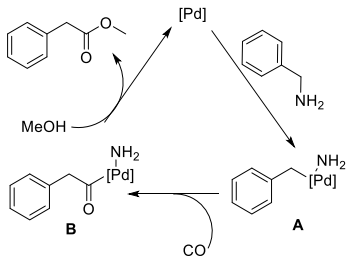
produced with $Pd(OAc)_2$ as the catalyst precursor (Table 1, entry 4). The reaction efficiency decreased when DPPP, DPPPe or Xantphos was applied instead of DPPB (Table 1, entries 5-7). To our surprise, no reaction occurred when using THF or 1,4-dioxane as reaction solvent (Table 1, entry 8). This phenomenon implies that DMC might have other role besides solvent. Carbon monoxide pressure or reaction temperature variations could not further improve the reaction outcomes (Table 1, entry 9). With lower amount of MeOH, yield of the desired ester slightly decreased (Table 1, entry 10).

At this stage, the optimum reaction conditions were established. However, the simple and sustainable conditions for such challenge benzyl amine activation motivated us to perform further control studies to get some understandings of the reaction pathway (Scheme 1). We suspect that the N*H*$_2$ group of benzyl amine could be methylated by methanol or DMC in the presence of palladium catalyst.[7,8] Then the *in situ* produced *N*-methyl or *N*,*N*-dimethyl product can be carbonylated to give the obtained ester. However, *N*-methyl benzyl amine or/and *N*,*N*-dimethyl benzyl amine could not be detected in the absence of CO or CO and MeOH (Scheme 1, eq 1 and 2). A control reaction without MeOH addition has been carried out as well (Scheme 1, eq 3). Under CO pressure, no methyl 2-phenylacetate can be detected, but 21% of methyl benzylcarbamate was formed which comes from the reaction between benzyl amine and DMC. The possibility that methyl benzylcarbamate acting as the reaction intermediate can be excluded by the control experiments shown in Scheme 1, eq 4 and 5. No methyl 2-phenylacetate can be detected under our standard conditions or in the absence of DMC with methyl benzylcarbamate as the starting material.




**Scheme 1.** Control experiments.

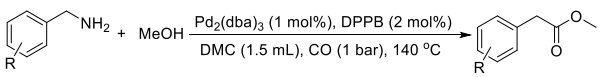
With all these results in our mind, a possible reaction pathway is proposed and shown in Scheme 2. Firstly, the benzylic C-N bond can be activated by palladium catalyst to give the corresponding organopalladium complex **A**. Secondary, acylpalladium intermediate **B** as the key intermediate will be produced after the coordination and insertion of CO to the Pd-C bond of complex **A**. Finally, the desired ester product will be eliminated after the nucleophilic attack of MeOH to the complex **B** and meanwhile regenerates the active palladium species for the next cycle. Concerning the roles of DMC, besides acting as solvent, a part of the DMC might be transformed into methyl hydrogen carbonate and acting as the activator of amines and then facile the oxidation step.

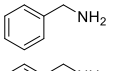
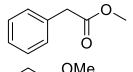
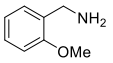
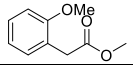



**Scheme 2. Proposed reaction mechanism.**

In order to proven the synthetic potential of this methodology, the testing of different benzyl amines were carried out under our standard condition as well (Table 2). Primary benzyl amines can be all effectively transformed in general (Table 2, entries 1-10). Substrates with substituent at *ortho* position or 2,6-positions can provide the corresponding products in excellent yields, 91% and 90% respectively (Table 2, entries 2,3). Either electron-donating or electron-withdrawing substituents at the *para* position, good yields of the desired esters can be isolated in general (Table 2, entries 4-7). In addition to naphthalen-1-ylmethanamine, pyridin-2-ylmethanamine and thiophen-2-ylmethanamine can be successfully carbonylated under our standard conditions as well (Table 2, entries 9 and 10). Additionally, secondary benzylic amines can also be applied (Table 2, entries 11-19). Various *N*-methyl benzyl amines were selectively transformed and provided the desired products in moderate to good yields. And other types of *N*-alkyl substituted benzyl amines are proven to be suitable substrates as well. In the case of dibenzylamine, both of the benzylic groups can be activated and utilized (Table 2, entry 19). Moreover, tertiary substituted benzyl amine can be applied without any problem. 80% of methyl 2-phenylacetate was produced from *N*,*N*-dimethyl benzyl amine under our standard conditions (Table 2, entry 20). Ethanol was tested in DMC in our model system as well, but a mixture of ethyl 2-phenylacetate and methyl 2-phenylacetate were obtained. The methanol for methyl 2-phenylacetate was from the reaction between ethanol and DMC. This problem can be overcome by using diethyl carbonate as the solvent for ethanol, good yield of the corresponding ester was produced (Table 2, entry 21). However, aliphatic amines failed in this system and only the corresponding ureas could be detected after reacted with DMC.

**Table 2.** Pd-catalysed carbonylative transformation of benzyl amines.[a]




| Entry | Benzyl amines | Products | Yield |
|---|---|---|---|
| 1 |  |  | 90% |
| 2 |  |  | 91% |

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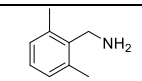
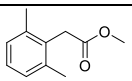
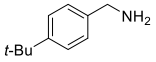
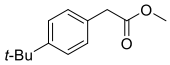
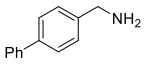
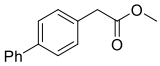
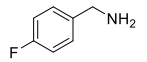
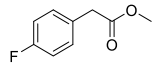
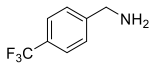
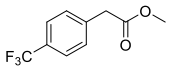
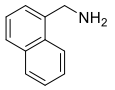
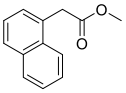
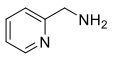
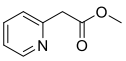
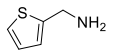
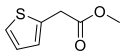
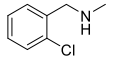
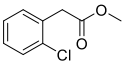
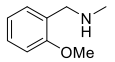
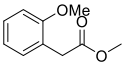
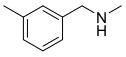
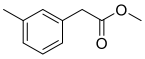
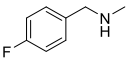
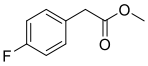
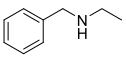
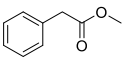
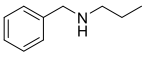
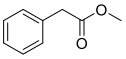
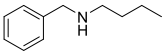
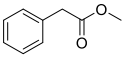
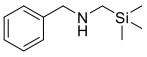
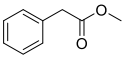
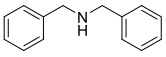
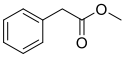
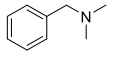
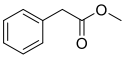
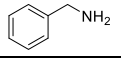
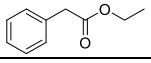
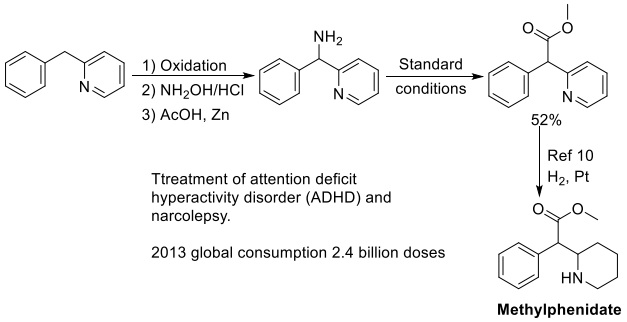
|---|---|---|---|
| 3 |  |  | 90% |
| 4 |  |  | 74% |
| 5 |  |  | 80% |
| 6 |  |  | 78% |
| 7 |  |  | 68% |
| 8 |  |  | 72% |
| 9 |  |  | 66% |
| 10 |  |  | 51% |
| 11 |  |  | 75% |
| 12 |  |  | 84% |
| 13 |  |  | 85% |
| 14 |  |  | 58% |
| 15 |  |  | 91% |
| 16 |  |  | 77% |
| 17 |  |  | 84% |
| 18 |  |  | 80% |
| 19 |  |  | 124% |
| 20 |  |  | 80% |
| 21 |  |  | 89%[b] |

[a] Substrate (0.25 mmol), $Pd_2(dba)_3$ (1 mol%), DPPB (2 mol%), CO (1 bar), $N_2$ (19 bar), MeOH (1.5 mL), DMC (1.5 mL), 24 h, isolated yield. [b] Diethyl carbonate (1.5 mL), EtOH (1.5 mL).

Methylphenidate with trade name Ritalin, has been used in the treatment of attention deficit hyperactivity disorder (ADHD) and narcolepsy.[9] It's traditionally synthetic procedure was started from 2-bromopyridine and 2-phenylacetonitrile with seven manipulation steps.[10] To our delight, our procedure can be applied in the synthesis of methylphenidate as well (Scheme 3). With phenyl(pyridin-2-yl)methanamine as the substrate, under our standard reaction conditions, 52% of the desired methyl 2-phenyl-2-(pyridin-2-yl)acetate can be produced without any further optimization which can be reduced to the final methylphenidate with one additional known procedure.




**Scheme 3.** Synthesis of methylphenidate.

In conclusion, an interesting palladium-catalysed procedure for the direct carbonylative transformation of various benzyl amines has been developed. Without any additive or even base, using dimethyl carbonate as the green solvent, the desired esters were produced in moderate to excellent yields. Not only primary benzyl amines, but also secondary and tertiary can all be applied. Additionally, our procedure can also be applied in the preparation of methylphenidate, which is a marketing drug and used in the treatment of attention deficit hyperactivity disorder (ADHD) and narcolepsy.

## ASSOCIATED CONTENT

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### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.
General comments, general procedure, analytic data and NMR spectrums of products (PDF)

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