# An Efficient Method for the Preparation of Tertiary Esters by Palladium-Catalyzed Alkoxycarbonylation of Aryl Bromides
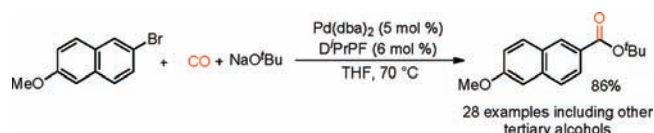
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**ABSTRACT**



The palladium-catalyzed alkoxycarbonylation of aryl bromides is described for the efficient preparation of tertiary esters. The protocol proved compatible with a wide variety of functionalized (hetero)aromatic bromides, as well as several different sterically hindered tertiary alcohols, affording the alkoxycarbonylated products in high yields. Finally, the formation of aromatic trityl esters is discussed.

Esterification is one of the most fundamental and important reactions widely employed in organic synthesis of bioactive compounds, synthetic materials, and as a means of installing protecting groups.[1,2] Despite numerous protocols reported in the literature, the formation of tertiary esters remains a persistent challenge. Specialized reagents and procedures are typically employed to obtain these sterically hindered esters from the carboxylic acid precursor.[3] Installing the carboxylic ester directly from an aromatic halide via transition-metal-catalyzed carbonylation in the presence of an alcohol represents a diverse and well-known strategy. Despite the fact that Pd-catalyzed carbonylative reactions are among the most studied, only a limited amount of work has been published regarding the formation of tertiary esters.[4] The obvious drawback in such reactions is the high steric bulk of the incoming alcohol impeding its coordination to the metal center. However, the high utility of tertiary esters, especially as protecting groups for the free carboxylic acid, calls for the continuous development toward their synthesis.

**Scheme 1.** Ex Situ Generation of CO for the Synthesis of Tertiary Esters
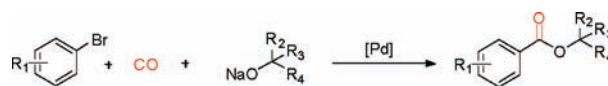


In this paper, we report on our findings in the palladium-catalyzed alkoxycarbonylation of aryl bromides using

(1) (a) Furniss, B. S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, A. R. *Vogel's Textbook of Practical Organic Chemistry*, 5th ed.; Wiley: New York, U.S., 1989; pp 1266–1269. (b) Larock, R. C. *Comprehensive Organic Transformations*, 2nd ed.; VCH: New York, U.S., 1989; pp 881–958.

(2) (a) Carmo, A. C.; Souza de, L. K. C.; Costa de, C. E. F.; Longo, E.; Zamian, J. R.; Rocha Filha da, G. N. *Fuel* **2009**, *88*, 461. (b) Nishikubo, T.; Kameyama, A.; Yamada, Y.; Yoshida, Y. *J. Polym. Sci., Part A: Polym. Chem.* **1996**, *34*, 3531. (c) Ansari, H. R.; Curtis, A. J. *J. Soc. Cosmet. Chem.* **1974**, *25*, 203.

(3) (a) Grasa, G. A.; Singh, R.; Nolan, S. P. *Synthesis* **2004**, 971. (b) Singh, R.; Kissling, R. M.; Letellier, M.-A.; Nolan, S. P. *J. Org. Chem.* **2004**, *69*, 209. (c) Tararov, V. I.; Korostylev, A.; König, G.; Börner, A. *Synth. Commun.* **2006**, *36*, 187. (d) Falck, J. R.; Sangrasa, B.; Capdevila, J. H. *Bioorg. Med. Chem.* **2007**, *15*, 1062. (e) Alizadeh, M. H.; Kermani, T.; Tayebee, R. *Monatsh. Chem.* **2007**, *138*, 165. (f) Salavati-Niasari, M.; Khosousi, T.; Hydarzadeh, S. *J. Mol. Catal. A: Chem.* **2005**, *235*, 150. (g) Liang, C. O.; Helms, B.; Hawker, C. J.; Fréchet, J. M. J. *Chem. Commun.* **2003**, 2524. (h) Mukaiyama, T.; Shintou, T.; Fukumoto, K. *J. Am. Chem. Soc.* **2003**, *125*, 10538.
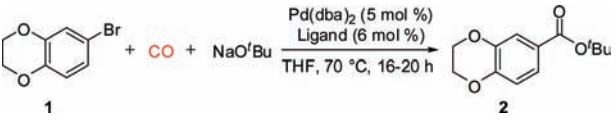
(4) (a) Kormos, C. M.; Leadbeater, N. E. *Org. Biomol. Chem.* **2007**, *5*, 65. (b) Yamamoto, Y. *Adv. Synth. Catal.* **2010**, *352*, 478.

(5) Hermange, P.; Lindhardt, A. T.; Taaning, R. H.; Bjerglund, K.; Lupp, D.; Skrydstrup, T. *J. Am. Chem. Soc.* **2011**, *133*, 6061. 9-Methyl-fluorene-9-carbonyl chloride and two-chamber glassware are commercially available; see Supporting Information.

tertiary alcohols as nucleophiles (Scheme 1). The ability to generate tertiary esters directly from aromatic bromides and an alcohol in the presence of a base would provide a simple access to this class of compounds.

We initiated a catalyst screening for the carbonylation of 6-bromo-1,4-benzodioxane (**1**) with sodium *tert*-butoxide using a slight excess (1.5 equiv) of carbon monoxide (CO). As the source of CO, the two-chamber technique recently developed in our laboratories was applied employing a carbon monoxide precursor (see Supporting Information

**Table 1.** Optimization of the Alkoxycarbonylation Reaction of Aryl Bromide **1** with Sodium *tert*-Butoxide[a]

| entry | ligands | yield [%][b] |
| --- | --- | --- |
| 1 | BINAP | 87 |
| 2 | Xantphos | 78 |
| 3 | DPPF | 87 |
| 4 | PPF-$^t$Bu | 88 |
| 5 | D$^i$PrPF | 90 |
| 6 | D$^t$BuPF | 0[c] |
| 7[d] | D$^i$PrPF | 77 |
| 8[e] | D$^i$PrPF | 89 |
| 9[e,f] | D$^i$PrPF | 87 |
| 10[e,g] | D$^i$PrPF | 88 |

[a] Chamber A: 9-Methyl-fluorene-9-carbonyl chloride (0.45 mmol), Pd(dba)$_2$ (5 mol %), HBF$_4$P($^t$Bu)$_3$ (5 mol %), DIPEA (1.5 equiv) in THF (2 mL). Chamber B: 6-Bromo-1,4-benzodioxane **1** (0.3 mmol), Pd(dba)$_2$ (5 mol %), L (6 mol %) in THF (2 mL). [b] Isolated yield after column chromatography. [c] Determined by $^1$H NMR analysis. [d] CO (0.33 mmol) [e] Pd(dba)$_2$ (1 mol %), HBF$_4$P($^t$Bu)$_3$ (1 mol %). [f] DIPEA (1.2 equiv). [g] CO (0.75 mmol), **1** (0.5 mmol). PPF-$^t$Bu: (*R*)-1-[(*S*$_P$)-2-(Diphenyl-phosphino)ferrocenyl]ethyldi-*tert*-butylphosphine. D$^i$PrPF: 1,1′-Bis-(diisopropylphosphino)ferrocene.

PPF-$^t$Bu          Xantphos          D$^i$PrPF
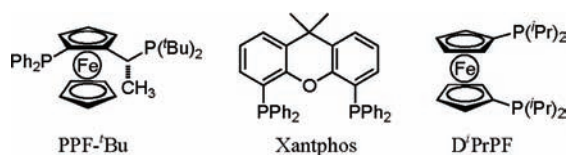
for further details).[5−7] Initial screenings revealed that bidentate ligands were superior in comparison to their monodentate counterparts such as PPh$_3$, PCy$_3$, and cat-aCXium A (results not shown).[8] All but one of the tested bidentate ligands led to desired product **2** in high isolated yields except D$^t$BuPF (entry 6) which, surprisingly resulted in no conversion at all (Table 1, entries 1−5 and 6).

From Table 1, PPF-$^t$Bu and D$^i$PrPF were selected to test the reaction of sodium *tert*-butoxide with 4-bromobenzonitrile to ensure that the developed method could be applied to both electron-rich and -poor aromatic systems. Whereas PPF-$^t$Bu afforded a 70% conversion of 4-bromobenzonitrile, D$^i$PrPF provided a more useful 90% conversion with a 76% isolated yield of 4-cyanobenzoic acid *tert*-butyl ester. D$^i$PrPF was chosen for further optimization, and next the amount of CO required was investigated. Decreasing the loading of CO to 1.1 equiv led to a drop in the yield (entry 7).[9] Lowering the catalytic loading in the CO-releasing chamber A to 1 mol % of both Pd(dba)$_2$ and HBF$_4$P($^t$Bu)$_3$ did not affect the isolated yield of **2** (entries 8−10). Increasing the concentration of reactants had no effect on the reaction outcome (entry 10). Changing the solvents to dioxane or toluene led to a decrease in isolated yield. Finally, applying potassium *tert*-butoxide as the nucleophile only afforded trace amounts of the desired alkoxycarbonylated coupling product.

Having established the optimum reaction conditions, the scope of the palladium-catalyzed alkoxycarbonylation of functionalized aryl bromides with sodium *tert*-butoxide was explored (Table 2). Simple substituted aryl bromides all provided the desired products in yields attaining 90% (entries 2−6) except bromobenzene, which only afforded a 60% isolated yield (entry 1). This lower yield was assigned to the product's relatively low boiling point.[10] Both electron-rich and -poor systems proved reactive toward the catalytic system, and the desired *tert*-butyl ester derivatives were obtained in yields ranging from 44% to 86% (entries 7−13).[11] Next, a handful of heteroaromatic bromides was tested, which satisfyingly afforded the desired products in good yields (entries 14−18). In the case of 4-bromoisoquinoline and 5-bromoisoquinoline, debromination was also observed in the crude reaction mixture leading to an overall decrease in isolated yield (entries 16 and 17).[12] Furthermore, *ortho*-substituents impeded the alkoxycarbonylation reaction, leading to trace amounts of the desired products (results not shown).

Attention was next turned to test the application of other sodium tertiary alkoxides as nucleophlies. Suspecting that several of the isolated esters in Table 2 were volatile, it was expected that an increase in overall molecular weight would be accompanied by an increase in isolated yield. Toward this end, the sodium salt of 1-adamantol was chosen, resembling the bulk of sodium *tert*-butoxide (Table 3). Not only did the catalytic system prove to be adaptable to other bulky alkoxides, but higher yields were obtained in all reactions except with 4-trifluoromethyl bromobenzene

(6) Hermange, P.; Gøgsig, T. M.; Lindhardt, A. T.; Taaning, R. H.; Skrydstrup, T. *Org. Lett.* **2011**, *13*, 2444.

(7) Nielsen, D. U.; Taaning, R. H; Lindhardt, A. T.; Gøgsig, T. M.; Skrydstrup, T. *Org. Lett.* **2011**, *13*, 4456.

(8) Mägerlein, W.; Indolese, A. F.; Beller, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 2856. cataXCium A: Di(1-adamantyl)-*n*-butylphosphine.

(9) Decreasing the catalytic loading in the CO-releasing chamber of Pd(dba)$_2$ and HBF$_4$P(*t*Bu)$_3$ to 1 mol % did not influence the yield (entries 8 and 9).

(10) The boiling point of **3** is 54 °C (1Torr). See: Kazuo, N.; Keiko, O.; Asami, Y.; Keiichi, I. *Chem. Lett.* **1994**, *2*, 209.

(11) The boiling point of **13** is 60 °C (1 Torr). See: Amin, H. B.; Taylor, R. *J. Chem. Soc., Perkin Trans. 2: Phys. Org. Chem. (1972−1999)* **1975**, 1802.

(12) **18** was obtained along with approximately 30% of the debro-minated isoquinoline according to crude $^1$H NMR analysis. **19** and its debrominated isoquinoline were obtained as an inseparable mixture (see Supporting Information).

**Table 2.** Alkoxycarbonylation Reaction of Aryl Bromides with Sodium *tert*-Butoxide[a]

$$ArBr + CO + NaO^tBu \xrightarrow[\text{THF, 70 °C, 16-20 h}]{\substack{Pd(dba)_2\ (5\ mol\ \%)\\ D^iPrPF\ (6\ mol\ \%)}} \underset{Ar}{\overset{O}{\diagdown}}O^tBu$$

| entry | ArBr | product | | yield[%][b] |
|---|---|---|---|---|
| 1 | | | 3 | 60 |
| 2 | | | 4 | 90 |
| 3 | | | 5 | 88 |
| 4 | | | 6 | 73 |
| 5 | | | 7 | 86 |
| 6 | | | 8 | 78 |
| 7 | | | 9 | 77[c,d] |
| 8 | | | 10 | 86 |
| 9 | | | 11 | 76[c,d] |
| 10 | | | 12 | 64 |
| 11 | | | 13 | 44 |
| 12 | | | 14 | 67 |
| 13 | | | 15 | 67 |
| 14 | | | 16 | 62 |
| 15 | | | 17 | 68 |
| 16 | | | 18 | 56 |
| 17 | | | 19 | 77 |
| 18 | | | 20 | 50 |

[a] Chamber A: 9-methyl-fluorene-9-carbonyl chloride (0.75 mmol), Pd(dba)$_2$ (1 mol %), HBF$_4$P($^t$Bu)$_3$ (1 mol %), DIPEA (1.2 equiv) in THF (2 mL). Chamber B: Aryl bromide (0.5 mmol), Pd(dba)$_2$ (5 mol %), D$^i$PrPF (6 mol %), NaO$^t$Bu (1.2 equiv) in THF (2 mL). [b] Isolated yield after column chromatography. [c] Calculated yield by $^1$H NMR analysis. [d] Obtained as an inseparable mixture of starting material and product.

**Table 3.** Alkoxycarbonylation Reaction of Aryl Bromides with Other Sodium *tert*-Alkoxides[a]

$$ArBr + CO + RONa \xrightarrow[\text{THF, 70 °C, 16-20 h}]{\substack{Pd(dba)_2\ (5\ mol\ \%)\\ D^iPrPF\ (6\ mol\ \%)}} \underset{Ar}{\overset{O}{\diagdown}}OR$$

| entry | ArBr | RONa | | yield[%][b] |
|---|---|---|---|---|
| 1 | | | 21 | 89 |
| 2 | | | 22 | 76 |
| 3 | | | 23 | 86 |
| 4 | | | 24 | 63 |
| 5 | | | 25 | 78 |
| 6 | | | 26 | 67 |
| 7 | | | 27 | 73 |
| 8 | | | 28 | 77 |
| 9 | | | 29 | 89 |
| 10 | | | 30 | 57 |

[a] Chamber A: 9-Methyl-fluorene-9-carbonyl chloride (0.75 mmol), Pd(dba)$_2$ (1 mol %), HBF$_4$P($t$Bu)$_3$ (1 mol %), DIPEA (1.2 equiv) in THF (2 mL). Chamber B: Aryl bromides (0.5 mmol), Pd(dba)$_2$ (5 mol %), D$^i$PrPF (6 mol %), NaOR (1.2 equiv) in THF (2 mL). [b] Isolated yield after column chromatography.

(entries 1−6). Even sodium 9-methyl-9-fluorenoxide proved reactive, affording the desired tertiary esters regardless of the electronic nature of the aryl bromide (7−9). Applying secondary alcohols, such as menthol, led to a significant drop in the product yield, indicating that a high degree of bulk might be mandatory for an efficient reductive elimination.[13]

Finally, the formation of the trityl ester was attempted using the sodium salt of triphenylmethanol. Applying aryl bromides carrying an electron-donating substitutent resulted in a good 57% isolated yield of the desired trityl ester **30** (entry 10). This last result is currently being investigated further in our laboratories since it provides straightforward access to trityl-protected carboxylic acids by an unprecedented method.

In conclusion, a simple and efficient method for the palladium-catalyzed alkoxycarbonylation of aryl bromides with sodium alkoxide forming tertiary esters was developed.

(13) Hartwig, J. F. *Inorg. Chem.* **2007**, *46*, 1936.

Near-stoichiometric loadings of carbon monoxide proved sufficient, and the system displayed good functional group tolerance. Four different bulky sodium alkoxides proved compatible with the catalytic system including sodium triphenyl methoxide, demonstrating an interesting approach for accessing trityl esters. This work is currently under further development in our laboratories and will be reported in due time.

**Supporting Information Available.** Experimental details and copies of $^{1}$H and $^{13}$C NMR spectra for all the coupling products. This material is available free of charge via the Internet at http://pubs.acs.org.