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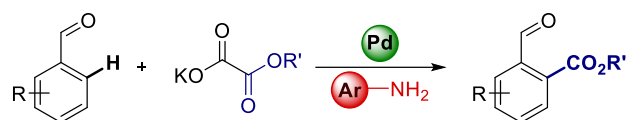
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Palladium-Catalyzed *ortho*-C–H Alkoxy carbonylation of Aromatic Aldehydes *via* a Transient Directing Group Strategy

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Supporting Information Placeholder



- 31 examples
- Aniline for TDG formation
- Up to 93% yield
- Access to phthalides and isoindolinones

ABSTRACT: Transient directing groups (TDGs) can be a powerful strategy to directly functionalized C–H bonds of aldehydes. We report a palladium-catalyzed *ortho*-C–H alkoxy carbonylation of benzaldehydes using catalytic amount of aromatic amine to form a transient imine which plays the role of monodentate TDG. The reaction conditions were applied to a broad range of aldehydes and corresponding 2-formyl benzoates were used as direct precursors for the synthesis of phthalides and 1-isoindolinones.

3*H*-Isobenzofuran-1-one or phthalide and 1-isoindolinone are ubiquitous scaffolds found in plenty of natural products and bioactive compounds (Figure 1).¹ Among them, (*S*)-cytosporene E and herbaric acid are known for their antibacterial activities,^{2,3} (+)-spiroloxine has shown helicobactericidal properties,⁴ cryphonetic acid inhibits the formation of tomato seedlings,⁵ alcyopterosin E exhibits cytotoxic activities and (*S*)-PD172938 is known as a dopamine D₄ ligand.^{6,7}

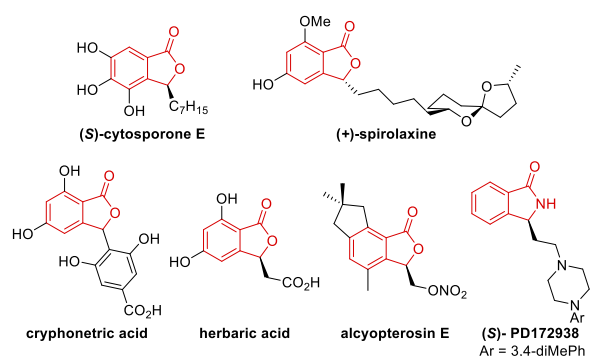


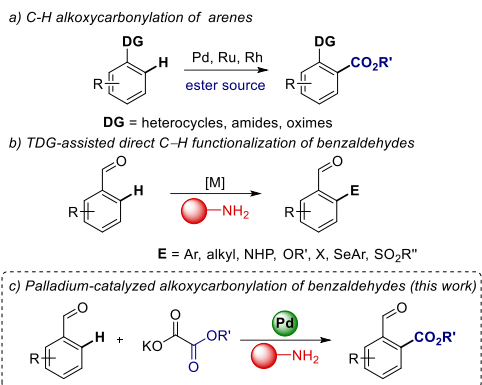
Figure 1. Natural products and bioactive compounds bearing a phthalide or isoindolinone moiety

Due to this wide range of biological properties, phthalide and isoindolinone natural products have attracted the attention of many research groups over the years and a lot of methodologies and syntheses have been reported.⁸ Among these syntheses, 2-formyl benzoates could be seen as key intermediates. Indeed, the addition of a nucleophile, in an asymmetric fashion or not, onto a 2-formylbenzoate allows a direct access to variously substituted phthalides or isoindolinone if an amine is added.^{9,10}

Therefore, a fast access to 2-formyl benzoate is of high importance.

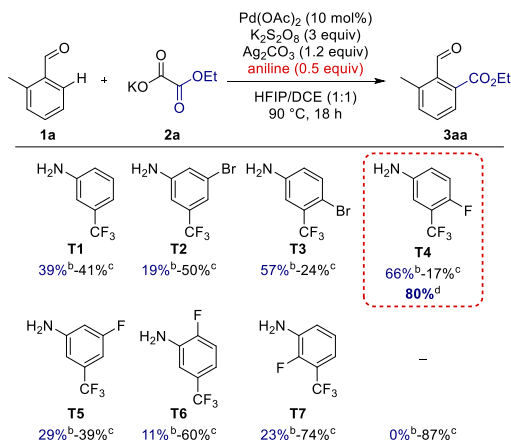
In this context, the development of an *ortho*-C–H alkoxy carbonylation of aromatic aldehydes is of considerable interest. For the last two decades, a lot of progress have been made on the functionalization of C–H bonds,¹¹ and some direct alkoxy carbonylation reactions of arenes based on palladium, ruthenium or rhodium catalysis have been reported (Scheme 1.a).¹² Different ester group providers, but often toxic such as diethyl azodicarboxylate, have been employed. Concerning directing groups, only N-heterocycles, amides and oximes have been successfully used. Regarding aromatic aldehydes, the *ortho*-C–H alkoxy carbonylation has never been described, but recently a strategy based on transient directing group (TDG) has emerged.¹³ Since pioneering works reported by Yu's group,¹⁴ several *ortho*-C–H functionalizations of benzaldehydes have been described using a catalytic amount of amine to *in situ* generate an imine directing group (Scheme 1.b).¹⁵ Thanks to this strategy, aryls, alkyls and different heteroatoms could be directly introduced onto aldehydes. Following our efforts on developing new C–H activation reactions,¹⁶ we were keen to develop a palladium-catalyzed *ortho*-C–H alkoxy carbonylation of benzaldehydes using a TDG strategy and potassium oxalate monoester as non-toxic ester provider (Scheme 1.c).^{12g}

Scheme 1. Metal-catalyzed *o*-C–H alkoxy carbonylation and *o*-C–H functionalization of benzaldehydes *via* a TDG strategy



At the onset of our investigation, we focused our attention on the alkoxycarbonylation of 2-methylbenzaldehyde **1a** and finding the suitable TDG for our transformation. Preliminary experiments showed us that 3-(trifluoromethyl)anilines could be suitable amines to form monodentate TDG with palladium diacetate (Pd(OAc)₂) as catalyst. Therefore, a series of 3-(trifluoromethyl)anilines were screened using Pd(OAc)₂ as catalyst, potassium oxalate monoethylester **2a** as ester provider, potassium persulfate as oxidant and silver carbonate to promote decarboxylation of potassium oxalate, and the best result (66% NMR yield) was observed using 4-fluoro-3-(trifluoromethyl)aniline **T4** (Scheme 2). Interestingly, when no amine was added, no desired product **3aa** was detected. Further optimizations were carried out (see the Supporting information for the details), and 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) was identified as a key solvent for the transformation.¹⁷ Finally, **3aa** was obtained in 80% NMR yield using a mixture DCE/HFIP (1:3) as solvent at 90 °C for 18 h.

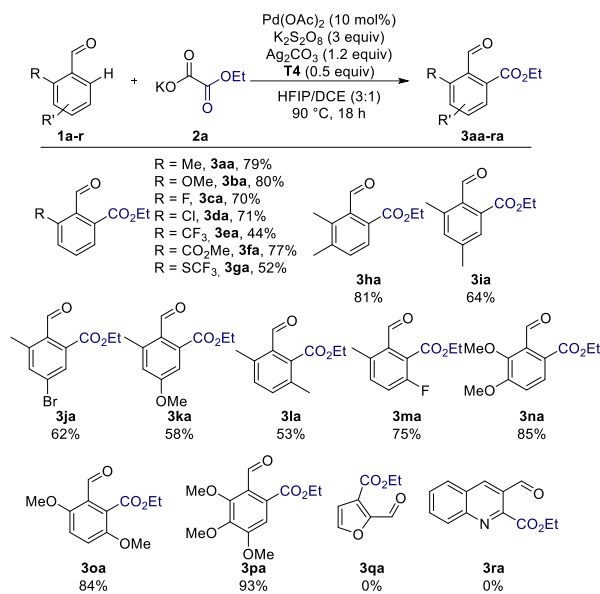
Scheme 2. Selected TDG screening for *o*-C-H alkoxycarbonylation of benzaldehydes^a



Having the optimized conditions in hand, we first evaluated the scope of the reaction regarding *ortho*-substituted benzaldehydes (Scheme 3). In line with the previously observed NMR yield, *ortho*-methylated ethoxycarbonylated product **3aa** was isolated in 79% yield. Several *ortho*-substituted aldehydes having both electron-donating and electron-withdrawing groups

were tested in our conditions and corresponding ethoxycarbonylated compounds **3ba-3ga** were obtained in moderate to good yields (44-80%). The reaction conditions were compatible with methoxy group, fluorine and chlorine atoms and strongly electron-withdrawing groups such as trifluoromethyl or ester. Then, many poly-substituted benzaldehydes were engaged in the reaction to furnished desired products **3ha-3pa** in good to very good yields (53-93%). Interestingly, the reaction was successfully conducted on *para*-bromo-substituted benzaldehyde **1j** which opens the door to further functionalizations. Unfortunately, when the reaction conditions were tested on heterocyclic aldehydes **1q** and **1r**, no expected esters could be observed.

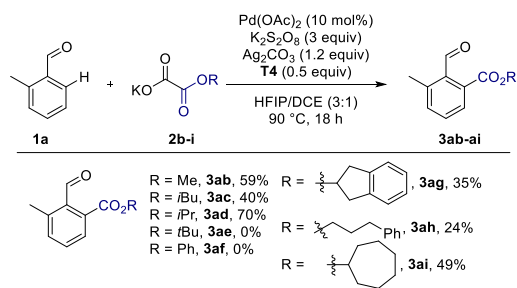
Scheme 3. Scope of the C-H alkoxycarbonylation of *ortho*-substituted benzaldehydes^{a,b}



Then, we turned our attention to the scope of ester group. Several potassium oxalate monoesters were easily synthesized from oxalyl chloride and tested in our reaction (Scheme 4). Products bearing a methyl (**3ab**), *iso*-butyl (**3ac**) and *iso*-propyl (**3ad**) ester group were obtained in good yields (40-70%). Unfortunately, when bulkier potassium oxalate *tert*-butyl-ester **2e** or aromatic phenyl-ester **2f** were engaged, no desired product was observed. Finally, more complex ester groups **3ag-3ai** were successfully introduced in moderate yields (24-49%).

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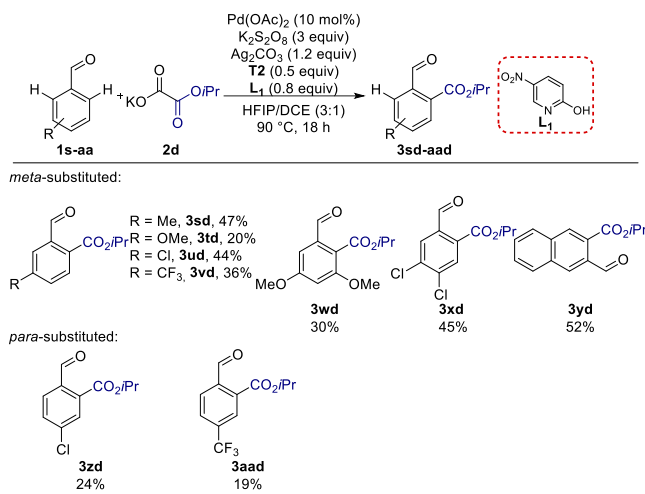
Scheme 4. Scope of potassium oxalate^{a,b}



^aReactions were carried out using **1a** (0.6 mmol, 1 equiv), **2** (2 equiv), Pd(OAc)₂ (0.1 equiv), K₂S₂O₈ (3 equiv), Ag₂CO₃ (1.2 equiv), **T4** (0.5 equiv) in HFIP/DCE (3:1, C = 0.2 M) at 90 °C for 18 h. ^bIsolated yields were reported.

Next, we tried the optimized conditions on 3-methylbenzaldehyde **1s** but a significant amount of difunctionalized benzaldehyde was observed as well as some unreacted starting material. To suppress difunctionalization, a new optimization was conducted (see the Supporting information), and new aniline **T2** was selected in combination with potassium oxalate *iso*-propylester **2d** as ester provider. Moreover, the addition of 2-hydroxy-5-nitropyridine **L1** as palladium ligand was beneficial for the reactivity. Indeed, electron-deficient 2-pyridones are known to displace OAc as ligand and accelerate the C–H activation step.¹⁸ With these newly optimized conditions in hand, the scope of *meta*- and *para*-substituted benzaldehydes was evaluated (Scheme 5). This time difunctionalization was suppressed and several *meta*-substituted *iso*-propoxycarbonylated benzaldehydes were isolated in moderate yields (20–47%) due to unreacted starting material. As previously, the reaction conditions were compatible with electron-donating and electron-withdrawing groups. Disubstituted products **3wd** and **3xd** were isolated in 30% and 45% yields respectively and, pleasingly, 3-formyl-2-naphthoate **3yd** was got in 52% yield. Unfortunately, when these conditions were applied to *para*-substituted benzaldehydes **1z–1aa**, only poor yields (19–24%) were observed due to significant amount of unreacted starting material and the appearance of dialkoxycarbonylated product.

Scheme 5. Scope of *meta*- and *para*-substituted benzaldehydes^{a,b}

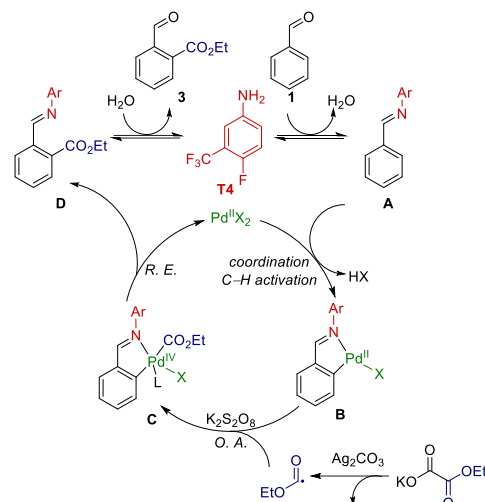


^aReactions were carried out using **1a** (0.6 mmol, 1 equiv), **2** (2 equiv), Pd(OAc)₂ (0.1 equiv), K₂S₂O₈ (3 equiv), Ag₂CO₃ (1.2 equiv), **T8** (0.5 equiv), **L1** (0.8 equiv) in HFIP/DCE (3:1, C = 0.2 M) at 90 °C for 18 h. ^bIsolated yields were reported.

In light of previous work and our experimental results (see the Supporting information),^{12g,15m} a plausible mechanism is proposed in scheme 6. Initially, benzaldehyde **1** condenses with **T4** to generate *in situ* transient imine **A**. Then, the imine group can coordinate to the palladium (II) catalyst to direct the C–H activation and provide palladacycle **B**. According to literature precedents, a palladium monomer-dimer equilibrium could take place at this stage.¹⁹ Next, palladacycle **B** reacts with the ethoxycarbonyl radical, generated from a silver promoted decarboxylation of **2**, in presence of an oxidant to form palladium (IV) complex

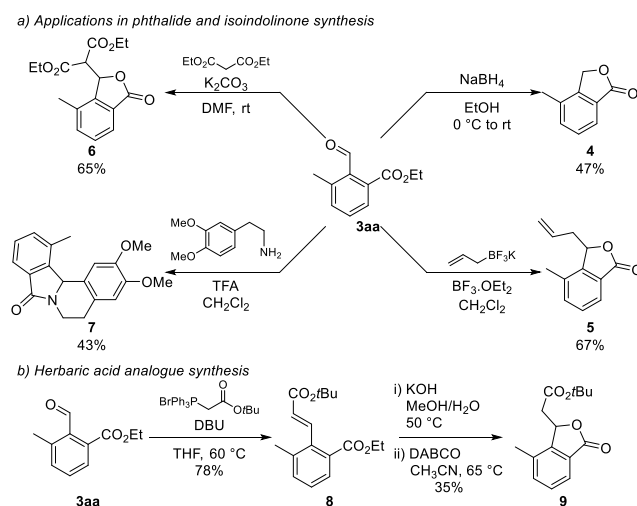
C. Finally, product **3** is obtained after reductive elimination to regenerate palladium (II) catalyst and imine hydrolysis which reform aniline **T4** for another cycle.

Scheme 6. Plausible reaction mechanism



To show the potential interest of our methodology in synthesis, several transformations were achieved on ethyl 2-formylbenzoate **3aa** (Scheme 7.a). First, reduction of aldehyde using sodium borohydride directly delivered phthalide **4**. Then, different nucleophiles were added onto aldehyde **3aa** and phthalides bearing an allyl or a malonate group in position 3 were easily synthesized. To extend synthetic applications, benzaldehyde **3aa** was reacted with 3,4-dimethoxyphenethylamine in presence of trifluoroacetic acid to furnish isoindolo[1,2-*a*]isoquinoline **7**.^{10g} In addition, a racemic synthesis of a herbaric acid analogue was achieved (Scheme 7.b). First, a Wittig reaction with (*tert*-butoxycarbonylmethyl)triphenylphosphonium bromide was conducted to deliver α,β -unsaturated *tert*-butyl ester **8** in 78% yield. Then, after selective hydrolysis of the ethyl ester group, followed by lactone formation through Michael addition, herbaric acid derivative **9** was obtained in 35% overall yield.

Scheme 7. Synthetic applications



In summary, a novel palladium-catalyzed *ortho*-alkoxycarbonylation of aromatic aldehydes was developed based on a TDG strategy. This method allows to extend the scope of C–H

alkoxycarbonylation reactions to aldehyde derivatives which could have a strong impact on natural product synthesis. This protocol tolerates a wide range of functional groups and could be applied to differently substituted benzaldehydes. Other C–H functionalizations of aldehydes using a TDG strategy are currently ongoing in our laboratory.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental details and characterization data for all new compounds, including NRM spectra (PDF)

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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