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A clean, palladium-catalyzed oxidative esterification of aldehydes using benzyl chloride

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ABSTRACT

A highly efficient, mild, simple and clean procedure is presented for the one-pot oxidation of aromatic and aliphatic aldehydes to their corresponding ethyl esters using benzyl chloride as the oxidant under palladium-catalyzed conditions. The reaction is complete in just 30 min under microwave irradiation and inert conditions are not required to obtain good to excellent yields (65–93%) of isolated products.

The ester functional group is not only widely abundant in natural products but is also required in many synthetic strategies. Esters are generally prepared by nucleophilic addition of an alcohol to activated carboxylic acid derivatives such as acid anhydrides and chlorides.[1] The direct conversion of aldehydes into esters is a valuable alternative, and much effort has been devoted to achieve this transformation.[2] Many methods, however, have restrictive requirements such as the use of stoichiometric transition metal oxidants[3] or the employment of co-oxidants in large excess,[4] and therefore greener methods have been sought and recently reported.[5]

Here we report a simple and effective catalytic procedure to oxidize aldehydes directly to the corresponding ethyl ester under low palladium loading, and using benzyl chloride in only slight excess generating toluene as the only by-product. The procedure is suitable for both electron-deficient and electron-rich aromatic aldehydes as well as aliphatic aldehydes, making it a practical alternative to the already described procedures.

Oxidative esterifications of aldehydes using transition metal catalysis in general,[4,5a,6] and palladium[7] in particular, are not new. Undoubtedly, the most environmentally friendly are those using molecular oxygen as the oxidizing agent.[6b,7a] However, this option could be problematic in cases where high oxygen pressures are required in reactions running in flammable organic solvents, and also for substrates containing oxygen-sensitive functionalities. Examples of oxidation reactions using halogen-based reagents as oxidants are less reported. Muzart[8] obtained mixtures of aldehydes, acids and chloroethyl esters when oxidizing primary alcohols using palladium chloride in refluxing 1,2-dichloroethane, and similarly using carbon tetrachloride as both solvent and co-oxidant, Tsuji[9] obtained mainly esters from the oxidation of alcohols. However, to the best of our knowledge, benzyl halides have not been previously used in the oxidative esterification of aldehydes. Instead, palladium-catalyzed transformations involving aryl halides are more frequently reported than the analogous reactions with benzylic derivatives[10] and examples of palladium-catalyzed oxidations of primary alcohols using halobenzenes have been described.[11] A procedure that takes advantage of a related hydrodehalogenation is that of Asensio[12] where an α-bromo sulfoxide is used to oxidize alcohols. However, this method is not compatible with benzylic alcohols containing electron-withdrawing groups and requires handling bromine in the synthesis of bromomethyl phenyl sulfoxide. Moreover, after the oxidation reaction, the sulfoxide by-product must be separated from the crude reaction mixture. Our method, on the other hand, relies on readily available reagents and a facile separation of the reduced by-product by simple evaporation of the crude reaction mixture.

During a dendrimer synthesis we required the cleavage of an aryl allyl ether and subsequent benzylation without isolation of the intermediate phenolic compound.[13] However, in an attempt to do a tandem deallylation–Williamson-type etherification,[14] 4-allyloxybenzaldehyde (**1**) was converted into a mixture of the transetherified compound **2** and the product derived from an oxidative esterification **3** (ratio 1:1) (Scheme 1).

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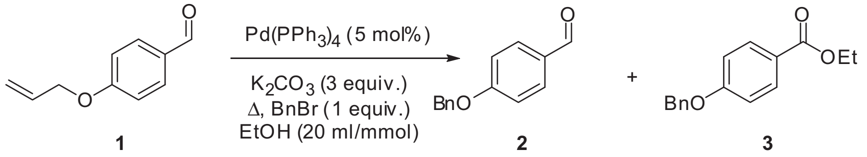


Scheme 1. Attempted tandem deallylation–Williamson-type etherification of 4-allyloxybenzaldehyde.

Intrigued by this outcome, we chose 4-nitrobenzaldehyde as a model substrate in order to establish the conditions required to efficiently oxidize the aldehyde to the ester. An electron-poor aromatic aldehyde was chosen as substrate since these were reported to be more reactive towards a palladium-catalyzed oxidative esterification when a more complex oxidant was used.[7c]

Under the initial reaction conditions, [Pd(PPh$_3$)$_4$ (5 mol %), K$_2$CO$_3$ (3 equiv), benzyl bromide (1 equiv) in refluxing ethanol] 4-nitrobenzaldehyde were fully converted into a mixture of ester **5a** and benzyl alcohol **6a** (Table 1, entry 1). This result resembled a Cannizzaro-type reaction which involves the redox conversion of aldehydes into their respective alcohols and carboxylic acids or esters in the presence of a strong base.[15] However, the observation that in our reaction the ester was produced in a yield above 50% suggested that another type of mechanism was involved.

We then performed two control experiments to prove unequivocally the role of the reagents/catalysts in the reaction mechanism. First, we examined the uncatalyzed reaction in which case the starting material was recovered quantitatively (entry 2). Exclusion of benzyl bromide from the reaction medium resulted in decomposition of the aldehyde (entry 3). Because of Pd(OAc)$_2$, a Pd(II) catalyst, can act as Lewis acid and catalyses the nucleophilic attack of alcohols to aldehydes,[16] we speculated that oxidative addition of Pd(0) to benzyl bromide to generate a Lewis acid Pd(II) salt occurs. With this in mind, other halides that would allow facile insertion of Pd(0) into the C–X bond were screened (entries 4–7), but all failed to improve the results.

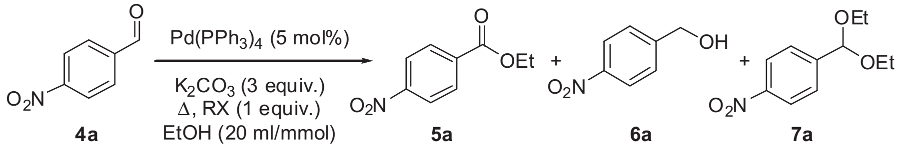
Addition of triphenylcarbenium tetrafluoroborate as a hydrogen acceptor (entry 8), added in order to decrease the amount of reduced benzyl alcohol, successfully suppressed its formation but altered the course of the reaction and acetal **7a** was obtained as the major product.[17] That this acetal was not an intermediate of our reaction was supported by the observation that an attempt to obtain the ester from the acetal under the initial reaction conditions failed. The ratio of the ester to benzyl alcohol could be increased by reducing the volume of ethanol[6d] (entry 9) and the reaction time could be reduced to 30 min by applying microwave irradiation (entry 10). Benzyl alcohol formation was totally suppressed when the volume of ethanol was further reduced to 5 equiv, although in this case acetal formation was predominant (entry 11).[18]

With optimized reaction conditions available, we proceeded to examine the scope of the Pd-catalyzed oxidative esterification of different aldehydes. These conditions led to total (Table 1, entry 10) or almost total conversion of only electron-poor aromatic aldehydes[19] and saturated aldehydes.[20] The conversion of electron-rich aromatic aldehydes was significantly lower,[21] possibly due to a lowering of the reactivity of the carbonyl group due to resonance effects of the electron-donating substituents. Notably, however, their lower reactivity also precluded their reduction and the corresponding benzyl alcohols were not generated.

We next examined conditions to improve the conversion of electron-rich aromatic aldehydes and chose 4-methoxybenzaldehyde (**4b**) for this purpose.

Doubling the reaction time (Table 2, entry 1) did not improve significantly either the conversion or yield. Changing the base to sodium carbonate, cesium carbonate or triethylamine (entries 2–4) resulted in no reaction and neither did the addition of sodium iodide (entry 5) as a solid additive.[22] Changing the oxidant to benzyl iodide (entry 6) or 4-methoxybenzyl bromide (entry 7) left the

Table 1
Optimization of the oxidative esterification of 4-nitrobenzaldehyde[a]



Entry	RX	Conv.[b] (%)	Yield[b] (%) **5a**/**6a**/**7a**
1	BnBr	100	75/23/0
2[c]	BnBr	0	—
3	—	100	0/0/0
4	EtBr	100	40/7/0
5	AllBr	100	21/6/0
6	PhBr	100	32/0/0
7	4-MeOPhI	84	12/0/0
8[d]	BnBr	100	10/0/90
9[e]	BnBr	100	82/18/0
10[e,f]	BnBr	100	87/10/0 (70/10/0)
11[f,g]	BnBr	80	6/0/60

[a] Aldehyde (1 equiv), RX (1 equiv), K$_2$CO$_3$ (3 equiv), Pd(PPh$_3$)$_4$ (5 mol %), EtOH (20 mL/mmol), 78 °C, 5 h.
[b] Conv. = conversion; conversions and yields were determined by NMR spectroscopy using an internal standard. Yield of isolated product shown in parentheses.
[c] Reaction carried out without Pd catalyst.
[d] Ph$_3$C$^+$BF$_4^-$ (0.5 equiv) was added to the reaction mixture.
[e] Two milliliters of EtOH was used per mmol of aldehyde.
[f] Reaction conducted under microwave irradiation for 30 min at 90 °C.
[g] Five equivalents of EtOH were used.

Table 2
Optimization of the oxidative esterification of 4-methoxybenzaldehyde[a] (**4b**)

Entry	RX	Base	Conv.[b] (%)	Yield[b] (**5b**) (%)
1[c]	BnBr	K_2CO_3	62	57
2	BnBr	Cs_2CO_3	0	—
3	BnBr	Na_2CO_3	0	—
4	BnBr	Et_3N	0	—
5[d]	BnBr	K_2CO_3	0	—
6	BnI	K_2CO_3	0	—
7	4-MeOBnBr	K_2CO_3	0	—
8	4-O_2NBnBr	K_2CO_3	50	48
9	BnCl	K_2CO_3	64	64
10[e]	BnCl	K_2CO_3	100	100 (88)
11[e]	BnBr	K_2CO_3	85	85

[a] Aldehyde (1 equiv), RX (1 equiv), K_2CO_3 (3 equiv), $Pd(PPh_3)_4$ (5 mol %), EtOH (2 mL/mmol), MW, 90 °C, 30 min.

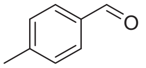
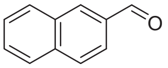
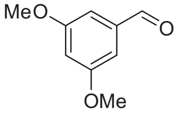
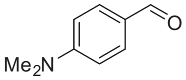
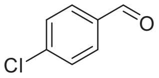
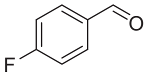
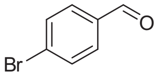
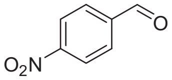
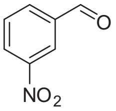
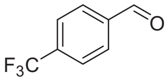
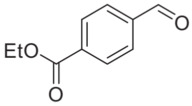
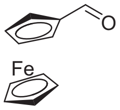
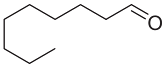
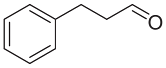
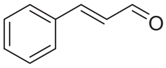
[b] Conv. = conversion; conversions and yields were determined by NMR spectroscopy using an internal standard. Yield of isolated product shown in parentheses.

[c] Reaction time was 60 min.

[d] NaI (1 equiv) was added to the reaction.

[e] Two equivalents of RX were used.

Table 3
Substrate scope in the palladium-catalyzed oxidative esterification with benzyl chloride[a]

Entry	Aldehyde	Product	Yield[b] (%) **5**/**6**
1		**5c**	77/0 (70/0)
2		**5d**	100/0 (93/0)
3		**5e**	100/0 (93/0)
4[c]		**5f**	70/0 (70/0)
5		**5g**	96/0 (81/0)
6		**5h**	100/0 (79/0)
7[d]		**5i**	0/0
8		**5a**	76/22 (65/18)
9		**5j**	80/20 (67/17)
10		**5k**	85/15 (79/15)
11		**5l**	82/18 (82/18)
12		**5m**	95/0 (93/0)
13		**5n**	100/0 (78/0)
14		**5o**	100/0 (80/0)
15[e]		**5p**	75/0

[a] Aldehyde (1 equiv), BnCl (1.2 equiv), K_2CO_3 (3 equiv), $Pd(PPh_3)_4$ (1 mol %), EtOH (2 mL/mmol), MW, 90 °C, 30 min.

[b] Yield determined by NMR spectroscopy using an internal standard. The yields in parentheses are the isolated yields.

[c] Starting material was recovered (27%).

[d] A mixture of ethyl benzoate (65%) and benzaldehyde (8%) was obtained (yields by NMR spectroscopy).

[e] Ethyl 3-phenylpropanoate was also formed in 25% yield.

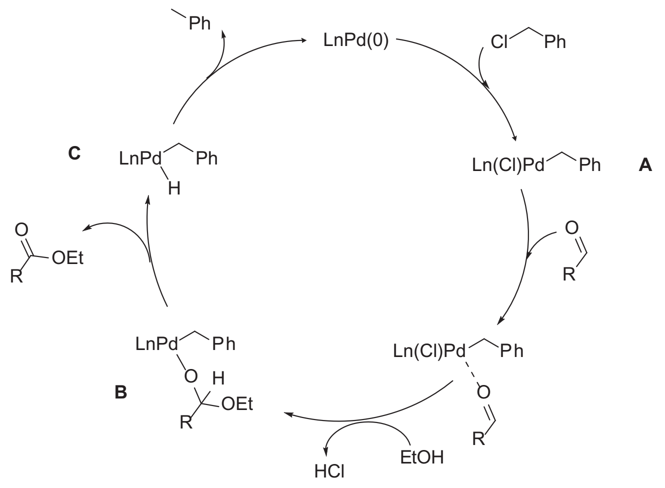
aldehyde unreacted and solvolysis of the benzyl halides occurred.[23] 4-Nitrobenzyl bromide (entry 8) and benzyl chloride (entry 9) gave similar results to benzyl bromide, but the competing solvolysis reaction did take place and finally, doubling the equivalents of benzyl chloride (entry 10) led to full conversion to ethyl 4-methoxybenzoate (**5b**) and toluene.[24] Using 2 equiv of benzyl bromide also increased the yield of the product but conversion was still not quantitative (entry 11) and ethoxymethylbenzene was obtained as a side-product[23] thereby complicating the purification and making the chloride analogue a better choice as co-oxidant.

Having found conditions that converted fully 4-methoxybenzaldehyde into its ethyl ester, we then successfully lowered the amount of catalyst from 5 to 1 mol %,[25] replaced absolute ethanol with 95% commercial ethanol, and with the new lower catalyst loading the equivalents of benzyl chloride could be reduced to 1.2 without any appreciable loss in yield. Other halogen-based co-oxidants were also examined but 1,2-dichloroethane[8] and chlorobenzene,[11a] both used in palladium- catalyzed oxidations of alcohols, and phenyl iodide, employed in a tandem addition-oxidation of 2-alkynylbenzaldehydes,[7d] led to recovery of the starting material when utilized under our optimized conditions. We also performed a control experiment in deoxygenated ethanol under argon and the reaction proceeded quantitatively, therefore excluding any involvement of aerial oxygen as co-oxidant in the reaction pathway.

Various aldehydes were subjected to the improved reaction conditions (Table 3). These proved to be effective for electron-rich aromatic aldehydes and gave the corresponding aromatic esters in good to excellent yields (entries 1–6), the least reactive being 4-dimethylaminobenzaldehyde which led to the recovery of starting material in 27% isolated yield (entry 4). Chloro- or fluoro-substituted benzaldehydes were compatible with the reaction conditions (entries 5 and 6) but, as expected,[26] reductive dehalogenation occurred for the bromo substituted derivative (entry 7), and ethyl benzoate was obtained instead.

Notably, 4-nitrobenzaldehyde gave a higher benzyl alcohol to ester ratio (22:78) (entry 8) than when benzyl bromide was used (11:89) (Table 1, entry 10). This trend can be generalized to electron-poor aromatic aldehydes since 3-nitrobenzaldehyde, 4-trifluoromethylbenzaldehyde and ethyl 4-formylbenzoate were also reduced in discernible yields (entries 9–11). This hydride transfer reaction to the deactivated aldehydes occurs possibly due to the slower reactivity of benzyl chloride compared to benzyl bromide which allows for the competing process to take place. Metallocene derivatives such as ferrocenecarboxaldehyde (entry 12) and aliphatic aldehydes (entries 13 and 14) also worked well and the corresponding esters were obtained in good yields. Oxidative esterification of cinnamaldehyde was satisfactory and no competitive Heck reaction took place,[27] but instead, ethyl 3-phenylpropanoate, the product from hydrogenation and oxidative esterification, was formed in 25% yield (entry 15).

A possible mechanism for the oxidative esterification reaction involves initial oxidative addition of the benzyl derivative to the



Scheme 2. Proposed reaction mechanism.

palladium(0) species to generate benzylpalladium complex **A**, which then undergoes coordination to the aldehyde and allows the addition of ethanol onto the carbonyl group to produce the oxypalladium complex **B**. β-Hydride elimination generates the ester and the palladium hydride species **C** which through reductive elimination affords toluene and regenerates the Pd catalyst (Scheme 2).

In summary, we have demonstrated a facile and mild palladium-catalyzed oxidation of aldehydes into esters. Our methodology employs a low loading of palladium and the readily available co-oxidant is fully transformed into toluene, resulting in an easy to work-up and purified reaction. Moreover, this method does not require inert conditions or the use of ligands and works well for aromatic, saturated and unsaturated aldehydes.[28]

Acknowledgment

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18. Acetal formation has been reported as a competing reaction when electron-deficient benzaldehydes were used in a gold-catalyzed oxidative esterification, see Ref. 6a.
19. Ninety two percent conversion for 3-nitrobenzaldehyde [ester (**5j**): benzyl alcohol (**6j**) 89:11] and 71% for 4-trifluoromethylbenzaldehyde [ester (**5k**): benzyl alcohol (**6k**) 96:4].
20. Ninety three percent conversion for both nonanal and 3-phenylpropionaldehyde.
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24. The ^{1}H NMR spectrum of the crude product showed no signal at 4.55 ppm corresponding to BnCl and the appearance of a singlet at 2.33 ppm corresponding to toluene.
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26. (a) Chen, J.; Zhang, Y.; Yang, L.; Zhang, X.; Liu, J.; Li, L.; Zhang, H. *Tetrahedron* **2007**, *63*, 4266–4270; (b) Zask, A.; Helquist, P. *J. Org. Chem.* **1978**, *43*, 1619–1620.
27. Heck reactions have been reported on unsaturated substrates when bromobenzene was used as co-oxidant, see Ref. 11b.
28. *General procedure*: A 10 mL reaction vessel was charged in air with $Pd(PPh_3)_4$ (6 mg, 1 mol %), aldehyde (0.5 mmol), K_2CO_3 (207 mg, 1.5 mmol), benzyl chloride (70 μL, 0.6 mmol) and EtOH (1 mL). The vessel was sealed and submitted to microwave irradiation for 30 min at 90 °C, using an initial power of 30 W. (Microwave reactions were carried out with a CEM Discover 300 W monomode microwave instrument. The closed vessels used were special glass tubes with self-sealing septa that controlled pressure with appropriate sensors on the top (outside the vial). The temperature was monitored through a non-contact infrared sensor centrally located beneath the cavity floor.) The mixture was then allowed to cool to room temperature, filtered over a pad of Celite® and rinsed with EtOH (5 mL). The filtrate was concentrated in vacuo and the product was purified by flash chromatography on silica gel (CH_2Cl_2/hexane).