Synthetic Methods

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Covalently Bound Benzyl Ligand Promotes Selective Palladium-Catalyzed Oxidative Esterification of Aldehydes with Alcohols**

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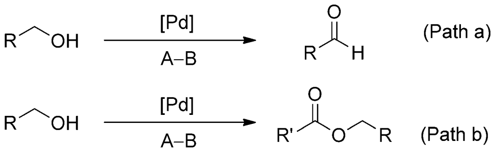
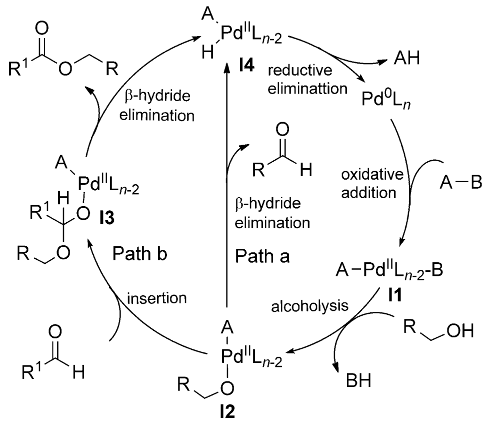
Esterification is a fundamental transformation in chemistry. The essential feature of esterification that particularly distinguishes it from other reactions lies in its broad utilization in industry. Up to now, esterification only largely occurs between carboxylic acid derivatives and alcohols.[1] Aldehydes are also readily available and are bulk scale raw chemicals in industry. Theoretically, esterification of aldehydes with alcohols is an attractive alternative. However, current methods to esterify an aldehyde with an alcohol require oxidation to the acid in advance. As a result, multiple steps are involved with production of toxic irremovable by-products, and is incongruent with the current demand of environmentally benign processes. Therefore, successful efforts during the past ten years have been focused on direct esterification of aldehydes with alcohols in the presence of an oxidant and catalyst.[2] However, challenges still remain. The key issue is the selectivity between esterification (aldehyde oxidation) and alcohol oxidation.

The oxidation of an alcohol to an aldehyde in the presence of palladium catalysts has been a fundamental research area in the chemical synthesis community.[3] In such transformations, the aldehyde is produced and remains unreacted, thus resulting in selective aldehyde formation (Path a, Scheme 1). These facts suggest that in most cases selective palladium-catalyzed oxidation of an alcohol into an aldehyde occurs before esterification of an aldehyde with an alcohol. Therefore, to find the factors that control the selectivity is essential for both selective palladium-catalyzed aldehyde formation and oxidative esterification (Path b, Scheme 1).



Scheme 1. Alcohol oxidation (Path a) and oxidative esterification (Path b).

We assume that the palladium-catalyzed oxidative esterification and alcohol oxidation to an aldehyde proceed through the catalytic cycles shown in Scheme 2. First, the oxidative addition of oxidant A−B to Pd^0 generates the intermediate A-Pd^{II}-B (**I1**). The following alcoholysis step selectively occurs at the Pd−B bond of **I1** with an alcohol to generate the alkoxy palladium intermediate **I2** with the aid of a base. Two pathways are available for intermediate **I2**. Path a describes a direct β-hydride elimination to afford the aldehyde and the palladium hydride intermediate **I4** which undergoes reductive elimination to regenerate Pd^0 species.[3c] This cylcle is the acknowledged pathway for oxidation of an alcohol into an aldehyde. Path b describes an oxidative esterification. Before the β-hydride elimination of **I2**, the aldehyde insertion occurs to result in the hemiacetal palladium intermediate **I3**. The β-hydride elimination of **I3** releases the ester and the palladium hydride intermediate **I4**.



Scheme 2. Proposed catalytic cycles for alcohol oxidation (Path a) and oxidative esterification (Path b).

Upon examination of the catalytic cycles, it becomes clear that a key challenge in developing a highly selective esterification is to control the rate of alcohol oxidation relative to formation of the hemiacetal palladium species (Path a versus Path b). In intermediates **I1**, **I2**, and **I3**, the A−Pd bond is preserved, and A will serve as a covalent ligand. Especially for **I2**, we believe that the structural and electronic

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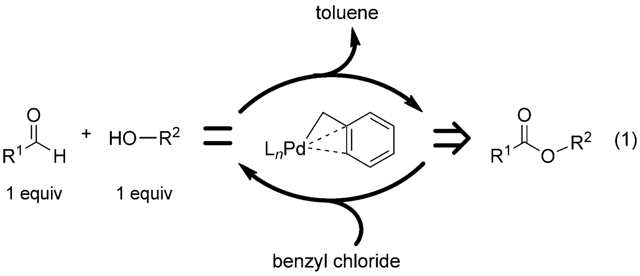
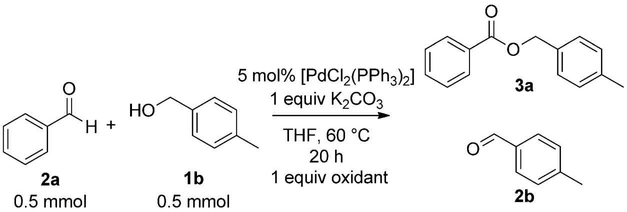
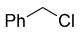
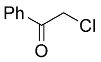
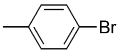
properties of A will strongly affect the selectivity between paths a and b.

N-ligands and P-ligands are normally considered for palladium-catalyzed alcohol oxidation processes. Actually, the oxidative addition of an organohalide (C−X) to Pd^0 generates a complex which contains a covalent C−Pd bond. Alcoholysis first occurs at the Pd−X bond, and the remaining organo group serves as a covalent ligand through a bond to a carbon atom (Scheme 2, A = R).[3c] The effect of this covalently bound carbon ligand in both alcohol oxidation and esterification has never been taken into account. Herein, we describe a novel report on a covalently bound benzyl ligand which promotes palladium-catalyzed oxidative esterification of aldehydes with alcohols in a selective manner [Eq. (1)].



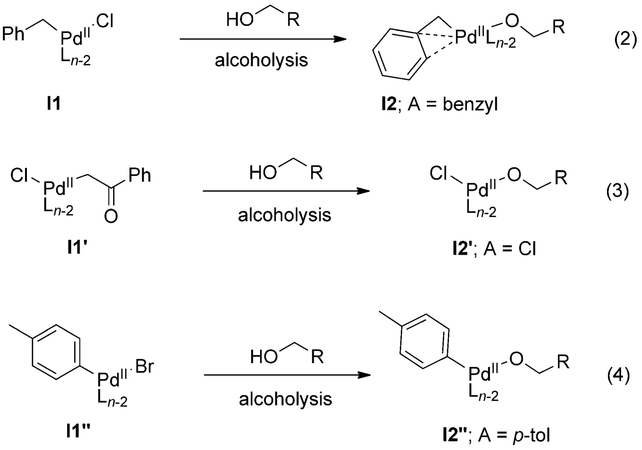
Recently, Beller and co-workers as well as our group simultaneously investigated the palladium-catalyzed oxidative esterification of benzylic alcohols with aliphatic alcohols.[4] Ligands were found to be essential for the success of both transformations. However, little was known about the ligand effect for the achievement of palladium-catalyzed oxidative esterification. Based on the above hypothesis, some organohalides were tested in the oxidative esterification of aldehydes with alcohols to get some information about ligand effects on palladium-catalyzed oxidative esterification (Scheme 3). Interestingly, by using benzyl chloride as the oxidant, benzaldehyde (**2a**) was selectively esterified with p-tolylmethanol (**1b**; with a 1:1 ratio) to afford **3a** in an excellent yield in the presence of 5 mol% $[PdCl_2(PPh_3)_2]$ and 1 equivalent K_2CO_3 in THF at 60 °C. However, when 2-chloroacetophenone was applied as the oxidant, **1b** was selectively converted into its corresponding 4-methylbenzaldehyde (**2b**) in a good yield without any observation of ester **3a**. The starting **2a** remained intact. Similarly, 4-bromotoluene also selectively afforded aldehyde **2b** in 72% with just a trace amount of **3a** observed.[5]



oxidant		Yield [%][a] 3a	Yield [%][a] 2b
	benzyl chloride	93 (96[b])	n.d.
	2-chloroacetophenone	n.d.	69
	4-bromotoluene	trace	72

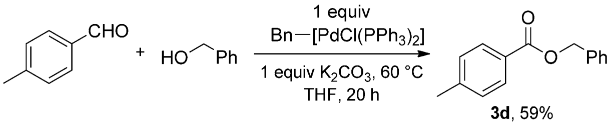
Scheme 3. Three oxidants tested in palladium-catalyzed oxidative esterification. [a] The yield was determined by GC analysis. [b] Yield of isolated product.

It has been shown that the alcoholysis of **I1** selectively occurred at the Pd−Cl bond (A−B = Bn−Cl, Bn = benzyl) [Eq. (2)],[6] whereas it selectively occurred at the Pd–enolate bond of **I1′** (generated from the oxidative addition of 2-chloroacetophenone with Pd^0, A−B = Cl−enolate) in the 2-chloroacetophenone system [Eq. (3)], and at the Pd−Br bond of **I1″** (generated from the oxidative addition of 4-bromotoluene with Pd^0, A−B = p-tol−Br) in the aryl bromide system [Eq. (4)].[7] As a result, the benzyl group is preserved in the selective oxidative esterification system [Eq. (2)] (we further confirmed it by an isotopic labeling experiment; see Scheme S2 in the Supporting Information), whereas the chloride and aryl groups are preserved in the selective alcohol oxidation systems [Eqs. (3) and (4)]. These results show that the benzyl group is the key for the selective esterification of aldehydes with alcohols.

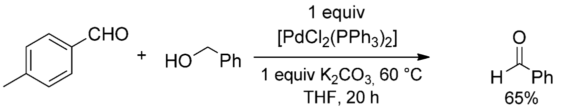


To further confirm the benzyl ligand effect, stoichiometric experiments were carried out by direct utilization of Bn-$[PdCl(PPh_3)_2]$ and $[PdCl_2(PPh_3)_2]$ as the oxidant in this oxidative esterification. In the presence of 1 equivalent of Bn-$[PdCl(PPh_3)_2]$, 4-methylbenzaldehyde and benzyl alcohol were converted into the corresponding ester **3d** in 59% yield without any observation of alcohol oxidation product [Eq. (5)], whereas use of 1 equivalent of $[PdCl_2(PPh_3)_2]$ led only to the conversion of benzyl alcohol into benzaldehyde with a yield of 65%; 4-methylbenzaldehyde was recovered and ester **3d** was not observed [Eq. (6)]. These stoichiometric experiments obviously show that the covalently bound benzyl group can control the selectivity and promote the ester formation.

Here, the covalently bound benzyl group is displayed as a carbon ligand (C−Pd), which can easily form η^3 coordination to palladium [Eq. (2)]. The η^3-coordination



(5)



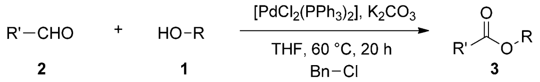
(6)

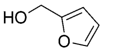
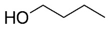
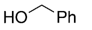
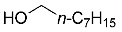
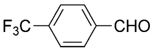
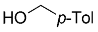
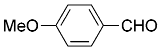
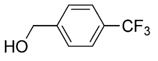
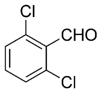
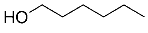
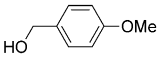
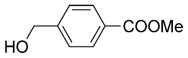
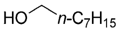
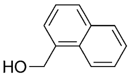
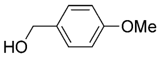
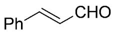
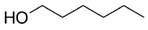
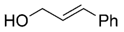
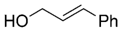
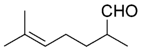
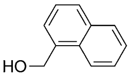
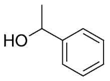
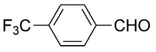
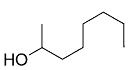
effect on palladium might lead to facile dissociation of PPh_3,[8] and will favor of the coordination of the aldehyde to the palladium center. To prove this η^3-coordination effect, a rigid bidentate ligand, 1,1′-bis(diphenylphosphino)ferrocene) (dppf), was tested in the oxidative esterification of **2a** with **1b**. Low yield (33%) of the ester was obtained with trace amounts of alcohol oxidation were observed (see Scheme S1 in the Supporting Information). This result may be due to the bidentate ligands having stronger binding to palladium and thus preventing the η^3 coordination, which indicates the importance of the phosphine ligand dissociation for the selective esterification.

As the precursor of the covalently bound benzyl ligand, benzyl chloride is a fundamental industrial chemical, which is cheap and easily obtained. The side product of this protocol is toluene which is a widely applied as a solvent and is easy to separate and recover [Eq. (1)]. This makes the oxidative esterification more applicable and practical. The reported oxidants, such as H_2O_2,[2f,g] $PhI(OAc)_2$,[2d] oxone,[2e] MnO_2,[9] TBHP,[2b] and O_2,[2h] for oxidative esterification of aldehydes with alcohols are usually too strong to control the selectivity between esterification and alcohol oxidation, therefore, excess alcohol, especially methanol, is usually applied as solvent to achieve full conversion of aldehydes. In contrast, benzyl chloride is a mild oxidant and allows the oxidative esterification in a 1:1 ratio.

We further tested the substrate scope and the data are listed in Table 1. Various aldehydes and alcohols could be used to give good to excellent product yields (72–100%). Aromatic aldehydes were well tolerated (entries 1–7, and 18). Both strong electron-withdrawing (p-CF_3) and strong electron-donating (p-OMe) groups could be used (entries 5, 6, and 18), and aromatic C−Cl bonds were well tolerated in this transformation (entry 7). Aliphatic aldehydes typically cannot survive strong oxidants, such as H_2O_2, TBHP, but they were oxidatively esterified in excellent yields with various alcohols by using the mild oxidant benzyl chloride (entries 8–12, 14–17). Aldehydes bearing a secondary aliphatic substituent also afforded the esterification product in excellent yields (entries 11, 12, and 15–17). As we know, aliphatic aldehydes easily undergo aldol condensations in the presence of a base, however, no such by-products were detected in these reaction systems. α,β-Unsaturated aldehydes, such as cinnamyl aldehyde, was also successfully employed in this oxidative esterification.[10] It was oxidatively esterified with pentan-1-ol to afford the desired ester in 76% yield (entry 13). In this system, the olefin reduction product of **3n** was observed in the yield of 15%. Aliphatic alcohols all afforded the corresponding esters in excellent yields (entries 2, 4, 7, 10, 13, and 18). In addition, benzylic alcohols are known to be readily oxidized into the corresponding aldehydes, however, both electron-rich and electron-poor benzylic alcohols were suitable for this transformation. No alcohol oxidation products were observed, which demonstrates an excellent selectivity towards esterification (entries 1, 3, 5, 6, 8, 9, 11, 12, and 16). Allylic alcohol was also successfully employed in this oxidative esterification.[10] Cinnamyl alcohol was selectively converted into the corresponding esters with decanal and cyclohexanecarbaldehyde in excellent yields (entries 14 and 15). No olefin reduction products were observed in these cases. It is worth noting that

Table 1: Palladium-catalyzed oxidative esterification of aldehyde with alcohol.[a]



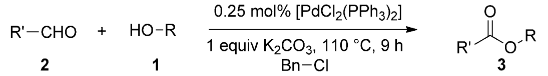
Entry	R′-CHO	HO-R	3	Yield [%][b]
1	Ph−CHO		**3b**	85
2	Ph−CHO		**3c**	96
3	p-Tol−CHO		**3d**	84
4	p-Tol−CHO		**3e**	98
5			**3f**	91
6			**3g**	74
7			**3h**	96
8	n-C_9H_{19}−CHO		**3i**	>99
9	n-C_5H_{11}−CHO		**3j**	98
10	n-C_9H_{19}−CHO		**3k**	90
11	Cy−CHO		**3l**	90
12	Cy−CHO		**3m**	>99
13[c]			**3n**	76
14	n-C_9H_{19}−CHO		**3o**	85
15	Cy−CHO		**3p**	95
16			**3q**	84
17	Cy−CHO		**3r**	74
18			**3s**	72

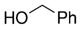
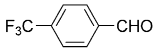
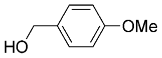
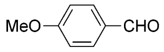
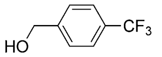
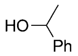
[a] Reaction conditions: **2** (0.5 mmol), **1** (0.5 mmol), $[PdCl_2(PPh_3)_2]$ (5 mol%), K_2CO_3 (0.5 mmol), BnCl (0.5 mmol) in THF (2 mL) at 60°C for 20 h. [b] Yield of isolated product. [c] 15% of olefin reduction product was observed.

nonconjugated alkenyl groups could also be tolerated in this oxidative cross-esterification (entry 16). Importantly, secondary alcohols, both benzylic and aliphatic types, were also suitable substrates to react with aldehydes to afford the corresponding esters in good yields (entries 17 and 18). To the best of knowledge, this is the most general and selective oxidative esterification of aldehyde with alcohol in a 1:1 ratio.

To our delight, this esterification could also proceed in the absence of the THF solvent (Table 2). We scaled up the amount of alcohol and aldehyde, yet lowered the catalyst loading at 110 °C. Various aldehydes and alcohols were esterified under these solvent-free conditions. Several typical examples are listed in Table 2 for a 5 mmol scale reaction of aldehydes and alcohols in the presence of 0.25 mol% of $[PdCl_2(PPh_3)_2]$. Good to excellent yields of the desired esters were obtained and contained various functional groups, such as p-OMe and p-CF_3 (entries 4 and 5). Aliphatic aldehydes and alcohols afforded excellent yields of the corresponding esters (entries 2 and 3). A secondary alcohol was also esterified in good yield (entry 6). To our knowledge, very few reported procedures could achieve such a low catalyst loading for oxidative esterifications.[11]

Table 2: Palladium-catalyzed oxidative esterification of aldehydes with alcohols under solvent-free conditions.[a]



Entry	R'-CHO	HO-R	3	Yield [%][b]
1	p-Tol–CHO		**3d**	97
2	n-C_9H_{19}–CHO	HO–n-C_8H_{17}	**3k**	>99
3	p-Tol–CHO	HO–n-C_8H_{17}	**3e**	99
4			**3t**	72
5			**3g**	83
6	Cy–CHO		**3r**	62

[a] Reaction conditions: **2** (5 mmol), **1** (5 mmol), $[PdCl_2(PPh_3)_2]$ (0.25 mol%), K_2CO_3 (5 mmol), BnCl (5 mmol), 110 °C, 9 h. [b] Yield of isolated product.

In conclusion, we have demonstrated that a covalently bound benzyl ligand promotes the selective palladium-catalyzed oxidative esterification of aldehydes with alcohols by using benzyl chloride as the oxidant. The covalently bound benzyl group is a carbon ligand which provides an η^3-coordination effect on palladium. The study of the substrate scope showed that various aldehydes and alcohols were selectively converted into the corresponding esters in high selectivity and good to excellent yields by using benzyl chloride as the oxidant. Moreover, the ratio of the aldehyde and alcohol is 1:1. Neither of the substrates needs to be excess. Under solvent-free reaction conditions large-scale reactions were carried out in the presence of a low catalyst loading. Importantly, the efect of the benzyl ligand provides information for the further design of ligands in achieving selective palladium-catalyzed oxidative esterification.

Experimental Section

General procedure (**3a**): $[PdCl_2(PPh_3)_2]$ (17.5 mg, 0.025 mmol) and K_2CO_3 (69.5 mg, 0.5 mmol) were placed in a oven-dried Shlenck tube, which was filled with nitrogen by using standard Schlenk techniques. THF (2.0 mL), aldehyde **2a** (0.50 mmol), and alcohol **1b** (0.50 mmol) were then added to the reaction tube. The reaction mixture was stirred at 60 °C for 20 h and the resulting mixture was quenched with water. The suspension was then extracted by ethyl acetate (3 × 5 mL), the organic layers were combined, and dried over sodium sulfate. The pure product was obtained by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 50:1). The yield of the siolated product was 96%. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.98$ (d, $J = 7.2$ Hz, 2H), 7.44 (t, $J = 7.5$ Hz, 1H), 7.32 (t, $J = 7.5$ Hz, 2H), 7.25 (d, $J = 8.1$ Hz, 2H), 7.15 (d, $J = 8.1$ Hz, 2H), 5.23 (s, 2H), 2.26 ppm (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 166.4$, 138.0, 132.8, 130.0, 129.5, 129.1, 128.2, 66.5, 21.0 ppm.

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