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Palladium-Catalyzed Carbonylative Esterification of Primary Alcohols with Aryl Chlorides through Dehydroxymethylative C–C Bond Cleavage

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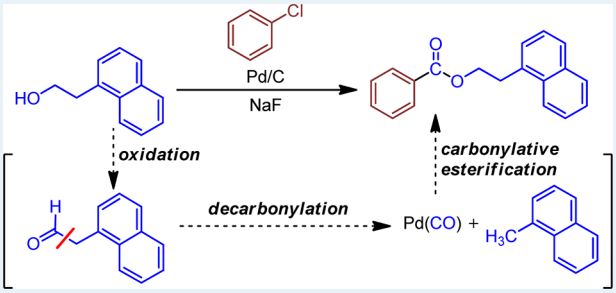
Supporting Information

ABSTRACT: Aryl chlorides in the presence of Pd/C catalyst and NaF react with primary alcohols to form esters, arenes, and alkanes. In this reaction, aryl chlorides act as both oxidants and coupling partners, whereas alcohols serve as both carbonyl sources and alkoxy components of the ester products



KEYWORDS: *C–C activation, carbonylative esterification, catalysis, decarbonylation, palladium*

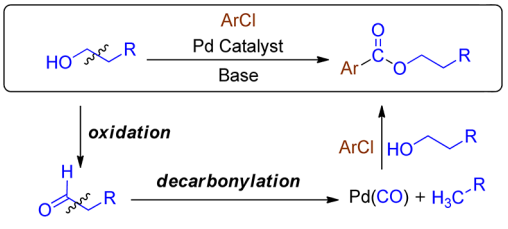
Carbonylative coupling reactions are of current interest in the chemical industry because they produce many carbonyl compounds such as esters, amides, and ketones.[1] Especially important are processes that produce esters, which serve as components of many industrial processes. One common method for synthesis of esters involves transition metal-catalyzed, carbonylative coupling reactions of aryl halides with alcohols using CO gas.[2] Owing to the toxic nature and pressure control problems associated with CO gas, other nontoxic and nongaseous carbonyl surrogates like alkyl formates,[3] chloroform,[4] and formic anhydrides[5] have been developed for use in carbonylative coupling reactions.

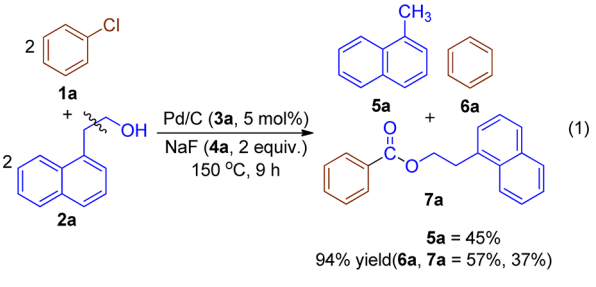
In the course of recent studies of palladium-catalyzed oxidations of primary alcohols, we observed that addition of aryl chlorides to the reaction mixture causes production of alkanes along with a mixture of arenes and of cross-coupled esters. We speculated that the carbonyl group of the ester product is derived from the alcohol through an oxidation and decarbonylation sequence (Scheme 1).

Herein, we describe the results of an investigation, which has confirmed this proposal by demonstrating that esters are generated in these reactions through a carbonylative esterification process. Specifically, the primary alcohol and aryl chloride participate in a Pd promoted dehydroxymethylative C–C bond cleavage reaction that produces Pd(0)CO, which is trapped sequentially by the aryl chloride and alcohol. This is a rare example of a process in which the reactants play dual roles with the aryl chloride serving as an oxidant and coupling partner and the alcohol as a source of the carbonyl and alkoxy group of the ester.

In initial experiments, we observed that reaction of chlorobenzene (**1a**) with 2-(naphth-1-yl)ethanol (**2a**) in the presence of Pd/C (**3a**, 5 mol %) and NaF (**4a**, 2 equiv) at 150 °C for 9 h leads to formation of benzene (**6a**) and ester **7a** in respective 57% and 37% yields based on **1a** (eq 1). Another interesting product, 1-methylnaphthalene (**5a**), is generated in a 45% yield based on **1a**, presuming that 1 equiv of **1a** dehydroxymethylates 1 equiv of **2a** to give **5a**.

Scheme 1. Concept of Carbonylative Esterification through Dehydroxymethylation





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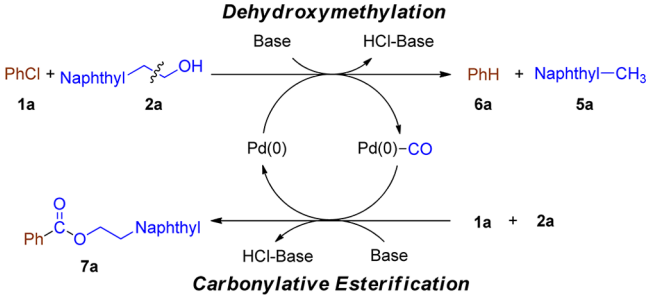
The nature and relative amounts of the products suggest that **5a** and **6a** arise from **2a** and **1a**, respectively, and that ester **7a** is derived from **1a** and **2a** (Scheme 2). In the initial step of the

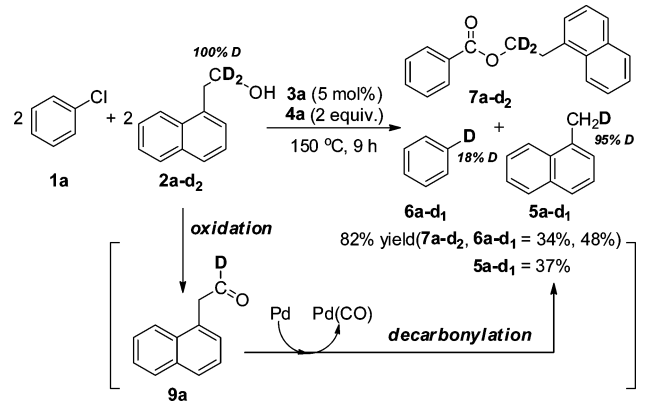
Scheme 2. Mechanistic Overview of Carbonylative Esterification of 1a and 2a



pathway for this process, alcohol **2a** undergoes chlorobenzene (**1a**) and Pd(0) promoted dehydroxymethylation by C–C bond cleavage to produce **6a** and **5a**. Pd(0)(CO), also generated in the initial step, then participates in carbonylative esterification with **1a** and the **2a** to form the ester **7a**. Using this pathway, the theoretical yields of **5a**, **6a**, and **7a** produced in the process based on **1a** are 50%, 50%, and 50%, respectively.

To demonstrate the validity of this mechanistic proposal and, specifically, that the carbonyl group in the ester product and methylnaphthalene both arise via oxidative cleavage of 2-(naphth-1-yl)ethanol followed by decarbonylation of resulting aldehyde, reaction using the 1,1-d_2 derivative **2a-d_2** was explored (Scheme 3).[6] In accord with the proposed mechanism

Scheme 3. Carbonylative Esterification with 1,1-d_2-Labeled 2-(Naphth-1-yl)ethanol



involving the intermediacy of d_1-aldehyde **9a**, reaction of **2a-d_2** leads to formation of **5a-d_1**, which contains 95% of deuterium in its methyl group.

To unambiguously identify the source of the ester carbonyl group, 1-^{13}C-2-phenylethanol (**2b***) was utilized as the starting material in the reaction. The results of ^{13}C NMR analysis of the products show that phenethyl ester **7b***, bearing the ^{13}C-labeled carbonyl group, is generated in this process (Figure 1). This observation demonstrates that the carbonyl group in **7b*** comes from hydroxymethyl group of **2b*** (eq 2).

The experimental results suggest that mechanism displayed in Scheme 4 is operating in the ester-forming reaction. Specifically, the aryl chloride along with Pd(0) oxidizes the primary alcohol **2** to form aldehyde **9**, arene **6** and HCl, which

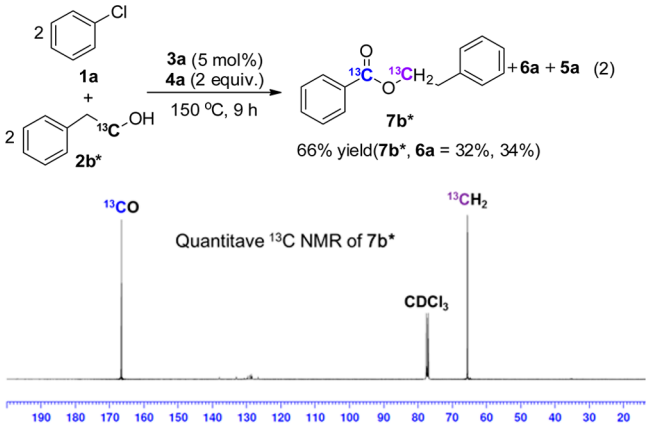
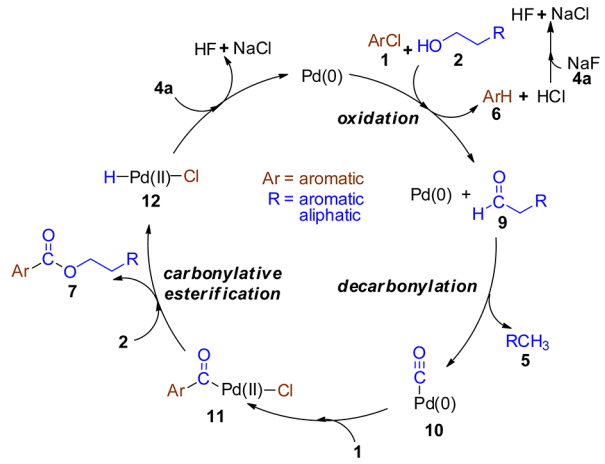


Figure 1. ^{13}C NMR analysis of **7b***.

Scheme 4. Catalytic Cycle for the Carbonylative Esterification Reaction



is neutralized by NaF (**4a**). Aldehyde **9** is then readily decarbonylated to generate alkane **5** and Pd(0)CO **10**, which undergoes oxidative addition with aryl chloride **1** followed by migratory insertion to form acyl-Pd(II)chloride **11**. Reaction of **11** with the alcohol produces the ester product **7** along with regenerated Pd(0) and HCl.

In order to uncover the optimal conditions for the ester-forming reaction, various transition metal catalysts were tested (Table 1). The results show that palladium catalysts such as **3a** and **3b** promote the process (entries 1, 2). However, in the reaction using **3b**, ligand decomposition (e.g., P–C bond cleavage) was observed to take place.[7] Other transition metals do not catalyze the ester-forming reaction (entries 3–4). As a result, Pd/C (**3a**) is the optimal catalyst for the esterification reaction. In this process, a base is required to neutralize HCl generated from the aryl chloride in both steps in which it participates. Among various bases tested (entries 1, 5–11), greater than 2 equiv of NaF (**4a**) displayed the best activity without causing the production of side products (entries 1, 5–6).[8] It is important to note that bases such as Na_2CO_3, $NaHCO_3$, and NaOH, which are commonly used in cross-coupling processes, promote reactions that generate only a low yield of ester **7a** and large amounts of side products such as biphenyl (**8a**) (entries 7–11).

The aryl chloride substrate scope of the process was explored next (Table 2). The results of this effort show that steric hindrance of the aryl group affects the ester-forming reaction as

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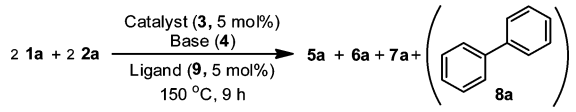
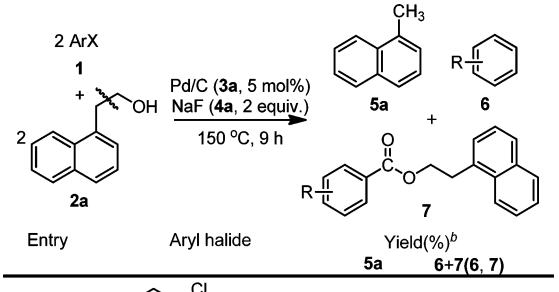
Table 1. Optimization of Carbonylative Esterification[a]

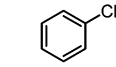
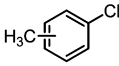
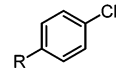
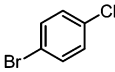


entry	catalyst	ligand	base (x equiv)	yield (%)[b] 5a	6a + 7a (6a, 7a)	8a
1	**3a**		NaF (**4a**, 2)	45	94 (57, 37)	0
2	$Pd(PPh_3)_4$ (**3b**)		**4a** (2)	40	95 (65, 30)	0
3	$RhCl(PPh_3)_3$ (**3c**)	PPh_3 (**9a**)	**4a** (2)	5	7 (7, 0)	0
4	$[Ir(COE)_2Cl_2]_2$ (**3d**)	PPh_3 (**9a**)	**4a** (2)	12	4 (4, 0)	0
5	**3a**		**4a** (1)	33	68 (39, 29)	0
6	**3a**		**4a** (3)	43	96 (61, 35)	0
7	**3a**		KF (**4b**, 2)	22	65 (45, 20)	32
8	**3a**		CsF(**4c**, 2)	34	64 (63, 1)	19
9[c]	**3a**		Na_2CO_3 (**4d**, 2)	28	64 (49, 15)	36
10[d]	**3a**		$NaHCO_3$ (**4e**, 2)	13	66 (53, 13)	34
11	**3a**		NaOH (**4f**, 2)	36	86 (85, 1)	8

Reaction conditions: **1a** (0.4 mmol), **2a** (0.56 mmol), **3** (0.02 mmol), **4** and **9a** (0.02 mmol) at 150 °C for 9 h and with yields calculated based on **1a** [a]Small amounts (<5%) of dehydroxylated product and Tishchenko type ester were formed. [b]**7a** is isolated yield. Yields of **5a** and **6a** were determined by GC-MS and ^{1}H NMR. [c]14% of Tishchenko type ester formed. [d]11% of Tishchenko product formed.

Table 2. Substrate Scope of Aryl Halide[a]



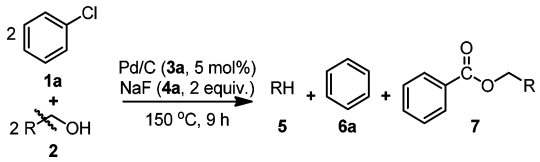
Entry	Aryl halide			Yield(%)[b] 5a	6+7(6, 7)
1			(**1a**)	45	94(**6a**, **7a**=57, 37)
2[c]		*para*-	(**1b**)	37	92(**6b**, **7c**=55, 37)
3		*meta*-	(**1c**)	32	71(**6c**, **7d**=42, 29)
4		*ortho*-	(**1d**)	27	54(**6d**, **7e**=33, 21)
5		R = OMe	(**1e**)	43	85(**6e**, **7f**=52, 33)
6		CF_3	(**1f**)	34	64(**6f**, **7g**=36, 28)
7		F	(**1g**)	35	64(**6g**, **7h**=38, 26)
8		X = F	(**1h**)	5	
9		Br	(**1i**)	0	5(**6a**, **7a**=5, 0)
10		I	(**1j**)	0	5(**6a**, **7a**=5, 0)
11[d]			(**1k**)	0	

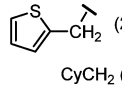
Reaction conditions: **1** (0.4 mmol), **2a** (0.56 mmol), **3a** (0.02 mmol) and **4a** (0.8 mmol) at 150 °C for 9 h and yields are based on **1**. [a]Small amounts (<5%) of dehydroxylated compounds and Tishchenko type esters are generated. [b]**7** is isolated yield. Yields of **5a** and **6** were determined by GC-MS and ^{1}H NMR. [c]14% of dehydroxylated compound was produced. [d]3% of **1a** and 10% of **8a** were obtained.

exemplified by the fact that *ortho*-methylchlorobenzene (**1d**) is much less reactive than is its para-substituted analogue **1b** (entries 2−4). In addition, aryl chlorides with electron-donating substituents (e.g., **1e**) are more reactive than their electron-withdrawing substituted counterparts (e.g., **1f** and **1g**) (entries 5−7). It is interesting to note that only chloroarenes participate in this reaction, while other haloarenes such as fuloro (**1h**), bromo (**1i**), and iodobenzene (**1j**) do not (entries 8−10). A likely reason for this selectivity is that chloroarenes oxidize primary alcohols more readily than do other haloarenes.[9] When 4-bromochlorobenzene was also applied in this reaction, any ester product was not obtained, implying that aryl bromide destroys the catalytic activity of Pd/C (entry 11).

The use of various alcohols for this transformation was also probed (Table 3). As expected based on the proposed

Table 3. Substrate Scope of Alcohol[a]



Entry	R	Yield(%)[b] 5	6+7(6, 7)
1	$C_6H_5CH_2$ (**2b**)	52(**5b**)	91(**6a**, **7b**=54, 37)
2[c]	C_6H_5 (**2c**)	58(**5c+6a**)	11(**7i**)
3[d]	$C_6H_5CH_2CH_2$ (**2d**)	39(**5d**)	79(**6a**, **7j**=53, 26)
4	$C_6H_5(CH_2)_2CH_2$ (**2e**)	26(**5e**)	66(**6a**, **7k**=49, 17)
5	4-$FC_6H_5CH_2$ (**2f**)	9(**5f**)	28(**6a**, **7l**=19, 9)
6	4-$CH_3OC_6H_5CH_2$ (**2g**)	55(**5g**)	91(**6a**, **7m**=61, 30)
7	 (**2h**)	14(**5h**)	28(**6a**, **7n**=19, 9)
8	$CyCH_2$ (**2i**)	8(**5i**)	20(**6a**, **7o**=15, 5)
9[e]	CH_3 (**2j**)	-	14(**6a**, **7p**=10, 4)

Reaction conditions: **1a** (0.4 mmol), **2** (0.56 mmol), **3a** (0.02 mmol) and **4a** (0.8 mmol) at 150 °C for 9 h and yields calculated based on **1a**. [a]Small amounts (<5%) of dehydroxylated compounds and Tishchenko type esters were produced. [b]**7** is isolated yield. Yields of **5** and **6a** were determined by GC-MS and ^{1}H NMR. [c]42% of dehydroxylated compound was produced. [d]18% of dehydroxylated compound and 23% of Tishchenko type ester were produced. [e]1,4-dioxane(50 μL) was used as solvent.

mechanism, only primary alcohols serve as substrates for the process owing to their capability to form key aldehyde intermediates that undergo decarbonylation to generate Pd(0)CO.[10] This type of dehydroxymethylation process is an interesting example of a C−C bond cleavage reactions.[11]

Primary alcohols containing aryl groups display higher reactivity than do their aliphatic alcohol analogues. In contrast

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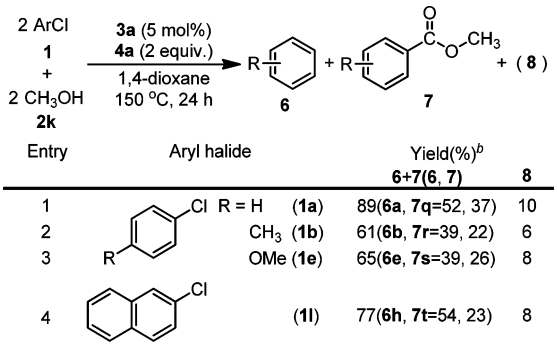
to other primary alcohols, including benzyl alcohol (**2c**), 3-phenyl propanol (**2d**), 4-phenyl butanol (**2e**), the ω-phenyl alkanol 2-phenylethanol (**2b**) participates in the highest yielding reactions to form ester **7b** (entries 1−4). We believe that phenylacetaldehyde formed from 2-phenylethanol (**2b**) is more readily dehydroxymethylated because it gives the more stable benzyl palladium complex. It should be noted that examples exist in which stable benzyl transition metal complexes are formed by C−C bond activation of benzyl ketones.[12] Among the 2-phenylethanols probed, electron-donating substituted members like the *p*-methoxy-derivative **2f** react more efficiently than do their electron-withdrawing group substituted analogues *p*-fluoro-derivative **2g** (entries 5, 6).

Methanol is a good carbonyl source owing to the fact that C−C bond cleavage is not required to form the Pd−CO complex. Reaction of chlorobenzene with methanol, carried out in the presence of Pd/C (**3a**) and NaF (**4a**) at 150 °C for 24 h, was observed to form benzene (**6a**) and methyl benzoate (**7q**) in 89% total yield (52/37 ratio) along with 10% of the homocoupling product **8a** (entry 1 in Table 4). Other aryl

Table 4. Carbonylative Esterification with Methanol[a]



Entry	Aryl halide	Yield(%)[b] 6+7(6, 7)	8
1	Cl R = H (**1a**)	89(**6a**, **7q**=52, 37)	10
2	CH_3 (**1b**)	61(**6b**, **7r**=39, 22)	6
3	OMe (**1e**)	65(**6e**, **7s**=39, 26)	8
4	Cl (**1l**)	77(**6h**, **7t**=54, 23)	8

Reaction conditions: **1** (0.4 mmol), **2k** (1.68 mmol), **3a** (0.02 mmol) and **4a** (0.8 mmol) at 150 °C for 24 h in 1,4-dioxane (50 μL) and yields are based on **1**. [a]*Less than* 1% of isomers of **7** are formed. [b]**7** is isolated yield. And yield of **6** was determined by GC-MS and ^{1}H NMR.

chlorides, such as 4-methyl (**1b**), 4-methoxy (**1e**), and 2-naphthyl chloride (**1l**), also participate in reactions with methanol to generate the corresponding arenes **6** and methyl arenoates **7** in moderate yields (entries 2−4). Thus, as anticipated Pd catalyzes the aryl chloride promoted oxidation reaction of methanol that forms Pd(0)CO, which is then converted to methyl ester **7**.

In summary, esters are directly produced in reactions of aryl chlorides and primary alcohols in the presence of Pd/C and NaF. In this process, the alcohol undergoes oxidative dehydroxymethylation to give an alkane and Pd(0)CO through a C−C bond cleavage pathway in which aryl chloride is reduced. In the last stage of the reaction, Pd(0)CO reacts with the aryl chloride and alcohol to form the ester product. Further applications of this protocol are under study.

■ ASSOCIATED CONTENT

Supporting Information

The following file is available free of charge on the ACS Publications website at DOI: 10.1021/cs501778q.

Compound characterization data, ^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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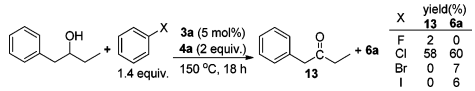
(6) We observed that 18% of deuterium is incorporated in benzene (**6a-d1**), determined by GC-MS. It is likely that the initially generated aryl-deuterium bond is partially exchanged with proton to give aryl-H on Pd/C. For a related report, see: Atzrodt, J.; Derdau, V.; Fey, T.; Zimmermann, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 7744−7765.

(7) Pd/C was chosen because benzene is also produced from P-C bond cleavage of PPh3. For a related reference, see: Kong, K. C.; Cheng, C. H. *J. Am. Chem. Soc.* **1991**, *113*, 6313−6315.

(8) For suppression of homocoupling product by NaF, see: Qi, C.; Sun, X.; Lu, C.; Yang, J.; Du, Y.; Wu, H.; Zhang, X.-M. J. *Organomet. Chem.* **2009**, *694*, 2912−2916.

(9) Among various aryl halides used for oxidation of *sec*-alcohols, only chlorobenzene is effective in forming the ketone (**13**) in 58% yield with formation of benzene (**6a**).



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