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Communication

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Catalytic Deoxygenative Coupling of Aromatic Esters with Organophosphorus Compounds

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ABSTRACT: We have developed a deoxygenative coupling of aromatic esters with diarylphosphine oxides/dialkyl phosphonates under palladium catalysis. In this reaction, aromatic esters can work as novel benzylation reagents to give the corresponding benzylic phosphorus compounds. The key of this reaction is the use of phenyl esters, an electron-rich diphosphine as a ligand, and sodium formate as a hydrogen source. Arylcarboxylic acids were also applicable in this reaction using $(Boc)_2O$ as an additive. Palladium/dcype worked to activate the acyl C–O bond of the ester and to support the reduction with sodium formate.

Aromatic esters are frequently used as abundant, inexpensive chemical feedstock in organic synthesis and can be derived into various aromatic molecules. Therefore, a significant number of substitution reactions from aromatic esters have been reported thus far. Conventionally, these reactions involve an aromatic ester with a nucleophile in a 1,2-addition reaction in which the nucleophile attacks the carbonyl on the ester to produce the corresponding aromatic ketones and alcohols (Figure 1A).

Recently, transition-metal-catalyzed non-decarbonylative and decarbonylative transformations of aromatic esters with various nucleophiles have received attention as an emerging method in synthetic organic chemistry (Figure 1B).[1–4] In these reactions, various nucleophiles can be introduced directly under the following mechanism: Oxidative addition of the acyl carbon–oxygen (C–O) bond of the phenyl arenoate to a transition metal (step A), followed by attack of the nucleophile to the metal (step B), and subsequent decarbonylation (step C) and/or reductive elimination (step D). Based on this plausible mechanism, we hypothesized that the reduction of the non-decarbonylative product (formally the same as the 1,2-adducts obtained conventionally) with an appropriate reducing agent is faster than decarbonylation (step C), giving a deoxygenative product (step E). Conventionally, this chemical transformation requires three steps; reduction of an ester, halogenation of the resulting alcohol, and nucleophilic substitution of the ensuing benzyl halide. However, under this hypothesis, aromatic esters should behave like benzyl halides, and react with nucleophiles in a single step. Additionally, it might be possible to use various nucleophiles that have been developed for non-decarbonylative and decarbonylative ester transformations. As our first step toward developing this new type of transformation, herein we report a deoxygenative carbon–phosphorus (C–P) bond formation reaction using aromatic esters as benzylating agents under palladium catalysis (Figure 1C). Such organophosphorus products could potentially be useful as synthetic intermediates, bioactive molecules and ligands for transition metal catalysis.[5]

Regarding the decarbonylative transformation of aromatic esters, our group has recently developed a nickel-catalyzed decarbonylative C–P bond formation between aromatic phenyl esters and organophosphorus compounds.[3e]

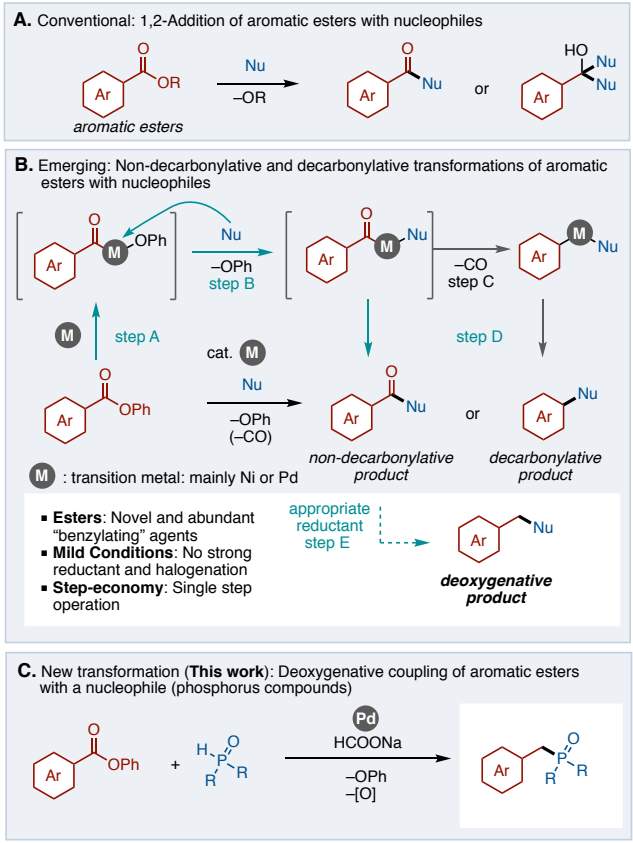
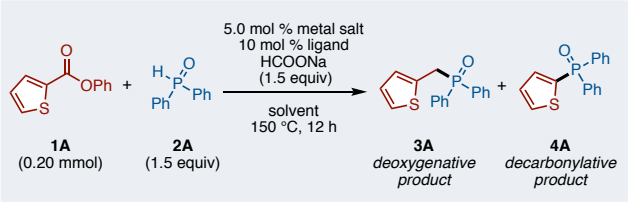


Figure 1. Chemical transformation of aromatic esters. (A) Conventional approach. (B) Emerging methods. (C) Deoxygenative coupling with phosphorus compounds

With a $Ni(OAc)_2$/dcypt [3,4-bis(dicyclohexylphosphino)thiophene] catalyst, aromatic esters can function as arylating agents to give the corresponding aromatic phosphorus compounds. For example, phenyl thiophene-2-

carboxylate (**1A**) and diphenylphosphine oxide (**2A**) with 5 mol % $Ni(OAc)_2$/dcypt catalyst and NaF (1.5 equiv) as an additive in ^{t}AmylOH at 170 °C only produced the undesired decarbonylative product **4A** in 64% yield (Table 1, entry 1). To realize the hypothesized deoxygenative coupling, we set out to change the reaction conditions. Using the same catalyst, 1.5 equiv of sodium formate (HCOONa) as a hydrogen source (a reductant) in ^{t}AmylOH at 150 °C for 12 h were used as the initial screening conditions (Table 1, entry 2). This successfully gave the desired deoxygenative product **3A** in 18% yield along with the decarbonylative product **4A** in 60% yield. Changing the solvent from ^{t}AmylOH to 1,4-dioxane as well as 1,2-dimethoxyethane (DME) increased the yield of desired **3A**, particularly when DME was used as the solvent, giving **3A** in 35% yield as a single product (Table 1, entries 3 and 4). However, nickel catalysis could not improve the yield of **3A** after extensive investigations.[6] To our delight, when nickel was changed to palladium salts such as $Pd(OAc)_2$, $Pd_2(dba)_3$·$CHCl_3$, and $PdCl_2$, the yield of **3A** significantly improved to 63% yield as the best result and no **4A** was observed (Table 1, entries 5–7). Furthermore, when the ligand was changed from dcypt to various phosphine ligands,the highest yield of **3A** was obtained (89% yield) without any decarbonylative product **4A** (using dcype, Table 1, entries 8–16). It should be noted that the reaction hardly proceeds without the Pd metal or the ligand (Table 1, entries 17–19).

Table 1. Screening of reaction conditions.[a]



entry	metal	ligand	solvent	3A/4A (%)
1[b]	$Ni(OAc)_2$	dcypt	^{t}AmylOH	0/64
2	$Ni(OAc)_2$	dcypt	^{t}AmylOH	18/60
3	$Ni(OAc)_2$	dcypt	dioxane	33/44
4	$Ni(OAc)_2$	dcypt	DME	35/0
5	$Pd(OAc)_2$	dcypt	DME	62/0
6	$Pd_2(dba)_3$[c]	dcypt	DME	60/0
7	$PdCl_2$	dcypt	DME	63/0
8	$PdCl_2$	dppe	DME	67/0
9	$PdCl_2$	dppbz	DME	46/0
10	$PdCl_2$	P^nBu_3	DME	60/0
11	$PdCl_2$	XPhos	DME	35/0
12	$PdCl_2$	BINAP	DME	31/0
13	$PdCl_2$	PPh_3	DME	16/0
14	$PdCl_2$	bipy	DME	15/0
15	$PdCl_2$	IPr·HCl	DME	55/0
16	$PdCl_2$	dcype	DME	89/0
17	–	–	DME	4/0
18	$PdCl_2$	–	DME	1/0
19	–	dcype	DME	0/0

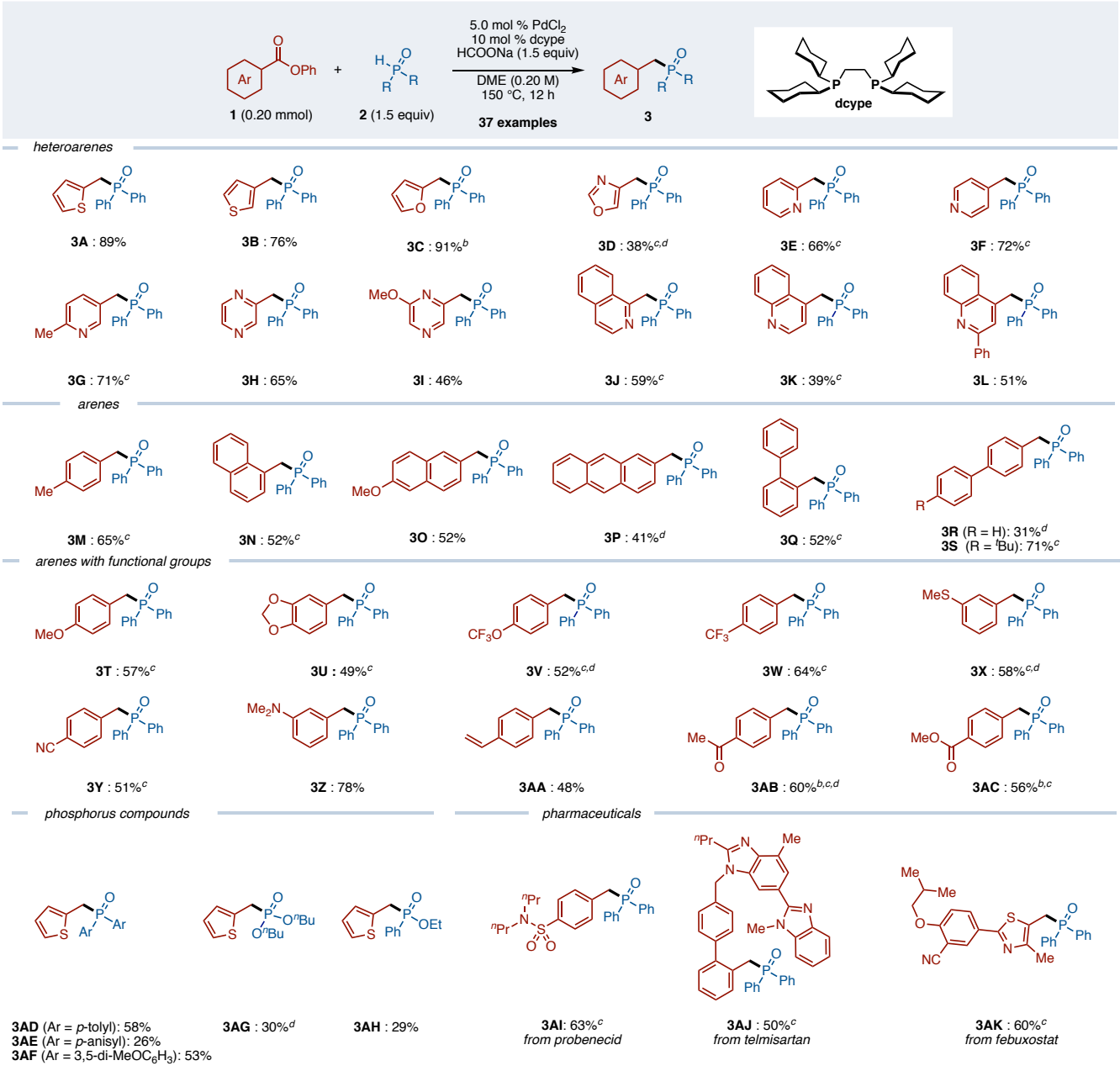
[a] Conditions; **1A** (0.20 mmol), **2A** (0.30 mmol), metal (5.0 mol %), ligand (monodentatel; 10 mol %, bidentate; 20 mol %), HCOONa (1.5 equiv), solvent (1.0 mL), 150 °C, 12 h. NMR yield, [b] NaF (1.5 equiv) instead of HCOONa was used at 170 °C for 18 h. [c] $Pd_2(dba)_3$·$CHCl_3$ (2.5 mol %) was used. dcype = 1,2-Bis(dicyclohexylphosphino)ethane.

With optimal conditions in hand, the substrate scope of aromatic esters **1** and organophosphorus compounds **2** was investigated (Scheme 1). This reaction was applicable to various heteroaromatic esters, not only to phenyl 2-thienoate (**1A**) but also to 3-thienoate (**1B**), 2-furanoate (**1C**), 2-picolinate (**1E**), isonicotinates and nicotinates (**1F** and **1G**), pyrazinoates (**1H** and **1I**), isoquinolinates (**1J**), and quinolinates (**1K** and **1L**) to give the corresponding deoxygenative products **3B**–**3L** in moderate to good yields. In terms of simple arenoates such as *p*-tolyl (**1M**), naphthyl (**1N**), anthracenyl (**1P**), and biphenyl (**1Q**–**1S**) as the aryl group, the deoxygenative coupling also worked well to afford the corresponding products **3M**–**3S** in moderate yields. Electron-withdrawing or electron-donating substituents at the *para* position of the phenoate, such as methoxy (**1T**), alkoxy (**1U**), trifluoromethoxy (**1V**), and trifluoromethyl (**1W**) groups did not affect the yields of products **3T**–**3W**. Next, we examined the functional group tolerance for this reaction. Indeed, this reaction showed high functional group tolerance and proceeded with aromatic phenyl esters bearing thiomethyl (**3X**), cyano (**3Y**), dimethylamino (**3Z**), vinyl (**3AA**), acetyl (**3AB**), and methyl carboxylate (**3AC**) groups. This deoxygenative coupling proceeded even when different diarylphosphine oxides were used instead of **2A**, affording the corresponding coupling products **3AD**–**3AF**. Although disubstituted phosphites and phosphinate were less applicable substrates compared with phosphine oxides, they reacted with **1A** to give the corresponding coupling products **3AG** and **3AH**. We also attempted this reaction with the phenyl ester of probenecid, telmisartan, and febuxostat, which are well-known pharmaceuticals, and succeeded in obtaining products **3AI**–**3AK** in moderate yields. It should be noted that several substrates required 2.0 equiv of sodium formate and higher temperatures to increase the yields. Regarding to the limitation of this protocol at this stage, alkyl (Alk–CO_2Ph) and alkenyl esters did not deliver the corresponding products (see the Supporting Information for details).

At this stage, it can be hypothesized following two routes; 1) direct reduction of **1A** and then coupling of the resulting etherific C–OPh bond of **5F** with **2A** under palladium catalysis;[7] 2) reduction to the aldehyde and addition with **2A**, followed by a phospha-Brook rearrangement[8,9] and transformation of the C–OP(O)Ph_2 bond by the palladium catalyst (Figure 2A). To understand the reaction mechanism, several control experiments were performed. Firstly, phenyl ester **1A** was changed to various other carbonyl compounds **5A**–**5H**, which includes possible reaction intermediates (Figure 2B). This reaction could not be accomplished with methyl ester **5A** and aldehyde **5B**. When 4-trifluorophenyl ester **5C**, acid chloride **5D** and thioester **5F** were used, the desired product **3A** was obtained, albeit in lower yields. These results indicate that this reaction can only be achieved using "activated" aroyl compounds. However, possible intermediates such as aldehyde **5B**, phenyl ether **5F**, and benzylic phosphine oxide **5G** did not affect the reaction, which means ruling out our mechanistic hypotheses 1 and 2.

On the other hand, acyl phosphine oxide **5H**, which was a moisture-sensitive compound, reacted to give **3A** in 49% yield. This result supports that **5H** is a reaction intermediate. Next, we

Scheme 1. Substrate scope[a]



[a] Conditions; **1** (0.20 mmol), **2** (0.30 mmol), $PdCl_2$ (5.0 mol %), dcype (10 mol %), HCOONa (1.5 equiv), DCE (1.0 mL), 150 °C, 12 h. [b] **2A** (3.0 equiv) was added. [c] HCOONa (2.0 equiv) was added. [d] The reaction was performed at 160 °C.

wondered whether acyl phosphine oxide **5H** was produced by a simple 1,2-addition reaction of aromatic phenyl ester **1** with diphenylphosphine oxide (**2A**) or not. Hence, we conducted a control experiment, in which **1A** was mixed with **2A** under optimal conditions without a palladium catalyst (Figure 2C). As a result, **5H** was not produced, and both starting materials were recovered. With this result, we speculate that **5H** is likely formed by a non-decarbonylative coupling pathway involved by the palladium catalysis (see Figure 1, step A and B, followed by step D).

We also confirmed that possible reduction intermediates such as **5H**, **5I** and **5J** can be transformed into **3A** (Figure 2D). In all cases, the desired product **3A** were given, which means that **5H** can be reduced under Pd/HCOONa catalytic system. Finally, the reaction was conducted using deuterated sodium formate (DCOONa) and/or diphenylphosphine oxide *d*-**2A** (Figure 2E).[10] When only DCOONa was used, a mixture of hydrogenated (**3A**) and deuterated (*d*$_1$-**3A** and *d*$_2$-**3A**) forms at the benzylic proton of **3A** was obtained with a ratio of 44:44:12 (**3A**:*d*$_1$-**3A**:*d*$_2$-**3A**). Subsequently, when only deuterated *d*-**2A** was used, the ratio of deuterated products was increased (22:39:39). Finally, both deuterated reagents were combined to give a product mixture with a ratio of (14:29:57). These experiments reveal that both sources of deuterium are involved in the reduction of the carbonyl group, and that other sources of hydrogen are seemingly present in the reaction system.

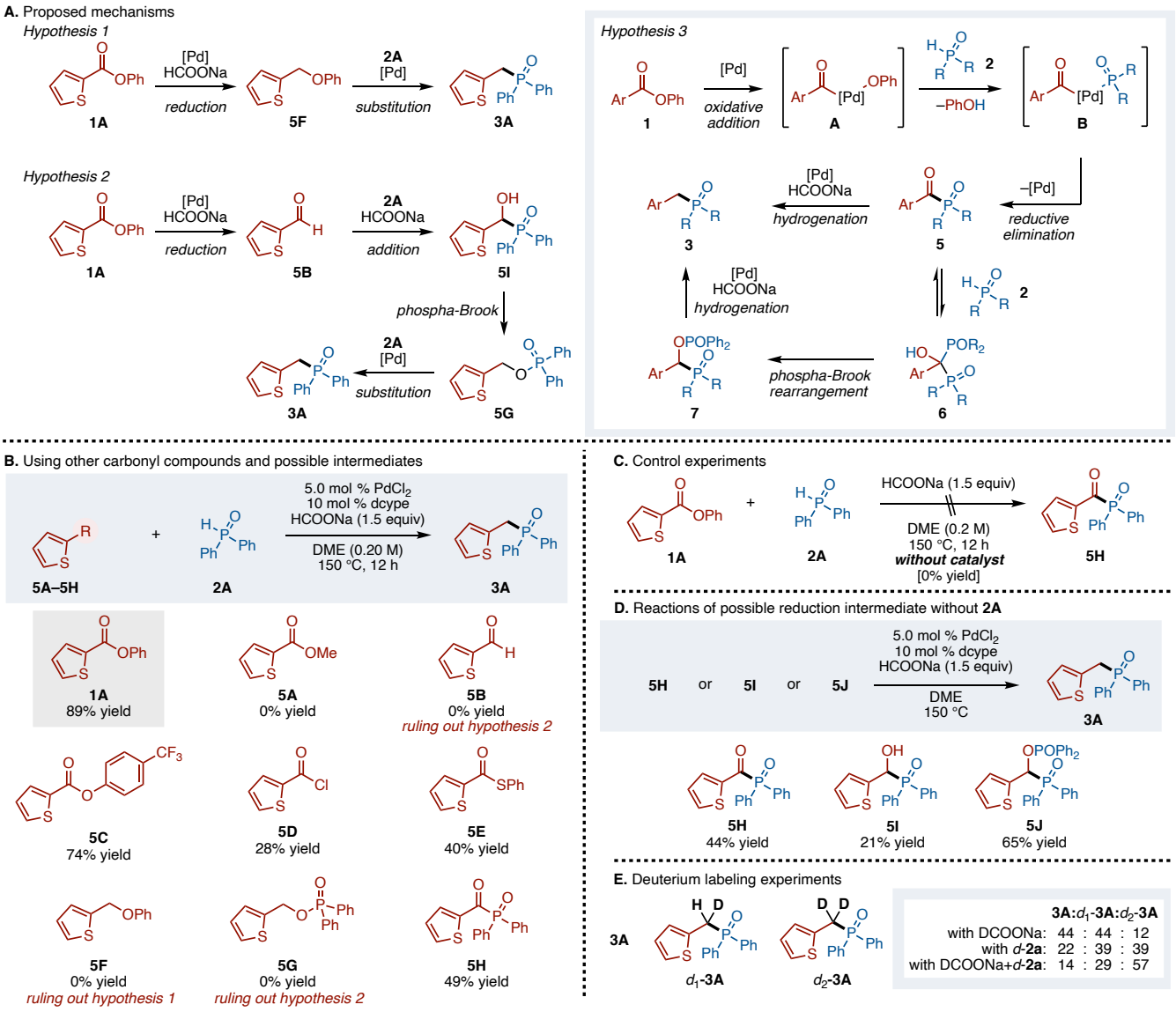
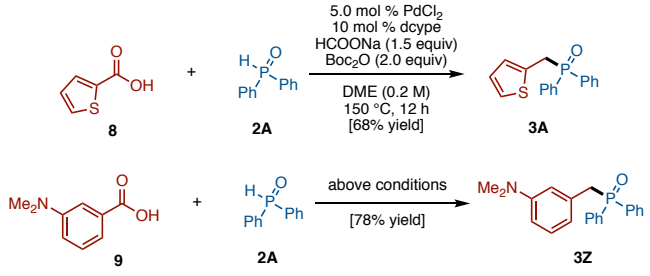


Figure 2. (A) Proposed mechanisms. (B) Deoxygenative coupling using other carbonyl compounds and possible intermediates. (C) Control experiments. (D) Reactions of possible reduction intermediates without **2A**. (E) Deuterium labeling experiments.

Based on the above experiments, a plausible mechanism is depicted in Figure 2A (Hypothesis 3). First, oxidative addition of the acyl C–O bond of phenyl ester **1** onto palladium produces palladium complex **A**. Then, ligand exchange from phenoxy (OPh) to diaryl phosphine oxide **2** produces complex **B** and phenol, followed by reductive elimination to give non-decarbonylative product **5**. Because the phosphine oxide bearing carbonyl group of **5** is electron-deficient, hydrogenation of **5** proceeds under palladium and sodium formate to afford the organophosphorus compound **3**. As a minor process of the hydrogenation, **5** can react with another molecule of **2**, thus forming **6**, followed by phospha-Brook rearrangement to give intermediate **7**.[8,9] Then, hydrogenation of **7** furnishes the deoxygenative product **3**.

Finally, we wanted to achieve this deoxygenative coupling directly from arylcarboxylic acids (Scheme 2). To our optimized conditions was added $(Boc)_2O$: 2-thiophenecarboxylic acid (**8**) as well as 3-dimethylaminobenzoic acid (**9**) were reacted with **2A** through *in situ* acid anhydride formation, resulting in the corresponding deoxygenative products **3A** and **3Z** in good yields.[11]

Scheme 2. Deoxygenative coupling from arylcarboxylic acids.



In summary, we succeeded in developing a deoxygenative carbon–phosphorus bond formation reaction between aromatic esters and organophosphorus compounds using a palladium catalyst. The catalyst has two roles: activation of the acyl C–O bond of the aromatic ester and catalytic reduction in conjunction with HCOONa. Expanding the range of substrates and nucleophiles for this new type of transformation is currently underway in our laboratory.[12]

ASSOCIATED CONTENT

Supporting Information

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

Experimental procedures and spectroscopic data for compounds including ^{1}H-, ^{13}C, ^{31}P NMR spectra (PDF)

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Notes

No competing financial interests have been declared.

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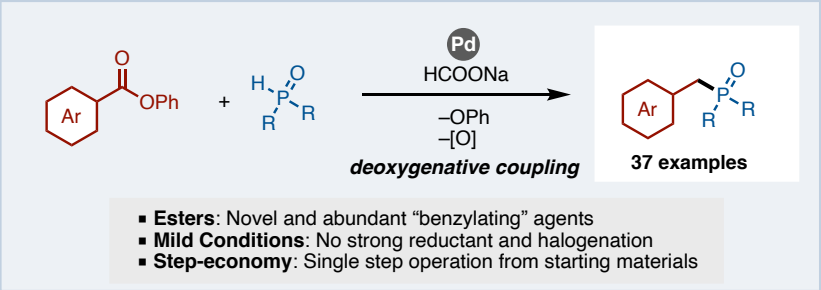
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37 examples
▪ Esters: Novel and abundant “benzylating” agents
▪ Mild Conditions: No strong reductant and halogenation
▪ Step-economy: Single step operation from starting materials