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Palladium-Catalyzed Ylidyl-Carbonylation of Aryl Halides To Produce α-Acylphosphoranes

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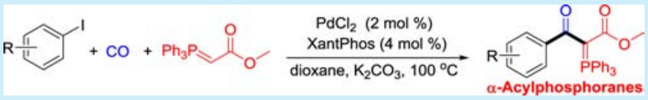
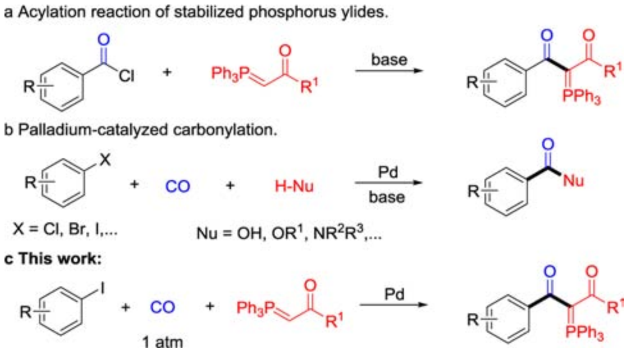
Supporting Information

ABSTRACT: An efficient synthesis of α-acylphosphoranes by palladium-catalyzed carbonylation of aryl iodides with carbon monoxide and stabilized phosphonium ylides has been developed. Featuring 44 examples, the protocol displayed a wide substrate scope under mild reaction conditions, showcasing its potential in synthetic organic chemistry.



α-Acylphosphoranes have attracted considerable attention in organic synthesis due to their participation in the synthesis of the Shell Higher Olefin Process (SHOP)-type catalysts,[1] carboxylic acids,[2] terminal alkynes,[3] acetylenic esters,[4] vicinal tricarbonyl compounds,[5] 2,3-diketo esters,[6] halogenated enol lactones,[7] cyclization compounds,[8] and heterocycles.[9] In particular, α-acylphosphoranes act as a key intermediate in the synthesis of GS-493,[6b] one of the most powerful selective inhibitors of the protein tyrosine phosphatase SHP2. These examples highlight the importance of α-acylphosphoranes in organic synthesis. Traditionally, α-acylphosphoranes have been synthesized by acylation reaction of carboxylic acid chlorides with stabilized phosphonium ylides (Scheme 1, a)[3a,9b,10] or using carboxylic acid derivatives,[5a,b,8c] cyclic anhydrides,[11] aldehydes,[5a] 1,3-dicarbonyl compounds,[4d] benzoic acid trimethylsilyl ester (TMSE),[5b] and tellurol esters.[12] However, an efficient and simple synthesis of α-acylphosphoranes via palladium-catalyzed carbonylation under atmospheric CO pressure has received no attention.

Scheme 1. Pd-Catalyzed Carbonylation of Aryl Iodides with Phosphonium Ylides



Since its initial discovery by Heck and co-workers in 1974,[13] the palladium-catalyzed carbonylation has become an efficient methodology for synthesizing a variety of highly valued compounds. In particular, it has been used for the selective synthesis of a wide range of aromatic acyl derivatives (Scheme 1, b),[14] such as carboxylic acids,[15] esters,[16] amides,[17] anhydrides,[18a] aldehydes,[19] ketones,[20] and heterocycles.[21] Despite the considerable attention that carbonylation reactions have received over the past several decades, to the best of our knowledge, carbonylative reactions of aryl halides with stabilized phosphonium ylides as nucleophiles via palladium catalysis to yield α-acylphosphoranes have not been described before.[22] Following our continued interest in palladium-catalyzed carbonylation reactions,[18] herein we describe an efficient synthesis of α-acylphosphoranes by palladium-catalyzed ylidyl carbonylation (Scheme 1, c).

We began our investigation by carrying out the reaction of methyl 4-iodobenzoate **1** (0.5 mmol) with methyl 2-(triphenylphosphoranylidene)acetate **2** (1 equiv) in the presence of DBU (1 equiv), 2 mol % of $Pd(OAc)_2$, and 4 mol % of triphenylphosphine in 1,4-dioxane (3 mL) under a CO (6 atm) atmosphere. After reaction at 100 °C for 12 h, to our delight, the desired product **3** was obtained in 34% isolated yield (Table 1, entry 1). Control experiments showed that both the CO and the $Pd(OAc)_2$ catalyst were essential for the reaction (Table 1, entries 2 and 3). Without the phosphine ligand and base, the yield of target product decreased compared to the initial conditions, indicating that the phosphine ligand and the base are beneficial to the reaction (Table 1, entries 4 and 5). Subsequently, different phosphine ligands (18 examples) were investigated and XantPhos was found to be the most efficient ligand.[23] In the presence of this ligand, various bases were also surveyed. Compared with organic bases, the inorganic ones improved the yield further.[23] Other Pd sources were also examined in the presence of 4 mol % of XantPhos. The results show $PdCl_2$ to be the more effective catalyst for this reaction compared to $Pd(OAc)_2$, $Pd(PhCN)_2Cl_2$, and $Pd(MeCN)_2Cl_2$.[23] In addition, different

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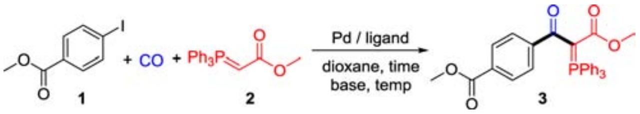
Table 1. Optimization of Reaction Conditions[a]



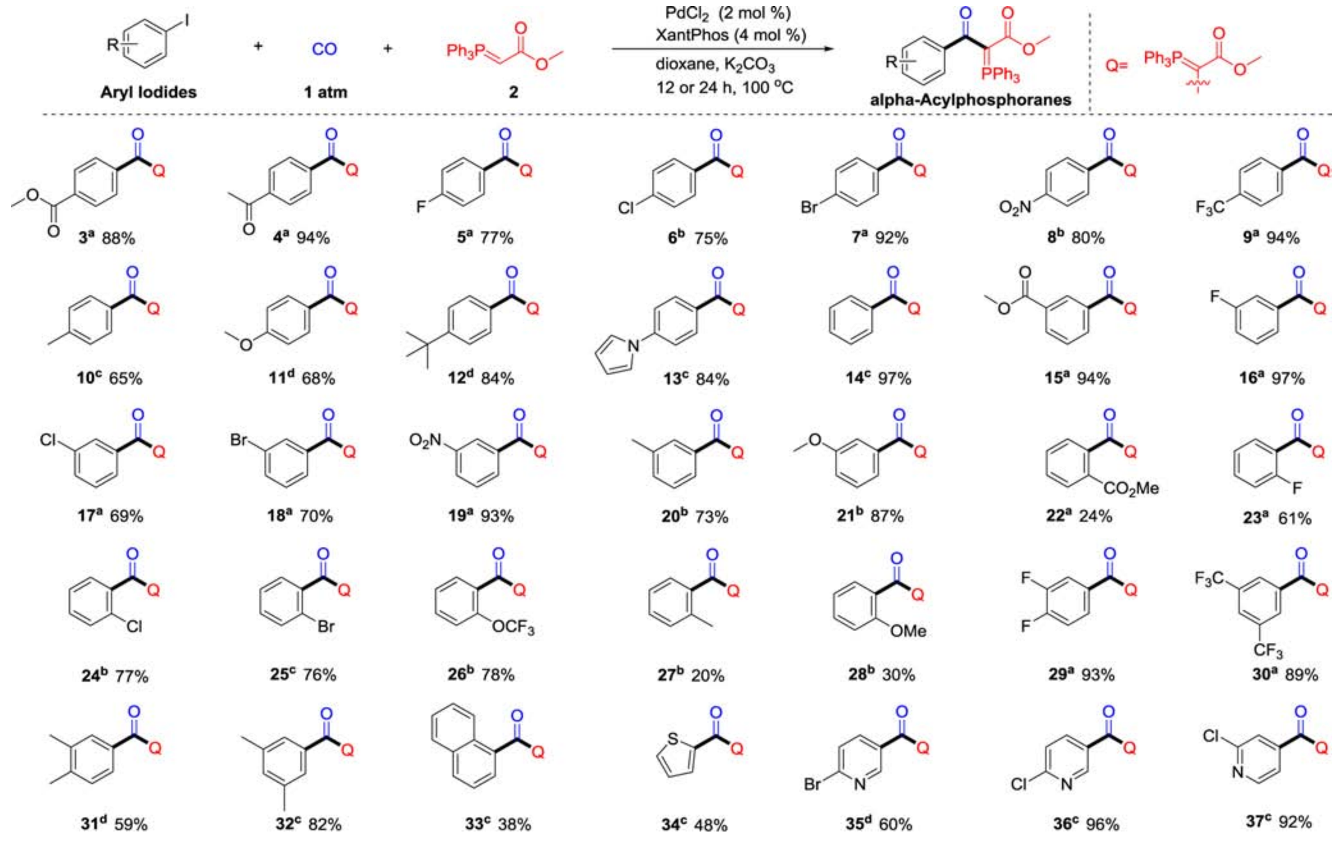
entry	cat.	ligand	base	yield (%)[b]
1	$Pd(OAc)_2$	PPh_3	DBU	45/34[c]
2[d]	$Pd(OAc)_2$	PPh_3	DBU	0
3	none	PPh_3	DBU	0
4	$Pd(OAc)_2$	none	DBU	36
5	$Pd(OAc)_2$	PPh_3	none	25
6	$Pd(OAc)_2$	XantPhos	K_2CO_3	76
7	$PdCl_2$	XantPhos	K_2CO_3	81
8[e,f]	$PdCl_2$	XantPhos	K_2CO_3	69
9[e,g]	$PdCl_2$	XantPhos	K_2CO_3	85
10[e,h]	$PdCl_2$	XantPhos	K_2CO_3	93
11[e,i]	$PdCl_2$	XantPhos	K_2CO_3	88

[a] **1** (0.5 mmol), **2** (0.5 mmol, 1 equiv), base (1 equiv), catalyst (2 mol %), and ligand (4 mol %) in 3 mL of solvent under CO (6 atm) at 100 °C for 12 h. [b] Yield determined by ^{1}H NMR with 1,3,5-trimethoxybenzene as internal standard. [c] Isolated yield. [d] Without CO. [e] CO (1 atm). [f] 0.8 equiv of **2**. [g] 1 equiv of **2**. [h] 1.2 equiv of **2**. [i] 1.4 equiv of **2**.

solvents were examined and dioxane was the best compared with other solvents.[23] Other reaction parameters, such as the CO pressure and the reaction temperature were also investigated. Delightfully, the reaction can work well under atmospheric CO pressure.[23] However, temperatures lower or higher than 100 °C reduced the yields of the target product.[23] Subsequently we varied the ratio of **1** to **2** and found that the yield of the target product **3** could rise to 93% when the ratio was 1/1.2 (Table 1, entries 8–11). These results led to the following optimized reaction conditions: **1** (0.5 mmol), **2** (1.2 equiv), 1 equiv of K_2CO_3 as the base, and 2 mol % of $PdCl_2$ and 4 mol % of XantPhos as the catalyst in 1,4-dioxane (3 mL) at 100 °C under CO (1 atm) for 12 h.

With the optimized reaction conditions in hand, the substrate scope of the carbonylation reaction was then explored. As summarized in Scheme 2, various aryl iodides equipped with diverse functional groups (ester, ketone, halogen, nitro, trifluoromethyl) were tolerated in this reaction. The reaction appears to be affected by the electronic properties of the para substituent of the aryl iodides with electron-withdrawing groups providing higher yields (Scheme 2, **3**–**13**). The protocol was found to work well when the substituent was at the meta position as well, in which case substrate bearing electron-withdrawing and -donating groups both afforded the corresponding α-acylphosphoranes in good to excellent yields (Scheme 2, **15**–**21**). However, the reaction of methyl 2-iodobenzoate, 1-iodo-2-methylbenzene, and 1-iodo-2-methoxybenzene (Scheme 2, **22**, **27**, **28**) resulted in poor yields, most likely because of the steric hindrance.[24] In contrast, aryl iodides bearing electron-withdrawing and relatively less sterically demanding ortho-halogen or ortho-trifluoromethoxy afforded

Scheme 2. Pd-Catalyzed Carbonylation of Aryl Iodides and Methyl 2-(Triphenylphosphoranylidene)acetate

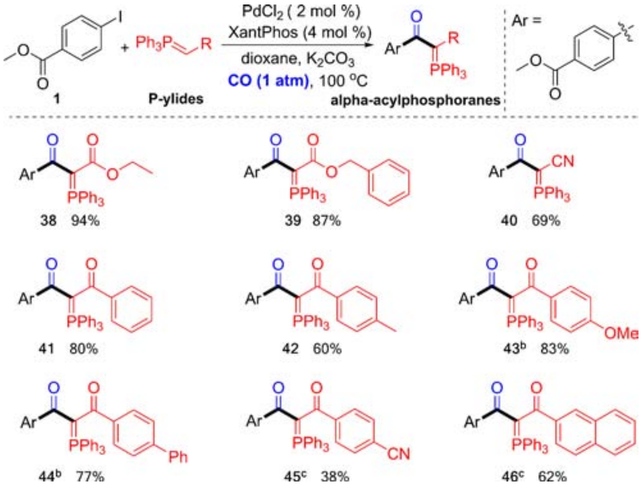


[a] $PdCl_2$ (0.01 mmol, 2 mol %), XantPhos (0.02 mmol, 4 mol %), aryl iodides (0.5 mmol, 1 equiv), **2** (0.6 mmol, 1.2 equiv), K_2CO_3 (0.5 mmol, 1 equiv), and dioxane (3 mL), CO (1 atm), 12 h, 100 °C; isolated yields. [b] **2** (0.8 mmol, 1.6 equiv), 12 h. [c] **2** (0.8 mmol, 1.6 equiv), 24 h. [d] **2** (1.0 mmol, 2 equiv), 24 h.

the target products in good yields (Scheme 2, **23**–**26**). Disubstituted aryl iodides were also tested, giving the corresponding products in good yields (Scheme 2, **29**–**32**). The substrate scope could also be extended to naphthyl or (hetero)aryl iodides, affording the corresponding products in moderate to excellent yields (Scheme 2, **33**–**37**). As shown in Scheme 2, prolonging the reaction time and increasing the amount of the reactant **2** could achieve high yields for the substrates with low activity, such as the aryl iodides carrying electron-donating groups and (hetero)aryl iodides.

Having demonstrated that the process is compatible with a wide range of aryl iodides, investigation of the scope with respect to stabilized phosphonium ylides was undertaken. Aside from the commercially available stabilized phosphonium ylides (Scheme 2 and Scheme 3, **38**), we also synthesized various stabilized phosphonium ylides on gram scale.[23] The α-acylphosphoranes derived from the carbonylation with these stabilized phosphonium ylides are summarized in Scheme 3. When the R group was CO_2Et, CO_2Bn, and cyano, the corresponding products were obtained in 94%, 87%, and 69% yields, respectively (Scheme 3, **38**–**40**). When the R group was PhCO, the target product was also obtained in high yields (Scheme 3, **41**). Electronic effects on the phenyl ring of the R unit affect the reaction yield significantly. Thus, whilst an electron-donating group such as methyl and methoxy gave moderate yields (Scheme 3, **42**–**43**), an electron-withdrawing group such as the cyano group decreased the yields to less than 40% (Scheme 3, **45**). This is in contrast to the effect observed with the aryl iodides and presumably reflects the ylide as a nucleophile while the aryl iodide as an electrophile.[25]

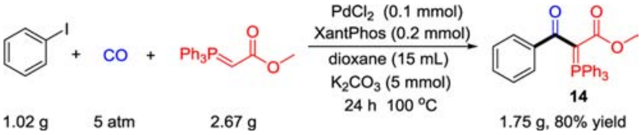
Scheme 3. Pd-Catalyzed Carbonylation of Methyl 4-Iodobenzoate 1 with Various Phosphonium Ylides[a]



[a] $PdCl_2$ (0.01 mmol, 2 mol %), XantPhos (0.02 mmol, 4 mol %), **1** (0.7 mmol, 1.4 equiv), P-ylides (0.5 mmol, 1 equiv), K_2CO_3 (0.5 mmol, 1 equiv), and dioxane (3 mL), CO (1 atm), 13 h, 100 °C; isolated yields. [b] 24 h. [c] **1** (1.0 mmol, 2 equiv), 24 h.

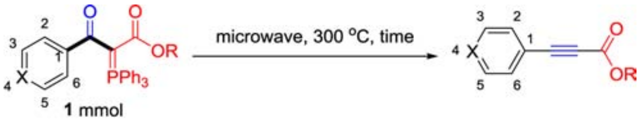
To demonstrate the utility of this palladium-catalyzed carbonylation, the reaction was carried out on gram scale. As shown in Scheme 4, methyl 3-oxo-3-phenyl-2-(triphenylphosphoranylidene)propanoate **14** was obtained in 80% isolated yield, showcasing the potential of the method in organic synthesis.

Scheme 4. A Gram-Scale Synthesis of 14



α-Acylphosphoranes have been applied to construct various highly valued compounds.[1−9] To highlight the utility of the products, we performed the transformation of α-acylphosphoranes into acetylenic esters, obtaining moderate to good yields (Scheme 5, **47**–**51**).[23] The acetylenic esters are important intermediates in organic synthesis. For instance, acetylenic esters **47** and **48** were vital substrates in the synthesis of α-pyrone derivatives found in various natural products,[26] and **47** and **49** were used in the synthesis of 2,3-diaryl-pyrazolo[1,5-*b*]pyridazines derivatives, which are potent and selective cyclooxygenase-2 inhibitors.[27] **51** is prepared for the first time with this methodology.

Scheme 5. Transformation of α-Acylphosphoranes to Acetylenic Esters



X = C, R = Me, 13 min	**47** (125 mg, 78%)
X = C, R = Et, 5 min	**48** (136 mg, 78%)
X = C, R = Me, 3-F,13 min	**49** (128 mg, 72%)
X = C, R = Me, 3-OMe, 8 min	**50** (91 mg, 48%)
X = N, R = Me, 3-Cl, 5 min	**51** (88 mg, 45%)

In summary, we have developed a new and efficient method for the preparation of α-acylphosphoranes. The palladium-catalyzed ylide carbonylation allows for the direct transformation of aryl iodides into the corresponding α-acylphosphoranes under atmospheric CO pressure. The wide scope, mild reaction conditions, and high yields showcase the potential of the method in chemical synthesis.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02278.

Experimental details and spectroscopic data for new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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