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A copper- and solvent-free coupling of acid chlorides with terminal alkynes catalyzed by a polystyrene-supported palladium(0) complex under aerobic conditions

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ABSTRACT

A polystyrene-supported palladium(0) complex [PS-dpp-Pd(0)] is an efficient catalyst for the copper- and solvent-free acylation of terminal alkynes with different acid chlorides in the presence of triethylamine as base, giving the corresponding ynones in good yields.

1. Introduction

α,β-Acetylenic carbonyl derivatives are compounds of considerable interest due to their occurrence in a wide variety of biologically active molecules and as key synthetic intermediates.[1] They have mainly been used for the preparation of important biologically active heterocycles.[2] Their preparation typically involves the reaction of alkynyl organometallic reagents of silver,[3] copper,[4] sodium,[5] lithium,[6] cadmium,[7] zinc,[8] silicon,[9] or tin[10] with acid chlorides. The direct coupling of alkynyl palladium reagents with acid chlorides is an important method for the preparation of alkynyl ketones. However, these methods require anhydrous solvents and inert atmospheres.[11]

The use of heterogeneous catalysts for coupling reactions leads to a reduction in waste. As such, highly active polymer-supported transition metal complexes have attracted significant interest because they can be easily recovered and reused.[12] As part of our continuing interest in palladium-catalyzed carbon–carbon cross-coupling reactions,[13] we recently reported a mild protocol for the copper-free Sonogashira coupling of aryl iodides with terminal alkynes under aerobic conditions.[14]

In this work, we describe a copper- and solvent-free method for the preparation of ynones via palladium-catalyzed reaction of terminal alkynes with various carboxylic acid chlorides, employing the heterogeneous palladium complex, [PS-dpp-Pd(0)] **1**[14] as the catalyst (Fig. 1) under aerobic conditions.

The catalytic activity of complex **1** (0.5 mol %) was studied at room temperature in a copper-free coupling reaction using *p*-chlorobenzoyl chloride and phenylacetylene (Tables 1 and 2).

We first tested the suitability of various solvents and bases for the coupling of *p*-chlorobenzoyl chloride with phenylacetylene (Table 1). *N*,*N*-Dimethylformamide and triethylamine proved to be good solvents for this coupling reaction (entries 1 and 10). Among the bases tested, triethylamine was the most efficient (entry 1). To our surprise, the highest yield of product was obtained when the reaction was performed under solvent-free conditions (Table 2). As shown in Table 2, when the reaction was performed with Et_3N as base, an excellent 98% yield of the product was obtained (entry 2). Increasing the amount of palladium catalyst (entry 5) and increasing the reaction time (entry 8) did not increase the yield of product further. A low palladium concentration resulted in a decreased yield (entry 6).

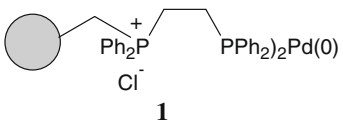

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Figure 1.

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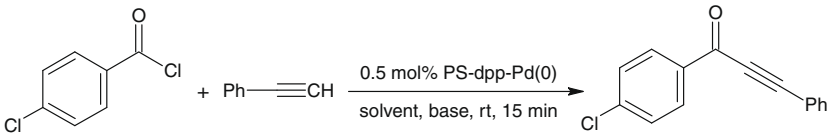
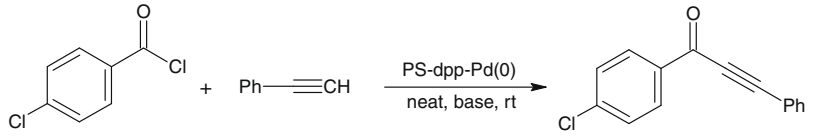
Table 1
Copper-free coupling reaction of *p*-chlorobenzoyl chloride with phenylacetylene in the presence of different bases and solvents[a]



Entry	Solvent	Base	Yield[b] (%)
1	DMF	Et_3N	92
2	DMF	DIPEA[c]	85
3	DMF	Pyridine	83
4	CH_3CN	Et_3N	80
5	CH_3CN	DIPEA	82
6	CH_3CN	Pyridine	77
7	Dioxane	Et_3N	75
8	Dioxane	DIPEA	72
9	Dioxane	Pyridine	78
10	Et_3N	—[d]	90
11	DIPEA	—[d]	88
12	Pyridine	—[d]	86

[a] Reaction conditions: *p*-chlorobenzoyl chloride (1.0 mmol), phenylacetylene (1.0 mmol), base (1.0 mmol), solvent (3 mL), room temperature and aerobic conditions.
[b] GC yield.
[c] Diisopropylethylamine
[d] Solvent employed as base.

Table 2
Copper- and solvent-free coupling reaction of *p*-chlorobenzoyl chloride with phenylacetylene in the presence of different bases[a]



Entry	Base	[PS-dpp-Pd(0)] (mol %)	Time (min)	Yield[b] (%)
1	DIPEA	0.5	15	96
2	Et_3N	0.5	15	98
3	Pyridine	0.5	15	95
4	Cs_2CO_3	0.5	15	94
5	Et_3N	1.0	15	98
6	Et_3N	0.2	15	92
7	Et_3N	0.5	30	98
8	Et_3N	0.5	60	98

[a] Reaction conditions: *p*-chlorobenzoyl chloride (1.0 mmol), phenylacetylene (1.0 mmol), base (1.0 mmol), room temperature and aerobic conditions.
[b] GC yield.

To examine the scope of this coupling reaction, various benzoyl chlorides **2** containing electron-withdrawing or electron-donating groups were coupled with different terminal alkynes **3** (Table 3). The results show that this reaction is equally facile with both electron-donating and electron-withdrawing substituents present on the aroyl chloride resulting in excellent yields of the corresponding ynones.

The stability of [PS-dpp-Pd(0)] was studied in recycling reactions of *p*-chlorobenzoyl chloride with phenylacetylene. The catalyst was separated from the reaction mixture by filtration after each experiment, washed with water and acetonitrile and dried carefully before use in subsequent runs. A yield of compound **4g** of 92% was obtained from the 10th catalyst recycle (Table 4, entry 3).

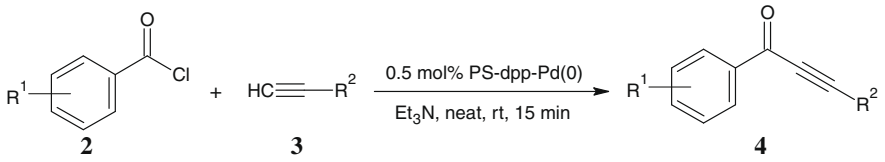
In conclusion, we have reported [PS-dpp-Pd(0)] as a reusable catalyst for the heterogeneous copper- and solvent-free synthesis of ynones at room temperature via coupling of various acid chlorides with terminal alkynes under aerobic conditions. The simple procedure, short reaction times, high selectivity and excellent isolated yields make this method well-suited for the generation of a combinatorial library of ynones.

2. Typical procedure for the preparation of 1-(4-chlorophenyl)-3-phenylpropynone (4g), (Table 3, entry 7)

A round-bottomed flask was charged with 4-chlorobenzoyl chloride (1.0 mmol), phenylacetylene (1.0 mmol), [PS-dpp-Pd(0)] (0.005 mmol) and Et_3N (1.0 mmol). The mixture was stirred at room temperature for 15 min under aerobic conditions. Upon completion of the reaction, the mixture was extracted with EtOAc (2×10 mL).

The organic layer was washed with water to remove the amine hydrochloride by-product. The organic layer was separated, dried over $MgSO_4$, filtered and concentrated under vacuum to afford the crude product. The residue was purified by column chromatography using $CHCl_3$–CH_3OH (98:2) as eluent to afford compound **4g**. Mp 105–106 °C; IR, ν (KBr): 2200, 1652 cm^{-1}; ^1H NMR δ (500 MHz, $CDCl_3$): 7.38–7.50 (m, 5H), 7.62–7.67 (m, 2H), 8.10 (d, 2H, $J = 8.70$); ^{13}C NMR δ (125 MHz, $CDCl_3$): 86.50, 93.44, 120.10, 128.54, 128.83, 130.65, 130.87, 132.90, 135.32, 140.56, 176.80. Anal. Calcd for $C_{15}H_9ClO$: C, 74.85; H, 3.77. Found: C, 74.68; H, 3.65.

Table 3
Copper- and solvent-free coupling reactions of various acyl chlorides with terminal alkynes[a]

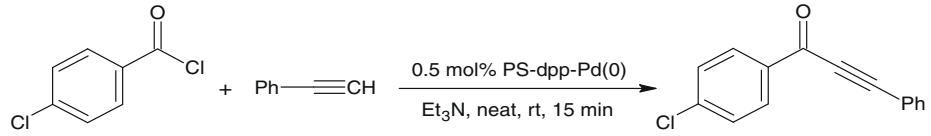


2 3 4

Entry	R^1	R^2	Product	Yield[b] (%)
1	H	Ph	**4a**	90
2	4-NO_2	Ph	**4b**	78
3	3-NO_2	Ph	**4c**	74
4	2-CH_3	Ph	**4d**	87
5	4-CH_3	Ph	**4e**	93
6	4-OCH_3	Ph	**4f**	87
7	4-Cl	Ph	**4g**	98
8	2-Cl	Ph	**4h**	95
9	H	*n*-C_4H_9	**4i**	97
10	4-NO_2	*n*-C_4H_9	**4j**	83
11	3-NO_2	*n*-C_4H_9	**4k**	80
12	2-CH_3	*n*-C_4H_9	**4l**	92
13	4-CH_3	*n*-C_4H_9	**4m**	94
14	4-OCH_3	*n*-C_4H_9	**4n**	90
15	4-Cl	*n*-C_4H_9	**4o**	92
16	2-Cl	*n*-C_4H_9	**4p**	94

[a] Reaction conditions: **2** (1.0 mmol), **3** (1.0 mmol), Et_3N (1.0 mmol), room temperature and aerobic conditions.
[b] GC yield.

Table 4
Copper-and solvent-free coupling reaction of *p*-chlorobenzoyl chloride with phenylacetylene catalyzed by the recycled catalyst[a]



Entry	Cycle	Yield[b] (%)
1	1	98
2	5	96
3	10	92

[a] Reaction conditions: *p*-chlorobenzoyl chloride (1.0 mmol), phenylacetylene (1.0 mmol), triethylamine (1.0 mmol), room temperature and aerobic conditions.
[b] GC yield.

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