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Using Pd–salen complex as an efficient catalyst for the copper- and solvent-free coupling of acyl chlorides with terminal alkynes under aerobic conditions

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Abstract

The palladium–salen complex palladium(II) *N*,*N*′-bis{[5-(triphenylphosphonium)-methyl]salicylidene}-1,2-ethanediamine chloride was found to be a highly active catalyst for the copper- and solvent-free coupling reaction of terminal alkynes with different acyl chlorides in the presence of triethylamine as base, giving excellent ynones under aerobic conditions.

Keywords: Copper-free; Ynones; Pd–salen complex; Neat

Alkynyl ketones appear in many biologically active molecules [1], and play crucial roles as intermediates in the synthesis of natural products [2] and drug-like molecules [3]. They have mainly been used in the preparation of heterocyclic derivatives such as pyrroles [4], furans [5], and quinolines [6]. Their preparation typically involves reaction of alkynyl organometallic reagents such as silver [7], and tin [8] with acyl chlorides. An alternative method for the synthesis of alkynyl ketones is the transition metal-catalyzed coupling of terminal alkynes or metalated derivatives with organic halides in the presence of carbon monoxide [9]. The direct coupling of alkynyl palladium reagents with acyl chlorides is an important method for the preparation of alkynyl ketones. However, these methods require anhydrous solvents and an inert atmosphere [10]. Moreover, these reactions need degassed organic solvents, and have to be carried out under an inert atmosphere. This is particularly inconvenient when the reactions are carried out in multiple vessels for library generation. Therefore, the development of a convenient method is an important objective in this effort. Taking these into consideration, we decided to concentrate on developing a new palladium catalyst which is highly active and air-stable. Our goal was to keep the reaction effective in the absence of solvent and copper salts as a co-catalyst under aerobic conditions.

Palladium(II) salts with bidentate N,O-ligands have proven to be efficient catalysts for C–C bond-forming reactions. [11] As part of our continuing interest in palladium catalyzed carbon–carbon cross-coupling reactions [12],

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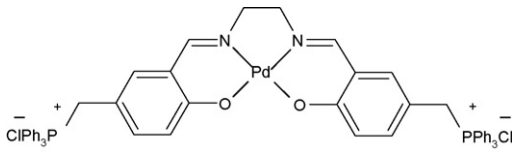


Fig. 1. The structure of compound **1**.

we have recently reported a mild protocol for the copper-free Sonogashira coupling reactions catalyzed by the Pd–salen complex under aerobic conditions [13].

In this paper, we wish to report the development of a mild protocol for the copper- and solvent-free coupling reaction of terminal alkynes with various acyl chlorides under aerobic conditions with the Palladium(II) *N*,*N*′-bis{[5(triphenylphosphonium)methyl]salicylidene}-1,2-ethanediamine chloride **1** [13] as catalyst (Fig. 1).

1. Experimental

A round-bottom flask was charged with acyl chloride (1.0 mmol), a terminal alkyne (1.0 mmol), Pd–salen complex (0.01 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 reaction mixture was extracted with EtOAc (2 × 10 mL). The organic layer was washed with water to remove the amine hydrochloride formed. The organic layer was separated, dried over $MgSO_4$, filtered, and concentrated under vacuum to obtain the crude product. The residue was purified by column chromatography using hexane/ethyl acetate (20:1) as eluent to afford the product [14].

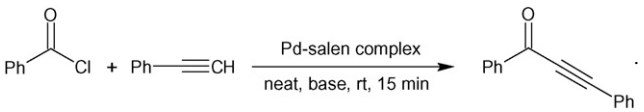
2. Result and discussion

The catalytic activity of palladium–salen complex **1** (1 mol%) was studied at room temperature under aerobic conditions in a copper- and solvent-free coupling reaction using acyl chlorides and terminal alkynes.

As a starting point for the development of the methodology, we chose to study the coupling of phenylacetylene with benzoyl chloride. Our optimization data is shown in Table 1. First several bases were screened for the coupling reaction in the presence of a catalytic amount of the Pd–salen complex. As shown in Table 2, dioxan proved to be a good solvent for this coupling reaction, and among the bases tested, triethylamine was the most efficient (entry 10).

To our surprise, under solvent-free conditions, the highest yield of product was obtained when the reaction was performed (Table 1). As shown in Table 1, when the reaction was performed with Et_3N as base, an excellent 97% yield

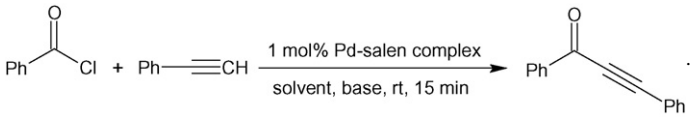
Table 1
Copper- and solvent-free coupling reaction of benzoyl chloride with phenylacetylene in the presence of different bases[a]



Entry	Base	Pd–salen complex (mol%)	Time (min)	Yield[b] (%)
1	Et_3N	1	15	97
2	DIPEA	1	15	84
3	pyridine	1	15	76
4	Cs_2CO_3	1	15	80
5	K_2CO_3	1	15	82
6	Et_3N	2	15	97
7	Et_3N	0.5	15	70
8	Et_3N	1	30	97
9	Et_3N	1	60	97

[a] Reaction conditions: benzoyl chloride (1.0 mmol), phenylacetylene (1.0 mmol), base (1.0 mmol), room temperature, aerobic conditions.
[b] GC yield.

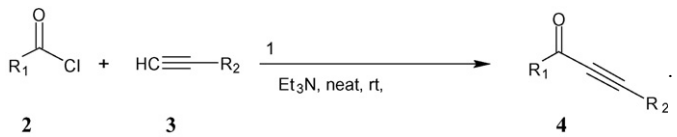
Table 2
Copper-free coupling reaction of benzoyl chloride with phenylacetylene in the presence of different base solvent[a]



Entry	Solvent	Base	Yield[b](%)
1	DMF	Et_3N	63
2	DMF	DIPEA[c]	54
3	DMF	Pyridine	46
4	CH_3CN	Et_3N	48
5	CH_3CN	DIPEA	42
6	CH_3CN	Pyridine	35
7	THF	Et_3N	70
8	THF	DIPEA	54
9	THF	Pyridine	46
10	Dioxane	Et_3N	78
11	Dioxane	DIPEA	75
12	Dioxane	Pyridine	64
13	Toluene	Et_3N	73
14	Toluene	DIPEA	69
15	Toluene	Pyridine	61
16	Pyrrolidine	—[d]	52

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

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



Entry	R^1	R^2	Product	Yield[b] (%)
1	Ph	Ph	**4a**	97
2	4-Cl-C_6H_4-	Ph	**4b**	85
3	4-MeO-C_6H_4-	Ph	**4c**	93
4	4-Me-C_6H_4-	Ph	**4d**	98
5	4-NO_2-C_6H_4-	Ph	**4e**	87
6	Cyclohexyl	Ph	**4f**	88
7	2-thiophene	Ph	**4g**	92
8	Ph	n-C_4H_9	**4h**	75
9	4-MeO-C_6H_4-	n-C_4H_9	**4i**	80
10	2-Me-C_6H_4-	n-C_4H_9	**4j**	85
11	Ph	n-C_6H_{13}	**4k**	69
12	4-MeO-C_6H_4-	n-C_6H_{13}	**4l**	75
13	4-Me-C_6H_4-	n-C_6H_{13}	**4m**	79
14	4-Cl-C_6H_4-	n-C_6H_{13}	**4n**	76

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

of the product was obtained (entry 1). Increasing the amount of palladium catalyst (entry 6) 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 7). Using the optimized reaction conditions, we explored the general applicability of the Pd–salen complex **1** with various benzoyl chlorides **2** containing electron-withdrawing or electron-donating groups and different terminal alkynes **3** (Table 3). Table 3 shows that the 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. Cyclohexane acid chloride also afforded the desired product in 88% yield (entry 6). A hetero-aryl acyl chloride such as 2-thiophene carbonyl chloride (entry 7) reacted smoothly with phenyl acetylene to give the products in 92% yield. The reaction was sluggish in the case of the aliphatic alkyne 1-octyne (entry 11), giving a relatively lower yield.

In conclusion, we showed that the air stable palladium–salen complex **1** efficiently catalyzed the copper- and solvent-free coupling reaction of various acyl chlorides with terminal alkynes under aerobic conditions. The simple procedure, short reaction time, high selectivity, and excellent isolated yields make this method well-suited for the generation of a combinatorial library of ynones.

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[14] Spectroscopic data **4a**: MP 45–46 °C (Lit. [15]) 46–48 °C; IR (KBr) (max cm^{-1}): 2200, 1642. ^1H NMR (500 MHz, $CDCl_3$): δ 7.45–7.70 (m, 8H), 8.22–8.26 (m, 2H). **4b**: MP 104–105C (Lit. [16]) 105–106C; IR (KBr) (max cm^{-1}): 2202, 1660. ^1H NMR (500 MHz, $CDCl_3$): δ 7.42–7.50 (m, 5H), 7.62–7.70 (m, 2H), 8.20 (d, 2H, J = 8.6 Hz). **4c**: MP 98–99 °C (Lit. [16]) 99 °C; IR (KBr) (max cm^{-1}): 2200, 1635. ^1H NMR (500 MHz, $CDCl_3$): δ 3.85 (s, 3H), 6.95 (d, 2H, J = 9.0 Hz), 7.41–7.51 (m, 3H), 7.65–7.69 (m, 2H), 8.18 (d, 2H, J = 8.9 Hz). **4d**: MP 69–70 °C (Lit. [17]) 70 °C; IR (KBr) (max cm^{-1}): 2203, 1640, 1610, 1570. ^1H NMR (500 MHz, $CDCl_3$): δ 2.43 (s, 3H), 7.30-7.42 (m, 5H), 7.68 (d, 2H, J = 8.6 Hz), 8.15 (d, 2H, J = 8.7 Hz). **4e**: MP 160–162 °C (Lit. [16]) 162–163 °C; IR (KBr) (max cm^{-1}): 2200, 1650, 1510, 1340. ^1H NMR (500 MHz, $CDCl_3$): δ 7.49–7.83 (m, 5H), 8.42 (s, 4H). **4f**: Colorless oil; [16] IR (neat (max cm^{-1}): 2200, 1660. ^1H NMR (500 MHz, $CDCl_3$): δ 1.20–2.14 (m, 10H), 2.42–2.55 (m, 1H), 7.30–7.42 (m, 3H), 7.57–7.60 (m, 2H). **4g**: MP 54–55 °C (Lit. [18]) 53–54 °C; IR (KBr) (max cm^{-1}): 3010, 2200, 1622, 1410. ^1H NMR (500 MHz, $CDCl_3$): δ 7.18–7.22 (m, 1H), 7.35–7.50 (m, 3H), 7.64–7.72 (m, 3H), 8.03 (d, 1H, J = 2.9 Hz). **4h**: Colorless oil; [19] IR neat (max cm^{-1}): 2950, 2200, 1645. ^1H NMR (500 MHz, $CDCl_3$): δ 0.95 (t, 3H, J = 7.2 Hz), 1.44–1.54 (m, 2H), 1.60–1.70 (m, 2H), 2.50 (t, 2H, J = 7.2 Hz), 7.46–7.52 (m, 2H), 7.55–7.60 (m, 1H), 8.12–8.15 (m, 2H). **4i**: Colorless oil; [20] IR neat (max cm^{-1}): 2930, 2850, 2200. ^1H NMR (500 MHz, $CDCl_3$): δ 0.97 (t, 3H, J = 6.3 Hz), 1.44–150 (m, 2H), 1.56–1.67 (m, 2H), 2.44 (t, 2H, J = 6.2 Hz), 3.88 (s, 3H), 6.94 (d, 2H, J = 8.3 Hz), 8.16 (d, 2H, J = 6.6 Hz). **4j**: Colorless oil; [21] IR neat (max cm^{-1}): 2955, 2860, 2202, 1645. ^1H NMR (500 MHz, $CDCl_3$): δ 0.95 (t, 3 H, J = 6.1 Hz), 1.42–1.52 (m, 2H), 1.61–1.66 (m, 2H), 2.46 (t, 2H, J = 6.8 Hz), 2.65 (s, 3H), 7.21–7.26 (m, 1H), 7.34–7.43 (m, 2H), 8.20–8.24 (m, 1H). **4k**: Colorless oil; [16] IR neat (max cm^{-1}): 2230, 2200, 1650. ^1H NMR (500 MHz, $CDCl_3$): δ 0.82–1.75 (m, 11H), 2.55(t, 2H, J = 7.2 Hz), 7.45–7.52 (m, 2H), 7.55–7.61 (m, 1H), 8.12–8.16 (m, 2H). **4l**: Colorless oil; [17] IR neat (max cm^{-1}): 2930, 2850, 2199, 1640. ^1H NMR (500 MHz, $CDCl_3$): δ 0.96 (t, 3H, J = 6.4 Hz), 1.32–1.68 (m, 8H), 2.45 (t, 2H, J = 6.9 Hz), 3.83 (s, 3H), 6.92 (d, 2H, J = 8.2 Hz), 8.11 (d, 2H, J = 6.6 Hz). **4m**: Colorless oil; [17] IR neat (max cm^{-1}): 2950, 2940, 2198, 1640. ^1H NMR (500 MHz, $CDCl_3$): δ 0.90 (t, 3H, J = 7.1 Hz), 1.23–1.78 (m, 8H), 2.52 (t, 2H, J = 7.4 Hz), 7.26 (d, 2H, J = 8.3 Hz), 8.05 (d, 2H, J = 7.2 Hz). **4n**: Colorless oil; [17] IR neat (max cm^{-1}): 2930, 2855, 2240, 2200, 1642, 1595, 1576. ^1H NMR (500 MHz, $CDCl_3$): δ 0.92 (s, 3H), 1.22–1.75 (m, 8H), 2.54 (t, 2H, J = 7.2 Hz), 7.42 (d, 2H, J = 8.2 Hz), 8.10 (d, 2H, J = 8.2 Hz).

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