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Pd-catalyzed coupling reaction of acid chlorides with terminal alkynes using 1-(2-pyridylethynyl)-2-(2-thienylethynyl)benzene ligand

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ABSTRACT

In the presence of 1-(2-pyridylethynyl)-2-(2-thienylethynyl)benzene as a ligand, the direct synthesis of alkynones has accomplished by a Pd-catalyzed coupling reaction of acid chlorides with terminal acetylenes under mild conditions.

Alkynones are useful intermediate in organic synthesis, especially for the synthesis of cyclic compounds such as N-heterocycles,[1] furans,[2] and others,[3,4] though the synthetic methods of alkynones have not been developed markedly. A general procedure for the synthesis of alkynones has been established by using an oxidation of propargylic alcohols which are obtained from a nucleophilic addition reaction of anionic acetylide to aldehydes.[5] With regard to a transition-metal-catalyzed reaction, Sonogashira et al. reported that a direct coupling reaction of acid chlorides with terminal acetylenes afforded various alkynones directly under mild conditions.[6,7] Despite of the convenience of this method, the reaction often suffered from the formation of diynes, generated from terminal acetylenes due to the presence of Cu co-catalysts. From this viewpoint, there are some reports of Pd-catalyzed coupling reactions of acid chlorides with acetylenes under copper-free conditions.[8] Recently, we have reported a copper-free Sonogashira coupling reaction[9] using a rigid *trans*-spanning ligand **1** or **2** (Fig. 1). In the course of the study, we examined the direct synthesis of alkynones using *trans*-spanning ligands. Here, we disclose a Pd-catalyzed coupling reaction of acid chlorides with terminal acetylenes using 1-(2-pyridylethynyl)-2-(2-thienylethynyl)benzene (**3**) as a *trans*-spanning ligand.[9b,10]

First, we examined a coupling reaction of benzoyl chloride (**4a**) with 1-octyne (**5a**) using the ligand **3**. When a mixture of **4a** (0.6 mmol), **5a** (0.5 mmol), $PdCl_2(PPh_3)_2$ (0.01 mmol), **3** (0.01 mmol), and triethylamine (1.7 mmol) was stirred in acetonitrile (1.5 mL) at 40 °C, the desired coupling product **6a** was obtained in 56% yield (Table 1, entry 1). To optimize the reaction conditions, several solvents, bases, or catalysts were also examined. The use of diisopropylethylamine, pyridine, or K_2CO_3 as a base was not effective for this reaction (entries 2–4). Chloroform and toluene were found to be favorable solvents. When the reaction was conducted in chloroform or toluene, **6a** was obtained in 71% or 81% yields, respectively, though the reaction in DMF did not proceed at all (entries 5–7). In the presence of $Pd(PPh_3)_4$ or $Pd(OAc)_2$ as a catalyst, the desired coupling reaction proceeded to give **6a** in 72% or 44% yield, respectively (entries 8 and 9). From these results, the reaction conditions in entry 7 were employed as the optimized conditions unless otherwise noted.

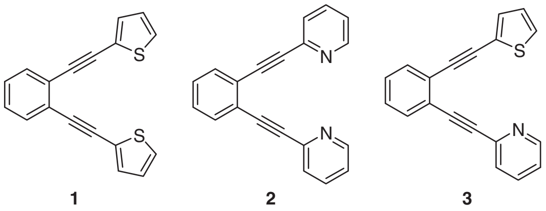

Figure 1. Rigid *trans*-spanning ligands.

Next, other *trans*-spanning ligands were employed under the optimized conditions (Scheme 1). In contrast to the result of the reaction using **3**, the use of ligand **1**, which would coordinate

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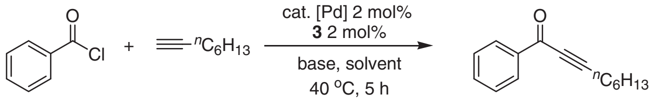
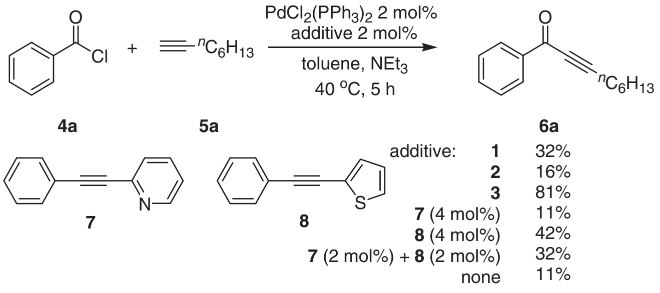
Table 1
Optimization of the reaction conditions



4a **5a** **6a**

Entry	Cat. [Pd]	Base	Solvent	Yield[a] (%)
1	$PdCl_2(PPh_3)_2$	NEt_3	CH_3CN	56
2	$PdCl_2(PPh_3)_2$	NEt^iPr_2	CH_3CN	ND
3	$PdCl_2(PPh_3)_2$	Pyridine	CH_3CN	9
4	$PdCl_2(PPh_3)_2$	K_2CO_3	CH_3CN	ND
5	$PdCl_2(PPh_3)_2$	NEt_3	DMF	ND
6	$PdCl_2(PPh_3)_2$	NEt_3	$CHCl_3$	71
7	$PdCl_2(PPh_3)_2$	NEt_3	Toluene	81
8	$Pd(PPh_3)_4$	NEt_3	Toluene	72
9	$Pd(OAc)_2$	NEt_3	Toluene	44

[a] Determined by ^{1}H NMR.

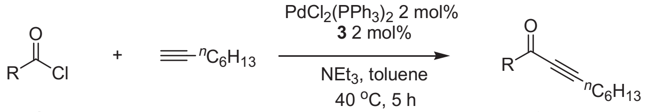


Scheme 1. Coupling reactions in the presence of ethynylbenzenes.

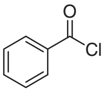
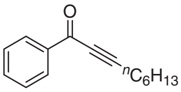
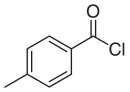
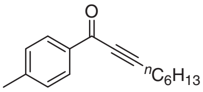
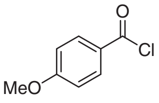
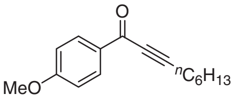
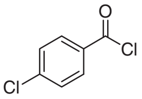
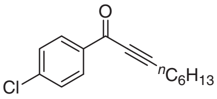
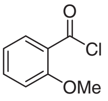
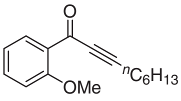
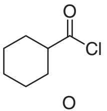
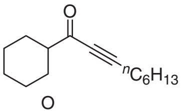
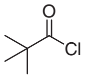
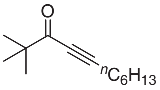
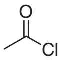
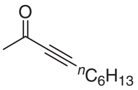
relatively weakly to palladium, or **2**, which would coordinate strongly, was found to be ineffective and most of the starting material **5a** was recovered. Both 2-(phenylethynyl)pyridine (**7**) and 2-(phenylethynyl)thiophene (**8**), which are the half structure of the bidentatable ligand **3**, were employed instead of **3** to give **6a** in 11% and 42% yields, respectively. Even when **7** and **8** were used simultaneously, an enhancement of the reactivity was not observed. This implied that the *trans*-bidentatable structure of the ligand was important for this coupling reaction. In the absence of any ligand, the desired product **6a** was obtained in 11% yield.

The reactions of various acid chlorides with 1-octyne were examined and the results were summarized in Table 2.[11] 4-Methylbenzoyl chloride (**4b**) showed good reactivity to give the corresponding product **6b** in 94% yield (entry 2). Both 4-methoxybenzoyl chloride (**4c**) and 4-chlorobenzoyl chloride (**4d**) were also converted into the corresponding products **6c** (99%) and **6d** (73%), respectively (entries 3 and 4). Unfortunately, the reaction of

Table 2
Coupling reaction using various acid chlorides

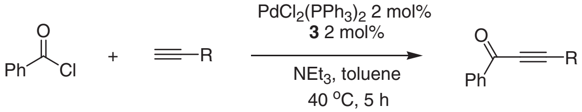


4 **5a** **6**

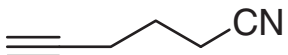
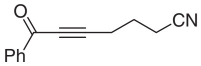
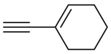
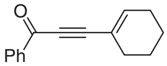
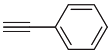
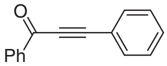
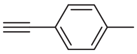
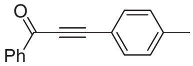
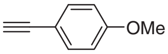
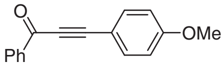
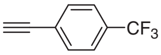
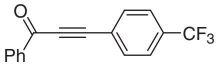
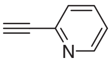
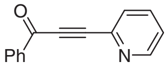
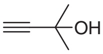
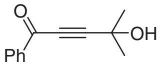
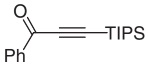
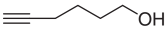
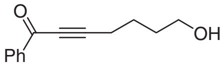
Entry	4	Product	Yield[a] (%)
1	 **4a**		**6a**, 78
2	 **4b**		**6b**, 94
3	 **4c**		**6c**, 99
4	 **4d**		**6d**, 73
5	 **4e**		**6e**, 15
6	 **4f**		**6f**, 77
7[b]	 **4g**		**6g**, 76
8	 **4h**		**6h**, Trace[c]

[a] Isolated yield.
[b] 80 °C, 17 h.
[c] Determined by ^{1}H NMR.

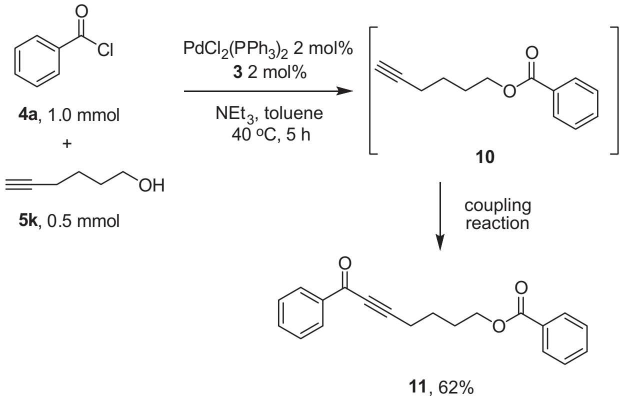
Table 3
Coupling reaction using various terminal acetylenes



4a **5** **9**

Entry	5		Product	Yield[a] (%)
1		**5b**		**9b**, 82
2		**5c**		**9c**, 68
3		**5d**		**9d**, 94
4		**5e**		**9e**, 85
5		**5f**		**9f**, 84
6		**5g**		**9g**, 85
7[b]		**5h**		**9h**, 39
8		**5i**		**9i**, 99
9		**5j**		**9j**, 71
10		**5k**		**9k**, Trace[c]

[a] Isolated yield.
[b] Ambient temperature, 2 h.
[c] Determined by ^{1}H NMR.



Scheme 2. A tandem esterification and coupling reaction of **5k**.

2-methoxybenzoyl chloride (**4e**) resulted in a formation of complex mixture including **6e** (15%) (entry 5). Aliphatic acid chloride such as cyclohexanecarboxylic acid chloride (**4f**) reacted with **5a** to give **6f** in good yield (77%) (entry 6). Although the reaction of sterically hindered pivaloyl chloride (**4g**) did not proceed at 40 °C, higher temperature (80 °C) and prolonged reaction time resulted in the formation of the corresponding product **6g** in 76% yield (entry 7). Acetyl chloride (**4h**) was found to be unsuitable for this reaction, and a complex mixture, including a trace amount of **6h**, was obtained (entry 8).

Next, the reactions of various terminal acetylenes with **4a** were examined. The results were summarized in Table 3.[11] 5-Hexynenitrile (**5b**) showed a good reactivity to give **9b** in good yield (entry 1). When 1-ethynylcyclohexene (**5c**) was employed as a conjugated enyne for this reaction, the corresponding coupling product **9c** was obtained in 68% yield (entry 2). Aromatic acetylenes, such as phenylacetylene (**5d**), 4-tolylacetylene (**5e**), 4-methoxyphenylacetylene (**5f**), and 4-trifluoromethylphenylacetylene (**5g**) were all favorable substrates and the corresponding products **9d**, **9e**, **9f**, and **9g** were obtained in high yields, respectively (entries 3–6). In contrast, the reaction of 2-ethynylpyridine (**5h**) with **4a** afforded the coupling product **9h** in relatively low yield (39%) (entry 7). A coordination of nitrogen atom in pyridine ring to the palladium might have inhibited the desired reaction. Both mono-protected alkynes, 2-methyl-3-butyn-2-ol (**5i**) and triisopropylsilyl acetylene (**5j**), reacted effectively with **4a** to give the corresponding alkynones **9i** and **9j**, which can be employed in further transformation after deprotection, in high yields, respectively (entries 8 and 9). In the case of the reaction of 5-hexyn-1-ol (**5k**) with **4a**, a trace amount of the desired product **9k** was detected (entry 10).[12] Interestingly, in this reaction an esterification of **4a** prior to the coupling reaction proceeded to afford an ester **10** and its coupling product **11** in 32% and 10% yields, respectively. Therefore, when the reaction was conducted by using 2 equiv of **4a**, a tandem esterification and the following coupling product **11** was obtained in 62% yield (Scheme 2).

Although a role of the *trans*-spanning ligand **3** is unclear, *trans*-[PdCl{C(=O)R}·**3**] complex, which would be formed after oxidative addition of acid chloride to palladium metal and the following isomerization from *cis*- to *trans*-form of complex by the aid of **3**, might be a key intermediate in the catalytic cycle.

In summary, we have developed the direct synthesis of the conjugated alkynones by the palladium-catalyzed coupling reaction of acid chlorides with terminal acetylenes using the rigid *trans*-spanning ligand **3**. Mechanistic studies to clarify the role of *trans*-spanning ligand are now in progress.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2012.01.105.

References and notes

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10. Unfortunately, we could not achieve the crystal structure analysis. However, DFT calculation indicated that *trans*-[Pd(PPh_3)$_2$·**3**] is comfortable than the *cis*-complex.
11. In most cases, neither diynes nor enynes, generated from **5**, were detected by ^{1}H NMR, whereas acid anhydrides, elaborated from acid chlorides, were observed.
12. Formation of the coupling product **9k** was confirmed by ^{1}H NMR, though it could not be isolated from the resulting reaction mixture.