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COMMUNICATION

Palladium/copper-cocatalyzed decarbonylative alkynylation of acyl fluorides with alkynylsilanes: Synthesis of unsymmetrical diarylethynes

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Palladium/copper-cocatalyzed decarbonylative alkynylation of acyl fluorides with alkynylsilanes is described. This reaction not only effectively inhibits the formation of undesired homocoupled products by avoiding the addition of the base, but also exhibits a wide substrate scope to provide a general access to diverse unsymmetrical diarylethynes.

Since Sonogashira-Hagihara (S-H) reaction[1] has been known as an effective method to prepare a variety of conjugated arylethynes and enynes, a large number of applications utilizing this reaction have been reported.[2] One of the purposes to optimize this protocol was to minimize the inevitable formation of homocoupled products that made the work-up process more tedious and the yields of the desired products lower.[3] To avoid the formation of homocoupled products, copper-free S-H reactions have been explored extensively.[4] Furthermore, the "sila"-S-H reactions employed trimethylsilylethynes as the coupling partner instead of conventional terminal alkynes, which succeeded in preventing the generation of undesired homocoupled products.[5-10] An array of reagents such as K_2CO_3,[5] CsF,[6] tetrabutylammonium chloride (TBAC),[7] and tetrabutylammonium fluoride (TBAF)[8] have been employed to activate trimethylsilylethynes in "sila"-S-H reactions. Besides, Ito and Hosomi,[9] and our group[10] disclosed that copper salts have specific reactivity for transmetalation, forming alkynylcopper species. More importantly, these reactions proceeded under the neutral conditions, which allows the base-sensitive functional groups to be tolerated.

In regard to the coupling partners in S-H reactions, general aryl or vinyl (pseudo)halides as well as sodium sulfonates,[11] arylhydrazines,[12] arylsulfonyl hydrazides,[13] and amides[14] have been employed. However, the development of other coupling partners derived from naturally abundant feedstocks is still highly demanded. Recently, since acyl fluorides have attracted much attention due to stability, ready availability from the corresponding carboxylic acids as well as their specific reactivity,[15] they have widely been applied in various transformations as an 'RCO'[16] or 'R' source[17-21] *via* non-decarbonylative or decarbonylative reaction pathway, respectively. In particular, since the decarbonylative trifluoromethylation of acid fluorides has been reported,[17] acyl fluorides showed unique reactivities which can participated in a large number of decarbonylative reactions, such as reduction,[18] Suzuki-Miyaura-type arylation,[19] and direct C–H arylation.[20] We also reported various decarbonylative transformations of acyl fluorides,[21] showing different reactivities from those of acyl chlorides. However, the construction of C(sp^2)–C(sp) bonds by decarbonylative alkynylation of acyl fluorides remains largely unexplored. We herein report the synthesis of unsymmetrical diarylethynes by Pd/Cu-cocatalyzed decarbonylative alkynylation of acyl fluorides with alkynylsilanes under the neutral conditions.

Initially, as a model reaction we conducted the reaction of benzoyl fluoride (**1a**) with (phenylethynyl)trimethylsilane (**2a**) under the $PdCl_2$ catalysis to optimize reaction conditions and the results are summarized in Table 1. Among a series of bidentate phosphorus ligands screened, 1,3-bis(diphenylphosphino)propane (DPPP) was the most efficient, giving diphenylethyne (**3aa**) in 58% GC yield (entries 1-3). In a sharp contrast, monodentate phosphine ligands gave poor yields of **3aa** (Table S1). Subsequently, the influence of pallidum catalysts was examined and a comparative yield of **3aa** was obtained when $Pd(OAc)_2$ (54%) and $Pd_2(dba)_3{\cdot}C_6H_6$ (56%) were employed. The combination of $Pd(PPh_3)_4$ or $PdCl_2(PPh_3)_2$ with 10 mol % of PPh_3, which showed a high activity in the former reports,[1,10] also had been tested, but only poor yield of **3aa** was observed (Table S2). Although the yield decreased as the DPPP loading decreased (entry 4), a comparable yield of 54% could be obtained even with 15 mol % of DPPP (entry 5). To our delight,

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† Electronic Supplementary Information (ESI) available: experimental procedures, spectroscopic data and copies of ^1H, $^{13}C\{^1H\}$ and $^{19}F\{^1H\}$ NMR spectra. See DOI: 10.1039/x0xx00000x

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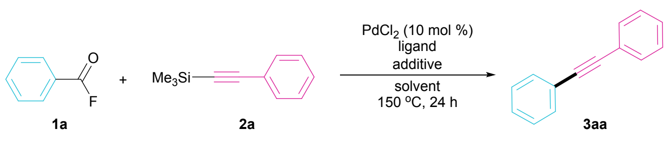
Table 1 Optimization of the reaction conditions[a]

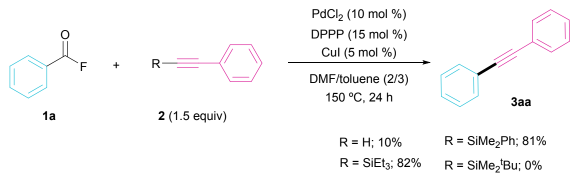


Entry	ligand	additive	solvent(s)	yield (%)[b]
1	DPPE	-	DMF	24
2	DPPP	-	DMF	58
3	DPPB	-	DMF	27
4[c]	DPPP	-	DMF	9
5[d]	DPPP	-	DMF	54
6[d]	DPPP	-	DMF/toluene (2/3)	74
7[d]	DPPP	CuI	DMF/toluene (2/3)	99
8[d,e]	DPPP	CuI	DMF/toluene (2/3)	89
9[d,e,f]	DPPP	CuI	DMF/toluene (2/3)	98 (84)
10[d,e,f,g]	DPPP	CuI	DMF/toluene (2/3)	14

[a] Conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), $PdCl_2$ (0.02 mmol), ligand (0.04 mmol), CuI (0.02 mmol), solvent (1 mL), 150 ºC, 24 h. [b] GC yields using 1-tetradecene as an internal standard and an isolated yield is shown in parentheses. [c] DPPP (0.02 mol). [d] DPPP (0.03 mmol). [e] **2a** (0.3 mmol). [f] CuI (0.01 mmol). [g] Benzoyl chloride instead of benzoyl fluoride.

after several optimization of the solvents (Table S4), a mixed solvent system of DMF and toluene in a 2:3 ratio increased the yield of **3aa** to 74% (entry 6). Furthermore, 10 mol % of CuI as the additional catalyst dramatically improved the yield of **3aa** (entry 7). A series of additives, such as $PhCO_2Li$, $PhCO_2Na$, and $PhCO_2K$ proved to be less efficient than CuI (Table S5). With a decrease of the amount of **2a** to 1.5 equiv, **3aa** was obtained in 89% yield (entry 8). Although the copper sources were screened, CuI was found to be the best (Table S6). Since the decreased loading of CuI to 5 mol % also resulted in 98% yield of **3aa**, the conditions in entry 9 was adopted to be optimum. It is worth noting that when benzoyl chloride was employed instead of benzoyl fluoride, only 14% of **3aa** was detected, which demonstrated the unique nature of acyl fluorides in the present decarbonylative alkynylation (entry 10). It is noteworthy to mention that no formation of alkynylketones without decarbonylation was observed in all cases.

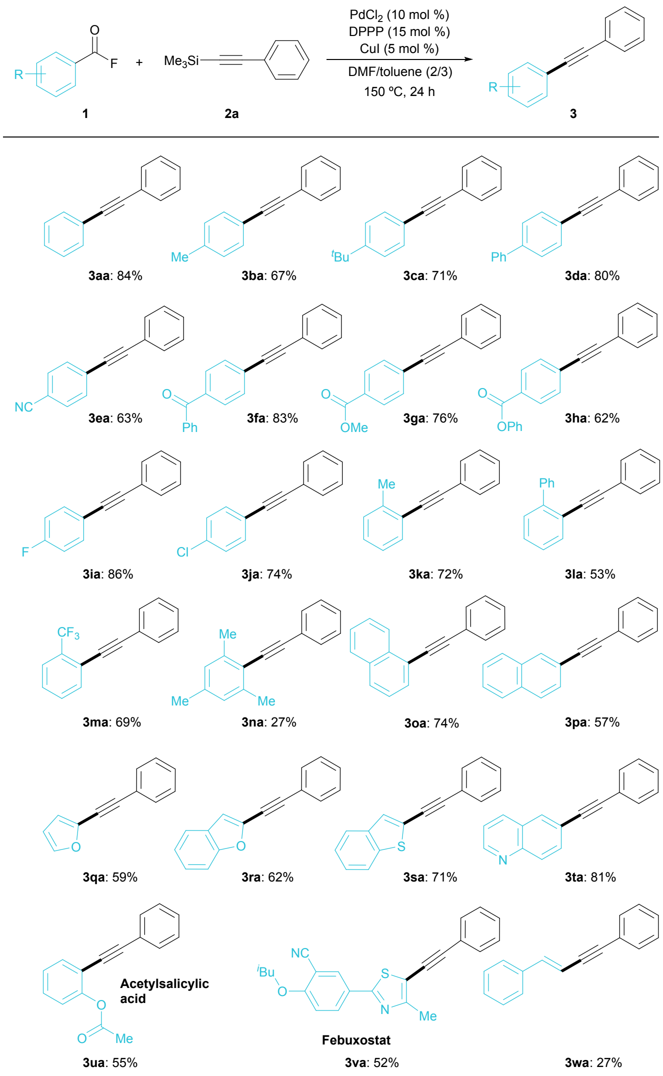
Next, we investigated the effect of substituents on alkynes. As shown in Scheme 1, when the reaction was conducted with a terminal alkyne (R = H), only 10% yield of **3aa** was obtained. The other silyl groups were also evaluated. As a result, as steric bulk of silyl groups increases, the reactivity slightly decreased to give **3aa** in 82% ($SiEt_3$) and 81% ($SiMe_2Ph$) yields. In a sharp contrast, when the bulkier $SiMe_2{}^tBu$ group was employed, no desired product was formed, indicating that the steric hindrance of the substituents might retard the coordination of copper to a triple bond in **2** and the subsequent transmetalation, forming alkynylcopper (I) species.



Scheme 1 The influence of substituents on alkynes. [a] Reaction conditions: **1** (0.2 mmol), **2** (0.3 mmol), $PdCl_2$ (0.02 mmol), DPPP (0.03 mmol), CuI (0.01 mmol), in DMF/toluene (2:3, 0.4 M) at 150 ºC for 24 h under Ar. GC yields using 1-tetradecene as an internal standard.

With the optimized reaction condition in hand, we performed the reactions of various acyl fluorides **1** with **2a** (Table 2). Aa a result, the desired unsymmetrical diarylethynes **3ba**-**3ha** bearing electron-donating or –withdrawing groups in the *para*-position were obtained in moderate to good yields. Accordingly, acyl fluorides **1** bearing fluoride and chloride groups could also be compatible for this transformation; **3ia** and **3ja** could be obtained in 86% and 74% yields, respectively. Furthermore, under the identical conditions, the steric effect was investigated with **1** bearing Me, Ph, and CF_3 substituents in the *ortho*-positions, which gave the products in 53-72% yields. However, 2,4,6-trimethylbenzoyl fluoride having a higher steric bulk, only 27% of **3na** was obtained.

Table 2 Scope of acyl fluorides[a]



[a] Reaction conditions: **1** (0.2 mmol), **2a** (0.3 mmol, 1.5 equiv), $PdCl_2$ (0.02 mmol), DPPP (0.03 mmol), CuI (0.01 mmol), in DMF/toluene (2:3, 0.4 M) at 150 ºC for 24 h under Ar. Isolated yields.

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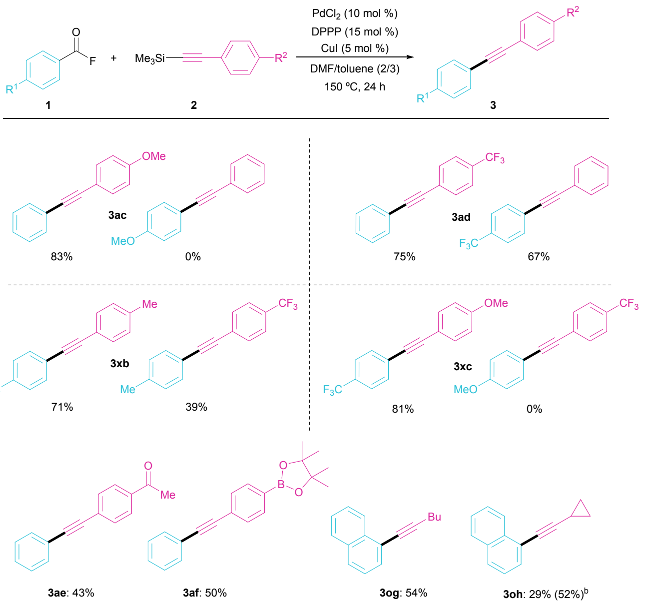
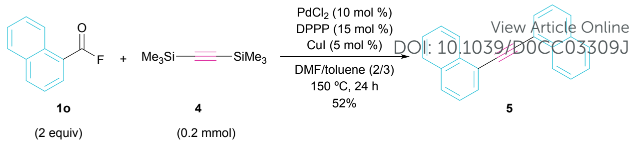
Besides, the cross-coupled products with polycyclic (**3oa**-**3pa**) and heterocyclic (**3qa**-**3ta**) scaffolds were afforded in moderate to high yields. In regard to the demonstration of the present reaction, acyl fluorides derived from biologically active molecules (**3ua**-**3va**) were also suitable substrates. We also tried to extend the scope of acyl fluorides to cinnamoyl fluoride (**1w**), but only 27% of conjugated enynes **3wa** was obtained. Unfortunately, benzoyl fluorides **1** bearing an OMe, NO_2, NMe_2, or Br group in the 4-position were not compatible in this reaction (see, ESI).

In order to elucidate an electronic effect of the substituents on the coupling partners **1** and **2**, we performed a series of substrate combinations that afford the identical products. As shown in Table 3, acyl fluorides **1** with electron-neutral and -withdrawing groups gave higher yield than that with electron-donating groups, indicating that electronically poor acyl fluorides can render oxidation addition to Pd(0) much easier, leading to the higher yields of **3**. To our surprise, when an acyl fluoride bearing an OMe group was employed, no trace of the desired products **3ac** and **3xc** were detected, along with the formation of **3aa** and **3ad** (up to 15% yield), which might be generated from the Ph-group transfer between acyl fluorides and the 1,3-bis(diphenylphosphino)propane (DPPP) ligand.[22] Whereas alkynylsilanes **2** with an OMe group could afford **3ac** and **3xc** in 83% and 81% yields, respectively. On the contrary, alkynylsilanes **2** with electron-deficient groups gave **3xb** and **3ae** in lower yield. We assumed that electron-rich alkynylsilanes can accelerate the coordination of copper to a triple bond in **2** to facilitate the transmetalation. These results suggest that the choice of the substrates is highly important for the success of complementary synthesis of the target molecules.

Table 3 Scope of alkynylsilanes[a]



[a] Reaction conditions: **1** (0.2 mmol), **2** (0.03 mmol 1.5 equiv), $PdCl_2$ (0.02 mmol), DPPP (0.03 mmol), CuI (0.01 mmol), in DMF/toluene (2:3, 0.4 M) at 150 ºC for 24 h under Ar. Isolated yields.

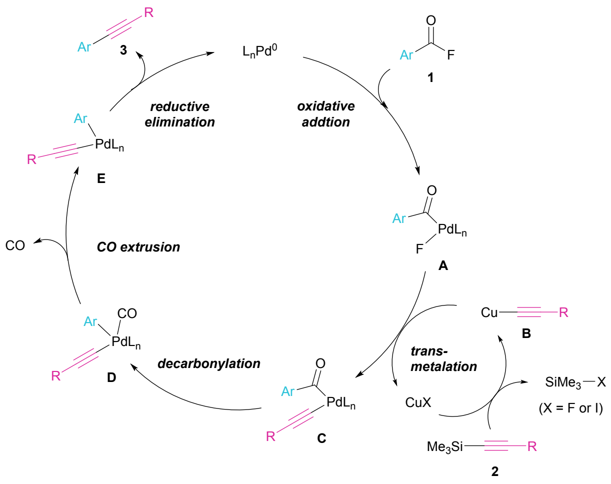


Scheme 2 Reaction of Benzoyl Fluoride with Bis(trimethylsilyl)acetylene. [a] Reaction conditions: **1o** (0.4 mmol), **4** (0.2 mmol), $PdCl_2$ (0.02 mmol %), DPPP (0.03 mmol), CuI (0.01 mmol), in DMF / toluene (2:3, 0.4 M) at 150 ºC for 24 h under Ar.

Because of non-basic conditions, the base-sensitive substrates could be tolerated to afford **3af** in 50% yield. Besides, aliphatic alkynylsilanes were also compatible to give **3og** and **3oh**, albeit in moderate yields. We successfully attained a large-scale synthesis by the reaction of **1a** with trimethyl(4-tolylethynyl)silane, giving 1.10 g of **3ba** in 57% yield.

In the "Sila"-S-H reactions, a $SiMe_3$ group not only can work as a directly reactive group for transmetalation with a copper salt, but can help us to handle volatile compounds. Based on this idea, we utilized a commercially available bis(trimethylsilyl)ethyne (**4**) as the ethyne gas surrogate (Scheme 2). The reaction **4** with 2 equiv of acyl fluoride **1o** gave **5** in 52% yield. This synthetic method demonstrated convenient usage of **4** for the synthesis of symmetrical diarylethynes.

Combining all the fundamental reactions reported in the catalytic cycle,[2,10,17,23] a plausible reaction mechanism is shown in Scheme 3. Initially, acyl fluorides **1** are subjected to oxidative addition with Pd(0) via C–F bond cleavage to provide complex **A**. Meanwhile, transmetalation between alkynylsilanes **2** and a copper salt takes place to form alkynylcopper species **B**.[24] Sequentially, a second transmetalation between **A** and **B**, which might be the rate-determining step, affords an acyl(alkynyl)palladium(II) complex **C**. The formation of intermediate **D** by decarbonylation from **C**, followed by CO extrusion from **D** may occur to produce intermediate **E**, from which reductive elimination produces the cross-coupled product **3**, regenerating the initial Pd(0) catalyst. Considering the result shown in Table 1, entry 6, where the product was obtained in 74% yield even in the absence of CuI, a direct transmetalation between the intermediate **A** and alkynylsilanes **2** certainly takes place with the assistance of the thermodynamically stable Si–F bond formation.[17,18]



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Scheme 3 Plausible catalytic cycle.

In conclusion, we have developed Pd/Cu-cocatalyzed decarbonylative alkynylation of various acyl fluorides with ether, halo, cyano, ketone, and ester functional groups and nitrogen, oxygen, sulfur-containing heterocyclic compounds in moderate to good yield. To clarify the orders of transmetalation and decarbonylation in the catalytic cycle, further mechanistic studies by isolating the intermediate complexes and by detailed DFT calculations are currently underway in our laboratory.

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Conflicts of interest

There are no conflicts to declare.

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