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Palladium-Catalyzed Regio- and Stereoselective Chlorothiolation of Terminal Alkynes with Sulfenyl Chlorides

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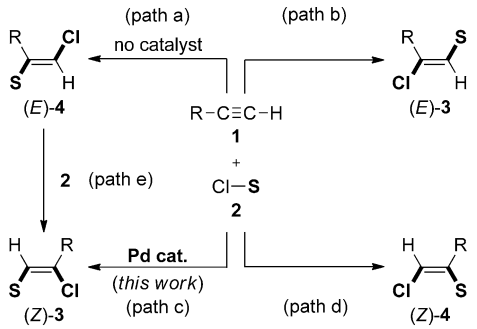
Abstract: Chlorothiolation of terminal alkynes with sulfenyl chlorides yields *anti*-adducts without transition-metal catalysts. In sharp contrast, transition-metal-catalyzed chlorothiolation has not been developed to date, possibly because organosulfur compounds can poison catalyst. Herein, the regio- and stereoselective palladium-catalyzed chlorothiolation of terminal alkynes with sulfenyl chlorides is described. *syn*-Chlorothiolation offers a complementary synthetic route to chloroalkenyl sulfides. 2-Chloroalkenyl sulfides can easily be transformed into various sulfur-containing products, most of which are often found in natural products and pharmaceuticals.



Scheme 1. Chlorothiolation of alkynes.

Addition of organosulfur compounds to alkynes is a straightforward synthetic approach to highly functionalized alkenyl sulfides that are a valuable and important class of compounds in organic synthesis.[1] Among them, successful additions of various carbon–sulfur bonds to alkynes (carbothiolation) have been developed with palladium, platinum, and rhodium catalysts in the past two decades.[2] Chlorothiolation of alkynes has also been studied for many years[3] because the chlorothiolation adducts, 2-chloroalkenyl sulfides, are versatile alternatives to the carbothiolation adducts, which can be converted into various complex alkenyl sulfides by further transformations. However, it is still difficult to control regio- and stereoselectivities of chlorothiolation. In principle, chlorothiolation of sulfenyl chlorides **2** across terminal alkynes **1** could give four regio- and stereoisomers, that is, (*E*)/(*Z*)-**3** and (*E*)/(*Z*)-**4** (Scheme 1). Although *anti*-addition can proceed without any transition-metal catalysts and gives (*E*)-2-chloroalkenyl sulfides (*E*)-**4** as sole products (path a)[3] and the formed adduct (*E*)-**4** prepared was reported to isomerize to (*Z*)-**3** in the presence of a catalytic amount of **2** (path e),[3d] only 3,3-dimethyl-1-butyne could be used in this reaction, and long isomerization time (1–3 days) is required. Therefore, a complementary, and more practical synthetic approach to other chlorothiolation adducts (*E*)/(*Z*)-**3** and (*Z*)-**4** (paths b–d) under mild conditions has been highly desirable. Meanwhile, as another example of the addition of chlorine–sulfur bonds to alkynes, transition-metal-catalyzed chlorosulfonylation of alkynes has been known to provide the corresponding adducts with high regio- and stereoselectivities. More recently, Nakamura and co-workers have investigated the iron-catalyzed chlorosulfonylation that delivers *anti*-addition via a radical pathway (path b).[4,5] In addition, the copper-catalyzed chlorosulfonylation has been communicated to afford *syn*-adducts (path c).[6] These examples prompted us to investigate the transition-metal-catalyzed chlorothiolation of alkynes, because it is difficult to prepare the resulting (*Z*)-**3** by reduction of the corresponding alkenyl sulfones synthesized by the copper-catalyzed chlorosulfonylation.[7] Herein, we report the highly regio- and stereoselective addition of sulfenyl chlorides **2** to terminal alkynes **1** under palladium catalysis to yield (*Z*)-2-chloroalkenyl sulfides (*Z*)-**3** with a high efficiency, according to path c.

We found that phenylacetylene (**1a**) reacted with benzenesulfenyl chloride (**2a**) in the presence of 10 mol% of Pd(tfa)$_2$ (tfa = trifluoroacetate) in toluene at 25 °C to give (*Z*)-2-chloro-2-phenylethenyl phenyl sulfide ((*Z*)-**3a**) in 84% yield, as determined by NMR spectroscopy, with high regio- and stereoselectivities (Table 1, entry 1). The reaction was completed within 2 h, while a prolonged reaction time of

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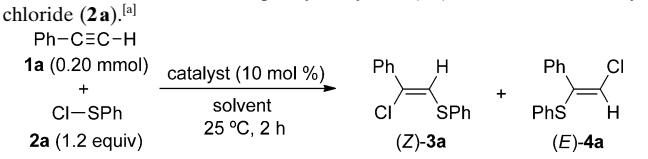
Table 1. Chlorothiolation of phenylacetylene (**1a**) with benzenesulfenyl chloride (**2a**).[a]

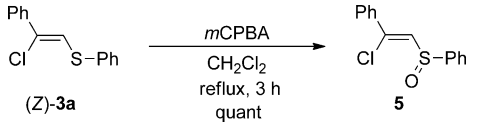


Entry	Catalyst	Solvent	Yield [%][b]	
			(*Z*)-**3a**	(*E*)-**4a**
1	$Pd(tfa)_2$	toluene	84 (79)	3
2[c]	$Pd(tfa)_2$	toluene	73	4
3	none	toluene	0	13
4[d]	none	toluene	0	67
5	$Pd(OAc)_2$	toluene	58	<1
6	$Pd(dba)_2$	toluene	36	<1
7	$PdCl_2$	toluene	10	5
8	CuCl	toluene	0	7
9	$CuCl_2$	toluene	0	11
10	$Pd(tfa)_2$	1,4-dioxane	67	0
11	$Pd(tfa)_2$	benzene	63	2
12	$Pd(tfa)_2$	EtOAc	63	2
13	$Pd(tfa)_2$	CH_2Cl_2	39	27
14	$Pd(tfa)_2$	hexane	5	5

[a] Conditions: **1a** (0.2 mmol), **2a** (0.24 mmol), catalyst (10 mol %), toluene (2.4 mL). [b] Yields were determined by the ^{1}H NMR spectroscopic analysis of a crude mixture using dibenzyl ether as an internal standard. An isolated yield based on **1a** after silica gel column chromatography is shown in parenthesis. [c] Performed for 12 h. [d] Performed at 110 °C for 12 h.

12 h did not improve the yield of (*Z*)-**3a** (Table 1, entry 2). By contrast, in the absence of the palladium catalyst, the *anti*-adduct (*E*)-**4a** was obtained as a sole product in 13% yield under identical conditions (Table 1, entry 3). We assume that without the palladium catalyst compound (*E*)-**4a** was formed through the formation of thiirenium intermediate and the subsequent nucleophilic attack of the counter chloride ion at the less hindered carbon, as proposed in the literature.[3] It is found that palladium-catalyzed *syn*-chlorothiolation was much faster than *anti*-addition, and indeed 61% of the palladium-catalyzed product (*Z*)-**3a** was formed after 5 min.[8] Although *anti*-chlorothiolation of an alkyne in polar ethyl acetate was known to proceed quantitatively at room temperature,[3d] it took 12 h to obtain (*E*)-**4a** in 67% yield in toluene even at reflux (Table 1, entry 4). $Pd(OAc)_2$, $Pd(dba)_2$ (dba = dibenzylideneacetone), and $PdCl_2$ were found to perform poorly (entries 5–7). It is noteworthy that the palladium catalysts suppress the formation of (*E*)-**4a**, probably due to a strong coordination of palladium to **1** (Table 1, entry 3 vs. entries 1, 5–7). Although copper salts CuCl and $CuCl_2$ are known to catalyze the chlorosulfonylation of alkynes,[4] they proved ineffective catalysts for chlorothiolation (Table 1, entries 8 and 9).[9] The addition of phosphine ligands (PPh_3, PCy_3, or dppf; dppf = 1,1′-bis(diphenylphosphino)ferrocene) decreased the yields of (*Z*)-**3a**. Toluene proved to be the best solvent, whereas 1,4-dioxane, benzene, ethyl acetate, dichloromethane, and hexane were inferior (Table 1, entries 10–14). At higher concentrations, decomposition of **2a** occurred and substantial amounts of diphenyl disulfide were detected.

To confirm the configuration of the adduct (*Z*)-**3a** unambiguously, the liquid (*Z*)-**3a** was oxidized with *m*CPBA (*m*-chloroperoxybenzoic acid) to the corresponding crystalline sulfoxide **5** (Scheme 2). X-ray crystallographic analysis revealed that sulfoxide **5** was in the (*Z*)-configuration (Figure 1).[10]



Scheme 2. Oxidation of (*Z*)-**3a**.

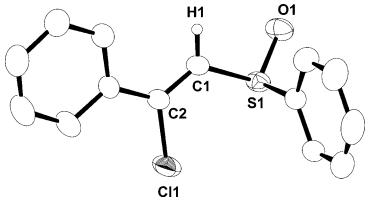
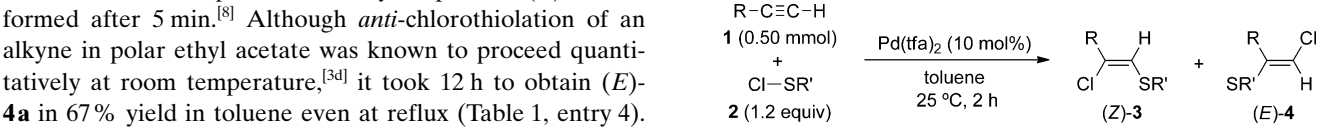


Figure 1. ORTEP drawing of **5** with thermal ellipsoids at the 50% probability level. Hydrogen atoms, except for that on C1, are omitted for clarity.

With the optimized reaction conditions in hand, we then introduced a range of terminal alkynes **1** into the reactions with sulfenyl chlorides **2**. Chlorothiolation of various aromatic alkynes gave the corresponding *syn*-adducts (*Z*)-**3a**–**3f** in moderate to good yields with high regio- and stereoselectivities (Table 2, entries 1–6). The reactions of electron-rich alkynes gave higher yields than those of electron-deficient alkynes, suggesting that a stronger coordination of **1** to palladium facilitates the migratory insertion step (see

Table 2. Palladium-catalyzed chlorothiolation of terminal alkynes **1** with sulfenyl chlorides **2**.[a]



Entry	R	R′	Product	Yield [%][b]
1	Ph	Ph (**2a**)	(*Z*)-**3a**	79
2	4-MeC_6H_4	Ph (**2a**)	(*Z*)-**3b**	79
3	4-$MeOC_6H_4$	Ph (**2a**)	(*Z*)-**3c**	62
4	4-ClC_6H_4	Ph (**2a**)	(*Z*)-**3d**	53
5	4-$F_3CC_6H_4$	Ph (**2a**)	(*Z*)-**3e**	41
6	4-NCC_6H_4	Ph (**2a**)	(*Z*)-**3f**	36
7	*t*Bu	Ph (**2a**)	(*Z*)-**3g**	55
8	Me_3Si	Ph (**2a**)	(*Z*)-**3h**	39
9	Ph (**1a**)	4-MeC_6H_4 (**2b**)	(*Z*)-**3i**	80
10	Ph (**1a**)	4-$MeOC_6H_4$ (**2c**)	(*Z*)-**3j**	64
11	Ph (**1a**)	4-BrC_6H_4 (**2d**)	(*Z*)-**3k**	37
12	Ph (**1a**)	4-$F_3CC_6H_4$ (**2e**)	(*Z*)-**3l**	42
13	Ph (**1a**)	2-MeC_6H_4 (**2f**)	(*Z*)-**3m**	66

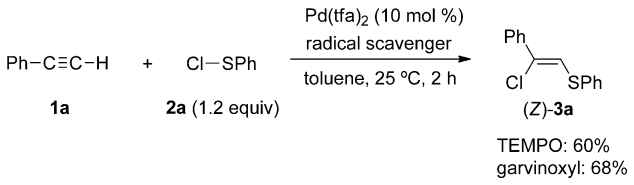
[a] Conditions: **1** (0.5 mmol), **2** (0.6 mmol), $Pd(tfa)_2$ (10 mol %), toluene (6 mL). Small amounts of (*E*)-**4** (1–9%) were present as minor products. [b] Isolated yields based on **1** after silica gel column chromatography.

below). The reaction of aliphatic terminal alkynes such as 1-octyne and propargylbenzene gave a mixture of the isomers (*Z*)-**3** and (*E*)-**4** with poor selectivity, whereas the sterically hindered terminal alkynes such as 3,3-dimethyl-1-butyne and trimethylsilylacetylene underwent the selective reaction to yield the corresponding adducts (*Z*)-**3g** and (*Z*)-**3h**, respectively (Table 2, entries 7 and 8). This selectivity can be rationalized by considering that the electron-rich aliphatic alkynes would accelerate non-catalyzed *anti*-addition, but that the steric bulkiness of the substituents would avoid the nucleophilic attack of the chloride counterion after the formation of the thiirenium species in the uncatalyzed pathway. On the other hand, internal alkynes such as 4-octyne and diphenylacetylene did not give the desired products (*Z*)-**3** under optimized reaction conditions and instead gave *anti*-products (*E*)-**4** in 78% and 3%, respectively. These results imply that two substituents of internal alkyne would suppress a coordination of palladium to the alkynes and consequently lead to an acceleration of the non-catalyzed *anti*-addition.

Next, a variety of sulfenyl chlorides **2** were examined for the chlorothiolation of **1a**. Electron-rich aromatic sulfenyl chlorides **2b** and **2c** reacted smoothly (Table 2, entries 9 and 10). The reaction of the brominated substrate **2d** occurred to provide the corresponding adduct (*Z*)-**3k**, and left the bromo substituent intact (Table 2, entry 11). Electron-deficient **2e** also participated in the reaction, albeit in low yield (Table 2, entry 12). A substituent at the *ortho*-position did not retard the reaction to afford (*Z*)-**3m** in 66% yield (entry 13).

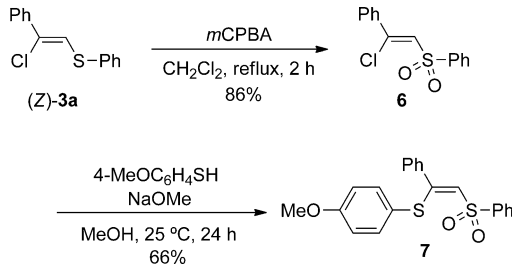
Although the reaction mechanism of the present chlorothiolation is not clear at this stage, one of the possible reaction mechanisms is a Pd^0/Pd^{II} pathway initiated by oxidative addition of the sulfenyl chlorides **2** to Pd^0, which has precedent in the transition-metal-catalyzed addition of thiocyanates[11] and disulfides[12] to alkynes. Therein, oxidative addition of **2** to Pd^0 would afford a chloropalladium(II) arenethiolate complex.[13] The subsequent chloropalladation of terminal alkynes **1** in a *syn*-fashion affords 2-chloro-1-alkenylpalladium species.[14] Sequential reductive elimination delivers **3** and regenerates the initial Pd^0 catalyst. We believe that high regioselectivity can be attributed to a steric control as the relatively bulky palladium moiety adds to the terminal carbon of the alkynes. Reported examples of the insertion of alkynes into a chlorine–palladium bond[15,16] are suggestive of this mechanism, although the other pathways through thiopalladation cannot be ruled out.[17,18] While it was reported *anti*-adduct (*E*)-**4** can isomerize into *syn*-adduct (*Z*)-**3** with a slight excess of sulfenyl chloride,[3d] no isomerization was observed under our reaction conditions.[19]

Homolytic cleavage of the chlorine–sulfur bond in **2** could occur,[4a–c,5,20] and so the reaction has the possibility to proceed via a radical pathway. Single-electron transfer (SET) from Pd^0 to sulfenyl chloride generates Pd^ICl and a sulfenyl radical. The subsequent radical addition at the less hindered position of terminal alkyne gives the corresponding alkenyl radical species. Recombination of Pd^ICl with carbon-centered radical forms divalent palladium species, in which coordination of sulfur to palladium controls the regioselectivity to form the (*Z*)-alkenylpalladium species. Finally, reductive elimination affords the adducts and regenerates Pd^0. We then investigated the reaction of **1a** with **2a** in the presence of a radical scavenger (Scheme 3). Consequently, we determined that even in the presence of TEMPO (2,2,6,6-tetramethylpiperidine 1-oxyl) or garvinoxyl the chlorothiolation proceeded smoothly to form (*Z*)-**3a** in 60% and 68% yields, respectively. We also did not observe any adduct of radical scavengers in both reactions. These results strongly rule out a radical process.



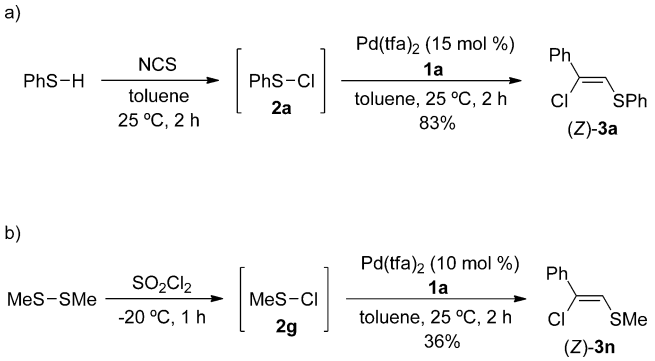
Scheme 3. Reactions in the presence of radical scavengers.

The utility of the chlorothiolation adducts (*Z*)-**3** is illustrated in Scheme 4. The adduct (*Z*)-**3a** was treated with *m*CPBA to afford the corresponding sulfone **6**, which was then treated with a thiol to give the *vic*-difunctionalized alkene **7**[21] bearing two different arylthio groups. Dithioalkene **7** is a potent ligand for transition-metal-catalyzed allylic substitution reactions,[22] which cannot be prepared from *anti*-adduct (*E*)-**4**.



Scheme 4. Transformation of (*Z*)-**3a**.

Since the in situ synthesis of **2** from the corresponding thiols and *N*-chlorosuccinimide (NCS) has been widely utilized,[23] a more practical sequence with chlorination of thiol and subsequent chlorothiolation of **1a** was envisaged. Thus, the in situ prepared **2a**, derived from chlorination of benzenethiol with NCS, was treated with **1a** and $Pd(tfa)_2$ to give (*Z*)-**3a** in 83% overall yield (Scheme 5a). Encouraged by the success of this one-pot synthesis of (*Z*)-**3a**, we thus investigated chlorothiolation with aliphatic sulfenyl chlorides. Since methanesulfenyl chloride (**2g**) was found to be unstable and to decompose easily on the bench top, we performed the one-pot reaction of phenylacetylene (**1a**), starting from dimethyl disulfide. To our delight, chlorothiolation proceeded to give the corresponding product (*Z*)-**3n** in 36%



Scheme 5. One-pot synthesis. a) Synthesis of (*Z*)-**3a**. b) Synthesis of (*Z*)-**3n**.

yield (Scheme 5b). These results suggest that various sulfenyl chlorides, even those that are difficult to isolate, could be utilized directly in the present reaction, which in turn would expand the generality of the chlorothiolation reaction.

In summary, we have developed the first regio- and stereoselective addition of sulfenyl chlorides to terminal alkynes catalyzed by a palladium complex under mild conditions. This synthetic approach can provide stereodefined alkenyl sulfides in a facile and straightforward manner. Studies on the detailed reaction mechanism and the application of this reaction to the synthesis of sulfur-containing complex molecules are currently in progress.

Experimental Section

A typical procedure for palladium-catalyzed addition of sulfenyl chlorides to terminal alkynes: Under an argon atmosphere, palladium trifluoroacetate (6.6 mg, 0.02 mmol) was placed in a 20 mL Schlenk tube. Toluene (0.80 mL) was then added at room temperature. The resulting suspension was stirred for 5 min, and benzenesulfenyl chloride (**2a**, 34.7 mg, 0.24 mmol) was added. Phenylacetylene (**1a**, 20.4 mg, 0.20 mmol) in toluene (1.6 mL) was added dropwise to the reaction mixture. The mixture was stirred at room temperature for 2 h. Saturated sodium thiosulfate solution (5 mL) was added to quench the reaction. The mixture was extracted with ethyl acetate (3×5 mL). The combined organic layers were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane) to give (*Z*)-2-chloro-2-phenylethenyl phenyl sulfide ((*Z*)-**3a**) (38.9 mg, 0.158 mmol, 79%).

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Keywords: addition · alkynes · chlorothiolation · homogeneous catalysis · palladium

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[9] See the Supporting Information for detailed optimization studies.

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COMMUNICATION

Synthetic Methods

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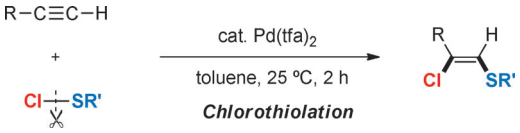
Palladium-Catalyzed Regio- and Stereoselective Chlorothiolation of Terminal Alkynes with Sulfenyl Chlorides



Pick and choose: The first chlorothiolation of alkynes in a *syn*-fashion is achieved by cleavage of the chlorine–sulfur bond in sulfenyl chlorides. Treatment of terminal alkynes with sulfenyl chlorides in the presence of palladium catalyst at ambient temperature leads to (*Z*)-2-chloroalkenyl sulfides with high regio- and stereoselectivities. tfa = trifluoroacetate.