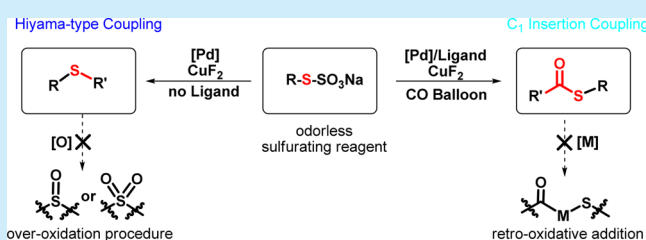


Ligand-Controlled Divergent Cross-Coupling Involving Organosilicon Compounds for Thioether and Thioester Synthesis

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Supporting Information

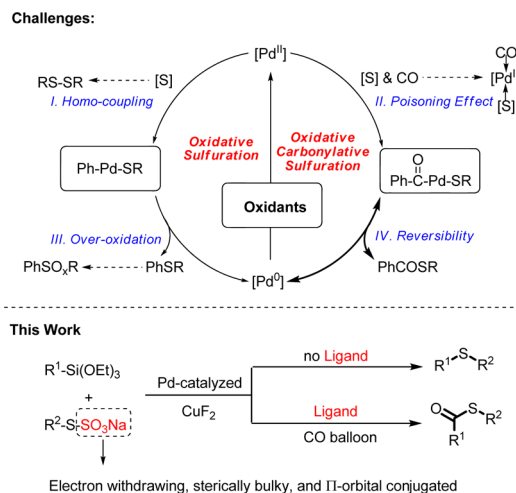
ABSTRACT: A divergent cross-coupling for both thioether and thioester construction from organosilicon compounds has been developed. Predominant selectivity for Hiyama-type coupling and C₁ insertion reaction was achieved under the guidance of ligands. Thioether was obtained under ligand-free conditions in which disulfide generated from homocoupling could be prevented. Meanwhile, application of bidentate phosphine ligands under carbon monoxide atmosphere (CO balloon) afforded the thioester with little decomposition, which was revealed through interval NMR tracking.



Organosulfur chemistry is vital in synthetic science since carbon–sulfur bonds are ubiquitous in the pharmaceutical industry,¹ material science,² and food chemistry.³ Notably, a vast array of research on carbon–sulfur bond formation has focused on coupling between nucleophilic sulfides and electrophilic reagents.⁴ Direct oxidative cross-coupling from nucleophilic sulfides and nucleophilic organometallic reagents is especially rare,⁵ mainly deflection on coupling with boronic acids. Organosilicon reagent(s), alternatives to commonly used organometallic reagents, are readily available, have low toxicity, and display good air/moisture stability.⁶ However, the employment of organosilicon reagents for sulfide synthesis also presents challenges such as (I) homocoupling to disulfide prior to cross-coupling;⁷ (II) catalyst poisoning due to strong coordination of thiol and CO;⁸ (III) overoxidation of product sulfide to sulfoxide/sulfone;⁹ (IV) reversible process for thioester with Pd catalysis of oxidative addition and reductive elimination (Scheme 1).¹⁰ As a continuation of our interest in sulfur atom transfer reactions from thiosulfate,¹¹ herein we report an oxidative cross-coupling reaction involving organosilicon reagent for both thioether and thioester formation through the concept of ligand control and odorless sulfuration.

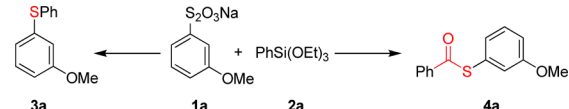
Model reaction between sodium S-3-methoxyphenyl sulfothioate **1a** and phenyltriethoxysilane **2a** was selected to perform in the presence of palladium catalyst without additional ligands, which intentionally frees coordinating space for sulfide with steric bulky thiosulfate (Table 1). Cupric fluoride serves as both oxidant and fluoride source, which afforded desired thioether **3a** in 22% (Table 1, entry 3). Palladium diacetate was the best catalyst in this protocol (Table 1, entries 6–8). The yield was improved to 60% when *N,N*-dimethylacetamide was selected as solvent (Table 1, entry 11). Trifluoromethanesulfonic acid,^{11f}

Scheme 1. Challenges in Pd-Catalyzed Thioetheration and Thioesteration



which activates the sulfothioate, elevated the yield to 82% (Table 1, entry 12). Carbon monoxide as ligand resulted in a diminished yield of **3a** along with thioester **4a** formation (Table 1, entry 13). To restrain poisonous catalyst properties, several phosphine ligands were applied, in which bidentate ligand dppp afforded 12% of **4a** (Table 1, entry 16). Further improvement was achieved through prepared PdCl₂/dppp with elevated yield of 70% (Table 2, entry 18). At the same time, thioether **3a** was diminished to 3% yield, which revealed that the ligand effect is

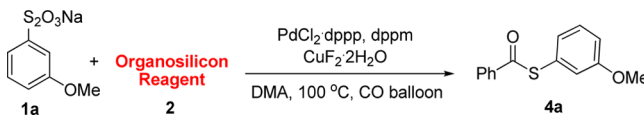
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Table 1. Optimization for Thioether and Thioester Formation^a


entry	[Pd]/ligand	additive	solvent	atmosphere	yield ^b of 3a (%)	yield ^b of 4a (%)
1	Pd(OAc) ₂	MnF ₃	DMF	N ₂	ND ^c	
2	Pd(OAc) ₂	FeF ₃	DMF	N ₂	ND ^c	
3	Pd(OAc) ₂	CuF ₂	DMF	N ₂	22	
4	Pd(OAc) ₂	CuF ₂ ·2H ₂ O	DMF	N ₂	21	
5	Pd(OAc) ₂	NiF ₂	DMF	N ₂	ND ^d	
6	PdCl ₂	CuF ₂ ·2H ₂ O	DMF	N ₂	5	
7	Pd(dba) ₂	CuF ₂ ·2H ₂ O	DMF	N ₂	14	
8	Pd(TFA) ₂	CuF ₂ ·2H ₂ O	DMF	N ₂	9	
9	Pd(OAc) ₂	CuF ₂ ·2H ₂ O	toluene	N ₂	<2	
10	Pd(OAc) ₂	CuF ₂ ·2H ₂ O	DMSO	N ₂	42	
11	Pd(OAc) ₂	CuF ₂ ·2H ₂ O	DMA	N ₂	60	
12 ^e	Pd(OAc) ₂	CuF ₂ ·2H ₂ O	DMA	N ₂	82	
13	Pd(OAc) ₂	CuF ₂ ·2H ₂ O	DMA	CO	47	trace
14	Pd(OAc) ₂ /PPh ₃	CuF ₂ ·2H ₂ O	DMA	CO	15	ND
15	Pd(OAc) ₂ /PCy ₃	CuF ₂ ·2H ₂ O	DMA	CO	trace	ND
16	Pd(OAc) ₂ /dppp	CuF ₂ ·2H ₂ O	DMA	CO	40	12
17	PdCl ₂ /dppp	CuF ₂ ·2H ₂ O	DMA	CO	23	36
18	PdCl ₂ /dppp	CuF ₂ ·2H ₂ O	DMA	CO	3	70
19	PdCl ₂ /dppp/dppm	CuF ₂ ·2H ₂ O	DMA	CO	5	85
20	PdCl ₂ /dppp/dppe	CuF ₂ ·2H ₂ O	DMA	CO	8	73
21	PdCl ₂ /dppp/dppb	CuF ₂ ·2H ₂ O	DMA	CO	2	80
22	PdCl ₂ /dppp/dppm	CuF ₂ ·2H ₂ O	DMA	CO	3	63
23	PdCl ₂ /dppm/dppp	CuF ₂ ·2H ₂ O	DMA	CO	2	24
24	PdCl ₂ /dppm/dppm	CuF ₂ ·2H ₂ O	DMA	CO	9	44

^aReaction conditions: **1** (0.1 mmol), **2** (0.2–0.3 mmol), [Pd] (5 mol %), Ligand (15 mol %), additive (0.11–0.2 mmol), and solvent (2.0 mL); 100 °C. ^bIsolated yields. ^c1 equiv of 1,2-bis(3-methoxyphenyl)-disulfane was obtained. ^d3-Methoxybenzenethiol was obtained in 73% yield. ^e0.15 mmol of CF₃SO₃H was added.

crucial for Pd-precursor stabilization and chemoselectivity (Supporting Information for more details). Encouraged by the above results, other bidentate ligands were tested (Table 1, entries 19–22). Finally, PdCl₂/dppp with additional dppm as the catalyst combination displayed an important role in thioester formation, providing **4a** in 85% yield.

Table 2. Different Types of Silicon Center^a


entry	reagent	yield (%)
1	PhSi(OEt) ₃	85
2	PhSi(OMe) ₃	42
3	Ph ₂ Si(OEt) ₂	34
4	Ph ₂ Si(OMe) ₂	24
5	PhSiMe ₃	ND

^aReaction conditions: **1a** (0.1 mmol), **2** (0.3 mmol), PdCl₂/dppp (5 mol %), dppm (15 mol %), CuF₂·2H₂O (0.15 mmol), DMA (2.0 mL), CO balloon; 100 °C.

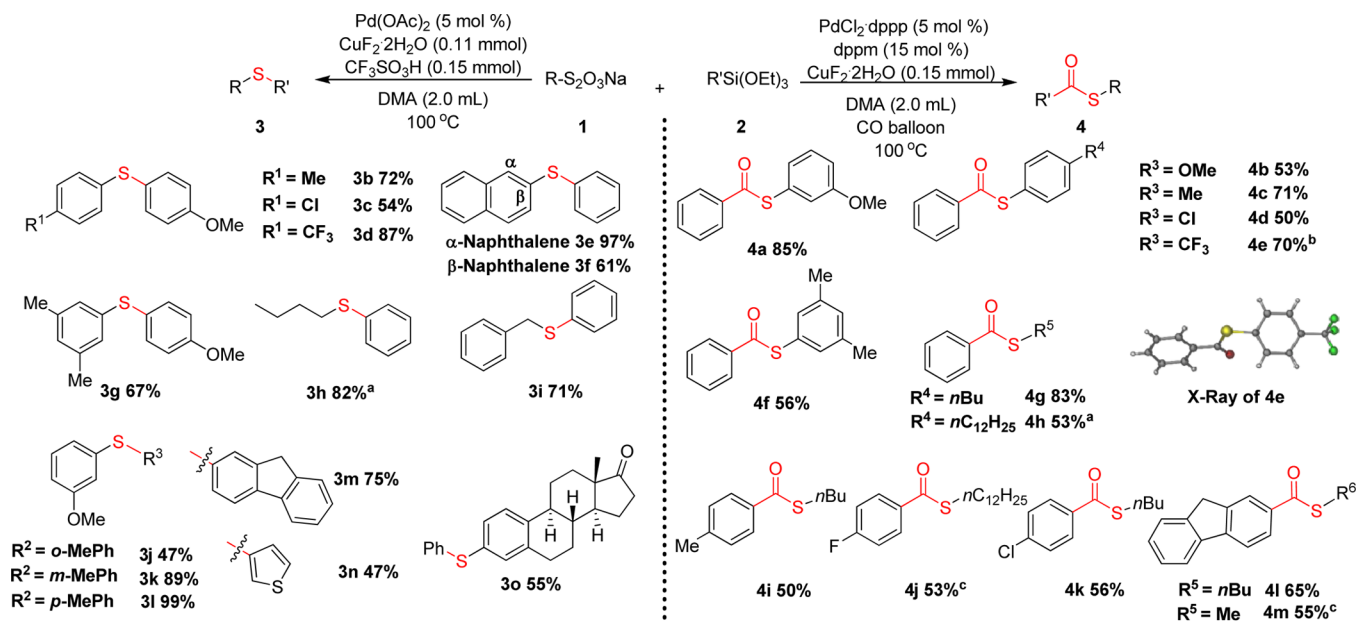
Different types of silicon show totally different reactivity for thioester formation (Table 2). The trimethoxy, diethoxy-(phenyl), and dimethoxy(phenyl) substituent organosilicon reagents provide desired product **4a** in 42%, 34%, and 24%, respectively. Trimethyl(phenyl)silane was not an effective coupling partner due to the transmetalation rate of silicon.

With the optimized conditions in hand, the scope of coupling was delineated in Scheme 2. In thioether formation, both electron-rich (**3b**) and electron-poor thiosulfate (**3c** and **3d**) performed well. Naphthalene sulfide was obtained in 97% yield on the α-position and 61% yield on the β-position (**3e** and **3f**), showcasing the effectiveness on condensed ring. Not only the butyl chain (**3h**) but also active benzyl thiosulfate (**3i**) could furnish good yields. Organosilicon components were versatile for the coupling as well (**3j–n**). Estratrien,¹² a kind of female hormone drug, was readily applied to late-stage diversification affording corresponding sulfur-modified estratrien **3o**. Thioesters are important building blocks widespread in biochemistry.¹³ Carbon monoxide, as a common and readily available C1 source, was targeted as the third component to directly construct thioester through free combination of organic thiosulfate salts and organosilicon reagent. On the right part of Scheme 2, thiosulfate salts both bearing electron-donating and -withdrawing substituents, such as methoxy (**4b**), methyl (**4c**), and trifluoromethyl (**4e**), gave corresponding coupling products in high yields, and the structure of thioester **4e** was further confirmed by X-ray analysis.¹⁴

To probe the crucial role of ligand for the successful carbonylative sulfuration, interval NMR experiments were conducted with different bidentate phosphine ligand (Figure 1). Most ligands exhibited a sharp decrease of thioester formation after 6 h, which indicated that product thioester has been consumed. Additional ligands, such as dppe, dppp, and dppb, could decrease the consumption of thioester by blocking Pd(0) species. Notably, dppm, with a four-membered ring catalytic center, presented a stable yield curve up to 14 h after reaching to the peak yield in 10 h, which implied that palladium catalyst was coordinated by two kinds of ligands to avoid further oxidative addition.

A proposed mechanism for thioesteration is illustrated in Scheme 3. In path a, a chelated catalytic center **A** was formed in the presence of bidentate phosphine ligand. Direct transmetalation with organosilicon compounds, by using CuF₂, could produce intermediate **B**, which then experienced a CO insertion process rather than further transmetalation by thiosulfate due to the steric hindrance of the catalytic center. Next, aryl Pd species **C** was formed and underwent reductive

Scheme 2. Thioether and Thioester Formation



^a10 mol % of Pd(OAc)₂ was added. ^b0.2 mmol of CuF₂·2H₂O was added. ^c0.25 mmol of CuF₂·2H₂O was added.

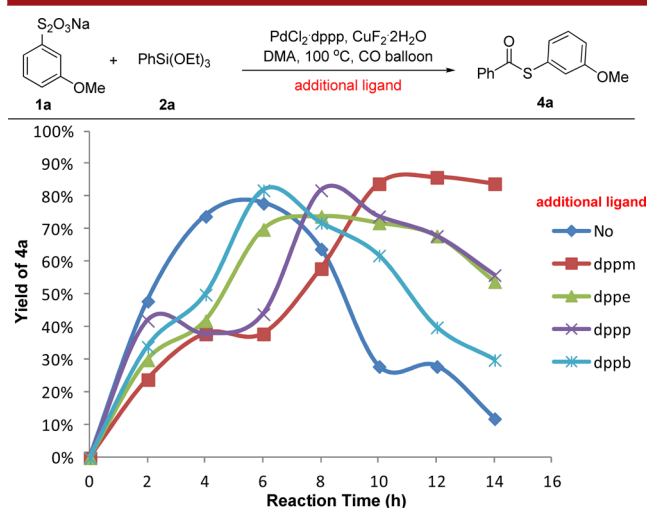


Figure 1. Ligand effect from dppm.

elimination to afford thioester. However, through control experiments in Table 3, Pd intermediate **B** was synthesized and subjected to several designed conditions. No desired product was formed, which excludes the pathway mentioned above. Alternatively, in path b, palladium complex **D** should be generated via transmetalation through Cl[−] displacement by RSSO₃[−] in advance, which was followed by CO insertion. Finally, loss of SO₃ and organosilicon reagent transmetalization could go from **E** to **F**. Intermediate **F** underwent reductive elimination to give the corresponding product.

Application of thioester¹⁵ for carbonyl compound synthesis is exemplified with several efficient transformations in Scheme 4. Ketone **5a**, alkynone **5c**, and carbonate ester **5d** were highly efficiently prepared through palladium oxidative addition of thioester by a cross-coupling protocol such as Fukuyama coupling,^{15a} Sonogashira coupling,^{15b} Hiyama–Denmark coupling,^{15c} etc. These transformations further proved that oxidation–addition of Pd complexes with thioester is effortless

Scheme 3. Proposed Mechanism

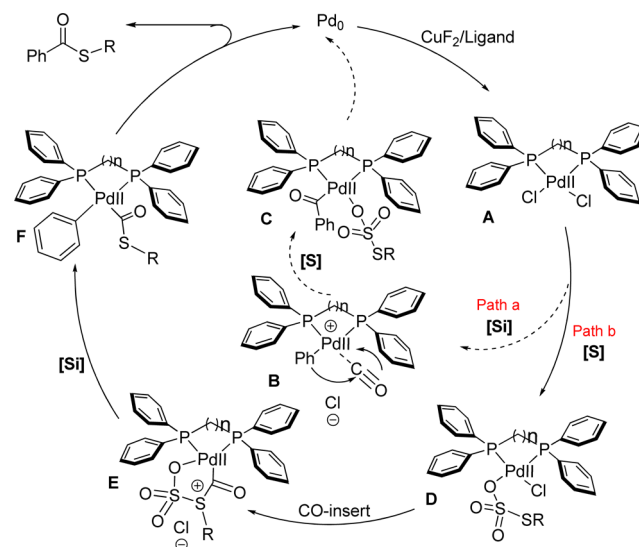


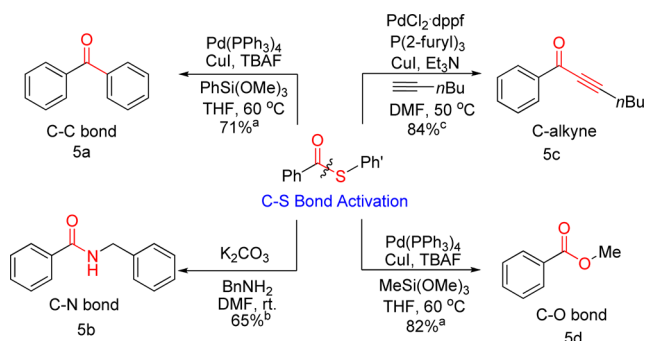
Table 3. Control Experiment

		conditions ^a	ND
R =	CuF ₂	atmosphere	result
COPh	X	N ₂	ND ^b
COPh	✓	N ₂	ND ^c
Ph	X	CO	ND ^b
Ph	✓	CO	ND ^b

^aReaction conditions: DMA (2.0 mL); 100 °C; X = Cl or I. ^bDisulfide was detected. ^cBenzophenone was obtained in 41% yield.

and protecting thioesters under Pd(0) conditions is not conventional.

Scheme 4. Thioester Transformation



^aPd(PPh₃)₄, CuI, TBAF, and THF; 60 °C; 0.5 h. ^bK₂CO₃ and DMF; rt; 10 h. ^cPdCl₂-dppf, P(2-furyl)₃, CuI, Et₃N, and DMF; 50 °C; 3 h.

In summary, we have developed a new and efficient Pd-catalyzed oxidative cross-coupling protocol to construct thioethers and thioesters that was tuned through ligands on palladium. A special ligand effect has been uncovered by interval NMR tracking. Meanwhile, thiosulfate exhibited unique powerful advantages of base-free, odorless, and compatibility with oxidizing reagent. Sole usage of copper salt as both fluoride anion and oxidant makes the protocol much more practical. Further application of the ligand control sulfuration and synthetic use are currently ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00324.

Procedure, NMR spectra, X-ray data, and analytical data for all new compounds (PDF)
X-ray data for 4e (CIF)

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Notes

The authors declare no competing financial interest.

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(14) CCDC 1433427: C₁₄H₉F₃OS, MW = 282.27, monoclinic, space group P2(1)/c, final R indices [I > 2σ(I)], R1 = 0.0851, wR2 = 0.2112 R indices (all data), R1 = 0.1833, wR2 = 0.2840, a = 5.701 (2) Å, b = 14.172 (5) Å, c = 16.101 (6) Å, α = 90°, β = 96.143 (12) deg, γ = 90°, V = 1293.4 (8) Å³, T = 296 (2) K, Z = 4, reflections collected/unique: 14285/2267 (R(int) = 0.1162).

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