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Palladium-Catalyzed Desulfitative C−C Cross-Coupling Reaction of (Hetero)Aryl Thioesters and Thioethers with Arylsiloxanes

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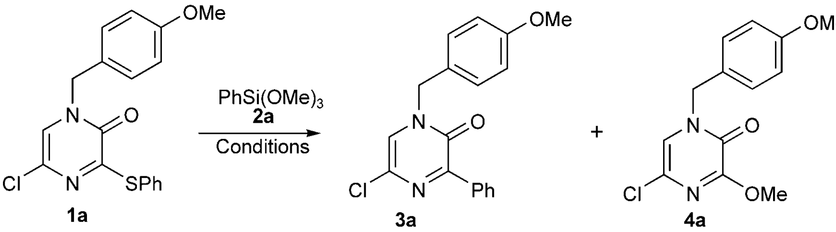
Abstract: The first desulfitative Hiyama-type cross-coupling protocol is reported and exemplified by the synthesis of substituted 5-chloro-3-arylpyrazinones. The method has also been successfully applied for the arylation of other (hetero)aryl thioethers and thioesters.

Keywords: copper(I); cross-coupling; desulfitative procedure; Hiyama reaction; homogeneous catalysis; pyrazinones

Palladium-catalyzed C−C and C−heteroatom bond-forming cross-coupling reactions are among the most powerful methods in organic synthesis.[1] Such procedures involve the coupling of an activated electrophilic partner with a nucleophilic organometallic donor through a palladium-assisted cross-coupling cascade. For this purpose a number of organometallic donors have been explored, mainly organoborons,[2] organostannanes,[3] and organozinc reagents.[4] Seminal work by Liebeskind and co-workers describes the coupling of aryl or heteroaryl thioethers with organoboron, organotin or organoindium compounds.[5] However instability, difficulty in preparation and, most importantly, toxicity of most organometallic reagents keep chemists searching for alternatives. Hiyama demonstrated the potential of the use of organosilicon reagents as nucleophilic coupling partners having the advantage of being environmentally safe and posing no toxicity hazards.[6] Since then, an increasing number of publications has appeared dealing with the coupling of activated (hetero)aromatic systems with organosilicon reagents, applying this Hiyama protocol.[7] Denmark et al. have successfully applied a variety of silanols as active transmetallating species.[8] However, nearly all Hiyama protocols have focused on the coupling of C−X electrophiles, X being halide or triflate. Until now, we are unaware of any example of Hiyama coupling with activated C_{sp^2}−S electrophiles. Pursuant to our long-standing interest in the synthesis and decoration of the pyrazin-2(1*H*)-one scaffold[9] and to our recently described protocol for the transition metal-catalyzed orthogonal decoration of the 2(1*H*)-pyrazinone scaffold using a sulfur linker,[10] we were keen to investigate whether a desulfitative Hiyama-type reaction at the C-3 position of 5-chloro-3-(phenylsulfanyl)pyrazin-2(1*H*)-ones would be possible. Tests were performed with 5-chloro-1-(4-methoxybenzyl)-3-(phenylsulfanyl)pyrazin-2(1*H*)-one (**1a**) and trimethoxyphenylsilane as a model system. Applying the standard conditions for the Hiyama process [5 mol% Pd(II), 10 mol% ligand, 2 equiv. TBAF, THF], 75% conversion of the starting material was observed (Table 1, entry 1). However, surprisingly, the major product turned out to be the C-3 methoxylated pyrazinone and only 35% of the expected C-3 arylated compound was observed.[11] To our satisfaction we found that addition of CuI[12] effectively suppressed the formation of **4a**, hence acting as a reaction switch between methoxylated and arylated products. After extensive investigation of the reaction parameters, we found that 1.5 equiv. of phenyltrimethoxysilane **2a**, 5 mol% of $Pd(PPh_3)_4$, 0.3 mmol of CuI (1.0 equiv.), 0.6 mmol of TBAF (1 M soln. in THF, 2 equiv.) in THF at 60 °C for 3 h under conventional heating is optimal for the formation of **3a** in 79% yield beside traces of **4a** (Table 1, entry 5).

Having optimized the conditions we reacted an array of differently substituted 5-chloro-3-(phenylsulfanyl)pyrazin-2(1*H*)-ones (**1a–f**) with trimethoxyarylsilanes (Table 2). The corresponding arylated products were obtained in excellent yields. The method was also evaluated for the application of alkylsiloxanes. Surprisingly, reaction of **1a** with methyl- or vinylsiloxane using the optimized protocol, provided the me-

Table 1. Optimization of the desulfitative arylation of thioether **1a** with silane **2a**.[a]



Entry	Pd catalyst [mol%]	Silane [equiv.]	Cu [equiv.]	Solvent	Time [h]	Conversion[b]	Yield **3a** [%][c]	Yield **4a** [%][c]
1	$PdCl_2$ (5)/PPh_3 (10)	1.5	–	THF	6	75%	35	40
2	$Pd(OAc)_2$ (5)	1.5	–	THF	6	60%	35	25
3	$Pd(PPh_3)_4$ (5)	1.5	–	THF	6	80%	50	29
4	$Pd(PPh_3)_4$ (5)	1.5	CuI (0.1)	THF	4	80%	55	20
5	**$Pd(PPh_3)_4$ (5)**	**1.1**	**CuI (1.0)**	**THF**	**3**	**100%**	**79**	**traces**
6	$Pd(PPh_3)_4$ (5)	1.2	CuI (2.0)	THF	2.5	100%	80	traces
7	$Pd(PPh_3)_4$ (5)	1.2	CuI (0.5)	THF	6	75%	64	traces
8	$Pd(PPh_3)_4$ (5)	1.2	CuBr (1.0)	THF	6	85%	69	traces
9	–		CuI (1.0)	THF	8	0%	0[d]	0[d]
10	$Pd(PPh_3)_4$ (2)	1.2	CuI (1.0)	THF	6	70%	60	-
11[e]	$Pd(PPh_3)_4$ (5)	1.1	CuI (1.0)	THF	5	50%	41	-
12	$Pd(PPh_3)_4$ (5)	1.2	CuI (1.0)	Toluene	4	100%	66	34
13	$Pd(PPh_3)_4$ (5)	1.5	CuI (1.0)	MeCN	4	100%	28	70
14	$Pd(PPh_3)_4$ (5)	1.5	CuI (1.0)	*o*-xylene	4	80%	39	39
15	$Pd(PPh_3)_4$ (5)	1.5	CuI (1.0)	PhCN	4	100%	56	44
16	$Pd(PPh_3)_4$ (5)	1.5	CuI (1.0)	–	5	50%	0	40
17	$Pd(PPh_3)Cl_2$ (5)	1.2	CuI (1.0)	THF	4	100%	49	51
18	$Pd_2(dba)_3$ (5)	1.2	CuI (1.0)	THF	4	100%	42	58
19	$Pd(dppf)Cl_2$ (5)	1.2	CuI (1.0)	THF	4	90%	36	54
20	$Pd(PhCN)_2Cl_2$ (5)	1.5	CuI (1.0)	THF	4	100%	60	40
21	Herrmann's palladacycle (5)	1.5	CuI (1.0)	THF	4	100%	65	35

[a] Reactions were run on a 0.3 mmol scale of **1a** in dry THF (4 mL) with phenyltrimethoxysilane **2a** (1.1–1.5 equiv.), Pd source, Cu (0.1–2.0 equiv.) (entries 5–21), TBAF (1 M solution in THF, 2 equiv.). The mixture was flushed 3 times with argon. Then it was kept in a preheated oil bath at a temperature of 60 °C for the stipulated time.

[b] Conversion based on GC-MS analysis.

[c] Isolated yield, single runs.

[d] Unreacted starting material recovered.

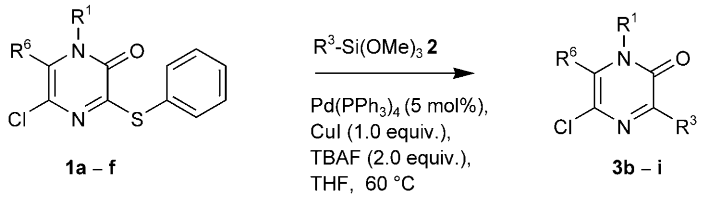
[e] 1.0 equiv of TBAF used.

thoxylated product in very high yield with no trace of the alkylated product (Table 2, entries 9 and 10).

Having successfully established the methodology for the pyrazine scaffold, we were keen to extend the protocol to substituted arylthioesters. Gratifyingly, the respective diaryl ketones were obtained in high yields (Table 3, entries 1–11). Moreover, when **5a** was reacted with $Me(SiOMe)_3$, the methyl ester was obtained in quantitative yield indicating the favoring of the methoxy group compared to the methyl group (Table 3, entry 18). Finally, the method was also evaluated for the heteroaromatic thioethers **6a–c**: applying substituted arylsiloxanes resulted in the formation of the corresponding arylated compounds in excellent yields (Table 3, entries 12–17).

In conclusion, for the first time conditions have been established allowing the desulfitative C–C cross-coupling of thioethers and thioesters with various arylsiloxanes. The judicious combination of a Cu(I) salt with $Pd(PPh_3)_4$ as catalytic system allows us to suppress efficiently the formation of the methoxylated compound in favor of the arylated one. High yields, tolerance towards a range of functional groups, applicability on a range of siloxanes and novelty are the merits of the protocol. The extension of the protocol toward different systems will be investigated in due course.

Table 2. Scope and limitations of the desulfitative arylative protocol.



2a, R^3 = Ph, **2b**, R^3 = 4-MeO-C_6H_4, **2c** R^3 = 4-Me-C_6H_4
2d, R^3 = 4-Cl-C_6H_4, **2e**, R^3 = Me, **2f**, R^3 = vinyl

Entry	R^1	R^6	R^3	Product	Time [h]	Yield [%][a]
1	Bn	Me	Ph	**3b**	2.5	88
2	$(CH_2)_3$-Ph	H	Ph	**3c**	1	89
3	CH_2-cyclohexyl	H	Ph	**3d**	1	90
4	PMB	4-MeO-C_6H_4	Ph	**3e**	1.5	90
5	PMB	Bn	Ph	**3f**	1.5	95
6	PMB	H	4-MeO-C_6H_4	**3g**	1	98
7	PMB	H	4-Me-C_6H_4	**3h**	2	89
8	PMB	H	4-Cl-C_6H_4	**3i**	1.5	92
9	PMB	H	Me	**4a**	1.5	90[b]
10	PMB	H	vinyl	**4a**	1.5	94[b]

[a] Isolated yields, single runs.

[b] Only formation of methoxylated products is observed. PMB = *p*-methoxybenzyl.

Experimental Section

General Methods

^{1}H NMR spectra were recorded on a Bruker Avance 300 MHz instrument using $CDCl_3$ and DMSO-d_6 as solvent unless otherwise stated. The ^{1}H and ^{13}C NMR chemical shifts are reported in parts per million relative to tetramethylsilane as an internal standard. Mass spectra were recorded by using a Kratos MS50TC and a Kratos Mach III system. The ion source temperature was 150–250 °C, as required. High-resolution EI-mass spectra were performed with a resolution of 10,000. The low-resolution spectra were obtained with an HP5989 A MS instrument. For thin-layer chromatography, analytical TLC plates [Alugram SIL G/ UV_{254} and 70–230 mesh silica gel (E. Merck)] were used. All the solvents were distilled prior to use. All chemicals were purchased and used as available.

Typical Procedure for the Synthesis of Representative Compound 3a

Under air, a vial equipped with a stir-bar was charged with thioether **1a**, (0.3 mmol, 1 equiv.), Pd source (5 mol%), CuI (0.3 mmol, 1.0 equiv.), sealed with septum and purged with argon. Distilled THF was added by syringe and the mixture stirred for 1–2 min, after which the siloxane reagent (0.33 mmol, 1.1 equiv.) was added in one shot by syringe and then tetrabutylammonium fluoride (TBAF) (0.6 mmol, 2 equiv) was added in one shot *via* syringe. The septum was replaced with a Teflon-lined screw cap under an argon atmosphere and the reaction mixture was allowed to stir for approximately 3 h at 65 °C prior to GC/MS and/or TLC analysis. Once the product was identified after complete conversion, the general work-up procedure for compound isolation was followed. The reaction mixture was cooled to room temperature, poured into water and extracted with dichloromethane (2×50 mL). The combined organic layers were washed with water and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was subjected to silica gel column chromatography from (5% to 20% EtOAc in heptane) to afford 5-chloro-3-phenyl-1-(4-methoxybenzyl)-2(1*H*)-pyrazinone (**3a**) as a yellow oil; yield: 79%. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.36$–8.33 (m, 2H), 7.44–7.42 (m, 3H), 7.31–7.28 (d, 2H, $J = 8.2$ Hz), 7.16 (s, 1H), 6.91–6.88 (d, 2H, $J = 9.12$ Hz), 5.04 (s, 2H), 3.79 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 160.10$, 154.50, 152.24, 134.94, 130.74, 130.46, 129.37, 128.21, 126.56, 126.35, 125.22, 114.68, 55.41, 52.48; HR-MS (EI): $m/z = 326.0817$, calcd. for $C_{18}H_{15}O_2N_2Cl$: 326.0822.

Supporting Information

Additional experimental procedure and spectra data for new compounds are available as Supporting Information.

Acknowledgements

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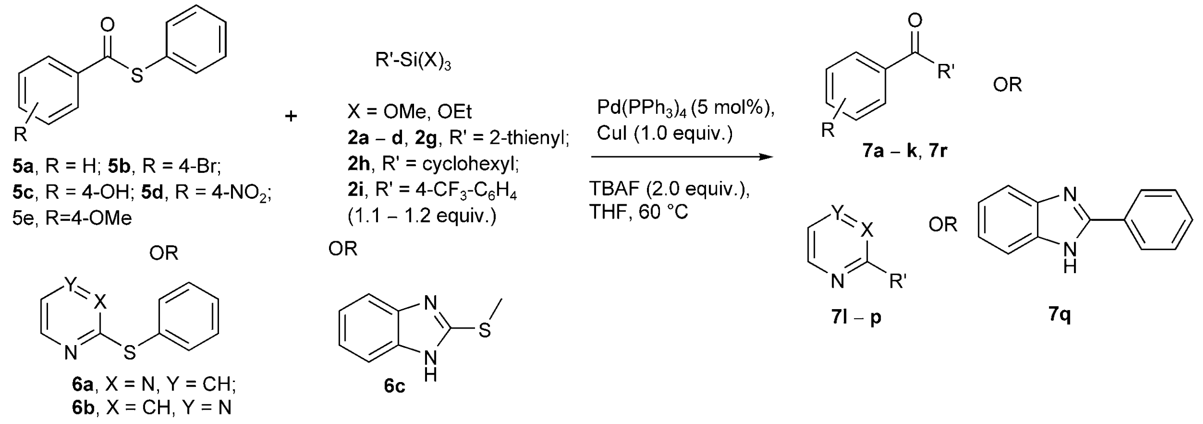
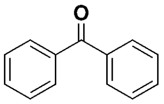
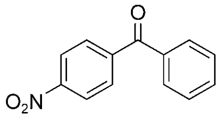
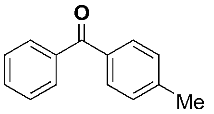
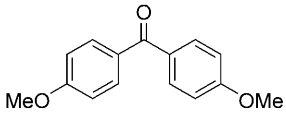
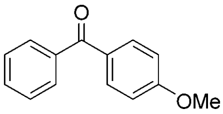
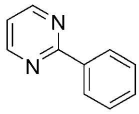
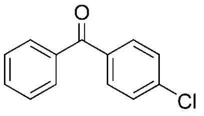
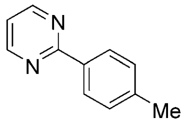
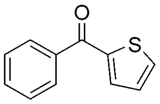
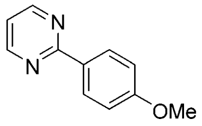
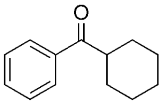
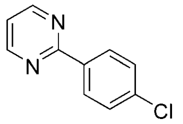
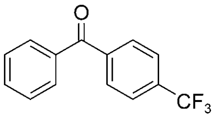
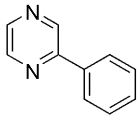
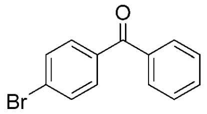
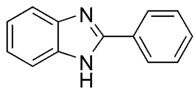
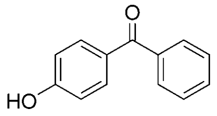
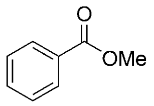
Table 3. Palladium-catalyzed desulfitative C-C cross coupling of thioethers and thioesters using silanes.



Entry	Substrate	Product		Time [h]	Yield[a] [%]	Entry	Substrate	Product		Time [h]	Yield[a] [%]
1	**5a**	**7a**		0.5	88	10	**5d**	**7j**		1.5	88
2	**5a**	**7b**		1	93	11	**5e**	**7k**		1.5	92
3	**5a**	**7c**		1	96	12	**6a**	**7l**		2	91
4	**5a**	**7d**		1.5	90	13	**6a**	**7m**		1.5	94
5	**5a**	**7e**		1	88	14	**6a**	**7n**		1.5	98
6	**5a**	**7f**		0.5	92	15	**6a**	**7o**		2.5	90
7	**5a**	**7g**		2	84	16	**6b**	**7p**			82
8	**5b**	**7h**		6	96	17	**6c**	**7q**		3.5	79
9	**5c**	**7i**		1.5	86	18	**5a**	**7r**		0.5	Quant

[a] Isolated yield are the average of two runs.

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