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Rapid palladium-catalyzed cross-coupling in the synthesis of aryl thioethers under microwave conditions

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Abstract—A Pd-catalyzed coupling of aromatic iodides or bromides and tin-thiolates under microwave conditions was developed to synthesize aromatic thioethers without concomitant formation of the reduced products. Ligand screening revealed DiPPF and BINAP-Tol as the most generally useful ligands for this transformation. A variety of iodides or bromides were coupled to give the thioethers rapidly (10 min) in 60–95% isolated yield.

Aromatic thiothers often feature as important synthetic intermediates and biologically interesting compounds, including several therapeutic drugs.[1,2] Homogeneous catalysts based on either copper(I) or palladium have been developed for their syntheses.[2–4] Mechanistic studies of palladium-catalyzed aromatic substitution of halo or triflate groups by thiolate show that both three and four coordinate intermediates might be involved.[5–7] Indeed, both mono and bidentate phosphine ligands have been developed for this type of reaction.[8–13] Copper(I)-based catalysts for similar syntheses are mechanistically much less clear.[14–18]

In our program to develop new IMPY [6-iodo-2-(4′-*N*, *N*-dimethylamino)phenylimidazo[1,2-*a*]pyridine] derivatives (**1**, Scheme 1) as radiotracers for imaging brain β-amyloid[19] with positron emission tomography (PET), we desired to synthesize several aryl thioethers as novel candidates. The most attractive approach is to introduce the thioether group in the last step in order to avoid manipulation and protection of this sensitive group in the synthesis of the IMPY skeleton. The required aromatic halide substrates (e.g., **1**) for potential substitution by thiolates are generally accessible in multiple step syntheses.[19] We needed a catalytic method of halogen substitution in aryl halides by thiolates that would satisfy a number of requirements. Some of these were not apparent until this study, such as avoidance of competing reductive removal of the halogen substituent. We set our goals to achieve the following for aryl thioether syntheses: (a) one-step introduction of a thioether group into a halogen position in an aryl ring; (b) selective introduction of a thioether group at an iodo position in the presence of other halogen substituents, such as bromo; (c) tolerance of functional groups, especially amino groups; and (d) fast microwave-assisted reaction conditions. Herein, we present a general, efficient, and operationally simple palladium-catalyzed aryl thioether synthesis.

4-(6-Iodoindolizin-2-yl)-*N*-methylbenzeneamine (**2**) plus 2-mercaptoacetamide or 2-mercaptoethanol were used as the prototypical substrate combination for preliminary investigation of the reaction conditions for aryl thioether synthesis (Schemes 1 and 2). Since copper(I) compounds are inexpensive and easily available, we initially selected CuI for investigation as a catalyst. Two ligands, ethylene glycol and ethylene diamine, were evaluated along with a variety of bases and solvents (Table 1). Low conversion of the iodo compound was observed with a catalytic amount of CuI. The reaction went to completion only when a greater than stoichiometric amount of CuI was used. For 2-mercaptoacetamide, the majority of the reaction product arose from reductive removal of the iodo group. For 2-mercaptoethanol, substitution of the iodo group was nearly

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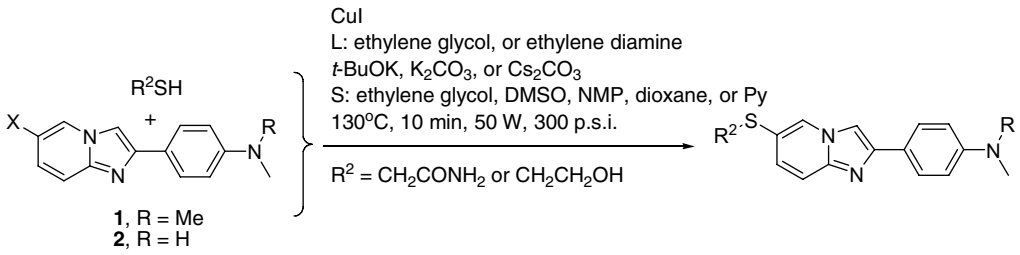
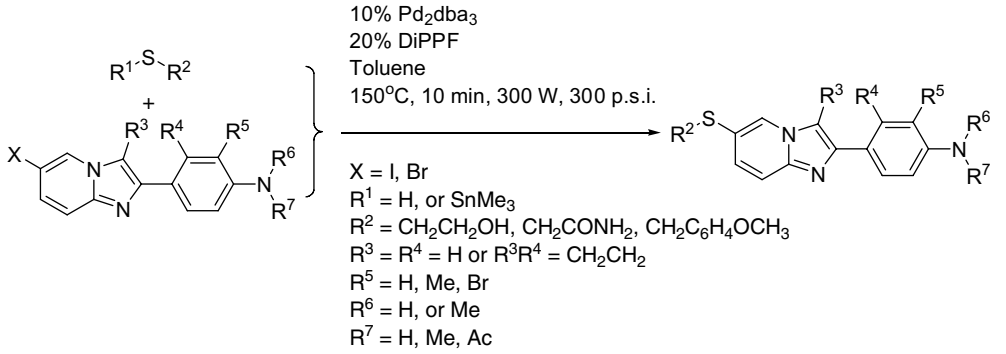


Scheme 1. Copper-mediated syntheses of aryl thioethers.



Scheme 2. Palladium-catalyzed syntheses of aryl thioethers.

Table 1. The copper(I)-mediated coupling of aryl iodides (**1** or **2**) with thiols (Scheme 1)

Entry	R	Method	Conversion (%)	Ratio of substitution:reduction
1	$R^2 = -CH_2CONH_2$, R = Me	A1	100	1.0:4.0
2	$R^2 = -CH_2CONH_2$, R = Me	A2	81	0:1
3	$R^2 = -CH_2CONH_2$, R = H	A1	81	1:8.3
4	$R^2 = -CH_2CONH_2$, R = H	A2	100	1:4.1[a,b]
5	$R^2 = -CH_2CONH_2$, R = H	A3	100	0:1
6	$R^2 = -CH_2CH_2OH$, R = Me	A1	60	Messy
7	$R^2 = -CH_2CH_2OH$, R = H	A1	96	1:0.038

Note: R, substituents shown in Scheme 1; general conditions: 130 °C, 10 min, 50 W, 300 psi, substrate:thiol = 1:1.2–5; A1, 1–5 equiv CuI, 2 equiv ethylene diamine, 2 equiv *t*-BuOK or K_2CO_3 in DMSO, *N*-methylpyrrolidin-2-one (NMP) or dioxane; A2, 1–5 equiv CuI, 2 equiv ethylene glycol, 2 equiv *t*-BuOK in Py; A3, 0.05 equiv CuI, 2 equiv Cs_2CO_3 in NMP.

[a] Without thiol, the reaction generated reduced and $HOCH_2CH_2O$-substituted products.

[b] No reaction was observed when 1,2-dimethoxyethane was used instead of ethylene glycol.

quantitative for one substrate when 5 equiv of CuI was used. However, no catalytic or general reaction was observed and so no further effort was expended on this approach for other substrates.

The palladium-catalyzed coupling of aryl iodides with thiols (Scheme 2) was evaluated using the protocol originally established by Buchwald et al.,[8] who used aryl bromides as substrates. Variations here included the use of (i) catalysts, such as $(DPPF)PdCl_2$; (ii) catalyst precursors, such as Pd_2dba_3 and $Pd(OAc)_2$; (iii) ligands (L) as shown in Figure 2; (iv) bases, such as NEt_3, *t*-BuOK; and (v) solvents, such as NMP, dioxane, or toluene. Multiple products in similar amounts were generated, including the desired substitution products. Given the success of a number of bulky monophosphines in the catalysis of aryl C–N and C–O formation,[7,20] we evaluated a number of bulky monophosphines (Fig. 1). In our general conditions (150 °C, 10 min, 300 W, 300 psi with 0.05 equiv Pd_2dba_3, 0.1 equiv L, 2–4 equiv of NEt_3 or *t*-BuOK, and ethanol or toluene as solvent), the new ligands behave similarly like PPh_3, giving less than 10% total conversion of aryl iodide and ratios of substitution and reduction ranging from 0.4 to 15. No further reaction progress was observed on extended reaction time.

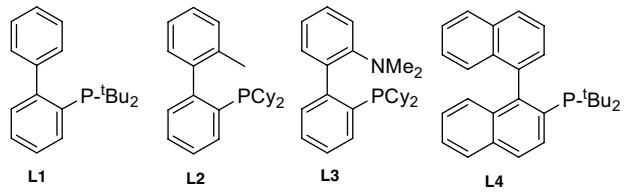


Figure 1. Mono-phosphine ligands.

A number of thiolates instead of free thiols have been used for the aromatic substitution reaction.[1,21] When

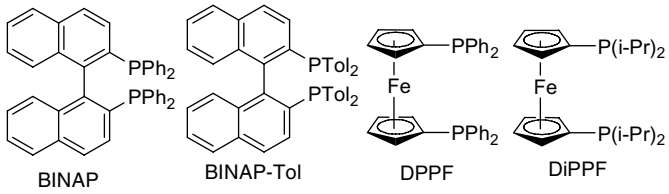


Figure 2. Bis-phosphine ligands.

Table 2. The palladium-catalyzed coupling of aryl iodides (**1** or **2**) with tin-thiolates (Scheme 2 with $R^1 = SnMe_3$, $R^3 = R^4 = R^5 = R^6 = H$, $R^7 = Me$, $X = I$)

Entry	R	Method	Ligand	Conversion (%)	Ratio of substitution:reduction
1	$R^2 = CH_2CH_2OH$, $R^6 = Me$	a	BINAP	17	1:0.13
2	$R^2 = CH_2CH_2OH$, $R^6 = Me$	b	BINAP-Tol	81	1:0.12
3	$R^2 = CH_2CH_2OH$, $R^6 = H$	c	DPPF	100	1:0
4	$R^2 = CH_2CH_2OH$, $R^6 = Me$	d	DPPF	56	1:0.15
5	$R^2 = CH_2CONH_2$, $R^6 = H$	e	DiPPF	51	1:0.19
6	$R^2 = CH_2CONH_2$, $R^6 = Me$	f	DiPPF	76	1:0.14
7	$R^2 = CH_2CH_2OH$, $R^6 = H$	g	DiPPF	6	1:0.083

Note: the ligand structures are shown in Figure 2; R, substituents as shown in Scheme 2; general conditions: 150 °C, 10 min, 300 W; 300 psi, substrate:thiolate = 1:1 in toluene; a, 0.1 equiv $Pd_2(dba)_3$, 0.1 equiv L; b, 0.2 equiv $Pd_2(dba)_3$, 0.4 equiv L; c, 0.11 equiv $Pd_2(dba)_3$, 0.14 equiv L; d, 0.1 equiv $Pd_2(dba)_3$, 0.1 equiv L; e, 0.1 equiv $Pd_2(dba)_3$, 0.2 equiv L; f, 0.2 equiv $Pd_2(dba)_3$, 0.4 equiv L; g, 0.2 equiv $Pd_2(dba)_3$, 0.4 equiv L.

the tin-thiolates were used in Scheme 2, mainly substitution products accompanied by minor reduction products were observed. Different kinds of bis-phosphine ligands were evaluated (Fig. 2, Table 2). BINAP-Tol, DPPF, and DiPPF are efficient ligands for the reaction. Since a number of chelating phosphines have been used in enantioselective hydrogenation,[22] they provide further excellent candidates for evaluation in this reaction (Table 3). Once again, ferrocene-based bis-phosphine, f-binaphane, provided the best combination of reactivity and selectivity.

Palladium catalysts based on phosphine oxide ligands are a new type of efficient, versatile, air-stable and preformed homogeneous catalysts for the C–S bond formation.[9–11] Ten of the most common catalysts were evaluated. Generally, low reactivities and selectivities were observed (Table 4).

When aryl bromides were used to compare the reactivity of thiols versus tin-thiolates, the thiols showed better reactivity but less selectivity (Table 5 and Scheme 2), as in reactions with the iodides.

Table 3. The palladium-catalyzed coupling of aryl iodide (**2**) with thiolates (Scheme 2 with $R^1 = SnMe_3$, $R^2 = CH_2CONH_2$, $R^3 = R^4 = R^5 = R^6 = H$, $R^7 = Me$, $X = I$)

Entry	Ligand	Conversion (%)	Ratio of substitution:reduction
1	T-Phos	22	1:0.91
2	TangPhos	7	1:0.71
3	Binapine	1	1:0.63
4	f-Binaphane	11	1:0.077
5	C4TunePhos	8	1:0.77
6	DuanPhos	0	0
7	Binaphane	0	0

Note: the ligand structures are shown in Ref. 21; method, 150 °C, 10 min, 300 W, 300 psi, substrate:thiolate = 1:1, 0.1 equiv $Pd_2(dba)_3$ and 0.1 equiv L in toluene.

The combination of Pd_2dba_3 as catalyst, DiPPF as ligand and tin-thiolate as reagent was used to synthesize several aryl thiolates in moderate to high yield (Table 6).

When bromo and iodo groups were both present in the same compound, selective substitution of the iodo group was realized using the same reaction conditions developed above, using stoichiometric quantities of tin-thiolates (Table 7).

Table 4. The palladium-catalyzed coupling of aryl iodide (**2**) with tin-thiolates (Scheme 2 with $R^1 = SnMe_3$, $R^2 = CH_2CONH_2$, $R^3 = R^4 = R^5 = R^6 = H$, $R^7 = Me$, $X = I$)

Entry	Catalyst	Method	Conversion (%)	Ratio of substitution: reduction
1	POPd	B1	0	
2	POPd	B3	0	
3	PXPd	B1	2	1:0.63
4	PXPd7	B1	7	1:0.77
5	PXPd7	B2	2	1:0.83
6	PXPd7	B3	3	1:0.50
7	POPd2	B1	0[a,b]	
8	POPd2	B2	0	
9	POPd2	B3	1	1:0
10	PXPd2	B1	2	1:1.7
11	POPd6	B1	0	
12	PXPd6	B1	2	1:2.5
13	POPd1	B1	0	
14	POPd1	B2	0	
15	POPd1	B3	0	
16	POPd7	B1	0	
17	POPd7	B2	0	
18	Ph1-Phoxide	B1	3	1:0.59

Note: the catalyst structures are shown in Refs. 8–10; general conditions: 150 °C, 10 min, 300 W, 300 psi, substrate:thiolate = 1:1.5 in toluene; B1, 2.5 equiv K_2CO_3; B2, 2.5 equiv K_2CO_3 and 2.5 equiv TEA; B3, 2 equiv *t*-BuOK.

[a] When thiol was used, no reaction was observed.

[b] Other thiols, such as $HSCH_2CH_2OH$, also did not react.

Table 5. The palladium-catalyzed coupling of aryl bromides with thiols or tin-thiolates (Scheme 2 with $R^3 = R^4 = H$, $R^5 = Me$, $R^6 = H$, $R^7 = Me$, $X = Br$)

Entry	R	Ligand	Method	Conversion (%)	Ratio of substitution:reduction
1	$R^1 = SnMe_3$, $R^2 = CH_2CH_2OH$	BINAP	a	6	1:0
2	$R^1 = SnMe_3$, $R^2 = CH_2CH_2OH$	BINAP-Tol	b	16	1:0
3	$R^1 = SnMe_3$, $R^2 = CH_2CH_2OH$	DPPF	c	0.4	1:0
4	$R^1 = SnMe_3$, $R^2 = CH_2CH_2OH$	DiPPF	d	14	1:0
5	$R^1 = SnMe_3$, $R^2 = CH_2CONH_2$	DiPPF	e	26	1:0
6	$R^1 = H$, $R^2 = CH_2CH_2OH$	DiPPF	f, g	100	1:0.06
7	$R^1 = H$, $R^2 = CH_2CONH_2$	DiPPF	h	26	1:0.67

Note: the ligand structures are as shown in Figure 2; R, substituents shown in Scheme 2. General conditions for tin-thiolate reaction: 150 °C, 10 min, 300 W, 300 psi, substrate:thiolate = 1:1 in toluene; a, 0.1 equiv $Pd_2(dba)_3$ and 0.1 equiv L; b, 0.2 equiv $Pd_2(dba)_3$ and 0.2 equiv L; c, 0.1 equiv $Pd_2(dba)_3$ and 0.1 equiv L; d, 0.2 equiv $Pd_2(dba)_3$ and 0.4 equiv L; e, 0.2 equiv $Pd_2(dba)_3$ and 0.4 equiv L. General conditions for thiol reaction: 150 °C, 10 min, 300 W, 300 psi, 11.2 equiv *t*-BuOK; f, 0.2 equiv $Pd(OAc)_2$ and 0.23 equiv L in dioxane; g, 0.2 equiv $Pd_2(dba)_3$ and 0.23 equiv L in toluene; h, 0.2 equiv $Pd_2(dba)_3$ and 0.23 equiv L in dioxane.

Table 6. Thioethers synthesized by palladium-based catalysis (Scheme 2 with $R^1 = SnMe_3$, $R^3 = R^4 = H$, $R^7 = Me$)

X	R^5	R^6	R^2	M	Yield (%)[a]
I	H	H	CH_2CONH_2	C1	78
I	H	Me	CH_2CONH_2	C2	85
I	H	H	CH_2CH_2OH	C1	91
I	H	Me	CH_2CH_2OH	C2	89
I	H	Me	$CH_2C_6H_4OCH_3$	C3	85[b]
Br	Me	H	CH_2CONH_2	C4	69
Br	Me	H	CH_2CH_2OH	C4	69

Note: general conditions: 150 °C, 10 min, 300 W, 300 psi, substrate:thiolate = 1:1–1.5 in toluene; L = DiPPF; method C1, 0.1 equiv $Pd_2(dba)_3$ and 0.1 equiv L; method C2, 0.2 equiv $Pd_2(dba)_3$ and 0.4 equiv L; method C3, 0.2 equiv $Pd_2(dba)_3$ and 0.2 equiv L; method C4, 0.2 equiv $Pd_2(dba)_3$ and 0.8 equiv L.

[a] Isolated yield of the substitution product from reverse phase HPLC.

[b] When B_2O_3 was used with the thiol instead of tin-thiolate, no reaction was observed.

Table 7. Thioethers synthesized by palladium-based catalysis (Scheme 2 with $R^1 = SnMe_3$, $R^3R^4 = CH_2CH_2$, $R^5 = Br$, $R^6 = Me$, $R^7 = Ac$)

X	R^2	Yield (%)[a]
I	CH_2CONH_2	60
I	CH_2CH_2OH	94

Note: general conditions: 150 °C, 10 min, 300 W, 300 psi, substrate:thiolate = 1:1, 0.1 equiv $Pd_2(dba)_3$, 0.1 equiv DiPPF in toluene.

[a] Isolated yield of the substitution product from reverse phase HPLC.

In summary, we have developed a method with microwave heating for the rapid, selective and efficient substitution of bromo or iodo groups in aryl halides by tin-thiolates. This procedure is applicable to substrates with an easily reducible iodo group, in either the presence or absence of a bromo group. Lower reactivity and higher selectivity were observed as compared with those using thiols as reagents. The corresponding reactions under conventional heating did not generate any appreciable amount of products except for those without any heteroatoms in the substrates (no data shown).

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