



Palladium-catalyzed C–S bond formation by using *N*-amido imidazolium salts as ligands



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ABSTRACT

N-Amido imidazolium salt was employed as a ligand in the palladium-catalyzed cross-coupling reaction of aryl halides and thiols, and showed good activity in the formation of thioether. The best combination for the coupling with aryl bromides was *N*-amido imidazolium salt **2** and NaHMDS, and that for the coupling with aryl iodides was *N*-amido imidazolium salt **1** and KO^tBu. The coupling reactions were conducted in the presence of Pd(OAc)₂ (1 mol %) in DMSO at 80 °C for 12 h.

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Palladium-catalyzed transformation is one of the most important methods in organic synthesis. A number of methods have been developed and applied in the pharmaceutical and material fields. Palladium-catalyzed coupling reactions such as C–C, C–N, C–S, and C–O bond formations have been studied intensively. The C–S bond formation provides thioether, which is one of the most important structures in functional organic compounds, such as pharmaceutical, bioactive, and electro materials.¹ Although Migita first reported the palladium-catalyzed C–S bond formation to produce thioether,² a number of related methodologies have been intensively developed using transition metal catalysts, including palladium,³ copper,⁴ nickel,⁵ cobalt,⁶ gold,⁷ indium,⁸ iron,⁹ and manganese.¹⁰ It is important to develop a suitable ligand due to the fact that thiol deactivates the palladium catalyst.¹¹ To address this issue, sterically bulky phosphines¹² and carbene¹³ compounds have been developed and employed as ligands. Among them, a variety of imidazolium salts which are precursors of carbene have also been developed. Recently, we reported on amido-type *N*-heterocyclic imidazolium salts, and used them as ligand precursors in Suzuki coupling reactions of the heteroaromatic compounds.¹⁴ They have several advantages, such as easy derivatization, simple preparation steps, and good activities in the coupling of aryl bromides. We planned to develop a catalytic system for the C–S bond formation by using amido-type *N*-heterocyclic imidazolium salts as ligands. As shown in Figure 1, four kinds of *N*-amido heterocyclic

imidazolium salts **1**, **2**, **3**, and **4** were employed as ligands. It is believed that compound **1**, which has two mesityl groups, shows the least sterically hindered property, and compound **4**, with 2,6-isopropylphenyl and 2,4,6-*tert*-butylphenyl groups, shows the most sterically bulky property.

Bromobenzene and thiophenol were chosen as model substrates and reacted in the presence of Pd(OAc)₂ and a base. We employed 6 kinds of bases: NaO^tBu, KO^tBu, NaHMDS, KHMDS, Cs₂CO₃, and K₂CO₃. The results are summarized in Table 1 and Figure 2.

The imidazolium salt bearing a small substituent of mesityl showed lower yields than the others (entries 1–6). The weak bases Cs₂CO₃ and K₂CO₃ exhibited no activity in this coupling reaction. Alkoxide bases NaO^tBu and KO^tBu provided the desired coupled product, but they did not show satisfactory results. 2,6-diisopropylphenyl-substituted imidazolium compounds **2**, **3**, and **4** showed good yields of product in the presence of NaHMDS or KHMDS. Among them, the combination of ligand **2** and NaHMDS showed the best result in the C–S bond formation.

Next, we evaluated these optimized conditions in the coupling reaction of aryl bromides and thiols. The results are summarized in Scheme 1.¹⁵ In the reaction with thiophenol, phenyl bromide provided the desired product **7a** in 90% isolated yield. Alkyl or alkoxy substituted aryl bromides showed good yields. 4-Bromobenzonitrile and 1-bromo-4-nitrobenzene were coupled with thiophenol and provided **7f** and **7g** in 77% and 67% yield, respectively. Aryl bromide bearing ketone group gave the desired product in 77% yield, but aryl bromides with ester or aldehyde group provided the corresponding coupled products in good yield by using NaO^tBu

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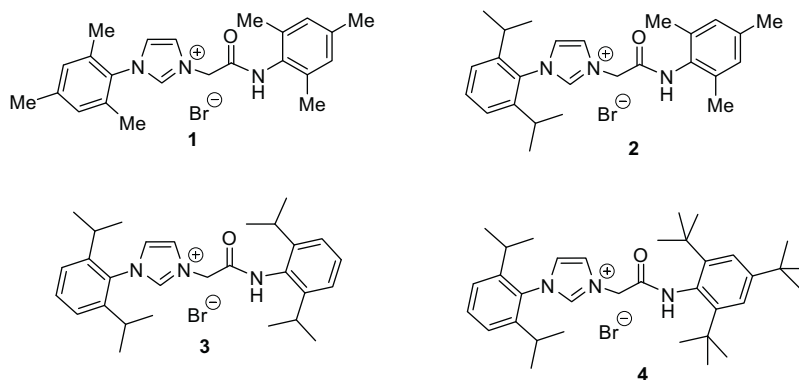
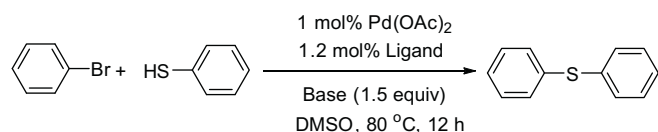
Figure 1. *N*-Amido imidazolium salts.

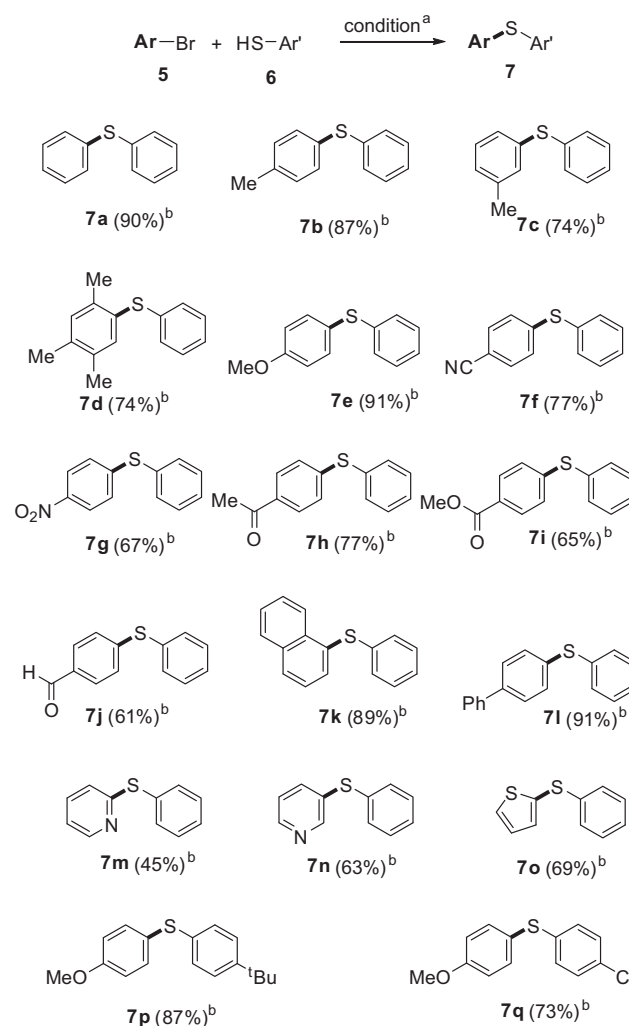
Table 1
The optimization conditions for the coupling of bromobenzene and thiophenol with *N*-amido imidazolium salts as ligands^a



Ligand	Base	NaO ^t Bu	KO ^t Bu	NaHMDS	KHMDS	Cs ₂ CO ₃	K ₂ CO ₃
1	Entry	1	2	3	4	5	6
	(yield) ^b	(9%)	(7%)	(11%)	(15%)	(–)	(–)
2	Entry	7	8	9	10	11	12
	(yield) ^b	(10%)	(9%)	(89%)	(79%)	(–)	(–)
3	Entry	13	14	15	16	17	18
	(yield) ^b	(19%)	(29%)	(77%)	(72%)	(–)	(–)
4	Entry	19	20	21	22	23	24
	(yield) ^b	(23%)	(13%)	(74%)	(73%)	(–)	(–)

^a Reaction conditions: PhBr (0.3 mmol), PhSH (0.3 mmol), Pd(OAc)₂ (1 mol %), and ligand (1.2 mol %) were reacted in DMSO at 80 °C for 12 h.

^b Yield was determined by GC with internal standard.



Scheme 1. The synthesis of thioethers from the coupling with a variety of aryl bromides. ^aReagents and conditions: ArBr (3.0 mmol), ArSH (3.0 mmol), Pd(OAc)₂ (0.03 mmol), ligand **2** (0.036 mmol), and NaHMDS (4.5 mmol) were reacted in DMSO at 80 °C for 12 h. ^bIsolated yield. ^cNaO^tBu was used instead of NaHMDS.

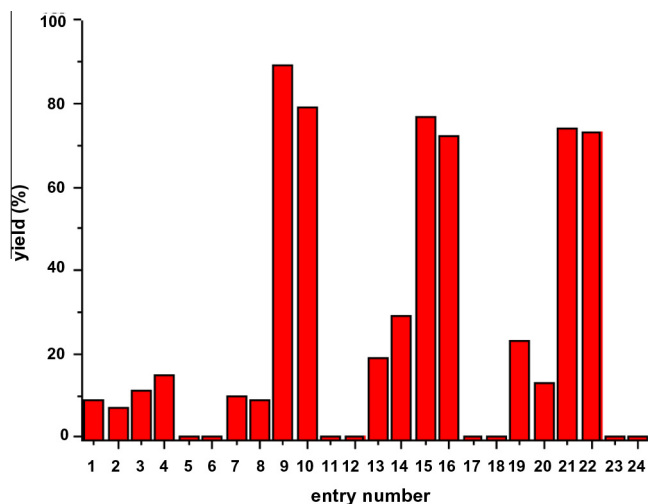


Figure 2. The yields of diphenylsulfide in the Table 1.

instead of NaHMDS. 1-Bromonaphthalene and 4-bromobiphenyl afforded **7k** and **7l** in 89% and 91% yield, respectively. Heteroaryl bromides such as 2-, 3-bromopyridine and 2-bromothiophene gave the desired products in moderate to good yields. Substituted thiols also showed good yields in these coupling conditions.

It was often found that the best ligand and base system which showed good reactivity toward aryl bromides was not always good for aryl bromides. We tested four kinds of *N*-amido imidazolium salts as ligands for the coupling reaction of iodobenzene and thiophenol. As shown in Table 2, strong bases were employed as the base.

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