

# Efficient ligand-free nickel-catalyzed C–S cross-coupling of thiols with aryl iodides

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## Abstract

NiCl<sub>2</sub>·6H<sub>2</sub>O efficiently catalyzes the C–S bond formation by the cross-coupling of aryl iodides with thiols in tetrabutylammonium bromide (TBAB) in excellent yield. The reaction functions in air and the NiLn-TBAB can be recovered and recycled without the loss of activity.

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**Keywords:** C–S bond formation; Cross-coupling; Thiols; Aryl iodides; Synthetic method

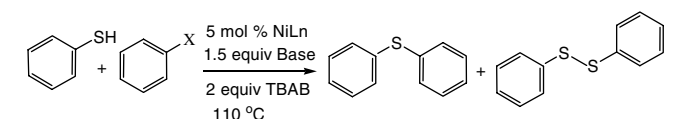
## 1. Introduction

Transition metal-catalyzed cross-coupling reactions of aryl halides with various nucleophilic compounds are now among the most prominent synthetic methods for the formation of carbon-heteroatom bonds.<sup>1</sup> Among these, the formation of C–S bond has received much attention due to the occurrence of this bond in many molecules that are of biological, pharmaceutical, and material interest.<sup>2</sup> In 1980, Migita and co-workers first reported the cross-coupling of aryl halides with thiols in the presence of [Pd(PPh<sub>3</sub>)<sub>4</sub>] as the catalyst and NaO<sup>t</sup>Bu as a base in polar solvents, such as ethanol at reflux or dimethyl sulfoxide (DMSO) at 90 °C.<sup>3</sup> Copper,<sup>4</sup> palladium,<sup>5</sup> nickel,<sup>6</sup> and cobalt-based<sup>7</sup> catalytic systems have since been studied for this purpose. Most of these studies have shown that the catalysts with electron-rich ligands are effective and usually function in anhydrous organic solvents under inert atmosphere.

The use of molten salt for organic reactions has been intensive in recent years,<sup>8</sup> because they provide simplified

product isolation, easy recovery and recyclability of the catalysts, excellent thermal stability, and low vapor pressure. Herein, we report that the readily available NiCl<sub>2</sub>·6H<sub>2</sub>O efficiently catalyzes the cross-coupling of thiols with aryl iodides in tetrabutylammonium bromide (TBAB) with excellent yield. It is ligand-free and the

Table 1  
The reaction of benzenethiol with aryl halides




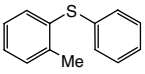

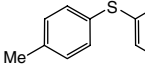

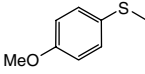

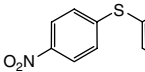

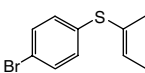

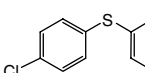

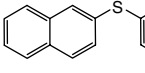

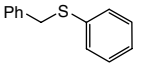

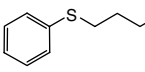
Catalyst	X	Base	Time (h)	PhSPh (%)	PhSSPh <sup>a,b</sup> (%)
Ni(OAc) <sub>2</sub> ·4H <sub>2</sub> O	I	KOH	10	80	—
NiNO <sub>3</sub> ·6H <sub>2</sub> O	I	KOH	10	85	—
NiCl <sub>2</sub> ·6H <sub>2</sub> O	I	KOH	10	99	—
NiCl <sub>2</sub> ·6H <sub>2</sub> O	Br	KOH	14	23	—
NiCl <sub>2</sub> ·6H <sub>2</sub> O	Cl	KOH	14	14	—
NiCl <sub>2</sub> ·6H <sub>2</sub> O	I	K <sub>2</sub> CO <sub>3</sub>	10	10	36
NiCl <sub>2</sub> ·6H <sub>2</sub> O	I	Pyridine	10	23	30

<sup>a</sup> Catalyst (5 mol %), benzenethiol (5 mmol), aryl halide (5.5 mmol), base (7.5 mmol) and TBAB (10 mmol) were stirred at 110 °C for 10 h under air.

<sup>b</sup> Isolated yield.

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Table 2  
The reaction of various thiols with iodobenzene

Entry	Thiol	Time (h)	Product	Yield <sup>a,b</sup> (%)
1		10		89
2		9		95
3		8		97
4		12		94
5		10		93
6		8		95
7		8		98
8		12		92
9		12		10

<sup>a</sup> NiCl<sub>2</sub>·6H<sub>2</sub>O (5 mol %), thiol (1 mmol), iodobenzene (1.1 mmol), KOH (1.5 mmol) and TBAB (2 mmol) were stirred at 110 °C under air.

<sup>b</sup> Isolated yield.

NiLn/TBAB can be recovered and recycled without the loss of activity.

We first studied the reaction of the model substrate benzenethiol with iodobenzene (Table 1).<sup>9</sup> The reaction occurred to provide the desired C–S cross-coupled diphenylsulfide in 99% yield when the substrate was stirred at 110 °C with 5 mol % of NiCl<sub>2</sub>·6H<sub>2</sub>O, 1.1 equiv of iodobenzene, and 1.5 equiv of KOH in 2 equiv of TBAB under air. Of the bases tested, KOH, K<sub>2</sub>CO<sub>3</sub>, and pyridine, the former provided the best result. Among the nickel(II) salts studied, NiCl<sub>2</sub>·6H<sub>2</sub>O was superior to Ni(OAc)<sub>2</sub>·4H<sub>2</sub>O and Ni(NO<sub>3</sub>)<sub>2</sub>·6H<sub>2</sub>O. Iodobenzene was a more reactive compared to chlorobenzene and bromobenzene.

Next, we studied the scope of the procedure for the cross-coupling of various thiols with iodobenzene (Table 2).<sup>9</sup> 2-Methyl-, 4-methyl-, 4-methoxy-, 4-nitro-, 4-bromo-, and 4-chlorobenzenethiol underwent reaction in 89–98% yield. Similar results were observed with 2-naphthyl and benzyl thiol affording the C–S cross-coupled products in 98% and 92% yields, respectively, while the substrate having

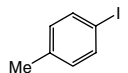
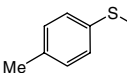
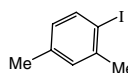
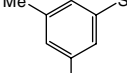
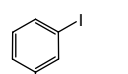
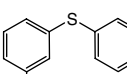
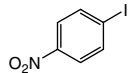
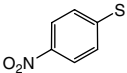
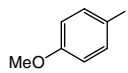
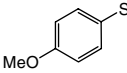
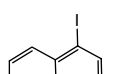
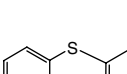
alkyl chain, 1-butanethiol, was less reactive providing butyl(phenyl)sulfide in 10% yield.

The reaction of substituted aryl iodides with benzenethiol was further examined (Table 3).<sup>9</sup> Aryl iodide having electron withdrawing group was more reactive in comparison to those with electron donating group. Thus, aryl iodide with methyl and methoxy substituents underwent reaction to give the corresponding C–S cross-coupled products in 70–99% yield, while the reaction of aryl iodides with nitro substituent completed in 94–98% yield. Under these conditions, 1-iodonaphthalene underwent reaction to give the respective cross-coupled product in 91% yield.

Finally, we investigated the reaction of various thiols with 1-iodo-4-nitrobenzene (Table 4). 2-Methyl-, 4-methyl-, 4-methoxy-, 4-nitro-, 4-bromo-, and 4-chlorobenzenethiol underwent reaction in 91–99% yield. Similar results were observed with 2-naphthyl and benzyl thiol providing the cross-coupled products in 94% and 90% yield, respectively.

The NiLn/TBAB is recyclable without the loss of activity (Table 5). After the completion of the reaction, the product was isolated from the reaction mixture by extracting with diethyl ether. The insoluble NiLn/TBAB was reused for the fresh reaction of 4-methylbenzenethiol with 1-iodo-4-nitrobenzene. The reaction occurred to afford the cross-coupled product in 99% yield. This process was

Table 3  
Reaction of benzenethiol with aryl and naphthyl iodides

Entry	Iodide	Product	Time (h)	Yield <sup>a,b</sup> (%)
1			10	99
2			12	91
3			4	94
4			3	98
5			10	70
6			10	91

<sup>a</sup> NiCl<sub>2</sub>·6H<sub>2</sub>O (5 mol %), benzenethiol (1 mmol), aryl/naphthyl iodide (1.1 mmol), base (1.5 mmol) and TBAB (2 mmol) were stirred at 110 °C under air.

<sup>b</sup> Isolated yield.

Table 4  
Reaction of various thiols with 1-iodo-4-nitrobenzene

Entry	Thiol	Product	Time (h)	Yield <sup>a,b</sup> (%)
1			6	92
2			3	97
3			2	99
4			5	96
5			6	91
6			4.5	95
7			4	98
8			4	94
9			7	90

<sup>a</sup> NiCl<sub>2</sub>·6H<sub>2</sub>O (5 mol %), thiol (1 mmol), 1-iodo-4-nitrobenzene (1.1 mmol), base (1.5 mmol) and TBAB (2 mmol) were stirred at 110 °C under air.

<sup>b</sup> Isolated yield.

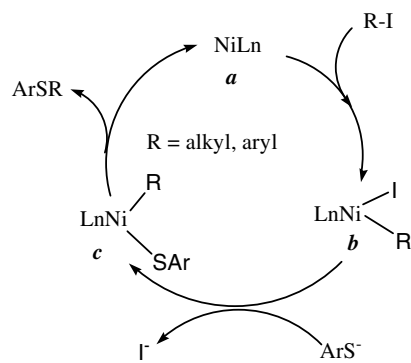
Table 5  
Recyclability of NiLn-TBAB

Run	NiLn-TBAB recovery (%)	Product (yield, %) <sup>a,b</sup>
1	>99	99
2	>99	99 <sup>c</sup>
3	>99	99 <sup>c</sup>
4	>99	99 <sup>c</sup>
5	99	98 <sup>c</sup>

<sup>a</sup> NiCl<sub>2</sub>·6H<sub>2</sub>O (5 mol %), 4-methylbenzenethiol (1 mmol), 1-iodo-4-nitrobenzene (1.1 mmol), base (1.5 mmol) and TBAB (2 mmol) were stirred under air.

<sup>b</sup> Isolated yield.

<sup>c</sup> Recovered and used.



Scheme 1. Proposed reaction pathway.

repeated up to five runs and no loss of activity was observed.

The proposed reaction pathway for these reactions is shown in Scheme 1. Oxidative addition of the aryl iodide with the catalyst may provide intermediate **b**, which on reaction with thiol can give intermediate **c**. Intermediate **c** can provide the desired C–S cross-coupled product by reductive elimination.

## 2. Conclusions

A simple and efficient procedure is described for the C–S cross-coupling of aromatic and benzyl thiols with aryl iodides using NiCl<sub>2</sub>·6H<sub>2</sub>O in TBAB under air. It is ligand-free and the NiLn/TBAB can be recovered and recycled without the loss of activity.

## Acknowledgments

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## References and notes

- (a) Hartwig, J. F. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley-Interscience: New York, 2002; Vol. 1, p 1051; (b) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131; (c) Prim, D.; Campagne, J.-M.; Joseph, D.; Andrioletti, B. *Tetrahedron* **2002**, *58*, 2041; (d) Kondo, T.; Mitsudo, T.-A. *Chem. Rev.* **2000**, *100*, 3205; (e) Hartwig, J. F. *Acc. Chem. Res.* **1998**, *31*, 852; (f) Beletskaya, I. P.; Ananikov, V. P. *Eur. J. Org. Chem.* **2007**, 3431.
- (a) Jones, D. N. In *Comprehensive Organic Chemistry*; Barton, D. H., Ollis, D. W., Eds.; Pergamon: New York, 1979; Vol. 3; (b) Tiecco, M. *Synthesis-Stuttgart* **1988**, 749; (c) Rayner, C. M. *Contemp. Org. Synth.* **1996**, *3*, 499; (d) Baird, C. P.; Rayner, C. M. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1973; (e) Procter, D. J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 641; (f) Procter, D. J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 335; (g) Frost, C. G.; Mendonca, P. J. *Chem. Soc., Perkin Trans. 1* **1998**, 2615; (h) Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359; (i) Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, *248*, 2337; (j) Corbet, J.-P.; Mignani, G. *Chem. Rev.* **2006**, *106*, 2651; (k) Ullmann, F. *Ber. Dtsch. Chem. Ges.* **1903**, *36*, 2382; (l) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400; (m) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*,

- 2046; (n) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805.
3. (a) Migita, T.; Shimizu, T.; Asami, Y.; Shiobara, J.; Kato, Y.; Kosugi, M. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1385; (b) Kosugi, M.; Ogata, T.; Terada, M.; Sano, H.; Migita, T. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 3657.
4. (a) Rout, L.; Sen, T. K.; Punniyamurthy, T. *Angew. Chem., Int. Ed.* **2007**, *37*, 2046; (b) Bates, C. G.; Gujadhur, R. K.; Venkataraman, D. *Org. Lett.* **2002**, *4*, 2803; (c) Kwong, F. Y.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 3517; (d) Wu, Y.-J.; He, H. *Synlett* **2003**, 1789; (e) Bates, C. G.; Saejueng, P.; Doherty, M. Q.; Venkataraman, D. *Org. Lett.* **2004**, *6*, 5005; (f) Deng, W.; Zou, Y.; Wang, Y.-F.; Liu, L.; Guo, Q.-X. *Synlett* **2004**, 1254; (g) Palomo, C.; Oiarbide, M.; Lopez, R.; Gomez-Bengoia, E. *Tetrahedron Lett.* **2000**, *41*, 1283; (h) Savarin, C.; Srogl, J.; Liebeskind, L. S. *Org. Lett.* **2002**, *4*, 4309; (i) Herradura, P. S.; Pendola, K. A.; Guy, R. K. *Org. Lett.* **2000**, *2*, 2019; (j) Chen, Y.-J.; Chen, H.-H. *Org. Lett.* **2006**, *8*, 5609; (k) Zhu, D.; Xu, L.; Wu, F.; Wan, B. *Tetrahedron Lett.* **2006**, *47*, 5781.
5. (a) Mispelaere-Canivet, C.; Spindler, J.-F.; Perrio, S.; Beslin, P. *Tetrahedron* **2005**, *61*, 5253; (b) Itoh, T.; Mase, T. *Org. Lett.* **2004**, *6*, 4587; (c) Fernandez-Rodriguez, M. A.; Shen, Q.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 2180; (d) Murata, M.; Buchwald, S. L. *Tetrahedron* **2004**, *60*, 7397; (e) Schopfer, U.; Schlapbach, A. *Tetrahedron* **2001**, *57*, 3069; (f) Li, G. Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 1513; (g) Barbieri, R. S.; Bellato, C. R.; Dias, A. K. C.; Massabni, A. C. *Catal. Lett.* **2006**, *109*, 171; (h) Dickens, M. J.; Gilday, J. P.; Mowlem, T. J.; Widdowson, D. A. *Tetrahedron* **1991**, *47*, 8621; (i) Ishiyama, T.; Mori, M.; Suzuki, A.; Miyaura, N. *J. Organomet. Chem.* **1996**, *525*, 225; (j) Zheng, N.; McWilliams, J. C.; Fleitz, F. J.; Armstrong, J. D.; Volante, R. P. *J. Org. Chem.* **1998**, *63*, 9606; (k) Mann, G.; Baranano, D.; Hartwig, J. F.; Rheingold, A. L.; Guzei, I. A. *J. Am. Chem. Soc.* **1998**, *120*, 9205.
6. (a) Cristau, H. J.; Chabaud, B.; Chene, A.; Christol, H. *Synthesis* **1981**, 892; (b) Millois, C.; Diaz, P. *Org. Lett.* **2000**, *2*, 1705; (c) Percec, V.; Bae, J.-Y.; Hill, D. H. *J. Org. Chem.* **1995**, *60*, 6895; (d) Takagi, K. *Chem. Lett.* **1987**, 2221.
7. Wong, Y.-C.; Jayanth, T. T.; Cheng, C.-H. *Org. Lett.* **2006**, *8*, 5613.
8. Parvulescu, V. I.; Hardacre, C. *Chem. Rev.* **2007**, *107*, 2615.
9. NiCl<sub>2</sub>·6H<sub>2</sub>O (12 mg, 5 mol %), TBAB (644 mg, 2 mmol), KOH (84 mg, 1.5 mmol), aryl iodide (1.1 mmol) and thiol (1 mmol) were stirred at 110 °C under air for the appropriate time until complete consumption of starting material. The progress of the reaction was monitored by TLC using ethyl acetate and hexane as eluent. The reaction mixture was then cooled to ambient temperature and extracted with diethyl ether. The insoluble NiLn/TBAB was recovered and recycled without the loss of activity. The combined diethyl ether solution was dried (Na<sub>2</sub>SO<sub>4</sub>), concentrated and passed through a short pad of silica gel to afford analytically pure C–S cross-coupled product.