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Nickel-Mediated Inter- and Intramolecular C–S Coupling of Thiols and Thioacetates with Aryl Iodides at Room Temperature

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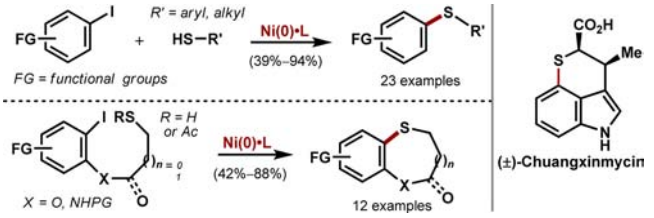
ABSTRACT



A Ni(0)-catalyzed intermolecular cross-coupling of various functionalized thiols and aryl iodides has been developed and successfully extended to less explored intramolecular versions, where thioacetates could also be utilized as the strategic surrogate. Air-stable precatalysts, very mild conditions, and an easy protocol allow rapid access to medicinally useful aryl thioethers, as demonstrated in the facile synthesis of (±)-chuangxinmycin as a key step.

Aryl thioether moieties are prevalent in a wide range of bioactive natural products and pharmaceuticals. As demonstrated in Figure 1: gemmacin[1] shows broad-spectrum Gram-positive antibacterial activity in vitro, including growth inhibition of vancomycin-intermediate *S. aureus* and vancomycin-resistant enterococci; diltiazem[2a] as a typical calcium antagonist has been used as a remedy for angina and hypertension; and F 15845[3] shows cardiac sodium current inhibition and antiischemic effects. Thus, there have already been some advances in aryl–sulfur bond construction,[4] among which transition-metal-catalyzed cross-coupling of aryl halides and thiols played an important role.[5] However, this progress is limited compared to that of well-established C–N and C–O coupling reactions,[6] since organic sulfur compounds easily poison the catalyst due to their superfluous coordination with the metal in the catalyst, and therefore most of the known methods often rely on harsh conditions such as strong bases (*t*-BuOK, *t*-BuONa, etc.), high reaction temperatures (80–135 °C),[5a–d,f–h] and use of expensive or air-sensitive ligands and excessive reagents. Consequently, an alternative protocol is still in high demand; in particular, intramolecular C–S cross-coupling remains much less explored.[7] Recently, we disclosed a C–C reductive cross-coupling reaction under mild conditions by using a readily

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(7) For an isolated example in which CuI/*N*,*N*-dimethylglycine catalyzed Ullmann-type coupling was utilized, see: Gan, J.; Ma, D. *Org. Lett.* **2009**, *11*, 2788.

(8) Yan, C.-S.; Peng, Y.; Xu, X.-B.; Wang, Y.-W. *Chem.—Eur. J* **2012**, *18*, 6039.

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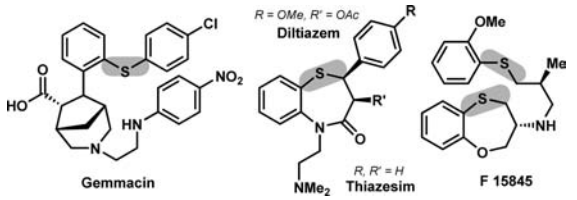
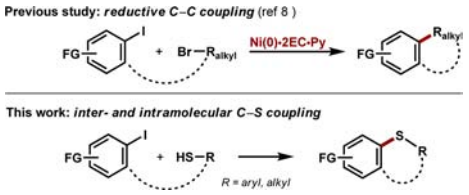


Figure 1. Bioactive aryl thioether molecules.

Scheme 1. C−C *versus* C−S Cross-Coupling



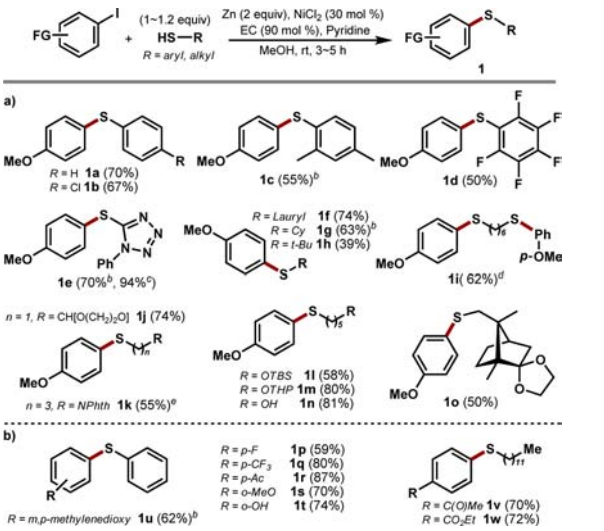
accessible and extremely cheap Ni(0) complex (Scheme 1, top);[8] herein, this versatile catalyst has been extended to inter- and intramolecular C−S coupling where broad tolerance to functional groups and practical application were demonstrated preliminarily.

Our studies commenced with examining intermolecular C−S coupling between *p*-iodoanisole and benzenethiol (see Table S1 in Supporting Information (SI)) using Ni(0)•2EC•Py as the catalyst, which is readily generated in situ from a mixture of Zn/$NiCl_2$/pyridine/ethyl crotonate (EC) at 55 °C according to a previously established procedure.[8] After screening the different solvents, MeOH was found to be the best choice. With a stoichiometric amount of this complex, the intended cross-coupling indeed occurred at rt, and the desired thioether **1a** was formed in 88% yield; its yield slightly decreased to 72% when 30 mol % Ni(0) complex was employed. The addition sequence of two coupling partners also proved to be important: first, the introduction of *p*-iodoanisole into the above Ni(0) catalyst followed by the addition of PhSH (1.2 equiv) could guarantee the efficient formation of a carbon−sulfur bond. The analogous Ni(0) catalyst generated by 2,2′-bipyridine[9] as a ligand afforded a comparable result.

With the above optimized conditions in hand, cross-couplings of various functionalized aryl thiols with *p*-iodoanisole were then investigated (Scheme 2a). To our delight, benzenethiols with Me and Cl groups, even pentafluorobenzenethiol, reacted smoothly, affording the corresponding unsymmetrical diaryl thioethers (**1b**−**1d**) in moderate yields. Moreover, 5-mercapto-1-phenyl-1*H*-tetrazole was also suitable, and the corresponding aryl-heteroaryl thioether **1e** could be isolated in 70% yield.

(9) For recent applications of this kind of ligands in Ni-catalyzed synthesis of trifluoromethyl thioethers and C−C coupling respectively, see: (a) Zhang, C.-P.; Vicic, D. A. *J. Am. Chem. Soc.* **2012**, *134*, 183. (b) Wang, S.; Qian, Q.; Gong, H. *Org. Lett.* **2012**, *14*, 3352.

Scheme 2. Intermolecular C−S Cross-Coupling[a]



[a] Reaction conducted on 1 mmol scale, and the isolated product yield is shown. [b] 2,2′-Bipyridine (36 mol %) as the ligand was employed instead of ethyl crotonate (EC). [c] Reaction conducted on 6 mmol (1.07 g) of thiol, Zn (0.5 equiv), $NiCl_2$ (10 mol %), and 2,2′-bipyridine (12 mol %), and the isolated yield of **1e** is 94%. [d] 2.4 equiv of 4-iodoanisole relative to 1,6-hexanedithiol, Zn (2 equiv), $NiCl_2$ (50 mol %), and 2,2′-bipyridine (60 mol %) were employed. The isolated yield of **1i** is 52% when EC (2 equiv) was employed. [e] Zn (2 equiv), $NiCl_2$ (50 mol %), and 2,2′-bipyridine (60 mol %) were employed for a corresponding thioester.

Importantly, this reaction can be also carried out in gram scale with a significant increase of efficiency even with 10 mol % Ni(0) catalyst (see SI). Aliphatic (1°, 2°, 3°) thiols, a class of relatively difficult substrates,[5f] were examined next, and all of the lauryl, cyclohexyl, and *tert*-butyl mercaptans[10,5e] gave the desired alkyl aryl thioethers (**1f**−**1h**) with good to moderate yields, respectively. Interestingly, double S-arylation[11] of 1,6-hexanedithiol proceeded smoothly, and symmetrical bisthioether **1i** was obtained in 62% yield. The present C−S cross-coupling showed excellent tolerance to a wide range of functional groups such as acetal (**1j**), NPhth (**1k**), OTBS (**1l**), and OTHP (**1m**). Especially, thioether **1n** with a free hydroxyl group was also formed in 81% yield without accident, obviously demonstrating the mild nature of this cross-coupling reaction since its acidic proton apparently cannot be compatible with the previous conditions with a strong base. Utilization of the neopentyl thiol in C−S cross-coupling is unprecedented due to its notorious steric hindrance; however, 9-mercaptan camphor ethylene ketal derived from (+)-camphor indeed can participate in the above-described coupling, leading to the chiral thioether **1o** that would be served as a potential ligand in asymmetric catalysis,[12] in 50% isolated yield. Besides *p*-iodoanisole,

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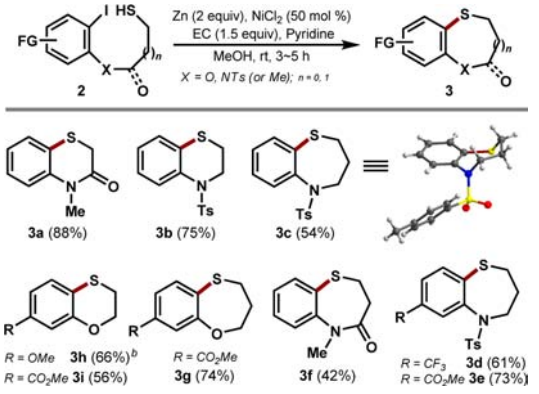
(11) For two examples where CuO nanoparticle catalyzed Ullmann coupling was utilized, see: (a) Xu, H.-J.; Liang, Y.-F.; Zhou, X.-F.; Feng, Y.-S. *Org. Biomol. Chem.* **2012**, *10*, 2562. (b) Rout, L.; Sen, T. K.; Punniyamurthy, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 5583.

(12) Gómez Arrayás, R.; Carretero, J. C. *Chem. Commun.* **2011**, *47*, 2207 and references cited therein.

Scheme 3. Intramolecular C−S Cross-Coupling[a]

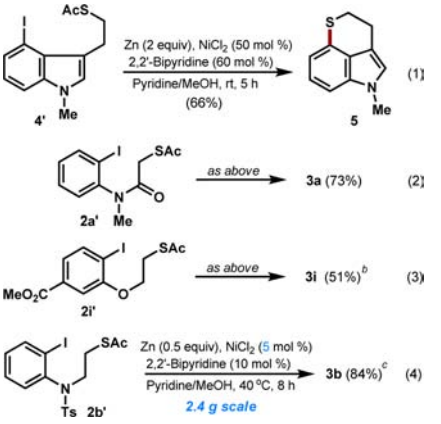


[a] Reaction conducted on 1 mmol scale, and the isolated product yield is shown. [b] 2,2′-Bipyridine (60 mol %) as a ligand was employed instead of ethyl crotonate (EC).

other electron-rich and -deficient phenyl iodides bearing (OMe, OH) and (F, CF_3, COMe, CO_2Et) groups, respectively, also worked well with either aryl or alkyl thiols (Scheme 2b), affording the corresponding cross-coupling products (**1p**−**1r** and **1u**−**1w**) in 59%−87% yields. Both hindered *o*-iodoanisole and *o*-iodophenol also furnished the desired thioethers **1s** and **1t** in good yields. Notably, the present method provided a complementary approach for the synthesis of 2-(phenylthio)phenols, which had already been obtained through Cu(I)-catalyzed tandem transformation of C−S coupling/C−H oxidation by Pan.[13]

Extension of the above intermolecular C−S cross-couplings to a less explored intramolecular version was then explored. The needed cyclization precursors **2** could be prepared conveniently according to procedures described in the SI. As shown in Scheme 3, two 1,4-benzothiazines (**3a** and **3b**) can be obtained in high yields through intramolecular C−S coupling. More challenging 1,5-benzothiazepine, a valuable structural unit in the pharmaceutical industry as aforementioned, also can be obtained in moderate yield, as exemplified in the case of **3c**, whose structure was confirmed by the X-ray diffraction of its single crystal.[14] Two additional 1,5-benzothiazepines **3d** and **3e** bearing CF_3 and CO_2Me groups on the benzene ring respectively were prepared in useful yields as well, indicating that the present C−S coupling is more efficient for the construction of a seven-membered ring than that by our previous C−C coupling.[8] Notably, the access to 1,5-benzothiazepine-4(5*H*)-one **3f** is feasible albeit in moderate yield, and this intramolecular C−S cross-coupling strategy provides a new approach which complements those based on Michael

Scheme 4. Intramolecular C−S Coupling with Thioacetates[a]



[a] Reaction conducted on 1 mmol scale, and the isolated product yield is shown. [b] The isolated yield of **3i** is 35% when K_2CO_3 (1.5 equiv) as an extra base was employed. [c] The isolated yield of **3b** is 92% at rt when $NiCl_2$ (10 mol %) and 2,2′-bipyridine (20 mol %) were employed.

addition[15a] or alkylation[15b,c] of thiols, to the core of two drugs, diltiazem and thiazesim. This catalytic system was also applicable in the efficient construction of 1,5-benzoxathiepines such as **3g**. Finally, two addional 1,4-benzoxathiine products **3h** and **3i** bearing either an electron-donating OMe group or electron-withdrawing CO_2Me group were also demonstrated.

The direct use of thiols has some drawbacks such as a foul smell and sensitivity of oxidation to disulfides. Thioacetate, as a superior surrogate over other sulfur sources due to ease of its installation and cleavage, has been applied in the C−S coupling but only to a limited extent in the intermolecular reactions with base.[16] We surmised that the intramolecular counterpart would be plausible. Gratifyingly, cyclization of thioacetate **4′** derived from 4-bromoindole (*vide infra*; see SI for preparation) proceeded smoothly under standard Ni(0)-mediated conditions except in the replacement of EC by 2,2′-bipyridine as a ligand, and the desired tricyclic thioether **5** with some strain could be isolated in 66% yield (Scheme 4, eq 1). Other examples were demonstrated in the cyclizations of thioacetates **2a′** and **2i′** (eqs 2 and 3), affording the corresponding thioethers in comparable or even better yields considering this essential two-step (deprotection and coupling) transformation. The unmasked thiol could be detected during the course of reaction; however, introduction of an extra base (e.g., K_2CO_3) in order to facilitate release of thiol led to the decreased yield of thioether (e.g., **3i**) instead, suggesting the mild nature imparted from this unique system. Notably, the above method worked even better on a gram-scale reaction with only 5 mol % Ni(0) catalyst as demonstrated in the case of **2b′** (eq 4), indicating that this protocol would be practically valuable.

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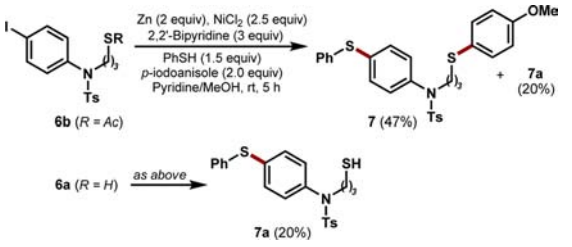
(14) See the CIF file in the Supporting Information for more details.

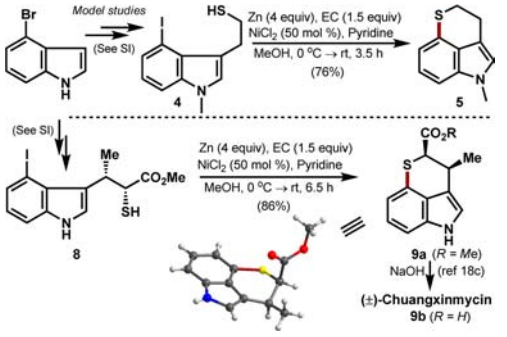
(15) (a) Ogawa, T.; Kumagai, N.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 8551. (b) Choudary, B. M.; Chowdari, N. S.; Madhi, S.; Kantam, M. L. *J. Org. Chem.* **2003**, *68*, 1736. (c) Watson, K. G.; Fung, Y. M.; Gredley, M.; Bird, G. J.; Jackson, W. R.; Gountzos, H.; Mattews, B. R. *J. Chem. Soc., Chem. Commun.* **1990**, 1018.

(16) (a) Wager, K. M.; Daniels, M. H. *Org. Lett.* **2011**, *13*, 4052. (b) Park, N.; Park, K.; Jang, M.; Lee, S. *J. Org. Chem.* **2011**, *76*, 4371.

Scheme 5. Sequential Twofold C−S Cross-Coupling



Scheme 6. Formal Synthesis of (±)-Chuangxinmycin



The unprecedented but interesting sequential twofold C−S cross-coupling reaction was investigated next (Scheme 5). This challenging transformation is orthogonal, distinctively different from the usual parallel double C−S bond construction as exemplified by **1i** and previous reports.[11] The expected bis-coupling product **7** cannot be detected when free thiol **6a** was employed, and only monocoupling thioether **7a** was obtained except for **1a** and some oligomeric substances. However, with thioacetate **6b** as the substrate, the desired bisthioether **7** was indeed formed in fairly good yield (*ca.* 70% per step) along with 20% of **7a**.

Chuangxinmycin **9b** with an arylthioether functionality was isolated from *Actinoplanes tsinanensis* n. sp. in China; it exhibits *in vitro* activity against a number of Gram-positive and -negative bacteria and is particularly effective for the treatment of *Escherichia coli* infection.[17] Its synthesis had been achieved by a variety of approaches.[18] We envisioned that this natural product would be served as a

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(18) (a) Chang, C.-P.; Hsu, H.-D.; Huang, L.-C.; Lin, Y.-C.; Li, H.-S.; Yu, C.-L.; Chao, C.-L. *Acta Chim. Sin.* **1976**, *34*, 133. *Chem. Abstr.* **1978**, *88*, 62309h. (b) Kozikowski, A. P.; Greco, M. N. *J. Am. Chem. Soc.* **1980**, *102*, 1165. (c) Kozikowski, A. P.; Greco, M. N.; Springer, J. P. *J. Am. Chem. Soc.* **1982**, *104*, 7622. (d) Ishibashi, H.; Tabata, T.; Hanaoka, K.; Iriyama, H.; Akamatsu, S.; Ikeda, M. *Tetrahedron Lett.* **1993**, *34*, 489. (e) Kato, K.; Ono, M.; Akita, H. *Tetrahedron Lett.* **1997**, *38*, 1805. (f) Dickens, M. J.; Mowlem, T. J.; Widdowson, D. A.; Slawin, A. M. Z.; Williams, D. J. *J. Chem. Soc., Perkin Trans. 1* **1992**, 323.

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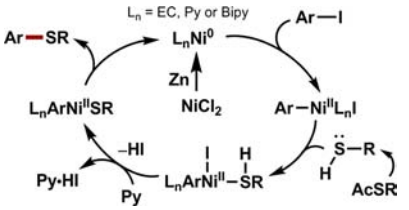
Scheme 7. Proposed Mechanism



effective platform to further evaluate our newly developed methodology. As shown in Scheme 6, model thiol **4** was subjected to an optimized Ni(0) system, and the desired **5** with a tricyclic thioether skeleton was produced in 76% isolated yield. It is noteworthy that this intramolecular reaction can proceed even at 0 °C, the lowest temperature for this kind of C−S coupling reaction, to the best of our knowledge. The successful synthesis of the core structure of chuangxinmycin prompted us to investigate the application in the secondary thiol **8**, which was prepared from 4-bromoindole in a few steps. Similar conditions afforded chuangxinmycin methyl **9a**[14] in a higher yield, and surprisingly the free amine group did not interfere the expected cyclization. Thus, formal synthesis of (±)-chuangxinmycin has already been accomplished.

Based on previous mechanistic hypotheses about Ni-[5h] or Pd-catalyzed[19] C−S coupling, a similar mechanism for the present reaction is proposed in Scheme 7. First, oxidative addition of aryl iodide to Ni^0 gives an $ArNi^{II}I$ species that is subjected to coordination by thiol. The resulting intermediate $IArNi^{II}S(H)R$ would proceed to the $ArNi^{II}SR$ species through elimination of HI assisted by excess pyridine. Subsequent reductive elimination of $ArNi^{II}SR$ furnishes the desired cross-coupling product Ar−SR while regenerating the Ni^0 catalyst.

In summary, we have developed a practical method for C−S bond construction catalyzed by a Ni(0) complex generated in situ under mild, convenient conditions. The less explored but more valuable intramolecular C−S cross-coupling of thiols or thioesters was also achieved, affording diverse medicinally useful aryl thioethers.

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Supporting Information Available. Experimental details; characterization data for new compounds; copies of ^1H, ^{13}C NMR; and crystallographic information files (CIFs) for **3c** and **9a**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.