

Transition-Metal-Free Cross-Coupling of Aryl and Heteroaryl Thiols with Arylzinc Reagents

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(5) Supporting Information

ABSTRACT: Cross-coupling of (hetero)arylthiols with arylzinc reagents via C-S cleavage was performed under transition-metal-free conditions. The reaction displays a wide scope of substrates and high functional-group tolerance. Electron-rich and -deficient



(hetero)arylthiols and arylzinc reagents can be employed in this transformation. Mg^{2+} and Li^+ ions were demonstrated to facilitate the reaction.

C ulfur-containing organic molecules exist widely in natural D products, pesticides, and proteins. The study on functionalization of the C-S bond is of significance in modifying the sulfur-containing molecules and developing synthetic methodology based on organosulfur compounds. Transition-metalcatalyzed C-S bond activation is a main method to achieve the goal.¹⁻⁵ However, the sulfur atom can be strongly bound to transition metals, which poison the catalysts and lead to deactivation.⁶ Hence, developing highly effective catalytic systems or searching for alternative methods is an important research topic. On the other hand, transition-metal-free reactions of unreactive substrates are receiving considerable attention because they are less costly and more environmentally friendly in comparison with transition-metal-catalyzed ones and can avoid any transition metal impurities in pharmaceutical products.⁷ Some examples of transition-metal-free cross-couplings have been reported. Nucleophiles used in the transformation included Grignard reagents,⁸ organozinc reagents,⁹ organoboron reagents,¹⁰ and organoaluminum reagents.¹¹ Electrophiles were mainly organic halides.^{8–11} Allylic alcohols and aryl cyanides were also employed as electrophilic partners.^{9e,10a} In view of the above results and the importance of C-S bond activation, we initiated a study on transition-metal-free cross-coupling of arylthiols with arylzinc reagents.

The reaction of benzenethiol (1a) with p-Me₂NC₆H₄ZnCl (2a) was employed to optimize reaction conditions. Because of the presence of the acidic proton in benzenethiol, excess organozinc reagent was used or a strong base was added to convert benzenethiol to its salt prior to performing the coupling reaction. When benzenethiol was treated with 2.8 equiv of p-Me₂NC₆H₄ZnCl in toluene at 120 °C (bath temperature) for 12 h, the expected product, *N*,*N*-dimethyl[1,1'-biphenyl]-4-amine (3a), was obtained in 93% yield (Table S1 in the SI, entry 1). Benzenethiol was treated with 1.2 equiv of MeMgCl, LiMe, or NaH or 0.6 equiv of Me₂Zn at first and then reacted with 1.6 equiv of p-Me₂NC₆H₄ZnCl to afford 3a in lower yields (Table S1 in the SI, entries 2–5). When benzenethiol was treated with 1.2

equiv of MeZnCl, the following reaction with 1.6 equiv of p-Me₂NC₆H₄ZnCl gave **3a** in 93% yield (Table S1 in the SI, entry 6). Reducing **2a** loading or lowering reaction temperature led to a decrease in yield (Table S1 in the SI, entries 7–10). Other solvents were also tested. The reaction in THF, toluene/iPr₂O (3:1) or toluene/nBu₂O (3:1) gave 85%, 90%, and 88% product yields, respectively. No reaction occurred when DMF or DMSO was employed as a solvent (Table S1 in the SI, entries 11–15). Finally, it was demonstrated that the reaction completed quantitatively when the reaction time was prolonged to 24 h (Table S1 in the SI, entry 16).

It has been reported that Mg²⁺ and Li⁺ ions often play important roles in the Negishi cross-coupling reaction.¹² In the current study, we also examined Mg²⁺ and Li⁺ ion effects. In the process of optimizing the reaction conditions p-Me₂NC₆H₄ZnCl was prepared by reaction of p-Me₂NC₆H₄MgBr with an equimolar amount of $ZnCl_2$ in the presence of 2 equiv of LiCl. In the absence of a LiCl additive, the reaction gave 43% product yield (Table S2 in the SI, entry 1). LiCl additive (1 equiv) led to 88% product yield (Table S2 in the SI, entry 2), being a little lower than that using 2 equiv of LiCl. LiCl additive (3 equiv) did not further improve the yield compared with that using 2 equiv of LiCl additive (Table S2 in the SI, entry 3). In the absence of Mg^{2+} ion, the reaction of p-Me2NC6H4ZnCl (prepared from p- $Me_2NC_6H_4Li$ and $ZnCl_2$) with benzenethiol resulted in 3a in 60% yield (Table S2 in the SI, entry 4). p-Me₂NC₆H₄ZnCl prepared from the reaction of *p*-Me₂NC₆H₄Li and ZnCl₂ in the presence of MgCl₂ showed the same reactivity as those prepared from p-Me₂NC₆H₄MgBr and ZnCl₂ in the presence of LiCl (Table S2 in the SI, entries 5 and 6). In this reaction, Mg^{2+} and Li⁺ ions may play multiple roles. On the one hand, action of ArZnX with MgX₂ can form ionic zincates which have higher reactivity than ArZnX.9b,13 The existence of LiX increases the solubility of the zinc reagents by forming a trimetallic adduct and

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produces reactive zincates.¹⁴ The higher reactivity of the zincates was also supported by the ¹³C NMR spectral study of *p*-MeC₆H₄ZnCl with various proportions of LiCl and MgCl₂ (see the SI).¹⁵ On the other hand, coordination of the sulfur atom of benzenethiolate salt to the Mg²⁺ and Li⁺ ions activates the C–S bond. Combination of the sulfur anion with the metal ions also increases its leaving propensity.

ICP-MS analysis of the reaction mixture (Table S1 in the SI, entry 16) showed the existence of transition-metal impurities (Mn, 28.0 ppm; Fe, 19.0 ppm; Co, 1.9 ppm; Ni, 5.2 ppm; Cu, 2.7 ppm; Ru, Rh, and Pd < 0.05 ppm). To rule out the possibility of transition-metal catalysis, we carried out the reaction using highly pure Mg (99.99%, Aladdin Industrial Corp.), ZnCl₂ (99.999%, Alfa Aesar), and LiCl (99.995%, Alfa Aesar) under the same conditions as shown in entry 16, Table S1 in the SI. The coupling product **3a** was obtained in 99% yield. ICP-MS analysis of the reaction mixture derived from the highly pure reagents showed that no transition-metal impurities were detected at the level of 1 ppb (the detection limit).

Next, we examined substrate scope of the reaction under the optimized conditions. Reaction of various (hetero)arylthiols with $p-Me_2NC_6H_4ZnCl$ (2a) was first tested. Thus, (hetero)arylthiols were treated with MeZnCl at room temperature for 30 min, and then the resultant thioates were reacted with $p-Me_2NC_6H_4ZnCl$ in toluene at 120 °C for 24 h. As shown in Scheme 1, a broad

Scheme 1. Cross-Coupling of (Hetero)arylthiols with p-Me₂NC₆H₄ZnCl^{*a*}



^{*a*}The reactions were carried out using 0.5 mmol (hetero)arylthiols and 1.6 equiv of **2a** according to the conditions indicated by the above equation. p-Me₂NC₆H₄ZnCl and MeZnCl were prepared from the corresponding Grignard reagents and ZnCl₂ in the presence of 2 equiv of LiCl. ^{*b*}2.0 equiv of **2a** was used. ^{*c*}Bath temperature was 140 °C. ^{*d*}1.8 equiv of **2a** was used. ^{*e*}2.5 equiv of **2a** was used.

range of (hetero)arylthiols was demonstrated to be suitable for the coupling. Both 2-methylbenzenethiol and 4-methylbenzenethiol exhibited reactivity similar to that of benzenethiol. Their reaction with 2a formed the corresponding coupling products (3b, 3c) in almost quantitative yields. The steric hindrance of *o*methyl group in 2-methylbenzenethiol did not affect the reaction result. 4-Methoxybenzenethiol showed lower reaction activity than benzenethiol. Its reaction with 2a gave 3d in 67% yield. Enhancing reaction temperature and increasing loading of the zinc reagent can increase product yield to some extent (77%). Both naphthalene-1-thiol and naphthalene-2-thiol were also highly reactive. They showed similar reactivity to benzenethiol and led to excellent coupling yields (3e, 3f). A series of benzenethiols with electron-withdrawing groups on the phenyl rings including p-F, p-Cl, p-Br, m-CF₃, p-CF₃, p-CN, p-COPh, p-CO₂Et, and p-CONEt₂ groups were also demonstrated to react with 2a under standard conditions, giving the corresponding coupling products (3g-o) in 30-91% yields. Among the halogen-substituted benzenethiols, 4-fluorobenzenethiol resulted in excellent coupling yield (85%), while 4-bromobenzenethiol gave relatively low coupling yield (36%). The low yield of the latter was due to the existence of side reactions. 1,4-(p- $Me_2NC_6H_4)_2C_6H_4$ as a main byproduct was detected by GC-MS in the reaction of 4-bromobenzenethiol with 2a. It was reported that the transition-metal-free reaction of arylzinc reagents with aryl iodides was a radical process.^{9a} In our reaction of 4-bromobenzenethiol, both the radical process and transitionmetal-catalyzed process were ruled out by adding a radical trap (2 equiv of 1,1-diphenylethene) and employing highly pure metal reagents (see the SI), respectively. Reaction of 3-(trifluoromethyl)benzenethiol with 2a afforded the desired product 3i in excellent yield (91%). Reaction of p-CF₂C₄H₄SH under the same conditions gave markedly lower product yield (3k, 57%), and unidentified byproducts were observed from TLC. Reaction of p-NCC₆H₄SH and p-PhC(O)C₆H₄SH with 2a resulted in the desired products (3l, 3m) in relatively low yields and unidentified byproducts. Respective reaction of p- $EtO_2CC_6H_4SH$ and *p*- $Et_2NC(O)C_6H_4SH$ with **2a** under standard conditions gave desired product (3n, 3o) in moderate yield. Higher 2a loading (up to 2.5 equiv) increased the product yield. Coordination of the CN or carbonyl group to Zn²⁺, Mg²⁺, or Li⁺ ions in these compounds may affect the reactivity of the thiolates or arylzinc reagents. Heteroarylthiols including benzo [d]oxazole-2-thiol, benzo d thiazole-2-thiol, pyridine-2-thiol, 4,6dimethylpyrimidine-2-thiol, and 1-phenyl-1H-tetrazole-5-thiol were also demonstrated to be suitable substrates in this transformation. Reaction of benzo[d]thiazole-2-thiol required higher 2a loading to achieve optimal product yield (3q). Reaction of the other heteroarylthiols proceeded smoothly under the standard conditions and gave good to excellent product yields (3p and 3r-t).

The scope of nucleophilic substrates was examined by the reaction with 4,6-dimethylpyrimidine-2-thiol (Scheme 2). We noticed that in the reaction with 4,6-dimethylpyrimidine-2-thiol 1.8 equiv of arylzinc reagent was necessary to achieve optimal yields. Reaction of both p-MeC₆H₄ZnCl and o-MeC₆H₄ZnCl gave the desired products in excellent yields. However, reaction of 2,4,6-Me₃C₆H₂ZnCl gave only 23% product yield (4c). This is ascribed to the steric hindrance of 2,4,6-Me₃C₆H₂ZnCl. Increasing the zinc reagent loading to 2 equiv and prolonging the reaction time to 48 h resulted in 38% product yield. Other electron-rich arylzinc reagents including (4-methoxyphenyl)zinc chloride, benzo[d][1,3]dioxol-5-ylzinc chloride, and (4-(methylthio)phenyl)zinc chloride showed good reactivity, and they led to desired products in good to excellent yields (4d-f). Naphthalen-1-ylzinc chloride exhibited lower reactivity than naphthalen-2-ylzinc chloride, probably due to the larger steric hindrance of the former. Increasing the naphthalen-1-ylzinc chloride loading can improve the product yield. Reaction of electron-poor arylzinc reagents such as p-CF₃C₆HZnCl and p- FC_6H_4ZnCl also gave excellent product yields (4i, 4j). This may result from high reactivity of 4,6-dimethylpyrimidine-2-thiol.

Scheme 2. Cross-Coupling of 4,6-Dimethylpyrimidine-2-thiol with Organozinc Reagents⁴



^{*a*}The reactions were carried out using 0.5 mmol of 4,6-dimethylpyrimidine-2-thiol and 1.8 equiv of (hetero)arylzinc reagents according to the conditions indicated by the above equation. Unless otherwise specified, the zinc reagents were prepared from corresponding Grignard reagents and ZnCl₂ in the presence of 2 equiv of LiCl. ^{*b*}1.6 equiv of zinc reagent was used. ^{*c*}2.0 equiv of zinc reagent was used. ^{*d*}Reaction time was 48 h. ^{*e*}The zinc reagents were prepared from furan-2-yllithium or thiophene-2-yllithium and 1.0 equiv of ZnCl₂ in the presence of 1.0 equiv of LiCl and 1.0 equiv of MgCl₂.

Heteroarylzinc reagents, furan-2-ylzinc chloride, and thiophene-2-ylzinc chloride also reacted smoothly with 4,6-dimethylpyrimidine-2-thiol to form the corresponding biheteroaryls in 87% and 78% yields, respectively (4k, 4l).

Reaction of benzenethiol and electron-rich arylthiols with various arylzinc reagents, especially electron-poor arylzinc reagents, was also tested (Scheme 3). p-MeOC₆H₄ZnCl and benzo[d][1,3]dioxol-5-ylzinc chloride were proven to effectively couple with benzenethiol to afford the desired products in

Scheme 3. Cross-Coupling of Benzenethiol and Electron-Rich Arylthiols with Organozinc Reagents⁴



^aThe reactions were carried out using 0.5 mmol of thiol and 1.8 equiv of zinc reagents according to the conditions indicated by the above equation. Unless otherwise specified, the zinc reagents were prepared from Grignard reagents and ZnCl₂ in the presence of 2 equiv of LiCl. ^bNMR yield. ^cThiophene-2-ylzinc chloride was prepared from thiophene-2-yllithium and 1.0 equiv of ZnCl₂ in the presence of 1.0 equiv of LiCl and 1.0 equiv of MgCl₂.

excellent yields (**5a**, **5b**), while reaction of electron-poor arylzinc reagents, p-FC₆H₄ZnCl and p-CF₃C₆H₄ZnCl, with benzenethiol, 4-methylbenzenethiol, or 4-methoxybenzenethiol generated corresponding products in markedly lower yields (**5c**-**h**). This is ascribed to weak nucleophilicity of the electron-poor arylzinc reagents. Finally, reaction of naphthalene-2-thiol with thiophene-2-ylzinc chloride was carried out, affording 2-(naphthalen-2yl)thiophene in 79% yield.

Preliminary experiments to evaluate the plausible reaction mechanism were carried out. The reaction of PhSH with p- $Me_2NC_6H_4ZnCl$ was not affected by 1,1-diphenylethene or (1cyclopropylvinyl)benzene additive. When 2.0 equiv of 1,1diphenylethene or (1-cyclopropylvinyl)benzene was added to the reaction system, the reaction gave the coupling product in 98% yield in each case. The recovery of 1,1-diphenylethene and (1-cyclopropylvinyl)benzene was 98% and 97%, respectively. Single-electron-donor lithium di-tert-butylbiphenyl (LiDBB) was reported to lead to a significant increase in the product yield for reaction of aryl or alkenyl halides with aryl Grignard reagents or arylzinc reagents.^{8b,d,9a} However, the same effect was not observed in the reaction of PhSH with p-Me₂NC₆H₄ZnCl or p-MeOC₆H₄SH with p-CF₃C₆H₄ZnCl (see the SI). The above experimental facts exclude a free-radical electron-transfer mechanism. On the other hand, the reaction of substituted benzenethiols with arylzinc reagents did not generate regioisomers, which rules out the aryne pathway.¹⁶ Furthermore, two intermolecular competition experiments were performed. When *p*-Me₂NC₆H₄ZnCl and *p*-CF₃C₆H₄ZnCl in 1:1 molar ratio reacted with 1 equiv of PhSZnCl, a mixture of p-Me₂NC₆H₄Ph and p-CF₂C₆H₄Ph was obtained in a \sim 2:1 ratio. This result demonstrated that the reaction was facilitated by a stronger nucleophilic reagent. When a mixture of p-FC₆H₄SZnCl and p-MeOC₆H₄SZnCl in 1:1 molar ratio was treated with 1.0 equiv of p-Me₂NC₆H₄ZnCl, 4'-fluoro-N,N-dimethylbiphenyl-4-amine and 4'-methoxy-N,N-dimethylbiphenyl-4-amine were obtained in a 1.46:1 ratio. This result showed that an electron-poor arylthiol was more reactive than an electron-rich one. These experimental facts support a nucleophilic aromatic substitution mechanism via an addition—elimination pathway.¹⁷ However, a nucleophilic aromatic substitution mechanism normally requires the presence of activating groups on the aromatic rings of the electrophilic substrates.¹⁸ In our reaction, unactivated arylthiols also showed good reactivity. This may result from an interaction of the metal ions with the π -cloud of aromatic ring which decreases the electron density of the aromatic ring. The theoretical calculation results proved the presence of cation $-\pi$ interaction between metal cations (Li⁺, Na⁺, K⁺, Be²⁺, Mg²⁺, and Ca^{2+}) and different π -systems such as para-substituted (F, Cl, OH, SH, CH₃, and NH₂) benzene derivatives.¹⁹ Each ¹H NMR spectrum of PhSLi, PhSMgCl, and PhSZnCl·MgCl₂·2LiCl showed an obvious downfield shift of the aromatic proton signals compared with those of PhSH (see the SI). The deshielding effect corresponds to a decrease of the electron density of the aromatic rings. Meanwhile, the metal ions also promote the reaction via (1) their complexation with the sulfur anion, which activates the C-S bond and (2) forms ionic zincates, which increases the nucleophilicity of the reagent. The low yields of the reaction of the electron-deficient arylthiols such as p-NCC₆H₄SH, p-PhC(O)C₆H₄SH, p-EtO₂CC₆H₄SH, and p- $Et_2NC(O)C_6H_4SH$ are ascribed to (1) the existence of side reactions and (2) the coordination of CN or carbonyl groups to Zn^{2+} , Mg^{2+} , or Li⁺ ions, which reduces the amount of the metal ions used to interact with the sulfur anion or the aromatic ring.

That higher loading of the zinc reagents resulted in higher product yields supported this assumption (Scheme 1, 3n and 3o). In addition, the aqueous-phase residue obtained after extraction of the reaction mixture with organic solvent can react with HgCl₂ to form a black-brown precipitate, which proved formation of S^{2-} in the reaction.

In summary, we developed a transition-metal-free coupling reaction of (hetero)arylthiols with arylzinc reagents to form bi(hetero)aryls. The reaction exhibited wide substrate scope and good compatibility of functional groups. Electron-rich and -poor aryl or heteroaryl thiols can be converted. Various arylzinc reagents, including electron-rich and electron-poor reagents, can be employed as the coupling partners. Preliminary mechanistic studies suggest a nucleophilic aromatic substitution pathway, and Mg^{2+} and Li^+ ions play important roles in the process of reaction. This study provides an example of S^{2-} as a leaving group in an aromatic system and an effective methodology for the synthesis of bi(hetero)aryls including pharmaceutical molecules without transition-metal impurities.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03145.

Experimental procedures, spectral data, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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