Cross-coupling of Aryl Sulfides Powered by *N*-Heterocyclic Carbene Ligands

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Abstract: Cross-coupling reactions of aryl sulfides are more difficult than they look. We have disclosed that transition metal–NHC complexes allow us to efficiently use a wide range of aryl sulfides as electrophilic coupling partners in various cross-coupling reactions and have thus significantly expanded the scope of aryl sulfides available for the cross-coupling technology. Newly introduced nucleophilic partners include arylzinc reagents, Grignard reagents such as alkynylmagnesium species, amines, ketimines, and diborons to achieve Negishi-type coupling, Kumada–Tamao–Corriu-type coupling, Buchwald–Hartwig-type amination, Buchwald–Hartwig–Miura-type carbonyl α -arylation, and Miyaura-type borylation, respectively. These cross-coupling reactions are particularly advantageous when combined with sulfur-specific transformations to prepare organosulfur substrates. Through the development of catalytic transformations of C–S bonds, sulfur-based organic synthesis has come to complement conventional halogen-based organic methodology.

1. Introduction

Cross-coupling reactions represent an indispensable class of transformations in organic synthesis, in which aryl halides have been typically employed as electrophilic partners. Phenol derivatives such as triflates and phosphates are also available as electrophilic substrates for cross-coupling reactions, and recent research has now realized efficient cross-coupling reactions of much less reactive, usually inert phenol derivatives such as esters, carbonates, and even ethers.¹ The scope of electrophilic partners in the cross-coupling continues to expand still further.

Organosulfur compounds are ubiquitous in nature as well as in industrial processes. They are also important as synthetic intermediates. Among them, aryl sulfides can be useful electrophilic partners, instead of aryl halides or pseudohalides, in cross-coupling reactions. In 1979, Takei and Wenkert independently reported the first cross-coupling of aryl or vinyl sulfides with Grignard reagents.² Since their discoveries, hundreds of cross-coupling reactions of aryl sulfides have been reported.³ It might seem that cross-coupling of aryl sulfides presents no difficulties nowadays.

During the course of our study on extended Pummerer reactions of sulfoxides,⁴ we often encountered difficulty in converting aryl sulfides through cross-coupling technology. After a careful literature survey, we realized that cross-coupling of aryl sulfides is still difficult and hence needs to be explored. In this Account, we describe our endeavors aimed at establishing universal cross-coupling of aryl sulfides with efficiency as high as that of aryl halides. Eventually, several cross-coupling reactions of aryl sulfides were invented, wherein *N*-heterocyclic carbene ligands (NHC ligands) play key roles.

2. With Organozinc Reagents

Organozinc reagents have been widely used as nucleophiles in the Negishi cross-coupling due to their high tolerance toward various functional groups. However, despite the pioneering work by Takei and Wenkert using Grignard reagents,² cross-coupling reaction of aryl sulfides with organozinc

reagents had for a long time remained challenging. In 1999, the first example of such a Negishi-type transformation was reported by Liebeskind (Scheme 1).⁵ In this report, the cross-coupling reaction of aryl sulfides with diarylzincs was accomplished by means of chelating thioglycolic acid as a specially designed leaving group that captures a zinc ion to facilitate transmetalation. After this finding, several Negishi-type coupling reactions of aryl sulfides were developed, though the aryl groups must be activated heteroaryls such as thioester mimics (2-pyridyl, 2-pyrimidyl, etc.).⁶

Scheme 1. Chelating leaving group in cross-coupling of aryl sulfides.

During the course of our research on sulfur-based benzofuran synthesis,^{4,7} we also became interested in C–S bond arylation of the initially produced 2-methylsulfanylbzofurans with arylzinc reagents. The benzofuryl sulfides often showed good reactivity, and Fukuyama's protocol using PdCl₂(dppf)⁸ worked satisfactorily to afford the corresponding 2-arylbzofurans.^{7b}

Having developed interest in the fluorescent properties of 2-arylbzofurans, we then started to construct a library of more π -extended 2-arylnaphthofurans.⁹ PdCl₂(dppf) usually worked nicely as a catalyst for the arylation. However, when it came to installing a bulky aryl group, the conventional protocol was ineffective. For instance, the reaction of 3-trifluoromethyl-2-methylsulfanylnaphtho[2,1-*b*]furan (**1**) with 9-anthrylzinc and 2,6-dimethylphenylzinc under PdCl₂(dppf) catalysis failed to afford the desired products **2a** and **2b**, respectively (Scheme 2). We thus had to find more powerful

conditions to achieve this goal. After screening of various transition metal complexes as catalysts, palladium complexes bearing an NHC ligand were found to be particularly effective. Thus the same reactions yielded 93% and 74% yields of **2a** and **2b**, respectively with Pd-PEPPSI-IPr precatalyst (Figure 1¹⁰).

Scheme 2. Arylation of **1** with bulky arylzinc reagents.

Figure 1. Transition metal NHC precatalysts in this account.

This finding encouraged us to develop cross-coupling reactions of more general aryl sulfides with arylzinc reagents.¹¹ After further optimization of reaction conditions, we found that an IPr- or SIPr-ligated Pd-NHC complex (Figure 1) uniquely catalyzes the cross-coupling reaction of simple *p*-methylthioanisole (**3**) with arylzinc reagent **4** even at room temperature (Table 1, entries 1 and 2). Notably, other palladium complexes (entries 3–5) or a Ni-NHC complex (entry 6) were totally ineffective.

Owing to the mild reactivity of organozinc reagents, a wide

Table 1. Catalyst screening for cross-coupling of *p*-methylthioanisole (**3**) with an arylzinc reagent **4**.

entry	cat.	NMR yield (%)
1	Pd-PEPPSI-IPr	85
2	Pd-PEPPSI-SIPr	94 (isolated yield)
3	Pd-PEPPSI-IMes	1
4	PdCl ₂ (PPh ₃) ₂	0
5	PdCl ₂ (dppf)	0
6	(IPr)NiCl ₂ (PPh ₃)	8

variety of sensitive functional groups, such as formyl (**5b**), succinimide (**5c**), acetyl (**5d**), and cyano (**5f**) groups, were well tolerated (Scheme 3). Alkenylzinc (**5g**) as well as heteroarylzinc (**5h**) reagents were also applicable to the coupling reactions. It is worth noting that Knochel's zinc reagents containing lithium chloride¹² are particularly useful in terms of reactivity as well as availability.

Scheme 3. Cross-coupling of aryl sulfides with organozinc reagents.

Surprisingly, our protocol has orthogonality to the conventional cross-coupling reactions of aryl tosylate and chloride (Scheme 4). By means of Pd-PEPPSI-SIPr and an arylzinc reagent, arylations of 4-tosyloxy- (**6**) and 4-chlorothioanisole (**7**) smoothly proceeded without affecting their tosyloxy and chloro groups to yield **9** and **11**, respectively. In contrast, cross-coupling reactions of these substrates proceeded selectively at the tosyloxy and chloro position with Buchwald's¹³ and Wolf's¹⁴ procedures affording **8** and **10**, respectively (Scheme 4).

We then turned our attention to direct C-H arylation of

Scheme 4. Orthogonal cross-coupling reactions.

arenes via deprotonative zincation with 2,2,6,6-tetramethylpiperidylzinc chloride·lithium chloride complex (TMPZnCl·LiCl) as base.¹⁵ Pd-PEPPSI-SIPr was again the best catalyst for this transformation, and the desired product was obtained quantitatively from **3** and pentafluorobenzene (**12a**) (Table 2).

Table 2. Catalyst screening for arylation of pentafluorobenzene (**12a**) with **3**.

entry	cat.	yield (%) ^a
1	Pd-PEPPSI-IPr	95
2	Pd-PEPPSI-SIPr	>99 (91)
3	PdCl ₂ (PPh ₃) ₂	0
4	PdCl ₂ (dppf)	0
5	(IPr)NiCl ₂ (PPh ₃)	0

^a Determined by ¹H NMR. Isolated yield is in parentheses.

TMPZnCl·LiCl was found to be an exquisitely effective base for deprotonation of electron-deficient arenes or heteroarenes to generate the corresponding arylzinc species.¹⁶ Compatibility of the *in-situ* generation of pentafluorophenylzinc species with the following cross-coupling of aryl sulfides allowed us to achieve the deprotonative C–H arylation under mild conditions. As another advantage, the resulting zinc methylthiolate species of moderate reactivity does not undergo S_NAr displacement of polyfluorinated compounds.

Various polyfluoro- and heteroarenes **12** could be used for this arylation (Scheme 5). The arylation of 1,2,4-trifluorobenzene took place at the most acidic 3 position exclusively to give **13c**. Oxazole, thiazole, and thiophene derivatives were also good substrates giving 2-arylated products **13e–h** in good to high yields.

Combined with the unique reactivity of organosulfur compounds, our palladium-catalyzed arylation protocols offer

Scheme 5. Deprotonative C–H arylation with aryl sulfide **3**.

interesting transformations that are otherwise difficult to achieve. For example, thiolate anions are so nucleophilic that they can replace the nitro group of electron-deficient nitroarenes **14** with an alkylsulfanyl group through an S_NAr mechanism.¹⁷ The subsequent palladium-catalyzed arylation allowed the nitro moiety to be arylated in two steps (Scheme 6).

Scheme 6. S_NAr Displacement of nitro group with dodecylsulfanyl followed by palladium-catalyzed arylation.

Another unique class of transformations of organosulfur compounds are extended Pummerer reactions. For instance, methyl 2-propargylphenyl sulfide **17** was readily synthesized from methyl phenyl sulfoxide (**16**) and propargylsilane (Scheme 7) according to Procter's protocol.¹⁸ With **17** available

Scheme 7. Propargylation via extended Pummerer reaction and subsequent arylation of sulfoxide **16**.

Scheme 8. Arylation of 3-carbonylthiophenes with **17** followed by condensation reaction.

through the sulfur-specific reaction, its arylation provided 2-propargylbiphenyls **18**, which can be viewed as promising precursors of phenanthrene analogues.¹⁹ In addition, C–H arylation of 3-carbonylthiophenes with **17** by means of $\text{TMPZnCl} \cdot \text{LiCl}$ followed by condensation provided naphthothiophene **19** or benzonaphthothiophene **20** (Scheme 8).

3. With Organomagnesium Reagents

Following our success in inventing a general cross-coupling of aryl sulfides with arylzincs and combining it with Pummerer chemistry, we envisioned a similar strategy utilizing Grignard reagents would be of importance. To this end, diphenylation of difuran **21** with phenylmagnesium bromide was examined as a model reaction (Table 3).^{7a} Catalyst screening revealed that a Ni–NHC precatalyst $(\text{IPr})\text{NiCl}_2(\text{PPh}_3)^{10c}$ (Figure 1) was the best affording **22** in 68% yield (entry 1). While a moderate yield of **22** was obtained with Pd–PEPPSI–IPr (entry 3), a nickel–diphosphine complex and other palladium complexes failed to perform the desired transformation efficiently (entries 2, 4 and 5).²⁰

Table 3. Catalyst screening for diphenylation of **21** with phenyl Grignard reagent.

entry	cat.	isolated yield (%)
1	$(\text{IPr})\text{NiCl}_2(\text{PPh}_3)$	68
2	$\text{NiCl}_2(\text{dppe})$	14
3	Pd–PEPPSI–IPr	54
4	Pd–PEPPSI–IMes	<10
5	$\text{PdCl}_2(\text{dppf})$	14

Treatment of benzofuran **23**, which was available through our annulation method, with 3,4-methylenedioxyphenylmagnesium bromide in the presence of $(\text{IPr})\text{NiCl}_2(\text{PPh}_3)$ furnished Eupomatenoid-3 (**24**) in 79% yield (Scheme 9).^{7a} Eupomatenoid-3 is a potent anti-cancer agent, the preparation of which highlights the synthetic potential of our cross-coupling protocol.

Scheme 9. Synthesis of Eupomatenoid-3 via C–S bond arylation with a Grignard reagent

In a similar fashion, alkylation was also achieved by the $(\text{IPr})\text{NiCl}_2(\text{PPh}_3)$ precatalyst, giving 2-alkylbenzofurans **26** in

good to excellent yields (Scheme 10). Indeed, by means of butylmagnesium bromide, butyl groups were smoothly introduced to 2-methylsulfanylbenzofurans **25a–d** to afford 2-butylbenzofurans **26a–d**.²¹ Other alkyl groups such as methyl, cyclohexyl, unsaturated 10-undecenyl, and THP-protected 11-hydroxyundecyl groups were also installed to give **26e–h** in nearly quantitative yields. The use of toluene as the solvent allowed stabilized anions such as Me_3SiCH_2 and PhCH_2 to react efficiently, giving **26i** and **26j**, respectively.

Scheme 10. Alkylation of 2-methylsulfanylbenzofurans.

^a 2 equiv Grignard reagent. ^b 10 mol % $(\text{IPr})\text{NiCl}_2(\text{PPh}_3)$.

^c 1 equiv Grignard reagent four times. ^d toluene. ^e 50 °C.

We applied this methodology to the synthesis of two precursors of potential PTP 1B inhibitors **29** (Scheme 11).²² Phenol underwent the extended Pummerer annulation with ketene dithioacetal monoxide **27** on treatment with trifluoroacetic anhydride to afford 2-methylsulfanylbenzofuran **28** in 61% yield. The following cross-coupling alkylations resulted in short syntheses of **29a** and **29b**.

Scheme 11. Pummerer annulation/alkylation protocol.

Considering the importance of alkynyl groups in organic chemistry, we then tackled desulfanylation/alkynylation of aryl sulfides using alkynyl Grignard reagents. In this case, Pd–PEPPSI–IPr was superior to the nickel complex as well as other Pd precatalysts.²³ The reaction with phenylethynylmagnesium chloride (**30a**) accommodates a broad scope of aromatic and heteroaromatic sulfides bearing diverse functionalities affording diarylacetylenes **31** (Scheme 12). The scope of alkynyl Grignard reagents **30** is wide (Scheme 13). Functional groups such as cyclopropyl, triisopropylsilyl and vinyl moieties survived.

Our alkynylation methodology is orthogonal to other conventional cross-coupling reactions. Indeed, Mizoroki–Heck alkenylation, Suzuki–Miyaura coupling, and Buchwald–Hartwig amination could be applied to 5-bromo-substituted

Scheme 12. Pd–NHC–Catalyzed alkynylation of aryl sulfides with **30a**.

^a 30% of aryl sulfide was recovered. ^b 10 mol % catalyst/IPr-HCl. ^c 2 equiv **30a** three times. ^d 4 equiv **30a**. ^e 65 °C.

Scheme 13. Scope of alkynyl Grignard reagents **30**.

^a 4 equiv **30**. ^b 10 mol % catalyst/IPr-HCl.

Scheme 14. Cross-coupling reactions followed by alkynylation.

[a] 4-vinylanisole, 10 mol % Pd(OAc)₂/SPhos, DMF/Et₃N, 100 °C. [b] 4-MeOC₆H₄B(OH)₂, 5 mol % Pd(PPh₃)₄, K₂CO₃, toluene/EtOH, 100 °C. [c] Ph₂NH, 5 mol % Pd(OAc)₂, 10 mol % tBu₃P, tBuONa, toluene, 100 °C. [d] Our standard alkynylation conditions.

benzofuran **32**, leaving the 2-methylsulfanyl group intact. Subsequent alkynylation at the 2 positions yielded multisubstituted benzofurans **33** (Scheme 14).

4. With Amines

Amines are coupling partners able to react with aryl halides as in the well-documented Buchwald–Hartwig amination reaction. We anticipated aryl sulfides should potentially be good surrogate coupling partners for amination reactions. Once again, NHC ligands were found to play a key role in the amination reaction of aryl sulfides.²⁴ Treatment of methyl phenyl sulfide (**34**) with *p*-toluidine (**35a**) by means of IPr-ligated Pd–NHC precatalysts gave the corresponding aminated product **36a** in good yields (Table 4, entries 2–6). Especially, SingaCycle–A3 proved to be the optimal precatalyst, and finally, a 91% yield of **36a** was isolated in the presence of KN(SiMe₃)₂ as base in dioxane at 100 °C (entries 5 and 6). The choice of IPr ligand was critical as other NHCs all exhibited detrimental effects (entries 7 and 8).

Table 4. Catalyst screening for amination of sulfide **34** with *p*-toluidine (**35a**).

entry	cat.	NMR yield (%) ^a
1	PdCl ₂ (dppf)	0
2	Pd-PEPPSI-IPr	76 ^a
3	[IPrPdCl(π-allyl)]	72
4	SingaCycle-A1	84
5	SingaCycle-A3	88 ^a
6	SingaCycle-A3	91 ^{a,b}
7	Pd-PEPPSI-SIPr	25
8	Pd-PEPPSI-IMes	0

^a Isolated yield. The reactions were performed at 0.3 M concentration of **34** unless otherwise noted. ^b 1.2 equiv **35a**, 2.5 mol % SingaCycle-A3, 2.5 equiv KN(SiMe₃)₂, dioxane (0.5 M).

The optimal reaction conditions were applied to various aryl sulfides and anilines **35** (Scheme 15). Functional groups such as protected phenol (**36b**) and aldehyde (**36d**) were tolerated. A wide scope of anilines including heterocyclic aniline also underwent the amination reaction in good yields. As for aliphatic amines **37**, SingaCycle–A1 was found to be the better catalyst, and the desired amination reactions proceeded with both secondary and primary aliphatic amines.²⁵

Based on this highly efficient amination of aryl sulfides, a modular synthesis of carbazoles was performed starting from 2-bromophenyl methyl sulfide (**39**) (Scheme 16). A Suzuki–Miyaura coupling reaction of **39** followed by an amination reaction of the C–S bond afforded biphenylamine **40**. Finally, palladium-catalyzed intramolecular oxidative C–H amination provided carbazole derivative **41**.

In Scheme 17 are shown two sets of transformations combining extended Pummerer annulation reactions with the C–S bond amination. Cyclization via Pummerer activation²⁶ formed benzothiophene **42**, the amination of which afforded 2-(4-tolylamino)benzothiophene **43**. More interestingly, 2-propargylphenyl sulfide, synthesized through Procter's propargylation,¹⁸

underwent tandem amination/cyclization to yield the corresponding indole **44** in 80% yield.

Scheme 15. Amination of aryl sulfides.

Scheme 16. Modular synthesis of carbazole **41**.

Scheme 17. Combination of extended Pummerer reactions with amination.

5. α -Arylation of Ketimines

On the basis of the successful amination of aryl sulfides, ketones appeared to be another possible option as the soft nucleophilic partner. However, all attempts to arylate ketones failed, and none of the corresponding α -arylation products were formed. One likely reason for this failure might be the low nucleophilicity of enolates. On the other hand, azaenolates generated from ketimine are known to be more reactive than enolates in $\text{S}_{\text{N}}2$ α -alkylation reactions. Hence we expected that azaenolates should be more reactive toward α -arylation than the corresponding enolates. To our delight, acetophenone *N*-methylimine derivatives **45** reacted with aryl sulfides to afford the corresponding α -arylation products **46** in the presence of a catalytic amount of SingaCycle-A1 after hydrolysis (Scheme 18).²⁷ In this arylation, a remarkably low catalyst loading of SingaCycle-A1 (0.5 mol %) was sufficient to achieve efficient new C–C bond formation via C–S bond cleavage. Strong bases such as LiN(SiMe₃)₂ or LiNⁱPr₂ were necessary to efficiently deprotonate ketimines. The choice of lithium counteranion is also important as KN(SiMe₃)₂ and NaN(SiMe₃)₂ were inferior.

Scheme 18. α -Arylation of ketimine **45** with aryl sulfides.

The reaction displayed interesting chemoselectivity. For instance, *p*-chlorothioanisole underwent α -arylation preferentially at the C–S bond to yield **46b**. Perfect chemoselectivity was observed when the α -arylation took place with *p*-acetylphenyl methyl sulfide, leaving the acetyl moiety in **46c** intact.

The initially produced α -arylated ketimines **47** could be utilized as synthetic intermediates. By adding DMF and KO^tBu after the palladium-catalyzed α -arylation and prior to hydrolysis, *N*-unprotected 2,3-diarylpyrroles **48** were furnished in high yields (Scheme 19).

The initially produced ketimine compound **47** also reacted with oxalyl chloride to afford pyrroledione **49** in 62% yield (Scheme 20). Furthermore, indole **50** was obtained in 61% yield by the reaction with *o*-fluorophenyl methyl sulfide through α -arylation/intramolecular $\text{S}_{\text{N}}\text{Ar}$ cyclization.

6. Borylation with Diboron Reagents

Due to the enormous versatility of organoboron compounds as reagents, functional materials, and bioactive agents, new methods for the formation of C–B bonds continues to be actively investigated.²⁸ The Miyaura borylation of aryl halides

Scheme 19. Synthesis of 2,3-diarylpyrroles **48**. **Scheme 20.** Synthesis of pyrroledione **49** and indole **50**.

offers a regioselective and reliable approach.²⁹ However, there had been no precedents for *ipso*-borylation of aryl sulfides.³⁰ As a part of our research interest in catalytic C–S bond cleavage, we developed the Miyaura-type borylation of aryl sulfides catalyzed by a Pd–NHC complex (Scheme 21).³¹

Scheme 21. Pd-Catalyzed borylation of aryl sulfides.

^a 10 h. ^b 15 mol % Pd-PEPPSI-IPr, 24 h. ^c 24 h.

By employing 10 mol % of Pd–PEPPSI–IPr as a precatalyst, aryl methyl sulfides were converted into borylated products **51** in the presence of bis(pinacolato)diboron (B₂pin₂) and LiN(SiMe₃)₂ as base. This reaction proceeds with various

para-substituted aryl sulfides though electron-rich ones required a larger amount (15 mol %) of the palladium precatalyst and a longer reaction time of 24 h to reach full conversions (**51e–h**). Azole units were tolerated under the reaction conditions and did not suppress the borylation (**51g** and **51h**). Notably, this transformation proceeded with sterically demanding substrates, including *ortho*-phenylthioanisole, to furnish the corresponding products **51i–k** after 24 h. This offers an advantage for synthetic chemistry because *ortho*-substituted aryl sulfides can be readily synthesized by *ortho*-lithiation of thio-phenols.³²

7. Conclusion

We have invented several cross-coupling reactions of aryl sulfides utilizing NHC ligands, especially IPr or SIPr as a magic ligand. Aryl sulfides can now serve as surrogates for aryl halides. In addition, taking advantage of intriguing organosulfur chemistry, one can perform sulfur-specific transformations that are otherwise difficult to achieve. Through development of catalytic transformations of C–S bonds, we continue to work to establish sulfur-based organic synthesis that can complement the classical halogen-based organic methods.

We should make some comments on the favorable effect of NHC ligands. (1) An NHC is known to coordinate to a transition metal center tightly. This strong coordination prevents catalyst deactivation through ligand dissociation and/or metal aggregation and keeps the complex catalytically active even in the presence of strongly poisonous organosulfur species. (2) Due to its strongly electron-donating property, an NHC ligand helps facile oxidative addition of a C–S bond. The equilibrium of the oxidative addition of a C–S bond would be shifted further toward the oxidative adduct than with phosphine ligands. However, simply considering bond dissociation energies enables us to sketch an explanation: we do not think oxidative addition of a carbon–sulfur bond to a low-valent metal is critically difficult. The bond dissociation energies of Ph–Cl, Ph–SMe, and Ph–Br decrease in this order and were determined to be 399.6±6.3, 357.3±6.3, and 336.4±6.3 kJmol^{−1}, respectively.³³ (3) We presume that the difficulty of cross-coupling of aryl sulfides could reside in the transmetalation step due to the affinity of a thiolate anion toward a transition metal center. It is known that an electron-withdrawing ligand facilitates transmetalation between Ar–Pd–X and an organometallic reagent by increasing the cationic character at the palladium center.³⁴ We conjecture that the situation is opposite in the transmetalation of Ar–Pd–SMe. The palladium center in Ar–Pd–SMe is not so cationic that transmetalation is sluggish. The NHC on the palladium would powerfully donate electron density to the metal. This donation may induce departure of the methylthiolate anion from the palladium with the aid of counter-cations such as zinc, lithium, and potassium. In other words, the transmetalation of Ar–Pd–SMe may proceed by a dissociative process. Further investigation is necessary from a theoretical and experimental viewpoint.

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