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<tr>
<td>Citation</td>
<td>Chemistry - A European Journal (2015), 21(42): 14703-14707</td>
</tr>
<tr>
<td>Issue Date</td>
<td>2015-10-12</td>
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<tr>
<td>URL</td>
<td><a href="http://hdl.handle.net/203038">http://hdl.handle.net/203038</a></td>
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<td>Rights</td>
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<td>Type</td>
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Kyoto University
Palladium-catalyzed Zinc-amide-mediated C–H Arylation of Fluoroarenes and Heteroarenes with Aryl Sulfides

Shinya Otsuka,[a] Hideki Yorimitsu,[a,b] and Atsuhiro Osuka[a]

Abstract: C–H arylation of polyfluoroarenes and heteroarenes with aryl sulfides proceeds smoothly with the aid of a palladium-N-heterocyclic carbene catalyst. A bulky zinc amide, TMPZnCl-LiCl, plays a key role as an effective base to generate the corresponding arylzinc species in situ. This arylation is practically much easier to perform than our previous method that necessitates preparation of arylzinc reagents in advance from the corresponding aryl halides. Aryl sulfides that are prepared through sulfur-specific reactions such as S$_2$Ar sulfanylation and extended Pummerer reactions undergo this direct arylation, which offers interesting transformations that are otherwise difficult to achieve with the conventional halogen-based organic synthesis.

Organsulfur compounds have played unique roles in organic chemistry owing to their intriguing reactivities, biological activities, or physical properties.[1] Among them, aryl sulfides occupy an important position, and new methods for the synthesis of aryl sulfides have hence been actively developed.[2] In contrast, development of new reactions of aryl sulfides has been reported only scatteringly. Transition-metal-catalyzed cross-coupling reactions of aryl sulfides[3] are difficult to achieve because sulfur atoms strongly poison catalysts and C(sp$^2$)-S bonds are rather strong to cleave. One can overcome these difficulties when Grignard reagents are employed as nucleophiles[4] or aryl sulfides have special structures that facilitate efficient conversions.[5-7] We are interested in catalytic transformations of organsulfur compounds[4c-9,8] and recently developed general cross-coupling reactions of aryl sulfides with arylzinc reagents, using a palladium-NHC complex as a catalyst.[8] Although our Negishi-type cross-coupling shows wide scope and proceeds under mild conditions, the reactions necessitate preparation of the arylzinc reagents from the corresponding haloarenes in advance.

Transition-metal-catalyzed direct C–H arylation of arenes with aryl halides has emerged as a promising alternative to the conventional cross-coupling.[9] However, due to the aforementioned difficulties in catalytically transforming aryl sulfides, it is just a few months ago that Wang admirably reported the first example of direct C–H arylation with aryl sulfides, wherein a palladium-diphosphine catalyst and sodium t-butoxide were employed.[10] Nevertheless, the arylation lacks generality: electron-neutral and -rich aryl sulfides reacted moderately even at 140 °C and only oxazole derivatives smoothly underwent the arylation. To expand the utility of aryl sulfides, here we report efficient and general conditions for C–H arylation of polyfluoroarenes[11,12] and heteroarenes[13] with aryl sulfides.

We chose the reaction of methyl p-tolyl sulfide (1a) with pentafluorobenzene (2a) as a model reaction. We screened palladium catalysts and bases (see the Supporting Information for optimization) to find that Pd-PePPSI-SIPr[14] and 2,2,6,6-tetramethylpiperidylzinc chloride-lithium chloride complex[15,16] (TMPZnCl-LiCl) are the best catalyst/base combination to afford 3a in 91% yield (Scheme 1). As we found previously,[17] Pd-PePPSI-SIPr, a palladium NHC complex, is again the key for the success. TMPZnCl-LiCl is known as an exquisite base for deprotonative zinication of electron-deficient or heteroarenes, tolerating various functional groups.[18] We are delighted to find that TMPZnCl-LiCl serves to generate pentafluorophenylzinc species in situ[19] compatibly with successive Negishi-type cross-coupling, which allowed us to achieve C–H arylation under mild conditions. Another advantage of using the zinc base is that the resulting zinc methylthiolate species is not nucleophilic enough to induce conceivable S$_2$Ar displacement of a fluoro group with a methylsulfanyl group.[19]

**Scheme 1. Scope of Polyfluoroarenes.**

A variety of polyfluoroarenes can be used for this reaction. Perfluorinated 2,3,5,6-tetrafluorobenzotrifluoride (2b) reacted smoothly to afford 3b in excellent yield. For the less fluorinated arenes, the efficiency of arylation is likely to depend heavily on the acidity of the proton that is deprotonated: the reactions of...
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1,2,4,5-tetrafluoro-, 1,2,3,5-tetrafluoro-, and 1,2,4-trifluorobenzene gave the corresponding products 3c, 3d, and 3f in high yields whereas less acidic 1,2,3,4-tetrafluoro- and 1,3,5-trifluorobenzene were converted less efficiently to 3e and 3g, respectively. The arylation of 2f took place regioselectively at the 4 position under the acidity control. 3,5-Difluoropyridine (2h) proved to be acidic enough to be arylated at the 4 position. A cyano group is also effectively electron-withdrawing to yield 3j in excellent yield with exclusive regioselectivity.

Not only polyfluoroarenes but also five-membered heteroarenes reacted under the reaction conditions (Scheme 2). Compared with Wang’s procedure, 4-methyl oxazole, thiazole, benzothiazole reacted much more smoothly to give 2-arylated products 5a–c in high yields with exclusive regioselectivity. Besides azoles, thiophene derivatives reacted at the 2 position to yield 5d–f in good yields. Six-membered coumarin and bioactive caffeine also gave the desired products 5g and 5h, respectively.

The scope of aryl sulfides is also broad (Scheme 3). Neither electron-donating methoxy group nor electron-withdrawing fluoro group retarded the reaction (6a and 6c). Acetal-protected aldehyde and ketone were compatible (6d and 6e). A toslyoxy group, which can be a leaving group of cross-coupling, was tolerated to yield 6f although 4-chlorothioanisole underwent twofold arylation to give terphenyl 6g. Interestingly, trimethylsilyl group and pinacolatoboryl group survived under the basic conditions (6h and 6i). When combined with reactions that are unique to organosulfur compounds, this direct arylation offers interesting transformations that are otherwise difficult to achieve.

Aryl sulfides 1j–l bearing a carbonyl or cyano group were synthesized via nucleophilic aromatic substitution of electron-deficient nitroarenes with dodecanethiol (Scheme 4). These aryl sulfides underwent catalytic pentfluorophenylation selectively at the dodecylsulfanyl unit with the polar functional groups untouched. The overall two-step transformation represents displacement of a nitro group with a perfluoroaryl group by using a unique reactivity of organosulfur species.

Our group reported the concise synthesis of multi-substituted benzothiophenes and benzofurans containing a methylsulfanyl group through extended Pummerer chemistry of ketene dithioacetal monoxides (Scheme 5). We found that compounds 7 thus synthesized are good substrates for the direct arylation with thiophene-3-carbaldehyde (4e) in spite of the steric hindrance of the neighboring phenyl group.

Padwa developed 3-allylation of 2-heteroaryl sulfilylimines under Pummerer-type conditions. According to this protocol, we synthesized 2-butylsulfanyl-3-allylfuran (9), which was then
subjected to the arylation conditions to yield the corresponding 3-allyl-2-thienylfuran 10 (Scheme 6).

Procter reported extended Pummerer reactions of aryl sulfoxides with propargylsilanes to provide 2-propargylaryl sulfides. We found that such a 2-propargylated product 11 is a useful precursor of naphthothiophene derivatives (Scheme 7). Arylation of thiophene derivatives 4e, 4f, and 4j bearing a carbonyl group at the 3 position with 11 proceeded smoothly despite steric repulsion. We were glad to find that treatment of 12a and 12b with LiOBU led to dehydration to yield alkylated naphthothiophene 13a and benzonaphthothiophene 13b, respectively. Similarly, treatment of naphthothiophene 12a resulted in condensation followed by tautomerization to yield hydroxynaphthothiophene 13c in high yield.

**Experimental Section**

The reaction of methyl p-tolyl sulfide (1a) and pentafluorobenzene (2a) is representative (Scheme 1, 3a). Pd(0)-PEPPSi-SiPPr (17.0 mg, 0.025 mmol) was placed in a 20-mL Schlenk tube under nitrogen. After additions of TMPZnCl-LiCl (1.0 mL, 1.0 mmol, 1.0 M in THF), pentafluorobenzene (168.1 mg, 1.0 mmol), methyl p-tolyl sulfide (69.1 mg, 0.50 mmol), and THF (1.0 mL), the resulting mixture was heated to 80 °C and stirred for 6 h at the same temperature. After being cooled to 20 °C, the reaction was quenched with saturated NaHCO₃ aq. (20 mL). Organic compounds were extracted with n-hexane (10 mL × 3). The combined organic layer was passed through pads of anhydrous sodium sulfate and activated alumina, and concentrated in vacuo. Purification by chromatography on silica gel (n-hexane) provided 3a (117.1 mg, 0.45 mmol, 91%).

**Acknowledgements**

This work was supported by Grants-in-Aid for Scientific Research from MEXT (No.: 25107002 “Science of Atomic Layers”) and from JSPS (Nos.: 24685007 (Young Scientists (A)) and 26620081 (Exploratory Research)). H.Y. thanks Japan Association for Chemical Innovation for financial support.

**Keywords:** C–H arylation • C–S bond activation • organosulfur compounds • palladium • organozinc compounds


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[17] We confirmed that deprotonation to form arylzinc species is faster than the successive arylation. See supporting information for details.

[18] MeSnA reacted with 3a smoothly to give a substituted product. See supporting information for details.


Efficient C–H arylation of polyfluoroarenes and heteroarenes with aryl sulfides proceeds with the aid of a palladium-NHC catalyst and a bulky zinc amide base to generate the corresponding arylzinc species in situ. Aryl sulfides that are prepared through sulfur-specific reactions such as S$_2$Ar sulfanylation and extended Pummerer reactions undergo this direct arylation, which offers interesting transformations that are otherwise difficult to achieve with the conventional halogen-based organic synthesis.