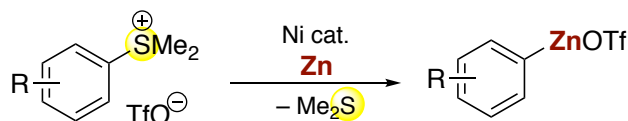


Generation of Organozinc Reagents from Arylsulfonium Salts Using a Nickel Catalyst and Zinc Dust

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efficient catalytic C–S cleavage to generate a wide range of synthetically useful arylzinc reagents under mild conditions

ABSTRACT: Readily available aryl dimethylsulfonium triflates react with zinc powder under nickel catalysis via the selective cleavage of the sp^2 -hybridized carbon–sulfur bond to produce salt-free arylzinc triflates under mild conditions. This zincation displays superb chemoselectivity and thus represents a protocol that is complementary or orthogonal to existing methods. The generated arylzinc reagents show both high reactivity and chemoselectivity in palladium-catalyzed and copper-mediated cross-coupling reactions.

Organometallic compounds are indispensable reagents in organic synthesis. Organozinc compounds show superb reactivity and have thus been widely used in highly chemoselective cross-coupling reactions and addition reactions across unsaturated bonds.¹ As the importance of organozinc reagents has increased, methods to efficiently prepare functionalized organozinc reagents under mild conditions have been diligently investigated.^{1d,1i,2} The insertion of zinc metal into the carbon–halogen bond of an organic halide represents a promising method for the preparation of functionalized organozinc reagents. It enables the regioselectivity to be set, offers a broad scope, and is a robust method. Zinc insertion without a catalyst^{1e,3} or in the presence of a stoichiometric amount of lithium chloride^{1d,1i,2,4} is commonly used to allow organic iodides, activated aryl bromides, and benzylic or allylic chlorides to serve as precursors for organozinc reagents. To expand the scope of zincations with respect to the organic halides that can be employed, the use of transition-metal catalysis has been investigated (Scheme 1a). Gosmini has pioneered and advanced zincation reactions using a cobalt catalyst,⁵ whilst Yoshikai has developed an improved method.⁶ Based on their combined efforts, such cobalt catalysis now accommodates aryl bromides, aryl chlorides and even phenol derivatives, i.e., aryl triflates.^{5d} Very recently, Hintermann has reported the nickel(diimine)-catalyzed formation of arylzinc reagents from general aryl sulfonates.⁷ These catalytic methods, as well as other examples,^{8,9} are the basis for further highly exciting catalytic zinc-insertion reactions.

Due to their ready availability and synthetic versatility,¹⁰ organosulfur compounds hold great potential as precursors of organozinc compounds. However, the strength of the C–S bond and the often catalytically poisonous nature of the sulfur fragments generated during the reaction render catalytic zinc-

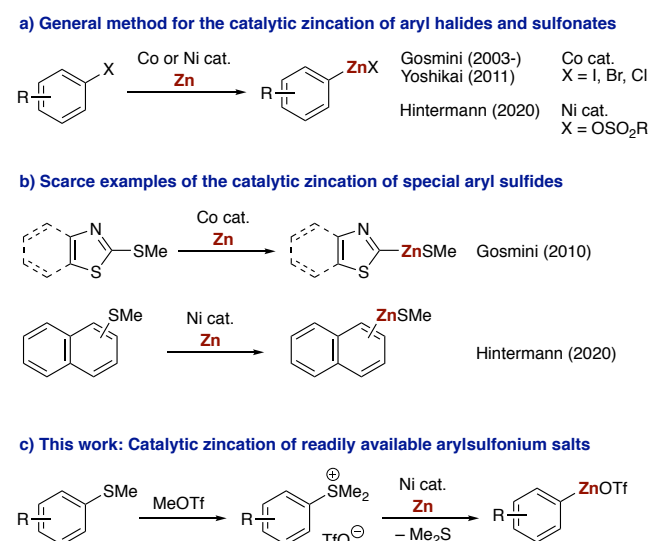
insertion reactions into C–S bonds challenging. Although Gosmini¹¹ and Hintermann⁷ have reported cobalt- and nickel-catalyzed zinc-insertion reactions into aryl sulfides, the available precursors are limited to particularly reactive (benzo)thiazoyl and naphthyl sulfides¹² (Scheme 1b). This underscores the difficulties associated with achieving the S-to-Zn transformation. In addition, the synthetic application of these arylzinc reagents has only been investigated for trivial iodinations and a small number of Negishi coupling reactions. The utility of organosulfur compounds as precursors of organozinc reagents is thus underdeveloped.

We are interested in the development of catalytic reactions of organosulfur compounds via the cleavage of the C–S bond.^{13–15} Recently, we have reported the nickel-catalyzed carboxylation of arylsulfonium salts using zinc powder with carbon dioxide.¹⁶ This study implied that an arylzinc species is the intermediate formed prior to the carboxylation event, although tangible evidence for this hypothesis had been elusive¹⁷ or deemed unlikely¹⁸ in nickel-catalyzed carboxylation reactions, which use a metallic reductant. Our previous success in preparing arylboronate esters from arylsulfonium salts and bis(pinacolato)di-boron^{14a} via a palladium-catalyzed reaction also encouraged us to develop another important *ipso*-metalation of arylsulfonium salts. With this in mind, we report here an efficient nickel-catalyzed preparation of arylzinc reagents from a variety of arylsulfonium salts (Scheme 1c).

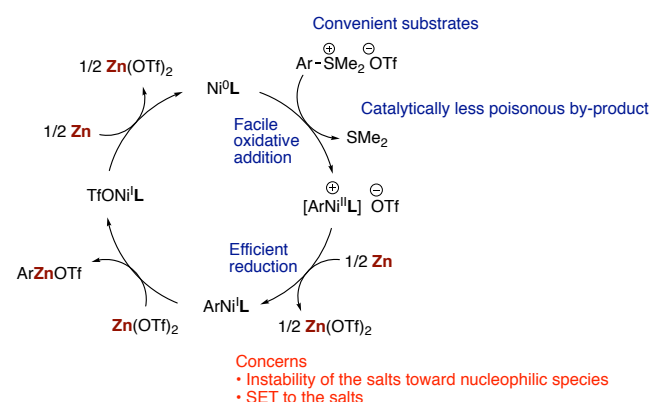
Encouraged by Liebeskind's original idea,^{19–21} we prefer using arylsulfonium salts as aryl pseudohalides. When compared to neutral aryl sulfides, arylsulfonium salts have several advantages for nickel-catalyzed zinc-insertion reactions that can be explained on the basis of the possible reaction

mechanism^{5,7,16} (Scheme 2): (1) Arylsulfonium salts are electron-deficient and undergo smoother oxidative addition; (2) the oxidative addition forms a cationic arylnickel intermediate that is more susceptible to reduction by metallic zinc;²² (3) instead of anionic sulfur fragments, a neutral and catalytically less poisonous sulfide is formed; (4) arylsulfonium salts, which can be readily prepared from aryl mercaptans or sulfides on a large scale, usually exhibit good crystallinity as well as bench-stability. We also had to pay attention to the possibility of the undesired degradation of the arylsulfonium salts into neutral aryl sulfides via demethylation. This could potentially occur via the action of a nucleophilic arylmetal species generated *in situ* or by a single-electron transfer (SET) from zinc or a low-valent nickel species.²³ Suppressing the SET is also important for controlling the regioselectivity of the C–S bond cleavage, where sp² C–S bond cleavage via two-electron oxidative insertion predominates over SET-induced sp³ C–S bond cleavage.

Scheme 1. Catalytic Zinc-Insertion Reactions into Aryl Halides and Pseudohalides.



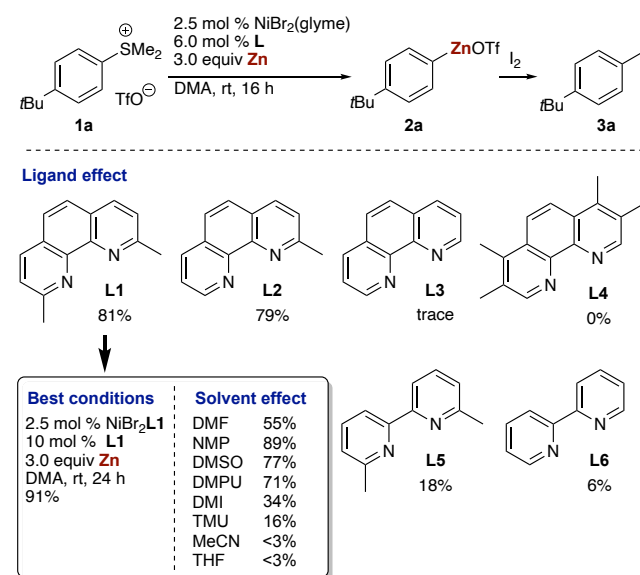
Scheme 2. Mechanistic Working Hypothesis.



Our investigations began by evaluating the catalytic zincation of **1a** (Scheme 3). The efficiency of the zincation was assessed using ¹H NMR spectroscopy to analyze the iodinated product **3a** after iodolysis. Simply applying the standard conditions from our previous carboxylation in the absence of carbon dioxide¹⁶ resulted in a zincation with poor reproducibility. After some experimentation, we found that the addition of 6.0 mol %

of a supporting ligand ensures reproducibility. Of the ligands tested, 2,9-dimethylphenanthroline (**L1**) proved to be the most effective.²³ While monomethylated **L2** showed comparable reactivity, neither the parent phenanthroline (**L3**) nor 3,4,7,8-tetramethylphenanthroline (**L4**) worked. The more flexible 2,2'-bipyridyl ligands **L5** and **L6** did not facilitate the zincation. In these four runs with **L3–L6**, low conversions were observed. Finally, using 2.5 mol % of the complex NiBr₂**L1** and an additional 10 mol % of **L1** provided **3a** in 91% yield. A screening of solvents revealed that *N,N*-dimethylacetamide (DMA) is the best while *N*-methylpyrrolidone (NMP), dimethyl sulfoxide (DMSO), and *N,N'*-dimethylpropyleneurea (DMPU) are almost comparable. Conversely, the zincation did not occur in other polar solvents such as acetonitrile or tetrahydrofuran (THF). *N,N'*-dimethyl-2-imidazolidinone (DMI) and tetramethylurea (TMU) showed moderate performance. The corresponding cobalt complex CoBr₂**L1** was not catalytically active in the zincation. In this case, as well as in the absence of any transition-metal complex, gradual demethylation of **1a** was observed, most likely via a SET directly from the zinc powder to **1a**.²⁴ The neutral sulfide *p*-*t*BuC₆H₄SMe did not undergo zincation, discarding the possibility of an aryl sulfide intermediate in the zincation.

Scheme 3. Optimization Study of the Zincation Reaction.

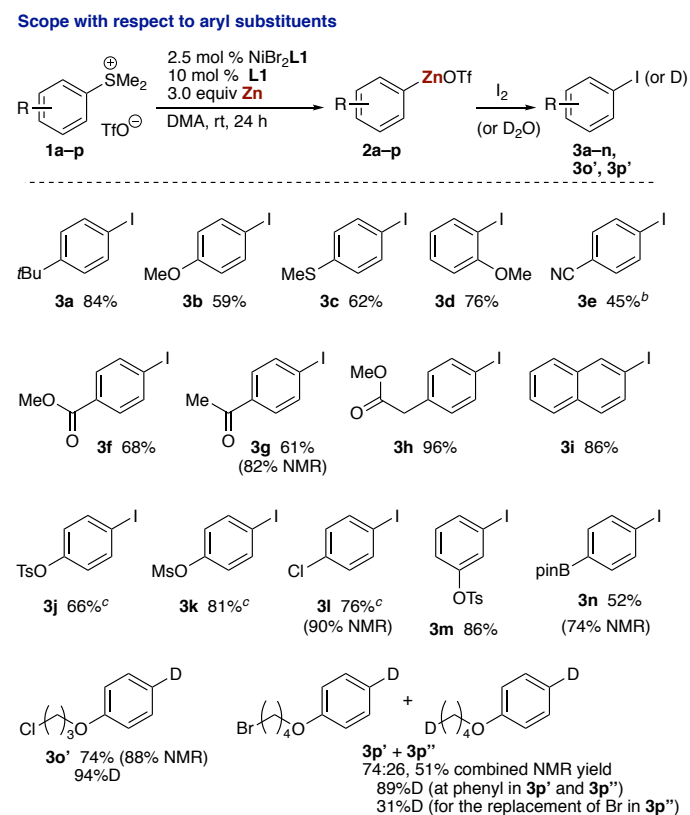


With the optimized conditions in hand, we investigated the reaction scope (Scheme 4). Electron-rich and -neutral arylsulfonium salts **1a–1d**, **1h**, and **1i** displayed good reactivity.²⁵ As expected, **1c**, which contains a methylsulfanyl group, was selectively zincated at the sulfonium moiety. The methoxy group at the *ortho* position in **1d** has little effect on the zinc insertion. Electron-deficient cyano-substituted **1e** suffered from competitive SET from either the zinc powder or a low-valent nickel species,²⁴ and thus demethylation of **1e** competed to yield 4-methylsulfanylbzonitrile and the yield of **3e** was moderate.²⁶ Notably, the zincation of the other electron-deficient arylsulfonium salts **1f–1g** proceeded efficiently under the standard conditions. The potentially reactive carbonyl groups in **3f–3h** were unaffected by the reaction conditions. Surprisingly, the acidic protons in **1h** have no detrimental effect on the reaction, and the corresponding zinc reagent **2h** was found, after filtration,

to be storable under an inert atmosphere at ambient temperature (*vide infra*). Interestingly, the potentially reactive sulfonate and chloro groups^{5–7} in **1j–1m** remained mostly intact and the C–S bond cleavage proceeded selectively. Small amounts of *p*-diiodobenzene were observed in the reactions of **1j–1l**, whilst no *m*-diiodobenzene was detected in the reaction of **1m**. The zincation tolerated a pinacolboronyl group, thus providing ample scope for further derivatization via orthogonal Suzuki–Miyaura cross-coupling reactions. Zincation in **1o** occurred predominately at the sp^2 C–S bond rather than at the sp^3 C–Cl bond to yield **3o'** after hydrolysis with D_2O . The bromo group in **1p** was partly reduced under the applied reaction conditions, and **1p** gave a mixture of **3p'** and **3p''**.

The counteranion of the sulfonium salts is not limited to triflate: $[BF_4]^-$, $[PF_6]^-$, or $[SbF_6]^-$ salts of **1q** showed similar

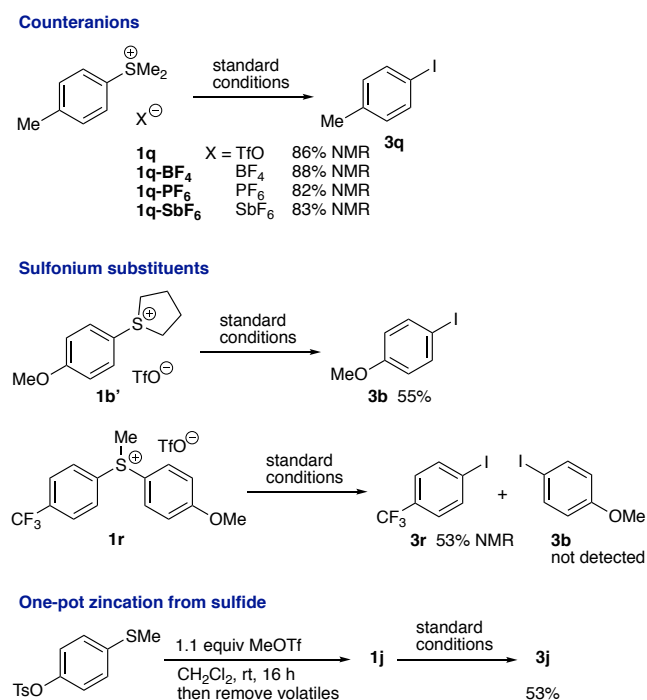
Scheme 4. Scope of the Catalytic Zincation of Arylsulfonium Salts.^a



^a Unless otherwise noted, isolated yields of **3** obtained from the arylsulfonium salts are shown. ^b *p*-Methylsulfanylbzenzonitrile was formed in 9% NMR yield. ^c *o*-Diiodobenzene was formed in 7% yield with **3j** and in <5% yield with **3k** and **3l**.

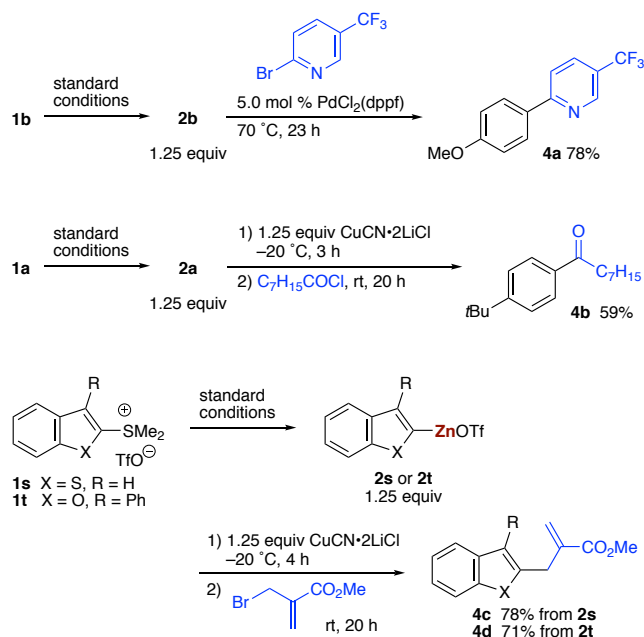
The behavior of the arylzinc species depends on the counteranion, solvent, and other coexisting reaction components.²⁷ In our case, dimethyl sulfide can act as a catalyst poison. Furthermore, nothing was known about the reactivity of the ‘accompanying salt-free arylzinc triflates’²⁸ except for their propensity to undergo iodolysis.^{5d,7} We thus investigated the reactivity of our arylzinc triflates, prepared from the sulfonium salts, with transition-metal complexes. Gratifyingly, the one-pot Negishi cross-coupling reaction of arylzinc triflate **2b** with 5-trifluoromethyl-2-bromopyridine proceeded smoothly to yield **4a** in 78% yield (Scheme 5).²⁹ In addition, arylzinc triflate **1a** underwent a copper-mediated coupling^{3e,30} with an acyl chloride. Heteroarylsulfonium salts **1s**³¹ and **1t**³² also successfully underwent the zincation followed by a subsequent copper-mediated coupling with an allylic bromide.

It should be noted here that accordingly, the arylzinc species generated from these salts should formally contain a $[BF_4]^-$, $[PF_6]^-$, or $[SbF_6]^-$ counteranion and would hence need further investigations from the viewpoint of coordination chemistry. Regarding the substituents on the cationic sulfur atom, dimethyl substituents would be the best in terms of reactivity, selectivity, atom-economy, and ease of preparation. When cyclic sulfonium salt **1b'** was used, the zincation proceeded to afford **3b** in 55% yield. Interestingly, unsymmetrically substituted diarylsulfonium salts **1r** underwent preferential zincation at the most electron-deficient C–S bond to yield **3r**. Starting from the parent aryl methyl sulfide, the zincation can be implemented in a one-pot procedure after simply removing volatiles upon completion of the methylation with methyl triflate.

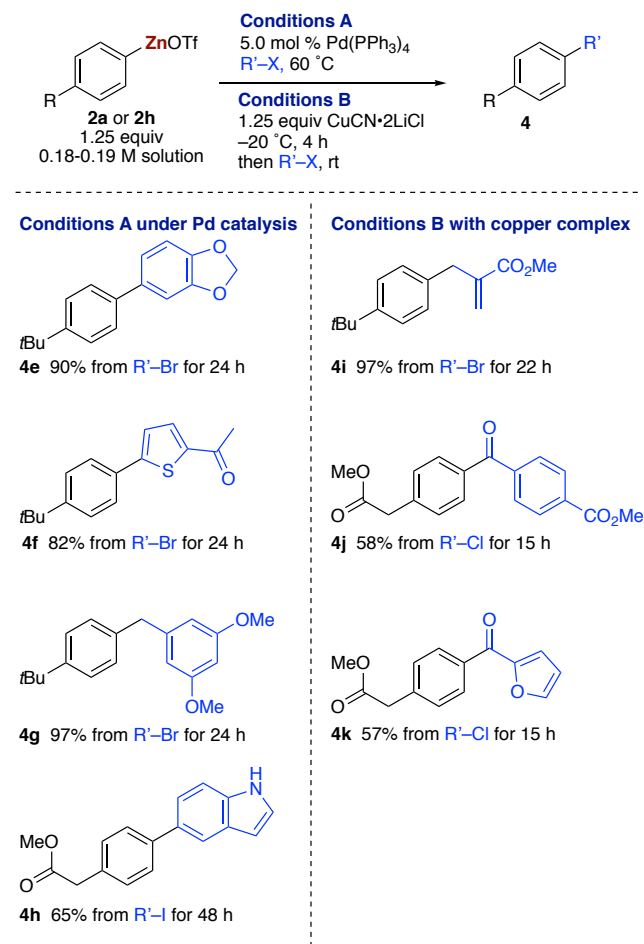


It is worth noting that we could, after removing the remaining zinc powder by filtration, store the arylzinc reagents under an inert atmosphere and use them efficiently for further cross-coupling reactions (Scheme 6). Stock solutions of **2a** and **2h** were stable at ambient temperature for a few weeks without significant degradation (**2a**: 0.181 M on April 4th, 2020; 0.165 M on June 1st, 2020. **2h**: 0.187 M on June 4th, 2020; 0.178 M on June 17th, 2020).

Scheme 5. One-pot Zincation/Cross-coupling.



Scheme 6. Cross-coupling Reactions with Arylzinc Stock Solutions.



In conclusion, we have demonstrated a highly effective method for the mild preparation of arylzinc triflates by developing a Ni-catalyzed insertion of zinc into the sp²-hybridized C–S bond of arylsulfonium salts. Sulfonium salts are readily

available from their corresponding aryl methyl sulfides and methyl triflate. This zincation has thus paved the way to use a wide range of aromatic sulfides via the cleavage of their chemically indolent C–S bonds. The zinc insertion takes place with superb chemoselectivity and offers a protocol that is complementary or orthogonal to existing methods for the generation of arylzinc reagents. The prepared arylzinc reagents exhibit consistent reactivity in palladium-catalyzed and copper-mediated cross-coupling reactions. This new zincation can be expected to find applications in the synthesis of bioactive compounds and functional π -conjugated materials as other known zincation methods have done previously.

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Supporting Information

Experimental procedures and spectral data (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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