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Desulfonylative Arylation of Redox-Active Alkyl Sulfones with Aryl Bromides

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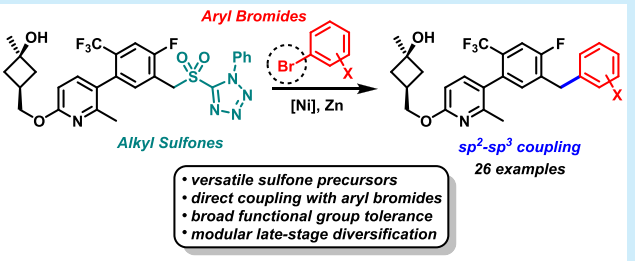
Supporting Information

ABSTRACT: We describe the development of the first reductive cross-electrophile coupling between alkyl sulfones and aryl bromides. The use of alkyl sulfones offers strategic advantages over other alkyl electrophiles as they can be incorporated into molecules in unique ways and permit α-functionalization prior to coupling. The conditions developed here enable incorporation of a wide array of aromatic rings onto (fluoro)alkyl scaffolds with broad functional group tolerance and generality, making this a practical method for late-stage diversification.



In drug discovery and development, the percentage of sp^3-hybridized carbons in drug candidates is positively correlated to success in the clinic.[1] This has been attributed to factors such as improved biological and physicochemical properties as well as reduced promiscuity relative to less saturated analogues.[1,2] Consequently, numerous synthetic methods have been developed that enable the cross-coupling of aliphatic motifs to facilitate access to sp^3-rich molecules.[3] Ni-catalyzed reductive cross-electrophile couplings have been particularly useful in this regard and have undergone extensive development in recent years (Figure 1A).[4,5] One attractive feature of these transformations is that they circumvent the need to preform nucleophilic reaction partners, resulting in simple reaction setups and broad functional group tolerance. As a result, cross-electrophile couplings have seen rapid uptake by synthetic chemists in recent years.

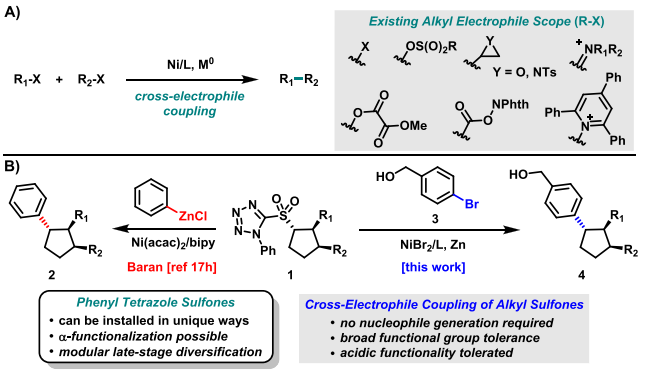


Figure 1. (A) General scheme for reductive cross-electrophile coupling. (B) Negishi-coupling of alkyl sulfone **1** with phenylzinc chloride and cross-electrophile coupling of **1** with aryl bromide **3**.

While seminal methods for cross-electrophile coupling employed alkyl halides as sp^3-coupling partners,[4,6] the scope has since expanded to include alkyl acetates,[7] carbonates,[8] sulfonates,[9] epoxides,[10] aziridines,[11] activated esters,[12] oxalates,[13] pyridinium salts,[14] iminiums,[15] and others (Figure 1A).[4,16] Such flexibility is valuable during synthetic planning, and further expansion to include alternative alkyl electrophiles is desirable. In this regard, we aimed to develop reductive coupling chemistry with alkyl sulfones due to their unique strategic advantages over other alkyl electrophiles.[17] In particular, alkyl sulfones can be deprotonated and functionalized at the α-position and can be prepared via cycloaddition or conjugate addition reactions. These diversifying bond formations can enable rapid exploration of chemical space, which is a vital aspect of drug discovery.

Our proposal to use alkyl sulfones as electrophiles in reductive cross-coupling was inspired by a recent report from the Baran laboratory describing Ni-catalyzed Negishi-type cross-coupling (Figure 1B, left),[17h] a method that we recently applied toward structure activity relationship (SAR) exploration on scaffold **1**. Notably, the use of an alkyl sulfone electrophile was advantageous here for several reasons, including the ability to perform α-functionalization prior to coupling and its greater stability compared to other alkyl electrophiles. While this method was enabling, the use of preformed organometallic reagents prevented direct incorporation of aryl groups with acidic hydrogens (e.g., **3**) and required several additional synthetic operations. To avoid protecting group manipulations and be able to use readily available aryl halides, we hypothesized that direct cross-electrophile coupling between sulfone **1** and aryl bromide **3** could be possible under reducing conditions. Although

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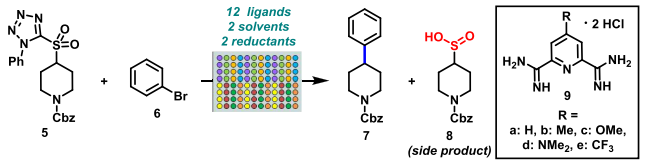
sulfones have not been previously used as electrophiles in reductive cross-coupling, phenyl tetrazole sulfones (e.g., **1**) are known to be redox active and capable of engaging in single electron transfer reactions.[17h] We herein describe the discovery and development of the first reductive cross-electrophile coupling reaction between alkyl sulfones and aryl bromides.

To assess the feasibility of using alkyl sulfones as substrates in cross-electrophile couplings, we studied the reaction between sulfone **5** and bromobenzene **6** (Scheme 1). A

Scheme 1. Initial Hit from High Throughput Screening and Final Reaction Conditions for the Cross-Coupling of Alkyl Sulfone 5 and Bromobenzene 6



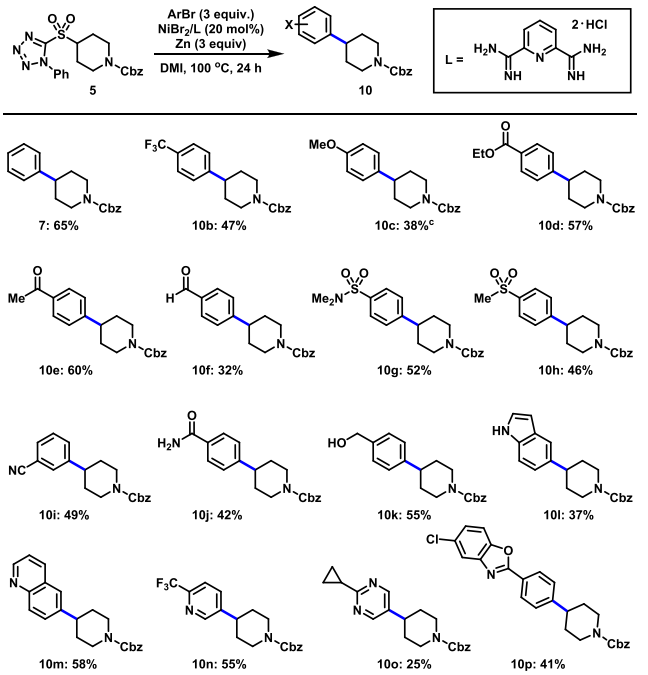
Initial Hit: $NiCl_2$·dme (10 mol %), **9a** (10 mol %), Zn (3 equiv.), DMPU (0.1 M), 80 °C (~10% yield)
Optimized Conditions: $NiBr_2$ (20 mol %), **9a** (20 mol %), Zn (3 equiv.), DMI (0.1 M), 100 °C (65% yield)

preliminary screen of 48 different reaction conditions (12 ligands, 2 solvents, and 2 reductants) using microscale high-throughput experimentation revealed that arylated product **7** could be formed in ca. 10% yield at 80 °C in DMPU in the presence of $NiCl_2$·dme/**9a** (10 mol %) and Zn (3 equiv) (see Supporting Information for details).[18] From this initial hit, further development led to the identification of DMI as being a particularly effective solvent for the reaction. Finally, a thorough screening of Ni sources and electronically differentiated ligands **9a**–**e** (R = H, Me, OMe, NMe_2, CF_3) revealed that the combination of $NiBr_2$ and **9a** enabled the formation of arylated product **7** in 65% yield (Scheme 1).

During reaction development, we identified sulfinate **8** as the major side product, which accounts for nearly all of the mass balance of **5**.[19] In attempts to reduce the formation of **8** during the reaction, we investigated the effects of several additives (bases, metal salts, TMSCl, etc.) on product distribution. However, none of these additives resulted in increased yields of cross-coupled product **7**. Control experiments revealed that the reaction does not proceed in the absence of Ni, **9a**, or Zn. Finally, the reaction was found to be largely insensitive toward both water and air, which simplifies material handling and reaction setup (see Supporting Information for details).

With reaction conditions in place, we explored the scope of this reductive cross-coupling reaction and found that a variety of electronically differentiated aryl bromides were competent coupling partners with sulfone **5** (Scheme 2). Several common functional groups were tolerated in the reaction, including esters (**10d**), ketones (**10e**), aldehydes (**10f**), sulfonamides (**10g**), sulfones (**10h**), nitriles (**10i**), and amides (**10j**). The synthesis of compound **10h** highlights the method's ability to chemoselectively differentiate between redox-active phenyl tetrazole sulfones and standard aryl sulfones. Moreover, aryl chlorides remain intact under the reaction conditions, thereby offering the potential to deliver products with a synthetic handle for further derivatization (**10p**). While *para*- and *meta*-substitution were both tolerated in this reaction, *ortho*-substituted aryl bromides were unreactive (see Supporting Information for details). The cross-coupling of several pharmaceutically relevant heteroaryl bromides also proceeded

Scheme 2. Aryl Bromide Scope[a,b]

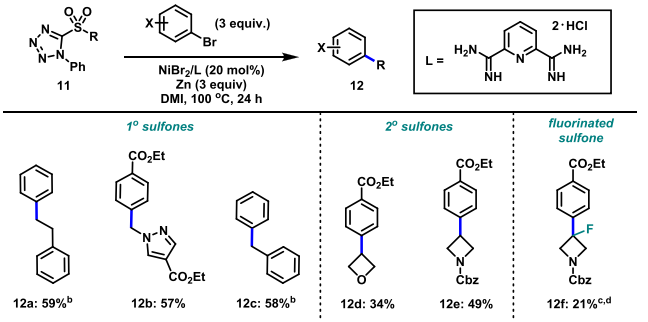


[a]Isolated yields shown for reactions conducted with 0.5 mmol of **5**. [b]In every reaction, the mass balance of limiting reagent **5** is sulfinate **8** (Scheme 1). [c]Ten equiv of 4-bromoanisole was used.

smoothly to form pyridine-, pyrimidine-, indole-, quinoline-, and benzoxazole-containing products in synthetically useful yields (**10l**–**p**). Of particular significance, functional groups with acidic hydrogens such as primary amides (**10j**), unprotected indoles (**10l**), and alcohols (**10k**) were well-tolerated in the reaction.

In addition to compound **5**, several other sulfones reacted under the standard conditions with similar levels of efficiency (Scheme 3). For example, primary (**12a**–**c**), secondary (**12d** and **e**), benzylic (**12c**), and α-heteroatom-containing (**12b**) sulfones all underwent cross-coupling to give arylated products in moderate to good yields. Notably, a fluorinated sulfone could also be employed in the reaction to deliver **12f** in 21% yield.[20] This example highlights the unique ability of alkyl sulfones to serve as handles for two-point diversification when

Scheme 3. Alkyl Sulfone Scope[a]



[a]Isolated yields shown for reactions conducted with 0.5 mmol of **11** unless otherwise stated. [b]Assay yield determined by HPLC analysis versus an authentic standard. [c]Five equiv of ethyl 4-bromobenzoate was used. [d]DMPU was used in place of DMI.

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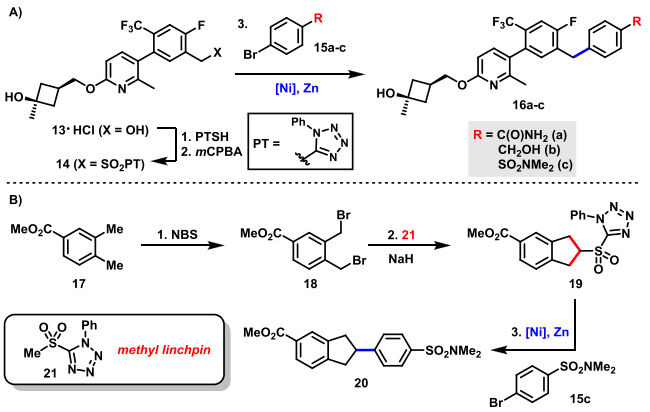
employed as electrophiles for cross-coupling reactions. However, at this time, the scope of α-fluorosulfones is limited due to the instability of the C−F bonds toward elimination under the reaction conditions.[21]

To highlight the utility of this method for late-stage diversification of complex molecules, we prepared several analogues from benzyl alcohol **13** (Scheme 4A). Common

Scheme 4. (A) Modular Synthesis of Diarylmethanes 16a−c and (B) Synthesis of Aryl Indane 20 Using a Methyl Linchpin/Reductive Cross-Coupling Strategy[a,b]

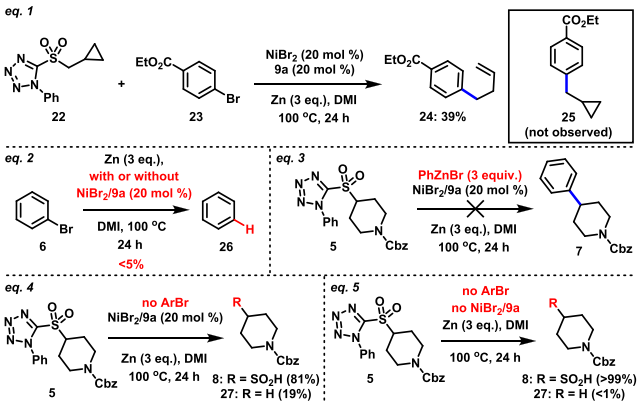


[a]Conditions and reagents for Scheme 4A: 1. Ph_3P (1.5 equiv), DIAD (1.5 equiv), PTSH (1.5 equiv), THF, 0 °C → rt (88%); 2. (i) *m*CPBA (6 equiv), 0 °C → rt; (ii) B_2Pin_2 (4 equiv), 0 °C → rt (91%); 3. optimized conditions from Scheme 1 with 5 equiv of **15a−c**. [b]Conditions and reagents for Scheme 4B: 1. NBS (2.2 equiv), $(PhCO_2)_2$ (7 mol %), CCl_4, 80 °C (90%); 2. NaH (2.2 equiv), **21** (1.1 equiv), rt (36% AY); 3. optimized conditions from Scheme 1 with 3 equiv of **15c** (20%).

intermediate sulfone **14** was prepared in two steps from **13** in 80% overall yield. Subsequent reductive coupling with aryl bromides **15a−c** proceeded smoothly to deliver diaryl methanes **16a−c** in 34−66% isolated yield. Importantly, each of these cross-couplings proceeded effectively in the presence of acidic functional groups (benzylic/tertiary alcohols and/or primary amide) without the need for protecting groups. Furthermore, the synthesis of 2-aryl indane **20** was accomplished via sequential annulation of dibromide **18** with methyl sulfone **21** followed by reductive coupling of the resulting sulfone **19** (Scheme 4B). This example highlights the ability of sulfone **21** to serve as a methyl linchpin and offers new opportunities for the installation of this versatile functional handle. Notably, this strategy is unique to the use of alkyl sulfones and has not been demonstrated with other alkyl electrophiles within the context of reductive cross-electrophile coupling.

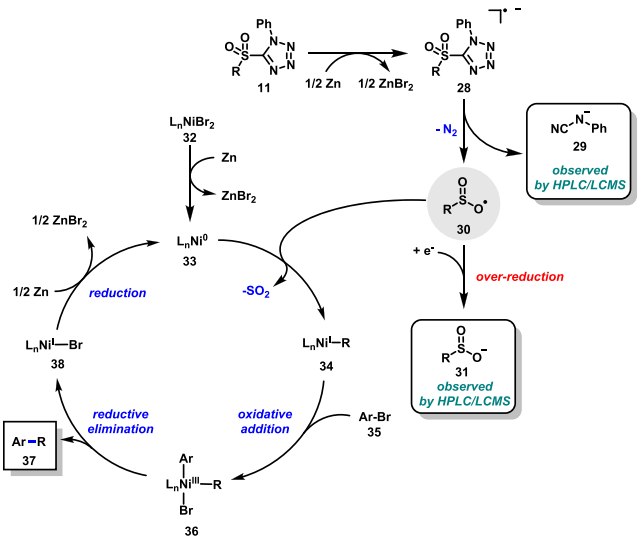
Several experiments and observations provided insight into the mechanism of this reaction (Scheme 5). First, conversion of (cyclopropyl)methyl sulfone **22** into ethyl 4-(3-butenyl)-benzoate (**24**) under the reaction conditions is consistent with the formation of a radical-like intermediate (eq 1). Moreover, control experiments confirmed that arylzinc halides are not generated under the reaction conditions (eq 2), and preformed arylzinc halides do not engage in cross-coupling under the standard conditions (eq 3).[22] The lack of conversion of bromobenzene (**6**) in eq 2 suggests a reaction between Ni and the alkyl component precedes oxidative addition into the aryl

Scheme 5. Selected Control Experiments



bromide bond. Furthermore, alkane **27** was formed in 19% yield when sulfone **5** was submitted to the standard reaction conditions in the absence of an aryl bromide coupling partner, providing further evidence in support of an initially generated alkyl-Ni species (eq 4). Notably, negligible amounts of alkane **27** are generated in the absence of Ni, which further supported this hypothesis (eq 5). On the basis of these experiments and literature precedent,[23] we propose a possible mechanism that involves an initial single electron reduction of sulfone **11** with Zn to generate radical anion **28** (Scheme 6).[24] Radical anion

Scheme 6. Possible Mechanism for the Reductive Cross-Coupling of Alkyl Sulfones and Aryl Bromides



28 can then undergo fragmentation to generate sulfinyl radical **30** and cyanamide **29** (consistently observed in crude reaction mixtures by HPLC/LCMS analysis).[25] Reaction of **30** with Ni(0) might then generate alkyl-Ni(I) species **34** via loss of SO_2.[26] Finally, reaction of **34** with aryl bromide **35** would lead to the formation of cross-coupled product **37** and Ni(I) species **38** via the intermediacy of Ni(III) species **36**. Reduction of **38** to Ni(0) would complete the catalytic cycle.[27−29]

In conclusion, we developed the first reductive cross-electrophile coupling reaction between alkyl sulfones and aryl bromides. This new method serves as a convenient approach to forge C(sp^3)-aryl bonds without the need for prefunctionalization of the aryl halide coupling partner. Moreover, in

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combination with well-established chemistry to functionalize alkyl sulfones, this method serves as a platform from which rapid diversification can be accomplished. As such, we anticipate that this method will have meaningful impacts within drug discovery and synthetic chemistry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01987.

Experimental procedures and characterization data for new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(18) For the discovery and utilization of ligand **9a** in the reductive cross-electrophile coupling between aryl halides and alkyl halides, see: (a) Hansen, E. C.; Pedro, D. J.; Wotal, A. C.; Gower, N. J.; Nelson, J. D.; Caron, S.; Weix, D. J. New ligands for nickel catalysis from diverse pharmaceutical heterocycle libraries. *Nat. Chem.* **2016**, *8*, 1126−1130. (b) Hansen, E. C.; Li, C.; Yang, S.; Pedro, D.; Weix, D. J. Coupling of Challenging Heteroaryl Halides with Alkyl Halides via Nickel-Catalyzed Cross-Electrophile Coupling. *J. Org. Chem.* **2017**, *82*, 7085−7092.
(19) Assigned based on LCMS analysis of the crude reaction mixture.
(20) While the standard cross-coupling conditions can be employed to deliver cross-coupled product **12f**, the use of DMPU in place of DMI was found to give a slightly improved yield.
(21) See the Supporting Information for a list of substrates that did not engage in cross-coupling under the current set of reaction conditions.
(22) Under the conditions shown in eq 3, sulfone **5** is completely converted to sulfinate **8**.
(23) For mechanistic studies of cross-electrophile couplings, see ref 15 and (a) Everson, D. A.; Jones, B. A.; Weix, D. J. Replacing Conventional Carbon Nucleophiles with Electrophiles: Nickel-Catalyzed Reductive Alkylation of Aryl Bromides and Chlorides. *J. Am. Chem. Soc.* **2012**, *134*, 6146−6159. (b) Biswas, S.; Weix, D. J. Mechanism and Selectivity in Nickel-Catalyzed Cross-Electrophile Coupling of Aryl Halides with Alkyl Halides. *J. Am. Chem. Soc.* **2013**, *135*, 16192−16197.
(24) Control experiments showed that sulfone **5** is cleanly reduced to sulfinate **8** in the presence of Zn. However, in the absence of Zn, no reduction of **5** occurs with $NiBr_2$/**9a** or $Ni(COD)_2$/**9a**.
(25) Alternatively, radical anion **28** could fragment to generate an alkyl radical and a phenyl tetrazole sulfinate (see ref 17h). Further fragmentation of the phenyl tetrazole sulfinate could generate cyanamide **29** via loss of N_2/SO_2 (see Supporting Information).
(26) Loss of SO_2 to generate alkyl radicals has been studied computationally and determined to be endergonic in many cases. Thus, while further mechanistic study is required to confirm this hypothesis, a Ni species (i.e. **33**) might assist in facilitating SO_2 extrusion from **30**: dos Passos Gomes, G.; Wimmer, A.; Smith, J. M.; Konig, B.; Alabugin, I. V. CO_2 or SO_2: Should It Stay, or Should It Go? *J. Org. Chem.* **2019**, *84*, 6232−6243.
(27) On the basis of our observation that alkyl sulfinates (e.g., **31**) are generated as side products in the reaction, competing reduction of sulfinyl radical **30** is proposed.
(28) At this time, an alternative mechanism involving fragmentation of **28** to generate an alkyl radical and a phenyl tetrazole sulfinate cannot be ruled out (see ref 25 and Supporting Information). Under such a scenario, the conversion of radical anion **28** to sulfinate **31** (via sulfinyl radical **30**) would represent an unproductive pathway.
(29) A catalytic cycle involving oxidative addition of an initially-generated alkyl-Ni(I) species into an aryl bromide bond has been proposed for a Ni-catalyzed cross-coupling of aryl bromides and photoredox-generated radicals: Gutierrez, O.; Tellis, J. C.; Primer, D. N.; Molander, G. A.; Kozlowski, M. C. Nickel-Catalyzed Cross-Coupling of Photoredox-Generated Radicals: Uncovering a General Manifold for Stereoconvergence in Nickel-Catalyzed Cross-Couplings. *J. Am. Chem. Soc.* **2015**, *137*, 4896−4899.

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