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Synthesis of Pyridylsulfonium Salts and Their Application in the Formation of Functionalized Bipyridines

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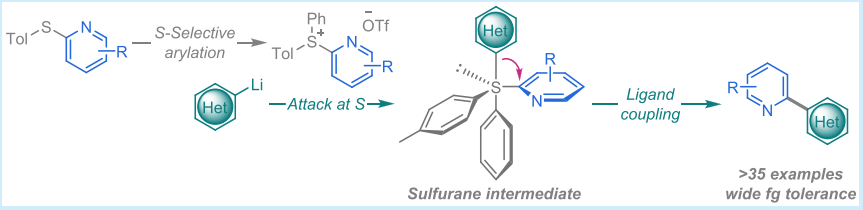
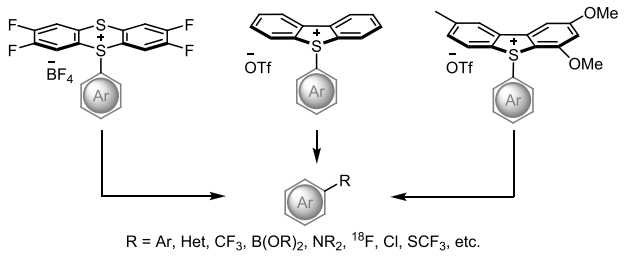


ABSTRACT: An S-selective arylation of pyridylsulfides with good functional group tolerance was developed. To demonstrate synthetic utility, the resulting pyridylsulfonium salts were used in a scalable transition-metal-free coupling protocol, yielding functionalized bipyridines with extensive functional group tolerance. This modular methodology permits selective introduction of functional groups from commercially available pyridyl halides, furnishing symmetrical and unsymmetrical 2,2′- and 2,3′-bipyridines. Iterative application of the methodology enabled the synthesis of a functionalized terpyridine with three different pyridine components.

Sulfur-mediated organic synthesis continues to be a rich area for exploration.[1] Sulfonium salts have garnered considerable attention of late in organic synthesis, especially for their utility in mediating C−C bond formation (Scheme 1).[2,3] Examples using sulfonium salts bearing sp^2-hybridized carbon substituents include reactions of vinylsulfonium salts to generate pharmaceutically relevant heterocycles,[4] cross-couplings,[5] and transformations using the extremely versatile thianthrenium and benzothiophenium salts.[2] Triarylsulfonium salts have been demonstrated to be particularly versatile reagents, capable of forming C−C bonds via various different methods.[2,3,6]

Scheme 1. Recent Reactions of Triarylsulfonium Salts[2,3b,6]



Methods of accessing synthetically useful arylsulfonium salts are limited in the literature;[3] this is especially true for 2- and 4-pyridylsulfonium salts,[5,7] and consequently their applications in organic chemistry remain underexplored. One such application of pyridylsulfonium salts which would be beneficial to the synthetic community involves their use in sulfur-mediated ligand-coupling reactions. Triarylsulfonium salts have previously demonstrated utility in transition-metal-free ligand-coupling reactions,[8] forming aryl−aryl products. However, limited examples of heteroaryl−aryl bond formations have been demonstrated[8f,9] and, to the best of our knowledge, no heteroaryl−heteroaryl bond formations resulting from the use of sulfonium salts in ligand-coupling reactions have been reported (in contrast ligand coupling via heteroarylsulfoxides has precedent).[8f,10,11] The lack of routes to access diarylpyridylsulfonium salts may be one reason for this. We postulated that a general route to diarylpyridylsulfonium salts would enable their subsequent reaction with lithiated pyridines in a transition-metal-free coupling protocol to access functionalized bipyridines. Bis-heteroaryls are common motifs in organic synthesis and drug targets, especially the bipyridine core. Bipyridines are highly sought after within the fields of synthetic chemistry, photochemistry, material sciences, and drug development.[12] This common structural motif can be found in biologically active natural products[13] (e.g., Caerulomycin F, Figure 1), but arguably, their most prevalent use is as ligands for transition metals, in both catalysts and photosensitizers.[12]

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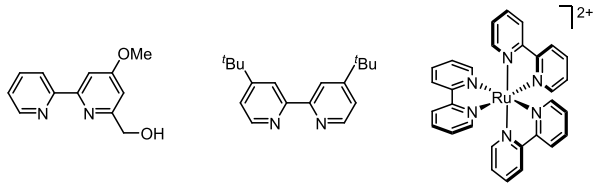
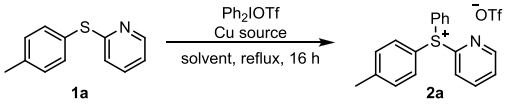


Figure 1. Exemplar molecules containing a bipyridine core.

When we started this project, existing methods for making bipyridines had limitations. They are commonly accessed using transition-metal-catalyzed methods (Scheme 2a); however, these processes have a significant number of constraints. Accessibility of cross-coupling precursors, high cost of transition metals, toxicity, and poor stability of reagents are examples of limitations. An analysis of Pfizer e-notebooks revealed that <8% of Suzuki–Miyaura cross-couplings with pyridyl boronic acids/esters gave >20% yield.[14] Willis and co-workers recently reported pyridyl sulfinates as improved coupling partners; however, this still requires costly transition metals.[14,15] The availability of transition-metal-free routes for the synthesis of bipyridines are limited, with contributions by McNally and co-workers being a notable advance.[16] Their phosphorane-mediated route provides access to an extensive range of bipyridines; however, there are still limitations such as poor EDG tolerance, limited access to fluorinated bipyridines, and no access to 2,3′-bipyridines. Examples of the analogous sulfur-mediated ligand-coupling processes are limited in the literature, especially for pyridine–pyridine coupling. A route with pyridylsulfoxides as the pyridine surrogate[10] was expanded upon significantly in a recent publication as we finalized this manuscript.[17] Qin and co-workers described using diisopropyldisulfide to mediate the coupling of heteroaryl Grignard reagents in good-to-excellent yield (Scheme 2c). They focused on 2-pyridyl-heteroaryl couplings e.g., 2,2′-bipyridines, but showed that 2,4′- and 2,3′-bipyridines could be accessed in moderate yields in several cases; it has been previously noted that ligand exchange processes can lead to undesired mixtures of coupling products with 3- and 4-pyridylsulfoxides.[8f,11] We envisioned that we could develop a simple method of accessing the synthetically useful pyridylsulfonium salts and apply them in effective ligand-coupling reactions to synthesize valuable functionalized bipyridines. This approach would involve the synthesis of diarylpyridylsulfonium salts, followed by reaction with lithiated pyridines forming a sulfurane intermediate, which would undergo heteroaryl–heteroaryl ligand-coupling to form the targeted bipyridines (Scheme 2d). The methodology reported herein further demonstrates the synthetic capabilities of sulfonium salts as versatile functional handles in organic synthesis.

The first challenge was to develop a synthetic route to the rare diarylpyridylsulfonium salts.[7d,e] Pyridylsulfides **1** were accessed easily through S_NAr reactions between the corresponding thiol and halopyridines. We focused on using *p*-methylthiophenol, as it is a solid with relatively low odor. The corresponding sulfonium salts **2** were obtained by copper-catalyzed S-selective arylation with Ph_2IOTf (Tables 1 and

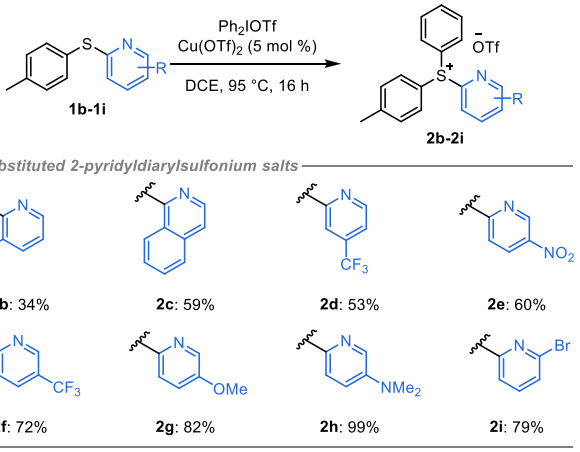
Table 1. Optimization of S-Selective Arylation of Pyridylsulfides[a]



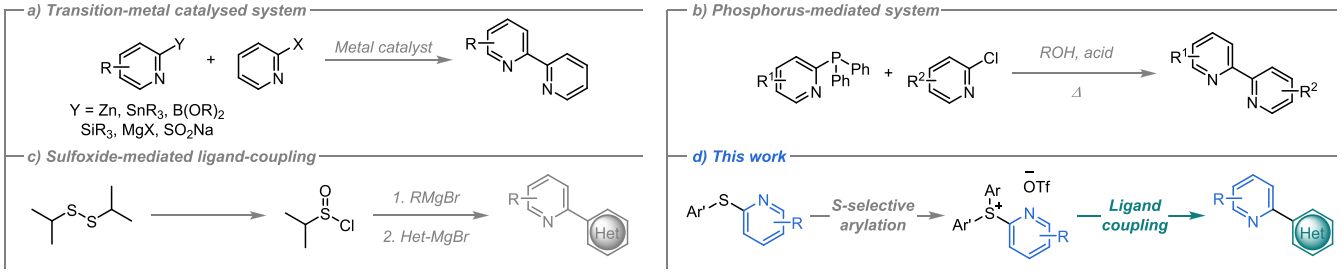
Entry	Cu source	Solvent	Ratio of S/N-arylation	Yield (%)[b]
1	Cu, CuCl	DCE	4:1	40
2	CuCl	Toluene	3:1	18
3	CuI	DCE	14:1	67
4	Cu(TC)	DCE	10:1	15
5	**$Cu(OTf)_2$**	**DCE**	**>20:1**	**69**
6	None	DCE	No reaction	0

[a]Using: **1a** (1.1 equiv), Ph_2IOTf (1 equiv), copper source (5 mol %) and solvent (0.6 M). [b]Isolated yield; Cu(TC) = Copper(I) 2-thiophene-2-carboxylate.

Table 2. Scope of S-Selective Arylation for the Synthesis of Substituted 2-Pyridyldiarylsulfonium Salts (Isolated Yields, 0.4–2.9 g)



Scheme 2. Current Bis-heteroaryl Syntheses and the System Reported Herein[14–17]



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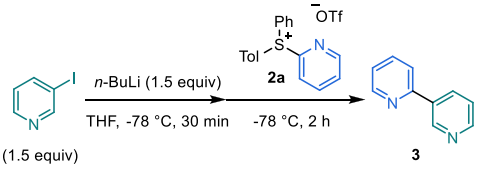
2).[18] The problem of competing S- vs N-arylation had been previously noted as a limitation.[7e] We discovered that the choice of copper source was important; e.g., an initial screening showed that the Cu/CuCl system used by Krief and co-workers[19] (Table 1, entry 1) gave the corresponding sulfonium salt in 40% yield along with N-arylated product, which proved to be difficult to remove by chromatography. Use of toluene as solvent gave some product but was less effective than DCE (entry 2). CuI gave S-selective arylation in Maruoka's sulfoximine synthesis[20] and also gave high levels of selectivity in our system (entry 3). Cu(TC) gave slightly reduced levels of selectivity compared to CuI, with isolation of **2a** again proving problematic (entry 4). Optimization of the copper source revealed that $Cu(OTf)_2$ produced the desired sulfonium salt **2a** in 69% yield with negligible amounts of competing N-arylation (entry 5). Using a modification of the copper-free method developed by Olofsson and co-workers for S-arylation of thioamides,[21] there was no reaction (entry 6). The factors influencing S- vs N-arylation remain a topic of investigation in our laboratory.

Using this new S-selective arylation method, various novel functionalized sulfonium salts **2b−2i** were furnished on multigram scale (Table 2) with no further optimization required. While the S-arylation of hindered sulfides (**1b,c**) was slightly lower yielding, it was pleasing to see that a range of electronically varied salts **2d−h** could be obtained in good-to-excellent yields. Bromo-substituted salt **2i** demonstrated the potential complementarity of the proposed ligand-coupling system. Sulfonium salts were bench-stable with no sign of degradation over a full year.

With a robust route to pyridylsulfonium salts in hand, we began investigating the ligand-coupling reaction (Table 3).

Table 3. Ligand-Coupling Optimization



Entry	Deviation from standard conditions	Yield (%)[a]
1	none	90[b]
2	3-bromopyridine in place of ArI	65
3	0.05 M	67
4	0.2 M	69
5	2 equiv of halopyridine	48

[a]Spectroscopic yield. [b]Isolated yield.

Reaction conditions were screened using sulfonium salt **2a** as the model substrate and 3-iodopyridine as the coupling partner. Under the best conditions found, lithiation at −78 °C with *n*-BuLi[22] was followed by the addition of sulfonium salt **2a** and the reaction was left to stir at −78 °C for 2 h. The corresponding 2,3′-bipyridine **3** was obtained in 90% yield. Changing to 3-bromopyridine gave a yield of 65% (entry 2). Varying the concentration from 0.1 to 0.05 or 0.2 M gave lower yields (entries 3 and 4). Use of two equivalents of iodopyridine also gave lower yields (entry 5).

Having identified suitable reaction conditions, we began to explore the functional group tolerance of our system. Sulfonium salt **2a** was subjected to reaction with various lithiated pyridines to produce a range of 2,2′- and 2,3′-bipyridines (Table 4). Both electron-rich and electron-poor systems were well tolerated in different substitution patterns. Dihalogenated pyridines were competent reaction partners (**8**, **13**, **17**, **29**, **30**). Functional groups such as amines, alkenes, alkynes, sulfides and acetals were also well tolerated. Thus, a wide range of further functionalization of the product bipyridines is possible. Ligand-coupling also proceeded efficiently in the presence of trifluoromethyl and fluoro groups, two functionalities that are prevalent in medicinal chemistry. Another noteworthy feature of the methodology is that it enables access to underexplored 2,3′-bipyridines which have potential in medicinal chemistry,[23] as ligands,[24] and have been proposed as scaffolds for N_2-fixation recently.[25] No modification of conditions was required, and the method did not seem to suffer from the problem of ligand exchange leading to undesired 2,2′-bipyridines that had been reported for coupling with some 3-pyridylsulfoxides[8f,11] (it is unclear if Qin's sulfoxide method[17] suffers from this problem, they report two examples of 2,3′-bipyridines). The method is complementary to previously reported methods, and as with any method there are limitations. In particular, to-date we have been unable to make 2,4′-bipyridines (whereas Qin[17] reports several successful examples) and certain functional groups are incompatible with organolithiums (see SI for further details). Although the method is not "pot-efficient", we note that the single set of arylation and coupling conditions will be useful for library synthesis. By contrast, Qin's method[17] is more "pot-efficient" but requires different conditions for different products.

Next, we explored the synthesis of bipyridines through variation of sulfonium salt coupling partner (Table 4). Substituted pyridylsulfonium salts **2b−2i** were reacted with various lithiated pyridines. A diverse range of symmetrical and unsymmetrical bipyridines were synthesized via this methodology. Electron-deficient and electron-rich bipyridines could be accessed successfully with various substitution patterns. Sterically hindered substituted bipyridines **23−26** could be accessed with no deleterious effect on yield, demonstrating the tolerance of sterically hindered ligands in the carbon−carbon bond formation step. Halogenated bipyridines were also synthesized, providing functional handles for further derivatization, highlighting the orthogonality of this process. A limitation was that reactions with nitro-substituted sulfonium salt **2e** gave complex mixtures of products that were difficult to separate.

With respect to the mechanism, the coupling reaction is proposed to proceed through the formation of a sulfurane intermediate: attack of the organolithium species at the electropositive sulfur center, followed by subsequent ligand-coupling of the two pyridine units forms the bipyridine product and phenyltolylsulfide (Scheme 3).[8] Sulfuranes bearing solely carbon substituents have been proposed and detected previously.[2,8] Recently they have been invoked in aryl−aryl, aryl−vinyl, and vinyl−vinyl couplings.[2b,d] In our case, the selectivity for bipyridine formation over pyridyl−aryl or phenyl−tolyl couplings can be rationalized as follows: the incoming nucleophile would be expected to occupy an apical position and ligand coupling with an equatorial pyridine would be favored over phenyl or tolyl groups.[10,11,16] The reaction pathway may involve pseudorotations if both pyridines occupy the apical positions in the initially formed intermediate.

Direct S_NAr attack could also lead to the formation of the bipyridine products. An initial probe of this possibility was

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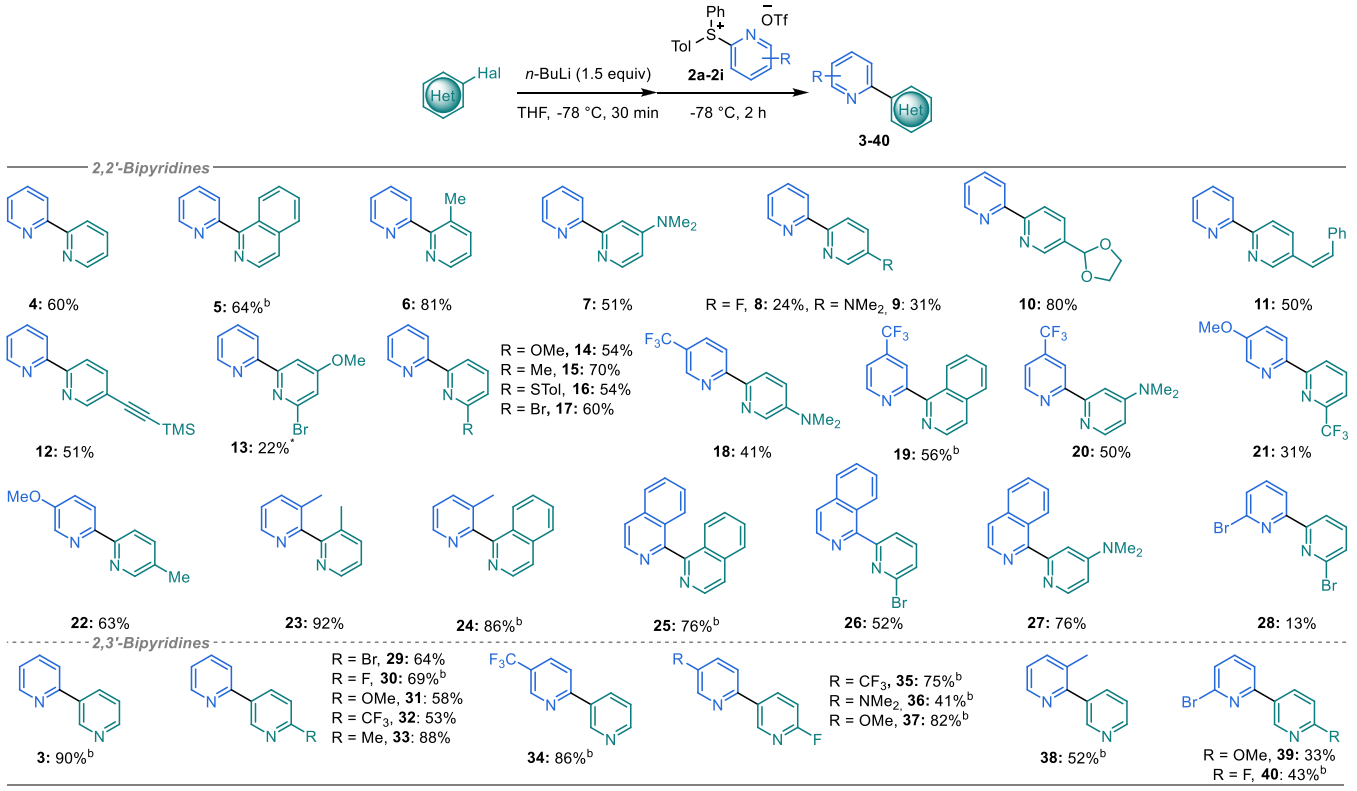
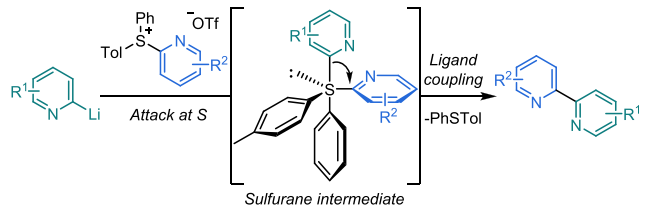
Table 4. Variation of Organolithium and Sulfonium Salt Coupling Partners[a]



[a]Lithiations were performed using bromopyridine starting materials except where stated. [b]Iodopyridine starting material was used. *Reaction performed at 0.1 mmol scale.

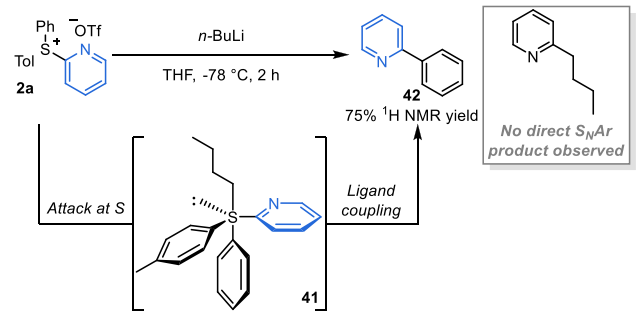
Scheme 3. Proposed Reaction Mechanism



conducted by reacting *n*-BuLi and sulfonium salt **2a**. The expected product from S_NAr would be 2-butylpyridine.

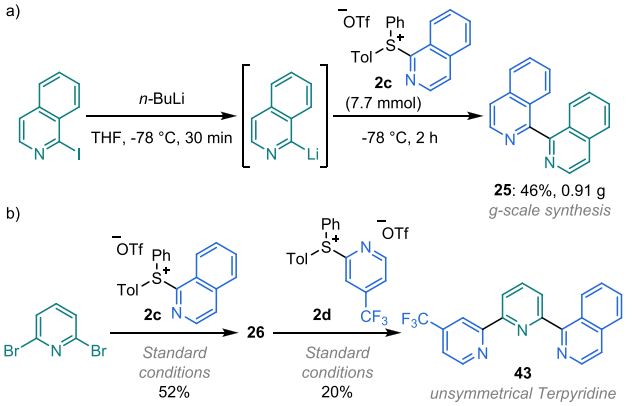
However, the formation of 2-phenylpyridine **42** was observed. This outcome is consistent with formation of a sulfurane intermediate **41** from reaction of the organolithium and **2a**, followed by ligand coupling to form the biaryl species **42** (Scheme 4).

Scheme 4. Testing the Possibility of Direct S_NAr



The coupling method can be scaled up, as demonstrated by the synthesis of 0.91 g of bisisoquinoline **25** without further optimization (Scheme 5a). With methodology in hand, we

Scheme 5. (a) Gram-Scale Synthesis of 25; (b) Modular Synthesis of an Unsymmetrical Terpyridine 43



proceeded to apply it to the synthesis of a privileged class of ligands, terpyridines (Scheme 5b).[26] Using our standard conditions, with no optimization, a novel unsymmetrically substituted terpyridine **43** was accessed through two sequential ligand coupling reactions starting from readily available 2,6-dibromopyridine. Different pyridine cores were integrated through iterative use of our methodology, exhibiting its synthetic potential.

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In summary, we have developed a transition-metal-free strategy for the synthesis of bipyridines using pyridylsulfonium salts.[27] We have also developed an S-selective arylation methodology to furnish these synthetically useful diarylpyridylsulfonium salts. The combination of these methods enables access to a wide range of symmetrical and unsymmetrical bipyridines in a modular fashion, offering a new complementary method to existing procedures, which we believe will be an attractive strategy for medicinal and catalysis chemists.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03048.

Experimental procedures, method limitations, compound characterization, copies of NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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