Synthesis of Pyridylsulfonium Salts and their Application in Transition Metal-Free Formation of Functionalized Bipyridines

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Abstract: An S-selective arylation of pyridylsulfides with good functional group tolerance has been developed. The resulting pyridylsulfonium salts have been used in a scalable transition metal-free coupling protocol yielding functionalized bipyridine scaffolds with extensive functional group tolerance and modularity. Pyridylsulfonium salts were coupled to lithiated pyridines in a sulfur-mediated synthesis of bipyridines. 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.

The bipyridine core is highly sought after within the fields of synthetic chemistry, photochemistry, material sciences and drug development.[1] This common structural motif can be found in biologically active natural products[2] (e.g., Caerulomycin F, Figure 1) but, arguably, their most prevalent use is as ligands for transition metals, both in catalysts and photosensitizers.[1]

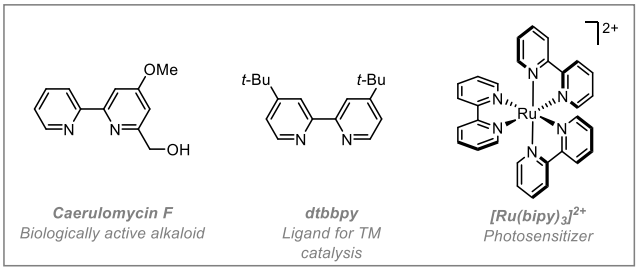
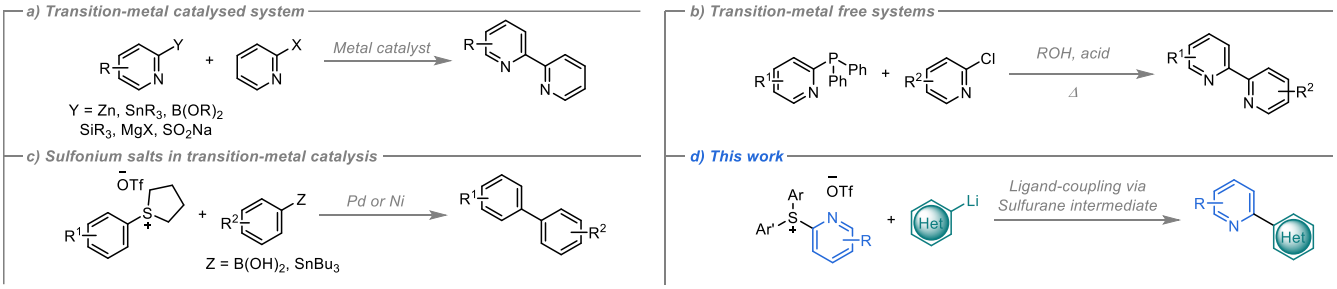


Figure 1. Exemplar molecules containing a bipyridine core.

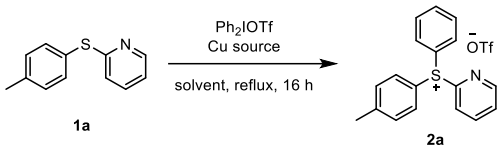
Existing methods for making bipyridines have limitations. They are commonly accessed using transition metal-catalyzed methods (Scheme 1a), however, these processes have a significant number of constraints. Accessibility of cross-coupling precursors, high cost of transition metals, toxicity and poor stability 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.[3] Willis and co-workers recently reported pyridyl sulfinates as improved coupling partners, however, this still requires costly transition metals.[3,4] The availability of transition metal-free routes for the synthesis of bipyridines are limited, with the method recently developed by McNally and co-workers as the most notable system (Scheme 1b).[5] 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 sulfur-mediated route with pyridyl-sulfoxides as the pyridine surrogate had limited scope and little demonstrated functional group tolerance,[6] until a very recent paper expanding significantly on this work was published as we finalized this manuscript.[7] Sulfonium salts have garnered considerable attention of late,[8] and their use in ligand coupling has been described previously, however, only with selected heteroaromatic examples and no examples in bipyridine formation.[9] Their use in transition metal-based cross-coupling has been explored[10] (Scheme 1c) but their potential as reagents in transition metal-free couplings has yet to be fully realized. We envisioned that they could facilitate such couplings to access functionalized bipyridine cores and offer a complementary transition metal-free system to McNally's method. This approach would involve the synthesis of pyridylsulfonium salts, followed by reaction with lithiated pyridines forming a sulfurane intermediate, which would undergo heteroaryl-heteroaryl ligand-coupling to form the target bipyridines (Scheme 1d). The methodology reported herein further demonstrates the synthetic capabilities of sulfonium salts as versatile functional handles in organic synthesis.



Scheme 1: Current methods and the system reported herein.

The first challenge was to develop a synthetic route to the rare pyridylsulfonium salts.[8e] Pyridylsulfides **1** were accessed easily through S_NAr reactions between the corresponding thiol and halopyridines. Subsequently, sulfonium salts **2** were obtained by copper-catalyzed S-selective arylation with Ph_2IOTf (Tables 1 and 2). The choice of copper source was important, e.g., an initial screening showed that the Cu/CuCl system used by Krief and co-workers[11] (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[12] and also gave high levels of selectivity in our system (entry 3). CuTC 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 modified copper-free method developed by Olofsson and co-workers,[13] there was no reaction (entry 6). The factors influencing S vs. N-arylation remain a topic of investigation in our laboratory.

Table 1. Optimization of S-selective arylation of pyridylsulfides.



Entry	Cu source	Solvent	Ratio of S/N-arylation	Yield (%)[a]
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

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

Using this new S-selective arylation method, various novel functionalized sulfonium salts **2b-2i** were furnished on multi-gram 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). 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[14] was followed by the addition of sulfonium salt **2a** and the reaction was left to stir at -78 °C for 2 hours. 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 M to 0.05 M or 0.2 M gave lower yields (entries 3 and 4). Use of two equivalents of iodopyridine also gave lower yields (entry 5).

Table 2. Scope of S-selective arylation for the synthesis of substituted 2-pyridylsulfonium salts.

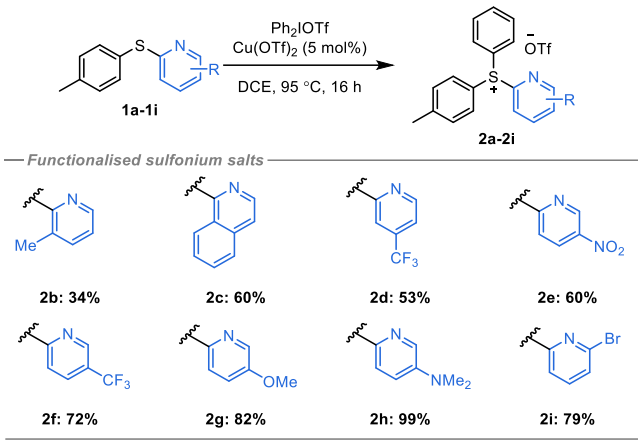
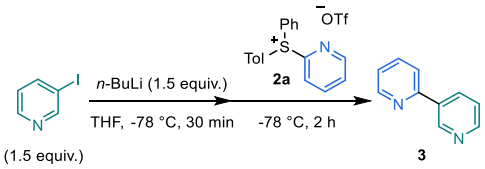


Table 3. Ligand-coupling optimization.

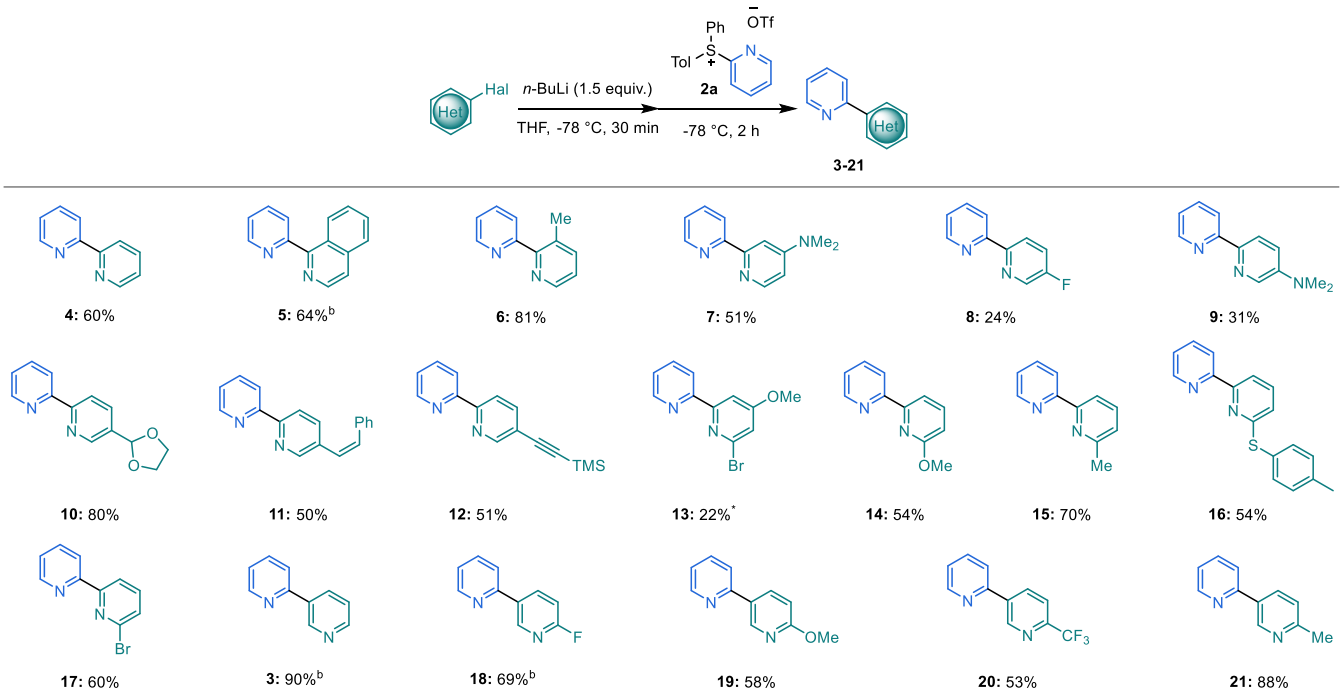


Entry	Deviation from standard conditions	Yield (%)[a]
1	none	90[b]
2	3-bromopyridine in place of ArI	65
3	0.05 M	67
4	0.2 M	69
5	2 equiv. of halopyridine	48

Reactions were run at a 0.1 mmol scale in THF (0.1 M wrt **2a**). [a] Determined by ^1H NMR spectroscopy with 1,2,4-trimethoxybenzene as an internal standard; [b] Isolated yield

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, 18**). 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,[15] as ligands,[16] and have been proposed as scaffolds for N_2-fixation recently.[17] The method is complementary to previously reported methods.

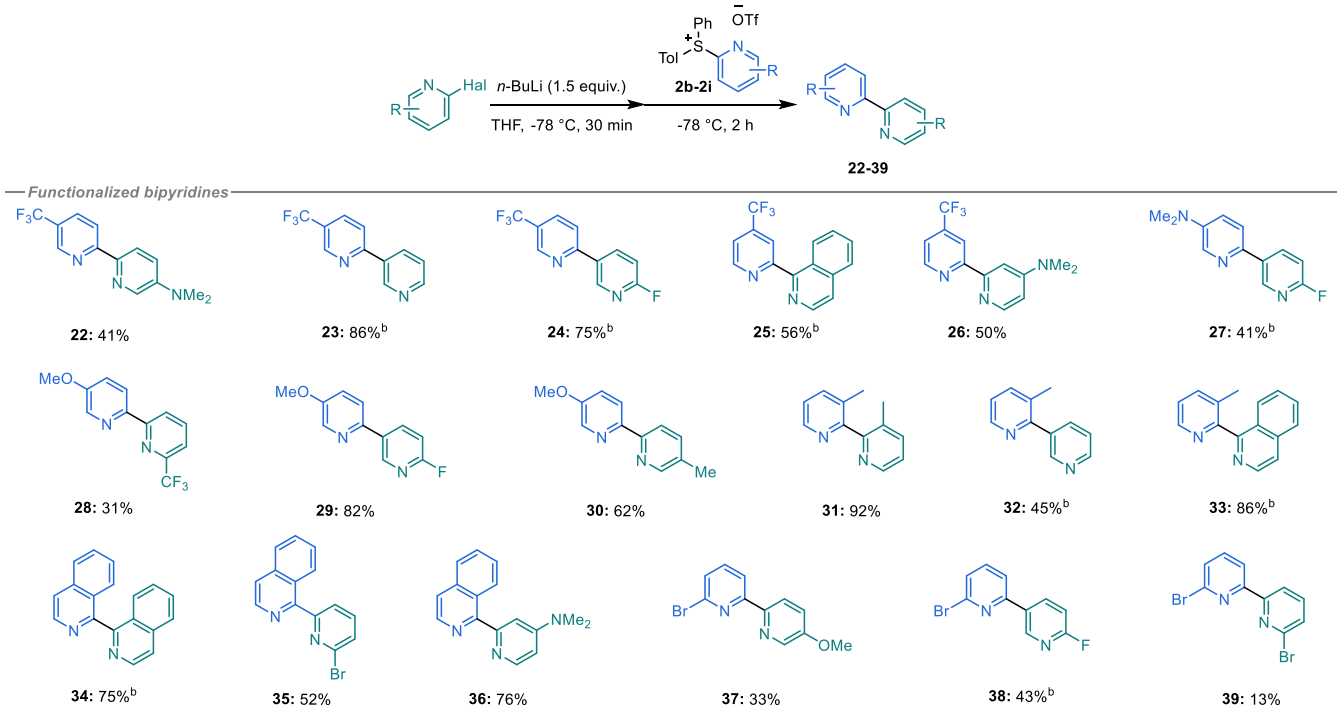
Table 4. Variation of organolithium coupling partner.[a]



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

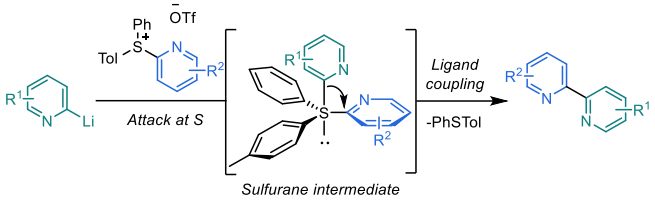
Next, we explored the synthesis of functionalized bipyridines through variation of sulfonium salt coupling partner (Table 5). Functionalized pyridylsulfonium salts **2b-2i** were reacted with various lithiated pyridines. A diverse range of symmetrical and unsymmetrical bipyridines **22-39** were synthesized via this methodology. Electron-deficient and electron-rich bipyridines could be accessed successfully with various substitution patterns. Sterically hindered substituted bipyridines **31-35** could be accessed with no deleterious effect on yield, demonstrating the tolerance of sterics in the carbon-carbon bond formation step. Halogenated bipyridines were also synthesized, providing functional handles for further derivatization, highlighting the orthogonality and modularity of this process. A limitation was that reactions with nitro-substituted sulfonium salt **2e** gave a complex mixture of products that were difficult to separate.

Table 5. Variation in sulfonium coupling partner to access a range of bipyridines.[a]



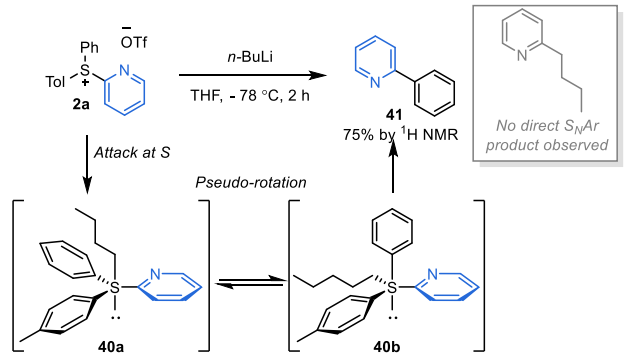
[a] Lithiation performed using corresponding bromopyridine starting material except where stated; [b] corresponding iodopyridine starting material was used.

With respect to the mechanism, the 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 2).[9]



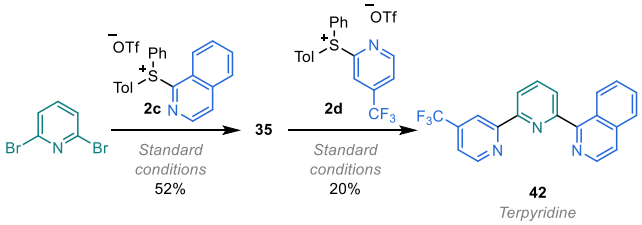
Scheme 2. Proposed reaction mechanism.

Direct S_NAr attack could also lead to the formation of the bipyridine products. An initial probe of this possibility was 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 **41** was observed. Presumably, a sulfurane intermediate **40a** was formed from reaction of the organolithium and **2a**, which then underwent pseudo-rotation to **40b**, followed by ligand coupling to form the biaryl species **41** (Scheme 3).



Scheme 3. Testing the possibility of direct S_NAr.

With methodology in hand, we proceeded to apply it to the synthesis of a privileged class of ligands, terpyridines (Scheme 4).[18] Using our standard conditions, with no optimization, a novel unsymmetrically substituted terpyridine **42** 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.



Scheme 4. Modular synthesis of an unsymmetrical terpyridine.

In summary, we have developed a transition metal-free strategy for the synthesis of bipyridines using pyridylsulfonium salts. We have also developed an S-selective arylation methodology to furnish these synthetically useful pyridylsulfonium 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.

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Conflicts of interest

The authors declare no conflict of interest.

Keywords: Sulfurane • Bipyridine • Sulfonium • S-Arylation • Ligand Coupling

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