Synthesis of Air-stable, Odorless Thiophenol Surrogates via Ni-Catalyzed C-S Cross-Coupling

Valentin Magné, and Liam T. Ball*

Abstract: Thiophenols are versatile synthetic intermediates whose practical appeal is marred by their air sensitivity, toxicity and extreme malodor. Herein we report an efficient catalytic method for the preparation of *S*-aryl isothiouronium salts, and demonstrate that these air-stable, odorless solids serve as user-friendly sources of thiophenols in synthesis. Diverse isothiouronium salts featuring synthetically useful functionality are readily accessible *via* nickel-catalyzed C-S cross-coupling of (hetero)aryl iodides and thiourea. Convenient, chromatography-free isolation of these salts is achieved *via* precipitation, allowing the methodology to be translated directly to large scales. Thiophenols are liberated from the corresponding isothiouronium salts upon treatment with a weak base, enabling an *in situ* release / *S*-functionalization strategy that entirely negates the need to isolate, purify or manipulate these noxious reagents.

Introduction

Aryl-sulfur motifs feature in numerous important compound classes, from materials and food additives to agrochemicals and pharmaceuticals (Figure 1).[1] Concise and general methods for the synthesis of these ubiquitous structural elements are therefore extremely valuable, and their development continues to be the subject of significant research effort.[2] In this regard, thiophenols represent universal precursors from which all other aryl-sulfur functionality can ultimately be accessed. However, despite occupying such a privileged position in synthetic strategy, the air sensitivity, toxicity and foul odor of many thiophenols renders them impractical as starting materials.[3] Furthermore, the relatively limited commercial availability of thiophenols[4] necessitates their synthesis prior to elaboration into the desired aryl-sulfur motif.

In the context of complex molecule synthesis, Migita-type[5] cross-coupling between a sulfur nucleophile and an aryl halide represents the most general and widely deployed approach to thiophenols. The identity of the sulfur nucleophile has consequences for not only the catalytic efficiency, cost, convenience and atom-economy of the process as a whole, but also the ease of subsequent thiophenol deprotection. This is illustrated in arguably the two best-in-class protocols (Scheme 1A): coupling of aryl halides with either a β-thiol ester[6] or triisopropylsilanethiol.[7] Despite being widely used, both methods rely on a precious metal catalyst and employ a strong base in either the cross-coupling itself or the subsequent

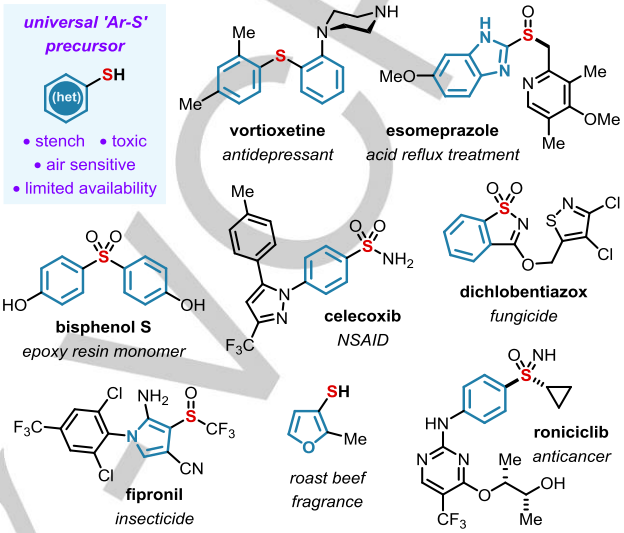

Figure 1. Thiophenols are universal precursors to structurally diverse aryl-sulfur motifs which form the core of numerous societally important compounds.

deprotection step. While the β-thiol esters employed in the former methodology are readily available and odorless, triisopropylsilanethiol is expensive, has limited availability on scale, and possesses a "pungent rotten egg odor".[8] Both sulfur nucleophiles offer poor atom economy[9] (<20%), which is compounded by the frequent need for chromatographic purification of the protected thiophenol prior to its liberation. New general methods for the convenient and scalable synthesis of thiophenols – or their chemical surrogates – would therefore greatly expedite the preparation of more complex aryl-sulfur motifs that form the core of important molecules.

Herein we report a general and practical method for the synthesis of *S*-aryl isothiouronium salts (Scheme 1B), and demonstrate that these air-stable, odorless compounds are convenient surrogates for thiophenols in synthesis. C_{aryl}-S bond formation is achieved *via* Ni-catalyzed coupling of structurally diverse aryl iodides with thiourea – a cheap, air-stable, odorless sulfur source – under mild, base-free conditions. The resulting isothiouronium salts can be precipitated directly from the reaction mixture *via* anion metathesis with a sodium benzoate salt, and liberate the corresponding thiophenols readily in the presence of a weak base. This ease of deprotection allows for *in situ* liberation / *S*-functionalisation of the thiophenols, thereby entirely negating the need to isolate or manipulate these noxious compounds.

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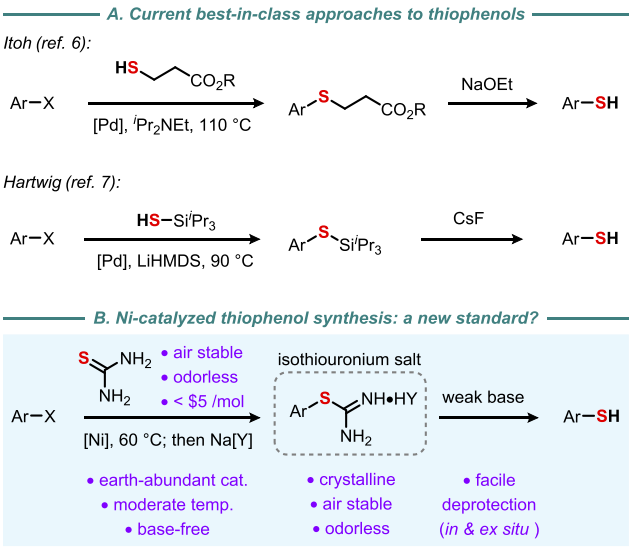
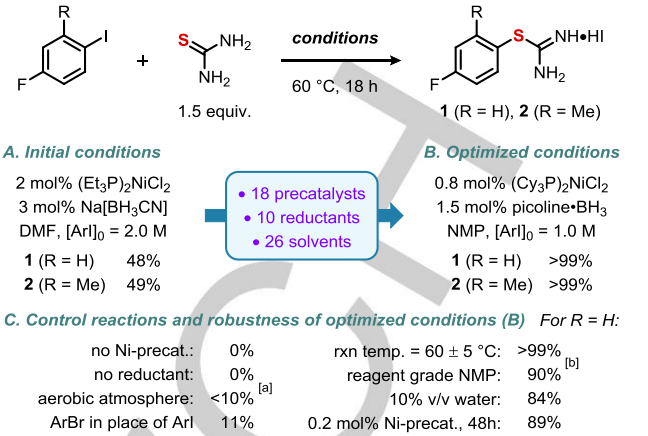


Scheme 1. (A) Preeminent cross-coupling approaches to thiophenols[6,7] and (B) advantages of the present Ni-catalyzed strategy.



Scheme 2. (A) Initial and (B) optimized conditions for Ni-catalyzed synthesis of *S*-aryl isothiouronium salts, and (C) selected control reactions. Yields determined by ^{19}F NMR spectroscopic analysis *vs* internal standard. [a] Air from a 1 mL syringe was injected into an otherwise standard reaction. [b] N_2-sparged reagent grade NMP employed without prior purification.

Results and Discussion

Thiourea has been employed previously as a sulfur source in both Pd- and Cu-catalyzed cross-coupling.[10] However, the use of forcing conditions and the presence of base in these reactions leads to *in situ* decomposition of the initially-formed isothiouronium salt, and the resulting thiophenol(ate) is then typically engaged in subsequent couplings. To date, Takagi's 1985 report of base-free thiourea cross-coupling is the sole exception to this trend.[11] However, although an important proof of concept, this methodology was demonstrated for only seven substrates, from which only three isothiouronium salts were isolated.[11,12]

Application of Takagi's[11] conditions to 4-fluoroiodobenzene – a substrate that had not been previously tested – proved disappointing (Scheme 2A). We therefore re-investigated the methodology, and identified the conditions illustrated in Scheme 2B as both general and convenient. The process of optimization[13] highlighted the need for a polar reaction medium and the superiority of monodentate phosphines over bidentate phosphine and non-phosphine ligands. Notably, excellent yields were achieved by using (1) lower loadings of an air-stable, commercially available precatalyst, and (2) picoline-borane as a benign and practical alternative to sodium cyanoborohydride,[14] the toxic, highly hygroscopic[15] catalyst activator employed by Takagi.[11]

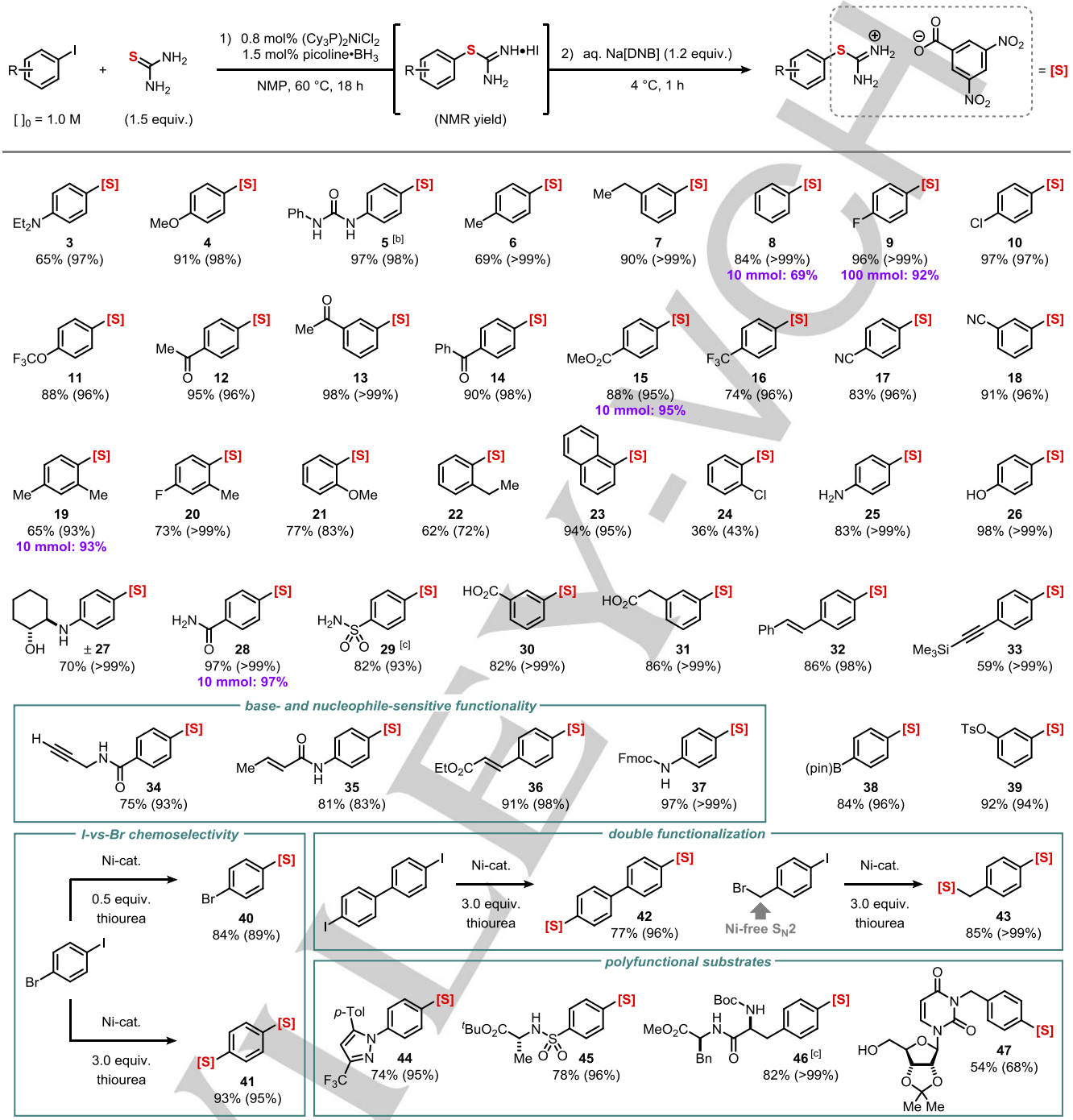
Control reactions (Scheme 2C) indicated that the Ni precatalyst, the reductant and an anaerobic atmosphere were essential, and that the optimized conditions could not be applied generally to aryl bromides. However, variations in reaction temperature were well-tolerated, and the reaction could be performed in unpurified, wet solvents without significant detriment. The excellent yield was maintained upon further reduction of the catalyst loading to 0.2 mol%, corresponding to a turnover number of 445. The robustness of the C-S cross-coupling to minor variations in process parameters, and its high catalytic efficiency, suggest that it will be readily reproducible on both discovery and process scales.

Having identified appropriate conditions for the C-S cross-coupling (Scheme 2B), we turned our attention to product isolation. Despite being salts, isothiouronium iodides **1** and **2** are soluble in NMP and their selective, high-yielding crystallization could not be achieved by addition of anti-solvents and / or by cooling. However, the corresponding isothiouronium 3,5-dinitrobenzoates[13] are precipitated rapidly upon anion metathesis, and can be isolated in excellent yield and purity simply by filtration.[16] The isolated isothiouronium dinitrobenzoates are stable to air, light and moisture at ambient temperature, with no decomposition observed in samples that had been stored on the bench for over 12 months. In addition to its practical convenience, this approach benefits from the thermal stability (onset temperature >330 °C)[17] and low cost of 3,5-dinitrobenzoic acid. We anticipate that the free-flowing, non-hygroscopic nature of the salts will render them appropriate for use in conjunction with automated weighing systems for high throughput experimentation, as well as in conventional synthesis.

An investigation of substrate scope indicated that the reaction is compatible with common electron-donating and -withdrawing functionality (Table 1, **3**-**18**), such as ureas, esters, ketones and nitriles. The uniformly excellent yields of these products determined by NMR spectroscopy are largely replicated in the isolated yields, although some disparities are observed (*e.g.*, **3**, **6** and **16**), reflecting the fact that the precipitation protocol was applied without substrate-specific reoptimization.

Aryl iodides featuring *ortho*-substitution undergo C-S coupling with varying efficiency: while simple *ortho*-substituents are perfectly compatible (**19**-**23**), the yield falls with increasing steric demand (**24**) to the extent that no reaction is observed for

Table 1. Scope of the Ni-catalyzed synthesis of *S*-aryl isothiouronium salts.[a]



[a] Yields are of isolated material from reactions performed on a 1 mmol scale; values in parenthesis refer to yields of isothiouronium iodides determined by NMR spectroscopic analysis prior to isolation. [b] Standard conditions, but with $[ArI]_0$= 0.75 M. [c] Reaction performed on a 0.5 mmol scale. DNB = 3,5-dinitrobenzoate.

di-*ortho*-substituted aryl iodides (*vide infra*). This trend is consistent with the significant retarding effect of *ortho*-substitution observed in other Ni-catalyzed cross-coupling reactions.[18]

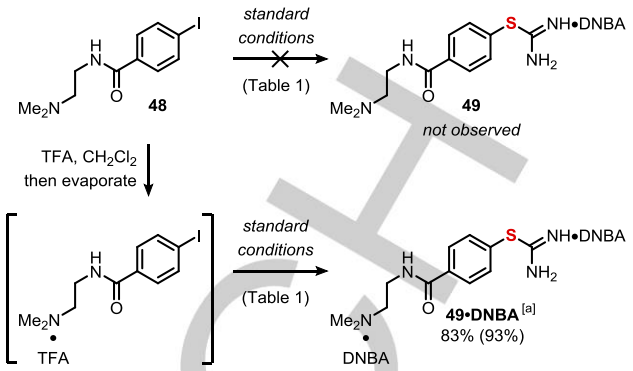
A broad range of functionality is well-tolerated, including unprotected anilines, phenols and alcohols (**25**-**27**). Substrates featuring aliphatic amines are more challenging, but can be employed successfully with minor changes to reaction conditions (*vide infra*). The substrate scope extends to synthetically

versatile substituents that would not necessarily be tolerated by the basic / nucleophilic conditions of conventional Migita couplings (**30**-**39**),[2] most notably a terminal alkyne (**34**), Michael acceptors (**35** and **36**)[19] and the Fmoc protecting group (**37**).

Furthermore, aryl boronic esters, halides and *pseudo*halides (**10**, **38** and **39**) are also compatible with the methodology, enabling it to be used in conjunction with other cross-coupling strategies to rapidly assemble more complex molecular architectures. It should be noted that, while aryl bromides are poor substrates for the C-S coupling (Scheme 2C), reaction of 4-bromoiodobenzene under our standard conditions occurred with low selectivity to form a mixture of *S*-(4-bromophenyl) isothiouronium salt **40** (60%) and diisothiouronium salt **41** (40%). Further investigation revealed that the rate of C-I bond activation is *ca* 10 times greater than the rate of C-Br activation,[13] such that good chemoselectivity for *S*-(4-bromophenyl) isothiouronium salt **40** could be achieved by using thiourea as the limiting reagent. Alternatively, diisothiouronium salt **41** is obtained in excellent yield following exhaustive coupling at both halides with an excess of thiourea. Diisothiouronium salts can be accessed more generally from substrates featuring two C_{aryl}-I bonds (**42**), or a C_{aryl}-I bond and an S_N2-reactive alkyl halide (**43**).

Gratifyingly, a series of polyfunctional aryl iodides afforded good to excellent yields of the corresponding isothiouronium salts (**44**-**47**), further emphasizing the generality and robustness of the methodology, and its applicability to complex molecule synthesis.

Although moderately basic functionality such as anilines and pyridines (*vide infra*) are well-tolerated by the C-S coupling, substrates incorporating aliphatic amines proved incompatible (Scheme 3). Given that triethylamine is sufficiently basic to promote the release of a thiophenol from the corresponding

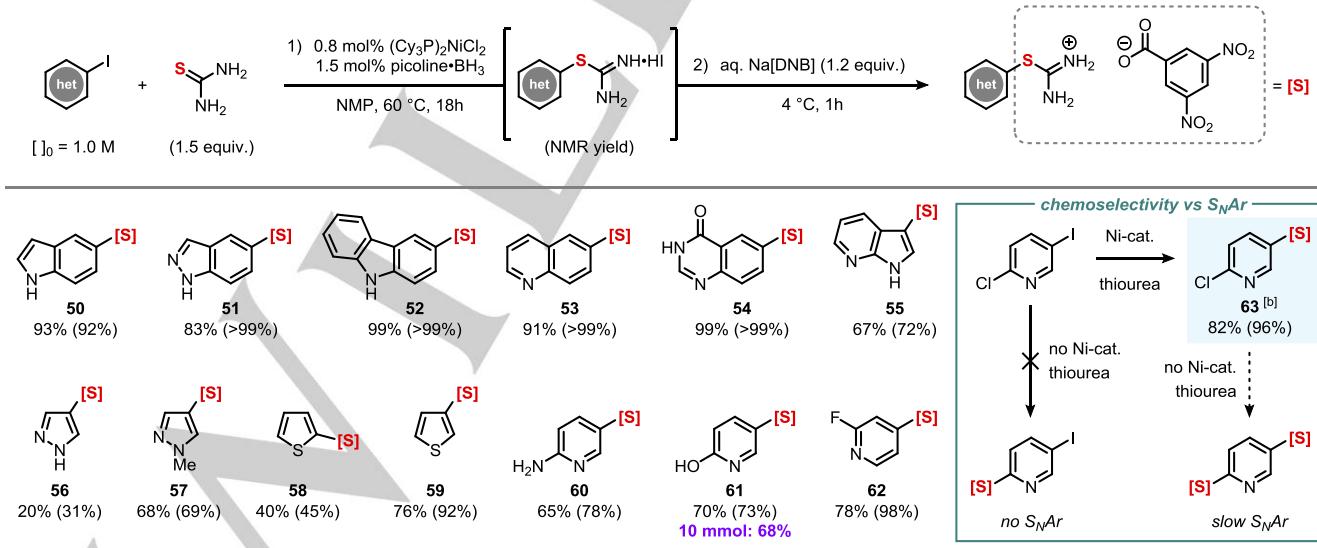


Scheme 3. Protection of aliphatic amines *via* protonation prior to Ni-catalyzed C-S coupling. Reaction conditions as Table 1. Yield is of isolated material; value in parenthesis refers to yield of isothiouronium iodide determined by NMR spectroscopic analysis prior to isolation. [a] Product precipitated with 2.4 equiv. aqueous sodium 3,5-dinitrobenzoate. TFA = trifluoroacetic acid; DNBA = 3,5-dinitrobenzoic acid.

isothiouronium salt, we assume that the tertiary amine in **48** promotes decomposition of isothiouronium salt **49** as soon as it is formed, and that the liberated thiophenol(ate) acts as an efficient catalyst poison. Fortunately, reactivity is restored simply by protonation of the basic nitrogen prior to cross-coupling, allowing the C-S coupling product to be isolated in good yield as bis(3,5-dinitrobenzoate) salt **49•DNBA**.

The utility of the C-S cross-coupling is significantly enhanced by its applicability to a range of aromatic heterocycles (Table 2), motifs that are ubiquitous in pharmaceuticals and agrochemicals.[20] Notably, unprotected azoles (**50**-**52**, **55** and **56**) and 2-aminopyridines (**60**) are well-tolerated by our methodology, despite being recognized as challenging

Table 2. Scope of the Ni-catalyzed synthesis of *S*-heteroaryl isothiouronium salts.[a]

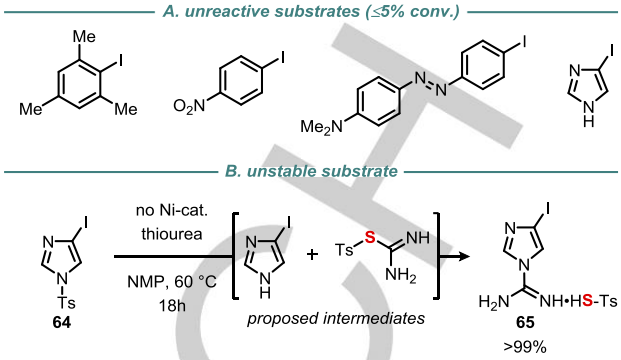


[a] Yields are of isolated material from reactions performed on a 1 mmol scale; values in parenthesis refer to yields of isothiouronium iodides determined by NMR spectroscopic analysis prior to isolation. [b] Standard conditions, but with 1.05 equiv. thiourea. DNB = 3,5-dinitrobenzoate.

substrates for other metal catalyzed coupling strategies.[21,22] While 2-iodopyridine (not shown) is subject to nucleophilic aromatic substitution (S_NAr) in the absence of the Ni precatalyst,[23] 2-fluoro-4-iodopyridine is inert towards direct C2-substitution and affords solely **62**, the product of Ni-catalyzed C-I bond activation. 2-Chloro-5-iodopyridine shows intermediate reactivity: although this substrate does not undergo S_NAr itself, the isothiouronium product of catalytic C-I bond activation (**63**) *does* undergo slow subsequent S_NAr at the 2-position. This competing process can, however, be entirely avoided simply by using 1.05 equiv. of thiourea under otherwise standard conditions.

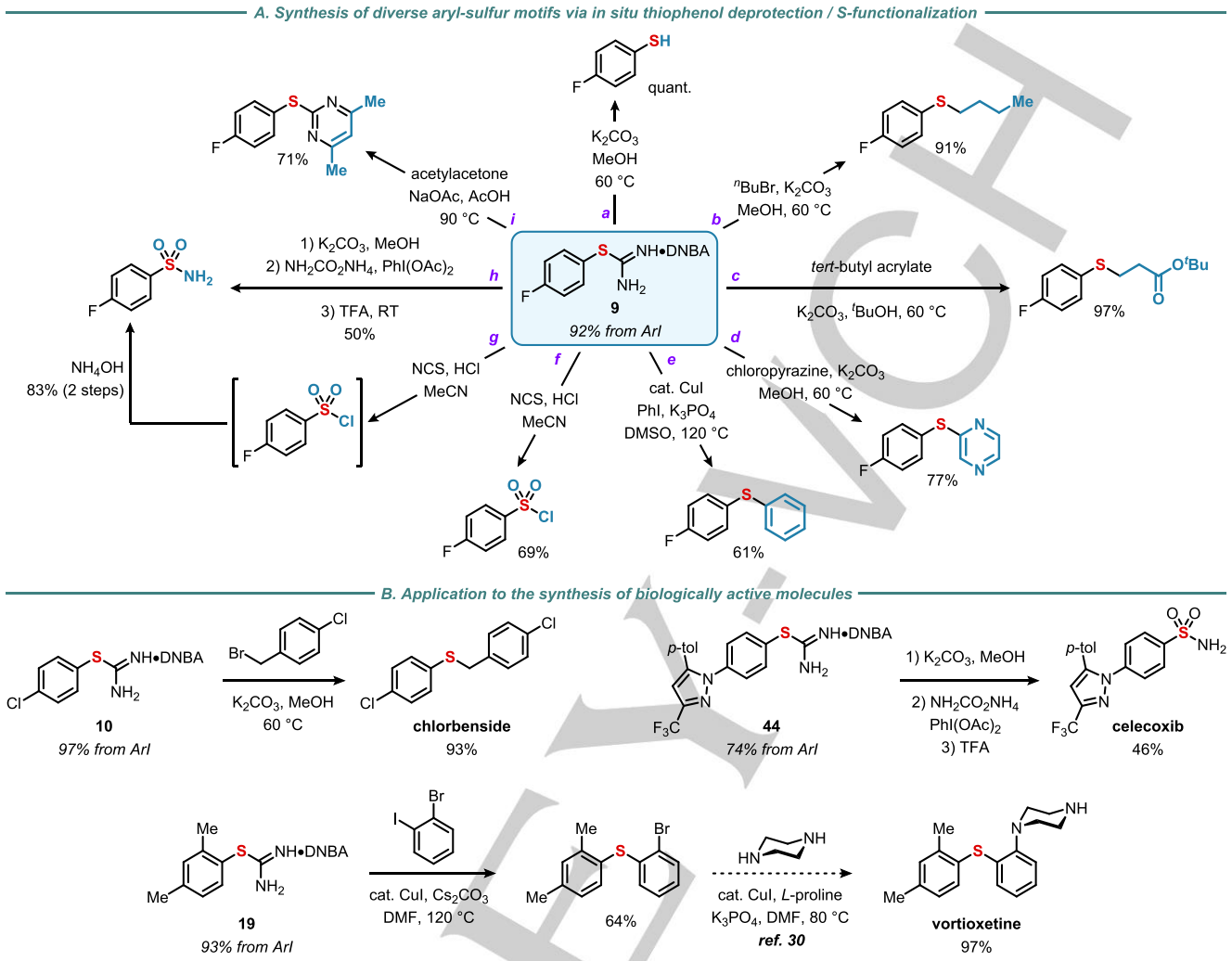
Due to the ease of product isolation, the atom economy of the sulfur source (43%) and the use of a base metal catalyst at low loadings, this methodology is well-suited to large scale applications. Indeed, performing the C-S coupling on a 10 or 100 mmol scale afforded excellent yields of the corresponding isothiouronium salts (10 mmol: **8**, **15**, **19**, **28** and **61**; 100 mmol: **9**) without modification of the experimental procedure. For **9** prepared at a 100 mmol scale, analysis by ICP-MS indicated that the isolated salt contained 106 ppm residual Ni. While this level is above the limits typically required for active pharmaceutical ingredients, it is acceptable for a synthetic intermediate and represents a >10-fold reduction in Ni content relative to the crude reaction mixture.

While the scope of our methodology is extensive (Tables 1 and 2), it is not without limitations (Scheme 4). As already noted, di-*ortho*-substitution is not tolerated and no conversion of 2-iodomesitylene is observed under our standard reaction conditions (Scheme 4A). Nitro- and azo-substituted aromatics, which are electronically activated towards cross-coupling,[24] and 4-iodoimidazole are also recovered unreacted. These observations have mechanistic implications and will be discussed later. In contrast, tosyl-protected 4-iodoimidazole **64** is unstable to the reaction conditions, and undergoes complete decomposition to carboxamidinium thiotosylate **65** in the absence of catalyst (Scheme 4B). This is consistent with the known sensitivity of *N*-sulfonyl imidazoles towards nucleophilic attack.[25]



Scheme 4. Limitations of the Ni-catalyzed synthesis of *S*-aryl isothiouronium salts.

Having identified general conditions for the preparation of structurally diverse *S*-aryl isothiouronium salts, we sought to demonstrate their utility as convenient precursors to ubiquitous aryl-sulfur motifs. Release of a thiophenol from the corresponding isothiouronium salt (pK_a <9.8)[26] is achieved by deprotonation with a weak base and subsequent elimination of cyanamide.[27,28] Thus the extensive chemistries of thiophenols can be accessed directly from isothiouronium salts simply by addition of one equivalent of base. This *in situ* release strategy was successfully applied to some of the most common thiophenol *S*-functionalizations (Scheme 5A), including alkylation *via* S_N2 (*b*) and conjugate addition (*c*), and arylation *via* S_NAr (*d*) and Ullman-type coupling (*e*). Redox adjustment at sulfur *via* oxychlorination (*f, g*) and a modification of Bull's oxyamination procedure[29] (*h*) provides direct access to synthetically valuable sulfonyl chlorides and primary sulfonamides. Finally, condensation of the isothiouronium salt with a diketone provides access to a 2-thiopyrimidine based on the isothiourea scaffold (*i*).

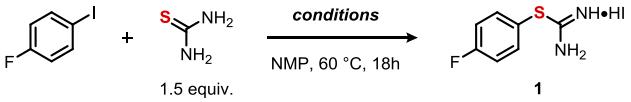


Scheme 5. *S*-Aryl isothiouronium salts are convenient synthetic surrogates for thiophenols in *S*-functionalization reactions. (A) Synthesis of common aryl-sulfur motifs, and (B) application to the concise synthesis of biologically active compounds.

The practicality of this *in situ* release / *S*-functionalization strategy was further demonstrated by the concise synthesis of chlorbenside and celecoxib, and a key intermediate *en route* to vortioxetine[30] (Scheme 5B), all of which were accessed in 2 steps from an aryl iodide without the need to handle noxious thiophenols.

Although it is premature to propose a detailed mechanism for the catalytic coupling of aryl iodides and thiourea, a number of experimental observations and preliminary investigations merit discussion with regards the possible operation of 1- or 2-electron manifolds. Firstly, the reaction is inhibited by known radical traps such as TEMPO and 1,4-dinitrobenzene (Table 3, entries 2 and 3).[31] This latter result is consistent with the lack of activity exhibited by nitro-substituted aryl iodides in both our C-S cross-coupling (Scheme 4A) and Ni-catalyzed Suzuki-Miyaura couplings.[32] While these results are consistent with operation of a single-electron process, caution must be exercised due to the known reactivity of TEMPO towards organometallic

Table 3. Mechanistically relevant control reactions.[a]



entry	conditions	yield **1** (%)
1	**std conds:** 0.8 mol% $(Cy_3P)_2NiCl_2$, 1.5 mol% picoline-BH_3	>99
2	std conditions (entry 1), with 1 equiv. TEMPO	0
3	std conditions (entry 1), with 0.2 equiv. 1,4-dinitrobenzene	0
4	0.8 mol% $(Cy_3P)_2NiCl$(*o*-tol)	0
5	0.8 mol% $(Cy_3P)_2NiCl$(*o*-tol), 1.5 mol% picoline-BH_3	>99
6	0.8 mol% $Ni(cod)_2$, 1.6 mol% PCy_3	35

[a] Yields determined by ^{19}F NMR spectroscopic analysis *vs* internal standard. TEMPO = (2,2,6,6-tetramethylpiperidin-1-yl)oxyl free radical; *o*-tol = *ortho*-tolyl; cod = 1,4-cyclooctadiene.

intermediates,[33] and of Ni(0) towards nitroarenes.[34] Similarly, azo-functionality – which is also not tolerated by the C-S coupling (Scheme 4A) – is known to act as both a radical chain inhibitor[35] and a π-acidic ligand for Ni(0).[36] The lack of reactivity of 4-iodoimidazole is unlikely to be due to its basicity,[37] but is consistent with its unsuitability in both conventional and photo-stimulated $S_{RN}1$ reactions.[38] This has been explained by formation of σ* radical anions that fragment to form imidazole anions, rather than radicals,[39] and suggests involvement of single electron processes in our methodology. However, based on these observations alone, it is not possible to distinguish unequivocally between operation of a 2-electron Ni(0/II) cycle or single electron processes.

Subsequent experiments were designed to probe the role of the co-catalytic reductant, and its consequences for the accessible oxidation states of Ni. Use of $(Cy_3P)_2NiCl(o\text{-tol})$[40] as a well-defined σ-aryl complex and a plausible intermediate in a Ni(0/II) cycle resulted in no reaction (Table 3, entry 4). Reactivity was, however, completely restored by addition of picoline-borane to the same σ-aryl complex (entry 5). Although an appreciable yield of isothiouronium salt **1** was obtained with a Ni(0) precatalyst (entry 6), this should not be taken as strong evidence in favor of a Ni(0/II) cycle: it is well documented that numerous oxidation states of Ni are accessible from the combination of Ni(0) and aryl halides (and especially iodides).[41] Together, these experiments suggest involvement of Ni(I) intermediates, although the significance of these species for either the precatalyst activation process or catalyst turnover are not yet clear.[42] Detailed studies into the mechanism of this reaction are ongoing, and will be reported in due course.

Conclusion

In summary, we have developed a general and expedient method for the catalytic preparation of *S*-aryl isothiouronium salts, and have demonstrated that these air-stable, odorless solids are convenient surrogates for thiophenols in synthesis.

The isothiouronium salts are prepared *via* Ni-catalyzed C-S coupling of aryl iodides with thiourea, and are isolated in high purity simply by precipitation. The methodology can be applied to structurally diverse substrates – including biologically relevant azines and unprotected azoles – and tolerates synthetically versatile functionality that would not necessarily be compatible with conventional Migita- or Ullman-type C-S couplings. The isothiouronium salts represent convenient sources of the corresponding thiophenol, as is illustrated by their *in situ* liberation and elaboration into common aryl-sulfur motifs. The wider relevance of this strategy is demonstrated by its application to the concise synthesis of biologically active molecules.

We anticipate that the chance to avoid handling malodorous, air-sensitive thiophenols will be widely appreciated by the synthetic community.

Experimental Section

An oven dried Schlenk tube containing $(Cy_3P)_2NiCl_2$ (5.5 mg, 0.008 mmol), picoline-borane (1.6 mg, 0.015 mmol), thiourea (114 mg, 1.5 mmol) and solid aryl iodide (1.0 mmol) was evacuated and back-filled with anhydrous dinitrogen three times. Liquid aryl iodides (1.0 mmol) were added subsequent to evacuation and back-filling. Anhydrous, degassed *N*-methylpyrolidinone (1 mL) was added, the Schlenk tube was sealed, and the reaction was stirred at 60 °C for 18 h. After cooling to room temperature, the extent of conversion was determined by ^{1}H NMR spectroscopic analysis of a 15 µL aliquot of the reaction mixture diluted with DMSO-d_6. The reaction mixture was then poured into a stirred aqueous solution of sodium 3,5-dinitrobenzoate (0.2 M, 6 mL, 1.2 mmol); residual reaction mixture was transferred from the Schlenk tube with water washes (2 × 0.5 mL). The resulting suspension was cooled to 4 °C for 1 h before the solid was collected by filtration. The filter-cake was dried by suction for 10 minutes, then washed with ice cold isopropanol (2 × 2 mL) and diethyl ether (4 × 2 mL). Drying *in vacuo* afforded the *S*-aryl isothiouronium 3,5-dinitrobenzoate salt as a free-flowing, non-hygroscopic solid.

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Keywords: Nickel • Sulfur • Cross-coupling • Homogeneous catalysis • Sulfonamides

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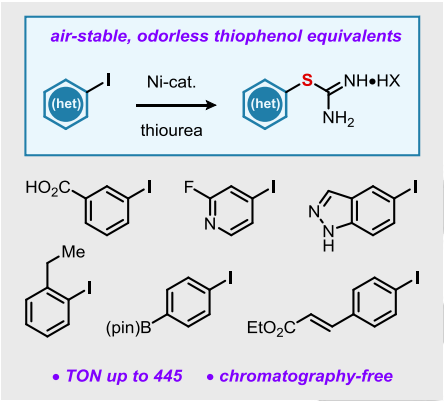
Entry for the Table of Contents

RESEARCH ARTICLE

Ni-catalyzed cross-coupling provides access to *S*-aryl isothiouronium salts under mild conditions. These air-stable, odorless solids are isolated without chromatography, and are convenient sources of thiophenols in synthesis. The scope and utility of the methodology is illustrated with 60 examples and is showcased through the concise synthesis of celecoxib.



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Synthesis of Air-stable, Odorless Thiophenol Surrogates *via* Ni-Catalyzed C-S Cross-Coupling