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Sulfur(IV)–Mediated Unsymmetrical Heterocycle Cross-Couplings

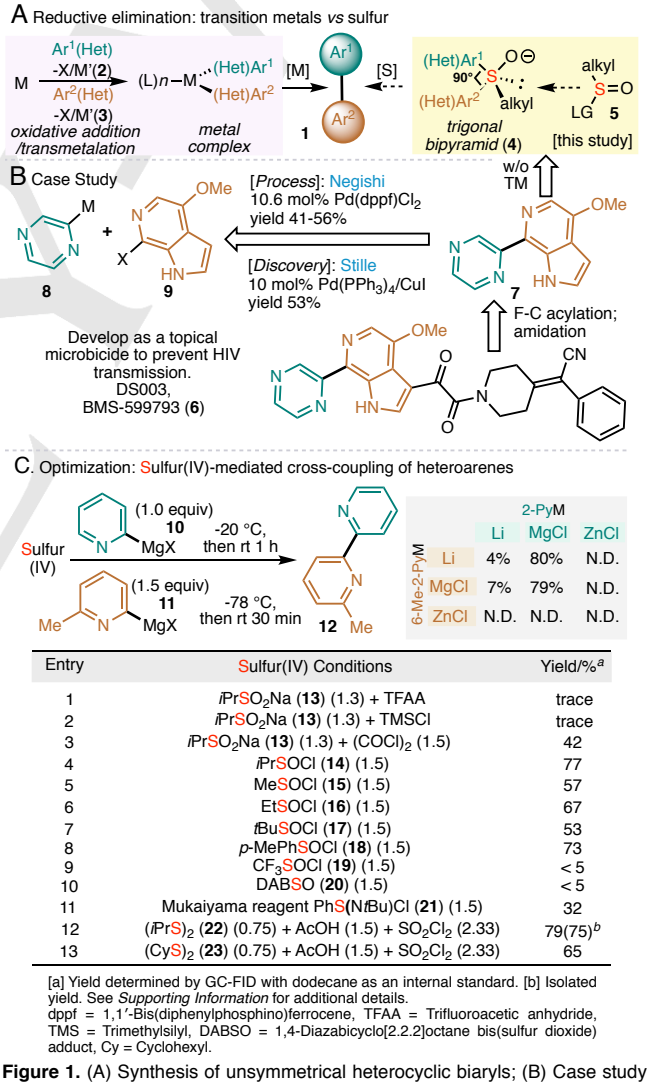
Min Zhou, Jet Tsien and Tian Qin *

Abstract: Despite the tremendous utilities of metal-mediated cross-couplings in modern organic chemistry, coupling reactions involving nitrogenous heteroarenes remain a challenging undertaking – coordination of Lewis basic atoms onto metal centers often necessitate elevated temperature, high catalyst loading, etc. Herein we report a sulfur (IV) mediated cross-coupling amendable for the efficient synthesis of heteroaromatic substrates. Addition of heteroaryl nucleophiles onto a simple, readily-accessible alkyl sulfinyl (IV) chloride allows formation of a trigonal bipyramidal sulfurane intermediate. Reductive elimination therefrom provides bis-heteroaryl products in a practical and efficient fashion.

The advent and popularization of transition-metal catalyzed cross-couplings in the later part of the 20th century heralded revolutionary changes in the synthesis of biaryls.[1] The fundamental steps of oxidative addition and transmetalation give rise to metal-aryl complexes, wherein the orbital overlap of aryl groups enable a new modality of C–C bond formation through reductive elimination in a three-center ligand coupling process.[2] Despite their tremendous utilities[3], these venerable reactions are not without limitations. Cross-coupling of substrates comprising Lewis basic functionalities (e.g., heteroarenes) has proven to be difficult, as the basic heteroatoms coordinate to the Lewis acidic metal center, thwarting reductive elimination (e.g., via catalyst deactivation).[4] Further, a number of heteroaryl nucleophiles are known to have poor stability under cross-coupling conditions – for example, boronic acids having azine nitrogen at the α-position are prone to proto-deborylation.[5,6] As an example, a high loading of palladium (> 10%) was required in the Negishi and Stille[7] couplings to access **7,** a key intermediate in the preparation of microbicide BMS-599793 (**6**), in both discovery[8] and process settings.[9] In light of the foregoing, development of an alternative and practical (and preferably transition-metal-free) method for cross-coupling, particularly one that is amendable for basic heterocyclic substrates remains desirable. Recently, the McNally group reported an elegant approach to access 2,2'-diazines through a phosphorous mediated cross-coupling.[10] Here, we show that stable and easily accessible sulfinyl (IV) chloride can facilitate the *oxidative* cross-coupling of heteroaryl building blocks, providing an assortment of unsymmetrical heterocycles expediently.

Fully–carbon linked sulfuranes have long been considered unstable and elusive species.[11] C–C ligand coupling was believed to be a major decomposition pathway. Extensive mechanistic studies by Trost[12] and Oae[13] established that that the trigonal bipyramidal geometries of sulfuranes allowed ligands to be placed at a dihedral angle of approximately 90°, thereby facilitating ligand coupling via reductive elimination.[14] A series of studies emanating from the Furukawa and Oae group[15, 16] demonstrated that addition of organometallic nucleophiles onto sulfoxides led to the formation of ligand coupling products via oxy-sulfurane intermediates (see Supporting Information for historical summary of sulfur mediated couplings). However, these hypervalent sulfur species have found little synthetic utility[17] until the seminal works by Stockman and Procter in recent years. Stockman and co-workers developed an approach for the enantioselective synthesis of diarylmethanes via C(sp^3)-C(sp^2) ligand coupling.[18] Procter and co-workers reported a method for the stereoselective synthesis of substituted (E,Z)-1,3-dienes via ligand coupling of all-carbon sulfurane intermediates.[19] Peng group described a benzyne-mediated desulfurized biaryl synthesis.[20] Inspired by these path-pointing efforts *(supra)*, we surmised that the ability of sulfuranes to undergo ligand coupling could be harnessed to provide a unique mode of cross-coupling. It is envisaged that the basic sulfur center is impervious to metal chelating, potentially making the process amendable for the coupling of basic heteroarenes.

We set out to identify a suitable sulfur(IV) precursor which could react with heteroaryl nucleophiles to provide a transitory sulfurane. Alkyl sulfinates were initially employed to avert compe-



Entry	Sulfur(IV) Conditions	Yield/%[a]
1	*i*PrSO$_2$Na (**13**) (1.3) + TFAA	trace
2	*i*PrSO$_2$Na (**13**) (1.3) + TMSCl	trace
3	*i*PrSO$_2$Na (**13**) (1.3) + (COCl)$_2$ (1.5)	42
4	*i*PrSOCl (**14**) (1.5)	77
5	MeSOCl (**15**) (1.5)	57
6	EtSOCl (**16**) (1.5)	67
7	*t*BuSOCl (**17**) (1.5)	53
8	*p*-MePhSOCl (**18**) (1.5)	73
9	CF$_3$SOCl (**19**) (1.5)	< 5
10	DABSO (**20**) (1.5)	< 5
11	Mukaiyama reagent PhS(N*t*Bu)Cl (**21**) (1.5)	32
12	(*i*PrS)$_2$ (**22**) (0.75) + AcOH (1.5) + SO_2Cl_2 (2.33)	79(75)[b]
13	(CyS)$_2$ (**23**) (0.75) + AcOH (1.5) + SO_2Cl_2 (2.33)	65

[a] Yield determined by GC-FID with dodecane as an internal standard. [b] Isolated yield. See *Supporting Information* for additional details.
dppf = 1,1′-Bis(diphenylphosphino)ferrocene, TFAA = Trifluoroacetic anhydride, TMS = Trimethylsilyl, DABSO = 1,4-Diazabicyclo[2.2.2]octane bis(sulfur dioxide) adduct, Cy = Cyclohexyl.

Figure 1. (A) Synthesis of unsymmetrical heterocyclic biaryls; (B) Case study of BMS-599793 (**6**): discovery and process route to access intermediate **7**; (C) Optimization of sulfur (IV) reaction conditions.

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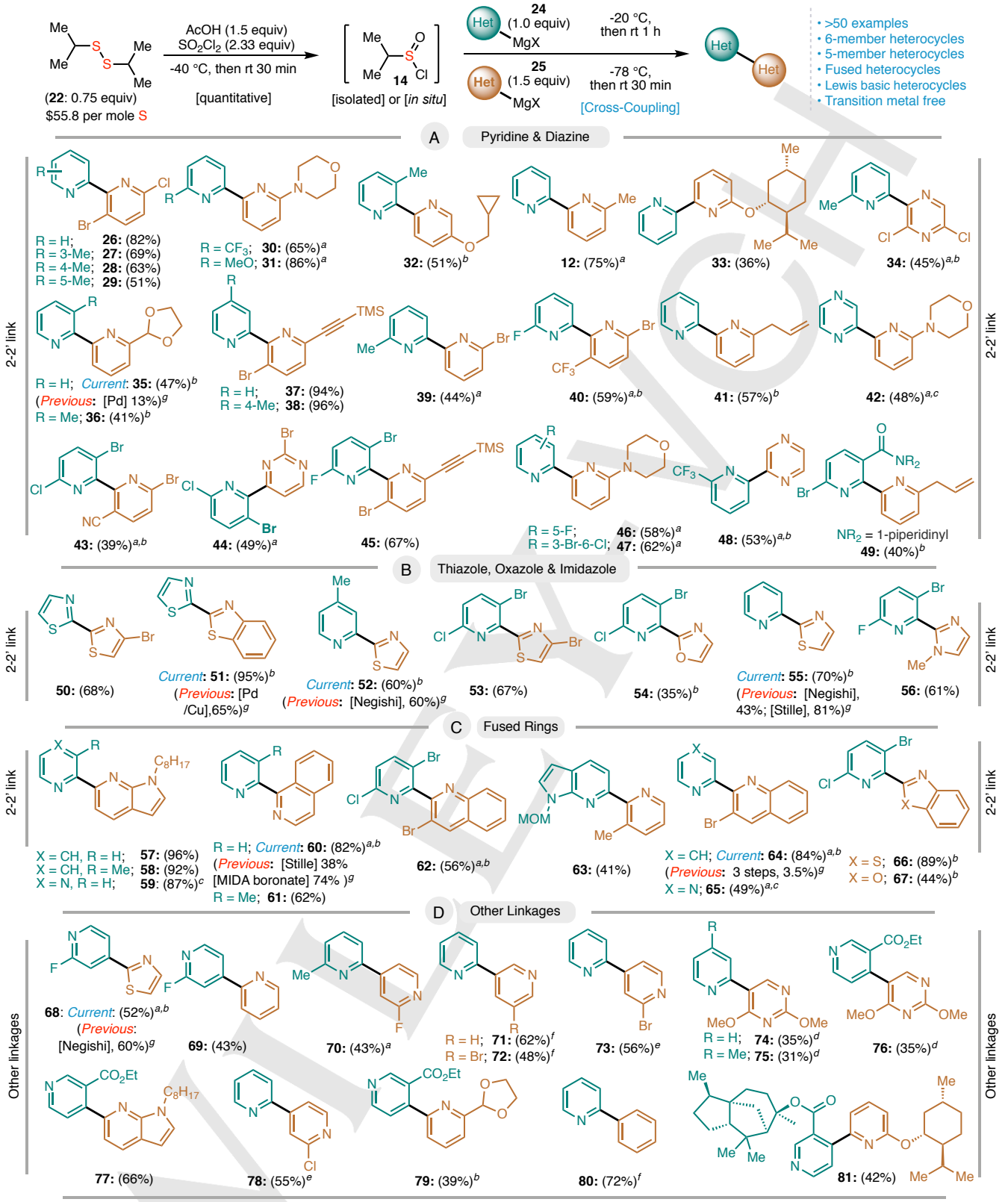

Scheme 1. Scope of the sulfur (IV) mediated unsymmetrical heterocyclic couplings. The first Grignard reagent is depicted in green and the second Grignard reagent in brown. Reaction condition: **14** (1.5 equiv), **24** (0.1 mmol, 1.0 equiv), -20 °C to rt 1 h; **25** (1.5 equiv), -78°C to 30 min. [a] 0.5 mmol scale, **14** was prepared *in situ*. [b] Using **25** (3.0 equiv of its precursor). [c] Adding **24** (1.5 equiv of its precursor) at -78 °C then warming to rt slowly and **25** (1.0 equiv) as the limiting reagent. [d] Using EtSOCl (1.5 equiv). [e] Using **14** (1.3 equiv) and **25** (2.0 equiv). [f] Using *t*BuSOCl (1.5 equiv) and **25** (2.5 equiv) was added at rt. [g] See SI for literature routes. The concentration of Grignard reagents were titrated by I_2. If it was too dark for titration, the concentration was assumed according to its precursor. For all the details regarding Grignards preparation, see SI. MIDA = *N*-methyliminodiacetic acid.

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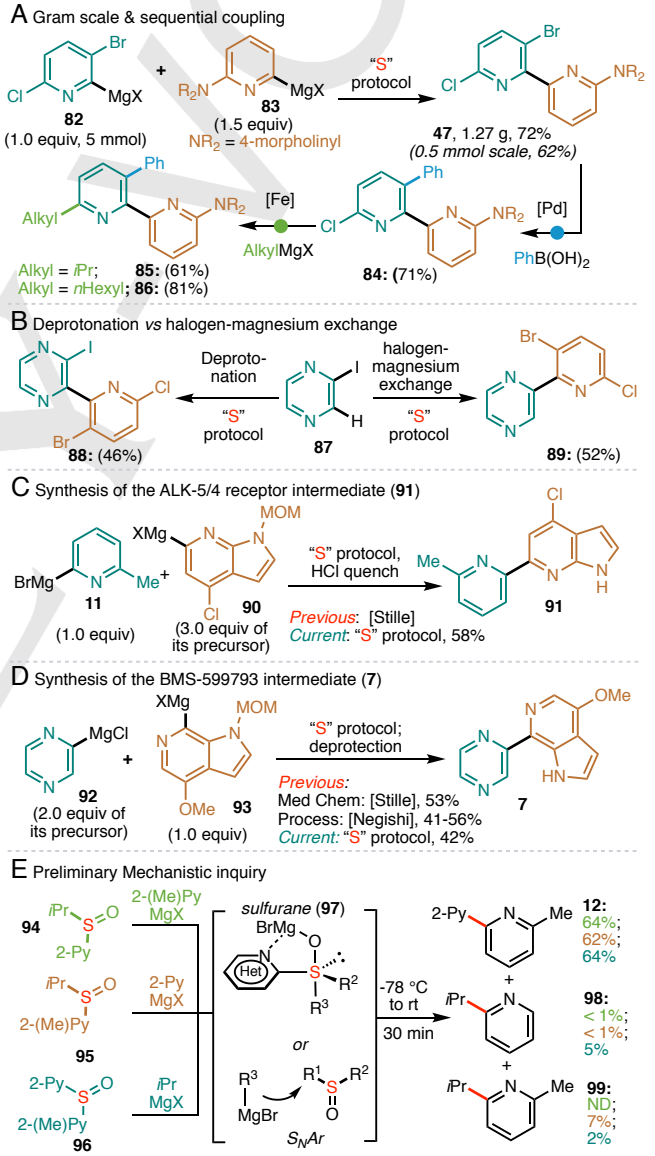
-ting coupling reaction. It was reasoned that activation of the sulfinate oxygen, followed by sequential reactions with 2-pyridyl Grignard **10** and **11** could afford a coupling product via a sulfurane intermediate. Sodium isopropyl sulfinate (**13**) were subjected to a variety of activating agents[21] – nevertheless, only trace amounts of coupling product were observed in most cases (see Supporting Information). After rigorous experimentation, it was discovered that oxalyl chloride could activate sulfinates to form sulfinyl chlorides, which could then react with **10** and **11** to furnish cross-coupling product **12** in 42% yield (entry 3). Direct application of sulfinyl chloride **14** led to an increased yield of 77% with only a trace amount of first homo-coupling. Application of other alkyl sulfinyl chlorides (e.g., **15**–**17**, **19**) resulted in diminished yields (entries 5-7, 9), while *para*-methylphenyl sulfinyl chloride **18** offering the slightly lower yield (entry 8). Furthermore, isopropylsulfinyl chloride **14** was proved to be a more general reagent than **18** after the side-by-side comparison reactions for selected substrates, see Supporting Information for additional details. This preference for secondary alkyl groups is possibly attributable to an interplay of the Thorpe–Ingold effect and sterics.[22] Use of the Mukaiyama reagent[23] (**21**) furnished the product in 32% yield (entry 11). Unsurprisingly, only trace amount of product was observed when DABSO[24] (**20**) (entry 10) or isopropylsulfonyl chloride was used. A one-pot procedure was then developed -- isopropylsulfinyl chloride (**14**) was prepared *in situ* from oxidation of diisopropyl sulfide (**22**) using Herrmann's protocol,[25] whereupon treatment with the nucleophiles in the same pot provided the coupling product in high yield (entry 12). The *in* situ formed sulfinyl chloride may be also be stored under refrigeration (+ 4°C) for future reactions without deterioration for months. A preliminary survey of nucleophilic heteroaryl reagents indicated a strong preference for Grignard reagents (Figure 1C, inset). Notably, neither Pummerer rearrangement byproducts[26,27] nor alkyl deprotonation[28] was observed under the optimized reaction conditions.

With the optimal conditions in hand, the substrate scope was explored. Heterocyclic Grignard reagents, either prepared by halogen-magnesium exchange[29] or deprotonation[30], were found to be compatible with the reaction conditions. Various 2,2'-linked diazines were generated in high yields accordingly (Scheme 1A). For example, pyridine, pyrimidine, and pyrazine-based nucleophiles all reacted smoothly in this cross-coupling reaction. Cross-couplings of thiazole, oxazole, and imidazole were also successfully demonstrated (Scheme 1B, **50**–**56**). It is of note that boronic acids of these 5-membered heteroaromatics are generally unstable – as such, Stille coupling using toxic stannane reagents is the go-to method for these coveted heteroarenes.[14] Fused heterocycles such as azaindoles, quinolines, isoquinolines, benzothiazole, and benzoxazole could also be successfully coupled under the present conditions (Scheme 1C). Due to the rapid reaction rate and low temperature, a gamut of functionalities remained unscathed. These include ether (**31**–**33**), alkene (**41**), alkyne (**37**–**38**, **45**), acetal (**35**–**36**), nitrile (**43**), ester (**76**–**77**), and amide (**49**). It is particularly noteworthy that aryl halides which are generally labile under transition-metal catalyzed cross-couplings were found to be compatible with the present reaction, allowing the possibility for further modification. Aside from the 2,2'-linked products (*supra*), the reaction manifold is amenable for the preparation of bis-heteroaryls with other linkages (Scheme 1D). On the other hand, organometallic nucleophiles derived from certain heterocycles such as quinoxaline were found to be unstable under the reaction conditions (see Supporting Information for complete list). Substrates having a neighboring nitrogen atom typically provide products in higher yields, akin to the reports by Oae and Furukawa.[16d-e,16i] Nevertheless, coupling product was still obtained (such as substrate **76**) in the absence of adjacent Lewis basic atom, albeit in a lower yield.

A distinct advantage of this methodology is the ability to procure coupling products of Lewis basic heteroarenes building blocks while obviating complications under transition-metal mediated reactions due to catalyst poisoning. The compatibility with halogenated compounds could also allow for modular and iterative reactions, enabling rapid assembly of highly functionalized heteroaryl scaffolds. Scheme 2A provides a case-in-point example emphasizing the applicability and the utility of the method described herein. Tri-substituted pyridines **85**/**86** were expeditiously synthesized using the sulfur(IV) mediated cross-coupling followed by sequential transition-metal couplings. Notably, compound **47** *en route* to **85**/**86** was synthesized in 5 mmol scale in good yield. The ability to generate organometallic species (the nucleophiles of the present reaction) under both



Scheme 2. (A) Gram scale and sequential transition metal-catalyzed coupling. (B) Diverse coupling products derived from the same heterocycle via deprotonation and halogen-magnesium exchange. (C) Synthesis of the ALK-5/4 receptor intermediate. (D) Synthesis of the BMS-599793 intermediate. (E) Preliminary mechanistic inquiry. For experimental details, see Supporting Information. MOM = Methoxymethyl.

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directed metalation and halogen-metal exchange further bolsters the versatility of this method. For example, 2-pyridyl 3-iodopyrazine **88** and 2-pyridyl pyrazine **89** were selectively and divergently obtained from **87** through TMPMgCl·LiCl (TMP = 2,2,6,6-tetramethylpiperidinyl) deprotonation[30] or *n*BuMgCl exchange[29] followed by the present cross-coupling protocol (Scheme 2B). It is worth noting that the *iodo* group was found intact under the deprotonation conditions to access **88**. Compound **91**, an advanced intermediate to access anaplastic lymphoma kinase (ALK) 4/5 inhibitor developed by Novartis, was obtained from the corresponding pyridyl Grignard **11** and azaindole partner **90** in a single step after acidic quench -- a Stille coupling[31] was previously required to access the same compound.[32] As noted in Figure 1B, *en route* to BMS-599793 (**6**) under process setting, a Negishi coupling utilizing a high load of palladium catalyst (10.6 mol%) was necessary to access intermediate **7**.[8] With the sulfur-mediated cross-coupling, this critical compound was prepared from pyrazine Grignard **92** and 6-azaindole Grignard **93** in 42% yield (Scheme 2D) in the absence of transition metal catalysts or ligands. The yield stayed consistent when the sequence of Grignard addition was reversed (see the Supporting Information).

To probe the mechanism of this transformation, a series of the sulfoxides (**94**–**96**) were prepared and treated with Grignards (Scheme 2E). The hetero-coupling product **12** was found to be the dominant species in all cases, possibly owing to favorable orbital overlap within the sulfurane intermediate (**97**).[16d-e,16i] However, the formation of byproducts **98** and **99** may suggest a partial S_NAr mechanism[33] leading to $C(sp^2)$–$C(sp^3)$ coupling product.

In summary, capitalizing on the unique reactivity of sulfuranes, a sulfinyl (IV) chloride–mediated cross-coupling between heteroarene Grignard reagents has been developed. Complementary to the venerable Kumada, Negishi, or Stille couplings, this reaction is uniquely suited for the preparation of Lewis basic substrates which are difficult to couple under classical conditions. A large number of functional groups are tolerated under the reaction condition, allowing modular and rapid access to molecular complexity.

Acknowledgements

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Keywords: heterocycle • cross-coupling • sulfurane

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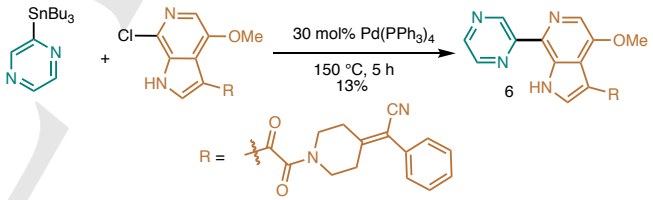

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