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Intermolecular Pummerer Coupling with Carbon Nucleophiles in Non-Electrophilic Media

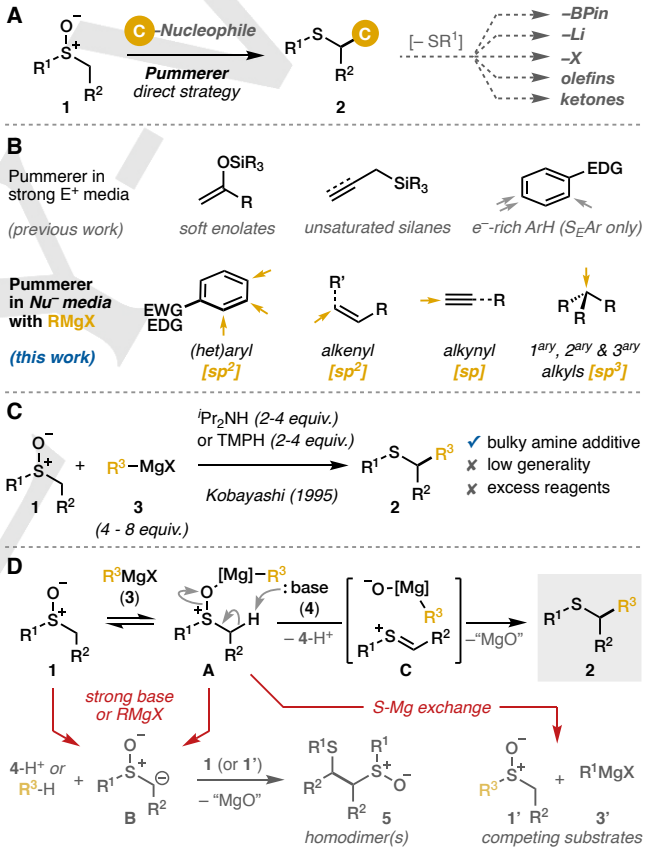
Kilian Colas,[a,b] Raúl Martín-Montero[a] and Abraham Mendoza*[a,b]

We dedicate this manuscript to Prof. F. J. Fañanás on the occasion of his 65th birthday.

Abstract: A new Pummerer-type C–C coupling protocol is introduced based on *turbo*-organomagnesium amides that unlike traditional Pummerer reactions, does not require strong electrophilic activators, engages a broad range of sp^3, sp^2 and *sp* *C*–nucleophiles and seamlessly integrates with C–H and C–X magnesiation. Due to the central character of sulfur compounds in organic chemistry, this protocol allows access to unrelated carbonyls, olefins, organometallics, halides and boronic esters through a single strategy.

The development of important new products and technologies has often relied on the unique properties of sulfur. For example, sulfur moieties are present in relevant medicines,[1] semiconductors,[2] catalysts[3] and biological probes.[4] Moreover, sulfur and particularly the carbon-sulfur bond are central in organic chemistry. Thioethers can be selectively activated through mild oxidation, participate in cross-coupling reactions,[5] be seamlessly transformed into dissimilar functions (including carbonyls, olefins, organometallics and halides),[6] and immobilized[7] through native 'click' methods.[8] Importantly, the balanced reactivity-stability profile of thioethers has been extensively battle-tested in the total synthesis of sulfur-containing and sulfur-free molecules.[9] Thioethers are often prepared through C–S coupling from custom fragments,[10] or multistep alkylation/reduction sequences. Tactically, the direct intermolecular reductive coupling of sulfoxides and carbon nucleophiles (Pummerer, Scheme 1a) provides access to thioethers bearing elaborate carbon frameworks from simple sulfur compounds in one step.

Despite a century of developments in Pummerer chemistry[9,11] the intermolecular reaction between sulfoxides and *C*-nucleophiles is still limited. Fundamental incompatibilities between electrophilic activation and strong *C*-nucleophiles is the main reason for the dominance in the literature of soft surrogates (Scheme 1b).[12] Electron-rich arenes,[12a-c] enolate equivalents,[12d,e] ene-donors[11,13] and silanes[12j,k] have been successful nucleophiles in electrophilic Pummerer reactions.[9,11] Nevertheless, arenes produce regioisomers dictated by electrophilic aromatic substitution (S_EAr), and olefins or alkynes act as allyl,[12k,13] propargyl,[12h,j] or enolate[12f,g,i] equivalents. As a result, Pummerer couplings engaging electron-poor (hetero)arenes, alkyls, vinyls or alkynyls are beyond scope. These shortcomings could be solved if common, powerful and localized *C*-nucleophiles, like Grignard reagents, could engage in this chemistry. However, reports on the reductive coupling of Grignard reagents with sulfoxides has only been testimonial, requiring large excess of reagents to compensate the native reactivity of these coupling partners (Scheme 1c).[14,15]



Scheme 1. Synthesis of thioethers *via* intermolecular Pummerer C–C coupling: (**A**) significance, (**B**) available and desired *C*-nucleophiles, (**C**) seminal work using Grignard nucleophiles, and (**D**) fundamental challenges to control their reactivity.

Namely, sulfoxides **1** undergo fast S-Mg exchange when exposed to Grignard reagents **3** (Scheme 1d) leading (*via* **A**) to recombination into sulfoxides **1'** and Grignard reagents **3'**.[14,16] This fast process consumes **1** and **3** and generates mixtures of alternative substrates **1'** and **3'**, thus eroding the efficiency of the desired coupling. Inspired by earlier work by Kobayashi (Scheme 1c),[15b-d] we recognized the key role of the base (**4**) that is required to deprotonate the sulfoxide for productive coupling (Scheme 1d).

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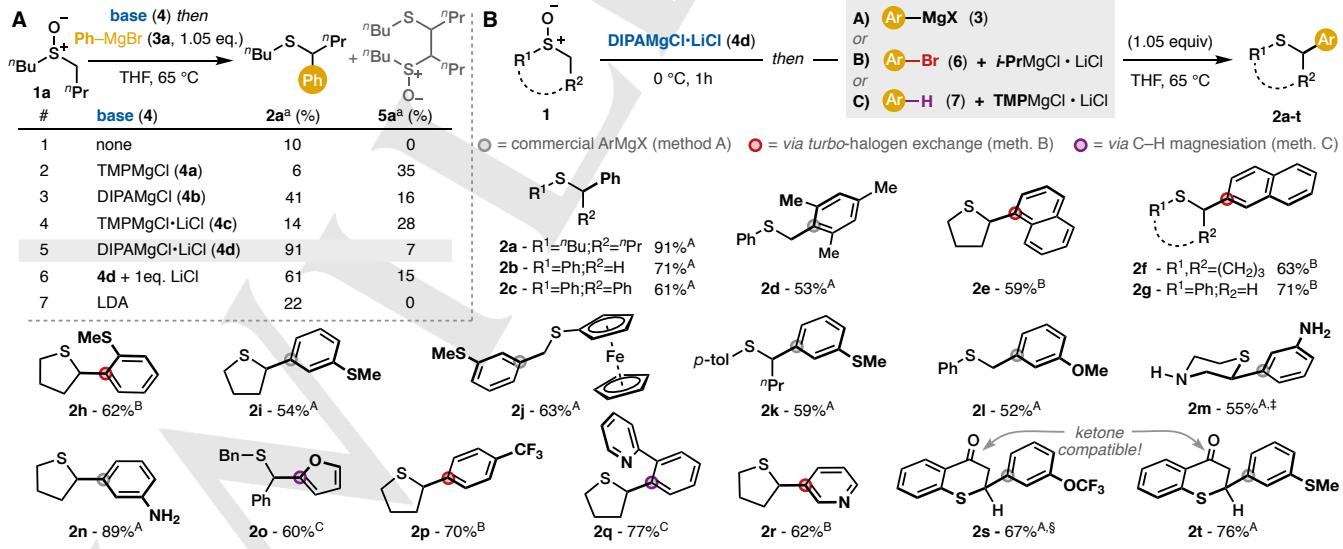
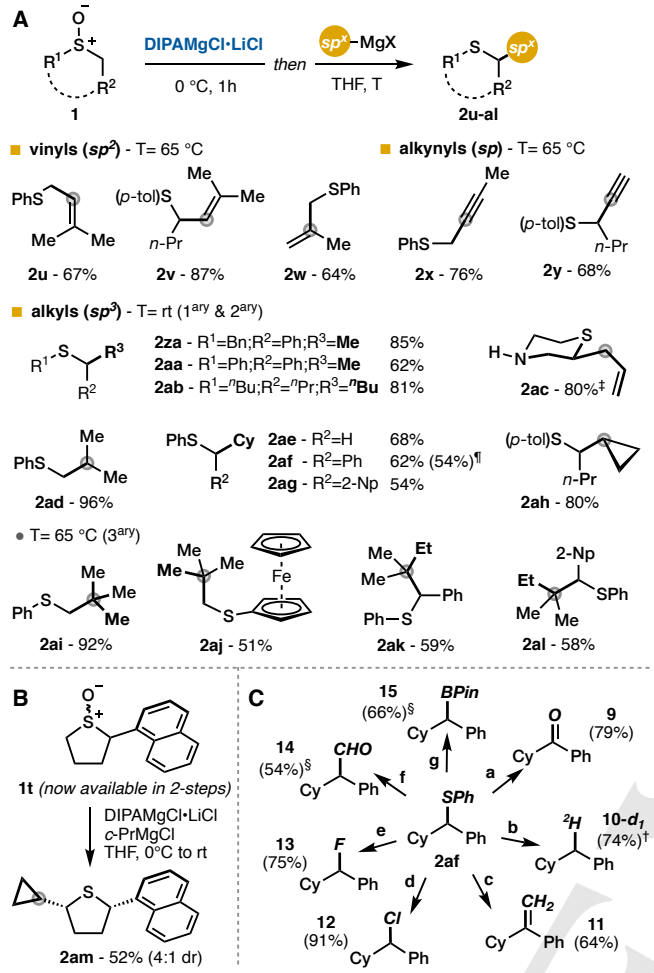
Too reactive bases produce sulfoxide anions **B** (**1**→**B**) that compete with the Grignard reagents as nucleophiles in the reductive coupling, thus leading to the homodimer **5** (or various crossover dimers if **1'** is formed through S-Mg exchange). However, if the base is not reactive enough, intermediate **A** would get irreversibly deprotonated by the basic magnesium alkyl (**A**→**B**). We hypothesized that a suitable base should thus readily deprotonate complex **A** - *but not the free sulfoxide **1*** - to promote the formation of the sulfonium intermediate **C** that would collapse into the desired thioether **2** (**A**→**C**→**2**). Therefore, an engineered base seemed the key to bypass the competing side-reactions and enable efficient Pummerer C-C coupling in nucleophilic media.[15]

Aromatic Grignard reagents are fundamental building blocks with the potential to surpass S_EAr-driven Pummerer arylations. However, due to their relatively low reactivity they are particularly rare in earlier reports on reductive couplings with sulfoxides.[9,11] We initially targeted the reductive arylation of the aliphatic sulfoxide **1a** with only 1.05 equiv. of PhMgBr (**3a**; Scheme 2a). Without base, only a small amount of the desired product **2a** is formed (entry 1). Unlike the TMP-derived Hauser base **4a** (entry 2), the presence of the DIPA-derivative **4b**[15b] has a positive effect under these restrictive conditions, but cannot produce satisfactory yields of **2a**. Inspired by the recent studies on Knochel-Hauser bases[17] (and in stark contrast to **4b**) to our surprise we found that the rare DIPAMgCl·LiCl (**4d**)[18] promoted the formation of **2a** in 91% yield (entry 5).[17b,18] The synergy between an optimal Li-Mg ratio (entry 6,7 and tables S1,S2) and the specific diisopropylamide base (entries 4,5) are both critical at enabling this reaction. We speculate that aggregation equilibria[17a] between the Grignard reagents and the base (likely involving organomagnesium amide species),[19] may be the origin of these experimental results. The efficiency of the system is remarkable considering the competing pathways available (Scheme 1d) and the limited Grignard reagent used.

The scope was studied with various aliphatic and aromatic sulfoxides that yielded arylated thioethers **2a-d** (Scheme 2b). The aromatic and heteroaromatic fragments that would be problematic (or impossible) in traditional S_EAr-Pummerer engage in this reaction. Thus, 1- or 2-naphthyl reagents (**2e-g**) are obtained selectively, and electron-rich (hetero)aryls bearing sulfur-, oxygen- and nitrogen-activating groups provide *ortho*- and *meta*-functionalized coupling products **2h-o**, as desired. Even electron-deficient (hetero)aryls (non S_EAr-reactive) readily participate to furnish products **2p-s**, including basic *N*-heterocycles (problematic with hard electrophiles), and medicinally-relevant fluorinated moieties (**2p,s**). Importantly, these nucleophilic Pummerer conditions enable integration with Knochel's magnesiations (see methods B and C).[18,21] This way, aryl bromides become viable nucleophiles in Pummerer coupling through *turbo*-halogen exchange (see **2e-h,p,r**).[21] Moreover, simple heteroarenes can be selectively C–H magnesiated to furnish products **2o,q**.[18] This feature allows to override the native S_EAr reactivity of the fragment introduced (see **2q**) in favor of proximity-induced activation that was unavailable before in the context of Pummerer chemistry. Regarding the Grignard coupling partners, we have only found a limitation with electron-poor reagents that are prone to decomposition upon gentle warming. At present, organolithiums do not engage in this reaction. On the sulfoxide side, substrates bearing a ferrocene (**2j**),[22] as well as thiomorpholine (**2m**) and thioflavanone heterocycles (**2s,t**) further expands the potential of this reaction to impact ligand[3,23] and drug design.[1b,24] Remarkably, β-heteroatoms and even unprotected ketones are tolerated (**2m,s,t**), further suggesting the unusual organometallic species that enable this reaction (entries 4,5; Scheme 2a).[19a] Despite these features, sterically hindered thioethers (neopentylic or α,α-disubstituted) are still a limitation, producing low yield of the thioether products.

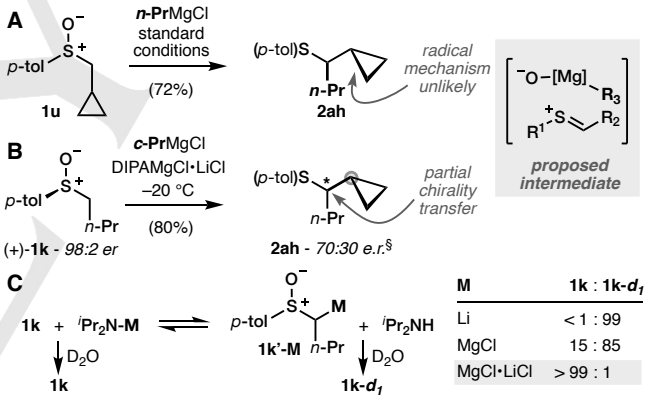


Scheme 3. Discovery and scope of the intermolecular (hetero)arylation including its Integration with *in situ* magnesation methods. **[A]** Conditions: **1a** (0.1 mmol), **4d** (0.11 mmol), THF (1 mL), 0 °C, 1 h; *then* **3** (0.105 mmol), 0 °C *then* 65 °C, 12 h. [a]Determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as internal standard. TMP, 2,2,6,6-tetramethylpiperid-1-yl; DIPA, diisopropylamide. **[B]** Conditions: Method A: **1** (0.3 mmol), **4d** (0.33 mmol), THF (2.5 mL), 0 °C, 1 h, *then* Grignard reagent **3** (0.315 mmol), 0 °C, *then* 65 °C, 14 h. Methods B and C.[20] ‡*N*-Boc thiomorpholine substrate. §Isolated as thioflavone due to auto-oxidation.[20]



Scheme 3. (**A**) Extension to various Grignard reagent classes. (**B**) Versatility of the method and (**C**) its products. **[A,B]** Method A (Scheme 3) at the temperature indicated.[20] ‡*N*-Boc thiomorpholine substrate. ¶Yield on gram-scale. **[C]** Conditions:[20] (a) Py·9HF, DBH, rt; (b) $NiCl_2$, $NaBD_4$, rt; (c) H_2O_2, Ac_2O, rt, *then* LDA, *then n*-BuLi, *then* $Zn(CH_2I)_2$, –50 °C to rt; (d) $PhICl_2$, rt; (e) $NiCl_2·6H_2O$, Py·9HF, DBH, rt; (f) LiNp, –78 °C *then* DMF; (g) LiNp, –78 °C *then* (*i*-PrO)BPin. †>95% deuterium (^2H) incorporation. §*Via* the organolithium intermediate. 2-Np, 2-naphthyl; DBH, 1,3-dibromo-5,5-dimethylhydantoin; LiNp, lithium naphthalenide; DMF, *N*,*N*-dimethylformamide.

After demonstrating the efficient and regioselective coupling of aryls, we explored the generality of these conditions with *sp*-, sp^2- and sp^3-hybridized Grignard reagents (Scheme 3a). Vinyl transfer can be undertaken to produce linear or branched allylic sulfides **2u-w**. Both internal and terminal C(*sp*)-alkynyl Grignard reagents also produce the corresponding propargyl sulfides **2x,y**. As far as we know, these are the first examples of vinyl- and alkynyl-transfer in Pummerer chemistry. The reactive C(sp^3)-Grignard reagents were expected to be more challenging to control due to their fast S-Mg exchange (Scheme 1d), but they engage in the reaction at room temperature. DIPAMgCl·LiCl is again superior to other similar bases (see SI). Different primary alkyls are transferred to form products **2z-ac** in the first examples of efficient Pummerer alkylation.[15] Acyclic or cyclic secondary alkyls (including cyclopropyl) yield the derivatives **2ad-ah**. The scalability of this reaction is illustrated by **2af** (54% yield in gram-scale). Even tertiary alkyls, which would not be accessible to sulfoxide alkylation–reduction strategies, do provide neopentyl sulfides **2ai-al** in a single operation. These reactions also allow the late-stage functionalization of relevant heterocycles and organometallics (**2ac,ak**).[1b] Moreover, the compound **2e** that is obtained through our reductive arylation (Scheme 2b) can be oxidized to the sulfoxide **1t** (Scheme 3b) and coupled with a second Grignard reagent to obtain product **2am**, which underscore the utility of the reaction in the late-stage edition of thioethers and its complete regioselectivity for the least hindered secondary position. Sulfur compounds are also central synthetic intermediates that can be used to mask both electrophilic and nucleophilic functions (Scheme 4c). For example, the oxidative hydrolysis of **2af** leads to the ketone **9**, while nickel boride gives access to the isotopically-labelled alkane **10**-d_1 (or unlabeled **10**, see SI).[6e] Marek's methylenation furnishes **11**,[6d] which can produce epoxides, aziridines and cross-metathesis products. Alkyl halides like the chloride **12**,[6c] and the fluoride **13** can be obtained (the latter through a new nickel-promoted reaction that we are currently studying). The reductive lithiation pioneered by Screttas,[6a,f] provides access to sp^3-organolithiums that can produce, for example, aldehydes and boronic esters for downstream manipulations (*i.e.* **14,15**).[25]



Scheme 4. Preliminary data on the mechanism.

Although the nature of the activation bestowed by the interplay between the Grignard reagent and the Knochel-Hauser base requires a discrete study, we have preliminarily investigated the mechanism of the reductive coupling with sulfoxides. Control experiments with the cyclopropylcarbinyl substrate **1u** (Scheme 4a), disfavor pathways involving radical intermediates that may be generated through SET from the Grignard reagent to the sulfoxide. The intermediacy of a loosely associated sulfonium ion pair is supported by the partial chirality transfer observed when using the unbiased enantiopure sulfoxide (+)-**1k** (Scheme 4b). This result also showcases the potential of this system to develop enantiospecific *S*-to-*C* chirality-transfer reactions in the future. The specific activation observed with the Knochel-Hauser bases can be attributed (in part) to their unexpected low basicity towards sulfoxides (Scheme 4c). The sulfoxide **1k** gets fully deprotonated when using LDA (as evidenced by deuteration into **1k-*d1***), while the optimal DIPAMgCl·LiCl (**4d**) base is completely unreactive. In

this light, **4d** seems to discern between the acidity of free sulfoxides **1** and their magnesium complexes **A** (Scheme 2). The lower concentration of sulfoxide nucleophiles **C** can explain the small amounts of homodimerization products **5** that we have observed using **4d**.

In summary, we report herein a protocol to engage sulfoxides in intermolecular reductive C–C coupling with sp^3-, sp^2-, and *sp*-Grignard nucleophiles. This transformation covers a gap in sulfur chemistry that has remained unsolved for decades, taking advantage of an unusual and specific *turbo*-Hauser base. To the best of our knowledge, this reaction is the first efficient Pummerer-type coupling occurring in non-electrophilic media. Its nucleophilic conditions allow integration with C–H and C–X metalation reactions and is naturally orthogonal to other Pummerer-type reactions. The new protocol has enabled the construction of complex thioethers, which are precursors of unrelated scaffolds such as carbonyls, olefins, halides, organometallics and boronic esters. This concept has preliminarily demonstrated its potential enantiospecificity, and will motivate further research in organomagnesium chemistry and downstream sulfur manipulations.

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NMR primary data for this article are freely available in Zenodo: https://doi.org/10.5281/zenodo.1033411

Keywords: Pummerer • Sulfur • Main group elements • C–C coupling • Hauser base

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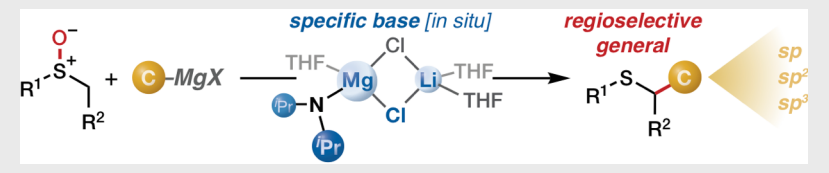

Sulfur-enabled C–C bond formation has been exploited over decades in the synthesis of both sulfur-containing and sulfur-free molecules. The Pummerer coupling allows this process to be performed in a single operation but it is limited by the need of electrophilic activators. Herein we unveil an efficient and orthogonal protocol for electrophile-free Pummerer C–C coupling that addresses the scope limitations of traditional approaches.

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Intermolecular Pummerer coupling with carbon nucleophiles in non-electrophilic media