Iterative Synthesis of Pluripotent Thioethers through Controlled Redox Fluctuation of Sulfur

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Dedicated to Prof. Kazuhiro Kobayashi

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Abstract Target- and diversity-oriented syntheses are based on diverse building blocks, whose preparation requires discrete design and constructive alignment of different chemistries. To enable future automation of the synthesis of small molecules, we have devised a unified strategy that serves the divergent synthesis of unrelated scaffolds such as carbonyls, olefins, organometallics, halides, and boronic esters. It is based on iterations of a nonelectrophilic Pummerer-type C–C coupling enabled by *turbo*-organomagnesium amides that we have recently reported. The pluripotency of sulfur allows the central building blocks to be obtained by regulating C–C bond formation through control of its redox state.

Key words sulfur, Pummerer coupling, iterative synthesis, Grignard reagents

One of the biggest challenges of modern organic synthesis is the acceleration of its own development.¹ Today, automatic synthesizers deliver large libraries of compounds in predictable time scales with minimal human input, thus enabling research campaigns in chemistry, medicine, and biology that would have been impossible otherwise.² The success of automatic synthesizers is inspired by the same principles of iterative activation and coupling that dominate in Nature.³ Despite their power to create C-N, C-O, and P-O bonds in peptides,^{2a} oligosaccharides,^{2c} and oligonucleotides,^{2b} the automatic synthesis of ubiquitous C-C bonds is still an ongoing endeavor.^{1a,2d,3e} In this regard, recent cutting-edge technologies have emerged to enable iterative activation/coupling strategies towards complex molecules (Scheme 1, A), albeit only valid for some types of C-C bonds. Metal-catalyzed cross-couplings dominate $C(sp^2)$ containing bonds;2d,3b,e while carbenoid-organoboron coupling excels at creating C(sp³)-C(sp³) bonds.⁴ All these strat-



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egies are aimed at growing carbon skeletons in each iteration. To the best of our knowledge, a strategy to decorate a single carbon atom (*ipso* functionalization) iteratively with diverse $C(sp^3)$, $C(sp^2)$, and C(sp) fragments is yet to be realized (Scheme 1, B). Unlike homologation strategies, the number of iterations possible for the *ipso* decoration of a single carbon atom is fundamentally restricted by its bond-

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ing possibilities (3–4 iterations in a *sp*³-hybridized carbon). Far from undermining the potential of this approach, this characteristic is complementary in the classes of molecules that it targets. We envisage that such technology could transform how building blocks are sourced, and thus how plan conventional or automatic approaches to both target-^{1b,2e} and diversity-oriented syntheses are planned.⁵



This technology requires a critically important chemical handle (grey circle; Scheme 1, B), which needs to be easily and orthogonally activated; sufficiently stable to be transported over several iterations and ideally primed for integration with solid-phase techniques.^{2a-c} Once the carbon framework is assembled, it needs to be replaced by distinct nucleophilic and electrophilic functional groups to deliver relevant building blocks, such as boronic esters, carbonyls, organometallics, halides, ketones, or olefins. In this regard, thioethers 1 (Scheme 2, A) attracted our attention for their innate synthetic potential to suit this purpose. Specifically, thioethers can be selectively activated through mild S-oxidation (favored over most functional groups), they can be used as substrates in cross-coupling methods⁶ and are pluripotent precursors of various functional groups.⁷ Additionally, they have a balanced reactivity-stability profile that has been extensively exploited in total synthesis,⁸ and are primed for immobilization.⁹ Taking advantage of these features, we envisioned an iterative C-C coupling strategy that would be enabled by controlled modification of the redox state of sulfur (Scheme 2, A). This way, a given thioether 1 would be oxidized to the corresponding sulfoxide 2 and then reductively coupled with a C-nucleophile to provide thioether 1' with concomitant transfer of the redox state from sulfur to the adjacent carbon. Thioether 1' could thus be a substrate for a new iteration, or be transformed into a different functional group, as desired.

Despite intense and creative research dedicated to intermolecular reductive coupling reactions between sulfoxides and *C*-nucleophiles (Pummerer processes),^{8,10} there were fundamental limitations that prevented the use of organometallic nucleophiles with traditional electrophilic activators.¹¹ In connection with our activity in unusual C-C coupling reactions promoted by main-group organometallics,¹² our group has contributed to widen the chemical space available to the Pummerer coupling by providing a preliminary solution to the above-mentioned incompatibility.¹³ Namely, we have reported a nonelectrophilic system based on a specific magnesium base (ⁱPr₂NMgCl·LiCl) that enables productive coupling with a wide range of aryl, alkyl, alkenyl, and alkynyl Grignard nucleophiles (Scheme 2, A). The resulting thioether products 1' could in principle be Soxidized to initiate a second round of iterative coupling, but the need for two separate reactions (S-oxidation and Pummerer) hindered the implementation of a practical iterative protocol. In this contribution, we disclose a procedure to perform S-oxidation followed by Pummerer C-C coupling without isolating the intermediate sulfoxide product.





Ph .	$S_{CH_3} \xrightarrow{H_2O_2, Ac_2O}_{then} F_{DCM, rt} F$	o ⁻ ^{L+} 2a 2a purification)	ⁱ Pr h-i Ti	2 NMgCl MgX (1.0 HF, rt to €	• <i>LiCl</i> 95 equiv) 	h ^{_S} _Ph 1b
#	work-up	purification		2a (%)	1b (from 2a; %)	1b (from 1a; %
1 2 3	extraction extraction solvent evaporation	chromatograph — —	ıy	92 ^a 98 ^b 98 ^b	73 ^b 68 ^b 65 ^b	67 ^b 66 ^b 64 ^b

Scheme 2 Iteration design based on nonelectrophilic Pummere C–C coupling and the discovery of its implementation in one-pot. ^a Isolated yield. ^b Yield determined after workup by ¹H NMR using 1,1,2,2-tetra-chloroethane as internal standard.

Among the various procedures to oxidize thioethers to sulfoxides,¹⁴ we found that the conditions developed by Kakarla and co-workers^{14a} were instrumental to obtain sulfoxides with minimal overoxidation to their sulfones. For example, thioether **1a** is efficiently oxidized to obtain the sulfoxide **2a**, which can be isolated in 92% yield after liquid extraction workup and chromatographic purification. As we reported earlier,¹³ **2a** engages in Pummerer coupling in nucleophilic media, producing the thioether **1b**. Using the purified sulfoxide **2a**, the Pummerer coupling produces **1b** in 73% yield (Scheme 2, B; entry 1). At first glance, the aqueous conditions of the oxidation reaction and its workup seemed reasonably challenging to be telescoped in combination with an organometallic reaction. To our surprise,

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the chromatographic purification of the sulfoxide was only marginally relevant for our Pummerer coupling (Scheme 2, B, entry 2). Moreover, we found that the reductive coupling was less sensitive than we initially anticipated, and simple high-vacuum treatment was sufficient to remove moisture permit subsequent Pummerer coupling with similar efficiency (Scheme 2, B, entry 3). This result is remarkable, taking into account that only 1.05 equiv of Grignard reagent were used in the C-C coupling reaction. Overall, the yield obtained for both telescoped operations compares well with the efficiency of the stepwise synthesis (Scheme 2, B; right column). From an engineering perspective, this result is particularly important as implementation of the vacuum operation would be relatively easy (as opposed to alternative workups and/or purification procedures) in a future automatic synthesizer.

To illustrate the viability of this telescoped protocol in the synthesis of pluripotent thioether intermediates, we selected thioanisole (**1a**) as a simple commercial substrate that, in this context, behaves as a single carbon (C_1) donor (Scheme 3). After *S*-oxidation, the crude sulfoxide was cross-coupled *in situ* with two different aryl sources: commercial PhMgBr and 2-naphthyl bromide. The latter exemplifies the capacity of our nonelectrophilic Pummerer protocol to integrate with Knochel's magnesium–halogen exchange (treating the bromide *in situ* with ⁱPrMgCl-LiCl).¹⁵ Both one-pot experiments yielded thioethers **1b** and **1c** in 64% and 52% yield over the two telescoped steps, respectively. These products were again *S*-oxidized and the crude products submitted to a second round of C–C coupling with secondary and tertiary alkyl Grignards. In this way, the products **1d–g** that arise from all four possible combinations in this sequence were seamlessly obtained in 50–56% yield. Despite the current moderate yields, the versatility of the concept allows the synthesis of four difunctionalized derivatives using only four different Grignard reagents. The efficiencies obtained in this telescoped procedure¹⁶ are similar to those observed using the stepwise protocol that required the isolation of the intermediate sulfoxide.¹³ Unfortunately, attempts to perform two iterations in a single flask or a third iterative coupling to create quaternary thioethers were not successful and will require further developments of this chemistry, which we are currently pursuing.

The versatility of the current protocol is well illustrated by **1e**, which can be used to deliver different small molecules bearing central functional groups. We have illustrated recently¹³ that **1e** can be oxidatively hydrolyzed into the corresponding ketone or reduced to a specifically deuterated alkane.^{7e} The olefin manifold can be accessed using the method reported by Marek, thus opening the door for epoxides, aziridines, and cross-metathesis products.^{7d} Oxidative chlorination^{7c} and fluorination allow the preparation of electrophiles and organofluorine products, respectively. Reductive lithiation pioneered by Screttas,^{7a,f} provides access to organometallic reagents that give rise, for example, to aldehydes or boronic esters for further manipulation, including the latest iterative carbenoid homologations.⁴ Thus,



Scheme 3 Iterative synthesis of diverse building blocks by controlled fluctuation of the redox state of sulfur. *Reagents and conditions*: H_2O_2 , Ac_2O , SiO_2 , DCM, rt, followed by vacuum evaporation, followed by DIPAMgCI-LiCl, RMgX (or ArX, ⁱPrMgCI-LiCl), THF, rt (to 65 °C). Derivatization conditions:¹³ (a) Olah's reagent, DBH, H_2O , DCM, rt; (b) NiCl₂·6H₂O, NaBD₄, THF, CD₃OD, rt; (c) H_2O_2 , Ac_2O , SiO_2 , DCM, rt, followed by LDA, THF, -78 °C to -40 °C, followed by "BuLi, THF, -78 °C to -50 °C, followed by Zn(CH₂))₂, THF, -50 °C to rt; (d) PhICl₂, DCM, rt; (e) NiCl₂·6H₂O, Olah's reagent, DBH, DCM, 0 °C to rt; (f) LiNp, THF, -78 °C to -20 °C, followed by DMF; (g) LiNp, THF, -78 °C to 0 °C followed by (ⁱPrO)BPin. 2-Np = 2-naphthyl; DBH = 1,3-dibromo-5,5-dimethylhydantoin; LiNp = lithium naphthalenide.

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the versatile chemistry of the C–S bond¹⁷ is primed to maximize the utility of the iterative C–C coupling strategy that we have introduced herein.

In summary, the iterative construction of complex carbon frameworks using sulfur compounds has been enabled by a one-pot S-oxidation/reductive-coupling protocol. This strategy is based on an intermolecular reductive C-C coupling between sulfoxides and sp³-, sp²-, and sp-Grignard nucleophiles that our group has recently developed.¹³ Herein we have introduced the sulfur moiety as control unit for C-C coupling through iterative fluctuation of its redox state. The choice of sulfur benefits from its rich chemistry, which can deliver unrelated scaffolds such as carbonyls, olefins, halides, organometallics and boronic esters, among others. Despite these features, important challenges remain to be solved to reach the goal of assembling in solid-phase guaternary carbon centers in an enantiospecific fashion. Our group is actively pursuing fundamental solutions to these challenges, thus aiming to complement current approaches towards iterative C-C assembly and to inspire further research in downstream sulfur manipulations.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1591864 and for download from Zenodo (https://doi.org/10.5281/zenodo.1033411); see Table S1 in the Supporting Information for details.

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