C(sp^3) Cross-Couplings of Benzyl and Tertiary Halides with Thiols or Alcohols Catalyzed by Iron

Julius Semenya[1], Yuanjie Yang[1], Kimberly A. Giannantonio[1], Rikhil Manduva[1], Hye Joon Lee[1], Elias Picazo[1]*

[1] Department of Chemistry, Loker Hydrocarbon Research Institute, University of Southern California, 837 Bloom Walk, Los Angeles, California 90089-1661, United States

*Corresponding author. Email: epicazo@usc.edu

Abstract:

Various metal catalysts have proven effective in carbon–heteroatom bond formation with softer heteroatomic nucleophiles, but examples remain largely limited to sp^2 hybridized carbon electrophiles. Here, we report the coupling of sp^3 hybridized benzyl or tertiary halides with soft thiol nucleophiles catalyzed by iron. The reaction is broad in substrate scope for both coupling partners and applicable in the construction of congested tri- and tetrasubstituted carbon-centers as well as β-quaternary thioethers. The synthetic utility is further emphasized by the coupling of alcohol nucleophiles, gram-scale synthesis, thiol bioconjugation, and rapid herbicide library synthesis. Results from mechanistic experiments are consistent with a stereoablative pathway that likely involves a carbon radical intermediate. Overall, we provide an efficient method to prepare pharmaceutically and materially relevant carbon–sulfur and carbon–oxygen bonds by expanding iron-catalyzed cross-coupling reactions to the coupling of sp^3 hybridized carbon electrophiles with soft nucleophiles.

Text:

The ubiquitous nature of C–S and C–O bonds in natural products,[1] pharmaceuticals,[2] agrochemicals,[3] and materials[4] drives the discovery of methods for their construction.[5] Select examples include chlorbenside, an acaricide used for mites and ticks,[6] lenalidomide analogs with anti-cancer activity,[7] and recently approved pretomanid for the treatment of multidrug-resistant tuberculosis (Figure 1A).[8] Despite its extensive utility, the Williamson (thio)ether synthesis (Figure 1B)[9] relies on additives to promote an S_N2 reaction. Such additives can generate inorganic salts, promote undesired side reactions, or limit substrate scope. For example, despite the utility of complex (thio)ethers,[10] S_N2 reactions are largely limited to primary alkyl (thio)ethers because secondary alkyl halides face elimination and tertiary halides are unreactive.[11] Though other methods for (thio)ether synthesis have been reported,[12] transition-metal catalyzed cross-couplings of sp^3 hybridized alkyl halides with soft nucleophiles remain a challenge.

Seminal studies in C–O[13] and C–N[14] bond construction through copper-catalyzed Ullmann-type cross-coupling reactions[15] demonstrated that strategies involving transition-metal catalysts present an opportunity for a finer approach to carbon–heteroatom bond formation. Beyond coupling reactions with hard metalated nucleophiles for C–C bond construction,[16] several transition-metal cross-coupling reactions that produce carbon–heteroatom bonds have been developed. Reactions to form C–N,[17] C–O,[18] and C–S,[19] bonds typically engage an sp^2 hybridized carbon electrophile, with sp^3 hybridized carbon electrophiles facing additional β-hydride elimination complications.[20] Further, C–S bond formation is impeded by thiol oxidative S–S coupling reactions,[21] thiol-mediated catalyst poisoning,[22] elimination reaction pathways, and thiol-mediated C–H bond formation through radical quenching,[23] rendering reactions that couple sp^3 carbon electrophiles

with soft nucleophiles challenging to develop (Figure 1C). Notably, the only example of a metal-catalyzed cross-coupling of C(sp^3)–halides with sulfur nucleophiles is limited to benzenesulfonothioates and thiosulfonates.[24]

Despite nature's ability to use iron and sulfur for target reduction,[25] iron-catalyzed cross-coupling reactions commonly couple an alkyl or aryl electrophile with a hard nucleophilic organometallic reagent. Grignard reagents for Kumada couplings in C–C bond formation have found great success and continue to inspire new reactivity.[26] In addition to reactivity, iron presents the advantage of being the most abundant transition metal in Earth's crust.[27]

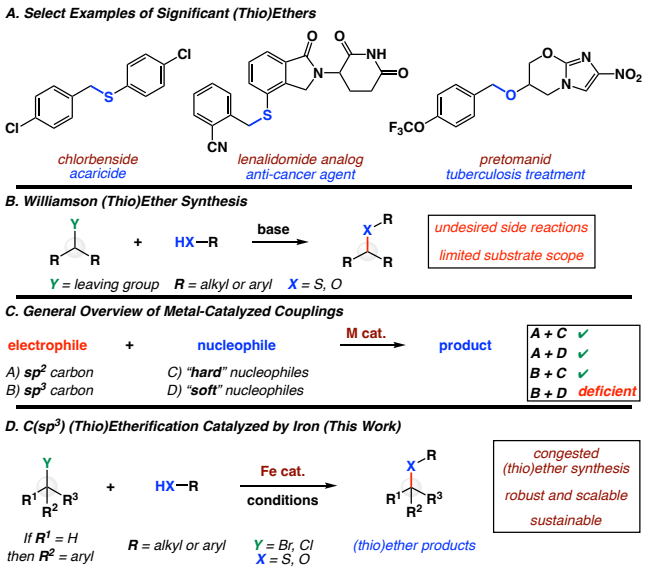
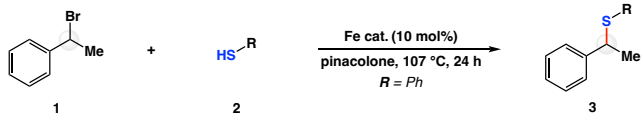


Figure 1. (A) Examples of significant (thio)ethers, (B) Williamson (thio)ether synthesis, (C) state of transition-metal-catalyzed cross-coupling reactions, (D) (thio)etherification of benzyl or tertiary halides with soft thiol or alcohol nucleophiles catalyzed by iron.

Given successful olefin hydrogenations in the presence of thiols[28] and a cross-electrophile coupling of benzyl halides with disulfides catalyzed by iron,[29] we wondered if iron's reactivity could be leveraged to couple C(sp^3)–halide electrophiles with sulfur nucleophiles. Herein, we report the realization of general cross-coupling reactions between benzyl or tertiary halides and soft thiol nucleophiles catalyzed by iron. The scope is broad, the system extends to ether synthesis, and the reaction can be applied in large-scale synthesis, thiol bioconjugation, rapid herbicide analog synthesis, and in the assembly of hindered (thio)ether products (Figure 1D).

After discovering that iron pentacarbonyl can activate (1-bromoethyl)benzene (**1**) and promote a coupling with soft thiophenol (**2**) without catalyst poisoning, we evaluated solvents, temperature, catalyst loading, iron sources, and additives. Select optimization studies are shown in Table 1.[30] Despite observing the formation of thioether **3** with various iron sources (entries 2–11) and conditions, optimal conditions using iron pentacarbonyl in pinacolone yield product in 91% isolated yield (entry 1). Only a trace amount of thioether **3** is observed when running the reaction in the absence of iron (Table 1, entry 12), verifying that the process is not functional in the absence of catalyst. Reducing catalyst to 5 mol% (entry 13) decreases the yield from 92 to 76%.



Entry	Iron Source (10 mol%)	NMR Yield[a] % (Isolated)
1	$Fe(CO)_5$	92 (91)
2	$Fe_2(CO)_9$[b]	72
3	$Fe(OAc)_2$	79
4	$Fe(OTf)_2$	75
5	FeF_2	76
6	$FeCl_2$	81
7	$FeBr_2$	70
8	$Fe(acac)_3$	76
9	FeF_3	79
10	$FeCl_3$	54
11	$FeBr_3$	68
12	no Fe cat.	trace
13	$Fe(CO)_5$ (5 mol%)	76

Table 1. Select Results from Optimization Studies. [a] ^{1}H NMR yields were determined using 1,3,5-trimethoxybenzene as internal standard. [b] 10 mol% of Fe was achieved by using 5 mol% of $Fe_2(CO)_9$.

As shown in Figure 2, a wide range of functional groups are applicable to the coupling between benzyl halides **4** and soft nucleophiles **5** in the presence of $Fe(CO)_5$ to yield (thio)ether products **6**. The generality across both coupling partners renders (thio)ether product **6** modular in 4 compartments. For example, unsubstituted and electron rich 4-methyl substituted

thioethers **7** and **8** form smoothly with isolated yields of 91 and 85%, respectively. It should be noted that overly donating groups on the arene, such as ethers, led to bromides that were unstable to chromatography. Electron-withdrawn thioethers in cyano-, nitro-, and fluoro-thioethers **9**, **10**, and **11** are also produced in high yield. Historically metal-reactive groups[31] are unaffected and 4-, 3-, and 2-substitutions are successful, as demonstrated with fluoro-, chloro-, and bromo-adducts **11**–**15**. Extension of the conjugated system is not detrimental to the reaction, represented by the synthesis of thioether **16** in 81% yield, and the reaction remains operable with diaryl and primary bromide substrates, demonstrated with the syntheses of **17**–**20** in high yields. The reaction extends beyond bromide starting materials, as exemplified by the synthesis of thioether **21** in 75% yield from the corresponding chloride starting material. A steric effect is observed when replacing the methyl group in product **7** with larger groups, as detailed with the production of thioethers **22**–**24**. Despite the steric effect, b-tertiary thioether **23** was isolated in 71% yield.

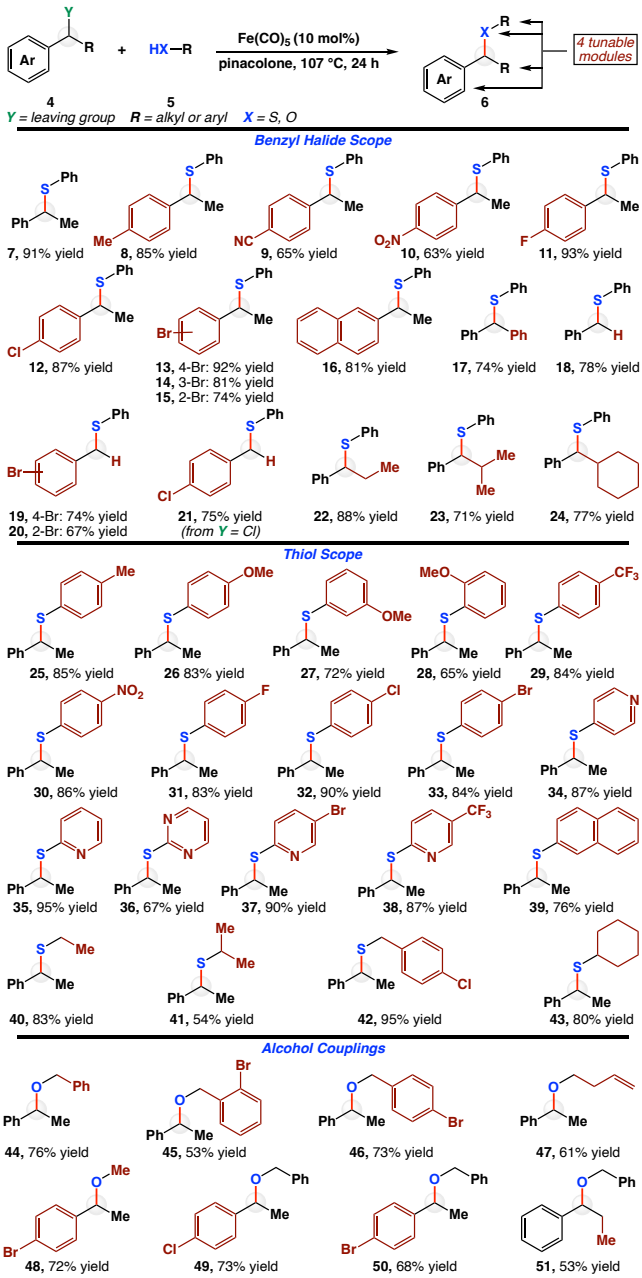


Figure 2. Reaction scope for the alkylation of thiols for thioether synthesis catalyzed by iron and its extension for ether synthesis.

The thiol coupling partner supports both aryl and alkyl thiols with varying substitutions. Thioethers bearing electron-donating and electron-withdrawing groups (e.g., **25**–**33**), including historically metal-reactive groups, are isolated in high yields. Further, inclusion of nitrogen within the aromatic backbone reliably affords pyridine and pyrimidine products **34**–**38**. Extending conjugation on the thiol group yields naphthyl thioether **39** in 76% yield. Increasing the steric profile of alkyl thiols results in lower yields, but increasingly encumbered thioethers **40**–**43** are still produced in synthetically useful yields. It should be noted that no elimination byproducts are observed in the construction of thioethers.

Given the success of thioether synthesis, we also performed experiments with amine and alcohol nucleophiles. It was found that amine nucleophiles such as aniline and piperidine undergo alkylation in the absence of iron.[32] Like the thiol nucleophiles, alcohols do not have an uncatalyzed reaction pathway. As such, we developed a representative scope (**44**–**51**) for the equivalent iron-catalyzed etherification reaction.[33] Similar modifications, including arene and alkyl variations on

the benzyl halide and alcohol coupling partners, are applicable. The yields for ether production are generally lower because of notable elimination byproduct formation due to relative heteroatomic basicity.

To emphasize the utility of the reaction, we performed a gram-scale synthesis of thioether **7**. The 6 mmol reaction yields desired product in 93% yield (Figure 3A). Given the prevalence of thiols in biomolecules, we also sought out to form a C–S bond between a fluorophore and a more complex cysteine derivative. Reaction between 9-anthracenyl substrate **52** and cysteine derivative **53** under standard conditions produces bioconjugated anthracene **54** in 81% yield (Figure 3B). Running the reaction at 40 °C for 24 hours, which are more favorable biological conditions, yields the desired labeled thioether **54** in 59% yield.

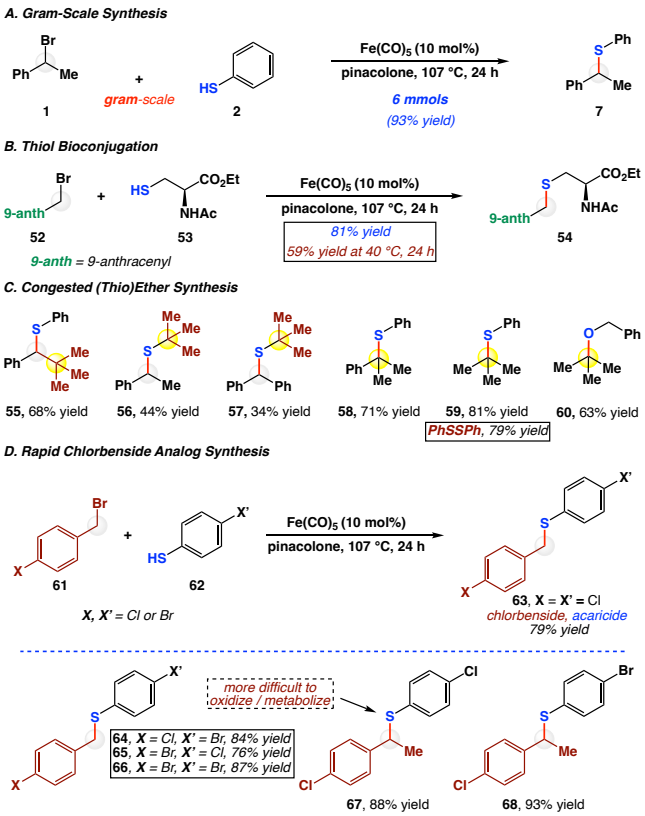


Figure 3. (A) Gram-scale thioether synthesis, (B) thiol coupling with 9-anthracenyl substrate, (C) synthesis of highly congested (thio)ethers, (D) rapid synthesis of chlorbenside and its analogs.

Interested in the successful synthesis of hindered thioethers **23** and **41**, we wondered if we could leverage this reaction for the synthesis of heavily congested thioethers (Figure 3C). To our gratification, the iron-catalyzed reaction produces sterically encumbered β-quaternary thioethers like **55** in 68% yield. Further, as represented by the production of thioethers **56** and **57** in synthetically useful yields, this method is amenable to tertiary thioether synthesis via tertiary thiol coupling. Using tertiary bromide as starting materials, we can also construct thioethers with tetrasubstituted carbon centers like **58** and **59** in high yields. Notably, using the corresponding disulfide, analogous to our previous study,[29] produces congested thioether **59** and the coupling of an alcohol with a tertiary bromide results in the formation of tertiary ether **60**. Interestingly, the (thio)etherification is limited to benzyl halides for primary and secondary halides with unactivated halides being unreactive (see Supporting Information), but tertiary bromide coupling partners do not present this limitation as represented by the synthesis of tertiary trialkyl (thio)ethers **59** and **60**.

Due to the prevalence of (thio)ethers in biologically active compounds, we sought to synthesize chlorbenside (**63**) and analogs. When coupling corresponding chlorides **61** and **62**, chlorbenside (**63**) is isolated in 79% yield (Figure 3D). The flexibility of the method enables the rapid synthesis of chlorbenside analogs **64**–**68** in high yields, emphasizing the ability to rapidly generate libraries of biologically active molecules from common precursors. While **64**–**66** demonstrate the facile exchange of aryl substituents, thioethers **67** and **68** introduce chemical complexity with greater steric profiles near the thioether center. It is known that some chlorbenside is excreted as the sulfoxide and sulfone equivalents[34] and methylated derivatives like **67** and **68** are likely to be oxidized and metabolized at slower rates.[10,35]

Mechanistic experiments of the iron-catalyzed protocol are consistent with the intermediacy of organic radicals derived from the electrophile (Figure 4). Enantioenriched bromide **69**, **ent** was prepared in 24 or 33% enantiomeric excess (ee) and reacted with thiophenol (**2**) or benzyl alcohol (**70**), respectively, to produce corresponding (thio)ether product **71** as a racemate (Figure 4A). We conducted a radical spin experiment to determine if the deterioration of stereochemical information is the result of a radical intermediate (Figure 4B). Reacting bromide **1** with thiophenol (**2**) or benzyl alcohol (**70**) in the presence of (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) under standard conditions results in a 39 or 45% (thio)ether **72** and 51 or 34% TEMPO-adduct **73** formation, respectively. An organic radical intermediate is further substantiated through the synthesis of acyclic (thio)ether **76** as opposed to cyclopropane-containing (thio)ether **75** in 76 or 100% yield when coupling radical clock substrate **68** with thiophenol (**2**) or benzyl alcohol (**70**), respectively (Figure 4C). Each nucleophile was evaluated under their respective optimal conditions and the difference in yield may be due to the difference in temperatures.

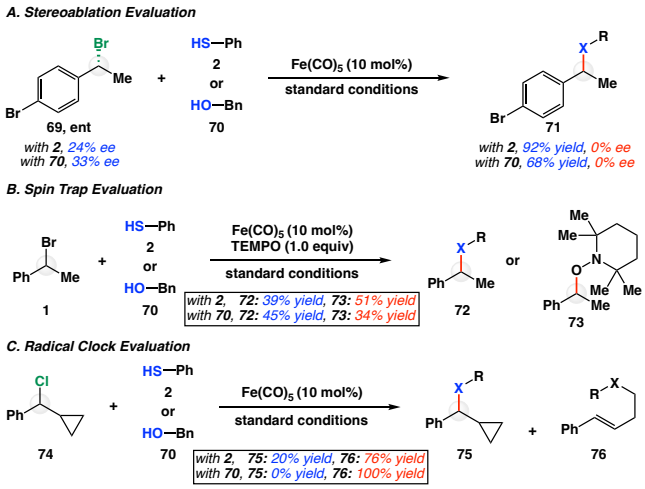


Figure 4. (A) Stereochemical examination, (B) spin trap examination, (C) radical clock examination.

In conclusion, we have developed a coupling of benzyl or tertiary alkyl halides with soft thiol nucleophiles for the synthesis of thioether products. The reaction is catalyzed by iron and avoids the use of exogenous acid or base. Good efficiency with a broad steric and electronic generality for each coupling partner is observed. The system expands to C–O bond construction, gram-scale synthesis, and thiol bioconjugation. Highly congested (thio)ethers can be constructed in high yields and tertiary alkyl halides break through the benzylic limitation. The reaction's generality enables rapid synthesis of compound libraries, exemplified by the synthesis of chlorbenside and its analogs. Results from mechanistic experiments are consistent with a stereoablative pathway that likely involves an organic radical intermediate. Due to several challenges associated with alternative methods for C–S and C–O bond construction and the importance of (thio)ether compounds in various fields, we expect this advance to be of interest to the broader scientific community.

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Supporting Information is available in the online version of the paper.

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Author Information Correspondence and requests for materials should be addressed to the corresponding author, E.P. (epicazo@usc.edu), Department of Chemistry, Loker Hydrocarbon Research Institute, University of Southern California, 837 Bloom Walk, Los Angeles, California 90089-1661, United States.