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Nickel-Catalyzed Decarbonylative Synthesis of Fluoroalkyl Thioethers

Conor E. Brigham, Christian A. Malapit, Naish Lalloo, and Melanie S. Sanford*

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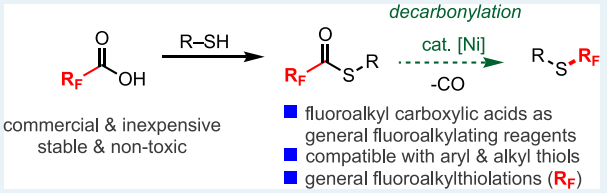
ABSTRACT: This report describes the development of a nickel-catalyzed decarbonylative reaction for the synthesis of fluoroalkyl thioethers (R_FSR) from the corresponding thioesters. Readily available, inexpensive, and stable fluoroalkyl carboxylic acids (R_FCO_2H) serve as the fluoroalkyl (R_F) source in this transformation. Stoichiometric organometallic studies reveal that R_F–S bond-forming reductive elimination is a challenging step in the catalytic cycle. This led to the identification of diphenylphosphinoferrocene as the optimal ligand for this transformation. Ultimately, this method was applied to the construction of diverse fluoroalkyl thioethers (R_FSR), with R = both aryl and alkyl.



KEYWORDS: *nickel-catalysis, decarbonylation, fluoroalkyl carboxylic acids, thioether synthesis, fluoroalkylation*

Fluoroalkyl thioethers (R_FSR) have emerged as increasingly common motifs in bioactive molecules due to their unique physiochemical properties.[1] As shown in Figure 1A, thioethers bearing diverse fluoroalkyl substituents (for example, CF_2H, CFH_2, and CH_2CF_3) appear in lead structures relevant to both medicinal and agricultural chemistry.[2,3] The most common synthetic routes to R_FSR involve either the electrophilic fluoroalkylation of thiols (Figure 1B, *i*)[3−5] or the coupling of aryl/alkyl electrophiles with [M]−SR_F nucleophiles (Figure 1B, *ii*).[3,6−8] Both approaches have significant limitations with respect to the breadth of R_F substituents that can be introduced, since very few of the necessary R_F-containing electrophiles/nucleophiles are commercially available.[6,7] Furthermore, many of these methods require other toxic, unstable, or expensive reagents.[3,4,6,7] Overall, more general synthetic approaches to fluoroalkyl thioethers are of high interest, and the use of readily available fluoroalkyl carboxylic acids as R_F precursors would be particularly enabling in this context.

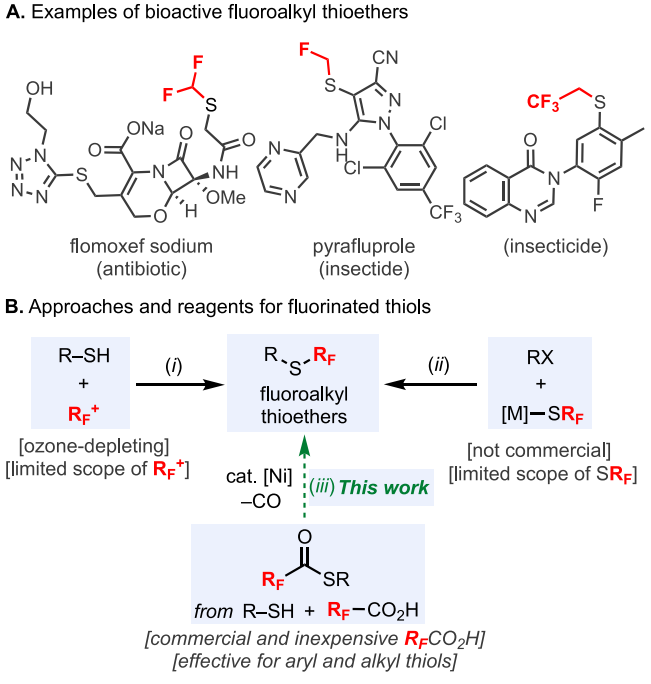


Figure 1. (A) Representative examples of bioactive molecules containing fluoroalkyl thioethers (R_FSR). (B) Existing synthetic approaches to R_FSR (*i*, *ii*) and our approach (*iii*).

This report describes the development of a Ni-catalyzed reaction for constructing fluoroalkyl thioethers from the corresponding thioesters (Figure 1B, *iii*). Our approach leverages fluoroalkyl carboxylic acids as inexpensive, stable, and commercially available R_F precursors.[9−12] As such, it enables the construction of a variety of different fluoroalkyl thioethers from a single thiol starting material.

Recent studies on Ni-catalyzed coupling reactions of carboxylic acid derivatives[13,14] led us to propose this decarbonylative route to fluoroalkyl thioethers. Recent reports from our group[13c] and others[15−17] have demonstrated that

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Ni(0) phosphine complexes catalyze decarbonylative C−S coupling reactions of (hetero)aryl thioesters to afford (hetero)aryl thioether products (for example, see Figure 2A).

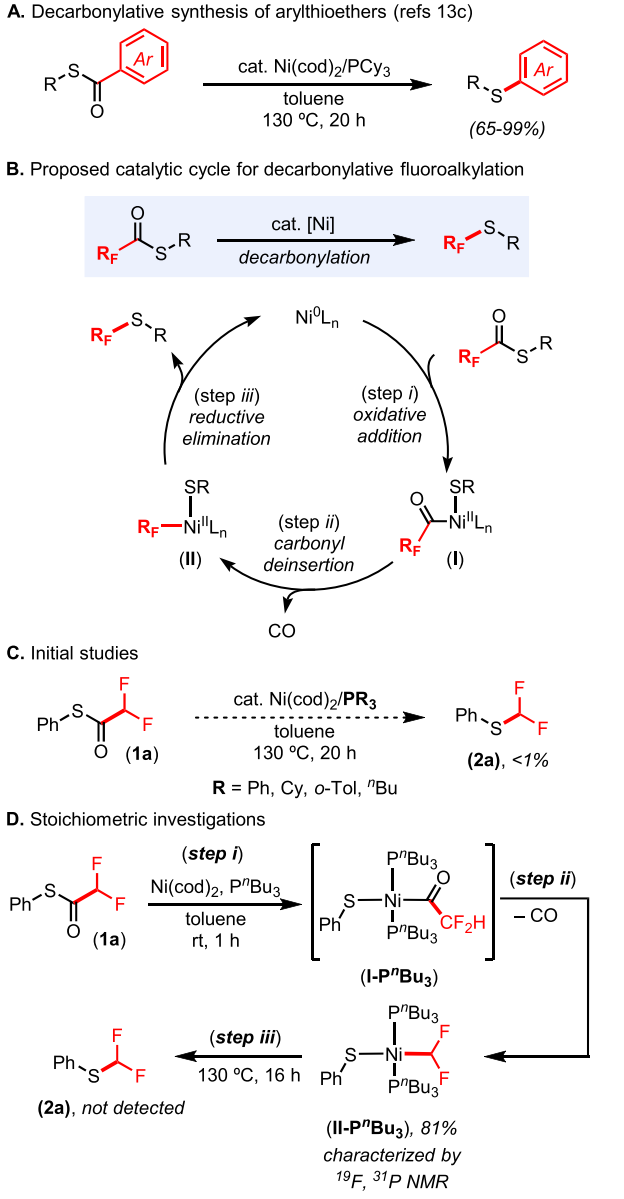

Figure 2. (A) Example of precedent for decarbonylative thioetherification. (B) Proposed catalytic cycle. (C) Initial catalysis studies. (D) Stoichiometric studies with P^nBu_3 as ligand.

We hypothesized that an analogous pathway, using fluoroalkyl thioesters as starting materials, could offer a route to R_FSR products. The proposed catalytic cycle (Figure 2B) involves initial oxidative addition of the fluoroalkyl thioester at a Ni(0) catalyst to form the acyl Ni(II)-intermediate, **I** (step *i*). Carbonyl deinsertion then generates the Ni(II)(fluoroalkyl)(thiolate) intermediate **II** (step *ii*). Finally, **II** undergoes C−S bond-forming reductive elimination (step *iii*) to yield the target fluoroalkyl thioether product and regenerate the Ni(0) catalyst.

We initiated these investigations by targeting the conversion of difluoromethyl thioester **1a** to thioether **2a** (Figure 2C). We focused on catalysts based on a combination of $Ni(cod)_2$ and monodentate phosphine ligands (PR_3), which were previously employed for the transformation in Figure 2A.[13c15−17] However, only traces (<1%) of product **2a** were detected using PPh_3, $P(o\text{-Tol})_3$, PCy_3, or PBu_3 (Figure 2C). In all of these systems, the majority of the mass balance was the unreacted starting material **1a**.

We next conducted stoichiometric studies to identify the problematic step(s) in this sequence. The treatment of a toluene solution of $Ni(cod)_2/P^nBu_3$ with 1 equiv of **1a** resulted in the formation of $(P^nBu_3)_2Ni(SPh)(CF_2H)$ (**II-P^{n}Bu$_3$**) within 1 h at ambient temperature (Figure 2D). Complex **II-P^{n}Bu$_3$** was characterized in situ via ^{19}F and ^{31}PNMR spectroscopy, which show resonances indicative of a trans configuration, with three-bond coupling between the CF_2H and P^nBu_3 ligands (J_{PF} = 26.5 Hz). The formation of **II-P^{n}Bu$_3$** implicates the feasibility of two key steps of the catalytic cycle: oxidative addition (step *i*) and carbonyl deinsertion (step *ii*). However, when in situ-generated **II-P^{n}Bu$_3$** was heated at 130 °C for 2 h, none of the thioether product **2a** was formed (step *iii*). Instead, the resonances associated with **II-P^{n}Bu$_3$** slowly decayed, without the observation of identifiable organic products. This suggests that F_2HC−S bond-forming reductive elimination is challenging in this system and that alternative ligands are required to enable this step.

Literature reports have shown that 1,1′-bis(diphenylphosphino)ferrocene (dppf) is particularly effective for promoting challenging reductive elimination reactions.[18] As such, we next conducted an analogous stoichiometric experiment with $Ni(cod)_2$/dppf. As shown in Figure 3A, the

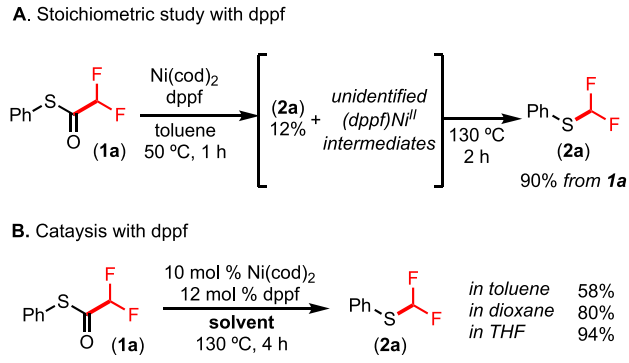

Figure 3. (A) Stoichiometric and (B) catalytic studies with dppf.

treatment of a toluene solution of $Ni(cod)_2$/dppf with 1 equiv of **1a** resulted in 70% consumption of **1a** within 1 h at 50 °C. This was accompanied by the formation of **2a** (in 12% yield) along with broad signals in the ^{19}F NMR spectrum. Based on previous reports,[18a] these broad signals are indicative of fluxional (dppf)Ni^{II} intermediates. Subsequent heating at 130 °C for 1 h resulted in S−CF_2H bond formation to generate **2a** in 90% yield by ^{19}F NMR spectroscopy (Figure 3A).[19] Dppf was next examined as a ligand for the catalytic transformation of **1a** to **2a**. As shown in Figure 3B, the combination of 10 mol % $Ni(cod)_2$ and 12 mol % dppf afforded **2a** in 58% yield over 20 h at 130 °C in toluene. Further optimization of the reaction solvent and time resulted in nearly quantitative yield over 4 h in THF (Figure 3B).[20]

The scope of this transformation was first explored with respect to the substitution on sulfur (Figure 4). The difluoromethyl thioester substrates **1a**−**1w** were prepared via the reaction of RSH with difluoroacetic anhydride. These were typically obtained in quantitative yield without the need for

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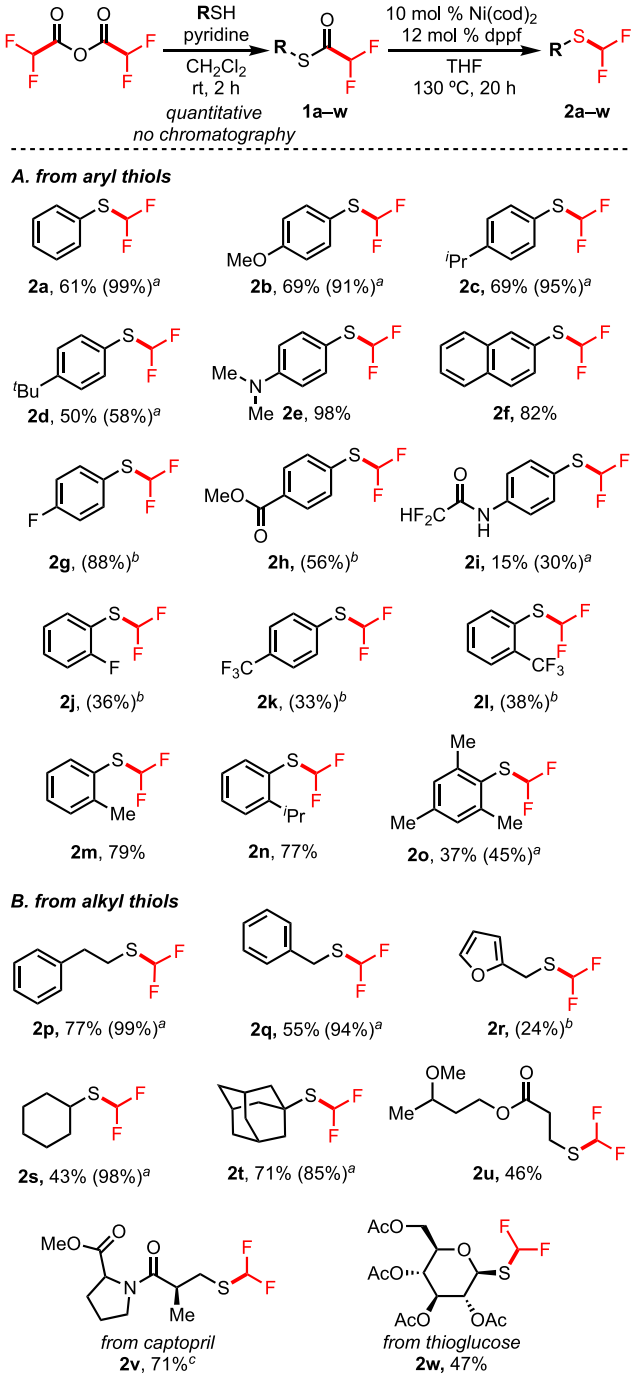

Figure 4. Scope of (A) aryl and (B) alkyl thioethers. [a]% conversion of **1** to **2** as determined by ^{19}F NMR spectroscopy. [b]Yield determined by ^{19}F NMR spectroscopy with 4-fluorotoluene as internal standard. [c]Catalyst loading was increased to 15 mol % Ni(cod)$_2$, 18 mol % dppf.

purification by column chromatography. Aryl thioesters bearing electron-donating and -neutral substituents (**1b**−**1f**) afforded good yields of the difluoromethyl thioether products (Figure 4A). Substituents such as ethers, amines, and amides were compatible. Aryl thioesters bearing electron-withdrawing groups resulted in lower yields (see products **2h**−**2l**), with the exception of 4-fluorothiophenol derivative, **2g**. In these systems, the major side products were diarylthioethers, which are likely formed via competing activation of the aryl−S bond of the product by the Ni(0) catalyst.[21] This transformation showed modest sensitivity to sterics on the aryl ring, and substrates containing either one or two electron-donating ortho-substituents afforded **2m**−**2o** in moderate to good yields.

Primary, secondary, and tertiary alkyl thiols were also effective substrates for this transformation (for example **2p**, **2s**, and **2t** in Figure 4B). Thiol-containing biologically active compounds such as captopril (**2v**) and thioglucose (**2w**) underwent conversion to the corresponding difluoromethyl thioethers in good yields. In these systems, unreacted starting material accounted for the remaining mass balance when the yields were modest. Importantly, the catalytic cycle does not require an exogenous base. This limits racemization of substrates like **2v** during catalysis.

Finally, we used this approach to synthesize a series of different fluoroalkyl thioethers. As shown in Figure 5, the

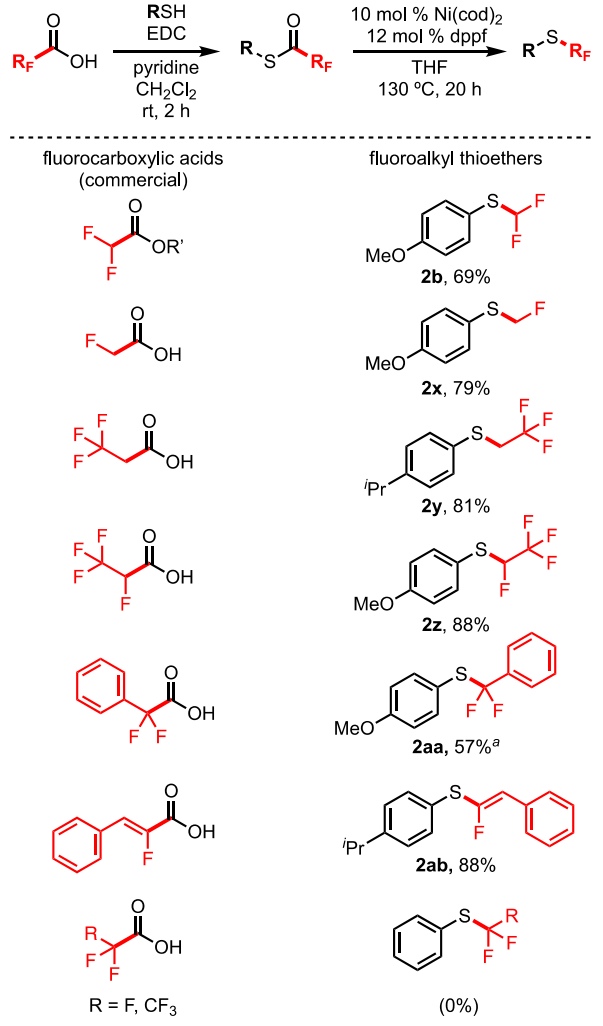

Figure 5. Scope of fluoroalkyl groups derived from commercial R_FCO_2H. Isolated yields. See the SI for details. [a]Catalyst loading was increased to 20 mol % Ni(cod)$_2$, and Xantphos was used as the ligand at 24 mol %.

substrates for this transformation were synthesized from commercially available R_FCO_2H and thiols. Catalytic decarbonylation then provided the partially fluorinated thioether products **2x**−**2ab** in good to excellent yields. Importantly, these products are challenging to access using most existing approaches (Figure 1B), because of the inaccessibility of the required fluoroalkylating reagents. One current limitation of

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this approach is that fluorinated derivatives (e.g., SCF_3, SCF_2CF_3) afford none of the desired fluoroalkyl thioether product.[22] A stoichiometric study of the CF_3 system showed the formation of Ni−CF_3 intermediates; however, no thioether product was detected upon heating these species. This result suggests that the S−R_F reductive elimination step remains a challenge in these systems.[23]

In summary, a nickel-catalyzed decarbonylative coupling reaction was developed to convert fluoroalkyl thioesters to the analogous thioethers. This method leverages readily available fluorocarboxylic acids as commercial and stable fluoroalkyl sources to install these functional groups, which are increasingly prevalent in biologically active molecules.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.0c02950.

Experimental details, characterization data, and NMR spectra of compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Melanie S. Sanford − *Department of Chemistry, University of Michigan, Ann Arbor, Michigan 48109, United States;* orcid.org/0000-0001-9342-9436; Email: mssanfor@umich.edu

Authors

Conor E. Brigham − *Department of Chemistry, University of Michigan, Ann Arbor, Michigan 48109, United States*

Christian A. Malapit − *Department of Chemistry, University of Michigan, Ann Arbor, Michigan 48109, United States;* orcid.org/0000-0002-8471-4208

Naish Lalloo − *Department of Chemistry, University of Michigan, Ann Arbor, Michigan 48109, United States*

Complete contact information is available at: https://pubs.acs.org/10.1021/acscatal.0c02950

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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(22) See SI for catalyst screening of the decarbonylative trifluoromethylation of thiophenol.
(23) Stoichiometric studies of the reaction between $Ni(cod)_2$/dppf and (trifluoromethyl)thioesters showed the formation of Ni-CF_3 intermediates by ^{19}F NMR spectroscopy (see SI), suggesting that oxidative addition and carbonyl deinsertion are taking place. However, no S-CF_3 coupling was observed by ^{19}F NMR spectroscopy or GCMS when these intermediates were heated.

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