Nickel-Catalyzed Light-Mediated Thioetherification

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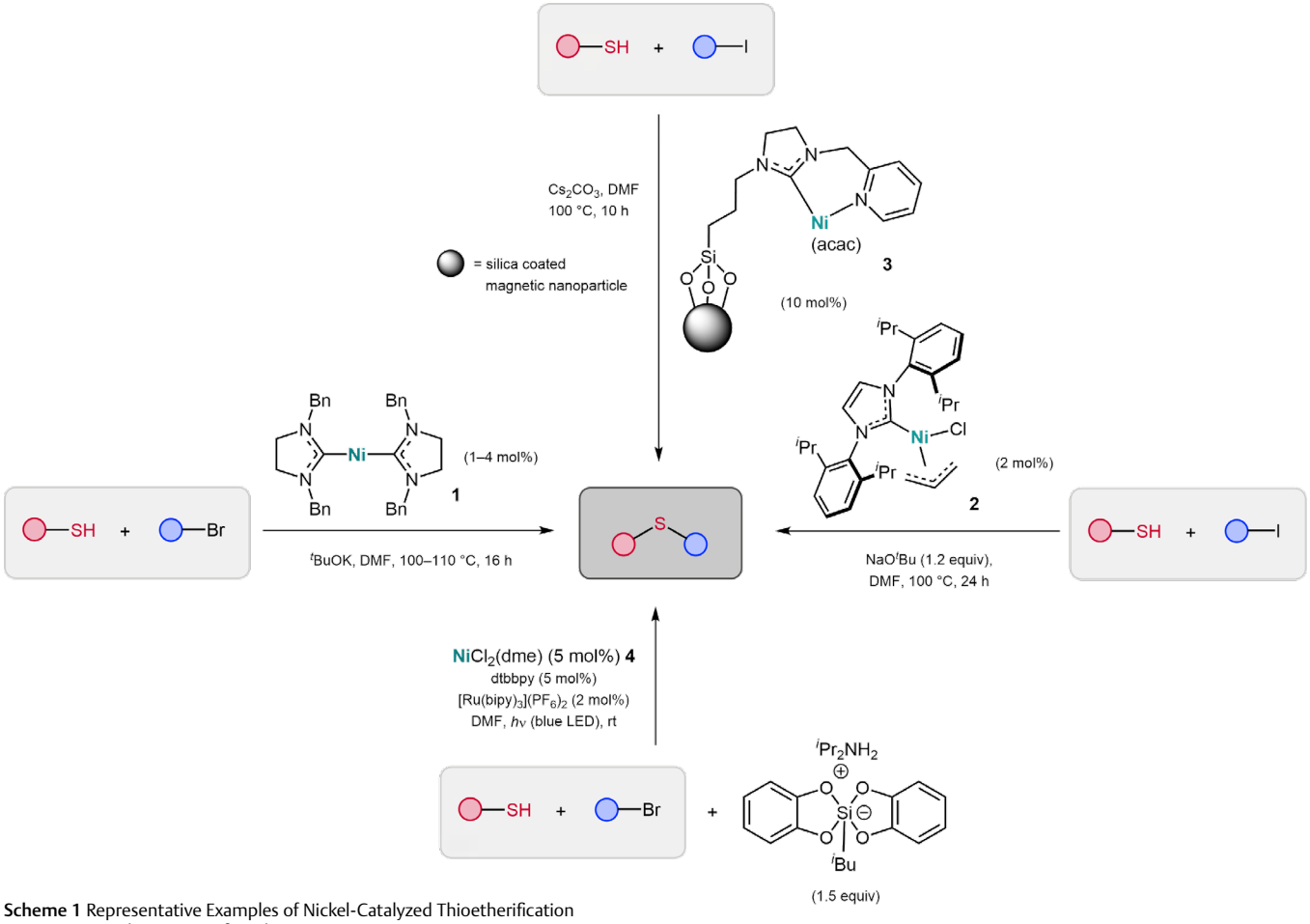
Abstract

One of our group's main objectives is to develop sustainable nickel-catalyzed methodologies to enable the facile formation of new C–heteroatom bonds from abundant building blocks. Recently, we envisioned a strategy using nickel catalysis under mild conditions to form the C–S bond connectivity present in thioethers. *Science of Synthesis* became a crucial tool in starting our project, where we utilized its structure- and text-search functionalities to obtain a comprehensive and quick overview of the synthetic methodologies currently available for nickel-catalyzed thioetherification.

Discussion

One of the most important aspects of the initial stage of any synthetic chemistry project is understanding the state of the art of the desired transformation. We turned to the critical reviews on synthetic methodology that are found in *Science of Synthesis* to gain an understanding of the organic and organometallic methods that are available for accessing thioethers; our searches quickly led us to a comprehensive review devoted to the *Aryl Sulfides* product class (Section 31.14).[1]

From further searches focusing on nickel-catalyzed methodologies for thioetherification, we found that aryl sulfides can be accessed through the cross-coupling of aryl bromides and thiols catalyzed by the pre-formed bis-NHC nickel(0) catalyst **1** (Scheme 1). In the presence of potassium *tert*-butoxide and with heating to 110 °C, several aryl and alkyl thioethers can be obtained in good yields (*Cross-Coupling and Heck-Type Reactions 2*, Section 2.3.1.5.1.1).[2]

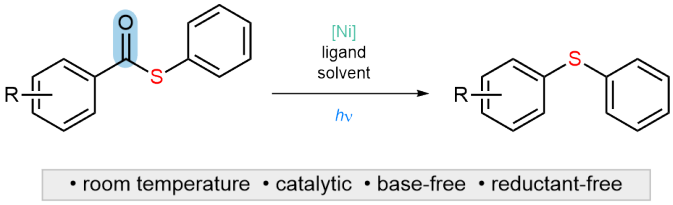


Scheme 1 Representative Examples of Nickel-Catalyzed Thioetherification Reactions Found in *Science of Synthesis*

Under similar conditions, reactions of aryl iodides with thiols can also be catalyzed by the isolable complex **2** to give sulfides with excellent functional-group tolerance and high yields by avoiding potential C–S activation side reactions (Scheme 1). A recyclable NHC-nickel catalyst has also been reported, which was supported on a silica-coated magnetic nanoparticle for ease of recovery. This complex **3** (Scheme 1) was able to catalyze the cross-coupling of aryl iodides and arenethiols in the presence of a base at 100 °C (*N-Heterocyclic Carbenes in Catalytic Organic Synthesis 1*, Section 1.2.4.2.2).[3]

An alternative approach for the formation of C(sp^2)–S bonds is based on nickel/photoredox dual catalysis. In the presence of blue light, alkyl silicates undergo facile homolysis to generate an alkyl radical, which then undergoes hydrogen-atom transfer with an alkanethiol to form a thiyl radical (Scheme 1). These newly formed sulfur-centered radicals then participate in cross-coupling with bromoarenes under the action of the nickel catalyst **4**, to afford thioethers in high yields (*Photocatalysis in Organic Synthesis*, Section 11.7.2).[4]

This comprehensive overview of prior nickel-catalyzed methods for accessing thioethers provided us with an understanding of the limitations in nickel-catalyzed thioether formation, guiding the design of our own methodology. Previously reported approaches typically involve the use of stoichiometric reductants, alkaline conditions, and/or temperatures above 100 °C. Our goal is to develop methods to access a wide range of thioethers via nickel-catalyzed intramolecular light-promoted decarbonylation while avoiding these constraints (Scheme 2).



Scheme 2 Desired Strategy for Accessing Thioethers under Nickel/Photoredox Dual Catalysis

Once we had established the system to study, the next step was to access aryl thioesters that would act as our substrates for the decarbonylative thioetherification. In *Science of Synthesis*, we found a variety of methods to furnish the thioester functionality, mainly through the acylation of thiols (Section 20.8.4.1.2).[5] We were able to synthesize a wide array of thioesters in good to excellent yields by reacting thiols with either pyridine or triethylamine as the base, followed by the addition of the corresponding acid chloride at 0 °C. This method was detailed in the procedure found in Section 20.8.4.1.2.1, which conveniently included relevant warnings about the reagents used in the synthesis as well as the full work-up procedure.

Additionally, *Science of Synthesis* also enabled us to get a solid understanding of the photophysical and photochemical processes involved in light-mediated reactions (*Photocatalysis in Organic Synthesis*, Section 2),[6] as well as the specific roles of nickel in photocatalytic systems (*Photocatalysis in Organic Synthesis*, Section 11).[7]

Conclusion

By using *Science of Synthesis*, we were able to access a curated library of chemical transformations relevant to our project, which helped us save time and resources by narrowing the search to the most representative examples of nickel-catalyzed C–S bond formation.

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