Developing and Exploiting New Photoreductants in Radical Chemistry

Shuo Wu (吴硕)

UNIVERSITAT ROVIRA i VIRGILI

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DOCTORAL THESIS
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Doctoral Thesis
Supervised by Prof. Paolo Melchiorre
ICIQ – Institut Català d'Investigació Química

Tarragona
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Professor Paolo Melchiorre, Professor at the University of Bologna, Italy,

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I STATE that the present study, entitled "Developing and Exploiting New Photoreductants in Radical Chemistry", presented by Shuo Wu for the award of the degree of Doctor of Philosophy, has been carried out under my supervision at the Institut Català d'Investigació Química (ICIQ).

Tarragona, 30 August, 2024

Doctoral Thesis Supervisor

Prof. Paolo Melchiorre

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List of Publications

Some of the results presented in this thesis have been published:

- **Wu, S.**; Melchiorre, P. "Photochemical Synthesis of Thioesters from Aryl Halides and Carboxylic Acids." *Angew. Chem. Int. Ed.* **2024**, e202407520.
- **Wu, S.**; Wong, T.H.-F.; Righi, P.; Melchiorre, P. "Photochemical Organocatalytic Synthesis of Thioethers from Aryl Halides and alcohols." *J. Am. Chem. Soc.* **2024,** *146*, 5, 2907–2912.
- **Wu, S.**;[+] Schiel, F.;[+] Melchiorre, P. "A General Light-Driven Organocatalytic Platform for the Activation of Inert Substrates." *Angew. Chem. Int. Ed.* **2023**, 62, e202306364.
- Zhou, W.; **Wu, S.**; Melchiorre, P. "Tetrachlorophthalimides as Organocatalytic Acceptors for Electron Donor–Acceptor Complex Photoactivation." *J. Am. Chem. Soc.* **2022**, 144, 20, 8914–8919.

[+] These authors contributed equally

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Chapter I

General Overview

The main focus of this doctoral thesis was the development of novel strong photoreductants capable of activating generally inert substrates through a single-electron transfer (SET) mechanism. Our overarching plan was to identify organic catalysts or intermediates that, upon excitation with visible light, could access a highly reducing excited state and subsequently act as potent SET reductants to activate a diverse range of inert compounds towards radical formation. Here, we introduce the basic concepts of photochemistry, illustrating how the light excitation of organic molecules can alter their reactivity, including the formation of strong reductants. This chapter discusses pioneering contributions that highlight the effectiveness of photochemical activation in radical-based transformations, which are not feasible under thermal conditions. It provides the background that has motivated this research.

1.1 Photochemistry

Photochemistry studies the chemical effects of light interacting with matter.[1] According to the Grotthuss–Draper law, "*only the light absorbed is effective in producing a photochemical change*." This means that a molecule must absorb a photon to reach an electronically excited state and undergo a photochemical reaction. The quantum mechanical description of matter also supports this principle, claiming that molecules exhibit quantized energy levels ranging from their low energy 'ground states' to a number of higher-order states. Upon absorbing light with adequate energy, an electron in a molecule can undergo transition from the highest occupied molecular orbital (HOMO, Figure 1.1.a) to its lowest unoccupied molecular orbital (LUMO), thereby bringing the molecule into an electronically excited state. In this process, the molecule has gained a specific amount of energy (E, the energy of the photon) to overcome the energy gap between the excited state E_f and the ground state E_i. This energy is

[1] Balzani, V., Ceroni, P., Juris, A. "Photochemistry and Photophysics: Concept, Research and Applications" Weinheim, Wiley-VCH, **2014**.

directly proportional to the frequency of the absorbed light ν, according to Planck's equation (*h* is the Planck's constant).

$$E = h \cdot \nu = E_f - E_i$$

The wave functions Ψ are used to describe electronic states, with Ψ_i referring to the ground state and Ψ_f to the excited state (Figure 1.1.b).

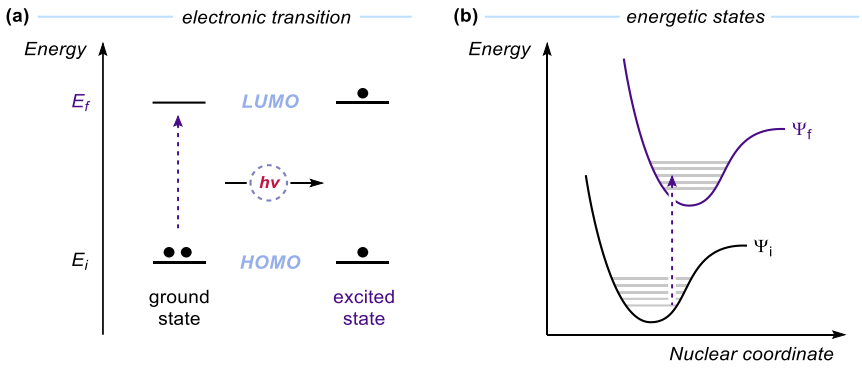

Figure 1.1. (**a**) Energy of the absorbed photon promotes the transition of an electron from the highest occupied molecular orbital (HOMO) to the lowest unoccupied molecular orbital (LUMO). (**b**) The electronic transition from the ground state Ψ_i to the excited state Ψ_f. Grey lines represent different rotation-vibrational levels.

Upon electronic transition, a molecule displays completely different chemical properties from its ground state. Therefore, an excited molecule can be regarded as a distinct chemical entity.[2] A variety of photophysical events occurs in the electronically excited state. For instance, the excited molecule can return to the ground state S_0 through thermal relaxation between vibrational levels ($S_1 \rightarrow S_0$, *non-radiative deactivation*, Figure 1.2). Furthermore, transition to ground state from different excited states (S_1: *singlet and* T_1: *triplet*) can lead to re-emission of a photon, releasing less energy than its incident counterpart ($S_1 \rightarrow S_0$, fluorescence; $T_1 \rightarrow S_0$, phosphorescence).[3] Such mechanism can also be applied for the bimolecular photochemical manifold, in which single-electron transfer (SET) or energy transfer (EnT) take place between the excited molecule and electron or energy acceptors,

[2] Albini, A., Fagnoni, M. "Photochemically Generated Intermediates in Synthesis" John Wiley & Sons, **2013**.

[3] Lakowicz, J. R. "Principles of Fluorescence Spectroscopy" Springer, **2006**.

resulting in activated radical species that offer new reactivity patterns unavailable under traditional thermal activation.

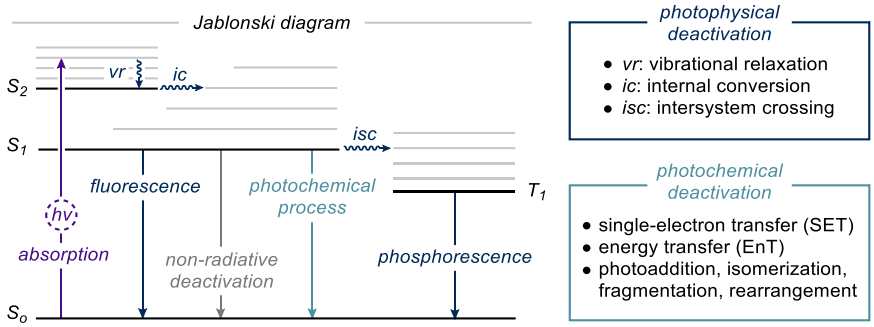

Figure 1.2. Photophysical and photochemical processes on a Jablonski diagram. *S*: singlet state; *T*: triplet state.

The origins of photochemistry can be traced back to the 18th century,[4] when Ciamician and Silber used sunlight to perform transformations of organic molecules in their pioneering studies.[5] However, organic photochemistry did not become a mainstream research field for a long time. This was mainly because the need of energetic ultraviolet (UV) light typically required for the photochemical activation of colorless substrates. Indeed, most organic compounds cannot absorb visible light. High-energy UV irradiation often led to inefficient and non-selective reactions, limiting the range of possible transformations. Additionally, the need for specialized equipment further restricted the widespread application of photochemistry.

The emergence of colored metal-based photocatalysts, capable of mediating the interactions between visible light and colorless substrates, has provided a strong impetus for the development of photochemical transformations (Figure 1.3). Independent reports from

[4] (a) Roth, H. D. "The Beginnings of Organic Photochemistry." *Angew. Chem., Int. Ed.* **1989**, *28*, 1193–1207; (b) König, B. "Chemical Photocatalysis", Berlin/Boston, Walter de Gruyter GmbH, 2013.

[5] (a) Ciamician, G.; Silber, P. "Chemische Lichtwirkungen" *Ber. Dtsch. Chem. Ges.* **1910**, *43*, 45; (b) Ciamician, G. "The Photochemistry of the Future." *Science*, **1912**, *926*, 385–394.

MacMillan, [6] Yoon, [7] and Stephenson [8] highlighted the utility of tris(bipyridine)ruthenium(II) complex [$Ru(bpy)_3^{2+}$],[9] which was previously used mainly for water splitting applications,[10] as an effective photocatalyst for mediating SET processes triggered by visible light, thereby generating radicals under mild conditions. Since then, the use of photoredox catalysts in organic synthesis has sparked a resurgence in radical chemistry. As cheaper, more sustainable, and environmentally benign alternatives, organic photocatalysts, including colored organic dyes (e.g., methylene blue[11] and eosin Y[12]), are also applied widely for radical generation.[13] In addition to their ready availability and low cost, these organic catalysts are often biocompatible and can be easily functionalized to adjust their spectroscopic and redox properties. Importantly, these photocatalysts require only inexpensive and readily available LED illumination for their activation, which has significantly contributed to the widespread development of the photoredox catalysis field.

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[6] Nicewicz, D. A.; MacMillan, D. W. C. "Merging Photoredox Catalysis with Organocatalysis: The Direct Asymmetric Alkylation of Aldehydes." *Science* **2008**, *322*, 77–80.

[7] Ischay, M. A.; Anzovino, M. E.; Du, J.; Yoon, T. P. "Efficient Visible Light Photocatalysis of [2+2] Enone Cycloadditions." *J. Am. Chem. Soc.* **2008**, *130*, 12886–12887.

[8] Narayanam, J. M. R.; Tucker, J. W.; Stephenson, C. R. J. "Electron-Transfer Photoredox Catalysis: Development of a Tin-Free Reductive Dehalogenation Reaction." *J. Am. Chem. Soc.* **2009**, *131*, 8756–8757.

[9] Paris, J. P.; Brandt, W. W. "Charge Transfer Luminescence of a Ruthenium(II) Chelate." *J. Am. Chem. Soc.* **1959**, *81*, 5001–5002.

[10] Balzani, V.; Juris, A. "Photochemistry and Photophysics of Ru(II) Polypyridine Complexes in the Bologna Group. From Early Studies to Recent Developments." *Coord. Chem. Rev.* **2001**, *211*, 97−115.

[11] Pitre, S. P.; McTiernan, C. D.; Ismaili, H.; Scaiano, J. C. "Mechanistic Insights and Kinetic Analysis for the Oxidative Hydroxylation of Arylboronic Acids by Visible Light Photoredox Catalysis: A Metal-Free Alternative." *J. Am. Chem. Soc.* **2013**, *135*, 13286–13289.

[12] Neumann, M.; Füldner, S.; König, B.; Zeitler, K. "Metal-Free, Cooperative Asymmetric Organophotoredox Catalysis with Visible Light." *Angew. Chem., Int. Ed.* **2011**, *50*, 951–954.

[13] Nicewicz, D. A.; Nguyen, T. M. "Recent Applications of Organic Dyes as Photoredox Catalysts in Organic Synthesis." *ACS Catal.* **2014**, *4*, 355−360.

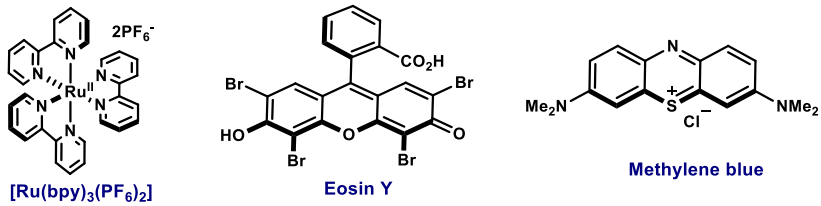

Figure 1.3. Applied photocatalysts for radical generation.

1.2 Direct Excitation of Organic Molecules

Photoredox catalysis is one of the significant achievements of modern photochemistry. However, relying on an external photocatalyst is not the only approach to harnessing radical chemistry. For a long time, direct excitation of organic molecules was the dominant approach in synthetic photochemistry. One example is the Paternò-Buchi reaction,[14] a light-driven [2+2] cycloaddition between an aldehyde **1** and an olefin **2** (Figure 1.4). The irradiation by UV light promotes the electronic transition ($\Psi_i \rightarrow \Psi_f$), bringing the aldehyde **1** into the excited state. This excitation enables the [2+2] cycloaddition to proceed, highlighting an early example of the synthetic potential of photochemistry.

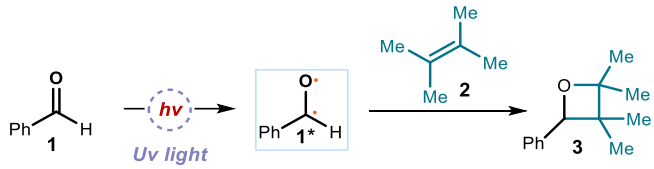

Figure 1.4. Paternò-Büchi reaction for the synthesis of oxetanes.

In the context of photochemistry enabled by direct excitation, our research group recently discovered that certain organocatalytic intermediates can absorb visible light to reach an electronically excited state, thereby enabling entirely different chemical processes compared to their ground-state reactivity. Interestingly, these intermediates showed a bathochromic shift in their UV-vis spectra compared to their progenitors, which permits the selective

[14] Büchi, G.; Inman, C. G.; Lipinsky, E. S. "Light-catalyzed Organic Reactions. I. The Reaction of Carbonyl Compounds with 2-Methyl-2-butene in the Presence of Ultraviolet Light." *J. Am. Chem. Soc.* **1954**, *76*, 4327–4331.

irradiation of the intermediate in the presence of the starting materials.[15] In 2013, it was discovered that enamines **I**, formed by the condensation of a chiral amine catalyst with aldehydes **1**, can interact with electron-poor benzyl bromides **4a** to form a ground-state aggregate (Figure 1.5a). This interaction causes a color change in the solution from colorless to bright yellow, indicating the formation of an electron donor-acceptor (EDA) complex.[16] In contrast to the individual components, which were transparent to visible light (aldehydes **1**, **4a**, and the amine catalyst), these complexes exhibited a bathochromic shift in their UV-vis spectra, allowing for selective excitation with visible light. Irradiation of the EDA complex promoted an intra-complex SET, ultimately releasing the benzylic radical **II**, which was trapped by the ground-state chiral enamine **I** to give the enantio-enriched chiral product **5a**.

Interestingly, when other radical precursors (**4b**, **4c**) were used, the formation of EDA complex was not observed (Figure 1.5b).[17] Nevertheless, enamine **I** alone could absorb in the near-UV region, reaching an excited-state **III***, which acts as a strong photo-reductant (estimated E(**III**$^{\cdot+}$/**III***) ~ −2.50 V versus Ag/AgCl). This excited state can reduce radical precursors, promoting the formation of radical **IV**. Subsequently, the radical was trapped by the ground-state enamine **I** following a similar mechanistic pathway to that proposed for EDA complex activation. Mechanistic investigations revealed that this transformation relied on a self-propagating radical chain mechanism. This study offered an example of how photoexcitation can significantly enhance the reduction power of excited molecules.

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[15] Silvi, M.; Melchiorre, P. "Enhancing the Potential of Enantioselective Organocatalysis with Light." *Nature* **2018**, *554*, 41–49.

[16] Arceo, E.; Jurberg, I. D.; Álvarez-Fernández, A.; Melchiorre, P. "Photochemical Activity of a Key Donor–Acceptor Complex Can Drive Stereoselective Catalytic α-alkylation of Aldehydes." *Nat. Chem.* **2013**, *5*, 750–756.

[17] (a) Silvi, M., Arceo, E., Jurberg, I. D., Cassani, C., Melchiorre, P. "Enantioselective Organocatalytic Alkylation of Aldehydes and Enals Driven by the Direct Photoexcitation of Enamines." *J. Am. Chem. Soc.* **2015**, *137*, 6120–6123. (b) Filippini, G., Silvi, M., Melchiorre, P. "Enantioselective Formal α-methylation and α-benzylation of Aldehydes by Means of Photo-Organocatalysis." *Angew. Chem. Int. Ed.* **2017**, *56*, 4447–4451.

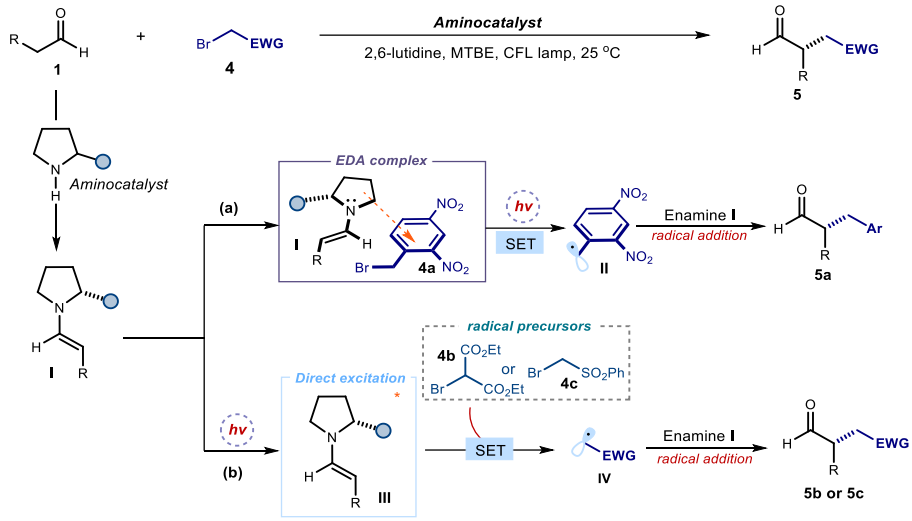


Figure 1.5. (**a**) Photochemical stereoselective alkylation of aldehydes promoted by the excitation of EDA (electron donor-acceptor) complexes. (**b**) Direct photoexcitation of enamine **I** that acts as a strong photoreductant. MTBE: Methyl *tert*-butyl ether.

The discovery of the photochemistry of enamine intermediates encouraged our group to explore the excited-state behavior of other established aminocatalytic intermediates. It was surmised that an electron-deficient iminium ion **V** may become a strong excited-state photo-oxidant upon irradiation (Scheme 1.6).[18] Acid-promoted condensation of cinnamaldehyde derivatives **6** and a chiral aminocatalyst led to the formation of the iminium ion **V**. We found that the excited iminium ion can induce the SET oxidation of benzyl silanes **7**, leading to the generation of the benzyl radical **VI** and the chiral allylic radical **VII**. A radical coupling then forged the new C-C bond while setting the stereogenic center. The direct excitation of iminium ions was used to activate different radical precursors, enabling a range of asymmetric transformations. Overall, this work highlighted how the direct excitation of organocatalytic intermediates can unlock new reactivity by generating radicals.

[18] Silvi, M.; Verrier, C.; Rey, Y. P.; Buzzetti, L.; Melchiorre, P. "Visible-Light Excitation of Iminium Ions Enables the Enantioselective Catalytic β-Alkylation of Enals." *Nat. Chem.* **2017**, *9*, 868–873.

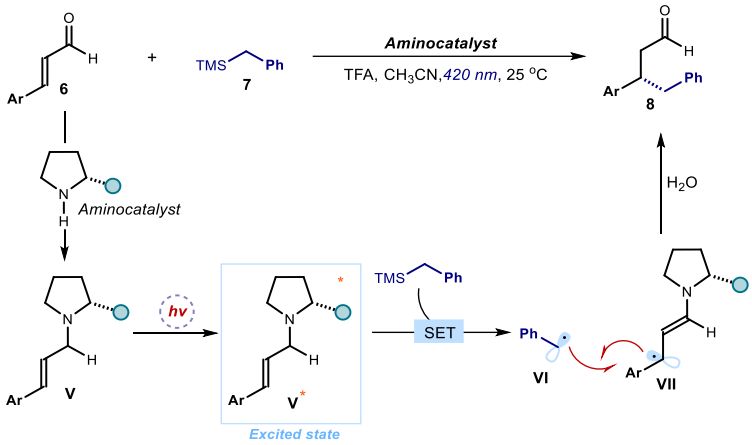


Figure 1.6. Photochemical β-alkylation of cinnamaldehyde derivatives enabled by the direct excitation of chiral iminium ions.

1.3 General Objectives

The activation of typically inert organic compounds via SET reduction is a significant goal in synthetic chemistry. This doctoral thesis focused on studying and developing novel photochemical strategies to activate a wide range of such compounds and generate radical species. The objective was to utilize these radicals to facilitate synthetically valuable transformations, enabling the construction of useful chemical bonds. To achieve this target, we designed and developed organic catalysts and intermediates that, upon light excitation, access a highly reducing excited state and subsequently function as potent SET reductants.

1.3.1 A General Light-Driven Organocatalytic Platform for the Activation of Inert Substrates

In chapter II, we introduce a simple indole thiolate organocatalyst **C** that becomes a potent reductant upon excitation.[19] Activating relatively inert substrates, such as fluoro- and chloro-arenes, alkyl chlorides, and unsubstituted arenes, via SET reduction is difficult due to their strong covalent bonds and low reduction potentials. Although a few strategies are available for the reduction of certain functional groups, each method typically targets only

[19] Wu, S.; Schiel, F.; and Melchiorre, P. "A General Light-Driven Organocatalytic Platform for the Activation of Inert Substrates". *Angew. Chem. Int. Ed.* **2023**, *62*, e202306364.

specific substrates. To develop a general and practical protocol based on a single photocatalyst capable of activating a wide variety of inert substrates, we identified a highly reducing anionic indole thiolate organocatalyst **C**. Upon excitation with visible light, this catalyst can consistently achieve the activation of inert C–F, C–Cl, and C–O bonds, as well as the Birch-type reduction of unfunctionalized arenes, all through SET reduction (Figure 1.7).

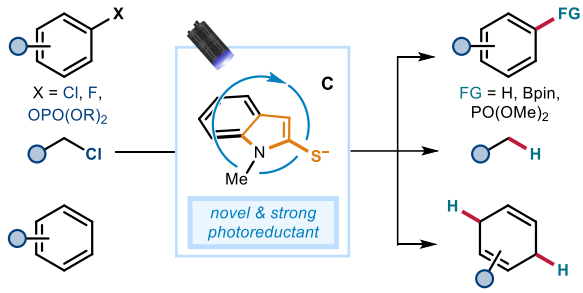


Figure 1.7. The new indole-thiolate photocatalyst suitable for the reduction of a wide range of difficult-to-activate molecules.

1.3.2 Photochemical Synthesis of Thioethers from Aryl Chlorides and Alcohols

Chapter III presents a photochemical, organocatalytic approach to synthesizing thioethers by integrating novel radical chemistry with an established polar deoxythiolation process. Leveraging the strongly reducing anionic indole thiolate organocatalyst **C**, which we previously designed for generating aryl radicals, we developed a thiol-free organocatalytic method that couples aryl chlorides **9** with alkyl alcohols **10** under mild conditions, producing a diverse array of aryl alkyl thioethers **11** (Figure 1.8). A key aspect of this method was the discovery that 1,1,3,3-tetramethylthiourea **12** can serve as a simple sulfur source, intercepting aryl radicals generated through SET activation of aryl chlorides **9**. The subsequent SET oxidation forms aryl isothiouronium ions **IX**, known polar intermediates in the thiol-free synthesis of thioethers via deoxythiolation with nucleophilic alcohols. Formation of **IX** under photochemical conditions allows for an intersection with the deoxythiolation pathway, leading directly to thioethers in a mild and selective manner.

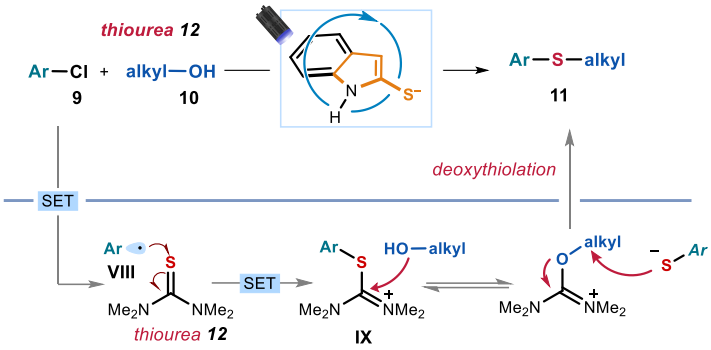


Figure 1.8. Photochemical organocatalytic synthesis of thioethers from aryl chlorides and alcohols

1.3.3 Photochemical Synthesis of Thioesters from Aryl Halides and Carboxylic Acids

Chapter IV introduces a thiol-free protocol for synthesizing a diverse array of thioesters, which are significant motifs in various natural products.[20] Traditional methods for their preparation predominantly rely on thiols, which often possess undesirable traits including unpleasant odor, limited commercial variety, and air instability. Building on our findings from Chapter III, where we demonstrated that isothiouronium salt **IX** can be easily generated by trapping aryl radicals with 1,1,3,3-tetramethylthiourea **12**, we aimed to extend this strategy to thioester synthesis by substituting alcohols with carboxylic acids as nucleophiles in the deoxythiolation path. Surprisingly, we discovered that 1,1,3,3-tetramethylthiourea **12** could be directly excited with light (Figure 1.9). Unlike the previous study, this protocol is centered on the direct excitation of 1,1,3,3-tetramethylthiourea **12** and its versatile role as both a sulfur source and a photoreductant. It facilitates the generation of aryl radicals via SET activation of aryl halides **13**, which are then trapped to form reactive isothiouronium ions **IX**. These intermediates, through the well-established polar deoxythiolation process, lead to the formation of the desired thioesters **15** under mild conditions.

[20] Wu, S.; Melchiorre, P. "Photochemical Synthesis of Thioesters from Aryl Halides and Carboxylic Acids". *Angew. Chem. Int. Ed.* 2024, *62*, e202306364.

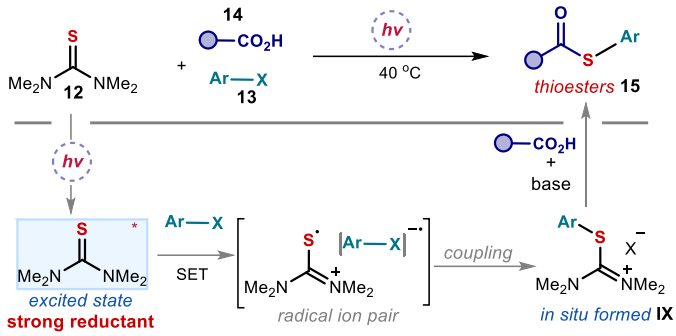


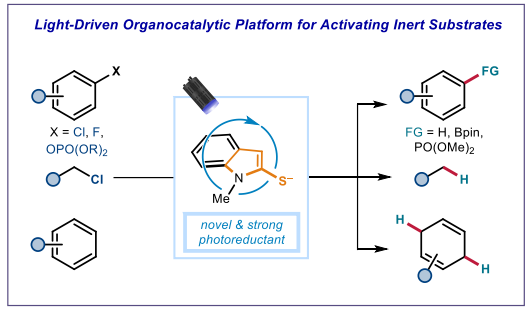
Figure 1.9. Photochemical synthesis of thioethers from aryl halides and carboxylic acids.

Chapter II

A General Light-Driven Organocatalytic Platform for the Activation of Inert Substrates

Target

To develop a new powerful photoreductant that, through single electron transfer reduction, can activate a variety of inert bonds, including strong C-F, C-Cl, C-O bonds, as well as perform Birch-type reductions of unfunctionalized arenes.



Tools

An indole thiolate catalyst, generated in situ upon deprotonation of a readily available cyclic thioamide pre-catalyst, which can be excited by 405 nm light to achieve a highly reducing excited state for the activation of inert substrates.[1]

2.1 Introduction

The activation of inert substrates by single-electron transfer (SET) reduction, including fluoro- and chloro-arenes, alkyl chlorides, and unsubstituted arenes, is difficult due to their strong bond dissociation energy (BDE) and highly negative reduction potentials (E_{red} < -2.5 V vs. SCE, see Figure 2.1a).[2] For instance, aryl chlorides **1** and fluorides **2** would be useful

[1] The project discussed in this chapter has been conducted in collaboration with Florian Schiel. I contributed to the conception of the catalyst design and modification, explored the substrate scope of the reaction, and conducted the mechanistic investigations. This study has been published: Wu, S.; Schiel, F.; and Melchiorre, P. "A General Light-Driven Organocatalytic Platform for the Activation of Inert Substrates". *Angew. Chem. Int. Ed.* **2023**, *62*, e202306364.

[2] (a) Amii, H.; Uneyama, K. "C−F Bond Activation in Organic Synthesis". *Chem. Rev.* **2009**, *109*, 2119–2183; (b) Cheng, L. J.; Mankad, N. P. "C–C and C–X coupling reactions of unactivated alkyl

precursors[3] for the generation of reactive aryl radicals **I**, as they are readily available. However, they have been scarcely employed for this purpose. Their activation generally requires strongly reducing alkali metals, transition metal complexes, or electrochemical methods.[4] While effective, these methods often involve harsh conditions, the use of flammable compounds, and the formation of undesired products. Therefore, it is desirable to develop a versatile and efficient strategy for the activation of **1** and **2** under mild conditions.

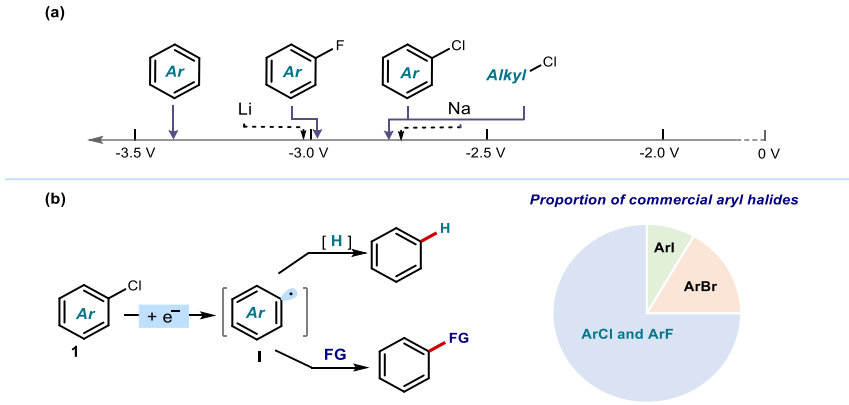


Figure 2.1. (a) Abundant but relatively inert radical precursors and their reduction potentials. **(b)** Overview of aryl radical application and the proportion of commercial aryl halides: the sum of aryl chlorides and fluorides accounts for more than 80%.[3]

Over the past years, photoredox catalysis has emerged as an effective technology for generating radicals under mild conditions.[5] In such systems, the energy of visible light is

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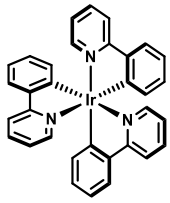
electrophiles using copper catalysis". *Chem. Soc. Rev*. **2020**, *49*, 8036–8064; (c) Rabideau, P. W.; Marcinow, Z. *Organic Reactions*, **1992**, 1–334.

[3] Huang, L.; Ackerman, L. K. G.; Kang, K.; Parsons, A. M.; Weix, D. J. "LiCl-Accelerated Multimetallic Cross-Coupling of Aryl Chlorides with Aryl Triflates". *J. Am. Chem. Soc.* **2019**, *141*, 10978−10983.

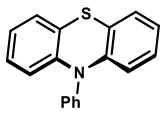
[4] Yan,M.; Kawamata, Y.; Baran, P. S. "Synthetic Organic Electrochemical Methods Since 2000: On the Verge of a Renaissance". *Chem. Rev*. **2017**, *117*, 13230–13319.

[5] (a) Yoon, T. P.; Ischay, M. A.; Du, J. "Visible light photocatalysis as a greener approach to photochemical synthesis". *Nat. Chem.* **2010**, *2*, 527−532. (b) Narayanam, J. M. R.; Stephenson, C. R. J. "Visible light photoredox catalysis: applications in organic synthesis". *Chem. Soc. Rev*. **2011**, *40*, 102−113. (c) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. "Visible Light Photoredox Catalysis with Transition Metal Complexes: Applications in Organic Synthesis". *Chem. Rev.* **2013**, *113*, 5322−5363.

used to enable photoredox catalysts to access their excited states, which have enhanced redox properties. These excited states facilitate SET events to activate substrates. However, traditional photocatalysts are limited by a relatively low reducing power (> –2.0 V, Figure 2.2), and therefore cannot activate relatively inert substrates.



fac-Ir(ppy)$_3$
Ered (Ir^{III}/Ir^{II}) = -2.19 V
*Eox ($Ir^{IV}/*Ir^{III}$) = -1.73 V



*EoxS^1 ($PTh^+/*PTh$) = -2.10 V
Eox (PTh^+/PTh) = +0.68 V

Figure 2.2. Redox potentials of some traditional photoredox catalysts.

Recently, innovative light-driven systems have been developed to overcome this limitation, providing effective methods for inert bond activation.[6] One of these methods involves the photoexcitation of radical anions, which enables the catalysts to achieve significantly high reducing power (Figure 2.3a). This mechanism primarily includes two patterns based on the generation of anionic radical intermediates (**PC**$^{\bullet-}$):

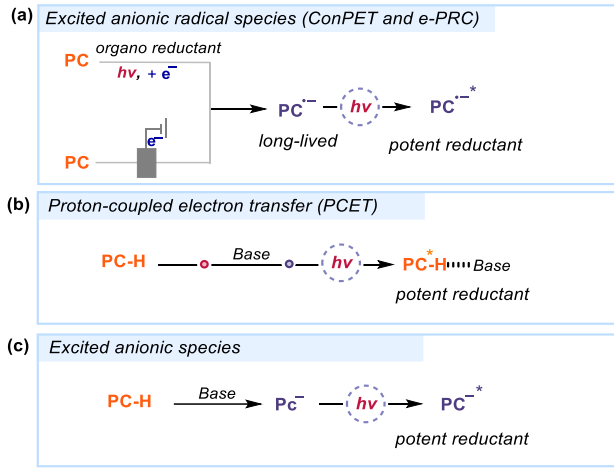
1) *Consecutive Photoinduced Electron Transfer (ConPET)*: This process relies on the use of reducing excited-state photocatalysts in combination with sacrificial organic reductants (Figure 2.3a, upper panel);

2) *Electrochemically Mediated Photoredox Catalysis (e-PRC)*: This involves the electrochemical cathodic reduction of ground-state photocatalysts (Figure 2.3a, lower panel). The central aspect of this approach is that the resulting transient radical anions are relatively stabilized and long-lived. This stability allows them to absorb visible light and reach an electronically excited state with a strong reducing character. Photoexcitation of radical anions was applied for the activation of aryl and alkyl chlorides, and arenes (Figure 2.3d).

In a different approach, a strategy that relies on the mechanism of proton-coupled electron transfer (PCET) between external Brönsted bases and photocatalysts was used to enhance the

[6] Liao, L.-L.; Song, L.; Yan, S.-S.; Ye, J.-H.; Yu, D.-G. "Highly reductive photocatalytic systems in organic synthesis". *Chem.* **2022**, *4*, 512−527.

reducing power of photocatalysts (Figure 2.3b), enabling the reduction of aryl chlorides. Photoexcitation of organic anionic intermediates, generated in situ upon deprotonation of stable catalysts, has also been found to be a powerful tool for the reductive activation of inert compounds (Figure 2.3c-d).[7] Compared to their neutral precursors, organic anions usually experience a significant bathochromic shift in their absorption spectra. This new absorption profile, which can be attributed to π-π* transitions, allows them to absorb visible light.



(d) Applications of recent photocatalytic strategies for the inert compound activation

substrate	ConPET	e-PRC	PCET	excited-state anions
Aryl-Cl	✓	✓	✓	✓
Alkyl-Cl	✓	✗	✗	✓
Aryl-F	✗	✗	✗	✓
Birch reduction	✓	✗	✗	✗

Figure 2.3. Recent photoredox strategies to enable highly reducing activities. **(a)** Excitation of anionic radicals. **(b)** Proton-coupled electron transfer processes. **(c)** Excitation of anionic species. PC: photocatalyst.

While these methodologies permit the reduction of relatively inert substrates, they are restricted to the activation of one or a few specific substrates. Therefore, the development of a general and practical protocol based on a simple catalyst capable to activate a large variety of inert substrates is desirable. In this chapter, we describe the development of a highly reducing anionic organocatalyst that, upon activation with light, can consistently activate an

[7] (a) Schmalzbauer, M.; Marcon, M.; König, B. "Excited State Anions in Organic Transformations". *Angew. Chem. Int. Ed*. **2021**, *60*, 6270–6292; (b) Wang, S.; Wang, H.; König, B. "Light-Induced Single-Electron Transfer Processes involving Sulfur Anions as Catalysts". *J. Am. Chem. Soc*. **2021**, *143*, 15530–15537.

array of strong chemical bonds through SET reduction. Specifically, we identified that a simple indole thiolate, generated in situ upon deprotonation of a readily available cyclic thioamide catalyst, could access a highly reducing excited state under light irradiation (Figure 2.4).

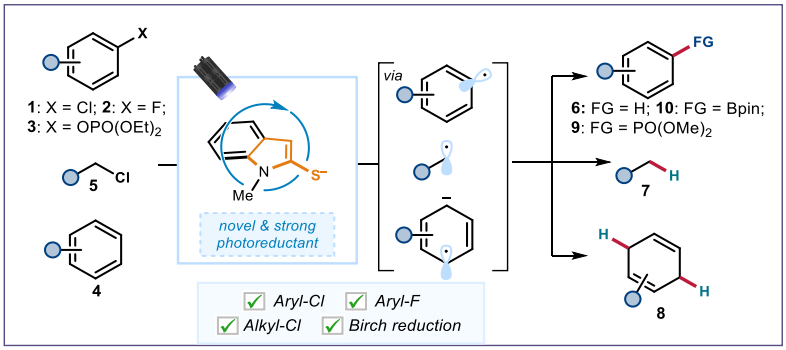


Figure 2.4. A new highly reducing excited-state thiolate catalyst for the SET activation of relatively inert compounds.

Previous photochemical methodologies for activating inert substrates will be detailed in the following section, with particular focus on the activation of strong chemical bonds within substrates with negative reduction potentials (E_{red} < -2.5 V vs. SCE).

2.2 Background

2.2.1 Photoexcitation of Radical Anions for Inert Substrate Activation

Consecutive photoinduced electron transfer (ConPET) is a powerful photochemical strategy for the activation of inert chemical bonds. In 2014, König[8] used an organic dye, namely *N*,*N*-bis(2,6-diisopropylphenyl)perylene3,4,9,10-bisdicarboximide (PDI), as photocatalyst. Upon excitation, PDI was capable of reducing a wide range of aryl halides **1**, including electron-poor aryl chlorides, to release aryl radicals **I** (Figure 2.5). Mechanistically, it was proposed that PDI absorbed the first photon to reach an excited state, which was then quenched via SET by a sacrificial reductant (e.g., Et_3N) to deliver the anionic radical state **II** of the photocatalyst. Subsequent absorption of another photon by **II** produced the highly reductive

[8] Ghosh, I.; Ghosh, T.; Bardagi, J. I.; König, B. "Reduction of Aryl Halides by Consecutive Visible Light-Induced Electron Transfer Processes." *Science* **2014**, *346*, 725−728.

species **III**, which was proposed as the actual SET reductant for the activation of aryl halides **1**.

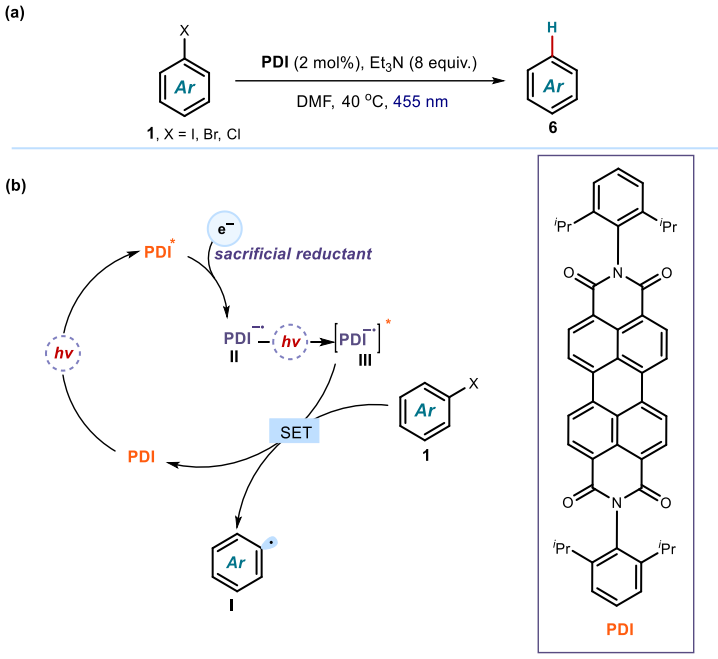


Figure 2.5. (a) Photochemical activation of aryl halides using **PDI** as catalyst. **(b)** Proposed mechanism for the ConPET (consecutive photoinduced electron transfer) process. DMF: dimethylformamide. PC: photocatalyst.

While effective, this PDI-based method could not affectively reduce electro-rich aryl bromides and chlorides. To address this shortcoming, in 2020 Nicewicz[9] reported that neutral acridine radical **IV**, upon photoexcitation under 390 nm, can reach an excited state and act as a super electron donor **V** (E = -3.36 V). Radical **IV** was generated from SET reduction of excited acridinium salts (Mes-Acr-BF_4). This system was effective not only for the hydrodehalogenation of electron-rich aryl chlorides **1** but also for the reductive deprotection of *N*-tosyl amines **11**. Mechanistic studies indicated that the formation of a twisted intramolecular charge-transfer species **V** enabled the population of higher-energy

[9] MacKenzie, I. A.; Wang, L.; Onuska, N. P. R.; Williams, O. F.; Begam, K.; Moran, A. M.; Dunietz, B. D.; Nicewicz, D. A. "Discovery and Characterization of an Acridine Radical Photoreductant." *Nature* **2020**, *580*, 76−80.

excited states upon excitation, leading to the observed potent photoreducing behavior (Figure 2.6).

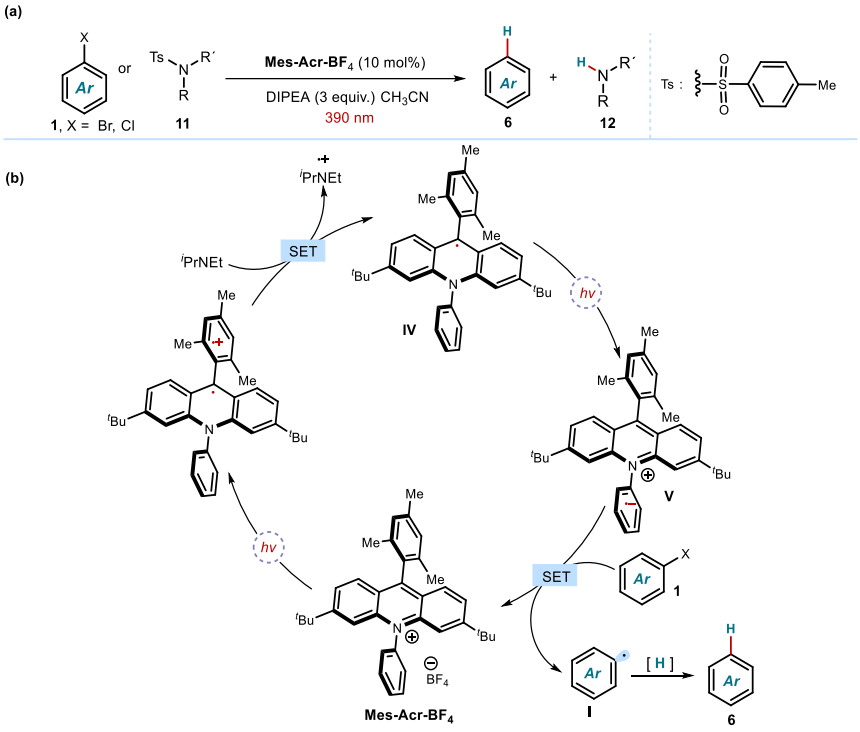


Figure 2.6. (a) Photoexcited **Mes-Acr-BF$_4$** for inert substrates activation. **(b)** Proposed mechanism for the photoexcitation of the acridine radical intermediate **IV**. DIPEA: *N,N*-diisopropylethylamine.

To further expand the activation of inert aryl chlorides **1**, alternative catalysts capable of initiating the ConPET process have been explored. These catalysts exhibit strong reducing power in their excited anionic radical state (Figure 2.7a-c).[10] In the resulting protocols, the generated aryl radicals are captured by various radical acceptors, such as pyrrole, phosphate,

[10] (a) Neumeier, M.; Sampedro, D.; Majek, M.; de la Pena O'Shea, V. A.; Jacobi von Wangelin, A.; Perez-Ruiz, R. "Dichromatic Photocatalytic Substitutions of Aryl Halides with a Small Organic Dye." *Chem. - Eur. J.* **2018**, *24*, 105−108.; (b) Chmiel, A. F.; Williams, O. P.; Chernowsky, C. P.; Yeung, C. S.; Wickens, Z. K. "Non-Innocent Radical Ion Intermediates in Photoredox Catalysis: Parallel Reduction Modes Enable Coupling of Diverse Aryl Chlorides." *J. Am. Chem. Soc.* **2021**, *143*, 10882−10889. (c) Xu, J.; Cao, J.; Wu, X.; Wang, H.; Yang, X.; Tang, X.; Toh, R. W.; Zhou, R.; Yeow, E. K. L.; Wu, J. "Unveiling Extreme Photoreduction Potentials of Donor-Acceptor Cyanoarenes to Access Aryl Radicals from Aryl Chlorides." *J. Am. Chem. Soc*. **2021**, *143*, 13266−13273.

B_2Pin_2, or alkenes, enabling the construction of C-C, C-P, and C-B chemical bonds from readily accessible feedstocks. A common step in these reactions is the use of sacrificial reductants, which are indispensable for the reductive quenching of excited photocatalysts to yield long-lived anionic radical intermediates.

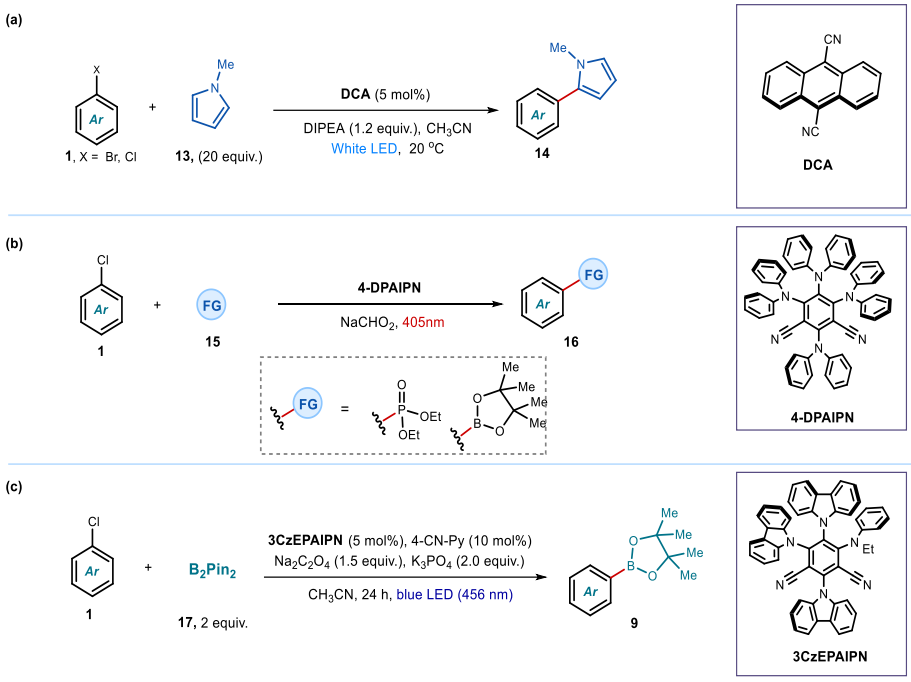


Figure 2.7. Alternative photocatalysts based on the ConPET mechanism for aryl halide activation and functionalization. **(a) DCA** (9,10-dicyanoanthracene) photocatalyst; **(b) 4-DPAIPN** (2,4,5,6-tetrakis(diphenylamino)isophthalonitrile) photocatalyst;**(c) 3CzEPAIPN** (2,4,5-tri(9H-carbazol-9-yl)-6-(ethyl(phenyl)amino)isophthalonitrile) photocatalyst. DIPEA: *N,N*-diisopropylethylamine.

Electrochemistry has also proven to be a useful and clean method for generating radicals, avoiding the use of toxic or expensive oxidants or reductants. Synergistic electrochemistry and photoredox catalysis has emerged as a promising field,[11] with electron primed photoredox chemistry (e-PRC) being useful for the activation of inert substrates.[12] In this

[11] Barham, J. P.; König, B. "Synthetic Photoelectrochemistry." *Angew. Chem., Int. Ed.* **2020**, *59*, 11732−11747.

[12] (a) Liu, J.; Lu, L.; Wood, D.; Lin, S. "New Redox Strategies in Organic Synthesis by Means of Electrochemistry and Photochemistry." *ACS Cent. Sci.* **2020**, *6*, 1317−1340; (b) Huang, H.; Steiniger,

approach, ground-state photocatalysts undergo cathodic reduction to produce radical anions, which then absorb photons to generate highly reducing excited radical anions. These species are capable of reducing recalcitrant substrates with low current density, offering an efficient approach to radical formation (Figure 2.8a).

In 2020, Lin, Lambert, and coworkers[13] reported a photoexcited dicyanoanthracene (DCA) radical anion, generated in situ from the cathodic reduction of ground-state DCA, as a strong electron-donor in photo-electrochemistry. Time-dependent density functional theory calculations revealed a low oxidation potential below –3.2 V for the excited DCA anionic radical, which enabled the reduction of the aryl halides (below –2.9 V) to deliver aryl radicals **I**. These radicals could then be effectively trapped by B_2pin_2, Sn_2Me_6, or (hetero)arenes (Figure 2.8b). Similarly, Wickens[14] reported that the naphthalenemonoimide catalyst (**NpMI**) can undergo the e-PRC process, exhibiting a strong redox potential below –2.90 V, suitable for the functionalization of aryl chlorides (Figure 2.8c).

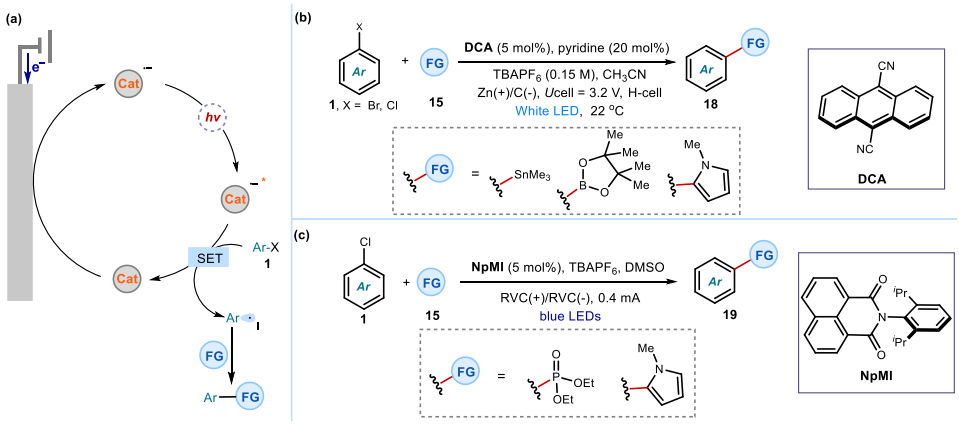


Figure 2.8. Reductive electrophotocatalysis for inert substrate activation via e-PRC mechanism. **(a)** General mechanism of e-PRC; **(b) DCA** (9,10-dicyanoanthracene) photocatalyst in combination with electrochemistry; **(c) NpMI (**naphthalenemonoimide analog) photocatalyst in combination.

K. A.; Lambert, T. H. "Electrophotocatalysis: Combining Light and Electricity to Catalyze Reactions." *J. Am. Chem. Soc.* **2022**, *144*, 12567−12583.

[13] Kim, H.; Kim, H.; Lambert, T.; Lin, S. "Reductive Electrophotocatalysis: Merging Electricity and Light to Achieve Extreme Reduction Potentials." *J. Am. Chem. Soc.* **2020**, *142*, 2087−2092.

[14] Cowper, N.; Chernowsky, C.; Williams, O.; Wickens, Z. "Potent Reductants via Electron-Primed Photoredox Catalysis: Unlocking ArylChlorides for Radical Coupling." *J. Am. Chem. Soc.* **2020**, *142*, 2093−2099.

with electrochemistry. $TBAPF_6$: tetrabutylammonium hexafluorophosphate; DMSO: dimethyl sulfoxide

Photoexcitation of radical anions has provided efficient methods for activating a wide range of inert substrates. Despite these advancements, the activation of aryl fluorides has not been achieved using this approach.

2.2.2 Proton-Coupled Electron Transfer Pattern for Inert Substrate Activation

Proton-coupled electron transfers (PCETs) play a crucial role in many significant biological redox processes and serve as a general mechanism for substrate activation in organic synthesis.[15] The classical mechanism of PCETs, involving a concerted exchange of protons and electrons, provides an alternative approach for the homolytic activation of σ-bonds, effectively overcoming energetic limitations (Figure 2.9a). This concerted elementary step has also inspired the development of advanced photochemical reduction processes, wherein the interaction typically occurring between the base and the substrate is instead directed towards the photocatalyst (Figure 2.9b). This interaction enhances the photocatalyst's redox potential, providing a promising method for the reduction of inert compounds.

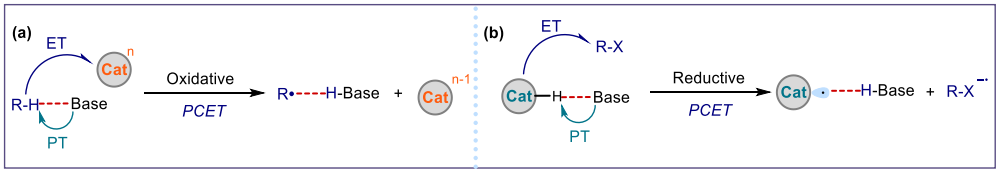


Figure 2.9. Proton-coupled electron transfer (PCET) mechanism. **(a)** Base/substrate interaction for σ-bonds oxidation; **(a)** Base/photocatalysts interaction for σ-bonds reduction. ET: Electron transfer; PT: Proton transfer.

In 2020, Larionov[16] disclosed an efficient photocatalytic platform that enables borylation of electron-rich derivatives, including phenols, anilines, and chloroarenes (Figure 2.10). The reaction is catalyzed by phenothiazine (**PTH**), a commercially available organic catalyst,

[15] Gentry, E. C.; Knowles, R. R. "Synthetic Applications of Proton-Coupled Electron Transfer." *Acc. Chem. Res*. **2016**, *49*, 1546−1556.

[16] Jin, S.; Dang, H. T.; Haug, G. C.; He, R.; Nguyen, V. D.; Nguyen, V. T.; Arman, H. D.; Schanze, K. S.; Larionov, O. V. "Visible Light-Induced Borylation of C−O, C−N, and C−X Bonds." *J. Am. Chem. Soc*. **2020**, *142*, 1603−1613.

which mediates the previously unachievable light-induced reduction of phenol derivatives with highly negative reduction potentials through a PCET mechanism. Mechanistic studies highlighted the crucial role of the interaction between the photocatalyst and the base.

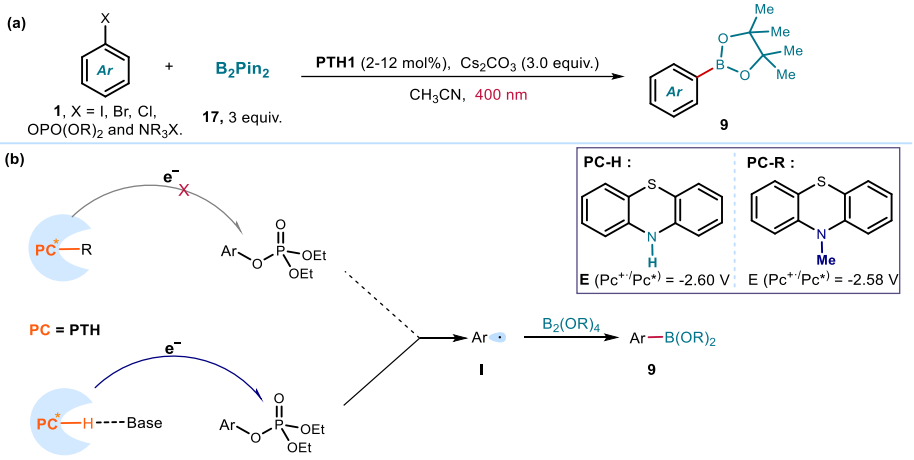


Figure 2.10. (a) PCET enabled photoinduced borylation of inert aryl derivatives. **(b)** Proposed mechanism.

Later on, a carbazole-based organic photocatalyst was reported for the activation of the alkyl aryl ether C−O bonds (E_{red} < −2.6 V vs SCE), which afforded the phenol derivatives **21** and alkyl radicals **VI** (Figure 2.11).[17] The reaction was proposed to occur via SET from the excited-state carbazole to the substrate involving a PCET mechanism that diminishes the required energy barrier.

[17] Yabuta, T.; Hayashi, M.; Matsubara, R. "Photocatalytic Reductive C−O Bond Cleavage of Alkyl Aryl Ethers by Using Carbazole Catalysts with Cesium Carbonate." *J. Org. Chem.* **2021**, *86*, 2545−2555.

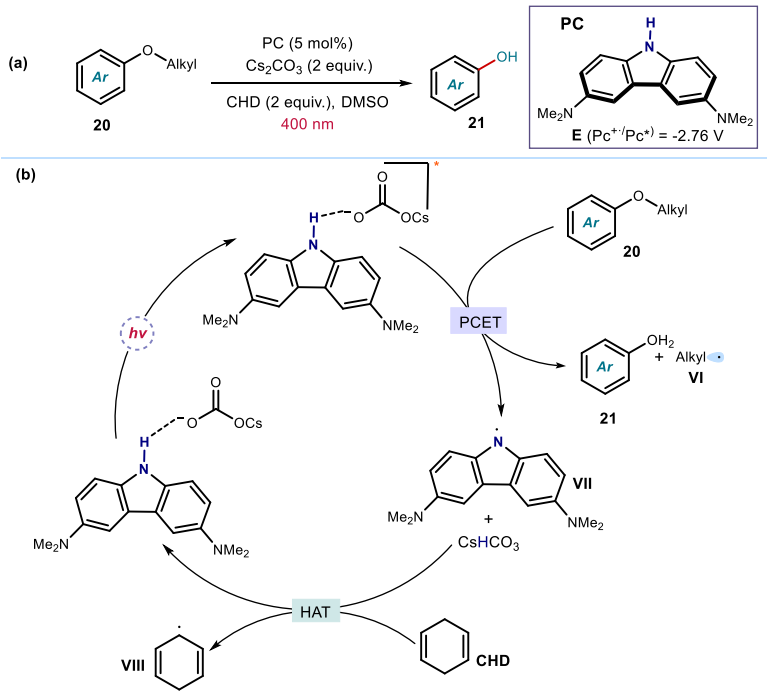


Figure 2.11. (a) Visible-light-induced photocatalytic C−O bonds cleavage of ethers. **(b)** Proposed mechanism.

PCET has been proven effective for increasing the reducing power of photocatalysts,[18] revealing a novel direction for the activation of inert substrates.

2.2.3 Photoexcitation of Organic Anionic Species for Inert Substrate Activation

Closed-shell organic anions have been shown to reach a significant redox potential upon light excitation, suitable for promoting SET reactions.[19] This pronounced absorption can be attributed to π-π* transitions, enabling the organic anions to absorb visible light effectively (Figure 2.12).

[18] Bortolato, T.; Simionato, G.; Vayer, M.; Rosso, C.; Paoloni, L.; Benetti, E. M.; Sartorel, A.; Leboeuf, D.; Dell'Amico, L. "The Rational Design of Reducing Organophotoredox Catalysts Unlocks Proton-Coupled Electron-Transfer and Atom Transfer Radical Polymerization Mechanisms." *J. Am. Chem. Soc.* **2023**, *145*, 1835−1846.

[19] Schmalzbauer, M.; Marcon, M.; König, B. "Excited State Anions in Organic Transformations". *Angew. Chem. Int. Ed*. **2021**, *60*, 6270–6292

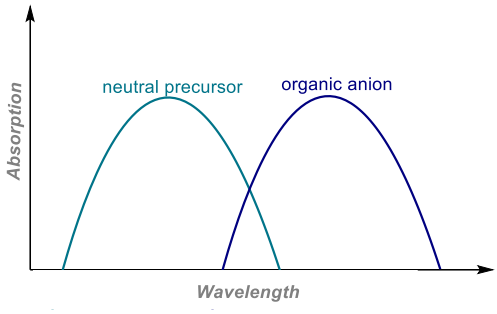


Figure 2.12. The absorption spectrum of organic anions and their neutral precursors.

Additionally, anionic species are considered superior electron donors compared to their neutral forms due to the increased electron-electron repulsion and reduced nuclear attraction.[19] As a result, the excess negative charge facilitates easier electron transfer. Upon photoinduced electron transfer (PET), an excited-state neutral donor (*D) transferring an electron to a neutral ground-state acceptor (A) causes charge separation, resulting in radical ion pairs that are electrostatically attracted, thereby increasing the likelihood of back-electron transfer (BET). Conversely, PET from an anionic excited-state donor to a neutral acceptor can be considered a charge shift, where the resulting products do not experience electrostatic attraction. This lack of attraction allows the products to diffuse freely, thereby reducing the likelihood of BET (Figure 2.13).

Figure 2.13. Charge separation with a neutral donor (left) and charge shift with an anionic donor (right).

The use of anionic species as potent reductants is achieved by direct photoexcitation. Chruma[20a] revealed that the colored azaallyl anion **IX**, a well-defined strong reductant in its ground state,[19b] enabled the reduction of inactive aryl bromides and chlorides **1** upon excitation by visible light, providing an approach for the preparation of 2-azaallyls **23** (major)

[20] (a)Wang, Q.; Poznik, M.; Li, M.; Walsh, P. J.; Chruma, J. J. "2-Azaallyl Anions as Light-Tunable Super-Electron-Donors: Coupling with Aryl Fluorides, Chlorides, and Bromides." *Adv. Synth. Catal.* **2018**, *360*, 2854−2868; (b) Li, M.; Berritt, S.; Matuszewski, L.; Deng, G.; Pascual-Escudero, A.; Panetti, G. B.; Poznik, M.; Yang, X.; Chruma, J. J.; Walsh, P. J. "Transition-Metal-Free Radical C(sp^3)−C(sp^2) and C(sp^3)−C(sp^3) Coupling Enabled by 2-Azaallyls as Super-Electron-Donors and Coupling-Partners." *J. Am. Chem. Soc.* **2017**, *139*, 16327−16333.

and **24**. The process occurs through radical coupling of the generated aryl radical **I** and azaallyl radical **X** (Figure 2.14).

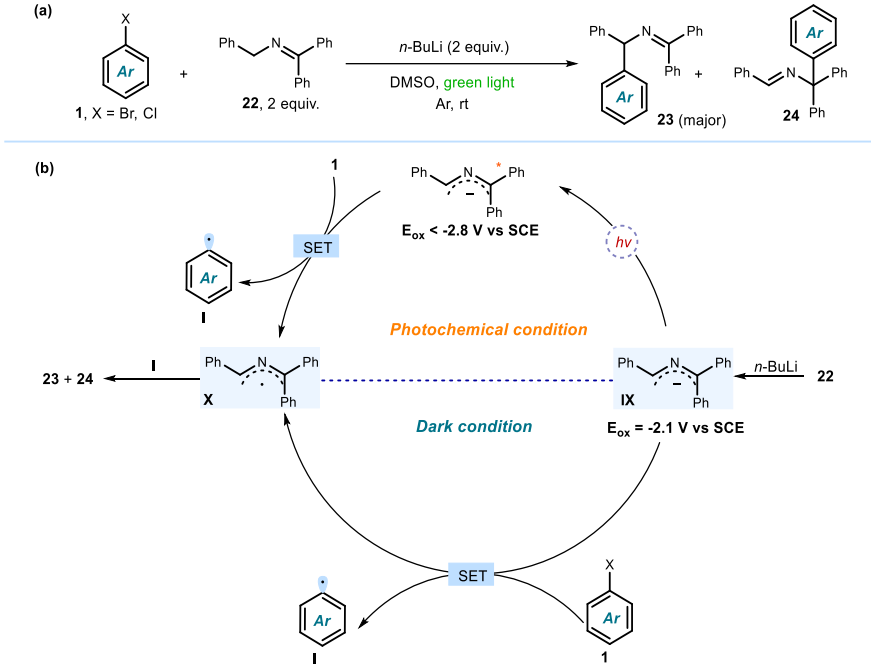


Figure 2.14. **(a)** Arylation of 2-azaallyl anions with non-activated (hetero)- aryl halides. **(b)** Proposed mechanism.

Later, Xia[21] applied another strong photo-reductant, the vinylphenolate anion (E_{ox}* = −2.48 V vs. SCE), generated in situ upon deprotonation of substrate **25**, for a photochemical Heck-type arylation under blue LED illumination. In this system, the addition of aryl radical **I** to the vinyl phenolate furnishes the desired product **26** (Figure 2.15).

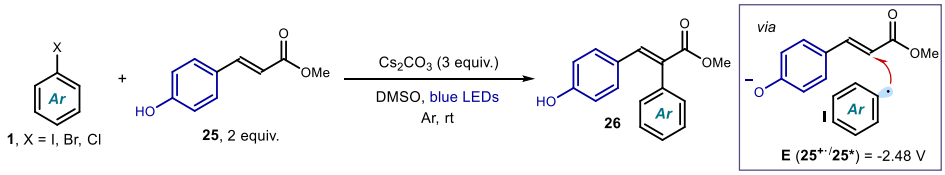


Figure 2.15. Photochemical Heck-type arylation of vinylphenols with (hetero)aryl halides.

[21] Liang, K.; Li, T.; Li, N.; Zhang, Y.; Shen, L.; Ma, Z.; Xia, C. "Redox-Neutral Photochemical Heck-type Arylation of Vinylphenols Activated by Visible Light." *Chem. Sci.* **2020**, *11*, 2130−2135.

This photochemical process was also extended into a catalytic manifold, using substituted 4-phenylphenol as a potent photocatalyst for the activation of aryl halides **1**[22a] and alkyl chlorides **5**.[21b] TEMPO-H was used as the radical trap and hydrogen donor to enable catalyst turn-over. Remarkably, the estimated excited-state oxidation potential (E_{ox} = -3.16 V) of the phenolate **XI** enabled the selective activation of electron-rich aryl and alkyl chlorides in the presence of styrene **27** and TEMPO-H (Figure 2.16). These findings allowed the use of abundant and inexpensive feedstocks as radical precursors in valuable synthetic reactions.

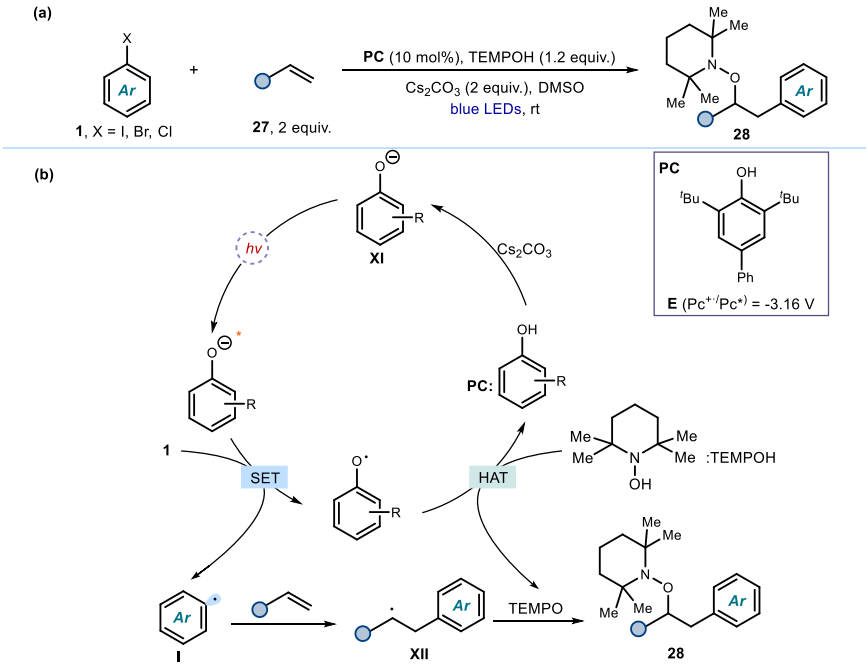


Figure 2.16. **(a)** Phenolate catalyzed oxyarylation under visible light. **(b)** Proposed mechanism.

Other organic anions have been exploited for the photochemical activation of inert aryl halides, expanding beyond the use of substituted phenolates as photocatalysts[23] (Figure

[22] (a) Liang, K.; Liu, Q.; Shen, L.; Li, X.;Wei, D.; Zheng, L.; Xia, C. "Intermolecular Oxyarylation of Olefins with Aryl Halides and TEMPOH Catalyzed by the Phenolate Anion under Visible Light." *Chem. Sci*. **2020**, *11*, 6996−7002; (b) Wei, D.; Li, X.; Shen, L.; Ding, Y.; Liang, K.; Xia, C. "Phenolate Anion-catalyzed Direct Activation of Inert Alkyl Chlorides Driven by Visible Light." *Org. Chem. Front.* **2021**, *8*, 6364−6370.

[23] (a)Liu, C.; Shen, N.; Shang, R. "Photocatalytic Defluoroalkylation and Hydrodefluorination of Trifluoromethyls using o-Phosphinophenolate." *Nat. Commun*. **2022**, *13*, 354; (b) Shen, N.; Li, R.; Liu,

2.17a). Notably, colored *N*-centered anions have proven effective for the reduction of inert aryl chlorides under visible light irradiation[24] (Figure 2.17b). Sulfur-based anionic species (e.g., sulfide, thiolate) have also found applications as electron donors in photochemical transformation. They can either form electron-donor-acceptor (EDA) complexes with substrates[25] or act as photocatalysts with moderate redox potentials.[26] Notably, polysulfide anions have been reported as visible light photoredox catalysts for the reduction of aryl halides, enabling aryl cross-coupling reactions (Figure 2.17c).[27]

C.; Shen, X.; Guan, W.; Shang, R. "Photocatalytic Cross-Couplings of Aryl Halides Enabled by o-Phosphinophenolate and o-Phosphinothiophenolate." *ACS Catal*. **2022**, *12*, 2788−2795.

[24] (a)Singh, V.; Singh, R.; Hazari, A. S.; Adhikari, D. "Unexplored Facet of Pincer Ligands: Super-Reductant Behavior Applied to Transition-Metal-Free Catalysis." *JACS Au.* **2023**, *3*, 1213−1220; (b)Shen, N.; Liu, C.; Zhang, X.; Shang, R. "o-Phosphinodiarylamides as Reductive Photocatalysts for Dehalogenative and Deaminative Cross-Couplings." *ACS Catal*. **2023**,*13*, 11753−11761;(c) Halder, S.; Mandal, S.; Kundu, A.; Mandal, B.; Adhikari, D. "Super-Reducing Behavior of Benzo[b]phenothiazine Anion Under Visible-Light Photoredox Condition." *J. Am. Chem. Soc*. **2023**, *145*, 22403−22412.

[25] (a) Liu, B.; Lim, C.-H.; Miyake, G. M. "Visible-Light-Promoted C-S Cross-Coupling via Intermolecular Charge Transfer." *J. Am. Chem. Soc*. **2017**, *139*, 13616−13619; (b) de Pedro Beato, E.; Spinnato, D.; Zhou, W.; Melchiorre, P. "A General Organocatalytic System for Electron Donor-Acceptor Complex Photoactivation and Its Use in Radical Processes." *J. Am. Chem. Soc.* **2021**, *143*, 12304−12314; (c) Le Saux, E.; Zanini, M.; Melchiorre, P. "Photochemical Organocatalytic Benzylation of Allylic C–H Bonds." *J. Am. Chem. Soc*. **2022**, *144*, 1113–1118.

[26](a) Kobayashi, F.; Fujita, M.; Ide, T.; Ito, Y.; Yamashita, K.; Egami, H.; Hamashima, Y. "Dual-Role Catalysis by Thiobenzoic Acid in Cα-H Arylation under Photoirradiation." *ACS Catal*. **2021**, *11*, 82−87; (b) Le Saux, E.; Georgiou, E.; Dmitriev, I. A.; Hartley, W. C.; Melchiorre, P. "Photochemical Organocatalytic Functionalization of Pyridines via Pyridinyl Radicals." *J. Am. Chem. Soc*. **2022**, *145*, 47-52.

[27] Li, H.; Tang, X.; Pang, J. H.; Wu, X.; Yeow, E. K. L.; Wu, J.; Chiba, S. "Polysulfide Anions as Visible Light Photoredox Catalysts for Aryl Cross-Couplings." *J. Am. Chem. Soc*. **2021**, *143*, 481−487.

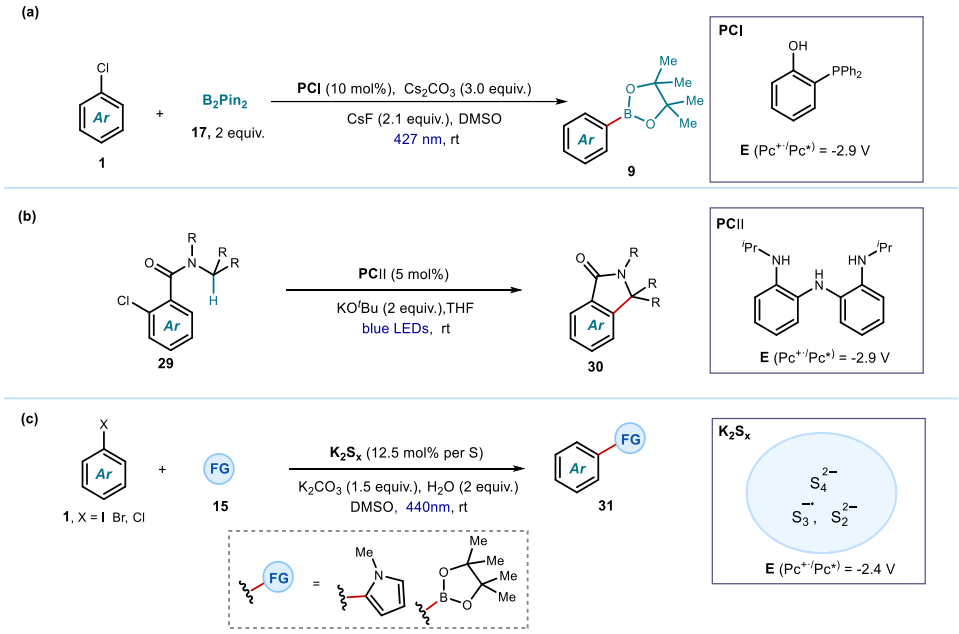


Figure 2.17. Excited-state organic anions for the activation of inert substrates. **(a)** Photoexcited phenolates; **(b)** Photoexcited *N*-center organic anions; **(c)** Photoinduced polysulfide anions.

Beyond the activation of aryl chlorides, photoinduced organic anion catalysis also shows potential towards the reduction of more challenging aryl fluorides **2** without involving pre-activation of C_{aryl}-F bond with transition metals. For example, König[28] has developed a photoinduced thiolate-catalyzed *ipso*-borylation of substituted arenes **1** with B_2pin_2. This approach provides a platform for the activation of strong chemical bonds (C–F, C–O, C–N, and C–S) and their transformation into synthetically valuable boronates. The formation of a charge transfer complex **XIII** was proposed to facilitate the reduction of the substrate, generating the aryl radical **I**. It is suggested that the activation of substrates with C–F, C–O, and C–S bonds by a [B_2pin_2-F^-] adduct plays a crucial role in the photoinduced electron-transfer process (Figure 2.18).

[28] Wang, S.; Wang, H.; König, B. "Photo-Induced Thiolate Catalytic Activation of Inert Caryl-Hetero Bonds for Radical Borylation." *Chem*. **2021**, *7*, 1653−1665.

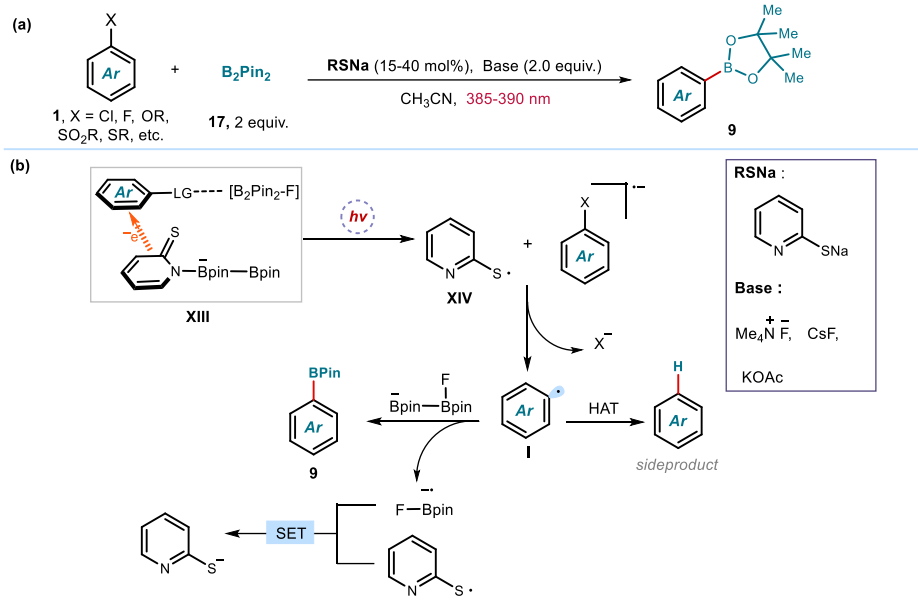


Figure 2.18. **(a)** Photoinduced thiolate-catalytic *ipso*-borylation of substituted arenes. **(b)** Proposed mechanism.

Subsequently, Chen disclosed a method involving light-induced *N*-heterocyclic carbene (NHC) catalysis for the SET reduction of mono-fluoroarenes **2**, which facilitates biaryl cross-couplings.[29] The NHC/*t*BuOK combination gave rise to the highly reducing NHC radical anion complex **XV** that, upon blue light irradiation, promoted the SET activation of C_{aryl}-F bonds (Figure 2.19).

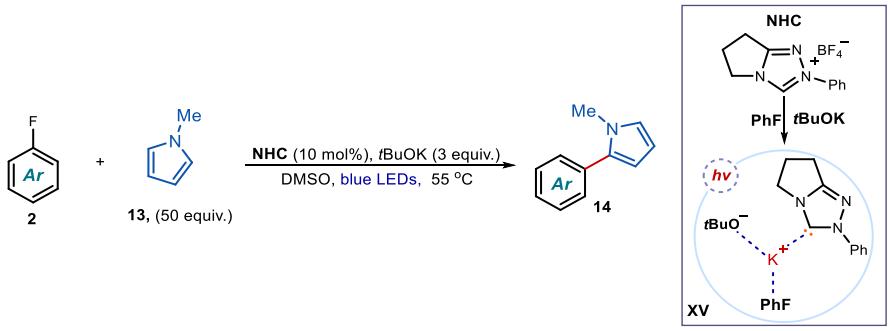


Figure 2.19. Photoinduced NHC-catalyzed biaryl cross-couplings of mono-fluoroarens.

[29] Sheng, H.; Liu, Q.; Zhang, B.-B.; Wang, Z.-X.; Chen, X.-Y. "Visible-Light-Induced N-Heterocyclic Carbene-Catalyzed Single Electron Reduction of Mono-Fluoroarenes." *Angew. Chem. Int. Ed.* **2023**, *62*, e202218468.

Photoexcitation of organic anions has also proven effective for achieving the Birch-type reduction of arens. In 2020, Miyake[30] introduced benzoperylene imide (BPI) as a new organic photoredox catalyst for the Birch reduction at ambient temperature and driven by visible light. In-depth mechanistic investigation[31] revealed that the catalyst BPI underwent thermal degradation, resulting in the formation of a ring-opened imide, which was then deprotonated to produce the actual anionic catalyst responsible for the reduction of arenes (Figure 2.20).

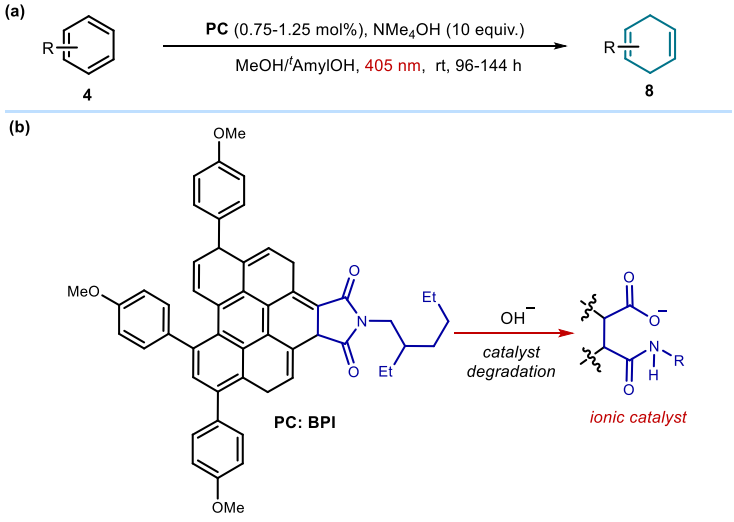


Figure 2.20. **(a)** Visible-light-driven Birch reduction of arenes. (**b**) Degradation of the catalyst. ^{t}AmylOH: 2-Methylbutan-2-ol.

Overall, the combination of organic anions and light facilitated useful synthetic transformations, enabling the synthesis of valuable architectures from simple and readily available feedstocks. In this context, we considered interesting to develop a new, general photochemical platform that leverages organic anions as efficient photocatalysts for activating a broad spectrum of inert compounds.

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[30] Cole, J. P.; Chen, D. F.; Kudisch, M.; Pearson, R. M.; Lim, C. H.; Miyake, G. M. "Organocatalyzed Birch Reduction Driven by Visible Light." *J. Am. Chem. Soc.* **2020**, *142*, 13573−13581.

[31] Sau, A.; Pompetti, N. F.; Green, A. R.; Popescu, M. V.; Paton, R. S.; Miyake, G. M.; Damrauer, N. H. "Mechanistic Investigation of a Photocatalyst Model Reveals Function by Perylene-Like Closed Shell Super-Photoreductant Capable of Reducing Unactivated Arenes." *ACS Catal.* **2024**, *14*, 2252–2263.

2.3 Design and Target of the Project

Inspired by recently reported studies on the use of excited thiolates as potent reductants[27-28] for inert substrates activation, we aimed to identify a new thiolate photocatalyst with potent reducing capability. The target was to develop a general photochemical platform for activating a diverse array of inert compounds. We found that the electron-rich indole thiolate anion **D**, generated in situ upon deprotonation of the cyclic thioamide catalyst **C1**, can access a highly reducing excited state under light irradiation (Figure 2.21). This excited-state reactivity served to activate, by SET reduction, strong C-F, C-Cl, and C-O bonds in both aromatic and aliphatic substrates. This catalytic platform was versatile enough to promote the reduction of generally recalcitrant electron-rich substrates (E_{red}<–3.0 V vs SCE), including arenes that afforded 1,4-cyclohexadienes. The protocol was also useful for the borylation and phosphorylation of inert substrates. Mechanistic studies identified an excited-state thiolate anion as responsible of the highly reducing reactivity. It is worth noting that the pre-catalyst **C1** can be readily prepared through oxygen-sulfur exchange of the commercially available *N*-methyl oxindole.

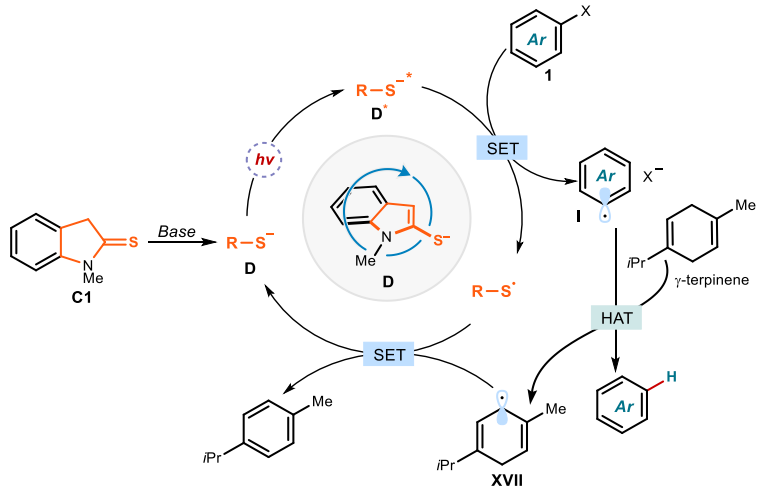


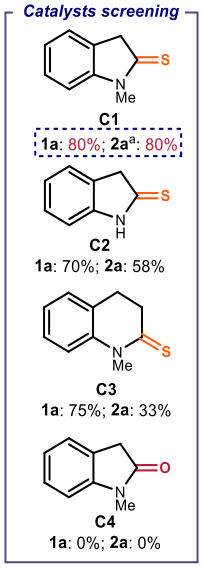
Figure 2.21. Proposed action of our new photoreducant catalyst.

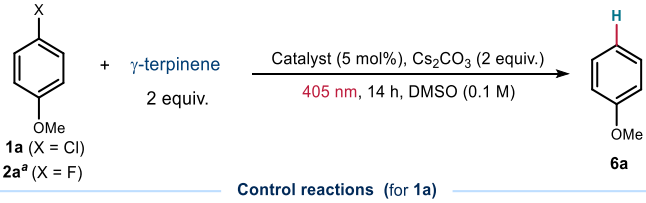
2.4 Results and Discussion

2.4.1 Optimization of the Reaction Conditions and Substrate Scope

To test the reducing efficacy of the excited-state thiolates, we examined cyclic thioamides **C1**–**C4** as catalysts in the hydrodechlorination of 4-chloroanisole **1a** (E_{red} = –2.9 V vs. SCE). The reactions were conducted using 5 mol% of the catalyst, Cs_2CO_3 as the base (3 equiv., needed to form the thiolate anion **D** in situ upon deprotonation), γ-terpinene as hydrogen donor and DMSO as solvent under 405 nm light irradiation (Table 2.1). Cyclic 1-methylindoline-2-thione **C1** offered the best result, affording the anisole product **6a** in 80% yield upon SET activation of the C(sp^2)-Cl bond (Table 2.1, entry 1). Structurally related thioamides **C2**–**3** also catalyzed the dechlorination reaction of **1a**, albeit with slightly diminished yield, while the analogous oxygen-containing catalyst **C4** was ineffective.

Table 2.1. Reaction optimization of the defunctionalisation of aryl chlorides





Control reactions (for 1a)

entry	deviation	[%] yield **3a**[b]
1	none	**80**
2	no catalyst, no light or no base	0
3	no γ-terpinene	30
4	*i*-Pr_2NEt instead of γ-terpinene	50
5	HCO_2Na instead of γ-terpinene, 6 h	70
6	CH_3CN as solvent	75
7	K_3PO_4 or K_2CO_3 as base	70
8	Na_2CO_3 as base	35
9	$NaHCO_3$ as base	0
10	TMG as base	40
11	Cs_2CO_3 (1 equiv.)	60
12	Cs_2CO_3 (0.5 equiv.)	50
13	425 nm irradiation	30

All reactions performed on a 0.2 mmol scale; yield of **6a** determined by ^{1}H NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as the internal standard. [a]γ-terpinene (1 equiv.), 390 nm irradiation, NMP as solvent. [b]NMR yield using 1,3,5-trimethoxybenzene as the internal standard. NMP: N-methyl-2-pyrrolidone.

Control experiments showed that the presence of catalyst, light and the base were all essential for reactivity (Table 2.1, entry 2). The reaction proceeded poorly in the absence of γ-terpinene (Table 2.1, entry 3), while replacement with *i*-Pr_2NEt or sodium formate (HCO_2Na) gave moderate yield (Table 2.1, entries 4-5). Other solvent (CH_3CN) and bases, including K_2CO_3 and K_3PO_4, could be used, but the results did not exceed those obtained with Cs_2CO_3 (Table

2.1, entries 6-10). Decreasing the amount of Cs_2CO_3 from 3 to 0.5 or 1 equiv. resulted in a significant decrease in reactivity. Using a different light for irradiation, namely 425 nm emission, offered low yield of product **6a**.

Notably, we found that our cyclic thioamide catalysts were also effective for the hydrodefluorination of the more challenging 4-fluoroanisole **2a** (E_{red} = <–3.0 V vs. SCE), indicating the powerful reducing ability of our catalysts. With a slight modification of the standard conditions (using 1 equiv. γ-terpinene as the hydrogen donor, NMP as the solvent, and irradiating with a 390 nm Kessil lamp), catalyst **C1** significantly outperformed other analogues in activating 4-fluoroanisole **2a**, yielding 80% of the anisole product **6a**.

Using the conditions described in entry 1 of Table 2.1, we then tested the generality of our light-driven organocatalytic platform (Figure 2.22). We first evaluated the possibility to activate aryl chlorides **1**. A series of difficult-to-reduce electron-rich substrates underwent hydrodechlorination to afford the corresponding arenes in high yields (products **6a–d**). Bis-chloroanisole was doubly-dechlorinated (**6e**) while electron-neutral and electron-deficient aryl chlorides, including the antidepressant drug *moclobemide*, were reduced efficiently (adducts **6f–k**). To further test the generality of organocatalyst **C1**, we then targeted aryl phosphates **3** and alkyl chlorides **5**. These substrates are particularly recalcitrant to SET activation because of their low redox potentials (E_{red} < -2.8 V vs. SCE). Electron-rich and electron-neutral phosphates were reduced in good yields to afford products **6a**, **6h**, **6l**, and **6m**, while primary, secondary, and tertiary alkyl chlorides **5** all afforded the reduced adducts in high yields using sodium formate (HCO_2Na) as hydrogen donor in combination with catalyst **C1** (products **7a–f**).

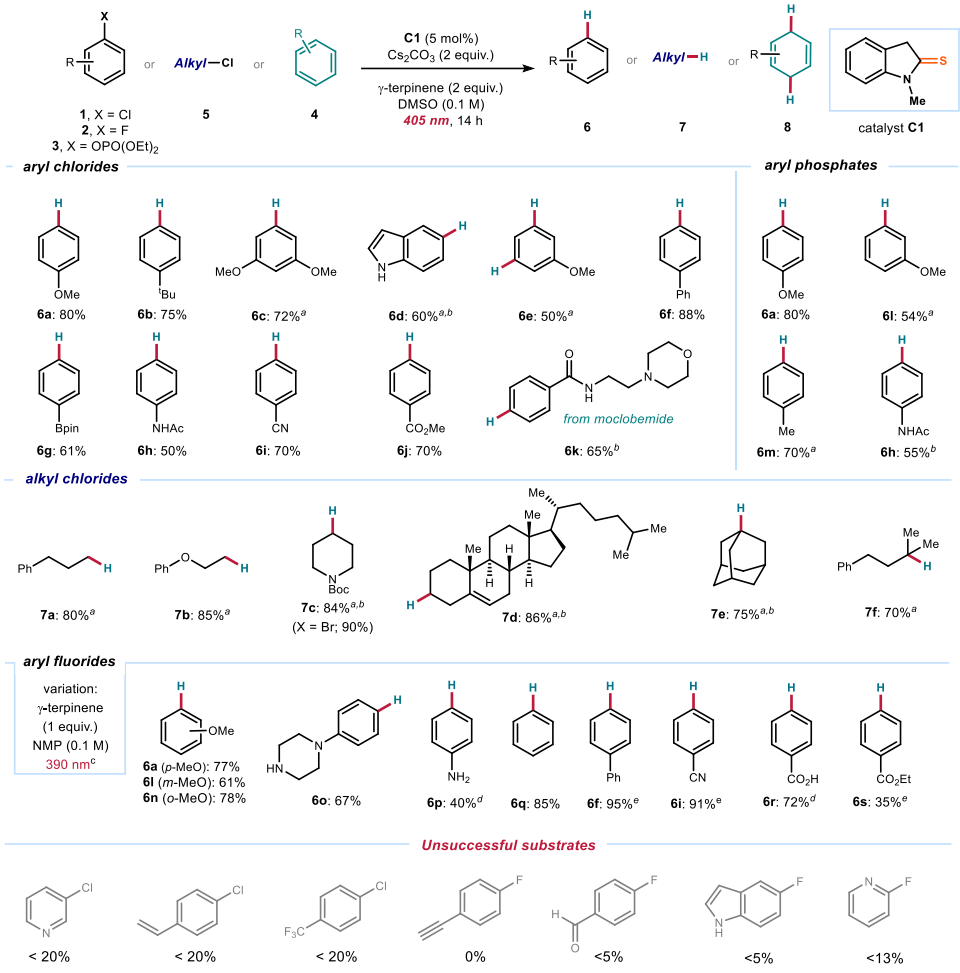


Figure 2.22. Photocatalytic reduction of inert substrates. Reactions performed on a 0.2 mmol scale at 40 °C. Yields of products **6**–**8** measured by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as the internal standard. [a] Performed using HCO_2Na instead of γ-terpinene. [b] Yields of isolated products. [c] Reactions with fluorides **2** performed using a 3-D printed reactor[32] with 390 nm irradiation. [d] Performed in the presence of H_2O (5 equiv.). [e] 40 equiv. of H_2O. NMP: *N*-methyl-2-pyrrolidone.

We then focused on the reductive defunctionalization of aryl fluorides **2**. Their activation is hampered by both the poor leaving group ability of the fluoride and the highly negative reduction potentials (E_{red} < -3 V vs. SCE). Notably, our protocol could achieve the activation

[32] Schiel, F.; Peinsipp, C.; Kornigg, S.; Böse, D. "A 3D-Printed Open Access Photoreactor Designed for Versatile Applications in Photoredox- and Photoelectrochemical Synthesis." *ChemPhotoChem* **2021**, *5*, 431−437.

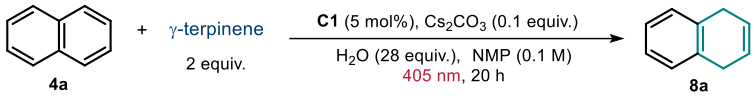
of neutral or electron-rich fluoride substrates under mild conditions, affording the hydrodefluorination products in high yield (adducts **6a**, **6l**, **6o**-**6q**). Interestingly, addition of water allowed us to reduce electron-poor aryl fluorides too, leading to products **6f**, **6i**, **6j** and **6r**. To the best of our knowledge, those substrates were previously beyond the reach of reported photochemical reduction protocols.[33] Synthetically, it is worth noting the tolerance of this highly reducing protocol towards a variety of functional groups, including unprotected amines (adducts **6o**-**6p**), amides (**6h**, **6k**), a carboxylic acid (**6r**), an ester (**6j**), a nitril (**6i**), and a boron-derivative (**6g**). On the other hand, substrates containing readily reducible functional groups, such as vinyl, trifluoromethyl, formyl and carbonyl or pyridine substituents, were not compatible.

2.4.2 Birch-Type Reduction

We also evaluated the potential of catalyst **C1** to promote the light-driven Birch reduction of arenes **4**. This process can be complicated by the absence of leaving groups in the aromatic substrates, which may lead to unproductive back-electron transfer. Using naphthalene **4a** as the model substrate, a solvent mixture of NMP/H_2O, and a catalytic amount of Cs_2CO_3 as the base, we successfully reduced naphthalene to the corresponding 1,4-dihydronaphthalene **8a** (Table 2.2, entry 1). Control experiments demonstrated the crucial roles of catalyst **C1**, the base, and light. Additionally, the inclusion of H_2O significantly improved the yield, as it served as a proton source (Table 2.2, entries 2-7).

[33] Toriumi, N.; Yamashita, K.; Iwasawa, N. "Metal-Free Photoredox-Catalyzed Hydrodefluorination of Fluoroarenes UtilizingAmide Solvent as Reductant." *Chem.-Eur. J.* **2021**, *27*, 12635−12641.

Table 2.2. Reaction optimization for the Birch-Type Reduction



entry	deviation	[%] yield **8a**
1	none	70
2	no catalyst **C1**	0
3	no Base	0
4	no light	0
5	HCO_2Na instead of γ-terpinene	0
6	no adding H_2O	40
7	10 equiv. H_2O	57
8	DMSO as solvent	30

All reactions were performed on a 0.2 mmol scale; yield of **8a** determined by ^{1}H NMR analysis of the crude reaction mixture by comparison with 1,3,5-trimethoxybenzene as internal standard.

We then explore the versatility of this light-driven platform for the Birch reduction of unactivated arenes **4** (Figure 2.23). We successfully activated naphthalene derivatives and phenanthrene, leading to the desired di-hydro products **8a-8f** in good yields. *N*-Methyl indole, anisole and benzene were also converted to the corresponding dienes (adducts **8g-i**). Overall, these results demonstrated that catalyst **C1** can activate, via SET reduction, electron-rich arenes with very negative redox potentials (E_{red} < -3.3 V vs. SCE). Additionally, while other arenes could be activated to afford good conversion under standard conditions, they did not yield the expected products due to deleterious side reactions, such as over-reduction or dimerization (see inset in Figure 2.23).

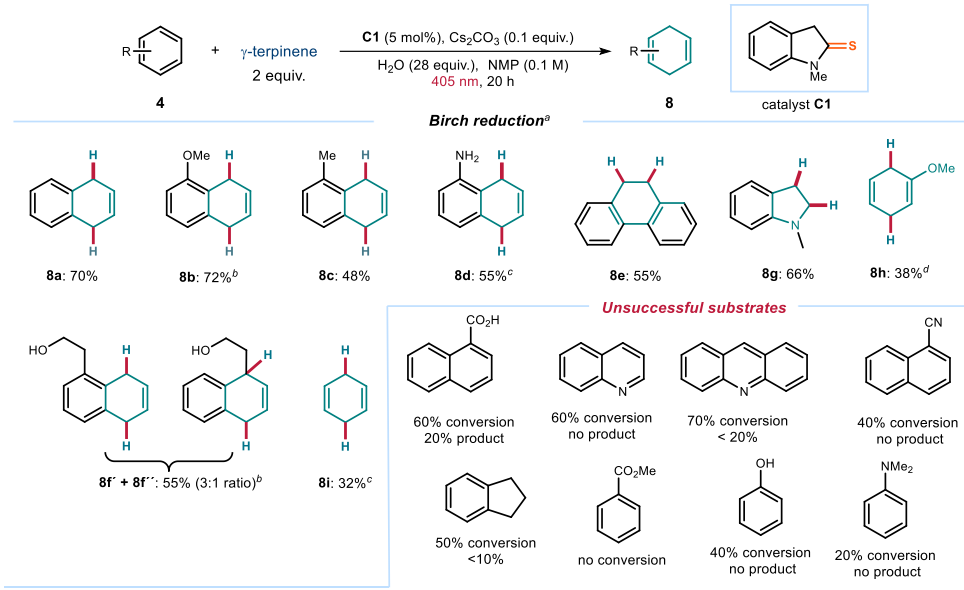


Figure 2.23. All reactions were performed on a 0.2 mmol scale; [a] yield of **8a** determined by ^{1}H NMR analysis of the crude reaction mixture by comparison with 1,3,5-trimethoxybenzene as internal standard. [b] Yields of isolated products. [c] Performed in the absence of H_2O for 20 h. [d] In the absence of H_2O for 6 h; NMP: *N*-methyl-2-pyrrolidone.

2.4.3 Substrate Scope for the Functionalization of Aryl Chlorides

We then used the highly reducing power of catalyst **C1** to functionalize aromatic chlorides (Figure 2.24). Phosphorylation of aryl chlorides **1** using trimethyl phosphite $P(OMe)_3$ was successfully achieved under standard conditions and using HCO_2Na instead of γ-terpenene (detailed optimization studies can be found in Table 2.9 and 2.10 of the Experimental Section). Aryl chlorides with electron-rich substituents at the *ortho*, *meta*, and *para* positions all reacted smoothly to afford the corresponding products **9a-9i**. Electron-neutral (adducts **9j-9m**), electron-poor (**9n-9o**), bicyclic, and heterocyclic (**9p-9u**) moieties were tolerated well. High functional group tolerance was observed, allowing the use of alkyl alcohols (**9h**), amides (**9l**), esters (**9o**), sulfones (**9n**), and amines (**9i**). The chemoselective activation of the C(sp^2)-Cl over C(sp^2)-F bond was demonstrated with the formation of product **9m**, which was formed in 46% yield leaving the C-F bond untouched. To probe the synthetic utility of the protocol, the phosphorylation reaction was conducted on a 5 mmol gram scale leading to product **9a** in 63% yield (680 mg of product **9a** isolated). The organocatalytic platform was also suitable for the borylation of aromatic chlorides using bis(pinacolato)diboron (B_2pin_2),

although a higher catalyst loading was needed (10 mol% of **C1**, Figure 2.25, bottom panel). Here, the use of acetonitrile as solvent minimized a competitive hydrodechlorination reaction. Electron-rich and neutral substrates were effectively converted into the borylated products **10a**-**10f**, while electron-poor aryl chlorides offered only low yields (*p*-CN and *p*-CO_2Me substituents offered less than 20% yield). The more challenging borylation of aryl fluorides was also possible, and products **10a** and **10b** were isolated in moderate yields.

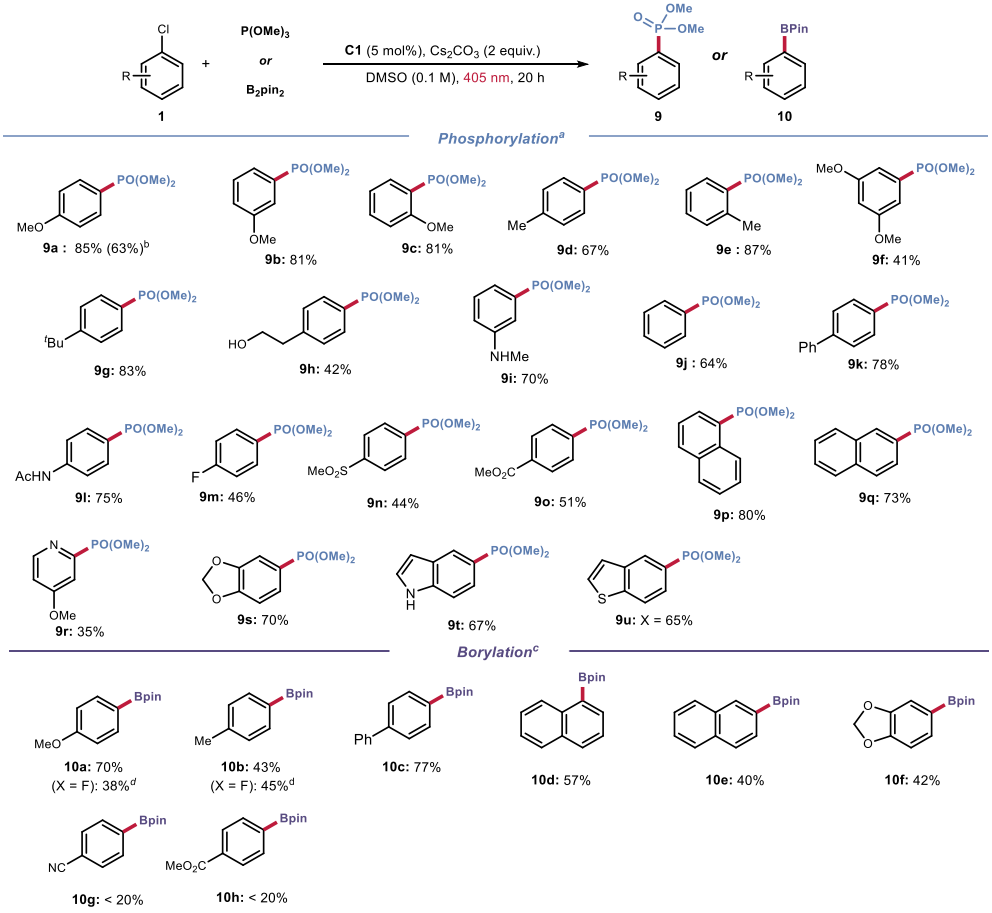


Figure 2.24. Photocatalytic phosphorylation and borylation of aryl chlorides **1**. Reactions performed on a 0.2 mmol scale. Yields refer to isolated product **9** and **10**. [a] Performed using $P(OMe)_3$ (5 equiv.), **C1** (5 mol%), and HCO_2Na (1 equiv.). [b] 5 mmol scale reaction. [c] Performed using B_2pin_2 (3 equiv.), catalyst **C1** (10 mol%) in CH_3CN/DMSO (3:1, 0.5 M) as solvent. [d] Using CH_3CN/NMP (3:1, 0.5 M) as solvent; NMP: *N*-methyl-2-pyrrolidone.

2.4.4 Mechanistic Investigations

To better elucidate our photocatalytic system, we conducted a series of mechanistic experiments.

Characterization of Precatalyst C1 and Thiolate Catalyst D

We confirmed that the thiolate **D** could be readily formed within a few minutes upon efficient deprotonation of cyclic thioamide catalyst **C1** by Cs_2CO_3 (detailed in Figure 2.36 of the Experimental Section), as inferred by ^1H NMR analysis (Figure 2.25a). Absorption spectroscopy investigations indicated that catalyst **C1** does not absorb visible light. However, the addition of Cs_2CO_3, leading to the formation of anion **D**, induced a clear bathochromic shift into the visible region (Figure 2.25b). Upon irradiating a DMSO solution of catalyst **C1** and Cs_2CO_3 (resulting in the in situ formation of **D**) at 350 nm, we detected emission centered at 401 nm (Figure 2.25c). This confirmed that the deprotonated catalyst **D** could access an electronically excited state. From the crossing point of the emission and absorption profiles at 375 nm, a 0-0 transition energy ($E_{0,0}$) of 3.3 eV could be inferred.[34] Next, the ground-state redox properties of the deprotonated catalyst **D** were determined by cyclic voltammetry (Figure 2.25d). A first irreversible oxidation peak was found at +0.01 V vs Ag/AgCl in DMSO, which was assigned to the formation of the resulting sulfur radical.[35] Following the reported equation($(E(\mathbf{Pc}^{\bullet}/\mathbf{Pc}^{*}) = E(\mathbf{Pc}^{\bullet}/\mathbf{Pc}^{-}) - E_{0\text{-}0}(\mathbf{Pc}^{-*})/(\mathbf{Pc}^{-}))$) for determining the redox potential of excited chromophores,[36] the redox potential of the excited thiolate $E(\mathbf{D}^{\bullet}/[\mathbf{D}^{-}]^{*})$ was estimated as –3.38 V vs. SCE. This confirmed that the anion of catalyst **C1** acquires a strongly reducing power upon excitation.

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[34] Buzzetti, L.; Crisenza, G. E. M.; Melchiorre, P. "Mechanistic Studies in Photocatalysis." *Angew. Chem., Int. Ed.* **2019**, *58*, 3730−3747

[35] The non-reversible behaviour of **D** can be rationalised with the fast formation of the S-S dimer once the sulfur radical is formed. We could not isolate the dimer of catalyst **D** but indirect evidence has been collected, see details in Figure 40-42 of the Experimental Section.

[36] Kavarnos, G. J. *Fundamentals of Photoinduced Electron Transfer.* chap. 1, pp. 29, VCH Publishers, **1993**.

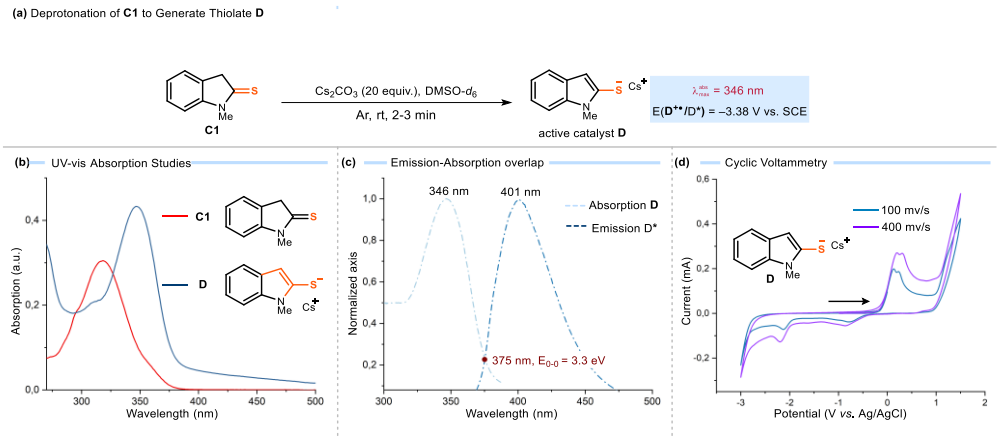


Figure 2.25. Characterizations of the thiolate **D**. **(a)** Deprotonation of **C1** to generate thiolate **D**; **(b)** UV-Vis absorption spectra of catalyst **C1** and thiolate salt **D** (formed in situ treating **C1** with Cs_2CO_3) measured in DMSO; **(c)** Emission of the excited thiolate salt **D*** in DMSO (formed in situ treating **C1** with Cs_2CO_3) upon irradiation at 350 nm and its intercept with the absorption spectrum at 375 nm, with a 0-0 transition energy ($E_{0,0}$) of 3.3 eV; **(d)** Cyclic voltammetry measurements of the thiolate salt **D** carried out in DMSO vs Ag/AgCl at a scan rate of 100 and 400 ms/V.

Reducing Activity of the Excited Thiolate D

We have conducted experiments to confirm that the exited catalyst **D** could activate the substrates via SET. Pre-stirring of the catalyst with Cs_2CO_3 for 30 min, followed by addition of aryl chloride **1a** and γ-terpinene via syringes, gave product **6a** in comparable yield (72%) as the one-pot procedure. No reaction was observed in the absence of base (Figure 2.26). These experiments confirmed that the deprotonated catalyst **D** is the active species.

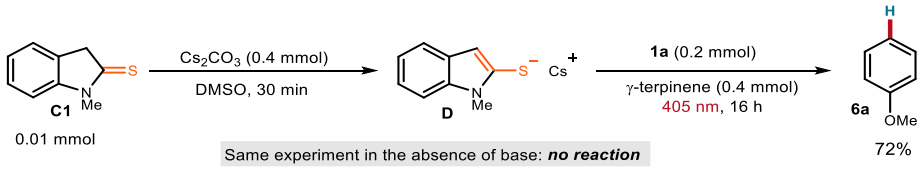


Figure 2.26. Hydrodechlorination of **1a** by pre-stirring catalyst **C1** with Cs_2CO_3.

Stern-Volmer studies also revealed that all the model substrates quenched the emission of the excited anionic catalyst **D*** with the following relative rate: 4-chloroanisole (**1a**)> chloro-N-

boc-piperidine (**5c**) > naphthalene (**4a**) > 4-fluoroanisole (**2a**) (detailed in Figure 2.46-49 of the Experimental Section).

Considering Alternative Mechanisms

Exclusion of EDA complex formation.

It has been reported[37] that thiolates could form electron-donor-acceptor (EDA) complexes with aryl halides. To investigate whether our catalytic thiolate **D** exhibits a similar behavior, we performed absorption spectroscopic studies (Figure 2.27). Our results showed no significant bathochromic shifts upon mixing catalyst **C1**, Cs_2CO_3, and aryl chloride **1a**, indicating that no EDA complexes were formed in the ground state.

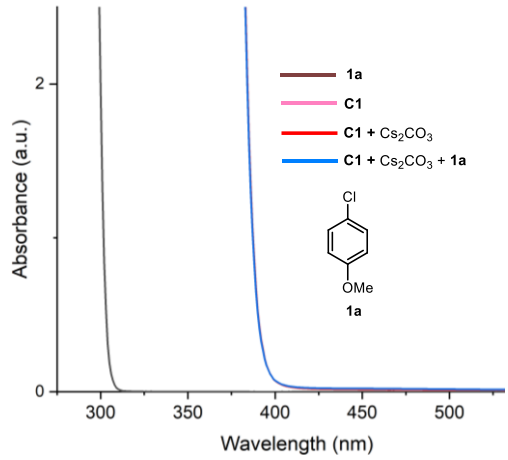


Figure 2.27. Absorption spectra recorded in DMSO of the mixture of catalyst **C1**, Cs_2CO_3 and substrate **1a**; note that the blue and red lines perfectly overlay.

Exclusion of a reduction mechanism enabled by $CO_2^{\bullet-}$

$CO_2^{\bullet-}$ is reported to be a strong reductant (E_{ox} = -2.2 V *vs.* SCE), useful for the cleavage of C-Br, C-Cl, and C-F bonds.[38] Control experiments were conducted to explore whether this

[37] Liu, B.; Lim, C.-H.; Miyake, G. M. "Visible-Light-Promoted C-S Cross-Coupling via Intermolecular Charge Transfer." *J. Am. Chem. Soc.* **2017**, *139*, 13616−13619.

[38] Hendy, C. M.; Smith, G. C.; Xu, Z.; Lian, T.; Jui, N. T. "Radical chain reduction via carbon dioxide radical anion ($CO_2^{\bullet-}$)." *J. Am. Chem. Soc.* **2021**, *143*, 8987−8992.

pathway might be operative in our system, specifically when using HCO_2Na as the hydrogen donor in combination with catalyst **C1**. We compared the reducing ability of $CO_2^{\bullet-}$ with that of catalyst **C1** (Figure 2.28). This comparison was based on literature reports that used a PhSSPh/HCO_2Na mixture as a $CO_2^{\bullet-}$-based reducing system.[39] $CO_2^{\bullet-}$ showed good reducing ability for electron-poor aryl chlorides and alkyl bromides affording low yield but complete conversion of the substrates. However, neither electron-rich aryl nor alkyl chlorides resulted in any conversion under the same condition. In contrast, these substrates were effectively reduced by our organocatalyst **C1**. Based on these observations, we can conclude that the reduction from $CO_2^{\bullet-}$ *is not operative* for electron-rich substrates, but it cannot be completely ruled out for electron-poor compounds, although reduction via catalyst **C1** is likely the major pathway.

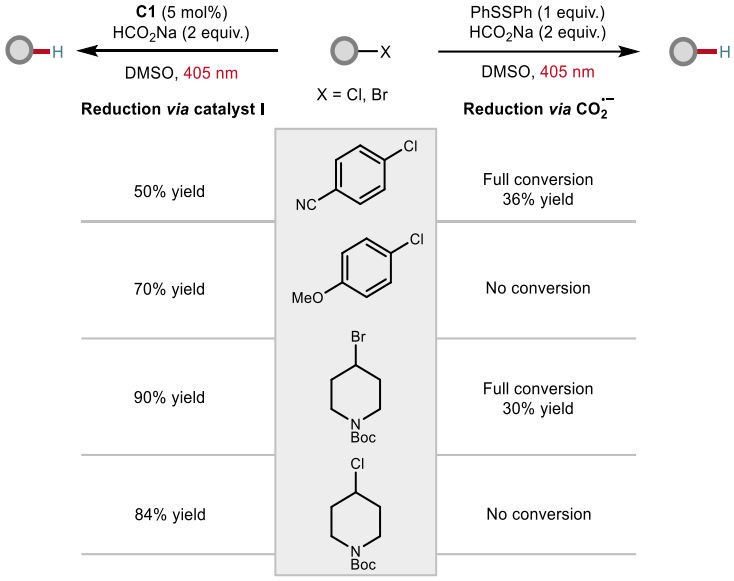


Figure 2.28. Comparison of the reducing ability of $CO_2^{\bullet-}$ and catalyst **C1**. Above results are obtained from experimental process.

Exclusion of XAT mechanism induced by hydrogen tunnelling

[39] Chmiel, A. F.; Williams, O. P.; Chernowsky, C. P.; Yeung, C. S.; Wickens, Z. K. "Non-innocent Radical Ion Intermediates in Photoredox Catalysis: Parallel Reduction Modes Enable Coupling of Diverse Aryl Chlorides." *J. Am. Chem. Soc.* **2021**, *143*, 10882−10889.

Recently, the Leonori group reported an efficient protocol for activating alkyl and aryl halides via a quantum mechanical tunneling mechanism, using γ-terpinene as the abstractor (Figure 2.29).[40] Given that γ-terpinene was also used in our work, we considered whether this potential mechanism could be operative in our system too. Based on our results, we can conclude that a γ-terpinene-induced XAT mechanism is unlikely to be operative in our system for the following reasons: (1) Replacing γ-terpinene with HCO_2Na or DIPEA still resulted in good yields for the hydrodechlorination reactions; (2) Aryl phosphates and Birch-type reactions can be activated exclusively by an SET process, which can be mastered only by our photocatalyst **C1**, thus ruling out the possibility of a terpinene-based XAT mechanism; (3) Hydrodefluorination of aryl fluorides have not been reported using an XAT system. Overall, these observations are inconsistent with a γ-terpinene-based XAT mechanism being operative under our conditions.

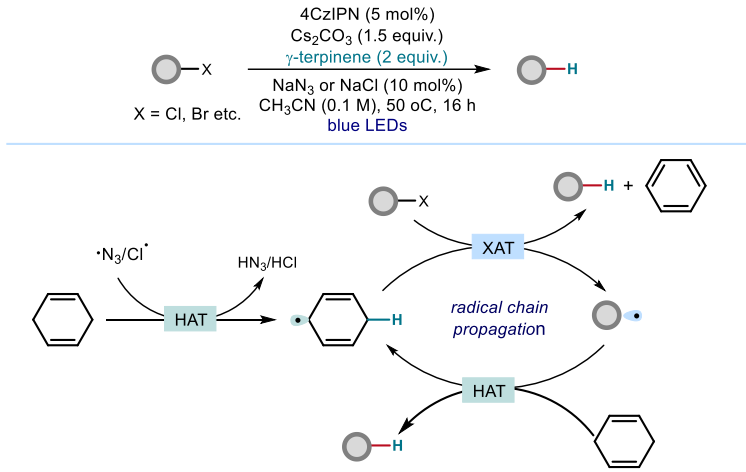


Figure 2.29. Leonora's work: halogen-atom and group transfer reactivity enabled by hydrogen tunnelling.

2.5 Conclusion

In summary, we have identified a simple indole thiolate organocatalyst that becomes a strong reductant upon deprotonation and light excitation. The resulting light–driven catalytic

[40] Constantin, T.; Górski, B.; Tilby, M. J.; Chelli, S.; Juliá, F.; Llaveria, J.; Gillen, K. J.; Zipse, H.; Lakhdar, S.; Leonori, D. "Halogen-Atom and Group Transfer Reactivity Enabled by Hydrogen Tunneling." *Science* **2022**, *377*, 1323–1328.

platform demonstrated a wide generality, since it could master the reductive activation of inert C-F, C-Cl and C-O bonds and the Birch-type reduction of unfunctionalized arenes. The mild conditions and the wide applicability suggest that this readily available organocatalyst could find widespread use for the photochemical activation of inert substrates.

2.6 Experimental Section

General Information.

The ^{1}H NMR, $^{19}F\{^{1}H\}$ NMR, $^{13}C\{^{1}H\}$ NMR spectra are available in the literature[1] and are not reported in the present dissertation.

The NMR spectra were recorded at 400 MHz and 500 MHz for ^{1}H, 101 or 126 MHz for $^{13}C\{^{1}H\}$ and 376 MHz for $^{19}F\{^{1}H\}$. The chemical shift (δ) for ^{1}H and $^{13}C\{^{1}H\}$ are given in ppm relative to residual signals of the solvents ($CHCl_3$ at 7.26 ppm for ^{1}H NMR and 77.16 ppm for $^{13}C\{^{1}H\}$ NMR). Coupling constants are given in Hertz. The following abbreviations are used to indicate the multiplicity: s, singlet; d, doublet; q, quartet; m, multiplet; br, broad signal

High resolution mass spectra (HRMS) were obtained from the ICIQ HRMS unit on MicroTOF Focus and Maxis Impact (Bruker Daltonics) with electrospray ionization (ESI) and Atmospheric-pressure chemical ionization (APCI). Optical rotations were measured on a Polarimeter Jasco P-1030 and are reported as follows: $[\alpha]_D$ ambient temperature (c in g per 100 mL, solvent). Cyclic voltammetry studies were carried out on a Princeton Applied Research PARSTAT 2273 potentiostat, offering compliance voltage up to ± 100 V (available at the counter electrode), ± 10 V scan range and ±2 A current range.

Yields refer to isolated materials of >95% purity as determined by ^{1}H NMR analysis.

General Procedures. All reactions were set up under an argon atmosphere in oven-dried glassware. Synthesis grade solvents were used as purchased, anhydrous solvents were taken from a commercial SPS solvent dispenser. Chromatographic purification of products was accomplished using forced-flow chromatography (FC) on silica gel (230-400 mesh). For thin layer chromatography (TLC) analysis throughout this work, Merck pre-coated TLC plates (silica gel 60 GF_{254}, 0.25 mm) were employed, using UV light as the visualizing agent and an acidic mixture of vanillin or basic aqueous potassium permanganate ($KMnO_4$) stain solutions, and heat as developing agents. Organic solutions were concentrated under reduced pressure on a Büchi rotatory evaporator.

Materials. Commercial grade reagents and solvents were purchased at the highest quality from commercial suppliers and used as received, unless otherwise stated.

2.6.1 Synthesis of Substrates and Catalysts

Substrate Synthesis

The following substrates were synthesized according to reported procedures (Figure 2.30).[41]

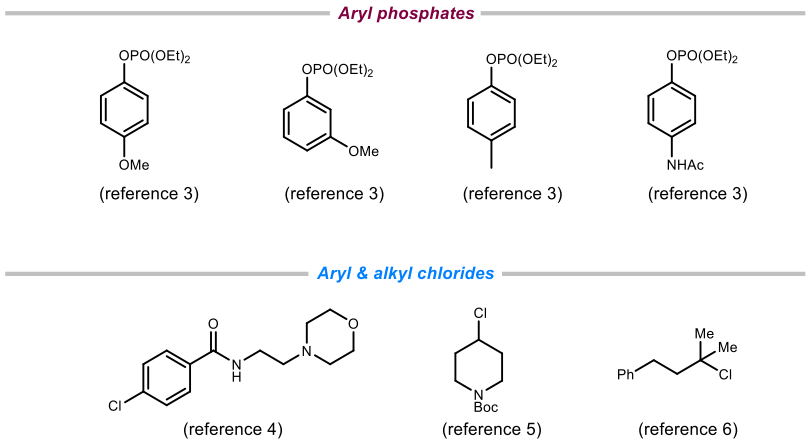
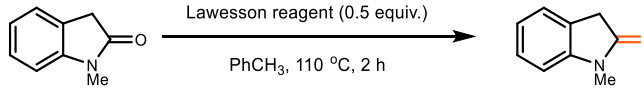


Figure 2.30. Starting materials synthesized according to known procedures.

Catalyst Synthesis

1-methylindoline-2-thione (C1):



[41] (a) Liu, T.; Neverov, A. A.; Tsang, J. S. W.; Brown, R. S. "Mechanistic Studies of La^{3+}- and Zn^{2+}-Catalyzed Methanolysis of Aryl Phosphate and Phosphorothioate Triesters. Development of Artificial Phosphotriesterase Systems." *Org. Biomol. Chem*. **2005**, *3*, 1525; (b) Li, G.; Ji, C. L.; Hong, X.; Szostak, M. "Highly Chemoselective, Transition-Metal-Free Transamidation of Unactivated Amides and Direct Amidation of Alkyl Esters by N-C/O-C Cleavage." *J. Am. Chem. Soc.* **2019**, *141*, 11161; (c) Villalpando, A.; Ayala, C. E.; Watson, C. B.; Kartika, R. "Triphosgene-Amine Base Promoted Chlorination of Unactivated Aliphatic Alcohols." *J. Org. Chem.* **2013**, *78*, 3989−3996; (d) Someya, H.; Yorimitsu, H.; Oshima, K. "Silver-Catalyzed Coupling Reactions of Alkyl Halides with Indenyllithiums." *Tetrahedron*. **2010**, *66*, 5993–5999.

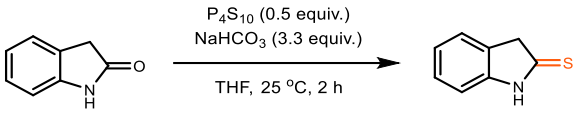
An oven dried flask was charged with 1-methylindolin-2-one (736.0 mg, 5.0 mmol, 1.0 equiv.), the Lawesson reagent (2.5 mmol, 0.5 equiv.) and toluene (20 mL). The flask was placed in an oil-bath preheated to 110 ºC. After 2 hours stirring, the solution was concentrated in vacuo and the crude mixture was purified by flash column chromatography on silica gel (1% ethyl acetate in hexanes as eluent) to afford the catalyst as light-yellow solid (620.5 mg, 76% yield).

^{1}H NMR (400 MHz, CDCl3) δ 7.37 – 7.28 (m, 2H), 7.19 – 7.14 (m, 1H), 6.97 (d, J = 8.0 Hz, 1H), 4.11 (s, 2H), 3.63 (s, 3H).

^{13}C NMR (101 MHz, CDCl3) δ 201.2, 146.6, 129.2, 128.0, 124.4, 124.0, 109.6, 49.1, 31.3.

Matching reported literature data.[42]

Indoline-2-thione (C2):



To a solution of 2-oxindole (0.50 g, 3.64 mmol, 1.0 equiv.) in THF (8 mL) was added P4S10 (0.83 g, 1.82 mmol, 0.50 equiv.). This mixture was stirred at 25 °C for 30 min before $NaHCO_3$ (1.0 g, 12 mmol, 3.3 equiv.) was added in three portions. Stirring was continued for additional 1.5 hours. The mixture was filtered and concentrated to dryness under reduced pressure. The crude was diluted with chloroform and water and extracted with chloroform. The combined organic phases were washed with saturated NaCl solution, dried over Na_2SO_4, filtered and concentrated to dryness under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (0-10% AcOEt in cyclohexane) to give indoline-2-thione as a yellow amorphous solid (160 mg, 30%).

^{1}H NMR (400 MHz, CDCl3) δ 7.30 – 7.23 (m, 2H), 7.15 – 7.09 (m, 1H), 7.06 – 6.99 (m, 1H), 4.08 (s, 2H).

^{13}C NMR (101 MHz, CDCl3) δ 203.5, 144.4, 130.4, 128.1, 124.2, 124.2, 110.2, 49.3.

Matching reported literature data.[43]

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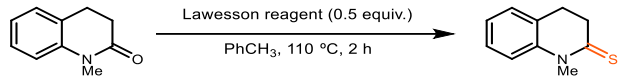
[42] Ransborg, L. K.; Albrecht, Ł.; Weise, C. F.; Bak, J. R.; Jørgensen, K. A. "Optically Active Thiophenes via an Organocatalytic One-Pot Methodology." *Org. Lett.* **2012**, *14*, 724–727.

[43] Lopes, A. B.; Choury, M.; Wagner, P.; Gulea, M. "Tandem Double-Cross-Coupling/Hydrothiolation Reaction of 2-Sulfenyl Benzimidazoles with Boronic Acids." *Org. Lett.* **2019**, *21*, 5943–5947.

1-methyl-3,4-dihydroquinoline-2(1H)-thione (C3):



An oven dried flask was charged with 1-methyl-3,4-dihydroquinolin-2(1H)-one (483.6 mg, 3.0 mmol, 1.0 equiv.), the Lawesson reagent (1.5 mmol, 0.5 equiv.) and toluene (10 mL). The flask was placed in an oil-bath preheated to 110 ºC. After 2 hours stirring, the solution was concentrated in vacuo and the crude mixture was purified by flash column chromatography on silica gel (1% ethyl acetate in hexanes as eluent) to afford the catalyst as light-yellow solid (319 mg, 70% yield).

^{1}H NMR (400 MHz, CDCl3) δ 7.33 – 7.26 (m, 1H), 7.21 – 7.05 (m, 3H), 3.91 (s, 3H), 3.23 – 3.16 (m, 2H), 2.84 – 2.78 (m, 2H).

^{13}C NMR (101 MHz, CDCl3) δ 200.8, 140.2, 129.0, 128.0, 127.6, 124.7, 116.4, 42.3, 38.6, 24.8.

Matching reported literature data.[44]

2.6.2 Experimental Procedures

Experimental Setup

- ***Set-up 1*** 405 nm EvoluChem setup (Figure 2.31)

Some of the reactions were performed using an EvoluChem P303-30-1 lamp (18 W, λ_{max} = 405 nm, 2-3 cm away), a fan was used to cool down the vials (the reaction temperature within the reaction vessel was measured to be between 40-42 ºC).

[44] Takahta, H.; Tomiguchi, A.; Hagiwara, A.; Yamazaki, T. "Activated Lactams. VI. The Cycloaddition Reaction of Cyclic Ketene-S, N-acetals with Dimethyl Acetylenedicarboxylate." *Chem. Pharm. Bull.* **1982**, *30*, 3959–3964.

Figure 2.31. Reaction setup using EvoluChem lamps emitting at 405 nm

- ***Set-up 2*** 390 nm Kessil Lamp setup (Figure 2.32)

Some of the reactions were performed under illumination by a *Kessil* lamp (PR160L-390 nm, 100% intensity), using a 3D-printed photoreactor reported in the literature[8] (the temperature in the reactor was set to 40 ºC).

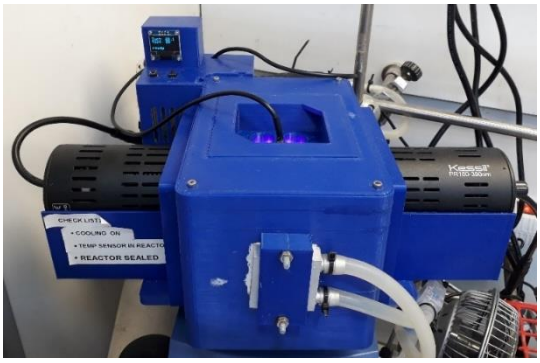


Figure 2.32. Reaction setup using a 3D-printed photoreactor under illumination at 390 nm by two Kessil lamps.

- ***Set-up 3*** Gram scale experiment (Figure 2.33)

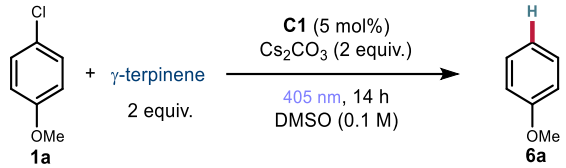
The gram scale reaction was performed under illumination by two EvoluChem P303-30-1 lamps (18 W, λ_{max}= 405 nm, 2-3 cm away from the reaction vessel) and using a fan to cool the flask.

Figure 2.33. Setup for the gram-scale experiment using two EvoluChem lamps emitting at 405 nm.

2.6.3 Dechlorination of Aryl Chlorides

Optimization Studies

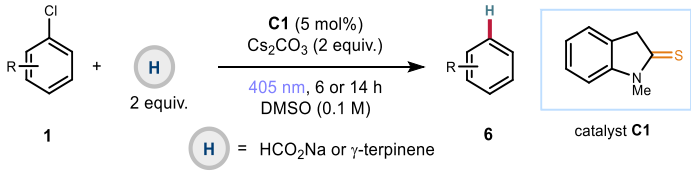
Table 2.3. Reaction optimization of the defunctionalisation of aryl chlorides



Entry	Deviations	NMRy **6a**
1	none	80%
2	No **C1**	trace
3	No light	0%
4	No base	0%
5	No γ-terpinene	30%
6	CH_3CN as solvent	75%
7	Cs_2CO_3 (1 equiv.)	60%
8	Cs_2CO_3 (0.5 equiv.)	50%
9	K_2CO_3 as base	75%
10	Na_2CO_3 as base	35%
11	$NaHCO_3$ as base	0%
12	K_3PO4 as base	73%
13	TMG as base	40%
14	HCO_2Na, 6 h	70%
15	3 mol% **C1**, HCO_2Na, 6 h	71%[a]
16	DIPEA instead of γ-terpinene	50%
17	DIPEA as base and HAT Source	10%
18	irradiation at 425 nm	30%

All reactions were performed on a 0.2 mmol scale; yield of **3a** determined by ^1H NMR analysis of the crude reaction mixture by comparison with 1,3,5-trimethoxybenzene as internal standard. [a]0.3 mmol scale.

General Procedure



To a 7 mL glass vial, catalyst **C1** (1.65 mg, 0.01 mmol, 0.05 equiv.), cesium carbonate (163 mg, 0.4 mmol, 2 equiv.), sodium formate (if sodium formate was the HAT source, 27.0 mg, 0.4 mmol, 2 equiv.) and aryl chlorides (if solid, 0.2 mmol, 1 equiv.) were sequentially added. The vial was sealed with a screw-top cap with septum and then vacuumed and backfilled with argon for 3 times. Afterwards, aryl chlorides **1** (if liquid, 0.2 mmol, 1 equiv.) and γ-terpinene (if γ-terpinene was the HAT source, 64 μL, 0.4 mmol, 2 equiv.) followed by argon-sparged DMSO (0.1 M) were added *via* syringe. The vial was sealed with Parafilm and then stirred under 405 nm for 6 hours (with sodium formate) or 14 hours (with γ-terpinene) using ***Set-up 1*** detailed in Figure 2.31.

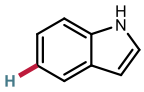
NMR analyses (products **6a-6c**, **6e-6j**): 1,3,5-trimethoxybenzene was added as the internal standard (33.6 mg, 0.2 mmol, 1 equiv.) to the crude reaction mixture, followed by 2 mL H_2O and 1 mL of brine. Then, the solution was extracted with 0.7 mL of $CDCl_3$ and the reactions were analysed *via* ^1H NMR of the $CDCl_3$ layer.

For the isolation of products **6d** and **6k***:* After reaction was completed, the reaction mixture was transferred to an extraction funnel, 10 mL of H_2O and 2 mL of brine were added and the organic layer was extracted with EtOAc. The organic layer was washed twice with brine, the combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The crude residue was purified by column chromatography to afford the corresponding products with the reported yields (>95% purity according to ^1H NMR analysis).

Characterization of Products

The crude ^1H NMR of adducts **6a-6c**, and **6e-6j** matched with reported literature data.[45]

[45] (a) MacKenzie, I. A.; Wang, L.; Onuska, N. P. R.; Williams, O. F.; Begam, K.; Moran, A. M.; Dunietz, B. D.; Nicewicz, D. A. "Discovery and Characterization of an Acridine Radical Photoreductant." *Nature* **2020**, *580*, 76−80; (b) Kuhlmann, J. H.; Dickoff, J. H.; Mancheño, O. G.; "Visible Light Thiyl Radical-

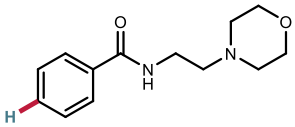


1H-indole (6d): Synthesized according to General Procedure using 5-chloro-1H-indole (30.5 mg, 0.2 mmol, 1.0 equiv.) and γ-terpinene (64 μL, 0.4 mmol, 2.0 equiv.) or sodium formate (27.2 mg, 0.4 mmol, 2.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (10% ethyl acetate in hexanes as eluent) to afford **6d** (11.8 mg, 50% yield using γ-terpinene; 14.1 mg, 60% yield using sodium formate) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (br, 1H), 7.76 – 7.71 (m, 1H), 7.46 – 7.41 (m, 1H), 7.31 – 7.25 (m, 1H), 7.24 – 7.18 (m, 2H), 6.65 – 6.61 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 135.8, 127.9, 124.1, 122.0, 120.8, 119.8, 111.0, 102.67.

Matching reported literature data.[46]



***N*-(2-morpholinoethyl)benzamide (6k):** Synthesized according to General Procedure using 4-chloro-*N*-(2-morpholinoethyl)benzamide (53.7 mg, 0.2 mmol, 1.0 equiv.) and γ-terpinene (64 μL, 0.4 mmol, 2.0 equiv.) or sodium formate (27.2 mg, 0.4 mmol, 2.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (20% ethyl acetate in hexanes as eluent) to afford **6k** (30.4 mg, 65% yield with γ-terpinene and 30.0 mg, 64% with from sodium formate) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 – 7.75 (m, 2H), 7.53 – 7.48 (m, 1H), 7.47 – 7.41 (m, 2H), 6.81 (br, 1H), 3.73 (t, *J* = 4.0 Hz, 4H), 3.59 – 3.53 (m, 2H), 2.63 – 2.59 (m, 2H), 2.54 – 2.48 (m, 4H)

^{13}C NMR (101 MHz, $CDCl_3$) δ 167.4, 134.6, 131.4, 128.6, 126.9, 67.0, 57.0, 53.4, 36.0.

Matching reported literature data.[47]

Mediated Desilylation of Arylsilanes." *Chem. Eur. J.* **2023**, *29*, e202203347; (c) Alassad, Z.; Aboraed, A.; Mizrachi, M. S.; PérezTemprano, M.; Milo, A. "Metal-Free Multicomponent Strategy for Amidine Synthesis." *J. Am. Chem. Soc.* **2022**, *144*, 20672−20679.

[46] Pankhurst, J. R.; Curcio, M.; Sproules, S.; Lloyd-Jones, G. C.; Love, J. B. "Earth-Abundant Mixed-Metal Catalysts for Hydrocarbon Oxygenation." *Inorg. Chem.* **2018**, *57*, 5915−5298

[47] Nicholson, W. I.; Barreteau, F.; Leitch, J. A.; Payne, R.; Priestley, I.; Godineau, E.; Battilocchio, C.; Browne, D. L. "Direct Amidation of Esters by Ball Milling." *Angew. Chemie Int. Ed.* **2021**, *60*, 21868–21874

Comparison of the Results using γ-terpinene and Sodium Formate

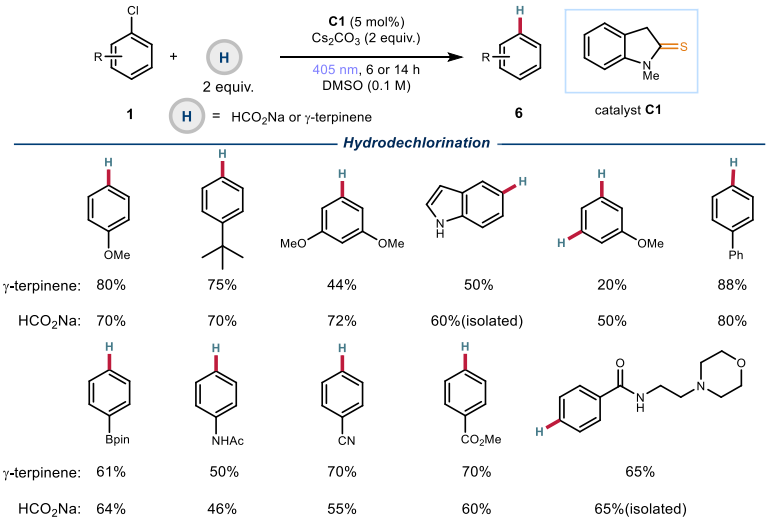
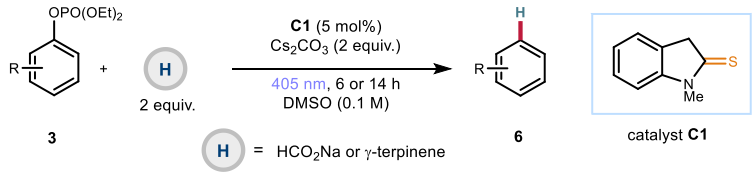


Figure 2.34. Hydrodechlorination scope using either γ-terpinene or sodium formate as the H donor.

2.6.4 Hydrogenation of Aryl Phosphates

General Procedure



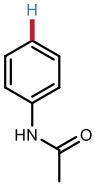
To a 7 mL glass vial, catalyst **C1** (1.65 mg, 0.01 mmol, 0.05 equiv.), cesium carbonate (163 mg, 0.4 mmol, 2 equiv.), sodium formate (if sodium formate was the HAT source, 27.0 mg, 0.4 mmol, 2 equiv.) and aryl phosphates **3** (if solid, 0.2 mmol, 1 equiv.) were sequentially added. The vial was sealed with a screw-top cap with septum and then vacuumed and backfilled with argon for 3 times. Afterwards, aryl phosphates (if liquid, 0.2 mmol, 1 equiv.) and γ-terpinene (if γ-terpinene was the HAT source, 64 μL, 0.4 mmol, 2 equiv.) followed by argon-sparged DMSO (0.1 M) were added *via* syringe. The vial was sealed with Parafilm and then stirred under 405 nm for 6 hours (with sodium formate) or 16 hours (with γ-terpinene) using ***Set-up 1*** detailed in Figure 2.31.

For NMR analyses (products **6a**, **6l**, **6m**): 1,3,5-trimethoxybenzene was added as the internal standard (33.6 mg, 0.2 mmol, 1 equiv.) to the crude reaction mixture, followed by addition of 2 mL of H_2O and 1 mL of brine. Then, the solution was extracted with 0.7 mL of $CDCl_3$ and the reactions were analysed *via* ^1H NMR of the $CDCl_3$ layer.

For the isolation of product **6h***:* After the reaction was completed, the reaction mixture was transferred to an extraction funnel, 10 mL of H_2O and 2 mL of brine were added and the organic layer was extracted with EtOAc. The organic layer was washed twice with brine, the combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The crude residue was purified by column chromatography to afford the corresponding product with the reported yields (>95% purity according to ^1H NMR analysis).

Characterization of Products

The crude ^1H NMR of products **6a**, **6l**, and **6m** matched the reported literature data.[45a]



***N*-phenylacetamide (6h):** Synthesized according to General Procedure using 4-acetamidophenyl diethyl phosphate (57.4 mg, 0.2 mmol, 1.0 equiv.) and γ-terpinene (64 μL, 0.4 mmol, 2.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (5% Ethyl acetate in hexanes as eluent) to afford **6h** (14.9 mg, 55% yield) as a white solid.

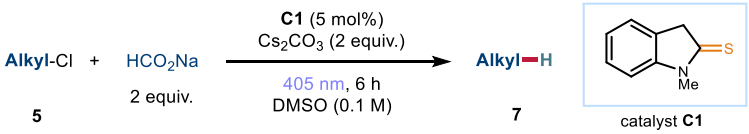
^1H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.5 Hz, 2H), 7.49 (br, 1H) 7.31 (t, *J* = 8.0 Hz, 2H), 7.10 (t, *J* = 7.4 Hz, 1H), 2.16 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.4, 137.9, 129.0, 124.3, 119.9, 24.6.

Matching reported literature data.[46]

2.6.5 Hydrodechlorination of Alkyl Chlorides

General Procedure



To a 7 mL glass vial, catalyst **C1** (1.65 mg, 0.01 mmol, 0.05 equiv.), cesium carbonate (163 mg, 0.4 mmol, 2 equiv.), sodium formate (27.0 mg, 0.4 mmol, 2 equiv.) and alkyl chlorides

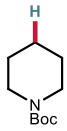
5 (if solid, 0.2 mmol, 1 equiv.) were added. The vial was sealed with a screw-top cap with septum and then vacuumed and backfill with argon for 3 times. Afterwards, alkyl chlorides (if liquid, 0.2 mmol, 1 equiv.) followed by argon-sparged DMSO (0.1 M) were added *via* syringe. The vial was sealed with Parafilm and then stirred under 405 nm illumination for 6 hours using ***Set-up 1*** detailed in Figure 2.31.

For NMR analyses of products **7a**, **7b**, and **7f**: 1,3,5-trimethoxybenzene was added as the internal standard (33.6 mg, 0.2 mmol, 1 equiv.) to the crude reaction mixture, followed by 2 mL of H_2O and 1 mL of brine. Then, the solution was extracted with 0.7 mL of $CDCl_3$ and the reactions were analysed *via* ^1H NMR of the $CDCl_3$ layer.

For the isolation of products **7c**-**7e***:* After the reaction was completed, the crude mixture was transferred to an extraction funnel, 10 ml of H_2O and 2 mL of brine were added and the organic layer was extracted with EtOAc. The organic layer was washed twice with brine, the combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The crude residue was purified by column chromatography to afford the corresponding product with the reported yields (>95% purity according to ^1H NMR analysis).

Characterization of Products

The crude ^1H NMR of adducts **7a-b**, and **7f** matched the reported literature data.[48]



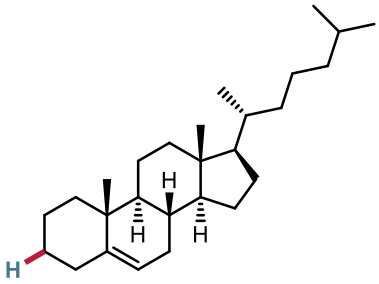
***Tert*-butyl piperidine-1-carboxylate (7c):** Synthesized according to the General Procedure using *tert*-butyl 4-chloropiperidine-1-carboxylate **5c** (43.9 mg, 0.2 mmol, 1.0 equiv.) and sodium formate (27.2 mg, 0.4 mmol, 2.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (5% ethyl acetate in hexanes as eluent) to afford **7c** (31.2 mg, 84%, and 33.3 mg, 90% from tert-butyl 4-bromopiperidine-1-carboxylate) as a colorless oil.

^1H NMR (400 MHz, $CDCl_3$) δ 3.36 – 3.31 (m, 4H), 1.58 – 1.46 (m, 6H), 1.44 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 155.0, 79.1, 44.7, 28.5, 25.7, 24.5.

[48] Okita, T.; Aida, K.; Tanaka, K.; Ota, E.; Yamaguchi, J. Chlorine Atom Transfer of Unactivated Alkyl Chlorides Enabled by Zirconocene and Photoredox Catalysis *Precis. Chem.* **2023**. Doi: 10.1021/prechem.2c00002.

Matching reported literature data.[49]

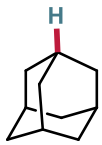


(8S,9S,10R,13R,14S,17R)-10,13-dimethyl-17-((R)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthrene (7d): Synthesized according to General Procedure using (3S,8S,9S,10R,13R,14S,17R)-3-chloro-10,13-dimethyl-17-((*R*)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthrene (80.8 mg, 0.2 mmol, 1.0 equiv.) and sodium formate (27.2 mg, 0.4 mmol, 2.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (hexanes as eluent) to afford **7d** (64.0 mg, 86%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.29 – 5.25 (m, 1H), 2.30 – 2.18 (m, 1H), 2.06 – 1.92 (m, 3H), 1.87 – 1.78 (m, 2H), 1.76 – 1.68 (m, 1H), 1.60 – 0.99 (m, 26H), 0.92 (d, *J* = 6.5 Hz, 3H), 0.88 (d, *J* = 1.8 Hz, 3H), 0.86 (d, *J* = 1.8 Hz, 3H), 0.68 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 143.7, 119.0, 56.9, 56.2, 50.6, 42.3, 39.9, 39.6, 37.6, 36.2, 35.8, 32.9, 31.9, 31.9, 28.3, 28.1, 28.0, 24.3, 23.9, 22.8, 22.6, 22.6, 20.8, 19.5, 18.8, 11.9.

Matching reported literature data.[50]



Adamantane (7e): Synthesized according to the General Procedure using 1-chloroadamantane (34.1 mg, 0.2 mmol, 1.0 equiv.) and sodium formate (27.2 mg, 0.4 mmol, 2.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (hexanes as eluent) to afford **7e** (20.5 mg, 75%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.91 – 1.84 (m, 4H), 1.78 – 1.73 (m, 12H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 37.8, 28.4.

Matching reported literature data.[50]

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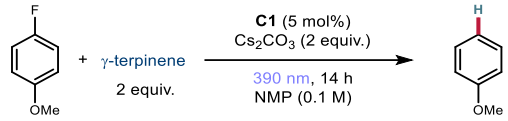
[49] Li, H.; Tang, X.; Pang, J. H.; Wu, X.; Yeow, E. K. L.; Wu, J.; Chiba, S. "Polysulfide Anions as Visible Light Photoredox Catalysts for Aryl Cross-Couplings." *J. Am. Chem. Soc*. **2021**, *143*, 481−487.

[50] Pilli, R.; Balakrishnan, V.; Chandrasekaran, R.; Rasappan, R. "Iron-Catalyzed Protodehalogenation of Alkyl and Aryl Halides using Hydrosilanes." *Org. Biomol. Chem*. **2019**, *17*, 1749–1753.

2.6.6 Hydrodefluorination of Aryl Fluorides

Optimization Studies

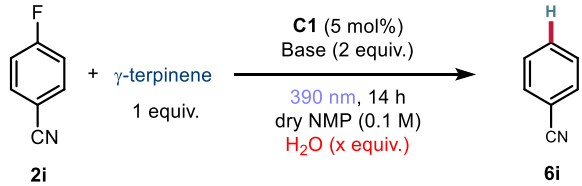
Table 2.4. Reaction optimization on the defluorination of aryl fluorides.



Entry	Deviations	NMRy **6a**
1	none[a]	80%
2	No **C1**	0%
3	No light	0%
4	No base	0%
5	No γ-terpinene	65%
6	405 nm, 10% Ith	63%
7	DIPEA	56%
8	$NaCO_2H$	57%
9	DMSO	35%
10	CH_3CN	70%
11	1 equiv. γ-terpinene[a]	77%

All reactions were performed on a 0.2 mmol scale; yield of **6a** determined by ^{1}H NMR analysis of the crude reaction mixture by comparison with 1,3,6-Mesitylene as internal standard. [a] In some cases, over reduction was observed when using 2 equiv. of γ-terpinene, depending on the water content of NMP. Over reduction was not observed when using 1 equiv. of γ-terpinene.

Table 2.5. Effect of water on the hydrodefluorination of electron-poor aryl fluorides



Entry	H_2O equiv.	Base	NMRy **3i**[a]
1	0	Cs_2CO_3	0%

2	5	Cs_2CO_3	18%
3	10	Cs_2CO_3	32%
4	15	Cs_2CO_3	43%
5	20	Cs_2CO_3	69%
6	40	Cs_2CO_3	93%
7	15	K_2CO_3	68%
8	15	$(NH_4)_2CO_3$	21%

All reactions were performed on a 0.2 mmol scale; yield of **6i** determined by ^{1}H NMR analysis of the crude reaction mixture by comparison with 1,3,6-mesitylene as internal standard. [a] Difference in mass balance is unreacted **2i**

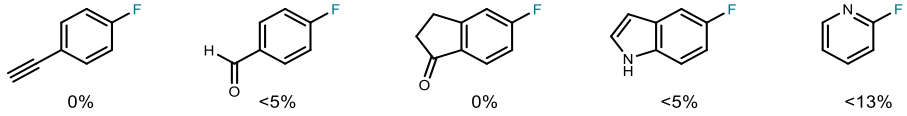
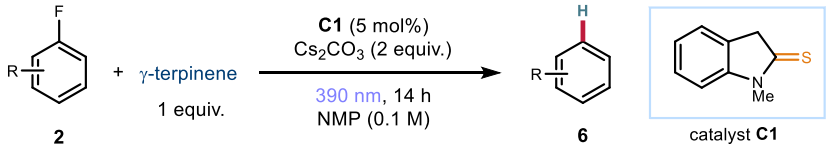


Figure 2.35. Unsuccessful substrates of the hydrodefluorination scope

General Procedure



To a 7 mL glass vial, catalyst **C1** (1.65 mg, 0.01 mmol, 0.05 equiv.), cesium carbonate (163 mg, 0.4 mmol, 2 equiv.) and aryl fluorides **2** (if solid, 0.2 mmol, 1 equiv.) were sequentially added. The vial was sealed with a screw-top cap with septum and then vacuumed and backfilled with argon for 3 times. Afterwards, aryl fluorides (if liquid, 0.2 mmol, 1 equiv.), γ-terpinene (64 μL, 0.4 mmol, 2 equiv.), degassed NMP (0.1 M) and, if necessary, H_2O (5 or 40 equiv.) were added *via* syringe. The vial was sealed with Parafilm, and then placed into the *3D printed reactor* under 390 nm irradiation for 14 hours using ***Set-up 2*** detailed in Figure 2.32.

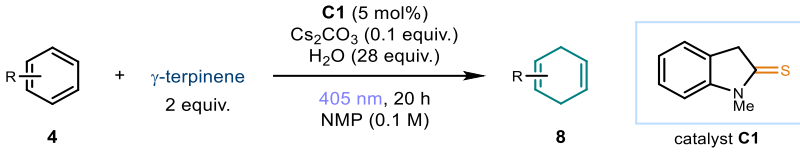
1,3,5-mesitylene was added as the internal standard (28 μl, 0.2 mmol, 1 equiv.) to the crude reaction mixture, followed by addition of 2 mL of H_2O and 1 mL of brine. Then, the solution was extracted with 0.7 mL of $CDCl_3$ and the reactions were analysed *via* ^{1}H NMR of the $CDCl_3$ layer.

Characterization of Products

The crude ^{1}H NMR of products **6a**, **6f**, **6i**, **6l**, and **6n-s** matched the reported literature data.[45,51]

2.6.7 Birch-type Reduction

General Procedure



To a 7 mL glass vial, catalyst **C1** (1.65 mg, 0.01 mmol, 0.05 equiv.), cesium carbonate (6.5 mg, 0.4 mmol, 2 equiv.) and arenes **4** (if solid, 0.2 mmol, 1 equiv.) were added sequentially. The vial was sealed with a screw-top cap with septum and then vacuumed and backfilled with argon for 3 times. Afterwards, arenes (if liquid, 0.2 mmol, 1 equiv.), γ-terpinene (64 μL, 0.4 mmol, 2 equiv.), H_2O (0.1 ml, 28 equiv.) followed by degassed NMP (0.1 M) were added *via* syringe. The vial was sealed with Parafilm and then stirred under 405 nm irradiation for 20 hours using ***Set-up 1*** detailed in Figure 2.31.

For NMR analyses of products **8a**, **8c-8e** and **8g-8i**: 1,3,5-trimethoxybenzene was added as the internal standard (33.6 mg, 0.2 mmol, 1 equiv.) to the crude reaction mixture, followed by 2 mL of H_2O and 1 mL of brine. Then, the solution was extracted with 0.7 mL of $CDCl_3$ and the reactions were analysed *via* ^{1}H NMR of the $CDCl_3$ layer.

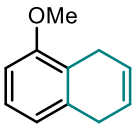
For the isolation of product **8b** and **8f***:* After the reaction was completed, the crude mixture was transferred to an extraction funnel, 10 mL of H_2O and 2 mL of brine were added and the organic layer was extracted with EtOAc. The organic layer was washed twice with brine, the combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated to

[51] (a) Sharma, U.; Kumar, P.; Kumar, N.; Kumar, V.; Singh, B. "Highly Chemo- and Regioselective Reduction of Aromatic Nitro Compounds Catalyzed by Recyclable Copper (II) as well as Cobalt (II) Phthalocyanines." *Adv. Synth. Catal.* **2010**, *352*, 1834–1840; (b) Lyons, D. J. M.; Dinh, A. H.; Ton, N. N. H.; Crocker, R. D.; Mai, B. K.; Nguyen, T. V. "Ring Contraction of Tropylium Ions into Benzenoid Derivatives." *Org. Lett.* **2022**, *24*, 2520–2525.

dryness. The crude residue was purified by column chromatography to afford the corresponding product with the reported yields (>95% purity according to ^{1}H NMR analysis).

Characterization of Products

The crude ^{1}H NMR of adducts **8a-8e, 8f´´** and **8g-8i** matched the reported literature data.[52]

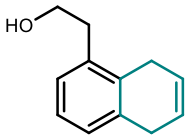


5-methoxy-1,4-dihydronaphthalene (8b): Synthesized according to the General Procedure using 1-methoxynaphthalene (31.6 mg, 0.2 mmol, 1.0 equiv.) and γ-terpinene (64 μL, mg, 0.4 mmol, 2.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (hexanes as eluent) to afford **8b** (23.1 mg, 72%) as a colorless oil.

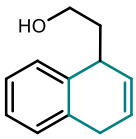
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (dd, *J* = 7.9, 7.9 Hz, 1H), 6.75 (d, *J* = 6.9 Hz, 1H), 6.70 (d, *J* = 8.1 Hz, 1H), 5.97 – 5.84 (m, 2H), 3.84 (s, 3H), 3.45 – 3.39 (m, 2H), 3.31 – 3.25 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 156.9, 135.3, 126.3, 124.5, 123.9, 123.2, 120.7, 107.0, 55.3, 29.5, 24.2.

Matching reported literature data.[52a]



8f´



8f´´

2-(5,8-dihydronaphthalen-1-yl)ethan-1-ol and **2-(1,4-dihydronaphthalen-1-yl)ethan-1-ol (8f´+ 8f´´):** Synthesized according to the General Procedure using 2-(naphthalen-1-yl)ethan-1-ol (34.4 mg, 0.2 mmol, 1.0

[52] (a) Yoshimi, Y.; Ishise, A.; Oda, H.; Moriguchi, Y.; Kanezaki, H.; Nakaya, Y.; Katsuno, K.; Itou, T. Inagaki, S. Morita, T.; Hatanaka, M. "Hydroxide Ion as Electron Source for Photochemical Birch-Type Reduction and Photodehalogenation." *Tetrahedron Lett.* **2008**, *49*, 3400–3404; (b) Yousuf, Z.; Richards, A. K.; Dwyer, A. N.; Linclaua, B.; Harrowven, D. C. "The Development of a Short Route to The API Ropinirole Hydrochloride." *Org. Biomol. Chem.* **2015**, *13*, 10532–10539; (c) O'Byrne, A.; Murray, C.; Keegan, D.; Palacio, C.; Evans, P.; Morgan, B. S. "The Thio-Adduct Facilitated, Enzymatic Kinetic Resolution of 4-hydroxycyclopentenone and 4-hydroxycyclohexenone." *Org. Biomol. Chem.* **2010**, *8*, 539–545. (d) Burrows, J.; Kamo, S.; Koide, K. "Scalable Birch Reduction with Lithium and Ethylenediamine in Tetrahydrofuran." *Science* **2021**, *374*, 741–746; (e) Guignard,R. F.; Petit, L.; Zard, S. Z. "A Method for the Net Contra-thermodynamic Isomerization of Cyclic Trisubstituted Alkenes." *Org. Lett*. **2013**, *15*, 4178–4181.

equiv.) and γ-terpinene (64 μL, mg, 0.4 mmol, 2.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (15% EtOAc in hexanes as eluent) to afford the mixture of both isomers **8f´+ 8f´´** (19 mg, 55%) in a ration 3:1 (**8f´:8f´´)** as a colorless oil. The isomers were partially separated by flash column chromatography on SiO_2/$AgNO_3$ (10% loading, 50% EtOAc in hexanes as eluent).

8f´: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 – 7.10 (m, 1H), 7.08 – 7.00 (m, 2H), 5.95 – 5.88 (m, 2H), 3.85 (t, *J* = 6.8 Hz, 2H), 3.47 – 3.34 (m, 4H), 2.89 (t, *J* = 6.8 Hz, 2H).

13C NMR (101 MHz, CDCl3) δ 136.08, 134.77, 132.85, 127.44, 127.30, 126.10, 124.63, 124.44, 62.89, 35.92, 30.35, 27.27.

8f´´: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 – 7.10 (m, 4H), 6.03 – 5.94 (m, 2H), 3.74 – 3.57 (m, 3H), 3.45 – 3.34 (m, 2H), 1.94 (q, *J* = 6.5 Hz, 2H). [Peak at 3.45 – 3.34 overlapped with **8f´**]

13C NMR (101 MHz, CDCl3) δ 138.09, 134.56, 129.33, 128.39, 127.97, 126.18, 125.96, 125.33, 60.51, 40.43, 36.52, 29.89. [Peak at 125.96 overlapped with **8f´**]

8f´´ is matching reported literature data.[52d]

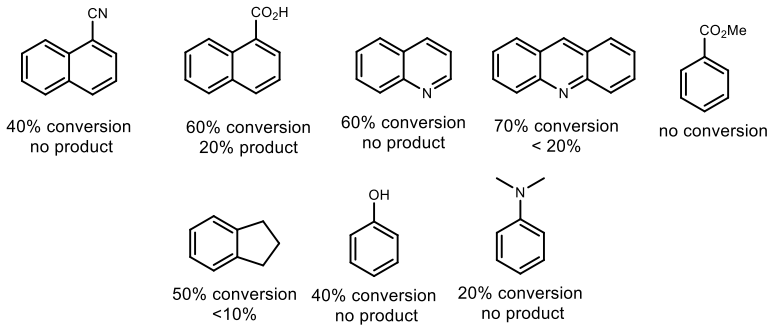
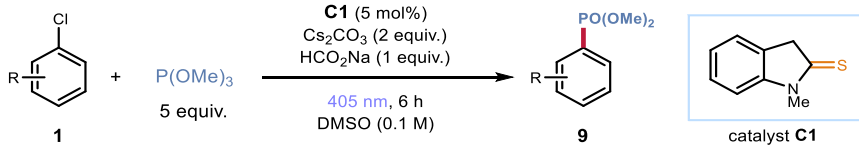


Figure 2.36. Unsuccessful substrates of the Birch-type reduction.

2.6.8 Phosphorylation of Aryl Chlorides

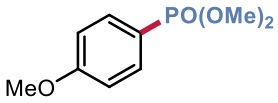
General Procedure



To a 7 mL argon-purged glass vial, catalyst **C1** (1.63 mg, 0.01 mmol, 0.05 equiv.), cesium carbonate (163 mg, 0.4 mmol, 2 equiv.), sodium formate (13.6 mg,0.2 mmol, 1 equiv.) and aryl chlorides **1** (if solid, 0.2 mmol, 1 equiv.) were added as solids. Then vacuum and backfill with argon for 3 times. Then, aryl chlorides (if liquid, 0.2 mmol, 1 equiv.) and trimethyl phosphite (118 μL, 1.0 mmol, 5.0 equiv.), followed by argon-sparged DMSO (0.1 M), were added *via* syringe. The vial was sealed with Parafilm, and then placed under 405 nm irradiation using a fan as cooling system according to ***Set-up 1*** detailed in Figure 2.31.

After 6 hours stirring, the reaction mixture was transferred to an extraction funnel, 10 mL of H_2O and 2 mL of brine were added and the organic layer was extracted with EtOAc. The organic layer was washed with brine twice. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness. The crude residue was purified by column chromatography to afford the corresponding product 3 in the stated yield with >95% purity according to 1H NMR analysis.

Characterization of Products



Dimethyl (4-methoxyphenyl)phosphonate (9a): Synthesized according to the General Procedure using 1-chloro-4-methoxybenzene (28.5 mg, 0.2 mmol, 1.0 equiv.) and trimethyl phosphite (124.0 mg, 1.0 mmol, 5.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (40% acetone in hexanes as eluent) to afford **9a** (36.9 mg, 85% yield, for the 5 mmol scale 681 mg, 63% yield) as a yellow liquid.

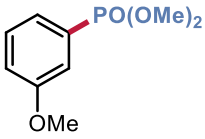
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 – 7.66 (m, 2H), 6.65 – 6.89 (m, 2H), 3.81 (s, 3H), 3.72 (s, 4H), 3.69 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 163.1 (d, J = 3.0 Hz), 133.9 (d, J = 11.1 Hz), 117.5 (d, J = 198.0 Hz), 114.2 (d, J = 16.2 Hz), 55.3, 52.7 (d, J = 6.1 Hz).

^{31}P NMR (162 MHz, $CDCl_3$) δ 25.3.

Matching reported literature data.[53]

[53] Zeng, H.; Dou, Q.; Li, C.-J. "Photoinduced Transition-Metal-Free Cross-Coupling of Aryl Halides with H-Phosphonates." *Org. Lett.* **2019**, *21*, 1301–1305.



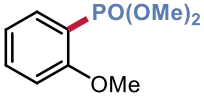
Dimethyl (3-methoxyphenyl)phosphonate (9b): Synthesized according to the General Procedure using 1-chloro-3-methoxybenzene (28.5 mg, 0.2 mmol, 1.0 equiv.) and trimethyl phosphite (124.1mg, 1.0 mmol, 5.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (40% acetone in hexanes as eluent) to afford **9b** (35.2 mg, 81% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.26 (m, 3H), 7.10 – 7.04 (m, 1H), 3.82 (s, 3H), 3.75 (s, 3H), 3.72 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.5 (d, *J* = 18.2 Hz), 129.9 (d, *J* = 18.2Hz), 128.0 (d, *J* = 188.9 Hz), 124.1 (d, *J* = 9.1 Hz), 119.1 (d, *J* = 3.0 Hz), 116.4 (d, *J* = 11.1 Hz), 55.4, 52.7 (d, *J* = 6.1 Hz).

^{31}P NMR (162 MHz, $CDCl_3$) δ 24.6.

Matching reported literature data.



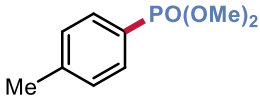
Dimethyl (2-methoxyphenyl)phosphonate (9c): Synthesized according to the General Procedure using 1-chloro-3-methoxybenzene (28.5 mg, 0.2 mmol, 1.0 equiv.) and trimethyl phosphite (124.0 mg, 1.0 mmol, 5.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (40% acetone in hexanes as eluent) to afford **9c** (36.0 mg, 83% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (ddd, *J* = 14.9, 7.6, 1.8 Hz, 1H), 7.55 – 7.45 (m, 1H), 7.05 – 6.98 (m, 1H), 6.98 – 6.91 (m, 1H), 3.90 (s, 3H), 3.80 (s, 3H), 3.77 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 161.4, 135.3 (d, *J* = 7.1 Hz), 134.9 (d, *J* = 2.0 Hz), 120.6 (d, *J* = 14.2 Hz), 114.3 (d, *J* = 193.9 Hz), 111.2 (d, *J* = 10.1 Hz), 55.9, 53.2 (d, *J* = 5.1 Hz).

^{31}P NMR (162 MHz, $CDCl_3$) δ 23.5.

Matching reported literature data.



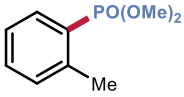
Dimethyl p-tolylphosphonate (9d): Synthesized according to the General Procedure using 1-chloro-4-methylbenzene (25.3 mg, 0.2 mmol, 1.0 equiv.) and trimethyl phosphite (124.0 mg, 1.0 mmol, 5.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (25% acetone in hexanes as eluent) to afford **9d** (35.0 mg, 87% yield) as a yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 – 7.62 (m, 2H), 7.29 – 7.23 (m, 2H), 3.73 (s, 3H), 3.70 (s, 4H), 2.38 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 143.3 (d, *J* = 3.0 Hz), 131.9 (d, *J* = 10.1 Hz), 129.3 (d, *J* = 16.2 Hz), 123.5 (d, *J* = 191.9 Hz), 52.6 (d, *J* = 5.05 Hz), 21.6 (d, *J* = 2.02 Hz).

^{31}P NMR (162 MHz, $CDCl_3$) δ 25.5.

Matching reported literature data.



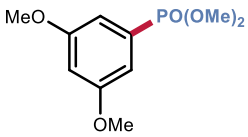
Dimethyl o-tolylphosphonate (9e): Synthesized according to the General Procedure using 1-chloro-2-methylbenzene (25.3 mg, 0.2 mmol, 1.0 equiv.) and trimethyl phosphite (124.0 mg, 1.0 mmol, 5.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (25% acetone in hexanes as eluent) to afford **9e** (27.2 mg, 67% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 – 7.83 (m, 1H), 7.46 – 7.39 (m, 1H), 7.29 – 7.22(m, 2H), 3.76 (s, 3H), 3.73 (s, 3H), 2.54 (d, *J* = 4.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 142.0 (d, *J* = 11.1 Hz), 134.1(d, *J* = 11.1 Hz), 132.7 (d, *J* = 3.0 Hz), 131.3 (d, *J* = 15.2 Hz), 125.5 (d, *J* = 14.1 Hz), 125.5 (d, *J* = 185.8 Hz), 52.5 (d, *J* = 6.1 Hz), 21.2 (d, *J* = 4.0 Hz).

^{31}P NMR (162 MHz, $CDCl_3$) δ 25.6.

Matching reported literature data.



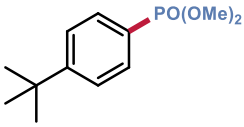
Dimethyl (3,5-dimethoxyphenyl)phosphonate (9f): Synthesized according to the General Procedure using 1-chloro-3,5-dimethoxybenzene (34.5 mg, 0.2 mmol, 1.0 equiv.) and trimethyl phosphite (124.0 mg, 1.0 mmol, 5.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (50% acetone in hexanes as eluent) to afford **9f** (18.8 mg, 46% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.90 (dd, *J* = 14.8, 2.3 Hz, 2H), 6.62 (dd, *J* = 2.3, 2.3 Hz, 1H), 3.81 (s, 6H), 3.76 (s, 3H), 3.73 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 160.9 (d, *J* = 22.2 Hz), 128.6 (d, *J* = 188.9 Hz), 109.3 (d, *J* = 11.1 Hz), 105.3 (d, *J* = 3.0 Hz), 55.6, 52.8 (d, *J* = 5.1 Hz).

^{31}P NMR (162 MHz, $CDCl_3$) δ 24.7.

HRMS: calculated for $C_{10}H_{16}O_5P$ ($M+H^+$): 247.0730, found 247.0740.



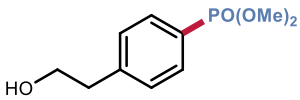
Dimethyl (4-(tert-butyl)phenyl)phosphonate (9g): Synthesized according to the General Procedure using 1-(tert-butyl)-4-chlorobenzene (33.7 mg, 0.2 mmol, 1.0 equiv.) and trimethyl phosphite (124.0 mg, 1.0 mmol, 5.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (25% acetone in hexanes as eluent) to afford **9g** (40.0 mg, 83% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 – 7.65 (m, 2H), 7.50 – 7.43 (m, 2H), 3.74 (s, 3H), 3.71 (s, 3H), 1.31 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 156.2 (d, *J* = 3.03 Hz), 131.8 (d, *J* = 10.1 Hz), 125.6 (d, *J* = 15.2 Hz), 123.5 (d, *J* = 191.9 Hz), 52.6 (d, *J* = 5.05 Hz), 35.1, 31.0.

^{31}P NMR (162 MHz, $CDCl_3$) δ 25.4.

Matching reported literature data.



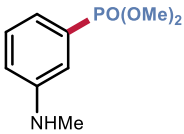
Dimethyl (4-(2-hydroxyethyl)phenyl)phosphonate (9h): Synthesized according to the General Procedure using 2-(4-chlorophenyl)ethan-1-ol (31.3 mg, 0.2 mmol, 1.0 equiv.) and trimethyl phosphite (124.0 mg, 1.0 mmol, 5.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (50% acetone in hexanes as eluent) to afford **9h** (19.5 mg, 42% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 – 7.69 (m, 2H), 7.38 – 7.32 (m, 2H), 3.89 (t, *J* = 8.0 Hz, 2H), 3.76 (s, 3H), 3.73 (s, 4H), 2.92 (t, *J* = 8.0 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 144.0 (d, *J* = 3.03 Hz), 132.2 (d, *J* = 10.1 Hz), 129.3 (d, *J* = 15.2 Hz), 124.8 (d, *J* = 190.9 Hz), 63.2, 52.7 (d, *J* = 5.1 Hz), 39.2.

^{31}P NMR (162 MHz, $CDCl_3$) δ 25.1.

HRMS: calculated for $C_{10}H_{15}NaO_4P$ ($M+Na^+$): 253.0600, found 253.0611.



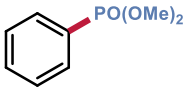
Dimethyl (3-(methylamino)phenyl)phosphonate (9i): Synthesized according to the General Procedure using 3-chloro-*N*-methylaniline (28.3 mg, 0.2 mmol, 1.0 equiv.) and trimethyl phosphite (124.0 mg, 1.0 mmol, 5.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (50% acetone in hexanes as eluent) to afford **9i** (29.8 mg, 69% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.22 (m, 1H), 7.11 – 6.98 (m, 2H), 6.80 – 6.73 (m, 1H), 3.76 (s, 3H), 3.73 (s, 3H), 2.86 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 149.2 (d, *J* = 18.2 Hz), 129.5 (d, *J* = 17.2Hz), 127.3 (d, *J* = 186.9 Hz), 120.2 (d, *J* = 9.1 Hz), 116.5 (d, *J* = 3.0 Hz), 115.2 (d, *J* = 12.1 Hz), 52.6 (d, *J* = 5.1 Hz), 30.6.

^{31}P NMR (162 MHz, $CDCl_3$) δ 26.0.

HRMS: calculated for $C_9H_{15}NO_3P$ ($M+H^+$): 216.0784, found 216.0794.



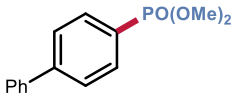
Dimethyl phenylphosphonate (9j): Synthesized according to the General Procedure using chlorobenzene (22.5 mg, 0.2 mmol, 1.0 equiv.) and trimethyl phosphite (124.0 mg, 1.0 mmol, 5.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (25% acetone in hexanes as eluent) to afford **9j** (24.1 mg, 64% yield) as a yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 – 7.74 (m, 2H), 7.59 – 7.52 (m, 1H), 7.50 – 7.42 (m, 2H), 3.76 (s, 3H), 3.73 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 132.7 (d, *J* = 3.0 Hz), 131.9 (d, *J* = 10.1 Hz), 128.6 (d, *J* = 15.2 Hz), 126.9 (d, *J* = 189.9 Hz), 52.7 (d, *J* = 6.1 Hz).

^{31}P NMR (162 MHz, $CDCl_3$) δ 24.8.

Matching reported literature data.



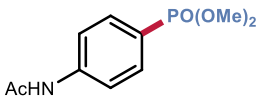
Dimethyl [1,1'-biphenyl]-4-ylphosphonate (9k): Synthesized according to the General Procedure using 4-chloro-1,1'-biphenyl (37.3 mg, 0.2 mmol, 1.0 equiv.) and trimethyl phosphite (124.0 mg, 1.0 mmol, 5.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (25% acetone in hexanes as eluent) to afford **9k** (41.0 mg, 78% yield) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 – 7.83 (m, 2H), 7.72 – 7.66 (m, 2H), 7.62 – 7.57 (m, 2H), 7.48 – 7.43 (m, 2H), 7.41 – 7.36 (m, 1H), 3.80 (s, 3H), 3.77(s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 145.6 (d, *J* = 4.04 Hz), 140, 132.5 (d, *J* = 10.1 Hz), 129.0, 128.3, 127.3 (d, *J* = 15.2 Hz), 127.3, 125.2 (d, *J* = 191.9 Hz), 52.8 (d, *J* = 6.1 Hz).

^{31}P NMR (162 MHz, $CDCl_3$) δ 24.9.

Matching reported literature data.



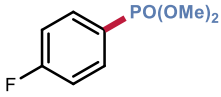
Dimethyl (4-acetamidophenyl)phosphonatebenzoate (9l): Synthesized according to the General Procedure using *N*-(4-chlorophenyl)acetamide (33.9 mg, 0.2 mmol, 1.0 equiv.) and trimethyl phosphite (124.0 mg, 1.0 mmol, 5.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (50% acetone in hexanes as eluent) to afford **9l** (46.1 mg, 75% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (s, 1H), 7.75 – 7.63 (m, 4H), 3.75 (s, 3H), 3.72 (s, 3H), 2.2 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.5, 143.0 (d, *J* = 11.1 Hz), 132.9 (d, *J* = 11.1 Hz), 120.5 (d, *J* = 193.9 Hz), 119.3 (d, *J* = 15.2 Hz), 52.7 (d, *J* = 6.1 Hz), 24.5.

^{31}P NMR (162 MHz, $CDCl_3$) δ 24.7.

HRMS: calculated for $C_{10}H_{14}NNaO_4P$ ($M+Na^+$): 266.0553, found 266.0561.



Dimethyl (4-fluorophenyl)phosphonate (9m): Synthesized according to the General Procedure using 1-chloro-4-fluorobenzene (26.1 mg, 0.2 mmol, 1.0 equiv.) and trimethyl phosphite (124.0 mg, 1.0 mmol, 5.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (25% acetone in hexanes as eluent) to afford **9m** (18.8 mg, 46% yield) as a yellow oil.

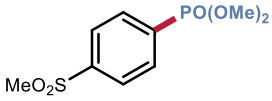
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 – 7.75 (m, 2H), 7.19 – 7.11 (m, 2H), 3.76 (s, 3H), 3.73 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 165.5 (dd, *J* = 255.5, 4.04 Hz), 134.5 (dd, *J* = 11.1, 9.1 Hz), 122.7 (dd, *J* = 194.9, 4.0 Hz), 116.0 (dd, *J* = 21.2, 16.2 Hz), 52.7 (d, *J* = 6.1 Hz).

^{31}P NMR (162 MHz, $CDCl_3$) δ 23.8.

^{19}F NMR (376 MHz, $CDCl_3$) δ -105.5

Matching reported literature data.



Dimethyl (4-(methylsulfonyl)phenyl)phosphonate (9n): Synthesized according to the General Procedure using 1-chloro-4-(methylsulfonyl)benzene(38.1 mg, 0.2 mmol, 1.0 equiv.) and trimethyl phosphite (124.0 mg, 1.0 mmol, 5.0 equiv.). The crude mixture was purified by

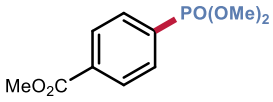
flash column chromatography on silica gel (50% acetone in hexanes as eluent) to afford **9n** (23.0 mg, 44% yield) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 – 7.97 (m, 4H), 3.81 (s, 3H), 3.79 (s, 3H), 3.08 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 144.3 (d, *J* = 4.04 Hz), 133.5 (d, *J* = 187.9 Hz), 132.9 (d, *J* = 10.1 Hz), 127.4 (d, *J* = 15.2 Hz), 53.1 (d, *J* = 6.1 Hz), 44.3.

^{31}P NMR (162 MHz, $CDCl_3$) δ 21.3.

HRMS: calculated for $C_9H_{13}NaO_5PS$ ($M+Na^+$): 287.0114, found 287.0117.



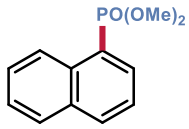
Methyl 4-(dimethoxyphosphoryl)benzoate (9o): Synthesized according to the General Procedure using 4-chlorobenzoate (34.1 mg, 0.2 mmol, 1.0 equiv.) and trimethyl phosphite (124.0 mg, 1.0 mmol, 5.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (40% acetone in hexanes as eluent) to afford **9o** (25.1 mg, 51% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 – 8.09 (m, 2H), 7.90 – 7.82 (m, 2H), 3.93 (s, 3H), 3.78 (s, 3H), 3.75 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.2, 133.8 (d, *J* = 3.03 Hz), 131.9 (d, *J* = 10.1 Hz), 131.8 (d, *J* = 188.9 Hz), 129.5 (d, *J* = 15.2 Hz), 52.9 (d, *J* = 6.1 Hz), 52.5.

^{31}P NMR (162 MHz, $CDCl_3$) δ 22.9.

Matching reported literature data.



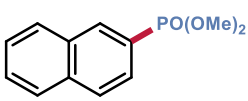
Dimethyl naphthalen-1-ylphosphonate (9p): Synthesized according to the General Procedure using 1-chloronaphthalene (32.5 mg, 0.2 mmol, 1.0 equiv.) and trimethyl phosphite (124.0 mg, 1.0 mmol, 5.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (25% acetone in hexanes as eluent) to afford **9p** (37.7 mg, 80% yield) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (d, *J* = 8.5 Hz, 1H), 8.23 (ddd, *J* = 16.4, 7.1, 1.4 Hz, 1H), 8.05 (d, *J* = 7.5 Hz, 1H), 7.92 – 7.81 (m, 1H), 7.64 – 7.48 (m, 3H), 3.80 (s, 3H), 3.77 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 135.0 (d, *J* = 9.1 Hz), 133.9 (d, *J* = 3.0 Hz), 133.6 (d, *J* = 13.1 Hz), 132.7 (d, *J* = 11.1 Hz), 128.8 (d, *J* = 2.0 Hz), 127.7, 126.5 (d, *J* = 4.0 Hz),126.5 124.5 (d, *J* = 17.2 Hz), 123.3 (d, *J* = 184.8 Hz), 52.7 (d, *J* = 5.1 Hz).

^{31}P NMR (162 MHz, $CDCl_3$) δ 25.4.

Matching reported literature data.



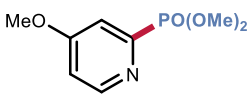
Dimethyl naphthalen-2-ylphosphonate (9q): Synthesized according to the General Procedure using 2-chloronaphthalene (32.5 mg, 0.2 mmol, 1.0 equiv.) and trimethyl phosphite (124.0 mg, 1.0 mmol, 5.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (25% acetone in hexanes as eluent) to afford **9q** (34.5 mg, 73% yield) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, *J* = 15.5 Hz, 1H), 7.96 – 7.83 (m, 3H), 7.77 – 7.68 (m, 1H), 7.63 – 7.50 (m, 2H), 3.79 (s, 3H), 3.77 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 135.1 (d, *J* = 3.0 Hz), 134.3 (d, *J* = 10.1 Hz), 132.4 (d, *J* = 17.2 Hz), 128.9, 128.6, 128.4, 127.8, 127.0 (d, *J* = 2.1 Hz), 126.4 (d, *J* = 9.1 Hz), 123.9 (d, *J* = 189.9 Hz), 52.8 (d, *J* = 6.1 Hz).

^{31}P NMR (162 MHz, $CDCl_3$) δ 25.1.

Matching reported literature data.



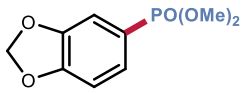
Dimethyl (4-methoxypyridin-2-yl)phosphonate (9r): Synthesized according to the General Procedure using 2-chloro-4-methoxypyridine (28.7 mg, 0.2 mmol, 1.0 equiv.) and trimethyl phosphite (124.0 mg, 1.0 mmol, 5.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (50% acetone in hexanes as eluent) to afford **9r** (15.1 mg, 35% yield) as a yellow oil.

^{1}H NMR (400 MHz, Acetone-d_6) δ 8.59 (d, *J* = 5.6 Hz, 1H), 7.46 (dd, *J* = 8.5, 2.7 Hz, 1H), 7.12 (ddd, *J* = 5.7, 2.7, 1.2 Hz, 1H), 3.97 (s, 3H), 3.82 (s, 3H), 3.79 (s, 3H).

^{13}C NMR (101 MHz, Acetone-d_6) δ 165.7 (d, *J* = 17.2 Hz), 153.1 (d, *J* = 225.2 Hz), 151.8 (d, *J* = 26.3 Hz), 114.7(d, *J* = 27.3 Hz), 111.7(d, *J* = 3.0 Hz), 55.2, 52.8 (d, *J* = 7.1 Hz).

^{31}P NMR (162 MHz, Acetone-d_6) δ 15.9.

HRMS: calculated for $C_8H_{13}NO_4P$ ($M+H^+$): 218.0577, found 218.0585.



Dimethyl benzo[d][1,3]dioxol-5-ylphosphonate (9s): Synthesized according to the General Procedure using 5-chlorobenzo[d] [1,3] dioxole (31.3 mg, 0.2 mmol, 1.0 equiv.) and

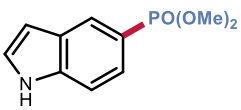
trimethyl phosphite (124.0 mg, 1.0 mmol, 5.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (50% acetone in hexanes as eluent) to afford **9s** (32.0 mg, 70% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (ddd, *J* = 14.0, 7.9, 1.5 Hz, 1H), 7.16 (dd, *J* = 12.9, 1.4 Hz, 1H), 6.87 (dd, *J* = 7.5, 3.7 Hz, 1H), 6.01 (s, 2H), 3.73 (s, 3H), 3.70 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 151.4 (d, *J* = 4.0 Hz), 147.9 (d, *J* = 22.2 Hz), 127.7 (d, *J* = 11.1 Hz), 119.7 (d, *J* = 195.9 Hz), 111.3 (d, *J* = 12.1 Hz), 108.7 (d, *J* = 18.2 Hz), 101.7, 52.7 (d, *J* = 5.1 Hz).

^{31}P NMR (162 MHz, $CDCl_3$) δ 24.9.

Matching reported literature data.



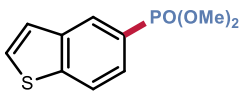
Dimethyl (1H-indol-5-yl)phosphonate (9t): Synthesized according to the General Procedure using 5-chloro-1H-indole (30.3 mg, 0.2 mmol, 1.0 equiv.) and trimethyl phosphite (124.0 mg, 1.0 mmol, 5.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (40% acetone in hexanes as eluent) to afford **9t** (30.0 mg, 67% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.99 (s, 1H), 8.41 (d, *J* = 15.5 Hz, 1H), 8.21 – 8.13 (m, 1H), 7.60 – 7.52(m, 1H), 7.51 – 7.45 (m, 1H), 7.33 – 7.28 (m, 1H), 3.77 (s, 3H), 3.74 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 138.2, 127.6 (d, *J* = 17.2 Hz), 126.4 (d, *J* = 11.1 Hz), 125.8, 124.6 (d, *J* = 12.1 Hz), 116.3 (d, *J* = 192.9 Hz), 111.6 (d, *J* = 16.2 Hz), 103.4 (d, *J* = 2.0 Hz), 52.6 (d, *J* = 6.1 Hz).

^{31}P NMR (162 MHz, $CDCl_3$) δ 28.3.

HRMS: calculated for $C_{10}H_{13}NO_3P$ ($M+H^+$): 226.0628, found 226.0631.



Dimethyl benzo[b]thiophen-5-ylphosphonate (9u): Synthesized according to the General Procedure using 5-chlorobenzo[b]thiophene (33.7 mg, 0.2 mmol, 1.0 equiv.) and trimethyl phosphite (124.0 mg, 1.0 mmol, 5.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (25% acetone in hexanes as eluent) to afford **9u** (31.4 mg, 65% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 – 8.29 (m, 1H), 8.00 – 7.93 (m, 1H), 7.72 – 7.65 (m, 1H), 7.53(d, *J* = 5.5 Hz, 1H), 7.40 (dd, *J* = 5.5, 0.8 Hz, 1H), 3.78 (s, 3H), 3.76 (s, 3H).

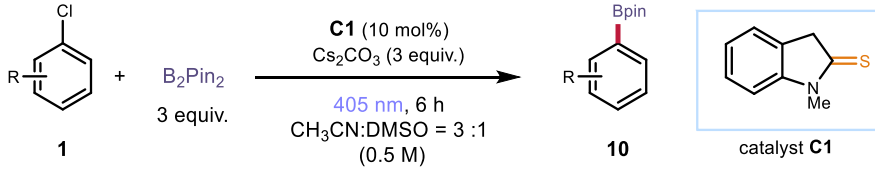
^{13}C NMR (101 MHz, $CDCl_3$) δ 144.0 (d, *J* = 4.0 Hz), 139.2 (d, *J* = 17.2 Hz), 128.4 (d, *J* = 10.1 Hz), 127.9, 126.1 (d, *J* = 11.1 Hz), 124.1 (d, *J* = 1.0 Hz), 122.9 (d, *J* = 16.2 Hz), 122.3 (d, *J* = 190.9 Hz), 52.8 (d, *J* = 5.1 Hz).

^{31}P NMR (162 MHz, $CDCl_3$) δ 25.7.

HRMS: calculated for $C_{10}H_{12}O_3PS$ ($M+H^+$): 243.0239, found 243.0246.

2.6.9 Phosphorylation of Aryl Chlorides

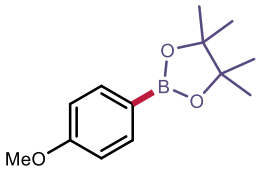
General Procedure



To a 7 mL argon-purged glass vial, catalyst **C1** (3.26 mg, 0.00 mmol, 0.1 equiv.), cesium carbonate (195 mg, 0.6 mmol, 3 equiv.), B_2Pin_2 (152 mg, 0.6 mmol, 3 equiv.) and aryl chlorides **1** (if solid, 0.2 mmol, 1 equiv.) were added as solids. Then vacuum and backfill with argon for 3 times. Then, aryl chlorides (if liquid, 0.2 mmol, 1 equiv.) followed by argon-sparged solvent (CH_3CN: DMSO = 3:1, 0.5 M) were added *via* syringe. The vial was sealed with Parafilm, and then placed under irradiation by a 405 nm light using a fan as cooling system according to ***Set-up 1*** detailed in Figure 2.31.

After 6 hours stirring, the reaction mixture was transferred to an extraction funnel, 10 ml of H_2O and 2 mL of brine were added and the organic layer was extracted with EtOAc. The organic layer was washed with brine twice. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness. The crude residue was purified by column chromatography to afford the corresponding product **10** in the stated yield with >95% purity according to 1H NMR analysis.

Characterization of Products



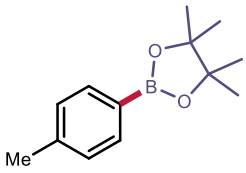
2-(4-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (10a): Synthesized according to the General Procedure using 1-chloro-4-methoxybenzene (28.5 mg, 0.2 mmol, 1.0 equiv.) and

4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (152.4 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (3% ethyl acetate in hexanes as eluent) to afford **10a** (32.7 mg, 70% yield, and 17.7 mg, 38% yield obtained from1-fluoro-4-methoxybenzene) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 – 7.73 (m, 2H), 6.92 – 6.88 (m, 2H), 3.83 (s, 3H), 1.34 (s, 12H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 162.2, 136.5, 113.3, 83.6, 55.1, 24.9.

Matching reported literature data.[54]

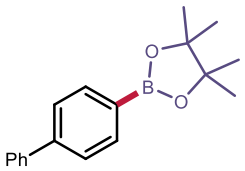


4,4,5,5-tetramethyl-2-(p-tolyl)-1,3,2-dioxaborolane (10b): Synthesized according to the General Procedure using 1-chloro-4-methylbenzene (25.3 mg, 0.2 mmol, 1.0 equiv.) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (152.4 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (2% Ethyl acetate in hexanes as eluent) to afford **10b** (18.8 mg, 43% yield and 19.7 mg, 45% yield obtained from 1-fluoro-4-methylbenzene) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 – 7.69 (m, 2H), 7.21 – 7.16 (m, 2H), 2.37 (s, 3H), 1.34 (s, 12H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 141.4, 134.8, 128.5, 83.6, 24.9, 21.7.

Matching reported literature data.



2-([1,1'-biphenyl]-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (10c): Synthesized according to the General Procedure using 4-chloro-1,1'-biphenyl (37.3 mg, 0.2 mmol, 1.0 equiv.) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (152.4 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (2% ethyl acetate in hexanes as eluent) to afford **10c** (43.0 mg, 77% yield) as a white solid.

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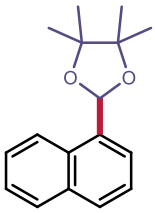
[54] Zhao, J.-H.; Zhou, Z.-Z.; Zhang, Y.; Su, X.; Chen, X.-M.; Liang, Y.-M. "Visible-Light-Mediated Borylation of Aryl and Alkyl Halides with A Palladium Complex." *Org. Biomol. Chem.* **2020**, *18*, 4390–4394.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 – 7.89 (m, 2H), 7.66 – 7.62 (m, 4H), 7.49 – 7.44 (m, 2H), 7.40 – 7.35 (m, 1H), 1.39 (s, 12H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 143.9, 141.1, 135.3, 128.8, 127.6, 127.3, 126.5, 83.9, 24.9.

Matching reported literature data.

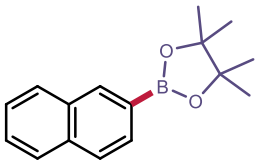


4,4,5,5-tetramethyl-2-(naphthalen-1-yl)-1,3-dioxolane (10d): Synthesized according to the General Procedure using 1-chloronaphthalene (32.5 mg, 0.2 mmol, 1.0 equiv.) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (152.4 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (2% Ethyl acetate in hexanes as eluent) to afford **10d** (29.5 mg, 58% yield) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (d, *J* = 9.3 Hz, 1H), 8.10 (dd, *J* = 6.9, 1.4 Hz, 1H), 7.95 (d, *J* = 8.3 Hz, 1H), 7.85 (d, *J* = 6.9 Hz, 1H), 7.58 – 7.52 (m, 1H), 7.51 – 7.46 (m, 2H), 1.44 (s, 12H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 137.0, 135.7, 133.2, 131.6, 128.4, 128.3, 126.4, 125.5, 125.0, 83.8, 25.0.

Matching reported literature data.

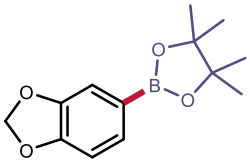


4,4,5,5-tetramethyl-2-(naphthalen-2-yl)-1,3,2-dioxaborolane (10e): Synthesized according to the General Procedure using 2-chloronaphthalene (32.5 mg, 0.2 mmol, 1.0 equiv.) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (152.4 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (2% ethyl acetate in hexanes as eluent) to afford **10e** (20.3 mg, 40% yield) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (s,1H), 7.92 – 7.81 (m, 4H), 7.55 – 7.45 (m, 2H), 1.40 (s, 12H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 136.3, 135.1, 132.8, 130.4, 128.7, 127.7, 127.0, 127.0 125.8, 83.9, 25.0.

Matching reported literature data.



2-(benzo[d][1,3]dioxol-5-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (10f): Synthesized according to the General Procedure using 5-chlorobenzo[d] [1,3] dioxole (31.3 mg, 0.2 mmol, 1.0 equiv.) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (152.4 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (5% ethyl acetate in hexanes as eluent) to afford **10f** (21.0 mg, 42% yield) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.24 (d, *J* = 1.1 Hz, 1H), 6.83 (d, *J* = 7.2 Hz, 1H), 5.95 (s, 2H), 1.33 (s, 12H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 150.2, 147.2, 129.7, 114.0, 108.3, 100.7, 83.7, 24.8.

Matching reported literature data.

2.6.10 Mechanistic Studies

Deprotonation Experiments

To a 7 mL glass vial, catalyst **C1** (0.2 mmol, 1 equiv.) and cesium carbonate (0.4 mmol, 2 equiv.) were added. The vial was sealed with a screw-top cap with septum, then vacuumed and backfilled with argon for 3 times and DMSO-d_6 (0.1 M) were added *via* syringe. The solution was stirred at room temperature for 2 min, transferred into an argon filled NMR tube *via* syringe and then the ^{1}H NMR was recorded (Figure 2.37).

Treatment of catalyst **C1** (0.02 mmol) with excess Cs_2CO_3 (0.4 mmol) resulted in full deprotonation of catalyst in less than 2 min.

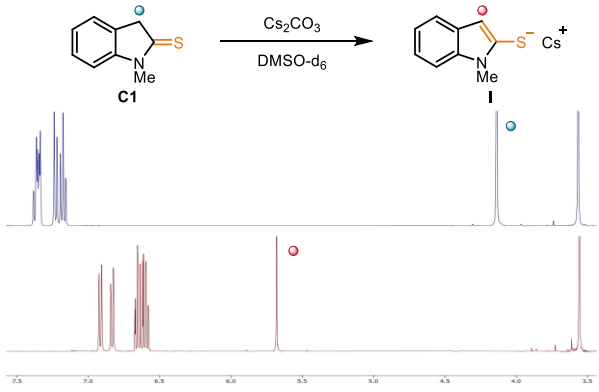
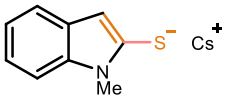


Figure 2.37. ^{1}H NMR analysis of catalyst **C1** before (blue spectrum) and after (red) treatment with Cs_2CO_3.



Cesium 1-methyl-1H-indole-2-thiolate (D):

^{1}H NMR (400 MHz, DMSO-d_6) δ 6.94 – 6.90 (m, 1H), 6.86 – 6.82 (m, 1H), 6.69 – 6.58 (m, 2H), 5.69 (d, J = 0.8 Hz, 1H), 3.56 (s, 3H).

^{13}C NMR (101 MHz, DMSO-d_6) δ 157.9, 137.3, 130.8, 117.8, 115.3, 114.3, 106.9, 98.2, 29.2.

Pre-stirring of the catalyst with Cs_2CO_3 for 30 min, followed by the addition of aryl chloride **1a** and γ-terpinene, gave product **3a** in comparable yield (72%) as the one-pot procedure while no reaction was observed *in the absences of base* (Figure 2.39). These experiments confirmed the deprotonated catalyst **D** as the active species.

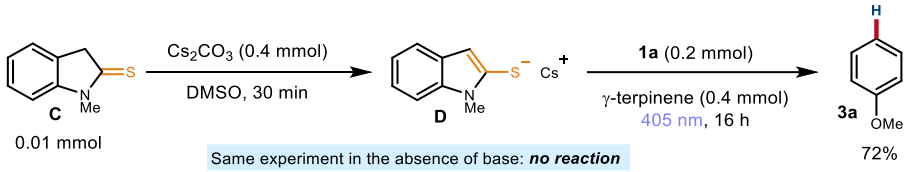


Figure 2.38. Hydrodechlorination of **1a** by pre-stirring of catalyst **C1** with Cs_2CO_3.

The degree of deprotonation for catalyst **C2-C4** was investigated by means of ^{1}H NMR analysis (Figure 2.39). While catalyst **C2** is also efficiently deprotonated, only 20% of the **C3** thiolate were detected after 12 hours and catalyst **C4** was completely unreactive.

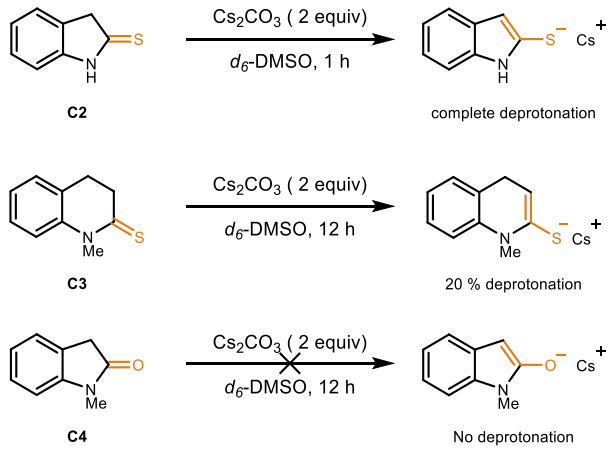


Figure 2.39. Deprotonation experiments of catalyst **C1**-**C4** with Cs_2CO_3 on a 0.1 mmol scale. Degree of deprotonation determined by ^{1}H NMR analysis.

Formation of the catalyst S-S Dimer

The non-reversible cyclic voltammetry behaviour of sulfur anions in the oxidation step is typically observed because of the possible formation of S-S dimers.[55] Efforts were made to synthesize the catalyst **C1**'s S-S dimer (**32**). Instead, the C-C dimer **33** was observed due to a fast thermal [3,3] dithia sigmatropic rearrangement (Figure 2.40).[56] Therefore, direct evidence of the **32** was not obtained but small quantities of the **33** were detected in the crude reaction mixture (Figure 2.42).

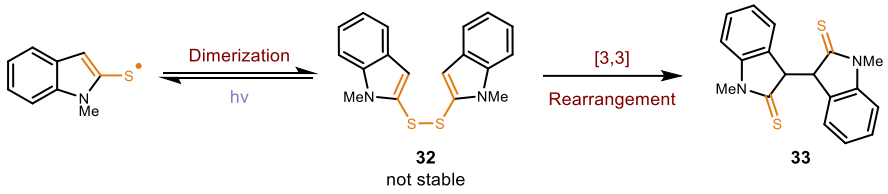


Figure 2.40. Formation of S-S and C-C Dimer of catalyst **C1**.

We then used an authentic sample of dimer **33** to catalyse the model reaction. We found that dimer **33** is catalytically active (Figure 2.41) upon deprotonation by Cs_2CO_3. The highly reducing power of the deprotonated catalyst **33** in the excited state was estimated to be -3.2 V vs Ag/AgCl in DMSO using the tail of the absorption spectrum and the first oxidation peak in the CV (see Figure 2.43 and 2.53 of the Experimental Section). However, dimer **33**, while being catalytically active, is only formed in small quantities upon dimerization of **C1** (ratio **33**/**C1** 1:99 after 2 h), as evaluated by NMR analysis (Figure 2.42). Therefore, the deprotonated catalyst **C1** is the main photoactive species responsible for reactivity.

[55] Roth, H. G.; Romero, N. A.; Nicewicz, D. A. "Experimental and Calculated Electrochemical Potentials of Common Organic Molecules for Applications to Single-Electron Redox Chemistry." *Synlett.* **2016**, *27*, 714–723.

[56] Tamaru, Y.; Harada, T.; Yoshida, Z. "Stereoselective Coupling Reaction of Thioamides via A Dithia-Cope Rearrangement." *J. Am. Chem. Soc.* **1978**, *100*, 1923–1925.

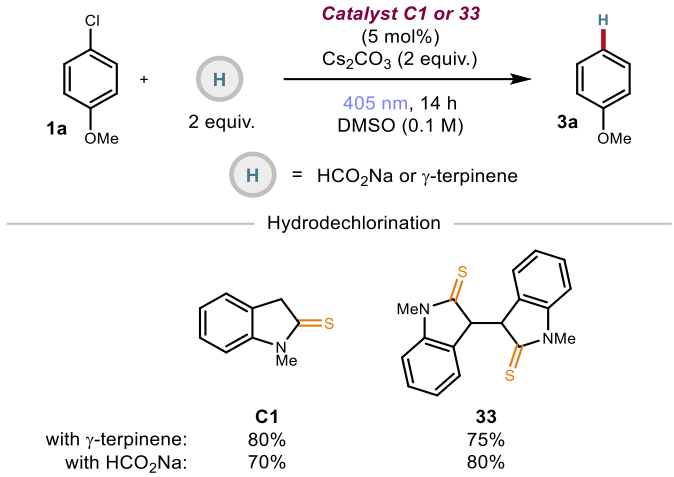


Figure 2.41. Investigation of the catalytic activity of catalyst **33**.

1,1'-dimethyl-[3,3'-biindoline]-2,2'-dithione (33):

To a solution of 1-methylindoline-2-thione **C1** (1.0 mmol, 1 equiv.) in MeOH (3 mL) was added a solution of I_2 (1 equiv.) in MeOH (7 mL) dropwise during 20 min, while stirring at room temperature. After each addition of I_2 solution, color of I_2 faded rapidly, and crystals precipitated. The mixture was further stirred at room temperature for 30 min until 1-methylindoline-2-thione **C1** was fully consumed (as detailed by TLC analysis). The crystals were collected to give crude dimer **33**, which was purified *via* recrystallization from benzene-hexane affording 43% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 – 7.11 (m, 2H), 6.97 (d, *J* = 7.4 Hz, 2H), 6.88 – 6.81 (m, 4H), 5.01 (s, 2H), 3.71 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 202.9, 145.7, 129.5, 128.5, 124.1, 123.5, 109.3, 61.3, 31.6.

Matching reported literature data.[57]

Detection of the dimer 33 by ^{1}H NMR analysis under the reaction conditions

The model reaction was performed according to the general procedure in a 25 mL flask with 15 mol% catalyst loading under complete exclusion of oxygen with Schlenk-line technique. After 2 hours, the reaction was stopped, the remaining solid was filtered off and small

[57]Tamaru, Y.; Harada, T.; Yoshida, Z. "Stereoselective Coupling Reaction of Thioamides via A Dithia-Cope Rearrangement." *J. Am. Chem. Soc.* **1978**, *100*, 1923–1925.

quantities of formic acid (2-4 drops, ~10-20 µl) were added to quench the remaining base until a neutral pH was reached. Afterwards, DMSO was removed under high vacuum (~40 °C and 0.02 mbar), the residue was dissolved in degassed $CDCl_3$ and transferred into an NMR tube.

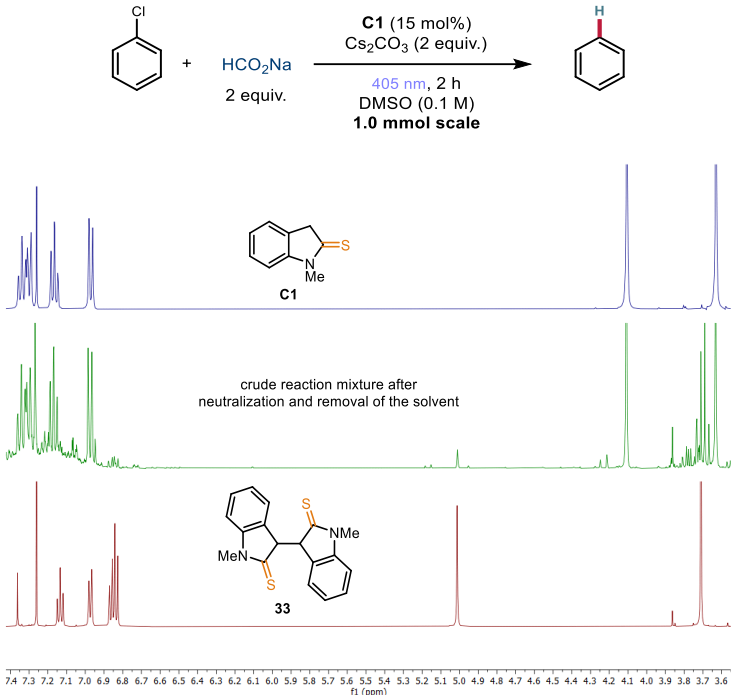


Figure 2.42. ^{1}H NMR analysis of the crude reaction mixture after 2 h, neutralization and removal of the solvent under inert atmosphere. Integration established a ratio of 1:99 for **33** to **C1**.

Photophysical studies

Sample Preparation:

- Neutral catalysts **C1**

A 25 mL glass vial containing catalyst **C1** (0.01 mmol) was sealed with a septum, vacuumed and backfilled with argon for 3 times, then degassed DMSO (5 mL, HPLC grade) was added *via* syringe ($2 \cdot 10^{-3}$ M solution). 40 µL of the stock solution were taken and diluted further with DMSO (4 mL) to obtain a $2 \cdot 10^{-5}$ M solution (20 µL were taken for a $1 \cdot 10^{-5}$ M solution). 3 mL of the solution was transferred into an argon filled quartz cuvette (10 x 10 mm light path) equipped with a septum.

- Deprotonated catalysts **D**

A 25 mL glass vial containing Cs_2CO_3 (130 mg) was sealed with a septum, vacuumed and backfilled with argon for 3 times, then degassed DMSO (16 mL, HPLC grade) was added *via* syringe. Addition of 160 µL of a freshly prepared neutral catalyst **C1** solution ($2 \cdot 10^{-3}$ M) gave a $2 \cdot 10^{-5}$ M solution (80 µL were taken for a $1 \cdot 10^{-5}$ M solution). The vial was sealed with Parafilm and stirred at room temperature for 0.5 hour. 3 mL of the solution was transferred into an argon filled quartz cuvette (10 x 10 mm light path) equipped with a septum.

Absorption measurements

UV-Vis measurements were carried out on an Agilent Cary 60 UV-Vis spectrophotometer equipped with two silicon diode detectors, double beam optics and Xenon pulse light.

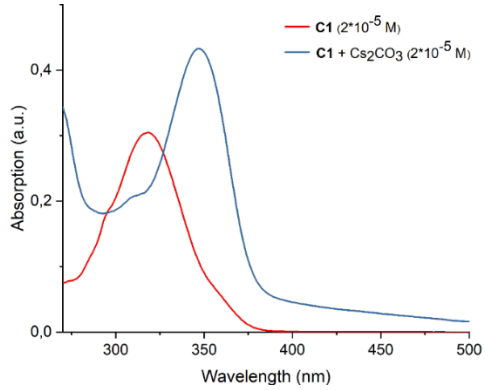


Figure 2.43. Absorption spectra recorded for catalyst **C1** in DMSO without (red line) and with (blue line) Cs_2CO_3 in a $2 \cdot 10^{-5}$ M solution.

We also recorded the absorption spectra of the dimer **33** in the absence and presence of Cs_2CO_3 (Figure 2.44).

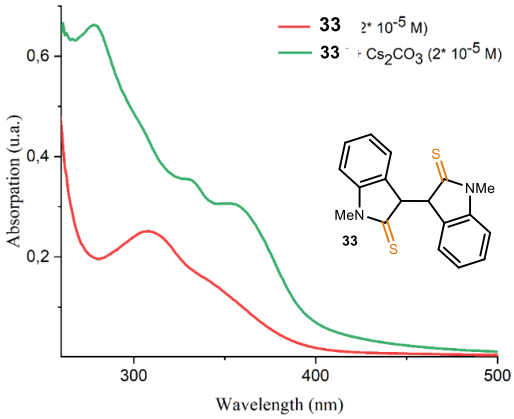


Figure 2.44. Absorption spectra recorded for catalyst **33** without (red line) and with Cs_2CO_3 (green line) in a $2 \cdot 10^{-5}$ M DMSO solution.

Emission Spectrum

Fluorescence measurements were carried out on an Aminco-Bowman Series 2 Luminescence spectrofluorimeter equipped with a high voltage PMT detector and continuum Xe light source. The emission spectrum of the deprotonated catalyst **C1** (formed in situ upon addition of Cs_2CO_3 in degassed DMSO according to the standard procedure) was recorded from 370 nm to 500 nm after excitation with a 350 nm laser (Figure 2.45 left). The emission spectrum of catalyst **C2** was measured following the same procedure (Figure 2.45 right).

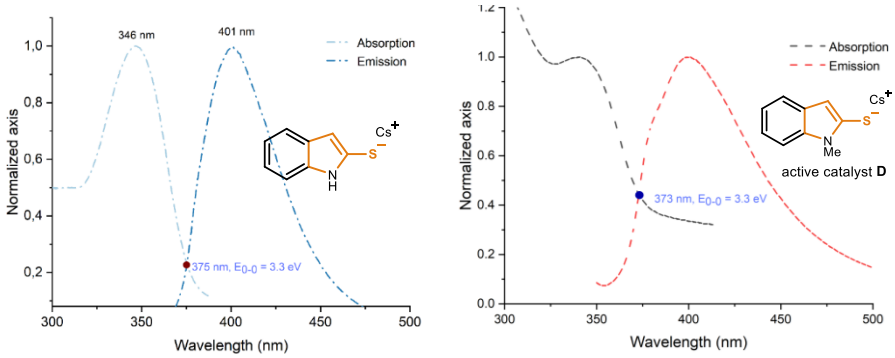


Figure 2.45. *left*) Normalized absorption and emission spectra of the active catalyst **D** (formed upon deprotonation of **C1**) in DMSO in a $1 \cdot 10^{-5}$ M solution. *right*) Normalized absorption and emission spectra of the deprotonated catalyst **C2.**

Stern-Volmer Quenching studies

Fluorescence measurements were carried out on an Aminco-Bowman Series 2 Luminescence spectrofluorimeter equipped with a high voltage PMT detector and continuum Xe light source. A 1.0 M solution of the quencher substrate in degassed DMSO (HPLC grade) was prepared and 20 μL of this stock solution were added to the solution of the active catalyst **D**, prepared according to the standard procedure. The addition of the substrate solution (the quencher) was repeated for four/five times. After each addition, the solution was mixed and the emission spectra of the excited catalyst was acquired from 380 nm to 500 nm (the excitation wavelength was fixed at 370 nm). A solvent blank was subtracted from all the measurements. The excitation wavelength was chosen in order to avoid saturation of the emission detector. The results shown in Figure 2.46-49 indicates that all substrates quenched the excited state emission of the deprotonated catalyst **C1** (anion **D**). The Stern-Volmer plot shows a linear correlation between the amounts of substrates and the ratio I_0/I, following the relationship: $I_0/I = 1 + KSV[Q]$ (Q = Quencher).

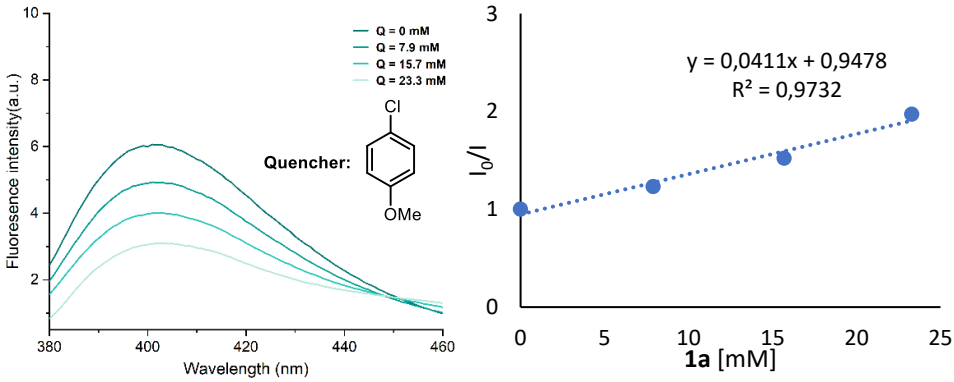


Figure 2.46. Stern-Volmer quenching studies with 1-chloro-4-methoxybenzene (**1a**).

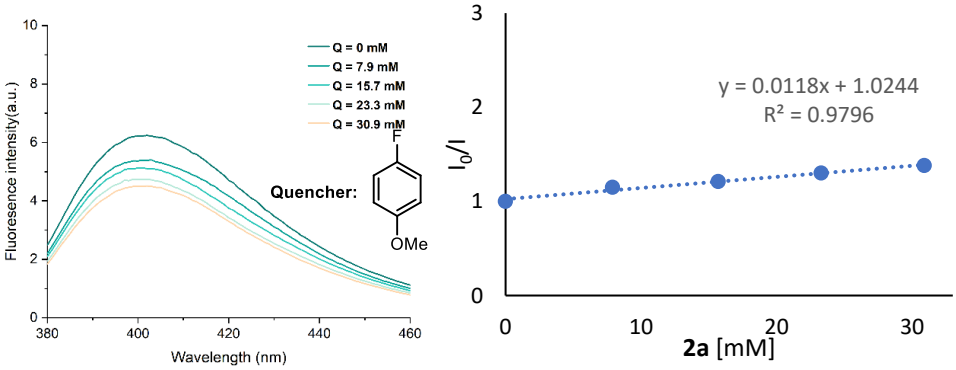


Figure 2.47. Stern-Volmer quenching studies with 1-fluoro-4-methoxybenzene (**2a**).

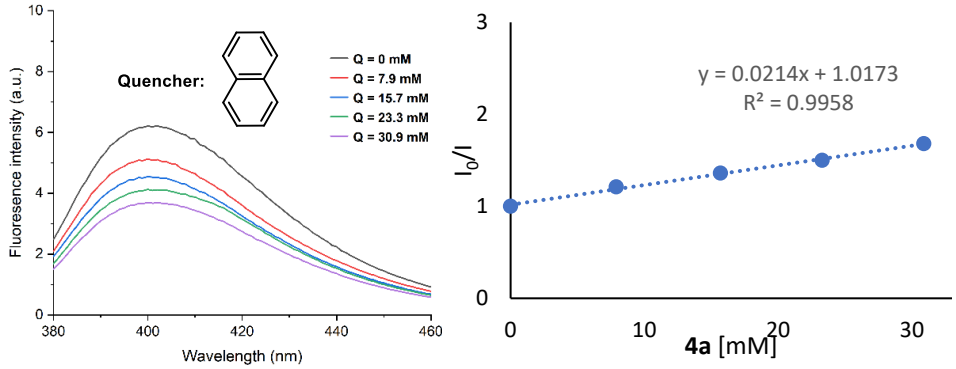


Figure 2.48. Stern-Volmer quenching studies with naphthalene (**4a**).

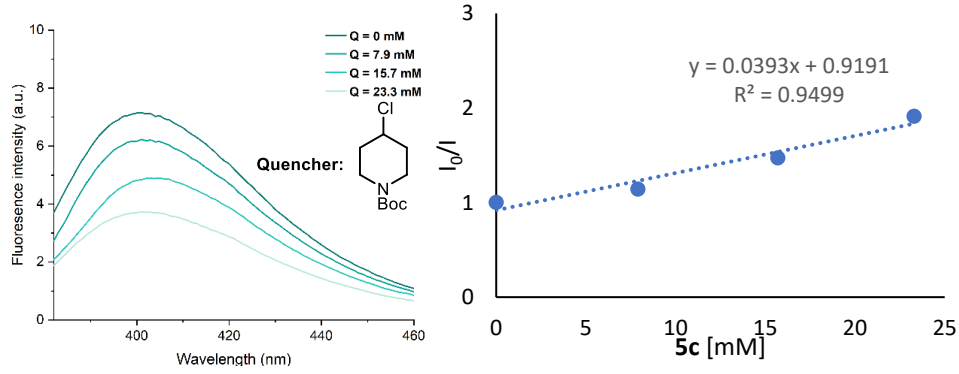


Figure 2.49. Stern-Volmer quenching studies with *N*-Boc-4-chloro-piperidine (**5c**).

Electrochemical Studies

Cyclic voltammetry (CV) measurements were carried out on a Princeton Applied Research PARSTAT 2273 instrument with a glassy carbon disk electrode (diameter: 3 mm) as working electrode. A silver wire coated with AgCl immersed in a 3.0 M aqueous solution of KCl and separated from the analyte by a fritted glass disk was employed as the reference electrode and a Pt wire counter-electrode completed the electrochemical setup. The scan rate was 100 mV/s unless otherwise stated. The substrates were measured at concentration of 0.02 M in DMSO with $TBAPF_6$ (0.1 M) as electrolyte. The preparation of the deprotonated catalyst solutions was carried out as described in the photophysics studies section (at a concentration of 0.02 M).

Potentials are quoted with the following notation: E_p^C (E_{Red}) refers to the cathodic peak potential, E_p^A (E_{Ox}) refers to the anodic peak potential.

Cyclic voltammetry measurements of the model substrates and pre-catalysts

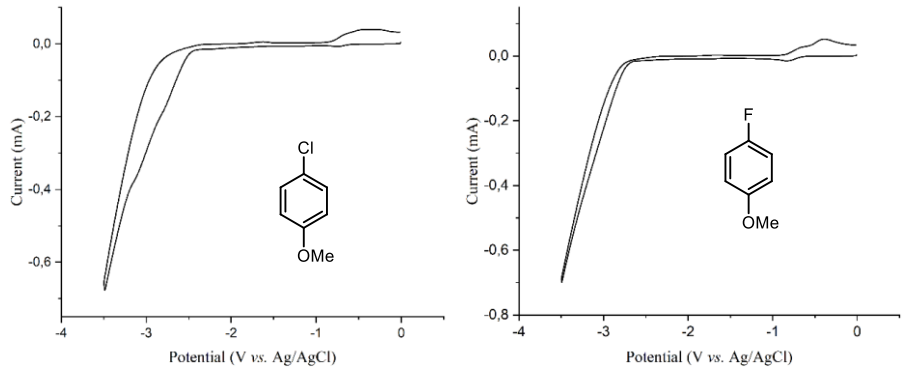


Figure 2.50 *left*) CV of 1-chloro-4-methoxybenzene (**1a**) in DMSO, reduction was not observed in the registered potential window. *right*) CV of 1-fluoro-4-methoxybenzene (**2a**) in DMSO, reduction was not observed in the registered potential window.

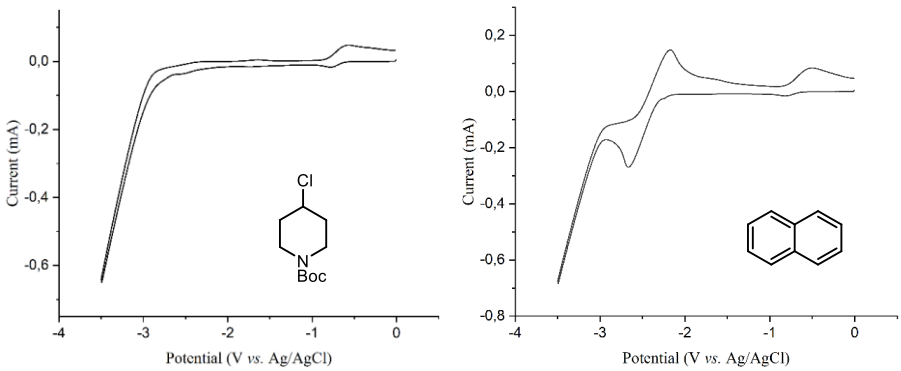


Figure 2.51. *left*) CV of *N*-Boc-4-chloro-piperidine (**5c**) in DMSO, reduction was not observed in the registered potential window. *right*) CV of Naphthalene (**4a**) in DMSO, reversible reduction $E_{1/2}$ = -2.43 V.

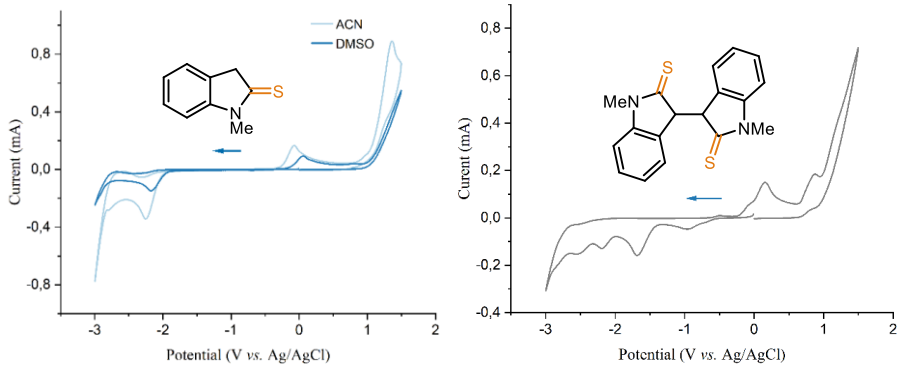


Figure 2.52. *left*) CV of catalyst **C1** in DMSO (dark blue) and in CH_3CN (light blue), irreversible reduction E_p^C = -2.20 V in DMSO; right) CV of dimer **33** in DMSO, irreversible reduction E_{p1}^C = -1.7 V, E_{p2}^C = -2.20 V and E_{p3}^C = -2.50 V.

Cyclic voltammetry measurements of catalytic active species

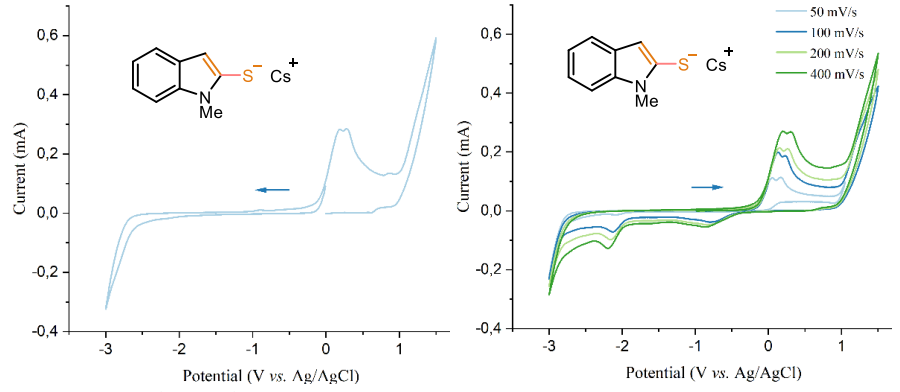


Figure 2.53. *left*) CV of the deprotonated catalyst **C1** (anion **D**) in DMSO starting with the reduction, irreversible oxidation E_{p1}^A = 0.13 V and E_{p2}^A = 0.27 V; *right*) CV of **D** DMSO starting with

the oxidation with a sweep rate from 50 to 400 mV/s, irreversible oxidation and reduction, E_p^A = 0.13 V, E_p^C = -2.22 V.

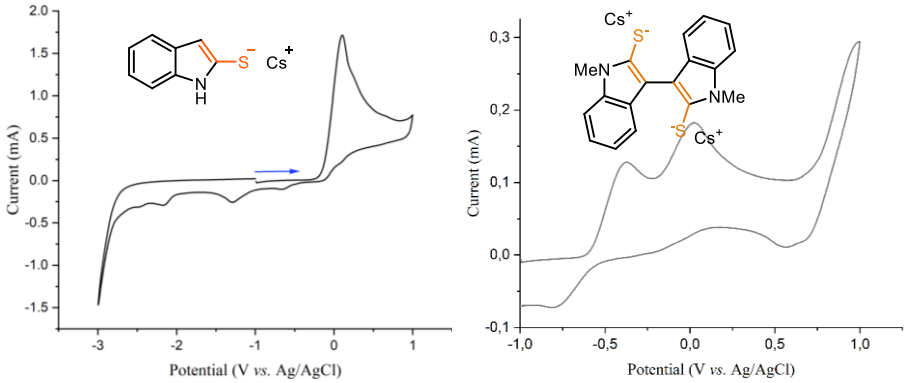


Figure 2.54 *left*) CV of the deprotonated catalyst **C2** in DMSO starting with the oxidation, irreversible oxidation E_p^A = 0.1 V; (*right*) CV of the deprotonated dimer **33** in DMSO, irreversible oxidation E_{p1}^A = -0.38 V and E_{p2}^A = 0.02 V.

Conversion of the potential from Ag/AgCl to SCE

The conversion of the redox potential from Ag/AgCl to SCE was done according to the literature by measuring the redox potential of ferrocene as reference in CH_3CN.[58]

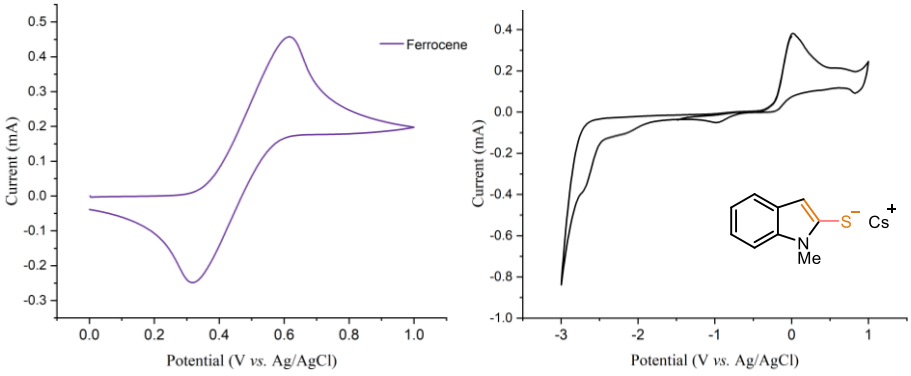


Figure 2.55. *left*) CV of ferrocene in CH_3CN, reversible reduction and oxidation $E_{1/2}$ = 0.46 V. *right*) CV of catalyst **C1** in CH_3CN, irreversible oxidation E_p^A = 0.01 V.

[58] Pavlishchuk, V. V.; Addison, A. W. "Conversion Constants for Redox Potentials Measured Versus Different Reference Electrodes in Acetonitrile Solutions at 25°C." *Inorganica Chim. Acta.* **2000**, *298*, 97–102.

With the reference CV, the redox potential *vs.* SCE in CH_3CN was calculated using the following equations:

$$E_p^A \text{ (Ag/AgCl to Fc/Fc}^+) = 0.01 - 0.46 = -0.45 \text{ V } vs. \text{ Fc/Fc}^+$$

$$E_p^A \text{ (Fc/Fc}^+ \text{ to SCE)} = (-0.45) + 0.38 = -0.07 \text{ V } vs. \text{ SCE}$$

Evaluation of the Excited-state Potential of the deprotonated catalyst C1 and C2

Using the data collected from the CV studies (Figure 2.53-54) and from the absorption and emission spectra (Figure 2.45) of the deprotonated catalyst **C1** (anion **D**) and **C2**, we could estimate the redox potential of the excited state with the following Equation: [59]

$$E(\mathbf{Pc}^{\bullet}/\mathbf{Pc}^{-*}) = E(\mathbf{Pc}^{\bullet}/\mathbf{Pc}^{-}) - E_{0\text{-}0}(\mathbf{Pc}^{-*})/(\mathbf{Pc}^{-})$$

Since the electrochemical oxidation of **D** is irreversible (Figure 2.52), the irreversible peak potential E_p anode was used for $E(Pc^{\bullet}/Pc^{-})$. The oxidation potential was calculated above to be -0.07 V *vs.* SCE (in ACN). $E_{0\text{-}0}(Pc^{-*})/(Pc^{-})$ was determined spectroscopically from the intersection of the normalized absorbance and emission spectra to have a value of 3.31 eV. The redox potential of excited-state **D**:

$$E(\mathbf{Pc}^{\bullet}/\mathbf{Pc}^{-*}) = 0.13 - 3.31 = \textbf{\textit{-3.18 V vs. Ag/AgCl}}$$

$$E(\mathbf{Pc}^{\bullet}/\mathbf{Pc}^{-*}) = (-0.07) - 3.31 = \textbf{\textit{-3.38 V vs. SCE}}$$

The redox potential of the excited-state deprotonated catalyst **C2** was calculated following the same equation.

$$E(\mathbf{Pc}^{\bullet}/\mathbf{Pc}^{-*}) = 0.10 - 3.31 = \textbf{\textit{-3.21 V vs. Ag/AgCl}}$$

[59] Buzzetti, L.; Crisenza, G. E. M.; Melchiorre, P. "Mechanistic Studies in Photocatalysis." *Angew. Chem. Int. Ed.* **2019**, *58*, 3730–3747.

Exclusion of EDA complex formation

The deprotonated catalyst was prepared and the absorption spectra measured as described in the photophysics studies section, with a catalyst concentration of 0.005 M and a substrate concentration of 0.1 M in DMSO.

There were not significant bathochromic shifts observed while mixing the catalyst and substrates, which indicated that no electron-donor-acceptor (EDA) complexes formed in the ground state (Figure 2.56-57).

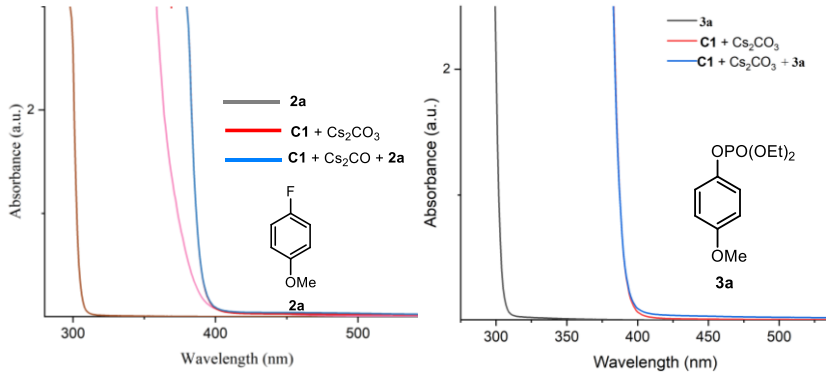


Figure 2.56. *left*) Absorption spectra recorded in DMSO of the mixture of catalyst **C1**, Cs_2CO_3 and substrate **2a**; *right*) Absorption spectra recorded in DMSO of the mixture of catalyst **C1**, Cs_2CO_3 and substrate **3a**.

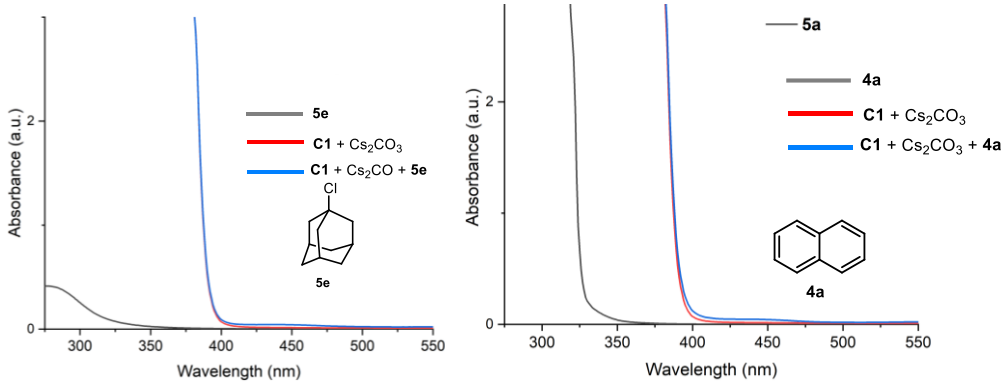


Figure 2.57. *left*) Absorption spectra recorded in DMSO of the mixture of catalyst **C1**, Cs_2CO_3 and substrate **5e**. *right*) Absorption spectra recorded in DMSO of the mixed catalyst **C1**, Cs_2CO_3 and substrate**4a**.

Proposed mechanism for the individual reactions

According to the reported literatures[60] and the discussions above, we propose the following mechanisms for the hydrogenation, phosphorylation and borylation exactions, and Birch-type reduction (Figure 2.58-61).

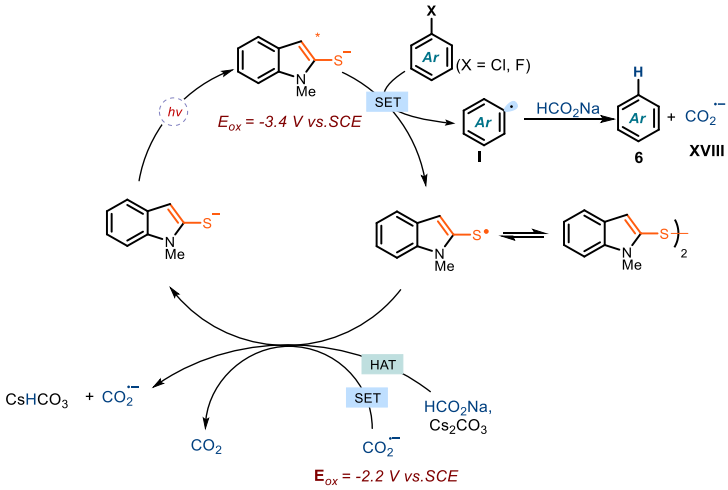


Figure 2.58. Proposed mechanism of the hydrogenation by using HCO_2Na as hydrogen donor.

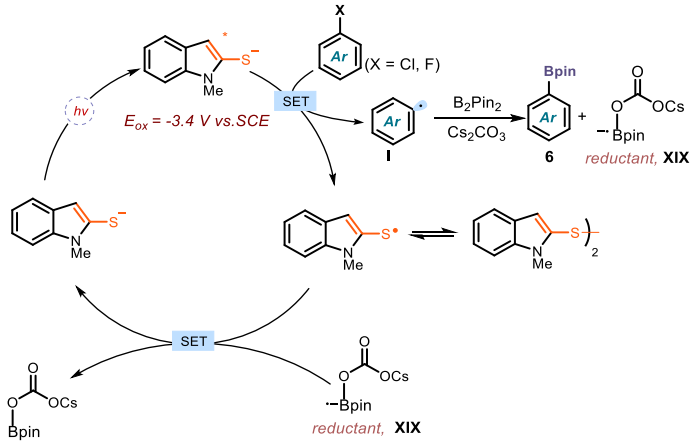


Figure 2.59. Proposed mechanism of the borylation process.

[60] Zhang, L.; Jiao, L. "Visible-Light-Induced Organocatalytic Borylation of Aryl Chlorides." *J. Am. Chem. Soc.* **2019**, *141*, 9124–9128.;

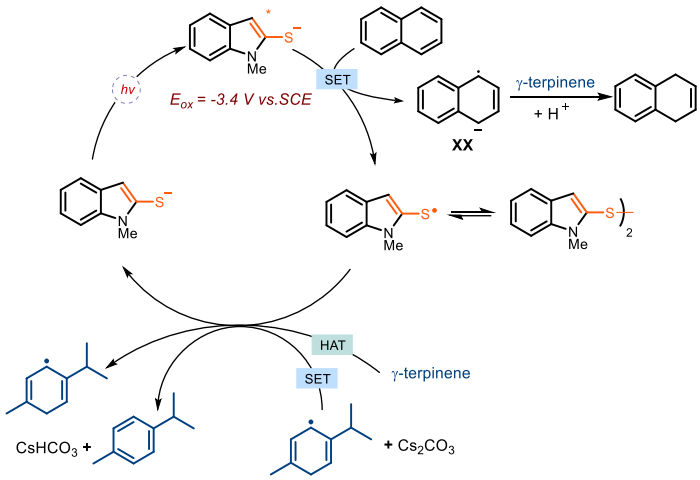


Figure 2.60. Proposed mechanism of the Birch-type reduction.

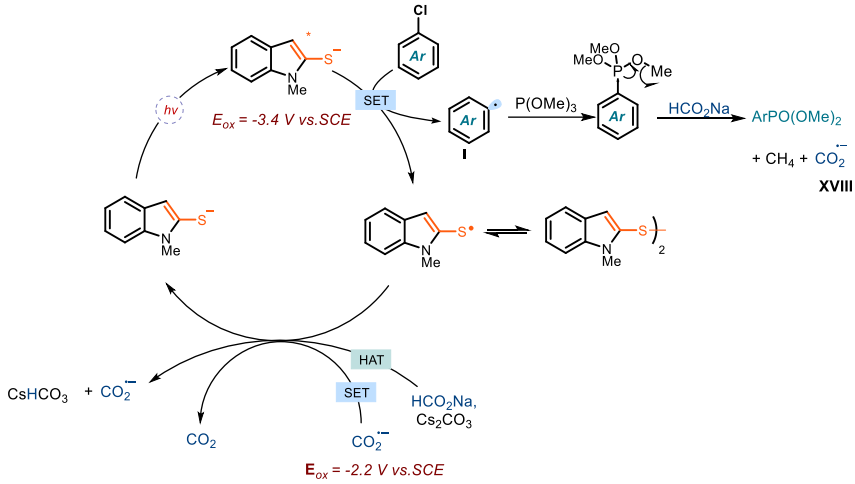
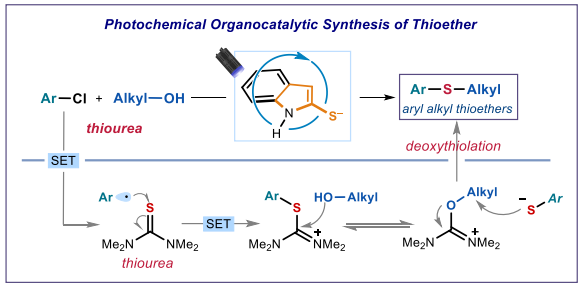


Figure 2.62. Proposed mechanism of the phosphorylation.

Chapter III

Photochemical Organocatalytic Synthesis of Thioethers from Aryl Chlorides and Alcohols

Target



To develop a thiol-free protocol for synthesizing aryl-alkyl thioethers from aryl chlorides and aliphatic alcohols by combining the photochemical organocatalytic reduction of aryl chlorides with a polar deoxythiolation step.

Tools

Using a cyclic thioamide as a strongly reducing organic photocatalyst to activate strong C(sp^2)-Cl bond in aryl chlorides, generating aryl radicals. 1,1,3,3-Tetramethylthiourea was then used to trap these aryl radicals, leading to the formation of the target thioethers via an overall radical-polar crossover deoxythiolation path with alcohols.[1]

3.1 Introduction

Thioethers are prevalent in natural products and pharmaceuticals with bioactivity against diseases like cancer, HIV, and Alzheimer's diseases.[2] Consequently, there has been

[1] The project discussed in this chapter has been conducted in collaboration with Dr. Thomas Hin-Fung Wong. I have contributed to the reaction design and development, the exploration of substrate scope, and the mechanistic investigations. This study has been published: Wu, S.; Wong, T. H.-F.; Righi, P.; Melchiorre, P. "Photochemical Organocatalytic Synthesis of Thioethers from Aryl Chlorides and Alcohols". *J. Am. Chem. Soc.* **2024**, *146*, 2907–2912.

[2] (a) Feng, M.; Tang, B.; Liang, S. H.; Jiang, X. "Sulfur Containing Scaffolds in Drugs: Synthesis and Application in Medicinal Chemistry." *Curr. Top. Med. Chem.* **2016**, *16*, 1200–1216; (b) Scott, K. A.; Njardarson, J. T. "Analysis of US FDA-Approved Drugs Containing Sulfur Atoms." *Top. Curr. Chem.* **2018**, *376*, 5; (c) Ilardi, E. A.; Vitaku, E.; Njardarson, J. T. "Data-Mining for Sulfur and Fluorine: An Evaluation of Pharmaceuticals to Reveal Opportunities for Drug Design and Discovery." *J. Med. Chem.*

substantial interest in developing synthetic methods for their efficient preparation. One valuable example is the thermal substitution of aryl (pseudo)halides **1** (where X is commonly I, Br, Cl, etc.) with aliphatic thiols (Figure 3.1a), leading to the construction of C(sp^2)-S bonds. This method provides a useful approach for preparing thioethers **3**.

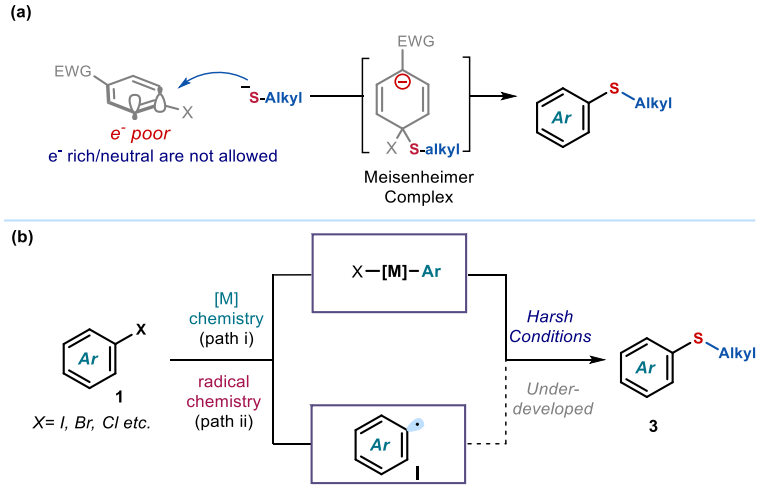


Figure 3.1. Strategies for aryl alkyl thioether synthesis. (**a**) Polar S_NAr reactions. **(b)** Transition-metal catalysis and photoredox ctalysis. EWG: electron-withdrawing groups.

In this process, the thiolate nucleophile adds to the π* orbitals of the arene, forming a dearomatized Meisenheimer intermediate. However, this reactivity typically occurs only with electronically deficient aryl fluorides at elevated temperature. Less activated aryl halides, such as more readily available aryl chlorides, are generally incompatible with this method. Another useful method for preparing aryl-alkyl thioethers **3** is based on transition-metal catalyzed C(sp^2)-S cross coupling reactions (Figure 3.1b).[3] In this approach, C-X bonds are

2014, *57*, 2832–2842; (d) Le Grand, B. L.; Pignier, C.; Letienne, R.; Cuisiat, F.; Rolland, F.; Mas, A.; Vacher, B. "Sodium Late Current Blockers in Ischemia Reperfusion: Is the Bullet Magic?" *J. Med. Chem.* **2008**, *51*, 3856–3866; (e) Chaffman, M.; Brogden, R. N. "Diltiazem: a review of its pharmacological properties and therapeutic efficacy." *Drugs* **1985**, *29*, 387–454; (f) Robinson, S. E.; Berney, S.; Mishra, R. and Sulser, F. "The relative role of dopamine and norepinephrine receptor blockade in the action of antipsychotic drugs: Metoclopramide, thiethylperazine, and molindone as pharmacological tools." *Psychopharm.* **1979**, *64*, 141–147.

[3] (a) Norris, T.; Leeman, K. "Development of a New Variant of the Migita Reaction for Carbon−Sulfur Bond Formation Used in the Manufacture of Tetrahydro-4-[3-[4-(2-methyl-1H-imidazol-1-yl)-

activated through oxidative addition with metals, forming a metal-aryl complex that can then react with thiolates. Although efficient, these organometallic protocols have some drawbacks, including the need for high catalyst loading, elevated temperatures, and strong bases. These issues are partly due to the limited ability of metal-based catalysts to activate C(sp^2)-Cl bonds in aryl chlorides, which restricts their general application to substrates with sensitive moieties. Overall, all these protocols rely on thiolates that, because of their undesirable traits—such as unpleasant odor, air instability, limited commercial availability, and the tendency to deactivate metal catalysts—are considered not preferred starting materials.

Photoinduced single-electron transfer (SET) process offers a mild alternative for activating C(sp^2)-X bonds, generating highly reactive aryl radicals from aryl halides (Figure 3.1b, path ii). In the previous chapter, we identified a strongly reducing organic photocatalyst, specifically a cyclic thioamide, that is effective in activating inert aryl chlorides upon excitation with purple light.[4] The resulting aryl radical species were used to form new C(sp^2)-B and C(sp^2)-P bonds through trapping. Given the existing limitations in thioether synthesis, which generally require thiols as substrates, this chapter explores the potential of using our strongly reducing photocatalyst to drive the photochemical, thiol-free organocatalytic synthesis of aryl-alkyl thioethers from aryl chlorides **1** (Figure 3.2). We aimed to avoid using thiols by instead employing widely available alkyl alcohols **2**. Central to this approach is tetramethylthiourea, which acts as a simple sulfur source by intercepting photochemically generated aryl radicals. Radical trapping by the thiourea, followed by an alcohol attack via a polar deoxythiolation pathway, leads to the formation of thioether products **3**.

phenyl]thio]phenyl-2H-pyran-4-carboxamide." *Org. Process Res. Dev.* **2008**, 12, 869–876; (b) de Koning, P. D.; Murtagh, L.; Lawson, J. P.; Vonder Embse, R. A.; Kunda, S. A.; Kong, W. "Development an Efficient Route to the 5-Lipoxygenase Inhibitor PF-04191834." *Org. Process Res. Dev.* **2011**, 15, 1046–1051.

[4] Wu, S.; Schiel, F.; Melchiorre, P. "A General Light-Driven Organocatalytic Platform for the Activation of Inert Substrates." *Angew. Chem., Int. Ed.* **2023**, 62, No. e202306364.

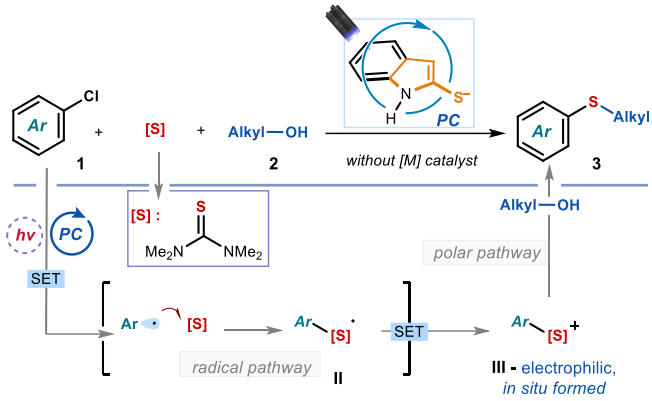


Figure 3.2. Proposed strategy for developing a thiol-free synthesis of aryl alkyl thioethers, enabled by combining radical and polar reactivity in a single sequence. SET: single-electron transfer, PC: photocatalyst.

To provide context for our research, the following section details previous methodologies for constructing aryl-alkyl thioethers using transition-metal catalysis and/or photochemical activation, with a particular focus on the formation of C(sp^2)-S bonds from C(sp^2)-Cl bonds.

3.2 Background

3.2.1 Transition-Metal Catalyzed Methods for the Synthesis of Aryl Alkyl Thioethers

Transition-metal catalyzed cross coupling reactions provide a useful approach for the synthesis of thioethers. The first C(sp^2)-S cross coupling catalyzed by a palladium catalyst was reported by Migita in 1978 (Figure 3.3).[5] It was proposed that the Pd(II) aryl complex **IV**, generated from the oxidative addition to aryl iodides **4**, could undergo transmetallation with sodium thiolate to provided Pd(II) sulfide species **V**. Subsequently, aryl alkyl thioethers **3** were obtained through carbon-sulfur reductive elimination.

[5] (a) Kosugi, M.; Shimizu, T.; Migita, T. "Reactions of Aryl Halides with Thiolate Anions in Presence of Catalytic Amounts of Tetrakis(Triphenylphosphine)Palladium Preparation of Aryl Sulfides." *Chem. Lett.* **1978**, 13–14; (b) Migita, T.; Shimizu, T.; Asami, Y.; Shiobara, J.; Kato, Y.; Kosugi, M. "The Palladium Catalyzed Nucleophilic-Substitution of Aryl Halides by Thiolate Anions." *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1385–1389.

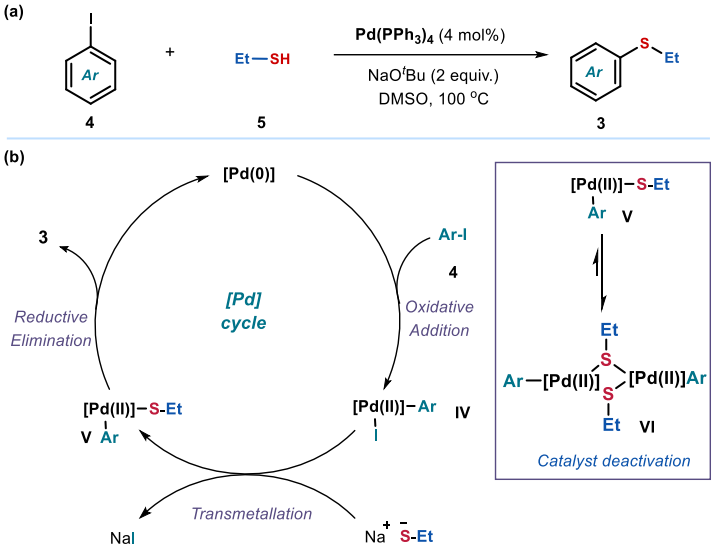


Figure 3.3. (a) Palladium-catalyzed C-S cross coupling. (**b**) Proposed catalytic cycle. Coordination of ligand to metal catalyst was not shown and was represented as brackets []. DMSO: dimethyl sulfoxide.

However, the formation of the deactivated metal sulfide dimer **VI**, arising from the coordination of thiolates with transition-metal catalysts, complicated the reactivity.[6] Additionally, activated aryl bromides and iodides, elevated temperatures (>90°C), and strong bases (such as NaOt-Bu) were required for this transformation. These harsh conditions limited the functional group tolerance and versatility of the method. This seminal work was followed by reports on nickel[7] and copper[8] catalysts performing the same transformation, but these methods suffered from similar limitations as their palladium counterparts.

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[6] (a) Hegedus, L. L.; McCabe, R. W. "Catalyst Poisoning." *Stud. Surf. Sci. Catal.* **1980,** *6*, 471–505; (b) Crabtree, R. H. *The Organometallic Chemistry of the Transition Metals*; John Wiley & Sons, Inc.: Hoboken, NJ, **2014**.

[7] (a) Cristau, H. J.; Chabaud, B.; Chene, A.; Christol, H. "Synthesis of Diaryl Sulfides by Nickel(II)-Catalyzed Arylation of Arenethiolates." *Synthesis* **1981**, *11*, 892–894; (b) Takagi, K. "Nickel(0)-catalyzed Synthesis of Diaryl Sulfides from Aryl Halides and Aromatic Thiols." *Chem. Lett.* **1987**, 2221–2224.

[8] Bates, C. G.; Gujadhur, R. K. and Venkataraman, D. "A General Method for the Formation of Aryl−Sulfur Bonds Using Copper(I) Catalysts." *Org. Lett.* **2002**, *4*, 2803– 2806; (d) Kwong, F. Y.; Buchwald, S. L. "A General, Efficient, and Inexpensive Catalyst System for the Coupling of Aryl Iodides and Thiols." *Org. Lett.* **2002**, 20, 3517–3520.

Later on, DuPont introduced a more effective C-S cross-coupling protocol by utilizing an uncommon phosphine oxide as a ligand.[9] This protocol could activate not only aryl bromides and iodides, but also less activated, more cost-effective, and readily available aryl chlorides,[10] although a single example was reported. Later, designing effective ligands for the activation of aryl chlorides became a growing trend.[11] By using bidentate DiPPF (1,1'-Bis(diisopropylphosphino)ferrocene) as ligand, Buchwald and co-workers[11a] developed a general aryl alkyl thioether synthesis from aryl chlorides (Figure 3.4a). This specific ligand secured the C(sp^2)-S cross coupling with reduced catalyst loading, using electron-rich and hindered aryl halides which were incompatible with earlier conditions. Meanwhile, Hartwig[11b] independently disclosed a similar system to prepare thioethers through activating aryl chlorides and coupled them with alkyl thiols (Figure 3.4b). A highly active and robust catalyst was generated using bidentate Josiphos ligand in the presence of a low loading of palladium pre-catalyst (down to 0.01%). The robust chelating ability of these bidentate phosphine ligands protected the metal center from deactivation and the formation of bridging thiolate complexes, thereby conferring high efficacy in the coupling process.[12]

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[9] Li, G. Y. "The First Phosphine Oxide Ligand Precursors for Transition Metal Catalyzed Cross Coupling Reactions: C-C, C-N, and C-S Bond Formation on Unactivated Aryl Chlorides." *Angew. Chem., Int. Ed.* **2001**, *40*, 1513–1516.

[10] Huang, L.; Ackerman, L. K. G.; Kang, K.; Parsons, A. M.; Weix, D. J. "LiCl-Accelerated Multimetallic Cross-Coupling of Aryl Chlorides with Aryl Triflates." *J. Am. Chem. Soc.* **2019**, *141*, 10978– 10983.

[11] (a) Murata, M.; Buchwald, S. L. "A general and efficient method for the palladium-catalyzed cross-coupling of thiols and secondary phosphines." *Tetrahedron.* **2004**, *60*, 7397– 7403; (b) Fernandez-Rodriguez, M. A.; Shen, Q. L.; Hartwig, J. F. "A General and Long-Lived Catalyst for the Palladium-Catalyzed Coupling of Aryl Halides with Thiols." *J. Am. Chem. Soc.* **2006**, *128*, 2180– 2181.

[12] Louie, J.; Hartwig, J. F. "Transmetalation, Involving Organotin Aryl, Thiolate, and Amide Compounds. An Unusual Type of Dissociative Ligand Substitution Reaction." *J. Am. Chem. Soc.* **1995**, *117*, 11598–11599.

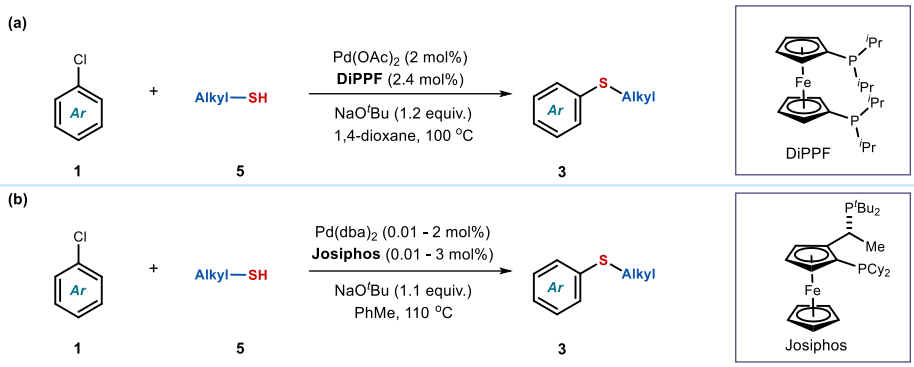


Figure 3.4. Palladium-catalyzed C-S cross coupling with specially designed ligands. **(a)** Use of the DiPPF ligand and **(b)** Josiphos ligand. DiPPF: (1,1′-Bis(diisopropylphosphino)ferrocene); Dba: dibenzylideneacetone.

Subsequent studies identified an air-stable, nickel-based oxidative addition complex that enables a mild cross-coupling reaction between aryl chlorides **1** and alkyl thiols **5** (Figure 3.5).[13] The reaction could readily occur at room temperature, providing thioethers in excellent yields. Relying on DFT computations, the proposed mechanism (depicted in Figure 3.5b) suggested that the pre-catalyst **[Ni]** would undergo ligand substitution, providing an acetate complex **VII** with thiol as a ligand. Through an event similar to a concerted metalation-deprotonation, the formed Ni(II) thiolate complex **VIII** can undergo reductive elimination to give the desired thioethers and release the active Ni(0) catalyst **IX**.

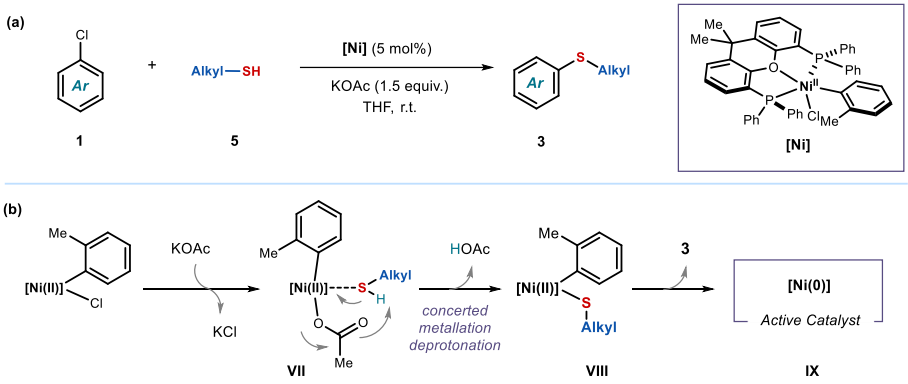


Figure 3.5. (a) Palladium-catalyzed C-S cross coupling using **[Ni]** precatalyst. **(b)** Proposed steps for catalyst activation. THF: tetrahydrofuran, r.t.: room temperature.

[13] Oechsner, R. M.; Wagner, J. P.; Fleischer, I. "Acetate Facilitated Nickel Catalyzed Coupling of Aryl Chlorides and Alkyl Thiols." *ACS Catal.* **2022**, *12*, 2233–2243.

Despite these advances, cross-coupling protocols largely relied on thiols **5**, which have undesirable traits such as unpleasant odor, air instability, and limited commercial variety. To circumvent the use of thiols, some metal-catalyzed approaches employed sulfur surrogates, where thiolates are generated in situ by reacting with aliphatic electrophiles (Figure 3.6).[14] However, elevated temperatures are still required, and some odorous sulfur reagents, like the Lawesson's reagent, cannot be avoided. Further improvements are needed to make these methods more generally applicable.

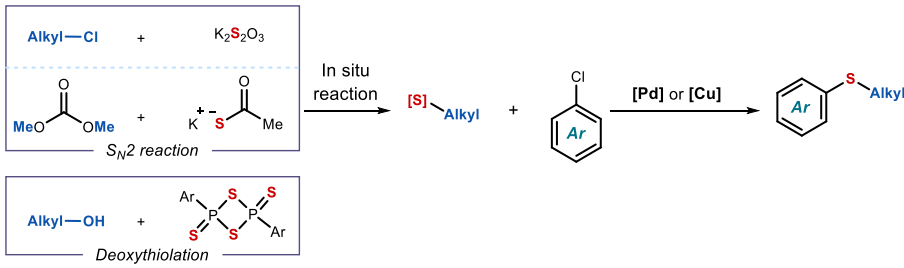


Figure 3.6. Metal-catalyzed C-S cross coupling using sulfur surrogates.

Alkyl-isothiouronium salt **III**, a bench stable and odorless reagent, has also been employed as sulfur surrogates to synthesize thioethers under mild condition (Figure 3.7). In 1985, Kajigaeshi [15] disclosed a general and transition metal-free strategy for the preparation of thioethers from primary alcohols **2** utilizing isothiouronium salts (Figure 3.7a). Alkyl-isothiouronium salts **III** were pre-formed via S_N2 nucleophilic substitution reaction between the nucleophilic tetramethylthiourea **A** and alkyl electrophiles (Figure 3.7b). Subsequent nucleophilic addition of common alkyl alcohols to the pre-synthesized salts **III** generates a hemithioacetal, which is in equilibrium with isouronium salt **X** upon extrusion of the thiolate. Eventually, the transiently formed thiolate nucleophile re-attacks the intermediate **X** at the alcoholic carbon, following a deoxythiolation polar pathway that leads to the formation of

[14] For selected examples: (a) Qiao, Z.; Wei, J.; Jiang, X. "Direct Cross-Coupling Access to Diverse Aromatic Sulfide: Palladium Catalyzed Double C−S Bond Construction Using $Na_2S_2O_3$ as a Sulfurating Reagent." *Org. Lett.* **2014**, *16*, 1212–1215; (b) Gholinejad, M. "One-Pot Copper-Catalysed Thioetherification of Aryl Halides Using Alcohols and Lawesson's Reagent in Diglyme." *Eur. J. Org. Chem.* **2015**, 4162. (c) Wang, M.; Qiao, Z.; Zhao, J.; Jiang, X. "Palladium-Catalyzed Thiomethylation via a Three-Component Cross-Coupling Strategy." *Org. Lett.* **2018**, *20*, 6193–6197.

[15] Fujisaki, S.; Fujiwara, I.; Norisue, Y.; Kajigaeshi, S. "A Facile One-pot Synthesis of Sulfides from Alkyl Halides and Alcohols Using Tetramethylthiourea." *Bull. Chem. Soc. Jpn.* **1985**, *58*, 2429– 2430.

the desired dialkyl thioethers. While demonstrating only a few examples with moderate yields, this reaction highlighted the potential of using thiouronium salts for the preparation of thioethers. Using these alkyl-isothiouronium salts, Maulide recently reported a simple and scalable method for the stereoselective synthesis of thioethers from alcohols, leveraging the stereospecificity of the deoxythiolation pathway (Figure 3.7c).

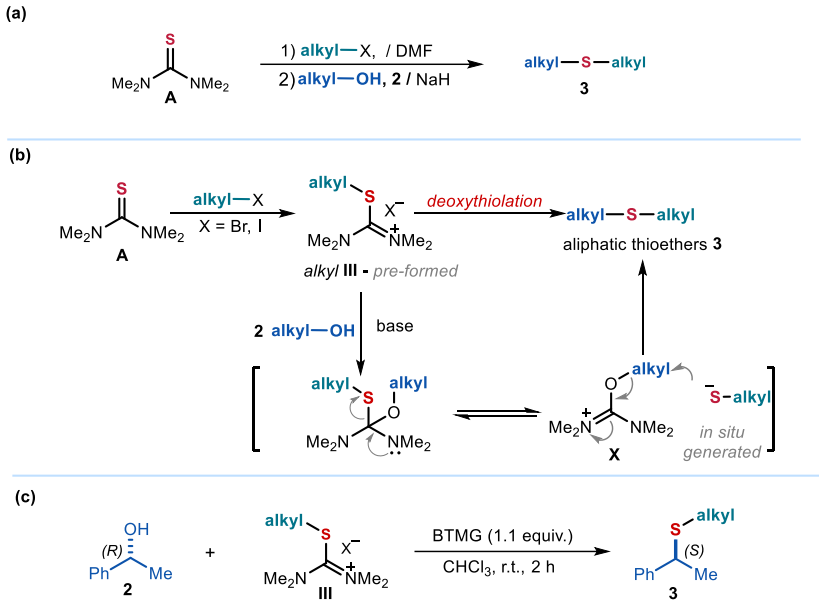


Figure 3.7. Synthesis of thioethers using alkyl-isothiouronium salts **III** as a sulfur surrogate. **(a)** Preliminary strategy for preparation of thioethers from alcohols. **(b)** Stereoselective synthesis of thioethers from alcohols. **(c)** Proposed steps for reaction. DMF: dimethylformamide; BTMG: 2-tert-Butyl-1,1,3,3-tetramethylguanidine; r.t.: room temperature.

While these methods employ readily available substrates, such as alkyl halides and alcohols, they necessitate the pre-synthesis of alkyl-isothiouronium salts **III** and are limited to the formation of aliphatic thoether products.

Photochemistry has recently emerged as efficient technology for the construction of C(sp^2)-S bonds.[16] An external photoredox catalyst can both induce an SET event under light

[16] (a) Chan, A. Y.; Perry, I. B.; Bissonnette, N. B.; Buksh, B. F.; Edwards, G. A.; Frye, L. I.; Garry, O. L.; Lavagnino, M. N.; Li, B. X.; Liang, Y.; Mao, E.; Millet, A.; Oakley, J. V.; Reed, N. L.; Sakai, H. A.; Seath, C. P.; MacMillan, D. W. C. "Metallaphotoredox: The Merger of Photoredox and Transition Metal Catalysis." *Chem. Rev.* **2022**, *122*, 1485–1542; (b) Beletskaya, I. P.; Ananikov, V. P. "Transition-Metal-Catalyzed C−S, C−Se, and C−Te Bond Formations via Cross-Coupling and Atom-Economic Addition Reactions. Achievements and Challenges." *Chem. Rev.* **2022**, *122*, 16110–16293.

excitation to generate radicals and modulate the oxidation states of metal catalysts, enabling specific elementary steps of the metal-catalyzed cycle (Figure 3.8). This method for cross coupling operates under mild condition, overcoming the high barrier in electrophile activation without requiring elevated temperatures or additional redox reagents.

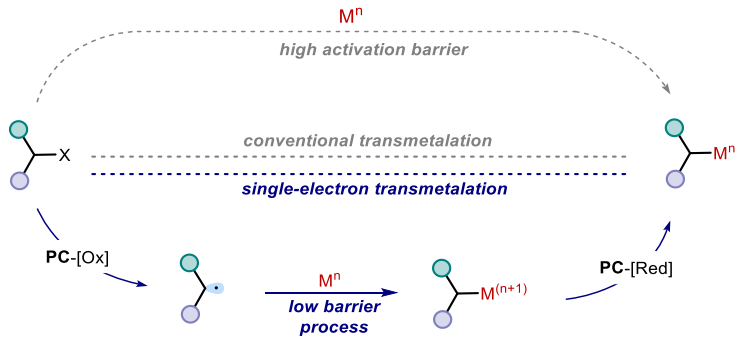


Figure 3.8. Coupling of photoredox and transition-metal catalysis.

This metallo-photoredox tactic was first applied to C-S cross coupling by Oderinde and Johannes.[17] A nickel pre-catalyst was employed in synergy with an external photocatalyst, promoting the formation of C-S bond from aryl iodides **4** and thiols **5** at ambient temperature (Figure 3.9a). This C−S cross-coupling method exhibits remarkable functional group tolerance, and the reactions can be carried out in the presence of molecular oxygen. Mechanistic investigations indicated that the reaction proceeded through a transient Ni(I)-species and thiyl radicals. However, aryl chlorides remained unreactive. Only in 2023, the first methodology based on aryl chlorides for metallophotoredox C(sp^2)-S-alkyl cross coupling was reported. This method combined nickel catalysis with an organic photocatalyst but still required the use of thiols (Figure 3.9b).[18c]

[17] For selected examples, see: (a) Oderinde, M. S.; Frenette, M.; Robbins, D. W.; Aquila, B.; Johannes, J. W. "Photoredox Mediated Nickel Catalyzed Cross-Coupling of Thiols with Aryl and Heteroaryl Iodides via Theil Radicals." *J. Am. Chem. Soc.* **2016**, *138*, 1760–1763; (b) Düker, J.; Ghosh, I.; Konig, B. "Sequential One-Pot (Het)arene Thioetherification and Amination with Nickel and Visible Light." *ACS Catal.* **2023**, *13*, 13618. (c) Ghosh, I.; Shlapakov, N.; Karl, T. A.; Düker, J.; Nikitin, M.; Burykina, J. V.; Ananikov, V. P.; König, B. "General cross-coupling reactions with adaptive dynamic homogeneous catalysis." *Nature* **2023**, *619*, 87–93.

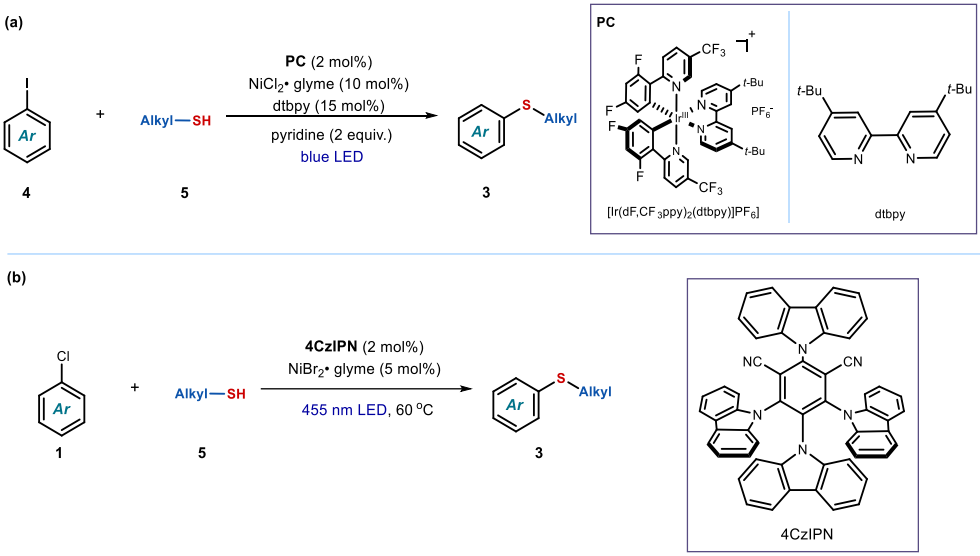


Figure 3.9. Metallophotoredox C-S cross coupling. **(a)** Photoredox mediated nickel catalyzed cross-coupling of thiols with aryl iodides; (**b**) Recently reported procedure for C-S cross coupling from aryl chlorides. LED: light-emitting diode.

3.2.2 Photochemical Methods for the Synthesis of Aryl Alkyl Thioethers

Researchers have recently explored methods for preparing thioethers that do not require transition metals. One such method involves the direct coupling of thiols with aryl moieties through photocatalyzed radical pathways (Figure 3.10), eliminating the need for a metal catalyst. An example of this is the thiyl radical-mediated thiol-ene click reaction, where thiyl radicals add to alkenes to produce alkyl radicals, which then undergo hydrogen atom transfer (HAT) from thiols, resulting in the formation of thioether products while propagating a radical chain (Figure 3.10a).[18] In this system, the key C(sp^2)-S bond is already pre-installed in thiophenol substrates.

[18] (a) Tyson, E. L.; Ament, M. S.; Yoon, T. P. "Transition Metal Photoredox Catalysis of Radical Thiol-Ene Reactions." *J. Org. Chem.* **2013**, *78*, 2046– 2050; (b) Das, A. K.; Thomas, R. J. "Facile Thiol−Ene Click Protocol Using Benzil as Sensitizer and White LED as Light Source." *Eur. J. Org. Chem.* **2020**, *2020*, 7214–7218; (c) Singh, M.; Yadav, A. K.; Yadav, L. D. S.; Singh, R. K. P. "Visible Light Photocatalysis with Benzophenone for Radical Thiol-Ene Reactions." *Tetrahedron Lett.* **2017**, *58*, 2206–2208.

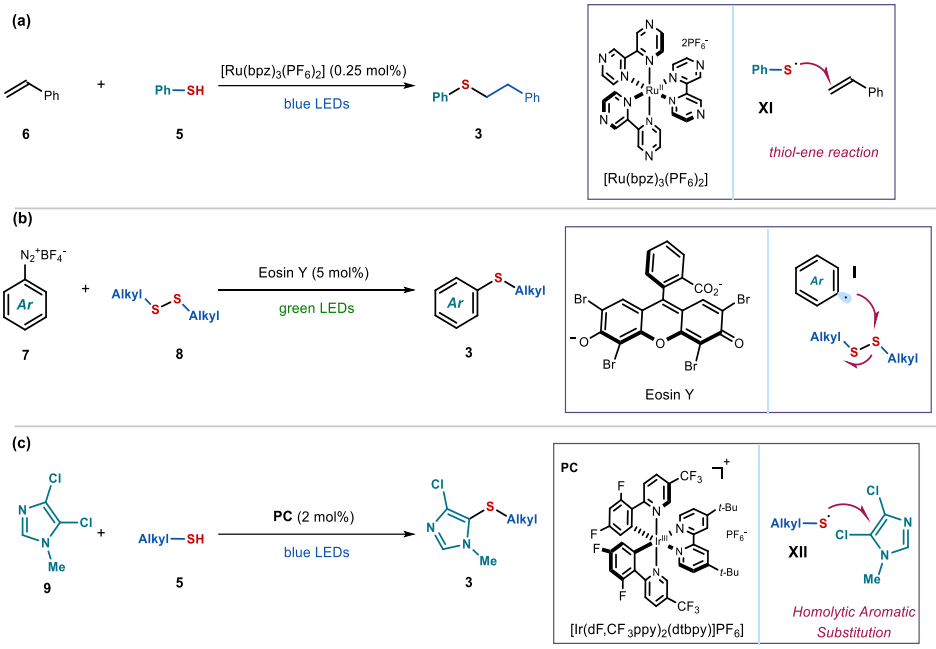


Figure 3.10. Metal-free photoredox C-S cross coupling. **(a)** Thiol-ene reactions; (**b**) A photoredox thioether synthesis via aryl radical **I** addition to disulfide; **(c)** A photoredox thioether synthesis via thiyl radical **XI** addition to halogenated heterocycles.

In an alternative approach, electrophilic aryl radicals **I**, generated from Eosin Y photocatalyst via SET reduction of aryl diazonium salts **7**, are trapped by alkyl disulfide **10**, forming the key C(sp^2)-S bond and produce alkyl aryl thioether products. However, the utility of this protocol is limited by the need for specialized starting materials (Figure 3.10).[19]

Thiyl radicals are also known to attack heterocyclic aryl chlorides,[20] providing the target products through site-selective homolytic aromatic substitution (Figure 3.10c). Electron-rich and neutral five-membered chlorinated heterocycles **9** were used as radical acceptors to form C(sp^2)-S bonds. Due to the electrophilic nature of the thiyl radicals, electron-deficient arenes were not suitable substrates. Additionally, the use of thiols as reactants was unavoidable.

[19] Majekz, M. and von Wangelin, A. J. "Organocatalytic visible light mediated synthesis of aryl sulfides." *Chem. Comm.*, **2013**, *49*, 5507– 5509.

[20] Sandfort, F.; Knecht, T.; Pinkert, T.; Daniliuc, C. G.; Glorius, F. "Site-Selective Thiolation of (Multi)halogenated Heteroarenes." *J. Am. Chem. Soc.* **2020**, *142*, 6913–6919.

Overall, both transition-metal-catalyzed and photochemical strategies for thioether synthesis have fallen short in practicality. It is desirable to develop a *metal- and thiol-free* protocol that uses widely accessible chemicals to construct aryl C(sp^2)-S bonds.

3.3 Design and Target of the Project

Our study aimed to develop a mild protocol for thioether synthesis using readily available aryl chlorides, without relying on thiols. To achieve this goal, we drew inspiration from two strategies. Firstly, we recently reported a highly reducing indole thiolate photocatalyst (detailed in Chapter II)[21] that can generate aryl radicals via SET activation of inert C(sp^2)-Cl bonds (Figure 3.11). Specifically, we found that the deprotonated cyclic thioamide catalyst absorbs purple light, becoming a strong reductant in its excited state (E(**PC**•/[**PC**$^-$]*) < -3.0 V). This redox power served to generate aryl radicals from the corresponding aryl chlorides, which were then intercepted to form new C-P and C-B bonds.

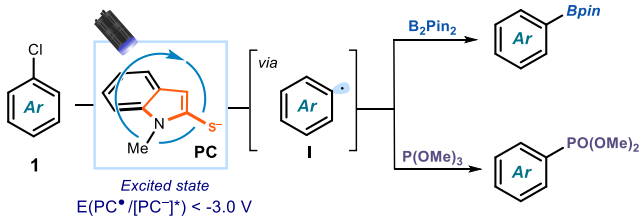


Figure 3.11. Photoredox activation of aryl chlorides, enabled by the excitation of an organic anion catalyst.

A second inspiration came from an approach to thioether synthesis that has the potential to avoid using thiols or metal catalysts, relying instead on widely accessible and stable chemicals, such as alcohols. This method relies on the reported chemistry of isothiouronium salts **III**, which was briefly discussed above in Figure 3.7.[22] Specifically, the pre-formed

[21] Wu, S.; Schiel, F.; Melchiorre, P. "A General Light-Driven Organocatalytic Platform for the Activation of Inert Substrates." *Angew. Chem., Int. Ed.* **2023**, 62, No. e202306364.

[22] (a) Fujisaki, S.; Fujiwara, I.; Norisue, Y.; Kajigaeshi, S. "A Facile One-pot Synthesis of Sulfides from Alkyl Halides and Alcohols Using Tetramethylthiourea." *Bull. Chem. Soc. Jpn.* **1985**, *58*, 2429–2430; (b) Alan Aitken, R.; Ali, K.; Mesher, S. T. E. "Kinetic Resolution of Secondary Alcohols Using Proline-Derived Bicyclic Iminium Salts." *Tetrahedron Lett.* **1997**, *38*, 4179–4182; (c) Merad, J.; Matyasovsky, J.; Stopka, T.; Brutiu, B. R.; Pinto, A.; Drescher, M.; Maulide, N. "Stable and Easily Available Sulfide Surrogates Allow a Stereoselective Activation of Alcohols." *Chem. Sci.* **2021**, *12*, 7770–7774.

alkyl-isothiouronium salts **III**, generated from a substitution reaction between tetramethylthiourea **A** and alkyl electrophiles, can undergo nucleophilic addition with common alkyl alcohols to produce a hemithioacetal **X'**. Such intermediate is in equilibrium with isouronium salt **X** upon extrusion of thiolate (Figure 3.12a). Subsequently, the transiently formed thiolate nucleophile re-attacks the intermediate **X** at the alcoholic carbon, following a *deoxythiolation polar* pathway that leads to the formation of the desired dialkyl thioethers. Although this method uses readily available substrates, it requires the pre-synthesis of alkyl-isothiouronium salts **III**.

We aimed to combine our strongly reducing organic photocatalyst with the polar deoxythiolation pathway to achieve the thiol-free photochemical synthesis of thioethers from aryl chlorides and alcohols. This idea required the design of a radical-polar sequence (Figure 3.12b). Central to our plan was the discovery that tetramethylthiourea **A** can intercept photochemically generated aryl radicals, leading to the in situ formation of aryl isothiouronium salts **III** upon SET oxidation of the resulting radical intermediate **II**. The subsequent reaction of alcohols with **II** then follows the established polar deoxythiolation path depicted in Figure 3.12a to yield the desired aryl-alkyl thioether product **3**.

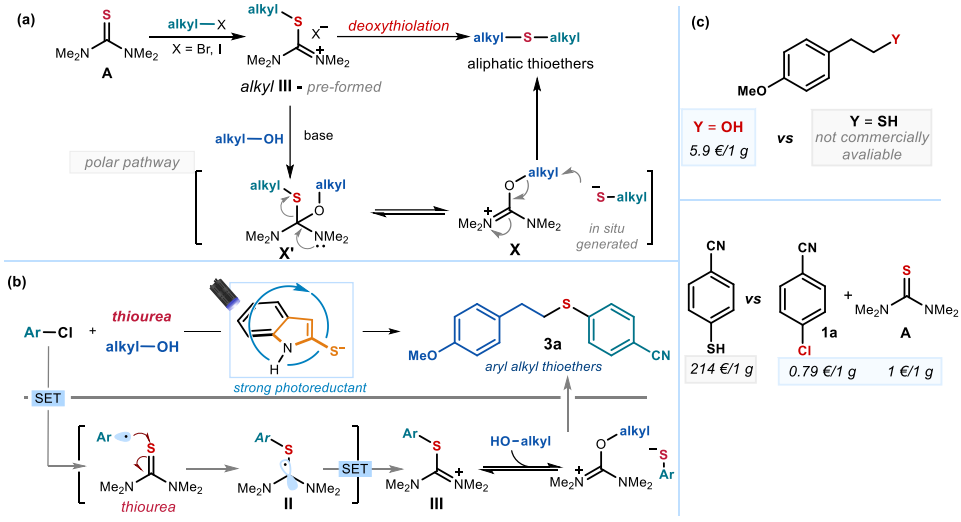


Figure 3.12. Our design plan for dialkyl thioether synthesis: **(a)** The polar deoxythiolation path; **(b)** The proposed strategy for combining photoredox activation of aryl chlorides with deoxythiolation; **(c)** Practical Considerations for thioether synthesis by price comparison of starting materials. Data from Sigma-Aldrich, accessed in November 2023.

The practical benefits of our method for thioether preparation can be appreciated when evaluating the commercial supply of precursors to access thioether **3a** (Figure 2.11c). While current methods necessitate costly or noncommercially available thiols for the one-step synthesis of the target product **3a**, our approach instead would capitalize on the affordability of a wide commercial assortment of aliphatic alcohols[23] and aryl chlorides.[24]

In the following section, we discuss the development and implementation of this photochemical organocatalytic method for synthesizing aryl-alkyl thioethers. The protocol requires low temperature (40 °C), purple light irradiation (405 nm), and inexpensive, widely available substrates such as aryl chlorides **1** and aliphatic alcohols **2**.

3.4 Results and Discussion

3.4.1 Optimization of Reaction Conditions and Substrate Scope

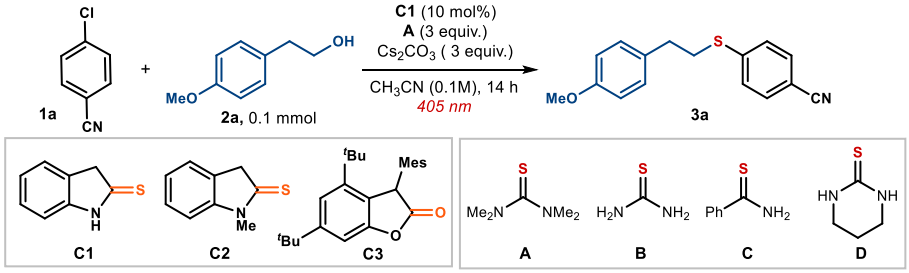
At the outset, we investigated the feasibility of our design plan by using 1,1,3,3-tetramethylthiourea **A** as the sulfur source and radical trap, 4-chlorobenzonitrile **1a** as the radical precursor [$E(\mathbf{1a}/\mathbf{1a}^{\bullet-})$ = -2.2 V vs Ag/AgCl], and 4-methoxyphenethyl alcohol **2a** as the nucleophile (Table 3.1). The experiments were performed in acetonitrile (CH_3CN) as the solvent under irradiation by a purple light-emitting-diode (LED, *evoluchem*, λ_{max} = 405 nm). We initially tested the highly reducing cyclic thioamide catalysts **C1** and **C2**, which we recently developed for C(sp^2)-Cl bonds activation.[21] The reactions, conducted using 10 mol% of photocatalysts **C1** and **C2** and in the presence of Cs_2CO_3 (3 equiv.) to facilitate the generation of the photoactive deprotonated intermediate, afforded the target product **3a** in 80% and 50% yield, respectively (Table 3.1, entries 1 and 2). We also tested catalyst **C3**, a newly synthesized photoreductant, which displayed significantly reduced reactivity (entry 3). Control experiments established that the presence of photocatalyst and light was essential for product formation (entries 4-5). When adding the radical scavenger TEMPO (2,2,6,6-

[23] Dong, Z.; MacMillan, D. W. C. "Metallaphotoredox-enabled deoxygenative arylation of alcohols." *Nature* **2021,** *598,* 451–456.

[24] In the current study, 35 different products were synthesized from aryl chloride/bromide substrates, all of which were directly procured from chemical suppliers. In contrast, only 10 of the corresponding thiophenols are commercially available, based on information from Sigma Aldrich, as of June 2024.

tetramethylpiperidine 1-oxyl, 2 equiv., entry 6), the reactivity was completely inhibited, which was congruent with a radical path being operative.

Table 3.1. Optimization studies.[a]



entry	deviation	yield [%][a]	entry	deviation	yield [%][a]
1	none	**80**	6	TEMPO (2 equiv.)	0
2	**C2** (10%)	50	7	**B-D**	0
3	**C3** (10%)	30	8	K_2CO_3	50
4	no light or no base	0	9	DMSO or DMF or DCM	0
5	dark, 70 °C	0	10	PhCl insetad of **1a**	5

[a] Reactions performed on a 0.1 mmol scale for 14 h using 3 equiv. of **1a**, 1 equiv. of **2a**, 10 mol% of **C1** photocatalyst, 3 equiv. of **A** and cesium carbonate, in 0.2 mL of MeCN under illumination by a purple LED (*EvoluChem*) at 405 nm, temperature kept constant at 45 °C using a fan. [a] Yield inferred by ^{1}H NMR analysis of the crude mixture using 1,3,5-trimethoxybenzene as an internal standard. Mes: mesityl.

When exploring other sulfur sources **B-D**, the desired thioether product **3a** was not formed. The lack of reactivity can be rationalized based on the following reason (Figure 3.13): (1) the presence of acidic protons in substrates **B-D**, which may be deprotonated to afford nucleophilic thiolates, significantly complicating the reaction; (2) compared to thiourea **A**, **B-D** are less electron-rich, potentially making them less reactive towards intercepting electrophilic aryl radicals; (3) the aryl-isothiouronium salt derived from tetramethylthiourea **A** is more electrophilic than the neutral adducts formed from **B-D**, making it more efficient in the deoxythiolation step with alcohols.

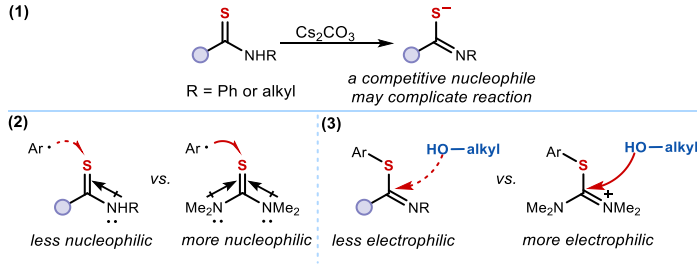


Figure 3.13. Rationalizing the poor performance of sulfur surrogates **B-D**.

Additional screening of bases and solvents resulted in inferior results (entries 8-9). Using chlorobenzene as radical precursor, which is more difficult to reduce (E_{red} < -2.9 V vs. SCE), afforded the corresponding product only in traces (5% yield, entry 10).

We then examined the scope of this photochemical thioetherification strategy by using the conditions reported in entry 1 of Table 3.1. Commercial aryl bromides were used when the corresponding chlorides were not commercially available. We initially explored the reactivity of diverse aryl chlorides **1** as radical precursors, using 4-methoxyphenethyl alcohol **2a** as the nucleophile (Figure 3.13). First, we demonstrated that the process was equally efficient on a 5 mmol scale, yielding 1.0 g of product **3a** (75% yield). Compound **3a** could be synthesized not only by SET activation of chloride **1a** but also upon reduction of the corresponding fluoride, bromide, and iodide. Aryl chlorides with diverse substituents at various positions on the phenyl ring were well tolerated, yielding products **3b**−**3h** in a high yield. It is noteworthy that, when multiple halides are present, only the weakest C-X bond was activated, and less reactive yet reducible halide(s) could be retained (adducts **3g** and **3h**).

The reaction was compatible with substrates containing polycyclic aromatic structures (adducts **3i**−**3k**) and valuable *N*-heterocyclic frameworks, encompassing pyridines, pyrimidines, and quinolines (products **3l**–**3q**). Notably, late-stage modification of chlorine-containing drug molecules, such as the selective COX-2 inhibitor *Etoricoxib* (product **3r**) and the antidepressant *Moclobemide* (**3s**), was achieved, albeit in moderate yields. Functional groups such as ketone (**3c**), sulfone (**3d**, **3r**), secondary amide and amine (**3s**), were tolerated, showcasing the chemoselectivity of the transformation.

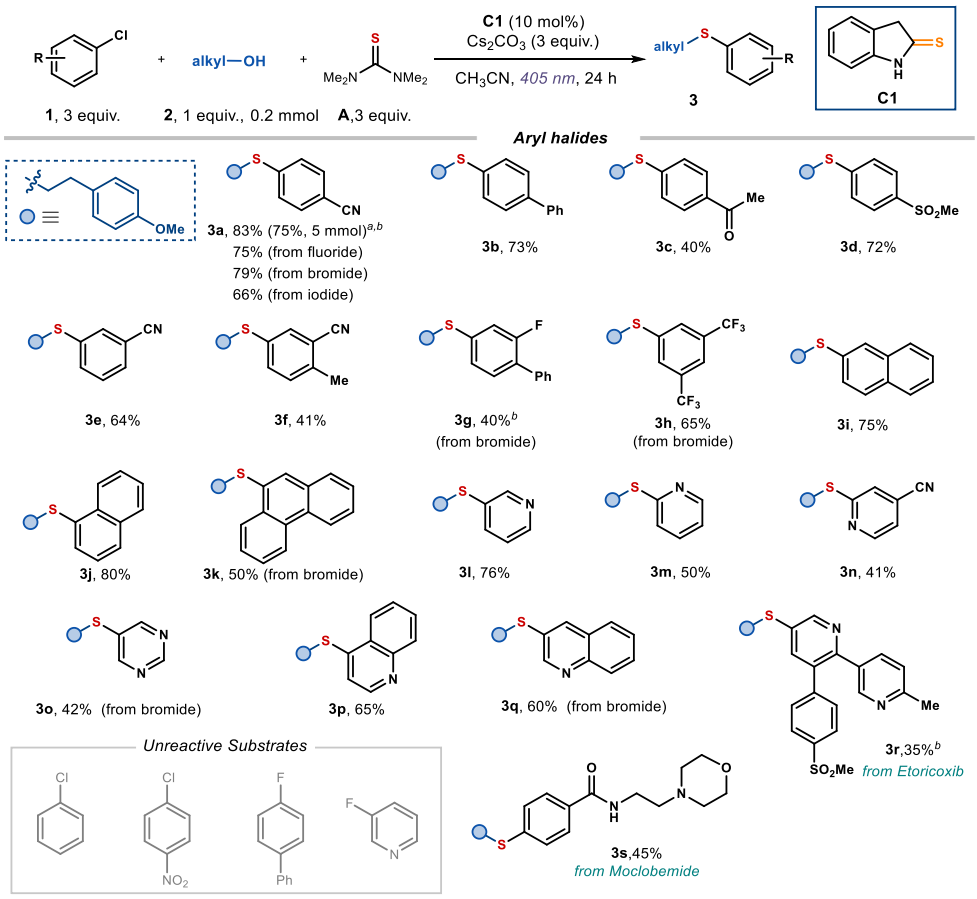


Figure 3.14. Aryl halides that can participate in the photochemical organocatalytic synthesis of thioethers from aryl chlorides and alcohols. Reactions performed on a 0.2 mmol scale at 40 °C using photocatalyst **C1** (10 mol %), 3 equiv of **1** and 3 equiv of thiourea **A** under illumination by a purple LED (*EvoluChem*) at 405 nm. Yields refer to isolated products **3** after purification. Aryl chlorides were used as radical precursors unless otherwise stated. [a]5 mmol scale reaction. [b]48 h reaction time. Boc: *tert*-butyloxycarbonyl.

A limitation of the method was that electron-neutral, such as chlorobenzene, or electron-rich aryl chlorides were not reactive. Strong C-F bonds were also reluctant to be activated, and nitro groups were not tolerated under this set of conditions (Figure 3.14, grey box).

We next examined the spectrum of alcohols compatible with this photochemical organocatalytic method (Figure 3.15). Primary alcohols **2**, bearing potentially reactive aromatic systems such as phenol, thiophene, and halogen substituents, underwent smooth reactions, producing thioethers **3t–3w**. A diverse array of functional groups was well-tolerated, including an ether (adduct **3aa**), tertiary amine (**3ab**), carbamate (**3ac**), and

thioether (**3ad**). Sensitive functional moieties were preserved, including trimethylsilane (**3ae**), silyl ether (**3af**), acrylate (**3ag**), and oxetane (**3ah**). Alkenes and alkynes, potentially susceptible to radical additions, showed compatibility (**3ai–3an**). Straightforward thioetherification of feedstock methanol, ethanol and benzyl alcohol was also achieved (**3ao–3aq**). Complex substrates such as natural products *myrtenol* (adduct **3aj**), *geraniol* (**3ak**), *perillol* (**3al**), *Lithocholic acid* derivative (**3ar**), and the pharmaceutical agent *Perphenazine* (**3as**) were efficiently functionalized.

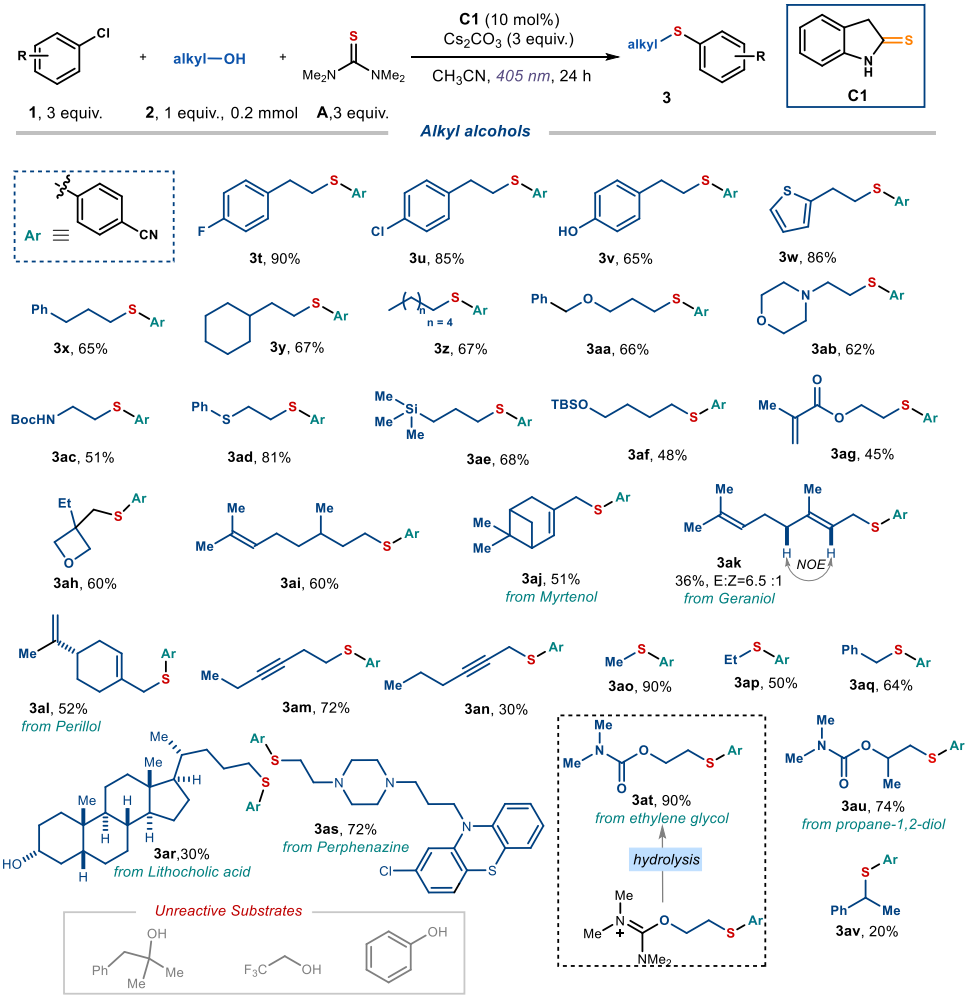


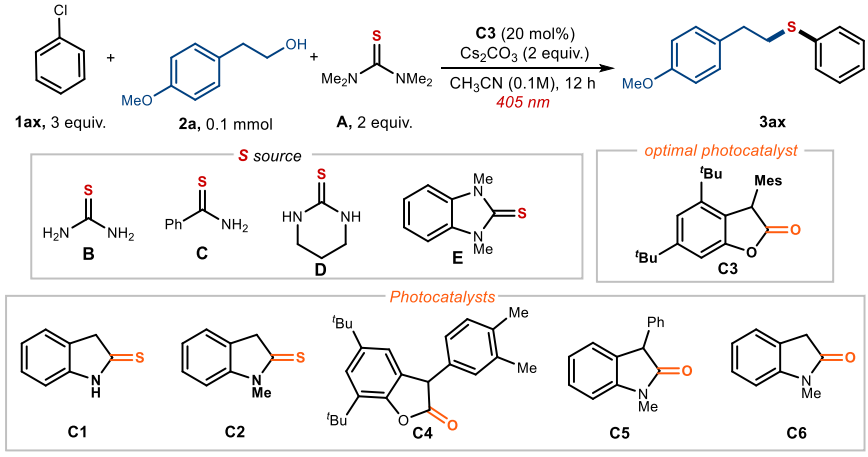
Figure 3.15. Alcohols that can participate in the photochemical organocatalytic synthesis. Reactions performed on a 0.2 mmol scale at 40 °C using photocatalyst **C1** (10 mol %), 3 equiv of **1** and 3 equiv of thiourea **A** under illumination by a purple LED (*EvoluChem*) at 405 nm. Yields refer to isolated products **3** after purification. TBS: butyl(dimethyl)silyl.

Interestingly, diols exhibited selective thioetherification of only one hydroxyl group, while the other alcohol moiety was converted into a carbamate (products **3at**–**3au**). This path likely arises from the hydrolysis of isouronium intermediates. As a limitation of the protocol, secondary alcohols, such as 1-phenylethanol, provided thioethers in moderate yield (**3av**), while phenol, polyfluorinated and tertiary alcohols remained completely unreactive, mainly because of their inability to undergo the polar deoxythiolation step.

3.4.2 Expanding the Scope to Electron Neutral and Rich Aryl Halides

Our studies highlighted that electronically neutral or electron-rich aryl chlorides remained unreactive under the photo-activity of catalyst **C1**.[21] To overcome this limitation, we explored the reactivity of the newly prepared dioxindole-based organocatalyst **C3**, which could act, upon deprotonation and excitation, as an effective photoreductant (E* ~ −3.35 V vs. SCE) to activate these substrates (optimization detailed in Table 3.2).

Table 3.2. Optimization studies.[a]



entry	deviation	yield [%][a]	entry	deviation	yield [%][a]
1	none	35	9	**C2** (10 mol%) as catalyst	5
2	**E** as S source	5	10	**C6** (10 mol%) as catalyst	0
3	**B-D** as S source	0	11	**C5** (10 mol%) as catalyst	10
4	no light or no base	0	12	**C4** (10 mol%), 3 equiv. PhCl	15
5	no **C3**	0	13	**C3** (10 mol%), 3 equiv. PhCl	20
6	DMSO or DMF or DCM	0	14	**C3** (20 mol%), 3 equiv. PhCl	45
7	K_2CO_3 or KHCO or K_3PO_4	0	15	**C3** (40 mol%), 3 equiv. PhCl	60
8	**C1** or **C2** (5 mol%) as catalyst	5	**16**	**C3 (40 mol%), 5 equiv. PhCl**	**70**[b]

[a] Reactions performed on a 0.1 mmol scale for 14 h under illumination by a purple LED (*EvoluChem*) at 405 nm, temperature kept constant at 45 °C using a fan. [a] Yield inferred by ^{1}H NMR analysis of the crude mixture using 1,3,5-trimethoxybenzene as an internal standard. [b] Isolated yield. Mes: mesityl.

Using the conditions described in Table 3.2 entry 16, we broadened the range of aryl chlorides amenable to thioetherification (Figure 3.16).

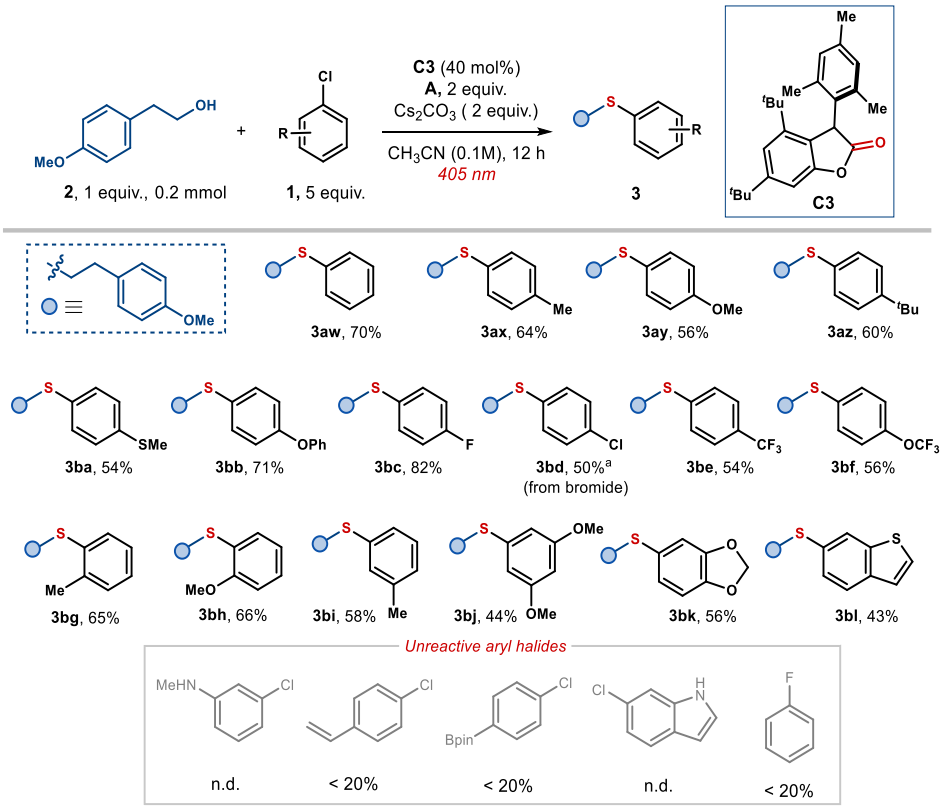


Figure 3.16. Thioetherification of electron-neutral or electron-rich aryl chlorides **1** with alcohol **2a**. Reactions performed on a 0.2 mmol scale at 40 °C using 5 equiv of **1** and 2 equiv of **A** under illumination by a purple LED at 405 nm. Yields refer to isolated products **3** after purification.

Electron-neutral chlorobenzene (product **3aw**) and substrates substituted with electron-donating groups (**3ax**–**3bb**, **3bj**) underwent successful transformations. Substitution patterns on the arene appeared to have insignificant effects, as *para*- (**3ax**), *meta*- (**3bg**) and *ortho*-tolyl (**3bi**) chlorides were all converted with good reactivity. Additionally, other substituents, including less active halides (e.g., fluoride **3bc** and chloride **3bd**), trifluoromethyl group (**3be**–**3bf**), benzodioxole (**3bk**) and thiophene (**3bl**), were well-tolerated. Some moderately reactive or unreactive substrates are also depicted in Figure 3.16 (grey box).

To figure out the reason why catalyst **C3** is superior to **C1-2** in the SET activation of these substrates, we estimated the redox potentials of the excited catalysts. They have comparable

photoproperties and redox potentials. **C1-3** could be all capable of reducing the substrates, generating aryl radicals and the oxidized catalyst **XIII** or **XIV** (Figure 3.17). Therefore, the difference in efficiency should not depend on their ability to activate aryl chlorides via SET reduction. Thus, we reasoned that the divergence in reactivity might be ascribed to the instability of catalyst **C1**, which could potentially undergo deactivation during the reaction, as the transient radical intermediate **XIII** might engage in undesirable side reactions. We hypothesize that the lactone catalyst **C3**, with its bulkier mesitylene group, may have effectively mitigated this issue. The presence of the mesitylene group could potentially stabilize the radical formed in the corresponding intermediate **XIV**, making it long-lived. To validate this initial proposal, further comprehensive investigations would be required.

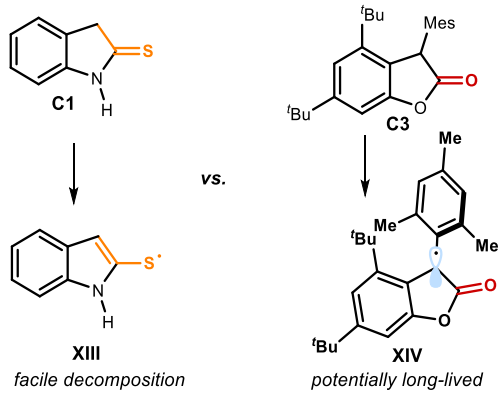


Figure 3.17. Rationale for the higher reactivity of catalyst **C3** in activating electron-rich aryl chlorides.

3.4.3 Mechanistic Investigations

We then performed investigations to gain mechanistic insights. Thorough characterization of photocatalysts **C1**-**C3** was carried out to elucidate their mechanism of action (experimental details are reported in Section 3.6.6 and 3.6.7). The thiolate anions, generated upon catalyst deprotonation, can absorb visible light to access an electronically excited state, which was proved by NMR studies and absorption spectroscopic investigations (Figure 3.18a-c). The UV-Vis spectrum of the deprotonated **C1** showed a significant bathochromic shift to the visible light region compared to its neutral progenitor **C1**. Upon excitation by a laser at 350

nm, fluorescence emission of deprotonated **C1** was recorded, indicating that it can access an electronically excited state (Figure 3.18c).

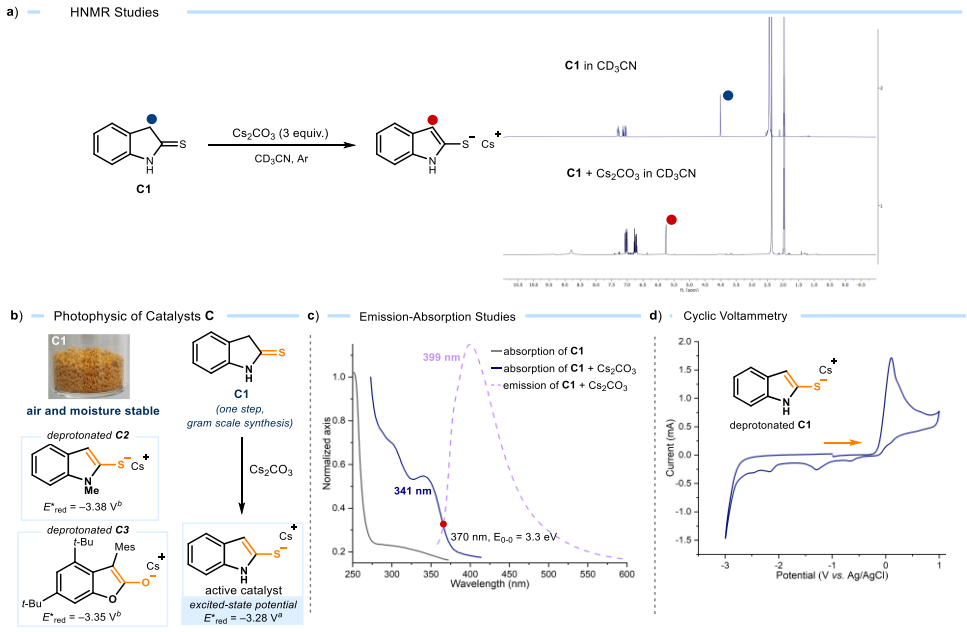


Figure 3.18. Photophysical and electrochemical properties of the photocatalysts. (**b**) ^{1}H NMR analysis of catalyst **C1** before (top) and after (bottom) treatment with Cs_2CO_3. (**b**) Deprotonation of **C1** and the estimated redox potential of the excited thiolates derived from catalysts **C1**–**C3**. **(c)** Emission of the excited thiolate (formed in situ treating **C1** with Cs_2CO_3) in CH_3CN upon irradiation at 350 nm and its intercept with the absorption spectrum at 373 nm, with a 0–0 transition energy ($E_{0,0}$) of 3.3 eV. **(d)** Cyclic voltammetry measurements of deprotonated catalyst C1 carried out in CH_3CN vs. Ag/AgCl. [a]Estimated redox potential vs. SCE in CH_3CN.

Emission spectroscopic studies and cyclic voltammetry (Figure 3.18b and c) were used to estimate the redox potential of the excited thiolates (with E* ranging from −3.28 to −3.38 V vs SCE in CH_3CN for deprotonated **C1**–**C3**).[25] This confirmed that the anions of catalysts **C1**–**C3** acquire a strongly reducing power upon excitation. Moreover, Stern–Volmer quenching studies showed that fluorescence of the deprotonated photocatalyst **C1**, excited by a laser at 350 nm, was effectively quenched by 4-chlorobenzonitrile **1a** (see detail in section 3.6.6). These observations are consonant with the ability of the excited deprotonated catalyst

[25] Farid, S.; Dinnocenzo, J. P.; Merkel, P. B.; Young, R. H.; Shukla, D.; Guirado, G. "Reexamination of the Rehm-Weller Data Set Reveals Electron Transfer Quenching that Follows a Sandros-Boltzmann Dependence on Free Energy." *J. Am. Chem. Soc.* **2011**, *133*, 11580–11587.

C1 (E* ~ −3.2 V vs. Ag/AgCl) to activate **1a** (E_{red} = -2.2 V vs. Ag/AgCl) through SET reduction (Figure 3.18a). The resulting aryl radical is trapped by tetramethylthiourea **A**, forming radical **II** (E(**III**/**II**) ~ −1.6 V vs. Ag/AgCl, as inferred by cyclic voltammetry studies of preformed **III**) with the appropriate redox potential to reduce the sulfur-centered radical **XIII** (**XIII**/**C1**$^{-}$) ~ +0.1 V vs. Ag/AgCl) via SET, thus turning over catalyst **C1**. An equivalent catalytic cycle can also be proposed for the action of **C3**.

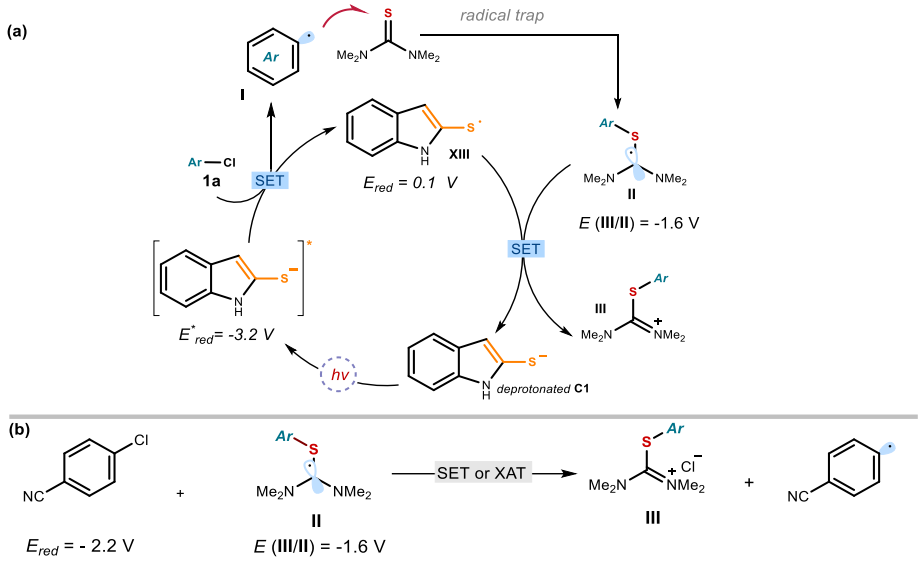


Figure 3.19. (**a**) Proposed photoredox catalytic cycle; **(b)** The possibility of a radical propagation step leading to a light-independent chain mechanism was deemed implausible.

In an alternative scenario, the light-driven SET reduction of aryl halide **1a** by the excited catalyst **C1** may serve merely as an initiating event for a radical chain propagation mechanism. For instance, the electron-rich radical **II** might hypothetically activate another equivalent of aryl halide **1a** (E_{red} = -2.2V vs Ag/AgCl) to generate the target aryl radical through either SET or halogen atom transfer (XAT) processes, thus providing a propagation step to sustain a light-independent radical chain (Figure 3.19b). Electrochemical measurement suggested that the radical intermediated **II**(E(III/II) ~ -1.6 V vs Ag/AgCl) is unable to reduce aryl halide **1a** (E_{red} = -2.2V vs Ag/AgCl), and this SET step is therefore endergonic. Moreover, we determined the quantum yield (Φ) of the model reaction between **1a** and **2a**, which stood at a low value of 0.017. This is consistent with the proposed closed

photoredox cycle, and suggests that a radical chain pathway has limited contribution to the conversion of starting materials, if any.

Polar Deoxythiolation Step

In our suggested mechanism, we propose that a radical pathway leading to the in-situ formation of the aryl isothiouronium ion **III**, followed by a polar deoxythiolation path involving alcohols **2** and yielding aryl alkyl thioethers **3**, is operative. This polar pattern was confirmed through an experiment using the preformed isothiouronium ion **III** (Figure 3.20a). Stirring **III** with alcohol **2a** in the presence of Cs_2CO_3 and in the dark resulted in the formation of product **3aw**, albeit in low yield. This is in agreement with our proposal that **III** is an intermediate in the reaction, and light is not necessary for the following deoxythiolation step. Additionally, subjecting the enantioenriched chiral alcohol **2av** ((*S*)-1-phenylethan-1-ol, 97% e.e.) and chlorobenzene **6** to standard reaction conditions led to the corresponding chiral thioether product **12** in poor yield, but maintaining the same enantiopurity (Figure 3.19b). Analysis of the absolute configuration via optical rotation[26] established that the process proceeded with complete stereoinversion, a signature of a stereospecific S_N2 ionic pathway. This is congruent with the proposed mechanism where thiophenolate would attack the isouronium intermediate, displacing urea as a leaving group.

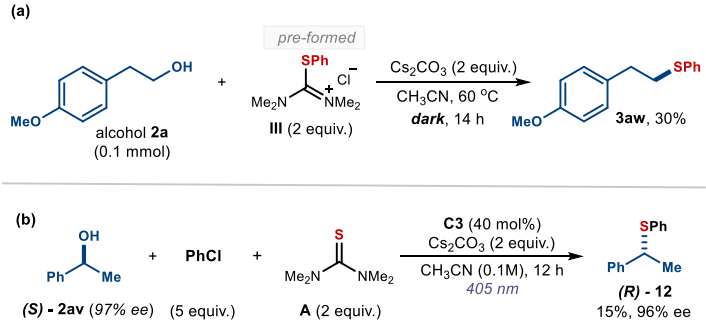


Figure 3.20. Mechanistic experiments to probe the polar pathway in the photochemical organocatalytic thioether synthesis. (**a**) Reaction between alcohol **2a** and pre-formed **III**. **(b)** Thioether synthesis from an enantioenriched chiral alcohol.

[26] Li, F.; Wang, D.; Chen, H.; He, Z.; Zhou, L.; Zeng, Q. "Transition Metal-Free Coupling Reactions of Benzylic Trimethylammonium Salts with Di(hetero)aryl Disulfides and Diselenides." *Chem. Commun.* **2020**, *56*, 13029–13032.

By-product Formation

We attempted to conduct GC-MS analyses to investigate why a large excess (5 equivalent) of aryl chlorides and 40 mol% of catalyst **C3** were needed for the thioetherification of electron-neutral and rich precursors. In the GC-MS analysis of the crude reaction mixture, we observed the signal of tetramethylurea, which is expected to be produced from the deoxythiolation process between alcohol and aryl isothiouronium ion. Trace amount of diphenyl disulfide was also observed, suggesting the generation of the aryl radical. An interesting finding was the detection of species **13**, assignable to **C3** modification with a phenyl group. Its formation can be justified by the coupling between the generated phenyl radical **I** and persistent radical **XIV**. This may explain the deleterious consumption of **C3** in the reaction. Regarding the reaction using **C1** as photocatalyst, a biaryl thioether side product **14** was found in the reaction mixture (Figure 3.21b). This compound might be produced from the radical coupling between aryl radical **I** and thiyl radical (from oxidation of thiophenolate). This observation implicated the intermediacies of phenyl radicals and thiophenol in the system.

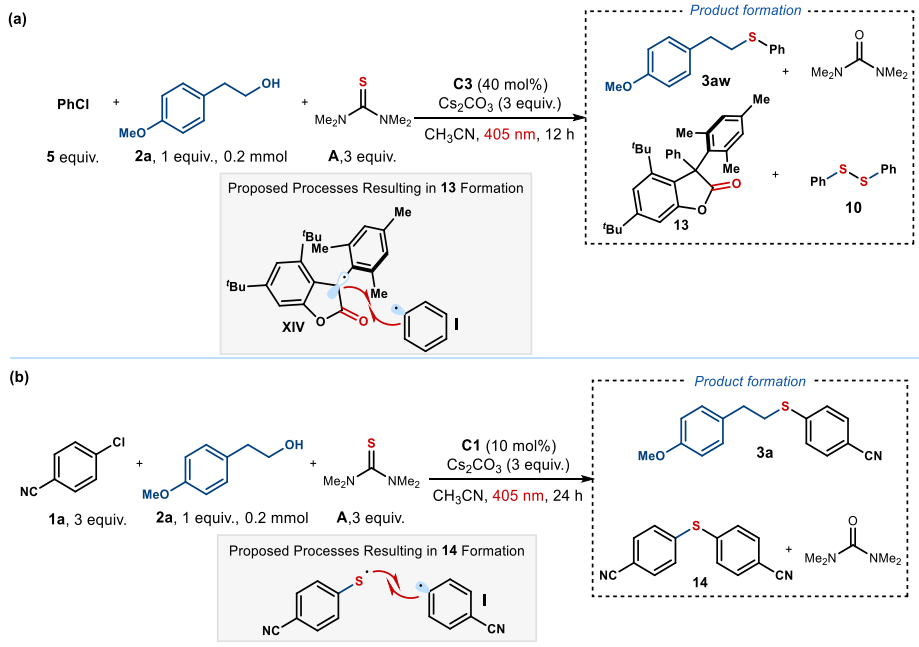


Figure 3.21. Detection of undesirable products in photochemical organocatalytic reaction. (**a**) GC-MS analyses of reaction mixture of thioether synthesis catalyzed by **C3**; **(b)** GC-MS analyses of reaction mixture of thioether synthesis catalyzed by **C1**.

3.5 Conclusions

In summary, we reported a photochemical catalytic protocol that enables the preparation of diverse alkyl aryl thioethers without thiol or transition metal involvement. The method operates under mild conditions using easily accessible, non-toxic and widespread aryl chlorides and alcohols as feedstocks. Its remarkable tolerance for functional groups allows for late-stage modifications of biorelevant compounds.

3.6 Experimental Section

General Information. The ^{1}H NMR, $^{19}F\{^{1}H\}$ NMR, $^{13}C\{^{1}H\}$ NMR spectra are available in the literature[1] and are not reported in the present dissertation.

The NMR spectra were recorded at 400 MHz and 500 MHz for ^{1}H, 101 or 126 MHz for $^{13}C\{^{1}H\}$ and 376 MHz for $^{19}F\{^{1}H\}$. The chemical shift (δ) for ^{1}H and $^{13}C\{^{1}H\}$ are given in ppm relative to residual signals of the solvents ($CHCl_3$ at 7.26 ppm for ^{1}H NMR and 77.16 ppm for $^{13}C\{^{1}H\}$ NMR). Coupling constants are given in Hertz. The following abbreviations are used to indicate the multiplicity: s, singlet; d, doublet; q, quartet; m, multiplet; br, broad signal

High resolution mass spectra (HRMS) were obtained from the ICIQ HRMS unit on MicroTOF Focus and Maxis Impact (Bruker Daltonics) with electrospray ionization (ESI) and Atmospheric-pressure chemical ionization (APCI). Optical rotations were measured on a Polarimeter Jasco P-1030 and are reported as follows: $[\alpha]_D$ ambient temperature (c in g per 100 mL, solvent). Cyclic voltammetry studies were carried out on a Princeton Applied Research PARSTAT 2273 potentiostat, offering compliance voltage up to ± 100 V (available at the counter electrode), ± 10 V scan range and ±2 A current range.

Yields refer to isolated materials of >95% purity as determined by ^{1}H NMR analysis.

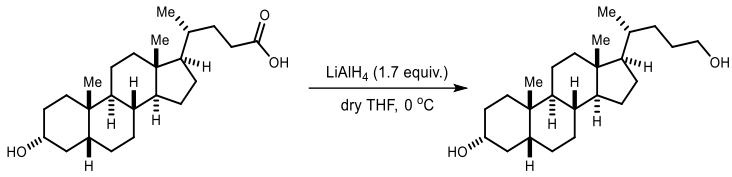
General Procedures. All reactions were set up under an argon atmosphere in oven-dried glassware. Synthesis grade solvents were used as purchased, anhydrous solvents were taken from a commercial SPS solvent dispenser. Chromatographic purification of products was accomplished using forced-flow chromatography (FC) on silica gel (230-400 mesh). For thin layer chromatography (TLC) analysis throughout this work, Merck pre-coated TLC plates (silica gel 60 GF_{254}, 0.25 mm) were employed, using UV light as the visualizing agent and an acidic mixture of vanillin or basic aqueous potassium permanganate ($KMnO_4$) stain

solutions, and heat as developing agents. Organic solutions were concentrated under reduced pressure on a Büchi rotatory evaporator.

Materials. Commercial grade reagents and solvents were purchased at the highest quality from commercial suppliers and used as received, unless otherwise stated.

3.6.1 Synthesis of the Substrates and Catalysts

Substrate Synthesis



An oven-dried 25 mL round-bottom flask equipped with magnetic stirring bar was charged with lithocholic acid (5 mmol, 1.0 equiv.). The flask was sealed, evacuated and refilled with nitrogen (3 times). Anhydrous THF (15 mL) was added and the resulting clear solution was cooled to 0 °C and stirred for 5 min at the same temperature. $LiAlH_4$ (8.5 mmol, 1.7 equiv.) was then added in small portions at 0 °C. After stirring at 0 °C for 1 hour, the mixture was allowed to stir at room temperature for additional 16 hours. The reaction was quenched by adding H_2O (1.4 mL) dropwise over 10 min. Then 15% w/w NaOH (1.4 mL) was added and the reaction was allowed to stirred at room temperature for 20 minutes. Then the resulting suspension was diluted with H_2O (15 mL) followed by extraction with ethyl acetate (3 ×20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness under reduced pressure. The crude residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 10: 1) to afford product as white solid (1.1g, 65% yield).

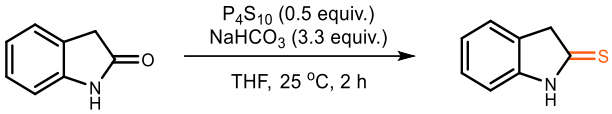
^{1}H NMR (400 MHz, CD_3OD): δ= 3.68 – 3.47 (m, 3H), 2.15 – 2.06 (m, 1H), 2.05 – 1.80 (m, 4H), 1.76 – 1.63 (m, 3H), 1.60 – 1.31 (m, 14H), 1.29 – 1.12 (m, 6H), 1.06 – 0.98 (m, 6H), 0.78 (s, 3H) ppm.

^{13}C{^{1}H} NMR (101 MHz, CD_3OD): δ= 71.1, 62.2, 56.6, 56.4, 42.5, 42.2, 40.6, 40.2, 35.9, 35.9, 35.6, 35.2, 34.4, 31.9, 29.9, 29.0, 28.0, 27.0, 26.3, 24.0, 22.6, 20.6, 17.9, 11.2 ppm.

HRMS (ESI): calculated for $C_{24}H_{42}NaO_2$ [M+Na^+]: 385.3077, found 385.3086.

Catalysts Synthesis

Indoline-2-thione (catalyst **C1):**

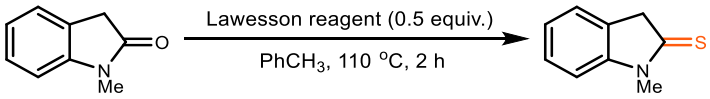


To a solution of 2-oxindole (5 mmol, 1.0 equiv.) in 15 mL of anhydrous THF, $NaHCO_3$ (10 mmol, 2.0 equiv.) was added and the reaction was stirred at room temperature for 10 minutes. P_4S_{10} (3 mmol, 0.6 equiv.) was then added portion wise and the resulting mixture was stirred at room temperature for 3 hours. On completion of the reaction, as indicated by TLC, the mixture was concentrated in vacuo to one fourth of its volume. Ice-cold water (10 mL) was then added in small portions to the oily residue with vigorous stirring, which resulted in precipitate formation. The mixture was left to stand in the ice-cold water for 15 minutes before vacuum filtration. The precipitates collected were washed with water followed by hexanes and air dried to yield product (597 mg, 80% yield). The purity was confirmed by ^{1}H NMR.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.30 – 7.23 (m, 2H), 7.15 – 7.09 (m, 1H), 7.06 – 6.99 (m, 1H), 4.08 (s, 2H) ppm

.**^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$):** δ= 203.5, 144.4, 130.5, 128.1, 124.2, 124.2, 110.2, 49.3 ppm. Matching reported literature data.[27]

1-Methylindoline-2-thione **(**catalyst **C2):**



An oven dried flask was charged with 1-methylindolin-2-one (736.0 mg, 5.0 mmol, 1.0 equiv.), the Lawesson reagent (2.5 mmol, 0.5 equiv.) and toluene (20 mL). The flask was placed in an oil-bath preheated to 110 ºC. After 2 hours stirring, the solution was concentrated in vacuo and the crude mixture was purified by flash column chromatography on silica gel

[27] Rhodes, S.; Short, S.; Sharma, S.; Kaur, R.; Jha, M. "One-Pot Mild and Efficient Synthesis of [1,3]thiazino[3,2-a]indol-4-ones and Their Anti-Proliferative Activity." *Org. Biomol. Chem.* **2019**, *17*, 3914–3920.

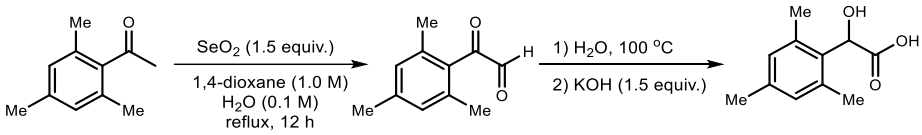
(1% ethyl acetate in hexanes as eluent) to afford the catalyst as light yellow solid (620.5 mg, 76% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.37 – 7.28 (m, 2H), 7.19 – 7.14 (m, 1H), 6.97 (d, *J* = 8.0 Hz, 1H), 4.11 (s, 2H), 3.63 (s, 3H) ppm.

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ= 201.2, 146.6, 129.2, 128.0, 124.4, 124.0, 109.6, 49.1, 31.3 ppm.

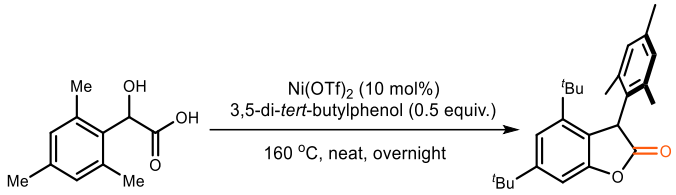
Matching reported literature data.[21]

1-Methyl-3,4-dihydroquinoline-2(1H)-thione **(**catalyst **C3):**



Based on a procedure reported in the literature [28] : a solution containing 2,4,6-trimethylacetophenone (10.0 mmol), SeO_2 (15.0 mol) and water (1 mL) in 1,4-dioxane (10 mL) was heated at reflux for 12 h. During the reaction, black selenium precipitated and was broken up to aid stirring. The solution was carefully decanted to separate free selenium. Removal of the solvent in vacuo gave a yellow oil which was used for the next step without further purification. Glyoxal was then added to water (20 mL) and heated until the yellow colour disappeared. White needle-like crystals of 2,4,6-trimethylphenylgloxal hydrate precipitated from water and were collected by filtration. Crude gloxal hydrate was heated with aqueous potassium hydroxide (10 mL, 1.5 M) at 100°C for 1 h and then cooled down to ambient temperature. The solution was filtered and acidified with conc. HCl to reach pH 1-3, when precipitation occurred. The solid was collected, carefully washed with water, air dried and recrystallised from ethanol to afford white crystalline 2,4,6-trimethylmandelic acid (1.77g, 91% yield).

[28] Allen, B. M.; Hegarty, A. F.; O'Neill, P.; Nguyen, M. T. "Hydration of Bis(pentamethylpheny1)- and Bismesityl-ketenes leading to Ene-1, 1 -diols (Enols of Carboxylic Acids)." *J. Chem. Soc., Perkin Trans* 2 **1992**, 927.



Based on a literature procedure[29]: 2-hydroxy-2-mesitylacetic acid (2.0 mmol), 3,5-di-*tert*-butylphenol (1.0 mmol, 0.5 equiv.), and $Ni(OTf)_2$ (0.1 mmol, 10 mol%) were added to an oven-dried 25 mL Schlenk tube equipped with a magnetic stirring bar. The mixture was vigorously stirred at 160 °C for 12 hours under argon conditions before being cooled to ambient temperature. Then 15 mL of water was added, and the resulting mixture was extracted with EtOAc (15 mL × 3). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. Further purification by flash column chromatography on silica gel (eluting with petroleum ether/ethyl acetate = 150: 1) provided catalyst **C3** as a white solid (310 mg, 85%).

^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.23 (d, *J* = 1.9 Hz, 1H), 7.05 (d, *J* = 1.9 Hz, 1H), 6.97 (s, 1H), 6.69 (s, 1H), 5.38 (s, 1H), 2.55 (s, 3H), 2.25 (s, 3H), 1.59 (s, 3H), 1.34 (s, 9H), 1.08 (s, 9H) ppm.

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ= 175.8, 154.7, 152.6, 147.9, 137.5, 137.2, 137.2, 131.3, 130.9, 130.0, 121.6, 119.5, 106.3, 46.5, 35.8, 35.2, 31.4, 30.5, 21.1, 20.9, 19.6 ppm.

HRMS (ESI): calculated for $C_{24}H_{42}NaO_2$ [M+Na^+]: 387.2295, found 387.2302.

3.6.2 Experimental Procedures

Experimental Setup

Set-up 1 *405 nm EvoluChem setup* (**Figure 3.22**)

The reactions were performed using an *EvoluChem* P303-30-1 lamp (18 W, λ_{max}= 405 nm, 2-3 cm away), and a fan to cool down the vials (under these conditions, the reaction temperature within the reaction vessel was measured to be between 40 - 42 ºC).

[29] Tang, Z.; Tong, Z.; Xu, Z.; Au, C.-T.; Qiu, R.; Yin, S.-F. "Recyclable Nickel-Catalyzed C–H/O–H Dual Functionalization of Phenols with Mandelic Acids for The Synthesis of 3-aryl benzofuran-2(3H)-ones Under Solvent-Free Conditions." *Green Chem*. **2019**, *21*, 2015–2022.

Figure 3.22. Reaction setup using *EvoluChem* lamps emitting at 405 nm.

Set-up 2 Gram scale experiment (**Figure 3.23**)

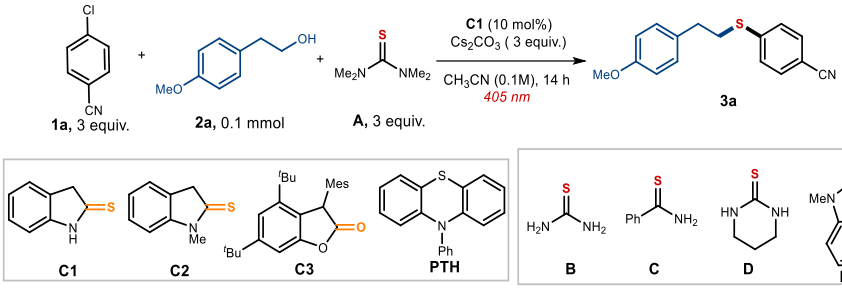
The gram scale reaction was performed under illumination by two EvoluChem P303-30-1 lamps (18 W, λ_{max}= 405 nm, 2-3 cm away from the reaction vessel) and using a fan to cool the flask.

Figure 3.23. Setup for the gram-scale experiment using two *EvoluChem* lamps emitting at 405 nm.

3.6.3 Preparation of Thioethers from Alcohols and Electron-Deficient Aryl Halides

Optimization Studies

Table 3.2. Optimization of the model reaction using **C1** as catalyst

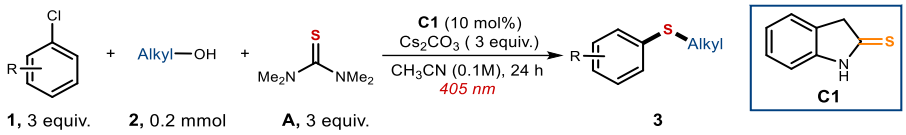


Entry	Deviations	Yield of 3a
1	none	80%
2	No light	0%
3	No base	0%
4	No **C1**	20%
5	No **C1** and light, 50 or 70 °C	0%
6	2 equiv. **1a**, **A** and Cs_2CO_3	60%
7	5 mol% **C1**	44%
8	**C2** (10 mol%)	50%
9	**C3** (10 mol%)	30%
10	PTH (10 mol%), 456 nm	57%
11	Ir-$(ppy)_3$ (3 mol%), 456 nm	45%
12	**B-D** or elemental S_8	0%

13	**E**	60%
14	DMSO, DMF, THF, DCM as solvent	0
15	Acetone as solvent	59%
16	$KHCO_3$, K_2CO_3, K_3PO_4, TMG as base	30-60%
17	PhCl as radical precursor	5%
18	With TEMPO	0%
19	0.2 mmol scale, 14 h	63% [a]
20	0.2 mmol scale, 24 h	85% (83%) [a]

All reactions were performed on a 0.1 mmol scale; yield of **3a** determined by ^{1}H NMR analysis of the crude reaction mixture by comparison with 1,3,5-trimethoxybenzene as internal standard. [a] Yield of isolated **3a**. Mes: mesityl.

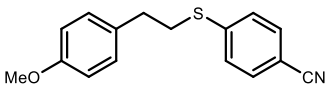
General Procedure A for Electron-Deficient Aryl halides



To a 7 mL glass vial, catalyst **C1** (3 mg, 0.02 mmol, 0.1 equiv.), cesium carbonate (196 mg, 0.6 mmol, 3.0 equiv.), 1,1,3,3-tetramethylthiourea (79.3 mg, 0.6 mmol, 3.0 equiv.), alcohols **2** (if solid, 0.2 mmol, 1 equiv.) and aryl chlorides **1** (if solid, 0.6 mmol, 3 equiv.) were sequentially added. The vial was sealed with a screw-top cap with septum and then vacuumed and backfilled with argon for 3 times. Afterwards, aryl chlorides **1** (if liquid, 0.6 mmol, 3.0 equiv.) and alcohols (if liquid, 0.2 mmol, 1 equiv.) followed by argon-sparged acetonitrile (0.1 M, 2.0 mL) were added *via* syringe. The vial was sealed with Parafilm and then stirred under 405 nm for 24 hours using ***Set-up 1*** detailed in Figure 4.21. After reaction was completed, the crude mixture was concentrated and purified by column chromatography to

afford the corresponding products with the reported yields (>95% purity according to ^{1}H NMR analysis).

Characterization of Products from Electron-Deficient Aryl Halides

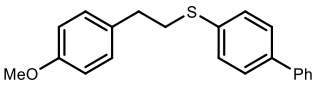


4-(4-Methoxyphenethyl)thio)benzonitrile (3a): Synthesized according to the General Procedure **A** using 2-(4-methoxyphenyl)ethan-1-ol (30.5 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and 4-fluorobenzonitrile (72.5 mg, 0.6 mmol, 3.0 equiv.) or 4-chlorobenzonitrile (82.5 mg, 0.6 mmol, 3.0 equiv.) or 4-bromobenzonitrile (109.0 mg, 0.6 mmol, 3.0 equiv.) or 4-iodobenzonitrile (137.5 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane: EtOAc = 30: 1 as eluent) to afford **3a** (40.5 mg, 75% yield with 4-fluorobenzonitrile; 44.7 mg, 83% yield with 4-chlorobenzonitrile; 42.5 mg, 79% yield with 4-bromobenzonitrile; 35.5 mg, 66% yield with 4-iodobenzonitrile and 1.0g, 75% yield was obtained from 5 mmol scale) as a pale yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ= 7.55 – 7.48 (m, 2H), 7.33 – 7.27 (m, 2H), 7.16 – 7.10 (m, 2H), 6.89 – 6.82 (m, 2H), 3.80 (s, 3H), 3.24 – 3.17 (m, 2H), 2.92 (t, *J* = 7.7 Hz, 2H) ppm.

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ= 158.5, 144.8, 132.3, 131.5, 129.5, 126.90, 118.9, 114.1, 108.2, 55.3, 34.1, 33.7 ppm.

HRMS (ESI): calculated for $C_{16}H_{15}NNaOS$ [M+Na^+]: 292.0767, found 292.0763.



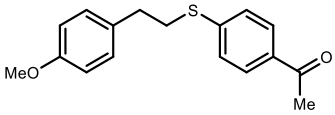
[1,1'-Biphenyl]-4-yl(4-methoxyphenethyl)sulfane (3b): Synthesized according to the General Procedure **A** using 2-(4-methoxyphenyl)ethan-1-ol (30.5 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and 4-chloro-1,1'-biphenyl (113.0 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (hexane:EtOAc = 500: 1 as eluent) to afford **3b** (47.0 mg, 73% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.61 – 7.56 (m, 2H), 7.55 – 7.51 (m, 2H), 7.47 – 7.39 (m, 4H), 7.37 – 7.31 (m, 1H), 7.17 – 7.11 (m, 2H), 6.89 – 6.82 (m, 2H), 3.80 (s, 3H), 3.22 – 3.15 (m, 2H), 2.95 – 2.88 (m, 2H) ppm.

$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ= 158.3, 140.5, 138.9, 135.6, 132.3, 129.5, 129.4, 128.8, 127.6, 127.3, 126.9, 114.0, 55.3, 35.4, 34.8 ppm.

HRMS (ESI): calculated for $C_{21}H_{21}OS$ [M+H$^+$]: 321.1308, found 321.1293.

1-(4-((4-Methoxyphenethyl)thio)phenyl)ethan-1-one (3c): Synthesized according to the

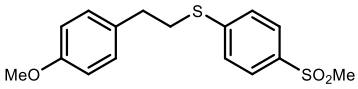


General Procedure **A** using 2-(4-methoxyphenyl)ethan-1-ol (30.5 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and 1-(4-chlorophenyl)ethan-1-one (93.0 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane: EtOAc = 30: 1 as eluent) to afford **3c** (23.0 mg, 40% yield) as a pale yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.89 – 7.83 (m, 2H), 7.35 – 7.29 (m, 2H), 7.17 – 7.11 (m, 2H), 6.89 – 6.82 (m, 2H), 3.80 (s, 3H), 3.24 – 3.18 (m, 2H), 2.96 – 2.89 (m, 2H), 2.57 (s, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ= 197.2, 158.4, 144.4, 134.0, 131.8, 129.5, 128.8, 126.5, 114.0, 55.3, 34.3, 33.8, 26.4 ppm.

HRMS (ESI): calculated for $C_{17}H_{18}NaO_2S$ [M+Na$^+$]: 309.0920, found 309.0930.

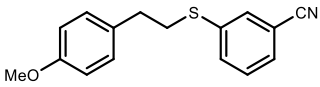


(4-Methoxyphenethyl)(4-(methylsulfonyl)phenyl)sulfane (3d): Synthesized according to the General Procedure **A** using 2-(4-methoxyphenyl)ethan-1-ol (30.5 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and 1-chloro-4-(methylsulfonyl)benzene (114.5 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane: DCM = 1:1 as eluent) to afford **3d** (46.5 mg, 72% yield) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.82 – 7.77 (m, 2H), 7.41 – 7.34 (m, 2H), 7.16 – 7.10 (m, 2H), 6.88 – 6.82 (m, 2H), 3.79 (s, 3H), 3.25 – 3.19 (m, 2H), 2.96 – 2.90 (m, 2H), 3.03 (s, 3H) ppm.

$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ= 158.5, 145.8, 136.7, 131.5, 129.5, 127.7, 126.9, 114.1, 55.3, 44.7, 34.2, 33.8 ppm.

HRMS (ESI): calculated for $C_{16}H_{18}NaO_3S_2$ [M+Na$^+$]: 345.0590, found 345.0592.

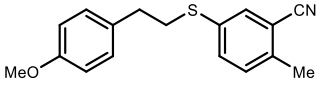


3-((4-Methoxyphenethyl)thio)benzonitrile (3e): Synthesized according to the General Procedure **A** using 2-(4-methoxyphenyl)ethan-1-ol (30.5 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and 3-chlorobenzonitrile (82.5 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane: EtOAc = 30: 1 as eluent) to afford **3e** (34.5 mg, 64% yield) as a pale yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.53 – 7.48 (m, 2H), 7.45 – 7.40 (m, 1H), 7.39 – 7.32 (m, 1H), 7.15 – 7.09 (m, 2H), 6.88 – 6.81 (m, 2H), 3.80 (s, 3H), 3.21 – 3.14 (m, 2H), 2.93 – 2.86 (m, 2H) ppm.

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ= 158.5, 139.3, 132.5, 131.5, 131.1, 129.5, 129.4, 129.0, 118.4, 114.1, 113.2, 55.3, 34.9, 34.4 ppm.

HRMS (ESI): calculated for $C_{16}H_{16}NOS$ [M+H$^+$]: 270.0947, found 270.0943.

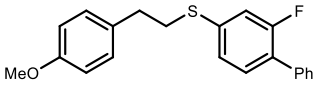


5-((4-Methoxyphenethyl)thio)-2-methylbenzonitrile (3f): Synthesized according to the General Procedure **A** using 2-(4-methoxyphenyl)ethan-1-ol (30.5 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and 5-chloro-2-methylbenzonitrile (91.0 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane: EtOAc = 30: 1 as eluent) to afford **3f** (23.5 mg, 41% yield) as a pale yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.50 (d, *J* = 2.1 Hz, 1H), 7.42 (dd, *J* = 8.1, 2.1 Hz, 1H). 7.24 – 7.19 (m, 1H), 7.12 – 7.07 (m, 2H), 6.87 – 6.81 (m, 2H), 3.79 (s, 3H), 3.16 – 3.10 (m, 2H), 2.89 – 2.83 (m, 2H), 2.51 (s, 3H) ppm.

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ= 158.4, 139.4, 135.3, 133.5, 132.4, 131.7, 130.7, 129.5, 117.7, 114.0, 113.6, 55.3, 35.5, 34.6, 20.0 ppm.

HRMS (ESI): calculated for $C_{17}H_{17}NNaOS$ [M+Na$^+$]: 306.0923, found 306.0928.



(2-Fluoro-[1,1'-biphenyl]-4-yl)(4-methoxyphenethyl)sulfane (3g): Synthesized according to the General Procedure **A** using 2-(4-methoxyphenyl)ethan-1-ol (30.5 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and 4-bromo-2-fluoro-1,1'-biphenyl (151.0 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash

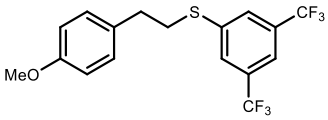
column chromatography on silica gel (Hexane:EtOAc = 200: 1 as eluent) to afford **3g** (27.0 mg, 40% yield) as a pale yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.57 – 7.53 (m, 2H), 7.49 – 7.42 (m, 3H), 7.39 – 7.34 (m, 2H), 7.17 – 7.13 (m, 3H), 6.89 – 6.84 (m, 2H), 3.80 (s, 3H), 3.22 – 3.16 (m, 2H), 2.97 – 2.90 (m, 2H) ppm.

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ= 161.0, 158.4, 138.1 (d, *J* = 8.3 Hz), 135.4 (d, *J* = 8.3 Hz), 132.0, 130.9 (d, *J* = 4.3 Hz), 129.5, 128.9 (d, *J* = 3.1 Hz), 128.5, 127.7, 126.4 (d, *J* = 13.9 Hz), 124.4 (d, *J* = 3.4 Hz), 115.8 (d, *J* = 25.1 Hz), 114.0, 55.3, 35.0, 34.6 ppm.

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ= -117.3 ppm.

HRMS (ESI): calculated for $C_{21}H_{19}FNaOS$ [M+Na^+]: 361.1033, found 361.1033.



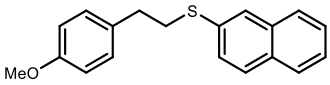
(3,5-Bis(trifluoromethyl)phenyl)(4-methoxyphenethyl)sulfane (3h): Synthesized according to the General Procedure **A** using 2-(4-methoxyphenyl)ethan-1-ol (30.5 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and 1-bromo-3,5-bis(trifluoromethyl)benzene (175.5 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane: EtOAc = 500: 1 as eluent) to afford **3h** (49.5 mg, 65% yield) as a pale yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.68 – 7.63 (m, 2H), 7.64 – 7.60 (m, 1H), 7.17 – 7.10 (m, 2H), 6.89 – 6.83 (m, 2H), 3.80 (s, 3H), 3.28 – 3.22 (m, 2H), 2.97 – 2.90 (m, 2H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ= 158.5, 140.9, 132.1 (q, *J* = 33.3 Hz), 131.2 129.5, 127.6 – 127.3 (m, 1C), 124.5(q, *J* = 273.7 Hz), 119.1 – 118.8 (m, 1C), 114.1, 55.2, 34.8, 34.3 ppm.

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ= -63.2 ppm.

HRMS (ESI): calculated for $C_{17}H_{13}F_6OS$ [M^+]: 379.0586, found 379.0588.

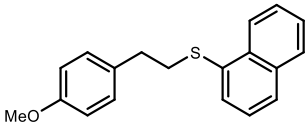


(4-Methoxyphenethyl)(naphthalen-2-yl)sulfane (3i): Synthesized according to the General Procedure **A** using 2-(4-methoxyphenyl)ethan-1-ol (30.5 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and 2-chloronaphthalene (97.5 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane: EtOAc = 300: 1 as eluent) to afford **3i** (44.5 mg, 75% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.83 – 7.73 (m, 4H), 7.52 – 7.42 (m, 3H), 7.18 – 7.13 (m, 2H), 6.90 – 6.83 (m, 2H), 3.80 (s, 3H), 3.29 – 3.23 (m, 2H), 2.97 – 2.91 (m, 2H) ppm.

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ= 158.3, 134.1, 133.8, 132.3, 131.8, 129.5, 128.4, 127.6, 127.4, 127.1, 126.8, 126.6, 125.6, 114.0, 55.3, 35.3, 34.7 ppm.

HRMS (ESI): calculated for $C_{19}H_{19}OS$ [M+H$^+$]: 295.1151, found 295.1138.

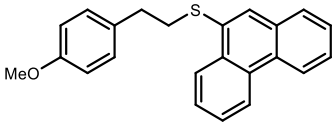


(4-Methoxyphenethyl)(naphthalen-1-yl)sulfane (3j): Synthesized according to the General Procedure **A** using 2-(4-methoxyphenyl)ethan-1-ol (30.5 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and 1-chloronaphthalene (97.5 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane: EtOAc = 300: 1 as eluent) to afford **3j** (47.0 mg, 80% yield) as a yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 8.44 – 8.40 (m, 1H), 7.89 – 7.85 (m, 1H), 7.77 – 7.74 (m, 1H), 7.63 – 7.60 (m, 1H), 7.59 – 7.51 (m, 2H), 7.45 – 7.41 (m, 1H), 7.14 – 7.10 (m, 2H), 6.86 – 6.82 (m, 2H), 3.80 (s, 3H), 3.24 – 3.19 (m, 2H), 2.94 – 2.89 (m, 2H) ppm.

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ= 158.2, 134.0, 133.7, 133.1, 132.4, 129.5, 128.6, 128.1, 127.2, 126.4, 126.2, 125.6, 125.1, 113.9, 55.3, 36.0, 34.8 ppm.

HRMS (ESI): calculated for $C_{19}H_{19}OS$ [M+H$^+$]: 295.1151, found 295.1137.

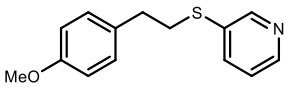


(4-Methoxyphenethyl)(phenanthren-9-yl)sulfane (3k): Synthesized according to the General Procedure **A** using 2-(4-methoxyphenyl)ethan-1-ol (30.5 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and 9-bromophenanthrene (154.5 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane: EtOAc = 300: 1 as eluent) to afford **3k** (34.5 mg, 50% yield) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 8.74 – 8.70 (m, 1H), 8.67 – 8.63 (m, 1H), 8.51 – 8.47 (m, 1H), 7.84 – 7.80 (m, 2H), 7.72 – 7.67 (m, 2H), 7.65 – 7.58 (m, 2H), 7.17 – 7.12 (m, 2H), 6.87 – 6.82 (m, 2H), 3.79 (s, 3H), 3.31 – 3.26 (m, 2H), 3.00 – 2.94 (m, 2H) ppm.

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ= 158.3, 134.1, 133.8, 132.3, 131.6, 129.5, 128.4, 127.8, 127.4, 127.1, 126.8, 126.6, 125.6, 114.0, 55.3, 35.3, 34.7 ppm.

HRMS (ESI): calculated for $C_{23}H_{21}OS$ [M+H$^+$]: 345.1308, found 345.1294.

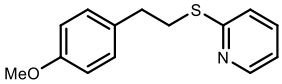


3-((4-Methoxyphenethyl)thio)pyridine (3l): Synthesized according to the General Procedure **A** using 2-(4-methoxyphenyl)ethan-1-ol (30.5 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and 3-chloropyridine (68.0 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (DCM as eluent) to afford **3l** (37.5 mg, 76% yield) as a yellow liquid.

^{1}H NMR (400 MHz, CDCl$_3$): δ= 8.58 (d, *J* = 1.6 Hz, 1H), 8.42 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.63 (ddd, *J* = 8.0, 2.4, 1.5 Hz, 1H), 7.20 (ddd, *J* = 8.0, 4.8, 0.8 Hz, 1H). 7.12 – 7.07 (m, 2H), 6.86 – 6.82 (m, 2H), 3.78 (s, 3H), 3.17 – 3.12 (m, 2H), 2.89 – 2.85 (m, 2H) ppm.

^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$): δ= 158.4, 150.3, 147.2, 136.9, 133.6, 131.7, 129.5, 123.6, 114.0, 55.3, 35.5, 34.7 ppm.

HRMS (ESI): calculated for $C_{14}H_{16}NOS$ [M+H$^+$]: 246.0947, found 246.0956.

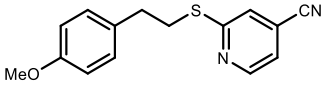


2-((4-Methoxyphenethyl)thio)pyridine (3m): Synthesized according to the General Procedure **A** using 2-(4-methoxyphenyl)ethan-1-ol (30.5 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and 2-chloropyridine (80.0 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane: EtOAc = 100: 1 as eluent) to afford **3m** (24.5 mg, 50% yield) as a yellow liquid.

^{1}H NMR (400 MHz, CDCl$_3$): δ= 8.47 – 8.42 (m, 1H), 7.50 – 7.43 (m, 1H), 7.22 – 7.14 (m, 3H), 7.01 – 6.94 (m, 1H), 6.88 – 6.82 (m, 2H), 3.80 (s, 3H), 3.43 – 3.36 (m, 2H), 3.00 – 2.92 (m, 2H) ppm.

^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$): δ= 159.1, 158.2, 149.5, 135.8, 132.7, 129.6, 122.4, 119.3, 113.9, 55.3, 34.9, 31.7 ppm.

HRMS (ESI): calculated for $C_{14}H_{16}NOS$ [M+H$^+$]: 246.0947, found 246.0957.



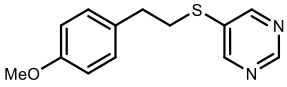
2-((4-Methoxyphenethyl)thio)isonicotinonitrile (3n): Synthesized according to the General Procedure **A** using 2-(4-methoxyphenyl)ethan-1-ol (30.5 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and 2-chloroisonicotinonitrile (83.0 mg, 0.6 mmol, 3.0

equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane: EtOAc = 50: 1 as eluent) to afford **3n** (22.0 mg, 41% yield) as a yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 8.57 (dd, *J* = 5.1, 1.0 Hz, 1H), 7.37 – 7.33 (m, 1H), 7.19 – 7.13 (m, 3H), 6.87 – 6.83 (m, 2H), 3.80 (s, 3H), 3.43 – 3.38 (m, 2H), 2.97 – 2.93 (m, 2H) ppm.

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ= 161.6, 158.3, 150.2, 132.1, 129.6, 124.0, 120.2, 119. 9, 116.3, 113.9, 55.3, 34.7, 31.8 ppm.

HRMS (ESI): calculated for $C_{15}H_{15}N_2OS$ [M+H$^+$]: 271.0900, found 271.0897.

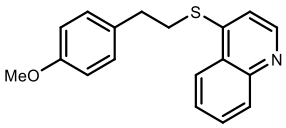


5-((4-Methoxyphenethyl)thio)pyrimidine (3o): Synthesized according to the General Procedure **A** using 2-(4-methoxyphenyl)ethan-1-ol (30.5 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and 5-bromopyrimidine (95.5 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (DCM: EtOAc = 50: 1 as eluent) to afford **3o** (20.5 mg, 42% yield) as a yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 9.02 (s, 1H), 8.66 (s, 2H), 7.13 – 7.07 (m, 2H), 6.87 – 6.81 (m, 2H), 3.79 (s, 3H), 3.22 – 3.15 (m, 2H), 2.93 – 2.87 (m, 2H) ppm.

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ= 158.5, 156.9, 155.9, 133.1, 131.1, 129.5, 114.1, 55.3, 35.3, 34.7 ppm.

HRMS (ESI): calculated for $C_{13}H_{15}N_2OS$ [M+H$^+$]: 247.0900, found 247.0896.

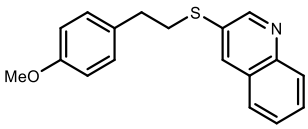


4-((4-Methoxyphenethyl)thio)quinoline (3p): Synthesized according to the General Procedure **A** using 2-(4-methoxyphenyl)ethan-1-ol (30.5 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and 4-chloroquinoline (98.5 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane: EtOAc = 3: 1 as eluent) to afford **3p** (38.5 mg, 65% yield) as a yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 8.71 (d, *J* = 4.8 Hz, 1H), 8.15 – 8.10 (m, 1H), 8.10 – 8.05 (m, 1H), 7.74 – 7.68 (m, 1H), 7.57 – 7.50 (m, 1H), 7.21 – 7.14 (m, 3H), 6.90 – 6.84 (m, 2H), 3.80 (s, 3H), 3.35 – 3.28 (m, 2H), 3.06 – 3.00 (m, 2H) ppm.

$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ= 158.5, 149.2, 147.6, 147.4, 131.6, 130.0, 129. 8, 129.5, 126.6, 126.3, 123.7, 115.9, 114.1, 55.3, 33. 8, 32.9 ppm.

HRMS (ESI): calculated for $C_{18}H_{18}NOS$ $[M+H^+]$: 296.1104, found 296.1115.

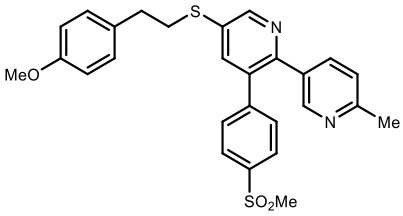


3-((4-Methoxyphenethyl)thio)quinoline (3q): Synthesized according to the General Procedure **A** using 2-(4-methoxyphenyl)ethan-1-ol (30.5 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and 3-bromoquinoline (124.5 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane: EtOAc = 20: 1 as eluent) to afford **3q** (35.5 mg, 60% yield) as a yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 8.85 (d, *J* = 2.3 Hz, 1H), 8.09 – 8.05 (m, 1H), 8.03 – 8.00 (m, 1H), 7.74 – 7.69 (m, 1H), 7.69 – 7.64 (m, 1H), 7.56 – 7.51 (m, 1H), 7.14 – 7.10 (m, 2H), 6.85 – 6.81 (m, 2H), 3.77 (s, 3H), 3.27 – 3.22 (m, 2H), 2.96 – 2.90 (m, 2H) ppm.

$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ=158.4, 151.6, 146.3, 135.1, 131.7, 130.6, 129.6, 129.3, 129.1, 128.2, 127.2, 127.0, 114.0, 55.3, 35.7, 34.8 ppm.

HRMS (ESI): calculated for $C_{18}H_{18}NOS$ $[M+H^+]$: 296.1104, found 296.1115.

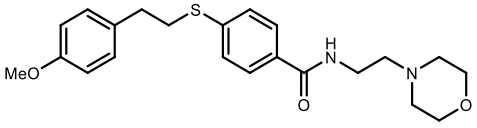


5-((4-Methoxyphenethyl)thio)-6'-methyl-3-(4-(methylsulfonyl)phenyl)-2,3'-bipyridine (3r): Synthesized according to the General Procedure b using 2-(4-methoxyphenyl)ethan-1-ol (30.5 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and 5-chloro-6'-methyl-3-(4-(methylsulfonyl)phenyl)-2,3'-bipyridine (215.5 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane: Acetone= 3: 1 as eluent) to afford **3r** (34.5 mg, 35% yield) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 8.66 (d, *J* = 2.2 Hz, 1H), 8.37 (s, 1H), 7.92 – 7.85 (m, 2H), 7.60 – 7.53 (m, 2H), 7.39 – 7.33 (m, 2H), 7.15 – 7.04 (m, 3H), 6.84 – 6.78 (m, 2H), 3.76 (s, 3H), 3.26 – 3.20 (m, 2H), 3.08 (s, 3H), 2.95 (t, *J* = 7.5 Hz, 2H), 2.52 (s, 3H) ppm.

$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ= 158.4, 158.1, 151.2, 149.8, 149.2, 144.7, 139.9, 138.4, 137.4, 134.3, 133.4, 131.8, 131.4, 130.5 , 129.6, 127.8, 122.8, 114.0, 55.3, 44.5, 35.3, 34.9, 24.2 ppm.

HRMS (ESI): calculated for $C_{27}H_{27}N_2O_3S_2$ $[M+H^+]$: 491.1458, found 491.1472 ppm.

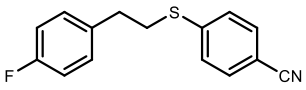


4-((4-Methoxyphenethyl)thio)-N-(2-morpholinoethyl)benzamide (3s): Synthesized according to the General Procedure **A** using 2-(4-methoxyphenyl)ethan-1-ol (30.5 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and 4-chloro-N-(2-morpholinoethyl)benzamide (161.5 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (EtOAc: MeOH= 50: 1 as eluent) to afford **3s** (36.0 mg, 45% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 8.12 – 8.06 (m, 2H), 7.77 – 7.70 (m, 2H), 7.55 – 7.50 (m, 2H), 7.28 – 7.23 (m, 2H), 7.18 (br, 1H), 4.19 (s, 3H), 4.14 (t, *J* = 4.7 Hz, 4H), 3.99 – 3.93 (m, 2H), 3.63 – 3.55 (m, 2H), 3.34 – 3.27 (m, 2H), 3.03 (t, *J* = 6.0 Hz, 2H), 2.94 (t, *J* = 4.0 Hz, 4H) ppm.

$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ= 166.9, 158.4, 141.7, 131.9, 131.4, 129.5, 127.4, 127.4, 114.0, 66.9, 56.96, 56.0, 53.3, 36.0, 34.4, 34.3 ppm.

HRMS (ESI): calculated for $C_{22}H_{29}N_2O_3S$ $[M+H^+]$: 401.1893, found 401.1891.



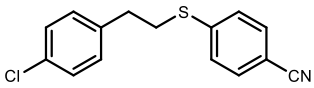
4-((4-Fluorophenethyl)thio)benzonitrile (3t): Synthesized according to the General Procedure **A** using 2-(4-fluorophenyl)ethan-1-ol (28.0 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and 4-chlorobenzonitrile (82.5 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane: EtOAc = 30: 1 as eluent) to afford **3t** (49.5 mg, 90% yield) as a pale yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.56 – 7.50 (m, 2H), 7.33 – 7.28 (m, 2H), 7.20 – 7.14 (m, 2H), 7.04 – 6.96 (m, 2H), 3.24 – 3.18 (m, 2H), 2.95 (t, *J* = 7.6 Hz, 2H) ppm.

$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ= 161.8 (d, *J* = 246.1 Hz), 144.4, 135.05 (d, *J* = 3.3 Hz), 132.3, 130.0 (d, *J* = 8.0 Hz), 127.0, 118.8, 115.5 (d, *J* = 21.3 Hz), 108.4, 34.2, 33.57 (d, *J* = 1.4 Hz) ppm.

$^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$): δ= -116.1 ppm.

HRMS (ESI): calculated for $C_{15}H_{12}FNNaS$ [M+Na^+]: 280.0567, found 280.0571.

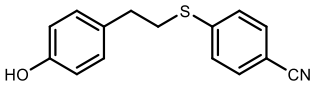


4-((4-Chlorophenethyl)thio)benzonitrile (3u): Synthesized according to the General Procedure **A** using 2-(4-chlorophenyl)ethan-1-ol (31.5 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (54.0 mg, 0.4 mmol, 2.0 equiv.) and 4-chlorobenzonitrile (82.5 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane: EtOAc = 30: 1 as eluent) to afford **3u** (46.5 mg, 85% yield) as a pale yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.55 – 7.49 (m, 2H), 7.33 – 7.25 (m, 4H), 7.16 – 7.11 (m, 2H), 3.24 – 3.18 (m, 2H), 2.95 (t, *J* = 7.6 Hz, 2H) ppm.

$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ= 144.3, 137.8, 132.3, 129.9, 128.8, 127.1, 118.8, 108.4, 34.3, 33.3.

HRMS (ESI): calculated for $C_{15}H_{12}ClNNaS$ [M+Na^+]: 296.0271, found 296.0276.

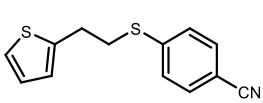


4-((4-Hydroxyphenethyl)thio)benzonitrile (3v): Synthesized according to the General Procedure **A** using 4-(2-hydroxyethyl)phenol (27.5 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and 4-chlorobenzonitrile (82.5 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane: EtOAc = 300: 1 as eluent) to afford **3v** (33.5 mg, 65% yield) as a yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.56 – 7.49 (m, 2H), 7.34 – 7.27 (m, 2H), 7.11 – 7.05 (m, 2H), 6.83 – 6.76 (m, 2H), 5.00 (br, 1H), 3.22 – 3.16 (m, 2H), 2.91 (t, *J* = 7.7 Hz, 2H) ppm.

$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ= 154.5, 144.8, 132.3, 131.6, 129.7, 126.9, 118.9, 115.5, 108.1, 34.1, 33.7 ppm.

HRMS (ESI): calculated for $C_{15}H_{13}NNaOS$ [M+Na^+]: 278.0610, found 278.0607.



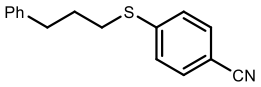
4-((2-(Thiophen-2-yl)ethyl)thio)benzonitrile (3w): Synthesized according to the General Procedure **A** using 2-(thiophen-2-yl)ethan-1-ol (25.5 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and 4-chlorobenzonitrile (82.5 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography

on silica gel (Hexane: EtOAc = 150: 1 as eluent) to afford **3w** (40.5 mg, 86% yield) as a yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.56 – 7.50 (m, 2H), 7.34 – 7.29 (m, 2H), 7.18 (dd, *J* = 5.1, 1.2 Hz, 1H), 6.97 – 6.93 (m, 1H), 6.89 – 6.85 (m, 1H), 3.31 – 3.24 (m, 2H), 3.23 – 3.16 (m, 2H) ppm.

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ= 144.2, 141.7, 132.4, 127.1, 127.0, 125.4, 124.1, 118.8, 108.5, 33.7, 29.4 ppm.

HRMS (ESI): calculated for $C_{13}H_{12}NS_2$ [M+H$^+$]: 246.0406, found 246.0405.

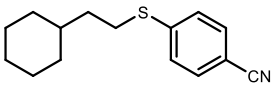


4-((3-Phenylpropyl)thio)benzonitrile (3x): Synthesized according to the General Procedure **A** using 3-phenylpropan-1-ol (27.2 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and 4-chlorobenzonitrile (82.5 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane: EtOAc = 200: 1 as eluent) to afford **3x** (33.0 mg, 65% yield) as a pale yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.53 – 7.46 (m, 2H), 7.34 – 7.28 (m, 2H), 7.26 – 7.21 (m, 3H), 7.21 – 7.17 (m, 2H), 2.97 (t, *J* = 7.4 Hz, 2H), 2.78 (t, *J* = 7.4 Hz, 2H), 2.02 – 1.97 (m, 2H) ppm.

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ= 144.8, 140.7, 132.2, 128.6, 128.5, 126.8, 126.3, 118.9, 108.1, 34.7, 31.0, 30.1 ppm.

HRMS (ESI): calculated for $C_{16}H_{15}NNaS$ [M+Na$^+$]: 276.0817, found 276.0824.

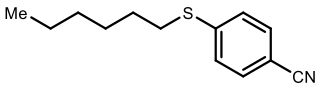


4-((2-Cyclohexylethyl)thio)benzonitrile (3y): Synthesized according to the General Procedure **A** using 2-cyclohexylethan-1-ol (25.6 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and 4-chlorobenzonitrile (82.5 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane: EtOAc = 300: 1 as eluent) to afford **3y** (33.0 mg, 67% yield) as a pale yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.54 – 7.49 (m, 2H), 7.30 – 7.26 (m, 2H), 3.01 – 2.95 (m, 2H), 1.78 – 1.64 (m, 5H), 1.60 – 1.56 (m, 2H), 1.45 – 1.37 (m, 1H), 1.26 – 1.14 (m, 3H), 0.98 – 0.90 (m, 2H) ppm.

$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ= 145.4, 132.2, 126.6, 119.0, 107.8, 37.0, 36.0, 33.0, 29.5, 26.5, 26.2 ppm.

HRMS (ESI): calculated for $C_{15}H_{19}NNaS$ [M+Na^+]: 268.1130, found 268.1131.



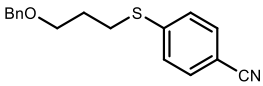
4-(Hexylthio)benzonitrile (3z): Synthesized according to the General Procedure **A** using hexan-1-ol (20.4 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and 4-chlorobenzonitrile (82.5 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane: EtOAc = 300: 1 as eluent) to afford **3z** (28.5 mg, 65% yield) as a pale yellow liquid.

^1H NMR (400 MHz, $CDCl_3$): δ 7.54 – 7.49 (m, 2H), 7.31 – 7.27 (m, 2H), 2.97 (t, *J* = 8.0 Hz, 2H),

1.72 – 1.66 (m, 2H), 1.48 – 1.41 (m, 2H), 1.33 – 1.28 (m, 4H), 0.91 – 0.87 (m, 3H) ppm.

$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ= 145.3, 132.2, 126.7, 119.0, 107.9, 31.9, 31.3, 28.6, 28.5, 22.5, 14.0 ppm.

HRMS (ESI): calculated for $C_{13}H_{17}NNaS$ [M+Na^+]: 242.0974, found 242.0977.

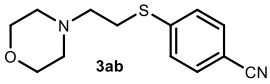


4-((3-(Benzyloxy)propyl)thio)benzonitrile (3aa): Synthesized according to the General Procedure A using 3-(benzyloxy)propan-1-ol (33.2 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and 4-chlorobenzonitrile (82.5 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane: EtOAc = 30: 1 as eluent) to afford **3aa** (37.4 mg, 66% yield) as a pale yellow liquid.

^1H NMR (400 MHz, $CDCl_3$): δ= 7.53 – 7.47 (m, 2H), 7.39 – 7.27 (m, 7H), 4.51 (s, 2H), 3.60 (t, *J* = 5.8 Hz, 2H), 3.12 (t, *J* = 5.8 Hz, 2H), 2.03 – 1.94 (m, 2H) ppm.

$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ= 144.9, 138.2, 132.2, 128.5, 127.7, 127.6, 126.8, 119.0, 108.0, 73.1, 68.2, 29.1, 28.7 ppm.

HRMS (ESI): calculated for $C_{17}H_{17}NNaOS$ [M+Na^+]: 306.0923, found 306.0924.



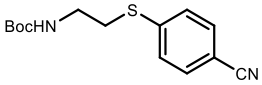
4-((2-Morpholinoethyl)thio)benzonitrile (3ab): Synthesized according to the General Procedure **A** using 2-morpholinoethan-1-ol (26.2 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0

equiv.) and 4-chlorobenzonitrile (82.5 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane: EtOAc = 1: 1 as eluent) to afford **3ab**) (31.0 mg, 62% yield) as a pale yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.54 – 7.48 (m, 2H), 7.34 – 7.28 (m, 2H), 3.74 – 3.68 (m, 4H), 3.15 – 3.08 (m, 2H), 2.70 – 2.64 (m, 2H), 2.54 – 2.44 (m, 4H) ppm.

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ= 144.7, 132.3, 126.9, 118.8, 108.3, 66.8, 57.2, 53.5, 29.3 ppm.

HRMS (ESI): calculated for $C_{13}H_{17}N_2OS$ [M+H$^+$]: 249.1056, found 249.1063.

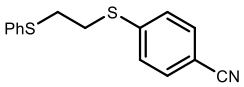


Tert-butyl (2-((4-cyanophenyl)thio)ethyl)carbamate (3ac): Synthesized according to the General Procedure **A** using tert-butyl (2-hydroxyethyl)carbamate (32.0 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and 4-chlorobenzonitrile (82.5 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane: EtOAc = 10: 1 as eluent) to afford **3ac** (28.5 mg, 51% yield) as a yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.57 – 7.49 (m, 2H), 7.40 – 7.34 (m, 2H), 4.89 (br, 1H), 3.38 (q, *J* = 6.6 Hz, 2H), 3.13 (t, *J* = 6.8 Hz, 2H), 1.44 (s, 9H) ppm.

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ= 155.7, 143.6, 132.4, 127.2, 118.8, 108.6, 79.8, 39.6, 32.0, 28.4 ppm.

HRMS (ESI): calculated for $C_{14}H_{18}N_2NaO_2S$ [M+Na$^+$]: 301.0981, found 301.0982.

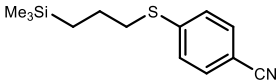


4-((2-(Phenylthio)ethyl)thio)benzonitrile (3ad): Synthesized according to the General Procedure **A** using 2-(phenylthio)ethan-1-ol (30.8 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and 4-chlorobenzonitrile (82.5 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane: EtOAc = 150: 1 as eluent) to afford **3ad** (44.5 mg, 81% yield) as a pale yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.50 – 7.45 (m, 2H), 7.42 – 7.37 (m, 2H), 7.36 – 7.30 (m, 2H), 7.30 – 7.24 (m, 1H), 7.22 – 7.15 (m, 2H), 3.18– 3.13(m, 2H), 3.13 – 3.07 (m, 2H) ppm.

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ= 143.4, 134.4, 132.4, 131.1, 129.2, 127.3, 127.3, 118.7, 108.7, 33.5, 31.5 ppm.

HRMS (ESI): calculated for $C_{15}H_{13}NNaS_2$ [M+Na$^+$]: 294.0382, found 294.0387.

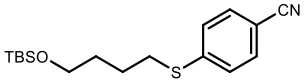


4-((3-(Trimethylsilyl)propyl)thio)benzonitrile (3ae): Synthesized according to the General Procedure **A** using 3-(trimethylsilyl)propan-1-ol (26.5 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and 4-chlorobenzonitrile (82.5 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane: EtOAc = 300: 1 as eluent) to afford **3ae** (34.0 mg, 68% yield) as a pale yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.54 – 7.48 (m, 2H), 7.31 – 7.26 (m, 2H), 3.01 – 2.94 (m, 2H), 1.72 – 1.64 (m, 2H), 0.69 – 0.61 (m, 2H), 0.01 (s, 9H) ppm.

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ= 145.3, 132.2, 126.7, 119.0, 107.9, 35.5, 23.5, 16.5, -1.8.

HRMS (ESI): calculated for $C_{13}H_{20}NSSi$ [M+H$^+$]: 250.1080, found 250.1076.

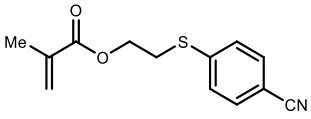


4-((4-((Tert-butyldimethylsilyl)oxy)butyl)thio)benzonitrile (3af): Synthesized according to the General Procedure **A** using 4-((tert-butyldimethylsilyl)oxy)butan-1-ol (41.0 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and 4-chlorobenzonitrile (82.5 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane: EtOAc = 150: 1 as eluent) to afford **3af** (31.0 mg, 48% yield) as a pale yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.54 – 7.47 (m, 2H), 7.32– 7.27 (m, 2H), 3.64 (t, *J* = 6.0 Hz, 2H), 3.00 (t, *J* = 6.0 Hz, 2H),1.82 – 1.73 (m, 2H), 1.69 – 1.63(m, 2H), 0.87 (s, 9H), 0.03 (s, 6H) ppm.

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ= 145.1, 132.2, 126.8, 119.0, 108.0, 62.4, 31.8, 31.8, 25.9, 25.3, 18.3, -5.3 ppm.

HRMS (ESI): calculated for $C_{17}H_{27}NNaOSSi$ [M+Na$^+$]: 344.1475, found 344.1482.



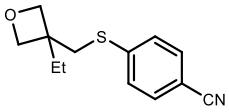
2-((4-Cyanophenyl)thio)ethyl methacrylate (3ag): Synthesized according to the General Procedure **A** using 2-hydroxyethyl methacrylate (26.0 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and 4-chlorobenzonitrile (82.5

mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane: EtOAc = 20: 1 as eluent) to afford **3ag** (22.5 mg, 45% yield) as a yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.58 – 7.51 (m, 2H), 7.44 – 7.37 (m, 2H), 6.09 – 6.05 (m, 1H), 5.61 – 5.55 (m, 1H), 4.36 (t, *J* = 6.9 Hz, 2H), 3.27 (t, *J* = 6.9 Hz, 2H), 1.94 – 1.89 (m, 3H) ppm.

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ= 167.1, 143.3, 135.8, 132.4, 127.3, 126.3, 118.7, 108.9, 62.6, 30.5, 18.2 ppm.

HRMS (ESI): calculated for $C_{13}H_{13}NNaO_2S$ [M+Na^+]: 270.0559, found 270.0558.



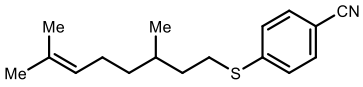
4-(((3-Ethyloxetan-3-yl)methyl)thio)benzonitrile (3ah): Synthesized according to the General Procedure **A** using (3-ethyloxetan-3-yl)methanol (23.2 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and 4-chlorobenzonitrile (82.5 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane: EtOAc = 30: 1 as eluent) to afford **3ah** (28.0 mg, 60% yield) as a yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.58 – 7.51 (m, 2H), 7.39 – 7.33 (m, 2H), 4.48 – 4.41 (m, 4H),

3.35 (s, 2H), 1.83 (q, *J* = 7.4 Hz, 2H), 0.92 (t, *J* = 7.4 Hz, 3H) ppm.

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ= 144.6, 132.3, 127.5, 118.7, 108.7, 80.0, 43.3, 38.6, 28.3, 8.2 ppm.

HRMS (ESI): calculated for $C_{13}H_{15}NNaOS$ [M+Na^+]: 256.0767, found 256.0764.

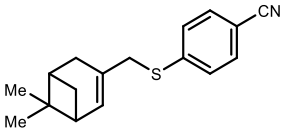


4-((3,7-Dimethyloct-6-en-1-yl)thio)benzonitrile (3ai): Synthesized according to the General Procedure **A** using 3,7-dimethyloct-6-en-1-ol (31.3 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and 4-chlorobenzonitrile (82.5 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane: EtOAc = 300: 1 as eluent) to afford **3ai** (33.0 mg, 60% yield) as a pale yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.54 – 7.49 (m, 2H), 7.31– 7.26 (m, 2H), 5.11 – 5.04 (m, 1H), 3.05 – 2.89 (m, 2H), 2.05 – 1.90 (m, 2H), 1.76 – 1.68 (m, 4H), 1.60 – 1.48 (m, 5H), 1.40 – 1.32 (m, 1H), 1.24 – 1.16 (m, 1H), 0.94 (d, *J* = 6.4 Hz, 3H) ppm.

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ= 145.3, 132.2, 131.6, 126.7, 124.4, 119.0, 107.9, 36.7, 35.6, 32.0, 29.8, 25.7, 25.4, 19.2, 17.7 ppm.

HRMS (ESI): calculated for $C_{17}H_{23}NNaS$ [M+Na$^+$]: 296.1443, found 296.1452.

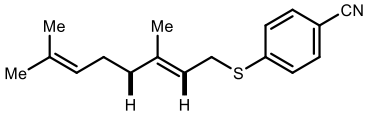


4-(((6,6-Dimethylbicyclo[3.1.1]hept-2-en-3-yl)methyl)thio)benzonitrile (3aj): Synthesized according to the General Procedure **A** using (6,6-dimethylbicyclo[3.1.1]hept-2-en-3-yl)methanol (30.5 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and 4-chlorobenzonitrile (82.5 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane: EtOAc = 150: 1 as eluent) to afford **3aj** (27.5 mg, 51% yield) as a yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.52 – 7.47 (m, 2H), 7.33 – 7.28 (m, 2H), 5.56 – 5.51 (m, 1H), 3.60 – 3.56 (m, 2H), 2.41 – 2.35 (m, 1H), 2.29 – 2.16 (m, 3H), 2.11 – 2.05 (m, 1H), 1.28 (s, 3H), 1.05 (d, *J* = 8.7 Hz, 1H), 0.73 (s, 3H) ppm.

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ= 145.1, 141.7, 132.0, 127.3, 121.7, 119.0, 108.1, 45.2, 40.4, 38.6, 38.2, 31.6, 31.3, 26.1, 21.1 ppm.

HRMS (ESI): calculated for $C_{17}H_{20}NS$ [M+H$^+$]: 270.1311, found 270.1307.

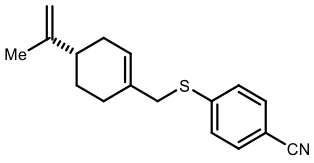


(E)-4-((3,7-Dimethylocta-2,6-dien-1-yl)thio)benzonitrile *(E: Z= 6.5 :1) (major isomer)* (3ak): Synthesized according to the General Procedure **A** using (E)-3,7-dimethylocta-2,6-dien-1-ol (31.0 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and 4-chlorobenzonitrile (82.5 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane: EtOAc = 300: 1 as eluent) to afford **3ak** (19.5 mg, 36% yield) as a yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.54 – 7.49 (m, 2H), 7.32– 7.27(m, 2H), 5.32 – 5.25 (m, 1H), 5.07 – 4.99 (m, 1H), 3.64 – 3.59 (m, 2H), 2.12 – 1.98 (m, 4H), 1.69 (s, 3H), 1.66 (s, 3H), 1.59 (s, 3H) ppm.

$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ= 145.3, 141.4, 132.1, 131.9, 127.2, 123.6, 119.0, 117.8, 108.1, 39.5, 30.5, 26.3, 25.7, 17.7, 16.3 ppm.

HRMS (ESI): calculated for $C_{17}H_{21}NNaS$ [M+Na^+]: 294.1287, found 294.1290.



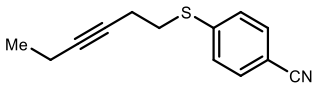
(S)-4-(((4-(Prop-1-en-2-yl)cyclohex-1-en-1-yl)methyl)thio)benzonitrile (3al): Synthesized according to the General Procedure **A** using (S)-(4-(prop-1-en-2-yl)cyclohex-1-en-1-yl)methanol (30.5 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and 4-chlorobenzonitrile (82.5 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane: EtOAc = 300: 1 as eluent) to afford **3al** (28.0 mg, 52% yield) as a yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.53 – 7.49 (m, 2H), 7.33 – 7.29 (m, 2H), 5.74 – 5.70 (m, 1H), 4.74 – 4.70 (m, 1H), 4.69 – 4.66(m, 1H), 3.57 (s, 2H), 2.19 – 2.06 (m, 4H), 2.00 – 1.88 (m, 1H), 1.88 – 1.80 (m, 1H), 1.73 – 1.71 (m, 3H), 1.53 – 1.42 (m, 1H) ppm.

$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ= 149.3, 145.1, 132.1, 131.7, 127.6, 126.0, 119.0, 108.9, 108.3, 40.6, 39.9, 30.7, 27.8, 27.5, 20.8 ppm.

HRMS (ESI): calculated for $C_{17}H_{19}NNaS$ [M+Na^+]: 292.1130, found 292.1137.

4-(Hex-3-yn-1-ylthio)benzonitrile (3am): Synthesized according to the General Procedure

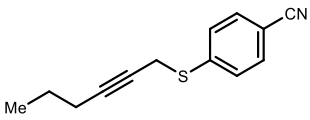


A using hex-3-yn-1-ol (19.6 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and 4-chlorobenzonitrile (82.5 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane: EtOAc = 200: 1 as eluent) to afford **3am** (31.0 mg, 72% yield) as a yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.55 – 7.49 (m, 2H), 7.35 – 7.29 (m, 2H), 3.11 (t, *J* = 7.5 Hz, 2H), 2.55 – 2.48 (m, 2H), 2.19 – 2.10 (m, 2H), 1.09 (t, *J* = 7.5 Hz, 3H) ppm.

$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ= 144.2, 132.3, 127.2, 118.8, 108.5, 84.0, 76.5, 31.5, 19.4, 14.0, 12.4 ppm.

HRMS (ESI): calculated for $C_{13}H_{13}NNaS$ [M+Na^+]: 238.0661, found 238.0655.

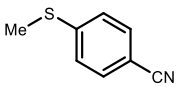


4-(Hex-2-yn-1-ylthio)benzonitrile (3an): Synthesized according to the General Procedure **A** using hex-2-yn-1-ol (19.6 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and 4-chlorobenzonitrile (82.5 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane: EtOAc = 300: 1 as eluent) to afford **3an** (13.0 mg, 30% yield) as a yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.58 – 7.53 (m, 2H), 7.44 – 7.39 (m, 2H), 3.70 (t, *J* = 2.4 Hz, 2H), 2.16 – 2.11 (m, 2H), 1.52 – 1.42 (m, 2H), 0.91 (t, *J* = 7.4 Hz, 3H) ppm.

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ= 143.6, 132.2, 127.3, 118.7, 108.7, 84.8, 74.3, 22.0, 21.3, 20.7, 13.4 ppm.

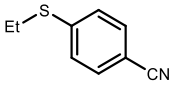
HRMS (ESI): calculated for $C_{13}H_{13}NNaS$ [M+Na^+]: 238.0661, found 238.0653.



4-(Methylthio)benzonitrile (3ao): Synthesized according to the General Procedure **A** using methanol (6.5 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and 4-chlorobenzonitrile (82.5 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane: EtOAc = 150: 1 as eluent) to afford **3ao** (27.0 mg, 90% yield) as a pale yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ =7.54 – 7.49 (m, 2H), 7.27 – 7.23 (m, 2H), 2.50 (s, 3H) ppm.

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 146.1, 132.2, 125.5, 119.0, 107.7, 14.7 ppm. Matching reported literature data[30].

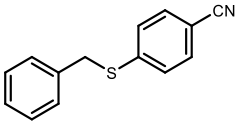


4-(Methylthio)benzonitrile (3ap): Synthesized according to the General Procedure **A** using ethanol (9.2 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and 4-chlorobenzonitrile (82.5 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane: EtOAc = 150: 1 as eluent) to afford **3ap** (16.5 mg, 50% yield) as a yellow liquid.

[30] Zhang, G.; Zhang, C.; Tian, Y.; Chen, F. "Fe-Catalyzed Direct Synthesis of Nitriles from Carboxylic Acids with Electron-Deficient *N*-Cyano-*N*-aryl–arylsulfonamide." *Org. Lett.* **2023**, 25, 917–922.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.55 – 7.49 (m, 2H), 7.31 – 7.27 (m, 2H), 3.01 (q, *J* = 7.4 Hz, 2H), 1.37 (t, *J* = 7.4 Hz, 3H) ppm.

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ= 145.0, 132.2, 126.7, 119.0, 108.0, 26.0, 13.8 ppm. Matching reported literature data[31].

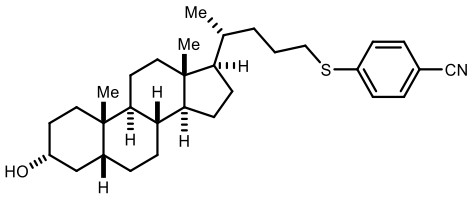


4-(Benzylthio)benzonitrile (3aq): Synthesized according to the General Procedure **A** using phenylmethanol (21.6 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and 4-chlorobenzonitrile (82.5 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane: EtOAc = 100: 1 as eluent) to afford **3aq** (29.0 mg, 64% yield) as a yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.52 – 7.47 (m, 2H), 7.39– 7.26 (m, 7H), 4.2 (s, 2H) ppm.

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ= 144.5, 135.8, 132.2, 128.8, 128.7, 127.7, 127.4, 118.8, 108.6, 37.1 ppm.

HRMS (ESI): calculated for $C_{14}H_{11}NNaS$ [M+Na^+]: 248.0504, found 248.0509.



4-(((4R)-4-((3R,5R,8R,9S,10S,13R)-3-Hydroxy-10,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)pentyl)thio)benzonitrile (3ar): Synthesized according to the General Procedure **A** using (3R,5R,8R,9S,10S,13R)-17-((R)-5-hydroxypentan-2-yl)-10,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-3-ol (72.5 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and 4-chlorobenzonitrile (82.5 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (DCM as eluent) to afford **3ar** (28.0 mg, 30% yield) as a yellow liquid.

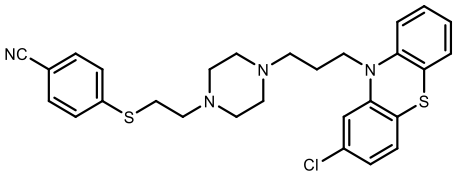
^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.55 – 7.49 (m, 2H), 7.30 – 7.27 (m, 2H), 3.66 – 3.58 (m, 1H), 3.01 – 2.86 (m, 2H), 1.98 – 1.92 (m, 1H), 1.88 – 1.72 (m, 5H), 1.60 – 1.52 (m, 6H), 1.43

[31] Scattolin, T.; Senol, E.; Yin, G.; Guo, Q.; Schoenebeck, F. "Site-Selective C−S Bond Formation at C−Br over C−OTf and C−Cl Enabled by an Air-Stable, Easily Recoverable, and Recyclable Palladium(I) Catalyst." *Angew. Chem., Int. Ed.* **2018**, *57*, 12425 –12429.

– 1.35 (m, 6H), 1.30 – 1.15 (m, 5H), 1.12 – 1.02 (m, 4H), 1.00 – 0.86 (m, 1H), 0.94 – 0.89 (m, 6H), 0.64 (s, 3H) ppm.

$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ= 145.4, 132.2, 126.7, 119.0, 107.9, 71.9, 56.5, 56.1, 42.7, 42.1, 40.5, 40.2, 36.5, 35.9, 35.5, 35.4, 35.2, 34.6, 32.4, 30.6, 28.3, 27.2, 26.4, 25.3, 24.2, 23.4, 20.8, 18.6, 12.1 ppm.

HRMS (ESI): calculated for $C_{31}H_{45}NNaOS$ [M+Na^+]: 502.3114, found 502.3127.

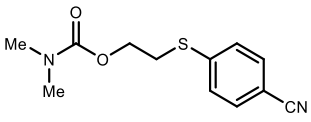


4-((2-(4-(3-(2-Chloro-10H-phenothiazin-10-yl)propyl)piperazin-1-yl)ethyl)thio)benzonitrile (3as): Synthesized according to the General Procedure **A** using 2-(4-(3-(2-chloro-10H-phenothiazin-10-yl)propyl)piperazin-1-yl)ethan-1-ol (81.0 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and 4-chlorobenzonitrile (82.5 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (EtOAc as eluent) to afford **3as** (73.0 mg, 72% yield) as a yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.54 – 7.48 (m, 2H), 7.32 – 7.28 (m, 2H), 7.18 – 7.09 (m, 2H), 7.03 – 6.99 (m, 1H), 6.98 – 6.82 (m, 4H), 3.90 (t, *J* = 6.7 Hz, 2H), 3.13 – 3.05 (m, 2H), 2.70 – 2.63 (m, 2H), 2.62 – 2.28 (m, 10H), 2.00 – 1.87 (m, 2H) ppm.

$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ= 146.5, 144.7, 144.5, 133.2, 132.3, 127.9, 127.5, 127.4, 126.9, 124.9, 123.6, 123.0, 122.3, 118.9, 115.9, 115.9, 108.3, 56.7, 55.4, 53.1, 52.8, 45.2, 29.4, 24.0 ppm.

HRMS (ESI): calculated for $C_{28}H_{30}ClN_4S_2$ [M+H^+]: 521.1595, found 521.1600.

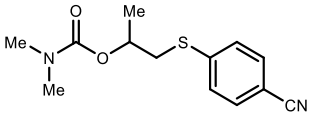


2-((4-Cyanophenyl)thio)ethyl dimethylcarbamate (3at): Synthesized according to the General Procedure **A** using ethane-1,2-diol (12.5 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and 4-chlorobenzonitrile (82.5 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane: EtOAc = 20: 1 as eluent) to afford **3at** (40.5 mg, 90% yield) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.56 – 7.50 (m, 2H), 7.42 – 7.36 (m, 2H), 4.26 (t, *J* = 6.9 Hz, 2H), 3.23 (t, *J* = 6.9 Hz, 2H), 2.89 (s, 3H), 2.82 (s, 3H) ppm.

$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ= 156.1, 143.7, 132.4, 127.1, 118.8, 108.6, 63.2, 36.5, 35.9, 30.8 ppm.

HRMS (ESI): calculated for $C_{12}H_{14}N_2NaO_2S$ [M+Na$^+$]: 273.0668, found 273.0662.

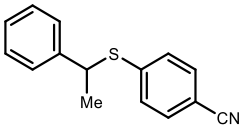


1-((4-Cyanophenyl)thio)propan-2-yl dimethylcarbamate (3au): Synthesized according to the General Procedure **A** using propane-1,2-diol (15.2 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and 4-chlorobenzonitrile (82.5 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane: EtOAc = 20: 1 as eluent) to afford **3au** (39.0 mg, 74% yield) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.55 – 7.48 (m, 2H), 7.44 – 7.39 (m, 2H), 5.01 – 4.91 (m, 1H), 3.31 (dd, *J* = 13.7, 5.3 Hz, 1H), 3.02 (dd, *J* = 13.8, 6.9 Hz, 1H), 2.88 (s, 3H), 2.79 (s, 3H), 1.36 (d, *J* = 6.3 Hz, 3H) ppm.

$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ= 155.8, 144.2, 132.3, 127.1, 118.8, 108.4, 69.8, 37.3, 36.4, 35.8, 19.4 ppm.

HRMS (ESI): calculated for $C_{13}H_{16}N_2NaO_2S$ [M+Na$^+$]: 287.0825, found 287.0824.



4-((1-Phenylethyl)thio)benzonitrile (3av): Synthesized according to the General Procedure **A** using 1-phenylethan-1-ol (24.4 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and 4-chlorobenzonitrile (82.5 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane: EtOAc = 100: 1 as eluent) to afford **3av** (9.6 mg, 20% yield) as a yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.47 – 7.42 (m, 2H), 7.39 – 7.34 (m, 2H), 7.33 – 7.27 (m, 3H), 7.28 – 7.21 (m, 2H), 4.50 (q, *J* = 7.0 Hz, 1H), 1.67 (d, *J* = 7.0 Hz, 3H) ppm.

$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ= 143.5, 142.2, 132.1, 129.4, 128.8, 127.6, 127.1, 118.8, 109.1, 46.6, 22.8 ppm.

HRMS (ESI): calculated for $C_{15}H_{13}NNaS$ [M+Na$^+$]: 262.0661, found 262.0668.

Unsuccessful Substrates

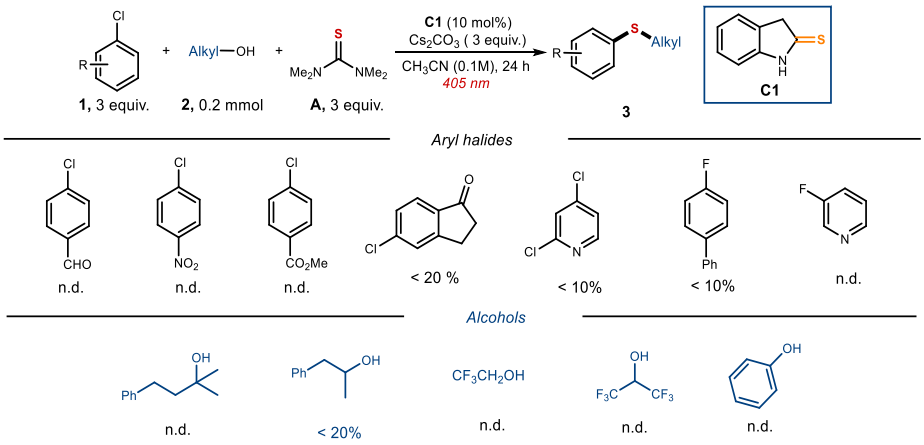


Figure 3.24. Unsuccessful aryl halides and alcohols, n.d. = product not detected

Other Aryl Halides as Precursors

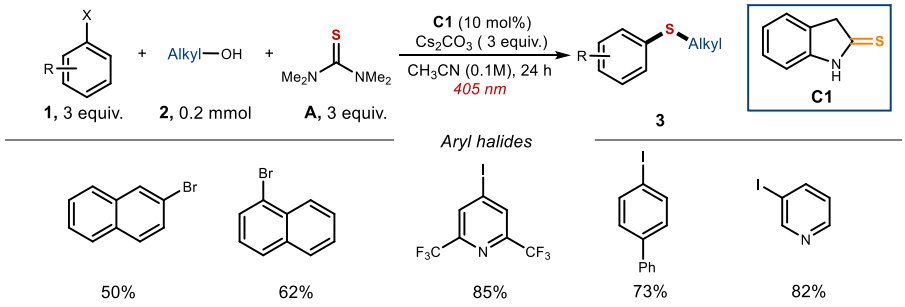
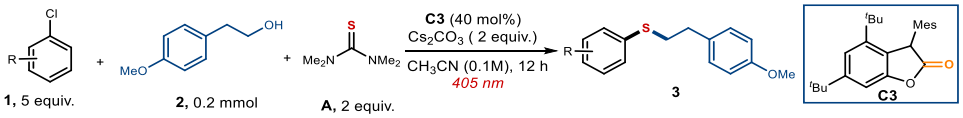


Figure 3.25. Reactivity of aryl bromides and iodides.

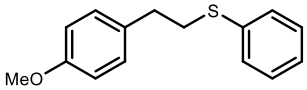
3.6.4 Preparation of Thioethers from Alcohols and Electron-Neutral and Rich Aryl Halides

General Procedure B for Neutral and Electron-Rich Aryl Halides



To a 7 mL glass vial, **C3** (29.5 mg, 0.08 mmol, 0.4 equiv.), cesium carbonate (130.0 mg, 0.4 mmol, 2 equiv.), 1,1,3,3-tetramethylthiourea **A** (53.0 mg, 0.4 mmol, 2.0 equiv.), alcohol **2** (30.5 mg, 0.2 mmol, 1 equiv.) and aryl chlorides **1** (if solid, 0.6 mmol, 5 equiv.) were sequentially added. The vial was sealed with a screw-top cap with septum and then vacuumed and backfilled with argon for 3 times. Afterwards, aryl chlorides **1** (if liquid, 0.6 mmol, 5 equiv.) followed by argon-sparged acetonitrile (0.1 M, 2.0 mL) were added *via* syringe. The vial was sealed with Parafilm and then stirred under 405 nm for 24 hours using ***Set-up 1*** detailed in Figure 3.21. After completion of the reaction, column chromatography purification afforded the corresponding products **3** with the reported yields

Characterization of Products from Electron-Neutral and Rich Aryl Halides

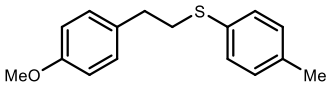


(4-Methoxyphenethyl)(phenyl)sulfane (3aw): Synthesized according to the General Procedure **B** using 2-(4-methoxyphenyl)ethan-1-ol (30.5 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (54.0 mg, 0.4 mmol, 2.0 equiv.) and chlorobenzene (112.5 mg, 1.0 mmol, 5.0 equiv.) or bromobenzene (157.0 mg, 1.0 mmol, 5.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane: EtOAc = 300: 1 as eluent) to afford **3aw** (34.0 mg, 70% yield with chlorobenzene and 33.2 mg, 68% yield with bromobenzene) as a yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.39 – 7.34 (m, 2H), 7.33 – 7.27 (m, 2H), 7.22 – 7.17 (m, 1H), 7.15 – 7.10 (m, 2H), 6.88 – 6.83 (m, 2H), 3.80 (s, 3H), 3.18 – 3.11 (m, 2H), 2.91 – 2.85 (m, 2H) ppm.

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ= 158.3, 136.5, 132.3, 129.5, 129.2, 128.9, 125.9, 114.0, 55.3, 35.4, 34.8 ppm.

Matching reported literature data[32].



(4-Methoxyphenethyl)(p-tolyl)sulfane (3ax): Synthesized according to the General Procedure **B** using 2-(4-methoxyphenyl)ethan-1-ol (30.5 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea

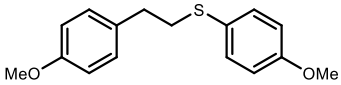
[32] Yang, Y.-Z.; Li, Y.; Lv, G.-F.; He, D.-L.; Li, J.-H. "Nickel-Catalyzed C-S Reductive Cross-Coupling of Alkyl Halides with Arylthiosilanes toward Alkyl Aryl Thioethers." *Org. Lett.* **2022**, *24*, 5115−5119.

(54.0 mg, 0.4 mmol, 2.0 equiv.) and 1-chloro-4-methylbenzene (126.6 mg, 1.0 mmol, 5.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane: EtOAc = 300: 1 as eluent) to afford **3ax** (33.2 mg, 64% yield) as a yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.31 – 7.27 (m, 2H), 7.15 – 7.08 (m, 4H), 6.87 – 6.82 (m, 2H), 3.80 (s, 3H), 3.13 – 3.08 (m, 2H), 2.88 – 2.82 (m, 2H), 2.34 (s, 3H) ppm.

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ= 158.2, 136.2, 132.6, 132.5, 130.1, 129.7, 129.5, 113.9, 55.3, 36.1, 34.9, 21.0 ppm.

Matching reported literature data[33].

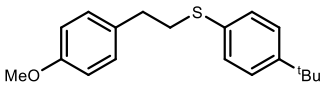


(4-Methoxyphenethyl)(4-methoxyphenyl)sulfane (3ay): Synthesized according to the General Procedure **B** using 2-(4-methoxyphenyl)ethan-1-ol (30.5 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (54.0 mg, 0.4 mmol, 2.0 equiv.) and 1-chloro-4-methoxybenzene (142.5 mg, 1.0 mmol, 5.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane: EtOAc = 100: 1 as eluent) to afford **3ay** (31.0 mg, 56% yield) as a yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.39 – 7.34 (m, 2H), 7.11 – 7.06 (m, 2H), 6.89 – 6.80 (m, 4H), 3.81 (s, 3H), 3.79 (s, 3H), 3.13 – 3.08 (m, 2H), 2.85 – 2.78 (m, 2H) ppm.

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ= 158.9, 158.2, 133.2, 132.5, 129.5, 126.4, 114.6, 113.9, 55.4, 55.3, 37.5, 35.0 ppm.

HRMS(APCI): calculated for $C_{16}H_{18}O_2S$ [M^+]: 274.1022, found 274.1021.



(4-(Tert-butyl)phenyl)(4-methoxyphenethyl)sulfane (3az): Synthesized according to the General Procedure B using 2-(4-methoxyphenyl)ethan-1-ol (30.5 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (54.0 mg, 0.4 mmol, 2.0 equiv.) and 1-(tert-butyl)-4-chlorobenzene (168.5 mg, 1.0 mmol, 5.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane: EtOAc = 300: 1 as eluent) to afford **3az** (36.5 mg, 60% yield) as a yellow liquid.

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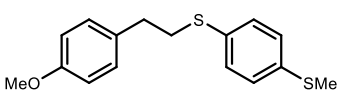
[33] Huang, Y.; Xin, Z.; Yao, W.; Hu, Q.; Li, Z.; Xiao, L.; Yang, B.; Zhang, J. A Recyclable Self-Assembled Composite Catalyst Consisting of Fe_3O_4-Rose bengal-Layered Double Hydroxides for Highly Efficient Visible Light Photocatalysis in Water. *Chem. Commun.* **2018**, *54*, 13587–13590.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.35 – 7.28 (m, 4H), 7.15 – 7.10 (m, 2H), 6.87 – 6.82 (m, 2H), 3.80 (s, 3H), 3.79 (s, 3H), 3.15 – 3.09 (m, 2H), 2.90 – 2.84 (m, 2H), 1.32 (s, 9H) ppm.

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ= 158.2, 149.3, 132.8, 132.5, 129.5, 129.4, 126.0, 113.9, 55.3, 35.8, 34.9, 34.5, 31.3 ppm.

HRMS (ESI): calculated for $C_{19}H_{24}NaOS$ [M+Na^+]: 323.1440, found 323.1445.

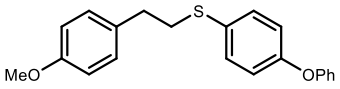


(4-Methoxyphenethyl)(4-(methylthio)phenyl)sulfane (3ba): Synthesized according to the General Procedure **B** using 2-(4-methoxyphenyl)ethan-1-ol (30.5 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (54.0 mg, 0.4 mmol, 2.0 equiv.) and (4-chlorophenyl)(methyl)sulfane (158.5 mg, 1.0 mmol, 5.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane: EtOAc = 300: 1 as eluent) to afford **3bb** (31.4 mg, 54% yield) as a yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.31 – 7.27 (m, 2H), 7.22 – 7.17 (m, 2H), 7.13 – 7.08 (m, 2H), 6.86 – 6.81 (m, 2H), 3.79 (s, 3H), 3.13 – 3.07 (m, 2H), 2.88 – 2.82 (m, 2H), 2.48 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 158.2, 136.5, 132.8, 132.3, 130.5, 129.5, 127.3, 113.9, 55.3, 36.0, 34.8, 16.1.

HRMS(APCI): calculated for $C_{16}H_{18}OS_2$ [M^+]: 290.0794, found 290.0791.

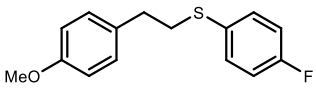


(4-Methoxyphenethyl)(4-phenoxyphenyl)sulfane (3bb): Synthesized according to the General Procedure **B** using 2-(4-methoxyphenyl)ethan-1-ol (30.5 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (54.0 mg, 0.4 mmol, 2.0 equiv.) and 1-chloro-4-phenoxybenzene (204.5 mg, 1.0 mmol, 5.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane: EtOAc = 200: 1 as eluent) to afford **3bb** (48.0 mg, 71% yield) as a pale yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.39 – 7.32 (m, 4H), 7.16 – 7.09 (m, 3H), 7.05 – 7.01 (m, 2H), 6.99 – 6.94 (m, 2H), 6.88 – 6.82 (m, 2H), 3.80 (s, 3H), 3.13 – 3.07 (m, 2H), 2.90 – 2.84 (m, 2H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ= 158.2, 157.0, 156.3, 132.3, 132.2, 130.0, 129.8, 129.5, 123.5, 119.4, 119.0, 113.9, 55.3, 36.8, 34.9 ppm.

HRMS (ESI): calculated for $C_{21}H_{20}NaO_2S$ [M+Na$^+$]: 359.1076, found 359.1074.



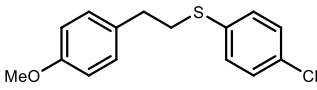
(4-Fluorophenyl)(4-methoxyphenethyl)sulfane (3bc): Synthesized according to the General Procedure **B** using 2-(4-methoxyphenyl)ethan-1-ol (30.5 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (54.0 mg, 0.4 mmol, 2.0 equiv.) and 1-chloro-4-fluorobenzene (130.5 mg, 1.0 mmol, 5.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane: EtOAc = 300: 1 as eluent) to afford **3bc** (43.0 mg, 82% yield) as a pale yellow liquid.

^{1}H NMR (400 MHz, CDCl$_3$): δ= 7.39 – 7.33 (m, 2H), 7.12 – 7.07 (m, 2H), 7.05 – 6.97 (m, 2H), 6.87 – 6.81 (m, 2H), 3.79 (s, 3H), 3.12 – 3.06 (m, 2H), 2.88 – 2.81 (m, 2H) ppm.

^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$): δ= 161.8 (d, *J* = 246.1 Hz), 158.3, 132.3(d, *J* = 8.1 Hz), 132.2, 131.2(d, *J* = 4.0 Hz), 129.5, 116.0 (d, *J* = 22.2 Hz), 113.9, 55.3, 36.8, 34.8 ppm.

^{19}F{^{1}H} NMR (376 MHz, CDCl$_3$): δ= -115.8 ppm.

HRMS(APCI): calculated for $C_{15}H_{15}FOS$ [M$^+$]: 262.0822, found 262.0826.



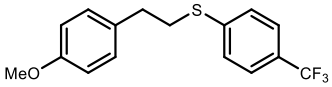
(4-Chlorophenyl)(4-methoxyphenethyl)sulfane (3bd): Synthesized according to the General Procedure **B** using 2-(4-methoxyphenyl)ethan-1-ol (30.5 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (54.0 mg, 0.4 mmol, 2.0 equiv.) and 1-bromo-4-chlorobenzene (191.5 mg, 1.0 mmol, 5.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane: EtOAc = 200: 1 as eluent) to afford **3bd** (27.9 mg, 50% yield) as a yellow liquid.

^{1}H NMR (400 MHz, CDCl$_3$): δ= 7.29 – 7.24 (m, 4H), 7.13 – 7.08 (m, 2H), 6.87 – 6.82 (m, 2H), 3.79 (s, 3H), 3.14 – 3.09 (m, 2H), 2.89 – 2.83 (m, 2H) ppm.

^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$): δ= 158.3, 135.0, 132.0, 131.9, 130.5, 129.5, 129.0, 114.0, 55.3, 35.7, 34.6 ppm.

HRMS (ESI): calculated for $C_{15}H_{15}ClNaO_2S$ [M+Na$^+$]: 317.0373, found 317.0365.

Note: The product may have oxidized upon storage, as only the mono-oxidized form of the product by HRMS. When freshly prepared product was analyzed, the molecule peak can be detected by GC-MS (calculated: 278.0, found 277.9).

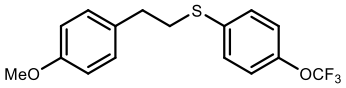
(4-Methoxyphenethyl)(4-(trifluoromethyl)phenyl)sulfane (3be): Synthesized according  to the General Procedure **B** using 2-(4-methoxyphenyl)ethan-1-ol (30.5 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (54.0 mg, 0.4 mmol, 2.0 equiv.) and 1-chloro-4-(trifluoromethyl)benzene (180.5 mg, 1.0 mmol, 5.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane: EtOAc = 200: 1 as eluent) to afford **3be** (34.0 mg, 54% yield) as a pale yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.54 – 7.49 (m, 2H), 7.39 – 7.34 (m, 2H), 7.16 – 7.11 (m, 2H), 6.88 – 6.53 (m, 2H), 3.80 (s, 3H), 3.23 – 3.17 (m, 2H), 2.95 – 2.89 (m, 2H) ppm.

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ= 158.4, 142.2, 131.8, 129.5, 127.5, 125.7 (q, *J* = 3.9 Hz). 124.2 (q, *J* = 273.7 Hz), 114.0, 55.3, 34.4, 34.3 ppm.

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ= -62.5 ppm.

HRMS (ESI): calculated for $C_{16}H_{16}F_3OS$ [M+H$^+$]: 313.0868, found 313.0855.

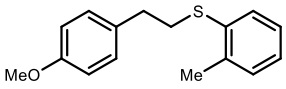
(4-Methoxyphenethyl)(4-(trifluoromethoxy)phenyl)sulfane (3bf): Synthesized according  to the General Procedure **B** using 2-(4-methoxyphenyl)ethan-1-ol (30.5 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (54.0 mg, 0.4 mmol, 2.0 equiv.) and 1-chloro-4-(trifluoromethoxy)benzene (196.5 mg, 1.0 mmol, 5.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane: EtOAc = 200: 1 as eluent) to afford **3bf** (37.0 mg, 56% yield) as a pale yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.37 – 7.33 (m, 2H), 7.17 – 7.09 (m, 4H), 6.87 – 6.82 (m, 2H), 3.79 (s, 3H), 3.17 – 3.11 (m, 2H), 2.91 – 2.84 (m, 2H) ppm.

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ= 158.3, 147.47 (q, *J* = 1.9 Hz), 135.4, 132.0, 130.5, 129.5, 121.6, 120.5 (q, *J* = 258.6 Hz), 114.0, 55.3, 36.7, 34.7 ppm.

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ= -58.1 ppm.

HRMS (ESI): calculated for $C_{16}H_{16}F_3O_2S$ [M+H$^+$]: 329.0818, found 329.0804.



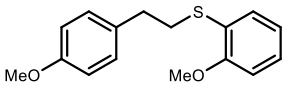
(4-Methoxyphenethyl)(p-tolyl)sulfane (3bg): Synthesized according to the General Procedure **B** using 2-(4-methoxyphenyl)ethan-1-ol (30.5 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (54.0 mg, 0.4 mmol, 2.0 equiv.) and 1-chloro-2-methylbenzene (126.5 mg, 1.0 mmol, 5.0

equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane: EtOAc = 300: 1 as eluent) to afford **3bg** (33.5 mg, 65% yield) as a yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.33 – 7.28 (m, 1H), 7.20 – 7.08 (m, 5H), 6.88 – 6.83 (m, 2H), 3.80 (s, 3H), 3.15 – 3.09 (m, 2H), 2.93 – 2.87 (m, 2H), 2.38 (s, 3H) ppm.

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ= 158.2, 137.6, 135.8, 132.4, 130.1, 129.5, 127.8, 126.4, 125.6, 113.9, 55.3, 34.6, 20.4 ppm.

HRMS(APCI): calculated for $C_{16}H_{18}OS$ [M^+]: 258.1073, found 258.1076.

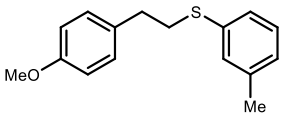


(4-Methoxyphenethyl)(2-methoxyphenyl)sulfane (3bh): Synthesized according to the General Procedure **B** using 2-(4-methoxyphenyl)ethan-1-ol (30.5 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (54.0 mg, 0.4 mmol, 2.0 equiv.) and 1-chloro-2-methoxybenzene (142.6 mg, 1.0 mmol, 5.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane: EtOAc = 100: 1 as eluent) to afford **3bh** (36.5 mg, 66% yield) as a yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.31 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.23 – 7.17 (m, 1H), 7.16 – 7.11 (m, 2H), 6.97 – 6.91 (m, 1H), 6.88 – 6.82 (m, 3H), 3.90 (s, 3H), 3.79 (s, 3H), 3.15 – 3.08 (m, 2H), 2.91 – 2.85 (m, 2H) ppm.

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ= 158.2, 157.4, 132.6, 129.5, 129.5, 127.2, 124.5, 121.1, 113.9, 110.5, 55.8, 55.3, 34.7, 33.8 ppm.

HRMS (ESI): calculated for $C_{16}H_{18}NaO_2S$ [M+Na^+]: 297.0920, found 297.0922.

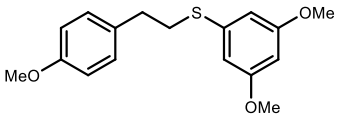


(4-Methoxyphenethyl)(p-tolyl)sulfane (3bi): Synthesized according to the General Procedure **B** using 2-(4-methoxyphenyl)ethan-1-ol (30.5 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (54.0 mg, 0.4 mmol, 2.0 equiv.) and 1-chloro-3-methylbenzene (126.5 mg, 1.0 mmol, 5.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane: EtOAc = 300: 1 as eluent) to afford **3bi** (30.0 mg, 58% yield) as a yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.22 – 7.10 (m, 5H), 7.02 – 6.98 (m, 1H), 6.87 – 6.82 (m, 2H), 3.80 (s, 3H), 3.16 – 3.11 (m, 2H), 2.91 – 2.84 (m, 2H), 2.33 (s, 3H) ppm.

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ= 158.2, 138.7, 136.2, 132.4, 129.8, 129.5, 128.8, 126.8, 126.1, 113.9, 55.3, 35.4, 34.8, 21.4 ppm.

HRMS (APCI): calculated for $C_{16}H_{18}OS$ [M^+]: 258.1073, found 258.1079.

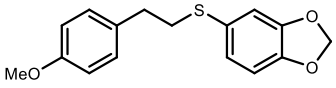


(3,5-Dimethoxyphenyl)(4-methoxyphenethyl)sulfane (3bj): Synthesized according to the General Procedure **B** using 2-(4-methoxyphenyl)ethan-1-ol (30.5 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (54.0 mg, 0.4 mmol, 2.0 equiv.) and 1-chloro-3,5-dimethoxybenzene (172.5 mg, 1.0 mmol, 5.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane: EtOAc = 100: 1 as eluent) to afford **3bj** (26.8 mg, 44% yield) as a yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.16 – 7.11 (m, 2H), 6.88 – 6.82 (m, 2H), 6.50 (d, *J* = 2.2 Hz, 2H), 6.29 (t, *J* = 2.2 Hz, 1H), 3.79 (s, 3H), 3.78 (s, 6H), 3.17 – 3.11 (m, 2H), 2.92 – 2.87 (m, 2H) ppm.

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ= 161.0, 158.3, 138.6, 132.3, 129.5, 113.9, 106.5, 98.3, 55.4, 55.3, 35.0, 34.7 ppm.

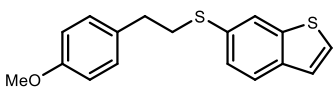
HRMS (ESI): calculated for $C_{17}H_{21}O_3S$ [$M+H^+$]: 305.1206, found 305.1194.



5-((4-Methoxyphenethyl)thio)benzo[d][1,3]dioxole (3bk): Synthesized according to the General Procedure **B** using 2-(4-methoxyphenyl)ethan-1-ol (30.5 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (54.0 mg, 0.4 mmol, 2.0 equiv.) and 5-chlorobenzo[d][1,3]dioxole (156.5 mg, 1.0 mmol, 5.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane: EtOAc = 100: 1 as eluent) to afford **3bk** (32.5 mg, 56% yield) as a pale yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.11 – 7.06 (m, 1H), 6.94 – 6.90 (m, 2H), 6.86 – 6.81 (m, 2H), 6.78 – 6.74 (m, 2H), 5.97 (s, 2H), 3.79 (s, 3H), 3.07 – 3.01(m, 2H), 2.86 – 2.79 (m, 2H) ppm. **^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)**: δ= 158.2, 148.0, 147.0, 132.3, 129.5, 128.1, 125.3, 113.9, 112.0, 108.7, 101.3, 55.3, 37.5, 34.9 ppm.

HRMS(APCI): calculated for $C_{16}H_{16}O_3S$ [M^+]: 288.0815, found 288.0816.



6-((4-Methoxyphenethyl)thio)benzo[b]thiophene (3bl): Synthesized according to the General Procedure **B** using 2-(4-methoxyphenyl)ethan-1-ol (30.5 mg, 0.2 mmol, 1.0

equiv.), 1,1,3,3-tetramethylthiourea (54.0 mg, 0.4 mmol, 2.0 equiv.) and 6-chlorobenzo[b]thiophene (168.5 mg, 1.0 mmol, 5.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane: EtOAc = 100: 1 as eluent) to afford **3bl** (26.0 mg, 43% yield) as a yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.84 (d, *J* = 1.9 Hz, 1H), 7.82 – 7.78 (m, 1H), 7.46 (dd, J = 5.4, 0.5 Hz, 1H), 7.40 – 7.35 (m, 1H), 7.28 (dd, *J* = 5.5, 0.8 Hz, 1H), 7.14 – 7.09 (m, 2H), 6.86 – 6.81 (m, 2H), 3.79 (s, 3H), 3.21 – 3.15 (m, 2H), 2.91 – 2.85 (m, 2H) ppm.

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ= 158.2, 140.4, 138.0, 132.4, 131.9, 129.5, 127.4, 126.7, 125.2, 123.4, 122.8, 113.9, 55.3, 36.6, 34.9 ppm.

HRMS (ESI): calculated for $C_{17}H_{17}OS_2$ [M+H$^+$]: 301.0715, found 301.0706.

Unsuccessful Substrates

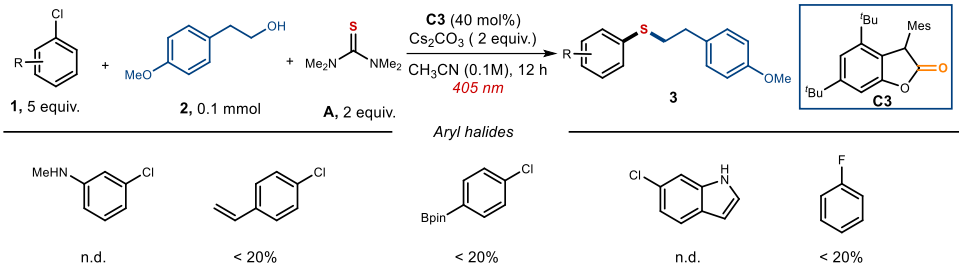


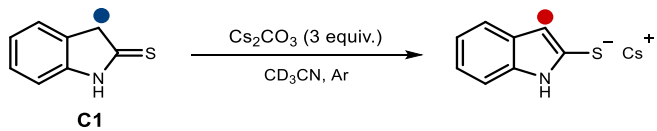
Figure 3.26. Unsuccessful aryl halides; n.d. = product not detected.

3.6.5 Reactivity Study of C1 and C3

Deprotonation Experiments for C1 and C3

- *Deprotonation of catalyst **C1**:*

To a 7 mL glass vial, catalyst **C1** (0.1 mmol, 1 equiv.) and cesium carbonate (0.3 mmol, 3 equiv.) were added. The vial was sealed with a screw-top cap with septum, then vacuumed and backfilled with argon for 3 times and CD_3CN (0.1 M) was added *via* syringe. The solution was stirred at ambient temperature for 10 min, transferred into an argon filled NMR tube *via* syringe and then the ^{1}H NMR spectrum was recorded (Figure 3.27).



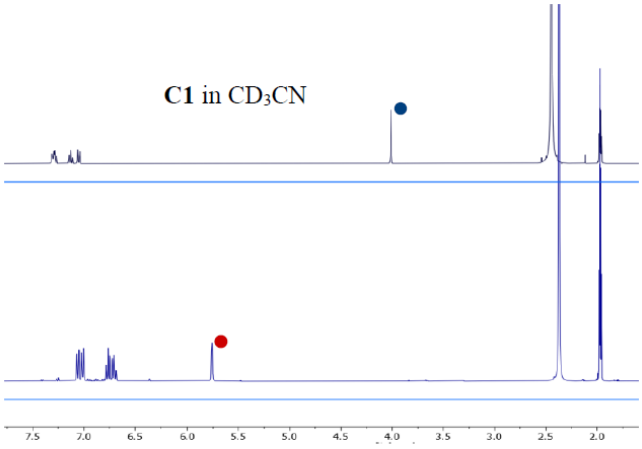
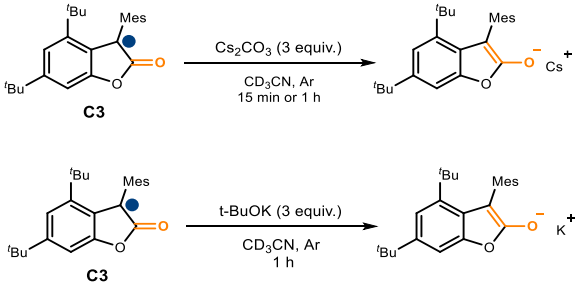


Figure 3.27. ^{1}H NMR analysis of catalyst **C1** before (*top*) and after (*bottom*) treatment with Cs_2CO_3.

- *Deprotonation of catalyst **C3**:*

To a 7 mL glass vial, catalyst **C3** (0.1 mmol, 1 equiv.) and cesium carbonate (0.3 mmol, 3 equiv.) or potassium *tert*-butoxide were added. The vial was sealed with a screw-top cap with septum, then vacuumed and backfilled with argon for 3 times and CD_3CN (0.1 M) were added *via* syringe. The solution was stirred at room temperature for 15 min or 1 h, transferred into an argon filled NMR tube *via* syringe and then the ^{1}H NMR spectrum was recorded (Figure 3.28 and 3.29).



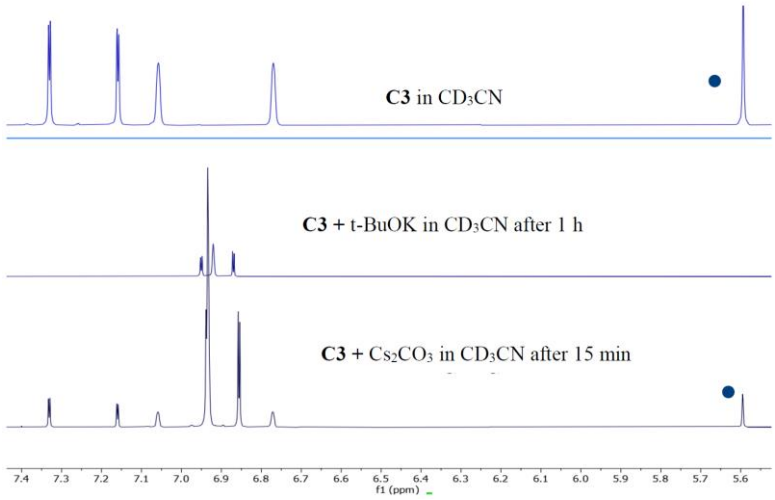


Figure 3.28. ^{1}H NMR analysis of catalyst **C1** before (*top*), after (*middle*) treatment with t-BuOK in 1 hour and after (*bottom*) treatment with Cs_2CO_3 in 15 min.

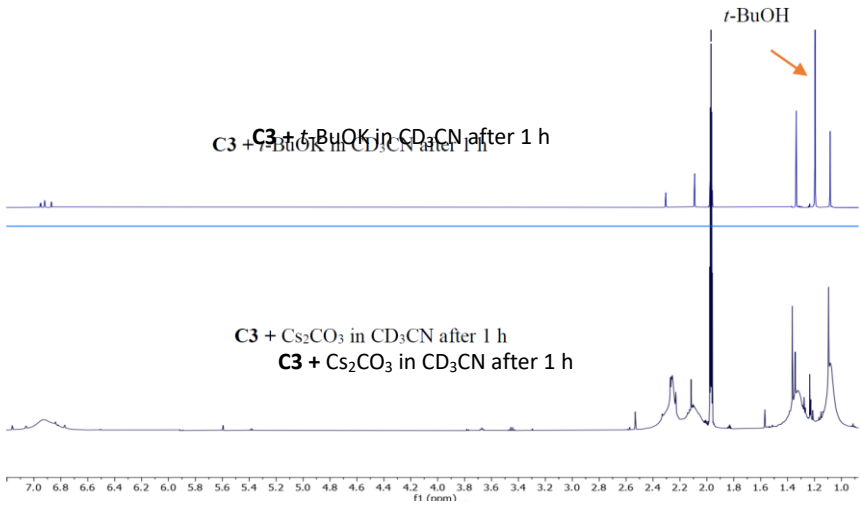


Figure 3.29. ^{1}H NMR analysis of catalyst **C1** after treatment with t-BuOK (*top*) and Cs_2CO_3 (*bottom*) in 1 hour.

Hydrodechlorination of Aryl Halides Catalyzed by C1 and C3

The reactivity of photocatalysts **C1** and **C3** in the hydrodechlorination of aryl halides were examined.[21] The results in Figure 3.30 demonstrated the necessity of Cs_2CO_3 to deprotonate **C1** and **C3**, providing the active photoreductants.

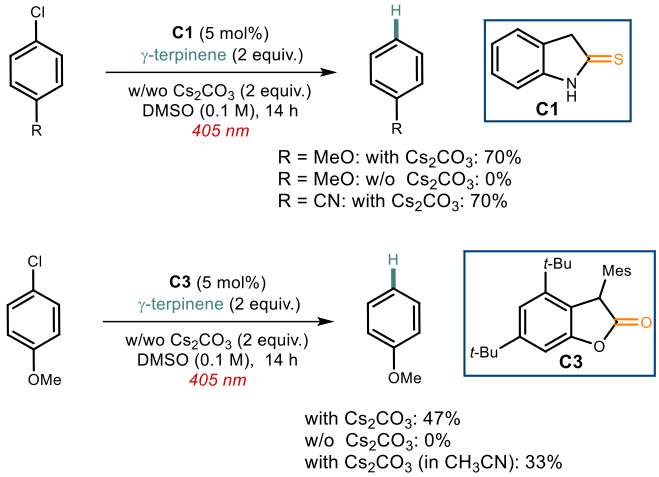


Figure 3.30. Effect of the base on the reactivity of catalysts **C1** and **C3** in the hydrodechlorination of aryl halides.

3.6.6 Photophysical Studies

The photophysical properties of C2 have been presented in our previous reports[21].

Sample Preparation:

- Neutral catalysts **C1** and **C3**

A 25 mL glass vial containing catalysts **C1** or **C3** (0.01 mmol) was sealed with a septum, vacuumed and backfilled with argon for 3 times, then degassed acetonitrile (5 mL, HPLC grade) was added via syringe to provide a 2 mM stock solution of catalyst. 20 μL of the stock solution were taken and diluted further with acetonitrile (4 mL) to obtain a 10 μM solution (200 μL were taken for a 0.1 mM solution). 2.5 mL of the solution was transferred into an argon filled quartz cuvette (10 x 10 mm light path) equipped with a septum.

- Deprotonated **C1** and **C3**

A 25 mL glass vial containing Cs_2CO_3 (130 mg) was sealed with a septum, vacuumed and backfilled with argon for 3 times, then degassed acetonitrile (8 mL, HPLC grade) was added via syringe. Addition of 40 μL of freshly prepared neutral **C1** or **C3** solution (2 mM) gave a 10 μM solution (400 μL were taken for a 0.1 mM solution). The vial was sealed with Parafilm and stirred at room temperature for 1 hour. 2.5 mL of the solution was transferred into an argon filled quartz cuvette (10 x 10 mm light path) equipped with a septum.

UV-visible Absorption Spectra

UV-Vis measurements were carried out on an Agilent Cary 60 UV-Vis spectrophotometer equipped with two silicon diode detectors, double beam optics and Xenon pulse light (Figure 3.31).

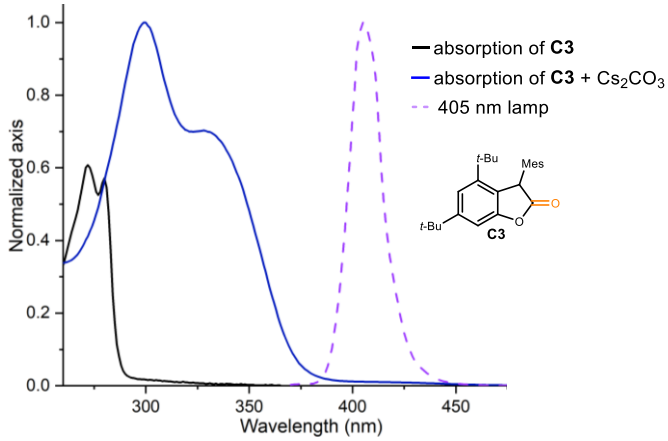


Figure 3.31. Normalized absorption spectra recorded for catalyst **C3** in CH_3CN, in absence (black line) or in presence (blue line) of Cs_2CO_3 in a 0.1 mM solution and 405 nm lamp spectrum (purple line).

Emission Spectra

Fluorescence measurements were carried out on an Fluorolog Horiba Jobin Yvon spectrofluorimeter equipped with a photomultiplier detector, a double monochromator, and a 450W xenon light source. The emission spectrum of the deprotonated **C1** and **C3** (formed in situ upon addition of Cs_2CO_3 in degassed CH_3CN) was recorded from 340 nm to 550 nm and 370 nm to 600 nm after excitation with 350 nm and 360 nm lasers respectively (Figure 3.32).

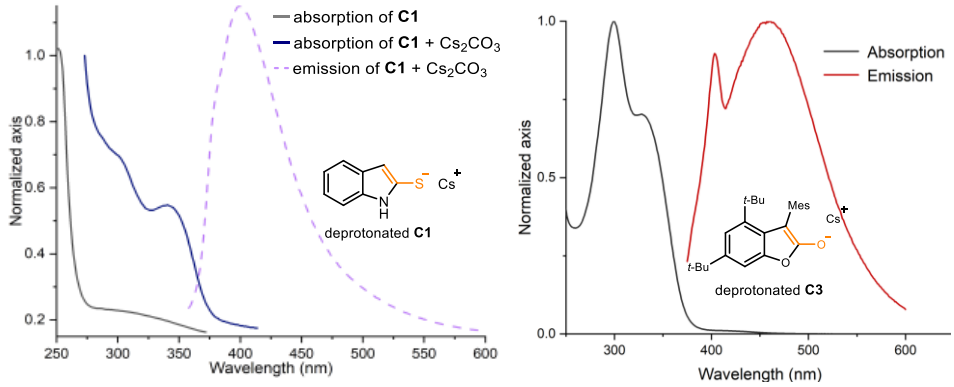


Figure 3.32. *left*) Normalized absorption of catalyst **C1**, absorption and emission spectra of the deprotonated **C1** (formed upon deprotonation with Cs_2CO_3) in CH_3CN in a 10 μM solution; *right*) Normalized absorption and emission spectra of the deprotonated catalyst **C3** (formed upon deprotonation with Cs_2CO_3 (3 equiv.)) in CH_3CN in a 0.1 mM solution.

Stern-Volmer Quenching Studies

Fluorescence measurements were carried out on an Fluorolog Horiba Jobin Yvon spectrofluorimeter equipped with a photomultiplier detector, a double monochromator, and a 450W xenon light source. A 1.0 M solution of the quencher substrate in degassed MeCN (HPLC grade) was prepared and 20 μL of this stock solution were added to the solution of the deprotonated catalyst. The addition of the substrate solution (the quencher) was repeated for four/five times. After each addition, the solution was mixed and the emission spectra of the excited catalyst was acquired from 365 nm to 500 nm (the excitation wavelength was fixed at 350 nm, slit width = 5 nm). A solvent blank was subtracted from all the measurements. The excitation wavelength was chosen in order to avoid saturation of the emission detector.

The results shown in Figure 3.33 indicates that 4-chlorobenzonitrile quenched the excited state emission of the deprotonated catalyst **C1**. The Stern-Volmer plot shows a linear correlation between the amounts of substrates and the ratio I_0/I, following the relationship: $I_0/I = 1 + K_{SV}[Q]$ (Q = Quencher).

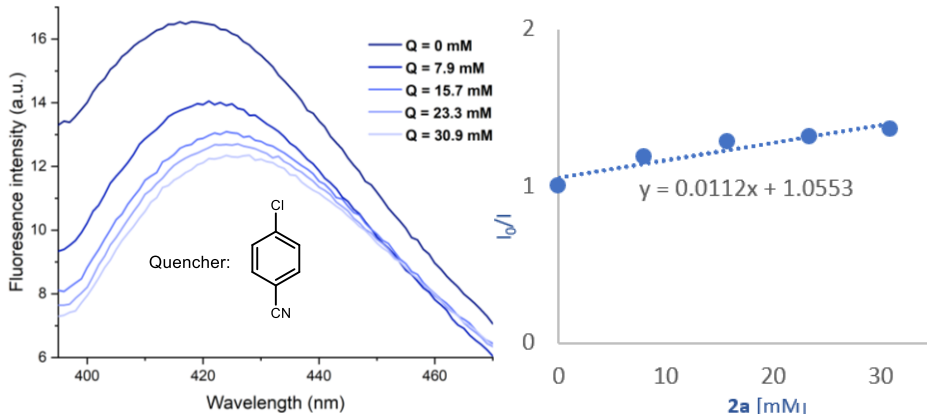


Figure 3.33. Stern-Volmer quenching studies with 4-chlorobenzonitrile (**1a**).

Quantum Yield Determination

-Experimental Setup

The experiments for the quantum yield determination were conducted under illumination by a 405 nm high-power single LED (setup depicted in Figure 3. 34), using an aluminum block on a 3D-printed holder, fitted with a 405 nm high-power single LED. The irradiance was fixed at 60±2 mW/cm^2, as controlled by an external power supply and measured using a photodiode light detector at the start of each reaction. This setup secured a reliable irradiation while keeping a distance of 1 cm between the reaction vessel and the light source.

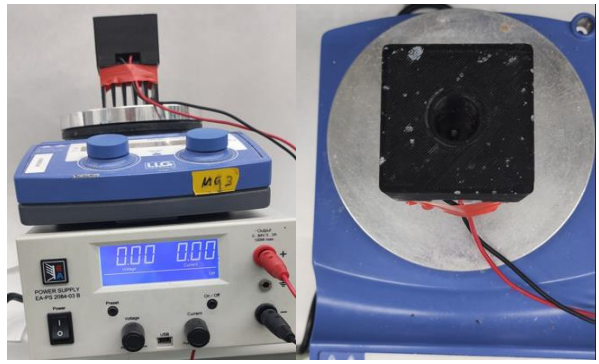


Figure 3.34. High-power single LED setup.

-General Procedure for photon Flux (F) determination[34]

$$\Phi = \frac{\mathrm{M}}{\mathrm{F} \times \mathrm{t}[1 - 10^{A(\lambda)}]} \cdots\cdots\cdots\cdots\cdots\cdots \boldsymbol{Eq.5}$$

M is the moles of product formed (mol), **F** is the number of photons emitted per second (einstein s^{-1}), **t** is the time (s) and **A(λ)** is the measured absorbance at 405 nm. The number of photons emitted per second was determined using azobenzene as actinometer. [35]

Using the reaction setup depicted in Figure 3.34, a glass vial was filled with a solution of *trans*-azobenzene (0.1 mmol) in CD_3OD (0.1M) and irradiated with a 405 nm light. The *trans-cis* isomerization was followed in time in ^{1}H-NMR using 1,3,5-trimethoxybenzene as internal standard.

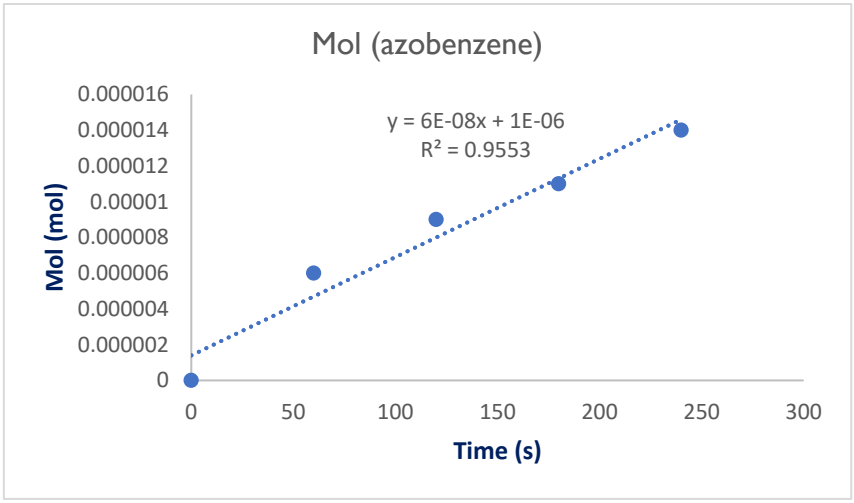


Figure 3.35. Plot of moles of *cis*-azobenzene formed vs irradiation time.

The actinometer solution was irradiated for 0 min, 1 min, 2 min, 3 min and 4 min. According to the eq. 1-2 and reported quantum yield of trans-cis isomerization process (Φ = 0.288) [35b],

[34] Cismesia, M. A.; Yoon, T. P. "Characterizing Chain Processes in Visible Light Photoredox Catalysis." *Chem. Sci.* **2015**, *6*, 5426–5434.

[35] (a) Leeuwen, T. v.; Buzzetti, L.; Perego, L. A.; Melchiorre, P. "A Redox-Active Nickel Complex that Acts as an Electron Mediator in Photochemical Giese Reactions." *Angew. Chem.,Int. Ed.* **2019**, *58*, 4953–4957. (b) Ladányi, V.; Dvořák, P.; Anshori, J. A.; Vetráková, Ľ.; Wirz, J.; Heger, D. "The Absorption Spectrum of Cis-azobenzene." *Photochem. Photobiol. Sci.* **2017**, *16*, 1749–1756.

the number of photons emitted per time unit (**F**) was determined (3.0×10^{-7} mol s^{-1}).

-*Quantum Yield Determination Using **C1** as Photocatalyst*

Following the general procedure A, five model thioetherification reactions between **1a** and **2a** were performed separately using catalyst **C1**. Each reaction mixture was irradiated for 0 min, 30 min, 60 min, 90 min and 120 min. After irradiation, the amount of product **3a** formed was determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as the internal standard. An absorbance of 0.216 was determined for the model reaction mixture (1:4 dilution). The moles of the formed product **3a** are plotted against the number of incident photons (Figure 3.36).

The quantum yield (Φ) was calculated to be Φ = 0.017 based on the slope and Eq. 5.

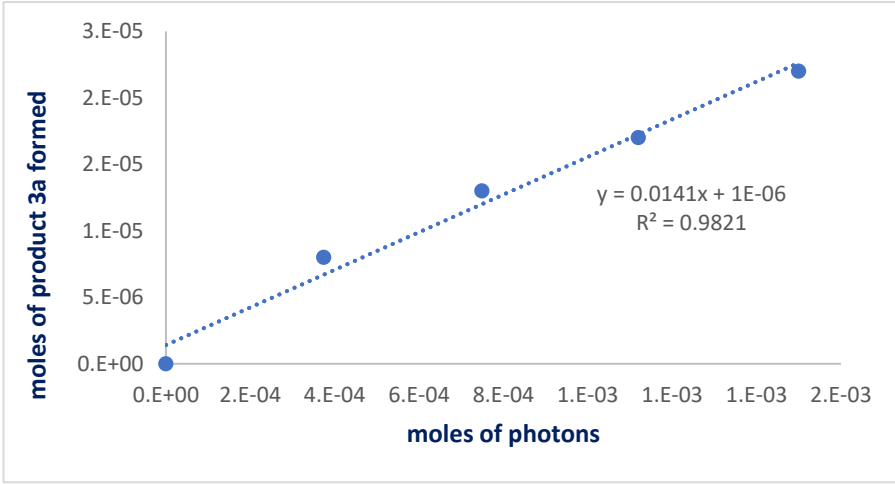


Figure 3.36. Plot of moles of incident photons vs moles of product **3a** formed.

-*Quantum Yield Determination Using **C3** as Photoreductant*

Following the general procedure B, five model thioetherification reactions between **1aw** and **2a** were performed separately under **C3** catalysis. Each reaction mixture was irradiated for 0 min, 30 min, 60 min, 90 min and 120 min. After irradiation, the amount of product **3aw** formed was determined by ^{1}H NMR measurement using 1,3,5-trimethoxybenzene as the internal standard. An absorbance of 0.084 was determined for the model reaction mixture

(1:4 dilution). The moles of the formed product are plotted against the number of incident photons (Figure 3.37).

The quantum yield (Φ) was calculated to be Φ = 0.052 based on the slope and Eq. 5.

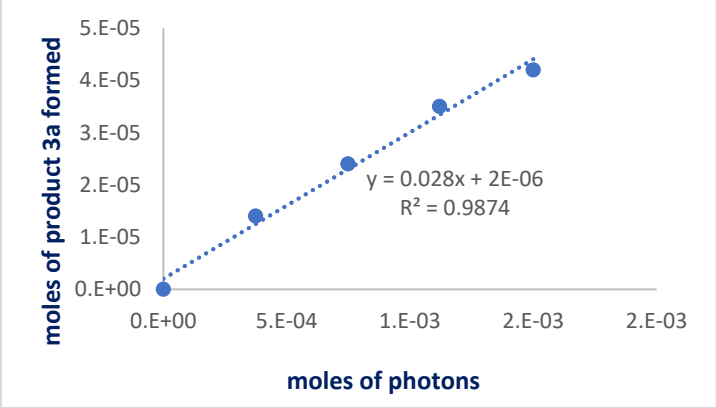


Figure 3.37. Plot of moles of incident photons vs moles of product **3aw** formed.

Light On-off Experiment

Experiments with successive intervals of irradiation and dark periods were performed following general procedure **A**, using alcohol **2a** as model substrate in the presence of aryl halide **1a**, photocatalyst **C1**, thiourea **A1** and Cs_2CO_3 ([**2a**] = 0.1 M in CH_3CN). Formation of product **3a** was determined by means of ^1H NMR analysis from aliquots taken under nitrogen atmosphere from the reaction mixture.

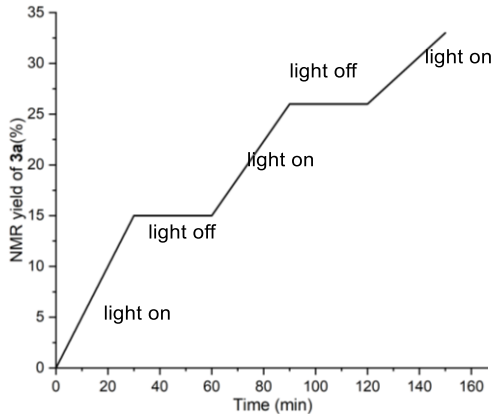


Figure 3.38. Light on-off experiment according to formation of **3a.**

3.6.7 Electrochemical Studies

Cyclic voltammetry (CV) measurements were carried out on a Princeton Applied Research PARSTAT 2273 instrument with a glassy carbon disk electrode (diameter: 3 mm) as working electrode. A silver wire coated with AgCl immersed in a 3.0 M aqueous solution of NaCl and separated from the analyte by a fritted glass disk was employed as the reference electrode and a Pt wire counter-electrode completed the electrochemical setup. The scan rate was 100 mV/s unless otherwise stated. The substrates were measured at concentration of 0.02 M in acetonitrile with NBu_4PF_6 (0.1 M) as electrolyte. The preparation of the deprotonated catalyst solutions was carried out as described in the photophysical studies section 3.6.6, at a concentration of 0.02 M.

Potentials are quoted with the following notation: E_p^C (E_{Red}) refers to the cathodic peak potential, E_p^A (E_{Ox}) refers to the anodic peak potential.

Cyclic Voltammetry Measurements of the Model Substrates

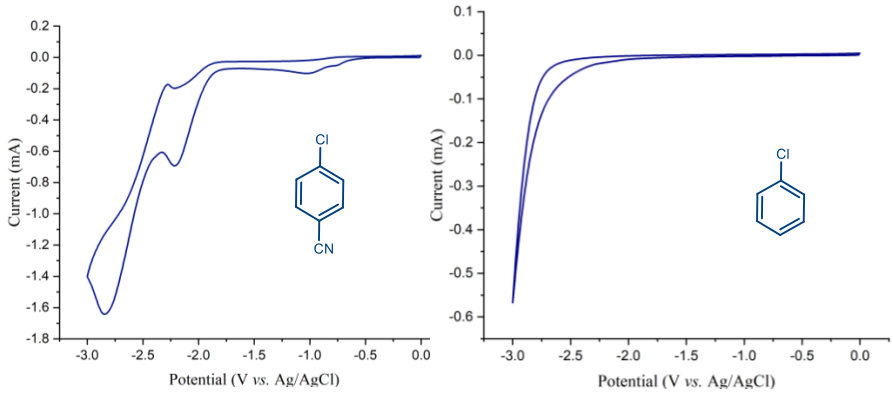


Figure 3.39. *left*) CV of 0.02M 4-chlorobenzonitrile **1a** in 0.1 M [NBu_4PF_6] in CH_3CN. irreversible reductions E_p = -2.2 V, E_p = -2.8 V. *right*) CV of 0.02M chlorobenzene **1aw** in 0.1 M [NBu_4PF_6] in CH_3CN. reduction was not observed in the registered potential window.

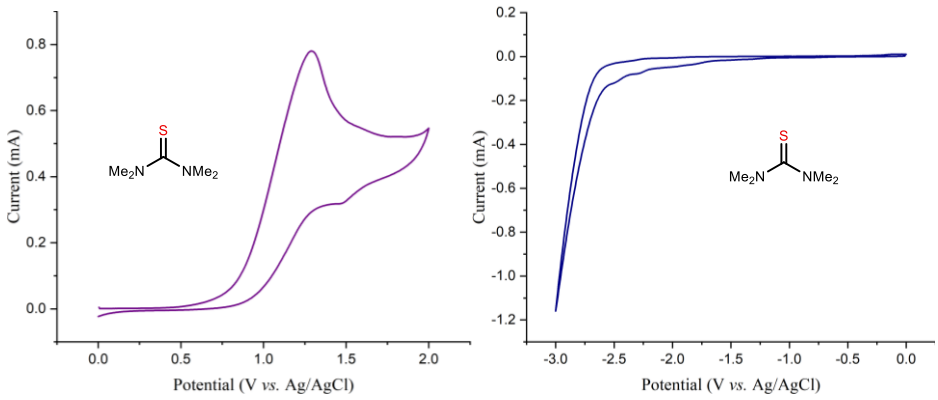


Figure 3.40. CV of 0.02M 1,1,3,3-tetramethylthiourea in 0.1 M [NBu_4PF_6] in CH_3CN, *left*) measurement between 0 to +3.0 V. irreversible oxidation, E_p = +1.29 V. *right*) Measurement between 0 to -3.0 V. reduction was not observed in the registered potential window.

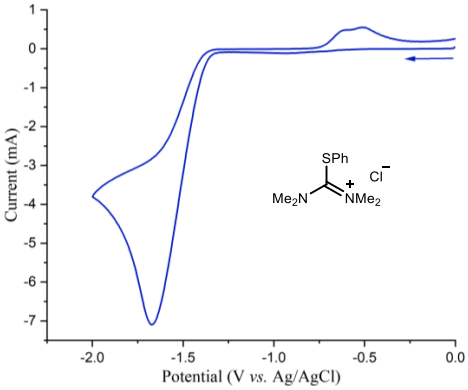


Figure 3.41. CV of 0.02M 1,1,3,3-tetramethyl-2-phenylisothiouronium chloride in 0.1 M [NBu_4PF_6] in CH_3CN., irreversible reduction E_p = -1.68 V.

Cyclic Voltammetry of Pre-catalysts and Catalytic Active Species

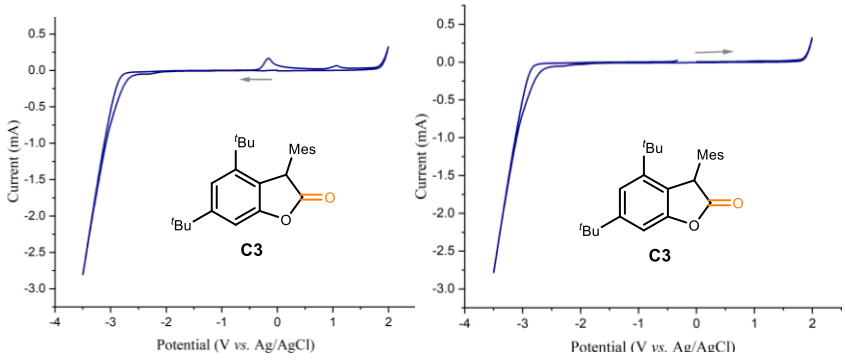


Figure 3.42. *left*) CV of 0.02M [**C1**] in 0.1 M [NBu_4PF_6] in CH_3CN, irreversible oxidation E_p^A = -0.16 V; *right*) CV of 0.02M [deprotonated **C1**] in 0.1 M [NBu_4PF_6] in CH_3CN, oxidation was not observed.

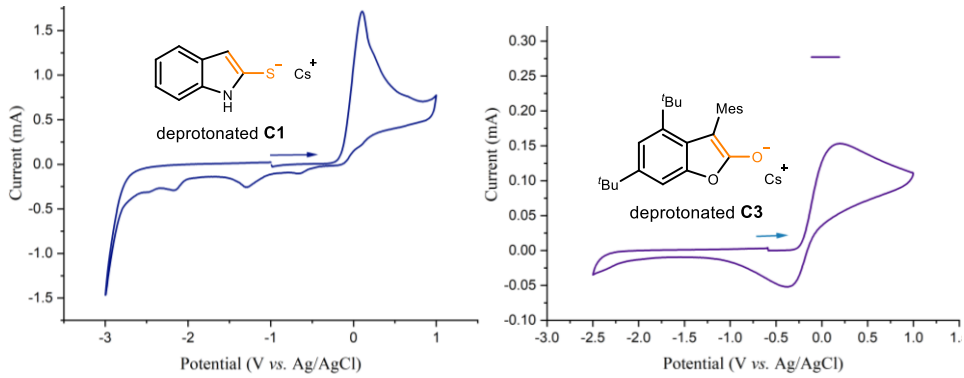


Figure 3.43. *left*) CV of 0.02M [deprotonated **C1**] in 0.1 M [NBu_4PF_6] in CH_3CN, irreversible oxidation E_p^A = +0.1 V *right*) CV of 0.02M [deprotonated **C3**] in 0.1 M [NBu_4PF_6] in CH_3CN, irreversible oxidation E_p^A = +0.17 V.

Conversion of the Potential from Ag/AgCl to SCE

The conversion of the redox potential from Ag/AgCl to SCE was done according to the literature by measuring the redox potential of ferrocene as reference in CH_3CN.[36]

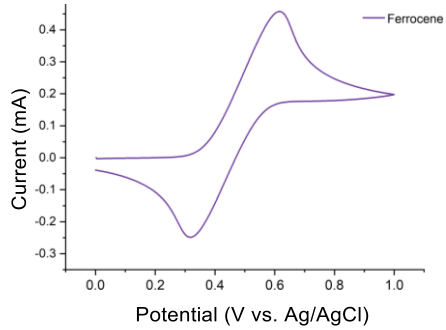


Figure 4.44. CV of ferrocene [0.02M] in [0.1 M] TBAPF6 in CH_3CN. Measurement started by oxidation from 0 V to +1.0 and finishing at -1 V. Platinum disk working electrode, Ag/AgCl (NaCl 3 M) referenceelectrode, Pt wire auxiliary electrode, one reversible reduction and oxidation $E_{1/2}$ = 0.46 V.

[36] Pavlishchuk, V. V.; Addison, A. W. "Conversion Constants for Redox Potentials Measured Versus Different Reference Electrodes in Acetonitrile Solutions at 25°C." *Inorganica Chim. Acta*. **2000**, 298, 97–102.

With the reference CV, the redox potential *vs.* SCE in CH_3CN was calculated using the following equations:

*For deprotonated **C1:***

$$E_p^A = -0.36 \text{ V } vs. \text{ Fc/Fc}^+; E_p^A = +0.02 \text{ V } vs. \text{ SCE}$$

*For deprotonated **C3:***

$$E_p^A = -0.29 \text{ V } vs. \text{ Fc/Fc}^+; E_p^A = +0.09 \text{ V } vs. \text{ SCE}$$

Evaluation of the Excited-State Potential of the Deprotonated Catalyst C1 and C3

Using the data collected from the CV studies (Figure 3.43) and from the absorption and emission spectra (Figure 3.18 and 3.32) of the deprotonated **C1** and **C3**, we could estimate the redox potential of the excited state with the following Equation[37]:

$$E(PC^{\bullet}/PC^{-*}) = E(PC^{\bullet}/PC^{-}) - E_{0-0}(PC^{-*}/PC^{-}) \cdots\cdots\cdots\cdots\cdots\cdots \boldsymbol{Eq.6}$$

Since the electrochemical oxidation of deprotonated **C1** and **C3** is irreversible (Figure 3.43), the irreversible peak potential E_p anode was used for $E(Pc^{\bullet}/Pc^{-})$. The oxidation potential was calculated to be +0.02 V *vs.* SCE (in MeCN) and +0.09 V *vs.* SCE (in MeCN) respectively. $E_{0\text{-}0}(PC^{-*})/(PC^{-})$ was approximately determined spectroscopically from the intersection of the normalized absorbance and emission spectra (roughly at 373 nm for deprotonated **C1** and 360 nm for deprotonated **C3**) to have values of 3.3 eV and 3.44 eV.

The oxidation potential of the excited deprotonated catalyst **C1**:

$$E(PC^{\bullet}/PC^{-*}) = 0.1 - 3.3 = \textbf{\textit{-3.2 V vs. Ag/AgCl}}$$

$$E(PC^{\bullet}/PC^{-*}) = 0.02 - 3.3 = \textbf{\textit{-3.28 V vs. SCE}}$$

The oxidation potential of excited deprotonated catalyst **C3**:

$$E(Pc^{\bullet}/Pc^{-*}) = 0.17 - 3.44 = \textbf{\textit{-3.27 V vs. Ag/AgCl}}$$

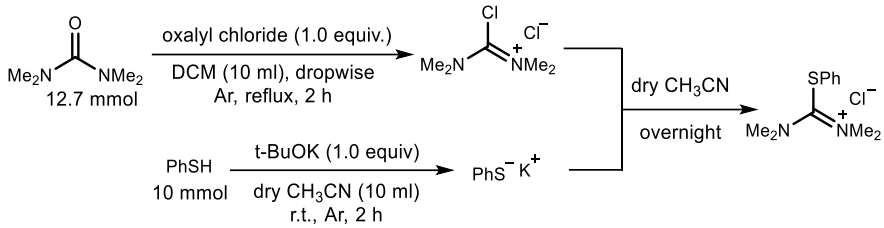
$$E(Pc^{\bullet}/Pc^{-*}) = 0.09 - 3.44 = \textbf{\textit{-3.35 V vs. SCE}}$$

[37] Buzzetti, L.; Crisenza, G. E. M.; Melchiorre, P. "Mechanistic Studies in Photocatalysis." *Angew. Chem., Int. Ed.* **2019**, *58*, 3730–3747.

3.6.8 Mechanistic Experiments for Probing Ionic Deoxythiolation

Reactions Between Prepared Aryl Isothiourea Salts and Alcohols

-Preparation of Aryl Isothiouronium salts[38]:

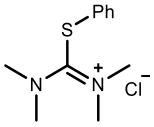


All manipulations were performed in anhydrous conditions under argon. Oxalyl chloride (1.1 mL, 1.0 equiv.) was added dropwise via syringe to a stirred solution of tetramethylurea (15.25 mL, 12.7 mmol) in DCM (10 mL). The reaction was refluxed for 2 hours, cooled to room temperature, and anhydrous ether (30 mL) was added. The tightly stoppered flask was refrigerated for 2 hours, then the precipitated intermediate was isolated by filtration under argon, and washed 3 times with anhydrous ether. In a separate flask, thiophenol (1.05 mL, 10 mmol) in dry acetonitrile (10 mL) was stirred vigorously and treated with potassium *tert*-butoxide (1.2 g). After 2 hours, the deprotonation reaction of thiophenol was evaporated to dryness in vacuo, and dried for a further 2 hours.

The filtered chloro-uronium salt without further drying, was mixed with newly obtained thiolate and washed in with 10 mL dry acetonitrile, and stirred vigorously. An exothermic reaction started immediately. The reaction was stirred overnight and resulting mixture was filtered (to remove precipitated KCl), and the residue washed 3 x with 5 mL dry acetonitrile. The filtrates were evaporated, anhydrous ether (~20 mL) added to the oily residue, and then refrigerated. After 2 hours, the crude product was isolated and washed with dry ether. The material was suspended in acetone (15 mL), sonicated and vortexed, which effectively extracted a yellow impurity from the product. The mixture was refrigerated, and the product isolated by filtration was washed with cold acetone and dried. The isothiourea salt was obtained as white solid in 82% yield (*which is sensitive to moisture, and therefore should be stored carefully under dry condition*).

[38] Biancalana, S.; Hudson, D.; Songster, M. F.; Thompson, S. A. "Fmoc Chemistry Compatible Thio-Ligation Assembly of Proteins." *Letters in Peptide Science*. **2001**, 7, 291–297.

1,1,3,3-tetramethyl-2-phenylisothiouronium chloride (III):



^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.49 – 7.42 (m, 2H), 7.42 – 7.32 (m, 3H), 3.30 (s, 12H) ppm.

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ= 174.1, 131.7, 130.6, 130.0, 127.8, 44.8 ppm.

Matching reported literature data.[37]

- *Thioetherification from preformed phenyl isothiouronium salt **III** and alcohol **2a***:

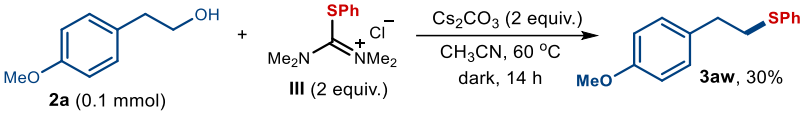
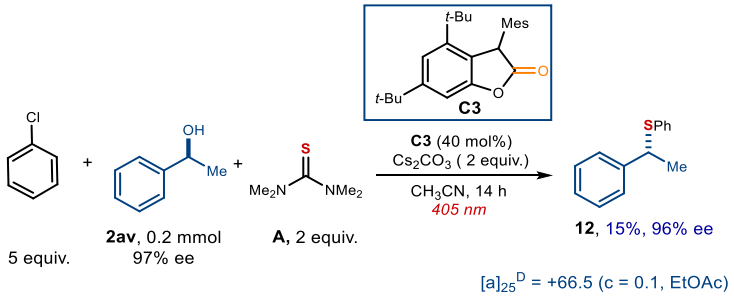


Figure 3.45. Thioetherification from pre-formed aryl Isothiouronium salts and alcohols

As shown above, primary alcohol **2a** can be converted into corresponding thioether **3aw** by reacting with isothiouronium salt **III** under dark conditions, while accompanying with 1,1,3,3-tetramethylurea as by-products.

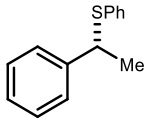
Stereospecific Displacement: Configuration Inversion

To verify the occurrence of *S_N2 substitution* process in the photochemical thioetherification, we subjected an enantioenriched alcohol to the standard condition and observed inversion of configuration (96% ee), which is consistent with an S_N2 polar manifold being operative. The optical rotation was in good agreement with the value reported in the literature.[39]



[39] Buzzetti, L.; Crisenza, G. E. M.; Melchiorre, P. "Mechanistic Studies in Photocatalysis." *Angew. Chem., Int. Ed.* **2019**, *58*, 3730–3747.

Figure 3.46. Stereospecific displacement of enantiopure alcohol **2av**.



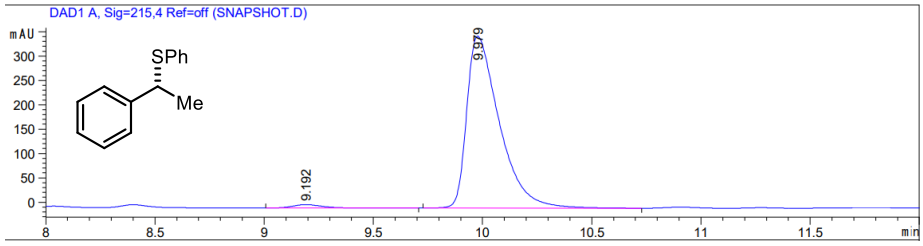
(*R*)-Phenyl(1-phenylethyl)sulfane (12): Synthesized according to the General Procedure using (*S*)-1-phenylethan-1-ol (*S*)-**5** (24.5 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea **A** (79.5 mg, 0.6 mmol, 3.0 equiv.) and chlorobenzene **6** (112.6 mg, 1.0 mmol, 5.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane: EtOAc = 300: 1 as eluent) to afford (*R*)-**12** (6.5 mg, 15% yield) as a yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ= 7.36 – 7.28 (m, 6H), 7.27 – 7.20 (m, 4H), 4.37 (qd, J = 7.0, 1.8 Hz, 1H), 1.66 (dd, J = 7.0, 1.8 Hz, 3H) ppm.

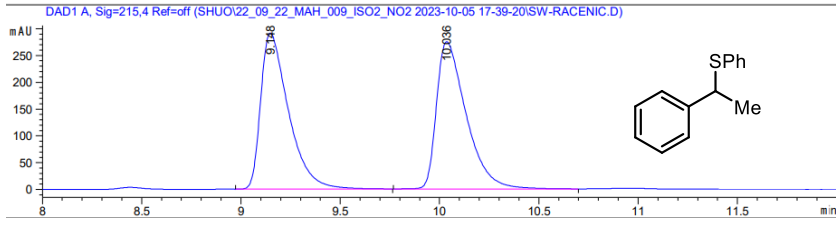
^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ= 143.3, 135.2, 132.5, 128.7, 128.4, 127.3, 127.2, 127.2, 48.0, 22.4 ppm. Matching reported literature data[Error! Bookmark not defined.].

The enantiomeric excess of the corresponding product was determined to be 96% by Agilient 1200 series HPLC, using Daicel Chiralpak IB-3 column (eluent: *n*-hexane; flow rate 1.0 mL/min; λ = 215 nm: t_R(major) = 9.98 min, t_R(minor) = 9.19 min)

$[\alpha]_D^{25}$ = +66.5 (c = 0.1, EtOAc), reported:[10] $[\alpha]_D^{26}$ = +41 (c = 1.1, EtOAc)



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.192	BB	0.1485	66.13474	6.85553	1.7704
2	9.979	BB	0.1562	3669.54980	353.21246	98.2296

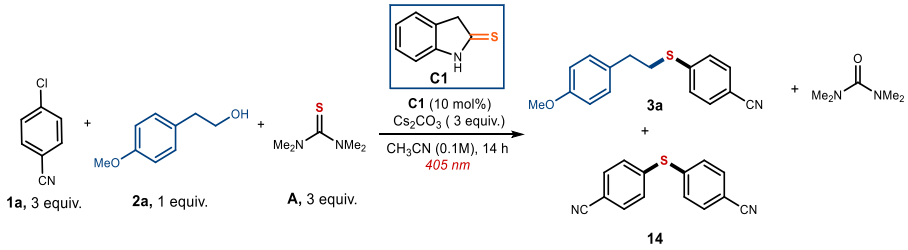


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.148	BB	0.1454	2829.27246	291.16721	49.8440
2	10.036	BB	0.1569	2846.97754	274.71118	50.1560

3.6.9 Detection and analyses of Side products

GC-MS Analyses of Reaction mixtures

Reaction between aryl chloride **1a** and alcohol **2a** was conducted according to general procedure **A**. After completion of reaction, the reaction mixture was diluted and injected into GC-MS. 1,1,3,3-tetramethylurea was confirmed as common co-byproduct of both conditions, as predicted side-product from deoxythiolation step. In addition, 4,4'-thiodibenzonitrile **14** can be detected as undesired product in the reaction using **C1** catalyst.



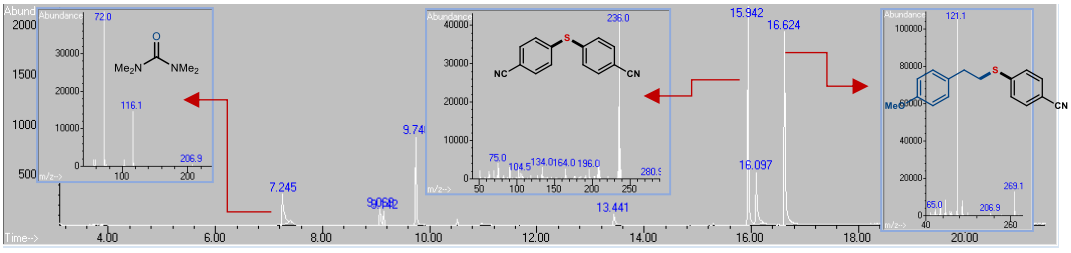


Figure 3.47. Assignment of species in reaction mixture by GC-MS analyses.

Reaction between chlorobenzene and alcohol **2a** was conducted according to general procedure **B**. After completion of reaction, the reaction mixture was diluted and injected into GC-MS. In addition to 1,1,4,4-tetramethylurea, diphenyl disulfide can be detected. Pertinently, a species with m/z= 440.3 can be detected, which can be assignable to **C3** modified by a phenyl group. Its formation can be justified by the coupling between phenyl radical and **C3** radical within the reaction mixture, accounting for its decomposition.

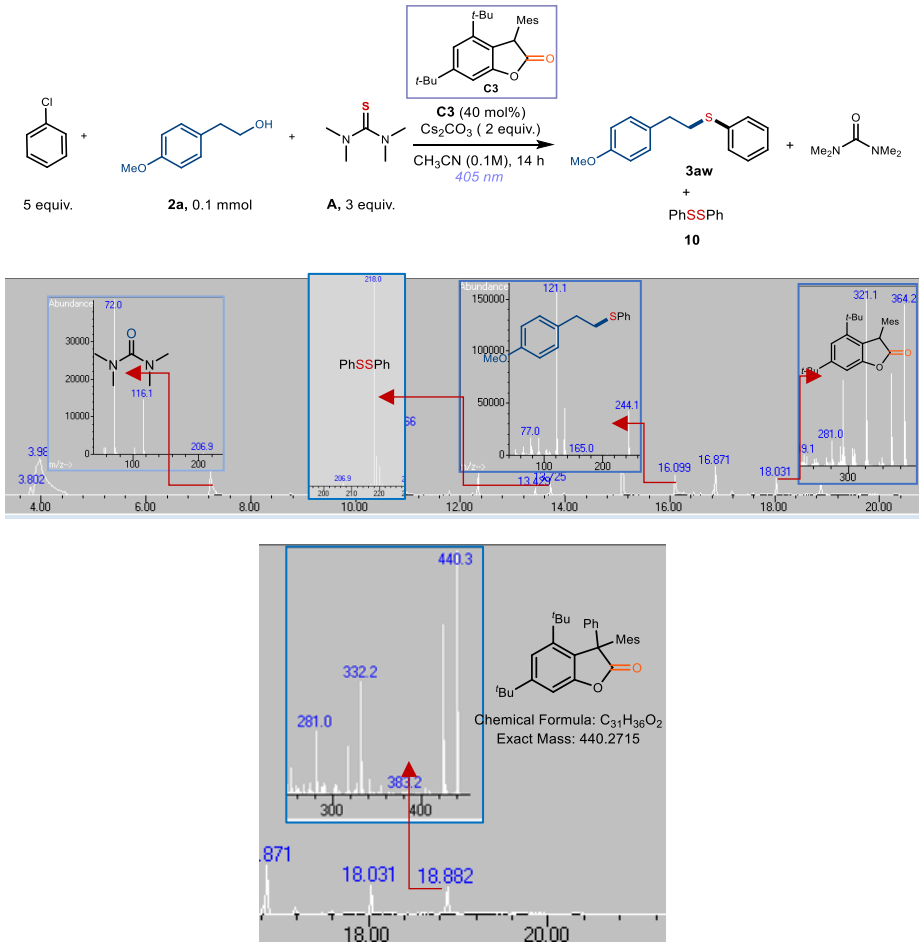


Figure 3.48 Assignment of species in reaction mixture by GC-MS analyses observation of coupling product in GC-MS.

To confirm the identity of the decomposition product, a stoichiometric reaction between **C3** and aryl chloride **1ay** (Figure 3.46)**:** To a 7 mL glass vial, **C3** (36.9 mg, 0.1 mmol, 1.0 equiv.), cesium carbonate (65.0 mg, 0.2 mmol, 2 equiv.) were added. The vial was sealed with a screw-top cap with septum and then vacuumed and backfilled with argon for 3 times. Afterwards, aryl chlorides **1ay** (0.2 mmol, 2 equiv.) followed by argon-sparged acetonitrile (0.1 M, 2.0 mL) were added *via* syringe. The vial was sealed with Parafilm and then stirred under 405 nm for 12 hours using ***Set-up 1***. After completion of the reaction, purification by preparative TLC afforded the predicted arylation product.

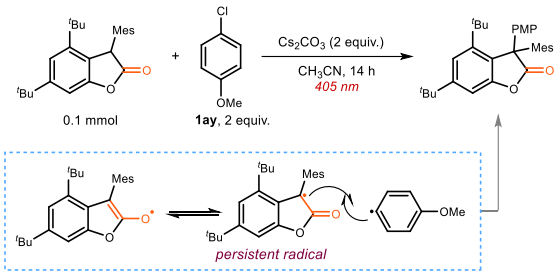
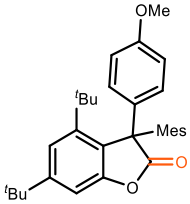


Figure 3.49. Stoichiometric reaction for characterization of decomposition product of **C3**.



4,6-di-tert-butyl-3-mesityl-3-(4-methoxyphenyl)benzofuran-2(3H)-one:

^{1}H NMR (500 MHz, $CDCl_3$): δ= 7.92 (dd, *J* = 9.0, 2.5 Hz, 1H), 7.37 (d, *J* = 2.0 Hz, 1H), 7.02 (d, *J* = 2.0 Hz, 1H), 6.87 (dd, *J* = 9.0, 2.6 Hz, 1H), 6.79 – 6.83 (m, 2H), 6.63 – 6.70 (m, 2H), 3.77 (s, 3H), 2.24 (s, 3H), 1.84 (s, 3H), 1.72 (s, 3H), 1.35 (s, 9H), 1.03 (s, 9H) ppm.

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ =178.7, 159.6, 153.7, 152.4, 149.2, 139.4, 138.3, 137.0, 134.1, 133.2, 131.7, 130.5, 130.4, 120.4, 114.0, 112.4, 107.3, 64.3, 55.2, 36.6, 35.1, 31.7, 31.3, 25.3, 21.6, 20.6 ppm.

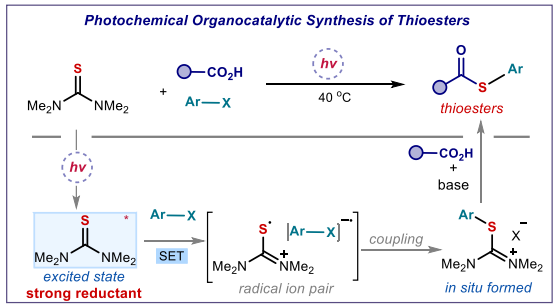
HRMS (ESI): calculated for $C_{32}H_{38}NaO_3$ [M+Na^+]: 493.2713, found 493.2718

Chapter IV

Photochemical Synthesis of Thioesters from Aryl Halides and Carboxylic Acids

Target

To develop a thiol-free protocol for the synthesis of thioesters by stitching together widespread carboxylic acids and aryl halides under mild photochemical conditions.



Tool

Using 1,1,3,3-tetramethylthiourea not only as a sulfur source but also as a strong reductant for activating aryl halides upon photoexcitation. This approach leads to the formation of the desired thioesters through our previously developed radical trap/deoxythiolation sequence.[1]

4.1 Introduction

The importance of thioesters extends beyond applications in synthetic chemistry to encompass fields such as materials and biology.[2] Thioesters are also typical motifs in various natural products.[3] Therefore, there is a need to develop efficient methods for their

[1] I conducted the research activities in the laboratory independently and contributed to the conception of the project design, explored the substrate scope of the reaction, and conducted mechanistic investigations. This study has been published: Wu, S.; Melchiorre, P. "Photochemical Synthesis of Thioesters from Aryl Halides and Carboxylic Acids". *Angew. Chem. Int. Ed.* **2024**, *62*, e202306364.

[2] (a) Agouridas, V.; Mahdi, O. E.; Diemer, V.; Cargoet, M.; Monbaliu, J. C. M.; Melnyk, O. "Native Chemical Ligation and Extended Methods: Mechanisms, Catalysis, Scope, and Limitations." *Chem. Rev.* **2019**, *119*, 7328−7443; (b) Bannin, T. J.; Kiesewetter, M. K. "Poly(thioester) by Organocatalytic Ring-Opening Polymerization." *Macromolecules* **2015**, *48*, 5481−5486; (c) Chandru, K.; Gilbert, A.; Butch, C.; Aono, M.; Cleaves, H. J. "The Abiotic Chemistry of Thiolated Acetate Derivatives and the Origin of Life." *Sci. Rep*. **2016**, *6*, 29883.

[3] (a) Barce Ferro, C. T.; dos Santos, B. F.; da Silva, C. D. G.; Brand, G.; da Silva, B. A. L.; Campos Domingues, N. L. de. "Review of the Syntheses and Activities of Some Sulfur-Containing Drugs."

preparation from readily available substrates and under mild conditions. As a classic method for their synthesis, the thioesterification of carboxylic acids with thiophenols provides a direct route to *S*-aryl thiocarboxylates,[4] but the required harsh dehydrating reagents restrict the versatility of this procedure. Thermal substitution of thiophenols with pre-activated acylating compounds (e.g., acyl chlorides and carboxylic anhydrides)[5] also offers a method for thioester **3** preparation (Figure 4.1a), but these acylating compounds are moisture sensitive and have limited availability. In addition, all these methods rely on using thiols, which are characterized by undesirable traits like unpleasant odor, limited commercial variety, and air instability.

Transition-metal catalyzed carbonylative coupling reactions with aryl halides have also been used to achieve *S*-aryl thiocarboxylates **3**,[6] where C(sp^2)-X (where X is commonly I, Br etc.) bond can be activated through oxidative addition by the metal. The ensuing metal-aryl complex can then react with thiolates to undergo carbonylative coupling reactions (Figure 4.1b). This method, while efficient, still involves the use of thiols while requiring elevated temperatures and specific ligands to overcome the high coordinating ability of thiols to transition metals.[7]

Curr. Org. Synth. **2020**, *17*, 192−210; (b) Wang, N.; Saidhareddy, P.; Jiang, X. "Construction of Sulfur-Containing Moieties in the Total Synthesis of Natural Products." *Nat. Prod. Rep.* **2020**, *37*, 246−275.

[4] Iimura, S.; Manabe, K.; Kobayashi, S. "Direct Thioesterification from Carboxylic Acids and Thiols Catalyzed by A Brønsted Acid." *Chem. Commun*. **2002**, 94−95.

[5] (a) For selected examples, see: (a) Santi, C.; Battistelli, B.; Testaferri, L.; Tiecco, M. "On Water Preparation of Phenylselenoesters." *Green Chem.* **2012**, *14*, 1277−1280; (b) Kazemi, M.; Shiri, L. "Thioesters Synthesis: Recent Adventures in the Esterification of Thiols." *J. Sulfur Chem.* **2015**, *36*, 613−623. and references therein.

[6] For selected examples, see: (a) Ogawa, A.; Kawakami, J.; Mihara, M.; Ikeda, T.; Sonoda, N.; Hirao, T. "Highly Regioselective Hydrothiocarboxylation of Acetylenes with Carbon Monoxide and Thiols Catalyzed by $Pt(PPh_3)_4$." *J. Am. Chem. Soc*. **1997**, *119*, 12380−12381; (b) Yi, C.-L.; Huang, Y.-T.; Lee, C.-F. "Synthesis of Thioesters Through Copper-Catalyzed Coupling of Aldehydes with Thiols in Water." *Green Chem.* **2013**, 15, 2476−2484; (c) Hirschbeck, V.; Gehrtz, P.H.; Fleischer, I. "Metal-Catalyzed Synthesis and Use of Thioesters: Recent Developments." *Chem. Eur. J.* **2018**, *24*, 7092–7107; (d) Luo, J.; Rauch, M.; Avram, L.; Diskin-Posner, Y.; Shmul, G.; Ben-David, Y.; Milstein, D. "Formation of Thioesters by Dehydrogenative Coupling of Thiols and Alcohols with H_2 Evolution." *Nat. Catal.* **2020**, *3*, 887−892.

[7] Crabtree, R. H. *The Organometallic Chemistry of the Transition Metals*; John Wiley & Sons, Inc.: Hoboken, NJ, 2014.

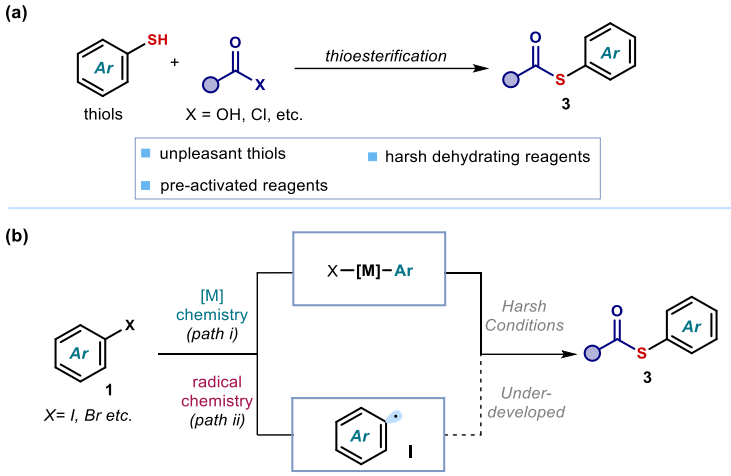


Figure 4.1. Strategy for thioesters synthesis. (**a**) Traditional methods for synthesizing thioesters relying on thiols; **(b)** Methods based on transition-metal catalysis and photoredox catalysis.

In view of the existing shortcomings associated with thioester synthesis, the development of a general and efficient method that does not involve odorous thiols would be valuable. As detailed in the previous chapter, we introduced a photochemical organocatalytic platform for synthesizing thioethers [8] by coupling widely available aryl chlorides and alcohols under mild conditions. A crucial step in this reaction is the use of odorless and stable 1,1,3,3-tetramethylthiourea **A**, which serves both as a sulfur source and a radical trap for the aryl radicals **I** generated from aryl chlorides. This radical trap forms isothiouronium salt **I** (Figure 4.2). Given the electrophilic nature of these intermediates, we hypothesized that the nucleophilic addition of carboxylic acids **2** would yield intermediate **II**, which equilibrates with isothiouronium salt **III** upon extrusion of thiolate **IV** (*path A*, lower panel of Figure 4.2). The transient thiolate **IV** would eventually reattack intermediate **III**, following a deoxythiolation polar pathway to form the desired thioesters **3**. Importantly, and in contrast to our previous study,[8] we discovered that tetramethylthiourea **A** is not only a sulfur source and aryl radical trap but can also be directly excited by absorbing purple light (405 nm) to acquire strong reducing power, which is useful for activating aryl halides via single-electron transfer (SET), thereby generating aryl radicals.

[8]Wu, S.; Wong, T. H.-F.; Righi, P.; Melchiorre, P. "Photochemical Organocatalytic Synthesis of Thioethers from Aryl Chlorides and Alcohols". *J. Am. Chem. Soc.* **2024**, *146*, 2907–2912.

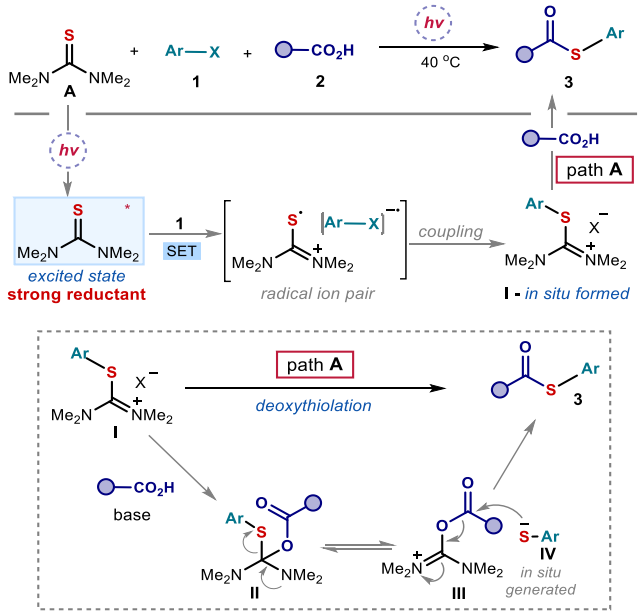


Figure 4.2. Proposed strategy for developing a thiol-free synthesis of thioesters, enabled by combining radical and polar reactivity in a single sequence. A polar deoxythiolation pathway (path A in the lower panel) involving carboxylic acids **2** then leads to thioesters **3**. SET: single-electron transfer.

The following section details methodologies for synthesizing thioesters using transition-metal-catalyzed activation of aryl halides. Additionally, previous studies that employed radical strategies or photoredox catalysis to prepare thioesters, which are relevant to the background of the present project, will also be discussed.

4.2 Background

4.2.1 Transition-Metal Catalyzed Methods for the Synthesis of Thioesters

Transition-metal catalyzed C(sp^2)-S cross coupling reaction is a traditional approach for the synthesis of *S*-aryl thiocarboxylates. In 1983, Osuka and Suzuki established coupling of aryl iodides with copper thiobenzoate **4**, pre-formed from thiols, offering a useful method for

thioester preparation (Figure 4.3a).[9] This reaction was improved later by Sawada,[10] using 10 mol% of CuI and thiobenzoic acid **5** as catalyst and coupling partner, respectively (Figure 4.3b). The improved condition is applicable to both electron-deficient and electron-rich aryl iodides, including sterically hindered substrates.

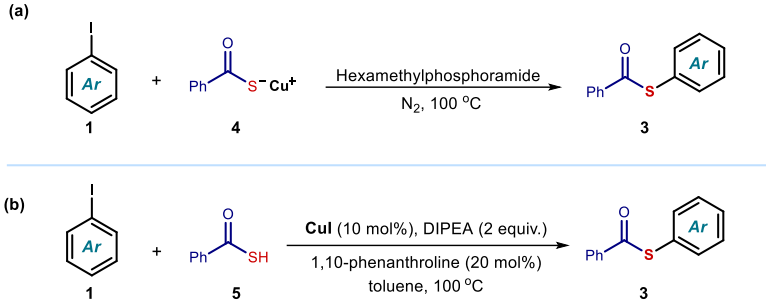


Figure 4.3. Cross-coupling reactions for thioester synthesis. (**a**) The direct coupling of aryl iodides with copper thiobenzoate; (**b**) Copper-catalyzed coupling of aryl iodides with thiobenzoate.

Carbonylation reaction catalyzed by transition metals is also a prevalent strategy for the thioester preparation. In this chemistry, the oxidative addition of aryl iodides with metals or the insertion of alkene to active transition metals, followed by CO insertion, produces an acyl palladium intermediate **V**, which is susceptible to the nucleophilic attack by thiols to yield thioesters via reductive elimination. In this approach, the S-aryl thiocarboxylate **3** is synthesized using pre-installed C_{aryl}-S bond in thiophenols. The first Pd-catalyzed thiocarbonylation of aryl iodides was published by Alper in 2008.[11] This catalytic system, consisting of 5 mol% $Pd(OAc)_2$ and PPh_3 as ligand, delivered aryl iodides **1**. Both thiophenols and aliphatic thiols **6** were suitable substrates leading to the corresponding thioesters (Figure 4.4a). Lei[12] also reported a similar palladium catalyzed thiocarbonylation of aryl iodides with sodium thiolates in a thiol/THF solvent mixture. Mechanistically, they proposed a

[9]Osuka, A.; Ohmasa, N.; Uno,Y.; Suzuki, H. "A Convenient Synthesis of S-Aryl Thiobenzoates from Copper(I) Thiobenzoate and Aryl Iodides." *Synthesis* **1983**, 68–69.

[10] Sawada,N.; Itoh, T.; Yasuda, N. "Efficient Copper-Catalyzed Coupling of Aryl Iodides and Thiobenzoic Acid." *Tetrahedron Lett.* **2006**, *47*, 6595– 6597.

[11]Cao, H.; McNamee, L.; Alper, H. "Palladium-Catalyzed Thiocarbonylation of Iodoarenes with Thiols in Phosphonium Salt Ionic Liquids." *J. Org. Chem.* **2008**, *73*, 3530 – 3534

[12]Hu,Y.; Liu, J.; Lu, Z.; Luo, X.; Zhang, H.; Lan, Y.; Lei, A. "Base-Induced Mechanistic Variation in Palladium-Catalyzed Carbonylation of Aryl Iodides." *J. Am. Chem. Soc.* **2010**, *132*, 3153 – 3158.

distinct catalytic cycle from the conventional path II, which consisted of oxidative addition, subsequent ArPdSR (**VIII**) formation, CO insertion to form ArCOPd-SR (**VII**), and final reductive elimination to give produce **3** (Path I).

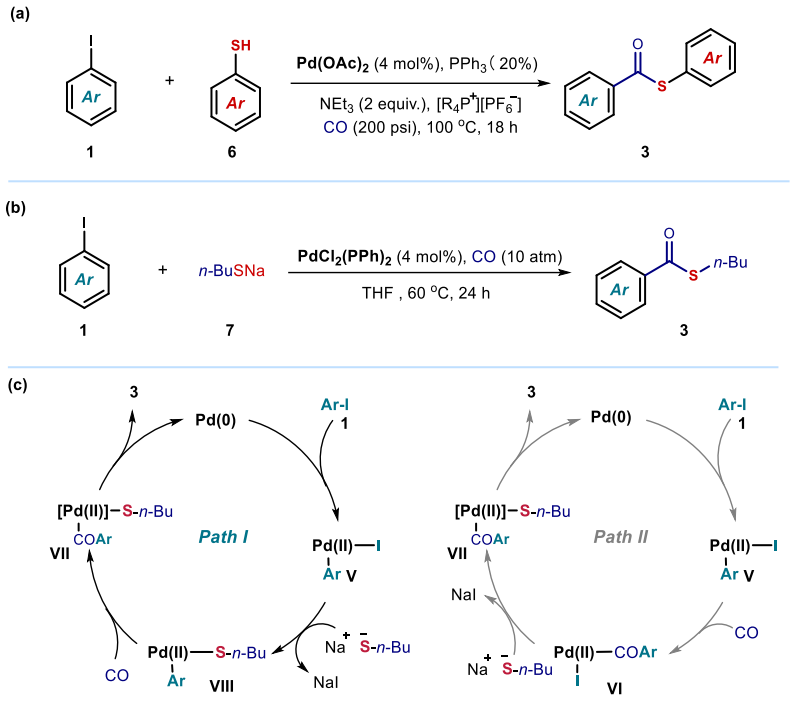


Figure 4.4. Transition-metal catalyzed thiocarbonylation of aryl iodides for thioesters synthesis. **(a)** First thiocarbonylation of aryl iodides reported by Alper; (**b**) Palladium catalyzed thiocarbonylation of aryl iodides with sodium thiolates; (**c**) Proposed catalytic cycle.

In addition to metal-catalyzed coupling reaction, catalytic hydrothiocarbonylation of alkenes, utilizing carbon monoxide (CO) and organic thiols, also offers the opportunity to access thioesters. In 2016, the first Pd-catalyzed thiocarbonylation of vinyl arenes with CO gas and free thiols towards branched thioesters synthesis was disclosed by Fleische (Figure 4.5).[13] This process involves the oxidative addition of palladium catalyst with thiophenols, resulting in organometallic complex **IX**, which subsequently engages in alkene and CO insertion. Product **3** is obtained through reductive elimination of intermediate **XI**. While aliphatic thiols

[13]Hirschbeck,V.; Gehrtz, P. H.; Fleischer, I. "Regioselective Thiocarbonylation of Vinyl Arenes." *J. Am. Chem. Soc*. **2016**, *138*, 16794–16799.

exhibited high efficiency and regioselectivity towards the formation of branched thioesters, aromatic thiophenols performed moderately with low regioselectivity.

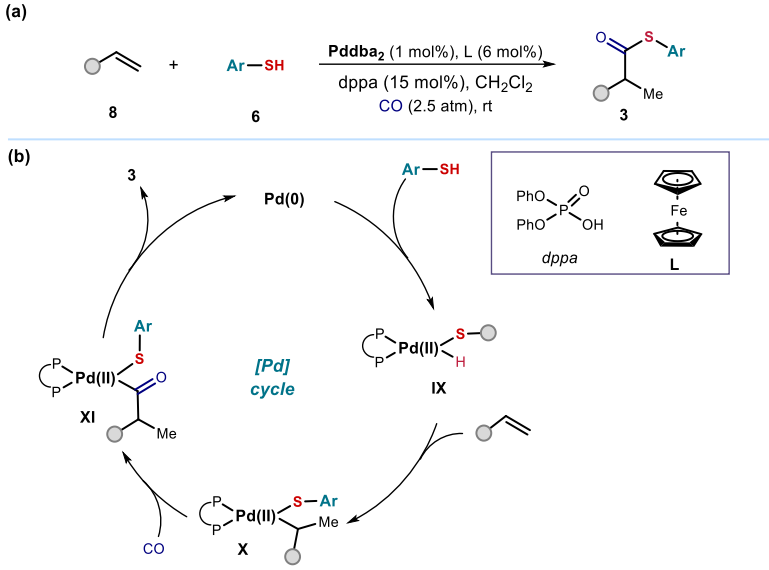


Figure 4.5. (a) Palladium catalyzed thiocarbonylation of olefins to prepare thioesters. (**b**) Proposed catalytic cycle.

The preceding methods are effective for synthesizing thioesters but require toxic CO gas or thiols. Therefore, methods that use CO surrogates and stable, user-friendly thiol progenitors have been developed.[14] *S*-aryl thiocarbonyl compounds containing C(sp^2)-S bonds and carbonyl motifs were developed for releasing CO and thiolates. For instance, easily accessible and storable reagents, such as *S*-aryl thioformate **9** [15] and oxalic acid monothioester **10**, [16] can undergo oxidative addition with palladium(0) yielding acyl palladium(II) complex **XII** and **XIV**, followed by decarbonylation to generate (CO)Pd(0) species **XIII** and thiolates. Then, thioesters can be obtained upon reaction of aryl iodides with **XIII** (Figure 4.6a-b).

[14]Pal, A.; Mondal, P. P.; Niloofar, F. Sahoo, B. "Synthetic Strategies for Versatile Thioester Building Blocks." *Eur. J. Org. Chem*. **2022**, e202201159.

[15]Yang, R.; Xie, Q.; Yan, Q.; Zhang, X.; Gao, B. "Palladium-Catalyzed Thiocarbonylation of Aryl Iodides with S-Aryl Thioformates via Thioester Transfer." *Org. Lett*. **2022**, *24*, 7555–7559.

[16]Zhao, B.; Fu, Y.; Shang, R. "Oxalic Acid Monothioester for Palladium-Catalyzed Decarboxylative Thiocarbonylation and Hydrothiocarbonylation." *Org. Lett*. **2019**, *21*, 9521–9526.

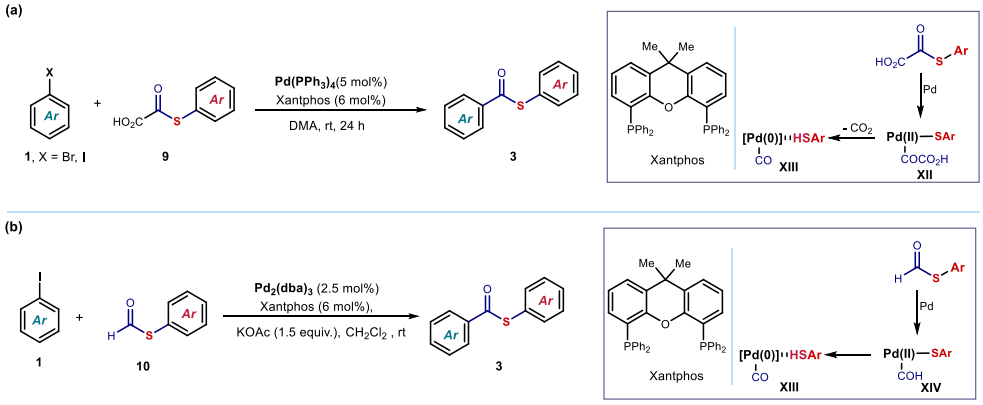


Figure 4.6. Transition-metal-catalyzed synthesis of thioesters using surrogates of toxic CO and thiols. (**a**) Palladium catalyzed synthesis of thioesters from aryl iodides and S-aryl thioformate; (**b**) Palladium-catalyzed synthesis of thioesters from aryl iodides and oxalic acid monothioester.

Aldehydes also served as CO surrogates for cross coupling reactions with organometallic thiolate complex **XVI** to access thioesters (Figure 4.7a). Acyl radical **XV**, generated from aldehyde, reacted with copper-thiolate in aqueous solution, generating the *S*-aryl thiocarboxylates **3**.[17] Alkyl alcohol-mediated dehydrogenative coupling was also applied for the preparation of thioesters and evolution of H_2 (Figure 4.7b). In this reaction, an acridine-based ruthenium pincer complex **XVII** promoted the dehydrogenation of alkyl alcohols, with in situ release of aldehydes. Here, the thiol not only serves as a reactant, but also as an assisting ligand for the metal.[18] This reaction was carried out using hexamethyldisiloxane (HMDSO) as solvent, yielding various thioesters using equivalent amounts of alcohols and thiols, with hydrogen gas as the only by-product.

[17] (a)Yi, C.-L.; Huang, Y.-T.; Lee, C.-F. "Synthesis of Thioesters through Copper-Catalyzed Coupling of Aldehydes with Thiols in Water." *Green Chem.* **2013**, *15*, 2476−2484; (b) Huang, Y.-T.; Lu, S.-Y.; Yi, C.-L.; Lee, C.-F. "Iron-Catalyzed Synthesis of Thioesters from Thiols and Aldehydes in Water." *J. Org. Chem.* **2014**, *79*, 4561−4568.

[18] Luo, J.; Rauch, M.; Avram, L.; Diskin-Posner, Y.; Shmul, G.; Ben-David, Y.; Milstein, D. "Formation of Thioesters by Dehydrogenative Coupling of Thiols and Alcohols with H_2 Evolution." *Nat. Catal.* **2020**, *3*, 887−892.

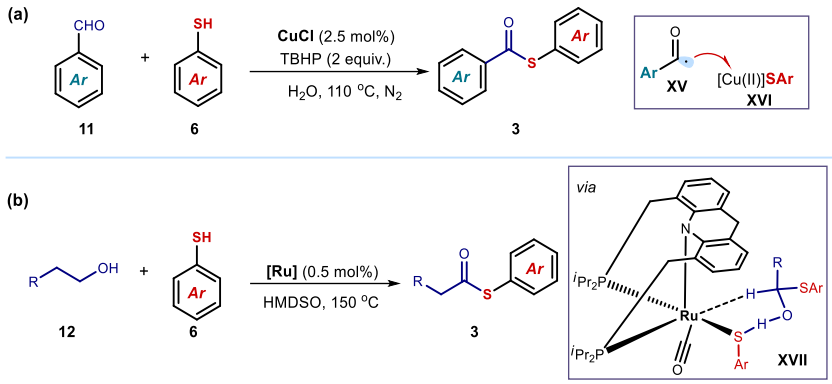


Figure 4.7. Transition-metal catalyzed coupling of aldehydes with thiophenols to prepare thioesters. **(a)** Copper-catalyzed coupling of aldehydes with thiols in water; (**b**) Dehydrogenative formation of thioesters from alcohols or aldehydes and thiols.

Overall, transition metal catalysis offered effective methods for thioester preparation. The utilization of sulfur surrogates can obviate the use of unpleasant thiols or toxic CO to some extent, but these surrogates are of limited access, and most of them are still pre-formed from thiols.

4.2.2 Photochemical Methods for the Synthesis of Thioesters

As a useful alternative, photocatalyzed radical reactions provide an efficient means to construct thioesters under mild condition, bypassing some of the problems associated with transition metal catalysis. Photocatalyzed thiol-ene click reaction is one of such protocols,[19] where thioacids are appropriate sulfur sources to generate carbonyl thiyl radical species **XVIII** via SET oxidation by excited photocatalysts, followed by thiyl radical addition to alkenes and hydrogen atom transfer (HAT) to form the desired thioesters (Figure 4.8a).

[19](a) Tyson, E. L.; Ament, M. S.; Yoon, T. P. "Transition Metal Photoredox Catalysis of Radical Thiol-Ene Reactions." *J. Org. Chem.* **2013**, 78, 2046−2050; (b) Levin, V. V.; Dilman, A. D. "Visible-Light-Mediated Organocatalyzed Thiolene Reaction Initiated by a Proton-Coupled Electron Transfer." *J. Org. Chem.* **2019**, *84*, 8337−8343.

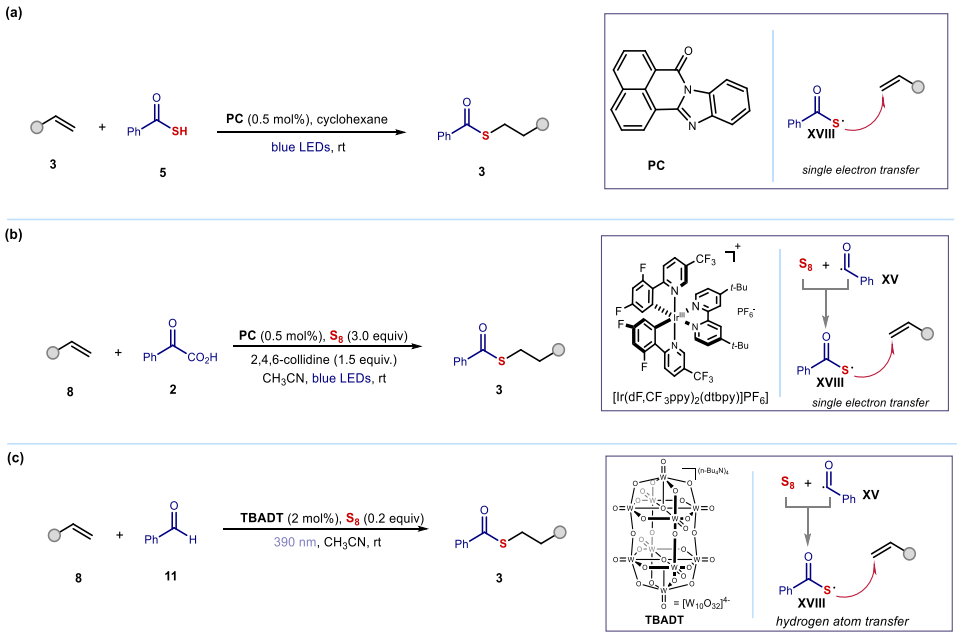


Figure 4.8. Photocatalyzed thiol-ene click type reaction for thioesters preparation. **(a)** Photocatalyzed thiol-ene click type reaction using thioacids as radical precursor; (**b**) Photocatalytic activation of elemental sulfur enables a chemoselective three-component thioesterification; **(c)** Photocatalyzed synthesis of thioesters from feedstock chemicals and elemental sulfur.

The identification of mild new strategies that do not rely on thiols are highly valuable. There are methods for the thiol-ene click type reaction based on the use of elemental sulfur S_8 as sulfur source to prepare thioesters.[20] Elemental sulfur S_8 was found to serve as radical trap, intercepting the acyl radicals to release carbonyl thiyl radicals **XVIII**, and then thiol-ene click type reaction would proceed following the traditional route. For the radical generation, α-ketoacids and aldehydes have been reported as progenitors undergoing SET or HAT to yield acyl radicals (Figure 4.8b-c).

[20](a) Murakami, S.; Nanjo, T.; Takemoto, Y. "Photocatalytic Activation of Elemental Sulfur Enables a Chemoselective ThreeComponent Thioesterification." *Org. Lett.* **2021**, 23, 7650−7655; (b) Tang, H.; Zhang, M.; Zhang, Y.; Luo, P.; Ravelli, D.; Wu, J. "Direct Synthesis of Thioesters from Feedstock Chemicals and Elemental Sulfur" *J. Am. Chem. Soc.* **2023**, *145*, 5846−5854.

Disulfides **13** are also applied as sulfur surrogates for synthesizing thioesters in radical chemistry (Figure 4.10a), yet they require elevated temperature.[21] Photocatalysis has provided a powerful platform for the formation of acyl radicals **XV** and thiyl radicals **XIX** from available carboxylic acids **2**[22] and disulfides,[23] which involves photoinduced energy transfer (PET) and SET mechanisms. Merging this reactivity with transition metal catalysis,[24] a Ni-catalyzed radical cross-thioesterification process has been developed to produce diverse methyl thioesters (Figure 4.9b)

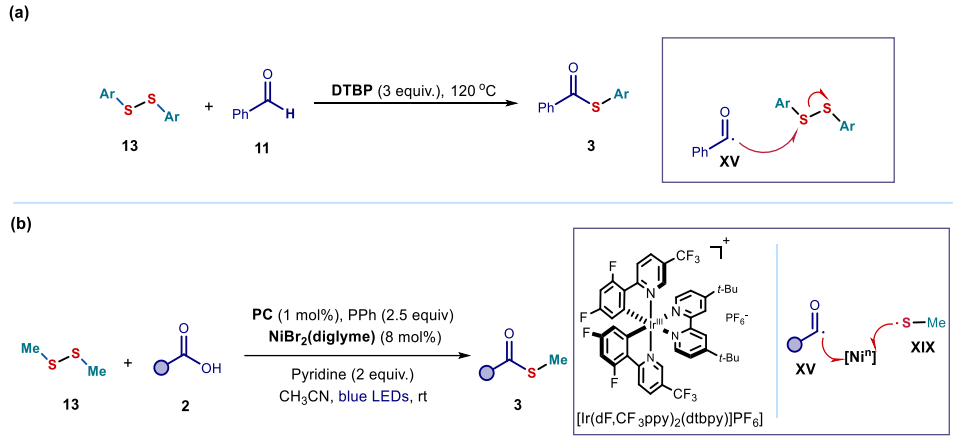


Figure 4.9. Disulfides are used as a sulfur source for the synthesis of thioesters. **(a)** DTBP-promoted synthesis of thioesters from diaryl disulfides and aldehydes; **(b)** Radical thioesterification via nickel-catalyzed sensitized electron transfer.

[21]Zeng, J.-W.; Liu, Y.-C.; Hsieh, P.-A.; Huang, Y.-T.; Yi, C.-L.; Badsara, S.; Lee, C.-F. "Metal-Free Cross-Coupling Reaction of Aldehydes with Disulfides by Using DTBP as An Oxidant under Solvent-Free Conditions." *Green Chem.* **2014**, *16*, 2644−2652.

[22](a) Rossi-Ashton, J. A.; Clarke, A. K.; Unsworth, W. P.; Taylor, R. J. K. "Phosphoranyl Radical Fragmentation Reactions Driven by Photoredox Catalysis." *ACS. Catal.* **2020**, *10*, 7250−7261; (b) Zhang, W.; Luo, H. T.; Yang, J. D. "Breakthrough in Phosphonylation of Alkyl Radicals: Alternative Access of Alkyl Phosphonates." *Chem*. **2023**, *9*, 2735−2737.

[23](a) Strieth-Kalthoff, F.; Glorius, F. "Triplet Energy Transfer Photocatalysis: Unlocking the Next Level." *Chem*. **2020**, *6*, 1888−1903; (b) Strieth-Kalthoff, F.; James, M. J.; Teders, M.; Pitzer, L.; Glorius, F. "Energy Transfer Catalysis Mediated by Visible Light: Principles, Applications, Directions." *Chem. Soc. Rev.* **2018**, 47, 7190−7202.

[24]Wang, H.; Liu, Z.; Das, A.; Bellotti, P.; Megow, S.; Temps, F.; Qi, X.; Glorius, F. "Radical Thioesterification via Nickel-Catalysed Sensitized Electron Transfer." *Nat. Syn*. **2023**, 2, 1116–1126.

4.3 Design and Target of the Project

In the previous chapter III, we introduced our recent finding that isothiouronium salt **I** can be readily prepared by trapping aryl radicals, generated from aryl chlorides, with tetramethylthiourea **A** by means of a radical-polar cross-over pattern.[8] We sought to expand this platform to the preparation of thioesters using readily available carboxylic acids. Specifically, given the electrophilic nature of the isothiouronium ion intermediates **I**, we surmised that carboxylic acids might behave as nucleophiles, similarly to the alcohols and in analogy to our previous study. We therefore hypothesized that carboxylic acids could react with **I** to form intermediate **II**, which is in equilibrium with isothiouronium salt **III** upon the extrusion of thiolate **IV** (Figure 4.10). The transiently formed **IV** would eventually reattack intermediate **III**, following the established deoxythiolation *polar* pathway that leads to the formation of the desired thioesters **3** and 1,1,3,3-tetramethylurea as the byproduct.

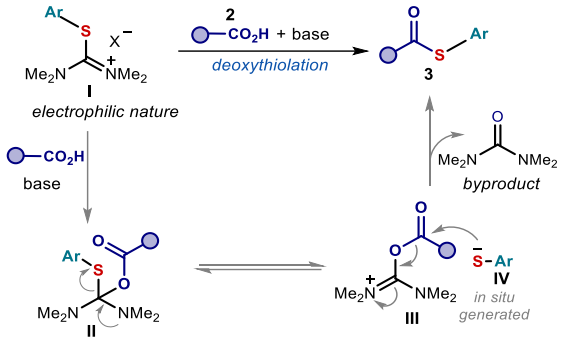


Figure 4.10. Design plan: a polar deoxythiolation pathway involving carboxylic acids **2** then leads to thioesters **3**.

A few reports on the reactivity of preformed stoichiometric isothiouronium salts further supported the feasibility of this plan.[25] For example, in 2003 it was reported (Figure 4.11) that the pre-synthesized 2-pyridinyl isothiouronium ion intermediates **I** were suitable for the

[25]For protocols requiring stoichiometric amounts of preformed isothiouronium salts: (a) Biancalana, S.; Hudson, D.; Songster, M. F.; Thompson, S. A. "Fmoc-Protein Synthesis: Preparation of Peptide Thioesters Using a Side-Chain Anchoring Strategy." *Lett. Pep. Sci.* **2001**, *7*, 291–297; (b) Scardovi, N.; Garner, P. P.; Protasiewicz, J. D. "S-(2-Pyridinyl)-1,1,3,3-Tetramethylthiouronium Hexafluorophosphate. A New Reagentfor the Synthesis of 2-Pyridinethiol Esters." *Org. Lett.* **2003**, *5*, 1633–1635.

conversion of various carboxylic acids into their corresponding 2-pyridinethiol ester derivatives.

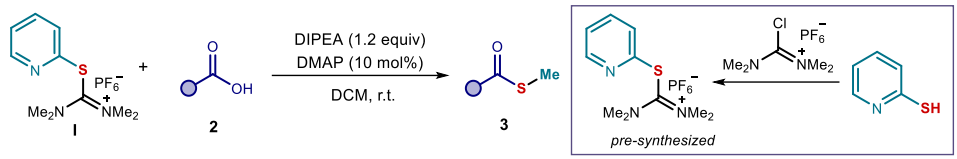


Figure 4.11. Synthesis of 2-Pyridinethiol Esters using 2-pyridinyl isothiouronium ions.

In the present chapter, we detail the realization of this design plan. We successfully developed a new protocol based on readily available 1,1,3,3-tetramethylthiourea **A** as the sulfur source, which uses purple light to stitch together widely available aryl halides **1** and carboxylic acids **2**, thus affording thioesters **3** (Figure 4.12). Importantly, and in contrast to our previous study detailed in Chapter III,[8] we found that tetramethylthiourea **A** does not act solely as a sulfur source and aryl radical trap. **A** can be directly excited upon absorption of purple light (405 nm) to acquire strong reducing power, useful for activating aryl halides **1** via SET. Therefore, in this protocol, we could avoid the use of an external photoredox catalyst for the generation of aryl radicals, which was instead required in our previous method.

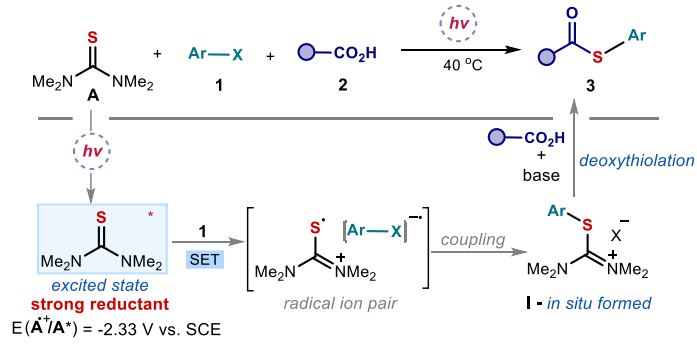


Figure 4.12. A new thiol-free strategy that uses the dual nature of tetramethylthiourea **A**, which serves as both sulfur source and potent photoreductant for aryl radical formation under purple light excitation.

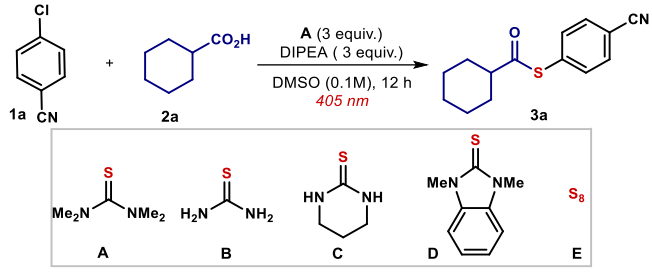
4.4 Results and Discussion

4.4.1 Optimization of Reaction Conditions and Substrate Scope

We started out our investigations using 1,1,3,3-tetramethylthiourea **A** as the sulfur source, 4-chlorobenzonitrile **1a** as the radical precursor (E (**1a**/**1a**$^{-\bullet}$) = −2.2 V vs. Ag/AgCl), and

cyclohexanecarboxylic acid **2a** as the nucleophile (Table 4.1). The reaction was conducted in DMSO as the solvent under irradiation by a purple light-emitting diode (LED, λ_{max} = 405 nm) and employing DIPEA (*N*,*N*-diisopropylethylamine) for deprotonation of acid **2a**. Initially, we aimed to apply the same conditions developed for the thioetherification process, as detailed in Chapter III. Our plan was to use photocatalysts with high reducing power, as we initially believed they were essential for generating aryl radicals via SET reduction of **1a**. Surprisingly, we observed that the photochemical reaction proceeded smoothly, yielding the thioester product **3a** in 83% yield (entry 1 in Table 4.1), without requiring any external photoredox catalysts. A mechanistic rationale for this unexpected photochemical reactivity is detailed in Section 4.2 below.

Table 4.1. Optimization of the reaction conditions with electrophilic aryl iodide 1a.[a]



entry	deviation	yield [%][a]	entry	deviation	yield [%][a]
1	none	**86 (83)**[b]	6	TEMPO (3 equiv.)	<10
2	K_3PO_4	80	7	465 nm	0
3	$NaHCO_3$	60	8	no light	0
4	CH_3CN	80	9	no base	0
5	**B - E**	0	10	dark, 60 °C	0

[a] Reactions performed on a 0.1 mmol scale for 12 h using 3 equiv. of **1a**, 1 equiv. of **2a**, 3 equiv. of **A** and DIPEA, in 0.2 mL of DMSO under illumination by a purple LED (*EvoluChem*) at 405 nm, ambient temperature. [a] Yield inferred by ^{1}H NMR analysis of the crude mixture using 1,3,5-trimethoxybenzene as an internal standard. DIPEA: *N*,*N*-diisopropylethylamine.

We then tested other bases and solvents, which offered product **3a** with comparable yet slightly lower efficiency (entries 2-4). Using different sulfur sources (**B-E**, entry 5) failed to produce **3a**. Similar results were observed in the previous chapter on the photocatalyzed synthesis of thioethers. This lack of reactivity can be attributed to the presence of acidic protons in **B** and **C**, which may be deprotonated to form nucleophilic thiolates, thereby complicating the reaction significantly (Figure 4.13). Aryl-isothiouronium salts from tetramethylthiourea **A** are more electrophilic than the neutral adducts from **B-D**, making them

more efficient in the deoxythiolation step with carboxylates. Finally, the formation of the key aryl-isothiouronium salts from **E** (S_8) was not possible. As for the reaction with thiourea **D**, we detected 4,4'-thiodibenzonitrile as a byproduct after reaction completion (Figure 4.13, lower panel), which suggests that the excitation of **D** and the generation of the aryl radical upon SET activation of **1a** were feasible, although to a minimal extent. We hypothesize that the lack of thioester product formation was a consequence of a difficult deoxythiolation process.

We then performed control experiments. Reactivity was completely inhibited by adding TEMPO as the radical scavenger (entry 6, Table 4.1), consistent with the involvement of a radical pathway. Further experiments indicated that both purple light illumination and the presence of a base were essential for reactivity (entries 7-10, Table 4.1).

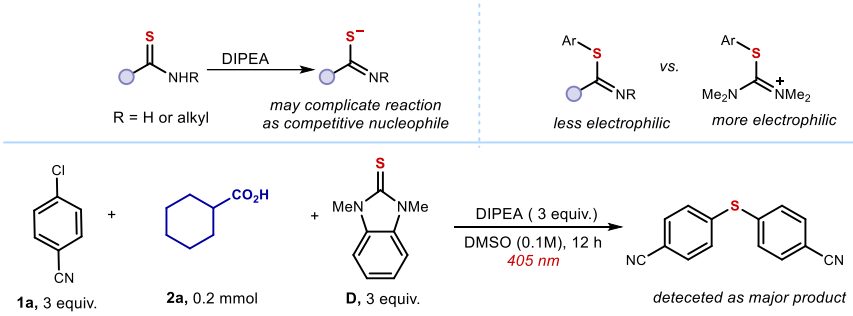


Figure 4.13. Rationalization of the poor performance of sulfur surrogates **B-D**.

Under the optimal conditions outlined in entry 1 of Table 4.1, we explored the scope of the photochemical thioesterification (Figure 4.14). Initially, we demonstrated the process's efficiency on a preparative scale (5 mmol scale), yielding 1.2 g of product **3a** (95% yield). We then investigated the reactivity of various aryl halides **1** as radical precursors using cyclohexanecarboxylic acid **2a** as the nucleophile. Notably, in addition to iodides, aryl bromides and chlorides, which are more challenging to activate by SET, were suitable substrates, yielding the corresponding thioesters **3a**–**c** in good yields. Aryl iodides with diverse substituents at various positions on the phenyl ring were well-tolerated, affording products **3d**–**3o** in good yields. The protocol exhibited tolerance towards sensitive functional groups, including aldehydes (products **3d**, **3m**), a ketone (product **3e**), and esters (products **3b**, **3k**), highlighting the mild conditions of the reaction. However, the method showed lower efficiency with electron-neutral and electron-rich aryl iodides (products **3g**, **3j**, and **3l**),

consistent with a difficult activation of these substrates by excited **A**. The reaction was also compatible with substrates containing polycyclic aromatic structures (products **3p**–**3q**) and valuable heterocyclic frameworks, including pyridines, quinoline, and thiophene (products **3r**–**3u**). Using more difficult-to-reduce aryl bromides, chlorides, and fluorides did not yield good results (grey box at the bottom of Figure 4.13). This is because their more negative reduction potentials exceed the redox capacity of the excited state of **A**. A complete list of unreactive or poorly reactive substrates is reported in Figure 4.21 within the Experimental Section.

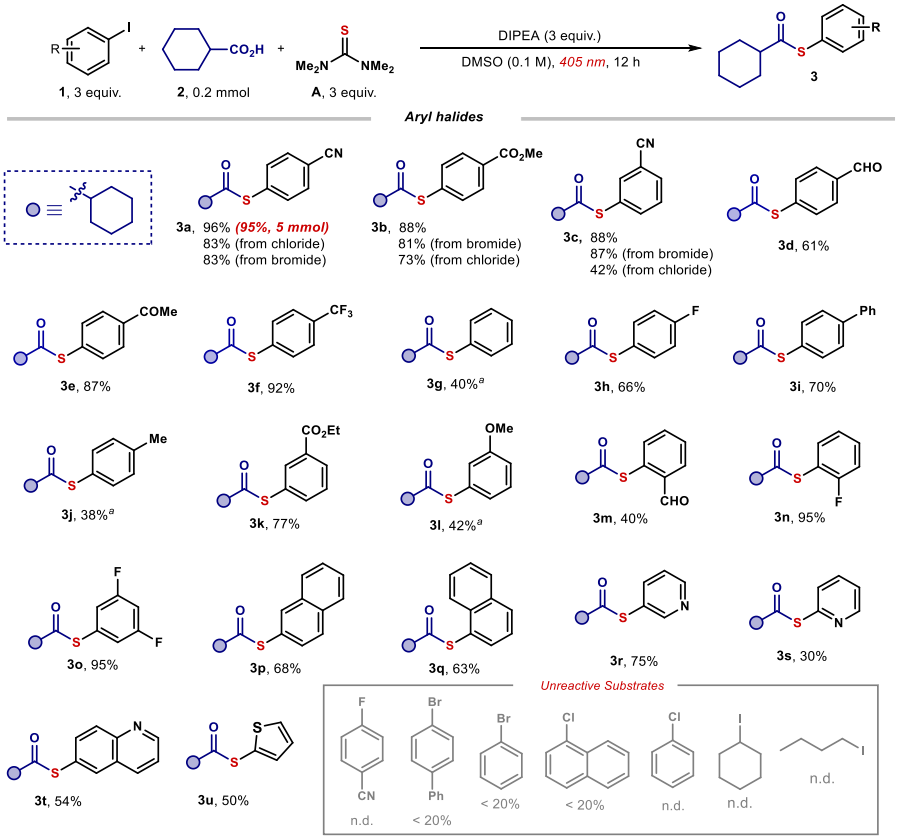


Figure 4.14. Substrate scope for aryl halides in the photochemical organocatalytic synthesis of thioesters with cyclohexanecarboxylic acid **2a**. Reactions performed on a 0.2 mmol scale at 40 °C using 3 equiv. of **1** and 3 equiv. of thiourea **A** under illumination by a purple LED (*EvoluChem*) at 405 nm. Yields refer to isolated products **3** after purification. [a]24 h reaction time.

Next, we explored the scope of widely available carboxylic acids **2** using 4-iodobenzonitrile **1a** as the radical precursor (Figure 4.15). Primary carboxylic acids, bearing various functional

groups such as carbonyl (product **3w**), cyclopropane (**3x**), phthalimide (**3y**), and ester (**3z**) moieties, were tolerated well. Thioesterification of simple acetic acid was straightforwardly achieved affording adduct **3aa**. A diverse array of secondary (**3ab**–**ae**) and tertiary (**3af**–**ag**) alkyl carboxylic acids, as well as aromatic acids (**3ah**–**ai**) and acrylic acid (**3aj**), were compatible with this photochemical transformation. Notably, pharmaceutical agents and natural products bearing a carboxylic acid functionality, such as *Oxaprozin* (product **3ak**), *citronellic acid* (**3al**), protected *sarcosine* (**3am**), *Lithocolic acid* (**3an**), *oleic acid* (**3ao**), *Flurbiprofen* (**3ap**), *Ibuprofen* (**3aq**), *Telmisartan* (**3ar**), *Probenecid* (**3as**), *dehydroabietic acid* (**3at**), *Indomethacin* (**3au**), *Loxoprofen* (**3av**), and *Gemfibrozil* (**3aw**) were efficiently functionalized. Interestingly, the dithioester **3ax** was also obtained from a diacid (*pimelic acid*).

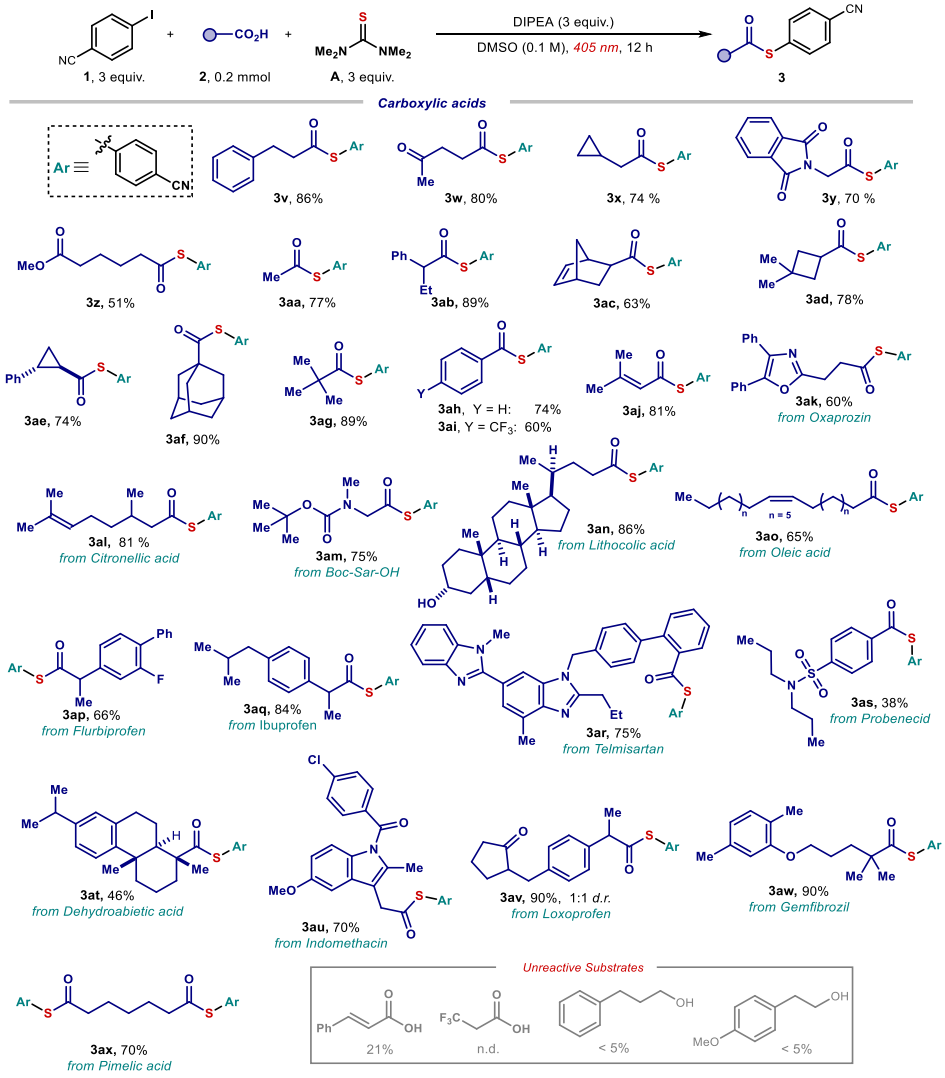


Figure 4.15. Substrate scope for carboxylic acids in the photochemical organocatalytic synthesis of thioethers from **1a**. Reactions performed on a 0.2 mmol scale at 40 °C using 3 equiv. of **1a** and 3 equiv. of thiourea **A** under illumination by a purple LED (*EvoluChem*) at 405 nm. Yields refer to isolated products **3** after purification.

As a limitation of the protocol, the cinnamic acids containing double bonds susceptible to radical addition offered low amount of thioester **3** (see grey inset in Figure 4.15). Using trifluoropropionic acid and alkyl alcohols as nucleophiles did not generate the desired products under standard condition.

4.4.2 Mechanistic Investigations

To better understand why light could trigger the radical generation process and to validate the potential mechanism of photoexcitation of thiourea **A**, a series of mechanistic experiments were conducted.

Photochemical reduction of aryl halides by direct photoexcitation of thiourea A

We initially performed photophysical characterization studies of 1,1,3,3-tetramethylthiourea **A** to evaluate whether its excitation with light could be responsible for the SET activation of aryl halides (see Figure 4.16). Full experimental details are reported in Section 4.6.3.

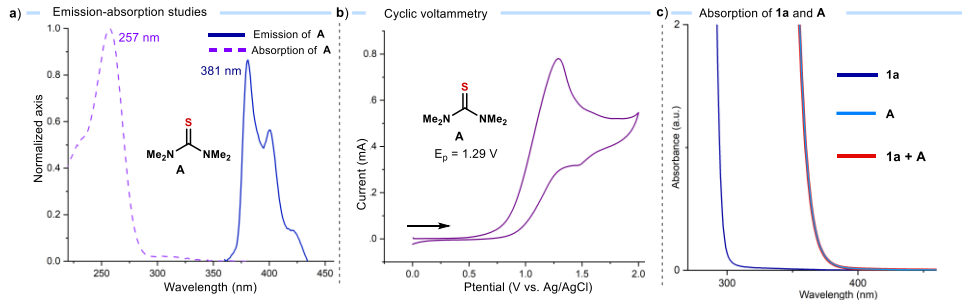


Figure 4.16. Photophysical and electrochemical properties of the 1,1,3,3-tetramethylthiourea **A**. (**a**) Emission of the excited tetramethylthiourea **A** in CH_3CN upon irradiation at 350 nm. A 0−0 transition energy ($E_{0,0}$) was determined to be 3.54 eV referring to the tail of absorption spectrum at 350 nm. **(b)** Cyclic voltammetry measurement of tetramethylthiourea **A** carried out in CH_3CN vs. Ag/AgCl. **(c)** Absorption spectra recorded for **A**, 4-chlorobenzonitrile (**1a**) and a mixture of **A** and **1a** in DMSO (0.3 M).

We investigated the photophysical behavior of 1,1,3,3-tetramethylthiourea **A**, the sole absorbing species at 405 nm, the wavelength of irradiation used in this study. Upon irradiation at 350 nm of a CH_3CN solution of **A**, we detected emission, confirming that **A** could access an electronically excited state (Figure 4.16a). The 0−0 transition energy ($E_{0,0}$) was determined to be 3.54 eV, referring to the tail of the absorption spectrum at 350 nm. Next, the ground-state redox property of **A** was determined by cyclic voltammetry (Figure 4.16b). An irreversible oxidation peak was found at +1.29 V vs Ag/AgCl in CH_3CN. Applying the reported equation ($(E(\mathbf{Pc}^{\bullet}/\mathbf{Pc}^{*}) = E(\mathbf{Pc}^{\bullet}/\mathbf{Pc}^{-}) - E_{0\text{-}0}(\mathbf{Pc}^{-*})/(\mathbf{Pc}^{-})$) for determining the redox potential of excited chromophores,[26] the redox potential of the excited **A**

[26] Kavarnos, G. J. *Fundamentals of Photoinduced Electron Transfer.* chap. 1, pp. 29, VCH Publishers, **1993**.

(E(**A**$^{\bullet+}$/**A***)) was estimated as − 2.33 V vs SCE. This confirmed that **A** acquires a strongly reducing power upon excitation. Stern−Volmer quenching studies revealed that the fluorescence of excited tetramethylthiourea **A**, induced by a laser at 350 nm, was effectively quenched by 4-chlorobenzonitrile **1a** [E_{red} = −2.1 V vs. Ag/AgCl] and iodobenzene [E_{red} = −2.3 V vs. Ag/AgCl], respectively (details in section 4.6.3, Figure 4.26-27). The possibility of ground-state aggregation was also excluded (e.g., no electron donor-acceptor complexes were detected) by spectroscopic analyses of the substrates (Figure 4.16c), as evidenced by the absence of any bathochromic shift in the UV-Vis spectroscopic profile of **1a**, **A**, and their mixture.

These observations suggest a mechanism in which the direct excitation of tetramethylthiourea **A** is responsible for the SET activation of aryl chlorides, leading to the generation of aryl radicals. This process would then trigger the formation of isothiouronium salts **I** (Figure 4.17). Two possible pathways for the formation of intermediates **I** can be considered:

1) SET activation of aryl halides **1** by the excited **A** generates a radical ion pair (*path I*, Figure 4.17). Within this pair, halide cleavage produces aryl radicals, which then recombine with the sulfur radical within the solvent cage to yield intermediate **I**.

2) In an alternative scenario, the aryl radical may exit the solvent cage and be intercepted by ground-state tetramethylthiourea **A**, forming the electron-rich radical intermediate **XX**. This intermediate could potentially propagate the chain reaction by SET reduction of aryl halides (Figure 4.17, *path II*).

However, the redox potential of intermediate **XX** [E = −1.6 V vs. Ag/AgCl] is insufficient to reduce aryl halides, and the quantum yield (Φ) of the overall photochemical process between **1a** and **2a** is low (0.067), indicating that a radical chain mechanism is unlikely. Overall, these studies suggest that *Path I* is more likely under the reaction conditions.

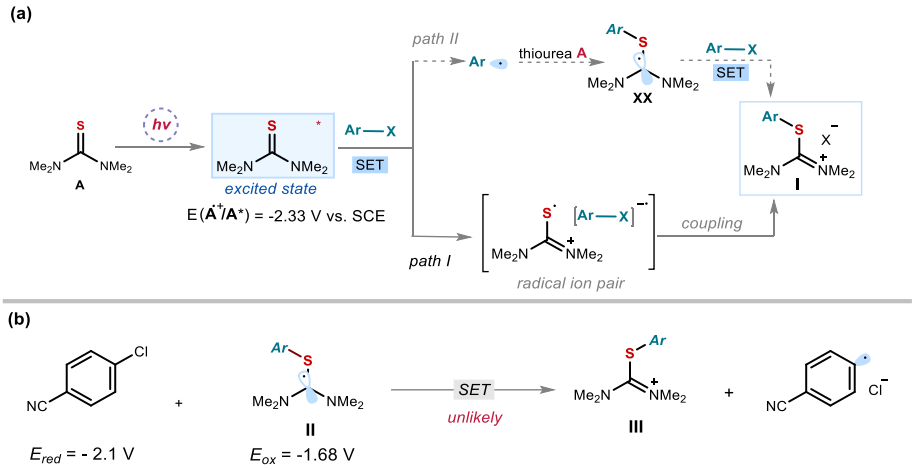


Figure 4.17. (**a**) Proposed mechanism. **(b)** A hypothetical radical propagation step leading to a light-independent chain mechanism found implausible.

Aryl Radical Capture and Polar Deoxythiolation Steps

To corroborate the generation of aryl radials in our system, we conducted the model reaction in the presence of 1,1-diphenylethylene (3 equiv.), an established radical trap. Adduct **15** was isolated in 15% yield, consistent with the formation of the aryl radical from **1a** (Figure 4.18a), while thioester **3a** remained the major product. We also performed an experiment reacting the preformed isothiouronium ion **16**, carboxylic acid **2a**, and DIPEA in the dark (Figure 4.18b). This experiment resulted in the formation of thioester **3g**, confirming that the proposed polar deoxythiolation path is indeed operational.

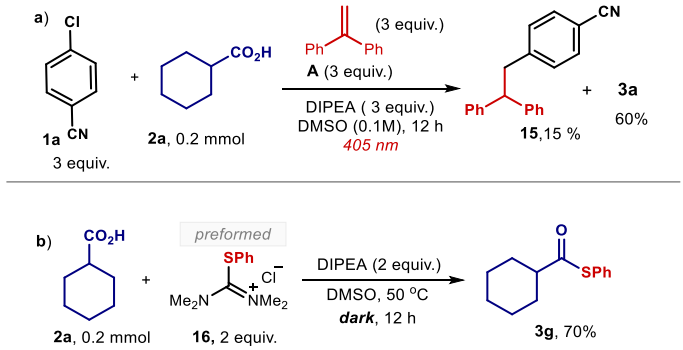


Figure 4.18. Mechanistic investigations: (**a**) capture of the aryl radical; (**b**) thioetherification from the preformed phenyl isothiouronium salt **16** via a deoxythiolation polar path.

4.5 Conclusions

In summary, we have reported a novel photochemical method for synthesizing thioesters from readily available aryl halides and carboxylic acids. This thiol-free protocol hinges on the direct excitation of 1,1,3,3-tetramethylthiourea **A** and its multifaceted ability to act as the sulfur source, generate aryl radicals upon SET reduction of halides, and trap them to produce reactive isothiouronium ions. A synthetic advantage of this method is its mild conditions, which enable remarkable tolerance for functional groups, facilitating late-stage modifications of biorelevant compounds.

4.6 Experimental Section

General Information. The ^{1}H NMR, $^{19}F\{^{1}H\}$ NMR, $^{13}C\{^{1}H\}$ NMR spectra are available in the literature[1] and are not reported in the present dissertation.

The NMR spectra were recorded at 400 MHz and 500 MHz for ^{1}H, 101 or 126 MHz for $^{13}C\{^{1}H\}$ and 376 MHz for $^{19}F\{^{1}H\}$. The chemical shift (δ) for ^{1}H and $^{13}C\{^{1}H\}$ are given in ppm relative to residual signals of the solvents ($CHCl_3$ at 7.26 ppm for ^{1}H NMR and 77.16 ppm for $^{13}C\{^{1}H\}$ NMR). Coupling constants are given in Hertz. The following abbreviations are used to indicate the multiplicity: s, singlet; d, doublet; q, quartet; m, multiplet; br, broad signal

High-resolution mass spectra (HRMS) were obtained from the ICIQ HRMS unit on MicroTOF Focus and Maxis Impact (Bruker Daltonics) with electrospray ionization (ESI) and Atmospheric-pressure chemical ionization (APCI). Optical rotations were measured on a Polarimeter Jasco P-1030 and are reported as follows: $[\alpha]_D$ ambient temperature (c in g per 100 mL, solvent). Cyclic voltammetry studies were carried out on a Princeton Applied Research PARSTAT 2273 potentiostat, offering compliance voltage up to ± 100 V (available at the counter electrode), ± 10 V scan range and ±2 A current range.

Yields refer to isolated materials of >95% purity as determined by ^{1}H NMR analysis.

General Procedures. All reactions were set up under an argon atmosphere in oven-dried glassware. Synthesis grade solvents were used as purchased, anhydrous solvents were taken from a commercial SPS solvent dispenser. Chromatographic purification of products was accomplished using forced-flow chromatography (FC) on silica gel (230-400 mesh). For thin layer chromatography (TLC) analysis throughout this work, Merck pre-coated TLC plates (silica gel 60 GF_{254}, 0.25 mm) were employed, using UV light as the visualizing agent and

an acidic mixture of vanillin or basic aqueous potassium permanganate ($KMnO_4$) stain solutions, and heat as developing agents. Organic solutions were concentrated under reduced pressure on a Büchi rotatory evaporator.

Materials. Commercial grade reagents and solvents were purchased at the highest quality from commercial suppliers and used as received, unless otherwise stated.

4.6.1 Experimental Procedures

Experimental Setup

Set-up 1 *405 nm EvoluChem setup* (**Figure 4.19**)

The reactions were performed using an *EvoluChem* P303-30-1 lamp (18 W, λ_{max}= 405 nm, 2-3 cm away), and a fan to cool down the vials (under these conditions, the reaction temperature within the reaction vessel was measured to be between 40 - 42 ºC).

Figure 4.19. Reaction setup using *EvoluChem* lamps emitting at 405 nm.

Set-up 2 Gram scale experiment (**Figure 4.20**)

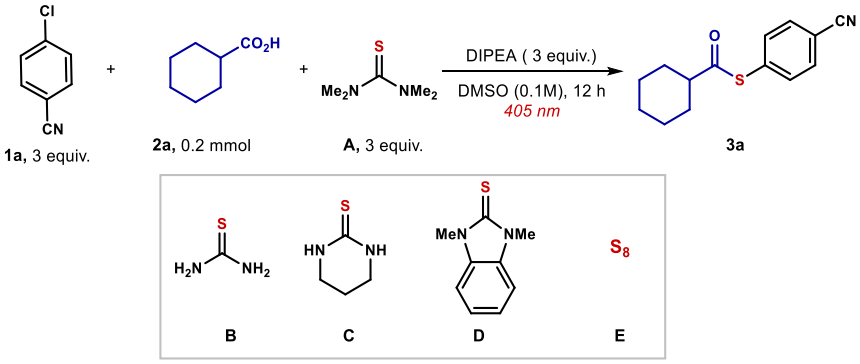
The gram scale reaction was performed under illumination by two EvoluChem P303-30-1 lamps (18 W, λ_{max}= 405 nm, 2-3 cm away from the reaction vessel) and using a fan to cool the flask.

Figure 4.20. Setup for the gram-scale experiment using two *EvoluChem* lamps emitting at 405 nm.

4.6.2 Preparation of Thioesters from Carboxylic Acids and Aryl Halides

Optimization Studies

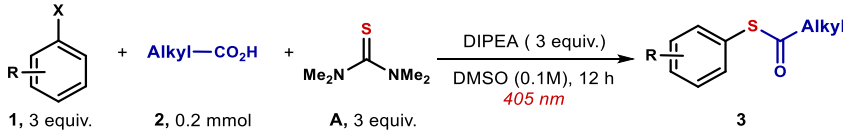
Table 4.2. Optimization of the model reaction



Entry	Deviations	NMRy **3a** (%)
1	none	86 (83)[a]
2	No light	0
3	No base	0
4	No light, 60 °C	0
5	**B-E**	0
6	2 equiv. **1a**, **A** and DIPEA	65
7	CH_3CN as solvent	80
8	DMA as solvent	76
9	DMF as solvent	80
10	K_3PO_4 as Base	80
11	K_2HPO_4 as Base	76
12	$NaHCO_3$ as Base	60
13	Et_3N as Base	70
14	465 nm LED	< 10
15	With TEMPO	0%

All reactions were performed on a 0.2 mmol scale; yield of **3a** determined by ^{1}H NMR analysis of the crude reaction mixture by comparison with 1,3,5-trimethoxybenzene as internal standard. [a] Yield of isolated **3a**. DIPEA: N,N-Diisopropylethylamine.

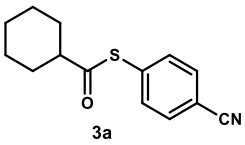
General Procedure for Preparation of Thioesters



To a 7 mL glass vial, 1,1,3,3-tetramethylthiourea **A** (79.0 mg, 0.6 mmol, 3.0 equiv.), carboxylic acids **2** (if solid, 0.2 mmol, 1 equiv.) and aryl halides **1** (if solid, 0.6 mmol, 3 equiv.) were sequentially added. The vial was sealed with a screw-top cap with septum and then vacuumed and backfilled with argon for 3 times. Afterwards, DIPEA (104 μL, 0.6 mmol, 3.0 equiv.), aryl halides **1** (if liquid, 0.6 mmol, 3.0 equiv.) or carboxylic acids (if liquid, 0.2 mmol, 1 equiv.) followed by argon-sparged DMSO (0.1 M, 2.0 mL) were added *via* syringe. The vial was sealed with Parafilm and then stirred under 405 nm for 12 hours using ***Set-up 1***

detailed in **Figure 4.19**. After the reaction was completed, the reaction mixture was transferred to an extraction funnel, 10 mL of H_2O and 2 mL of brine were added and the organic layer was extracted with EtOAc. The organic layer was washed with brine twice. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness. The crude residue was purified by column chromatography to afford the corresponding product **3** in the stated yield with >95% purity according to ^{1}H NMR analysis.

Characterization of Products



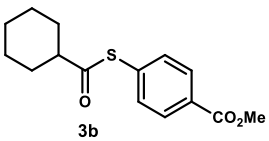
3a

S-(4-cyanophenyl) cyclohexanecarbothioate (3a): Synthesized according to the General Procedure using cyclohexanecarboxylic acid (25.6 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and 4-chlorobenzonitrile (82.5 mg, 0.6 mmol, 3.0 equiv.) or 4-bromobenzonitrile (109.0 mg, 0.6 mmol, 3.0 equiv.) or 4-iodobenzonitrile (137.5 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane: EtOAc = 100: 1 as eluent) to afford **3a** (40.8 mg, 83% yield) with 4-chlorobenzonitrile; (40.8 mg, 83% yield) with 4-bromobenzonitrile; (37.2 mg, 96% yield) with 4-iodobenzonitrile and 1.16g, 95% yield was obtained from 5 mmol scale) as a pale yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 – 7.64 (m, 2H), 7.54 – 7.49 (m, 2H), 2.67 – 2.57 (m, 1H), 2.05 – 1.98 (m, 2H), 1.86 – 1.78 (m, 2H), 1.72 – 1.65 (m, 1H), 1.57 – 1.47 (m, 2H), 1.40 – 1.20 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 198.8, 134.8, 134.6, 132.4, 118.3, 112.7, 52.9, 29.5, 25.5, 25.4.

HRMS: calculated for $C_{14}H_{15}NNaOS$ ($M+Na^+$): 268.0767, found 268.0768.



3b

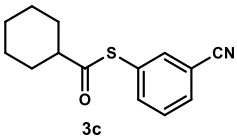
Methyl 4-((cyclohexanecarbonyl)thio)benzoate (3b): Synthesized according to the General Procedure using cyclohexanecarboxylic acid (25.6 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and methyl 4-chlorobenzoate (102.0 mg, 0.6 mmol, 3.0 equiv.) or 4-bromobenzoate (129.0 mg, 0.6 mmol, 3.0 equiv.) or 4-iodobenzoate (157.0 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane:EtOAc = 100: 1 as eluent) to afford **3b** (40.5

mg, 73% yield) with methyl 4-chlorobenzoate; (45.0 mg, 81% yield) with methyl 4-bromobenzoate; (49.0 mg, 88% yield) with methyl 4-Iodobenzoate as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 – 8.01 (m, 2H), 7.50 – 7.45 (m, 2H), 3.92 (s, 3H), 2.66 – 2.56 (m, 1H), 2.06 – 1.96 (m, 2H), 1.87 – 1.77 (m, 2H), 1.71 – 1.64 (m, 1H), 1.58 – 1.47 (m, 2H), 1.38 – 1.20 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 199.5, 166.5, 134.1, 133.9, 130.5, 130.0, 52.8, 52.3, 29.5, 25.6, 25.5.

HRMS: calculated for $C_{15}H_{18}NaO_3S$ ($M+Na^+$): 301.0869, found 301.0866.



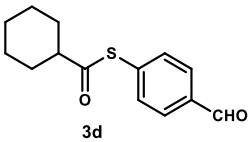
3c

S-(3-cyanophenyl) cyclohexanecarbothioate (3c): Synthesized according to the General Procedure using cyclohexanecarboxylic acid (25.6 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and 3-chlorobenzonitrile (82.5 mg, 0.6 mmol, 3.0 equiv.) or 3-bromobenzonitrile (109.0 mg) or 3-Iodomobenzonitrile (137.5 mg). The crude mixture was purified by flash column chromatography on silica gel (Hexane:EtOAc = 100: 1 as eluent) to afford **3c** (20.5 mg, 42% yield) with 3-chlorobenzonitrile; (42.8 mg, 87% yield) with 3-bromobenzonitrile; (45.1 mg, 92% yield) with 3-iodobenzonitrile with as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 – 7.64(m, 2H), 7.63– 7.59 (m, 1H), 7.53 – 7.48 (m, 2H), 2.66 – 2.56 (m, 1H), 2.04 – 1.97 (m, 2H), 1.87 – 1.79 (m, 2H), 1.72 – 1.65 (m, 1H), 1.58 – 1.47 (m, 2H), 1.38 – 1.22 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 199.2, 138.9, 137.8, 132.5, 130.2, 129.7, 117.9, 113.4, 52.7, 29.5, 25.5, 25.4.

HRMS: calculated for $C_{14}H_{15}NNaOS$ ($M+Na^+$): 268.0767, found 268.0770.



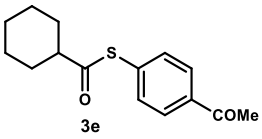
3d

S-(4-formylphenyl) cyclohexanecarbothioate (3d): Synthesized according to the General Procedure using cyclohexanecarboxylic acid (25.5 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and 4-iodobenzaldehyde (139.0 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane:EtOAc = 75:1 as eluent) to afford **3d** (30.0 mg, 61% yield) as a yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.02 (s, 1H), 7.90 – 7.86 (m, 2H), 7.59 – 7.55 (m, 2H), 2.65 – 2.58 (m, 1H), 2.05 – 1.98 (m, 2H), 1.86 – 1.79 (m, 2H), 1.71 – 1.65 (m, 1H), 1.58 – 1.48 (m, 2H), 1.36 – 1.20 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 199.2, 191.5, 136.3, 135.8, 134.7, 129.9, 52.9, 29.5, 25.5, 25.4.

HRMS: calculated for $C_{14}H_{17}O_2S$ ($M+H^+$): 249.0944, found 249.0944.



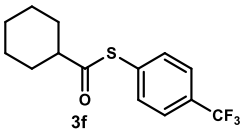
3e

S-(4-acetylphenyl) cyclohexanecarbothioate (3e): Synthesized according to the General Procedure using cyclohexanecarboxylic acid (25.5 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and 1-(4-iodophenyl)ethan-1-one (147.5 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane:EtOAc = 50: 1 as eluent) to afford **3e** (45.6 mg, 87% yield) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 – 7.92 (m, 2H), 7.51 – 7.47 (m, 2H), 2.60 (s, 3H), 2.64 – 2.57 (m, 1H), 2.03 – 1.96 (m, 2H), 1.85 – 1.78 (m, 2H), 1.70 – 1.65 (m, 1H), 1.57 – 1.47 (m, 2H), 1.37 – 1.18 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 199.5, 197.4, 137.2, 134.4, 134.1, 128.7, 52.8, 29.5, 26.7, 25.6, 25.4.

HRMS: calculated for $C_{15}H_{19}O_2S$ ($M+H^+$): 263.1100, found 263.1098.



3f

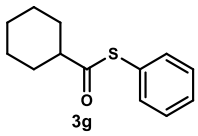
S-(4-(trifluoromethyl)phenyl) cyclohexanecarbothioate (3f): Synthesized according to the General Procedure using cyclohexanecarboxylic acid (25.5 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and 1-iodo-4-(trifluoromethyl)benzene (163.0 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane:EtOAc = 300: 1 as eluent) to afford **3f** (53.0 mg, 92% yield) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 – 7.62 (m, 2H), 7.55 – 7.50 (m, 2H), 2.67 – 2.58 (m, 1H), 2.06 – 1.98 (m, 2H), 1.87 – 1.79 (m, 2H), 1.73 – 1.66 (m, 1H), 1.58 – 1.48 (m, 2H), 1.37 – 1.20 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 199.4, 134.6, 132.8, 131.07 (q, J = 32.7 Hz), 125.82 (q, J = 3.8 Hz), 123.86 (q, J = 272.3 Hz), 52.8, 29.5, 25.5, 25.4.

$^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$) δ -63.0.

HRMS: calculated for $C_{14}H_{16}F_3OS$ ($M+H^+$): 289.0868, found 289.0869.



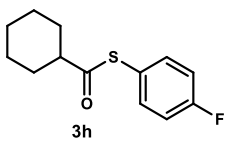
3g

S-phenyl cyclohexanecarbothioate (3g): Synthesized according to the General Procedure using cyclohexanecarboxylic acid (25.5 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and iodobenzene (122.4 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane:EtOAc = 300: 1 as eluent) to afford **3g** (15.0 mg, 40% yield) as a yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.35 (m, 5H), 2.65 – 2.55 (m, 1H), 2.05 – 1.95 (m, 2H), 1.87 – 1.77 (m, 2H), 1.72 – 1.65 (m, 1H), 1.58 – 1.47 (m, 2H), 1.38 – 1.17 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 200.8, 134.6, 129.1, 129.1, 128.0, 52.5, 29.6, 25.6, 25.5.

Matching reported literature data. [27]



3h

S-(4-fluorophenyl) cyclohexanecarbothioate (3h): Synthesized according to the General Procedure using cyclohexanecarboxylic acid (25.5 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and 1-fluoro-4-iodobenzene (133.0 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane:EtOAc = 300: 1 as eluent) to afford **3h** (31.5 mg, 66% yield) as a yellow solid.

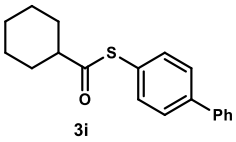
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.33 (m, 2H), 7.13 – 7.07 (m, 2H), 2.64 – 2.56 (m, 1H), 2.02 – 1.96 (m, 2H), 1.85 – 1.78 (m, 2H), 1.71 – 1.65 (m, 1H), 1.58 – 1.47 (m, 2H), 1.36 – 1.20 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 200.8, 163.4 (d, J = 249.6 Hz), 136.6 (d, J = 8.5 Hz), 123.3 (d, J = 3.4 Hz), 116.3 (d, J = 22.0 Hz), 52.5, 29.5, 25.6, 25.5.

$^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$) δ -111.7.

HRMS: calculated for $C_{13}H_{16}FOS$ ($M+H^+$): 239.0900, found 239.0900.

[27] Su, J.; Chen, A.; Zhang, G.; Jiang, Z.; Zhao, J. "Photocatalytic Phosphine-Mediated Thioesterification of Carboxylic Acids with Disulfides." *Org. Lett.* **2023**, 25, 8033−8037.

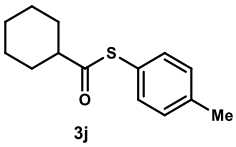


3i

S-([1,1'-biphenyl]-4-yl) cyclohexanecarbothioate (3i): Synthesized according to the General Procedure using cyclohexanecarboxylic acid (25.5 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and 4-iodo-1,1'-biphenyl (168.0 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane:EtOAc = 300: 1 as eluent) to afford **3i** (41.5 mg, 70% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 – 7.56 (m, 4H), 7.49 – 7.41 (m, 4H), 7.39 – 7.34 (m, 1H), 2.68 – 2.58 (m, 1H), 2.08 – 1.97 (m, 2H), 1.88 – 1.79 (m, 2H), 1.72 – 1.64 (m, 1H), 1.61 – 1.48 (m, 2H), 1.39 – 1.22 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 200.9, 142.1, 140.3, 134.9, 128.9, 127.8, 127.7, 127.2, 126.8, 52.6, 29.6, 25.6, 25.5. HRMS: calculated for $C_{19}H_{21}OS$ ($M+H^+$): 297.1308, found 297.1305.

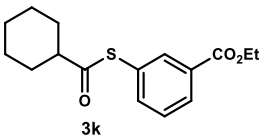


3j

S-(p-tolyl) cyclohexanecarbothioate (3j): Synthesized according to the General Procedure using cyclohexanecarboxylic acid (25.5 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and 1-iodo-4-methylbenzene (131 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane:EtOAc = 300: 1 as eluent) to afford **3j** (17.8 mg, 38% yield) as a yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.26 (m, 2H), 7.23 – 7.18 (m, 2H), 2.64 – 2.55 (m, 1H), 2.37 (s, 3H), 2.03 – 1.95(m, 2H), 1.86 – 1.77 (m, 2H), 1.70 – 1.64 (m, 1H), 1.57 – 1.46 (m, 2H), 1.37 – 1.17 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 201.2, 139.4, 134.6, 129.9, 124.4, 52.4, 29.6, 25.6, 25.5, 21.3. Matching reported literature data. [28]



3k

Ethyl 3-((cyclohexanecarbonyl)thio)benzoate (3k): Synthesized according to the General Procedure using cyclohexanecarboxylic acid (25.5 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and ethyl 3-iodobenzoate (166.0

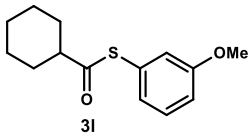
[28]Zhao, B.; Fu, Y.; Shang, R. "Oxalic Acid Monothioester for Palladium-Catalyzed Decarboxylative Thiocarbonylation and Hydrothiocarbonylation." *Org. Lett.* **2019**, *21*, 9521−9526.

mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane:EtOAc = 50: 1 as eluent) to afford **3k** (45.0 mg, 77% yield) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 – 8.03 (m, 2H), 7.60 – 7.55 (m, 1H), 7.51 – 7.44 (m, 1H), 4.38 (q, *J* = 7.1 Hz, 2H), 2.66 – 2.57 (m, 1H), 2.05 – 1.96 (m, 2H), 1.85 – 1.78 (m, 2H), 1.71 – 1.64 (m, 1H), 1.58 – 1.47 (m, 2H), 1.39 (t, *J* = 7.1 Hz, 3H), 1.35 – 1.20 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 200.2, 165.8, 139.0, 135.6, 131.5, 130.3, 129.0, 128.6, 61.2, 52.6, 29.5, 25.6, 25.5, 14.3.

HRMS: calculated for $C_{16}H_{20}NaO_3S$ ($M+Na^+$): 315.1025, found 315.1032.



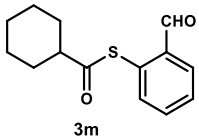
3l

S-(3-methoxyphenyl) cyclohexanecarbothioate (3l): Synthesized according to the General Procedure using cyclohexanecarboxylic acid (25.5 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and 1-iodo-3-methoxybenzene (140.0 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane:EtOAc = 300: 1 as eluent) to afford **3l** (21.5 mg, 42% yield) as a yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.28 (m, 1H), 7.01 – 6.97 (m, 1H), 6.97 – 6.91 (m, 2H), 3.81 (s, 3H), 2.64 – 2.56 (m, 1H), 2.04 – 1.97 (m, 2H), 1.85 – 1.79 (m, 2H), 1.70 – 1.65 (m, 1H), 1.58 – 1.47 (m, 2H), 1.36 – 1.18 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 200.7, 159.8, 129.8, 128.9, 126.8, 119.6, 115.4, 55.4, 52.6, 29.6, 25.6, 25.5.

HRMS: calculated for $C_{14}H_{18}NaO_2S$ ($M+Na^+$): 273.0920, found 273.0923.



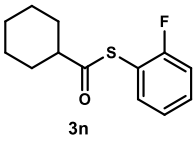
3m

S-(2-formylphenyl) cyclohexanecarbothioate (3m): Synthesized according to the General Procedure using cyclohexanecarboxylic acid (25.5 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and 2-iodobenzaldehyde (139.0 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane:EtOAc = 70: 1 as eluent) to afford **3m** (20.0 mg, 40% yield) as a yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.20 (s, 1H), 8.06 – 8.00 (m, 1H), 7.64 – 7.58 (m, 1H), 7.58 – 7.53 (m, 1H), 7.50 – 7.46 (m, 1H), 2.74 – 2.64 (m, 1H), 2.07 – 1.98 (m, 2H), 1.88 – 1.78 (m, 2H), 1.73 – 1.65 (m, 1H), 1.60 – 1.50 (m, 2H), 1.40 – 1.18 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 199.5, 190.9, 136.9, 136.7, 134.1, 131.3, 130.1, 129.0, 52.8, 29.5, 25.5, 25.4.

HRMS: calculated for $C_{14}H_{16}NaO_2S$ ($M+Na^+$): 271.0763, found 271.0771.



3n

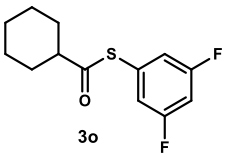
S-(2-fluorophenyl) cyclohexanecarbothioate (3n): Synthesized according to the General Procedure using cyclohexanecarboxylic acid (25.5 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and 1-fluoro-2-iodobenzene (133.0 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane:EtOAc = 300: 1 as eluent) to afford **3n** (45 mg, 95% yield) as a yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.36 (m, 2H), 7.20 – 7.11 (m, 2H), 2.70 – 2.60 (m, 1H), 2.07 – 1.99 (m, 2H), 1.87 – 1.78 (m, 2H), 1.72 – 1.64 (m, 1H), 1.60– 1.50 (m, 2H), 1.39 – 1.20 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 198.9, 162.17 (d, J = 249.2 Hz), 136.8, 131.82 (d, J = 8.1 Hz), 124.55 (d, J = 3.8 Hz), 116.13 (d, J = 22.9 Hz), 115.45 (d, J = 18.7 Hz), 52.5, 29.5, 25.6, 25.5.

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ -106.8.

HRMS: calculated for $C_{13}H_{16}FOS$ ($M+H^+$): 239.0900, found 239.0904.

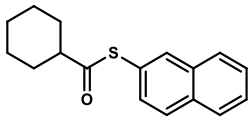


3o

S-(3,5-difluorophenyl) cyclohexanecarbothioate (3o): Synthesized according to the General Procedure using cyclohexanecarboxylic acid (25.5 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and 1,3-difluoro-5-iodobenzene (144.0 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane:EtOAc = 300: 1 as eluent) to afford **3o** (49.2mg, 95% yield) as a yellow liquid.

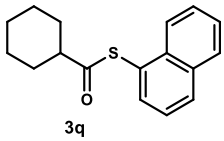
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 – 6.92 (m, 2H), 6.89 – 6.79 (m, 1H), 2.64 – 2.54 (m, 1H), 2.04 – 1.96 (m, 2H), 1.86 – 1.78 (m, 2H), 1.71 – 1.65 (m, 1H), 1.58– 1.46 (m, 2H), 1.38 – 1.20 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 199.0, 162.68 (dd, *J* = 251.1, 12.7 Hz), 131.19 (dd, *J* = 10.2, 10.2 Hz), 117.3 (dd, *J* = 26.3, 12.1 Hz), 104.90 (dd, *J* = 25.1, 25.1 Hz), 52.7, 29.4, 25.5, 25.4.
^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ -109.1.
HRMS: calculated for $C_{13}H_{15}F_2OS$ ($M+H^+$): 257.0806, found 257.0807.



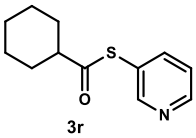
3p

S-(naphthalen-2-yl) cyclohexanecarbothioate (3p): Synthesized according to the General Procedure using cyclohexanecarboxylic acid (25.5 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and 2-iodonaphthalene (152.5 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane:EtOAc = 300: 1 as eluent) to afford **3p** (37.0 mg, 68% yield) as a yellow solid.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 – 7.92 (m, 1H), 7.89 – 7.80 (m, 3H), 7.56 – 7.47 (m, 2H), 7.44 (dd, *J* = 8.5, 1.8 Hz, 1H), 2.71– 2.60 (m, 1H), 2.09 – 2.00 (m, 2H), 1.88 – 1.80 (m, 2H), 1.73 – 1.66 (m, 1H), 1.61 – 1.52 (m, 2H), 1.39 – 1.22 (m, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 201.0, 134.4, 133.6, 133.3, 131.1, 128.64, 127.9, 127.8, 127.0, 126.5, 125.4, 52.6, 29.6, 25.6, 25.5.
HRMS: calculated for $C_{17}H_{18}NaOS$ ($M+Na^+$): 293.0971, found 293.0973.



3q

S-(naphthalen-1-yl) cyclohexanecarbothioate (3q): Synthesized according to the General Procedure using cyclohexanecarboxylic acid (25.5 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and 1-iodonaphthalene (152.5 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane:EtOAc = 300: 1 as eluent) to afford **3q** (34.0 mg, 63% yield) as a yellow solid.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 – 8.11 (m, 1H), 7.97 – 7.84 (m, 2H), 7.74 – 7.64 (m, 1H), 7.60 – 7.46 (m, 3H), 2.80– 2.69 (m, 1H), 2.14 – 2.06 (m, 2H), 1.90 – 1.82 (m, 2H), 1.76 – 1.67 (m, 1H), 1.66 – 1.54 (m, 2H), 1.43 – 1.20 (m, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 200.4, 135.1, 134.4, 134.2, 130.7, 128.6, 127.1, 126.3, 125.6, 125.4, 125.3, 52.7, 29.6, 25.6, 25.6.
HRMS: calculated for $C_{17}H_{18}NaOS$ ($M+Na^+$): 293.0971, found 293.0978.



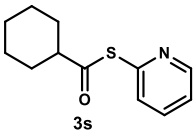
3r

S-(pyridin-3-yl) cyclohexanecarbothioate (3r): Synthesized according to the General Procedure using cyclohexanecarboxylic acid (25.5 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and 3-iodopyridine (123.0 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane:EtOAc = 20: 1 as eluent) to afford **3r** (33.0 mg, 75% yield) as a yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 – 8.47 (m, 2H), 7.74 – 7.67 (m, 1H), 7.33 (dd, *J* = 7.9, 4.7 Hz, 1H), 2.67 – 2.57 (m, 1H), 2.05 – 1.96 (m, 2H), 1.87 – 1.77 (m, 2H), 1.72 – 1.64 (m, 1H), 1.58 – 1.47 (m, 2H), 1.38 – 1.21 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 199.5, 154.2, 149.9, 142.2, 125.6, 123.9, 52.7, 29.5, 25.5, 25.4.

HRMS: calculated for $C_{12}H_{16}NOS$ ($M+H^+$): 222.0947, found 222.0955.



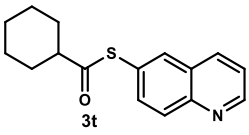
3s

S-(pyridin-2-yl) cyclohexanecarbothioate (3s): Synthesized according to the General Procedure using cyclohexanecarboxylic acid (25.5 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and 2-iodopyridine (123.0 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane:EtOAc = 50: 1 as eluent) to afford **3s** (13.3 mg, 30% yield) as a yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 – 8.58 (m, 1H), 7.76 – 7.69 (m, 1H), 7.62 – 7.56 (m, 1H), 7.29 – 7.26 (m, 1H), 2.69 – 2.58 (m, 1H), 2.06 – 1.98 (m, 2H), 1.86 – 1.79 (m, 2H), 1.70 – 1.66 (m, 1H), 1.58 – 1.48(m, 2H), 1.37 – 1.20 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 199.9, 151.8, 150.4 137.0, 130.3, 123.3, 53.0, 29.4, 25.6, 25.5.

HRMS: calculated for $C_{12}H_{15}NNaOS$ ($M+Na^+$): 244.0767, found 244.0769.

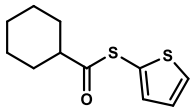


3t

S-(quinolin-6-yl) cyclohexanecarbothioate (3t): Synthesized according to the General Procedure using cyclohexanecarboxylic acid (25.5 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and 6-iodoquinoline (153.0 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane:EtOAc = 15: 1 as eluent) to afford **3t** (29.3 mg, 54% yield) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.95 (dd, *J* = 4.3, 1.7 Hz, 1H), 8.16 – 8.08 (m, 2H), 7.93 (d, *J* = 2.0 Hz, 1H), 7.67 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.43 (dd, *J* = 8.3, 4.2 Hz, 1H), 2.71– 2.61 (m, 1H), 2.10 – 2.00 (m, 2H), 1.87 – 1.80 (m, 2H), 1.73 – 1.66 (m, 1H), 1.60 – 1.50 (m, 2H), 1.40 – 1.20 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 200.4, 151.34, 148.1, 136.0, 134.8, 134.2, 130.2, 128.5, 126.6, 121.6, 52.7, 29.6, 25.6, 25.5.HRMS: calculated for $C_{16}H_{18}NOS$ ($M+H^+$): 272.1104, found 272.1108.



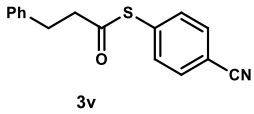
3u

S-(thiophen-2-yl) cyclohexanecarbothioate (3u): Synthesized according to the General Procedure using cyclohexanecarboxylic acid (25.5 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and 2-iodothiophene (126.0 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane:EtOAc = 70: 1 as eluent) to afford **3u** (22.5 mg, 50% yield) as a yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 – 7.51 (m, 1H), 7.15 – 7.12 (m, 1H), 7.12 – 7.08 (m, 1H), 2.66 – 2.56 (m, 1H), 2.04 – 1.97 (m, 2H), 1.86 – 1.78 (m, 2H), 1.70 – 1.63 (m, 1H), 1.58 – 1.47 (m, 2H), 1.36 – 1.20 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 200.5, 135.5, 131.5, 127.7, 125.1, 52.1, 29.4, 25.6, 25.4.

HRMS: calculated for $C_{11}H_{14}NaOS_2$ ($M+Na^+$): 249.0378, found 249.0375.

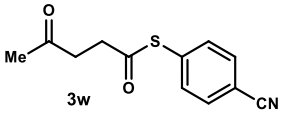


3v

S-(4-cyanophenyl) 3-phenylpropanethioate (3v): Synthesized according to the General Procedure using 3-phenylpropanoic acid (30.0 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and 4-iodobenzonitrile (137.5 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane:EtOAc = 70: 1 as eluent) to afford **3v** (46.0 mg, 86% yield) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 – 7.63 (m, 2H), 7.53 – 7.47 (m, 2H), 7.35 – 7.29 (m, 2H), 7.27 – 7.18 (m, 3H), 3.08 – 2.98 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 194.6, 139.5, 134.6, 134.1, 132.5, 128.7, 128.4, 126.6, 118.2, 113.0, 45.5, 31.3. HRMS: calculated for $C_{16}H_{13}NNaOS$ ($M+Na^+$): 290.0610, found 290.0609.



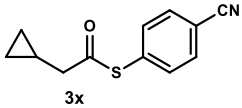
3w

S-(4-cyanophenyl) 4-oxopentanethioate (3w): Synthesized according to the General Procedure using 4-oxopentanoic acid (23.0 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and 4-iodobenzonitrile (137.5 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane:EtOAc = 10: 1 as eluent) to afford **3w** (37.3 mg, 80% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 – 7.63 (m, 2H), 7.55 – 7.49 (m, 2H), 2.98 (t, *J* = 6.5 Hz, 2H), 2.83 (t, *J* = 6.4 Hz, 2H), 2.19 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 205.7, 194.7, 134.7, 133.9, 132.5, 118.2, 113.0, 37.9, 37.5, 29.8.

HRMS: calculated for $C_{12}H_{11}NNaO_2S$ ($M+Na^+$): 256.0403, found 256.0403.



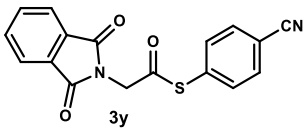
3x

S-(4-cyanophenyl) 2-cyclopropylethanethioate (3x): Synthesized according to the General Procedure using 2-cyclopropylacetic acid (20.0 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and 4-iodobenzonitrile (137.5 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane:EtOAc = 70: 1 as eluent) to afford **3x** (32.0 mg, 74% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 – 7.64 (m, 2H), 7.57 – 7.50 (m, 2H), 2.56 (d, *J* = 7.2 Hz, 2H), 1.17 – 1.04 (m, 1H), 0.72 – 0.60 (m, 2H), 0.35 – 0.21 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 195.2, 134.7, 134.5, 132.4, 118.3, 112.9, 48.9, 7.2, 5.0.

HRMS: calculated for $C_{12}H_{11}NNaOS$ ($M+Na^+$): 240.0454, found 240.0462.



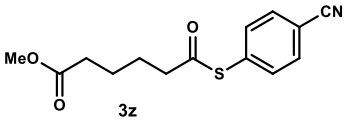
3y

S-(4-cyanophenyl) 2-(1,3-dioxoisoindolin-2-yl)ethanethioate (3y): Synthesized according to the General Procedure using 2-(1,3-dioxoisoindolin-2-yl)acetic acid (41.0 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and 4-iodobenzonitrile (137.5 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane:EtOAc = 10: 1 as eluent) to afford **3y** (45.1 mg, 70% yield) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 – 7.89 (m, 2H), 7.81 – 7.75 (m, 2H), 7.70 – 7.64 (m, 2H), 7.58 – 7.52 (m, 2H), 4.72 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 190.6, 167.2, 135.0, 134.6, 132.7, 132.2, 131.8, 123.9, 118.0, 113.6, 46.5.

HRMS: calculated for $C_{17}H_{10}N_2NaO_3S$ ($M+Na^+$): 345.0304, found 345.0304.

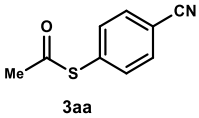


Methyl 6-((4-cyanophenyl)thio)-6-oxohexanoate (3z): Synthesized according to the General Procedure using 6-methoxy-6-oxohexanoic acid (32.0 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and 4-iodobenzonitrile (137.5 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane:EtOAc = 20: 1 as eluent) to afford **3z** (28.3 mg, 51% yield) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 – 7.64 (m, 2H), 7.55 – 7.49 (m, 2H), 3.67 (s, 3H), 2.72 (t, *J* = 7.0 Hz, 2H), 2.35 (t, *J* = 7.0 Hz, 2H), 1.80 – 1.65 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 195.0, 173.5, 134.6, 134.1, 132.5, 118.2, 113.0, 51.6, 43.6, 33.5, 24.8, 24.1.

HRMS: calculated for $C_{14}H_{15}NNaO_3S$ ($M+Na^+$): 300.0665, found 300.0665.

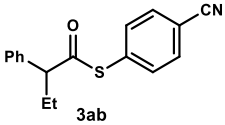


S-(4-cyanophenyl) ethanethioate (3aa): Synthesized according to the General Procedure using acetic acid (12.0 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and 4-iodobenzonitrile (137.5 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane:EtOAc = 100: 1 as eluent) to afford **3aa** (27.5 mg, 77% yield) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 – 7.64 (m, 2H), 7.56 – 7.50 (m, 2H), 2.46 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 191.8, 134. 6, 134.3, 132.5, 118.2, 113.0, 30.5.

HRMS: calculated for C_9H_7NNaOS ($M+Na^+$): 200.0141, found 200.0141.



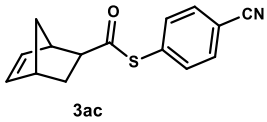
S-(4-cyanophenyl) 2-phenylbutanethioate (3ab): Synthesized according to the General Procedure using 2-phenylbutanoic acid (33.0 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and 4-iodobenzonitrile (137.5 mg, 0.6 mmol, 3.0 equiv.). The

crude mixture was purified by flash column chromatography on silica gel (Hexane:EtOAc = 70: 1 as eluent) to afford **3ab** (50.0 mg, 89% yield) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 – 7.60 (m, 2H), 7.49 – 7.44 (m, 2H), 7.41 – 7.30 (m, 5H), 3.76 (t, *J* = 7.5 Hz, 1H), 2.29 – 2.14 (m, 1H), 1.97 – 1.82 (m, 1H), 0.94 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 196.6, 137.5, 134.5, 134.5, 132.4, 128.92, 128.4, 127.9, 118.2, 112.8, 62.4, 26.9, 12.1.

HRMS: calculated for $C_{17}H_{15}NNaOS$ ($M+Na^+$): 304.0767, found 304.0770.



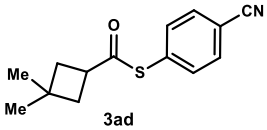
3ac

S-(4-cyanophenyl) (1R,4R)-bicyclo[2.2.1]hept-5-ene-2-carbothioate (3ac): Synthesized according to the General Procedure using (1R,4R)-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid (27.5 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and 4-iodobenzonitrile (137.5 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane:EtOAc = 100: 1 as eluent) to afford **3ac** (32.0 mg, 63% yield) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 – 7.61 (m, 2H), 7.53 – 7.45 (m, 2H), 6.23 (dd, *J* = 5.7, 3.1 Hz, 1H), 5.99 (dd, *J* = 5.7, 2.8 Hz, 1H), 3.40 – 3.30 (m, 2H), 3.00 – 2.95 (m, 1H), 1.99 – 1.90 (m, 1H), 1.60 – 1.49 (m, 2H), 1.38 – 1.32 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 196.7, 138.3, 134.7, 134.6, 132.4, 131.6, 118.3, 112.6, 53.4, 49.59, 47.3, 42.8, 29.7.

HRMS: calculated for $C_{15}H_{13}NNaOS$ ($M+Na^+$): 278.0610, found 278.0609.



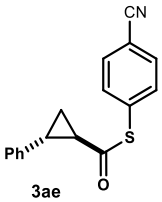
3ad

S-(4-cyanophenyl) 3,3-dimethylcyclobutane-1-carbothioate (3ad): Synthesized according to the General Procedure using 3,3-dimethylcyclobutane-1-carboxylic acidacid (25.5 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and 4-iodobenzonitrile (137.5 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane:EtOAc = 200: 1 as eluent) to afford **3ad** (35.0 mg, 81% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 – 7.63 (m, 2H), 7.55 – 7.50 (m, 2H), 3.45 – 3.34 (m, 1H), 2.20 – 2.13 (m, 2H), 2.09 – 2.01 (m, 2H), 1.19 (s, 3H), 1.10 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 197.8, 134.6, 134.6, 132.4, 118.3, 112.67, 40.7, 38.4, 31.9, 29.9, 28.3.

HRMS: calculated for C14H15NNaOS ($M+Na^+$): 268.0767, found 268.0774.



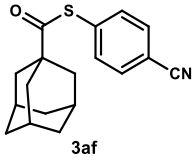
3ae

S-(4-cyanophenyl) (1R,2R)-2-phenylcyclopropane-1-carbothioate (3ae): Synthesized according to the General Procedure using (1R,2R)-2-phenylcyclopropane-1-carboxylic acid (32.5 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and 4-iodobenzonitrile (137.5 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane:EtOAc = 100: 1 as eluent) to afford **3ae** (41.5 mg, 74% yield) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 – 7.66 (m, 2H), 7.61 – 7.53 (m, 2H), 7.35 – 7.29 (m, 2H), 7.27 – 7.22 (m, 1H), 7.16 – 7.10 (m, 2H), 2.78 – 2.70 (m, 1H), 2.37 – 2.30 (m, 1H), 1.88 – 1.81 (m, 1H), 1.59 – 1.52 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 193.7, 139.1, 134.6, 134.2, 132.5, 128.67, 127.0, 126.3, 118.2, 113.0, 33.6, 29.5, 19.5.

HRMS: calculated for $C_{17}H_{13}NNaOS$ ($M+Na^+$): 302.0610, found 302.0612.



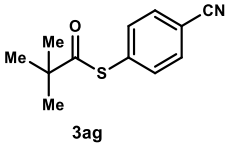
3af

S-(4-cyanophenyl) (3r,5r,7r)-adamantane-1-carbothioate (3af): Synthesized according to the General Procedure using (3r,5r,7r)-adamantane-1-carboxylic acid (36.0 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and 4-iodobenzonitrile (137.5 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane:EtOAc = 100: 1 as eluent) to afford **3af** (53.6 mg, 90% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 – 7.62 (m, 2H), 7.54 – 7.45 (m, 2H), 2.12 – 2.06 (m, 3H), 2.01 – 1.96 (m, 6H), 1.80 – 1.68 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 202.2, 135.3, 134.9, 132.3, 118.4, 112.6, 49.5, 39.2, 36.3, 28.2.

HRMS: calculated for $C_{18}H_{19}NNaOS$ ($M+Na^+$): 240.0454, found 240.0462.



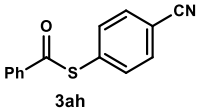
3ag

S-(4-cyanophenyl) 2,2-dimethylpropanethioate (3ag): Synthesized according to the General Procedure using pivalic acid (20.5 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and 4-iodobenzonitrile (137.5 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane:EtOAc = 100: 1 as eluent) to afford **3ag** (39.0 mg, 89% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 – 7.63 (m, 2H), 7.53 – 7.48 (m, 2H), 1.32(s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 202.7, 135.2, 134.8, 132.3, 118.3, 112.7, 47.4, 27.3.

HRMS: calculated for $C_{12}H_{13}NNaOS$ ($M+Na^+$): 242.0610, found 242.0605.



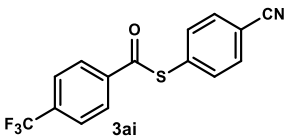
3ah

S-(4-cyanophenyl) benzothioate (3ah): Synthesized according to the General Procedure using benzoic acid (24.5 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and 4-iodobenzonitrile (137.5 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane:EtOAc = 70: 1 as eluent) to afford **3ah** (35.4 mg, 74% yield) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 – 7.97 (m, 2H), 7.75 – 7.69 (m, 2H), 7.68 – 7.61 (m, 3H), 7.55 – 7.48 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 188.2, 136.1, 135.3, 134.3, 134.0, 132.5, 129.0, 127.6, 118.3, 113.1.

Matching reported literature data. [29]



3ai

S-(4-cyanophenyl) 4-(trifluoromethyl)benzothioate (3ai): Synthesized according to the General Procedure using 4-(trifluoromethyl)benzoic acid (38.0 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and 4-iodobenzonitrile (137.5 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane:EtOAc = 100: 1 as eluent) to afford **3ai** (37.0 mg, 60% yield) as a white solid.

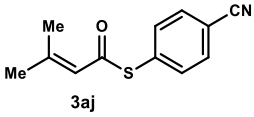
[29] Xu, J.-X.; Wang, L.-C.; Wu, X.-F. "Palladium-Catalyzed Desulfonative Carbonylation of Thiosulfonates: Elimination of SO2 and Insertion of CO." *Org. Lett.* **2022**, 24, 4820−4824.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 – 8.08 (m, 2H), 7.82 – 7.72 (m, 4H), 7.69 – 7.62 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 187.5, 138.8, 135.8 (q, *J* = 32.9 Hz), 135.28, 133.1, 132.7, 128.0, 126.1 (q, *J* = 3.7 Hz), 123.4 (q, *J* = 272.9 Hz), 118.1, 113.6.

19F{1H} NMR (376 MHz, CDCl3) δ -63.3.

HRMS: calculated for $C_{15}H_8F_3NNaOS$ ($M+Na^+$): 330.0171, found 330.0176.



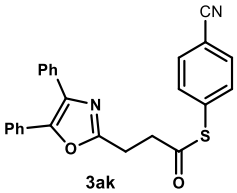
3aj

S-(4-cyanophenyl) 3-methylbut-2-enethioate (3aj): Synthesized according to the General Procedure using 3-methylbut-2-enoic acid (20.0 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and 4-iodobenzonitrile (137.5 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane:EtOAc = 100: 1 as eluent) to afford **3aj** (35.0 mg, 81% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 – 7.64 (m, 2H), 7.57 – 7.52 (m, 2H), 6.07 – 6.02 (m, 1H), 2.16 (d, *J* = 1.2 Hz, 3H), 1.94 (d, *J* = 1.3 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 184.9, 157.7, 135.2, 134.8, 132.3, 121.9, 118.4, 112.6, 27.5, 21.6.

HRMS: calculated for $C_{12}H_{11}NNaOS$ ($M+Na^+$): 240.0454, found 240.0460.



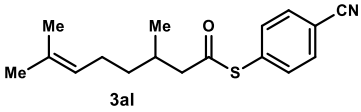
3ak

S-(4-cyanophenyl) 3-(4,5-diphenyloxazol-2-yl)propanethioate (3ak): Synthesized according to the General Procedure using 3-(4,5-diphenyloxazol-2-yl)propanoic acid (59.0 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and 4-iodobenzonitrile (137.5 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane:EtOAc = 15: 1 as eluent) to afford **3ak** (49.3 mg, 60% yield) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 – 7.60 (m, 4H), 7.60 – 7.52 (m, 4H), 7.40 – 7.30 (m, 6H), 3.35 – 3.22 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 193.9, 160.9, 145.7, 135.2, 134.7, 133.7, 132.6, 132.3, 128.8, 128.7, 128.6, 128.6, 128.2, 127.9, 126.5, 118.2, 113.1, 40.4, 23.6.

HRMS: calculated for $C_{25}H_{18}N_2NaO_2S$ ($M+Na^+$): 433.0981, found 433.0991.



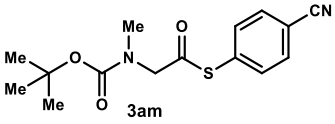
3al

S-(4-cyanophenyl) 3,7-dimethyloct-6-enethioate (3al): Synthesized according to the General Procedure using 3,7-dimethyloct-6-enoic acid (34.1 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and 4-iodobenzonitrile (137.5 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane:EtOAc = 100: 1 as eluent) to afford **3al** (46.5 mg, 81% yield) as a yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 – 7.64 (m, 2H), 7.55 – 7.48 (m, 2H), 5.12 – 5.03 (m, 1H), 2.69 (dd, *J* = 14.8, 5.9 Hz, 1H), 2.50 (dd, *J* = 14.8, 8.1 Hz, 1H), 2.12 – 1.93 (m, 3H), 1.68 (s, 3H), 1.61 (s, 3H),1.45 – 1.35 (m, 1H), 1.32 – 1.22 (m, 1H), 1.00 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 194.9, 134.5, 134.5, 132.4, 131.9, 123.92, 118.2, 112.8, 51.2, 36.6, 30.8, 25.7, 25.4, 19.5, 17.7.

HRMS: calculated for $C_{17}H_{21}NNaOS$ ($M+Na^+$): 310.1236, found 310.1246.



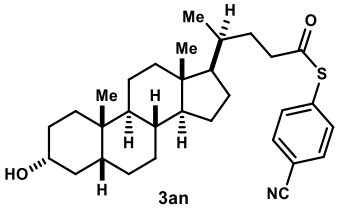
3am

S-(4-cyanophenyl) 2-((tert-butoxycarbonyl)(methyl)amino)ethanethioate (*rotamer = 1:1*) (3am): Synthesized according to the General Procedure using N-(tert-butoxycarbonyl)-N-methylglycine (38.0 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and 4-iodobenzonitrile (137.5 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane:EtOAc = 15: 1 as eluent) to afford **3am** (46.0 mg, 75% yield) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 – 7.64 (m, 4H), 7.56 – 7.48 (m, 4H), 4.22 (s, 2H), 4.13 (s, 2H), 3.04 (s, 3H), 3.01 (s, 3H), 1.50 (s, 9H), 1.48 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 195.3, 195.1, 155.8, 154.8, 135.0, 134.8, 133.6, 132.6, 132.5, 118.2, 113.2, 113.1, 81.2, 81.0, 59.2, 58.5, 36.2, 36.2, 28.3.

HRMS: calculated for $C_{15}H_{18}N_2NaO_3S$ ($M+Na^+$): 329.0930, found 329.0929.



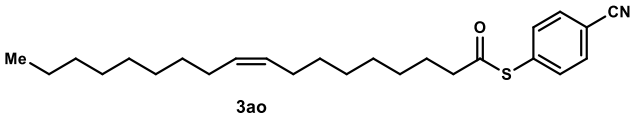
3an

S-(4-cyanophenyl) (S)-4-((3R,5R,8R,9S,10S,13R,14S,17R)-3-hydroxy-10,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)pentanethioate (3an): Synthesized according to the General Procedure using (S)-4-((3R,5R,8R,9S,10S,13R,14S,17R)-3-hydroxy-10,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)pentanoic acid (75.5 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and 4-iodobenzonitrile (137.5 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane:EtOAc = 10: 1 as eluent) to afford **3an** (85.0 mg, 86% yield) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 – 7.63 (m, 2H), 7.54 – 7.49 (m, 2H), 3.66 – 3.56 (m, 1H), 2.76 – 2.66 (m, 1H), 2.64 – 2.54 (m, 1H), 1.98 – 1.90 (m, 1H), 1.88 – 1.72 (m, 5H), 1.67 – 1.62 (m, 1H), 1.60 – 1.53 (m, 1H), 1.52 – 1.32 (m, 9H), 1.30 – 1.20 (m, 4H), 1.15 – 1.01 (m, 5H), 0.95 – 0.92 (m, 1H), 0.93 (d, *J* = 6.2 Hz, 3H), 0.90 (s, 3H), 0.63 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 195.9, 134.6, 134.5, 132.4, 118.2, 112.8, 71.8, 56.5, 55.8, 42.8, 42.1, 41.2, 40.4, 40.2, 36.4, 35.8, 35.4, 35.3, 34.6, 31.5, 30.5, 28.2, 27.2, 26.4, 24.2, 23.4, 20.8, 18.4, 12.1.

HRMS: calculated for $C_{31}H_{43}NNaO_2S$ ($M+Na^+$): 516.2907, found 516.2909.



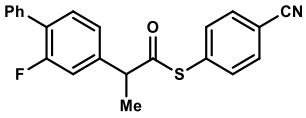
3ao

S-(4-cyanophenyl) (Z)-octadec-9-enethioate (3ao): Synthesized according to the General Procedure using oleic acid (56.5 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and 4-iodobenzonitrile (137.5 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane:DCM = 10: 1 as eluent) to afford **3ao** (52.0 mg, 65% yield) as a yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 – 7.64 (m, 2H), 7.55 – 7.48 (m, 2H), 5.44 – 5.27 (m, 2H), 2.68 (t, *J* = 7.5 Hz, 2H), 2.08 – 1.93 (m, 3H), 1.77 – 1.66 (m, 2H), 1.41 – 1.19 (m, 21H), 0.88 (t, *J* = 6.8 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 195.4, 134.6, 132.4, 130.6 130.1, 129.7, 118.2, 112.8, 44.1, 32.61, 32.5, 31.9, 29.8, 29.7, 29.5, 29.3, 29.1, 29.0, 28.9, 27.2, 27.1, 25.5, 22.7, 14.1.

HRMS: calculated for $C_{25}H_{37}NNaOS$ ($M+Na^+$): 422.2488, found 422.2502.



3ap

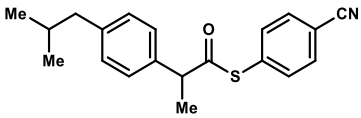
S-(4-cyanophenyl) 2-(2-fluoro-[1,1'-biphenyl]-4-yl)propanethioate (3ap): Synthesized according to the General Procedure using 2-(2-fluoro-[1,1'-biphenyl]-4-yl)propanoic acid (49.0 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and 4-iodobenzonitrile (137.5 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane:EtOAc = 70: 1 as eluent) to afford **3ap** (48.0 mg, 66% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 – 7.63 (m, 2H), 7.58 – 7.54 (m, 2H), 7.53 – 7.42 (m, 5H), 7.41 – 7.35 (m, 1H), 7.24– 7.14 (m, 2H), 4.04 (q, *J* = 7.1 Hz, 1H), 1.64 (d, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 196.6, 159.8 (d, *J* = 249.2 Hz), 140.0 (d, *J* = 7.6 Hz), 135.2, 134.6, 134.1, 132.5, 131.2 (d, *J* = 4.0 Hz), 128.7 (d, *J* = 13.6 Hz) 128.5, 129.0 (d, *J* = 2.9 Hz), 127.9, 124.1 (d, *J* = 3.4 Hz), 118.2, 115.7 (d, *J* = 23.8 Hz), 113.0, 53.90 (d, *J* = 1.5 Hz), 18.4.

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ -116.9.

HRMS: calculated for $C_{22}H_{16}FNNaOS$ ($M+Na^+$): 384.0829, found 384.0826.



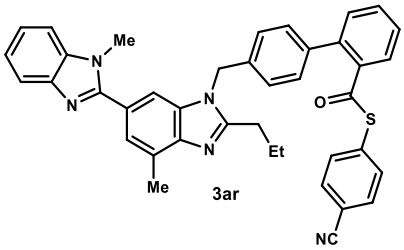
3aq

S-(4-cyanophenyl) 2-(4-isobutylphenyl)propanethioate (3aq): Synthesized according to the General Procedure using 2-(4-isobutylphenyl)propanoic acid (41.0 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and 4-iodobenzonitrile (137.5 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane:EtOAc = 100: 1 as eluent) to afford **3aq** (54.5 mg, 84% yield) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 – 7.60 (m, 2H), 7.50 – 7.43 (m, 2H), 7.28 – 7.22 (m, 2H), 7.18 – 7.12 (m, 2H), 3.97 (q, *J* = 7.1 Hz, 1H), 2.48 (d, *J* = 7.2 Hz, 2H), 1.93 – 1.80 (m, 1H),1.59 (d, *J* = 7.1 Hz, 3H), 0.91 (d, *J* = 6.6 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 197.4, 141.5, 136.0, 134.7, 134.6, 132.4, 129.7, 127.8, 118.3, 112.7, 54.3, 45.1, 30.2, 22.4, 18.4.

HRMS: calculated for $C_{20}H_{21}NNaOS$ ($M+Na^+$): 346.1236, found 346.1239.



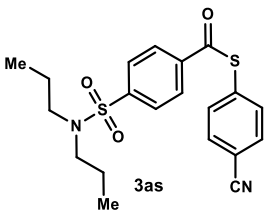
3ar

S-(4-cyanophenyl) 4'-((1,7'-dimethyl-2'-propyl-1H,3'H-[2,5'-bibenzo[d]imidazol]-3'-yl)methyl)-[1,1'-biphenyl]-2-carbothioate (3ar): Synthesized according to the General Procedure using 4'-((1,7'-dimethyl-2'-propyl-1H,3'H-[2,5'-bibenzo[d]imidazol]-3'-yl)methyl)-[1,1'-biphenyl]-2-carboxylic acid (103.0 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and 4-iodobenzonitrile (137.5 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (EtOAc as eluent) to afford **3ar** (95.0 mg, 75% yield) as a yellow solid.

^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 7.72 – 7.54 (m, 6H), 7.50 – 7.43 (m, 2H), 7.42 – 7.28 (m, 6H), 7.23 – 7.14 (m, 4H), 5.54 (s, 2H), 3.70 (s, 3H), 2.87 (t, *J* = 7.6 Hz, 2H), 2.65 (s, 3H), 1.90 – 1.76 (m, 2H), 0.94 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $(CD_3)_2CO$) δ 190.8, 156.2, 154.4, 143.4, 143.1, 139.7, 139.2, 137.6, 137.0, 136.8, 135.1, 134.8, 134.2, 132.6, 132.1, 130.9, 129.4, 128.9, 127.9, 127.8, 126.8, 123.90, 123.5, 122.1, 121.8, 119.0, 117.9 112.8, 109.9, 109.1, 46.4, 38.0, 31.4, 20.9, 16.0, 13.5.

HRMS: calculated for $C_{40}H_{34}N_5OS$ ($M+H^+$): 632.2479, found 632.2485.



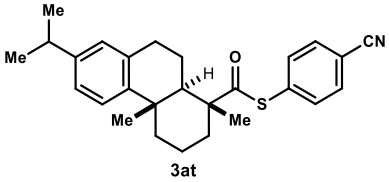
3as

S-(4-cyanophenyl) 4-(N,N-dipropylsulfamoyl)benzothioate (3as): Synthesized according to the General Procedure using 4-(N,N-dipropylsulfamoyl)benzoic acid (57.0 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and 4-iodobenzonitrile (137.5 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane:EtOAc = 20: 1 as eluent) to afford **3as** (31.0 mg, 38% yield) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 – 8.08 (m, 2H),7.96 – 7.91 (m, 2H), 7.78 – 7.72 (m, 2H), 7.67 – 7.62 (m, 2H), 3.15 – 3.09 (m, 4H), 1.61 – 1.51 (m, 4H), 0.88 (t, *J* = 7.4 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 187.4, 145.4, 138.7, 135.3, 133.0, 132.7, 128.2, 127. 6, 118.1, 113.6, 50.0, 22.0, 11.2.

HRMS: calculated for $C_{20}H_{23}N_2O_3S_2$ ($M+Na^+$): 403.1145, found 403.1151.



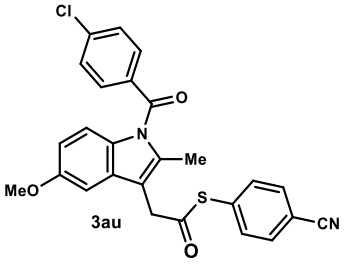
3at

S-(4-cyanophenyl) (1R,4aS,10aR)-7-isopropyl-1,4a-dimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene-1-carbothioate (3at): Synthesized according to the General Procedure using (1R,4aS,10aR)-7-isopropyl-1,4a-dimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene-1-carboxylic acid (60.0 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and 4-iodobenzonitrile (137.5 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane:EtOAc = 200: 1 as eluent) to afford **3at** (39.0 mg, 46% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 – 7.64 (m, 2H), 7.54 – 7.47 (m, 2H), 7.19 (d, *J* = 8.2 Hz, 1H), 7.04 (dd, *J* = 8.3, 2.0 Hz, 1H), 6.94 – 6.89 (m, 1H), 3.03 – 2.79 (m, 3H), 2.40 – 2.27 (m, 2H), 1.96 – 1.75 (m, 5H), 1.63 – 1.51 (m, 2H), 1.41 (s, 3H), 1.27 (s, 3H), 1.24 (d, *J* = 7.0 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 203.9, 146.4, 146.0, 135.5, 135.3, 134.5, 132.4, 127.0, 124.2, 124.1, 118.3, 112.7, 56.1, 45.7, 37.8, 37.7, 37.4, 33.5, 30.0, 25.5, 24.0, 24.0, 21.7, 18.7, 16.8.

HRMS: calculated for $C_{27}H_{31}NNaOS$ ($M+Na^+$): 440.2019, found 440.2007.



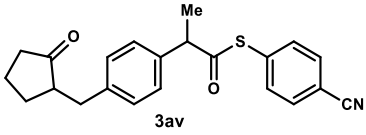
3au

S-(4-cyanophenyl) 2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)ethanethioate (3au): Synthesized according to the General Procedure using 2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid (71.5 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and 4-iodobenzonitrile (137.5 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane:EtOAc = 20: 1 as eluent) to afford **3au** (66.5 mg, 70% yield) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 – 7.63 (m, 4H), 7.52 – 7.46 (m, 4H), 6.97 (d, *J* = 2.5 Hz, 1H), 6.88 (d, *J* = 9.0 Hz, 1H), 6.71 (dd, *J* = 9.0, 2.5 Hz, 1H), 3.99 (s, 2H), 3.85 (s, 3H), 2.47 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 193.5, 168.3, 156.3, 139.6, 137.3, 134.6, 134.2, 133.6, 132.5, 131.3, 130.9, 130.3, 129.2, 118.1, 115.1, 113.0, 111.9, 111.0, 101.2, 55.8, 39.4, 13.5.

HRMS: calculated for $C_{26}H_{20}ClN_2O_3S$ ($M+H^+$): 475.0878, found 475.0870.



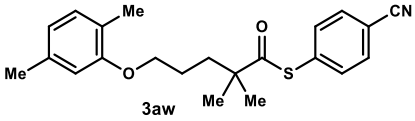
3av

S-(4-cyanophenyl) 2-(4-((2-oxocyclopentyl)methyl)phenyl)propanethioate (3av): Synthesized according to the General Procedure using 2-(4-((2-oxocyclopentyl)methyl)phenyl)propanoic acid (49.0 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and 4-iodobenzonitrile (137.5 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane:EtOAc = 15: 1 as eluent) to afford **3av** (66.0 mg, 90% yield, 1:1 *d.r.*) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 – 7.59 (m, 2H), 7.49 – 7.43 (m, 2H), 7.28 – 7.22 (m, 2H), 7.20 – 7.14 (m, 2H), 3.97 (q, *J* = 7.0 Hz, 1H), 3.14 (dd, *J* = 13.9, 4.1 Hz, 1H), 2.53 (dd, *J* = 13.9, 9.4 Hz, 1H), 2.39 – 2.28 (m, 2H), 2.16 – 2.04 (m, 2H), 2.00 – 1.90 (m, 1H), 1.80 – 1.65 (m, 1H), 1.60 – 1.50 (m, 1H), 1.57 (d, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 220.0, 197.3, 139.9, 136.6, 134.6, 132.4, 129.5, 128.2, 118.2, 112.8, 54.2, 50.9, 38.2, 35.3, 29.3, 20.6, 18.4.

HRMS: calculated for $C_{22}H_{21}NNaO_2S$ ($M+Na^+$): 386.1185, found 386.1195.



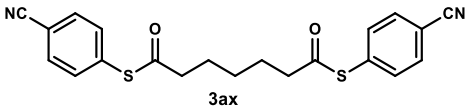
3aw

S-(4-cyanophenyl) 5-(2,5-dimethylphenoxy)-2,2-dimethylpentanethioate (3aw): Synthesized according to the General Procedure using 5-(2,5-dimethylphenoxy)-2,2-dimethylpentanoic acid (50.0 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and 4-iodobenzonitrile (137.5 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane:EtOAc = 100: 1 as eluent) to afford **3aw** (66.4 mg, 90% yield) as a yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 – 7.63 (m, 2H), 7.51 – 7.44 (m, 2H), 7.03 (d, *J* = 7.4 Hz, 1H), 6.69 (d, *J* = 6.8 Hz, 1H), 6.63 (s, 1H), 3.97 (t, *J* = 5.8 Hz, 2H), 2.32 (s, 3H), 2.21 (s, 3H), 1.91 – 1.76 (m, 4H), 1.37 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 202.3, 156.8, 136.5, 135.3, 134.7, 132.4, 130.4, 123.6, 120.9, 118.3, 112.8, 111.9, 67.5, 50.6, 37.6, 25.3, 24.9, 21.5, 15.9.

HRMS: calculated for $C_{22}H_{25}NNaO_2S$ ($M+Na^+$): 390.1498, found 390.1510.



3ax

S,S-bis(4-cyanophenyl) heptanebis(thioate) (3ax): Synthesized according to the General Procedure using heptanedioic acid (32.0 mg, 0.2 mmol, 1.0 equiv.), 1,1,3,3-tetramethylthiourea (79.5 mg, 0.6 mmol, 3.0 equiv.) and 4-iodobenzonitrile (137.5 mg, 0.6 mmol, 3.0 equiv.). The crude mixture was purified by flash column chromatography on silica gel (Hexane:EtOAc = 20: 1 as eluent) to afford **3ax** (55.0 mg, 70% yield) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 – 7.64 (m, 4H), 7.54 – 7.48 (m, 4H), 2.71 (t, *J* = 7.4 Hz, 4H), 1.79 – 1.71 (m, 4H), 1.50 – 1.40 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 195.1, 134.6, 134.1, 132.5, 118.2, 112.9, 43.7, 28.1, 25.0.

HRMS: calculated for $C_{21}H_{18}N_2NaO_2S_2$ ($M+Na^+$): 417.0702, found 417.0701.

Unsuccessful Substrates

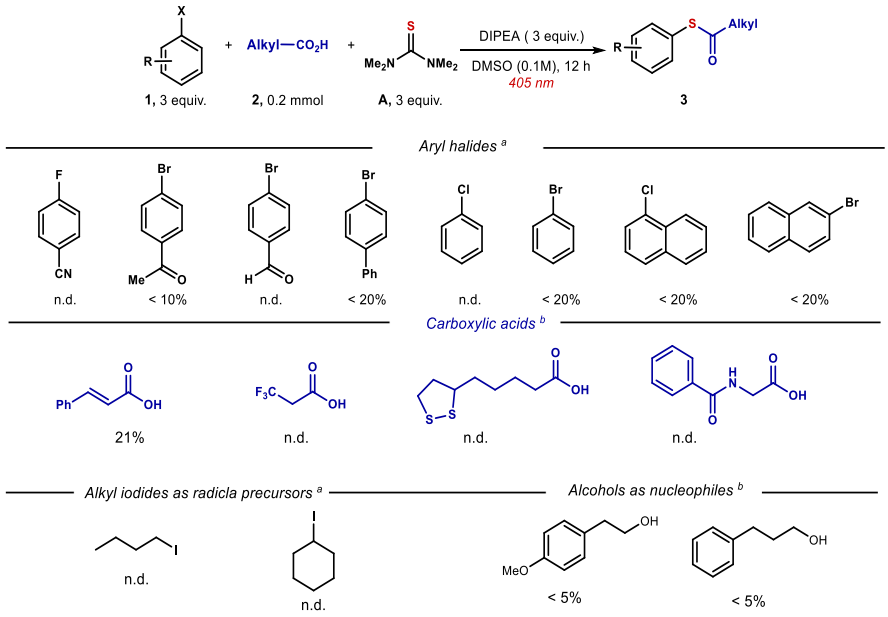


Figure 4.21. Unsuccessful and poorly reactive aryl halides and carboxylic acids, n.d. = product not detected. [a] cyclohexanecarboxylic acid was used as nucleophile while testing various aryl halides or alkyl iodies. [b] 4-iodobenzonitrile was used as radical precursor while testing various carboxylic acids or alcohols.

4.6.3 Mechanistic Studies

Capture of Radical Intermediate

An attempt to trap the aryl radical was conducted by adding ethene-1,1-diyldibenzene to the standard reaction. After 12 hours, thioester **3a** was the main product. Additionally, a product resulting from the addition of the phenyl radical to ethene-1,1-diyldibenzene was also detected, providing strong support for the generation of the aryl radical (Figure 4.22).

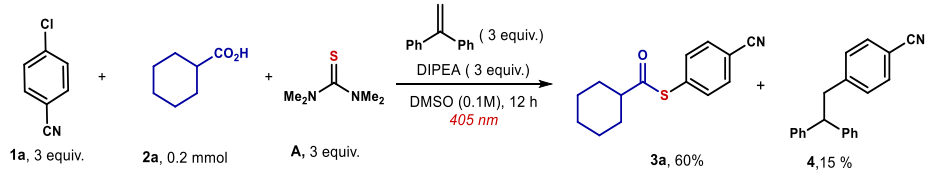
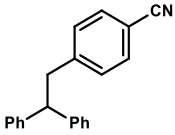


Figure 4.22. Capture of aryl radical with ethene-1,1-diyldibenzene.



4-(2,2-diphenylethyl)benzonitrile (15):

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.42 (m, 2H), 7.30 – 7.24 (m, 4H), 7.22– 7.15 (m, 6H), 7.11 – 7.06 (m, 2H), 4.20 (t, *J* = 7.9 Hz, 1H), 3.42 (d, *J* = 7.9 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 146.0, 143.6, 131.9, 130.0, 128.6, 127.90, 126.6, 119.0, 109.9, 52.8, 42.2.

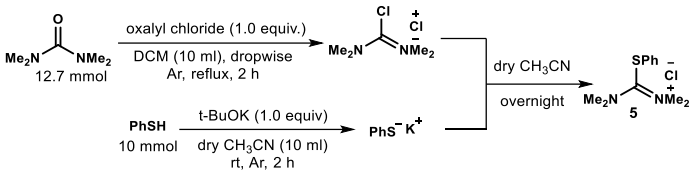
Matching reported literature data.[30]

Reactions between a Preformed Aryl Isothiourea Salt and the Carboxylic Acid

- *preparation of Aryl Isothiouronium salts* ***16***[31]*:*

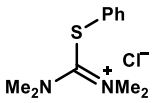
[30]Li, H.; Li, S.; Hu, H.; Sun, R.; Liu, M.; Ding, A.; Liu, X.; Luo, W.; Fu, Z.; Cai, Guo. S. "Visible-light-Induced C(sp^3)–C(sp^3) Bond Formation via Radical/Radical Cross-Coupling." *Chem. Commun.* **2023**, *59*, 1205–1208.

[31]Biancalana, S.; Hudson, D.; Songster, M. F.; Thompson, S. A. "Fmoc Chemistry Compatible Thio-Ligation Assembly of Proteins." *Letters in Peptide Science*. **2001**, *7*, 291.



All manipulations were performed in anhydrous conditions under argon. Oxalyl chloride (1.1 mL, 1.0 equiv.) was added dropwise via syringe to a stirred solution of tetramethylurea (15.25 mL, 12.7 mmol) in DCM (10 mL). The reaction was refluxed for 2 hours, cooled to room temperature, and anhydrous ether (30 mL) was added. The tightly stoppered flask was refrigerated for 2 hours, then the precipitated intermediate was isolated by filtration under argon, and washed 3 times with anhydrous ether. In a separate flask, thiophenol (1.05 mL, 10 mmol) in dry acetonitrile (10 mL) was stirred vigorously and treated with potassium *tert*-butoxide (1.2 g). After 2 hours, the deprotonation reaction of thiophenol was evaporated to dryness in vacuo, and dried for a further 2 hours.

The filtered chloro-uronium salt without further drying, was mixed with newly obtained thiolate and washed in with 10 mL dry acetonitrile, and stirred vigorously. An exothermic reaction started immediately. The reaction was stirred overnight and resulting mixture was filtered (to remove precipitated KCl), and the residue washed 3 x with 5 mL dry acetonitrile. The filtrates were evaporated, anhydrous ether (~20 mL) added to the oily residue, and then refrigerated. After 2 hours, the crude product was isolated and washed with dry ether. The material was suspended in acetone (15 mL), sonicated and vortexed, which effectively extracted a yellow impurity from the product. The mixture was refrigerated, and the product isolated by filtration was washed with cold acetone and dried. The isothiourea salt **16** was obtained as white solid in 82% yield (*which is sensitive to moisture, and therefore should be stored carefully under dry condition*).



1,1,3,3-tetramethyl-2-phenylisothiouronium chloride (16):

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.42 (m, 2H), 7.42 – 7.32 (m, 3H), 3.30 (s, 12H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.1, 131.7, 130.6, 130.0, 127.8, 44.8.

Matching reported literature data.[32]

*- thioesterification from preformed phenyl isothiouronium salt **16** and carboxylic acid **2a**:*

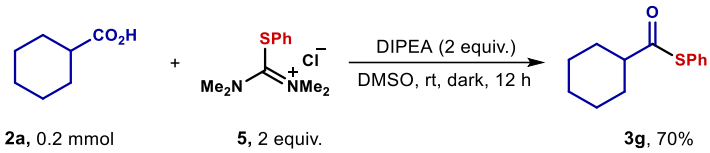


Figure 4.23. Thioetherification from prepared aryl isothiouronium salt **16** and carboxylic acid **2a**.

The carboxylic acid **2a** was converted into the corresponding thioester **3g** by reacting with isothiouronium salt **16** under dark conditions (**Figure 4.23**). This confirmed that the polar deoxythiolation path can provide the desired thioester.

Photophysical Studies

Sample Preparation:

A 25 mL glass vial containing 1,1,3,3-tetramethylthiourea **A** (0.01 mmol) was sealed with a septum, vacuumed and backfilled with argon for 3 times, then degassed DMSO or CH_3CN (5 mL, HPLC grade) was added via syringe to provide a $2 \cdot 10^{-3}$ M stock solution of catalyst. 200 µL of the stock solution were taken and diluted further with DMSO or CH_3CN (4 mL) to obtain a $0.95 \cdot 10^{-4}$ M solution. 2.5 mL of the solution was transferred into an argon filled quartz cuvette (10 x 10 mm light path) equipped with a septum.

Absorption Studies

UV-Vis measurements were carried out on an Agilent Cary 60 UV-Vis spectrophotometer equipped with two silicon diode detectors, double beam optics and Xenon pulse light.

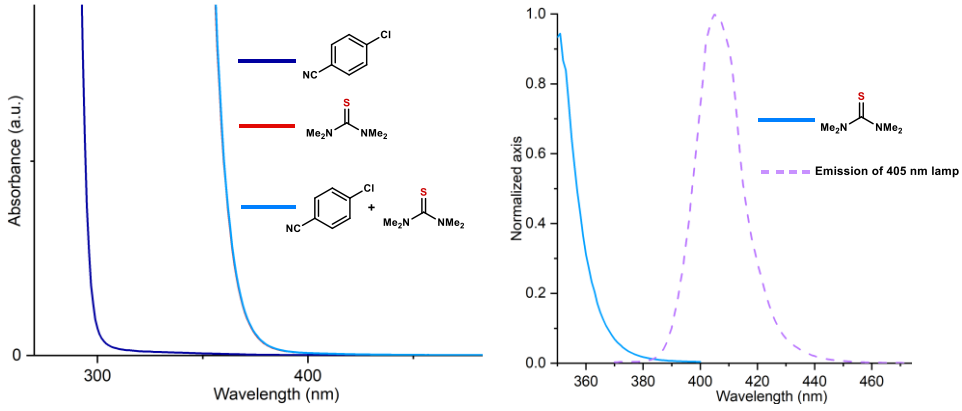


Figure 4.24. *left*) Absorption spectra recorded for 1,1,3,3-tetramethylthiourea **A**, 4-chlorobenzonitrile (**1a**) and a mixture of **A** with **1a** in DMSO (0.3 M); right) Normalized spectra recorded for 1,1,3,3-tetramethylthiourea **A** in DMSO (0.3 M) and emission of 405 nm lamp.

Emission Studies

Fluorescence measurements were carried out on an Fluorolog Horiba Jobin Yvon spectrofluorimeter equipped with a photomultiplier detector, a double monochromator, and a 450W xenon light source. The emission spectrum of 1,1,3,3-tetramethylthiourea **A** was recorded from 360 nm to 440 nm after excitation with 350 nm laser.

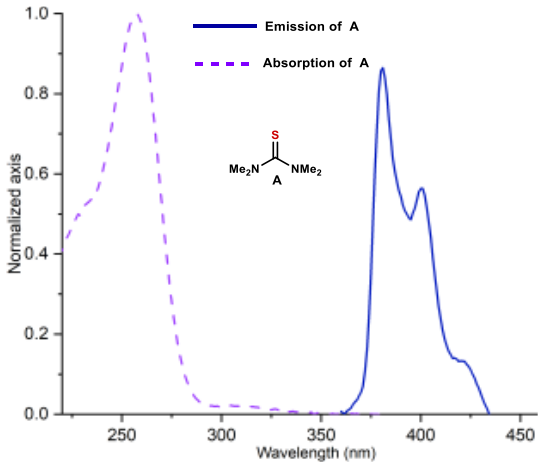


Figure 4.25. Normalized absorption and emission spectra of 1,1,3,3-tetramethylthiourea **A** in CH_3CN in a $0.95 \cdot 10^{-4}$ M solution.

Stern-Volmer Quenching Studies

Fluorescence measurements were carried out on an Fluorolog Horiba Jobin Yvon spectrofluorimeter equipped with a photomultiplier detector, a double monochromator, and a 450W xenon light source. A 1.0 M solution of the quencher substrate in degassed CH_3CN (HPLC grade) was prepared and 20 μL of this stock solution were added to the solution of the deprotonated catalyst, prepared according to the procedure detailed in page S22. The addition of the substrate solution (the quencher) was repeated for four/five times. After each addition, the solution was mixed and the emission spectra of the excited catalyst was acquired from 360 nm to 440 nm (the excitation wavelength was fixed at 350 nm, slit width= 5 nm).

A solvent blank was subtracted from all the measurements. The excitation wavelength was chosen in order to avoid saturation of the emission detector.

The results shown in **Figure 4.26-27** indicates that 4-chlorobenzonitrile **2a** and iodobenzene **2g** quenched the excited state emission of 1,1,3,3-tetramethylthiourea **A**. The Stern-Volmer plot shows a linear correlation between the amounts of substrates and the ratio I_0/I, following the relationship: $I_0/I = 1 + K_{SV}[Q]$ (Q = Quencher).

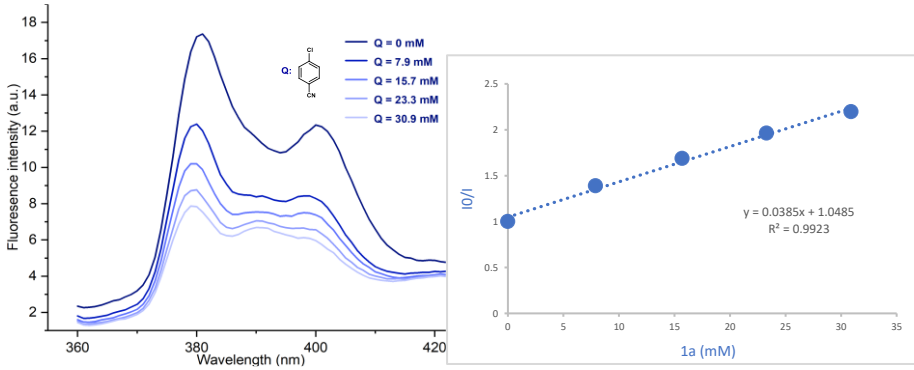


Figure 4.26. Stern-Volmer quenching studies with 4-chlorobenzonitrile (**1a**).

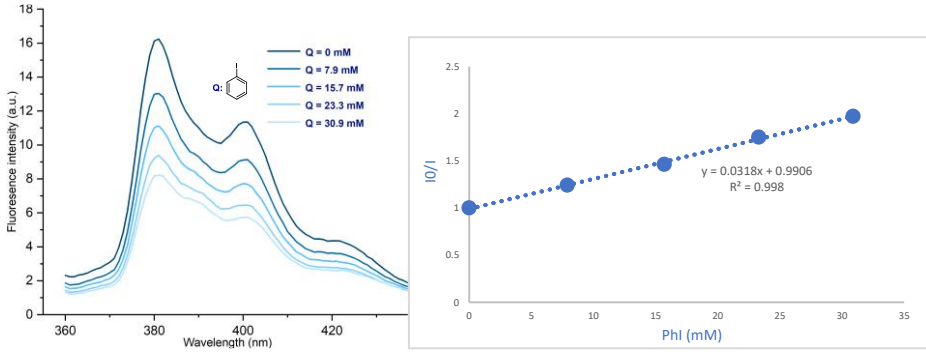


Figure 4.27. Stern-Volmer quenching studies with iodobenzene (**1g**).

Quantum Yield Determination

-Experimental Setup

The experiments for the quantum yield determination were conducted under illumination by a 405 nm high-power single LED (setup depicted in Figure 4. 28), using an aluminum block on a 3D-printed holder, fitted with a 405 nm high-power single LED. The irradiance was fixed at 60±2 mW/cm^2, as controlled by an external power supply and measured using a

photodiode light detector at the start of each reaction. This setup secured a reliable irradiation while keeping a distance of 1 cm between the reaction vessel and the light source.

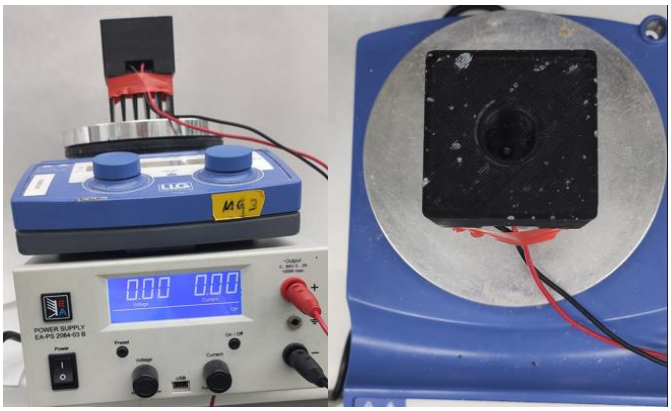


Figure 4.28. High-power single LED setup.

-General Procedure for photon Flux (F) determination[32]

$$\Phi = \frac{\mathrm{M}}{\mathrm{F} \times \mathrm{t}[1 - 10^{A(\lambda)}]} \ldots\ldots\ldots\ldots\ldots\ldots\ldots \boldsymbol{Eq.5}$$

M is the moles of product formed (mol), **F** is the number of photons emitted per second (einstein s^{-1}), **t** is the time (s) and **A(λ)** is the measured absorbance at 405 nm.The number of photons emitted per second was determined using azobenzene as actinometer[33].

Using the reaction setup depicted in Figure 4.34, a glass vial was filled with a solution of *trans*-azobenzene (0.1 mmol) in CD_3OD (0.1M) and irradiated with a 405 nm light. The *trans-cis* isomerization was followed in time in ^{1}H-NMR using 1,3,5-trimethoxybenzene as internal standard.

[32] Cismesia, M. A.; Yoon, T. P. "Characterizing Chain Processes in Visible Light Photoredox Catalysis." *Chem. Sci.* **2015**, *6*, 5426.

[33] (a) Leeuwen, T. v.; Buzzetti, L.; Perego, L. A.; Melchiorre, P. "A Redox-Active Nickel Complex that Acts as an Electron Mediator in Photochemical Giese Reactions." *Angew. Chem.,Int. Ed.* **2019**, *58*, 4953, (b) Ladányi, V.; Dvořák, P.; Anshori, J. A.; Vetráková, Ľ.; Wirz, J.; Heger, D. "The Absorption Spectrum of Cis-azobenzene." *Photochem. Photobiol. Sci.* **2017**, *16*, 17

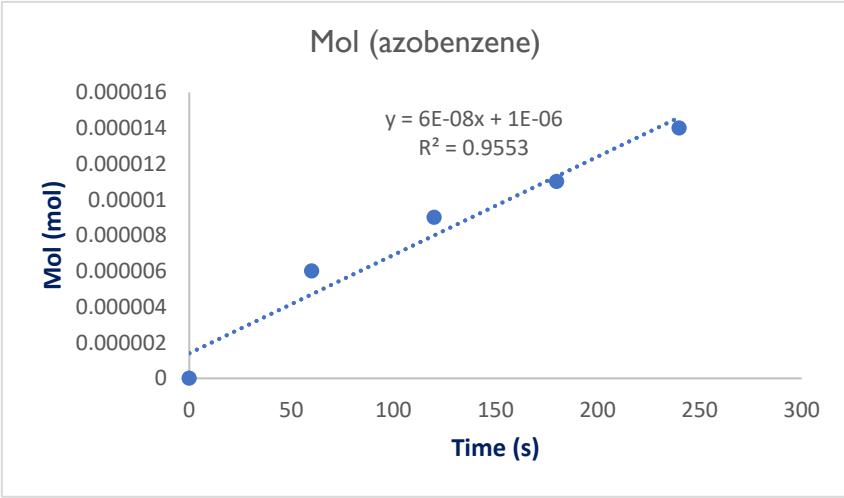


Figure 4.29. Plot of moles of *cis*-azobenzene formed vs irradiation time.

The actinometer solution was irradiated for 0 min, 1 min, 2 min, 3 min and 4 min. According to the eq. 1-2 and reported quantum yield of trans-cis isomerization process ($\Phi = 0.288$),[34] the number of photons emitted per time unit (**F**) was determined (3.0×10^{-7} mol s^{-1}).

-*Quantum Yield Determination*

Following the general procedure, five model thioetherification reactions between **1a**, **2a** and 1,1,3,3-tetramethylthiourea **A** were performed separately. Each reaction mixture was irradiated for 0 min, 20 min, 40 min, 60 min and 80 min. After irradiation, the amount of product **3a** formed was determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as the internal standard. Fraction of light absorbed *f* was recognized as 1. The moles of the formed product **3a** are plotted against the number of incident photons (**Figure S30**). The quantum yield (Φ) was calculated to be $\Phi = 0.067$ based on the slope and eq. 1-2.

[34] (a) Leeuwen, T. v.; Buzzetti, L.; Perego, L. A.; Melchiorre, P. "A Redox-Active Nickel Complex that Acts as an Electron Mediator in Photochemical Giese Reactions." *Angew. Chem.,Int. Ed.* **2019**, *58*, 4953, (b) Ladányi, V.; Dvořák, P.; Anshori, J. A.; Vetráková, Ľ.; Wirz, J.; Heger, D. "The Absorption Spectrum of Cis-azobenzene." *Photochem. Photobiol. Sci.* **2017**, *16*, 17

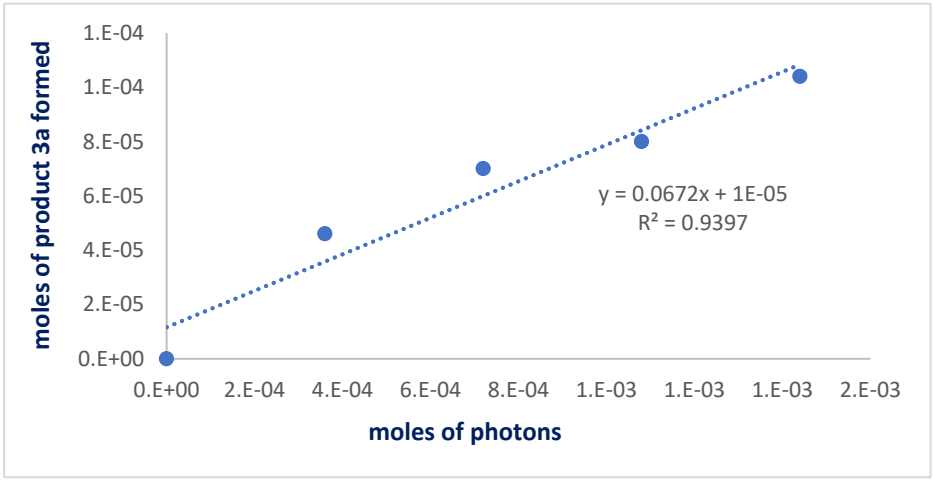


Figure 4.30. Plot of moles of incident photons vs moles of product **3a** formed.

4.6.4 Electrochemical Studies

Cyclic voltammetry (CV) measurements were carried out on a Princeton Applied Research PARSTAT 2273 instrument with a glassy carbon disk electrode (diameter: 3 mm) as working electrode. A silver wire coated with AgCl immersed in a 3.0 M aqueous solution of NaCl and separated from the analyte by a fritted glass disk was employed as the reference electrode and a Pt wire counter-electrode completed the electrochemical setup. The scan rate was 100 mV/s unless otherwise stated. The substrates were measured at concentration of 0.02 M in acetonitrile with $TBAPF_6$ (0.1 M) as electrolyte. The preparation of the deprotonated catalyst solutions was carried out as described in the photophysical studies section.

Potentials are quoted with the following notation: E_p^C (E_{Red}) refers to the cathodic peak potential, E_p^A (E_{Ox}) refers to the anodic peak potential.

Cyclic Voltammetry Measurements of the Model Substrates

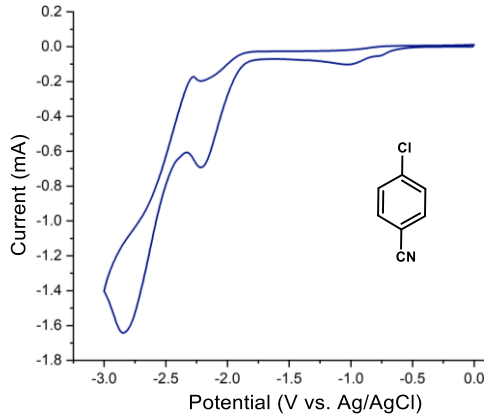


Figure 4.31. CV of 4-chlorobenzonitrile [0.02M] in [0.1 M] TBAPF6 in CH_3CN. Measurement started by reduction from 0 to -3.0 V and finishing at 0 V. Platinum disk working electrode, Ag/AgCl (NaCl 3 M) referenceelectrode, Pt wire auxiliary electrode. irreversible reduction E_p = -2.1 V, E_p = -2.8 V.

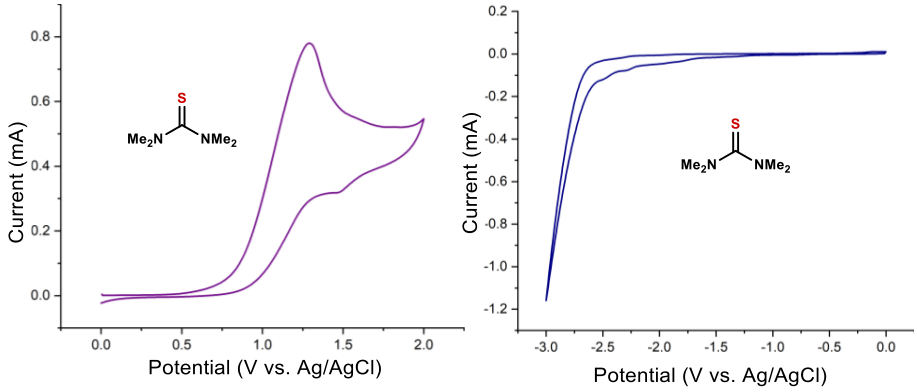


Figure 4.32. *left*) CV of 1,1,3,3-tetramethylthiourea [0.02M] in [0.1 M] TBAPF6 in CH_3CN. Measurement started by oxidation from 0 to +2.0 V and finishing at 0 V. Platinum disk working electrode, Ag/AgCl (NaCl 3 M) referenceelectrode, Pt wire auxiliary electrode, one irreversible oxidation E_p = 1.29 V. *right*) CV of 1,1,3,3-tetramethylthiourea [0.02M] in [0.1 M] TBAPF6 in CH_3CN. Measurement started by reduction from 0 to -3.0 V and finishing at 0 V. Platinum disk working electrode, Ag/AgCl (NaCl 3 M) reference electrode, Pt wire auxiliary electrode, reduction was not observed in the registered potential window.

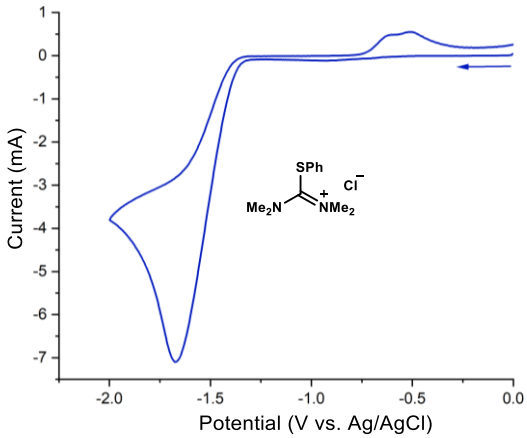


Figure 4.33. CV of 1,1,3,3-tetramethyl-2-phenylisothiouronium chloride [0.02M] in [0.1 M] TBAPF6 in CH_3CN. Measurement started by reduction from 0 to -2.5 V and finishing at 0 V. Platinum disk working electrode, Ag/AgCl (NaCl 3 M) referenceelectrode, Pt wire auxiliary electrode, one irreversible reduction E_p = -1.68 V.

Conversion of the Potential from Ag/AgCl to SCE

The conversion of the redox potential from Ag/AgCl to SCE was done according to the literature by measuring the redox potential of ferrocene as reference in CH_3CN.[35]

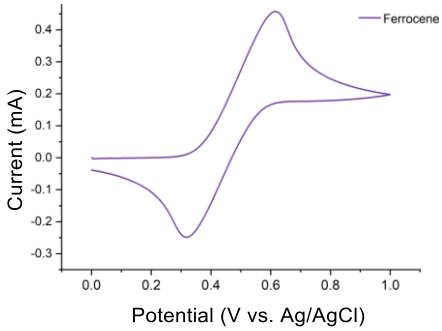


Figure 4.34. CV of ferrocene [0.02M] in [0.1 M] TBAPF6 in CH_3CN. Measurement started by oxidation from 0 V to +1.0 and finishing at -1 V. Platinum disk working electrode, Ag/AgCl (NaCl 3 M) referenceelectrode, Pt wire auxiliary electrode, one reversible reduction and oxidation $E_{1/2}$ = 0.46 V.

[35] Pavlishchuk, V. V.; Addison, A. W. "Conversion Constants for Redox Potentials Measured Versus Different Reference Electrodes in Acetonitrile Solutions at 25°C." *Inorganica Chim. Acta*. **2000**, 298, 97–102.

With the reference CV, the redox potential *vs.* SCE in CH_3CN was calculated using the following equations:

For1,1,3,3-tetramethylthiourea:

$$E_p^A\,(Ag/AgCl \text{ to } Fc/Fc^+) = 1.29 - 0.46 = 0.83 \text{ V } vs.\ Fc/Fc^+$$
$$E_p^A\,(Fc/Fc^+ \text{ to SCE}) = 0.83 + 0.38 = 1.21 \text{ V } vs.\ \text{SCE}$$

Evaluation of the Excited-State Potential of Excited 1,1,3,3-tetramethylthiourea A

Using the data collected from the CV studies (**Figure 4.32**) and from the absorption and emission spectra (**Figure 4.25**) of 1,1,3,3-tetramethylthiourea **A**, we could estimate the redox potential of the excited state with the following Equation:[36]

$$E(Pc^{\bullet+}/Pc^*) = E(Pc^{\bullet+}/Pc) - E_{0\text{-}0}(Pc^*)/(Pc)$$

Since the electrochemical oxidation of 1,1,3,3-tetramethylthiourea **A** is irreversible, the irreversible peak potential E_p anode was used for $E(Pc^{\bullet+}/Pc)$. The oxidation potential was calculated to be 1.21 V *vs.* SCE (in ACN). $E_{0\text{-}0}(Pc^*)/(Pc)$ was approximately determined spectroscopically from the tail of absorption spectrum(roughly at 350 nm for 1,1,3,3-tetramethylthiourea **A**) to have values of 3.54 eV.

The oxidation potential of the excited **A**:

$$E(Pc^{\bullet+}/Pc^*) = 1.29 - 3.54 = \textbf{\textit{-2.25 V vs. Ag/AgCl}}$$
$$E(Pc^{\bullet+}/Pc^*) = 1.21 - 3.54 = \textbf{\textit{-2.33 V vs. SCE}}$$

Rationale for the Higher Reactivity Tetramethylthiourea A compared to B-D

A possible explanation for the higher reactivity of tetramethylthiourea **A** compared to **B-D** can be ascribed to the presence of acidic protons in the latter substrates. **B-D** possess acidic

[36] Buzzetti, L.; Crisenza, G. E. M.; Melchiorre, P. "Mechanistic Studies in Photocatalysis." *Angew. Chem., Int. Ed.* **2019**, *58*, 3730.

protons within NH_2 or NHR moieties that, upon deprotonation, can form nucleophilic thiolates, significantly complicating the reaction (see Figure 4.35, bottom left). Additionally, aryl-isothiouronium salts derived from tetramethylthiourea **A** are more electrophilic than salts from **B-D**, making them more efficient towards nucleophilic attack by the carboxylic acids to undergo deoxythiolation (see Figure 4.35, bottom right). Finally, the formation of the key aryl-isothiouronium salts from S_8 was not possible.

As for the reaction with thiourea **D**, we detected 4,4'-thiodibenzonitrile as a byproduct after reaction completion (Figure 4.35, lower panel), which suggests that the excitation of **D** and the generation of the aryl radical upon SET activation of **1a** were feasible, although to a minimal extent. We hypothesized that the lack of thioester product formation was a consequence of a difficult deoxythiolation process.

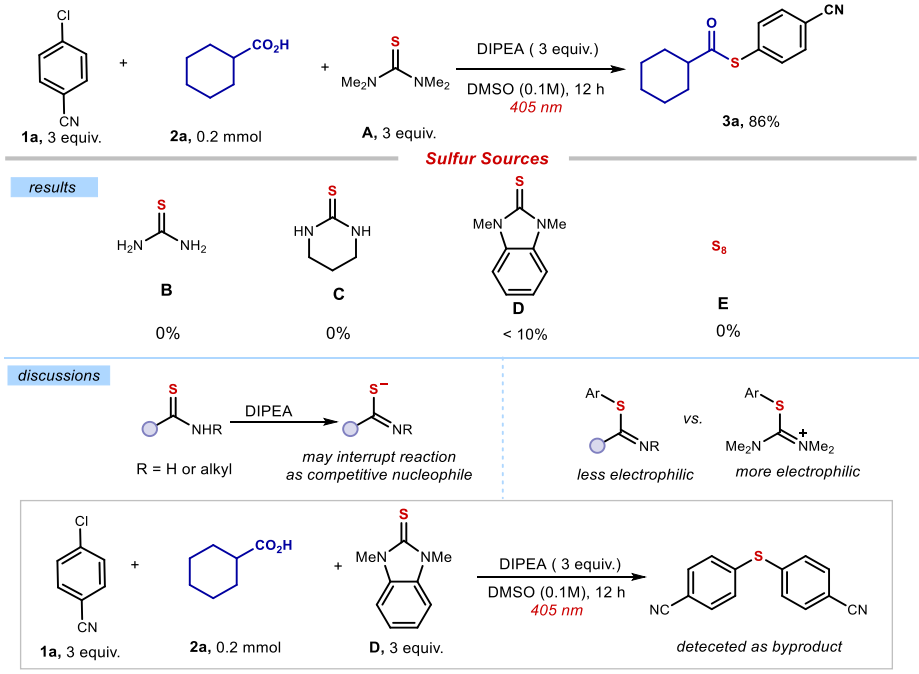


Figure 4.35. Rationale for the higher reactivity of tetramethylthiourea **A** as the sulfur source.

We have measured the absorption spectra of thiourea **B-D**, also in the presence **1a**. As depicted in Figure 18 below, we observed bathochromic shifts when mixing thiourea **B-C** with **1a**. Additionally, note that thiourea **D** could absorb in the visible light region. These studies established the possibility for these substrates (in particular **D**) to get excited by light.

The byproduct formation observed when using **D** is also in line with the visible-light-absorbing property of this substrate.

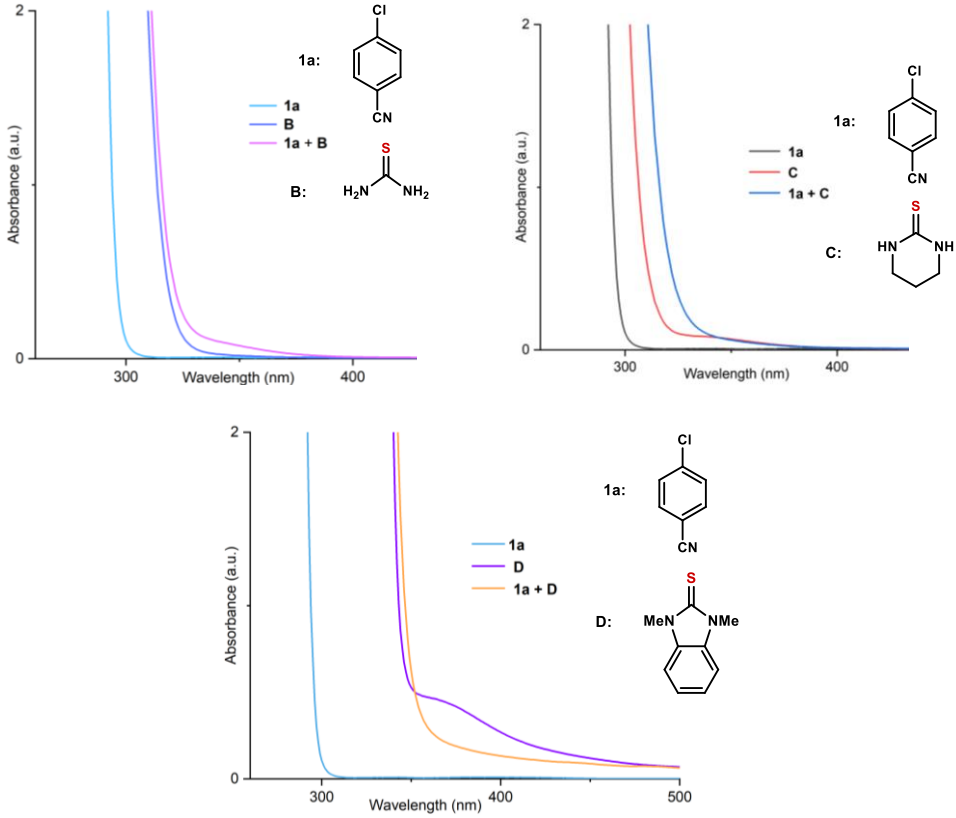


Figure 18. Absorption spectra recorded for thiourea **B-D**, 4-chlorobenzonitrile (**1a**) and their mixtures in DMSO (0.3 M).

Chapter V

General Conclusions

The work carried out in this doctoral thesis has identified new organic catalysts or intermediates that, upon excitation with visible light, could access a highly reducing excited state and subsequently act as potent single-electron transfer (SET) reductants to activate a diverse range of inert compounds towards radical formation, including aryl halides, alkyl chlorides and arenes. This opened up new opportunities for transformation of diverse chemical bonds, e.g. C-X (X = F, Cl, Br, I), C-C, and C-O bonds, yielding diverse scaffolds.

In Chapter II, we developed a versatile photochemical catalytic platform for activating diverse inert substrates. The key discovery was identifying a simple indole thiolate organocatalyst that, upon deprotonation and light excitation, becomes a powerful reductant. This light-driven catalytic platform exhibited broad generality, effectively enabling the reductive activation of inert C-F, C-Cl, and C-O bonds, as well as the Birch-type reduction of unfunctionalized arenes. The mild reaction conditions and wide applicability suggest that this readily available organocatalyst could have widespread utility in the photochemical activation of inert substrates.

Building on the photochemical catalytic platform developed in Chapter II, Chapter III explores the photochemical synthesis of thioethers using readily accessible, non-toxic, and widely available aryl chlorides and alcohols as feedstocks—without the need for thiols or transition metals. Leveraging our strongly reducing indole thiolate organic photocatalyst, we achieved the cleavage of unreactive C(sp^2)-Cl bonds to generate aryl radicals. These radicals are subsequently captured by tetramethylthiourea, forming an aryl isothiouronium intermediate. This intermediate then undergoes an established ionic dexythiolation pathway with alkyl alcohols in a single sequence, resulting in the formation of aryl alkyl thioethers. The protocol's reliance on abundant commercial substrates and its remarkable functional group tolerance offer broad synthetic utility, ranging from the transformation of simple feedstock chemicals to late-stage modifications of biorelevant compounds.

Our thiol-free photochemical method for thioether synthesis can also be applied to the

preparation of thioesters. Chapter IV introduces a novel photochemical approach for synthesizing thioesters from readily available aryl halides and carboxylic acids. Unlike in our previous study, 1,1,3,3-tetramethylthiourea serves not only as a sulfur source and aryl radical trap but also as a photoactive catalyst. Upon absorption of purple light (405 nm), 1,1,3,3-tetramethylthiourea is directly excited, acquiring strong reducing power that activates aryl halides via SET. The key advantage of this thiol-free protocol is its mild reaction conditions, which enable remarkable functional group tolerance and facilitate late-stage modifications of biorelevant compounds.

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Developing and Exploiting New Photoreductants in Radical Chemistry
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