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ADVANCED SYNTHESIS & CATALYSIS

Photoredox/Nickel Dual Catalytic C(sp^2)—S Cross-coupling of Bromoanilines Enabled by Mineral Acids

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Abstract: Cross-coupling reactions are essential tools in modern organic synthesis, enabling the formation of carbon—heteroatom (C—X) bonds. Despite significant advancements in method development, particularly with palladium, copper, and nickel catalysis, including recent progress in photoredox catalysis, their efficiency is often limited when sensitive functional groups, such as thiols and amines, are present in the nucleophile or electrophile, and typically requires extensive protection–deprotection strategies. Herein, a practical synthetic approach is reported that employs mineral acids as unconventional reagents to facilitate C(sp^2)—S cross-coupling between bromoanilines (or other electrophiles bearing free primary amines as functional groups) and thiols, thereby eliminating the need for protecting group manipulations. Additionally, protonation alters the electronic influence of the aniline moiety, transforming it from an electron-donating to an electron-withdrawing group, which promotes oxidative addition, and the acidic medium suppresses polythiolate formation, enhancing nickel catalysts' accessibility and reducing inner filter effects in photocatalysis. This strategy enables efficient and high-yielding synthesis of amino thioethers across a broad substrate scope, underscoring the value of acid-assisted cross-coupling as a streamlined and robust photoredox methodology for C(sp^2)—S bond formation.

Keywords: acid, AD-HoC, bromoaniline, C(sp²)–S coupling, cross-coupling, photoredox

1. Introduction

Over the past five decades, cross-coupling reactions have become a cornerstone of modern organic synthesis, enabling the efficient construction of carbon—carbon (C—C) and carbon—heteroatom (C—X) bonds.[1–6] These transformations are indispensable for the synthesis of natural products, pharmaceuticals, and advanced materials.[3] Although significant progress has been made in transition metal-catalyzed methodologies, particularly those employing palladium,[1–3] copper,[5,6] and nickel catalysts,[4,7] as well as in emerging photoredox dual catalytic systems,[8–13] broadly applicable methods that are compatible with sensitive functional groups remain limited.[14–17]

This limitation is especially evident in the direct cross-coupling of bromoanilines with thiols for the synthesis of amino thioethers, a class of compounds frequently encountered in biologically active molecules.[18] For instance, a recent study by Fleischer and coworkers[14] demonstrated the use of a flexible bidentate phosphine ligand to promote C(sp^2)—S cross-coupling, including for sterically hindered substrates. However, this method proved ineffective for amine- and amide-substituted triflates, with no observed conversion to the desired products.

Several key challenges hinder this transformation. Thiols have a strong tendency to coordinate to metal centers,[19,20] forming often catalytically inactive complexes that reduce reactivity. Additionally, bromoanilines—being electron-rich aryl halides—exhibit reduced reactivity in

oxidative addition steps due to the strongly electron-donating nature of the free —NH_2 group. Unprotected anilines also promote the formation of higher-order polythiolates, which sequester active nickel species and compromise catalytic turnover. In photoredox systems, this issue is exacerbated: polythiolates absorb visible light, disrupting efficient photon transfer[21] and inhibiting the reduction of Ni(II) intermediates. These combined effects derail both the nickel and photocatalytic cycles, leading to diminished conversions. To address these challenges, *N*-protection strategies (e.g., acylation of the aniline) are frequently employed to reduce the electron density of the aryl halide, thereby enhancing oxidative addition and overall reactivity. While effective in some cases, these approaches introduce additional synthetic steps for protection and deprotection, which reduce atom economy, increase purification requirements, and complicate the overall process. Moreover, many of the developed methods still fail to deliver the desired product,[14] highlighting the need for a more general and robust approach. Overcoming these persistent limitations would represent a significant advancement in synthetic methodology, enabling direct C(sp^2)—S cross-coupling of bromoanilines with thiols, without the need for protecting groups.

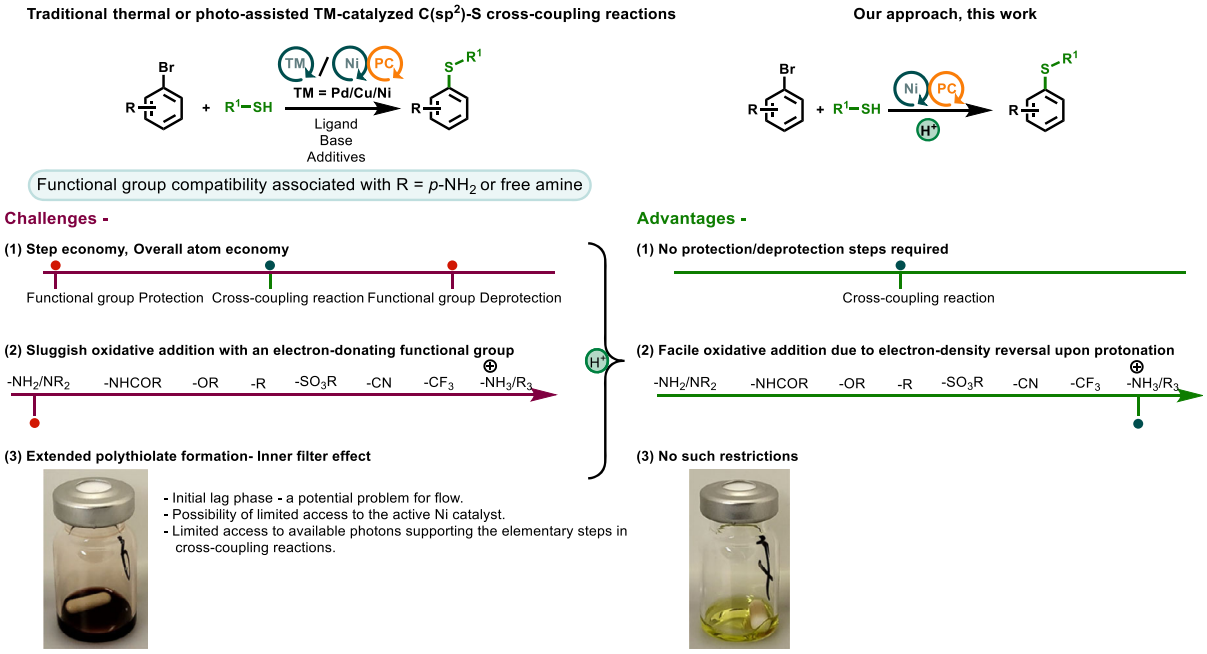
Here, we report a general and practical acid-assisted protocol for the cross-coupling of unprotected bromoanilines with a broad range of thiol nucleophiles. Rather than relying on protecting group strategies, we envisioned whether a simple mineral acid additive could overcome the inherent challenges associated with these substrates. This idea was inspired by our recent observations under adaptive dynamic homogeneous catalytic conditions,[11] where in situ acid formation did not inhibit C(sp^2)—S coupling reaction but, in some cases, significantly enhanced reaction rates.[11,22–24] Notably, this approach also translated well to flow systems, enabling scalable and efficient synthesis of (het)aryl thioethers.[21]

We propose that mineral acid additives play three crucial roles in enabling this transformation. First, protonation of the aniline moiety serves as a noncovalent protective strategy, obviating the need for additional synthetic steps. Second, protonation reduces the electron-donating nature of the aniline group, thereby facilitating oxidative addition. Third, the acidic environment suppresses the formation of polythiolates, increasing the availability of active nickel species and minimizing inner filter effects during photocatalysis (**Scheme 1**).

This straightforward strategy proved highly effective in delivering C(sp^2)—S cross-coupling products in high yields across a broad range of bromoanilines and thiol nucleophiles. Moreover, by eliminating the need for protecting group manipulations and suppressing polythiolate formation, the methodology offers a robust, scalable, and operationally streamlined solution to a longstanding challenge in the direct synthesis of amino thioethers.

2. Results and Discussion

We began our synthetic investigations using 4-bromoaniline as the electrophile and ethyl 3-mercaptopropionate

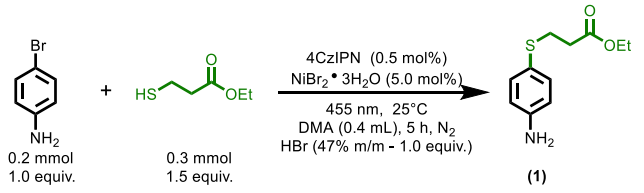


Scheme 1. A schematic illustrating the role of mineral acids as a trimodal reagent in the C(sp^2)—S cross-coupling of amino aryl bromides highlights three key benefits.

as the nucleophile. The cross-coupling reaction was ineffective in the absence of acid. However, the addition of just 1.0 equivalent of 47% (w/w) aqueous hydrobromic acid (HBr) as a mineral acid led to the formation of the desired cross-coupled product in an excellent 93% yield (see Entry 1 in **Table 1**). Notably, the reaction conditions are remarkably simple, requiring only the mixing of reagents (i.e., the coupling partners and aqueous HBr) followed by irradiation of the reaction mixture under an inert atmosphere using a low-power LED to afford the desired product. Other mineral acids, such as hydrochloric and sulfuric acid, as well as strong organic acids like triflic acid, also proved effective in promoting the cross-coupling reaction, delivering comparable yields and efficiencies (see Table 1, Entries 6–8). Optimization experiments confirmed that ≈1.0 equivalent of acid was optimal, maximizing both the yield and reaction rate (cf., **Figure 1**). The sequence of acid addition—whether before or after the thiol—had no significant effect on the overall efficiency of the cross-coupling, in terms of both product yield and reaction kinetics (see Figure S6–S8, Supporting Information for further details). Additionally, a slight increase in reaction temperature did not adversely affect the outcome of the C(sp^2)─S cross-coupling and generally accelerated the reaction rate, enabling shorter reaction times (Entry 11, Table 1). The cross-coupling reaction was generally effective with most nickel bromide salts (see Table 1, Entries 12–14). However, given the aqueous nature of the acid, we selected $NiBr_2 \cdot 3H_2O$ as the nickel source, offering a more economical alternative to other nickel catalysts such as $NiBr_2 \cdot$glyme. Control experiments confirmed the essential roles of light, $NiBr_2 \cdot 3H_2O$, and 4CzIPN as the photocatalyst in this transformation.

With the optimized reaction condition established, we next explored the general synthetic applicability of the C(sp^2)─S cross-coupling method by evaluating a diverse set of thiol nucleophiles and electrophiles (**Figure 2**). To our delight, a wide range of thiols—including both primary and secondary types—proved to be highly effective, delivering the desired products in good to excellent isolated yields using only a single low-power LED (≈600 mW; see Section 2 in the Supporting Information for further details). Notably, the cross-coupling reaction proceeded efficiently with low-boiling ethanethiol, affording the corresponding product in 69% isolated yield. When 2-(pyridin-4-yl) ethane-1-thiol was employed as the nucleophile, the

Table 1. Optimization of reaction conditions and results from the control experiments. See table S1, Supporting Information for additional details.



Entry	Deviation from the standard reaction condition	1 (% yield)[a]
1	None	93
Control experiments		
2	No 4CzIPN	0
3	No $NiBr_2 \cdot 3H_2O$	2
4	No light	0
5	No HBr	0
Influence of other acids		
6	HCl (1.0 equiv.)	80
7	H_2SO_4 (1.0 equiv.)	86
8	TfOH (1.0 equiv.)	93
Effect of HBr equivalent and temperature		
9	1.2 equiv. HBr	88
10	1.5 equiv. HBr	76
11	60 °C, 1 h	91
Effect of other Ni-salts as catalysts		
12	$NiBr_2 \cdot$glyme	88
13	$NiCl_2 \cdot$glyme	85
14	$NiCl_2 \cdot 6H_2O$	72
Others		
15	Addition of H_2O (23.0 µL) w/o HBr	0
16	Addition of H_2O (23.0 µL)	21
17	No degassing	0[b]
18	20 µL of DMA w/o HBr	0
19	20 µL of DMA	85

[a] Yields were determined (within analytical errors, ± 10%) by GC-FID using 1,3,5-trimethoxybenzene as an internal standard; [b] The cross-coupling reaction was performed just by closing the reaction vial without degassing.

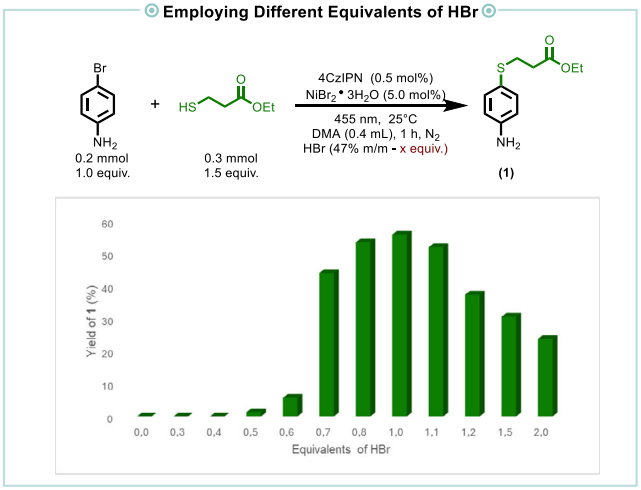


Figure 1. Influence of HBr equivalents on the yield of the desired product in the C(sp^2)─S cross-coupling reaction. The cross-coupling of 4-bromoaniline (0.2 mmol, 1.0 equiv.) with ethyl 3-mercaptopropionate (0.3 mmol, 1.5 equiv.) was carried out under a nitrogen atmosphere at 25 °C in DMA for 1 h. Yields were determined by GC-FID using 1,3,5-trimethoxybenzene as the internal standard.

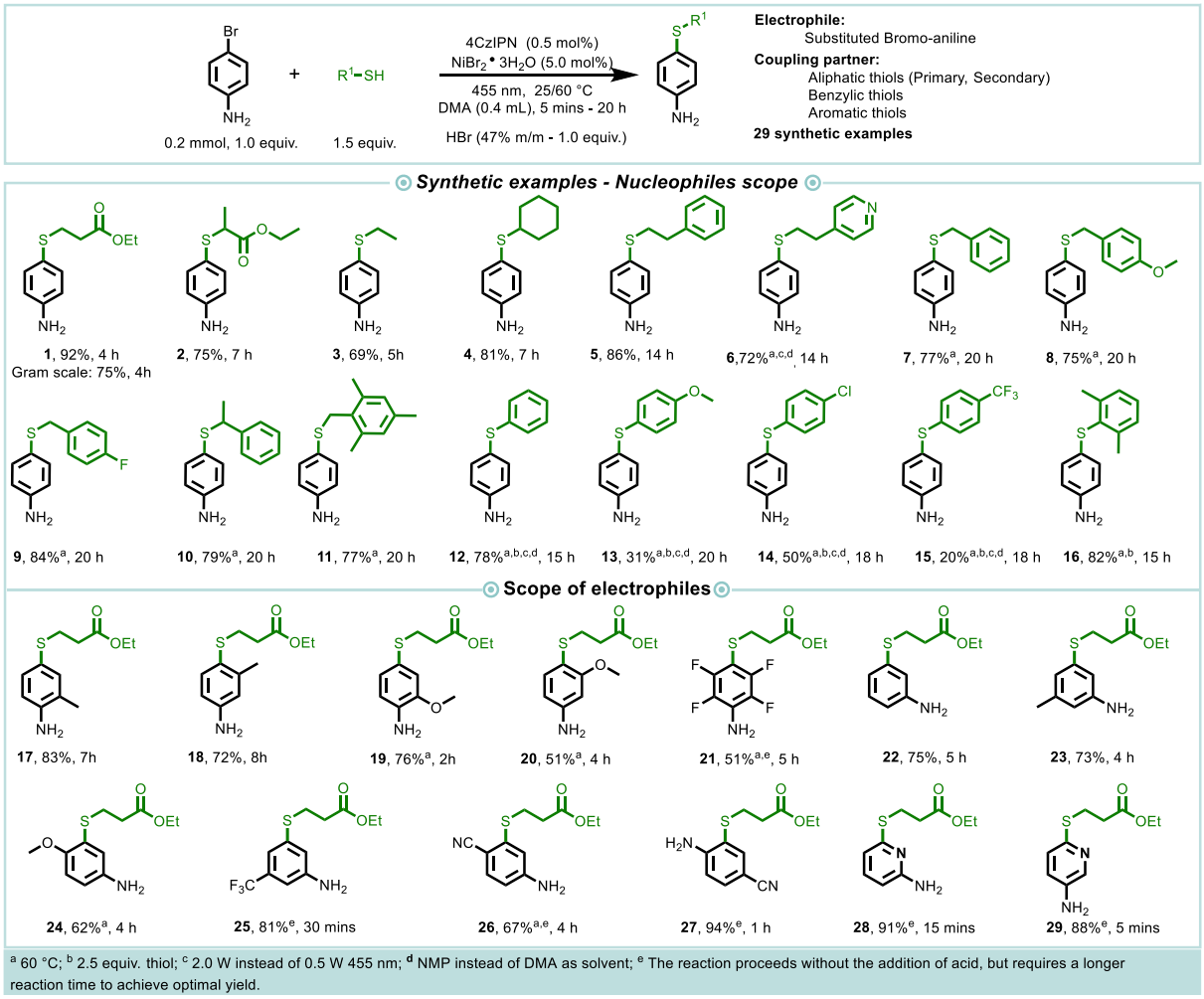


Figure 2. Synthetic examples of C(sp^2)─S cross-coupling reactions exploring nucleophiles' and electrophiles' scope. Isolated yields are reported unless noted otherwise.

product (**6**) was obtained in 72% yield. Steric hindrance at the *α*-position to the sulfur center also did not adversely affect the transformation; for instance, when ethyl 2-mercaptopropanoate was used as a nucleophile partner, the corresponding product (**2**) was isolated in 75% yield.

A variety of benzylic thiols were also successfully employed as nucleophiles, providing the desired cross-coupled products in consistently high yields. Benzylic thiols bearing neutral (**7**), electron-rich (**8**), and electron-deficient (**9**) substituents on the aromatic ring all afforded very good isolated yields. Furthermore, steric hindrance at both the benzylic position and the arene core, such as in 1-phenylethane-1-thiol and mesitylmethanethiol, had no detrimental impact on the reaction outcome, leading to high yields of the corresponding products (see synthetic examples **10** and **11**).

Thiophenols also proved to be effective coupling partners, although a slight increase in reaction temperature was found to be beneficial to accelerate these transformations. In addition, switching the solvent from DMA to *N*-methyl-2-pyrrolidone (NMP) further improved reaction efficiency for this class of substrates (see Scheme S1 in the Supporting Information for further details). Thiophenols featuring electron-neutral, electron-rich, and electron-deficient substituents afforded the desired products in moderate to good isolated yields (Figure 2, examples **12**–**15**). Remarkably, a chloro substituent on the thiophenol ring was well tolerated, providing the desired product in 50% yield and suggesting potential for subsequent coupling transformations. Even sterically hindered thiophenols, such as 2,6-dimethylbenzenethiol, exhibited no adverse effects on the reaction, affording the corresponding product (**16**) in an impressive 82% isolated yield.

The C(sp^2)─S cross-coupling reactions were effective with electrophiles bearing functional groups such as ─Me, ─OMe, ─F, ─CF_3, and ─CN at different positions on the arene core. These substrates successfully furnished the corresponding C(sp^2)─S products in good to excellent isolated yields (Figure 2). Notably, steric

hindrance at the *ortho* position was well tolerated, as exemplified by substrates **18**, **20**, **21**, **24**, and **26**, which afforded the desired products in 51%–72% isolated yields.

Even *ortho*-substituted electrophiles containing adjacent functional groups with heteroatoms, such as 4-amino-3-bromobenzonitrile, underwent efficient coupling, delivering product **27** in a near-quantitative 94% isolated yield. Electron-deficient electrophiles, including 4-bromo-2,3,5,6-tetrafluoroaniline, also performed well under the optimized conditions, affording the corresponding products in good to excellent yields. Notably, these electron-poor bromoaniline substrates—likely due to the increased acidity of the aniline moiety and relatively more facile oxidative addition—exhibited reactivity even in the absence of added acid; however, the presence of acid significantly enhanced the reaction rate (see Section 8 in the Supporting Information for additional details).

Encouragingly, the C(sp^2)─S cross-coupling protocol also proved effective for (hetero)aryl bromides, including 6-bromopyridin-2-amine and 6-bromopyridin-3-amine, which provided the desired products in excellent yields (Figure 2, examples **28** and **29**).[25] The inherent simplicity and robustness of this acid-promoted C(sp^2)─S cross-coupling methodology were further underscored by its successful application to electrophiles bearing free primary amine groups (see **Figure 3**). Substrates such as **33**, **34**, and **35** underwent smooth cross-coupling, affording their respective products in moderate isolated yields, highlighting the utility of the method for amine-containing substrates.

The simplicity and practicality of the reaction conditions—requiring only the mixing of starting materials, followed by irradiation under an inert atmosphere—enabled the successful execution of the C(sp^2)–S cross-coupling reactions across various photochemical setups. Notably, recent reports have highlighted that the efficiency and kinetics of photochemical reactions can be highly sensitive to the choice of photoreactor,[26] raising concerns about reproducibility.[27] However, such complications were not encountered in our system. The cross-coupling reactions consistently delivered comparable yields across different photochemical setups, demonstrating excellent reproducibility. Moreover, the use of commercial photoreactors or Kessil lamps further accelerated the reaction kinetics by enhancing photon flux, thereby facilitating faster transformations. Importantly, the methodology also proved amenable to scale-up, enabling efficient gram-scale synthesis (cf., product **1** in Figure 1) in standard batch setups without compromising yield or efficiency.

While a comprehensive mechanistic picture, particularly considering the interplay of redox events and acid effects, has yet to be fully elucidated, the proposed catalytic cycle under photoredox conditions involving

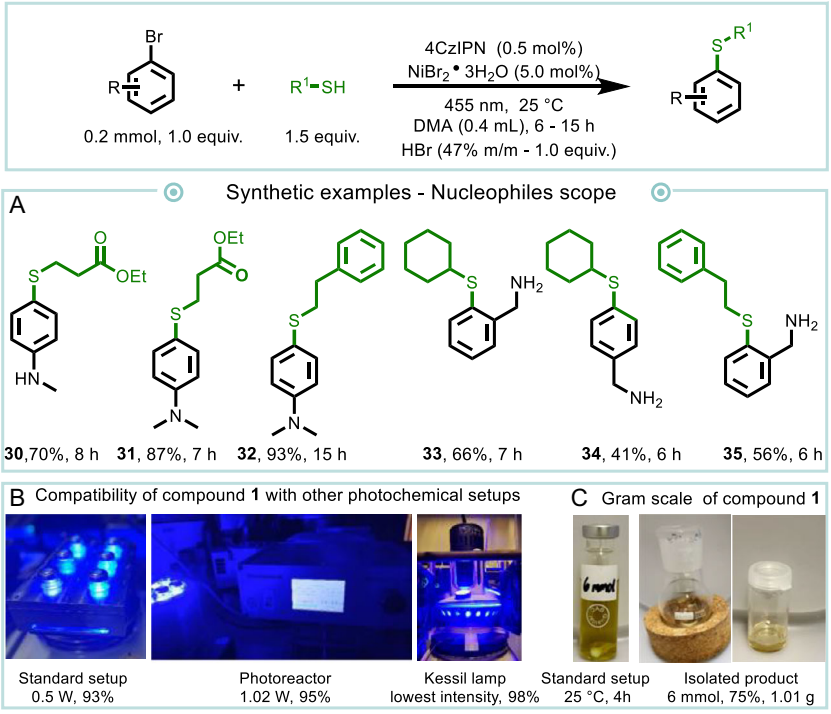


Figure 3. A) Compatibility with other functional groups in C(sp^2)─S cross-coupling reaction is demonstrated. B,C) The simplicity of gram-scale reactions and compatibility with other photochemical setups, such as the Kessil lamp and commercial photoreactor, are also shown (see supporting information for additional details).

4CzIPN begins with single-electron transfer reduction of Ni(II) to Ni(I).[11,28] The resulting Ni(I) species undergoes oxidative addition with the (hetero)aryl bromide, forming a Ni(III) intermediate. This Ni(III) species subsequently undergoes ligand exchange, followed by reductive elimination to deliver the desired C(sp^2)─S cross-coupled product and regenerate the catalytically active Ni(I) species (see Scheme S2, Supporting Information for further details).

It is worth noting that, depending on the thiol nucleophile used, the ligated nickel species (in this case, coordinated with the nucleophile) can form prior to the oxidative addition step and may play a significant role in facilitating the transformation by modulating the electronic environment of the metal center.

3. Conclusion

In conclusion, we report here the use of mineral acids as unconventional yet effective reagents in nickel-catalyzed C(sp^2)─S cross-coupling reactions with substituted bromoanilines and electrophiles bearing free primary amine groups, effectively eliminating the need for synthetically demanding protection–deprotection strategies. This approach capitalizes on the protonation of aniline derivatives, converting an electron-donating group into an electron-withdrawing one, thereby facilitating the key oxidative addition step within the catalytic cycle. Moreover, the acidic environment suppresses the formation of nickel-thiolate complexes, enhancing the availability of active nickel species and mitigating inner filter effects in photoredox dual metal-catalyzed cross-coupling reactions. The methodology accommodates a broad range of thiol nucleophiles—including aliphatic, benzylic, and thiophenol derivatives—and delivers the desired products in high yields. Challenging substrates, such as *ortho*-substituted bromoanilines and sterically hindered nucleophiles, were also efficiently cross-coupled with excellent isolated yields. Finally, the protocol demonstrates compatibility with various photochemical setups and is readily scalable, underscoring its practical utility in the direct synthesis of amino thioethers.

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Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

Indrajit Ghosh *and* ***Burkhard König*** *conceived and supervised the project.* ***Florence Babawale***, ***Maksim Nikitin***, *and* ***Indrajit Ghosh*** *designed the experiments with valuable and critical input from* ***Burkhard König***, ***Florence Babawale*** *and* ***Maksim Nikitin*** *performed the optimization, scope, and mechanistic studies.* ***Florence Babawale*** *and* ***Maksim Nikitin*** *analyzed the experimental results with input from* ***Indrajit Ghosh***, ***Florence Babawale***, *and* ***Burkhard König*** *wrote the manuscript with input from all authors.*

Data Availability Statement

Research data are not shared.

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