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Direct utilization of hydrogen sulfide gas for aryl thiol synthesis *via* adaptive dynamic homogeneous catalysis in a flow system

 Hiroshi Kitamura,^a Maksim Nikitin,^{id b} Indrajit Ghosh,^{id bc} Burkhard König,^{id b} C. Oliver Kappe^{id ad} and Sándor B. Ötvös^{id *ad}

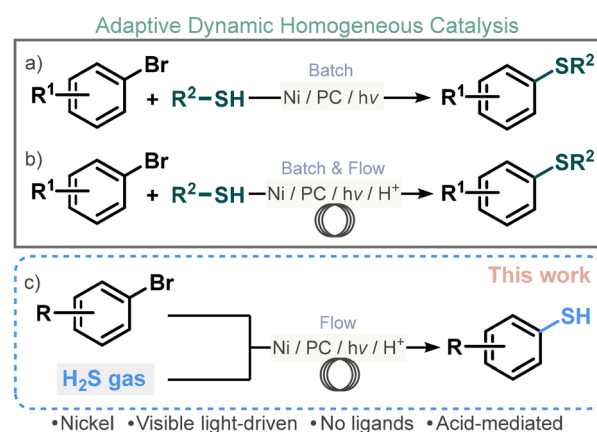
We present our initial results on C(sp²)-S cross-couplings employing the adaptive dynamic homogeneous catalysis (AD-HoC) strategy in combination with H₂S gas as an economically viable reagent for aryl thiol synthesis. To ensure the safe and efficient use of toxic H₂S gas, process development was carried out in a commercially available continuous flow photoreactor under visible-light irradiation, with a simple Brønsted acid playing a key role in promoting the reaction.

The utilization of hydrogen sulfide gas (H₂S) might represent one of the most straightforward and atom-economical approaches to incorporating sulfur atoms into organic molecules.¹ However, the high toxicity of H₂S restricts its practical synthetic applications, especially on larger scales.² Beyond the inherent challenges of gas-liquid reactions due to inadequate mixing and mass transfer,³ a further technical difficulty is that moist H₂S is highly corrosive to many metals, often necessitating specialized reactor designs.⁴ As a result, safer surrogates for H₂S are commonly employed in practice.⁵ While these alternatives can mitigate some safety and handling issues, they typically generate stoichiometric amounts of waste (often including toxic metal residues), which compromises atom economy and significantly reduces the environmental sustainability of such processes, particularly at scale.

Adaptive dynamic homogeneous catalysis (AD-HoC) has recently emerged as a powerful strategy for constructing molecular complexity through diverse nickel-catalyzed cross-coupling reactions driven by visible-light and an organic photosensitizer.⁶ This approach leverages the dynamic *in situ* assembly of various nickel complexes, enabling multiple catalytic pathways without

the need for additional bases or ligands. Remarkably, the reaction predominantly proceeds *via* a Ni(I)/Ni(III) catalytic cycle, providing easy access to Ni(I) species from inexpensive, bench-stable Ni(II) salts. The method has proven particularly effective for C(sp²)-S cross-coupling reactions of various (het)aryl bromides with thiols and thiophenols as nucleophiles (Scheme 1a and b). These thioetherifications have also been demonstrated using mesoporous graphitic carbon nitride as an organic heterogeneous photocatalyst.⁷ Notably, the reaction operates under ligand- and base-free conditions and is facilitated by catalytic amounts of a Brønsted acid.⁸ This is a rare feature, as traditional cross-couplings are typically incompatible with acidic media due to the protonation of the nucleophile component.⁹ The Brønsted acid-promoted thioetherification protocol has been successfully scaled to multigram quantities using a commercially available continuous flow photoreactor, underscoring its potential for practical synthetic applications.⁸

Building on the promising results of thioetherification cross-couplings,⁸ we sought to extend the scope of AD-HoC conditions by exploring H₂S as a nucleophile in C(sp²)-S cross-couplings,


 Scheme 1 Overview of AD-HoC strategies for C(sp²)-S cross-couplings.

^a Institute of Chemistry, University of Graz, NAWI Graz, Heinrichstrasse 28, A-8010 Graz, Austria

^b Fakultät für Chemie und Pharmazie, Universität Regensburg, 93053 Regensburg, Germany

^c Nanotechnology Centre, Centre for Energy and Environmental Technologies, VSB – Technical University of Ostrava, Ostrava-Poruba 708 00, Czech Republic

^d Continuous Flow Synthesis and Processing (CCFLOW), Research Center Pharmaceutical Engineering GmbH (RCPE), Inffeldgasse 13, A-8010 Graz, Austria. E-mail: sandor.oetvoes@rcpe.at


enabling access to valuable aryl thiols from simple aryl halide precursors. Initial experiments with a commercially available H₂S solution in THF gave unsatisfactory results (see SI for details); moreover, to achieve high atom economy and minimize solvent use, we opted to employ H₂S gas directly as the sulfur source (Scheme 1c). Because of the hazards and technical challenges associated with handling H₂S gas, we aimed to employ a photochemical flow reactor that is capable of safely managing gas-phase reagents. Continuous flow reactors offer key advantages for gas–liquid reactions, including enhanced heat and mass transfer and precise, safe gas dosing.¹⁰ In contrast, handling H₂S gas under batch conditions would pose considerable safety and operational challenges, while mass transfer and stoichiometric control would be substantially more difficult to maintain. Importantly, photochemical transformations also benefit significantly from flow processing due to short optical path lengths in narrow channels, enabling faster reaction times, higher productivity, and straightforward scalability.¹¹

A corning advanced-flow lab photo reactor, equipped with a glass plate-based fluidic module, high-intensity LED light source, and high-capacity temperature control, was used for process development (Fig. 1). The reaction mixture, consisting of the electrophile (1 equiv., 0.5 M), an acid additive, the nickel catalyst, and 1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene (4CzIPN) as the photocatalyst in DMA, was delivered as a single liquid stream at 0.25 mL min⁻¹ using a syringe pump. H₂S gas was supplied from a cylinder *via* a calibrated mass flow controller (MFC) at a fixed flow rate of 3.05 mL_N min⁻¹, corresponding to 1.1 equiv. relative to the electrophile, thereby minimizing its excess and enhancing both safety and system efficiency. The two streams were combined in a Y-mixer before entering the photoreactor (2.77 mL volume). The system was pressurized at 5 bar by using an adjustable backpressure regulator (BPR). Under these conditions, H₂S gas dissolved completely in the liquid phase, enabling stable single-phase operation and providing a residence time of approx. 10 min within the irradiated reactor zone. To prevent corrosion of the MFC caused by contact with H₂S in the presence of residual moisture, a nitrogen gas purge was implemented *via* a gas inlet switch. The system was purged with nitrogen before and after each use to ensure the MFC was not exposed to moist H₂S.

Using ethyl 4-bromobenzoate as a model substrate, we first examined the influence of various reaction parameters (Table 1).

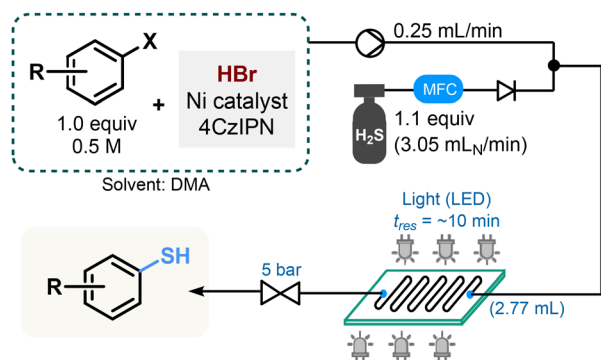


Fig. 1 Representation of the flow reactor setup used in this study.

Based on our previous findings,⁸ certain acids as additives can promote C(sp²)-S cross-couplings under AD-HoC reaction conditions. In fact, under original non-acidic AD-HoC conditions, HBr accumulates over the reaction course, accelerating the cross-coupling and therefore suggesting the autocatalytic nature of the system.^{6a} Accordingly, HBr was tested first as an acidic additive, conveniently applied as a commercially available 47 wt% aqueous solution, due to the tolerance of the system towards moisture. To our satisfaction, the desired thiol product, ethyl 4-mercaptobenzoate, was formed under typical AD-HoC conditions even during the first few trials. Screening nickel sources revealed that (1,2-dimethoxyethane)nickel dibromide (NiBr₂·glyme) performed better than NiBr₂·3H₂O, with 5 mol% catalyst loading proving optimal. Remarkably, the photocatalyst loading could be reduced to just 0.5 mol%, with irradiation at 450 nm identified as ideal, consistent with previous C(sp²)-S cross-couplings under AD-HoC conditions. In contrast, shorter wavelengths significantly decreased conversion, while longer wavelengths afforded only trace product. As was anticipated, no product formation was detected in the absence of light. It was observed that the reaction also required gentle heating, as no product formation occurred at 25 °C despite the irradiation.

One of the major technical challenges of this reaction lies in the subsequent formation of symmetrical thioethers, due to the fact that the generated thiophenol exhibits higher nucleophilic reactivity toward aryl bromides than H₂S itself. As a result, some of our attempts to increase the reaction rate occasionally led to increased side product formation. Nevertheless, by carefully fine-tuning the reaction parameters, we were able to suppress this competing pathway under optimized conditions, achieving a chemical selectivity of 81% while maintaining a reasonable conversion of over 50% (see Table 1, entry 3).

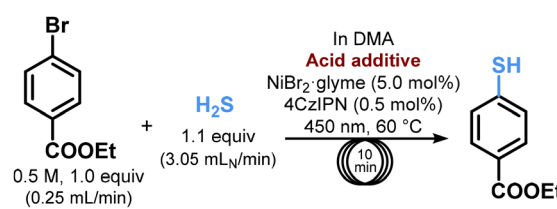
Table 1 Parameter optimization under flow conditions

# ^a	Ni catalyst		4CzIPN [mol%]	λ [nm]	T [°C]	Conv. ^b [%]	Sel. ^b [%]
	Name	[mol%]					
1	NiBr ₂ ·3H ₂ O	5	0.5	450	60	26	90
2	NiBr ₂ ·glyme	2.5	0.25	450	60	Traces	nd
3	NiBr ₂ ·glyme	5	0.5	450	60	51	81
4	NiBr ₂ ·glyme	10	1.0	450	60	56	76
5	NiBr ₂ ·glyme	10	2.0	450	60	57	74
6	NiBr ₂ ·glyme	10	5.0	450	60	51	78
7	NiBr ₂ ·glyme	5	0.5	385	60	38	91
8	NiBr ₂ ·glyme	5	0.5	405	60	41	87
9	NiBr ₂ ·glyme	5	0.5	475	60	<5	nd
10	NiBr ₂ ·glyme	5	0.5	450	25	<5	nd
11 ^c	NiBr ₂ ·glyme	5	0.5	450	60	41	87
12	NiBr ₂ ·glyme	5	0.5	Dark	60	0	—

^a HBr was used as a 47 m/m% aqueous solution. ^b Determined by HPLC-UV at 275 nm. ^c Light intensity was reduced to 50%.



Table 2 Exploring the effects of various acid additives



# ^a	Acid additive Name	[Equiv.]	Conv. ^b [%]	Sel. ^b [%]
1	HBr	0	< 5	nd
2	HBr	1.1	51	81
3	HBr	2.0	< 5	nd
4	HCl	1.1	< 5	nd
5	H ₂ SO ₄	0.5	6	98
6	H ₂ SO ₄	1.1	8	98
7	HNO ₃	1.1	< 5	nd
8	H ₃ PO ₄	1.1	0	—
9	CF ₃ SO ₃ H	1.1	42	83
10	CH ₃ COOH	1.1	8	97

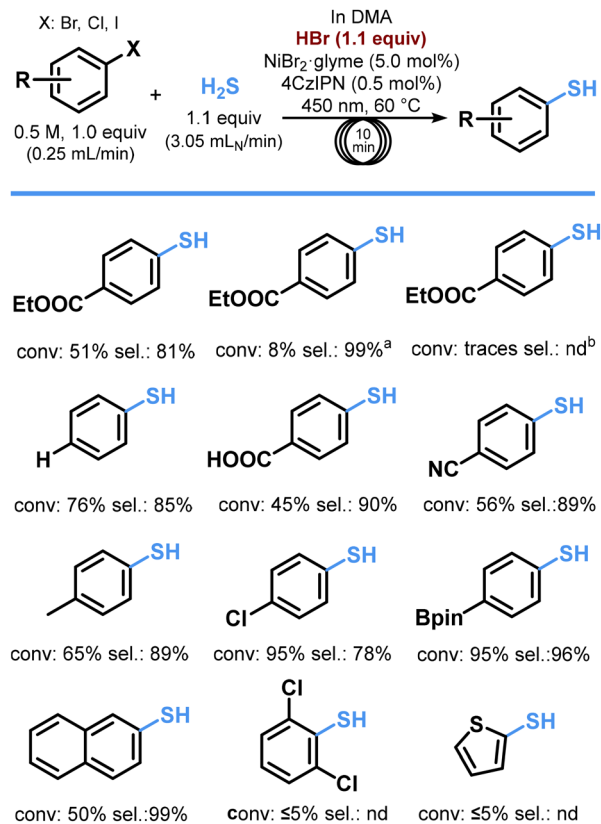
^a HBr was used as a 47 m/m% aqueous solution. HCl, H₂SO₄ and HNO₃ in a concentrated form. ^b Determined by HPLC-UV at 275 nm.

A pronounced influence of the acid additive was observed, as confirmed by a control experiment conducted without any added HBr but otherwise under identical conditions (Table 2, entry 1 vs. 2). In the absence of the acid, the conversion dropped drastically to below 5%, rendering the reaction essentially unproductive. This highlights the beneficial role of HBr in this reaction system.

With more conventional nucleophiles such as thiols and thiophenols, acceptable conversions were obtained even without an external acid, although the addition of HBr still significantly accelerated the reaction.⁸ In contrast, H₂S lacks the steric bulk of thiols and thiophenols, and both of its protons can be readily removed upon deprotonation. As a result, H₂S binds very strongly to the nickel centre and shows a pronounced tendency to form catalytically inactive species with nickel, such as polythiolates and sulfides.¹² The presence of an external acid is therefore crucial, as it prevents strong coordination of H₂S, thereby maintaining a higher concentration of catalytically active species.^{6a,8} Notably, when the amount of HBr was increased from 1.1 equiv. to 2.0 equiv., a significant drop in conversion was observed, likely due to the partial protonation of H₂S (Table 2, entry 3).

In addition to HBr, other Brønsted and carboxylic acids were evaluated as additives (Table 2, entries 4–10). Using HCl, H₂SO₄, HNO₃, H₃PO₄, or CH₃COOH resulted in only very low conversions, which can be possibly explained by their significantly different pK_a values, potential coordination to the catalytically active nickel species, or their redox non-innocence. In contrast, trifluoromethanesulfonic acid (CF₃SO₃H) provided 42% conversion with 83% chemical selectivity, comparable to the results obtained with HBr.

Finally, to gain deeper insight into the reactivity trends under the developed conditions, a series of additional aryl



Scheme 2 Substrate scope for C(sp²)-S cross-coupling reactions with H₂S gas. HBr was used as a 47 m/m% aqueous solution. ^aThe corresponding aryl iodide was used as electrophile. ^bThe corresponding aryl chloride was used as electrophile.

halides were investigated as electrophiles in reactions with H₂S gas (Scheme 2). All experiments were conducted under identical conditions, employing NiBr₂·glyme as the nickel source, 4CzIPN as the photocatalyst, and HBr as the acid additive, at 60 °C under 450 nm irradiation, while maintaining a slight excess of H₂S (1.1 equiv.). Compared to ethyl 4-bromobenzoate, the corresponding iodide exhibited markedly lower reactivity, affording only 8% conversion, and the chloride analogue produced only trace amounts of product under the same conditions. Nonetheless, the ability to selectively activate aryl bromides represents a practical and advantageous feature of this method. The protocol showed high tolerance toward diverse 4-substituted bromobenzene derivatives, irrespective of electronic or steric effects. Conversions of 45–95% and chemical selectivities of up to 96% were obtained with bromobenzene, 4-bromobenzoic acid, 4-bromobenzonitrile, as well as the corresponding 4-methyl-, 4-chloro-, and 4-boronic acid pinacol ester (Bpin) derivatives. Moreover, the bulkier 2-bromonaphthalene was converted to the corresponding thiol with nearly perfect selectivity and 50% conversion. Notably, the major side product observed in some of these reactions was the corresponding symmetrical thioether, formed *via* subsequent coupling with the produced thiophenol product. Among the tested substrates, sterically hindered 2,6-dichlorobromobenzene and 2-bromonaphthalene proved incompatible



with the developed protocol, giving conversions below 5%. A current limitation of the methodology is some reactor fouling, which slowly decreases light penetration over time. This is likely caused by the accumulation and adhesion of certain nickel species on the borosilicate glass reactor walls and can potentially be mitigated by using an alternative reactor material.¹³

In summary, we report our preliminary findings on the direct application of H₂S gas as a useful reagent for aryl thiol synthesis *via* C(sp²)-S cross-coupling under AD-HoC conditions. Continuous flow chemistry was employed as an enabling tool to ensure the safe handling of H₂S gas while achieving an effective and highly controlled transformation under visible-light irradiation. The role of HBr as an acid additive proved crucial in this challenging reaction system, as acid-free conditions resulted in negligible product formation. The reaction utilizes a readily available nickel catalyst and a low loading of 4CzIPN as the photocatalyst. Through precise tuning of the reaction parameters, the formation of symmetrical thioether side products was effectively minimized. Under optimized conditions, the process required only a slight excess of H₂S and a short residence time of 10 min in the photoreactor. This study represents the first instance of an AD-HoC strategy employing H₂S for cross-coupling and offers a simple yet atom-economical method for incorporating sulfur atoms into organic compounds.

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Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the supplementary information (SI). Supplementary information containing general procedures, additional reaction data, compound characterization data and copies of NMR spectra, is available at DOI: <https://doi.org/10.1039/d5cc04825g>.

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