Volume 26
Number 10
21 May 2024
Pages 5585-6220

Green Chemistry

Cutting-edge research for a greener sustainable future

rsc.li/greenchem

ISSN 1463-9262

ROYAL SOCIETY OF CHEMISTRY

PAPER

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Cite this: *Green Chem.*, 2024, **26**, 5845

C(sp^2)–S cross-coupling reactions with nickel, visible light, and mesoporous graphitic carbon nitride†

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Cross-coupling reactions play a vital role in modern organic synthesis, enabling the construction of necessary C–C or C–(het)atom bonds for synthetic transformations. Although C(sp^2)–C and C(sp^2)–N cross-coupling reactions have received significant attention, recent advancements have also highlighted the significance of C(sp^2)–S cross-coupling reactions. These reactions lead to the synthesis of valuable compounds, including pharmaceuticals and materials. In a recent report, we introduced Adaptive Dynamic Homogeneous Catalysis (AD-HoC) as an efficient method for C(sp^2)–S cross-coupling reactions. This method operates without the need for any ligands, base, or additional additives, relying solely on essential parameters. In this report, we discuss the use of mesoporous graphitic carbon nitride (mpg-CN) as an all-organic heterogeneous photocatalyst in such transformations. The versatility and robustness of the reaction are showcased with fifty synthetic examples, achieving up to a 98% yield. The use of mpg-CN as a catalyst additionally enables the easy recovery of the photocatalyst from the reaction mixture and facilitates the sequential execution of multiple cross-coupling reactions with consistent yields of the desired products using a simple setup. This approach is a significant advancement in the field, both in terms of operational simplicity and environmental impact, traits that we all envision for sustainability.

Received 20th November 2023,
Accepted 15th January 2024

DOI: 10.1039/d3gc04517j

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Introduction

Transition-metal-mediated C(sp^2)–(hetero)atom coupling reactions represent extensively explored organic transformations, enabling the efficient construction of molecules and providing access to molecular complexity for a wide range of applications. While C(sp^2)–C[1,2] and C(sp^2)–N[3,4] cross-coupling reactions have gained significant recognition in the synthetic organic community, C(sp^2)–S cross-coupling reactions have also recently emerged as crucial transformations leading to the production of valuable products, including pharmaceuticals and materials.[5–8] Traditionally, palladium has been the catalyst of choice for these transformations.[9–12] However, concerns have arisen regarding the sustainability and toxicity of palladium,[13] prompting the exploration of alternative catalysts, particularly nickel.[14] In this context, visible light photoredox catalysis offers an alternative approach, allowing easy manipulation of the redox state of the transition metal catalyst with the introduction of a photocatalyst.[15–23] Oderinde, Johannes, and co-workers reported C(sp^2)–S cross-coupling reactions using nickel, visible light, and an iridium-based photocatalyst.[24] Subsequently, other photocatalytic protocols have also been reported, including the use of the most stable allotrope of carbon nitride and graphitic carbon nitrides[25] to provide a more sustainable approach for such transformations. Despite considerable progress in this field, whether using transition metals or graphitic carbon nitrides as photocatalysts, these reactions often require extensive optimization processes including various ligands, bases, and/or additives.[24,25] Moreover, the cross-coupling reactions are often limited to (het)aryl iodides as electrophiles,[24,25] with only specific instances where the use of additional additives, such as pyridinium iodide, has enabled the coupling of (het)aryl bromides.[26] Furthermore, many of the reported protocols rely primarily on iridium or ruthenium-based photocatalysts, which are both costly and potential sources of toxic contaminants in the resulting product.[14] Therefore, the alternative use of redox-active organic dyes for such transformations under visible light excitations is considered to be more desirable; however, their relatively low stability under photocatalytic reaction

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†Electronic supplementary information (ESI) available. See DOI: https://doi.org/10.1039/d3gc04517j

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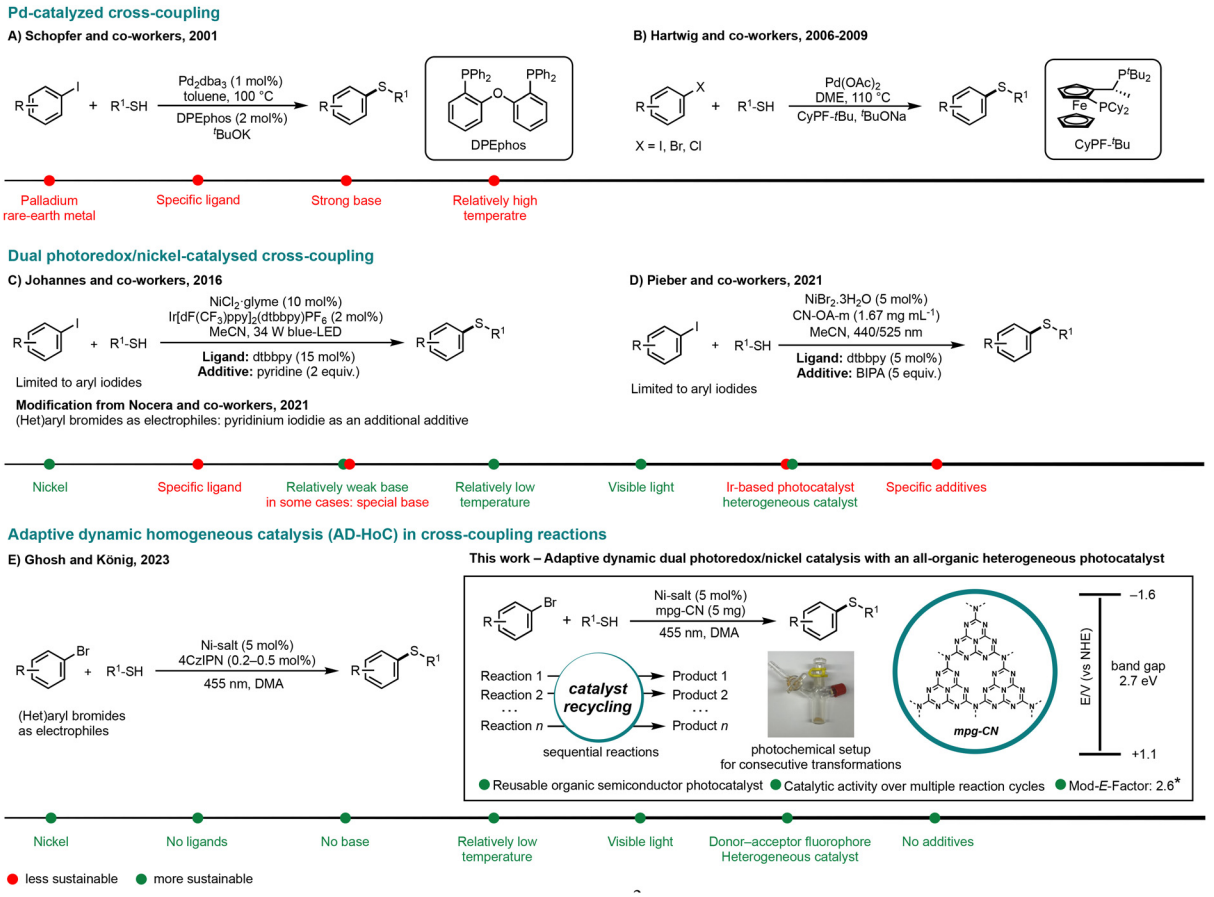


Scheme 1 Representative literature reports on C(sp^2)–S cross-coupling transformations either using palladium or nickel under photoredox dual catalytic conditions with specific ligands and this work. *See ref. 35 and section 5 in the ESI† for more details.

conditions is noteworthy. Depending on the substrates, chemical reaction, and photocatalyst used, the presence of the photocatalyst decomposition product in the reaction mixture often poses challenges during the purification step of the desired product, especially when considering the eventual application of the desired product in bio-related contexts. This necessity often leads to an additional purification step, aspects that are frequently overlooked, contributing to the environmental footprint.

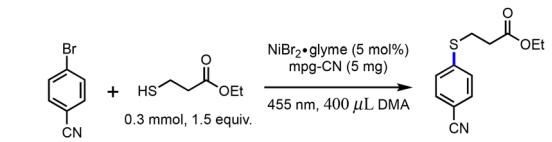
Recently, we introduced Adaptive Dynamic Homogeneous Catalysis (AD-HoC) in C(sp^2)–S cross-coupling reactions–a general, practical approach that eliminates the need for ligands, bases, or additional additives commonly used in traditional cross-coupling reactions.[20] This method facilitates cross-coupling between various (het)aryl bromides with thiols and thiophenols, exclusively powered by visible light and a donor–acceptor fluorophore, namely 1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene (4CzIPN).[20] Mesoporous graphitic carbon nitride (mpg-CN), a purely organic semiconductor material composed of the earth-abundant elements carbon and nitrogen,[27–29] has recently garnered attention as a semiconductor photocatalyst for its straightforward synthesis from readily available and inexpensive starting materials like urea. Therefore, it also boasts a low cost, just a few euros per kilogram.[30] Under visible-light excitation, mpg-CN exhibits a redox window of approximately 2.7 V, ranging from about +1.1 V to −1.6 V *versus* the normal hydrogen electrode (NHE).[31] This redox window is comparable to those of commonly used transition metal complexes, such as $Ru(bpy)_3^{2+}$, eosin Y as an organic dye, or 4CzIPN used as a donor–acceptor complex (see ref. 27 and 28 for additional details on the properties of mpg-CN). Recent studies have demonstrated that the electronic band structures of mpg-CN can be readily tuned through nanomorphology modification or doping.[32] One of its most important advantages is its pure organic and heterogeneous nature, coupled with photo and chemical stability under diverse reaction conditions.[28] Each of these features provides distinct advantages. For instance, (1) the pure organic nature eliminates the potential risk of the presence of toxic transition metal contamination in the final product;[14] (2) the photo and chemical stability of mpg-CN under diverse reaction conditions, as opposed to organic photoredox dyes, facilitates the straightforward attainment of the desired product without contamination from the decomposed photocatalyst–an essential consideration for biomedical applications; and (3) the heterogeneous nature, combined with photochemical stability, not only simplifies the separation of the photocatalyst from the reaction mixture but also enables multiple uses.[28,33]

Considering the simplicity of the C(sp^2)–S cross-coupling reactions under the reported AD-HoC reaction conditions[20] and the attributes of mpg-CN as a sustainable photocatalyst,[28] we envisioned the feasibility of employing mpg-CN for C(sp^2)–S cross-coupling reactions with nickel and visible light alone, without additional additives. Additionally, the photochemical stability and the heterogeneous nature allowing recyclability of the photocatalyst inspired us to devise a more sustainable method, enabling the sequential execution of reactions in a self-made reactor with a straightforward filtration step for each cross-coupling reaction. This approach aligns with an eco-friendly and efficient strategy for organic synthesis, presenting promising prospects for sustainable advancements in the field. The significance of mpg-CN as a photocatalyst is underscored by its recycling capability, influencing the modified Sheldon's environmental impact factor (*E*-factor[34]).

We began our synthetic investigation using mpg-CN as a photocatalyst in C(sp^2)–S cross-coupling reactions with 4-bromobenzonitrile as the test aryl bromide directly with three different classes of thiol nucleophiles: ethyl 3-mercaptopropionate representing primary thiols and a thiol surrogate,[36] benzylthiol, and thiophenol. To our delight, employing the AD-HoC reaction conditions[20] with mpg-CN as the photocatalyst resulted in high yields of the corresponding cross-coupled products for each nucleophile. Control experiments, where light, mpg-CN as a photocatalyst, or $NiBr_2$·glyme were omitted, confirmed the necessity of all components for efficient cross-coupling reactions (*cf.* Table 1, entries 3–5, and the ESI† for additional details). Notably, these reactions remained highly effective with various nickel salts, including different nickel chlorides and their respective hydrates. Moreover, the reactions were successful with reduced solvent quantities (0.2 mmol-scale/40 μL, Table 1, entry 16), demonstrating the simplicity of the reaction conditions, involving just the mere mixing of reaction components and irradiation with a blue LED under a nitrogen atmosphere. Importantly, the cross-coupling reactions were efficiently conducted in different reaction setups, including a commercial photo-setup, allowing rapid completion within an hour (*cf.* Table S3 in the ESI†). The reactions were also effective under an air atmosphere; however, the substrate conversion (in this case, the respective aryl bromide) was relatively poor due to the rapid consumption of the thiol nucleophile, leading to the formation of disulfides. Using an excess of thiol nucleophile (for example, 3.0 equiv. or more) gives the desired cross-coupling product in good yield (*cf.* Table 1, entries 17 and 18).

With the optimized reaction conditions in hand, the scope for C(sp^2)–S cross-coupling reactions was explored with a range of thiols and thiophenols as nucleophiles and different (het) aryl bromides as electrophiles (*cf.*, Fig. 1 and 2). To our delight, numerous thiols, both primary and secondary, proved effective in giving the desired products in good to excellent, and in some instances, nearly quantitative yields. Noteworthy is the near-quantitative yield achieved when using ethanethiol, a low-boiling liquid, as a coupling partner. Both primary and secondary thiols allowed the completion of the cross-coupling reactions within just a few hours in some cases, using a single low-power LED (*ca.* 600 mW, see ESI† for further details).

Table 1 Control reactions and optimization of reaction conditions



Entry	Deviation from the standard reaction condition	1 (% yield)[a]
1	None	94
2	1.0 equiv. thiol	79
3	No mpg-CN	0
4	No $NiBr_2$·glyme	17
5	No light	0
6	2.0 equiv. thiol	93
7	1.0 mg mpg-CN	92[b]
8	2.5 mg mpg-CN	91[b]
9	$NiBr_2·3H_2O$	97
10	$NiCl_2$·glyme	93
11	$NiCl_2·xH_2O$	87
12	Dimethylformamide (DMF) as a solvent	89
13	Dimethyl sulfoxide (DMSO) as a solvent	3
14	Pyridine as a solvent	8
15	Acetonitrile (MeCN) as a solvent	1
16	Dimethylacetamide (DMA) – 40 μL	79[c]
17	No degassing – 1.5 equiv. of nuclophile	36[d]
18	No degassing – 3.0 equiv. of nuclophile	79[d]

[a] Yields were determined (within analytical errors, ±5%) by GC-FID using 1,3,5-trimethoxybenzene as an internal standard. [b] It should be noted that while the cross-coupling reaction yielding compound **1** can be performed with a lower amount of catalyst loading, the use of 5.0 mg of mpg-CN was found to be beneficial for cross-coupling reactions in general with thiophenols (see ESI† for further details). [c] The cross-coupling reaction was performed only using 40 μL DMA as a solvent, see ESI† for further details. [d] The cross-coupling reaction was performed just by closing the reaction vial without degassing.

Benzylic thiols, when used as nucleophiles, were also of no exception in giving the desired products: neutral (**6**), electron-deficient (**7**), and electron-rich (**8**) benzylic thiols all exhibited near-quantitative yields. Importantly, the presence of steric bulk at the arene core of the benzyl thiol had only minimal influence on the reaction outcome. This was evident when mesitylmethanethiol was used as a representative nucleophile, yielding the desired product **9** in 93% isolated yield. The photochemical reaction can also be performed on a gram-scale, giving the desired product in nearly identical yield (see Fig. 1 and ESI† for further details). When steric hindrance was introduced, however, at the benzylic position (for example, using 1-phenylethane-1-thiol as a nucleophile), there was a slight decrease in the yield, which we attribute to the increased steric demand on the nickel species (*cf.*, ref. 37). Nevertheless, a synthetically useful amount of the desired cross-coupling product (**10**) was obtained. Additionally, the presence of a bromo substituent on the phenyl ring (**11**) of the nucleophile was well-tolerated[38] yielding the desired product with a good 71% isolated yield, providing potential avenues for multifunctionalization reactions.[39]

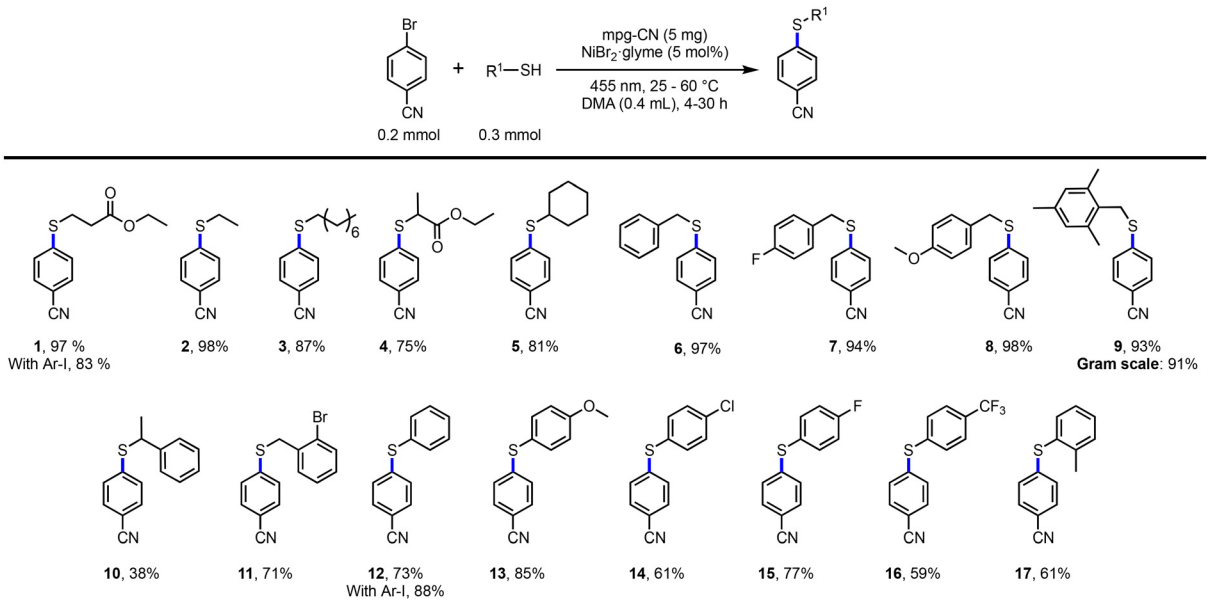


Fig. 1 Nucleophiles scope in C(sp^2)–S cross-coupling reactions using mpg-CN as a photocatalyst. Aliphatic, benzylic, and thiophenols are used as nucleophiles. Isolated yields are reported unless noted otherwise. See also Fig. 3 for additional synthetic examples and ESI† for further details.

The cross-coupling reactions also yielded favorable results when thiophenols were used as coupling partners. Various thiophenols, including electron-neutral, electron-rich, and electron-deficient variants, produced the desired products in good to excellent yields (Fig. 1, **12–17**). Interestingly, the chloro substituent in the thiophenol core was well-tolerated, resulting in a 61% yield of the desired product. Lastly, sterically demanding thiophenols, such as 2-methylthiophenol as a coupling partner, posed only a minor hindrance to achieving the desired product.[40]

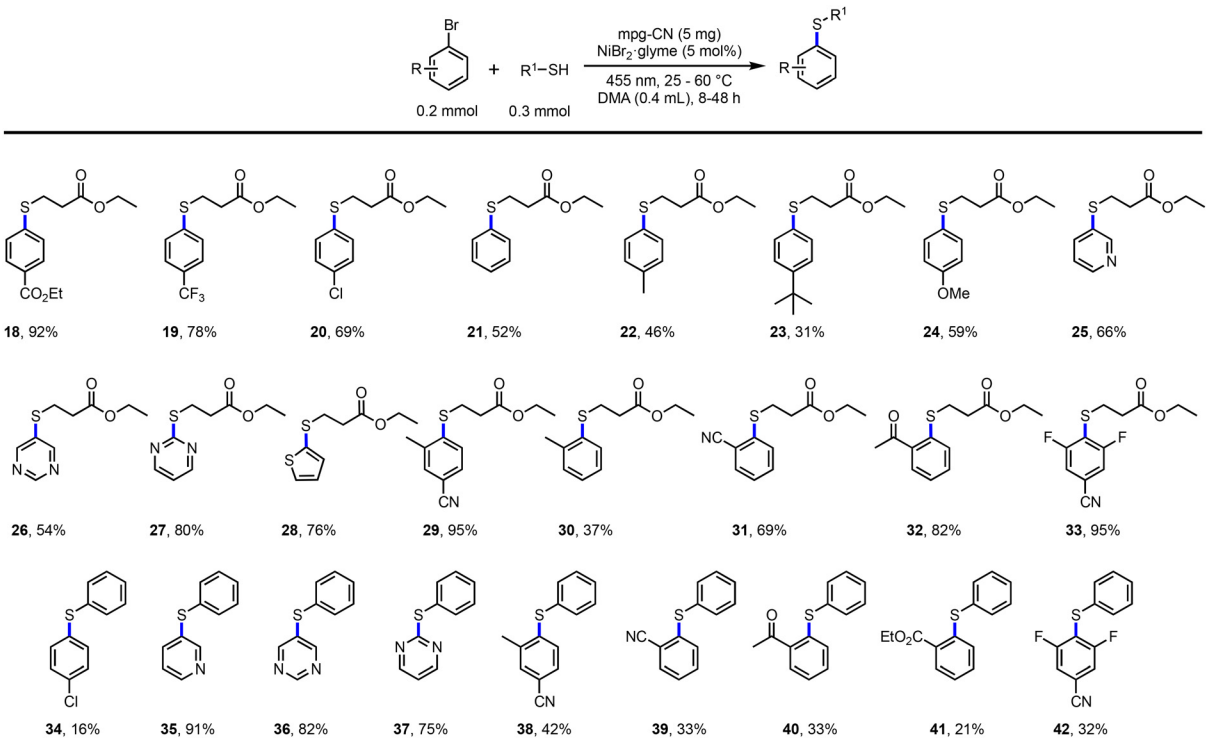


Fig. 2 Electrophiles scope for C(sp^2)–S cross-coupling reactions using mpg-CN as a photocatalyst. Isolated yields are reported unless noted otherwise. For further details see ESI.†

Although relatively complex, the dual photoredox cross-coupling reaction likely follows the mechanism involving a Ni(I)/Ni(III) catalytic cycle, as recently proposed in the literature,[14,26] and also with 4CzIPN as a photocatalyst.[20] The dynamic nature of the photoredox catalytic system was also observed in the present study. Under photoredox reaction conditions, the Ni(II) complex forms Ni(I) species, which undergo oxidative addition with the (het)aryl halides, generating Ni(III) species. Subsequently, the Ni(III) species undergo reductive elimination to form the desired product.

A diverse range of electrophiles bearing various functional groups, such as –CN, $–COCH_3$, $–CO_2Et$, $–CF_3$, –F, and –Cl produced the desired C(sp^2)–S coupling products in good to excellent yields. While electron-deficient electrophiles were expected to yield the desired products in good yields due to their facile oxidative addition, to our delight, electron-neutral electrophiles, like 1-bromo-4-*tert*-butylbenzene and 4-bromotoluene, also yielded the desired product in moderate yields. More importantly, electron-rich electrophiles, which exhibit relatively slower oxidative addition, particularly 1-bromo-4-methoxybenzene, could be used as an electrophile in the cross-coupling reaction, providing the desired products in good yield, albeit over a longer reaction time.

The C(sp^2)–S cross-coupling reactions were equally effective when heteroaryl bromides were used as electrophiles. Among the (het)aryl bromides, 3-bromopyridine, 5-bromopyrimidine, 2-bromopyrimidine, and 2-bromothiophene, each possessing a biologically relevant heterocyclic core,[41] yielded the desired products in good to excellent yields (Fig. 2, **25–28**; **35–37**). The *ortho*-substituted aryl bromides were also well-tolerated in the cross-coupling reactions, especially when primary thiols (**29–33**) were employed as nucleophiles, resulting in moderate to good yields, and in some cases, excellent yields were achieved. When thiophenols were used as nucleophiles, the influence of steric hindrance at the *ortho* position became more prominent. Nevertheless, the desired products (**38–42**) were all isolated in synthetically useful yields.

The significance of mpg-CN as a photocatalyst for C(sp^2)–S cross-coupling becomes more prominent when we turn our attention toward its recycling capability and the associated impact on the modified environmental impact factor (mod-*E*-factor, *cf.*, ref. 34 and 35; for further details, see section 5 in the ESI†) of the reaction. The amalgamation of photo and chemical stability, complemented by its heterogeneous nature, facilitates the straightforward separation and recovery of mpg-CN from the reaction mixture through processes such as simple centrifugation or filtration (see ESI† for further details). This, along with the simplicity of the dual metal photoredox catalytic reaction conditions (*i.e.*, absence of ligands, organic bases, and other additives), ultimately bypasses additional complications in the product purification–an aspect of paramount importance in bio-related applications. Kinetic studies confirmed a consistent performance (in this case, formation of the desired product over time, *cf.* Fig. 3B) of recovered mpg-CN within the experimental error. Furthermore, the recovered mpg-CN was successfully applied in eleven different C(sp^2)–S cross-coupling reactions, each yielding distinct products without any reduction in yield (Fig. 3C).

Of even greater significance, the facile recovery of the catalyst through simple filtration has enabled the development of a streamlined photochemical setup for consecutive transformations in sequence, as illustrated over eighteen cycles for the

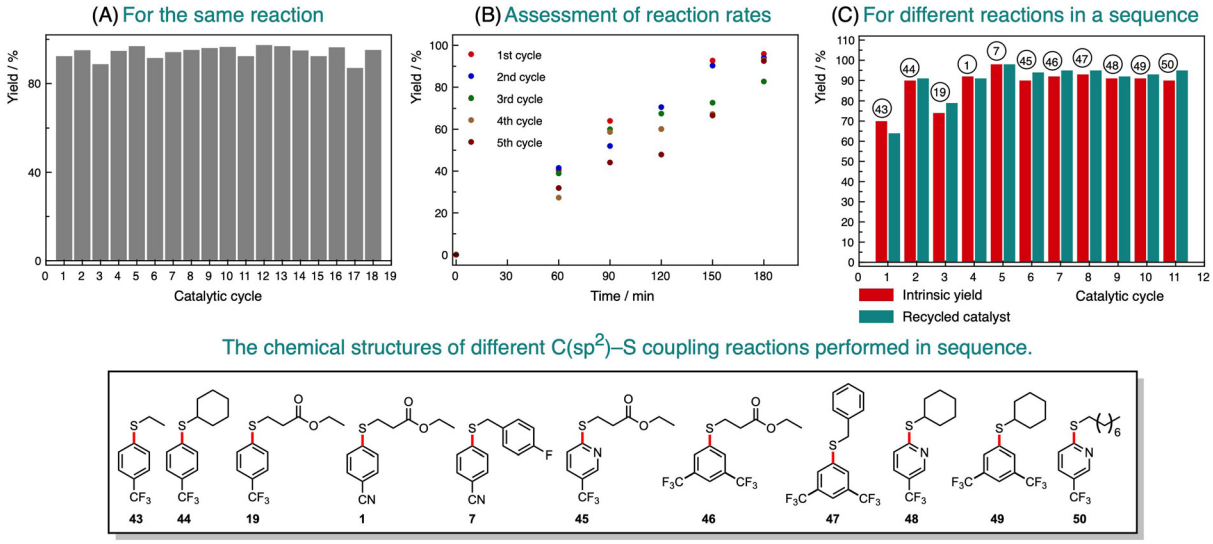


Fig. 3 (a) Evaluation of catalyst recycling for the C(sp^2)–S cross-coupling reaction of 4-bromobenzonitrile with ethyl 3-mercaptopronionate. The yields were determined by GC-FID using 1,3,5-trimethoxybenzene as an internal standard. The flat-bottom 10 mL Schlenk flask equipped with a glass frit was used (see ESI† for further details). (b) Evaluation of the kinetic profile (in this case, the yield of the desired product with time) on the catalyst recycling for C(sp^2)–S cross-coupling reactions using 4-bromobenzonitrile and ethyl 3-mercaptopronionate. (c) Evaluation of catalyst recycling for different C(sp^2)–S cross-coupling reactions. The yields were determined by either ^{19}F NMR spectroscopy using 2,2,2-trifluoroethan-1-ol as an internal standard or by GC-FID using 1,3,5-trimethoxybenzene as an internal standard. For further details see ESI.†

synthesis of product **1** (see Fig. 3A). This setup involves just a flat-bottom 10 mL Schlenk flask equipped with a glass frit (Scheme 1 and Fig. S4†). After each reaction cycle, the photocatalyst can be easily recovered through filtration using the glass frit and promptly reused after a simple rinsing step to prevent product contamination (see ESI† for more details). It is to be noted here that the straightforward cross-coupling reaction conditions (*i.e.*, relying solely on essential parameters) also contribute to the sustainability of the method, as the simplicity and predictability reduce the consumption of materials and solvents during optimization, aspects often overlooked in methodology development but crucial for fostering a sustainable transformation in chemical processes.

Taken together, the use of mpg-CN for C(sp^2)–S cross-coupling reactions under AD-HoC reaction conditions[20] not only emphasizes the operational simplicity of the catalytic system but also highlights its impact on the mod-*E*-factor.[35] For instance, when calculated for a 40 μL reaction with catalyst recovery (*cf.*, entry 16 in Table 1), the mod-*E*-factor is approximately 2.2. We believe that further reduction can be achieved by developing next-generation photocatalytic systems, especially those that incorporate nickel into the mpg-CN framework.[42,43] This incorporation may enable the recovery of all necessary components from the reaction mixtures, leaving only HBr as the by-product of the cross-coupling reaction.

Conclusions

Mesoporous graphitic carbon nitride (mpg-CN) is an organic and recyclable photocatalyst that enables the nickel-mediated construction of C(sp^2)–S bonds through visible light irradiation without the need for ligands, bases, or additives. This cross-coupling protocol is versatile, accommodating a wide range of substrates, including aliphatic, benzylic, and various thiophenols, even those with steric bulk, resulting in high yields. The photo and chemical stability of mpg-CN facilitate the photocatalyst separation process from the reaction mixture without leaving any undesired (decomposed) catalyst components in the product, and the heterogeneous nature of mpg-CN makes it easy to recover and reuse, streamlining the execution of diverse cross-coupling reactions sequentially. The integration of nickel into the mpg-CN framework could further enhance the sustainability of the transformation, enabling the recovery of all essential components from the reaction mixture, leaving only HBr as the by-product. This approach aligns with the drive for improved atom economy in chemical transformations, promoting sustainable and efficient synthetic processes. We anticipate that this work will inspire the development of next-generation more sustainable photocatalytic systems.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgements

This work was supported by the Deutsche Forschungsgemeinschaft (DFG, German Science Foundation)–TRR 325–444632635. We thank Dr Rudolf Vasold (University of Regensburg) for his assistance in GC–MS measurements, Ms. Regina Hoheisel (University of Regensburg) for her assistance in cyclic voltammetry measurements, and Mr Ernest Lautenschlager (University of Regensburg) for his assistance in solving technical issues. M. N. thanks Anastasia Dmitrievna and Olga Kuznetsova for their support.

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