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Recent Advances in Nickel-Catalyzed C-Heteroatom Cross-Coupling Reactions under Mild Conditions via Facilitated Reductive Elimination

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Abstract: The formation of C-heteroatom bonds represents an important type of bond-forming reaction in organic synthesis and often provides a fast and efficient access to privileged structures found in pharmaceuticals, agrochemical and materials. In contrast to conventional Pd- or Cu-catalyzed C-heteroatom cross-couplings under high-temperature conditions, recent advances in homo- and heterogeneous Ni-catalyzed C-heteroatom formations under mild conditions are particularly attractive from the standpoint of sustainability and practicability. The generation of Ni^{III} and excited Ni^{II} intermediates facilitate the reductive elimination step to achieve mild cross-couplings. This minireview provides an overview of the state-of-the-art approaches for mild C-heteroatom bond formations highlights the developments in photoredox and nickel dual catalysis involving SET and energy transfer processes; photoexcited nickel catalysis; electro and nickel dual catalysis; heterogeneous photoredox and nickel dual catalysis involving graphitic carbon nitride (mpg-CN), metal organic frameworks (MOFs) or semiconductor quantum dots (QDs); as well as more conventional zinc and nickel dual catalyzed reactions.

1. Introduction

Over the past several decades, transition metal-catalyzed cross-coupling reactions have made vital contributions in the field of organic synthesis.^[1] A wide range of valuable pharmaceutical agents, materials, and fine chemicals bearing diverse functionalities have been accessed via the formation of C-C or C-heteroatom bonds through coupling chemistry. In this regard, palladium^[2]- and copper^[3]-catalyzed C-heteroatom cross-couplings are well established. However, the reductive elimination from the palladium catalyst and the oxidative addition to the copper catalyst have high energy barriers. Therefore, high temperature or specialized ligands are usually required in C-heteroatom cross-couplings. In recent years, increasing attention has been devoted to earth-abundant nickel catalysis.^[4] Compared to palladium, nickel is more nucleophilic and thus more easily undergoes oxidative addition. In contrast, the reductive elimination step from nickel is endothermic, making the C-heteroatom bond formation more difficult. To overcome these difficulties, a series of methodologies have been developed to generate unstable nickel intermediates, including Ni^{III} and excited Ni^{II} complexes, thus facilitating reductive elimination (Scheme 1). The generality of this phenomenon is supported by the DFT calculation of the reductive elimination energy barriers for a series of Ni^{II} and Ni^{III} intermediates bearing different types of nucleophiles (Scheme 2).^[5] In this review, we summarize different approaches for nickel-catalyzed C-heteroatom cross-coupling reactions under mild conditions, which mainly include i) photoredox and nickel dual-catalyzed reactions involving single-electron transfer (SET); ii) photoredox and nickel dual-catalyzed reactions involving energy transfer; iii) photoinduced nickel-catalyzed reactions; iv) electro and nickel dual-catalyzed reactions; v) heterogeneous photoredox and nickel dual catalysis; and vi) light irradiation-free zinc and nickel dual catalysis.

Conventional:**Ullmann Reaction:**

high energy barrier of oxidative addition

Buchwald-Hartwig Reaction:

high energy barrier of reductive elimination

Nickel-Catalyzed Cross-Coupling Reaction: **Approaches facilitating the reductive elimination in Ni catalysis**

Scheme 1. Different types of C-heteroatom cross-coupling reactions.

2. Photoredox and nickel dual-catalyzed reactions involving SET

A general mechanism for photoredox and nickel dual-catalyzed reactions involving SET is shown in Scheme 3. First, the oxidative addition of aryl halide to the active Ni⁰ species gives an aryl-Ni^{II}-halide complex, which then undergoes transmetalation with a nucleophile, with or without the aid of a base, to form an aryl-Ni^{II}-Nuc complex. Next, the newly formed Ni^{II} complex is oxidized by the excited photocatalyst to furnish an aryl-Ni^{III}-X-Nuc intermediate that easily undergoes reductive elimination to deliver the C-heteroatom cross-coupling product and the Ni^I-X intermediate. Last, the reduction of the Ni^I-X intermediate regenerates the active Ni⁰ species and completes the catalytic cycle.

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	$\Delta\Delta G^\ddagger$ required for reductive elimination at Ni^{II} [kcal/mol]	$\Delta\Delta G^\ddagger$ required for reductive elimination at Ni^{III} [kcal/mol]
	19.8	0.7
	17.9	2.2
	31.1	4.8
	29.5	10.0
	33.2	10.5
	33.1	2.2
	20.3	3.8
	32.6	0.2

Scheme 2. The reductive elimination energy barrier for different types of C-heteroatom cross-couplings at Ni^{II} and Ni^{III} .

Scheme 3. General mechanism of photoredox and nickel dual catalyzed reactions involving SET.

2.1 Photoredox and nickel dual-catalyzed C-N bond cross-coupling

An initial breakthrough was made in 2015 by Jamison and coworkers, who reported a photoredox and nickel dual-catalyzed indoline synthesis with high regioselectivity (Scheme 4A).^[6] One $C(sp^3)$ -N bond along with one $C(sp^2)$ - $C(sp^2)$ bond were generated in one synthetic operation involving the reaction of iodoacetanilides and alkenes. The success of this transformation is attributed to the dual functions of the photocatalyst: i) oxidation of the Ni^{II} amido complex to an unstable Ni^{III} amido complex in the absence of an exogenous ligand and ii) reduction of the Ni^I intermediate to regenerate active Ni^0 species and complete the nickel catalytic cycle. Particularly, the oxidative addition of iodoacetanilides to Ni^0 produces a Ni^{II} complex, which

coordinates with an alkene and undergoes migratory insertion to generate another Ni^{II} complex. Subsequently, this newly generated Ni^{II} complex undergoes ligand exchange with a pendent NH group and is then oxidized by an excited Ru photocatalyst to a Ni^{III} complex. This Ni^{III} amido complex then undergoes reductive elimination to deliver the desired indoline product and Ni^I intermediate. Active Ni^0 species are regenerated via reduction by the photocatalyst. Unlike previous reports in which the photocatalyst was used to oxidize a radical precursor to give a radical and reduce the nickel intermediate to a lower valence state, the whole photoredox cycle in this protocol was used to modulate the oxidation state of the nickel center directly for the first time. Notably, the use of a Ni^0 catalyst in the presence of the N-heterocyclic carbene (NHC) ligand IPr is crucial for β -H elimination suppression and highly selective alkene migratory insertion. A number of 4- or 5-substituted 2-iodoacetanilides underwent this protocol smoothly, while 3- or 6-substituted 2-iodoacetanilides gave substantially lower yields. Aliphatic alkenes containing trimethylsilyl groups, protected alcohols and amines, ketones, and alkyl chlorides as well as electron-rich and electron-poor styrenes were all suitable coupling partners, giving the corresponding product in good to excellent yields. However, internal and 1,1-disubstituted alkenes gave not the desired products, which is a limitation of this protocol.

In 2016, MacMillan, Buchwald, and coworkers developed a photoredox and nickel dual-catalyzed amination reaction of aryl halides (Scheme 4B).^[7] This catalytic aryl amination protocol has high efficiency and selectivity without specialized ligands and proceeds under very mild reaction conditions. Moreover, the need for low photocatalyst loadings (≤ 0.02 mol %) makes it an appealing and practical methodology. A series of primary and secondary aliphatic amines and diverse (hetero)aryl bromides could participate in chemoselective amination in good yields, and functional groups, including trifluoromethyl, fluoride, hydroxyl, vinyl, amide, chloro, ester, and sulfonamide groups, were all tolerated. α -substituted alkylamines and aryl bromides could be coupled in moderate to good yields, while more hindered *tert*-butylamine and 2,6-disubstituted arene showed no activity. A protodehalogenation byproduct, trace phenol, and an aryl ether or aryl chloride were observed for substrates that gave lower yields, and lowering the photocatalyst loading (0.002 mol %) increased the reaction efficiency and inhibited competitive protodehalogenation by electron-rich arenes. Notably, amines lacking α -hydrogens such as sulfonamides and anilines failed to give the corresponding products under the standard reaction conditions, while the addition of a catalytic amount (10 mol%) of pyrrolidine possessing α -hydrogens resulted in good efficiency. The authors proposed that to initiate the nickel catalytic cycle, a β -hydride elimination event is a prerequisite for generating the active Ni^0 species from a stable Ni^{II} catalyst. A computational work by Ma and coworkers provided some insight into the requirement for α -hydrogen-containing pyrrolidine.^[8] Moreover, the reactions of 18 drug-like aryl halides were tested in a high-throughput fashion with a microscale informer plate, and 78% of these substrates could undergo this aryl amination protocol to give the desired products in optimizable yields. Additionally, this mild aryl amination was evaluated as a flow chemistry protocol via the reaction of 4-bromobenzotrifluoride and pyrrolidine, and a 95% yield was obtained in only 15 min, showing its advantages over traditional palladium-catalyzed amination reactions. The scope of

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the amination under continuous flow conditions was also explored.^[9]

In the same year, Johannes, Oderinde, and coworkers developed a photoredox and nickel dual-catalyzed cross-coupling procedure for C-N bond formation by emphasizing the reactions of primary aryl amines with aryl halides (Scheme 4C).^[10] This protocol proceeded with high chemoselectivity and broad functional group compatibility under very mild conditions without rigorous degassing of molecular oxygen, showing the practical utility of this amination methodology. A wide range of electron-rich and electron-poor aryl iodides bearing synthetically useful functional groups or *ortho* substituents as well as heteroaryl iodides could be coupled with aniline in moderate to excellent yields. In addition to anilines containing hydroxy, vinyl, acetylene, chloro, and methoxy groups, sulfonamides and heteroaryl amines could also be engaged. The tolerance of the active functional groups allows further functionalization of the generated amine products. Notably, no subsequent arylation of the generated secondary amine products occurred in any of the reactions, and little to no amination products were observed when N-methylaniline and diphenylamine were coupled with 1-chloro-4-iodobenzene, which may be partially due to steric hindrance. The main side reaction of this protocol is hydrodehalogenation of aryl halides to deliver the reduced arenes, and trace biaryl byproducts were observed in some cases, which indicates an aryl radical-involved mechanism. Benzyl amine and alkyl amines bearing α -hydrogens participated in this protocol with very low yields, which can be attributed to the competitive deprotonation of the corresponding aminium radical cation or β -hydride elimination from the formed Ni^I-amido complex. Based on these observations, the authors proposed a Ni^{III/II} mechanism. First, aniline is oxidized by an excited Ir photocatalyst to an aniline radical cation that is deprotonated by Et₃N to give an aniline radical. Rapid interception of the aniline radical by the pregenerated Ni^I-halide complex delivers an amido-Ni^{II}-halide intermediate that is then reduced by the photocatalyst to form another Ni^I-amido complex. Oxidative addition of the Ni^I-amido complex with aryl halide forms an unstable Ar-Ni^{III}-amido intermediate, which is prone to undergo reductive elimination to deliver the amination product and regenerate the active Ni^I-halide complex.

Extensive work was reported by Vannucci and coworkers.^[11] In this work, in addition to the successful coupling of primary aryl amines with aryl halides, secondary amines and sulfonamides were also used as efficient coupling partners, making it the first photoredox and nickel dual-catalyzed protocol capable of accessing both bi- and triaryl amines.

Additionally, steric *ortho*- and highly substituted anilines could be coupled successfully to give the corresponding products in good yields. Stern-Volmer fluorescence quenching experiments showed that aniline could quench the Ru photocatalyst with or without base, suggesting the formation of aniline nitrogen radicals. Although these methods have provided efficient ways to access structurally diverse amines bearing various functionalities, the applications of heteroaryl amines and more complex heterocycles as coupling partners still represent limitations. The work recently reported by Johannes, Konev, and coworkers overcame some of these limitations via the development of a procedure for the photoredox and nickel dual-catalyzed reductive cross-coupling of aryl azides and aryl electrophiles, including heteroaryl iodides, bromides, chlorides, and triflates (Scheme 4D).^[12]

A. Indoline synthesis

key intermediates

B. C-N bond cross-coupling using aliphatic amine

selected examples

C. C-N bond cross-coupling using aniline

selected examples

D. C-N bond cross-coupling using aryl azide

X = Cl, Br, I, OTf

key intermediates

selected examples

Scheme 4. Photoredox and nickel dual-catalyzed C-N bond cross-coupling involving SET.

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This protocol also proceeded without the exclusion of oxygen under mild conditions, making it practical. A wide range of heteroaryl electrophiles bearing pyridine, diazine, azole, and thiazole motifs were all competent coupling partners. A series of synthetically useful functional groups, including ketone, ester, cyano, boronate ester, and even unprotected NH groups, were well tolerated. Electron-neutral and electron-rich azides, including those bearing steric functionalities and heterocycles, performed well in this reductive amination coupling. Moreover, some complex drug-like diarylamines were synthesized from heterocyclic aryl iodides and azides in synthetically useful yields. For the mechanism, a $\text{Ni}^{0/\text{I}/\text{II}/\text{III}}$ coupling cycle was proposed. First, the oxidative addition of aryl electrophiles to active Ni^0 species gives an aryl- Ni^{II} -halide complex, which then coordinates to an aryl azide. Next, the coordinated azide was reduced by the photocatalyst to the corresponding radical anion, which undergoes subsequent protonation and loss of N_2 to deliver an anilino radical. This anilino radical is then trapped rapidly by the Ni^{II} complex to form a Ni^{III} amido complex, which undergoes reductive elimination to afford the desired diarylamine products and Ni -halide complex. Finally, the active Ni^0 species is regenerated via the reduction of this Ni^{I} complex by the photocatalyst. A control experiment that strongly supports this proposed mechanism was conducted. A direct diarylamine product was obtained from an *ortho*-allylic-substituted azide in excellent yield, while no 5-exo-trig cyclization product was observed, suggesting the formation of the coordinated aryl- Ni^{II} azide complex.

2.2 Photoredox and nickel dual-catalyzed C-O bond cross-coupling

Similar to C-N bond formation, the reductive elimination of the Ar- Ni^{II} alkoxide is also endothermic and thus does not readily occur at room or elevated temperature. However, with the assistance of stoichiometric oxidants, an unstable Ni^{III} alkoxide species could be accessed to facilitate the C-O bond formation.^[13] Inspired by this result, Macmillan and coworkers developed an efficient C-O coupling protocol under mild conditions by merging photoredox and nickel catalysis (Scheme 5A).^[14] Herein, the Ir photocatalyst acted not only as an oxidant to oxidize Ni^{II} to the elusive Ni^{III} -alkoxide complex but also as a reductant to reduce Ni^{I} to Ni^0 , thus completing the catalytic cycle. A computational work by Su, Guan, and coworkers investigated the proposed mechanism in detail.^[15] A wide range of electron-deficient and electron-rich aryl bromides, as well as pyridines with substituents at different positions, could be coupled in good to excellent yields. Additionally, primary and secondary alcohols, including complex and medicinally relevant motifs as well as the weakly nucleophilic trifluoroethanol, could all undergo this etherification protocol with good efficiency. Notably, H_2O could also be coupled smoothly with electron-poor aryl bromides to generate the corresponding phenol product. A stable Ar- Ni^{II} alkoxide was synthesized, and the control experiment showed that the photocatalyst and visible light are essential for the formation of the corresponding ether product. Moreover, cyclic voltammetry (CV) measurements of the Ni^{II} complex (irreversible oxidation at +0.83 V versus SCE in CH_3CN) showed that the $^*\text{Ir}^{\text{III}}$ photocatalyst ($E_{1/2}^{\text{red}} [^*\text{Ir}^{\text{III}}/\text{Ir}^{\text{II}}] = +1.21$ V versus SCE) is able to oxidize the Ni^{II} complex, and Stern-Volmer fluorescence quenching experiments indicated that the $^*\text{Ir}^{\text{III}}$ photocatalyst could be quenched by the Ni^{II} complex. All these results strongly

suggest that a transient Ni^{III} complex is involved in the catalytic process.

Later, Xue and coworkers also realized the hydroxylation reaction of aryl halides with water via organophotoredox and nickel dual catalysis (Scheme 5B).^[16]

A. C-O bond cross-coupling using an alcohol

selected examples

B. C-O bond cross-coupling using water

selected examples

C. C-O bond cross-coupling using a peptide

selected examples

Scheme 5. Photoredox and nickel dual-catalyzed C-O bond cross-coupling involving SET.

The use of BODIPY in lieu of expensive noble metals as photocatalysts and the avoidance of strong inorganic bases make this protocol appealing and practical for the synthesis of phenols. The elaborate introduction of neighboring amino groups enhanced the nucleophilic property of H_2O via the intramolecular hydrogen-bond effect. The scope of this protocol is broad, and a large number of electron-poor, electron-neutral, and electron-rich aryl bromides, including heterocyclic and drug-like substrates as well as aryl chlorides, can undergo this hydroxylation reaction with moderate to high efficiency. It is important to point out that to obtain good results, a higher temperature (120 °C) or longer reaction time (36 h) was required for the aryl chlorides, electroneutral and electron-rich aryl bromides than for the other substrates. Recently, this dual catalysis strategy was extended to challenging and valuable peptide C-O cross-coupling (Scheme 5C).^[17] Intermolecular etherification between amino acids

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containing alcohols and bromobenzoyl-capped peptides as well as side chain-to-tail macrocyclization of peptides via intramolecular C–O bond formation were realized, providing a general and efficient methodology for the late-stage diversification of linear and macrocyclic peptides.

2.3 Photoredox and nickel dual-catalyzed C–S bond cross-coupling

Ir/Ni-dual-catalyzed C–S bond formation was first realized by Oderinde, Johannes, and coworkers via cross-coupling of aryl and heteroaryl iodides with aryl, benzyl, and alkyl thiols under mild conditions (Scheme 6A).^[18] Different from C–N and C–O bond cross-couplings, the SET oxidation step of the photocatalyst was used to generate thiyl radicals from thiols rather than modulate the oxidation state of Ni intermediates. A successful radical trapping experiment with olefins and the fact that Stern–Volmer quenching between the thiol and $^*Ir^{III}$ showed excellent linear regression both confirmed thiyl radical generation. CV analysis of $NiCl_2 \cdot dtbbpy$ indicated that the reduction of the Ni^{II} complex to the Ni^I intermediate by Ir^I is thermodynamically and kinetically favored. Additionally, a good coupling yield was observed in the presence of O_2 , while almost no product was obtained when using the Ni^0 catalyst. All these results suggest that Ni^I species, rather than Ni^0 species are the active catalyst in this protocol. Therefore, a $Ni^{II/III}$ mechanism was proposed. Under optimal reaction conditions, a wide range of aryl iodides bearing useful functionalities and heteroaryl iodides could all participate in this protocol with high chemoselectivity and good efficiency. In addition, electron-rich thiophenols and simple and functionalized primary, secondary and tertiary alkyl thiols were all suitable substrates and gave the corresponding thioether products in moderate to excellent yields. However, the electron-poor thiophenols seemed inapplicable to this transformation.

In 2017, the photoredox/Ni-dual-catalyzed C–S coupling was extended to bromoalkynes, providing a good method for the alkylation of thiols to form structurally diverse alkynyl sulfides (Scheme 6B).^[19] The application of a soluble and inexpensive organic carbazole-based 4CzIPN photocatalyst and bipyridine-based, ligand-free, and continuous flow techniques make this protocol more practical than its predecessor. Generally, this transformation was completed in short reaction times (30 min), and a gram-scale reaction could be realized with high reproducibility. The mechanism was proposed to be similar to the thioetherification of aryl iodides via the $Ni^{II/III}$ catalytic cycle. The scope was broad, and a series of alkynyl sulfides could be generated from electronically and sterically diverse aromatic alkynes and thiols. Notably, the chirality was completely preserved after the reaction of an enantiomerically pure substrate. Interestingly, a 19-membered macrocyclic structure was also obtained in synthetically useful yield via intramolecular C(sp)–S bond formation. Moreover, diverse synthesis applications of the generated alkynyl sulfides, such as hydration, reduction, oxidation, intermolecular [2+2] cycloaddition, and azide-alkyne cycloaddition, were successfully achieved in good to high yields. Molander and coworkers also reported the photoredox/Ni-dual-catalyzed thioetherification of aryl bromides under mild conditions (Scheme 7A).^[20] Different from the aforementioned cases, in this protocol, thiyl was generated not by direct photoredox oxidation of thiol but via intra- or intermolecular hydrogen-atom transfer (HAT) with alkyl radicals from alkylbis(catecholato)silicate

precursors. The thiyl radical was then involved in the nickel-catalyzed coupling of aryl halides to give the thioetherification product via a $Ni^{0/II/I}$ catalytic cycle. The driving force of the selectivity for C–S bond formation rather than C–C bond formation may be the different bond-dissociation energies (BDEs) of the C–H and S–H bonds (ethane 1 °C–H BDE = 101.1 kcal mol^{−1} versus methanethiol S–H BDE = 87–88 kcal mol^{−1}). Under the optimal conditions based on a Ru-based photocatalyst, a primary alkyl thiol bearing a distal alkyl silicate could couple with various electron-poor and electron-neutral aryl bromides as well as heteroaryl bromides containing pyridine, quinoline, isoquinoline, thiophene, caffeine, and indazole motifs with good efficiencies. In addition, using an external isobutylsilicate as a traceless HAT reagent, a series of simple primary, secondary, and tertiary thiols were smoothly coupled with diverse aryl and heteroaryl bromides. The tolerance of NH_2 , OH , and SO_2NH_2 groups indicates that thioetherification outcompeted etherification or amination, which is a significant advantage over Pd-catalyzed methods.

A. C–S bond cross-coupling using aryl halide and thiol

proposed mechanism

selected examples

B. C–S bond cross-coupling using (bromoethynyl)benzene and thiol

selected examples

Scheme 6. Photoredox and nickel dual-catalyzed C–S bond cross-coupling involving SET.

Two years later, the same group extended this protocol to the thioarylation of unprotected peptides and biomolecules (Scheme 7B).^[21] Peptides bearing primary, secondary, and tertiary alkyl thiols could undergo Ru/Ni dual-catalyzed thioetherification with

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functionalized aryl/heteroaryl bromides, including those containing linkers, biologic probes, and drug molecules. In addition, microscale high-throughput experimentation (HTE) was conducted to evaluate more complex and drug-like aryl bromides, and most of them showed reactivity 'hits' with the peptide thiol. These encouraging results, along with successful gram-scale experiments, make this an appealing platform for protein bioconjugation.

A. C-S bond cross-coupling via HAT **B. C-S bond cross-coupling using a peptide**

Scheme 7. Photoredox and nickel dual-catalyzed C-S bond cross-coupling via HAT.

2.4 Photoredox and nickel dual-catalyzed C-SO₂ bond cross-coupling

In 2018, Rueping and coworkers developed an efficient protocol for the sulfonylation of organic halides via photoredox/nickel catalysis (Scheme 8).^[22] Different types of aromatic sulfones were synthesized via the coupling of aryl, heteroaryl, and vinyl halides with sulfinate salts as radical precursors at room temperature. The substrate scope of aryl halides, including aryl iodides, aryl bromides, and even less-reactive aryl chlorides and sodium sulfonates, was broad. A wide array of functional groups, including reactive primary amine and hydroxy groups on the aromatic ring, were tolerated. The smooth scaled-up reaction in the presence of 0.5 mol% photocatalyst indicated the scalability and practicability

of the mild dual-catalyzed sulfonylation protocol. Regarding the mechanism, a Ni^{0/II/III} catalytic cycle was proposed. Almost simultaneously, the groups of Molander and Manolikakes also reported similar protocols for dual-catalyzed sulfonylation, albeit the scope focused on only aryl iodides or aryl bromides.^[23] In Molander's work, thioethers were observed as side products, and DFT calculations were conducted to rationalize the observation and competition between thioethers and sulfones. Moreover, the authors applied this protocol to prepare the precursor for the 5-HT₆ receptor antagonist RVT-101, highlighting the utility of this mild dual-catalytic approach again.

C-SO₂-R bond cross-coupling using sodium sulfinate **2.5 Photoredox and nickel dual-catalyzed C-P bond cross-coupling**

C-P bond formation has also been realized via photoredox/Ni-dual-catalyzed cross-coupling. In 2015, Xiao and coworkers developed the coupling of diaryl phosphine oxides with aryl iodides by merging Ru-base photocatalysts and active Ni⁰ catalysts (Scheme 9).^[24] A series of aryl iodides bearing various substituents and some heteroaryl iodides were converted to the corresponding triarylphosphine oxides in good to excellent yields. Later, in 2017, Yu and coworkers extended the coupling partners to alkenyl and aryl C-O bonds and more diverse P sources after modification of the dual-catalytic conditions.^[25] A series of alkenyl phosphonates and aryl phosphine oxides were synthesized in moderate to excellent yields, and the scale-up reaction was also realized with excellent efficiency.

C-P bond cross-coupling

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3. Photoredox and nickel dual-catalyzed reactions involving an energy transfer process

In addition to the SET pathway between the photocatalyst and nickel catalyst, another important energy-transfer pathway between them has been demonstrated, in which an excited-state nickel complex is generated via energy-transfer photosensitization to facilitate the formation of C-heteroatom bonds. Mechanistically, the oxidative addition of an aryl halide to active Ni^0 gives the aryl- Ni^{II} -Br intermediate that undergoes rapid ligand exchange with a nucleophile to afford an aryl- Ni^{II} -Nuc complex. The subsequent triplet-triplet energy transfer from the excited photocatalyst to the aryl- Ni^{II} -Nuc complex produces an excited-state aryl- Ni^{II} -Nuc species that readily undergoes reductive elimination to deliver the C-heteroatom coupling product and regenerate the active Ni^0 catalyst (Scheme 10).

Scheme 10. The general mechanism for photoredox and nickel dual-catalyzed reactions involving an energy-transfer process.

The efficient and mild coupling of aryl halides and carboxylic acids was first established to generate O-aryl ester products via this catalytic mode by MacMillan, McCusker, and coworkers in 2017 (Scheme 11A).^[26] To demonstrate that this transformation occurs via an energy-transfer process rather than an SET event, a series of mechanistic investigations were performed. Initial experiments showed that the use of the organic sensitizer benzophenone in lieu of an Ir-based photocatalyst also gave the C-O coupling product, and this transformation could also proceed with moderate efficiency via direct excitation with a high-intensity light source in the absence of a photocatalyst after a longer reaction time (120 h), suggesting the involvement of an excited-state Ni complex. Moreover, a library of Ir-based photocatalysts bearing different triplet-state energies and oxidation potentials were prepared and tested in this reaction. The results showed that the higher the triplet state energy of the photocatalyst was, the higher the yield obtained, while the higher the oxidation potential of the photocatalyst was, the lower the yield observed. The positive correlation with triplet-state energies and negative correlation with oxidation potentials also suggest that this transformation is facilitated by an energy-transfer process rather than SET.

A. Esterification

selected examples

B. Sulfonamidation

selected examples

C. C-N bond cross-coupling using NH-sulfoximines

selected examples

D. C-N bond cross-coupling using sulfamate esters

selected examples

E. C-N bond cross-coupling using carbamates

selected examples

Scheme 11. Photoredox and nickel dual-catalyzed C-heteroatom cross-coupling involving an energy-transfer process.

The proposed mechanism was also well rationalized by Chen's work using theoretical modeling, in which the enhanced reductive

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elimination activity from excited-state aryl-Ni^{II}* carboxylate species benefits from the Ni^{III} character of the metal-to-ligand charge transfer (MLCT) excited state.^[27] The primary, secondary, and tertiary carboxylic acids, as well as benzoic acid derivatives and N-H-bearing amino acids, were all suitable substrates for this mild coupling. For electrophiles, electron-deficient aryl- and pyridine-derived heteroaryl bromides could be applied to give the corresponding products in good to excellent yields. However, no electron-rich aryl bromides were shown, which may have been due to their difficult oxidative addition to nickel catalysts under mild conditions. In addition, the C-O cross-coupling of (hetero)aryl halides with acids, alcohols, or water via an energy-transfer pathway was also realized by several other research groups using different types of photosensitizers, including donor-acceptor fluorophores based on carbazoyl-cyanobenzene (4DPAPN),^[28] thioxanthen-9-one (TXO),^[29] and aminoquinolate diarylboron (AQDAB) complexes.^[30] One year later, the same group extended this platform to the preparation of sulfonamides via the sulfonamidation of aryl and heteroaryl halides (Scheme 11B).^[31] The proposed key intermediate was an excited-state aryl-Ni^{II}*-SO₂R complex via energy transfer with the excited photocatalyst. The beneficial effect of the organic sensitizer benzophenone again indicated the generation of the triplet excited-state Ni^{II}* complex and the involvement of the energy-transfer process. Interestingly, this reaction could proceed with or without bipyridine ligands. The addition of dtbbpy (1 mol%) in DMSO allowed this reaction to be performed at room temperature and was beneficial to the oxidative addition of electron-rich aryl halides, whereas the ligand-free conditions in CH₃CN required an elevated reaction temperature (68 °C). Under these optimized conditions, a wide range of electron-neutral, electron-rich, and electron-poor aryl halides, including some *ortho*-substituted aryl halides and heteroaryl halides bearing pyridine, pyrimidine, and pyrazine motifs, gave moderate to excellent yields. Additionally, a number of aryl, heteroaryl, and alkyl sulfonamides could participate in this reaction with good to excellent efficiency. Later, this mild strategy was applied to other N-nucleophiles, such as carbamates, O-alkyl sulfamate esters, sulfamides, and NH-sulfoximines, providing an efficient way to access valuable N-containing organic compounds (Scheme 11C-E).^[32]

In 2019, Miyake, Thordarson, and coworkers reported light-driven nickel-catalyzed C-N bond cross-couplings via an energy-transfer pathway (Scheme 12).^[33] In this protocol, NiBr₂·H₂O and [Ru(bpy)₃]Cl₂/organic phenoxazine were used as dual catalysts, and a series of techniques and quantitative Förster theory were utilized to provide deep insights into the reaction mechanism, strongly suggesting a Förster-type energy transfer from the excited-state photocatalyst to the Ni-amine complex. First, quenching experiments showed that the Ni-morpholine complex generated *in situ* could quench the excited state of [Ru(bpy)₃]Cl₂ directly to its ground state since kinetic traces of the Ru photocatalyst at all wavelengths from λ = 300 - 800 nm returned fully to baseline. These observations are consistent with an energy-transfer pathway. Second, CV measurements showed that SET events, including oxidation and reduction between an excited-state photocatalyst and Ni-morpholine complex, are thermodynamically unfavorable. Third, the excited-state lifetime of the Ru photocatalyst was reduced significantly from 870 ± 40 ns to 360 ± 20 ns in the presence of the Ni-morpholine complex, while no electron-transfer product was observed. Structure identification of the Ni-morpholine complexes via single-crystal X-

ray powder diffraction (XRD) along with UV-visible absorption spectroscopy confirmed them as EnT acceptors. All these results suggest that an excited Ni-amine intermediate was formed during the reaction via energy transfer from an excited photocatalyst. Regarding the substrate scope, the organic phenoxazine photocatalyst was more effective for almost all substrates, likely because the blueshifted band facilitated the EnT process, which is also in line with quantitative results from Förster theory. Moreover, the thioetherification of aryl bromides was realized by the same group using this strategy.^[34]

C-N, C-S and C-O bond formation via energy transfer

Scheme 12. C-N, C-S, and C-O bond cross-coupling via energy transfer.

Very recently, Johannes and Escobar developed a general and practical photo/nickel dual-catalyzed carbon-heteroatom cross-coupling reaction for C-N, C-O, and C-S bond formation in a non-degassed solvent under air (Scheme 12).^[35] Photocatalyst screening showed that Ir(ppy)₃ ($E_{1/2}^{\text{red}} \text{ Ir}^{\text{III}}/\text{Ir}^{\text{II}} = +0.31 \text{ V}$) was optimal, while photocatalysts with higher oxidation potentials, such as [Ir(dF(CF₃)ppy)₃(dtbbpy)]PF₆ ($E_{1/2}^{\text{red}} \text{ Ir}^{\text{III}}/\text{Ir}^{\text{II}} = +1.21 \text{ V}$) and [Ru(bpy)₃]Cl₂ ($E_{1/2}^{\text{red}} \text{ Ru}^{\text{II}}/\text{Ru}^{\text{I}} = +0.77 \text{ V}$), gave no product. Additionally, a phenoxazine-based photocatalyst known as a photosensitizer could also give a quantitative yield. Moreover, ligand screening indicated that bipyridine ligands bearing electron-donating groups led to high reaction efficiencies, which may be due to the increase in the molecular orbital overlap between the ground-state Ni^{II} complex and excited photocatalyst, thus facilitating energy transfer. All these results suggest that the preferred pathway may involve an energy-transfer process rather than a photoredox SET event. Aryl bromides, iodides, and even chlorides could be coupled with diverse nucleophiles, including alcohols, amines, thiols, carbamates, and sulfonamides. Moreover, due to the avoidance of photocatalysts with high oxidation potential, the substrate scope is broad, and a wide range of functional groups, including some active groups, could be well tolerated. Notably, the scalability of the reaction was demonstrated to be feasible using a VaporTech flow apparatus.

4. Photoinduced nickel-catalyzed reactions

Although photoredox and nickel dual catalysis has been developed as an appealing strategy for C-heteroatom couplings,

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the general use of metal complexes of expensive precious metals such as Ru and Ir as photocatalysts largely limits its application. Notably, photoinduced nickel-catalyzed C-O and C-N cross-couplings have been realized in the absence of external photoredox catalysts or oxidants. The general mechanism is shown in Scheme 13. In this regard, Doyle and coworkers realized photoinduced nickel-catalyzed C-O cross-coupling without external photoredox catalysts under irradiation by blue LEDs at room temperature (Scheme 14A).^[36] The fundamental photophysics of the Ni^{II}-aryl halide complexes was initially explored via computational and ultrafast spectroscopic studies. The preliminary results imply that the Ni^{II}-aryl halide complex generates a long-lived ³MLCT excited state that undergoes bimolecular electron transfer to the ground-state Ni^{II} complex (disproportionation of Ni^{II}) to generate an active Ni^I bromide catalyst. This resultant Ni^I bromide then undergoes ligand exchange with an alcohol, oxidative addition with aryl bromide, and facile reductive elimination from the Ni^{III} intermediate to afford the C-O cross-coupling product.

Scheme 13. General mechanism of photoexcited nickel-catalyzed reactions.

However, two years later, the same group revised the assignment of the long-lived excited states as ³d-d rather than ³MLCT based on further experimental studies and proposed that the active Ni^I species was generated via the homolysis of the long-lived ³d-d excited Ni^{II}-aryl halide complex.^[37] To investigate the photophysics and geometry of the excited Ni^{II} complexes, several Ni(R¹bpy)(R²o-Tol)Cl complexes bearing electron-donating or electron-withdrawing groups were synthesized to reveal the structure-activity relationships. First, since the (π,π*) transition had been previously verified experimentally, the authors recorded the electronic UV-Vis absorption spectra for the Ni^{II} complexes while varying the R¹bpy and R²o-Tol parts. The bathochromic shift caused by OMe¹bpy → CO₂Et¹bpy or CF₃o-Tol → OMe²o-Tol variation, the smaller shift in the visible absorption band (1180 cm⁻¹) caused by R²o-Tol than that (2810 cm⁻¹) caused by the R¹bpy variation, and the higher extinction coefficients for the variants bearing more extensively conjugated Ph¹bpy and CO₂Et¹bpy ligands together suggested that an MLCT state was indeed generated initially upon excitation. Transient absorption (TA) spectroscopy showed that one of the two absorptions by bpy⁻ disappeared, meaning that the MLCT state evolved to a different excited state. The relatively constant lifetimes of different substituted Ni^{II} excited states were also inconsistent with the trend in the MLCT states. The fact that the Lewis basicity of the solvent had a small effect on the excited-state lifetimes implies that the initially generated MLCT state may

evolve into a long-lived tetrahedral ³d-d excited state. The increased ν_{C=O} observed after ~10 ps in the time-resolved infrared (TRIR) spectroscopy study of Ni(CO₂Et¹bpy)(o-Tol)Cl ruled out bpy ligand reduction and a long-lived MLCT state. Cross-peaks in 2D exchange spectroscopy (EXSY) were observed for the *t*-Bu groups in Ni(*t*-Bu¹bpy)(o-Tol)Cl, indicating the existence of a tetrahedral ³d-d excited state. Moreover, by combining EXSY and TA data, the energy of the ³d-d state was determined to be 0.50 eV (12 kcal/mol) above the ground state. The same ¹H NMR peaks of blue light-irradiated Ni(*t*-Bu¹bpy)(o-Tol)Cl with the prepared Ni^I dimer Ni₂(*t*-Bu¹bpy)₂(μ-Cl)₂ and the successful trapping of an *o*-tolyl radical but not a Cl⁻ via electron paramagnetic resonance (EPR) spectroscopy strongly supported the photoinduced homolysis of the Ni^{II}-aryl bond to produce active Ni^I species.

Very recently, Xue and coworkers reported photoinduced nickel-catalyzed C-O couplings using a Ni^{II}-aryl complex as the catalyst without any additional photosensitizer (Scheme 14B).^[38] The reactions were performed with a soluble amine as the base under irradiation by longwave UV (390-395 nm) at an elevated temperature of 80 °C. The mechanism was similar to that proposed by Doyle, in which active Ni^I species were generated via the light-promoted homolysis of the Ni^{II}-aryl complex through a long-lived ³d-d excited state. The signals at g_{||}=2.25 and g_⊥=2.07 from an EPR study of the irradiated Ni^{II}-aryl complex also indicated the formation of a d⁹ Ni^I species. It is noteworthy that continuous irradiation was needed, likely because the comproportionation of Ni^{III} and Ni^I could generate the Ni^{II} species, which would require a photocatalytic step for the regeneration of the active Ni^I species. Compared to Doyle's work, this protocol possesses a broader substrate scope. A series of primary and secondary aliphatic alcohols could couple smoothly with a wide range of (hetero)aryl bromides as well as more challenging (hetero)aryl chlorides and several types of sulfonates. It should be pointed out that for electron-neutral aryl chlorides and secondary aliphatic alcohols, a higher catalytic loading (15 mol %) was required, and electron-rich aryl chlorides were inactive in this protocol. Interestingly, intramolecular C-O couplings were realized to form a series of important five- and six-membered O-containing heterocycles, and the gram-scale reaction was conducted in excellent yield.

A C-N bond formation was also realized via photoinduced nickel-catalyzed cross-coupling of aryl halides and amines using inexpensive NiBr₂·3H₂O as the catalyst under irradiation with a 365 nm LED at room temperature without any exogenous photoredox catalyst (Scheme 14C).^[39] The reaction was performed under ligand- and base-free conditions with oxygen and water tolerance and consisted of direct photoexcitation of the nickel-amine complex, thus having a broad substrate scope and functional group tolerance. Mechanistically, NiBr₂·3H₂O first exchanges three water molecules for three morpholine molecules to generate [NiBr₂(morph)₃], which absorbs photons from 365 nm LED irradiation to undergo electron transfer from electron-rich morpholine to the electron-poor Ni^{II} metal center to give a reduced Ni^I and oxidized morpholine radical cation. This species could dissociate rapidly into the corresponding ion pairs with a 57.0 kcal/mol endergonic free energy cost that can be supplied by photon absorption (365 nm or 78.3 kcal/mol).

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A. C-O bond cross coupling using $\text{Ni}(\text{cod})_2$

● key intermediates

B. C-O bond cross coupling using $\text{Ni}(\text{Ar})\text{X}$

X = Cl, Br, OMs, OTs, OTf

● selected examples

C. C-N bond cross coupling

● selected examples

Scheme 14. Photoexcited nickel-catalyzed C-O/C-N bond cross-coupling without photocatalyst.

The resulting morpholine radical cation is deprotonated by the excess morpholine to afford the corresponding reactive Ni^{I} and morpholine radical, which can add to the aryl halide to deliver the desired product through bromine atom displacement along with the formation of Ni^{I} and $\text{Br}^{\cdot}$. The $\text{Br}^{\cdot}$ then adds to Ni^{I} with an energy loss of 55.6 kcal/mol ($n = 3$) to give a closed-shell $[\text{NiBr}_2(\text{morph})_{n-1}]$ complex that can be coordinated with another morpholine to regenerate the initial active Ni^{I} catalyst. In another possible pathway, once the reactive Ni^{I} and morpholine radical are generated, the oxidative addition of aryl halide to the reactive

Ni^{I} may occur to form the Ni^{III} and morpholine radical, which undergo reductive elimination to readily deliver the amination product and the $[\text{NiBr}_2(\text{morph})_{n-1}]$ complex. The kinetic isotope effect (KIE) was studied, and the large KIE value (4.9 for piperidine) indicates that the dissociation of an N-H(D) bond to generate the amino radical is the rate-determining step. Notably, primary, secondary alkyl amines, and weakly nucleophilic anilines could all couple smoothly with aryl halides bearing diverse electronic functionalities. Moreover, sequential multistep synthesis via photocatalyzed C-S and C-N bond formations was realized. Notably, primary alkyl- and aryl amines typically required longer reaction times, and the couplings of weakly basic aryl amines also required the addition of 1.5 equiv of quinuclidine as a base to obtain satisfactory yields.

5. Heterogeneous photoredox and nickel dual catalysis

5.1 Mesoporous graphitic carbon nitride as the heterogeneous photocatalyst

Because of the high cost of photocatalysts based on the precious metal Ir/Ru, there is a high demand for the development of more inexpensive and general photocatalysts. In this regard, heterogeneous photocatalysts represent a practical and attractive alternative. As one of the most attractive organic semiconductor materials, mesoporous graphitic carbon nitride (mpg-CN) can generate surface redox centers as electron-hole pairs upon photoexcitation and thus allow two aligned redox transformations to occur simultaneously on the same particle surface. The general mpg-CN catalysts absorb light in the visible region with a band gap of less than 2.7 eV, and adjusting the C/N ratio, the polymerization degree, or the crystallinity could also alter the band gap and position of the valence and conduction bands, thus allowing for oxidation and reduction of diverse redox-active substrates. Moreover, the metal-free mpg-CN materials feature ease of preparation, low cost, low toxicity, reusability, and stability against the action of reactive radicals, strong nucleophiles, and intense light irradiation, thus providing a sustainable alternative to noble-metal complexes in photocatalysis.^[40]

In 2019, König, Antonietti, and coworkers reported several photoredox reactions of arenes and heteroarenes using mpg-CN materials as efficient and sustainable photoredox catalysts (Scheme 15).^[41]

In particular, C-N bond-forming cross-coupling was realized via mpg-CN and nickel dual-catalyzed amination of electron-poor aryl bromides and aryl chlorides. The heterogeneous photoinduced mpg-CN/nickel dual-catalyzed transformation was conducted in the absence of ligand under irradiation by blue LEDs at room temperature. A number of o-/m-/p-substituted aryl bromides along with one aryl chloride could be coupled with aliphatic amines, aniline, and benzenesulfonamide in moderate to high yields. mpg-CN materials could be readily recycled by filtration or centrifugation, and the low cost, chemical stability, and photostability of these organic semiconductors make their scalability practical. However, the substrate scope was limited to aryl halides bearing electron-withdrawing groups.

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mpg-CN

Scheme 15. mpg-CN as a photocatalyst in photoredox and nickel dual catalysis.

Very recently, Pieber and coworkers investigated the carbon nitride CN-OA-m and nickel dual-catalyzed amination reactions and found that catalyst deactivation to inactive nickel black is responsible for this limitation (Scheme 16A). The optimal carbon nitride CN-OA-m for this protocol was synthesized via condensation of urea and oxamide followed by postcalcination in a molten salt. Several measures were found to be effective at suppressing nickel-black formation when the relative rate of oxidative addition (OA) was equal to or higher than the relative rate of reductive elimination (RE). First, switching the light source from 450 nm blue LEDs to 520 nm green LEDs decelerated the light-mediated RE step. Second, increasing the concentration of the reaction mixture could increase the rate of the OA step and reduce the adverse solvent (DMAc)-catalyst interactions. Third, some additives, such as MTBD (7-methyl-1,5,7-triazabicyclo(4.4.0)dec-5-ene), could coordinate to the active, low-valent nickel species, thus stabilizing it to afford a longer lifetime before nickel-black formation and facilitating the OA step. The combined use of these three approaches enabled the application of the challenging electron-neutral and electron-rich aryl bromides and less nucleophilic primary amines in the photoredox and nickel dual-catalyzed amination reactions.^[42] In addition, overcoming the challenges of the use of heterogeneous catalysts in the flow setup, the same group also realized the scaled-up reaction (up to 12 g) using an oscillatory plug flow photoreactor. High efficiency was achieved in a short reaction time, and the CN-OA-m catalyst could be recycled and reused for more than 10 cycles with no loss of activity.^[43] Pieber and coworkers developed a heterogeneous carbon nitride/Ni-dual-catalyzed esterification of carboxylic acids with aryl iodides via C-O coupling (Scheme 16A).^[44] The combination of CN-OA-m, NiCl₂·glyme, dtbbpy, and N-*tert*-butylisopropylamine (BIPA) in DMSO under irradiation by white LEDs was found to give the best result. The generation of esterification products without any detectable decarboxylative alkylation product indicates the involvement of an energy-transfer pathway rather

than a SET event, which is similar to the homogeneous counter protocol.

A. CN-OA-m

CN-OA-m: co-condensation of urea and oxamide followed by post-calcination in a molten salt

B. NCN_x Scheme 16. CN-OA-m and NCN_x as the photocatalyst in photoredox and nickel dual catalysis.

A series of aryl iodides bearing electron-withdrawing groups could participate and gave high yields. Additionally, aliphatic, olefinic, and benzylic carboxylic acids; benzoic acids; and biotin, could all be coupled with moderate to high efficiency. However, the application of some aryl iodides containing *ortho* substituents, electron-neutral and electron-rich aryl iodides, and electron-poor

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and complex carboxylic acids gave lower or no yields. The CN-OA-m catalyst could be recycled three times by straightforward centrifugation and washing, without any loss of catalytic efficiency. However, a slight reduction in yield was observed when the catalyst was used more than three times, potentially due to nickel decomposition or small amounts of photocatalyst loss during the operation. The same characteristic XRD peaks and identical FTIR and UV/Vis spectra were obtained for CN-OA-m before and after the reaction, which showed that the photocatalytic properties of the recovered CN-OA-m remained unchanged. However, 5–8% of the nickel was deposited on the organic semiconductor, as confirmed by X-ray photoelectron spectroscopy (XPS), ICP-OES analysis, and scanning transmission electron microscopy (STEM). In addition, real-time monitoring via *in situ* FTIR analysis indicated that the CN-OA-m catalyst could absorb a broad range of visible light wavelengths (up to ca. 600 nm). A comprehensive kinetic mechanistic study revealed that the heterogeneous graphitic carbon nitride gave higher carboxylative O-arylation selectivity compared to the homogeneous photocatalyst Ir(ppy)₃. In addition, the rate determination steps in the heterogeneous dual catalysis system include not only the reductive elimination but also the oxidative addition.^[45] Shortly afterward, the same group reported CN-OA-m/Ni-dual-catalyzed (thio)etherification of aryl halides via a SET pathway.^[46] Intermolecular and intramolecular C–O coupling and intermolecular C–S coupling were successfully realized. Similarly, the scope of aryl halides was also limited to electron-poor aryl bromides. Another drawback is the long reaction time for many cases. Very recently, Nocera and coworkers developed a new type of surface-modified carbon nitride, ^{NCN}CN_x, which absorbs sunlight over an extended spectral range (Scheme 16B).^[47] Thus, efficient and sustainable photoredox nickel-catalyzed aryl amination and etherification driven by readily available sunlight using ^{NCN}CN_x as the heterogeneous photocatalyst was realized.

5.2 Semiconductor quantum dots (QDs) as the heterogeneous photocatalyst

SET events can also occur between photoexcited semiconductor QDs and organic molecules or metal centers. In 2017, Weix, Krauss, and coworkers reported the application of CdSe QDs as efficient and robust heterogeneous photocatalysts in diverse photoredox reactions due to their inherent advantages, including the photostability, high photoabsorption efficiency, long-lived excited states and broad absorption spectra of QDs (Scheme 17A).^[48] They found that a single CdSe QD (3.0 ± 0.2 nm) could act as an effective surrogate in five different reported photoredox reactions, such as β-alkylation, β-amino alkylation, amine arylation, dehalogenation, and decarboxylative radical addition to styrene, without further reaction optimization. Notably, good to excellent yields could be obtained even at extremely low loadings (down to 0.0008 mol %). The excited-state reduction potentials (excited-state E_{1/2} from –1.43 to –1.80 V vs. SCE) allow the CdSe QD catalyst to replace three of the most commonly used Ir/Ru-based catalysts [Ir(ppy)₂(bpy)X, Ru(bpy)₃X₂, and Ir(ppy)₃] in pure photoredox reactions or dual catalysis combined with an organic catalyst or a transition metal catalyst. The addition of a small amount of oleic acid could prevent the harmful effect caused by QD surface capping ligands and thus stabilize the QD photocatalysts. In particular, for the heterogeneous photoinduced CdSe QD and nickel dual catalysis, C–N bond cross-coupling outcompeted the C–O bond formation, giving the aryl amination

product in 58% yield. In 2019, this practical heterogeneous photoredox/nickel dual catalysis was expanded significantly by Xiao, Lu, and coworkers to C–N and C–O bond formations using bench-stable CdS as a photocatalyst (Scheme 17B).^[49] The cocatalysts CdS and NiCl₂·6H₂O in DMA with 6 W of blue LED irradiation were found to be optimal for amination coupling, and the addition of DBU base at an elevated temperature of 55 °C could promote the conversion of aryl bromides in many cases. In addition to secondary and primary aliphatic amines, sulfonamides, alcohols, and water could be used as effective nucleophiles to couple with electron-poor aryl and heteroaryl bromides. Notably, scale-up reactions for both amination and etherification were achieved in excellent yields. Due to the easy isolation of the CdS catalyst, reactions with recycled CdS were performed, and almost the same efficiency was observed even after 10 cycles. Mechanistically, a Ni⁰/Ni^{II}/Ni^{III}/Ni^I catalytic cycle was proposed, in which the oxidizing holes in the valence band (VB) of photoexcited CdS oxidize the Ni^{II} complex to afford Ni^{III} species, while the conduction band (CB) of photoexcited CdS reduces the Ni^I intermediate to the active Ni⁰ species.

A. CdSe quantum dot photoredox catalysis

B. CdS quantum dot photoredox catalysis

Scheme 17. semiconductor QDs as the photocatalyst in photoredox and nickel dual catalysis.

5.3 Metal-organic-framework (MOFs) or metal-organic layers (MOLs) as the heterogeneous photocatalyst

As an excellent multifunctional material, MOFs have been employed in photoredox and nickel dual catalysis. In 2018, Lin and coworkers reported the photoinduced thioetherification of aryl iodides using a dual catalyst Zr₁₂-Ir-Ni that formed via the incorporation of an Ir photoredox catalyst and a Ni cross-coupling catalyst into a stable Zr₁₂ MOF (Scheme 18A).^[50]

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A. Metal-Organic Framework (MOF)

B. Metal-Organic Layers (MOL)

Metal-Organic Layers: a **dispersible monolayered** version of MOFs

Scheme 18. MOFs or MOLs as photocatalysts in photoredox and nickel dual catalysis.

The recycling and reusability of the dual MOF catalyst make this protocol practicable. For the preparation of the $\text{Zr}_{12}\text{-Ir-Ni}$ MOF, a solvothermal reaction among ZrCl_4 , H_2DBB ($\text{DBB}=4,4'$ -di(4-benzoate)-2,2'-bipyridine) and $[\text{Ir}^{\text{III}}(\text{dFCF}_3\text{ppy})_2(\text{H}_2\text{DBB})]\text{Cl}$ in DMF at 80°C using acetic acid as the modulator gave $\text{Zr}_{12}\text{-Ir}$ MOF, followed by metalation of $\text{Zr}_{12}\text{-Ir}$ with $\text{NiCl}_2\cdot 6\text{H}_2\text{O}$ to form $\text{Zr}_{12}\text{-Ir-Ni}$ MOF catalyst. The TEM image and PXRD pattern of this $\text{Zr}_{12}\text{-Ir-Ni}$ MOF were the same as those of the $\text{Zr}_{12}\text{-Ir}$ MOF, which adopts hexagonal plate morphology and is an isostructure of the reported $\text{Hf}_{12}\text{-DBP}$ MOF. Additionally, the extended X-ray absorption fine structure (EXAFS) spectrum of $\text{Zr}_{12}\text{-Ir-Ni}$ suggests that the Ni^{II} centers have a tetrahedral coordination environment. The combination of 0.02 mol% $\text{Zr}_{12}\text{-Ir-Ni}$ MOF catalyst and 2 equiv. of 2,6-lutidine in acetonitrile under radiation from blue LEDs allows the efficient coupling of various aryl iodides and thiols with a turnover number of up to 38500. In addition, the $\text{Zr}_{12}\text{-Ir-Ni}$ dual catalyst could be recovered and reused for at least five cycles without loss of catalytic activity. The effective quenching of the $[\text{Ir}^{\text{III}}]^*$ luminescence of $\text{Zr}_{12}\text{-Ir}$ by 4-methoxythiophenol and the corresponding CV measurements show that the thiyl radical was initially generated via the oxidation of 4-methoxythiophenol ($E_P = 0.50 \text{ V}$ vs. SCE with lutidine) by the $[\text{Ir}^{\text{III}}]^*$ species ($E^0 = +1.27 \text{ V}$ vs. SCE). On the other hand, $(\text{Me}_2\text{DBB})\text{NiCl}_2$ could also quench the luminescence of the $[\text{Ir}^{\text{III}}]^*$ species, and CV measurements showed that the reversible reduction peak of $\text{Ir}^{\text{III/IV}}$ was located at -1.10 V , which is between -0.93 V ($\text{Ni}^{\text{II/I}}$) and -1.28 V ($\text{Ni}^{\text{I/0}}$), implying that $\text{Ir}^{\text{III}}(\text{DBB})$ can reduce Ni^{II} to Ni^{I} but cannot further reduce Ni^{I} to Ni^0 . Based on these results, a $\text{Ni}^{\text{I/II/III}}$ mechanism similar to its homogeneous counterpart by was proposed

Johannes *et al.* The periodic arrangements and the close proximity (ca. 0.6 nm) of Ir^{III} and Ni^{II} in the MOF greatly facilitate electron and thiyl radical transfers between the Ir and Ni centers, thus accelerating the whole catalytic cycle.

At almost the same time, the same group also reported $\text{Hf}_{12}\text{-Ir-Ni}$ metal-organic layers (MOLs), dispersible monolayered versions of MOFs, as a novel class of molecular two dimensional (2D) materials for photoinduced C-heteroatom bond-forming cross-couplings (Scheme 18B).^[51] The newly designed $\text{Hf}_{12}\text{-Ir-Ni}$ MOL catalyst was synthesized by linking Hf_{12} secondary building units (SBUs) with photosensitizing $\text{Ir}(\text{DBB})[\text{dF}(\text{CF}_3)\text{ppy}]^{2+}$ bridging ligands and subsequent termination with $\text{Ni}(\text{MBA})\text{Cl}_2$. Similar to the aforementioned $\text{Zr}_{12}\text{-Ir-Ni}$ MOF catalysis, the proximity between the Ir and Ni centers (ca. 0.85 nm) in the $\text{Hf}_{12}\text{-Ir-Ni}$ MOL also facilitated SET and thus led to enhanced efficiency for photocatalytic C-S and C-O bond formations with turnover numbers of ~ 4500 and ~ 1900 , respectively.

5.4 Perovskites as heterogeneous photocatalysts

In 2019, perovskites were applied in photocatalytic organic synthesis due to their strong light absorption, long excited-state lifetimes, efficient charge separation and transfer, and electron-hole diffusion.^[52] In this protocol, photoinduced C-C, C-O, and C-N bond formations were achieved using Pb-halide perovskites as photocatalysts. Specifically, perovskite nanocrystal and nickel dual-catalyzed esterification of aryl bromides with carboxylic acids was realized (Scheme 19). To optimize the catalytic activity, the size and stability of the CsPbBr_3 nanocrystals, as well as the solvent type, ions, and acidity, were first investigated. Small nanocrystals resulted in a faster initial reaction rate with a rapid decrease in catalytic reactivity, while large nanocrystals usually gave a higher yield but required longer reaction time. The less polar organic solvents and non-halide organic acids could stabilize the CsPbBr_3 nanocrystals.

Perovskites

Scheme 19. Perovskites as the photocatalyst in photoredox and nickel dual catalysis.

Unlike most homogeneous photocatalyzed reactions, perovskite-catalyzed reactions showed high tolerance to air, and this protocol proceeds without the need for N_2 sparging. The superior catalytic performance of Pb-halide perovskites can be attributed to the avoidance of electron and hole trapping and fast interfacial electron and hole transfer. During C-O formation, the use of $\text{NiBr}_2\text{-dtbbpy}$ in lieu of $\text{NiCl}_2\text{-dtbbpy}$ (78% yield) resulted in trace conversion, which can be explained by the fact that *in situ* ion exchange from NiCl_2 may lead to a larger bandgap for perovskite. This is in line with the trend in the homogeneous counter protocol

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in which an Ir photocatalyst with a higher triplet excited state gave a higher yield. Moreover, the intentional or *in situ* band-tuning of perovskite nanocrystals may enable the use of previously inaccessible substrates in photoredox organic synthesis.

6. Electro- and nickel dual-catalyzed reactions

Due to the simultaneous occurrence of anodic oxidation and cathodic reduction, electrocatalysis could usually be carried out without exogenous oxidants or reductants under mild conditions, thus reducing the consumption of chemicals and energy. In addition, organic electrocatalysis still has several advantages, such as high reactivity, good functional group tolerance, easy operation, and scalability.^[53] Notably, the adjustability of the current or voltage allows some unprecedented transformations that cannot occur with chemical oxidants or reductants.^[54] The mechanism is similar to that of photoredox/nickel catalysis, in which both the anode and cathode are used to directly or indirectly modulate the oxidation state of nickel (Scheme 20).

Scheme 20. General mechanism of electro and nickel dual-catalyzed reactions.

In 2017, Baran and coworkers developed a nickela-electrocatalyzed amination reaction of aryl halides and triflates (Scheme 21A).^[55] The reactions were performed under constant-current conditions in an undivided cell without the addition of an external base at room temperature, and the optimal conditions were assigned as follows: $\text{NiCl}_2 \cdot \text{glyme}$ as the catalyst, dtbbpy as the ligand, LiBr as the electrolyte, reticulated vitreous carbon (RVC) as the anode and Ni foam as the cathode, in DMA solvent under constant current $I = 4 \text{ mA}$ for generally 4.5 h. Cyclic and acyclic secondary and primary amines such as pyrrolidine, piperazine, morpholine, piperidine, dibutylamine, and 2-(2-aminoethoxy)ethanol bearing diverse substituents, including hydroxy groups, were successfully coupled with aryl bromides in moderate to high yields. Additionally, a series of electron-poor and electron-neutral aryl bromides, as well as heteroaryl bromides, aryl iodides, chlorides, and triflates, could participate in the transformation with good efficiencies. Notably, the coupling of 4-

bromobenzotrifluoride and N-Boc-piperazine on a decagram scale was complete in 7 h with 66% yield, and the N-arylation of the bioactive molecules amoxapine and paroxetine was accomplished using the amines as the limiting reagents with the addition of 2 equiv of DBU. Moreover, the addition of an external DBU base enabled the application of a primary alcohol and pyrrolidinone as nucleophilic coupling partners. However, the application of the current method to electron-rich aryl halides; other types of heteroaryl halides; anilines; and complex amines, including amino acids and oligopeptides, remains problematic.

To address these issues, the same group explored the reaction mechanism in detail via the combination of nuanced electrochemical analysis and DFT calculations. Based on the obtained insights into the mechanism, the authors also performed further optimization of the nickela-electro-catalyzed amination protocol and developed a more general catalytic amination system with a greatly expanded substrate scope.^[56]

A UV-Vis study of different ligand/ Ni^{II} ratios suggested that a higher ligand loading may improve the catalytic efficiency, and DFT calculations showed that facile ligand association/dissociation is thermodynamically feasible and that the content of different Ni^{II} complexes depends on the molar fractions of the ligand, DMF, and amine nucleophile. Furthermore, CV measurements of $\text{Ni}^{\text{II}}(\text{Mebpy})\text{Br}_2$ in the absence and presence of 4-bromoanisole as well as DFT calculations both suggested rapid oxidative addition and the feasibility of reduction from $\text{Ni}^{\text{III}}(\text{Mebpy})(4\text{-CF}_3\text{C}_6\text{H}_4)\text{Br}_2$ to $\text{Ni}^{\text{II}}(\text{Mebpy})(4\text{-CF}_3\text{C}_6\text{H}_4)\text{Br}$. Furthermore, a sluggish reaction with steric *t*-butyl amine and DFT results for the coupling of morpholine and 4-bromobenzotrifluoride implied that the coordination/deprotonation of the amine is the rate-determining step and that the excess free amine molecules as the base could compensate for the large energy increase ($\Delta E = 193 \text{ kJ/mol}$) of the deprotonation step. Mechanistically, cathodic reduction of the Ni^{II} complex gives a Ni^{I} -Br species, which undergoes rapid oxidative addition with an aryl halide to afford a transient $\text{Ar-Ni}^{\text{III}}\text{-Br}_2$ species. This Ni^{III} species undergoes cathodic reduction or comproportionation with the Ni^{I} -Br species to furnish an $\text{Ar-Ni}^{\text{II}}\text{-Br}$ species that coordinates with amine via assistance from a base to generate an $\text{Ar-Ni}^{\text{II}}\text{-amino}$ species. Anodic oxidation of the $\text{Ar-Ni}^{\text{II}}\text{-amino}$ species forms an $\text{Ar-Ni}^{\text{III}}\text{-amino}$ intermediate that easily undergoes reductive elimination to deliver the amination product and regenerate the active Ni^{I} -Br species. Based on the results, the amination efficiency may be improved by adjusting the ligand/ Ni^{II} ratio to avoid Ni^0 deposition and adding an external base to facilitate the rate-limiting deprotonation step. After reoptimization, the combination of $\text{Ni}(\text{bpy})_3\text{Br}_2$ as the catalyst and tetra-*n*-butylammonium bromide as the electrolyte with the addition of 2 or 3 equiv. of DBU as the base allowed for the efficient arylation of amino acid esters and amination of diverse heteroaryl bromides. Additionally, C-N bond formation with more challenging substrates, such as nucleosides and oligopeptides, were also realized with satisfactory to good yields. For oligopeptide modification, the use of excess amine coupling partner, the omission of DBU, and the use of LiBr electrolyte in lieu of $^t\text{Bu}_4\text{NBr}$ led to higher yields. Notably, a 100 g-scale reaction for the preparation of vilazodone intermediate was successfully carried out using carbon felt electrodes and NaBr electrolyte via a flow technique.

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A. C-N and C-O bond cross-coupling

selected examples

further optimization:

selected examples

B. C-P and C-Se bond cross-coupling

selected examples

C. C-S bond cross-coupling

selected examples

Scheme 21. Electro and nickel dual-catalyzed C-heteroatom cross-coupling.

Recently, Rueping and coworkers developed a nickel-electrocatalyzed redox-neutral cross-coupling for C-P and C-Se bond formations (Scheme 21B).^[5] In this economic and sustainable electrochemical protocol, the simultaneous anodic oxidation of Ni^{II} to Ni^{III} and cathodic reduction of Ni^{II} to Ni⁰ in an undivided cell lead to high reaction efficiency. A Ni⁰/Ni^{II}/Ni^{III}/Ni^I catalytic cycle was proposed, and a series of experimental mechanistic investigations were carried out to rationalize it. No oxidation peak for diphenylphosphine oxide was observed in the CV measurements, suggesting that the phosphorus radical may not be involved in the reaction. In addition, the *in situ*-prepared Ar-Ni^{II}-Br complex produced a reversible peak at 0.41 V vs. Ag/AgNO₃, which corresponds to the Ni^{II}/Ni^{III} redox potential, and the subsequent addition of diphenylphosphine oxide and base led to a higher potential peak and current increase, showing the formation of a new Ar-Ni^{II}-P(O)Ph₂ species after transmetalation. Providing 20 min of electricity for the whole 12 h reaction led to a dramatically lower yield, indicating that electricity is necessary for the reaction to regenerate the Ni^I and Ni^{III} complexes, which could undergo thermodynamically favored comproportionation and back-convert to Ni^{II} complexes. DFT calculation results also supported these experimental mechanistic studies and the whole proposed mechanism. A wide range of electron-poor and electron-rich aryl halides, including aryl bromides, aryl iodides, and even aryl chlorides, as well as vinyl halides and heteroaryl halides containing quinoline, pyridine, and thiophene groups, could be smoothly transformed to the corresponding products in good to excellent yields. Additionally, the *ortho* substituents, active free amines, and complex motifs could all be tolerated. This mild electrochemical cross-coupling could be readily extended to C-Se bond formation for electron-poor, electron-rich, and even sterically hindered aryl halides, and the gram-scale reaction was successfully realized with excellent yield in only 3 h. Notably, DFT calculations for different C-heteroatom bond formations were conducted, and the results show a general trend that electricity reduces the energy barrier in Ni-catalyzed electrochemical transformations. Simultaneously, Xiang, Cui, and coworkers also realized the similar nickel-catalyzed electrochemical phosphorylation of aryl bromides.^[57] In 2019, Wang and coworkers reported the nickel-electrocatalyzed Ullmann thiolation of aryl iodides (Scheme 21C).^[58] The optimal reaction conditions were found to be NiCl₂·glyme as the catalyst, dtbbpy as the ligand, graphite felt and nickel foam as the electrodes, LiBr as the electrolyte with the addition of a pyridine base in DMA solvent in a simple undivided cell with a cell voltage of 3 V. Diverse aryl and alkyl thiols were coupled successfully with a wide range of functionalized aryl and heteroaryl iodides in moderate to high yields under mild conditions. The addition of 3 equiv. of TEMPO completely suppressed the coupling and resulted in the formation of disulfide, and the trapping of thiyl radical with diphenylacetylene gave a thiolated olefin in 52% yield, which suggests the generation of thiyl radical from the direct anodic oxidation of thiol. CV measurements of the substrates/base and Ni/ligand showed that the addition of pyridine as the base is beneficial for the initial anodic oxidation of thiol to its radical, and the Ni⁰ complex is the active species. Based on these results, the mechanism was proposed as follows: First, the cathodic reduction of NiCl₂·dtbbpy gives an active Ni⁰ species that undergoes oxidative addition to an aryl halide to deliver an Ar-Ni^{II}-X species. This resulting Ni^{II} intermediate then traps the thiyl radical generated from anodic oxidation/deprotonation of the thiol, forming an unstable Ni^{III}

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complex that readily undergoes reductive elimination to furnish the C-S product along with a Ni^{I} species. Finally, the active Ni^0 species is regenerated by cathodic reduction of the Ni^{I} species. Almost at the same time, Mei and coworkers realized the nickel-catalyzed thiolation of aryl and heteroaryl bromides and chlorides under mild electrochemical conditions.^[59] Distinct from Wang's work, this protocol was conducted using a sacrificial Mg anode and Ni-foam cathode without an external base under constant-current conditions. Due to these differences and the consumption of the Mg anode (Mg^0 to Mg^{2+}), another mechanism is proposed even though the formation of disulfide and TEMPO trapping products were observed. The initial cathodic reduction of Ni^{II} or Ni^{I} gives an active Ni^0 species that undergoes oxidative addition with an aryl halide to afford an $\text{Ar-Ni}^{\text{II}}\text{-Br}$ complex. Next, the thiolate generated from cathodic reduction of a thiol reacts with this $\text{Ar-Ni}^{\text{II}}\text{-Br}$ complex to furnish another $\text{Ar-Ni}^{\text{II}}\text{-SR}$ complex, followed by reductive elimination to form the thiolation product and regenerate the active Ni^0 species. For both protocols, a series of electron-poor aryl halides and heteroaryl halides worked well, while electron-rich arenes were not effective.

Very recently, a series of redox-neutral reactions, including nickel-catalyzed esterification, have been realized by Jensen, Buchwald, and coworkers via a microfluidic redox-neutral electrochemical ($\mu\text{RN-eChem}$) platform (Scheme 22).^[60] In traditional electrochemistry, the electrode distance, which ranges from millimeters to centimeters, is not beneficial for the mixing of the two reactive intermediates generated on the two electrodes and thus leads to undesirable radical decomposition. However, in a microfluidic parallel flow channel, the extremely thin interelectrode gap flow cell enabled rapid species transport within the micrometer-scale channel, delivering the cross-coupling products efficiently.

Microfluidic electrochemistry for C-O bond cross-coupling

Microflow: using 25 μm FEP as space between electrodes

→ Enhance the conductivity

→ Avoid the decomposition of the generated radical from both electrodes

Switching polarity: Switching the anode and cathode after certain time

→ Avoid the gradual passivation of the electrode surface

selected examples

Scheme 22. Microfluidic electrochemistry for C-O bond cross-coupling.

Moreover, the anode and cathode were switched after a certain time during the reaction to avoid gradual passivation of the electrode surface. Reaction optimization showed that the yields of the cross-coupling products increased with decreasing interelectrode distance, and the smallest interelectrode distance (25 mm) gave the best result because the molecular diffusion time was exceptionally shorter than the lifetime of the corresponding reactive intermediate. Microfluidic nickel-electro-catalyzed C-O cross-coupling of carboxylic acids and aryl bromides was

achieved efficiently via the $\mu\text{RN-eChem}$ platform. Mechanistically, after oxidative addition and transmetalation, the resultant Ar-Ni^{II} carboxylate is transported rapidly to the anode and undergoes anodic oxidation to form an unstable Ni^{III} intermediate, while the cathodic reduction of the Ni^{I} intermediate regenerates the active Ni^0 species.

7. Light-free zinc and nickel dual-catalyzed reactions

Very recently, Nocera and coworkers reported light-free nickel-catalyzed C-N and C-O cross-coupling under mild conditions without the use of any photocatalysts or elaborate ligands (Scheme 23).^[61] Notably, the efficient amination, etherification, and esterification of aryl bromides were all achieved under thermal conditions. The photoredox-like thermal reactivity involving the $\text{Ni}^{\text{II/III}}$ redox couple is attributed to the addition of a catalytic amount of an earth-abundant zinc powder as a reductant. Mechanistically, the reduction of the Ni^{II} precursor gives a Ni^{I} intermediate that undergoes subsequent OA with aryl bromide to furnish an $\text{Ar-Ni}^{\text{III}}\text{-Br}$ intermediate. The resultant Ni^{III} intermediate then undergoes ligand exchange with the nucleophiles with the assistance of base to form a new type of $\text{Ar-Ni}^{\text{III}}\text{-Nuc}$ complex. The RE of $\text{Ar-Ni}^{\text{III}}\text{-Nuc}$ delivers the coupling product, along with the generation of the active Ni^{I} intermediate. Notably, the heterogeneity of the reduction process enabled access to a $\text{Ni}^{\text{II/III}}$ catalytic pathway by maintaining the concentrations of the Ni^{I} and Ni^{III} intermediates at sufficiently low levels to suppress comproportionation.

Zinc and nickel dual-catalyzed cross-coupling

Scheme 23. Light-free zinc and nickel dual-catalyzed C-heteroatom cross-coupling.

The observation of a high etherification yield using only 0.01 equivalents of Zn powder and 1 mol% (dtbbpy)- NiCl_2 also

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supported this judgment. In addition, the use of only a Ni^0 source gave very low yields, while the combination of Ni^0 and Zn powder significantly improved the yields, indicating that Ni^{II} could not undergo carbon-heteroatom RE and that the $\text{Ni}^{\text{I/III}}$ catalytic cycle was dominant. Different from the homogeneous counter protocol, the absence of light during esterification precludes any possibility of the Ni^{II} excited-state mechanism. A series of aliphatic amines; anilines; alcohols, even including the weakly nucleophilic 2,2,2-trifluoroethanol; water; Boc-protected amino acids; and benzoic acid could all successfully be coupled. In general, electron-deficient aryl halides showed high efficiency, while the application of aryl halides without electron-withdrawing groups seemed to be inefficient.

8. Summary and Outlook

Ni-catalyzed C-heteroatom cross-couplings under mild conditions have been significantly developed for C-N, C-O, C-S, C-Se, and C-P bond formations in recent years. The Ni^{II} and excited Ni^{II} intermediates could be accessed with the assistance of photocatalysts, electricity, or catalytic amounts of zinc powder, thus facilitating the RE from the Ni centers to form the desired products. Diverse types of photocatalysts, including Ir-/Ru-based complexes, organic dyes, BODIPY, thioxanthene-9-one (TXO), aminoquinolate diarylboron (AQDAB) complexes, mpg-CN, CdS/CdSe QDs, MOFs, and perovskites, have been employed. Both homogeneous and heterogeneous catalytic modes via a SET event or an energy-transfer pathway have been reported, providing protocols with high practicability. However, despite these experimental advances a better understanding of the detailed mechanisms is required. To date, four main mechanistic pathways have been proposed (Scheme 24): i) the oxidative addition to Ni^0 and generation of Ni^{II} -species that undergoes transmetalation with the nucleophile, followed by SET oxidation to give the unstable Ni^{III} -intermediate that undergoes a facilitated reductive elimination; ii) SET generated radical addition to Ni^0 to form a Ni^{I} -intermediate which undergoes oxidative addition with aryl halide to furnish the unstable Ni^{III} -species that undergoes a facilitated reductive elimination; iii) the SET generated radical is firstly trapped by Ni^{I} to form a Ni^{II} -intermediate which is reduced back to a Ni^{I} -species, which undergoes oxidative addition to form the unstable Ni^{III} -intermediate that undergoes a facilitated reductive elimination; and iv) oxidative addition to Ni^0 with subsequent transmetalation to give a Ni^{II} -complex which is then excited by the photocatalyst to generate the unstable excited Ni^{II} intermediate. Although preliminary supportive spectroscopic and kinetic investigations as well as DFT calculations have been conducted,^[62] the underlying mechanisms are not fully understood and require further detailed investigations.

Future developments should also be focused on the following aspects. Generally, independent of the method used, i.e. photo-, electro- or photoelectrochemistry, more efficient ligands remain to be developed to also include electron-rich aryl halides since most current variants are limited to aryl halides bearing electron-withdrawing groups. With regard to more sustainable and practicable Ni-catalyzed C-heteroatom bond formations less expensive and reusable heterogeneous photocatalysts, or electrochemical or photo-/photocatalyst-free procedures need to be developed. Regarding the photocatalytic processes, nickel complexes that can be excited by long-wavelength visible light should be developed in order to further improve the functional

group tolerance and reaction diversity for photoinduced Ni-catalyzed C-heteroatom bond formations leading to more practical methods which do not need external photocatalysts.

Different possible mechanistic pathways involved in the reactions

Scheme 24. Proposed mechanistic pathways for the dual catalyzed C-heteroatom bond cross-coupling reactions.

Regarding the electrochemical methods future work should be directed to the switching current strategy as well as to the challenging paired electrolysis involving short-lived intermediates resulting in favorable operations and the avoidance of intermediate quenching. Furthermore, multicomponent reactions^[63] involving C-heteroatom bonds deserve further attention and finally efforts to apply of these powerful platforms to the functionalization of complex molecules or even to total syntheses at larger scale are important future goals in this exciting area of research.

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**Recent Advances in Nickel-Catalyzed
C-Heteroatom Cross-Coupling under
Mild Conditions by Facilitating the
Reductive Elimination**

The generation of Ni^{III} and excited Ni^{II} intermediates facilitates the reductive elimination step leading to the mild cross-couplings. This review provides an overview of the state-of-the-art approaches for mild C-heteroatom bond formations via homo- and heterogeneous photoredox and nickel dual catalysis; electro- and nickel dual catalysis; as well as conventional zinc and nickel dual catalysis.