Photoredox Catalysis

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Visible-Light-Promoted Nickel- and Organic-Dye-Cocatalyzed Formylation Reaction of Aryl Halides and Triflates and Vinyl Bromides with Diethoxyacetic Acid as a Formyl Equivalent

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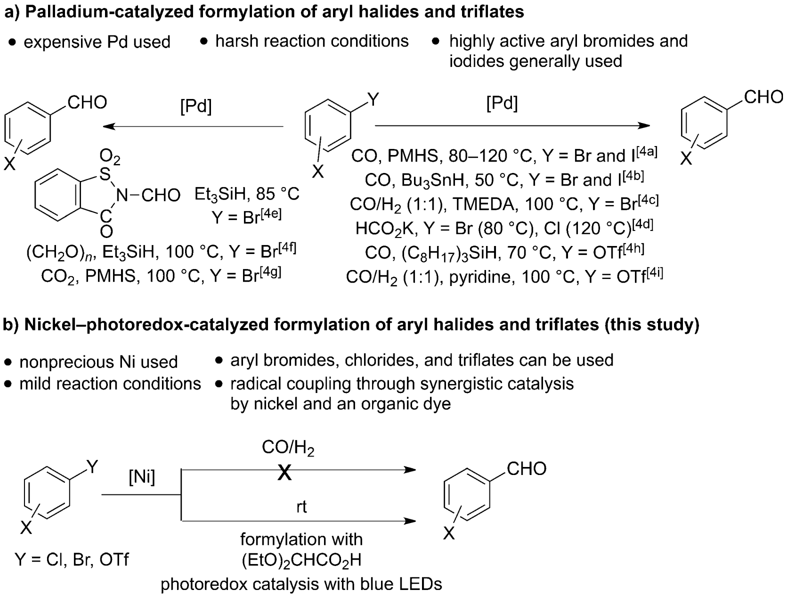
Abstract: *A simple formylation reaction of aryl halides, aryl triflates, and vinyl bromides under synergistic nickel- and organic-dye-mediated photoredox catalysis is reported. Distinct from widely used palladium-catalyzed formylation processes, this reaction proceeds by a two-step mechanistic sequence involving initial in situ generation of the diethoxymethyl radical from diethoxyacetic acid by a 4CzIPN-mediated photoredox reaction. The formyl-radical equivalent then undergoes nickel-catalyzed substitution reactions with aryl halides and triflates and vinyl bromides to form the corresponding aldehyde products. Significantly, besides aryl bromides, less reactive aryl chlorides and triflates and vinyl halides serve as effective substrates for this process. Since the mild conditions involved in this reaction tolerate a plethora of functional groups, the process can be applied to the efficient preparation of diverse aromatic aldehydes.*

Arguably, aromatic aldehydes are the most fundamentally important substances used in organic synthesis.[1] Therefore, the availability of predictable and chemoselective methods for the formylation of aromatic compounds will continue to have a profound impact on chemical synthesis. Classical methods for the preparation of aromatic aldehydes, such as the Reimer–Tiemann, Vielsmeier–Haack, Gattermann–Koch, and Duff reactions,[2] are not atom- and step-economical. Furthermore, the lack of control of the regiochemical course of these reactions makes it difficult to employ them to introduce an aldehyde functionality at desired positions. As a result of these limitations, state-of-the-art formylation technologies employing transition-metal catalysts have been developed. The pioneering study on the palladium-catalyzed formylation of aryl halides with CO and H_2 by Heck and co-workers[3] triggered significant interest in the development of more efficient protocols. Impressive results from studies of this topic have come from the laboratories of Pri-Bar, Stille, Beller, Manabe, Skrydstrup, Kotsuki, and Liu (Scheme 1 a).[4] However, the approaches developed by these groups generally require high reaction temperatures, aryl bromides or iodides as substrates, and precious palladium complexes as promoters.[5] Moreover, in some cases, toxic CO gas[4a–c,h,i] and tin compounds[4b] are used. These issues highlight the demand for more cost-effective, environmentally friendly, and mild protocols for aryl aldehyde synthesis.



Scheme 1. Methods based on palladium and nickel catalysis for the formylation of aryl halides and triflates. PMHS = poly(methylhydrosiloxane), TMEDA = tetramethylethylenediamine.

Although significant advances have been made in the development of inexpensive nickel-catalyzed cross-coupling reactions,[6] nickel-catalyzed formylation reactions have not been described. This deficiency results from low reactivity in the reductive elimination of CO, as demonstrated by Heck and co-workers (Scheme 1 b).[1c,3] Furthermore, very few studies have focused on the palladium-catalyzed formylation of aryl chlorides,[4,7] which are more broadly available and

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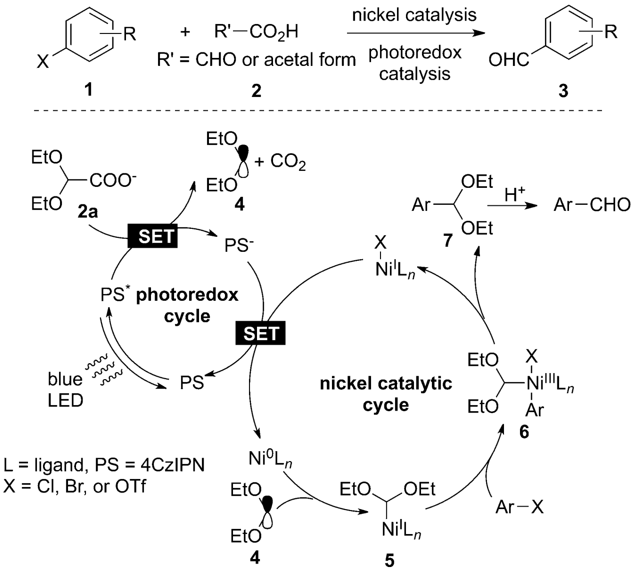
cheaper. Clearly, a new nickel-promoted formylation strategy, which would enable aryl chlorides to serve as coupling partners, would have substantial synthetic utility within both academic and industrial settings. In this context, we recently uncovered a formylation process under synergistic photoredox catalysis with nickel and organic catalysts. 2,2-Diethoxyacetic acid served as the formylation reagent, thus avoiding the need for CO. The process combines an organic-dye-mediated photoredox-catalyzed formyl-radical-forming reaction with a nickel-promoted radical coupling process. Moreover, readily available aryl chlorides can serve as substrates (Scheme 1 b). The transformation proceeds under straightforward and mild conditions that tolerate a plethora of functional groups, and does not produce abundant amounts of chemical waste.

Although nickel-catalyzed reactions of aryl halides with CO/H_2 fail to generate formylation products,[3] the capacity of Ni catalysts to activate C−Cl bonds of aryl chlorides[6] to produce highly reactive organic radicals in cross-coupling reactions is highly attractive.[8] We reasoned that the generation of a formyl-radical equivalent in the presence of an aryl chloride and a Ni catalyst might lead to a cross-coupling process corresponding to the long-sought-after nickel-promoted formylation reaction. Accordingly, the key to the successful development of this process was the identification of a new reagent that would efficiently produce a formyl-radical equivalent under conditions that are compatible with nickel catalysis. The results of studies of photochemical decarboxylation reactions of glyoxylic acid and its acetals by us,[9] and related recent efforts by the research groups of MacMillan, Doyle, and Overman,[10] indicated that these inexpensive and abundant substances might be ideal precursors of formyl-radical equivalents. This consideration suggested that the merging of visible-light photoredox catalysis with nickel catalysis, in a manner earlier demonstrated by the research groups of MacMillan, Doyle, and Molander,[11,12] could serve as the foundation for the new transformation. Specifically, we hypothesized that photoredox-mediated single-electron-transfer (SET) oxidation of glyoxylic acid or its acetals, followed by the loss of CO_2, would form a formyl-radical equivalent **4** (Scheme 2, with a diacetal as an example). Reaction of the Ni^0 complex with radical **4** would form the diacetal–nickel(I) intermediate **5**.[12d] Oxidative activation of aryl halide **1** to **5** would then generate the putative Ni^{III} complex **6**, which should undergo reductive elimination to produce the desired aryl diacetal **7**, a substance that can be readily converted into aryl aldehyde **3** through workup with an aqueous acid.

Thus far, ruthenium and iridium complexes have typically been used as photocatalysts in photoredox nickel-catalyzed reactions. It is somewhat surprising that far fewer reports exist describing reactions of this type in which organic dyes serve as photocatalysts, despite the lower cost, wider availability, higher stability, and superior properties of these substances as compared to those of their inorganic and organometallic counterparts in many cases.[13] Because of this comparison, we decided to exploit organic dyes as photoredox catalysts for the new formylation reaction. Among the family of carbazoyl dicyanobenzenes reported by Adachi and co-workers as light harvesters in organic light-emitting diodes, we were attracted to readily available 1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene (4CzIPN).[14,15] The high reduction potential of the photoexcited state of 4CzIPN ($E^{*\mathrm{red}} = +1.35$ V vs. SCE) augurs well for the use of this substance to promote photo-oxidative decarboxylation reactions.

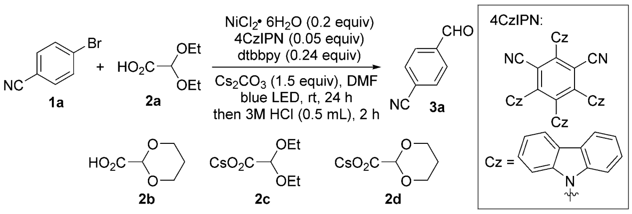


Scheme 2. Proposed nickel–photoredox-catalyzed formylation of aryl halides and triflates.

In initial studies to probe the feasibility of the new formylation reaction, we used glyoxylic acid as the formyl-radical source. Unfortunately, none of the desired aldehyde product **3a** was produced when a mixture of 4-bromobenzonitrile (**1a**), glyoxylic acid monohydrate, $NiCl_2$·glyme (glyme = ethylene glycol dimethyl ether), 4CzIPN, 4,4′-di-*tert*-butyl-2,2′-bipyridine (dtbbpy), and Cs_2CO_3 in *N*,*N*-dimethylformamide (DMF) at room temperature was irradiated with blue-light-emitting diodes (LEDs) for 24 h (Table 1, entry 1). We reasoned that the failure of this reaction might be associated with the difficulty of promoting SET oxidation of glyoxylic acid because of its high oxidation potential ($E^{\mathrm{ox}} = +1.33$ V vs. SCE, CH_3CN; see Figure S1 in the Supporting Information) and lability.[16] A careful search uncovered the fact that the readily available and inexpensive diethyl acetal derivative of glyoxylic acid **2a**, generated by the hydrolysis of ethyl diethoxyacetate ($0.56 g^{-1}),[17] has a much lower oxidation potential [E^{ox}(**2a** Cs salt) $= +0.95$ V vs. SCE, CH_3CN (see Figure S2). Thus, this acetal should be more readily oxidized by SET to the excited state of 4CzIPN. Significantly, the irradiation of a mixture containing **1a**, **2a**, $NiCl_2$·glyme, 4CzIPN, dtbbpy, and Cs_2CO_3 in DMF at room temperature with blue-light-emitting diodes (LEDs) led to smooth formation of the formylation product **3a** in 72 % yield (Table 1, entry 2).

Encouraged by this preliminary result, we evaluated the effects of several parameters, including the Ni salt, photosensitizer, base, solvent, ligand, and light source on this transformation (Table 1; see also Table S1 in the Supporting Information). Slightly higher efficiency was observed when

Table 1: Exploration and optimization.

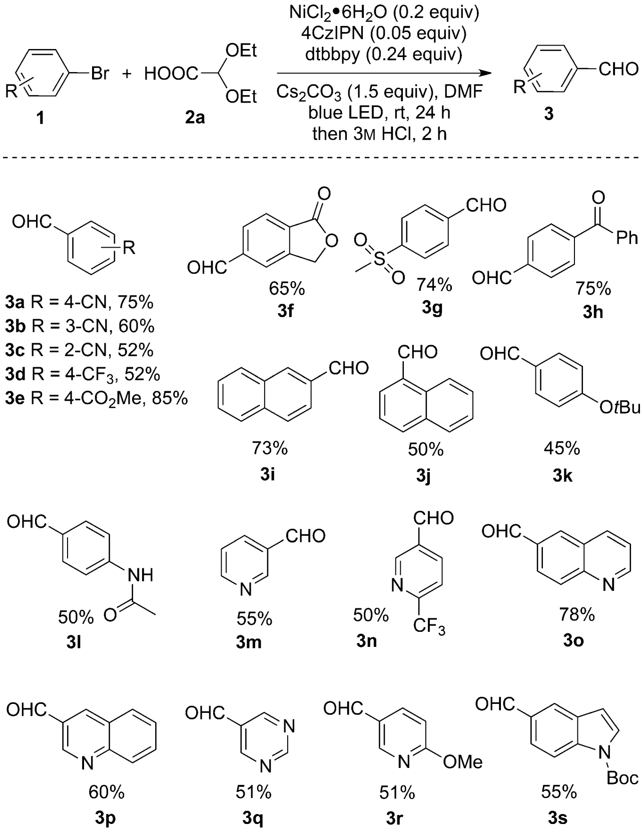


Entry	Deviation from the standard conditions[a]	Yield [%][b]
1	CHOCO$_2$H·H$_2$O instead of **2a**	0
2	NiCl$_2$·glyme instead of NiCl$_2$·6H$_2$O	72
3	none	75 (75)[c]
4	9-mesityl-10-methylacridinium instead of 4CzIPN	0
5	Eosin Y instead of 4CzIPN	0
6	Na$_2$CO$_3$ instead of Cs$_2$CO$_3$	0
7	[**1a**] was 0.2 M instead of 0.02 M	19
8	[**1a**] was 0.04 M instead of 0.02 M	45
9	**2b** instead of **2a**	25
10	**2c** instead of **2a**	0
11	**2d** instead of **2a**	0
12	no light	trace
13	without NiCl$_2$·6H$_2$O	0
14	without 4CzIPN	trace
15	without N$_2$ protective atmosphere	30

[a] Standard reaction conditions: A mixture of **1a** (0.2 mmol), **2a** (0.3 mmol), NiCl$_2$·6H$_2$O (0.04 mmol), dtbbpy (0.048 mmol), 4CzIPN (0.01 mmol), and Cs$_2$CO$_3$ (0.3 mmol) in DMF (10 mL) was irradiated with blue LEDs at rt for 24 h, and then 3 N HCl (0.5 mL) was added (see the Supporting Information for details). [b] The yield was determined by using ^{1}H NMR spectroscopy with dimethyl maleate as an internal standard. [c] Yield of the isolated product.

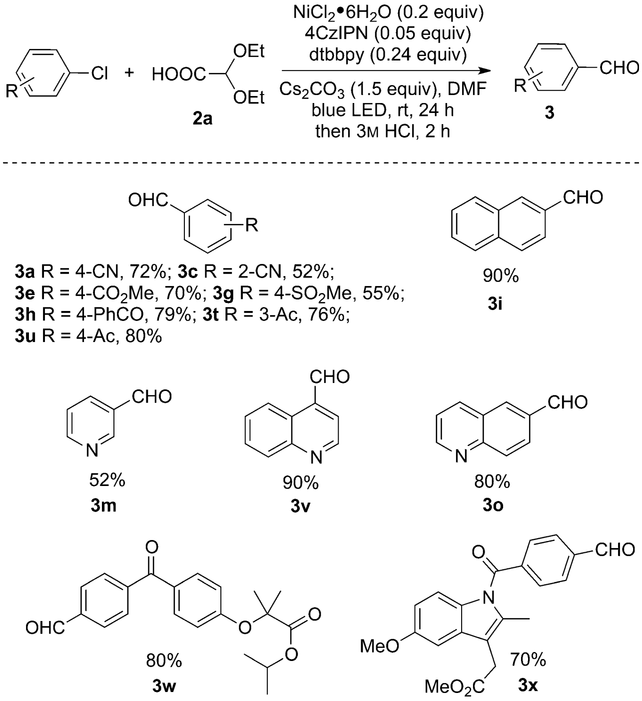
NiCl$_2$·glyme was replaced with less expensive NiCl$_2$·6H$_2$O (entry 3, 75% yield). The photocatalyst 4CzIPN was found to play a crucial role in the process. Other photocatalysts, including commonly used dyes, such as 9-mesityl-10-methylacridinium and eosin Y (entries 4 and 5; for the other dyes screened, see Table S1), failed to promote aldehyde formation. Other observations showed that Cs$_2$CO$_3$ was the best base for the process (entry 6; see also Table S1) and that the concentration of aryl bromide **1a** strongly influenced the efficiency of the reaction. Specifically, the irradiation of 0.02, 0.04, and 0.2 M solutions of **1a** generated **3a** in 75, 45, and 19% yield, respectively (Table 1; entries 3, 7, and 8). Interestingly, the cyclic acetal acid **2b** participated in this reaction, but the yield was appreciably lower (entry 9). Furthermore, when the Cs salts **2c** and **2d** were utilized, the formylation reaction did not take place (entries 10 and 11). We observed the facile generation of the corresponding highly active radicals, which caused rapid decomposition and other side reactions. As expected, light irradiation and the nickel and 4CzIPN catalysts were essential for the success of the process (entries 12–14). Finally, the presence of molecular oxygen led to decreased reaction efficiency (entry 15).

The scope of the transformation with respect to the aryl bromide was explored under the optimized reaction conditions (Table 1, entry 3). A series of structurally diverse aryl bromides were found to undergo highly efficient formylation reactions with diethoxyacetic acid as the formyl equivalent (Scheme 3). Although substituents at the *meta* and *para* positions of the aryl ring in these substrates had little effect on the efficiency of the process (e.g. products **3a** and **3b**), *ortho* substitution resulted in diminished yields (product **3c**). Furthermore, the process tolerated a variety of functionalities, including a trifluoromethyl (product **3d**), ester (products **3e** and **3f**), methanesulfonyl (product **3g**), ketone (product **3h**), ether (product **3k**), and amide group (product **3l**). Polyaromatic bromides also served as effective substrates in this reaction, with the production of the corresponding aldehydes **3i** and **3j** in moderate to good yields. Moreover, electron-rich aryl bromides reacted under the optimized conditions to give **3k** and **3l**, but in only moderate yields. Significantly, the formylation method could be employed to transform a broad range of pharmaceutically relevant heteroaromatic bromides, including those containing pyridine, quinoline, pyrimidine, and indole ring systems, into the corresponding aldehydes **3m–s**.



Scheme 3. Scope of the formylation reaction with aryl bromides. Standard reaction conditions: A mixture of **1** (0.2 mmol), **2a** (0.3 mmol), NiCl$_2$·6H$_2$O (0.04 mmol), dtbbpy (0.048 mmol), 4CzIPN (0.01 mmol), and Cs$_2$CO$_3$ (0.3 mmol) in DMF (10 mL) was irradiated with blue LEDs at room temperature for 24 h, then 3 N HCl (0.5 mL) was added, and the mixture was stirred for 2 h (see the Supporting Information for details). Yields are for the isolated product. Boc = *tert*-butoxycarbonyl.

We next expanded the scope of the process to include more readily available and less expensive aryl chlorides (Scheme 4). As mentioned above, the development of methods to promote the formylation of the chloride substrates with previously developed catalysts has been unsuc-

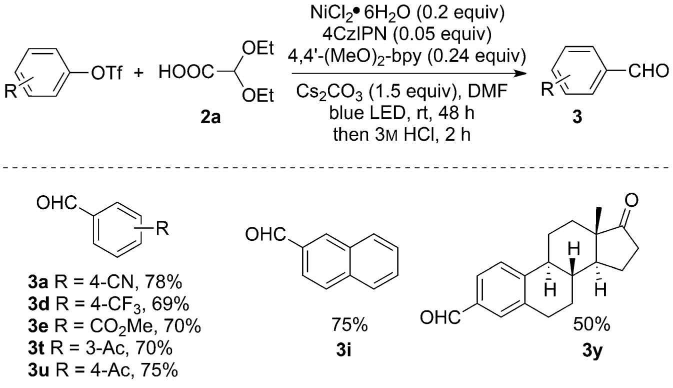


Scheme 4. Formylation reactions of aryl chlorides. For the reaction conditions, see Scheme 3 and the Supporting Information. Yields are for the isolated product.

cessful.[1c,3] We observed that under the optimal conditions for reactions of their bromide counterparts, a broad range of aryl chlorides underwent formylation to form the corresponding aldehyde products in similarly high yields. Again, the reaction can be applied to generate aldehydes from aryl chlorides containing pharmaceutically relevant functionality, such as nitrile (products **3a** and **3c**), ketone (products **3h**, **3t**, and **3u**), ester (product **3e**), and methanesulfonyl groups (product **3g**), as well as fused-aromatic (product **3i**) and hetereoaromatic moieties (products **3m**, **3v**, and **3o**). Finally, we demonstrated that the mild reaction conditions enable the process to be employed for late-stage synthetic elaboration of biologically relevant substances, including fenofibrate (product **3w**) and indomethacin methyl ester (product **3x**).

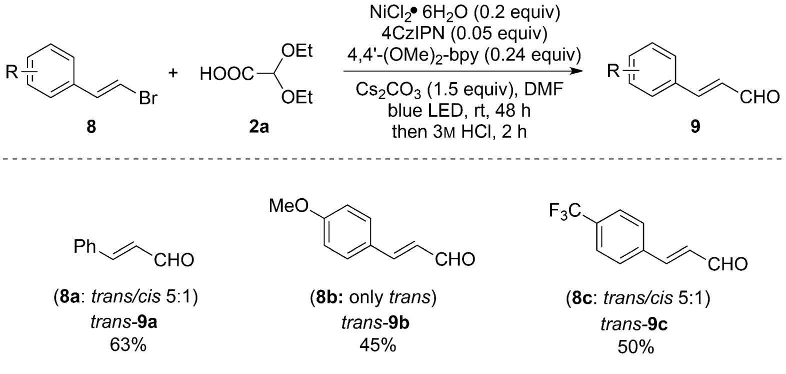
Having established an efficient protocol for the synthesis of aldehydes from aryl halides, we next investigated the use of aryl triflates as coupling partners. Substrates of this type have not been used previously for formylation reactions. Significantly, when the more electron rich ligand 4,4′-dimethoxy-2,2′-bipyridine (4,4′-(MeO)$_2$-bpy) was used in conjunction with the optimized conditions described above, a variety of aryl triflates were converted into the corresponding aromatic aldehydes **3a**, **3d**, **3e**, **3i**, **3t**, and **3u** (Scheme 5; see Scheme S1 for the results of optimization studies). Moreover, the new formylation procedure is applicable to late-stage synthetic elaboration of biologically relevant substances, such as estrone (product **3y**).

Finally, the protocol was used to transform vinyl bromides into α,β-unsaturated aldehydes **9a–c** in moderate to good yields (Scheme 6). Notably, only the *trans* products **9a** and **9c** were formed, even when a mixture of *trans* and *cis* bromides were used. To the best of our knowledge, these reactions are the first examples of the use of non-precious-metal catalysts for the formylation of vinyl bromides.[18]

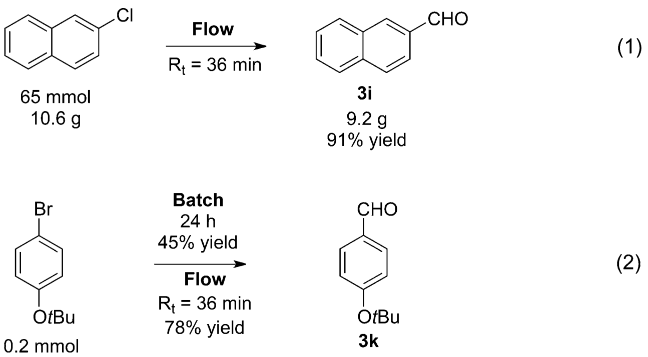


Scheme 5. Formylation reactions of aryl triflates. Standard reaction conditions: A mixture of aryl chloride (0.2 mmol), **2a** (0.3 mmol), $NiCl_2 \cdot 6H_2O$ (0.04 mmol), 4,4′-(OMe)$_2$-bpy (0.048 mmol), 4CzIPN (0.01 mmol), and Cs_2CO_3 (0.3 mmol) in DMF (10 mL) was irradiated with blue LEDs at room temperature for 48 h, then 3 N HCl (0.5 mL) was added, and the mixture was stirred for 2 h (see the Supporting Information for details). Yields are for the isolated product.

In the final phase of this investigation, we assessed the practical utility of the new formylation protocol in a potential industrial-process-scale setting. An attractive approach to large-scale synthesis involves the use of a continuous-flow procedure.[19] We found that the new formylation methodology is compatible with continuous-flow technology (see Figure S3 and Scheme S2). Thus, the reaction of 2-chloronaphthalene (10.6 g) in a flow system with a short residence time of 36 min produced the corresponding aldehyde **3i** in 91% yield [9.2 g; Scheme 7, Eq. (1)]. Furthermore, the reactant concentration, whose variation had a pronounced effect on the efficiency of the batch process (see above), did not affect the reaction in the continuous-flow system. Specifically, even the reaction of a 0.5 M solution (1 mmol scale) of 2-chloronaphthalene gave **3i** in 93% yield. The



Scheme 6. Formylation reactions of vinyl bromides. For the reaction conditions, see Scheme 5 and the Supporting Information. Yield of the isolated product.



Scheme 7. Reactions performed in a flow system. For the reaction conditions, see Scheme 3 and the Supporting Information. Yields are for the isolated product.

improved efficiency associated with the continuous-flow technique was also demonstrated by the efficient formylation of 4-*tert*-butoxybromobenzene [product **3k**, 45% in batch versus 78% in flow; Scheme 7, Eq. (2)].

In summary, a novel, cost-effective formylation strategy has been developed. Distinct from extensively studied palladium-catalyzed methods, this process takes place through nickel-promoted coupling between aryl halides, aryl triflates, or vinyl bromides and a formyl-radical equivalent derived from readily available diethoxyacetic acid by photoredox catalysis. The synergistic metal–organic catalytic process occurs at room temperature and tolerates a wide range of functional groups. The results of this study expand the scope of nickel and photoredox catalysis by providing a practical approach to the preparation of members of the fundamentally important family of aromatic aldehydes.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: flow chemistry · formylation · nickel catalysis · photoredox catalysis · synthetic methods

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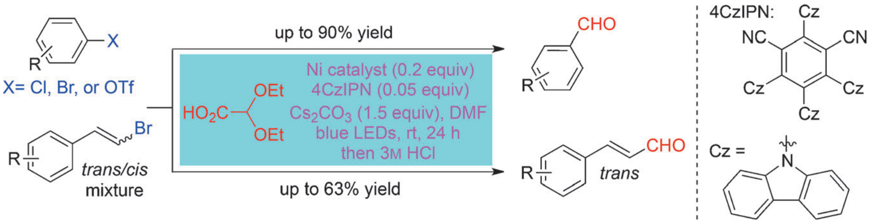
Communications

Photoredox Catalysis

H. Huang, X.-M. Li, C.-G. Yu, Y.-T. Zhang, P. S. Mariano,* W. Wang* ——— ▮▮▮–▮▮▮

Visible-Light-Promoted Nickel- and Organic-Dye-Cocatalyzed Formylation Reaction of Aryl Halides and Triflates and Vinyl Bromides with Diethoxyacetic Acid as a Formyl Equivalent



Masked beauty: Whereas palladium-catalyzed formylation reactions require harsh reaction conditions, aryl halides, aryl triflates, and vinyl bromides underwent formylation with diethoxyacetic acid under mild conditions through synergistic photoredox catalysis in the presence of a nickel complex and the organic dye 4CzIPN (see scheme). Even aryl chlorides could be used as substrates, and the transformation tolerated a wide range of functional groups.