C–H Functionalization

International Edition: DOI: 10.1002/anie.201702079
German Edition: DOI: 10.1002/ange.201702079

Mild, Redox-Neutral Formylation of Aryl Chlorides through the Photocatalytic Generation of Chlorine Radicals

*Matthew K. Nielsen[+], Benjamin J. Shields[+], Junyi Liu, Michael J. Williams, Michael J. Zacuto, and Abigail G. Doyle**

Abstract: *We report a redox-neutral formylation of aryl chlorides that proceeds through selective 2-functionalization of 1,3-dioxolane through nickel and photoredox catalysis. This scalable benchtop approach provides a distinct advantage over traditional reductive carbonylation in that no carbon monoxide, pressurized gas, or stoichiometric reductant is employed. The mild conditions give unprecedented scope from abundant and complex aryl chloride starting materials.*

Aromatic aldehydes are among the most versatile intermediates in the synthesis of pharmaceuticals, fragrances, fine chemicals, and natural products.[1] Indeed, the functional group can be rapidly elaborated through an ever growing host of C–C and C–X bond forming reactions. Despite the ubiquitous application of aryl aldehydes, synthetic methods for their preparation are limited. Classical approaches such as the Vilsmeier–Haack and Duff reactions proceed through electrophilic aromatic substitution; therefore their reactivity and regioselectivity are endogenous to the particular aryl substrate (Figure 1 A).[2] As an alternative, traditional organometallic methods, such as the addition of Grignard reagents to DMF at cryogenic temperatures, impart regiocontrol at the expense of functional group compatibility.[3] To date, the most general method for the synthesis of aryl aldehydes is the palladium-catalyzed reductive carbonylation of aryl iodides and bromides, first reported by Heck in 1974 under 100 atm of syngas (1:1 H_2/CO) at 150 °C.[4] Although this procedure has been performed on a multi-ton scale,[5] the conditions are not ideal for benchtop synthesis owing to the hazards associated with carbon monoxide and the specialized equipment required for handling high-pressure syngas. To develop user-friendly methods, several laboratories have reported alternative condensed-phase reductants[6] and CO surrogates[7] such as the crystalline *N*-formylsaccharin.[7b] Nevertheless, reductive formylations are still limited to simple arenes owing to the general requirements of high reaction temperatures and stoichiometric reducing agents. Moreover, most methods are incapable of employing aryl chlorides,[8] which are by far the most abundant and diverse class of aryl halides.[9]

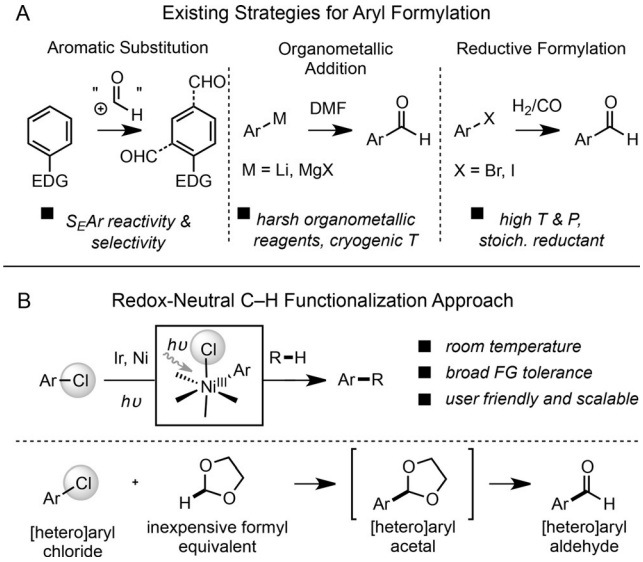


Figure 1. A) Prior art in aryl formylation. B) Proposed redox-neutral formylation of aryl chlorides through C–H activation of 1,3-dioxolane.

Recently, our group[10] and others reported directing-group-free Csp^3–H cross-coupling platforms capable of carrying out C–H arylations at room temperature. In contrast to systems reported by MacMillan[11] and Molander,[12] which primarily employ aryl bromides and iodides, our method utilizes aryl chlorides by design. Here, we demonstrate that this manifold can be leveraged to enable redox-neutral formylation through selective 2-arylation of the inexpensive and abundant solvent 1,3-dioxolane with aryl chlorides followed by a mild acidic workup (Figure 1 B). Importantly this strategy overcomes the challenges of positional selectivity and functional-group compatibility associated with classical formylation reactions and obviates the need for the gaseous reagents, stoichiometric reductants, and high reaction temperatures that are required for reductive carbonylation.

We envisioned that oxidative addition of Ni^0 (Figure 2, **1**) into an aryl chloride would produce Ni^{II} intermediate **2**. Simultaneously, visible-light irradiation of Ir^{III} photocatalyst **3** would generate triplet excited $*Ir^{III}$ (**4**; $\tau_0 = 2.3$ μs, $*E_{1/2} = 1.21$ V vs. SCE in MeCN) which could engage **2** ($E_P = 0.85$ V vs. SCE in THF) in photoinduced electron transfer to give presumed Ni^{III} intermediate **5**.[10,13] According to our prior studies,[10] photolysis of **5** produces Ni^{II} species **6** and a chlorine radical capable of abstracting a hydrogen atom from 1,3-dioxolane. A concern in developing this reaction was

[*] M. K. Nielsen,[+] B. J. Shields,[+] J. Liu, Prof. A. G. Doyle
Department of Chemistry, Princeton University
120 Washington Road, Princeton, NJ 08544 (USA)
E-mail: agdoyle@princeton.edu
Dr. M. J. Williams, Dr. M. J. Zacuto
Drug Substance Development, Celgene Corporation
556 Morris Ave., Summit, NJ 07901 (USA)
[+] These authors contributed equally to this work.
Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under: https://doi.org/10.1002/anie.201702079.

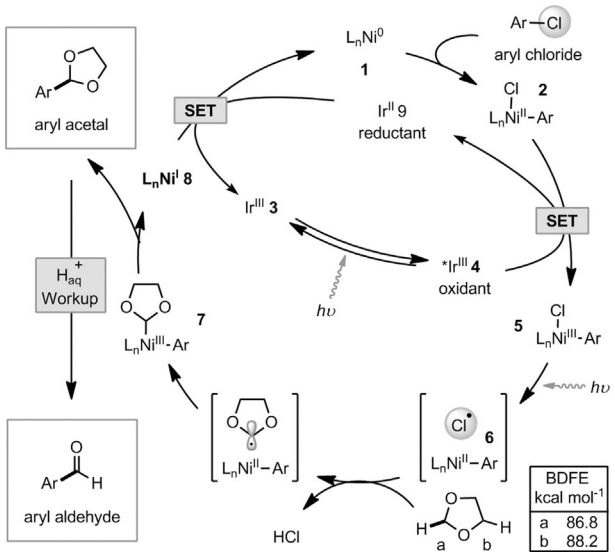


Figure 2. Proposed catalytic cycle.

that 1,3-dioxolane has two sets of chemically distinct α-oxy C–H bonds. Thermodynamic computations imply a moderate driving force for 2-functionalization ($\Delta BDFE = 1.4$ kcal mol^{-1}), which we expected could be influenced by the Ni catalyst that accepts the resultant carbon-centered radical. Reductive elimination from Ni^{III} species **7** would then give the aryldioxolane acetal, and hydrolytic workup would furnish the desired aryl aldehyde product. Finally, to close both cycles, Ni^I species **8** ($E_{1/2}[Ni^{II}/(0)] = -1.2$ V vs. SCE in DMF) can be reduced by Ir^{II} species **9** ($E_{1/2} = -1.37$ V vs. SCE in MeCN).[13,14]

We began studying the proposed formylation reaction with emphasis on the development of a user-friendly and scalable method. We were pleased to find that the commercial bench-stable precatalyst systems $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$[15] and $NiCl_2$·DME with 4,4′-di-*t*-butyl-2,2′-bipyridine ligand (dtbbpy), combined with two equivalents of potassium phosphate under irradiation with blue LEDs enabled the selective 2-functionalization of 1,3-dioxolane with numerous aryl chlorides. A subsequent mild acidic workup gave the desired aryl (Figure 3, **10**–**18**), heteroaryl

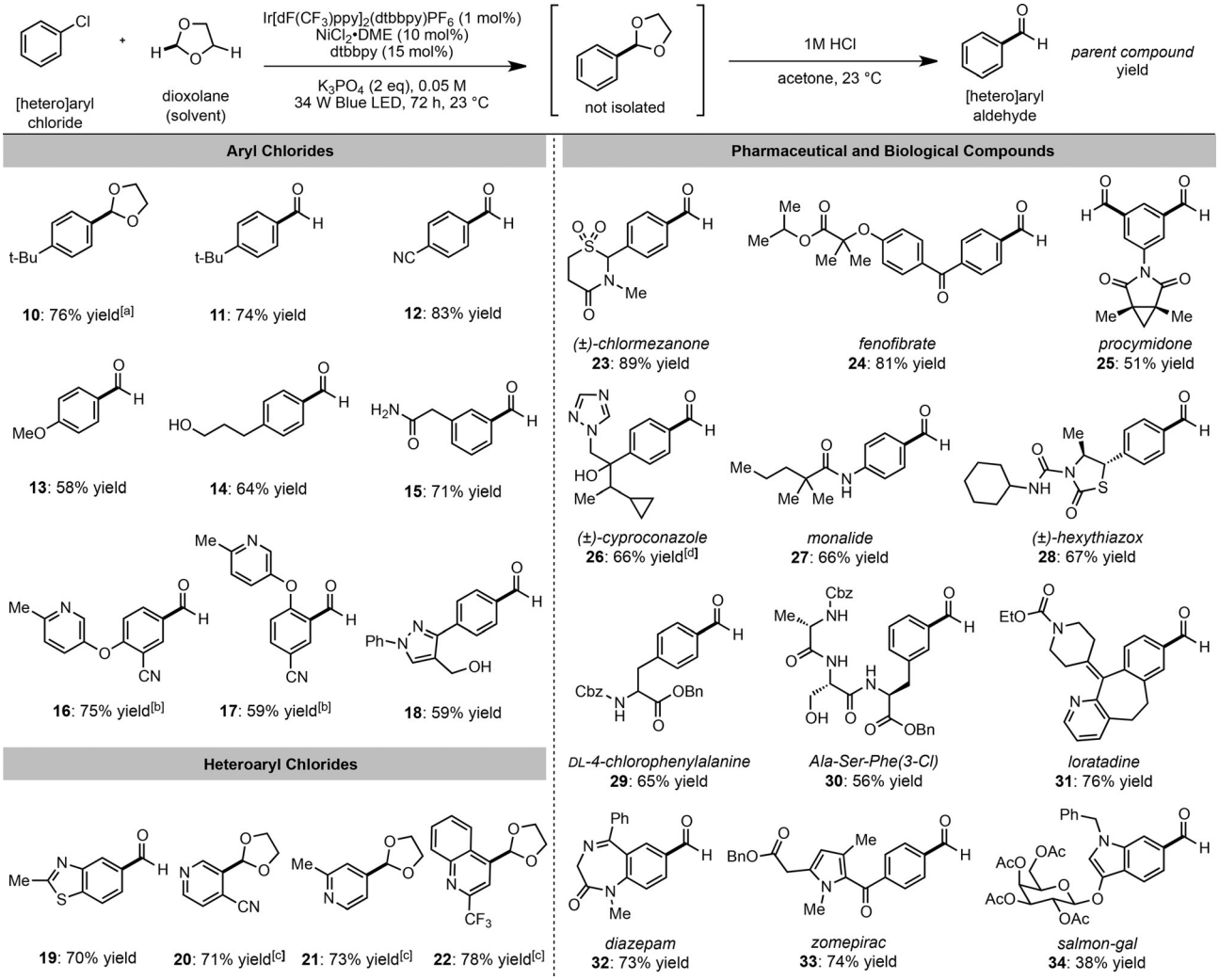


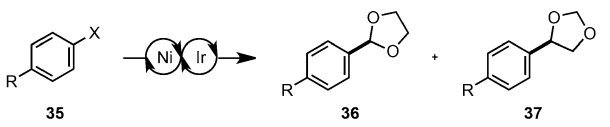
Figure 3. Formylation of aryl chlorides: substrate scope. Yields are an average of two runs on 0.25 mmol scale. For **23**–**34**, the name of the parent compound is listed. [a] Acid hydrolysis omitted. [b] Benchtop setup; single run. [c] Aldehyde does not form under hydrolysis conditions. [d] 2.3:1 d.r. (conserved from starting material).

(**19**–**22**) and biologically relevant (**23**–**34**) aldehydes in good to excellent yields with minimal loss of material upon acetal hydrolysis (76% yield **10** vs. 74% yield **11**). Interestingly, the average selectivity for the cross-coupling step favored methylene over ethylene C–H functionalization by 9:1. This observation is in qualitative agreement with computed C–H BDFEs, which predict a selectivity of 5:1 purely based on thermodynamics and stoichiometry. However, the disparity suggests that other factors such as polar effects in the rebound of the radical to Ni^{II} may also be important. Based on these observations, it is noteworthy that the reaction of chlormezanone afforded **23** in 89% yield, which is the maximum theoretical yield based on average selectivity. For most substrates, simple silica gel column chromatography was sufficient to obtain the desired product in high purity (see the Supporting Information for details). However, in some cases, a mixture of aryl aldehyde and isomeric acetal resulting from 4-functionalization of dioxolane was isolated. Notably, regioisomerism can be avoided by employing 1,3,5-trioxane as a formyl source; for example, by using 50 equivalents of 1,3,5-trioxane and benzene as a solvent, the trioxanyl acetal of **12** can be prepared in 57% yield under otherwise identical conditions. Control reactions demonstrated that in the absence of light, nickel, or photoredox catalyst, no product was formed. Reactions carried out on the benchtop afforded comparable yields to those set up in a glovebox; for example, **23** was obtained in 81% yield (vs. 89% yield) when using Schlenk techniques. In addition, the reaction is amenable to operationally simple batch scale-up; fenofibrate gave 1.47 g of **24** in 83% yield on 5 mmol scale. Moreover, benchtop scale-up reactions of **16** and **17** gave 64% yield and 70% yield, respectively, on the gram scale.

Reaction scope investigations indicate that the method is general across a broad range of electronically differentiated aryl chlorides. It was observed that electron-deficient aryl chlorides generally afforded higher yields than electron-rich substrates over the 72 hour reaction time. Time-point experiments showed that while the reaction of 4-chlorobenzonitrile reached nearly full conversion within 48 h, 4-chloroanisole continued to undergo cross-coupling for the duration of the 96 h monitoring period (Figure S5), thus indicating that electron-rich substrates react at a reduced rate. Sterically encumbered chloroarenes bearing *ortho* substituents underwent coupling to give the corresponding formylated products (**17**, **21**). Additionally, the dichloride fungicide procymidone underwent multiple functionalizations to form dialdehyde **25**.

A broad range of reactive functional groups were well tolerated, thus highlighting the exceptionally mild reaction conditions. Aryl chlorides containing protic functionality underwent efficient formylation to yield primary alcohols **14** and **30**, primary and tertiary benzylic alcohols **18** and **26**, primary amide **15**, and secondary amides **27**–**30**. Functional groups susceptible to hydrogenation under typical reductive carbonylation conditions can be accommodated, such as alkene **31** and imine **32**. Furthermore, formylation proceeds in the presence of diverse heterocycles, both distal and proximal, including pyridines **16**, **17**, **20**, **21,** and **31**, pyrazole **18**, benzothiazole **19**, quinoline **22**, triazole **26**, thiazolidinone **28**, benzodiazepine **32**, pyrrole **33**, and indole **34**. We were pleased to find that numerous pharmaceuticals (**23**, **24**, **31**–**33**) and agrochemicals (**25**–**28**) were accommodated. Formylations that yielded amino ester **29**, tripeptide **30**, and glycoside **34** are particularly noteworthy, demonstrating a new strategy for synthesizing biomolecular aldehydes, a desirable functional handle in the field of bioconjugation.[16] More generally, the unparalleled scope of this transformation offers the possibility of late-stage formylation of typically inert aryl chlorides and thus the potential to disrupt current trends in synthesis in which aryl aldehydes are employed early in a synthetic sequence.[1a,b]

We recognized that in some instances, it may be advantageous to employ aryl bromides or iodides in this transformation. 4-Bromobenzonitrile and 4-bromobiphenyl performed modestly well in the coupling reaction, giving the corresponding aryl acetals (**36**-CN and **36**-Ph) in 52% and 36% yield, respectively (Figure 4). Notably, aryl bromides are



35 **36** **37**

Entry	R	X	Yield **36**	**36**/**37**	Entry	R	X	Yield **36**	**36**/**37**
1	CN	Cl	73%	7.1:1	4	Ph	Cl	65%	9.0:1
2	CN	Br	52%	15.8:1	5	Ph	Br	36%	18.1:1
3[a]	CN	I	18%	5.0:1	6[a]	Ph	I	25%	7.7:1

Figure 4. Aryl halide selectivity studies. Yields determined by GC-FID using 1-fluoronaphthalene as an external standard. See Tables S2 and S3 for additional experiments and reaction conditions. [a] With addition of 1 equiv TBACl.

significantly more selective for 2-functionalization, in both cases doubling the regioisomeric ratio. This observation is consistent with a halogen radical abstraction mechanism wherein selectivity for the initial C–H functionalization is governed by Hammond's postulate, that is, that the late transition state in bromine abstraction ($BDE_{H\text{-}Br} = 88$ kcal mol^{-1} vs. $BDE_{H\text{-}Cl} = 103$ kcal mol^{-1}) results in higher selectivity for the thermodynamically favored alkyl radical product. Interestingly, the change in selectivity for each set of aryl chlorides and aryl bromides was moderately substituent-dependent (Entry 1/Entry 4 = 1:1.3, Entry 2/Entry 5 = 1:1.1), which is in agreement with the proposed role of aryl Ni^{II} (Figure 2, species **6**) in the radical rebound step. Together these observations suggest the potential for both halide and substrate control over C–H functionalization selectivity. Although aryl iodides alone are incompetent ($BDE_{H\text{-}I} =$ 71 kcal mol^{-1}), moderate yield can be attained through halide exchange with tetrabutylammonium chloride (TBACl).

In a preliminary evaluation of other substrate classes under unoptimized conditions, alkyl bromide (3-bromopropyl)benzene afforded 4-phenylbutanal in 6% yield, thus demonstrating the potential of this strategy to convert alkyl halides into homologated aldehydes. Moreover, the acyl chloride 4-methylbenzoyl chloride underwent coupling to give the corresponding protected glyoxal in 39% yield (see

the Supporting Information for details). By comparison, under reductive carbonylation conditions, acid halides are protodehalogenated to form aldehydes,[4] and the aryl glyoxals are typically only accessible through oxidative methods.

Although various oxidation states (e.g., alcohol and carboxylic acid derivative) can be accessed from aldehydes, redox manipulations are not ideal for step economy and require stoichiometric oxidants or reductants. We recognized the generality of the redox-neutral Csp^3–H functionalization strategy underlying our formylation reaction and hypothesized that direct access to other oxidation states could be afforded through judicious selection of the C–H coupling partner. Gratifyingly, under unoptimized conditions, the methyl ester and benzyl alcohol of 4-chlorobiphenyl could be accessed by direct arylation of trimethyl orthoformate through a tertiary radical intermediate and trimethyl orthoacetate to give **39** and **40** in 14% and 42% yield, respectively (Figure 5). These preliminary examples provided promising results for further development.

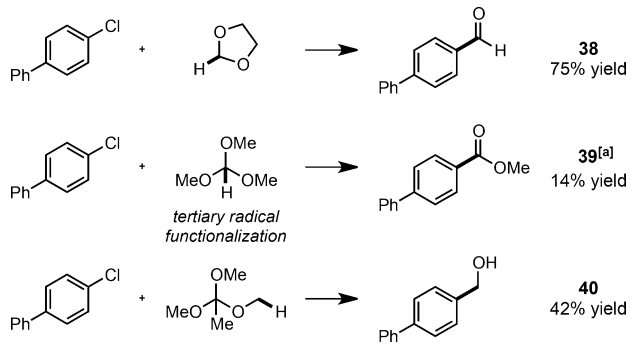


Figure 5. Direct access to formyl oxidation and reduction analogues through redox-neutral Csp^3–H functionalization. Yield of isolated product are given. [a] Generates methoxy functionalization product in 15% yield. See the Supporting Information for experimental details.

In conclusion, we have demonstrated a redox-neutral C–H functionalization approach to aryl formylation that proceeds under exceptionally mild conditions to give numerous aryl, heteroaryl, and biologically relevant aldehydes.

Acknowledgements

Financial support was provided by NIGMS (R01 GM100985) and Celgene Corporation.

Conflict of interest

The authors declare no conflict of interest.

Keywords: C–H functionalization · formylation · nickel · photocatalysis · redox reactions

How to cite: *Angew. Chem. Int. Ed.* **2017**, *56*, 7191–7194
Angew. Chem. **2017**, *129*, 7297–7300

[1] a) K. L. Baumann, D. E. Butler, C. F. Deering, K. E. Mennen, A. Millar, T. N. Nanninga, C. W. Palmer, B. D. Roth, *Tetrahedron Lett.* **1992**, *33*, 2283–2284; b) J. M. McNamara, J. L. Leazer, M. Bhupathy, J. S. Amato, R. A. Reamer, P. J. Reider, E. J. J. Grabowski, *J. Org. Chem.* **1989**, *54*, 3718–3721; c) G. Fráter, J. A. Bajgrowicz, P. Kraft, *Tetrahedron* **1998**, *54*, 7633–7703; d) R. B. Woodward, M. P. Cava, W. D. Ollis, A. Hunger, H. U. Daeniker, K. Schenker, *J. Am. Chem. Soc.* **1954**, *76*, 4749–4751; e) P. Magnus, N. Sane, B. P. Fauber, V. Lynch, *J. Am. Chem. Soc.* **2009**, *131*, 16045–16047.

[2] a) K. Reimer, F. Tiemann, *Ber. Dtsch. Chem. Ges.* **1876**, *9*, 1268–1278; b) L. Gattermann, J. A. Koch, *Chem. Ber.* **1897**, *30*, 1622–1624; c) L. Gattermann, W. Berchelmann, *Ber. Dtsch. Chem. Ges.* **1898**, *31*, 1765–1769; d) A. Vilsmeier, A. Haack, *Chem. Ber.* **1927**, *60*, 119–122; e) J. C. Duff, E. J. Bills, *J. Chem. Soc.* **1932**, 1987–1988.

[3] L. Bouveault, *Bull. Soc. Chim. Fr.* **1904**, *31*, 1306–1322.

[4] A. Schoenberg, R. F. Heck, *J. Am. Chem. Soc.* **1974**, *96*, 7761–7764.

[5] S. Klaus, H. Neumann, A. Zapf, D. Strübing, S. Hübner, J. Almena, T. Riermeier, P. Groß, M. Sarich, W.-R. Krahnert, K. Rossen, M. Beller, *Angew. Chem. Int. Ed.* **2006**, *45*, 154–158; *Angew. Chem.* **2006**, *118*, 161–165.

[6] a) V. P. Baillargeon, J. K. Stille, *J. Am. Chem. Soc.* **1983**, *105*, 7175–7176; b) I. Pri-Bar, O. Buchman, *J. Org. Chem.* **1984**, *49*, 4009–4011.

[7] a) T. Okano, N. Harada, J. Kiji, *Bull. Chem. Soc. Jpn.* **1994**, *67*, 2329–2332; b) T. Ueda, H. Konishi, K. Manabe, *Angew. Chem. Int. Ed.* **2013**, *52*, 8611–8615; *Angew. Chem.* **2013**, *125*, 8773–8777; c) B. Yu, Y. Zhao, H. Zhang, J. Xu, L. Hao, X. Gao, Z. Liu, *Chem. Commun.* **2014**, *50*, 2330–2333; d) X. Jiang, J.-M. Wang, Y. Zhang, Z. Chen, Y.-M. Zhu, S.-J. Ji, *Org. Lett.* **2014**, *16*, 3492–3495; e) K. Natte, A. Dumrath, H. Neumann, M. Beller, *Angew. Chem. Int. Ed.* **2014**, *53*, 10090–10094; *Angew. Chem.* **2014**, *126*, 10254–10258; f) N. Iranpoor, H. Firouzabadi, E. Etemadi-Davan, A. Rostami, K. R. Moghadam, *Appl. Organomet. Chem.* **2015**, *29*, 719–724.

[8] Y. Ben-David, M. Portnoy, D. Milstein, *J. Am. Chem. Soc.* **1989**, *111*, 8742–8744.

[9] A Ni/photoredox decarboxylative approach for formylating activated aryl chlorides was recently reported. H. Huang, X. Li, C. Yu, Y. Zhang, P. Mariano, W. Wang, *Angew. Chem. Int. Ed.* **2017**, *56*, 1500–1505; *Angew. Chem.* **2017**, *129*, 1522–1527.

[10] B. J. Shields, A. G. Doyle, *J. Am. Chem. Soc.* **2016**, *138*, 12719–12722.

[11] M. H. Shaw, V. W. Shurtleff, J. A. Terrett, J. D. Cuthbertson, D. W. C. MacMillan, *Science* **2016**, *352*, 1304–1308.

[12] D. R. Heitz, J. C. Tellis, G. A. Molander, *J. Am. Chem. Soc.* **2016**, *138*, 12715–12718.

[13] M. S. Lowry, J. I. Goldsmith, J. D. Slinker, R. Rohl, R. A. Pascal, G. G. Malliaras, S. Bernhard, *Chem. Mater.* **2005**, *17*, 5712–5719.

[14] M. Durandetti, M. Devaud, J. Perichon, *New J. Chem.* **1996**, *20*, 659–667.

[15] (4,4′-Di-*t*-butyl-2,2′-bipyridine)bis[3,5-difluoro-2-[5-trifluoromethyl-2-pyridinyl-κ*N*)phenyl-κ*C*]iridium(III) hexafluorophosphate [870987-870963-6].

[16] I. S. Carrico, B. L. Carlson, C. R. Bertozzi, *Nat. Chem. Biol.* **2007**, *3*, 321–322.

Manuscript received: February 25, 2017
Revised manuscript received: April 7, 2017
Version of record online: May 23, 2017

