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Visible-Light-Mediated Deaminative Three-Component Dicarbofunctionalization of Styrenes with Benzylic Radicals

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ABSTRACT: The visible-light-mediated three-component dicarbofunctionalization of styrenes using simple benzylic radicals is described. Notably, this work describes a rare example of undirected dicarbofunctionalization using unsubstituted benzyl radicals. Key to the success of this strategy was the rational design and use of benzylic pyridinium salts as radical precursors. Using this approach, abundant styrenes, electron-rich heterocycles and benzylic amines were combined to rapidly afford a number of densely functionalized 1,1-diarylalkanes. A dipeptide derived pyridinium salt was applied to that transformation, which resembles a visible-light mediated deaminative generation of radicals from peptides.
KEYWORDS: dicarbofunctionalization • deamination • redox-active • photoredox catalysis • visible-light

The utilization of carboxylic acids[1] and their derivatives[2] in decarboxylative reactions are well-explored and have gained considerable attention. However, strategies utilizing other abundant functionalities, such as amines, remain scarce.[3] Amines can be readily synthesized,[4] carried through a synthetic sequence in protected forms[5] and even serve as directing groups in regioselective transformations.[6] In contrast to the well-explored formation and conservation of C–N bonds, the majority of deaminative radical reactions employ diazonium salts, which are potentially hazardous and can only reliably be synthesized from aromatic amines.[7] Alternatively, condensation of amines with pyrylium salts gives pyridinium salts which are active for nucleophilic displacement.[8]

Recently, the scope of pyridinium salts in deaminative nickel-catalyzed cross-coupling reactions has been explored by Watson and co-workers.[9] In our efforts to develop visible-light-mediated transformations of abundant functional groups we developed a mild, additive-free method to generate alkyl radicals from Katritzky pyridinium salts, showcasing the synthetic potential of (naturally) abundant amines, including amino acid derivatives, in synthesis.[10] These salts can be prepared in a single step and are mostly obtained after a simple filtration as bench-stable, free-flowing solids in a pure form.

The difunctionalization of olefins is another powerful strategy in organic synthesis that utilizes abundant olefin feedstocks to provide rapid access to densely functionalized molecules. For that reason intense research into metal-catalyzed[11] and light-mediated[12] protocols is of great interest. As part of this family, dicarbofunctionalization reactions construct elaborate carbon frameworks in a single step. Classically, these reactions have been realized by the addition of carbon nucleophiles to Michael acceptors with subsequent electrophilic trapping[13] or by metal-catalyzed protocols,

wherein β-hydride elimination is supressed.[14] Renewed interest in recent years has given rise to the development of intramolecular and directed approaches.[15] However, efficient undirected intermolecular three-component dicarbofunctionalization reactions remain an on-going challenge in organic synthesis (Scheme 1). These processes typically require an appropriate combination of radical precursors, olefins and arene partners. In catalytic transformations, Liu, Masson and Zhang have shown that reactive perfluoroalkyl iodides can be used as radical precursors to great effect.[16] The groups of Baran, Nevado, Li and Zhu have shown that precursors for tertiary alkyl and α-carbonyl radicals can also be employed in intermolecular olefin dicarbofunctionalization reactions.[2g,17] More recently, Giri et al. described an intermolecular nickel-catalyzed dicarbofunctionalization method using alkyl iodides, styrenes and arylzinc
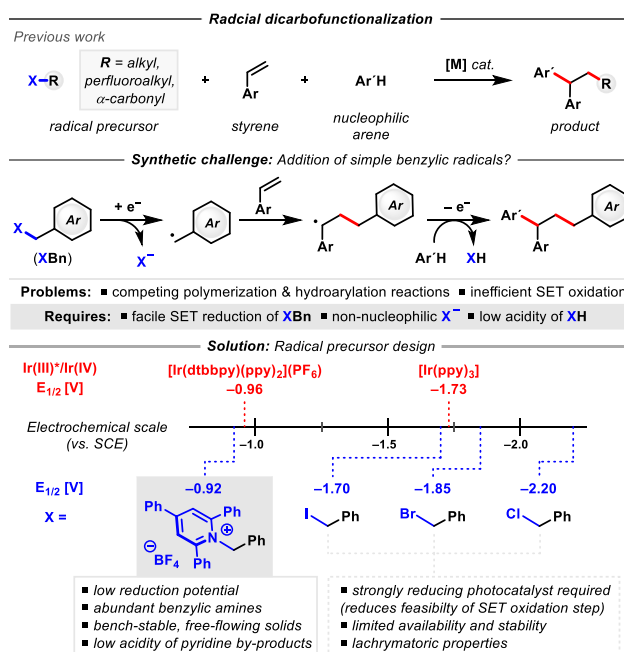
reagents.[18] Despite the significant advances in this field, there is, to the best of our knowledge, no method that efficiently introduces simple benzyl groups to generate densely functionalized polyaromatic frameworks in a three-component, undirected strategy. Considering this, we felt that the development of such a method would be highly desirable for the rapid and efficient synthesis of these product motifs and would foster further development towards more general undirected dicarbofunctionalization protocols.

Scheme 1. Activated amines as radical precursors and dicarbofunctionalization of olefins.

We rationalized that in order to realize this highly challenging transformation, the identification of a suitable radical precursor would be crucial. We reasoned that benzylic Katritzky salts might serve as suitable substrates to enable a visible-light-mediated mild protocol for the three-component dicarbofunctionalization of olefins.[19] In comparison to benzylic bromides, which are the classical precursors to benzylic radicals in a reductive fashion, benzylic Katritzky salts have a considerably more positive reduction potential ($E_{1/2}$ = –1.85 V vs. SCE in MeCN[20] against $E_{1/2}$ = –0.92 V vs. SCE in DMF[21]). Thus their reduction is expected to be more favourable by excited state photocatalysts or radical intermediates en route to product formation, which might reduce polymerization side reactions of radical intermediates. Moreover, a dicarbofunctionalization reaction will liberate stoichiometric amounts of the strong acid HBr using BnBr as radical precursor, potentially leading to extensive hydroarylation side reactions.

Table 1. Three-component dicarbofunctionalization
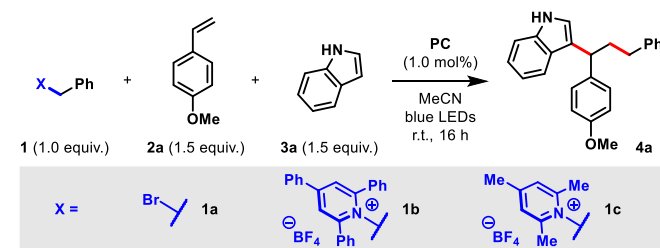
using benzylic radicals.

Entry	X	PC	Additive	Yield[f]
1[a]	1a	[Ir(dtbbpy)(ppy)₂](PF₆)	-	Traces
2[a]	1a	fac-Ir(ppy)₃	-	Traces
3[a]	1a	[Ir(dtbbpy)(ppy)₂](PF₆)	K_2CO_3[d]	15%
4[a]	1a	fac-Ir(ppy)₃	K_2CO_3[d]	18%
5[a]	1b	[Ir(dtbbpy)(ppy)₂](PF₆)	-	48%
6[b]	1b	[Ir(dtbbpy)(ppy)₂](PF₆)	-	63%[g]
7[b]	1b	[Ir(dtbbpy)(ppy)₂](PF₆)	NaCl[e]	29%
8[b]	1b	[Ir(dtbbpy)(ppy)₂](PF₆)	NaI[e]	3%
9[b, c]	1c	[Ir(dtbbpy)(ppy)₂](PF₆)	-	20%

[a]Conditions: 1 (0.10 mmol), 2a (0.15 mmol), 3a (0.15 mmol) and PC (1.0 mol%) in MeCN (0.2 M) under argon. [b]Conditions: 1 (0.20 mmol), 2a (0.30 mmol), 3a (0.30 mmol) and PC (1.0 mol%) in MeCN (1.0 M) under argon. [c]Reaction on a 0.30 mmol scale. [d]Additive (2.0 equiv.). [e]Additive (1.0 equiv.). [f]Yield determined by calibrated GC-FID analysis with mesitylene as internal standard. [g]Isolated yield on a 0.30 mmol scale: 56%; For a qualitative analysis on side-products in this protocol, see Supporting Information.

To test this hypothesis we first irradiated a mixture of benzyl bromide (1a), 4-methoxystyrene (2a), indole (3a) and common photocatalysts in MeCN for 16 h. As expected, primarily hydroarylation was observed and only traces of the desired dicarbofunctionalization product were obtained (Table 1, Entries 1, 2). To neutralize the liberated acid, K_2CO_3 was added as a base leading to unsatisfactory yields of the desired product (Table 1, Entries 3, 4). In support of our hypothesis, the desired dicarbofunctionalization product was obtained in 48% yield using benzylic Katritzky salt (1b) as radical precursor in the absence of additives (Table 1, Entry 5). Further optimization showed that more concentrated conditions lead to an increased yield (for further optimization studies see Supporting Information). Under these optimized reaction conditions the desired product (4a) could be obtained in 63% yield using 1.0 equiv. of benzyl Katritzky salt (1b), 1.5 equiv. of styrene (2a), 1.5 equiv. indole (3a) and 1.0 mol% of [Ir(dtbbpy)(ppy)₂](PF₆) in a MeCN solution (1.0 M) under irradiation with visible-light (λ_{max} = 455 nm, 5W) for 16 h (Table 1, Entry 6). The addition of halide additives, such as NaCl or NaI, was shown to significantly decrease the yields, potentially due to competing nucleophilic capture of cationic intermediates by the halides (Table 1, Entries 7, 8), indicating that other benzylic halides are presumably not suitable precursors in this method. When trimethylpyridinium salt derivative (1c) was employed the product was also obtained, but again in reduced yield (Table 1, Entry 9). In the absence of either light or photocatalyst, no formation of the desired product was observed (see Supporting Information).

Having established that benzyl Katritzky salts can be used as radical precursors to enable challenging dicarbofunctionalization reactions, we explored the scope of the newly developed protocol. A range of benzylic Katritzky salts were synthesized in this study and the corresponding radicals were employed to achieve an efficient dicarbofunctionalization reaction to yield polyaromatic carbon frameworks (Scheme 2). In this regard, a range of para-substituted products were obtained in good to moderate yield (4a–4f). Sterically demanding ortho-bromo substituents, that are possible reactive sites for further functionalizations, are well tolerated as exemplified by the formation of products 4g–4h. A meta-trifluoromethyl substituent could be incorporated into the

product structure (**4i**). Pyridine containing products **4j–4k**, which might be challenging to access via transition metal-catalyzed protocols, were obtained in good yield. Variation on the styrene coupling partner led to generation of protected amine substituted diarylmethane **4m**.[22] Valuable all carbon quarternary centers are successfully generated by this method, as showcased by the formation of product **4o**. The nucleophilic arene partner was then varied (Scheme 2c) to provide access to a range of 3-substituted indoles (**4p–4r**), which is a prominent architecture found in numerous natural products and bioactive substances such as tryptamine, serotonine and indomethacine.[23]
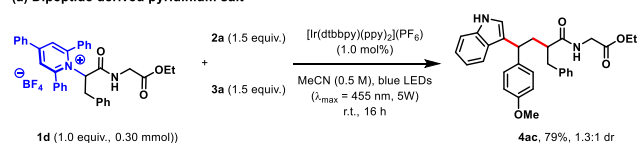
Furthermore, N-methylaniline also couples to give exclusively the *para*-C–H functionalized product **4s**, albeit with a diminished yield.[24] Katritzky salts derived from naturally abundant amino acid derivatives can be applied in this transformation and deliver complex γ-diarylated carboxylic acid derivatives in good to excellent yield (**4t–4ab**). Remarkably the use of methionine derived Katritzky salt allows for the incorporation of a thioether moiety into the final product (**4aa**), which would presumably be challenging in transition metal-catalyzed methods, due to catalyst poisoning.

Scheme 2. Scope of the visible-light-mediated deaminative dicarbofunctionalization. Reactions performed on a 0.30 mmol scale in 0.3 mL of solvent. Diastereomeric ratios determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [a]Reaction performed with **2** (2.0 equiv.) and **3** (2.0 equiv.). [b]24 h reaction time.

Having demonstrated the functional group tolerance of the protocol we searched to establish applications of our newly developed method. Dipeptide derived Katritzky salt **1d** was synthesized and applied in this transformation, showcasing the potential of this method for the highly challenging deaminative functionalization of peptides (Scheme 3a). Furthermore bromo-substituted derivative **4r** was shown to engage in a highly diastereoselective
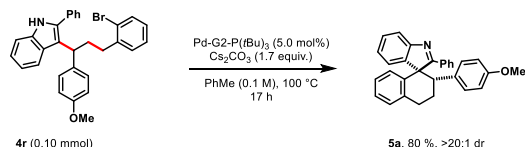
intramolecular dearomative spirocyclization reaction to form **5a** (Scheme 3b).[25]

To shine light on the mechanistic intricacies of this three-component reaction we first performed a radical trapping experiment by adding TEMPO (2.0 equiv.) to the reaction under standard conditions. No formation of the desired product was observed, supporting the involvement of radical intermediates in product formation. From crude [1]H

NMR spectroscopy, the formation of a radical adduct of the benzylic radical was not observed. Rather, under these conditions, only trace amounts of the pyridinium salt **1b** were converted. When styrene **2b** was used the ring opened product **5b** was isolated from the reaction mixture, suggesting the presence of a benzylic radical after radical addition to the styrene (Scheme 3c). Next, Stern-Volmer luminescence quenching studies revealed that the benzylic Katritzky salt **1b** is the only quencher of the excited photocatalyst in the reaction mixture.
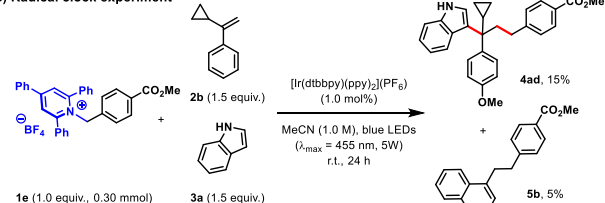
III, which then reduces the oxidized photocatalyst or another molecule of pyridinium salt **1b** to maintain a chain reaction. The resulting cation **IV** is subsequently trapped by indole (**3a**) to form the desired dicarbofunctionalization product (**4**).

Scheme 4. Proposed mechanism of the deaminative dicarbofunctionalization using Katritzky salts as radical precursors.

In summary, we have developed the first undirected three-component dicarbofunctionalization reaction of styrenes with benzylic radicals. The reaction utilizes highly abundant amine derivatives, styrenes and non-prefunctionalized arenes and forges them into an elaborate carbon framework in a single step operation. This reaction process was enabled by the use of versatile benzylic pyridinium salts as radical precursors. Notably pyridine moieties, as well as thioethers were well tolerated in this protocol. Furthermore, highly challenging all carbon quaternary centers were also readily accessed by this method. A dipeptide derived pyridinium salt was applied to that transformation, which resembles the first visible-light mediated deaminative generation of radicals from peptides. Overall, we hope that this work, and the design of other radical precursors, will enable a range of other previously challenging olefin difunctionalization reactions to be performed.
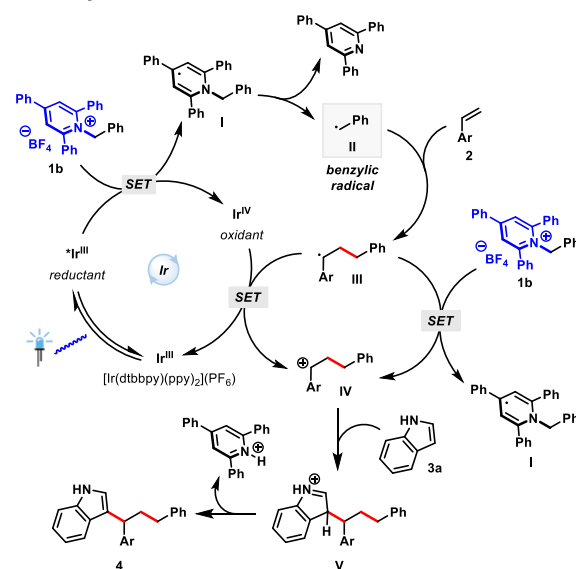

Scheme 3. Applications of the deaminative dicarbofunctionalization of styrenes and radical clock experiment. Diastereomeric ratios determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture.

Based on these mechanistic studies and literature precedence[17a,17b] we propose the following mechanism (Scheme 4). The excited state photocatalyst initiates the reaction by the reduction of Katritzky salt **1b**. This process is predicted to be thermodynamically feasible (potentials: [Ir(dtbbpy)(ppy)$_2$](PF$_6$), Ir(III)*/Ir(IV): −0.96 V[26] vs. **1b**: −0.92 V[21]) and the interaction of the excited catalyst was proven by Stern-Volmer quenching studies. Pyridinyl radical **I** fragments and delivers benzylic radical **II**.[21] This species adds to the styrene producing radical intermediate

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Notes
The authors declare no competing financial interest.

ASSOCIATED CONTENT
Supporting Information

REFERENCES

(1) (a) Johnson, R. G.; Ingham, R. K. The Degradation Of Carboxylic Acid Salts By Means Of Halogen - The Hunsdiecker Reaction. *Chem. Rev.* **1956**, *56*, 219–269. (b) Gooßen, L. J.; Rodriguez, N.; Gooßen, K. Carboxylic Acids as Substrates in Homogeneous Catalysis. *Angew. Chem. Int. Ed.* **2008**, *47*, 3100–3120. (c) Miyake, Y.; Nakajima, K.; Nishibayashi, Y. Visible light-mediated oxidative decarboxylation of arylacetic acids into benzyl radicals: addition to electron-deficient alkenes by using photoredox catalysts. *Chem. Commun.* **2013**, *49*, 7854–7856. (d) Zuo, Z.; MacMillan, D. W. C. Decarboxylative Arylation of α-Amino Acids via Photoredox Catalysis: A One-Step Conversion of Biomass to Drug Pharmacophore. *J. Am. Chem. Soc.* **2014**, *136*, 5257–5260. (e) Noble, A.; MacMillan, D. W. C. Photoredox α-Vinylation of α-Amino Acids and N-Aryl Amines. *J. Am. Chem. Soc.* **2014**, *136*, 11602–11605. (f) Xuan, J.; Zhang, Z.-G.; Xiao, W.-J. Visible-Light-Induced Decarboxylative Functionalization of Carboxylic Acids and Their Derivatives. *Angew. Chem. Int. Ed.* **2015**, *54*, 15632–15641. (g) Candish, L.; Standley, E. A.; Gomez-Suárez, A.; Mukherjee, S.; Glorius, F. Catalytic Access to Alkyl Bromides, Chlorides and Iodides via Visible Light-Promoted Decarboxylative Halogenation. *Chem. Eur. J.* **2016**, *22*, 9971–9974. (h) Candish, L.; Pitzer, L.; Gomez-Suárez, A; Glorius, F. Visible Light-Promoted Decarboxylative Di- and Trifluoromethylthiolation of Alkyl Carboxylic Acids. *Chem. Eur. J.* **2016**, *22*, 4753–4756.

(2) (a) Barton, D. H. R.; Crich, D.; Motherwell, W. B. New and improved methods for the radical decarboxylation of acids. *J. Chem. Soc., Chem. Commun.* **1983**, 939–941. (b) Okada, K.; Okamoto, K.; Oda, M. A new and practical method of decarboxylation: photosensitized decarboxylation of N-acyloxyphthalimides via electron-transfer mechanism. *J. Am. Chem. Soc.* **1988**, *110*, 8736–8738. (c) Okada, K.; Okamoto, K.; Morita, N.; Okubo, K.; Oda, M. Photosensitized decarboxylative Michael addition through N-(acyloxy)phthalimides via an electron-transfer mechanism. *J. Am. Chem. Soc.* **1991**, *113*, 9401–9402. (d) Schnermann, M. J.; Overman, L. E. A Concise Synthesis of (−)-Aplyviolene Facilitated by a Strategic Tertiary Radical Conjugate Addition. *Angew. Chem. Int. Ed.* **2012**, *51*, 9576–9580. (e) Candish, L.; Teders, M.; Glorius, F. Transition-Metal-Free, Visible-Light-Enabled Decarboxylative Borylation of Aryl N-Hydroxyphthalimide Esters. *J. Am. Chem. Soc.* **2017**, *139*, 7440–7443. (f) Tlahuext-Aca, A.; Garza-Sanchez, R. A.; Glorius, F. Multicomponent Oxyalkylation of Styrenes Enabled by Hydrogen-Bond-Assisted Photoinduced Electron Transfer. *Angew. Chem. Int. Ed.* **2017**, *56*, 3708–3711. (g) Qin, T.; Cornella, J.; Li, C.; Malins, L. R.; Edwards, J. T.; Kawamura, S.; Maxwell, B. D.; Eastgate, M. D.; Baran, P. S. A general alkyl-alkyl cross-coupling enabled by redox-active esters and alkylzinc reagents. *Science* **2016**, *352*, 801–805. (h) Suzuki, N.; Hofstra, J. L.; Poremba, K. E.; Reisman, S. E. Nickel-Catalyzed Enantioselective Cross-Coupling of N-Hydroxyphthalimide Esters with Vinyl Bromides. *Org. Lett.* **2017**, *19*, 2150–2153. (i) Huihui, K. M. M.; Caputo, J. A.; Melchor, Z.; Olivares, A. M.; Spiewak, A. M.; Johnson, K. A.; DiBenedetto, T. A.; Kim, S.; Ackerman, L. K. G.; Weix, D. J. Decarboxylative Cross-Electrophile Coupling of N-Hydroxyphthalimide Esters with Aryl Iodides. *J. Am. Chem. Soc.* **2016**, *138*, 5016–5019. (j) Proctor, R. S. J.; Davis, H. J.; Phipps, R. J. Catalytic enantioselective Minisci-type addition to heteroarenes. *Science* **2018**, *360*, 419–422.

(3) (a) McGrath, N. A.; Brichacek, M.; Njardarson, J. T. A Graphical Journey of Innovative Organic Architectures That Have Improved Our Lives. *J. Chem. Educ.* **2010**, *87*, 1348–1349. (b) Hamley, I. W. Small Bioactive Peptides for Biomaterials Design and Therapeutics. *Chem. Rev.* **2017**, *117*, 14015–14041. (c) Zhang, L.; Fu, N.; Luo, S. Pushing the Limits of Aminocatalysis: Enantioselective Transformations of α-Branched β-Ketocarbonyls and Vinyl Ketones by Chiral Primary Amines. *Acc. Chem. Res.* **2015**, *48*, 986–997.

(4) (a) Gibson, M. S.; Bradshaw, R.W. The Gabriel Synthesis of Primary Amines. *Angew. Chem. Int. Ed.* **1968**, *7*, 919–930. (b) Gomez, S.; Peters, J. A.; Maschmeyer, T. The Reductive Amination of Aldehydes and Ketones and the Hydrogenation of Nitriles: Mechanistic Aspects and Selectivity Control. *Adv. Synth. Catal.* **2002**, *10*, 1037–1057. (c) Klinkenberg, J. L.; Hartwig, J. F. Catalytic Organometallic Reactions of Ammonia. *Angew. Chem. Int. Ed.* **2011**, *50*, 86–95.

(5) Green, T. W.; Wuts, P. G. M. Protective Groups in Organic Synthesis, Wiley-Interscience, New York, **2007**, 696–926.

(6) (a) Xu, Y.; Young, M. C.; Wang, C.; Magness, D. M.; Dong, G. Catalytic C(sp^3)–H Arylation of Free Primary Amines with an *exo* Directing Group Generated In Situ. *Angew. Chem. Int. Ed.* **2016**, *55*, 9084-9087. (b) Liu, Y.; Ge, H. Site-selective C–H arylation of primary aliphatic amines enabled by a catalytic transient directing group. *Nat. Chem.* **2016**, *9*, 26–32. (c) St John-Campbell, S.; Bull, J. A. Transient imines as 'next generation' directing groups for the catalytic functionalisation of C–H bonds in a single operation. *Org. Biomol. Chem.* **2018**, *16*, 4582–4595.

(7) (a) Griefs, P. Vorläufige Notiz über die Einwirkung von salpetriger Säure auf Amidinitro- und Aminitrophenylsäure. *Justus Liebigs Ann. Chem.* **1858**, *106*, 123–125. (b) Oger, N.; d'Halluin, M.; Le Grognec, E.; Felpin, F.-X. Using Aryl Diazonium Salts in Palladium-Catalyzed Reactions under Safer Conditions. *Org. Process Res. Dev.* **2014**, *18*, 1786–1801. (c) Hari, D. P.; Schroll, P.; König, B. Metal-Free, Visible-Light-Mediated Direct C–H Arylation of Heteroarenes with Aryl Diazonium Salts. *J. Am. Chem. Soc.* **2012**, *134*, 2958–2961. (d) Hari, D. P.; Hering, T.; König, B. The Photoredox-Catalyzed Meerwein Addition Reaction: Intermolecular Amino-Arylation of Alkenes. *Angew. Chem. Int. Ed.* **2014**, *53*, 725–728.

(8) (a) Katritzky, A. R.; Marson, C. M. Pyrylium Mediated Transformations of Primary Amino Groups into Other Functional Groups. New Synthetic Methods (41). *Angew.Chem. Int. Ed. Engl.* **1984**, *23*, 420–429. (b) Katritzky, A. R.; Kashmiri, M. A.; de Viile, G. Z.; Patel, R. C. Kinetics and mechanism of the C-alkylation of nitroalkane anions by 1-alkyl-2,4,6-triphenylpyridiniums: a nonchain reaction with radicaloid characteristics. *J. Am. Chem. Soc.* **1983**, *105*, 90–96. (c) Moser, D.; Duan, Y.; Wang, F.; Ma, Y.; O'Neill, M. J.; Cornella, J. Selective Functionalization of Aminoheterocycles by a Pyrylium Salt. *Angew. Chem. Int. Ed.* **2018**, *57*, 11035–11039.

(9) (a) Basch, C. H.; Liao, J.; Xu, J.; Piane, J. J.; Watson, M. P. Harnessing Alkyl Amines as Electrophiles for Nickel-Catalyzed Cross Couplings via C–N Bond Activation. *J. Am. Chem. Soc.* **2017**, *139*, 5313–5316. (b) Liao, J.; Guan, W.; Boscoe, B. P.; Tucker, J. W.; Tomlin, J. W.; Garnsey, M. R.; Watson, M. P. Transforming Benzylic Amines into Diarylmethanes: Cross-Couplings of Benzylic Pyridinium Salts via C–N Bond Activation. *Org. Lett.* **2018**, *20*, 3030–3033. (c) Guan, W.; Liao, J.; Watson, M. P. Vinylation of Benzylic Amines via C–N Bond Functionalization of Benzylic Pyridinium Salts. *Synthesis* **2018**, *50*, 3231–3237.

(10) (a) Klauck, F. J. R.; James, M. J.; Glorius, F. Deaminative Strategy for the Visible-Light-Mediated Generation of Alkyl Radicals. *Angew. Chem. Int. Ed.* **2017**, *56*, 12336–12339. (b) Wu, J.; He, L.; Noble, A.; Aggarwal, V. K. Photoinduced Deaminative Borylation of Alkylamines. *J. Am. Chem. Soc.* **2018**, *140*, 10700–10704. (c) Sandfort, F.; Strieth-Kalthoff, F.; Klauck, F. J. R.; James, M. J.; Glorius, F. Deaminative Borylation of Aliphatic Amines Enabled by Visible Light Excitation of an Electron-Donor-Acceptor Complex. *Chem. Eur. J.* **2018**, DOI: 10.1002/chem.201804246. (d) Ociepa, M.; Turkowska, J.; Gryko, D. Redox-activated amines in C(sp3)-C(sp) and C(sp3)-C(sp)2 bond formation enabled by metal-free photoredox catalysis. *ACS Catal.* **2018**, *8*, 11362–11367.

(11) Zhang, J.; Liu, L.; Chen, T.; Han, L. Transition-Metal-Catalyzed Three-Component Difunctionalizations of Alkenes. *Chem. Asian J.* **2018**, *13*, 2277–2291.

(12) Courant, T.; Masson, G. Recent Progress in Visible-Light Photoredox-Catalyzed Intermolecular 1,2-Difunctionalization of Double Bonds via an ATRA-Type Mechanism. *J. Org. Chem.* **2016**, *81*, 6945–6952.

(13) (a) Chapdelaine, M. J.; Hulce, M. Tandem Vicinal Difunctionalization: β-Addition to α,β-Unsaturated Carbonyl Substrates Followed by α-Functionalization. *Org. React.* **1990**, *38*, 227–294. (b) Ihara, M.; Fukumoto, K. Syntheses of Polycyclic Natural Products Employing the Intramolecular Double Michael Reaction. *Angew Chem. Int. Ed. Engl.* **1993**, *32*, 1010–1022.

(14) (a) Catellani, M.; Chiusoli, G. P. One-pot palladium-catalyzed synthesis of 2,3-disubstituted bicyclo[2.2.1]heptanes and bicyclo[2.2.1]hept-5-enes. *Tetrahedron Lett.* **1982**, *23*, 4517–4520. (b) Larock, R. C.; Hershberger, S. S.; Takagi, K.; Mitchell, M. A. Synthesis and chemistry of alkylpalladium compounds prepared via vinylpalladation of bicyclic alkenes. *J. Org. Chem.* **1986**, *51*, 2450–2457. (c) Liao, L.; Jana, R.; Urkalan, K. B.; Sigman, M. S. A Palladium-Catalyzed Three-Component Cross-Coupling of Conjugated Dienes or Terminal Alkenes with Vinyl Triflates and Boronic Acids. *J. Am. Chem. Soc.* **2011**, *133*, 5784–5787. (d) Wu, X.; Lin, H.-C.; Li, M.-L.; Li, L.-L.; Han, Z.-Y.; Gong, L.-Z. Enantioselective 1,2-Difunctionalization of Dienes Enabled by Chiral Palladium Complex-Catalyzed Cascade Arylation/Allylic Alkylation Reaction. *J. Am. Chem. Soc.* **2015**, *137*, 13476–13479.

(15) (a) Giri, R.; KC, S. Strategies toward Dicarbofunctionalization of Unactivated Olefins by Combined Heck Carbometalation and Cross-Coupling. *J. Org. Chem.* **2018**, *83*, 3013–3022. (b) Tour, J. M.; Negishi, E. Metal promoted cyclization. 9. Controlled and catalytic acylpalladation. A novel route to cyclopentenone and cyclohexenone derivatives. *J. Am. Chem. Soc.* **1985**, *107*, 8289–8291. (c) Shrestha, B.; Basnet, P.; Dhungana, R. K.; KC, S.; Thapa, S.; Sears, J. M.; Giri, R.. Ni-Catalyzed Regioselective 1,2-Dicarbofunctionalization of Olefins by Intercepting Heck Intermediates as Imine-Stabilized Transient Metallacycles. *J. Am. Chem. Soc.* **2017**, *139*, 10653–10656. (d) Thapa, S.; Basnet, P.; Giri, R. Copper-Catalyzed Dicarbofunctionalization of Unactivated Olefins by Tandem Cyclization/Cross-Coupling. *J. Am. Chem. Soc.* **2017**, *139*, 5700–5703. (e) Derosa, J.; Tran, V. T.; Boulous, M. N.; Chen, J. S.; Engle, K. M. Nickel-Catalyzed β,γ-Dicarbofunctionalization of Alkenyl Carbonyl Compounds via Conjunctive Cross-Coupling. *J. Am. Chem. Soc.* **2017**, *139*, 10657–10660. (f) Derosa, J.; van der Puyl, V. A.; Tran, V. T.; Liu, M.; Engle, K. M. Directed nickel-catalyzed 1,2-dialkylation of alkenyl carbonyl compounds. *Chem. Sci.* **2018**, *9*, 5278–5283. (g) Yu, H.; Hu, B.; Huang, H. Nickel-Catalyzed Alkylarylation of Activated Alkenes with Benzyl-amines via C−N Bond Activation. *Chem. Eur. J.* **2018**, *24*, 7114–7117.

(16) (a) Wang, F.; Wang, D.; Mu, X.; Chen, P.; Liu, G. Copper-Catalyzed Intermolecular Trifluoromethylarylation of Alkenes: Mutual Activation of Arylboronic Acid and CF$_3^+$ Reagent. *J. Am. Chem. Soc.* **2014**, *136*, 10202–10205. (b) Carboni, A.; Dagousset, G.;

Magnier, E.; Masson, G. One pot and selective intermolecular aryl- and heteroaryl-trifluoromethylation of alkenes by photoredox catalysis. *Chem. Commun.* **2014**, *50*, 14197–14200. (c) Gu, J.-W.; Min, Q.-Q.; Yu, L.-C.; Zhang, X. Tandem Difluoroalkylation-Arylation of Enamides Catalyzed by Nickel. *Angew. Chem. Int. Ed.* **2016**, *55*, 12270–12274.

(17) (a) Ouyang, X.-H.; Song, R.-J.; Hu, M.; Yang, Y.; Li, J.-H. Silver-Mediated Intermolecular 1,2-Alkylarylation of Styrenes with α-Carbonyl Alkyl Bromides and Indoles. *Angew. Chem. Int. Ed.* **2016**, *55*, 3187–3191. (b) Li, M.; Yang, J.; Ouyang, X.-H.; Yang, Y.; Hu, M.; Song, R.-J.; Li, J.-H. 1,2-Alkylarylation of Styrenes with α-Carbonyl Alkyl Bromides and Indoles Using Visible-Light Catalysis. *J. Org. Chem.* **2016**, *81*, 7148–7154. (c) García-Domínguez, A.; Li, Z.; Nevado, C. Nickel-Catalyzed Reductive Dicarbofunctionalization of Alkenes. *J. Am. Chem. Soc.* **2017**, *139*, 6835–6838.

(18) KC, S.; Dhungana, R. K.; Shrestha, B.; Thapa, S.; Khanal, N.; Basnet, P.; Lebrun, R. W.; Giri, R. Ni-Catalyzed Regioselective Alkylarylation of Vinylarenes via C(sp3)–C(sp3)/C(sp3)–C(sp2) Bond Formation and Mechanistic Studies. *J. Am. Chem. Soc.* **2018**, *140*, 9801–9805. For a recent nickel-catalyzed diarylation protocol: Gao, P.; Chen, L.-A.; Brown, M. K. Nickel-Catalyzed Stereoselective Diarylation of Alkenylarenes. *J. Am. Chem. Soc.* **2018**, *140*, 10653–10657.

(19) Selected reviews on visible-light photoredox catalysis: (a) Yoon, T. P.; Ischay, M. A.; Du, J. Visible light photocatalysis as a greener approach to photochemical synthesis. *Nat. Chem.* **2010**, *2*, 527–532. (b) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. Visible Light Photoredox Catalysis with Transition Metal Complexes: Applications in Organic Synthesis. *Chem. Rev.* **2013**, *113*, 5322–5363. (c) Narayanam, J. M. R.; Stephenson, C. R. J. Visible light photoredox catalysis: applications in organic synthesis. *Chem. Soc. Rev.* **2011**, *40*, 102–113. (d) Xuan, J.; Xiao, W.-J. Visible-Light Photoredox Catalysis. *Angew. Chem. Int. Ed.* **2012**, *51*, 6828–6838. (e) Tucker, J. W.; Stephenson, C. R. J. Shining Light on Photoredox Catalysis: Theory and Synthetic Applications. *J. Org. Chem.* **2012**, *77*, 1617–1622. (f) Shaw, M. H.; Twilton, J.; MacMillan, D. W. C. Photoredox Catalysis in Organic Chemistry. *J. Org. Chem.* **2016**, *81*, 6898–6926. (g) Marzo, L.; Pagire, S. K.; Reiser, O.; König, B. Visible-Light Photocatalysis: Does It Make a Difference in Organic Synthesis? *Angew. Chem. Int. Ed.* **2018**, *57*, 10034–10072.

(20) Koch, D. A.; Henne, B. J.; Bartak, D. E. Carbanion and Radical Intermediacy in the Electrochemical Reduction of Benzyl Halides in Acetonitrile. *J. Electrochem. Soc.* **1987**, *134*, 3062–3067.

(21) Grimshaw, J.; Moore, S.; Grimshaw, J. T. Electrochemical Reactions. Part 26. Radicals Derived by Reduction of N-Alkylpyridinium Salts and Homologous N,N'-Polymethylenebispyridinium Salts. Cleavage of the Carbon--Nitrogen Bond. *Acta Chem. Scand. B.* **1983**, *37*, 485–489.

(22) Electron neutral styrene as alkene component gave a low yield (<10%) of the desired dicarbofunctionalization product as determined by the 1H NMR spectrum of the crude reaction mixture with dibromomethane as an internal standard. With 1-octene no formation of the desired product was observed by GC-MS analysis of the crude reaction mixture.

(23) (a) Jones, R. S. G. Tryptamine: a neuromodulator or neurotransmitter in mammalian brain? *Progress Neurobiol.* **1982**, *19*, 117–139. b) Berger, M.; Gray, J. A.; Roth, B. L. The expanded biology of serotonin. *Annu. Rev. Med.* **2009**, *60*, 355–366. c) Ferreira, S.; Moncada, S.; Vane, J. Indomethacin and aspirin abolish prostaglandin release from the spleen. *Nat. New Biol.* **1971**, *231*, 237–239.

(24) Using 2-n-butylfuran as aromatic coupling partner, the dicarbofunctionalization product was detected in low yield (<20%) as determined by the 1H NMR spectrum of the crude reaction mixture with dibromomethane as an internal standard. Using 3-

acetyl-2,4-dimethylpyrrole as a coupling partner, the purification of the desired product yet remained unsuccessful.

(25) Wu., K.-J.; Dai, L.-X.; You, S.-L. Palladium(0)-Catalyzed Dearomative Arylation of Indoles: Convenient Access to Spiroindolenine Derivatives. *Org. Lett.* **2012**, *14*, 3772–3775.

(26) Slinker, J. D.; Gorodetsky, A. A.; Lowry, M. S.; Wang, J.; Parker, S.; Rohl, R.; Bernhard, S.; Malliaras, G. G. Efficient Yellow Electroluminescence from a Single Layer of a Cyclometalated Iridium Complex. *J. Am. Chem. Soc.* **2004**, *126*, 2763–2767.

- benzylic radicals
- highly abundant starting materials
- bench-stable radical precursors

- complex polyaromatic frameworks in a single step

three-component

additive-free

visible-light

30 examples 25-95% yield