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

Felix J. R. Klauck[a], Hyung Yoon[b], Michael J. James[a], Mark Lautens*[b] and Frank Glorius*[a]

[a]Organisch-Chemisches Institut, Westfälische Wilhelms-Universität Münster, Corrensstraße 40, 48149 Münster, Germany.

[b]Department of Chemistry, Davenport Chemical Laboratories, University of Toronto, 80 St. George Street, Toronto, Ontario M5S 3H6, Canada.

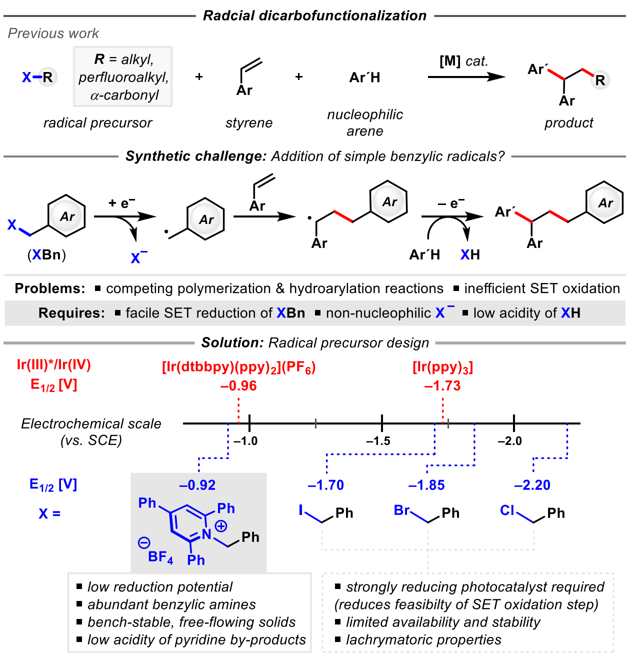
ABSTRACT: The visible-light-mediated three-component dicarbofunctionalization of styrenes using simple benzylic radicals is described. Notably, this work describes a rare example of undirected dicarbofunctionalization using unsubstituted benzyl radicals. Key to the success of this strategy was the rational 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

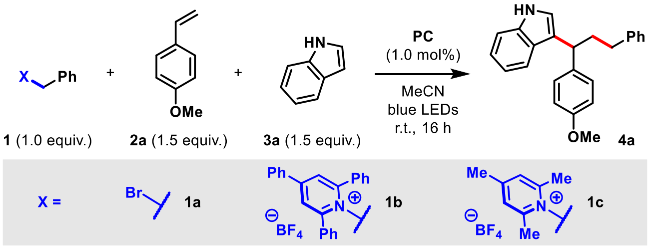


reagents.[18] Despite the significant advances in this field, there is, to the best of our knowledge, no method that efficiently introduces simple benzyl groups to generate densely functionalized polyaromatic frameworks in a three-component, undirected strategy. Considering this, we felt that the development 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.

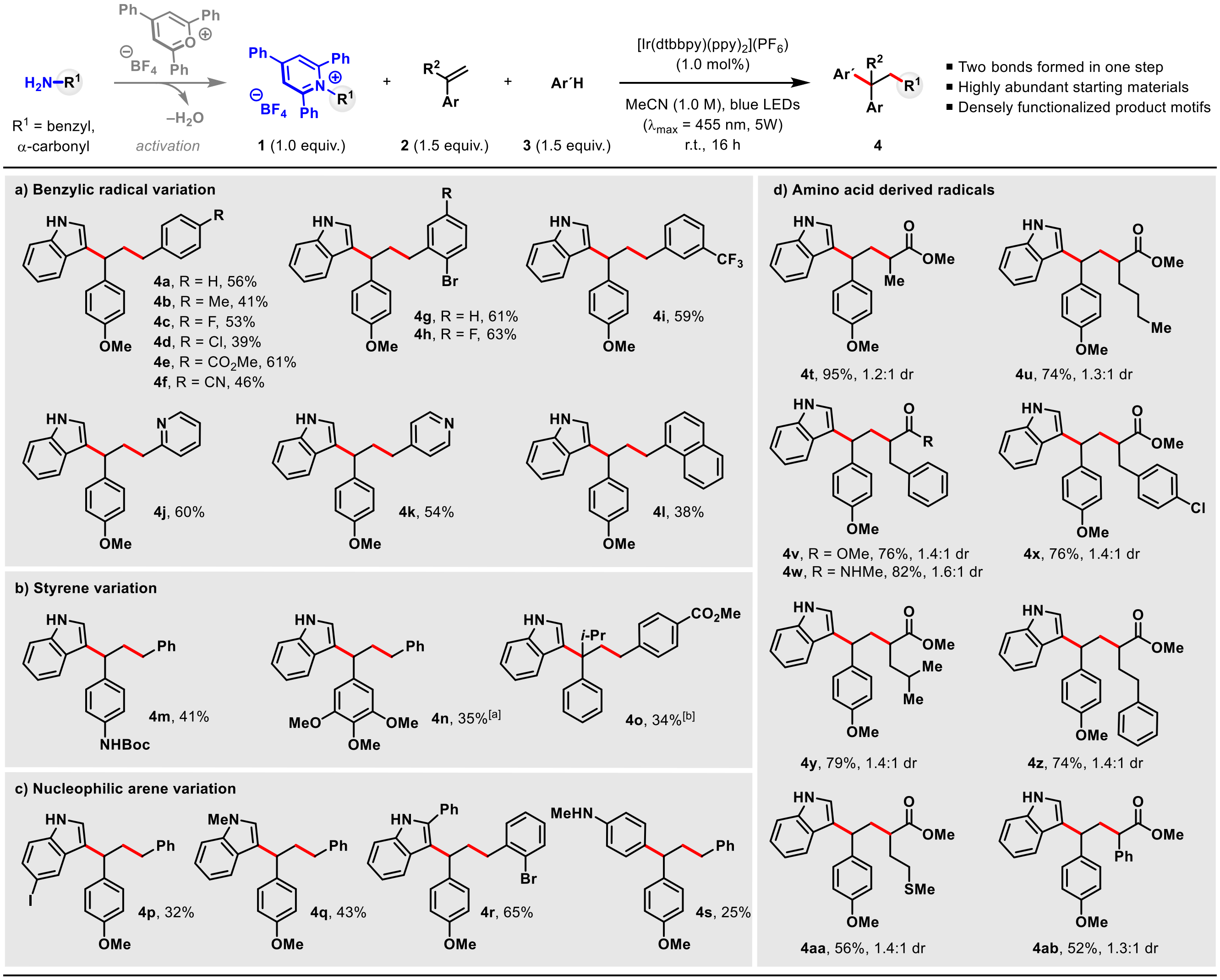


Entry	X	PC	Additive	Yield[f]
1[a]	**1a**	$[Ir(dtbbpy)(ppy)_2](PF_6)$	-	Traces
2[a]	**1a**	*fac*-$Ir(ppy)_3$	-	Traces
3[a]	**1a**	$[Ir(dtbbpy)(ppy)_2](PF_6)$	K_2CO_3[d]	15%
4[a]	**1a**	*fac*-$Ir(ppy)_3$	K_2CO_3[d]	18%
5[a]	**1b**	$[Ir(dtbbpy)(ppy)_2](PF_6)$	-	48%
6[b]	**1b**	$[Ir(dtbbpy)(ppy)_2](PF_6)$	-	**63%**[g]
7[b]	**1b**	$[Ir(dtbbpy)(ppy)_2](PF_6)$	NaCl[e]	29%
8[b]	**1b**	$[Ir(dtbbpy)(ppy)_2](PF_6)$	NaI[e]	3%
9[b, c]	**1c**	$[Ir(dtbbpy)(ppy)_2](PF_6)$	-	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 $[Ir(dtbbpy)(ppy)_2](PF_6)$ 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 quaternary 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.

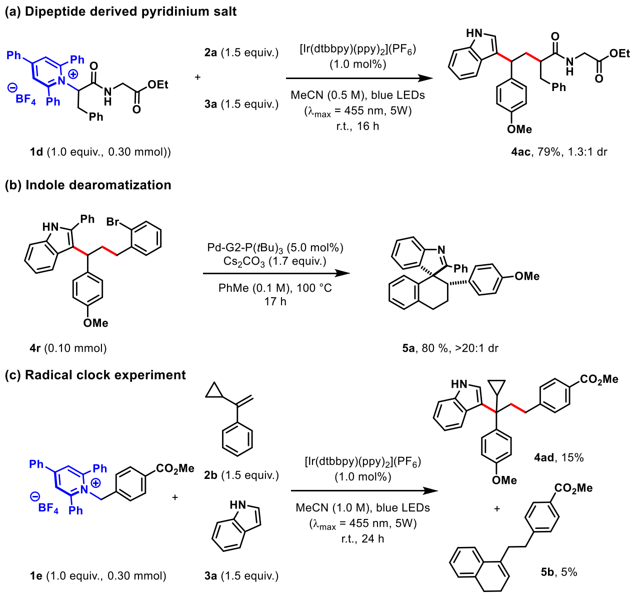


Scheme 2. Scope of the visible-light-mediated deaminative dicarbofunctionalization. Reactions performed on a 0.30 mmol scale in 0.3 mL of solvent. Diastereomeric ratios determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [a]Reaction performed with **2** (2.0 equiv.) and **3**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

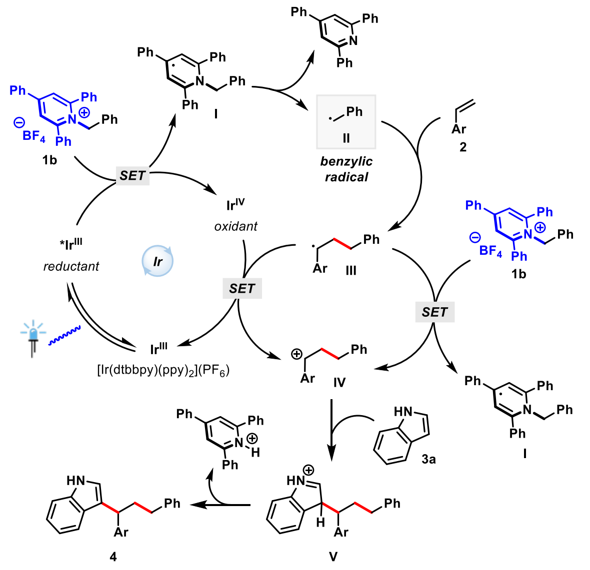
To shine light on the mechanistic intricacies of this three-component reaction we first performed a radical trapping experiment by adding TEMPO (2.0 equiv.) to the reaction under standard conditions. No formation of the desired product was observed, supporting the involvement of radical intermediates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



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 **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.

AUTHOR INFORMATION

Corresponding Author

glorius@uni-muenster.de

mlautens@chem.utoronto.ca

Author Contributions

Notes

The authors declare no competing financial interest.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge via the Internet at http://pubs.acs.org, which included NMR data and characterization (PDF).

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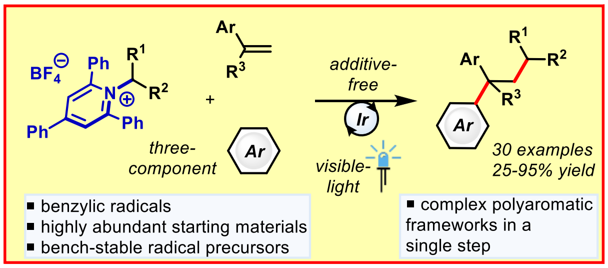
TOC graphic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30 examples
25-95% yield
■ benzylic radicals
■ highly abundant starting materials
■ bench-stable radical precursors
■ complex polyaromatic frameworks in a single step