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To be cited as: *Chem. Eur. J.* 10.1002/chem.201800813

Link to VoR: http://dx.doi.org/10.1002/chem.201800813

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Palladium-Catalyzed Decarboxylative Heck-Type Coupling of Activated Aliphatic Carboxylic Acids Enabled by Visible Light

Maximilian Koy[+], Frederik Sandfort[+], Adrian Tlahuext-Aca, Linda Quach, Constantin G. Daniliuc and Frank Glorius*

Abstract: The palladium-catalyzed coupling reaction of *N*-hydroxyphthalimide esters and styrenes to deliver exclusively (*E*)-substituted olefins under irradiation with visible light is reported. This method tolerates *N*-hydroxyphthalimide esters derived from primary, secondary, tertiary as well as benzylic carboxylic acids. Notably, $Pd(PPh_3)_4$ is employed as an inexpensive palladium source and no addition of base or classical photocatalyst is required. Mechanistic studies suggest a light-mediated single electron reduction of the activated acid by a photoexcited palladium(0) species to access alkyl radicals via decarboxylation.

The palladium-catalyzed reaction between olefins and aryl or alkenyl halides to deliver substituted olefins with high (*E*)-selectivity – generally known as the Mizoroki-Heck reaction – is one of the most fundamental reactions in cross-coupling chemistry.[1] Detailed investigations have revealed a Pd^0/Pd^{II} mechanistic cycle, initiated by oxidative addition of the respective aryl or alkenyl halide (Figure 1a).[2] The extension of Heck methodology to the analogous coupling of alkyl halides is not trivial due to challenging oxidative addition of palladium(0) and fast β-hydride elimination of the intermediate palladium(II) alkyl species.[3] Pioneering work by the groups of Alexanian and J. Zhou suggests a single electron transfer (SET) from palladium(0) to the respective alkyl halide, thereby generating a palladium(I) species and an alkyl radical, which then adds to the olefin.[4] After recombination, β-hydride elimination and reductive elimination is proposed to occur in analogy to standard Heck coupling chemistry. Recently, the groups of Gevorgyan and Y. Fu reported on mild Heck-type couplings with an impressively expanded scope of alkyl halides under visible light irradiation (Figure 1b).[5] Carboxylic acids are a cheap, stable, non-toxic and often naturally abundant feedstock for organic synthesis. Therefore, they present an attractive replacement for organic halides. In 2002, Myers reported on the decarboxylative Heck-type coupling of aryl carboxylic acids with olefins (Figure 1c).[6] Mechanistic investigations support a palladium(II)-mediated decarboxylation to access palladium(II) aryl species.[7] This Pd^{II}/Pd^0 mechanistic paradigm has only been applied to sp^2-sp^2 couplings, presumably due to fast β-hydride elimination of related palladium(II) alkyl species.

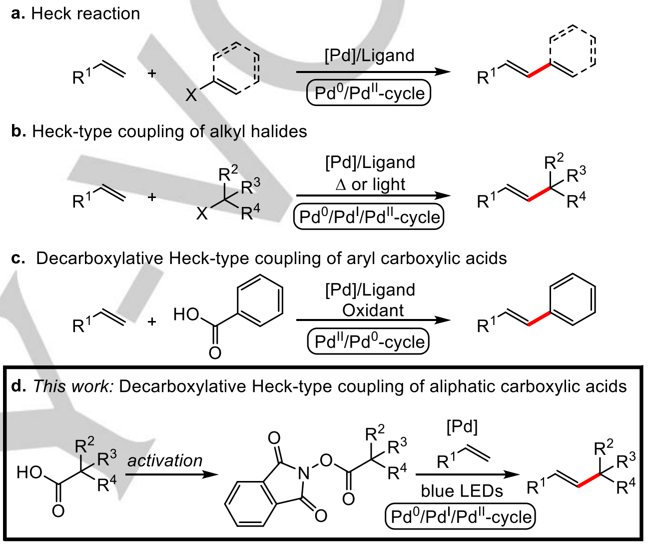

Figure 1. a. – c. Overview of classical and decarboxylative Heck(-type) methodology (X = halide). **d.** Expansion to alkyl carboxylic acids.

Thus, we sought to develop a process that would enable the combination of the broad structural diversity of alkyl carboxylic acids with Heck coupling methodology to deliver highly valuable (*E*)-substituted olefins. We envisioned a radical process initiated by SET between a palladium species and an alkyl carboxylic acid or its derivative.[8] Motivated by various reports about reduction of easily accessible *N*-hydroxyphthalimide esters **2** – also known as redox active esters – by organometallic nickel,[9] iron,[9f,h,10] iridium[11] and copper[12] species to access alkyl radicals; and of an emerging number of reports about SET processes from palladium(0) species to organic halides,[13] we wondered whether a photochemically or thermally induced SET could also occur between a palladium(0) species and *N*-hydroxyphthalimide esters **2** (Figure 1d).[14]

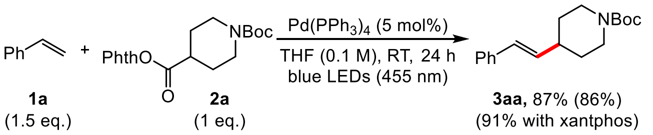

Figure 2. General reaction conditions. Phth = Phthalimide, Boc = *tert*-butyloxycarbonyl. Yields determined by ^1H NMR, isolated yield in parentheses.

We started our investigations with the reaction of styrene (**1a**) and *N*-hydroxyphthalimide ester **2a**. Pleasingly, the (*E*)-substituted olefin **3aa** was exclusively obtained in 86% isolated yield (87% ^1H NMR yield) by reaction with $Pd(PPh_3)_4$ (5 mol%) in THF (0.1 M) under irradiation with blue LEDs (455 nm, 5 W, Figure 2). No

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Supporting information for this article is given via a link at the end of the document.((Please delete this text if not appropriate)) product formation was observed in the dark or in the absence of the palladium catalyst (see the Supporting Information for further details). Notably, under these conditions $Pd(PPh_3)_4$ could be employed as a commercially available and inexpensive palladium source without requiring additional use of base or ligand. However, inspired by the work of Gevorgyan and Y. Fu, who reported on a beneficial effect of xantphos in light mediated palladium(0) chemistry, we also investigated the effect of a bidentate ligand and product **3aa** was observed in slightly improved yield with 6 mol% of xantphos (91% NMR yield).[5] For simplicity of the system and to avoid the use of an expensive ligand, we decided to use xantphos only in exceptional cases.

An additive-based robustness screen[15] revealed high functional group tolerance for synthetically important functional groups like free alcohols, terminal alkynes, carbonyl compounds and nitriles. However, this screen indicated that sulfur and bromide containing substrates are not suitable for this transformation (Figure 3a and see the Supporting Information). The substrate scope of the transformation was evaluated using 15 different styrene coupling partners. Electron-donating as well as electron-withdrawing groups were tolerated on the arene ring and (*E*)-substituted olefins (**3aa** – **3ja**) were isolated in high yields. Notably, heteroaromatic 2-vinylpyridine was tolerated and product **3ka** was isolated in high yield. Expansion of the aromatic ring gave product **3la** in good yield, while two *ortho*-substituents of the styrenyl coupling partner led to diminished yield of product **3ma**. Reaction with an α-substituted styrene was also successful, as exemplified by product **3na** (Figure 3b).

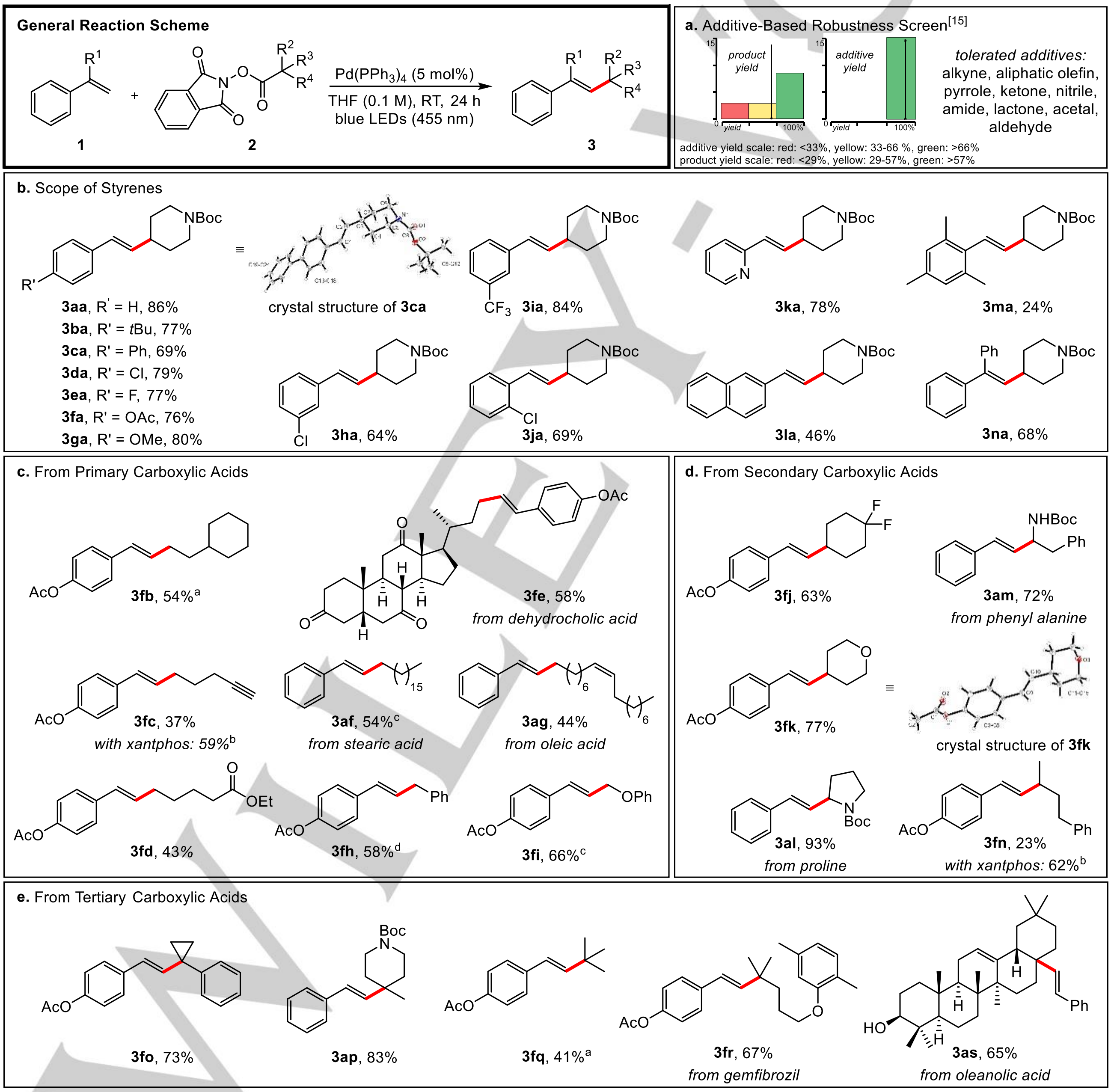
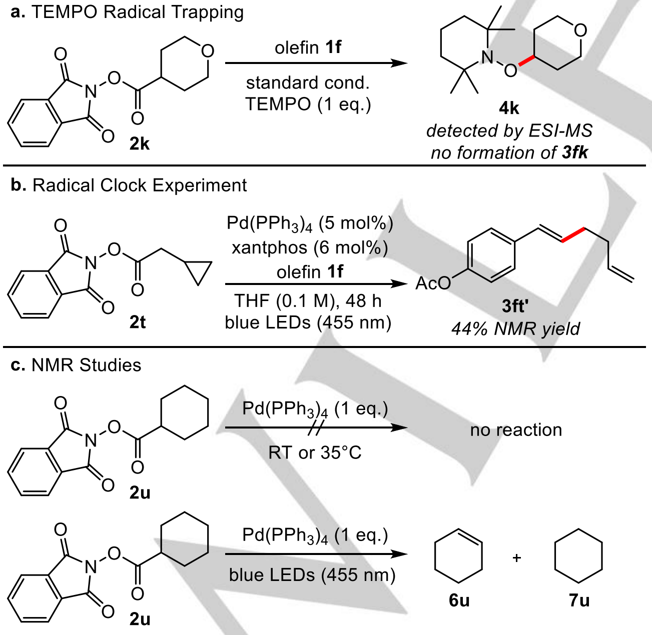


Figure 3. Additive–based robustness screen (a.) and scope of the decarboxylative Heck-type coupling (b.-e.). Standard conditions: **2** (0.3 mmol, 1 eq.), **1** (0.45 mmol, 1.5 eq.), $Pd(PPh_3)_4$ (5 mol%), THF (3.0 mL), RT, 24 h, 455 nm LEDs (5 W). a 0.1 mmol scale. b With xantphos (6 mol%). c 48 h reaction time. d Irradiation with Kessil lights (32 W).

A wide variety of *N*-hydroxyphthalimide esters derived from primary, secondary and tertiary carboxylic acids were also compatible coupling partners. While product **3fb**, derived from a primary carboxylic acid, was isolated in synthetically useful yield under the standard conditions, the addition of xantphos was essential to obtain olefin **3fc** containing a terminal alkyne in 59% isolated yield. Product **3fd** with an ester group was isolated in 43% yield, where no beneficial effect of added xantphos was observed. Esters of naturally abundant molecules such as dehydrocholic acid and fatty acids could be derivatized in high and satisfying yield, respectively (**3fe**, **3af** and **3ag**). A benzylic substrate could also be used to prepare product **3fh** in a synthetically useful yield of 58% by irradiation with higher intensity blue Kessil lights (32 W). Additionally, activated phenoxyacetic acid gave access to β-unsaturated ether **3fi** in good yield. Both, cyclic and acyclic, secondary carboxylic acid esters were successfully coupled (**3fj** – **3fn**). However, acyclic compound **3fn** required the addition of xantphos to obtain a good yield. Notably, esters derived from naturally occurring amino acids proline and phenyl alanine gave the corresponding products (**3al** and **3am**) in high yield. Tertiary acids could also be used to give access to synthetically valuable quaternary carbon centers. Olefinated products (**3fo** – **3as**) were isolated in good yields. To show the utility of this methodology, esters from natural products gemfibrozil and oleanolic acid, containing a free alcohol, were successfully coupled in good yield (**3fr** and **3as**).

For all olefins, we exclusively obtained the (*E*)-isomer and no (*Z*)-isomer was detectable by NMR. The (*E*)-substitution pattern was additionally verified by crystal structures of compounds **3ca** and **3fk**.[16] For analogous reactions with organic alkyl halides, especially with primary halides, the formation of a small amount of the (*Z*)-isomer was observed.[5a-c]


a. TEMPO Radical Trapping

b. Radical Clock Experiment

c. NMR Studies

Figure 4. Selected mechanistic studies.

To shed light on the mechanism of this light-mediated, decarboxylative Heck-type coupling, TEMPO trapping and radical clock experiments were conducted to verify a radical-type mechanism being operative. In these studies, the formation of adduct **4k** between TEMPO and the alkyl radical stemming from decarboxylation of *N*-hydroxyphthalimide **2k** was observed, while the corresponding product **3fk** was not detected (Figure 4a). Additionally, rapid ring-opening of the cyclopropyl moiety of redox active ester **2t** was found upon decarboxylation to give product **3ft'** in 44% NMR yield (Figure 4b and see the Supporting Information). UV/vis spectroscopic analysis of each individual reaction component indicated that $Pd(PPh_3)_4$ is the only light absorbing species at 455 nm. Furthermore, the UV/vis spectrum of the reaction mixture with all components and the spectrum only of $Pd(PPh_3)_4$ were nearly identical, which indicates that no chemical modification of the palladium catalyst occurs prior to photoexcitation (see the Supporting Information for details). To verify this hypothesis, $Pd(PPh_3)_4$ and *N*-hydroxyphthalimide ester **2u** were stirred in THF-d_8 at room temperature (72 h) and at 35 °C (12 h). No reaction was observed in either case by ^1H and ^{31}P NMR spectroscopy. Upon irradiation with 455 nm light for 12 h, complete conversion of **2u** to cyclohexene **6u** from direct β-hydride elimination and to cyclohexane **7u** from hydrogen-atom abstraction was detected by ^1H NMR spectroscopy (Figure 4c). Finally, the quantum yield of the reaction was determined to be 0.21.

Based on these studies and on literature precedence,[5] a mechanistic proposal is depicted in Figure 5. The catalytic cycle is initiated by photoexcitation of the palladium(0) catalyst, followed by single electron transfer to *N*-hydroxyphthalimide ester **2a**, which forms the corresponding alkyl radical upon release of CO_2. Addition of the radical to the corresponding styrene gives the more stabilized radical species **9a**. Recombination followed by β-hydride elimination gives the product and palladium(II) hydride species **10**. Formal reductive elimination of phthalimide regenerates the catalyst.

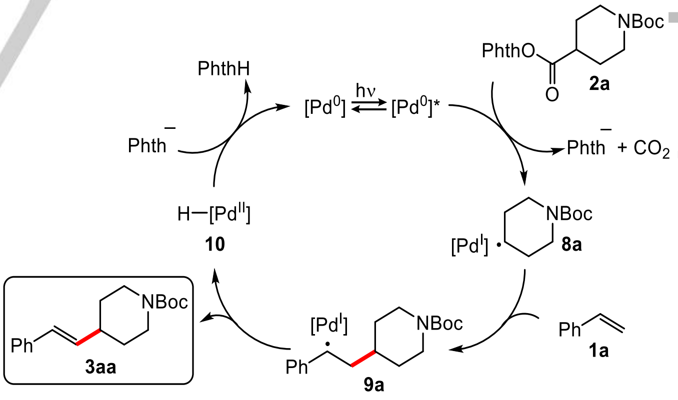


Figure 5. Proposed mechanistic cycle.

In conclusion, we have developed the Heck-type coupling of activated aliphatic acids with styrenes. Primary, secondary, tertiary and benzylic carboxylic acids are tolerated and the reaction proceeds in the absence of base under irradiation with commercially available and cheap blue LED lights to give access to valuable (*E*)-substituted olefins in perfect selectivity. The applicability of the methodology was demonstrated through the functionalization of various naturally occurring carboxylic acids. Mechanistic studies revealed a radical mechanism being operative and that a single electron transfer between the photoexcited palladium catalyst and the *N*-hydroxyphthalimide ester occurs as the initial step.

Acknowledgements

Generous financial support by the Deutsche Forschungsgemeinschaft (Leibniz Award) and the Graduate School of Chemistry NRW (A. T.-A.) is gratefully acknowledged. We are thankful to Dr. Michael J. James and Andreas Lerchen for helpful discussions.

Keywords: Palladium • Heck-Type Coupling • Carboxylic Acids • Decarboxylation • Redox-Active Esters

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[14] We estimated the oxidation potential of photoexcited $Pd(PPh_3)_4$ to be $E(M^+/M^*) = -1.72$ V vs. SCE. A single electron reduction of *N*-hydroxyphthalimide esters ($E_{1/2} = -1.4$ V) should therefore be thermodynamically feasible. See the Supporting Information for details.

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[16] CCDC 1818039 and CCDC 1823949 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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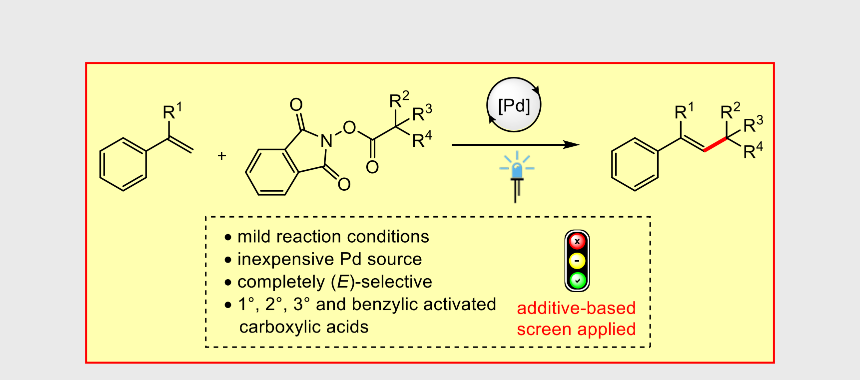

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