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Synthesis of All-Carbon Quaternary Centers by Palladium-Catalyzed Olefin Dicarbofunctionalization

Maximilian Koy[+], Peter Bellotti[+], Felix Katzenburg, Constantin G. Daniliuc and Frank Glorius*[a]

Dedicated to Prof. Roland Winter on the occasion of his 65th birthday

Abstract: The redox-neutral dicarbofunctionalization of tri- and tetrasubstituted olefins to form a variety of (hetero)cyclic compounds using photoinduced palladium catalysis is described. This cascade reaction process was used to couple a broad range of highly decorated olefins tethered to aryl or alkyl bromides with styrenes or acryl amides (> 50 examples). Through this protocol, one or two contiguous all-carbon quaternary centers can be formed in a single step. The products were readily diversified and applied in the synthesis of a bioactive oxindole analogue.

Dicarbofunctionalization reactions provide a powerful method to access complex molecular frameworks in a single operational step.[1] Long standing challenges, such as unwanted β-hydride elimination of intermediate metal species have been addressed through ligand design, tailored substrates or the use of early transition metals, which are less prone to β-hydride elimination.[2] Numerous elegant intramolecular versions to access valuable cyclic motifs have been developed, but reports using highly decorated olefins are still limited.[3] This limitation may be due to the formation of C(sp^3)-metal species **A**, which is challenging to form with higher substituted olefins due to steric repulsion or fast β-hydride elimination.[1a] Additionally, existing methods are typically either suitable for only aryl or alkyl electrophiles, while general methods for both classes are rare (see Scheme 1a).[4]

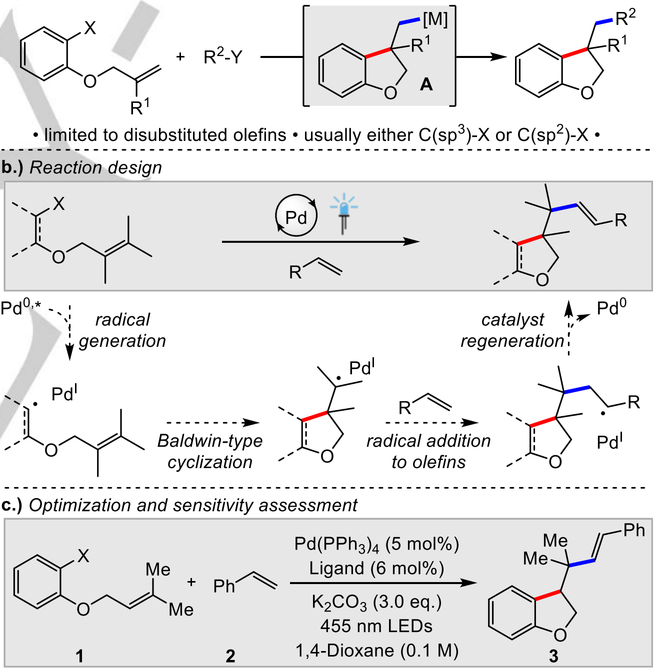
Palladium catalyzed cross-coupling manifolds to construct carbon-carbon or carbon-heteroatom bonds have reached remarkable levels of versatility.[5] Classically, these reactions occur mostly through two-electron processes. Conversely, reactions occurring through radical intermediates involving palladium(I) hybrid species are less well explored.[6] Recently, several elegant protocols using palladium catalysts as single electron donors have been reported. Single electron transfer from a palladium species can either be triggered thermally[7] or through photoexcitation[8] and used to generate radicals from various alkyl or aryl halides and activated carboxylic acids.

As the formation of highly-substituted moieties is generally hampered by classical two-electron cross-coupling processes, we questioned whether open-shell palladium chemistry could be used to enable dicarbofunctionalization reactions with tri- and tetrasubstituted olefins. It should be noted that there are very few methods available for the transition-metal catalyzed dicarbofunctionalization of trisubstituted olefins and, to the best of our knowledge, *none* for tetrasubstituted olefins.[9] Here, we envisioned that a photoexcited palladium catalyst could be used to generate a radical intermediate *via* single electron transfer, which could then rapidly undergo an intramolecular Baldwin-type cyclization to afford a tertiary radical species. This tertiary radical could then be trapped by an olefin coupling partner to form a secondary radical, which would recombine with the palladium(I) catalyst species and undergo β-hydride elimination to regenerate the palladium(0) catalyst and close the catalytic cycle in a redox neutral fashion (see Scheme 1b).

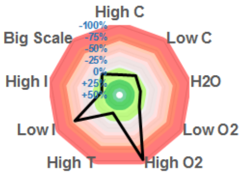
a.) *Dicarbofunctionalization of tethered olefins*

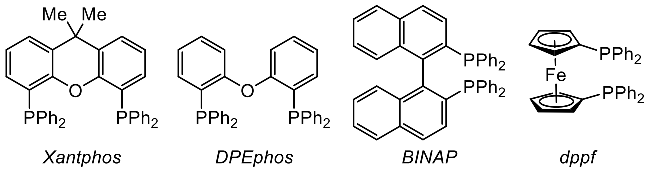
b.) *Reaction design*

c.) *Optimization and sensitivity assessment*



Entry	Variation	yield (%)^a
1	with Xantphos	82 (80%)
2	without additional ligand	16
3	with DPEphos, BINAP, dppf	18/9/0
4	no $Pd(PPh_3)_4$	0
5	no light	0
6	corresponding chloride/iodide	0/10
7	no base	6
8	classical photocatalysts	0
9	TEMPO	0^b





Scheme 1. a) Dicarbofunctionalization methodology. b) Reaction design. c) Optimization parameters and sensitivity assessment. ^{a}determined by GC-FID analysis. ^{b}determined by ^{1}H NMR analysis. TEMPO = 2,2,6,6-tetramethylpiperidine-1-oxyl.

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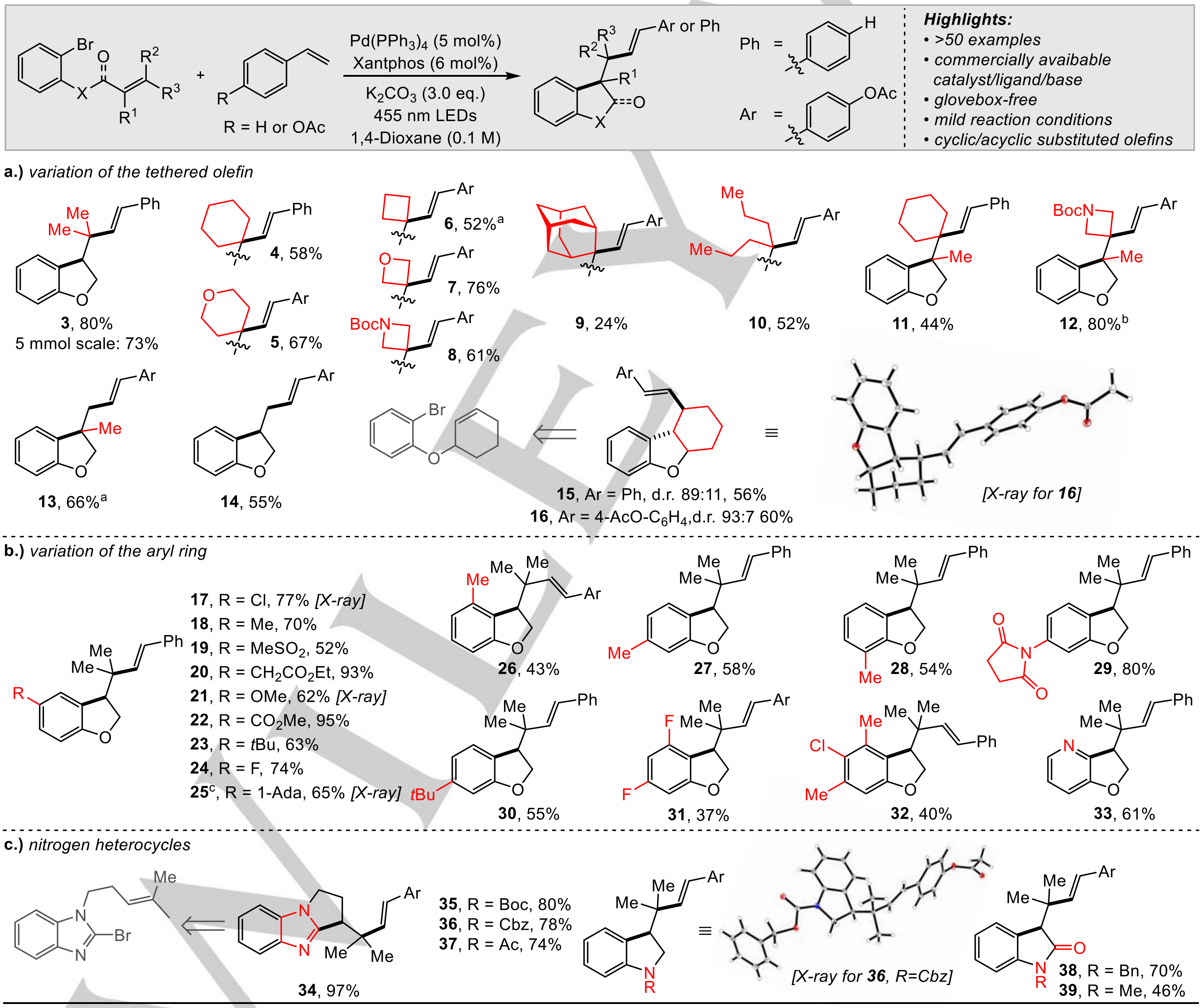
Potential pitfalls of this reaction design include: i) unproductive protodehalogenation, or ii) premature recombination of the initial cyclization radical with palladium. However if successful, this reaction cascade would provide a powerful method to access various unstrained cyclic scaffolds decorated with one or even two quaternary centers adjacent to each other within a single operational step from easily accessible olefins. Such structurally dense motifs are still highly challenging targets in synthetic organic chemistry, especially in related transition metal catalyzed reactions.[10]

We started our investigations by reacting prenylated 2-bromophenol **1** and styrene **2** with various palladium catalysts under visible light irradiation. After optimization, we were delighted to obtain the desired cross-coupled product **3** in 80% isolated yield and complete (*E*)-selectivity using commercially available $Pd(PPh_3)_4$, xantphos as an ancillary ligand and potassium carbonate as a base in 1,4-dioxane under irradiation with blue LEDs. Interestingly, in the absence of xantphos, or with other bidentate ligands, the product was formed in diminished yield. No product was obtained without $Pd(PPh_3)_4$, base or light. Dihydrobenzofurane **3** was obtained in 10% yield from the corresponding iodide, while the corresponding chloride was not reactive at all. Notably, classical photocatalysts based on ruthenium or iridium completely failed to afford the corresponding product, highlighting the unique reactivity of palladium under visible light irradiation. Finally, the addition of TEMPO completely inhibited product formation. Nevertheless, a TEMPO adduct of a cyclized intermediate was detected, which suggests a radical mechanism was in operation (for further preliminary mechanistic experiments, see the Supporting Information). The reaction was assessed to be sensitive towards the presence of oxygen and low light intensity, while other parameters, such as wet solvent and reaction scale, had no significant effect on the outcome of the reaction (see radar diagram in Scheme 1c).[11]



Scheme 2. Scope of aryl bromides. Yields of isolated product are given. For experimental details, see the Supporting Information. [a]Yield was determined by ^1H NMR spectroscopy using an internal standard. [b]Contains an inseparable impurity of approx. 8%. [c]4-Acetoxystyrene was used as olefin. Ph = Phenyl, Ar = 4-Acetoxyphenyl, 1-Ada = 1-Adamantyl, Boc = *tert*-butyloxycarbonyl, Cbz = benzyloxycarbonyl, Ac = acetyl.

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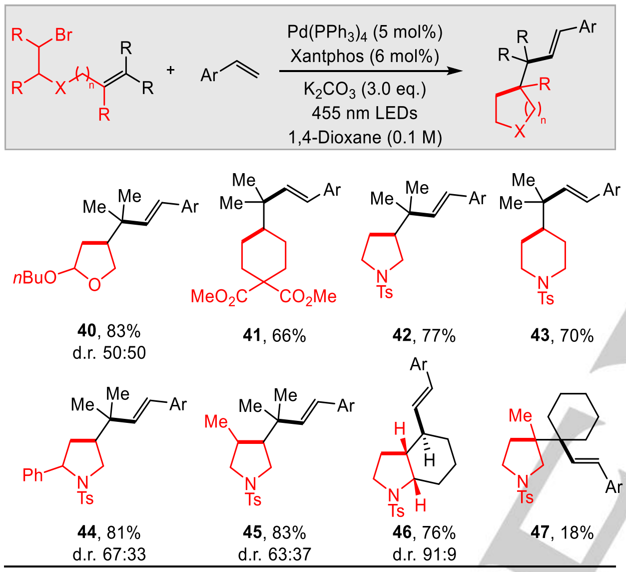
To examine the generality of our developed reaction conditions, we initiated scope and limitation studies, from which we were pleased to observe that these conditions were widely applicable (>50 examples). Furthermore, the *E*/*Z* selectivity was >99:1 for all entries. We first examined different olefin substitution patterns with a special emphasis on cyclic motifs. Four and six membered rings containing different heteroatoms were readily converted the products (**4** – **8**) in generally good yields. Oxetane **8**, was particularly pleasing to obtain as oxetanes are frequently used in medicinal chemistry as prominent bioisosteres of carbonyl and *gem*-dimethyl groups.[12] The highly sterically demanding adamantyl motif (**9**) could also be installed following our developed methodology. Acyclic substitution patterns at the newly formed quaternary carbon center was also well tolerated (**10**).

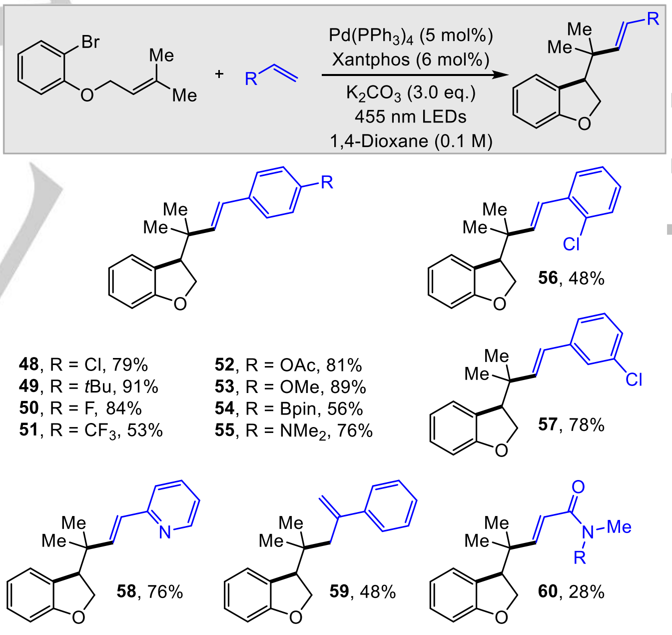
Scheme 3. Scope of alkyl bromides. Yields of isolated product are given. For experimental details, see the Supporting Information. Ar = 4-Acetoxyphenyl.



We next turned our attention to tetrasubstituted olefins, which are generally challenging substrates in metal catalyzed reactions,[10d, f] and were not previously amenable to dicarbofunctionalization reactions. Thus, we were delighted to obtain products **11** and **12** in synthetically useful yield. Notably, both compounds contain two contiguous quaternary centers – each of them within a cyclic scaffold – which are highly challenging targets in natural product synthesis.[13] Di- and monosubstituted olefins – generally used for related dicarbofunctionalization reactions – are also suitable substrates (**13** – **16**). The structure of product **16** was additionally verified through single crystal X-ray diffraction, confirming the *anti*-stereochemistry at the cyclohexyl fragment.[14] It should be noted that the fused tricyclic scaffold of **15** and **16** can also be found in various natural products *e.g.* Cannabielsoin or Linderol A (see Scheme 2a).[15] Substitution patterns on the aryl ring of the bromide (**17** – **33**) were similarly tolerated. Substrates bearing either electron-donating or electron-withdrawing groups at different positions of the aryl ring were all converted into the corresponding products in moderate to excellent yields (37 – 95%). Medicinally relevant pyridine and benzimidazole derivatives (**33**, **34**) were also readily prepared. Furthermore, indolines (**35** – **37**) and oxindoles (**38**, **39**) containing different protecting groups, were accessible through this method. The structure of Cbz-protected indoline **36** was validated by single-crystal X-ray diffraction (see Scheme 2c).[14]

We next examined alkyl electrophiles, which are typically challenging substrates in the field of palladium catalysis due to their sluggish oxidative addition and fast β-hydride elimination. Here, we were pleased to find that complex tetrahydrofuran **40**, carbocyclic compound **41**, pyrrolidines (**42**, **44** – **47**) and piperidine **43** were all accessible in generally good yields from the respective alkyl bromides. These products were formed with moderate (**44**, **45**) to good (**46**) diastereoselectivities, as expected with open-shell intermediates. Finally, highly congested pyrrolidine **47** was prepared through the challenging dicarbofunctionalization of a tetrasubstituted olefin, albeit in diminished yield (18%, see Scheme 3).

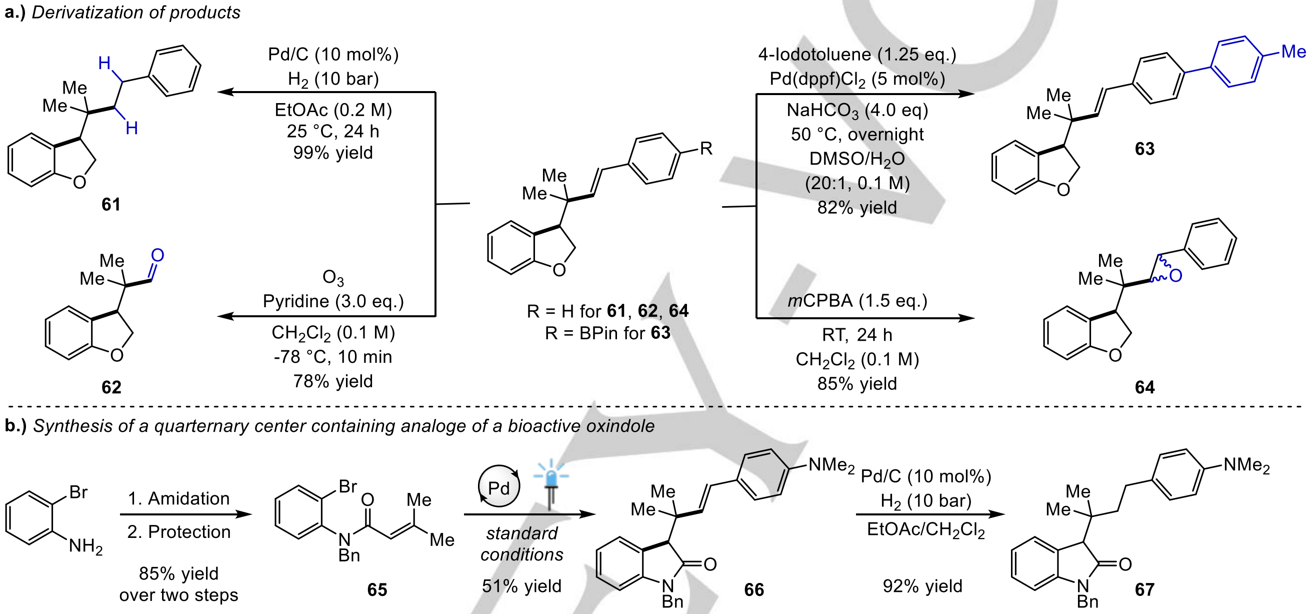
Next, the accepting olefins were evaluated under our reaction conditions. Styryl compounds bearing various electron-donating as well as -withdrawing substituents and heteroatoms were well tolerated (**48** – **59**). Interestingly, α-methyl styrene reacted to selectively afford the terminal olefin product **59**, while the thermodynamically more favourable internal olefin was not detected. Pleasingly, acryl amides were also suitable reaction partners in the synthetic manifold to access the product in fair yield (**60**) (see Scheme 4).



Scheme 4. Scope of accepting olefins. Yields of isolated product are given. For experimental details, see the Supporting Information.

The scalability of the reaction was shown through a large-scale reaction (5 mmol), in which product **3** was prepared in a slightly diminished yield of 73%. Finally, the products were further derivatized to illustrate potential synthetic applications (see Scheme 5a): Hydrogenation (**61**), ozonolysis (**62**), Suzuki-Miyaura coupling (**63**) and epoxidation (**64**) reactions all proceeded in high yields. Importantly, cleavage of the double bond through ozonolysis offers a synthetic handle for further transformations directly at the newly formed quaternary carbon center. Furthermore, an analogue of a dimethylaminophenyl oxindole **67** – which are reported to have neurological activity – was easily synthesized with this protocol in four linear steps from inexpensive 2-bromoaniline. Notably, in previous studies of these neurologically active compounds, quaternary centers α-to the oxindole core were not accessible through the reported multistep synthesis (see Scheme 5b).[16]

In conclusion, we have developed a general method for the dicarbofunctionalization of tri- and tetrasubstituted olefins *via* open-shell intermediates using palladium as a non-classical photocatalyst. Impressively, aryl bromides as well as alkyl bromides were both suitable to the developed reaction conditions. Various (hetero)cyclic compounds with different cyclic and acyclic quaternary carbon centers adjacent to the newly formed ring were prepared. The products were further modified through selected transformations. Finally, an analogue of a class of neurologically active oxindoles was prepared with this dicarbofunctionalization protocol as the key step. We believe that this approach enables the synthesis of more highly complex and congested cyclic frameworks in a fast and facile fashion.



Scheme 5. a.) Diversification of products. b.) Synthesis of an analogue of a bioactive oxindole containing a quaternary carbon center.

Acknowledgements

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Keywords: dicarbofunctionalization • palladium catalysis • quaternary centers • radicals • heterocycles

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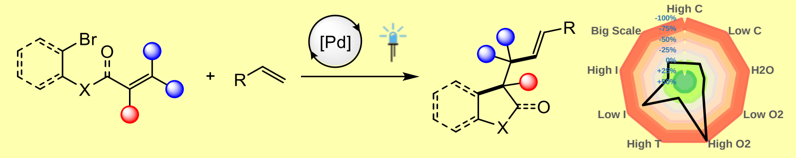

- tri- and tetrasubstituted olefins
- one or two quaternary centers in one step
- aryl or alkyl bromides with one set of conditions
- diverse (hetero)cyclic compounds

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Synthesis of All-Carbon Quaternary Centers by Palladium-Catalyzed Olefin Dicarbofunctionalization

The dicarbofunctionalization of tri- and tetrasubstituted olefins to form (hetero)cyclic compounds using photoinduced palladium catalysis is described. A broad range of highly decorated olefins tethered to aryl or alkyl bromides were coupled with styrenes or acryl amides (> 50 examples). Through this protocol, one or two contiguous all-carbon quaternary centers can be formed in a single step. The products were readily diversified and applied in the synthesis of a bioactive oxindole analogue.