

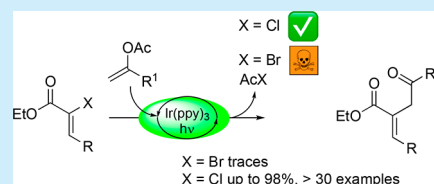
# Ir(ppy)<sub>3</sub>-Catalyzed, Visible-Light-Mediated Reaction of $\alpha$ -Chloro Cinnamates with Enol Acetates: An Apparent Halogen Paradox

Thomas Föll, Julia Rehbein,<sup>1b</sup> and Oliver Reiser\*<sup>1b</sup>

Institute of Organic Chemistry, University of Regensburg, Universitätsstraße 31, 93053 Regensburg, Germany

**S** Supporting Information

**ABSTRACT:** The visible-light-mediated activation of vinyl chlorides derived from  $\alpha$ -chloro ethyl cinnamates via oxidative quenching of excited photocatalyst *fac*-Ir(ppy)<sub>3</sub> is described. Upon photoelectron transfer and chloride extrusion, the corresponding vinyl radical can be efficiently trapped by enol acetates, giving rise to synthetically useful 1,4-dicarbonyl compounds in good to excellent yields. This transformation is distinguished by mild and environmentally benign reaction conditions and can be performed on a multigram scale, in sharp contrast to contrasting  $\alpha$ -bromo ethyl cinnamates, which show low conversion under the various conditions applied.



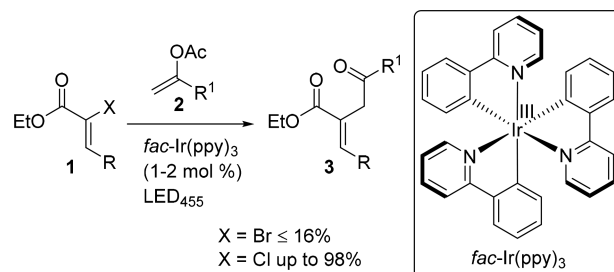
One key aspect of modern organic synthesis represents the selective activation of C(sp<sup>2</sup>)-halogen bonds via transition metal catalysis. As a reliable approach, palladium-catalyzed cross-coupling reactions proved to be a powerful method to construct C–C bonds and have been well studied over the past 50 years.<sup>1</sup> Reactivity strictly correlates with the dissociation energies of the C–halogen bond. While oxidative addition to C(sp<sup>2</sup>)-iodides and bromides is generally facile, unactivated C(sp<sup>2</sup>)-chlorides are considered to be challenging substrates, requiring specially designed catalysts and forcing reaction conditions.<sup>2</sup> Nevertheless, chloro-substituted compounds are greatly preferred as substrates since they are readily available at a lower cost compared to the bromides and iodides.

As an alternative approach, C(sp<sup>2</sup>)-halogen bonds can be activated by an electron-induced bond cleavage to form a carbon-centered radical and a halide anion. This principle was first realized via electrochemical methods<sup>3</sup> and more recently via visible-light-mediated photoredox catalysis,<sup>4</sup> which has emerged as a versatile tool in organic synthesis.<sup>5</sup> In this context, our group reported the generation of vinyl radicals via visible-light-mediated single electron transfer of vinyl bromides with extended  $\pi$ -systems such as chalcones, which were shown to be excellent precursors for the synthesis of 1,2-dihydronaphthalenes,<sup>4d</sup> polycyclic aromatic scaffolds,<sup>4e</sup> or indenones.<sup>4f</sup>

However, substrates with smaller  $\pi$ -systems such as  $\alpha$ -bromo ethyl cinnamate (**1a-Br**) show only poor conversion at best in these transformations, which could be attributed to the decrease in reduction potential in comparison to the corresponding chalcones ( $E_{\text{RX/RX}^-}^{\circ} = -0.88$  V vs SCE for (*E*)- $\alpha$ -bromo chalcone;<sup>4e</sup>  $E_{\text{RX/RX}^-}^{\circ} = -1.54$  V vs SCE for **1a-Br**). Established photocatalysts such as Ir(ppy)<sub>2</sub>(dtb-bpy)PF<sub>6</sub> (dtb-bpy = 4,4'-di-*tert*-butyl-2,2'-bipyridine, Ir[dF(CF<sub>3</sub>)ppy]<sub>2</sub>(dtb-bpy)PF<sub>6</sub> (dF(CF<sub>3</sub>)ppy = 2-(2,4-difluorophenyl)-5-(trifluoromethyl)pyridine), Ru(bpy)<sub>3</sub>Cl<sub>2</sub> (bpy = 2,2'-bipyridine), and Cu(dap)<sub>2</sub>Cl (dap = 2,9-bis(p-anisyl)-1,10-phenanthroline) led to no product formation, being in line with their more positive reduction potential ( $E_{\text{M}^+/\text{M}^*}^{\circ}$  = between  $-0.81$  and  $-1.43$  V vs SCE).<sup>6</sup> We therefore considered the strongly

reducing *fac*-Ir(ppy)<sub>3</sub> ( $E_{\text{Ir(IV)/Ir(III)*}^{\circ}} = -1.73$  V vs SCE, ppy = 2-phenylpyridine) as catalyst and chose enol acetates as trapping reagents (Scheme 1) because they are highly efficient in the

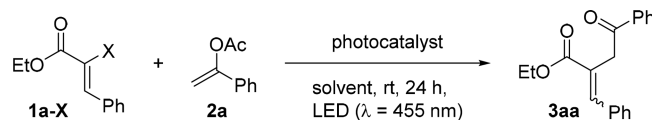
## Scheme 1. Visible-Light-Mediated Activation of Vinyl Halides



reaction with radicals.<sup>7</sup> However, only low yields at best of the desired 1,4-dicarbonyl **3aa** were observed (Table 1, entries 1, 2). Further screening revealed that surprisingly  $\alpha$ -chloro ethyl cinnamate (**1a-Cl**), having an even more negative reduction potential ( $E_{\text{RX/RX}^-}^{\circ} = -1.64$  V vs SCE) and a less favorable leaving group based on bond dissociation energies (BDE C–Cl = 91.7 kcal/mol; C–Br = 79.4 kcal/mol), gave rise to **3aa** in up to 98% yield (entry 5).

Again, *fac*-Ir(ppy)<sub>3</sub> proved to be necessary for the reaction to take place, while other catalysts tested (entries 7–10) were unsuccessful in this transformation. Moreover, all attempts to run the reaction in the presence of a sacrificial electron donor, i.e., utilizing the reductive quenching cycle, only resulted in undesired hydrodehalogenation.<sup>8</sup> Control experiments proved a photochemically driven process as no product was obtained when neither a photocatalyst was used nor the reaction was carried out in the dark (entries 11 and 12).

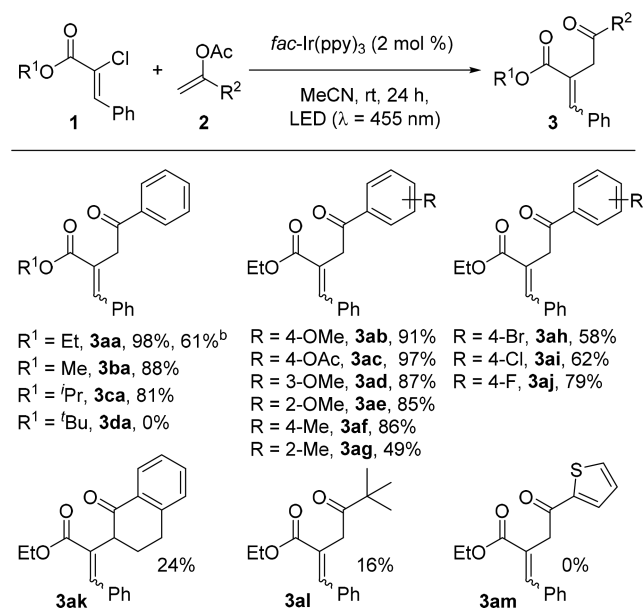
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Table 1. Catalyst Screening and Reaction Optimization<sup>a</sup>


entry	photocatalyst	$E^{\circ}_{M^{\bullet}/M^*}$ (V vs SCE)	X	solvent	yield (%) <sup>b</sup>
1	<i>fac</i> -Ir(ppy) <sub>3</sub>	-1.73	Br	DMF	16
2	<i>fac</i> -Ir(ppy) <sub>3</sub>		Br	MeCN	8
3	<i>fac</i> -Ir(ppy) <sub>3</sub>		Cl	DMF	43
4	<i>fac</i> -Ir(ppy) <sub>3</sub>		Cl	MeCN	58
5 <sup>c</sup>	<i>fac</i> -Ir(ppy) <sub>3</sub>		Cl	MeCN	98
6 <sup>d</sup>	<i>fac</i> -Ir(ppy) <sub>3</sub>		Cl	MeCN	15
7	Ir(ppy) <sub>2</sub> (dtb-bpy)PF <sub>6</sub>	-0.96	Cl	MeCN	-
8	Ir[dF(CF <sub>3</sub> )ppy] <sub>2</sub> (dtb-bpy)PF <sub>6</sub>	-0.89	Cl	MeCN	-
9	Ru(bpy) <sub>3</sub> Cl <sub>2</sub>	-0.81	Cl	MeCN	-
10 <sup>e</sup>	Cu(dap) <sub>2</sub> Cl	-1.43	Cl	MeCN	-
11 <sup>f</sup>	-		Cl	MeCN	-
12 <sup>g</sup>	<i>fac</i> -Ir(ppy) <sub>3</sub>		Cl	MeCN	-

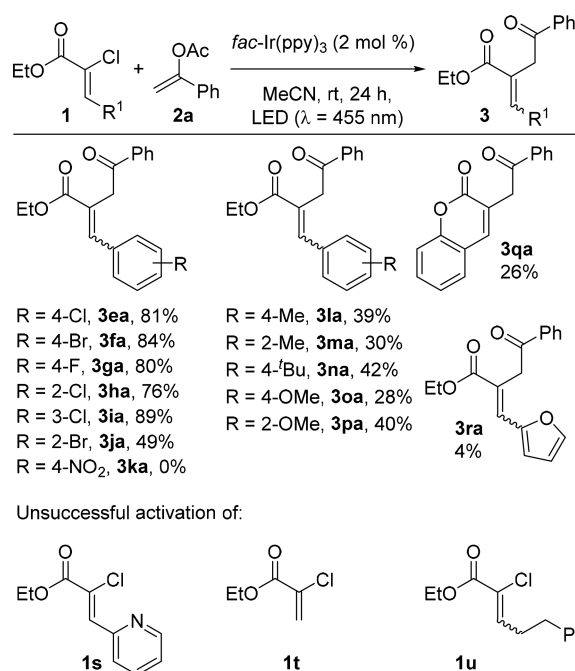
<sup>a</sup>Standard reaction conditions: **1a-X** (0.5 mmol, 1.0 equiv), **2a** (2.5 mmol, 5.0 equiv), photocatalyst (1 mol %), solvent (*c* = 0.1 M), N<sub>2</sub> atmosphere, rt, 24 h, blue LED ( $\lambda$  = 455 nm). <sup>b</sup>Isolated yield after purification via column chromatography. *E/Z* ratio of approximately 1:1 in all cases. For details see SI. <sup>c</sup>2 mol % catalyst. <sup>d</sup>Under O<sub>2</sub> atmosphere. <sup>e</sup>Green LED ( $\lambda$  = 530 nm) was used. <sup>f</sup>No photocatalyst. <sup>g</sup>No light.

Under the optimized reaction conditions (Table 1, entry 5) we next established that ester substitution in **1-Cl** is tolerated well (Scheme 2, **3aa–3ca**) with the exception of a sterically

Scheme 2. Scope of Enol Acetates **2** in the Coupling with  $\alpha$ -Chloro Cinnamates **1-Cl**<sup>a</sup>

<sup>a</sup>Standard reaction conditions: **1** (0.5 mmol, 1.0 equiv), **2** (2.5 mmol, 5.0 equiv), *fac*-Ir(ppy)<sub>3</sub> (2 mol %) in 5 mL of MeCN. Combined isolated yields of separated *E* and *Z* isomer after purification via column chromatography. *E/Z* ratio of approximately 1:1 in all cases. For details see SI. <sup>b</sup>20 mmol scale, 0.5 mol % [Ir], 48 h.

bulky <sup>t</sup>Bu-ester, which disrupts conjugation of the system sufficiently to prevent the photocoupling (**3da**). Focusing on **1a-Cl**, various enol acetates were subsequently subjected to this visible-light-mediated transformation. Excellent results were obtained using electron-rich enol acetates (**3ab–3af**), reflecting the electrophilic nature of the vinyl radical intermediate. Nevertheless, moderately electron-deficient substituents still gave

Scheme 3. Scope of  $\alpha$ -Chloro Cinnamates **1-Cl**<sup>a</sup>

<sup>a</sup>Standard reaction conditions, see Scheme 2. Combined isolated yields of separated *E* and *Z* isomer after purification via column chromatography. *E/Z* ratio of approximately 1:1 to 2:1 in all cases. For details see SI.

appreciable yields of the coupling products (**3ah–3aj**), and no cross reactivity with halogen substituents in aromatic moieties of the enol acetates was observed. The reaction is sensitive to sterically more demanding enol acetates (**3ag**, **3ak**), and also alkyl substitution in the enol acetate was not tolerated well (**3al**). Furthermore, heterocyclic coupling partners were not amenable substrates (**3am**; also **3ra**, **1s** in Scheme 3) due to the cross reactivity for direct addition of the vinyl radical to such moieties.<sup>4e,9</sup>

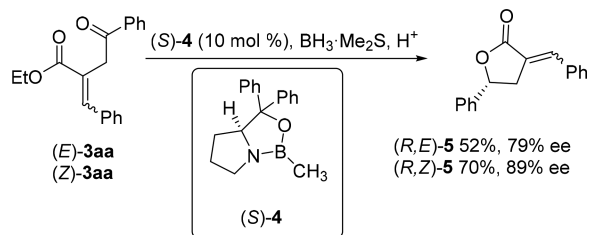
The reaction could also be run on a 20 mmol scale: using a setup with 30 high power LEDs and internal water cooling to

maintain ambient temperature, 61% of **3aa** could be readily prepared in 48 h. It is important to note that in this experiment the catalyst loading was greatly reduced to 0.5 mol % compared to the original 2 mol % (see [Supporting Information \(SI\)](#) for details). In all cases, we observed an *E/Z* distribution of close to 1:1 for the products **3**; control experiments (see [SI](#)) showed that both starting materials **1** as well as products **3** undergo rapid photoisomerization; moreover, vinyl radicals are known to have a very low barrier of rotation.<sup>10</sup>

Electron-deficient cinnamates ([Scheme 3](#)) were also proven to be excellent coupling partners given that electron-withdrawing groups make the single electron reduction more feasible (**3ea–3ja**). Notably, chemoselectivity prevailed as both bromide (**3fa**, **3ja**) as well as chloride substituents (**3ea**, **3ha**, **3ia**) attached on the aromatic ring showed no cross reactivity.<sup>4c</sup> As observed in related processes before,<sup>4d,e</sup> nitro-substitution (**3ka**) was not possible, presumably due to efficient quenching of excited states by this moiety. The limitation of this coupling process was found for electron-donating substituents, resulting in a sharp decrease in yield (**3la–3pa**). Again, heterocyclic substrates were not amenable due to side reactions occurring directly on the aromatic core (**3ra**, **1s**). Finally, conjugation of the vinyl chloride with an arene substituent is necessary as can be seen from the unsuccessful activation of **1t** or **1u**.

1,4-Dicarbonyl compounds including those of type **3** have been broadly applied for the synthesis of furans and pyrroles.<sup>11</sup> A different application of products **3** is demonstrated with the CBS reduction<sup>12</sup> of **3aa** to enantioenriched  $\alpha$ -alkylidene- $\gamma$ -aryl- $\gamma$ -butyrolactone **5** ([Scheme 4](#)), a class of substrates being of

#### Scheme 4. Synthesis of Enantioenriched $\alpha$ -Alkylidene- $\gamma$ -aryl- $\gamma$ -butyrolactone **5**<sup>a</sup>



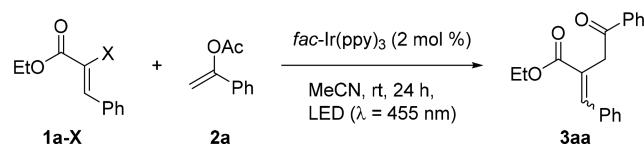
<sup>a</sup>Standard reaction conditions: **3aa** (1.0 mmol, 1.0 equiv),  $\text{BH}_3 \cdot \text{Me}_2\text{S}$  (1.3 mmol, 1.3 equiv), (**S**)-**4** (0.1 mmol, 10 mol %), toluene,  $-15^\circ\text{C}$ , 23 h. Isolated yield after purification via column chromatography. ee determined via chiral HPLC.

interest due to its biologically active properties including anti-inflammatory, phytotoxic, or cytotoxic activities.<sup>13</sup> The absolute stereochemistry of (*R,Z*)-**5** was confirmed by X-ray crystallography and is in line with the predictive model for CBS reductions.<sup>12</sup>

The overall mechanism of the coupling reaction developed here follows the established modes discussed before,<sup>4d,e,7</sup> however, the trend in reactivity observed for the  $\alpha$ -halo cinnamates is puzzling. Nevertheless, the reversal for the ease in C–X (X = Cl, Br) bond dissociation moving from benzyl halides to their corresponding radical anions has been suggested.<sup>14</sup>

In agreement with reduction potentials and bond dissociation energies (BDEs), the  $\alpha$ -fluoro cinnamate **1a-F** does not allow vinyl radical formation to take place ([Table 2](#)). In turn, we have been unable to synthesize **1a-I**, for which vinyl radical formation should have been most facile. While the reduction potential of **1a-Cl** is only slightly more negative than for **1a-Br**,

**Table 2.** Comparison of  $\alpha$ -Halo Cinnamates<sup>a</sup>

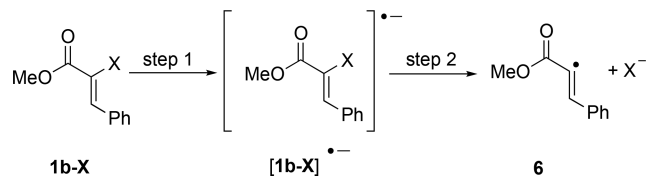


entry	X	BDE vinyl–X (kcal mol <sup>-1</sup> )	$E_{\text{RX/RX}^{\bullet-}}^{\circ}$ <sup>b</sup>	conv (%) <sup>c</sup> /yield (%) <sup>c</sup>
1	F	123.7	–1.93 V	0/0
2	Cl	91.7	–1.64 V	100/98
3	Br	79.4	–1.54 V	23/23
4	I	61.9	n.d.	–

<sup>a</sup>Reactions were performed using optimized reaction conditions ([Table 1](#), entry 5). <sup>b</sup>Reduction potentials were measured in MeCN vs SCE. <sup>c</sup>Conversion and yield were determined by <sup>1</sup>H NMR analysis using 1,3,5-trimethoxybenzene as internal standard.

the BDE of the vinyl halide is approximately 12 kcal/mol higher for the chloride than for the bromide. Still, **1a-Br** gave rise to significantly lower yield of **3aa** under the optimized reaction conditions for **1a-Cl** ([Table 2](#), entries 2 and 3). By computing the driving forces and relative stabilities of key intermediates in the two elemental steps ([Table 3](#)) we tried to elucidate if

**Table 3.** Computed Enthalpies and Gibbs Free Energies Associated with the Two Key Elemental Steps of Radical Anion Formation and Fragmentation<sup>a</sup>



X	gas phase		PCM (MeCN)	
	$\Delta H$ (kcal/mol)	$\Delta G$ (kcal/mol)	$\Delta H$ (kcal/mol)	$\Delta G$ (kcal/mol)
Step 1: $\Delta E_{[\text{1b-X}]^{\bullet-}}^{\circ} - \Delta E_{\text{1b-X}}$				
Br	–25.2	–26.2	–66.0	–68.1
Cl	–24.4	–25.1	–66.6	–65.4
Step 2: $\{\Delta E_{\text{6}} + \Delta E_{\text{X}^-}\} - \Delta E_{[\text{1b-X}]^{\bullet-}}$				
Br	13.3	4.5	–8.9	–18.5
Cl	21.8	12.4	–4.5	–15.8

<sup>a</sup>*E*: Either being enthalpy, *H*, or Gibbs free energy, *G*. See [SI](#) for further details.

indeed the different overall reactivity in the catalyzed transformation is only due to differences in the fragmentation of the radical anions.

In the gas phase, the radical anion formation (Step 1) is favorable, independently of X. The dissociation into carbon radical and the halide anion (Step 2) however is unfavorable in both cases. The latter reflects that gas phase structures with evolving or fully established charges cannot be stabilized. Using a simple polarizable continuum model (PCM, solvent = MeCN, for other solvents see [SI](#)) to mimic the dielectric effects of the solvent, now both elemental steps become exergonic. While the driving force for the release of the bromide is still favored over the chloride, the free energies become more convergent ( $\Delta\Delta G = 3$  kcal/mol), whereas in the gas phase there was a more than 3-fold higher driving force to cleave the C–Br bond. Interestingly, the computed reaction enthalpies indicated that MeCN is likely to be the most suitable solvent. And indeed, further

screening of different solvents for the reaction did not bring further improvement: while unipolar solvents did not allow a conversion neither with **1a-Cl** nor with **1a-Br**, more polar solvents (DMF, DMSO, MeCN/water, see SI for details) allowed significantly better conversions of the former, but overall the yield decreased for both substrates compared to pure acetonitrile. While these calculations suggest that in polar solvents the photochemical activation of vinyl-C–Cl becomes more feasible, nevertheless, the vinyl bromides should be more reactive. Conducting an experiment in which **1a-Br** and **1a-Cl** were employed in a 1:1 ratio confirmed this: while the conversion and the yield of coupling product **3aa** were now low, analysis of the crude reaction mixture revealed an approximately 3 times faster conversion of **1a-Br** compared to **1a-Cl** (see SI for details). Thus, we concluded that AcBr, being formed upon reaction of **1a-Br** and enol acetates might be an efficient catalyst poison for *fac*-Ir(ppy)<sub>3</sub>, while the corresponding AcCl formed in the reaction of **1a-Cl** is not. Indeed, adding AcBr (0.5 equiv, reflecting 50% conversion) to the reaction mixture under conditions used to convert **1a-Cl** (Table 1, entry 5) gave rise to **3aa** only in a strongly diminished yield of 22%. All attempts to reverse this process by adding various inorganic bases to prevent the catalyst poison proved to be unsuccessful (see SI for details). Studies by König and co-workers<sup>15a</sup> as well as by Stephenson and co-workers<sup>15b</sup> had shown the susceptibility of *fac*-Ir(ppy)<sub>3</sub> toward degradation. In particular, the work by Stephenson<sup>15b</sup> showed that radical functionalization of the ppy ligand is responsible. Since in our case the same radical is formed from either **1a-Br** or **1a-Cl**, we suggest here that a (Lewis)-acid-induced deactivation of *fac*-Ir(ppy)<sub>3</sub> by AcBr or HBr is the culprit that makes **1a-Br** unsuitable in the title transformation.

In summary, a visible-light-mediated activation of  $\alpha$ -chloro cinnamates was achieved. Based on the oxidative quenching of *fac*-Ir(ppy)<sub>3</sub>, vinyl radicals were generated after single electron reduction and efficiently trapped by enol acetates, giving rise to a broad range of valuable 1,4-dicarbonyl compounds. Calculations revealed that vinyl radical formation from their corresponding radical anions in general is more facile with vinyl bromides than with vinyl chlorides, but differences diminish in polar solvents like acetonitrile. With this tuning of reactivities the problem of catalyst poisoning of *fac*-Ir(ppy)<sub>3</sub> through acetyl bromide, being the stoichiometric side product in the reaction of vinyl bromides, could be overcome.

## ■ ASSOCIATED CONTENT

### 📄 Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02484.

Experimental details, characterization data, NMR spectra of all compounds, HPLC chromatograms, X-ray data, and computational details (PDF)

### Accession Codes

CCDC 1860111 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif), or by emailing [data\\_request@ccdc.cam.ac.uk](mailto:data_request@ccdc.cam.ac.uk), or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

## ■ AUTHOR INFORMATION

### Corresponding Author

\*E-mail: [oliver.reiser@chemie.uni-regensburg.de](mailto:oliver.reiser@chemie.uni-regensburg.de).

### ORCID

Julia Rehbein: 0000-0001-9241-0637

Oliver Reiser: 0000-0003-1430-573X

### Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

### Notes

The authors declare no competing financial interest.

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