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A synergistic LUMO lowering strategy using Lewis acid catalysis in water to enable photoredox catalytic, functionalizing C–C cross-coupling of styrenes†

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Easily available α -carbonyl acetates serve as convenient alkyl radical source for an efficient, photocatalytic cross-coupling with a great variety of styrenes. Activation of electronically different α -acetylated acetophenone derivatives could be effected *via* LUMO lowering catalysis using a superior, synergistic combination of water and (water-compatible) Lewis acids. Deliberate application of *fac*-Ir(ppy)₃ as photocatalyst to enforce an oxidative quenching cycle is crucial to the success of this (umpolung type) transformation. Mechanistic particulars of this dual catalytic coupling reaction have been studied in detail using both Stern–Volmer and cyclic voltammetry experiments. As demonstrated in more than 30 examples, our water-assisted LA/photoredox catalytic activation strategy allows for excess-free, equimolar radical cross-coupling and subsequent formal Markovnikov hydroxylation to versatile 1,4-difunctionalized products in good to excellent yields.

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Introduction

Visible light photocatalysis as a powerful tool for the selective generation of radicals has given rise to numerous unprecedented C–C-coupling reactions in recent years.¹ Especially alkyl radicals² have attracted great interest for the formation of highly functionalized natural products and pharmaceuticals.³ Back in 1985, Kellogg, one of the early pioneers of visible light photocatalysis, explored the reactivity of the electron deficient phenacyl radical generated by the photocatalytic single electron reduction of the corresponding phenacyl bromide.⁴ Since then, this electrophilic radical species has enabled the access to a variety of interesting radical trapping reactions for the implementation of new C–C-coupling transformations.⁵ However, phenacyl bromide is well known to promote radical polymerizations and also to be susceptible to nucleophilic substitutions (and hence enabling undesired polar reaction pathways) as for example, demonstrated for pyridines⁶ or under basic conditions.⁷ We hence assumed, that less activated α -acetoxy acetophenone could be a promising alternative for radical C–C coupling reactions avoiding undesired pathways.

Especially, in addition, bromide itself cannot be considered as a photochemically innocent leaving group based on its

redox properties: with an oxidation potential of only 0.66 V *vs.* SCE ($E_{\text{ox}}(\text{Br}^{\bullet}/\text{Br}^-) = 0.66 \text{ V}$) mesolytically cleaved bromide anions can easily get oxidized to the corresponding bromine radicals and hence potentially may also form elemental Br₂ by most common photocatalysts.^{8–10} Although, as the reduction potential of the corresponding α -acetoxy acetophenone ($E_{\text{red}} = -1.72 \text{ V vs. SCE}$) is more negative than the reduction potential of bromo acetophenone ($E_{\text{red}} = -1.45 \text{ V vs. SCE}$), we considered based on our recent C–O-bond cleaving studies,¹¹ that this reduced affinity to accept electrons could, in addition, be beneficially utilized as a promising, assistant tool to enhance reaction control and selectivity by deliberate lowering of the carbonyl LUMO.

Using synergistic photoredox catalysis with amino organocatalysis MacMillan and co-workers could already demonstrate that α -alkylation of aldehydes can be achieved with common α -bromo acetophenone¹² and, very recently, as well as with significantly less reactive α -acetoxy derivatives as non-traditional radical precursors.^{13,14} We hence questioned, if such α -acetoxy derived radicals as “alkylation reagent” could provide the required selectivity for a photocatalytic sp³–sp² C–C cross-coupling with styrenes followed by an oxidation to give the respective Markovnikov-type functionalized products (Scheme 1). This challenging photocatalytic/radical polar crossover reaction would offer unprecedented access to 1,4-functionalized synthons, such as γ -hydroxyketones, being versatile building blocks for the synthesis of a variety of bioactive compounds.¹⁶

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Scheme 1 Design plan for a functionalizing sp^3 - sp^2 -photocatalytic cross-coupling reaction.

Results and discussion

Based on our previous experience in C–O-bond activation,¹¹ we approached our cross-coupling investigations right from the beginning with a focus on mechanism, especially considering



Scheme 2 Oxidative vs. reductive quenching conditions for the C–C coupling of α -acetoxy acetophenone and 1,1-diphenylethylene and simplified comparison of the corresponding different reaction pathways. **Oxidative quenching** conditions: fac -Ir(ppy)₃, 0.5 mmol 1, 1.0 mmol 2 in MeCN/H₂O 4 : 1, irradiation with blue LEDs; yield of isolated product 4: 33%. **Reductive quenching** conditions: 4CzIPN,¹⁵ 1.5 equiv. NBu₃, 0.5 mmol 1, 1.0 mmol 2 in MeCN/H₂O 4 : 1, irradiation with blue LEDs; yield of isolated product 3: 83%.

the crucial role of the quenching cycles of the photocatalyst (Scheme 2).¹⁷ Initial test reactions employing simple oxidative (Scheme 2/left) and reductive quenching conditions (Scheme 2/right) for the coupling of α -acetoxy acetophenone (1) as radical precursor and 1,1-diphenylethylene (2) as well-established activated coupling partner,¹⁸ confirmed our hypothesis, that a reductive quenching cycle would be inappropriate for this intended reaction.

Using tertiary amines as reductive quenchers typically offers the great advantage of an extensive LUMO-lowering of the carbonyl group *via* hydrogen bond/PCET¹⁹ activation or 2-center/3-electron interaction,²⁰ respectively, effected by the tertiary amine's radical cation. However, we expected that such a reductive quenching cycle would impede the necessary oxidation of the benzylic radical to the corresponding benzylic cation being crucial for achieving the targeted, additional Markovnikov functionalization. Two possible pathways for this supposed limitation could be considered to be operating: apart from a competitive oxidation of the reductive quencher (*e.g.* R₃N), well-established HAT (hydrogen atom transfer) from the tertiary amine's radical cation, being present in increasing concentrations during the progress of the reaction, could operate as an additional detrimental pathway. As anticipated, no Markovnikov product was obtained while conducting the reaction with tributylamine as electron donor, following a reductive quenching cycle (Scheme 2/right). Instead, hydrogen atom abstraction took place as subsequent reaction step after the catalytic cycle to provide the coupling product 3 in an isolated yield of 83%. However, our attempts to transfer these promising, "reductive quenching coupling conditions", which albeit miss the targeted additional functionalization, to less reactive styrenes (instead of our initial test substrate 1,1-diphenylethylene 2) were not met with success. Further competitive reaction pathways (Scheme 3) impede the coupling with styrene, such as the direct abstraction of a hydrogen atom from the reductive quencher by the phenacyl radical (product 5) (HAT), as well as the radical addition onto an enamine species derived from the degradation of the amine quencher providing the alternative aldehyde coupling product 6 *via* aminocatalysis (Scheme 3).

Fortunately, employing fac -Ir(ppy)₃ as photocatalyst in a redox neutral oxidative quenching cycle mediates the targeted functionalizing C–C coupling reaction to yield the desired 1,4-functionalized product 4. Remarkably, the α -acetoxy acetophenone (1) was reduced by fac -Ir(ppy)₃ ($E_{1/2}(\text{Ir(III)}^*/\text{Ir(IV)}) = -1.73 \text{ V vs. SCE}$)^{17b} without further attempts to lower the



Scheme 3 Undesired side products present in cross-coupling reactions following a reductive quenching cycle.



carbonyl LUMO. Although the reduction potential of **1** seems to be too negative for a direct reduction ($E_{\text{red}} = -1.72$ V vs. SCE), we could already obtain 33% of the desired functionalized coupling product **4**. Notably, this preliminary finding indicated, that the carbonyl group may here even be significantly activated for reduction, respectively for a PCET-type reduction with water as omnipresent hydrogen bond donor under our aqueous conditions.²¹

Having this in mind, we initiated a detailed screening, again using styrene (**7**) as a more challenging, less activated coupling partner (Table 1). Additional to water as H-bond donor present in our solvent mixture, we evaluated different activation modes for the LUMO lowering of carbonyl group,²² including Schreiner's thiourea,²³ as well as different lanthanide-based, water-compatible Lewis acids.^{24,25} Interestingly, the choice of the activation mode (entries 2 and 3), as well as the choice of the lanthanide Lewis acid (entries 5–9) seems to be insignificant for the coupling product's yield.

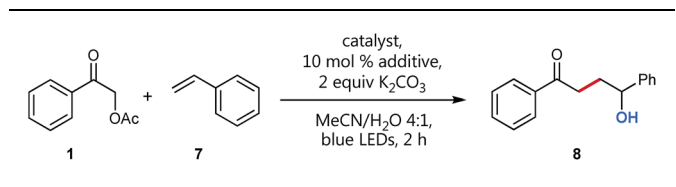
However, Schreiner's thiourea catalyst proved to be rather unstable under these photocatalytic conditions. To avoid large catalyst loadings and additional side products formed *via* the degradation of the thiourea catalyst, we decided to continue our investigations with neodymium triflate as Lewis acid in a dual activation, synergistic catalysis.²⁶ Furthermore, the yield of coupling product could be dramatically increased by degassing the reaction mixture (entries 4 and 5), to 91% (entry 9). Additionally, decreasing the styrene equivalents to an equimolar amount, as well as lowering the catalyst loading to 0.5 mol% had no negative influence nor on the yield neither on the reaction time (2 h) (entry 10 (92%)). Notably, these optimized reaction conditions allow for equimolar cross-coupling of radical precursor **1** and styrene **7** to the 1,4-functionalized

product in excellent yield, avoiding typical side reactions, such as styrene polymerization or hydrogen abstraction of the α -acetylated acetophenone.

The control reactions (Table 2) confirmed the decisive role of both catalyst and visible light, as without each no reaction occurred during 48 h of elongated reaction time (entries 1 and 2). The omission of Lewis acid (entry 3) decreases the yield to only 64%. An experiment performed in acetonitrile without water, but offering MeOH as alternative nucleophile (entry 4), did not provide any of the corresponding methoxy adduct. In combination with entry 3 this clearly shows the synergistic interaction of both activation modes.^{21,26} Water can lower the carbonyl LUMO only by weak hydrogen bonds, however greatly contributes to the success of the reaction by creating a two-phase system, which additionally shifts the equilibrium to the cross-coupling process.

The catalytic amount of Lewis acid strongly enhances the effect on lowering the carbonyl's LUMO; this may also be in the context of the formation of Lewis acid water complexes to promote PCETs as well-known for SmI₂-water systems.^{27,28} However, without the addition of water Nd(OTf)₃ is almost insoluble in acetonitrile and therefore cannot effectively contribute to the carbonyl activation (entry 4). The exchange of the acetate leaving group with bromide (entry 6) significantly decreased the yield of the desired coupling product **8** to 38%. While full conversion of the bromo acetophenone was still reached after 2 h of irradiation, numerous, not further determined side products were formed, clearly proving the crucial role of the radical source for this cross-coupling/functionalization protocol. An additional test reaction using Ir(dtbbpy)(ppy)₂(PF₆) as strongly reductive catalyst for reductive quenching cycles, but weaker reductive power of its excited state ($E(\text{Ir(III)}/\text{Ir(II)}) = -1.51$ V vs. SCE; $E(\text{Ir(III)}^*/\text{Ir(IV)}) = -0.96$ V vs.

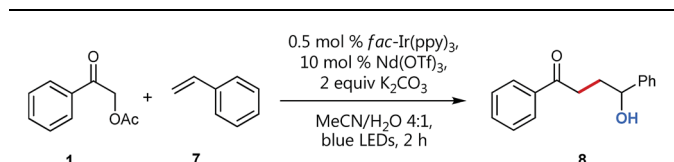
Table 1 Optimization of oxidative quenching conditions for styrene cross-coupling



Entry	Catalyst	Additive	1 : 7	Yield ^a
1 ^{b,c,d}	1 mol% <i>fac</i> -Ir(ppy) ₃	Thiourea ^e	1 : 4	19%
2 ^{b,c}	1 mol% <i>fac</i> -Ir(ppy) ₃	Thiourea ^e	1 : 4	45%
3 ^{b,c}	1 mol% <i>fac</i> -Ir(ppy) ₃	Yb(OTf) ₃	1 : 4	46%
4 ^c	1 mol% <i>fac</i> -Ir(ppy) ₃	Yb(OTf) ₃	1 : 2	58%
5	1 mol% <i>fac</i> -Ir(ppy) ₃	Yb(OTf) ₃	1 : 2	82%
6	1 mol% <i>fac</i> -Ir(ppy) ₃	Er(OTf) ₃	1 : 2	85%
7	1 mol% <i>fac</i> -Ir(ppy) ₃	Gd(OTf) ₃	1 : 2	88%
8	1 mol% <i>fac</i> -Ir(ppy) ₃	Dy(OTf) ₃	1 : 2	90%
9	1 mol% <i>fac</i> -Ir(ppy) ₃	Nd(OTf) ₃	1 : 2	91%
10	0.5 mol% <i>fac</i> -Ir(ppy) ₃	Nd(OTf) ₃	1 : 1	92%

^a Conditions: catalyst, 10 mol% additive, 2 equiv. K₂CO₃, 0.25 mmol **1**, 0.25 mmol **7** in 1 mL MeCN/H₂O 4 : 1, degassed, irradiation with blue LEDs, 2 h, yield determined by GC-FID using mesitylene as internal standard. ^b 20 mol% additive. ^c Without degassing. ^d MeCN as solvent. ^e Schreiner's thiourea catalyst.

Table 2 Control experiments



Entry	Deviation from the standard conditions	Yield ^a
1 ^b	No catalyst	0%
2 ^b	No light	0%
3	No Lewis acid	64%
4	No water, but MeOH	0% ^c
5	No base	61%
6	Bromoacetophenone as radical source	38%
7	Ir(dtbbpy)(ppy) ₂ (PF ₆) as catalyst	0%

^a Conditions: 0.5 mol% *fac*-Ir(ppy)₃, 10 mol% Nd(OTf)₃, 2 equiv. K₂CO₃, 0.25 mmol **1**, 0.25 mmol **7** in 1 mL MeCN/H₂O 4 : 1, degassed, irradiation with blue LEDs, 2 h, yield determined by GC-FID using mesitylene as internal standard. ^b 48 h reaction time. ^c Only minor conversion of **1**; traces of 1,4-diphenylbut-3-en-1-one (corresp. alkene to **8**) and dimerization product 1,4-diphenylbutane-1,4-dione were detected by GC/MS.



SCE)^{17b} failed to provide any product and further confirms the oxidative quenching cycle of this cross-coupling.

We then set out to prove the synergistic combination of water and Lewis acid in a series of mechanistic studies. Initially, we wanted to “visualize” and somewhat quantify the LUMO lowering effect by cyclic voltammetry measurements²⁹ to monitor the influence of different additives on the reduction potential (Fig. 1) and hence to gain a more detailed mechanistic understanding.

Insightfully, both the addition of water as well as of neodymium triflate results in a significant decrease of the measured reduction potential of α -acetoxy acetophenone **1**. While without any additive the potential of **1** is slightly too high for a thermodynamically favorable reduction with *fac*-Ir(ppy)₃, the solvent mixture (MeCN/water 4 : 1 (v/v)) already lowers the reduction potential sufficiently to enable the reduction of **1** and hence points to the often neglected, however crucial role of solvents, especially water, for (photo)redox processes.³⁰

Notably, the combination of both activation modes, the aqueous solvent system plus a water-compatible Lewis acid,²⁷ significantly lowers the potential by 0.5 V and hence contributes to an even more exergonic electron transfer process.

Furthermore, we could confirm these observations by Stern–Volmer experiments (Fig. 2), also corroborating our initial studies with diphenylethylene (see also Scheme 2).

While quenching study A shows no relevant decrease in the photocatalyst's fluorescence with increasing concentrations of **1** in pure (dry) acetonitrile, only in quenching study B, performed in an acetonitrile/water mixture (4 : 1 (v/v)), the emission of *fac*-Ir(ppy)₃ is clearly quenched by α -acetoxy acetophenone **1**. We further proved the importance of the exclusion of oxygen (Table 1, entries 4 and 5) in this reaction: quenching study C shows energy transfer to O₂ for the singlet oxygen production³¹ to be a strongly preferred quenching pathway of *fac*-Ir(ppy)₃ in these solvent conditions.



Fig. 1 LUMO-lowering effects on reduction potential of **1** subject to different conditions. For details on electrodes, concentration and measurement conditions see ESI.†

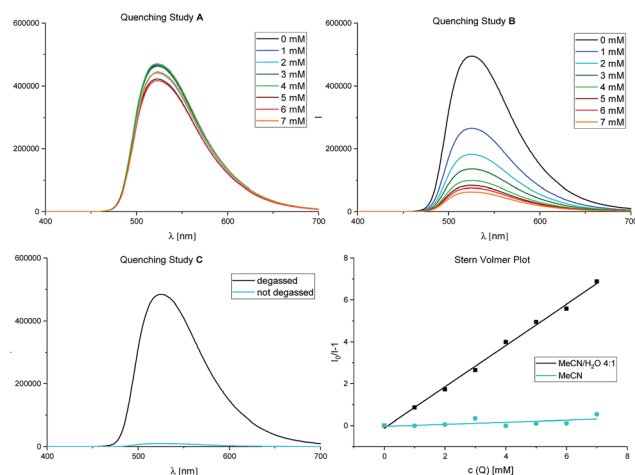
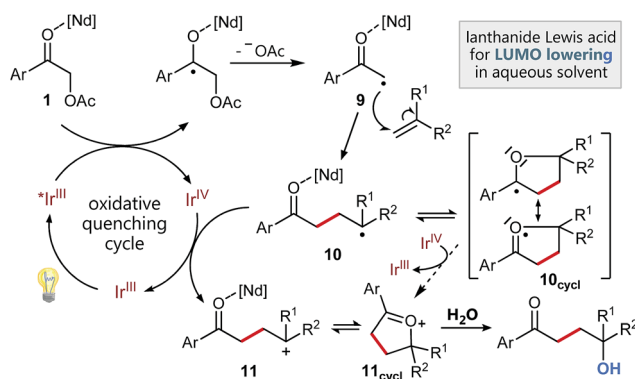


Fig. 2 Stern–Volmer quenching studies. Fluorescence spectra for *fac*-Ir(ppy)₃ (50 μM) with increasing amounts of α -acetoxy acetophenone **1** (0–7 mM) as quencher. Quenching study A: in MeCN; quenching study B: in MeCN/H₂O 4 : 1; quenching study C: presence of oxygen. For further details, see ESI.†

Based on these studies and our experimental results, we propose the following mechanism for this functionalizing, radical C–C-coupling reaction (Scheme 4) starting with the excitation of the Ir catalyst followed by an oxidative quenching *via* single electron transfer to the activated carbonyl group of **1**. The mesolytic cleavage of the C–O-bond leads to electron deficient radical **9**, which can now attack the styrene. Subsequently, the newly created benzylic radical **10**, which may be stabilized by intramolecular cyclization^{5g} to radical **10_{cycl}** and hence suppress possible, undesired side reactions (polymerization *etc.*), can be oxidized by the Ir(IV) species. Upon regeneration of the photocatalyst this results in a radical polar crossover to benzylic cation **11**, respectively its cyclized variant **11_{cycl}**. Final attack of water can then lead to the formation of the 1,4-keto-hydroxy product.

Having optimized conditions and a mechanistic understanding at hand, we set out to examine the scope of the reaction starting with different styrenes (Scheme 5). Notably, all tested vinyl benzenes could successfully be coupled with the



Scheme 4 Proposed mechanism.





Scheme 5 Substrate scope for C–C-coupling with styrene derivatives. Conditions: 0.5 mol% *fac*-Ir(ppy)₃, 10 mol% Nd(OTf)₃, 2 equiv. K₂CO₃, 0.5 mmol **1**, 0.5 mmol styrene derivative in 2 mL MeCN/H₂O 4 : 1, degassed, irradiation with blue LEDs; isolated yields.

acetophenone radical. With exception of product **17**, whose styrene precursor is known to be strongly prone to polymerization, all coupling products were obtained in good to excellent yields (up to 96%). Interestingly, there is no recognizable difference for the coupling of styrenes with electron withdrawing (**12–15**) and electron donating substituents (**16, 18, 19**). The direct comparison of the three different regioisomeric bromo styrenes (**12–14**) nicely shows the insensitivity of the transformation towards sterically hindrance being a typical advantage of radical coupling reactions.³²

Even quaternary centers (e.g. tertiary alcohols) could be generated in excellent yields by either employing α -methylstyrene (product **20**) or 1,1-diphenylethylene (product **4**). To further elucidate the broad scope of our approach for radical cross-couplings with styrenes, we then investigated the trapping of radicals derived from different substituted α -acetoxy acetophenone precursors with a selection of four different styrenes (Scheme 6). Gratifyingly, we could obtain the desired products for all tested combinations within our “4 × 5 matrix”. While the yields for the combination of α -acetoxy acetophenone **1** with these styrenes are all consistently very good to excellent (82–96%; see Scheme 5 products: **8, 15, 16, 19**) the difference in performance becomes more apparent for other, substituted α -acetylated acetophenones (Scheme 6: acetophenones **I–V**). The cross-coupling of styrenes with α -tetralone derivative **I**, as precursor for secondary radicals, tolerates styrenes bearing an electron withdrawing group (**21**) as well as a mesomeric electron donating effect (**22**) (77–89%). However, the yield decreases to 53% in combination with the sterically demanding and inductive electron donating *tert*-butyl substituent present (**23**). Interestingly, the electron donating methyl group (**II**) and the

electron withdrawing chloro-substituent (**III**) did not show an opposing trend for their performance as coupling partners. According to this observed reactivity, the polarity match seems to be of minor importance for the success of this radical



Scheme 6 Substrate scope for functionalizing, radical polar cross-coupling reaction with styrenes. Conditions: 0.5 mol% *fac*-Ir(ppy)₃, 10 mol% Nd(OTf)₃, 2 equiv. K₂CO₃, 0.5 mmol acetoxy substrate, 0.5 mmol styrene derivative in 2 mL MeCN/H₂O 4 : 1, degassed, irradiation with blue LEDs; isolated yields.



transformation. However, the mesomeric effect of the *para*-methoxy substituent (acetophenone **IV**) shows a notable decrease of all yields being best explained by the lowering of the electron deficiency of the attacking alkyl radical, respectively of the substrate's carbonyl group for the initial SET reduction.

Altering the position of the substituent further illustrates this effect with the observed increased yield for the coupling with *meta*-methoxy substituted radical source **V** (Scheme 6/line 5: $-I$ effect only).

Conclusions

In summary, we have developed a novel equimolar cross-coupling reaction of α -acetoxy acetophenones and styrene derivatives with a subsequent Markovnikov functionalization to provide efficient access to versatile 1,4-substituted building blocks in good to excellent yields. The reaction was realized by the oxidative quenching of *fac*-Ir(ppy)₃ in combination with effective synergistic activation of the carbonyl group with water and Nd(OTf)₃. Detailed mechanistic investigations were performed, including cyclic voltammetry and Stern–Volmer experiments, to examine the LUMO-lowering effect in detail. Our mechanistic studies reveal the impact of radical source and choice of photocatalyst on both reactivity and selectivity and support the crucial importance of the deliberate application of *fac*-Ir(ppy)₃ as an “oxidative quenching cycle”-only catalyst for this challenging functionalizing cross-coupling reaction. Moreover, our studies shed further light on the often neglected, but critical role of aqueous solvent systems in photoredox reactions.

Conflicts of interest

There are no conflicts to declare.

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