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Reduction of electron-deficient alkenes enabled by a photoinduced hydrogen atom transfer

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Abstract. Direct hydrogen atom transfer from a photoredox-generated Hantzsch ester radical cation to electron-deficient alkenes has enabled the development of an efficient formal hydrogenation under mild, operationally simple conditions. The HAT-driven mechanism is supported by experimental and computational studies. The reaction is applied to a variety of cinnamate derivatives and related structures,

irrespective of the presence of electron-donating or electron-withdrawing substituents in the aromatic ring and with good functional group compatibility.

Keywords: Alkenes; Transfer hydrogenation; Hydrogen atom transfer; Photocatalysis; Photoredox; DFT

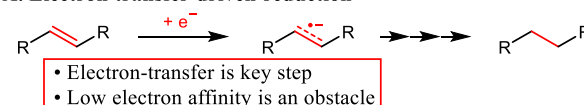
Introduction

The hydrogenation of C-C multiple bonds and related reductive transformations are among the most important processes in chemical industry.^[1] In particular, transfer hydrogenation, which avoids the use of hydrogen gas, is of much practical interest in both industrial and laboratory settings, and the development of new methods and strategies is of continued importance.^[2]

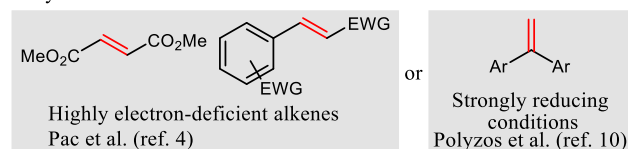
The recent fast development of photocatalysis has resulted in the discovery of a wide variety of reductive, oxidative and redox-neutral transformations.^[3] Photocatalytic reduction methods have been explored in a number of instances, and actually some of the pioneering research in photocatalysis dealt with the formal hydrogenation of alkenes using a dihydropyridine (*N*-benzyl 1,4-dihydronicotinamide, BNAH) as the reductant.^[4] However, this early work was handicapped by a very narrow substrate scope—the reaction only worked on extremely electron-deficient alkenes bearing at least two electron-withdrawing groups (Figure 1A).^[5] This limitation is consistent with the proposed mechanism, where the alkene reduction starts with a single electron transfer to give the corresponding radical anion. Thus, the scope was limited by the reduction potentials of the alkene and the catalyst in its reduced form.^[6] For other functional groups, similar limitations have been overcome by activating the substrate with Lewis or Brønsted acid additives or co-catalysts to make it more electron-deficient.^[7] However, to the best of our knowledge, little success has been obtained with such strategies in the formal

hydrogenation of alkenes.^[8] On a different approach, reduction could be forced by using catalytic systems with increased reductive power, for example by the exploitation of two-photon excited states^[9] or combining electro- and photocatalysis.^[10] Nevertheless, the possible reduction of other functional groups under these very strongly reducing conditions limits the scope of such strategies. One recent report has described the application of a two-photon strategy for the formal hydrogenation of 1,2-diarylethylenes by sequential electron and proton transfer reactions (Figure 1A).^[11]

A. Electron transfer-driven reduction



Only feasible with:



B. HAT-driven reduction (this work)

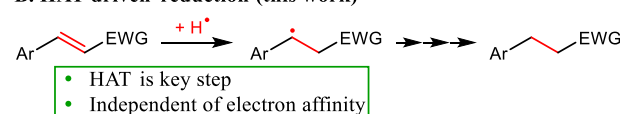


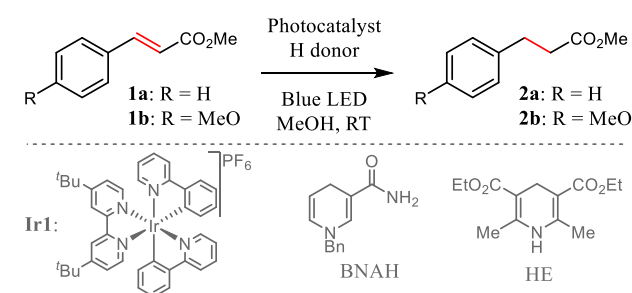
Figure 1. Strategies for the photoreduction of alkenes promoted by visible light.

An alternative strategy for the reduction of alkenes would be to circumvent formation of the radical anion by exploiting light-promoted hydrogen atom transfer (HAT) reactions.^[12] Thus, a catalytic system capable of promoting the transference of a H atom to an alkene could provide an easy route for their reduction under mild reaction conditions (Figure 1B). Hantzsch ester (HE) and related compounds have been applied before as versatile reductants acting as hydride, hydrogen atom and/or electron donors.^[13,14] Although HAT is frequently invoked in light-promoted hydrofunctionalisation, it is invariably proposed to occur in a *termination* step where an organic radical abstracts a H atom from the HE or its radical cation.^[15] However, HAT from a HE derivative to a stable, closed-shell compound has not been described in this context.^[16] Herein we report an efficient and operationally simple reduction of cinnamate derivatives under mild conditions, initiated by HAT from a photoredox-generated Hantzsch ester radical cation.

Results and Discussion

We started our investigation by studying the reduction of methyl cinnamate (**1a**) as a model substrate with combinations of known photocatalysts and potential hydrogen atom donors^[17] (summary in Table 1, entries 1-5). Gratifyingly, we found that [Ir(ppy)₂(dtbbpy)]PF₆ (**Ir1**) was indeed capable of promoting the reaction with either ^tPr₂NEt, 1,4-dihydronicotinamide (BNAH) or Hantzsch ester (HE)

Table 1. Summary of reaction optimisation.^a



Entry	Substrate	Conditions	Yield (%) ^b
1	1a	[1] = 50 mM, Ir1 2.5 mol%, HE (2 equiv)	100
2		Ru(bpy) ₃ Cl ₂ as the catalyst	1
3		Ir(ppy) ₃ as the catalyst	2
4		EtN ^t Pr ₂ as the reductant	36
5		BNAH as the reductant	42
6	1b	As entry 1	70
7		[1] = 25 mM	89
8		[1] = 12.5 mM	91
9	1a	As entry 7, no photocatalyst	0
10		As entry 7, dark	0

Ir1: [Ir(ppy)₂(dtbbpy)]PF₆. ^a Reactions run with substrate **1** (0.1 mmol), reductant (2 equiv) and catalyst (2.5 mol%) at RT in MeOH, following general procedure B (see ESI). ^b Yield determined by ¹H NMR using an internal standard.

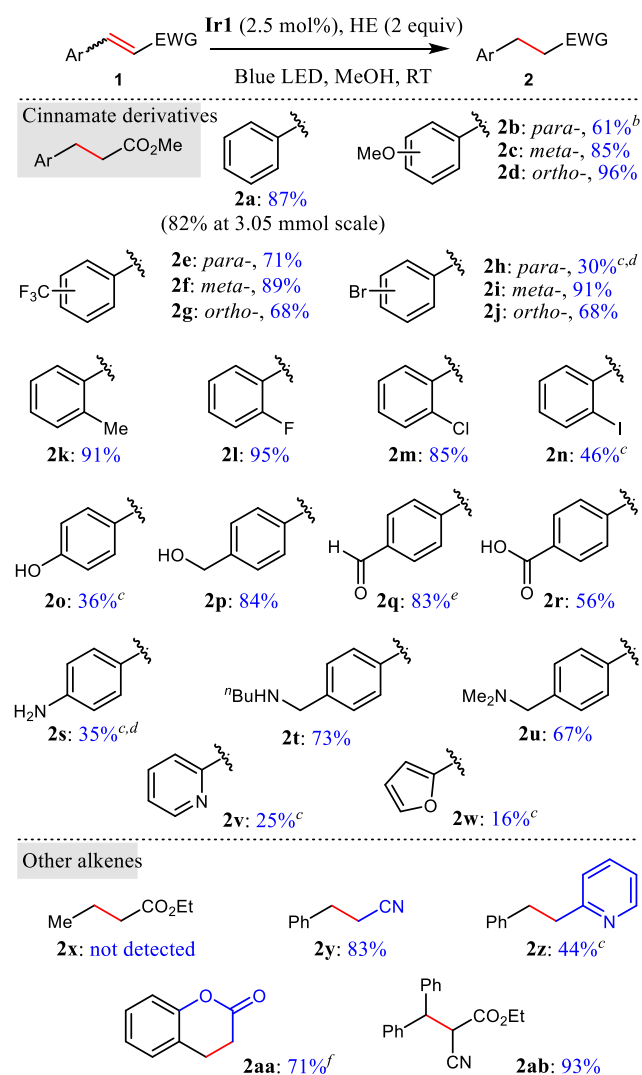
as the reductant and H atom donor, with HE providing quantitative yield of the reduced product **2a** (entry 1). Other similar photocatalysts such as Ru(bpy)₃Cl₂ and Ir(ppy)₃ did not provide virtually any conversion to **2a**.^[18]

Application of these conditions to the more electron-rich substrate **1b** resulted initially in a significant erosion of the yield (entry 6). Nonetheless, decreasing the concentration of the reaction mixture resulted in a recovery of the yield to satisfactory levels of 89 and 91%, respectively, at 25 and 12.5 mM (entries 7 and 8). To avoid using excessive solvent, we chose 25 mM as the most appropriate concentration, given the very small increase obtained by further dilution. As expected, control experiments in the absence of the Ir photocatalyst (entry 9) or in the dark (entry 10) showed that both are essential for the reaction to proceed.

Then, we set out to explore the substrate scope and limitations of our method (Table 2). The photoreduction worked to high yields with a wide variety of cinnamate derivatives bearing different substituents on the aryl ring (**2a-u**). Electron-donating MeO group was tolerated at all three possible positions (**2b-d**, 61-96%), as well as electron-withdrawing CF₃ (**2e-g**, 68-89%). Likewise, no steric influence on reaction yield was apparent from substitution at the *ortho*- position (**2k-m**, 85-95%). The reaction was compatible with halogen substituents (**2h-j**, **2l-2n**), although a lower yield for **2n** (46%) may suggest a competing reduction of the C-I bond. In the case of Br, *para*-substituted compound was only obtained in moderate yield (**2h**, 30%), in contrast with the good results for the *ortho*- and *meta*- analogues (68% and 91%, respectively, for **2j** and **2i**). The reaction tolerated unprotected alcohol (**2p**, 84%), carboxylic acid (**2r**, 56%) and amines, even when containing free NH bonds (**2t** and **2u**, 73 and 67%, respectively), although phenol and aniline provided decreased yields (**2o** and **2s**, 36 and 35%, respectively). Aldehyde-substituted product **2q** could be obtained in 83% yield by performing the reaction with the corresponding ethyleneglycol acetal, which was deprotected *in situ* during work-up.

Replacing the aryl group in the cinnamate ester structure for heterocycles such as pyridyl or furyl resulted in low yields of product (**2v** and **2w**, 25 and 16%) and the reaction did not proceed at all in the absence of an aromatic group (**2x**).

Moving away from the methyl cinnamate structure, cinnamitrile (**1y**) and coumarin (**1aa**) were both efficiently reduced under our reaction conditions to the corresponding alkanes in 83 and 73% yield, respectively. 2-Styrylpyridine (**1z**), with just the pyridyl group as electron-withdrawing group, was also reduced albeit in an only moderate yield (44%). Finally, a tetrasubstituted alkene (**1ab**) was efficiently reduced (93% yield), highlighting the robustness of this method with respect to steric hindrance. A preparative experiment under standard conditions with 3.05 mol (0.5 g) of substrate **1a** provided **2a** in 82% isolated yield.

Table 2. Substrate scope and limitations.^a

a) Unless stated otherwise, reactions were run with substrate **1** (0.2 mmol, 25 mM), HE (2 equiv) and catalyst **Ir1** (2.5 mol%) following general procedure B (see ESI). Yields are of isolated product unless otherwise noted.

b) NMR yield in this case was significantly higher (89%), however isolation was challenging. ^c Yield determined by ¹H NMR using an internal standard. ^d The ethyl ester was used in this case instead of methyl. ^e Starting from the corresponding ethyleneglycol acetal. ^f MeCN was used as the solvent.

Next we turned our attention to studying the reaction mechanism. Stern-Volmer fluorescence quenching studies (Figure 2B) showed that HE is an efficient quencher for the excited catalyst,^[19] in a well precedented process giving place to the reduced form of the catalyst [**Ir1**]⁻ and the Hantzsch ester radical cation [HE]^{•+}.^[20]

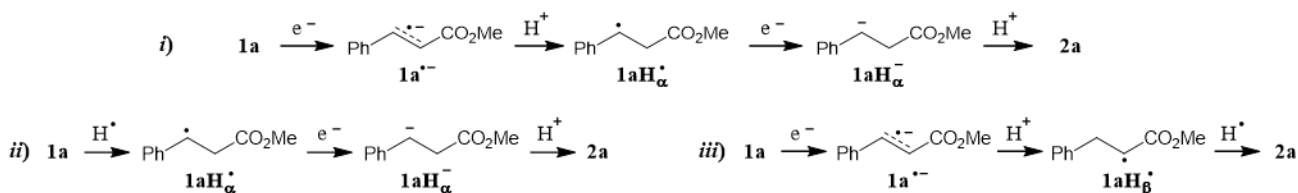
Regarding the manner of activation of the alkene, previously reported methods for the photoreduction of alkenes^[4,11a] were proposed to proceed through sequential single electron transfer (SET) and protonation events (Figure 2A, *i*), with the solvent acting as the H⁺ source. To explore this possibility, we performed a series of experiments using

deuterium labelling (Figure 2C). Thus, the photoreduction of **1a** using MeOD as the solvent led to formation of product **2a** with 88% incorporation of D at the alkene β-position, but a very poor 18% at α.^[21] Conversely, the use of 4,4-d₂-HE in MeOH resulted in 50% deuterium incorporation exclusively at the α-position, with no deuteration detected at β. These results show that the β-hydrogen in **2a** has its source in the solvent, while the α-hydrogen comes preferentially from the reductant. These data contrast with similar experiments carried in other alkene photoreduction systems, where both hydrogens were incorporated from the solvent,^[22] and are inconsistent with a reduction through sequential electron and proton transfer events. The use of CD₃OH as the solvent did not result in any detectable D incorporation (see ESI, Figure S3), ruling out a possible role of the solvent as a H atom donor.^[23] In addition, an experiment at low conversion using the monodeuterated analogue 4-d-HE resulted in a significantly lower D-incorporation to the product than statistically predicted, showing a faster transfer of H compared to D (apparent *k_H/k_D* ≈ 4.2, Figure 2B). These observations rule out a SET/protonation sequence, and strongly support a HAT step for incorporation of the α-H.

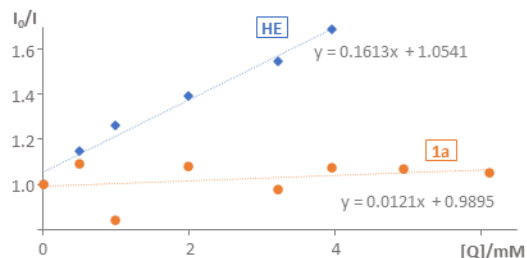
Then, we used DFT calculations to explore the feasibility of a HAT from [HE]^{•+} to substrate **1a** (Figure 2A, *ii*).^[24] Pleasingly, we found that the reaction was thermodynamically favourable and kinetically accessible at both positions of the alkene. Importantly, our computational model predicted HAT to the α position to be significantly faster than that at β ($\Delta G^\ddagger = 14.9$ and 19.0 kcal/mol, respectively), which is consistent with the observed regioselectivity in deuteration experiments (Figure 2E; see also Figure S6 for a complete reaction profile). The radical obtained after HAT (**1aH_α•**) would then be easily reduced by [**Ir1**]⁻ to its corresponding carbanion (calculated potential for **1aH_α•**: *E*_{1aH_α•} = -1.43 V, Figure 2D),^[25,26] which could abstract H⁺ from the solvent to give the reduced product **2a**.

The only alternative remaining in view of the D labelling experiments would be that described in Figure 2A, *iii*, where after an initial SET reduction of **1a**, the radical anion would be protonated at the β-position to give enolyl radical **1aH_β•**. Then, HAT from HE^{•+} to **1aH_β•** would lead to product **2a**. However, this mechanism presents a number of issues which allow us to rule it out too. Firstly, **1a** is not a good quencher for the excited **Ir1** catalyst as shown by quenching experiments (Figure 2B).^[19] Its reduced form [**Ir1**]⁻ is not a strong enough reductant to directly engage in SET with **1a** to form the key radical anion **1a^{-•}** (*E*_{Ir1} = -1.54 V, *E*_{1a} = -1.87 V).^[3d,27] As an alternative, we considered the possibility of an excited HE species performing the reduction of **1a** to **1a^{-•}**.^[28] However, the involvement of such species under the reaction conditions is unlikely in this case: The involvement of HE* formed by direct absorption of light is ruled out by control experiments showing that the reaction does not work

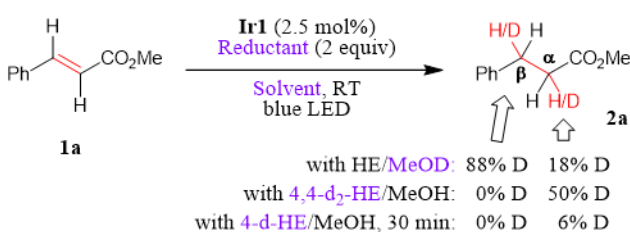
A. Potential mechanisms for the reduction of electron-deficient alkenes



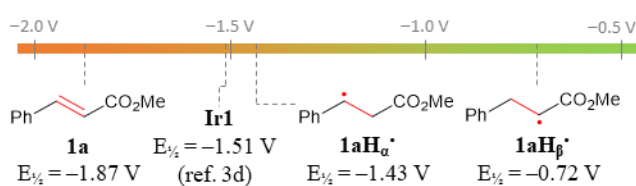
B. Fluorescence quenching studies^a



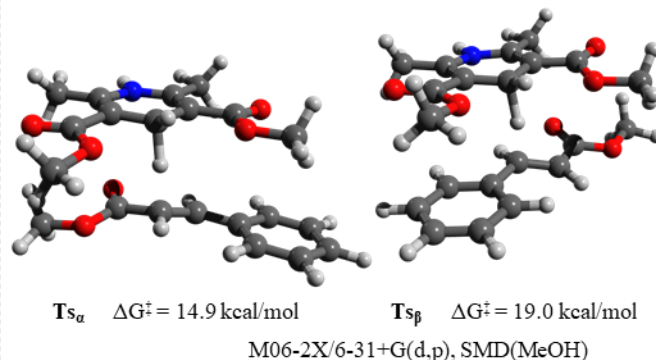
C. Deuterium labelling^b



D. Reduction potentials^c



E. Calculated transition states for HAT from HE⁺⁺ to 1a^d



F. Proposed mechanism

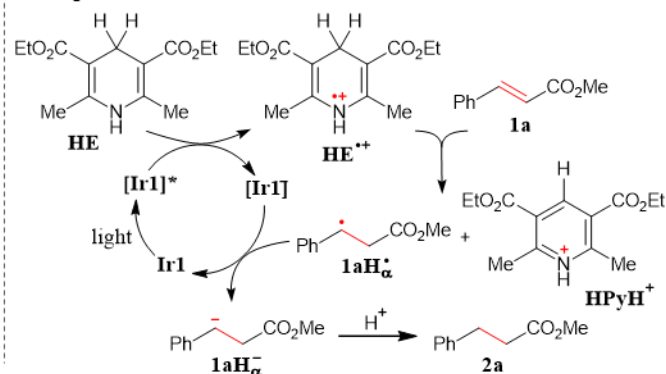


Figure 2. Mechanistic elucidation of the HAT-based photoreduction. ^a Experiments performed at 0.01 mM concentration of Ir1 in a quartz cuvette. ^b Conditions as in Table 2. ^c Reduction potentials are in MeCN vs. saturated calomel electrode (SCE). $1a$, $1aH_{\alpha}^{\bullet}$ and $1aH_{\beta}^{\bullet}$ are calculated by DFT (M06-2X/6-31+G(d,p) with SMD solvent model, see ESI for details). ^d Relative energies respect of independent starting materials (M06-2X/6-31+G(d,p), SMD, see ESI for details).

at all in the absence of catalyst Ir1 (Table 1, entry 9). Likewise, sensitisation of HE by direct energy transfer from [Ir1]* can be discarded considering the large difference between the triplet state energies of both species (70.8 kcal/mol for HE and 49.2 kcal/mol for Ir1).^[29,30] In addition to this, even if intermediate $1a^{--}$ were to be formed by some yet unknown pathway, it was expected that its protonation would not proceed preferentially at the β position, as required for this mechanism to fit the D-labelling experiments.^[31] This was indeed confirmed by DFT calculations, which showed the protonation of $1a^{--}$ by MeOH to be strongly disfavoured thermodynamically and with protonation at α being preferred by 4.5 kcal/mol or ca. 3.3 pK_a units (see ESI, Figure S5 for further details). Thus, a mechanism of this type would result in opposite selectivity to that experimentally observed in the D-labelling experiments.

Overall, our combined experimental and computational data provide strong support for a mechanism as depicted in Figure 2F, where excitation of Ir1 by visible light enables it to oxidise HE to its radical cation [HE]⁺⁺. Subsequently, [HE]⁺⁺ transfers a H atom to the alkene 1a giving place to a benzylic radical [$1aH_{\alpha}^{\bullet}$], which is finally further reduced by SET from [Ir1]⁻ and protonated to give the reduced product 2a.

Conclusion

In conclusion, we have developed a simple method for the photoreduction of olefins which enables the use of moderately electron-deficient, synthetically meaningful substrates with good functional group compatibility. Our mechanistic investigations support a hydrogen atom transfer to the substrate as the key

step which enables the reduction to proceed without requiring the generation of a very highly reducing medium. We believe this unprecedented mode of substrate activation offers new opportunities for photoredox transformations by enabling the generation of radical intermediates that otherwise are not easily accessible.

Experimental Section

General method for the photoreduction of electron-deficient alkenes: Substrate (0.2 mmol), Hantzsch ester (2 eq., 0.4 mmol) and $[\text{Ir}(\text{dtbbpy})(\text{ppy})_2]\text{PF}_6$ (2.5 mol%) were weighted out into a microwave vial equipped with a magnetic stirrer. Dry methanol (8 mL) was added and the vial was quickly capped. The mixture was degassed with argon for 10 minutes and the septum was covered with parafilm. The vial was placed in a photoreactor and irradiated under blue light for 16 hours. Thereafter, the mixture was transferred to a round bottom flask, the vial washed with Et_2O and the solvent was evaporated. 0.5 mL of HCl in Et_2O (1.0-1.7M) were added to the residue and the resulting mixture was filtered through a packed layer of silica. The solution was neutralized with a saturated NaHCO_3 solution and the extracted organic layer washed with water. The organic phase was dried over MgSO_4 , filtered and concentrated *in vacuo*. The resulting residue was further purified when necessary by flash column chromatography.

Acknowledgements

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- [22] For example in ref. 4b, photoreduction of dimethyl fumarate by BNAH catalysed by **Ru1** in MeOD gave 59% *d*₂- and 37% *d*-dimethyl succinate, with only 4% non-deuterated product, while reaction with 4,4-*d*₂-BNAH in MeOH gave 6% mono- and 94% non-deuterated product. Similar numbers were reported for dimethyl maleate.
- [23] In addition, although MeOH provided in most cases the best results, the reaction worked well in a variety of solvents, including MeCN and DMF (see ESI, table S1)
- [24] Calculations performed using M06-2X functional and 6-31+G(d,p) basis set as implemented in Gaussian 16, revision A03, with SMD solvent model. See ESI, section 3 for full Gaussian citation and full details on computational methods.
- [25] Calculated reduction potential for the isomeric radical **1aH_β•**, obtained from H addition on the β position, was $E_{\text{1aH}\beta} = -0.72$ V.
- [26] Method for calculating reduction potentials: H. G. Roth, N. A. Romero, D. A. Nicewicz, *Synlett* **2016**, *27*, 714–723.
- [27] Calculated value for **1a** in MeCN for consistency with other literature values. Compare to -1.98 V experimental in MeOH, see: T. Shiragami, H. Ankyu, S. Fukami, C. Pac, S. Yanagida, H. Mori, H. Fujita, *J. Chem. Soc. Faraday Trans.* **1992**, *88*, 1055–1061.
- [28] A reduction potential as low as -2.28 V has been proposed for the pair [HE]^{•+}/HE*. This value was calculated based on a ground state oxidation potential of 0.79 V vs. SCE in DMF and a band gap energy of 3.07 eV obtained from absorption spectrum in DMSO: J. Jung, J. Kim, G. Park, Y. You, E. J. Cho, *Adv. Synth. Catal.* **2016**, *358*, 74–80.
- [29] Triplet state energy value estimated based on the 3.07 eV band gap reported by Cho *et al.* (ref. 28).
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