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Organocatalytic Enantioselective Alkylation of Aldehydes with $[\text{Fe}(\text{bpy})_3]\text{Br}_2$ Catalyst and Visible Light.

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ABSTRACT: Catalytic amounts (2.5 mol%) of $[\text{Fe}(\text{bpy})_3]\text{Br}_2$ complex in the presence of visible light, and the MacMillan catalyst **3** (20 mol%), are highly effective in promoting an enantioselective organocatalytic photoredox alkylation of aldehydes with various α -bromo carbonyl compounds. Reaction yields of isolated compounds and enantioselectivities are very good and comparable to the ones obtained by $[\text{Ru}(\text{bpy})_3]^{2+}$, organic dyes, or semiconductors, in the presence of the same organocatalysts. The use of first row abundant and cheap metals in photocatalyzed reactions can open new perspectives in stereoselective organic synthesis.

KEYWORDS Photocatalysis, $[\text{Fe}(\text{bpy})_3]\text{Br}_2$, Organocatalysis, Stereoselective alkylations, Aldehydes, Radicals.

Due to the mild reaction conditions and the high enantiomeric excesses obtained, asymmetric catalysis promoted by visible light, a sustainable and economical source of energy, is emerging as an active new field of investigation.¹ There are basically three leading strategies to promote enantioselective chemical reactions by light with enamine organocatalysts and bromo derivatives,² and all of them are based on photoinduced electron transfer (ET) processes.³ In 2008, MacMillan's group reported the first example of merging visible light induced photoredox catalysis in asymmetric organocatalysis by using $[\text{Ru}(\text{bpy})_3]^{2+}$ as photosensitizer (Figure 1, A).⁴ Chiral enamines formed *in situ* as nucleophilic partners are able to intercept the radical species generated by the photoredox event. Similarly, radical species can be generated by other photosensitizers as organic dyes,⁵ semiconductors,⁶ or chiral iridium complexes.⁷ A variant for the generation of radical species was disclosed by Melchiorre, that used chiral enamines able to form electron donor-acceptor (EDA) complexes with benzyl halides electrophiles. The resulting EDA complexes are capable of absorbing visible light and inducing a charge transfer (Figure 1, B).⁸ Melchiorre was also reporting that quite nucleophilic enamines⁹ can photoreduce species that are not forming with them EDA complexes (Figure 1, C).¹⁰ In all these processes three general events are occurring in order to drive the chemical reaction: i) a photo driven-initiation step; ii) the electron transfer (ET) involving the photosensitizer (or the EDA complexes, or enamine); iii) the oxidation of generated α -amino radicals to iminium ions (Figure 1).

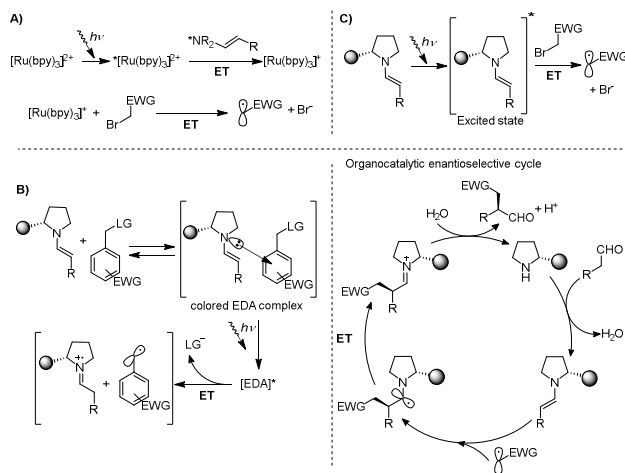
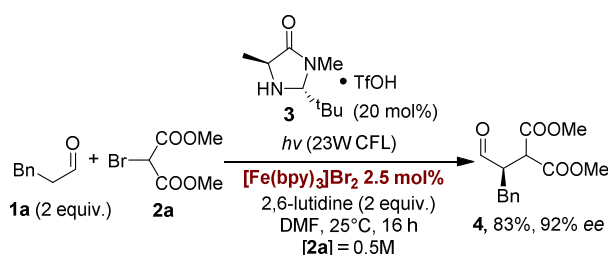


FIGURE 1. Strategies in stereoselective photocatalytic addition of bromo derivatives: A, asymmetric photocatalysis with $\text{Ru}(\text{bpy})_3^{2+}$; B, asymmetric photocatalysis induced by EDA complex; C, enamine photo-induced electron transfer.

Most commonly employed photosensitizers are based on rare and expensive ruthenium and iridium complexes, although interesting processes based on copper^{11,12} and chromium¹³ photosensitizers have been described. The discovery and employment of metal complexes as alternative, earth-abundant, first-row transition metals for photoinduced synthetic organic transformations¹³ would be a major advance in the area of photocatalysis. Particularly, the use of iron(II) complexes would be in fact quite attractive for photocatalytic stereoselective reactions as iron is inexpensive, and very abundant.

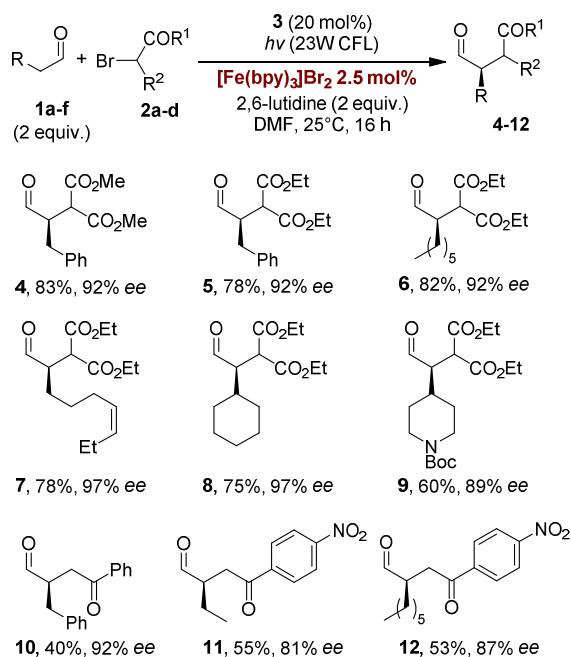
Photophysical properties of iron(II) polypyridyl complexes were fully investigated.¹⁴ The prototypical $[\text{Fe}(\text{bpy})_3]^{2+}$ complex displays a metal-to-ligand charge-transfer (MLCT) band in the visible region. The lowest energy excited state is a metal-centered (MC) state, which is formed within a hundred femtoseconds from the MLCT excited states and it is not luminescent, due to fast non-radiative decay to the ground state (ca. 650 ps lifetime).^{14f} $[\text{Fe}(\text{bpy})_3]^{2+}$ is not a good candidate for dynamic electron-transfer processes because of the extremely short lifetime of the lowest energy excited state. Nevertheless, iron(II) polypyridyl complexes have been reported as photosensitizers of TiO_2 demonstrating ultrafast electron injection.¹⁵ In this communication, we report that the combination of 2.5 mol% of $[\text{Fe}(\text{bpy})_3]\text{Br}_2$ and visible light can effectively replace $[\text{Ru}(\text{bpy})_3]^{2+}$ or other photosensitizers in practical and effective organocatalytic stereoselective reactions.



SCHEME 1. Optimized conditions for the $[\text{Fe}(\text{bpy})_3]\text{Br}_2$ photocatalyzed reaction.

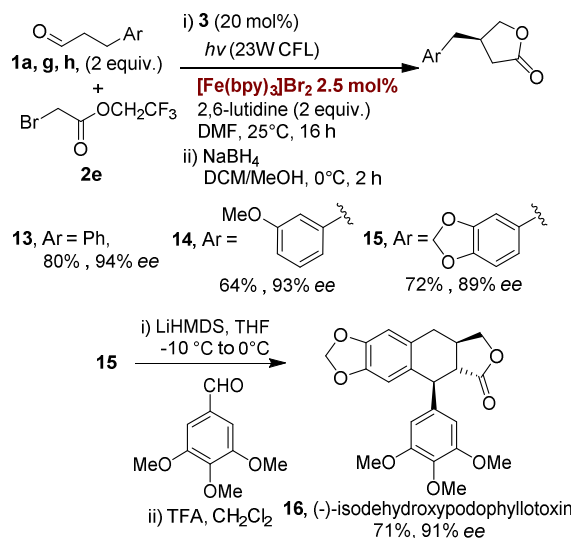
In order to investigate the possibility to use iron(II) polypyridyl complexes in photocatalysis we have selected, as benchmark reaction, the α -alkylation of aldehydes developed by MacMillan (Scheme 1).^{4a} Various Fe(II) complexes were tested in the model reaction with chiral (racemic and enantiopure) organocatalysts (see SI for details). We discovered that $[\text{Fe}(\text{bpy})_3]\text{Br}_2$ used in catalytic amount (2.5 mol%) was a compelling and effective photosensitizer for promoting the reaction between hydrocinnamaldehyde and dimethyl bromomalonate, in the presence of 20 mol% of the organocatalyst **3** (Scheme 1) and upon irradiation with visible light.

Isolated yields and enantiomeric excesses obtained were comparable to the reaction promoted by $[\text{Ru}(\text{bpy})_3]^{2+}$. No decomposition of the photosensitizer was observed at the end of the reaction, as monitored by the absorption band in the visible region (Figure S11). Among all the iron complexes investigated (see SI) $[\text{Fe}(\text{bpy})_3]\text{Br}_2$ gave the maximum yields, and from various solvent investigated, DMF was the solvent of choice; enantioselectivity was optimal at room temperature. The reaction was investigated in detail with various aldehydes and bromo derivatives. The salient results are reported in Scheme 2. In general, a good scope for the reaction was observed. It was possible to employ in the reaction various bromo-substituted carbonyl compounds as the reaction tolerates various functional and protecting groups. No side reaction is observed with aldehydes bearing alkene functional groups.



SCHEME 2. Scope of the stereoselective alkylation promoted by $[\text{Fe}(\text{bpy})_3]\text{Br}_2$.

In addition, we have investigated the practical use of photoinduced iron(II) reaction to access useful synthetic intermediates. The addition of bromo ester **2e** to hydrocinnamaldehydes **1a, g, h** (see SI for preparation) gave in a straightforward manner the lactons **13–15**, key intermediates for the synthesis of biologically active compounds.

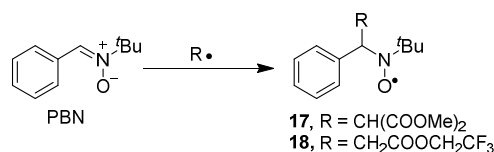


SCHEME 3. Preparation of enantioenriched lactones via alkylation of aldehydes and synthesis of (-)-isodehydroxypodophyllotoxin.

The lacton **15** was transformed into the natural product **16** by a straightforward transformation as illustrated in Scheme 3.^{16,17,18}

To clarify mechanistic details about our reaction, we conducted some control experiments. As CFL lamp emits also in the UV region (Figure S14) where reagents absorb light (green line in Figure S12 is the reaction mixture without the photosensitizer), we ruled out a UV-induced mechanism by testing the reaction upon visible irradiation ($\lambda > 420$ nm) (Table S6), where only the photosensitizer $[\text{Fe}(\text{bpy})_3]\text{Br}_2$ absorbs light and effectively promotes the reaction.¹⁹ On the other hand, in the presence of the iron sensitizer and in the absence of light, the reaction does not proceed. (Table S6).

In order to prove the formation of radical species under the combined action of light and $[\text{Fe}(\text{bpy})_3]\text{Br}_2$ we undertook the study of the formation of radicals with EPR, in the presence of a radical trap.^{20,21} The spin trap experiments were performed in the presence of PBN (see Scheme 4). In order to get a good EPR signal for the correct characterization of the spin adduct, we initially irradiated the reaction mixture with light containing also near UV ($\lambda > 320$ nm). Actually, irradiation at these wavelengths of a deoxygenated DMF solution containing bromomalonate **2a** (0.5 M), $[\text{Fe}(\text{bpy})_3]\text{Br}_2$ (10 mol%) and PBN (0.1 M), resulted in a strong EPR signal consisting of a characteristic doublet of triplets (Figure 2a). The spectrum was attributed to spin adduct **17** (Scheme 4), resulting from addition of malonate alkyl radical to PBN, as suggested by the values of the EPR parameters²² ($a_N = 14.95$ G, $a_H = 4.75$ G, $g = 2.0057$) which are typical for PBN adducts with alkyl radicals having carbonyl groups in α -position.¹⁷



SCHEME 4. A Radical trap experiment demonstrates the formation of radical induced by iron and visible light.

We then repeated the same experiment by employing visible light ($\lambda > 420$ nm), thus mimicking the synthetic reaction conditions (Figure 2b). Also in this case the signal due to the radical adduct **17** was clearly detected although the intensity of the signals was weaker with respect to that recorded in the presence of UV-visible light. No signals were observed in the absence of light or after irradiation of a solution containing only the photosensitizer and the spin trap (Figure 2c).

A similar trend was also observed in the presence of bromoester **2e** (Figure S15). The PBN-adduct (**18**) was characterized by slightly different EPR parameters: $a_N = 14.85$ G, $a_H = 5.55$ G, $g = 2.0057$. In this case, however, the intensities of EPR spectra were lower if compared to those observed in the spectra recorded with bromomalonate **2a** under the same experimental conditions. This indicates that the formation of the less stable alkyl radical from **2e** is more difficult.²³

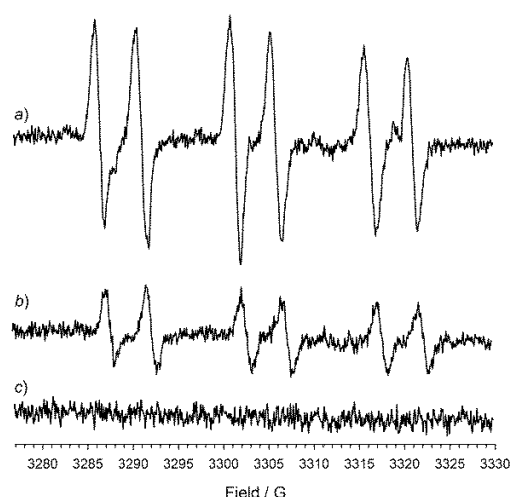
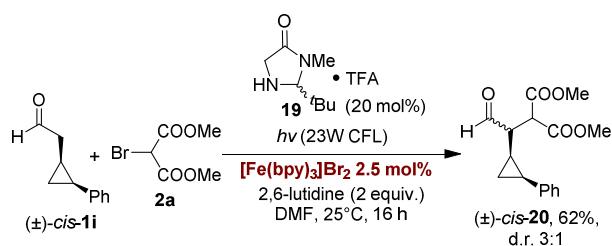


FIGURE 2. EPR spectra of spin adduct **17** generated in DMF in the presence of dimethyl bromomalonate **2a** (0.5 M) and PBN (0.1 M) as the spin trap at room temperature. Reaction conditions: a) $[\text{Fe}(\text{bpy})_3]\text{Br}_2$ (10 mol%), irradiation with UV-visible light ($\lambda > 320$ nm); b) $[\text{Fe}(\text{bpy})_3]\text{Br}_2$ (10 mol%), irradiation with visible light ($\lambda > 420$ nm); c) $[\text{Fe}(\text{bpy})_3]\text{Br}_2$ (10 mol%) no irradiation.

From these experiments it is clear that visible light and iron(II) polypyridyl complexes are necessary to drive the reaction to completion. Furthermore, EPR studies with a radical trap evidence the formation of a radical and the reaction is completely shut down in the presence of TEMPO ~~catalytic amount~~ (20 mol% and 100 mol%) of TEMPO. To get more insights onto the mechanism, an experiment with light turned off and on (Figures S1-2) was performed and showed that reaction is proceeding also when light is switched off, suggesting the existence of a radical chain mechanism.²⁴ The photosensitizer is capable of promoting, upon excitation, a chain radical reaction in which the photochemical event is only the starting step (Figure 3),^{10,19} in agreement with the results obtained by femtosecond laser absorption spectroscopy (see SI for details).²²

We also examined if the proposed chain process would proceed through enamine catalysis with a radical clock-containing aldehydes. If an α -cyclopropylcarbonyl radical is formed during the iron(II) induced photocatalytic process by ET, the aldehyde **1i**, containing a *cis*-cyclopropane ring, will be leading to the more stable *trans*-cyclopropyl product **2o** by opening-closure of the cyclopropyl ring. The formation of only *cis*-**2o** provides a strong evidence that an enamine addition mechanism is operating (Scheme 5).



SCHEME 5. Alkylation reaction performed in the presence of a radical-clock.

Therefore, we propose that the reaction is proceeding through a radical chain propagation pathway (see Figure 3).¹⁰ The addition of the radical **III** to enamine **II** is the enantio-discriminating step.

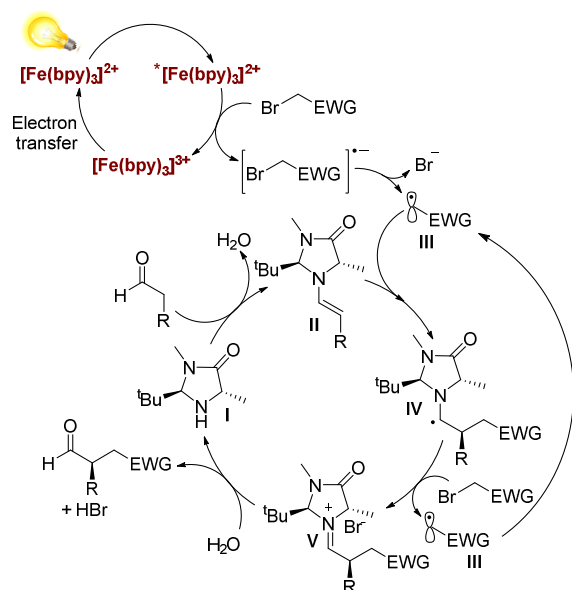


FIGURE 3. Suggested catalytic cycle for the Fe(II) alkylation.

The $[\text{Fe}(\text{bpy})_3]\text{Br}_2$ photosensitizer acts as a reductant for initiating the chain mechanism, as proposed in Figure 3. The ability of the amidoalkyl radical **IV** to behave as strong reducing agent²⁶ induces the reduction of bromo-malonate, regenerating the radical **III**.^{27,28}

In conclusion, we discovered another class of valuable photosensitizers based on first-row transition metals in the arena of light-activated catalysis for synthetic transformations. To our knowledge, this work represents the first report of the use of iron(II) polypyridyl complexes being applied in stereoselective photocatalysis. Not only this work opens new perspectives in the area of asymmetric transformations, but raises new questions about the use of cobalt, and manganese complexes as alternative photosensitizers based on earth-abundant metals. Further synthetic applications in photocatalysis of iron complexes, and other first row metals will be reported in due course.

ASSOCIATED CONTENT

Supporting Information. Screening tests, and light effect tests. Photophysical measurements and EPR studies. Detailed procedures. Copies of NMR spectra for all compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript. A. G. was involved in the discovery and development of the photochemical reaction. A. G. and L. M. performed the experiments. M. M., M. N. and P. C. designed and performed the photophysical measurements. M. L. designed and performed the EPR experiments. P. G. C. conceived and directed the project and wrote the manuscript with contributions from all the authors.

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ABBREVIATIONS

Bpy, 2,2'-bipyridine; DCM, dichloromethane; DMF, *N,N*-dimethylformamide; PBN, *N-tert*-butyl- α -phenylnitron; TEMPO, 2,2,6,6-tetramethyl-1-piperidinyloxy.

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- (28) The [Fe(bpy)₃]Br₂ is not decomposed or oxidized during the reaction. As possible steps for the reduction of Fe(III) to Fe(II) we propose that the α -aminoalkyl radical produced after the addition of the malonate, or the oxidation of sacrificial enamine are the compelling reductants. For SOMO chemistry performed with Fe polypyridyl complexes in which Fe(III) complexes are used as stoichiometric oxidants of enamines, see: Comito, R. J.; Finelli, F. G.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2013**, 135, 9358-9361.

SYNOPSIS TOC

Strike the iron...while is hot! Iron polypyridyl complexes are efficient catalysts (2.5 mol%) for the photocatalytic synergistic enantioselective alkylation of aldehydes performed with a MacMillan catalyst (20 mol%). The application of low cost and abundant metals will be next frontier in organic photocatalysis for ET, radical reactions, and photoinduced mediated organic processes.

