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ABSTRACT: Catalytic amounts (2.5 mol%) of [Fe(bpy)$_3$]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 [Ru(bpy)$_3$]$_2^{2+}$, 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.

Due to the mild reaction conditions and the high enantioselective process observed, 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 [Ru(bpy)$_3$]$_2^{2+}$ as photosensitizer (Scheme 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 (Scheme 1, B).⁸ Melchiorre was also reporting that quite nucleophilic enamines⁹ can photoreduce species that are not forming with EDA complexes (Scheme 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).

Most commonly employed photosensitizers are based on rare and expensive ruthenium and iridium complexes, although interesting processes based on copper¹¹ and chromium¹² photosensitizers have been described. The discovery and employment of metal complexes as alternative, earth-abundant, first-row transition metals for photoinuced synthetic organic transformations¹² 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, non-toxic, and very abundant.

FIGURE 1. Strategies in stereoselective photocatalytic addition of bromo derivatives.
Photophysical properties of iron(II) polypyridine complexes were fully investigated. The prototypical [Fe(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). [Fe(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) polypyridine complexes have been reported as photosensitizers of TiO$_2$ demonstrating ultrafast electron injection. In this communication, we report that the combination of 2.5 mol% of [Fe(bpy)$_3$]Br$_2$ and visible light can effectively replace [Ru(bpy)$_3$]$^{2+}$ or other photosensitizers in practical and effective organocatalytic stereoselective reactions.

**SCHEME 1.** Optimized conditions for the [Fe(bpy)$_3$]Br$_2$ photocatalyzed reaction.

In order to investigate the possibility to use iron(II) polypyridine complexes in photocatalysis we have selected, as benchmark reaction, the $\alpha$-alkylation of aldehydes developed by MacMillan (Scheme 1). Various Fe(II) complexes were tested in the model reaction with chiral (racemic and enantiopure) organocatalysts (see SI for details). We discovered that [Fe(bpy)$_3$]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 and upon irradiation with visible light.

Isolated yields and enantiomeric excesses obtained were comparable to the reaction promoted by [Ru(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 S9). Among all the iron complexes investigated (see SI) [Fe(bpy)$_3$]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. 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 [Fe(bpy)$_3$]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 hydrocinnamic aldehydes 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 dehydroxypodophyllotoxin.

The lactone 15 was transformed into the natural product 16 by a straightforward transformation as illustrated in Scheme 3.
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 S10 is the reaction mixture without the photosensitizer), we ruled out a UV-induced mechanism by testing the reaction upon visible irradiation ($\lambda > 320$ nm) (Table S6), where only the photosensitizer $[\text{Fe(bpy)}]_3\text{Br}_2$ absorbs light. On the other hand, in the presence of the iron sensitizer and in the absence of light, the reaction does not proceed. (see Table S6, entries 2 and 8, and EPR experiments).

In order to prove the formation of radical species under the combined action of light and $[\text{Fe(bpy)}]_3\text{Br}_2$, we undertook the study of the formation of radicals with EPR, in the presence of a radical trap.\(^\text{17,18}\) 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 $2\text{a}$ (0.5 M), $[\text{Fe(bpy)}]_3\text{Br}_2$ (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 parameters\(^\text{19}\) ($a_{\alpha} = 14.95$ G, $a_{\beta} = 4.75$ G, $g = 2.0057$) which are typical for PBN adducts with alkyl radicals having carbonyl groups in $\alpha$-position.\(^\text{17}\)

We then repeated the same experiment by employing visible light ($\lambda > 420$ nm), thus mimicking the synthetic reaction conditions. 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 (Figure 2b). 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 $2\text{e}$ (see SI). The PBN-adduct $18$ was characterized by slightly different EPR parameters: $a_{\alpha} = 14.85$ G, $a_{\beta} = 5.55$ 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 $2\text{a}$ under the same experimental conditions. This indicates that the formation of the less stable alkyl radical from $2\text{e}$ is more difficult.\(^\text{20}\)

From these experiments it is clear that visible light and iron(II) polypyrindine complexes are necessary to drive the reaction to completion.\(^\text{21}\) Furthermore, EPR studies with a radical trap evidence the formation of a radical and the reaction is completely shut down in the presence of 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 SX) was performed and showed that reaction is proceeding also when light is switched off, suggesting the existence of a radical chain mechanism.\(^\text{22}\) The photosensitizer is capable of promoting, upon excitation, a chain radical reaction in which the photochemical event is only the starting step (Figure 2),\(^\text{20,16}\) in agreement with the results obtained by femtosecond laser absorption spectroscopy (see SI for details).

We also examined if the proposed chain process would proceed through enamine catalysis with a radical clock-containing aldehydes. If an $\alpha$-cyclopropylcarbinyl radical is formed during the iron(II) induced photocatalytic process by ET, the aldehyde $1\text{i}$, containing a $\text{ciscyclopropyl}$ ring, will be leading to the more stable $\text{transcyclopropyl}$ product $2\text{o}$ by opening-closure of the cyclopropyl ring. The formation of only $\text{cis-2o}$ 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). 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 [Fe(bpy)₃]Br₂ photosensitizer acts as a reductant for initiating the chain mechanism, as proposed in Figure 2. The ability of the amidoalkyl radical IV to behave as strong reducing agent induces the reduction of bromomalonate, regenerating the radical III.

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) polypyridine 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 test. 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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Notes
Any additional relevant notes should be placed here.

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ABBREVIATIONS
Bpy, 2,2'-bipyridine; DCM, dichloromethane; DMF, N,N-dimethylformamide; PBN, N-tert-butyl-α-phenylnitrone.

REFERENCES


(16) Although enamines derived from Hayashi-jørgensen catalysts are able to promote the stereoselective alkylation reaction with bromo-malonates (ref (10)) in absence of any photosensitizers, the less nucleophilic enamines derived from MacMillan imidazolidinone 3 are quite poor catalyst for this reaction giving low yields after prolonged reaction time (see SI published by Melchiorre, ref. (10), for details).


(20) The C-H bond dissociation energies in H-CH(COOEt) and H-CH(COOMe) are 96 and 90.5 kcal mol⁻¹, respectively (Luo, Y.-R. in “Bond Dissociation Energies in Organic Compounds”, 2003, CRC Press).

(21) We were unable to observe by ultrafast spectroscopy the electron transfer quenching of the iron complex excited state in the presence of enamine and bromomalonate at different concentration. However, the uncertainty accompanying the ultrafast measurement, in particular in the sub-ps region (i.e., in the time scale of the MLCT lifetime), suggests that the quenching process takes place with a rather low efficiency (5% or even less). For a detailed discussion, see SI.

(22) For an important study concerning the off-on experiments, and photochemical processes, see: Cismesia, M. A.; Yoon, T. P. Chem. Sci. 2015; DOI: 10.1039/C5SC02185E.


(24) An atom transfer mechanism, in which the α-aminoalkyl radical is abstracting a bromine atom, has been also suggested as key step for ruthenium catalyzed reaction, see ref 23. In this alternative mechanism, the α-amidoalkyl radical after abstractation of the bromine is forming a α-bromo amine adduct, that is decomposed to the iminium ion pair.

(25) The [Fe(bpy)]Br₃ 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.
SYNOPSIS TOC

Strike the iron…while is hot! Iron polypiridyl 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, non-toxic, and abundant metals will be next frontier in organic photocatalysis for ET, radical reactions, and photoinduced mediated organic processes.